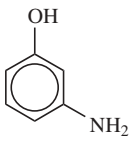
AMINOPHENOLS

1. Introduction

Aminophenols and their derivatives are of commercial importance, both in their own right and as intermediates in the photographic, pharmaceutical, and chemical dye industries. They are amphoteric and can behave either as weak acids or weak bases, but the basic character usually predominates. 3-Aminophenol (1) is fairly stable in air unlike 2-aminophenol (2) and 4-aminophenol (3) that easily undergo oxidation to colored products. The former are generally converted to their acid salts, whereas 4-aminophenol is usually formulated with low concentrations of antioxidants which act as inhibitors against undesired oxidation.



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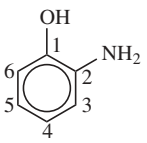

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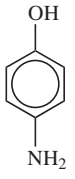

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2. Physical Properties

The simple aminophenols exist in three isomeric forms depending on the relative positions of the amino and hydroxyl groups around the benzene ring. At room temperature they are solid crystalline compounds. In the past, the commercial-grade materials were usually impure and colored because of contamination with oxidation products, but now virtually colorless, high purity commercial grades are available. The partitioning of aminophenols between aqueous and organic solvent systems has been studied; 2-aminophenol behaves anomalously because of intramolecular hydrogen bonding (1,2). The solubilities of these compounds in common solvents of differing polarities (dielectric constants) are given in Table 1 and their spectral characteristics in Table 2. In acidic solution all isomers exhibit fluorescence. 4-Aminophenol shows two bands; one at 300 nm common to all the isomers, and the second at 370 nm attributed to the existence of an additional aqueous ionic species. Fluorescence also exists in neutral solution, but is abolished at high pH values (3–13).

2.1. 2-Aminophenol. This compound forms white orthorhombic bipyramidal needles when crystallized from water or benzene, which readily become yellow-brown on exposure to air and light. The crystals have eight molecules to the elementary cell and a density of 1.328 g/cm^3 (1.29 also quoted) (14–16). The molecules are hydrogen bonded from OH to N to form chains parallel to the b-axis; these chains are linked together to form sheets by NH to O hydrogen bonds essentially parallel to the c-axis. There are large cavities between the sheets permitting the intercalation of small foreign molecules (17) (see Tables 3–5).

2.2. 3-Aminophenol. This is the most stable of the isomers under atmospheric conditions. It forms white prisms when crystallized from water or toluene. The orthorhombic crystals have a tetramolecular unit and a density of 1.195 g/cm^3 (1.206 and 1.269 also quoted) (15,16) (see Tables 3–5).

Table 1. **Solubility[a] of Aminophenols in Common Solvents Arranged in Order of Increasing Polarity (Dielectric Constant)[b]**

Solvent	2-Aminophenol	3-Aminophenol	4-Aminophenol
benzene	1	1	0
toluene	1	1	1
acetonitrile	3	3	2
diethyl ether	2	3	1
chloroform	1	1	0
ethyl acetate	3	3	2
acetone	3	3	2
ethanol	2	3	1
dimethyl sulfoxide	3	3	3
water			
hot	2	3	2
cold	1	2	1

[a] 0, insoluble; 1, slightly soluble; 2, soluble; 3, very soluble.
[b] Eluotropic series.

Table 2. **Spectral Characteristics of the Aminophenol Isomers**

	2-Aminophenol	3-Aminophenol	4-Aminophenol
uv[a] nm			
absorption	233,285 (methanol)	287 (methanol)	234,301 (methanol)
	229,281 (water)	270 (0.1 *M* HCl)	229,294 (water)
	235,288 (cyclohexane)	234,284 (cyclohexane)	235,304 (cyclohexane)
emission	λ_{cx} λ_{em}	λ_{cx} λ_{em}	λ_{cx} λ_{em}
fluorescence	291 336 (ethanol)	287 333 (ethanol)	302 364.5 (ethanol)
	286 338–344 (water)	286 331–334 (water)	301 367–374 (water)
	283 330 (cyclohexane)	290 320 (cyclohexane)	270 330 (cyclohexane)
phosphorescence	291 440 (ethanol)	287 425 (ethanol)	302 470 (ethanol)
ir[b] cm^{-1}	3380,3300,1600,1510,1470,1270, 900,740	3370,3310,1600,1470,1390,1260, 1180,910	3050–2580,1500,1470,1240,970,830, 750
ms[c]	109 (100)	109 (100)	109 (100)
	80 (39)	80 (23)	80 (31)
	53 (12)	81 (10)	107 (23)
	28 (11)	53 (6)	53 (20)
nmr[d] ppm	6.9–7.5,8.6 (TFA)	4.7,6.0,6.1,6.8,8.8 (DMSO)	7.1,7.4,8.7 (TFA)

[a] ultraviolet (uv) spectra: λ_{cx}, excitatory wavelength; λ_{em}, emission wavelength (3, 4, 7–9).

[b] Only infrared (ir) absorption bands reported as very strong are included (accuracy $\pm$ 10 cm^{-1}) (5, 6).

[c] Values quoted are ion (m/z) followed by relative abundance in parentheses. After m/z 109 and 80, the other ions may vary in abundance order dependent upon conditions employed (10).

[d] Proton chemical shift spectra over the range of 0–15 ppm ($\pm$0.1 ppm): TFA, trifuoroacetic acid; DMSO, dimethyl sulfoxide. When complex spectra caused by second-order effects or overlapping resonances were encountered, the range was recorded (11,12). Nuclear magnetic resonance = nmr.

Table 3. **General Properties of Aminophenols**

Property	2-Aminophenol	3-Aminophenol	4-Aminophenol
alternative names	2-hydroxyaniline 2-amino-1-hydroxy-benzene	3-hydroxyaniline 3-amino-1-hydroxy-benzene	4-hydroxyaniline 4-hydroxy-1-aminobenzene
C.I. designation	76,520		
CAS Registry Number	[95-55-6]	[591-27-5]	[123-30-8]
molecular formula	C_6H_7NO	C_6H_7NO	C_6H_7NO
molecular weight	109.13	109.13	109.13
melting point, °C	174	122–123	189–190[a]
boiling point, °C			
0.04 kPa			130[a], 110[b]
0.4 kPa			150
1.07 kPa			167
1.47 kPa	153[b,c]	164[c]	174
101.3 kPa			284
ΔH_f, kJ/mol[d]	−191.0 ± 0.9	−194.1 ± 1.0	−190.6 ± 0.9[e]

[a] Decomposes.
[b] Sublimes. To convert kPa to mm Hg, multiply by 7.5.
[c] Ref. 18.
[d] In the crystalline state (19). To convert kJ to kcal, divide by 4.184.
[e] −179.1 is also quoted (20).

