SALICYLIC ACID AND RELATED COMPOUNDS

1. Introduction

o-Hydroxybenzoic acid [69-72-7] (salicylic acid) appears very early in the historical recognition and preparation of organic compounds. The extract of roots, bark, leaves, and fruit of many common, widely distributed plants and trees contains the glucosides of methyl salicylate [119-38-6] and salicyl alcohol [90-01-7]. Salicylic acid does not appear in nature in large amounts, but is easily derived from the glucosides by extraction and mild oxidation. As an indicator of early knowledge of the analgesic nature of these materials, Hippocrates, about 400 BC, recommended the extract of willow leaves for relief of pain in childbirth.

Related to salicylic acid as isomers are *m*-hydroxybenzoic acid [99-06-9] and *p*-hydroxybenzoic acid [99-96-7]. The three are commonly known as the monohydroxybenzoic acids; because of the shared chemical reactions, the three isomers are discussed together herein. These monohydroxybenzoic acids have a broad range of applications from paper coatings and liquid crystal preparations to drugs. Salicylic acid and its derivatives are interesting because of their demonstrated activity as analgesics, antipyretics, and antiinflammatory agents, whereas the para-substituted acids and esters known as parabens have activity as preservatives for food.

2. Physical Properties

o-Hydroxybenzoic acid is obtained as white crystals, fine needles, or fluffy white crystalline powder. It is stable in air and may discolor gradually in sunlight. The synthetic form is white and odorless. When prepared from natural methyl salicylate, it may have a light yellow or pink tint and a faint, wintergreen-like odor. *m*-Hydroxybenzoic acid crystallizes from water in the form of white needles and from alcohol as platelets or rhombic prisms. *p*-Hydroxybenzoic acid crystallizes in the form of monoclinic prisms. Various physical properties of hydroxybenzoic acids are listed in Tables 1–4.

3. Reactions

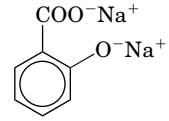
The hydroxybenzoic acids have both hydroxyl and the carboxyl groups and, therefore, participate in chemical reactions characteristic of each of these moieties. In addition, these acids can undergo electrophilic ring substitution. The following reactions are discussed in terms of salicylic acid, but are characteristic of all the hydroxybenzoic acids.

3.1. Carboxylic Acid Group. Reactions of the carboxyl group include decarboxylation, reduction to alcohols, and the formation of salts, acyl halides, amides, and esters.

Generally, the carboxyl group is not readily reduced. Lithium aluminum hydride is one of the few reagents that can reduce these organic acids to alcohols.

The scheme involves the formation of an alkoxide, which is hydrolyzed to the alcohol. Commercially, the alternative to direct reduction involves esterification of the acid followed by the reduction of the ester.

The acid dissolves in aqueous sodium carbonate or sodium bicarbonate to form sodium salicylate [54-21-7]. However, if salicylic acid is dissolved in the presence of alkali metals or excess sodium hydroxide, the disodium compound [13639-21-9] is formed.



Salicylic acid can be converted to salicyloyl chloride [1441-87-8] by reaction with thionyl chloride in boiling benzene. The formation of acyl halide may also extend to reaction with the phenolic hydroxyl. The reaction with phosphorus tri- and pentachlorides is not restricted to the formation of the acid chloride. Further interaction of the phosphorus halide and the phenolic hydroxyl results in the formation of the phosphoric or phosphorous esters.

The formation of amides can be accomplished by dehydration of the ammonium salts of salicylic acid. The more common method for amines is the reaction of the ester, acyl halide, or anhydride with an amine or ammonia. Each step is fast and essentially irreversible.

Esterification is frequently carried out by direct reaction of the carboxylic acid with an alcohol in the presence of a small amount of mineral acid, usually concentrated sulfuric or hydrochloric acid. The esters of commercial importance in both *o*- and *p*-hydroxybenzoic acid are the methyl esters. Direct esterification has the advantage of being a single-step synthesis, but being an equilibrium it is easily reversed. The reaction to the ester is driven by either of the reactants in large excess or by removal of the reaction product during the course of the reaction. Another esterification method infrequently used is to react the acid chloride with the appropriate alcohol. Still another method is to react the alkali salt with an alkyl or an arylalkyl halide.

Decarboxylation of salicylic acid takes place with slow heating because of the presence of the electronic configuration of the carboxyl group ortho to the hydroxyl group, but does not occur in the other isomers of hydroxybenzoic acid. On rapid heating, salicylic acid sublimes because of its low vapor pressure. This property allows commercial separation from the other isomers as a means of purification analogous to distillation. The differences in the vapor pressures are shown in Table 4.

3.2. Hydroxyl Group. Reactions of the phenolic hydroxyl group include the formation of salts, esters, and ethers. The sodium salt of the hydroxyl group is alkylated readily by an alkyl halide (Williamson ether synthesis). Normally, only alkylation of the hydroxyl is observed. However, phenolate ions are ambident nucleophiles and under certain conditions, ring alkylation can also occur. Proper choice of reaction conditions can produce essentially exclusive sub-

stitution. Polar solvents favor formation of the ether; nonpolar solvents favor ring substitution.

Esters of the phenolic hydroxyl are obtained easily by the Schotten-Baumann reaction. The reaction in many cases involves an acid chloride as the acylating agent. However, acylation is achieved more commonly by reaction with an acid anhydride. The single most important commercial reaction of this type is the acetylation of salicylic acid with acetic anhydride to produce acetylsalicylic acid [50-78-2] (aspirin).

3.3. Ring-Substitution Reactions. In the introduction of a third group into a disubstituted benzene, the position the group takes depends on the other groups present. In the case of salicylic acid, the hydroxyl directs ortho- and para-, and the carboxyl directs meta-substitution. The ortho–para director prevails because unlike the meta director it activates the ring. Specifically, the electron-donating hydroxyl group increases the electron density in the 3- and 5-positions. The electron withdrawal nature of the carboxyl group decreases the electron density around the 4- and 6-positions, which further enhances the electron density of the 3- and 5-positions. As a rule, direct substitution occurs more easily in the less sterically hindered 5-position with formation of only small amounts of the 3-substituted and 3,5-disubstituted product. High yields of the 3-substituted salicylic acid usually can only be prepared indirectly.

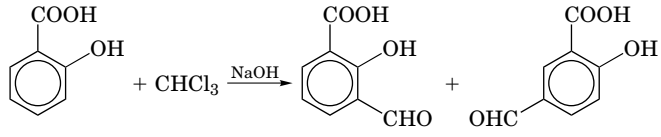
Direct halogenation of salicylic acid is generally carried out in glacial acetic acid. As expected, the main product is the 5-halo-salicylic acid with small quantities of the 3-halo and 3,5-dihalosalicylic acids.

Reaction with cold nitric acid results primarily in the formation of 5-nitrosalicylic acid [96-97-9]. However, reaction with fuming nitric acid results in decarboxylation as well as the formation of 2,4,6-trinitrophenol [88-89-1] (picric acid). Sulfonation with chlorosulfonic acid at 160°C yields 5-sulfosalicylic acid [56507-30-3]. At higher temperatures (180°C) and with an excess of chlorosulfonic acid, 3,5-disulfosalicylic acid forms. Sulfonation with liquid sulfur trioxide in tetrachloroethylene leads to a nearly quantitative yield of 5-sulfosalicylc acid (1).

Because salicylic acid contains the deactivating meta-directing carboxyl group, Friedel-Crafts reactions are generally inhibited. This effect is somewhat offset by the presence of the activating hydroxyl group. Salicylic acid reacts with isobutyl or *t*-butyl alcohol in 80 wt % sulfuric acid at 75°C to yield 5-*t*-butylsalicylic acid [16094-31-8]. In the case of isobutyl alcohol, the intermediate carbonium ion rearranges to $(CH_3)_3C^+$.

