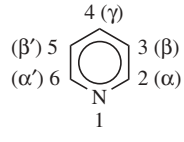
PYRIDINE AND PYRIDINE DERIVATIVES

1. Introduction

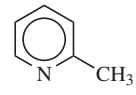
Since the early twentieth century, pyridine derivatives have been commercially important, but most prominently so during World War II and thereafter. Many pyridines of commercial interest find application in market areas where bioactivity is important, as in medicinal drugs and in agricultural products, eg, herbicides, insecticides, fungicides, and plant growth regulators. However, pyridines also have significant market applications outside the realm of bioactive ingredients. For example, polymers made from pyridine-containing monomers are generally sold on the basis of their unique physical properties and function, rather than for any bioactivity. Pyridines can be classified as specialty chemicals because of a relatively lower sales volume than commodity chemicals. They are most often sold in the marketplace as chemical intermediates used to manufacture final consumer products.

Pyridine compounds are defined by the presence of a six-membered heterocyclic ring consisting of five carbon atoms and one nitrogen atom. The carbon valencies not taken up in forming the ring are satisfied by hydrogen atoms. The arrangement of atoms is similar to benzene except that one of the carbon–hydrogen ring sets has been replaced by a nitrogen atom. The parent compound is pyridine itself (**1**). Substituents are indicated either by the numbering shown, 1–6, or by the Greek letters, α, β, or γ. The Greek symbols refer to the position of the substituent relative to the ring nitrogen atom, and are usually used for naming monosubstituted pyridines. The ortho, meta, and para nomenclature commonly used for disubstituted benzenes is not used in naming pyridine compounds.



(**1**)

Important commercial alkylpyridine compounds are α-picoline (**2**), β-picoline (**3**), γ-picoline (**4**), 2,6-lutidine (**5**), 3,5-lutidine (**6**), 5-ethyl-2-methylpyridine (**7**), and 2,4,6-collidine (**8**). In general, the alkylpyridines serve as precursors of many other substituted pyridines used in commerce. These further substituted pyridine compounds derived from alkylpyridines are in turn often used as intermediates in the manufacture of commercially useful final products.



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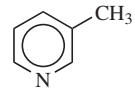

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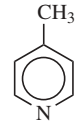

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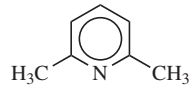

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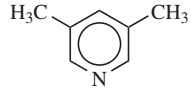

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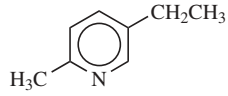

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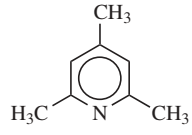


(**8**)

Pyridine was first synthesized in 1876 (1) from acetylene and hydrogen cyanide. However, α-picoline (**2**) was the first pyridine compound reported to be isolated in pure form (2). Interestingly, it was the market need for (**2**) that motivated the development of synthetic processes for pyridines during the 1940s, in preference to their isolation from coal-tar sources. The basis for most commercial pyridine syntheses in use can be found in the early work of Chichibabin (3). There are few selective commercial processes for pyridine (**1**) and its derivatives, and almost all manufacturing processes produce (**1**) along with a ser-

ies of alkylated pyridines in admixture. The chemistry of pyridines is significantly different from that of benzenoids. Pyridines undergo some types of reaction that only highly electron-deficient benzenoids undergo, and do not undergo some facile reactions of benzenoids, such as Friedel-Crafts alkylation and C-acylation, eg. However, nitration of pyridine under mild conditions are reported and mentioned in later section. These mild nitrations are explained using the nucleophilic addition, elimination mechanism.

2. Physical Properties

The physical properties of pyridines are the consequence of a stable, cyclic, 6- π-electron, π-deficient, aromatic structure containing a ring nitrogen atom. The ring nitrogen is more electronegative than the ring carbons, making the two-, four-, and six-ring carbons more electropositive than otherwise would be expected from a knowledge of benzenoid chemistries. The aromatic π-electron system does not require the participation of the lone pair of electrons on the nitrogen atom; hence the terms weakly basic and π-deficient used to describe pyridine compounds. The ring nitrogen of most pyridines undergoes reactions typical of weak, tertiary organic amines such as protonation, alkylation (qv), and acylation.

Liquid pyridine and alkylpyridines are considered to be dipolar, aprotic solvents, similar to dimethylformamide (dml) or dimethyl sulfoxide (dmas). Most pyridines form a significant azeotrope with water, allowing separation of mixtures of pyridines by steam distillation that could not be separated by simple distillation alone. The same azeotropic effect with water also allows rapid drying of wet pyridines by distillation of a small forecut of water azeotrope.

2.1. Pyridine. Many physical properties of pyridine are unlike those of benzene, its homocyclic counterpart. For example, pyridine has a boiling point 35.2°C higher than benzene (115.3 vs. 80.1°C), and unlike benzene, it is miscible with water in all proportions at ambient temperatures. The much higher dipole moment of pyridine relative to benzene is responsible, in significant part, for the higher boiling point and water solubility. Benzene and pyridine are aromatic compounds having resonance energies of similar magnitude, and both are miscible with most other organic solvents. Pyridine is a weak organic base ($pK_a = 5.22$), being both an electron-pair donor and a proton acceptor, whereas benzene has little tendency to donate electron pairs or accept protons. Pyridine is less basic than aliphatic, tertiary amines. Table 1 lists some physical properties of pyridine, and Table 2 compares physical properties of pyridine to some alkyl- and alkenylpyridine bases.

2.2. Other Pyridine Bases. The nucleophilicity and basicity of pyridines can be reduced by large, sterically bulky groups around the nitrogen atom, such as *tert*-butyl in the 2- and 6-positions. Sterically undemanding groups like methyl tend to increase basicity relative to parent pyridine, as expected. Electron-withdrawing substituents can also reduce pyridine basicity and nucleophilicity. 2,6-Dichloropyridine [2402-78-0] is sterically hindered and also contains strong electron-withdrawing substituents. As such, it cannot be titrated

by acid, even by using extremely acidic media such as perchloric acid in acetic acid solvent.

Generally, hydrophobic substituents on the pyridine ring reduce water solubility, polar ones capable of hydrogen bonding as acceptor or donor, increase it.

Table 3 gives the corresponding physical properties of some commercially important substituted pyridines having halogen, carboxylic acid, ester, carboxamide, nitrile, carbinol, aminomethyl, amino, thiol, and hydroxyl substituents.

2.3. Quantitative Structure–Property Relationships. A useful way to predict physical property data has become available, based only on a knowledge of molecular structure, that seems to work well for pyridine compounds. Such a prediction can be used to estimate real physical properties of pyridines without having to synthesize and purify the substance, and then measure the physical property.

The relationship between the structure of a molecule and its physical properties can be understood by finding a quantitative structure–property relationship (QSPR) (10). A basis set of similar compounds is used to derive an equation that relates the physical property, eg, melting point or boiling point, to structure. Each physical property requires its own unique QSPR equation. The compounds in the basis set used for QSPRs with pyridines have sometimes been quite widely divergent in respect to structural similarity or lack of it, yet the technique still seems to work well. The terms of the equation are composed of a coefficient and an independent variable called a descriptor. The descriptors can offer insight into the physical basis for changes in the physical property with changes in structure.

The same strategy can be used to relate chemical reactivity, catalytic ability, and bioactivity (10) of pyridine compounds with their structure. Although such a prediction is still in its formative stage, early results have been encouraging.

3. Chemical Properties

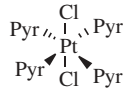
Chemical reactivity of pyridines is a function of ring aromaticity, presence of a basic ring nitrogen atom, π-deficient character of the ring, large permanent dipole moment, easy polarizability of the π-electrons, activation of functional groups attached to the ring, and presence of electron-deficient carbon atom centers at the α- and γ- positions. Depending on the conditions of the chemical transformation, one or more of these factors can give rise to the observed chemistry. The chemistry of pyridines can be divided into two categories: reactions at the ring-atomic centers, and reactions at substituents attached to the ring-atomic centers.

3.1. Reactions at Ring Atoms. Ring-atomic centers can undergo attack by electrophiles, easily at the ring nitrogen and less easily at ring carbons. Nucleophilic attack is also possible at ring carbons or hydrogens.

Electrophilic Attack at Nitrogen. The lone pair on pyridine (**1**) ($pK_a = 5.22$) reacts with electrophiles under mild conditions, with protonic acids to give simple salts, with Lewis acids to form coordination compounds, eg, (**9**) [2903-67-5], and with transition metals to form complex ions, eg, (**10**,**11**) [24444-58-4]. The complex ion pyridinium chlorochromate [67369-53-3] (**12**) is a mild oxidizing agent suitable

for the conversion of alcohols to carbonyl compounds.

(**9**)



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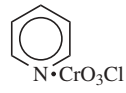

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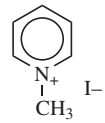
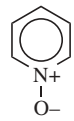


(**12**)

Reactive halogen compounds, alkyl halides, and activated alkenes give quaternary pyridinium salts, eg, (**13**). Oxidation with peracids gives pyridine *N*-oxides, eg, pyridine *N*-oxide itself [694-59-7] (**14**), which are useful for further synthetic transformations (11).

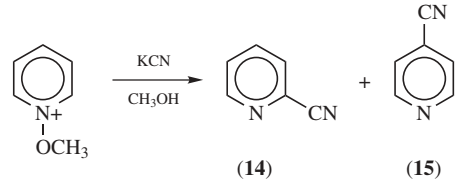


(**13**)

Electrophilic Attack at Carbon. Electrophilic attack at a C atom in pyridines is particularly difficult unless one or more strong electron-donating substituents are attached to the ring. Knowledge of this fact has resulted in the widespread use of pyridine as a solvent for reactions involving electrophilic species. Pyridine undergoes nitration in low yield (15%) to give 3-nitropyridine [2530-26-9] (13), whereas pyridine *N*-oxide is nitrated at position 4 to give 4-nitropyridine *N*-oxide [1124-33-0] in high yield, and 2- and 4-aminopyridines may be dinitrated (14). Better yields of nitropyridines are obtained by newer nitrating methods (15–17). Here the electrophile (NO_2^+) rearranges from the

nitrogen to the C-3 (or C-5) carbon with the help from nucleophiles like sulfites that undergo addition to the initial 1-nitropyridinium species and elimination after the rearrangement of the nitro group from the *N*-nitropyridinium derivative. The chlorination of pyridine and picolines (**2–4**), is of great commercial importance (18).

Nucleophilic Attack at Carbon or Hydrogen. Only the strongest of nucleophiles (eg, $-NH_2$) can replace a hydrogen in pyridine. However, *N*-oxides and quaternary salts rapidly undergo addition, followed by subsequent transformations (13). Recently, softer nucleophiles like cyanide ion (CN^-) have been used for the nucleophilic displacement of hydrogen to form 2-cyanopyridines (19). This reaction involves *N*-nitropyridinium intermediates.



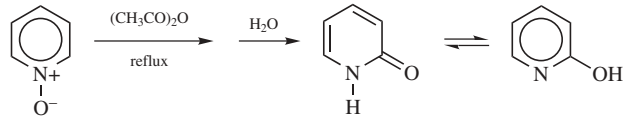
(**14**) (**15**) (1)

The Feely-Beavers procedure (eq. 1) provides a method for the introduction of a cyano group (9), principally at the 2-position, to give compounds, eg, **14** and **15**. Pyridylpyridinium salts have been used in the introduction of nucleophiles onto a pyridine ring. Here the pyridine ring would be the leaving group instead of a hydrogen, and hence good yields of the 4-substituted pyridine derivatives are obtained (20,21).

A modification of the Reissert-Henze reaction employing benzoyl chloride and $(CH_3)_3SiCN$ gives good yields of 2-cyano pyridine (**14**) from pyridine *N*-oxide (**13**) (22).

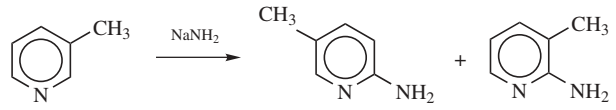
Methylpyridinium quaternary salts, eg, **12** undergo oxidation in alkaline solution in the presence of potassium ferricyanide to give 2-pyridones, eg, *N*-methyl-2-pyridone [694-85-9] (20). Frequently nucleophilic attack at position 2 by excess hydroxide leads to ring opening; this and synthetically useful recyclizations have been reviewed (24).

Treatment of pyridine *N*-oxide (**13**) with acetic anhydride leads chiefly to 2-pyridone (**16**) formation (eq. 2) (12).



