PYRIDINE
and Its Derivatives
Part Three

Erwin Klingsberg, *Editor*
American Cyanamid Company, Bound Brook, New Jersey

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PYRIDINE AND ITS DERIVATIVES

In Four Parts

PART THREE

This is Part Three of the fourteenth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds and accommodate the specific interests of the authors.

Research Laboratories
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Rochester, New York

ARNOLD WEISSBERGER

Preface

It is hoped that the organization of this monograph will prove to be self-explanatory, but a few general observations are in order.

Chemical compounds are tabulated exhaustively by the principle of latest position. Thus halogenated pyridinecarboxylic acids are found in Chapter X rather than VI, but hydroxy acids in Chapter XII. The principal exceptions are the quaternary compounds, which proved too numerous to be catalogued, and the N-oxides, which are included in Chapter IV irrespective of nuclear substitution. Other exceptions are explained where they occur.

The principle of latest position does not apply to reactions. All reactions for obtaining pyridine derivatives from non-pyridinoid starting materials are covered in Chapter II irrespective of substitution. If the starting material *is* a pyridine derivative, the reaction is discussed instead in the appropriate later chapter or chapters. Thus the conversion of aminopyridines to pyridinols is discussed in Chapters IX and XII.

Nomenclature follows Chemical Abstracts.

The editor wishes to express his gratitude to Prof. D. S. Tarbell of the University of Rochester for the impetus he gave to this undertaking, to the chemists in many parts of the world who have been so generous with reprints, to the staff of Interscience Publishers for their cooperation, and finally to Dr. R. S. Long and Dr. J. J. Leavitt of American Cyanamid for their patience.

Bound Brook Laboratories
American Cyanamid Co.
Bound Brook, N.J.

ERWIN KLINGSBERG

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CHAPTER IX

Aminopyridines

By Andrew S. Tomcufcik and Lee N. Starker

Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York

The aminopyridines occupy an important position in the field of pyridine chemistry. They serve as useful intermediates for medicinals and dyes, and as starting materials for further synthesis.

A. NUCLEAR

1. Preparation

a. From Nonpyridine Starting Materials

Examples of the preparation of aminopyridine derivatives from nonpyridine sources are relatively rare. Cairns *et al.* (*1*) obtained a 12.5% yield of a product said to be either 2-amino-6-ethyl-3-picoline or 4-amino-2-ethyl-3-picoline by the action of acetylene upon propionitrile in the presence of potassium at 180° and fourteen atmospheres pressure.

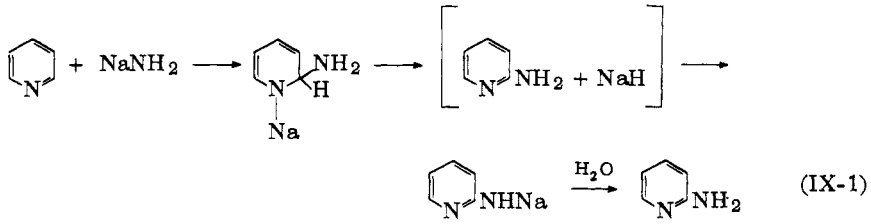
Moir (*2*) heated diacetonitrile with the zinc chloride–ammonia complex and obtained 6-amino-2,4-dimethylnicotinonitrile. Acyl derivatives of substituted diacetonitriles are cyclized by sodium amide in dioxane to 3,5,6-trisubstituted 4-amino-2-pyridinols (*3,4*). An analogous reaction is the cyclization of a 2-acyliminocyclopentanonitrile by sodium amide in liquid ammonia to give a 3-substituted 4-amino-5,6-trimethylene-2-pyridinol (*5*).

Fanta (*6*) obtained a 35% yield of ethyl 2-methyl-5-nitronicotinate by the reaction of ethyl β-aminocrotonate and sodium nitromalondialdehyde. The amine derivative was prepared by reduction.

b. Amination with Sodium Amide

In 1914, Chichibabin and Seide (*7*) reported the synthesis of 2-aminopyridine by the action of sodium amide upon pyridine in an inert solvent at elevated temperatures. This reaction has since become one of the most important in pyridine chemistry, since 2-aminopyridine is a useful starting material for further synthesis.

The suggested mechanism for this reaction involves the addition of sodium amide to a $-CH=N-$ linkage of pyridine, the resultant adduct then rearranging or decomposing to the sodium derivative of 2-aminopyridine. Hydrolysis yields the free amine (*8*) (IX-1).



(IX-1)

This mechanism also explains the simultaneous formation of small amounts of 4-aminopyridine, via 1,4-addition, and the absence of 3-aminopyridine. (*Cf.* Chapter I, pp. 26 ff.)