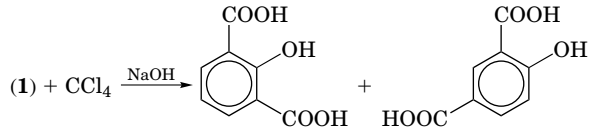
3.4. Miscellaneous Reactions. The Reimer-Tiemann reaction of salicylic acid (**1**) with chloroform and alkali (eq. 1) results in the 3- and 5-formyl derivatives. If the reaction is carried out with carbon tetrachloride, the corresponding dicarboxylic acids form (eq. 2). The products (2) and (3) are 2-hydroxy-1,3-benzenedicarboxylic acid [606-19-2] and 4-hydroxy-1,3-benzenedi-

carboxylic acid [636-46-4], respectively.



(1)

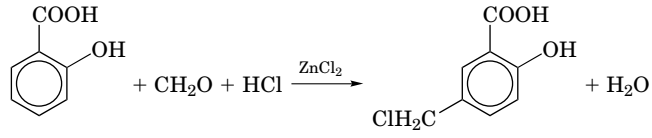
(**1**)



(2)

(**2**) (**3**)

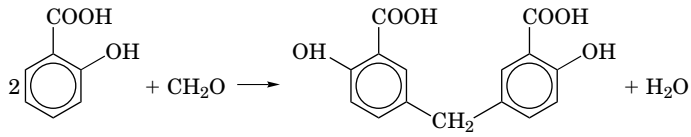
Alkylation involving formaldehyde in the presence of hydrogen chloride is known as chloromethylation (eq. 3). The reagent may be a mixture of formalin and hydrochloric acid, paraformaldehyde and hydrochloric acid, a chloromethyl ether, or a formal. Zinc chloride is commonly employed as a catalyst, although many other Lewis acids can be used. Chloromethylation of salicylic acids yields primarily the 5-substituted product 5-chloromethylsalicylic acid [10192-87-7] (**4**).



(3)

(**4**)

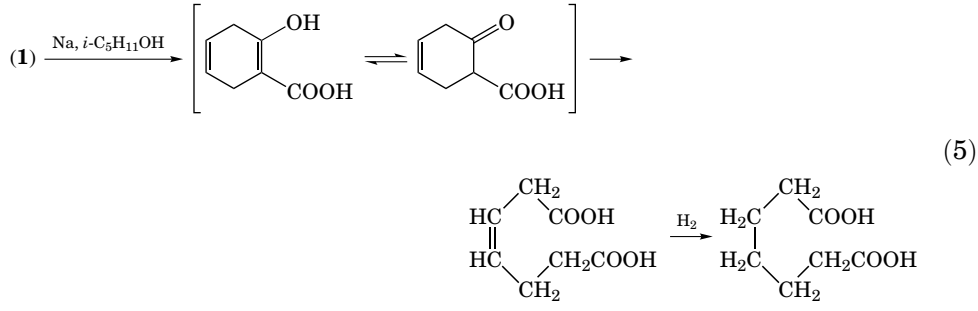
The reaction of salicylic acid with formaldehyde in the presence of catalytic amounts of strong mineral acid results in the condensation product methylene-5,5′-disalicylic acid [122-25-8] (eq. 4).



(4)

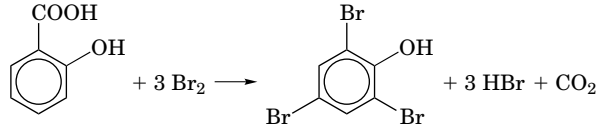
Salicylic acid, upon reaction with amyl alcohol and sodium, reduces to a ring-opened aliphatic dicarboxylic acid, ie, pimelic acid (eq. 5). The reaction proceeds through the intermediate cyclohexanone-2-carboxylic acid. This novel reaction involves the fission of the aromatic ring to *cis*-hexahydrosalicylic acid when salicylic acid is heated to 310°C in an autoclave with strong alkali. Pimelic acid is

formed in 35–38% yield and is isolated as the diethyl ester.



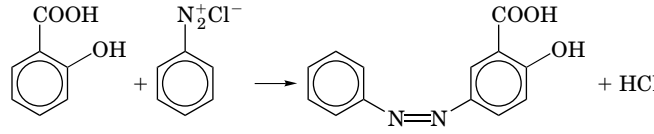
(5)

During certain substitution reactions, the carboxyl group is often replaced by the entering group. An example is fuming nitric acid, which results in the formation of trinitrophenol. Another is the bromination of salicylic acid in aqueous solution to yield 2,4,6-tribromophenol [25376-38-9] (eq. 6).



(6)

Salicylic acid couples with diazonium salts in the expected manner. With diazotized aniline, ie, benzenediazonium chloride, the primary product is 5-phenylazosalicylic acid [3147-53-3] (eq. 7).



(7)

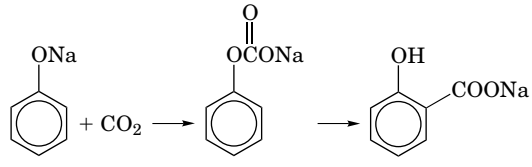
The close proximity of the carboxyl and the hydroxyl groups can be used for heterocylic synthesis, as in the preparation of hydroxyxanthones (2).

4. Manufacture of Salicylic Acid

4.1. Natural Occurrence. Salicyl alcohol glucosides [138-52-3] (salicin) occur in *Populus balsamifera* (poplar) and *Salix helix* (willow) trees. Methyl salicylate glucosides occur in *Betula* (birch) and *Fagus* (beech) trees. A more familiar source of methyl salicylate is the leaves of *Gaultheria procumbens* (wintergreen). The color reaction exhibited by iron salts with the salicylates was reported in 1798 (3), which made identification and a crude estimation of the concentration or strength of salicylates in botanical extracts routine for the apothecary. The original name, *Acidium spiricum*, was derived from its identification with one source, the roots, blossoms, and fruit of *Spiraea ulmaria*. During

the early history of laboratory chemical synthesis, salicylic acid was first prepared in 1837 through the action of potassium hydroxide on the naturally occurring salicin, a glucoside of salicyl alcohol (4,5).

4.2. Early Synthesis. Reported by Kolbe in 1859, the synthetic route for preparing the acid was by treating phenol with carbon dioxide in the presence of metallic sodium (6). During this early period, the only practical route for large quantities of salicylic acid was the saponification of methyl salicylate obtained from the leaves of wintergreen or the bark of sweet birch. The first suitable commercial synthetic process was introduced by Kolbe 15 years later in 1874 and is the route most commonly used in the 1990s. In this process, dry sodium phenate reacts with carbon dioxide under pressure at elevated (180–200°C) temperature (7). There were limitations, however; not only was the reaction reversible, but the best possible yield of salicylic acid was 50%. An improvement by Schmitt was the control of temperature, and the separation of the reaction into two parts. At lower (120–140°C) temperatures and under pressures of 500–700 kPa (5–7 atm), the absorption of carbon dioxide forms the intermediate phenyl carbonate almost quantitatively (8,9). The sodium phenyl carbonate rearranges predominately to the *ortho*-isomer, sodium salicylate (eq. 8).



(8)

4.3. Current Methods. The general outline of the Kolbe-Schmitt reaction, is as follows. In the first step, phenol and hot aqueous caustic are mixed to produce the sodium phenate which is taken to dryness. Next, the phenate and dry carbon dioxide are introduced into the carbonator. Air is excluded to minimize oxidation and the formation of colored compounds. The gas–solid mixture is agitated and heated, first at low temperature, followed by several hours at higher temperatures, to complete the formation of sodium salicylate. Variations of this reaction have been noted in the literature and are still being investigated (10,11). One reported scheme produces salicylic acid or substituted salicylic acids by reaction of a granulated alkali metal salt of the respective phenolic compound with CO_2 in a fluidized bed at 20–130°C until at least 50–80% of the metal salt has been converted to the corresponding carbonate. In a second step, the temperature of the fluidized bed is increased to 140–210°C to complete the reaction to sodium salicylate or substituted sodium salicylate. These intermediate products are converted to the corresponding acid by acidification with mineral acid. High yields with less interference by tackiness is the claimed advantage (12,13). In most commercial processes, the crude sodium salicylate is cooled and then dissolved in water. If desired, dissolved color bodies can be eliminated via reduction by treating the solution with zinc dust on activated carbon. Finally, the water solution of sodium salicylate is filtered, and then acidified, to precipitate technical-grade salicylic acid. The technical-grade salicylic acid may be further purified by sublimation or recrystallization. During the sublimation

and recovery, the risk of dust explosions is minimized by circulating an inert gas through the sublimation chambers.