(**13**) (**16**) (2)

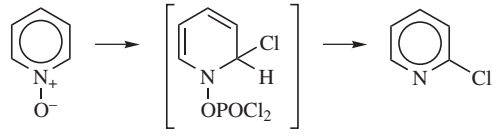
Pyridine and its methyl derivatives, (**2–4**), undergo amination with sodium amide at the 2-position eg, 2-amino-3-methylpyridine [1603-40-3] and 2-amino-5-methylpyridine [1603-41-4] from **3** (eq. 3). This Chichibabin reaction is most important for introduction of a 2-amino substituent, which may be replaced readily by many other groups (25).



(3)

(**3**)

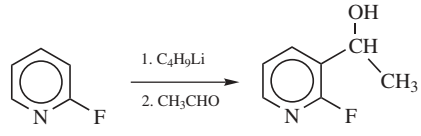
The *N*-oxides readily undergo nucleophilic addition followed by elimination, which forms the basis of several useful syntheses of 2-substituted pyridines. Chlorination of **13** with $POCl_3$ to give 2-chloropyridine (**17**) is a good example (eq. 4); some chlorination may occur also at C-4 (12).



(4)

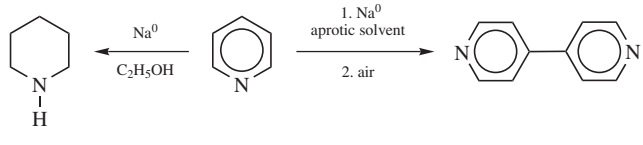
(**13**) (**17**)

Pyridine undergoes 2- and 4-alkylation with Grignard reagents, depending on whether free metal is present (26). Free metal gives mixtures or exclusive 4-alkylation. Substituent-directed metallation (eq. 5) has become an important approach to the synthesis of disubstituted pyridines (13). For example, 2-fluoropyridine [372-48-5] reacts with butyllithium and acetaldehyde to give a 93% yield of alcohol [79527-61-1].



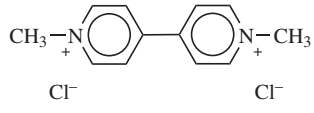
(5)

Treatment of pyridine (**1**) with sodium metal in ethanol gives piperidine [1910-42-5] (**18**); however, dimerization to 4,4′-bipyridine [553-26-4] (**19**) is favored in aprotic solvents (13). Piperidine ring is one of the most common motifs found in natural products and biologically active agents. The scope and limitations of [3+3]cycloaddition reactions to make piperidines is reviewed (13).



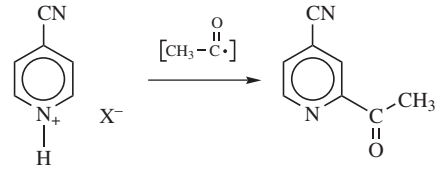
(**18**) (**1**) (**19**)

The 4,4′-bipyridine (**19**) formed is a precursor of the important herbicide Paraquat [1910-42-5] (**20**) (27).



(**20**)

Free-Radical Attack at Carbon. Homolytic substitution of pyridines has not been as thoroughly studied as heterolytic processes have been, owing to low conversions and poor selectivity (28). However, some pyridinium salts have been found to undergo potentially useful regiospecific reactions (29). Protonated pyridines readily undergo acylation by acyl radicals, generated by abstracting a hydrogen atom from an aldehyde, eg, 2-acetyl-4-cyanopyridine [37398-49-5] from protonated 4-cyanopyridine (eq. 6).

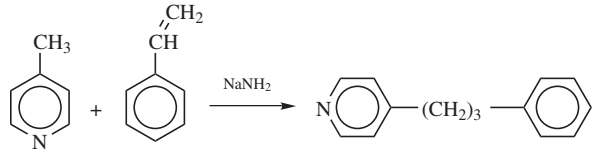


(6)

4-Cyanopyridine (**15**) reacts with ketones not bearing an α-hydrogen in the presence of sodium metal to afford a tertiary alcohol (a precursor of azacyclonol) in high yield, eg, the reaction of (**15**) and benzophenone yields the tertiary benzyl alcohol [1620-30-0] (30).

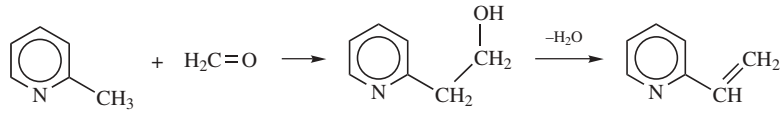
3.2. Reactions of Substituted Pyridines

Carbon Substituents. Alkyl groups at positions 2 and 4 of a pyridine ring are more reactive than either those at the 3-position of a pyridine ring or those attached to a benzene ring. Carbanions can be formed readily at alkyl carbons attached at the 2- and 4-positions. This increased chemical reactivity has been used to form 2- and 4-(phenylpropyl)pyridines, eg, 4-(3-phenylpropyl)pyridine [2057-49-0] (**21**) (31).



(**4**) (**21**)

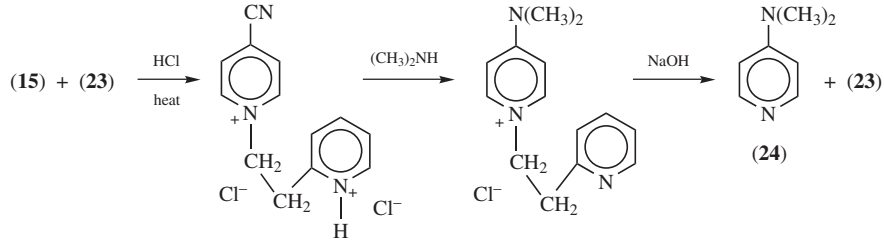
An industrially important example is the condensation of α- **2** or γ- picoline (**4**) with aqueous formaldehyde to form the corresponding ethanolpyridines, 2-ethanolpyridine [104-74-2] (**22**) and 4-ethanolpyridine [5344-27-4], respectively, followed by dehydration of the alcohols to give 2- **23** or 4-vinylpyridine.



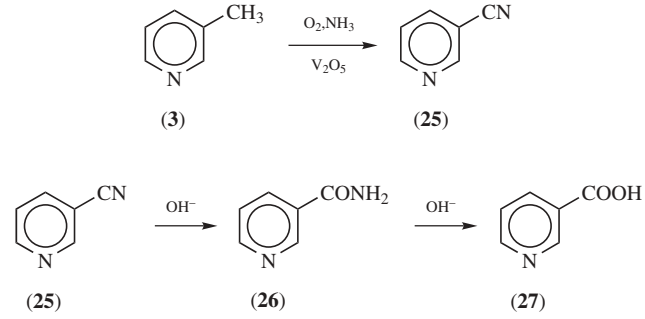
(**2**) (**22**) (**23**)

2-Vinylpyridine (**23**) came into prominence ~ 1950 as a component of latex. Butadiene and styrene monomers were used with **23** to make a terpolymer that bonded fabric cords to the rubber matrix of automobile tires (32). The ability of **23**

to act as a Michael acceptor has been exploited for the manufacture of 4-dimethylaminopyridine (DMAP) (**24**) (33). The sequence consists of a Michael addition of **23** to 4-cyanopyridine (**15**), replacement of the 4-cyano substituent by dimethylamine (taking advantage of the activation of the cyano group by quaternization of the pyridine ring), and base-catalyzed dequaternization (retro-Michael addition). 4-Dimethylaminopyridine is one of the most effective acylation catalysts known (24). Commercial synthesis of DMAP involve the nucleophilic displacement with dimethylamine on pyridylpyridinium salt (20) and the use of acrylamide or acrylic acid with 4-cyanopyridine (**15**) instead of 2-vinylpyridine (**23**) and 4-cyanopyridine (**15**) as described above, in comparable processes (35,36).

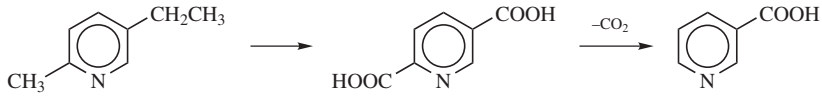


Cyanopyridines are usually manufactured from the corresponding picoline by catalytic, vapor-phase ammoxidation (eq. 7) in a fixed- or fluid-bed reactor (37). 3-Cyanopyridine (**25**) is the most important nitrile, as it undergoes partial or complete hydrolysis under basic conditions to give niacinamide [98-92-0] (**26**) or niacin (nicotinic acid) (**27**), respectively (38).



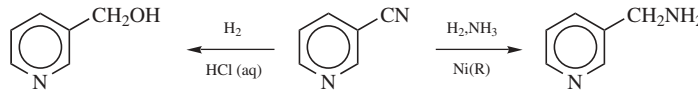
(7)

Compound 27 may also be obtained directly by oxidation of β-picoline (**3**) or by exhaustive oxidation of 5-ethyl-2-methylpyridine (**7**), followed by decarboxylation of the initially formed pyridine-2,5-dicarboxylic acid [100-26-5] (**28**) (eq. 8) (39–42). The technology of the catalytic processes involved in the production of niacin (**27**) is discussed (39).



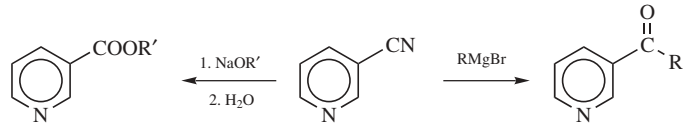
(7) (28) (27) (8)

Hydrogenation of 3-cyanopyridine (**25**) in the presence of ammonia gives 3-picolylamine [3731-52-0] (**29**); however, hydrogenation in the presence of hydrogen chloride affords the corresponding 3-carbinol (**30**)(43).



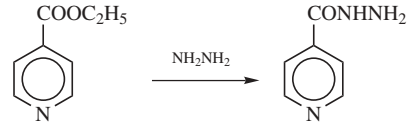
(**30**) (**25**) (**29**)

Treatment of cyanopyridines, eg, **25** with a Grignard reagent yields a ketone (44). A carboxylic ester is obtained by reaction of the nitrile **25** with sodium alkoxide, followed by hydrolysis (45).



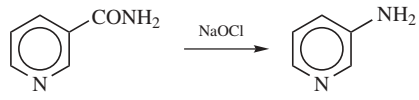
(**25**)

Isonicotinic hydrazide [54-83-3] (isoniazid) (**31**) is still an important tuberculostat (46). It may be obtained by reaction of isonicotinic esters, eg, ethyl isonicotinate [1570-45-2], or the 4-nitrile (**15**), with hydrazine.

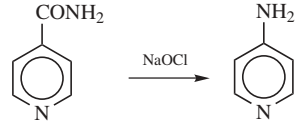


(**31**)

Nicotinamide [98-92-0] (**26**) and isonicotinamide [1453-82-3] (**32**) undergo Hofmann rearrangements to form 3- (**33**) and 4-aminopyridine (**34**), respectively (47). This provides an important route for the manufacture of these amines.

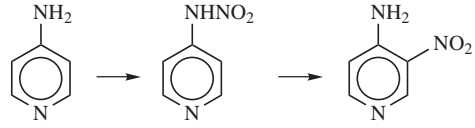


(**26**) (**33**)



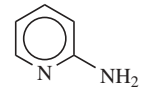
(**32**) (**34**)

Nitrogen Substituents. 4-Aminopyridine (**34**) and 2-aminopyridine (**35**) react with cold nitric acid to give the corresponding nitramines, which are insoluble in the media. On heating, these nitramines rearrange intermolecularly to nitroaminopyridines having the nitro group mainly adjacent to the amino group (14). From **34** the products are the intermediate 4-nitraminopyridine [26482-55-3] and 4-amino-3-nitropyridine [1681-37-4] (eq. 9).

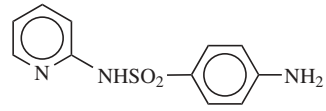


(**34**) (9)

Reaction of 2-aminopyridine (**35**) with *N*-acetylsulfanilyl chloride, followed by hydrolysis, gives sulfapyridine [144-83-2] (**36**), an antibacterial (48).

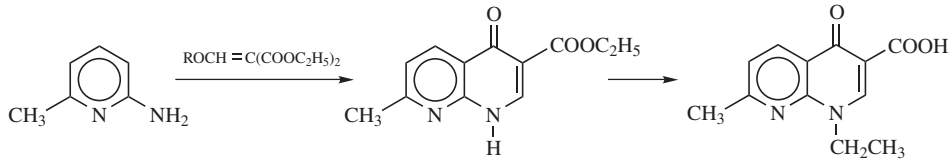


(**35**)



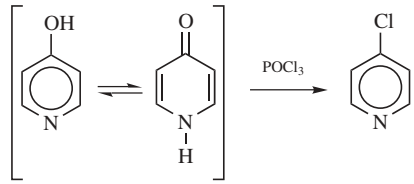
(**36**)

The antibacterial agent nalidixic acid [389-08-2] (**37**) is formed by reaction of 2-amino-6-methylpyridine [1824-81-3] with an alkoxymethylenemalonic ester to form the 1,8-naphthyridine carboxylic ester followed by alkylation and ester hydrolysis (49).