The importance of 2-aminopyridine as an intermediate, for example in the preparation of sulfapyridine, has led to a thorough study of the experimental conditions of the amination reaction. A summary of the older patent literature is given by Maier-Bode and Altpeter (*9*). The use of dialkylanilines as solvents, with careful control of the temperature at 90–115°, has given 70–80% yields of 2-aminopyridine (*10,11*). Higher temperatures and an excess of sodium amide lead to the formation of 2,6-diaminopyridine and 2,4,6-triaminopyridine (*10*). The improvement in yield obtained by the use of the dialkylanilines is probably due to their solvent action upon sodium amide and the sodium amide–pyridine adduct.

The preparation of 4-aminopyridines by the amination reaction is of minor importance. 4-Aminopyridine itself has been isolated in small quantity from the by-products of the preparation of 2-aminopyridine (*12*). 2,6-Dimethylpyridine is converted to the 4-amino derivative by sodium amide (*13,14*).

A large number of alkylpyridines have been aminated by the sodium amide procedure. In liquid ammonia, the 2- and 4-alkylpyridines form a sodium salt, but at higher temperatures in inert solvents, amino derivatives are obtained. (Aminoalkylpyridines prepared in this manner are listed in Tables IX-10, IX-11, and IX-12, pp. 82 f.). The reaction of pyridine and *N,N*-dialkylaminoethylamines in the presence of sodium powder in refluxing toluene gives poor to fair yields of 2-(dialkylaminoethylamino)pyridines (*796*).

Diamino derivatives are obtained from 2,2′- and 4,4′-bipyridyl by the action of sodium amide in xylene (*15,16*).

2-Pyridinol is reported to yield 6-amino-2-pyridinol by treatment with sodium amide (*17*), but 3-pyridinol gave 2,6-diaminopyridine

solely, reduction having occurred (*18*). 3,4-Pyridinediol is converted to 2-amino-3,4-pyridinediol in 40% yield (*19*).

Aminopyridines are aminated to polyamino derivatives, as shown by the preparation of 2,6-diamino- and 2,4,6-triaminopyridines by the strenuous amination of pyridine (*10*). 3-Aminopyridine is converted in very low yield to 2,3-diaminopyridine (*20*), and 3-methylaminopyridine to the corresponding 2-amino derivative (*21*). Nicotine (*22*), anabasine, and *N*-methylanabasine (*24*) all yield mixtures of monoamino derivatives (2- and 6-substitution) when treated with sodium amide.

Nicotinamide gives 2-aminonicotinamide in 20–25% yield (*23*). A survey of the literature on the amination of heterocyclic bases has been given by Leffler (*11*).

c. Ammonolysis of Halopyridines

The ammonolysis of halopyridines at high temperatures, usually in the presence of metallic salt catalysts, yields the corresponding amino derivatives. 2-Aminopyridine has been obtained in 50% yield by the action of ammonia upon 2-chloropyridine at 250° in the presence of copper sulfate (*25*) or nickel sulfate (*26*). In the absence of a catalyst, replacement does not occur (*27*). Treatment of 2-chloropyridine with the zinc chloride–ammonia complex at 200° gave a quantitative yield of 2-aminopyridine (*28*), but rigorously anhydrous conditions must be observed (*26*). Ammonolysis of 2-bromopyridine at 200–250° with copper sulfate as catalyst (*22,29*) yields 2-aminopyridine. This reaction is also accomplished by the action of sodium or potassium amide upon the bromopyridine in liquid ammonia (*30*).

Surprisingly, 3-bromopyridine reacts more readily with ammonia than the 2-isomer. At 140° in the presence of copper sulfate, 75–85% yields of 3-aminopyridine are obtained (*31–33*). 5-Amino-2-picoline is obtained from the 5-iodo compound in a similar manner (*34*).

The relative inaccessibility of 4-halopyridines has limited ammonolysis studies with these compounds. 4-Chloropyridine is converted to the 4-amino derivative by treatment with the zinc chloride–ammonia complex at 220° (*35*), or by heating with ammonia in phenol at 170° (*36*).

3-Bromopyridine 1-oxide is ammonolyzed (copper sulfate catalyst) to 3-aminopyridine 1-oxide. Subsequent reduction with iron and acetic acid gives 3-aminopyridine (*37*).

The presence of other substituent groups usually does not interfere with the ammonolysis reaction. This is illustrated by the preparation of 6-amino-2-ethoxypyridine from the the 6-bromo derivative (*32*), 2-amino-3-ethoxy-6-nitropyridine from the 2-bromo derivative (*38*), and 2-amino-6-ethoxy-3-nitropyridine from the 2-bromo derivative (*38*). 3-Aminopyridine derivatives are obtained from 3-bromopyridines bearing an ethoxy (*39*) or hydroxy (*40*) group in the 5 position.