The carbonation of dried sodium phenate to sodium salicylate, followed by reaction with gaseous hydrogen chloride in a simultaneous neutralization–sublimation has been patented (14). The identified advantages are the minimization of the amount of heat needed for the sublimation process and the elimination of water during acidification, thus saving wastewater cleanup in this process. The heat liberated during the acidification provides the energy needed to sublime the salicylic acid because the heat of acidification and the heat of sublimation are opposite and nearly equal. The subliming chamber in this patented process for salicylic acid is much smaller in volume than the traditional sublimation chambers.

A manufacturing process has been described in which the *o*- and *p*-isomer ratio of the aromatic hydroxycarboxylic acid products resulting from the reaction of an alkali metal phenolate with CO_2 in an organic phosphine oxide solvent is controlled. The mole ratio of the organic phosphine oxide to the alkali metal phenolate is varied from 1 to 4, with the higher ratio favoring para-substitution. The monovalent phenols may be ring-substituted with a 2–12 carbon alkyl or 6–12 carbon aryl group (15). Other syntheses have been reported. The fusion of 2-sulfo- and 2-halobenzoic acid with alkali, and the oxidation of the cresols, *o*-hydroxybenzyl alcohol, and *o*-hydroxybenzaldehyde result in salicylic acid.

An interesting biochemical method of manufacture is the utilization of bioengineered *Pseudomonad* plasmid (16) or *Pseudomonas stutzeri* (17) in a culture medium to oxidize naphthalene or alkyl-substituted naphthalene. The metabolic oxidation products, unsubstituted or substituted salicylic acid, respectively, are recovered from the medium. DNA coding sequences in a strain of *Pseudomonad* plasmid are engineered to optimize the microbiological oxidation product yield. *P. stutzeri 5A* is cultured at 10–41°C at pH 6–9, and 25–35°C for 7–10 days. Surfactant is added to disperse the sparingly water-soluble naphthalene compound.

5. Specifications and Analysis

Specifications for salicylic acid are given in Table 5. The comparison of USP 23 (19), EP 84 (20), and BP 93 (21) shows the somewhat different requirements of these monographs. In monographed ingredient manufacturing, Current Good Manufacturing Practice (CGMP) should be followed. Typical salicylic acid specifications for technical and technical sublimed are given in Table 6.

6. Health and Safety Factors

Because salicylic acid is a moderate respiratory irritant, skin and eye contact should be avoided and dust mask protection should be used. General good hygiene and good housekeeping should be incorporated into procedures. If large quantities are to be handled, protective clothing with long sleeves and gauntlets as well as approved dust respirators should be used. A further consid-

eration is that dust concentrations as low as $9\,g/m^2$ can ignite. For safe practice, ignition and arcing sources should be recognized and eliminated.

The single-dose oral toxicity of salicylic acid is moderate. The LD_{50} in rats is 400–800 mg/kg.

It is a poison by ingestion, intravenous, and intraperitoneal routes. It is moderately toxic by subcutaneous routes (22).

Chemical goggles should be worn when handling salicylic acid because eye contact with the chemical can produce irritation and marked pain. If the eyes should come into contact with salicylic acid or its dusts, they should be irrigated promptly and continuously with water for at least 15 minutes before medical attention is sought. Single short exposures are not expected to cause significant irritation, but prolonged or repeated exposures may cause peeling of the skin, rash, itching, or blisters. If the acid contacts the skin, it should be washed off the skin promptly with soap and water. Contaminated clothing should be washed before reuse. If a rash appears, the patient should seek medical attention. Breathing of dusts generated in handling salicylic acid should be avoided. Handlers should wear approved air-purifying respirators. If the product is handled with reasonable care and dusts are controlled by ventilation, there is little likelihood of injury resulting from inhalation.

7. Uses of Salicylic Acid

During the late 1980s and early 1990s, approximately 60% of the salicylic acid produced in the United States has been consumed in the manufacture of aspirin [50-78-2]. However, several applications of the acid grew while the production of aspirin reached a plateau.

Salicylic acid USP, EP, and other pharmacopeial grades are used medically as antiseptic, disinfectant, antifungal, keratolytic agents and antiviral and antibacterial agents (23). Salicylic acid is formulated in lotion or ointment formulations for the treatment of dandruff, eczema, psoriasis, and various parasitic skin diseases. Because the keratolytic property of this aromatic acid has use in the safe removal of dead skin cells from the surface of healthy skin, the acid is used in concentrated salicylic acid solutions or suspensions to remove warts and corns. In more dilute form, salicylic acid preparations have found use in dandruff and eczema treatment. It is also used in antiaging formulations (24). Salicylic acid has been considered and found effective by the Advisory Committees to the FDA in various over-the-counter (OTC) drug regulated uses. Among these are acne products, dermatitis, dry skin, dandruff and psoriasis products, and foot care products (25).

Carbonless copypaper using salicylic acid and alkyl salicylic acid derivatives has become an active application area. The salicylic acid is incorporated into a resin or is encapsulated as one of the agents for pressure or thermally activated imaging. The pressure-sensitive dyes used are fluorane and phthalide compounds such as crystal violet lactone, malachite green lactone, benzoyl leuco methylene blue, Japanese pink, dibenzyl green, and One-Dye Black. The developers are mostly metal salts of alkylphenol resins or salicylic acid derivatives. The trend toward high sensitivity thermal color materials is exemplified by pro-

ducts for high speed fax and high brightness labels. A survey of more recent patents shows that improvements in near-infrared-absorbing color former resins are claimed for agents made by the introduction of zinc in the aromatic hydrocarbon resins, including salicylic acid–benzyl chloride derivative–styrene condensates, and carbonylated *p*-substituted phenol–mesitylene resins. Phenolic resins containing zinc salicylate successfully eliminate the reddening of black images (26,27). Salicylic acid derivatives form surfactants that can influence the rheologic properties of solutions. They impart controllable and useful viscous and elastic properties to aqueous liquids (28).

Several patents of interest include the use of salicylic acid with a quaternary ammonium salt of a long-chain alkyl compound as drag-reducing agents in aqueous media being transported under turbulent flow conditions. One stated application is in hot-water heating systems in large buildings. The large surfactant molecules reduce drag at low (0.2% and lower) concentrations and some of the compounds retain their activity for a year or more even above 90°C (29). Salicylic acid has been used as a cross-linking agent in the phenol–formaldehyde resin used in glue for plywood to give faster cures and in the same phenol–formaldehyde resins as a sand core and mold binder imparting higher tensile strength. Salicylic acid is also used as an intermediate in the manufacture of dyes. It is a coupling agent for azo dyes (qv) and a chelating agent in chromium dyes. An alkylation reaction to produce lubricating ore additives has been reported (30).

8. Related Compounds

8.1. Salts of Salicylic Acid. A large number of salts of salicylic acid have been prepared and evaluated for therapeutic or other commercial use. Table 7 lists those most frequently referenced. Sodium salicylate has analgesic, antiinflammatory, and antipyretic activities and was used extensively in the sixteenth and seventeenth centuries as a remedy, prepared from natural sources, for arthritis and rheumatism. The salt can be obtained directly from Kolbe-Schmitt carboxylation or by the reaction of salicylic acid with either aqueous sodium bicarbonate or sodium carbonate. The resulting mixture is heated until effervescence stops; the salt is then isolated by filtration and evaporation to dryness at low temperatures. Generally, the solution must be kept slightly acidic so that a white product is obtained; if the mixture is basic, a colored product results. The USP product contains 99.5–100.5% $NaC_7H_5O_3$ (anhydrous).

