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

ARNOLD WEISSBERGER, *Consulting Editor*

Contributors to This Part

John C. Godfrey

Bristol Laboratories
Syracuse, New York

Herbert Meislich

The City University of New York,
New York City

Eugene P. Oliveto

Schering Corporation
Bloomfield, New Jersey

Lee N. Starker

Warner-Lambert Research Institute
Morris Plains, New Jersey

Andrew S. Tomcufcik

Lederle Laboratories Division
American Cyanamid Company
Pearl River, New York

PYRIDINE
and Its Derivatives
Part Three

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

1962
INTERSCIENCE PUBLISHERS
A DIVISION OF JOHN WILEY & SONS, NEW YORK-LONDON

Library of Congress Catalog Card Number 59-13038

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
Eastman Kodak Company
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

Contents of Other Parts

Part One

Part Two

Part Four

Contents of Part Three

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.

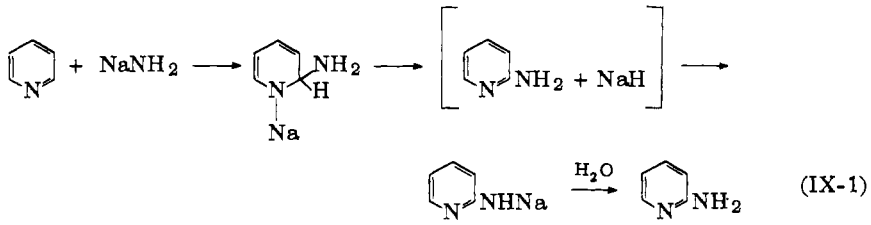
Moir (*2*) heated diacetonitrile with the zinc chloride–ammonia complex and obtained 6-amino-2,4-dimethylnicotinonitrile. Acyl derivatives of substituted diacetonitriles are cyclized by sodium amide in dioxane to 3,5,6-trisubstituted 4-amino-2-pyridinols (*3,4*). An analogous reaction is the cyclization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

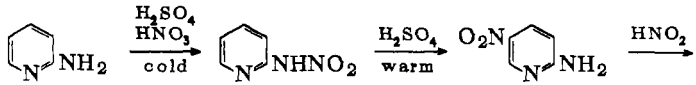
e. Reduction of Nitro Compounds

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*).

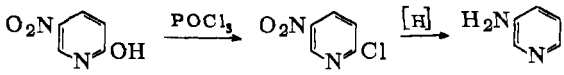
The nitro derivatives of alkylpyridines have also been reduced to the corresponding amino compounds. These include 5-nitro-2-picoline (*81*) and 2-*n*-propyl-5-nitropyridine (*82*) with stannous chloride, and 4-nitro-3-picoline (*83*) by catalytic reduction over palladium. The 6-methyl, 2,6-dimethyl,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

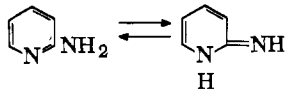
Nienburg (*141*) subjected the α-oxime of 5-benzoyl-2-phenylpyridine to the Beckman rearrangement (PCl_5) and isolated 5-amino-2-phenylpyridine from the reaction products after acid hydrolysis.

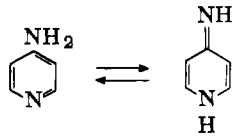
2-Benzylaminopyridine has been prepared by the treatment of 2-aminopyridine with sodium hydroxide in refluxing benzyl alcohol. The yield is essentially quantitative (*799*).

2. Structure and Properties

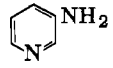
The striking difference in chemical properties between 3-aminopyridine and 2- and 4-aminopyridines has occasioned considerable study of their structure. The previous interpretations (*142*) of this

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).





(IX-3)



(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.

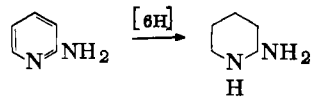
2-Aminopyridine yields only the sulfate ester of 2-amino-3-pyridol (*801*).

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

c. Hydrogenation to Piperidine Derivatives

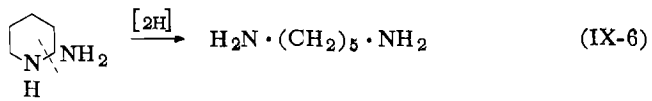
Nuclear reduction of the aminopyridines can be accomplished by a number of methods. 3-Aminopyridine (*160*) has been reduced to 3-aminopiperidine in quantitative yield, using platinum oxide in hydrochloric acid. A previous report of the preparation of 3-aminopiperidine from 2,5-diaminopyridine using 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*).

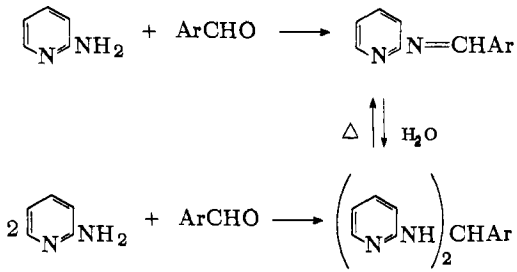
d. Reactions with Aldehydes and Ketones

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,

1-(6-alkoxy-3-pyridylamino)glucose sulfonates are formed (*186*). Both series of compounds are reported to be active against tuberculosis.

e. Acylation

(a) Carbonyl Derivatives. The acylation of the aminopyridines usually proceeds in a normal manner. For example, 2-aminopyridine (*187*) and 3-amino-2,6-lutidine (*188*) are formylated by formic acid; the 3-methyl and 3-ethyl derivatives of 2-aminopyridine are formylated by the action of acetic anhydride upon their formic acid salts (*22,189,190*).

Acetylation has been accomplished by the action of acetic anhydride, alone or in a solvent such as acetic acid, benzene, or ligroin (*54*). Thermal decarboxylation of *N*-(5-halo-2-pyridyl)malonamic acid yields the corresponding 2-acetamido-5-halopyridines (*191*).

2-Amino-3-ethoxypyridine could be acetylated with ketene in ether solution, but not with acetic anhydride in refluxing benzene; acetic anhydride at 215° gave a 2-diacetamido derivative (*106*).

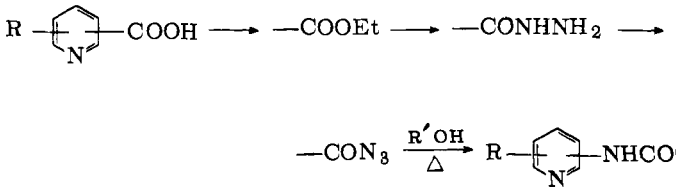
6-Amino-5-ethyl-3-picoline is also reported to yield a diacetamido derivative (*192*).

2-Haloacetamidopyridines (*193,194*) and 4-bromoacetamidopyridine (*178*) have been prepared by the use of haloacetyl halides in pyridine solution.

Fusion of 2-amino-6-bromopyridine and glycolic acid yields the 2-hydroxyacetamido derivative (*195*).

The preparation of the higher alkanoyl derivatives of 2-aminopyridines has been accomplished by two procedures. Fusion of the acids with a slight excess of 2-aminopyridine at 200–10° gives the amides in 50–70% yields (*196*). Bis(2-pyridyl)carbodiimide and the fatty acid when fused at 180–200° give comparable yields of the amides (*746*). A series of 3-acylamido-6-alkoxypyridines, prepared by "the usual methods," are described in two patents (*197,198*).

N-Carboalkoxy derivatives of aminopyridines are readily obtained by the action of chloroformic esters in benzene solution (*199*) or in alkaline solution (*117*). Before the aminopyridines had become readily available, these urethans were generally prepared by the Curtius reaction (IX-8). A variety of alkyl- and halogen-substituted

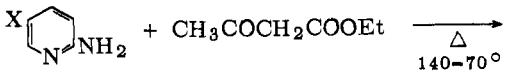


(IX-8)

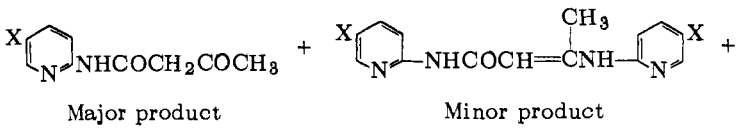
pyridinecarboxylic acids have been converted into urethans by this procedure (*72,74,200*).

N-Pyridylmalonamic esters have been obtained from monoalkyl malonyl chloride and 2- and 4-aminopyridines (*781,201,202*). The action of diethyl malonate upon 2-aminopyridine at 165–95° yields a pyridopyrimidine derivative (*191,203*). The 5-halo derivatives of 2-aminopyridine, under the same conditions, yield only the non-cyclic products, ethyl *N*-(5-halo-2-pyridyl)malonamate and *N,N'*-di-(5-halo-2-pyridyl)malonamide, the former predominating. 2-Amino-5-nitropyridine and the 2-amino-3,5-dihalopyridines fail to react under these conditions (*191*).

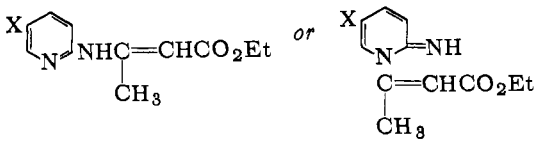
The reaction of ethyl acetoacetate and 2- and 3-aminopyridines gives low yields of the corresponding acetoacetamidopyridines (*204, 205*). Ethyl benzoylacetate reacts in a similar manner (*178,205*).



X = Cl, Br, I



Major product Minor product



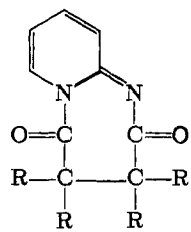
Minor product

(IX-9)

The 5-halo-2-aminopyridines and ethyl acetoacetate give a mixture of products when the reactants are heated at 140–70° (*206,207*). When the reaction is carried out with 2-amino-5-iodopyridine in ethanol in the presence of sulfuric acid as catalyst, ethyl 1,2-dihydro-2-imino-5-iodo-β-methyl-1-pyridineacrylate is formed in fair yield (*207*) (IX-9).

2-Aminopyridine (*208*) and 3-amino-6-butoxypyridine (*209*) react with succinic anhydride in ethanol to yield the *N*-(2-pyridyl)-succinamic acid derivatives. Treatment of the former compound with acetic anhydride yields *N*-(2-pyridyl)succinimide (*208*). *N*-Pyridylsuccinimide and -glutarimide derivatives are also obtainable directly from the anhydride (*210*). α-Methyl-β-dodecylsuccinic anhydride and 2-aminopyridine react similarly to yield an *N*-(2-pyridyl)succinamic derivative of unknown structure (*211*).

The reaction of tetramethyl-, tetraethyl-, and diethyldimethylsuccinic anhydrides with 2-aminopyridine is reported to yield bicyclic products of the structure IX-10 (*747*).



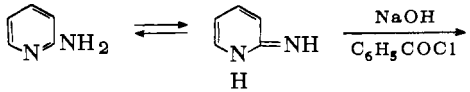
(IX-10)

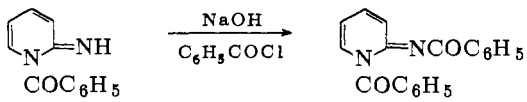
Diethyl azodicarboxylate and 2-aminopyridine react, depending on the experimental conditions, to yield either the mono- or di-*N*-(3-pyridyl)amide of azodicarboxylic acid (*213*).

Physical properties of the aliphatic acylaminopyridines are summarized in Tables IX-78, IX-79, IX-81, IX-84, and IX-87 (pp. 137 *et seq.*).

The benzoylation of 2-aminopyridine has been studied since 1894, but the mechanism of the reaction and the nature of the products remain points of controversy to the present day. In 1948, Huntress and Walter (*748*) reviewed the older literature and re-

solved some of the discrepancies. They found that under Schotten-Baumann conditions, 2-aminopyridine and benzoyl chloride yielded a dibenzoyl derivative, to which they ascribed the 2-(dibenzoylamino)pyridine structure. Hydrolysis with ethanolic sodium carbonate gave 2-benzamidopyridine, which was also prepared by the action of benzoic anhydride upon 2-aminopyridine in ether solution. The structure of the latter compound was proved by its preparation from *syn*-phenyl-2-pyridyl ketoxime by the Beckmann rearrangement, using thionyl chloride. However, Angyal *et al.* (*214*) disagree with the 2-(dibenzoylamino)pyridine structure. They were unable to introduce a second benzoyl group into 2-benzamidopyridine under Schotten-Baumann conditions, proving that it could not be an intermediate in the formation of the dibenzoyl derivative which they accordingly formulate as the *N,N'*-dibenzoyl derivative of 1,2-pyridonimine (IX-11). The definitive characterization of the dibenzoyl





(IX-11)

derivative of 2-aminopyridine must, however, await the preparation of either 2-(dibenzoylamino)pyridine or 1-benzoyl-2-benzoylimino-1,2-dihydropyridine by an independent synthesis not complicated by the tautomerism inherent in the 2-aminopyridine structure.

2-Benzamidopyridine may be prepared from 2-aminopyridine and benzoyl chloride in good yield by the use of pyridine as an acid binder or solvent (*215*). This technique has been applied to many substituted benzoyl chlorides (*216–221*).

2-Aminopyridine, when treated with the phenyl esters of benzoic acid and salicylic acid in 1-methylnapthalene at 200–30°, yields 2-benzamido- (*222*) and 2-salicylamidopyridine (*223,224*), respectively. The methyl ester of *N*-(4-sulfamylphenyl)glycine and 2-aminopyridine at 180° yield the *N*-(2-pyridyl)glycinamide derivative (*225*).

A variety of heterocyclic acid chlorides and esters have been reacted with 2-aminopyridine to yield the amides, which are listed in Table IX-80 (p. 139).

The reaction of phthalic anhydride and 2-aminopyridine by direct fusion or in a solvent may yield either the *N*-(2-pyridyl)-phthalamic acid or *N*-(2-pyridyl)phthalimide (*120,208,227*), which are easily separable by alkali extraction. Fusion of phthalimide or thiophthalic anhydride with 2-aminopyridine similarly yields *N*-(2-pyridyl)phthalimide (*224*), which may also be obtained from potassium phthalimide and 2-chloropyridine (*208*).

The action of aromatic acid chlorides upon 3-aminopyridine and its derivatives leads to 3-aroylaminopyridines readily and in good yield, without the complications presented by the 2-isomer (*cf.* Table IX-85, p. 143). Phthalic anhydride yields either the *N*-(3-pyridyl)-phthalamic acid or *N*-(3-pyridyl)phthalimide derivatives (*209,228*).

The aroyl derivatives of 4-aminopyridine are but little known at the present time. Fusion of 4-aminopyridine and phthalic anhydride yields *N*-(4-pyridyl)phthalimide (*120*). The nicotinoyl derivative of 4-aminopyridine has been prepared (*229*). *Cf.* Table IX-87 (p. 144).

Acyl derivatives of 2-aminopyridines, such as 2-acetamidopyridine (*230,231*), its 5-iodo derivative (*232*), and 2-benzamidopyridine (*230*), are converted to the corresponding thioamides by the action of phosphorus pentasulfide in a neutral high-boiling solvent, such as xylene. 2-Chloro-5-nitropyridine and thioacetamide react to yield 5-nitro-2-thioacetamidopyridine (*233*).

The acylamidopyridines have not been widely applied as synthetic intermediates, since in most cases the free amino derivatives serve equally well. Bromination of 2-acetamidopyridine in water solution yields the 5-bromo derivative (*234*). 2-Acetamido-4,6-lutidine is brominated to the 5-derivative by *N*-bromosuccinimide in the presence of benzoyl peroxide (*235*).

2-Acetamidopyridine is very resistant to nitration. Under mild conditions the nitrate salt is obtained, while more strenuous conditions result in deacetylation, with the formation of the 3- and 5-nitro derivatives. The same result is obtained by the nitration of the free amine (*234*). However, ethyl *N*-(2-pyridyl)carbamate is nitrated

with nitric acid–sulfuric acid to the 5-nitro derivative, while ethyl *N*-(3-pyridyl)carbamate is converted to ethyl *N*-(2-nitro-3-pyridyl)-carbamate in good yield (*236*).

Neither 2-acetamidopyridine nor its methiodide can be converted into an *N*-nitroso derivative (*237,238*), but 3-acetamidopyridines (*238*) and 3-*i*-butyramidopyridine (*239*) undergo this reaction successfully. These latter compounds on heating in benzene solution yield the 3-phenylpyridine derivatives.

2-Acetamido-5-nitropyridine is reported resistant to reduction under conditions that convert 2-amino-5-nitropyridine to 2,5-diaminopyridine (*240*).

2- and 3-Acetamidopyridines (*241*) and 2-benzamidopyridine (*242*) readily yield stable methiodides.

2-Benzamido- and 2-*p*-methoxybenzamidopyridines are converted to their sodium salts by the action of sodium amide. Subsequent reaction with dialkylaminoalkyl halides yields the *N*-dialkylaminoalkyl derivatives (*243*).

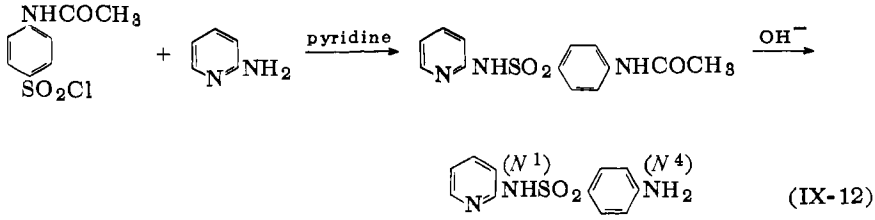
(b) Sulfonyl Derivatives. Alkylsulfonyl halides react normally with 2-aminopyridine in refluxing benzene or acetone solution (*244*); other amines have not been reported. In a study of pantoyltauramides as possible antimalarials, a series of 2-(*N*-benzamidoalkylsulfonamido)-, 2-(*N*-*o*-carboxybenzamidoalkylsulfonamido)-, 2-(*N*-phthalimidoalkylsulfonamido)-, 2-aminoalkylsulfonamido-, and 2-(*N*-pantoylamidoalkylsulfonamido)pyridines were prepared for testing (*245–248*). The corresponding 5-chloro- and 5-bromo-2-pyridyl derivatives were also prepared (*247,248*). *Cf.* Table IX-82 (p. 140).

2-Aminopyridine reacts normally with β-styrylsulfonyl chloride in benzene–pyridine (*749*) and with the *d-*, *l-*, and racemic forms of β-camphorylsulfonyl chloride (*750*), while sulfur trioxide in methylene chloride yields 2-pyridylsulfamic acid (*249*).

In contrast to the alkylsulfonamido derivatives, a voluminous literature exists on the chemistry of arylsulfonamidopyridines. Of these, by far the largest number are derivatives of 2-(4′-aminobenzenesulfonamido)pyridine (sulfapyridine), which was the first heterocyclic derivative of sulfanilamide to be synthesized. Its outstanding curative effect in pneumonia spurred intensive study not only on new pyridine derivatives, but on the other heterocyclic nuclei

as well. Sulfapyridine has now been displaced by other less toxic sulfa drugs, and by the broad-spectrum antibiotics. A history of the development of the sulfa drugs and a compilation of substituted sulfapyridines are given in Northey's extensive monograph (*250*); the present review is accordingly limited to sulfonamidopyridines which are *not* sulfanilamide derivatives (*cf.* Tables IX-83, p. 141, and IX-86, p. 143).

The reaction of 2-aminopyridine with arylsulfonyl chlorides has been accomplished under a variety of experimental conditions. Under Schotten-Baumann conditions, only the 2-arylsulfonamido derivative is obtained, in contrast to the dibenzoyl derivative discussed previously. This is primarily due to the lability of the second arylsulfonyl group in the presence of hydroxylic solvents, especially under strongly alkaline conditions. Angyal *et al.* (*752*) have isolated a bis-*p*-toluenesulfonyl derivative from 2-aminopyridine by carrying out the reaction in acetone solution in the presence of sodium bicarbonate. Mere recrystallization from ethanol removed one tosyl group to give the 2-*p*-toluenesulfonamidopyridine. The use of pyridine as a solvent and acid acceptor leads directly to the 2-arylsulfonamidopyridines. This is the usual method employed in the synthesis of sulfapyridine from *p*-acetamidobenzenesulfonyl chloride and 2-aminopyridine. The N^4-acetyl derivative is then hydrolyzed to the sulfa drug under alkaline conditions (IX-12).



(IX-12)

Sulfapyridine

A number of miscellaneous procedures for the preparation of sulfapyridine are described in Northey's monograph (*250*). Most of these were designed to avoid patents covering the synthesis of sulfapyridine, and are of little practical value.

The methylation of sulfapyridine with diazomethane yields a

mixture of the N^1-methyl (70%) and ring-methylated (30%) derivatives (*252*). Angyal and Warburton (*253*) were unable to repeat this work, but by using N^4-acetylsulfapyridine, and hydrolyzing the reaction product with ethanolic sodium hydroxide, they were able to isolate the N^1-methyl derivative in low yield. By the use of dimethyl sulfate and alkali, the latter authors were also able to isolate the ring-nitrogen methylated derivative, 1-methyl-2-sulfanilimido-1,2-dihydropyridine, in good yield; see also Kelly and Short (*751*). Their paper discusses the application of ultraviolet absorption spectra to the study of the parent sulfapyridine and the two methylated derivatives.

The reaction of sodium sulfapyridine and ω-halo aliphatic esters yields products whose properties "indicate a pyridonimine structure" (*255*).

Sulfapyridine and ethyl chlorocarbonate react in pyridine to yield a carbethoxy derivative of unspecified structure (*256*).

The unequivocal synthesis of N^1-substituted sulfapyridines may be accomplished by the action of 4-acetamidobenzenesulfonyl chloride upon the substituted amino derivative followed by hydrolysis (*252,257*). Similarly, 1-alkyl-1,2-dihydro-2-pyridonimines may be converted to 1-alkyl-2-sulfanilimido-1,2-dihydropyridines (*258*).

The preparation of arylsulfonyl derivatives from 3-aminopyridine and its derivatives offers no difficulty, and a large variety of alkyl-, (*259–261,797*), alkoxy- (*262,263*), carbethoxy-, carbamoyl- (*264*), dialkylamino- (*265*), and halo- (*263,266,267*) substituted 3-sulfanilamidopyridines have been reported.

4-Aminopyridine behaves like the 2-isomer in the synthesis of sulfanilyl derivatives (*269–271*).

(c) Ureas, Thioureas, Guanidines, Amidines, and Carbodiimides. 2-Pyridylurea was first prepared by Fischer (*28*), by heating an aqueous solution of 2-aminopyridine hydrochloride and potassium cyanate. However, Gerchuk and Taĭts (*272*) obtained 1-(2-pyridyl)-biuret by this procedure, and 2- and 3-pyridylureas by the fusion of the aminopyridines and urea.

The action of potassium cyanate upon the acid solutions of 2-carboxy (*273*) and 4-carboxy (*274*) derivatives of 3-aminopyridine gives the corresponding urea derivatives in good yield.

The action of alkyl and aryl isocyanates upon a wide variety of

substituted 2- and 3-aminopyridines yields the expected mixed urea derivatives (see ref. *803* for typical examples).

Symmetrical dipyridylureas have been obtained by the action of phosgene upon the aminopyridine (*54,272*), by fusion of ethyl urethane (*272*) or urea (*272,275*) with the aminopyridine, and by heating pyridyl isocyanates and pyridylcarbonylazides in the presence of a little water (*70,72*).

The action of mercuric oxide upon 1,3-bis(2-pyridyl)thiourea yields the urea derivative (*275*).

Pyridylthioureas may be prepared by the action of carbon disulfide or thiophosgene upon aminopyridines under alkaline conditions, or in general by reactions analogous to the preparation of the ureas themselves (*28,54,275,276*).

Pyridylurea and -thiourea derivatives are summarized in Tables IX-88 to IX-90 (pp. 145 f.).

Hydrazinopyridines are readily converted into semicarbazides by treatment with potassium cyanate and acid (*277*), or by heating aminopyridines with acetone semicarbazone, followed by acid hydrolysis (*182*). Many more thiosemicarbazides are known; they are prepared from hydrazinopyridines by reaction with thiocyanates and acid (*278*) or with alkyl and aryl isothiocyanates (*277,279*). The reaction of 2-aminopyridine, carbon disulfide, and potassium hydroxide yields the potassium salt of *N*-2-pyridyldithiocarbamic acid, which on treatment with hydrazine in warm water, gives 4-(2-pyridyl)thiosemicarbazide (*280*).

N-(Pyridyl)amidines have been prepared from the aminopyridines by reaction with iminoether hydrochlorides (*281*), fusion with nitriles in the presence of aluminum chloride (*282,283*), or refluxing with nitriles in the presence of sodium in benzene solution (*284*). Treatment of α-alkylamino-α,α-dichloromethylfuran with aminopyridines yields the *N*-pyridyl-*N'*-furylamidine derivatives (*285*). *Cf.* Tables IX-92 (p. 147) and IX-97 (p. 151).

Symmetrical *N,N'*-dipyridylformamidines are readily prepared from the aminopyridine derivatives by refluxing with ethyl orthoformate (*285–287*). (*Cf.* Table IX-92, p. 147.) *N,N'*-Bis(5-iodo-2-pyridyl)acetamidine has been prepared by the action of phosphorus pentoxide (*231*) or phosphorus pentasulfide (*232*) upon 2-acetamido-5-iodopyridine.

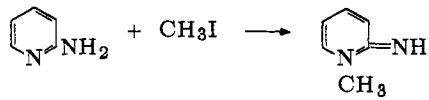
The action of cyanogen upon 2-aminopyridine gives *N*-(2-pyridyl)cyanoformamidine or *N,N'*-bis(2-pyridyl)oxamidine, depending on the reaction conditions employed. The 3-, 4-, and 5-methyl derivatives of 2-aminopyridine gave only the cyanoformamidines, while 6-amino-2-picoline gave only the oxamidine (*289*).

N-(2-Pyridyl)-*N'*-alkyl- or -arylthioureas and *N,N'*-bis(2-pyridyl)-thioureas yield guanidine derivatives when heated with amines in a solvent in the presence of mercuric oxide (*279*) or basic lead carbonate (*288,290*). The action of 2-aminopyridine and its 5- and 6-methyl derivatives upon 1-methyl-1-nitroso-3-nitroguanidine gives rise to the corresponding 1-(2-pyridyl)-3-nitroguanidines (*291*). *Cf.* Table IX-91 (p. 147).

Refluxing a toluene solution of *N,N'*-bis(2-pyridyl)thiourea with litharge yields *N,N'*-bis(2-pyridyl)carbodiimide (*292*).

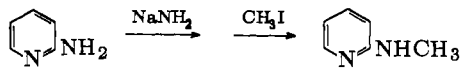
f. Preparation of Secondary and Tertiary Amines

When aminopyridines are treated with alkyl halides, alkyl sulfates, or diazomethane, the expected alkylaminopyridines are obtained in poor yield. The major product is usually a pyridonimine derivative, the result of reaction with the ring nitrogen (IX-13).



(IX-13)

By carrying out the reaction in the presence of sodamide, however, Chichibabin *et al.* (*146*) were able to obtain the desired 2-methylaminopyridine in good yield (IX-14). Other alkyl and dialkylamino

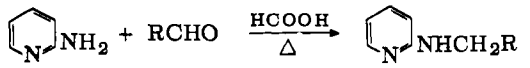


(IX-14)

derivatives have been prepared in a similar manner (*804*). The reaction of sodio-2-aminopyridine with styrene oxide gave 2-hydroxy-2-phenylethylaminopyridine (*805*).

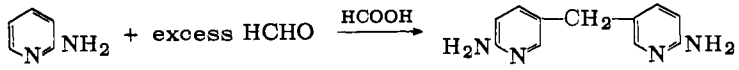
These reactions have also been carried out by replacing the sodamide with potassium methoxide, sodium methoxide (*293*), lithium amide (*294*), and potassium amide (*295*).

The amine nitrogen may also be subjected to reductive alkylation with a carbonyl compound in the presence of formic acid, usually in favorable yields. For example, benzaldehyde gave 2-benzylaminopyridine in 90% yield (*187*), while a series of other aromatic and heterocyclic aldehydes gave 76–96% yields (*174*) (IX-15). When



(IX-15)

a large excess of formaldehyde was used (*168*), the dipyridylmethane (IX-16) was formed, however.



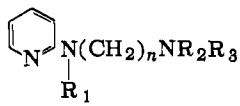
(IX-16)

Alkylation with alcohols in the presence of alumina at high temperatures has been reported in the patent literature (*318*) to give a mixture of monoalkyl and dialkylamines as well as pyridines and pyridonimines. With a large excess of methanol, the product was 2-dimethylaminopyridine in 70% yield. Similar results were reported with 4-aminopyridine.

2-Amino-5-chloropyridine, sodium methoxide, and methanol in the presence of cupric sulfate at 300° resulted in about 50% yields of 2-methylaminopyridine (*297*).

Longer chain groups (propyl, butyl) have been placed on the amino nitrogen by the action of the appropriate alkyl *p*-toluenesulfonate ester on the sodium salt of the aminopyridine (*298*).

The great amount of work in the antihistamine field in the last ten to fifteen years resulted in the preparation of a large number of alkylaminoalkylaminopyridines (IX-17). Many of these compounds



(IX-17)

were prepared by the reaction of the required dialkylaminoalkylamine with a halopyridine in the presence of potassium carbonate,

copper bronze (*299*), and sodium carbonate in refluxing cymene (*300*), or under other conditions (*302,303*). These reactions are more fully discussed on p. 31.

In contrast to alkylation, which requires the sodium salt of the amine, arylations can be performed on the base itself. Thus Chichibabin (*304*) reported that 2-aminopyridine and bromobenzene yielded 2-anilinopyridine under the conditions of the Ullman reaction. However, later workers (*305*) were not able to duplicate his results, but were successful when they substituted iodobenzene for the bromobenzene. 2-Anilinopyridine has also been prepared from 2,2-dichloro-1,2-dihydro-1-phenylpyridine (prepared from 2-pyridone and phosgene) and liquid ammonia (*306*), and from pyridine and the sodium salt of aniline (*7*).

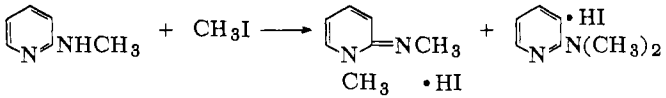
Other arylations have been carried out with α- and β-naphthols (*307*), 2,4-dichlorobenzoic acid (*308*), and 2,4-dinitrochlorobenzene (*309*). The attempted reaction between 2,4-dinitrobromobenzene and 2-amino-4-picoline failed under a wide variety of conditions (*310*).

The arylaminopyridines have also been made by the reaction of a halopyridine and the aromatic amine. These reactions may be catalyzed by potassium carbonate and copper (*311, 312*), potassium acetate (*313,314*), or zinc chloride (*28*), or performed without catalyst or added base (*312,315,316*).

Dialkylaminopyridines are formed by further alkylation of monoalkylaminopyridines. Some of the tertiary amine is almost always obtained in the monoalkylation of aminopyridines, but where excess of the alkylating agent is used, fair to good yields of the tertiary amine can be obtained. 2-Dimethylaminopyridine is thus formed in 65% yields from 2-aminopyridine and methyl iodide in the presence of sodamide (*317*), or in 70% yield by the use of a large excess of methanol in the presence of alumina at 360° (*318*). Alkylation with methyl sulfate (*319*) gives less satisfactory results.

2-Methylaminopyridine reacts with alkylating agents as does the parent 2-aminopyridine, in the absence of alkali. The main product (*146*) is the result of alkylation on the ring nitrogen, although some of the tertiary amine is formed (IX-18).

N,N-Bis(2-pyridyl)aniline has been prepared in 14% yield by the action of 2-bromopyridine on 2-anilinopyridine in mesitylene in the

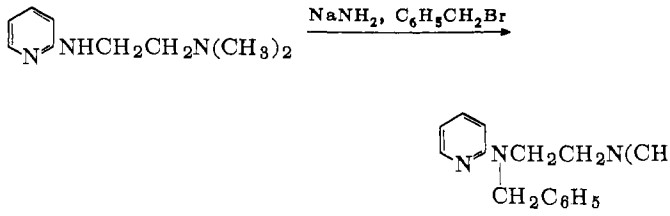


(IX-18)

Main product

presence of a copper catalyst (*316*). A 17% yield of 2-diphenylaminopyridine was obtained by the reaction between 2-bromopyridine and the sodium salt of diphenylamine (*30*).

Most of the known tertiary aminopyridines have been made in the search for new antihistamine agents. Many hundreds of these compounds have been prepared by similar procedures. A secondary aminopyridine is prepared by any of the previously described procedures and then alkylated, usually by conversion to an alkali metal salt followed by treatment with the required halide. The last step is illustrated for the synthesis of pyribenzamine (IX-19) (*301*), which



(IX-19)

Pyribenzamine

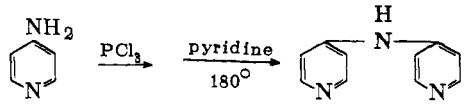
was found to counteract about fifty times its weight of histamine phosphate (*330*). Table IX-1 (p. 77) lists several additional antihistamine agents.

Lithium amide (*320*), sodium hydride (*321*), and potassium carbonate (*302,322,323*) have been used as well as sodium amide (*324,325*). Simpler tertiary amines have also been prepared by the action of secondary amines such as methylaniline on a halopyridine. These reactions (*312*) are catalyzed by copper or copper salts and potassium carbonate.

Bis-(2-pyridyl)amine has been synthesized by the reaction between 2-aminopyridine and its hydrochloride (*326*), and from 2-chloropyridine and 2-aminopyridine in the presence of zinc chloride (*326,327*).

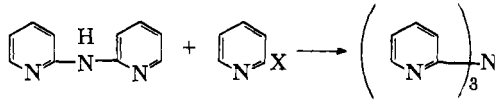
The 4-amino analog has been prepared (*328*) by the treatment of 4-aminopyridine with phosphorus trichloride followed by refluxing

in pyridine (IX-20). This reaction is analogous to the preparation of diphenylamine from aniline and phosphorus trichloride (*753*). 2-Aminopyridine fails, however, to undergo this reaction.



(IX-20)

The tripyridylamine (IX-21) can be prepared from bis-2-pyridylamine and a 2-halopyridine (*329*).



(IX-21)

Secondary and tertiary aminopyridines are listed in Tables IX-24 to IX-40 (pp. 89 ff.).

In addition to alkylation, the secondary aminopyridines undergo the usual reactions of secondary amines, such as arylation and nitrosation.

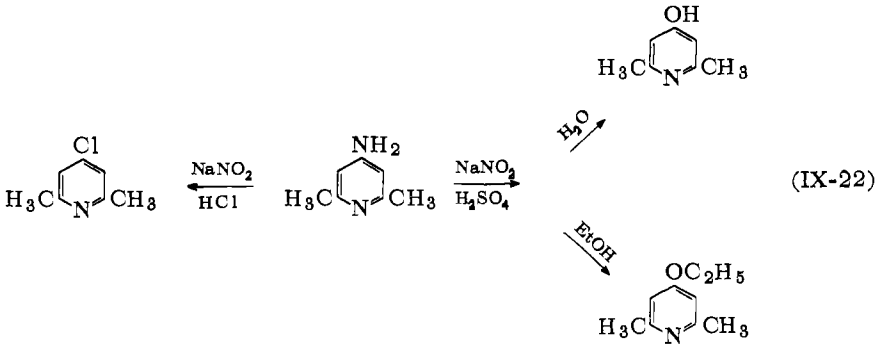
g. Diazotization Reactions

(a) **Diazotization and Replacement.** 2-Amino- and 4-aminopyridines can be diazotized only in the presence of a strong acid. In weak acid, these amines apparently go directly to the hydroxy compound (*33*).

Marckwald (*41*) diazotized 4-amino-2,6-lutidine in concentrated hydrochloric acid and obtained the 4-chloro compound. On diazotization in concentrated sulfuric acid, followed by treatment with water or ethanol, he obtained the corresponding 4-hydroxy or 4-ethoxy compounds, respectively (IX-22). 2-Methyl-, 2,6-dimethyl-, and 2,6-dichloro-4-aminopyridines can be readily diazotized and the diazo group replaced by halogen, cyano, or thiocyano groups in low yield (*806*).

Chichibabin and Rjazancev (*331*) treated 2-aminopyridine with concentrated hydrochloric acid and obtained no more than 50% of 2-chloropyridine. In concentrated hydrofluoric acid, 2-fluoropyridine was obtained in but 25% yield.

2,6-Diaminopyridine is nitrosated and not diazotized, giving 2,6-diamino-3-nitrosopyridine (*332*). The diamine does, however, couple



(IX-22)

readily with a large number of diazonium compounds (*333–340*). 2,3-Diaminopyridine and 2,5-diaminopyridine are diazotized at the 3- or 5-amino group (*341*).

Like aniline and its derivatives, 3-aminopyridine, on diazotization and subsequent treatment with copper or a cuprous salt plus the appropriate halide, gives (*276*) 3-fluoro- (22%), 3-chloro- (65%), 3-bromo- (56%), or 3-iodopyridine (50%). Some other conversions are shown in Table IX-2 (p. 77).

The 2-amino- and 4-aminopyridines, once diazotized in strong acid, may also be converted to the various halo derivatives. Of particular interest is the procedure developed by Craig (*342*) for the preparation of 2-bromopyridine from 2-aminopyridine by diazotization in hydrobromic acid solution in the presence of excess bromine. Yields of up to 87% were obtained when at least two moles of bromine were used. Whitmore *et al.* (*343*) noted that if the temperature of this reaction was allowed to rise to 10°, a 10% yield of 2,5-dibromopyridine was also obtained. The chloro compounds, as was noted above, can be prepared by diazotization of the amine in concentrated hydrochloric acid. The conversion of several 2-aminopyridines to 2-halopyridines is listed in Table IX-3 (p. 78). *Cf.* Chapter VI (p. 334).

Table IX-4 (p. 79) lists the conversion of several representative pyridinediazonium compounds to the hydroxy compounds, generally by diazotization in sulfuric acid followed by dilution or heat (*cf.* Chapter XII, pp. 585 ff.).

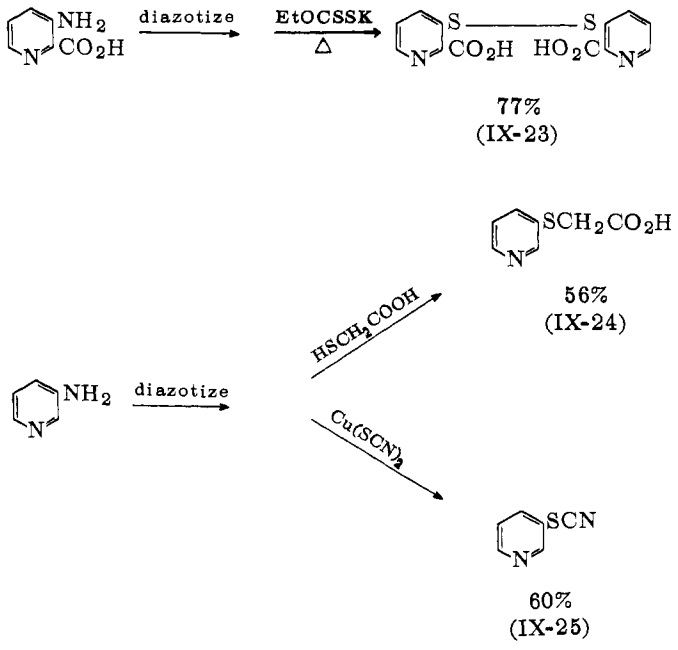
Although a number of 3-aminopyridine compounds have been converted to the corresponding nitriles in fair yield via the Sand-

meyer reaction, there are no reports of a similar conversion of either 2-aminopyridines or 4-aminopyridines. Some of the reagents used in these reactions are shown in Table IX-5 (p. 79).

(b) Reduction. Like benzenediazonium compounds and by similar procedures, the pyridinediazonium analogs can be deaminated or reduced to the hydrazine. The reduction to the hydrazine is carried out with stannous chloride in the presence of hydrochloric acid. 3-Aminopyridine thus gave 3-hydrazinopyridine in 60–70% yield (*276*). Similarly reduced were the diazonium salts of 5-amino-2-chloropyridine (*356*) and 3-amino-5-bromopyridine (*33*).

The deamination reaction has been effected with ethanol (*352*) on diazotized 4-amino-3-pyridinesulfonic acid, and with hypophosphorous acid on diazotized ethyl 5-amino-2-methylnicotinate (*6*) in 62% yield.

Other replacements, generally analogous to procedures in benzene chemistry, have been reported. Potassium ethyl xanthate (*357*) gives the disulfide (IX-23), mercaptoacetic acid (*358*) gives pyridylmercaptoacetic acid (IX-24), and copper thiocyanate gives 3-thiocyanopyridine (IX-25).



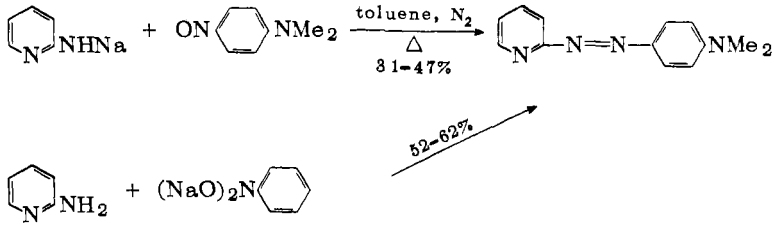
The Bart reaction has given the expected arsonic and stibonic acids (*88,359–362*). These reactions fail, however, when the aminopyridine is unsubstituted (*276*). The Bart-Scheller reaction has also been successfully applied to aminopyridines (*363*).

(c) **Coupling.** Diazotized 2-aminopyridine does not couple with aromatic amines or phenols. Diazotized 3-aminopyridines do, however, couple with a variety of amines and phenols to give the corresponding azo compounds. Thus naphthol gives a dark red dye (*276*), and dimethylaniline gives a yellow-red dye (*276*).

There are two reports (*117,352*) of coupling reaction between diazotized 4-aminopyridines and resorcinol, dimethylaniline, and *m*-phenylenediamine to give dyes. Other methods have been generally employed to prepare both the 2- and 4-arylazopyridines.

2,6-Dimethyl-4-phenylazopyridine was prepared by the oxidation, with mercuric oxide (*296*), of 2,6-dimethyl-4-phenylhydrazinopyridine. Similar oxidations of 4-hydrazino derivatives have been carried out with air (*364,365*) or potassium ferricyanide (*365*).

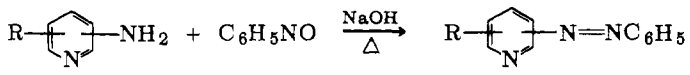
Faessinger and Brown (*366*) developed an interesting approach to the preparation of 2- or 4-arylazopyridines. The sodium salt of the aminopyridine reacts with 4-nitrosodimethylaniline in refluxing toluene to yield the 2-(4-dimethylaminophenylazo)pyridine (IX-26). Alternatively, the disodium salt of 4-nitrodimethylaniline reacts with 2-aminopyridine to give the same product (IX-26).



(IX-26)

These procedures served equally well for 4-aminopyridines, but an attempt to apply the reaction to 3-aminopyridine was unsuccessful.

Similarly, Campbell *et al.* (*156*) reacted a number of 2-, 3-, and 4-aminopyridines with nitrosobenzene in the presence of alkali to give the corresponding phenylazopyridines (IX-27).



(IX-27)

This reaction failed with 2,6-diaminopyridine. Some of the products that were obtained are shown in Table IX-6 (p. 80). The yields reported here were substantially better than those obtained by Faessinger and Brown.

Azopyridines are discussed in detail in Chapter VIII (pp. 483 ff.) and are tabulated in Tables IX-45 to IX-49 (pp. 108 ff.).

h. Nuclear Substitution Reactions

(a) Halogenation. In contrast with pyridine itself, aminopyridines halogenate very readily, and the halogen derivatives thus obtained are useful intermediates for synthesis. Their physical properties are summarized in Tables IX-13 to IX-19 (pp. 83 ff.).

Chlorination of 2-aminopyridine in ice-cold ethanol gives 2-amino-5-chloropyridine in 68% yield (*367*). Continued chlorination under these conditions gives 2-amino-3,5-dichloropyridine in 75% yield. The structure of the monochloro derivative was proved by its preparation from 2,5-diaminopyridine by the Sandmeyer reaction (*341*). 6-Amino-3-nitro-2-picoline yields the 5-chloro derivative (*91*).

Bromo derivatives of 2-aminopyridine were first obtained as by-products from the Hofmann reaction of 2-picolinamide and potassium hyprobromite (*54*). The 2-aminopyridine initially formed was probably brominated by excess hypobromite. The reported melting points indicate that the 5-bromo and 3,5-dibromo derivatives of 2-aminopyridine were present. The bromination of 2-aminopyridine in 20% sulfuric acid solution also gives a mixture of the 5-bromo and 3,5-dibromo derivatives (*368,369*). Extraction of the reaction product with petroleum ether removes the more soluble dibromo compound. Bromination in cold ethanol gives slightly lower yields (46 against 59%) of the 5-bromo derivative (*348,370*). Excess bromine in dilute sulfuric acid solution gives 2-amino-3,5-dibromopyridine in 90% yields (*371*). Bromination at 500° gives a 25% yield of brominated derivatives, 55–75% of which consists of equal parts of

the 3-, 5-, and 6-bromo-2-aminopyridines (*372*). 2-Acetamidopyridine brominates in the 5 position (*23,234*).

Nuclear alkyl derivatives brominate normally. 2-Amino-4-ethylpyridine in 20% sulfuric acid yields the 3,5-dibromo derivative (*373*), while 2-amino-4,6-lutidine with bromine in acetic acid or with *N*-bromosuccinimide in chloroform also yields the 3,5-dibromo derivative (*235*). The latter reagents convert 2-acetamido-4,6-lutidine to the 5-bromo derivative in quantitative yield (*235*). 6-Amino-2-picoline gives the 3-bromo and 3,5-dibromo derivatives (*351*).

2-Alkylaminopyridines are also readily brominated. 2-Methylaminopyridine yields a 5-bromo derivative and the 3,5-dibromo derivative (*371*). 2-Dimethylaminopyridine behaves similarly (*319*). The monobromo derivative was shown to be 2-dimethylamino-5-bromopyridine by the methylation of 2-amino-5-bromopyridine with dimethyl sulfate in the presence of sodamide.

Den Hertog (*53,126*) has prepared all of the possible bromo derivatives of 2-amino- and 4-aminopyridines.

Bromination of 2-acetamido-3,5-diethoxypyridine in acetic acid gives the 6-bromo derivative (*374*).

Nitro derivatives of 2-aminopyridines have been successfully brominated. Among compounds so prepared are 2-amino-3-bromo-5-nitropyridine (*375*), 2-amino-5-bromo-3-nitropyridine (*375*), 6-amino-5-bromo-3-nitro-2-picoline (*91*), 2-methylamino-3-bromo-5-nitropyridine, and 2-methylamino-5-bromo-3-nitropyridine (*376*).

The action of bromine upon 2-amino-5-pyridinesulfonic acid in water solution yields the 3-bromo derivative (*377*).

The iodination of 2-aminopyridine has been carried out under a wide variety of experimental condition. The most convenient procedure for the preparation of 2-amino-5-iodopyridine appears to be that of Caldwell *et al.* (*23*), who added iodine to an aqueous solution of 2-aminopyridine and, after addition of potassium hydroxide, obtained the iodo derivative in 90% yield. Iodination in aqueous solution in the presence of mercuric acetate gives a 60% yield, while the use of two moles of iodine gives a 20% yield of 2-amino-3,5-diiodopyridine (*767,378*). The action of alkaline agents upon the 2-aminopyridine–iodine monochloride adduct yields the 5-iodo derivative (*379,380*). Iodine in the presence of hydrogen peroxide or po-

tassium iodide gives a periodide of 2-aminopyridine, which yields the 5-iodo derivative upon treatment with potassium hydroxide solution (*381,382*). The same product may be obtained by electrolysis in aqueous iodide solution (*383*) or iodination over pumice at 510° (*384*).

2-Aminopyridine and a number of *N*-monoalkyl and *N,N*-dialkyl derivatives yield 5-iodo derivatives when their iodine monochloride adducts are treated with alkali (*380*).

With 3-aminopyridines, halogenation is more difficult to control than with the 2-amino derivatives. Chlorination of 3-aminopyridine in hydrochloric acid solution yields primarily 3-amino-2,6-dichloropyridine together with a little 3-amino-2-chloropyridine. However, the action of hydrochloric acid and hydrogen peroxide upon 3-aminopyridine at 80° gives an 88% yield of 3-amino-2-chloropyridine and a little 3-amino-2,6-dichloropyridine. When this reaction is carried out at 110°, 3-amino-2-chloropyridine is still the main product, but 5.7% of 3-amino-2,6-dichloropyridine and 4% of 3-amino-2,4,5,6-tetrachloropyridine are also obtained. Both 2-chloro- and 6-chloro-3-aminopyridines are chlorinated to 3-amino-2,6-dichloropyridine by the action of hydrogen peroxide and hydrochloric acid at 80–90° (*152*).

Like picolinamide, nicotinamide yields a dibromoamine as a by-product when treated with potassium hypobromite (*54*). The same product appears to be formed by the action of bromine upon 3-aminopyridine in methanol solution (*385*), and by the action of hydrogen peroxide and hydrobromic acid upon 3-aminopyridine (*152*). This compound is assigned the structure 3-amino-2,6-dibromopyridine, but no proof is available. A tribromo derivative (2,4,6-?) is also obtained by the bromination of 3-aminopyridine in ethanol (*385*).

5-Amino-2-chloro-6-methylnicotinonitrile is brominated to the 4-bromo derivative in excellent yield (*386*).

3-Aminopyridine and 3-aminopicolinic acid react with iodine monochloride in strong hydrochloric acid solution to give a low yield of 2,6-diiodo-3-aminopyridine. This structure was proved by reductive deamination to a diiodo derivative, which, upon ammonolysis, gave 2,6-diaminopyridine (*387*).

The chlorination and bromination of 4-aminopyridine do not appear to have been investigated. A dibromo-4-aminopyridine is obtained as a by-product from the reaction of isonicotinamide and potassium hypobromite (*54*). Bromination of 4-amino-2,6-lutidine in water yields the 3-bromo and 3,5-dibromo derivatives (*41*). Den Hertog (*53*) has studied the bromination of various mono- and dibromo derivatives of 4-aminopyridine, the bromine atoms always entering the 3 or 5 position, or both if excess bromine is used. The necessary brominated 4-aminopyridine intermediates were prepared by the preferential ammonolysis of the 4-bromo subtituent in the various polybromopyridine derivatives.

The bromination of 4-amino-3-nitropyridine in acetic acid gives the 5-bromo derivative (*388*).

The action of iodine chloride upon 4-aminopyridine in strong hydrochloric acid solution, followed by treatment with alkali, gives a mixture of the 3-iodo and 3,5-diiodo derivatives (*389,390*). 4-Amino-2,6-lutidine and iodine monochloride yield the 3-iodo derivative in hydrochloric acid solution, and the 3,5-diiodo derivative in acetic acid (*180*).

Halogenation is also discussed in Chapter VI (pp. 308, 316 f., 320 f.).

(b) Sulfonation. The sole sulfonation product of 2-aminopyridine, under a wide variety of experimental conditions, is 2-amino-5-pyridinesulfonic acid. The 3-sulfonic acid has not been reported. Among the conditions employed were 20% oleum at 140–45° for sixteen hours (70% yield) (*49*); concentrated sulfuric acid and a little oleum at 180–90° for five hours (60% yield) (*273*); 100% sulfuric acid and aluminum powder at 200–10° (60% yield) (*391*); and sulfuric acid in diphenyl sulfone at 250° for fifteen hours (32% yield) (*392*).

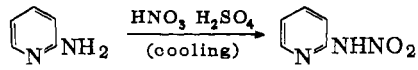
3-Aminopyridine is not sulfonated directly with sulfuric acid, but heating with chlorosulfonic acid gives 3-amino-2-pyridinesulfonic acid. This structure was proved by reductive deamination to 2-pyridinesulfonic acid, and by its nonidentity with 5-amino-2-pyridinesulfonic acid, prepared by an unambiguous method (*385,393*).

Heating 4-aminopyridine with a mixture of oleum and concentrated sulfuric acid at 275° for four hours gives 4-amino-3-pyridine-

sulfonic acid in excellent yield. Reductive deamination yields 3-pyridinesulfonic acid (*352*).

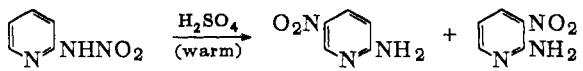
Sulfonation is also discussed in Chapter XV.

(c) **Nitration.** The nitration of 2- and 4-aminopyridine derivatives constitutes a most important synthetic reaction. The nitration proceeds in two distinct steps, as shown with 2-aminopyridine (IX-28). 3- and 4-Aminopyridines yield similar *N*-nitro derivatives.



(IX-28)

Warming a sulfuric acid solution of 2-nitraminopyridine to 27° results in exothermic rearrangement to the 3- and 5-nitro derivatives (1:8 ratio) (IX-29). If the rearrangement is carried out at a higher



(IX-29)

Major product Minor product

temperature, the amount of the 3-isomer is increased slightly (*273,394*). The behavior of 3- and 4-nitraminopyridines under these conditions will be discussed later (p. 50).

The 3- and 5-nitro derivatives of 2-aminopyridine are readily separated by steam distillation, the former compound being volatile while the latter is not (*273*). This technique is extremely useful in the separation of the isomers formed by nitration of 2-aminopyridines with both the 3 and 5 positions free. When either position is occupied by a stable group, the nitro group enters the free position exclusively.

The nitration of 2-acetamidopyridine gives 3- and 5-nitro-2-aminopyridine. 2-Nitraminopyridine can also be isolated, indicating that deacylation occurs before nitration (*234*). However, the nitration of ethyl 2-pyridylcarbamate gives a 46% yield of the 5-nitro derivative (*236*).

Pino and Zehrung (*396*) have prepared all of the possible mononitro derivatives of the four 2-aminopicolines. Separation of the 3- and 5-nitro isomers was accomplished by sublimation of a current of air at 120°. Surprisingly, the nitration of 2-amino-4,6-lutidine

gave 2-nitramino-5-nitro-4,6-lutidine as the sole isolated product (*397*). On the other hand, 6-amino-5-ethyl-2-picoline gave a mixture of 6-amino-5-ethyl-3-nitro-2-picoline and 6-nitramino-5-ethyl-2-picoline. Warming the nitramino derivative in sulfuric acid failed to effect a rearrangement of the nitro group (*398*).

2-Methylaminopyridine yields an *N*-nitro derivative, which rearranges in sulfuric acid to the 3-nitro and 5-nitro derivatives in a ratio of 1:10. A small amount of *N*-nitroso-2-methylaminopyridine was also formed (*376*). 2-Dimethylaminopyridine, which cannot form a nitramino derivative, nevertheless nitrated in high yield to a mixture of the 3- and 5-nitro derivatives in a ratio of 1:9 (*317,319*).

2-Amino-5-chloropyridine (*376,399*) and the corresponding 5-bromo compound (*368,370*) are easily nitrated to the 3-nitro derivatives. An attempt to isomerize 2-nitramino-5-iodopyridine to the 3-nitro derivative was unsuccessful (*382*). The nitration of 2-amino-3,5-dibromopyridine yields 2-amino-3-bromo-5-nitropyridine as a minor product, while the expected 2-nitramino derivative is obtained in good yield (*371*).

6-Aminonicotinic acid gives the 6-nitramino derivative with a cold mixture of nitric and sulfuric acids. Rearrangement to 6-amino-5-nitronicotinic acid requires heating in sulfuric acid at 100° for fifteen hours (*353*). 6-Amino-3-pyridinesulfonic acid nitrates readily in the 5 position (*377,273*).

2-Amino-5-nitropyridine, one of the rearrangement products of 2-nitraminopyridine, itself may be converted to a nitramino derivative. The rearrangement to 2-amino-3,5-dinitropyridine is very difficult, requiring heating in sulfuric acid at 150° (*394*). However, 2-nitramino-3-nitropyridine rearranges to 2-amino-3,5-dinitropyridine at room temperature in 90% yield.

The *N*-methylamino derivatives behave similarly (*376*). 2-Dimethylaminopyridine gives the 3,5-dinitro derivative (*319*).

Räth and Prange (*437,353*) have reported the formation of 2-pyridones in the rearrangements of 6-nitraminonicotinic acid and 2-nitramino-5-nitropyridine. Both of these nitramino derivatives require rather severe conditions to effect rearrangement, and the pyridones may arise by cleavage of nitrous oxide from the nitramino group.

4-Aminopyridine resembles the 2-derivative in its behavior to-

wards nitration. It forms an *N*-nitro derivative (*33*), which rearranges to 4-amino-3-nitropyridine upon warming in sulfuric acid (*33,388*). With two moles of nitric acid in sulfuric acid at 85–90°, 4-nitramino-3-nitropyridine is obtained. This compound is also formed by the nitration of 4-nitraminopyridine, but not from 4-amino-3-nitropyridine. Nitration at 170–75° gives 4-amino-3,5-dinitropyridine (*388*).

3-Aminopyridine forms an *N*-nitro derivative, but attempted rearrangement in warm sulfuric acid results in decomposition to 3-pyridinol (*400*). Treatment of 3-aminopyridine nitrate with fluorosulfonic acid or liquid hydrogen fluoride gave very low yields of mononitro derivatives of undetermined structure (*33*). Attempts to nitrate 3-acetamidopyridine likewise were fruitless (*401*), but ethyl 3-pyridylcarbamate gave a 61% yield of ethyl (2-nitro-3-pyridyl)carbamate (*236*), which can be hydrolyzed by mild alkaline treatment to 3-amino-2-nitropyridine. An attempt to nitrate 3-amino-2,6-lutidine was unsuccessful (*402*).

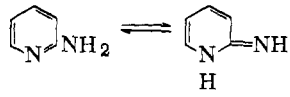
3-Methylaminopyridine yields an *N*-nitro derivative that rearranges in cold sulfuric acid to 3-methylamino-2-nitropyridine (*21*).

Physical properties of nuclear nitro derivatives of primary aminopyridines are summarized in Tables IX-20 to IX-23 (pp. 87 f.).

(d) Miscellaneous Substitutions of Aminopyridines. 2-Aminopyridine and 2-pyridone are claimed to yield 5-arsonic acid derivatives when treated with arsenic acid (*403*). Similarly, "mercuration" of 2-aminopyridine is said to yield the 5-substituted derivative (*404*), while the treatment of 4-aminopyridine with mercuric oxide in acetic acid, followed by the addition of sodium chloride, gave a mixture of 3-chloromercuri- and 3,5-bischloromercuri-4-aminopyridines (*807*). The chloromercuri substituents were readily replaced by bromine or iodine on treatment with the corresponding halogen in acetic acid solution. For a recent review of procedures for effecting substitution in the pyridine ring see Thomas and Jerchel (*794*).

i. Synthesis of Polycylic Systems

The aminopyridines have served as useful starting materials for the synthesis of condensed-ring heterocycles. The two reactive nitrogen centers in the tautomeric form (IX-30) of 2-aminopyridine



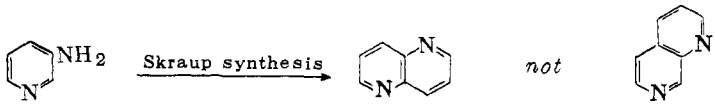
(IX-30)

(which may be considered as an amidine) make possible the formation of compounds containing a bridgehead nitrogen. Examples of these are the pyridopyrimidines and the pyridoimidazoles. Other types of heterocycles are formed by more conventional types of closures, either on the pyridine ring or a substituent on the ring.

The present discussion, which is supplemented by that (p. 64) of the conversion of diaminopyridines to condensed-ring heterocycles, is limited to heterocycles formed from monoaminopyridines or from diaminopyridines in which only one amino group is affected.

(a) **Naphthyridines.** The naphthyridines are among the best-known heterocyclic condensed-ring systems which are based on aminopyridines. Excellent reviews of their chemistry have been published (*405,406*).

1,5-Naphthyridines (IX-31) have been prepared from 3-aminopyridine in a Skraup reaction (*408,808*) using glycerin and sulfuric acid at 170°. It is interesting to note that this reaction does not give the isomeric 1,7-naphthyridine (IX-32). 3-Amino-2-chloropyridine

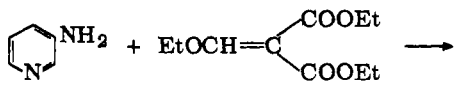


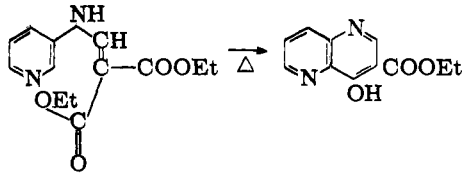
1,5-Naphthyridine (IX-31) 1,7-Naphthyridine (IX-32)

also gives 1,5-naphthyridine, the halogen being eliminated, but if the blocking group in the 2 position is not readily removable, no naphthyridine is formed.

In another procedure, due to Price and Roberts (*407*), the condensation product of 3-aminopyridine and diethyl ethoxymethylenemalonate is heated to give 3-carbethoxy-4-hydroxy-1,5-naphthyridine (IX-33).

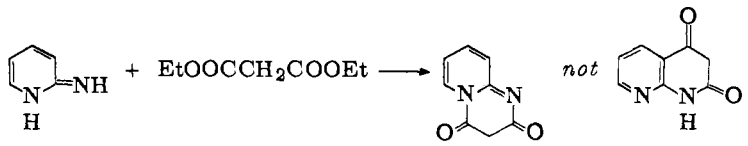
The 1,8-naphthyridines cannot generally be prepared from simple 2-aminopyridines. In this case, the amidine character of 2-aminopyridine becomes obvious and ring closure onto the ring





(IX-33)

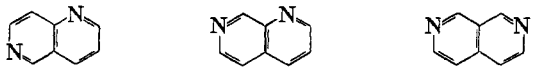
nitrogen is observed. Thus the reaction between 2-aminopyridine and diethyl malonate (*203*) gave the pyridopyrimidine (IX-34) and not the naphthyridine (IX-35).



(IX-34) (IX-35)

Lappin (*212,409*) has since shown that 1,8-naphthyridines are formed, however, from 6-substituted 2-aminopyridines by ring closure at the 3 position. With substituents in other positions of the pyridine ring, the pyridopyrimidine is again formed.

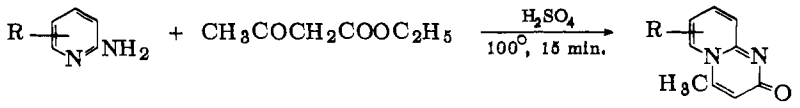
1,6-Naphthyridine (IX-36) has been prepared in seven steps from 4-aminopyridine and ethyl ethoxymethylenemalonate (*808*). 1,7-Naphthyridine (IX-37) has been prepared by a similar sequence of reactions starting with 3-aminopyridine 1-oxide (*808*). 2,7-Naphthyridine (IX-38) cannot be derived from a nuclear aminopyridine.



(IX-36) (IX-37) (IX-38)

(b) Pyridopyrimidines. As was indicated in the naphthyridine section, 2-aminopyridines can be converted into either naphthyridines

or pyridopyrimidines. With reagents such as diethyl malonate (*212,410*), ethyl acetoacetate (*179,206,207,411*), or diethyl ethoxymethylenemalonate (*409*), the pyridopyrimidone (IX-39) is formed



(IX-39)
x-Alkyl-4-methyl-2*H*-pyrido-[1,2-*a*]-pyrimidin-2-one

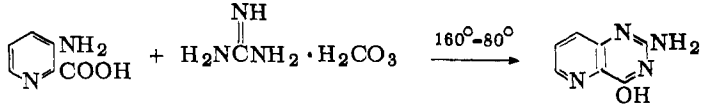
if the 2-aminopyridine has no substituent in the 6 position. When this position is occupied, the naphthyridine is formed.

The same general type of reaction has been carried out with 2-aminopyridine and ethyl 3-aminocrotonate (*412*) or ethyl 3-halopropionates (*413,809*). The preparation of pyrido[1,2-a]pyrimidines from 2-aminopyridine and 2-bromoacrylic acid or ethyl acrylate has been described (*180*). The same authors reported that no cyclization occurred with acrylic acid.

It should be pointed out that in the reaction between 2-aminopyridine and ethyl benzoylacetate, Palazzo and Tamberini (*204*) reported isolation of an intermediate which on cyclization yielded a 1,8-naphthyridine. Seide (*414*) later showed that the product was not the naphthyridine, but the expected pyridopyrimidine.

2-Aminonicotinic acid was heated at 170–210° with formamide, urea, or thiourea to give, respectively, 4-hydroxy-, 2,4-dihydroxy-, or 4-hydroxy-2-mercaptopyrido[2,3-d]pyrimidine (*754*). The use of acetamide yielded 4-hydroxy-2-methylpyrido[2,3-d]pyrimidine (*415*).

When the positions of the amino and carboxy groups are reversed, the pyrido[2,3-e]pyrimidines are obtained (IX-40) (*273*).

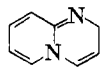


(IX-40)

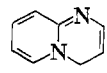
40%

The pyrido[4,3-d]pyrimidines are prepared in analogous ways from 3-aminoisonicotinic acid (*64,416*).

While the reactions starting with 2-aminopyridine all yield the 2*H*-pyrido[1,2-a]pyrimidine (IX-41) or the 4*H*-pyrido[1,2-a]pyrimidine (IX-42), the use of an aminopyridinecarboxylic acid and urea or

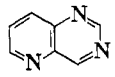


(IX-41)

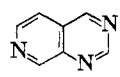


(IX-42)

a urea derivative leads to pyrido[2,3-d]pyrimidines (IX-43) or pyrido-[4,3-d]pyrimidines (IX-44).

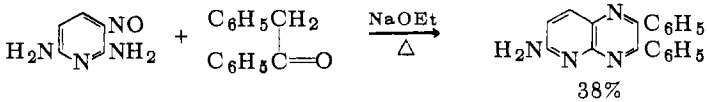


(IX-43)



(IX-44)

(c) **Pyridopyrazines.** These compounds are generally prepared from diaminopyridines and are discussed under the reactions of those compounds (p. 64). There is one report, however, of the treatment of an aminonitrosopyridine with several different active hydrogen compounds to give the pyrido[2,3]pyrazine (IX-45) in yields of 30–40% (*417*).

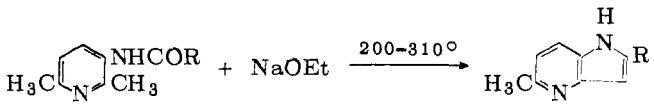


38%

(IX-45)

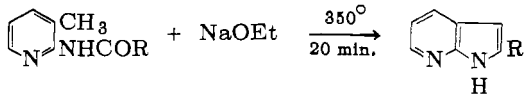
(d) **Pyrrolopyridines.** These compounds are generally prepared from acylamino- or formylaminomethylpyridines by alkaline ring closure at high temperatures. The yields in these reactions are extremely varied and range from traces to nearly theoretical quantities.

The reaction of 3-acetamido-2,6-lutidine at 200–310° in the presence of sodium ethoxide gave 2,5-dimethyl-1*H*-pyrrolo[3,2-b]-pyridine (*188*) in 55% yield. The benzoylamino analog gave the 2-phenyl derivative in 67% yield while 3-formamido-2,6-lutidine under the same conditions gave 5-methyl-1*H*-pyrrolo[3,2-b]pyridine (IX-46) in 12% yield. The parent compound was prepared by the reaction of 3-formamido-2-picoline with sodium amide at 300° (*810*).



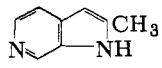
(IX-46)
R = H, CH_3, Ph
1*H*-Pyrrolo[3,2-b]pyridines

On reversal of the position of the amino and methyl groups, the 1*H*-pyrrolo[2,3-b]pyridine (IX-47) is obtained (*22,189,810*).

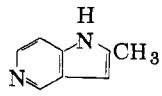


R = H, Me, Et (IX-47)

In a similar manner, 3-acetamido-4-picoline yielded a 1*H*-pyrrolo[2,3-c]pyridine (IX-48) (*792*), and 4-acetamido-3-picoline yielded IX-49 (*418*).

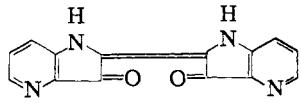


(IX-48)



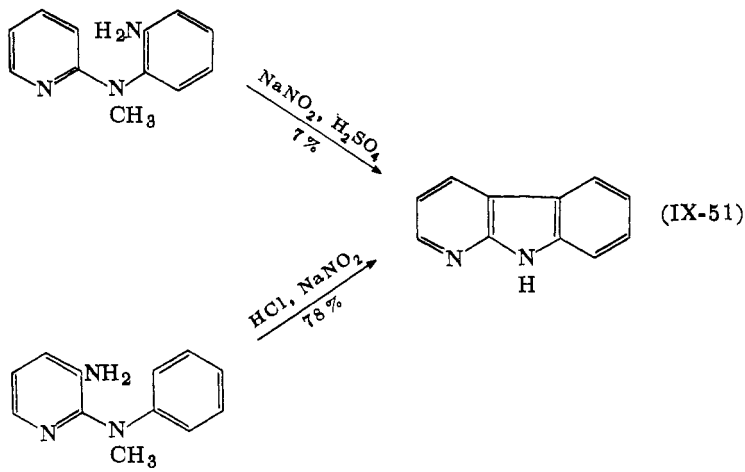
(IX-49)

Pyrrolopyridines have also been prepared by the action of benzoin on a mixture of 2,6-diaminopyridine and its hydrochloride salt (*281*). On heating with potassium hydroxide at 260°, 3-carboxymethylaminopicolinic acid yielded a compound that on air oxidation gave the blue dye IX-50, which Sucharda (*419*) called γ-pyrindigo.



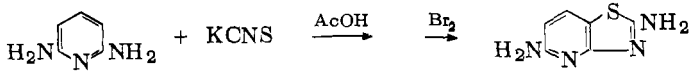
(IX-50)

Several pyrrolo[2,3-b]pyridines containing a benzene ring fused to the pyrrole portion of the molecule have been prepared from *N*-methyl-*N*-(2-pyridyl)-*o*-phenylenediamine or its isomer, 3-amino-2-(*N*-methylanilino)pyridine, by diazotization (IX-51) (*312*).



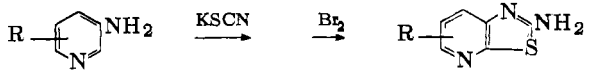
(IX-51)

(e) **Pyridothiazoles.** 2,5-Diaminopyrido[2,3-d]thiazole (IX-52) was obtained in poor yield from 2,6-diaminopyridine by the action of potassium thiocyanate (*281*) followed by bromine at −5 to −10°.



(IX-52)

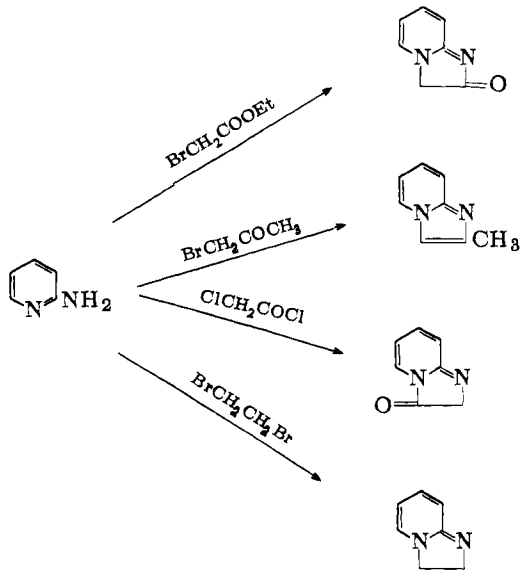
The reaction has also been carried out with copper thiocyanate; in this instance bromine is not used (*420,421*). Under similar conditions 3-aminopyridine and many of its derivatives yield the pyrido-[3,2-d]thiazole (IX-53) (*96,422*).



(IX-53)

3,5-Diamino-2-pyridinethiol may also be converted to a pyrido-thiazole (*423*).

(f) **Imidazopyridines.** 2-Aminopyridine has been treated with α-halo esters (*178,193,424,425*), α-halo ketones (*424–428,803,811*), α-haloacyl chlorides (*193,429*), 1,2-dihaloalkanes (*178,425*), and a β-halo alcohol (*178*) to yield imidazo[1,2-a]pyridines (IX-54).



(IX-54)

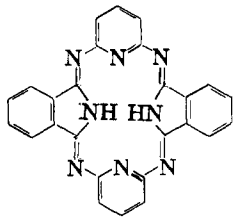
These reactions are generally carried out under relatively mild conditions, by refluxing in various solvents up to about 120°. The reaction between α-bromoacetophenone and the lithium salt of 2-aminopyridine was reported (*428*) to take place at room temperature.

Imidazopyridines in which a benzene ring is fused to the imidazole portion of the molecule have also been reported (*430, 431*).

(g) Miscellaneous Systems. A number of other condensed heterocyclic systems have been prepared from aminopyridine intermediates. Among these are pyridoxazines (*432*), pyridoxazoles (*433*), azaacridines (*434*), pyridoquinoxalines (*435*), a triazafluorene (*435*), and a 1-azaphenothiazine (*812*). The reaction of 2-aminopyridine with 2,3-dichloro-1,4-naphthoquinone gives either 5*H*,6*H*-benzo[e]pyrido-[a]benzimidazole-5,6-dione or 5,6-dihydro-5-oxo-6-(2-pyridylimino)-benzo[e]pyrido[a]benzimidazole, depending on the relative amounts of the reactants (*813*).

2-Pyridyl isothiocyanate is reported to exist as the dimer dipyrido-[1,2-a, 1′,2′-e][1,3,5,7]tetrazocine-6,13-dithione, but reacts as the monomer with aniline at 100° to yield *N*-phenyl-*N*′-2-pyridylthiourea (*814*).

The interesting azaporphyrin IX-55 was obtained (*436*) by the reaction between two moles of 1,3-diiminoisoindoline and two moles of 2,6-diaminopyridine. This compound is a high-melting, orange-red material that closely resembles the phthalocyanines in its ability to form complexes with a number of metals.

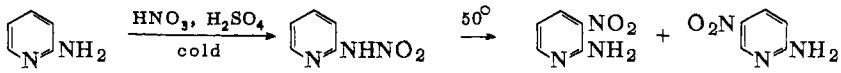


(IX-55)

4. Nitraminopyridines and Nitrosoaminopyridines

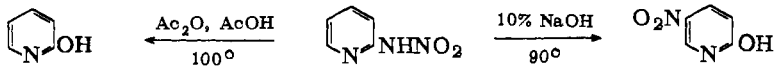
When an aminopyridine is treated with a mixture of nitric and sulfuric acids in the cold, a nitraminopyridine is formed. Temperature control is important in these reactions. At elevated temperatures, rearrangement occurs and the nitro group enters the nucleus to give a nitraminopyridine (*394*).

Thus, 2-nitraminopyridine (IX-56) on warming to 50° in sulfuric acid gives a mixture of 2-amino-3-nitro- (IX-57) and 2-amino-5-nitropyridines (IX-58). Pino and Zehrung (*396*) used a fractional sublimation technique to resolve the mixture into 20% of IX-57 and 63% of IX-58. The ortho isomer chelates as expected, and Korte (*273*) was able to separate the isomers by steam distillation.



(IX-56) (IX-57) (IX-58)

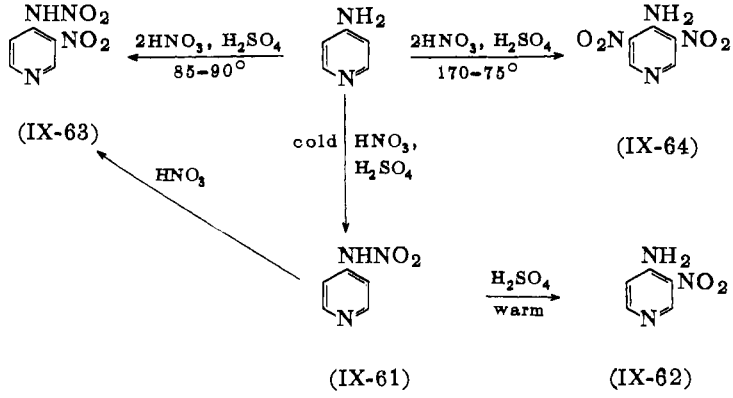
When IX-56 is heated to 100° in a mixture of acetic acid–acetic anhydride, the pyridinol (IX-59) is isolated in 60% yield (*400*). The action of 10% alkali at 90° resulted in rearrangement of the nitro group, but the amino group was replaced by hydroxyl to give 5-nitro-2-pyridinol (IX-60) (*437*).



(IX-59) (IX-56) (IX-60)

The 4-nitraminopyridine (IX-61) can also rearrange under the influence of heat and sulfuric acid to a nuclearly substituted nitroaminopyridine (IX-62) (*33*). When nitric acid is present during the rearrangement, additional nitration can also occur (*388*).

In the presence of nitric acid, IX-61 yields only 4-nitramino-3-nitropyridine (IX-63) and no IX-62. 4-Nitramino-3-nitropyridine can also be obtained directly from 4-aminopyridine by the use of mixed acid at 85–90°, while two moles of nitric acid at 170–75° gives 3,5-dinitro-4-aminopyridine (IX-64) (*388*).

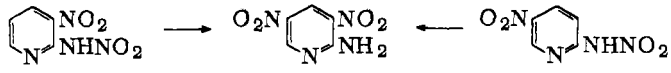


(IX-61) (IX-62)

4-Halopyridines can be prepared from the corresponding nitramino compound (IX-61) by the use of hydrochloric or hydrobromic acid in the presence of sodium nitrite (*388,438*). When concentrated hydrochloric acid and elevated temperatures are used, IX-61 is converted to the 4-chloro compound, as well as a dichloropyridine.

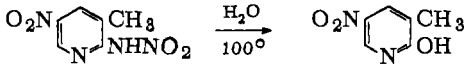
3-Nitraminopyridine, which can be prepared by the use of nitric and sulfuric acids at 0° (*400*), does not rearrange to an aminonitropyridine. Under forcing conditions, nitrous oxide is evolved and 3-pyridinol is isolated (*33,400*). Reduction of this nitramine with zinc and alkali gives mainly 3-aminopyridine (*400*).

Several substituted 2-aminopyridines have been converted to the nitramino compounds and rearranged or otherwise converted to new products. 2-Amino-3,5-dinitropyridine (IX-65) has been prepared from both 2-nitramino-3-nitropyridine (IX-66) and the 5-nitro isomer (IX-67). 2-Nitramino-3-nitropyridine was reported to rearrange more readily than the 5-nitro isomer (*376*).



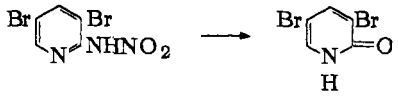
(IX-66) (IX-65) (IX-67)

The nitramino group was removed completely by heating 2-nitramino-5-nitro-3-picoline (IX-68) in water at 100°, the corresponding pyridinol (IX-69) being isolated (*92*).



(IX-68) (IX-69)

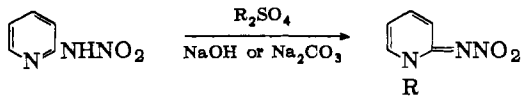
The 3,5-dibromo compound (IX-70) yielded the pyridone (IX-71) when it was allowed to remain in contact with sulfuric acid for two to three days at room temperature (*371*).



(IX-70) (IX-71)

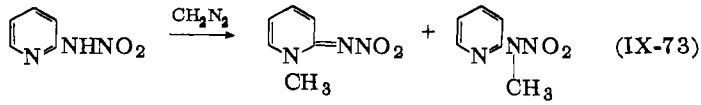
Chichibabin and Widonowa (*398*) reported that 5-ethyl-6-nitramino-2-picoline could not be rearranged to the nuclear nitro compound.

2-Nitraminopyridine (IX-56) is sufficiently acidic to permit ready alkylation with alkyl sulfates or diazoalkanes. The use of methyl or ethyl sulfate in the presence of alkali or sodium carbonate resulted in alkylation of the ring nitrogen to give 1-methyl- or 1-ethyl-2-nitrimino-1,2-dihydropyridine (IX-72) (*439*).

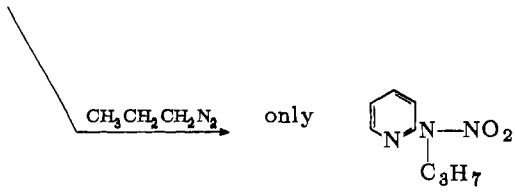


(IX-56) (IX-72)

Diazoalkanes alkylate both at the ring and side-chain nitrogen (IX-73). As the size of the alkyl group increases, the percentage of the ring nitrogen product decreases, so that with diazopropane, the only product is 2-(*N*-propylnitramino)pyridine (IX-74) (*397*). The



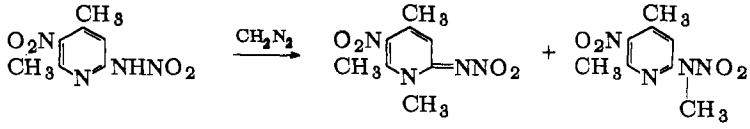
(IX-56) 56% 11.6% (IX-73)



(IX-74)

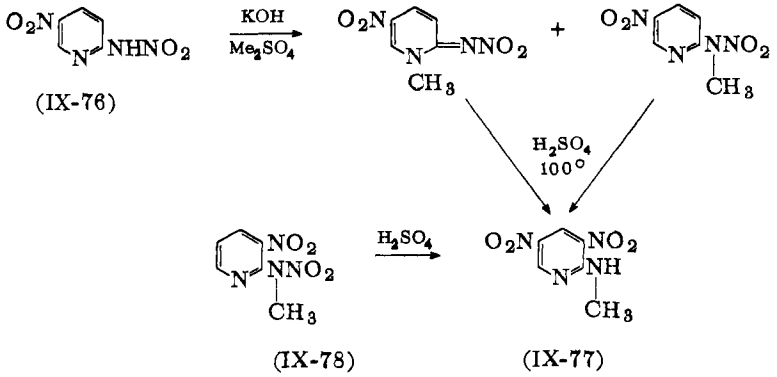
same type of results were noted when 2-nitramino-4-picoline was treated with diazomethane and diazoethane. In this instance, however, while diazomethane resulted in a mixture of the two types of products, diazoethane yielded only 2-(*N*-ethylnitramino)-4-picoline.

With the more highly substituted 2-nitramino-5-nitro-4,6-lutidine, diazomethane gave both types of products (IX-75) in poor yield, although alkylation of the nitramino side-chain was preferred (*397*).



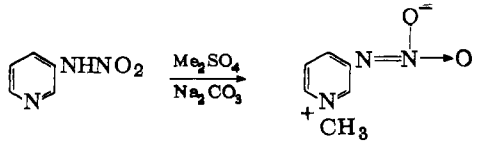
(IX-75)

The use of methyl sulfate and potassium hydroxide with 2-nitramino-5-nitropyridine (IX-76) has been reported (*376*) to give both ring and side-chain alkylation. Both products rearrange in sulfuric acid at 100° to give the same compound (IX-77), which is also obtained from 3-nitro-2-(*N*-methylnitramino)pyridine (IX-78) (*440*) in sulfuric acid at room temperature (*376*).



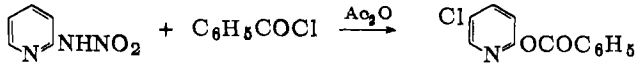
(IX-76) (IX-78) (IX-77)

Only one attempt to methylate 3-nitraminopyridine (IX-79) has been reported (*400*). This resulted in a betaine-like compound (IX-80).



(IX-79) (IX-80)

An interesting reaction of 2-nitraminopyridine (IX-56) is encountered with acyl chlorides. Benzoyl chloride in acetic acid or acetic anhydride gives a compound which has been represented as being either IX-81 or its 1-benzoyl isomer (*441*).

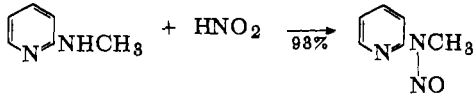


(IX-56) (IX-81)

The same type of product is obtained with *p*-nitrobenzoyl chloride. The reaction was also carried out with acetyl chloride.

A study of the effect of aluminum chloride on IX-56 has been made (*442*). In nitrobenzene or hexane, only tars were obtained. When benzene was used as a solvent, 3-phenyl-1-methylcyclopentane, 2-chloropyridine, 2-phenylpyridine, and 2-anilinopyridine were obtained.

On treatment with nitrous acid, 2-methylaminopyridine is readily converted to the *N*-nitroso compound (IX-82) (*586*). Unlike its

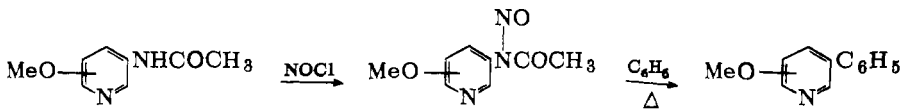


(IX-82)

benzene analog, *N*-methyl-*N*-nitrosoaniline, when IX-82 is warmed with sulfuric acid, it does not rearrange to give a nuclear nitroso derivative. 2-(*N*-Nitrosoanilino)pyridine, prepared similarly, also fails to rearrange (*306*).

Failure to convert 2-acetamidopyridine to the nitroso compound has been reported (*237,238*), although this reaction goes smoothly with 3-acetamidopyridines.

3-Acetamido-2-, -4-, and -6-methoxypyridines (IX-83) have all been converted to the corresponding *N*-nitroso derivatives (IX-84) by the use of nitrosyl chloride (*238*). These compounds on heating in benzene for twenty-four hours all gave the corresponding 3-phenylpyridines (IX-85).



(IX-83) (IX-84) (IX-85)

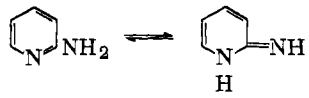
In a similar manner (*239*), the 3-(*N*-nitroso-*i*-butyramido)pyridine was converted to 3-phenylpyridine.

Physical properties of nitramino and nitrosoaminopyridines are summarized in Tables IX-41 to IX-44 (pp. 106 f.).

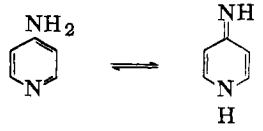
5. Pyridonimines

In the discussion of the chemical structure of the 2- and 4-aminopyridines as compared to 3-aminopyridine, the reactions of the former were explained on the basis of two reactive tautomeric forms.

Derivatives of structures IX-86 and IX-87 are termed 2- and 4-pyridonimines, respectively, and are named systematically as derivatives of 1,2-dihydro-2-iminopyridine and 1,4-dihydro-4-iminopyridine.



(IX-86)

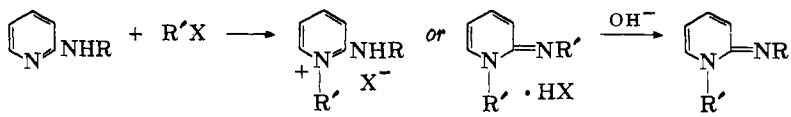


(IX-87)

The pyridonimines contrast sharply with the isomeric substituted aminopyridines in their behavior. Thus, the former are strong bases and unstable in air, yield crystalline salts, and are hydrolyzed by aqueous alkali to the corresponding pyridone derivatives. 2(and 4)-Monosubstituted aminopyridines are weak bases and relatively stable in air and aqueous alkali. A study of the ultraviolet absorption spectra of these two types of compounds has been made by Gol'dfarb and co-workers (*443*). Physical properties of pyridonimines are summarized in Tables IX-98 and IX-99 (pp. 152 ff.).

The synthesis of pyridonimines has been accomplished by a variety of procedures. Because of the relative inaccessibility of 4-aminopyridine until recently, the majority of these procedures deal with the preparation of 2-pyridonimines.

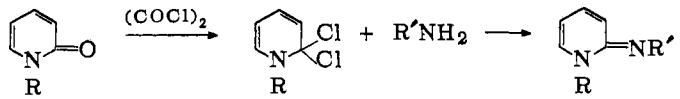
The addition of alkyl halides to a 2-aminopyridine derivative yields a water-soluble quaternary salt which, on treatment with aqueous alkali or silver oxide, gives a 1,2-dihydro-2-imino-1-alkylpyridine (IX-88) (*146,172,444*). A similar synthesis gives 1,4-dihy-



(IX-88)

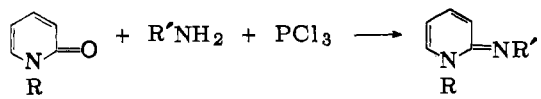
dro-4-imino-1-methylpyridine (*445,446*), which is also obtained by the action of methyl iodide upon 4-aminopyridine in the presence of sodium amide (*446*). 2-Aminopyridine is methylated on the amino group under these conditions (*327*). Similarly, the reaction of 4-aminopyridine and 2,4-dinitrochlorobenzene yields a quaternary salt, which by treatment with aqueous alkali is converted to the unstable 1,4-dihydro-1-(2,4-dinitrophenyl)-4-iminopyridine (*447,309*). 2-Aminopyridine, under the same reaction conditions, gives the stable 2-(2,4-dinitroanilino)pyridine (*431*).

1-Substituted 2-pyridones are converted into 2,2-dichloro derivatives by treatment with oxalyl chloride. Subsequent reaction with a primary amine then yields the 2-pyridonimine derivative (IX-89) (*306,448,449*).



(IX-89)

The simultaneous reaction of a 1-substituted 2-pyridone derivative, phosphorus trichloride, and a primary amine leads to the formation of a 1-substituted 2-pyridonime (IX-90) (*450*).

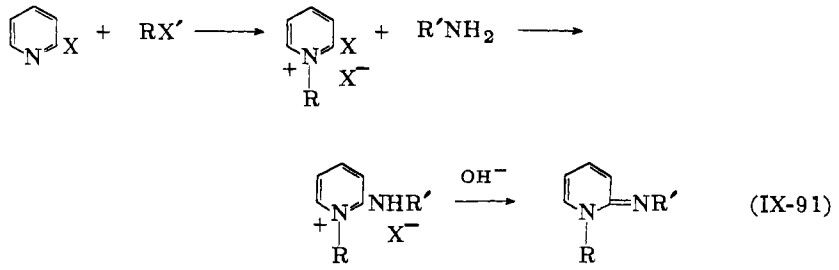


(IX-90)

2- and 4-Halopyridine derivatives are readily quaternized by reaction with alkyl halides. The nuclear halogen atoms in these quaternary compounds are very labile, and react readily with primary amines to yield compounds identical with those obtained by the action of alkyl halides on the substituted 2- and 4-aminopyridines. Subsequent treatment with alkali yields the pyridonimine derivative (IX-91) (*451*).

The reaction of 1-substituted 2-pyridinethiones and ammonia in the presence of mercuric oxide or other "desulfurizing" agents yields 1-substituted 2-pyridonimines (*452*). The use of alkyl- or arylamines in this reaction apparently has not been investigated.

1-Substituted 2-pyridonimines have been obtained by a number of miscellaneous procedures. Passing a mixture of 2-aminopyridine



(IX-91)

and methanol over alumina at 360° gives a low yield of 1,2-dihydro-2-imino-1-methylpyridine (*318*). This compound is also obtained in 29% yield by the action of dimethylphosphoric monochloride upon 2-aminopyridine (*453*). Treatment of the methiodide of 2-acetamidopyridine with hydriodic acid is also said to yield this pyridonimine derivative (*381*).

The reaction of 2-nitraminopyridine and dialkyl sulfates in alkaline solution results in the formation of 1-alkyl-2-nitrimino-1,2-dihydropyridines (*439*). 5-Nitro-2-nitraminopyridine reacts similarly (*376,440*). 2-Aminopyridine and styrene oxide give 1-(2-hydroxy-2-phenylethyl)-2-pyridonimine (*805,815*).

1,4-Dihydro-4-imino-1-(4-pyridyl)pyridine is obtained by treating the reaction product from sodium 4-pyridinesulfonate and phosphorus pentachloride first with ammonia, and then with hydrochloric acid (*454*).

The unsubstituted imino group in the 2- and 4-pyridonimines reacts readily with alkyl halides (*146,306*), acid chlorides (*146,242, 455*), aryl isocyanates (*146*), and nitric acid in sulfuric acid (*440*) to yield the imino-substituted derivatives. The imino group in 1,2-dihydro-2-imino-1-methylpyridine adds to ethylene oxide and acrylonitrile to yield the 2-(2′-hydroxyethylimino) and 2-(2′-cyanoethylimino) derivatives (*456*).

The reaction of 3- and 5-nitro-2-aminopyridines and methyl iodide leads to direct methylation of the amino group rather than quaternization of the ring nitrogen atom (*376*).

1,2-Dihydro-1-methyl-2-nitriminopyridine rearranges in concentrated sulfuric acid at room temperature to a mixture of 3- and 5-nitro-2-methylaminopyridines (*376*).

6. Diamino- and Triaminopyridines

Six diaminopyridine isomers are possible, and all have been prepared. Of the six possible triaminopyridines, all but the 2,4,5-isomer have been reported. The preparation and reactions of these compounds, in general, parallel those of the monoamino compounds. A significant difference lies in the use of the di- and triaminopyridines as intermediates in the preparation of a large number of condensed-ring heterocyclic compounds. These reactions will be discussed subsequently.

a. Preparation

(a) Reduction of a Nitro Group. Catalytic reduction of an aminonitropyridine has been carried out under a variety of conditions to yield the corresponding diamine. The reduction of 2-amino-5-bromo-3-nitropyridine with Raney nickel in an alkaline medium gave (*370*) 2,3-diaminopyridine. In a similar reaction, the 5-chloro analog was reduced with platinum to give a good yield of 2,3-diamino-5-chloropyridine (*457*).

The reduction of 2-amino-3-nitropyridine over platinum gave an 89% yield of the diamine (*457*). Other isomers prepared by catalytic reduction are the 3,5-, over palladium (*458*), the 2,5-, over palladium (*38*), and a number of 2,3-diamino-6-alkyl derivatives by reduction over palladium (*459,395*).

Reduction with tin and an acid or with stannous chloride has been a commonly used procedure that often leads to chlorinated reduction products. Thus, the reduction of 2-amino-3-nitropyridine with stannous chloride in hydrochloric acid gave (*273*) both the 2,3-diamino- and the 2,3-diamino-4(or 6)-chloropyridine, while the treatment of 2-amino-5-chloro-3-nitropyridine (*341*) with tin and hydrochloric acid gave 2,3-diamino-5-chloropyridine and a dichloro diamine.

The reduction of 4-alkylamino-3-nitropyridines with tin and hydrochloric acid gave the 2-chloro derivative of the diamine (*462*), although the 6-chloro isomer has also been reported (*388*). Reductions with these reagents in which no chlorinated product was isolated have also been reported (*21,117,319,463*).

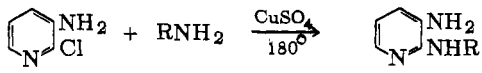
A series of reductions of 2-amino-5-nitropyridines (*353*), 2-amino-3-nitropyridines (*464*), and 4-alkylamino-3-nitropyridines (*465*) with iron and acetic or hydrochloric acid have given the corresponding diamino compounds in 75–95% yields.

A long series of compounds have been reduced with sodium hydrosulfite. The yields in these reactions have been generally good (*466–469*).

Other reductions of aminonitro compounds have been carried out with sodium sulfide (*470*), ammonium sulfide, tin and hydrochloric acid (*41*), zinc and hydrochloric acid (*437*), and zinc and alkali (*471*).

Triaminopyridines have been prepared by similar reductions and some of these procedures are listed in Table IX-7 (p. 80).

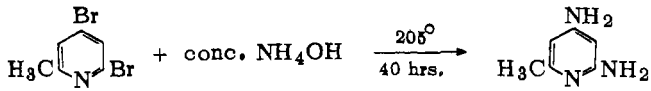
(b) Ammonolysis. The replacement of a halogen with ammonia or an amine takes place much more rapidly in the pyridine series than in the benzene series. These reactions are often assisted by the use of catalysts such as copper sulfate. 3-Amino-2-chloropyridine reacts with ammonia or an alkylamine at 180° in the presence of copper sulfate (IX-92) (*472–475*).



(IX-92)

R = H, Me, Ph, Pr, cyclohexyl

A 2,4-diamine was prepared by the action of alcoholic ammonia for eleven hours at 100° on 2,4-dichloro-3-nitropyridine (*51,476*). To obtain 4,6-diamino-2-picoline in 54% yield, the corresponding dibromo compound was heated with aqueous ammonia at 205° for forty hours (IX-93) (*477*).

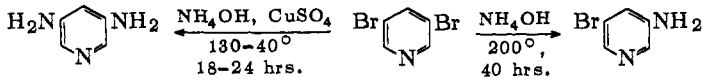


(IX-93)

54%

3,5-Diaminopyridine has been prepared by ammonolysis of both the dibromo- and diiodopyridines. The effects of temperature and catalyst are strikingly shown in the reaction of ammonia with the

dibromo compound (IX-94) (*31,33*). 3,5-Diiodopyridine gave the diamine under similar conditions (*480*).

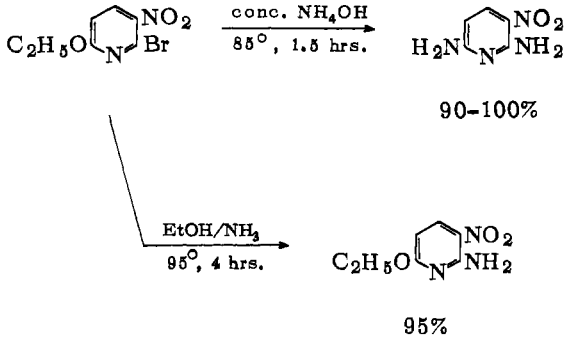


(IX-94)

15–20%

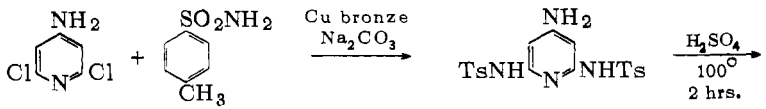
The preparation of 2,6-diaminopyridines from the 2,6-dihalo compounds has not in general been a very successful procedure. 2,6-Dibromopyridine when treated with ammonium hydroxide at 180° for four hours gave 70–80% yields of 2-amino-6-bromopyridine; in ten hours at 200° it gave a small yield of the diamine (*29*). Similar results were obtained with the dichloro analog (*25*). The diiodo compound gave 2,6-diaminopyridine in unspecified yield when heated with ammonium hydroxide (*387*).

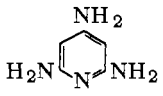
Depending on conditions, 2-bromo-6-ethoxy-3-nitropyridine gives either monoamine or diamine (IX-95) (*38*).



(IX-95)

Piperidine replaces one halogen of 2,6-dibromopyridine at 160°, while at 180° the second halogen is replaced to give 2,6-dipiperidinopyridine (*32*). The reaction of 4-amino-2,6-dichloropyridine with *p*-toluenesulfonamide in the presence of copper bronze and sodium carbonate has been reported (*200*) to give 4-amino-2,6-bis(*p*-toluenesulfonamido)pyridine, which was then hydrolyzed to the triamine (IX-96).





(IX-96)

(c) Direct Amination. Many attempts have been made to convert pyridine to 2,6-diaminopyridine by the action of sodium amide in a high-boiling solvent. The best procedure to be developed (*481*) is the treatment of pyridine with sodium amide at 170° for six to eight hours in a ball mill. The yield of the diamine under these conditions is 55%. A number of other attempts have been reported (*7,327,482–484*). Many of these reactions resulted in mixtures of mono- and diamines.

The direct introduction of a second amino group into an aminopyridine has been reported a number of times, but is not a satisfactory route to the diaminopyridines. The treatment of 3-aminopyridine with sodium amide at 210° gave the 2,3-diamine in less than 10% yield (*20*), while amination of 3-pyridinol under essentially the same conditions gave some 2,6-diaminopyridine (*485*) with reduction of the hydroxyl group. 2-Picoline, when heated at 200–300° for several hours with sodium amide, gave a mixture of the 4,6- and 3,6-diamines (*486*).

In an attempt to introduce a second amino group with hydroxylamine at 50–60°, 2-amino-3-nitropyridine was converted to 2,6-diamino-3-nitropyridine in 9% yield, while 6-amino-5-nitro-3-picoline was converted to 2,6-diamino-5-nitro-3-picoline in 21% yield (*487*).

(d) Hofmann and Curtius Degradations. Five of the six diaminopyridines have been prepared by either the Hofmann (*488,489*) or Curtius (*69,490–492*) degradation from the corresponding amides or hydrazides.

b. Properties and Reactions

The physical properties of the diaminopyridines are given in Tables IX-50 to IX-55 (pp. 113 ff.), the triamines in Table IX-56 (p. 118).

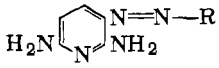
(a) **Hydrolysis.** 2,6-Diaminopyridine is stable to base even under severe conditions. In acid, however, the amine groups tend to hydrolyze. By control of the conditions, either 6-amino-2-pyridinol or 2,6-pyridinediol may be obtained (*494–496*).

Some of the data which have been obtained for this reaction are given in Table IX-8 (p. 81).

(b) Diazotization and Coupling. Diaminopyridines such as the 2,3- and the 2,5-isomers may be diazotized on the 3- or 5-amino group (see p. 33), and the resulting diazo compounds subjected to the usual replacement reactions to give 3- or 5-substituted 2-aminopyridines. Thus 2,5-diaminopyridine has been converted to the 5-chloro, 5-iodo, and 5-arsonic acid derivatives of 2-aminopyridine (*341*); 2,3-diaminopyridine was similarly converted to 2-amino-3-chloropyridine (*341*).

These diazotized diamines also couple, in the usual fashion, with amines and phenols (*341*).

2,6-Diaminopyridine has been used as a coupling agent for a great number of diazonium compounds. Coupling occurs in the 3 position to yield compounds of the type IX-97 (*332,340*), which generally have bactericidal properties.



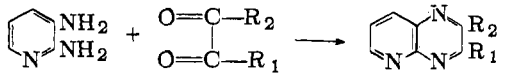
(IX-97)

(c) **Substitution Reactions.** 2,6-Diaminopyridine has been nitrated at –3° (*493*) to give 2,6-diamino-3-nitropyridine in 60% yield. Somewhat better results were obtained by the nitration of the diacetyl derivative; the 3-nitro compound is obtained in 70% yield (*332*) and may be hydrolyzed to the diamine.

The bromination of 3,5-diacetamidopyridine (*33*) in hot acetic acid has been reported to give 3,5-diacetamido-2,6-dibromopyridine in poor yield, while the bromination of 2,6-diaminopyridine yielded 2,6-diamino-3-bromopyridine (*340*).

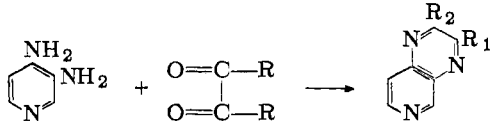
A large number of acyl and alkyl derivatives of 2,6-diaminopyridine are reported by Bernstein *et al.* (*281,664*).

(d) Synthesis of Condensed Heterocyclic Systems. Perhaps the most characteristic reaction of *o*-diaminopyridines is the formation of heterocyclic condensed-ring systems. The reaction of a 2,3-diaminopyridine with an α-dicarbonyl compound gives the corresponding pyrido[2,3]pyrazine (IX-98).



(IX-98)

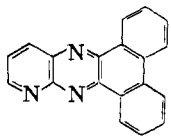
With 3,4-diaminopyridines the product is a pyrido[3,4]pyrazine (IX-99).



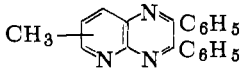
(IX-99)

2,3-Diaminopyridine has been treated with glyoxal to give the unsubstituted pyrido[2,3]pyrazine (IX-98, $R_1 = R_2 = H$) (*273,464*), with benzil to give the 2,3-diphenyl derivative (IX-98, $R_1 = R_2 = C_6H_5$) (*341*), and with pyruvic acid to give 2-methyl-3-hydroxypyrido[2,3]pyrazine (IX-98, $R_1 = CH_3$, $R_2 = OH$) (*273*). 7-Chloro- and 6,7-dichloropyrido[2,3]pyrazines, as well as other derivatives, were prepared from the appropriate halo-2,3-diaminopyridines and various α-diketo compounds (*816*). The reactions of 3-amino-2-anilinopyridine are described by Ried and Grabosch (*817*).

The reaction of the diamine with phenanthraquinone gives compound IX-100 (*341*), while the reaction of 5,6-diaminopicolines with benzil gave 2,3-diphenyl-6(7 or 8)-methylpyrido[2,3]pyrazine (IX-101) (*461*).

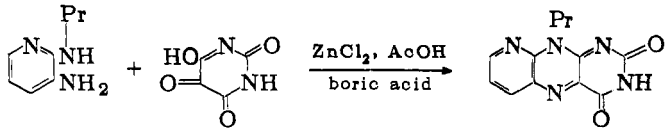


(IX-100)



(IX-101)

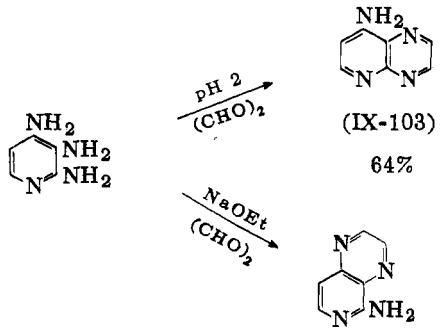
The synthesis of 9-propyl-8-azaflavine was accomplished (*472*) by a slight modification of this reaction (IX-102).



(IX-102)

Similar reactions with 3,4-diaminopyridine and glyoxal have given the unsubstituted pyrido[3,4]pyrazine (IX-99, $R_1 = R_2 = H$) (*117,470*).

In the triamine series, 2,3,4-triaminopyridine can give either 8-aminopyrido[2,3]pyrazine or 5-aminopyrido[3,4]pyrazine. The linear product (IX-103) is obtained in acid medium, the angular product (IX-104) under basic conditions (*497*).



(IX-103)

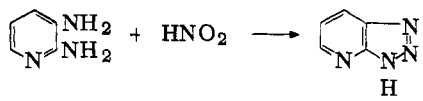
64%

(IX-104)

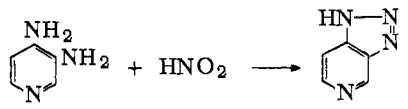
20%

Where the three amino groups are not vicinal, obviously only two ortho groups can participate in such reactions (*273*).

The reaction between 2,3- (*41,341,467,468*) or 3-4-diaminopyridine (*466*) and nitrous acid gives the corresponding pyridotriazole (IX-105, IX-106).

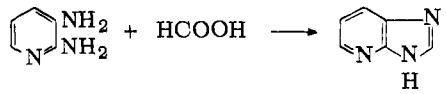


(IX-105)



(IX-106)

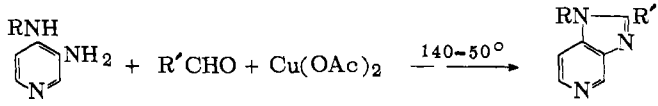
A variety of pyrido[2,3]imidazoles have been prepared from 2,3-diaminopyridines. When the diamine is treated with formic acid (*273,464,467,816*), the parent compound results in yields up to 84% (IX-107).



(IX-107)

Various 2-substituted derivatives may be obtained by the substitution of the appropriate reactant for formic acid. Phosgene (*467*) yielded the 2-oxo derivative, while thiophosgene yielded the thio analog (*467*). Urea and carbon disulfide gave the 2-hydroxy and the 2-mercapto derivatives, respectively (*464*). The 2-methylpyrido[2,3]-imidazole was obtained (*464*) from 2,3-diacetamido-5-bromopyridine in 50% yield.

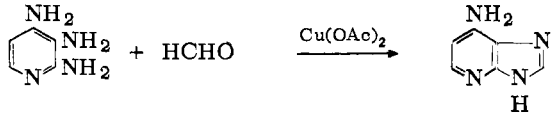
3-Amino-4-thioformylaminopyridine was converted (*498*) to pyrido[3,4]imidazole. A series of pyrido[3,4]imidazoles were prepared (*465,499*) by the reaction between a 4-alkylamino-3-aminopyridine, an aldehyde, and cupric acetate at 140–50° (IX-108). The yields in these reactions ranged between 39 and 71%.



(IX-108)

R = Me, Et, Pr, Bu; R′ = alkyl, aryl, or heteroaryl

A similar reaction with 2,3,4-triaminopyridine and formaldehyde (*498*) yielded 7-aminopyrido[2,3]imidazole (1-desazaadenine) (IX-109).



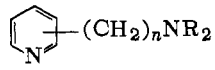
(IX-109)

B. SIDE-CHAIN AMINES

1. Preparation

For the purpose of this discussion, side-chain amines will be defined as those compounds in which an amine group is separated from the pyridine ring by a carbon skeleton uninterrupted by any other element. Those compounds in which the amine function is part of an alicyclic system (piperidyl, morpholinyl, etc.) will be included in this definition.

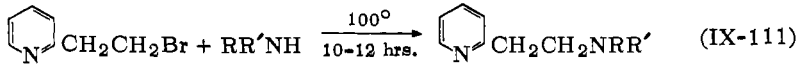
It will be seen that, for the most part, aminoalkylpyridines (IX-110) are prepared by simple extensions of well-known reactions.



(IX-110)

a. Aminolysis of Side-Chain Halides and Related Compounds

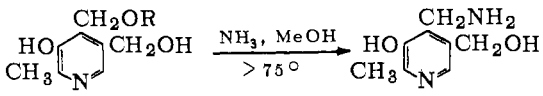
Primary, secondary, and tertiary amines may all be prepared by aminolysis of halomethylpyridines (*500*) or higher haloalkylpyridines (*501*) (IX-111). Similar reactions have been reported by Hamlin *et al.* (*502*) and others (*503–506,818*).



(IX-111)

R = R′ = H
R = H, R′ = Me
R = R′ = Et

Pyridylcarbinols and their ethers may also be aminolyzed to the methylamine derivative (*507–509*); this reaction has been widely applied to the synthesis of vitamin B_6 intermediates (*510*) (IX-112).



(IX-112)

R = alkyl, aralkyl, aryl

2-(2-Aminopropyl)pyridine has been prepared by ammonolysis of the tosyl ester of the corresponding carbinol (*511*).

b. Reduction of Nitriles

All of the cyanopyridine isomers have been reduced to the corresponding aminomethyl compounds.

Picolinonitrile and isonicotinonitrile have been reduced by chromous acetate in about 70% yields (*512–515*). Several of their derivatives have been similarly reduced in fairly good yields (*513*). In the presence of excess chromous acetate, however, picolinonitrile gave only 2-picoline (*512*). The 4-aminomethyl isomer has also been prepared by the nickel-catalyzed reduction of the nitrile in methanolic ammonia at 85 atmospheres and 70° in 70% yield (*516*). Neither the 2- nor the 4-nitrile could be reduced by sodium amalgam or aluminum amalgam (*515*).

Nicotinonitrile has been reduced to 3-aminomethylpyridine in yields as high as 89% by the use of ammonia to repress the formation of the secondary amine (*517,547*) in the Raney nickel-catalyzed hydrogenation reaction. Chromous acetate gave decidedly inferior results (*513,518*).

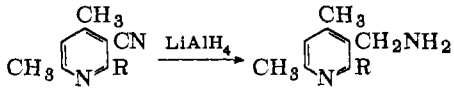
A wide variety of cyanopyridines have been hydrogenated to the amines in the presence of Raney nickel, palladium, platinum, etc. Much of this work was done in the course of synthetic studies on vitamin B_6. This work resulted in some interesting examples of the selective reduction of one or more reducible groups on the pyridine ring. Thus, while palladium on charcoal catalyzes the reduction of the nitrile group in ethyl 2-chloro-3-cyano-6-methylisonicotinate (*519*), the use of palladium on barium carbonate resulted only in the removal of the halogen (*489*).

Although platinum oxide generally fails to reduce a nitrile function to the aminomethyl group (*520,521*) examples have been reported in which this reduction did occur (*520,522–524*).

Numerous examples exist where combinations of palladium and platinum catalysts were used to reduce other groups as well as the nitrile function (*525–527*).

An electrolytic reduction in the presence of palladium has been reported to give 6-amino-5-aminomethyl-2-picoline (*528*) from 2-amino-6-methylnicotinonitrile.

Reduction of the nicotinonitrile derivative with lithium aluminum hydride gave 2-amino-3-aminomethyl-4,6-dimethylpyridine in 68% yield (*529*), while 2-diethylamino- and 2-methoxy-4,6-dimethylnicotinonitriles were reduced to the corresponding aminomethyl compounds in 88 and 93% yields, respectively (*530*) (IX-113).



(IX-113)

R = Et_2N or CH_3O

2,6-Dichloroisonicotinonitrile (*512*) and 2,3,5,6-tetrachloroisonicotinonitrile (*513*) have been reduced with chromous acetate to the amine with retention of halogen. The former nitrile also gave the amine in 79% yield, rather than the expected aldehyde, under the conditions of the Stephen reduction (*531*).

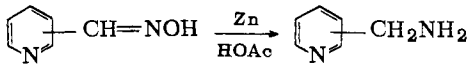
c. Reduction of Amides

Lithium aluminum hydride affords ready conversion of pyridine amides to the side-chain amine. *N,N*-Diethylnicotinamide gave *N,N*-diethylaminomethylpyridine in 84% yield (*532*). A bis-amide has also been reduced by the use of lithium aluminum hydride (*533*). A thioamide was converted to the 4-(morpholinylethyl)pyridine by the use of Raney nickel (*534*). In an attempted reduction of *N*-ethylnicotinamide under Sonn-Mueller conditions, 3-(ethylaminomethyl)pyridine as well as the expected aldehyde was obtained (*535*).

d. Reduction of Oximes or Hydrazones

A number of aminoalkylpyridines have been prepared by the reduction of an oxime or phenylhydrazone. The oximes of 2- and 3-

pyridinealdehydes have been converted to the corresponding aminomethyl compounds in about 80% yields by the use of zinc and acetic acid (*536*) (IX-114). The oxime of 3-hydroxy-5-hydroxymethyl-2-

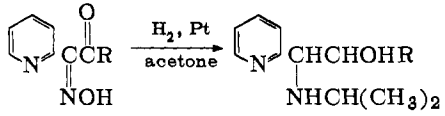


(IX-114)

methylisonicotinaldehyde was reduced catalytically to the 4-aminomethyl derivative in 87% yield (*537*).

A number of oximes of alkyl pyridyl ketones have been reduced by zinc and acetic acid (*538–542*), zinc and hydrochloric acid (*543*), and catalytic hydrogenation (*500,544–547*). The yields in most instances were good to excellent, although the presence of some secondary amine, usually in small amounts, can be expected.

The reduction of oximes in acetone or cyclohexanone resulted (IX-115) in the preparation of substituted amines (*545*). The yields in this reaction were about 95%.



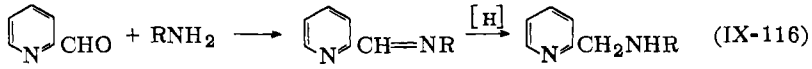
(IX-115)

R = 2-Py or C_6H_5

The phenylhydrazone of 3-pyridyl propyl ketone has been reduced to 1-(3-pyridyl)butylamine (*541*).

e. Reduction of Schiff Bases

A relatively unexplored source of side-chain aminopyridines lies in the reduction of the Schiff base that may be obtained by the reaction of a pyridine aldehyde and an amine (IX-116). Yields up to

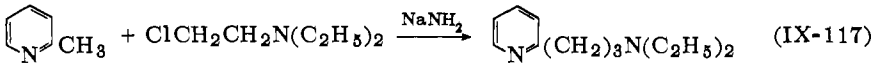


(IX-116)

100% have been reported for this reaction (*548–550*). Several instances of the reductive amination of pyridyl ketones have also been reported (*320,551*).

f. Alkylation with Aminoalkyl Halides

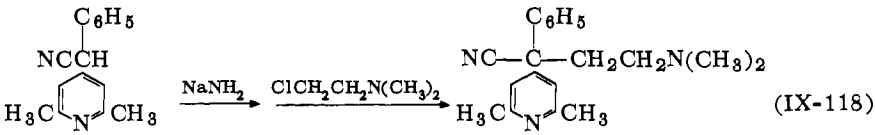
2-Picoline has been alkylated with diethylaminoethyl chloride in the presence of sodamide (*704*) (IX-117).



(IX-117)

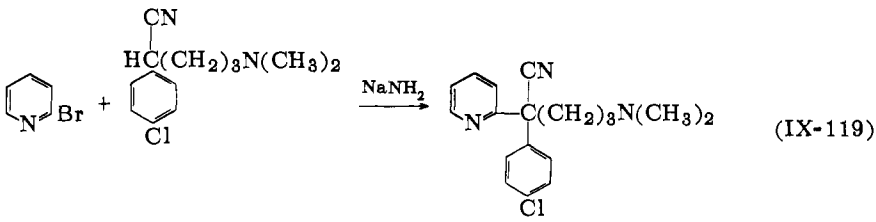
Although 4-picoline has not been aminoalkylated in this way, it does react with ethoxyethyl chloride to give 4-(ethoxypropyl)pyridine. The use of methylene iodide or 1,2-diiodoethane gave negative results.

Activated side-chains may also be alkylated in this manner (*102,553,554*) (IX-118).



(IX-118)

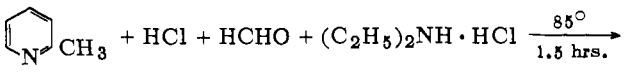
The inverse type of coupling reaction may be carried out between halopyridines and dialkylamino compounds which are capable of being converted to a carbanion (*718*) (IX-119).



(IX-119)

g. Mannich Reactions

The Mannich reaction has been used in a number of instances to aminoalkylate alkyl- or hydroxypyridines. The reported yields vary. When a 2- or 4-alkylpyridine is used as the starting material, the reaction site is on the alkyl group. In a series of reactions with 2-picoline (*555*), both mono- and diamines were obtained (IX-120). The substitution of piperidine hydrochloride for diethylamine hy-

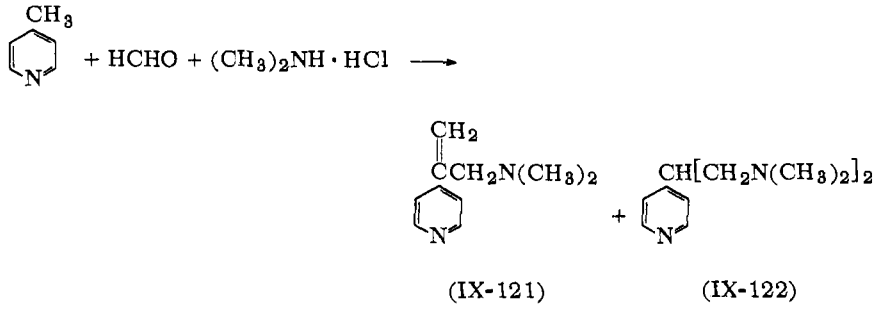


(IX-120)

54% 37%

drochloride gave the bispiperidyl compound in 78% yield. Under the same conditions, however, 2-ethylpyridine gave a quantitative yield of *N,N*-diethyl-2-(2-pyridyl)propylamine. Under neutral conditions, 2-picoline, formaldehyde, and diethylamine (*556*) gave an 80% yield of 2-diethylaminoethylpyridine.

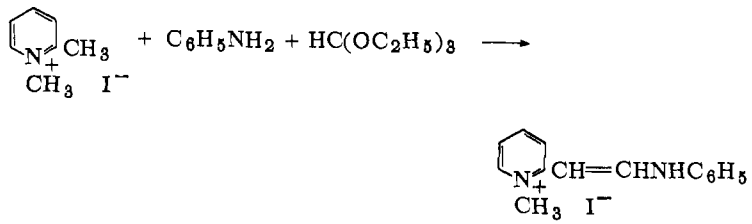
Matuszko and Taurins (*557*) found that 4-picoline gave a methylene derivative (IX-121) as well as the diamine (IX-122). A series of reactions was also carried out in neutral or acetic acid medium to give the normal product, 4-Py$CH_2CH_2NR_2$, in very poor yields.



(IX-121) (IX-122)

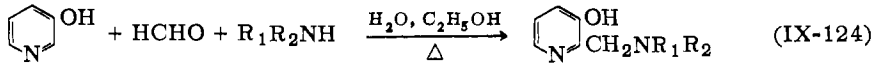
As might be expected, no similar reactions with 3-alkylpyridines have been reported.

A number of quaternary pyridine compounds have been treated with ethyl orthoformate and an amine to yield unsaturated side-chain amines (*558–560*) (IX-123).



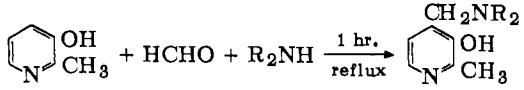
(IX-123)

3-Pyridinol, under the conditions of the Mannich reaction, undergoes nuclear substitution to give the 2-dialkylaminoalkyl-3-hydroxy compound (*561*) (IX-124). 2-Methyl-3-pyridinol reacted with



(IX-124)

several amines to give a series of 4-dialkylaminoalkylpyridines (IX-125) in 28–65% yield (*562*).

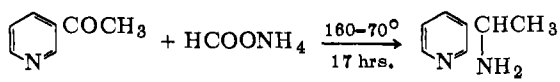


(IX-125)

R = Et, Bu; NR_2 = piperidyl

h. Leuckart Reaction

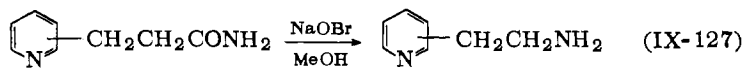
Burger and Ullyot (*563*) and Burger and Walter (*564*) have applied the Leuckart reaction to pyridyl ketones. The use of ammonium formate with 3-pyridyl ketones gave the amine in low yields (IX-126). A series of 2-picolyl ketones was treated (*563*) with formic acid and formamide to give the amine in higher yields.



(IX-126)

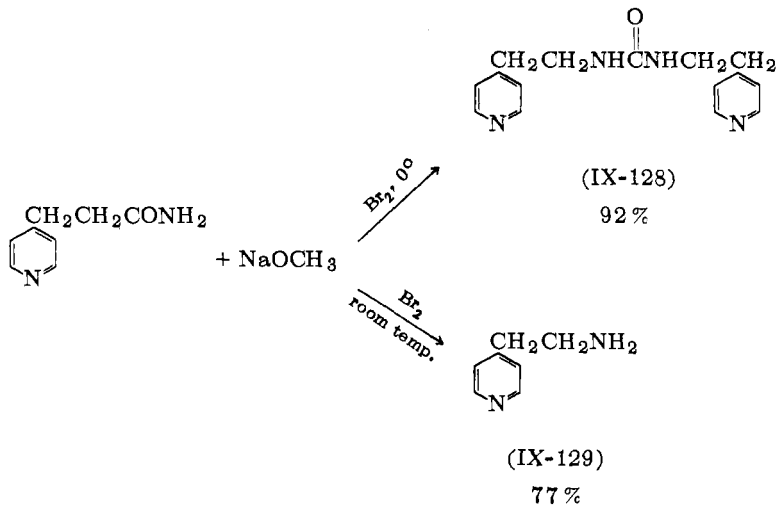
i. Hofmann Rearrangement

The Hofmann rearrangement of amides to amines (IX-127) has generally given good to excellent yields. The 2- and the 3-pyridyl



(IX-127)

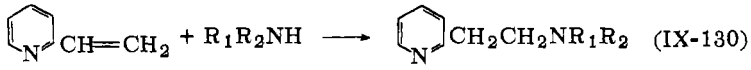
compounds were readily prepared (*504,565*) by this method, but 4-pyridinepropionamide, under the usual conditions, gave a 92% yield of the diacylurea (IX-128). The expected amine was obtained on rapid addition of bromine at room temperature (IX-129) (*566*); the urethane was obtained in methanol (*504*).



The urea (IX-128) was presumably formed by interaction between the amide and the intermediate isocyanate through which the Hofmann rearrangement proceeds.

j. Addition of Amines to Vinylpyridines

A versatile method for the preparation of secondary or tertiary aminoethylpyridines has been developed in the addition of amines to vinylpyridines (IX-130).



(IX-130)

Much of the work on 2-vinylpyridines has been done by Reich and Levine (*567,568*). Although several secondary amines were successfully pyridylethylated with no catalyst, the general results were uniformly better with an acetic acid-catalyzed procedure. Weakly basic amines such as pyrrole and 2,5-dimethylpyrrole failed to react under acid catalysis; in the presence of sodium these gave 89 and 53% yields, respectively, of the pyridylethylated product.

These workers also treated 2-vinylpyridine with a number of primary amines, including aniline, 2-aminofuran, and 2-aminothiophene. These reactions likewise required acid catalysis. 2-Aminopyridine failed to react.

Pyridylethylation with 4-vinylpyridine was first reported by Matuszko and Taurins (*557*). Profft (*569*) treated a wide variety of primary and secondary amines with 4-vinylpyridine and 6-vinyl-2-picoline at 120–40° for three to four hours in the presence of acid catalysts. 6-Vinyl-2,4-lutidine gives similar results (*819*). In a recent study, a number of primary and secondary amines were treated at 100° for twenty hours without a catalyst. The addition of either acetic acid or a little water almost invariably caused sluggish reactions to proceed well (*570*). 3-Vinylpyridine does not enter into the pyridylethylation reaction.

Phthalimide adds normally to 2-vinylpyridine and the product may be hydrolyzed to 2-(2-aminoethyl)pyridine (*571,572*).

The base-catalyzed addition of nitroalkanes to vinylpyridines yields substituted 2-nitroethylpyridines (*820*), which are readily reduced to amines by hydrogenation (Raney nickel in ethanolic ammonia) (*821*).

k. Miscellaneous Preparations

Nicotinaldehyde has been treated with *N*-benzoylglycine to give, via the azlactone, 3-(3-pyridyl)alanine (*573*).

2-Aminometanicotine, on treatment with hydrogen and platinum, gave 2-amino-3-(dimethylaminobutyl)pyridine (*138*).

The coreduction of imines and pyridine by aluminum or magnesium amalgam gives good yields of *N*-substituted aminomethylpyridine derivatives (*822*).

The three pyridine aldehydes and primary nitroalkanes yield nitro alcohols that are reducible to the corresponding amino alcohols in 50–60% yields (*823*).

2. Properties and Reactions

The properties and reactions of the side-chain aminopyridines are, in general, those to be expected of similarly substituted aliphatic amines. Side-chain aminopyridines are listed in Tables IX-57 to IX-77 (pp. 119 ff.).

a. Alkylation and Acylation

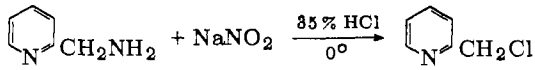
Alkylation reactions have been reported by Craig (*540*) and La Forge (*541*). Normal reactions are given with acyl halides and an-

hydrides (*529,530,538*), aroyl halides (*386,529,545*), heterocyclic acid chlorides (*574*), chloroformic esters (*529,537*), and *p*-toluenesulfonyl chloride (*540,575,576*). *Cf.* Tables IX-94 to IX-97 (pp. 149 ff.). A number of N^1-(pyridylalkyl)sulfanilamides have also been reported (*544*).

Like other amines, aminoalkylpyridines react with cyanamide to form the guanidine (*577*) and with isocyanates (*190,530*) or nitrourea (*571*) to give ureas.

b. Conversion of the Amine to a Hydroxyl Group

Nitrous acid converts the aminoalkyl to a hydroxyalkyl side-chain. A comprehensive study of the effect of various acids with sodium nitrite or silver nitrite (*578*) showed that 3-(aminomethyl)-pyridine gave best results with sodium nitrite and aqueous acetic acid. Concentrated hydrohalic acids (*579–581*) give the halomethyl compound instead (IX-131).



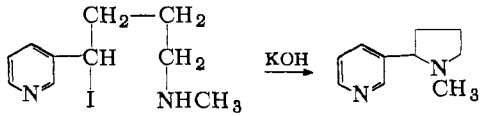
(IX-131)

c. Oxidation

Potassium permanganate (*582*) or manganese dioxide (*583*) converts 4-(aminomethyl)pyridine compounds to the corresponding aldehydes. 3-(Aminomethyl)pyridine gives excellent yields of nicotinaldehyde by the Sommelet reaction (*584*).

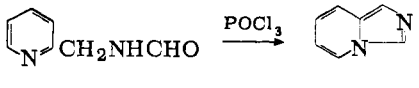
d. Cyclization Reactions

Appropriately substituted aminoalkylpyridines undergo cyclization reactions, which may or may not involve the pyridine nucleus. Nicotine (IX-132) was prepared by allowing 3-(1-iodo-4-methylaminobutyl)pyridine to stand over potassium hydroxide at room temperature (*585*).



(IX-132)

Bower and Ramage (*538*) have prepared a series of [2,3a]diazaindenes (IX-133) from acyl- or formylaminomethylpyridines.

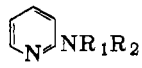


(IX-133)

(80 %)

[2,3a]Diazaindene

C. TABLES

TABLE IX-1. Antihistaminic Compounds 

Name	R_1	R_2
Pyribenzamine	benzyl	dimethylaminoethyl
Neoantergan	*p*-methoxybenzyl	dimethylaminoethyl
Thenylenehistadyl	2-thienylmethyl	dimethylaminoethyl
Chlorothen	5-chloro-2-thienylmethyl	dimethylaminoethyl

TABLE IX-2. Conversion of Diazotized 3-Aminopyridines to 3-Halopyridines

Diazotized pyridine	Reagent	Product (yield)	Ref.
5-Amino-2-picoline	HCl	5-chloro-2-picoline (20%)	72
3-Aminonicotinic acid	HCl	3-chloronicotinic acid (18%)	45
	40% HBF_4	methyl 3-fluoronicotinate	344
	H_2SO_4, MeOH, HBF_4	no reaction	344
3-Amino-5-bromo-2-chloropyridine	HCl	5-bromo-2,3-dichloropyridine	345
3-Amino-2-picoline	HI	3-iodo-2-picoline	60
Ethyl 5-amino-2-methylnicotinate	KI	ethyl 5-iodo-2-methylnicotinate (55%)	6
5-Aminonicotinic acid	CuBr	5-bromonicotinic acid	346
5-Amino-3-picoline	HBF_4	5-fluoro-3-picoline (60%)	92
3-Aminopyridine	HBF_4	3-fluoropyridine (50%)	58
3-Aminopyridine	30% H_2SiF_6	3-fluoropyridine (36%)	347

TABLE IX-3. Conversion of Diazotized 2-Aminopyridines to 2-Halopyridines

Diazotized pyridine	Reagent	Product (yield)	Ref.
2-Aminonicotinic acid	40% HBF_4	2-fluoronicotinic acid	344
2-Amino-5-chloro-3-nitropyridine	HCl	2,5-dichloro-3-nitropyridine ("fair")	345
2-Amino-4-picoline	HBr, Br_2	2-bromo-4-picoline (77%)	348
2-Amino-3-picoline	HBr, Br_2	2-bromo-3-picoline (46%)	348
2-Amino-5-bromopyridine	HBr, Br_2	2,5-dibromopyridine	348
2-Amino-5-nitropyridine	KI	2-iodo-5-nitropyridine (14%)	348
2-Amino-4,6-dichloropyridine	HCl	2,4,6-trichloropyridine	75
2-Aminopyridine	HBF_4	2-fluoropyridine (34%)	58
6-Amino-2-picoline	KBr, AcOH	6-bromo-2-picoline (20%)	349
2-Amino-5-nitropyridine	60% HF	2-fluoro-5-nitropyridine (22%)	315
2-Aminopyridine	30% H_2SiF_6	2-fluoropyridine (42%)	347
4-Aminopyridine	HBF_4	no reaction	58
2-Amino-4-ethylpyridine	HBr,Br_2	2-bromo-4-ethylpyridine	795

TABLE IX-4. Conversion of Diazotized Aminopyridines to Pyridinols

Diazotized pyridine	Reagent	Product (yield)	Ref.
3-Amino-6-methoxypyridine	$CuSO_4$, H_2O	3-hydroxy-6-methoxypyridine (low)	350
6-Amino-2-picoline	H_2SO_4	6-hydroxy-2-picoline (93%)	351
2-Amino-4-picoline	H_2SO_4	2-hydroxy-4-picoline (78%)	351
2-Aminoisonicotinic acid	H_2SO_4	2-hydroxyisonicotinic acid (90%)	43
3-Amino-2,5-dibromopyridine	HCl	2,5-dibromo-3-hydroxypyridine	345
3-Amino-2-picoline	H_2SO_4	3-hydroxy-2-picoline	60
Ethyl 5-amino-2-methylnicotinate	H_2SO_4	ethyl 5-hydroxy-2-methylnicotinate (low)	6
4-Amino-3-pyridinesulfonic acid	H_2O	4-hydroxy-3-pyridinesulfonic acid	352

TABLE IX-5. Conversion of Diazotized 3-Aminopyridines to 3-Cyanopyridines

Diazotized pyridine	Reagent	Product (yield)	Ref.
3-Aminopyridine	$KCu(CN)_2$	3-cyanopyridine (50%)	276
2,5-Diaminopyridine	CuCN	2-amino-5-cyanopyridine (50%)	353
5-Amino-2-picoline	KCN, $CuSO_4$	5-cyano-2-picoline (40%)	354
3-Amino-2-picoline	KCN, CuCN, pH 4.5	3-cyano-2-picoline	355
3-Amino-5-bromopyridine	$KCu(CN)_2$	5-bromo-3-cyanopyridine (50%)	33
5-Amino-2-pyridinol	KCN, $CuSO_4$	5-cyano-2-pyridinol	354

TABLE IX-6. Phenylazopyridines Prepared by the Method of Campbell *et al.* (*156*)

Starting material	Product (yield)
2-Amino-5-bromopyridine	5-bromo-2-phenylazopyridine (86%)
2-Amino-3,5-dibromopyridine	3,5-dibromo-2-phenylazopyridine (84%)
2-Amino-4-picoline	2-phenylazo-4-picoline (68%)
2-Aminopyridine	2-(*o*-chlorophenylazo)pyridine[a] (48%)
3-Aminopyridine	3-phenylazopyridine (60%)
4-Aminopyridine	4-phenylazopyridine (69%)

[a] *o*-Chloronitrosobenzene was used instead of nitrosobenzene.

TABLE IX-7. Triaminopyridines by Reduction

Starting material	Reducing agent	Product (yield)	Ref.
4,6-Diamino-5-nitro-2-picoline	Na_2S	4,5,6-triamino-2-picoline (80%)	459
2,6-Diamino-3-nitropyridine	Sn,HCl	2,3,6-triaminopyridine (80%)	478
2,6-Diamino-3-(*p*-tolylazo)pyridine	Sn,HCl	2,3,6-triaminopyridine (80%)	478
2,6-Diamino-3-(*p*-tolylazo)pyridine	Zn,HCl	2,3,6-triaminopyridine (70%)	478
2,6-Diamino-3-(*p*-tolylazo)pyridine	Fe,HCl	2,3,6-triaminopyridine (60%)	478
2,6-Diacetamido-3-nitropyridine	H_2/Pd; H_2/Ni	3-amino-2,6-diacetamidopyridine (80–85%)	478
4-Amino-3,5-dinitropyridine	H_2/Ni	3,4,5-triaminopyridine	479
4-Amino-3,5-dinitropyridine	$SnCl_2$, HCl	2,6-dichloro-3,4,5-triaminopyridine	388

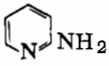
TABLE IX-8. Hydrolysis of 2,6-Diaminopyridine

Medium	Temp.	Time	Product (yield)	Ref.
10% HCl	Reflux	3 hours	6-amino-2-pyridinol (85%)	494
50% H_2SO_4	100°	5 hours	6-amino-2-pyridinol (93%)	495
70% H_2SO_4	100°	2 hours	6-amino-2-pyridinol (100%)	495
65% H_2SO_4	155°	4½ hours	2,6-pyridinediol (50%)	496
70% H_2SO_4	175°	"prolonged"	cleavage products	496
Conc. HCl/EtOH	15°	12 days	3-nitroso-2,6-pyridinediol[a] (90%)	493
Dil. H_2SO_4, $NaNO_2$	0°	10 days	3-nitroso-2,6-pyridinediol[a] (90%)	493

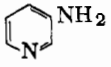
[a]The starting material was 2,6-diamino-3-nitrosopyridine.

TABLE IX-9. Monoaminopyridines

Compound	Physical properties	Ref.
2-Aminopyridine	m.p. 56°; b.p. 204°	27,41
	m.p. 56°; b.p. 210°	17,28,113,591,755
	m.p. 57.5°; b.p. 204°	7,55,327
	m.p. 59–60°	756
	m.p. 55–57°; b.p. 118–20°/36 mm.	30
3-Aminopyridine	m.p. 65°; b.p. 250°	755
	m.p. 64°	32
	m.p. 64°; b.p. 131–32°/12 mm.	88
	m.p. 64°; b.p. 115°/12 mm.	33
4-Aminopyridine	m.p. 157°	757
	m.p. 158°	54,99,124,135
	m.p. 159°	104,123

TABLE IX-10. Alkyl-2-aminopyridines 

Substituents and positions				Physical properties	Ref.
3	4	5	6		
Me				b.p. 103°/11 mm.	758
				b.p. 95°/8 mm.	687
				m.p. 33.5°; b.p. 221.5°	759
	Me			m.p. 98°	688
		Me		m.p. 76.5–79.5°	760
			Me	m.p. 36.5°; b.p. 208–9°	7,17
				m.p. 40°; b.p. 208–9°	613
				m.p. 41°; b.p. 205–6°	56
Et				m.p. 43–45°	189
	Et			b.p. 134–39°/16 mm.	16
				m.p. 66.5–67.5°; 69–70°	373,795
	Pr			m.p. 37–47°; b.p. 151–56°/29 mm.	761
n-Bu				m.p. 46–47°	138
	Me		Me	m.p. 69–70°	57,235
Et			Me	m.p. 51°; b.p. 110–12°/4 mm.	16

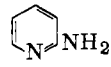
TABLE IX-11. Alkyl- and Aryl-3-aminopyridines 

Substituents and positions				Physical properties	Ref.
2	4	5	6		
Me				m.p. 113°	355
				m.p. 112–16°	89,91
	Me			m.p. 104–5°	71,689
		Me		m.p. 57–59°; b.p. 153°/21 mm.	92,93
			Me	m.p. 96–97°	89,91
				m.p. 97–98°	34
			Pr	b.p. 134–36°/11 mm.	73
				b.p. 50–60°/.005 mm.	724
Me			Me	m.p. 124°; b.p. 230°/738 mm.	81
				m.p. 122°	116
Me	Ph		Me	m.p. 87–87.5°	762
Me	Me		Me	m.p. 66°; b.p. 244°/744 mm.	81,797
			Ph	m.p. 105–6°	141

TABLE IX-12. Alkyl-4-aminopyridines 

Substituents and positions				M.p., °C.	Ref.
2	3	5	6		
Me				95.5-96	105,106
	Me			107.4-8.6	83
Me			Me	186-88	41,108
				191-92	109
Me		Et		hydrochloride: 258	107
(Et?)	Me			55-60[a]; b.p. 116°/15 mm.	1

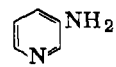
[a]Positions of ethyl and amino groups uncertain.