Halopyridinecarboxylic acids are smoothly ammonolyzed to amino derivatives. The homogeneous solution is readily handled in the autoclave, and good yields are usually obtained. Among the halopyridine acids which have been converted to the corresponding amines are the following: 6-chloronicotinic (*27,41*), 6-chloropicolinic (*42*), 2-chloroisonicotinic (*43*), 5-chloronicotinic (*44*), 5-bromonicotinic (*45*), 5-bromo-3,4-pyridinedicarboxylic (*46*), 4-chloro-2,6-pyridinedicarboxylic, and 4-chloro-2,6-dimethyl-3,5-pyridinedicarboxylic (*41*).

6-Chloronicotinamide (*23,47*) and 6-chloro-3-pyridinesulfonamide (*48,49*) are likewise readily ammonolyzed.

4-Chloro-3-nitropyridine is converted under relatively mild conditions to the 4-amino compound (*50*). Both chlorine groups are readily replaced in 2,4-dichloro-3-nitropyridine (*51*).

The ammonolysis of polyhalogen pyridine derivatives has been studied in considerable detail, particularly by the Dutch school. 2,6-Dichloropyridine yields 2-amino-6-chloropyridine, but the second chlorine cannot be replaced (*25*). 2,6-Dibromopyridine, on the other hand, can be converted to 2,6-diaminopyridine in low yield under forcing conditions (*25,29,32*).

2,4-Dichloropyridine gives rise to both 2-amino-4-chloro- and 4-amino-2-chloropyridines, the second compound predominating. 2,4,5-Trichloropyridine, however, yields only 4-amino-2,5-dichloropyridine (*52*), while 2-chloro-3,5-diiodopyridine gives 2-amino-3,5-diiodopyridine (*23*).

Den Hertog (*53*) summarizes his extensive investigation of the ammonolysis of polybromopyridines as follows: (*a*) 2-, 4-, and 6-

bromine substituents are easily replaced, 3- and 5-bromine substituents difficultly so; (*b*) 2- and 4-bromines are almost equally active, the 4-derivative being slightly more so; (*c*) the presence of other bromine substituents increases the activity of the 2- and 4-bromine.

The original literature may be consulted for further details (*29,31,53,126,175,589,590*).

d. Hofmann and Curtius Reactions

Historically, the three monoaminopyridines were first prepared from the corresponding carboxamides by the Hofmann reaction. Thus, picolinamide, upon treatment with potassium hypobromite (*54*) or sodium hypochlorite (*55*), yields 2-aminopyridine. 6-Amino-2-picoline (*56*) and 6-amino-2,4-lutidine (*57*) were similarly prepared.

The most important preparative method for 3-aminopyridine is from nicotinamide by the Hofmann reaction. This synthesis has been studied in considerable detail, since nicotinic acid is readily available. Potassium hypobromite has been the reagent of choice (*54,58,59*), giving yields of 50–60%. 2-Methylnicotinamide is converted to 3-amino-2-picoline by sodium hypochlorite (*60*), and 6-methylnicotinamide to 5-amino-2-picoline by the same reagent.

4-Aminopyridine has been obtained from isonicotinamide in excellent yield by treatment with potassium hypobromite (*36,54,58*).

Bromination sometimes occurs during the Hofmann reaction, giving aminobromopyridines which have usually not been studied further (*54,59*).

Halogenated pyridinecarboxamides (*61–63*) have been successfully converted to aminohalopyridines by the Hofmann reaction. Monoamides of pyridinedicarboxylic acids (*64–67,113*) yield the aminocarboxylic acid.

A summary of the application of the Hofmann reaction to the preparation of heterocyclic amines is included in the review by Wallis and Lane (*68*).

The Curtius reaction has been less widely utilized than the Hofmann reaction in the preparation of monoaminopyridine derivatives, primarily because of the reactivity of hydrazine toward labile substituents on the pyridine nucleus. Its main application has been

to the synthesis of diaminopyridines, which will be discussed later in this chapter (p. 62).

Picolinic (*69*) and nicotinic hydrazides (*70,71*) have been converted to the corresponding amines. In the latter case, an over-all yield of 60% of 3-aminopyridine was obtained, based on the hydrazide. The 4-methyl (*71*), 6-methyl (*72*), and 6-*n*-propyl (*73*) derivatives of nicotinic hydrazide have been similarly converted to the corresponding 3-aminopyridine derivatives.

In a similar manner, Graf was able to convert the following halogenated derivatives of picolinic hydrazide to the corresponding 2-aminopyridines: 4-chloro (*74*), 4-iodo (*74*), and 2,4-dichloro (*75*).

The application of the Curtius reaction to the preparation of aminopyridines is included in the survey by Smith (*76*).