Magnesium salicylate, an analgesic and antiinflammatory agent, appears to have exceptional ability to relieve backaches. It is also used for the symptomatic relief of arthritis. Magnesium salicylate is prepared in a similar manner as sodium salicylate, using the appropriate magnesium carbonate salt.

Bismuth subsalicylate [5798-98-1] is employed as an antidiarrheal agent. It is taken orally in combination with other ingredients for protective, antacid action as well as antidiarrheal and antiseptic effects. Other salts of salicylic acid that are of interest are aluminum salicylate [18921-11-4], ammonium salicylate [528-94-9], calcium salicylate, lead salicylate [15748-73-9], lithium salicylate, mercury salicylate [5970-32-1], potassium salicylate, and strontium

salicylate [526-26-1]. In the past, many of these salicylates have been used in medicinal applications. These properties as pain-relieving agents have been reviewed by the Internal Analgesic Panel of the FDA using the established advisory panel procedure for the Tentative Final Monograph for Internal Analgesics (31). Only magnesium salts of salicylic acid and sodium are judged safe and effective (Category I). The salts in general also have a few nonmedical applications, eg, uv absorber systems for paints and coatings. However, interest has waned as nonextractable, more efficient uv agents have found their way into commerce. Commercially, the salts of salicylic acid account for less than 5% of the salicylic acid produced.

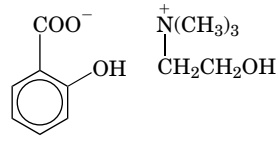
8.2. Esters of Salicylic Acid. The esters of salicylic acid account for an increasing fraction of the salicylic acid produced. Typically, the esters are commercially produced by esterification of salicylic acid with the appropriate alcohol using a strong mineral acid such as sulfuric as a catalyst. To complete the esterification, the excess alcohol and water are distilled away and recovered. The crude product is further purified, generally by distillation. For the manufacture of higher esters of salicylic acid, transesterification of methyl salicylate with the appropriate alcohol is the usual route of choice. However, another reaction method uses sodium salicylate and the corresponding alkyl halide to form the desired ester.

The main commercial applications for salicylate esters are as uv sunscreen agents and as flavor and fragrance agents. Several have application as topical analgesics. A number of salicylate esters of commercial interest and their physical properties are listed in Table 8.

Methyl salicylate is produced synthetically for commercial purposes by the esterification of salicylic acid with methanol or by extraction by steam distillation of wintergreen leaves or sweet birch bark. The source, natural or synthetic, is declared on the label. The methyl salicylate NF must assay not less than 98.0% and not more than 100.5% and be processed by Good Manufacturing Practice described in USP (19).

As a pharmaceutical, methyl salicylate is used in liniments and ointments for the relief of pain and for rheumatic conditions. As a flavor and fragrance agent, it is used in confectioneries, dentifrices, cosmetics, and perfumes. Other commercial applications for methyl salicylate are as a dye carrier, as a uv-light stabilizer in acrylic resins, and as a chemical intermediate.

Choline salicylate ((2-hydroxyethyl)trimethylammonium salicylate) is contained in a list of safe and effective compounds (31). Choline salicylate [2016-36-6] (**5**) is the only liquid salicylate preparation available and is often useful for arthritic patients who have difficulty swallowing tablets.

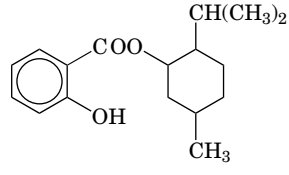


(**5**)

Phenyl salicylate (salol) is manufactured by heating salicylic acid and phenol in the presence of phosphorus oxychloride for 4–5 hours at 110–115°C. The molten product is separated, mixed with water, dried, and distilled under vacuum. Another process involves the transesterification of a salicylate such as methyl, with phenol in the presence of an alkali or alkaline-earth phenate. Medicinally, phenyl salicylate was formerly used as an intestinal antiseptic. However, the main applications of phenyl salicylate have been related to the ability to absorb uv light over the wavelengths of 290–325 nm. As an effective uv-light absorber, phenyl salicylate was incorporated in alkyd paints, waxes, and polishes, but has been largely replaced in this application by less extractable, more effective compounds.

Benzyl salicylate can be prepared by the reaction of benzyl chloride with an alkali salt of salicylic acid at 130–140°C or by the transesterification of methyl salicylate with benzyl alcohol. It is used as a fixative and solvent for nitro musks and as a fragrance for detergents.

Homomenthyl salicylate (homosalate), employed as a sunscreen agent, is on a list of 21 compounds for OTC sunscreen products, recommended by the FDA advisory review panel on OTC burn and sunburn prevention as both "safe and effective" (31). Menthyl salicylate (**6**) is also a sunscreen agent.



(**6**)

2-Ethylhexyl salicylate [118-60-5] is another compound listed as an accepted sunscreen agent for OTC regulated sunscreen products. The definition of such an agent is "an active ingredient that absorbs 95% or more of the radiation in the uv range at wavelengths from 290 to 320 nm and thereby removes the sunburning rays." By varying the concentration of the agent in the sunscreen vehicle, the sun protection factor (SPF) is developed. It is derived by dividing the exposure response of protected skin by the response of unprotected skin. Standard procedures have been set up to determine the appropriate SPF for these products which are OTC drugs by regulation (32).

Isoamyl salicylate is perhaps the most important ester of salicylic acid for perfumery purposes. Generally, it is manufactured by the transesterification of methyl salicylate. It has a characteristic flowery aroma and is useful in soap fragrances. Other salicylates of commercial interest as flavor and fragrance agents include isopropyl, isobutyl, phenethyl [87-22-9], and 2-ethylhexyl salicylates.

Salicylsalicylic acid [532-94-3] (salsalate) is prepared by the action of phosphorus trichloride, phosphorus oxychloride, or thionyl chloride on salicylic acid at low temperatures in an appropriate solvent. The crude product is recrystallized rapidly from ethyl alcohol to avoid hydrolysis and esterification. It is used as an analgesic and an antipyretic, as well as in the treatment of acute and chronic rheumatism and arthritis. It does not induce gastric disturbances

because it is only slowly hydrolyzed in the intestine. Owing to the slowness of its hydrolysis (two molecules of salicylic acid per molecule of the ester), the action of salicylsalicylic acid is less prompt but more persistent than that of other salicylates. Other salicylates of interest include ethylene glycol monosalicylate [87-28-5], dipropylene glycol monomethylether salicylate, bornyl salicylate [560-88-3], and *p*-acetamidophenyl salicylate [118-57-0].

8.3. Other Derivatives of Salicylic Acid. *p*-Aminosalicylic acid and its salts have been used in the treatment of tuberculosis. *p*-Aminosalicylic acid can be prepared by the carboxylation of *m*-aminophenol (33). Aminosalicylic acid USP assays not less than 98.5% and not more than 100.5%, calculated on the anhydrous basis. The antitubercular agents are likely to be used as the more tolerated salts: calcium [133-15-3], potassium [133-09-5], sodium [133-10-8], and the ethyl [6069-17-2] and phenyl [133-11-9] esters of *p*-aminosalicylic acid.

Methylene-5,5-disalicylic acid is produced by heating two parts salicylic acid with 1–1.5 parts of 30–40 wt % formaldehyde in the presence of an acid catalyst (34). The resulting product is a mixture of isomers, primarily the 5,5′-isomer and small amounts of low molecular weight polymers. It is used as an intermediate in the production of bacitracin methylenedisalicylate, which is used in a feed supplement to promote growth and as a medicament in swine, feedlot cattle, as well as chickens, turkeys, pheasants, and quail.