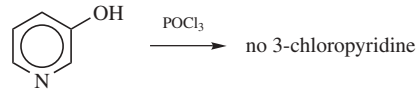


(**37**)

Oxygen Substituents. The presence of oxygen or sulfur attached to the ring can affect the chemistry of those compounds through tautomerism. This phenomenon in the pyridine series has been well studied and reviewed (50,51). An example of 2-pyridone-2-pyridinol tautomerism was shown in equation 2, compound **16**.



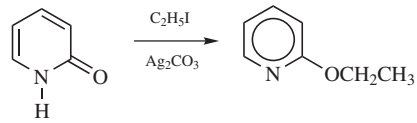
(**38**)



(**39**)

The compounds 2- (**16**) and 4-pyridone (**38**) undergo chlorination with phosphorus oxychloride; however, 3-pyridinol (**39**) is not chlorinated similarly. The product from **38** is 4-chloropyridine [626-61-9]. The 2- **16** and 4-oxo **38** isomers behave like the keto form of the keto–enol tautomers, whereas the 3-oxo **39** isomer is largely phenolic-like, and fails to be chlorinated (50,51).

Exclusive O-alkylation of **16** (eq. 10) may be achieved using ethyl iodide and silver carbonate (44), the product is 2-ethoxypyridine [14529-53-4]. Heating 2- or 4-alkoxypyridines, with or without acid catalyst, induces intermolecular migration of the alkyl group on oxygen to the ring nitrogen to form *N*-alkyl-2- or *N*-alkyl-4-pyridones (52).

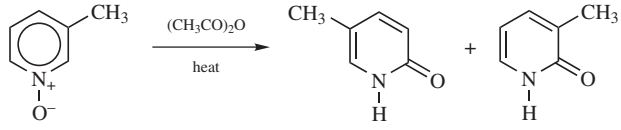


(10)

(**16**)

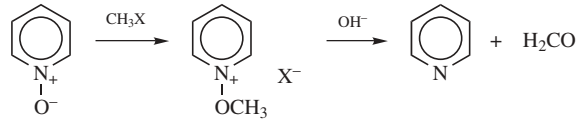
The *N*-oxide function has proved useful for the activation of the pyridine ring, directed toward both nucleophilic and electrophilic attack (see Amine oxides). However, pyridine *N*-oxides have not been used widely in industrial

practice, because reactions involving them almost invariably produce at least some isomeric by-products, adding to the cost of purification of the desired isomer. Frequently, attack takes place first at the *O*-substituent, with subsequent rearrangement into the ring. For example, 3-picoline *N*-oxide [1003-73-2] (**40**) reacts with acetic anhydride to give a mixture of pyridone products in equal amounts, 5-methyl-2-pyridone [1003-68-5] and 3-methyl-2-pyridone [1003-56-1] (12).



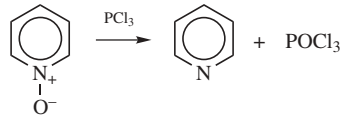
(**40**)

Alkylation at the oxygen atom of *N*-oxides is also a facile process, and the entire N-substituent may be removed with base (eq. 11).



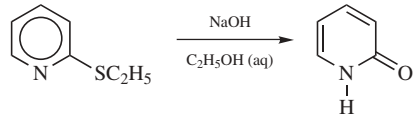
(**13**) (**1**) (11)

Treatment of *N*-oxides with phosphorus trichloride provides a good method for deoxygenation (eq. 12) to obtain the free base.



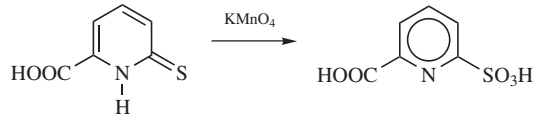
(12)

Sulfur Substituents. Acetylation and alkylation of pyridinethiones usually take place on sulfur (52–54). An exception to this is 4-pyridinethione [19829-29-9], which is acetylated on nitrogen. Displacement of thioethers can be achieved with hydroxide or amines (eq. 13) (55). Thioether functional groups can also be removed by reduction (52–54).



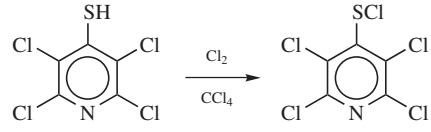
(**16**) (13)

Oxidation of a pyridinethione gives the corresponding sulfonic acid, eg, 6-carboxy-2-pyridinesulfonic acid [18616-02-9] from 6-carboxy-2-pyridinethione [14716-87-1] (eq. 14) (56).



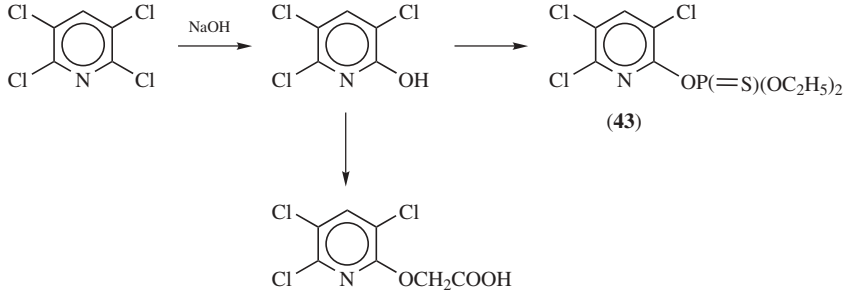
(14)

Tetrachloropyridine-4-thiol [10357-06-1] (**41**) reacts with chlorine in carbon tetrachloride to give a sulfenyl chloride (**42**), which is fairly stable. The sulfenyl chloride may be converted into a number of derivatives (52–54).



(**41**) (**42**)

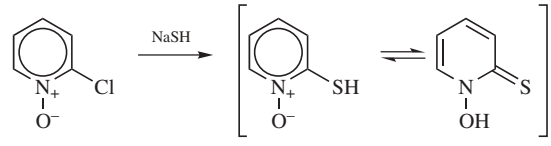
Halogen Substituents. Halogen functional groups are readily replaced by nucleophiles, eg, hydroxide ion, especially when they are attached at the α- or ?-position of the pyridine ring. This reaction has been exploited in the synthesis of the insecticide chlorpyrifos [2921-88-2] (**43**) (57), and the insecticide triclopyr [55335-06-3] (**44**) (18,58). 2,3,5,6-Tetrachloropyridine [2402-79-1] reacts with caustic to form the hydroxylated material [6515-38-4], which then can be used to form (**44**) and (**43**).



(**43**)

(**44**)

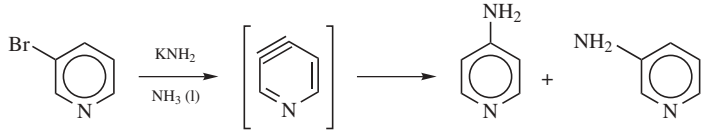
2-Chloropyridine *N*-oxide [20295-64-1] reacts with sodium hydrosulfide to give pyrithione [1121-31-9] (**45**), the zinc salt of which is used as an antifungal agent, most prominently in shampoos (59,60).



(**45**)

Amines or ammonia replace activated halogens on the ring, but competing pyridyne [7129-66-0] (**46**) formation is observed for attack at 3- and 4-halo sub-

stituents, eg, in 3-bromopyridine [626-55-1](52–54). The most acidic hydrogen in 3-halopyridines (except 3-fluoropyridine) has been shown to be the one in the 4-position. Hence, the 3,4-pyridyne is usually postulated to be an intermediate instead of a 2,3-pyridyne. Product distribution (40% **33** and 20% **34**) tends to support the 3,4-pyridyne also.

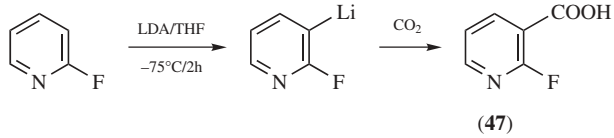


(**46**) (**34**) (**33**)

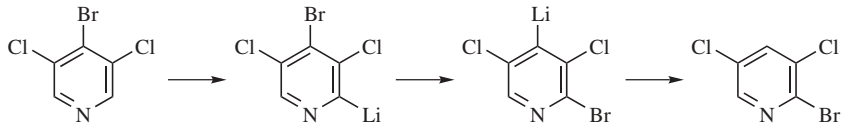
The 4-chloro group can be removed selectively when pentachloropyridine [2176-62-7] (**47**) is treated with zinc to form symmetrical 2,3,5,6-tetrachloropyridine (61).

Organometallics. The scope of synthetic approaches in pyridine chemistry have been dramatically boosted by the development of organolithium methods and metal-catalyzed cross-coupling reactions over the last 20 years. Now it is possible to introduce electrophiles or their equivalents at the α, β, or γ positions of pyridine with relative ease, previously this was difficult or virtually impossible to achieve using the traditional reactions of aromatic chemistry. These areas have been excellently reviewed (62,63).

Schlosser and co-worker (64) introduced a carboxyl function into the 3-, 4-, 5-, or 6- positions regioselectively using reaction sequences based on lithium–hydrogen exchange. 2-Fluoronicotinic acid (**47**) was made directly from 2-fluoropyridine (eq. 15). The others have been made by sequential metalation, chlorination (and or trimethylsilylation), metalation, and finally CO_2 treatment. Bromine and iodine migrations have been initiated by metal–halogen exchange (65). For example, isomerization of 3,5-dichloro-4-bromopyridine to its isomer, 3,5-dichloro-2-bromopyridine (**48**) was observed in a metalation reaction by lithium reagents. Halogen–metal exchange and directed metalation have been reviewed (63,65–67).

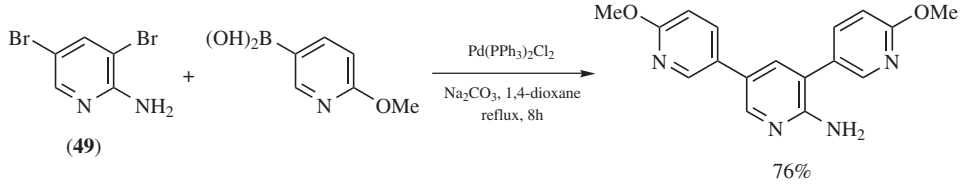


(**47**) (15)



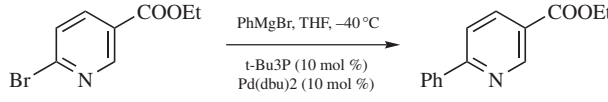
(**48**)

Examples of recently reported cross-coupling reactions undergone by pyridines include Suzuki (68), Sonogashira (69), Pd-catalyzed Negishi (70), Hartwig-Buchwald (71), and Kumada (72) reactions. A recent example extends this approach to the Suzuki cross-coupling of pyridylboronic acids with heteroarylhalide **49** bearing a primary amine group (73).



(**49**) 76%

Selection of the appropriate reaction to use depending on the synthetic target is well discussed by Gribble and co-workers (62). Another interesting coupling is that between an aryl Grignard reagent and a halopyridine (**50**) (74).

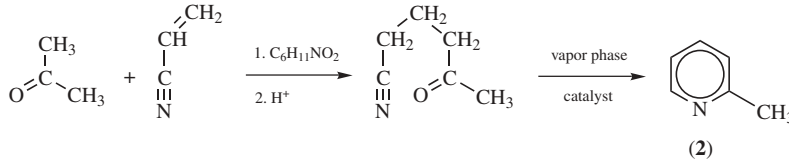


(**50**) 95%

4. Synthesis

Pyridine ring syntheses (75) can be classified into essentially two categories: ring synthesis from nonheterocyclic compounds, and synthesis from other ring systems. The synthesis of pyridine derivatives by transformations on the pyridine ring atoms and side-chain atoms have been considered in the previous section. Achieving positional selectivity in pyridine synthesis to make either 2,3- or 2,5- substituted pyridine is discussed (75).

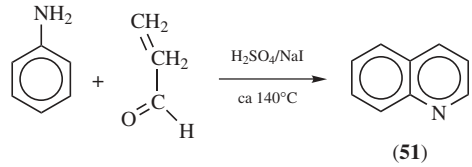
4.1. Ring Synthesis from Nonheterocyclic Compounds. These methods may be further classified based on the number of bonds formed during the pyridine ring formation. Synthesis of α-picoline (**2**) from 5-oxohexanenitrile is a one-bond formation reaction (eq. 16) (77). The nitrile is obtained by reaction between acetone and acrylonitrile (78). If both reaction steps are considered together, the synthesis must be considered a two-bond forming one, ie, formation of **2** from acetone and acrylonitrile in a single step comes under the category of two-bond formation reaction.