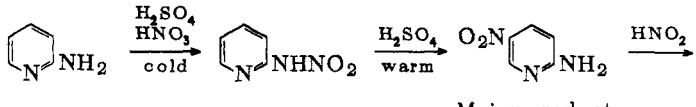
e. Reduction of Nitro Compounds

Although the reduction of nitropyridines to the amines usually proceeds normally, the relative inaccessibility of the starting materials makes this method less important than in the benzene series. 2-Nitropyridine is reduced to 2-aminopyridine by stannous chloride in hydrochloric acid (*591*). 3-Nitropyridine (obtained in 15% yield by the vigorous nitration of pyridine) is reduced quantitatively to the amine under the same conditions (*77*). In the latter case, reduction with activated aluminum in aqueous ether (*78*) and catalytic reduction over Raney nickel (*592*) have also been employed. 4-Nitropyridine has likewise been reduced catalytically to the amine (*80*).

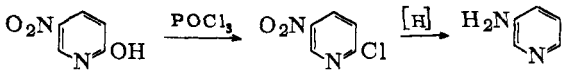
The nitro derivatives of alkylpyridines have also been reduced to the corresponding amino compounds. These include 5-nitro-2-picoline (*81*) and 2-*n*-propyl-5-nitropyridine (*82*) with stannous chloride, and 4-nitro-3-picoline (*83*) by catalytic reduction over palladium. The 6-methyl, 2,6-dimethyl, and 2,4,6-trimethyl derivatives of 3-nitropyridine yield the amines by stannous chloride reduction (*81*). Catalytic reduction of 4-nitro-2-picoline (*726*) and 4-nitro-3-picoline (*83*) yields the corresponding amines.

The direct nitration of pyridine proceeds with difficulty as noted previously; however, the presence of an activating group facilitates nitration, as in the case of 2-aminopyridine (*85*). The resultant 2-amino-5-nitropyridine is readily converted to the 2-chloro derivative

(*594*). Catalytic reduction then results in excellent yields of 3-aminopyridine, the chlorine group suffering simultaneous reductive elimination (*86–88*) (IX-2). Generally, nitropyridines carrying a halo-



Major product



(IX-2)

gen substituent in the 2 or 4 position may be catalytically reduced to the dehalogenated amino compound (*86*). 4-Chloro-3-nitropyridine (*86*) is reduced to 3-aminopyridine, while the 4-chloro (*89*) and 6-chloro (*90*) derivatives of 3-nitro-2-picoline both yield 3-amino-2-picoline. In like fashion, the 4-chloro (*89*) and 6-chloro (*91*) derivatives of 5-nitro-2-picoline are both reduced to 5-amino-2-picoline; 2-chloro-5-nitro-3-picoline to 3-amino-5-picoline (*92,93*); and a mixture of 3-nitro- and 5-nitro-2-chloro-4-picolines to 3-amino-4-picoline (*94*).

Halonitropyridines may be reduced to haloaminopyridines by noncatalytic techniques. For example, 2-chloro-5-nitropyridine is reduced to the corresponding amine in 93% yield by iron and water (*95*). This reduction is also effected by electrolysis in dilute sulfuric acid (*88*). Stannous chloride in hydrochloric acid reduces 2-bromo-5-nitropyridine to 5-amino-2-bromopyridine (*88,96*). All three halogens in 5-bromo-2,4-dichloro-3-nitropyridine are retained during reduction with iron–acetic acid to 3-amino-5-bromo-2,4-dichloropyridine (*97*). The 5-bromo, 5-chloro, and 5-iodo derivatives of 3-nitropyridine are reduced by stannous chloride to the corresponding amines (*98*).

The discovery (*99,100*) that pyridine 1-oxides are readily nitrated to 4-nitro derivatives has spurred interest in the hitherto unavailable 4-aminopyridines. 4-Nitropyridine 1-oxide is easily reduced to 4-aminopyridine in excellent yield by iron–acetic acid (*99*), zinc–sodium hydroxide (*101*), or by catalytic hydrogenation (*80,102,104*).

Under proper conditions the reduction can be stopped at the 4-aminopyridine 1-oxide stage (*103*), and then continued to the 4-aminopyridine (*101*).

A wide variety of substituted 4-nitropyridine 1-oxides have been reduced to the corresponding 4-aminopyridines. These include the 2-methyl (*105*), 3-methyl (*83*), 5-ethyl-2-methyl (*107*), and 2,6-dimethyl (*108,109*) derivatives. The 2-bromo (*106*), 3-bromo (*99*), and 3,5-dibromo (*110*) derivatives of 4-nitropyridine 1-oxide have been reduced to the corresponding bromo-4-aminopyridines. 2-Ethoxy-4-nitropyridine 1-oxide yields 4-amino-2-ethoxypyridine upon reduction (*106*).