Salicylamide [65-45-2] is prepared by the reaction of methyl salicylate with ammonia. Salicylamide has mild analgesic, antiinflammatory, and antipyretic properties. Salicylamide is unlike other salicylates in that it causes sedation and central nervous system depression. Salicylamide is not hydrolyzed to salicylate and its action depends on the entire molecule. Salicylamide has been useful for protection against mildew and fungus in a variety of soaps, salves, lotions, and oils.

Salicylanilide [87-17-2] is prepared by heating salicylic acid and aniline in the presence of phosphorus trichloride (35). It is used as an intermediate in the production of other chemicals and as a slimicide, fungicide, and medicament. As an active fungicide and antimildew agent, it is used in cotton fabrics, cordage, paints, and lacquers. It is also reported to be a fungistatic agent for plastics. As a medicament, salicylanilide is an active ingredient in creams used to treat fungus infections of the scalp. 3,4,5-Tribromosalicylanilide is an antimicrobial with reported application in soaps, shampoos, textiles, melamine–formaldehyde and polyethylene plastics, synthetic fibers, paints, adhesives, and paper.

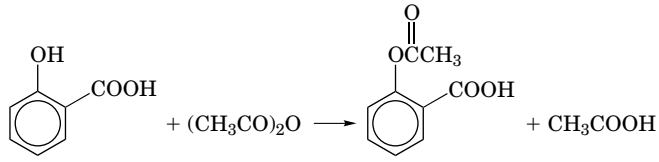
5-Sulfosalicylic acid is prepared by heating 10 parts of salicylic acid with 50 parts of concentrated sulfuric acid, by chlorosulfonation of salicylic acid and subsequent hydrolysis of the acid chloride, or by sulfonation with liquid sulfur trioxide in tetrachloroethylene. It is used as an intermediate in the production of dyestuffs, grease additives, catalysts, and surfactants. It is also useful as a colorimetric reagent for ferric iron and as a reagent for albumin. Table 9 shows the physical properties of salicylic acid derivatives.

8.4. Acetylsalicylic Acid (Aspirin). Acetylsalicylic acid [50-78-2] (*o*-acetyoxybenzoic acid) was first synthesized in 1853 by reaction of acetyl chloride with sodium salicylate. As a drug, acetylsalicylic acid was introduced in Germany in 1899 and into the United States in 1900. The first U.S. patent (36) for the manufacture of acetylsalicylic acid expired in 1917. Aspirin is a registered

trademark of Bayer in many nations, but in the United States and the United Kingdom, aspirin is accepted as the generic name for acetylsalicylic acid (37).

Physical Properties. Aspirin normally occurs in the form of white, flat platelets or needle-like crystals, or as a crystalline powder. It melts at 135–137°C and decomposes at 140°C. The solubility of aspirin is about 1 g/300 mL of water at 25°C, about 1 g/5 mL of ethanol at 25°C, 1 g/3.5 mL of acetone at 20°C, and 1 g/17 mL of chloroform at 25°C.

Manufacture. Aspirin [50-78-2] is manufactured by the acetylation of salicylic acid with acetic anhydride (eq. 9) (38,39).



(9)

Salicylic acid and acetic anhydride are introduced into a glass-lined or stainless steel reactor. The reactor temperature is kept below 100°C for two to three hours to complete the esterification. The resulting solution is pumped through a filter to remove extraneous solids that interfere with the crystallization, and then into a crystallizer vessel having a reliable temperature control. The temperature is gradually reduced to induce crystallization of the aspirin from the acetic acid/acetic anhydride mother liquor. The resulting suspension is centrifuged. The crystals are washed with water, dried to less than 0.5% by weight moisture, and then separated by particle size. In some processes, the crystals from the centrifuge are recrystallized prior to washing.

Various processes involve acetic acid or hydrocarbons as solvents for either acetylation or washing. Normal operation involves the recovery or recycle of acetic acid, any solvent, and the mother liquor. Other methods of preparing aspirin, which are not of commercial significance, involve acetyl chloride and salicylic acid, salicylic acid and acetic anhydride with sulfuric acid as the catalyst, reaction of salicylic acid and ketene, and the reaction of sodium salicylate with acetyl chloride or acetic anhydride.

Production and Economic Aspects. As of February 2003, there were no United States producers of acetylsalicyclic acid. Rhodia, the leading global aspirin producer has facilities in France and Thailand. Aspirin is considered a mature market and it was thought that only population increases and new uses would affect production and demand. With the discovery of new indications, aspirin may eventually enter a new period of growth. Early studies suggest that anti-inflammatories such as aspirin may delay the onset of Alzheimer's disease and slow it in those diagnosed earlier. It may also prevent myocardial infarction, several cancers (colon, pancreas, and prostate), and used in migraine and herpes treatments. U.S. demand for 2006 is predicted to be 11,000 t, up from 10,800 t in 2002 (40).

Specifications. Table 10 shows the tests required to satisfy the demands of the *Pharmacopeias* of the United States, Europe, and Japan (19–21).

Health and Safety Factors. Aspirin is a poison by ingestion, intraperitoneal, and possibly other routes. Human effects include: acute pulmonary edema, body temperature increase, changes in kidney tubules, coma, constipation, somnolence, nausea or vomiting to name a few. A 10-gram dose to an adult may be fatal. Aspirin is also an allergen, skin contact, inhalation or ingestion can cause asthma, sneezing, irritation of eyes and nose, hives and eczema (22).

Uses. Aspirin has analgesic, antiinflammatory, and antipyretic activity. It is used for the relief of less severe types of pain, such as headache, neuritis, acute and chronic rheumatoid arthritis, and toothache. Aspirin can be purchased in a variety of OTC and prescription dosage forms made and formulated by many companies. Tablets, ie, buffered, plain, or enteric-coated, are the most familiar in the United States, but other forms such as powder and effervescent formulations are of considerable importance in other parts of the world.

There has been a rebirth of interest in aspirin between the 1970s and through 2003 as evidence accumulated from a number of clinical trials that aspirin ingestion lowers the incidence of myocardial infarction (41,42), unstable angina (43,44), stroke (45), diabetic microangiopathy (40), and some cancers (40,46).

These actions of aspirin are thought to result from its ability to reduce the production of prostaglandin formed by platelet cells without appreciably affecting the other important functions in these blood factors (47).

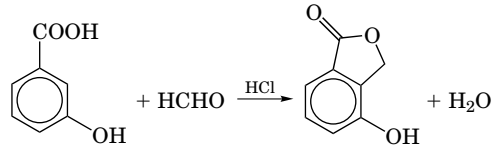
The understanding of these actions of aspirin started in 1971 (48) and resulted in the recommendations of the medical community that small doses of aspirin, used under the care of the doctor, may be a prevention measure for heart attack, and stroke for those considered at risk in the population.

8.5. *m*-Hydroxybenzoic Acid. Of the three hydroxybenzoic acids, the metaisomer is of least commercial importance. It offers no outstanding points of chemical interest and is used industrially in small quantities in a limited number of applications.

Reactions. *m*-Hydroxybenzoic acid affords a variety of products, depending on the catalyst and conditions employed. Catalytic reduction over platinum black or platinum oxide in alkaline solution gives 3-hydroxycyclohexanecarboxylic acid [22267-35-2]. Reduction of a warm aqueous solution over platinum oxide or over colloidal platinum yields cyclohexanecarboxylic acid. *m*-Hydroxybenzaldehyde can be prepared by reducing *m*-hydroxybenzoic acid with sodium amalgam. Finally, reduction over Raney nickel gives cyclohexanol.