TABLE IX-13. Monohalo-2-aminopyridines 

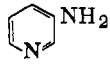
Substituents and positions				M.p., °C.	Ref.
3	4	5	6		
Cl				134.5	341
	Cl			130-31	52,74
		Cl		130-32	457,766
			Cl	75	25
Br				64.5-65.5	126
	Br			143-44.5	126
		Br		137-38	38,53,234
			Br	89-90	32,53
	I			158-60	477
				163-64	74
		I		129	380,381, 477,767

TABLE IX-14. Polyhalo-2-aminopyridines 

Substituents and positions				M.p., °C.	Ref.
3	4	5	6		
Cl		Cl		84	766
	Cl		Cl	108	75
Br	Br			128-29	126
Br		Br		104-4.5	768
Br			Br	105-6	53
	Br	Br		145-45.5	53
	Br		Br	135-36	53
		Br	Br	154-55	53
Br	Br	Br		178-79	53
Br	Br		Br	160.5-61.5	53
Br		Br	Br	178-79	53
	Br	Br	Br	172-73	53
Br	Br	Br	Br	214-15	53
	Cl		I	137	75
I		I		147-48	268,767

TABLE IX-15. Monohalo-3-aminopyridines 

Substituents and positions				M.p., °C.	Ref.
2	4	5	6		
Cl				79-80	152,345
		Cl		82	98
			Cl	83	88,593
Br				79	345
		Br		65-67	98,346
			Br	77	88
		I		70	98

TABLE IX-16. Polyhalo-3-aminopyridines 

Substituents and positions				M.p., °C.	Ref.
2	4	5	6		
Cl		Cl		129	345
Cl			Cl	119	152
Cl	Cl	Br		85.5-86	97
Cl	Cl	Cl	Cl	143	152
Br		Cl		142	345
Cl		Br		131	345
Br		Br		153	345
Br			Br	142	385
Br	Br		Br	115	385
I			I	150-52	387

TABLE IX-17. Monohalo-4-aminopyridines 

Substituents and positions		M.p., °C.	Ref.
2	3		
Cl		91-91.5	52
Br		97.5-98.5	126
	Br	235-36	126
	I	100	389

TABLE IX-18. Polyhalo-4-aminopyridines 

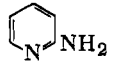
Substituents and positions				M.p., °C.	Ref.
2	3	5	6		
Cl		Cl		125.5-26	52
Cl			Cl	176	200
	Cl	Cl			769
Cl	Cl	Br		148-48.5	770
Cl		Br		147.5-48	770
Br	Br			173-73.5	126
Br		Br		147-48	126
Br			Br	212-13	53
	Br	Br		169-70	53
Br	Cl	Br		156.5-57.5	770
Br	Br	Br		148-48.5	53
Br	Br		Br	191.5-92.5	53
Br	Br	Br	Br	249-50	53
	I	I		134	389

TABLE IX-19. Alkylhaloaminopyridines 

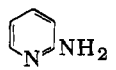
Substituents and positions					M.p., °C.	Ref.
2	3	4	5	6		
NH_2			Br	Me	83-84	351
NH_2	Br		Br	Me	144	351
NH_2	Br	Et	Br		113.5-14	373
Cl	NH_2			Me	82-83	91
Me	NH_2			Cl	93-94	91
Me	NH_2		Br	Cl	162.5-64	91
Me	Br	NH_2		Me	129	41
NH_2		Me	Br	Me	145-46	235
Me	Br	NH_2	Br	Me	152	41
Me	I	NH_2		Me	hydrochloride: 262	108
NH_2	Et		I	Me	159	380
Me	I	NH_2	I	Me	154-55	108
NH_2	Br	Me	Br	Me	136-36.5	235

TABLE IX-20. Nitroaminopyridines 

Substituents and positions					M.p., °C.	Ref.
2	3	4	5	6		
NH_2	NO_2				162-64	17,396,471
NH_2			NO_2		187-88	17,236,396,471
NH_2	NO_2		NO_2		190-91	376
NO_2	NH_2				203-4	38
	NH_2			NO_2	234-35	38
	NO_2	NH_2			200	388,676,763
	NO_2	NH_2	NO_2		170-71	388

TABLE IX-21. Alkylnitro-2-aminopyridines 

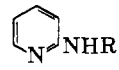
Substituents and positions				M.p., °C.	Ref.
3	4	5	6		
NO_2	Me			134-36	396,688
NO_2		Me		190-91	396
				192-94	691
NO_2			Me	141	396,692
				150-53, 154	91,764
Me		NO_2		255	396,687
	Me	NO_2		220	396,688
		NO_2	Me	187-88	396,692
Et		NO_2	Me	195	398

TABLE IX-22. Alkylhalonitro-2-aminopyridines 

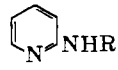
Substituents and positions				M.p., °C.	Ref.
3	4	5	6		
Cl		NO_2	Me	215.4-16	91
Br		NO_2	Me	211.6-12.4	91

TABLE IX-23. Halonitroaminopyridines 

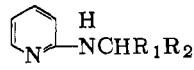
Substituents and positions					M.p., °C.	Ref.
2	3	4	5	6		
NH_2	Cl		NO_2		211–13	765
NH_2	NO_2		Cl		194–96	399,467
NH_2	Br		NO_2		215	375
NH_2	NO_2		Br		205	375
Br	NH_2			NO_2	213–13.5	38
	Br	NH_2	NO_2		181	469

TABLE IX-24. 2-Alkylaminopyridines 

R	Physical properties, derivatives	Ref.
Amyl	m.p. 43°	257
Butyl	m.p. 47–49°	596
	m.p. 45°	298
Cetyl	m.p. 67°	257
Cyclohexyl		597
2-(Cyclohexyl)ethyl	m.p. 97–98°	598
Decyl	m.p. 51–52°	599
1-(2,2-Dibutyl)hexyl	b.p. 172–74°/2 mm.	300
1-(2,2-Dicylohexylamino)ethyl	hydrobromide, m.p. 198°	444
1-(2,2-Diethoxy)ethyl	b.p. 115–18°/0.6 mm.	600
2-(5-Diethylamino)pentyl	b.p. 182°/14 mm.	299
1-(3-Diethylamino)propyl	b.p. 136–38°/3.5 mm.	601
1-(2,2-Dimethoxy)ethyl	picrate, m.p. 133–34°	602
(2-Dimethylamino)cyclohexyl	b.p. 131–33°/0.01 mm.	622
1-(2-Dimethylamino)ethyl	b.p. 150–55°/1–2 mm.; hydrochloride, m.p. 223–25°	596,603, 604
1-(3-Dimethylamino)propyl	b.p. 109–110°/2 mm.	605
Dodecyl	m.p. 60°	599
Ethyl	sulfate, m.p. 111–13°	598
Geranyl	picrate, m.p. 125°	257
Hexyl	hydrochloride, m.p. 112–14°	598
Methyl	m.p. 15°; picrate, m.p. 190°	7,146, 586
Octadecyl	m.p. 66–67°	257
2-Piperidinoethyl	picrate, m.p. 163°	257,298
Propyl	picrate, m.p. 194–95°	606
Tetradecyl	m.p. 69°	599
Tridecyl	m.p. 65–66°	599
Undecyl	m.p. 60–61°	599

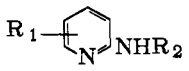
TABLE IX-25. 2-Aryl- or Heteroarylaminopyridines 

R	M.p., °C.	Ref.
5-Bromo-2-thenyl	83–85	607
5-Chloro-2-nitrophenyl	152.5–53.5	608
2,4-Diaminophenyl	150	431
2,4-Dinitro-1-naphthyl	192	430
2-Ethoxyphenyl	94	609
2-Hydroxyphenyl	154	172
2-Methoxyphenyl	92	172
	63–64	609
4-Methoxyphenyl	85	609
1-Naphthyl	115	609
	116	307
2-Naphthyl	133	609
	135	307
Phenyl	108	7,306,28,610, 304,316
Picryl	135	431
4-Sulfonamidophenyl	223–24	611
	235	612

TABLE IX-26. 2-Aralkylaminopyridines 

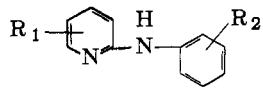
R_1	R_2	M.p., °C.	Ref.
3-Benzothiazolyl	H	101–3	614
Benzoyl	phenyl	106–8	427
Benzyl	H	51	596,603
5-Bromo-2-furyl	H	72	615
5-Bromo-2-thienyl	H	81–83	616
5-Chloro-2-thienyl	H	84–86	616
3,4-Dimethoxyphenyl	H	165, 102–3	597,617
2-Furyl	methyl	b.p. 110–12/1.6 mm.	615
Methyl	phenyl	91–92	173
3,4-Methylenedioxyphenyl	H	96, 99–100	187,617
4-Methoxyphenyl	H	120–21, 128	187,617
Phenyl	H	94, 98	187,599
Phenyl	phenyl	94–96, 101–2	173,604,618
4-*i*-Propoxyphenyl	H	101–2	294
4-*i*-Propylphenyl	H	104–5	603
2-Thienyl	H	81–82, 80–83	605,607

TABLE IX-27. Nuclear-Substituted 2-Alkyl- and 2-Aralkylaminopyridines

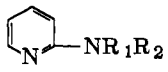


R_1	R_2	M.p., °C.	Ref.
3-Amino	cyclohexyl	119	474
3-Amino	methyl	100–1	152
5-Bromo	dimethylaminoethyl	hydrochloride: 226–28	616
5-Bromo	methyl	70–71	371
3-Bromo-5-nitro	hydroxyethyl	136	619
3-Bromo-5-nitro	methyl	163–64	376
5-Bromo-3-nitro	methyl	149–50	376
5-Chloro	4-methoxybenzyl	158–59	294
3,5-Dibromo	methyl	56.5–57	371
3,5-Dinitro	methyl	147–48	376
6-Methyl	benzyl	66	613
6-Methyl	2-hydroxybenzyl	97	620
6-Methyl	2-methoxybenzyl	69	620
3-Methyl	methyl	b.p. 113/21 mm..	190
6-Methyl	methyl	chloroplatinate: 178–79; picrate: 192	7,613
6-Methyl	3,4-methylenedioxybenzyl	80	620
6-Methyl	octadecyl	46	257
5-Nitro	allyl	97	619
5-Nitro	aminoethyl	123	619
5-Nitro	2-bromopropyl		619
5-Nitro	diethylaminoethyl		619
5-Nitro	hydroxyethyl	hydrochloride: 131–32	619
3-Nitro	methyl	63–64	376
5-Nitro	methyl	181	376

TABLE IX-28. Nuclear-Substituted 2-Arylaminopyridines

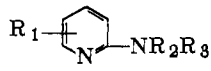


R_1	R_2	M.p., °C.	Ref.
3-Amino	H	141	152
		142–43	474
5-Amino	4-acetamido	242–43	313
3-Methyl	2,4,6-trinitro	142–43	431
5-Nitro	H	134	469
		135–36	314
5-Nitro	4-acetamido	239–40	313
5-Nitro	4-ethoxy	140–41	314
5-Nitro	4-hydroxy	211–12	314
5-Nitro	4-methoxy	160–61	314
5-Nitro	2-methyl	137–39	315

TABLE IX-29. Tertiary 2-Aminopyridines 

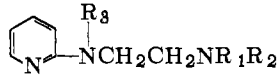
R_1	R_2	Physical properties, derivatives	Ref.
i-Amyl	*i*-amyl	b.p. 168–69°/20 mm.	318
Benzyhydryl	benzyhydryl	m.p. 181–82°	618
Benzyl	2,2-dimethoxyethyl	hydrochloride, m.p. 215.5–16.5°	602
Benzyl	2-dimethylaminocyclohexyl	b.p. 153–160°/0.06 mm.	622
Benzyl	1-ethyl-3-piperidyl	picrate, m.p. 217–18°	621,623
Benzyl	1-methyl-3-piperidyl	hydrochloride, m.p. 256–60°	621
Butyl	butyl	m.p. 136–37°; picrate, m.p. 130–35°	30,298
4-Chlorobenzyl	2-dimethylaminocyclohexyl	m.p. 139–40°	622
Ethyl	ethyl	b.p. 205–8°	318
Ethyl	formyl	b.p. 114–15°/3 mm.	598
Ethyl	2,4,6-trinitrophenyl	m.p. 234–36°	310
2-Hydroxyphenyl	methyl	m.p. 153°	172
2-Methoxyphenyl	methyl	m.p. 25–30°	172
Methyl	methyl	picrate, m.p. 182°	7,146
Methyl	2-aminophenyl	m.p. 66–67°	312
Methyl	phenyl	b.p. 147–48°/3 mm.	30
Methyl	2,4,6-trinitrophenyl	m.p. 240–42°	310
Phenyl	phenyl	m.p. 95–99°, 104°, 105°	30,304 624
Phenyl	2,4,6-trinitrophenyl	229–31°	310
Propyl	propyl	picrate, m.p. 138.5°	298
—pentamethylene—		picrate, m.p. 137.5–38.5°	316

TABLE IX-30. Nuclear-Substituted Tertiary 2-Aminopyridines



R_1	R_2	R_3	Physical properties, derivatives	Ref.
5-Amino	methyl	methyl	m.p. 55–56°	319
3-Amino	methyl	phenyl	m.p. 80–81°	312
3-Amino-6-methyl	methyl	phenyl	m.p. 100°	312
5-Bromo	methyl	methyl	m.p. 42–43°	319
5-Chloro	dimethyl-aminoethyl	4-methoxy-phenyl	hydrochloride, m.p. 141–42°	294
5-Chloro	dimethyl-aminoethyl	phenyl	hydrochloride, m.p. 179–80°	294
3,5-Dibromo	methyl	methyl	picrate, m.p. 185–86°	319,371
5-(4-Dimethyl-amino)benzyl	methyl	methyl	m.p. 80°, 82°	167,625
3,5-Dinitro	methyl	methyl	m.p. 125–26°	319
5-Hydroxymethyl	methyl	methyl	m.p. 45.5°	625
5-Iodo	methyl	methyl	m.p. 55°	319
3-Methyl	benzyl	dimethyl-aminoethyl	b.p. 150–88°/ 14 mm.	626
6-Methyl	methyl	methyl	picrate, m.p. 153°	7,318
6-Methyl-3-nitro	methyl	phenyl	b.p. 140–42°/ 0.4 mm.	312
5-Nitro	ethyl	hydroxyethyl	m.p. 59–60°	619
3-Nitro	methyl	methyl	m.p. 31°	317
5-Nitro	methyl	methyl	m.p. 154–55°	319
3-Nitro	methyl	phenyl	b.p. 108°/0.7 mm.	312

TABLE IX-31. 2-(Dialkylaminoethylamino)pyridines

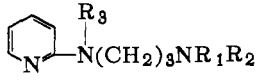


R_1	R_2	R_3	Physical properties, derivatives	Ref.
H	H	benzyl	sulfate, m.p. 156–58°	627
Benzyl	benzyl	benzyl	b.p. 200–4°/0.05 mm.	628
Benzyl	benzyl	4-chlorobenzyl	b.p. 212–13°/0.08 mm.	628
Benzyl	benzyl	4-methoxybenzyl	b.p. 234–36°/0.01 mm.	628
Ethyl	ethyl	1-(2,2-dibutyl)hexyl	hydrochloride, m.p. 205–5.5	300
Ethyl	ethyl	phenyl	b.p. 135–49°/0.08 mm.	626
Ethyl	ethyl	2-thenyl	b.p. 187–90°/4 mm.	607
Methyl	methyl	1-acenaphthenyl	b.p. 182–92°/1 mm.	629
Methyl	methyl	benzhydryl	b.p. 195–98°/1 mm.	173
Methyl	methyl	2-benzothienyl	m.p. 80–81°	630
Methyl	methyl	3-benzothienyl	hydrochloride, m.p. 186–87°	614
Methyl	methyl	benzyl	hydrochloride, m.p. 182°, 189–91	603,596,243
Methyl	methyl	4-bromobenzyl	b.p. 162°/0.1 mm.	322
Methyl	methyl	5-bromo-2-furfuryl	b.p. 156–58°/0.5 mm.	321
Methyl	methyl	3-bromo-2-thenyl	b.p. 184–85°/1 mm.	616
Methyl	methyl	5-bromo-2-thenyl	hydrochloride, m.p. 184–86°	295,616
Methyl	methyl	butyl	hydrochloride, m.p. 187°	596
Methyl	methyl	4-chlorobenzyl	hydrochloride, m.p. 172–74°	302
Methyl	methyl	5-chloro-2-furfuryl	oil	615
Methyl	methyl	5-carboxy-2-thenyl	picrate, m.p. 198–200°	616
Methyl	methyl	5-chloro-3-thenyl	hydrochloride, m.p. 106–8°	295,616
Methyl	methyl	cyclopentenyl	hydrochloride, m.p. 163–65°	631
Methyl	methyl	1-(2,2-dibutyl)hexyl	hydrochloride, m.p. 184.5–85.5°	300
Methyl	methyl	2,5-dichloro-3-thenyl	b.p. 174–180°/1 mm.	616

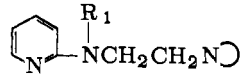
TABLE IX-31 (*continued*)

R_1	R_2	R_3	Physical properties, derivatives	Ref.
Methyl	methyl	ethoxyethyl	b.p. 160–5°/1.7 mm.	633,324
Methyl	methyl	4-fluorobenzyl	b.p. 132°/0.1 mm.	323
Methyl	methyl	2-furfuryl	b.p. 146–49°/2 mm.	615,321
Methyl	methyl	2-furyl	hydrochloride, m.p. 117–19°	635
Methyl	methyl	4-methoxybenzyl	hydrochloride, m.p. 135°	634
Methyl	methyl	α-methylbenzyl	picrate, m.p. 162–63°	632,173
Methyl	methyl	4-methyl-2-thienyl	b.p. 185–90°/2 mm.	596
Methyl	methyl	2-methyl-4-thiazolylmethyl	b.p. 185–90°/2 mm.	603
Methyl	methyl	phenethyl	hydrochloride, m.p. 143°	603
Methyl	methyl	*i*-propyl	b.p. 120–25°/1 mm.	626
Methyl	methyl	4-*i*-propylbenzyl	b.p. 190–95°/1.9 mm.	596,603
Methyl	methyl	4-*i*-propyloxyphenyl	hydrochloride, m.p. 151–52°	294
Methyl	methyl	2-thenyl	b.p. 166–68°/2 mm.	251,637,638
Methyl	*i*-propyl	phenyl	b.p. 155–56°/0.075 mm.	294

TABLE IX-32. 2-(Dialkylaminopropylamino)pyridines

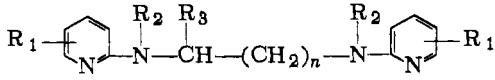


R_1	R_2	R_3	B.p., °C./mm.	Ref.
Ethyl	ethyl	phenyl	185–95/5	30
Methyl	methyl	benzyl	200–5/3	603
Methyl	methyl	4-methoxybenzyl	195–200/2.5	596,603
Methyl	methyl	phenyl	200–5/3	596
Methyl	methyl	2-thenyl	171–74/4	251

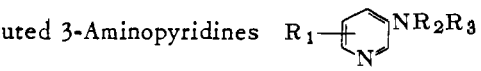
TABLE IX-33. 2-(Cycloalkylaminoethyl)pyridines 

R_1	—N◯	Physical properties, derivatives	Ref.
Benzyl	morpholinyl	hydrochloride, m.p. 206–10°	243
Benzyl	phthalimido	m.p. 121–2°	627
Benzyl	piperidyl	b.p. 195–203°/0.7 mm.	243
4-Chlorobenzyl	pyrrolidyl	hydrochloride, m.p. 163–65°	636
4-Methoxybenzyl	piperidyl	hydrochloride, m.p. 123–23.5°	639
Pyrrolidylethyl	pyrrolidyl	b.p. 178–79°/0.45 mm.	640
2-Thenyl	morpholinyl	hydrochloride, m.p. 195–5.5°	605
2-Thenyl	piperidyl	hydrochloride, m.p. 135–36°	251

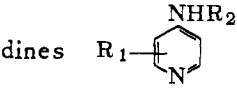
TABLE IX-34. Bis(2-pyridylamino)alkanes



n	R_1	R_2	R_3	M.p., °C.	Ref.
0	H	H	2-furyl	94–97	615
0	H	H	2-hydroxyphenyl	66–67	172
0	H	H	phenyl	105–6	172
0	H	H	trichloromethyl	160	172
0	5-nitro	H	H	262–64	168
1	H	H	H	134–35	641
4	H	H	H	150	641,598
4	H	butyl	H	sulfate: 170–71	598
4	H	ethyl	H	hydrochloride: 177–79	598
4	H	hexyl	H	hydrochloride: 93–94	598
5	H	H	H	152–54	641
6	H	H	H	104–5	641
7	H	H	H	110–12	641
8	H	H	H	140–41	641
9	H	H	H	122–24	641

TABLE IX-35. *N*- and *N,N*-Substituted 3-Aminopyridines 

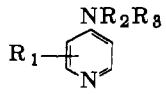
R_1	R_2	R_3	Physical properties, derivatives	Ref.
H	H	2-aminophenyl	m.p. 125.5–26°	642
H	H	2-carboxy-5 chlorophenyl	m.p. 263–65°	308
H	H	2-carboxy-phenyl	m.p. 237–38°	643,311
H	H	2-(5-diethyl-amino)-pentyl	b.p. 175–78°/0.5 mm.	299
H	H	4-dimethyl-aminophenyl	b.p. 200–20°/14 mm.	644
H	H	ethyl	b.p. 246–47°	644
H	H	methyl	b.p. 118–20°/12 mm.	21
H	H	phenyl	m.p. 200°	642
H	H	2-tetrahydro-furfuryl	picrate, m.p. 161°	645
H	dimethyl-amino-ethyl	methyl	b.p. 145–47°/10 mm.	646
H	methyl	methyl	hydrochloride, m.p. 143°	88
H	methyl	phenyl	b.p. 245–50°/25 mm.	644
2-Amino	H	methyl	m.p. 124°	21
6-Amino	H	methyl	m.p. 70°	21
2-Nitro	H	methyl	m.p. 110°	21
2,6-Dibromo	methyl	methyl	b.p. 113–15°/0.5 mm.	21

TABLE IX-36. Secondary 4-Aminopyridines 

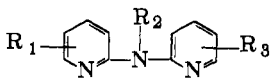
R_1	R_2	Physical properties, derivatives	Ref.
H	benzyl	m.p. 108–9.5°	647
H	2-carboxyphenyl	m.p. 283–84°	311,643
H	4-chlorobenzyl	m.p. 137.5–38.5°	648
H	diethylaminobutyl	b.p. 145°/0.4 mm.	649
H	2-(4-diethylamino)-butyl	b.p. 135°/0.4 mm.	303,650
H	diethylaminoethyl	b.p. 130°/0.4 mm.	649
H	diethylaminohexyl	b.p. 160°/0.5 mm.	649
H	diethylaminopentyl	b.p. 160°/0.4 mm.	649
H	2-(5-diethylamino)-pentyl	picrate, m.p. 150–51°	303,650
H	diethylaminopropyl	b.p. 135°/0.4 mm.	649
H	2-diethylamino-propyl	b.p. 125°/0.25 mm.	650
H	methyl	m.p. 117–18°	318
H	phenyl	m.p. 173°	643
		m.p. 175–76°	311
H	2-piperidylethyl	b.p. 150°/0.05 mm.	650
H	3-piperidylpropyl	b.p. 155°/0.05 mm.	650
3-Amino	4-acetamidophenyl	m.p. 159°	466
3-Amino	benzyl	m.p. 67–68°	469
3-Amino	butyl	m.p. 72–73°	469
3-Amino	2-chloroethyl	m.p. 85–86°	619
3-Amino	2-diethylamino-ethyl	b.p. 181–5°/1 mm.	469
3-Amino	ethyl	m.p. 129–30°	469
3-Amino	6-methoxy-8-quinolinyl	m.p. 163–64°	466
3-Amino	methyl	m.p. 169°	465
3-Amino	phenyl	m.p. 170°	466
3-Amino	propyl	m.p. 93°	465
3-Bromo-5-nitro	2-hydroxyethyl	m.p. 120–21°	651
3,5-Dinitro	2-aminophenyl	m.p. 222°	435
3,5-Dinitro	2-anilinophenyl	m.p. 180–82°	435
2,6-Dimethyl	benzyl	picrate, m.p. 169°	647
2,6-Dimethyl	4-chlorobenzyl	m.p. 179–81.5°	648

TABLE IX-36 (*continued*)

R_1	R_2	Physical properties, derivatives	Ref.
2,6-Dimethyl	2-dimethylamino-ethyl	b.p. 175–85°/5 mm.	647
2,6-Dimethyl	phenyl	m.p. 148–49°	652
		m.p. 150°	653
3-Nitro	4-acetamidophenyl	m.p. 235–36°	466
3-Nitro	2-aminoethyl	hydrochloride, m.p. 169°	469
3-Nitro	4-aminophenyl	m.p. 163°	466
3-Nitro	benzyl	m.p. 103°	469
3-Nitro	butyl	m.p. 47–48°	469
3-Nitro	2-chloroethyl	m.p. 104°	619
3-Nitro	2-diethylamino-ethyl	b.p. 166°/1 mm.	469
3-Nitro	2-hydroxyethyl	hydrochloride, m.p. 205–6°	469
3-Nitro	6-methoxy-8-quinolinyl	m.p. 203°	466
3-Nitro	phenyl	m.p. 118°	466
3-Nitro	propyl	m.p. 70°	465

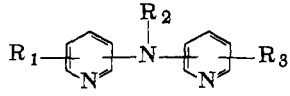
TABLE IX-37. Tertiary 4-Aminopyridines 

R_1	R_2	R_3	Physical properties, derivatives	Ref.
H	benzyl	2-dimethylaminoethyl	b.p. 174–78°	647
H	methyl	methyl	m.p. 114°	318,655
2,6-Dimethyl	2-dimethylaminoethyl	4-methoxybenzyl	picrate, m.p. 194–96°	654
2,6-Dimethyl	benzyl	2-diethylaminoethyl	b.p. 175–95°/7 mm.	654
2,6-Dimethyl	benzyl	2-dimethylaminoethyl	b.p. 174–78°/4 mm.	647
2,6-Dimethyl	benzyl	2-piperidylethyl	hydrobromide, m.p. 192°	654
2,6-Dimethyl	2-diethylaminomethyl	furfuryl	b.p. 170–80°/4 mm.	648
2,6-Dimethyl	2-dimethylaminoethyl	furfuryl	picrate, m.p. 172–75°	648
2-Methyl	benzyl	2-diethylaminoethyl	picrate, m.p. 186.5°	654
2-Methyl	benzyl	2-dimethylaminoethyl	b.p. 194–96°/10 mm.	647
2-Methyl	benzyl	2-piperidylethyl	b.p. 230–40°/4 mm.	654
2-Methyl	2-dimethylaminoethyl	phenyl	picrate, m.p. 192°	654

TABLE IX-38. Bis(2-pyridyl)amines 

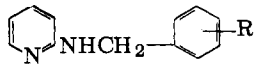
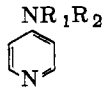
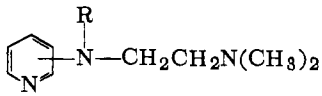
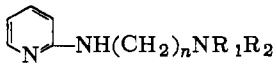
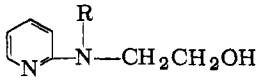
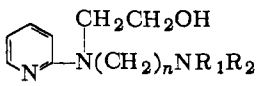
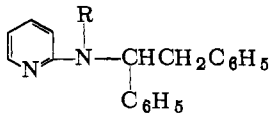
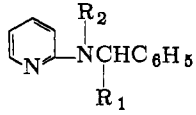
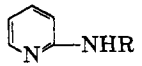
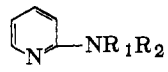
R_1	R_2	R_3	M.p., °C.	Ref.
H	H	H	94–95	172,656
H	H	5-amino	91	431
H	H	5-(2,4-diaminoanilino)	187	431
H	H	5-(2,4-dinitroanilino)	198	431
H	H	5-nitro	196–97	326
H	H	5-picrylamino	224	431
H	Ph	H	93	316
			94	624
5-Amino	H	5-amino	hydrochloride: 256–58	657
3,5-Dinitro	H	3,5-dinitro	140–41	326
3,5-Dinitro	H	5-nitro	197	326
3-Nitro	H	3-nitro	179–80	326
5-Nitro	H	5-nitro	219–20	326

TABLE IX-39. Miscellaneous Di- and Tripyridylamines

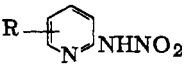


R_1	R_2	R_3	M.p., °C.	Ref.
5-Amino-2-pyridyl	H	6-amino-3-pyridyl	hydrochloride: 275	657
5-Nitro-2-pyridyl	H	6-amino-3-pyridyl	hydrochloride: 239–40	657
2-Pyridyl	H	3-pyridyl	143.8–44.8	658
2-Pyridyl	2-dimethylaminoethyl	3-pyridyl	b.p. 138–43 °/ 0.04 mm.	626
2-Pyridyl	H	3-amino-4-pyridyl	148–49	466
2-Pyridyl	H	3,5-dinitro-4-pyridyl	184–85	435
2-Pyridyl	H	3-nitro-4-pyridyl	131–32	466
2-Pyridyl	H	4-pyridyl	183–84	658
3-Pyridyl	H	3-pyridyl	128.6–29.6	658
3-Pyridyl	H	4-pyridyl	154–55	658
3-Amino-4-pyridyl	H	3-amino-4-pyridyl	244–45	328
3-Bromo-5-nitro-4-pyridyl	H	3,5-dibromo-4-pyridyl	181	328
3-Bromo-5-nitro-4-pyridyl	H	3-bromo-5-nitro-4-pyridyl	222–23	328
3,5-Dibromo-4-pyridyl	H	3,5-dibromo-4-pyridyl	222	328
3-Nitro-4-pyridyl	H	3-nitro-4-pyridyl	195–96	328
4-Pyridyl	H	3-amino-4-pyridyl	239	328
4-Pyridyl	H	3-nitro	122–23	328
4-Pyridyl	H	4-pyridyl	273–75	328
2-Pyridyl	2-pyridyl	2-pyridyl	130	329,624

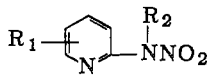
TABLE IX-40. Miscellaneous Secondary and Tertiary Aminopyridines[a]

General structure	Substituents	Ref.
	R = various substituents	174
	R_1 = benzyl and substituted benzyl R_2 = dialkylaminoethyl	648
	R = various thenyl substituents	659
		343
		
and		660
		
	R = dialkylaminoalkyl	661
	R_2 = hetero or aryl R_1 = H or dimethylaminoethyl	662
	R = various aminoalkyl derivatives	663
	R_1 or R_2 = various alkyl, aryl, hetero substituents. R_1 or R_2 may be H.	477,281, 664

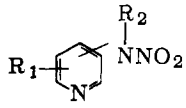
[a]This table summarizes compounds of the indicated structures which have not been included in preceding tables.

TABLE IX-41. 2-Nitraminopyridines 

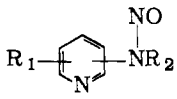
R	M.p., °C.	Ref.
H	185–89	396,394,234
6-Acetamido	193	281
6-Amino	240–50	281
5-Bromo		368
3-Chloro	159–60	367
5-Chloro-3-nitro	148	399
3,5-Dibromo	123	371
4,6-Dimethyl-5-nitro	174–75	397
4-Ethyl	171–72	373
3-Ethyl-6-methyl	221.5–22	398
5-Iodo	189	381,382
3-Methyl	154	687
3-Methyl-5-nitro		92
4-Methyl	182	688,689,397
5-Methyl	183–83.5	690,691
6-Methyl	94	692
3-Nitro	137	440
5-Nitro		394,376

TABLE IX-42. *N*-Substituted 2-Nitraminopyridines 

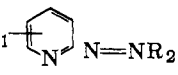
R_1	R_2	Physical properties, derivatives	Ref.
H	Et	mercuric chloride, m.p. 125.5–26.5°	397
H	Me	m.p. 30–31°	376,397
H	Pr	mercuric chloride, m.p. 122.5–23.5°	397
3,5-Dibromo	Me	m.p. 101°	371
4,6-Dimethyl-5-nitro	Me	m.p. 104.5°	397
4-Me	Et	mercuric chloride, m.p. 131–32°	397
4-Me	Me	picrate, m.p. 92–93°	397
3-Nitro	Me		376
5-Nitro	Me	m.p. 59–60°	376

TABLE IX-43. 3- and 4-Nitraminopyridines 

Position of —N(R2)—NO2	R_1	R_2	M.p., °C.	Ref.
3	H	H	170–75	400
3	H	methyl	54–55	21
4	H	H	243–44	117,438
4	3-nitro	H	202	388
4	H	benzoyl	226	117

TABLE IX-44. *N*-Nitrosoaminopyridines 

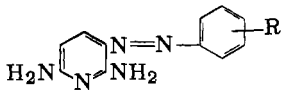
Position of —NR2	R_1	R_2	M.p., °C.	Ref.
2	H	methyl	picrate: 186–87	586
2	H	phenyl	102	306,28
2	3,5-dibromo	methyl	56–57	371
2	3-nitro	methyl	102–3	376
2	5-nitro	H	240	437
2	5-nitro	methyl	112–13	376
3	H	methyl	b.p. 135°/10 mm.	21
3	H	*i*-butyryl		239,694
3	2-methoxy	acetyl	oil	238
3	4-methoxy	acetyl	84	238
3	6-methoxy	acetyl	51.5–52.5	238

TABLE IX-45. 2-Azopyridines[a] 

R_1	R_2	M.p., °C.	Ref.
H	2-chlorophenyl	54–55	156
H	4-chlorophenyl	115–18	366
H	2,5-dihydroxyphenyl	186–88	665
H	4-dimethylaminophenyl, *cis*	108–9	366
	4-dimethylaminophenyl, *trans*	111–12	366,666
H	α-(2-hydroxynaphthyl)	137	665
H	4-methoxyphenyl	50–52	366
H	phenyl	32–34	156,366
H	2-pyridyl	85–86	156
		81	158
H	*p*-tolyl	72–74	366
5-Bromo	2-(5-bromopyridyl)	260	156
5-Bromo	phenyl	115	156
5-Chloro	2-(5-chloropyridyl)	248	157
5-Chloro	2-pyridyl	135	157
3,5-Dibromo	2-(3,5-dibromopyridyl)	103	156
3,5-Dibromo	phenyl	112	156
3-Methyl	4-dimethylaminophenyl	158–60	366
4-Methyl	4-dimethylaminophenyl	151–53	366
4-Methyl	2-(4-methylpyridyl)	149–51	156
4-Methyl	phenyl	55	156
5-Methyl	4-dimethylaminophenyl	154–57	366
6-Methyl	4-dimethylaminophenyl	107–8	366
3-Nitro	2-(3-nitropyridyl)	220	156

[a] *Cf.* Chapter VIII, pp. 520 ff.

TABLE IX-46. 2,6-Diamino-3-phenylazopyridines[a]



R	M.p., °C.	Ref.
H	137	332,668
H	diacetyl: 213–14	669
2-Carboxy	270	670,671
4-Carboxy-3-hydroxy	262	672
4-Dimethylaminophenyl	hydrochloride	335
2-Ethoxy	hydrochloride: 127	339
3-Ethoxy	hydrochloride: 116–17	339
4-Ethoxy	hydrochloride: 176–77	670,339
2-Hydroxy	186	338
3-Hydroxy	212–13	338
4-Hydroxy	218–20	338
	hydrochloride: 214–15	670
4-Methoxy	hydrochloride: 192	670
	hydrochloride: 182	339

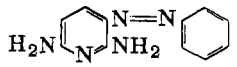
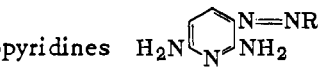
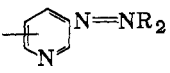
[a]For more compounds of the general formula:  see refs. 334,673,333,674,675,290,672,267.

TABLE IX-47. 2,6-Diamino-3-heteroarylazopyridines 

R	M.p., °C.	Ref.
6-Acetamido-3-pyridyl	253	340
6-Amino-3-pyridyl	260	340
6-Butoxy-3-pyridyl	129	340
6-*i*-Butylmercapto-3-pyridyl	146–47	678
6-Carbethoxy-2-benzothiazolyl	235	677
6-Chloro-3-pyridyl	242	340,679,267
2-Ethoxy-3-pyridyl	154	340
6-Ethoxy-3-pyridyl	181	340
6-Ethoxy-5-quinolinyl	239	340
2-Ethylmercapto-6-benzothiazolyl	154–55	675
6-Ethylmercapto-3-pyridyl	143–44	678,362
6-Hydroxy-3-pyridyl	290	340
4-Methyl-2-benzothiazolyl	274–75	681
5-Methyl-2-benzothiazolyl	248–50	681
6-Methyl-2-benzothiazoyl	264	681
7-Methyl-2-benzothiazolyl	275–76	681
6-Methylmercapto-3-pyridyl	130	678
2-Pyridyl	167	665
2-Thiazolyl	226–27	681

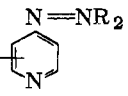
TABLE IX-48. Other 3-Azopyridines[a] 

R_1	R_2	M.p., °C.	Ref.
H	2-chlorophenyl	60	156
H	4-dimethylaminophenyl	121	276
H	α-(2-hydroxynaphthyl)	152	276
H	phenyl	52–53	156
H	3-pyridyl	140	156,152
2-Acetamido-5-amino	6-chloro-3-pyridyl	160	340
6-Amino	α-(2-hydroxynaphthyl)	188–89	240
5-Bromo	α-(2-hydroxynaphthyl)	145–46	33
5-Bromo-2,6-diamino	6-chloro-3-pyridyl	255	340
6-Chloro	α-(2-hydroxynaphthyl)	185	667
2,4-Diamino-6-methyl	3-hydroxy-4-tolyl[b]	177	486
2,5-Diamino-6-methyl	3-hydroxy-4-tolyl[c]	143	486
2,4-Diamino-6-methyl	4-methoxyphenyl[b]	155	486
2,4-Diamino-6-methyl	phenyl[b]	182	486
2,6-Dimethyl	2,6-dimethyl-3-pyridyl	137–38	402
2,6-Dimethyl	4-hydroxyphenyl	240	116
2,6-Dimethyl	4-methoxyphenyl	81–82	116

[a] *Cf.* Chapter VIII, pp. 520 ff.

[b] Structure not definite. This group may be in the 5 position.

[c] Structure not definite. This group may be in the 4 position.

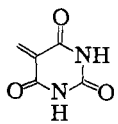
TABLE IX-49. 4-Azopyridines[a] 

R_1	R_2	M.p., °C.	Ref.
H	4-chlorophenyl	99–100	365
H	2,4-dihydroxyphenyl		352,117
H	4-dimethylaminophenyl	dinitrate: 176–77	117
H	phenyl	98–99	365,156
H	4-pyridyl	108–9	156,682
2,6-Diamino	phenyl	203	668
3,5-Diamino	4-bromphenyl	217–18[b]	683
3,5-Diamino	6-butoxy-3-pyridyl	169–70[b]	684
3,5-Diamino	2-carboxyphenyl		683,685
3,5-Diamino	2-chlorophenyl	237[b]	683
3,5-Diamino	3-chlorophenyl	186[b]	683
3,5-Diamino	4-chlorophenyl	209[b]	683,685
3,5-Diamino	6-chloro-3-pyridyl	221[b]	684
3,5-Diamino	6-ethoxy-3-pyridyl	221[b]	684
3,5-Diamino	4-methoxyphenyl	245[b]	683,685
3,5-Diamino	6-methoxy-3-pyridyl	230[b]	684
3,5-Diamino	β-naphthyl	192[b]	683,685
3,5-Diamino	phenyl	178[b]	683,685
3,5-Diamino	8-quinolinyl	> 260[b]	684
2,6-Dimethyl	4-chlorophenyl	99–100	365
2,6-Dimethyl	phenyl		365

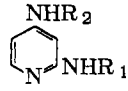
[a] *Cf.* Chapter VIII, pp. 520 ff.

[b] Position of coupling not certain.

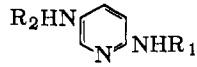
TABLE IX-50. 2,3-Diaminopyridines 

R_1	R_2	Substituents and positions 4	5	6	M.p., °C.	Ref.
H	H	H	H	H	112-13, 111, 112, 113-14; picrate: 247-49	341,370, 475,457, 498
H	H	Me			115-16	395
H	H		Me		85-86	395
H	H			Me	69-70	395,459
H	H		Br		164-65	464
H	H		Cl		174-76, 164.5-65	467,457, 341
H	H			Cl		459
H	H	Cl(?)	Br		164	345
H	H			Nitro	214-14.5	38
Acetyl	acetyl		Br		214-15	464
Cyclohexyl	H				119	474
Dimethyl[a]	H				60	473
Methyl	H				100-1	475,152
H	Me				124	475,21
Phenyl	H				142-43	474,475
Propyl	H				58	472
Propyl					243	473

[a] 3-Amino-2-dimethylaminopyridine.

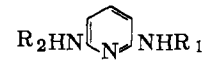
TABLE IX-51. 2,4-Diaminopyridines 

R_1	R_2	Substituents and positions 3	5	6	M.p., °C.	Ref.
H	H				107, 106-7	491,477
H	H			Br	155-56	589
H	H			Me	117-18	477,486
H	H	nitro			212	497,51,498,476
H	H	nitro		Me	186-87	459
Acetyl	acetyl				200-2	477
Carbethoxy	carbethoxy				170	491

TABLE IX-52. 2,5-Diaminopyridines 

R_1	R_2	Substituents	M.p., °C.	Ref.
H	H		103.5-4.5, 107-9, 108-10	38,471,490, 437,353
H	H	6-Me		486
H	2-amino-4-methoxy-phenyl		132-33	477
H	methyl		70	21
Acetyl	acetyl		289-90	341
Benzoyl	benzoyl		229-30	490
Butyl	acetyl		155	460
Carbethoxy	carbethoxy		198-99	490
Carbomethoxy	carbomethoxy		206-7	490
Dimethyl[a]	H		55-56	319

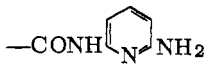
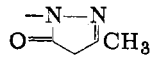
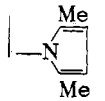
[a] 5-Amino-2-dimethylaminopyridine.

TABLE IX-53. 2,6-Diaminopyridines 

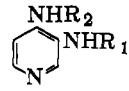
R_1	R_2	Substituents and positions			M.p., °C.	Ref.
		3	4	5		
H	H				119-20	492,481
					121-22	484,482, 483
					122	7,327
H	H	4-Amino-phenyl			155-57	695
H	H	Br			174-75, 176	696,340
H	H	4-chloro-phenyl			186-87	695
H	H	I		I	209-10	281
H	H	Me			149-50	281
H	H		Me		110-11	281
H	H	nitro		Me	282	487
H	H	nitro			237-38	38,493, 332,487
H	H	nitroso			indef.	332
H	H	Ph			114-15	695
H	acetyl				156-57	281
H	6-amino-2-pyridyl					281
H	butyryl				152-53	281
H	carbamoyl				175-76	281
H	carbethoxy				111-12	281
H	cyanoacetyl				152-53	281
H	diethyl[a]				hydrochloride: 143-44	281
H	diethylamino-propyl				dihydrochloride: 65-75	281
H	2-hydroxy-benzoyl				178-79	281
H	piperidyl[b]				38-39	32,697

(*continued*)

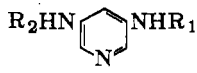
TABLE IX-53. 2,6-Diaminopyridines (*continued*)

R_1	R_2	Substituents and positions			M.p., °C.	Ref.
		3	4	5		
H	succinoyl				174–75	281
H	—COCHPh OAc				151–53	281
H						281
H					188–89.5	281
Acetyl	acetyl				202–3	281,332
Acetyl	acetyl	I			210–11	281
Acetyl	acetyl	methoxy			173.5–74.5	281
Acetyl	acetyl	nitro			192–93	332
Acetyl-glycyl	acetylglycyl				260–61	281
Acetyl	carbethoxy-acetyl				150–51.5	281
Acetyl	2-(5-diethylamino-pentyl)				106–8	281
Acetyl	nitro				193	281
Benzoyl	benzoyl				176	492
Carbamoyl	carbamoyl					281
Carbethoxy	carbethoxy				132.5–33.5	281,69
Diethyl	diethyl[c]				hydrochloride: 120–22	281
N,*N*-Diethylglycyl	*N*,*N*-diethylglycyl				109.5–10.5	281
Methyl	methyl				70–71	281
Piperidyl	piperidyl[d]				39–40	32
Phthaloyl	phthaloyl				340	488
p-Tosyl	*p*-tosyl		amino		360	200
Acetyl	 (≡ —NHR_2)				147.5–48.5	281

[a] 2-Amino-6-Diethylaminopyridine.
[b] 2-Amino-6-piperidylpyridine.
[c] 2,6-Bis(diethylamino)pyridine.
[d] 2,6-Dipiperidylpyridine.

TABLE IX-54. 3,4-Diaminopyridines 

R_1	R_2	Substituents and positions			Physical properties, derivatives	Ref.
		2	5	6		
H	H				m.p. 218–19°, 215–16°	470,469
H	H		Br		m.p. 141.5°	469
H	H			Cl	m.p. 157–58°, 162°	469,388, 470
H	H			Me	dihydrochloride, m.p. 250°	489
H	*p*-acetamidophenyl				m.p. 159°	466
H	benzyl				m.p. 67–68°	469
H	Bu				m.p. 72–73°	469,465
H	Bu		Br		m.p. 46°	462
H	Bu	Cl			m.p. 107–8°	462
H	Bu	Cl	Br		m.p. 45°	462
H	Bu	Cl	Cl		b.p. 163–64°/3 mm.	462
H	2-diethylaminoethyl				b.p. 181.5°/1 mm.	469
H	Et				m.p. 129–30°	469,465
H	6-methoxy-8-quinolinyl				m.p. 163–64°	466
H	Me				m.p. 169°	465
H	Ph				m.p. 170°	466
H	Pr				monohydrate, m.p. 93°	465
H	2-Py				m.p. 148–49°	466
H	thioformyl					
or	*or*				m.p. 154°	498
Thioformyl	H					
Benzoyl	benzoyl				m.p. 213°, 222–23°	117,470

TABLE IX-55. 3,5-Diaminopyridines 

R_1	R_2	Substituents and positions			M.p., °C.	Ref.
		2	4	6		
H	H				109–10	33
					110–11	31,458,480
H	dimethyl[a]					40
H	Me					40
Acetyl	acetyl				247–8,	458,33
					251–2	33
Acetyl	acetyl	Br		Br	233–4	33
Benzoyl	benzoyl				211–12	492
Carbethoxy	carbethoxy				179–81	492

[a] 3-Amino-5-dimethylaminopyridine.

TABLE IX-56. Triaminopyridines 

Substituents and positions					M.p., °C.	Ref.
2	3	4	5	6		
Amino	amino	amino			dihydrochloride: 246–48	497
Amino	amino	amino		methyl	hydrochloride: 240–45	459
Amino	amino			amino	dihydrochloride: 230	698, 273, 468,467
Acetamido	amino			acetamido	171–75	699,478
Acetamido	acetamido			acetamido	251–52	464,698
Amino		amino		amino	185	200
Chloro	amino	amino	amino	chloro	206	388

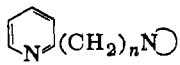
TABLE IX-57. Simple 2-(Aminoalkyl)pyridines 

n	R_1	R_2	Physical properties, derivatives	Ref.
1	H	H	b.p. 78–80°/12 mm., 82°/12 mm., 95–98°/20 mm.	512,513,538
1	H	acetyl	m.p. 59–60°	538
1	H	benzoyl		538
1	H	butyl	b.p. 112–14°/8 mm.	548
1	H	formyl	b.p. 160–61°/4 mm.	538
1	aminopropyl	butyl	b.p. 137–40°/1 mm.	548
1	butyl	2-cyanoethyl	b.p. 182–83°/10 mm.	548
1	butyl	3-(2′-cyanoethylamino)-propyl	b.p. 205–11°/2 mm.	548
1	H	6-purinyl	m.p. 257°	702
2	H	H	b.p. 92–93°/12 mm.; hydrochloride, m.p. 185–86°	501,571,504
2	H	amyl		700
2	H	benzyl	b.p. 140–41°/1.7 mm.	568
2	H	butyl	b.p. 132–33°/12 mm.	568
2	H	*i*-butyl	b.p. 85–87°/1.5 mm.	568
2	H	carbamoyl	m.p. 143°	571
2	H	carbomethoxy	m.p. 53–54°	504
2	H	cyclohexyl	b.p. 134–35°/1.5 mm.	568,701
2	H	ethyl	b.p. 109–10°/12 mm.	568
2	H	2-furfuryl	b.p. 120–21°/1 mm.	568
2	H	hydroxy	b.p. 105.9–6.8°	568
2	H	2-hydroxyethyl		700
2	H	methyl	b.p. 113–14°/30 mm., 117–18°/25 mm.; dihydrochloride, m.p. 148–49°	501,568,504
2	H	phenyl	m.p. 40.6–41.5°; b.p. 175°/2 mm.	568,700
2	H	propyl	b.p. 79–80°/1 mm.	568
2	H	2-pyridylethyl	b.p. 192°/8 mm.	501
2	H	2-thenyl	b.p. 144–46°/1.7 mm.	568
2	benzyl	chloroethyl	hydrochloride, m.p. 171–72°	505

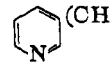
(*continued*)

TABLE IX-57. Simple 2-(Aminoalkyl)pyridines (*continued*)

n	R_1	R_2	Physical properties, derivatives	Ref.
2	benzyl	hydroxyethyl	b.p. 198–202°/5 mm.	505
2	butyl	butyl	b.p. 120–21°/1.8 mm.	567
2	*i*-butyl	*i*-butyl	b.p. 144–45°/12 mm.	567
2	carbamoyl	nitroso	m.p. 108°	571
2	ethyl	ethyl	b.p. 118°/15 mm.; picrate, m.p. 164°; b.p. 82–83°/2 mm.; b.p. 79–80°/2 mm.; hydrochloride, m.p. 171–72°	555,556, 567,703, 504
2	methyl	methyl	b.p. 101–3°/17 mm.	567
2	methyl	phenyl	b.p. 141–43°/1.1 mm.	567
2	propyl	propyl	b.p. 140–41°/16 mm.	567
2	ethyl	ethyl	b.p. 142°/24 mm.	704

TABLE IX-58. Cyclic 2-(Aminoalkyl)pyridines 

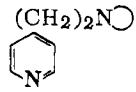
n	—N⌒	Physical properties, derivatives	Ref.
1	piperidyl	b.p. 122–24°/10 mm.	705
		b.p. 121–27°/4 mm.	703
2	(2,5-dimethyl)pyrryl	b.p. 124–25°/1 mm.	567
2	2-methylpiperidyl	b.p. 152°/15 mm.	706
2	4-methylpiperazyl	b.p. 128–29°/2.7 mm.	705
2	morpholinyl	b.p. 105–6°/0.5 mm.	567
		b.p. 163–71°/17–18 mm.	705
2	phthalimido	m.p. 95–97°	571,572
2	piperidyl	b.p. 115°/3 mm.	700
		b.p. 116–18°/3.7 mm.	567
2	pyrrolidinyl	b.p. 96–97°/2.2 mm.	567
2	1-pyrryl	b.p. 148–50°/10 mm.	567

TABLE IX-59. Simple 3-(Aminoalkyl)pyridines 

n	R_1	R_2	Physical properties, derivatives	Ref.
1	H	H	b.p. 88–90°/2 mm.	707
			b.p. 102–3°/14 mm.	513
			b.p. 102–3°/14 mm.	517
			b.p. 112°/18 mm.	547,536
			hydrochloride, m.p. 224°	518,708
1	H	benzyl	hydrochloride, m.p. 246–47°	708
1	H	ethyl	hydrochloride, m.p. 159–60°	708
			picrate, m.p. 207°	535
1	H	6-purinyl	m.p. 259°	702
1	H	3-pyridylcarbonyl	m.p. 108°	574
1	H	3-pyridylmethyl	b.p. 147–48°/? mm.	547
			b.p. 168°/0.55 mm.	708
			b.p. 184–87°/2–3 mm.	707
1	ethyl	ethyl	b.p. 108–9°/14 mm.	532
			b.p. 99–100°/12 mm.	709
1	methyl	methyl	hydrochloride, m.p. 178–79°	708
1	methyl	3-pyridylmethyl	hydrochloride, m.p. 193–94°	708
1	3-pyridylmethyl	3-pyridylmethyl	hydrochloride, m.p. 247–48°	708
2	H	H	b.p. 117°/15 mm.	708
			b.p. 117–18°/15 mm.	565
			b.p. 114–19°/15 mm.	190
2	H	4-chlorobenzoyl	monohydrate, m.p. 173–75°	710
2	H	*N*-phenylcarbamoyl	m.p. 112.5–14.5°	190
4	H	H		543
4	acetyl	methyl	b.p. 164°/1 mm.	711
4	diethylcarbamoyl	methyl	b.p. 174–77°/1 mm.	711
4	formyl	methyl	b.p. 240–6°/35 mm.	711
4	methyl	3-pyridylcarbonyl	b.p. 215–30°/1 mm.	711
4	methyl	*i*-valeryl	b.p. 175°/1 mm.	711

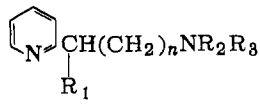
TABLE IX-60. Simple 4-(Aminoalkyl)pyridines 

n	R_1	R_2	Physical properties, derivatives	Ref.
1	H	H	b.p. 103°/11 mm.	513
			b.p. 120–25°/12 mm.	516
1	H	6-purinyl	m.p. 265–66°	702
2	H	H	hydrochloride, m.p. 226–29°	566
2	H	butyl	b.p. 162–67°/0.2 mm.	569
2	H	carbomethoxy	hydrochloride, m.p. 132–33.	504
2	H	2-carbomethoxyphenyl	b.p. 166°/0.6 mm.	569
2	H	cyclohexyl	b.p. 175–82°/15 mm.	570
2	H	ethyl	hydrochloride, m.p. 154–55°	570
2	H	hydroxyethyl	b.p. 188–93°/15 mm.	570
2	H	2-methoxyphenyl	b.p. 176–77°/0.3 mm.	569
2	H	methyl	hydrochloride, m.p. 215–18°	570
2	H	1-naphthyl	b.p. 226–28°/0.8 mm.	569
2	H	phenyl	m.p. 61.5°	569
2	H	2-propoxyphenyl	b.p. 179–85°/0.6 mm.	569
2	H	3-(4-pyridyl)propionyl	m.p. 144–46°	566
2	H	2-tolyl	m.p. 66–67°	569
2	H	3-tolyl	b.p. 184–87°/2 mm.	569
2	H	4-tolyl	b.p. 180–85°/0.5 mm.	569
2	benzyl	butyl	b.p. 167–68°/2 mm.	570
2	benzyl	ethyl	b.p. 180–81°/7 mm.	570
2	benzyl	methyl	b.p. 158–60°/3–4 mm.	570
2	benzyl	phenyl	b.p. 203–5°/0.3 mm.	569
2	butyl	butyl	b.p. 171–75°/19 mm.	569
			b.p. 111–13°/0.5 mm.	557
2	ethyl	ethyl	b.p. 80–81°/0.5 mm.	557
			hydrochloride, m.p. 234–35°	570
2	methyl	methyl	b.p. 63–64°/0.5 mm.	557
			hydrochloride, m.p. 223–24°	570
2	methyl	phenyl	b.p. 158–60°/1–2 mm.	570
2	*i*-propyl	*i*-propyl	b.p. 116°/0.5 mm.	557

TABLE IX-61. Cyclic 4-(Aminoalkyl)pyridines 

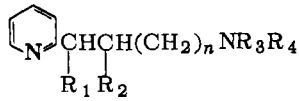
—N◯	Physical properties, derivatives	Ref.
1-(4-Methylpiperazyl)	b.p. 167-68°/12 mm.	570
Morpholinyl	b.p. 117-19°/0.5 mm.	557
	hydrochloride, m.p. 215-15.7°	534
	hydrochloride, m.p. 224-26°	570
Piperidyl	b.p. 156-60°/16 mm.	569
	hydrochloride, m.p. 225-26°	570
Pyrrolidyl	hydrochloride, m.p. 216-17°	570
	b.p. 93°/0.5 mm.	557
Tetrahydroquinolyl	b.p. 171-73°/0.2 mm.	569

TABLE IX-62. 2-(Aminoalkyl)pyridines (with chain branching adjacent to the ring)

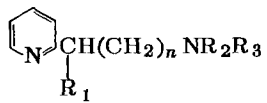


n	R_1	R_2	R_3	Physical properties, derivatives	Ref.
0	3-Ethoxypropyl	H	H	b.p. 133°/5 mm.	540
0	3-Ethoxypropyl	methyl	4-tosyl		540
0	3-Ethoxypropyl	H	4-tosyl	m.p. 96°	540
0	Ethyl	H	H	b.p. 110°/31 mm.	538
0	Ethyl	acetyl	H	m.p. 83°	538
0	Ethyl	formyl	H	b.p. 146°/2 mm.	538
0	Methyl	H	H	b.p. 197-201°,194-96°	538,544
0	Methyl	acetyl	H	m.p. 107°	538
0	Methyl	benzoyl	H	m.p. 93°	538
0	Methyl	formyl	H	b.p. 156°/4 mm.	538
1	Diethylaminomethyl	ethyl	ethyl	picrate, m.p. 164°	555
1	Methyl	ethyl	ethyl	b.p. 129°/18 mm.	555
2	Benzyl	methyl	methyl	b.p. 135°/0.5 mm.	712,713
2	4-Bromobenzyl	methyl	methyl		712
2	5-Bromo-2-thenyl	methyl	methyl		713
2	Cyclohexyl	methyl	methyl	145-50°/2 mm.	712
2	Cycholexylmethyl	methyl	methyl		712,713
2	Pentyl	methyl	methyl	104-5°/1.5 mm.	712
2	2-Thenyl	methyl	methyl	130-33°/0.1 mm.	712
3	Amino	ethyl	ethyl	145-47°/5 mm.	714
3	4-Bromobenzyl	methyl	methyl		713
3	Cyclohexylmethyl	methyl	methyl		713
0	Piperidylmethyl	—pentamethylene—		b.p. 192°/8 mm.	555

TABLE IX-63. 2-(Aminoalkyl)pyridines (with chain branching not adjacent to the ring)



n	R_1	R_2	R_3	R_4	Physical properties, derivatives	Ref.
0	H	methyl	H	H	b.p. 49°[a]/0.016 mm.	511
					b.p. 75°[b]/0.5 mm.	511
					b.p. 96.5–97°/12 mm.	563
					b.p. 103–4°/13 mm.	706
0	H	methyl	ethyl	H	b.p. 108–9°/13 mm.	706
0	H	methyl	ethyl	ethyl	b.p. 122°/12 mm.	706
0	H	methyl	methyl	H	hydrochloride, m.p. 158–58.5°	504
0	butyl	methyl	H	H	b.p. 129–30°/2.5 mm.	563
1	phenyl	methyl	methyl	methyl		712
2-Py—CH(C_6H_5)—$(CH_2)_2$—CH(CH_3)—$N(CH_3)_2$						715

TABLE IX-64. 2-(Aminoalkyl)pyridines (with side-chain arylation) 

n	R_1	R_2	R_3	Physical properties, derivatives	Ref.
0	Phenyl	2-dimethylaminoethyl	H	b.p. 140–43°/0.5 mm.	320,351
0	Phenyl	2-dimethylaminoethyl	methyl	b.p. 160–63°/1 mm.	320,551
0	Phenyl	2-dimethylaminoethyl	2-pyridyl	b.p. 185–90°/0.2 mm.	320,551
0	Phenyl	methyl	H	b.p. 120–22°/0.5 mm.	320
0	Phenyl	2-pyridyl	H	b.p. 145–47°/0.2 mm.	320,551
0	Phenyl	2-pyrimidyl	H		551
0	3-Methoxyphenyl	H	H	hydrochloride, m.p. 210–11°	717
1	Phenyl	H	H	b.p. 130°/0.15 mm.; hydrochloride, m.p. 210–11°	717 577
1	Phenyl	guanyl	H	acetate, m.p. 202°	577,717
1	Phenyl	methyl	methyl	hydrochloride, m.p. 190°	717
1	Phenyl	3-pyridylmethyl	H	b.p. 190–95°/0.25 mm.	717
1	Phenyl	2-Py—CH(C$_6$H$_5$)—CH$_2$—	H	m.p. 84–85°	717
2	3-(Acetamido)phenyl	methyl	methyl		715,712
2	4-Aminophenyl	methyl	methyl		712
2	4-Bromophenyl	methyl	methyl	b.p. 147–52°/0.5 mm.	715
2	5-Bromo-2-thenyl	methyl	methyl	b.p. 145–48°/0.5 mm.	712
2	5-Chloro-3-methyl-2-thienyl	methyl	methyl	b.p. 149–52°/1 mm.	712
2	2-Chlorophenyl	methyl	methyl		712
2	4-Chlorophenyl	ethyl	H	b.p. 187–90°/2 mm.	718

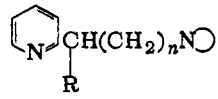
2	4-Chlorophenyl	ethyl	ethyl	b.p. 187–89°/4 mm.	718
2	4-Chlorophenyl	methyl	H	b.p. 178–80°/2 mm.	718
2	4-Chlorophenyl	methyl	methyl	b.p. 142°/1 mm.	715
2	5-Chloro-2-thenyl	methyl	methyl	b.p. 140–44°/0.5 mm.	712
2	2,4-Dichlorophenyl	methyl	methyl		712,715
2	2,3-Dimethoxyphenyl	methyl	methyl	b.p. 195–200°/1–2 mm.	715
2	3,4-Dimethoxyphenyl	methyl	methyl		712,715
2	4-Dimethylaminophenyl	methyl	methyl	b.p. 183–85°/1 mm.	715,712
2	2,4-Dimethylphenyl	methyl	methyl		715,712
2	2-Furyl	methyl	methyl		712
2	4-Hydroxyphenyl	methyl	methyl	b.p. 210°/2 mm.	715
2	4-Methoxyphenyl	methyl	methyl	b.p. 137–42°/0.5 mm.	713
2	3-Methyl-2-thienyl	ethyl	ethyl	b.p. 138–42°/2–3 mm.	712
2	5-Methyl-2-thienyl	methyl	methyl	b.p. 134–37°/1 mm.	712
2	3-Nitrophenyl	methyl	methyl		715
2	Phenyl	H	H	b.p. 150–54°/2 mm.	718
2	Phenyl	ethyl	ethyl	b.p. 156°/1 mm.	713,715,712
2	Phenyl	methyl	methyl	b.p. 104–6°/0.05 mm.	719,720
				b.p. 139–42°/1–2 mm.	713,715,712
				b.p. 140–45°/3 mm.	718
2	4-*i*-Propylphenyl	methyl	methyl	b.p. 144–47°/1 mm.	713,715,712
2	2-Pyridyl	methyl	methyl	b.p. 129–32°/0.5 mm.	712
2	2-Pyrimidyl	methyl	methyl	b.p. 135–40°/1 mm.	712
2	2-Thiazolyl	ethyl	ethyl		712
2	2-Thiazolyl	methyl	methyl		712
2	2-Thienyl	ethyl	ethyl	b.p. 130–32°/1 mm.	712

(*continued*)

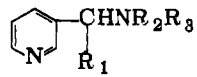
TABLE IX-64. 2-(Aminoalkyl)pyridines (with side-chain arylation) (*continued*)

n	R_1	R_2	R_3	Physical properties, derivatives	Ref.
2	2-Thienyl	methyl	methyl	b.p. 125–28°/1 mm.	712
				b.p. 154°/2 mm.	713
2	3-Thienyl	methyl	methyl	b.p. 134–37°/2–3 mm.	712
2	4-Tolyl	methyl	methyl	b.p. 130–35°/0.5 mm.	713,715,712
3	Phenyl	methyl	methyl	b.p. 135°/0.5 mm.	713,712,715
3	2-Thienyl	methyl	methyl	b.p. 130–33°/0.1 mm.	713

TABLE IX-65. Cyclic 2-(Aminoalkyl)pyridines (with side-chain arylation)

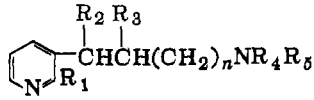


n	R	—N◯	Physical properties	Ref.
0	phenyl	4-methylpiperazyl	m.p. 95–7°	502
2	4-chlorophenyl	piperidyl	b.p. 155–60°/0.01 mm	720
2	5-methyl-2-thienyl	piperidyl	b.p. 140–44°/0.5–1 mm.	712
2	phenyl	morpholinyl		712,715
2	phenyl	piperidyl	b.p. 120–22°/0.01 mm.	720
			b.p. 160–64°/0.25 mm.	553
			b.p. 160–65°/1–2 mm.	715

TABLE IX-66. 3-(Aminoalkyl)pyridines 

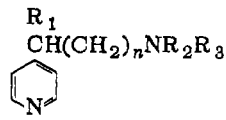
R_1	R_2	R_3	B.p., °C./mm.	Ref.
Benzyl	H	H	155–60/0.5	564
3-Ethoxypropyl	H	H	151–52/5	539
Methyl	H	H	219–21	541
			216–19	544
			223	547
Methyl	ethyl	H	223–26	541
Methyl	(3-pyridyl)ethyl	H	152–53/1	547
Phenyl	H	H	329–31	542
Propyl	H	H	247–51	541
Propyl	methyl	H	244–47	541

TABLE IX-67. Longer Chain 3-(Aminoalkyl)pyridines



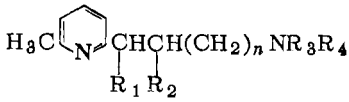
n	R_1	R_2	R_3	R_4	R_5	Physical properties	Ref.
0	H	H	Me	H	H	b.p. 83–88°/1 mm.	564
2	H	amino	H	Et	Et	b.p. 146–48°/4 mm.	714
2	H	H	Br	Me	H	unstable	721
2	H	H	Cl	Me	H	b.p. 126–30°/0.2 mm.	721
2	H	I	H	Me	H		585
2	amino	H	H	Me	H	m.p. 85–85.5°	722
2	amino	H	H	Me	Me	m.p. 84–85°	138

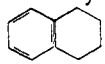
TABLE IX-68. 4-(Aminoalkyl)pyridines (with branched or arylated side chain)



n	R_1	R_2	R_3	Physical properties, derivatives	Ref.
0	Me	H	H	b.p. 221–23°	544
0	2-carbethoxy-phenyl	pentamethylene			723
1	dimethylamino-methyl	Me	Me	b.p. 84–88°/0.5 mm.	557
1	methylene	Me	Me	b.p. 65–66°/0.5 mm.	557
1	Ph	H	H	b.p. 130–35°/0.2 mm.; hydrochloride, m.p. 200°	717 577
1	Ph	[2-phenyl-2-(4′-pyridyl)]ethyl	H	picrate, m.p. 187°	717
1	methylene	—pentamethylene—		b.p. 105–6°/0.5 mm.	557
3	amino	Et	Et	b.p. 162–70°/5 mm.	714

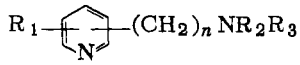
TABLE IX-69. 2-(Aminoalkyl)-6-methylpyridines



n	R_1	R_2	R_3	R_4	Physical properties	Ref.
0	H	H	H	H	b.p. 102-4°/3 mm.	506
0	H	H	benzyl	phenyl	b.p. 202-4°/0.6 mm.	569
0	H	H	butyl	H	b.p. 88-92°/0.6 mm.	569
0	H	H	butyl	butyl	b.p. 122-26°/1.2 mm.	569
0	H	H	2-carbomethoxyphenyl	H	b.p. 179-82°/0.2 mm.	569
0	H	H	*i*-hexyl	*i*-hexyl	b.p. 148-54°/1.1 mm.	569
0	H	H	2-methoxyphenyl	H	b.p. 164°/0.2 mm.	569
0	H	H	1-naphthyl	H	b.p. 211°/0.8 mm.	569
0	H	H	phenyl	H	m.p. 59°	569
0	H	H	propyl	propyl	b.p. 145-48°/12 mm.	569
0	H	H	*o*-tolyl	H	b.p. 160-63°/0.7 mm.	569
0	H	H	*m*-tolyl	H	b.p. 152-54°/0.8 mm.	569
0	H	H	*p*-tolyl	H	b.p. 176°/0.5 mm.	569
0	H	methyl	H	H	b.p. 72°/0.5 mm.	563
1	phenyl	H	methyl	methyl	b.p. 171-75°/1 mm.	712,713, 715
1	2-thienyl	H	methyl	methyl	b.p. 133-37°/1-2 mm.	712
0	H	H	—($CH_2(CH_2)_3CH(CH_3)$)—		b.p. 160-61°/12 mm.	569
0	H	H	—pentamethylene—		b.p. 151-52°/12 mm.	569
0	H	H	 [a]		b.p. 152°/0.15 mm.	569

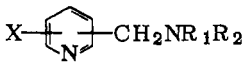
[a] Tetrahydroquinolinyl residue.

TABLE IX-70. Miscellaneous 3- and 4-(Aminoalkyl)pyridines



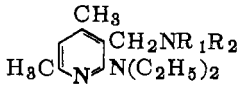
Position of aminoalkyl group	n	R_1	R_2	R_3	Physical properties, derivatives	Ref.
3	1	6-methyl	H	H	b.p. 118-20°/ 14 mm.	513
					hydrochloride, m.p. 278-80°	386
3	1	6-propyl	H	H	picrate, m.p. 193-95°	724
3	1	2,4-dimethyl	H	H	hydrochloride, m.p. 204-6°	725
3	1	2,4-dimethyl-6-chloro	acetyl	H	m.p. 136.5-38°	530
3	1	5,6-dimethyl	H	H	hydrochloride, m.p. 216-18°	725
3	2	2-methyl	H	H	b.p. 130-32°/ 20 mm.	522,523
3	2	2-methyl	2-methyl-3-pyridyl	H	b.p. 206-8°/ 12 mm.	522
4	1	2-methyl	H	H	hydrochloride, m.p. 274°	726
4	1	2-methyl	6-methyl-4-pyridylmethyl	H	hydrochloride, m.p. 218-20°	726

TABLE IX-71. Halogen-Substituted (Aminomethyl)pyridines



Position of aminomethyl group	X	R_1	R_2	M.p., °C.	Ref.
3	6-chloro	H	6-chloro-3-pyridylmethyl	104	727
4	2,6-dibromo	H	H	92-93	531
4	2,6-dibromo	acetyl	H	116-18	531
4	2,6-dichloro	H	H	70	531
				73	512
4	2,6-dichloro	acetyl	H	102	531
4	2,3,5,6-tetrachloro	H	H	62-63	513

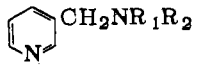
TABLE IX-72. 2-Diethylamino-3-(aminomethyl)-4,6-dimethylpyridines



R_1	R_2	Physical properties	Ref.
H[a]	H	m.p. 135-38°	529
Acetyl[a]	H	m.p. 185-87°	529
Benzoyl[a]	H	m.p. 156-58°	529
H	H	b.p. 123-24.5°/4.5 mm.	530
Acetyl	H	m.p. 126.5-127°	530
Benzoyl	H	m.p. 134.5-35.5°	530
Benzyl	chloroacetyl	m.p. 62-64°	530
Benzyl	2-diethylaminoethyl	b.p. 175-78°/0.45 mm.	530
Benzyl	dimethylaminoacetyl	b.p. 201-5°/0.5 mm.	530
Chloroacetyl	H	m.p. 110-12°	530
Cyclohexylaminoacetyl	H	m.p. 76-78°	530
2-Diethylaminoethyl	H	b.p. 147-50°/0.38 mm.	530
Diethylaminoacetyl	H	b.p. 191-93°/0.5 mm.	530
Morpholinylacetyl	H	m.p. 73-75°	530
Phenylcarbamoyl	H	m.p. 205.5-7°	530

[a]These compounds have an unsubstituted 2-amino group.

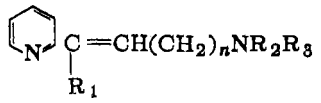
TABLE IX-73. Miscellaneous 3-(Aminomethyl)pyridines (with amino and methyl ring substituents)



Substituents and positions				R_1	R_2	Physical properties, derivatives	Ref.
2	4	5	6				
Amino	H	H	methyl	H	H	hydrochloride, m.p. 273–73.5°	528
Amino	H	H	methyl	formyl	H	m.p. 165–65.5°	528
Amino	H	H	methyl	thioformyl	H	m.p. 130°	528
H	amino	H	methyl	H	H		728
H	H	amino	methyl	H	H	hydrochloride, m.p. 295–97°	368
H	bromomethyl	amino	methyl	H	H	hydrobromide, m.p. 260–65°	729,731
H	methyl	amino	methyl	H	H	picrate, m.p. 244°	520
H	methyl	amino	bromomethyl	H	H	hydrobromide, m.p. 244–45°	527

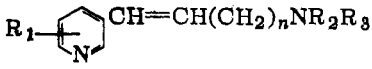
TABLE IX-74. Bis(aminomethyl)pyridines 

Substituents and positions					Physical properties, derivatives	Ref.
2	3	4	5	6		
N-Benzyl-*N*-ethylaminomethyl	*N*-benzyl-*N*-ethylaminomethyl	H	H	H	b.p. 78–80°/12 mm.	533
Aminomethyl	H	H	H	aminomethyl	hydrochloride, m.p. 250°	513
H	aminomethyl	aminomethyl	amino	methyl		732,733, 734
					hydrochloride, m.p. > 300°	735,736
Methyl	aminomethyl	aminomethyl	H	methyl	hydrochloride, m.p. > 290°	737

TABLE IX-75. 2-(Aminoalkenyl)pyridines 

n	R_1	R_2	R_3	Physical properties, derivatives	Ref.
0	H	Me	Ph	methiodide, m.p. 249°	558
0	H	Ph	H	ethiodide, m.p. 206–7°	560
				methiodide, m.p. 210°	558,559
0	H	2-Py	H	ethiodide, m.p. 271°	558
0	H	4-Py	H	methiodide, m.p. 220°	558
0	H	2-thiazolyl	H		558
0	H	—$(CH_2)_2$—O—$(CH_2)_2$—		perchlorate, m.p. 176°	558
0	H	—pentamethylene—		perchlorate, m.p. 160°	558
1	4-chlorophenyl	Et	Et	b.p. 136–38°/0.01 mm.	720
1	4-chlorophenyl	Me	Me	b.p. 118–20°/0.01 mm.	720
1	4-methoxyphenyl	Me	Me	b.p. 156–58°/0.3 mm.	720
1	Ph	Et	Et	b.p. 119–21°/0.01 mm.	720
1	Ph	Me	Me	b.p. 108°/0.05 mm.	720,738
1	2-thienyl	Me	Me	b.p. 116–22°/0.5 mm.	720
1	4-chlorophenyl	—$(CH_2)_2$—O—$(CH_2)_2$—		b.p. 186–88°/0.01 mm.	720
1	4-chlorophenyl	—pentamethylene—		b.p. 182–84°/0.01 mm.	720
1	4-chlorophenyl	—tetramethylene—		b.p. 165–69°/0.01 mm.	720
1	Ph	—pentamethylene—		b.p. 128–35°/0.01 mm.	720

TABLE IX-76. 3-(Aminoalkenyl)pyridines[a]

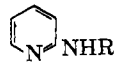


n	R_1	R_2	R_3	Physical properties, derivatives	Ref.
0	H	carbomethoxy	H	m. p. 145°	739
2	H	Me	H	picrate, m.p. 163–64°	721,740
2	2-amino	Me	H	m.p. 81.5–82°	722,741
2	6-amino	Me	H		741
2	6-amino	Me	Me	m.p. 96–97°	742

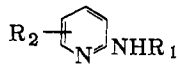
[a]Only one 4-pyridyl analog is known: 4 Py-CH=CHNHPh ethiodide trihydrate, m.p. 65° (558).

TABLE IX-77. Properties of Some Nicotine Analogs

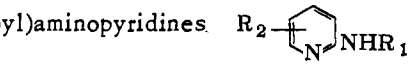
	Physical properties, derivatives	Ref.
2-Py derivatives		
1-Methyl-2-(2-pyridyl)pyrrolidine	b.p. 122°/25 mm.	540
2-(2-Pyridyl)pyrrolidine	b.p. 120°/12 mm.	540
1-Methyl-3-(2-pyridyl)pyrrolidine	picrate, m.p. 175–77°	743
3-(2-Pyridyl)pyrrolidine	picrate, m.p. 214–16°	743
3-Py derivatives		
2-(3-Pyridyl)pyrrolidine	b.p. 139–40°/12 mm.	539
	b.p. 266–67°	721
1-Methyl-2-(3-pyridyl)pyrrolidine	b.p. 113–15°/10 mm.	539
3-(3-Pyridyl)pyrrolidine	picrate, m.p. 236–37°	743
1-Methyl-3-(3-pyridyl)pyrrolidine	picrate, m.p. 193–95°	743
1-Methyl-2-(2-amino-3-pyridyl)pyrrolidine	m.p. 97–98°	22
1-Methyl-2-(2-acetamido-3-pyridyl)pyrrolidine	m.p. 35–37°	744
2-(3-Pyridyl)piperidine	b.p. 120–21°/6 mm.	745
1-Methyl-2-(3-pyridyl)piperidine	b.p. 130–35°/6 mm.	745

TABLE IX-78. 2-Acylaminopyridines 

R	M.p., °C.	Ref.
Acetoacetyl	110-13	204
Acetyl	71	192
Acrylyl		780
Benzoylacetyl	113-15	178
Bromoacetyl	91	193
Caproyl	oil	196
Carbethoxy	104-5	199
Carbethoxyacetyl	hydrochloride: 129-31	781
Carbobutoxy	62-63	199
Carboisobutoxy	74-76	199
Carboisopropoxy	82-83	199
Carbomethoxy	131-32	199
Carbomethoxyacetyl	oil	202
Carbopropoxy	74-75	199
Carboxyacrylyl		208
3-Carboxy-2-methylacrylyl	264	208
Carboxypropionyl	184	208
Chloroacetyl	110	193
Crotonyl	79	746
Formyl	71	187
Guanylthioacetyl	hydrochloride: 225	194
Lauroyl	46-47	196
Linoleyl	picrate: 57	746
Myristoyl	62	196
Oleyl	picrate: 68	746
Palmitoyl	70-71	196
Stearoyl	76-77	196
Thioacetyl	108	230

TABLE IX-79. Ring-Substituted 2-Acylaminipyridines 

R_1	R_2	M.p., °C.	Ref.
Acetyl	5-bromo	175	234
Acetyl	5-bromo-4,6-dimethyl	216–7	235
Acetyl	5-chloro	171	191
Acetyl	3,5-dibromo	102	175
Acetyl	4,6-dichloro	218–19	75
Acetyl	4,6-dimethyl	157–58	235
Acetyl	5-iodo	154–55	191
Acetyl	3-methyl	64	687
Acetyl	4-methyl	102–3	688
Acetyl	5-methyl	103–4	477
Acetyl	6-methyl	88	56
Acetyl	3-nitro	135–36	782
Acetyl	5-nitro	196	240
Acetyl	4-*n*-propyl	74–75	761
Carboxyacetyl	5-bromo	152–53	191
Carboxyacetyl	5-chloro	155–55.5	191
Carboxyacetyl	5-iodo	144–45	191
Carbethoxy	4-chloro	161	74
Carbethoxy	4,6-dichloro	75	75
Carbethoxy	4-iodo	167	74
Carbethoxy	5-iodo	192–94	477
Carbethoxy	5-nitro	209–10	236
Formyl	3-ethyl	113–14.5	189
Formyl	3-methyl	138–39	793
Hydroxyacetyl	6-bromo		195
Propionyl	3-methyl	picrate: 157	793
Thioacetyl	5-iodo	151	232
Thioacetyl	5-nitro	113–14	233

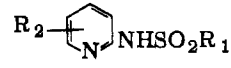
TABLE IX-80. 2-(Aroyl and Heteroyl)aminopyridines 

R_1	R_2	M.p., °C.	Ref.
4-Aminobenzoyl	H	168	783
4-Amino-2-bromobenzoyl	H		220
4-Amino-2-chlorobenzoyl	H	171–72	220
4-Arsenosobenzoyl	H		784
2-Benzothienoyl	H	132–32.5	785
Benzoyl	H	82–83	748
Benzoyl	R-chloro	120–21	74
Benzoyl	3,5-dibromo	181–82	768
Benzoyl	4-iodo	167–68	74
Benzoyl	4-methyl	114	688
2-Benzyloxy-4-nitrobenzoyl	H	144	217
2-Bromo-4-nitrobenzoyl	H	154–55	220
2-Carboxybenzoyl	H	168	208
2-Chloro-4-nitrobenzoyl	H	166–68	220
3,5-Dibromo-2-hydroxybenzoyl	H	205	221
3,5-Dichloro-2-hydroxybenzoyl	H	217	219
4-Fluorobenzoyl	H	123.6–24.3	786
2-Hydroxy-3-naphthoyl	5-bromo	278	787
2-Hydroxy-3-naphthoyl	5-nitro	> 300	787
2-Hydroxy-4-nitrobenzoyl	H	263	218
4-Methoxybenzoyl	H	158	243
Nicotinoyl	H	139–39.5	788
4-Nitrobenzoyl	H	244	783
1-Phenyl-2,3-dimethyl-5-keto-4-pyrazolinoyl	H	197	789
Picolinoyl	5-nitro	223	790
2-Thienoyl	H	b.p. 165–70/2 mm.	791

TABLE IX-81. 2-(*N,N*-Diacyl and Diaroyl)aminopyridines 

R_1	R_2	R_3	M.p., °C.	Ref.
Acetyl	acetyl	3-ethyl-6-methyl	108	192
—$OC(CH_2)_2CO$—		H	137	210
—$OC(CH_2)_2CO$—		3-methyl	118	210
—$OC(CH_2)_2CO$—		4-methyl	117	210
—$OC(CH_2)_2CO$—		5-methyl	168	210
—$OC(CH_2)_2CO$—		6-methyl	143	210
—$OC(CH_2)_3CO$—		6-methyl	192	210
Benzoyl	benzoyl	H		
Benzoyl	benzoyl	4-methyl	182–83	688
Benzoyl	benzoyl	4-chloro	165–66	74
Benzoyl	benzoyl	4-iodo	176–77	74
Phthaloyl[a]			227	120,208

[a] *N,N*-Disubstituted derivative.

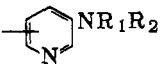
TABLE IX-82. 2-(Alkylsulfonyl)aminopyridines 

R_1	R_2	M.p., °C.	Ref.
2-Aminoethyl		140–41	245
2-Aminoethyl	5-bromo		247
2-Aminoethyl	5-chloro		247
3-Aminopropyl		182.5–83.5	246
i-Amyl		108	244
n-Butyl		97	244
i-Butyl		103	244
d-β-Camphor		208–10	750
l-β-Camphor		209–10	750
dl-β-Camphor		216–18	750
Ethyl		163	244
Methyl		194	244
2-Phthalimidoethyl		213–15	245
2-Phthalimidoethyl	5-bromo		247
2-Phthalimidoethyl	5-chloro		247
i-Propyl		203	244
β-Styryl		185	749

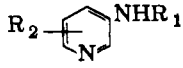
TABLE IX-83. 2-(Arylsulfonyl and Heteroarylsulfonyl)aminopyridines[a]

R_1	M.p., °C.	Ref.
5-Acetamido-2,4-xylyl	260.5–61	461
4-Acetamido-2,5-xylyl	243.5–44.5	461
4-Acetoxyphenyl	196–97	401
4-Benzoyloxyphenyl	213–13.5	680
4-Carbethoxyphenyl	167.9–68.8	401
6-Chloro-3-pyridyl	237–39	378
4-Fluorophenyl	151.2–51.7	786
4-Hydroxyphenyl	226–28	401,680
Phenyl	171–72	103
3-Pyridyl	187	111
p-Tosyloxy	202.5–4.5	401

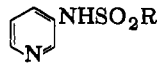
[a]Other than derivatives of sulfanilamide, for which ref. 250 may be consulted.

TABLE IX-84. 3-Acylaminopyridines 

R_1	R_2	R_3	M.p., °C.	Ref.
Acetyl	H	H	130–32	71
			133–34	37
Acetyl	H	2-chloro	90–91	152
Acetyl	H	2,6-diiodo		387
Acetyl	H	2,6-dimethyl	hydrate: 79–80	188
Acetyl	H	2,6-dimethyl-4-phenyl	162–63	762
Acetyl	H	4-methyl	84	792
Acetyl	H	6-methyl	122–23	72
Acetyl	acetyl	2-chloro	67–68	152
Acetyl	acetyl	2-methyl		418
Acetyl	methyl	H	64	21
Acetyl	H	6-phenyl	148–49	141
i-Butyryl	H	H	78–79	239
Carbethoxy	H	H	91–92	199
Carbethoxy	H	5-bromo	150–51	346
Carbethoxy	H	6-methyl	132–33	72
Carbethoxy	H	2-nitro	83–84	236
Carbethoxy	H	6-*n*-propyl	70	73
Carbisobutoxy	H	H	103–5	199
Carbisopropoxy	H	H	137–39	199
Carbobenzyloxy	H	H	164–65	71
Carbobenzyloxy	H	4-methyl	122–23	71
Carbobutoxy	H	H	71–72	199
Carbomethoxy	H	H	120–22	199
Carbomethoxy	H	5-bromo	169–70	346
Carbopropoxy	H	H	82–83	199
Cinnamoyl	H	2,6-dimethyl	189–90	188
Formyl	H	2,6-dimethyl	97–98	188
Formyl	H	2-methyl	b.p. 150/2 mm.	418
3-Phenylpropionyl	H	2,6-dimethyl	134	188

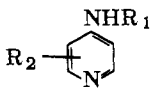
TABLE IX-85. 3-(Aroyl and Heteroaroyl)aminopyridines 

R_1	R_2	M.p., °C.	Ref.
Benzoyl	H	119	276
Benzoyl	2,6-dimethyl	169–70	188
Benzoyl	2,6-dimethy-4-phenyl	213–14	762
Benzoyl	2-methyl	114–15	60
Benzoyl	4-methyl	81	792
Benzoyl	6-methyl	110–11	72
6-Methylnicotinoyl	6-methyl	275–77	72
Nicotinoyl	H	188	47
Nicotinoyl	2-methyl	108	552
Benzoyl	6-phenyl	201	141

TABLE IX-86. 3-(Arylsulfonyl)aminopyridines[a] 

R	M.p., °C.	Ref.
3-Pyridyl	182	111
4-Tolyl	190–91.5	623

[a]Other than the two compounds in this table, all known sulfonamides of 3- and 4-aminopyridines are apparently sulfanilamide derivatives; see ref. 250.

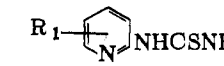
TABLE IX-87. 4-Acylaminopyridines 

R_1	R_2	M.p., °C.	Ref.
Acetyl	H	150	54
Acetyl	2,6-dimethyl	113	41
Acetyl	3-methyl	151-52	83
Acetyl	3-nitro	115	676
Benzoyl	H	202	117
Bromoacetyl	H		178
Carbethoxy	H	129	54
Carbethoxy	2,6-dichloro	132	200
Carbethoxyacetyl	H		201
Nicotinoyl	H	187	229
Phthaloyl[a]	H	232-33	120
Thiocarbethoxy	3-nitro		763
Thiocarb*iso*propoxy	3-nitro	hydrochloride: 176 (dec.)	763
Thiocarbobutoxy	3-nitro	148 (dec.)	763
Thiocarbomethoxy	3-nitro		763
Thiocarbopropoxy	3-nitro		763

[a] *N,N*-Disubstituted.

TABLE IX-88. 2-Pyridylureas 

R_1	R_2	M.p., °C.	Ref.
H	H	195	28
		173	272
H	allyl	102	171
H	amino		84
H	*i*-butyl	102	171
H	carbamoyl	175	272
H	methyl	148	171
H	4-methyl-2-thiazolyl	175–77	772
H	phenyl	187	171,771
H	2-pyridyl	175	272,275
6-Amino	H	175–76	281
6-Amino	*p*-ethoxyphenyl	168–69	281
6-(Carbamoylamino)	H		281
4,6-Dichloro	*m*-nitrophenyl	230–31	773
5-Iodo	amino	174–77	84
6-Methyl	allyl	139	620
6-Methyl	phenyl	186	620

TABLE IX-89. 2-Pyridylthioureas 

R_1	R_2	M.p., °C	Ref.
H	allyl	98	171
H	amino	194	280
H	*i*-butyl	97	171
H	4-carbomethoxy-3-hydroxyphenyl	212	774
H	*p*-chlorophenyl	188	279
H	*p*-hydroxyphenyl	218	775
H	phenyl	167	279
H	*i*-propyl	129–30	279
H	2-pyridyl	163	275
H	*m*-tolyl	168–70	279
H	*p*-tolyl	182	279
6-Methyl	H	170	620
6-Methyl	6-methyl-2-pyridyl	209	620
6-Methyl	phenyl	196	620

TABLE IX-90. 3- and 4-Pyridylureas and Thioureas

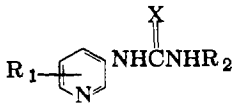
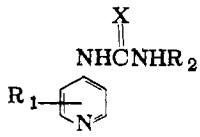
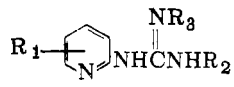
R_1	R_2	X	M.p., °C.	Ref.
				
H	H	O	178–79	272
H	amino	O		84
H	carbamoyl	O	216	776
H	carbomethoxy	O	218	776
H	phenyl	S	164	54
H	3-pyridyl	O	225	54
H	3-pyridyl	S	176	276
6-Dimethylamino	6-dimethylamino-3-pyridyl	O	252	272
6-Methyl	6-methyl-3-pyridyl	O	285–88	72
				
H	phenyl	S	148	54
H	4-pyridyl	O	208	54

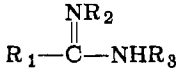
TABLE IX-91. 2-Pyridylguanidines 

R_1	R_2	R_3	M.p., °C.	Ref.
H	H	nitro		279
H	*sec*-butyl	H	80–81	279
H	*p*-chlorophenyl	H	175–76	279
H	nitro	H	229	291
H	phenyl	H	108–9	279
H	*n*-propyl	H	63–65	279
H	*i*-propyl	H	82	279
H	2-pyridyl	*p*-acetylsulfamoylphenyl	212	288
H	2-pyridyl	6-carbethoxy-2-benzothiazolyl	237	288
H	2-pyridyl	*p*-carbethoxyphenyl	89–91	288
H	2-pyridyl	*p*-ethoxyphenyl	113	288
H	2-pyridyl	*p*-methoxyphenyl	109	288
H	2-pyridyl	6-methoxy-3-pyridyl	88–91	288
H	2-pyridyl	6-methyl-2-benzothiazolyl	b.p. 94/13 mm.	288
H	2-pyridyl	*p*-sulfamoylphenyl		288
H	*m*-tolyl	H	134–35	279
H	*p*-tolyl	H	148	279
5-Methyl	nitro	H	219	291
6-Methyl	nitro	H	204–5	291

TABLE IX-92. *N,N*^{1}-Dipyridylformamidines 

R	M.p., °C.	Ref.
5-Bromo-2-pyridyl	184–86	286
5-Chloro-2-pyridyl	195–96	286
6-Chloro-3-pyridyl	194–95	149
3,5-Dibromo-2-pyridyl	226	286
5-Iodo-2-pyridyl	209	286
6-Methoxy-3-pyridyl	123	149
3-Nitro-2-pyridyl	150	118
5-Nitro-2-pyridyl	213	118
2-Pyridyl	210	287

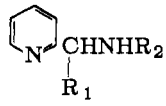
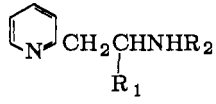
TABLE IX-93. *N*-Pyridylbenzamidines and Heterocyclic Amidines



R_1	R_2	R_3	Physical properties	Ref.
3-Aminophenyl	H	2-pyridyl		779
4-Aminophenyl	H	2-pyridyl		779
3-Chlorophenyl	H	2-pyridyl		779
4-Chlorophenyl	H	2-pyridyl		779
2-Furyl	allyl	2-pyridyl	b.p. 130–35°/4 mm.	285
2-Furyl	ethyl	3-pyridyl	b.p. 126–28°/8 mm.	285
4-Hydroxyphenyl	H	2-pyridyl		779
4-Methylsulfonylphenyl	H	2-pyridyl	m.p. 170.5°	282
3-Nitrophenyl	H	2-pyridyl		779
4-Nitrophenyl	H	2-pyridyl		779
Phenyl	H	2-pyridyl	m.p. 99–99.5°	282
2-Pyridyl	H	diphenyl[a]	m.p. 129–30°	282

[a] 2-Py$\underset{\displaystyle N(C_6H_5)_2}{\overset{\displaystyle |}{C}}$=NH

TABLE IX-94. *N*-Acyl and *N*-Sulfonyl Derivatives of 2-Aminoalkylpyridines

R_1	R_2	Physical properties	Ref.
			
H	acetyl	m.p. 59–60°	538
H	*p*-aminobenzoyl	m.p. 94°	513
H	formyl	b.p. 160–61°/4 mm.	538
H	*p*-nitrobenzoyl	m.p. 136°	513
Ethyl	acetyl	m.p. 83°	538
Ethyl	formyl	b.p. 146°/2 mm.	538
Methyl	acetyl	m.p. 107°	538
Methyl	benzoyl	m.p. 93°	538
Methyl	formyl	b.p. 156°/4 mm.	538
			
H	acetyl	b.p. 175°	501
H	carbomethoxy	m.p. 53–54°	504
H	phthalimido[a]	m.p. 95–97°	571
Methyl	carbobenzyloxy		511
Methyl	*p*-toluenesulfonyl	m.p. 133.5–34.5°	511

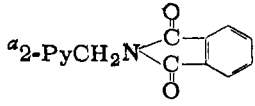
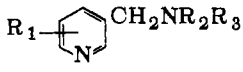
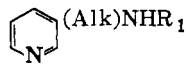
[a] 

TABLE IX-95. *N*-Acyl and *N*-Sulfonyl Derivatives of 3-Aminoalkylpyridines



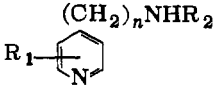
R_1	R_2	R_3	M.p., °C.	Ref.
H	nicotinoyl	H	108	574
H	*p*-nitrobenzoyl	H	188–89	513
2-Amino-6-methyl	formyl	H	165–65.5	528
2-Amino-6-methyl	thioformyl	H	130	528
5-Benzamido-6-methyl	benzoyl	H	204–5	386
2-Chloro-4,6-dimethyl	acetyl	H	136.5–38	530
2-Diethylamino-4,6-dimethyl-5-nitro	acetyl	H	148–48.5	530
2-Diethylamino-4,6-dimethyl	acetyl	H	126.5–27	530
2-Diethylamino-4,6-dimethyl	benzyl	chloracetyl	62–64	530
2-Diethylamino-4,6-dimethyl	benzyl	dimethylamino-acetyl	picrate: 168–69.5	530
2-Diethylamino-4,6-dimethyl	benzoyl	H	134.5–35.5	530
2-Diethylamino-4,6-dimethyl	chloroacetyl	H	110–12	530
2-Diethylamino-4,6-dimethyl	diethylamino-acetyl	H	picrate: 149	530
2-Diethylamino-4,6-dimethyl	cyclohexylamino-acetyl	H	76–78	530
2-Diethylamino-4,6-dimethyl	—phthalimido—		73–75	530
6-Methyl	benzoyl	H	121–22	513
6-Methyl	*p*-nitrobenzoyl	H	171	513

TABLE IX-95 (*continued*)



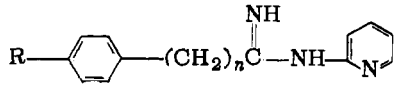
Alk	R_1	M.p., °C.	Ref.
—CH=CH—	carbomethoxy	145	739
$—CH_2CH_2—$	*p*-chlorobenzoyl	monohydrate: 173–75	710
$—(CH_2)_4—$	benzenesulfonyl	112.5–13.5	543
$—CH_2CH(CH_3)—$	*m*-nitrobenzenesulfonyl	167–68.5	564

TABLE IX-96. 4-(*N*-Acyl)alkylaminopyridines

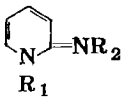


n	R_1	R_2	M.p., °C.	Ref.
1	H	benzoyl	108	513
1	2,6-dibromo	acetyl	116–18	531
1	2,6-dichloro	acetyl	102	531
1	2,6-dichloro	benzoyl	61–63	512
2	H	carbomethoxy	hydrochloride: 132–33	504

TABLE IX-97. *N*-(2-Pyridyl)aralkylamidines



n	R	Ref.
1	H	779
1	nitro	779
2	H	779
2	nitro	779
3	H	779

TABLE IX-98. 1,2-Dihydro-2-pyridonimines 

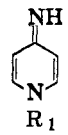
R_1	R_2	3	4	5	Physical properties, derivatives	Ref.
Benzyl	H				m.p. 37–39°	146
Benzyl	acetyl					455
Benzyl	phenyl				m.p. 92.5–93.5°	306
n-Butyl	H				hydrochloride, m.p. 180–81°	452
n-Butyl	benzoyl					455
n-Butyl	oleyl					455
Carboxyethyl	H				m.p. 260°	777
Carboxymethyl	H				m.p. 249–50°	193
2-Dicyclohexylaminoethyl	H				hydrochloride, m.p. 230°	444
2-Di(cyclohexylmethyl)aminoethyl	H				hydrochloride, m.p. 236°	444
4-Dicyclohexylamino-2-methylbutyl	H				hydrochloride, m.p. 233°	444
2-(3-Ethoxy-9-perhydrocarbazolyl)-ethyl	H				hydrochloride, m.p. 236°	778
Ethyl	H				hydrochloride, m.p. 150–51°	452
Ethyl	nitro				m.p. 139°	439
Ethyl	phenyl				picrate, m.p. 131–32°	306
Methyl	*i*-amyl				b.p. 122–25°/12 mm.	451
Methyl	benzoyl				m.p. 70°	146
Methyl	benzyl				picrate, m.p. 123.5–24.5°	
Methyl	cyanoethyl					456
Methyl	4-diethylamino-1-methylbutyl				chloraurate-hydrochloride, m.p. 128–29°	449

Methyl	4-ethoxyphenyl			m.p. 88–89°	451
Methyl	6-ethoxy-3-pyridyl			b.p. 219°/16 mm.	451
Methyl	H			picrate, m.p. 201°	146
Methyl	H	bromo	bromo	m.p. 99–100°	371
Methyl	H		nitro	m.p. 181°	440
Methyl	hydroxyethyl				456
Methyl	methyl			b.p. 138°/38 mm.	451
Methyl	2-naphthyl			m.p. 141–42°	451
Methyl	nitro			m.p. 161°	439
Methyl	nitro	bromo	bromo	m.p. 186–87°	371
Methyl	nitro	nitro		m.p. 209°	440
Methyl	nitro		nitro	m.p. 182°	440
Methyl	palmitoyl				455
Methyl	phenyl			m.p. 69–70°	451
Methyl	phenyl	chloro	chloro	b.p. 219°/15 mm.	451
Methyl	phenylcarbamoyl			m.p. 148°	146
Methyl	2-pyridyl				450
Methyl	stearoyl				455
Methyl	4-sulfamoyl-phenyl			m.p. 245–46°	449
2-Di(4′-methylcyclohexyl)aminoethyl	H			hydrochloride, m.p. 256°	444
2-(2′-Methyl-9′-perhydrocarbazolyl)-ethyl	H			hydrochloride, m.p. 217°	778
2-(9′-Perhydroacridinyl)ethyl	H			hydrochloride, m.p. 202°	444

(*continued*)

TABLE IX-98. 1,2-Dihydro-2-pyridonimines (*continued*)

R_1	R_2	3	4	5	Physical properties, derivatives	Ref.
2-(9′-Perhydrocarbazolyl)-3-(diethylamino)propyl	H				hydrochloride, m.p. 247°	778
2-(9′-Perhydrocarbazolyl)ethyl	H				hydrochloride, m.p. 274°	778
2-(9′-Perhydrocarbazolyl)ethyl	H		methyl		hydrochloride, m.p. 258°	778
Phenethyl	H					779
Phenyl	benzyl				picrate, m.p. 259–60°	306
Phenyl	ethyl				picrate, m.p. 254–55°	306
Phenyl	phenyl				m.p. 129–29.5°	306
Phenyl	propyl				picrate, m.p. 131.5–132.5°	306
Propyl	H				hydrochloride, 176–77°	452

TABLE IX-99. 1,4-Dihydro-4-pyridonimines 

R_1	M.p., °C.	Ref.
2,4-Dinitrophenyl	hydrochloride: 263	309
Methyl	picrate: 188–89	446
2-(9′-Perhydrocarbazolyl)ethyl	hydrochloride: 245	778
4-Pyridyl	hydrochloride: 280	454

D. BIBLIOGRAPHY

1. Cairns, Sauer, and Wilkinson, *J. Am. Chem. Soc.*, **74**, 3989 (1952).
2. Moir, *J. Chem. Soc.*, **81**, 100 (1902).
3. Reynolds, Humphlett, Swamer, and Hauser, *J. Org. Chem.*, **16**, 165 (1951).
4. U.S. patent 2,333,493; *C.A.*, **38**, 2507 (1944).
5. Schroeder and Rigby, *J. Am. Chem. Soc.*, **71**, 2205 (1949).
6. Fanta, *J. Am. Chem. Soc.*, **75**, 737 (1953).
7. Chichibabin and Seide, *J. Russ. Phys. Chem. Soc.*, **46**, 1216 (1914); *Chem. Zentr.*, **1915, II**, 1064.
8. Ziegler and Zeiser, *Ber.*, **63**, 1847 (1930).
9. Maier-Bode and Altpeter, *Das Pyridin und seine Derivative in Wissenschaft und Technik*, Knapp, Halle, Germany, 1934, pp. 94-97.
10. German patent 663,891; *C.A.*, **33**, 175 (1939).
11. Leffler in R. Adams, ed., *Organic Reactions*, Wiley, New York, 1942, Vol. I, Chap. 4, pp. 91-104.
12. German patent 358,397; *C.A.*, **17**, 2118 (1923).
13. Chichibabin, *J. Russ. Phys. Chem. Soc.*, **47**, 835 (1915); *C.A.*, **9**, 2896 (1915).
14. Chichibabin and Vidonova, *J. Russ. Phys. Chem. Soc.*, **53**, 238 (1921); *Chem. Zentr.*, **1923, III**, 1025.
15. Willink and Wibaut, *Rev. trav. chim.*, **54**, 275 (1935).
16. German patent 398,204; *Chem. Zentr.*, **1924, II**, 1409.
17. German patent 374,291; *Chem. Zentr.*, **1923, IV**, 725.
18. Plazek, *Roczniki Chem.*, **16**, 403 (1936); *C.A.*, **31**, 1808 (1937).
19. Belonosov, *Zhur. Priklad. Khim.*, **22**, 1103 (1949); *C.A.*, **45**, 5650 (1951).
20. Konopnicki and Plazek, *Ber.*, **60**, 2045 (1927).
21. Plazek, Marcinikow, and Stammer, *Roczniki Chem.*, **15**, 365 (1935); *C.A.*, **30**, 1377 (1936).
22. Chichibabin and Kirssanow, *Ber.*, **57**, 1163 (1924).
23. Caldwell, Tyson, and Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).
24. Menschikoff, Grigorovitch, and Orechoff, *Ber.*, **67**, 289 (1934).
25. Wibaut and Nicolai, *Rec. trav. chim.*, **58**, 709 (1939).

26. German patent 510,432; *C.A.*, **25**, 974 (1931).
27. Marckwald, *Ber.*, **26**, 2187 (1893).
28. Fischer, *Ber.*, **32**, 1297 (1899).
29. Den Hertog and Wibaut, *Rec. trav. chim.*, **51**, 381 (1932).
30. Hauser and Weiss, *J. Org. Chem.*, **14**, 310 (1949).
31. Maier-Bode, *Ber.*, **69**, 1543 (1936).
32. Den Hertog and Wibaut, *Rec. trav. chim.*, **55**, 122 (1936).
33. Zwart and Wibaut, *Rec. trav. chim.*, **74**, 1062 (1955).
34. Plazek and Rodewald, *Roczniki Chem.*, **21**, 150 (1947); *C.A.*, **42**, 5456 (1948).
35. Emmert and Dorn, *Ber.*, **48**, 687 (1915).
36. Hauser and Reynolds, *J. Org. Chem.*, **15**, 1224 (1950).
37. Murray and Hauser, *J. Org. Chem.*, **19**, 2008 (1954).
38. Den Hertog and Jouwersma, *Rec. trav. chim.*, **72**, 125 (1953).
39. Den Hertog, Falter, and van der Linde, *Rec. trav. chim.*, **67**, 377 (1948).
40. Marcinikow and Plazek, *Roczniki Chem.*, **16**, 136 (1936); *C.A.*, **31**, 2216 (1937).
41. Marckwald, *Ber.*, **27**, 1317 (1894).
42. Swiss patent 227,124; *C.A.*, **43**, 3471 (1949).
43. Baumler, Sorkin, and Erlenmeyer, *Helv. Chim. Acta*, **34**, 496 (1951).
44. Meyer and Graf, *Ber.*, **61**, 2202 (1928).
45. Bachman and Micucci, *J. Am. Chem. Soc.*, **70**, 2381 (1948).
46. Reed and Shive, *J. Am. Chem. Soc.*, **68**, 2740 (1946).
47. Kushner, Dalalian, Cassell, Sanjurjo, McKenzie, and Subbarow, *J. Org. Chem.*, **13**, 834 (1948).
48. U.S. patent 2,170,209; *C.A.*, **34**, 1134 (1940).
49. Chichibabin and Vialatout, *Bull. Soc. chim. France*, [5], **6**, 736 (1939).
50. Koenigs and Freter, *Ber.*, **57**, 1187 (1924).
51. British patent 629,439; *C.A.*, **44**, 7354 (1950).
52. Kolder and den Hertog, *Rec. trav. chim.*, **72**, 285 (1953).
53. Den Hertog, *Rec. trav. chim.*, **65**, 129 (1946).
54. Camps, *Arch. Pharm.*, **240**, 345 (1902); *Chem. Zentr.*, **1902, II**, 647.
55. Japanese patent 2669(50); *C.A.*, **47**, 2772 (1953).
56. Meyer, *Rec. trav. chim.*, **44**, 323 (1925).
57. Takahashi and Saikachi, *J. Pharm. Soc. Japan*, **62**, 40 (1942); *C.A.*, **45**, 620 (1951).
58. Roe and Hawkins, *J. Am. Chem. Soc.*, **69**, 2443 (1947).
59. Pollak, *Monatsh.*, **16**, 45 (1895).
60. Dornow, *Ber.*, **73**, 78 (1940).
61. Mills and Widdows, *J. Chem. Soc.*, **93**, 1372 (1908).
62. Sell, *J. Chem. Soc.*, **87**, 799 (1905).
63. Sell, *J. Chem. Soc.*, **93**, 2001 (1908).
64. Gabriel and Colman, *Ber.*, **35**, 2831 (1902).
65. Kirpal, *Monatsh.*, **29**, 228 (1908).
66. Kirpal, *Monatsh.*, **23**, 243 (1902).

67. Gabriel and Colman, *Ber.*, **35**, 3847 (1902).
68. Wallis and Lane, *Org. Reactions*, **III**, Ch. 7.
69. Meyer and Molly, *Monatsh.*, **33**, 393 (1912).
70. Curtius and Molu, *Ber.*, **31**, 2493 (1898).
71. Sugasawa, Akahoshi, Toda, and Tomisawa, *J. Pharm. Soc. Japan*, **72**, 192 (1952); *C.A.*, **47**, 6418 (1953).
72. Graf, *J. prakt. Chem.*, **133**, 19 (1932).
73. Sŏrm and Sicher, *Collection Czechoslov. Chem. Communs.*, **14**, 331 (1949); *C.A.*, **44**, 1505 (1950).
74. Graf, *Ber.*, **64**, 21 (1931).
75. Graf, *J. prakt. Chem.*, **133**, 36 (1932).
76. Smith, *Org. Reactions*, **III**, Ch. 9.
77. Friedl, *Ber.*, **45**, 428 (1912).
78. Kirpal and Reiter, *Ber.*, **58**, 699 (1925).
79. Kucherov and Kocheskov, *J. Gen Chem. U.S.S.R.*, **16**, 1137 (1946); *C.A.*, **41**, 2703 (1947).
80. Hamana, *J. Pharm. Soc. Japan*, **71**, 263 (1951); *C.A.*, **46**, 4542 (1952).
81. Plazek, *Ber.*, **72**, 577 (1939).
82. Gruber and Schlögl, *Monatsh.*, **80**, 499 (1949).
83. Herz and Tsai, *J. Am. Chem. Soc.*, **76**, 4184 (1954).
84. Saikachi and Yoshina, *J. Pharm. Soc. Japan*, **72**, 30 (1952); *C.A.*, **46**, 11176 (1952).
85. Chichibabin and Rasorenov, *J. Russ. Phys. Chem. Soc.*, **47**, 1286 (1915); *Chem. Zentr.*, **1916, II**, 15.
86. German patent 622,345; *C.A.*, **30**, 1396 (1936).
87. German patent 653,200; *C.A.*, **32**, 4180 (1938).
88. Binz and v. Schickh, *Ber.*, **68**, 315 (1935).
89. Suzuki, *J. Pharm. Soc. Japan*, **71**, 789 (1951); *C.A.*, **46**, 4004 (1952).
90. Clemo and Holt, *J. Chem. Soc.*, **1953**, 1313.
91. Parker and Shive, *J. Am. Chem. Soc.*, **69**, 63 (1947).
92. Hawkins and Roe, *J. Org. Chem.*, **14**, 328 (1949).
93. U.S. patent 2,516,830; *C.A.*, **45**, 669 (1951).
94. Papa, Sperber, and Sherlock, *J. Am. Chem. Soc.*, **73**, 1279 (1951).
95. Cragoe and Hamilton, *J. Am. Chem. Soc.*, **67**, 536 (1945).
96. Yamamoto, *J. Pharm. Soc. Japan*, **71**, 662 (1951); *C.A.*, **46**, 8109 (1952).
97. Kolder and den Hertog, *Rec. trav. chim.*, **72**, 853 (1953).
98. Plazek, Sorokowska, and Tolopka, *Roczniki Chem.*, **18**, 210 (1938); *Chem. Zentr.*, **1939, II**, 2779.
99. Den Hertog and Overhoff, *Rec. trav. chim.*, **69**, 468 (1950).
100. Ochiai, Arima, and Ishikawa, *J. Pharm. Soc. Japan*, **63**, 79 (1943); *C. A.*, **45**, 5151 (1951).
101. Ochiai and Katada, *J. Pharm. Soc. Japan*, **63**, 186 (1943); *C.A.*, **45**, 5151 (1951).
102. Kato, *J. Pharm. Soc. Japan*, **73**, 149 (1953); *C.A.*, **47**, 11191 (1953).
103. English, Chappell, Bell, and Roblin, *J. Am. Chem. Soc.*, **64**, 2516 (1942).

104. Tomita, *J. Pharm. Soc. Japan,* **71,** 1053 (1951); *C.A.,* **46,** 5044 (1952).
105. Ochiai and Suzuki, *J. Pharm. Soc. Japan,* **67,** 158 (1947); *C.A.,* **45,** 9541 (1951).
106. Den Hertog, Kolder, and Combé, *Rec. trav. chim.,* **70,** 591 (1951).
107. Berson and Cohen, *J. Org. Chem.,* **20,** 1461 (1955).
108. Ochiai and Fujimoto, *Pharm. Bull. (Tokyo),* **2, #2,** 131 (1954); *C.A.,* 50, 990 (1956).
109. Ochiai and Katoh, *J. Pharm. Soc. Japan,* **71,** 156 (1951); *C.A.,* **45,** 9542 (1951).
110. Den Hertog, Henkens, and Dilz, *Rec. trav. chim.,* **72,** 296 (1953).
111. Reinhart, *J. Franklin Inst.,* **236,** 316 (1943).
112. Hayashi, *J. Pharm. Soc. Japan,* **70,** 142 (1950); *C.A.,* **44,** 5880 (1950).
113. Phillips, *Ber.,* **27,** 839 (1894).
114. McLean and Spring, *J. Chem. Soc.,* **1949,** 2582.
115. Blumenfeld, *Monatsh.,* **16,** 693 (1895).
116. Gulland and Robinson, *J. Chem. Soc.,* **127,** 1493 (1925).
117. Koenigs, Kinne, and Weiss, *Ber.,* **57,** 1172 (1924).
118. Takahashi, Senda, and Zenno, *J. Pharm. Soc. Japan,* **69,** 104 (1949); *C.A.,* **44,** 3450 (1950).
119. Carboni, *Gazz. chim. Ital.,* **83,** 637 (1953).
120. Koenigs and Greiner, *Ber.,* **64,** 1049 (1931).
121. U.S. patent 1,879,324; *C.A.,* **27,** 313 (1933).
122. Mosher, in R. C. Elderfield, Ed., *Heterocyclic Compounds,* Wiley, New York, 1950, Vol. 1, p. 552.
123. Wibaut, Herzberg, and Schlatmann, *Rec. trav. chim.,* **73,** 140 (1954).
124. Albert, *J. Chem. Soc.,* **1951,** 1376.
125. Rodewald and Plazek, *Roczniki Chem.,* **16,** 444 (1936); *C.A.,* **31,** 1808 (1937).
126. Den Hertog, *Rec. trav. chim.,* **64,** 85 (1945).
127. Den Hertog and Wibaut, *Rec. trav. chim.,* **51,** 940 (1932).
128. Fischer and Riemerschmied, *Ber.,* **16,** 1183 (1883).
129. Sell and Dootson, *J. Chem. Soc.,* **75,** 979 (1899).
130. U.S. patent 2,643,256; *C.A.,* **48,** 4597 (1954).
131. Wibaut and van de Lande, *Verslag. Gewone Vergader. Afdeel. Natuurk. Ned. Akad. Wetenschap. Amsterdam,* **36,** 1238 (1928); *C.A.,* **22,** 2357 (1928).
132. Wibaut and van de Lande, *Rec. trav. chim.,* **48,** 1005 (1929).
133. Wibaut and van de Lande, *Rec. trav. chim.,* **50,** 1056 (1931).
134. Ochiai, Itai, and Yoshino, *Proc. Imp. Acad. (Tokyo),* **20,** 141 (1944); *C.A.,* **48,** 12,100 (1954).
135. Levine and Leake, *Science,* **121,** 780 (1955).
136. Sunagawa, Kushima, and Ichii, *J. Pharm. Soc. Japan,* **72,** 1570 (1952); *C.A.,* **47,** 9285 (1953).
137. Goldfarb and Kondakova, *Compt. rend. acad. sci. U.S.S.R.,* **55,** 613 (1947); *C.A.,* **42,** 571 (1948).

138. Zhukova, Kondakova, and Goldfarb, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk,* **1952,** 743; *C.A.,* **47,** 401 (1953).
139. Ochiai, Katada, and Naito, *J. Pharm. Soc. Japan,* **64,** 210 (1944); *C.A.,* **45,** 5154 (1951).
140. Mangini and Colonna, *Gazz. chim. Ital.,* **73,** 313 (1943); *C.A.,* **41,** 1224 (1947).
141. Nienburg, *Ber.,* **67,** 874 (1934).
142. Ref. 9, p. 91.
143. Anderson and Seeger, *J. Am. Chem. Soc.,* **71,** 340 (1949).
144. Steck and Ewing, *J. Am. Chem. Soc.,* **70,** 3397 (1948).
145. Angyal and Angyal, *J. Chem. Soc.,* **1952,** 1461.
146. Chichibabin, Konowalowa, and Konowalowa, *Ber.,* **54,** 814 (1921).
147. Angyal and Werner, *J. Chem. Soc.,* **1952,** 2911.
148. Goulden, *J. Chem. Soc.,* **1952,** 2939.
149. Takahashi, Ichikawa, and Yatsuka, *J. Pharm. Soc. Japan,* **65, No. 2A,** 14 (1945); *C.A.,* **45,** 8531 (1951).
150. Kirpal and Bohm, *Ber.,* **65,** 680 (1932).
151. Kirpal and Bohm, *Ber.,* **64,** 767 (1931).
152. v. Schickh, Binz, and Schulz, *Ber.,* **69,** 2593 (1936).
153. Wiley and Hartman, *J. Am. Chem. Soc.,* **73,** 494 (1951).
154. Bystritskaya and Kirsanov, *J. Gen. Chem. U.S.S.R.,* **10,** 1101 (1940); *C.A.,* **35,** 4023 (1941).
155. Den Hertog, Jouwersma, van der Wal, and Willebrands-Schogt, *Rec. trav. chim.,* **68,** 275 (1949).
156. Campbell, Henderson, and Taylor, *J. Chem. Soc.,* **1953,** 1281.
157. Kirpal, *Ber.,* **67,** 70 (1934).
158. Kirpal and Reiter, *Ber.,* **60,** 664 (1927).
159. Bystritskaya and Kirsanov, *J. Gen. Chem. U.S.S.R.,* **10,** 1827 (1940); *C.A.,* **35,** 4380 (1941).
160. Nienburg, *Ber.,* **70,** 635 (1937).
161. Chichibabin and Gertschuk, *Ber.,* **63,** 1153 (1930).
162. Koenigs and Neumann, *Ber.,* **48,** 956 (1915).
163. Orthner, *Ann.,* **456,** 225 (1927).
164. Grave, *J. Am. Chem. Soc.,* **46,** 1460 (1924).
165. Kirsanov and Ivastchenko, *Bull. soc. chim.,* [5], **3,** 2279 (1936).
166. Kahn and Petrow, *J. Chem. Soc.,* **1945,** 858.
167. Titov and Baryshnikova, *Zhur. Obscheĭ Khim.,* **23,** 290 (1953); *C.A.,* **48,** 2704 (1954).
168. Chichibabin and Knunjanz, *Ber.,* **62,** 3048 (1929).
169. Zalukajevs, *Latvijas P.S.R. Zinātnu Akad. Vēstis,* **1951,** 747; *C.A.,* **48,** 10024 (1954).
170. Schmidt and Becker, *Monatsh.,* **46,** 675 (1926).
171. Feist, Awe, Schultz, and Klatt, *Arch. Pharm.,* **272,** 100 (1934); *C.A.,* **28,** 3407 (1934).
172. Steinhauser and Diepolder, *J. prakt. Chem.,* **93,** 387 (1916).

173. Villani, King, and Papa, *J. Am. Chem. Soc.*, **73**, 5916 (1951).
174. Kaye and Kogon, *Rec. trav. chim.*, **71**, 309 (1952).
175. Fischer and Chur, *J. prakt. Chem.*, **93**, 363 (1916).
176. Schmid and Bangler, *Ber.*, **58**, 1971 (1925).
177. Gilman, Stuckwisch, and Nobis, *J. Am. Chem. Soc.*, **68**, 326 (1946).
178. German patent 451,733; *Chem. Zentr.*, **1928, I**, 586.
179. Hauser and Weiss, *J. Org. Chem.*, **14**, 453 (1949).
180. Adams and Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).
181. Takahashi, Saikachi, Yoshina, and Mizuno, *J. Pharm. Soc. Japan*, **69**, 284 (1949); *C.A.*, **44**, 5372 (1950).
182. Saikachi and Yoshina, *J. Pharm. Soc. Japan*, **71**, 982 (1952); *C.A.*, **46**, 8082 (1952).
183. British patent 625,327; *C.A.*, **44**, 2571 (1950).
184. Tien and Hunsberger, *J. Am. Chem. Soc.*, **77**, 6604 (1955).
185. U.S. patent 2,426,012; *C.A.*, **42**, 225 (1948).
186. U.S. patent 2,426,011; *C.A.*, **42**, 225 (1948).
187. Chichibabin and Knunjanz, *Ber.*, **64**, 2839 (1931).
188. Clayton and Kenyon, *J. Chem. Soc.*, **1950**, 2952.
189. Robison and Robison, *J. Am. Chem. Soc.*, **77**, 457 (1955).
190. Robison and Robison, *J. Am. Chem. Soc.*, **77**, 6554 (1955).
191. Kucherova, Kucherov, and Kocheskov, *J. Gen. Chem. U.S.S.R.*, **16**, 1706 (1946); *C.A.*, **41**, 6243 (1947).
192. German patent 406,206; *Chem. Zentr.*, **1925, I**, 1534.
193. Chichibabin, *Ber.*, **57**, 2092 (1924).
194. U.S. patent 2,461,987; *C.A.*, **43**, 4155 (1949).
195. U.S. patent 2,461,119; *C.A.*, **43**, 3853 (1949).
196. Takase, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **74**, 60 (1953); *C.A.*, **48**, 10570 (1954).
197. French patent 769,688; *C.A.*, **29**, 1435 (1935).
198. German patent 607,662; British patent 424,032; *C.A.*, **29**, 4523 (1935).
199. Shriner and Child, *J. Am. Chem. Soc.*, **74**, 549 (1952).
200. Meyer and von Beck, *Monatsh.*, **36**, 731 (1915).
201. Snyder and Robison, *J. Am. Chem. Soc.*, **74**, 5945 (1952).
202. Synder and Robison, *J. Am. Chem. Soc.*, **74**, 4910 (1952).
203. Chichibabin, *Ber.*, **57**, 1168 (1924).
204. Pallazzo and Tamburini, *Att real. accad. Lincei*, [5], **20, I**, 37 (1911); *Chem. Zentr.*, **1911, I**, 987.
205. Palazzo and Macogna, *Chem. Zentr.*, **1913, I**, 171.
206. Kucherov, *Zhur. Obscheĭ Khim.*, **20**, 1890 (1950); *C.A.*, **45**, 2951 (1951).
207. Kucherov, *Zhur. Obscheĭ Khim.*, **21**, 1145 (1951); *C.A.*, **46**, 5043 (1952).
208. Schmid and Mann, *Monatsh.*, **85**, 864 (1954).
209. Friedman, Braitberg, Tolstoouhov, and Tisza, *J. Am. Chem. Soc.*, **69**, 1795 (1947).
210. Hoey and Lester, *J. Am. Chem. Soc.*, **73**, 4473 (1951).

211. Barry and Twomey, *Proc. Roy. Irish Acad.*, **51B**, 152 (1947); *C.A.*, **41**, 4454 (1947).
212. Lappin, Petersen, and Wheeler, *J. Org. Chem.*, **15**, 377 (1950).
213. Diels and Behnen, *Ber.*, **56**, 561 (1923).
214. Angyal, Morris, and Warburton, *Australian J. Sci. Res.*, **A5**, **No. 2**, 368 (1952).
215. Lur'e, *Zhur. Obscheĭ Khim.*, **20**, 195 (1950); *C.A.*, **44**, 5880 (1950).
216. Clauder and Toldy, *Magyar Kem. Folyóirat*, **56**, 61 (1950); *C.A.*, **47**, 117 (1953).
217. Jensen and Ingvorsen, *Acta Chem. Scand.*, **6**, 161 (1952).
218. U.S. patent 2,554,186; *C.A.*, **46**, 531 (1952).
219. Swiss patent 253,645; *C.A.*, **43**, 7513 (1949).
220. Jensen and Ploug, *Acta Chem. Scand.*, **3**, 13 (1949).
221. Swiss patent 253,644; *C.A.*, **43**, 7513 (1949).
222. Takatori and Ueda, *J. Pharm. Soc. Japan*, **71**, 1373 (1951); *C.A.*, **46**, 8052 (1952).
223. Allen and Van Allan, *Org. Synthesis*, **26**, 92 (1946).
224. Feist and Schultz, *Arch. Pharm.*, **272**, 785 (1934); *C.A.*, **29**, 792 (1935).
225. Rubtsov and Klimko, *J. Gen. Chem. U.S.S.R.*, **16**, 1865 (1946); *C.A.*, **41**, 6218 (1947).
226. Saikachi and Yoshina, *J. Pharm. Soc. Japan*, **72**, 30 (1952); *C.A.*, **46**, 11176 (1952).
227. Wanag, *Acta Univ. Latviensis, Chem. Sec.*, **4**, 405 (1939); *Chem. Zentr.*, **1939, II**, 3815.
228. U.S. patent 2,474,893; *C.A.*, **44**, 2041 (1950).
229. Vejdělek, Trčka, and Protiva, *Chem. listy*, **46**, 423 (1952); *C.A.*, **47**, 8069 (1953).
230. Knunyants and Katrenko, *J. Gen. Chem. U.S.S.R.*, **10**, 1167 (1940); *C.A.*, **35**, 2893 (1941).
231. Takahashi, Yatsuka, and Onuma, *J. Pharm. Soc. Japan*, **64**, 235 (1944); *C.A.*, **45**, 4717 (1951).
232. Takahashi, Yoshikawa, and Shirai, *J. Pharm. Soc. Japan*, **65**, **No. 2A**, 13 (1945); *C.A.*, **46**, 110 (1952).
233. Takahashi and Taniyama, *J. Pharm. Soc. Japan*, **64**, **No. 10A**, 49 (1944); *C.A.*, **46**, 110 (1952).
234. Plazek and Sucharda, *Ber.*, **61**, 1813 (1928).
235. Mariella and Belcher, *J. Am. Chem. Soc.*, **74**, 1916 (1952).
236. Curry and Mason, *J. Am. Chem. Soc.*, **73**, 5043 (1951).
237. Haworth, Heilbron, and Hey, *J. Chem. Soc.*, **1940**, 372.
238. Ahmad and Hey, *J. Chem. Soc.*, **1954**, 4516.
239. Rapoport, Look, and Keely, *J. Am. Chem. Soc.*, **74**, 6293 (1952).
240. Chichibabin and Posdnijakow, *J. Russ. Phys. Chem. Soc.*, **57**, 297 (1925); *Chem. Zentr.*, **1926, I**, 3335.
241. Renshaw and Shand, *J. Am. Chem. Soc.*, **54**, 1474 (1932).

242. Chichibabin and Bylinkin, *Ber.*, **55**, 998 (1922).
243. Rericha and Protiva, *Chem. Listy*, **43**, 176 (1949); *C.A.*, **45**, 576 (1951).
244. Kostsova, *J. Gen. Chem. U.S.S.R.*, **22**, 1430 (1952); *C.A.*, **47**, 4862 (1953).
245. Mead, Rapport, Senear, Maynard, and Koepfli, *J. Biol. Chem.*, **163**, 465 (1946).
246. Griffin and Hey, *J. Chem. Soc.*, **1952**, 3334.
247. Winterbottom, Clapp, Miller, English, and Roblin, *J. Am. Chem. Soc.*, **69**, 1393 (1947).
248. U.S. patent 2,459,111; *C.A.*, **43**, 3450 (1949).
249. Hurd and Kharasch, *J. Am. Chem. Soc.*, **68**, 653 (1946).
250. Northey, *The Sulfonamides and Allied Compounds*, Reinhold Publishing Co., New York, 1948.
251. Leonard and Solmssen, *J. Am. Chem. Soc.*, **70**, 2064 (1948).
252. Shepherd, Bratton, and Blanchard, *J. Am. Chem. Soc.*, **64**, 2532 (1942).
253. Angyal and Warburton, *Australia J. Sci. Res.*, **A, 4**, 93 (1951).
254. English, Clark, Shepherd, Marson, Krapcho, and Roblin, *J. Am. Chem. Soc.*, **68**, 1039 (1946).
255. Magidson and Elina, *J. Gen. Chem. U.S.S.R.*, **16**, 1933 (1946); *C.A.*, **41**, 6219 (1947).
256. Raffa, *Farm. Sci. e tec. (Pavia)*, **3**, 29 (1948); *C.A.*, **42**, 4163 (1948).
257. Spring and Young, *J. Chem. Soc.*, **1944**, 248.
258. Polyakova and Kirsanov, *J. Appl. Chem. (U.S.S.R.)*, **13**, 1215 (1940); *C.A.*, **35**, 2145 (1941).
259. Belgian patent 447,660; *C.A.*, **39**, 944 (1945).
260. Ochiai and Arai, *J. Pharm. Soc. Japan*, **59**, 458 (1939); *C.A.*, **34**, 108 (1940).
261. Plazek and Richter, *Roczniki Chem.*, **21**, 55 (1947); *C.A.*, **42**, 1907 (1948).
262. Raiziss, Clemence, and Freifelder, *J. Am. Chem. Soc.*, **63**, 2739 (1941).
263. Roblin and Winnek, *J. Am. Chem. Soc.*, **62**, 1999 (1940).
264. British patent 562,349; *C.A.*, **40**, 903 (1946).
265. Plazek and Rikhter, *Zhur. Obscheĭ Khim.*, **18**, 1154 (1948).
266. U.S. patent, 2,295,867; *C.A.*, **37**, 1229 (1943).
267. Takahashi and Senda, *J. Pharm. Soc. Japan*, **66**, 26 (1946); *C.A.*, **46**, 111 (1952).
268. Shepherd and Fellows, *J. Am. Chem. Soc.*, **70**, 157 (1948).
269. Swiss patent 220,959; *C.A.*, **43**, 364 (1949).
270. Ochiai, Teshigawara, Oda, and Naito, *J. Pharm. Soc. Japan*, **64**, No. 5/6A, 1 (1944); *C.A.*, **45**, 8527 (1951).
271. U.S. patent 2,335,221; *C.A.*, **38**, 2796 (1944).
272. Gerchuk and Taito, *Zhur. Obshcheĭ Khim.*, **20**, 910 (1950); *C.A.*, **44**, 9443 (1950).
273. Korte, *Chem. Ber.*, **85**, 1012 (1952).
274. Fox, *J. Org. Chem.*, **17**, 542 (1952).
275. Schmidt and Becker, *Monatsh.*, **46**, 671 (1926).
276. Binz and Räth, *Ann.*, **486**, 95 (1931).
277. Marckwald and Rudzik, *Ber.*, **36**, 1111 (1903).

278. Gardner, Smith, Wenis, and Lee, *J. Am. Chem. Soc.*, **74**, 2106 (1952).
279. Roy and Guha, *J. Sci. Indian Research*, **9B**, 262 (1950); *C.A.*, **45**, 6636 (1951).
280. German patent 832,891; *C.A.*, **47**, 3343 (1953).
281. Bernstein, Stearns, Shaw, and Lott, *J. Am. Chem. Soc.*, **69**, 1151 (1947).
282. Oxley, Partridge, and Short, *J. Chem. Soc.*, **1947**, 1110.
283. British patent 598,453; *C.A.*, **42**, 6854 (1948).
284. Cooper and Partridge, *J. Chem. Soc.*, **1953**, 255.
285. Takahashi, Saikachi, Kimura, and Yoshina, *J. Pharm. Soc. Japan*, **68**, 42 (1948); *C. A.*, **44**, 1954 (1950).
286. Takahashi, Saikachi, Goto, and Satake, *J. Pharm. Soc. Japan*, **64**, No. 11A, 55 (1944); *C. A.* **45**, 8530 (1951).
287. Katayanagi, *J. Pharm. Soc. Japan*, **68**, 228 (1948); *C.A.*, **48**, 4545 (1954).
288. Takahashi and Taniyama, *J. Pharm. Soc. Japan*, **66**, 38 (1946); *C.A.*, **45**, 8533 (1951).
289. Woodburn and Pino, *J. Org. Chem.*, **16**, 1389 (1951).
290. Takahashi, Yoshikawa, and Okada, *J. Pharm. Soc. Japan*, **66**, 33 (1946); *C.A.*, **46**, 112 (1952).
291. Henry, *J. Am. Chem. Soc.*, **72**, 5343 (1950).
292. Zetsche, Meyer, Overbeck, and Nerger, *Ber.*, **71**, 1512 (1938).
293. U.S. patent 2,512,249; *C.A.*, **44**, 8961 (1950).
294. Biel, *J. Am. Chem. Soc.*, **71**, 1306 (1949).
295. Clapp, Clark, Vaughan, English, and Anderson, *J. Am. Chem. Soc.*, **69**, 1549 (1947).
296. Marckwald, *Ber.*, **31**, 2496 (1898).
297. Jones, Jenkins, and Christian, *J. Am. Pharm. Assoc.*, **38**, 70 (1949).
298. Slotta and Franke, *Ber.*, **63**, 678 (1930).
299. Ashley and Grove, *J. Chem. Soc.*, **1945**, 768.
300. Sperber and Papa, *J. Am. Chem. Soc.*, **71**, 886 (1949).
301. Huttrer, Djerassi, Beears, Mayer, and Scholz, *J. Am. Chem. Soc.*, **68**, 1999 (1946).
302. Swiss patent 264,754; *C.A.*, **45**, 176 (1951).
303. Rubtsov and Klimko, *J. Gen. Chem. U.S.S.R.*, **16**, 1860 (1946); *C.A.*, **41**, 6245 (1947).
304. Chichibabin, *J. Russ. Phys. Chem. Soc.*, **50**, 497 (1918); *Chem. Zentr.*, **1923, III**, 1021.
305. Gibson, Johnson, and Vining, *Rec. trav. chim.*, **49**, 1006 (1930).
306. Danyushevskii and Goldfarb, *Doklady Akad. Nauk. S.S.S.R.*, **72**, 899 (1950); *C.A.*, **44**, 9446 (1950).
307. Buu-Hoï, *J. Chem. Soc.*, **1952**, 4346.
308. Price and Roberts, *J. Org. Chem.*, **11**, 463 (1946).
309. Turitsyna and Vompe, *Doklady Akad. Nauk. S.S.S.R.*, **74**, 509 (1950); *C.A.*, **45**, 3846 (1951).
310. Berg and Petrow, *J. Chem. Soc.*, **1952**, 784.
311. Petrow, *J. Chem. Soc.*, **1945**, 927.

312. Abramovitch, Hey, and Mulley, *J. Chem. Soc.*, **1954**, 4263.
313. Petrow and Rewald, *J. Chem. Soc.*, **1945**, 591.
314. Mangini, *Ricerca sci.*, **8, I**, 427 (1937); *Chem. Zentr.*, **1938, I**, 2181.
315. Gruber, *Can. J. Chem.*, **31**, 1020 (1953).
316. Wibaut and Tilman, *Rec. trav. chim.*, **52**, 987 (1933).
317. Chichibabin and Knunjanz, *Ber.*, **62**, 3053 (1929).
318. German patent 489,184; *Chem. Zentr.*, **1930, I**, 2012.
319. Chichibabin and Knunjanz, *Ber.*, **61**, 427 (1928).
320. Tilford, Shelton, and Van Campen, *J. Am. Chem. Soc.*, **70**, 4001 (1948).
321. Vaughan and Anderson, *J. Am. Chem. Soc.*, **70**, 2607 (1948).
322. Swiss patent 267,632; *C.A.*, **45**, 7139 (1951).
323. Swiss patent 267,633; *C.A.*, **45**, 7139 (1951).
324. U.S. patent 2,489,777; *C.A.*, **44**, 7353 (1950).
325. Swiss patent 266,235; *C.A.*, **44**, 9487 (1950).
326. Chichibabin and Preobrashensky, *Ber.*, **61**, 199 (1928).
327. Chichibabin, Konowalowa, and Konowalowa, *J. Russ. Phys. Chem. Soc.*, **53**, 193 (1921); *Chem. Zentr.*, **1923, II**, 1023.
328. Koenigs and Jung, *J. prakt. Chem.*, **137**, 141 (1933).
329. Wibaut and La Bastide, *Rec. trav. chim.*, **52**, 493 (1933).
330. Mayer, Huttrer, and Scholz, *Science*, **102**, 93 (1945).
331. Chichibabin and Rjazancev, *J. Russ. Phys. Chem. Soc.*, **46**, 1571 (1915); *C.A.*, **10**, 2898 (1916).
332. Chichibabin and Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 522 (1920); *C.A.*, **18**, 1496 (1924).
333. Mangini, *Boll. sci. facolta chim. ind. Bolgna*, **No. 4**, 127 (1940); *C.A.*, **34**, 7286 (1940).
334. Mangini, *Atti acad. Italia, Rend. classe sci. fis. mat. nat.*, **(7), 1**, 452 (1940); *C.A.*, **37**, 98 (1943).
335. Prelog and Kohlbach, *Collection Czechoslov. Chem. Communs.*, **8**, 377 (1936).
336. Shreve, Swaney, and Richers, *J. Am. Chem. Soc.*, **65**, 2241 (1943).
337. U.S. Patent 1,680,108; *C.A.*, **23**, 2723 (1929).
338. U.S. Patent 1,830,300; *C.A.*, **26**, 808 (1932).
339. U.S. Patent 1,856,602; *C.A.*, **26**, 3522 (1932).
340. German patent 543,288; *C.A.*, **26**, 2470 (1932).
341. Chichibabin and Kirsanov, *J. Russ. Phys. Chem. Soc.*, **59**, 405 (1927); *C.A.*, **22**, 2563 (1928).
342. Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934).
343. Whitmore, Mosher, Goldsmith, and Rytina, *J. Am. Chem. Soc.*, **67**, 393 (1945).
344. Beaty and Musgrave, *J. Chem. Soc.*, **1951**, 3512.
345. Berrie, Newbold, and Spring, *J. Chem. Soc.*, **1952**, 2042.
346. Graf, *J. prakt. Chem.*, **138**, 244 (1933).
347. Beaty and Musgrave, *J. Chem. Soc.*, **1952**, 875.

348. Case, *J. Am. Chem. Soc.*, **68**, 2574 (1946).
349. Willink and Wibaut, *Rec. trav. chim.*, **53**, 416 (1934).
350. Adams and Govindachari, *J. Am. Chem. Soc.*, **69**, 1806 (1947).
351. Adams and Schreiber, *J. Am. Chem. Soc.*, **71**, 1186 (1949).
352. Koenigs and Jungfer, *Ber.*, **57**, 2080 (1924).
353. Räth and Prange, *Ann.*, **467**, 1 (1928).
354. Räth and Schiffman, *Ann.*, **487**, 127 (1931).
355. Schmelkes and Joiner, *J. Am. Chem. Soc.*, **61**, 2562 (1939).
356. U.S. patent 1,671,257; *C.A.*, **22**, 2572 (1928).
357. Katz, Schroeder, and Cohen, *J. Org. Chem.*, **19**, 711 (1954).
358. Chichibabin and Woroshtzow, *Ber.*, **66**, 364 (1933).
359. Binz and Maier-Bode, *Ann.*, **487**, 119 (1931).
360. Binz and Räth, *Ann.*, **455**, 127 (1927).
361. German patent 523,113; *C.A.*, **25**, 4558 (1931).
362. Takahashi and Morita, *J. Pharm. Soc. Japan*, **64**, **No. 7A**, 11 (1944); *C.A.*, **45**, 8014 (1951).
363. Binz and v. Schickh, *Ber.*, **69**, 1527 (1936).
364. Chichibabin and Ossetrowa, *J. Am. Chem. Soc.*, **56**, 1711 (1934).
365. Koenigs, Freigang, Lobmayer, and Zscharn, *Ber.*, **59**, 321 (1926).
366. Faessinger and Brown, *J. Am. Chem. Soc.*, **73**, 4606 (1951).
367. Chichibabin and Egorov, *J. Russ. Phys. Chem. Soc.*, **60**, 683 (1928); *C.A.*, **23**, 2182 (1929).
368. Chichibabin and Tjashelowa, *J. Russ. Phys. Chem. Soc.*, **50**, 483 (1918); *Chem. Zentr.*, **1923, III**, 1021.
369. Bradlow and Vanderwerf, *J. Org. Chem.*, **16**, 73 (1951).
370. Leese and Rydon, *J. Chem. Soc.*, **1954**, 4039.
371. Chichibabin and Kirssanow, *Ber.*, **61**, 1236 (1928).
372. Den Hertog and Bruin, *Rec. trav. chim.*, **65**, 385 (1946).
373. Halvarson, *Arkiv. Kemi*, **7**, 225 (1954); *C.A.*, **50**, 335 (1956).
374. Den Hertog and Mulder, *Rec. trav. chim.*, **67**, 957 (1948).
375. Chichibabin, *J. Russ. Phys. Chem. Soc.*, **50**, 492 (1918); *Chem. Zentr.*, **1923, III**, 1021.
376. Chichibabin and Kirssanow, *Ber.*, **61**, 1223 (1928).
377. Räth, *Ann.*, **487**, 105 (1931).
378. Adams, Hine, and Campbell, *J. Am. Chem. Soc.*, **71**, 387 (1949).
379. German patent 513,293; *C.A.*, **25**, 1263 (1931).
380. German patent 503,920; *C.A.*, **24**, 5769 (1930).
381. Magidson and Menschikoff, *Ber.*, **58**, 113 (1925).
382. Magidson and Menshikoff, *Trans. Sci. Chem.-Pharm. Inst. (Moscow)*, **No. 16**, 23 (1926); *C.A.*, **23**, 1640 (1929).
383. German patent 526,803; *C.A.*, **25**, 4807 (1931).
384. German patent 574,655; *C.A.*, **27**, 4542 (1933).
385. Plazek and Marcinkow, *Roczniki Chem.*, **14**, 326 (1934); *C.A.*, **29**, 2535 (1935).

386. Perez-Medina, Mariella, and McElvain, *J. Am. Chem. Soc.*, **69**, 2574 (1947).
387. Rodewald and Plazek, *Roczniki Chem.*, **16**, 130 (1936); *C.A.*, **31**, 2215 (1937).
388. Koenigs, Mields, and Gurlt, *Ber.*, **57**, 1179 (1924).
389. German patent 579,224; *C.A.*, **27**, 4880 (1933).
390. French patent 728,634; *C.A.*, **26**, 6071 (1932).
391. Naegeli, Kundig, and Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938).
392. Skrowaczewska, *Trav. soc. sci. et lettres Wroclaw, Ser. B*, **No. 61**, 5 (1953).
393. E. Plazek, *Roczniki Chem.*, **17**, 97 (1937); *C.A.*, **31**, 4669 (1937).
394. Chichibabin and Rasorenow, *J. Russ. Phys. Chem. Soc.*, **47**, 1286 (1915); *Chem. Zentr.*, **1916, II**, 15.
395. Lappin and Slezak, *J. Am. Chem. Soc.*, **72**, 2806 (1950).
396. Pino and Zehrung, *J. Am. Chem. Soc.*, **77**, 3154 (1955).
397. Taurins and Viron, *Can. J. of Chem.*, **31**, 1048 (1953).
398. Chichibabin and Widonowa, *J. Russ. Phys. Chem. Soc.*, **53**, 238 (1921); *Chem. Zentr.*, **1923, III**, 1025.
399. Takahashi and Shibasaki, *J. Pharm. Soc. Japan*, **72**, 431 (1952); *C.A.*, **47**, 6404 (1953).
400. Chichibabin and Kirssanow, *Ber.*, **60**, 2433 (1927).
401. British patent 662,798; *C.A.*, **46**, 11241 (1952).
402. Ochiai, Iwai, and Negoro, *J. Pharm. Soc. Japan*, **61**, 230 (1941); *C.A.*, **45**, 2941 (1951).
403. German patent 537,896; *C.A.*, **26**, 1301 (1932).
404. Nesmeyanov, *Uspekhi Khim. (U.S.S.R.)*, **3**, 34 (1934); *C.A.*, **29**, 1075 (1935).
405. Allen, *Chem. Revs.*, **47**, 275 (1950).
406. Weiss and Hauser, in R. C. Elderfield, ed., *Heterocyclic Compounds*, Wiley, New York, Vol. VII, 1961, p. 198.
407. Price and Roberts, *J. Am. Chem. Soc.*, **68**, 1204 (1946).
408. Bobranski and Sucharda, *Ber.*, **60**, 1081 (1927).
409. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).
410. Buu-Hoï and Declercq, *Rec. trav. chim.*, **73**, 376 (1954).
411. Crippa and Scevola, *Gazz. chim. ital.*, **67**, 327 (1937); *C. A.*, **32**, 166 (1938).
412. Antaki and Petrow, *J. Chem. Soc.*, **1951**, 551.
413. Adams and Pachter, *J. Am. Chem. Soc.*, **74**, 4906 (1952).
414. Seide, *Ber.*, **58**, 352 (1925).
415. Klisiecki and Sucharda, *Roczniki Chem.*, **3**, 251 (1923); *Chem. Zentr.*, **1924, II**, 660.
416. Fox, *J. Org. Chem.*, **17**, 547 (1952).
417. Leese and Rydon, *J. Chem. Soc.*, **1955**, 303.
418. Clemo and Swan, *J. Chem. Soc.*, **1948**, 198.
419. Sucharda, *Ber.*, **58**, 1724 (1925).
420. Takahashi, Yoshikawa, and Yatsuka, *J. Pharm. Soc. Japan*, **66**, 32 (1946); *C.A.*, **46**, 112 (1952).
421. Takahashi, Senda, and Yatsuka, *J. Pharm. Soc. Japan*, **66**, 26 (1946); *C.A.*, **46**, 111 (1952).

422. Yamamoto and Takahashi, *J. Pharm. Soc. Japan,* **71,** 169 (1951); *C.A.,* **46,** 8108 (1952).
423. Takahashi and Yamamoto, *J. Pharm. Soc. Japan,* **70,** 187 (1950); *C.A.,* **44,** 7320 (1950).
424. Reindel and Rauch, *Ber.,* **59,** 2921 (1926).
425. Takahashi and Shibasaki, *J. Pharm. Soc. Japan,* **69,** 496 (1949); *C.A.,* **44,** 4474 (1950).
426. Campbell and McCall, *J. Chem. Soc.,* **1951,** 2411.
427. Kaye, Parris, and Burlant, *J. Am. Chem. Soc.,* **75,** 746 (1953).
428. Kröhnke, Kickhofen, and Thoma, *Chem. Ber.,* **88,** 1117 (1955).
429. Finger and Kraft, *Ber.,* **57,** 1950 (1924).
430. Morgan and Stewart, *J. Chem. Soc.,* **1939,** 1057.
431. Morgan and Stewart, *J. Chem. Soc.,* **1938,** 1292.
432. Plazek and Rodewald, *Roczniki Chem.,* **16,** 502 (1936); *C.A.,* **31,** 3918 (1937).
433. Ames, Bowman, and Grey, *J. Chem. Soc.,* **1953,** 3008.
434. Takahashi and Hayase, *J. Pharm. Soc. Japan,* **65, No. 5-6A,** 9 (1945); *C.A.,* **45,** 8530 (1951).
435. Petrow and Saper, *J. Chem. Soc.,* **1946,** 588.
436. Elvidge and Linstead, *J. Chem. Soc.,* **1952,** 5008.
437. Räth and Prange, *Ber.,* **58,** 1208 (1925).
438. Wibaut, Overhoff, and Geldof, *Rec. trav. chim.,* **54,** 807 (1935).
439. Chichibabin and Menschikow, *Ber.,* **58,** 406 (1925).
440. Chichibabin and Konowalowa, *Ber.,* **58,** 1712 (1925).
441. Kabachnik, *J. Gen. Chem. U.S.S.R.,* **7,** 1749 (1937); *C.A.,* **32,** 560 (1938).
442. Kursanov and Ignat'eva, *J. Gen. Chem. U.S.S.R.,* **13,** 62 (1943); *C.A.,* **38,** 356 (1944).
443. Gol'dfarb, Setkina, and Danyushevskii, *Zhur. Obscheĭ Khim.,* **18,** 124 (1948); *C.A.,* **43,** 4137 (1949).
444. U.S. patent 1,936,547; *C.A.,* **28,** 858 (1934).
445. Tomita, *Pharmazie,* **7,** 497 (1952); *C.A.,* **48,** 10020 (1954).
446. Chichibabin and Ossetrowa, *Ber.,* **58,** 1708 (1925).
447. Vompe and Turitsyna, *Doklady Akad. Nauk S.S.S.R.,* **74,** 509 (1950); *C.A.,* **45,** 3846 (1951).
448. El'kina and Shemyakin, *J. Gen. Chem. U.S.S.R.,* **13,** 164 (1943); *C.A.,* **38,** 1504 (1944).
449. Shemyakin and El'kina, *J. Gen. Chem. U.S.S.S.R.,* **11,** 349 (1941); *C.A.,* **35,** 5893 (1941).
450. German patent 567,751; *C.A.,* **27,** 2761 (1933).
451. German patent 595,361; *C.A.,* **28,** 4069 (1934).
452. Gautier and Renault, *Compt. rend.,* **234,** 2081 (1952).
453. Lugovkin and Arbuzov, *Zhur. Obscheĭ Khim.,* **22,** 2041 (1952); *C.A.,* **47,** 9283 (1953).
454. King and Ware, *J. Chem. Soc.,* **1939,** 873.
455. German patent 613,122; *C.A.,* **29,** 5547 (1935).

456. Gol'dfarb and Pryanishnikova, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk.*, **1951**, 457; *C.A.*, **46**, 8108 (1952).
457. Ziegler, *J. Am. Chem. Soc.*, **71**, 1891 (1949).
458. Ochiai and Futaki, *J. Pharm. Soc. Japan*, **72**, 274 (1952); *C.A.*, **47**, 6417 (1953).
459. Salemink and van der Want, *Rec. trav. chim.*, **68**, 1013 (1949).
460. Yamamoto, *J. Pharm. Soc. Japan*, **72**, 1017 (1952); *C.A.*, **46**, 10285 (1952).
461. Savitskii and Rodionovskaya, *J. Gen. Chem. U.S.S.R.*, **10**, 2091 (1940); *C.A.*, **35**, 3988 (1941).
462. Bremer, *Ann.*, **539**, 276 (1939).
463. Koenigs, Gerdes, and Sirot, *Ber.*, **61**, 1022 (1928).
464. Petrow and Saper, *J. Chem. Soc.*, **1948**, 1389.
465. Weidenhagen and Train, *Ber.*, **75**, 1936 (1942).
466. Bremer, *Ann.*, **514**, 279 (1934).
467. Vaughan, Krapcho, and English, *J. Am. Chem. Soc.*, **71**, 1885 (1949).
468. U.S. patent 2,637,731; *C.A.*, **48**, 5228 (1954).
469. Bremer, *Ann.*, **518**, 274 (1935).
470. Koenigs, Beuren, and Jung, *Ber.*, **69**, 2690 (1936).
471. Chichibabin, *J. Russ. Phys. Chem. Soc.*, **46**, 1236 (1914); *Chem. Zentr.*, **1915, I**, 1066.
472. Rudy and Majer, *Ber.*, **71**, 1243 (1938).
473. Rudy and Majer, *Ber.*, **71**, 1323 (1938).
474. Rudy and Majer, *Ber.*, **72**, 933 (1939).
475. German patent 667,219; *C.A.*, **33**, 2150 (1939).
476. Swiss patent 260,573; *C.A.*, **44**, 2040 (1950).
477. Bernstein, Dexter, and Lott, *J. Am. Chem. Soc.*, **69**, 1147 (1947).
478. German patent 628,605; *C.A.*, **30**, 6137 (1936).
479. German patent 670,920; *C.A.*, **33**, 6351 (1939).
480. Rodewald and Plazek, *Ber.*, **70**, 1159 (1937).
481. Shreve, Riechers, Rubenkoenig, and Goodman, *Ind. Eng. Chem.*, **32**, 173 (1940).
482. German patent 399,902; *Chem. Zentr.*, **1924, II**, 2788.
483. German patent 400,638; *Chem. Zentr.*, **1925, I**, 303.
484. Swiss patent 239,755; *C.A.*, **43**, 7972 (1949).
485. Plazek, *Roczniki Chem.*, **16**, 403 (1936); *C.A.*, **31**, 1808 (1937).
486. U.S. patent 2,068,353; *C.A.*, **31**, 1959 (1937).
487. Boyer and Schoen, *J. Am. Chem. Soc.*, **78**, 423 (1956).
488. Crippa, Long, and de Martini, *Gazz. chim. ital.*, **64**, 83 (1934); *C.A.*, **28**, 4732 (1934).
489. Reider and Elderfield, *J. Org. Chem.*, **7**, 286 (1942).
490. Meyer and Staffen, *Monatsh.*, **34**, 517 (1913).
491. Meyer and Tropsch, *Monatsh.*, **35**, 189 (1914).
492. Meyer and Tropsch, *Monatsh.*, **35**, 207 (1914).
493. Titov, *J. Gen. Chem. U.S.S.R.*, **8**, 1483 (1938); *C.A.*, **33**, 4248 (1939).
494. U.S. patent 1,863,676; *C.A.*, **26**, 4347 (1932).

495. Seide and Titow, *Ber.*, **69**, 1884 (1936).
496. Titov and Levin, *J. Gen. Chem. U.S.S.R.*, **11**, 9 (1941); *C.A.*, **35**, 5501 (1941).
497. Albert and Hampton, *J. Chem. Soc.*, **1952**, 4985.
498. Kögl, van der Want, and Salemink, *Rec. trav. chim.*, **67**, 29 (1948).
499. Weidenhagen and Weeden, *Ber.*, **71**, 2347 (1938).
500. Harris, Heyl, and Folkers, *J. Biol. Chem.*, **154**, 315 (1944).
501. Löffler, *Ber.*, **37**, 161 (1904).
502. Hamlin, Weston, Fischer, and Michaels, *J. Am. Chem. Soc.*, **71**, 2731 (1949).
503. Cohen and Hughes, *J. Chem. Soc.*, **1952**, 4384.
504. Walter, Hunt, and Fosbinder, *J. Am. Chem. Soc.*, **63**, 2771 (1941).
505. U.S. patent 2,533,243; *C.A.*, **45**, 4271 (1951).
506. Takahashi, Nishigaki, and Taniyama, *J. Pharm. Soc. Japan*, **64**, 237 (1944); *C.A.*, **45**, 1997 (1951).
507. British patent 600,676; *C.A.*, **42**, 7344 (1948).
508. British patent 603,289; *C.A.*, **43**, 725 (1949).
509. Heyl, Harris, and Folkers, *J. Am. Chem. Soc.*, **75**, 653 (1953).
510. U.S. patent 2,497,730; *C.A.*, **44**, 5923 (1950).
511. Chapman and Williams, *J. Chem. Soc.*, **1953**, 2797.
512. Graf, *J. prakt. Chem.*, **140**, 39 (1934).
513. Graf, *J. prakt. Chem.*, **146**, 88 (1936).
514. Norton, Benson, Seibert, and Bergstrom, *J. Am. Chem. Soc.*, **68**, 1330 (1946).
515. Camps, *Arch. Pharm.*, **240**, 366 (1902); *Chem. Zentr.*, **1902, II**, 649.
516. Prijs, Lutz, and Erlenmeyer, *Helv. Chim. Acta*, **31**, 571 (1948).
517. Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).
518. Erlenmeyer and Epprecht, *Helv. chim. Acta*, **20**, 690 (1937).
519. Henecka, *Chem. Ber.*, **82**, 36 (1949).
520. Van Wagtendonk and Wibaut, *Rec. trav. chim.*, **61**, 728 (1942).
521. Martin, Avakian, and Moss, *J. Biol. Chem.*, **174**, 495 (1948).
522. Dornow and Schacht, *Chem. Ber.*, **82**, 117 (1949).
523. Dornow, *Angew. Chem.*, **60A**, 72 (1948).
524. U.S. patent 2,516,673; *C.A.*, **45**, 670 (1951).
525. Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 1245 (1939).
526. Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 3307 (1939).
527. Swiss patent 224,314; *C.A.*, **43**, 1811 (1949).
528. Matsukawa and Matsuno, *J. Pharm. Soc. Japan*, **64**, 145 (1944); *C.A.*, **45**, 4724 (1951).
529. Vanderhorst and Hamilton, *J. Am. Chem. Soc.*, **75**, 656 (1953).
530. Sculley and Hamilton, *J. Am. Chem. Soc.*, **75**, 3400 (1953).
531. Wibaut and Overhoff, *Rec. trav. chim.*, **52**, 55 (1933).
532. Micovic and Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).
533. Swiss patent 273,953; *C.A.*, **46**, 3556 (1952).
534. Burger, Rector, and Schmalz, *J. Am. Chem. Soc.*, **74**, 3175 (1952).

535. Work, *J. Chem. Soc.*, **1942**, 429.
536. Craig and Hixon, *J. Am. Chem. Soc.*, **53**, 4367 (1931).
537. Karrer, Viscontini, and Forster, *Helv. Chim. Acta*, **31**, 1004 (1948).
538. Bower and Ramage, *J. Chem. Soc.*, **1955**, 2834.
539. Craig, *J. Am. Chem. Soc.*, **55**, 2854 (1933).
540. Craig, *J. Am. Chem. Soc.*, **56**, 1144 (1934).
541. Laforge, *J. Am. Chem. Soc.*, **50**, 2477 (1928).
542. Laforge, *J. Am. Chem. Soc.*, **50**, 2484 (1928).
543. Haines, Eisner, and Woodward, *J. Am. Chem. Soc.*, **67**, 1258 (1945).
544. Kolloff and Hunter, *J. Am. Chem. Soc.*, **63**, 490 (1941).
545. Dornow and Bruncken, *Chem. Ber.*, **83**, 189 (1950).
546. Dornow, Machens, and Bruncken, *Chem. Ber.*, **84**, 147 (1951).
547. Adkins, Wolff, Pavlic, and Hutchinson, *J. Am. Chem. Soc.*, **66**, 1293 (1944).
548. Profft, *Chem. Tech.*, **6**, 484 (1954); *C.A.*, **50**, 332 (1956).
549. Heyl, Luz, Harris, and Folkers, *J. Am. Chem. Soc.*, **70**, 3669 (1948).
550. Heyl, Luz, Harris, and Folkers, *J. Am. Chem. Soc.*, **74**, 414 (1952).
551. Tilford, Shelton, and Van Campen, *J. Am. Chem. Soc.*, **70**, 4001 (1948).
552. U.S. patent 2,493,645; *C.A.*, **44**, 9575 (1950).
553. British patent 692,931; *C.A.*, **48**, 10776 (1954).
554. Mosher and Tessieri, *J. Am. Chem. Soc.*, **73**, 4925 (1951).
555. Heou-Feo, *Bull. soc. chim. (France)*, [5], **2**, 103 (1935).
556. Heou-Feo, *Compt. rend.*, **192**, 1242 (1931).
557. Matuszko and Taurins, *Can. J. Chem.*, **32**, 538 (1954).
558. U.S. patent 2,500,127; *C.A.*, **44**, 6158 (1950).
559. U.S. patent 2,500,128; *C.A.*, **44**, 6158 (1950).
560. British patent 585,708; *C.A.*, **45**, 6517 (1951).
561. U.S. patent 2,512,732; *C.A.*, **44**, 8961 (1950).
562. Brown and Miller, *J. Org. Chem.*, **11**, 388 (1946).
563. Burger and Ullyot, *J. Org. Chem.*, **12**, 342 (1947).
564. Burger and Walter, *J. Am. Chem. Soc.*, **72**, 1988 (1950).
565. Dornow and Schacht, *Chem. Ber.*, **80**, 505 (1947).
566. Katritzky, *J. Chem., Soc.*, **1955**, 2581.
567. Reich and Levine, *J. Am. Chem. Soc.*, **77**, 4913 (1955).
568. Reich and Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955).
569. Profft, *J. prakt. chem.* [4], **4**, 19 (1956).
570. Phillips, *J. Am. Chem. Soc.*, **78**, 4441 (1956).
571. Kirchner, McCormick, Cavallito, and Miller, *J. Org. Chem.*, **14**, 388 (1949).
572. British patent 667,457;*C.A.*, **47**, 616 (1953).
573. Wibaut, Wallingsford, Rang, and Kettenes, *Rec. trav. chim.*, **74**, 1049 (1955).
574. Swiss patent 257,245; *C.A.*, **44**, 286 (1950).
575. U.S. patent 2,519,470; *C.A.*, **44**, 10739 (1950).
576. Heyl, Luz, Harris, and Folkers, *J. Am. Chem. Soc.*, **73**, 3436 (1951).
577. Panizzon, *Helv. Chim. Acta*, **29**, 324 (1946).
578. Swiss patent 249,970; *C.A.*, **43**, 7973 (1949).

579. Niemann, Lewis, and Hays, *J. Am. Chem. Soc.*, **64**, 1678 (1942).
580. Overhoff, Boeke, and Gorter, *Rec. trav. chim.*, **55**, 293 (1936).
581. German patent 707,704; *C.A.*, **37**, 2745 (1943).
582. Peterson and Sober, *J. Am. Chem. Soc.*, **76**, 169 (1954).
583. Wilson and Harris, *J. Am. Chem. Soc.*, **73**, 4693 (1951).
584. Angyal, Barlin, and Wailes, *J. Chem. Soc.*, **1953**, 1740.
585. Späth and Bretschneider, *Ber.*, **61**, 327 (1928).
586. Chichibabin and Knunjanz, *Ber.*, **61**, 2215 (1928).
587. Osdene and Timmis, *J. Chem. Soc.*, **1955**, 2032.
588. Osdene and Timmis, *J. Chem. Soc.*, **1955**, 2214
589. Den Hertog and Jouwersma, *Rec. trav. chim.*, **72**, 44 (1953).
590. Wibaut, Bickel, and Brandon, *Rec. trav. chim.*, **58**, 1124 (1939).
591. Den Hertog and Overhoff, *Rec. trav. chim.*, **49**, 552 (1930).
592. Jenkins and Taylor, *J. Chem. Soc.*, **1937**, 495.
593. Chichibabin and Builinkin, *J. Russ. Phys. Chem. Soc.*, **50**, 471 (1920); *C.A.*, **18**, 1494 (1924).
594. Caldwell and Kornfeld, *J. Am. Chem. Soc.*, **64**, 1695 (1942).
595. Brooks and Rudner, *J. Am. Chem. Soc.*, **78**, 2339 (1956).
596. British patent 606,181; *C.A.*, **43**, 3471 (1949).
597. Baltzly and Kauder, *J. Org. Chem.*, **16**, 173 (1951).
598. Blicke and Tsao, *J. Am. Chem. Soc.*, **68**, 905 (1946).
599. Sharp, *J. Chem. Soc.*, **1939**, 1855.
600. Jones, Kornfeld, McLaughlin, and Anderson, *J. Am. Chem. Soc.*, **71**, 4000 (1949).
601. Weiss and Hauser, *J. Am. Chem., Soc.*, **72**, 1858 (1950).
602. Kaye, *J. Am. Chem. Soc.*, **72**, 5467 (1951).
603. U.S. patent 2,502,151; *C.A.*, **44**, 5921 (1950).
604. Hall and Burckhalter, *J. Am. Chem. Soc.*, **73**, 473 (1951).
605. Kyrides, Meyer, Zienty, Harvey, and Bannister, *J. Am. Chem. Soc.*, **72**, 745 (1950).
606. Ochiai, Tsuda, and Ikuma, *Ber.*, **69**, 2238 (1936).
607. British patent 673,633; *C.A.*, **47**, 5454 (1953).
608. Mangini, *Gazz. chim. ital.*, **65**, 1191 (1935); *C.A.*, **30**, 5221 (1936).
609. Fischer, *Ber.*, **35**, 3674 (1902).
610. Seide, *Ann.*, **440**, 311 (1924).
611. Phillips, *J. Chem. Soc.*, **1941**, 9.
612. Gray, *J. Chem. Soc.*, **1939**, 1202.
613. Feist, Auwe, and Kuklinski, *Arch. Pharm.*, **274**, 418 (1936); *C.A.*, **31**, 687 (1937).
614. Blicke and Sheets, *J. Am. Chem. Soc.*, **70**, 3768 (1948).
615. Hayes, Giver, and Orcutt, *J. Am. Chem. Soc.*, **72**, 1205 (1950).
616. Clark, Clapp, Vaughn, Sutherland, Winterbottom, Anderson, Forsythe, Blodinger, Eberlin, and English, *J. Org. Chem.*, **14**, 216 (1949).
617. Mercier, Mousseron, and Mercier, *Trav. soc. pharm. Montpellier*, **6**, 131 (1946); *C.A.*, **42**, 5562 (1948).

618. Gol'dfarb and Danushevskii, *Doklady Akad. Nauk. S.S.S.R.*, **87**, 223 (1952); *C.A.*, **48**, 679 (1954).
619. Bremer, *Ann.*, **521**, 286 (1936).
620. Feist and Kuklinski, *Arch. Pharm.*, **274**, 425 (1936); *C.A.*, **31**, 687 (1937).
621. U.S. patent 2,496,957; *C.A.*, **44**, 5397 (1950).
622. Stoll and Morel, *Helv. Chim. Acta*, **34**, 1937 (1951).
623. Reitsema and Hunter, *J. Am. Chem. Soc.*, **71**, 1680 (1949).
624. Mann and Watson, *J. Org. Chem.*, **13**, 502 (1948).
625. Berezovskii, *J. Gen. Chem., U.S.S.R.*, **21**, 1903 (1951); *C.A.*, **46**, 3282 (1952).
626. U.S. patent 2,406,594; *C.A.*, **41**, 488 (1947).
627. Gardner and Stevens, *J. Am. Chem. Soc.*, **71**, 1868 (1949).
628. Kaye and Horn, *J. Am. Chem. Soc.*, **74**, 838 (1952).
629. Campbell, Corrigan, and Campbell, *J. Org. Chem.*, **16**, 1712 (1951).
630. U.S. patent 2,530,358; *C.A.*, **45**, 1735 (1951).
631. U.S. patent 2,512,293; *C.A.*, **44**, 8948 (1950).
632. Protiva, Pliml, Borovička, and Řeřicha, *Chem. listy*, **46**, 346 (1952); *C.A.*, **47**, 4299 (1953).
633. British patent 606,182; *C.A.*, **43**, 3471 (1949).
634. British patent 606,187; *C.A.*, **43**, 3470 (1949).
635. Kyrides and Zienty, *J. Am. Chem. Soc.*, **71**, 1122 (1949).
636. British patent 668,779; *C.A.*, **47**, 5454 (1953).
637. U.S. patent 2,581,868; *C.A.*, **46**, 7592 (1952).
638. Weston, *J. Am. Chem. Soc.*, **69**, 980 (1947).
639. Austrian patent 170,862; *C.A.*, **47**, 9370 (1953).
640. Lincoln, Heinzelman, and Hunter, *J. Am. Chem. Soc.*, **71**, 2902 (1949).
641. Sharp, *J. Chem. Soc.*, **1938**, 1191.
642. Späth and Eiter, *Chem. Ber.*, **73**, 719 (1940).
643. Kermack and Weatherhead, *J. Chem. Soc.*, **1942**, 726.
644. German patent 586,879; *C.A.*, **28**, 1359 (1934).
645. Paul and Tchelitcheff, *Compt. rend.*, **221**, 560 (1945).
646. Grail and Tenenbaum, *J. Am. Chem. Soc.*, **74**, 1313 (1952).
647. Kato and Ohta, *J. Pharm. Soc. Japan*, **71**, 217 (1951); *C.A.*, **46**, 4541 (1952).
648. Kato and Hagiwara, *J. Pharm. Soc. Japan*, **73**, 145 (1953); *C.A.*, **47**, 11192 (1953).
649. Kalthod and Linnell, *Quarterly J. Pharm. and Pharmacol.*, **20**, 546 (1947).
650. Kalthod and Linnell, *Quarterly J. Pharm. and Pharmacol.*, **21**, 63 (1948).
651. Bremer, *Ann.*, **529**, 290 (1937).
652. Michaelis, *Ann.*, **366**, 324 (1909).
653. Conrad and Epstein, *Ber.*, **20**, 162 (1887).
654. Kato, *J. Pharm. Soc. Japan*, **71**, 1381 (1951); *C.A.*, **46**, 7100 (1952).
655. Koenigs, Friederich, and Jurany, *Ber.*, **58**, 2571 (1925).
656. Chichibabin and Worabjew, *J. Russ. Phys. Chem. Soc.*, **50**, 519 (1918); *Chem. Zentr.*, **1923, III**, 1022.
657. Takahashi, Saikachi, and Tabata, *J. Pharm. Soc. Japan*, **66**, 25 (1946); *C.A.*, **45**, 8532 (1951).