(16)

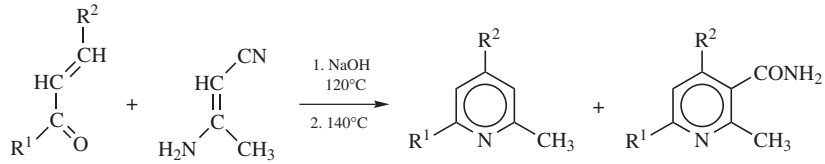
(**2**)

The formation of quinoline [91-22-5] (**51**) from aniline and acrolein involves formation of two bonds during the ring synthesis.



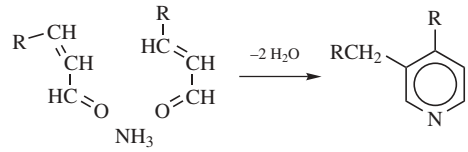
(**51**)

Synthesis of 4,6-disubstituted- 2-picolines and their corresponding nicotinamides has been developed using β-aminocrotonitrile (**52**) and α, β-unsaturated compounds, where $R^1 = R^2 =$ aryl (79).



(**52**)

The formation of pyridine derivatives from α, β-unsaturated aldehydes and ammonia involves formation of three bonds during the ring synthesis. For example, with an α, β-unsaturated aldehyde, both 2,5-substituted as well as 3,4-substituted pyridines can be obtained, depending on whether a 1,2- (eq. 17) or 1,4-addition (eq. 18) occurs with ammonia. Reactions are performed in the vapor phase with catalysts.



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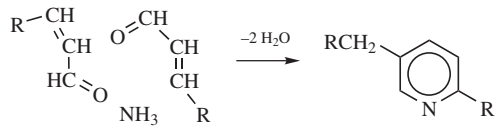
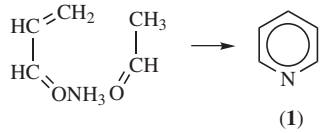
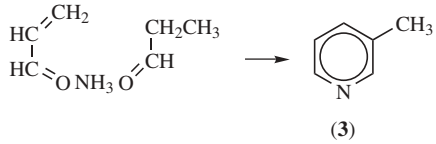


(18)

Acrolein and ammonia give β-picoline (**3**, R = H) (eq. 17). Acrolein, ammonia, and acetaldehyde give pyridine (**1**) (eq. 19). Acrolein, ammonia, and propionaldehyde give **3** (eq. 20) (80–84). Reactions are performed in the vapor phase with proprietary catalysts.



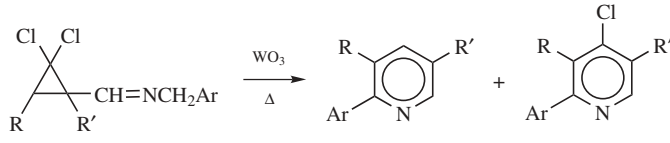
(**1**) (19)



(**3**) (20)

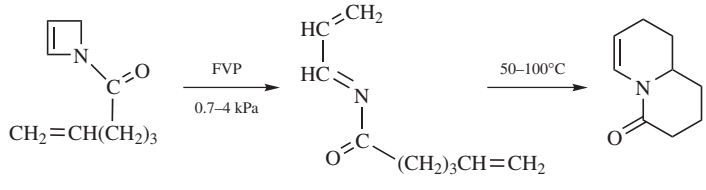
The vapor-phase synthesis of pyridines and picolines from formaldehyde, acetaldehyde, and ammonia falls in the category of four-bond formation reactions (Fig. 1). Reactions are performed in the vapor phase with proprietary catalysts. The mechanism of these reactions have been studied recently by using labeled compounds (91).

4.2. Synthesis from Other Ring Systems. These syntheses are further classified based on the number of atoms in the starting ring. Ring expansion of dichlorocyclopropane carbaldimine (**53**), where R = H and R′ = aryl, on pyrolysis gives 2-arylpyridines. Thermal rearrangement to substituted pyridines occurs in the presence of tungsten(VI) oxide. In most instances, the nonchlorinated product is the primary product obtained (92).

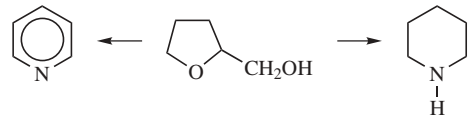


(**53**)

Azacyclobutenes have been used to generate 1-azabutadienes, which are intramolecularly as well as intermolecularly cyclized to give tetrahydropyridines, eg, hexahydroquinolizin-4-one [87842-80-6] (93,94). In the following, FVP = flash vacuum pyrolysis.

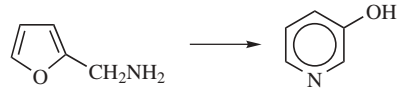


Ring expansion of five-membered ring heterocyclic compounds has been accomplished to form pyridine derivatives. Reaction of tetrahydrofurfuryl alcohol with ammonia gives pyridine (**1**) under dehydrogenating conditions, and gives piperidine (**18**) under reductive conditions.



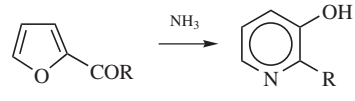
(**1**) (**18**)

Furfurylamine reacts with hydrogen peroxide and acid to give 3-hydroxypyridine (**39**).



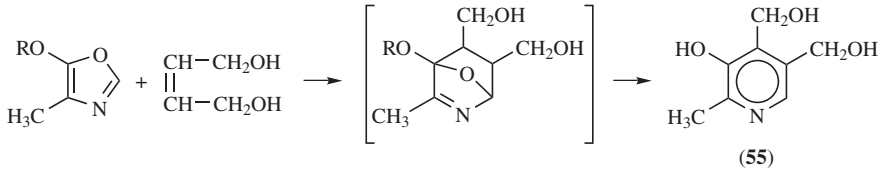
(**39**)

2-Alkyl-3-pyridinols (**54**) are reported to be formed from acyl furans and ammonia under pressure (95–97).



(**54**)

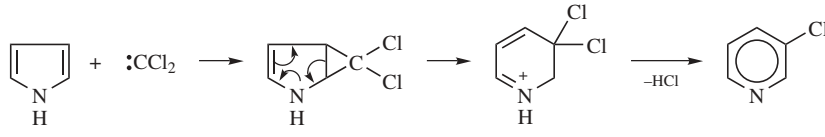
Oxazoles react with dienophiles to give pyridines after dehydration or other aromatization reactions (98,99). A commercially important example is the reaction of a 5-alkoxy-4-methyloxazole with 1,4-butenediol to yield pyridoxine (**55**), which is vitamin B_6.



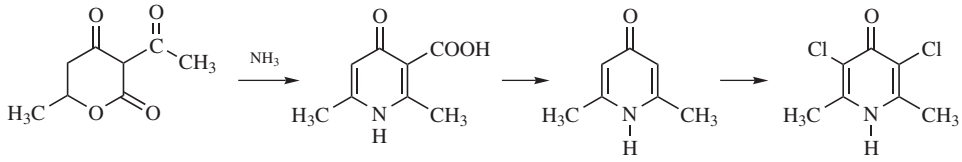
(**55**)

Pyrroles may be ring-expanded to pyridines in reactions having a greater academic than practical interest. Treatment of pyrrole with chloroform and sodium ethoxide (in effect, with dichlorocarbene,: CCl_2) gives a low yield of 3-chloropyridine [626-60-8]. A much better yield (33%) is obtained if chloroform and pyrrole are heated together in the vapor phase at 550°C; some 2-chloropyridine (**17**) is also formed (100).

A large number of pyridine derivatives have been obtained by the dehydrogenation of suitable piperidines.



Pyrans and related compounds react with ammonia to give pyridines. A commercially useful example is the reaction of dehydroacetic acid (derived from diketene) with ammonia to give 2,6-dimethyl-4-pyridinone [7516-31-6] via 2,6-dimethyl-4-pyridinone-3-carboxylic acid [52403-25-5]. Chlorination of the pyridone gives clopidol [2971-90-6] (**56**), a coccidiostat (101,102).



(**56**)

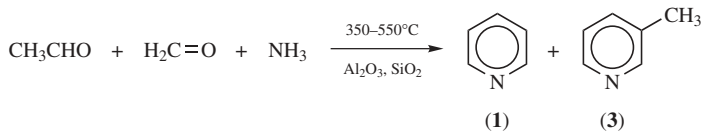
5. Manufacture and Processing

There are no natural sources of pyridine compounds that are either a single pyridine isomer or just one compound. For example, coal tar contains a mixture of bases, mostly alkylpyridines, in low concentrations. Few commercial synthetic methods produce a single pyridine compound, either; most produce a mixture of alkylpyridines, usually with some pyridine (**1**). Those that produce mono- or disubstituted pyridines as principal components also usually make a mixture of isomeric compounds along with the desired material.

5.1. Historical. Pyridines were first isolated by destructive distillation of animal bones in the mid-nineteenth century (2). A more plentiful source was found in coal tar, the condensate from coking ovens, which served the steel industry. Coal tar contains roughly 0.01% pyridine bases by weight. Although present in minute quantities, any basic organics can be easily extracted as an acid-soluble fraction in water and separated from the acid-insoluble tar. The acidic, aqueous phase can then be neutralized with base to liberate the pyridines, and distilled into separate compounds. Only a small percentage of worldwide production of pyridine bases can be accounted for by isolation from coal tar. Almost all pyridine bases are made by synthesis.

Most processes currently in use make pyridines by condensation of ammonia with aldehydes or ketones either in the vapor phase or in the liquid phase. These processes are based on the pioneering work of Chichibabin (1905) (3). Commercial practice of that process was not realized until some 50 years after its discovery (103,104).

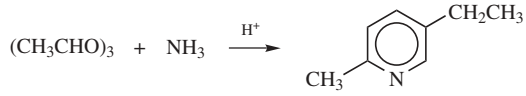
5.2. Commercial Manufacture of Pyridine. There are two vapor-phase processes used in the industry for the synthesis of pyridines. The first process (eq. 21) utilizes formaldehyde and acetaldehyde as a cofeed with ammonia, and the principal products are pyridine (**1**) and 3-picoline (**3**). The second process produces only alkylated pyridines as products.



(1) (3) (21)

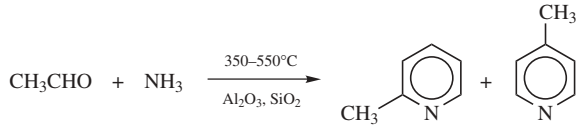
Acrolein ($CH_2=CHCHO$) can be substituted for formaldehyde and acetaldehyde in the above reaction to give similar results, but the proportion of (**3**) is higher than when acetaldehyde and formaldehyde are fed separately. Acrolein may be formed as one of the first steps to pyridine (**1**) and β-picoline (**3**) formation. There are many variations on the vapor-phase synthesis of pyridine itself. These variations are the subject of many patents in the field.

5.3. Commercial Manufacture of Specific Pyridine Bases. Condensation of paraldehyde with ammonia at 230°C and autogenous pressure (eq. 22) is used to manufacture 5-ethyl-2-methylpyridine (**7**). This is one of the few liquid-phase processes used in the industry to make relatively simple alkylpyridines, and one of the few processes known to make a single alkylpyridine product selectively.



(7) (22)

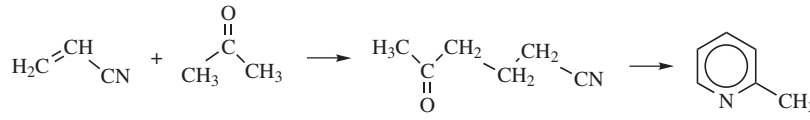
The vapor-phase analogue of this liquid-phase reaction (eq. 22) is used to make α- **2** and γ- picoline (**4**) (eq. 23). The gas-phase products are different from the liquid-phase products, because acetaldehyde is used in place of its trimer, paraldehyde, and a multivalent metal oxide catalyst is used. Heterogeneous catalysts used in the synthesis of various heterocycles including pyridines has been reviewed (105).