Nitration of *m*-hydroxybenzoic acid with fuming nitric acid in the presence of sulfuric acid and acetic anhydride gives a mixture of the 2-nitro [602-00-6] and 4-nitro [619-14-7] substitution products. Bromination and iodination yield the 4-halogenated derivatives (4-bromo [14348-38-0] and 4-iodo [58123-77-6]). When *m*-hydroxybenzoic acid is treated with formalin in the presence of hydrochloric

acid, 4-hydroxyphthalide [13161-32-5] is obtained as shown in equation 10.

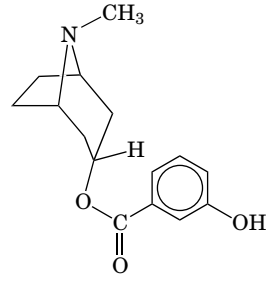


(10)

Unlike salicylic acid, *m*-hydroxybenzoic acid does not undergo the Friedel-Crafts reaction. It can be converted in 80% yield to *m*-aminophenol by the Schmidt reaction, which involves treating the acid with hydrazoic acid in trichloroethylene in the presence of sulfuric acid at 40°C (49).

Manufacture. *m*-Hydroxybenzoic acid was first obtained by the action of nitrous acid on *m*-aminobenzoic acid (50). It is more conveniently prepared by the sulfonation of benzoic acid with fuming sulfuric acid. The resulting *m*-sulfobenzoic acid is mixed with salt and fused with caustic soda at 210–220°C. The fusion melt is dissolved in water and acidified with hydrochloric acid to precipitate the crude product. Final purification is generally achieved by recrystallization from water.

Uses. *m*-Hydroxybenzoic acid is reported as an intermediate in the manufacture of germicides, preservatives, pharmaceuticals, and plasticizer. In the production of pharmaceuticals, the *m*-hydroxybenzoic acid ester of tropine, ie, (*m*-hydroxybenzoyl)tropeine [52418-07-2] (**7**), is claimed to cause dilation of the pupils (mydriatic effect), whereas the sodium salt [81256-75-9] is a cholegogic agent promoting the discharge of bile. Esters and metal salts of *m*-hydroxybenzoic acid have been used as germicides and preservatives in foods and meats. Ethers of alkyl esters and carbonates of glycol esters of the acid have been patented as plasticizers for vinyl and cellulosic plastics. It is useful in the manufacture of B-stage epoxy resins having long shelf lives and short curing times (51).



(**7**)

8.6. *p*-Hydroxybenzoic Acid. *p*-Hydroxybenzoic acid is of significant commercial importance. The most familiar application is the use of several of its esters as preservatives, known as parabens. Also of interest is the use in liquid crystal polymer applications.

Reactions. *p*-Hydroxybenzoic acid undergoes the typical reactions of the carboxyl and hydroxyl moieties. When heated above its melting point, it decomposes almost completely into phenol and carbon dioxide. It reacts with electrophilic reagents in the predicted manner and does not undergo the Friedel-Crafts reaction. Nitration, halogenation, and sulfonation afford the 3-substituted products. Heating *p*-hydroxybenzoic acid with 8 *N*-nitric acid results in a 95% yield of picric acid. In a similar fashion, treatment with chlorine water yields 2,4,6-trichlorophenol (52).

Manufacture. Several methods have been described for the preparation of *p*-hydroxybenzoic acid. The commercial technique is similar to that of salicylic acid, ie, Kolbe-Schmitt carboxylation of phenol. The modification includes the use of potassium hydroxide in place of caustic (53). The dried potassium phenate is heated under pressure, 270 kPa (2.7 atm) or more, with dry carbon dioxide at 180–250°C. The potassium salt [16782-08-4] of *p*-hydroxybenzoic acid forms almost quantitatively and can be converted to free acid by using a mineral acid.

Other reported syntheses include the Reimer-Tiemann reaction, in which carbon tetrachloride is condensed with phenol in the presence of potassium hydroxide. A mixture of the ortho- and para-isomers is obtained; the para-isomer predominates. *p*-Hydroxybenzoic acid can be synthesized from phenol, carbon monoxide, and an alkali carbonate (54). It can also be obtained by heating alkali salts of *p*-cresol at high temperatures (260–270°C) over metallic oxides, eg, lead dioxide, manganese dioxide, iron oxide, or copper oxide, or with mixed alkali and a copper catalyst (55). Heating potassium salicylate at 240°C for 1–1.5 h results in a 70–80% yield of *p*-hydroxybenzoic acid (56). When the dipotassium salt of salicylic acid is heated in an atmosphere of carbon dioxide, an almost complete conversion to *p*-hydroxybenzoic acid results. The *p*-aminobenzoic acid can be converted to the diazo acid with nitrous acid followed by hydrolysis. Finally, the sulfo- and halogenobenzoic acids can be fused with alkali. Patents report a process for preparing *p*-hydroxybenzoic acid by fermentation (57) and high level production in green plants (58).

Uses. There are many polymer and plastic applications for *p*-hydroxybenzoic acid. A linear polymer of *p*-hydroxybenzoic acid displays long-term stability in air at over 325°C (59). In addition, the polymer has a self-lubricating character combined with a high elastic modulus, thermal conductivity, electrical insulating character, and solvent resistance. These properties make useful metal coatings that are durable. Another application of interest is in liquid crystal preparation. *p*-Hydroxybenzoic acid has been studied in liquid crystal systems either as part of a rod- or disk-shaped surfactant molecule in a solvent, or as a monomer in a polymer, such as a polyester, that exhibits a degree of order lower than the crystalline solid, but higher than the normal isotropic liquid. Such materials are known as liquid crystals because they combine in a single phase the typical flow of a liquid with the anisotropy of properties found in noncubic crystals (60–62) (see LIQUID CRYSTALLINE MATERIALS).

p-Hydroxy benzoic acid is used in the manufacture of the methyl, ethyl, *n*-propyl, *n*-butyl, and benzyl esters called parabens. These esters have been used as preservatives for food, pharmaceuticals, and cosmetics for many years. Physical properties are listed in Table 11. These esters are effective bacteriostatic and fungistatic agents against a wide variety of microorganisms. The specifications

for the food ingredient chemicals are given in the *Food Chemicals Codex* (63). The compilation of standards for food-grade chemicals was brought together by the Food Protection Committee of the National Academy of Sciences and the National Research Council effort in the early 1960s to provide standards similar to the USP and NF for drug ingredients. Unlike the USP–NF, the *Food Chemicals Codex* does not have the same legal status as the USP–NF compilation. The exception to this involves definitions and interpretive regulations relating to the eligibility of substances for classification as GRAS (generally recognized as safe) published in 1971.

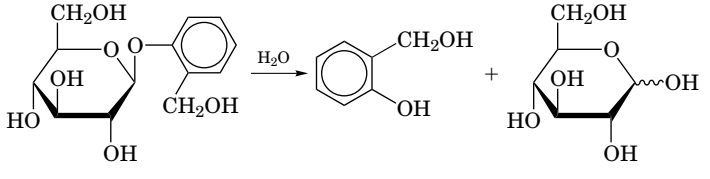
8.7. Salicyl Alcohol. Salicyl alcohol [90-01-7] (saligenin, *o*-hydroxybenzyl alcohol) crystallizes from water in the form of needles or white rhombic crystals. It occurs in nature as the bitter glycoside, salicin [138-52-3], which is isolated from the bark of *Salix helix*, *S. pentandra*, *S. praecos*, some other species of willow trees, and the bark of a number of species of poplar trees such as *Populus balsamifera*, *P. candicans*, and *P. nigra*.

Physical Properties. The alcohol, which sublimes readily and is very soluble in alcohol and ether, has the following properties: melting point, 86°C; density 13°/25°, 1.161 g/cm^3; heat of combustion, 3.542 mJ/mol (846.6 kcal/mol); and solubility in 100 mL water at 22°C, 6.7 g.