658. Zwart and Wibaut, *Rec. trav. chim.*, **74**, 1081 (1955).
659. U.S. patent 2,581,869; *C.A.*, **46**, 7592 (1952).
660. Weiner and Kaye, *J. Org. Chem.*, **14**, 868 (1949).
661. Kaye and Parris, *J. Am. Chem. Soc.*, **74**, 1566 (1952).
662. Kaye, Kogon, and Parris, *J. Am. Chem. Soc.*, **74**, 403 (1952).
663. Huttrer, Djerassi, Beears, Mayer, and Scholz, *J. Am. Chem. Soc.*, **68**, 1999 (1946).
664. Bernstein, Pribyl, Losee, and Lott, *J. Am. Chem. Soc.*, **69**, 1158 (1947).
665. Chichibabin, *J. Russ. Phys. Chem. Soc.*, **50**, 512 (1918); *Chem. Zentr.*, **1923, III**, 1022.
666. Klotz and Ming, *J. Am. Chem. Soc.*, **75**, 4159 (1953).
667. Pieroni, *Atti. accad. Lincei*, (**6**), **2**, 125 (1925); *C.A.*, **20**, 764 (1926).
668. U.S. patent 1,680,109; *C.A.*, **22**, 3736 (1928).
669. U.S. patent 1,874,656; *C.A.*, **26**, 6070 (1932).
670. Ostromislensky, *J. Am. Chem. Soc.*, **56**, 1713 (1934).
671. U.S. patent 1,680,110; *C.A.*, **22**, 3736 (1928).
672. Swiss patent 270,987; *C.A.*, **46**, 4575 (1952).
673. Mangini, *Boll. sci. fac. chim. ind. Bologna*, **1940**, 143; *Chem. Zentr.*, **1941, I**, 891.
674. Takahashi and Yamamota, *J. Pharm. Soc. Japan*, **66**, 27 (1946); *C.A.*, **46**, 111 (1952).
675. Takahashi and Taniyama, *J. Pharm. Soc. Japan*, **66**, 63 (1946); *C.A.*, **45**, 8534 (1951).
676. Takahashi and Ueda, *Pharm. Bull. (Tokyo)*, **2**, 34 (1954); *C.A.*, **50**, 335 (1956).
677. Takahashi and Taniyama, *J. Pharm. Soc. Japan*, **66**, 3 (1946); *C.A.*, **45**, 8532 (1951).
678. Takahashi and Saikachi, *J. Pharm. Soc. Japan*, **62**, 140, 143 (1942); *C.A.*, **45**, 1592, 1593 (1951).
679. British patent 341,598; *C.A.*, **25**, 4892 (1931).
680. Matsukawa, Ban, and Kawasaki, *J. Pharm. Soc. Japan*, **70**, 557 (1950); *C.A.*, **45**, 5651 (1951).
681. Colonna and Risaliti, *Gazz. chim. ital.*, **82**, 31 (1952); *C.A.*, **47**, 3297 (1953).
682. Den Hertog and Combé, *Rec. trav. chim.*, **70**, 581 (1951).
683. U.S. patent 2,156,141; *C.A.*, **33**, 5998 (1929).
684. U.S. patent 2,145,579; *C.A.*, **33**, 3599 (1929).
685. German patent 640,724; *C.A.*, **31**, 5382 (1937).
686. Chichibabin and Tjashelova, *J. Russ. Phys. Chem. Soc.*, **50**, 495 (1918); *Chem. Zentr.*, **1923, III**, 1021.
687. Seide, *Ber.*, **57**, 1803 (1924).
688. Seide, *Ber.*, **57**, 791 (1924).
689. Roe and Seligman, *J. Org. Chem.*, **20**, 1729 (1955).
690. Hall and VanderWerf, *J. Am. Chem. Soc.*, **73**, 4466 (1951).
691. Childress and McKee, *J. Am. Chem. Soc.*, **73**, 3504 (1951).

692. Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 534 (1918); *Chem. Zentr.*, **1923, III**, 1022.
693. Feist, Awe, and Völksen, *Arch. Pharm.*, **273**, 476 (1935); *C.A.*, **30**, 1377 (1936).
694. Rapaport and Look, *J. Am. Chem. Soc.*, **75**, 4605 (1953).
695. Chase and Walker, *J. Chem. Soc.*, **1953**, 3548.
696. U.S. patent 1,830,301; *C.A.*, **26**, 735 (1932).
697. U.S. patent 2,129,294; *C.A.*, **32**, 8707 (1938).
698. Chichibabin and Hoffman, *Compt. rend.*, **205**, 153 (1937).
699. Swiss patent 212,197; *C.A.*, **36**, 3632 (1942).
700. U.S. patent 2,615,892; *C.A.*, **47**, 10011 (1953).
701. Swiss patent 268,094; *C.A.*, **45**, 4399 (1951).
702. Skinner and Shive, *J. Am. Chem. Soc.*, **77**, 6692 (1955).
703. Doering and Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).
704. Chichibabin, *Bull. soc. chim.*, (5), **5**, 436 (1938).
705. Sommers, Freifelder, Wright, and Weston, *J. Am. Chem. Soc.*, **75**, 57 (1953).
706. Löffler and Kirschner, *Ber.*, **38**, 3329 (1905).
707. Vejdělek and Protiva, *Chem. Listy*, **45**, 451 (1951); *C.A.*, **47**, 8068 (1953).
708. Fromherz and Spiegelberg, *Helv. Physiol. Acta*, **6**, 42 (1948).
709. Uffer and Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).
710. Burrus and Powell, *J. Am. Chem. Soc.*, **67**, 1468 (1945).
711. Hromatka, *Chem. Ber.*, **75**, 522 (1942).
712. U.S. patent 2,604,473; *C.A.*, **48**, 12811 (1954).
713. British patent 690,274; *C.A.*, **48**, 6472 (1954).
714. Bloom, Breslow, and Hauser, *J. Am. Chem. Soc.*, **67**, 2206 (1945).
715. U.S. patent 2,567,245; *C.A.*, **46**, 4574 (1952).
716. Wibaut and Beyerman, *Rec. trav. chim.*, **70**, 977 (1951).
717. U.S. patent 2,508,332; *C.A.*, **44**, 7352 (1950).
718. Sunagawa, Hamatsu, and Murayama, *J. Pharm. Soc. Japan*, **73**, 882 (1953); *C.A.*, **48**, 8778 (1954).
719. British patent 689,289; *C.A.*, **48**, 4008 (1954).
720. Adamson and Billinghurst, *J. Chem. Soc.*, **1950**, 1039.
721. Von Braun and Weissbach, *Ber.*, **63**, 2018 (1930).
722. Gol'dfarb and Karaulova, *J. Gen. Chem. U.S.S.R.*, **18**, 117 (1948); *C.A.*, **42**, 5020 (1948).
723. U.S. patent 2,442,865; *C.A.*, **42**, 7796 (1948).
724. Gruber and Schlögl, *Monatsh.*, **81**, 83 (1950).
725. Mariella and Leech, *J. Am. Chem. Soc.*, **71**, 331 (1949).
726. Ochiai and Suzuki, *Pharm. Bull. (Tokyo)*, **2**, 147 (1954); *C.A.*, **50**, 1015 (1956).
727. Räth, *Ann.*, **489**, 107 (1931).
728. Swiss patent 244,837; *C.A.*, **43**, 6652 (1949).
729. Japanese patent 161,769; *C.A.*, **43**, 2645 (1949).
730. Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 3307 (1939).

731. U.S. patent 2,272,198; *C.A.*, **36**, 3634 (1942).
732. British patent 626,368; *C.A.*, **44**, 2570 (1950).
733. Mowat, Pilgrim, and Carlson, *J. Am. Chem. Soc.*, **65**, 954 (1943).
734. British patent 567,611; *C.A.*, **41**, 2755 (1947).
735. Ichiba, Emoto, and Nagai, *J. Sci. Research Inst.*, **43**, 23 (1948); *C.A.*, **43**, 4673 (1949).
736. U.S. patent 2,520,038; *C.A.*, **45**, 671 (1951).
737. Ichiba and Emoto, *J. Sci. Research Inst.*, **43**, 30 (1948); *C.A.*, **43**, 4670 (1949).
738. British patent 689,288; *C.A.*, **48**, 4008 (1954).
739. Heyl and Williams, *J. Chem. Soc.*, **1950**, 1678.
740. Rayburn, Harlan, and Hammer, *J. Am. Chem. Soc.*, **72**, 1721 (1950).
741. Gol'dfarb and Karaulova, *Doklady Akad. Nauk. S.S.S.R.*, **65**, 843 (1949); *C.A.*, **43**, 6626 (1949).
742. Gol'dfarb and Kondakova, *Compt. rend. acad. sci. U.R.S.S.*, **48**, 484 (1945); *C.A.*, **40**, 4732 (1946).
743. Gitsels and Wibaut, *Rec. trav. chim.*, **60**, 176 (1941).
744. Gol'dfarb, *Arch. Pharm.*, **274**, 490 (1936); *C.A.*, **31**, 1817 (1937).
745. Sadykov, *J. Gen. Chem. U.S.S.R.*, **17**, 1710 (1947); *C.A.*, **42**, 2610 (1948).
746. Zetsche, Mayer, Overbeck, and Lindlar, *Chem. Ber.*, **71**, 1516 (1938).
747. Ott and Hess, *Arch. Pharm.*, **276**, 181 (1938); *Chem. Zentr.*, **1938, I**, 4323.
748. Huntress and Walter, *J. Org. Chem.*, **13**, 735 (1948).
749. Terent'ev and Dombrovskii, *Zhur. obscheĭ. Khim.*, **20**, 1875 (1950); *C.A.*, **45**, 2892 (1951).
750. Singh and Manhas, *Proc. Indian Acad. Sci.*, **A30**, 87 (1949); *C.A.*, **45**, 2910 (1951).
751. Kelly and Short, *J. Chem. Soc.*, **1945**, 242.
752. Angyal, Morris, and Warburton, *Australian J. Sci. Research*, **A5**, 368 (1952); *C.A.*, **47**, 4877 (1953).
753. Lemoult, *Compt. rend.*, **138**, 1224 (1904).
754. Robins and Hitchings, *J. Am. Chem. Soc.*, **77**, 2256 (1955).
755. Philips, *Ann.*, **288**, 253 (1895).
756. German patent 362,446; *Chem. Zentr.*, **1923, II**, 808.
757. Ishii, *J. Pharm. Soc. Japan*, **72**, 1315 (1952); *C.A.*, **47**, 12386 (1953).
758. Seide, *Ber.*, **58**, 1733 (1925).
759. U.S. patent 2,456,379; *C.A.*, **43**, 7050 (1949).
760. Leonard and Ryder, *J. Org. Chem.*, **18**, 598 (1953).
761. Solomon, *J. Chem. Soc.*, **1946**, 934.
762. Petrow, *J. Chem. Soc.*, **1946**, 200.
763. Takahashi and Ueda, *Pharm. Bull. (Tokyo)*, **2**, 78 (1954); *C.A.*, **50**, 336 (1956).
764. Takahashi, Shibasaki, Hamada, and Okuda, *J. Pharm. Soc. Japan*, **72**, 434 (1952); *C.A.*, **47**, 6404 (1953).
765. Berrie, Newbold and Spring, *J. Chem. Soc.*, **1951**, 2590.
766. German patent 400,191; *Chem. Zentr.*, **1925, I**, 303.

767. U.S. patent 2,521,544; *C.A.*, **44**, 10739 (1950).
768. Wibaut and Kraay, *Rec. trav. chim.*, **42**, 1084 (1923).
769. Den Hertog, Schogt, De Bruyn, and De Klerk, *Rec. trav. chim.*, **69**, 673 (1950).
770. Den Hertog and Schogt, *Rec. trav. chim.*, **70**, 353 (1951).
771. Gerchuk, Livshits, and Taits, *Zhur. Obscheĭ. Khim.*, **20**, 924 (1950); *C.A.*, **44**, 9444 (1950).
772. Gerchuk, *Zhur. Obscheĭ. Khim.*, **20**, 917 (1950); *C.A.*, **44**, 9443 (1950).
773. Karrman, *Svensk Kem. Tidskr.*, **60**, 61 (1948); *C.A.*, **42**, 5804 (1948).
774. Aumuller and Horner, *Chem. Ber.*, **85**, 760 (1952).
775. German patent 553,278; *C.A.*, **26**, 4683 (1932).
776. French patent 974,085; *C.A.*, **47**, 12421 (1953).
777. Kirpal and Wojnar, *Chem. Ber.*, **71**, 1261 (1938).
778. German patent 586,802; *C.A.*, **28**, 1472 (1934).
779. Goodwin and Marshall, *J. Pharm. Exptl. Therap.*, **84**, 16 (1945).
780. U.S. patent 2,649,438; *C.A.*, **47**, 10863 (1953).
781. Thiers and van Dormall, *Bull. soc. chim. Belges*, **61**, 245 (1952).
782. Chichibabin and Kirssanow, *Ber.*, **61**, 206 (1928).
783. Kuhn, Moller, Wendt, and Beinert, *Chem. Ber.*, **75**, 711 (1942).
784. Doak, Steinman, and Eagle, *J. Am. Chem. Soc.*, **62**, 3012 (1940).
785. Shirley and Cameron, *J. Am. Chem. Soc.*, **74**, 664 (1952).
786. Sveinbjornsson and Vanderwerf. *J. Am. Chem. Soc.*, **73**, 869 (1951).
787. Mangini, Andrisano, and Colonna, *Pubbl. ist. chim. ind. univ. Bologna*, **No. 9**, 3 (1943); *C.A.*, **41**, 682 (1947).
788. Swiss patent 212,061; *C.A.*, **36**, 3512 (1942).
789. Kaufmann and Huang, *Chem. Ber.*, **75**, 1214 (1942).
790. Takahashi, Saikachi, and Sasaki, *J. Pharm. Soc. Japan*, **66**, 221 (1946); *C.A.*, **46**, 112 (1952).
791. Kyrides, Meyer, and Zienty, *J. Am. Chem. Soc.*, **69**, 2239 (1947).
792. Koenigs and Fulde, *Ber.*, **60**, 2106 (1927).
793. Clemo and Swan, *J. Chem. Soc.*, **1945**, 603.
794. Thomas and Jerchel, *Angew. Chem.*, **70**, 719 (1958).
795. Foldi, *Acta chim. Acad. Sci. Hung.*, **19**, 205 (1959); *C.A.*, **54**, 2325 (1960).
796. Kovacs and Najda, *Chem. and Ind.*, **1959**, 259.
797. Adams and Dunbar, *J. Am. Chem. Soc.*, **80**, 3649 (1958).
798. Jerchel and Jakob, *Chem. Ber.*, **91**, 1266 (1958).
799. Sprinzak, *Org. Syntheses*, **38**, 3 (1958).
800. Grammaticakis, *Bull. soc. chim. France*, **1959**, 480.
801. Boyland and Sims, *J. Chem. Soc.*, **1958**, 4198.
802. Savich, Pikaev, Lebedev, and Spitsyn, *Vestnik Moskov. Univ.*, **11**, *Ser. Mat. Mekh, Astron., Fiz., Khim., No. 1*, 225 (1956); *C.A.*, **53**, 1334 (1959).
803. Buu-Hoï, Xuong, and Suu, *J. Chem. Soc.*, **1958**, 2815.
804. Furst and Feustel, *Chem. Tech.*, **10**, 693 (1958); *C.A.*, **53**, 18951 (1959).
805. Gray, Heitmeier, and Spinner, *J. Am. Chem. Soc.*, **81**, 4351 (1959).

806. Talik and Plazek, *Roczniki Chem.*, **33**, 387 (1959); *C.A.*, **53**, 18954 (1959).
807. Profft and Otto, *J. prakt. Chem.*, [8], 156 (1959).
808. Albert, *J. Chem. Soc.*, **1960**, 1790.
809. Lappin, *J. Org. Chem.*, **23**, 1358 (1958).
810. Adler and Albert, *J. Chem. Soc.*, **1960**, 1794.
811. Adams and Dix, *J. Am. Chem. Soc.*, **80**, 4618 (1958).
812. Gennaro, *J. Org. Chem.*, **24**, 1156 (1959).
813. Mosby and Boyle, *ibid.*, **24**, 374 (1959).
814. Howard and Michels, *ibid.*, **25**, 829 (1960).
815. Klosa, *J. prakt. Chem.*, [8], 168 (1959).
816. Israel and Day, *J. Org. Chem.*, **24**, 1455 (1959).
817. Ried and Grabosch, *Chem. Ber.*, **89**, 2684 (1956).
818. Vitali and Craneri, *Chimica (Milan)*, **34**, 146 (1958); *C.A.*, **53**, 354 (1959).
819. Profft, *Chem. Ber.*, **91**, 957 (1958).
820. Profft, *Chem. Tech.*, **8**, 705 (1956); *C.A.*, **52**, 11040 (1958).
821. Profft, *Chem. Ber.*, **90**, 1734 (1957).
822. Bachman and Karickhoff, *J. Org. Chem.*, **24**, 1696 (1959).
823. Zymalkowski, *Arch. Pharm.*, **291**, 12 (1958); *C.A.*, **53**, 10209 (1959).

CHAPTER X

Pyridinecarboxylic Acids

By Eugene P. Oliveto
Schering Corporation, Bloomfield, New Jersey

The pyridinecarboxylic acids and their derivatives are present in many natural products (*e.g.*, vitamins, coenzymes, alkaloids). They are also of special interest to the medicinal chemist because

of the wide variety of physiological properties displayed by the natural as well as many synthetic acids. In addition, the stability of the pyridine ring to oxidation is such that pyridine acids are often the end product in degradation studies of many nitrogen-containing natural substances.

A. PREPARATION

1. From Nonpyridine Starting Materials

A thorough discussion of the synthesis of the pyridine ring system from nonpyridine starting materials has already been given in Chapter II, and many of these methods can be used for the preparation of pyridine acids and their derivatives.

The classical synthesis of pyridine from glutaconic dialdehyde and ammonia has been modified (especially in the Hantzsch method) to yield pyridine acids, esters, amides, or nitriles. The method consists of the condensation of a 1,5-diketone or potential 1,5-diketone with ammonia to give a dihydropyridine, which is easily oxidized to the pyridine derivative. If hydroxylamine is used instead of ammonia, the pyridine derivative is formed directly. The necessary diketone is usually formed *in situ*, for example, by the condensation between two moles of a β-keto ester and one mole of an aldehyde, and the product, after reaction with ammonia, is a pyridinedicarboxylic ester. One modification of the Hantzsch synthesis is the reaction between one mole of β-keto ester, two moles of an aldehyde, and ammonia to give a pyridinemonocarboxylic acid ester directly rather than the dihydro compound; excess aldehyde apparently can act as the oxidizing agent.

In another modification (the Guareschi synthesis) the aldehyde is omitted, and the β-keto ester condenses either with itself or with another such compound.

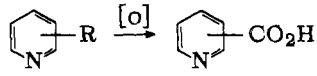
The keto ester can be replaced by β-keto amides or nitriles in any of the above methods to give pyridine amides and nitriles instead of acids.

Instead of ammonia and a β-keto ester, a compound such as β-aminocrotonic ester may be employed. This may be treated with an aldehyde or a β-keto ester separately, and makes possible the synthesis of unsymmetrical pyridine compounds.

2. From Pyridine Starting Materials

a. Oxidation of Monoalkyl- or Monoarylpyridines

Because of the high degree of stability of the pyridine ring, a large variety of derivatives yield pyridinecarboxylic acids upon oxidation, and indeed this type of reaction represents the most common method for preparing the simple acids (X-1). *Cf.* Chapter V, pp. 184 ff., 222.



(X-1)

R = alkyl, aryl, aralkyl, condensed ring, heterocycle

The alkylpyridines, which are readily available from coal tar and from the condensation of aliphatic aldehydes and ketones with ammonia (*cf.* Chapter II) are the most widely used intermediates, and potassium permanganate in neutral, acid, or alkaline medium the most common oxidizing agent for laboratory preparative purposes. The monoalkylpyridines can obviously give only one acid upon oxidation; 2-picoline has been oxidized to picolinic acid in 73% yield with hot neutral permanganate. Similarly, 3-picoline gives 83% of nicotinic acid, and 4-picoline gives 76% of isonicotinic acid (*1*). These yields are based on starting material consumed; about 8% of unreacted picoline is recovered in each case. The oxidations are carried out for 6 hours at 70–90°, the unoxidized base removed by steam distillation, and the residue acidified to the isoelectric point of the acid. Nicotinic and isonicotinic acids can be crystallized directly from the resulting hot aqueous solutions. Picolinic acid, however, is much too water-soluble (9 g. in 10 ml. of water at 9°); therefore, the aqueous acid mixture is distilled with benzene until all the water is removed, and the product crystallized from benzene.

Dilute nitric acid at temperatures of about 200° and pressures of 30–40 kg./cm.^{2} has converted 3-picoline to nicotinic acid in 50–60% yield, and 4-picoline to isonicotinic acid in 93% yield (*2*).

Other oxidants which have been reported include mixtures of nitric and sulfuric acids alone (*3*), or with selenium (*4*) or copper

and mercury salts (*5*), nitrogen tetroxide, sulfuric acid and selenium dioxide (*6*), selenium dioxide alone (*7*), mercuric sulfate or selenium in sulfuric acid (*8*), manganese dioxide in 70% sulfuric acid (*9*), chromium trioxide or potassium dichromate (*10*), and catalytic air oxidation (*11,12*). Electrolytic oxidation of 3-picoline with a lead anode has given 60% of nicotinic acid (*40*). Selenium dioxide appears to be selective in its action, oxidizing 2- or 4-picoline in 74–80% yield to the corresponding acid at temperatures of 110–120°, but not attacking 3-picoline (*13–15*). The oxidation of 3-picoline with selenium dioxide had, however, been reported in an earlier paper (*7*).

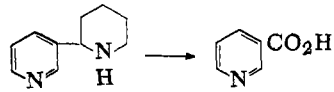
Higher monoalkylpyridines behave in a similar fashion, giving good yields of the corresponding monocarboxylic acids. For example, 4-ethylpyridine with dilute nitric acid gives 90% of isonicotinic acid (*2*), and 2-*i*-butylpyridine with alkaline permanganate gives picolinic acid (*16*).

Aryl and heterocyclic derivatives of pyridine are also converted to pyridine acids, demonstrating the higher degree of stability of the pyridine ring towards oxidation. The classical example is the preparation of nicotinic acid from nicotine (X-2), for which excellent

(X-2)

Nicotine

yields can be realized using potassium permanganate (*17*), nitric acid (*18,19*), sodium hypochlorite (*20*), or sulfuric acid containing mercuric sulfate or selenium (*8*). A similar example is the oxidation of the alkaloid anabasine to nicotinic acid (X-3) (*21*). Interestingly,

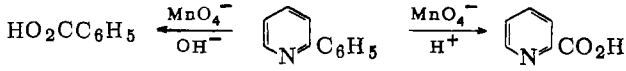


(X-3)

Anabasine

while the oxidation of 2-phenylpyridine with acid permanganate gives good yields of picolinic acid, basic permanganate gives mostly

benzoic acid (X-4) (*22*). Similar results are obtained if a mixture of 2- and 4-phenylpyridines is used (*23*).



(X-4)

b. Oxidation of Polyalkylpyridines or Benzopyridines

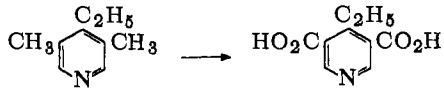
The oxidation of polysubstituted pyridines is a somewhat more complicated problem than that of the simple derivatives. Actually, three different reaction paths may be realized, depending on the experimental conditions and the starting materials: (*a*) partial oxidation to a mono- or polycarboxylic acid in which one or more of the original side-chain substituents has survived oxidation; (*b*) complete oxidation to a polycarboxylic acid; (*c*) complete oxidation to a polycarboxylic acid followed immediately by decarboxylation to give a lower acid.

The choice of oxidizing agent, its concentration, time, and temperature are all important factors in determining which of these three pathways will predominate (*cf.* Chapter II, pp. 251 ff., 257 ff.).

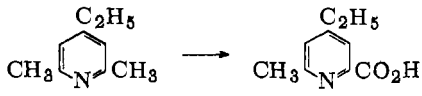
Few real generalizations can be made regarding the course of partial oxidations, but a methyl group (especially at position 3) seems to be oxidized somewhat more readily than a higher alkyl group (*1108*). As examples, we may cite the permanganate oxidation of 4-*i*-butyl-2,6-dimethyl-3,5-pyridinedicarboxylic acid (X-5) to 4-*i*-butyl-6-methyl-2,3,5-pyridinetricarboxylic acid (X-6) (*24*), the oxi-

(X-5) (X-6)

dation of 4-ethyl-3,5-lutidine to 4-ethyl-3,5-pyridinedicarboxylic acid (X-7) (*25*), the preparation of 4-ethyl-6-methylpicolinic acid from 4-ethyl-2,6-lutidine (X-8) (*26*), and the isolation, in 76% yield, of

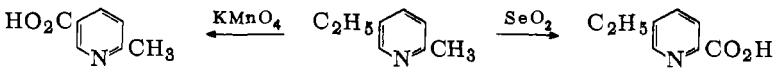


(X-7)



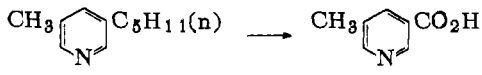
(X-8)

5-ethylpicolinic acid from the selenium dioxide oxidation of 5-ethyl-2-picoline (aldehyde collidine) (*15*). However, with other oxidizing agents (*e.g.*, permanganate), aldehyde collidine gives principally 6-methylnicotinic acid (X-9) (*76*). Other exceptions include the



(X-9)

oxidations of 2-propyl-3,5-lutidine to 3,5-dimethylpicolinic acid (*27*) and the isolation of 5-methylnicotinic acid after permanganate treatment of 5-*n*-amyl-3-picoline (X-10) (*28*).



(X-10)

With some exceptions, the ease of attack seems to increase in the order 4 < 2 < 3 positions (although selenium dioxide oxidation follows exactly the reverse order, 3 < 2 < 4 positions (*15*)). This can be seen in some of the reactions already cited and in the oxidation of 2,4,6-trimethylnicotinic acid to 2,4-dimethyl-3,6-pyridinedicarboxylic acid (*31*). However, the permanganate oxidation of 2,4-lutidine gives a 30% yield of 2-methylisonicotinic acid (isolated as ethyl ester) along with only a small amount of 4-methylpicolinic acid and the diacid (*29*).

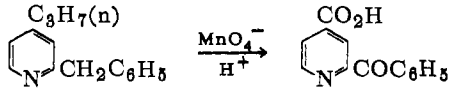
The extensive researches of Oparina on polyalkylpyridines provide further reactions: (*a*) 2,3,5,6-tetramethylpyridine was oxidized with permanganate to a mixture of 2,6-dimethyl-3,5-pyridinedicarboxylic acid and 2,5-dimethyl-3,6-pyridinedicarboxylic acid (*32*); (*b*) 2,3,4,-trimethylpyridine gave, with sufficient permanganate, 2,3,4-pyridinetricarboxylic acid and 2-methyl-3,4-pyridinedicarboxylic acid; with insufficient oxidizing agent 4-methylquinolinic acid (4-methyl-2,3-pyridinedicarboxylic acid) was isolated (*33*); (*c*) 2,3,5-trimethylpyridine gave a mixture of the tricarboxylic acid and 2,5-dimethylnicotinic acid (*34*); (*d*) 2,3,6-trimethylpyridine gave, besides

the tricarboxylic acid, 2-methyl-3,6-pyridinedicarboxylic acid; under similar conditions 2,4,5-trimethylpyridine gave some 4-methyl-2,5-pyridinedicarboxylic acid (*35*).

When the methyl groups are symmetrically placed, the problem is simplified: 2,6-lutidine gives a good yield (59%) of 6-methylpicolinic acid (*1*).

It is obvious that a great deal of work must still be done before truly definitive rules for predicting the course of partial oxidation of polyalkylpyridines can be outlined. Many of the previous investigations were aimed merely at the isolation of a single product (which might not necessarily be the most plentiful one, but merely the most insoluble, or the easiest to isolate) without regard for a true material balance.

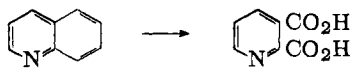
Alkyl groups are much more prone to oxidation than aryl groups. For example, 2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylic acid is oxidized with aqueous permanganate to 4-phenyl-2,3,5,6-pyridinetetracarboxylic acid in 72% yield (*36*) and 6-phenylpicolinic acid can be obtained from the oxidation of 6-phenyl-2-picoline (*37*). An interesting variation is the acid permanganate oxidation of 2-benzyl-4-propylpyridine to 2-benzoylisonicotinic acid in 60% yield (X-11) (*38*). 2-Phenyl- and 6-phenylnicotinic acids are obtained from the corresponding phenylpicolines (*1099*).



(X-11)

The oxidation of polyalkylpyridines to the corresponding pyridinepolycarboxylic acids presents no particular difficulties, provided sufficient oxidizing agent is used and reaction temperatures kept as low as possible to minimize side reactions. Selenium dioxide oxidation (*7,15*) is particularly worthy of note, because of the satisfactory yields of pyridinedi- and -tricarboxylic acids from 2,4- and 2,6-lutidines and *s*-collidine. Also, aqueous copper nitrate at 205° and 280 atmospheres oxidizes aldehyde collidine to 2,5-pyridinedicarboxylic acid in 98.5% yield (*30*).

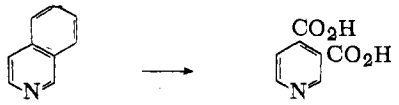
Oxidation of fused ring systems such as the quinolines and isoquinolines proceeds very readily to give 2,3-pyridinedicarboxylic acid (quinolinic acid) (X-12) and 3,4-pyridinedicarboxylic acid



(X-12)

Quinoline Quinolinic acid

(cinchomeronic acid) (X-13). The former acid has been prepared from quinoline in 70% yield by means of hydrogen peroxide, sul-



(X-13)

Isoquinoline Cinchomeronic acid

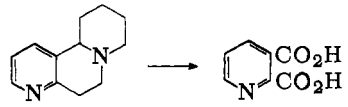
furic acid, and copper sulfate at 60–70° for 11 hours (*39*), and 77% yield by electrolytic oxidation in 75% sulfuric acid with a platinum anode (*40*), and in 89.5% yield by means of nitrogen tetroxide and selenium dioxide in 96% sulfuric acid at 200–300° (*6*). If the selenium dioxide is omitted from this last reaction, the yield drops to 63%. Cinchomeronic acid may be prepared from isoquinoline by treatment with sulfuric acid in the presence of a selenium compound (*42*), in 48% yield by treatment with manganese dioxide and sulfuric acid at 170° (*43*), and in 45% yield by ozonolysis in acetic acid (*44*).

Substitution in the benzene ring of quinoline does not change the course of the reaction, and, in fact, the presence of certain groups may actually aid in the oxidation. For example, oxidation of the readily available 8-hydroxyquinoline with nitric acid gives up to 85% of quinolinic acid (*45*) or up to 94% of a mixture of quinolinic and nicotinic acids (*46*). The ozonolysis of 6-substituted quinoline derivatives, however, gives much lower yields of quinolinic acid (*44*): 8-hydroxyquinoline (90–95%), 6-aminoquinoline (65%), 6-fluoroquinoline (15%), 6-nitroquinoline (6%).

Pyridinetri- and -tetracarboxylic acids may be obtained by oxidation of quinolinecarboxylic acids. Thus permanganate oxidation of 2,4-quinolinedicarboxylic acid or ozonolysis of 8-hydroxy-2,4-quinolinedicarboxylic acid gives an excellent yield of 2,3,4,6-pyridinetetracarboxylic acid. Similarly, 4-quinolinecarboxylic acid is oxidized to 2,3,4-pyridinetricarboxylic acid (*1044*).

Saturated fused rings are likewise attacked much more readily

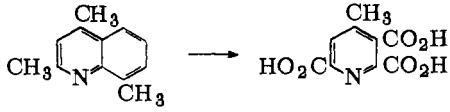
than the pyridine nucleus: 4,5-(α,β-pyridylene)norlupinane has been converted to quinolinic acid in 68% yield with hot aqueous permanganate (X-14) (*47*).



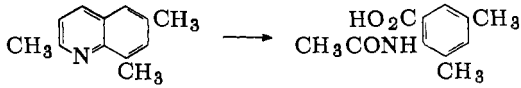
(X-14)

The benzene portion of quinoline (or isoquinoline) is oxidized so readily that aryl and even alkyl substituents on the pyridine ring easily survive. Thus, 4-phenylquinoline, upon oxidation with hot permanganate for 6 hours, gives a 61% yield of 4-phenylquinolinic acid (*48*); 2-propyl-8-hydroxyquinoline yields 41% of 6-propylquinolinic acid (*49*); and 3-methylisoquinoline gives 11% of 6-methylcinchomeronic acid (isolated as the diethyl ester) (*50*).

An unusual series of oxidations has been described by Kruber and Rappen (*51*). While 6,8-dimethylquinoline gives the expected product (quinolinic acid) upon permanganate oxidation, and 2,4,8-trimethylquinoline gives 4-methyl-2,3,6-pyridinetricarboxylic acid (X-15), 2,6,8-trimethylquinoline gives no pyridine acid; instead, 2-acetamido-3,5-dimethylbenzoic acid is the sole product (X-16).



(X-15)



(X-16)

By slight changes in reaction condition (*e.g.*, raising the temperature) polysubstituted pyridines, instead of yielding the expected polycarboxylic acids, can often be made to give lower acids through loss of carbon dioxide during the reaction. Carboxyl groups in positions 2 and 4 are especially prone to loss. Quinoline then becomes an important source of nicotinic acid, for while quinolinic acid is the primary oxidation product at temperatures in the range of 150–190° (*5,52,53*), nicotinic acid can be obtained in yields up to

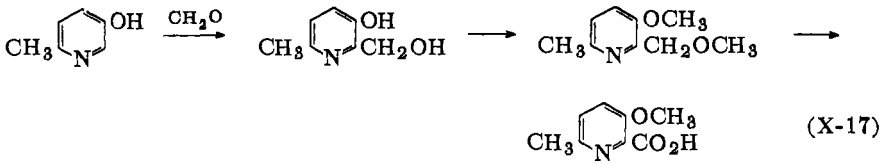
88% if the reaction temperature is raised above 210° (*5,8,52–54*). Aldehyde collidine (5-ethyl-2-picoline) also can be readily converted to nicotinic acid in good yield (*55*). Carboxyl groups in position 2 are the easiest of all to eliminate: permanganate oxidation of 4-*i*-butyl-2-picoline gives isonicotinic acid (*23*), nitric acid treatment of 2,4-lutidine or *s*-collidine gives 40–45% of isonicotinic acid (*2*), and 6-*i*-propyl-2,3-lutidine gives 2,5-pyridinedicarboxylic acid on permanganate oxidation (*56*). In the last case, only one of the sensitive α-carboxyl groups is lost, the other being retained. Carboxyl groups at position 2 are labilized by the presence of substituents at position 3 (*1044*).

The decarboxylation reaction may be carried out as a separate step, allowing, perhaps, somewhat better control. As already mentioned, the order of ease of decarboxylation is $2 > 4 > 3$. The reaction is usually carried out by heating the polyacid to an elevated temperature, either with or without a solvent. Much work has been done on the conversion of 2,5-pyridinedicarboxylic acid (readily available from aldehyde collidine) to nicotinic acid, and 90–95% yields have been obtained by heating with nitrobenzene at reflux for ¾–1 hour (*61,62*), or with steam at 190° and 28 atmospheres for 2 hours (*63*). The lability of a carboxyl in position 2 and the relative inertness of a carboxyl in position 3 may be illustrated by several examples: (*a*) triethyl 3-acetyl-2-methyl-4,5,6-pyridinetricarboxylate, when hydrolyzed with hydrochloric acid and then heated to 150° in diethylene glycol, gives a 56% yield of 3-acetyl-2-methyl-4,5-pyridinedicarboxylic acid; the corresponding 3-cyano compound does not hydrolyze and decarboxylate, while the corresponding 3-amino compound decarboxylates in abnormally low yield with the loss of the 5-carboxyl group rather than the 4-carboxyl, and 3-amino-2-methylisonicotinic acid was isolated in low yield (*64*); (*b*) 2,4-pyridinedicarboxylic acid, upon heating above its melting point (*65*), or with superheated steam (*66*), readily gives isonicotinic acid; (*c*) 2-methyl-4,6-pyridinedicarboxylic acid, upon heating to 280°, gives a 65% yield of 2-methylisonicotinic acid; (*67*); (*d*) 2,3,5-pyridinetricarboxylic acid, after ½ hour heating at 150°, gives 3,5-pyridinedicarboxylic acid (*68*); (*e*) 6-propylquinolinic acid gives 6-propylnicotinic acid by heating in propionic acid (*49*).

c. Oxidation of Partially Oxidized Derivatives

Derivatives in which the substituents are already in a higher oxidation state than alkyl or aryl groups can be good sources of acids. In particular, they offer an opportunity to use mild oxidizing conditions, permitting much higher selectivity in partial oxidations than is possible with polyalkylpyridines.

This selectivity is well shown by hydroxymethylpyridine derivatives. For example, 6-methyl-3-pyridinol reacts with formaldehyde to give a 75% yield of 3-hydroxy-6-methyl-2-pyridinemethanol. After methylation, the resulting compound can be oxidized in 40% yield with alkaline permanganate to 3-methoxy-6-methylpicolinic acid (X-17) (*57*). Other examples are the oxidation of 3-hydroxy-2-

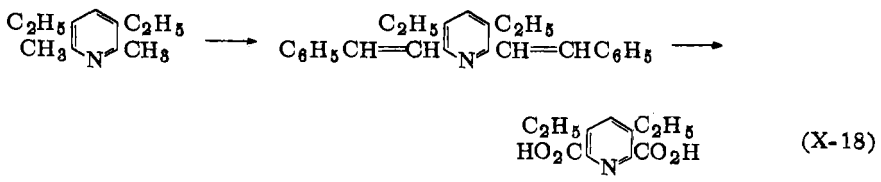


(X-17)

pyridinemethanol to 3-hydroxypicolinic acid in 60% yield (*58*), and the oxidation of 4-hydroxy-5-methoxy-2-pyridinemethanol with nitric acid to give a 70–85% yield of 4-hydroxy-5-methoxypicolinic acid (*59*).

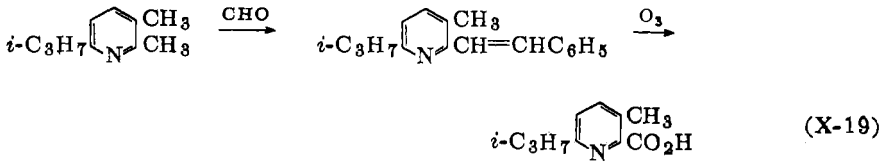
Both 2-pyridinemethanol and 4-pyridinemethanol are oxidized to the corresponding acids with selenium dioxide at 110–150° in the absence of solvent. Under these conditions 3-pyridinemethanol gives mostly aldehyde (*1043*).

Methyl groups in positions 2 and 4 of the pyridine nucleus undergo aldol-type condensations with a variety of carbonyl compounds, including benzaldehyde, *p*-nitrobenzaldehyde, cinnamaldehyde, formaldehyde, acetaldehyde, ethyl oxalate, and chloral. The resulting carbinol (or olefin, depending on reaction conditions) can, in many cases, be selectively oxidized to acid without affecting alkyl groups which have not reacted with the aldehyde. Thus, 3,5-diethyl-2,6-lutidine reacts with benzaldehyde and acetic anhydride only at positions 2 and 6, to give 3,5-diethyl-2,6-distyrylpyridine. This, upon permanganate oxidation at 0°, yields 3,5-diethyl-2,6-pyridinedicarboxylic acid (X-18) (*60*). Another example is the condensation of



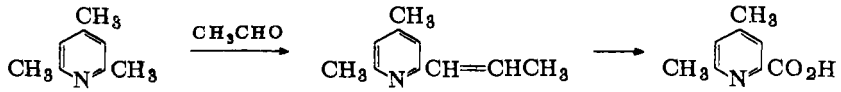
(X-18)

6-*i*-propyl-2,3-lutidine with benzaldehyde to give 3-methyl-6-*i*-propyl-2-stilbazole, followed by ozonolysis to give a 40% yield of 3-methyl-6-*i*-propylpicolinic acid (X-19) (*56*).



(X-19)

In *s*-collidine, only the 2-methyl group can be made to react with acetaldehyde (*70*) or chloral (*71*) to give, respectively, 2-propenyl-4,6-lutidine (X-20) and 2-(3-trichloro-2-hydroxypropyl)-4,6-lutidine.



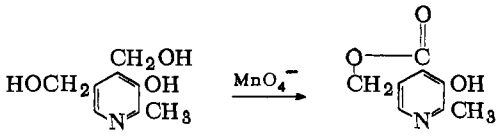
(X-20)

Both of these can be oxidized to 4,6-dimethylpicolinic acid, although some difficulties have been encountered in the oxidation of chloral derivatives (*72*). 4-Ethyl-2,6-lutidine and 4-propyl-2,6-lutidine react with benzaldehyde at only one methyl group to give the 2-styryl derivatives; these, upon oxidation, yield, respectively, 4-ethyl-6-methylpicolinic acid (*73*) and 6-methyl-4-propylpicolinic acid (*74*). A study has been made of the condensation of benzaldehyde with 2- and 4-picolines; the resulting stilbazoles could be ozonized in acetic acid to picolinic or isonicotinic acid in 75–95% yield (*75*).

A number of reactions carried out by Plattner, Keller, and Baller (*76*) well exemplify the preparation of acids, otherwise difficultly accessible, by this type of condensation and oxidation. Three 2-picolines, substituted at position 5 with ethyl, *n*-butyl, or *n*-hexyl, were condensed with benzaldehyde in the presence of acetic anhydride

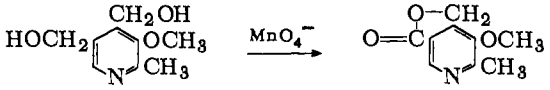
to give excellent yields of the 2-styryl derivatives; these were then oxidized to the 5-alkylpicolinic acids with permanganate in 65–67% yield. Thus, by this sequence, 5-ethyl-2-picoline (aldehyde collidine) gives 5-ethylpicolinic acid, but by direct permanganate oxidation, 6-methylnicotinic acid is obtained in 57% yield (*76*).

An interesting anomaly has been reported in the Vitamin B_6 series. While pyridoxine (Vitamin B_6) gives with permanganate the lactone of 3-hydroxy-5-(hydroxymethyl)-2-methylisonicotinic acid (X-21), oxidation of pyridoxine 3-methyl ether gives the lactone of 4-hydroxymethyl-5-methoxy-6-methylnicotinic acid (X-22) (*77–79*).



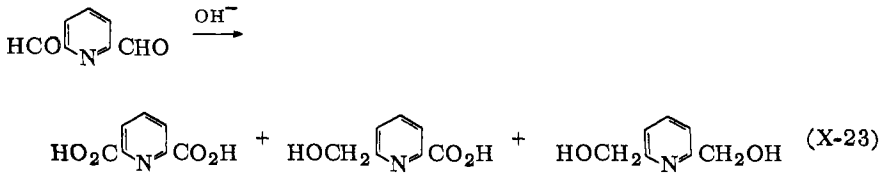
(X-21)

Pyridoxine



(X-22)

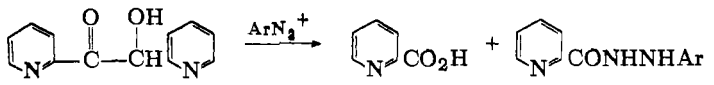
As might be expected, the pyridine aldehydes are very easily transformed into the corresponding acids. For example, 2,6-pyridinedicarboxaldehyde gives a good yield of 2,6-pyridinedicarboxylic acid (*80*). Of academic interest, but of little preparative value, is the Cannizzaro reaction with pyridine aldehydes (*80,81*); 2,6-pyridinedicarboxaldehyde gives all three expected products: 2,6-pyridinedicarboxylic acid, 6-(hydroxymethyl)picolinic acid, and 2,6-pyridinedimethanol (X-23).



(X-23)

The reaction of diazonium salts with 2-pyridoin has been studied by Eistert (*82,83*). One portion of the pyridoin molecule is con-

verted to picolinic acid, the other half to 1-aryl-2-(2-pyridoyl)hydrazines in good yield (X-24). 2-Pyridoin may also be readily converted



(X-24)

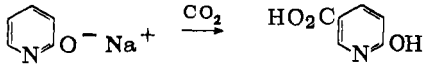
to picolinic acid by oxidation with ferric chloride, and to picolinic acid 1-oxide with hydrogen peroxide. With this latter reagent, 2-pyridil gives picolinic acid (*84*).

An unusual oxidation is the conversion of potassium 1-methyl-2(1*H*)-pyridone-6-pyruvate by means of hydrogen peroxide to 1-methyl-2(1*H*)-pyridone-6-carboxylic acid in 58% yield (*85*). If the ethyl ester is used instead of the potassium salt, 1-methyl-2(1*H*)-pyridone-6-acetic acid is obtained instead, in 84–87% yield.

Pinacol rearrangement of 1,2-bis(2-pyridyl)-1,2-diphenyl-1,2-ethanediol produces the expected pinacolone, which is hydrolyzed to picolinic acid in 80% yield, along with 60% 2-pyridyldiphenylmethane (*86*). A similar result is obtained with the 3-pyridyl derivative.

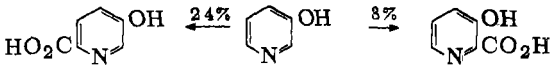
d. Carbonation of Pyridinols

Little has appeared in the literature on this type of reaction. The first report was by Chichibabin (*87*), who converted 2-pyridinol (sodium salt) to 6-hydroxynicotinic acid (X-25). This has been re-



(X-25)

peated more recently in 60% yield (*41*). 3-Pyridinol (sodium salt) when heated at 215–220° and 45 atmospheres with carbon dioxide, gives 22% of 3-hydroxypicolinic acid (*88*). This resembles the original Kolbe synthesis in that the entering carboxyl group is ortho to the hydroxyl. However, under the same conditions, the potassium salt of 3-pyridinol is reported to give 24% of 5-hydroxypicolinic acid, and only 3% of the 3-hydroxy isomer (X-26) (*88*). The same



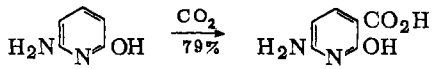
(X-26)

investigators report an optimal yield of 85–87% of 5-hydroxypicolinic acid from 3-pyridinol.

There is some discrepancy regarding the products obtained on treatment of 3-pyridinol with potassium carbonate. One group (*943*) claims the isolation of 70% of 5-hydroxypicolinic acid and only 1% of 3-hydroxypicolinic acid, while others (*944*) have obtained 28% of the latter acid and only 21% of the former.

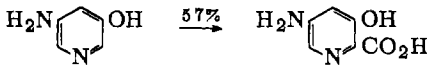
The sodium or potassium salt of 4-pyridinol with carbon dioxide gives mixtures of 4-hydroxynicotinic acid and 4-hydroxy-3,5-pyridinedicarboxylic acid; the proportion of the two acids formed is dependent on the time and temperature of the reaction and the particular salt used as starting material (*1075*).

In the aminopyridinols which have been studied, the carboxyl group enters ortho to the hydroxyl: 6-amino-2-pyridinol, with potassium carbonate and carbon dioxide at 200° for 3–4 hours, gives 79% of the 3-carboxyl derivative (X-27), while 5-amino-3-pyridinol,



(X-27)

on somewhat longer treatment, gives 57% of the 2-carboxyl derivative (X-28) (*89*).



(X-28)

e. Carbonation of Organometallic Derivatives

All three pyridinemonocarboxylic acids have been prepared by the action of carbon dioxide on the appropriate pyridyllithium compound (*90–95*). The latter are prepared by the exchange reaction between an alkyllithium (usually butyllithium) and a halopyridine (either bromo- or iodopyridine). By this method, nicotinic (*91,94*) and isonicotinic (*95*) acids have been prepared in which the carboxyl carbon is isotopically labeled.

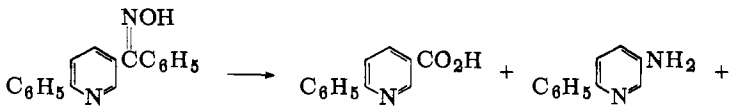
Although many side reactions are possible, reasonably good yields can be obtained with short reaction times and low temperatures. In a study made by Gilman and Spatz (*90*), using a variety of alkyllithiums, 3-iodopyridine gave better and more consistent yields than 3-bromopyridine. Both 3,5-dibromopyridine and 2,6-dibromopyridine react at only one of the halogens, giving, respectively, 41% of 5-bromonicotinic acid and 45% of 6-bromopicolinic acid (*90*). The

pyridyllithium obtained from 2-bromo-3,4,6-triphenylpyridine and butyllithium gives, after carbonation, 67% of 3,4,6-triphenylpicolinic acid (*96*).

The preparation and reactions of pyridyllithium compounds are fully discussed in Chapter VII (pp. 422 ff.).

f. Beckmann Rearrangement

Pyridyl ketones behave in the Beckmann rearrangement exactly like their aliphatic counterparts; that is, two possible oximes may be formed, each of which gives a different product in the rearrangement. Although Benary and Psille (*97*) were able to isolate only *syn*-oxime of 3-benzoyl-6-phenylpyridine, Nienburg (*98*) obtained both forms. The *anti* form gives, on rearrangement with phosphorus pentachloride followed by hydrolysis, a mixture of 6-phenylnicotinic acid and aniline. The *syn* form gives these two products, plus benzoic acid and 3-amino-6-phenylpyridine (X-29). This ap-



$$C_6H_5CO_2H + C_6H_5NH_2 \qquad \text{(X-29)}$$

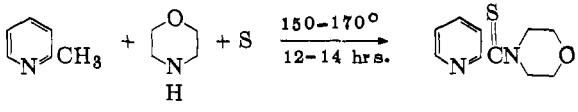
parent anomaly was demonstrated to be the result of partial conversion of the *syn* to the *anti* form under the rearrangement conditions. Comparable results are obtained in the rearrangement with thionyl chloride of the oximes of 2-benzoylpyridine: the *anti*-oxime gives picolinic acid and aniline, while the *syn*-oxime gives benzoic acid and 2-aminopyridine. With sulfuric acid, either isomer gives only the former two products, again demonstrating the ease with which the *syn* can be converted to the *anti* form (*99*).

With a symmetrical ketone such as bis(2-dimethylamino-5-pyridyl) ketone, only one oxime is possible, and after rearrangement and hydrolysis, excellent yields of 6-dimethylaminonicotinic acid are obtained (*100*).

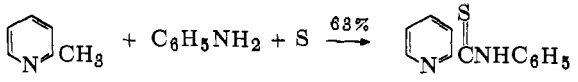
g. Willgerodt Reaction

Both 2- and 4-picolines undergo the Willgerodt reaction, while 3-picoline does not. One of the products obtained by the action of

sulfur and an amine on 2- or 4-picoline is a thioamide, which can be oxidized by permanganate to the amide, or easily hydrolyzed to the acid. Unfortunately, the yields of thioamides vary because at least two other products can sometimes be formed. Morpholine, sulfur, and 2(or 4)-picoline, heated together 12–14 hours at 150–170°, give 22% thiopicolinoylmorpholine (X-30) (or 40% thioisonicotinoylmorpholine) (*101,953*). Aniline, sulfur, and 2-picoline give a good yield (63%) of thiopicolinanilide (X-31), but 4-picoline,

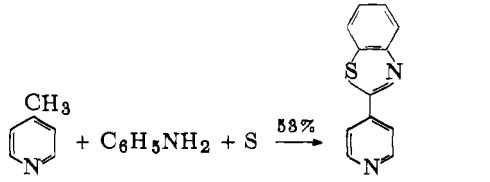


22% (X-30)



(X-31)

under these conditions, gives a 53% yield of 2-(4-pyridyl)benzothiazole (X-32) (*101*). With longer reflux times even 2-picoline gives



(X-32)

some 2-(2-pyridyl)benzothiazole (*102*), while 4-picoline begins to give appreciable quantities of *N,N'*-diphenylisonicotinamidine (which can be hydrolyzed to isonicotinic acid with concentrated hydrobromic acid). From 100 g. of 4-picoline, 100 g. of aniline, and 50 g. of sulfur, refluxed 40 hours, Emmert and Holz (*103*) obtained 20–40 g. of the thioanilide, 60 g. of the amidine, and 10–15 g. of the benzothiazole. α-Naphthylamine gives both the thioamide and 2-(2-pyridyl)naphthothiazole, while β-naphthylamine gives mainly the naphthothiazole (*102,103*).

2-Picoline, sulfur, and *t*-octylamine gave a good yield of *N*-*t*-octylthiopicolinamide; 2,4-lutidine reacted only at the 2-methyl group (*1098*).

Nitrobenzene can replace aniline in the Willgerodt reaction, the nitro group suffering reduction. Other amines and nitroaromatics which have been used include *p*-nitro- or *p*-aminotoluenes, α-nitronaphthalene, *p*-nitrophenol, *p*-nitroaniline, methylaniline, and *p*-nitrodimethylaniline.

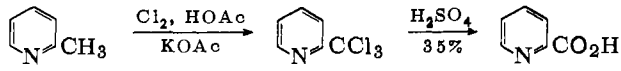
h. Hydrolysis of Nitriles

The cyanopyridines generally are good sources of carboxylic acids (or amides) because they can be hydrolyzed, usually in good yields, to these products. The hydrolysis may be carried out by a variety of procedures, including acid, alkaline, and neutral conditions. Specific reactions will be discussed under the cyanopyridines later in this chapter (p. 232).

i. Hydrolysis of Trichloromethyl Derivatives

All three pyridinemonocarboxylic acids have been prepared by the hydrolysis of trichloromethylpyridines. These, in turn, are prepared from the picolines by chlorination. Under proper conditions, the hydrolysis may occur during the chlorination step so that the intermediate trichloromethyl derivative need not be isolated.

In order to limit attack to the side chain, 2-picoline is chlorinated with chlorine in acetic acid heavily buffered with potassium acetate; the yield of 2-trichloromethylpyridine is 25%. Hydrolysis to picolinic acid is then accomplished in 35% yield by refluxing with 30% sulfuric acid for 8 hours (X-33) (*104*). A 64% yield of tri-



(X-33)

chloromethyl compound can be obtained if the chlorination is carried out in the presence of ultraviolet light (*105*). Chlorine and ultraviolet light convert 3-ethylpyridine to 3-trichloroacetylpyridine, easily hydrolyzed to nicotinic acid (*106*). Chlorine, ultraviolet light, and hydrochloric acid convert 3-picoline directly to nicotinic acid in 15% yield (*107*).

Graf and Zettl (*108*) have studied the reaction of refluxing thionyl chloride with 6-methylpicolinic acid, 6-methylnicotinic acid, 6-methyl-2,4-pyridinedicarboxylic acid, and 2,6-lutidine. With the first three compounds, the products of reaction were first esterified

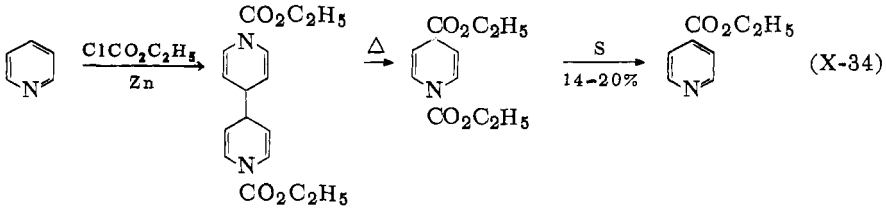
with methanol and then separated. In each case, they obtained a mixture of the trichloromethyl derivative and the acid (or ester) which would be derived from it by hydrolysis. For example, 4 g. of 6-methyl-2,4-pyridinedicarboxylic acid gives 2 g. of 6-trichloromethyl-2,4-pyridinedicarboxylic acid and 0.2 g. of 2,4,6-pyridinetricarboxylic acid. The only product isolated from 2,6-lutidine is 2,6-bis(trichloromethyl)pyridine, which, with 80% sulfuric acid, gives 2,6-pyridinedicarboxylic acid.

Trichloromethyl derivatives may also be hydrolyzed with boiling water (*109*) or with silver nitrate in acetic acid (*110*). An unusual example of the latter reaction is the hydrolysis (followed by oxidation) of 4-dichloromethylpyridine to isonicotinic acid in 55% yield, while 4-trichloromethylpyridine gives only 32% of this acid (*110*).

j. Miscellaneous

The sulfonic acid group in 4-ethyl-3-pyridinesulfonic acid can be replaced directly with the carboxyl group by means of sodium formate; the yield, however, is low (*111*).

An interesting transformation is described by van Dorp and Arens (*112*). Pyridine reacts with ethyl chloroformate and zinc to give 1,1′-dicarbethoxy-1,1′,4,4′-tetrahydro-4,4′-bipyridine; this breaks down on distillation to 1,4-dicarbethoxy-1,4-dihydropyridine which, when heated with sulfur, gives 14–20% yields of ethyl isonicotinate (X-34).



(X-34)

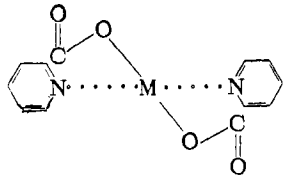
B. PROPERTIES

The pyridinecarboxylic acids are all white crystalline solids. Nicotinic and isonicotinic acids can be crystallized from water, but picolinic acid is too soluble to permit this. The polycarboxylic acids

are relatively insoluble. The unsubstituted mono- and polyacids are listed in Table X-1 (pp. 250 ff.) and Table X-2 (p. 266 ff.).

The monocarboxylic acids appear to be weaker acids than benzoic when the ionization constant is determined in the usual way. Nicotinic and isonicotinic acids have approximately the same acid strength as the aminobenzoic acids, but all three pyridine acids are much weaker than the nitrobenzoic acids. (For a discussion of the true acidity of the pyridine acids, see Chapter I, p. 74).

The pyridine acids and their derivatives form complexes with a variety of bivalent metallic ions (*113,115*), for which structures such as (X-35) are postulated. Pyridine compounds with a free carboxyl



(X-35)

group in the 2 (or 6) position form reddish complexes with ferrous salts, while carboxyls in other positions give no such colors. This test has been used to help identify the position of a carboxyl group in an unknown substance, and the intensity of the color used as a measure of the total number of carboxyl groups present (*116*).

C. REACTIONS

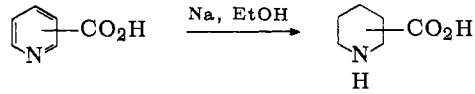
1. Reduction

a. Chemical

The pyridine acids may undergo many different types of reduction, including partial or complete reduction of the carboxyl group or the ring, ring opening, ring coupling, and combinations of these.

The early reductions were carried out mostly by chemical agents. These include aluminum, aluminum amalgam, sodium amalgam, and sodium in alcohol. Picolinic, nicotinic, and isonicotinic acids

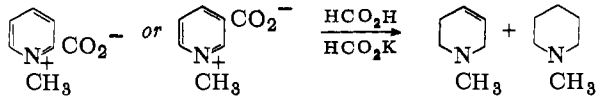
have all been reduced by the last reagent to the corresponding piperidinecarboxylic acids in good yield (X-36) (*65,117,118*).



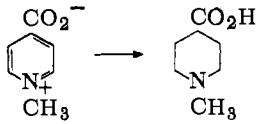
(X-36)

Aluminum, aluminum amalgam, and sodium amalgam have been reported to reduce various dicarboxylic acids either to dihydro products or tetrahydro bimolecular products (*120,121*). Sodium amalgam is also reported to open the ring of 2-methyl-6-phenylcinchomeronic acid, giving mostly nitrogen-free acids or lactones (*122*).

Homarine (picolinic acid methyl betaine) and trigonelline (nicotinic acid methyl betaine) are both reduced by refluxing potassium formate and formic acid to 1-methyl-1,2,5,6-tetrahydropyridine and 1-methylpiperidine (X-37); isonicotinic acid methyl betaine, however, gives only 1-methylisonipecotinic acid (X-38) (*137*).



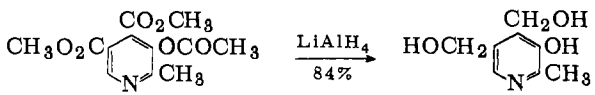
(X-37)



(X-38)

The introduction of lithium aluminum hydride into preparative organic chemistry has provided an elegant method for the reduction of pyridine esters to hydroxymethylpyridines; for example, the ethyl esters of the three pyridinemonocarboxylic acids are reduced to the corresponding hydroxymethylpyridines in 70–80% yields (*50,119,138,582*).

This type of reaction has provided a relatively simple synthesis of pyridoxine (Vitamin B_6): dimethyl 5-acetoxy-6-methyl-3,4-pyridinedicarboxylate was reduced with lithium aluminum hydride to Vitamin B_6 in 84% yield (X-39) (*50*). Other reductions which have



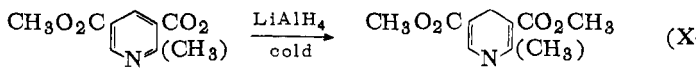
(X-39)

been accomplished are: diethyl 6-methyl-3,4-pyridinedicarboxylate to 6-methyl-3,4-pyridinedimethanol (60%) (*50*); ethyl 2-hydroxy-4,6-dimethylnicotinate to 2-hydroxy-4,6-dimethyl-3-pyridinemethanol (60%) (*193*); and diethyl 2,6-dimethyl-3,4-pyridinedicarboxylate to 2,6-dimethyl-3,4-pyridinedimethanol (50%) (*50*). Reduction of this latter ester, under more vigorous conditions, results in the formation of 20% of 2,3,6-trimethyl-4-pyridinemethanol. The structure of this product was indicated by its nonidentity with the reduction product of ethyl 2,4,6-trimethylnicotinate (*583*).

Various diesters of 5-amino-6-methyl-3,4-pyridinedicarboxylic acid give quite different yields of 5-amino-6-methyl-3,4-pyridinedimethanol on lithium aluminum hydride reduction: dimethyl ester 90%, dibutyl 75%, and dibenzyl 26% (*584*).

Lithium aluminum hydride reductions, while simple, are not always completely successful. Methyl 2-hydroxy-6-methylnicotinate gives a product of unknown structure (*141*), while ethyl 2,6-pyridinedicarboxylate gives only a 5% yield of 2,6-pyridinedimethanol (*140*).

Both diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate and diethyl 2,4,6-trimethyl-3,5-pyridinedicarboxylate react normally to give good yields of the 3,5-bis(hydroxymethyl) analogues (*142,587,588*); reduction of the former in the cold (rather than at reflux) gives a 40% yield of ethyl 5-hydroxymethyl-2,6-dimethylnicotinate (*142*). However, reduction in the cold of dimethyl 3,5-pyridinedicarboxylate or dimethyl 2-methyl-3,5-pyridinedicarboxylate gives, respectively, 50% of dimethyl 1,4-dihydro-3,5-pyridinecarboxylate and 35% of dimethyl 1,4-dihydro-2-methyl-3,5-pyridinedicarboxylate (X-40) (*142*).



(X-40)

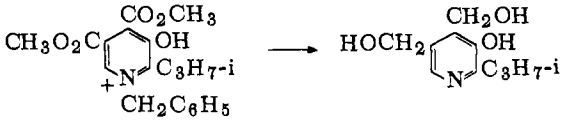
More vigorous reduction of the 2-methyl 3,5-diester yields 1,4-dihydro-2-methyl-3,5-pyridinedimethanol, which, on treatment with thionyl chloride, gives 3,5-bis(chloromethyl)-2-picoline (*589*).

The preparation of pyridine alcohols by these reduction reactions is also discussed in Chapter XIII.

Reductions of quaternary compounds with potassium borohydride take a quite different course, for the carboxyl group is retained while the pyridine ring is reduced to the tetrahydro or dihydro form

(*585,586*). Methyl nicotinate methiodide gives 32–36% of arecoline (methyl 1-methyl-1,2,5,6-tetrahydronicotinate), while nicotinic acid methiodide and nicotinamide methiodide give, respectively, arecaidine (1-methyl-1,2,5,6-tetrahydronicotinic acid) and arecaidinamide (*585*). No evidence was found for the formation of 1,2,3,6-tetrahydro analogues. Isonicotinic acid derivatives give the 1,2,3,6-tetrahydro compounds in this reduction (*586*). However, a similar reduction of 1-tetraacetylglucosidyl-3-carbamylpyridinium bromide gives the 1,2-dihydro derivative (*585*).

Lithium aluminum hydride also reacts with quaternary compounds: 1-benzyl-4,5-dicarbomethoxy-3-hydroxy-2-*i*-propylpyridinium chloride is reduced to 5-hydroxy-6-*i*-propyl-3,4-pyridinedimethanol (X-41) (*590*).

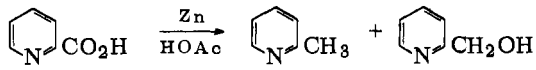


(X-41)

b. Catalytic

Both platinum and nickel have been successfully used for the hydrogenation of pyridinecarboxylic acids (or derivatives) to the piperidine analogues (*123–132*). The reductions are carried out in such solvents as acetic acid, dioxane, and methanol; reductions with nickel are usually performed at high pressure, while platinum can be used over a wide pressure range. Yields are generally excellent, but occasionally side products can be isolated in substantial quantities. For example, reduction of ethyl nicotinate with nickel at 165° and 200–300 atmospheres gives, besides the normal product (ethyl nipecotinate), a 27% yield of 3-methyl-2-piperidone (*125*). A similar reduction in ethanol gives 20% of ethyl 1-ethylnipecotinate (*124*). In some instances, the reduction may proceed further than expected, as, for example, the reduction of picolinic acid 1-oxide to pipecolinic acid (*123*) and the Raney nickel conversion of ethyl picolinate to 2-hydroxymethylpiperidine in 92% yield (*128*). In the reduction of 4-carbethoxy-1-methylpyridinium iodide, it has been possible to isolate a tetrahydro derivative by stopping the reaction before it has gone to completion (*133*).

F. Šorm (*134*) has made a study of the reduction of the monocarboxylic acids under various conditions, and has found that nicotinic acid behaves quite differently from picolinic and isonicotinic acids. The hydrogenation of nicotinic acid over platinum in acetic acid gives, besides the expected saturated product, some piperidine; ethyl nicotinate, however, gives no piperidine. Reductions of picolinic and isonicotinic acids with zinc and acetic acid give mixtures of the picolines and hydroxymethylpyridines (X-42) (*134,135*).

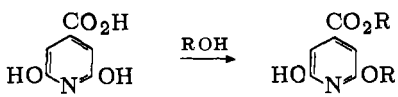


(X-42)

Electrolytic reduction of all three acids gives a complex mixture of products (*134*). It has been possible, however, to effect electrolytic reduction of picolinic and isonicotinic acids to the corresponding picolines in 30–35% yield (*136*), and zinc–hydrochloric acid reduction of 2,6-dichloroisonicotinic acid gives a fair yield (36%) of 2,6-dichloro-4-pyridinemethanol (*69*).

2. Esterification

No difficulties are ordinarily encountered in the esterification of pyridine acids, and several good methods are available to the organic chemist. These include direct esterification with diazomethane or with alcohol and an acid, or conversion first to the acid chloride followed by reaction with an alcohol. While these are generally satisfactory, the choice in any particular case is influenced by other substituents if present. Thus, the use of a strong acid catalyst (usually sulfuric or hydrochloric acid) with an alcohol would be contraindicated if a group such as cyano or 2-chloro were present, for these could be at least partially hydrolyzed. Apparently, ether formation can also occur, for a United States patent (*147*) describes the conversion of citrazinic acid (2,6-dihydroxyisonicotinic acid) to its ester monoether (X-43) by reaction with an alcohol and condensing agent



(X-43)

such as sulfuric acid, perchloric acid, phosphoric acid, or thionyl chloride.

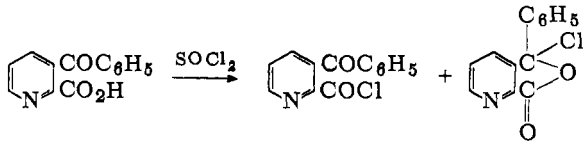
Although an extra step is required, the best yields are usually obtained by first converting the acid to the acid chloride with thionyl chloride and then reacting with an alcohol.

Care must be taken in the preparation of the acid chloride, for excessive heating may result in replacement of ring hydrogen or hydroxyl groups by halogen (*e.g.*, the conversion of 4-hydroxy-5-methoxypicolinic acid to 4-chloro-5-methoxypicolinic acid chloride) (*59,222*). An interesting reaction is the conversion of 1,4-dihydro-5-methoxy-1-methyl-4-oxopicolinic acid to the acid chloride of 4,6-dichloro-5-methoxypicolinic acid in 87% yield by means of refluxing thionyl chloride (X-44) (*143*). Phosphorus tribromide (or trichlo-

(X-44)

ride) or a mixture of phosphorus oxychloride and phosphorus pentachloride has also been used for the conversion of an acid to its acid halide, but hydroxyl groups in position 2 are replaced by chlorine or bromine (*144,145*).

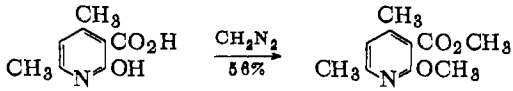
Thionyl chloride and 3-benzoylpicolinic acid give, besides the normal acid chloride, a pseudo acid chloride of structure X-45 (*591*).



(X-45)

Diazomethane is an excellent reagent for the conversion of an acid to its methyl ester, and is often the method of choice when other methods are unsatisfactory, particularly if the carboxyl groups are somewhat hindered. 5-Amino-6-methyl-3,4-pyridinedicarboxylic acid gives a low yield of dimethyl ester with methanol and hydrochloric acid, but a 90% yield with diazomethane (*50*). 5-Amino-

6-methyl-2,3,4-pyridinetricarboxylic acid gives with methanol and hydrogen chloride no isolable ester, with ethanol and sulfuric acid only the 2,3-diester, but with diazomethane the normal triester (*251*). 2-Cyanonicotinic acid with thionyl chloride gives mostly quinolinimide, while diazomethane gives the desired methyl 2-cyanonicotinate (*146*). Occasional side reactions have been encountered: diazomethane gives a 78% yield of methyl ester from 2-hydroxy-6-methylnicotinic acid (*141*), but with 2-hydroxy-4,6-dimethylnicotinic acid the 2-methoxy methyl ester is obtained in 56% yield (X-46) (*139*). The reaction of diazomethane with 2-ethyl-6-



(X-46)

hydroxyisonicotinic acid gives only the 6-methoxy compound and no ester (*154*).

A study has been made (*148*) of the esterification of picolinic acid under three different reaction conditions: (*a*) the acid and an alcohol refluxed with sulfuric acid; (*b*) the acid, an alkyl iodide, and silver oxide refluxed in xylene; and (*c*) the acid, an alcohol, and gaseous hydrochloric acid at room temperature. Method (*b*) gave much the best yields. Ethyl picolinate was prepared in 49% yield by method (*a*), and 100% yield by method (*b*). Cetyl picolinate was prepared in 39% yield by method (*c*), and 88% yield by method (*b*). The reaction of lower alcohols and picolinic acid in the presence of phosphorus oxychloride is reported to give 90–95% yields of esters (*1077*).

Isonicotinic acid was converted to its ethyl ester in 45% yield by means of ethanol and sulfuric acid, 68% yield by means of ethanol and gaseous hydrochloric acid, and 90% yield by first converting to the acid chloride and then reacting with ethanol (*149*).

Esterification of the silver salt of an acid with an alkyl halide may also result in alkylation of free hydroxy groups (*592,593*).

Esters of nicotinic acid can be obtained directly from the oxidation of quinoline with selenium and sulfuric acid if the appropriate alcohol is added to the reaction mixture after the oxidation is complete (*150*).

The choline ester of nicotinic acid may be prepared in 74–82% yield by the action of ethylene oxide and trimethylamine on nicotinic acid (*151*).

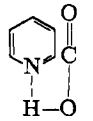
An ester preparation of only academic interest is the pyrolysis of quaternary ammonium pyridinecarboxylates. Thus, tetramethylammonium nicotinate, heated 6 hours at 180–200°, gives trimethylamine and methyl nicotinate (*594*).

3. Decarboxylation

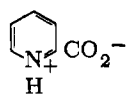
Some aspects of the decarboxylation of pyridine acids have been discussed earlier in this chapter (p. 184). In comparison to the aromatic acids, the pyridine acids lose carbon dioxide with relative ease. Decarboxylation has been carried out by heating the acid alone, in a solvent, or with lime, soda lime, or copper. Dry distillation of the silver salt has also been employed. Of the three pyridinemonocarboxylic acids, picolinic acid is by far the easiest to decarboxylate; it begins to lose carbon dioxide at about 160°, while nicotinic and isonicotinic acids require heating above 250° (*152*). Of the latter two, isonicotinic acid is somewhat easier to decarboxylate. This is best illustrated by the stepwise decarboxylation of 2,3,4-pyridinetricarboxylic acid (*153*). At 185–190° this is smoothly converted to 3,4-pyridinedicarboxylic acid (cinchomeronic acid) without significant amounts of impurities. Heating this diacid above its melting point gives mostly nicotinic acid, with some isonicotinic acid.

Occasional acids resist decarboxylation: neither 2-ethyl-6-hydroxyisonicotinic acid nor 2-ethylisonicotinic acid lost carbon dioxide on treatment with calcium hydroxide, soda lime, or copper (*154*).

In a study of picolinic acid and some methyl-substituted derivatives, Cantwell and Brown (*155,156*) observed that the rate of decarboxylation decreased in acidic or basic solvents, and concluded that the reactive form of picolinic acid is either X-47 or, more likely, the zwitterion X-48.



(X-47)



(X-48)

4. Hammick Reaction

When picolinic acid is decarboxylated in the presence of an aromatic aldehyde or ketone, a coupling reaction takes place and a pyridylcarbinol is formed (X-49). Thus, heating picolinic acid and

(X-49)

benzaldehyde at 140° for 1½ hours gives α-phenyl-2-pyridinemethanol (*157*). Representative aromatic compounds which have been successfully used in this reaction include benzophenone, acetophenone, *p*-methoxybenzaldehyde, *m*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde, veratraldehyde, and *p*-*i*-propylbenzaldehyde (*158–160*). Although the reaction can be run simply by refluxing the two reactants together, optimum yields (30–60%) are obtained in a solvent such as *p*-cymene (*158–160*).

If the decarboxylation of picolinic acid is assumed to proceed through an ionic intermediate such as X-50 (*157*), this intermediate

(X-50)

bears a resemblance to the cyanide ion $[C{\equiv}N]^-$, and the Hammick reaction then becomes a special case of cyanhydrin formation. To state it more generally, X-50 is a typical carbanion and undergoes aldol condensations with aldehydes and ketones. By the principle of vinylogy, isonicotinic acid might be expected to take part in the Hammick reaction. Only one example has been reported in the literature (*161*), the reaction with benzophenone, but the yield of product (α,α-diphenyl-4-pyridinemethanol) was so low (3.5%) as to be of little preparative value.

All of the monomethylpicolinic acids and 4,6-dimethylpicolinic acid react with anisaldehyde in *p*-cymene (*160*), the yields of carbinols ranging from 35 to 57%. Only one nonaromatic ketone has been reported (*159*) as participating in the Hammick reaction: picolinic acid and cyclohexanone give 30% of 1-(2-pyridyl)cyclohexanol.

Dipicolinic acid (2,6-pyridinedicarboxylic acid) with an aldehyde or ketone gives the same products obtained from picolinic acid, *i.e.*, the monocarbinol. The one exception is the reaction with benzaldehyde, where a 30% yield of the dicarbinol, 2,6-bis(α-hydroxybenzyl)pyridine is obtained (*163*). Quinolinic acid, however, does not undergo the Hammick reaction; instead, only nicotinic acid is formed (*162*).

The Hammick reaction is also discussed in Chapter XIII (Table XIII-7).

A preliminary communication (*164*) has indicated that picolinic acid reacts with esters, exchanging the alkoxy group of the ester with a pyridyl group to give pyridyl ketones, but no experimental details have appeared in the literature.

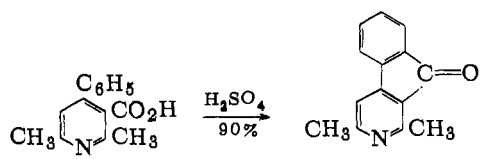
5. Betaine Formation

The pyridine acids, like the amino acids, react with alkyl halides and alkali to give inner salts called betaines. Trigonelline, formed from nicotinic acid and methyl iodide, occurs naturally in a variety of plants.

An unusual difference in reactivity has been observed between nicotinic acid and its ethyl ester: the latter reacts normally with 2-bromo-1-fluoroethane to give a quaternary bromide, while the former gives no reaction (*600*).

6. Formation of Polynuclear Systems

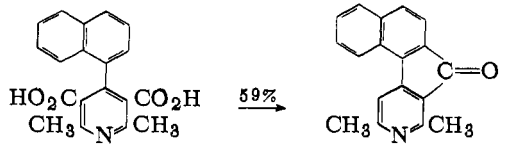
Suitably substituted pyridine acids undergo intramolecular cyclization to give polycyclic products. One of the simplest examples is the conversion of 2,6-dimethyl-4-phenylnicotinic acid to 1,3-dimethyl-2-azafluorenone (X-51) (*165–167*). The reaction may be



(X-51)

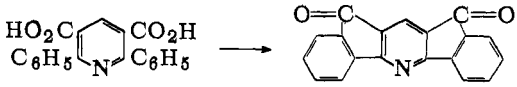
carried out in 90% yield (*166*) in one step by heating with sulfuric acid, or in 70% yield by first converting to the acid chloride and

then reacting with aluminum chloride (*165*). Other similar conversions which have been reported are: 2,6-dimethyl-4-(1-naphthyl)-3,5-pyridinedicarboxylic acid to 1,3-dimethyl-2-aza-5,6-benzfluorenone (59%) (X-52) (*166*); 2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylic



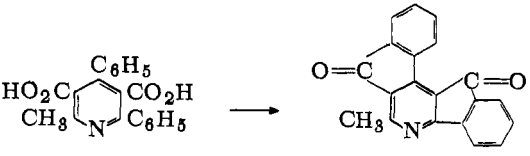
(X-52)

acid to 4-carboxy-1,3-dimethyl-2-azafluorenone (*168*); 2,6-dimethyl-4-(4-methoxyphenyl)nicotinic acid to 1,3-dimethyl-7-methoxy-2-azafluorenone (*165*); 2,6-diphenyl-3,5-pyridinedicarboxylic acid to 2,3,-5,6-dibenzoylenepyridine (X-53) (*165*); 2,4-diphenyl-6-methyl-3,5-



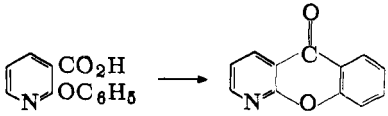
(X-53)

pyridinedicarboxylic acid to 2,3,4,5-dibenzoylene-6-methylpyridine (X-54) (*169*); and 4-phenylquinolinic acid to 2-azafluorenone-1-carboxylic acid (*48*).



(X-54)

Cyclization of 2-phenoxynicotinic acid and 2-phenylthionicotinic acid with phosphorus oxychloride produces, respectively, 9-oxa-1-azaanthrone (X-55) and 9-thia-1-azaanthrone (*170,171*). 4-Phenyl-

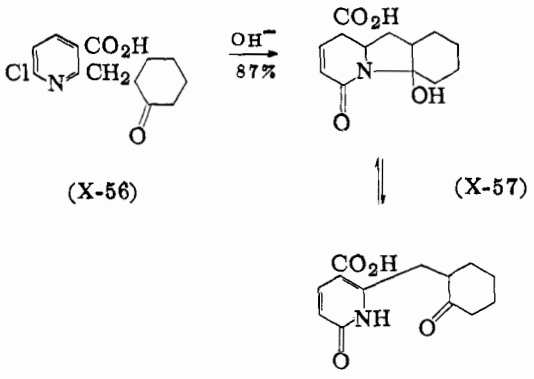


(X-55)

9-Oxa-1-azaanthrone

thionicotinic acid, converted first to the acid chloride, is cyclized with aluminum chloride to 9-thia-3-azaanthrone in 89% yield (*595*).

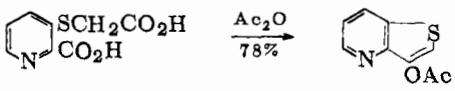
An unusual ring system is formed by the reaction of 6-chloro-2-(2-oxochlorohexyl)methylnicotinic acid (X-56) with alkali to give 87% of 9-carboxy-4a-hydroxy-1,2,3,4,4a,10a-hexahydrobenzo[b]pyrrocoline-6(10*H*)-one (X-57) (*172*), which is the enol tautomer of the pyridone (X-58).



(X-56) (X-57)

(X-58)

Cyclization of 3-(carboxymethylthio)picolinic acid with refluxing acetic anhydride produces 78% of 3-thieno[3,2-b]pyridyl acetate (X-59) (*596*). This may be considered as a Dieckmann condensation



(X-59)

followed by decarboxylation of the β-keto acid and conversion of the ketone to the enol acetate. A similar condensation has been carried out on methyl 2-(carbomethoxymethylthio)nicotinate, using sodium methoxide as the condensing agent (*195*).

7. Substitution Reactions

Because of the deactivating effects of the ring nitrogen and the carboxyl group, pyridine acids do not react well with the ordinary electrophilic substitution reagents. However, a surprising, but general, reaction of pyridine acids is their nuclear chlorination by

thionyl chloride at elevated temperatures or prolonged reaction times. Picolinic acid hydrochloride yields up to 50–55% of 4-chloropicolinic acid (*174–371*); under more severe conditions, a 35% yield of 4,6-dichloropicolinic acid is obtained (*173*). Sulfur dioxide in the chlorination mixture favors 4-chloropicolinic acid formation (*174*). Nicotinic acid gives up to 60% of about an equal mixture of 5-chloro- and 5,6-dichloronicotinic acids (*371*), while isonicotinic acid gives the 3-chloro derivative, which chlorinates further to 3,5-dichloroisonicotinic acid (*173*). Nicotinoyl chloride and bromine for 10 hours at 150–170° produce an excellent yield (87%) of 5-bromonicotinic acid (*176*). Possible mechanisms of these reactions are discussed in Chapter I (p. 45).

8. Miscellaneous

There are a few examples in the literature of the conversion of a pyridine acid to a dipyridyl ketone, and the reaction appears to be generally unsatisfactory. Dry distillation of calcium nicotinate (*177*) or treatment of nicotinic acid vapors with thorium or aluminum oxide (*178*) gave a very small yield of bis(3-pyridyl) ketone. A low yield of methyl 3-pyridyl ketone can also be obtained by the dry distillation of calcium acetate and calcium nicotinate (*597*); similar results are obtained with calcium propionate and butyrate (*598*).

A carboxyl group can be replaced by a halogen by treatment of the silver salt with bromine in carbon tetrachloride. By this method the silver salt of 2-hydroxy-4,6-dimethylnicotinic acid is converted to 3-bromo-4,6-dimethyl-2-pyridinol (*179*). This reaction, however, is far from general, for neither silver nicotinate nor isonicotinate reacts with bromine in nitrobenzene at 110–200°, while silver picolinate gives only a trace of 2-bromopyridine, along with 2,2′-bipyridyl and pyridine (*599*).

An interesting reaction is the conversion of picolinic acid 1-oxide to a mixture of 2-pyridinol and 2-pyridyl ether by *p*-toluenesulfonyl chloride at 115–120° (*180*).

Dimethyl 3,5-pyridinedicarboxylate, when heated with the half-ester of glutaroyl peroxide at 150°, produces the triester of 3,5-dicarboxy-2-pyridinebutyric acid in a yield of about 20% (*951*).

D. FUNCTIONAL DERIVATIVES

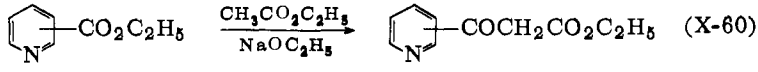
1. Esters

The preparation of esters has already been discussed. They are usually colorless, high-boiling liquids with slight aromatic odor, or relatively low melting solids, slightly soluble in water. Their reactions (including hydrolysis, amide formation, and ester condensations) do not differ significantly from those of their benzene counterparts.

a. Ester Condensations

These reactions are of interest for two reasons: they usually proceed in relatively good yield, and they offer a route to compounds which, in the aromatic series, are available by Friedel-Crafts reactions, but cannot be formed by this route in the pyridine series.

Esters of all three pyridinemonocarboxylic acids condense under the usual conditions with a large variety of compounds containing an active hydrogen. Ethyl picolinate, nicotinate, and isonicotinate have all been condensed with ethyl acetate in the presence of an alkaline catalyst such as sodium ethoxide to give the corresponding ethyl pyridoylacetate in excellent yields (X-60) (*180–188,601,602*).



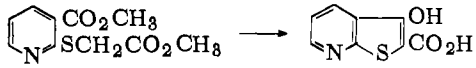
(X-60)

Some investigators report that under comparable conditions, esters of nicotinic acid give slightly lower yields (*185,186*) than the other isomers, but with careful control of reaction conditions there is essentially no difference (*188*). Esters other than ethyl acetate (*e.g.*, *t*-butyl butyrate, *i*-propyl propionate, butyrolactone) also behave satisfactorily, while ethyl malonate and ethyl glutarate give somewhat lower yields (*189,190*). *Cf.* Chapter XI, Table XI-11 (pp. 388 ff.).

Many alkylpyridinecarboxylic esters have been successfully condensed with ethyl acetate (or other lower aliphatic esters). These include ethyl 4-methylnicotinate, (*109,193*), ethyl 4-ethylpicolinate (*194*), ethyl 6-methylpicolinate (*181*), ethyl 3,5-dimethylpicolinate (*196*), and ethyl 2,6-dimethylnicotinate (*197*). The condensation of one pyridine diester has been reported: diethyl 2,5-pyridinedicar-

boxylate gives, after reaction with ethyl acetate and cleavage with acid, 23% of 2,5-diacetylpyridine (*194*).

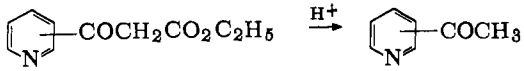
The cyclization of methyl (2-carbomethoxymethylthio)nicotinate to the α,β-pyridylthioindoxylic acid methyl ester is an example of an internal ester condensation (X-61) (*195*).



(X-61)

Ethyl γ-diethylaminobutyrate has been condensed with the three ethyl pyridinecarboxylates; the highest yield (58%) of product [4-diethylamino-1-(pyridyl)-1-butanone] was obtained with the isonicotinic ester and the lowest yield (40%) with the nicotinic ester (*186*).

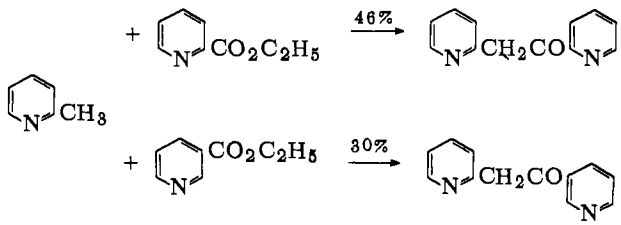
The β-keto esters, which are the first products of reaction, are very easily cleaved to ketones through the loss of carbon dioxide by heating with dilute acid (X-62). In many cases, the intermediate



(X-62)

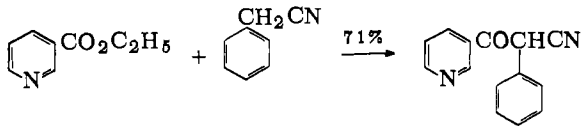
keto ester is not isolated, but carried directly into the decarboxylation step.

The pyridine esters react with many other types of compounds besides aliphatic esters. 2-Picoline is acylated by ethyl picolinate in 46% yield and by ethyl nicotinate in 30% yield (X-63) (*198,199*).



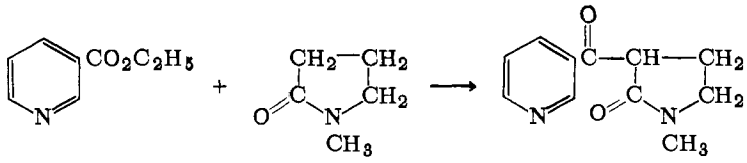
(X-63)

Ethyl nicotinate and phenylacetonitrile give 71% of α-(3-nicotinoyl)-phenylacetonitrile (X-64) (*200*); ethyl nicotinate and *N*-methyl-2-



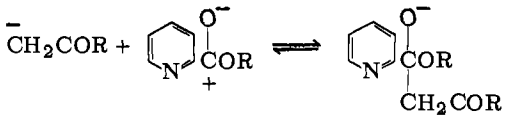
(X-64)

pyrrolidine give 3-pyridyl 3-(*N*-methyl-2-pyrrolidonyl) ketone (X-65) (*201*).



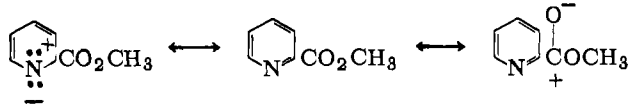
(X-65)

The relative reactivities of the three methyl pyridinecarboxylates in the acylation of three different ketones (acetone, acetophenone, and pinacolone) using sodium methylate have been studied by Levine and Sneed (*202*). In each case the order of reactivity is picolinate > isonicotinate > nicotinate ~ benzoate. Since the rate-determining step is the condensation of the ketone anion with the polarized ester molecule (X-66), the ester with the most electrophilic



(X-66)

carbon will react most easily. In picolinates and isonicotinates, resonance structures which decrease the electron density on the ester carbon can be pictured (X-67); similar structures cannot be drawn



(X-67)

for nicotinates. Since the electron-withdrawing effect decreases with the distance from the ring nitrogen, the influence on isonicotinates is less than with picolinates.

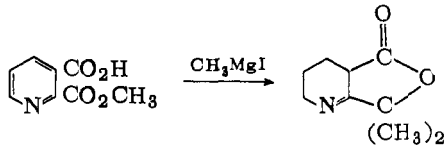
Pyridine esters condense not only with aliphatic and aromatic ketones, but also with heterocylic ketones, *e.g.*, tetrahydro-4-pyrone and methyl 3-pyridyl ketone (*203,204*), in excellent yields. A table of representative condensations has been compiled (*603*).

An interesting method for the preparation of certain 3-pyridyl ketones consists of passing methyl or ethyl nicotinate and a lower aliphatic acid over thorium oxide at 520–540°C. The yield of 3-

pyridyl alkyl ketone is about 30–40%; picolinates and isonicotinates fail in the reaction, giving mostly pyridine as product (*205*).

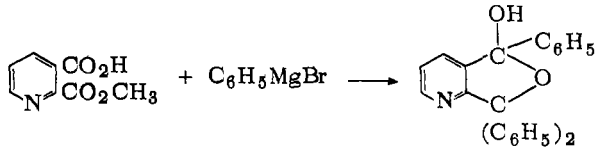
b. Reaction with Organometallic Compounds

Pyridine esters react normally with organometallic compounds, except that when the organometallic group is large, the reaction may proceed only to the ketone, or give only a small amount of tertiary carbinol. Ethyl nicotinate and picolinate with methylmagnesium iodide or ethylmagnesium bromide give good yields of the corresponding pyridyldialkylcarbinols (*206–208*). (*Cf.* Chapter XIII). However, 2-pyridylmagnesium iodide and ethyl picolinate give 10% of bis(2-pyridyl) ketone and a smaller amount of tris(2-pyridyl)-carbinol (*208*). The same result is obtained from the reaction of 2-pyridyllithium and ethyl picolinate (*209*). With 3-pyridyllithium, only ethyl picolinate gives any quantity (24%) of the tertiary carbinol, bis(3-pyridyl)-2-pyridylcarbinol; ethyl nicotinate and isonicotinate give mostly (19–29%) bis(3-pyridyl) ketone and 3-pyridyl 4-pyridyl ketone, respectively (*209*). 4-Pyridyllithium reacts in a similar fashion with ethyl picolinate and isonicotinate; only the dipyridyl ketones are formed (15–31%) (*604*). The 2-monomethyl ester of quinolinic acid reacts with methylmagnesium iodide to give dimethylpyridophthalide (X-68). Ethylmagnesium bromide gives



(X-68)

the corresponding diethyl compound, while phenylmagnesium bromide reacts further to yield triphenyloxypyridophthalane (X-69) (*210*). *Cf.* Chapter XIII, Table XIII-3.



(X-69)

2. Acid Chlorides

Pyridinecarboxylic acid chlorides are generally prepared from the corresponding acid and thionyl chloride. Although they are rela-

tively unstable and cannot be kept for any length of time, they readily undergo the usual reactions of acid chlorides, *e.g.*, ester formation with alcohols, and amide formation with amines.

a. Friedel-Crafts Reaction

This is of special interest, for, while pyridine will not react with aromatic acid halides, pyridine acid chlorides condense with a variety of aromatic compounds. The formation of some condensed rings via intramolecular Friedel-Crafts condensation has already been described (p. 208). Phenyl pyridyl ketones are readily formed in yields up to 91% from benzene and pyridine acid chlorides (*211, 605*). Naphthalene gives a mixture of α-naphthyl and β-naphthyl ketones which may be difficult to separate; with picolinic acid chloride the β-isomer predominates, while with nicotinic or isonicotinic acid chloride the α-isomer predominates (*212*). 2,5-Pyridinedicarboxylic acid chloride and 2,6-pyridinedicarboxylic acid chloride react normally with aluminum chloride and benzene to give the corresponding dibenzoylpyridines (*211,606*). The preparation of ketones by this reaction is discussed in Chapter XIV.

b. Reaction with Diazomethane

Pyridine acid chlorides react normally with diazomethane to give diazoacetylpyridines (*213–217,607,608*), which react with hydrochloric acid, hydrobromic acid, acetic acid, and sulfuric acid to give, respectively, the chloroacetylpyridine, bromoacetylpyridine, acetoxyacetylpyridine, and the sulfate ester of the hydroxyacetylpyridine. However, the Wolff rearrangement (Arndt-Eistert synthesis) of diazoacetylpyridines is not consistently satisfactory: 2-amino-3-diazoacetylpyridine does not rearrange with silver oxide, and 3-diazoacetylpyridine gives only a very small yield of 3-pyridineacetic acid, while 2-carbomethoxy-3-diazoacetylpyridine gives the dimethyl ester of 2-carboxy-3-pyridineacetic acid in yields of 50–70% based on the acid chloride (*216*).

c. Reduction

The Rosenmund reduction of carboxylic acid chlorides to aldehydes fails with picolinic, nicotinic, and isonicotinic acids (*218–220*).

It has been suggested (*219*) that the reaction requires electron-withdrawing groups on the pyridine nucleus to decrease the basicity of the ring nitrogen and thus render quaternary salt formation less likely. In support of this hypothesis, several polyhalogenated pyridine acid chlorides react very well: 4,6-dichloropicolinoyl chloride, 5,6-dichloronicotinoyl chloride, and 2,6-dichloroisonicotinoyl chloride all give yields of over 50% of the corresponding aldehyde. However, 5-bromo- and 5-chloronicotinoyl chlorides give low yields of aldehyde (*221*), and 4-chloro-5-methoxypicolinoyl chloride and 2,6-dibromoisonicotinoyl chloride give none at all (*222,223*). A common side reaction is the complete loss of the —COCl group, leaving only the halogenated pyridine. Thus, 4,5,6-trichloropicolinoyl chloride gives, besides the expected aldehyde, 2,3,4-trichloropyridine (*221*). *Cf.* Chapter XIV.

The reduction of nicotinoyl chloride with the relatively new reducing agent lithium tri-*t*-butoxyaluminohydride produces 69% of nicotinaldehyde (isolated as the 2,4-dinitrophenylhydrazone) (*1072*). Since this reagent does not attack many groups attached to an aromatic nucleus (*e.g.*, nitro, cyano, carbethoxy), it may prove valuable in preparing hitherto inaccessible compounds.

d. Reaction with Organometallic Compounds

With Grignard reagents, pyridine acid chlorides give tertiary alcohols: 5-bromonicotinoyl chloride and methylmagnesium iodide yield 5-bromo-α,α-dimethyl-3-pyridinemethanol (*176*). Alkylcadmium chlorides react with 2,6-pyridinedicarboxylic acid chloride to give 22–43% yields of 2,6-diacylpyridines (*609*). Nicotinoyl chloride also reacts with dipropylcadmium to give a 40% yield of propyl 3-pyridyl ketone (*610*).

3. Anhydrides

Anhydrides of the three pyridinemonocarboxylic acids are conveniently prepared by heating together the acid chloride and the potassium or sodium salt (*224,226,227,272*). The acid chloride may be formed *in situ* from thionyl chloride and the acid in nitrobenzene (*226*) or from oxalyl chloride and the potassium salt of the acid (*225,227*).

As might be expected, the anhydrides react with alcohols to give esters (*228*) and with amines to give amides (*229,230*), but these reactions offer no advantages over other conventional methods.

4. Amides

a. Preparation

Pyridinecarboxamides are generally prepared by (*a*) the interaction of a pyridine acid, acid chloride, or ester with an amine or (*b*) the partial hydrolysis of a cyanopyridine. In the direct reaction between an acid and an amine, provision may be made for removal of water, for example, by codistillation with xylene or by the use of a dehydrating agent. Otherwise, fairly high temperatures are used, limiting the method to higher amines (*231,232*) unless pressure vessels are employed. Nicotinic acid and ammonia in a sealed reactor at 200–270° and 800 p.s.i. gives 96–99% yields of nicotinamide (*233*), while nicotinic acid and diethylamine in the presence of one mole of phosphorus pentoxide give 90–94% yields of *N,N*-diethylnicotinamide (coramine) (*234*). Amides may be used instead of amines (*235–238*). For example, nicotinic acid and *N,N*-diethylbenzenesulfonamide, heated together for 3 hours at 225°, produce a 50% yield of coramine (*235*). Nicotinic acid reacts with urea and boric acid to give nicotinamide (*236*) and with *N*-acetyl-*p*-toluidine at 250–260° to give a good yield of *p*-nicotinotoluidide (*238*).

The interaction of an acid chloride and an amine to produce an amide is generally satisfactory, and the reaction temperatures are usually low. Aliphatic, aromatic, and heterocyclic primary and secondary amines all react smoothly.

Amides may be obtained directly from the acid by the use of ethyl chlorocarbonate in dioxane (*1104*).

The preparation of amides from amines and pyridine esters also does not require special comment, and all three pyridinecarboxamides were prepared by this route some time ago (*239*). The reaction temperatures range from room temperature to reflux; when liquid ammonia is used, high pressures may be developed.

The conversion of nicotinonitrile to nicotinamide is an important commercial process. For this reason much of the information on this reaction appears in the patent literature, and most of it is

intended for large-scale operation. For example, nicotinonitrile is hydrolyzed to nicotinamide by heating with water at 250° for 8 hours (*240*). Addition of an amine to the mixture produces the substituted amide. For laboratory preparative purposes, aqueous sodium hydroxide (*241,242*) alkaline hydrogen peroxide (*243–245, 250*), aqueous ammonia (*246,247*), and dilute (*248,249*) or concentrated (*250–252*) acid have all been used. However, acid hydrolysis does not always give satisfactory yields (*250*), and alkaline hydrolysis can give some pyridine acid salt as an impurity. To avoid these difficulties, the use of an alkaline ion-exchange resin (IRA-400) has been recommended (*253*).

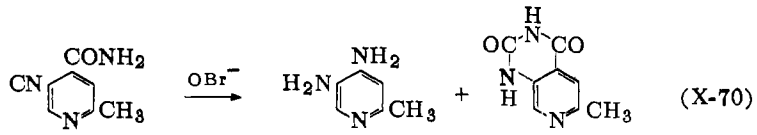
Amides can also be obtained in small yield by the air oxidation of alkylpyridines in the presence of ammonia and a catalyst (*254,255*).

b. Reactions

(a) **Hydrolysis.** The conversion of a pyridinecarboxamide to the corresponding acid may be accomplished by hot acid or alkaline hydrolysis (*245,248,256,258*) or by treatment with nitrous acid (*257–260*). This latter reagent is very mild and does not disturb other sensitive groups in the molecule; however, it replaces amino groups with hydroxyl.

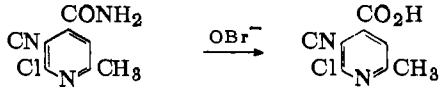
(b) **Dehydration.** Pyridinecarboxamides are readily dehydrated to nitriles by heating with acetic anhydride (*261,262*), phosphorus pentoxide (*248,263*), phosphorus oxychloride (*76,146,264–266*), thionyl chloride (*267,384*), or diammonium acid phosphate (*241*). Yields are generally good.

(c) **Hofmann Reaction.** The Hofmann degradation of the unsubstituted and simply substituted pyridinecarboxamides proceeds without difficulty to the aminopyridines (*269–283*). Even relatively complicated molecules may react normally with alkaline hypohalite, as in the conversion of 3-carboxy-4-chloropicolinamide to 2-amino-4-chloronicotinic acid (*284*) and of 5,6-dicarbethoxy-2-methylnicotinamide in 86% yield to 5-amino-6-methylquinolinic acid (*251*). However, 3,4-pyridinedicarboxamide gives 3-aminoisonicotinic acid (*285,286*), and, while 5-cyano-2-methylisonicotinamide gives the normal product as well as 2-methyldioxycopazaline (X-70), the corresponding 6-chloro compound does not give an amine; instead, only



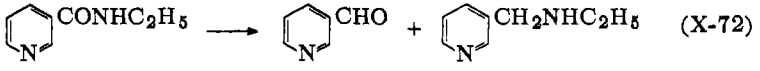
(X-70)

the hydrolysis product of the amide is isolated (X-71) (*256*). The preparation of aminopyridines by this reaction is discussed in Chapter IX (p. 7).



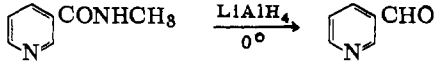
(X-71)

(d) **Reduction.** The Sonn-Müller method (*287*) for the preparation of aldehydes from amides does not appear to be particularly useful in the pyridine series. *N*-Ethylnicotinamide gave only a small amount of nicotinaldehyde, contaminated with 3-ethylaminomethylpyridine (X-72) (*288*). However, lithium aluminum hydride



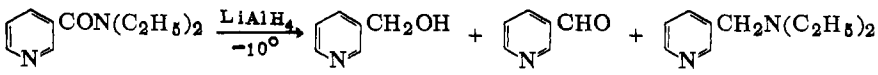
(X-72)

reduction of pyridinecarboxamides may produce pyridine aldehydes under certain conditions. For example, reduction of *N*-methylnicotinamide with 1/3 mole of lithium aluminum hydride at 0° for 10 hours gives a 65% yield of nicotinaldehyde (X-73) (*289*). Reduction



(X-73)

of coramine with 0.25 mole of lithium aluminum hydride at about −10° gave a mixture containing 25% starting material, 28% 3-pyridinemethanol, 5% 3-(diethylaminomethyl)pyridine, and 13% nicotinaldehyde (X-74) (*290*). At higher temperatures and with excess

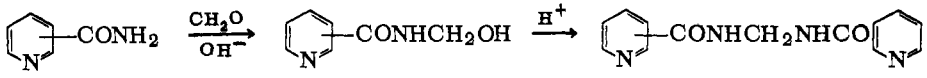


(X-74)

hydride, amides are reduced normally to the amines: coramine yields 84% of 3-(diethylaminomethyl)pyridine (*290,291*); 1-picolinoylpiperidine gives 55% of 2-(piperidylmethyl)pyridine (*292*); and *N,N'*-diethyl-*N,N'*-diphenyl-2,3-pyridinedicarboxamide gives 2,3-bis[(*N*-benzyl-*N*-ethyl)aminomethyl]pyridine (*293*). The preparation of side-chain amines by reduction of amides is discussed in Chapter IX (p. 69).

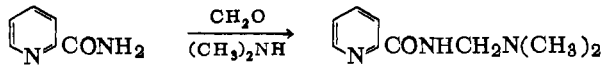
(e) ***N*-Substitution Reactions.** Nicotinamide reacts with alkyl and aryl isocyanates to produce substituted ureas (*294,295*). Phenyl isocyanate produces a 94% yield of 1-nicotinoyl-3-phenylurea and 2-naphthyl isocyanate gives a 96% yield of 1-nicotinoyl-3-(2-naphthyl)-urea, while with ethyl isocyanate the yield drops to 34%.

Pyridinecarboxamides react with formaldehyde in alkaline solution to produce the corresponding *N*-(hydroxymethyl)pyridinecarboxamides (X-75) (*296–299*). These latter compounds, on treatment with sulfuric acid, condense to give bis(pyridylcarbamyl)methanes (X-76). Picolinamide and isonicotinamide also react with formalde-



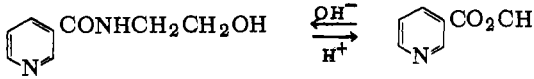
(X-75) (X-76)

hyde and dimethylamine to give the corresponding *N*-dimethylaminomethyl derivatives (X-77) (*299*).

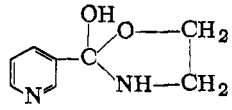


(X-77)

An interesting rearrangement of *N*-hydroxyethylnicotinamide (and picolinamide) occurs when these compounds are treated with acid, giving the isomeric 2-aminoethyl nicotinate and picolinate in 65% yield. Above pH 7.5 the latter revert to the starting amide (X-78) (*300*). An intermediate such as X-79 is postulated.

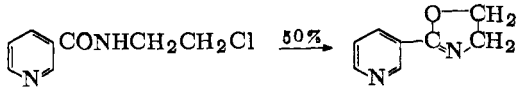


(X-78)



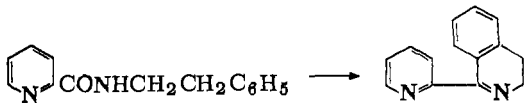
(X-79)

(f) Formation of Polynuclear Systems. A variety of condensed ring systems can be formed from substituted pyridinecarboxamides. *N*-(2-Chloroethyl)nicotinamide is converted to 2-(3-pyridyl)-Δ^2-oxazoline (X-80) in 50% yield on heating in aqueous ethanol (*301*).



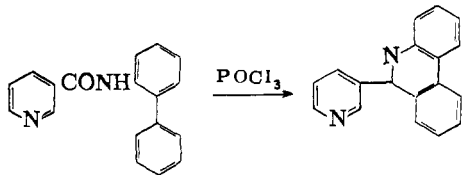
(X-80)

Several 1-pyridyl-3,4-dihydroisoquinolines have been prepared by cyclizing pyridine acid amides of 2-phenethylamine or substituted phenethylamines (X-81) (*302,303*). In the cyclization of amides of



(X-81)

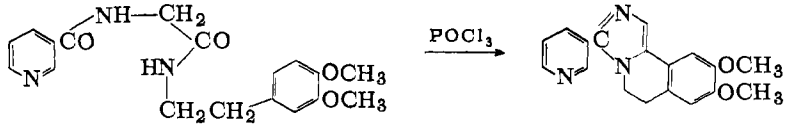
nicotinic acid or of aromatic amides containing electron-withdrawing groups, phosphorus pentachloride gives best results when mixed with aluminum chloride; in other cases, it may be used alone. Neither phosphorus pentoxide nor phosphorus oxychloride can be substituted for phosphorus pentachloride. Phosphorus oxychloride cyclization of 2-nicotinamidodiphenyl and its substitution products produces phenanthridines in good yield (X-82) (*304*). Without



(X-82)

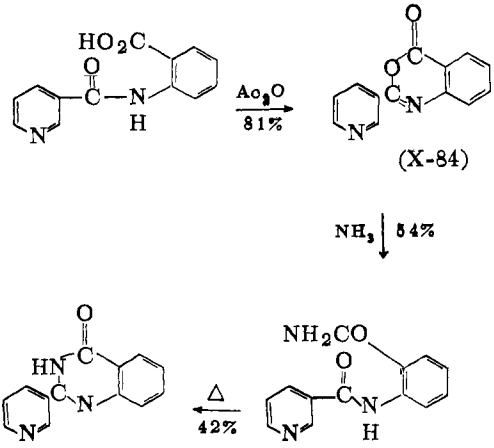
nitrobenzene as a solvent, the reaction fails. Condensation of α-nicotinoyl-*N*-(3,4-dimethoxyphenethyl)acetamide with phosphorus

oxychloride in toluene produces 9,10-dimethoxy-3-(3-pyridyl)-5,6-dihydrobenzoglyoxalocoline (X-83) (*305*). The 2- and 4-pyridyl analogues have also been prepared (*306,307*) by the same route.



(X-83)

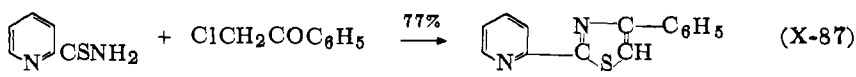
Treatment of *o*-nicotinoylaminobenzoic acid with acetic anhydride produces an 81% yield of 2-(3-pyridyl)-3,1(4*H*)-benzoxazine-4-one (X-84). Reaction with ammonia opens the ring in 54% yield to *o*-nicotinoylaminobenzamide (X-85), and recyclizing by heating at 240° produces 42% of 2-(3-pyridyl)-4-quinazolone (X-86). The same



(X-86) (X-85)

reactions using aniline instead of ammonia gives 2-(3-pyridyl)-3-phenyl-4-quinazolone (*308*).

Thiopicolinamide and ω-chloroacetophenone, heated together for 4 hours, yield 77% of 2-(2-pyridyl)-4-phenylthiazole (X-87) (*309*).



N,N-Diethylnicotinamide (coramine, nikethamide) is widely used in medicine as an analeptic and respiratory stimulant.

5. Hydrazides

The discovery that isonicotinic acid hydrazide (INH, isoniazid) is a potent drug for the treatment of tuberculosis has stimulated research in related compounds of the pyridine and other series.

Recently, several N^2-substituted isonicotinic acid hydrazides have been found to be potent monoamine oxidase inhibitors in animals, and some are now used clinically as antidepressants (*1109*).

a. Preparation and Properties

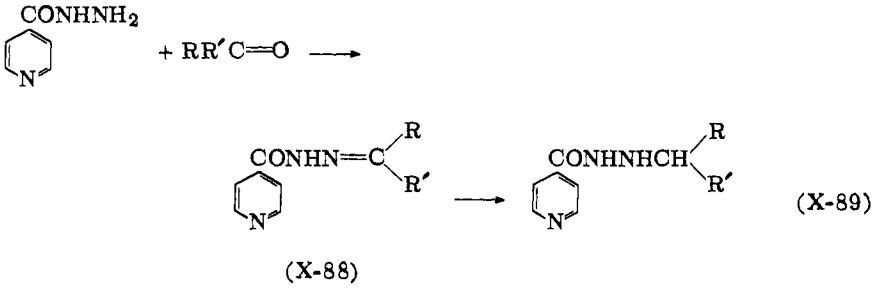
Pyridinecarboxylic acid hydrazides are prepared by the same general methods used to prepare amides, *i.e.*, by the reaction of an ester or an acid chloride with hydrazine or substituted hydrazines. For the preparation of the unsubstituted pyridinecarbohydrazides, the reaction between an ester and hydrazine gives excellent yields (*311,372*). If the acid chloride is used, a dipyridoylhydrazine may be formed (*192,336*). One possible source of difficulty is the replacement of active halogens (*e.g.*, in positions 2 and 4) by hydrazine (*312, 368–371*).

Literally thousands of isoniazid derivatives and analogues have been prepared in the last few years in an attempt to improve its therapeutic properties, and while many compounds have been found that possess significant anti-tubercular activity, none so far has challenged the parent compound for clinical purposes. These derivatives proved too numerous to be listed completely in tables; they fall roughly into five classes:

1. Alkylidene and arylidene derivatives (X-88) are very readily prepared from isoniazid and an aliphatic, aromatic, or heterocyclic aldehyde or ketone, either at room temperature or with brief warming (*313–328,611*). Most of these derivatives are very easily hydrolyzed to the starting materials, and in general they still possess significant anti-tubercular activity (*317,320,323,327*), with diminished toxicity in some cases. For example, the derivatives formed from isoniazid and 2-formylphenoxyacetic acid or 6-methoxy-2-formylphenoxyacetic acid are reported to have 35–50% of the activity of isoniazid with only 1/25 to 1/40 the toxicity (*329*). The veratralde-

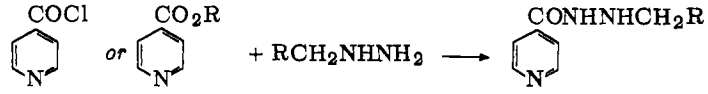
hyde derivative is said to be very active and is only 1/3 as toxic as isoniazid (*330*), and the condensation product of isoniazid and isonicotinaldehyde is said to be 5–10 times more effective than the parent hydrazide (*331*), but this report has not been confirmed (*612*). Sugar derivatives of isoniazid also retain high activity while exhibiting a lower order of toxicity (*332–337*).

2. Alkyl and aryl derivatives of the type 4-PyCONHNHCHRR are readily prepared by addition of a Grignard reagent to an alkylidene derivative (*322*), by hydrogenation of the corresponding alkylidene derivative with a platinum catalyst (X-89) (*318,320,322,338*),



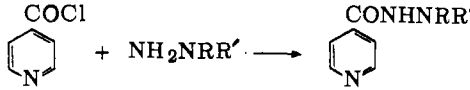
(X-88) (X-89)

by reaction between isonicotinoyl chloride (X-90) and a monosubstituted hydrazine (*322,338*), or by the interaction of an isonicotinic ester (X-91) with a monosubstituted hydrazine (*338,339*). N^2-Di-



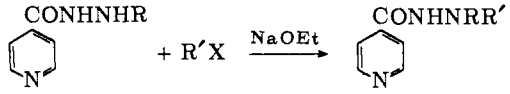
(X-90) (X-91)

alkyl derivatives of the type 4-PyCONHNRR′ are prepared by the reaction between isonicotinoyl chloride and an unsymmetrical dialkylhydrazine (X-92) (*322,340*) or by alkylation of an N^2-alkyliso-



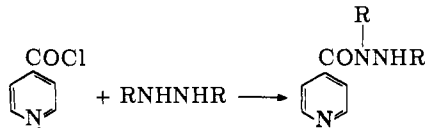
(X-92)

nicotinic acid hydrazide (X-93) (*340*). Acylation of a symmetrically substituted hydrazine gives an N^1,N^2-disubstituted isonicotinic acid



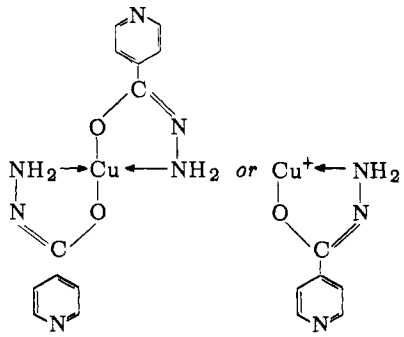
(X-93)

hydrazide (X-94) (*340*). The N^2-mono- or disubstituted derivatives still retain much of the parent activity, but the N^1-substituted hy-



(X-94)

drazides are relatively inactive. Isoniazid and its N^2 derivatives are able to form copper complexes of the type X-95 (*341–344*). It has

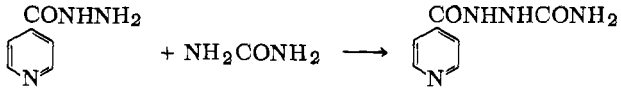


(X-95)

been postulated (*344*) that N^1-substituted derivatives, lacking a hydrogen at N^1, cannot form such complexes and that this explains their inactivity. Fox and Gibas (*946*) have pointed out, however, that N^1-isopropylisoniazid still retains a high degree of activity even though it cannot form a copper complex through binding with an N^1-hydrogen.

3. Acyl derivatives are prepared by reacting isoniazid with an acylating agent such as an acid chloride or anhydride (*345,346*). Acetic anhydride alone gives 1-isonicotinoyl-2,2-diacetylhydrazine, while a mixture of acetic anhydride and acetic acid gives only the monoacetyl derivative (*346*). 1,2-Diisonicotinoylhydrazine can be prepared by the reaction of isonicotinoyl chloride with hydrazine

(*336*), by the oxidation of isoniazid with mercuric oxide (*322,347*), or by the reaction of isoniazid with isonicotinoyl chloride (*612*). The N^2-benzenesulfonyl derivative, prepared from isoniazid and benzesulfonyl chloride, is inactive (*336*). Isonicotinoylsemicarbazide and related compounds are formed from isoniazid and urea (X-96)

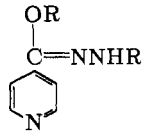


(X-96)

(*612*) or isocyanates (*345,348*) or by the reaction between isonicotinoyl chloride and semicarbazide (*322*). Thiosemicarbazides are prepared in a similar fashion (*349,350*).

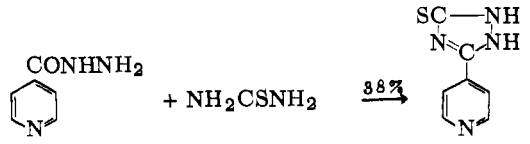
4. A variety of ring-substituted derivatives and isomers have been prepared by conventional methods. Nicotinic acid hydrazide is inactive, while picolinic acid hydrazide is active but toxic (*336*). 6-Aminonicotinic acid hydrazide is said to have strong *in vivo* antitubercular activity (*246*), but in general, ring substitution of isoniazid by functional groups usually produces inactive compounds (*611*). However, some 2-alkylisoniazids, especially 2-methyl- and 2-amylisoniazids, are reported to have significant activity (*352–355*), but 2,3-dialkyl derivatives are inactive (*355*).

It was originally thought that the action of an alkyl halide on the sodium salt of isoniazid produced an O,N^2-dialkyl derivative (X-97) (*356,357*). More recent work has shown that these are N^2,N^2-dialkyl compounds (*945*).



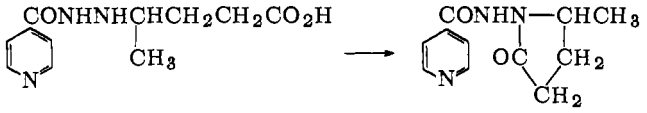
(X-97)

5. Cyclization of isoniazid by different methods produces a variety of heterocyclic derivatives. Heating isoniazid with thiourea gives a 38% yield of 3-(4-pyridyl)-Δ^2-1,2,4-triazoline-5-thione (X-98) (*612*); the same product is obtained by heating isonicotinoylthiosemicarbazide in tetralin (*358*). 4-(Isonicotinoylhydrazino)valeric acid is converted by heating in ethanol to *N*-(2-oxo-5-methyl-1-pyrrolidyl)-

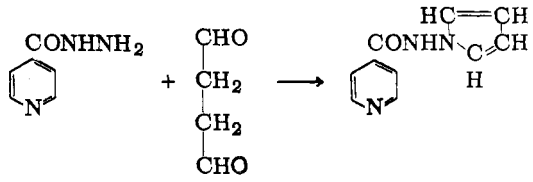


(X-98)

isonicotinamide (X-99) (*320*), while isoniazid and succinaldehyde give 1-isonicotinamidopyrrole (X-100) (*322*). The N^2-isopropylidene

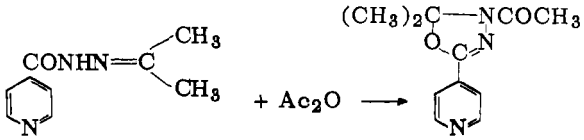


(X-99)



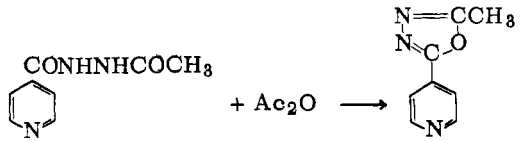
(X-100)

derivative of isoniazid is converted by acetic anhydride to 2,2-dimethyl-3-acetyl-5-(4-pyridyl)-1,3,4-oxadiazoline (X-101) (*322*) and the



(X-101)

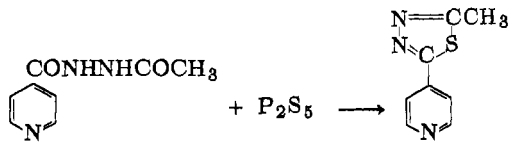
same reagent gives 2-methyl-5-(4-pyridyl)-1,3,4-oxadiazole (X-102) from 1-acetyl-2-isonicotinoylhydrazine (*318*). This latter compound



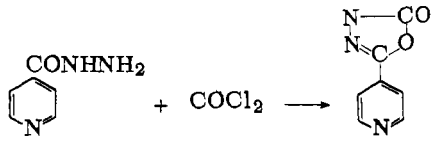
(X-102)

and phosphorus pentasulfide produce the corresponding thiadiazole (X-103). Isoniazid reacts with phosgene (*359*) or dialkylcarbamyl chlorides (*345*) to give 5-(4-pyridyl)-1,3,4-oxadiazol-2(3*H*)-one (X-104).

The nuclear-substituted pyridinecarboxylic acid hydrazides are listed in Table X-3 (pp. 269 ff.).



(X-103)



(X-104)

b. Reduction

Pyridinecarbohydrazides may be converted into aldehydes by two different procedures. The first is treatment with sodium metaperiodate or potassium ferricyanide in alkaline solution (*359,360,1097*). The second method is the familiar McFadyen-Stevens procedure (*287*) of converting an acid hydrazide to the benzesulfonyl derivative and then treating with alkali. Both 2- and 3-pyridinecarbohydrazides react to give 20–36% yields of the corresponding aldehyde (*351,362,363*), while isonicotinic acid hydrazide produces only a trace of aldehyde (*363*). This recalls the benzene series, for *m*-nitrobenzaldehyde can be prepared by the McFadyen-Stevens procedure, but not *p*-nitrobenzaldehyde. However, isonicotinaldehyde can be obtained in 31% yield by this method if it is isolated as the thiosemicarbazone (*364*). 2-Methylnicotinic acid hydrazide reacts normally to give a 31% yield of 2-methylnicotinaldehyde (*365*). A slight variation in procedure is the use of benzoyl chloride instead of benzenesulfonyl chloride. Treatment of 1-benzoyl-2-nicotinoylhydrazine with sodium carbonate gives 28–30% of the aldehyde (*366*). A surprisingly good yield (56%) of 2-hydroxy-4,6-dimethylnicotinaldehyde is obtained from the corresponding nicotinic hydrazide by the McFadyen-Stevens procedure (*622*).

The preparation of aldehydes is discussed in Chapter XIV.

6. Acid Azides

Pyridine acid azides ($PyCON_3$) are prepared by the action of sodium azide on an acid chloride (*367*), or more generally by the

action of nitrous acid on an acid hydrazide (*49,361,368,369,371–383*): $PyCONHNH_2 + HNO_2 \rightarrow PyCON_3 + H_2O$. Acid azides are useful for the preparation of other derivatives, *e.g.*, they react with amines under relatively mild conditions to produce amides (*361,376,378, 379,383*): $PyCON_3 + RR'CHNH_2 \rightarrow PyCONHCHRR^1$. In absolute alcohol at reflux they give urethanes (*49,368,369,371–377,381,382*), which are easily hydrolyzed to the amine: $PyCON_3 + EtOH \rightarrow PyNHCO_2Et \rightarrow PyNH_2$. The azide may be converted to amine in one step by refluxing in dilute acetic acid (*371,376,380*).

7. Nitriles

a. Preparation

Cyanopyridines are conveniently prepared by a variety of methods. The dehydration of pyridinecarboxamides to nitriles has already been mentioned (p. 219). If thionyl chloride is used as the dehydrating agent, bromine atoms on the nucleus may be replaced. 2,6-Dibromoisonicotinamide is converted in this way to 2,6-dichloroisonicotinonitrile (*384*).

A related preparation is the high temperature treatment of pyridine acids with ammonia and a dehydration catalyst (*385–387*). Good yields are claimed, but at the high temperatures necessary, carboxyl groups in position 2 are lost. In a similar fashion, treatment of 2,4-pyridinedicarboxylic acid or 2,4,6-pyridinetricarboxylic acid with *p*-toluenesulfonamide at 280–320° produces isonicotinonitrile (*1070*).

Alkylpyridines can be oxidized to nitriles in the presence of ammonia and a catalyst (*388–391*). With a vanadium catalyst a 60% yield of nicotinonitrile from 3-picoline has been reported (*388*).

Pyridinesulfonic acids are converted to the corresponding cyanopyridines by fusion with sodium or potassium cyanide (*392–394,1071*). This method is only of limited usefulness, because only the 3- and 5-pyridinesulfonic acids are readily available and because yields in the replacement are low.

A general method for the preparation of pyridine nitriles is the replacement of a nuclear halogen with cyanide. This is accomplished satisfactorily by heating a chloro-, bromo-, or iodopyridine with cuprous cyanide alone or with a solvent (*395–402,613*). From

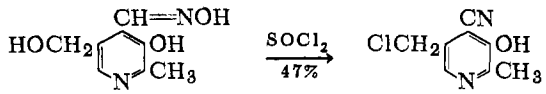
3-bromopyridine, a 74% yield of nicotinonitrile has been realized (*396*). Sodium cyanide fails in the reaction (*403*).

Some anomalous reactions have been noted with cuprous cyanide. Thus, while 4-chloro-3,5-dinitropyridine is converted to the 4-cyano compound in 42% yield, the corresponding 2-methyl derivative does not react (*614*). Similarly, the halogen atoms in 2,4-dichloro-6-methyl-5-nitronicotinonitrile, 5-amino-2,4-dichloro-6-methylnicotinonitrile, and 5-amino-4-bromo-2-chloro-6-methylnicotinonitrile do not react with cuprous cyanide (*615*).

The replacement of an amino group by a cyano group (Sandmeyer reaction) is successful only with 3- or 5-aminopyridines, for amino groups in positions 2 and 4 do not diazotize in the normal fashion (*404–407*). By this method, nicotinonitrile can be prepared in 50% yield (*407*), and several ring-substituted derivatives (*e.g.*, 6-hydroxy, 6-chloro, 6-methyl, 5,6-dichloro) have been made in 30–50% yields (*406*). 2,5-Diaminopyridine, since it diazotizes at only position 5, easily gives a 50% yield of 6-aminonicotinonitrile (*404*). While 4-aminopyridine does not diazotize normally, its 1-oxide does, and smoothly undergoes the Sandmeyer reaction to give isonicotinonitrile 1-oxide (*408*).

Pyridine 1-oxides, after alkylation with methyl iodide or dimethyl sulfate, react with potassium cyanide to introduce cyano groups at positions 2 and 4. The 1-oxides of pyridine, 2-, 3-, and 4-picolines, 2,6-lutidine, and 4,6-lutidine give 6–73% yields of the various 2- and 4-cyanopyridines (*1073,1074*). Even isonicotinonitrile 1-oxide gives a 54% yield of 2,4-dicyanopyridine, indicating that the presence of an electron-withdrawing group does not seriously inhibit the reaction (*1074*).

The dehydration of pyridine aldoximes with acetic anhydride or thionyl chloride produces cyanopyridines (*409*). With the latter reagent pyridoxal oxime is converted to 5-chloromethyl-3-hydroxy-2-methylisonicotinonitrile (X-105) in 47% yield (*249*).



(X-105)

Another method with little laboratory usefulness is the reaction between cyanogen and butadiene (or substituted butadienes) to give

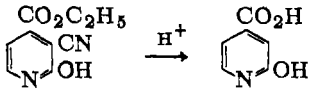
derivatives of picolinonitrile (*410–415*). Cyanogen and butadiene at 480° give an 18% yield of picolinonitrile, while 1,3-dimethylbutadiene gives a 61% yield of 4,6-dimethylpicolinonitrile (*415*).

Recently, a variety of 3,5-dicyanopyridines have been prepared in good yield by the reaction of 1,1,3,3-tetracyanopropenes and their salts with hydrogen halides (*1041*).

The cyanopyridines are listed in Table X-4 (pp. 272 ff.).

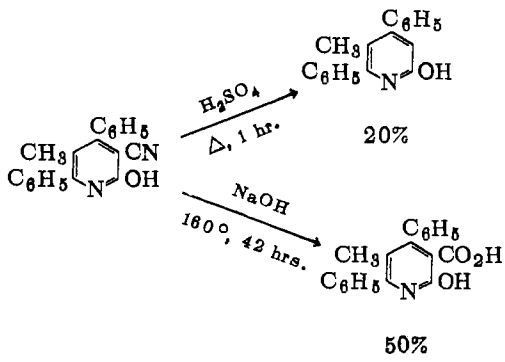
b. Reactions

(a) Hydrolysis. Cyanopyridines may be hydrolyzed under either alkaline or acid conditions, and depending on the conditions and starting material, either the amide, the acid, or the decarboxylated acid may be obtained. In general, alkaline is somewhat more difficult than acid hydrolysis, but there is a greater tendency for decarboxylation under acid conditions, especially with a 3-carboxyl ortho to a hydroxyl group. For example, derivatives of ethyl 3-cyano-2-hydroxyisonicotinate on refluxing with hydrochloric or sulfuric acid yield derivatives of 2-hydroxyisonicotinic acid (X-106)



(X-106)

(*355,417*). The presence of the hydroxyl in position 2 reverses the usual order of ease of decarboxylation (*473*). The tendency towards decarboxylation is somewhat less during alkaline hydrolysis. Treatment of 2-hydroxy-6-propylnicotinonitrile with sodium hydroxide gives a 90% yield of 2-hydroxy-6-propylnicotinic acid (*418*). Hydrolysis of 2-hydroxy-5-methyl-4,6-diphenylnicotinonitrile with hot dilute sulfuric acid for 1 hour produces about a 20% yield of 5-methyl-4,6-diphenyl-2-pyridinol, while hydrolysis with aqueous sodium hydroxide for 42 hours at 160° gives about a 50% yield of 2-hydroxy-5-methyl-4,6-diphenylnicotinic acid (*419*) (X-107). With less hindered nitriles, alkaline hydrolysis is satisfactory under much less severe conditions. Alkaline treatment of 4- or 5-methylnicotinonitrile in refluxing aqueous ethanol produces 80–90% yields of the corresponding nicotinic acid (*392*).



(X-107)

Pyridine nitriles can be hydrolyzed to amides in the normal fashion with strong acid (*400,401*).

Hindered nitriles may either refuse to hydrolyze at all or, more generally, give only amides under acid or alkaline conditions (*420–422*). Alkaline treatment of 2,4-dimethylnicotinonitrile gives only the amide (*420*) as does alkali fusion of 2-hydroxy-4,6-dimethylnicotinonitrile (*421*). An interesting study has been made of the hydrolysis of a hindered nitrile, 6-ethoxymethyl-2-hydroxy-4-methylnicotinonitrile (*423*). With refluxing 50% sulfuric acid for 5 hours, 5% of the corresponding nicotinic acid and 25% of the decarboxylated acid are formed, and 30% of starting material is recovered. With fuming sulfuric acid at 5–10°, only the ether is split, but at 100° the amide is also formed. The compound is unattacked by refluxing aqueous alkali, but at 150–170° for 3–5 hours, the acid is formed.

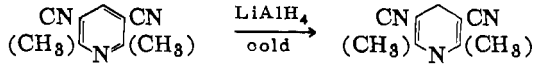
An interesting reaction which combines both hydrolysis and reduction is the treatment of nicotinonitrile in aqueous hydrochloric acid with palladium and hydrogen at atmospheric pressure to produce a 90% yield of 3-pyridinemethanol (*947*).

(b) Reduction. Cyanopyridines are reduced to aminomethylpyridines ($PyCN \rightarrow PyCH_2NH_2$) by chromous acetate, lithium aluminum hydride, hydrogen, and a catalyst (platinum, palladium, nickel), or electrolytic reduction, but sodium amalgam and aluminum amalgam apparently fail (*424*).

Chromous acetate reduces picolinonitrile and isonicotinonitrile to the aminomethyl compound in 70–73% yield and nicotinonitrile

in 30% yield. Excess chromous acetate, however, causes cleavage of the amine. The one advantage of this reagent over the more convenient catalytic methods is that halogen atoms on the ring can be retained (*425–427*).

Lithium aluminum hydride reduces substituted nicotinonitriles to the amines in excellent yields (*428,429*). However, 3,5-pyridinedicarbonitrile and its 2,6-dimethyl derivative are reduced in the cold only to the dihydropyridine stage (X-108) without affecting the nitrile groups (*142*).



(X-108)

The reduction of 3-cyano-1-methylpyridinium iodide with sodium borohydride produces 40–45% of 3-cyano-1-methyl-1,2,5,6-tetrahydropyridine and an equal amount of 3-cyano-1-methyl-1,6-dihydropyridine (*1093*).

At a dropping mercury electrode, cyanopyridines are significantly easier to reduce than benzenoid and aliphatic nitriles (*1106*).

Raney nickel reductions of cyanopyridines to the aminomethyl compounds require no special comment (*430–443,616*). The nitrile group does not always reduce over platinum catalyst alone: 2-chloro-6-methyl-5-nitro-3,4-pyridinedicarbonitrile is converted only to the 5-amino compound (*434*), while 2-hydroxy-4,6-dimethyl-5-nitronicotinonitrile yields 5-amino-3-aminomethyl-4,6-dimethyl-2-pyridinol (*435*). Palladium is a much more consistent catalyst, and has been used most frequently in strong acid solution (*434,436–439*), and occasionally on a calcium carbonate carrier (*440,441*). Mixtures of palladium and platinum have also been used (*439,442–446*). These reductions can be done in acetic acid, thus avoiding the use of a strong acid.

The preparation of side-chain amines from nitriles is discussed in Chapter IX (p. 68).

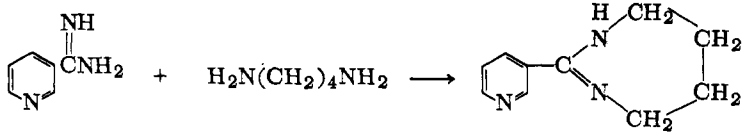
The Stephen method for the production of aldehydes (addition of hydrogen chloride to a nitrile, followed by reduction of the imino chloride with stannous chloride) has been successful only with 3-cyanopyridines (*1056*). Nicotinonitrile itself gives 83% yields of nicotinaldehyde thiosemicarbazone, while 4-ethoxymethyl-2-hydroxy-

6-methylnicotinonitrile gives a much lower yield of the corresponding aldehyde thiosemicarbazone (*463*). Picolinonitrile and isonicotinonitrile do not react, but 2,6-dichloroisonicotinonitrile gives a 79% yield of 4-aminomethyl-2,6-dichloropyridine rather than the aldehyde (*464,465*). 4-Methylnicotinonitrile failed (*1097*).

Nicotinaldehyde has been prepared in 83% yield by the reaction of nicotinonitrile with sodium triethoxyaluminum hydride (*952*).

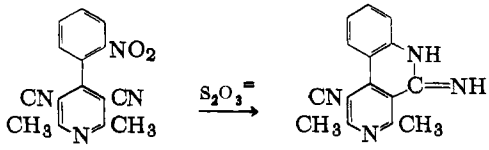
(c) Addition Reactions. Nitriles add hydrogen sulfide in the presence of ammonia and methanol, producing excellent yields of thioamides after twenty-four to forty-eight hours (*268,447,448,581*): $PyCN + H_2S \rightarrow PyCSNH_2$. The use of potassium acid sulfide in refluxing methanol reduces the reaction time considerably, but yields are somewhat lower (*449*).

Nitriles add ammonia or a primary or secondary amine in the presence of an acid catalyst, producing amidines: $PyCN + RNH_2 \rightarrow PyC(:NH)NHR$. Among the catalysts which have been successfully used are hydrochloric acid (*450,451*), aluminum chloride (*452,453*) and ammonium or amine sulfonates (*454–457*). One amidine may be transformed into another by heating with ammonia or an amine. Thus, *N*-phenylpicolinamidine and ammonia give picolinamidine (*458*), while nicotinamidine and tetramethylenediamine yield 1-(3-pyridyl)-2,7-diazacycloheptene (X-109) (*459*). Cyclic amidines may



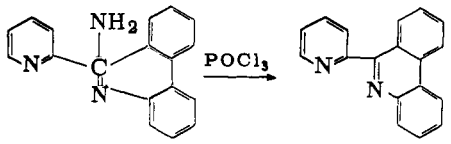
(X-109)

also be formed from suitable aminonitriles: 2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarbonitrile, on reduction of the nitro group with sodium dithionite, produces 10-amino-4-cyano-1,3-dimethyl-2,9-diazaphenanthrene (X-110) (*460*). Amidines containing a phenyl



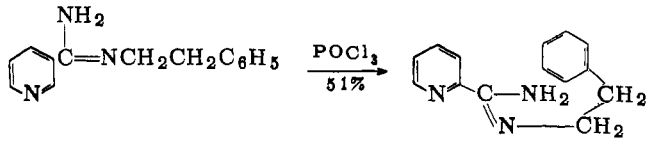
(X-110)

group may form condensed ring systems by cyclization with phosphorus oxychloride. By this method, *N*-(2-biphenyl)picolinamidine yields 6-(2-pyridyl)phenanthridine (X-111) (*461*), and *N*-(phenethyl)-



(X-111)

nicotinamidine gives 3,4-dihydro-1-(3-pyridyl)isoquinoline (X-112) (*462*) in 51% yield.

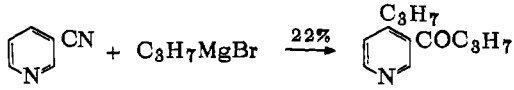


(X-112)

Another method for the preparation of *N*,*N*-dialkylpyridinecarboxamidines is the addition of dialkylaminomagnesium bromide to a cyanopyridine. In the few reported examples the yields are excellent (*617,618*).

Organometallic reagents react with cyanopyridines, giving fair to good yields of pyridyl ketones. 4-Pyridyllithium reacts with 2-, 3-, and 4-cyanopyridine to give, respectively, 28% of 2-pyridyl 4-pyridyl ketone, 5% of 3-pyridyl 4-pyridyl ketone and 29% of bis(4-pyridyl) ketone (*604*). The first compound can be prepared in 63% yield from 2-pyridyllithium and 4-cyanopyridine. Bis(2-pyridyl) ketone is prepared in 46% yield by this method, and bis(3-pyridyl) ketone in 13% yield (*209*). Alkyl and aryl Grignard reagents react fairly well with pyridine nitriles: PyCN + RMgX → PyC(:NH)R → PyCOR (*76,208,402,407,466,467,601*). In some cases, the intermediate imine can be isolated in good yield (*468*).

An unusual reaction between nicotinonitrile and excess propylmagnesium bromide produces a 22% yield of 3-butyryl-4-propylpyridine (X-113). Excess methylmagnesium iodide gives only the normal



(X-113)

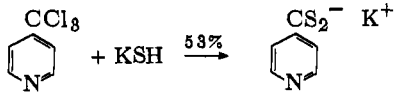
product, 3-acetylpyridine, and one equivalent of propylmagnesium bromide also gives only the expected 3-butyrylpyridine (*610*).

The preparation of ketones from nitriles is also discussed in Chapter XIV.

Cyanopyridines react with sodium azide to give pyridyltetrazoles (*1102*).

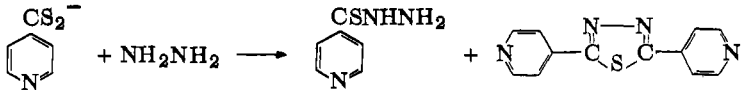
8. Thioacids and Derivatives

These compounds are prepared by the usual synthetic routes. Thiolnicotinic acid has been prepared in 56% yield from nicotinoyl chloride and potassium acid sulfide (*469*). It is very easily hydrolyzed in hot water to nicotinic acid. 4-Trichloromethylpyridine reacts with potassium acid sulfide to give a 53% yield of potassium dithioisonicotinate (X-114) (*470*). This reacts with amines to give



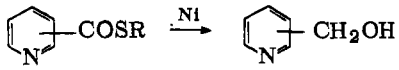
(X-114)

thioamides, with hydroxylamine to give 4-pyridylthiohydroxamic acid, and with hydrazine to give thioisonicotinic acid hydrazide and 2,5-bis(4-pyridyl)-1,3,4-thiadiazole (X-115) (*470*).



(X-115)

Thioesters are prepared either by the alkylation of salts of thioacids (*469*) or by the action of an alkyl mercaptan on a pyridine acid chloride (*471,472*). Reduction of thioesters with Raney nickel in hot ethanol produces good yields of pyridine methanols (X-116) (*471–*



(X-116)

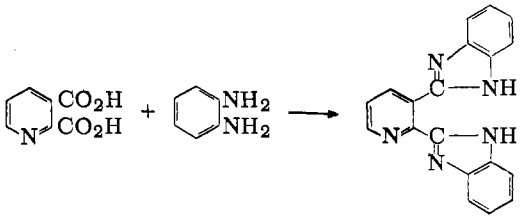
473). The preparation of thioamides via the Willgerodt reaction has been discussed on page 195.

E. PYRIDINE POLYCARBOXYLIC ACIDS

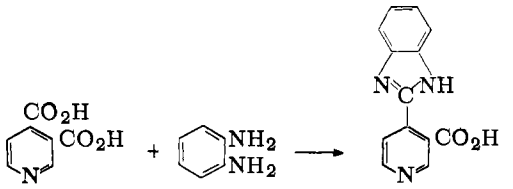
1. Reactions

Polyacids in which the carboxyl groups are not vicinal behave like the monoacids. Vicinal compounds are, however, affected by steric factors and the possibility of ring formation, and their reactions resemble those of phthalic acid.

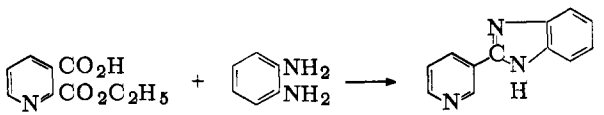
The reaction of *o*-phenylenediamine and quinolinic and cinchomeronic acids gives substituted benzimidazoles (X-117, X-118) (*521–523*). In addition, 2-ethyl hydrogen quinolinate gives the imidazole which would be expected if the ethyl group migrated first from position 2 to 3 and the resulting carboxyl at position 2 is lost (X-119) (*524*). Diethyl quinolinate does not react.



(X-117)

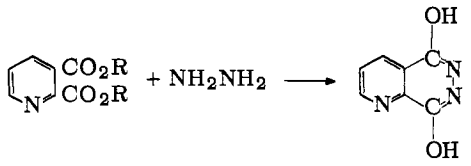


(X-118)

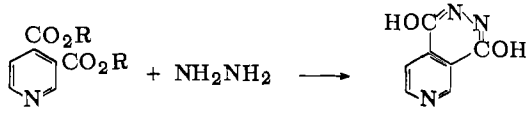


(X-119)

Diesters of quinolinic and cinchomeronic acids react with hydrazine to form pyridopyridazines (X-120, X-121) instead of dihydrazides (*322,654*).



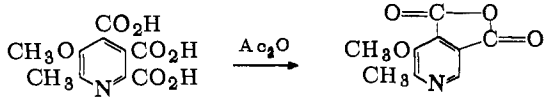
(X-120)



(X-121)

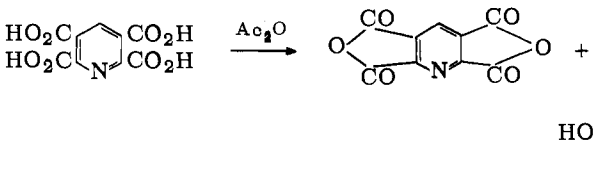
2. Cyclic Anhydrides

Anhydrides form readily from *o*-dicarboxylic acids on heating in acetic anhydride (*474–482*). Decarboxylation occasionally occurs simultaneously. For example, 5-methoxy-6-methyl-2,3,4-pyridinetricarboxylic acid on heating with acetic anhydride gives 5-methoxy-6-methylcinchomeronic anhydride (X-122) (*483*), and 2,3,5,6-pyridine-



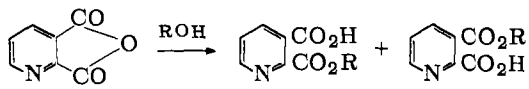
(X-122)

tetracarboxylic acid when heated ten minutes with acetic anhydride gives a mixture of the bis-anhydride and 3,5-pyridinedicarboxylic acid (X-123) (*416*).



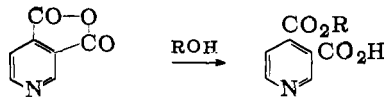
(X-123)

Reaction of quinolinic anhydride (or its substituted derivatives) with an alcohol gives mixtures of the 2-carbalkoxynicotinic acid and the 3-carbalkoxypicolinic acid (X-124) (*481,484,489–491*). The 3-



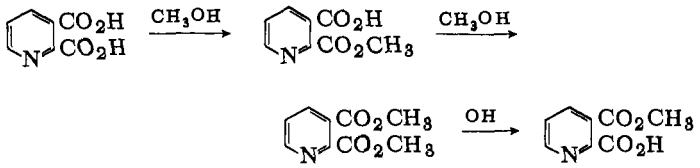
(X-124)

ester is converted to the 2-ester by heating in solution (*1039*). When cinchomeronic acid reacts with alcohols, 4-carbalkoxynicotinic acids are formed almost exclusively (X-125) (*485–488,490–493*). Partial



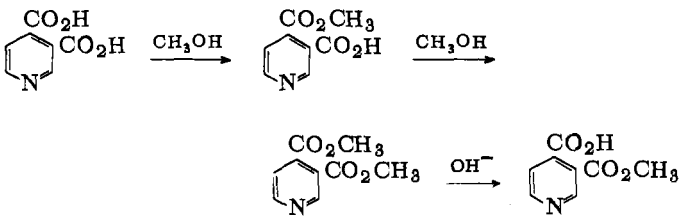
(X-125)

esterification of quinolinic acids gives mostly the 2-monomethyl ester (*491*), while partial saponification of the dimethyl ester gives the 3-monomethyl ester (X-126). Cinchomeronic anhydride and



(X-126)

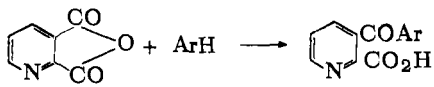
methanol yield the 4-monomethyl ester; the 3-monomethyl ester is obtained from the diester on treatment with alkali (X-127) (*490*).



(X-127)

Quinolinic anhydride reacts with amines to give the *N*-substituted 3-carboxypicolinamides (*496*) or 2-carboxynicotinamides (*504, 505*). There is some doubt whether both types of compounds actually form or whether some structure proofs are inadequate.

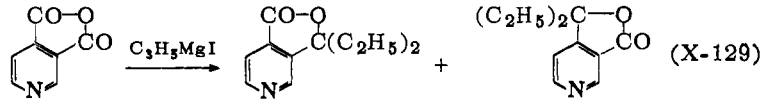
Anhydrides of pyridinepolycarboxylic acids undergo Friedel-Craft reactions with benzene, toluene, naphthalene, and other hydrocarbons. Quinolinic anhydride invariably gives the picolinic acid derivative (X-128) (*475,509–514*). Cinchomeronic anhydride, benzene, and aluminum chloride produce, however, a mixture of 4-



(X-128)

benzoylnicotinic and 3-benzoylisonicotinic acids (*514–517*). The anhydride of 2,3,5,6-pyridinetetracarboxylic acid gives, with benzene and aluminum chloride a 64% yield of mixed dibenzoylpyridinedicarboxylic acids. These, on further treatment, first with thionyl chloride and then with benzene and aluminum chloride, give a 57% yield of 2,3,5,6-tetrabenzoylpyridine (*416*).

Cinchomeronic anhydride behaves like phthalic anhydride with ethylmagnesium iodide, giving a mixture of the lactones of 3-(3-hydroxy-3-amyl)isonicotinic acid and 4-(3-hydroxy-3-amyl)nicotinic acid (X-129) (*520*).



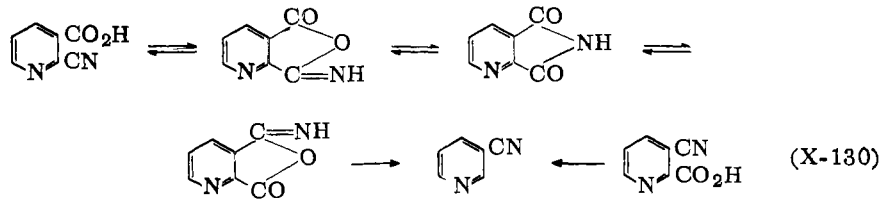
(X-129)

3. Cyclic Imides

Quinolinic and cinchomeronic acids are converted to their cyclic imides by heating with acetic acid and acetamide (*497–501*). The imide may also be prepared from the ammonium salt (*486,895*), the monoamide (*495,496*), or the diamide (*494,619*).

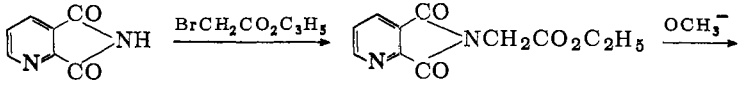
The Hofmann reaction on the imides is of some importance for the preparation of aminopyridine acids: quinolinimide and sodium hypobromite yields predominantly 3-aminopicolinic acid (*487,502*), with some 2-aminonicotinic acid (*500*), while cinchomeronimide gives 3-aminoisonicotinic acid (*479,498,503,823*). However, the reaction of the anhydrides with ammonia produces 3-carboxypicolinamide and 3-carboxyisonicotinamide, which, on Hofmann degradation, yield 2-aminonicotinic acid and 4-aminonicotinic acid, respectively (*171,478,479,482*).

An unusual fact which may be explained by the formation of an intermediate imide is the isolation of nicotinonitrile from the decarboxylation of *both* 3-cyanopicolinic and 2-cyanonicotinic acids (X-130) (*146*).

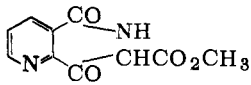


(X-130)

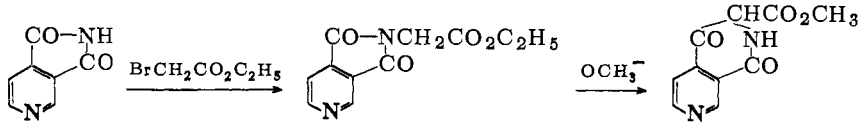
Both quinolinimide and cinchomeronimide react (as *N*-potassium salts) with ethyl bromoacetate to yield the substituted glycine esters X-131 and X-133 (*506–508*), respectively. Both rearrange on treatment with sodium methoxide, the former to give 7-carbomethoxy-5,8-dihydroxy-1,6-naphthyridine (X-132) and the latter to give 3-carbomethoxy-1,4-dihydroxy-2,7-naphthyridine (X-134).



(X-131)

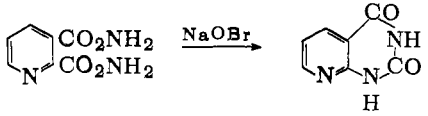


(X-132)



(X-133) (X-134)

Both quinolinamide and cinchomeronamide react abnormally with excess sodium hypobromite, giving pyridinopyrimidines (copazolines) (X-135) instead of the expected diamines (*518,519*).



(X-135)

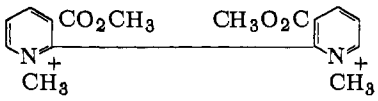
F. SUBSTITUTED PYRIDINECARBOXYLIC ACIDS

1. Alkyl and Aryl Derivatives

These are prepared by several of the general methods already discussed, *e.g.*, the condensation of suitably substituted aliphatic compounds, partial oxidation of polyalkylated pyridines, incomplete oxidation of certain condensed systems, and the hydrolysis of alkylcyanopyridines. Their reactions are normal, except that ortho sub-

stituted pyridine acids may exhibit some steric effects. The alkyl- and arylpyridine acids are listed in Tables X-5 to X-8 (pp. 283 ff.).

Several dipyridyl carboxylic acids have been prepared, by the oxidation either of dialkyl dipyridyls (prepared by the Ullman reaction) (*525*) or of substituted phenanthrolines (*68,527*). Some (*e.g.*, (X-136)) exhibit restricted rotation analogous to that found in substituted biphenyls (*527*).



(X-136)

2. Halogen Derivatives

These are prepared by (*a*) oxidation of ring halogenated alkylpyridines or condensed ring systems, (*b*) replacement of the hydroxyl group in hydroxypyridinecarboxylic acids, (*c*) replacement of the amino group in aminopyridinecarboxylic acids, (*d*) direct halogenation of pyridinecarboxylic acids, (*e*) interchange of halogens in halopyridinecarboxylic acids, and (*f*) hydrolysis of halocyanopyridines.

The oxidation of halogenated pyridines or higher ring systems requires little comment. Fluorine, chlorine, bromine, and iodine in any position easily survive oxidation, and yields of acids are generally good (*528–535*). For example, 2-chloronicotine gives 70% of 2-chloronicotinic acid (*539*). Polyhalogenated compounds, however, may be difficult to oxidize: 3,5,6-tribromo-2-picoline with neutral permanganate gives a very poor yield of acid with recovery of considerable starting material (*536*). Similarly, permanganate oxidation of 2,3,4-trichloroquinoline gives only 23% yields of 4,5,6-trichloroquinolinic acid (*537*), while 4-bromoisoquinoline gives a "fair yield" of 5-bromocinchomeronic acid (*538*).

Hydroxyl groups in positions 2 and 4 are readily replaced with bromine or chlorine by treatment with the appropriate phosphorus oxyhalide, phosphorus trihalide, phosphorus pentahalide, or mixtures; a 3-hydroxyl cannot be replaced by this method.

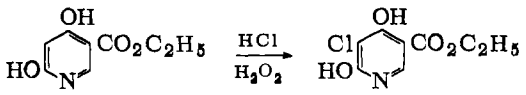
Mono- and polyhalogenated acids can be prepared satisfactorily in this manner (*540–546*). A related reaction is the preparation of a mixture of 2-chloronicotinic acid (41%) and 4-chloronicotinic acid

(5%) from nicotinic acid 1-oxide and a phosphorus oxychloride–phosphorus pentachloride mixture (*526*).

An amino group in any position of a pyridinecarboxylic acid can be replaced by halogen (*545,549*). 3-Aminopyridines react normally in the conventional Sandmeyer reaction, as in the benzene series. The 2- and 4-aminopyridines, however, require special conditions (*547,548*).

The introduction of halogen into a pyridinecarboxylic acid by means of thionyl chloride or bromine has already been discussed (p. 211).

An interesting variation is the treatment of ethyl 4,6-dihydroxynicotinate with hydrochloric acid and hydrogen peroxide to give the 5-chloro derivative (X-137) (*620*).



(X-137)

Halogen atoms in positions 2 and 4 are rather readily interchanged by other halogens. For example, 6-chloronicotinic acid is quantitatively converted to the 6-iodo acid by sodium iodide in methyl ethyl ketone (*550*). Hydriodic acid and red phosphorus also replace chlorine by iodine (*551,552*); this reaction is more satisfactory with 4-chloro than with 2-chloro acids, for the latter tend to undergo reductive removal of halogen (*548*). Hydrochloric acid and hydrogen peroxide convert ethyl 5-bromo-4,6-dihydroxynicotinate to the 5-chloro derivative (*620*), and thionyl chloride with 6-bromonicotinic acid yields 6-chloronicotinoyl chloride. However, 2-bromonicotinic acid gives the normal product (*552*).