2.3. 4-Aminophenol. This compound forms white plates when crystallized from water. The base is difficult to maintain in the free state and deteriorates rapidly under the influence of air to pink–purple oxidation products. The crystals exist in two forms. The α-form (from alcohol, water, or ethyl acetate) is the more stable and has an orthorhombic pyramidal structure containing four molecules per unit cell. It has a density of 1.290 g/cm^3 (1.305 also quoted). The less stable β-form (from acetone) exists as acicular crystals that turn into the α-form on standing: they are orthorhombic bipyramidal or pyramidal and have a hexamolecular unit (15,16,24) (see Tables 3–5).

Table 4. **Acid Dissociation Constants[a] of Aminophenols[b]**

Compound	pK_1	pK_2	Temperature, °C
2-aminophenol	4.72		21
	4.66[c]		25
		9.66	15
		9.71	22
3-aminophenol	4.17		21
	4.31c		25
		9.87	22
4-aminophenol	5.5		21
	4.86	10.60	30
	5.48c		25
		10.30	22

[a] In water unless otherwise noted.
[b] Refs. 21–23.
[c] 1 vol% ethyl alcohol in water.

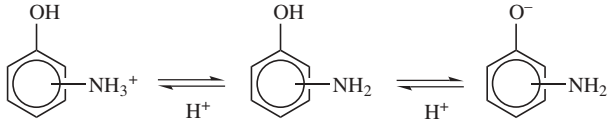
Table 5. **Salts of the Aminophenols**

Salt	2-Aminophenol	3-Aminophenol	4-Aminophenol
hydrochloride			
CAS Registry Number	[51-19-4]	[51-81-0]	[51-78-5]
melting point, °C	207	224	306[a]
crystal form	needles	prisms	prisms
hydroiodide			
CAS Registry Number			[33576-76-0]
melting point, °C		209	
crystal form		prisms	
oxalate			
melting point, °C	167.5[a]	275	183
acetate			
CAS Registry Number	[97777-54-3]	[97777-55-4]	[13871-68-6]
melting point, °C	150[b]		183
chloroacetate			
melting point, °C			148
crystal form			needles
trichloroacetate			
CAS Registry Number	[97777-57-6]	[97777-56-5]	
melting point, °C			166
crystal form			needles
sulfate			
CAS Registry Number		[66671-80-5]	[54646-39-8]
melting point, °C		152	
crystal form		plates or needles	
hydrosulfate			
CAS Registry Number	[40712-56-9]		[15658-52-3]
melting point, °C			272
crystal form			needles

[a] Decomposes.
[b] The formate salt melts at 120°C.

3. Chemical Properties

The chemical properties and reactions of the aminophenols and their derivatives are to be found in detail in many standard chemical texts (25). The acidity of the hydroxyl function is depressed by the presence of an amino group on the benzene ring; this phenomenon is most pronounced with 4-aminophenol. The amino group behaves as a weak base, giving salts with both mineral and organic acids. The aminophenols are true ampholytes, with no zwitterion structure; hence they exist either as neutral molecules (4), or as ammonium cations (5), or phenolate ions (6), depending on the pH value of the solution.



(**5**) (**4**) (**6**)

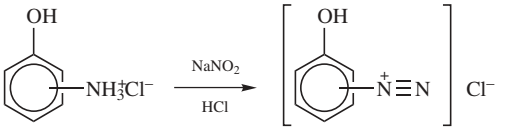
The existence of half-salt complex cations $B^{+}{}_{2}$, formed by the association of an ammonium cation B^{+}, with a neutral molecule, B, has also been postulated. This association phenomenon is most apparent with 4-aminophenol, but is also displayed by the other isomers (23).

The aminophenols are chemically reactive, undergoing reactions involving both the aromatic amino group and the phenolic hydroxyl moiety, as well as substitution on the benzene ring. Oxidation leads to the formation of highly colored polymeric quinoid structures. 2-Aminophenol undergoes a variety of cyclization reactions.

3.1. Alkylation. All the possible mono-, di-, and trimethylated aminophenols are known. *N*-Monoalkylation occurs when the aminophenol is heated with the appropriate alkyl halide or with an alcohol and Raney nickel; equal or even better results can be achieved using aldehydes or ketones in place of the alcohol. Specific alkylation of the hydroxyl group to form methoxyanilines (anisidines) or ethoxyanilines (phenetidines) is difficult because of the reactivity of the amino group; mixed alkylated products usually are obtained. 3-Methoxyanilines may be prepared by methylation of 3-aminophenol under alkaline conditions, but it is more usual to protect the amino group and to methylate 3-acetylaminophenol, followed by hydrolysis. The other anisidines and phenetidines are prepared indirectly by reduction of the nitro analogue.

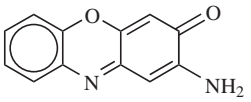
3.2. Acylation. Reaction conditions employed to acylate an aminophenol (using acetic anhydride in alkali or pyridine, acetyl chloride and pyridine in toluene, or ketene in ethanol) usually lead to involvement of the amino function. If an excess of reagent is used, however, especially with 2-aminophenol, O,N-diacylated products are formed. Aminophenol carboxylates (O-acylated aminophenols) normally are prepared by the reduction of the corresponding nitrophenyl carboxylates, which is of particular importance with the 4-aminophenol derivatives. A migration of the acyl group from the O to the N position is known to occur for some 2- and 4-aminophenol acylated products. Whereas ethyl 4-aminophenyl carbonate is relatively stable in dilute acid, the 2-derivative has been shown to rearrange slowly to give ethyl 2-hydroxyphenyl carbamate [35580-89-3] (26).

3.3. Diazonium Salt Formation. The aromatic amino group of aminophenols can be converted to the diazonium salt using sodium nitrite in aqueous acid, although difficulties may be encountered when the aminophenol is of low solubility or easily oxidized. Crystalline diazonium salts have been isolated using the hydrochloride or sulfate of the appropriate aminophenol under anhydrous conditions. Such diazo derivatives find extensive use in the dye industry (27,28).