Reactions. Saligenin [90-01-7] undergoes the typical reactions of phenols and benzyl alcohol. When heated above 100°C, it transforms into a pale yellow resinous material. Amorphous condensation products are obtained when saligenin reacts with acetic anhydride, phosphorus pentachloride, or mineral acids. Upon boiling with dilute acids, saligenin is converted into a resinous body, saliretin, a condensed form of saligenin. Condensation reactions of saligenin with itself in the absence of any catalysts and in the presence of bases have also been studied.

Oxidation of saligenin with chromic acid or silver oxide yields salicyladehyde as the first product. Further oxidation results in the formation of salicylic acid, which is also obtained when saligenin is heated with sodium hydroxide at 200–240°C. Chlorination of an aqueous solution of the alcohol gives 2,4,6-trichlorophenol, and bromination in an alkaline medium yields 2,4,6-tribromophenol and tribromosaligenin. When saligenin is heated with one mole of resorcinol in the presence of anhydrous zinc chloride, 3-hydroxyxanthene forms.

Manufacture. The hydrolysis of the naturally occurring β-glycoside (salicin) (**8**) with hydrochloric or sulfuric acid affords saligenin (**9**) and glucose (**10**) (eq. 11).



(**8**) (**9**) (**10**) (11)

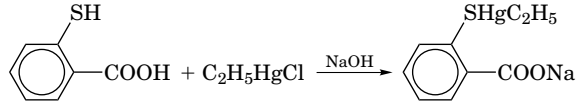
Numerous methods for the synthesis of salicyl alcohol exist. These involve the reduction of salicylaldehyde or of salicylic acid and its derivatives. The alco-

hol can be prepared in almost theoretical yield by the reduction of salicylaldehyde with sodium amalgam, sodium borohydride, or lithium aluminum hydride; by catalytic hydrogenation over platinum black or Raney nickel; or by hydrogenation over platinum and ferrous chloride in alcohol. The electrolytic reduction of salicylaldehyde in sodium bicarbonate solution at a mercury cathode with carbon dioxide passed into the mixture also yields saligenin. It is formed by the electrolytic reduction at lead electrodes of salicylic acids in aqueous alcoholic solution or sodium salicylate in the presence of boric acid and sodium sulfate. Salicylamide in aqueous alcohol solution acidified with acetic acid is reduced to salicyl alcohol by sodium amalgam in 63% yield. Salicyl alcohol forms along with *p*-hydroxybenzyl alcohol by the action of formaldehyde on phenol in the presence of sodium hydroxide or calcium oxide. High yields of salicyl alcohol from phenol and formaldehyde in the presence of a molar equivalent of ether additives have been reported (64). Phenyl metaborate prepared from phenol and boric acid yields salicyl alcohol after treatment with formaldehyde and hydrolysis (65).

Uses. Saligenin has been used medically as an antipyretic and appears to possess marked topical analgesic powers in concentrations of 4–10%. Saligenin's taste is pungent at first and then numbing. Unsymmetrical diphenylolmethanes prepared from salicyl alcohol and substituted phenol at 160–170°C in the presence of alkaline catalysts have been claimed as resin components and resin-hardening agents (66).

8.8. Thiosalicylic Acid. Thiosalicylic acid [147-93-3] (*o*-mercaptobenzoic acid), a sulfur-yellow solid that softens at 158°C, has a melting point of 164°C. It sublimes, is slightly soluble in hot water but freely soluble in glacial acetic acid and alcohol, and yields dithiosalicylic acid [527-89-9] upon exposure to air.

Reactions. Thiosalicylic acids reacts with ethylmercuric chloride in alcohol and in the presence of sodium hydroxide to yield sodium ethylmercurithiosalicylate [54-64-8] (thimerosal; Merthiolate, Eli Lilly and Company) (67) (eq. 12).



(12)

Uses. Thiosalicylic acid has been used as an anthelmintic, bactericide, and fungicide. It has also been used as a rust remover, a corrosion inhibitor for steel, and a polymerization inhibitor. In photography, it has application in print-out emulsions and as an activator for photographic emulsions.

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Table 1. **Physical Properties of Hydroxybenzoic Acids**

	Isomer value		
Property	Ortho	Meta	Para
molecular weight	138.12	138.12	138.12
melting point, °C	159	201.5–203	214.5–215.5
boiling point, °C	211 sub		
density	1.443_{4}^{20}	1.473_{25}^{25}	1.497_{20}^{20}
refractive index	1.565		
flash point (Tag closed-cup), °C	157		
acid dissociation, K_a, at 25°C	1.05×10^{-3}	8.3×10^{-5}	2.6×10^{-5}
heat of combustion, mJ/mol[a]	3.026	3.038	3.035
heat of sublimation, kJ/mol[a]	95.14		116.1

[a]To convert J to cal, divide by 4.184.

Table 2. **Solubilities of the Hydroxybenzoic Acids in Water, Wt %[a]**

	Isomer		
Temperature, °C	Ortho	Meta	Para
0°C	0.12	0.35	0.25
10°C	0.14	0.55	0.50
20°C	0.20	0.85	0.81
30°C	0.30	1.35	0.81
40°C	0.42	2.0	1.23
50°C	0.64	3.0	2.3
60°C	0.90	4.3	4.2
70°C	1.37	7.0	7.0
80°C	2.21	11.0	12.0

[a]Ref. 1.

Table 3. **Solubilities of the Hydroxybenzoic Acids in Nonaqueous Solvents, Wt %**

	Isomer[a]		
Solvent	Ortho	Meta	Para
acetone at 23°C	396	327	285
benzene at 25°C	0.775	0.010	0.0035
1-butanol	28.8_{38}	$20.7_{36.5}$	$19.5_{32.5}$
ethanol (99 wt %)	40.6_{41}	39.6_{65}	38.75_{67}
n-heptane	$2.09_{92.2}$	2.0_{197}	1.5_{197}
methanol at 15°C	39.87	40.38	36.22
carbon tetrachloride at 25°C	0.262		
chloroform (satd in H_2O) at 25°C	1.84		
ethanol (abs) at 21°C	34.87		
1-propanol at 21°C	27.36		

[a]Subscripts are temperature in °C.

Table 4. **Saturated Vapor Pressure, *p*, of *o*- and *p*-Hydroxybenzoic Acids**

	p, Pa[a]	
Temperature, °C	*o*-Hydroxybenzoic acid	*p*-Hydroxybenzoic acid
20°C	0.0	0.0
40°C	0.1	0.0
60°C	1.1	0.0
80°C	8.1	0.0
100°C	46.4	0.3
120°C	222.3	1.9
140°C	909.1	10.6

[a]To convert Pa to mm Hg, divide by 133.3.

Table 5. **Salicylic Acid Comparison[a]**

Property	USP 23	EP 84, BP 93, and PF X
identification		
A	Fe test for salicylates	melting point
B	Fe test for salicylates	ir spectrum
C	Fe test for salicylates	Fe test for salicylates
melting range	158–161°C	no test
melting point	no test	158–161°C
loss on drying	0.5% max	0.5% max
assay	99.5–101.0%	99.0–100.5%
heavy metals	0.002% max	20 ppm max
chlorides	0.014% max	100 ppm max
sulfates	0.02% max	200 ppm max
residue on ignition[b]	0.05% max	0.1% max
clarity and color	no test	clean and colorless (1 g in 10-mL alcohol R)
related compounds		
4-hydroxybenzoic acid	0.1% max	no test
4-hydroxyisophthalic acid	0.05% max	no test
phenol	0.02% max	no test
other	0.05% max	no test
sum	0.2% max	no test

[a]From *United States Pharmacopeia* (USP) and *European* (EP), *British* (BP), and *French* (PF) *Pharmacopeias*.

[b]Sulfated ash tests found in BP and EP are considered equivalent to the USP residue on ignition test, except where noted (18).