(2) (4) (23)

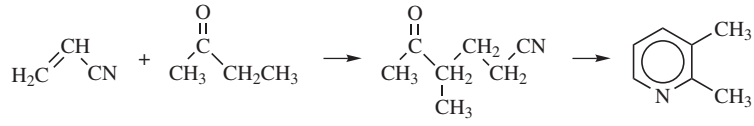
Replacing acetaldehyde with acetone and using a cofeed of formaldehyde and ammonia give mainly 2,6-lutidine (**5**). However, leaving out the formaldehyde results in production of 2,4,6-collidine (**8**) as the primary product.

Another of the few selective syntheses of alkylpyridines is one for α-picoline (**2**) (106). This is a two-step process (eq. 24) where acrylonitrile is used to monocyanoethylate acetone in the liquid phase at 180°C and at autogenous pressure, 2 MPa (300 psig). The monoadduct, 5-cyano-2-pentanone (**57**), is then passed over a palladium-containing catalyst to reduce, cyclize, and dehydrogenate, in sequence.



(24)

The same methodology can be used to prepare 2,3-lutidine (**58**) by using methyl ethyl ketone in place of acetone.



(**58**)

5.4. By-Products. Almost all commercial manufacture of pyridine compounds involves the concomitant manufacture of various side products. Liquid- and vapor-phase synthesis of pyridines from ammonia and aldehydes or ketones produces pyridine or an alkylated pyridine as a primary product, as well as isomeric alkylpyridines and higher substituted alkylpyridines, along with their isomers. Furthermore, self-condensation of aldehydes and ketones can produce substituted benzenes. Condensation of ammonia with the aldehydes can produce certain alkyl or unsaturated nitrile side products. Lastly, self-condensation of the aldehydes and ketones, perhaps with reduction, can lead to alkanes and alkenes.

Raw Material and Energy Aspects to Pyridine Manufacture. The majority of pyridine and pyridine derivatives are based on raw materials like aldehydes or ketones. These are petroleum-derived starting materials and their manufacture entails cracking and distillation of alkanes and alkenes, and oxidation of alkanes, alkenes, or alcohols. Ammonia is usually the source of the nitrogen atom in pyridine compounds. Gas-phase synthesis of pyridines requires high temperatures (350–550°C) and is therefore somewhat energy intensive.

6. Production and Shipment

Worldwide production of pyridine bases in the late 1990s was estimated at tens of thousands of tons a year. Production was initially concentrated mainly in the United States, Western Europe, and Japan and moved slowly into other parts of Asia like China, Taiwan, and India. Production statistics are not complete for any of the principal producing areas and trade statistics are also incomplete.

The relative production volumes of pyridine compounds can be ranked in the following order: pyridine (**1**) > β-picoline (**3**) > α-picoline (**2**) > niacin (**27**), or niacinamide (**26**) > 2-vinylpyridine (**23**) > piperidine (**18**). The U.S. and Japanese production was consumed internally as well as being exported, mainly to Europe. European production is mostly consumed internally.

6.1. Shipment Methods and Packaging. Pyridine (**1**) and pyridine compounds can be shipped in bulk containers, eg, tank cars, rail cars, and

super-sacks, or in smaller containers like fiber or steel drums. The appropriate U.S. Department of Transportation (DOT) requirements for labeling are given in Table 4. Certain temperature-sensitive pyridines, eg, 2-vinylpyridine (**23**) and 4-vinylpyridine are shipped cold ($<-10^{\circ}C$) to inhibit polymerization. Piperidine (**18**) and certain piperidine salts are regulated within the United States by the Drug Enforcement Agency (DEA) (107). Pyridines subject to facile oxidation, like those containing aldehyde and carbinol functionality, can be shipped under an inert atmosphere.

7. Economic Aspects

Although the volume of commercial pyridine compounds is relatively large, economic aspects resemble those of specialty markets more than those of commodities. Commercial transactions occur with little publicity, trade secrets are carefully guarded, and patents proliferate, thus obscuring the industrial processes used for their manufacture.

Pyridine bases are produced in three principal areas of the world: the United States, Western Europe, and Asia. In the United States, there is one principal producer of synthetic pyridine compounds: Reilly Industries, Inc. (Indianapolis, Indiana). Reilly Industries is the world's largest producer. Coal-tar-derived pyridine bases are made in only small amounts. In Europe, synthetic pyridine compounds are manufactured by Lonza AG (Switzerland), and DSM (the Netherlands). Small amounts of natural pyridine bases from coal tar can be obtained from a number of sources, including Raschig and Rütgerswerke AG (Germany). In Japan, synthetic pyridines are produced by Koei Chemical Company, Ltd., and by Daicel, Ltd.; natural pyridine bases can be obtained from Nippon Steel. Other main producers are, in China, Nantong-Reilly Chemical Co; in Taiwan, Chang Chung Petrochemical; in India, Jubilant Organosys and Armour Polymer Ltd.

Prices of pyridine compounds reflect two sources of manufacturing cost. One source is the cost of petroleum-based raw materials used in the manufacture of the pyridine base itself. This factor varies according to the current pricing of petroleum feedstocks in the country of manufacture, and can vary from country to country simultaneously. Long term, the variation in cost tracks the variation in market price of ethylene. The second source is related to the chemistry performed on a pyridine-based raw material to arrive at the desired compound. This cost can be variable, depending on the chemical technology used and the cost of reagents and solvents for the transformation. As a group of compounds, pyridine bases are considered specialty chemical products with prices generally no lower than $\sim$ \$5/kg and going up to \$100–150/kg, with an expected inverse relationship between price and volume sold. Because pyridine compounds are specialty products and manufacture is concentrated among a few suppliers, competition between producers is significant. Pricing information on specific products is generally considered proprietary information.

8. Specifications, Standards, and Quality Control

Most pyridine compounds are sold on the basis of a >98wt% criterion as analyzed by gas chromatography (gc), freezing point, titration, or hplc analysis. Because many pyridines are sold for specific applications by a single customer, or by a small group of customers, specification for those products is set by agreement. They are not generally published. However, specifications for pyridine products sold to a large group of customers, eg, pyridine (**1**) itself; the picolines, **2**, **3**, or **4**; and niacin (**27**) or niacinamide (**26**), are publicly known. The standards for ACS reagent grade pyridine are shown in Table 5.

Pyridine is also sold as a 1° grade, which means that the boiling point range of 98% of the sample will fall in a 1°C range, which includes the normal boiling point of **1** (115.3±0.1°C). Niacin (**27**) and niacinamide (**26**), equivalent forms of vitamin B_3, are generally sold under a *U.S. Pharmacopeia* (USP) specification (108). They are also sold as a feed-grade supplement (see Vitamins).

9. Analytical and Test Methods, and Storage

Most common analytical methods for analysis of the major component or minor components of organic products are used for pyridines. These include gas chromatography, titration, freezing point, nuclear magnetic resonance (nmr), infrared (ir), high performance liquid chromatography (hplc), and gas chromatography/mass spectrometry (gc/ms).

As a class, pyridine compounds tend to darken with storage. The color change is related to the conditions of storage; it is more rapid at higher temperatures and becomes more intense with increasing storage time. Pyridines with certain functional groups tend to be unstable on long storage. Aldehyde and carbinol groups tend to oxidize on exposure to air, and vinyl groups tend to polymerize. Hence, these compounds are stored at low temperature (<-10°C for the vinylpyridines), or under an inert atmosphere (aldehydes and carbinols). Storing vinylpyridines under inert atmosphere is not recommended, because the shelf life can be shortened by doing so.

10. Health and Safety Factors

10.1. Pyridine Acute Toxicology. Pyridine causes gastrointestinal upset and central nervous system (CNS) depression at high levels of exposure. The odor of pyridine can be detected at extremely low concentrations (12 ppb). The LD_{50} (oral, rats) is 891 mg/kg, the LC_{50} (inhalation, rats) is 4000/4 (ppm/h), and the TLV is 15 mg/m^3 (109,110).

10.2. Pyridine Chronic Toxicology. All mutagenicity tests have been negative and **1** is not considered a carcinogen or potential carcinogen. There have been no reports of adverse health effects on long-term exposure to **1** at low concentrations.

10.3. Acute Toxicology of Pyridine Derivatives. Table 6 shows the known acute health and safety factors for pyridine derivatives. In general, many pyridines are reasonably safe to handle and do not represent a serious hazard. However, some types of aminopyridines are poisons. For example, 4-aminopyridine (**34**) is highly poisonous to mammals and is commercially sold as a bird poison under the name avitrol (111). Quaternary salts of pyridines can also be toxic. Special care should be exercised when handling bis-quaternary salts, eg, **20**, of 4,4′-bipyridine (**19**), as the fatal effect cannot be reversed after ingestion or exposure. Chloropyridines, especially polychloropyridines, can potentially be mutagenic, teratogenic, and carcinogenic.

10.4. Safety Aspects in Handling and Exposure. Pyridine compounds are ubiquitous in the natural environment, and are often found in foods as minor flavor and fragrance components. Some synthetic pyridines are used as food additives (qv) (111). A high proportion of pyridine compounds show some type of bioactivity, albeit mostly minor, eg, herbicidal, insecticidal, or medicinal activity. Therefore, all the normal precautions should be exercised when handling pyridines that would be used when handling other organic products that are potentially bioactive. Care should be taken to avoid skin or eye contact, ingestion, or inhalation of vapors and dusts. Protective garments and respirators should be worn when handling these materials. Specific and more complete recommendations are available from the manufacturers of each pyridine base.

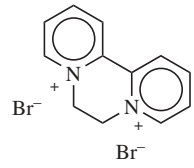
Particular attention should be paid to aminopyridines, especially unsubstituted ones, which tend to exert severe neurotoxic effects on exposure. Most of them are generally classified as poisons. Exceptions to this rule are known. A notable one is DMAP (**24**), which is widely used in industry as a superior acylation catalyst (34). Quaternary salts of pyridines are usually toxic, and in particular paraquat (**20**) exposure can have fatal consequences. Some chloropyridines, especially polychlorinated ones, should be handled with extra care because of their potential mutagenic effects. Vinylpyridines are corrosive to the skin, and can act as a sensitizer for some susceptible individuals. Niacin (**27**), niacinamide (**26**), and some pyridinecarbaldehydes can cause skin flushing.

Pyridine and alkylpyridines are excellent solvents for many materials, a property that must be taken into account when selecting O-rings, gaskets, and other sealants that are in contact with liquids. Generally, only polytetrafluoroethylene, graphite, and asbestos-based gasket and O-ring materials are acceptable. Most rubbers are rapidly swollen or degraded by liquid alkylpyridines.

11. Uses

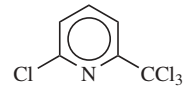
11.1. Pyridine and Picolines. These have been widely used as solvents in organic chemistry and, with increasing frequency, in industrial practice. Pyridine itself is a good solvent that is rather unreactive. The basic nature of pyridine and the picolines makes them ideal acid scavengers. Typically, pyridine is the solvent of choice for acylations (113). Furthermore, for dehydrochlorination reactions and extraction of antibiotics, pyridine is an excellent solvent. Large amounts of pyridine are used as the starting material for agrochemicals and

pharmaceuticals (qv). For example, pyridine is a precursor for herbicides such as diquat [2764-72-9] (**59**) (27) and paraquat (**20**) (108), insecticides, eg, chlorpyrifos (**43**), and antifungal agents, eg, the zinc salt of pyrithione (**45**) (61).

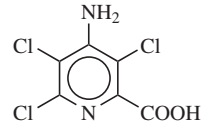


(**59**)

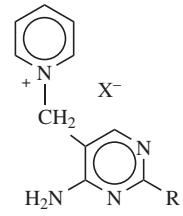
The primary use of α-picoline (**2**) is as a precursor of 2-vinylpyridine (**23**). It is also used in a variety of agrochemicals and pharmaceuticals, eg, nitrapyrin [1929-82-4] (**60**) to prevent loss of ammonia from fertilizers; picloram [1918-02-1] (**61**), a herbicide; and amprolium [121-25-5] (**62**), a coccidiostat.



(**60**)

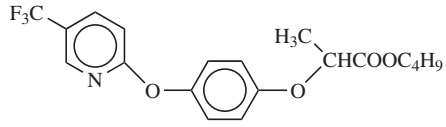


(**61**)



(**62**)

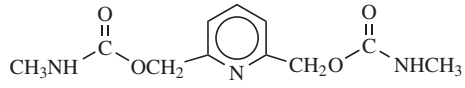
The predominant use of β-picoline (**3**) is as a starting material for agrochemicals and pharmaceuticals. For example, it is used to make insecticides such as chlorpyrifos (**43**), food additives, eg, niacin (**27**) and its amide (**26**), and herbicides, eg, fluazifop-butyl [69806-50-4] (**63**).