3.4. Cyclization Reactions. 2-Aminophenol is particularly susceptible to cyclization and condensation reactions because of the close proximity of the amino and hydroxyl groups attached to the benzene ring. A nonspecific oxidative

environment (ferric chloride, light, enzymes, autooxidation on silica thin-layer plates) gives 2-aminophenoxazin-3-one [1916-59-2] (7), further oxidation (ferric cyanide, heating in ethanolic potassium hydroxide) gives a pentacyclic structure, triphenoxdioxazine (benzoxazinophenoxazine) [258-72-0] (8). 2-Aminophenol and its derivatives are useful starting materials for the synthesis of phenoxazines, phenoxazones, benzoxazoles, and thiobenzoxazoles. Most of these condensation reactions involve heating at 200–300°C with a suitable catalyst (25).



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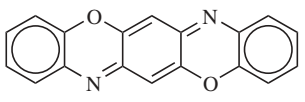


(8)

3.5. Condensation Reactions. Condensation of substituted benzaldehydes with 2-aminophenol in the presence of a catalyst (aluminum, iron, zinc or phosphorus chlorides) yields a Schiff base, with the elimination of water, in 52–88% yields (29). In general, substituted diphenylamines or diphenyl ethers are obtained from aminophenols and suitable reactants by elimination of ammonia or hydrogen chloride.

3.6. Reactions of the Benzene Ring. Both the amino and hydroxyl groups attached to the benzene nucleus are electron-donating because of resonance effects, which predominate over electron-withdrawing inductive effects. Many substituted derivatives are known. The controlled interaction of aminophenols with chlorine or bromine in glacial acetic acid can give a variety of mono-, di-, tri-, or tetrahalogenated products. The use of concentrated sulfuric acid or oleum, with or without heat, gives aromatic sulfonic acids. The sulfonic acid group enters the 2- or 4-position relative to the hydroxyl group. Further treatment with oleum leads to the formation of disulfonated compounds. The carboxylation of 3-aminophenol leads to the formation of 4-aminosalicyclic acid.

4. Manufacture and Processing

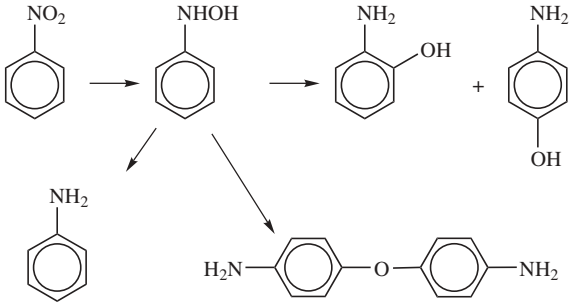
Aminophenols are either made by reduction of nitrophenols or by substitution. Reduction is accomplished with iron or hydrogen in the presence of a catalyst. Catalytic reduction is the method of choice for the production of 2- and 4-aminophenol (see AMINES BY REDUCTION). Electrolytic reduction is also under industrial consideration and substitution reactions provide the major source of 3-aminophenol.

4.1. Reduction. *Iron Reduction.* The reduction of nitrophenols with iron filings or turnings takes place in weakly acidic solution or suspension (30). The aminophenol formed is converted to the water soluble sodium aminophenolate by adding sodium hydroxide before the iron–iron oxide sludge is separated from the reaction mixture (31). Adjustment of the solution pH leads to the precipitation of aminophenols, a procedure performed in the absence of air because the salts are very susceptible to oxidation in aqueous solution.

Insoluble red lakes are formed as by-products that decrease yields when 2-nitrophenol [88-75-5] is reduced with iron. Consequently, the iron reduction of this nitro compound to 2-aminophenol is of minor industrial importance today.

Catalytic Reduction. Catalytic reduction usually takes place in solution, emulsion, or suspension in autoclaves or pressurized vessels; after the catalyst is added, the vessel is pressurized with hydrogen (32,33). Water and methanol are the preferred solvents. In water the addition of alkali hydroxide (34), alkali carbonate (35), or acid (36) has been recommended.

The chemical production of aminophenols via the reduction of nitrobenzene occurs in two stages. Nitrobenzene [98-95-3] is first selectively reduced with hydrogen in the presence of Raney copper to phenylhydroxylamine in an organic solvent such as 2-propanol (37). With the addition of dilute sulfuric acid, nucleophilic attack by water on the aromatic ring of *N*-phenylhydroxylamine [100-65-2] takes place to form 2- and 4-aminophenol. The by-product, 4,4′-diaminodiphenyl ether [13174-32-8], presumably arises in a similar manner from attack on the ring by a molecule of 4-aminophenol (38,39). Aniline [62-53-3] is produced via further reduction (40,41).



In past years, metals in dilute sulfuric acid were used to produce the nascent hydrogen reductant (42). Today, the reducing agent is hydrogen in the presence of a catalyst. Nickel, preferably Raney nickel (34), chromium or molybdenum promoted nickel (43), or supported precious metals such as platinum or palladium (35,44) on activated carbon, or the oxides of these metals (36,45), are used as catalysts. Other catalysts have been suggested such as molybdenum and platinum sulfide (46,47), or a platinum–ruthenium mixture (48).

The addition of "wetting agents" increases the aminophenol yield. These agents must be water soluble and stable in the presence of sulfuric acid (49). Quaternary ammonium salts that contain at least one alkyl group with at least ten carbon atoms are suitable (49,50). Dimethylalkylamine oxide increases the hydrogenation rate and improves the selectivity of the reaction for 4-aminophenol (51). The reaction temperature does not usually exceed 100–110°C, and is performed either at atmospheric or at a higher pressure, preferably around 2 MPa (20 atm) (up to 6 MPa). Hydrogen is added during the reaction as it is consumed. The addition of an inert organic solvent, not miscible with water, further increases the yield of 4-aminophenol and product quality (34,35), and the presence of an organic divalent sulfur compound inhibits the formation of aniline (40,41,52).

In another process variant, only 88% of the nitrobenzene is reduced, and the reaction mixture then consists of two phases; the precious metal catalyst (palladium on activated carbon) remains in the unreacted nitrobenzene phase. Therefore, phase separation is sufficient as work-up, and the nitrobenzene phase can be recycled directly to the next batch. The aqueous sulfuric acid phase contains 4-aminophenol and by-product aniline. After neutralization, the aniline is stripped, and the aminophenol is obtained by crystallization after the aqueous phase is purified with activated carbon (53).