4-Chloro-3-nitropyridine 1-oxide is simultaneously reduced and dehalogenated to 3-aminopyridine (*112*).

f. Decarboxylation

A characteristic behavior of aminopyridinecarboxylic acids is their tendency to decarboxylate at or above the melting point, giving the aminopyridine as a volatile distillate. The aminopyridinecarboxylic acids are obtainable by a number of routes, such as the oxidation and subsequent reduction of alkylnitropyridines, the conversion of a pyridonecarboxylic acid to the chloro derivative, followed by ammonolysis, and the Hofmann reaction upon the imides or monoamides of pyridinedicarboxylic acids.

2-Aminopyridine has been obtained by the thermal decarboxylation of 6-aminonicotinic acid (*27,41,113*) and 6-aminopicolinic acid (*42*). Treatment of 2,4-dihydroxy-1,3,8-triazanaphthalene with concentrated sulfuric acid at 250–60° yields 2-aminopyridine, probably via an initial hydrolysis to the amino acid and subsequent decarboxylation (*114*).

Similarly, 3-aminopyridine has been obtained by the decarboxylation of 3-aminopicolinic acid (*20*) and 3-aminoisonicotinic acid (*64,115*). 5-Amino-2-methylisonicotinic acid yields 5-amino-2-picoline (*114*), and 3-amino-2,6-dimethylisonicotinic acid yields 3-amino-2,6-lutidine (*116*) by this procedure.

Decarboxylation of 4-aminonicotinic acid (*64*) and 4-amino-2,6-pyridinedicarboxylic acid (*117*) yields 4-aminopyridine. 4-Amino-2,6-lutidine has been obtained from 4-amino-2,6-dimethyl-3,5-pyridinedicarboxylic acid in this manner (*41*).

2-Amino-5-nitronicotinic acid is decarboxylated at 275–80° to 2-amino-5-nitropyridine (*119*).

g. Ammonolysis of Pyridylpyridinium Salts

The first convenient synthesis of 4-aminopyridine was based on the work of Koenigs and Greiner (*120,121*), who found that pyridine and thionyl chloride reacted to yield 1-(4-pyridyl)pyridinium chloride hydrochloride, which on treatment with alkali or concentrated ammonia at 150° gave 4-aminopyridine in 36–40% yields. Subsequent attempts to duplicate this preparation were not successful (*122*), until Wibaut and co-workers (*123*) carefully delineated the reaction conditions necessary to achieve the yields obtained by Koenigs and Greiner. Albert (*124*) obtained an 80% yield by ammonolyzing the 1-(4-pyridyl)pyridinium salt in phenol at 180–90°. The reaction of 4-pyridylpyridinium chloride with an amine hydrochloride at elevated temperatures gives excellent yields, in most cases, of the corresponding 4-(substituted amino)pyridines. 4-Phenoxy- or 4-phenylthiopyridine gives similar results (*798*).

The preparation of 2-aminopyridine derivatives by the Koenigs-Greiner reaction is of little significance. When 2-chloropyridine is heated with pyridine or 3-picoline (*62*) at 200°, low yields of 2-aminopyridine are obtained by hydrolysis of the reaction product. Pyridine hydrochloride and iodine monochloride at 250° yield "iodo-2-pyridylpyridine," which gives 2-aminopyridine on treatment with ammonia (*125*).

3,4-Dibromopyridine, after standing at room temperature for eight months, yields a pyridylpyridinium salt which upon ammonolysis at 200° yields 4-amino-3-bromopyridine (*126*).

High temperature halogenation of pyridine occasionally forms pyridylpyridinium salts which are hydrolyzable to aminopyridines. In this manner, the reaction of pyridine and bromine at 250°, followed by hydrolysis, gave 4-amino-3,5-dibromopyridine (*127*). This compound is also obtained by the bromination of 3-pyridinesulfonic acid (*128*). Chlorination of pyridine at 270° gives a low yield of a pyridylpyridinium salt that can be hydrolyzed to 2-aminopyridine (*25*). Chlorination of fused pyridine hydrochloride for several weeks gives rise to an unidentified aminotrichloropyridine (*129*).

h. Miscellaneous Methods

The passage of pyridine and ammonia over dehydrogenation catalysts produces low yields of 2-aminopyridine (*130–133*). 2-Picoline yields an amino derivative by this procedure, which is *not* 6-amino-2-picoline (*133*).

Pyridine and chloramine at room temperature are reported to produce some 2-aminopyridine (*595*).

The action of sodium amide upon a mixture of 3-bromopyridine and acetophenone gives a low yield of 4-aminopyridine, besides 4-phenacylpyridine. The formation of these products is explained by the intermediate formation of a "pyridyne" derivative, which then adds either sodium amide or sodioacetophenone, the anion ending on the 4 position (*135*).