The hydrolysis of chlorocyanopyridines to chloropyridine acids cannot be considered a generally useful reaction because 2 and 4 halogens are easily hydrolyzed. Treatment of 6-chloronicotinonitrile with hydrochloric acid for eight hours at 100° produces an 80% yield of 6-chloronicotinic acid; in five hours at 150°, however, a 100% yield of 6-hydroxynicotinic acid is obtained (*621*). The halopyridine acids are listed in Table X-9 (pp. 303 ff.).

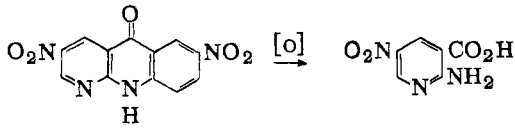
3. Nitro Derivatives

All of the mononitropyridine monocarboxylic acids have been prepared by Brown by oxidation of the corresponding nitropicolines

with permanganate; the yields range from 30–52% (*553*). The 2-nitropicolines were prepared from the 2-amines by persulfate oxidation (*554*), the 4-nitropicolines were prepared via nitration of the *N*-oxides, and the 3-nitropicolines were made by indirect methods. One of the acids (5-nitropicolinic acid) had been prepared previously by acid hydrolysis of 5-nitropicolinonitrile (*248*). The nitro acids are listed in Table X-10 (p. 309).

4. Amino Derivatives

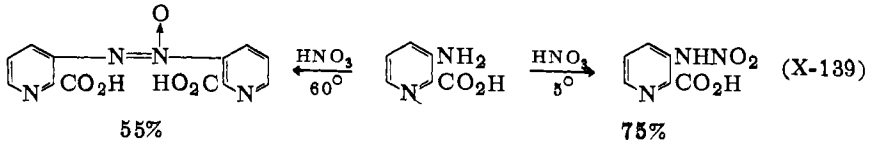
The *o*-aminopyridine monocarboxylic acids are readily prepared by Hofmann degradation of quinolinic or cinchomeronic imides, or of *o*-dicarboxylic acid monoamides, as discussed above (p. 219). They may also be prepared by replacement of halogens in positions 2 and 4 with ammonia or an amine (*526,555–561*). Even the relatively inert halogens at position 3 undergo replacement (*557,562,563*). The hydrolysis of amino nitriles (*564,621*) and the partial reduction of nitroacids (*248,564*), while satisfactory methods, do not have general applicability because the starting materials are relatively unavailable. Oxidation of certain condensed ring systems (*565,566*) or acylaminoalkylpyridines also yield aminopyridine acids (X-138) (*526,567*).



(X-138)

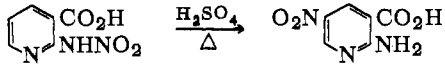
One example of direct amination has been reported: treatment of nicotinamide with sodium amide produces 20–25% of the 2-amino derivative. Nicotinonitrile does not react (*1076*). However, vigorous treatment of either nicotinic or isonicotinic acid or their amides with sodium amide gives 2,6-diaminopyridine as the only product (*1084*).

Nitration at low temperatures with mixtures of nitric and sulfuric acid give first the nitramino acid (*497,564*). Nitration at higher temperatures, or heating the nitramine in sulfuric acid, gives azoxy compounds. Thus, 3-aminopicolinic acid nitrated at 5° gives 75% of 3-nitraminopicolinic acid, while at 60° 55% of 3,3′-azoxypicolinic acid is obtained (X-139) (*497*). The latter can be reduced with zinc to 3,3′-azopicolinic acid. Similar results are obtained with 3-aminoisonicotinic acid. However, when 2-nitramines are heated in sul-



(X-139)

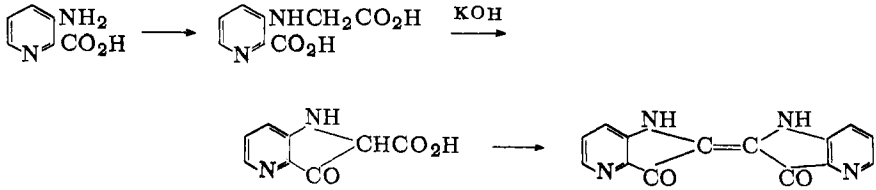
furic acid, the nitro group rearranges to position 3 or 5: 6-nitraminonicotinic acid yields 6-amino-5-nitronicotinic acid, and 2-nitraminonicotinic acid yields 2-amino-5-nitronicotinic acid (X-140) (*564*).



(X-140)

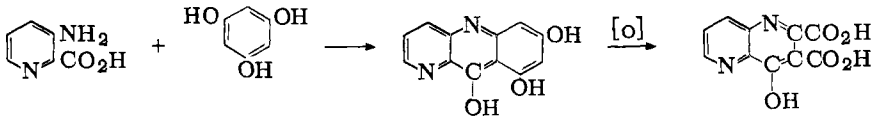
Recently a new synthesis of substituted 2-aminonicotinamides has been described involving Raney nickel cleavage of pyrazole[3,4-*b*]-pyridines (*1042*).

o-Aminopyridinecarboxylic acids undergo cyclization reactions to give several types of condensed ring systems. For example, 3-aminopicolinic acid, after first condensing with chloroacetic acid to give the secondary amine, cyclizes with alkali to the acid (X-141) (*568*). On decarboxylation and air oxidation this gives a dye similar to indigo (X-142); with amino groups in positions 2 and 4, dyes are not obtained.



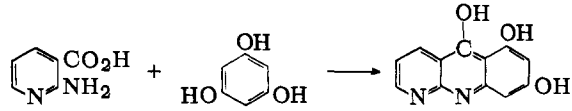
(X-141) (X-142)

Phloroglucinol and 3-aminopicolinic acid condense to give 7,9,10-trihydroxy-1,5-diazanthracene (X-143) (*569,570*); this, on oxidation, yields 4-hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid (X-144).



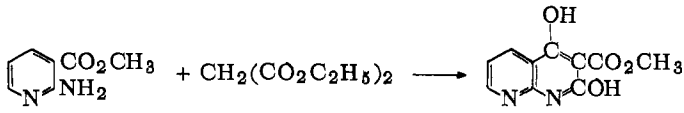
(X-143) (X-144)

Phloroglucinol and 2-aminonicotinic acid react in a similar fashion to give 5,6,8-trihydroxy-1,10-diazanthracene (X-145) (*572*).



(X-145)

Methyl 2-aminonicotinate and ethyl malonate condense to give methyl 2,4-dihydroxy-1,8-naphthyridine-3-carboxylate (X-146) (*571*). In the absence of the carboxyl group, ring closure takes place through the ring nitrogen.



(X-146)

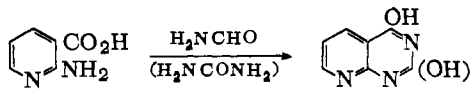
Attempted cyclization of 3-anilinoisonicotinic acid or 2-anilinonicotinic acid with sulfuric acid or phosphorus oxychloride, in order to obtain pyridoquinolones, has thus far failed (*479,556*). However, if activating groups are present, the reaction succeeds: 4-anilino-2,6-dimethylisonicotinic acid gives an excellent yield of 1,3-dimethylpyrido(3,4-*b*)quinoline (X-147) (*479*). In contrast, 2-anilinonicotinic

(X-147)

acid cyclizes readily with polyphosphoric acid to give pyrido[2,3-*b*]-quinolin-5(10*H*)-one (*1004*).

2-Aminonicotinic acid condenses in the same fashion with formamide, urea, and thiourea to yield, respectively, 4-hydroxy-2,4-dihydroxy, and 2-mercapto-4-hydroxypyrido(2,3-*d*)pyrimidine (X-148) (*567,573*).

The amino acids are listed in Table X-11 (pp. 310 ff.).

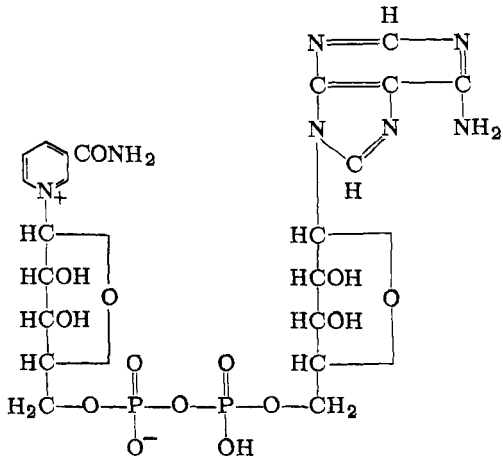


(X-148)

G. NICOTINIC ACID AND NICOTINAMIDE

The total production of nicotinic acid (niacin) and nicotinamide (niacinamide) was almost 2¼ million pounds in 1954; most of this production was intended for use in vitamin preparations. A discussion of the biology, pharmacology, and biochemistry of niacin can be found in a number of texts on the vitamins (*574*).

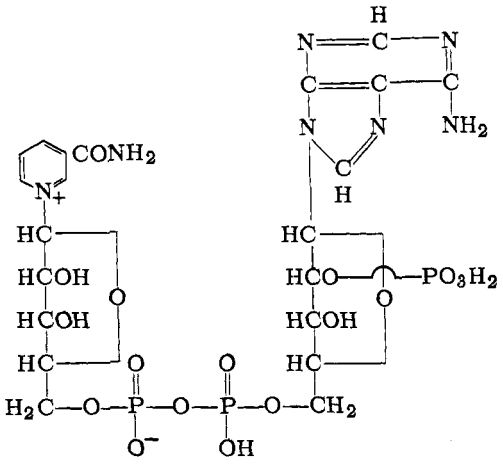
Niacin (or a derivative capable of giving niacin, such as the amide) is apparently needed in man for the biochemical synthesis of two important coenzymes, DPN (diphosphopyridine nucleotide, coenzyme I, codehydrogenase I) (X-149) and TPN (triphosphopyridine



DPN

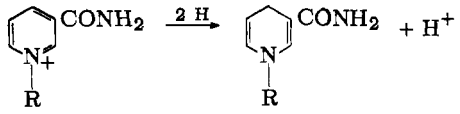
(X-149)

nucleotide, coenzyme II, codehydrogenase II) (X-150). These function by their ability to accept hydrogen from one substrate and transfer it to another (X-151). While it was originally believed that reduction occurred at position 6, recent evidence has shown the reduction takes place at position 4 (*575*). These coenzymes have been discussed more fully in Chapter III (p. 51). They are necessary for normal metabolism; a deficiency of nicotinic acid in the diet produces abnormal states, and if severe enough, even death. The disease pellagra is specifically caused by a lack of nicotinic acid and can be cured by administration of either this material or a derivative.



TPN

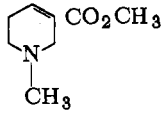
(X-150)



(X-151)

H. ALKALOIDS DERIVED FROM PYRIDINECARBOXYLIC ACIDS (*576*)

Arecoline, arecaidine, and guvacine are among the alkaloids found in the betel nut. The former has been shown to be methyl 1-methyl-1,2,5,6-tetrahydronicotinate (X-152) (*577*), while arecaidine



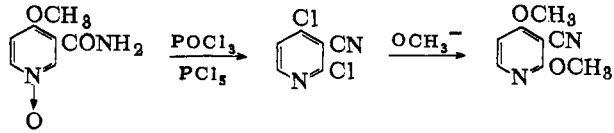
(X-152)

is the free acid. Guvacine is de-*N*-methylarecaidine (*i.e.*, 1,2,5,6-tetrahydronicotinic acid). Its methyl ester, guvacoline, is also present in small quantities in the betel nut.

Trigonelline, the methylbetaine of nicotinic acid, is found in coffee, potatoes, soybean, and several other plants. While it is ex-

creted by man, it is not a product of nicotinic acid metabolism in man, as it is in dogs.

Ricinine, a toxic alkaloid found in the oil of castor bean, has been shown to be 3-cyano-4-methoxy-1-methyl-2(1*H*)pyridone. 2,4-Dimethoxynicotinonitrile, obtained by different routes (*578,579*), gives ricinine when treated with methyl iodide. A recent synthesis (*580*) of the dimethoxynitrile makes use of the properties of the pyridine 1-oxides. 3-Picoline 1-oxide is nitrated to the 4-nitro derivative, and then oxidized by sodium dichromate in concentrated sulfuric acid to 4-nitronicotinic acid 1-oxide. Sodium methoxide treatment replaces the 4-nitro group by methoxy, and the acid is converted to the amide via the methyl ester. Treatment of this compound (4-methoxynicotinamide 1-oxide) with phosphorus oxychloride gives a 33% yield of 2,4-dichloronicotinonitrile, which is converted to the 2,4-dimethoxynitrile with sodium methoxide (X-153).



(X-153)

The chemistry of ricinine is discussed at length in Chapter XII (pp. 715 ff.).

I. TABLES

TABLE X-1. Pyridinemonocarboxylic Acids and Their Derivatives

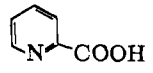
Derivative	M.p., °C.	B.p., °C.	Ref.
 Picolinic acid m.p. 134–35 °C.			
Me ester	14	232	14,148,310, 623–626
Et ester	0–2	240–41	
Amide	107		
Chloride	45–47		
Anhydride	124		272
Hexyl ester		162/13 mm.	148

TABLE X-1 (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
Octyl ester		184/13 mm.	148
Decyl ester		203/13 mm.	148
Dodecyl ester	31.5		148
Cetyl ester	35.5		148
2-$PyCO_2(CH_2)_4OCOPy$-2	81–82		977
Ph ester	82		272
Methylamide		128/12 mm.	1030
Ethylamide		133/11 mm.	1030
Piperidide	76–77	131–35/0.3 mm.	292
2-$PyCONHCH_2CBu_3$		184–85/0.5 mm.	1011
2-$PyCONHCH_2CO_2H$	165		976
2-$PyCONHCH_2CO_2Et$	71		976
2-$PyCONHCH_2CONH_2$	184–85		976
2-$PyCONHCH_2OH$	104–6		192,299
Hydrochloride	202–4		192,299
2-$PyCONHCH_2NHCOPy$-2	124–26		299
2-$PyCONHCH_2NMe_2$			299
Hydrochloride	159–61		299
Picrate	160–62		299
Anilide	76–77		99
p-Toluidide	104		102
Phenetide	120–22		1104
2,6-Xylidide	105–6		1104
o-Carboxyanilide	171–72		976
o-Carbomethoxyanilide	84–85		976
m-Nitroanilide	167		999
2-Methyl-5-nitroanilide	182		999
2-Methyl-5-aminoanilide	145		999
2-Methoxy-4-nitroanilide	209		999
2-Methoxy-4-aminoanilide	134		999
2-Chloro-4-nitroanilide	236		999
2,5-Diethoxy-4-nitroanilide	172		999
2,5-Diethoxy-4-aminoanilide	113		999
Phenethylamide	36	156–58/4 mm.	302
2-$PyCONHCH_2OC_{10}H_7$-1	176–77.5		299
2-PyCCl : NPh · HCl	128–31		99
2-PyCONHNHCOPy-2	218–19		192
2-PyC(: NH)$NHNH_2$	97–98		1003
2-PyCONHOH	120		1016,1050
Hydrochloride	190–91		1016,1050
Thioamide	137		447

(*continued*)

TABLE X-1. Pyridinemonocarboxylic Acids (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref
Picolinic acid (*continued*)			
Thiodiethylamide	50–51	171–72/2.5 mm.	1038
Picrolonate	157 (dec.)		1038
Thiomorpholide	104–6		101,1018
Thioanilide	51–52		101,102
Picrate	114–15		101,102
Thio-*p*-toluidide	99–101		102
Thio-*o*-toluidide	68		102
Picrate	153–55		102
Thio-*N*-methylanilide	85–86		102
Thio-*p*-dimethylaminoanilide	124–25		102
Thio-2-pyridylamide	82		1096
Thio-*t*-octylamide		128–33/0.6 mm.	1098
Thio-*p*-hydroxyanilide	144–45		102
Thio-1-naphthylamide	131–32		102
2-PyCSNH(C_6H_4-*p*)NHCSPy-2	215		102
2-PyC(:NH)NH_2			457
Picrate	207–8		457
Benzenesulfonate	145		457
2-PyC(:NH)NPh_2	129–30		453
Picrate	164.5–65.5		453
Nicotinic acid m.p. 235.5–36.5 °C.			
Me ester	38	204	225,231, 239,253, 310,624, 626
Et ester		223–24	
Picrate	148		
Amide	128.5–29.5		
Chloride hydrochloride	155.5–56.5		
Anhydride	124		224,226, 227,272
Azide	48		1024
Propyl ester		72–73/0.2 mm.	231
Picrate	130		231

TABLE X-1 (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
Butyl ester		75–76/0.15 mm.	124,231
Picrate	114		124,231
sec-Butyl ester		92/2 mm.	1039
Amyl ester		93/0.22 mm.	231,994
Picrate	99		231,994
Hexyl ester		103/0.2 mm.	231,994
Picrate	88		231,994
Heptyl ester		116/0.19 mm.	231,994
Picrate	93		231,994
Octyl ester		116/0.2 mm.	231,994
Picrate	90		231,994
Nonyl ester		133.5/0.28 mm.	231,994
Picrate	100		231,994
Decyl ester		140/0.25 mm.	231,994
Picrate	94		231,994
Undecyl ester		160/0.5 mm.	231,994
Picrate	104		231,994
Dodecyl ester	f.p. 22.7		231
Picrate	100		231
Tetradecyl ester	40.2–40.8		231
Picrate	103		231
Hexadecyl ester	47		231
Picrate	103		231
Octadecyl ester	56		231
Picrate	108		231
Cyclohexyl ester		144.5/4 mm.	228,1025
Methiodide	115		228,1025
Hydrochloride	120		228,1025
Picrate	116		228,1025
Isopropylidene glyceryl ester	42	144/1.2 mm.	228
Ph ester	75		228,272, 1025
1-Naphthyl ester	70		228

(*continued*)

TABLE X-1. Pyridinemonocarboxylic Acids (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
Nicotinic acid (*continued*)			
2-Naphthyl ester	160		1025
Methiodide	191–94		1025
Hydrochloride	191–94		1025
Picrate	178		1025
3-$PyCO_2CH_2Ph$		180–82/2 mm.	432,1025
Picrolonate	169		432,1025
Methiodide	159–60		432,1025
Hydrochloride	72–74		432,1025
3-$PyCO_2CH(Me)Ph$		145/0.5 mm.	432
Picrate	124–25		432
3-$PyCO_2CH(Bu)Ph$		165–68/1 mm.	432
Picrate	79–80		432
3-$PyCO_2CH(Am)Ph$		165–68/1 mm.	432
Picrate	79–80		432
3-$PyCO_2CHPh_2$		201–202/ 0.8 mm.	432
Hydrochloride	164–65		432
Picrate	138		432
3-$PyCO_2CH(Ph)C_6H_4Me$-*o*		203–4/1 mm.	432
Picrate	130–31		432
3-$PyCO_2CH(Ph)C_6H_4Me$-*m*		198–200/ 0.5 mm.	432
Picrate	139		432
3-$PyCO_2CH(Ph)C_6H_4Me$-*p*		202–3/0.3 mm.	432
Picrate	127–28		432
3-$PyCO_2CH_2CH_2Cl$	29	128–30/3–4 mm.	989
Hydrochloride	108		989
3-$PyCO_2CH_2CH_2OH$		143/2 mm.	988
Picrate	138		988
3-$PyCO_2CH_2CH_2OCH_2Py$-3		161–63/1 mm.	989
Dipicrate	181		989
3-$PyCO_2(CH_2)_3OH$		144/0.7 mm.	988
Picrate	106		988

TABLE X-1 (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
3-$PyCO_2(CH_2)_5OH$		160/0.5 mm.	988
Picrate	196		988
3-$PyCO_2(CH_2)_6OH$		178/0.5 mm.	988
Picrate	68		988
3-$PyCO_2(CH_2)_2OCOPy$-3	128		228,977, 988
3-$PyCO_2(CH_2)_3OCOPy$-3	95		988,989
Dipicrolonate	181		988,989
3-$PyCO_2(CH_2)_4OCOPy$-3	99		988
3-$PyCO_2(CH_2)_5OCOPy$-3	43		988
3-$PyCO_2(CH_2)_6OCOPy$-3	59		988
Pentaerythritol tetraester	162-63		228
Inositol tetraester	255		228
α-Monomyristin dinicotinin	59		228
3-$PyCO_2(CH_2)_2NMe_2$		118-19/2 mm.	988
Hydrochloride	168		988
3-$PyCO_2(CH_2)_2NEt_2$		131/2 mm.	988
Hydrochloride	138.5		988
3-$PyCO_2CHMeCH_2NEt_2$		134-35/2 mm.	988
Dipicrate	143		988
3-$PyCO_2CH_2CH_2NH_2 \cdot HCl$	213-14		300,1067
3-$PyCO_2CH_2CMe_2NHC_5H_{11} \cdot H_2SO_4$	153-53.5		1034
Choline ester	58-60		151
Furfuryl ester	32-34	141-42/3 mm.	1025
Hydrochloride	130		1025
Picrate	128		1025
Tetrahydrofuryl ester		114-16/ 0.25 mm.	997
Morpholinoethyl ester		192-94/17 mm.	996
Cholesteryl ester	152-54		1002
7-Dehydrocholesteryl ester	160-62		1002
Ergosteryl ester	162-66		1002
Phytosteryl ester	108-15		1002
Glyceryl triester	88		228,1012
Trihydrochloride	192-93		228,1012
α-Methyl-D-glucopyranoside tetraester	137		1012
D-Glucose tetraester	141-42		1012
D-Galactose pentanicotinate tetrapicrate	123		1012

(*continued*)

TABLE X-1. Pyridinemonocarboxylic Acids (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
	Nicotinic acid (*continued*)		
3-$PyCO_2CH_2CH_2SMe$		122/0.5 mm.	987,988
Picrate	105		987,988
Hydrochloride	111		987,988
3-$PyCO_2CH_2CH_2SEt$		132/2 mm.	987
Picrate	106		987
3-$PyCO_2CH_2CH_2SPr$		144/2 mm.	987
Picrate	100		987
3-$PyCO_2CH_2CH_2S(i\text{-}Pr)$		138/2 mm.	987
Picrate	117		987
3-$PyCO_2CH_2CH_2SBu$		146/2 mm.	987
Picrate	86		987
3-$PyCO_2CH_2CH_2S(i\text{-}Bu)$		140/2 mm.	987
Picrate	109		987
3-$PyCO_2CH_2CH_2S(i\text{-}Am)$		145/2 mm.	987
Picrate	92		987
3-$PyCO_2CH_2CH_2SC_6H_{13}$		173/2 mm.	987
Picrate	78		987
3-$PyCO_2CH_2CH_2SC_{16}H_{33}$	47	220/2 mm.	987
Picrate	94		987
Hydrochloride	86		987
3-$PyCO_2CH_2CH_2S$(cyclohexyl)		182/2 mm.	987
Picrate	116		987
Hydrochloride	86–89		987
3-$PyCO_2CH_2CH_2SPh$		188/2 mm.	987
Picrolonate	158		987
Hydrochloride	91		987
3-$PyCO_2CH_2CH_2SCH_2Ph$		198/2 mm.	987
Picrate	107		987
Hydrochloride	109		987
3-$PyCO_2CH_2CH_2SCH_2CH_2Ph$		204/2 mm.	987
Picrate	188		987
3-$PyCO_2CH_2CH_2SCHPh_2$	71		987
Picrate	118		987
Hydrochloride	151–52		987
3-$PyCO_2CH_2CH_2SCH_2Py\text{-}3$		190/2 mm.	987
Dipicrolonate	171		987
Methylamide	115		1030
Ethylamide	65–67	152/12 mm.	288,1030
Diethylamide		163–68/11 mm.	1014
Propylamide	89–92		1007
i-Propylamide	85–86.5		1007
Butylamide	34–37		1007

TABLE X-1 (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
Amylamide		90–95/reduced pressure	240
Hexylamide	45		231
Picrate	147		231
Heptylamide	52		231
Picrate	151		231
Octylamide	62		231
Picrate	145		231
Nonylamide	73		231
Picrate	148		231
Decylamide	72		231
Picrate	151		231
Undecylamide	72		231
Picrate	153		231
Dodecylamide	78		231,1007
Picrate	154		231,1007
Tridecylamide	82		231
Picrate	154		231
Tetradecylamide	81		231,1011
Picrate	154		231,1011
Hexadecylamide	88		231
Picrate	156		231
Octadecylamide	92		231
Picrate	155		231
Methoxypropylamide		235–40/14 mm.	1007
3-PyCONHCBu$_3$	103–3.5		1011
3-PyCONHCH$_2$CEtPr$_2$		200–2/3 mm.	1011
3-PyCONHCH$_2$CBu$_3$	104–4.5		1011
3-PyCONHCH$_2$CH$_2$Cl · HCl	142–43		1013,1067
3-PyCON(CH$_2$CH$_2$Cl)$_2$	62–64		1013,1087
Hydrochloride	202		1013,1087
Cyclohexylamide	140–42		231,1007
Picrate	199		231,1007
Morpholide		196–200/10 mm.	1014
3-PyCONHCH$_2$OH	141–42 (dec.)		192,299
Picrate	141–42		192,299
3-PyCONHCH$_2$NHCOPy-3	244–46		299
3-PyCONHCH$_2$CH$_2$OH	92	185–95/0.5 mm.	300,1013
Hydrochloride	172		300,1013
Picrate	123–24		300,1013

(*continued*)

TABLE X-1. Pyridinemonocarboxylic Acids (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
	Nicotinic acid (*continued*)		
3-PyCON(CH_2CH_2OH)$_2$	oil		1013
3-PyCONHCOCH$_3$	110–11		979
3-PyCONHCSNH$_2$ · HCl	195		982
3-PyCONHCH$_2$CH$_2$NHPh	141–43		978
3-PyCONHCH$_2$CH$_2$Ph	80		303,988, 1033, 1104
Picrate	156		303,988, 1033, 1104
3-PyCONHCHPhCH$_2$Ph	158		984
3-PyCONHCHPh$_2$	181–81.5		984
3-PyCONHCH$_2$CHPh$_2$	144–45		984
3-PyCONHCH$_2$Ph	85	205/4 mm.	984,988, 1007, 1011, 1033
Picrate	177		984,988, 1007, 1011, 1033
3-PyCONHCHPhCH(OH)Ph	225–26		984
3-PyCONHC(Ph)Bu$_2$	156.5–57		1011
3-PyCONHCH$_2$C(Ph)Bu$_2$	132.3–33		1011
Nicotinoyltyramine	183–84		1104
3-PyCONHCH$_2$CH$_2$CH$_2$Ph		221/4 mm.	1033
Picrate	120		1033
3-PyCONHCHMeCH$_2$Ph	88–90	205/4 mm.	1033
Picrate	176		1033
3-PyCONHCHMeCH$_2$C$_6$H$_4$OMe-*p*		207/4 mm.	1033
Picrate	136		1033
3-PyCON(Me)CHMeCH$_2$Ph		203/5 mm.	1033
Picrate	181		1033
3-PyCON(Me)CHMeCH$_2$C$_6$H$_4$OMe-*p*		224/3 mm.	1033
Picrate	139		1033
3-PyCON(Me)CHMeCH$_2$C$_6$H$_4$OH-*p*		240/6 mm.	1033
Picrate	106–7		1033
3-PyCON(Et)CHMeCH$_2$Ph		185/4 mm.	1033
Picrate	208		1033

TABLE X-1 (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
3-PyCON(Et)CHMeCONEt$_2$		163–65/ 0.15 mm.	998
3-PyCON(Et)CH$_2$CH$_2$CONEt$_2$		178–80/ 0.21 mm.	998
3-PyCON(Et)CHEtCONEt$_2$		162–64/ 0.15 mm.	998
3-PyCON(*i*-Pr)CHEtCONEt$_2$		170/0.25 mm.	998
3-PyCON(Et)CMe$_2$CONEt$_2$		175/0.3 mm.	998
3-PyCONHCONHC$_{10}$H$_7$-1	222–23		294
3-PyCONHCONHEt	120.5–22.5		294
3-PyCONHCHMeCH$_2$Ph	98		303
3-PyCONHCH$_2$CHMePh	73		303
3-PyCONHCH$_2$CH$_2$C$_6$H$_4$(OMe)-*p*	116		303
3-PyCONHCH$_2$CH$_2$C$_6$H$_3$(O$_2$CH$_2$)-3,4	129		303
3-PyCONHCHMeCH$_2$C$_6$H$_3$(O$_2$CH$_2$)-3,4	129		303
3-PyCONHCH$_2$CH$_2$C$_6$H$_4$Cl-*p*	133		303
3-PyCON(CH$_2$CBu$_3$)CH$_2$CH$_2$NEt$_2$		212–14/1 mm.	1011
Dihydrochloride	187–87.5		1011
Nicotinoyl *dl*-phenylalanine			383,1104
Me ester	63		383,1104
dl-Amide	193–94		383,1104
l-Amide	185		383,1104
Nicotinoyl *d*-tyrosine ethyl ester	147		383
Amide	226–27		383
Nicotinoyl 4-chloro-*dl*-phenylalanine			383
Me ester	89–90		383
Amide	220–21		383
Nicotinoyl-*l*-tryptophan			383
Amide	180–81		383
dl-Amide	237		383
Nicotinoyl-*dl*-methionine			383,1104
Me ester	60–61		383,1104
Amide	146–47		383,1104
Nicotinoyl-*l*-histidine amide	237–38		383
3-PyCONHCH(CH$_2$Ph)CONHC$_6$H$_4$OMe-*p*	215–18		1031
3-PyCONHCH(CH$_2$Ph)CO$_2$H	198		1031
3-PyCONHCH(CH$_2$Ph)CONHNH$_2$	185		1031
3-PyCONHCH(CH$_2$Ph)NHCONHC$_{10}$H$_7$-2	227		1031
3-PyCONHCH(CH$_2$Ph)CONHC$_{10}$H$_7$-2	199		1031
3-PyCONHCH$_2$CH$_2$NHCOMe	170–71		1006

(*continued*)

TABLE X-1. Pyridinemonocarboxylic Acids (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
	Nicotinic acid (*continued*)		
3-PyCONHCH$_2$CH$_2$NHCOEt	126–27		1006
3-PyCONHCH$_2$CH$_2$NHCOPr	157–59		1006
3-PyCONHCH$_2$CH$_2$NHCOBu	141–42		1006
3-PyCONHCH$_2$CH$_2$NHCOAm	124–25		1006
3-PyCONHCH$_2$CH$_2$NHCOPy-3	>250		1020
α-2-Camphorylamide	144–45		1026
α-2-Bornylethylamide	89–90		1026
3-PyCONHCONH$_2$	223–24		1047
3-PyCONHCH(OH)CCl$_3$	163–64		1058
3-PyCONHCH$_2$CO$_2$H	240		378,379, 976
3-PyCONHCH$_2$CO$_2$Me	67–68		976
3-PyCONHCH$_2$CO$_2$Et	54–55		305,976
3-PyCONHCH$_2$CONH$_2$	193–95		976
3-PyCONHCH$_2$CONHNH$_2$	178		305
3-PyCONHCH$_2$CONHCH$_2$CH$_2$C$_6$H$_3$-(OMe)$_2$-3,4	157–58		305
3-PyCONHCH$_2$CONHCH$_2$CO$_2$H	232 (dec.)		976
3-PyCONHCH$_2$CONHCH$_2$CO$_2$Et	144–45		976
Anilide	132		231,456, 993,1033
Picrate	187		231,456, 993,1033
p-Toluidide	146–47		238
2,6-Xylidide	213–15		1104
p-Chloranilide	169.5–70		456
p-Cyclohexylanilide	203–3.5		456
p-Dimethylaminoanilide	227–29		1015
o-Hydroxyanilide	200 (dec.)		1007
m-Hydroxyanilide	215–18		1007
p-Hydroxyanilide	203–5		1007
p-Phenoxyanilide	149.5–50		456
3-Hydroxy-4-carboxyanilide	195 (dec.)		1007
p-Acetamidoanilide	275–78		1007
o-Anisidide		204/4 mm.	1033
Picrate	204		1033
p-Anisidide	144		1033
p-Carboxyanilide	298–99		238,1007
2,5-Diethoxy-4-nitroanilide	127		999
p-Sulfamylanilide	207		972
o-Carboxyanilide	263–64		308,976

TABLE X-1 (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
3-PyCONH(C_6H_4-*o*)CONHPh	256		308
3-PyCONH(C_6H_4-*o*)$CONH_2$	211		308
o-Carbomethoxyanilide	127		976
p-Carboxyanilide	300-302		237,982
3-PyCONH(C_6H_4-*o*)$CONHC_6H_4CO_2H$-*o*	222		976
3-PyCONH(C_6H_4-*o*)$CONHC_6H_4CO_2Me$-*o*	181 (dec.)		976
3-PyCONH(C_6H_4-*p*)SO_2(C_6H_4-*p*)-NHCOPy-3	346		990
3-PyCONEtPh	63	186-90/3 mm.	980
Picrate	154-55		980
Methiodide	215 (dec.)		980
o-Phenylanilide	173-74		304
p-Phenylanilide	217		456
Hydrochloride	267		456
o-Phenyl-*p*-nitroanilide	160-61		304
o-(*p*-Nitrophenyl)anilide	226-27		304
3-PyCONH(C_6H_4-*p*)SO_2NHAc	250		982
3-PyCONHPy-2	141-43		231,980, 988,995, 1007, 1026
Picrate	225		231,980, 988,995, 1007, 1026
Methiodide	192-93		231,980, 988,995, 1007, 1026
3-PyCONHPy-3	191		988,1007
3-PyCONHPy-4	187		988
3-PyCONHCH_2Py-3	108		1023
3-PyCONH$SO_2C_6H_4NH_2$-*p*	256-57		980
3-PyCONH(C_6H_4-*p*)SO_2(C_6H_4-*p*)-NHCOPy-3	365		1028
3-PyCONH$SO_2C_6H_4NHAc$-*p*	213-15		980
3-PyCONH$SO_2C_6H_4NHEt$-*p*	229-30		980
3-PyCONPh_2	150-51		1054
3-PyCONH$SO_2C_6H_4NEtAc$-*p*	242-43		980
3-PyCONH(C_6H_4-*p*)SO_2NHPy-2	185-86		980
Dinicotinoylsulfaguanidine	219-20		980
Nicotinoyldicyandiamide	170-75		1007
3-PyCONH(C_6H_4-*p*)CH:NNHCSNH_2	252		237

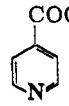
(*continued*)

TABLE X-1. Pyridinemonocarboxylic Acids (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
Nicotinic acid (*continued*)			
1-Anthraquinonylamide	205		1007
2-Methyl-5-coumaranylamide	240		1007
2-Dibenzofurylamide	220		456
2-Pyrimidylamide	173–75		1007
2-Thiazolyamide	210–11		982,1007
5-Carbethoxy-2-thiazolylamide	187–92		1007
Tetrazolylamide	>300		1104
3-PyCONHNHCSNH$_2$	182–84		1104
3-PyCONHOH	167		981,1016, 1050
Hydrochloride	186–87		981,1016, 1050
3-PyC(:NH)NHNH$_2$	97–98		1003
Amidine hydrochloride	190		451
p-Chlorophenylamidine	190		456
p-Ethoxyphenylamidine	218–19		456
p-Toluenesulfonate	220		456
p-Cyclohexylphenylamidine	172		456
p-Toluenesulfonate	178		456
p-Phenoxyphenylamidine	163–64		456
p-Toluenesulfonate	170		456
p-Diphenylylamidine	162–65		456
p-Toluenesulfonate	213		456
Benzylamidine	131–31.5		452
2-Dibenzofurylamidine	217.5		456
p-Toluenesulfonate	213		456
3-PyC(:NH)NBu$_2$	139		618
3-PyC(:NH)N(Et)CH$_2$Ph	153		618
3-PyC(:NH)N(Me)C$_{10}$H$_7$-1	242 (dec.)		618
3-PyCONHNHCOPy-3	227–28		192,1035
Dihydrochloride	235 (dec.)		192,1035
Dihydroiodide	248 (dec.)		192,1035
3-PyCOSH	145–47		469,1021
(3-PyCOS)$_2$	88–89		1021
3-PyCOSEt		122/10 mm.	469,471
Picrate	134–35		469,471
3-PyCOSCH$_2$CH$_2$SCOPy-3	115–16		469
3-PyCOSCH$_2$CH$_2$NEt$_2$		142–43/3 mm.	469
Oxalate	144–46		469

TABLE X-1 (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
3-PyCSNH$_2$	209–10		447,1019, 1020
3-PyCOSϕ	48–49		1078
3-PyC^{13}O$_2$H			94



Isonicotinic acid
m.p. 317 °C.

Me ester		207–8/8.5 mm.	14,132,271, 626,959, 1005, 1045
Hydrochloride	143–44		
Et ester		218	
Hydrochloride	245		
Picrate	126–27		
Amide	156–57		
Picrate	214–15		
Chloride hydrochloride	143–44		
Anhydride	114		224,227,272
Azide	45–46		283
Ph ester	70		272
Hydrochloride	177–78		272
Propyl ester		117–22/10 mm.	1048
4-PyCO$_2$CH$_2$NH$_2$ · HCl	213–14		300
4-PyCO$_2$CH$_2$CH$_2$NEt$_2$ · 2HCl	151–52		1032
4-PyCO$_2$CH$_2$CH$_2$N(S) · 2HCl	79–80		1032
4-PyCO$_2$CH$_2$CMe$_2$CH$_2$NEt$_2$ · HCl	180–81		1032
4-PyCO$_2$CMe$_2$CH$_2$NEt$_2$ · HCl	216		1032
Methylamide	116.5–17		959,1019
Hydrochloride	205–206		959,1019
Picrate	165		959,1019
Dimethylamide	58.5–59.5		1019
i-Propylamide	108.5–10.5		1019
4-PyCONHCH$_2$OH	145–47		299
Picrate	146–48 (dec.)		299
2,6-Xylidide	161–62		1104

(*continued*)

TABLE X-1. Pyridinemonocarboxylic Acids (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
	Isonicotinic acid (*continued*)		
4-PyCONHCH$_2$NHCOPy-4	326–28		299
Picrate	255–57		299
4-PyCONHCH$_2$NMe$_2$ · HCl	166–68		299
Picrate	188–89		299
4-PyCONHCH$_2$CBu$_3$	91.5–92		1011
4-PyCONHCH$_2$CH$_2$Cl · HCl	170–71.5		1013
4-PyCON(CH$_2$CH$_2$Cl)$_2$	95–97		1013,1086
Hydrochloride	186.5–87.5		1013,1086
4-PyCONHCH$_2$CO$_2$H	230–32		976,1020
4-PyCONHCH$_2$CO$_2$Et	89–90		976
4-PyCONHCH$_2$CONH$_2$	227–28		976
4-PyCONHCO$_2$Et · HCl	193–95		1020
4-PyCONHCONH$_2$	240–41		1047
4-PyCONHCONHEt	170–72		1047
4-PyCONHCONHCHMe$_2$	163–65		1047
4-PyCONHCH$_2$CH$_2$OH	134.5	220/1 mm.	300,1013
Hydrochloride	182.5		300,1013
Picrate	144		300,1013
4-PyCON(CH$_2$CH$_2$OH)$_2$ · HCl	153.5		1013
4-PyCONHCH(CO$_2$H)CHMeEt	200–210		1020
4-PyCONHCH(CO$_2$H)CH$_2$Ph	>250		1020
4-PyCONHCH$_2$CH$_2$NEt$_2$		175/1 mm.	1022,1032
Hydrochloride	245–47		1022,1032
4-PyCONH(CH$_2$)$_3$NEt$_2$		179/1 mm.	1022
4-PyCONHCHMeCH$_2$NEt$_2$ · HCl	134		1022
4-PyCONHCHMe(CH$_2$)$_3$NEt$_2$		185/1 mm.	1022
4-PyCONH(CH$_2$)$_6$NEt$_2$		190–92/1 mm.	1022
4-PyCON		135/0.3 mm.	1032
4-PyCONHCH$_2$CH$_2$Ph	123		303
4-PyCONHCHMeCH$_2$Ph	109		303
4-PyCONHCH$_2$CHMePh	83		303
4-PyCONHCH$_2$CH$_2$C$_6$H$_4$(OMe)-*p*	130		303
4-PyCONHCH$_2$CH$_2$C$_6$H$_3$(O$_2$CH$_2$)-3,4	138		303
4-PyCONHCH$_2$CH$_2$C$_6$H$_4$Cl-*p*	108		303
4-PyCONHPy-4	193–94		1020
4-PyCONHC$_6$H$_4$NMe$_2$-*p*	225		1096
4-PyCOSMe	50–51	120–22/14 mm.	472
Picrate	145–46		472

TABLE X-1 (*continued*)

Derivative	M.p., °C.	B.p., °C.	Ref.
4-PyCOSPh	64–65		1078
Thioamide	210 (dec.)		1000,1017, 1019, 1020
Thiomethylamide	105–5.5		1019
Thiodimethylamide	67.5–68		1019
Thio-*i*-propylamide	145.5–46.5		1019
Thiomorpholide	153		101,1018
Thiopiperidide	117		1017
Thiobutylamide	80		1017
Thiocyclohexylamide	174		1017
Thioanilide	181–82		1017,1037
Thio-*p*-dimethylaminoanilide	193–94		1096
Thio-*p*-toluidide	181		1037
Thiobenzylamide	134		1017
Thiohydrazide	134 (dec.)		1017
4-PyCONHNHCOPy-4	259–61		192,347
4-PyC(:NH)NH_2 · HCl	242–44		1020
4-PyCONHOH	171		322,342, 981,1016, 1050
Hydrochloride	206–7		322,342, 981,1016, 1050
4-PyCSNHOH	~180		1017
4-PyC(:NH)$NHNH_2$	127–28		1003
Hydrochloride	~280 (dec.)		1003
4-PyC(:NH)NHNHC(:NH)Py-4	> 280 (dec.)		1036
N,N'-Diphenylamidine	191–92		1037
N,N'-Di-*p*-tolylamidine	199–200		1037
Ring C^{14} derivative			1028
4-Py$C^{14}O_2H$			91,95

TABLE X-2. Pyridinepolycarboxylic Acids

Position of carboxyls	Common name	M.p., °C.	Derivatives	Ref.
			DICARBOXYLIC	
2,3	quinolinic	190	Me ester: m.p. 55–56°; Et ester: b.p. 280–85°; amide: m.p. 209°	44,45,239, 627,628
			2-amide-3-Et ester: m.p. 98°	506,1039
			imide: m.p. 233°	506,1039
			2-*sec*-butyl ester: m.p. 149–50°	1039
			3-*sec*-butyl ester: m.p. 129–30°	1039
			cyclic hydrazide: m.p. 309°	499
			2-amide-3-Me ester: m.p. 114–16°	146
			3-amide-2-Me ester: m.p. 126–28°	146
			2-anilide-3-Me ester: m.p. 137°	1054
			3-anilide-2-Me ester: m.p. 159°, 209°	1054
			2-*N*-Me anilide: m.p. 165° (dec.)	1054
			2-*N*-Me anilide-3-Me ester: m.p. 96°	1054
			3-*N*-Me anilide-2-Me ester: m.p. 85–86°	1054
			2-diphenylamide: m.p. 212–13° (dec.)	1054
			2-diphenylamide-3-Me ester: m.p. 167–68°	1054
			3-diphenylamide-2-Me ester: m.p. 165°	1054
			3-*p*-sulfamylanilide: m.p. 210°	505
			bis-*p*-sulfamylanilide: m.p. 293° (dec.)	505
			p-sulfamylphenylimide: m.p. 310–11° (dec.)	505
			 CONHSO$_2$C$_6$H$_4$NHAc-*p* CONHSO$_2$C$_6$H$_4$NHAc-*p* : m.p. 308°	505
			 CONHCH$_2$CBu$_3$ CO$_2$H : m.p. 128–29°; Me ester: m.p. 116–16.5°	1011

TABLE X-2 (*continued*)

Position of carboxyls	Common name	M.p., °C.	Derivatives	Ref.
2,4	lutidinic	248–50	Me ester: m.p. 58°; Et ester: b.p. 168°/11 mm.; amide: m.p. 254–55°; chloride: m.p. 54–56°; Ph ester: m.p. 136°; azide: m.p. 98° (dec.)	29,65,272, 629,630
2,5	isocincho-meronic	256–58	Me ester: m.p. 164°; Et ester: m.p. 164°, b.p. 181°/17 mm.; amide: m.p. 319–21°; diethylamide: m.p. 122–23°; Ph ester: m.p. 156°	29,37,56, 194,272, 629,631, 1008, 1026, 1056
2,6	dipicolinic	236–37 (252)	mono-Me ester: m.p. 151°; Me ester: m.p. 124–25°; Et ester: m.p. 44–46°; acid chloride: m.p. 60°; diethylamide: m.p. 82°; b.p. 196°/0.8 mm.; Ph ester: m.p. 179°; thiodiethylamide: m.p. 129–30°	7,29,67,80, 130,140, 272,632, 633,971, 1038, 1056, 1066
3,4	cincho-meronic	266–68	Et ester: b.p. 181–82°/28 mm.; amide: m.p. 175–76°; 4-monoamide: m.p. 170–71°; imide: m.p. 229–30°	44,239,286, 479,498, 634
3,5	dinicotinic	320–23	Me ester: m.p. 84–85°; monoamide: m.p. 265–66°; diamide: 303–4°; tetraethyldiamide: m.p. 73–75°; Et ester: m.p. 51°, b.p. 145°/1 mm.	28,68,635, 637,919, 967,1057
			TRICARBOXYLIC	
2,3,4	α-carboxy-cincho-meronic	249–50	Me ester: m.p. 101–2°; Et ester: b.p. 300–5°	239,480, 638–640
2,3,5	α-carboxy-dinico-tinic	324		35,68,635, 641
2,3,6		245 (dec.)		35,56,640, 642
2,4,5	berberonic	249		35,310,643, 644,1105
2,4,6	α-carboxy-lutidinic	227	Me ester: m.p. 154.5°; Et ester: m.p. 127.5°	108,640, 645,1056

(*continued*)

TABLE X-2. Pyridinepolycarboxylic Acids (*continued*)

Position of carboxyls	Common name	M.p., °C.	Derivatives	Ref.
		TRICARBOXYLIC (*continued*)		
3,4,5	β-carboxy-cincho-meronic	261		646–648
		TETRACARBOXYLIC		
2,3,4,5				646,647
2,3,4,6		236	Me ester: m.p. 135–36°	642,649, 650,963
2,3,5,6		200	Me ester: m.p. 118–19°; dian-hydride: (dec.) 277–80°	651–653, 975
		PENTACARBOXYLIC		
2,3,4,5,6				646,647

TABLE X-3. Nuclear-Substituted Pyridinecarboxylic Acid Hydrazides

Substituent and position					M.p., °C.	Ref.
2	3	4	5	6		
$CONHNH_2$					101–2	611
$CONHNH_2$	$CONHNH_2$				224	969
$CONHNH_2$		$CONHNH_2$			258	29,375
$CONHNH_2$		CH_3			71	29
$CONHNH_2$		Cl			166.5–68	312,371
$CONHNH_2$		I			160–61	371
$CONHNH_2$		NH_2			265	312
$CONHNH_2$	NH_2				103	1068
$CONHNH_2$		n-C_3H_7			picrate: 111; hydrochloride: 200	1086
$CONHNH_2$		Cl		$CONHNH_2$	>300	1082
$CONHNH_2$		$NHNH_2$			186.5–88.5	312
$CONHNH_2$		OCH_3			152–54	312
$CONHNH_2$		OH	OH		>270	927
$CONHNH_2$		CH_3		CH_3	77	37,960
$CONHNH_2$		Cl		Cl	154	368
$CONHNH_2$		$CONHNH_2$		CH_3	297, 239–40	29,948
$CONHNH_2$		$N_2C_6H_5$		$CONHNH_2$	228	377
$CONHNH_2$			CH_3		oil	37
$CONHNH_2$				C_6H_5	136–38	37
$CONHNH_2$				CH_2OH	185	80
$CONHNH_2$				$CONHNH_2$	298	29
	$CONHNH_2$				159–61; dihydrochloride: 227	310,956
NH_2	$CONHNH_2$				186.5–87.5	928,1068
SH	$CONHNH_2$				330	937
CH_2	$CONHNH_2$				120	939
OH	$CONHNH_2$	OH		$NHNH_2$		936

(*continued*)

TABLE X-3. Nuclear-Substituted Pyridinecarboxylic Acid Hydrazides (*continued*)

Substituent and position					M.p., °C.	Ref.
2	3	4	5	6		
OH	$CONHNH_2$	$CH_2OCH_2CH_3$		CH_3	220–22	948
CH_3	$CONHNH_2$	$CH_2OC_6H_5$	CN	Cl	114–15	935
NH_2	$CONHNH_2$			CH_3	179–80	1088
NH_2	$CONHNH_2$			C_6H_5	172	1088
CH_3	$CONHNH_2$		$CONHNH_2$	CH_3	230-5–32.5	373,928
OH	$CONHNH_2$			CH_3	>300	948
	$CONHNH_2$	NH_2			206–8	928
	$CONHNH_2$	CH_3			176.5–77.3	381,1097
	$CONHNH_2$	CO_2H			>300	948
	$CONHNH_2$		Cl		178	933
	$CONHNH_2$		Br		193–94	549
	$CONHNH_2$		Cl	$NHNH_2$	238–40	549
	$CONHNH_2$			OH	310	941
	$CONHNH_2$			NH_2	225	246,1059
	$CONHNH_2$			$C_3H_7(n)$	90–91	49
	$CONHNH_2$			CH_3	133–35	282
	$CONHNH_2$			SCH_2CH_3	126–27	948
		$CONHNH_2$			168.5–70.5	928,1104
F		$CONHNH_2$			110–12	929
Cl		$CONHNH_2$			166–68	934
Br		$CONHNH_2$			177–78	929
CH_3		$CONHNH_2$			120–22; dihydrochloride: 180	67,355,930
C_2H_5		$CONHNH_2$			76–78	355
$C_2H_7(n)$		$CONHNH_2$			74–76	355
$C_3H_7(i)$		$CONHNH_2$			oil	355
$C_4H_9(i)$		$CONHNH_2$			74–76	355
$C_4H_9(tert)$		$CONHNH_2$			92–93	355

C_5H_{11}		$CONHNH_2$			87–88	930
C_6H_5		$CONHNH_2$			127–28	355
OH		$CONHNH_2$			256–58	934
OCH_3		$CONHNH_2$			135–38	355
OC_2H_5		$CONHNH_2$			146.9	355
NH_2		$CONHNH_2$			194.5–95	1040,1062
$NHC_4H_9(n)$		$CONHNH_2$			134–36	941
NO_2		$CONHNH_2$			181.5–83.5	1040
	OH	$CONHNH_2$			320	928
	Cl	$CONHNH_2$			145–47	929
	F	$CONHNH_2$			146.8–47.8	940
	CH_3	$CONHNH_2$			127–28	355,929
	CO_2H	$CONHNH_2$			300	611
	NH_2	$CONHNH_2$			190–92	929,1068
	SH	$CONHNH_2$			239–40	937
CH_3		$CONHNH_2$	C_2H_5		150–52	355
CH_3	OH	$CONHNH_2$	CH_2OH		184–86	355,929
Cl	CN	$CONHNH_2$		CH_3	>360	256
CH_3	NH_2	$CONHNH_2$		CH_3	132	355
CH_3		$CONHNH_2$		CH_3	151–52	355,960
CH_3		$CONHNH_2$		OH	275–80	355
CH_3		$CONHNH_2$		Cl	147–48	355
OH		$CONHNH_2$		OH	235	611,931,941
NH_2		$CONHNH_2$		NH_2	260	932
Cl		$CONHNH_2$		Cl	184	611,932
$OC_4H_9(n)$		$CONHNH_2$			104	1062
$OC_4H_9(n)$		$CONHNH_2$		$OC_4H_9(n)$	96–98	355,929
OCH_3		$CONHNH_2$		OCH_3	170–71	318,355
OC_2H_5		$CONHNH_2$		OC_2H_5	128.5–32	355
Cl		$CONHNH_2$		$NHNH_2$	226	355,932
Cl		$CONHNH_2$		OC_2H_5	188–90	355
Cl		$CONHNH_2$		$OCH_2CH{:}CH_2$	126–30	355
C_5H_{11}		$CONHNH_2$		Cl	108–9	930

TABLE X-4. Cyanopyridines

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CN					26; b.p. 222.5–23.5, 118–20/25 mm.		271,425, 845
		CN			50–51; b.p. 204–8	hydrochloride: m.p. 267–69°; picrate:m.p. 224–26°	271, 299, 426,849
	CN				83	picrate:m.p. 197–99°	271,426, 626,876 1073
CN	CH_3				87–90		1073,1074
CN	NO_2				78		252
CN	NH_2				149		252
CN	CO_2H					Me ester:m.p. 89–90°; acid chloride:m.p. 60–62°	924
CN		CH_3			89–91		1073,1074, 1081
CN		C_2H_5			b.p. 123–4/11 mm.		1081
CN		$C_3H_7(n)$					38
CN		C_6H_5			99–100		1081
CN			CH_3		73–75		1074
CN			C_2H_5		b.p. 132/20 mm.		949
CN			Cl		83–84		922

CN			NO_2		43		248
CN			$CONH_2$		275–77		255,925
CN				CH_3	72–72.5		255,847, 848, 1073
CN				C_6H_5	64–66		1081
CN				$CONH_2$	184–87		255,925
CN	NO_2		Cl		98		252
CN	NO_2		Br		102		252
CN	NH_2		Br		175		252
CN	NH_2		Cl		175		252
CN		CH_3		CH_3	53–53.5		846,922
CH_3	CN				58	picrate:m.p. 170°	666,850
Cl	CN				106–7		245,851
NH_2	CN				131–33		245
CO_2H	CN				184	acid chloride: m.p. 85–87°; Me ester:m.p. 150–51°	906,924
	CN	CH_3			43–44; b.p. 64/1–2 mm.	picrate:m.p. 184.5–85.5°; hydrochloride: m.p. 208–9°	193,919, 1097
	CN	C_2H_5			b.p. 72–74/2 mm.	picrate:m.p. 153–5°	926,1089
	CN	OC_6H_5			104–5		938
	CN	SC_6H_5			63–63.5		938
	CN		CH_3		84–85	hydrochloride: m.p. 210°	406,919

(*continued*)

TABLE X-4. Cyanopyridines (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
	CN		Cl		60		908
	CN		Br		105–6		1052
	CN			CH_3	90; b.p. 216–17/750 mm.	hydrochloride: m.p. 210°	76,406,422, 722,919, 1049
	CN			Cl	117–18		264,406
	CN			NH_2	164; b.p. 240–50/15 mm.	*p*-nitrobenzene-sulfonyl:m.p. 224–25°	41,404, 991
	CN			SH	255		264
	CN			SCH_3	78		264
	CN			SO_2CH_3	133		264
	CN			*p*-$SC_6H_4NO_2$	133–35		875
CH_3	CN	CH_3			53; b.p. 218	hydrochloride: m.p. 187°	852
Cl	CN	Cl			114–15		575,580
Cl	CN		Cl		118–19		406
Cl	CN		NO_2		121–22		861
CH_3	CN			CH_3	83	picrate:m.p. 179–80°	870
Cl	CN			CH_3	117; b.p. 140–45°/1 mm.		422,615, 871, 1046
NH_2	CN			CH_3		185.5–86	871,1046
Cl	CN			$C_3H_7(n)$	b.p. 90–100/0.005 mm.		671

	CN	CH_3	$CH{:}CH_2$		b.p. 98/2 mm.	picrate:m.p. 141–143°	1090
	CN	C_2H_5	C_2H_5		115–16		1089
	CN	CH_3	CH_2CH_2Cl		b.p. 144–5/3 mm.	picrate:m.p. 143–44°	1090
	CN	CH_3	$CH_2CH_2NEt_2$		b.p. 134/2 mm.	picrate:m.p. 172–73°	1090
	CN	Cl		Cl	134–36		872
	CN	CO_2H		CH_3	230	Et ester:m.p. 58°; amide; m.p. 275° (dec.)	422
	CN	CO_2H		$C_3H_7(n)$	187–90	Et ester:b.p. 70–80°/ 0.005 mm.	671
	CN		NO_2	CH_3	145		1064
CH_3	CN	CH_3		Cl	65		852
CH_3	CN	CH_3		NH_2	222–23		852,907
CH_3	CN	C_6H_5		CH_3	105–106		719
CH_3	CN	C_6H_5		C_6H_5	115–16		719,852
CH_3	CN	C_6H_5		*p*-$CH_3C_6H_4$	165		852
CH_3	CN	*p*-ClC_6H_4		C_6H_5	173		725
CH_3	CN	*o*-$O_2NC_6H_4$		CH_3	160.5–61.5	picrate:m.p. 216.5–17.5°	866
CH_3	CN	*o*-ClC_6H_4	C_6H_5		144–5		725
CH_3	CN	*m*-ClC_6H_4	C_6H_5		141–2		725
CH_3	CN	*p*-ClC_6H_4	C_6H_5		173		725
CH_3	CN	*p*-$C_2H_5OC_6H_4$	C_6H_5		141–2		725
CH_3	CN	2,4,5-$O_2N(CH_2O)_2$-C_6H_2	CH_3		173–74		866
CH_3	CN	*o*-$CH_3OC_6H_4$	C_6H_5		128–29		725

(*continued*)

TABLE X-4. Cyanopyridines (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CH_3	CN	2,3,4-O_2N-$(OCH_3)_2C_6H_2$	CH_3		182–83	picrate:m.p. 190.5–91.5°	866
C_6H_5	CN	C_6H_5	C_6H_5		220		852,860
p-$CH_3C_6H_4$	CN	C_6H_5	C_6H_5		185		852
C_6H_5	CN	$CH{:}CHC_6H_5$	C_6H_5		184		852
C_6H_5	CN	$CH{:}CHC_6H_5$	*p*-$CH_3C_6H_4$		181		852
Cl	CN	CH_3	CH_3		104		429,436, 853, 1069
Cl	CN	CH_3	Cl		110–10.5		1097
Cl	CN	CH_3	CO_2H			Et ester:m.p. 90–91°	855
Cl	CN	C_6H_5	C_6H_5		154.5		909
Br	CN	C_6H_5	C_6H_5		169–70		909
Cl	CN	Cl	CH_3		101–102		579
Cl	CN	Cl	$CH{:}CHC_6H_5$		168–69		579
Cl	CN	Cl	$CH{:}CHC_6H_5$-Cl-*m*		182–83		857
Cl	CN	Cl	$CH{:}CHC_6H_4$-NO_2-*m*		263–64		857
Cl	CN	Cl	Cl		112–13		858
Cl	CN	Cl	CO_2H		180		579
Cl	CN	CH_2OCH_3	CH_3		66–67		439
Cl	CN	$CH_2OC_2H_5$	CH_3		35.5–36.5; b.p. 160–61/12 mm.		854,856
Cl	CN	CH_2OCH_3	CH_2OCH_3		77.5		859

Cl	CN	CO_2H		CH_3	198.5	Me ester:m.p. 168.5°; Et ester:m.p. 62°; b.p. 136°/0.5 mm. amide:m.p. 233°; acid chloride:m.p. 98–103°; *N*-bromoamide: m.p. 199°	422,855
Cl	CN	CO_2H		$C_3H_7(n)$		Et ester:b.p. 90–100°/0.005 mm.	793
NH_2	CN	CH_3		CH_3	253		429,1069
NEt_2	CN	CH_3		CH_3	b.p. 125.5–29/1.5 mm.	picrate:m.p. 94.5–96.5°	853
Cl	CN		CH_3	CH_3	b.p. 141.5–42.5/12 mm.		436
Cl	CN		Cl	CH_3	103–4		615
Cl	CN		NO_2	CH_3	98–99		615
Cl	CN		C_6H_5	NH_2	216–17		869
CH_3	CN		CO_2H	CO_2H		Et ester:m.p. 92–93°; b.p. 140–45°/0.5 mm.	651,694, 739
Cl	CN		NH_2	CH_3	224–25	*N*-acetyl m.p. 183–85°	615
CH_3	CN		$COCH_3$	CO_2H	154–56	Et ester:m.p. 94.5–95°	843

(*continued*)

TABLE X-4. (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CH_3	CN		CO_2H	CF_3		Et ester:b.p. 130–40°/4 mm.	744
C_6H_5	CN		CO_2H	CH_3		Et ester:m.p. 86–88°	694
C_6H_5	CN		CO_2H	C_6H_5		Et ester:m.p. 145°	694
C_6H_5	CN		CO_2H	CO_2H	202–4	Et ester:m.p. 92–93°	694
NH_2	CN		CH_3	CH_3	218	picrate:m.p. 200–1°	1069
	CN	CH_3	CH_3	CH_3	90–91		844
	CN	CH_3	NO_2	CH_3	223 (dec.)		1064
	CN	CH_3	NH_2	CH_3	192–94		923
	CN	CO_2H	NH_2	CH_3		Et ester:m.p. 131–32.5°	616,862
	CN	$CH_2OC_2H_5$	NH_2	CH_3	80		873
	CN	$CH_2OC_6H_5$	$NHCOC_2H_5$	CH_3	167		874
CH_3	CN	C_6H_5	CO_2H	CH_3	236–37	Et ester:m.p. 101–2°	719,865
CH_3	CN	o-$O_2NC_6H_4$	CO_2H	CH_3	232–3 (dec.)	Et ester:m.p. 115.5–16.5°	866
CH_3	CN	o-$O_3NC_6H_4$	$COCH_3$	CH_3	117.5–18.5		871
CH_3	CN	3,4-$(CH_3O)_2$-C_6H_3	CO_2H	CH_3		Et ester:m.p. 148–49°	866
CH_3	CN	2,5-$CH_3O(NO_2)$-C_6H_3	$COCH_3$	CH_3	166		880

CH_3	CN	3,4-OMe(OH)-C_6H_3	CO_2H	CH_3		Et ester:m.p. 132.5–32.5°; *O*-acetyl Et ester:m.p. 165–66°	866
CH_3	CN	2,3,4-O_2N(OMe)-(OH)C_6H_2	CO_2H	CH_3		Et ester:m.p. 187.5–88.5°; *O*-acetyl Et ester:m.p. 112–13°	866
CH_3	CN	2,4,5-O_2N-$(CH_2O_2)C_6H_2$		CH_3		Et ester:m.p. 153–54°	866
CH_3	CN	2,3,4-O_2N-$(OMe)_2C_6H_2$	CO_2H	CH_3		Et ester:m.p. 131.5–32.5°	866
CH_3	CN	CO_2H	CO_2H	CO_2H		Et ester:b.p. 177–79°/1 mm.	697
C_6H_5	CN	C_6H_5	CO_2H	CH_3		Et ester:m.p. 189°	913
Cl	CN	CH_3	NO_2	CH_3	114–15		920
Cl	CN	CH_3	NH_2	CH_3	149–49.2		920
Cl	CN	CH_3	NO_2	CH_2OCH_3	78–9		1079
Cl	Cl	CN	Cl	Cl	138		912
Cl	CN	CO_2H	NO_2	CH_3		Et ester:m.p. 61–62°	616,862, 864
Cl	CN	CO_2H	NH_2	CH_3		Et ester:m.p. 175°	616,862, 864
Cl	CN	Cl	NO_2	CH_3	199–200		266
Cl	CN	Cl	NH_2	CH_3	179–80		266,615
Cl	CN	Br	NH_2	CH_3	185–86		615

(*continued*)

TABLE X-4. Cyanopyridines (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
Cl	CN	C_6H_5	Br	C_6H_5	181–82		863
Cl	CN	CH_2OCH_3	NO_2	CH_3	70–73		915,921
Cl	CN	CH_2OCH_3	NO_2	C_2H_5	56–57		917
Cl	CN	$CH_2OC_2H_5$	NO_2	CH_3	47–48		914,915
Cl	CN	$CH_2OC_2H_5$	NH_2	CH_3	146–48		914,915
Cl	CN	$CH_2OC_6H_5$	$CONHNH_2$	CH_3	114–15		867
Cl	CN	3,4-(CH_2O_2)-C_6H_3	CO_2H	CH_3		Et ester:m.p. 132.5–33.5°	866
Cl	CN	$CH_2OC_6H_5$	$NHCO_2C_2H_5$	CH_3	167		868
Br	CN	C_6H_5	Br	C_6H_5	189–90		863
I	CN	I	NH_2	CH_3	209–11		266
CH_3		CN			45.5–46.5; b.p. 75/11–15 mm.	picrate:m.p. 163–64°	950,1073, 1074
$C_3H_7(n)$		CN			b.p. 90–95/4 mm.		1080
$C_4H_9(i)$		CN			b.p. 107–17/6 mm.		1080
Cl		CN			49		1063
	CH_3	CN			51–52.5	picrate:m.p. 154–6°	1073,1074
CH_3		CN		CH_3	81–2	picrate:m.p. 175–7.5°	1071,1073
$C_3H_7(n)$		CN		Cl	b.p. 112–22/4 mm.		1080
Cl		CN		Cl	95.5–96		542,986

Br		CN		Br	139–40	542
	NO_2	CN	NO_2		140	614
	CN		Cl	Cl	150	406
	CN		Br	Cl	160	406
	CN		I	Cl	148	406
CN	CN				130	877
CN		CN			88–91	1074
CN				CN	123°	426
	CN		CN		113	142,852
	CN	CN	Br		125	261,916
CH_3	CN	CN		CH_3	64	262
CH_3	CN		CN	CH_3	112	852
NH_2	CN		CN	Cl	subl. >200	1041
NH_2	CN		CN	Br	subl. >200	1041
NH_2	CN		CN	NH_2	subl. >200	1041
	CN	CN	NH_2	CH_3	193–94	878
Cl	CN	CN	NO_2	CH_3	88–89	878,918
Cl	CN	CN	NH_2	CH_3	224–25	878,918
CH_3	CN	CH_3	CN	CH_3	111	852
CH_3	CN	C_6H_5	CN	C_6H_5	116	852
CH_3	CN	*o*-$CH_3OC_6H_4$	CN	CH_3	177	880
C_6H_5	CN	*o*-$CH_3OC_6H_4$	CN	C_6H_5	219–20	880
CH_3	CN	*o*-$O_2NC_6H_4$	CN	CH_3	146.5–47.5	881
CH_3	CN	2,4-$(NO_2)_2C_6H_3$	CN	CH_3	159.5	881
CH_3	CN	2,4-$(CH_3O)_2$-C_6H_3	CN	CH_3	138.5	880
CH_3	CN	2,5-(CH_3O)-$(NO_2)C_6H_3$	CN	CH_3	222.5–23	880
CH_3	CN	2,4,5-$(CH_3O)_2$-$NO_2C_6H_2$	CN_3	CH_3	229	880

(*continued*)

TABLE X-4. Cyanopyridines (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CH_3	CN	2,3,4-$NO_2(CH_3O)$-$(AcO)C_6H_2$	CN	CH_3	190.5		881
C_6H_5	CN	CH_2Cl	CN	C_6H_5	177		879
C_6H_5	CN	CH_2OH	CN	C_6H_5	176		879
C_6H_5	CN	C_6H_5	CN	C_6H_5	238		852
C_6H_5	CN	*o*-$O_2NC_6H_4$	CN	C_6H_5	232–33		881
C_6H_5	CN	*p*-HOC_6H_4	CN	CH_3	265		882
C_6H_5	CN	2,4-$(NO_2)_2$-C_6H_3	CN	C_6H_5	211		881
C_6H_5	CN	2,3,4-$NO_2(CH_3O)$-$(OAc)C_6H_2$	CN	C_6H_5	184–85		881
p-$H_3CC_6H_4$	CN	*p*-HOC_6H_4	CN	*p*-$H_3CC_6H_4$	245–46		882
p-$CH_3OC_6H_4$	CN	*p*-HOC_6H_4	CN	*p*-$CH_3OC_6H_4$	248–50		882
NH_2	CN	Br	CN	Br	>300		1041
NH_2	CN	C_6H_5	CN	Cl	303–8		1041
NH_2	CN	NH_2	CN	Cl	>300		1041
NH_2	CN	NH_2	CN	Br	subl. >270		1041
NH_2	CN	NH_2	CN	I	>300		1041
NH_2	CN	$(CH_3)_2N$	CN	Cl	244–45		1041
NH_2	CN	*p*-$(CH_3)_2NC_6H_4$	CN	Cl	>320		1041
CH_3	CN	CH_2CN	CN	CH_3	230 (dec.)		879
NH_2	CN	CN	CN	Cl	227–28		1041
NH_2	CN	CN	CN	Br	229–30		1041
NH_2	CN	CN	CN	NH_2	subl. >250		1041
NH_2	CN	CN	CN	$NHCH_3$	subl. >250		1041
NH_2	CN	CN	CN	$NH(CH_2)_4CH_2$	218		1041
NH_2	CN	CN	CN	NHC_6H_5	275		1041
NH_2	CN	CN	CN	NHC_6H_4Cl-*p*	315–16		1041

TABLE X-5. Monoalkyl or Aryl Pyridinemonocarboxylic Acids

Substituents and positions					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CO_2H	CH_3				111		655,656
CO_2H	COC_6H_5				148		840
CO_2H	$CH(C_6H_5)_2$				153	Me ester: m.p. 109°	830
CO_2H	$CHPhC_6H_4$-Me(*p*)				161		830
CO_2H	*o*-$HO_2CC_6H_4$				207		664
CO_2H	$COC_6H_4Cl(p)$				147		836
CO_2H	*p*-phenylbenzoyl				170–71		513
CO_2H	1-naphthoyl				155	Me ester: m.p. 100–1°; hydrochloride: m.p. 179–80°	513
CO_2H	2-naphthoyl				145	Me ester: m.p. 80–82°; hydrochloride: m.p. 172–73°	513
CO_2H		CH_3			140	Me ester: b.p. 129–34°/17 mm.; Et ester: b.p. 105°/1 mm.	29,656–658,960
CO_2H		$C_3H_7(n)$			104–107	Cu salt: m.p. 305° (dec.); Et ester: m.p. 80°	38,1086
CO_2H		C_6H_5				Et ester: m.p. 60–61°	1081
CO_2H		C_2H_5			112–14		1091
CO_2H		$C_4H_9(n)$			101–3		1091
CO_2H		$C_4H_9(i)$			112–13		1091
CO_2H		$C_5H_{11}(n)$			102–3		1091

(*continued*)

TABLE X-5. Monoalkyl or Aryl Pyridinemonocarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CO_2H			CH_3		163–64	Et ester:b.p. 123–24° 15 mm.; amide: m.p. 179°; chloroplatinate: 189–90°	37,656,659
CO_2H			C_2H_5		110.5–12	Et ester: b.p. 151°/16 mm.; amide: m.p. 147–48°; *t*-butylthio-amide: b.p. 120–23°/ 0.4 mm.	76,194,949, 1098
CO_2H			$C_4H_9(n)$		102–4	Et ester: b.p. 176–79°/ 17 mm.; Et ester picrate:m.p. 85–86°; Me ester picrate:m.p. 83–86°; amide:m.p. 127–28°	76,957
$C^{14}O_2H$			$C_4H_9(n)$				957
CO_2H			$C_6H_{13}(n)$		97–99		76
CO_2H			C_6H_5		156–57		958
CO_2H				CH_3	129	Hydrate: m.p. 96°; Me ester: m.p. 29°, b.p. 137°/29 mm.; Et ester: b.p. 245°; amide: m.p. 116°; hydrochloride: m.p. 128–29°; acid chloride: m.p. 195°; hydroxymethylamide: m.p. 90–95°; amidrazone: m.p. 115–16°;	80,108,192 309,656, 660–662, 1003, 1066, 1098

				thioamide: m.p. 103–4°; Et ester hydrochloride: m.p. 74–75°; *t*-octylthioamide: b.p. 136–51°/0.6	
CO_2H		$C_4H_9(n)$			659
CO_2H		$C_3H_7(n)$	127–28		1061
CO_2H		$C_5H_{11}(n)$	101–2		1061
CO_2H		CHO	165	Me ester: m.p. 102°	80,964
CO_2H		C_6H_5	109	methylamide: m.p. 129.5°; ethylamide: m.p. 84°; Me ester: m.p. 47°; amide: m.p.179°; Et ester: m.p. 56–57°	37,663, 1081
CO_2H		CCl_3	140–43	Me ester: m.p. 108–10°; amide: m.p. 119–22°	108
CH_3	CO_2H		226–27	hydrochloride: m.p. 226°; Et ester: b.p. 118°/20 mm.; amide: m.p. 158°; Et ester picrate: m.p. 146–47°; amide picrate: m.p. 180–81°; diethylamide: b.p. 167°/12 mm.	29,273,666, 939,1094
$CCl{:}CHCl$	CO_2H		139		910
$CCl{:}CCl_2$	CO_2H		153–54		910
$C_3H_7(n)$	CO_2H		124–25		667
$C(:CH_2)\text{-}CH_3$	CO_2H		107–8		827
$COCH_3$	CO_2H		130		1095

(*continued*)

TABLE X-5. Monoalkyl or Aryl Pyridinemonocarboxylic Acids

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
2,6-CO_2H-$(Cl)C_6H_3$	CO_2H				252–56		899
o-HO_2C-C_6H_4	CO_2H				238–39		664
C_6H_5	CO_2H				167–69		1099
3-Py	CO_2H				183	Me ester: m.p. 83°	1060
o-HOC_6H_4-CH_2CH_2	CO_2H					lactone: m.p. 142–43 lactone-HCl: m.p. 183–84	1105
m-$NO_2C_6H_4$-CH:CH	CO_2H				230–32		1105
m-$NO_2C_6H_4$	CO_2H				176–77		1105
	CO_2H	CH_3			215–16	acid chloride: m.p. 135–38°; Me ester; b.p. 57–58°/1–2 mm.; Et ester: b.p. 118°/12 mm.; amide: m.p. 167–67.5°; diaroylhydrazine: m.p. 249–49.5°; Et ester picrate: m.p. 137–38°; Et ester chloroplatinate: m.p. 183° (dec.); Me ester hydrochloride: m.p. 145–45.5°; Me ester picrate: m.p. 148–49°	109,193, 669,1097

CO_2H	C_2H_5			137–38		111,668
CO_2H	CCl_3			161–62		109
CO_2H	$CH{:}CHC_6H_5$				Et ester picrate: m.p. 167–68.5	834
CO_2H	$CH_2CH_2C_6H_5$			156–57	picrate: m.p. 166–67°; Et ester picrate: m.p. 134–34.5°	824,834
CO_2H		CH_3		215–16		28,635,919
CO_2H		C_6H_5		267–69		958
CO_2H			CH_3	212–13	Me ester: m.p. 38°; Et ester: b.p. 222–24°; amide: m.p. 194–96°; diethylamide: b.p. 160–64°/12 mm.; anilide: m.p. 134–37°; 2-methyl-5-pyridylamide: m.p. 275–77° (dec.); azide: m.p. 44–45°; urethan: m.p. 132–33°; diaroylurea: m.p. 285–88° (dec.); diaroylhydrazine: m.p. 247–50°	76,106,282, 406,633, 919,967, 1049, 1094
CO_2H			CCl_3	183–84	Me ester: m.p. 82–84°; Ph ester: m.p. 87–88°; acid chloride: m.p. 33–35°	108
CO_2H			$C_3H_7(n)$	129–30	Et ester: b.p. 135–36°/13 mm.; amide: m.p. 150–52°	49,667,793
CO_2H			CH_2CHMe_2		Et ester: b.p. 103–5°/2 mm.	1094

(*continued*)

TABLE X-5. Monoalkyl or Aryl Pyridinemonocarboxylic Acids

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
	CO_2H			C_6H_5	232–33	anilide: m.p. 199°	98,672,673, 1099
	CO_2H			$CH{:}CHC_6H_5$	223		674
	CO_2H			$CH_2CH_2C_6H_5$	148–49		674
	CO_2H			$CH{:}CHC_6H_4NO_2(o)$	240	Et ester: m.p. 128–30°; hydrochloride: m.p. 184°	674
	CO_2H			$CH_2CH_2C_6H_4NH_2(o)$	223	Et ester: m.p. 70°; *N*-acetyl: m.p. 212°; *N*-acetyl Et ester: m.p. 118–19°	674
	CO_2H			$CH{:}CHC_6H_4NH_2(o)$		dihydrochloride: >300°; Et ester: m.p. 242°; *N*-acetyl Et ester: m.p. 196–97°	674
	CO_2H			$CH{:}CHC_6H_4Br(o)$	235		674
	CO_2H			$CH{:}CHC_6H_4OH(o)$	282		674
	CO_2H			$CH_2CH_2C_6H_4OH(o)$	233		674
	CO_2H			CHO		Et ester phenylhydrazone: m.p. 161°	674
CH_3		CO_2H			292	Me ester: b.p. 139–43°/17 mm.; Et ester: b.p. 119–22°/17 mm.; amide: m.p. 163°; thioamide: m.p. 190°	67,355,675, 676,1080, 1094

$C_4H_9(i)$		CO_2H		Et ester: b.p. 146–47°/ 23 mm.;amide: m.p. 106°; thioamide: m.p. 153°	355,1080
$C_4H_9(tert)$		CO_2H		Me ester: b.p. 129–30°/ 23 mm.	355
C_2H_5		CO_2H	233–35	Me ester: b.p. 107–8/9 mm.; Et ester: b.p. 130–31°/23 mm.; amide: m.p. 131°; thioamide: m.p. 166°	355,677, 1080, 1094
C_3H_7		CO_2H		Me ester: b.p. 130–31°/ 20 mm.; amide: m.p. 135°; thioamide: m.p. 142°	355,1080
$C_3H_7(i)$		CO_2H		Me ester: b.p. 127–28°/ 25 mm.	355
C_6H_5		CO_2H	270–71	Et ester: m.p. 42–43°	355,672
COC_6H_5		CO_2H	225–30		835
3-quinolyl		CO_2H	290		842
	CH_3	CO_2H		Et ester: b.p. 120–22°/ 20 mm.	355,1094
	C_2H_5	CO_2H	216–17		684

TABLE X-6. Monalkyl or Aryl Pyridinepolycarboxylic Acids

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CO_2H	CO_2H	CH_3			190		480,679,680
CO_2H	CO_2H	C_6H_5			173–75	Me ester: m.p. 114.5–15.5°	681
CO_2H	CO_2H			$C_3H_7(n)$	142–43		49
CO_2H	CO_2H		C_6H_5			NH_4 salt: m.p. 230° (dec.) imide: m.p. 78–79°	958
CO_2H	CO_2H			C_6H_5	148–50		682
CO_2H	CH_3	CO_2H			216–17		480
CO_2H	o-$HO_2CC_6H_4$	CO_2H		C_6H_5	202		899
CO_2H		CO_2H	C_2H_5		241–42		904
CO_2H		CO_2H		CH_3	282 (> 330)	Me ester: m.p. 119°	67,675,683, 684,960
CO_2H		CO_2H		CCl_3		Me ester: m.p. 114–16°	108
CO_2H	CH_3		CO_2H		245–50		635,645
CO_2H	$C_3H_7(i)$		CO_2H		208		685
CO_2H		CH_3	CO_2H		237–45		35,686
CO_2H			CO_2H	CH_3	247		35
CO_2H		CH_3		CO_2H	248		686,960
CO_2H		$CH(CO_2H)_2$		CO_2H		tetra-Et ester: m.p. 70–72°	898
CO_2H		$C(C_2H_5)(CO_2H)_2$		CO_2H	250–55		898
CH_3	CO_2H	CO_2H			260–68	anhydride m.p. 118–9°	480,650,687
	CO_2H	CO_2H	C_6H_5		225–30		688
	CO_2H	CO_2H		CH_3	249–51	Et ester: b.p. 119–21°/0.5 mm.; Et ester hydrochloride: m.p. 90–93°; Me ester: m.p. 68–69°; amide: m.p. 215–20°, 273–78°; imide: m.p. 277–78°; imide 3-imine: m.p. 225–60° (dec.)	50,689
	CO_2H	CO_2H		C_6H_5	248–50	Me ester: m.p. 74°	690
CH_3	CO_2H		CO_2H		245–46	Me ester: m.p. 88°	589,646

$(CH_2)_3CO_2H$	CO_2H		CO_2H			tri-Me ester: b.p. 160–70°/0.01 mm.	951
	CO_2H	CH_3	CO_2H		282–84 (dec.)	Et ester: b.p. 115–20°/0.5 mm.; Et ester picrate: m.p. 117.5°	693,1108
	CO_2H	C_2H_5	CO_2H		261	Et ester: b.p. 126–27°/1 mm.	25,635,692,
	CO_2H	C_6H_5	CO_2H		245–46		646,1108
	CO_2H	$CH_2C_6H_5$	CO_2H			Et ester: b.p. 154–56°/0.3 mm.; Et ester picrate: m.p. 155–57°	1108
CO_2H	CO_2H	CO_2H		CH_3	230		650,693
CO_2H	CO_2H	CO_2H		C_6H_5	183–85		690
CO_2H	CO_2H	CH_3	CO_2H		204–5		646
CO_2H	CO_2H		CO_2H	CH_3	226	Me ester: m.p. 78–79°; Et ester: b.p. 160°/0.5 mm.; 2,3-di-Et ester; 5-amide: m.p. 140°	251,646,651
CO_2H	CO_2H		CO_2H	C_6H_5	256–57	3-amide: m.p. 295°	694
CO_2H	CO_2H	CH_3		CO_2H	238		51,695,696
CO_2H		CO_2H	CO_2H	CH_3	226	Me ester: m.p. 83–84°; 2-Me ester 4,5-imide: m.p. 176–77°	650,687,697
CO_2H	CH_3	CO_2H	CO_2H		208		698,699
CH_3	CO_2H	CO_2H	CO_2H			Me ester: m.p. 61–62°; Et ester: b.p. 157–60°/0.5 mm.; 3-mono-Me-4,5-di-Et ester: b.p. 140–43/5 mm.	739
CO_2H	CO_2H	CO_2H	CO_2H	CH_3		Me ester: m.p. 73°; Et ester: b.p. 190–92°/1 mm.; 2,3,4-tri-Et ester 5-amide: m.p. 117–117.5°; 2,3-di-Et ester 4,5-imide: m.p. 145–46°; 2-mono-Et ester 4,5-imide: m.p. 227–28°	697,700
CO_2H	CO_2H	CO_2H	CO_2H	C_6H_5		Me ester: m.p. 152°	901
CO_2H	CO_2H	CH_3	CO_2H	CO_2H	200 (dec.)		646,649,693
CO_2H	CO_2H	C_6H_5	CO_2H	CO_2H	205–207		646,691,701

TABLE X-7. Polyalkyl or Aryl Pyridinemonocarboxylic Acids

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CO_2H	CH_3		CH_3		157	Et ester: m.p. 45–46°, b.p. 120°/10 mm.; Et ester picrate: m.p. 111–12°	27,28,196, 635,702
CO_2H	C_6H_5		C_6H_5		155–56		958
CO_2H	CH_3			$C_3H_7(i)$	Oil		841
CO_2H	o-HO_2C-C_6H_4			CH_3	201		706
CO_2H	$COCH_3$		$COCH_3$	CH_3	139–40	Et ester: m.p. 96–97°	843
CO_2H	C_6H_5	C_6H_5		C_6H_5	166–68 (dec.)	Me ester: m.p. 117–18°	832,833
CO_2H		CH_3	CH_2OH			Et ester: m.p. 98–100°	855
CO_2H		C_2H_5	C_2H_5		147–48	Et ester: b.p. 140–45°/3 mm.; Et ester picrate: m.p. 88–90°; amide: m.p. 177–78°	839,949
CO_2H		CH_3		CH_3	157	Me ester: b.p. 133–35°/15 mm.; Et ester: b.p. 262–64°; amide: m.p. 113–14°; platinate: m.p. 221° dec.; methylamide: b.p. 168–70°/16 mm.; ethylamide: b.p. 160.5°/15 mm.	37,71,656, 702,703, 960
CO_2H		C_2H_5		CH_3	194–95		683
CO_2H		$C_3H_7(n)$		CH_3	60		704
CO_2H		C_6H_5		C_6H_5	150		705
CH_3	CO_2H	CH_3			158–60	Et ester: b.p. 246–48°; amide: m.p. 191°	707–709, 1094

CH_3	CO_2H		CH_3		185–86	Et ester: m.p. 27–28°, b.p. 255–57°; Et ester picrate: m.p. 143°	32,34,844
CH_3	CO_2H			CH_3	170–71	Et ester: b.p. 255–57°; Et ester picrate: m.p. 137–38°	34,695,710, 713,1094, 1105
CH_3	CO_2H			t-C_4H_9	137–38	Et ester: b.p. 180°/17 mm.	714
CH_3	CO_2H			C_6H_5	196	Et ester: m.p. 46–46.5°, b.p. 185°/13 mm.	714,715
CH_3	CO_2H			p-$CH_3C_6H_4$	207–8	Et ester: m.p. 54°; Et ester picrate: m.p. 33°	717
CH_2	CO_2H	CH_3	$COCH_3$			Et ester: m.p. 122–23°	837
CH_3	CO_2H	CH_3		CH_3	155	Et ester: b.p. 255–56°	695, 718, 1094
CH_3	CO_2H	C_7H_{15}		CH_3			903
CH_3	CO_2H	C_6H_5		CH_3	207	Et ester: b.p. 316–20°; amide: m.p. 198–99° hydrochloride: m.p. 248°	276,701, 719,756
CH_3	CO_2H	C_6H_5		C_6H_5	264	amide: m.p. 216°	826
CH_3	CO_2H	o-$O_2NC_6H_4$		CH_3		Et ester picrate: m.p. 172–73°	720
CH_3	CO_2H	m-$O_2NC_6H_4$		CH_3	263 (dec.)	Et ester: m.p. 57°; Et ester picrate: m.p. 160°	838
CH_3	CO_2H	p-$O_2NC_6H_4$		CH_3	274.5	Et ester picrate: m.p. 201–3°	838
CH_3	CO_2H	o-ClC_6H_4		C_6H_5	244		725

(*continued*)

TABLE X-7. Polyalkyl or Aryl Pyridinemonocarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CH_3	CO_2H	*p*-ClC_6H_4		C_6H_5	237–38		725
CH_3	CO_2H	*m*-ClC_6H_4		C_6H_5	247		725
CH_3	CO_2H	3,4-CH_2O_2-C_6H_3		CH_3	250		721
CH_3	CO_2H	*o*-$CH_3OC_6H_4$		CH_3		Et ester: b.p. 238°/30 mm.; sulfate: m.p. 170°	838
CH_3	CO_2H	*m*-$CH_3OC_6H_4$		CH_3	261 (dec.)	Et ester: b.p. 245°/40 mm.	838
CH_3	CO_2H	*p*-$CH_3OC_6H_4$		CH_3	230	Et ester: b.p. 218–19°/20 mm.; sulfate: m.p. 161–62°	721,838
CH_3	CO_2H	$CH{:}CHC_6H_5$		CH_3	253	Et ester: b.p. 240–45°/14 mm.	721–723
CH_3	CO_2H	$CH_2CH_2C_6H_5$		CH_3	183–86	Et ester picrate: m.p. 132–33°	721,724
CH_3	CO_2H	1-naphthyl		CH_3	265	Et ester: b.p. 264–66°/20 mm.	838
CH_3	CO_2H		CH_3	CH_3	217–18 (dec.)	Et ester: b.p. 134–36°/11 mm.; Et ester picrate: m.p. 157°; Et ester mercurichloride: m.p. 118.5°	717
CH_3	CO_2H		CH_3	C_2H_5	193–94	Et ester: b.p. 145°/10 mm.	831
CH_3	CO_2H		$COCH_3$	CH_3		Et ester: b.p. 133–43°/3 mm.	837

CH_3	CO_2H		CH_3	C_6H_5	140 (dec.)	Et ester: m.p. 59°; Et ester picrate: m.p. 146°	717
CH_3	CO_2H	4-quinolinyl	$COCH_3$	CH_3		Et ester: m.p. 113.5°–14.5°	726
CH_3	CO_2H	C_6H_5	$COCH_3$	CH_3	264	Et ester:m.p. 85–86°	727,838
CH_3	CO_2H	CH_3	COC_6H_5	CH_3		Et ester hydrochloride: m.p. 192°	728
o-$HOC_6H_4CH_2$-CH_2	CO_2H			C_6H_5CH:CH		lactone: m.p. 200–1°	1105
o-$HOC_6H_4CH_2$-CH_2	CO_2H			C_6H_5CHBr-CHBr		lactone: m.p. 236–38°	1105
CH_3	CO_2H			C_6H_5CH:CH	192–94	Et ester: m.p. 68–69°; Et ester HCl: m.p. 222–23°	1105
CH_3	CO_2H			C_6H_5CHBr-CHBr		Et ester: m.p. 138–39°	1105
2-HO-3-NO_2-$C_6H_4CH_2CH_2$	CO_2H			m-$NO_2C_6H_4$-CH:CH		lactone: m.p. 230–32°	1105
CH_3	CO_2H			m-$NO_2C_6H_4$-CH:CH	238–39	Et ester-HCl: m.p. 234–35	1105
	CO_2H	CH_3		C_6H_5CH:CH	249–51	Et ester-HCl: m.p. 203–4	1105
	CO_2H	C_6H_5CH:CH		C_6H_5CH:CH	233–34		1105
	CO_2H	m-$NO_2C_6H_4$-CH:CH		m-$NO_2C_6H_4$-CH:CH	330		1105
	CO_2H	CH_3		m-$NO_2C_6H_4$-CH:CH	298–300	Et ester-HCl: m.p. 211–12°; Et ester: m.p. 130–310°	1105
	CO_2H	CH_3	CH_3			Et ester: b.p. 89–91°/0.5 mm.; Et ester picrate: m.p. 100–1°	1108

(continued)

TABLE X-7. (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
	CO_2H	C_2H_5	CH_3			Et ester: b.p. 88–90/0.4 mm.; Et ester picrate: m.p. 130–1°	1108
	CO_2H	C_4H_9	CH_3			Et ester: b.p. 115–17°/0.4 mm.; Et ester picrate: m.p. 89°	1108
	CO_2H	CH_3	$CH{:}CH_2$		178–80		1090
	CO_2H	CH_3	C_2H_5		163–65		1089
	CO_2H	C_2H_5	C_2H_5		115–16		1089
	CO_2H	CH_3		CH_3		Et ester: b.p. 111–13°/5 mm.	1094
C_2H_5	CO_2H			C_2H_5		Et ester: b.p. 121–24°/7 mm.	1094
	CO_2H		CH_3	CH_3	195–97		34
	CO_2H		p-$CH_3OC_6H_4$	CH_3	254		716,844
	CO_2H	CH_3	CH_3	CH_3	257		693

CH_3		CO_2H		CH_3		Me ester: m.p. 45°; Et ester: m.p. 38–39, b.p. 68–73°/0.05 mm.	355,960, 1094
CH_3		CO_2H		t-C_4H_9	219	Et ester: b.p. 170–80°/14 mm.	714,729
C_6H_5		CO_2H		C_6H_5	278–79		730,825
CH_3		CO_2H		C_6H_5	272	Et ester: b.p. 194°/16 mm.	714
CH_3		CO_2H	CH_2NH_2			Et ester picrate: m.p. 170°	422
CH_3		CO_2H	C_2H_5		226–28	Me ester picrate: m.p. 114.2–15.5°; Et ester: b.p. 130–40°/20 mm.; Et ester picrate: m.p. 129–30°	355,949, 955
CH_3	$COCH_3$	CO_2H		CH_3	206–7	Et ester: m.p. 30–31°	731
CH_3	COC_6H_5	CO_2H		CH_3	255–58	Et ester: m.p. 66°	732
CH_3	$COCH_3$	CO_2H		C_6H_5	163–64.5	Et ester: m.p. 65–66°	1051
2-Picolyl		CO_2H	C_2H_5			thioamide: m.p. 106°	1080

TABLE X-8. Polyalkyl or Aryl Pyridinepolycarboxylic Acids

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CO_2H	CO_2H		$COCH_3$	CH_3	165–66 (dec.)	Et ester: m.p. 62–63°, b. p. 165–70°/0.5 mm.	651
CO_2H	CO_2H	CH_3	C_2H_5				889
CO_2H	CO_2H	C_6H_5		CH_3	100 (dec.)		733
CO_2H	CO_2H	C_6H_5		C_6H_5	185		860
CO_2H	CO_2H		CH_3	CH_3		imide dioxime: m.p. 293° (dec.)	985
CO_2H	CO_2H	CH_3	CH_3	CH_3	194–95		693
CO_2H	*o*-$HO_2CC_6H_4$	CO_2H		*o*-$O_2NC_6H_4$	287		902
CO_2H	*o*-$HO_2CC_6H_4$	CO_2H		*m*-$O_2NC_6H_4$	115		902
CO_2H	*o*-$HO_2CC_6H_4$	CO_2H		*p*-$O_2NC_6H_4$	170		902
CO_2H	*o*-$HO_2CC_6H_4$	CO_2H		C_6H_5	202	tri-Me ester: oil	899
CO_2H	$COCH_3$	CO_2H	$COCH_3$	CH_3		Et ester: m.p. 96–97°	697
CO_2H	CH_3		CO_2H	CH_3	238		32
CO_2H	$COCH_3$		CO_2H	CH_3	210–13 (dec.)	Et ester: m.p. 67–68°, b.p. 180–85°/2.5 mm.	843
CO_2H		CH_3	CO_2H	CH_3	245		695
CO_2H	C_2H_5		C_2H_5	CO_2H			60
CO_2H	$COCH_3$	CH_3		CO_2H	175		735
CH_3	CO_2H	CO_2H		CH_3	275	Et ester: m.p. 16°, b.p. 270°; amide: m.p. 210°; Me ester: m.p. 48°; imide: m.p. 230°	501,712, 736,737
CH_3	CO_2H	CO_2H		C_2H_5	258–59	Et ester: b.p. 140–45°/0.4–0.8 mm.	714,732
CH_3	CO_2H	CO_2H		$C_3H_7(n)$	212 (dec.)	Et ester: b.p. 174–76°/12 mm.	714,732
CH_3	CO_2H	CO_2H		$C_3H_7(i)$	210	Et ester: b.p. 178°/13 mm.; Et ester picrate: m.p. 116°	714,732

CH_3	CO_2H	CO_2H		C_4H_9(*tert*)	208	Et ester: b.p. 172°/13 mm.; 4-mono-Et ester: m.p. 105°; 3-mono-Et ester: m.p. 116°; anhydride: m.p. 75°	714,732
CH_3	CO_2H	CO_2H		C_6H_5	219	Et ester: m.p. 73°; 4-mono-Et ester: m.p. 185°; 3-mono-Et ester: m.p. 145°; 4-mono-amide: m.p. 199°; anhydride: m.p. 196°	714,1051
CH_3	CO_2H	CO_2H		$CH:CHC_6H_5$	220–21	Et ester picrate: m.p. 147.5–48°	897
o-HO_2C-C_6H_4	CO_2H	CO_2H		C_6H_5	250		738
	CO_2H	CO_2H	$COCH_3$	CH_3	230–32	Et ester: b.p. 147–48°/1 mm.; 3-mono-Et ester: m.p. 138–39°	697,739
CH_3	CO_2H	CH_3	CO_2H		260		646,693, 718,886
CH_3	CO_2H		CO_2H	CH_3	315–20	Et ester: m.p. 75–76°, b.p. 301–2°; amide: m.p. > 300°; bis-diethylamide: m.p. 82–83°, b.p. 236°/12 mm.; monoamide mono-Et ester: m.p. 159–60.5°	32,646, 740–743, 887,888, 967
CH_3	CO_2H		CO_2H	CF_3		Et ester: b.p. 115–17°/1 mm.; 3-amide: m.p. 167–68°; 3-amide 5-Et ester: m.p. 167–68°	251,651
C_6H_5	CO_2H		CO_2H	CH_3	211–12		694
C_6H_5	CO_2H		CO_2H	C_6H_5	283		694,721

(*continued*)

TABLE X-8. Polyalkyl or Aryl Pyridinepolycarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CH_3	CO_2H	CH_3	CO_2H	CH_3		Me ester: m.p. 142°, b.p. 285–87°; Et ester: b.p. 308–310°, m.p. 170–73°; Bis-*p*-sulfamylanilide: m.p. 260° (dec.)	505,649, 695,745, 746,890
C_6H_5	CO_2H	CH_3	CO_2H	C_6H_5	287–88	Et ester: m.p. 105–6°	725,747
CH_3	CO_2H	C_2H_5	CO_2H	CH_3	289–90	Et ester: b.p. 305–8°, 135–40°/0.5 mm.; Et ester picrate: m.p. 116°	740,749
CH_3	CO_2H	$C_3H_7(n)$	CO_2H	CH_3	247	Et ester: b.p. 308°/714.5 mm.; Et ester picrate: m.p. 90–91°	74,750
CH_3	CO_2H	$C_3H_7(i)$	CO_2H	CH_3		Et ester: b.p. 183°/11 mm.	751
CH_3	CO_2H	CH_2Cl	CO_2H	CH_3		Et ester: b.p. 197–98°/10 mm.	894
CH_3	CO_2H	CH_2I	CO_2H	CH_3		Et ester: m.p. 77–78°	894
CH_3	CO_2H	CH_2CN	CO_2H	CH_3		Et ester: m.p. 66–67°	911
CH_3	CO_2H	$CH:CHCH_3$	CO_2H	CH_3	205		752
CH_3	CO_2H	CH_2NH_2	CO_2H	CH_3		lactam: m.p. 300° (dec.); lactam Et ester: m.p. 168–69°	911
CH_3	CO_2H	$C_4H_9(i)$	CO_2H	CH_3	273	Et ester: b.p. 312–18°	740,750, 751
CH_3	CO_2H	$C_6H_{13}(n)$	CO_2H	CH_3		Et ester chloroplatinate: m.p. 141°	750
CH_3	CO_2H	$C_7H_{15}(n)$	CO_2H	CH_3			903
CH_3	CO_2H	$C_{13}H_{27}(n)$	CO_2H	CH_3		Et ester: b.p. 265°/10 mm.	748
CH_3	CO_2H	$C_{15}H_{31}(n)$	CO_2H	CH_3	61	hydrochloride: m.p. 123–24°; Et ester: b.p. 267–69°/10 mm.; Et ester hydrochloride: m.p. 88–89°; Et ester chloroplatinate: m.p. 120°	753

CH_3	CO_2H	$CH_2C_6H_5$	CO_2H	CH_3	257–58	Et ester: m.p. 47–48.5°, b.p. 199–200°	754
CH_3	CO_2H	$CH:CHC_6H_5$	CO_2H	CH_3	253	Et ester: m.p. 39°	721,722, 723
CH_3	CO_2H	$CH_2CH_2C_6H_5$	CO_2H	CH_3	208	Et ester: m.p. 34°	721,751
CH_3	CO_2H	C_6H_5	CO_2H	CH_3	296	Me ester: m.p. 139–40°; Et ester: m.p. 66°; mono-Et ester: m.p. 177–79°; mono-Et ester monoamide: m.p. 180–81°	276,701, 721,755, 756
CH_3	CO_2H	C_6H_5	CO_2H	C_6H_5	287–88		747
CH_3	CO_2H	o-$O_2NC_6H_4$	CO_2H	CH_3		Et ester: m.p. 92.5–93.5°; mono-Et ester: m.p. 216–17°	866,905
CH_3	CO_2H	m-$O_2NC_6H_5$	CO_2H	CH_3	65	Et ester: m.p. 63°; mono-Et ester: m.p. 220.5°	758,759, 838
CH_3	CO_2H	p-$O_2NC_6H_4$	CO_2H	CH_3		Et ester: m.p. 117°; mono-Et ester: m.p. 232°	759,838, 883,892
CH_3	CO_2H	m-HOC_6H_4	CO_2H	CH_3		Et ester: m.p. 202°; mono-Et ester: m.p. 279°	760,884
CH_2	CO_2H	p-HOC_6H_4	CO_2H	CH_3		Et ester: m.p. 171°	759
CH_3	CO_2H	o-$CH_3OC_6H_4$	CO_2H	CH_3	314	Et ester: m.p. 65°; mono-Et ester: m.p. 195–96°	760,884
CH_3	CO_2H	m-$CH_3OC_6H_4$	CO_2H	CH_3		Et ester: m.p. 82°; mono-Et ester: m.p. 195°	760,884
CH_3	CO_2H	p-$CH_3OC_6H_4$	CO_2H	CH_3	295–96	Et ester: m.p. 51–53°; mono-Et ester: m.p. 189.5–91.5°	721,759, 760,838
CH_3	CO_2H	o-ClC_6H_4	CO_2H	CH_3		Et ester: m.p. 62°	760
CH_3	CO_2H	m-ClC_6H_4	CO_2H	CH_3		Et ester: m.p. 53°	760
CH_3	CO_2H	p-ClC_6H_4	CO_2H	CH_3	274	Et ester: m.p. 67°	760,891

(*continued*)

TABLE X-8. Polyalkyl or Aryl Pyridinecarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CH_3	CO_2H	*p*-$H_2NC_6H_4$	CO_2H	CH_3	>360	Et ester: m.p. 146°	759,883
CH_3	CO_2H	*p*-$Me_2NC_6H_4$	CO_2H	CH_3		Et ester: m.p. 124.5°	970
CH_3	CO_2H	*p*-$H_3CC_6H_4$	CO_2H	CH_3		Et ester: b.p. 220°/20 mm.	884
CH_3	CO_2H	3,4-$(CH_3O)_2$-C_6H_3	CO_2H	CH_3		Et ester: m.p. 101–2°	884
CH_3	CO_2H	4-Me_2N-3-BrC_6H_3	CO_2H	CH_3		Et ester: m.p. 91°	761
CH_3	CO_2H	4-Me_2N-3-$NO_2C_6H_5$	CO_2H	CH_3		Et ester: m.p. 109°	761
CH_3	CO_2H	3,4-CH_2O_2-C_6H_3	CO_2H	CH_3		Et ester: m.p. 134°	721
CH_3	CO_2H	2-quinolyl	CO_2H	CH_3		Et ester: m.p. 91°	883
CH_3	CO_2H	3-quinolyl	CO_2H	CH_3		Et ester: m.p. 77°	883
CH_3	CO_2H	4-quinolyl	CO_2H	CH_3		Et ester: m.p. 122°	883
CH_3	CO_2H	5-quinolyl	CO_2H	CH_3		Et ester: m.p. 79°	883
CH_3	CO_2H	6-quinolyl	CO_2H	CH_3		Et ester: m.p. 97°	883
CH_3	CO_2H	furfuryl	CO_2H	CH_3		Et ester: m.p. 40–41°	966
CH_3	CO_2H	4-piperonyl	CO_2H	CH_3			900
CH_3	CO_2H	1-naphthyl	CO_2H	CH_3		mono-Et ester: m.p. 238–39°; Et ester: m.p. 58°	838
C_6H_5	CO_2H	C_6H_5	CO_2H	C_6H_5	297–98	Et ester: m.p. 149–50°	725,762
CO_2H	CO_2H	CO_2H	$COCH_3$	CH_3		Et ester: b.p. 190–92°/1 mm.	697
CO_2H	CO_2H	CH_3	CO_2H	CH_3	220	anhydride: m.p. 232° (dec.); imide: m.p. >300° (dec.); 2-Et ester: m.p. 100°; 2-amide: m.p. 240°; 2,3-di-Et ester: m.p. 107°	481,646, 693,893
CO_2H	CO_2H	$C_4H_9(i)$	CO_2H	CH_3	120	Me ester: b.p. 175°/4 mm.	24
CH_3	CO_2H	CO_2H	CO_2H	CH_3	220	3,5-di Et ester: m.p. 181°	722,896

TABLE X-9. Halopyridinecarboxylic Acids

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CO_2H	Cl				121 (dec.)	amide: m.p. 140°	368
CO_2H	I				137–38	hydroiodide: m.p. 188°	545
CO_2H		Cl			182	hydrochloride: m.p. 184–87°; acid chloride: m.p. 46°; Me ester: m.p. 57–58°; amide: m.p. 158°; azide: m.p. 92° (dec.)	173,312,368,371
CO_2H		I			169 (dec.)	Me ester: m.p. 75–76°; amide: m.p. 158°; azide: m.p. 89°	173,371
CO_2H			Cl		169–70	acid chloride: m.p. 94°; Me ester: m.p. 85–87°; amide: m.p. 200–1°; Ph ester: m.p. 92°	282,368
CO_2H			Br		175		282
CO_2H			I		204		282,530
CO_2H				F	135–37	Me ester: m.p. 53–54.5°; amide: m.p. 134–35°	533
CO_2H				Cl	190		766,784
CO_2H				Br	192–94	Me ester: m.p. 93–94°	93
CO_2H	NO_2		Cl			amide: m.p. 230°	252
CO_2H	NO_2		Br			amide: m.p. 232–33° (dec.)	252
CO_2H	Cl		Cl		153–54	Me ester: m.p. 82°; amide: m.p. 175–76°	545,785,811
CO_2H	Br		Br		144–45	Me ester: m.p. 96–97°; Ph ester: m.p. 65°; amide: m.p. 172°	545
CO_2H		Cl	Cl		180		368,783
CO_2H		I	Cl		159 (dec.)		368
CO_2H		Cl		Cl	111–12	Me ester: m.p. 73–74°; amide: m.p. 172–74°; Ph ester: m.p. 90–91°; azide: m.p. 74°; diaroylhydrazine: m.p. > 300°	173,219,368

(*continued*)

TABLE X-9. Halopyridinecarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CO_2H	Cl	Cl	Cl		164-65	acid chloride: m.p. 24-25°; Me ester: m.p. 84-85°; Et ester: m.p. 34-35°; amide: m.p. 185°; Ph ester: m.p. 93-94°	545,812
CO_2H	Br	Cl	Br		163-64 (dec.)	Me ester: m.p. 105°; amide: m.p. 194°	545
CO_2H	I	Cl	I			Me ester: m.p. 106°	545
CO_2H	Br		Br	Br	144.5-45.0		536
CO_2H		Cl	Cl	Cl	123	acid chloride: m.p. 70°; Me ester: m.p. 125°; amide: m.p. 169°; Ph ester: m.p. 138°	368
CO_2H		CH_3		Cl	98		786,816
CO_2H		Cl		CH_3	93-94		817
F	CO_2H				164-65	Me ester: m.p. 74-75°; amide: m.p. 124°; diethylamide: b.p. 131°/2 mm.; 2-thiazolyamide: m.p. 159°; dicyandiamide: m.p. 191°	532,547,1009
Cl	CO_2H				194	acid chloride: m.p. 56°; amide: m.p. 164-65°; anilide: m.p. 125°; *p*-phenetidide: m.p. 115°; Me ester: b.p. 87-88°/3 mm.	245,529,535,544, 851,965,1055
Br	CO_2H				249.1-50.4°	Me ester: m.p. 107.2-108.3°, b.p. 95-97°/1.4 mm.; amide: m.p. 171-72/260°	552
	CO_2H	Cl			164	hydrochloride: m.p. 200-1°	245,1083
	CO_2H		F		195-97	Me ester: m.p. 48°; amide: m.p. 173-75°	531,547,787
	CO_2H		Cl		171	acid chloride: m.p. 53°; Me ester: m.p. 88-89°; amide: m.p. 205-6°; Ph ester: m.p. 79°	173,176,549,788

	CO_2H		Br		182–83	acid chloride: m.p. 75°; Me ester: m.p. 98–99°; Et ester: m.p. 42°; amide: m.p. 218°; diethylamide: b.p. 189°/12 mm.; Ph ester: m.p. 86–87°; azide: m.p. 88–89°(dec.), diaroylhydrazine: m.p. 308°	93,176,549,967
	CO_2H		I		220	Ph ester: m.p. 100–1°; Me ester: m.p. 121°; Et ester: m.p. 86–87°; amide: m.p. 221–22°	777
	CO_2H			F	146–47	diethylamide: b.p. 136°/3 mm.; 2-thiazolyamide: m.p. 249°; amide: m.p. 166.2–67.0°; 2-pyrimidylamide: m.p. 173°; 2-pyridylamide: m.p. 146°	532,1009
	CO_2H			Cl	199	Me ester: m.p. 86–89°; amide: m.p. 213.5–14.2°; acid chloride: m.p. 49–51°; anilide: m.p. 171–72°	406,450,552,789, 813,965,1007
	CO_2H			Br	193.0–93.9	Me ester: m.p. 108.5–10°, b.p. 107–10°/4 mm.	552
	CO_2H			I	189–90		550
Cl	CO_2H	Cl				amide: m.p. 181–82°	284
Cl	CO_2H			Cl	144		814
	CO_2H	Cl		Cl	152–53	Et ester: m.p. 31.5–32°	620
	CO_2H		Cl	Cl	168	acid chloride: m.p. 48–49°; Me ester: m.p. 67–68°; amide: m.p. 218–20°; diethylamide: b.p. 191–92°/12 mm.	173,219,777,788, 790,967
	CO_2H		NO_2	Cl	126.5–27.5	Me ester: m.p. 86°; Et ester: m.p. 61°	791,1065
	CO_2H		NO_2	Br		Me ester: m.p. 98°; Et ester: m.p. 85°	791
	CO_2H	Cl	Cl	Cl		Et ester: m.p. 34°	620

(*continued*)

TABLE X-9. Halopyridinecarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CH_3	CO_2H	CH_3		Cl	148	Et ester: b.p. 288–90°, 97–105°/2 mm.	479,792
CH_3	CO_2H	Cl		CH_3	183	Et ester: b.p. 263–64°	795–797,817
CH_3	CO_2H		CH_3	Cl		Et ester: m.p. 45°	844
Cl	CO_2H		NO_2	CH_3	261–62		141
CH_3	CO_2H		I			Et ester: m.p. 92.5–93.5°	798
CH_3	CO_2H			Cl		Et ester: m.p. 41–42°	799
CH_2Br	CO_2H			Cl		Et ester: b.p. 95–103°/0.2 mm.	799
Cl	CO_2H			$C_3H_7(n)$		Et ester: b.p. 80–90°/0.005 mm.	793
C_2H_5	CO_2H	Cl		C_2H_5		Et ester: b.p. 109–12°/2 mm.	1094
Cl	CO_2H			$CH(CH_3)_2$		Et ester: b.p. 109–14°/1 mm.	1094
Cl	CO_2H			$CHCH_2 \cdot (CH_3)_2$		Et ester: b.p. 120–26°/0.5 mm.	1094
F		CO_2H			195–97	Me ester: b.p. 91°/13 mm.; amide: m.p. 173–74°	533
Cl		CO_2H			245	acid chloride: b.p. 101°/10 mm.; Me ester: m.p. 30–31°, b.p. 84–88°/15 mm.; azide: m.p. 46–47°	800,818, 1032
Cl		CO_2H		$C_3H_7(n)$	108	Me ester: b.p. 150–53°/16 mm.	355,1080
Cl		CO_2H		$C_3H_7(i)$		Me ester: b.p. 80–83°/0.04 mm.	355
Cl		CO_2H		CH_3	214	Me ester: m.p. 60–61°	355,786,801,816
Cl		CO_2H		C_4H_9 (*tert*)		Me ester: m.p. 60–61°	355
Cl		CO_2H		C_6H_5		Et ester: m.p. 89°	355
Cl		CO_2H		C_2H_5	136–37	Et ester: b.p. 82–90°/0.2 mm.; Me ester: b.p. 104–5°/2.5 mm.	154,355,1094
Cl		CO_2H		$C_4H_9(i)$		Et ester: b.p. 105–10°/0.6 mm.	355
	F	CO_2H			256–57 (dec.)	Et ester: b.p. 215°/752 mm.; Et ester picrate: m.p. 110°	885
	Cl	CO_2H			235	Me ester: m.p. 32°	173
	I	CO_2H			244–44.5°		479,534,1011

	I	CO_2H	I		231–32		1101
Cl		CO_2H		Cl	210	acid chloride: m.p. 25–27°, b.p. 243–46°/760 mm.; Me ester: m.p. 82°; Et ester: m.p. 65–66°; amide: m.p. 207–8°	219,802,804, 1103
Br		CO_2H		Br	184–85	acid chloride: b.p. 256–58°; amide: m.p. 202–4°	803,804, 1092
I		CO_2H		I	195–96		803
	Cl	CO_2H	Cl		223–24		173,545
Cl	Cl	CO_2H	Cl		188–89		815
Cl	Cl	CO_2H	Cl	Cl	224–25	acid chloride: m.p. 47–48°; Et ester: m.p. 66–67°; amide: m.p. 235–36°	803
CO_2H	CO_2H	Cl			173	2-amide: m.p. 148–50°; anhydride: m.p. 200–2°	284
CO_2H	CO_2H		Br		165		819,820
CO_2H	CO_2H	CH_3		Cl	183–84		805
CO_2H	CO_2H	Cl	Cl	Cl	190–91		806
CO_2H	CO_2H	CH_3	C_2H_5	Cl			889
CO_2H	I			CO_2H	163		962
CO_2H		Cl		CO_2H	220 (ca.)	Et ester: m.p. 92–94°; Me ester: m.p. 142–43°	686,817,1082 1103
CO_2H		I		CO_2H	208	Me ester: m.p. 168°; amide: m.p. 297°	545
CO_2H	Cl	Cl	Cl	CO_2H	150 (dec.)	Et ester: m.p. 35°	541
CO_2H	Br	Br	Br	CO_2H	180 (dec.)	Et ester: m.p. 67°	541
CO_2H	I	Cl	I	CO_2H	232 (dec.)	Me ester: m.p. 144°; Et ester: m.p. 111°	541,545,942
CO_2H	I	Br	I	CO_2H	186 (dec.)	Et ester: m.p. 98–99°	541
CO_2H	I	I	I	CO_2H	242 (dec.)		942
	CO_2H	CO_2H	Br		236–37	Me ester: m.p. 75.5–76.5°	538

(*continued*)

TABLE X-9. Halopyridinecarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
Cl	CO_2H	CO_2H		CH_3	205	Me ester: m.p. 85°	256
Cl	CO_2H		CO_2H	Cl	230	Et ester: m.p. 75–76°	807
CH_3	CO_2H	Cl	CO_2H	CH_3	224		808
CO_2H	CO_2H	CO_2H		Cl	212	3-Et ester: m.p. 169°	809
CO_2H	Br	CO_2H	Br	CO_2H	204–6		810

TABLE X-10. Nitropyridinecarboxylic Acids

Substituent and position					M.p., °C.	Ref.
2	3	4	5	6		
CO_2H	NO_2				105; amide: 211	252,553
CO_2H		NO_2			152	553
CO_2H			NO_2		211–12; amide: 246–47	248,553
CO_2H				NO_2	168	553
NO_2	CO_2H				156	553
	CO_2H	NO_2			120	553
	CO_2H		NO_2		172	553
	CO_2H			NO_2	183	553
NO_2		CO_2H			175; Me ester: 80–81	553,1040
	NO_2	CO_2H			222	553
CO_2H	NO_2		Cl		amide: 230	252
CO_2H	NO_2		Br		amide: 232 (dec.)	252
CO_2H		CH_3	NO_2	CH_3	136	806
CO_2H	CH_3		NO_2	CH_3	166	961
Cl	CO_2H		NO_2	CH_3	261–62	141
	CO_2H		NO_2	Cl	Me ester: 76; Et ester: 61	791
	CO_2H		NO_2	Br	Me ester: 98; Et ester: 85	791
Cl	CN	CO_2H	NO_2	CH_3	Et ester: 61–62	616,862,864

TABLE X-11. Aminopyridlinecarboxylic Acids

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CO_2H	NH_2				210	amide: m.p. 184°; *N*-NO_2: m.p. 178-80°; Et ester of sulfanilyl derivative: m.p. 182°; amide of sulfanilyl derivative: m.p. 205°; 2-nitroethylidene derivative: m.p. 255°; Et ester: m.p. 132°; amide picrate: m.p. 214°	283,506, 763,764, 1001, 1010, 1027,1068
CO_2H	NH_2		CH_3		205		1085
CO_2H	NH_2		Cl			amide: m.p. 168°	252
CO_2H	NH_2		Br			amide: m.p. 168°	252
CO_2H	NH_2		NO_2		233		765
CO_2H	$NHCH_2$-COOH				245 (dec.)		568
CO_2H		NH_2			260	hydrochloride: m.p. 240° (dec.); Me ester: m.p. 129°	173
CO_2H		1-piperidino			219 (dec.)	hydrochloride: m.p. 225° (dec.); hydroiodide: m.p. 200–210° (dec.); Me ester: m.p. 52–53°	968
CO_2H	Cl	NH_2	Cl		172		821
CO_2H			NH_2		218–19	Et ester: m.p. 131–32°	248
CO_2H				NH_2	315		766

NH_2	CO_2H				310	hydrochloride: m.p. 214–16°; picrate: m.p. 229–30°; acid chloride: m.p. 110° (dec.); Me ester: m.p. 85°; Et ester: m.p. 94–96°; amide: m.p. 199°; *N*-NO_2; m.p. 180° Et ester picrate: m.p. 199°; *N*-benzenesulfonyl: m.p. 178°	216,245, 257,270, 567,763, 767–772, 779,974, 1068
NH_2	CO_2H	CH_3		CH_3	258	picrate: m.p. 227–28°; Et ester: m.p. 110°; amide: m.p. 156.6°; Et ester picrate: m.p. 163°	771,772, 1107
NH_2	CO_2H	Cl			173		578
NH_2	CO_2H		NO_2		318		770
NH_2	CO_2H			CH_3	298 (dec.)	Et ester: m.p. 84°; b.p. 140°/15 mm.; amide: m.p. 220°; Et ester picrate: m.p. 185–86°; amide picrate: m.p. 253–54°	771,772
NH_2	CO_2H			C_6H_5	243	picrate: m.p. 189–90°; Et ester: m.p. 108°; amide: m.p. 220–21°; Et ester picrate: m.p. 201–2°; amide picrate: m.p. 229–30°	771,772
NHPh	CO_2H				154–56		556, 1004

(*continued*)

TABLE X-11. Aminopyridinecarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
NHC_6H_4-OMe-*p*	CO_2H				295		556
NH_2	CO_2H		CH_3	CH_3		amide: m.p. 230–31°; amide picrate: m.p. 269–70°	771,1042, 1107
NH_2	CO_2H	CH_2OCH_3		CH_3		amide: m.p. 128–30°	1042
NHC_6H_5	CO_2H	CH_3		CH_3		amide: m.p. 136–37°	1042
NHC_6H_5	CO_2H	CH_2OCH_3		CH_3		amide: m.p. 123–24°	1042
NH_2	CO_2H	CH_3		CH_3		N-phenylamide: m.p. 207–208°	1042
NH_2	CO_2H	CH_3	CH_3	CH_3	118	Et ester: m.p. 130°; Et ester hydrochloride: m.p. 171°; amide: m.p. 208–9°	1088
NH_2	CO_2H	CH_3	Br	CH_3	112	amide: m.p. 170–71	1088
NH_2	CO_2H	CH_3		C_6H_5	267	Et ester: m.p. 129°; amide: m.p. 227°; hydrochloride: m.p. 171–72°; Et ester hydrochloride: m.p. 205° (dec.)	771
$NHCH_2$-CO_2H	CO_2H				218–19 (dec.)		983
	CO_2H	NH_2			338–41	Me ester: m.p. 173°; Et ester: m.p. 109–111°; amide: m.p. 229.5–30.5°	245,285, 479,769

	CO_2H	NHC_6H_4-(OCH_3)-*p*			290–91		479
	CO_2H		NH_2		292–94	Me ester: m.p. 137°	173,176, 531,549
CH_3	CO_2H	NHC_6H_5		CH_3	244–45	hydrochloride: m.p. 167–68°	479
CH_3	CO_2H	NHC_6H_4-(OCH_3)-*p*		CH_3	271–272	Et ester: m.p. 92–93°	479
CH_3	CO_2H	$NHC_{10}H_7$-2		CH_3	263–63		479
CF_3	CO_2H		NH_2	CH_3	215–16 (dec.)		773
CH_3	CO_2H	$NHCH_2CO_2H$		CO_2H	184	anhydride: m.p. 100–101°; anhydride hydrochloride: m.p. 221°;	973
CH_3	CO_2H	6-methoxy-8-quinolylamino		CH_3		Et ester: m.p. 149–50°; Et ester hydrochloride: m.p. 247–48°	479
CH_3	CO_2H	C_6H_5	NH_2	CH_3		Et ester: m.p. 124.5–25.5°; *N*-Bz: m.p. 276–77° (dec.); *N*, *N*-Ac_2: m.p. 240–41°	276
	CO_2H			NH_2	312 (dec.)	HNO_3: m.p. 242°; Et ester: m.p. 155° *N*-NO_2: m.p. 233° (dec.); *N*,*N*-diMe: m.p. 220–22°; amide: m.p. 243–44° (312°); Et ester HCl: m.p. 194–95°	41,100,246, 404,774–776,790, 1007, 1059
	CO_2H			p-$NO_2C_6H_4$-SO_2NH		amide: m.p. 184–85°	991

(*continued*)

TABLE X-11. Aminopyridinecarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
	CO_2H			*p*-$NH_2C_6H_4$-SO_2NH		amide: m.p. 203°	991
	CO_2H			EtNH		Et ester hydrochloride: m.p. 191–92°	992
	CO_2H			Et_2N		diethylaminoethyl ester monohydrochloride: m.p. 118–21°	992
	CO_2H			PrNH		dimethylaminoethyl ester monohydrochloride: m.p. 112–14°	992
						diethylaminoethyl ester dihydrochloride: m.p. 170–172°	992
	CO_2H			BuNH		Et ester: m.p. 77–78°; Et ester hydrochloride: m.p. 166–67°; diethylaminoethyl ester: m.p. 31–32°; diethylaminoethyl ester monohydrochloride: m.p. 118–21°; dihydrochloride: m.p. 198–201°; piperidinoethyl ester monohydrochloride: m.p. 167–68°	992
	CO_2H			$NH_2(C_6H_4$-*p*$)SO_2(C_6H_4$-*p*$)NH$	228°		1028
	CO_2H		Cl	NH_2	323 (dec.)	Me ester: m.p. 163–65°	777

	CO_2H		NO_2	NH_2	300–1 (dec.)		404
	CO_2H		NH_2	NH_2	300		404,774
	CO_2H		Cl	$NHNH_2$	248–49	Et ester: m.p. 137–38°	777
NH_2		CO_2H			300–50 (dec.)	Me ester: m.p. 149.5–51°; Et ester: m.p. 25°	380,1040, 1062
NH_2		CO_2H		Cl			803
	NH_2	CO_2H			319–20	*N*-acetyl derivative: m.p. 266–67°; dihydrochloride: m.p. 244–45°; Me ester: m.p. 86–87°; Et ester: m.p. 64–66°; amide: m.p. 151–52°; *i*-Pr ester: m.p. 78–79°; *i*-Pr ester hydrochloride: m.p. 185.5° (dec.); *N*-acetyl Me ester: m.p. 78.5–80.5°; *N*-carbamyl derivative: m.p. > 300°; *N*-NO_2: m.p. 202–4°	286,479, 498,743, 764,769, 778
	2-carboxy-4-methoxyanilino	CO_2H			317–19 (dec.)		479
	$N(C_6H_4$-OMe-$p)_2$	CO_2H			239–40		479
	NHC_6H_5	CO_2H			305–306 (dec.)		479
	NHC_6H_4-OMe-p	CO_2H			310–12 (dec.)		479

(*continued*)

TABLE X-11. Aminopyridinecarboxylic Acids (*continued*)

Substituent and position					M.p., °C.	Derivatives	Ref.
2	3	4	5	6			
CH_3	NH_2	CO_2H	CH_2NH_2		280 (dec.)	Et ester: m.p. 183° (dec.); lactam: m.p. 260°; lactam hydrochloride: m.p. 290° (dec.)	616,780
CH_3	NH_2	CO_2H		CH_3	295	hydrochloride: m.p. 253–54°; Me ester: m.p. 61°	355,501
CH_3		CO_2H	NH_2		> 290 (dec.)	Me ester: m.p. 150–55°	779
NH_2		CO_2H		NH_2		Me ester: m.p. 173°; amide: m.p. 256°	822
CO_2H	CO_2H		NH_2	CH_3	241–43	Me ester: m.p. 88–88.5°; Et ester: m.p. 86.5–87°	773
CO_2H		CO_2H	NH_2	CH_3	270–71	Me ester: m.p. 110–10.5° (dec.)	697
CO_2H		NH_2	CO_2H	CH_3	270–71 (dec.)	Me ester: m.p. 136.5–37°	697

CO_2H		NH_2		CO_2H	297	Et ester: m.p. 149–51°; *N*-Me: m.p. 245–55° (dec.); *N,N*-diMe: m.p. 248° (dec.); *N*-4-pyridyl: m.p. 255° (dec.); *N*-(2,6-dicarboxy-4-pyridyl) m.p. 272° (dec.)	555,781
	CO_2H	CO_2H	NH_2		223–24		538
	CO_2H	CO_2H	NH_2	CH_3	241–42	Me ester: m.p. 94–95°	50,739,862, 1053
CH_3	CO_2H	NH_2	CO_2H	CH_3	263		774
CH_3	CO_2H	CH_3	CO_2H	NH_2	242		782
CO_2H	CO_2H	CO_2H	NH_2	CH_3	235–40 (dec.)	Me ester: m.p. 132.5–35.5°; 2,3-di Et ester: m.p. 100–102°	697,773
	CH_2NH_3	CO_2H		CH_3		Et ester picrate: m.p. 170° (dec.); lactam: m.p. 250°; lactam hydrochloride: sublimes > 258°; lactam picrate: m.p. 205.5°	256,855

Acknowledgment. I wish to express my appreciation to Miss Margaret Sherlock for reading the manuscript and offering much helpful advice.

J. BIBLIOGRAPHY

1. Black, Depp, and Corson, *J. Org. Chem.*, **14**, 14 (1949).
2. Bengtsson, *Acta Chem. Scand.*, **9**, 832 (1955).
3. U.S. patent 2,522,163, Cislak and Wheeler, Sept. 12, 1950.
4. U.S. patent 2,449,906, Mueller, Dec. 21, 1948.
5. U.S. patent 2,513,099, Mueller, June 27, 1950.
6. U.S. patent 2,513,251, Porter, Bumpus, and Cosby, June 27, 1950.
7. Henze, *Ber.*, **67**, 750 (1934).
8. Woodward, Badgett, and Kaufman, *Ind. Eng. Chem.*, **36**, 544 (1944).
9. Spanish patent 202,450, May 28, 1952.
10. French patent 976,594, March 20, 1951.
11. U.S. patent 2,437,938, Cislak and Wheeler, March 16, 1948.
12. Ishiguro and Utsumi, *J. Pharm. Soc. Japan*, **72**, 709 (1952); through *C.A.*, **47**, 2174 (1953).
13. Rubtsov, Nikitskaya, and Yanina, *Zhur. Obshcheĭ Khim.*, **24**, 1648 (1954).
14. Cook and Yunghans, *J. Am. Chem. Soc.*, **74**, 5515 (1952).
15. Jerchel, Bauer, and Hippchen, *Chem. Ber.*, **88**, 156 (1955).
16. Mariella, *J. Am. Chem. Soc.*, **69**, 2670 (1947).
17. Laiblin, *Ann.*, **196**, 129 (1879).
18. Weidel, *Ann.*, **165**, 328 (1873).
19. McElvain and Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923).
20. Weijlard, *J. Am. Chem. Soc.*, **67**, 1031 (1945).
21. Matveev, *J. Gen. Chem. U.S.S.R.*, **17**, 482 (1947); through *C.A.*, **42**, 571 (1948).
22. Tronov and Kikonova, *J. Russ. Phys. Chem. Soc.*, **61**, 541 (1929).
23. Chichibabin, *Ber.*, **37**, 1373 (1904).
24. Cardani, Bassarov, and Piozzi, *Atti accad. nazl. Lincei. Rend. Classe sci. fis. mat. e nat.*, **13**, 257 (1952); through *C.A.*, **48**, 4534 (1954).
25. Chichibabin and Oparina, *J. Russ. Phys. Chem. Soc.*, **54**, 428 (1922); through *C.A.*, **18**, 2495 (1924).
26. Altar, *Ann.*, **237**, 182 (1886).
27. Späth and Galinovsky, *Ber.*, **69**, 761 (1936).
28. Späth and Galinovsky, *Ber.*, **66**, 1338 (1933).
29. Efimovsky and Rumpf, *Bull. soc. chim. France*, **1954**, 648.
30. Japanese patent 2730, Tanabe and Arai, June 16, 1953; through *C.A.*, **49**, 2523 (1955).
31. Michael, *Ann.*, **225**, 121 (1921).

32. Oparina, *Zhur. Obshcheĭ Khim.*, **19**, 1351 (1949); through *C.A.*, **44**, 1108 (1950).
33. Oparina, *Ber.*, **64**, 569 (1931).
34. Oparina, *J. Russ. Phys. Chem. Soc.*, **61**, 2001 (1929); through *C.A.*, **24**, 3790 (1930).
35. Oparina, *Ber.*, **64**, 562 (1931).
36. Forsyth and Pyman, *J. Chem. Soc.*, **1926**, 2912.
37. Häring, Prijs, and Erlenmeyer, *Helv. Chim. Acta*, **37**, 147 (1954).
38. Solomon, *J. Chem. Soc.*, **1946**, 934.
39. Stix and Bulgatsch, *Ber.*, **65**, 11 (1932).
40. Kulka, *J. Am. Chem. Soc.*, **68**, 2472 (1946).
41. Caldwell, Tyson and Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).
42. U.S. patent 2,436,660, Mueller, Feb. 24, 1948.
43. Bachman and Barker, *J. Org. Chem.*, **14**, 97 (1949); *cf.* van de Kamp and Sletzinger, U.S. patent 2,392,437.
44. Lindenstruth and VanderWerf, *J. Am. Chem. Soc.*, **71**, 3020 (1949).
45. Sucharda, *Ber.*, **58**, 1727 (1925).
46. Skrowaczewska, *Rocznicki Chem.*, **22**, 134 (1948); through *C.A.*, **44**, 3494 (1950).
47. Sadykov, Otroshchenko, and Yusupov, *Zhur. Obschcheĭ Khim.*, **23**, 968 (1953); through *C.A.*, **48**, 7617 (1954).
48. Koelsch and Steinhauer, *J. Org. Chem.*, **18**, 1516 (1953).
49. Šorm and Sicher, *Collection Czechoslov. Chem. Communs.*, **14**, 331 (1949); through *C.A.*, **44**, 1505 (1950).
50. Jones and Kornfeld, *J. Am. Chem. Soc.*, **73**, 107 (1951).
51. Kruber and Rappen, *Chem. Ber.*, **81**, 483 (1948).
52. U.S. patent 2,505,568, Mueller, April 25, 1950.
53. U.S. patent 2,586,555, Mueller, Feb,. 19, 1952.
54. U.S. patent 2,475,969, Larrison, July 12, 1949.
55. Jordan, *Ind. Eng. Chem.*, **44**, 332 (1952).
56. Lochte, Barton, Roberts and Bailey, *J. Am. Chem. Soc.*, **72**, 3007 (1950).
57. Urbanski, *J. Chem. Soc.*, **1947**, 132.
58. Urbanski, *J. Chem. Soc.*, **1946**, 1104.
59. Heyns and Vogelsang, *Chem. Ber.*, **87**, 13 (1954).
60. Prostenik and Filipovic, *Arkiv. Kem.*, **21**, 175 (1949); through *C.A.*, **45**, 8520 (1951).
61. Murahashi and Otuka, *Mem. Inst. Sci. Ind. Research Osaka Univ.*, **7**, 127 (1950); through *C.A.*, **45**, 9054 (1951).
62. Japanese patent 2720, Murahashi and Otuka, May 26, 1951; through *C.A.*, **47**, 4919 (1953).
63. Japanese patent 2734, Tanabe and Arai, June 16, 1953; through *C.A.*, **49**, 2523 (1955).
64. Jones, *J. Am. Chem. Soc.*, **73**, 5610 (1951).
65. Clemo and Metcalfe, *J. Chem. Soc.*, **1937**, 1523.
66. Clemo and Hoggarth, *J. Chem. Soc.*, **1941**, 41.

67. Efimovsky and Rumpf, *Bull. soc. chim. France,* **1954,** 648.
68. Searles and Warren, *J. Org. Chem.,* **18,** 1317 (1953).
69. Rabe, Spreckelsen, Wilhelm, and Hoter, *J. prakt. Chem.,* **151,** 65 (1938).
70. Kondo and Takahashi, *J. Pharm. Soc. Japan,* **487,** 775 (1922); through *C.A.,* **17,** 1473 (1923).
71. Takahashi, *J. Pharm. Soc. Japan,* **49,** 1048 (1929); through *C.A.,* **24,** 1380 (1930).
72. Brand and Reuter, *Ber.,* **72,** 1668 (1939).
73. Siddiqui and Khan, *J. Indian Chem. Soc.,* **16,** 415 (1939).
74. Siddiqui, Usmani, and Ali, *J. Indian Chem. Soc.,* **21,** 245 (1944); through *C.A.,* **39,** 2997 (1945).
75. Kaslow and Stayner, *J. Am. Chem. Soc.,* **67,** 1716 (1945).
76. Plattner, Keller, and Boller, *Helv. Chim. Acta,* **37,** 1379 (1954).
77. Huff and Perlzweig, *J. Biol. Chem.,* **155,** 345 (1944).
78. Harris, Heyl, and Folkers, *J. Am. Chem. Soc.,* **66,** 2088 (1944).
79. Stiller, Keresztesy, and Stevens, *J. Am. Chem. Soc.,* **61,** 1237 (1939); U.S. patent 2,380,478, July 31, 1945.
80. Mathes, Sauermilch, and Klein, *Chem. Ber.,* **86,** 584 (1953).
81. Wibaut, Kooyman, and Boer, *Rec. trav. chem.,* **64,** 30 (1945).
82. Eistert, *Bull. soc. chim. France,* **1955,** 288.
83. Eistert and Munder, *Chem. Ber.,* **88,** 226 (1955).
84. Mathes, Sauermilch, and Klein, *Chem. Ber.,* **84,** 452 (1951).
85. Adams and Schrecker, *J. Am. Chem. Soc.,* **71,** 1186 (1949).
86. Kegelman and Brown, *J. Am. Chem. Soc.,* **75,** 4649 (1953).
87. Chichibabin and Kirssanow, *Ber.,* **57,** 1161 (1924).
88. Bojarska-Dahlig and Urbanski, *Prace Placówek Nauk-Badawcz. Ministerstiva Przemyslu Chem.,* **1952** (No. 1), 1; through *C.A.,* **48,** 1337 (1954).
89. Talik and Talik, *Acta Polon. Pharm.,* **11,** 71 (1954); through *C.A.,* **49,** 8273 (1955).
90. Gilman and Spatz, *J. Am. Chem. Soc.,* **62,** 446 (1940).
91. Murray, Foreman, and Langham, *Science,* **106,** 277 (1947).
92. Adamson and Billinghurst, *J. Chem. Soc.,* **1950,** 1039.
93. Gilman and Spatz, *J. Org. Chem.,* **16,** 1485 (1951).
94. Beher, Holliday and Gaebler, *J. Biol. Chem.,* **198,** 573 (1952).
95. Murray and Langham, *J. Am. Chem. Soc.,* **74,** 6289 (1952).
96. Gilman and Melstrom, *J. Am. Chem. Soc.,* **68,** 103 (1946).
97. Benary and Psille, *Ber.,* **57,** 828 (1924).
98. Nienburg, *Ber.,* **67,** 874 (1934).
99. Huntress and Walter, *J. Am. Chem. Soc.,* **70,** 3702 (1948).
100. Chichibabin and Knunjanz, *Ber.,* **62,** 3048 (1929).
101. Porter, *J. Am. Chem. Soc.,* **76,** 127 (1954).
102. Emmert and Groll, *Chem. Ber.,* **86,** 208 (1953).
103. Emmert and Holz, *Chem. Ber.,* **87,** 676 (1954).
104. Dyson and Hammick, *J. Chem. Soc.,* **1939,** 781.

105. Ochiai and Okuda, *J. Pharm. Soc. Japan,* **70,** 156 (1950); through *C.A.,* **44,** 5878 (1950).
106. U.S. patent 2,670,352, Fand and Lutomski, Feb. 23, 1954.
107. U.S. patent 2,515,593, Engel and Hoog, July 18, 1950.
108. Graf and Zettl, *J. prakt. Chem.,* **147,** 188 (1936).
109. Preobrazhenskii and Beer, *J. Gen. Chem. U.S.S.R.,* **15,** 667 (1945); through *C.A.,* **40,** 5724 (1946).
110. Brown, Hammick, and Thewlis, *J. Chem. Soc.,* **1951,** 1145.
111. Wawzonek, Nelson, and Thelen, *J. Am. Chem. Soc.,* **74,** 2894 (1952).
112. van Dorp and Arens, *Rec. trav. chim.,* **66,** 189 (1947).
113. Sacconi, *Ann. chim. (Rome),* **40,** 386 (1950); through *C.A.,* **45,** 9053 (1951).
114. Chylik and Tamchyma, *Chem. zvesti,* **4,** 282 (1950); through *C.A.,* **45,** 6348 (1951).
115. Lukeš and Jurecek, *Collection Czechoslov. Chem. Communs.,* **13,** 131 (1948); through *C.A.,* **42,** 8102 (1948).
116. Maier-Bode and Altpeter, *Das Pyridin und seine Derivate,* Wilhelm Knappe Halle, Saale, 1934, p. 213.
117. Clemo and Ramage, *J. Chem. Soc.,* **1931,** 437.
118. Clemo, Ormstom, and Ramage, *J. Chem. Soc.,* **1931,** 3185.
119. Micovic and Mihailovic, *Rec. trav. chim.,* **71,** 970 (1952).
120. Mumm and Beth, *Ber.,* **54,** 1591 (1921).
121. Mumm, Roder, and Ludwig, *Ber.,* **57,** 865 (1924).
122. Mumm and Brodersen, *Ber.,* **56,** 2295 (1923).
123. Diels and Alder, *Ann.,* **505,** 103 (1933).
124. Adkins, Kuick, Farlow, and Wojcik, *J. Am. Chem. Soc.,* **56,** 2425 (1934).
125. Folkers and Adkins, *J. Am. Chem. Soc.,* **54,** 1145 (1932).
126. Singer and McElvain, *J. Am. Chem. Soc.,* **57,** 1134 (1935).
127. McElvain and Adams, *J. Am. Chem. Soc.,* **45,** 2738 (1923).
128. Adkins and Pavlic, *J. Am. Chem. Soc.,* **69,** 3039 (1947).
129. Clarke, Mooradian, Lucas, and Slauson, *J. Am. Chem. Soc.,* **71,** 2821 (1949).
130. Andersson and Soine, *J. Am. Pharm. Assoc.,* **39,** 460 (1950).
131. Feldkamp, Faust, and Cushman, *J. Am. Chem. Soc.,* **74,** 3831 (1952).
132. Grob and Renk, *Helv. Chim. Acta,* **37,** 1672 (1954).
133. Supniewski and Serafinowna, *Arch. Chem. Farm.,* **3,** 109 (1936); through *C.A.,* **33,** 7301 (1939).
134. Šorm, *Collection Czechoslov. Chem. Communs.,* **13,** 57 (1948); *C.A.,* **42,** 7298 (1948).
135. Šorm and Sedivy, *Collection Czechoslov. Chem. Communs.,* **13,** 289 (1948); *C.A.,* **43,** 2996 (1949).
136. Wibaut and Boer, *Rec. trav. chim.,* **68,** 72 (1949).
137. Lukeš, Jizba, Pliml, and Step, *Collection Czechoslov. Chem. Communs.,* **19,** 949 (1954); *C.A.,* **49,** 4642 (1955).

138. U.S. patent 2,520,037, Cohen, Aug. 22, 1950.
139. Mariella and Belcher, *J. Am. Chem. Soc.*, **73**, 2616 (1951).
140. Barnes and Fales, *J. Am. Chem. Soc.*, **75**, 975, 3830 (1953).
141. Mariella and Havlik, *J. Am. Chem. Soc.*, **74**, 1915 (1952).
142. Bohlmann and Bohlmann, *Chem. Ber.*, **86**, 1419 (1953).
143. Heyns and Vogelsang, *Chem. Ber.*, **87**, 1377 (1954).
144. Berrie, Newbold, and Spring, *J. Chem. Soc.*, **1951**, 2590.
145. Sugasawa and Ban, *J. Pharm. Soc. Japan*, **72**, 1336 (1952); through *C.A.*, **47**, 4336 (1953).
146. Fallab and Erlenmeyer, *Helv. Chim. Acta*, **34**, 488 (1951).
147. U.S. patent 2,190,444, Dohrn and Nahme, Feb. 13, 1940.
148. Furst and Jelesaroff, *Arch. Pharm.*, **283**, 238 (1950); through *C.A.*, **45**, 5687 (1951).
149. Lock, *Pharm. Ind.*, **14**, 366 (1952); through *C.A.*, **47**, 10531 (1953).
150. Kaufman, *J. Am. Chem. Soc.*, **67**, 497 (1945).
151. Štěpán, Král, and Jureček, *Chem. Listy*, **47**, 223 (1953); through *C.A.*, **49**, 314 (1955).
152. Schenkel and Klein, *Helv. Chim. Acta*, **28**, 1211 (1945).
153. Hoogewerff and van Dorp, *Ber.*, **13**, 61 (1880).
154. Tracy and Elderfield, *J. Org. Chem.*, **6**, 70 (1941).
155. Cantwell and Brown, *J. Am. Chem. Soc.*, **74**, 5967 (1952).
156. Cantwell and Brown, *J. Am. Chem. Soc.*, **75**, 4466 (1953).
157. Ashworth, Daffern and Hammick, *J. Chem. Soc.*, **1939**, 809.
158. Sperber, Papa, Schwenk, and Sherlock, *J. Am. Chem. Soc.*, **71**, 887 (1949).
159. Brown, *J. Chem. Soc.*, **1949**, 2577.
160. Cantwell and Brown, *J. Am. Chem. Soc.*, **75**, 1489 (1953).
161. Mislow, *J. Am. Chem. Soc.*, **69**, 2559 (1947).
162. Leko and Bastic, *Bull. soc. chim. Belgrade*, **13**, 203 (1948); through *C.A.*, **46**, 8655 (1952).
163. Buchdahl and Soine, *J. Am. Pharm. Assoc.*, **41**, 225 (1952).
164. Brown, Hammick, and Thewlis, *Nature*, **162**, 73 (1948).
165. Borsche and Hahn, *Ann.*, **537**, 219 (1939).
166. Kahn, Petrow, Rewald, and Sturgeon, *J. Chem. Soc.*, **1949**, 2128.
167. Chatterjea, *J. Indian Chem. Soc.*, **29**, 323 (1952).
168. Mills, Palmer, and Tomkinson, *J. Chem. Soc.*, **125**, 2365 (1924).
169. Palit and Chatterjea, *J. Indian Chem. Soc.*, **27**, 667 (1950).
170. Mann and Turnbull, *J. Chem. Soc.*, **1951**, 761.
171. Mann and Reid, *J. Chem. Soc.*, **1952**, 2057.
172. Ramirez and Paul, *J. Am. Chem. Soc.*, **77**, 3337, (1955).
173. Meyer and Graf, *Ber.*, **61**, 2202 (1928).
174. Mosher and Look, *J. Org. Chem.*, **20**, 283 (1955).
175. Graf, Lederer-Ponzer, Kopetz, Purkert, and Laszlo, *J. prakt. Chem.*, **138**, 244 (1933).
176. Bachmann and Micucci, *J. Am. Chem. Soc.*, **70**, 2381 (1948).

177. Laiblin, *Ann.*, **196**, 129 (1879).
178. Linsker and Evans, *J. Am. Chem. Soc.*, **68**, 907 (1946).
179. Mariella and Belcher, *J. Am. Chem. Soc.*, **74**, 1916 (1952).
180. Matsumura, *J. Chem. Soc. Japan Pure Chem. Soc.*, **74**, 547 (1953); through *C.A.*, **48**, 13687 (1954).
181. Pinner, *Ber.*, **33**, 1225 (1900).
182. Pinner, *Ber.*, **34**, 4234 (1901).
183. Hurd and Webb, *J. Am. Chem. Soc.*, **49**, 546 (1927).
184. Strong and McElvain, *J. Am. Chem. Soc.*, **55**, 816 (1933).
185. Burrus and Powell, *J. Am. Chem. Soc.*, **67**, 1468 (1945).
186. Bloom, Breslow, and Hausser, *J. Am. Chem. Soc.*, **67**, 2206 (1945).
187. Massie, *Iowa State Coll. J. Sci.*, **21**, 41 (1946).
188. Gilman and Broadbent, *J. Am. Chem. Soc.*, **70**, 2755 (1948).
189. Shivers, Dillon, and Hauser, *J. Am. Chem. Soc.*, **69**, 119 (1947).
190. Winterfeld and Müller, *Ann.*, **581**, 77 (1953).
191. Rabe and Jantzen, *Ber.*, **54**, 925 (1921).
192. Graf, *J. prakt. Chem.*, **138**, 288 (1933).
193. Webb and Corwin, *J. Am. Chem. Soc.*, **66**, 1456 (1944).
194. Prostenick and Filipovic, *Arkiv. Kemi.*, **18**, 3 (1946); through *C.A.*, **42**, 3398 (1948).
195. Chichibabin and Woroshtzow, *Ber.*, **66**, 364 (1933).
196. Späth and Galinovsky, *Ber.*, **71**, 721 (1938).
197. Dornow and Machens, *Ber.*, **73**, 355 (1940).
198. Dornow and Bruncken, *Chem. Ber.*, **83**, 189 (1950).
199. Dornow, Machens, and Bruncken, *Chem. Ber.*, **84**, 147 (1951).
200. Burger and Walter, *J. Am. Chem. Soc.*, **72**, 1988 (1950).
201. Spath and Bretschneider, *Ber.*, **61**, 327 (1928).
202. Levine and Sneed, *J. Am. Chem. Soc.*, **73**, 5614 (1951).
203. Winterfeld and Rink, *Arch. Pharm.*, **285**, 89 (1952); through *C.A.*, **47**, 7494 (1953).
204. Kuick and Adkins, *J. Am. Chem. Soc.*, **57**, 143 (1935).
205. Webb and Webb, *J. Am. Chem. Soc.*, **71**, 2285 (1949).
206. Sobecky, *Ber.*, **41**, 4103 (1908).
207. Graf, *J. prakt. Chem.*, **146**, 88 (1936).
208. DeJonge, den Hertog, and Wibaut, *Rec. trav. chim.*, **70**, 989 (1951).
209. Wibaut, deJonge, van der Voort, and Otto, *Rec. trav. chim.*, **70**, 1054 (1951).
210. Simonis and Cohn, *Ber.*, **47**, 1238 (1914).
211. Wolfenstein and Hartwich, *Ber.*, **48**, 2043 (1915).
212. Ghigi, *Ber.*, **75**, 1318 (1942).
213. Dornow, *Ber.*, **73**, 156 (1940).
214. Dornow, *Ber.*, **73**, 185 (1940).
215. Winterfeld and Cosel, *Arch. Pharm.*, **278**, 70 (1940); through *C.A.*, **34**, 5847 (1940).

216. Miescher and Kägi, *Helv. Chim. Acta,* **24,** 1471 (1941).
217. Dornow, *Angew. Chem.,* **60A,** 72 (1948).
218. Rojahn and Schulten, *Arch. Pharm.,* **264,** 348 (1926); through *C.A.,* **20,** 2857 (1926).
219. Graf, *J. prakt. Chem.,* **134,** 177 (1932).
220. Graf, *J. prakt. Chem.,* **134,** 187 (1932).
221. Graf and Laszlo, *J. prakt, Chem.,* **138,** 231 (1933).
222. Yubuta, *J. Chem. Soc.,* **125,** 575 (1924).
223. Graf and Laszlo, *J. prakt. Chem.,* **138,** 238 (1933).
224. Graf, *Biochem. Z.,* **229,** 164 (1930); through *C.A.,* **25,** 3000 (1931).
225. Wingfield, Harlan, and Hanmer, *J. Am. Chem. Soc.,* **75,** 4364 (1953).
226. Badgett, *J. Am. Chem. Soc.,* **69,** 2231 (1947).
227. Schrecker and Maury, *J. Am. Chem. Soc.,* **76,** 5803 (1954).
228. Badgett and Woodward, *J. Am. Chem. Soc.,* **69,** 2907 (1947).
229. U.S. patent 2,593,563, Huffman, April 22, 1952.
230. British patent 699,560, Nov. 11, 1953.
231. Badgett, Provost, Ogg, and Woodward, *J. Am. Chem. Soc.,* **67,** 1135 (1945).
232. Billman and Rendall, *J. Am. Chem. Soc.,* **66,** 540 (1944).
233. U.S. patent 2,617,805, Wissow, Nov. 11, 1952.
234. Swedish patent 133,694, Nylander, Nov. 27, 1951.
235. British patent 587,810, Short and Oxley, May 6, 1947.
236. U.S. patent 2,460,002, Garbo, Jan. 22, 1949.
237. Selmiciu, *Pharm. Zentralhalle,* **90,** 370 (1951); through *C.A.,* **46,** 6645 (1952).
238. Mazover, *Zhur. Obshcheĭ Khim.,* **19,** 356 (1949); through *C.A.,* **43,** 6622 (1949).
239. Camps, *Arch. Pharm.,* **240,** 345 (1902).
240. U.S. patent 2,446,957, Rosenberg, Aug. 10, 1948.
241. U.S. patent 2,685,586, Benner and Hochhauser, Aug. 3, 1954.
242. U.S. patent 2,471,518, Deusel and Friedman, May 31, 1949.
243. U.S. patent 2,453,496, Couch and Krewson, Nov. 9, 1948.
244. Jujo, *J. Pharm. Soc. Japan,* **66,** 21 (1946); through *C.A.,* **45,** 6201 (1951).
245. Taylor and Crovetti, *J. Org. Chem.,* **19,** 1633 (1954).
246. Vejdelek, *Chem. Listy,* **46,** 770 (1952); through *C.A.,* **47,** 11191 (1953).
247. Krewson and Couch, *J. Am. Chem. Soc.,* **65,** 2256 (1943).
248. Schmidt-Thomé and Goebel, *Z. physiol. Chem.,* **288,** 237 (1951).
249. Heyl, *J. Am. Chem. Soc.,* **70,** 3434 (1948).
250. Georg and Bachmann, *Helv. Chim. Acta,* **26,** 358 (1943).
251. Jones, *J. Am. Chem. Soc.,* **74,** 1489 (1952).
252. Berrie, Newbold, and Spring, *J. Chem. Soc.,* **1952,** 2042.
253. Galat, *J. Am. Chem. Soc.,* **70,** 3945 (1948).
254. British patent 671,763, May 7, 1952.
255. Mayŭrnik, Moschetto, Bloch, and Scudi, *Ind. Eng. Chem.,* **44,** 1630 (1952).

256. Reider and Elderfield, *J. Org. Chem.*, **7**, 286 (1942).
257. Dornow and Peterlein, *Ber.*, **82**, 257 (1949).
258. Dornow and Neuse, *Chem. Ber.*, **84**, 296 (1951).
259. U.S. patent 2,417,541, Carlson and Pilgrim, Mar. 18, 1947.
260. U.S. patent 2,431,463, Carlson and Pilgrim, Nov. 25, 1947.
261. U.S. patent 2,371,694, Kuhn and Westphal, Mar. 20, 1945.
262. Ichiba and Emoto, *J. Sci. Research Inst. (Tokyo)*, **43**, 30 (1948); through *C.A.*, **43**, 4670 (1949).
263. Teague and Short, *Org. Syntheses*, **33**, 52 (1953).
264. Forrest and Walker, *J. Chem. Soc.*, **1948**, 1939.
265. U.S. patent 2,459,128, Fahrenbach, Jan. 11, 1949.
266. Bruce and Perez-Medina, *J. Am. Chem. Soc.*, **69**, 2571 (1947).
267. Levelt and Wibaut, *Rec. trav. chim.*, **48**, 466 (1929).
268. Gabriel and Heymann, *Ber.*, **23**, 157 (1890).
269. Pollak, *Monatsh.*, **16**, 54 (1895).
270. Philips, *Ann.*, **288**, 254 (1895).
271. Camps, *Arch. Pharm.*, **240**, 345 (1902).
272. Meyer, *Rec. trav. chim.*, **44**, 323 (1925).
273. Dornow, *Ber.*, **73**, 78 (1940).
274. Newbold and Spring, *J. Chem. Soc.*, **1949**, S 133.
275. Shriner and Child, *J. Am. Chem. Soc.*, **74**, 549 (1952).
276. Petrow, *J. Chem. Soc.*, **1946**, 200.
277. Ettel and Hebký, *Collection Czechoslov. Chem. Communs.*, **15**, 356 (1950); through *C.A.*, **45**, 3847 (1951).
278. Meyer, *Monatsh.*, **15**, 173 (1894).
279. Mills and Widdows, *J. Chem. Soc.*, **93**, 1372 (1908).
280. Sell, *J. Chem. Soc.*, **93**, 2002 (1908).
281. Sell, *J. Chem. Soc.*, **87**, 804 (1905).
282. Graf, *J. prakt. Chem.*, **133**, 19 (1932).
283. Kirpal, *Monatsh.*, **29**, 227 (1908).
284. Späth and Koller, *Ber.*, **56**, 2454 (1923).
285. Kirpal, *Monatsh.*, **23**, 243 (1902).
286. Gabriel and Colman, *Ber.*, **35**, 2831, 3847 (1902).
287. Mosettig, *Organic Reactions*, Vol. VIII, Chapter 5, Wiley, New York, 1954.
288. Work, *J. Chem. Soc.*, **1942**, 429.
289. Weygand, Eberhardt, Linden, Schafer, and Eigen, *Angew. Chem.*, **65**, 525 (1953).
290. Mićović and Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).
291. Uffer and Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).
292. Sommers, Freifelder, Wright, and Weston, *J. Am. Chem. Soc.*, **75**, 57 (1953).
293. Swiss patent 273,953, June 1, 1951.
294. Wiley, *J. Am. Chem. Soc.*, **71**, 1310 (1949).
295. Huber, Boehme, and Laskowski, *J. Am. Chem. Soc.*, **68**, 187 (1946).