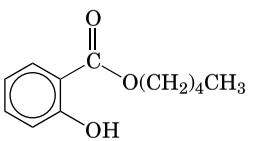
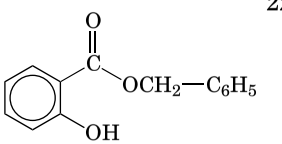
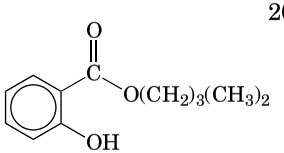
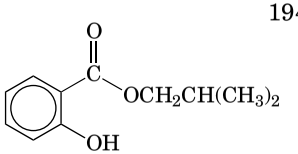
Table 6. **Typical Salicylic Acid Specifications**

Type	Melting range, °C	Assay, %	Ash, wt %	Water, wt %
technical	157–161	98.5	1.0	0.4
technical sublimed	157–161	99.5	0.1	0.1

Table 7. **Physical Properties of Salicylic Acid Salts**

Salt	CAS Registry Number	Formula	Mol wt	Crystalline form
bismuth salicylate, basic	[5798-98-1]	$Bi(C_7H_5O_3)_3{\cdot}Bi_2O_3$	877.3	white microcrystal
calcium salicylate dihydrate	[824-35-1]	$Ca(C_7H_5O_3)_2{\cdot}2H_2O$	350.34	white octahedral
lithium salicylate	[552-38-5]	$LiC_7H_5O_3$	144.05	white powder
magnesium salicylate tetrahydrate	[18917-89-0]	$Mg(C_7H_5O_3)_2{\cdot}4H_2O$	370.60	slightly red crystalline powder
potassium salicylate	[578-36-9]	$KC_7H_5O_3$	176.22	white powder
sodium salicylate	[54-21-7]	$NaC_7H_5O_3$	160.11	white crystalline powder

Table 8. **Physical Properties of Salicylic Acid Esters**

Ester	CAS Registry Number	R	Mol wt	Mp, °C	Bp, °C[kPa]	Density g/cm^3	Refractive index, n_D	Solubility[a]				
								Water	Methanol	Ether	Acetone	Benzene
amyl salicylate	[2050-08-0]		208.24		265							
benzyl salicylate	[118-58-1]		228.25	25	320	$1.1799^{30}{}_4$	1.5805^{20}		sl sol	sl sol		
isoamyl salicylate[c]	[87-20-7]		208.24		276–277[99]	$1.0535^{20}{}_4$	1.5080^{20}	insol	v	sl sol		
isobutyl salicylate	[87-19-4]		194.23	5.9	260–262	$1.0639^{20}{}_4$	1.5807^{20}	insol	sl sol	sl sol		

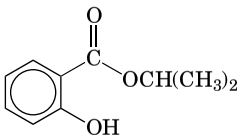
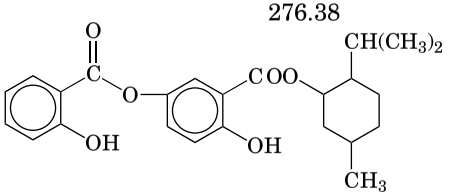
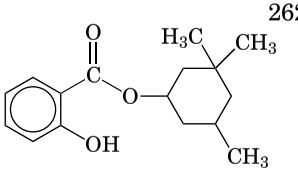
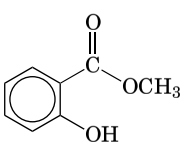
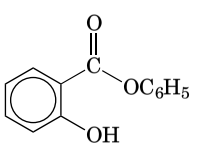
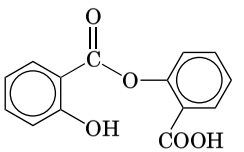
isopropyl salicylate	[607-85-2]		180.21		240–242	1.0729^{20}_{4}	1.5065^{20}	insol	∞	∞		
menthyl salicylate	[89-46-3]	 (**6**)	276.38		190^{2}	1.0467^{20}	1.5198^{26}	insol	∞	v	v	∞
homomenthyl salicylate	[118-56-9]		262.38	4.1								
methyl salicylate	[119-36-8]		152.16	−8.6	223.3	1.1738^{20}_{4}	1.5369^{20}		v	v		
phenyl salicylate[d]	[118-55-8]		214.22	43	$173^{1.6}$	1.2614^{20}_{4}		insol	v	sl sol	v	v

Table 8. (*Continued*)

Ester	CAS Registry Number	R	Mol wt	Mp, °C	Bp, °C[kPa]	Density g/cm^3	Refractive index, n_D	Solubility[a]				
								Water	Methanol	Ether	Acetone	Benzene
salicylsalicylic acid[e]	[552-94-3]		258.23	149				insol	v	sl sol		

[a] δ = partially soluble; v = very soluble; ∞ = infinitely soluble.
[b] To convert kPa to mm Hg, multiply by 7.5.
[c] Soluble in chloroform.
[d] Soluble in CCl_4.
[e] Soluble in CH_3OH.

Table 9. **Physical Properties of Salicylic Acid Derivatives**

Derivative	CAS Registry Number	Mol wt	Mp, °C	Solubility[a]				
				Water	Methanol	Ether	Acetone	Benzene
p-aminosalicylic acid	[65-49-6]	153.14	150–151 dec	sol	sol	sol	sol	insol
methylene-5,5-disalicylic acid	[27496-82-8]	228.26	243–244	δ	sol	sol	sol	δ
salicylamide[b]	[65-45-2]	137.13	142	δ	sol	δ		
salicylanilide[c]	[87-17-2]	213.24	135.8–136.2	sol	δ	δ		δ
5-sulfosalicylic acid	[97-05-2]	218.18	120 (anhydrous)	v	v	v		

[a] δ = partially soluble; v = very soluble.
[b] Bp at 14 kPa (105 mm Hg) = 181.5°C; density = 1.175_4^{140}.
[c] Also partially soluble in chloroform.

Table 10. **Acetylsalicylic Acid Comparison**[a]

Property	USP 23	EP 84, BP 93, and PF X
assay	99.5–100.5%	99.5–101.0%
identification		
A	color test	ir spectrum
B	ir spectrum	hydrolyzation, mp of salicylic acid
C	no test	W/Ca $(OH)_2$, color test
D	no test	color test
instantaneous melting point[b]	no test	~143°C
loss on drying	0.5% max (silica gel)	0.5% max (vacuo)
readily carbonizable substances	passes Q color	no test
residue on ignition[c]	0.05% max	0.1% max
clarity of solution	clear (500 mg in 10-mL Na_2CO_3 solution)	clear (1 g in 10-mL alcohol R)
color of solution	no test	colorless (1 g in 10-mL alcohol R)
chloride	0.014% max	no test
sulfate	0.04% max	no test
heavy metals	0.001% max	20 ppm max
free salicylic acid	0.1% max	500 ppm max
related substances	no test	0.1% max as acetylsalicylsalicylic acid
organic volatile impurities	meets requirements	no test

[a]From *United States Pharmacopeia* (USP) and *European* (EP), *British* (BP), and *French* (PF) *Pharmacopeias*.
[b]This is a product character, not a specification.
[c]Sulfated ash tests found in BP and EP are considered equivalent to the USP residue on ignition test, except where noted (18).

Table 11. **Physical Properties of Alkyl *p*-Hydroxybenzoates (Parabens)**

Property	Methyl	Ethyl	*n*-Propyl	Butyl	Benzyl
CAS Registry Number	[99-76-3]	[120-47-8]	[94-13-3]	[94-26-8]	[94-18-8]
mp, °C	125–128	116–119	95–98	68–72	108–113
assay (min), %	99.0	99.0	99.0	99.0	99.0
solubility, at 25°C, g/100 g solvent					
water	0.25	0.17	0.05	0.02	0.006
water (at 80°C)	2	0.86	0.30	0.15	0.09
methanol	59	115	124	220	79
ethanol	52	70	95	210	72
propylene glycol	22	25	26	110	13
peanut oil	0.5	1	1.4	5	0.5
acetone	64	84	105	240	102
benzene	0.7	1.65	3	40	2.6
ether	23	43	50	150	52
carbon tetrachloride	0.1	0.9	0.8	1	0.08