Electrolytic Reduction. Electrochemical reduction is finding commercial favor and causes less concern over pollution than metal–acid reduction systems (42,54–56). Electrolysis of nitrobenzene, phenylhydroxylamine, or azoxybenzene [495-48-7] in deoxygenated acid solutions, using graphite or copper–mercury cathodes at potential differences of −300 to −600 mV and temperatures of 60–90°C, produces 4-aminophenol in yields of 65–99% (57,58). Aniline is produced as a by-product (59). The use of 2-nitrophenol yields 2-aminophenol (60); the process does not appear satisfactory for the production of 3-aminophenol (61). The use of bismuth, tin, or titanium salts as additives (62), electrolyte agitation (63), flow-through cells with rotating copper-amalgamated electrodes, and square-wave pulsed current control are increasing the efficiency, product selectivity, and scale up of the process (64,65). Electrocatalytic oxidation of aniline to 4-aminophenol by electrochemically activated molecular oxygen via direct electron transfer from the cathode, in the presence of iron compounds, is also possible (66).

4.2. Substitution. Substitution of various groups by amino or hydroxyl functions is industrially unimportant for the production of 2- and 4-aminophenol, but this type of reaction is used for the synthesis of 2- and 4-aminophenol derivatives. However, 3-aminophenol cannot be obtained easily by reduction. It is made by the reaction of 3-aminobenzenesulfonic acid [121-47-1] with sodium hydroxide under fusion conditions (5–6 h; 240–245°C). The product is purified by vacuum distillation (25).

In an alternative industrial process, resorcinol [108-46-3] is autoclaved with ammonia for 2–6 h at 200–230°C under a pressurized nitrogen atmosphere, 2.2–3.5 MPa (22–35 atm). Diammonium phosphate, ammonium molybdate, ammonium sulfite, or arsenic pentoxide may be used as a catalyst to give yields of 60–94% with 85–90% selectivity for 3-aminophenol (67,68). A vapor-phase system operating at 320°C using a silicon dioxide catalyst impregnated with gallium sesquioxide gives a 26–31% conversion of resorcinol with a 96–99% selectivity for 3-aminophenol (69).

The direct conversion of aniline into aminophenols may be achieved by hydrogen peroxide hydroxylation in SbF_5–HF at −20 to −40°C. The reaction yields all possible aminophenols via the action of $H_3O^+_2$ on the anilinium ions; the major product is 3-aminophenol (64% yield) (70,71). This isomer may also be made by the hydrolysis of 3-aminoaniline [108-45-2] in dilute acid at 190°C (72). Another method of limited importance, but useful in the synthesis of derivatives, is the dehydrogenation of aminocyclohexenones (73).

4.3. Purification. Contaminants and by-products that are usually present in 2- and 4-aminophenol made by catalytic reduction can be reduced or even removed completely by a variety of procedures. These include treatment

with 2-propanol (74), with aliphatic, cycloaliphatic, or aromatic ketones (75), with aromatic amines (76), with toluene or low mass alkyl acetates (77), or with phosphoric acid, hydroxyacetic acid, hydroxypropionic acid, or citric acid (78). In addition, purity may be enhanced by extraction with methylene chloride, chloroform (79), or nitrobenzene (80).

Another method employed is the treatment of aqueous solutions of aminophenols with activated carbon (81,82). During this procedure, sodium sulfite, sodium dithionite, or disodium ethylenediaminotetraacetate (82) is added to increase the quality and stability of the products and to chelate heavy-metal ions that would catalyze oxidation. Addition of sodium dithionite, hydrazine (82), or sodium hydrosulfite (83) also is recommended during precipitation or crystallization of aminophenols.

Generally, aminophenols of high purity may be obtained by sublimation at reduced pressure. 3-Aminophenol may be purified by vacuum distillation and a colorless product obtained by adding sulfur dioxide during the distillation (84) or by collecting the distillate under a blanket of unreactive liquid of lower density such as water (85). During shipment contact with metal surfaces should be avoided as they promote oxidation. Transport of the technical grade material usually occurs in heavy duty, plastic-lined paper sacks. The fine chemicals are usually shipped in smaller quantities in brown, air-tight glass bottles.

5. Economic Aspects

Production figures for the aminophenols are scarce, the compounds usually being classified along with many other aniline derivatives (86). Most production of the technical grade materials (95% purity) occurs on-site as they are chiefly used as intermediate reactants in continuous chemical syntheses. World production of the fine chemicals (99% purity) is probably no more than a few hundred metric tons yearly, at prices ranging between \$40–70 per kg in 2000 with 4-aminophenol being the least expensive.

6. Analytical and Test Methods, Storage

Aminophenols have been detected in waste water by investigating uv absorptions at 220, 254, and 275 nm (87). These compounds can also be detected spectrophotometrically after derivatization at concentrations of 1 part per 100 million by reaction in acid solution with *N*-(1-naphthyl)ethylenediamine [551-09-7] (88) or 4-(dimethylamino)benzaldehyde [100-10-7] (89), and the Schiff base formed can be stabilized in chloroform by chelation to increase detection limits (90).

Reaction with 1,3-benzenediamine-periodate (91) or with a hypochlorite–alkaline phenol (Berthelot) reagent enables the detection of both 2- and 4-aminophenol, the latter reagent giving distinguishable blue and dark green products, respectively (92). 4-Aminophenol itself has been shown to react in alkaline solution with both the 2- and 3-aminophenol isomers, a reaction exploited for their detection (93).

More specifically, 2-aminophenol can be detected in solution using an iron(II) sulfate–hydrogen peroxide reagent (94) or dimerized in acidic solution to 2-hydroxyisophenoxazine-3-one, an intensively colored dye (95). 3-Aminophenol has been analyzed colorimetrically by oxidation in base and subsequent extraction of a violet quinoneimide dye (96). A colorimetric method using 3-cyano-*N*-methoxypyridinium perchlorate as reagent detects 4-aminophenol in the presence of *N*-acetyl-4-aminophenol (97). 4-Aminophenol has also been detected spectrophotometrically after conversion to indophenol [500-85-6] with alkaline phenol, a method quoted as detecting as little as 10^{-18}mol/L (98), and fluorimetrically after reaction with 3-amino-2(1*H*)-quinolinethione to give a yellow-green fluorescent product (99).

Filter paper impregnated with dicarbonyl(benz-2,1,3-thiadiazole)rhodium chloride gives characteristic colorations with the aminophenol isomers after fixation and can be used as an indicator paper (100).

The potentiometric microdetection of all aminophenol isomers can be done by titration in two-phase chloroform–water medium (101), or by reaction with iodates or periodates, and the back-titration of excess unreacted compound using a silver amalgam and SCE electrode combination (102). Microamounts of 2-aminophenol can be detected by potentiometric titration with cupric ions using a copper-ion-selective electrode; the 3- and 4-aminophenol isomers could not be detected by this method (103). Polarographic detection of 4-aminophenol is possible after conversion to the diazonium salt with sodium nitrite (104) and this isomer can also be analyzed by voltametry (105).