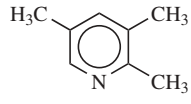
(**63**)

The main use of γ-picoline (**4**) is in the production of the antituberculosis agent, isoniazid (**31**). Compound (**4**) is also used to make 4-vinylpyridine, and subsequently polymers.

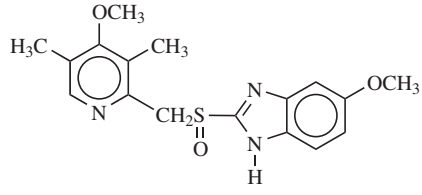
5-Ethyl-2-methylpyridine (**7**) is used as starting material for niacin (**27**). 2,6-Dimethylpyridine (**5**) is used for the antiarteriosclerotic pyridinol carbamate [1882-26-4] (**64**). 2,3,5-Collidine [695-98-7] (**65**) is used in the manufacture of the antiulcer drug, omeprazole [73590-58-6] (**66**) 114.



(**64**)



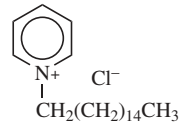
(**65**)



(**66**)

11.2. Quaternary Salts. Herbicides paraquat (**20**) and diquat (**59**) are the quaternary salts of 4,4′-bipyridine (**19**) and 2,2′-bipyridine with methyl chloride and 1,2-dibromoethane, respectively. Higher alkylpyridinium salts are used in the textile industry as dye ancillaries and spin bath additives. The higher alkylpyridinium salt, hexadecylpyridinium chloride [123-03-5] (**67**) (cetylpyridinium chloride) is a topical antiseptic. Amprolium (**62**), a quaternary salt of β-picoline (**2**), is a coccidiostat. Bisaryl salts of butylpyridinium bromide (or its lower 1-alkyl homologues) with aluminum chloride have been used as battery electrolytes (115), in aluminum electroplating baths (116), as Friedel-Crafts catalysts (117), and for the formylation of toluene by carbon monoxide (118) (see Quaternary ammonium compounds). The new application of pyridinium salts have been in their use as ionic liquids. *Ionic liquids* are compounds consisting of only ions and are low melting (around room temperature),

less viscous and preferably less corrosive and toxic. There are four types of ionic liquids studied, which are the salts of pyridinium, imidazolium, ammonium, and phosphonium. Books and reviews have been published on the subject of ionic liquids covering the full breath of areas of importance, starting from their preparation, to properties, and their applications in various fields (119–121).



(**67**)

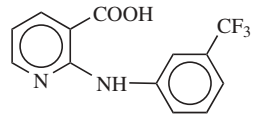
Pyridine has been the most studied of all the known heterocycles. For example, cetylpyridinium chloride salt has been used as a topical antiseptic in mouth wash and paraquat and diquat has been used as a herbicide by farmers for a long time (122,123).

Some of the other useful pyridine quaternary salts known in the literature are, amprolium (**62**) as a coccidiostat as seen earlier and others like pyridostigmine bromide, distigmine bromide, and pralidoxime iodide shown in later sections. The simple salt pyridine hydrochloride or pyridinium chloride is a very useful reagent in the demethylation of aromatic methyl ethers and has also been used as an acid catalyst (124). Pyridine has been used to abstract acid in many reactions and in this regard it should be mentioned here that pyridine would be able to do as good a job as it is reported for 1-methylimidazole.

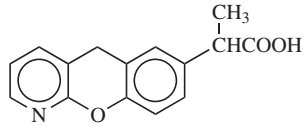
The pyridine derived ionic liquid halides are readily made by quaternization of the corresponding pyridine derivative with the right halide derivative. The exchange of the halide for another anion is readily achieved using the metathesis approach.

The pyridine based ionic liquids are as good as the more common imidazole based ionic liquids in many applications. In some instances the pyridine based ionic liquids have been found to be better than that of the imidazolium salts (125).

11.3. Pyridine *N*-Oxides. Analgesic and antiinflammatory drugs niflumic acid [4394-00-7] (**68**) and pranoprofen [52549-17-4] (**69**) are manufactured from nicotinic acid *N*-oxide [2398-81-4]. The antiulcer drug omeprazole (**66**) is produced from 2,3,5-trimethylpyridine *N*-oxide [74409-42-0]. Zinc pyrithione, the zinc salt of pyrithione (**45**), is a fungicide derived from 2-chloropyridine *N*-oxide (61).



(**68**)



(**69**)

11.4. Aminopyridines. Aminopyridines are key intermediates for the synthesis of important pharmaceutical and agricultural products (126,127). 2-Aminopyridine (**35**) is used in the production of sulfasalazine [599-79-1] (**70**), an antibacterial used for veterinary purposes (128). Compound **35** is also used in the synthesis of a number of antihistamines, including methapyrilene hydrochloride [135-23-9] (**71**) and pyrilamine maleate [59-33-6] (**72**) (129). Picoxicam [36322-90-4] (**73**), a nonsteroidal antiinflammatory agent, is based on **35** (see Fig. 2) (130).

The synthesis of aldipem [82626-01-5] (**74**), an anxiolytic, is based on 2-amino-5-chloropyridine [1072-98-6] (131). 2,6-Diaminopyridine [141-86-6] is used in the preparation of the urinary tract analgesic phenazopyridine hydrochloride [136-40-3] (**75**) (132). Nalidixic acid [389-08-2] (**76**), a quinolone carboxylic acid, is derived from 2-amino-6-methylpyridine [1824-81-3]. 2-Amino-3-methylpyridine [1603-40-3] is used in the synthesis of pemirolast potassium (**77**), an antiallergic and antiasthmatic medication. 2-Amino-4-methylpyridine [695-34-1] is used in the preparation of piketoprofen [60576-13-8] (**78**), a nonsteroidal antiinflammatory drug (133). Zopidem [82626-48-0] (**79**) is a hypnotic medication based on 2-amino-5-methylpyridine [1603-41-4] (134). The synthesis of pirenzepine [28797-61-7] (**80**), an antiulcerative drug, proceeds via 2-chloro-3-aminopyridine [629819-4], an intermediate derived from chlorination of 3-aminopyridine (**33**) (135). 3-Amino-2-chloro-4-methylpyridine [133627-45-9] and 2-chloronicotinic acid [2942-59-8] are used in the preparation of nevirapine [129618-40-2] (**81**), a drug for treatment of acquired immunodeficiency syndrome (AIDS) (136). Cephapirin sodium [24356-60-3] (**82**) is an antibacterial medicine derived from 4-aminopyridine (**34**) (137). Compound (**34**) is also used in the preparation of the antihypertensive pinacidil [60560-33-0] (**83**).

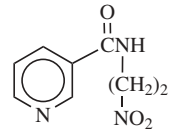
4-Dimethylaminopyridine [1122-58-3] (**24**) has emerged as the preferred catalyst for a variety of synthetic transformations under mild conditions, particularly acylations, alkylations, silylations, esterifications, polymerizations, Baylis-Hillman reaction, and rearrangements (138,140). POLYDMAP resin [1122-58-3], a polymeric version of DMAP, is available, and is as effective as DMAP as a catalyst for acylation reactions. Furthermore, it can be recycled without regeneration >20 times with very little loss in activity. POLYDMAP is a trademark of Reilly Industries, Inc. A phase selective soluble dendritic derivative of

DMAP was reported to be an easily recyclable catalyst for the Baylis-Hillman reaction (143).

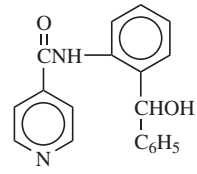
11.5. Chloropyridines. Figure 3 shows structures arising from chloropyridines, important intermediates in pharmaceuticals and agrochemicals. A significant use of 2-chloropyridine (**17**) is in the production of pyrithione (**49**). The zinc salt is a widely used antifungal agent (61). Phenylacetonitriles and (**17**) have been used in making pheniramine [86-21-5] (**84**) and dipyramide [3737-09-5] (**85**), both antihistamines. 2,6-Dichloropyridine is used for 8-azaquinoline antibiotics, eg, enoxalin [74011-58-8] (**86**). 2-Chloro-6-trichloromethylpyridine [1929-82-4] is the agrochemical nitrapyrin (**60**), which prevents the loss of ammonia from fertilizers. 2,5-Dichloro-6-trichloromethylpyridine [1817-13-6] is converted to the herbicide clopyralid [1702-17-6] (**87**). 2,3,4,5-Tetrachloro-6-trichloromethylpyridine [1134-04-9] is a precursor of the herbicide picloram (**61**). 2,3,5,6-Tetrachloropyridine is used for producing the insecticide chloropyrifos (**43**) and the herbicide triclopyr (**44**). 2-Chloro-5-trifluoromethylpyridine [52334-81-3] is used for the herbicide fluazifop-butyl (**63**). Significant use of 2-chloronicotinic acid is for production of herbicides, eg, diflufenican [83164-33-4] (**88**). 2-Chloro-5-methylpyridine [18368-64-4] is used in the manufacture of the insecticide imidacloprid [105827-78-9] (**89**).

11.6. Pyridinecarbonitriles, -Carboxamides, and -Carboxylic Acids. 3-Cyanopyridine (**25**) is used for the production of niacin (**27**), or vitamin B_3. 4-Cyanopyridine (**15**) is used for making the antitubercular drug isoniazid (**31**) (144).

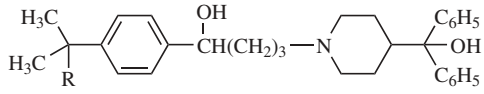
3- (**26**) and 4-Pyridinecarboxamides (**32**) are used in making the corresponding aminopyridines (**33**) and (**34**), respectively, by Hofmann degradation reactions. Niacin (**27**) can be used to make the vasodilator nicorandil [65141-46-0] (**90**). Inabenfide [82211-24-3] (**91**), a plant growth regulator, is an amide of isonicotinic acid. Terfenadine [50679-08-8] (**92**; R = CH_3), an antihistamine, along with its metabolite, fexofenadine (**92**; R = COOH), a better antihistamine, and nialamide [51-12-1] (**93**), an antidepressant, are also made from isonicotinic acid (4-carboxypyridine). Picolinic acid (2-carboxypyridine) is an intermediate for local anesthetics such as mepivacaine [96-88-8] (**94**; R = CH_3) and bupivacaine [2180-92-9] (**94**; R = n-C_4H_9) hydrochlorides. Quinolinic acid [89-00-9] (**95**) goes into the herbicide imazapyr [81334-34-1] (**96**).



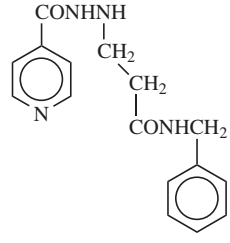
(**90**)



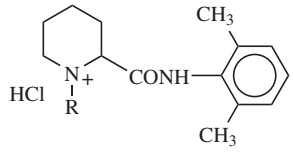
(**91**)



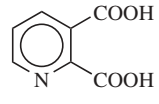
(**92**)



(**93**)



(**94**)



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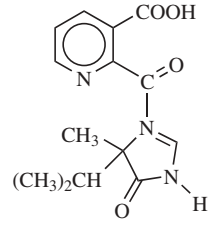


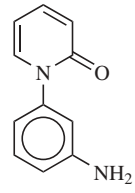
(**96**)

11.7. Nitropyridines. With the introduction of milder and easier approaches now available to make nitropyridines, more applications are beginning to appear as well as more new types of reactions on nitropyridine compounds (145). Various unique 3,4-disubstituted (by nitrating 4-substituted pyridines) and 2,5-disubstituted pyridines (by nucleophilic substitution of 3-

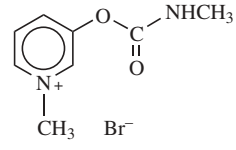
nitropyridine) were synthesized readily using this new nitration method in the synthetic sequence.

11.8. Hydroxy-, Hydroxyalkyl-, and Aminoalkylpyridines. A full discussion of the tautomerism occurring in heterocycles with oxygen and sulfur substituents has been published (50). Equation 2 shows the tautomerism expected in 2-pyridone (**16**) and 4-pyridone (**38**).

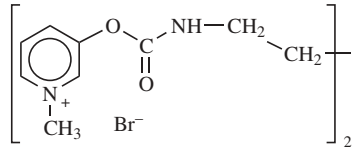
2-Pyridone (**16**) is used in the synthesis of the tranquilizer amphenidone [134-37-2] (**97**). 3-Pyridiniol (**39**) serves as a precursor to the cholinesterase inhibitors, pyridostigmine bromide [101-26-8] (**98**) and distigmine bromide [15876-67-2] (**99**). 4-Pyridone (**38**) is a precursor for propyliodone [587-61-1] (**100**), an X-ray contrast agent; it is also used as an intermediate for pericyazine [2622-26-6] (**101**), a psychotropic agent.