296. Swiss patent 283,644, Oct. 1, 1952.
297. Swiss patent 283,316, Sept. 16, 1952.
298. Graf, *J. prakt. Chem.*, **138**, 282 (1933).
299. Chechelska and Urbanski, *Roczniki Chem.*, **27**, 396 (1953); through *C.A.*, **49**, 1033 (1955).
300. Phillips and Baltzly, *J. Am. Chem. Soc.*, **69**, 200 (1947).
301. Drefahl and König, *Chem. Ber.*, **87**, 1628 (1954).
302. Irving and Hampton, *J. Chem. Soc.*, **1955**, 430.
303. Hey and Williams, *J. Chem. Soc.*, **1951**, 1527.
304. Petrow and Wragg, *J. Chem. Soc.*, **1947**, 1410.
305. Kametani and Iida, *J. Pharm. Soc. Japan*, **71**, 995 (1951); through *C.A.*, **46**, 8119 (1952).
306. Kametani and Iida, *J. Pharm. Soc. Japan*, **71**, 998 (1951); through *C.A.*, **46**, 8119 (1952).
307. Kametani and Iida, *J. Pharm. Soc. Japan*, **71**, 1000 (1951); through *C.A.*, **46**, 8119 (1952)
308. Zentmeyer and Wagner, *J. Org. Chem.*, **14**, 967 (1949).
309. Knott and Breckenridge, *Can. J. Chem.*, **32**, 512 (1954).
310. Weidel, *Ber.*, **12**, 1989 (1879).
311. Meyer and Mally, *Monatsh.*, **33**, 393 (1912).
312. Mosher and Look, *J. Org. Chem.*, **20**, 283 (1955).
313. Carrara, Chiancone, D'Amato, Ginoulhiac, Martinuzzi, Teotino, and Visconti, *Gazz. chim. ital.*, **82**, 652 (1952).
314. Mattu and Pirisi, *Chimica (Milan)*, **7**, 239 (1952); through *C.A.*, **47**, 1545 (1953).
315. Cavallini, Massarani, Mazzuchi, and Ravenna, *Farm. sci. e tec. (Pavia)*, **7**, 397 (1952); through *C.A.*, **47**, 8015 (1953).
316. Mattu, Pirisi and Manca, *Ann. chim. (Rome)*, **42**, 623 (1952); *C.A.*, **47**, 13382 (1953).
317. Cavallini, Massarani, Mazzucchi, and Ravenna, *Farm. sci. e tec. (Pavia)*, **7**, 138 (1952); through *C.A.*, **47**, 6943 (1953).
318. McMillan, Leonard, Meltzer, and King, *J. Am. Pharm. Assoc.*, **42**, 457 (1953).
319. Matsukawa, Ban, Shirakawa, and Yoneda, *J. Pharm. Soc. Japan*, **73**, 159 (1953); through *C.A.*, **47**, 11185 (1953).
320. Wenner, *J. Org. Chem.*, **18**, 1333 (1953).
321. Giovambattista and Sangra, *Rev. assoc. bioquim. arg.*, **18**, 222 (1953); through *C.A.*, **49**, 324 (1955).
322. Yale, Losee, Martins, Holsing, Perry, and Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953).
323. Fox and Gibas, *J. Org. Chem.*, **18**, 983 (1953).
324. Colonna and Runti, *Ann. Chim. (Rome)*, **43**, 87 (1953); *C.A.*, **48**, 3359 (1954).
325. Buu-Hoï, Xuong, Royer, and Lavit, *J. Chem. Soc.*, **1953**, 547.

326. Barry and Mitchell, *J. Chem. Soc.*, **1953**, 3723.
327. Sah, *J. Am. Chem. Soc.*, **76**, 300 (1954).
328. Efimovsky and Rumpf, *Bull. soc. chim. France*, **1954**, 1401.
329. Zubrys and Siebenmann, *Can. J. Chem.*, **33**, 11 (1955).
330. Rubbo and Cymerman-Craig, *Nature*, **1955**, 887.
331. Kakimoto and Yamamoto, *J. Pharm. Soc. Japan*, **74**, 997 (1954); through *C.A.*, **49**, 11650 (1955).
332. Sah, *J. Am. Chem. Soc.*, **75**, 2512 (1953).
333. Sah and Peoples, *J. Am. Pharm. Assoc.*, **42**, 612 (1953).
334. Sah and Peoples, *J. Am. Pharm. Assoc.*, **43**, 513 (1954).
335. Brown, Bond, Peoples, and Sah, *J. Am. Pharm. Assoc.*, **44**, 591 (1955).
336. Fox and Gibas, *J. Org. Chem.*, **17**, 1653 (1952).
337. Fox, *J. Org. Chem.*, **18**, 990 (1953).
338. Fox and Gibas, *J. Org. Chem.*, **18**, 994 (1953).
339. Gansser and Rumpf, *Helv. Chim. Acta*, **36**, 1423 (1953).
340. Fox and Gibas, *J. Org. Chem.*, **20**, 60 (1955).
341. Fallab and Erlenmeyer, *Experientia*, **8**, 298 (1952).
342. Sorkin, Roth, and Erlenmeyer, *Helv. Chim. Acta*, **35**, 1736 (1952).
343. Albert, *Experientia*, **9**, 370 (1953).
344. Cymerman-Craig, Willis, Rubbo, and Edgar, *Nature*, **176**, 34 (1955).
345. Yale, Losee, Perry, and Bernstein, *J. Am. Chem. Soc.*, **76**, 2208 (1954).
346. Fox and Gibas, *J. Org. Chem.*, **18**, 1375 (1953).
347. Soldi, Gialdi, and Ponci, *Farmaco (Pavia), Ed. sci.*, **8**, 204 (1953); through *C.A.*, **48**, 3974 (1954).
348. Vitale and Sardella, *Chimica (Milan)*, **7**, 229 (1952); through *C.A.*, **47**, 6414 (1953).
349. Buu-Hoï, Xuong, and Nam, *Compt. rend.*, **238**, 295 (1954).
350. Yoshida and Asai, *J. Pharm. Soc. Japan*, **74**, 946 (1954); through *C.A.*, **49**, 10937 (1955).
351. Dornow and Schacht, *Ber.*, **80**, 505 (1947).
352. Efimovsky and Rumpf, *Bull. soc. chim. France*, **1954**, 648.
353. Maruyama and Imamura, *Ann. Repts. Takeda Research Lab.*, **12**, 62 (1953); through *C.A.*, **48**, 4695 (1954).
354. Isler, Gutmann, Straub, Fust, Böhni, and Studer, *Helv. Chim. Acta*, **38**, 1046 (1955).
355. Isler, Gutmann, Straub, Fust, Böhni, and Studer, *Helv. Chim. Acta*, **38**, 1033 (1955).
356. Libermann, Grumbach, and Rist, *Compt. rend.*, **237**, 338 (1953).
357. Libermann, *Bull. soc. chim. France*, **1954**, 195.
358. Yoshida and Asai, *J. Pharm. Soc. Japan*, **74**, 948 (1954); through *C.A.*, **49**, 10937 (1955).
359. Kalb and Gross, *Ber.*, **59**, 727 (1926).
360. Wingfield, Harlan, and Hanmer, *J. Am. Chem. Soc.*, **74**, 5796 (1952).
361. Gardner, Wenis, and Lee, *J. Org. Chem.*, **19**, 753, (1954).

362. Panizzon, *Helv. Chim. Acta,* **24,** 24E (1941).
363. Niemann, Lewis, and Hays, *J. Am. Chem. Soc.,* **64,** 1678 (1942).
364. Fox, *J. Org. Chem.,* **17,** 555 (1952).
365. Dornow and Bormann, *Ber.,* **82,** 216 (1949).
366. Livshits, Evstigneeva, Bainova, and Probrazhenskii, *Zhur. Obshcheĭ Khim.,* **43,** 1360 (1951); through *C.A.,* **46,** 5051 (1952).
367. Swiss patent 222,990, April 2, 1942.
368. Graf, *J. prakt. Chem.,* **133,** 36 (1932).
369. Meyer and von Beck, *Monatsh.,* **36,** 731 (1915).
370. Schroeter and Finck, *Ber.,* **71,** 671 (1938).
371. Graf. *Ber.,* **64,** 21 (1931).
372. Curtius and Mohr, *Ber.,* **31,** 2493 (1898).
373. Mohr, *Ber.,* **33,** 1114 (1900).
374. Meyer and Staffen, *Monatsh.,* **34,** 517 (1913).
375. Meyer and Tropsch, *Monatsh.,* **35,** 189 (1914).
376. Graf, *J. prakt. Chem.,* **133,** 19 (1932).
377. Chichibabin and Ossetrowa, *J. Am. Chem. Soc.,* **56,** 1711 (1934).
378. Fox and Field, *J. Biol. Chem.,* **147,** 651 (1943).
379. Rohrlich, *Arch. Pharm.,* **284,** 6 (1951); through *C.A.,* **45,** 10245 (1951).
380. Bäumler, Sorkin, and Erlenmeyer, *Helv. Chim. Acta,* **34,** 496 (1951).
381. Sugasawa, Akahoshi, Toda, and Tomisawa, *J. Pharm. Soc. Japan,* **72,** 192 (1952); through *C.A.,* **47,** 6418 (1953).
382. Carrara, D'Amato, Rolland, and Fusarpoli, *Gazz. chim. ital.,* **83,** 459 (1953).
383. Iselin, Huang, McAllister, and Nieman, *J. Am. Chem. Soc.,* **72,** 1729 (1950).
384. Levelt and Wibaut, *Rec. trav. chim.,* **48,** 466 (1929).
385. U.S. patent 2,680,742, Sendi, Maschetto, and Mayŭrnik, June 8, 1954.
386. U.S. patent 2,710,869, Duesel and Berman, June 14, 1955.
387. British patent 721,905, March 25, 1955.
388. Mayŭrnik, Moschetto, Bloch, and Sendi, *Ind. Eng. Chem.,* **44,** 1630 (1952).
389. U.S. patent 2,592,123, Denton and Bishop, April 8, 1952.
390. U.S. patent 2,510,605, Porter, Erchak, and Cosby, June 6, 1950.
391. British patent 671,763, May 7, 1952.
392. McElvain and Goese, *J. Am. Chem. Soc.,* **65,** 2233 (1943).
393. Webb and Corwin, *J. Am. Chem. Soc.,* **66,** 1956 (1944).
394. Wawzonek, Nelson, and Thelen, *J. Am. Chem. Soc.,* **74,** 2894 (1952).
395. McElvain and Goese, *J. Am. Chem. Soc.,* **63,** 2283 (1941).
396. Craig, *J. Am. Chem. Soc.,* **56,** 231 (1934).
397. Caldwell, Tyson, and Lauer, *J. Am. Chem. Soc.,* **66,** 1479 (1944).
398. Solomon, *J. Chem. Soc.,* **1946,** 934.
399. U.S. patent 2,491,253, Crossley, King, Northey, and Scholz, Dec. 13, 1949.
400. Schmidt-Thomé and Goebel, *Z. physiol. Chem.,* **288,** 237 (1951).

401. Berrie, Newbold, and Spring, *J. Chem. Soc.*, **1952**, 2042.
402. Teague, Ballentine, and Rushton, *J. Am. Chem. Soc.*, **75**, 3429 (1953).
403. Bystritskaya and Kirsanov, *J. Gen. Chem. U.S.S.R.*, **10**, 1101 (1940); through *C.A.*, **35**, 4023 (1941).
404. Räth and Prange, *Ann.*, **467**, 1 (1928).
405. Reitmann, *Med. u. Chem. Abh. med.-chem., Forschungsstätten I. G. Farbenind.*, **2**, 384 (1934); through *C.A.*, **29**, 4359 (1935).
406. Räth and Schiffman, *Ann.*, **487**, 127 (1931).
407. Räth, *Ann.*, **486**, 95 (1931).
408. Ochiai, Teshigawara, Oda, and Naito, *J. Pharm. Soc. Japan*, **65**, 1 (1945); through *C.A.*, **45**, 8527 (1951).
409. U.S. patent 2,583,774, Heyl, Jan. 29, 1952.
410. Janz, Ascah, and Keenan, *Can. J. Research*, **25**, 272 (1947).
411. Janz and Keenan, *Can. J. Research*, **25**, 283 (1947).
412. Hawkins and Janz, *J. Am. Chem. Soc.*, **74**, 1790 (1952).
413. Hawkins and Janz, *J. Chem. Soc.*, **1949**, 1479.
414. Hawkins and Janz, *J. Chem. Soc.*, **1949**, 1485.
415. U.S. patent 2,494,204, Robinson and Janz, January 10, 1950.
416. Machek, *Monatsh.*, **59**, 175 (1932).
417. Bardhan, *J. Chem. Soc.*, **1929**, 2223.
418. Gruber and Schlögl, *Monatsh.*, **81**, 83 (1950).
419. Plati and Wenner, *J. Org. Chem.*, **15**, 1165 (1950).
420. Meyer, *J. prakt. Chem.*, **78**, 519 (1908).
421. Moir, *J. Chem. Soc.*, **81**, 114 (1902).
422. Reider and Elderfield, *J. Org. Chem.*, **7**, 286 (1942).
423. Wenner and Plati, *J. Org. Chem.*, **11**, 751 (1946).
424. Camps, *Arch. Pharm.*, **240**, 266 (1902).
425. Graf, *J. prakt. Chem.*, **140**, 39 (1934).
426. Graf, *J. prakt. Chem.*, **146**, 88 (1936).
427. Norton, Benson, Seibert, and Bergstrom, *J. Am. Chem. Soc.*, **68**, 1330 (1946).
428. Sculley and Hamilton, *J. Am. Chem. Soc.*, **75**, 3400 (1953).
429. Vanderhorst and Hamilton, *J. Am. Chem. Soc.*, **75**, 656 (1953).
430. Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).
431. Prijs, Lutz, and Erlenmeyer, *Helv. Chim. Acta*, **31**, 571 (1948).
432. Vejdelek and Protiva, *Chem. Listy*, **45**, 451 (1951); through *C.A.*, **47**, 8068 (1953); *cf. Collection Czechoslov. Chem. Communs.*, **16**, 344 (1951).
433. Bruce and Coover, *J. Am. Chem. Soc.*, **66**, 2092 (1944).
434. Mowat, Pilgrim, and Carlson, *J. Am. Chem. Soc.*, **65**, 954 (1943).
435. U.S. patent 2,516,673, Bruce, July 25, 1950.
436. Mariella and Leech, *J. Am. Chem. Soc.*, **71**, 331 (1949).
437. Heyl, Luz, Harris, and Folkers, *J. Am. Chem. Soc.*, **75**, 4079 (1953).
438. U.S. patent 2,615,896, Chase, October 28, 1952.
439. Mariella and Belcher, *J. Am. Chem. Soc.*, **74**, 4049 (1952).

440. Gruber and Schlögl, *Monatsh.*, **81**, 83 (1950).
441. Tsuda, Ikekawa, Mishima, Iini, and Morishige, *Pharm. Bull. (Tokyo)*, **1**, 122 (1953); through *C.A.*, **49**, 1719 (1955).
442. Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 1245 (1939).
443. Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 3307 (1939).
444. Ichiba and Emoto, *J. Sci. Res. Inst. (Tokyo)*, **43**, 30 (1948); through *C.A.*, **43**, 4670 (1949).
445. Mariella and Havlik, *J. Am. Chem. Soc.*, **74**, 1915 (1952).
446. Mariella and Belcher, *J. Am. Chem. Soc.*, **73**, 2616 (1951).
447. Karrer and Schukri, *Helv. Chim. Acta*, **28**, 820 (1945).
448. Gardner, Wenis, and Lee, *J. Org. Chem.*, **19**, 753 (1954).
449. Räth, *Ann.*, **487**, 105 (1931).
450. Forrest and Walker, *J. Chem. Soc.*, **1948**, 1939.
451. Barber and Slack, *J. Am. Chem. Soc.*, **66**, 1607 (1944).
452. Broderick and Short, *J. Chem. Soc.*, **1951**, 1343.
453. Oxley, Partridge, and Short, *J. Chem. Soc.*, **1947**, 1110.
454. Oxley and Short, *J. Chem. Soc.*, **1946**, 147.
455. U.S. patent 2,433,489, Short and Oxley, December 30, 1947.
456. Baxter and Cymerman-Craig, *J. Chem. Soc.*, **1953**, 1490.
457. Oxley, Partridge and Short, *J. Chem. Soc.*, **1948**, 303.
458. Oxley and Short, *J. Chem. Soc.*, **1949**, 449.
459. British patent 614,032, Short and Oxley, December 8, 1948.
460. Courts and Petrow, *J. Chem. Soc.*, **1952**, 1.
461. Cymerman and Short, *J. Chem. Soc.*, **1949**, 703.
462. Broderick and Short, *J. Chem. Soc.*, **1951**, 1343.
463. Gardner, Smith, Wenis, and Lee, *J. Org. Chem.*, **16**, 1121 (1951).
464. Wibaut and Overhoff, *Rec. trav. chim.*, **52**, 55 (1933).
465. Fox, *J. Org. Chem.*, **17**, 555 (1952).
466. LaForge, *J. Am. Chem. Soc.*, **50**, 2477 (1928).
467. Badger and Pettit, *J. Chem. Soc.*, **1953**, 2774.
468. Piper and Wright, *J. Am. Chem. Soc.*, **72**, 1669 (1950).
469. Grigorovskii and Kimen, *J. Gen. Chem. U.S.S.R.*, **18**, 171 (1948); through *C.A.*, **42**, 7296 (1948).
470. König, Siefken, and Offe, *Chem. Ber.*, **87**, 825 (1954).
471. Jeger, Norymberski, Szpilfogel, and Prelog, *Helv. Chim. Acta*, **29**, 684 (1946).
472. Prijs, Lutz, and Erlenmeyer, *Helv. Chim. Acta*, **31**, 571 (1948).
473. U.S. patent 2,509,171, Ruzicka and Prelog, May 23, 1950.
474. Philips, *Ann.*, **288**, 253 (1896).
475. Bernthsen and Mettegang, *Ber.*, **20**, 1208 (1887).
476. Goldschmiedt and Strache, *Monatsh.*, **11**, 133 (1890).
477. Fels, *Ber.*, **37**, 2137 (1904).
478. Späth and Koller, *Ber.*, **56**, 2454 (1923).
479. Bachmann and Barker, *J. Org. Chem.*, **14**, 97, (1949).

480. Oparina, *Ber.*, **64**, 569 (1931).
481. Kirpal and Reimann, *Monatsh.*, **38**, 249 (1917).
482. Carboni, *Gazz. chim. ital.*, **83**, 637 (1953).
483. U.S. patent 2,345,633, Salzer and Henecka, April 4, 1944.
484. Kirpal, *Monatsh.*, **21**, 957 (1900).
485. Kirpal, *Monatsh.*, **23**, 929 (1902).
486. Goldschmiedt and Strache, *Monatsh.*, **10**, 156 (1889).
487. Strache, *Monatsh.*, **11**, 133 (1890).
488. Ternajgo, *Monatsh.*, **21**, 446 (1900).
489. Kirpal, *Monatsh.*, **27**, 363 (1906).
490. Kirpal, *Monatsh.*, **28**, 439 (1907).
491. Kirpal, *Monatsh.*, **20**, 766 (1899).
492. Kaas, *Monatsh.*, **23**, 250 (1902).
493. Kaas, *Monatsh.*, **23**, 681 (1902).
494. Linstead, Noble, and Wright, *J. Chem. Soc.*, **1937**, 911.
495. Jindra, *Chem. Listy*, **41**, 221 (1947); through *C.A.*, **47**, 4339 (1953).
496. Jindra, *Collection Czechslov. Chem. Communs.*, **12**, 541 (1947).
497. Carboni and Berti, *Gazz. chim. ital.*, **84**, 683 (1954).
498. Blanchard, Dearborn, Lasagna, and Buhle, *Bull. Johns Hopkins Hosp.*, **91**, 339 (1952); through *C.A.*, **47**, 10535 (1953).
499. Gleu and Wackernagel, *J. prakt. Chem.*, **148**, 72 (1937).
500. Sucharda, *Ber.*, **58**, 1727 (1925).
501. Gulland and Robinson, *J. Chem. Soc.*, **127**, 1493 (1925).
502. Kirpal, *Monatsh.*, **29**, 227 (1908).
503. Gabriel and Colman, *Ber.*, **35**, 2831 (1902).
504. Swiss patent 232,604, August 16, 1944.
505. Jain, Iyer, and Guha, *Science and Culture*, **11**, 270 (1945); through *C.A.*, **40**, 2125 (1946).
506. Ochiai and Arai, *J. Pharm. Soc. Japan*, **59**, 458 (1939); through *C.A.*, **34**, 108 (1940).
507. Fels, *Ber.*, **37**, 2137 (1904).
508. Gabriel and Colman, *Ber.*, **35**, 1358 (1902).
509. Kogan and Shchukina, *J. Appl. Chem. (U.S.S.R.)*, **19**, 925 (1946); through *C.A.*, **42**, 572 (1948).
510. Kirpal, *Monatsh.*, **31**, 295 (1910).
511. Just, *Monatsh.*, **18**, 452 (1897).
512. Halla, *Monatsh.*, **32**, 747 (1911).
513. Jephcott, *J. Am. Chem. Soc.*, **50**, 1189 (1928).
514. Kirpal, *Monatsh.*, **30**, 355 (1909).
515. Freund, *Monatsh.*, **18**, 447 (1897).
516. Philips, *Ber.*, **27**, 1923 (1894).
517. Fulda, *Monatsh.*, **20**, 762 (1899).
518. Gabriel and Colman, *Ber.*, **35**, 2831 (1902).
519. McLean and Spring, *J. Chem. Soc.*, **1949**, 2582.

520. Mazza, *Rend. accad. sci. Napoli,* **34,** 59 (1928); through *C.A.,* **23,** 2976 (1929).
521. Bistrzycki and Leko, *Helv. Chim. Acta,* **4,** 425 (1921).
522. Leko and Dimitrijevic, *Bull. soc. chim. Belgrade,* **11,** 41 (1946); through *C.A.,* **42,** 3400 (1948).
523. Leko and Bastic, *Bull. soc. chim. Belgrade,* **16,** 175 (1951); through *C.A.,* **48,** 9366 (1954).
524. Leko and Bastic, *Bull. soc. chim. Belgrade,* **14,** 105 (1949); through *C.A.,* **46,** 8655 (1952).
525. Case, *J. Am. Chem. Soc.,* **68,** 2574 (1946).
526. Taylor and Crovetti, *J. Org. Chem.,* **19,** 1633 (1954).
527. Aziz and Breckenridge, *Can. J. Research,* **28,** 26 (1950).
528. Graf, *J. prakt. Chem.,* **133,** 19 (1932).
529. Seide, *Ber.,* **57,** 1802 (1924).
530. Plazek and Rodewald, *Roczniki Chem.,* **21,** 150 (1947); through *C.A.,* **42,** 5456 (1948).
531. Hawkins and Roe, *J. Org. Chem.,* **14,** 328 (1949).
532. Minor, Hawkins, Vanderwerf, and Roe, *J. Am. Chem. Soc.,* **71,** 1125 (1949).
533. Roe, Cheek, and Hawkins, *J. Am. Chem. Soc.,* **71,** 4152 (1949).
534. Plazek, Dohanink, and Grzyb, *Roczniki Chem.,* **26,** 106 (1952); through *C.A.,* **47,** 7497 (1953).
535. Robison and Robison, *J. Am. Chem. Soc.,* **77,** 457 (1955).
536. Willink and Wilbaut, *Rec. trav. chim.,* **53,** 416 (1934).
537. Kögl, van der Want, and Salemink, *Rec. trav. chim.,* **67,** 29 (1948).
538. Reed and Shive, *J. Am. Chem. Soc.,* **68,** 2740 (1946).
539. Chichibabin and Kirssanow, *Ber.,* **57,** 1163 (1924).
540. Koenigs and Jaeschke, *Ber.,* **54,** 1351 (1921).
541. Dohrn and Diedrich, *Ann.,* **494,** 284 (1932).
542. Levelt and Wibaut, *Rec. trav. chim.,* **48,** 466 (1929).
543. Chichibabin, *Ber.,* **57,** 1802 (1924).
544. Fibel and Spoerri, *J. Am. Chem. Soc.,* **70,** 3908 (1948).
545. Graf and Stauch, *J. prakt. Chem.,* **148,** 13 (1937).
546. Den Hertog, Schogt, de Bruyn, and de Klerk, *Rec. trav. chim.,* **69,** 673 (1950).
547. Beaty and Musgrave, *J. Chem. Soc.,* **1951,** 3512.
548. Graf, *J. prakt. Chem.,* **133,** 36 (1932).
549. Graf, *J. prakt. Chem.,* **138,** 244 (1933).
550. Klingsberg, *J. Am. Chem. Soc.,* **72,** 1031 (1950).
551. Graf, *Ber.,* **64,** 21 (1931).
552. Bradlow and Vanderwerf, *J. Org. Chem.,* **14,** 509 (1949).
553. Brown, *J. Am. Chem. Soc.,* **76,** 3167 (1954).
554. Wiley and Hartmann, *J. Am. Chem. Soc.,* **73,** 494 (1951).
555. Koenigs, Friedrich, and Jurany, *Ber.,* **58,** 2571 (1925).

556. Kermack and Weatherhead, *J. Chem. Soc.*, **1942**, 726.
557. Meyer and Graf, *Ber.*, **61**, 2202 (1928).
558. Marckwald, *Ber.*, **27**, 1317 (1894).
559. Michaelis, *Ann.*, **366**, 324 (1909).
560. Meyer and von Beck, *Monatsh.*, **36**, 731 (1915).
561. Koenigs, Kinne, and Weiss, *Ber.*, **57**, 1172 (1924).
562. Den Hertog and Wibaut, *Rec. trav. chim.*, **55**, 122 (1936).
563. Marcinkow and Plazek, *Roczniki Chem.*, **16**, 136 (1936); through *C.A.*, **31**, 2216 (1937).
564. Räth and Prange, *Ann.*, **467**, 1 (1928).
565. Clemo and Swan, *J. Chem. Soc.*, **1945**, 603.
566. Räth, *Ann.*, **486**, 284 (1931).
567. Robins and Hitchings, *J. Am. Chem. Soc.*, **77**, 2256 (1955).
568. Sucharda, *Ber.*, **58**, 1724 (1925).
569. Bobranski and Sucharda, *Ber.*, **60**, 1081 (1927).
570. Klisiecki and Sucharda, *Roczniki Chem.*, **7**, 204 (1927); through *C.A.*, **22**, 777 (1928).
571. Koller, *Ber.*, **60**, 1572 (1927).
572. Sucharda, *Kosmos*, **1920**, 15 pp.; through *C.A.*, **22**, 2948 (1928).
573. Fox, *J. Org. Chem.*, **17**, 547 (1952).
574. See, for example, Sebrell and Harris, *The Vitamins*, Vol. II, Academic Press, New York, 1954.
575. Pullman, San Pietro, and Colowick, *J. Biol. Chem.*, **206**, 129 (1954).
576. For a complete discussion of pyridine alkaloids, see Manske and Holmes, *The Alkaloids*, Vol. I, Academic Press, New York, 1950.
577. Wohl and Johnson, *Ber.*, **40**, 4712 (1907).
578. Späth and Koller, *Ber.*, **56**, 2454 (1923).
579. Späth and Koller, *Ber.*, **58**, 2124 (1925).
580. Taylor and Crovetti, *J. Am. Chem. Soc.*, **78**, 214 (1956).
581. Meltzer, Lewis, and King, *J. Am. Chem. Soc.*, **77**, 4062 (1955).
582. British patent 631,078, October 26, 1949.
583. Kornfeld, *J. Am. Chem. Soc.*, **77**, 4425 (1955).
584. U.S. patent 2,650,232, Jones, August 25, 1953.
585. Panouse, *Compt. rend.*, **233**, 260 (1951).
586. Lyle, Perlowski, Troscianic, and Lyle, *J. Org. Chem.*, **20**, 1761 (1955).
587. Karrer and Mainoni, *Helv. Chim. Acta*, **34**, 2151 (1951).
588. Tsuda, Ikekawa, Mishima, Iino, and Marischige, *Pharm. Bull. (Tokyo)*, **1**, 122 (1953); through *C.A.*, **49**, 1719 (1955).
589. Bohlmann, Englisch, Politt, Sander, and Weise, *Chem. Ber.*, **88**, 183 (1955).
590. Davoll and Kipping, *J. Chem. Soc.*, **1953**, 1395.
591. Kirpal and Kunze, *Ber.*, **60**, 138 (1927).
592. Dohrn and Diedrich, *Ann.*, **494**, 284 (1932).
593. Crippa, Long, and de Martini, *Gazz. chim. ital.*, **64**, 83 (1934).

594. Simon, *Sbornik Statei Obshchei Khim. Akad. Nauk S.S.S.R.*, **1**, 672 (1953); through *C.A.*, **49**, 1071 (1955).
595. Kruger and Mann, *J. Chem. Soc.*, **1955**, 2755.
596. Sheehan and Leitner, *J. Am. Chem. Soc.*, **74**, 5501 (1952).
597. Engler and Kiby, *Ber.*, **22**, 597 (1889).
598. Engler, *Ber.*, **24**, 2539 (1891).
599. Kuffner and Russo, *Monatsh.*, **85**, 1097 (1954).
600. Saunders and Wilding, *J. Chem. Soc.*, **1949**, 1279.
601. Kolloff and Hunter, *J. Am. Chem. Soc.*, **63**, 490 (1941).
602. Clemo and Holmes, *J. Chem. Soc.*, **1934**, 1739.
603. Koelsch, *J. Org. Chem.*, **10**, 34 (1945).
604. Wibaut and Heeringa, *Rec. trav. chim.*, **74**, 1003 (1955).
605. Villani, King, and Papa, *J. Org. Chem.*, **17**, 249 (1952).
606. Andersson and Soine, *J. Am. Pharm. Assoc.*, **39**, 463 (1950).
607. Baumgarten and Dornow, *Ber.*, **73**, 44 (1940).
608. Burger, Alfriend, and Deinet, *J. Am. Chem. Soc.*, **66**, 1327 (1944).
609. Bachmann and Jenkins, *J. Am. Pharm. Assoc.*, **40**, 44 (1951).
610. Frank and Weatherbee, *J. Am. Chem. Soc.*, **70**, 3482 (1948).
611. Libermann, Rist, Grumbach, Moyeux, Gauthier, Rouaix, Maillard, Himbert, and Cals, *Bull. soc. chim. France*, **1954**, 1430.
612. Beyerman, Bontekoe, Van der Burg, and Veer, *Rec. trav. chim.*, **73**, 109 (1954).
613. Den Hertog and Mulder, *Rec. trav. chim.*, **67**, 957 (1948).
614. Ochiai, Suzuki, and Futaki, *J. Pharm. Soc. Japan*, **74**, 666 (1954); through *C.A.*, **48**, 10746 (1954).
615. Perez-Medina, Mariella, and McElvain, *J. Am. Chem. Soc.*, **69**, 2574 (1947).
616. Velluz and Amiard, *Bull. soc. chim. France*, **1947**, 136.
617. Lorz and Baltzly, *J. Am. Chem. Soc.*, **70**, 1904 (1948).
618. Lorz, Albro, and Baltzly, *J. Am. Chem. Soc.*, **73**, 483 (1951).
619. Philips, *Ber.*, **27**, 839 (1894).
620. Den Hertog, Schogt, de Bruyn, and de Klerk, *Rec. trav. chim.*, **69**, 673 (1950).
621. Räth and Schiffman, *Ann.*, **487**, 127 (1931).
622. Geissman, Schlatter, Webb, and Roberts, *J. Org. Chem.*, **11**, 741 (1946).
623. Fischer, Hess, and Stahlschmidt, *Ber.*, **45**, 2456 (1912).
624. Engler, *Ber.*, **27**, 1784 (1894).
625. Brode and Bremer, *J. Am. Chem. Soc.*, **56**, 993 (1934).
626. Späth and Spitzer, *Ber.*, **59**, 1477 (1926).
627. Engler, *Ber.*, **27**, 1784 (1894).
628. Ochiai, Miyaki, and Sato, *Ber.*, **70**, 2018 (1937).
629. Weidel and Herzig, *Monatsh.*, **1**, 1 (1880).
630. Meyer and Tropsch, *Monatsh.*, **35**, 189 (1914).
631. Soine, *J. Am. Pharm. Assoc.*, **33**, 223 (1944).

632. Soine and Buchdahl, *J. Am. Pharm. Assoc.*, **39**, 421 (1950).
633. Ladenburg, *Ann.*, **247**, 1 (1888).
634. Weidel and Schmidt, *Ber.*, **12**, 1146 (1879).
635. Dürkopf and Göttsch, *Ber.*, **23**, 1110 (1890).
636. Meyer, *J. prakt. Chem.*, **78**, 511 (1908).
637. Swiss patent 284,073, Nov. 17, 1952.
638. Weidel, *Ann.*, **173**, 11 (1874).
639. Weidel, *Monatsh.*, **2**, 565 (1881).
640. Eckert and Loria, *Monatsh.*, **38**, 225 (1917).
641. Patrick, *J. Am. Chem. Soc.*, **74**, 2984 (1952).
642. Eguchi, *Bull. Chem. Soc. Japan*, **3**, 227, 235 (1928).
643. Barger and Scholz, *Helv. Chim. Acta*, **16**, 1343 (1933).
644. Scholz, *Helv. Chim. Acta*, **18**, 923 (1935).
645. Dürkopf and Schlaugk, *Ber.*, **21**, 834, 2707 (1888).
646. Weber, *Ann.*, **241**, 1 (1887).
647. Ahrens, *Ber.*, **28**, 798 (1895).
648. Rugheimer and Friling, *Ann.*, **326**, 267 (1903).
649. Hantzsch, *Ann.*, **215**, 1 (1882).
650. Mumm and Huneke, *Ber.*, **51**, 150 (1918).
651. Bottorf, Jones, Kornfeld, and Mann, *J. Am. Chem. Soc.*, **73**, 4380 (1951).
652. Machek, *Monatsh.*, **59**, 175 (1932).
653. Hantzsch and Weiss, *Ber.*, **19**, 284 (1886).
654. Jones, *J. Am. Chem. Soc.*, **78**, 159 (1956).
655. Zinke and Winzheimer, *Ann.*, **290**, 355 (1896).
656. Cantwell and Brown, *J. Am. Chem. Soc.*, **74**, 5967 (1952).
657. Arens, van Dorp, and van Dyk, *Rec. trav. chim.*, **69**, 287 (1950).
658. Clemo and Gourley, *J. Chem. Soc.*, **1938**, 478.
659. Winterfield and Holschneider, *Ber.*, **64**, 137 (1931).
660. Meyer, *Rec. trav. chim.*, **44**, 323 (1925).
661. Ladenburg and Scholtze, *Ber.*, **33**, 1081 (1900).
662. Turnau, *Monatsh.*, **29**, 845 (1908).
663. Scholtz, *Ber.*, **28**, 1726 (1895).
664. Skraup and Cobenzl, *Monatsh.*, **4**, 436 (1883).
665. Graf and Lehmann, *J. prakt. Chem.*, **138**, 240 (1933).
666. Baumgarten and Dornow, *Ber.*, **72**, 563 (1939).
667. Benary, *Ber.*, **60**, 914 (1927).
668. Gabriel and Colman, *Ber.*, **35**, 1358 (1902).
669. Rabe and Jantzen, *Ber.*, **54**, 925 (1921).
670. Schubert, *Ber.*, **27**, 86 (1894).
671. Gruber and Schlögl, *Monatsh.*, **81**, 83 (1950).
672. Ciusa and Masazo, *Chem. Zentr.*, **1931, II**, 719.
673. Benary and Psille, *Ber.*, **57**, 828 (1924).
674. Plieninger and Suehiro, *Ber.*, **87**, 882 (1954).
675. Böttinger, *Ber.*, **14**, 67 (1881).

676. Böttinger, *Ber.*, **17**, 93 (1884).
677. Tracy and Elderfield, *J. Org. Chem.*, **6**, 70 (1941).
678. Königs, *Ber.*, **35**, 1349 (1902).
679. Königs, *Ber.*, **14**, 103 (1881).
680. Hoogewerf and van Dorp, *Ber.*, **16**, 1381 (1883).
681. Koelsch and Steinhauer, *J. Org. Chem.*, **18**, 1516 (1953).
682. Späth and Burger, *Monatsh.*, **49**, 265 (1928).
683. Altar, *Ann.*, **237**, 182, 201 (1887).
684. Böttinger, *Ann.*, **188**, 328 (1877).
685. Oparina, *J. Russ. Phys. Chem. Soc.*, **57**, 319 (1925).
686. Königs and Jaeschke, *Ber.*, **54**, 1351 (1921).
687. Lawson, Perkin, and Robinson, *J. Chem. Soc.*, **125**, 616 (1924).
688. Krabbe, Bohlk, and Schmidt, *Ber.*, **71**, 64 (1938).
689. McLean and Spring, *J. Chem. Soc.*, **1949**, 2582.
690. Boehm and Bournot, *Ber.*, **48**, 1573 (1915).
691. Forsyth and Pyman, *J. Chem. Soc.*, **1926**, 2912.
692. Chichibabin and Oparina, *J. Russ. Phys. Chem. Soc.*, **54**, 428 (1924).
693. Wolff, *Ann.*, **322**, 351 (1902).
694. Chatterjea and Prasad, *J. Indian Chem. Soc.*, **32**, 371 (1955).
695. Michael, *Ann.*, **225**, 121 (1884).
696. Fischer and Besthorn, *Ber.*, **16**, 71 (1883).
697. Jones, *J. Am. Chem. Soc.*, **73**, 5610 (1951).
698. Marsden, *J. Chem. Soc.*, **71**, 663 (1897).
699. Dobbie and Lander, *J. Chem. Soc.*, **81**, 151 (1902).
700. Diels and Alder, *Ann.*, **498**, 1 (1932).
701. Hantzsch, *Ber.*, **17**, 1512, 2903 (1884).
702. Takahashi and Saikachi, *J. Pharm. Soc. Japan*, **62**, 40 (1942); through *C.A.*, **45**, 620 (1951).
703. Koenigs and Bentheim, *Ber.*, **38**, 3907 (1905).
704. Siddiqui, Usmani, and Ali, *J. Indian Chem. Soc.*, **21**, 245 (1944).
705. Gastaldi, *Gazz. chim. ital.*, **52**, 169 (1922).
706. Seitz, *Ber.*, **22**, 254 (1889).
707. Michael, *Ber.*, **18**, 2020 (1885).
708. Collie, *J. Chem. Soc.*, **71**, 306 (1897).
709. Meyer, *J. prakt. Chem.*, **78**, 519 (1908).
710. Weiss, *Ber.*, **19**, 1305 (1886).
711. Knoevenagel and Fuchs, *Ber.*, **36**, 2857 (1903).
712. Mumm and Gottschaldt, *Ber.*, **55**, 2064 (1922).
713. Dornow, *Ber.*, **72**, 1548 (1939).
714. Mumm and Neumann, *Ber.*, **59**, 1616 (1926).
715. Späth and Burger, *Monatsh.*, **49**, 265 (1928).
716. Pleininger, *Chem. Ber.*, **86**, 25 (1953).
717. Basu, *J. Indian Chem. Soc.*, **12**, 289 (1935).
718. Königs and Mengel, *Ber.*, **37**, 1322 (1904).

719. Chatterjea, *J. Indian Chem. Soc.*, **29**, 323 (1952).
720. Petrow, *J. Chem. Soc.*, **1946**, 884.
721. Borsche and Hahn, *Ann.*, **537**, 219 (1939).
722. Epstein, *Ann.*, **231**, 1 (1885).
723. Biginelli, *Gazz. chim. ital.*, **23**, 386 (1893).
724. Hinkel and Hey, *Rec. trav. chim.*, **48**, 1280 (1929).
725. Chatterjea and Prasad, *J. Sci. Ind. Research (India)*, **14B**, 383 (1955).
726. Berson and Brown, *J. Am. Chem. Soc.*, **77**, 444 (1955).
727. Knoevenagel and Ruschhaupt, *Ber.*, **31**, 1025 (1898).
728. Beyer, *Ber.*, **24**, 1662 (1891).
729. Alberts and Bachman, *J. Am. Chem. Soc.*, **57**, 1285 (1935).
730. Paal and Strasser, *Ber.*, **20**, 2750 (1887).
731. Mumm and Böhme, *Ber.*, **20**, 2756 (1887).
732. Mumm and Böhme, *Ber.*, **54**, 726 (1921).
733. Bülow and Issler, *Ber.*, **36**, 2447 (1903).
734. Palit, *J. Indian Chem. Soc.*, **27**, 71 (1950).
735. Mumm and Bergell, *Ber.*, **45**, 3040 (1912).
736. Mumm and Huneke, *Ber.*, **50**, 1568 (1917).
737. Wegscheider, *Ber.*, **51**, 1478 (1918).
738. Doebner and Kunze, *Ann.*, **249**, 119 (1888).
739. Jones, *J. Am. Chem. Soc.*, **73**, 5244 (1951).
740. Engelman, *Ann.*, **231**, 37 (1885).
741. Meyer and Tropsch, *Monatsh.*, **35**, 207 (1914).
742. Mohr and Schneider, *J. prakt. Chem.*, **69**, 245 (1904).
743. Fox, *J. Org. Chem.*, **17**, 542 (1952).
744. Jones, *J. Am. Chem. Soc.*, **74**, 1489 (1952).
745. Skraup, *Ann.*, **419**, 1 (1919).
746. Mumm and Brodersen, *Ber.*, **56**, 2301 (1923).
747. Palit and Chatterjea, *J. Indian Chem. Soc.*, **27**, 667 (1950).
748. Krafft and Mai, *Ber.*, **22**, 1758 (1889).
749. Siddiqui, *J. Indian Chem. Soc.*, **16**, 410 (1939); *C.A.*, **34**, 2377, (1940).
750. Jaeckle, *Ann.*, **246**, 32 (1888).
751. Ayling, *J. Chem. Soc.*, **1938**, 1014.
752. Gryschkevitsch-Trochiniowsky and Pawlowskaia, *J. Russ. Phys. Chem. Soc.*, **42**, 1378 (1910); *ibid.*, **45**, 944 (1913).
753. Gottfried and Ulzer, *Wiss. Mitt. Oesterr, Heilmittelstelle,* **1926**, No. 1, 1; No. 2, 1; **1927**, No. 3, 1; No. 4, 1; through *C.A.*, **23**, 1902 (1929).
754. Huntress and Shaw, *J. Org. Chem.*, **13**, 674 (1948).
755. Mills, Palmer, and Tomkinson, *J. Chem. Soc.*, **1924**, 2369.
756. Fox, Lewis, and Wenner, *J. Org. Chem.*, **16**, 1259 (1951).
757. Petrow, *J. Chem. Soc.*, **1946**, 884.
758. Lepetit, *Ber.*, **20**, 1338 (1887).
759. Emmert, Diefenbach, and Eck, *Ber.*, **60**, 2216 (1927).
760. Hinkel and Madel, *J. Chem. Soc.*, **1929**, 750.

761. Hinkel and Madel, *J. Chem. Soc.*, **1926**, 161.
762. Knoevenagel, *Ann.*, **281**, 25 (1894).
763. Sucharda, *Ber.*, **58**, 1727 (1925).
764. Carboni and Berti, *Gazz. chim. ital.*, **84**, 683 (1954).
765. Räth, *Ann.*, **486**, 284 (1931).
766. Swiss patent 227,174, Aug. 2, 1948.
767. Kirpal, *Monatsh.*, **21**, 957 (1900).
768. Robins and Hitchings, *J. Am. Chem. Soc.*, **77**, 2257 (1955).
769. Fox, *J. Org. Chem.*, **17**, 547 (1952).
770. Carboni, *Gazz. chim. ital.*, **83**, 637 (1953).
771. Dornow and Neuse, *Ber.*, **84**, 296 (1951).
772. Dornow and Karlson, *Ber.*, **73**, 542 (1940).
773. Jones, *J. Am. Chem. Soc.*, **74**, 1489 (1952).
774. Marckwald, *Ber.*, **26**, 2187 (1893); **27**, 1317 (1894).
775. Rath and Schiffmann, *Ann.*, **487**, 127 (1931).
776. Khaletskiĭ and Gurevich, *Zhur. Obschcheĭ Khim.*, **24**, 369 (1954); *C.A.*, **49**, 4643 (1955).
777. Graf, Lederer-Ponzer, Kopetz, Purkert, and László, *J. prakt. Chem.*, **138**, 244 (1933).
778. Kirpal, *Monatsh.*, **23**, 929 (1902).
779. McLean and Spring, *J. Chem. Soc.*, **1949**, 2582.
780. Scott, Norris, Heuser, and Bruce, *J. Am. Chem. Soc.*, **67**, 157 (1945).
781. Koenigs, Kinne, and Weiss, *Ber.*, **57**, 1172 (1924).
782. Kirpal and Reimann, *Monatsh.*, **38**, 249 (1917).
783. Ost, *J. prakt. Chem.*, **27**, 257 (1883).
784. Fischer, Hess, and Stahlschmidt, *Ber.*, **45**, 2456 (1912).
785. Sell, *J. Chem. Soc.*, **93**, 1993 (1908).
786. Aston and Collie, *J. Chem. Soc.*, **1929**, 2223.
787. Beaty and Musgrave, *J. Chem. Soc.*, **1951**, 3512.
788. von Pechmann and Mills, *Ber.*, **37**, 3829 (1904).
789. Chichibabin, *Ber.*, **57**, 1163 (1924).
790. Räth and Schiffmann, *Ann.*, **487**, 127 (1931).
791. Berrie, Newbold, and Spring, *J. Chem. Soc.*, **1951**, 2590.
792. Collie and Lean, *J. Chem. Soc.*, **73**, 588 (1898).
793. Gruber and Schlögl, *Monatsh.*, **81**, 83 (1950).
794. Koenigs and Kantrowitz, *Ber.*, **60**, 2097 (1927).
795. Collie, *J. Chem. Soc.*, **59**, 176 (1890).
796. Michaelis and Arend, *Ber.*, **34**, 2283 (1901).
797. Michaelis and Hanisch, *Ber.*, **35**, 3156 (1902).
798. Fanta, *J. Am. Chem. Soc.*, **75**, 737 (1953).
799. Ramirez and Paul, *J. Org. Chem.*, **19**, 183 (1954).
800. Bäumler, Sorkin, and Erlenmeyer, *Helv. Chim. Acta*, **34**, 496 (1951).
801. Bardhan, *J. Chem. Soc.*, **1929**, 2223.
802. Behrmann and Hofmann, *Ber.*, **17**, 2681 (1884).
803. Sell and Dootson, *J. Chem. Soc.*, **71**, 1076 (1897).

804. Levelt and Wibaut, *Rec. trav. chim.*, **48**, 466 (1929).
805. Besthorn and Byvanck, *Ber.*, **31**, 796 (1898).
806. Kögl, van der Want, and Salemink, *Rec. trav. chim.*, **67**, 29 (1948).
807. Guthzeit and Dressel, *Ann.*, **262**, 89 (1890); *Ber.*, **26**, 2795 (1893).
808. Conrad and Epstein, *Ber.*, **20**, 162 (1887).
809. Collie and Lean, *J. Chem. Soc.*, **73**, 588 (1898).
810. Pfeifer, *Ber.*, **20**, 1343 (1887).
811. Sell, *J. Chem. Soc.*, **93**, 1993 (1908).
812. Sell, *J. Chem. Soc.*, **87**, 799 (1905).
813. Reissert, *Ber.*, **28**, 121 (1895).
814. Guthzeit and Laska, *J. prakt. Chem.*, **58**, 403 (1898).
815. Sell and Dootson, *J. Chem. Soc.*, **83**, 396 (1903).
816. Aston and Collie, *J. Chem. Soc.*, **71**, 653 (1897).
817. Sedgwick and Collie, *J. Chem. Soc.*, **67**, 399 (1895).
818. Thielepape and Spreckelsen, *Ber.*, **55**, 2929 (1922).
819. Srpek, *Monatsh.*, **10**, 701 (1889).
820. Claus and Collischonn, *Ber.*, **19**, 2767 (1886).
821. Sell, *J. Chem. Soc.*, **99**, 1683 (1911).
822. Meyer and von Beck, *Monatsh.*, **36**, 731 (1915).
823. Gulland and Robinson, *J. Chem. Soc.*, **127**, 1494 (1925).
824. Fels, *Ber.*, **37**, 2146 (1904).
825. Klobb, *Bull. soc. chim. France*, **29**, 407 (1921).
826. Von Meyer, *J. prakt. Chem.*, **78**, 528 (1908).
827. Simonis and Cohn, *Ber.*, **47**, 1238 (1914).
828. Benary, *Ber.*, **60**, 915 (1927).
829. Adam, *Wiss. Ind.*, **2**, 7 (1923); *Chem. Zentr.*, **1923, I**, 1951.
830. Jephcott, *J. Am. Chem. Soc.*, **50**, 1189 (1928).
831. Basu and Banerjee, *J. Indian Chem. Soc.*, **12**, 665 (1935).
832. Melstrom, *Iowa State Coll. J. Sci.*, **18**, 65 (1943); *C.A.*, **38**, 727 (1944).
833. Gilman and Melstrom, *J. Am. Chem. Soc.*, **68**, 103 (1946).
834. Beer and Preobrazhenskiĭ, *J. Gen. Chem. U.S.S.R.*, **16**, 858 (1945); through *C.A.*, **41**, 122 (1947).
835. Solomon, *J. Chem. Soc.*, **1946**, 934.
836. Kogan and Shchukina, *J. Appl. Chem. (U.S.S.R.)*, **19**, 925 (1946); through *C.A.*, **42**, 572 (1948).
837. Henecka, *Chem. Ber.*, **82**, 41 (1949).
838. Kahn, Petrow, Rewald, and Sturgeon, *J. Chem. Soc.*, **1949**, 2128.
839. Karrer and Enslin, *Helv. Chim. Acta*, **32**, 1390 (1949).
840. British patent 629,177, Sept. 14, 1949.
841. Lochte, Barton, Roberts, and Bailey, *J. Am. Chem. Soc.*, **72**, 3007 (1950).
842. Hey and Williams, *J. Chem. Soc.*, **1950**, 1678.
843. Bottorff, Jones, Kornfeld, and Mann, *J. Am. Chem. Soc.*, **73**, 4380 (1951).
844. Tsuda, Ikekawa, Iino, Furukawa, and Hattori, *Pharm. Bull. (Tokyo)*, **1**, 126 (1953); through *C.A.*, **49**, 3190 (1955).
845. Craig, *J. Am. Chem. Soc.*, **56**, 231, 1144 (1934).

846. U.S. patent 2,494,204, Robinson and Janz, Jan. 10, 1950.
847. Knott and Breckenridge, *Can. J. Chem.*, **32**, 512 (1954).
848. British patent 671,763, May 7, 1952.
849. Teague, Ballantine, and Rushton, *J. Am. Chem. Soc.*, **75**, 3429 (1953).
850. Schmelkes and Joiner, *J. Am. Chem. Soc.*, **61**, 2562 (1939).
851. Späth and Koller, *Ber.*, **56**, 880 (1923).
852. Meyer, *J. prakt. Chem.*, **78**, 497 (1908).
853. Sculley and Hamilton, *J. Am. Chem. Soc.*, **75**, 3400 (1953).
854. Swiss patent 220,214, June 16, 1942.
855. Henecka, *Chem. Ber.*, **82**, 36 (1949).
856. Ichiba, Michi, and Emoto, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **39**, 126 (1941); through *C.A.*, **41**, 6246 (1947).
857. Koller, *Ber.*, **60**, 1920 (1927).
858. Schroeter, Seidler, Sulzbacher, and Kanitz, *Ber.*, **65**, 432 (1932).
859. Mariella and Havlik, *J. Am. Chem. Soc.*, **73**, 1864 (1951).
860. Palit, *J. Indian Chem. Soc.*, **27**, 71 (1950).
861. Fanta and Stein, *J. Am. Chem. Soc.*, **77**, 1045 (1955).
862. Itiba and Emoto, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **38**, 347 (1941); through *C.A.*, **35**, 6960 (1941).
863. Kohler and Souther, *J. Am. Chem. Soc.*, **44**, 2903 (1922).
864. Scott, Norris, Heuser, and Bruce, *J. Am. Chem. Soc.*, **67**, 157 (1945).
865. Petrow, *J. Chem. Soc.*, **1946**, 888.
866. Petrow, *J. Chem. Soc.*, **1946**, 884.
867. Swiss patent 217,228, February 16, 1942.
868. Swiss patent 217,229, February 2, 1942.
869. Chase and Walker, *J. Chem. Soc.*, **1953**, 3548.
870. Dornow, *Ber.*, **72**, 563, 1548 (1939).
871. Matsukawa and Matsuno, *J. Pharm. Soc. Japan*, **64**, 145 (1944); through *C.A.*, **45**, 4724 (1951).
872. Taylor, Crovetti, and Loux, *J. Am. Chem. Soc.*, **77**, 5445 (1955).
873. Japanese patent 7726, Matsukawa and Shirakawa, December 18, 1951; through *C.A.*, **48**, 738 (1954).
874. Swiss patent 222,900, April 2, 1942.
875. Reinhart, *J. Franklin Inst.*, **249**, 427 (1950).
876. Meyer, *Monatsh.*, **23**, 437, 897 (1902).
877. Linstead, Noble, and Wright, *J. Chem. Soc.*, **1937**, 911.
878. Ichiba, Emoto, and Nagai, *J. Sci. Research Inst. (Tokyo)*, **43**, 23 (1948); through *C.A.*, **43**, 4673 (1949).
879. Benary and Lowenthal, *Ber.*, **55**, 3429 (1922).
880. Courts and Petrow, *J. Chem. Soc.*, **1952**, 334.
881. Courts and Petrow, *J. Chem. Soc.*, **1952**, 1.
882. Palit, *J. Indian Chem. Soc.*, **10**, 529 (1933).
883. Cook, Heilbron, and Steger, *J. Chem. Soc.*, **1943**, 413.
884. Kahn, Petrow, Rewald, and Sturgeon, *J. Chem. Soc.*, **1949**, 2128.
885. Roe and Seligman, *J. Org. Chem.*, **20**, 1729 (1955).

886. Wolff, *Ann.*, **322**, 351 (1902).
887. Weber, *Ann.*, **241**, 1 (1887).
888. Knoevenagel, *Ann.*, **281**, 25 (1894).
889. Byvanck, *Ber.*, **31**, 2143 (1898).
890. Hantzsch, *Ber.*, **16**, 1946 (1883).
891. Von Walther and Raetze, *J. prakt. Chem.*, **65**, 289 (1855).
892. Lepetit, *Ber.*, **20**, 1338 (1887).
893. Hantzsch, *Ann.*, **215**, 1 (1882).
894. Benary, *Ber.*, **44**, 489 (1911).
895. Kirpal and Riemann, *Monatsh.*, **38**, 249 (1917).
896. Benary, *Ber.*, **44**, 489 (1911).
897. Lawson, Perkin, and Robinson, *J. Chem. Soc.*, **125**, 626.
898. Koenigs and Jaeschke, *Ber.*, **54**, 1351 (1921).
899. Steele and Adams, *J. Am. Chem. Soc.*, **52**, 4528 (1930).
900. Stein and Ulzer, *Wiss. Mitt. Oesterr. Heilmittelstelle*, **1928**, 15; *ibid.*, **1929**, 1; through *C.A.*, **24**, 3511 (1930).
901. Diels and Harms, *Ann.*, **525**, 73 (1936).
902. Colonna, *Gazz. chim. ital.*, **66**, 528 (1936).
903. Schalit, *Wiss. Mitt. Oesterr. Heilmittelstelle*, **No. 11**, 11; **No. 12**, 6 (1934); through *C.A.*, **34**, 6279 (1940).
904. Battersby and Openshaw, *J. Chem. Soc.*, **1949**, 3207.
905. Hinkel, Ayling, and Morgan, *J. Chem. Soc.*, **1931**, 1835.
906. Scheiber and Knothe, *Ber.*, **45**, 2252 (1912).
907. Holtzwart, *J. prakt. Chem.*, **39**, 236 (1846).
908. U.S. patent 1,702,334, Binz and Räth, *Chem. Zentr.*, **1929, II**, 489.
909. Kohler and Souther, *J. Am. Chem. Soc.*, **44**, 2903 (1923).
910. Zincke and Wiederhold, *Ann.*, **290**, 359 (1896).
911. Benary, *Ber.*, **51**, 567 (1918).
912. Graf, Perathoner, and Tatzel, *J. prakt. Chem.*, **146**, 88 (1936).
913. Palit, *J. Indian Chem. Soc.*, **14**, 354 (1937).
914. Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 1245 (1939).
915. Morii and Makino, *Enzymologia*, **7**, 385 (1939); through *C.A.*, **34**, 6279 (1940).
916. German patent 701,955, Kuhn and Westphal, January 2, 1941.
917. Harris and Wilson, *J. Am. Chem. Soc.*, **63**, 2526 (1941).
918. Mowat, Pilgrim, and Carlson, *J. Am. Chem. Soc.*, **65**, 954 (1943).
919. McElvain and Goese, *J. Am. Chem. Soc.*, **65**, 2233 (1943).
920. Van Wagtendonk and Wibaut, *Rec. trav. chim.*, **61**, 728 (1942).
921. Bruce and Coover, *J. Am. Chem. Soc.*, **66**, 2092 (1944).
922. Janz and Keenan, *Can. J. Research*, **25B**, 283 (1947).
923. Ichiba, Emoto, and Nagai, *J. Sci. Research Inst. (Tokyo)*, **43**, 23 (1948); through *C.A.*, **43**, 4673 (1949).
924. Fallab and Erlenmeyer, *Helv. Chim. Acta*, **34**, 488 (1951).
925. British patent 671,763, May 7, 1952.
926. Wawzonek, Nelson, and Thelen, *J. Am. Chem. Soc.*, **74**, 2894 (1952).

927. Takeuchi and Kaneko, *Japan J. Pharm. and Chem.*, **25**, 22 (1953); through *C.A.*, **48**, 676 (1954).
928. Fox and Gibas, *J. Org. Chem.*, **17**, 1653 (1952).
929. Yale, Losee, Martins, Holsing, Perry, and Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953).
930. Maruyama and Imamura, *Ann. Repts. Takeda Research Lab.*, **12**, 62 (1953); through *C.A.*, **48**, 4695 (1954).
931. Beyerman and Bontekoe, *Rec. trav. chim.*, **72**, 262 (1953).
932. Meyer and von Beck, *Monatsh.*, **36**, 731 (1915).
933. Meyer and Graf, *Ber.*, **61**, 2202 (1928).
934. Bäumler, Sorkin, and Erlenmeyer, *Helv. Chim. Acta*, **34**, 496 (1951).
935. Swiss patent 217,228, Feb. 16, 1942; U.S. patent 2,410,938, Nov. 12, 1946.
936. Schroeter and Finck, *Ber.*, **71**, 671 (1938).
937. Katz, Schroeder, and Cohen, *J. Org. Chem.*, **19**, 711 (1954).
938. Kruger and Mann, *J. Chem. Soc.*, **1956**, 2754.
939. Dornow and Borman, *Ber.*, **82**, 216 (1949).
940. Roe and Seligman, *J. Org. Chem.*, **20**, 1729 (1955).
941. Anderson, Grail, Leonard, Tenenbaum, Hart, and Barkley, *J. Am. Pharm. Assoc.*, **45**, 348 (1956).
942. Ochiai and Fujimoto, *Pharm. Bull. (Tokyo)*, **2**, 131 (1954); through *C.A.*, **50**, 990 (1956).
943. Bojarska-Dahlig and Urbanski, *Roczniki Chem.*, **26**, 158 (1952); through *C.A.*, **50**, 338 (1956).
944. Baine, Adamson, Barton, Fitch, Swayampati, and Jeskey, *J. Org. Chem.*, **19**, 510 (1954).
945. Fox, Gibas, and Motchane, *J. Org. Chem.*, **21**, 349 (1956).
946. Fox and Gibas, *J. Org. Chem.*, **21**, 356 (1956).
947. British patent 717,172, Chase, Oct. 20, 1954.
948. Gardner, Smith, Wenis, and Lee, *J. Org. Chem.*, **21**, 530 (1956).
949. Lee and Swan, *J. Chem. Soc.*, **1956**, 711.
950. Ochiai and Suzuki, *Pharm. Bull. (Tokyo)*, **2**, 147, (1954).
951. Bohlmann, Englisch, Ottowa, Sander, and Weise, *Chem. Ber.*, **89**, 792 (1956).
952. Hesse and Schrödel, *Angew. Chem.*, **68**, 438 (1956).
953. Schmitt and Suquet, *Bull. soc. chim. France*, **1956**, 755.
954. Lyle, Perlowski, Troscianiec, and Lyle, *J. Org. Chem.*, **20**, 1761 (1955).
955. Berson and Cohen, *J. Org. Chem.*, **20**, 1461 (1955).
956. Meyer and Mally, *Monatsh.*, **33**, 400 (1912).
957. Hardegger and Nikles, *Helv. Chim. Acta*, **39**, 223 (1956).
958. Farley and Eliel, *J. Am. Chem. Soc.*, **78**, 3477 (1956).
959. Cymerman-Craig and Willis, *J. Chem. Soc.*, **1955**, 4315.
960. Mathes and Sauermilch, *Chem. Ber.*, **88**, 1276 (1955).
961. Melichar, *Chem. Ber.*, **88**, 1208 (1955).
962. Batkowski and Plazek, *Roczniki Chem.*, **25**, 251 (1951); through *C.A.*, **46**, 6127 (1952).

963. Koelsch and Sundet, *J. Am. Chem. Soc.*, **72**, 1681 (1950).
964. Mathes and Sauermilch, *Chem. Ber.*, **87**, 1868 (1954).
965. U.S. patent 1,881,236, Miescher and Urech, Oct. 4, 1932.
966. Heiber, *Ber.*, **25**, 2405 (1892).
967. Graf, *J. prakt. Chem.*, **138**, 259 (1933).
968. Graf, *J. prakt. Chem.*, **138**, 239 (1933).
969. Meyer and Mally, *Monatsh.*, **33**, 408 (1912).
970. Hinkel and Cremer, *J. Chem. Soc.*, **117**, 137 (1920).
971. Inasinki and Plazek, *Roczniki Chem.*, **25**, 142 (1951); *C.A.*, **47**, 4885 (1953).
972. Jain, Iyer, and Guha, *J. Indian Chem. Soc.*, **24**, 177 (1947).
973. Koenigs and Kantrowitz, *Ber.*, **60**, 2097 (1927).
974. Kruber, *Ber.*, **76**, 128 (1943).
975. Machek, *Monatsh.*, **59**, 175 (1932).
976. Meyer and Graf, *Biochem. Z.*, **229**, 154 (1930); *C.A.*, **25**, 2999 (1931).
977. Pliml and Protiva, *Chem. Listy*, **47**, 1204 (1953); *C.A.*, **49**, 1034 (1955).
978. Protiva and Urban, *Chem. Listy*, **44**, 91 (1950); *C.A.*, **45**, 8013 (1951).
979. Rayet, *Ind. chim. belge*, **17**, 478 (1952); *C.A.*, **46**, 10445 (1952).
980. Sadykov and Maksimov, *J. Gen. Chem. U.S.S.R.*, **16**, 1719 (1946); *C.A.*, **41**, 5864 (1947).
981. Sharel, Leonard, McMillan, and King, *J. Am. Pharm. Assoc.*, **42**, 402 (1953).
982. Simon, *Zhur. Obshcheĭ. Khim.*, **21**, 1537 (1951); *C.A.*, **46**, 2544 (1952).
983. Sucharda, *Roczniki Chem.*, **3**, 236 (1923); *Chem. Zentr.*, **1924, II**, 659.
984. Suter, *Schweiz. med. Wochsch.*, **78**, 843 (1948); *C.A.*, **48**, 3360 (1954).
985. Wibaut and Boer, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **53**, 19 (1950); *C.A.*, **44**, 6860 (1950).
986. Wibaut and Overhoff, *Rec. trav. chim.*, **52**, 55 (1933).
987. Vejdelék, Trčka, Chybová, and Tůma, *Chem. Listy*, **47**, 49 (1953); *C.A.*, **49**, 336 (1955).
988. Vejdelék, Trčka, and Protiva, *Chem. Listy*, **46**, 423 (1952); *C.A.*, **47**, 8068 (1953).
989. Vejdelék, Trčka, Hejný, and Vysatova, *Chem. Listy*, **48**, 435 (1954); *C.A.*, **49**, 3958 (1955); *Collection Czechoslov. Chem. Communs.*, **19**, 274 (1954).
990. Zasosov, *J. Gen. Chem. U.S.S.R.*, **17**, 471 (1947); *C.A.*, **42**, 534 (1948).
991. U.S. patent 2,381,873, Braker and Pribyl, Aug. 14, 1945.
992. U.S. patent 2,194,567, Renshaw and Dreisbach, Mar. 26, 1940.
993. U.S. patent 2,509,594, Grimmel and Guenther, May 30, 1950.
994. U.S. patent 2,510,164, Woodward and Badgett, June 6, 1950.
995. Swiss patent 212,061, Jan. 16, 1941.
996. Swiss patent 248,343, Feb. 2, 1948.
997. Swiss patent 258,714, June 1, 1949.
998. British patent 586,136, March 4, 1947.
999. U.S. patent 2,439,728, Gross, April 13, 1948.
1000. U.S. patent 2,653,942, Lee, Sept. 29, 1953.
1001. British patent 562,349, Henry and Gorvin, June 28, 1944.

1002. U.S. patent 2,586,438, Rosenberg, Feb. 19, 1952.
1003. Van der Burg, *Rec. trav. chim.*, **74**, 257 (1955).
1004. Carboni, *Gazz. chim. ital.*, **85**, 1201 (1955).
1005. Van Dorp and Arens, *Rec. trav. chim.*, **66**, 189 (1947).
1006. Hodnett and Stewart, *J. Am. Chem. Soc.*, **65**, 254 (1943).
1007. Kushner, Dalalian, Cassell, Sanjurjo, McKenzie, and Subbarow, *J. Org. Chem.*, **13**, 834 (1948).
1008. Miller, Osuch, Goldberg, and Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).
1009. Minor and Vanderwerf, *J. Org. Chem.*, **17**, 1425 (1952).
1010. Robins and Hitchings, *J. Am. Chem. Soc.*, **78**, 973 (1956).
1011. Sperber, Papa, and Schwenk, *J. Am. Chem. Soc.*, **72**, 2012 (1950).
1012. Strong, Lutwak, and Farooqee, *Arch. Biochem.*, **18**, 297 (1948).
1013. Drefahl and Konig, *Chem. Ber.*, **87**, 1628 (1954).
1014. Zienty, *J. Am. Pharm. Assoc.*, **37**, 99 (1948).
1015. Beyerman, Bontekoe, Van der Burg, and Veer, *Rec. trav. chim.*, **73**, 109 (1954).
1016. Gardner, Wenis, and Smith, *J. Am. Chem. Soc.*, **73**, 5455 (1951).
1017. König, Siefken, and Offe, *Chem. Ber.*, **87**, 825 (1954).
1018. Schmitt and Suquet, *Bull. soc. chim. France*, **1956**, 755.
1019. Meltzer, Lewis, and King, *J. Am. Chem. Soc.*, **77**, 4062 (1955).
1020. Gardner, Wenis, and Lee, *J. Org. Chem.*, **19**, 753 (1954).
1021. Böhm and Michalski, *Roczniki Chem.*, **28**, 501 (1954); *C.A.*, **50**, 329 (1956).
1022. Linnell and Vyas, *Quart. J. Pharm. and Pharmacol.*, **20**, 119 (1947).
1023. Swiss patent 257,245, April 16, 1949.
1024. Breslow, *J. Am. Chem. Soc.*, **72**, 4244 (1950).
1025. Gol'dfarb, *J. Appl. Chem. (U.S.S.R.)*, **10**, 515 (1937); *C.A.*, **31**, 6657 (1937).
1026. Gryskiewicz-Trochimowski, *Roczniki Chem.*, **14**, 335 (1930); *Arhiv. chemi. i farm.*, **1**, 65 (1934).
1027. Hart, *J. Chem. Soc.*, **1956**, 212.
1028. Pichat, Bovet, and Audinot, *Bull. soc. chim. France*, **1954**, 88.
1029. Bauer, *J. Am. Chem. Soc.*, **73**, 2113 (1951).
1030. Prijs, Gall, Hinderling, and Erlenmeyer, *Helv. Chim. Acta*, **37**, 90 (1954).
1031. Seligman and Wolf, *J. Am. Chem. Soc.*, **73**, 2086 (1951).
1032. Büchi, Labhart, and Ragaz, *Helv. Chim. Acta*, **30**, 507 (1947).
1033. Calo and Evdomikoff, *Gazz. chim. ital.*, **80**, 456 (1950); *C.A.*, **45**, 4243 (1951).
1034. Pierce and Rutter, *J. Am. Chem. Soc.*, **74**, 3954 (1952).
1035. Gautier, *Compt. rend.*, **222**, 384 (1946).
1036. Libmann and Slack, *J. Chem. Soc.*, **1956**, 2253.
1037. Emmert and Holz, *Chem. Ber.*, **87**, 676 (1954).
1038. Profft, Schneider, and Beyer, *J. prakt. Chem.*, **2**, 147 (1955).
1039. Kenyon and Thaker, *J. Chem. Soc.*, **1957**, 2531.
1040. Stanonis, *J. Org. Chem.*, **22**, 475 (1957).

1041. Little, Middleton, Coffman, Engelhardt, and Sausen, *J. Am. Chem. Soc.*, **80,** 2832 (1958).
1042. Taylor and Barton, *J. Am. Chem. Soc.*, **81,** 2448 (1959).
1043. Jerchel and Heck, *Ann.*, **613,** 180 (1958).
1044. Cole, *Afinidad,* **31,** 441 (1954); through *C.A.*, **50,** 326 (1956).
1045. Japanese patent 6723, Sugimoto and Shigematsu, Oct. 20, 1954.
1046. Lespagnol, Cuinguet, and Beerens, *Bull. soc. pharm. Lille,* **1955,** No. 1, 60; through *C.A.*, **50,** 3438 (1956).
1047. Stempel, Zelauskas, and Aeschlimann, *J. Org. Chem.*, **20,** 412 (1955).
1048. British patent 724,256, Feb. 16, 1955.
1049. Nakashima, *J. Pharm. Soc. Japan,* **75,** 1010 (1955).
1050. Hackley, Plapinger, Stolberg, and Wagner-Jauregg, *J. Am. Chem. Soc.*, **77,** 3651 (1955).
1051. Kao and Robinson, *J. Chem. Soc.*, **1955,** 2865.
1052. Zwart and Wibaut, *Rec. trav. chim.*, **74,** 1062 (1955).
1053. British patent 721,299, Jan. 5, 1955.
1054. Dimitrijević and Tadić, *Glasnik Khemiskog Drushtva, Beograd,* **20,** 187 (1955); through *C.A.*, **50,** 7109 (1956).
1055. U.S. patent 2,713,049, Bernstein and Losee, July 12, 1955.
1056. Supniewski, *Bull. acad. polon. sci.,* Classe II, **3,** 55 (1955); through *C.A.*, **50,** 7800 (1956).
1057. Stetter and Henning, *Chem. Ber.*, **88,** 789 (1955).
1058. U.S. patent 2,721,203, Meyer, Oct. 18, 1955.
1059. Aramaki and Aoki, *Pharm. Bull. (Japan),* **3,** 194 (1955).
1060. Lukeš and Pliml, *Chem. Listy,* **49,** 1836 (1955).
1061. Nakashima, *J. Pharm. Soc. Japan,* **76,** 215 (1956).
1062. Kakimoto and Nishie, *Japan J. Tuberc.*, **2,** 334 (1954); through *C.A.*, **50,** 14744 (1956).
1063. Talik and Plazek, *Roczniki Chem.*, **29,** 1019 (1955); through *C.A.*, **50,** 12045 (1956).
1064. Mariella, Callahan, and Jibril, *J. Org. Chem.*, **20,** 1721 (1955).
1065. Boyer and Schoen, *J. Am. Chem. Soc.*, **78,** 423 (1956).
1066. Rubtsov, Nikitskaya, and Usovskaya, *Zhur. Obshcheĭ Khim.*, **26,** 130 (1956); through *C.A.*, **50,** 13904 (1956).
1067. Braz and Skorodumov, *Zhur. Obshcheĭ Khim.*, **26,** 770 (1956); through *C.A.*, **50,** 14711 (1956).
1068. Oakes, Pascoe, and Rydon, *J. Chem. Soc.*, **1956,** 1045.
1069. Dornow and Neuse, *Arch. Pharm.*, **288,** 174 (1955).
1070. Japanese patent 6722, Hiraga, Kubota, and Akita, Oct. 20, 1954.
1071. Ochiai and Suzuki, *Pharm. Bull. (Japan),* **2,** 147 (1954).
1072. Brown and Subba Rao, *J. Am. Chem. Soc.*, **80,** 5377 (1958).
1073. Okamoto and Tani, *Chem. and Pharm. Bull. (Japan),* **7,** 130 (1959).
1074. Feely and Beavers, *J. Am. Chem. Soc.*, **81,** 4004 (1959).
1075. Bojarska-Dahling and Nantka-Namirski, *Roczniki Chem.*, **29,** 1007 (1955).

1076. Caldwell, Tyson, and Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).
1077. Klosa, *Arch. Pharm.*, **289**, 125 (1956).
1078. Mujaki and Yamagishi, *J. Pharm. Soc. Japan*, **76**, 1196 (1956).
1079. Heyl, Luz, and Harris, *J. Am. Chem. Soc.*, **78**, 4474 (1956).
1080. Libermann, Moyeux, Rist, and Grumbach, *Compt. rend.*, **242**, 2409 (1956).
1081. Case and Kasper, *J. Am. Chem. Soc.*, **78**, 5842 (1956).
1082. Markees and Kidder, *J. Am. Chem. Soc.*, **78**, 4130 (1956).
1083. Nantka-Namirski and Bojarska-Dahlig, *Roczniki Chem.*, **30**, 641 (1956).
1084. Bojarska-Dahlig and Nantka-Namirski, *Roczniki Chem.*, **30**, 621 (1956).
1085. Oakes and Rydon, *J. Chem. Soc.*, **1956**, 4433.
1086. Rees, *J. Chem. Soc.*, **1956**, 3684.
1087. Mikkailov and Kozminskaya, *Zhur. Obshcheĭ Khim.*, **26**, 2042 (1956); through *C.A.*, **51**, 5072 (1957).
1088. Dornow and Hahmann, *Arch. Pharm.*, **290**, 20 (1957).
1089. Govindachari, Nagarajan, and Rajappa, *J. Chem. Soc.*, **1957**, 551.
1090. Govindachari, Nagarajan, and Rajappa, *J. Chem. Soc.*, **1957**, 2725.
1091. Nakashima, *Yakugaku Zasshi*, **77**, 698 (1957); through *C.A.*, **51**, 16462 (1957).
1092. Japanese patent 4234, Abe, Kitagawa, and Ishimura, June 22, 1955.
1093. Schenker and Druey, *Helv. Chim. Acta*, **42**, 1960 (1959).
1094. Sperber, Sherlock, Papa, and Kender, *J. Am. Chem. Soc.*, **81**, 704 (1959).
1095. Wibaut and Boer, *Rec. trav. chim.*, **74**, 241 (1955).
1096. Emmert, *Chem. Ber.*, **91**, 1388 (1958).
1097. Bobbitt and Scola, *J. Org. Chem.*, **25**, 560 (1960).
1098. Mansfield, *J. Org. Chem.*, **24**, 1111 (1959).
1099. Abramovitch, Seng, and Notation, *Can. J. Chem.*, **38**, 761 (1960).
1100. Dawson, Christman, D'Adamo, Solt, and Wolf, *J. Am. Chem. Soc.*, **82**, 2628 (1960).
1101. Palát, Čeladnik, Nováček, and Urbančík, *Rozhledy tuberk.*, **19**, 716 (1959); through *C.A.*, **54**, 11016 (1960).
1102. McManus and Herbst, *J. Org. Chem.*, **24**, 1462 (1959).
1103. Robison, *J. Am. Chem. Soc.*, **80**, 5481 (1958).
1104. Rinderknecht, *Helv. Chim. Acta*, **42**, 1324 (1959).
1105. Tittensor and Wibberley, *J. Chem. Soc.*, **1958**, 3161.
1106. Volke, Kubíček, and Šantavý, *Collection Czechoslov. Chem. Communs.*, **25**, 1510 (1960).
1107. Dornow and Siebrecht, *Chem. Ber.*, **93**, 1106 (1960).
1108. Vaculík and Kuthan, *Collection Czechoslov. Chem. Communs.*, **25**, 1591 (1960).
1109. *Ann. N. Y. Acad. Sci.*, **80**, 551–1045 (1959).

CHAPTER XI

Pyridine Side-Chain Carboxylic Acids

By John C. Godfrey
Bristol Laboratories, Syracuse, New York

Since about 1946, the once narrow field of pyridine side-chain carboxylic acids has been expanding rapidly. Some of the reasons for this sudden growth were the discoveries, during the latter years of the war, of the valuable properties of substituted pyridines as analgesics, antihistaminics, and regulators of blood pressure; the availability of new synthetic methods, such as reductions with complex metal hydrides; and interest in the synthesis of natural products containing structures derivable from pyridine, *e.g.*, carpaine and sparteine.

A. PREPARATION

1. From Nonpyridine Starting Materials

Only eight syntheses of this type were found in the literature; these are summarized in Table XI-1 (p. 366). These syntheses are representative of the types that are discussed exhaustively in Chapter II. They are mostly condensation reactions, but include the dehydrogenation of naturally occurring carpaine and its derivative, ethyl carpamate, to give high yields of deoxycarpyrinic acid and ethyl carpyrinate, respectively (*137,140,185*).

2. From Pyridine Starting Materials

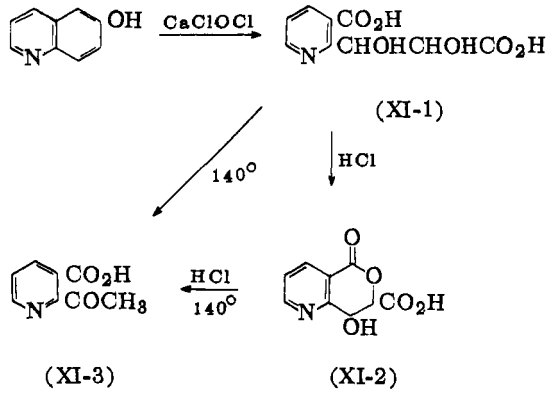
The preparations to be considered here include those which lead directly to esters and amides, as well as those which yield acids.

a. Side-Chain Oxidation

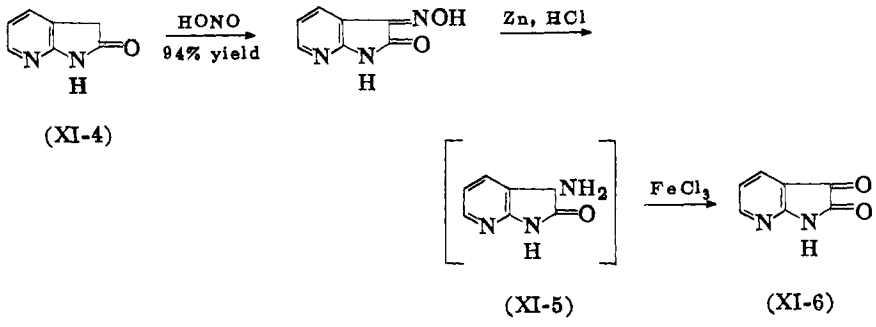
Oxidative degradation, with loss of all carbons not attached directly to the ring, is a valuable method for preparing nuclear pyridinecarboxylic acids, as described in Chapter X (pp. 182 ff.). When a side chain is branched, unsaturated, or already partially oxidized, it is often possible, by controlling the conditions, to effect oxidation to a carboxylic acid with retention of part or all of the chain. The product is a "side-chain" acid.

Oxidative preparations are summarized in Table XI-2 (p. 368). Permanganate is the most commonly used reagent. Nitric acid has also been employed (*7*); the structure assignments of the products from the oxidation of trisubstituted pyridines (*7*) (see Table XI-2) may be open to question, since these two substances survived prolonged refluxing in concentrated nitric acid.

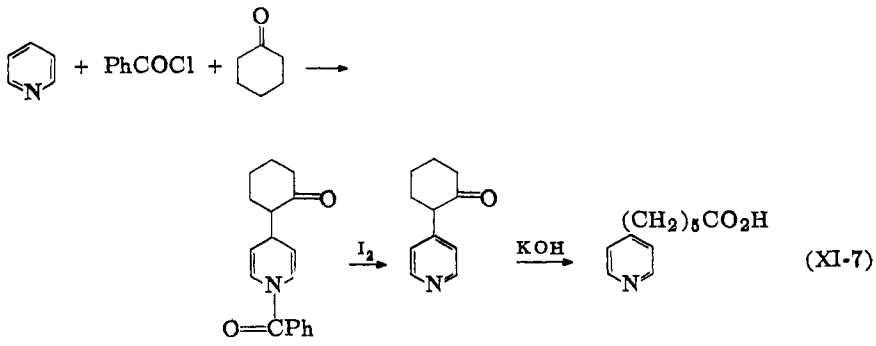
Hypochlorite has been used in a typical haloform reaction (*5*) (see Table XI-2) and also in the oxidation of 6-quinolinol to β-(3-carboxy-2-pyridine)glyceric acid (XI-1) (*6*). This unstable, hygroscopic acid was converted to lactone (XI-2) (60% over-all yield) by warming with concentrated hydrochloric acid. 2-Acetylnicotinic acid (XI-3) was obtained directly from the acid (XI-1) by heating at 140° or from the lactone (XI-2) in aqueous hydrochloric acid at 140°.



One example of the preparation of a side-chain acid derivative by ferric chloride oxidation was found in the literature. Treatment of 3-amino-7-pyroxindole (XI-5) with 42% aqueous ferric chloride yielded 7-pyrisatin (XI-6). The preparation of 7-pyroxindole (XI-4) is described in Table XI-4 (p. 373).



A unique example of oxidation with iodine which leads to 4-pyridinecaproic acid after potassium hydroxide fusion is shown in equation XI-7. The over-all yield from pyridine was about 4% of theory.



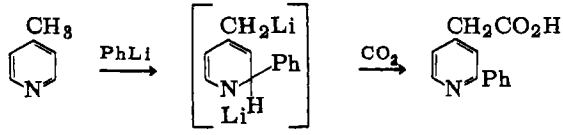
b. Carbonation of Organometallic Compounds

The preparation of 2- and 4-pyridineacetic acids by the carbonation of lithium derivatives of the corresponding picolines has been found to proceed in moderate yield. Table XI-3 (p. 372) summarizes these carbonations. Direct esterification is usually employed to sepa-

rate the products from the large volume of lithium carbonate formed. As expected, the reaction succeeds only with 2- and 4-picolines, and not with the 3-isomer.

2-Ethylpyridine gives a much smaller yield than 2-picoline (*31*), and only the starting material was recovered when the reaction was attempted with 2-(*sec*-butyl)pyridine. The unreactivity of these higher alkylated pyridines is probably due to three causes: (*a*) the smaller statistical factor resulting from the replacement of the methyl hydrogens; (*b*) the increasingly adverse steric factor as the number of alkyl groups on the methyl is increased; and (*c*) reduced acidity with increasing alkylation of the methyl group, resulting from the electron-releasing character of alkyl groups.

The phenylation of 4-picoline by excess phenyllithium in refluxing ether (*36*) is a reaction of particular interest. Carbonation of the resulting mixture produced 2-phenyl-4-pyridineacetic acid in unstated yield, presumably through the intermediate XI-8.



(XI-8)

c. Increase of Chain Length by the Arndt-Eistert Method

This synthesis (see Table XI-4, p. 373) does not give the expected products when applied to simple nuclear pyridinecarboxylic acids (*8,128*), but gives good yields when an α-position of the pyridine is substituted. The reaction proceeds normally with 2-pyridinedecanoic acid (*4*).

d. Condensation of Halogenated Pyridines with Active Methylene Compounds

Halopyridines, halomethylpyridines, and haloalkylpyridines have been condensed with sodium derivatives of β-dicarbonyl compounds, often by heating the sodio derivative with the halide at 100–150° for several hours. Inert solvents, such as toluene or de-

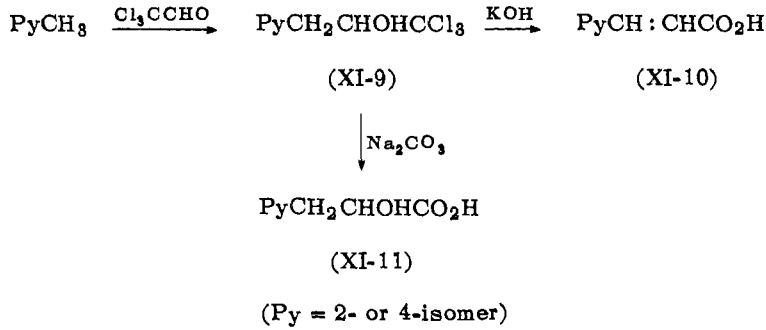
calin, may be advantageous in some cases, since the better yields, reported in Table XI-5 (p. 374), were usually obtained with a solvent. However, the yields are generally low. Unsubstituted picolyl halides are very unstable, and the authors referred to in Table XI-5 usually found it advantageous to employ the crude, freshly prepared picolyl halide, rather than to attempt purification.

A special case of nucleophilic displacement on pyridine is the replacement of the methoxyl group of 4-methoxy-3-nitropyridine by the diethyl malonyl moiety under basic conditions (*133*).

e. Condensations of Picolines and Related Compounds

The most widely used method for the preparation of pyridineacrylic acids was first described in 1887 by Einhorn (*62*). By his procedure, 2- or 4-picoline is heated with chloral, usually in the presence of zinc chloride. The intermediate *α*-trichloromethyl-2(or 4)-pyridineethanols (XI-9) are produced in satisfactory yields, and are stable, well-characterized compounds. They are readily convertible to 2- or 4-pyridineacrylic acids (XI-10) by the action of hot ethanolic potassium hydroxide. It is possible to conduct the condensation without a catalyst, but higher temperatures are required.

If the hydrolysis of the trichloropropane intermediate is carried out in warm, dilute, aqueous sodium carbonate, the product is an *α*-hydroxy-2(or 4)-pyridinepropionic acid (XI-11), alternatively called a 2(or 4)-pyridinelactic acid.



The condensations of chloral with picolines are listed in Table XI-6 (p. 377), and the hydrolysis of the products in Table XI-7 (p. 379).

One of the most generally applicable (and most tedious) methods for the preparation of 2- and 4-pyridineacetic acids (XI-12) was origi-

$$\mathrm{PyCH_3} \xrightarrow{\mathrm{PhCHO}} \mathrm{PyCH{:}CHPh} \xrightarrow{\mathrm{Br_2}} \mathrm{PyCHBrCHBrPh} \xrightarrow{\mathrm{KOH}}$$

$$\mathrm{PyC{\vdots}CPh} \xrightarrow{\mathrm{H_2O}} \mathrm{PyCH_2COPh} \xrightarrow{\mathrm{NH_2OH}}$$

$$\mathrm{PyCH_2(:NOH)Ph} \xrightarrow{\text{rearrangement}}$$

$$\mathrm{PyCH_2CONHPh} \xrightarrow{\mathrm{H_2O}} \mathrm{PyCH_2CO_2H} \qquad \text{(XI-12)}$$

(Py = 2- or 4-isomer)

nated by Oparina in 1934 (*80*). This synthesis has been found to be of greatest value in the preparation of pyridineacetic acids having nuclear alkyl substituents, difficult to obtain by other methods. The acids and esters that have been synthesized in this way are summarized in Table XI-15 (p. 398), under "Solvolysis of Anilides."

Under the influence of sodamide, a number of α-phenyl-2-pyridineacetonitriles have been condensed with bromoacetic and β-bromopropionic esters to yield the β-phenyl-β-cyanopyridinepropionic and γ-phenyl-γ-cyano-2-pyridinebutyric esters, respectively (*85,86*). (See eq. XI-13 and Table XI-8, p. 380). The butyric ester ($n = 2$)

$$\text{2-PyCHPhCN} + \mathrm{Br(CH_2)_nCO_2R} \xrightarrow{\mathrm{NaNH_2}}$$

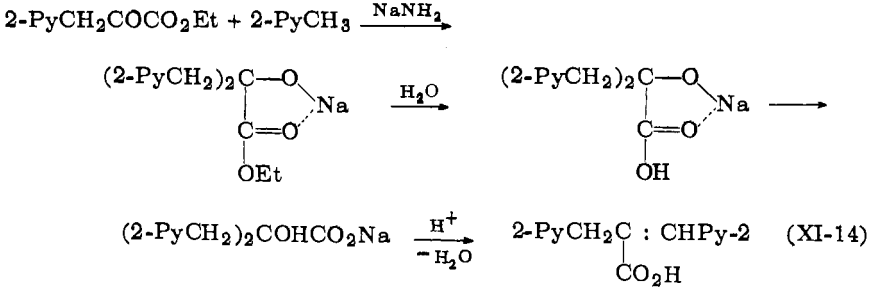
$$\text{2-PyCPhCN}(\mathrm{CH_2})_n\mathrm{CO_2R} \sim \qquad \text{(XI-13)}$$

was also obtained on condensation with acrylic ester under the same conditions (*85*).

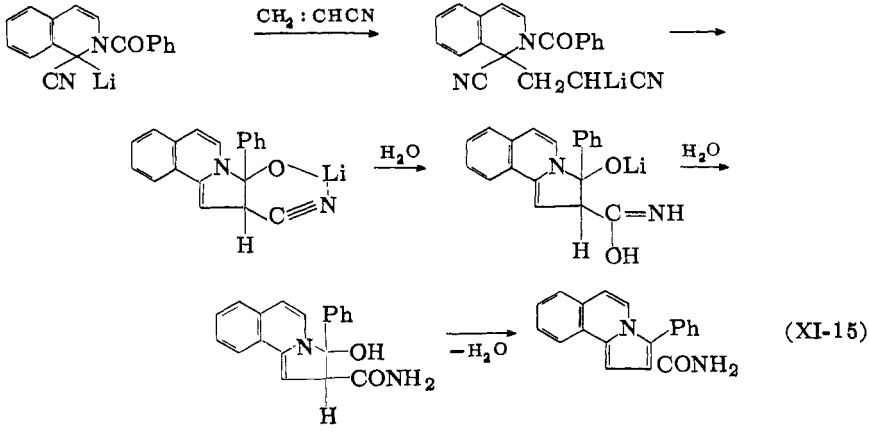
Condensations of 2- or 4-picolines with activated ketones, such as ethyl mesoxalate or barbituric acid, have been found to give yields of only about 30% of theory under a variety of conditions, both with and without a catalyst (*87,89–91*). More reactive ketones give much better yields. Thus ethyl benzoylglyoxylate gives a 74% yield of the condensation product when heated to 140° for two hours with 2-picoline (*90*) (Table XI-8, p. 380).

It is of interest that the strongly activated picoline 4-benzylpyridine yields ethyl β-phenyl-4-pyridinepyruvate when treated

with ethyl oxalate and potassium ethoxide in ethanol at 25° (*89*), whereas the *less* activated 2-picoline condenses twice with ethyl oxalate under the influence of sodamide in boiling ether, to yield α-(2-pyridylmethyl)-2-pyridineacrylic acid (*88*). These observations may indicate merely that the reaction takes different courses under different conditions, or that 4-benzylpyridine fails to react with its condensation product for steric reasons. The isolation of the free acid rather than the ester in the reaction with 2-picoline may have been the result of hydrolysis during the work-up of the reaction mixture with water. Such hydrolysis might be facilitated by chelation with a sodium ion (XI-14). A similar explanation has been



advanced for the hydrolysis of a nitrile to an amide in the 7,8-benzopyrrocoline series (*94*). After addition of acrylonitrile to an ethereal solution of the lithium salt of isoquinoline Reissert compound, the product isolated was always the amide; the nitrile could not be obtained (XI-15).



f. Condensations of Vinylpyridines with Esters

Malonic ester, acetoacetic ester, and other active methylene esters add across the double bond of 2-vinylpyridine (Michael addition), generally by several hours refluxing with excess ester in absolute ethanol containing sodium ethoxide. Occasionally the ester has been employed in place of ethanol as solvent; yields are fair to good. Boekelheide (*116,118*) discovered that condensation of one molecule of malonic ester with two molecules of 2-vinylpyridine is the main reaction if equimolar quantities of reactants are used; the simple monoadduct is obtained if an excess of malonic ester is employed. Ethyl *i*-butyrate is apparently the only simple aliphatic ester that has been added to a vinylpyridine (*5*).

Two references to the Michael additions of esters to ethyl 4-pyridineacrylate (*126*) and 4-vinylpyridine (*231*) were found. In the reaction between ethyl malonate and ethyl 4-pyridineacrylate, the usual order of addition to the double bond is reversed (see Table XI-9, p. 382).

The derivatives of malonic ester and acetoacetic ester listed in Table XI-9 may, in general, be hydrolyzed and decarboxylated in the normal way.

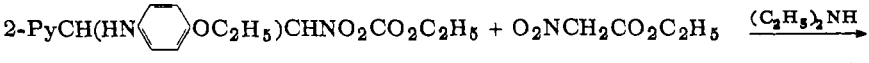
g. Condensations of Pyridine Aldehydes and Ketones

Pyridine aldehydes condense with active methylene compounds under the general conditions of the Perkin reaction, usually in good yield. If malonic acid is employed instead of the ester, the product usually decarboxylates *in situ* to the pyridineacrylic acid. Basic catalysts are almost always used; however, Rubtsov (*98*) condensed isonicotinaldehyde with malonic acid in hot acetic acid.

In a few cases, pyridine ketones have also been reported to engage in carbonyl condensation reactions, giving lower yields than the aldehydes, as would be expected.

It is interesting that picolinal-*p*-phenetidine condenses readily with nitroacetic ester. Treatment of the product with excess nitroacetic ester results in displacement of the phenetidine moiety (XI-16) (*103*).

These condensations are summarized in Table XI-10 (p. 384).



(XI-16)

h. Condensations of Pyridinecarboxylic Esters

Pyridinecarboxylic esters have been employed extensively in condensations of the Claisen type, under the usual conditions, to give β-pyridine-substituted β-keto esters. These reactions are summarized in Table XI-11 (p. 388), and require no further comment.

The β-oxopyridinepropionic esters listed in Table XI-11 undergo the normal reactions of β-keto esters. They may be alkylated in basic media with alkyl halides (*37,39,49*), converted to phenylhydrazones and pyridine-substituted pyrazolones (*37,50*), and saponified and decarboxylated (*39,40,43,49,50*). All of the isomeric acetylpyridines (*40*) and a few other acylated pyridines (*49,50*) have been prepared by the latter method. Catalytic and chemical reductions of the β-keto function are discussed below.

i. Condensations of Pyridineacetic Esters

Table XI-12 (p. 391) summarizes the condensations of pyridineacetic esters with activated ethylenic compounds (Michael addition), aldehydes, alkyl halides, and orthoesters. Basic catalysis has been the rule, except for the reaction of 2-pyridineacetic esters with ethyl orthoformate in acetic anhydride (*60,61*).

j. Reduction of Side-Chain Functions

Many pyridine-substituted aliphatic acids have been prepared by reduction of side-chain acids containing ethylenic or carbonyl unsaturation, such as may be prepared by methods previously discussed. Table XI-13 (p. 394) summarizes both complete reduction and partial reduction of keto acids to hydroxy acids. Both chemical and catalytic methods can be used, and yields are often excellent. With platinum catalyst, care must be taken to stop the reaction before nuclear reduction occurs.

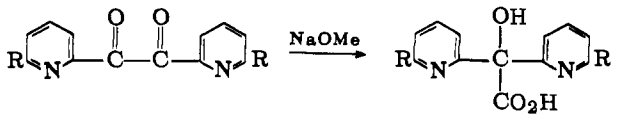
k. Willgerodt Reaction

Acetylpyridines are converted to pyridineacetic acid derivatives in good yield by means of the Willgerodt reaction and its variations (see Table XI-14, p. 397). 4-Ethylpyridine (*28*) and 2- and 4-vinylpyridines (*24–27*) may also be used as starting materials, although they give somewhat lower yields. Higher homologous pyridine aliphatic acids do not seem to have been prepared by this method.

The amides obtained by the Willgerodt reaction may be readily converted to acids or esters by the usual methods. These conversions are summarized in Table XI-15 (p. 398).

l. Benzilic Acid Rearrangement

The only recorded examples of the benzilic acid rearrangement applied to pyridine derivatives are due to Klosa (*271*) (XI-17).



(XI-17)

(R = H or CH_3)

B. PROPERTIES AND REACTIONS

The physical properties of the known side-chain acids are summarized in Tables XI-33, XI-34, and XI-35 (pp. 445 ff.).

1. Esterification and Ester Hydrolyses

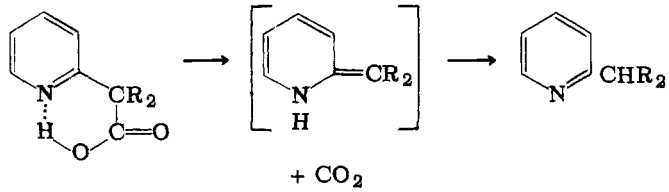
Pyridine side-chain acids may be esterified almost as easily as ordinary aliphatic acids, employing the same reagents. The only major difficulty is encountered with 2-pyridineacetic acid, which readily decarboxylates in solution above 60° (*145*). However, yields of the order of 50% of theoretical have been obtained under carefully controlled conditions. Diazomethane, which might be expected to give nearly quantitative yields, appears not to have been used to esterify 2-pyridineacetic acid.

Many pyridine side-chain acids have been prepared by hydrolysis of their esters, obtained through ester condensations or other reactions. In a few cases where the primary hydrolysis product is malonic, acetoacetic, or α-substituted 2-pyridineacetic acid, the hydrolysis is usually accompanied by decarboxylation to yield non-acidic products.

2. Decarboxylation

2-Pyridineacetic acid readily decarboxylates in neutral aqueous solution at 50–60° (*145*). A successful variation of the Japp-Klingemann reaction converts 1-(2-pyridyl)-3-carbethoxypentan-4-one to the

phenylhydrazone of ethyl 2-oxo-4-(2-pyridyl)butyrate (Tables XI-33 and XI-36, pp. 445 and 453). Strong evidence in support of a cyclic mechanism for this reaction (XI-18) was furnished by Doering and



(XI-18)

Pasternak (*32*) who found that optically active α-ethyl-α-methyl-2-pyridineacetic acid is rapidly decarboxylated to racemic 2-(1-methylpropyl)pyridine on neutralization of an aqueous solution of the hydrochloride of the acid with dilute base at room temperature. By contrast, prolonged boiling of either acidic or basic aqueous solutions of this acid produced little or no decarboxylation or racemization.

4-Pyridineacetic acids decarboxylate in high yield when an aqueous solution of the hydrochloride is heated to dryness (*154*). The reaction is facilitated by electron-withdrawing substituents on the ring (*112,113*) or the α carbon (*89*). No mechanistic study of this reaction appears to have been reported.

Decarboxylation reactions are summarized in Tables XI-16 and XI-17 (pp. 401 and 404).

3. Active Methylene Reactions

2-Pyridineacetic acid and its α-propyl derivative give very good yields in the Japp-Klingemann reaction (XI-19) (*31*). Ethyl 2-pyri-

$$\text{2-PyCHRCO}_2\text{H} + \text{ArN}_2\text{Cl} \xrightarrow[0^\circ]{} \text{2-PyCR:NNHAr}$$

R = H; Ar = *p*-$NO_2C_6H_4$, *p*-$HO_3SC_6H_4$, *p*-$HO_2CC_6H_4$: (XI-19)

R = *n*-propyl; Ar = *p*-$HO_2CC_6H_4$

dineacetate is readily monobrominated in the α-position in carbon bisulfide at 25°; it is converted by lead tetraacetate to the α-acetoxy derivative in 25% yield (*114*).

Ethyl 3-pyridineacetate is converted to its benzylidene derivative by treatment with benzaldehyde in ether in the presence of sodium (*20*).

4. Reduction

These reactions may be divided into three classes (see Table XI-18, p. 410).

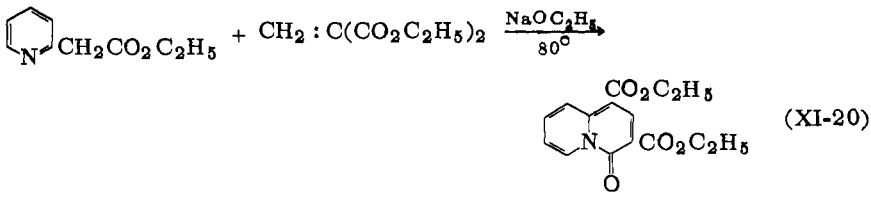
a. Chemical or catalytic reduction of the pyridine to a piperidine nucleus, with concurrent reduction of any side chain unsaturation. Phenyl substituents are not reduced by these methods.

b. Reduction of the carboxyl function summarized in Table XI-18. Reduction accompanied by quinolizidine ring closure is discussed in the next section.

c. Other substituents including dehalogenation (*132,139*) and reduction of a nitro to an amino function (*100*).

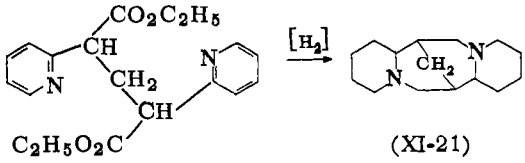
5. Syntheses of Condensed Heterocycles

2-Pyridineacetic esters may be cyclized at the ring nitrogen by condensation reactions, illustrated in XI-20, or by catalytic reduc-



(XI-20)

tion. An outstanding example of the latter reaction is the synthesis of *d,l*-sparteine (XI-21) from diethyl α,α'-di(2-pyridyl)glutarate (*59,*



(XI-21)

60). All of the compounds that have been prepared by these methods are quinolizidine derivatives, and are summarized in Table XI-19 (p. 413).

The syntheses of other condensed heterocyclic systems from pyridine side-chain acid derivatives are listed in Table XI-20.

C. FUNCTIONAL DERIVATIVES

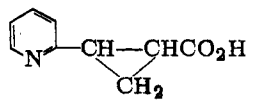
1. Esters

The esterification of side-chain acids has been discussed on p. 357. The known esters are given in Tables XI-36, XI-37, and XI-38 (pp. 453 ff.).

Reactions of esters have been discussed on pp. 356 ff. Further details are given in Table XI-12 (p. 391) and other tables.

2. Acid Chlorides and Anhydrides

A few acid chlorides have been prepared by the use of thionyl chloride, but none have been characterized. See Table XI-21 (p. 420). In one instance, the acid chloride prepared from an ester was treated with water, yielding 2-(2′-pyridyl)cyclopropanecarboxylic acid (XI-22), m.p. 99°; hydrochloride, m.p. 89° (*117*).



(XI-22)

No anhydrides of pyridine side-chain acids have been reported.

3. Amides

Many amides have been prepared from the side-chain acids, acid chlorides, and esters by the usual methods, often in excellent yield. Amides may also be prepared by the Willgerodt reaction (p. 356; Table XI-14, p. 397) and solvolysis of nitriles (p. 361; Table XI-27, pp. 435 ff.). Most of the amides obtained by the latter reactions have been hydrolyzed to the corresponding acids (Table XI-15, pp. 398 ff.). Physical properties of the side-chain amides found in the literature are reported in Tables XI-39, XI-40, and XI-41 (pp. 472 ff.).

Sodium hypobromite in methanol has been used to effect Hofmann rearrangement of 2- and 4-pyridinepropionamides to the

urethanes (*70*). Similarly, 3-pyridineacrylamide rearranges normally in the presence of sodium hypochlorite in methanol (*57*). Yields are not stated.

The synthesis of picolylisoquinolines is summarized in Table XI-20 (p. 419).

4. Hydrazides, Hydroxamic Acids, and Amidines

A few simple hydrazides have been prepared in moderate yield from side-chain esters and hydrazine. See Table XI-42, p. 486. They have been found to possess no tuberculostatic activity.

The only side-chain hydroxamic acid found in the literature is 3-$PyCH_2CONHOH$ (*169*).

The few known amidines were all prepared from nitriles, and are also listed in Table XI-42. Only one simple amidine appears to be known, the remaining compounds being 2-imidazoline derivatives.

5. Nitriles

a. Synthesis

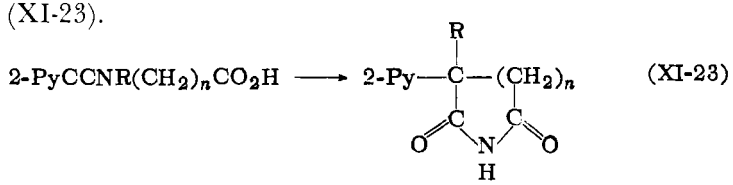
Many side-chain nitriles have been synthesized in recent years as intermediates for potential chemotherapeutic agents such as antihistamines and analgesics. Synthetic methods include pyridylation of nitriles with halopyridines (Table XI-22, p. 421); alkylation of pyridineacetonitriles with alkyl halides (Table XI-23, p. 426); Michael additions of vinylpyridine to hydrogen cyanide or activated nitriles and of vinyl compounds to pyridineacetic acid derivatives (Table XI-24, p. 429); Knoevenagel condensations with pyridine aldehydes (Table XI-25, p. 431); dehydration of pyridineacetamides; halogen-cyanide exchange; and lithium-cyanide exchange (Table XI-26, p. 433).

The physical properties of the known side-chain nitriles are given in Tables XI-43, XI-44, and XI-45 (pp. 488 ff.).

b. Solvolysis and Aminolysis

Many pyridine side-chain acids, amides, and esters have been prepared by the solvolysis of the corresponding nitriles. The products thus obtained are summarized in Table XI-27 (p. 435). In

acidic medium, the products are generally amides or esters, depending upon the solvent, while basic media favor the formation of acids. Decarboxylation was found to accompany hydrolysis in a few cases in which the starting material was a derivative of 2-pyridineacetonitrile (*86,123*). Of particular interest is the formation of cyclic five-, six-, and seven-membered imides in unstated yield (*85,147*) by hydrolysis of the corresponding nitrile derivatives under carefully controlled conditions (XI-23).



(XI-23)

(n = 1, 2, or 3)

Nearly all of the known derivatives of pyridineacetonitriles have been hydrolyzed under conditions such that the product was decarboxylated, *i.e.*, strong sulfuric acid above 130°, or strong alkali near 200°. These reactions have already been considered, and are summarized in Table XI-17 (p. 404). Aminolysis has been reported with ammonia (*160*) and ethylenediamine (*15*).

c. Reduction

This reaction has received little attention. The few examples which have been investigated are listed in Table XI-28 (p. 438). Secondary amine formation, due to reductive alkylation (*19,22,158*), and lactam formation (*86*) have been observed.

d. Reactions with Organometallic Compounds

α-Methyl-α-phenyl-2-pyridineacetonitrile reacts normally with alkyl Grignard reagents to yield ketones (*158*). See Table XI-29 (p. 439). However, the reaction of α-aryl-α-dimethylaminoethyl-2-pyridineacetonitriles with sodamide, ethyllithium, or ethylmagnesium bromide under a variety of conditions results in replacement of the cyano group, ultimately by hydrogen (*168*). It may be surmised from the few known examples that this reaction involves initial displacement of CN *as a positive ion* (XI-24).

$$\text{2-PyCRR'CN} + \text{R''}^{-}\text{M}^{+} \longrightarrow \text{2-PyCRR'}^{-}\text{M}^{+} + \text{R''}^{-}\text{CN}^{+}$$

$$\text{2-PyCRR'}^{-}\text{M}^{+} \xrightarrow{\text{H}_2\text{O}} \text{2-PyCRR'H} + \text{MOH}$$

R = Aryl
R' = $CH_2CH_2NMe_2$
R'' = C_2H_5, C_4H_9, or NH_2
M = Li, MgBr, or Na

(XI-24)

D. DERIVATIVES WITH SIDE CHAINS OF MIXED FUNCTION

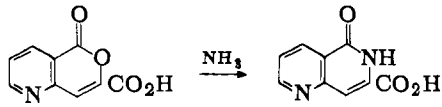
These compounds and their physical properties are not tabulated separately, but are incorporated into the tables of the simpler parent compounds. However, their chemistry presents a number of points of interest.

1. Carbonyl Derivatives

Side-chain acids containing a carbonyl function, prepared by methods described above (pp. 351 and 356), often form normal carbonyl derivatives. This property has been used to advantage in the formation of a number of pyrazolone derivatives (*37,39*). See Table XI-30 (p. 440). An interesting and useful variation of this reaction is the substitution of an amidine for hydrazine, resulting in the formation of 3-hydroxypyrazines (*37*). β-Keto esters have been nitrosated (*155*), and substituted on the α-carbon atom with aliphatic halides (*39,162*).

2. Hydroxyl Derivatives

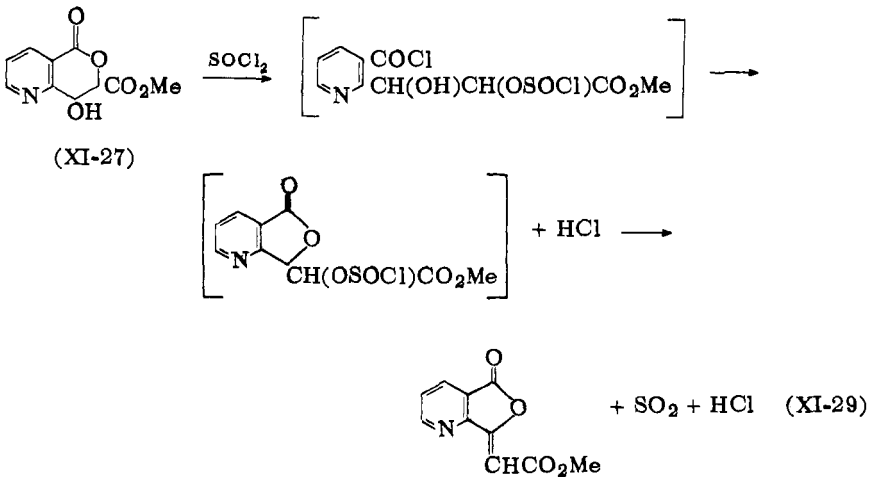
Side chains carrying a hydroxyl function, obtained by reactions described above (p. 356), give the usual ester derivatives. The formation of a lactone (*6,155*) should be noted, as well as its ready conversion to a lactam (XI-26) on heating with ammonia (*6*). The simple amide structure, derived from XI-25, was ruled out by the unequivocally acidic properties of the product.



(XI-25) (XI-26)

3. Ethylenic Derivatives

Introduction of a double bond (Table XI-31, p. 442) has been accomplished in the usual manner by dehydration (*63,75*), dehydrohalogenation (*63*), and the Tschugaeff reaction (*51*). The dehydration of lactone ester (XI-27) does not proceed normally. The authors (*155*) present convincing evidence that the product has structure XI-28, but do not propose a mechanism for its formation. A possible explanation is provided by equation XI-29.



(XI-27)

(XI-28)

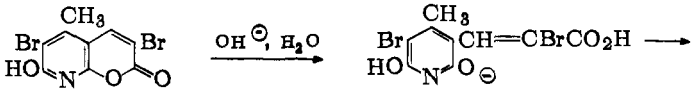
(XI-29)

The attempted double dehydrohalogenation of α,β-dibromo-4-pyridinepropionic acid (*69*) under a variety of conditions led only to 4-pyridineacrylic acid, with no trace of the desired acetylenic acid. The authors could find no precedent for such an observation, and therefore considered the possibility that the dibromide was actually an *N*-perbromide. Its properties, however, proved that it was not an *N*-perbromide.

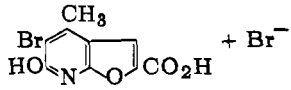
The addition reactions of unsaturated side-chains are summarized in Table XI-32 (p. 443). Either substitution (*132*) or addition to an olefinic double bond (*63,67,69*) may occur, depending upon the starting material. Michael addition has been observed in the presence of basic catalysts (*99,101*).

4. Displacement of Side-Chain Substituents

Side-chain halogen has been displaced by the action of dilute alkali (*63*) (Table XI-31, p. 442) or sodium acetate (*114*), the product being an alcohol or an acetate. Displacement of bromide from compound XI-30 results in formation of XI-31, presumably by the mechanism shown.



(XI-30)

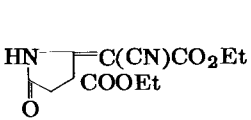
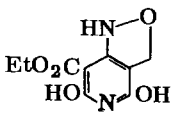
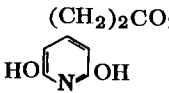
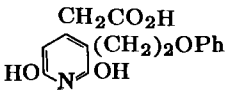
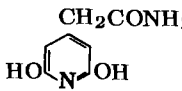


(XI-31)

E. TABLES

The following pages provide a thorough tabulation for the preparation, condensation, etc., of pyridine side-chain acids and their derivatives.

TABLE XI-1. Preparation of Side-Chain Acids from Nonpyridine Starting Materials

Starting materials	Conditions	Product	Yield	Ref.
	10% H_2SO_4, reflux			135
$EtO_2C(CH_2)_2C(CHCO_2Et)(EtO_2CCHCN)$	conc. H_2SO_4, 5 days, 25°; then + H_2O and reflux 12 hr.			136
$EtO_2CCH_2C(CHCO_2Et)(PhOCH_2CH_2CHCN)$	conc. HCl, reflux 12 hr.		45%	132
$EtO_2CCH:C(CH_2CO_2Et)_2$ + NH_4OH	sealed tube, 1 week, 25°			138

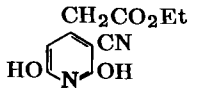
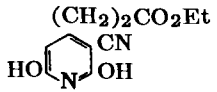
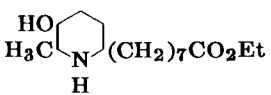
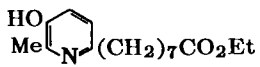
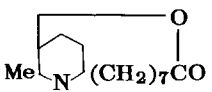
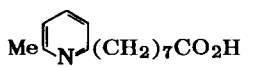
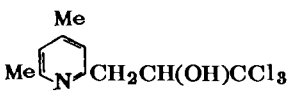
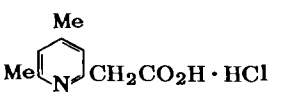
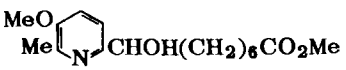
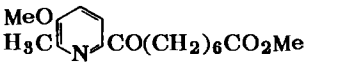
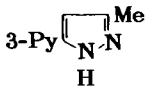
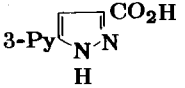
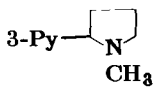
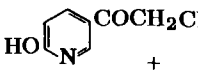
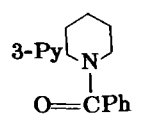
$O:C(CH_2CO_2Et)_2$ + $NCCH_2CONH_2$	piperidine, reflux 6 hr.		31%	139
$EtO_2CCH_2COCH_2CH_2CO_2Et$ + $NCCH_2CONH_2$	piperidine, 16 hr., 85°		36%	139
 Ethyl carpamate	Pd–C, refluxing *p*-cymene	 Ethyl carpyrinate	91%	137,185
 Carpaine	Pd–C, refluxing *p*-cymene	 Desoxycarpyrinic acid	85%	140

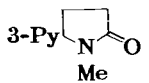
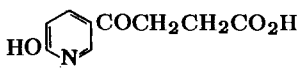
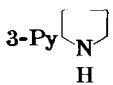
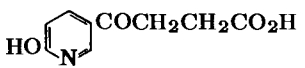
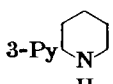
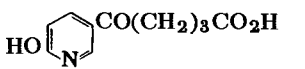
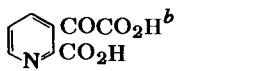
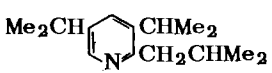
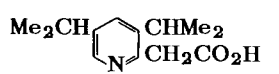
TABLE XI-2. Preparation of Side-Chain Acids by Oxidation

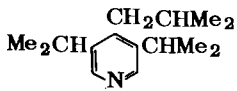
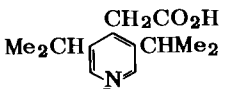
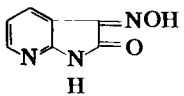
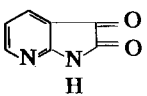
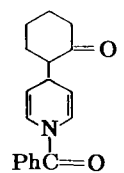
Starting material	Oxidant	Conditions	Product	Yield	Ref.
	$KMnO_4$	not stated			3
2-Py$(CH_2)_2CH(OEt)_2$	$KMnO_4$	not stated	2-Py$(CH_2)_2CO_2H$		84
2-PyCOCHNaCO_2Et	I_2		(2-PyCOCH$CO_2Et)_2$		270
2-PyCH$(CH_2CH_2OH)_2$	conc. HNO_3		2-PyCH$(CH_2CO_2H)_2$		218
2-PyCH(*p*-ClC_6H_4)CH : $CHCOCH_3$	CrO_3, H_2O-HOAc 100°, 10 min.		2-PyCH(*p*-ClC_6H_4)CO_2H	27%	262
2-PyCH$(CH_2OH)CH_2CH_2OH$	conc. HNO_3		2-PyCH$(CO_2H)CH_2CO_2H$		218
	conc. HNO_3				218
2-Py$(CH_2)_2CH$: $CClCH_3$	O_3, −10°; H_2O_2		2-Py$(CH_2)_2CO_2H$	81%	252
2-Py$(CH_2)_3COCH_3$	NaOBr		2-Py$(CH_2)_2CO_2H$ + 2-Py$(CH_2)_3CO_2H$	20% 21%	252
2-Py$(CH_2)_3OH$	$KMnO_4$	aq. H_2SO_4, 80°	2-Py$(CH_2)_2CO_2H$	37%	2
			2-Py$(CH_2)_2CO_2Et$[a]	14%	
2-Py$(CH_2)_9CH$: CHMe	$KMnO_4$	dry acetone, 4 hr., 35°	2-Py$(CH_2)_9CO_2H$	43%	4
2-Py$(CH_2)_{10}CH$: CH_2	$KMnO_4$	dry acetone, 4 hr., 35°	2-Py$(CH_2)_{10}CO_2H$	50%	4

	MnO_2	$CHCl_3$, 25°		71%	185
	$KMnO_4$	H_2O, 2 hr., 100°		50%	184,39
Nicotine	bacteria	culture, 5 days, 30°	$3\text{-PyCOCH}_2\text{CH}_2\text{CO}_2\text{H}$		190,205, 247
 (nicotine)	*Pseudomonas*	not stated	 + $3\text{-PyCOCH}_2\text{CH}_2\text{CO}_2\text{H}$	13% 25%	216,275
Nicotine		intravenous injection in dogs; extracted from urine	$3\text{-PyCH(NHCH}_3)\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$		253
Nicotine	roots of *Lapsans Communis*		$3\text{-PyCO(CH}_2)_2\text{CO}_2\text{H}$		276
	$KMnO_4$	H_2O, 2 hr., 100°	$3\text{-PyCHNH}_2(\text{CH}_2)_3\text{CO}_2\text{H}$	35%	1
$2\text{-Py(CH}_2)_2\text{CMe}_2\text{COMe}$	KOCl	H_2O, 60°	$2\text{-Py(CH}_2)_2\text{CMe}_2\text{CO}_2\text{H}$	78%	5

(*continued*)

TABLE XI-2. Preparation of Side-Chain Acids by Oxidation (*continued*)

Starting material	Oxidant	Conditions	Product	Yield	Ref.
6-Quinolinol	CaClOCl	H_2O, 20°		60%	6
Nicotine	O_2 (air)	several years, 25°			189
3-PyCH(CH_2CH_2OH)$_2$	conc. HNO_3		3-PyCH(CH_2CO_2H)$_2$		218
3-PyCO$CH_2CH_2CO_2H$	soil bacteria				247
 (nomicotine)	soil bacteria				247
 (anabasine)	soil bacteria				247
8-quinolinol	HNO_3	18 hr., 100°	 [b]	20%	150
	HNO_3	19 hr., reflux		40%	7

	HNO_3	19 hr., reflux			7
	$FeCl_3$	Zn + HCl, then aq. 42% $FeCl_3$		78%	8
4-PyCHPhCOCO$_2$Na	H_2O_2	not stated	4-PyCHPhCO$_2$Na		89
4-Py(CH$_2$)$_3$OH	$KMnO_4$	dil. H_2SO_4, 80°	4-Py(CH$_2$)$_2$CO$_2$H	61%	217
4-PyCH(CH$_2$CH$_2$OH)$_2$	conc. HNO_3		4-PyCH(CH$_2$CO$_2$H)$_2$		218
4-Py(CH$_2$)$_2$C(CH$_3$)$_2$COCH$_3$	KOCl		4-Py(CH$_2$)$_2$C(CH$_3$)$_2$CO$_2$H	11%	231
2-PyCH$_2$CH : CH$_2$	O_3, H_2O_2	O_3 in aq. HCl, 45 min.; then + H_2O_2	2-PyCH$_2$CO$_2$H · HCl	100%	9
	I_2	C_6H_6, 3 hr., reflux; fuse with KOH, 10 min.	4-Py(CH$_2$)$_5$CO$_2$H	10.5%	10

[a] Resulted on crystallization of crude 2-Py(CH$_2$)$_2$CO$_2$H from ethanol.
[b] Oxidation of 5,7-dinitro-8-hydroxyquinoline gave same product in minute yield.

TABLE XI-3. Carbonation of Organometallic Compounds

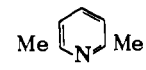
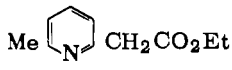
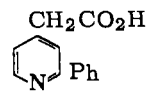
Starting materials	Conditions	Product	Yield	Ref.
2-PyMe	PhLi below 35°, + dry ice; CH_3OH + HCl esterification	2-$PyCH_2CO_2Me$	55%	29,33, 207
2-PyMe	PhLi in ether, 30 min.; + dry ice, EtOH + HCl esterification	2-$PyCH_2CO_2Et$	40%	30,31, 32
	same as above			81,210
4-PyMe	same as above; EtOH + HCl esterification	4-$PyCH_2CO_2Et$	34%	34,35, 225
4-PyMe	PhLi, $ClCO_2Et$; EtOH + HCl	4-$PyCH_2CO_2Et$	32%	225
2-PyEt	same as above	2-$PyCHMeCO_2Et$	15%	31
2-PyCHMeEt	same as above; also tried Ph_3CNa	starting material		32
4-PyMe	excess PhLi, ether, 10 hr. reflux; pour onto excess dry ice			36

TABLE XI-4. Arndt-Eistert Synthesis

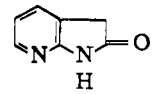
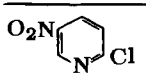
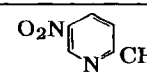
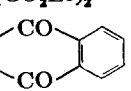
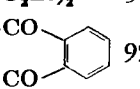
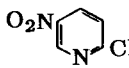
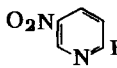
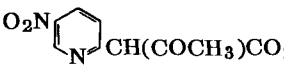
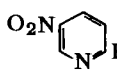
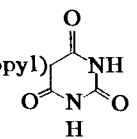
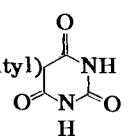
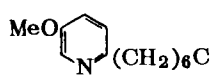
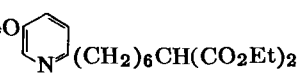
Starting material	Conditions	Product	Yield	Ref.
2-Py$(CH_2)_9COCl$	CH_2N_2, ether; then $Ag_2O + NH_4OH$, dioxane, 2 hr. 100°	2-Py$(CH_2)_{10}CONH_2$		4
	$PhN(CH_2)_2$, 180° 20 minutes		83%	8
	CH_2N_2, CH_2Cl_2; Ag_2O, MeOH		70%	127,128, 129
	CH_2N_2, CH_2Cl_2; Ag_2O, BuOH			129
4-Py$COCHN_2$	Ag_2O, EtOH	4-PyCH_2CO_2Et		233

TABLE XI-5. Condensation of Halopyridines with Active Methylene Compounds

Halide	Condensed with	Conditions	Product	Yield	Ref.
	$NaCH(CO_2Et)_2$, dry solid	1 hr., 120°		53%	33
2-PyBr	p-$ClC_6H_4CH_2CONMe_2$	$NaNH_2$, PhMe, 1 hr., 85°	2-PyCH(p-ClC_6H_4)$CONMe_2$		281
2-PyBr	$PhCH_2CONMe_2$	same as above	2-PyCHPh$CONMe_2$		281
2-PyBr	p-$ClC_6H_4CH_2CONEt_2$	same as above	2-PyCH(p-ClC_6H_4)$CONEt_2$		281
2-PyBr	p-$BrC_6H_4CH_2CON$ 	same as above	2-PyCH(p-BrC_6H_4)CON		281
2-PyBr	p-$BrC_6H_4CH_2CONEt_2$	same as above	2-PyCH(p-BrC_6H_4)$CONEt_2$		281
2-PyBr	p-$ClC_6H_4CH_2CON$ 	same as above	2-PyCH(p-BrC_6H_4)CON		281
2-PyBr	p-$MeC_6H_4CH_2CONMe_2$	same as above	2-PyCH(p-MeC_6H_4)$CONMe_2$		281
2-PyBr	o-$ClC_6H_4CH_2CONMe_2$	same as above	2-PyCH(o-ClC_6H_4)$CONMe_2$		281
2-PyBr	m-$MeOC_6H_4CH_2CONMe_2$	same as above	2-PyCH(m-$MeOC_6H_4$)$CONMe_2$		281
2-PyBr	p-$MeOC_6H_4CH_2CONMe_2$	same as above	2-PyCH(p-$MeOC_6H_4$)$CONMe_2$		281
2-PyBr	$NaCEt(CO_2Et)_2$, dry solid	30 hr., 140–150°	2-PyCHEtCO_2Et + 2-PyCEt$(CO_2Et)_2$	14% 10%	109
2-PyBr	Me_2CHCO_2Et	Ph_3CNa, decalin, 19 hr., 183°	2-PyCMe_2CO_2Et		32
2-$PyCH_2Cl$	$NaC(NHCOPh)(CO_2Et)_2$	EtOH, 6 hr., reflux	2-$PyCH_2C(NHCOPh)(CO_2Et)_2$	30%	115
2-$PyCH_2Cl$	$NaC(CO_2Et)_2N$ 	6 hr., 150°	2-$PyCH_2C(CO_2Et)_2N$ 	9%	17

	$NaCCH_3(CO_2Et)_2$ dry solid	1 hr., 150°		58%	111
	$CH_3COCHNaCO_2Et$ dry solid	45 min., 110–140°		22%	110
2-PyBr	$CH_2CH(Et)CO_2Et$	Ph_3CNa, decalin, 19 hr., 183°	2-$PyCMeEtCO_2Et$		32
2-$PyCH_2CH_2Cl$	$NaCH(CO_2Et)_2$	PhMe, 30 hr., 110°	2-$Py(CH_2)_2CH(CO_2Et)_2$	20%	124
2-$PyCHBrCO_2Et$	$NaCH(CO_2Et)_2$	absolute EtOH	2-$PyCH(CO_2Et)CH(CO_2Et)_2$	low	114
	$NaCEt(CO_2Et)_2$, dry solid	1 hr., 100–150°		44%	110
2-PyBr	5-*n*-propylbarbituric acid	$PhNMe_2$, 6 hr., 170°		29%	31
2-PyBr	5-*n*-butylbarbituric acid	same as above		29%	31
2-$Py(CH_2)_6Br$	$CH_2(CO_2Et)_2$	NaOEt, EtOH, trace KI	2-$Py(CH_2)_6CH(CO_2Et)_2$		237
	$CH_2(CO_2Et)_2$	NaOEt, EtOH, trace KI			237

(*continued*)

TABLE XI-5. Condensation of Halopyridines with Active Methylene Compounds (*continued*)

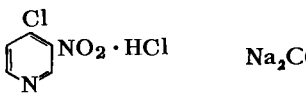
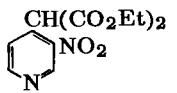
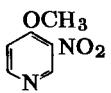
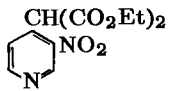
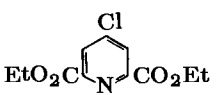
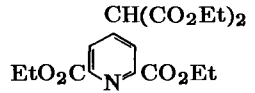
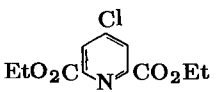
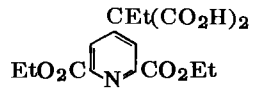
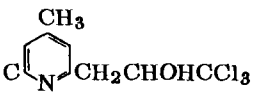
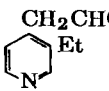
Halide	Condensed with	Conditions	Product	Yield	Ref.
2-Py$(CH_2)_{11}Br \cdot HBr$	$CH_2(CO_2Et)_2$	NaOEt, EtOH, 17 hr. reflux; then 10% KOH in MeOH	2-Py$(CH_2)_{11}CH(CO_2H)_2$	95%	143
3-PyCH_2Br	$EtCH(CO_2Et)_2$	NaOEt, EtOH, 1 hr., 100°	3-Py$CH_2CEt(CO_2Et)_2$		153
4-Py$CH_2Br \cdot HBr$	$NaC(NHCOPh)(CO_2Et)_2$	EtOH, 6 hr. reflux, hydrolyze, decarboxylate	4-Py$CH_2CHNH_2CO_2H$	6%	115
4-PyCH_2Br	$MeCONHCH(CO_2Et)_2$	NaOEt, C_6H_6, 2 hr., 80°	4-Py$CH_2C(CO_2Et)_2NHCOMe$	70%	267
	$Na_2C(CO_2Et)_2$	EtOH, 2 hr., 25°			113
	$CH_2(CO_2Et)_2$	NaOEt, EtOH, reflux 1 hr.			133
	$NaCH(CO_2Et)_2$	PhMe, 4 hr., 110°		50%	112
	$NaCEt(CO_2Et)_2$	same as above; 10% HCl, reflux 2 hr.			112

TABLE XI-6. Condensation of Chloral with Picolines

Picoline	Conditions	Product	Yield	Ref.
2-PyMe	heat, $ZnCl_2$, 10 hr.	2-$PyCH_2CHOHCCl_3$		62
2-PyMe	amyl acetate, 12 hr., 150°	same as above	45%	63,65
2-PyMe	38 hr., 112°	same as above	67%	64,273
2,4,6-Collidine	not stated			3,75
4-PyMe	16 hr., 90°	4-$PyCH_2CHOHCCl_3$	8%	66
4-PyMe	heat	same as above	35%	70
4-PyMe	$ZnCl_2$, 2 hr., 100°	same as above	43%	69,72,74
4-PyMe	Nuchar + Filter-cel 4 days, 40°; then 1 day, 70°	same as above	70%	61
4-PyMe	$ZnCl_3$, 16 hr., 85°	same as above	52%	73
4-PyMe	butyl acetate, 9 hr., 135°	same as above	42%	73
	$ZnCl_2$, 5 days, 36°		22%	67
	18 hr., 86°	same as above	67%	68

(continued)

TABLE XI-6. Condensation of Chloral with Picolines (*continued*)

Picoline	Conditions	Product	Yield	Ref.
4-PyEt	piperidine acetate, 16 hr., 80°	4-PyCH(CH_3)CHOHCCl_3	48%	234
4-Py(CH_2)$_2$OCOCH_3	piperidine acetate, C_6H_6, 16 hr.,	4-PyCH(CH_2OH)CHOHCCl_3 + 4-PyC(CH_2)CHOHCCl_3	10% + 29%	266
4-Py(CH_2)$_2$OMe	piperidine acetate, 29 hr., 55°	4-PyCH(CH_2OMe)CHOHCCl_3	46%	266

TABLE XI-7. Hydrolysis of $PyCH_2CHOHCCl_3$

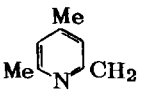
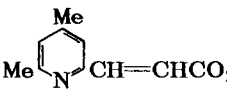
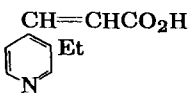
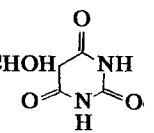
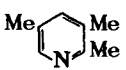
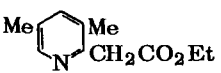
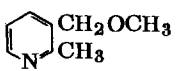
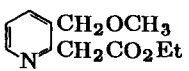
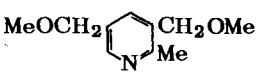
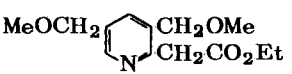
Py isomer	Conditions	Product	Yield	Ref.
2-Py	hot alcoholic KOH	2-PyCH : $CHCO_2H \cdot HCl$		62,77,79
2-Py	dilute aq. Na_2CO_3	2-$PyCH_2CHOHCO_2H$		63,64
2-Py	absolute ethanol, KOH	2-PyCH : $CHCO_2H$	50%	63,70
2-Py	EtOH, KOH, 65°	same as above	74%	76
2-Py	EtOH, KOH, reflux; EtOH + HCl esterification	2-PyCH : $CHCO_2Et$	56%	78,273
	aq. Na_2CO_3			3,75
4-Py	absolute EtOH, KOH, 65°	4-PyCH : $CHCO_2H$	70%	66
4-Py	absolute EtOH, KOH	same as above	74%	71,73,74
4-Py	EtOH, NaOEt, 60°	same as above	73%	69,72
	same as above		88%	68
	absolute EtOH, KOH	same as above	50%	67
4-$PyCH(CH_3)CHOHCCl_3$	alc. KOH, boil 2 hr.	4-$PyC(CH_3)$: $CHCO_2H$	24%	234
4-$PyCH(CH_2OMe)CHOHCCl_3$	alc. KOH, 50°, 2 hr.; EtOH, HCl, 3 hr., 80°	4-$PyC(CH_2OMe)$: $CHCO_2Et$	63%	266

TABLE XI-8. Condensations with Picolines to Give Side-Chain Acids and Esters

Picoline	Condensed with	Conditions	Product	Yield	Ref.
2-PyMe	$(CO_2Et)_2$	KNH_2 or $NaNH_2$, ether, 2 hr., 36°	2-$PyCH_2C(COOH):CHPy$-2′	23%	88
2-PyMe	$CO(CO_2Et)_2$	2 hr., 140°	2-$PyCH_2COH(CO_2Et)_2$	33%	90,91
2-PyMe	$PhCOCOCO_2Et$	1 hr., 140°	2-$PyCH_2COH(COPh)CO_2Et$	74%	90,91
2-PyMe	barbituric acid	2.5 hr., 140°		30%	90,91
2-PyMe	$CO(OEt)_2$	5–10 hr., ether, 36°	2-$PyCH_2CO_2Et$	25%	92
2-PyMe	$CO(OEt)_2$	PhLi, ether heat to 36°	2-$PyCH_2CO_2Et$	44%	93
	$CO(OEt)_2$	PhLi, ether 1 hr., 25°		30%	121
	$CO(CO_2Et)_2$	KNH_2			272
	$CO(OEt)_2$	KNH_2, ether, 2 hr, 36°		36%	121
2-PyCHMeEt	$ClCO_2Et$	PhLi, hexane, 2.5 hr., 58°	2-$PyCMeEtCO_2Et$	low	32

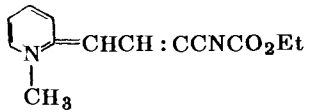
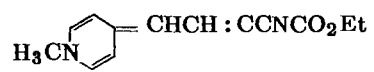
2-PyMe · CH_3I	$EtOCH:CCNCO_2Et$	KOH, MeOH			194
2-PyCHPhCN	$BrCH_2CO_2Et$	$NaNH_2$, ether	2-PyCPh(CN)CH_2CO_2Et		85
2-PyCHPhCN	$CH_2:CHCO_2CH_3$	$NaNH_2$, ether	2-PyCPhCN$(CH_2)_2CO_2Et$		85
2-PyCHPhCN	$BrCH_2CO_2Et$	$NaNH_2$, 2 hr., 100°	2-PyCPhCNCH_2CO_2Et	80%	86
2-PyCHPhCN	$Br(CH_2)_2CO_2Et$	$NaNH_2$, 2 hr., 100°	2-PyCHPhCN$(CH_2)_2CO_2Et$	71%	86
2-PyCH(*p*-ClC_6H_4)CN	$CH_2:CHCO_2Et$	$NaNH_2$, ether	2-PyCCN(*p*-ClC_6H_4)$(CH_2)_2CO_2Et$		85
2-PyCH(*p*-ClC_6H_4)CN	$BrCH_2CO_2Et$	$NaNH_2$, 2 hr., 100°	same as above	70%	86
2-PyCHPh$(CH_2)_2NMe_2$	$CO(OEt)_2$		2-PyCPh$(CO_2Et)(CH_2)_2NMe_2$		224
$(2\text{-Py})_2CH_2$	$Br(CH_2)_2CO_2Et$	PhLi	$(2\text{-Py})_2CH(CH_2)_2CO_2Et$	14%	256
2-PyCH$_2$Ph	$ClCH_2CONMe_2$	$NaNH_2$	2-PyCHPhCH_2CONMe_2		269
4-PyMe	$CO(CO_2Et)_2$	piperidine acetate 100°	4-PyCH$_2$COH$(CO_2Et)_2$	30%	87
4-PyMe	CO_2	PhLi; MeOH, HCl	4-PyCH$_2CO_2Me$	25%	244
4-PyMe	$ClCO_2Et$	PhLi, $ClCO_2Et$; EtOH + HCl	4-PyCHCO_2Et	32%	225
4-PyEt	$(HO)_2C(CO_2Et)_2$	Ac_2O, 10 hr., 90°	4-PyCH(CH_3)COH$(CO_2Et)_2$	66%	234
4-PyMe	$CO(CO_2Et)_2$	heated in Ac_2O	4-PyCH:C$(CO_2Et)_2$	30%	87
4-PyCH$_2$Ph	$(CO_2Et)_2$	KOEt, EtOH, 12 hr., 25°	4-PyCHPhCOCO_2Et	33%	89
4-PyCH$_3$ · CH_3I	$EtOCH:CCNCO_2Et$	KOH, CH_3OH			194
4-PyCHPh$(CH_2)_2NMe_2$	$CO(OEt)_2$		4-PyCPh$(CO_2Et)(CH_2)_2NMe_2$		224

TABLE XI-9. Condensations of Vinylpyridines with Esters

Condensed with	Conditions	Product	Yield	Ref.
$CH_2(CO_2Et)_2$, excess	not stated	2-Py$(CH_2)_2CH(CO_2Et)_2$	43%	116
$CH_2(CO_2Et)_2$, 1.0 equivalent	not stated	$(2\text{-PyCH}_2CH_2)_2C(CO_2Et)_2$		116,118
$CH_2(CO_2Et)_2$, 2.0 equivalent	NaOEt, EtOH, 2 hr., reflux	2-Py$(CH_2)_2CH(CO_2Et)_2$	53%	118,122, 124
$NaCH(CO_2Et)_2$	EtOH, trace hydroquinone, 6 hr. reflux	2-Py$(CH_2)_2CH(CO_2Et)_2$	33%	11
$EtCH(CO_2Et)_2$, 2.0 equivalent	NaOEt, EtOH, 2 hr., reflux	2-Py$(CH_2)_2CHEtCO_2Et$	47%	118
$EtCH(CO_2Et)_2$, 1.5 equivalent	same as above	2-Py$(CH_2)_2CEt(CO_2Et)_2$	39%	118
$NCCH_2CO_2Et$	Na, 100°, 5 hr.	2-Py$(CH_2)_2CHCNCO_2Et$	48%	53
Me_2CHCO_2Et	Na, 6 hr., reflux	2-Py$(CH_2)_2CMe_2CO_2Et$	48%	5
2-PyCH_2CO_2Et	NaOEt, 6 hr., 80°	2-Py$(CH_2)_2CH$(2-Py)CO_2Et	61%	55,197
$PhCH_2CO_2Et$	NaOEt, 5 hr., 130°	2-Py$(CH_2)_2CHPhCO_2Et$	60%	198
$CH_3COCH_2CO_2Et$	dry HCl, 10 min.; 3 hr. reflux	2-Py$(CH_2)_2CH(COMe)CO_2Et$	50%	118
$CH_3COCHNaCO_2Et$	$CH_2COCH_2CO_2Et$ solvent; 6 hr., reflux	2-Py$(CH_2)_2CH(COMe)CO_2Et$	58%	11
$CH_2CH_2CH(COCH_3)COO$	Na, 3 hr., reflux	2-Py$(CH_2)_2$C(COMe)CO CH_2CH_2O	40%	119
$CH_3COCHCNCO_2Et$	NaOEt, Ph, 7 hr., reflux	2-Py$(CH_2)_2$CCNCO_2Et COMe	58%	123
$PhCOCH_2CO_2Et$	Na, 5 hr., reflux	2-Py$(CH_2)_2CH(COPh)CO_2Et$	70%	119
N_2CHCO_2Et	xylene, 0.5 hr., 130°	CH_2 2-PyCH—$CHCO_2Et$	63%	117,125

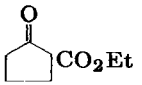
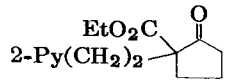
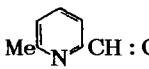
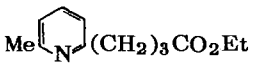
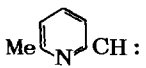
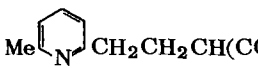
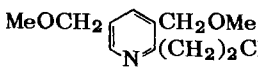
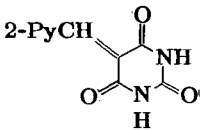
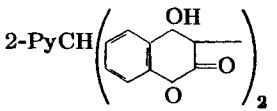
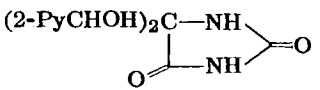
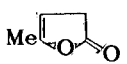
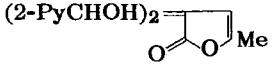
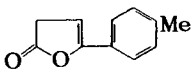
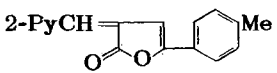
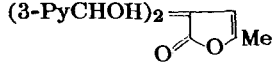
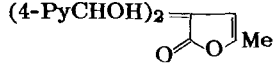
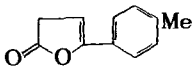
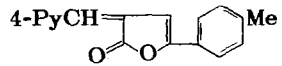
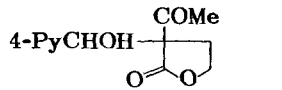
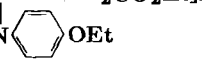
				240
 condensed with ethyl acetate	not stated			246
 condensed with acetoacetic ester	not stated			260
 condensed with $CH_2(CO_2Et)_2$	NaOEt, EtOH, 1 hr., reflux		25%	148
3-PyCH : $CHCO_2Et$ condensed with $NaCH(CO_2Et)_2$	EtOH, 1 hr., 63°	2-PyCH[$CH(CO_2Et)_2$]CH_2CO_2Et	93%	268
4-PyCH : $CHCO_2Et$ condensed with $CH_2(CO_2Et)_2$	NaOEt, 1 hr., 60°	4-PyCH(CH_2CO_2Et)$CH(CO_2Et)_2$	94%	126
2-PyC(: CH_2)CH_2O_2CMe condensed with $CH_2(CO_2Et)_2$	NaOEt, 1.5 hr., reflux	2-PyC(: CH_2)$CH_2CH(CO_2Et)_2$	75%	208
4-PyCH : CH_2 condensed with $CH_3COCH_2CO_2Et$	Na, reflux 6 hr.	4-Py$(CH_2)_2CH(COCH_3)CO_2Et$	67%	231
4-PyCH : CH_2 condensed with $CH_3COCH(CH_3)CO_2Et$	Na, reflux 24 hr.	4-Py$(CH_2)_2C(CH_3)(COCH_3)CO_2Et$	29%	231
4-PyCH : CH_2 condensed with $(CH_3)_2CHCO_2Et$	Na, reflux 3 hr.	4-Py$(CH_2)_2C(CH_3)_2CO_2Et$	28%	231

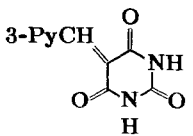
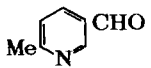
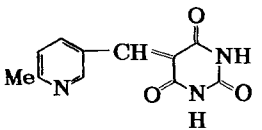
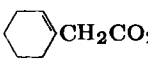
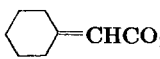
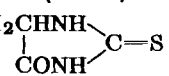
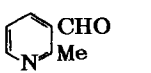
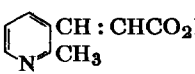
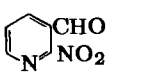
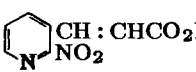
TABLE XI-10. Condensation of Pyridine Aldehydes and Ketones Yielding Side-Chain Acid Derivatives

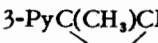
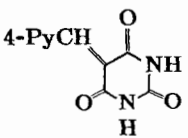
Aldehyde	Condensed with	Conditions	Product	Yield	Ref.
2-PyCHO	$CH_2(CO_2H)_2$	PyH, piperdine, 2 hr., 100°	2-PyCH : $CHCO_2H$	45%	149
2-PyCHO	$CH_2(CO_2H)_2$	Py, piperidine	2-PyCH : $CHCO_2H$	83%	227
2-PyCHO	$PhCOCH_2CO_2Et$	Piperidine, 25°	2-PyCH : $CPhCO_2Et$	58%	289
2-PyCHO	barbituric acid	H_2O, 90°		90%	289
2-PyCHO	$MeCOCH_2CO_2Et$	Et_2NH	2-PyCH : $C(COMe)CO_2Et$	80%	289
2-PyCHO	$NCCH_2CO_2Et$	EtOH, Et_2NH	2-PyCH : $C(CN)CO_2Et$	87%	289
2-PyCHO	4-hydroxycoumarin	MeOH		85%	289
2-PyCHO	hydantoin			55%	289
2-PyCHO	$O_2NCH_2CO_2Et$	Et_2NH, EtOH, 7 days, 20°	$[2\text{-PyCH}(CHNO_2CO_2Et)_2]Et_2NH$[a]	83%	103,104
2-PyCHO		ether, $EtNH_2$, 0°		60%	188
2-PyCHO		same as above		76%	188

3-PyCHO		same as above		43%	188
4-PyCHO	same as above	same as above		60%	188
4-PyCHO		same as above		78%	188
4-PyCHO		same as above		62%	188
2-PyCH : N⟨⟩OEt	$O_2NCH_2CO_2Et$	Et_2NH, 0°	[2-PyCHCHNO$_2$CO$_2$Et]Et$_2$NH[a] 	95%	103
2-PyCOPh	$NCCH_2CO_2Et$	NaOEt	2-PyCPh : $CCNCO_2Et$	24%	107
3-PyCHO	$CH_2(CO_2H)_2$	PyH, piperidine, 2 hr., 100°	3-PyCH : $CHCO_2H$	74–90%	95–97, 99,149
3-PyCHO	$CH_2(CO_2H)_2$	$MeNH_2 \cdot HOAc$, abs. EtOH, 2 hr., reflux	3-PyCH(NHMe)CH_2CO_2H	20%	99
3-PyCHO	$CH_2(CO_2Et)_2$	piperidine, 9 hr., 25°	3-PyCH : $C(CO_2Et)_2$	71%	101
3-PyCHO	$CH_2(CO_2Et)_2$	piperidine, 7 days, 25°	3-PyCHOHCH$(CO_2Et)_2$	77%	277
3-PyCHO	$NCCH_2CO_2Et$	Et_2NH, heat	3-PyCH : $C(CN)CO_2Et$		226
3-PyCHO	$NCCH_2CO_2CH_2Ph$	piperidine, EtOH, HOAc, reflux 2 hr.	3-PyCH : $C(CN)CO_2CH_2Ph$	77%	274

(*continued*)

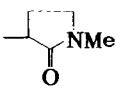
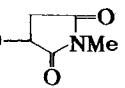
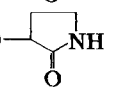
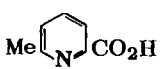
TABLE XI-10. Condensation of Pyridine Aldehydes and Ketones Yielding Side-Chain Acid Derivatives (*continued*)

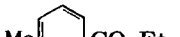
Aldehyde	Condensed with	Conditions	Product	Yield	Ref.
3-PyCHO	barbituric acid				226
	barbituric acid				226
3-PyCHO	*p*-$MeOC_6H_4CH_2CO_2H$	Et_3N	3-PyCH : C(*p*-$MeOC_6H_4$)CO_2H		105
3-PyCHO		Et_3N, Ac_2O, 15 hr., 110°	3-PyCH : C()CO_2H	52%	106,108
3-PyCHO		same as above	3-PyCH : C()CO_2H		106
3-PyCHO	acetylthiohydantoin	NaOAc, 1/2 hr., 115°; Ac_2O, red P, HI, 6 hr., reflux		60%	115
	$CH_2(CO_2H)_2$	PyH, piperidine, 3 hr., 100°		50%	102
	$CH_2(CO_2H)_2$	piperidine, 3 hr. reflux		43%	100

3-PyCOCH$_3$	$(CO_2Et)_2$	NaOEt, PhMe, 1.5 hr., 0–5°	3-PyCOCH$_2$COCO$_2$Et	51%	146
3-PyCOCH$_3$	BrCH$_2$CO$_2$Et	NaOEt, PhMe, 7 hr., 0–5°		30%	146
4-PyCHO	CH$_2$(CO$_2$H)$_2$	PyH, piperidine, 2 hr., 100°	4-PyCH:CHCO$_2$H	49%	149
4-PyCHO · HCl	CH$_2$(CO$_2$H)$_2$	HOAc, 3/4 hr., 90°	4-PyCH:C(CO$_2$H)$_2$ · 1.5 H$_2$O	81%	98
4-PyCHO · HCl	CH$_2$(CO$_2$Et)$_2$	PyH, piperidine, 4 days, 25°	4-PyCH:C(CO$_2$Et)$_2$	62%	98
4-PyCHO	NCCH$_2$CO$_2$Et		4-PyCH:C(CN)CO$_2$Et		226
4-PyCHO	NCCH$_2$CO$_2$CH$_2$Ph	piperidine, EtOH, HOAc, reflux 2 hr.	4-PyCH:C(CN)CO$_2$CH$_2$Ph	62%	274
4-PyCHO	barbituric acid				226

[a]Diethylamine salt of the nitronic acid.