Acid hydrolysis of 2-(*p*-methoxybenzylamino)pyridine gives rise to 2-aminopyridine (*136*).

The Hofmann degradation of 2- and 6-aminonicotine yields the corresponding 2- and 6-amino derivatives of 1-(3-pyridyl)butadiene (*137*). Catalytic reduction of the former compound gives 2-amino-3-*n*-butylpyridine (*138*).

4-Aminopyridine 1-oxide readily forms adducts with alkyl halides, which on treatment with alkali or silver oxide yield 4-aminopyridine and an aldehyde (*139*). This reaction may serve as a convenient synthesis of an aldehyde from an alkyl iodide.

A sulfonic group in the 2 position of a pyridine derivative is readily replaced by an amino group under ammonolysis conditions (*140*). However, this method has little practical value.

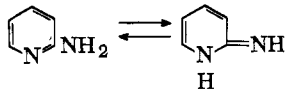
Nienburg (*141*) subjected the α-oxime of 5-benzoyl-2-phenylpyridine to the Beckman rearrangement (PCl_5) and isolated 5-amino-2-phenylpyridine from the reaction products after acid hydrolysis.

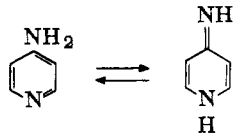
2-Benzylaminopyridine has been prepared by the treatment of 2-aminopyridine with sodium hydroxide in refluxing benzyl alcohol. The yield is essentially quantitative (*799*).

2. Structure and Properties

The striking difference in chemical properties between 3-aminopyridine and 2- and 4-aminopyridines has occasioned considerable study of their structure. The previous interpretations (*142*) of this

difference were based entirely on the ability of the 2- and 4-aminopyridines to exist in tautomeric forms (IX-3). 3-Aminopyridine, on the other hand, can only exist in one form (IX-4).





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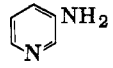


(IX-4)

Attempts to establish the presence of the tautomeric imino forms of 2- and 4-aminopyridines on the basis of ultraviolet absorption spectra have been inconclusive (*143,144*).

In an important paper, Angyal and Angyal (*145*) have reviewed the literature on the tautomerism of *N*-heterocyclic amines, and discuss the case for the imino and amino forms on the basis of physical and chemical evidence.

The direct reaction of methyl iodide and 2-aminopyridine yields a product which on careful neutralization yields 1,2-dihydro-2-imino-1-methylpyridine (*146*); this result has been cited as evidence for the imino form, the ring nitrogen being preferentially alkylated. However, by consideration of the electron distribution in 2-aminopyridine, and of the results of alkylation of amidines, Angyal and Angyal concluded that the ring nitrogen in 2-aminopyridine should have an enhanced nucleophilic reactivity, and thus should be the preferred site for substitution in the amino form.

The failure of 2- and 4-aminopyridines (unlike the 3-isomer) to yield stable diazonium salts in dilute acid solution is evidence of their special character. Angyal and Angyal regard this behavior as

an indication that resonance stabilization between the diazonium group and the aromatic ring is lacking in these diazonium salts because of the strong electron attraction of the ring nitrogen; thus they become as unstable as aliphatic derivatives.

The tendency of some potentially tautomeric *N*-heterocyclic amines to yield the corresponding hydroxy or carbonyl derivative upon hydrolysis has been cited as evidence for the imino form. However, 5-dimethylaminoacridine, which cannot, of course, tautomerize, is even more readily hydrolyzed to acridone than the corresponding amino or methylamino derivatives.

Ease of hydrolysis probably indicates a low electron density on the carbon atom bearing the amino group. Since 2- and 4-halo and other derivatives can be hydrolyzed to the corresponding pyridone, the lessened electron density may be the determining factor, rather than any tautomerization.

One important feature of the tautomerization (IX-3) is the loss of the aromatic resonance energy in going from the amino to the imino form. As a consequence, the amino form would be expected to be more stable.

From the dissociation constants of the cationic forms of 2-aminopyridine and 1,2-dihydro-2-imino-1-methylpyridine, Angyal and Angyal have calculated that the ratio of amino form to imino form in 2-aminopyridine exceeds 1000:1.

Two recent studies (*147,148*) show that the infrared spectra of all three monoaminopyridines closely resemble those of aniline and 2-naphthylamine, whereas that of 1,2-dihydro-2-imino-1-methylpyridine is sharply dissimilar. No evidence for the presence of an appreciable amount of the imino form was obtained.

A comprehensive study of the ultraviolet and visible absorption spectra of 2-, 3-, and 4-aminopyridine derivatives has been reported by Grammaticakis (*800*).

Physical properties of the monoaminopyridines and their nuclear alkyl derivatives are summarized in Tables IX-9 to IX-12 (pp. 81 ff.).