Chromatographic methods for the separation, identification, and quantification of aminophenols also have been described (106). Thin-layer chromatography (tlc) provides a rapid and convenient method of separating the isomers from many derivatives, and subsequent spraying with a variety of chromogenic reagents gives additional information (107,108). Impregnation of plates with nitrite (109) or the use of high performance plates and subsequent densitometry (110) provide quantification to the level of 0.1 μg.

Several gas–liquid chromatographic procedures, using electron-capture detectors after suitable derivatization of the aminophenol isomers, have been cited for the determination of impurities within products and their detection within environmental and wastewater samples (111,112). Modern high pressure liquid chromatographic (hplc) separation techniques employing fluorescence (113) and electrochemical (114) detectors in the 0.01-μg range have been described and should meet the needs of most analytical problems (115,116). The use of selected-ion mass spectrometry also greatly increases detection sensitivity (117,118).

Under atmospheric conditions, 3-aminophenol is the most stable of the three isomers. Both 2- and 4-aminophenol are unstable; they darken on exposure to air and light and should be stored in brown glass containers, preferably in an atmosphere of nitrogen. The use of activated iron oxide in a separate cellophane bag inside the storage container (119), or the addition of stannous chloride (120), or sodium bisulfite (121) inhibits the discoloration of aminophenols. The salts, especially the hydrochlorides, are more resistant to oxidation and should be used where possible.

7. Health and Safety Factors

In general, aminophenols are irritants. Their toxic hazard rating is slight to moderate and their acute oral toxicities in the rat (LD_{50}) are quoted as 1.3, 1.0, and 0.375 g/kg body weight for the 2-, 3-, and 4-isomer, respectively (122). Repeated contamination may cause general itching, skin sensitization, dermatitis, and allergic reactions (123). Immunogenic conjugates are spontaneously produced upon exposure to 2- and 4-aminophenol (124). Methemoglobin formation with subsequent cyanosis is another possible complication (125). Inhalation of aminophenols causes irritation of the mucosal membranes and may precipitate allergic bronchial asthma. Thermal decomposition will release toxic fumes of carbon monoxide and nitrogen oxides.

2-Aminophenol is neuroactive, inducing spike discharges when instilled into the cerebroventricle of the rat (126). 4-Aminophenol is a selective nephrotoxic agent and interrupts proximal tubular function (127,129). Disagreement exists concerning the nephrotoxity of the other isomers although they are not as potent as 4-aminophenol (130,131). Respiration, oxidative phosphorylation, and ATPase activity are inhibited in rat kidney mitochondria (132). The aminophenols and their derivatives are inhibitors of 5-lipoxygenase (133) and prostaglandin synthetase (134) and are being investigated as therapeutic and prophylactic agents for leukotriene or prostaglandin-induced allergic bronchial, tracheal, and lung disease (135).

Teratogenic effects have been noted with 2- and 4-aminophenol in the hamster, but 3-aminophenol was without effect in the hamster and rat (136,137). 2-Aminophenol causes DNA damage in the presence of copper(II) ions (138). 4-Aminophenol is known to inhibit DNA synthesis and alter DNA structure in human lymphoblasts (139,140) and is mutagenic in mouse micronuclei tests (141). The aminophenols have been shown to be genotoxic, as evidenced by the induction of sister chromatid exchanges (142,143), but they also exert a protective effect against DNA interaction with other noxious chemicals (144). After assessment of available data a recent report stated that the aminophenols were safe as cosmetic ingredients in their present uses and concentrations (145).

Obviously, care should be taken in handling these compounds with the wearing of chemical-resistant gloves and safety goggles; prolonged exposure should be avoided. Contaminated clothing should be removed immediately and the affected area washed thoroughly with running water for at least 10 minutes.

Since the aminophenols are oxidized easily, they tend to remove oxygen from solutions. Hence, if they are released from industrial waste waters into streams and rivers, they will deplete the capacity of these environments to sustain aquatic life. Concern has also been raised that chlorination of drinking water may enhance the toxicity of aminophenols present as pollutants (146); chlorinated aminophenols are known to be more toxic (147).

The addition of slaked lime (148) and the initiation of polymerization reactions with H_2O_2 and ferric or stannous salts (149) are techniques employed to remove aminophenols from waste waters. The adsorption of aminophenols onto metal ferrocyanides and activated carbons from bituminous coal has met with limited success but also may provide a possible means of removal (150,151).

An enzymatic method using horseradish peroxidase to cross link and precipitate the compounds as insoluble polymers has also been studied (152). Biological degradation of 3-aminophenol has been carried out in aeration tanks using adapted microflora (>4 month period) from activated sludge (153); and other microbial degradation techniques are under investigation (154–159) including the immobilization of microbial cells onto calcium-alginate (polymannuronate) beads (160).

8. Uses

The aminophenols are versatile intermediates and their principal use is as synthesis precursors; their products are represented among virtually every class of stain and dye.

Both 2- and 4-aminophenols are strong reducing agents and are employed as photographic developers under the trade names of Atomal and Ortol (2-aminophenol); Activol, Azol, Certinal, Citol, Paranol, Rodinol, Unal, and Ursol P (4-aminophenol); they may be used alone or in combination with hydroquinone. The oxalate salt of 4-aminophenol is marketed under the name of Kodelon. They also act as corrosion inhibitors in paints (161) and as anticorrosion-lubricating agents in two-cycle engine fuels (162).

As a result of the close proximity of the amino and hydroxyl groups on the benzene ring and their ease of condensation with suitable reagents, 2-aminophenol is a principal intermediate in the synthesis of such heterocyclic systems as oxyquinolines, phenoxazines, and benzoxazoles. The last-named compounds have been used as inflammation inhibitors (163), and other derivatives have potential as antiallergic agents (164). In addition, 2-aminophenol is specifically used for shading leather, fur, and hair from grays to yellowish brown. It has also found application in the determination and extraction of certain precious metals (165,166).

3-Aminophenol has been used as a stabilizer of chlorine-containing thermoplastics (167), although its principal use is as an intermediate in the production of 4-amino-2-hydroxybenzoic acid [65-49-6], a tuberculostat. This isomer is also employed as a hair colorant and as a coupler molecule in hair dyes (168,169).

Nitrogen-substituted 4-aminophenols have long been known as antipyretics and analgesics, and the production of these derivatives represents significant use of this compound. 4-Aminophenol is also used as a wood stain, imparting a roselike color to timber (170), and as a dyeing agent for fur and feathers.