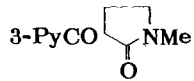
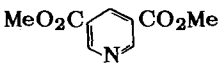
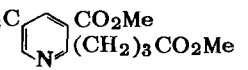
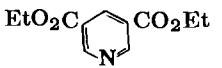
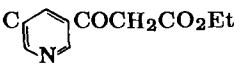
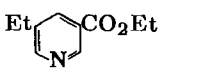
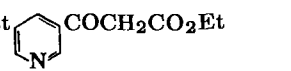
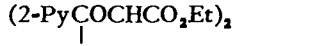
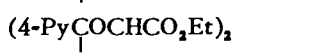
TABLE XI-11. Condensations of Pyridinecarboxylic Esters Yielding Side-Chain Acid Derivatives

Pyridine ester	Condensed with	Conditions	Product	Yields	Ref.
2-$PyCO_2Et$	$MeCO_2Et$	NaOEt, EtOH	2-$PyCOCH_2CO_2Et$		37,270
2-$PyCO_2Et$	$MeCO_2Et$	same as above	2-$PyCOCH_2CO_2Et$	(50%)[a]	40
2-$PyCO_2Et$	$MeCO_2Et$	same as above	same as above	70%	42
2-$PyCO_2Et$	$MeCO_2Et$	NaOMe, PhH 6 hr. reflux	same as above	84%	120
2-$PyCO_2Et$	$(CH_2CO_2Et)_2$	NaOEt, 1 hr., reflux; HCl hydrol. and re-esterification	2-$PyCO(CH_2)_2CO_2Et$	32%	46
2-$PyCO_2Et$	*N*-methylpyrrolidone	NaOEt, PhH, 8 hr., reflux		87%	48
2-$PyCO_2Et$	*N*-methylsuccinimide	Na, PhH, 15 hr., 110°		91%	49
2-$PyCO_2Et$	2-pyrrolidone	same as above		67%	49
2-$PyCO_2Et$	γ-butyrolactone	NaOMe, PhH, 15 hr., 110°	$CH_2CH_2CH(2\text{-}PyCO)COO$	83%	49
2-$PyCO_2Et$	$CH_2CH(OEt)(CH_2)_2COO$	Na, PhH, 15 hr., 110°	$CH_2CH(OEt)CH_2CH(2\text{-}PyCO)COO$		50
	$HOC(CH_2)_6CO_2Me$	*p*-cymene, 25 hr., reflux		9%	185

	$MeCO_2Et$	NaOEt, EtOH			37
	$HOC(CH_2)_6CO_2Me$	*p*-cymene, 25 hr., reflux		25%	185
	$(CH_2CO_2Et)_2$	NaOEt, PhH, 1 hr., 100°; HCl hydrol. and re-esterification		50%	45
2-Py$(CH_2)_3CO_2Et$	$(CO_2Et)_2$	KOEt	2-Py$(CH_2)_2CH(CO_2Et)COCO_2Et$	82%	236
3-PyCO_2Et	$MeCO_2Et$	NaOEt, EtOH, 6 hr., reflux	3-Py$COCH_2CO_2Et$	70%	37,38, 39
3-PyCO_2Et	$MeCO_2Et$	same as above	same as above	(81%)[a]	40
3-PyCO_2Et	$MeCO_2Et$	same as above	same as above	37%	42
3-PyCO_2Et	$MeCO_2Et$	NaOMe, 6.5 hr., 115°	same as above	74%	120
3-Py$C^{18}O_2Et$	$MeCO_2Et$	not stated	3-Py$C^{18}OCH_2CO_2Et$		43
3-PyCO_2Et	$MeCH_2CO_2Et$	NaOEt, EtOH	3-Py$COCHMeCO_2Et$		42
3-PyCO_2Et	$Me(CH_2)_2CO_2Et$	ground with NaH at 110° until gas evolution ceased	3-Py$COCHEtCO_2Et$	68%	44
3-PyCO_2Et	$(Me)_2CHCH_2CO_2Et$	same as above	3-Py$COCH(i\text{-}Pr)CO_2Et$	34%	44
3-PyCO_2Et	$(CH_2CO_2Et)_2$	$NaNH_2$, ether 2.5 hr., 36°	3-Py$COCH(CO_2Et)CH_2CO_2Et$	56%	99

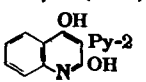
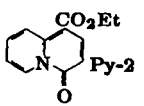
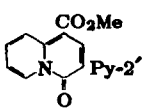
(*continued*)

TABLE XI-11. Condensations of Pyridinecarboxylic Esters Yielding Side-Chain Acid Derivatives (*continued*)

Pyridine ester	Condensed with	Conditions	Product	Yield	Ref.
3-$PyCO_2Et$	$(CH_2CO_2Et)_2$	NaOEt, PhMe, 3 hr., 80°	3-$PyCOCH(CO_2Et)CH_2CO_2Et$	20%	202,263
3-$PyCO_2Et$	*N*-methylpyrrolidone	NaOEt, PhH, 8 hr., reflux		70%	47,144
3-$PyCO_2Et$	$CH_3COCH(NA)COEt$	4 hr., 160°	3-$PyCOCH_2CO_2Et$	4%	52
3-$PyCOCH_2CO_2Et$	$BrCH_2CO_2Et$	KOEt	3-$PyCOCH(CO_2Et)CH_2CO_2Et$	67%	202
	$[OOC(CH_2)_3CO_2Me]_2$	3 hr., 150°		15%	148
	$MeCO_2Et$	NaOEt, PhMe, 2 days		87%	249
	$MeCO_2Et$	same as above		56%	249
4-$PyCO_2Et$	CH_3CO_2Et	NaOEt, EtOH	4-$PyCOCH_2CO_2Et$		37
4-$PyCO_2Et$	CH_3CO_2Et	same as above	same as above	(79%)[a]	40
4-$PyCO_2Et$	CH_3CO_2Et	same as above	same as above	53%	41
4-$PyCO_2Et$	CH_3CO_2Et	same as above	same as above	80%	42
2-$PyCOCH(K)CO_2Et$	itself	I_2, ether			37
4-$PyCOCH(K)CO_2Et$	itself	same as above			37

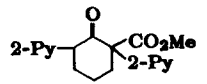
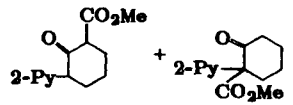
[a]The esters were not isolated, but were used in further syntheses which gave the over-all yields shown in parentheses.

TABLE XI-12. Condensations of Pyridineacetic Acids and Esters to Longer-Chain Acid Derivatives

Pyridine ester	Condensed with	Conditions	Product	Yield	Ref.
2-$PyCH_2CO_2Et$	$CH_2:CHCN$	Na, 2 hr., 180°	2-$PyCH(CO_2Et)(CH_2)_2CN$	74%	53
2-$PyCH_2CO_2Et$	$CH_2:CHCO_2Et$	Na, 2 hr., 140°	2-$PyCH(CO_2Et)(CH_2)_2CO_2Et$	82%	53
2-$PyCH_2CO_2Et$	$CH_2CH:CHCO_2Et$	NaOEt, EtOH, 2 hr., reflux	2-$PyCH(CO_2Et)CHMeCG_2CO_2Et$	59%	54
2-$PyCH_2CO_2Et$	2-$PyCH:CH_2$	NaOEt, 6 hr., 80°	2-$PyCH(CO_2Et)(CH_2)_2$Py-2	61%	55
2-$PyCH_2CO_2Et$	HCO_2Et	KOEt, EtOH, 18 hr., 25°	2-$PyCH(CHO)CO_2Et$	64%	56
2-$PyCH_2CO_2Et$	$ClCH_2CO_2Et$	same as above	2-$PyCH(CO_2Et)CH_2CO_2Et$	17%	56
2-$PyCH_2CO_2Et$	$Br(CH_2)_2OPh$	K, ether, 6 hr., 36°	2-$PyCH(CO_2Et)(CH_2)_2OPh$	33%	56
2-$PyCH_2CO_2Et$	HCO_2Et	Na, ether	2-$PyCH(CHO)CO_2Et$	60%	57
2-$PyCH_2CO_2Et$	methyl anthranilate	Na, 100–20°		74%	57
2-$PyCH_2CO_2Et$	CH_2I_2	K^+ salt, PhH, 0.5 hr. 80°	$(2\text{-PyCHCO}_2\text{Et})_2CH_2$	32%	59
2-$PyCH_2CO_2Et$	$HC(OEt)_3$	Ac_2O, 2 hr., "heat"		65%	60,61
2-$PyCH_2CO_2Et$	$PhO(CH_2)_2Br$		2-$PyCH[(CH_2)_2OPh]CO_2Et$		195
2-$PyCH_2CO_2Me$	CH_2I_2	K, PhH	$(2\text{-PyCHCO}_2\text{Me})_2CH_2$		141
2-$PyCH_2CO_2Me$	CH_2O	piperidine, 5 min., 120°	$(2\text{-PyCHCO}_2\text{Et})_2CH_2$	58%	59
2-$PyCH_2CO_2Me$	$HC(OEt)_3$	Ac_2O, 2 hr., "heat"		65%	61

(*continued*)

TABLE XI-12. Condensations of Pyridineacetic Acids and Esters to Longer-Chain Acid Derivatives (*continued*)

Pyridine ester	Condensed with	Conditions	Product	Yield	Ref.
2-PyCHKCO$_2$Et	Cl(CH$_2$)$_3$OCH$_2$Ph	PhMe$_2$, reflux 2 hr.	2-PyCH(CO$_2$Et)(CH$_2$)$_3$OCH$_2$Ph	39%	254
2-PyCH$_2$CO$_2$Me	CH$_2$(CH$_2$Br)$_2$	KNH$_2$, ether, 48 hr., 36°	[2-PyCH(CO$_2$Et)CH$_2$]$_2$CH$_2$	76%	248
[2-PyCH(CO$_2$Et)CH$_2$]$_2$CH$_2$	Dieckmann cyc.			30%	248
2-PyCH$_2$CO$_2$Me	Br(CH$_2$)$_4$CO$_2$Me	KNH$_2$, ether, 48 hr., 36°	2-PyCH(CO$_2$Me)(CH$_2$)$_4$CO$_2$Me	49%	248
2-PyCH(CO$_2$Me)(CH$_2$)$_4$CO$_2$Me	Dieckmann cyc.				248
2-PyCH(*p*-ClC$_6$H$_4$)CONMe$_2$	ClCH$_2$CH$_2$NMe$_2$	NaNH$_2$	2-PyC(*p*-ClC$_6$H$_4$)(CONMe$_2$)CH$_2$CH$_2$NMe$_2$		281
2-PyCHPhCONMe$_2$	ClCH$_2$CH$_2$NMe$_2$	same as above	2-PyCPh(CONMe$_2$)CH$_2$CH$_2$NMe$_2$		281
2-PyCH(*p*-ClC$_6$H$_4$)CONEt$_2$	ClCH$_2$CH$_2$NMe$_2$	same as above	2-PyC(*p*-ClC$_6$H$_4$)(CONEt$_2$)CH$_2$CH$_2$NMe$_2$		281
2-PyCH(*p*-BrC$_6$H$_4$)CON 	ClCH$_2$CH$_2$NMe$_2$	same as above	2-PyC(*p*-BrC$_6$H$_4$)(CON )CH$_2$CH$_2$NMe$_2$		281
2-PyCH(*p*-ClC$_6$H$_4$)CON 	ClCH$_2$CH$_2$NMe$_2$	same as above	2-PyC(*p*-ClC$_6$H$_4$)(CON)CH$_2$CH$_2$NMe$_2$		281

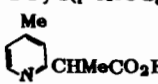
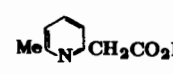
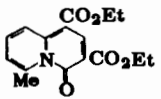
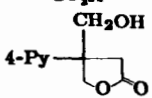
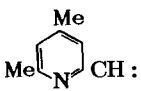
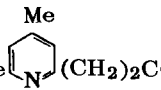
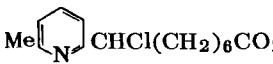
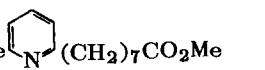
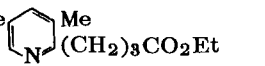
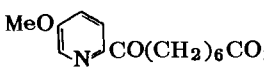
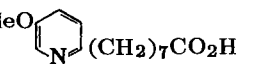
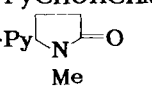
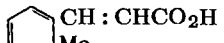
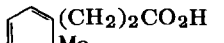
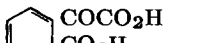
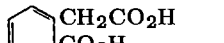
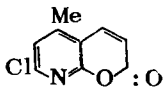
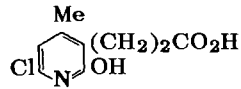
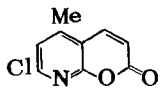
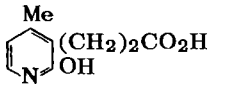
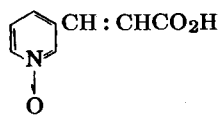
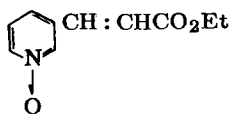
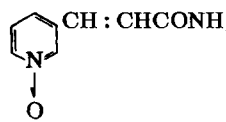
2-PyCHPhCONMe$_2$	ClCH$_2$CH$_2$N⟨O⟩	same as above	2-PyCPh(CONMe$_2$)CH$_2$CH$_2$N⟨O⟩		281
2-PyCH(*p*-BrC$_6$H$_4$)CONEt$_2$	ClCH$_2$CH$_2$N⟨⟩	same as above	2-PyC(*p*-BrC$_6$H$_4$)(CONEt$_2$)CH$_2$CH$_2$N⟨⟩		281
2-PyCH(*p*-ClC$_6$H$_4$)CON⟨⟩	ClCH$_2$CH$_2$N⟨⟩	same as above	2-PyC(*p*-ClC$_6$H$_4$)(CON⟨⟩)CH$_2$CH$_2$N⟨⟩		281
2-PyCH(*p*-MeC$_6$H$_4$)CONMe$_2$	ClCH$_2$CH$_2$NMe$_2$	same as above	2-PyC(*p*-MeC$_6$H$_4$)(CONMe$_2$)CH$_2$CH$_2$NMe$_2$		281
2-PyCH(*o*-ClC$_6$H$_4$)CONMe$_2$	ClCH$_2$CH$_2$NMe$_2$	same as above	2-PyC(*o*-ClC$_6$H$_4$)(CONMe$_2$)CH$_2$CH$_2$NMe$_2$		281
2-PyCH(*m*-MeOC$_6$H$_4$)CONMe$_2$	ClCH$_2$CH$_2$NMe$_2$	same as above	2-PyC(*m*-MeOC$_6$H$_4$)(CONMe$_2$)CH$_2$CH$_2$NMe$_2$		281
2-PyCH(*p*-MeOC$_6$H$_4$)CONMe$_2$	ClCH$_2$CH$_2$NMe$_2$	same as above	2-PyC(*p*-MeOC$_6$H$_4$)(CONMe$_2$)CH$_2$CH$_2$NMe$_2$		281
	CH_3I	K^+ salt, ether. 10 hr., 36°		73%	58
	EtOCH : C(CO$_2$Et)$_2$	185° until no more EtOH distilled			81
3-PyCH$_2$CO$_2$Me	PhCHO	Na, ether, 30 hr., 36°	PhCH : C(3-Py)CO$_2$Me		20
3-PyCH$_2$CO$_2$H	PhCHO	piperidine-py, 48 hr., reflux	3-PyC(CO$_2$H) : CHPh	40%	257
4-Py(CH$_2$)$_2$CO$_2$Et	CH_2O	H_2O, reflux 24 hr.		69%	220

TABLE XI-13. Preparation of Acids and Derivatives by Reduction of Side-Chain Functions

Starting material	Conditions	Product	Yield	Ref.
2-PyCH(O_2CPh)$CONH_2$	Pd-$BaSO_4$, EtOH, H_2, 25°	2-PyCH_2CONH_2	89%	241
2-PyCH(CHO)CO_2Et	HOAc, PtO_2, H_2 (100 p.s.i.), 40 hr., 25°	2-PyCHMeCO_2Et	low	56
2-PyCH : $CHCO_2H \cdot HCl$	EtOH, Pd-$BaSO_4$, H_2	2-Py$(CH_2)_2CO_2H$		77
2-PyCH : $CHCO_2H$	H_2, Ni, 20°, 3 hr.	2-Py$(CH_2)_2CO_2H$	85%	227
2-PyCPh : $CCNCO_2$Et	MeOH, Pt, H_2	2-PyCHPhCHCNCO_2Et	100%	107
2-Py$CO(CH_2)_2CO_2$Et	Zn · Hg, HCl, 6 hr., reflux	2-Py$(CH_2)_3CO_2$Et	52%	46
2-Py$(CH_2)_3COCO_2H$	H_2, PtO_2, base	2-Py$(CH_2)_3$CHOHCO_2H	95%	236
	metal catalyst, H_2			75
	Zn, HOAc			185
	Zn · Hg, HCl		91%	45
	N_2H_4, KOH, $(CH_2OH)_2$		52%	185
3-PyCH : $CHCO_2H$	aq. alkali, Ni, H_2 (40 p.s.i.), 25°; esterify	3-Py$(CH_2)_2CO_2$Me		70
3-PyCH : $CHCO_2H$	Pt, H_2	3-Py$(CH_2)_2CO_2H$	100%	96
3-PyCH : $CHCO_2H$	red P, HI, HOAc	3-Py$(CH_2)_2CO_2H$	90%	97
3-PyCH : $CHCO_2$Et	H_2, Pd-C, EtOH, 2 hr., 25°	3-Py$CH_2CH_2CO_2$Et	84%	265
3-Py$COCH_2CO_2$Et	Ni, H_2, 85°, distil product	3-PyCH : $CHCO_2$Et	40%	130
3-Py$COCH_2CO_2$Et	HOAc, ($HClO_4$), Pd-$BaSO_4$, H_2	3-Py$(CH_2)_2CO_2$Et	92%	131
3-PyCOCHMeCO_2Et	HOAc, Pd-$BaSO_4$, H_2; or EtOH, PtO_2, H_2	3-PyCHOHCHMeCO_2Et	63%	51
3-Py$CO(CH_2)_2CO_2$Et	H_2, Ni, $MeNH_2$			202

3-PyC(:NOH)$(CH_2)_2CO_2H$	Zn, HOAc-EtOH	3-PyCHN$H_2(CH_2)_2CO_2H$		263
	H_2O, PtO_2, H_2, 2 hr., 25°		100%	102
	red P, HI, 4 hr., 100°		50%	150
	Zn, HCl			132
	red P, HI		good	132
	H_2, Pd-C, EtOH, 25°	3-PyC$H_2CH_2CO_2H$	63%	265
	same as above	3-PyC$H_2CH_2CO_2Et$	58%	265
	same as above	3-PyC$H_2CH_2CONH_2$	80%	265
4-PyCH:CHCO_2H	aq. alkali, Ni, H_2 (40 p.s.i.), 25°; esterify	4-Py$(CH_2)_2CO_2Me$		70
4-PyCH:CHCO_2H	Pt, H_2	4-Py$(CH_2)_2CO_2H$	60%	73

(*continued*)

TABLE XI-13. Preparation of Acids and Derivatives by Reduction of Side-Chain Functions (*continued*)

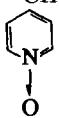
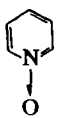
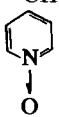
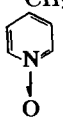
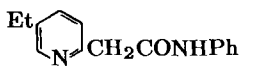
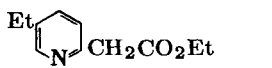
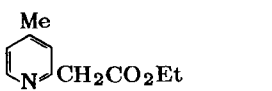
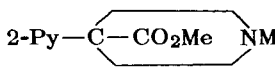
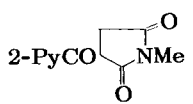
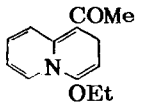
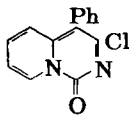
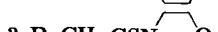
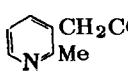
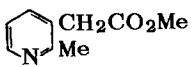
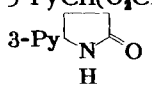
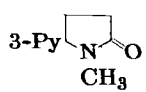
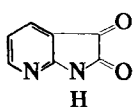
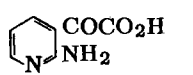
Starting material	Conditions	Product	Yield	Ref.
4-PyCH : $CHCONH_2$	H_2, Pd-C, EtOH, 25°	4-$PyCH_2CH_2CONH_2$	83%	265
4-PyCH : $CHCO_2Et$	H_2, Pd-C, EtOH, 2 hr., 25°	4-$PyCH_2CH_2CO_2Et$	88%	265
4-PyCH : $C(CO_2Et)_2$	H_2, Ni, 50 atm., 8 hr.. 25°	$[4\text{-}PyCH_2C(CO_2Et)_2]_2$ + 4-$PyCH_2CH(CO_2Et)_2$	14% 63%	230
4-$PyCOCH_2CO_2Et$	Ni, H_2 (2200 p.s.i.), 100°	4-$PyCHOHCH_2CO_2Et$		41
CH : $CHCO_2H$ 	H_2, Pd-C, EtOH, 25°	4-$PyCH_2CH_2CO_2H$	15%	265
CH : $CHCONH_2$ 	same as above	4-$PyCH_2CH_2CONH_2$	77%	265
CH : $CHCO_2Et$ 	H_2, Pd-C, EtOH, 5.5 hr., 25°	4-$PyCH_2CH_2CO_2Et$	75%	265
$CH_2CH_2CONH_2$ 	H_2, Pd-C, EtOH, 6 hr., 25°	4-$PyCH_2CH_2CONH_2$	88%	265

TABLE XI-14. The Willgerodt Reaction

Starting material	Conditions	Product	Yield	Ref.
2-PyCOMe	S, morpholine, 12 hr., reflux	2-PyCH$_2$CSN⟨O⟩	63%	18
2-PyCH : CH$_2$	NH$_3$, S, Py, 4 hr., 150°	2-PyCH$_2$CONH$_2$	26%	24
2-PyCH : CH$_2$	(NH$_4$)$_2$S, Py, (NH$_4$)$_2$S$_2$O$_3$, 4 hr., 150°	2-PyCH$_2$CONH$_2$	38%	25
2-PyCH : CH$_2$	NH$_3$, S, Py, 4 hr., 165°	2-PyCH$_2$CONH$_2$	60%	26
2-Py(CH$_2$)$_3$COMe	S, morpholine, 3 hr., 200°; boil in 50% H$_2$SO$_4$	2-Py(CH$_2$)$_4$CO$_2$H	23%	252
3-PyCOMe	aq. (NH$_4$)$_2$S, S, dioxane, 6 hr., 170°	3-PyCH$_2$CONH$_2$		20
3-PyCOCH$_2$CO$_2$Et	NH$_4$OH, H$_2$S, 2 hr., 180°	3-PyCH$_2$CONH$_2$		206
3-PyCOMe	S, morpholine, 6 hr., reflux	3-PyCH$_2$CSN⟨O⟩	65%	21
3-PyCOMe	S, morpholine, 12 hr., reflux	3-PyCH$_2$CSN⟨O⟩	80%	18
3-PyCOMe	same as above; hydrolysis and esterification	3-PyCH$_2$CO$_2$Me	70%	23
3-PyCOMe	same as above	3-PyCH$_2$CO$_2$Et	40%	15
	(NH$_4$)$_2$S, S, dioxane, 6 hr., 180°		83%	19,22
4-PyCOMe	S, morpholine, 12 hr., reflux	4-PyCH$_2$CSN⟨O⟩	76%	18
4-PyCH : CH$_2$	NH$_3$, S, dioxane, 4.5 hr., 165°	4-PyCH$_2$CONH$_2$	45%	27
4-PyCH$_2$Me	S, morpholine, 8 hr., 160°	4-PyCH$_2$CSN⟨O⟩	50%	28

TABLE XI-15. Solvolysis of Amides

Amide	Conditions	Product	Yield	Ref.
2-$PyCH_2CONH_2$	EtOH, HCl, reflux 4 hr.	2-$PyCH_2CO_2Et$	75%	241
2-$PyCH_2CONH_2$	$(EtO)_2CO$, NaOEt, EtOH, reflux 14 hr.	2-$PyCH_2CO_2Et$	90%	261
2-$PyCH(O_2CPh)CONH_2$	EtOH, HCl, reflux	2-$PyCHOHCO_2Et$	25%	250
2-$PyCH_2CONH_2$	aq. NaOH	2-$PyCH_2CO_2H$		25
2-$PyCHPhCONH_2$	MeOH, HCl, 6 hr., 100°	2-$PyCHPhCO_2Me$		13,14, 142
2-$PyCH_2CONHPh$	hydrolytic, unspecified	2-$PyCH_2CO_2H$		80
2-$PyCH_2CONHPh$	EtOH, HCl	2-$PyCH_2CO_2Et$	75%	33,82, 14,142
2-$PyCH_2CONHPh$	same as above	2-$PyCH_2CO_2Et$	80%	61,201
	same as above			58
	same as above			58
2-$PyCH_2C(NHCOPh)(CO_2Et)_2$	49% HBr, 9 hr., reflux	2-$PyCH_2CHNH_2CO_2H$	56%	115
2-$PyCPh(CH_2CH_2NEt_2)CONH_2$	EtOH, HCl, 6 hr., 100°	2-$PyCPh(CH_2CH_2NEt_2)CO_2Et$		14
2-$PyCH_2C[N(CO)_2C_6H_4](CO_2Et)_2$	35% HCl, 3 hr., 170°	2-$PyCH_2CHNH_2CO_2H$	100%	17
	MeOH, HCl, 8 hr., reflux		34%	187
	conc. HCl, 20 hr., reflux; esterify	2-$PyCO(CH_2)_2CO_2Et$	70%	49

	conc. HCl, 2 hr., 90°	2-PyCH(COMe)CH_2CO_2H		259
	NaOMe, MeOH, heat 14 hr.	2-PyCHPhCN		261
	KOH, EtOH, 3 days, reflux	2-PyCH_2CO_2H	low	18
	same as above	3-PyCH_2CO_2H	74%	18
	NaOH, EtOH; MeOH, HCl	3-PyCH_2CO_2Me	53%	21
	MeOH, H_2SO_4, 3 hr., reflux		64%	19
3-PyCH(O_2CPh)$CONH_2$	EtOH, HCl, reflux	3-PyCHOHCO_2Et	25%	250
	16% $Ba(OH)_2$, reflux 15 hr.	3-PyCH$NH_2(CH_2)_2CO_2H$		263
 (cotinine)	33% $Ba(OH)_2$, reflux 20 hr.	3-PyCH(NHMe)$(CH_2)_2CO_2H$	54%	263
	dil. NaOH; HOAc			8

(*continued*)

TABLE XI-15. Solvolysis of Amides (*continued*)

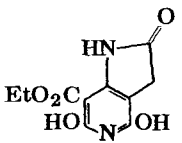
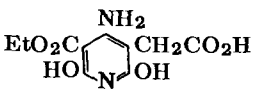
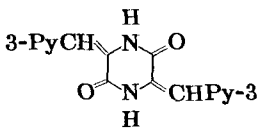
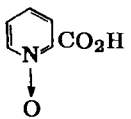
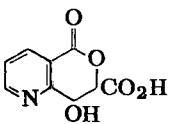
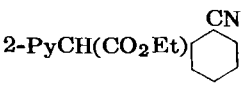
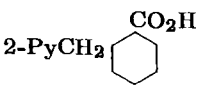
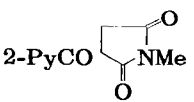
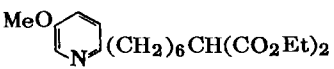
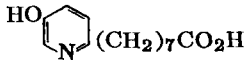
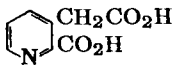
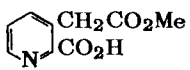
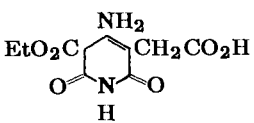
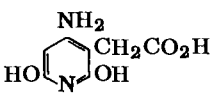
Amide	Conditions	Product	Yield	Ref.
	dil. Na_2CO_3, reflux			135
	Ac_2O, red P, HI, reflux	3-$PyCH_2CHNH_2CO_2H$	69%	115
4-$PyCH_2CONH_2$	EtOH, HCl, reflux, 4 hr.	4-$PyCH_2CO_2Et$	85%	241
4-PyCHPhCONH$_2$	MeOH, HCl, 6 hr., 100°	4-PyCHPhCO_2Me		13,14
4-$PyCH_2C(NHCOPh)(CO_2Et)_2$	49% HBr, 8 hr., reflux	4-$PyCH_2CHNH_2CO_2H$	8.7%	115
4-$PyCH_2CONHPh$	EtOH, HCl	4-$PyCH_2CO_2Et$		83
4-$PyCH_2CSN$ 	KOH, EtOH, 3 days, reflux	4-$PyCH_2CO_2H$	86%	18
4-$PyCH_2CSN$ 	same as above	4-$PyCH_2CON$ 	80%	193
5-Et-5-(4′-Py)barbituric acid	NH_3, $(NH_4)_2CO_3$, heat in H_2O	4-PyCHEtCO_2H		16
5-CH_3-5-(4′-Py)barbituric acid	same as above	4-PyCHMeCO_2H		16
2,6-$Py(CH_2CONHPh)_2$	hydrolytic, unspecified	2,6-$Py(CH_2CO_2H)_2$		80

TABLE XI-16. Decarboxylation Reactions Yielding Acidic Products

Starting material	Conditions	Product	Yield	Ref.
2-$PyCH_2CO_2Et$	H_2O_2, HOAc			54
	HCl, 140°			6
	HCl, reflux		20%	191
2-$PyCH_2C(NHCOPh)(CO_2Et)_2$	49% HBr, 8 hr., reflux	2-$PyCH_2CHNH_2CO_2H$	17%	115
2-$Py(CH_2)_2CH(CO_2H)_2$	heat at 160°	2-$Py(CH_2)_2CO_2H$	75%	11,208
2-$PyC(Et)(CO_2Et)_2$	NaOH, EtOH; urea, 100°	2-$PyCHEtCONH_2$	80%	109
2-$PyCH(CO_2Et)CH(CO_4Et)_2$	NaOH, H_2O; HCl	2-$Py(CH_2)_2CO_2H$	25%	114
	HCl, EtOH, 80°	2-$PyCO(CH_2)_2CO_2Et$	70%	49
2-$Py(CH_2)_2CEt(CO_2Et)_2$	HCl, reflux	2-$Py(CH_2)_2CHEtCO_2H$	50%	118
2-$Py(CH_2)_2CH(CO_2Et)COCO_2Et$	dil. H_2SO_4, reflux 16 hr.	2-$Py(CH_2)_3COCO_2H$	90%	236

(*continued*)

TABLE XI-16. Decarboxylation Reactions Yielding Acidic Products (*continued*)

Starting material	Conditions	Product	Yield	Ref.
	60% HBr., reflux 45 hr.			237
2-Py$(CH_2)_{11}CH(CO_2H)_2$	140°/12 mm.	2-Py$(CH_2)_{12}CO_2H$	75%	143
	$PhNMe_2$, 160–180°	3-PyCH_2CO_2H		127,129
	heat above m.p.	3-PyCH_2CO_2Me		128
	30% KOH, H_2O, reflux			135

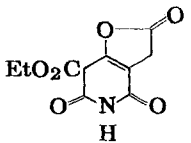
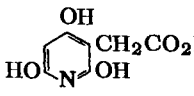
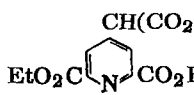
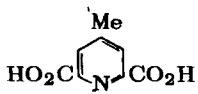
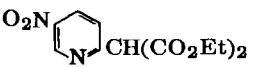
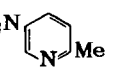
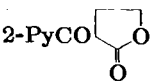
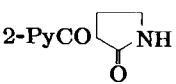
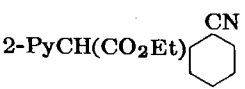
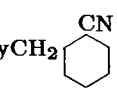
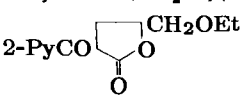
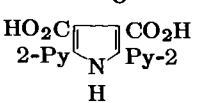
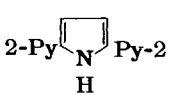
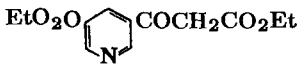
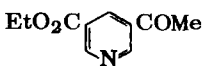
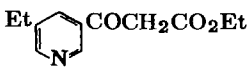
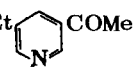
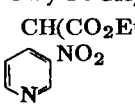
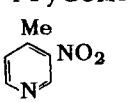
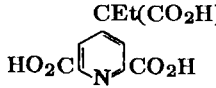
	same as above			135
3-PyCOCH(CO_2Et)CH_2CO_2Et	H_2SO_4, H_2O, 2 days, reflux	3-PyCO$(CH_2)_2CO_2H$	76%	99,263
3-PyCOCH(CO_2Et)CH_2CO_2Et	5% HCl, reflux	3-PyCO$(CH_2)_2CO_2Et$		202
3-PyCOCH_2CHPhCH(CO_2H)$_2$	heat at 180°	3-PyCOCH_2CHPhCH_2CO_2H	93%	243
4-PyCHPhCOCO_2Na	30% H_2O_2, H_2O, cold	4-PyCHPhCO_2Na		89
4-PyCH : C(CO_2H)$_2$ · HCl	HCl, EtOH, heat	4-PyCH : CHCO_2Et		98
4-PyCH_2CH(NHCOPh)(CO_2Et)$_2$	49% HBr, 8 hr., reflux	4-PyCH_2CHNH_2CO_2H	8.7%	115
4-PyCH_2C(NHCOMe)(CO_2Et)$_2$	48% HBr, reflux 6 hr.	4-PyCH_2CHNH_2CO_2H	76%	267
4-PyCH(CH_2CO_2Et)CH(CO_2Et)$_2$	HCl, 8 hr., reflux	4-PyCH(CH_2CO_2H)$_2$	84%	126,268
	HCl, reflux		50%	112

TABLE XI-17. Decarboxylation Reactions Yielding Nonacidic Products

Starting material	Conditions	Product	Yield	Ref.
	A. Side-chain acid derivatives			
2-$PyCH_2CO_2H$	H_2O, 50–60°	2-PyMe		145
$(2\text{-}PyCH_2CO_2)_2Ba$	dry distillation	2-PyMe		151
2-$PyCOCH_2CO_2Et$	HCl, reflux	2-PyCOMe	50%	40
	same as above			33
	same as above	2-$PyCO(CH_2)_3OH$		49
	same as above	2-$PyCO(CH_2)_3NH_2$		49
	KOH, MeOH, reflux, 6 hr.		86%	191
2-$PyCMeEtCO_2H \cdot HCl$	neutralize aq. soln.	2-PyCHMeEt	90%	32
2-$PyCOCH(CO_2Et)(CH_2)_2OMe$	HCl, reflux	2-$PyCO(CH_2)_3OMe$		49
	same as above	2-$PyCO(CH_2)_2CHOHCH_2OEt$		50
	reflux in ethanolamine, 1.5 hr.			270
3-$PyCOCH_2CO_2Et$	HCl, reflux	3-PyCOMe	95%	39,40,43

	heat in dil. H_2SO_4			249
	same as above		97%	249
4-PyCHPhCO$_2$Na	neutralize aq. soln.	4-PyCH$_2$Ph		89
4-PyCOCH$_2$CO$_2$Et	HCl, reflux	4-PyCOMe	80%	40
	same as above			113
4-PyCMe(CONH)$_2$CO	saponify with conc. NaOH, acidify with HCl, evap. to dryness	4-PyEt	99%	154
4-PyCEt(CONH)$_2$CO	same as above	4-PyPr	99%	154
	Distil at 1 atm.	4-PyPr		112
4-PyC(CH$_2$CHMe$_2$)(CONH)$_2$CO	saponify with conc. NaOH, acidify with HCl, evap. to dryness	4-Py(CH$_2$)$_2$CHMe$_2$	40%	154

B. Hydrolysis and decarboxylation of pyridineacetonitriles

(Starting material is the	70–75% H_2SO_4, 6 hr., 130–150°	(2-Py)$_2$CH$_2$	71%	167
pyridineacetonitrile corre-	70–75% H_2SO_4, 6 hr., 130–150°	2-PyCH$_2$Ph	70%	13,204
sponding to the product)	70–75% H_2SO_4, 6 hr., 130–150°	α-C$_{10}$H$_7$CH$_2$Py-2		13

(*continued*)

TABLE XI-17. Decarboxylation Reactions Yielding Nonacidic Products (*continued*)

Starting material	Conditions	Product	Yield	Ref.
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPh$_2$		181,235
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCH(*p*-ClC$_6$H$_4$)$_2$		181
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCH(*p*-MeC$_6$H$_4$)$_2$		181
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCH(*p*-MeOC$_6$H$_4$)$_2$		181
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCH(*p*-ClC$_6$H$_4$)Ph		181
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCH[2,4-Me$_2$C$_6$H$_3$]Ph		181
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHMePh		181
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPhCH$_2$Ph		181

70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHEtPh		181
70–75% H_2SO_4, 6 hr., 130–150°	2-PyCHPh$(CH_2)_2NMe_2$	88%	168,200
70–75% H_2SO_4, 6 hr., 130–150°	2-PyCHPh$(CH_2)_2NEt_2$	85%	168
70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPh$(CH_2)_2$N⟨⟩	68%	164,168 178
70–75% H_2SO_4, 6 hr., 130–150°	2-PyCH(*o*-ClC_6H_4)$(CH_2)_2NMe_2$	63%	168
20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCH(*m*-$MeOC_6H_4$)$(CH_2)_2NMe_2$		178
70–75% H_2SO_4, 6 hr., 130–150°	2-PyCH(*m*-ClC_6H_4)$(CH_2)_2NMe_2$	85%	168
70–75% H_2SO_4, 6 hr., 130–150°	2-PyCH(*p*-ClC_6H_4)$(CH_2)_2NMe_2$	50%	168,200
70–75% H_2SO_4, 6 hr., 130–150°	(2-Py)$_2$CH$(CH_2)_2NMe_2$	91%	168
70–75% H_2SO_4, 6 hr., 130–150°	2-PyCH(3-Py)$(CH_2)_2NMe_2$	79%	168
70–75% H_2SO_4, 6 hr., 130–150°	2-PyCH(2-C_4H_3S)$(CH_2)_2NMe_2$	30%	168
70–75% H_2SO_4, 6 hr., 130–150°	Me⟨N⟩CHPh$(CH_2)_2NMe_2$	72%	168
70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPh Pr		181
70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPhCHMe$_2$		181
70–75% H_2SO_4, 6 hr., 130–150°	2-PyCHPhCHMeCH_2NMe_2	66%	168

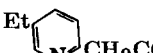
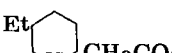
(*continued*)

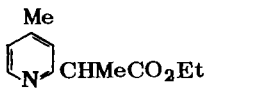
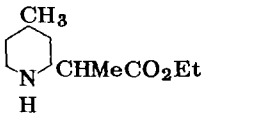
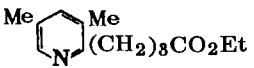
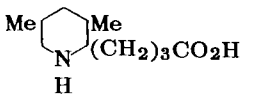
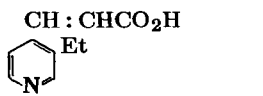
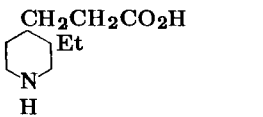
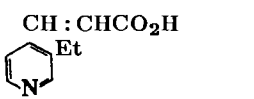
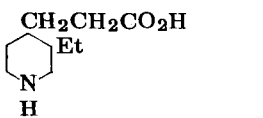
TABLE XI-17. Decarboxylation Reactions Yielding Nonacidic Products (*continued*)

Starting material	Conditions	Product	Yield	Ref.
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPh$(CH_2)_3$N⟨⟩		181
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCH(*p*-ClC_6H_4)$CHMe_2$		181
	70–75% H_2SO_4, 6 hr., 130–150°	2-PyCHPh$(CH_2)_3NMe_2$	89%	168,282
	70–75% H_2SO_4, 6 hr., 130–150°	2-PyCH$(CH_2Ph)(CH_2)_2NMe_2$	55%	168
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPhCH_2CHMe_2		181
	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPh$(CH_2)_2CHMe_2$		181

	70–75% H_2SO_4, 6 hr., 130–150°; 20% KOH, MeOH (or EtOH), H_2O, 6 hr., 220–230°	2-PyCHPh(cyclo-C_6H_{11})		181
(Starting material is the pyridineacetamide corresponding to the product)	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*p*-ClC_6H_4)$CH_2CH_2NMe_2$		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCHPh$CH_2CH_2NMe_2$		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*p*-BrC_6H_4)$CH_2CH_2NMe_2$		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*p*-ClC_6H_4)CH_2CH_2N⟨ ⟩		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCHPhCH_2CH_2N⟨ ⟩O		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*p*-BrC_6H_4)CH_2CH_2N⟨ ⟩		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*p*-ClC_6H_4)CH_2CH_2N⟨ ⟩		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*p*-MeC_6H_4)$CH_2CH_2NMe_2$		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*o*-ClC_6H_4)$CH_2CH_2NMe_2$		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*m*-$MeOC_6H_4$)$CH_2CH_2NMe_2$		281
	KOH, EtOH, or 80% H_2SO_4	2-PyCH(*p*-$MeOC_6H_4$)$CH_2CH_2NMe_2$		281
	70–75% H_2SO_4, 6 hr., 130–150°	4-PyCH_2Ph		13
	70–75% H_2SO_4, 6 hr., 130–150°	4-PyCHPh$(CH_2)_2NMe_2$	82%	168

TABLE XI-18. Reduction of Side-Chain Acids

Starting material	Conditions	Product (Pip = piperidine)	Yield	Ref.
	NUCLEAR REDUCTION			
2-$PyCH_2CO_2Et$	HOAc (or EtOH), PtO_2, H_2 (3 atm.), 20–50°	2-$PipCH_2CO_2Et$	75%	82
2-$PyCH(O_2CPh)CONH_2$	Pd-$BaSO_4$, EtOH, 25°, 1 atm. H_2	2-$PyCH_2CONH_2$	89%	241
2-$PyCHPhCONH_2$	catalytic, not further specified	2-$PipCHPhCO_2H$		161
2-$PyCHPhCONH_2$	same as above	2-$PipCHPhCONH_2$		142
2-$PyCHPhCO_2Me$	same as above	2-$PipCHPhCO_2Me$		142
	HOAc, PtO_2, H_2 (3 atm.), 20–50°		97%	58
2-$PyCH:CHCO_2Et$	EtOH, Na	2-$Pip(CH_2)_3OH$		152
2-$PyCH:CHCO_2H$	HCl, PtO_2, H_2 (3 atm.), 20–50°	2-$Pip(CH_2)_2CO_2H$		79
2-$PyCH:CHCO_2H$	HOAc, PtO_2, H_2 (3 atm.), 20–50°	2-$Pip(CH_2)_2CO_2H$	78%	76
2-$Py(CH_2)_2CONH(n\text{-}Bu)$	same as above	2-$Pip(CH_2)_2CONH(n\text{-}Bu)$	51%	2
2-$Py(CH_2)_2CONHPh$	same as above	2-$Pip(CH_2)_2CONHPh$	60%	2
2-$Py(CH_2)_2CONMe_2$	same as above	2-$Pip(CH_2)_2CONMe_2$	34%	2,76
2-$Py(CH_2)_2CONEt_2$	same as above	2-$Pip(CH_2)_2CONEt_2$	60%	2
2-$Py(CH_2)_2CON(n\text{-}Pr)_2$	same as above	2-$Pip(CH_2)_2CON(n\text{-}Pr)_2$	71%	2
2-$Py(CH_2)_2CON(n\text{-}Bu)_2$	same as above	2-$Pip(CH_2)_2CON(n\text{-}Bu)_2$	71%	2
2-$Py(CH_2)_2CONMePh$	same as above	2-$Pip(CH_2)_2CONMePh$	71%	2
2-$Py(CH_2)_2CON$ 	same as above	2-$Pip(CH_2)_2CON$ 	69%	2
2-$PyCPhEtCONH_2$	catalytic, not further specified	2-$PipCPhEtCONH_2$		142

	HOAc, PtO_2, H_2 (3 atm.), 20–50°		90%	58
	HCl, PtO_2, H_2 (3 atm.), 20–50°			45
3-PyCHPhCONH$_2$	HOAc, PtO_2, H_2 (3 atm.), 20–50°	3-PipCHPhCONH$_2$	30%	12
4-PyCHPhCONH$_2$	same as above	4-PipCHPhCONH$_2$	90%	13
4-PyCHPhCO$_2$Me	catalytic, not further specified	4-PipCHPhCO$_2$Me		142
4-Py(CH$_2$)$_2$CO$_2$Et	EtOH, PtO_2, H_2 (3 atm.), 20–50°	4-Pip(CH$_2$)$_2$CO$_2$Et		73
4-PyCH : CHCO$_2$H	HCl, PtO_2, H_2 (3 atm.), 20–50°	4-Pip(CH$_2$)$_2$CO$_2$H		71
4-PyCH : CHCO$_2$NH$_4$	H_2O, Ni, H_2 (600 p.s.i.), 20–50°	4-Pip(CH$_2$)$_2$CO$_2$Et	50%	72
4-PyCH : CHCO$_2$H	amyl alcohol, Na	4-Pip(CH$_2$)$_2$CO$_2$H	70%	66
	same as above		40%	67
	HCl, PtO_2, H_2 (3 atm.), 20–50°			68

REDUCTION OF CARBOXYL FUNCTION

2-PyCH$_2$CO$_2$Me	$LiAlH_4$, ether	2-Py(CH$_2$)$_2$OH	15%	179
2-Py(CH$_2$)$_2$CH(CO$_2$Et)$_2$	same as above	2-Py(CH$_2$)$_2$CH(CH$_2$OH)$_2$	53%	118,122
3-PyCH$_2$CO$_2$Et	EtOH, Na	3-Pip(CH$_2$)$_2$OH	25%	18
4-PyCH$_2$CO$_2$Et	same as above	4-Pip(CH$_2$)$_2$OH	10%	18

(*continued*)

TABLE XI-18. Reduction of Side-Chain Acids (*continued*)

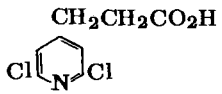
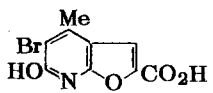
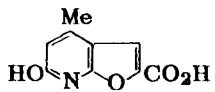
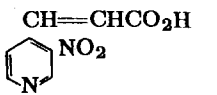
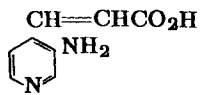
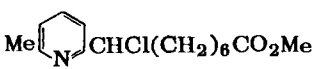
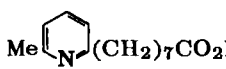
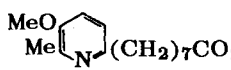
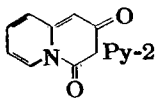
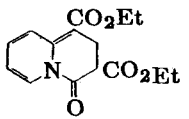
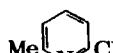
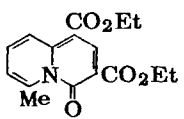
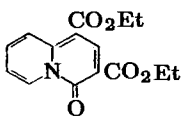
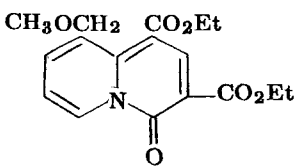
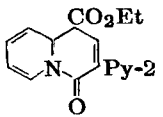
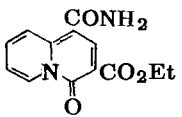
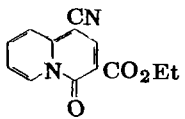
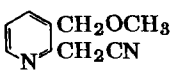
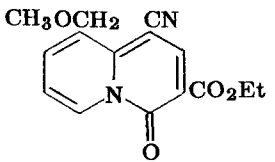
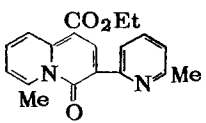
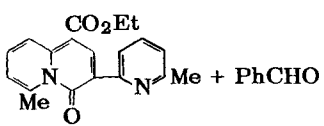
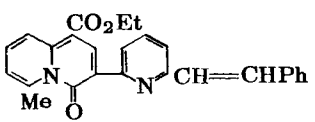
Starting material	Conditions	Product (Pip = piperidine)	Yield	Ref.
	REDUCTION OF OTHER SUBSTITUENTS			
	CH_3OH, Pd-C, H_2 (2 atm.)	4-Py$(CH_2)_2CO_2H$	77%	139
	10% NaOH, Zn dust, reflux 4 hr.			132
	NH_4OH, $FeSO_4$		92%	100
	Zn, HOAc			185
	Wolff-Kishner method		52%	185
4-PyCH$(O_2CPh)CONH_2$	Pd-$BaSO_4$, EtOH, 25°, 1 atm. H_2	4-PyCH_2CONH_2	75%	241

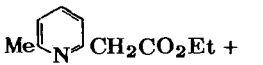
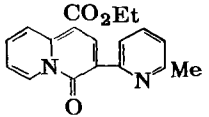
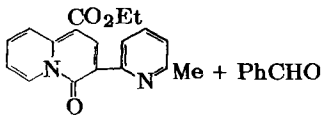
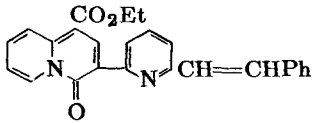
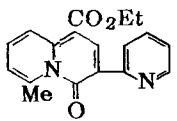
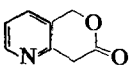
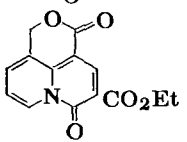
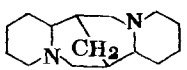
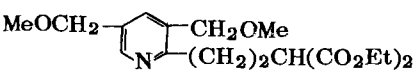
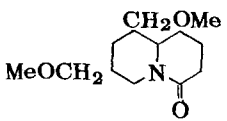
TABLE XI-19. Synthesis of Quinolizidines

Starting material	Conditions	Product	Yield	Ref.
2-$PyCH_2CO_2Et$ + 2PyCH : CH_2	NaOEt, 6 hr., 80°			55
2-$PyCH_2CO_2Et$ + CH_2 : $C(CO_2Et)_2$	NaOEt, EtOH, 3 hr., 80°		6.5%	54
 + EtOCH : $C(CO_2Et)_2$	185°, distil off EtOH		80%	81
2-$PyCH_2CO_2Et$ + EtOCH : $C(CO_2Et)_2$	same as above		50%	166,208
 + EtOCH : $C(CO_2Et)_2$	reflux			272

(*continued*)

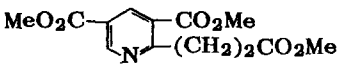
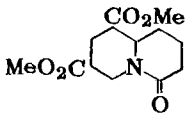
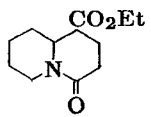
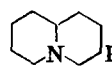
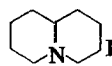
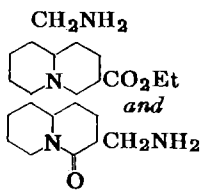
TABLE XI-19. Synthesis of Quinolizidines (*continued*)

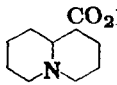
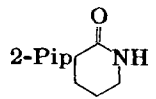
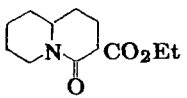
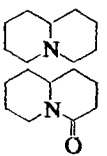
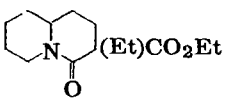
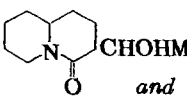
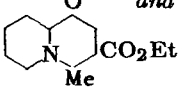
Starting material	Conditions	Product	Yield	Ref.
2-$PyCH_2CO_2Et$ + $HC(OEt)_3$	Ac_2O, 2 hr., reflux		65%	59,60,61 151, 210
2-$PyCH_2CO_2Et$ + $EtOCH:C(CONH_2)CO_2Et$	NaOEt, EtOH, 25°		67%	208
2-$PyCH_2CO_2Et$ + $EtOCH:CCNCO_2Et$	same as above			208
 + $EtOCH:C(CO_2Et)_2$	reflux			272
	Ac_2O, 3 hr., reflux		50%	210
	Ac_2O, 3 days, reflux		20%	210

 2-PyC(:CHOH)CO_2Et	Ac_2, 1.5 hr., reflux		75%	210
	Ac_2O, 3 days, reflux		40%	210
 2-PyCH_2CO_2Et	Ac_2O, 2 hr., reflux		75%	210
 + EtOCH : $C(CO_2Et)_2$	1 hr., 180°			264
$(2\text{-PyCHCO}_2\text{Et})_2CH_2$	copper chromite, H_2, 300 atm., 265°	 *d,l*-sparteine + *d,l*-α-isosparteine	31%	59,60
	Ni, H_2, 200 atm., 185°		70%	148

(continued)

TABLE XI-19. Synthesis of Quinolizidines (*continued*)

Starting material	Conditions	Product	Yield	Ref.
	Ni, H_2, 200 atm., 210°		60%	148
2-PyCH(CO_2Et)$(CH_2)_2CO_2Et$	Ni, H_2, 100 atm., 175°		80%	53
2-Py$(CH_2)_2$CHPhCN	Ni, H_2, 150 atm., 200°		15%	53
2-Py$(CH_2)_2$CHPhCN	PtO_2, H_2, 1 atm., HCl, 25°	 *and* 2-Py$(CH_2)_2$CHPh	30%	53
2-Py$(CH_2)_2$CHCNCO_2Et	same as above		25% 20%	53

2-PyCH(CO_2Et)$(CH_2)_2CN$	same as above	 *and* 	29%	53
2-Py$(CH_2)_2$CH$(CO_2Et)_2$	Ni, H_2, 200 atm., 145°		97%	188,116
2-Py$(CH_2)_2$CH$(CO_2Et)_2$	copper chromite, H_2, 250 atm., 260°	 *and*	65% 13%	118,116
2-Py$(CH_2)_2$CH$(CO_2Et)_2$	Ni, H_2, 200 atm., 145°		84%	118
2-Py$(CH_2)_2$CH(COMe)CO_2Et	same as above	 *and* 	15–75% 36–14%	118

(*continued*)

TABLE XI-19. Synthesis of Quinolizidines (*continued*)

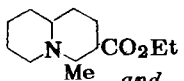
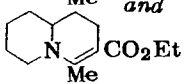
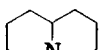
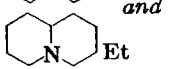
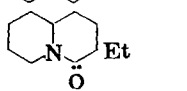
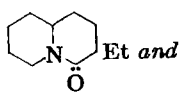
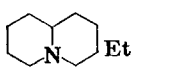
Starting material	Conditions	Product	Yield	Ref.
2-Py$(CH_2)_2$CH(COMe)CO_2Et	PtO_2, H_2, 1 atm., 25°	 *and* 	42% 38%	118
2-PyCH(COMe)CO_2Et	copper chromite, H_2, 250 atm., 260°	 *and* 	27% 31%	118
2-Py$(CH_2)_2$CHEtCO_2Et	Ni, H_2, 200 atm., 145°		78%	118
2-Py$(CH_2)_2$CHEtCO_2Et	copper chromite, H_2, 250 atm., 260°	 *and* 	35% 43%	118

TABLE XI-20. Synthesis of Condensed Heterocycles Other Than Quinolizidines

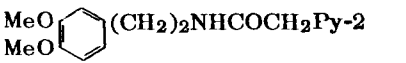
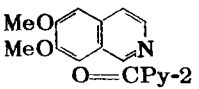
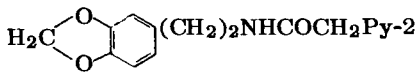
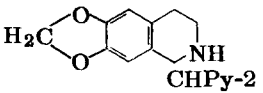
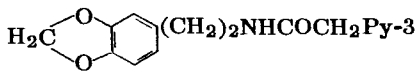
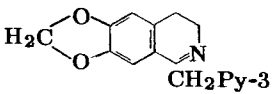
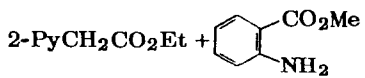
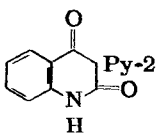
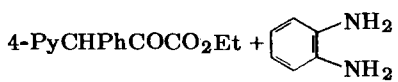
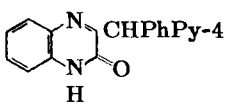
Starting materials	Conditions	Product	Yield	Ref.
	$POCl_3$; KOH + air		70%	27
	$POCl_3$, MePh, 1.5 hr., reflux			29
	same as above		89%	23
	Na, 100–20°		74%	57
	EtOH, 2 hr., reflux			89

TABLE XI-21. Side-Chain Acid Chlorides

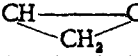
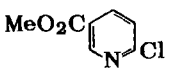
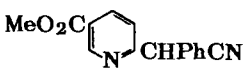
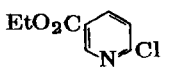
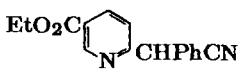
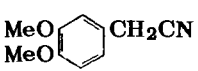
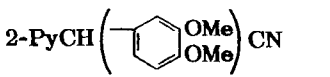
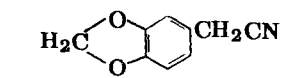
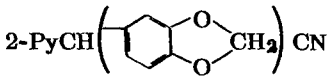
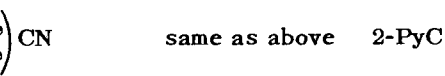
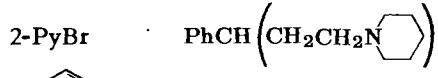
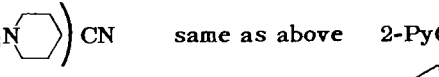
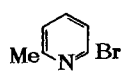
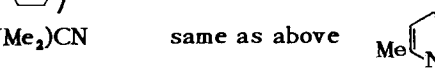
Acid chloride	Ref.
2-PyCH(CH_2Ph)COCl	15
2-PyCH : CPhCOCl	134
2-PyCH  CHCOCl	117,125
2-Py(CH_2)$_4$COCl	4
2-Py(CH_2)$_{10}$COCl	4

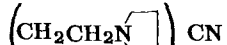
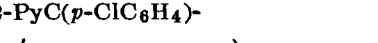
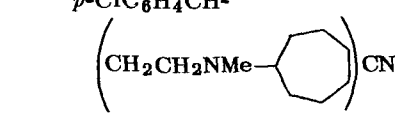
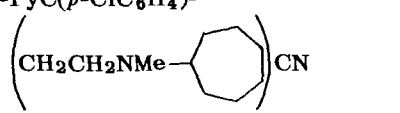
TABLE XI-22. Pyridylation of Nitriles

Pyridine halide	Nitrile	Conditions	Product	Yield	Ref.
2-PyBr	$PhCH_2CN$	$NaNH_2$, toluene, (*or* ether), reflux several hr.	2-PyCHPhCN	40%	85,204,282, 235
2-PyCl	$PhCH_2CN$	$NaNH_2$, toluene, reflux several hr.	2-PyCHPhCN	65%	13,107,142, 163
	$PhCH_2CN$	same as above		5%	12
	$PhCH_2CN$	same as above		44%	12
	$PhCH_2CN$	same as above		68%	168
2-PyBr	o-$ClC_6H_4CH_2CN$	same as above	2-PyCH(o-ClC_6H_4)CN	42%	168
2-PyBr	p-$ClC_6H_4CH_2CN$	same as above	2-PyCH(p-ClC_6H_4)CN	73%	168,282,284
2-PyCl	m-$MeOC_6H_4CH_2CN$	same as above	2-PyCH(m-$MeOC_6H_4$)CN		142,163
2-PyCl		same as above			142,163
2-PyCl		same as above			142,163
2-PyCl	α-$C_{10}H_7CH_2CN$	same as above	2-PyCH(α-$C_{10}H_7$)CN		142,163

(*continued*)

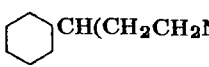
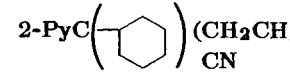
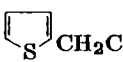
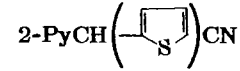
TABLE XI-22. Pyridylation of Nitriles (*continued*)

Pyridine halide	Nitrile	Conditions	Product	Yield	Ref.
2-PyBr	Ph_2CHCN	$NaNH_2$, dioxane, 4 hr., 120°	2-PyCPh_2CN		180,181
2-PyBr	$(p\text{-}ClC_6H_4)_2CHCN$	same as above	2-PyC$(p\text{-}ClC_6H_4)_2$CN		181
2-PyBr	$(p\text{-}MeC_6H_4)_2CHCN$	same as above	2-PyC$(p\text{-}MeC_6H_4)_2$CN		181
2-PyBr	$(p\text{-}MeOC_6H_4)_2CHCN$	same as above	2-PyC$(p\text{-}MeOC_6H_4)_2$CN		181
2-PyBr	$p\text{-}ClC_6H_4CHPhCN$	same as above	2-PyC$(p\text{-}ClC_6H_4)$PhCN		181
2-PyBr		same as above			181
2-PyBr	CH_3CN	NH_2, toluene, reflux several hr.	$(2\text{-Py})_2CHCN$	12%	167
2-PyCl	PhCHMeCN	same as above	2-PyCMePhCN		142,163
2-PyBr	$Me_2N(CH_2)_2CN$	same as above	2-PyCH$(CH_2CH_2NMe_2)$CN	48%	168
2-PyBr	PhCH$(CH_2CH_2NMe_2)$CN	same as above	2-PyC$(CH_2CH_2NMe_2)$PhCN	78%	173,168,200
2-PyBr	PhCH$(CH_2CH_2NEt_2)$CN	same as above	2-PyC$(CH_2CH_2NEt_2)$PhCN	92%	168
2-PyBr		same as above		89%	178
	PhCH$(CH_2CH_2NMe_2)$CN	same as above		74%	168
2-PyBr	$o\text{-}ClC_6H_4CH(CH_2CH_2NMe_2)CN$	same as above	2-PyC$(o\text{-}ClC_6H_4)(CH_2CH_2NMe_2)$CN	33%	168
2-PyBr	$p\text{-}ClC_6H_4CH(CH_2CH_2NMe_2)CN$	same as above	2-PyC$(p\text{-}ClC_6H_4)(CH_2CH_2NMe_2)$CN	67%	168,200

2-PyBr	*p*-$ClC_6H_4CH(CH_2CH_2NEt_2)CN$	$NaNH_2$, *benzene*, reflux several hr.	2-PyC(*p*-ClC_6H_4)($CH_2CH_2NMe_2$)CN		172
2-PyBr	*p*-ClC_6H_4CH()CN	same as above	2-PyC(*p*-ClC_6H_4)-()CN		172
2-PyBr	*p*-ClC_6H_4CH-()CN	same as above	2-PyC(*p*-ClC_6H_4)-()CN		172
2-PyBr	*p*-ClC_6H_4CH-()CN	same as above	2-PyC(*p*-ClC_6H_4)-()CN		172
2-PyBr	*p*-$MeC_6H_4CH(CH_2CH_2NMe_2)CN$	$NaNH_2$, toluene, reflux several hr.	2-PyC(*p*-MeC_6H_4)($CH_2CH_2NMe_2$)CN	44%	168,173
2-PyBr	*p*-cumyl $CH(CH_2CH_2NMe_2)CN$	same as above	2-PyC(*p*-cumyl)($CH_2CH_2NMe_2$)CN		173
2-PyBr	$PhCH_2CH(CH_2NMe_2)CN$	same as above	2-PyC(CH_2Ph)(CH_2NMe_2)CN	46%	168
2-PyBr	*p*-$MeOC_6H_4CH(CH_2CH_2NMe_2)$-CN	same as above	2-PyC(*p*-$MeOC_6H_4$)($CH_2CH_2NMe_2$)CN	80%	173,178
2-PyBr	α-$C_{10}H_7CH(CH_2CH_2NMe_2)CN$	same as above	2-PyC(α-$C_{10}H_7$)($CH_2CH_2NMe_2$)CN	76%	168
2-PyBr	2-$PyCH(CH_2CH_2NMe_2)CN$	same as above	$(2\text{-Py})_2C(CH_2CH_2NMe_2)CN$	78%	168
2-PyBr	3-$PyCH(CH_2CH_2NMe_2)CN$	same as above	2-PyC(3-Py)($CH_2CH_2NMe_2$)-CN	35%	168

(*continued*)

TABLE XI-22. Pyridylation of Nitriles (*continued*)

Pyridine halide	Nitrile	Conditions	Product	Yield	Ref.
2-PyBr	$(2\text{-}C_4H_3S)CH(CH_2CH_2NMe_2)CN$	same as above	$2\text{-}PyC(2\text{-}C_4H_3S)(CH_2CH_2NMe_2)CN$	36%	173,168
2-PyBr	$(3\text{-}C_4H_3S)CH(CH_2CH_2NMe_2)CN$	same as above	$2\text{-}PyC(3\text{-}C_4H_3S)(CH_2CH_2NMe_2)CN$		173
2-PyBr	$PhCH(CH_2CH_2CH_2NMe_2)CN$	same as above	$2\text{-}PyC(CH_2CH_2CH_2NMe_2)PhCN$	82%	168
2-PyBr	$PhCH(CH_2CHMeNMe_2)CN$	same as above	$2\text{-}PyC(CH_2CHMeNMe_2)PhCN$	63%	168
2-PyBr	$PhCH(CHMeCH_2NMe_2)CN$	same as above	$2\text{-}PyC(CHMeCH_2NMe_2)PhCN$	48%	168
2-PyBr	$PhCH_2CH(CH_2CH_2NMe_2)CN$	same as above	$2\text{-}PyC(CH_2CH_2NMe_2)(CH_2Ph)CN$	41%	168
2-PyBr		same as above		50%	168
2-PyBr		$NaNH_2$, 60°, C_6H_6		66%	282

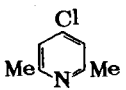
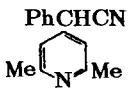
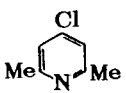
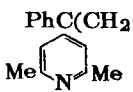
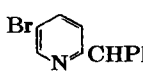
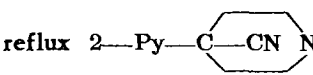
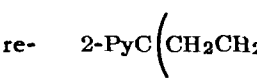
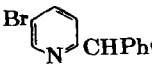
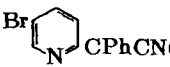
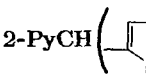
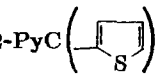
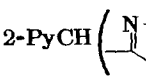
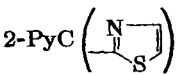
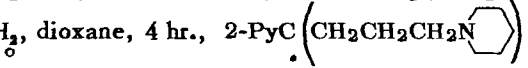
3-PyBr	$Me_2N(CH_2)_3CN$	$NaNH_2$, toluene, reflux several hr.	3-PyCH($CH_2CH_2NMe_2$)CN	40%	168
3-PyBr	$PhCH_2CN$	same as above	3-PyCHPhCN	36%	165
4-PyCl	$PhCH_2CN$	same as above	4-PyCHPhCN		142,163
4-PyCl	EtCHPhCN	same as above	4-PyCEtPhCN		142,163
4-PyBr	$PhCH(CH_2CH_2NMe_2)CN$	same as above	4-PyC($CH_2CH_2NMe_2$)PhCN	76%	168
	$PhCH_2CN$	same as above		40%	176
	$PhCH(CH_2CH_2NMe_2)CN$	same as above		40%	176
$2,5\text{-PyBr}_2$	$PhCH_2CN$	$NaNH_2$, 60°, C_6H_6		72%	282

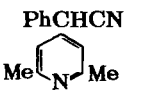
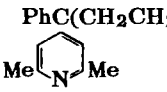
TABLE XI-23. Alkylation of Pyridineacetonitriles

2-PyCHRCN	$R'X$[a]	Conditions	Product	Yield	Ref.
2-PyCHPhCN	CH_3I	$NaNH_2$, *not further specified*	2-PyCMePhCN		158
2-PyCHPhCN	CH_3I	$NaNH_2$, dioxane, 4 hr., 120°	2-PyCMePhCN		181
2-PyCHPhCN	$PhCH_2X$	*same as above*	2-PyC(CH_2Ph)PhCN		181
2-$PyCH_2CN$	$Cl(CH_2)_2NMe_2$	$NaNH_2$, benzene, reflux several hr.	2-PyCH($CH_2CH_2NMe_2$)CN		147
2-PyCHPhCN	EtX	$NaNH_2$, dioxane, 4 hr., 120°	2-PyCEtPhCN		181,13
2-PyCHPhCN	$BrCH_2CO_2Et$	$NaNH_2$, toluene, 100°, several hr.	2-PyC(CH_2CO_2Et)PhCN	80%	85,86
2-$PyCH(CN)_2$	Me_2SO_4	$NaNH_2$, not further *specified*	2-PyCMe$(CN)_2$		159
2-$PyCH_2CN$	$(ClCH_2CH_2)_2$-NMe	$NaNH_2$, toluene, reflux several hr.		44%	187
2-PyCHPhCN	$Cl(CH_2)_2N$ 	$NaNH_2$, benzene, reflux several hr.	2-PyC  PhCN	78%	107,164 178
2-PyCHPhCN	$Br(CH_2)_2CN$	$NaNH_2$, toluene, reflux several hr.	2-PyC(CH_2CH_2CN)PhCN	72%	86
2-PyCH(*p*-ClC_6H_4)CN	$BrCH_2CO_2Et$	$NaNH_2$, toluene, 100°, several hr.	2-PyC(CH_2CO_2Et)(*p*-ClC_6H_4)CN	70%	86
2-PyCHPhCN	$Cl(CH_2)_2NMe_2$	$NaNH_2$, benzene, reflux several hr.	2-PyC($CH_2CH_2NMe_2$)PhCN	59%	107,196, 283

2-PyCHPhCN	$Cl(CH_2)_2NEt_2$	same as above	2-PyC($CH_2CH_2NEt_2$)PhCN	84%	107,196
2-PyCH(*m*-$MeOC_6H_4$)-CN	$X(CH_2)_2NMe_2$	$NaNH_2$, not further specified	2-PyC(*m*-$MeOC_6H_4$)(CH_2CH_2-NMe_2)CN		178
	$Cl(CH_2)_2NMe_2$	$NaNH_2$ in C_6H_6		72%	282
	$Cl(CH_2)_2NMe_2$	same as above		66%	282
2-PyCH(*p*-ClC_6H_4)CN	$Cl(CH_2)_2NMe_2$	same as above	2-PyC(*p*-ClC_6H_4)$CN(CH_2)_2NMe_2$	70%	282,284
	$Cl(CH_2)_3NMe_2$	$NaNH_2$, PhMe, 2 hr., reflux			283
2-PyCHPhCN	$Cl(CH_2)_3NMe_2$	$NaNH_2$ in C_6H_6	2-PyCPhCN$(CH_2)_3NMe_2$	97%	282
2-PyCHPhCN	$X(CH_2)_3$	$NaNH_2$, dioxane, 4 hr., 120°	2-PyC( PhCN		181,283
2-PyCHPhCN	$Me(CH_2)_2X$	same as above	2-PyC(CH_2CH_2Me)PhCN		181
2-PyCHPhCN	Me_2CHX	same as above	2-PyC($CHMe_2$)PhCN		181
2-PyCH(*p*-ClC_6H_4)CN	Me_2CHX	same as above	2-PyC(CHMe)(*p*-ClC_6H_4)CN		181
2-PyCHPhCN	$Br(CH_2)_2CO_2Et$	$NaNH_2$, toluene, 100°, several hr.	2-PyC($CH_2CH_2CO_2Et$)PhCN	71%	86
2-PyCHPhCN	Me_2CHCH_2X	$NaNH_2$, dioxane, 4 hr., 120°	2-PyC(CH_2CHMe_2)PhCN		181
2-PyCHPhCN	$Cl(CH_2)_3CN$	$NaNH_2$, not further specified	2-PyC($CH_2CH_2CH_2CN$)PhCN		85

(*continued*)

TABLE XI-23. Alkylation of Pyridineacetonitriles (*continued*)

2-PyCHRCN	R′X[a]	Conditions	Product	Yield	Ref.
2-PyCHPhCN	$Me_2CH(CH_2)_2X$	$NaNH_2$, dioxane, 4 hr., 120°	2-PyC($CH_2CH_2CHMe_2$)PhCN		181
2-PyCHPhCN	cyclohexyl-X	same as above	2-PyC(cyclohexyl)PhCN		181
3-$PyCH_2CN$	$PhCH_2I$	$NaNH_2$, benzene, reflux several hr.	3-PyCH(CH_2Ph)CN	53%	15
3-$PyCH_2CN$	$Et_2N(CH_2)_2I$	same as above	3-PyCH($CH_2CH_2NEt_2$)CN	20%	15
3-$PyCH_2CN$	$MeCO_2Et$	NaOEt, EtOH, 4 hr., 80°	3-PyCH(COMe)CN	56%	51
3-PyCHPhCN	$Me_2N(CH_2)_2Cl$	$NaNH_2$, benzene, reflux several hr.	3-PyC($CH_2CH_2NMe_2$)PhCN	59%	165
3-$PyCH_2CN$	$Me(CH_2)_2I$	same as above	3-PyCH($CH_2CH_2CH_2Me$)CN	48%	15
3-$PyCH_2CN$	n-$C_6H_{13}I$	same as above	3-PyCH(n-C_6H_{13})CN	40%	15
3-$PyCH_2CN$	$CH_2:CHCH_2I$	same as above	3-PyC($CH_2CH:CH_2$)$_2$CN	66%	15
	$Me_2N(CH_2)_2Cl$	$NaNH_2$, not further specified		25%	176

[a]Where not specified, X may be either Cl, Br, or I.

TABLE XI-24. Synthesis of Side-Chain Nitriles by Michael Addition

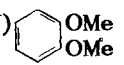
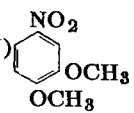
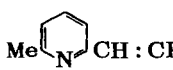
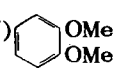
Vinyl compound	Addend	Conditions	Product	Yield	Ref.
2-PyCH : CH_2	HCN	20 hr., 77°	2-Py$(CH_2)_2$CN	42%	11
2-PyCH : CH_2	KCN	trace H_2O, Ac_2O, 16 hr., 100°	2-Py$(CH_2)_2$CN	67%	53
2-PyCH : CH_2	$PhCH_2CN$	Na, 5 hr., 160°	2-Py$(CH_2)_2$CHPhCN and (2-Py$CH_2CH_2)_2$CPhCN	77%	53,198, 219
2-PyCH : CH_2	Ph_2CHCN	not stated	2-Py$(CH_2)_2$CPh_2CN		177
2-PyCH : CH_2	$CNCH_2CO_2Et$	Na, 5 hr., 100°	2-Py$(CH_2)_2$CHCNCO_2Et	48%	53
CH_2 : CHCN	2-PyCH_2CO_2Et	Na, 2 hr., 180°	2-PyCCO_2Et$(CH_2)_2$CN	72%	53
CH_2 : $CHCO_2$Me	2-PyCHPhCN	Triton B, dioxane, 1 hr., 75–90°	2-PyC$(CH_2CH_2CO_2$Me)PhCN		85
CH_2 : $CHCO_2$Me	2-PyCH(*p*-ClC_6H_4)CN	same as above	2-PyC$(CH_2CH_2CO_2$Me)(*p*-ClC_6H_4)CN		85
2-PyCH : CH_2	$CNCH(HNCOCH_3)CO_2Et$	NaOEt, PhH 6 hr., reflux	2-Py$(CH_2)_2$C(HNCOMe)-$CNCO_2$Et	58%	123
CH_2 : CHCN	2-Py$CH(CH_2CH_2NMe_2)$CN	Triton B, dioxane, 1 hr., 75–90°	2-PyC$(CH_2CH_2NMe_2)(CH_2$-$CH_2CN)$CN		147
	2-PyCH_2CO_2Et	NaOMe, EtOH, 1 day, reflux	2-PyCH(CO_2Et) 	44%	191
2-PyCH : CH_2	Me_2CHCN	Na	2-Py$(CH_2)_2$C$(CH_3)_2$CN	27%	219
CH_2 : CHCN	2-PyCH_2COCH_3	KOH	2-PyCH$(COCH_3)CH_2CH_2$CN	44%	239
CH_2 : CHCN (excess)	2-PyCH_2COCH_3	same as above	2-PyC$(CH_2CH_2CN)_2COCH_3$	82%	239

(*continued*)

TABLE XI-24. Synthesis of Side-Chain Nitriles by Michael Addition (*continued*)

Vinyl compound	Addend	Conditions	Product	Yield	Ref.
$CH_2:CHCN$	$2\text{-}PyCH_2COPh$	same as above	$2\text{-}PyCH(COPh)CH_2CH_2CN$	48%	239
$CH_2:CHCN$	$2\text{-}PyCH_2CO\text{-}2\text{-}Py$	same as above	$2\text{-}PyCH(CH_2CH_2CN)COPy\text{-}2$	51%	239
$CH_2:CHCN$	2-PyCHPhCN	KOH, CH_3OH	$2\text{-}PyC(CH_2CH_2CN)PhCN$		211
$CH_2:CHCO_2Me$	2-PyCHPhCN	same as above	$2\text{-}PyC(CH_2CH_2CO_2Me)PhCN$	85%	211
$CH_2:CHCONH_2$	2-PyCHPhCN	same as above	$2\text{-}PyC(CH_2CH_2CONH_2)PhCN$	70%	211
$2\text{-}PyCH:CH_2$	CH_3CN	Na	$2\text{-}Py(CH_2)_3CN$	8%	219
$3\text{-}PyCH:CH_2$	HCN	2 hr., 145°	decomposition		11
$4\text{-}PyCH:CH_2$	HCN	same as above	$4\text{-}Py(CH_2)_2CN$	26%	11
$CH_2:CHCN$	3-PyCHEtCN	not stated	$3\text{-}PyCEtCNCH_2CH_2CN$		203
$4\text{-}PyCH:CH_2$	CH_3CN	Na	$4\text{-}Py(CH_2)_3CN$	8%	219
$4\text{-}PyCH:CH_2$	$PhCH_2CN$	same as above	$4\text{-}Py(CH_2)_2CHPhCN$	58%	219

TABLE XI-25. Synthesis of Side-Chain Nitriles by Knoevenagel Condensation

Carbonyl component	Methylene component	Conditions	Product	Yield	Ref.
2-PyCHO	$PhCH_2CN$	MeOH, NaOMe, 50°, 1 hr.	2-PyCH : CPhCN	74%	183,226, 257
2-PyCHO	p-$ClC_6H_4CH_2CN$	same as above	2-PyCH : C(p-ClC_6H_4)CN	91%	183
2-PyCHO		same as above	2-PyCH : C(CN) 	75%	183
2-PyCOPh	$CNCH_2CO_2Et$	EtOH, NaOEt	2-PyCPh : $CCNCO_2Et$	24%	107
2-PyCHO	$MeCOCH_2CO_2Et$	piperidine, ether, −20°	2-PyCHOHCH(COMe)CO_2Et	86%	258
2-PyCHO	2-nitro-4,5-dimethoxyphenylacetonitrile	heat in piperidine	2-PyCH : C(CN) 	96%	214
	$PhCH_2CN$				226
3-PyCHO	$PhCH_2CN$	MeOH, NaOMe, 50°, 1 hr.	3-PyCH : CPhCN	42%	183,226
3-PyCHO	o-$ClC_6H_4CH_2CN$	same as above	3-PyCH : C(o-ClC_6H_4)CN	86%	183
3-PyCHO	p-$ClC_6H_4CH_2CN$	same as above	3-PyCH : C(p-ClC_6H_4)CN	95%	183
3-PyCHO		same as above	3-PyCH : C(CN) 	83%	183,242
3-PyCHO	$MeCOCH_2CO_2Et$	piperidine, ether, −20°	3-PyCHOHCH(COMe)CO_2Et		258
4-PyCHO	$PhCH_2CN$	MeOH, NaOMe, 50°, 1 hr.	4-PyCH : CPhCN	30%	183,226

(*continued*)

TABLE XI-25. Synthesis of Side-Chain Nitriles by Knoevenagel Condensation (*continued*)

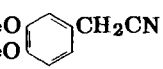
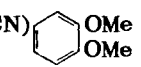
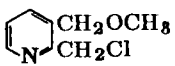
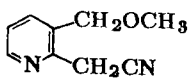
Carbonyl component	Methylene component	Conditions	Product	Yield	Ref.
4-PyCHO	*p*-$ClC_6H_4CH_2CN$	same as above	4-PyCH : C(*p*-ClC_6H_4)CN	91%	183
4-PyCHO		same as above		64%	183,242
4-PyCHO	O_2NCH_2CN		4-PyCH : $C(CN)NO_2$	35%	215
4-PyCHO	$MeCOCH_2CO_2Et$	piperidine, ether, −20°	4-PyCH : $C(COMe)CO_2Et$		258
2,6-$Py(CHO)_2$	$CH_2(CO_2H)_2$	piperidine, Py, reflux 4 hr.	2,6-$Py(CH:CHCO_2H)_2$	78%	251

TABLE XI-26. Side-Chain Nitrile Syntheses: Miscellaneous Methods

Starting material	Conditions	Product	Yield	Ref.
	DEHYDRATION			
3-$PyCH_2CONH_2$	$POCl_3$, reflux	3-$PyCH_2CN$	34%	15,51
	P_2O_5, 15 min., full flame		35%	19
	Ac_2O, reflux			22
	METATHESIS			
2-$Py(CH_2)_2Br$	NaCN, EtOH, 7 hr., 80°	2-$Py(CH_2)_2CN$	65%	70
	NaCN			272
3-$PyCH_2Cl$	KCN, MeOH, H_2O, 1 hr., reflux	3-$PyCH_2CN$	34%	165
	STRECKER SYNTHESIS			
2-PyCHO	KCN, NH_4Cl, H_2O	2-PyCHOHCN	48%	250
2-PyCHO	PhCOCl, KCN, Et_2O, H_2O, −10°	2-$PyCH(O_2CPh)CN$	81%	241,257
3-PyCHO	same as above	3-$PyCH(O_2CPh)CN$	50%	241
4-PyCHO	KCN, NH_4Cl, H_2O	4-PyCHOHCN	87%	250
4-PyCHO	PhCOCl, KCN, Et_2O, H_2O, −10°	4-$PyCH(O_2CPh)CN$	78%	241

(*continued*)

TABLE XI-26. Side-Chain Nitrile Syntheses: Miscellaneous Methods (*continued*)

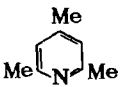
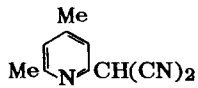
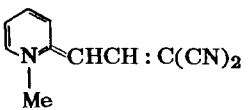
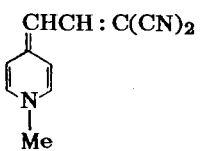
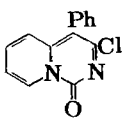
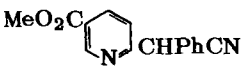
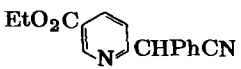
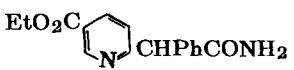
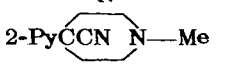
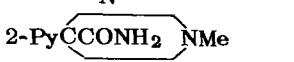
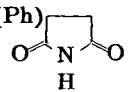
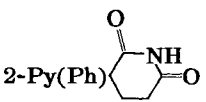
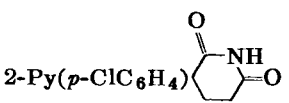
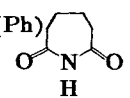
Starting material	Conditions	Product	Yield	Ref.
		OTHER		
2-PyMe	PhNMeCN. PhLi, ether, −15°	2-PyCH(CN)$_2$	70%	159,174
	same as above		70%	174
3-PyCO$_2$Et	PhCH$_2$CN, NaOEt, EtOH, 4 hr., 80°	3-PyCOCHPhCN	71%	51
3-PyCH$_2$CN	CH$_3$CO$_2$Et, NaOEt, EtOH, 4 hr., 80°	3-PyCH(COMe)CN	56%	51
2-PyMe · CH$_3$I	EtOCH : C(CN)$_2$, KOH, MeOH			194
4-PyMe · CH$_3$I	same as above			194
	NaOMe, MeOH, heat 14 hr.	2-PyCHPhCN		261

TABLE XI-27. Solvolysis of Side-Chain Nitriles

Nitrile	Conditions	Product	Yield	Ref.
2-PyCHPhCN	conc. H_2SO_4, 2 hr., 50°	2-PyCHPhCONH$_2$	90%	13,14,107,142
2-PyCH$_2$CN	dry HCl, EtOH	2-PyCH$_2$CO$_2$Et	72%	232
2-PyCH(O$_2$CPh)CN	conc. H_2SO_4, −15°, 5 hr.	2-PyCH(O$_2$CPh)CONH$_2$	85%	241
2-PyCHPhCN	MeOH, HCl, 100°	2-PyCHPhCO$_2$Me	70%	14,204
2-PyCHPhCN	Me$_2$CHOH, HCl, 60°	2-PyCHPhCO$_2$CHMe$_2$		204
2-PyCHPhCN	EtOH, HCl, 100°	2-PyCHPhCO$_2$Et		14,204
2-PyCHPhCN	H_2SO_4, 24 hr., 25°	2-PyCHPhCONH$_2$		204
	conc. H_2SO_4, 14 hr., 25°		52%	12
	same as above		70%	12
	same as above		94%	187
2-Py(CH$_2$)$_2$CN	hot, dil. HCl	2-Py(CH$_2$)$_2$CO$_2$H	75%	11
2-Py(CH$_2$)$_2$CHPhCN	EtOH, dry HCl	2-Py(CH$_2$)$_2$CHPhC(:NH)OEt		198
2-Py(CH$_2$)$_2$CN	KOH, H_2O_2, 40°	2-Py(CH$_2$)$_2$CONH$_2$	66%	70
2-PyC(CH$_2$CO$_2$Et)PhCN	70% H_2SO_4, 9 hr., 130°	2-PyCHPhCH$_2$CO$_2$Et	70%	86
2-PyC(CH$_2$CO$_2$Et)(*p*-ClC$_6$H$_4$)CN	same as above	2-PyCH(*p*-ClC$_6$H$_4$)CH$_2$CO$_2$Et	57%	86
2-PyCMePhCN	conc. H_2SO_4, 14 hr., 25°	2-PyCMePhCONH$_2$		14,142
2-PyCPhCN(CH$_2$)$_2$CO$_2$Et	70% H_2SO_4, 9 hr., 130°	2-PyCHPh(CH$_2$)$_2$CO$_2$Et	68%	86
2-Py(CH$_2$)$_2$C(HNCOMe)CNCO$_2$Et	conc., HCl, 6 hr. reflux	2-Py(CH$_2$)$_2$CHNH$_2$CO$_2$H	50%	123
2-PyCEtPhCN	conc. H_2SO_4, 14 hr., 25°	2-PyCEtPhCONH$_2$		13,14,142

(*continued*)

TABLE XI-27. Solvolysis of Side-Chain Nitriles (*continued*)

Nitrile	Conditions	Product	Yield	Ref.
	HCl, H_2O, reflux		95%	191
2-PyC($CH_2CH_2NEt_2$)PhCN	EtOH, HCl, 100°	2-PyC($CH_2CH_2NEt_2$)$PhCO_2Et$		14
2-PyC($CH_2CH_2NMe_2$)PhCN	90% H_2SO_4, 100°, 3/4 hr.	2-PyC($CH_2CH_2NMe_2$)$PhCONH_2$	76%	196
2-PyC($CH_2CH_2NEt_2$)PhCN	same as above	2-PyC($CH_2CH_2NEt_2$)$PhCONH_2$	72%	196,288
2-PyCPhCN$CH_2CO_2NH_4$	20 min., 180–220°			85
2-PyCPhCN$(CH_2)_2CO_2H$	Ac_2O, HOAc, $SnCl_4$ 20 min., reflux			85
2-PyC(*p*-ClC_6H_4)CN$(CH_2)_2CO_2H$	same as above			85
2-PyCPhCN$(CH_2)_3CO_2NH_4$	15 min., 180–220°			85

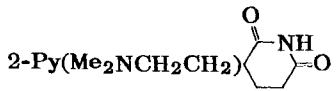
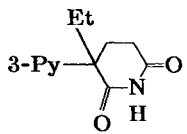
2-PyCH(COPh)CH_2CH_2CN	heat in 60% KOH; or conc. H_2SO_4, reflux	2-Py$(CH_2)_3CO_2H$	79%	239
		2-PyCH(COPh)$CH_2CH_2CO_2H$	89%	239
2-PyCH(CO-2-Py)CH_2CH_2CN	conc. H_2SO_4, reflux	2-PyCH(CO-2-Py)$CH_2CH_2CO_2H$	90%	239
2-PyCPhCN$(CH_2)_2CN$	dry HCl, CH_3OH	2-PyCPhCN$(CH_2)_2CO_2Me$	85%	211
2-PyCH$(COCH_3)CH_2CH_2CN$	conc. H_2SO_4, reflux	2-PyCH$(COCH_3)CH_2CH_2CO_2H$	83%	239
2-PyCPhCN$(CH_2)_3CN$	KOH, EtOH, reflux	2-PyCPhCN$(CH_2)_3CO_2H$		85
2-PyC$(CH_2CH_2NMe_2)CN(CH_2)_2$-CN	HOAc, 125–35°, add conc. H_2SO_4 during 10 min.			147
3-PyCEtCNCH_2CH_2CN	HOAc, H_2SO_4, 3/4 hr., 60–100°			203
3-PyCHPhCN	conc., H_2SO_4, 2 hr., 60°	3-PyCHPhCONH_2	45%	12
3-PyCH$(CH_2Ph)CN$	not stated	3-PyCH$(CH_2Ph)CO_2H$		15
3-PyCH$(O_2CPh)CN$	conc. H_2SO_4, 5 hr., −15°	3-PyCH$(O_2CPh)CONH_2$	69%	241
4-PyCH$(O_2CPh)CN$	same as above	4-PyCH$(O_2CPh)CONH_2$	78%	241
4-Py$(CH_2)_2CN$	20% NaOH	4-Py$(CH_2)_2CO_2H$	80%	11
4-PyCHPhCN	conc. H_2SO_4, 2 hr., 50°	4-PyCHPhCONH_2		13,14,142
4-PyCH$(CH_2Ph)CN$	MeOH, HCl, 100°	4-PyCH$(CH_2Ph)CO_2Me$		14

TABLE XI-28. Reduction of Side-Chain Nitriles

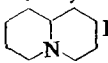
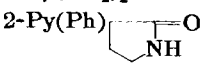
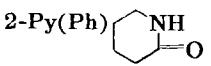
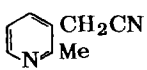
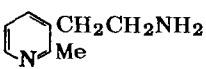
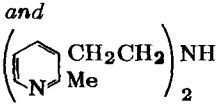
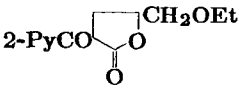
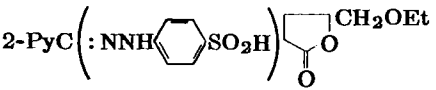
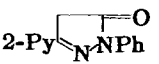
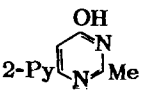
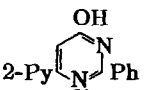
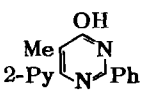
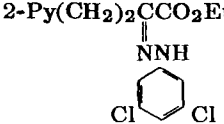
Nitrile	Conditions	Product	Yield	Ref.
2-PyCHPhCN	Ni, H_2 (500 p.s.i.), EtOH, 60–70°	2-PyCHPhCH$_2$NH$_2$ *and* (2-PyCHPhCH$_2$)$_2$NH		158
2-Py(CH$_2$)$_2$CHPhCN	PtO_2, H_2 (1 atm.), HCl, 25°	 *and* 2-Py(CH$_2$)$_2$CHPhCH$_2$NH$_2$	20%	53
2-Py(CH$_2$)$_2$CHPhCN	$LiAlH_4$, ether, reflux several hr.	2-Py(CH$_2$)$_2$CHPhCH$_2$NH$_2$	65%	53
2-PyC(CH$_2$CO$_2$Et)PhCN	same as above		64%	86
2-PyC(CH$_2$CH$_2$CO$_2$Et)PhCN	same as above		71%	86
	PtO_2 (or Pd), H_2 (1 atm.), H_2O, 16 hr.	 *and* 	35% 35%	19,22

TABLE XI-29. Reactions of 2-Pyridineacetonitriles with Organometallic Reagents

Starting material	Reagent	Conditions	Product	Yield	Ref.
2-PyCMePhCN	EtMgBr	ether, 3 hr., *reflux*	2-PyCMePhCOEt	85%	158
2-PyCMePhCN	PrMgBr	same as above	2-PyCMePhCOPr	65%	158
2-PyC(α-$C_{10}H_7$)($CH_2CH_2NMe_2$)CN	$NaNH_2$	xylene, 28 hr., reflux	2-PyCH(α-$C_{10}H_7$)(CH_2)$_2$$NMe_2$	68%	168
2-PyCPh($CH_2CH_2NMe_2$)CN	$NaNH_2$	same as above	2-PyCHPh(CH_2)$_2$$NMe_2$	60%	168
2-PyCPh($CH_2CH_2NMe_2$)CN	EtLi	ether, 4 hr., 25°	2-PyCHPh(CH_2)$_2$$NMe_2$	63%	168
2-PyCPh($CH_2CH_2NMe_2$)CN	EtMgBr	anisole, 2 hr., 60–70°	2-PyCHPh(CH_2)$_2$$NMe_2$	35%	168,283
2-PyCPh(CH_2CH_2N⬡)CN	EtMgBr	C_6H_6, reflux 1 hr.	2-PyCHPh(CH_2)$_2$N⬡		283
2-PyCPh($CH_2CH_2CH_2N$⬠)CN	EtMgBr	same as above	2-PyCHPh(CH_2)$_3$N⬠		283

TABLE XI-30. Carbonyl Reactions of Keto Acids

Starting material	Reagent and conditions	Product	Yield	Ref.
2-$PyCOCH_2CO_2Et$	NH_4OH, 3 days, 25°	2-PyC(:NM)CH_2CO_2Et		37
2-$PyCOCH_2CO_2Et$	$PhNHNH_2$	2-PyC(:NNHPh)CH_2CO_2Et		37
	*p*-$HO_3SC_6H_4NHNH_2$			50
2-PyC(:NNHPh)CH_2CO_2Et	heat in dilute HOAc			37
2-$PyCOCHNaCO_2Et$	$CH_3C(:NH)NH_2 \cdot HCl$ stand 4 days at 25°			37
2-$PyCOCHNaCO_2Et$	$C_6H_5C(:NH)NH_2 \cdot HCl$, stand 4 days at 25°			37
2-$PyCOCMeNaCO_2Et$	$CH_3C(:NH)NH_2 \cdot HCl$, stand 4 days at 25°			37
2-$Py(CH_2)_2COCH_2CO_2Et$	PhN_2Cl, NaOH, HCl	2-$Py(CH_2)_2$C(:NNHPh)(CO_2Et)	50%	209
2-$Py(CH_2)_2COCH_2CO_2Et$	$3,5\text{-}Cl_2C_6H_3N_2Cl$, NaOH, HCl		50%	209

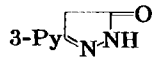
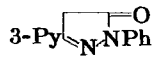
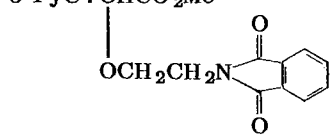
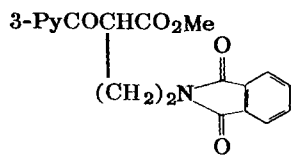
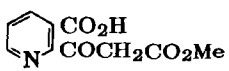
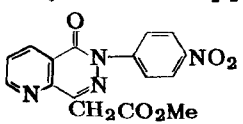
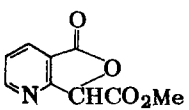
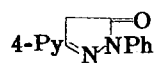
3-$PyCOCH_2CO_2Et$	$N_2H_4 \cdot H_2O$, MeOH, 4 hr., reflux			39
3-$PyCOCH_2CH_2CO_2Et$	NH_2OH, PyH EtOH, 2 hr., reflux	3-$PyC(:NOH)CH_2CH_2CO_2Et$	95%	190
3-$PyCOCH_2CO_2Et$	$PhNHNH_2$, HOAc, 1/2 hr., 100°			39
3-$PyCOCH_2CO_2Me$	KOMe, $C_8H_6O_2N(CH_2)_2Br$		25%	228
		+ 		228
3-$PyCO(CH_2)_2CO_2H$	NH_2OH	3-$PyC(:NOH)(CH_2)_2CO_2H$		263
	*p*-$O_2NC_6H_4NHNH_2$, HOAc			155
	same as above	same as above		155
4-$PyCOCH_2CO_2Et$	$PhNHNH_2$			37

TABLE XI-31. Introduction of a Double Bond

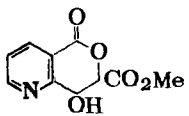
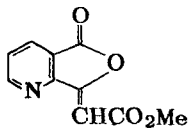
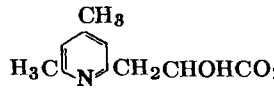
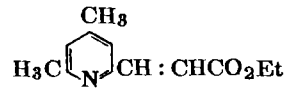
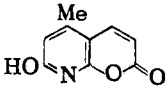
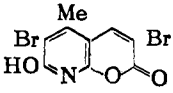
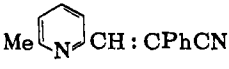
Starting material	Conditions	Product	Yield	Ref.
2-$PyCH_2CHOHCO_2H$	vacuum, 140°	2-$PyCH:CHCO_2H$		63
2-$PyCHBrCH_2CO_2H$	Na_2CO_3, H_2O, 100°	2-$PyCH:CHCO_2H$ *and* 2-$PyCHOHCH_2CO_2H$	20% 20%	63
	$SOCl_2$, PyH, $C_6H_5CH_3$ 2 hr., reflux		65%	155
	PCl_5			75
2-$PyCHOHCH(COMe)CO_2Et$	vacuum, 24 hr., 25°	2-$PyCH:C(COMe)CO_2Et$	86%	258
3-$PyCHOHCH(COMe)CO_2Et$	stand at 25°	3-$PyCH:C(COMe)CO_2Et$		258
3-$PyCHOHCH(CO_2Et)_2$	heat 2 hr. in Ac_2O	3-$PyCH:C(CO_2Et)_2$	77%	277
3-$PyCH(OCOCH_3)CHMeCO_2Et$	distil, 760 mm.	3-$PyCH:CMeCO_2Et$	86%	51
4-$Py(CHBr)_2CO_2H$	Na_2CO_3, H_2O; *or* PyH; *or* NaOEt; *or* H_2O	4-$PyCH:CHCO_2H$	85%	69

TABLE XI-32. Addition Reactions of Unsaturated Side-Chains

Starting material	Reagent and conditions	Product	Yield	Ref.
2-PyCH : $CHCO_2H$	HBr, HOAc, 1 hr., 100°	2-PyCHBrCH_2CO_2H		63
2-PyCH : $CHCO_2H$	Br_2, HOAc, 100°	2-Py$(CHBr)_2CO_2H$		63
3-PyCH : $CHCO_2H$	NH_2OH, 9 hr., reflux	3-PyCHN$H_2CH_2CO_2H$	10%	99
3-PyCH : $C(CO_2Et)_2$	$O_2NCH_2CO_2$-Et, Et_2NH, 2 days, 25°	3-PyCHCH$(CO_2Et)_2$ | EtO_2CCHNO_2	91%	101
3-PyCH : $C(CO_2Et)_2$	O_2NCH_2Ph, Et_2NH, 3 days, 25°	3-PyCHCH$(CO_2Et)_2$ | $PhCHNO_2$	84%	101
	Br_2, HOAc			132
2-PyCH : CPhCN	Br_2	2-PyCHBrCBrPhCN		226
	same as above			226
2-PyCH : $CHCO_2H$	NH_4OH, 50 hr., 130°	2-PyCHN$H_2CH_2CO_2H$		227
3-PyCOCH : CHPh	$CH_2(CO_2Me)_2$, 2 days, 25° in CH_3OH	3-PyCOCH_2CHPhCH$(CO_2Me)_2$	98%	243
3-PyCOCH : CHPh	same as above	3-PyCOCH_2CHPhCH$(CO_2Et)_2$	68%	243

(*continued*)

TABLE XI-32. Addition Reactions of Unsaturated Side-Chains (*continued*)

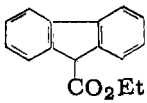
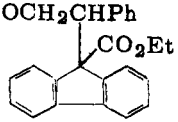
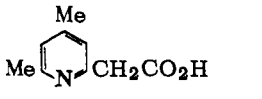
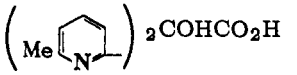
Starting material	Reagent and conditions	Product	Yield	Ref.
3-PyCOCH : CHPh	 + Et_2NH in EtOH, 2 days, 25°	3-PyCOCH$_2$CHPh 	100%	243
3-PyCH : CPhCN	Br_2	3-PyCHBrCBrPhCN		226
4-PyCH : CPhCN	same as above	4-PyCHBrCBrPhCN		226
4-PyCH : CHCO$_2$H	Br_2, HOAc, 100°	4-Py(CHBr)$_2$CO$_2$H	96%	69
	Br_2, $CHCl_3$, HOAc			67

TABLE XI-33. 2-Pyridine Side-Chain Acids

Acid	M.p.	Derivative	Ref.
2-$PyCH_2CO_2H$	98°	hydrochloride, M.p. 154°; picrate, m.p. 141°	9,18,25, 32,80
	146°		7
		hydrochloride, m.p. 107°	3
	140°·		80
$(2\text{-Py})_2COHCO_2H$	199°(dec.)		271
	239°		271
2-$PyCH(p\text{-}ClC_6H_4)CO_2H$	117°		262
2-$Py(CH_2)_2CO_2H$	138°, 140°		2,11,14, 77,84, 114, 227, 252
2-$PyCH:CHCO_2H$	203° (dec.), 198°	hydrochloride, m.p. 220°; picrate, m.p. 223°	62,63,70, 76,77, 79,149, 227
2-$PyCH_2CHNH_2CO_2H$	217° (dec.), 206°	hydrochloride, m.p. 191°; dihydrochloride, m.p. 210°; picrate, m.p. 165°	17,115
2-$PyCH_2CHOHCO_2H$	125°	hydrochloride, m.p. 86°; hydrobromide, m.p. 126°	63,64
2-$PyCH_2CH(O_2CPh)CO_2H$	145°		63

(*continued*)

TABLE XI-33. 2-Pyridine Side-Chain Acids (*continued*)

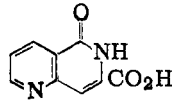
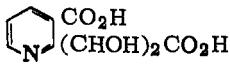
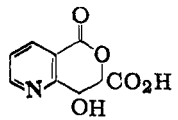
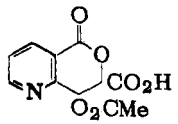
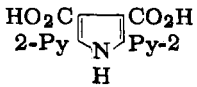
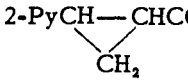
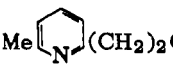
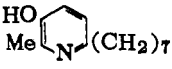
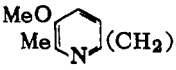
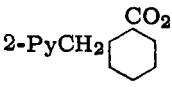
Acid	M.p.	Derivative	Ref.
	321° (dec.)		6
2-PyCHNH$_2$CH$_2$CO$_2$H	206° (dec.)		99,227
2-PyCHOHCH$_2$CO$_2$H	86°		63
2-PyCHBrCH$_2$CO$_2$H · HO$_2$CMe	164°		63
2-PyCHPhCH$_2$CO$_2$H	111°		86
2-PyCH(O$_2$CPh)CH$_2$CO$_2$H	135°		63
2-Py(CHBr)$_2$CO$_2$H	127°		63
	*a*		6
	210° (dec.)		6,155
	177°		6
			270
2,6-Py(CH : CHCO$_2$H)$_2$	315°		251
2-Py(CH$_2$)$_3$CO$_2$H	85°	hydrochloride, m.p. 112°	11,208, 239, 252
2-Py(CH$_2$)$_2$CHNH$_2$CO$_2$H	280°		123
	99°	hydrochloride, m.p. 89°	117,125
2-PyCHPh(CH$_2$)$_2$CO$_2$H	112°		86
2-PyCH : C(CO$_2$H)CH$_2$Py-2	164°	picrate, m.p. 147°	88
2-Py(CH$_2$)$_2$C(: NNHPh)CO$_2$H	160°		280
2-PyCH(CH$_2$CO$_2$H)CO$_2$H			218

TABLE XI-33 (*continued*)

Acid	M.p.	Derivative	Ref.
			218
2-Py$(CH_2)_4CO_2H$	97°		252
2-PyCMeEtCO_2H		hydrochloride, m.p. 104°	32
2-PyCH$(CH_2CO_2H)_2$			218
2-Py$(CH_2)_2$CH$(CO_2H)_2$	138°	hydrochloride, m.p. 180°	11
2-Py$(CH_2)_2$CHEtCO_2H	129°		118
2-Py$(CH_2)_2CMe_2CO_2H$	163°		5
2-Py$(CH_2)_3COCO_2H$			236
2-Py$(CH_2)_3$CHOHCO_2H	139°		236
2-PyCH(COPh)$CH_2CH_2CO_2H$	135°		239
2-PyCH(COPy-2)$CH_2CH_2CO_2H$	108°		239
2-PyCH(COMe)CH_2CO_2H		hydrochloride, m.p. 156°	278,279, 259
		hydrochloride, m.p. 97°	140,185
2-PyCH$(COCH_3)CH_2CH_2CO_2H$	121°		239
			237
	86°	hydrochloride, m.p. 111°	137,185
		hydrochloride, m.p. 135°	137,185
	138°		191
2-Py$(CH_2)_9CO_2H$	56°	picrate, m.p. 83°	4
2-Py$(CH_2)_{10}CO_2H$	69°		4
2-Py$(CH_2)_{12}CO_2H$	77°		143
2-Py$(CH_2)_{11}$CH$(CO_2H)_2$	100° (dec.)		143

[a]Dehydrates to δ-lactone at 140°.

TABLE XI-34. 3-Pyridine Side-Chain Acids

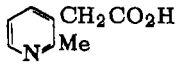
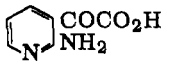
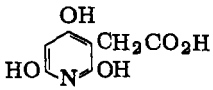
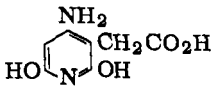
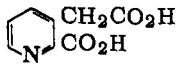
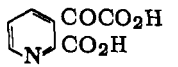
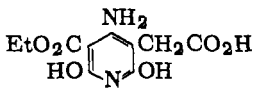
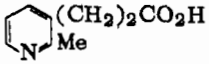
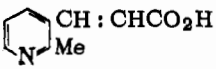
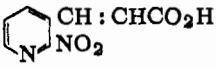
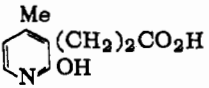
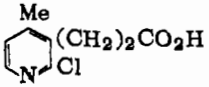
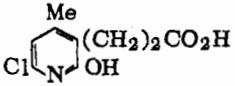
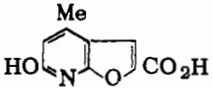
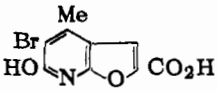
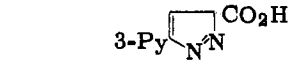
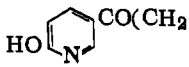
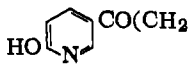
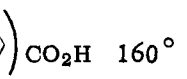
Acid	M.p.	Derivative	Ref.
3-$PyCH_2CO_2H$	145°	hydrochloride, m.p. 154°; picrate, m.p. 100°	18,127, 129,257
	207°		19
	198°		8
	220° (dec.)		135
	270°		135
	184°	monohydrate, m.p. 187° (dec.)	127–129, 150
		hydrazone, m.p. 306°; semicarbazone, m.p. 286°	150
	*a*		135
3-$Py(CH_2)_2CO_2H$	158°		97
	161°	hydroiodide, m.p. 164°	96,265
3-$PyCH:CHCO_2H$	233°	hydrobromide, m.p. 264°	95–97,99, 149
3-$PyCH_2CHNH_2CO_2H$	263°		115
3-$PyCH:C(p\text{-}MeOC_6H_4)CO_2H$	192°		105
3-$PyCHNH_2CH_2CO_2H$	206° (dec.)		99
3-$PyCH(NHMe)CH_2CO_2H$	171°		99

TABLE XI-34 (*continued*)

Acid	M.p.	Derivative	Ref.
3-PyCH(CH_2Ph)CO_2H	175°		15
3-PyC(:CHPh)CO_2H	233° (dec.)		20,257
	148°		102
	214°		102
	251°		100
	214°		132
	128°		132
	204–206°		132
	278° (dec.)		132
	245°		132
3-PyCO(CH_2)$_2CO_2$H	163°	acetylhydrazone, m.p. 197°; oxime, m.p. 166°; semicarbazone, m.p. 229°; picrate, m.p. 140°; oxime, m.p. 165°	99,190,205, 216,263, 247,275, 276

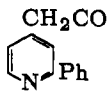
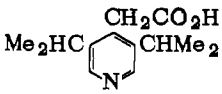
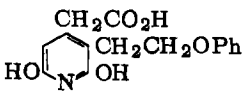
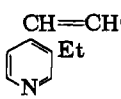
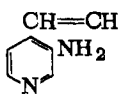
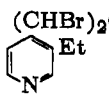
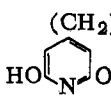
(*continued*)

TABLE XI-34. 3-Pyridine Side-Chain Acids (*continued*)

Acid	M.p.	Derivative	Ref.
	309°	picrate, m.p. 224°	184
$3\text{-PyCHNH}_2(CH_2)_3CO_2H$	146°		1
$3\text{-PyCH(NHMe)}(CH_2)_2CO_2H$	133°		263,253
$3\text{-PyCHNH}_2(CH_2)_2CO_2H$		monohydrate, m.p. 167°	263
	288°	oxime, m.p. 211°	216,247,275
$3\text{-PyCH(CH}_2CO_2H)_2$		hydrochloride, m.p. 135°	218,268
	241°	oxime, m.p. 242°	247
$3\text{-PyCOCH : COHCH}_2CO_2K$		dipotassium salt, m.p. 240–50° (dec.)	245
$3\text{-PyCOCH}_2CHPhCH_2CO_2H$	148°		243
$3\text{-PyCOCH}_2CHPhCH(CO_2H)_2$	149°		243
3-PyCH : C  CO_2H	160°		106,108

[a]Dehydrates to γ-lactam on heating.

TABLE XI-35. 4-Pyridine Side-Chain Acids

Acid	M.p.	Derivative	Ref.
4-PyCH$_2$CO$_2$H		hydrochloride, m.p. 131°	18
4-PyCHPhCO$_2$H	no data		89
	245°		36
	no data		7
	146°		132
4-Py(CH$_2$)$_2$CO$_2$H	232°	hydrochloride, m.p. 209°	11,73,139
4-PyCH : CHCO$_2$H	296° (dec.)	hydrochloride, m.p. 190° (dec.); chloraurate, m.p. 235° (dec.)	41,66,68, 69,71–74,149
4-PyCHMeCO$_2$H	90° (dec.)		16
4-PyCH$_2$CHNH$_2$CO$_2$H	236° (dec.)		115
4-PyCHOHCH$_2$CO$_2$H	202° (dec.)	hydrochloride, m.p. 174°, cupric salt, m.p. 208°	41
4-PyCHPhCOCO$_2$H	110° (dec.)	oxime hydrochloride, m.p. 53°	89
4-Py(CHBr)$_2$CO$_2$H	259°		69
	248° (dec.)	hydrochloride, m.p. 176°; chloraurate, m.p. 202°	67,68
	243°		100
	148°		67
	257° (dec.) 269°		136 139

(*continued*)

TABLE XI-35. 4-Pyridine Side-Chain Acids (*continued*)

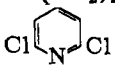
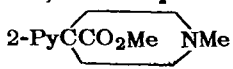
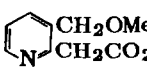
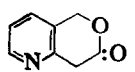
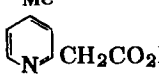
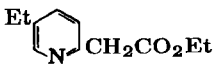
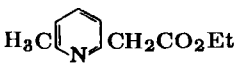
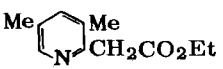
Acid	M.p.	Derivative	Ref.
	127°		139
4-PyC(CHOH)$_2$C(COCH$_3$)CO$_2$H			188
4-PyCHEtCO$_2$H	89° (dec.)		16
4-PyCH(CH$_2$CO$_2$H)$_2$		hydrochloride, m.p. 220°; cupric salt, m.p. 269°	99,126
4-Py(CH$_2$)$_5$CO$_2$H · 2H$_2$O	198°		10

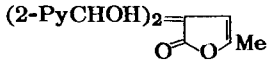
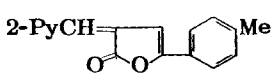
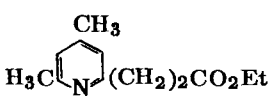
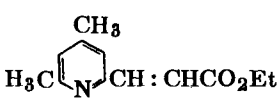
TABLE XI-36. 2-Pyridine Side-Chain Esters

Ester	B.p./mm.	M.p.	Derivative	Ref.
2-$PyCH_2CO_2Me$	126–27°/15			29,207
2-$PyCH_2CO_2Et$	120–22°/10		picrate, m.p. 141°; picrolonate, m. p. 157°	18,56,201, 232,254, 261,241
2-$PyCH_2CO_2$-*i*-Pr			picrolonate, m.p. 187°	56
2-$PyCHPhCO_2Me$		75°		14,142,204
2-$PyCHPhCO_2Et$	155–60°/0.4	68°		14,142,204
2-$PyCHPhCO_2CHMe_2$		62°		204
2-$PyCH(O_2CCH_3)CO_2Et$	97°/0.2			114
2-$PyCHPhCO_2(CH_2)_2NEt_2$	160–63°/0.2			142
2-$PyCHBrCO_2Me$	90°/0.2			114
2-$PyCHBrCO_2Et$	90°/0.2			114
		46°		187
2-$PyCHOHCO_2Et$		82°		250
	148°/8		picrate, m.p. 117°	272
	120–30°/0.08	88°		264
	96–97°/1		picrate, m.p. 116°; picrolonate, m.p. 166°	58

(*continued*)

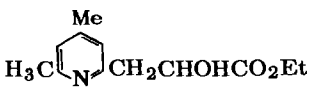
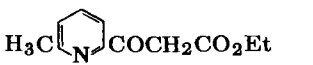
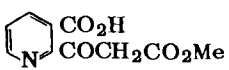
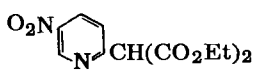
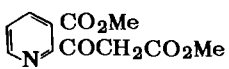
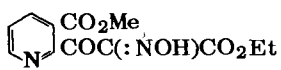
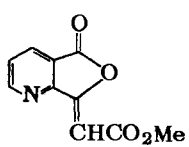
TABLE XI-36. 2-Pyridine Side-Chain Esters (*continued*)

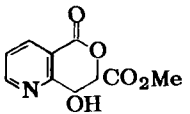
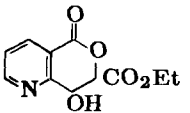
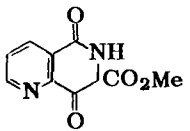
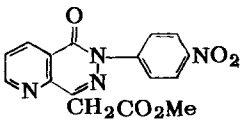
Ester	B.p./mm.	M.p.	Derivative	Ref.
	97–98°/1		picrate, m.p. 144°; picrolonate, m.p. 142°	58
				81
	125–35°/0.2			121
	120–25°/0.02		picrate, m.p. 114°	121
2-Py(CH_2)$_2CO_2Me$	102–103°/2			70
2-Py(CH_2)$_2CO_2Et$	103–104°/0.7, 145–50°/18			2,46
2-PyCH : $CHCO_2Me$			hydrochloride, m.p. 186°	63
2-PyCH : $CHCO_2Et$	142–45°/11		chloraurate, m.p. 149°	64,78,152, 273
2-Py$CH_2CHOHCO_2Me$		34°	chloraurate, m.p. 119°	63
2-Py$CH_2CH(O_2CPh)CO_2Me$		41°	chloroplatinate, m.p. 193°	63
2-PyCHOHCH_2CO_2Me			chloroplatinate, m.p. 178°	63
2-PyCHOHCH_2CO_2Et	no data			63
2-PyCHPhCH_2CO_2Et	140–42°/15			86
2-PyCHPh$CH_2CO_2(CH_2)_2NEt_2$	165–70°/2			86
2-PyCH(*p*-ClC_6H_4)CH_2CO_2Et	174–76°/1			86
2-Py$COCH_2CO_2Et$	92–97°/0.1		hydrochloride, m.p. 118°; chloroplatinate, m.p. 175°	37,40,42, 120,270

2-PyC(:NH)CH_2CO_2Et		63°		37
2-PyC(:NNHPh)CH_2CO_2Et		122°		37
			diethylamine salt, m.p. 86° (dec.)	103
2-PyCHMe CO_2Et	74°/14		picrate, m.p. 105°; picrolonate, m.p. 124°	31,56
2-PyCH(CHO)CO_2Et		98°		56,57
2-PyCH(CHO)CO_2-*i*-Pr		78°		56
$(2\text{-PyCOCHCO}_2\text{Et})_2$				270
2-PyCH : $CHCO_2(CH_2)_2Cl$		153°	picrate, m.p. 152°	213
2-Py$(CH_2)_2CO_2(CH_2)_2Cl$			picrate, m.p. 94°	213
2-PyCH : $CHCO_2(CH_2)_2\overset{+}{N}Me_3Pic.^-$		192°		213
2-Py$(CH_2)_2CO_2(CH_2)_2\overset{+}{N}Me_3Pic.^-$		93°		213
		150°		118
		268°		188
	91–92°/13			75
	125°/7		hydrochloride, m.p. 180°	3,75

(*continued*)

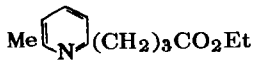
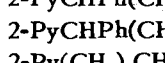
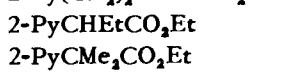
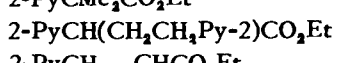
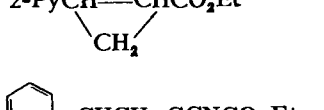
TABLE XI-36. 2-Pyridine Side-Chain Esters (*continued*)

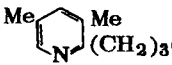
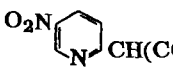
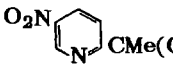
Ester	B.p./mm.	M.p.	Derivative	Ref.
	131–32°/4			75
	no data			37
	75–78°/1		picrate, m.p. 103°	58
		94°		155
		98°		33
	150–55°/0.04			155
		186° (dec.)		155
		161°		155

		152° (dec.)		6,155
		136° (dec.)		6
		220° (dec.)		155
		180°		155
2-Py(CH$_2$)$_3$CO$_2$Et	106°/0.5			236
2-PyCO(CH$_2$)$_2$CO$_2$Et	163°/11		picrolonate, m.p. 104°; chloroplatinate, m.p. 178°	46,49
2-PyCPh(CH$_2$CH$_2$NMe$_2$)CO$_2$Et	175–80°/2.5			224
2-Py(CH$_2$)$_2$C(:NNHPh)CO$_2$Et			hydrochloride, m.p. 197°	280
2-PyCH:C(COPh)CO$_2$Et		99°		289
(2-Py)$_2$CH(CH$_2$)$_2$CO$_2$Et	150–60°/0.06		dipicrate, m.p. 189°	256
(2-PyCH(CO$_2$Et)CH$_2$)$_2$CH$_2$			diamide, m.p. 228° dihydrazide, m.p. 166°	248

(*continued*)

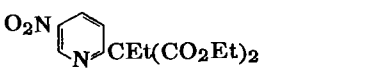
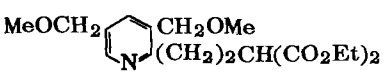
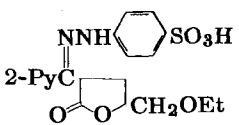
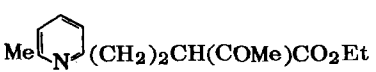
TABLE XI-36. 2-Pyridine Side-Chain Esters (*continued*)

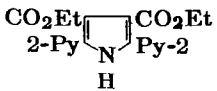
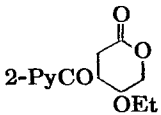
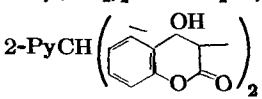
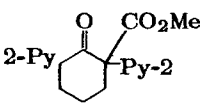
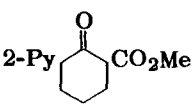
Ester	B.p./mm.	M.p.	Derivative	Ref.
				246
2-PyCHPh$(CH_2)_2CO_2Et$	144–52°/0.5			86
2-PyCHPh$(CH_2)_2CO_2(CH_2)_2NEt_2$	183–85°/1			86
2-Py$(CH_2)_2$CHPhCO_2Et	165–68°/2			198
2-PyCHEtCO_2Et	98°/2			109
2-PyCMe_2CO_2Et	70–78°/0.6			32
2-PyCH$(CH_2CH_2$Py-2$)CO_2Et$	154–56°/0.05			55
	116°/3		picrate, m.p. 123°	117,125
		146°		194
	162–63°/2			117,125
	no data			125
2-PyCH_2COH(COPh)CO_2Et		101°		90,91
2-PyC$(CH_2CH_2NEt_2)$PhCO_2Et	160–63°/0.2			14

	90°/0.01			45
	110–20°/0.01	69°		45
	120°/0.005			110
2-$PyCH_2COH(CO_2Et)_2$		39°		90,91
2-$PyCH(CO_2Et)CH_2CO_2Et$	143.7°/1		picrolonate, m.p. 95°	56
2-$PyCH_2C(NHCOPh)(CO_2Et)_2$	no data			115
2-$PyCH_2C[N(CO)_2C_6H_4](CO_2Et)_2$		120°		17
	150°/1			111
2-$Py(CH_2)_2CH(COPh)CO_2Et$	170–75°/0.3		picrolonate, m.p. 145°	119
2-PyCO 		57°		49
2-$PyCMeEtCO_2Et$	99–105°/3		picrate, m.p. 144.5°	32
2-$PyCH[(CH_2)_3OPh]CO_2Et$	205–207°/1			56,254
2-$PyCEt(CO_2Et)_2$	137°/2			109
2-$Py(CH_2)_2CH(CO_2Et)_2$	135–40°/0.02		picrate, m.p. 85°	11,116,118, 122,124
2-$PyCH(CO_2Et)CH(CO_2Et)_2$			sodium salt, m.p. 250° (dec.)	114
2-$PyCH(CHNO_2CO_2Et)_2$			diethylamine salt, m.p. 140.5°	103,104

(*continued*)

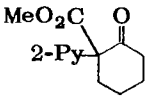
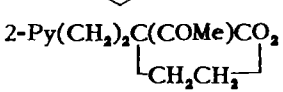
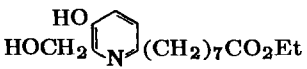
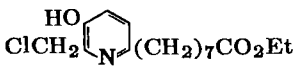
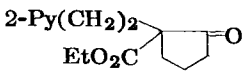
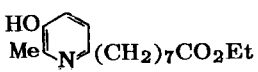
TABLE XI-36. 2-Pyridine Side-Chain Esters (*continued*)

Ester	B.p./mm.	M.p.	Derivative	Ref.
2-PyCHCO$_2$Me CH$_2$ 2-PyCHCO$_2$Me	212–20°/5		picrate, m.p. 195°	141
2-PyCHCO$_2$Et CH$_2$ 2-PyCHCO$_2$Et	175–85°/0.3		picrolonate, m.p. 147°; picrate, m.p. 154°	59
2-PyCPhCN(CH$_2$)$_2$CO$_2$Me	205°/0.8			211
2-PyCH(CO$_2$Et)(CH$_2$)$_3$OCH$_2$Ph	178–82°/0.6			254
2-PyCHOHCH(COMe)CO$_2$Et		54°		258
2-PyCH : CO(COMe)CO$_2$Et		116° (86°)		258,289
	120–40°/0.005			110
	165–75°/0.005			148
		235°		50
				260

				270
	173–75°/0.4		Reineckate, m.p. 129°	50
2-PyC(:CH_2)$CH_2CH(CO_2Et)_2$	130–50°/0.01			208
2-Py$(CH_2)_2CHEtCO_2Et$	115–22°/0.5			118
2-Py$(CH_2)_2CH(COMe)CO_2Et$	138–58°/1			11,118
2-Py$(CH_2)_2CMe_2CO_2Et$	127–29°/2		picrate, m.p. 88°	5
2-PyCH$(CO_2Et)CHMeCH_2CO_2Et$	143–45°/1.5			54
2-PyCOCHCO_2Et | 2-PyCOCHCO_2Et		137°		37
$(2\text{-PyCH}_2CH_2)_2C(CO_2Et)_2$	190°/1		picrate, m.p. 172°	116,118
2-Py$(CH_2)_2CEt(CO_2Et)_2$	138–50°/0.2		picrate, m.p. 89°	118
		253°		289
				248
2-PyCH$(CO_2Me)(CH_2)_4CO_2Me$	164°/0.01			248
				248

(*continued*)

TABLE XI-36. 2-Pyridine Side-Chain Esters (*continued*)

Ester	B.p./mm.	M.p.	Derivative	Ref.
				248
	178–80°/1		picrate, m.p. 112°	119
			picrate, m.p. 115°	237
				237
	120°/0.1			240
 (ethyl carpyrinate)		80°		137

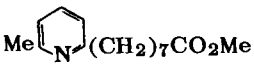
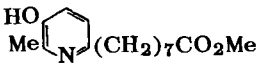
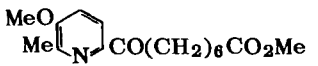
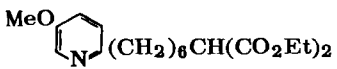
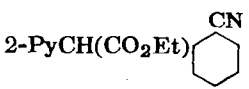
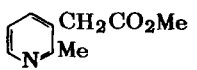
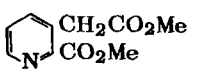
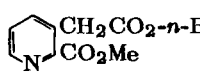
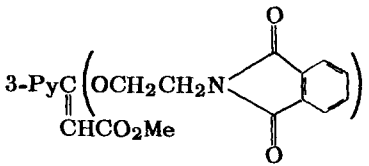
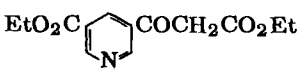
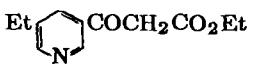
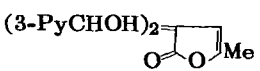
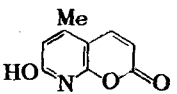
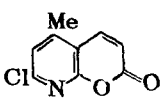
	152.5–55°/3.5		185
	172–73.5°/1.3		185
		126°	185
	181.5–82.5°/0.7		185
		57°	185
$2\text{-Py}(CH_2)_6CH(CO_2Et)_2$	160°/0.5		237
	204°/1.5		237
	166–70°/0.5		191
$2\text{-Py}(CH_2)_{12}CO_2Et$	185°/0.1		143

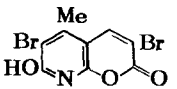
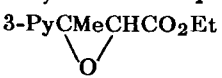
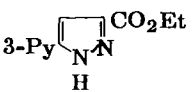
TABLE XI-37. 3-Pyridine Side-Chain Esters

Ester	B.p./mm.	M.p.	Derivative	Ref.
3-$PyCH_2CO_2Me$	85°/2, 112°/11		picrate, m.p. 111°	20,21,23,128,129, 157
3-$PyCH_2CO_2Et$	110–11°/2.5			15,18,20,51,157
	121–22°/10			128,129,157
3-$PyCH_2CO_2$-*n*-Pr	140°/10			128,129,157
3-$PyCH_2CO_2$-*i*-Pr	134°/10			128,129,157
3-$PyCH_2CO_2CH_2CH:CH_2$	138°/14			128,129,157
3-$PyCH_2CO_2CH_2CHMe_2$	142°/13			128,129,157
3-$PyCH_2CO_2(CH_2)_2NEt_2$	144°/12			157
3-$PyCHOHCO_2Et$	112°/0.1			250
	128–29°/14			19
	105°0.05			127–129
	125–30°/0.05			129
3-$Py(CH_2)_2CO_2Me$	102–3°/2, 134°/12			70,96
3-$Py(CH_2)_2CO_2Et$	140°/3, 129–30°/7	78°	picrate, m.p. 104°, 82°; hydrochloride, m.p. 96°	97,131,265,286
3-$PyCH:CHCO_2Et$	136–38°/3		hydrochloride, m.p. 186°	130

3-PyCOCH$_2$CO$_2$Et	125–35°/1, 122–32°/0.7		hydrochloride, m.p. 157°	37–40,42,43,52,120
3-PyCH(CH$_2$Ph)CO$_2$(CH$_2$)$_2$NEt$_2$	175-85°/0.06			15
3-PyC(:CHPh)CO$_2$Me	157°/2			20
3-PyC(:CHPh)CO$_2$Et	157°/0.2			20
		144°		228
		68°	picrate, m.p. 77°	249
	130°/0.5		picrate, m.p. 136°	249
		158°		188
		295°		132
		175°		132

(*continued*)

TABLE XI-37. 3-Pyridine Side-Chain Esters (*continued*)

Ester	B.p./mm.	M.p.	Derivative	Ref.
		297°		132
3-PyCO(CH$_2$)$_2$CO$_2$Me		67°		99
3-PyCO(CH$_2$)$_2$CO$_2$Et	142-45°/4		picrate, m.p. 108°	190,202
3-PyCOCH$_2$COCO$_2$Et		66°		146
3-PyCHOHCHMeCO$_2$Et		96°	hydrochloride, m.p. 131°	51
3-PyCOCHMeCO$_2$Et			hydrochloride, m.p. 127°	42
3-PyCH(O$_2$CCH$_3$)CHMeCO$_2$Et	130-31°/1			51
3-PyCO(CH$_2$CHO)CO$_2$Et		116°		39
3-PyCH : CMeCO$_2$Et	115-17°/0.5			51
	110-12°/2			146
		170°		39
3-PyCH : C(CO$_2$Et)$_2$	140°/4.5		hydrochloride, m.p. 153°	101,277
3-PyCH : C(CN)CO$_2$CH$_2$Ph		125°		274
3-PyCHOHCH(CO$_2$Et)$_2$				277
3-PyCH : C(CN)CO$_2$Et		80°		226
3-PyCOCH(CO$_2$Et)CH$_2$CO$_2$Et$_2$	152-54°/0.08		picrate, m.p. 95°	99,202,263

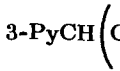
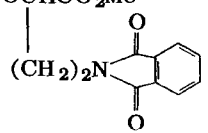
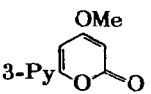
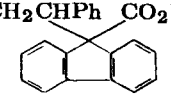
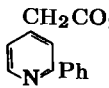
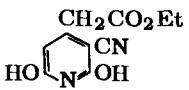
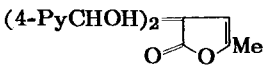
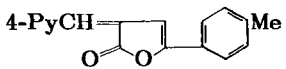
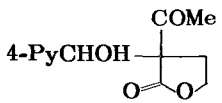
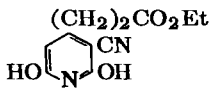
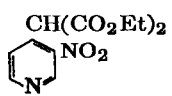
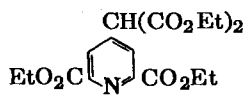
3-PyCH()-$CH(CO_2Et)_2$		120.5°	101
3-PyCH($CHNO_2CONEt_2$)CH-$(CO_2Et)_2$		117°	101
3-PyCOCHEtCO_2Et	138–40°/2.5		44
3-PyCOCH(CH_2CH_2SMe)CO_2Et	190–95°/1		162
3-PyCOCH($CHMe_2$)CO_2Et	138–40°/3		44
3-PyCHOHCH(COMe)CO_2Et		74°	258
3-PyCH : C(COMe)CO_2Et	93°/0.07		258
3-PyCH(CH_2CO_2Et)$_2$	148°/0.25		268
3-PyCOCHCO_2Me 		160°	228
3-Py 		180°	245
3-PyCOCH_2CHPh CO_2Et 		92°	243
3-PyCH[CH(CO_2Et)$_2$]CH_2CO_2Et	167°/0.2	hydrochloride, m.p. 120°	268
3-PyCOCH_2CHPhCH(CO_2Me)$_2$		96°	243
3-PyCOCH_2CHPhCH(CO_2Et)$_2$		77°	243

TABLE XI-38. 4-Pyridine Side-Chain Esters

Ester	B.p./mm.	M.p.	Derivative	Ref.
4-$PyCH_2CO_2Me$	103–105°/3		hydrochloride, m.p. 207° picrate, m.p. 147°	171,244
4-$PyCH_2CO_2Et$	107–108°/3, 73.5°/15	19°	picrate, m.p. 122°	18,34,35,83,225, 233
4-PyCHPhCO_2Me	150°/0.2			13,14,142
		79°		36
		239°		139
4-$Py(CH_2)_2CO_2Me$	95°/2			70
4-$Py(CH_2)_2CO_2Et$		164°		265
4-PyCH : $CHCO_2Me$		77°		192
4-PyCH : $CHCO_2Et$		64°		98,170
4-PyCH : $CHCO_2(CH_2)_2Cl$		209°	picrate, m.p. 160°	213
4-$Py(CH_2)_2CO_2(CH_2)_2Cl$			picrate, m.p. 113°	213
4-PyCH : $CHCO_2(CH_2)_2\overset{+}{N}Me_3Pic.^-$			picrate, m.p. 207°	213
4-$Py(CH_2)_2CO_2(CH_2)_2\overset{+}{N}Me_3Pic.^-$			picrate, m.p. 135°	213
4-PyCHOHCH_2CO_2Et			hydrochloride, m.p. 156°	41
4-PyCOCH_2CO_2Et		58°	hydrochloride, m.p. 174°; chloroplatinate, m.p. 156°; cupric salt, m.p. 184°	37,40–42

		192°		188
		230°		188
		93°		188
4-PyCHPhCOCO$_2$Et		124°		89
4-PyCHMeCO$_2$Et	145–8°/22			16
4-PyCH(CH$_2$Ph)CO$_2$Me	150°/0.2			14
		247°		139
4-PyCOH(CO$_2$Et)$_2$		80°	hydrochloride, m.p. 162–64°	87
	157°/3		sodium salt, m.p. 250° (dec.)	113,133
		71°		112
4-PyCH : C(CO$_2$Et)$_2$	162–4°/5		hydrochloride, m.p. 181°	87,98

(*continued*)

TABLE XI-38. 4-Pyridine Side-Chain Esters (*continued*)

Ester	B.p./mm.	M.p.	Derivative	Ref.
4-PyCPh($CH_2CH_2NMe_2$)-CO_2Et	153–58°/0.3			224
4-PyCH : C(CN)CO_2Et		105°		226
[4-PyCH_2C(CO_2Et)$_2$]$_2$		147°		230
4-PyCH_2CH(CO_2Et)$_2$	156–57°/5		hydrochloride, m.p. 148°	230
4-PyC(CH_2OMe): $CHCO_2Et$	119°/0.1			266
4-PyCH_2C(NHCOMe)(CO_2Et)$_2$		122°		267
4-PyCMe : $CHCO_2Et$	145°/0.5			234
4-PyCH : C(CN)CO_2CH_2Ph		97°		274
4-PyCHEtCO_2Et	130–5°/12			16
4-PyCH($CHMe_2$)CO_2Et	240°/760			16
4-PyCH : C(COMe)CO_2Et	113°/0.03			258
4-PyCH($CH_2CO_2CH_2CH_2NEt_2$)$_2$	195–97°/0.2			238
4-PyCHMeC(OH)(CO_2Et)$_2$	160–62°/0.45			234

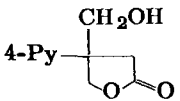
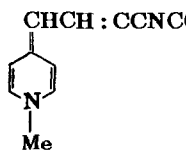
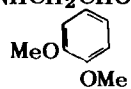
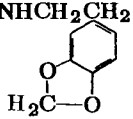
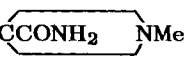
		134°		220
$4\text{-Py(CH}_2\text{)}_2\text{CMe}_2\text{CO}_2\text{Et}$	118–20°/1.5			231
$4\text{-Py(CH}_2\text{)}_2\text{CH(COCH}_3\text{)CO}_2\text{Et}$	162–64°/2			231
$4\text{-PyCH(}n\text{-Bu)CO}_2\text{Et}$	148–50°/13			16
$4\text{-PyCH(CH}_2\text{CO}_2\text{Et)CH(CO}_2\text{Et)}_2$	173–75°/0.2		hydrochloride, m.p. 122°	126
$4\text{-PyCOCHCO}_2\text{Et}$ $4\text{-PyCOCHCO}_2\text{Et}$			197°	37
			190°	194
$4\text{-Py(CH}_2\text{)}_2\text{CMe(COCH}_3\text{)CO}_2\text{Et}$	154–57°/1.5			231

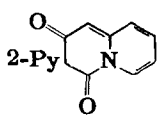
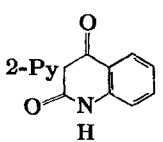
TABLE XI-39. 2-Pyridine Side-Chain Amides

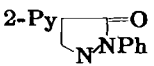
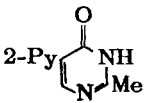
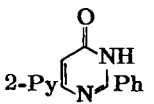
Amide	B.p./mm.	M.p.	Derivative	Ref.
2-$PyCH_2CONH_2$		122°		24–26,241
2-$PyCH_2CONHPh$		135°		33,201
2-$PyCH_2CONHCH_2CHOHPh$		115°	picrate, m.p. 132°	29
2-$PyCH_2CSNH_2$			hydrochloride, m.p. 194°	193
		66°	picrate, m.p. 179° (dec.)	18
2-$PyCH_2CONHCH_2CHOH$ 			hydrochloride, m.p. 105–10°	29
2-$PyCH_2CONHCH_2CH_2$ 		91°		29
		161°		187
2-$PyCHPhCONH_2$		134°		13,14,107,142,204
2-$PyCHPhCONMe_2$	185°/1			281
2-$PyCH(m\text{-}MeOC_6H_4)CONMe_2$				281
2-$PyCH(p\text{-}MeOC_6H_4)CONMe_2$				281
2-$PyCH(O_2CPh)CONH_2$		141°		241
2-$PyCH(p\text{-}ClC_6H_4)CONH_2$		107°		261
2-$PyCH(o\text{-}ClC_6H_4)CONMe_2$	185°/1			281

2-PyCH(*p*-ClC_6H_4)$CONMe_2$	190°/1		281
2-PyCH(*p*-ClC_6H_4)$CONEt_2$	183°/1		281
2-PyCH(2,4-$Cl_2C_6H_3$)$CONH_2$		178°	261
2-PyCH(*p*-BrC_6H_4)$CONEt_2$	190°/1		281
2-PyCH(*p*-MeC_6H_4)$CONMe_2$	180°/1		281
2-PyCH(*p*-ClC_6H_4)CON⟨ ⟩	200°/1		281
2-PyCH(*p*-BrC_6H_4)CON⟨ ⟩	210°/1		281
MeO_2C-Py-$CHPhCONH_2$	110–20°		12
EtO_2C-Py-$CHPhCONH_2$		128°	12
2-Py$(CH_2)_2CONH_2$		129°	2,70
2-Py$(CH_2)_2CONHMe$	132°/0.4	64°	2
2-Py$(CH_2)_2CONHEt$	120°/0.15	48°	2
2-Py$(CH_2)_2$CONH-*n*-Pr	115°/0.1		2
2-Py$(CH_2)_2$CONH-*i*-Pr		76°	2
2-Py$(CH_2)_2$CONH-*n*-Bu	130°/0.15		2
2-Py$(CH_2)_2CONHPh$		110°	2

(continued)

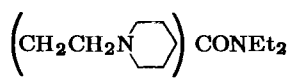
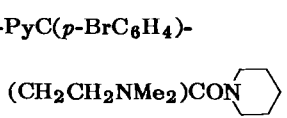
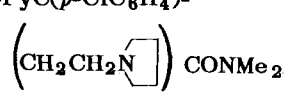
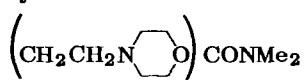
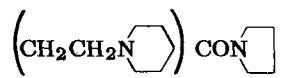
TABLE XI-39. 2-Pyridine Side-Chain Amides (*continued*)

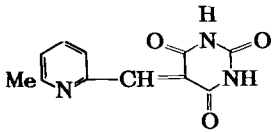
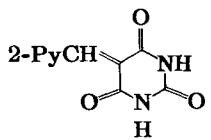
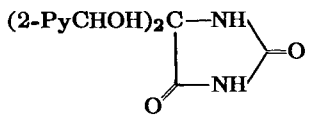
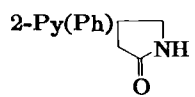
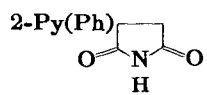
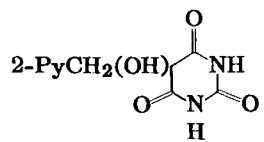
Amide	B.p./mm.	M.p.	Derivative	Ref.
2-Py$(CH_2)_2CONH(CH_2)_2OH$		103°		2
2-Py$(CH_2)_2CONH(CH_2)_2NEt_2$	150°/0.06			2
2-Py$(CH_2)_2CONMe_2$	116°/0.8			2,76
2-Py$(CH_2)_2CONEt_2$	107°/0.1			2,134
2-Py$(CH_2)_2CON(n\text{-}Pr)_2$	122°/0.5			2
2-Py$(CH_2)_2CON(i\text{-}Pr)_2$	103°/0.15			2
2-Py$(CH_2)_2CON(n\text{-}Bu)_2$	122°/0.1			2
2-Py$(CH_2)_2CONMePh$	154°/0.3	68°		2
2-Py$(CH_2)_2CON$ 	134°/0.4			2
2-Py$(CH_2)_2CON$ 	128°/0.2			2
2-PyCHPhCH_2CONMe_2	no data			269
2-PyCH : CPh$CONEt_2$		81°		134
2-PyCMePh$CONH_2$		130°		14,42
		no data		55
		290°		57

		179°		37
		270°		37
		268°		37
2-PyC($CH_2CH_2NMe_2$)PhCONH$_2$			methiodide, m.p. 178° (dec.); ethiodide, m.p. 142°	96,288
2-PyC($CH_2CH_2NEt_2$)PhCONH$_2$		65°	methiodide, m.p. 158°	196,288
2-PyCHEtCONH$_2$		126°		109
2-PyCHEtCONHCONH$_2$		123°		156
2-PyCEtPhCONH$_2$		108°		13,14,142
2-PyCPh($CH_2CH_2NMe_2$)CONMe$_2$	200°/1			281
2-PyC(*p*-MeC_6H_4)($CH_2CH_2NMe_2$)-CONMe$_2$	185°/1			281
2-PyC(*m*-$MeOC_6H_4$)-($CH_2CH_2NMe_2$)CONMe$_2$	210°/3			281
2-PyC(*p*-$MeOC_6H_4$)-($CH_2CH_2NMe_2$)CONMe$_2$	208°/2			281
2-PyC(o-ClC_6H_4)($CH_2CH_2NMe_2$)-CONMe$_2$	205°/2			281

(*continued*)

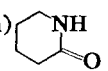
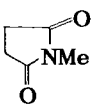
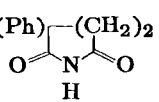
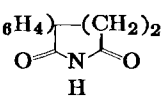
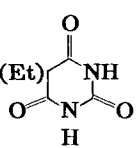
TABLE XI-39. 2-Pyridine Side-Chain Amides (*continued*)

Amide	B.p./mm.	M.p.	Derivative	Ref.
2-PyC(*p*-ClC_6H_4)($CH_2CH_2NMe_2$)-$CONMe_2$	205°/1			281
2-PyC(*p*-ClC_6H_4)($CH_2CH_2NMe_2$)-$CONEt_2$	205°/1			281
2-PyC(*p*-BrC_6H_4)- 	210°/1			281
2-PyC(*p*-BrC_6H_4)- 	220°/1			281
2-PyC(*p*-ClC_6H_4)- 	210°/1			281
2-PyCPh- 	220°/2			281
2-PyC(*p*-ClC_6H_4)- 	215°/1			281

	270°	226
	275° (dec.)	289
	203°	289
	166°	86
	128°	85
	231°	90,91

(*continued*)

TABLE XI-39. 2-Pyridine Side-Chain Amides (*continued*)

Amide	B.p./mm.	M.p.	Derivative	Ref.
2-PyCPhCN$(CH_2)_2$CONH$_2$		109°		211
2-PyCO 	175°/11	127°		49
2-PyCO 		83°	picrate, m.p. 138°	48
2-Py(Ph) 		193°		86
2-PyCO 		91°		49
2-Py(Ph) 		183°		85
2-Py(*p*-ClC$_6$H$_4$) 		186°		85
(2-PyCH$(CONH_2)CH_2)_2CH_2$		228°		248
2-Py(Et) 		258°		156

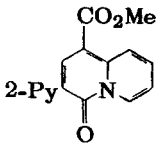
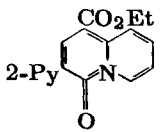
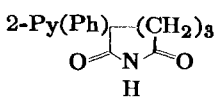
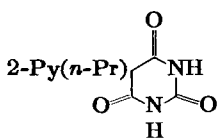
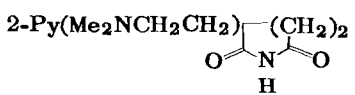
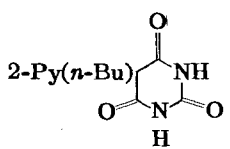
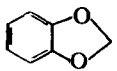
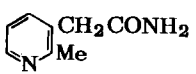
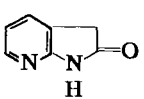
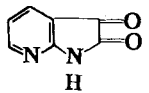
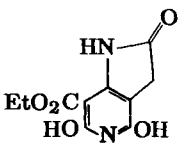
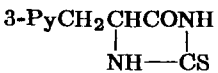
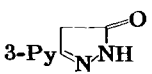
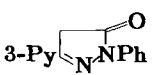
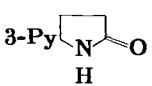
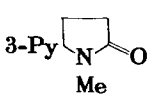
	172°	picrate, m.p. 243°	61
	126°	picrate, m.p. 216°	59–61,151
	147°		85
	250°		31
	106°	dihydrochloride, m.p. 150–56°	147
	265°		31
$2\text{-Py}(CH_2)_{10}CONH_2$	97°	picrate, m.p. 113°	4

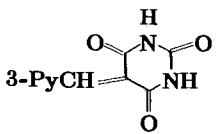
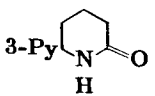
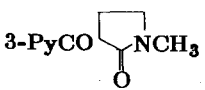
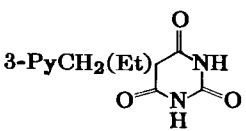
TABLE XI-40. 3-Pyridine Side-Chain Amides

Amide	B.p./mm.	M.p.	Derivative	Ref.
3-$PyCH_2CONH_2$		122°		15,20,51,206
3-$PyCH_2CONEt_2$	175°/12			20
3-$PyCH_2CONH(CH_2)_2$ 		100°		23
3-$PyCH_2CSN$		79°	picrate, m.p. 168°	18,21
3-$PyCH_2CSNH_2$		134°		193
3-$PyCHPhCONH_2$		159°		12
3-$PyCH_2CONHMe$		63°	picrate, m.p. 178°	212
3-$PyCHOHCONH_2$		155°		241
3-$PyCH(O_2CPh)CONH_2$		164°		241
		191°		19,22
		175°		8

		230° (dec.)		8
		350° (dec.)		135
3-Py$(CH_2)_2CONH_2$		119°, 137°		96,131,265
		249–52°		115
		268°		39
		188°		39
		115°	hydrate, m.p. 67° picrate, m.p. 163°	263
	(continine)	160–80°/0.03		189,202

(*continued*)

TABLE XI-40. 3-Pyridine Side-Chain Amides (*continued*)

Amide	B.p./mm.	M.p.	Derivative	Ref.
		296°		226
		147°		1
	152–154°/0.2		picrate, m.p. 155°	47,144
		214°		153

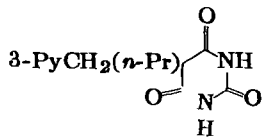
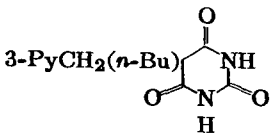
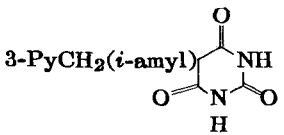
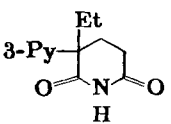
		250° (dec.)	153
		219°	153
		230°	153
		128–30°/0.1	203

TABLE XI-41. 4-Pyridine Side-Chain Amides

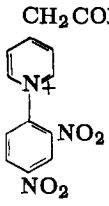
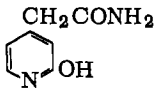
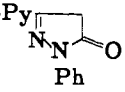
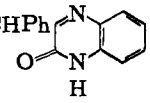
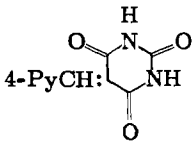
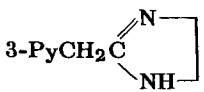
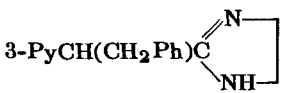
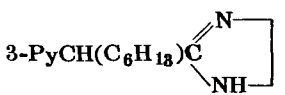
Amide	M.p.	Ref.
4-$PyCH_2CONH_2$	144°	27,171,241
4-$PyCH_2CONH(CH_2)_2$ 	111°	27
4-$PyCH_2CSN$ 	105°; picrate: 185° (dec.)	18,28
4-$PyCH_2CSNH_2$	179°	193
4-PyCHPhCONH$_2$	154°	13,14,142
4-$PyCH(O_2CPh)CONH_2$	197°	241
	224°	255
	228°	138
4-$Py(CH_2)_2CONH_2$	167°	70, 265
4-$Py(CH_2)_2CONMe_2$	b.p. 144°/0.35	217
4-$Py(CH_2)_2CSNH_2$	175°	193
4-Py 	215°	37
4-PyCHPh 	295°	89
4-$PyCH_2CON$ 	205°	193
4-PyCH: 	330°	226

TABLE XI-41 (*continued*)

Amide	M.p.	Ref.
4-PyCH(CH_2CONH_2)$_2$	194°	238
4-PyCH($CH_2CONHCH_2Ph$)$_2$	153°	238
4-PyCH[$CH_2CONH(CH_2)_2NEt_2$]$_2$	102°	238
4-PyCH[$CH_2CONH(CH_2)_3NEt_2$]$_2$	b.p. 220–90°/0.3	238

TABLE XI-42. Pyridine Side-Chain Hydrazides, Hydroxamic Acids, Amidines, and Imides

Compound	B.p./mm.	M.p.	Derivative	Ref.
2-$PyCH_2CONHNH_2$		121°		175
$[2\text{-}PyCH(CON_2H_3)CH_2]_2CH_2$		166°		248
$2\text{-}Py(CH_2)_2CHPhC(:NH)OEt$		118°		198
$3\text{-}PyCH_2CONHOH$		178°		169
$3\text{-}PyCH_2CNHNH_2$			dihydrochloride, m.p. 164–67°	160,222
	165–70°/1	69°	dipicrate, m.p. 196°; dihydrochloride, m.p. 234°	15
$3\text{-}PyCH(CH_2CON_2H_3)_2$		150°		268
	190–200°/0.4	94°	dihydrochloride, m.p. 246°	15
	160–75°/0.4	83°	dihydrochloride, m.p. 146°	15
$4\text{-}PyCH_2CONHNH_2$		86°, 91°	dihydrochloride, m.p. 214°	175,182,199, 222,223,233
$4\text{-}Py(CH_2)_2CONHNH_2$		65°	dihydrochloride, m.p. 225°	182,222
$4\text{-}PyCH:CHCONHNH_2$		151°	dipicrate, m.p. 80–90°	182,192,222
4-PyCH : CHCONHN : CHPh		187°		182
$4\text{-}PyCH_2CONHNHPh$		180°		223

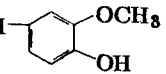
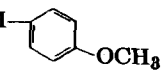
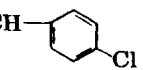
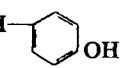
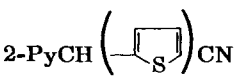
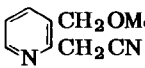
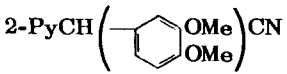
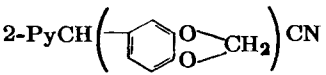
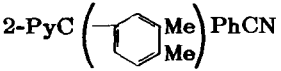
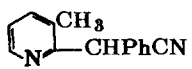
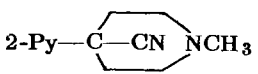
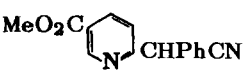
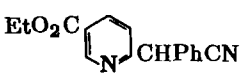
4-$PyCH_2CONHN:CHPh$	199°	223
4-$PyCH_2CONHN:CHCH:CHPh$	179°	223
4-$PyCH_2CONHN:CH(CH_2)_2Ph$	130°	223
4-$PyCH_2CONHN:CH$ 	221°	223
4-$PyCH_2CONHN:CH$ 	164°	223
4-$PyCH_2CONHN:CH$ 	194°	223
4-$PyCH_2CONHN:CH$ 	194°	223
4-$PyCH_2CONHN:CH$ 	199°	223
4-$PyCH_2CONHN:CH$ 	248°	223
4-$PyCH_2CONHN:CMePh$	161°	223
4-$PyCH(CH_2CON_2H_3)_2$	190°	238

TABLE XI-43. 2-Pyridine Side-Chain Nitriles

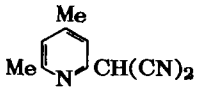
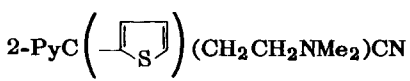
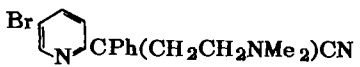
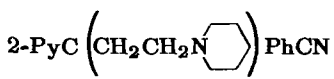
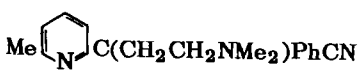
Nitrile	B.p./mm.	M.p.	Derivative	Ref.
2-PyCH$_2$CN	79–81°/0.4			232
2-PyCH(2,4-Cl$_2$C$_6$H$_3$)CN		74°		261
2-PyCHOHCN		132°		250
2-PyCH(O$_2$CPh)CN		101°		241,257
				282
	110–15°/0.05		picrate, m.p. 146°	272
				282
2-PyCHPhCN	150–5°/0.5	89°	picrate, m.p. 144°	13,85,107, 282,261
2-PyCH(*o*-ClC$_6$H$_4$)CN	165–70°/2.0			168
2-PyCH(*p*-ClC$_6$H$_4$)CN	163–7°/7.5	69° (30°)		168,282,261, 284
2-PyCH(*m*-MeOC$_6$H$_4$)CN		55°		142,163,261
	192–5°/0.2			142,163

2-PyCH()CN	170–80°/0.15			142,163
2-PyCH(α-$C_{10}H_7$)CN		87°		142,163
2-PyCPh_2CN		124°		180,181,235
2-PyC(*p*-ClC_6H_4)$_2$CN	no data			181
2-PyC(*p*-MeC_6H_4)$_2$CN	no data			181
2-PyC(*p*-MeOC_6H_4)$_2$CN		121°		181
2-PyC(*p*-ClC_6H_4)PhCN		83°		181
2-PyC()PhCN	no data			181
(2-Py)$_2$CHCN		139°		167
	162–70°/0.5	120°		168
		45°	picrate, m.p. 203–8°; hydrochloride, m.p. 183°	187
		81°		12
		84°		12

(*continued*)

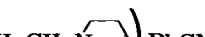
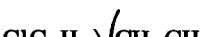
TABLE XI-43. 2-Pyridine Side-Chain Nitriles (*continued*)

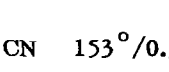
Nitrile	B.p./mm.	M.p.	Derivative	Ref.
2-Py$(CH_2)_2$CN	97–99°/2		picrate, m.p. 142° (dec.)	11,53
2-PyCH : CPhCN		65°	picrate, m.p. 160°	183,257
2-PyCH : C(*p*-ClC_6H_4)CN		125°		183,186,226
2-PyCH : C(3,4-$(OMe)_2C_6H_3$)CN		111°		183
2-PyCH : C(*p*-BrC_6H_4)CN		128°		186
2-PyCH : C(α-naphthyl)CN		127°		186
2-PyCHBrCBrPhCN		110–118°		226
Me-Py-CHBrCBrPhCN		170°		226
Me-Py-CH : CPhCN			hydrochloride, m.p. 120°; picrate, m.p. 138°	226
2-PyCH : CCN-(2,4-$(NO_2)_2$-5-CH_3O-6-OCH_3)C_6H		190°		215
2-PyCMePhCN	186–90°/12 145–50°/2			158,181,142, 163
2-PyC(CH_2Ph)PhCN		109°		181
2-PyCH$(CN)_2$		250–60° (dec.)		159,174

		260–70° (dec.)		174
2-Py$(CH_2)_3CN$	95–97°/1			219
2-PyCOCHMeCN	126–27°/0.75			229
2-PyCH : $CCNCO_2Et$		97°		289
				282
				282
2-Py$(CH_2)_2CHPhCN$	149–51°/0.5		picrate, m.p. 136°	53,198,219
2-Py$(CH_2)_2CPh_2CN$	no data			177
2-PyCH$(CH_2CH_2NMe_2)CN$	112–16°/15			147
2-PyCEtPhCN	193°/11			13,181
2-PyCH$(CH_2CH_2NMe_2)CN$	108–12°/0.5			168
2-PyC$(CH_2CH_2NMe_2)$PhCN	162–65°/0.5			173,168,283
2-PyC$(CH_2CH_2NEt_2)$PhCN	162–64°/0.3			168
	175–80°/1.0			178
	173–78°/2.5			168
2-PyC(*o*-ClC_6H_4)$(CH_2CH_2NMe_2)CN$	195–202°/2.0			168

(*continued*)

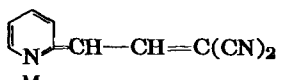
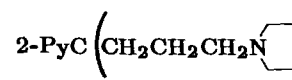
TABLE XI-43. 2-Pyridine Side-Chain Nitriles (*continued*)

Nitrile	B.p./mm.	M.p.	Derivative	Ref.
2-PyC()PhCN	187–89°/1.4			107,164,178
2-PyC($CH_2CH_2NMe_2$)PhCN	168°/2.8			107
2-PyC($CH_2CH_2NEt_2$)PhCN	160°/0.5			107
2-PyC(*m*-$MeOC_6H_4$)($CH_2CH_2NMe_2$)CN	168–70°/0.3			178
2-PyC(*p*-ClC_6H_4)($CH_2CH_2NMe_2$)CN	183–88°/3.0			172,168,282 284
2-PyC(*p*-ClC_6H_4)()CN	178–84°/0.3			172
2-PyC(*p*-ClC_6H_4)()CN	185–91°/0.2			172
2-PyC(*p*-ClC_6H_4)-()CN	210–18°/0.2			172
2-PyC(*p*-MeC_6H_4)($CH_2CH_2NMe_2$)CN	170–73°/0.5			173,168
2-PyC(*p*-Cumyl)($CH_2CH_2NMe_2$)CN	162–66°/0.5			173
2-PyC(CH_2Ph)(CH_2NMe_2)CN	147–52°/0.5			168
2-PyC(*p*-$MeOC_6H_4$)($CH_2CH_2NMe_2$)CN	180–85°/1.0			173,168
2-PyC(α-naphthyl)($CH_2CH_2NMe_2$)CN	205–20°/1.5			168
(2-Py)$_2$C($CH_2CH_2NMe_2$)CN	167–73°/0.5			168

2-PyC(3-Py)($CH_2CH_2NMe_2$)CN	172–80°/1.0			168
2-PyC(2-C_4H_3S)($CH_2CH_2NMe_2$)CN	150–58°/1.0			173,168
2-PyC(3-C_4H_3S)($CH_2CH_2NMe_2$)CN	178–82°/1.5			173
2-PyCMe$(CN)_2$	no data			159
2-PyCPhCNCH_2CO_2H		97–108° (dec.)		85
2-PyCHPhCHCNCO_2Et			picrate, m.p. 172°	107
2-PyCPh : CCNCO_2Et			picrate, m.p. 127°	107
2-PyC(*p*-ClC_6H_4)(CH_2CO_2Et)CN		68°		86
2-PyC($CH_2CH_2CH_2NMe_2$)PhCN	168–70°/1.0			168
2-PyC($CH_2CHMeNMe_2$)PhCN	179–84°/3.5			168
2-PyC($CHMeCH_2NMe_2$)PhCN	159–65°/0.5			168
2-PyCPhCN $(CH_2)_2CONH_2$		109°		211
2-PyCH(COPh)-CH_2CH_2CN		75°		239
2-PyCH(COPy-2)CH_2CH_2CN		72°		239
2-PyCH(PhCHCN)$_2$		172°	picrate, m.p. 126°	289
2-PyC($CH_2CH_2CH_2NMe_2$)()CN	153°/0.3			283
2-PyC()PhCN		83°		283

(*continued*)

TABLE XI-43. 2-Pyridine Side-Chain Nitriles (*continued*)

Nitrile	B.p./mm.	M.p.	Derivative	Ref.
		222°		194
2-PyC($CH_2CH_2NMe_2$)(CH_2Ph)CN	150–55°/0.5			168,173
2-PyC  PhCN	198–204°/ 0.05			181,283
2-PyC(CH_2CH_2Me)PhCN	139–44°/0.02			181
2-PyC($CHMe_2$)PhCN	138–40°/0.02			181
2-PyC($CHMe_2$)(*p*-ClC_6H_4)CN		90°		181
2-PyC(*p*-ClC_6H_4)($CH_2CH_2CO_2Me$)CN	187–92°/0.8			85
2-PyCH(CO_2Et)(CH_2)$_2$CN	137–40°/0.7		picrate, m.p. 83°	53
2-Py(CH_2)$_2$CHCNCO_2Et	136–38°/0.3		picrate, m.p. 103°	53
2-PyCPhCN(CH_2)$_2CO_2Et$	190–93°/2.5			85,86
2-Py(CH_2)$_2$CHCNCO_2Et	136–38°/0.3			53
2-Py(CH_2)$_2$C(HN$COCH_3$)CNCO_2Et		121°	picrate, m.p. 84°	123
2-PyCPhCN(CH_2)$_2CO_2H$		70°		85

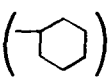
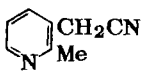
2-PyC(*p*-ClC_6H_4)$CN(CH_2)_2CO_2H$	no data			85
2-PyC($CH_2CH_2CO_2Me$)PhCN	187-90°/0.4			85,211
2-PyC(CH_2CH_2CN)PhCN		83°	dipicrate, m.p. 172°	86,211
(2-PyCH_2CH_2)$_2$CPhCN	220–40°/0.04			198
2-PyC(CH_2CHMe_2)PhCN	135–43°/0.01			181
2-PyC($CH_2CH_2CH_2CO_2H$)PhCN		117°		85
2-PyC($CH_2CH_2CH_2CN$)PhCN		41°		85
2-PyC($CH_2CH_2NMe_2$)(CH_2CH_2CN)CN	174–83°/0.18			147
2-PyC($CH_2CH_2CHMe_2$)PhCN	153-55°/0.02			181
2-PyCH($COCH_3$)CH_2CH_2CN	188–92°/15	34°		239
2-Py$(CH_2)_2CMe_2CN$	95–97°/1.5			219
2-PyCH_2 	149–52°/0.1			191
2-PyC(cyclohexyl)PhCN	135°			181
2-PyC 	158–63°/1.5			168
($CH_2CH_2NMe_2$)CN				
2-PyC($COCH_3$)(CH_2CH_2CN)$_2$		111°		239

TABLE XI-44. 3-Pyridine Side-Chain Nitriles

Nitrile	B.p./mm.	M.p.	Derivative	Ref.
3-$PyCH_2CN$	91°/2		picrate, m.p. 163°	15,51,165
3-PyCHPhCN	152–57°/2	64°	hydrochloride, m.p. 166°	165
3-$PyCH(O_2CPh)CN$		94°		241
3-PyCHCN 	180–3°/12		hydrochloride, m.p. 188°	226
3-$PyCH(NH_2)CN$			hydrochloride, m.p. 162°	226
3-$PyCH(NMe_2)CN$			hydrochloride, m.p. 167°	226
	138°/12	54°		19,22
3-$Py(CH_2)_2CN$	85–87°/1			70
3-PyCH : CPhCN		92°	picrate, m.p. 196°	183,226
3-PyCH : C(*o*-ClC_6H_4)CN		113°		183
3-PyCH : C(*p*-ClC_6H_4)CN		139°		183

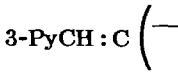
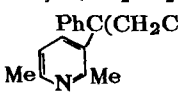
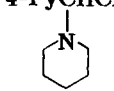
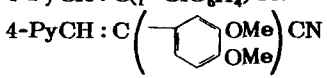
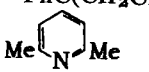
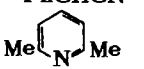
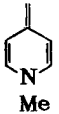
3-PyCH : C()CN		142°		183,242
3-PyCHBrCBrPhCN		168°		226
3-PyCOCHPhCN		143°		51
3-PyCH(CH_2Ph)CN	160–64°/1	65°	hydrochloride, m.p. 174°	15
3-PyCH($CH_2CH_2NMe_2$)CN	112–16°/1.0			168
3-PyCH($CH_2CH_2NEt_2$)CN	150–55°/0.5			15
3-PyCH(COMe)CN		195°		51
3-PyCH : C(CO_2CH_2Ph)CN		125°		274
3-PyC($CH_2CH_2NMe_2$)PhCN	152°/12		dipicrate, m.p. 195°	165
	175–80°/2		picrate, m.p. 140°	176
3-PyCH($CH_2CH_2CH_2Me$)CN	127°/1.5		hydrochloride, m.p. 110°	15
3-PyCEtCNCH_2CH_2CN	73–75°/0.1			203
3-PyCH(n-C_6H_{11})CN	125–35°/0.5		hydrochloride, m.p. 126°	15
3-PyC($CH_2CH : CH_2$)$_2$CN	123–27°/1		picrate, m.p. 109°	15

TABLE XI-45. 4-Pyridine Side-Chain Nitriles

Nitriles	B.p./mm.	M.p.	Derivative	Ref.
4-PyCHPhCN		77°		142,163
4-PyCHOHCN		140°		250
4-PyCH(O_2CPh)CN		131°	hydrochloride, m.p. 180°	241
		96°	hydrochloride, m.p. 175°	226
4-PyCH(NH_2)CN		150° (dec.)		226
4-PyCH(NMe_2)CN		155°	hydrochloride, m.p. 205°	226
4-Py(CH_2)$_2$CN	103°/25		picrate, m.p. 171°	11
4-PyCH : CPhCN		129°	picrate, m.p. 230°	183,226
4-PyCH : C(*p*-ClC_6H_4)CN		139°		183
		139°		183,242

4-PyCHBrCBrPhCN		260°	226
4-PyCH : $C(NO_2)CN$		100° (dec.)	215
4-Py$(CH_2)_3CN$	122–5°/1		219
4-Py$(CH_2)_2CHPhCN$	185–7°/2		219
4-PyCH : $C(CO_2CH_2Ph)CN$		97°	274
4-PyCEtPhCN	193°/11		142,163
4-PyC$(CH_2CH_2NMe_2)PhCN$	166–169°/1.0		168
PhC$(CH_2CH_2NMe_2)CN$ 		105°	176
PhCHCN 		105°	176
CHCH : $C(CN)_2$ 		266°	194

F. BIBLIOGRAPHY

1. Menshikov, Losik, and Orekhov, *Khim.-Pharm. Prom.*, **1934, No. 6,** 7; *C.A.*, **30,** 2196[3] (1936).
2. McMillan and King, *J. Am. Chem. Soc.*, **73,** 3165 (1951).
3. Takahashi and Saikachi, *J. Pharm. Soc. Japan,* **62,** 38 (1942); *C.A.*, **45,** 620*g* (1951).
4. Brody and Bogert, *J. Am. Chem. Soc.*, **65,** 1075 (1943).
5. Wilt and Levine, *ibid.*, **75,** 1368 (1953).
6. Rosenheim and Tafel, *Ber.*, **26,** 1501 (1893).
7. Oparina, *J. Russ. Phys. Chem. Soc.*, **57,** 319 (1925); *Chem. Zentr.*, **1926, I,** 3336.
8. Kägi, *Helv. Chim. Acta,* **24,** 141E (1941).
9. Wibaut and Beyerman, *Rec. trav. chim.*, **70,** 977 (1951).
10. Doering and McEwen, *J. Am. Chem. Soc.*, **73,** 2104 (1951).
11. Doering and Weil, *ibid.*, **69,** 2461 (1947).
12. Scholz and Panizzon, *Helv. Chim. Acta,* **37,** 1605 (1954).
13. Panizzon, *ibid.*, **27,** 1748 (1944).
14. British patent 589,625, Hartmann and Panizzon, June 25, 1947; *C.A.*, **42,** 225*f* (1948).
15. Protiva, Jilek, and Pliml, *Chem. Listy,* **46,** 640 (1952); *C.A.*, **47,** 8069*c* (1953).
16. German patent 638,821, Räth, Gebauer, and Falta, Nov. 23, 1936; *C.A.*, **31,** 3066[3] (1937).
17. Overhoff, Boeke, and Gorter, *Rec. trav. chim.*, **55,** 293 (1936).
18. Malan and Dean, *J. Am. Chem. Soc.*, **69,** 1797 (1947).
19. Dornow and Schacht, *Ber.*, **82,** 117 (1949).
20. Hartmann and Bosshard, *Helv. Chim. Acta,* **24,** 28E (1941).
21. Schwenk and Papa, *J. Org. Chem.*, **11,** 798 (1946).
22. Dornow, *Angew. Chem.*, **60A,** 72 (1948).
23. Noller and Azima, *J. Am. Chem. Soc.*, **72,** 17 (1950).
24. U.S. patent 2,495,567, Carmack and Detar, Jan. 24, 1950; *C.A.*, **44,** 7868*b* (1950).
25. Pattison and Carmack, *J. Am. Chem. Soc.*, **68,** 2033 (1946).
26. British patent 607,765, Rohm & Haas Co., Sept. 3, 1948; *C.A.*, **43,** 2233*b* (1949).
27. Noller and Wunderlich, *J. Am. Chem. Soc.*, **74,** 3835 (1952).
28. Porter, *ibid.*, **76,** 127 (1954).
29. Bills and Noller, *ibid.*, **70,** 957 (1948).
30. Woodward and Kornfeld, *Org. Syntheses,* **29,** 44 (1949).
31. Frank and Phillips, *J. Am. Chem. Soc.*, **71,** 2804 (1949).
32. Doering and Pasternak, *ibid.*, **72,** 143 (1950).
33. Gruber and Schlögl, *Monatsh.*, **81,** 473 (1950).
34. Wibaut and Hey, *Chem. Weekblad,* **49,** 169 (1953); *C.A.*, **48,** 2704*f* (1954).
35. Hey and Wibaut, *Rec. trav. chim.*, **72,** 522 (1953).