3. Reactions

a. Oxidation to Nitropyridines

The unsubstituted pyridine nucleus is very resistant to nitration. Under rather strenuous conditions, low yields of the 3-nitro deriva-

tive are obtained, along with some 2-nitropyridine (*77*). However, the nitropyridines are obtainable by an alternative method; oxidation of the corresponding amine with hydrogen peroxide. Thus 2-nitro- and 4-nitropyridines are obtained by oxidation with hydrogen peroxide in fuming sulfuric acid (*150*). Hydrogen peroxide and ammonium persulfate in concentrated sulfuric acid give 2-nitropyridine in inferior yield (*151*). 3-Nitropyridine is obtained from the amine in low yield by the action of hydrogen peroxide in concentrated sulfuric acid solution (*152*). When fuming sulfuric acid was employed, 3,3′-azoxypyridine was obtained (*153*).

Halogenated 2-aminopyridines are also oxidized to the corresponding 2-nitro derivatives with hydrogen peroxide in concentrated or fuming sulfuric acid. The 5-chloro (*154*), 5-bromo (*154,155*), and 3,5-dibromo (*155*) derivatives were prepared by this procedure.

The four 2-aminopicolines have been oxidized to 2-nitropicolines with hydrogen peroxide and fuming sulfuric acid (*153*).

This reaction is also discussed in Chapter VIII (pp. 476 f.).

b. Oxidation to Azopyridines

Azopyridines have been prepared by the alkaline arsenite reduction of nitropyridines (*150,156*) and the alkaline hypochlorite oxidation of aminopyridines (*150,156*). In the latter case, the simultaneous formation of chlorination products of azopyridines gives difficultly separable mixtures (*157*).

By the alkaline hypochlorite oxidation procedure, 2-amino- (*158*), 3-amino- (*156*), and 4-aminopyridines (*156*) have been converted to the corresponding azopyridines. Chloro (*157*), bromo (*156,159*), and nitro (*156*) derivatives of 2-aminopyridine have similarly been converted into substituted azopyridines. Hypochlorite oxidation of a mixture of 2-aminopyridine and 2-amino-5-chloropyridine yielded the unsymmetrical monochloroazopyridines along with the expected symmetrical azopyridines (*157*).

The action of sodium hypochlorite upon 2-amino-5-nitropyridine at a pH of 3–6 yields an *N,N*-dichloro derivative (*159*).

The action of hydrogen peroxide and hydriodic acid upon 3-aminopyridine gave 3,3′-azodipyridine in low yield (*152*).

Potassium persulfate oxidation of 4-aminopyridine yields a mixture of 4,4′-azoxypyridine and the sulfate ester of 4-amino-3-pyridol.

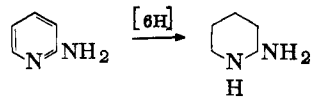
2-Aminopyridine yields only the sulfate ester of 2-amino-3-pyridol (*801*).

This reaction is also discussed in Chapter VIII (p. 485).

c. Hydrogenation to Piperidine Derivatives

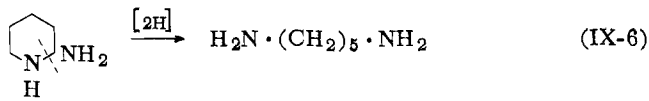
Nuclear reduction of the aminopyridines can be accomplished by a number of methods. 3-Aminopyridine (*160*) has been reduced to 3-aminopiperidine in quantitative yield, using platinum oxide in hydrochloric acid. A previous report of the preparation of 3-aminopiperidine from 2,5-diaminopyridine using sodium and ethanol (*161*) was shown to be erroneous. This latter reduction procedure converts 4-aminopyridine into 4-aminopiperidine in good yield (*35,162,163*). Electrolytic reduction of 4-aminopyridine in dilute sulfuric acid solution gave a low yield of 4-aminopiperidine (*35*), while catalytic reduction over platinum or platinum oxide was unsuccessful (*163*). The reduction of 4-amino-2,6-lutidine by tin and hydrochloric acid gave a complex mixture from which a very low yield of a compound analyzing for 4-amino-2,6-dimethylpiperidine was isolated (*41*).

Unlike the clear-cut reduction of 3- and 4-aminopyridines to the corresponding aminopiperidines, the reduction of 2-aminopyridine leads to a mixture of products. This is due to the unstable nature of the presumed intermediate, 2-aminopiperidine (IX-5), a diamino-



(IX-5)

methane derivative that would be expected as such to lose ammonia readily. Subsequent reduction of the resulting tetrahydropyridine yields piperidine. Indeed, piperidine and ammonia have been isolated among the products of the sodium-ethanol reduction of 2-aminopyridine (*41,164*). The formation of cadaverine (*161,165*) is explained by reductive ring scission of the intermediate 2-aminopiperidine (IX-6).