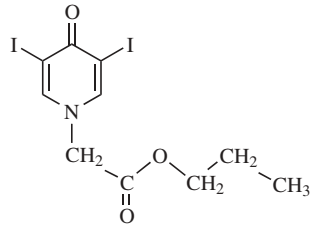
(**97**)



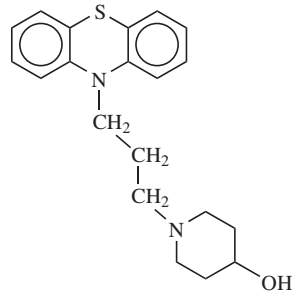
(**98**)



(**99**)

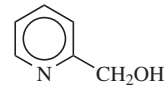


(**100**)

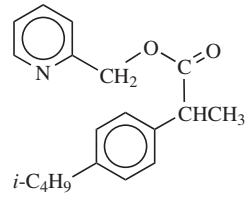


(**101**)

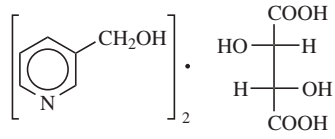
2-Pyridylcarbinol [586-98-1] (**102**) is used for the preparation of ibuprophenpiconol [64622-45-3] (**103**), an antiinflammatory drug. 3-Pyridylcarbinol (**30**) is the active component of the vasodilator nicotinyl tartrate [100-55-0] (**104**). The bis(carbamate) (**64**) of pyridine-2,6-dimethanol [6231-18-1] is an antiarteriosclerotic drug. The urea derivative **105** [38641-94-0] of 3-picolylamine (**29**) is a rodenticide.



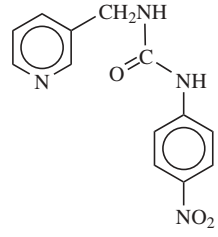
(**102**)



(**103**)

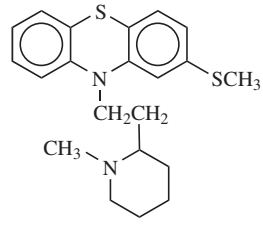


(**104**)

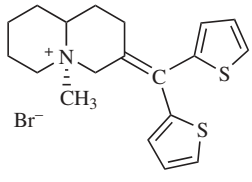


(**105**)

Ethanolpyridines are used mainly for vinylpyridine manufacture. However, 2-ethanolpyridine (**22**) is used to make the psychotropic agent thioridazine [50-52-2] (**106**), and the antispasmodic agent triquizium bromide [71731-58-3] (**107**).

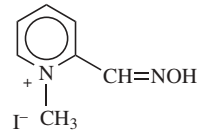


(**106**)

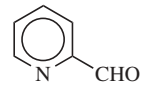


(**107**)

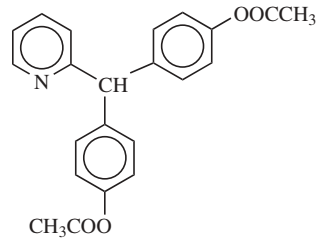
11.9. Pyridinecarbaldehydes. Pralidoxime iodide [51-15-0] (**108**), a derivative of 2-pyridinecarbaldehyde (**109**), is used as an antidote against organophosphorus nerve agents (acetylcholinesterase inhibitors). Compound **109** is also used in making the laxative bisacodyl [603-50-9] (**110**).



(**108**)



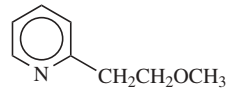
(**109**)



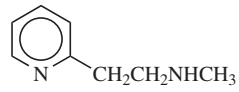
(**110**)

11.10. Bipyridines. Since the 1960s, the most important commercial agrochemical-based on pyridine has been the herbicide paraquat (**20**), which is made from 4,4′-bipyridine (**19**). The isomeric herbicide diquat (**59**) is made by an analogous route, but utilizing 2,2′-bipyridine [366-18-7] as a precursor.

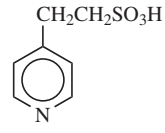
11.11. Vinylpyridines. 2-Vinylpyridine (**23**) is a large-volume specialty chemical used primarily for manufacturing terpolymers, eg, styrene, butadiene, and vinylpyridine, used to coat fabric cords of tires and fabric-reinforced rubber products, eg, belts (32). Vinylpyridines undergo Michael addition easily, and two of those products using **23** as a starting material, **111** [114-91-0], and **112** [5638-76-6], find use as a veterinary anthelmintic and a vasodilator, respectively (147). 4-Vinylpyridine is used to make 2-(4-pyridyl)ethanesulfonic acid [53054-76-5] (**113**), which serves as a coagulation accelerator for the gelatin layer of photographic plates (148).



(**111**)

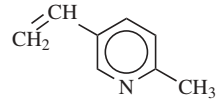


(**112**)



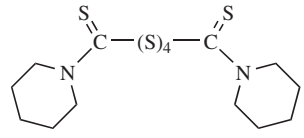
(**113**)

Homopolymers of vinylpyridines find many uses. These homopolymers are soluble in many organic solvents and retain the basic functionality of the pyridine ring. For example, homopolymers of pyridine can be made with great control of molecular weight. These pyridine homopolymer derivatives like *N*-oxides and quaternary salts have been used as dye transfer inhibitors in laundry and similar applications (149). 2-Methyl-5-vinylpyridine [140-76-1] (**114**) was once manufactured and polymerized to form coatings for medicinal tablets. Crosslinked vinylpyridine polymers are generally insoluble in all solvents and can be utilized as catalysts for acylation reactions, as basic tertiary amine catalysts, or as an acid scavenger in reactions, where acid is a troublesome by-product. These insoluble catalysts and acid scavengers are especially easy to regenerate to the free-base form for reuse. A recent article reviews the applications with these systems (152).

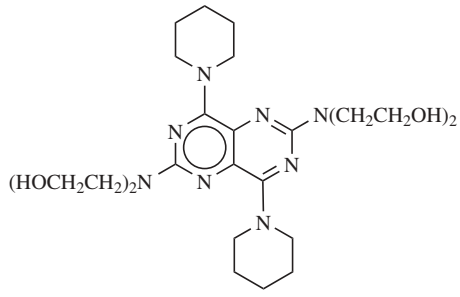


(**114**)

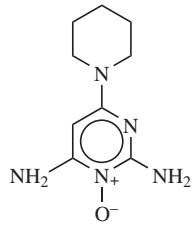
11.12. Piperidines. A significant use of piperidine (**18**) has been in the manufacture of vulcanization accelerators, eg, thiuram disulfide [120-54-7] (**115**) (see Rubber chemicals). Mepiquat dichloride [24307-26-4], the dimethyl quaternary salt of **18**, is used as a plant growth regulator for cotton (qv). Piperidine is used to make vasodilators, eg, dipyridamole [58-32-2] (**116**) and minoxidil [38304-91-5] (**117**), and diuretics, eg, etozoline [73-09-6] (**118**).



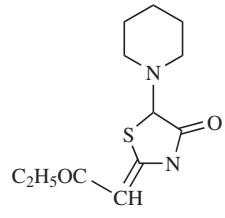
(**115**)



(**116**)



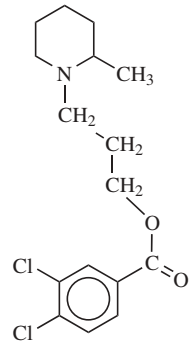
(**117**)



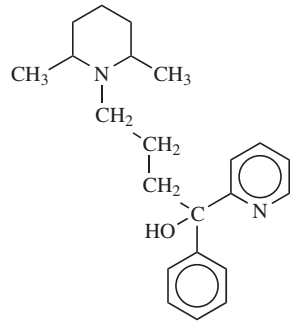
(**118**)

Both piperidine (**18**) and *N*-formylpiperidine [2591-86-8] are used as solvents. *N*-Formylpiperidine is a dipolar, aprotic solvent that has considerably better hydrocarbon solubility than other dipolar, aprotic solvents having formamide or acetamide functionality.

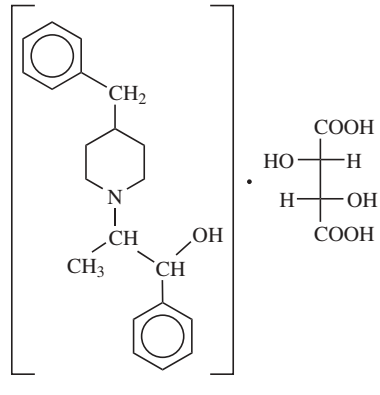
2-Methylpiperidine [109-05-7] is employed for making fungicides such as piperalin [3478-94-2] (**119**). 2,6-Dimethylpiperidine [766-17-6] is used for the antiarrhythmic pirmenol [61477-94-9] (**120**). 4-Benzyl piperidine is used to produce ifenprodil tartrate [23210-56-2] (**121**), a cerebral vasodilator.



(**119**)



(**120**)



(**121**)

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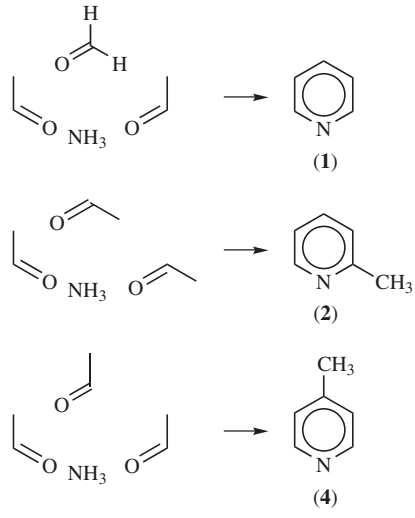

Fig. 1. Four-bond reactions: formaldehyde, acetaldehyde, and ammonia mainly give pyridine (**1**), and acetaldehyde and ammonia give α- (**2**) and γ-picoline (**4**) (72-77).

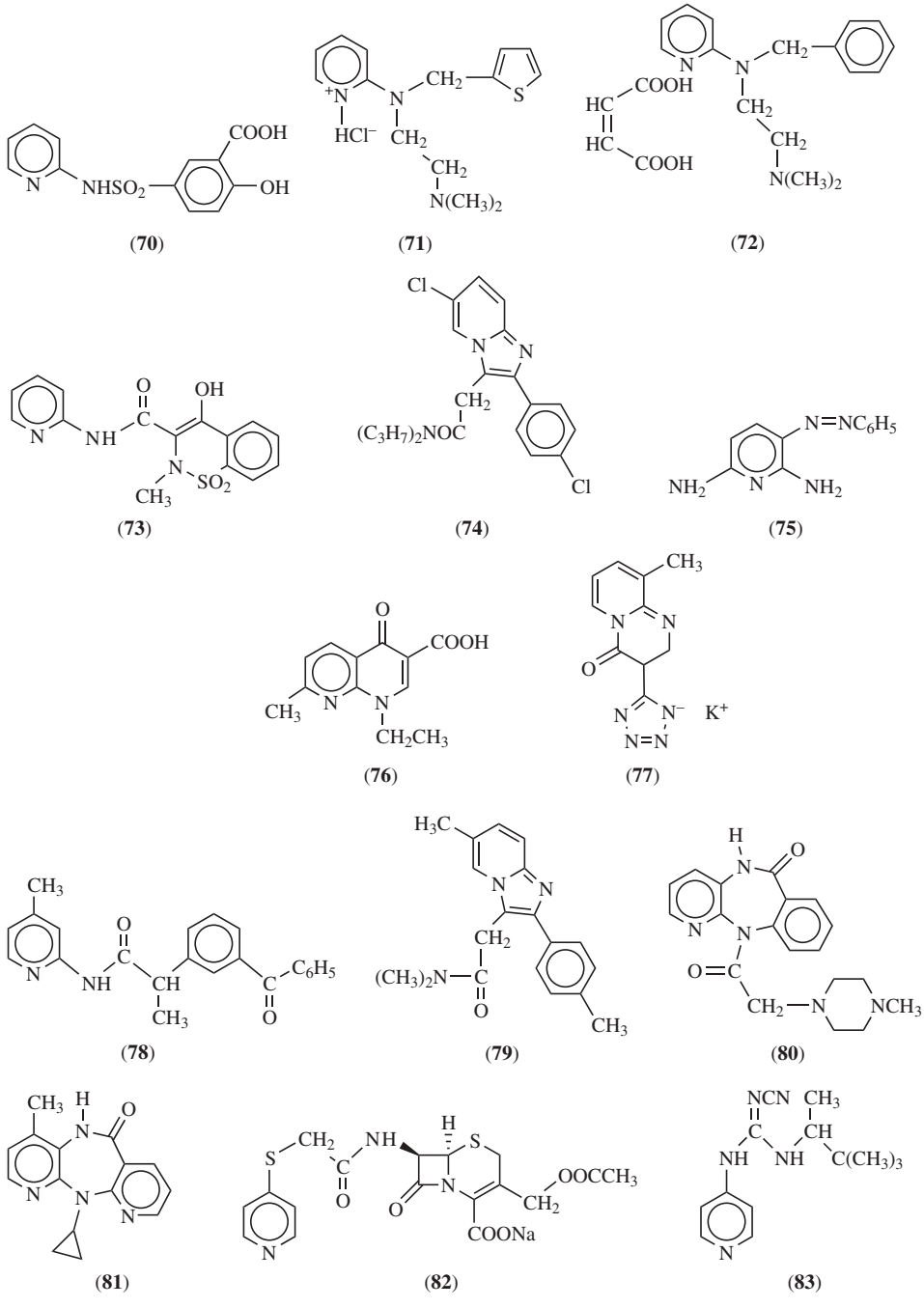

Fig. 2. Pharmaceutical products from aminopyridines.