36. Prijs, Lutz, and Erlenmeyer, *Helv. Chim. Acta,* **31,** 571 (1948).
37. Pinner, *Ber.,* **34,** 4234 (1901).
38. Strong and McElvain, *J. Am. Chem. Soc.,* **55,** 816 (1933).
39. Clemo and Holmes, *J. Chem. Soc.,* **1934,** 1739.
40. Kolloff and Hunter, *J. Am. Chem. Soc.,* **63,** 490 (1941).
41. Koelsch, *ibid.,* **65,** 2460 (1943).
42. Burrus and Powell, *ibid.,* **67,** 1468 (1945).
43. Beher, Holliday, and Gaebler, *J. Biol. Chem.,* **198,** 573 (1952).
44. Swamer and Hauser, *J. Am. Chem. Soc.,* **72,** 1352 (1950).
45. Späth and Galinovsky, *Ber.,* **71,** 721 (1938).
46. Clemo, Ramage, and Raper, *J. Chem. Soc.,* **1932,** 2959.
47. Späth and Bretschneider, *Ber.,* **61,** 327 (1928).
48. Winterfeld and Holschneider, *Ann.,* **499,** 109 (1932).
49. Winterfeld and Holschneider, *Arch. Pharm.,* **273,** 305 (1935).
50. Winterfeld and Holschneider, *ibid.,* **277,** 221 (1939); *C.A.,* **34,** 1112 (1940).
51. Burger and Walter, Jr., *J. Am. Chem. Soc.,* **72,** 1988 (1950).
52. McElvain and Weber, *ibid.,* **63,** 2192 (1941).
53. Boekelheide, Linn, O'Grady, and Lamborg, *ibid.,* **75,** 3243 (1953).
54. Adams and Miyano, *ibid.,* **76,** 3168 (1954).
55. Winterfeld, Wald, and Rink, *Ann.,* **588,** 125 (1954).
56. Clemo, Morgan, and Raper, *J. Chem. Soc.,* **1937,** 965.
57. Hey and Williams, *ibid.,* **1950,** 1678.
58. Clemo, Fletcher, Fulton, and Raper, *ibid.,* **1950,** 1140.
59. Leonard and Beyler, *J. Am. Chem. Soc.,* **72,** 1316 (1950).
60. Leonard and Beyler, *ibid.,* **70,** 2298 (1948).
61. Galinovsky and Kainz, *Monatsh.,* **77,** 137 (1947).
62. Einhorn and Liebrecht, *Ber.,* **20,** 1592 (1887).
63. Einhorn, *Ann.,* **265,** 208 (1891).
64. Tullock and McElvain, *J. Am. Chem. Soc.,* **61,** 961 (1939).
65. Koller, *Monatsh.,* **47,** 393 (1926).
66. Rabe and Kindler, *Ber.,* **52,** 1842 (1919).
67. Koenigs and Ottmann, *ibid.,* **54,** 1343 (1921).
68. Rabe, Huntenburg, Schultze, and Volger, *ibid.,* **64,** 2487 (1931).
69. Alberts and Bachman, *J. Am. Chem. Soc.,* **57,** 1284 (1935).
70. Walter, Hunt, and Fosbinder, *ibid.,* **63,** 2771 (1941).
71. Kleiman and Weinhouse, *J. Org. Chem.,* **10,** 562 (1945).
72. Webb and Corwin, *J. Am. Chem. Soc.,* **66,** 1456 (1944).
73. Rubtsov, *J. Gen. Chem. U.S.S.R.,* **16,** 461 (1946); *C.A.,* **41,** 762*d* (1947).
74. Renk and Grob, *Helv. Chim. Acta,* **37,** 2119 (1954).
75. Takahashi, Nishigaki, and Taniyama, *J. Pharm. Soc. Japan,* **63,** 235 (1943); *C.A.,* **45,** 2940*a* (1951).
76. King, Hofmann, and McMillan, *J. Org. Chem.,* **16,** 1100 (1951).
77. Winterfeld and Holschneider, *Arch. Pharm.,* **277,** 192 (1939); *C.A.,* **34,** 2853[6] (1940).
78. Clemo and Ramage, *J. Chem. Soc.,* **1932,** 2969.

79. Galinovsky, Vogl, and Weiser, *Monatsh.*, **83**, 114 (1952).
80. Oparina, *Khim.-Pharm. Prom.*, **1934, No. 4**, 12; *C.A.*, **29**, 1820[6] (1935).
81. Boekelheide and Gall, *J. Org. Chem.*, **19**, 499 (1954).
82. Clemo, Morgan, and Raper, *J. Chem. Soc.*, **1935**, 1743.
83. Lukeš and Ernest, *Collection Czechoslov. Chem. Communs.*, **14**, 679 (1949).
84. Spielman, Swadesh, and Mortenson, *J. Org. Chem.*, **6**, 780 (1941).
85. Tagmann, Sury, and Hoffmann, *Helv. Chim: Acta*, **35**, 1541 (1952).
86. Sperber and Fricano, *J. Am. Chem. Soc.*, **75**, 2986 (1953).
87. Rubtsov and Dorokhova, *Doklady Akad. Nauk. S.S.S.R.*, **88**, 843 (1953); *C.A.*, **48**, 3975*d* (1954). Rubtsov and Dorokhova, *J. Gen. Chem. U.S.S.R.*, **23**, 706 (1953); *C.A.*, **48**, 7610*a* (1954).
88. Hauser and Humphlett, *J. Am. Chem. Soc.*, **72**, 3805 (1950).
89. Singh, *J. Chem. Soc.*, **1925**, 2445.
90. McElvain and Johnson, *J. Am. Chem. Soc.*, **63**, 2213 (1941).
91. Franklin and Bergstrom, *Chem. Revs.*, **35**, 77 (1944).
92. Weiss and Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).
93. Goldberg, Perfetti, and Levine, *ibid.*, **75**, 3843 (1953).
94. Boekelheide and Godfrey, *ibid.*, **75**, 3679 (1953). Godfrey, Ph.D. thesis, University of Rochester, p. 13 (1954).
95. Panizzon, *Helv. Chim. Acta*, **24**, 24E (1941).
96. Dornow and Schacht, *Ber.*, **80**, 505 (1947).
97. Livshits, Evstigneeva, Bainova, and Preobrazhenskii, *J. Gen. Chem. U.S.S.R.*, **21**, 1360 (1951); *C.A.*, **46**, 5051*b* (1952).
98. Rubtsov, Nikitskaya, and Yanina, *ibid.*, **23**, 963 (1953); *C.A.*, **48**, 8781*e* (1954). Rubtsov, Nikitskaya, and Yanina, *Doklady Akad. Nauk. S.S.S.R.*, **89**, 81 (1953); *C.A.*, **48**, 4532*g* (1954).
99. Castle and Burger, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 163 (1954).
100. Baumgarten and Krieger, *J. Am. Chem. Soc.*, **77**, 2438 (1955).
101. Dornow and Boberg, *Ann.*, **578**, 101 (1952).
102. Dornow and Borman, *Ber.*, **82**, 216 (1949).
103. Dornow and Wiehler, *Ann.*, **578**, 113 (1952).
104. Dornow and Frese, *ibid.*, **578**, 122 (1952).
105. U.S. patent 2,606,922, Papa, Klingsberg, and Schwenk, August 12, 1952; *C.A.*, **47**, P6442g (1953).
106. Schwenk and Papa, *J. Am. Chem. Soc.*, **67**, 1432 (1945); *C.A.*, **40**, 5613 (1946).
107. Exner, *et al.*, *Chem. Listy*, **47**, 863 (1953).
108. U.S. patent 2,516,153, Schwenk and Papa, July 7, 1950; *C.A.*, **45**, 648*f* (1951).
109. Walter and McElvain, *J. Am. Chem. Soc.*, **57**, 1891 (1935).
110. Gruber and Schlögl, *Monatsh.*, **80**, 499 (1949).
111. Gruber, *Can. J. Chem.*, **31**, 1181 (1953).
112. Koenigs and Jaeschke, *Ber.*, **54**, 1351 (1921).
113. Koenigs and Fulde, *ibid.*, **60**, 2106 (1927).

114. Edwards, Chaput, Clarke, and Singh, *Can. J. Chem.*, **32**, 785 (1954).
115. Niemann, Lewis, and Hays, *J. Am. Chem. Soc.*, **64**, 1678 (1942).
116. Boekelheide and Rothchild, *ibid.*, **69**, 3149 (1947).
117. Burger, Markees, Nes, and Yost, *ibid.*, **71**, 3307 (1949).
118. Boekelheide and Rothchild, *ibid.*, **71**, 879 (1949).
119. Boekelheide and Agnello, *ibid.*, **72**, 5005 (1950).
120. Wunderlich, *J. prakt. Chem.*, **274**, 302 (1955).
121. Bohlmann, *et al.*, *Ber.*, **88**, 1831 (1955).
122. Winterfeld and Heinen, *Ann.*, **573**, 85 (1951).
123. Burkhalter and Stephens, *J. Am. Chem. Soc.*, **73**, 4460 (1951).
124. Ohki and Noike, *J. Pharm. Soc. Japan*, **72**, 490 (1952); *C.A.*, **47**, 6418*i* (1953).
125. U.S. patent 2,638,471, Burger, May 12, 1953; *C.A.*, **48**, 7641*b* (1954).
126. Rubtsov and Mikhlina, *J. Gen. Chem. U.S.S.R.*, **23**, 823 (1953); *C.A.*, **48**, 3978*a* (1954).
127. Miescher and Kägi, *Helv. Chim. Acta*, **24**, 1471 (1941).
128. U.S. patent 2,408,020, Hartmann, Miescher, Kaegi, and Bosshard, Sept. 24, 1946; *C.A.*, **41**, 780*d* (1947).
129. British patent 560,449, April 5, 1944; *C.A.*, **40**, 1635 (1946).
130. Adkins, Wolff, Pavlic, and Hutchinson, *J. Am. Chem. Soc.*, **66**, 1293 (1944).
131. Graef, Fredericksen, and Burger, *J. Org. Chem.*, **11**, 257 (1945).
132. Robinson and Watt, *J. Chem. Soc.*, **1934**, 1536.
133. Bremer, *Ann.*, **529**, 290 (1937).
134. Papa, Schwenk, Villani, and Klingsberg, *J. Am. Chem. Soc.*, **72**, 3885 (1950).
135. Best and Thorpe, *J. Chem. Soc.*, **1909**, 1506.
136. Farmer, *ibid.*, **1922**, 2015.
137. Govindachari and Narasimhan, *ibid.*, **1953**, 2635.
138. Ingold and Nickolls, *ibid.*, **1922**, 1638.
139. Stevens and Beutel, *J. Am. Chem. Soc.*, **65**, 449 (1943).
140. Rapoport and Baldridge, *ibid.*, **74**, 5365 (1952).
141. Sorm and Keil, *Collection Czechoslov. Chem. Communs.*, **12**, 655 (1947).
142. U.S. patent 2,507,631, Hartmann and Panizzon, May 16, 1950; *C.A.*, **44**, 8379*d* (1950). Also Swiss patent 269,338, October 2, 1950; *C.A.*, **45**, 3426*e* (1951).
143. Prelog, Wirth, and Schönbaum, *Helv. Chim. Acta*, **29**, 1204 (1946).
144. Haines and Eisner, *J. Am. Chem. Soc.*, **72**, 1719 (1950).
145. Oparina, *Khim. Pharm. Prom.*, **1936**, **No. 2**, 98; *C.A.*, **30**, 1789[7] (1936).
146. Kipnis, Levy, and Ornfelt, *J. Am. Chem. Soc.*, **70**, 4265 (1948).
147. Tagmann, Sury, and Hoffmann, *Helv. Chim. Acta*, **35**, 1235 (1952).
148. Bohlmann, *et al.*, *Ber.*, **89**, 792 (1956).
149. Marvel, Coleman, and Scott, *J. Org. Chem.*, **20**, 1785 (1955).
150. Carboni, *Gazz. chim. ital.*, **85**, 1194 (1955).
151. Clemo, Morgan, and Raper, *J. Chem. Soc.*, **1936**, 1025.

152. Löffler and Flügel, *Ber.*, **42**, 3420 (1909).
153. Kuhn and Richter, *J. Am. Chem. Soc.*, **57**, 1927 (1935).
154. German patent 638,596, Gebauer, Nov. 19, 1936; *C. A.*, **31**, 3067[6], 6257[6] (1937).
155. Ochiai, Miyaki, and Sato, *Ber.*, **70**, 2018 (1937).
156. McElvain and Goese, *J. Am. Chem. Soc.*, **65**, 2226 (1943).
157. British patent 563,171, Aug. 2, 1944; *C.A.*, **40**, 2471 (1946).
158. Panizzon, *Helv. Chim. Acta*, **29**, 324 (1946).
159. Jungmann, *Angew. Chem.*, **60A**, 72 (1948).
160. Fromherz and Spiegelberg, *Helv. Physiol. et Pharmacol. Acta*, **6**, 12 (1948); *C.A.*, **42**, 8956*i* (1948).
161. Swiss patent 269,656, CIBA Ltd., Oct. 16, 1950; *C.A.*, **46**, 4575*d* (1952).
162. Protiva, *Chem. Listy*, **44**, 91 (1950); *C.A.*, **45**, 8013*b* (1951).
163. U.S. patent 2,508,332, Hartmann and Panizzon, May 16, 1950; *C.A.*, **44**, 7352*f* (1950).
164. U.S. patent 2,567,245, Sperber, Papa, and Schwenk, Sept. 11, 1951; *C.A.*, **46**, 4574*a* (1952).
165. Mosher and Tessieri, *J. Am. Chem. Soc.*, **73**, 4925 (1951).
166. Boekelheide and Lodge, Jr., *ibid.*, **73**, 3681 (1951).
167. Sperber, Papa, Schwenk, and Sherlock, *ibid.*, **73**, 3856 (1951).
168. Sperber, *et al.*, *ibid.*, **73**, 5752 (1951).
169. Gardner, Wenis, and Smith, *ibid.*, **73**, 5455 (1951).
170. Clemo and Popli, *J. Chem. Soc.*, **1951**, 1406.
171. Burger, Rector, and Schmalz, *J. Am. Chem. Soc.*, **74**, 3175 (1952).
172. U.S. patent 2,585,550, Hoffmann and Tagmann, Feb. 12, 1952; *C.A.*, **47**, 2217*a* (1953).
173. British patent 666,778, Sperber, Papa, and Schwenk, Feb. 20, 1952; *C.A.*, **47**, 5454 (1953).
174. Lettré, Jungmann, and Salfeld, *Ber.*, **85**, 397 (1952).
175. Yale, *et al.*, *J. Am. Chem. Soc.*, **75**, 1933 (1953).
176. Kato, *J. Pharm. Soc. Japan*, **73**, 149 (1953); *C.A.*, **47**, 11191*c* (1953).
177. U.S. patent 2,649,455, Walter, Barry, and Clark, Aug. 8, 1953; *C.A.*, **48**, 8827*h* (1954).
178. British patent 692,931, Erlenbach and Sieglitz, June 17, 1953; *C.A.*, **48**, 10776*g* (1954).
179. Exner, *Chem. Listy*, **47**, 869 (1953).
180. Tripod, Sury, and Hoffmann, *Experientia*, **10**, 261 (1954); *C.A.*, **48**, 10920*g* (1954).
181. Sury and Hoffmann, *Helv. Chim. Acta*, **37**, 2133 (1954).
182. Katritzky, *J. Chem. Soc.*, **1954**, 4038.
183. Castle and Seese, *J. Org. Chem.*, **20**, 987 (1955).
184. Gough and King, *J. Chem. Soc.*, **1933**, 350.
185. Rapoport and Volcheck, Jr., *J. Am. Chem. Soc.*, **78**, 2451 (1956).
186. Buu-Hoï, Huls, and Xuong, *J. Org. Chem.*, **20**, 1407 (1955).

187. Dummel, Wrinkle, and Mosher, *J. Am. Chem. Soc.*, **78**, 1936 (1956).
188. Dornow and Wedekind, *Arch. Pharm.*, **286**, 338 (1953).
189. Frankenburg and Vaitekunas, *J. Am. Chem. Soc.*, **79**, 149 (1957).
190. Wada and Yamasaki, *ibid.*, **76**, 155 (1954).
191. Van Tamelen, Hughes, and Taylor, *ibid.*, **78**, 4625 (1956).
192. Byerman, *et al.*, *Rec. trav. chim.*, **73**, 109 (1954).
193. Gardner, Wenis, and Lee, *J. Org. Chem.*, **19**, 753 (1954).
194. Strell, Braunbruck, and Reithmayr, *Ann.*, **587**, 195 (1954).
195. Winterfeld and Augstein, *Naturwissenschaften*, **40**, 362 (1953); *C.A.*, **49**, 3210*c* (1955).
196. Wheatley, *et al.*, *J. Org. Chem.*, **19**, 794 (1954).
197. Winterfeld, Wald, and Rink, *Naturwissenschaften*, **41**, 230 (1954); *C.A.*, **49**, 14759*e* (1955).
198. Ohki and Yamakawa, *Pharm. Bull.* (*Tokyo*), **1**, 114 (1953); *C.A.*, **49**, 1728*a* (1955).
199. Carrara, *et al.*, *Gazz. chim. ital.*, **83**, 459 (1953); *C.A.*, **49**, 319*b* (1955).
200. Japanese patent 2489/53, Chokushigawara, June 2; *C.A.*, **49**, 3267*i* (1955).
201. Ohki, Noike, and Yamakawa, *Pharm. Bull.* (*Tokyo*), **1**, 391 (1953); *C.A.*, **49**, 10947*i* (1955).
202. Sugasawa, Tatsuno, and Kamiya, *ibid.*, **2**, 39 (1954); *C.A.*, **49**, 12460 (1955).
203. U.S. patent 2,673,205, Hoffmann and Tagmann, March 23, 1954; *C.A.*, **49**, 6318*d* (1955).
204. Klosa, *Arch. Pharm.*, **286**, 433 (1953); *C.A.*, **49**, 8273*g* (1955).
205. Frankenburg, *Nature*, **175**, 945 (1955).
206. British patent 706,798, Ruhrchemie A.-G., April 7, 1954; *C.A.*, **49**, 9043 (1955).
207. Tilford and Van Campen, Jr., *J. Am. Chem. Soc.*, **76**, 2431 (1954).
208. Bohlmann, Ottowa, and Keller, *Ann.*, **587**, 162 (1954).
209. Clemo and Seaton, *J. Chem. Soc.*, **1954**, 2582.
210. Clemo, Fox, and Raper, *ibid.*, **1954**, 2693.
211. British patent 765,868, Farbwerke Hoechst A.-G., January 16, 1957; *C.A.*, **51**, 13939*b* (1957).
212. Robison, Butler, and Robison, *J. Am. Chem. Soc.*, **79**, 2573 (1957).
213. Pasini, Vercellone, and Erspamer, *Gazz. chim. ital.*, **86**, 266 (1956); *C.A.*, **51**, 2799*f* (1957).
214. Walker, *J. Am. Chem. Soc.*, **78**, 3698 (1956).
215. Reid, *Ann.*, **598**, 145 (1956).
216. Wada, *Arch. Biochem. and Biophys.*, **64**, 244 (1956); *C.A.*, **51**, 553*e* (1957).
217. McMillan, *et al.*, *J. Am. Chem. Soc.*, **78**, 4077 (1956).
218. U.S. patent 2,763,658, Cislak, September 18, 1956; *C.A.*, **51**, 3670*e* (1957).
219. Magnus and Levine, *J. Am. Chem. Soc.*, **78**, 4127 (1956).
220. Mikhlina and Rubtsov, *Zhur. Obshcheĭ Khim.*, **27**, 691 (1957); *C.A.*, **51**, 16463*f* (1957).
221. Van Tamelen, Hughes, and Taylor, *J. Am. Chem. Soc.*, **78**, 4625 (1956).

222. Gardner, *et al., J. Org. Chem.*, **21,** 530 (1956).
223. Zimmer and George, *Naturwissenschaften,* **42,** 415 (1955).
224. U.S. patent 2,774,767, Ehrhart, Schmitt, and Ott, December 18, 1956; *C.A.,* **51,** 7433*g* (1957).
225. Zimmer and George, *Ber.,* **89,** 2285 (1956).
226. Klosa, *Arch. Pharm.,* **289,** 177 (1956); *C.A.,* **51,** 7373*e* (1957).
227. Reid and Keller, *Ber.,* **89,** 2578 (1956).
228. Stein and Burger, *J. Am. Chem. Soc.,* **79,** 154 (1957).
229. Eby and Hauser, *ibid.,* **79,** 723 (1957).
230. Nikitskaya and Rubtsov, *Zhur. Obshcheĭ Khim.,* **26,** 3119 (1956); *C.A.,* **51,** 8084 (1957).
231. Magnus and Levine, *J. Org. Chem.,* **22,** 270 (1957).
232. Winterfeld and Flick, *Arch. Pharm.,* **26,** 448 (1956); *C.A.,* **51,** 11346*c* (1957).
233. Yakhontov and Rubtsov, *Zhur. Obshcheĭ Khim.,* **27,** 72 (1957); *C.A.,* **51,** 12085*a* (1957).
234. Mikhlina and Rubtsov, *ibid.,* **27,** 77 (1957); *C.A.,* **51,** 12085*f* (1957).
235. British patent 756,713, CIBA Ltd., September 5, 1956; *C.A.,* **51,** 9712*i* (1957).
236. Ernest and Pitha, *Chem. Listy,* **51,** 543 (1957); *C.A.,* **51,** 10525*a* (1957).
237. Govindachari, Narasimhan, and Rajadurai, *J. Chem. Soc.,* **1957,** 560.
238. Rubtsov, Mikhlina, and Furshtatova, *Zhur. Obshcheĭ Khim.,* **26,** 445 (1956); *C.A.,* **50,** 13905*c* (1956).
239. Beyer, Lässig, and Schudy, *Ber.,* **90,** 592 (1957).
240. Boekelheide and Mason, *J. Am. Chem. Soc.,* **73,** 2356 (1951).
241. Zymalkowski and Schauer, *Arch. Pharm.,* **290,** 218 (1957).
242. Lavagnino and Shepard, *J. Org. Chem.,* **22,** 457 (1957).
243. Kloetzel and Chubb, *J. Am. Chem. Soc.,* **79,** 4226 (1957).
244. Thesing, Ramloch, and Willersinn, *Ber.,* **89,** 2896 (1956).
245. Mors, Gottlieb, and Djerassi, *J. Am. Chem. Soc.,* **79,** 4507 (1957).
246. Dubravkova, *et al., Chem. zvesti,* **11,** 394 (1957); *C.A.,* **52,** 406*b* (1958).
247. Wada, *Arch. Biochem. Biophys.,* **72,** 145 (1957); *C.A.,* **52,** 3025*d* (1958).
248. Funke and Rissi, *Compt. rend.,* **239,** 713 (1954); *C.A.,* **52,** 2010*h* (1958).
249. Lukes and Vaculik, *Chem. Listy,* **51,** 1510 (1957); *C.A.,* **52,** 1163*c* (1958).
250. Zymalkowski and Schauer, *Arch. Pharm.,* **290,** 267 (1957); *C.A.,* **52,** 1167*b* (1958).
251. Leonard, Morrow, and Rogers, *J. Am. Chem. Soc.,* **79,** 5476 (1957).
252. Hudlicky and Mares, *Chem. Listy,* **51,** 1875 (1957); *C.A.,* **52,** 4628*b* (1958).
253. McKennis, Turnbull, and Bowman, *J. Am. Chem. Soc.,* **79,** 6342 (1957).
254. Winterfeld and Augstein, *Ber.,* **90,** 863 (1957).
255. Vompe and Turitsyna, *Zhur. Obshcheĭ Khim.,* **27,** 3282 (1957); *C.A.,* **52,** 9110*d* (1958).
256. Sato, *Pharm. Bull.,* **5,** 412 (1957); *C.A.,* **52,** 9115*b* (1958).
257. Katritzky and Monro, *J. Chem. Soc.,* **1958,** 150.
258. Marvel and Stille, *J. Org. Chem.,* **22,** 1451 (1957).

259. Leonard, Conrow, and Fulmer, *ibid.*, **22**, 1445 (1957).
260. Dubravkova, *et al., Chem. zvesti,* **11**, 656 (1957); *C.A.*, **52**, 9168*h* (1958).
261. Hunger and Hoffmann, *Helv. Chim. Acta,* **40**, 1319 (1957); *C.A.*, **52**, 9144*b* (1958).
262. Barrett, *et al., J. Chem. Soc.*, **1958**, 325.
263. McKennis, *et al., J. Am. Chem. Soc.*, **80**, 1634 (1958).
264. Bohlmann and Rahtz, *Abhandl. braunschweig. wiss. Ges.*, **9**, 170 (1957); *C.A.*, **52**, 11056*i* (1958).
265. Katritzky and Monro, *J. Chem. Soc.*, **1958**, 1263.
266. Mikhlina and Rubtsov, *Zhur. Obshchei Khim.*, **28**, 103 (1958); *C.A.*, **52**, 1263*i* (1958).
267. Bixler and Niemann, *J. Org. Chem.*, **23**, 575 (1958).
268. Furshtatova, Mikhlina, and Rubtsov, *Zhur. Obshcheĭ Khim.*, **28**, 668 (1958); *C.A.*, **52**, 17264*b* (1958).
269. Kraut, *et al., Magyar Kem Folyoirat,* **63**, 1 (1957); *C.A.*, **52**, 15516*b* (1958).
270. Hein and Beierlein, *Pharm. Zentralhalle,* **96**, 401 (1957); *C.A.*, **52**, 14608*d* (1958).
271. Klosa, *Naturwissenschaften,* **44**, 558 (1957); *C.A.*, **52**, 18406*g* (1958).
272. Sato, *Chem. Pharm. Bull. (Tokyo)*, **6**, 222 (1958); *C.A.*, **52**, 20164*h* (1958).
273. Murakoski, *Yakagaku Zasshi,* **78**, 598 (1958); *C.A.*, **52**, 18409*f* (1958).
274. McKusick, *et al., J. Am. Chem. Soc.*, **80**, 2806 (1958).
275. Tabuchi, *Nippon Nōgei-kagaku Kaishi,* **28**, 222 (1955); *C.A.*, **52**, 20378*i* (1958).
276. Kuffner and Kallina, *Monatsh.*, **89**, 270 (1958); *C.A.*, **52**, 20452*h* (1958).
277. Chizhov and Rubtsov, *Zhur. Obshcheĭ Khim.*, **28**, 1181 (1958); *C.A.*, **52**, 20194*d* (1958).
278. Winterfeld and Schneider, *Ann.*, **581**, 66 (1953).
279. Winterfeld and Schneider, *Naturwissenschaften,* **40**, 109 (1953).
280. U.S. patent 2,773,875, Finklestein and Lee, December 11, 1956.
281. British patent 771,814, Aktiebolaget Pharmacia, April 3, 1957; *C.A.*, **52**, 1279*g* (1958).
282. German patent 922,824, Ehrhart and Bestian, January 27, 1955; *C.A.*, **52**, 2932*i* (1958).
283. German patent 830,193, Ehrhart and Bestian, February 4, 1952; *C.A.*, **52**, 11956*h* (1958).
284. Spanish patent 236,259, April 11, 1957; *C.A.*, **52**, 15596*b* (1958).
285. Zymalkowski, *Arch. Pharm.*, **291**, 436 (1958); *C.A.*, **53**, 6224*g* (1959).
286. U.S. patent 2,833,776, Ruddy, May 6, 1958; *C.A.*, **52**, 15594*b* (1958).
287. U.S. patent 2,823,233, Speeter, February 11, 1958; *C.A.*, **52**, 18473 (1958).
288. Profft, Schneider, and Beyer, *J. prakt. Chem.*, [4] **2**, 147 (1955).

CHAPTER XII

Pyridinols and Pyridones

By Herbert Meislich
The City University of New York

A. PREPARATION

The methods for preparing pyridinols and pyridones can be grouped into three main categories: (1) ring closure of acyclic compounds, (2) alteration of other heterocyclic ring systems, and (3) sub-

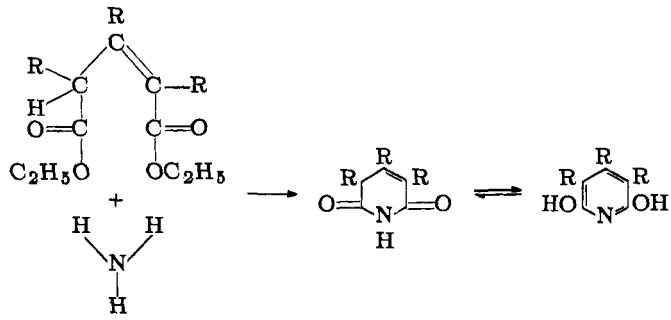
stitution and displacement on pyridine and its derivatives. For the first two methods, see also Chapter II, pp. 152 ff.

1. Ring Closure of Acyclic Compounds

Many of these methods employ a compound which has at least a five-carbon chain, the proper degree of unsaturation, and groups on carbons 1 and 5 which can undergo condensation with ammonia or amines. If carbon 1 or 5 is part of a nitrile or an amide group, intramolecular cyclization can readily occur and ammonia is not needed.

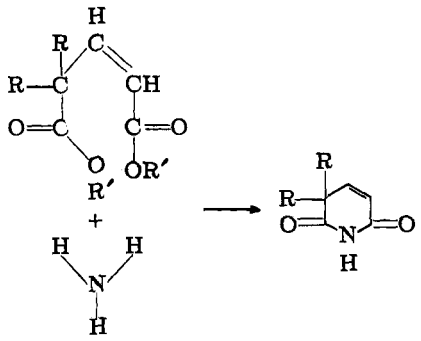
a. Glutaconic Acid Derivatives

Typical examples of such compounds are the substituted glutaconic acid derivatives. Ethyl glutaconate itself (XII-1, R = H) undoubtedly gives 2,6-pyridinediol when treated with ammonia. When the reaction was attempted by Thorpe, he could not isolate the product because it was susceptible to rapid air oxidation (*1*). However, the reactions of various substituted glutaconic esters (XII-1,



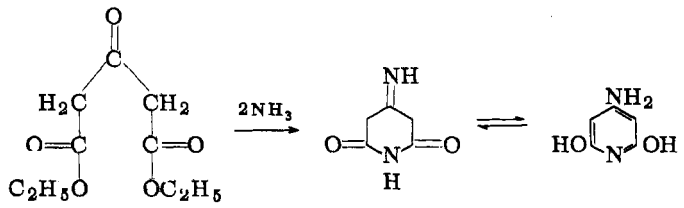
(XII-1)

R = alkyl, aryl) have been reported to proceed quite smoothly (*1–4a*). The substituted glutaconimides, which are expected products from such a reaction, are really tautomers of the 2,6-pyridinediols. To obtain a pyridine derivative, there must be at least one hydrogen atom on the *α*-methylene carbon. If this carbon is disubstituted, the product obtained is a 2,6-diketo 3,3-disubstituted tetrahydropyridine, which is incapable of undergoing complete enolization to the pyridinediol (XII-2).



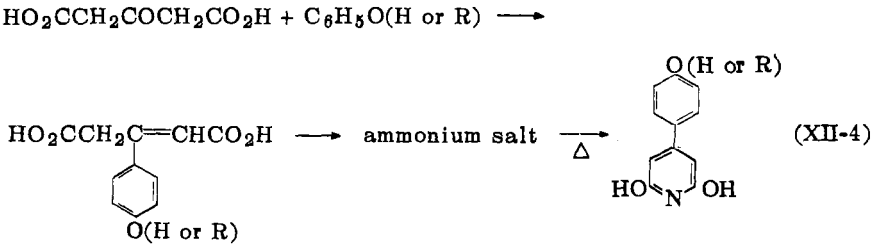
(XII-2)

Ethyl acetonedicarboxylate, which in its enolic form is a hydroxyglutaconate, should react with ammonia to form 2,4,6-pyridinetriol. However, ammonia reacts with the keto group to give an imine, and the final product is 4-amino-2,6-pyridinediol or glutazine (XII-3) (*5,5a*).



(XII-3)

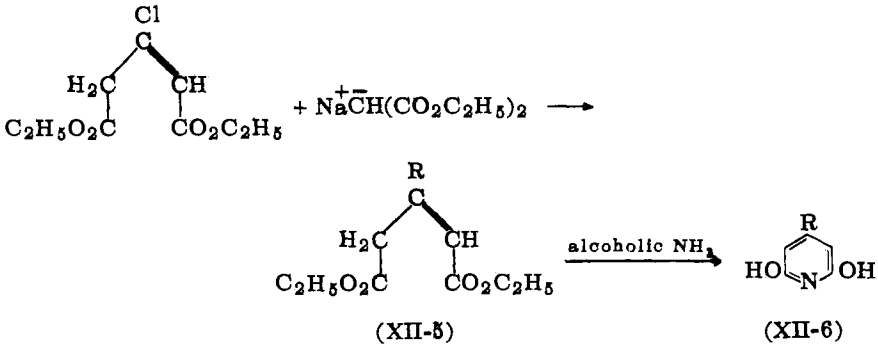
Acetonedicarboxylic acid itself condenses with phenols and phenolic ethers, and the ammonium salts of the resulting β-substituted glutaconic acids, on being heated, give good yields of the 4-(*p*-hydroxy(or alkoxy)phenyl)pyridinediols (XII-4) (*7,8*).



(XII-4)

Diethyl β-chloroglutaconate reacts with sodium diethylmalonate to give diethyl β-dicarbethoxymethylglutaconate (XII-5, R = CH-

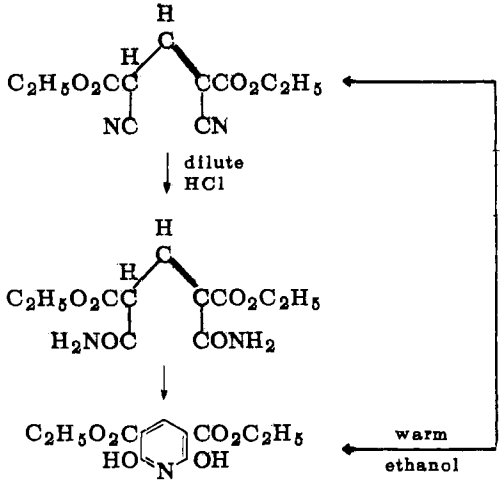
$(COOC_2H_5)_2$), which is converted to 2,6-dihydroxy-4-pyridineacetamide (XII-6, R = CH_2CONH_2) in refluxing alcoholic ammonia (*6*).



(XII-5) (XII-6)

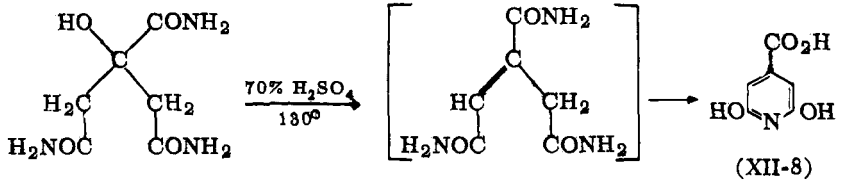
Similarly, triethyl aconitate (XII-5, R = $COOC_2H_5$) with ammonia is converted to citrazinamide (XII-6, R = $CONH_2$) (*114*).

If the glutaconic acid is changed to an amide or a nitrile, ammonia is not required to effect the ring closure. Ethyl α,γ-dicyanoglutaconate, formed from ethyl cyanoacetate and chloroform in sodium ethoxide, is hydrolyzed with dilute hydrochloric acid to the amide, which cyclizes in refluxing alcohol to diethyl 2,6-dihydroxy-3,5-pyridinedicarboxylate (XII-7) (*14*). The dinitrile itself gives the same product when refluxed in ethanol (*111*).



(XII-7)

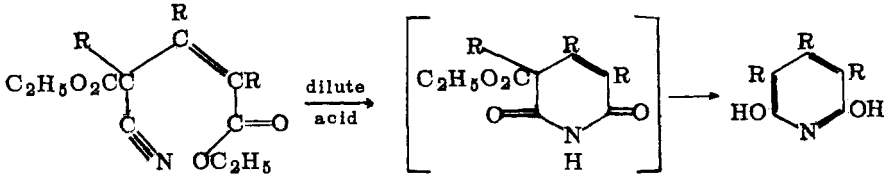
When the triamide of citric acid is heated with sulfuric acid, it is converted to citrazinic acid (XII-8) (*10,11,11a*). Since dehydra-



(XII-8)

tion can occur under these conditions, aconitic acid triamide, a carboxamido derivative of glutaconic acid, is a likely intermediate. Citrazinic acid has assumed importance as a precursor for synthesizing isoniazid, a valuable antituberculosis drug. It has been prepared in 44% yield by refluxing anhydrous citric acid in anhydrous methanol and then autoclaving with ammonium hydroxide (*833*). Its amide was prepared in 60–70% yield by treating citric acid under pressure with urea at 130–150°C. (*834*). *Cf.* Chapter II, p. 293.

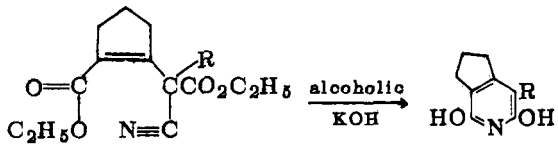
When the nitrogen of the pyridine ring is provided by a cyano group in the α-position of a glutaconic acid derivative (XII-9), the ring closure is greatly facilitated. This innovation was introduced by Rogerson and Thorpe (*12*) in 1905, and has since been used extensively. There is evidence to indicate that the 3-alkyl-3-carbethoxy derivative (XII-10) is an intermediate, which loses the car-



(XII-9) (XII-10)

bethoxy group via hydrolysis and decarboxylation. The tendency for the ring closure to occur is quite marked, since, for example, the attempt to hydrolyze diethyl α-cyano-α,β,γ-trimethylglutaconate (XII-9, R = CH_3) to the corresponding acid gave instead 3,4,5-trimethyl-2,6-pyridinediol exclusively in 56% yield (*12a*). When this synthetic route was attempted for the preparation of 3-ethyl-4,5-

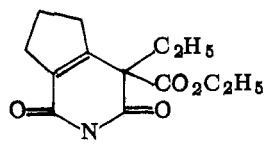
dimethyl- and 3,5-diethyl-4-methyl-2,6-pyridinediols, the yields were inferior, ranging from 9 to 37%, depending on the particular trisubstituted cyanoglutaconic ester (*827*). The esters were cyclized under both alkaline and acid conditions. An interesting application of this synthesis is the preparation of 3,4-trimethylene-2,6-pyridinediol (XII-12) by Kon and Nanjii (*15*), who hydrolyzed XII-11 (R = H)



(XII-11) (XII-12)

R = H, CH_3, C_2H_5

with alcoholic potassium hydroxide. When R = C_2H_5, an intermediate diketocarbethoxy compound (XII-12a) was isolated by treating

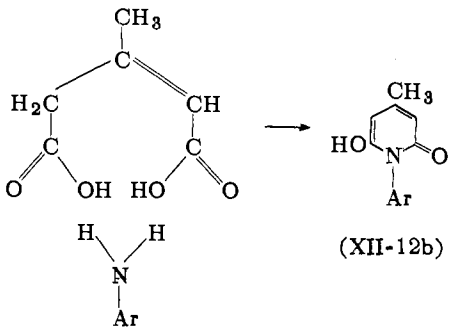


(XII-12a)

XII-11 (R = C_2H_5) with sulfuric acid at room temperature for twenty-four hours (*30*). In refluxing hydrochloric acid, the diketo compound loses the carbethoxy group, yielding the product XII-12 (R = C_2H_5).

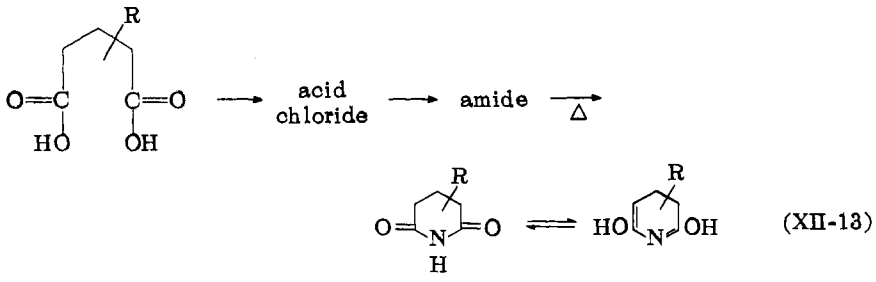
Substituting amines for ammonia affords 6-hydroxy-2(1*H*)-pyridones. This reaction was utilized to prepare several 1-aryl-4-methyl-6-hydroxy-2(1*H*)-pyridones (XII-12b). The same product (XII-12b) also results when the preformed half anilide is heated (*835*).

If substituted glutaric acid derivatives are utilized for cyclization, the degree of unsaturation is insufficient, and dihydropyridines are formed. These compounds are, however, convertible to pyridine derivatives by methods to be discussed later. In a typical example,



(XII-12b)

α- or β-cyclopentylglutaric acid is converted to the amide, which, when heated, yields 3- or 4-cyclopentyl-2,6-pyridinediol (XII-13) (*31*).



(XII-13)

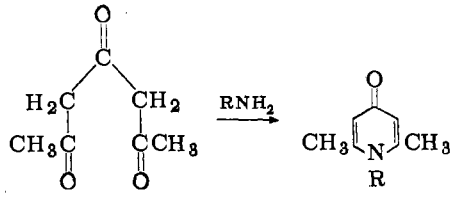
R = cyclopentyl

It is evident from the aforementioned examples that when glutaconates are used for cyclization, 2,6-pyridinediols are always formed (*cf.* Chapter II, pp. 295 f. and 329 ff.).

b. δ-Diketones and δ-Ketoacid Derivatives

To prepare pyridinols from δ-diketones, there must be an oxygen function elsewhere on the carbon chain to provide the hydroxyl group. A δ-diketone of this type which has been used extensively is diacetylacetone. It has been condensed with ammonia (*9a*) and with a variety of aliphatic, aromatic, and cyclic primary amines to give lutidone and its derivatives (XII-14).

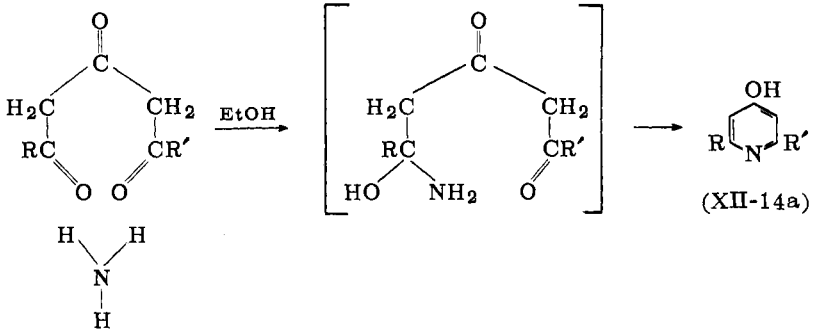
Light and Hauser (*819*) extended this reaction by combining other β,δ-triketones with ammonia to prepare 4-pyridinols (XII-14a)



(XII-14)

R = H, alkyl, cycloalkyl, aryl

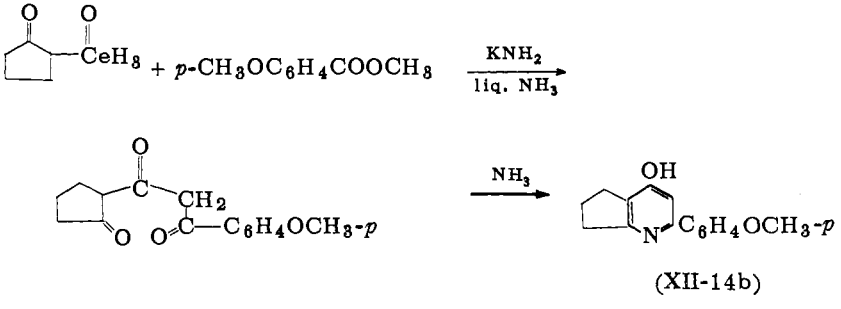
in yields up to 76%. In each case, R′ was an aroyl group, the starting material having been prepared by aroylation of a β-diketone.



(XII-14a)

R = Me, Ph
R′ = Ph, *p*-ClC$_6$H$_4$, *p*-CH$_3$OC$_6$H$_4$, 3-Py

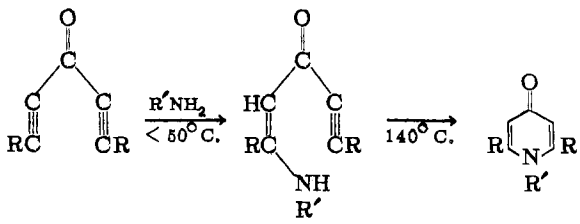
Cyclopenteno-[b]-6-(*p*-methoxyphenyl)-4-pyridinol (XII-14b) was obtained by cyclizing the triketone formed by aroylation of 2-acetylcyclopentanone with methyl anisate (*819,879*). Finally, the triketone



(XII-14b)

1,5-diphenyl-1,3,5-pentanetrione was cyclized with methylamine to form the expected *N*-methyl-4-pyridone in 42% yield (*cf.* Chapter II, pp. 276 and 305).

Since acetylenic compounds are in the same state of oxidation as ketones, it is not surprising that α-diacetylenic ketones react with ammonia or amines to give γ-pyridones (*16*). This reaction has been utilized for the identification of a large number of primary amines (*17*). The condensation proceeds through two successive Michael-type additions of the nucleophilic nitrogen of the amine to the α,β-unsaturated ketone. When the reaction is performed below 50°C., it is possible to isolate XII-15, the intermediate formed by the

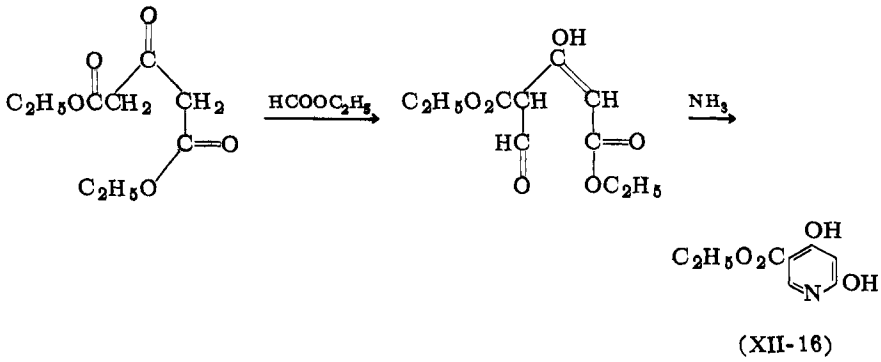


(XII-15)

first addition. When R = phenyl, the isomerization of XII-15 to the pyridone is complicated by the simultaneous formation of a well-defined orange derivative, believed to be a nitrogen-containing β-naphthol of undetermined structure (*17*). *Cf.* Chapter II, pp. 300 and 345.

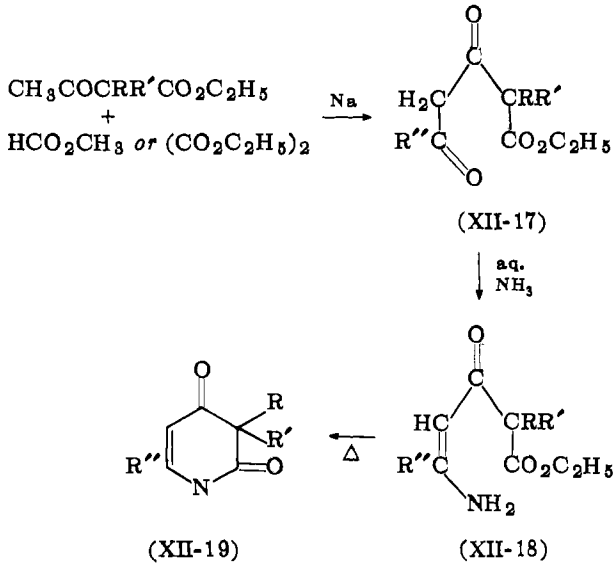
δ-Keto α,β(or β,γ)-unsaturated acid derivatives should serve as suitable starting materials for the synthesis of 2-pyridinols. They have been little used, however, probably because they are difficult to obtain. Schneider (*32*) reported the formylation of diethyl acetonedicarboxylate with ethyl formate in the presence of sodium, and the reaction of the resulting product, a β,δ-diketoester, with ammonia to give ethyl 4,6-dihydroxynicotinate (XII-16).

Dialkylacetoacetic ester derivatives are similarly formylated with methyl formate, and the condensation product (XII-17, R″ = H) yields a stable δ-amino-β-keto γ,δ-unsaturated ester (XII-18, R″ = H) on treatment with aqueous ammonia at room temperature. On being heated, XII-18 (R″ = H) cyclizes to a 2,4-diketo-3,3-dialkyltetra-



(XII-16)

hydropyridine (XII-19, R″ = H) (*33*). A similar synthesis involving the condensation of dialkylacetoacetic ester with diethyl oxalate leads to a series of compounds, XII-19, where R″ = $COOC_2H_5$ (*34*).



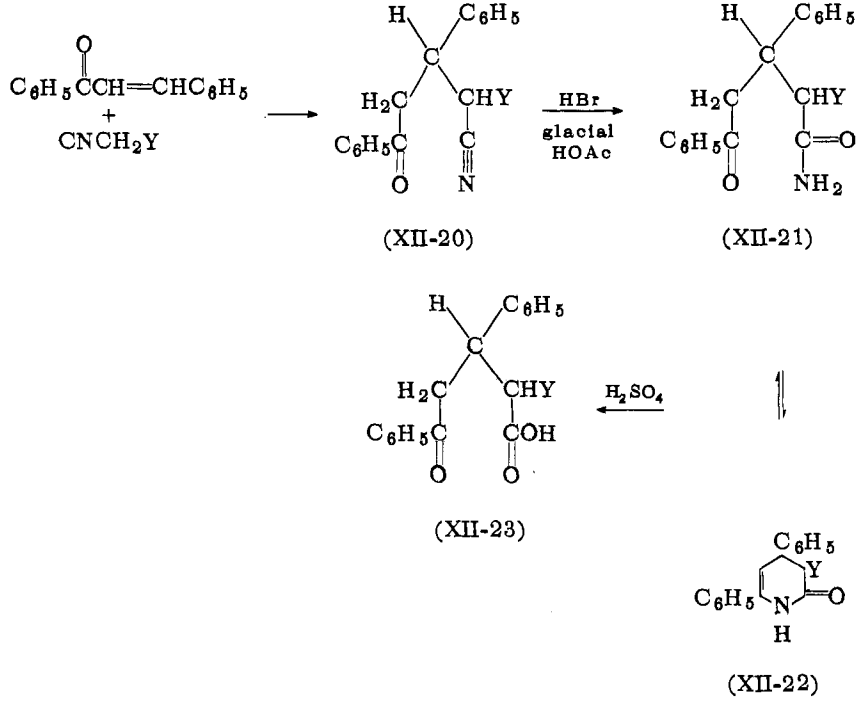
(XII-17)

(XII-19) (XII-18)

Whereas the δ-ketoesters have not been used extensively for the synthesis of substituted 2-pyridinols, the δ-ketonitriles have been successfully exploited by Kohler and Allen as starting materials. They are conveniently prepared by condensing cyanoacetic ester or amide, malononitrile, or benzyl cyanide with unsaturated ketones in the presence of sodium ethoxide. The saturated δ-ketonitriles

prepared in this manner are cyclized by treatment with hydrogen bromide in a small volume of chloroform or glacial acetic acid to dihydropyridinols, which are then aromatized. The first example (*18*) reported the condensation of methyl cyanoacetate with benzalacetophenone in the presence of sodium ethoxide to give XII-20 (Y = $COOCH_3$).

If acetic anhydride or acetyl chloride is introduced into the glacial acetic acid, the cyclization does not occur. From this evidence, it is concluded that a trace of water is essential to partially hydrolyze XII-20 to the amide (XII-21). The ring closure is reversible, and both the open-chain adduct (XII-21) and its ring isomer (XII-22) hydrolyze to the same free acid (XII-23) in sulfuric acid.



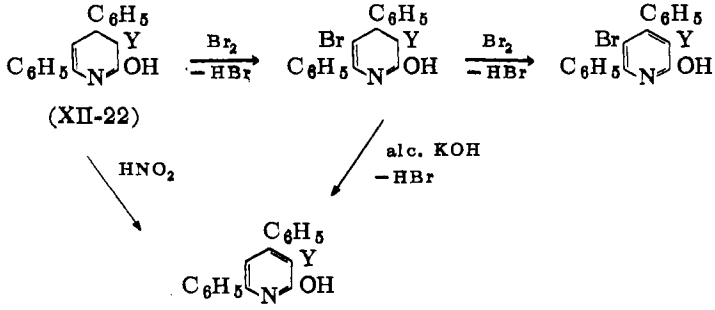
(XII-20) (XII-21)

(XII-23)

(XII-22)

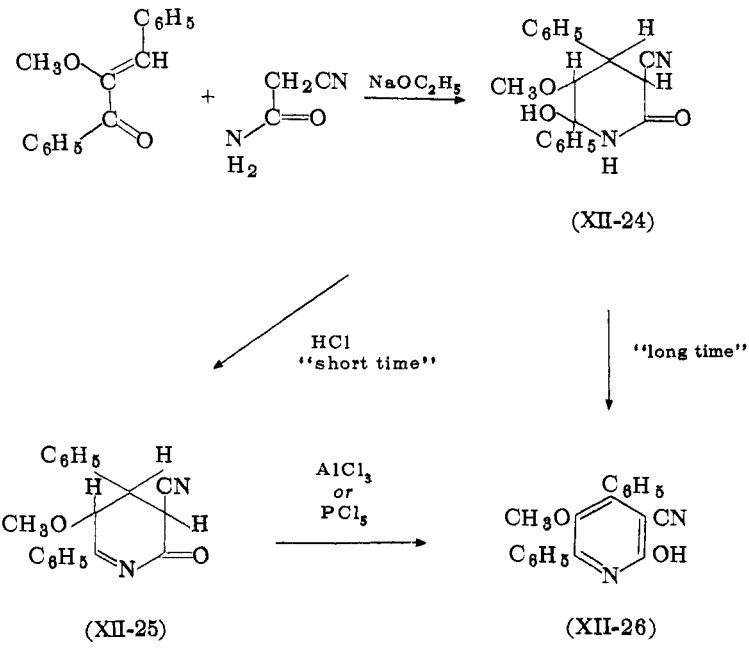
Kohler and Souther (*19*) used malononitrile instead of methyl cyanoacetate, and obtained the dinitrile adduct (XII-20, Y = CN). Although this compound does not ring-close to a dihydropyridinol with hydrohalic acids, treatment with alcoholic potassium hydrox-

ide gives, unexpectedly, 2-ethoxy-4,6-diphenylnicotinonitrile directly. Although not demonstrated by the authors, it may very well be that the aromatization of the expected intermediate dihydro compound (XII-22, Y = CN) was due to air oxidation. These authors also found that nitrous acid is an effective oxidant for the transformation of XII-22 to the pyridinol. Also noteworthy is the fact



that the adduct of cyanoacetamide (XII-20, Y = $CONH_2$) ring-closes through the amido group and not through the nitrile to give XII-22 (Y = CN) directly. This observation is in accord with the assumption that the nitrile group must first be partially hydrolyzed to an amido group (which is already present in XII-20, Y = $CONH_2$) before undergoing ring closure. Allen further extended this reaction by using benzyl cyanide (*20*) and aryl-substituted benzyl cyanides (*21,22*) and obtained the adduct XII-20 (Y = aryl). *Cf.* Chapter II, pp. 288 ff. and 318 ff.

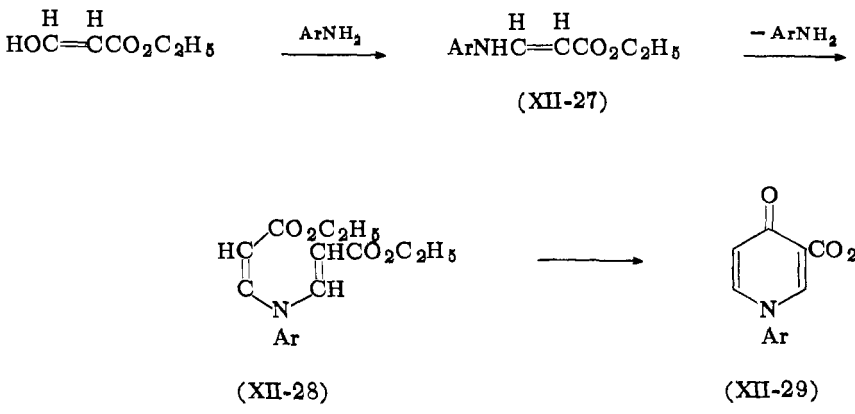
The course of the reaction is somewhat different when cyanoacetamide is condensed with benzal-α-methoxyacetophenone in the presence of a trace of sodium methoxide (*23*). Instead of the usual open-chain adduct (XII-20), a cyclic product (XII-24) is obtained which, on treatment with phosphorus pentachloride or aluminum chloride, yields XII-26. In all likelihood, the dehydrated product (XII-25) is an intermediate, which gives XII-26 on air oxidation. This inference is based on the observation that with hydrogen chloride in chloroform XII-25 was first obtained, but after several weeks XII-26 was isolated. Barat (*25*) has also studied the condensation of cyanoacetamide and arylidene ketones with both piperidine



and sodium ethoxide as basic catalysts (*cf.* Chapter II, pp. 443 ff. and 456 ff.).

c. Nitrogen-Containing Chains

The reactions which have been discussed previously involved compounds with an intact five-carbon skeleton, where the cyclization requires formation of a carbon-nitrogen bond. There are, however, instances where the nitrogen is part of the chain, and ring closure necessitates formation of a carbon-carbon bond (*cf.* Chapter II, pp. 533 ff.). Ethyl β-hydroxyacrylate (formylacetate) is condensed with arylamines in dilute acetic acid to give ethyl β-arylaminoacrylates (XII-27), which, on heating *in vacuo* 10–15° below their melting point, dimerize with the loss of arylamine to yield β-arylimino-diacrylic esters (XII-28). On saponification of XII-28 with alcoholic potassium hydroxide, 1,4-dihydro-4-oxo-1-phenylnicotinic acid (XII-29) results. When Ar = phenyl or 2-naphthyl (*43*), XII-28 is not isolated, and XII-29 is obtained directly on saponification of XII-27. However, when Ar = *p*-anisyl (*44*), XII-28 is isolated. This reaction has also been performed with Ar = 6-quinolyl (*43*).

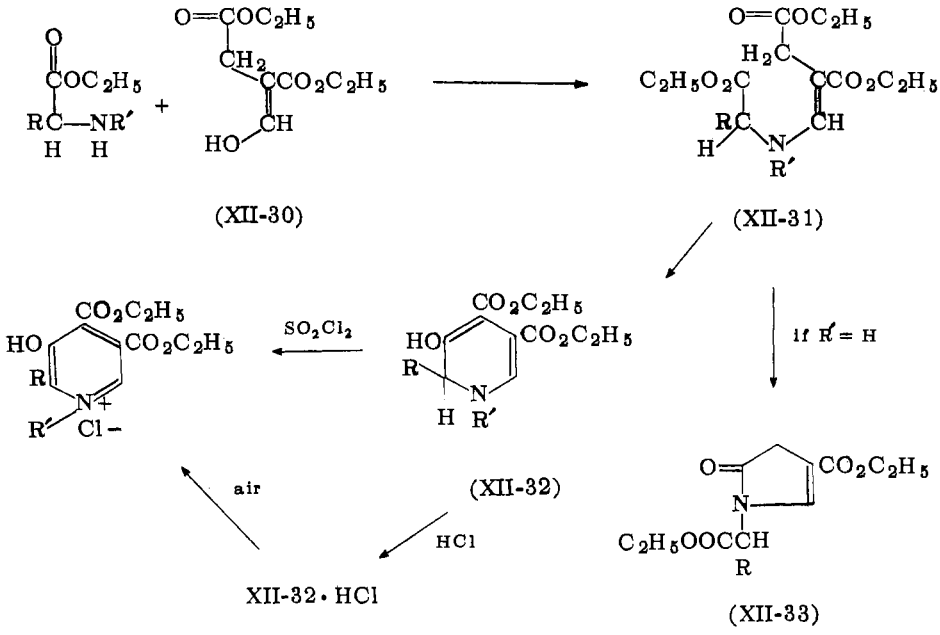


(XII-27)

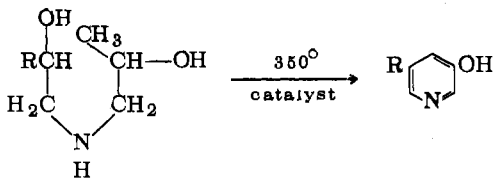
(XII-28) (XII-29)

Several dihydropyridinols have also been prepared by cyclization of a nitrogen-containing chain. The method developed by A. Cohen (*45*) requires mild heating of a mixture of an α-aminoester and ethyl α-(hydroxymethylene)succinate (XII-30). This reaction leads to the production in good yields of a series of carbethoxyalkylaminoitaconic esters (XII-31) which undergo the Dieckmann reaction in the presence of sodium, sodium ethoxide, or sodamide to form the dihydropyridinol (XII-32). If R′ = H, cyclization yields derivatives of 5-keto-4,5-dihydropyrrole (XII-33). Although the dihydropyridinol (XII-32) could not be simply dehydrogenated to a pyridine derivative, its hydrochloride was easily aromatized by air oxidation to the corresponding pyridinium salt. A more effective reagent for this conversion, however, is sulfuryl chloride. To utilize this synthetic route for the preparation of pyridine derivatives, R′ was made a benzyl group, which was subsequently removed by hydrogenolysis. The resulting product, a dialkyl 2-methyl-3-hydroxy-4,5-pyridinedicarboxylate, serves as an intermediate for the synthesis of pyridoxine. This series of reactions has been carried out with compounds where R = methyl (*45*), benzyl (*46*), *i*-propyl (*47*), *i*-butyl (*47*), and phenyl (*47*). In an attempt to simplify the pyridoxine synthesis, nitrile groups were substituted for one or both of the carbethoxy groups in XII-30 by using ethyl β-cyano-α-formylpropionate and hydroxymethylenesuccinodinitrile as starting materials. Although the con-

densation product (XII-31) was obtained, attempts to cyclize it to XII-32 were futile.



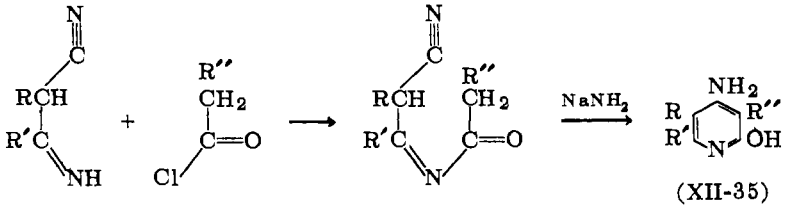
3-Pyridinol and 5-alkyl-3-pyridinols were prepared by vapor phase treatment of dialkanolamines with a hydrogenation-dehydrogenation catalyst of copper, nickel, and chromium in a hydrogen atmosphere at elevated temperatures (*102*). With XII-34 (R = CH_3),



(XII-34)

the yield was 42%, but with R = H, only 10% of product was obtained.

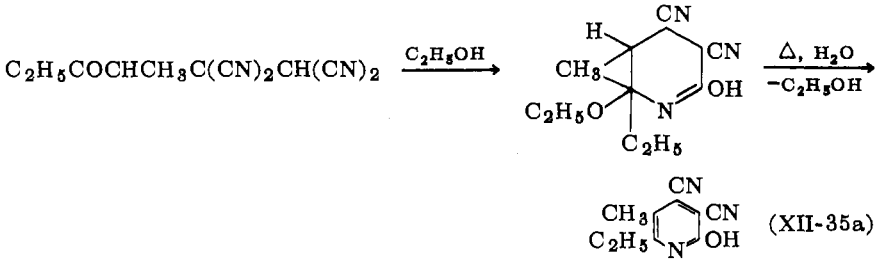
β-Iminonitriles can be acylated with acyl chlorides or anhydrides, and the intermediate nitrogen-containing chain cyclized by strong base to give substituted 4-amino-2-pyridinols (XII-35) (*155,158*).



(XII-35)

R and R′ can be a carbocyclic ring (*156*), in which case the yield is as high as 95%.

3,4-Dicyano-2-pyridinols have been prepared by heating β,β,γ,γ-tetracyanoketones in boiling ethanol (*822*). The only limitation is that the ketone must possess an α-hydrogen between the carbonyl and the dicyanomethylene groups. A typical example is shown in XII-35a; the tetracyanoketone is formed from diethyl ketone and



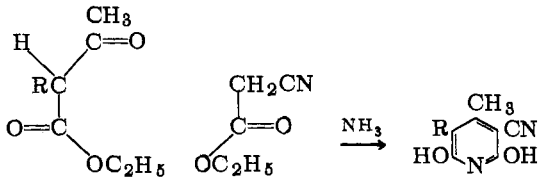
(XII-35a)

tetracyanoethylene (*823*). A dihydropyridinol that contains one mole of ethanol is formed as an intermediate. The ethanol is readily eliminated in boiling water, and the 2-pyridinol results. In the case of aromatic ketones, the intermediate was not isolated and the pyridinol was obtained directly. The yields ranged from 7% for the 5,6-diphenyl compound to 60% for the 6-phenyl compound.

d. β-Diketones and β-Ketoacid Derivatives with Malonic Acid Derivatives

Since the number of five-carbon chain compounds available for cyclization is limited, methods have been devised for the synthesis

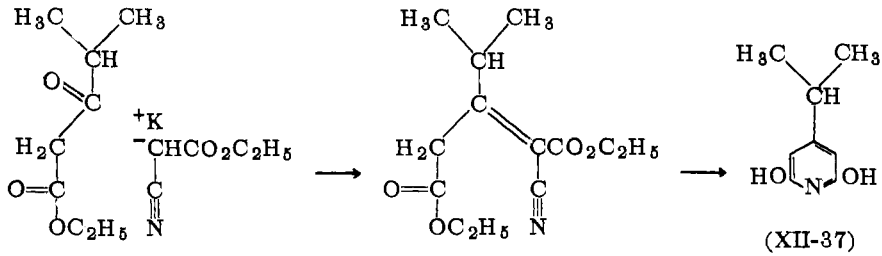
of pyridinols using two or more carbon-containing compounds directly. In one of the most important methods of this type, β-dicarbonyl compounds are condensed with cyanoacetic acid, its ester, or amide, or malononitrile. With the acid and ester, ammonia is sometimes used to furnish the ring nitrogen. Cyanoacetamide is most often utilized because it obviates the use of ammonia and, in general, gives the best yields. Piperidine, diethylamine, and (less frequently) sodium ethoxide serve as catalysts. Guareschi (*36*) reported condensing ethyl acetoacetate with ethyl cyanoacetate in ammonia to give 2,6-dihydroxy-4-methylnicotinonitrile (XII-36, R = H).



(XII-36)

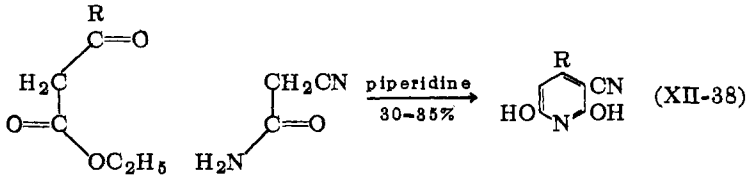
Another example is the condensation of ethyl α-ethylacetoacetate to yield XII-36 where R = C_2H_5 (*26*). This reaction has been performed with R representing other alkyl groups, including butyl, allyl, benzyl, and β-hydroxyethyl (*cf.* Chapter II, pp. 361 ff. and 398 ff.).

If other ketoesters are used, the alkyl group in the 4 position of the pyridine ring can be varied. Thus ethyl β-keto-γ-methylvalerate condensed with the potassium salt of ethyl cyanoacetate to give ethyl α-cyano-β-*i*-propylglutaconate as an intermediate, which, after hydrolysis and decarboxylation, yielded 4-*i*-propyl-2,6-pyridinediol (XII-37) (*37*). In place of ethyl cyanoacetate, Stevens and



(XII-37)

Beutel (*38*) condensed cyanoacetamide with diethyl acetonedicarboxylate (R = $CH_2COOC_2H_5$), ethyl oxaloacetate (R = $COOC_2H_5$), and diethyl β-ketoadipate (R = $CH_2CH_2COOC_2H_5$) as shown (XII-38). An interesting modification of this type of ring closure is the



(XII-38)

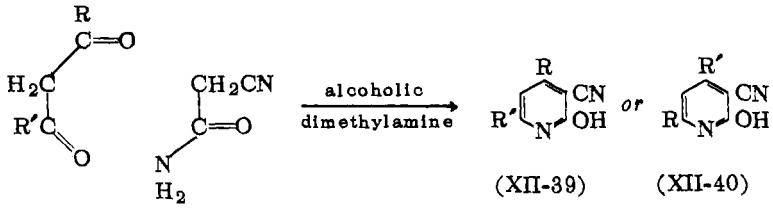
condensation of cyanoacetamide with α-acetylbutyrolactone in concentrated ammonium hydroxide, to yield 2,6-dihydroxy-5-(β-hydroxyethyl)-4-methylnicotinonitrile (XII-36, R = β-hydroxyethyl) (*39*).

The yield of XII-36 (R = H) obtained from ethyl acetoacetate and cyanoacetamide was increased to 85–95% by Bobbith and Scola (*820*). The condensation was effected in the presence of a mole of piperidine or potassium hydroxide, but, in contrast to previous work (*821*), the intermediate piperidinium or potassium salts were isolated. The diol itself was obtained in essentially quantitative yield by acidification of the salts.

The condensation of diethyl acetonedicarboxylate and ethyl cyanoacetate is effected by diethylamine. In the presence of concentrated sulfuric acid, the intermediate product undergoes hydration of the cyano group and cyclization to yield ethyl 3-carbethoxy-2,6-dihydroxy-4-pyridineacetate (*883*).

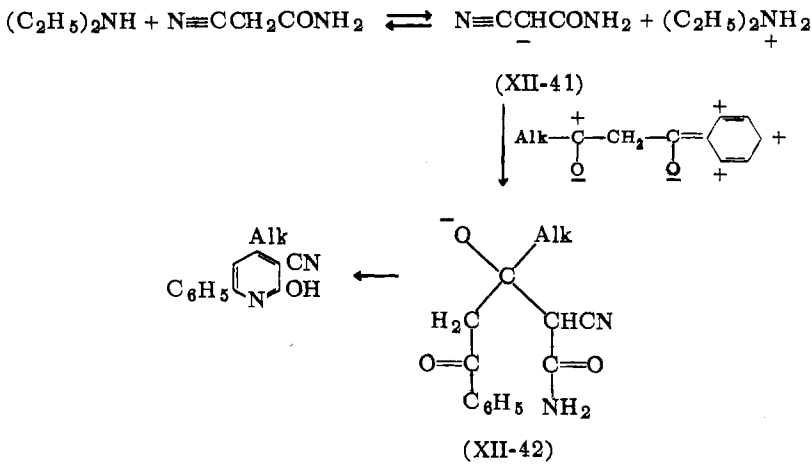
β-Ketoamides can be substituted for β-ketoesters. In the presence of ammonium hydroxide, α-methylacetoacetamide is condensed with ethyl cyanoacetate to give a 90% yield of 2,6-dihydroxy-4,5-dimethylnicotinonitrile (XII-36, R = CH_3) (*40*). α-Phenylacetoacetamide is condensed with ethyl cyanoacetate in the presence of piperidine to afford 2,6-dihydroxy-4-methyl-5-phenylnicotinonitrile (XII-36, R = C_6H_5) (*853*).

When β-diketones replace the β-ketoesters, 2-pyridinols rather than the 2,6-diols are obtained. Pentane-2,4-dione (R = R′ = CH_3) reacts with cyanoacetamide (*41*) to give 2-hydroxy-4,6-dimethylnicotinonitrile (XII-39) in 87% yield. Similarly, dibenzoylmethane



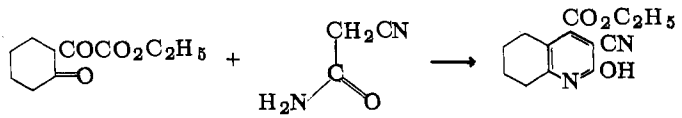
(XII-39) (XII-40)

($R = R' = C_6H_5$) gives the corresponding 4,6-diphenyl derivative in 60% yield, and heptane-3,5-dione gives a 90% yield of XII-39 where $R = R' = C_2H_5$ (*27*). The variation in yield may be explained on the basis of the greater reactivity of the alkyl *vs.* the aryl ketones. In these instances, the diketones are symmetrical, and only a single pyridinol can be formed. However, with unsymmetrical β-diketones, two isomeric products can result in which the two R groups are interchanged. Bardhan (*41*) reacted both benzoylacetone ($R = CH_3$, $R' = CH_6H_5$) and propionylacetophenone ($R = C_2H_5$, $R' = C_6H_5$) with cyanoacetamide, and in each case obtained the two expected products, XII-39 and its isomer. The major product was the 4-alkyl-6-phenyl isomer. He and Basu (*81*) were much concerned as to whether the reaction was of the aldol type (attack on a carbonyl group) or the Michael type (1,4 addition to the enol form, R–C(=O)–CH=C(OH)–R'). However, these results can be interpreted in terms of modern electronic theory. The catalyst, diethylamine, abstracts a proton from the active methylene group of cyanoacetamide. The resulting carbanion (XII-41) has a choice of bonding with either of the two electrophilic carbonyl carbons, and will undoubtedly select the one with the greater concentration of positive charge. Since the phenyl group, in this instance, is electron-donating, the carbonyl group adjacent to it will be less electrophilic than the one next to the alkyl group. Therefore, the intermediate (XII-42) forms to a greater extent, and the ring closes to place the aryl group in position 6 as the major product. When R and R' are both alkyl groups, *i.e.*, in acetylmethyl ethyl ketone (XII-40, $R = CH_3$, $R' = C_2H_5$), one might expect the steric environment of the two carbonyl groups to determine the order of bonding. The least hindered carbonyl should react preferentially, so that the major product has the bulkier



(XII-42)

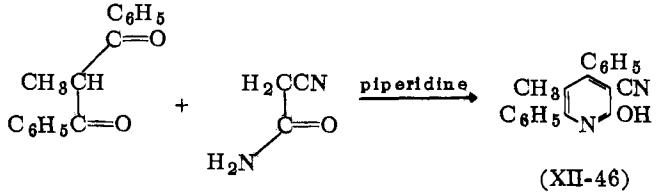
group in position 6. Thus, cyclization with sodium cyanoacetamide gave predominantly the 6-ethyl-4-methyl isomer (XII-39, R = CH_3, R′ = C_2H_5) (*41*). When R = $C_2H_5OCH_2$ and R′ = CH_3, *i.e.*, in ethoxyacetylacetone, ring closure with cyanoacetamide results in a 75% yield of a 2-pyridinol with the larger group in the 4 position, and a 15% yield with the same group in the 6 position (*48*). This distribution of isomers may be accounted for by the increased electron deficiency of the carbonyl group because of the pronounced electron-withdrawing inductive effect of the ethoxy group near it. When R = $COOC_2H_5$, it similarly enhances the activity of the carbonyl group adjacent to it, resulting exclusively in the isomer with the carbethoxy group in the 4 position. Thus ethyl acetylpyruvate gives 4-carbethoxy-2-hydroxy-6-methylnicotinonitrile (*41,100,837*). Ethyl benzoylpyruvate gives the analogous 6-phenyl-4-carbethoxy derivative (*50*), and ethyl butyrylpyruvate gives the 6-propyl derivative (*58*). A novel adaptation of this synthesis utilizes ethyl cyclohexanone-2-oxalate to give ethyl 3-cyano-5,6,7,8-tetrahydro-2-hydroxyquinoline-4-carboxylate (XII-45).



(XII-45)

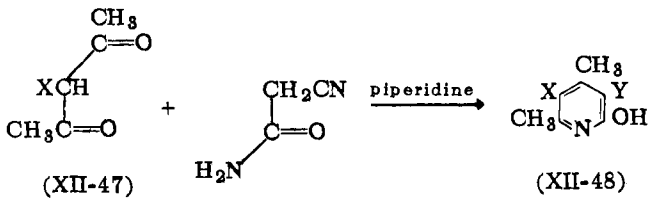
Further light may be shed on the course of reaction of unsymmetrical diketones by considering compounds where R and R′ are phenyl and *p*-substituted phenyl groups. *p*-Toluylacetophenone gives with cyanoacetamide a 34% yield of 2-hydroxy-4-phenyl-6-*p*-tolylnicotinonitrile (XII-39, R = C_6H_5, R′ = *p*-$CH_3C_6H_4$) and a 17% yield of the isomer (XII-40) in which the phenyl and *p*-tolyl groups are interchanged (*42*). In this case, there is no difference in the steric environment about each of the two carbonyl groups to account for the isomer ratio. However, the methyl group in the para position of the benzene ring, can, by hyperconjugative resonance, distribute the positive charge away from the ketonic carbon, thus deactivating it more than does the unsubstituted phenyl group. The attack by the carbanion (XII-41) will be predominantly on the carbonyl group adjacent to the phenyl group. In summary, when unsymmetrical β-diketones are used, the group adjacent to the more active carbonyl carbon ends up preferentially in the 4 position of the pyridinol.

Trialkyl-, aryl-, or alkaryl-substituted 3-cyano-2-pyridinols may be prepared by using β-diketones alkylated or arylated on the methylene group. Plati and Wenner (*51*) prepared 2-hydroxy-5-methyl-4,6-diphenylnicotinonitrile (XII-46) by the reaction of 1,1-dibenzoyl-



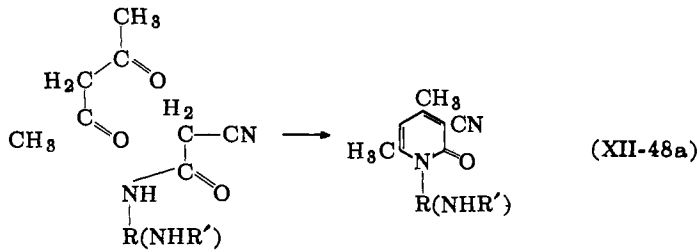
(XII-46)

ethane and cyanoacetamide. The versatility of this type of synthesis becomes further apparent in the work of Coover and Bowman (*84*). Cyanoacetamide was condensed with substituted 2,4-pentanediones (XII-47) yielding 5-substituted 4,6-dimethyl-3-cyano-2-pyridinols (XII-48, Y = CN). When XII-47 (X = $OCOCH_3$) reacted with ethyl cyanoacetate and ammonia, XII-48 (X = $OCOCH_3$, Y = $CONH_2$) was obtained. 2,4,5-Trihydroxy-6-methylnicotinonitrile was the product isolated when cyanoacetamide reacted with ethyl acetoxyacetoacetate in a sealed tube containing sodium ethoxide at 150° C.



X = Cl, $OCOCH_3$

N-Substituted cyanoacetamides and cyanoacetyl hydrazides were condensed with acetylacetone to give *N*-substituted α-pyridones (XII-48a) (*855*).



(XII-48a)

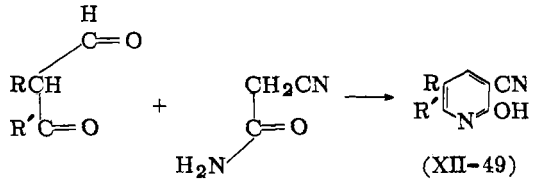
R = Ph, 4-antipyryl
R′ = Ph, phenylacetyl, tosyl, cyanoacetyl

β-Ketoaldehydes have been extensively used as starting materials, and in all instances the first attack by the carbanion is on the formyl-group carbon, while the second is on the keto-group carbon. The product is always a 2-pyridinol unsubstituted in the 4 position (XII-49, Table XII-1).

Malononitrile and malonamide can both be used instead of cyanoacetamide; the latter compound gives a 3-carboxamido derivative (*27*).

Errera (*96*) was the first to condense enol ethers of α,γ-diketones with cyanoacetamide. The reaction is initiated by displacement of the alkoxy group; consequently, the group adjacent to the carbonyl group ends up in the 6 position of the pyridinol (XII-51, Table XII-2). The original synthesis involved cyanoacetamide sodium salt and ethyl ethoxymethyleneacetoacetate (R = H, R′ = CH_3, R″ = $COOC_2H_5$), which is prepared from acetoacetic ester and methyl

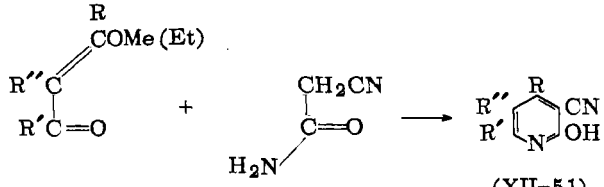
TABLE XII-1. Condensation of β-Ketoaldehydes with Cyanoacetamide



(XII-49)

R	R′	Ref.
CH_3	CH_3	52,53
H	n-C_3H_7	54,58
H	i-C_4H_9	55
CH_3	n-C_4H_9	56
H	cyclopropyl	57
H	CH_3	59
H	$C_6H_5(CH_2)_2$	53
NO_2	H	63
	$-(CH_2)_3-$	60
	$-(CH_2)_4-$	42
	$-(CH_2)_5-$	829
	$-(CH_2)_{13}-$	61

TABLE XII-2. Condensation of Enol Ethers of α,γ-Diketones with Cyanoacetamide

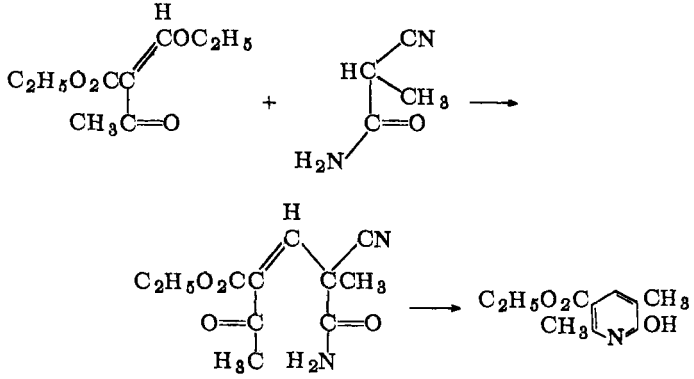


(XII-51)

R	R′	R″	Ref.
H	CH_3	$COOC_2H_3$	96
CH_3	C_6H_5	H	42
C_6H_5	C_6H_5	CH_3	42
C_6H_5	p-$CH_3C_6H_4$	H	27
CH_3	p-$CH_3C_6H_4$	H	50
p-$CH_3OC_6H_4$	C_6H_5	H	50
C_6H_5	CH_3	H	42

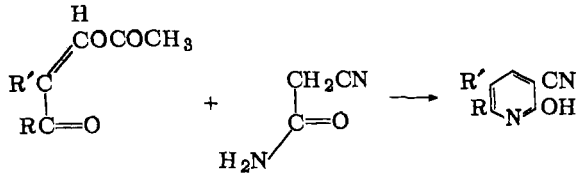
orthoformate. The unambiguous nature of the product is a distinct advantage of this reaction. Basu ran the reaction with methoxyphenylmethylene-*p*-methylacetophenone. In contrast to the mixture of isomers obtained from the parent diketone, the enol ether gave exclusively 2-hydroxy-4-phenyl-6-*p*-tolynicotinonitrile (*27*).

If α-cyanopropionamide is condensed with ethyl ethoxymethyleneacetoacetate, an acyclic intermediate is isolated which cyclizes in refluxing hydrochloric acid with concomitant hydrolysis and decarboxylation of the cyano group as shown (XII-52).



(XII-52)

Similarly, enol acetates have been condensed with cyanoacetamide, according to the general equation XII-53, also to give only one isomer (*62*). *Cf.* Chapter II, pp. 374 f. and 414 f.

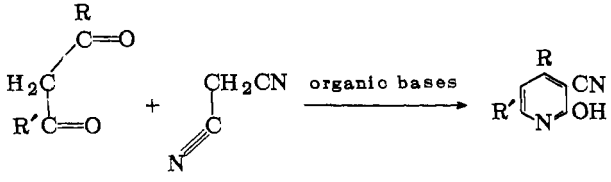


(XII-53)

R	R′
H	C_6H_5
H	*p*-$CH_3C_6H_4$

Ethyl cyanoacetate and ammonia can replace cyanoacetamide, resulting in 3-cyano-2-pyridinols (*64*). If ammonia is not used, the

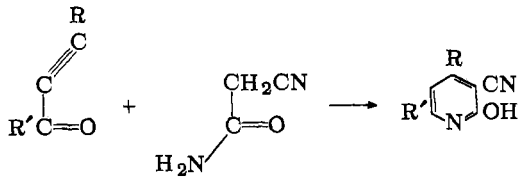
nitrogen of the cyano group enters the ring and the pyridinol produced has a carbethoxy group in the 3 position rather than a cyano group. The condensation of ethyl cyanoacetate and acetylacetone gives ethyl 2-hydroxy-4,6-dimethylnicotinate (*65,66*). Malononitrile has also been utilized in condensations with β-diketones (XII-54).



(XII-54)

R	R′	Ref.
CH_3	CH_3	27
CH_3	C_6H_5	27
CH_3	CH_3 or $ROCH_2$	29

Maintaining the same order of unsaturation as in β-diketones, Barat (*67*) used a series of acetylenic ketones in condensations with cyanoacetamide (XII-55). Whereas the yields from the diaryl ketones

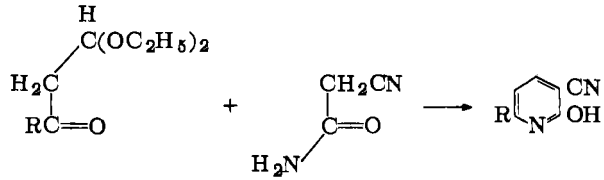


(XII-55)

R	R′
C_6H_5	C_6H_5
	CH_3
	C_2H_5
	p-$CH_3C_6H_4$
	p-$NO_2C_6H_4$

were good, those from the aryl alkyl ketones were poor. This reaction undoubtedly proceeds via a Michael-type condensation on the β-carbon (*cf.* Chapter II, pp. 445 and 460).

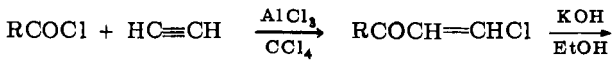
Another modification of the β-diketone synthesis utilizes keto-acetals (XII-56) as starting materials (*68*); these are elegantly pre-



(XII-56)

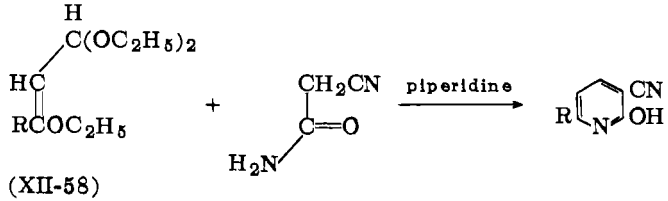
$$R = CH_3,\ n\text{-}C_3H_7,\ i\text{-}C_3H_7,\ n\text{-}C_5H_{11}$$

pared as shown in XII-57. β-Ethoxyacrolein diethylacetal (XII-58, R = H) (a functional derivative of malomaldehyde) and β-ethoxy-



(XII-57)

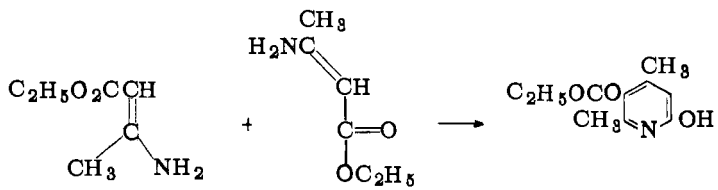
crotonaldehyde diethylacetal (XII-58, R = CH_3) also serve as satisfactory starting materials (*69*).



(XII-58)

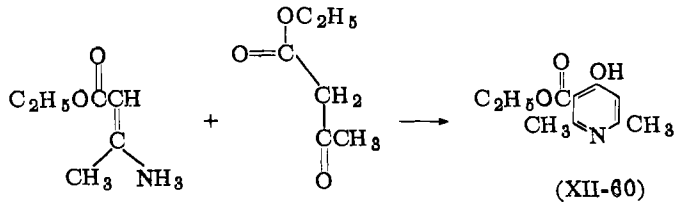
e. β-Iminocarbonyl Compounds

Another very useful variation dates back to the early work of Collie and Knoevenagel, who utilized β-iminoesters and β-iminoketones. Collie (*70,71*) in 1884 self-condensed the hydrochloride of ethyl iminoacetate (ethyl β-aminocrotonate, XII-59) to obtain ethyl



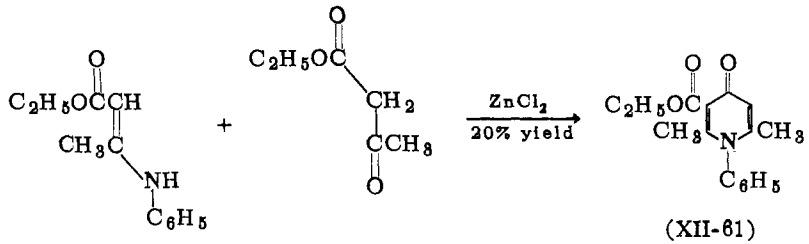
(XII-59)

6-hydroxy-2,4-dimethylnicotinate. This compound can also be prepared from XII-59 and ethyl acetoacetate in the presence of stannous chloride. However, if the amino group reacts with the keto rather than the ester group, the isomeric ethyl 4-hydroxy-2,6-dimethylnicotinate (XII-60) can form. This latter course is taken in the



(XII-60)

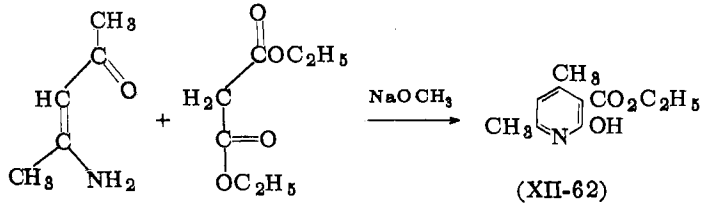
presence of phosphorus oxychloride, resulting in the formation of the 4-chloro analog of XII-60 (*72,73*). *Cf.* Chapter II, pp. 387 f. and 429. Similarly, ethyl β-anilinocrotonate condenses with ethyl acetoacetate to give ethyl 1,4-dihydro-2,6-dimethyl-1-phenylnicotinate (XII-61) (*76*). (It is noteworthy that if XII-59 reacts with a β-di-



(XII-61)

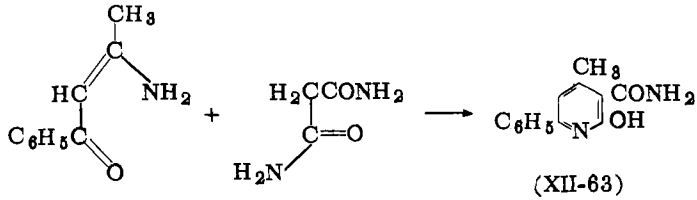
ketone, *e.g.*, formylacetophenone, rather than a β-ketoester, the oxidative state is insufficient, and a pyridine derivative, ethyl 2-methyl-6-phenylnicotinate, devoid of a nuclear oxygen function, is obtained (*75*).)

Knoevenagel and Cremer (*74*) condensed acetylacetonimine and ethyl malonate in the presence of sodium methoxide to give a 65% yield of ethyl 2-hydroxy-4,6-dimethylnicotinate (XII-62). Other



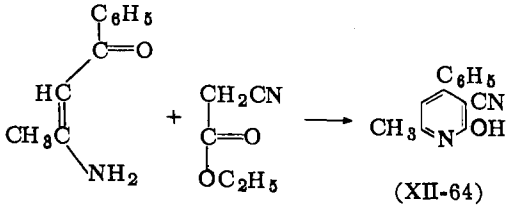
(XII-62)

derivatives of malonic acid can be used instead of the ester, *e.g.*, malonamide, cyanoacetic ester, and cyanoacetamide. Basu (*81*) condensed benzoylacetoneamine with malonamide and obtained almost exclusively 2-hydroxy-4-methyl-6-phenylnicotinamide (XII-63) re-



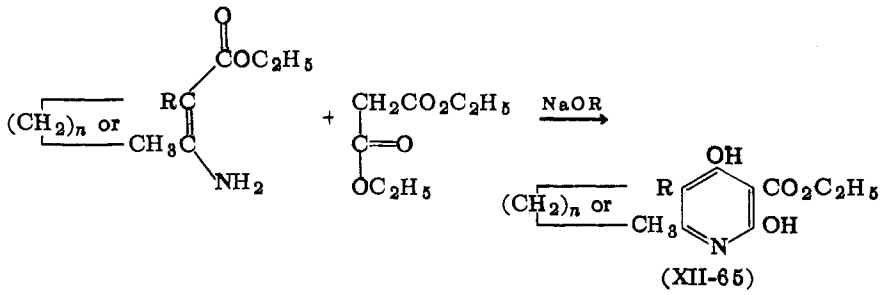
(XII-63)

sulting from a 1,4 addition. The same compound condensed with ethyl cyanoacetate in a 1,2 addition to give 2-hydroxy-6-methyl-4-phenylnicotinonitrile (XII-64). *Cf.* Chapter II, pp. 419 f.



(XII-64)

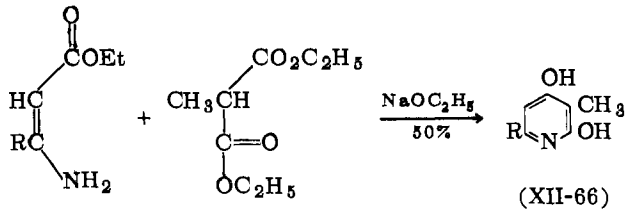
Whereas malonic ester and derivatives with β-iminoketones give 2-pyridinols, β-iminoesters lead to the higher oxidation stage 2,4-pyridinediols. The ring closure between ethyl malonate and ethyl β-aminocrotonate gives, in the presence of sodium ethoxide (*35*) or, with better yields, of sodium *n*-amylate (*77*), ethyl 2,4-dihydroxy-6-methylnicotinate (XII-65, R = H). This synthesis has been adapted



(XII-65)

n = 5 (*79*); 13 (*80*)
R = CH_3, C_2H_5 (*40*)

by Prelog and co-workers to prepare several 5,6-cycloalkeno-2,4-pyridinediols in about 40% yield. Alkyl-substituted malonic esters were condensed with β-iminoesters to yield 3,6-dialkyl-2,4-pyridinediols (XII-66) (*78,854*). Aromatization, in this instance, requires loss of a

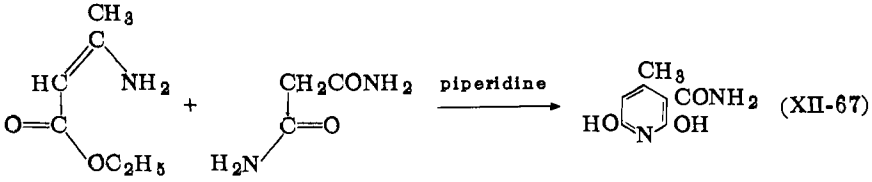


(XII-66)

R = CH_3, C_2H_5

carbethoxy group from the malonate moiety of the intermediate condensation product (*cf.* Chapter II, p. 426).

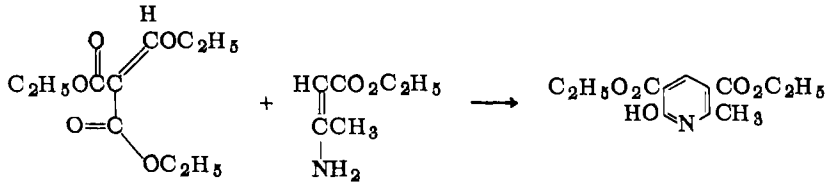
With malonamide in place of ethyl malonate, the course of the reaction is altered to give a 2,6-pyridinediol (XII-67) instead of the



(XII-67)

2,4 isomer (*81*). Whereas the ethyl malonate carbanion attacks the carbethoxy group, the malonamide carbanion probably joins by 1,4 addition, accounting for the formation of the 2,6-diol. This result is another indication that the nature of the carbanion determines whether the addition is the 1,2 aldol type or the 1,4 Michael type.

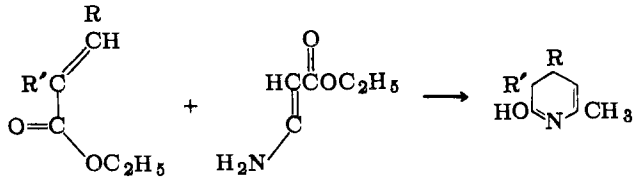
Ethyl ethoxymethylenemalonate (XII-68) reacts with ethyl aminocrotonate to yield diethyl 2-hydroxy-6-methyl-3,5-pyridine-



(XII-68)

dicarboxylate (*82*). Since XII-68 reacts as a β-ketoester derivative, the combined oxidation states are sufficient to give a pyridinol, but not a diol, which would be formed if it reacted as a β-dicarbalkoxy compound (*cf.* Chapter II, pp. 385 and 425).

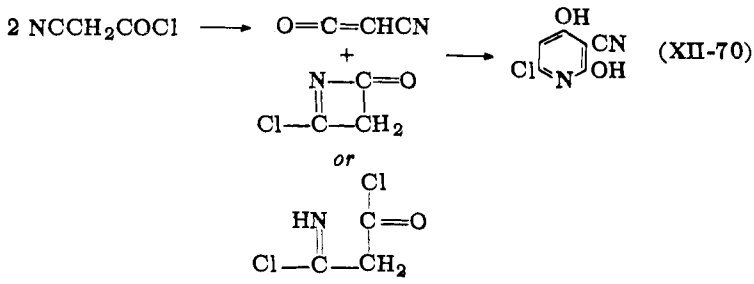
When an α,β-unsaturated ester, *i.e.*, ethyl ethylidenemalonate (XII-69, R = CH_3, R′ = $COOC_2H_5$), is condensed with ethyl amino-



(XII-69)

R = CH_3 (*35*); C_6H_5 (*83*)
R′ = $COOC_2H_5$

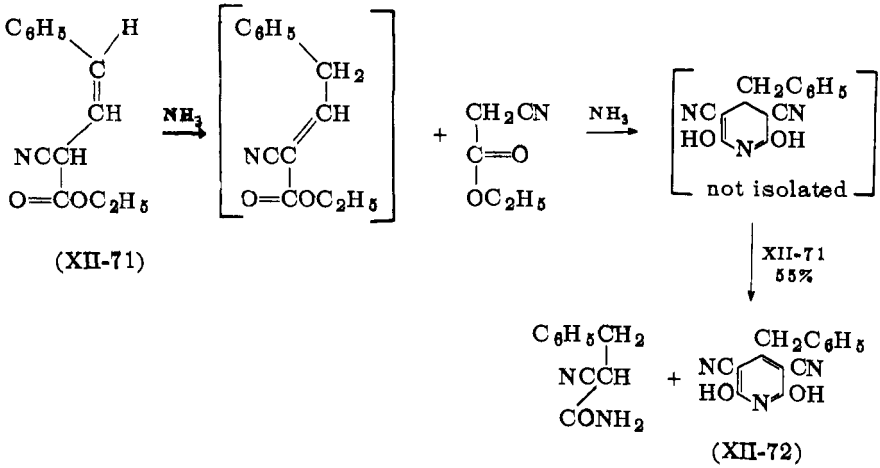
crotonate, the product is a dihydro-2-pyridinol. Cyanoacetyl chloride itself undergoes gradual dimerization at room temperature, and violent reaction when distilled (*159*). From the thick resinous residue, 6-chloro-2,4-dihydroxynicotinonitrile was isolated (XII-70).



(XII-70)

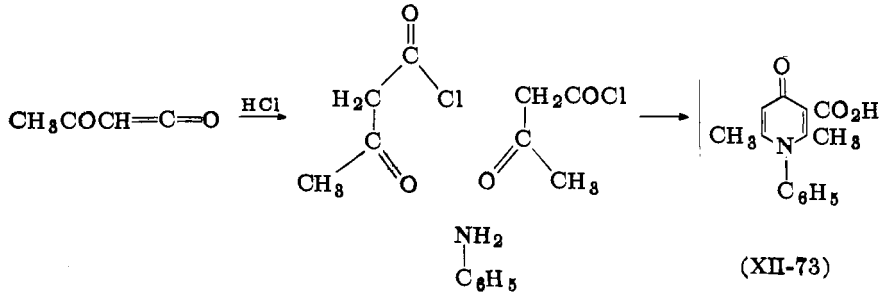
In a later paper, Schroeter (*160*) proposed a mechanism which requires the formation of cyanoketene and malonimide chloride. The former intermediate results from loss of hydrogen chloride, and the latter from the addition of hydrogen chloride to the nitrile group.

An interesting reaction was reported by Linstead and Williams (*112*) in which ethyl α-cyanostyrylacetate (XII-71) reacted with ethyl cyanoacetate and ammonia at 0° C. to give two compounds: 4-benzyl-2,6-dihydroxy-3,5-pyridinedicarbonitrile (XII-72) and 2-cyano-4-phenylbutyramide. To account for the formation of XII-72, it is



necessary to postulate that the double bond of XII-71 undergoes isomerization to the α,β position. The new isomer cyclizes with the other reactants to give a dihydro intermediate which is not isolated, but undergoes an oxidation-reduction with either XII-71 or its α,β isomer (*cf.* Chapter II, pp. 468 f.).

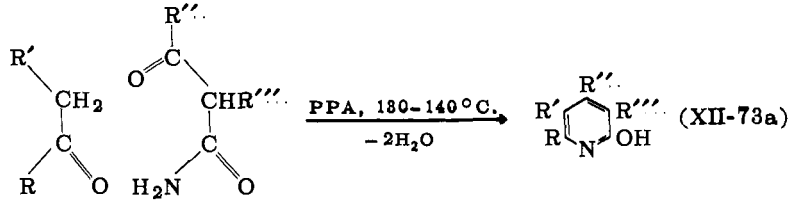
Acetoacetyl chloride, prepared from acetylketene and hydrogen chloride at temperatures below –20° C., reacts with aniline at room temperature to yield 1,4-dihydro-2,6-dimethyl-4-oxo-1-phenylnicotinic acid (XII-73) (*99*).



f. β-Ketoamides and Ketones

A new example of cyclization leading to 2-pyridinols was reported by Hauser and Eby (*824*) in 1957. β-Ketoamides were condensed

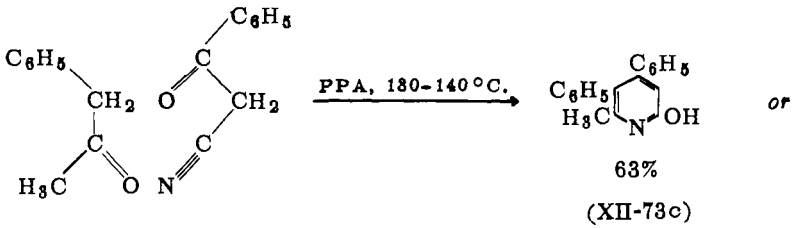
with ketones in the presence of polyphosphoric acid (PPA), as formulated in XII-73a. The method is the best one known for the syn-

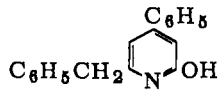


thesis of highly substituted 2-pyridinols. Since β-ketonitriles are hydrated to the corresponding amides by polyphosphoric acid, the amides were used directly in the ring closure. The yields of 2-pyridinols are, however, 5–10% higher with the β-ketonitriles than with the β-ketoamides, which indicates that the nitrile condenses directly without being first converted to the ketoamide. The β-ketonitriles are obtained by a mixed Claisen-type condensation of an ester and a nitrile, using sodamide as the basic catalyst (XII-73b).

$$RCOOCH_3 + R'CH_2CN \xrightarrow{NaNH_2} RCOCHR'CN \qquad \text{(XII-73b)}$$

In the condensation of phenylacetone and benzoylacetonitrile, two isomeric products can be formed. On mechanistic grounds, it is expected that the trisubstituted pyridinol (XII-73c) is more likely,

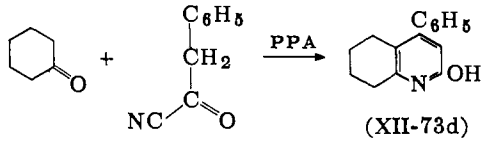




since the phenyl group has an acidifying effect, making the methylene hydrogens of the ketone more reactive than the methyl hydrogens. On this basis, and by analogy with acid-catalyzed condensations

with phenylacetonitrile, structure XII-73c was assigned. However, if the ketone is not symmetrical and R′ in XII-73a is an alkyl group, a mixture of products might be obtained. Table XII-3 lists the cyclizations which were carried out.

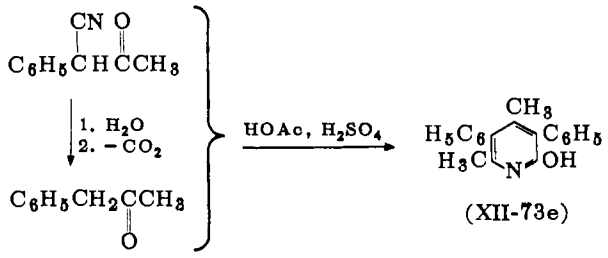
A modification which utilized cyclohexanone as the ketone affords a tetrahydroquinolinol (XII-73d), which can be dehydrogenated to



(XII-73d)

give 4-phenyl-2-quinolinol. Attempts to extend the reaction to esters and aldehydes were unsuccessful.

In the same year, Wajon and Arens (*831*) isolated 4,6-dimethyl-3,5-diphenyl-2-pyridinol (XII-73e) from an acid-catalyzed dimeric



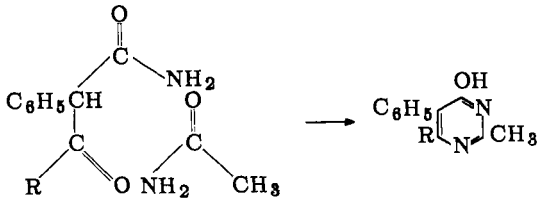
(XII-73e)

condensation of α-acetylbenzyl cyanide. They rationalized the reaction sequence as being hydrolysis of the α-cyanoketone, decarboxylation of the resulting β-ketoacid, and then condensation of the product, benzyl methyl ketone, with the original substrate to give the 2-pyridinol as shown. The isolation of XII-73b from the reaction of preformed benzyl methyl ketone with either the original nitrile or its corresponding amide established the plausibility of this suggested reaction sequence. The reaction was extended to other α-acyl and α-aroyl benzyl cyanides, $C_6H_5CH(CN)COR$. α-Propionylbenzyl cyanide ($R = C_2H_5$) and α-phenylacetylbenzyl cyanide ($R = CH_2C_6H_5$) appeared to give pyrimidinols as products. The authors suggested (*832*) that the pyrimidinols arise from a condensation of a β-keto-

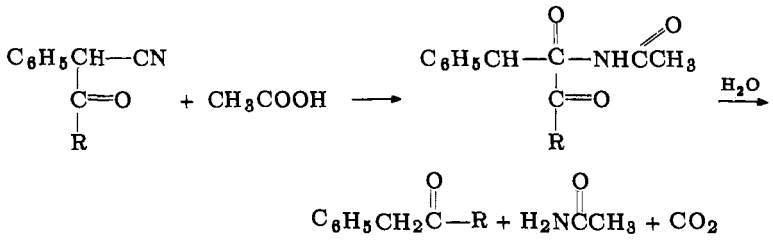
TABLE XII-3. Cyclization of β-Ketonitriles with Ketones by PPA

β-Ketonitrile	Ketone	2-Pyridinol	Yield, %
Benzoylacetonitrile	acetone	4-phenyl-6-methyl	68
α-Acetyl-α-toluonitrile	acetone	3-phenyl-4, 6-dimethyl	29
α-Benzoylpropionitrile	acetone	3,6-dimethyl-4-phenyl	43
Benzoylacetonitrile	phenylacetone	4,5-diphenyl-6-methyl	63
α-Acetyl-α-toluonitrile	phenylacetone	3,5-diphenyl-4,6-dimethyl	58
α-Benzoylpropionitrile	phenylacetone	4,5-diphenyl-3,6-dimethyl	60
α-Nicotincylpropionitrile	phenylacetone	3,6-dimethyl-4-(3-pyridyl)-5-phenyl	34
Benzoylacetonirile	acetophenone	4,6-diphenyl	5

amide (partial hydrolysis of the nitrile) and acetamide (XII-73f). The acetamide is formed by the sequence shown in XII-73g. α-Formylbenzyl cyanide gave no well-defined reaction product.

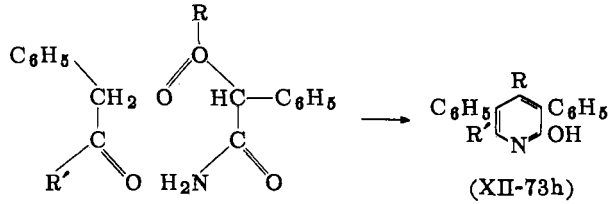


(XII-73f)



(XII-73g)

Several benzyl ketones and α-acylbenzyl cyanides were condensed to give tetrasubstituted 2-pyridinols (XII-73h). In almost every case,



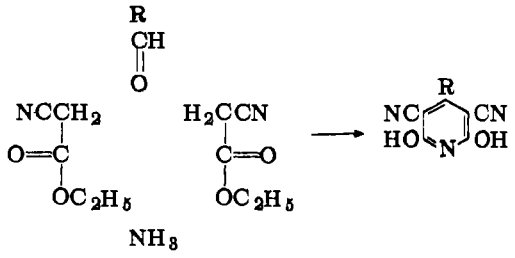
(XII-73h)

as expected, the benzyl methylene group, rather than the R′ methylene group, entered the condensation. One exception was the condensation of α-propionylbenzyl cyanide (R = C_2H_5) and benzyl ethyl ketone (R′ = C_2H_5). Two products were obtained; one was the expected product XII-73h (R = R′ = C_2H_5). The other product, 3-phenyl-4-ethyl-5-methyl-6-benzyl-2-pyridinol, arose from participation in the condensation of the ethyl methylene group.

g. Reactions of Three Molecules of Acyclic Compounds; Hantzsch-Type Syntheses

Several syntheses of pyridinols involve the condensation of three organic molecules. Probably the most important illustration of

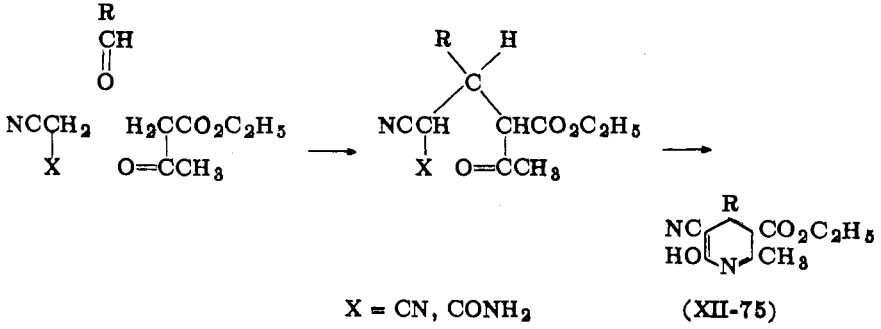
such a reaction is a contribution of Guareschi, a modification of the Hantzsch synthesis (*cf.* Chapter I, p. 503). One mole of aldehyde and two moles of ethyl cyanoacetate in the presence of ammonia yield a 3,5-dicyano-4-alkyl(or aryl)-2,6-pyridinediol (XII-74) (*873*). When



(XII-74)

R = CH_3 (*36,85*), $(CH_3)_2CH$ (*85*), $(CH_3)_2CHCH_2$ (*89*)

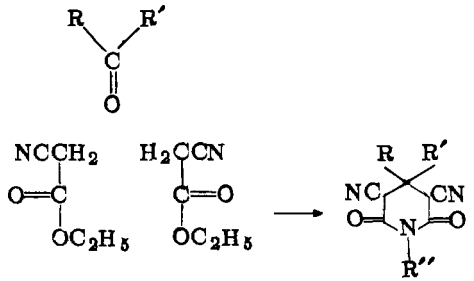
the reaction is run with a trace of alkali hydroxide, 90% yields of open-chain cyanoamides, $RCH(\overset{CN}{\overset{|}{C}}H{-}CONH_2)_2$, are isolated (*88*). When aldehydes are simultaneously condensed with ethyl acetoacetate and cyanoacetamide or malononitrile, in the presence of a secondary amine, an acyclic adduct is obtained, which is readily cyclized by mineral acids to a dihydro-2-pyridinol derivative (XII-75) in al-



X = CN, $CONH_2$ (XII-75)

most quantitative yield (*90*). The same product (XII-75) can also be obtained by substituting ethyl cyanoacetate and ammonia for cyanoacetamide or malononitrile (*86*). When R = phenyl, XII-75 can also be synthesized by the use of ethyl benzylideneacetoacetate in place of benzaldehyde and acetoacetic ester (*82*). *Cf.* Chapter II, pp. 503 ff. and 528 ff.

Guareschi reacted ketones with ethyl cyanoacetate in the presence of ammonia or amines and obtained 4,4-dialkyl-3,5-dicyano-2,6-diketopiperidines (XII-76) (*91,92*). In some instances where R″= H,



(XII-76)

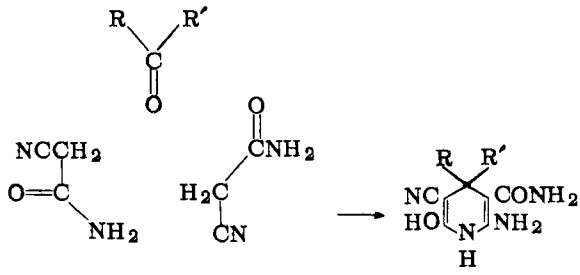
R, R′	R″
alkyl	H
aryl	CH_3
alkaryl	etc.

solutions of XII-76, made basic with ammonia or magnesium hydroxide, aromatize by losing a hydrocarbon. The following table summarizes the results reported for the aromatization of XII-76.

R	R′	Hydrocarbon lost
CH_3	C_2H_5	ethane
CH_3	C_3H_7	propane
CH_3	C_4H_9	butane
CH_3	C_9H_{19}	nonane
C_2H_5	C_3H_7	mixture of ethane and propane
CH_3	$C_6H_5CH_2CH_3$	ethylbenzene

Obviously, there is a consistency in the loss of the bulkier group. Sterically hindered ketones (*e.g.*, R = $C_6H_5CH_2$, R′ = $(CH_3)_2CHCH_2$) fail to condense to form the piperidinedione.

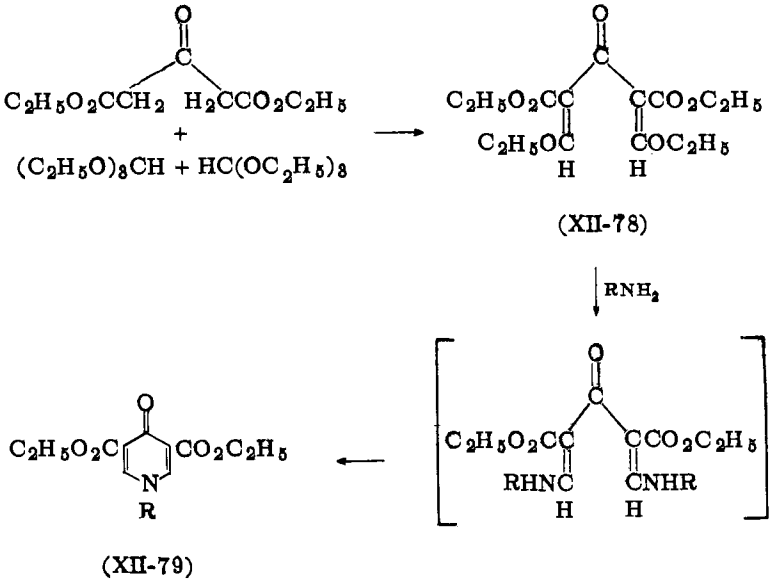
Thorpe and co-workers (*94,95,88*) effected the condensation of ketones with cyanoacetamide, and obtained mixtures of diketopiperidines. What might be called a head-to-head condensation of the two cyanoacetamide molecules gives the Guareschi product (XII-76), while a head-to-tail condensation (XII-77) leads to a hydroxyamino-



(XII-77)

dihydropyridine derivative. Ketones give much less acyclic by-product in this reaction than do aldehydes.

Errera (*96*) made another valuable addition to the field of pyridinol synthesis by showing that when ethyl acetonedicarboxylate is refluxed with two moles of ethyl orthoformate in acetic anhydride, the diethoxymethylene derivative (XII-78) can be isolated; this ring closes with ammonia to give a 3,5-dicarbethoxy-4-pyridone (XII-79). This reaction is similar to another one of Errera's (*96*) in which the starting materials are the same but only one mole of ethyl orthoformate is used. Thus a monoethoxymethylene derivative of

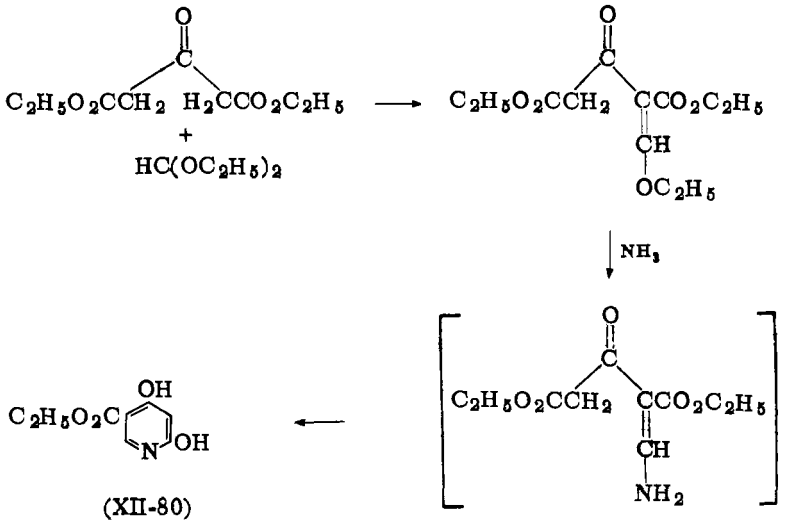


(XII-78)

(XII-79)

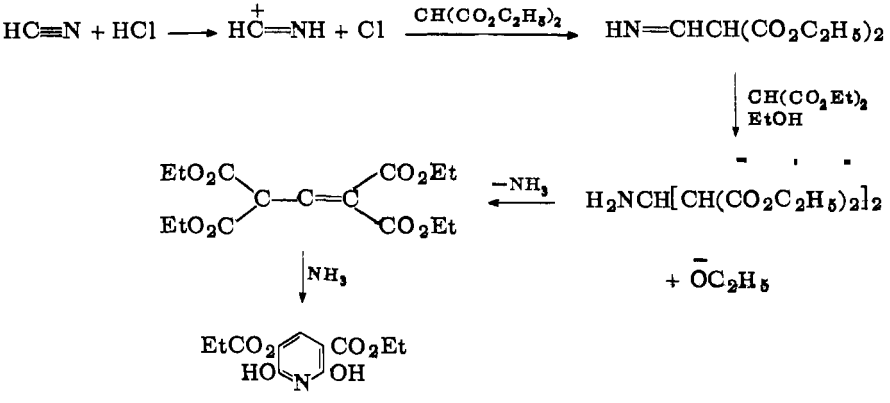
R = H (*96*), *m*-ClC_6H_4 (*97*)

ethyl acetonedicarboxylate is formed, which, on reaction with ammonia, gives most probably the β-aminocrotonate. This then undergoes cyclization to yield ethyl 4,6-dihydroxynicotinate (XII-80). *Cf.* Chapter II, pp. 349 and 473 f.



(XII-80)

An interesting synthesis of ethyl 2,6-dihydroxy-3,5-pyridinedicarboxylate (XII-82) is the reaction of sodium diethylmalonate and a mixture of hydrogen cyanide and hydrogen chloride (*98*). A possible mechanism in terms of modern theory involving the formation of a glutaconic acid derivative is given (XII-81).

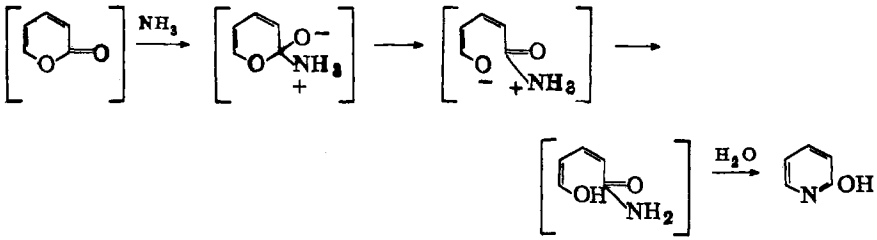


(XII-82) (XII-81)

2. From Other Ring Compounds

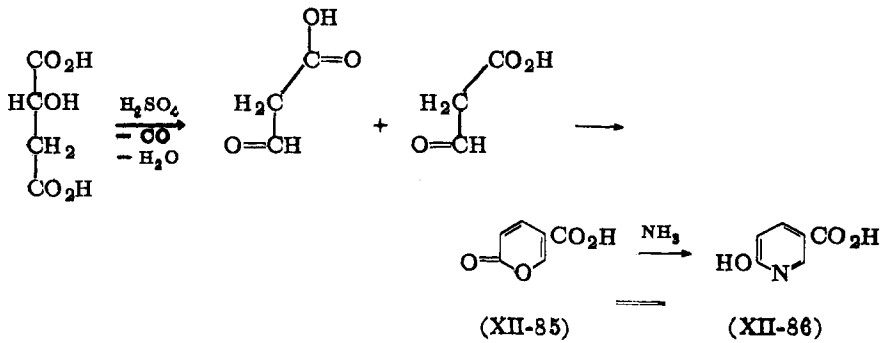
a. α- and γ-Pyrones

One of the oldest and commonest ring conversions involves the ammonolysis and aminolysis of α- and γ-pyrones. α-Pyrone, which is actually an unsaturated lactone, should react with ammonia to give 2-pyridinol, which, in turn, is actually an unsaturated lactam. Ammonia, a nucleophilic agent, bonds with the electrophilic carbon of the carbonyl group to give an intermediate that undergoes ring opening. A double exchange of protons with the solvent gives a δ-hydroxyamide (aldehydoglutaconamide) (XII-83), which dehydrates to the product (XII-84). *Cf.* Chapter II, pp. 177 ff.



(XII-83) (XII-84)

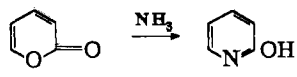
In 1884, von Pechmann and Welsh (103) warmed an ammoniacal solution of coumalic acid (XII-85) and obtained 6-hydroxynicotinic acid (XII-86). Coumalic acid has been prepared by cyclization of formylacetic acid (from heating malic acid with sulfuric acid). The ester of XII-85 also reacts with ammonia to give XII-86 (*104*). This reaction has been utilized to prepare N^{15}-2-pyridinol by the use of



(XII-85) (XII-86)

$N^{15}H_3$ (*105*). Other pyrones which have undergone this reaction are listed in Table XII-4. The conditions for ammonolysis vary considerably. Compounds XII-88 and XII-89, which have an alkyl substituent in the 6 position, react with difficulty. Kohler (*107*) reported obtaining ammonium salts of amines of unknown constitution when XII-88 (R = R′ = C_6H_5) was heated with aqueous ammonia. When heated with concentrated alcoholic ammonia, the pyrone passes slowly but completely into a mixture of the corresponding pyridinol ester and the decarboxylated pyridinol. At room temperature, concentrated aqueous ammonia acts very slowly, but after several months, a quantitative yield of the decarboxylated product, 4,6-diphenyl-2-pyridinol, was obtained. A refluxing mixture of ammonium acetate in acetic acid served for the conversion of XII-91 to the corresponding pyridinol.

TABLE XII-4. Conversion of α-Pyrones to 2-Pyridinols

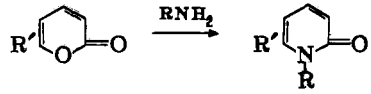


(XII-87)

Formula number	Substituent and position				Ref.
	3	4	5	6	
XII-87a		CH_3	$CO_2C_2H_5$	CH_3	106
		C_6H_5	$CO_2C_2H_5$	C_6H_5	113
		CH_3	$CO_2C_2H_5$	C_6H_5	113
		CH_3		CH_3	106
XII-88[a]	$CO_2C_2H_5$	C_6H_5		C_6H_5	107
	CO_2CH_3	$C_6H_5CH_2$		*p*-ClC_6H_4	109
XII-89	$CO_2C_2H_5$	*i*-C_3H_7		CH_3	389
XII-90	$CO_2C_2H_5$		$CO_2C_2H_5$	$CH_2CO_2C_2H_5$	108
				CO_2H	110
XII-91			CH_3	CO_2H	110
		$C_6H_5CH_2$		C_6H_5	389
		i-C_3H_7		C_6H_5	389
	CO_2H	C_2H_5	CH_3	C_6H_5	389
			C_6H_5CO		403
			p-$CH_3C_6H_4CO$		403
			p-$C_2H_5C_6H_4CO$		403
			p-BrC_6H_4CO		403
			p-ClC_6H_4CO		403
				C_6H_5	115

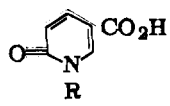
[a]In the course of the reaction, the carbethoxy group was lost.

Amines can replace ammonia to give a variety of *N*-substituted 2-pyridones (XII-92). Thus, XII-90 was reacted with amines (RNH_2),

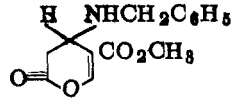


(XII-92)

when R = CH_3, C_2H_5, CH_2CH_2OH, $CH_2CH_2COOC_2H_5$ (*108*). 6-Phenyl-α-pyrone reacts with ammonia to give 6-phenyl-2-pyridinol (XII-92, R = H, R′ = C_6H_5) and with aniline to give 1,6-diphenyl-2(1*H*)-pyridone (R = R′ = C_6H_5) (*115*). R. H. Wiley and co-workers, in a series of recent papers, reported on the reaction of XII-87a (see Table XII-4) with amines. Benzylamine, *p*-methoxybenzylamine, β-phenylethylamine, β-(3,4-dimethoxyphenyl)ethylamine, and benzedrine all failed to react under a variety of conditions, or else formed a bis-urea, RNHCONHR, in yields up to 93% when the reactants were heated together at 200° C. (*116*). This is in contrast to the yields of 14–81% of 1-substituted 5-carboxy-2-pyridones (XII-93) formed from methyl coumalate (XII-85) and these amines (*117*). Benzylamine first gives an isolable addition product, to which is assigned the structure XII-94. This adduct is converted by alkali in



(XII-93)

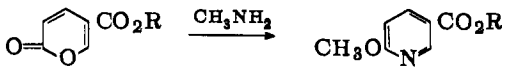


(XII-94)

20% yield to XII-93 (R = $C_6H_5CH_2$). It is the only instance in which an addition product is isolated. The reaction is generally carried out by adding one mole of the pyrone to three moles of the amine in methanol solution, and, after eight days at room temperature, refluxing the mixture with aqueous sodium hydroxide. In the case of benzylamine, XII-94 precipitates out after only 1.5 hours, in 56% yield. This adduct is converted in refluxing base to XII-93 in only 20% yield. It is possible that all the amines form soluble adducts of this type, and that a second mole of amine then adds to the

carbonyl carbon. Ring conversion then takes place, and aromatization is effected by base-catalyzed elimination of the first mole of amine. The requirement of an extra mole of amine would explain the low yield of 20% of the pyridone obtained on alkaline treatment of XII-94, where a 1:1 molar ratio of reactants exists. The authors attributed the resistance of XII-87a to ring conversion (as compared to ease of conversion of XII-85) to the distribution of the necessary electron deficiency of the ring carbonyl carbon to the two methyl groups through hyperconjugation (*118*).

An unexpected reaction occurs between coumalic acid (XII-95) (*103*) or its ethyl ester (*119*) and methylamine in alcohol at 0° C.



(XII-95)

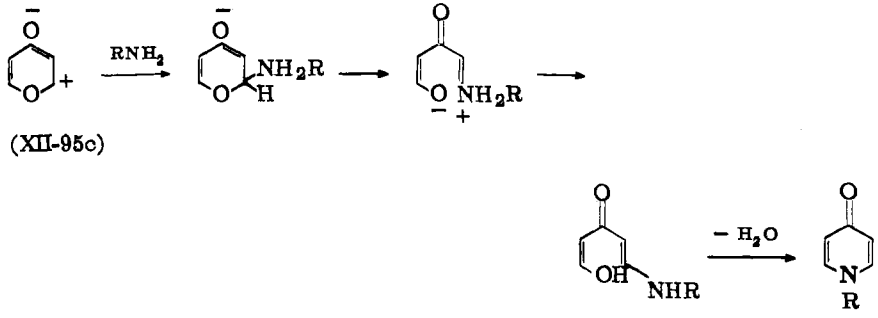
R = H, CH_3

Instead of the expected 1-methyl-2-pyridone derivative, 6-methoxynicotinic acid or its ester was obtained.

Even more versatile than the α-pyrones are the γ-pyrones, which can be considered as vinylogs of lactones. Considering the resonance structures of γ-pyrone itself (XII-95a–d), it is obvious that am-

(XII-95a) (XII-95b) (XII-95c) (XII-95d)

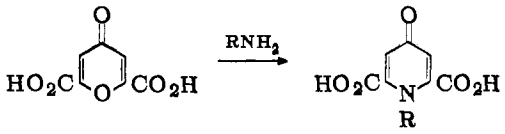
monia or amines can attack the nucleus at either of the α positions, initiating a series of changes, leading to 4-pyridinol, or a 1-substituted 4-pyridone. Whereas many of the α-pyrones react with ammonia at room temperature and below, the γ-pyrones require temperatures as high as 140° C. Carbethoxy groups in the α position render the nucleus more reactive. The reaction may be conducted in aqueous (*93,121*) or alcoholic (*132*) solution. Many γ-pyrones have been used; only a few of the more important ones are cited



(XII-95c)

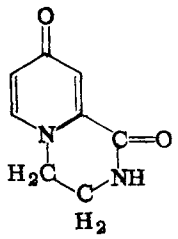
R = H, alkyl, aryl

here. Chelidonic acid (XII-96) can be heated with concentrated ammonia to give chelidamic acid (XII-97, R = H) (*120*), with



(XII-96) (XII-97)

methylamine (*121,122*) to give the *N*-methyl derivative in 90% yield, with aniline (*121*), *p*-substituted anilines (*123*), aralkylamines (77–84% yields) (*124*), nitroanilines (*129*) and amino acids (*127*). The ester of XII-96 reacts with iodo-, hydroxy-, and aminoanilines in acetic acid (32–85% yields) (*125,126*) to give a variety of *N*-substituted chelidamic acids (XII-97). When the ethylenediamine salt of XII-96 is treated with dilute hydrochloric acid in refluxing ethanol, the lactam of *N*-(β-aminoethyl)chelidamic acid (XII-98)



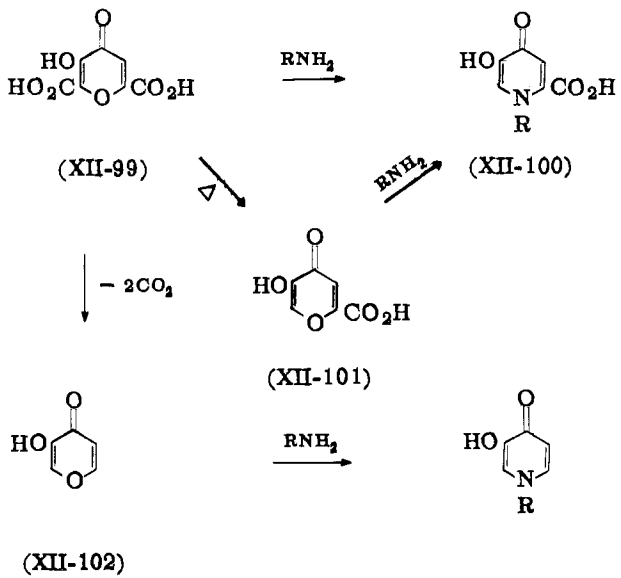
(XII-98)

precipitates instead of the expected 1,1′-ethylenebis(2,6-dicarboxy-4(1*H*)-pyridone) (*128*).

With *p*-phenylenediamine and the ethyl ester of chelidonic acid, the expected bis compound is obtained in 7.8% yield (*126*).

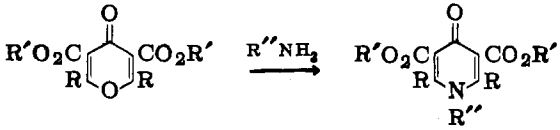
γ-Pyrone itself reacts with aniline (*130*), *p*-substituted anilines (*862*) (yields of 75–92%), aralkylamines (*124*) (yields of 31–42%), 1-amino-2-diethylaminoethane (*131*), β-aminopropionic acid (81% yield), and ethyl β-aminopropionate (10% yield) (*139*). The higher yields given by chelidonic acid with the aralkylamines emphasize the enhanced activation imparted by the two carboxyl groups.

Meconic acid (XII-99) is a valuable starting material. It can be treated with concentrated ammonia (*134,141*), alkylamines (R = CH_3, C_2H_5, *i*-C_3H_7) (15–40% yields) (*135,136*), and glycine (47% yield) (*136*) to give the corresponding *N*-substituted comenamic acids (XII-100), one carboxyl group being lost. Decarboxylation can be effected first, by heating meconic acid in dilute hydrochloric acid (*133*) to give comenic acid (XII-101), which can be aminated in 61% yield (*140*). Complete decarboxylation of XII-99 gives pyromeconic acid (XII-102), which reacts with methyl- (*137*), ethyl-, propyl-, and *i*-propylamines (*136*), as well as with 2-aminoethyl acetal



(*138*), to give the corresponding *N*-substituted-3-hydroxy-4-pyridones. Pyridones could not be obtained from *n*-butylamine, α(or β)-phenylethylamine, or α,β-diaminopropionic acid with XII-99, XII-102, or the XII-102 methyl ether. To show further the inconsistency of the reaction, XII-99 gives a pyridone with glycine, but XII-102 does not (*136*).

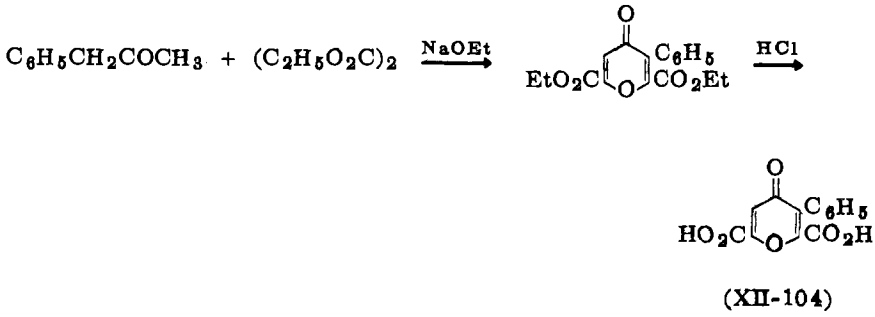
Diethyl 2,6-disubstituted 4-pyrone-3,5-dicarboxylate (XII-103, R = CH_3, C_2H_5; R′ = C_2H_5) reacts with a series of arylamines (*126*) and XII-103 (R = styryl, R′ = H) reacts with ammonia (95% yield)



(XII-103)

(*142*). The yields are higher than those given by chelidonic acid (XII-96), indicating that a carboxy or carbalkoxy group α to the carbonyl is more highly activating than when β to it. The difference in the reactivity of the two pyrones was conspicuous in the reaction with *p*-phenylenediamine. Compound XII-103 gave the bis-substituted 4-pyridone in 78% yield, whereas chelidonic acid (XII-96) gave only an 8% yield.

3-Phenylchelidonic acid (XII-104), prepared as shown, has been aminated with ammonia, alkylamines (*143*), arylamines (*144*), and various sulfanilamide derivatives (*145*).



(XII-104)

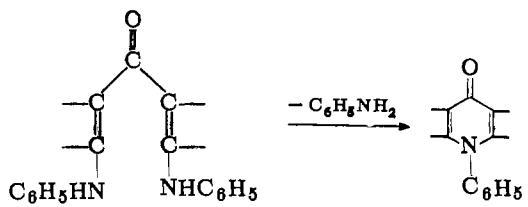
Various other substituted γ-pyrones which react successfully with ammonia and amines are listed in Table XII-5 (p. 556).

TABLE XII-5. Conversion of γ Pyrones to 4-Pyridinols

γ-Pyrone	Base	Ref.
2,6-Dimethyl	amines	150
2,6-Dimethyl	ammonia	132
2,6-Diethyl	ammonia	146
2,6-Dipropyl	ammonia	146
3,5-Diphenyl	ammonia	147
2-Phenyl	ammonia	148
5-Methoxy-2-methyl	ammonia	149
2-Carboxyl	ammonia	149
2,6-Dimethyl	methylamine	844
2,6-Dimethyl	ethylamine	844
2,6-Diphenyl	methylamine	844
2,6-Diphenyl	ethylamine	844
2,Phenyl-6-*p*-methoxyphenyl	methylamine	844
2-Phenyl-6-*p*-methoxyphenyl	ethylamine	844

It is noteworthy that 2,6-di-*p*-methoxyphenyl-4-pyrone does not undergo the typical aminolysis reaction (*844*). This nonreactivity is attributable to the electron-donating influence of the *p*-methoxy group, which dissipates the positive charge (XII-95c) at C_2. This finding substantiates the suggested mechanism.

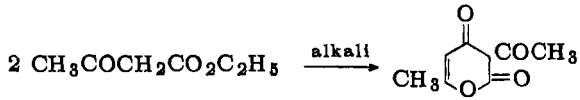
In the reaction with aniline, both γ-pyrone itself (*130*) and XII-103 (R = CH_3, R′ = C_2H_5) (*126*) gave isolable dianilinoketones (XII-105) which readily cyclized to the expected pyridones. It should be



(XII-105)

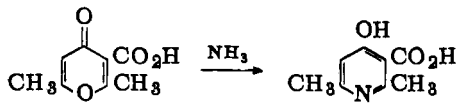
emphasized that XII-105 need not be an intermediate in pyridone formation, but may be a by-product.