9. Derivatives

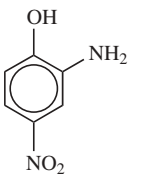
The derivatives of the aminophenols have important uses both in the photographic and the pharmaceutical industries. They are also extensively employed as precursors and intermediates in the synthesis of more complicated molecules, especially those used in the staining and dye industry. All of the major classes of dyes have representatives that incorporate substituted aminophenols; these compounds produced commercially as dye intermediates have been reviewed

(171). Details of the more commonly encountered derivatives of the aminophenols can be found in standard organic chemistry texts (25,172). A few examples, which have specific uses or are manufactured in large quantities, are discussed in detail in the following (see Table 6).

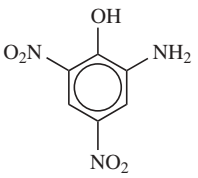
9.1. Derivatives of 2-Aminophenol. *2-Amino-4-nitrophenol.* This derivative, 2-hydroxy-5-nitroaniline (9), forms orange prisms from water. These prisms are hydrated with one water of crystallization, mp 80–90°C, and can be dehydrated over sulfuric acid to the anhydrous form, mp 143–145°C. The compound is soluble in ethanol, diethyl ether, acetic acid, and warm benzene and slightly soluble in water.

2-Amino-4-nitrophenol is produced commercially by the partial reduction of 2,4-dinitrophenol. This reduction may be achieved electrolytically using vanadium (173) or chemically with polysulfide, sodium hydrosulfide, or hydrazine and copper (174). Alternatively, 2-acetamidophenol or 2-methylbenzoxazole may be nitrated in sulfuric acid to yield a mixture of 4- and 5-nitro derivatives that are then separated and hydrolyzed with sodium hydroxide (175).

The major use of this compound is in the production of mordant and acid dyes. 2-Amino-4-nitrophenol also has found limited use as an antioxidant and light stabilizer in butyl rubbers and as a catalyst in the manufacture of hexadiene. The compound has been shown to be a skin irritant and continuous exposure should be avoided. Toxicological studies indicate that it is nonaccumulative (176) but suggest that it may be carcinogenic (177).



(**9**)



(**10**)

2-Amino-4,6-dinitrophenol. This derivative (10), also known as picramic acid, forms dark red needles from ethanol and prisms from chloroform. The compound flashes at 210°C in contact with an open flame, ignites rapidly and burns relatively fast. 2-Amino-4,6-dinitrophenol is soluble in glacial acetic acid, water, ethanol, benzene, and aniline and is sparingly soluble in diethyl ether and chloroform.

The compound can be prepared from 2,4,6-trinitrophenol (picric acid [88-89-1]) by reduction with sodium hydrosulfide (178), with ammonia-hydrogen sulfide followed by acetic acid neutralization of the ammonium salt (179), with ethanolic hydrazine and copper (180), or electrolytically with vanadium sulfate in alcoholic sulfuric acid (173). Heating 4,6-dinitro-2-benzamidophenol in concentrated HCl at 140°C also yields picramic acid (181).

2-Amino-4, 6-dinitrophenol is an important intermediate in the manufacture of colorants, especially mordant dyes. It has also been used as an indicator dye in titrations (yellow with acid, red with alkali) and as a reagent for albumin determination. The compound induces sister chromatid exchange and micronuclei formation suggesting potential health hazards (182,183).

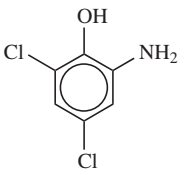
Table 6. **Derivatives of Aminophenols**

Common name	Structure number	CAS Registry Number	Molecular formula	Molecular weight	Melting point, °C	Boiling point[a], °C
			Derivatives of 2-aminophenol			
2-amino-4-nitrophenol	(9)	[99-57-0]	$C_6H_6N_2O_3$	154.13	80–90	
2-amino-4,6-dinitrophenol	(10)	[96-91-3]	$C_6H_5N_3O_5$	199.13	169–170	
2-amino-4,6-dichlorophenol	(11)	[527-62-8]	$C_6H_5Cl_2NO$	168.15	95–96	
2,4-diaminophenol	(12)	[95-86-3]	$C_6H_8N_2O$	124.14	78–80[b]	
acetarsone	(13)	[97-44-9]	$C_8H_{10}AsNO_5$	275.08	240–250[b]	
			Derivatives of 3-aminophenol			
3-(*N*,*N*-dimethylamino)phenol	(14)	[99-07-0]	$C_8H_{11}NO$	137.18	87	265–268 206 (13.3) 194 (6.7) 153 (0.7)
3-(*N*-methylamino)phenol	(15)	[14703-69-6]	C_7H_9NO	123.15		170 (1.6)
3-(*N*,*N*-diethylamino)phenol	(16)	[91-68-9]	$C_{10}H_{15}NO$	165.23	78	276–280 209–211 (1.6)
3-(*N*-phenylamino)phenol	(17)	[101-18-8]	$C_{12}H_{11}NO$	185.22	81.5–82	340
4-amino-2-hydroxybenzoic acid	(18)	[65-49-6]	$C_7H_7NO_3$	153.13	150–151	
			Derivatives of 4-aminophenol			
4-(*N*-methylamino)phenol	(19)	[150-75-4]	C_7H_9NO	123.15	87	168–169 (2)
4-(*N*,*N*-dimethylamino)phenol	(20)	[619-60-3]	$C_8H_{11}NO$	137.18	75–76	101–103 (0.067)
4-hydroxyacetanilide	(21)	[103-90-2]	$C_8H_9NO_2$	151.15	169–171	
4-ethoxyacetanilide	(22)	[62-44-2]	$C_{10}H_{13}NO_2$	179.21	134–135	
N-(4-hydroxyphenyl)glycine	(23)	[122-87-2]	$C_8H_9NO_3$	167.16	245–247[b]	

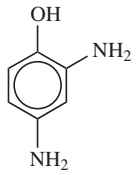
[a] At 101.3 kPa = 760 mm Hg unless otherwise noted in parentheses. Values in parentheses are in the kPa. To convert kPa to mm Hg, multiply by 7.5.
[b] Decomposes.

2-Amino-4,6-dichlorophenol. This compound (11) forms long white needles from carbon disulfide, and aggregate spheres from benzene. It sublimes at 70–80°C (8 Pa = 0.06 mm Hg) and decomposes >109°C. It is freely soluble in benzene and carbon disulfide, and is sparingly soluble in petroleum ether, water, and ethanol. The free base is unstable and the hydrochloride salt (mp 280–285°C, dec) is employed commercially.

Industrial production is by reduction of the corresponding nitrophenol with iron or hydrazine (184,185). 2-Amino-4,6-dichlorophenol finds important use as an azo-dye intermediate (see AZO DYES).