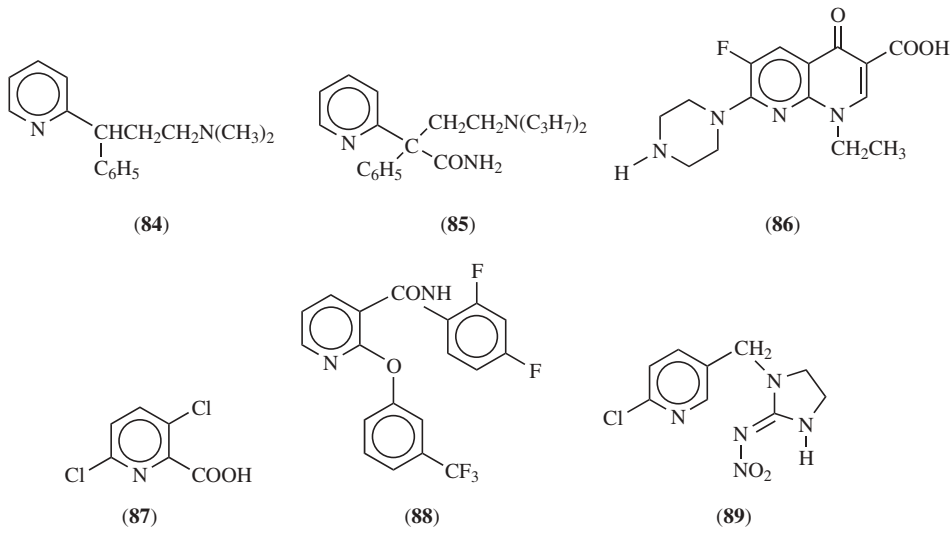

Fig. 3. Pharmaceuticals and agrochemicals from chloropyridines.

Table 1. **Physical Properties of Pyridine**[a]

Physical property	Value
enthalpy of fusion at −41.6°C, kJ/mol[b]	8.2785
enthalpy of vaporization, kJ/mol[b]	
at 25°C	40.2
115.26°C	35.11
critical temperature, °C	346.8
critical pressure, MPa[c]	5.63
enthalpy of formation, gas at 25°C, kJ/mol[b]	140.37
Gibbs free energy of formation, gas at 25°C, kJ/mol[b]	190.48
heat capacity, gas at 25°C, J/(K·mol)	78.23
ignition temperature, °C	550
explosion limit, %	1.7–10.6
surface tension, liquid at 25°C, mN/m(= dyn/cm)	36.6
viscosity, liquid at 25°C, mPa(= cP)	0.878
dielectric constant, liquid at 25°C, ϵ	13.5
thermal conductivity, liquid at 25°C, W/(K·m)	0.165

[a]Ref. 4.

[b]To convert kJ to cal, divide by 4.184.

[c]To convert MPa to atm, multiply by 9.87.

Table 2. **Physical Properties of Pyridine, Alkyl-, and Alkenylpyridine Derivatives**[a]

Compound	CAS Registry Number	Structure number	Mol wt	Freezing point, °C	Boiling point, °C	Density, d_4^{20}	Index of refraction, n_D^{20}	Water solubility[b] at 20°C, g/100 mL	pK_a at 20°C, in water[c]	Water azeotrope	
										Bp,[d] °C	Water, %
pyridine	[110-86-1]	**1**	79.10	−41.6	115.3	0.9830	1.5102	[e]	5.22	93.6	41.3
2-picoline[f, g]	[109-06-8]	**2**	93.13	−66.7	129.5	0.9462	1.5010	[e]	5.96	93.5	48
3-picoline[g]	[108-99-6]	**3**	93.13	−18.3	143.9	0.957	1.5043	[e]	5.63	96.7	63
4-picoline[f, g]	[108-89-4]	**4**	93.13	3.7	144.9	0.9558	1.5058	[e]	5.98	97.4	63.5
2,3-lutidine	[83-61-9]	**58**	107.16	−15.5	161.5	0.9491	1.5085	13.3	6.57		
2,4-lutidine	[108-47-4]		107.16	−64	158.7	0.9325	1.5000	[e]	6.63	71.5	67.4
2,5-lutidine	[589-93-5]		107.16	−15.7	157	0.9331	1.5005	10.0	6.40		
2,6-lutidine	[108-48-5]	**5**	107.16	−6.1	143.7	0.923	1.4977	[e]	6.72	93.3	51.5
3,4-lutidine	[583-58-4]		107.16	−10.6	179.1	0.9534	1.5081	5.2	6.46		
3,5-lutidine	[591-22-0]	**6**	107.16	−6.6	172.7	0.944	1.5049	3.3	6.15		
2,4,6-collidine	[108-75-8]	**8**	121.18	−44.5	170.4	0.913	1.4981	3.6	7.43		
5-ethyl-2-methyl-pyridine	[104-90-5]	**7**	121.18	−70.9	178.3	0.9208	1.4974	1.2		98.4	72
2-vinylpyridine	[100-69-6]	**23**	105.14		110[h]	0.9746	1.5509	2.75	4.98	97.0	62.0
4-vinylpyridine	[100-43-6]		105.14		121[h]	0.988	1.5525	2.91	5.62	98.0	76.6

[a] Ref. 5, unless otherwise noted.
[b] Ref. 6.
[c] Ref. 7.
[d] Ref. 8.
[e] Miscible.
[f] Ignition temperature = 535°C for **2** and 500°C for **4**.

Table 3. **Physical Properties of Substituted Pyridines**[a]

Compound	CAS Registry Number	Structure number	Mol wt	Freezing point, °C	Boiling point, °C	Density, d_4^{20}	Index of refraction, n_D^{20}	Water solubility[b] at 20°C, g/100 mL	pK_a[c] at 20°C in water
2-chloropyridine	[109-09-1]	**17**	113.55	−46.5	168–170	1.205[d]	1.532	2.5	0.5
2,6-dichloropyridine	[2402-78-0]		147.99	87–89	211			[e]	[f]
2-bromopyridine	[109-04-6]		158.00	192–194	194.8	1.627	1.5714	2.1	0.9
picolinic acid[g]	[98-98-6]		123.11	134–136	[h]	1.48		96	5.39
nicotinic acid[i]	[59-67-6]	**27**	123.11	236–239	[h]	1.473		1.7	4.81
isonicotinic acid[j]	[55-55-1]		123.11	314–315	[h]			0.5	4.86
methyl picolinate	[2459-07-6]		137.14	18.7	92[k]	1.166	1.519		2.21
ethyl nicotinate	[614-18-6]		151.17	8–10	223–224	1.107	1.5040	5.0	4.48
picolinamide	[1452-77-3]		122.13	110 dec	143[l]	1.39		18	2.10
nicotinamide	[98-92-0]	**26**	122.13	128–131		1.401		120	3.33
2-cyanopyridine	[100-70-9]	**14**	104.11	26–28	212–215	1.081	1.5290		−0.26
3-cyanopyridine	[100-54-9]	**25**	104.11	50-52	206	1.159	1.5252[m]	13.5	1.36
4-cyanopyridine	[100-48-1]	**15**	104.11	79	195	1.03[n]		4.0	1.90
3-pyridylcarbinol	[100-55-0]	**30**	109.13	−6.5	266	1.124	1.5455	[o]	4.90
4-pyridylcarbinol	[586-95-8]		109.13	57–59	146[p]			[o]	5.33
2-picolylamine	[3731-51-9]		108.14	81	203	1.053	1.5431	[o]	8.8
4-picolylamine	[3731-53-1]		108.14	−7.6	229	1.066	1.5493	[o]	4.39
2-mercaptopyridine	[2637-34-5]		111.17	128–130					−1.07
4-mercaptopyridine	[4556-23-4]		111.17	184–186					1.43
2-pyridone	[142-08-5]	**16**	95.10	107	294			>100	1.25
3-hydroxypyridine	[109-00-2]	**40**	95.10	126				3.6	4.9
4-pyridone	[626-64-2]	**38**	95.10	150	181[q]			>100	3.23

2-aminopyridine	[504-29-0]	**35**	94.12	58	211	1.065	>100	6.9
3-aminopyridine	[462-08-8]	**33**	94.12	62.2	248	1.24	>100	5.98
4-aminopyridine	[504-24-5]	**34**	94.12	159	273	1.250	8.3	9.2
4-dimethylamino-pyridine	[1122-58-3]	**24**	122.17	112	162[r]		7.6	9.5

[a]Measured in the laboratories of Reilly Industries, Inc., unless otherwise noted.
[b]Ref. 6.
[c]Ref. 7.
[d]Ref. 9.
[e]Insoluble.
[f]Cannot be protonated.
[g]2-Carboxypyridine.
[h]Sublimes.
[i]3-Carboxypyridine.
[j]4-Carboxypyridine.
[k]At 4 Pa (0.03 mmHg).
[l]At 2.7 kPa (20 mmHg).
[m]At 50°C.
[n]At 80°C.
[o]Miscible.
[p]At 1.3 kPa (10 mmHg).
[q]At 0.133 kPa (1 mmHg).
[r]At 6.7 kPa (50 mmHg).

Table 4. **U.S. DOT Labeling Regulations**

Compound	Structure number	Flash point,[a] °C	DOT label[b]
pyridine	**1**	19	red
2-methylpyridine	**2**	27	red
3-methylpyridine	**3**	38	red
4-methylpyridine	**4**	39	red
2-vinylpyridine	**23**	50	white red
4-vinylpyridine	**23**	56	white red
piperidine	**18**	12	white red
2-aminopyridine	**35**	104[c]	poison B

[a]Tagliabue closed cup (TCC) unless otherwise noted.
[b]Red is flammable; white, corrosive.
[c]Cleveland open cup (COC).

Table 5. **Specifications for ACS Reagent Grade Pyridine**

Physical properties	Specification
assay, wt % by gc	≥ 99.97
boiling point range, °C	2.0 including 115.3 ± 0.1
solubility in water	no turbidity noted in a 10 wt % soln[a]
residue after evaporation, ppm	≤ 20
water content, wt %	≤ 0.1
chloride content, ppm	≤ 10
sulfate content, ppm	≤ 10
ammonia content, ppm	≤ 20
copper content, ppm	$\leq \sim 5$
reducing substances	5 mL of pyridine does not entirely discharge the color of 0.5 mL of 0.1 *N* $KMnO_4$ solution[a]

[a]Within 30 min.

Table 6. **Acute Toxicity of Pyridine Derivatives**

Compound	Structure number	Oral LD_{50} rats, mg/kg	Inhalation LC_{50}, rats, ppm/h	TLV, mg/m^3
2-methylpyridine	**2**	790	4000/4	*a*
3-methylpyridine	**3**	400–800	8700/2	*a*
4-methylpyridine	**4**	1290	1000/4	*a*
2,6-dimethylpyridine	**5**	400	7500/1[b]	*a*
5-ethyl-2-methylpyridine	**7**	1540	1800/3.7[b]	2
2-vinylpyridine	**23**	100–200	5500/1.5[b]	0.05
4-vinylpyridine		100–200	2000/2[b]	*a*
nicotinic acid	**27**	7000		*a*
nicotinamide	**26**	7000		*a*
2-aminopyridine	**35**	200	5/5[c]	0.5
2-chloropyridine	**17**	140	100/4[d]	
3-cyanopyridine	**25**	1100		
N,*N*′-dimethyl-4,4′-bipyridinium chloride	**20**	57		
cetylpyridinium chloride	**67**	200		

[a]Not established.
[b]LC_{100}.
[c]TC_{LO}.
[d]LC_{LO}.