(IX-6)

Stable derivatives of 2-aminopiperidine are known. The reduction of 2-aminopyridine in a mixture of acetic anhydride and acetic acid in the presence of platinum oxide yields *N*-acetyl-2-acetamidopiperidine, while 2-diphenylaminopiperidine was obtained by the catalytic reduction of 2-diphenylaminopyridine in acetic acid solution (*165*).

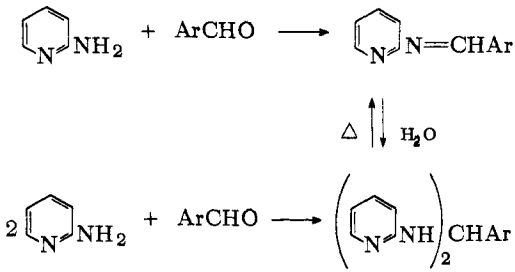
d. Reactions with Aldehydes and Ketones

Kahn and Petrow (*166*) heated a mixture of 2-aminopyridine and formalin to dryness and obtained a 20% yield of a compound formulated as 1,3,5-tris(2-pyridyl)hexahydro-*s*-triazine. Titov and Baryshnikova (*167*) heated 2-aminopyridine and paraformaldehyde at 150° and isolated a product formulated as bis(2-pyridylamino)methane. The reactions of 2-aminopyridine and formaldehyde in the presence of formic acid will be discussed later (p. 29).

The 3- and 5-nitro derivatives of 2-aminopyridine react with aqueous formaldehyde to yield the corresponding bis(nitropyridylamino)methanes (*154,168*).

2-Aminopyridine reacts with acetaldehyde and propionaldehyde to yield products of the general structure $(2\text{-PyNH})_2\text{CHR}$ (*169,170*). Trichloroacetaldehyde is reported to yield the mono addition product, 2-PyNHCHOHCCl_3 (*170,171*), and also the 1,1-bis(pyridylamino- product, $(2\text{-PyNH})_2\text{CHCCl}_3$ (*171,172*), but in neither case do the physical constants reported by the different authors agree.

The reaction of 2-aminopyridine with aromatic or heterocyclic aldehydes can lead to two different products, depending on the experimental conditions (IX-7). At room temperature, 2-aminopyri-



(IX-7)

dine and benzaldehyde yield the benzylidenedipyridylamine derivative (*158,172*) which upon heating above its melting point is

converted to 2-benzalaminopyridine (*158,173*). The latter compound is very susceptible to water, the benzylidenedipyridylamine being formed. This behavior is typical of many substituted 2-benzalaminopyridines (*28,158*). When the reaction between 2-aminopyridine and aromatic or heterocyclic aldehydes is carried out in refluxing cumene, with continuous removal of the water formed, excellent yields of the 2-benzalaminopyridines are obtained (*174*). 2-Aminopyridines substituted in the 3 and/or 5 position with halogens yield Schiff bases on condensation with salicylaldehyde (*175,802*).

Acetophenone and 2-aminopyridine do not yield a ketimine under any conditions, but the diethyl acetal of acetophenone yields the 2-(α-methylbenzalamino)pyridine in good yield (*176*).

The reaction of 2-aminopyridine and 2,5-hexanedione in the presence of hydrogen chloride as catalyst yields 1-(2-pyridyl)-2,5-dimethylpyrrole (*177*). The corresponding reaction with acetylacetone or benzil yields products of undescribed nature (*178*). Acetylacetone reacts with one mole of 6-amino-2-picoline to give the ketimine (*179*).

2-Amino-3,5-dibromopyridine and ethyl acetoacetate heated at 100° yield ethyl β-(3,5-dibromo-2-pyridylamino)crotonate (*180*).

The reactions of 2-aminopyridines with other ketoesters which lead to the synthesis of heterocyclic structures will be discussed later in this chapter (p. 45).

3-Aminopyridine resembles aniline in its reactions with aldehydes and ketones. Formaldehyde yields a polymer of 3-methylenaminopyridine, which resembles anhydroformaldehydeaniline (*88*). Stable Schiff bases have been obtained from aromatic (*158*) and heterocyclic (*181*) aldehydes. Similar derivatives have been obtained from the 6-alkoxy (*182,183*) and 6-alkylmercapto (*181*) derivatives of 3-aminopyridine.

3-Aminopyridine may react with ethyl glyoxylate to yield either the normal Schiff base or ethyl bis(2-pyridylamino)acetate. On reduction and hydrolysis, both compounds yield *N*-(3-pyridyl)glycine (*184*).

6-Alkoxy derivatives of 3-aminopyridine react with glucose in the presence of ammonium chloride as catalyst to give 1-(6-alkoxy-3-pyridylamino)glucosides (*185*). In the presence of sodium bisulfite,