(**11**)

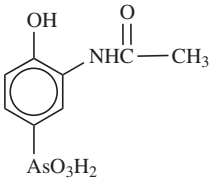


(**12**)

2,4-Diaminophenol. 4-Hydroxy-*m*-phenylenediamine [95-86-3] (12) forms leaflets that darken on exposure to air. It is soluble in acid, alkali, ethanol, and acetone and is sparingly soluble in chloroform, diethyl ether, and ligroin. 2,4-Diaminophenol usually is sold as the sulfate [74283-34-4] (Diamol) or dihydrochloride salt [137-09-7] (Acrol, Amidol). 2,4-Diaminophenol can be prepared from 2,4-dinitrophenol by catalytic hydrogenation or, less conveniently, by metal reduction in acid solution (Béchamp method) (186,187). Alternatively, electrolytic reduction and subsequent hydroxylation of 1,3-dinitrobenzene or 3-nitroaniline in sulfuric acid can be undertaken (188,189).

The dihydrochloride salt is used as a photographic developer. It also is employed as an intermediate in the manufacture of fur dyes, in hair dyeing, as a reagent in testing for ammonia and formaldehyde, and as an oxygen scavenger in water to prevent boiler corrosion (190).

Acetarsone. Acetarsone (3-acetamido-4-hydroxyphenyl arsonic acid) (13), also known as acetarsol, stovarsol, and Ehrlich 594, forms white prisms from water.



(**13**)

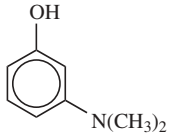
This compound is odorless with a faintly acidic taste; it is practically insoluble in water, ethanol and dilute acids but freely soluble in dilute aqueous alkali with dissociation constants, pK_a, 3.73, 7.9, 9.3. The compound is prepared by sodium hydrosulfite reduction of 3-nitro-4-hydroxyphenylarsonic acid [121-19-7] and

then acetylation in aqueous suspension with acetic anhydride at 50–55°C for 2 h (191,192).

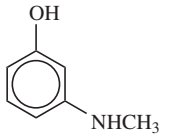
Salts of acetarsone are used in the treatment of intestinal amoebiasis, vaginal trichomoniasis, and necrotizing ulcerative gingivitis (Vincent's angina). The diethylamine salt (acetylarsan [534-33-8]) has antisyphilitic properties. Owing to toxicity problems, safer drugs have been developed. Oral LD_{50} in rabbits is 150 mg/kg.

9.2. Derivatives of 3-Aminophenol. *3-(N,N-Dimethylamino)phenol.* 3-Hydroxy-*N,N*-dimethylaniline (14) forms white needles and is soluble in alkali, mineral acid, ethanol, diethyl ether, acetone, and benzene and practically insoluble in water.

It can be prepared by heating resorcinol with an aqueous solution of dimethylamine and its hydrochloride at 200°C under pressure for 12 h (193). The treatment of dimethylaniline with oleum at 55–60°C, followed by fusion with sodium hydroxide at 270–300°C, also gives 3-(*N,N*-dimethylamino)phenol (194). In addition, 3-aminophenol may be methylated with dimethyl sulfate under neutral conditions, or its hydrochloride salt heated with methanol at 170°C under pressure for 8 h to give the desired product (195). The compound is used primarily as an intermediate in the production of basic (Red 3 and 11) and mordant (Red 77) dyes.



(**14**)



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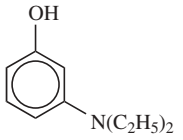
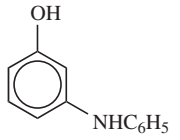


(**16**)



(**17**)

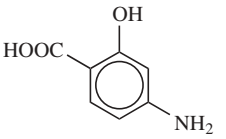
3-(N-Methylamino)phenol. This derivative (15) is easily soluble in ethyl acetate, ethanol, diethyl ether, and benzene. It is also soluble in hot water, but only sparingly soluble in cold water. Industrial synthesis is by heating 3-(*N*-methylamino)benzenesulfonic acid with sodium hydroxide at 200–220°C (196) or by the reaction of resorcinol with methylamine in the presence of aqueous phosphoric acid at 200°C (197).

3-(N,N-Diethylamino)phenol. This derivative (16) forms rhombic bipyramidal crystals. Industrial synthesis is analogous to the previously described synthesis of 3-(*N,N*-dimethylamino)phenol from resorcinol and diethylamine, by reaction of 3-(*N,N*-diethylamino)benzenesulfonic acid with sodium hydroxide, or by alkylation of 3-aminophenol hydrochloride with ethanol.

3-(N-Phenylamino)phenol. This phenol (17) is slightly soluble in ethanol, diethyl ether, acetone, benzene, and water. The compound is made by heating resorcinol and aniline at 200°C in the presence of aqueous phosphoric acid or calcium chloride. In another process, 3-aminophenol is heated with aniline hydrochloride at 210–215°C (198).

4-Amino-2-hydroxybenzoic acid. This derivative (18) more commonly known as 4-aminosalicylic acid, forms white crystals from ethanol, melts with effervescence and darkens on exposure to light and air. A reddish-brown crystalline powder is obtained on recrystallization from ethanol–diethyl ether. The

compound is soluble in dilute solutions of nitric acid and sodium hydroxide, ethanol, and acetone; slightly soluble in water and diethyl ether; and virtually insoluble in benzene, chloroform or carbon tetrachloride. It is unstable in aqueous solution and decarboxylates to form 3-aminophenol. Because of the instability of the free acid, it is usually prepared as the hydrochloride salt, mp 224°C (dec), dissociation constant pK_a 3.25.



(**18**)

4-Amino-2-hydroxybenzoic acid is manufactured by carboxylation of 3-aminophenol under pressure with ammonium carbonate at 110°C (199) or with potassium bicarbonate and carbon dioxide at 85–90°C (200) with subsequent acidification.

The major use of this compound is as a bacteriostatic agent against tubercle bacilii. This compound also is used as an adjunct to streptomycin and isoniazid. The free acid and its sodium, potassium, and calcium salts are marketed under many trade names (eg, Aminox, Apacil, Deapasil, Paramycin, Parasalicil, Pasnodia, Rezipas, Sanipirol-4, Tubersan). Up to 10–15 g of the sodium salt may be administered each day, although prolonged use may give rise to toxic symptoms. Oral LD_{50} of the free acid in mice is 4 g/kg.

9.3. Derivatives of 4-Aminophenol. *4-(N-Methylamino)phenol.* This derivative, also named 4-hydroxy-*N*-methylaniline (19), forms needles from benzene that are slightly soluble in ethanol and insoluble in diethyl ether. Industrial synthesis involves decarboxylation of *N*-(4-hydroxyphenyl)glycine [122-87-2] at elevated temperature in such solvents as chlorobenzene–cyclohexanone (201,202). It also can be prepared by the methylation of 4-aminophenol, or from methylamine [74-89-5] by heating with 4-chlorophenol [106-48-9] and copper sulfate at 135°C in aqueous solution, or with hydroquinone [123-31-9] at 200–250°C in alcoholic solution (203).

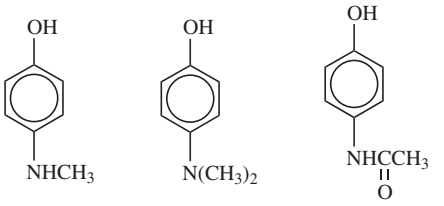
Its chief use is as a component in photographic developers. Because the free compound is unstable in air and light, it is usually marketed as the sulfate salt [55-55-0], Metol, mp 260°C (dec). It also finds application as an intermediate for fur and hair dyes and, under certain circumstances, as a corrosion inhibitor for steel. Prolonged exposure to 4-(*N*-methylamino)phenol has been associated with the development of dermatitis and allergies.

4-(N,N-Dimethylamino)phenol. 4-Hydroxy-*N,N*-dimethylaniline (20) forms large rhombic crystals from diethyl ether–hexane or diethyl ether–ligroin. It forms a salt with sulfuric acid, mp 208–210°C (204).

Methylation of 4-aminophenol with a methyl halide under pressure produces 4-(*N,N*-dimethylamino)phenol. The competing product, 4-hydroxyphenyltrimethyl ammonium halide (or the corresponding base), also yields 4-(*N,N*-dimethylamino)phenol on distillation. Alternatively, it can be synthesized by dealkylation of 4-methoxy-*N,N*-dimethylaniline [701-56-4] with hydroiodic acid

at reflux temperature for 10 h (205) or by the photodecomposition of 4-dimethylaminobenzene diazonium tetrafluoroborate [24564-52-1] (204).

The compound is an intermediate in several synthetic reactions and recently has found extensive use in experimental toxicity studies in animals. It has been shown to cause methemoglobinemia; its metabolism in humans has been discussed (206,207).



(**19**) (**20**) (**21**)

4-Hydroxyacetanilide. This derivative (21), also known as 4-acetamidophenol, acetaminophen, or paracetamol, forms large white monoclinic prisms from water. This compound is odorless and has a bitter taste. 4-Hydroxyacetanilide is insoluble in petroleum ether, pentane, and benzene; slightly soluble in diethyl ether and cold water; and soluble in hot water, alcohols, dimethylformamide, 1,2-dichloroethane, acetone, and ethyl acetate. The dissociation constant, pK_a, is 9.5 (25°C).

Production is by the acetylation of 4-aminophenol, which can be achieved with acetic acid and acetic anhydride at 80°C (208), with acetic acid anhydride in pyridine at 100°C (209), with acetyl chloride and pyridine in toluene at 60°C (210), or by the action of ketene in alcoholic suspension. 4-Hydroxyacetanilide also may be synthesized directly from 4-nitrophenol. The available reduction–acetylation systems include tin with acetic acid, hydrogenation over Pd–C in acetic anhydride, and hydrogenation over platinum in acetic acid (211,212). Other routes include rearrangement of 4-hydroxyacetophenone hydrazone with sodium nitrite in sulfuric acid and the electrolytic hydroxylation of acetanilide [103-84-4] (213).

4-Hydroxyacetanilide is used as an intermediate in the manufacture of azo dyes (qv) and photographic chemicals. The compound possesses antipyretic and analgesic properties and is used widely in this context. Typical formulations containing 4-hydroxyacetanilide include Acetalgin, Cetadol, Dirox, Febrilix, Hedex, Panadol, Tylenol, and Valadol. The oral LD_{50} in rats is 3.7 g/kg.

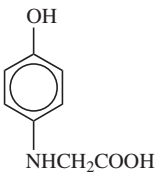
4-Ethoxyacetanilide. This compound (22), also known as phenacetin, is a white crystalline powder. The compound is odorless and has a slightly bitter taste. It is sparingly soluble in cold water and more soluble in hot water, ethanol, diethyl ether, and chloroform. At relative humidities between 15 and 90% the equilibrium moisture content is about 2% (25°C).

The main production route to 4-ethoxyacetanilide is by catalytic reduction of 4-nitrophenetole [100-29-8] with hydrogen and subsequent acetylation using acetic anhydride. The compound also can be synthesized by ethylating 4-nitrophenol with ethyl sulfate in alkali, reducing the nitro group to an amino group with iron in acid and then acetylating by boiling with glacial acetic acid (214).

Alternatively, 4-aminophenol may be ethylated with ethyl iodide in alcoholic alkali and the resulting 4-phenetidine [156-43-4] then acetylated. The acetylation also may be carried out first, followed by the ethylation.

4-Ethoxyacetanilide possesses both antipyretic and analgesic properties, but it is of little value for the relief of severe pain. Its use for prolonged periods should be avoided because one of its minor metabolites (2-hydroxyphenetidine) is nephrotoxic and may be involved in the formation of methemoglobinemia. The oral LD_{50} in rats is 1.65 g/kg (215).

(**22**)



(**23**)

N-(4-Hydroxyphenyl)glycine. This derivative (23) forms aggregate spheres or shiny leaflets from water. It turns brown at 200°C, begins to melt at 220°C, and melts completely with decomposition at 245–247°C. The compound is soluble in alkali and mineral acid and sparingly soluble in water, glacial acetic acid, ethyl acetate, ethanol, diethyl ether, acetone, chloroform, and benzene.

N-(4-Hydroxyphenyl)glycine can be prepared from 4-aminophenol and chloracetic acid (216,217) or by alkaline hydrolysis of the corresponding nitrile with subsequent elimination of ammonia (218).

N-(4-Hydroxyphenyl)glycine is used as a photographic developer under the trade names of Glycine, Iconyl, and Monazol. It is also applied as a photoresist in the dye industry and serves as an intermediate in the production of 4-(*N*-methylamino)phenol (Metol) by liberation of CO_2. *N*-(4-Hydroxyphenyl)glycine is used in analytical chemistry for the determination of iron, phosphorus , and silicon, and as an acid indicator in bacteriology. Prolonged exposure to this compound may result in kidney damage (219).

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