Pyrones with carbonyl groups in both the α and γ positions are also useful starting materials. The most important one from a practical and historical point of view is dehydroacetic acid (XII-106), prepared by the self-condensation of acetoacetic ester in the presence



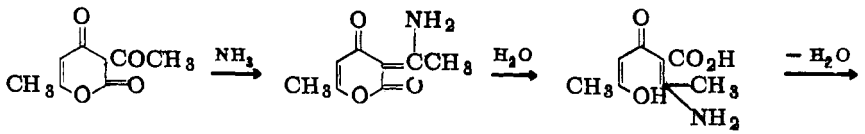
(XII-106)

of small amounts of alkali (*150*). It was first prepared in 1866, and controversy concerning its structure flourished until 1924, when Rassweiler and Adams finally proved it convincingly (*151*). Originally the structure proposed for it was XII-107, mainly because of the formation of lutidonecarboxylic acid (XII-108) by the action of am-

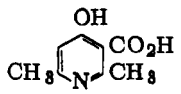


(XII-107) (XII-108)

monia (*152,153*). The weak acidity of dehydroacetic acid was not in accord with structure XII-107. Feist (*154*) proposed structure XII-106, explaining the formation of XII-108 by the mechanism shown (XII-109). An alternative structure (XII-110) was proposed by



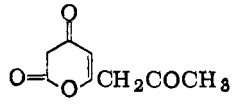
(XII-106)



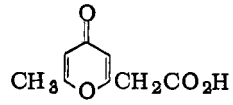
(XII-109)

(XII-108)

Collie (*161*). Treatment of dehydroacetic acid with 85% sulfuric acid gives an isomeric acid, for which Feist suggested the structure XII-107 and Collie the structure XII-111. The uncertainty was resolved in favor of Feist's formula when the pyridinol resulting from ammonolysis of the isomeric acid was shown to be XII-108, by in-

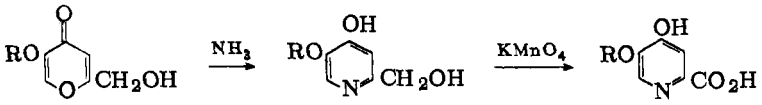


(XII-110)



(XII-111)

dependent synthesis from XII-103 ($R' = C_2H_5$, $R = CH_3$) (*151*). It is evident that the ring conversion of pyrones to pyridinols is not only a useful synthetic tool, but also a convenient device for structure proofs of naturally and synthetically occurring pyrones. The structure of kojic acid (XII-112, R = H) was elucidated by conversion of



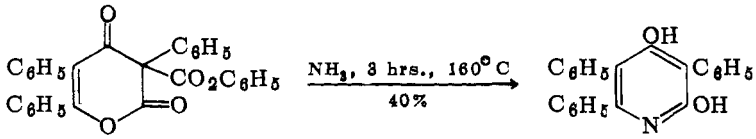
(XII-112)

its methyl ether into a 4-pyridinol, which was oxidized to the known methyl ether of comenamic acid (*149*). Several 6-substituted 2,4-diketopyrones (XII-113, $R = C_6H_5$ (*150*), C_2H_5 (*162*), and $COOC_2H_5$

(XII-113)

(*163*)) reacted with ammonia to give the corresponding 2,4-pyridinediol. The 2,4,6-triketo compound (XII-113, R = OH) and aniline gave (*164*) the expected 1-phenyl-2,6-dihydroxy-4(1*H*)-pyridone. However, unless anhydrous zinc chloride was added to remove the water, ring-opened products resulted instead.

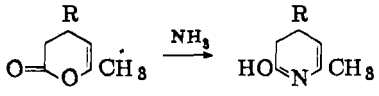
3,5,6-Triphenyl-3-benzoyl-2,4-diketopyrone (XII-114) aromatizes with loss of the benzoyl group when treated with concentrated am-



(XII-114)

$C_6H_5CONH_2$

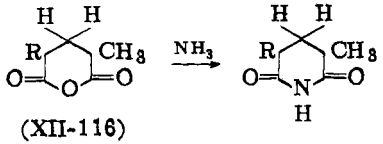
monia (*165*). As expected, dihydropyrones (XII-115) on ammonolysis yield dihydropyridinols. Glutaric anhydrides can also be



(XII-115)

R = H (*166*), C_6H_5 (*83*)

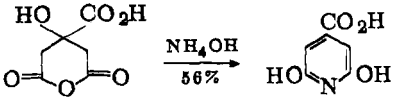
considered as dihydropyrones. α,α'-Dialkylglutaric anhydrides (XII-116) have been converted with liquid ammonia to the glutamides



(XII-116)

R = C_2H_5, cyclopentyl

(*167*). Hydroxyglutaric anhydrides, which are in a higher oxidation state, dehydrate to give pyridinediols rather than dihydropyridinetriols. An example of such a reaction is the formation of 2,6-dihydroxyisonicotinic acid (XII-117) when β-hydroxy-β-carboxyglutaric

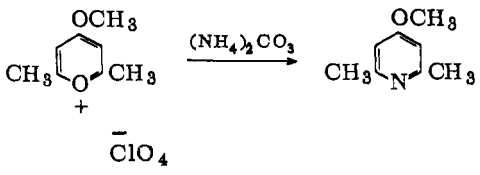


(XII-117)

anhydride is autoclaved with ammonium hydroxide at 130–135° C. (*168*).

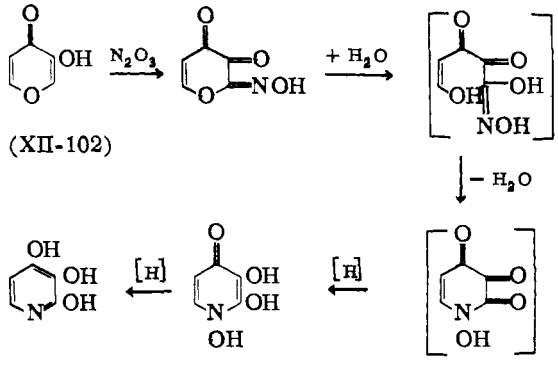
Alkoxypyrylium salts are convertible into the related pyridinol ethers. Thus, Baeyer (*169*) succeeded in preparing 2,6-dimethyl-4-methoxypyridine from 2,6-dimethyl-4-methoxypyrylium perchlorate (XII-118). This reaction has considerable historical significance because it led to the correct formulation of the structure of the pyrone salts (*cf.* Chapter II, p. 211).

A reaction unique in not requiring ammonia or amines for the introduction of the ring nitrogen was reported by Ost (*170*). Py-



(XII-118)

romeconic acid (XII-102) was nitrosated and the intermediate isonitrosopyromeconic acid rearranged during reduction with sulfur dioxide to give 1,2,3-trihydroxy-4(1*H*)-pyridone (XII-119). Further



(XII-102)

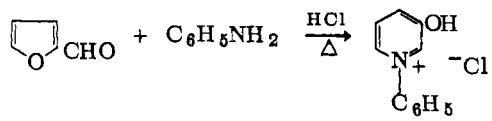
(XII-119)

reduction of XII-119 with tin and hydrochloric acid or hydriodic acid gave, as the final product, 2,3,4-pyridinetriol.

4-Dicyanomethylene-4*H*-pyranes have been converted by amines to the corresponding pyridine derivatives (*875,876*). This reaction may offer a convenient route to 4(1*H*)-pyridones.

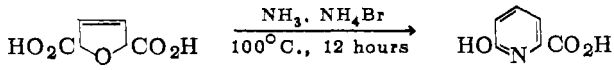
b. Furans

As early as 1905, a furan was converted into a pyridine. Heating an alcoholic solution of aniline, or hydrochloride, and furfural gave 3-hydroxy-1-phenylpyridinium chloride (XII-120) (*171*). The first



(XII-120)

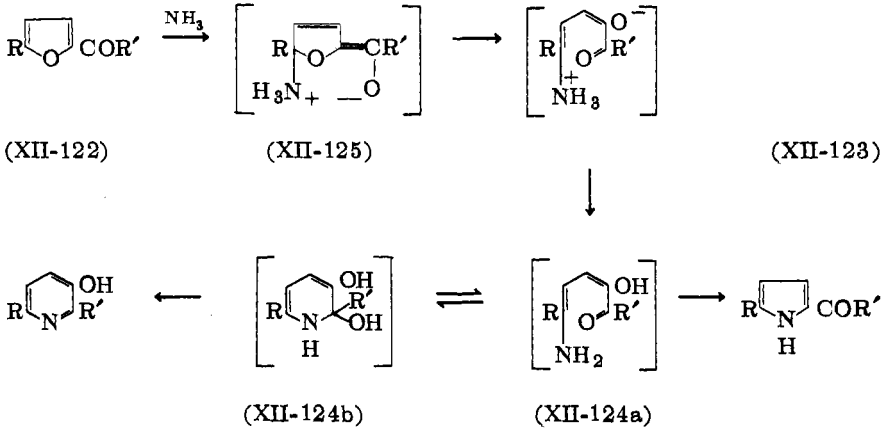
example (*172*) of the formation of nonquaternary pyridinols was the rearrangement of 2,5-dihydrofuran-2,5-dicarboxylic acid to 6-hydroxypicolinic acid (XII-121). It was only recently that this type of



(XII-121)

40%

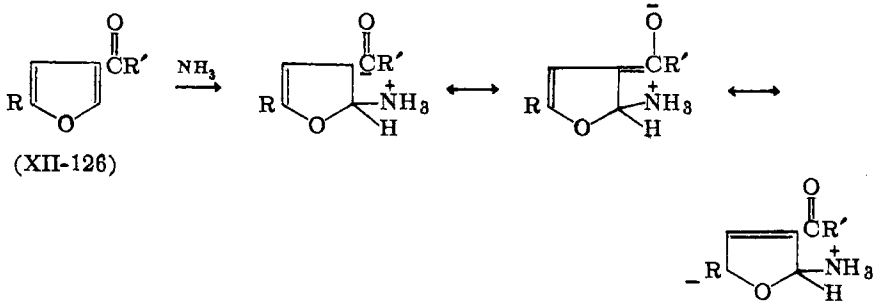
conversion has been exploited synthetically. The reaction has been developed by international contributions: Aso in Japan, Clauson-Kaas in Denmark, Leditschke in Germany, Gruber in Canada, and Dunlop in the United States. In 1939 Aso (*195*) reported the isolation of 6-methyl-3-pyridinol in low yields when 5-methylfurfural (XII-122, R = CH_3, R′ = H) was heated with ammonium sulfate at elevated temperatures. The mechanism proposed by Aso is outlined in XII-123. Since the transformation is initiated by a nucleophilic attack at the 5 position, an electron-withdrawing substituent, *e.g.*, carbonyl, is needed to stabilize the transition state leading to the first adduct. In the mechanism proposed by Leditschke (*173*), the first step is the formation of the ketimine of XII-122, which then traverses the steps depicted (XII-123). Nitrogen is less electronegative than oxygen, and the imine should be less effective than the original carbonyl in stabilizing the transition state leading to XII-125. Consequently, the initial reaction is probably directly on XII-122, not on its imine.



(XII-122) (XII-125) (XII-123)

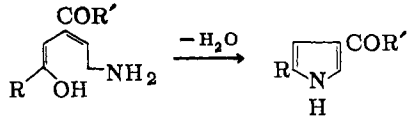
(XII-124b) (XII-124a)

An electron-withdrawing group in the β position would stabilize the transition state for attack on the C_2, rather than C_5, as shown by resonance structures of the adduct from XII-126. The open-chain



(XII-126)

intermediate (XII-127) resulting from attack by ammonia at the C_2 of XII-126, however, can only recyclize to a pyrrole, not a pyridinol.



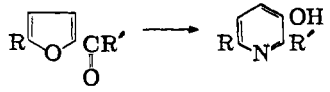
(XII-127)

Even in reaction XII-123, there is an alternate ring closure leading to an α-acylpyrrole. It has been shown (*174*) that an aqueous medium favors pyridinol formation, while an alcoholic solvent gives increased yields of pyrroles. Any electron-releasing group (*e.g.*, alkyl) in the 5 position should inhibit the reaction as shown by 2-acetylfuran (XII-122, R = H, R′ = CH_3) giving higher yields of pyridinol than its 5-methyl homolog (XII-122, R = R′ = CH_3). Although never demonstrated experimentally, it is conceivable that as the bulkiness of the alkyl group in the 5 position increases, the susceptibility to nucleophilic attack at that position would correspondingly diminish. Amines cannot be used in this synthesis, for then the intermediate (XII-124b) could not aromatize by dehydration. Instead, the reaction would reverse to the open-chain isomer (XII-124a) which would lose water irreversibly to give an *N*-substituted pyrrole. This was demonstrated by reacting butylamine with 2-acetylfuran, giving *N*-butyl-2-acetylpyrrole (*476*). The most favor-

able conditions, then, for the conversion of furans to pyridinols are (1) an electron-withdrawing group in the 2 and not the 3 position, (2) no electron-donating group in the 5 position, (3) no bulky alkyl group in the 5 position, (4) solvent condition to favor pyridinol over pyrrole formation, and (5) use of ammonia, but not amines.

A large variety of 2-acylfurans have been successfully transformed into the corresponding pyridinols, as listed in Table XII-6. Aso treated furfural (*196*) and its 5-methyl homolog (*186*) with hydroxyl-

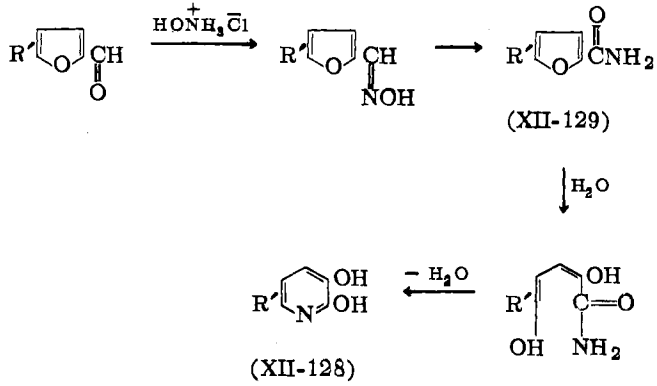
TABLE XII-6. Conversion of 2-Acylfurans to 3-Pyridinols



(XII–122)

R	R′	Reagent	Yield	Ref.
H	C_6H_5	NH_4OAc	59%	173
H	C_6H_5	NH_4OH, EtOH	65	174
H	*p*-$CH_3OC_6H_4$	NH_4Cl, NH_3, EtOH	33	173
H	*p*-$CH_3C_6H_4$	NH_4Cl, NH_3, EtOH	47	173
H	*p*-ClC_6H_4	NH_4OAc	73	173
H	3,4-$Cl_2C_6H_3$	NH_4OAc	77	173
H	CH_3	NH_3, H_2O, EtOH, liq. NH_3, 180°	47, 4.6	174,176, 836,828
H	C_2H_5	NH_3, H_2O, EtOH, NH_3EtOH	20, 10	174,176
H	*n*-C_3H_7	NH_3, EtOH	74	176
H	*i*-C_3H_7	NH_3	81	176
H	*n*-C_4H_9	NH_3	78	176
H	*sec*-C_4H_9	NH_3	60	176
H	*tert*-C_4H_9	NH_3	71	176
CH_3	CH_3	NH_3, H_2O, EtOH	9	174
CH_3	C_2H_5	NH_3, EtOH	80	176
H	$CH_2C_6H_5$	NH_3, EtOH	5.4	176
H	$(CH_2)_2CO_2H$	NH_3, EtOH, NH_4Cl		177
H	$(CH_2)_7CO_2H$	NH_3, EtOH, NH_4Cl	54	177
CH_3	$(CH_2)_3CO_2H$	NH_3, EtOH, NH_4Cl		177
CH_3	$(CH_2)_7CO_2H$	NH_3, EtOH, NH_4Cl	54	177
$(CH_2)_2CO_2H$	CH_3	NH_3, EtOH, NH_4Cl	34	177
$(CH_2)_7CO_2H$	CH_3	NH_3, EtOH, NH_4Cl	30	177
H	3-dibenzofuranyl	NH_3, EtOH, NH_4Cl	58	175
H	2-carbazolyl	NH_3, EtOH, NH_4Cl	66	175
H	2-methyl-3-indolyl	NH_3, EtOH, NH_4Cl	54	175

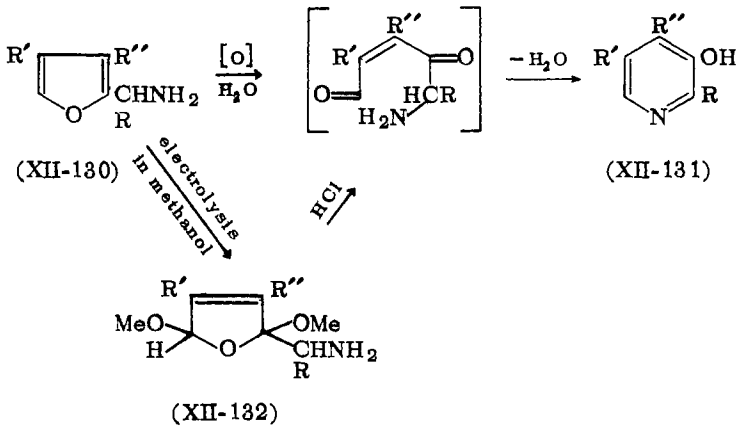
amine hydrochloride at elevated temperatures under pressure and isolated 2,3-pyridinediol (XII-128) and its 6-methyl derivative, respectively. He postulated that the initially formed aldoxime rearranged to the corresponding furoamide (XII-129, R′ = H), which cleaves hydrolytically and then recyclizes to XII-128. To confirm



this, it was shown that XII-128 (R′ = H) was obtained in low yield from 2-furamide in aqueous HCl under similar conditions of time and temperature. However, the lower yield from XII-129 (R′ = H) than from the oxime raises doubt concerning this proposed path.

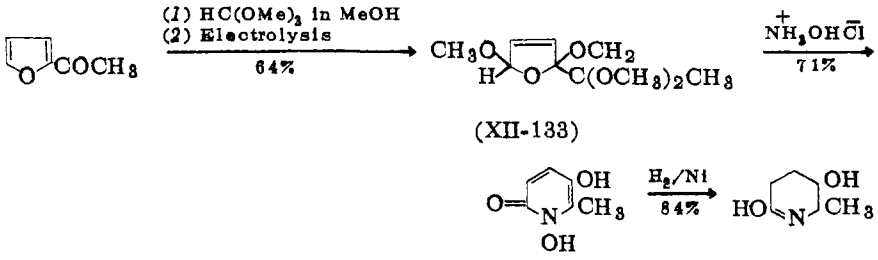
Hydrazine sulfate and furfural (XII-122, R = R′ = H) under pressure at 152° C. gave a mixture of 3-pyridinol and 2,3-pyridinediol (*197*). The products were accounted for by assuming that the reagent undergoes hydrolysis to ammonia and hydroxylamine, which then react independently.

Clauson-Kaas and co-workers (*179*) showed the feasibility of transforming various furfurylamines (XII-130, R′ = R″ = H, R = H or CH_3) by oxidative hydrolytic conditions into intermediate aminodiketones which condense intramolecularly to yield 3-pyridinols (XII-131). XII-130 is easily obtained by reductive amination of 2-formylfurans or 2-acylfurans. Since direct methods failed, XII-130 was oxidized electrolytically in methanol to yield the 2,5-dimethoxy-2,5-dihydrofuran (XII-132, R′ = R″ = H) derivative, which was subsequently hydrolyzed to XII-131 in yields from 60–95%. With the free amine the yields were inferior. Consequently, the amine was protected by acylation with either acetic anhydride, methyl chloro-

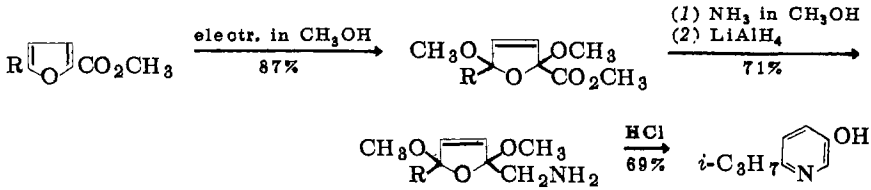


formate, or urea, giving respectively the $NHCOCH_3$, $NHCOOCH_3$, and $NHCONH_2$ or $(NH)_2C{=}O$ derivatives. This method seems applicable when there are substituents in the 3 and 4 positions, *i.e.*, $R' = R'' = CH_2OCOCH_3$, $R = CH_3$. The final product in this case is pyridoxine diacetate (XII-131, $R' = R'' = CH_2OCOCH_3$, $R = CH_3$) formed in 76% over-all yield from the furan XII-130 (*182*). This is in contrast to unsuccessful attempts (*198,199*) to prepare pyridoxine from 3,4-bis(hydroxymethyl)-2-acetylfuran with ammonia.

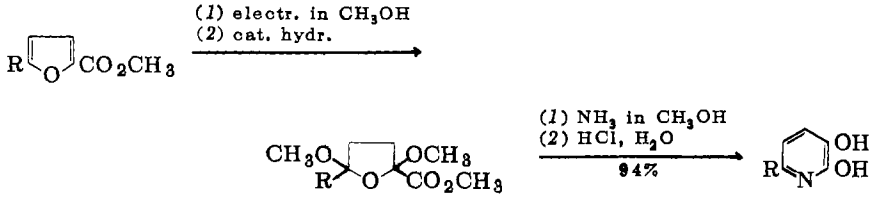
Several modifications of this method have been devised. In one (*180*) the 2-acetylfuran was ketalized in methanol with methyl orthoformate and a trace of *p*-toluenesulfonic acid. The resulting solution was then electrolyzed to form 2,5-dimethoxy-2-(α,α-dimethoxyethyl)-2,5-dihydrofuran (XII-133). Reaction of XII-133 with hydroxylamine hydrochloride led to 1,5-dihydroxy-6-methyl-2(1*H*)-pyridone (XII-134) (*183*), which was reduced to 5-hydroxy-6-methyl-



2-piperidone. The other modification (*181*) converts methyl furoates by two routes. In the first (XII-135), R = *i*-C_3H_7 and 6-*i*-propyl-3-pyridinol results; in route XII-135a, where R = H, the product is

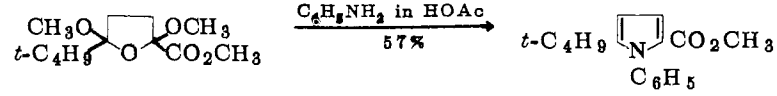


(XII-135)



(XII-135a)

2,3-pyridinediol. It was previously noted that when amines react with acylfurans, *N*-substituted pyrroles are formed. The same is true for the 2,5-dimethoxy-2,5-tetrahydrofurans (*200*) as shown by the isolation of methyl 1-phenyl-5-*t*-butyl-2-pyrrolecarboxylate from XII-136 and aniline.



(XII-136)

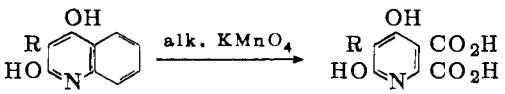
The usefulness of furan derivatives as starting materials leads to the intriguing thought that mono-, di-, and polysaccharides may be valuable sources for pyridinols. In fact, 3-pyridinol has been isolated from the hydrolytic products of algae with dilute sulfuric acid at 155–160° C. (*184*). The same product was obtained from ammonium salts and alginic acid, xylose, or 2-furaldehyde. Glucose and sucrose have been converted by similar treatment (with am-

monium salts) into poor yields of 2-methyl-3-pyridinol, 2-hydroxymethyl-5-pyridinol (*185*) and 6-methyl-2,3-pyridinediol (*186*).

The conversion of furans to pyridines is discussed in Chapter II (pp. 154 ff.).

c. Other Nitrogen-Containing Heterocycles

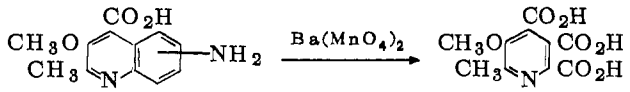
When benzopyridines are oxidized, the nitrogen atom stabilizes the pyridine ring, and the benzene nucleus is destroyed, leaving substituted pyridinedicarboxylic acids. By starting with hydroxy or alkoxy substituents on the pyridine nucleus, this method becomes adaptable for the synthesis of pyridinols or their ethers. Quinolines or isoquinolines can be used. Thus, 2,4-quinolinediol (XII-137, R = H) and its 3-bromo derivative (XII-137, R = Br) were oxidized



(XII-137)

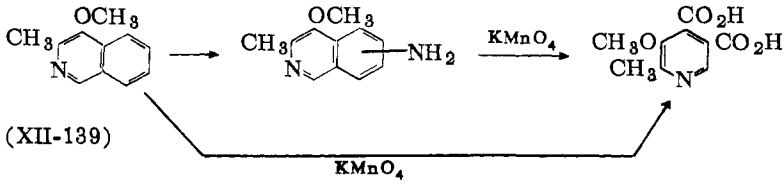
with hot alkaline permanganate to the corresponding 4,6-dihydroxyquinolinic acids (*187*).

To prepare intermediates needed to synthesize pyridoxine (XII-131, R = CH_3, R′ = R″ = CH_2OH), 2-methyl-3-methoxy-4-quinolinecarboxylic acid was nitrated in the benzene ring, and the nitro group reduced to amino (XII-138) in order to sensitize the benzene nucleus



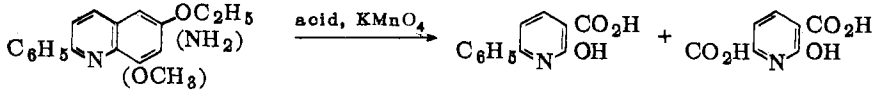
(XII-138)

(*188*). Likewise, 3-methyl-4-methoxyisoquinoline (XII-139) has proved to be a valuable starting material for synthesizing pyridoxine,



Vitamin B_6. It has been oxidatively degraded directly (*189*) or by first converting it to a Bz-amine derivative (*190*).

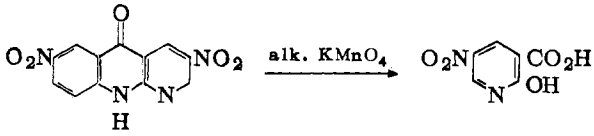
In acid medium, the oxidation of a quinoline nucleus leads to a 2-hydroxy-3-carboxyl derivative, rather than a 2,3-dicarboxy derivative. Thus, 2-phenylquinolines (XII-140) substituted in the benzene nucleus are oxidized in acid permanganate to give mainly 2-hydroxy-6-phenylnicotinic acid and as a by-product 2-hydroxy-3,6-pyridinedicarboxylic acid (XII-141) formed by oxidation of the phenyl



(XII-140) (XII-141)

group (*191*). XII-141 was also obtained as the sole product when 2-quinolinecarboxylic acid was oxidized (*192*). *Cf.* Chapter II, p. 253.

There are a few isolated instances of the conversion of other nitrogen ring systems to pyridinols. The structure proof of a pyracridone derivative (XII-142) was aided by isolating 2-hydroxy-5-nitronicotinic acid after alkaline permanganate oxidation (*193*).

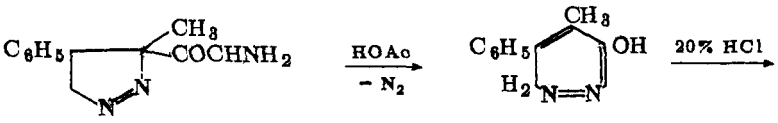


(XII-142)

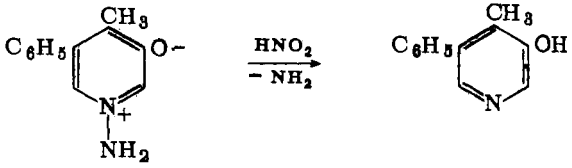
A novel series of reactions was recently communicated (*194*) starting with 3-diazoacetyl-3-methyl-4-phenyl-Δ^1-pyrazoline (XII-143), which was rearranged in acetic acid with loss of nitrogen to 4-hydroxy-5-methyl-6-phenyl-(7*H*)-1,2-diazepine (XII-144). This rearranges in warm 20% hydrochloric acid to the zwitterion of 1-amino-4-methyl-5-phenyl-3-pyridinol (XII-145), which, in turn, is deaminated with nitrous acid to 4-methyl-5-phenyl-3-pyridinol (*cf.* Chapter II, pp. 268 f.).

d. Benzene Derivatives

Benzene derivatives have been converted to pyridine derivatives by cleavage of the carbocyclic ring and recyclization (*852*), as ex-

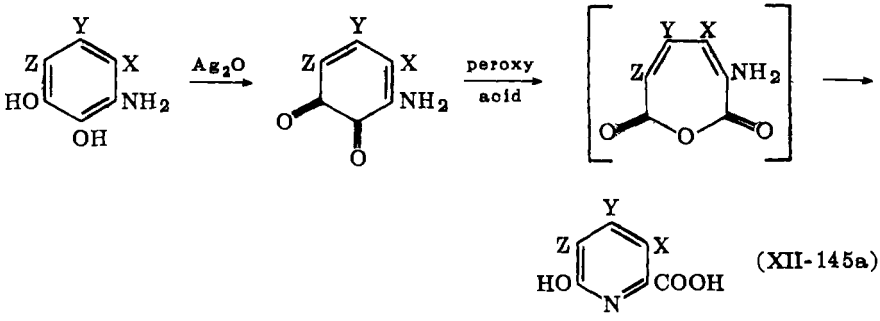


(XII-143) (XII-144)



(XII-145)

emplified by the conversion of 3-aminocatechols to 6-hydroxy-picolinic acid (XII-145a). The initial oxidant is silver oxide in anhy-



(XII-145a)

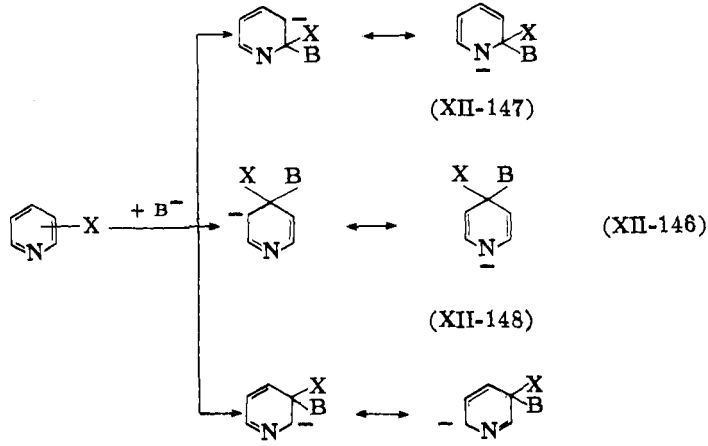
(a) X = Y = Z = H
(b) X = COOH; Y = Z = H
(c) X = NH_2; Y = CH_3; Z = H

drous ethyl acetate. The intermediate amino-*o*-quinone is further oxidized with a peroxy organic acid to give a Baeyer-Villiger reaction product, a muconic acid anhydride which isomerizes to a 6-hydroxypicolinic acid.

3. From Other Pyridine Derivatives

This method is most versatile for the synthesis of pyridinols. Its applicability is dependent on the electronic distribution of the pyridine nucleus. It has been shown from molecular orbital calculations that positions 2 and 4 are most susceptible to nucleophilic attack, the former being somewhat more reactive. This conclusion is also reached from an examination of the resonance structures of

the intermediates resulting from such an attack at the 2, 4, and 3 positions as shown in XII-146. Attack at position 2 or 4 gives a resonance hybrid which has the negative charge distributed to the electronegative nitrogen, thus stabilizing the intermediate. The structure resulting from the attack at the 3 position has the negative charge on carbon, and is of higher energy, making displacement on this position more difficult. (The 4 position is somewhat more reactive because the *p*-quinoid structure (XII-148) is more stable than the *o*-quinoid structure (XII-147).) Therefore, if group X forms a



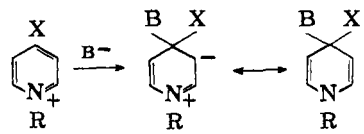
(XII-147)

(XII-148)

(XII-146)

weak base when displaced, *e.g.*, Cl^-, Br^-, I^-, NO_2^-, N_2, NH_3, it can be replaced by the stronger bases OH^-, OR^-, and OAr^- to give pyridinols and their ethers (*cf.* Chapter I, p. 28).

The displaceability of a group in the 2 or 4 position is further enhanced in pyridinium compounds. In this case, the intermediate (XII-149) is greatly stabilized by becoming neutral. (The same is

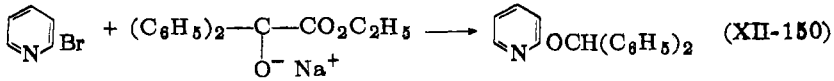


(XII-149)

true for bond formation in the 2 position.) The increased reactivity of group X enables it to be displaced by solvent, *e.g.*, H_2O, ROH (*cf.* Chapter II, p. 34).

a. Halopyridines

Owing to the difficulties encountered in the direct halogenation of pyridine, this method is not too suitable for the preparation of pyridinols. It is most useful, however, for the preparation of pyridinol ethers. On occasion, the pyridinol is converted first to the halo derivative, and then back to the ether. In contrast to the severe conditions required to hydrolyze chlorobenzene to phenol by the Dow process (sodium carbonate, copper, 350° C.), 2-chloropyridine is converted to 2-pyridinol quantitatively when heated with potassium hydroxide at 170° C. (*201*). Various aryl ethers have been prepared (*203,204*) in excellent yields by heating the phenols with 2-bromopyridine and anhydrous potassium carbonate for six hours at 150–160° C. This procedure failed for several benzoic and naphthoic esters, *e.g.*, methyl salicylate and ethyl-2-hydroxy-3-naphthoate. Ethers of these hydroxy compounds were successfully prepared by heating the appropriate dry sodium phenoxide with 2-bromopyridine and catalytic amounts of copper powder. The salutary effect of the catalyst was especially evident in the reaction of sodium veratryl alcoholate with 2-bromopyridine. In the absence of copper powder the reactants could be heated to 210–220° C. without evidence of reaction, whereas with the catalyst present, a vigorous reaction occurred at 150° C. (*204*). Ethers of α-hydroxy acids, *e.g.*, ethyl lactate, glycolate, and mandelate, have been prepared in 25% yield at 110–120° C. from an excess of 2-bromopyridine and the sodium alkoxide of the ester. When ethyl benzilate is used, the carbethoxy group is lost and the benzhydryl ether is isolated (XII-150); the normal product could not be obtained.



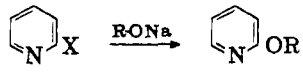
(XII-150)

Several 2-pyridyl alkyl ethers were prepared in 60% yields from 2-bromopyridine and the alcohol (*903*).

Several 2-halopyridines which have substituents that do not activate the halogen have been reacted (XII-151) as shown in Table XII-7. The yields in these reactions are all about 70%.

When the reduction of 2,6-dichloro-3,4,5-trimethylpyridine was attempted with hydrazine hydrate and cupric sulfate, in addition to

TABLE XII-7. Reaction of 2-Halopyridines with Alkoxides



(XII-151)

R	X	Substituent and position				Ref.
		3	4	5	6	
n-C_4H_9	Br	C_6H_5	C_6H_5	C_6H_5	C_6H_5	20
n-C_3H_7	Cl		CO_2H			206
n-C_4H_9	Cl		CO_2H			206
C_2H_5	Br			OC_2H_5		207
C_2H_5	Br	OC_2H_5				207
C_2H_5	Br				NH_2	216

the expected 3,4,5-trimethylpyridine, a small yield of 3,4,5-trimethyl-2-pyridinol was isolated (*827*).

4-Pyridinol is not made from 4-halopyridines, but its ethers are. 4-Chloropyridine is actually prepared from 4-pyridinol and then converted to the alkoxy compound, since direct etherification leads to a mixture of *O*- and *N*-alkylation products. This method (XII-152) is used for the preparation of both alkyl and aryl ethers, but mostly for the former (Table XII-8). Several 4-alkoxy- and 4-aryloxy-2,6-lutidines were prepared by this method (*871*).

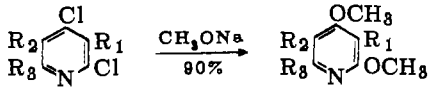
Although the 3-substituted halides are not as active as the 2- or 4-halides, they do undergo displacement. 3-Pyridinol can be obtained from 3-bromopyridine by treatment with aqueous sodium hydroxide at 200° C., with cupric sulfate as a catalyst (*212*). The poor yield of 20% and the difficulty of preparing the starting material make this an unsuitable preparative method. The less severe conditions of this reaction as compared to those of the Dow process for preparing phenol (200° C. *vs.* 350° C.) indicate that the ring nitrogen does exert an activating influence inductively on the 3 position, which, however, is much weaker than the resonance stabilization afforded to attack at the 2 and 4 positions. The methyl (*207*) and ethyl (*213*) ethers of 3-pyridinol have been prepared from 3-bromopyridine by heating with sodium methoxide and ethanolic potassium hydroxide, respectively.

Dihalides of the 3,5 and 2,6 type undergo displacements to give monochloroethers and diethers. Weidel and Blau (*213*) obtained a

TABLE XII-3. Reaction of 4-Chloropyridines with Alkoxides

(XII-152)

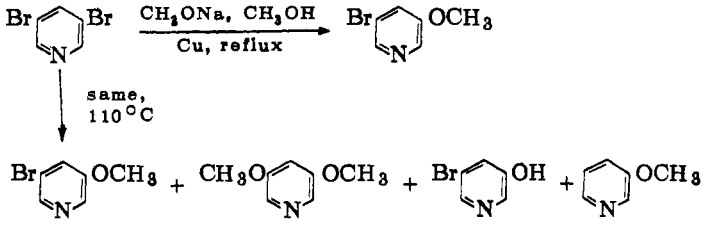
R′	R	Ref.
H	CH_3	121
H	C_6H_5	208
H	C_2H_5	209
COOH	H	210
COOH	CH_3	211



(XII-157)

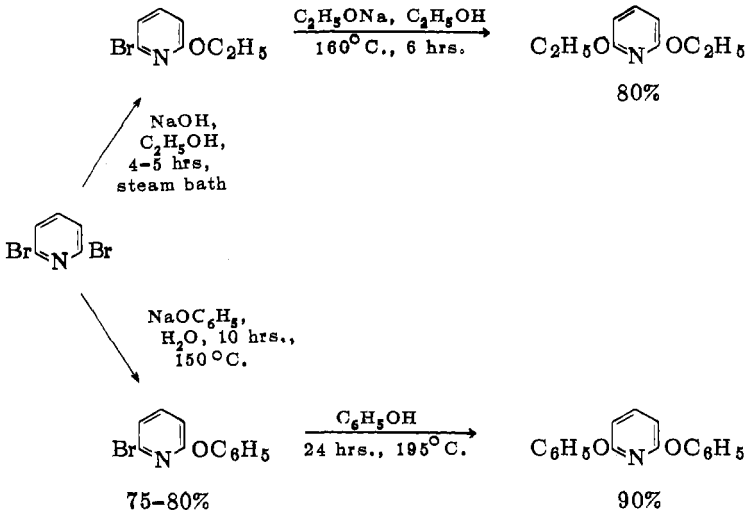
R_1	R_2	R_3	Ref.
H	H	H	221
CN	H	H	222
H	CN	H	223
H	H	H	224 (C_2H_5O Na used)

40% yield of 3,5-diethoxypyridine and a 10% yield of 5-ethoxy-3-pyridinol from the reaction of 3,5-dibromopyridine with sodium hydroxide in ethanol. More recently, repetition of this experiment (*214*) permitted isolation of 3-bromo-5-ethoxypyridine in 50% yield. The methoxy analog was likewise isolated after refluxing for two days in methanol (XII-153). When the reaction is performed in a sealed tube at 110° C., a variety of products, among them the unexpected 3-methoxypyridine (*215*), are isolated.



(XII-153)

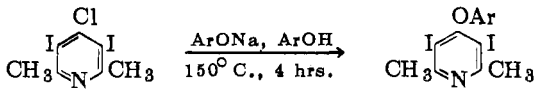
2,6-Dibromopyridine can also be made to react stepwise (XII-154) with sodium hydroxide in ethanol (*216*) or with sodium phen-



(XII-154)

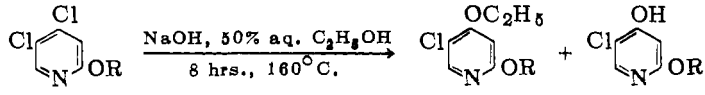
oxide (*227*). Similarly, 2,6-dichloroisonicotinic acid reacts with alkoxides up to *i*-amyl (*206*).

When dihalides of the α,β or β,γ type are used as starting materials, the greater reactivity of the 2- and 4-substituents is quite apparent. A methanolic solution of sodium methoxide and 5-iodo-2-chloropyridine gives 5-iodo-2-pyridinol (*218*). 2,3-Dichloropyridine with sodium *n*-butoxide gave 3-chloro-2-butoxypyridine (*865*). Several 4-aryl ethers of 3,5-diiodolutidine were prepared (XII-155) from



(XII-155)

the 4-chloro compound (*219*). The relative ease of this reaction is unexpected, since the bulk of the two ortho iodo groups should make it difficult for the nucleophilic group OAr^- to approach the 4 position. Treatment of 4,5-dichloro-2-ethoxypyridine (XII-156,

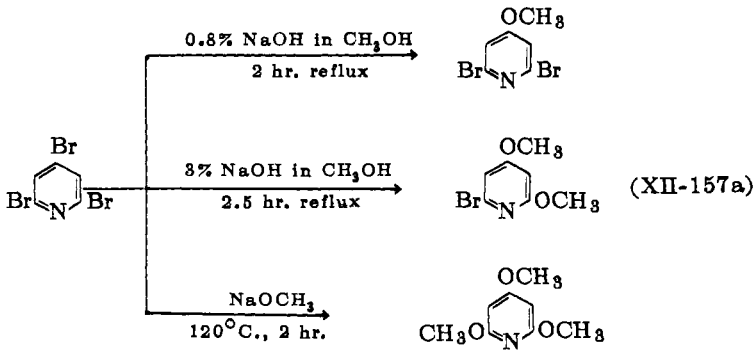


(XII-156) 60% 35–40%

R = C_2H_5) with base gives a mixture of products in which the 4-chlorine is displaced by either ethoxyl or hydroxyl (*220*). The alcohol (XII-156, R = H) gives a similar mixture.

In almost all cases where α,γ-dihalides react, both halogens are displaced simultaneously (XII-157). There is a report (*225*) of the replacement of only one chlorine by methoxyl in the reaction of 4,6-dichloro-2-picoline with sodium methoxide (Table XII-8). However, the authors gave no proof of structure, and the analysis is poor for the calculated formula for this product.

A better comparison of the reactivity of α- and γ-halides is obtained from a study of 2,4,6-tribromopyridine. Its reaction with sodium methoxide (*226*) reveals that the bromines are readily replaced in the order 4 > 2 > 6 (XII-157a).

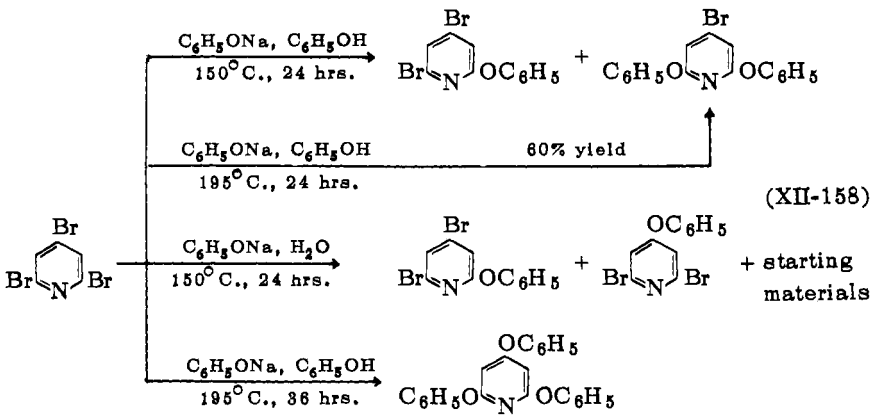


(XII-157a)

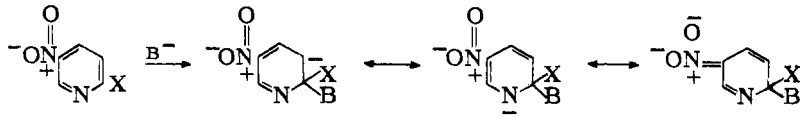
Atom localization energies for nucleophilic attack at C_2 = 2.40 and C_4 = 2.36. This difference must therefore be significant enough to overcome the 2:1 statistical advantage that the two α positions have over the γ position. However, with sodium phenoxide (*227*) the order is different (XII-158). It appears that the replacement order depends to some extent on the solvent.

Pentachloropyridine, boiled with a solution of sodium hydroxide in aqueous ethanol, gives 2,3,5,6-tetrachloro-4-pyridinol (*228*). In this case, not only is the 4 position at a statistical disadvantage, but it is also more sterically hindered by the 3- and 5-chloro groups than is either the 2 or the 6 position; nevertheless, the 4-chloro is displaced.

An electron-withdrawing group, *e.g.*, NO_2, CN, COX, SO_2NH_2, placed ortho or para to a halo group further facilitates displacement,



as would be expected by examining the intermediate (XII-159a,b,c) formed when a 5-nitro-2-halopyridine is attacked by a nucleophilic



(XII-159a) (XII-159b) (XII-159c)

ion, B^-. The anion formed is stabilized by having its charge distributed not only to the ring nitrogen (XII-159b), but also to the nitro group (XII-159c). A nitrile or carboxy derivative (ester, amide) can likewise effect this stabilization by interaction with the ring. 5-Nitro-2-halopyridines have been converted to a large variety of ethers (XII-160, Table XII-9) under much milder conditions (ca. 2–3 hours, at 70–80° C.) than those for the unnitrated halopyridines.

An attempt (*385*) was made to prepare 5-nitro-2-pyridinesulfonic acid by treating 5-nitro-2-chloropyridine with sodium sulfite in dilute methanol. The only isolable product was 2-methoxy-5-nitropyridine, resulting from solvolysis.

The chloro group of 3-nitro-4-chloropyridine is especially reactive, as evidenced by the fact that warming in water converts it to 3-nitro-4-pyridinol, and sodium methoxide converts it to the methyl ether at 50° C. (*238*), although in low yield and with considerable decomposition. When it was found (*235*) that 6-chloro-5-nitro-2-

TABLE XII-9. Alcoholysis of 5-Nitro-2-halopyridines

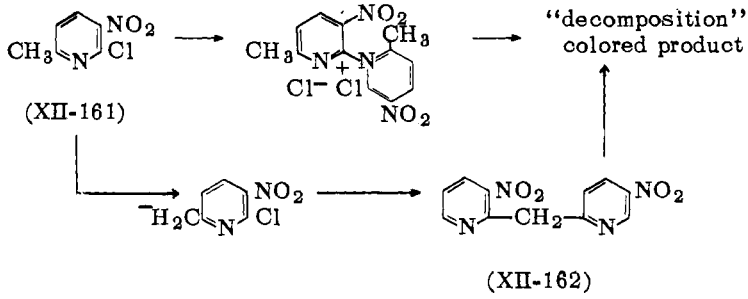
(XII-160)

X	R′	R	Yield, %	Ref.
Cl	H	H		201
Cl	H	CH_3		229
Cl	H	*n*-hexyl	67	230
Cl	H	CH_3 through $C_{10}H_{21}$		230
Cl	H	allyl[a]		231
Cl	H	hydroxyalkyl		230
Cl	H	alkoxyalkyl		230
Cl	H	aryloxyalkyl		230
Cl	H	phenyl		230
Cl	H	β-naphthyl	63	230
Cl	H	nitrophenyl		705
Cl	H	monochlorophenyl	53–68	232
Cl	H	dichlorophenyl	21–67	232
Cl	H	trichlorophenyl	25–68	232
Cl	H	2-chloro-4-nitrophenyl	45	232
Cl	H	benzyl		230
Cl	H	3-pyridyl		230
Cl	H	tetrahydrofurfuryl	90	230
Cl	H	cyclohexyl		230
I	H	CH_3		233
F[b]	H	CH_3	94	234
Cl	CH_3	CH_3	82	235
Cl	CH_3	aryl		236

[a] Used K_2CO_3 and the alcohol.
[b] Reaction instantaneous at 10 °C.

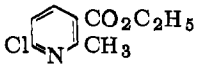
picoline (XII-161) decomposes in sodium hydroxide, it was generalized that all *o*-nitrochloropyridines were extremely reactive. The decomposition was attributed to ring opening of the nitropyridylpyridinium compound formed when XII-161 reacts with itself. This conclusion was found to be erroneous by Gruber (*237*), who obtained a 65% yield of 2-methoxy-3-nitropyridine from 2-chloro-3-nitropyridine. These results are difficult to reconcile. One would expect that XII-161 would less easily react with itself than would 2-chloro-3-nitropyridine. The methyl and chloro groups in positions 6 and 2 of XII-161 should decrease its nucleophilicity by increasing

the F-strain (*246*) about the ring nitrogen. Another puzzling point is that the self-condensation would be expected to occur in the absence of base (*235*). It is likely that the methyl group, activated by the nitro group para to it, forms a carbanion by protolysis. The carbanion then displaces the chloro group from another molecule of XII-161 to give XII-162, which should give the colored anion by loss

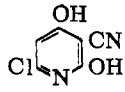


of a proton from the methylene group. Any further conjecture must await the accurate identification of the colored product from XII 161 and sodium ethoxide, which was not attempted.

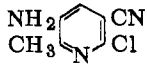
As expected, both 5-nitro-2,3-dichloropyridine (*239*) and 3-nitro-2,5-dichloropyridine (*240*) react with aryl oxide ion to yield monoaryl ethers by displacement of the 2-chloro group. Carboxy groups and their derivatives are efficient activators of halo groups. 3-Chloroisonicotinic acid is readily converted to 3-hydroxyisonicotinic acid by four hours refluxing with 50% potassium hydroxide (*243*). 6-Chloronicotinamide (*241*) and 2-chloro-*N*-phenylnicotinamide (*242*) react with sodium butoxide under mild conditions to give the corresponding ethers. Ethyl 2-methyl-6-chloronicotinate (XII-163) reacts with sodium ethoxide (*244*) and 6-chloro-2,4-dihydroxynicotinonitrile (XII-164) reacts with sodium methoxide (*159*), the expected ethers being obtained. In contrast to the decomposition of XII-161, 2-chloro-6-methylnicotinotrile reacts smoothly with sodium methoxide in 59% yield (*245*). To add to the complexity, 6-methyl-5-amino-2-chloronicotinotrile (XII-165) is recovered unchanged after treatment with alkoxides (*245*). The explanation offered (*247*) is that the electron-releasing effect of the amino group offsets the effect of the nitrile group and results in a deactivation of the 2-chloro sub-



(XII-163)

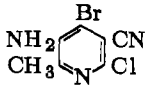


(XII-164)



(XII-165)

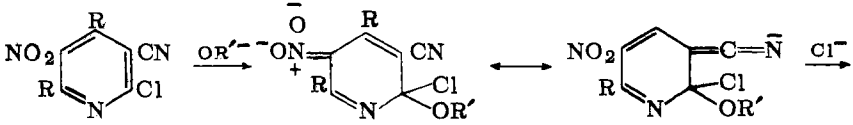
stituent with respect to displacement. However, 2-chloro-4-bromo-5-amino-6-methylnicotinotrile (XII-166) reacts with potassium ethox-



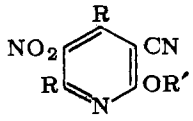
(XII-166)

ide to give an 87% crude yield of the 4-ethoxy derivative (*59*). 2-Methoxypyridine-5-sulfonamide was prepared from the corresponding 2-chloro compound and sodium methoxide in 77% yield (*467*).

As expected, two electron-withdrawing groups situated ortho or para to the halogen greatly facilitate its displacement. Both 2-chloro-5-nitronicotinotrile (XII-167, R = H) (*63*) and 2-chloro-4,6-dimethyl-5-nitronicotinotrile (XII-167, R = CH_3) (*247*) give a red or purple-brown color on treatment with alkoxides. Addition of water discharges the color, and the corresponding ethers (XII-169) are isolated. The color is ascribed (*247*) to the formation of an unusually stable quinone-type ion (XII-168a,b). More contribution might



(XII-167) (XII-168a) (XII-168b)



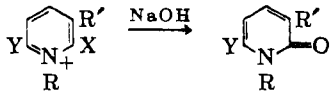
(XII-169)

be expected from XII-168b when R = CH_3 than from XII-168a, because of the steric inhibition of resonance by the two methyl groups.

The ether (XII-169) also gives a color with alkoxide, undoubtedly via formation of XII-168a,b, where instead of chlorine, there is an OR group. The formation of this intermediate can also account for the conversion of the methyl ether (XII-169, R = R′ = CH_3) to the ethyl ether (XII-169, R = CH_3, R′ = C_2H_5) (*247*). The pyridinol itself (XII-169, R′ = H) gives no color because the base removes the proton from the hydroxy group and the stable 2-pyridinoxy ion formed resists further nucleophilic attack.

After discussing the complexities of the nucleophilic displacement of halogen, it should be emphasized that in planning a synthesis using this reaction, it is necessary to take into account the electronic effects of all the ring substituents, and how these effects relate to the reactivity of the halide.

Introduction of a positive charge on the ring nitrogen further augments the reactivity of the halogen by increasing the electron-withdrawing power of the nitrogen. Thus, 1-alkyl-2-halopyridinium salts give 1-alkyl-2(1*H*)-pyridones (XII-170). Protonation is another



(XII-170)

R	R′	X	Y	Ref.
CH_3	H	Br	Br	248
$C_6H_5COCH_2$	H	Cl	H	249
C_2H_5	CH_3	I	H	250

effective way of placing a positive charge on the ring nitrogen and therefore acid-catalyzed hydrolysis of halopyridines should occur. With hydrochloric acid at elevated temperatures, several 2-halopyridines were converted to 2-pyridinols, *e.g.*, 2-chloro-, 2-chloro-5-nitro-, 2,5-dichloro-, 2,3-dichloro-5-nitro- (*251*), 2-chloro-5-cyano- (*252*), 2-chloro-4-carboxy- (*253*), 2-bromo-3-nitro-, and 2,3-dibromo-3-nitro- (*390*). Wibaut, Haayman, and van Dijk (*254*), using 2,6-dibromopyridine, made an extensive study of conditions required for acid hydrolysis. Concentrated aqueous solutions of sulfuric, phosphoric, acetic, and formic acids gave 6-bromo-2-pyridinol at 160°C. In a typical run with 70% sulfuric acid, the yield after four hours was 12% based on starting material taken, but 31% if allowance is made

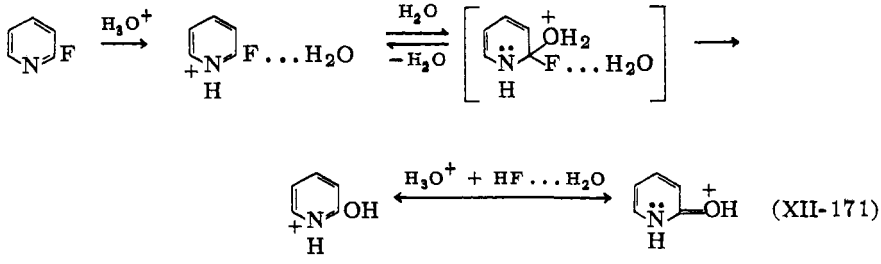
for recovery. Displacement did not occur if the dibromo compound was warmed with 50% sulfuric acid in a boiling water bath. In contrast, 2,6-pyridinediol was obtained from an aqueous alcoholic sodium hydroxide solution at 90°C.

A comparison of the reactivity of fluoro, chloro, and bromo groups toward acid hydrolysis was made by Bradlow and Van der Werf (*250*). All the compounds tested were refluxed for twenty-four hours in 6*N* hydrochloric acid and the results are summarized in Table XII-10. Examination of the results reveals that the fluoro

TABLE XII-10. Effect of Refluxing 6*N* Hydrochloric Acid on Halopyridines

Hydrolysis	No hydrolysis
2-Fluoropyridine	2-chloropyridine
2-Fluoro-3-methylpyridine	2-bromopyridine
2-Fluoro-5-methylpyridine	2-bromo-3-methylpyridine
2-Fluoronicotinic acid	2-bromo-5-methylpyridine
6-Fluoronicotinic acid	
2-Bromonicotinic acid	
6-Bromonicotinic acid	

group is most reactive, and that the bromo group reacts only if it is activated by an ortho or para carboxyl group. The authors propose a mechanism having hydrogen bonding of fluorine with water as a salient feature (XII-171). They argue that both the lower tendency

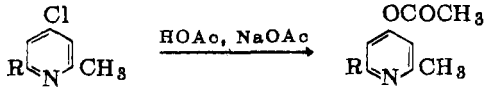


(XII-171)

of chlorine and bromine to form hydrogen bonds and their lower electronegativity operate to decrease their liability as compared to fluorine.

4-Halopyridines are far more reactive than the 2 isomers. Moist 4-chloropyridine is converted to the hydrochloride of 4-pyridinol (*121*). Undoubtedly, the formation of hydrochloric acid as a product makes this an autocatalytic reaction. Surprisingly, therefore, there are two reports of acid hydrolysis of 2,4-dichloropyridines at C_2 rather than C_4. Thus, 2,4-dichloro-6-carboxypyridine (4,6-dichloropicolinic acid) in sulfuric acid is reported (*257*) to give 4-chloro-6-carboxy-2-pyridinol (4-chloro-6-hydroxypicolinic acid), and from 2,4-dichloro-6-methylpyridine with benzaldehyde in the presence of zinc chloride is isolated (*258*) 6-styryl-4-chloro-2-pyridinol. In the latter reaction, the zinc chloride acts as the electrophilic agent which bonds to the ring nitrogen. In both cases, however, the structures assigned to the products are based on the assumption that the 2- or 6-chloro group is more active than the 4-chloro. Therefore these results are suspect until a proof of structure is forthcoming.

4-Chloropyridines have also been converted to 4-pyridyl acetates (XII-172). Treatment of 4,6-dichloro-3-(β-chloroethyl)-2-picoline



(XII-172)

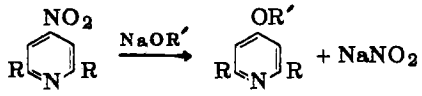
R = CH_3 (*259*), H (*260*)

with potassium acetate and acetic acid at 160°C. for six hours resulted in the displacement of one of the nuclear chlorines by a hydroxyl group. It was not determined whether the C_4 or C_6 chlorine reacted, but the side-chain group definitely did not (*392*).

The hydrolysis and alcoholysis of halopyridines are also discussed in Chapter VI (pp. 349 ff.).

b. Nitropyridines

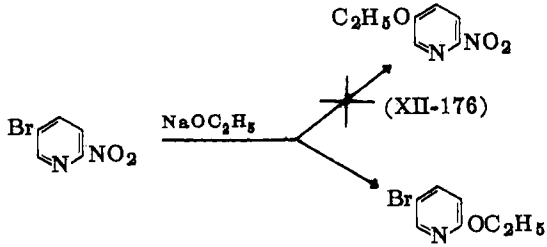
This reaction has not been as well exploited as the halo displacements. The first report was the reaction of 4-nitro-2,6-lutidine (XII-173, R = CH_3) with sodium ethoxide to give 4-ethoxy-2,6-lutidine (XII-174, R = CH_3, R′ = C_2H_5) (*261*). When R = H, the bases used were sodium ethoxide, concentrated ammonium hydroxide at 150°C.,



(XII-173) (XII-174)

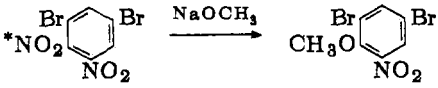
and sodium phenolate, to give XII-174, R = H, R′ = C_2H_5, H, and C_6H_5, respectively (*262*). Refluxing with 50% potassium hydroxide likewise gave the 4-pyridinol, but 10% potassium hydroxide on a steam bath proved too mild to cause the transformation. While 2-nitropyridine gives 2-ethoxypyridine with sodium ethoxide, no reaction takes place with sodium phenolate or with ammonium hydroxide at elevated temperatures (*263*). In contrast to the 4-nitro derivative, 2-nitropyridine reacts with 10% potassium hydroxide to give 2-pyridinol (*263*). The nitro group in the 2 position is susceptible to ionic attack under basic but not acidic conditions. The attempt to react 3-nitro-2,6-lutidine with sodium ethoxide led to resins (*261*).

Some interesting results are obtained when certain nitrohalopyridines are used as starting materials. In an attempt to prepare 5-ethoxy-2-nitropyridine (XII-176), 5-bromo-2-nitropyridine was reacted with sodium ethoxide. Instead of the bromo group, the nitro group was displaced (*264*) to give 5-bromo-2-ethoxypyridine (XII-175). In the starting material, the bromine is activated by the



(XII-175)

p-nitro group, while the nitro group is activated by the ring nitrogen. This competition is resolved in favor of the pyridine ring. Similar results were obtained with 3,5-dibromo-2-nitropyridine. The authors (*264*) assert that this reaction is analogous to the reaction of 1,3-dibromo-4,5-dinitrobenzene (XII-177) under the same



(XII-177)

conditions to give 4,6-dibromo-2-nitroanisole (*265*). This analogy is a poor one, however, and illustrates the possible pitfalls in such reasoning. The nitro group marked by an asterisk in XII-177 is the only one which is in a position to activate the two bromines. But because of steric inhibition of resonance, due to inability to become planar with the ring, it is incapable of doing so. It is itself, however, activated by the nitro group ortho to it, which can resonate with the ring, and it is thus displaced by the ethoxide ion. Obviously, then, this situation is quite different from the one leading to the formation of XII-175, in which steric inhibition of resonance is not involved. In acid, the nitro group of 5-bromo-2-nitropyridine undergoes hydrolysis, to give a mixture of 3,5-dibromo-2-pyridinol and 2-pyridinol (*266*). This reaction is complicated by a disproportionation of bromine. A very unexpected result was reported recently by Shibasaki (*267*). 2-Halo-5-nitropyridines (XII-178) un-

(XII-178)

R	X
CH_3	Cl
C_2H_5	Br
i-C_3H_7	
n-C_4H_9	

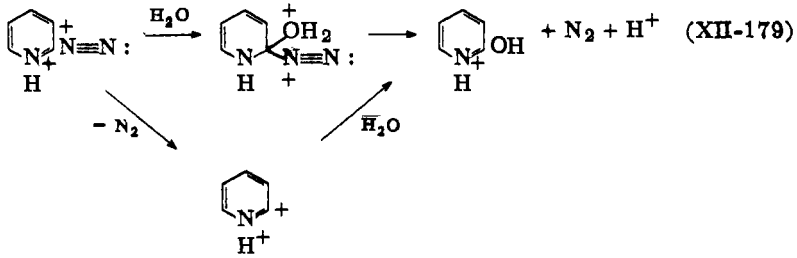
dergo displacement of the nitro group with alkoxides to give 2-halo-5-alkoxypyridines. On the basis of the electronic theory previously discussed, the α-halo group and not the β-nitro group should be displaced. These results are contrary to the findings previously discussed and are perhaps open to question.

For replacement reactions of nitro groups, see Chapter VIII (pp. 478 f.).

c. Aminopyridines

Aminopyridines are readily converted to pyridinols by two general methods, diazotization and hydrolysis. In several cases where the pyridinols are known, the structure of amines has been determined by such a conversion (*cf.* Chapter IX, pp. 32 f.).

The diazotization technique is applicable to the α, β, and γ isomers. The course of this reaction probably involves the displacement of nitrogen by water as shown in XII-179. In view of the

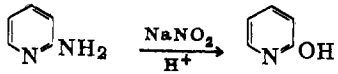


large heat of formation of nitrogen, the diazonium ion could lose N_2 to give a carbonium ion, which would then form the product by solvation. The high energy of the carbonium ion, due to lack of resonance stabilization and an adjacent positive charge in the ring, makes this alternate route less likely. In phenyldiazonium decompositions, however, it may be operative (*388*). Table XII-11 lists several alkyl- and halo-2-aminopyridines which have been converted to pyridinols (XII-180).

In the conversion of 2,4-dimethyl-5-aminomethyl-3-aminopyridine to the corresponding diol, it was found that barium rather than sodium nitrite gives a more easily purified product (*861*).

Several 3-nitro- (*277*), halo-3-nitro- (*278,279*), alkyl-3-nitro- (*280, 281*), 5-nitro- (*282*) and 5-nitroalkyl-2-aminopyridines (*280,304*) have been transformed to the corresponding 2-pyridinols in acceptable yields. Similarly, 3-carboxy- (*283*), 3-carboxy-4-chloro- (*222*), 3-carboxamidoalkyl- (*285*), and 3-chloro-5-carboxy-2-pyridinols (*284*) have been prepared in good yields. When, however, two ortho or para electron-withdrawing groups are present, conflicting results are reported. It has been claimed, for example (*286*), that 5-nitro-6-aminonicotinic acid (XII-181) is recovered unchanged after nitrous acid

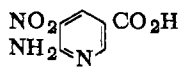
TABLE XII-11. Conversion of 2-Aminopyridines to 2-Pyridinols with Nitrous Acid



(XII-180)

Substituent and position				Yield, %	Ref.
3	4	5	6		
H	CH_3	H	H	78	268,274
CH_3	H	H	H		269
H	H	H	CH_3	93	270,274
C_2H_5	H	H	CH_3		271
H	H	H	PhCH=CH	48	274
H	H	Br	H		272
H	H	Cl	H	83	273
H	H	I	H		218
H	Cl	H	H		275
H	I	H	H		275
H	Cl	H	Cl		257
Br	H	Br	H		272
Cl	H	Cl	H		273
H	H	H	Br		276
H	H	H	Cl		865

treatment, while 5-nitro-2-aminonicotinic acid (XII-182) reacts readily (*287*). The successful preparation of 3,5-dinitro-2-pyridinol



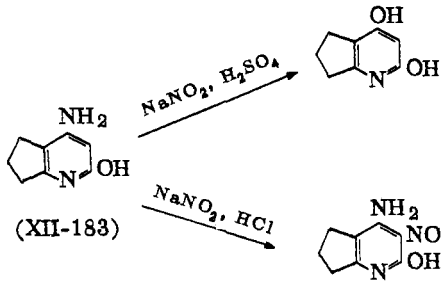
(XII-181)

(XII-182)

(*279*) and 4,6-dimethyl-3,5-dicarboxy-2-pyridinol (*288*) from the corresponding amines suggests that the failure of XII-181 to undergo diazotization may be due to conditions used, and not to the reduced basicity of the amino group.

A few 4-aminopyridines have been converted to the 4-pyridinols by nitrous acid, *viz.*, 4-amino-3-picoline (*289*), 2,6-dibromo-4-aminopyridine (*226*), and 4-aminopicolinic acid (*243*). The hindered amino group in 4-amino-2,3,5,6-tetrachloropyridine has been converted to a hydroxy group (*228*) with nitrosylsulfuric acid but in only 15% yield. With certain compounds the conditions are very

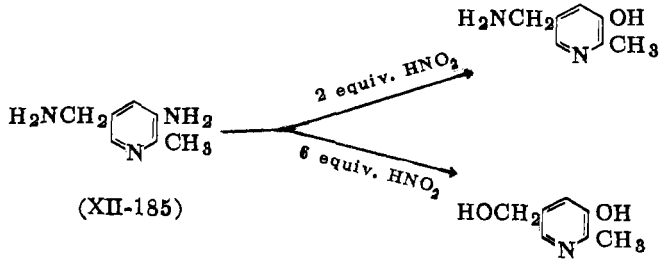
critical. Thus, 4-amino-2-hydroxy-6,7-dihydropyrindine (XII-183) can give the diol or 3-nitroso-4-amino-2-hydroxy-6,7-dihydropyrin-



dine, depending on whether sulfuric or hydrochloric acid is used (*156*).

The 3-aminopyridines are easily diazotized and hydroxylated (XII-184) as might be expected from the generally "normal" aromatic character of the 3 position. Table XII-12 lists some examples.

When an aminomethyl group (CH_2NH_2) is a substituent on a 3-aminopyridine, under competitive conditions the ring amino group is more reactive. With two equivalents of nitrous acid, 3-amino-5-aminomethyl-2-picoline (XII-185) gives 2-methyl-5-aminomethyl-3-pyridinol. To diazotize both amino groups, six equiva-



lents of nitrous acid are needed (*59*). At 0–5°C., treatment of 2-methyl-3-amino-5-aminomethylisonicotinic acid (XII-186) with nitrous acid results only in diazotization of the ring amino group; at 60°C., both diazotize.

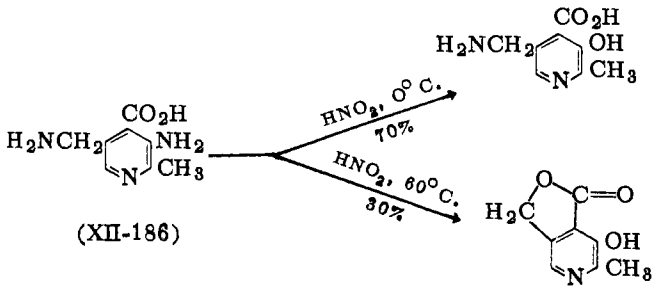
TABLE XII-12. Conversion of 3-Aminopyridines to 3-Pyridinols with Nitrous Acid

(XII-184)

Substituent and position				Ref.
2	4	5	6	
H	H	H	CH_3	290,281
H	H	Br	H	291
H	H	CO_2H	H	284
CH_3	H	H	CH_3	292
CH_3	CH_3	H	CH_3	292
H	CO_2H	CO_2H	H	293[a]
COOH	H	H	H	294
H	CO_2H	H	H	295
H	CO_2CH_3	H	H	296
Cl	H	H	CH_3	281
CH_3	H	H	Cl	281
H	H	H	C_3H_7	297
H	H	$CO_2C_2H_5$	CH_3	298
CH_3	Cl	CN	Cl	59
CH_3	CO_2H	CO_2H	H	49[b]
CH_3	CO_2H	CO_2H	CO_2H	299[b]
CH_3	H	CO_2H	CO_2H	391

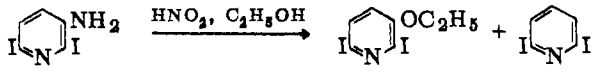
[a] Nitrosylsulfuric acid used.

[b] These two 3-pyridinols were prepared as intermediates for pyridoxine syntheses.



(XII-186)

Diazotization in concentrated hydrochloric acid often leads to the chloro- rather than the hydroxypyridine as the major product, as was found for 3-chloro-, 3,5-dichloro- (*273*) and 3-nitro-6-methyl-2-aminopyridines (*281*). When the reaction with nitrite is performed in alcohol, ethers are formed. The mineral acid salts of 2-aminopyridine in ethanol yield 2-ethoxypyridine when treated with alkyl nitrites (*301*). When diazotized in the presence of phenol, 2-aminopyridine forms 2-phenoxypyridine (*302*). Reduction of the intermediate diazonium salt as a side reaction is exemplified by the formation of both 2,6-diiodo-3-ethoxypyridine and 2,6-diiodopyridine from 3-amino-2,6-diiodopyridine (XII-187).

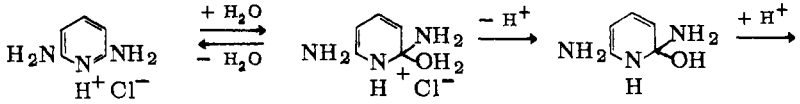


(XII-187)

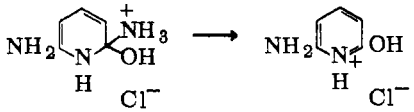
An alternate method of replacing amino by hydroxyl is direct acid- or base-catalyzed hydrolysis. This reaction is limited to 2- or 4-amino groups. 2,6-Diaminopyridine, refluxed for three hours in 10% hydrochloric acid (*305*) or for two hours in 70% sulfuric acid (*308*), gives excellent yields of 6-amino-2-pyridinol. Further study of this reaction (*306*) reveals that the second amino group can also be displaced to give the diol, but at a much slower rate. Excessive heating causes rupture of the ring. However, the diamine is stable in strongly alkaline solutions. 2-Aminopyridine itself does not react with either acid or alkali.

A modification in terms of ionic intermediates of the mechanism originally proposed by Seide and Titov (*308*) is shown (XII-188). The stability of the diamine toward base is probably due to two main factors: (1) the lack of formation of a neutral intermediate (XII-189) and (2) the need for displacing NH_2, a much stronger base than NH_3.

To account for the different behavior of the di- and monoaminopyridines an explanation was offered (*308*) based on the naive assumption that the two Kekulé structures of pyridine are discrete entities. It is, however, understandable in terms of modern resonance theory. Rather than exhibit typical amine-like properties, the 2-amino group is incorporated in an amidine system which has con-



(XII-189)



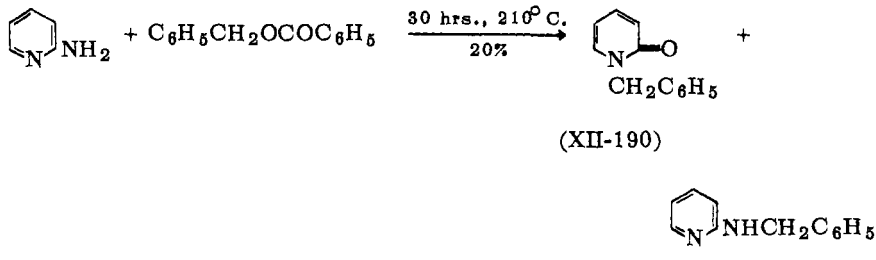
(XII-188)

siderable resonance stabilization in acid. Attack at C_2 is resisted because it interferes with the resonating system and because the 2 position has diminished electrophilic character. In the diamine both amino groups participate, but not to the same extent as a monoamino group. The positive charge on either carbon is greater than in the monoamine and hydrolysis can occur. The substitution of a hydroxyl group diminishes the replaceability of the remaining amino group. However, since there is some resonance interaction of the OH group with the ring, the amino group of 6-amino-2-pyridinol is somewhat more easily displaced than the one in 2-aminopyridine itself.

As expected, a C_3 nitroso or nitro group facilitates the hydrolysis of the diamine and hydroxyamine. The nitroso group increases the rate in both acid and base, while the nitro group has an appreciable effect only in base (*307*).

3-Nitro-4-pyridinol is formed smoothly from 3-nitro-4-aminopyridine and barium hydroxide (*309*), and 5-nitro-6-aminonicotinic acid, which could not be diazotized, was readily hydrolyzed with warm 10% sodium hydroxide (*286*).

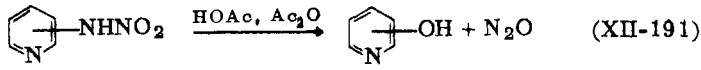
One advantage of hydrolysis over diazotization is the utility of methylamines as starting materials. Both 3- and 5-nitro-2-methylaminopyridines are quantitatively converted in boiling 5% sodium hydroxide to the corresponding 2-pyridinols and methylamine (*310*). Under the same conditions, 2-dimethylamino-5-nitropyridine is also hydrolyzed (*310*). A unique conversion of an aminopyridine is the reported formation (*311*) of 1-benzyl-2(1*H*)-pyridone (XII-190) when an anhydrous mixture of 2-aminopyridine and benzyl benzoate is heated.



(XII-190)

d. Nitramines

The use of these compounds for the preparation of oxypyridines is another major contribution of Chichibabin to the field of pyridine chemistry. All three aminopyridines can be nitrated on the amino group under controlled conditions. When 2-nitraminopyridine is treated with concentrated sulfuric acid, the nitro group migrates to the ring; however, a trace of 2-pyridinol is found. The yield of the oxypyridine can be improved to 60% by refluxing the nitramine in an acetic acid–acetic anhydride mixture (XII-191). The

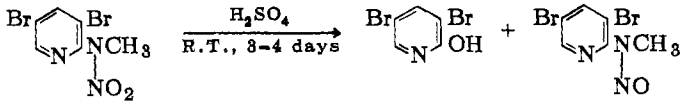


(XII-191)

3-nitramine undergoes pyridinol formation predominantly, rather than nitro group migration, in either concentrated sulfuric acid or the acetic acid–anhydride mixture (*312*). When the 3 and 5 positions are blocked, even the 2-nitraminopyridine forms the 2-pyridinol in good yield, when left for several days in concentrated sulfuric acid. This is exemplified by 3,5-dibromo-2-nitraminopyridine (*314*). No one has proposed a mechanism for this transformation. However, because of the anhydrous conditions and the formation of nitrous oxide, one can speculate that the reaction proceeds via an intramolecular attack of the nitro group oxygen on the ring carbon.

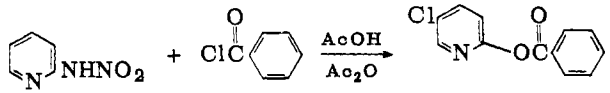
There have been reports of direct conversion of an amino to a hydroxy group during nitration with a concentrated nitric-sulfuric acid mixture. In each case there is an electron-withdrawing group para to the amino group, *e.g.*, 5-nitro-2-amino-3-picoline (*304*), 5-nitro-2-aminopyridine (*313*), and 6-aminonicotinic acid (*286*). Di-

azotization conditions were used for the conversion of 2-nitraminonicotinic acid to the hydroxy compound (*287*). Nitromethylaminopyridines are also converted to the corresponding oxypyridines, as exemplified (*314*) by the reaction of 3,5-dibromo-2-nitromethylaminopyridine (XII-192).



(XII-192)

An unusual result is the reported isolation (*315*) of 5-chloro-2-pyridyl benzoate from a mixture of 2-nitraminopyridine and benzoyl chloride, as shown (XII-193). The reaction with aliphatic acyl hal-



(XII-193)

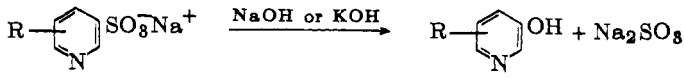
ides is less smooth. The ring chlorination and formation of nitrogen led to the speculation that an oxidation-reduction reaction occurred involving the expected by-products, nitrous oxide and hydrogen chloride.

e. Sulfonic Acids

The alkali fusion of salts of pyridinesulfonic acids is a useful synthesis of pyridinols. This is another example of the displacement of a weak base, sulfite ion, by a strong base, hydroxide or alkoxide ion. This is the conventional method (XII-194, Table XII-13) for preparing 3-pyridinol (*316,320*), and in general, is most applicable for 3-pyridinols because of the difficulties encountered in obtaining 2- and 4-sulfonic acids. The reaction has been extended to the preparation of ethers by fusing the sulfonic acid salts with sodium alkoxides. In this manner, 2-methoxy- and 2-ethoxy-5-nitropyridines (*322*) and 3-methoxypyridine (*323*) were prepared from the sulfonic acids.

Phosphorus pentachloride reacts with sodium 4-pyridinesulfonate to give a low yield of 4-pyridinol (*324*). Since the major product

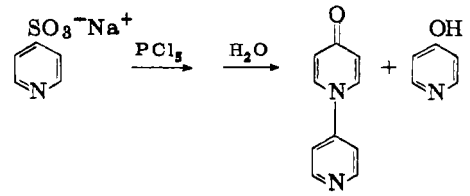
TABLE XII-13. Alkali Fusion of Sulfonic Acid Salts



(XII-194)

R	Ref.
6-CH_3	316,317
2-CH_3	316,318
5-CH_3	319
4-CH_3	316
2-CH_3, 5-C_2H_5	316
6-COOH	316
	321

of this reaction is 1-(4-pyridyl)-4(1*H*)-pyridone (XII-195), its hydrolysis probably accounts for the formation of 4-pyridinol.



(XII-195)

2,6-Di-*t*-butylpyridine-4-sulfonic acid is hydrolyzed to the 4-pyridinol when heated with water for ten hours at 240°C. in a sealed tube (*860*).

When pyridine is sulfonated at 330° C. with 100% sulfuric acid and mercuric sulfate, in addition to the expected pyridine-3-sulfonic acid, some 4-sulfonic acid and 4-pyridinol are isolated. Under the same reaction conditions, the 3-sulfonic acid is converted to 4-sulfonic acid and 4-pyridinol (15–20% yield). The authors exclude the possibility that 4-pyridinol arises from hydrolysis of the 4-sulfonic acid during isolation of the products. Rather, they believe the hydroxy compound is formed during the reaction, although they offer

no mechanism (*882*). Conceivably, it could result from a nucleophilic displacement by sulfate of the sulfo group at C_4. It would be of interest to treat the 4-sulfonic acid under the same conditions to detect any 4-pyridinol. For further discussion of the sulfonation and hydrolysis reactions, see Chapter XV.

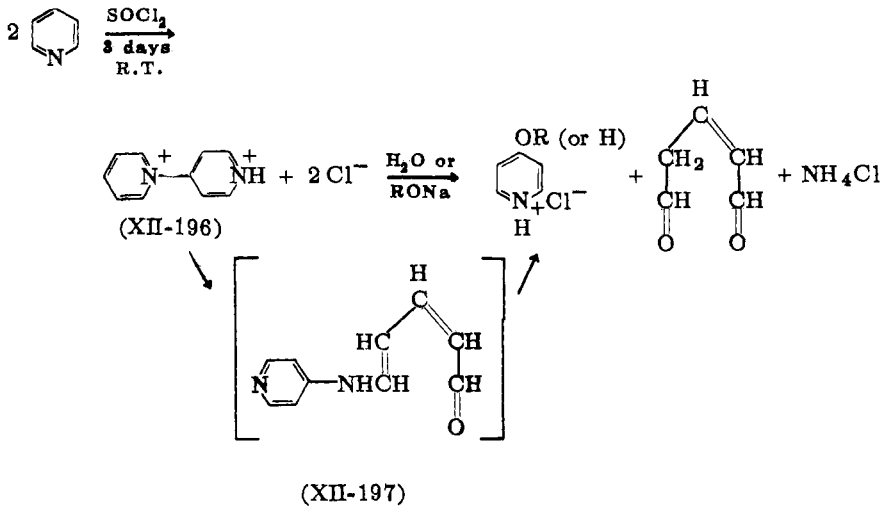
f. Pyridylpyridinium Salts

This reaction, introduced by Koenigs and Greiner (*325*), has proved to be very useful for the preparation of 4-pyridinol and its ethers. Pyridine, on standing for several days with thionyl chloride, yields crude 1-(4-pyridyl)pyridinium chloride hydrochloride (XII-196), which is hydrolyzed, without previous purification, to 4-pyridinol and glutaconic dialdehyde or some derivative of the latter (*325*). The hydrolysis of XII-196 can be effected with water at 150°C. for eight hours (*325*) or at reflux temperatures for seventy-two hours (*326*). This reaction has been considered (*326*) to be best from the point of view of yield and labor for the preparation of 4-pyridinol, being superior to the decarboxylation of chelidamic acid (formed from chelidonic acid and ammonia) (*120*). The yield of highly purified product calculated from pyridine is 20% (*326*). In a modification of this reaction, pyridine containing 2% of dissolved aluminum chloride was treated with bromine in tetrachloroethane at room temperature for forty-eight hours (*327*). 1-(4-Pyridyl)pyridinium bromide hydrobromide, so formed, was autoclaved at 150° to give 4-pyridinol. The hydrobromide on hydrolysis is reported to give better yields than the hydrochloride (XII-196).

Treatment of XII-196 with sodium alkoxides or aryloxides in the presence of the alcohol or phenol gives the corresponding 4-pyridyl ether, where R = methyl, *n*-butyl (*203*), benzyl (*205*), phenyl (*325, 203*), or *o*-, *m*-, and *p*-tolyl (*203*). The yields of the aryl ethers are about 70%, but those of the alkyl ethers were below 40%.

The isolation of glutaconic dialdehyde indicates the opening of one of the rings of XII-196 to give the intermediate XII-197, which undergoes hydrolysis to the products.

The chemistry of pyridylpyridinium salts is also discussed in Chapter III (pp. 11 ff.)

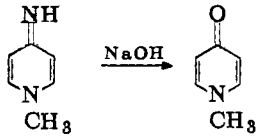


(XII-196)

(XII-197)

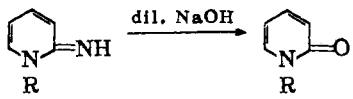
g. Pyridonimines

The use of these compounds was also pioneered by Chichibabin, no doubt as a result of his interest in the chemistry of aminopyridines. Both 2- and 4-pyridonimines have been hydrolyzed to the respective pyridones. 1,4-Dihydro-4-imino-1-methylpyridine is easily hydrolyzed in alkali (XII-198) to the 4-pyridone (*328*). When 2-



(XII-198)

aminopyridine and methanol are passed over aluminum oxide above 300°, 1-methyl-2(1*H*)-pyridone is isolated (*329*). The likely intermediate in this reaction is the pyridonimine. Several α-pyridonimines have been hydrolyzed by base (XII-199). This reaction was



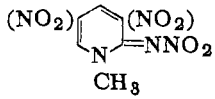
(XII-199)

R = CH_2COOH (*330*), $C_{12}H_{25}$ (*332*), CH_2CH_2OH (*331*), $CH_2C_6H_5$ (*334*)

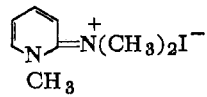
utilized to distinguish between the two alkylation products of 2-aminopyridine, since only the ring *N*-alkylated product gives a 1-alkyl-2(1*H*)-pyridone.

The pyridonimines are generally prepared by treating the 2- or 4-aminopyridines successively with methyl iodide and silver oxide (*334*). The utility of this method therefore depends on the availability of amino compounds (*cf.* Chapter IX).

Nitropyridonimines readily hydrolyze in boiling water, as exemplified by the reaction of 1,2-dihydro-1-methyl-3(and 5)-nitro-2-nitroiminopyridine (XII-200) (*333a*) and the 3,5-dibromo derivative (*314*) to give the corresponding pyridone and nitrous oxide. The alkylated derivative of 1,2-dihydro-1-methyl-2-methyliminopyridine, probably XII-201, reacts with silver oxide to give 1-methyl-2(1*H*)-pyridone (*333b*).



(XII-200)



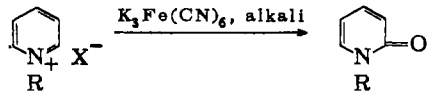
(XII-201)

h. Quaternary Salts

An important reaction of these compounds is their oxidation with potassium ferricyanide in alkali to give 1-substituted-2(1*H*)-pyridones (XII-202). (X is usually iodide or methosulfate.) Some typical compounds oxidized in this manner are listed in Table XII-14. This reaction was first developed by Decker (*335a,b,c*) who obtained 1-methyl-2(1*H*)-pyridone (XII-202, R = CH_3) in 75–80% yield. Improved conditions raised the yield to 90–95% (*336*). Electrolytic methods (*337*) offer no advantage over the chemical methods. It is necessary to add potassium ferricyanide to the anolyte, and the yields are of the order of 90–95%. The attempted oxidation of methylene-bis-pyridinium dibromide was unsuccessful, and pyridine was regenerated (*343*).

The reaction of N-substituted esters of isonicotinic acid gives good yields of the 2(1*H*)-pyridone. The product isolated is the free

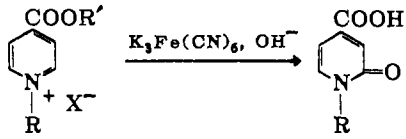
TABLE XII-14. Alkaline Ferricyanide Oxidation of Pyridinium Salts



(XII-202)

R	Yield, %	Ref.
CH_3	90–95	336,338
C_2H_5		335[b]
n-C_3H_7, i-C_4H_9, i-C_5H_{11}		335[c]
n-C_4H_9		339
$(CH_2CH_2)_2O$	40	340
$CH_2CH_2C_6H_5$	90	341
$CH_2CH_2C_6H_4(OCH_3)$		342
$(CH_2)_n$—N⟨◯⟩ (n = 2 – 6)		343
$CH_2CHOHC_6H_5$	80	344a
-Alkoxyhydroxy		344b

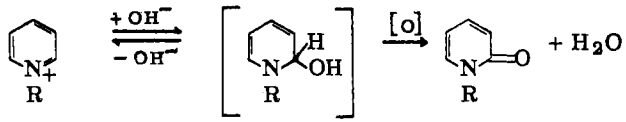
acid (XII-202a). The yield of pyridone increases with increasing size of the ester group, and with a slower, constant rate of addition of the reagents (*847*).



(XII-202a)

R = Me, R′ = Me, Et, i-Pr (*847,856*)
R = CH_2CH_2Ph, R′ = Me (*846*)

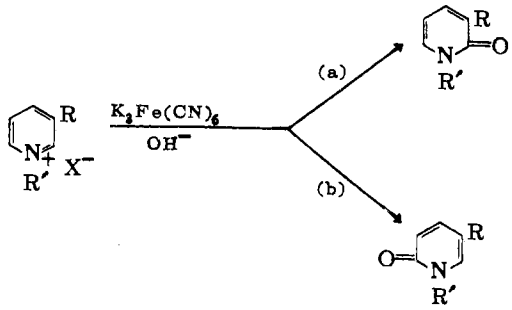
The mechanism proposed for this reaction (*345*) requires the formation of a pseudo- or carbinol-base (XII-203), which is in equili-



(XII-203)

brium with the pyridinium salt. Although the equilibrium strongly favors the pyridinium salt, the irreversible oxidation of XII-203 shifts it to the right. The formation of the transitory pseudo-base is facilitated by the activation of the α position by the positively charged nitrogen toward nucleophilic attack. In reality, therefore, this is another example of a displacement reaction, where hydroxide ion displaces hydride ion, whose removal is encouraged by its oxidation to water. This mechanism does not give a complete picture of the reaction, since it does not account for the absence of any γ-pyridone. Molecular orbital calculations reveal that the 4 position should be more predisposed toward attack by base than the 2 position. The explanation may be revealed if the actual mode of oxidation were elucidated. Possibly the close proximity of the ring nitrogen assists the reaction (*cf.* Chapter III, pp. 32 ff.).

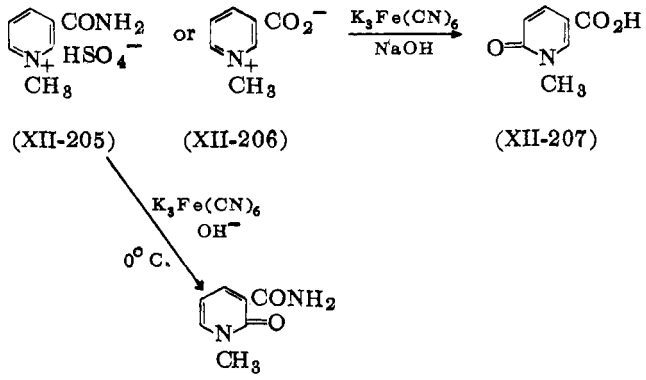
When there is a substituent in the 3 position, two isomeric pyridones can be formed, 2 and 6 (XII-204). Bradlow and Vanderwerf



(XII-204)

(*346*) have shown that the nature of the R group has a profound effect on the course of the reaction. When R = CH_3, $CONH_2$, Br (R′= CH_3), and R = CH_3 (R′= C_2H_5), oxidation occurs predominantly in the 2 position (XII-204a). Nicotinonitrile methiodide appeared to be oxidized in both positions, whereas nicotinic acid methosulfate was oxidized mainly in the 6 position (XII-204b). This work clarified a discrepancy in the literature. Huff (*347*) had reported isolating 1-methyl-2(1*H*)-pyridone-5-carboxylic acid (XII-207) by oxidizing either trigonelline (XII-206) or 1-methylnicotinamide bisulfate (XII-205). Shortly afterwards, it was reported (*348*) that at low temperatures XII-205 is oxidized to 1-methyl-2(1*H*)-pyridone-3-

carboxamide (XII-207a). Since the acid (XII-206) and the amide (XII-205) have since been shown to give different isomers (*346*), it



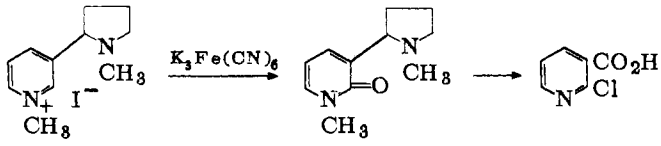
(XII-207a)

appears that in Huff's experiment the amide first underwent hydrolysis to the acid, which was then oxidized. The interest in these reactions stems from the isolation of XII-207 from human urine after ingestion of nicotinamide (*349*). Likewise, the amide of XII-207 has been obtained by the reaction of XII-205 with a quinone-oxidizing enzyme obtained from rabbit liver (*349*). This is an instance where synthetic and biochemical paths led to different isomers.

To bring order to these somewhat confusing results, the mechanism of the reaction was considered (*346*) in terms of the resonance stabilization of the pseudo-bases formed by reaction at C_2 and C_6. Regardless of whether the C_3 substituent is electron donating or withdrawing, more resonance structures can be written for attack at C_2. This explains why methyl, bromo and carboxamido groups favor oxidation at the 2 position. The claim is further made that the carboxylate and cyano groups, because of the presence of either a full or partial negative charge, electrostatically inhibit the oxidation of the C_2 pseudo-base, thus favoring reaction at C_6.

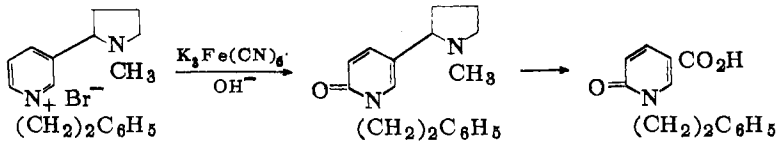
That this analysis is an oversimplification is apparent from the work of Sugasawa and his co-workers. He emphasizes the need to consider the steric influence of the ring substituent (*350*). The oxidation of 1-methyl-3-phenylpyridinium methosulfate gives the 6(1*H*)-

pyridone (*350*) as does the 3-(α-ethylene dioxyethyl) derivative (*352*). Sugasawa stresses the point that the nature of the *N*-alkyl group has no directive influence. This, however, is not borne out by results reported in the literature. The methiodide of nicotine (XII-208)



(XII-208)

was oxidized to the 2-pyridone, whose structure was proved by degradation to 2-chloronicotinic acid (*353*). The same position was oxidized when the ethiodide, propiodide, and butiodide were used. However, when the phenethyl bromide (XII-209) was oxidized, the



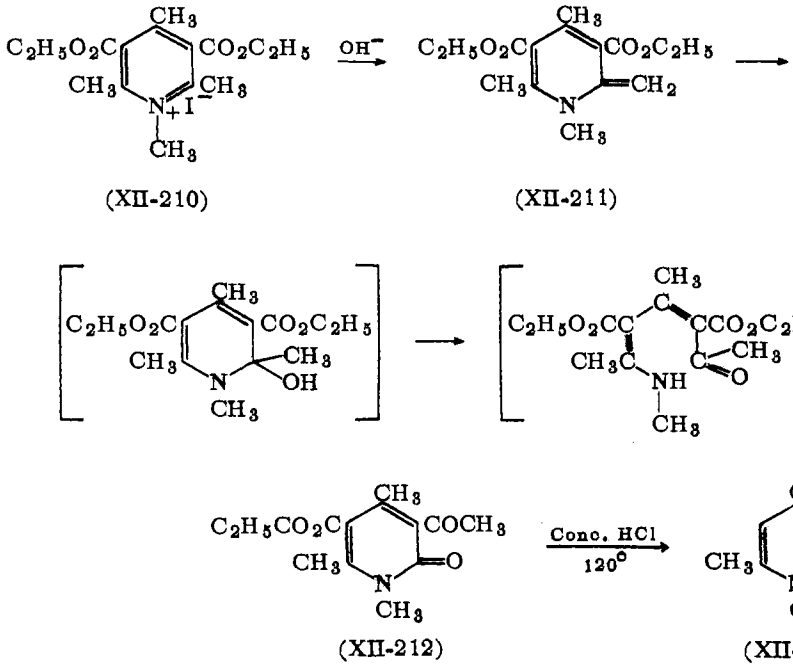
(XII-209)

6-pyridone was isolated, which was then degraded to 1-phenethyl-2(1*H*)-pyridone-5-carboxylic acid (*354*). This discrepancy may be attributed to the greater steric effect of the 1-phenethyl group, promoting hydroxylation of the less-hindered 6 position. It is evident, therefore, that the alkaline ferricyanide oxidation of 3-substituted pyridinium compounds is controlled not only by the resonance interaction and the electrostatic effects, but by the bulkiness of the *N*-substituent as well.

The confusion in this area is evident from the work of Tomisawa (*845*). He asserts that the oxidation of 1-phenethyl-3-phenoxypyridinium salts gives the 6-pyridone, while the corresponding 3-bromo and 3-cyano compounds give good yields of the 2-pyridone. Proof of structure, however, is based only on dipole moments.

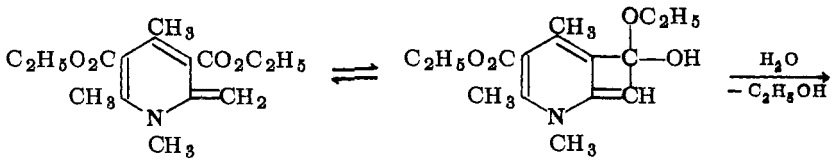
If one of the α positions is blocked by an alkyl group, *e.g.*, 1-phenethyl-2-picolinium bromide, the other α position is oxidized,

but the yields are poor (*364*). Where both α positions are blocked, conversion to α-pyridones can still occur via formation of intermediate pyridone methides. The action of alkali upon the methiodide of collidine-3,5-dicarboxylic ester (XII-210) is an example. This reaction was reported by Mumm and Hingst (*355*) to give 3-acetyl-5-carbethoxy-1,4.6-trimethyl-2(1*H*)-pyridone (XII-212) by a series of reactions involving formation of the pyridone methide (XII-211), its hydrolysis, ring fission, and subsequent ring closure in an alternate fashion. In a later publication (*356*), Mumm modified the structure assigned to the final product (XII-212), because whereas 1-methyl-2(1*H*)-pyridones fluoresce, XII-212 does not and the molecular refraction does not agree with the formula. Since XII-212 can be degraded to 1,4,6-trimethyl-2(1*H*)-pyridone (XII-213), the

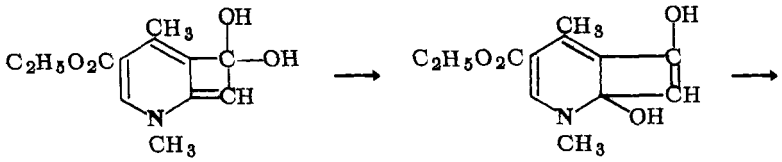


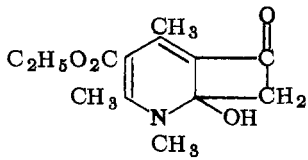
only doubtful substituents in XII-212 are in the 2 and 3 positions. However, any proposed structure must have an oxygen function in the 2 position to account for the formation of XII-213. Mumm

suggested the alternative structure XII-214 and a mechanism for its formation which avoids the ring opening.



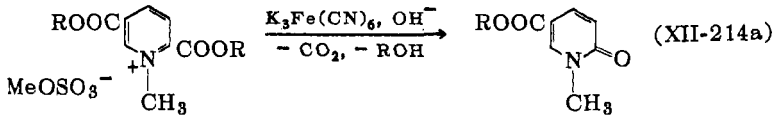
(XII-211)





(XII-214)

When 2,5-dicarbomethoxy-*N*-methylpyridinium methosulfate is treated with potassium ferricyanide in basic solution, a rapid exothermic reaction occurs, resulting in a displacement of the 2-carbomethoxy group by an oxo group (XII-214a). A similar reaction occurs when the free dicarboxylic acid is used (*848*).

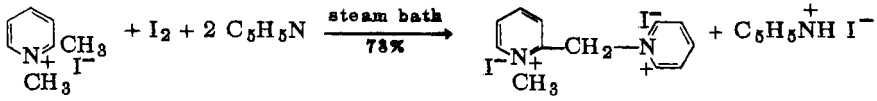


(XII-214a)

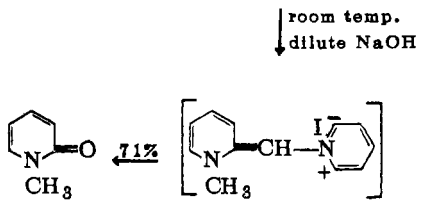
R = H, CH_3

A unique conversion of 1,2-dimethylpyridinium iodide to 1-methyl-2(1*H*)-pyridone has recently been reported by Berson and Cohen (*357*). The basis for the reaction is the analogous behavior of methyl ketones and 2-methylpyridines. Thus the change

$O{=}C{-}CH_3 \rightarrow O{=}C{-}OH$ is electronically related to $R{-}N{=}C{-}CH_3 \rightarrow R{-}N{=}C{-}OH$. Equimolar amounts of *N*-methyl-2-picolinium iodide and iodine were warmed in pyridine solution to give XII-215. Treatment of this with dilute sodium hydroxide gave a transient red color (attributed to the presence of XII-216, the

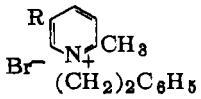


(XII-215)



(XII-216)

anhydro base) and then yielded 1-methyl-2(1*H*)-pyridone. This reaction is related to the cleavage of *N*-phenacylpyridinium salts. It was successfully extended to 1-phenethyl-2-picolinium bromide (XII-216a, R = H), there being no Hofmann elimination of the



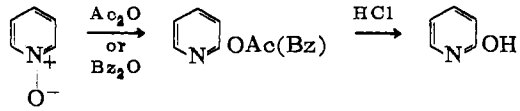
(XII-216a)

2-phenethyl group, and to 5-ethyl-1-phenethyl-2-picolinium bromide (XII-216a, R = C_2H_5).

i. N-Oxides

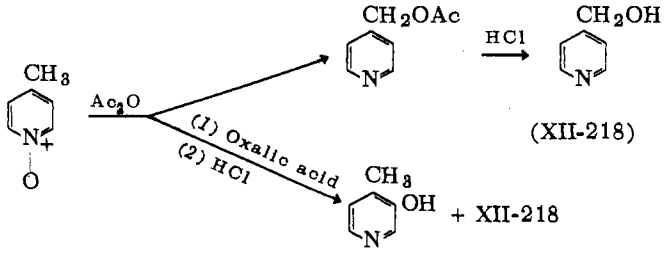
All three isomeric pyridinols have been prepared from *N*-oxides, either by rearrangement of the oxygen function from the nitrogen to the ring, or via an intermediate which requires removal of the nitrogen-bonded oxygen as the final step (*cf.* Chapter IV, pp. 125 ff.).

In 1947, Katada (*359*) reported the reaction of pyridine 1-oxide with either acetic or benzoic anhydride to give the 2-acyloxypyridine, which on hydrolysis yields 2-pyridinol in excellent yields (XII-217). Similarly, 3-picoline 1-oxide gives 3-methyl-2-pyridinol (*360*), and 4-ethoxypyridine 1-oxide gives 4-ethoxy-2-pyridinol (*361*).



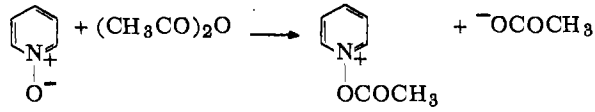
(XII-217)

In the case of 2-picoline 1-oxide, the reports are conflicting. One claim is that the oxygen function does not rearrange to the ring, but rather to the side chain methyl group, forming 2-pyridinemethanol (*360,362*). Another claim is made (*393*) that a 20% yield of 6-methyl-2(1*H*)-pyridone is obtained along with a 50% yield of 2-pyridinemethanol. Benzoic anhydride gives the same mixture as acetic anhydride, but in smaller yields. 4-Picoline 1-oxide was also found (*360,362*) to form the 4-pyridinemethanol (XII-218). How-



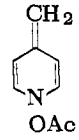
(XII-218)

ever, by changing the isolation procedure, Berson and Cohen (*363*) also obtained 4-methyl-3-pyridinol. The mechanism of the reaction is still obscure, although suggestions have been advanced. The first step is logically assumed by Boekelheide and Linn (*360*) to be the formation of the acetate salt of the acetylated *N*-oxide (XII-219).



(XII-219)

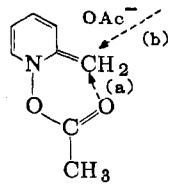
An induction period, followed by an exothermic reaction, suggests to these authors a chain reaction involving radicals, initiated by the homolytic cleavage of the thermally unstable N-O bond of XII-219. To account for the mixed products obtained from 4-picoline 1-oxide, an ionic mechanism was proposed (*363*) involving the anhydro base (XII-220) which is susceptible to attack by acetate ion either at the



(XII-220)

methylene group or at carbon-3. In either case, the acetoxy group bound to nitrogen would be cleaved simultaneously.

Traynelis and Martello (*849*) have made a careful study to test the free radical mechanism first proposed by Boekelheide and Harrington (*850a*). The products from the reaction of 2-picoline 1-oxide and acetic anhydride were carefully isolated and shown to be 2-pyridylmethyl acetate (87%), 2-picoline (0.14%), and gas, the major components of which were carbon dioxide and methane. It was argued that these gases were formed from acetoxy radicals. The presence of radicals is also supported by the formation of polystyrene when styrene is added to the reaction mixture (*850*). Added free radical scavengers such as *m*-dinitrobenzene or *p*-benzoquinone surprisingly had little effect on the yield of 2-pyridylmethyl acetate, but drastically reduced the amount of polystyrene and methane. The conclusion drawn was that although free radicals are present, they are not responsible for the formation of the rearranged product. An ionic mechanism was suggested involving the anhydro base (XII-220a).

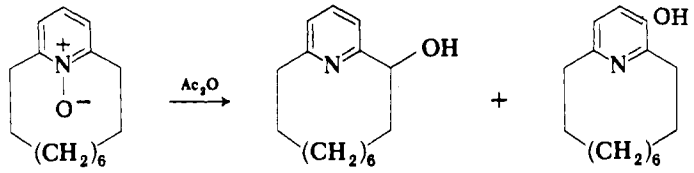


(XII-220a)

Two pathways are possible: (*a*) an intramolecular attack by the carbonyl oxygen of the acetoxy group on the methylene group giving the product directly or (*b*) a bimolecular process involving attack by an acetate ion on the methylene group followed by loss of the acetate group from the ring nitrogen to give the product. The two pathways were tested by reacting 2-picoline 1-oxide and butyric anhydride in the presence of sodium acetate. The sole product was 2-pyridylmethyl butyrate; no acetate was formed. Hence, the intramolecular pathway (*a*) is correct.

A similar study was made with 4-picoline 1-oxide (*850*), which confirmed the previous observation (*363*) that the major product was 4-pyridylmethyl acetate, with some 3-acetoxy-4-methylpyridine. Addition of *m*-dinitrobenzene gave some surprising results. Although the yields of ester products did not change when 10% of this free radical scavenger was introduced, there was a sharp drop in yield when 20% was added. To rationalize the results, an intramolecular process is postulated which involves a homolytic cleavage of nitrogen-oxygen bond in XII-220, with the formation of a radical pair. This pair may recombine either at C_3 or at the exocyclic methylene group to give a mixture of esters. In addition, some of the acetoxy and picolyl radicals may separate and give rise to the very small amounts of side products such as 4-methyl-, 4-ethyl-, and 2,4-dimethylpyridines. The intramolecular nature of the rearrangement was established again by using butyric anhydride and sodium acetate.

A novel application of this reaction was the synthesis of α-hydroxy-2,6-decamethylenepyridine (XII-220b) (*857*). From the reac-



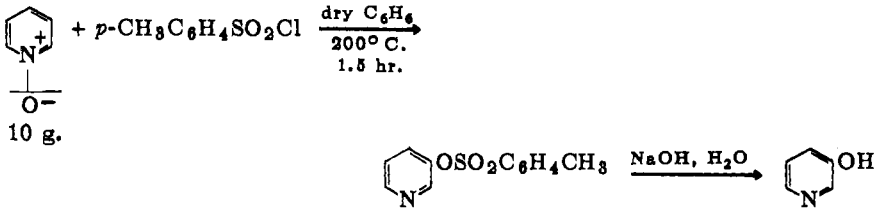
(XII-220b)

tion of nicotinic acid 1-oxide and acetic anhydride were obtained 2-acetylnicotinic acid 1-oxide (25–30%), 2-hydroxynicotinic acid (10%), and 6-hydroxynicotinic acid (3%). In contrast, rearrangement of 3-picoline 1-oxide gave 3- and 5-methyl-2(1*H*)-pyridones

(40% each) and 3-methyl-*N*-(5-methyl-2-pyridyl)-2(1*H*)-pyridone (4%), whose structure was proven by independent synthesis (*874*). No ketonic derivatives were isolated. The proposed mechanism for the formation of a ketonic product from nicotinic acid 1-oxide involves an intramolecular rearrangement of a mixed anhydride of the *N*-oxide and acetic acid via a cyclic transition state. The mechanism accounts for the absence of any 6-acetylnicotinic acid 1-oxide and also the nonformation of ketonic products from a similar reaction of isonicotinic acid 1-oxide.

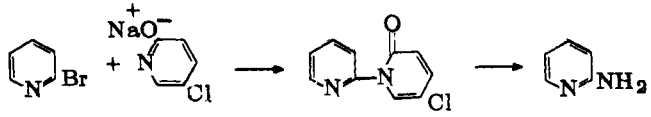
3-Nitropyridine 1-oxide rearranges in 50% yield to 3-nitro-2-pyridinol upon heating with acetic anhydride (*884*).

The reaction of *p*-toluenesulfonyl chloride with pyridine 1-oxide yields 3-(*p*-toluenesulfonyloxy)pyridine (XII-221) which gives 3-



(XII-221)

pyridinol on hydrolysis (*365*). Recently (*539*) a compound which analyzed for $C_{10}H_7ClN_2O$ was obtained in 10–15% yield along with XII-221 and a trace of pyridine. Its structure (XII-222) was estab-

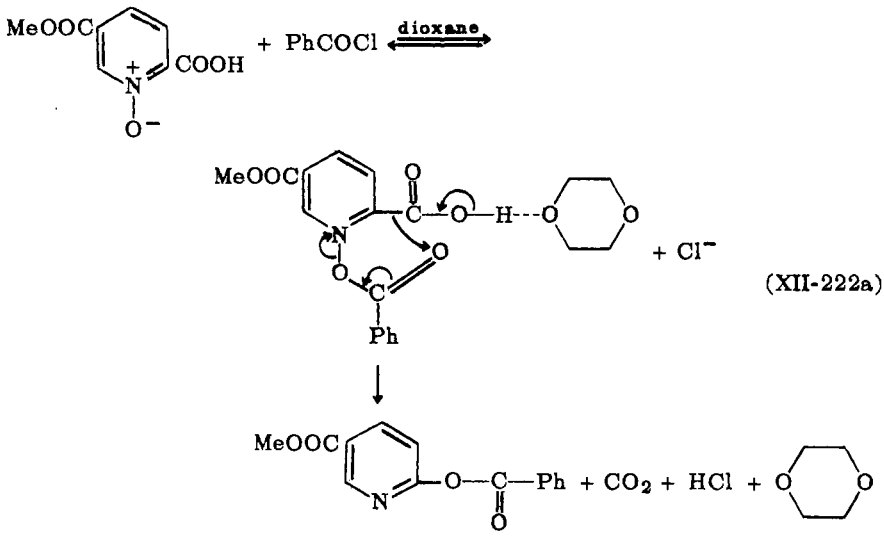


(XII-222)

lished by degradation to 2-aminopyridine under a variety of conditions and by independent synthesis. 3-Picoline 1-oxide behaves in an analogous manner to give 5-methyl-3-pyridinol (*366*). Conceivably, this reaction can proceed through tosylation of the oxygen. Another example of a rearrangement of the oxygen function from the nitrogen to the ring is the isolation of a small amount of 3,4-

dichloro-2-pyridinol (*228*) as a by-product from the reaction of 3,4-dichloropyridine 1-oxide with sulfuryl chloride.

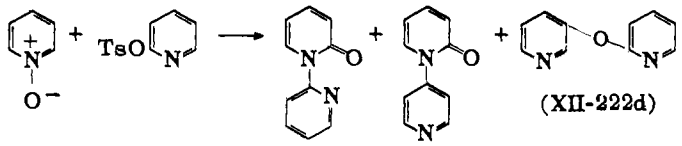
When benzoyl chloride was added to a dioxane solution of 5-carbomethoxypicolinic acid 1-oxide at 90° C., a rapid exothermic reaction occurred in which carbon dioxide was evolved (*848*). After hydrolysis, 6-hydroxynicotinic acid was isolated. The reaction does not proceed in benzene; a polar solvent is necessary. The reaction is formulated as shown (XII-222a). A similar reaction occurs with



(XII-222a)

acetic anhydride (*848*), but 4-hydroxynicotinic acid is obtained rather than the 6-hydroxy isomer. No explanation was offered for this unexpected result.

To see if 2-pyridyltoluenesulfonate is an intermediate in the reaction of pyridine 1-oxide with tosyl chloride, this compound was heated with the oxide. The products isolated are shown (XII-222b). To show the origin of the pyridine rings in the *N*-pyridyl products, 3-bromopyridine 1-oxide was reacted with 2-tosylpyridine. The product isolated was XII-222c, with a Br atom at the position ortho to the linkage to the nitrogen. Since some XII-222c and XII-222d are isolated in small amounts from the reaction of pyridine 1-oxide and tosyl chloride, it is conceivable that 2-tosylpyridine is an

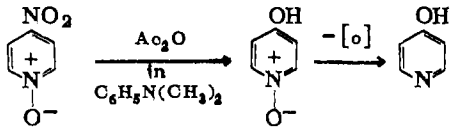


(XII-222b)

(XII-222c) (XII-222d)

intermediate. The 3-tosylpyridine is recovered unchanged when heated with pyridine 1-oxide (*851*).

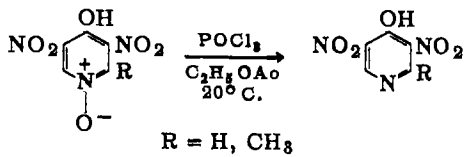
The activation of the ring by the *N*-oxide function offers a useful route to the synthesis of pyridinols, especially the 4 isomers. A typical synthesis (*367*) is shown in equation XII-223. The nitro



(XII-223)

63%

group can be displaced by methoxy, ethoxy, and phenoxy groups, by using the appropriate base (*368*). The success of this method depends on the deoxygenation of the *N*-oxide, and various methods have been devised. Both 4-ethoxy- and 4-phenoxypyridine 1-oxide have been reduced catalytically with palladium on charcoal under pressure (*368*). 4-Pyridinol 1-oxide and its methyl ether are reduced with Raney nickel in methanol at elevated temperatures or at room temperature under pressure (*369*). When nickel chloride is added to the reduction medium, the methyl ether yields 1-methyl-4(1*H*)-pyridone instead of 4-methoxypyridine (*369,387*). 3,5-Dinitro-4-pyridinol 1-oxide (*370*) and its 2-methyl homolog (*371*) are reduced (XII-224) with phosphorus oxychloride or phosphorus trichloride in

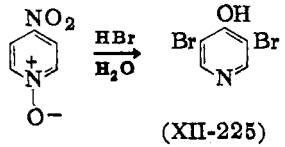


(XII-224)

R = H, CH_3

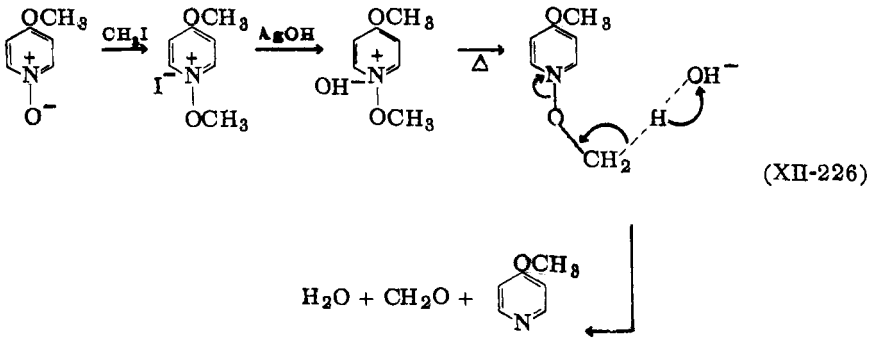
ethyl acetate. Thermal decomposition of the N—O bond has been accomplished by heating 4-ethoxypyridine 1-oxide with copper dust

at 160° C. (*263*). A more radical change was observed when 3,5-dibromo-4-pyridinol (XII-225) was isolated from the treatment of 4-nitropyridine 1-oxide with hydrobromic acid (*374*).



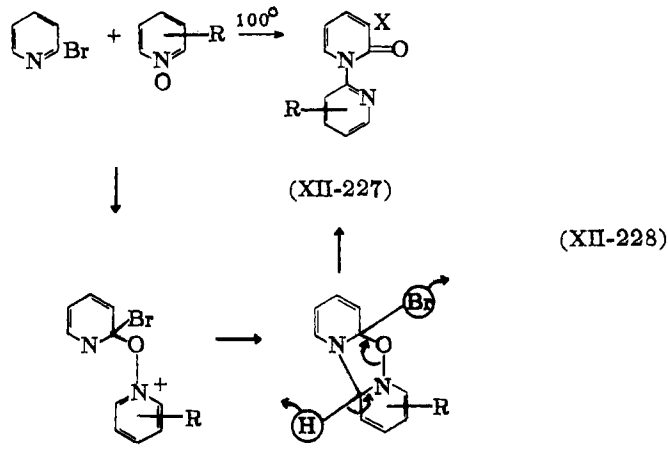
(XII-225)

When the methyl iodide adduct of 4-methoxypyridine 1-oxide was heated with silver oxide, 4-methoxypyridine and formaldehyde were obtained (*373*). Although the authors do not discuss the reaction, it is probably analogous to the Hofmann elimination reaction of quaternary ammonium hydroxides (XII-226).



(XII-226)

An unusual reaction was reported (*372*) between pyridine 1-oxide and 2-bromopyridine. 1-(2-Pyridyl)-2(1*H*)-pyridone (XII-227, R = X = H) and a second product of unknown structure were isolated. The reaction and its mechanism have been extensively studied by Ramirez and von Ostwalden (*375*). While a trace of mineral acid practically eliminates the usual induction period, base inhibits the reaction. In addition to XII-227 (R = X = H), a bromine-containing compound (XII-227, R = H, X = Br) was isolated. The path (XII-228) suggested for the formation of XII-227 (R = X = H) requires the oxide group to act initially as a nucleophile on 2-bromopyridine. This reaction should be facilitated by protonation of the ring nitrogen as was found. The bromo product (XII-227, R = H, X = Br) is considered to be formed in a secondary reaction from



XII-227 (R = X = H) by oxidative bromination involving the *N*-oxide and hydrogen bromide. This was substantiated by isolating XII-227 (R = H, X = Br) when XII-227 (R = X = H) and the hydrobromide of pyridine 1-oxide were heated. When toluene is used to moderate the initial reaction and some hydrobromic acid is used to initiate it, the brominated products are greatly minimized. The origin of the rings in the product was demonstrated by using picoline 1-oxides. Thus with 3-picoline 1-oxide, XII-227 is isolated where R = 5-CH_3. Similarly, 4- and 2-picoline 1-oxides gave the 4- and 6-methyl derivatives, respectively. These methyl products were synthesized for comparison purposes by *N*-pyridylation of 2-pyridinol with the corresponding 2-bromopicoline. That the bromine in XII-227 was at C_3 and not C_5 was likewise demonstrated by synthesis of the authentic compound from 5-bromo-2-pyridinol and 2-bromopyridine.

j. Direct Hydroxylation

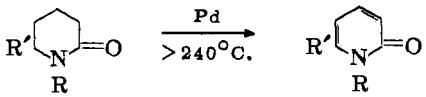
The first instance of nuclear hydroxylation of pyridine itself was reported by Chichibabin (*376*) who passed its vapors over molten potassium hydroxide at 300–320° C., and obtained 2-pyridinol and hydrogen. This reaction is related to the direct amination reaction, but the yields are inferior. This is attributed to the poorer nucleophilic properties of hydroxide ion. As a consequence of the low yield of product, this method has only limited synthetic value.

Similarly, 2-picoline is converted to 6-methyl-2-pyridinol (*377*). There are earlier references to the introduction of hydroxyl groups on pyridine derivatives. Thus, quinolinic acid is reported (*378*) to give 6-hydroxyquinolinic acid. Alkaline fusion of 3-pyridinol gives 40–50% yields of a pyridinediol (*379*). Originally it was believed to be the 2,5 isomer, but it is now known to be the 2,3 isomer (*380*). By fusion with sodium hydroxide at 200° C., 4-pyridinol is converted to 2,4-pyridinediol in good yield.

Mention has been made (*381*) of the formation of 3-pyridinol on treatment of pyridine with hydrogen peroxide. If *N*-oxide formation can be minimized, the availability of starting materials makes further study of this reaction worthwhile.

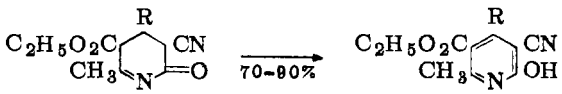
k. Hydropyridinols

Partially or totally reduced pyridinols or pyridones can be conveniently dehydrogenated to give the aromatic system. Thus, 2-piperidone, 6-methyl-2-piperidone, and *N*-methyl-2-piperidone have been dehydrogenated with palladium black at elevated temperatures (XII-229) (*382*). α-Dihydropyridinols (XII-230) have been aroma-



(XII-229)

R, R′ = H, CH_3

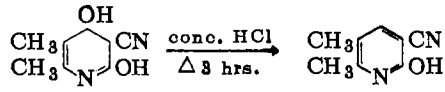


(XII-230)

R = C_6H_5, *p*-$NO_2C_6H_4$, $C_6H_5OCH_2$

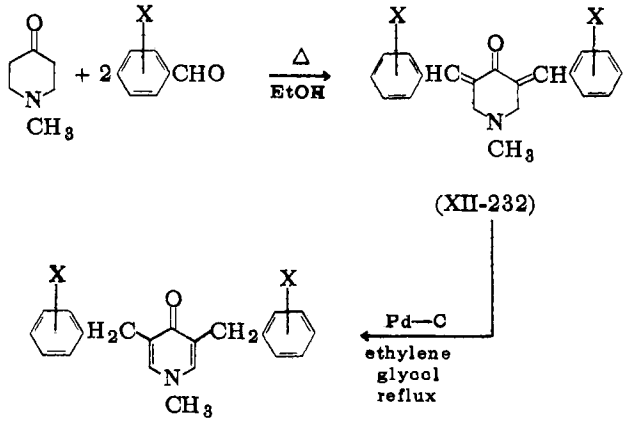
tized with a variety of dehydrogenating agents, *e.g.*, thionyl chloride, nitrous and nitric acids, nitrous esters, and alkaline ferricyanide (*383*), to 2-pyridinols. As previously mentioned (XII-22), dihydropyridinols can be dehydrogenated with bromine or sodium nitrite in acetic acid (*19,20*). Dihydropyridinediols are aromatized to pyri-

dinols (*52*) by dehydration, as illustrated by 5,6-dimethyl-3-cyano-2,4-dihydropyridinediol (XII-231).



(XII-231)

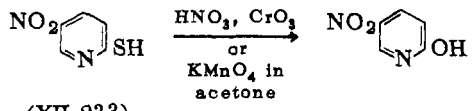
The conversion of 2,6-dibenzylidenecyclohexanone to 2,6-dibenzylphenol has been adapted to the analogous heterocyclic systems (*384*) under much milder conditions than those required for the carbocyclic systems. Accordingly, 1-methyl-3,5-dibenzylidene-4-piperidones (XII-232) were isomerized to the corresponding 1-



methyl-3,5-dibenzyl-4-pyridones. The 4-piperidones were prepared by condensing 1-methyl-4-piperidone, which acts as the basic catalyst, with the corresponding aldehyde in refluxing ethanol.

l. Miscellaneous Methods

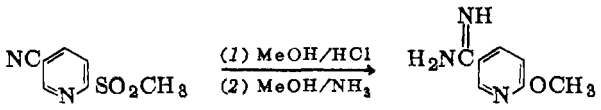
Some sulfur-containing groups have been displaced by hydroxyl groups. The attempt (*385*) to oxidize 5-nitro-2-pyridinethiol (XII-233) to the sulfonic acid gave the corresponding pyridinol instead. The activation of C_2 by the nitro group toward nucleophilic attack undoubtedly favors the loss of the sulfur group. It is not known at which stage of the oxidation the displacement occurs. 3,5-Dihalo-4-



(XII-233)

pyridinethiols are reported to give the corresponding 4-pyridinols on treatment with nitric acid (*443*).

An activated sulfur group was unexpectedly replaced by a methoxy group during the attempted conversion of 5-cyano-2-methylsulfonylpyridine (XII-234) to an amidine (*386*). It was indicated



(XII-234)

that the displacement occurred during step 2. When 5-nitro-2-methylsulfonylpyridine, in which activating forces are comparable to those in XII-234, was submitted to conditions used for imino-ether formation, it was recovered unchanged. Treatment with methanolic ammonia (step 2), however, afforded 5-nitro-2-aminopyridine, together with a small amount of 5-nitro-2-methoxypyridine.

The conversion of a methyl group to a hydroxyl group was effected by passing the vapors of 2-picoline and steam (1:3 ratio) over a mixture of the oxides of vanadium, molybdenum, and silver at elevated temperatures. The compounds isolated were α-pyridoin and 2-pyridinol. The yields, however, were not given (*394*).

B. PROPERTIES AND STRUCTURE

1. 3-Pyridinol and Derivatives

One might expect that the pyridinols should behave as typical phenols, altered somewhat by the presence of the ring nitrogen. This expectation is realized for 3-pyridinol. It gives a purple color with ferric chloride, undergoes nuclear electrophilic substitution, *i.e.*, halogenation, nitration, sulfonation, diazo coupling, and hydroxymethylation, and participates in the Mannich condensation. Acylation and alkylation of the hydroxyl group gives stable products

in good yields. The easily controlled hydroxymethylation with formaldehyde is evidence that the ring nitrogen does deactivate. This is in sharp contrast to the facile polymer formation occurring with phenol under similar conditions. 3-Pyridinol also resists nitrosation.

The ultraviolet spectral analysis of 3-pyridinol and its methyl ether at varying pH best reveals its intimate structure. The phenolic structure is supported by Specker and Gawrosch (*396*), who found that the spectra of 3-pyridinol and its methyl ether are identical to each other in neutral and acid methanolic solutions. In acid the ether shows a bathochromic shift of about 6 mμ (Table XII-15). In alkaline medium (dilute sodium methoxide), although the contour of the curves is similar, the maxima shift 22–34 mμ to the higher wavelengths. This behavior is also characteristic of phenol. The

TABLE XII-15. Ultraviolet Absorption of Pyridinol and Pyridone Derivatives

Compound	Conditions	λ_{max}, mμ	log *E*	λ_{max}, mμ	log *E*	Ref.
2-Pyridinol	MeOH	227	4.0	297	3.9	396
1-Methyl-2(1*H*)-pyridone	MeOH	227	3.9	300	3.9	396
2-Ethoxypyridine	MeOH			270	3.9	396
2-Pyridinol	MeONa (similar to spectrum in neut. MeOH)					396
2-Pyridinol	HCl					396
1-Methyl-2(1*H*)-pyridone	HCl (similar—no data)					396
2-Ethoxypyridine	HCl					396
3-Pyridinol	MeOH	243	2.68	277	3.6	396
3-Methoxypyridine	MeOH			277	3.6	396
3-Pyridinol	MeOH, 0.1*N* HCl	245	2.22	283	3.8	396
3-Methoxypyridine	MeOH, 0.1*N* HCl			283	3.8	396
3-Pyridinol	0.1*N* MeONa	238,235	4.0, 3.9	298	3.6	396
1-Methyl-3-pyridinol	0.1*N* HCl			288		397
1-Methyl-3-pyridinol	0.1*N* NaOH	245		322		397
6-Methyl-3-pyridinol	0.1*N* HCl			293		397
6-Methyl-3-pyridinol	0.1*N* NaOH	239	3.9	308	3.5	397
2-Methyl-5-ethyl-3-pyridinol	0.1*N* HCl			292		397
2-Methyl-5-ethyl-3-pyridinol	0.1*N* NaOH	240	5.5	305	5.9	397

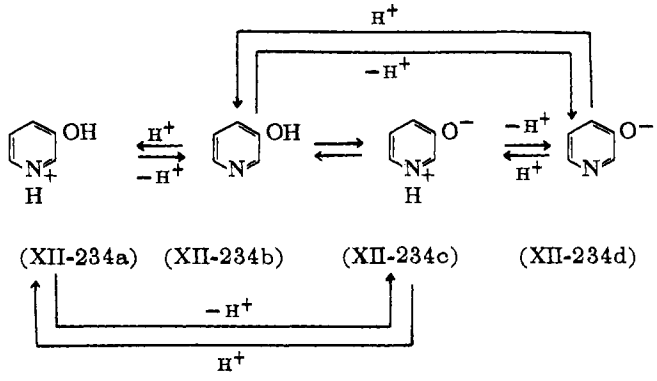
(*continued*)

TABLE XII-15 (*continued*)

Compound	Conditions	λ_{max}, mμ	log E	λ'_{max}, mμ	log E	Ref.
4-Methyl-3-pyridinol	EtOH			276	3.6	363
4-Methyl-3-pyridinol	EtOH, KOH	244	4.0	300	3.7	363
6-Methyl-2-pyridinol	90% EtOH	228	3.9	306	3.9	244
Ethyl 2-methyl-6-hydroxynicotinate	90% EtOH	264	4.2	300	3.8	244
2-Methyl-6-hydroxynicotinic acid	90% EtOH	261	4.1	303	3.8	244
Ethyl 2-methyl-5-bromohydroxynicotinate[a]	90% EtOH	271	4.2	307	3.9	244
Ethyl 2-methyl-6-ethoxynicotinate[b]	90% EtOH	248		275		419
4-Pyridinol	EtOH	256	4.2			419
4-Pyridinol	EtONa, EtOH	243	4.1	260s[c]	3.9	419
4-Pyridinol	EtOH, HCl	235				419
4-Methoxypyridine	MeOH	218	3.9	245s[c]	3.0	396
4-Methoxypyridine	MeOH, HCl			240	4.1	396
1-Methyl-4(1*H*)-pyridone	MeOH			260	4.2	396
1-Methyl-4(1*H*)-pyridone	MeOH, HCl			237	4.0	396
5-Benzoyl-2-pyridinol	EtOH	251	3.8	290	4.1	407
5-*p*-Toluoyl-2-pyridinol	EtOH	263s[c]		292	4.3	407
5-*p*-Bromobenzoyl-2-pyridinol	EtOH	265	4.2	293	4.3	407
5-*p*-Chlorobenzoyl-2-pyridinol	EtOH	260	4.0	293	4.2	407
2,4-Pyridinediol	H_2O	273	3.75			868
3-Bromo-2,4-pyridinediol	H_2O	277	3.8			868
4-Ethoxy-2-pyridinediol	H_2O	275	3.55			868
3-Bromo-4-ethoxy-2-pyridinol	H_2O	291	3.8			868
2-Ethoxy-4-pyridinol	H_2O	248	3.85			868
3-Bromo-2-ethoxy-4-pyridinol	H_2O	262	3.8			868
2,4-Diethoxypyridine	H_2O	261	3.4			868
3-Bromo-2,4-diethoxypyridine	H_2O	267	3.35			868
5-Bromo-2,4-diethoxypyridine	H_2O	272	3.35			868

[a] λ'' = 317, log E = 3.9
[b] λ'' = 283s
[c] "s" indicates shoulder

effect of pH changes on 3-pyridinol is illustrated in formulas XII-234a–d. In acid, the cation (XII-234a) exists, while in base, the anion (XII-234d) is found.



The presence of both the uncharged (XII-234b) and the dipolar (XII-234c) forms in neutral solutions (pH = 6–8) was demonstrated (*397*) by using dioxane-water mixtures. Increased additions of dioxane result in a gradual decrease in intensity at 313 mμ, attributable to XII-234c, and a corresponding increase in intensity at 277 mμ, due to XII-234b. An equilibrium constant of the ratio XII-234b to XII-234c was roughly calculated, and, by extrapolation, the percentage of XII-234b in aqueous solution was 46%. The addition of alcohol causes the peak of XII-234c (313 mμ) to diminish.

Further proof of the equilibrium stems from pK measurements (*398*) (Table XII-16). When alkali is added to 3-hydroxy-1-methylpyridinium chloride, a pK_a of 4.96 is obtained, representing the loss of the proton from oxygen. This pK_a is similar to that (4.86) obtained by dissociation of a proton from 3-pyridinol hydrochloride, where the loss can be from oxygen or nitrogen. It is also the same as the pK_a obtained from the ionization of 3-methoxypyridine hydrochloride (4.86), where the process represents loss of the proton from nitrogen. These results indicate that comparable energy changes are associated with the loss of a proton from either oxygen (XII-234a → XII-234c) or nitrogen (XII-234a → XII-234b), and therefore both processes occur simultaneously. Consequently, a neutral aqueous

TABLE XII-16. pK_a's of Pyridinol and Pyridone Derivatives

Substance	pK_a (proton lost)	Ref.	pK_a' (proton gained)	Ref.
2-Pyridinol	11.62	417	0.75	398
3-Pyridinol	8.72, 8.60 ± 0.08	398,397	4.86, 5.10 ± 0.16, 4.76	398,397, 418
4-Pyridinol	11.09	417	3.27	398
2,4-Pyridinediol	6.50 13	398	1.37	398
2,4,6-Pyridinetriol	4.6 9.0 13	398		
2-Methoxypyridine			3.28	398
3-Methoxypyridine			4.88	398
4-Methoxypyridine			6.62	398
3-Hydroxy-1-methylpyridinium chloride	4.96	398		
1-Methyl-2(1*H*)-pyridone			0.32	398
1-Methyl-4(1*H*)-pyridone			3.33	398

solution of 3-pyridinol must be an equilibrium mixture of XII-234b and XII-234c.

In a nonpolar solvent such as benzene, the dipole moment of 3-pyridinol was found by Albert and Phillips to be 2.00 D. (Table XII-17), indicating that XII-234b is the principal species, since the dipole moment of XII-234c would be of the order of 16 D. (*398*). These authors attribute the high proportion of the dipolar ion (XII-234c) in aqueous solutions to the mutual inductive effect of the two groups; the cationic charge strengthens the acidic group, and the anionic charge strengthens the basic group. However, increased

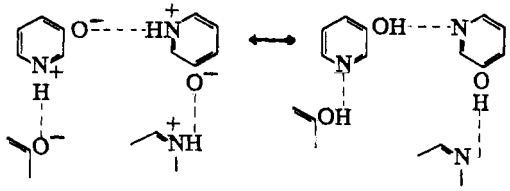
TABLE XII-17. Dipole Moments of Pyridinol and Pyridone Derivatives in Benzene at 25 °C. (*398*)

Substance	2	3	4
Pyridinol	1.95 D.	2.00 D.	5.3 D.[a]
O-Methyl derivative	1.15	2.75	3.00
N-Methyl derivative	4.15		6.9

[a]Too insoluble in benzene, value calculated from dioxane solution.

solvation by the polar solvent should increase the stability of the dipolar form.

The infrared spectral analysis of 3-pyridinol and its hydrochloride and of the same compounds after exchange with D_2O (*399*) is very revealing. The conclusion drawn from comparison of the spectra is that 3-pyridinol exists in the zwitterion form XII-234c, which is extensively hydrogen-bonded. The structure proposed incorporates XII-234b and XII-234c as polymeric "proton resonance" hybrids (*400*) as shown (XII-235), with the dipolar form making the



(XII-235)

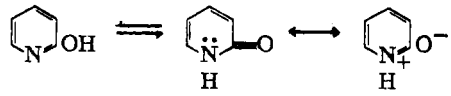
major contribution. A band at 4.06 μ is attributed to the stretching vibration of the O—H group; its intensity is greatly diminished in the deuteriated compound. The spectra were determined in Nujol mulls, and therefore represent the state of the solid, rather than the solution.

2. 2- and 4-Pyridinols and Derivatives

2-Pyridinol (XII-236) also shows certain phenolic properties. Thus it undergoes electrophilic substitution. It gives a color test with ferric chloride, although fainter than the 3 isomer gives; color formation is suppressed by an electron-withdrawing group in the 5 position (*402*). This effect is to be expected, since the color depends on complex formation between the nucleophilic oxygen and ferric ion. Any diminution of electron density on oxygen should inhibit the test.

In other important respects, 2-pyridinol behaves very differently from 3-pyridinol. For example, it gives both *O*- and *N*-alkylation, depending on reagents and conditions. Acylation gives esters which are very sensitive to moisture. Phosphorus halides and thionyl chloride can be used to replace the hydroxyl group by halogen. These properties led to the postulate that it consisted of tautomers XII-236 and XII-236a. The early workers also suggested (*401*) a betaine

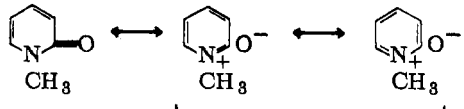
structure, and incorrectly assigned to it a pentavalent nitrogen. The modern formulation of the betaine is XII-236b, a dipolar ion.



(XII-236) (XII-236a) (XII-236b)

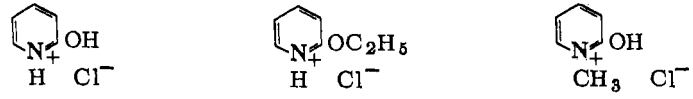
That 2-pyridinol exists as these tautomers with XII-236a predominating has been amply corroborated by ultraviolet, infrared, crystallographic, pK, dipole moment, and nuclear magnetic resonance measurements.

The analysis of the ultraviolet absorption spectra reveals that the predominant tautomer depends on the pH. The curves for 2-pyridinol and 1-methyl-2(1*H*)-pyridone (XII-237) in neutral meth-



(XII-237) (XII-237a)

anolic solutions are almost identical (see Table XII-15) (*396*). Since XII-237 is fixed in the lactam or pyridone form, this must be the form preferred by 2-pyridinol. This conclusion is further substantiated by the observation that the absorption spectrum of 2-ethoxypyridine, which must exist in the lactim or pyridinol form, differs in neutral solution from that of 2-pyridinol. The addition of sodium methoxide has little effect on the absorption of 2-pyridinol. In hydrochloric acid, the spectra of 2-pyridinol and its *O*-ethyl and *N*-methyl derivatives show striking similarity, leaving no doubt that the conjugate acids of these three compounds have similar structures XII-238, XII-239, and XII-240, respectively.



(XII-238) (XII-239) (XII-240)

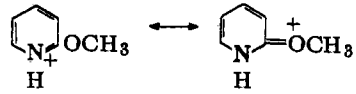
Electron-withdrawing groups at C_3 or C_5 alter the ultraviolet spectrum. 5-Aroyl-2-pyridinols (*407*) show maxima at 251–265 mμ (log E = 3.83–4.16) and 291–293 mμ (log E = 4.14–4.37). 5-Carbethoxy-2-pyridinols (*244*) have maxima at 264 (log E = 4) and 300 mμ (log E = 3) (see Table XII-15). It is evident that the first maximum undergoes a bathochromic shift of about 30 mμ with an increase in intensity. However, there is little change in the second maximum.

Contrary to the findings of Specker and Gawrosch (*396*) for 2-pyridinol, the spectrum of ethyl 2-methyl-6-hydroxynicotinate was found to differ markedly in neutral and alkaline ethanolic solutions. Thus, only one maximum (at 290 mμ) (log E = 4.36) is exhibited in 95% ethanol containing 0.1N aqueous sodium hydroxide (*244*).

An excellent analysis of the structural characteristics of 2-pyridinol and its N- and O-methyl derivatives is offered by Albert and Phillips from a study of pK_a values (*398*). From the data in Table XII-16, it is evident that the O-methyl derivative of 2-pyridinol is more basic than the parent compound or its N-methyl derivative. The latter two compounds have a similar proton affinity. These results have been explained in terms of resonance characteristics of the neutral molecules and their ions. In 2-methoxypyridine (XII-241), the base-weakening inductive effect of the methoxy group is greatly modified by the resonance interaction of the group with the ring. In the neutral molecule, resonance involving XII-241a should

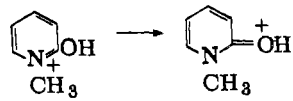
(XII-241) (XII-241a)

be slight because the oxygen and nitrogen carry charges contrary to the natural order of electronegativities, and in the cation XII-242 there should be a moderate amount of resonance with XII-242a.



(XII-242) (XII-242a)

This increased resonance stabilization of the cation is a base-strengthening effect. The *N*-methyl derivative (XII-237) has a different electronic arrangement from the *O*-methyl compound (XII-241). On the other hand, the derived cation hybrids XII-242 and XII-242a differ from XII-243 and XII-243a only by an interchange

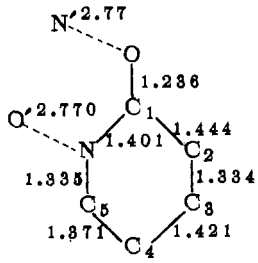


(XII-243) (XII-243a)

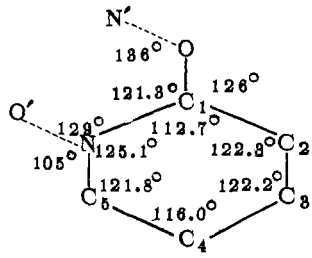
of H and methyl. The resonance XII-237 ⟷ XII-237a must be appreciable, because the charges borne by the oxygen and nitrogen atoms are in line with their respective electronegativities. Dipole moment measurements (Table XII-17) confirm that the *N*-methyl derivative is more highly polar than the *O*-methyl isomer. Since XII-237 is stabilized by resonance to a greater extent than XII-241, while their conjugate acids are electronically almost identical, the smaller proton affinity of XII-237 is not surprising.

The similar basicity of 2-pyridinol and its *N*-methyl derivative leads to the conclusion that they have a common electronic configuration. Thus the equilibrium between the lactim (XII-236) and the lactam (XII-236a) tautomers must favor the lactam form. This equilibrium state is favored by strong resonance between the pyridone form XII-236a and the dipolar form XII-237b. This discussion disregards those canonical forms that have a charge on carbon. The ratio of pyridone to pyridinol was calculated to be 340:1.

The structure of 2-pyridinol in the crystalline state has been determined (*404*) by measuring the electron densities in two projections. The bond lengths and bond angles are depicted in XII-244 and XII-245, respectively. Although the pyridine ring departs considerably from regular hexagonal shape, it is planar within experimental error. The pyridone structure is the stable one, and there is a strong intermolecular hydrogen bond between the nitrogen of one molecule and the oxygen of another, which is repeated throughout the structure, linking molecules in endless helices. This conclusion is based on the fact that the N–H distance is 1.02 A., very



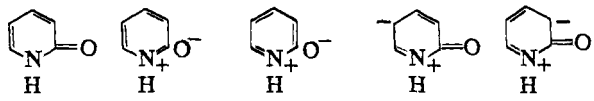
(XII-244)



(XII-245)

nearly the normal covalent bond length of 1.00 A., whereas the observed O–H distance greatly exceeds the normal covalent distance. This obviates the possibility that 2(1*H*)-pyridone exists as a hydrogen-bonded dimer.

The resonance structures of 2-pyridinol and their percent contribution (as shown in XII-246) were calculated to give the best



50% 15% 20% 10% 5%

(XII-246)

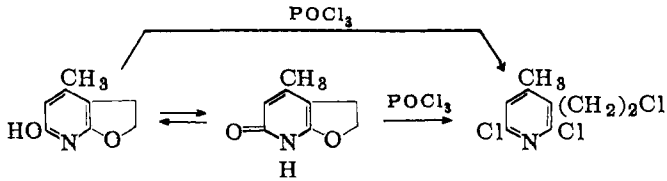
correspondence with the observed bond lengths and angles. As expected on the basis of electronegativity trends, the dipolar forms with negative charge on oxygen have much greater significance than those with the negative charge on carbon. These latter forms, however, do account for electrophilic substitutions at positions ortho and para to the CO group. The large contribution from the dipolar forms with negative charge on oxygen bestows a high polarity on the N···H···O hydrogen bond.

Infrared analyses (*399*) substantiate the findings from ultraviolet, pK_a, and crystallographic studies The spectra of 2-pyridinol (in Nujol) and its *N*-methyl derivative (liquid) contain bands at 6.06 μ characteristic of the carbonyl group. The former compound also has a band at 3.27 μ characteristic of stretching vibration of the N-H linkage. The carbonyl band and the N-H stretching bands are both

missing in the spectrum of 2-ethoxypyridine. 2-Alkoxypyridines show bands at 6.3 and 6.4 μ attributed to the pyridine ring, but absent from the spectra of both 2-pyridinol itself and its *N*-methyl derivative (*244*). The hydrochloride of 2-pyridinol shows the characteristics of the lactim structure, since the carbonyl band at 6.06 μ is missing. The infrared spectra of 2-pyridinol and its *N*-methyl and *O*-methyl derivatives have been compared in carbon tetrachloride (*405*). The first two compounds exhibit a strong absorption band at 6.0 μ which is absent in the *O*-methyl derivative.

When the 5 position is substituted by an electron-withdrawing group, *e.g.*, carboxyl (*406*), carbethoxyl (*244*), or aroyl (*407*), there is an additional very strong band characteristic of the pyridone carbonyl at 6.12 μ (Nujol), 6.14–6.15 μ (KBr pellets), or 6.08–6.10 μ (solution). α-Pyridones, with a free N-H function, have a broad band at 3.0–4.0 μ. This band has been attributed to the N-H stretching frequencies in the tautomeric imide-amide structure, indicating possible intramolecular hydrogen-bonding (*407*).

The lactam-lactim tautomers have never been isolated. The names used depend on the characteristics of the compound to be emphasized. (In this chapter, the term pyridinol is used extensively.) There is one fairly well documented report of the isolation of two tautomers. This occurred when 2,3-(2′,3′-dihydrofurano)-4-methyl-6-pyridinol (XII-247b and a) was prepared (*39*). The isomer XII-247a is lower melting and very soluble in ethyl acetate; it gives no color with ferric chloride. The higher melting isomer (XII-247b) is much less soluble in ethyl acetate and gives a positive ferric chloride test. The compounds can be equilibrated in a short time in 10% sodium hydroxide or by heating with concentrated hydrochloric acid at 150°C. for four hours. Both isomers are converted to the same trichloride, XII-248. The ultraviolet absorption

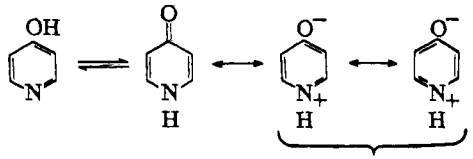


(XII-247b) m.p. 250°C. (XII-247a) m.p. 177.5–79°C. (XII-248)

spectra of the two compounds are appreciably different, and correspond to the assigned formulas.

4-Pyridinol (XII-249) is similar in chemical properties to the 2-isomer; it appears to be even somewhat less phenolic. Whereas 2-pyridinol gives a red color with ferric chloride, the 4-isomer gives a yellow color (*121*). It gives the *N*-methyl derivative when treated with diazomethane (*409*), whereas the 2-isomer yields mainly the *O*-methyl derivative (*408*).

The ultraviolet spectrum indicates that in neutral solution the predominant form is the pyridone structure (XII-250) with contributions from the dipolar resonance forms (XII-250a) (*396*). 4-Pyri-



(XII-249) (XII-250) (XII-250a)

dinol and its *N*-methyl derivative have very similar spectra, which are entirely different from the spectrum of the *O*-methyl derivative. The hydrochlorides of these three compounds are very similar to each other, clearly indicating that they all exist in the pyridinol, benzenoid form. These findings are completely analogous to those for 2-pyridinol (*396*), the exception being that in base, the absorption curve of 4-pyridinol differs greatly from that of 1-methyl-4(1*H*)-pyridone. It does, however, have the same characteristic shape as 4-methoxypyridine, although shifted toward higher wave lengths. Berson (*410*) has made a qualitative correlation of the ultraviolet spectra of α- and γ-pyridones. The α compounds absorb at pronouncedly longer wavelengths but with lower intensities than the γ-compounds. This difference is interpreted in terms of a qualitative quantum mechanical picture of the absorption process. The absorption by the γ compound at lower wavelengths is ascribed to the fact that the dipolar resonance forms (XII-250a) are of a higher energy than those for the α-pyridone (XII-236b), because of greater charge separation. The higher extinction coefficients of the γ series is attributed to this same greater charge separation, since the in-

tensity is a function of the dipole strength of the chromophore and is therefore proportional to the square of the length of the absorbing system.

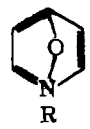
The pK_a measurements of Albert and Phillips (*398*) further elucidate the structure of 4-pyridinol. The findings (see Table XII-16) and interpretation resemble those for 2-pyridinol (see page 000). The conclusion reached is that the pyridone (XII-250) is the predominant form with appreciable resonance contribution from XII-250a. The ratio of amide to enol tautomers is 2200:1, about 6.5 times greater than for the α isomer. This is attributed to its more stable *p*-quinoidal structure, as compared to the *o*-quinoidal form of α-pyridone. The infrared data of Sensi and Gallo (*399*) corroborate the predominance of the γ-pyridone form. The spectra were taken in Nujol mulls and therefore pertain to the solid state.

The analysis of nuclear magnetic resonance spectra is an excellent method for investigating tautomeric equilibria. In aqueous solution the NMR spectrum of 4-pyridinol resembles that of 1-methyl-4(1*H*)-pyridone, confirming the predominance of the pyridone form. In 20*N* sulfuric acid the NMR spectrum supports the belief that 4-hydroxypyridinium ion is the major structure (*890*), formed as a result of *O*-protonation of the pyridone form. These findings of Katritzky and his co-workers are at variance with those of Spinner, who interpreted Raman, infrared (*891*), and ultraviolet (*892*) spectra as indicating that in acid *N*-protonation of the pyridone occurs. Katritzky considers Spinner's spectral evidence as inconclusive. His NMR spectrum of 4-pyridone in sulfuric acid does not permit an unequivocal assignment of *O*-protonation because the exchange of the labile protons occurs quickly and the protons cannot be distinguished from those of the solvent. To eliminate this uncertainty, he and R. A. Y. Jones took spectra in liquid sulfur dioxide, a solvent free of protons. The spectrum is again interpreted as indicating *O*-protonation (*893*). These authors admit that the equilibrium may be shifted in other solvents, but assert that, regardless of the solvent, the shift in equilibrium could never be so great as to cause the *N*-protonated form to predominate.

Katritzky and Jones have extended the analysis of infrared spectra of pyridines and pyridine *N*-oxides (*894*) to 2- and 4-pyridones and

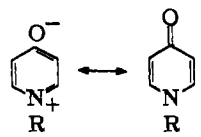
thiopyridones (*895*). They give a tentative assignment to nearly all the bands, and support the conclusion that the pyridone rather than the hydroxy form predominates.

The early researchers in this field did not expect α-pyridones to give ketonic derivatives, since they recognized them as cyclic amides. However, it was perplexing that the γ-pyridones lack ketonic properties and do not form quaternary salts. The reaction of 1-phenyl-4(1*H*)-pyridone with methyl iodide in a sealed tube gave a small amount of solid product which decomposed in water to give starting material and methanol (*130*). Methylmagnesium iodide also gave an unstable addition product, which decomposed in hydrochloric acid to the original pyridone. This led Smirnoff (*123*) to propose an amine oxide structure (*401*) containing pentavalent nitrogen (XII-251). This structure is in fact an incorrect representation of the



(XII-251)

betaine form (XII-252), which is a resonance form of the neutral pyridone. Actually it is the contribution of the canonical form (XII-252) that accounts for the lack of ketonic properties, since it

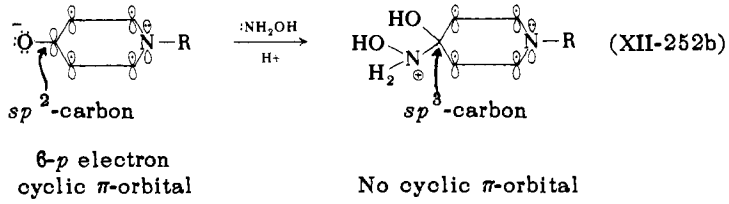


(XII-252) (XII-252a)

distributes the electron deficiency toward the nitrogen atom and away from the carbonyl carbon, which then becomes less susceptible to attack by nucleophilic reagents, *e.g.*, hydroxylamine and phenylhydrazine.

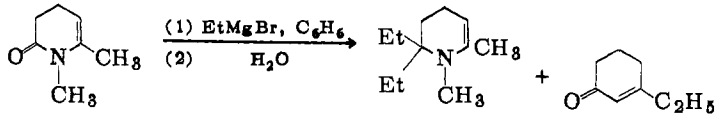
It is also possible to rationalize the lack of ketonic behavior of both the α- and γ-pyridones by applying molecular orbital theory

and Hückel's rule of aromaticity. According to this rule, a monocyclic system is aromatic if it possesses $(4n + 2)$ π electrons (n is an integer) which are in overlapping p orbitals. The six electrons of the pyridone come from the two double bonds and the unshared pair of electrons of the nitrogen atom. But to enable these six electrons to be present in a cyclically overlapping π bond, the carbon of the C=O group must be sp^2 hybridized and thus possess an electron-deficient p orbital. Attachment of another atom, *i.e.*, the nitrogen atom of hydroxylamine, to this carbon would necessitate a hybridization change from sp^2 to sp^3. The empty p orbital would no longer be present to permit cyclical overlap, as shown in XII-252b for a



(XII-252b)

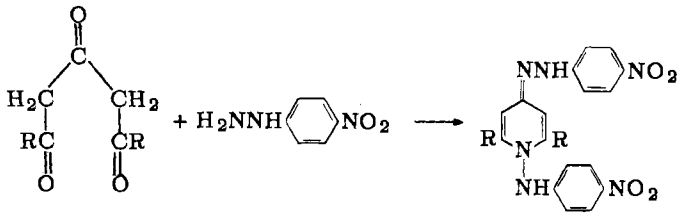
typical γ-pyridone. The typical ketonic reactions would all necessitate the loss of aromaticity, which arises from the six-electron cyclic π orbital, and hence they do not readily occur. The dihydropyridones, which do not fit Huckel's rule, do undergo reactions at the carbonyl group. Thus, 1-methyl-6-alkyl-3,4-dihydro-2(1*H*)-pyridone behaves as a lactam toward Grignard reagents. With ethylmagnesium bromide, the major product is 1,6-dimethyl-2,2-diethyl-1,2,3,4-tetrahydropyridine (XII-252c), the minor product, 1-ethyl-1-cyclohexen-3-one (*904*).



(XII-252c)

A phenylhydrazone of 1-(*p*-tolyl)chelidamic acid was reported (*123*) but was later shown to be a phenylhydrazine salt (*411*). Although ketonic derivatives cannot be made directly from the γ-pyri-

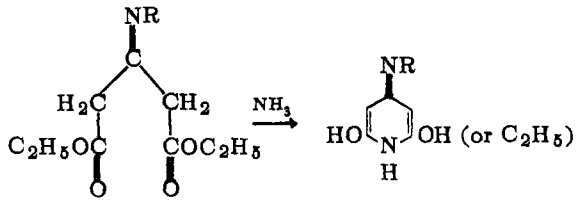
dones, some have been prepared indirectly by ring closure methods. Ethyl acetonedioxalate (XII-253, R = $COOC_2H_5$) reacts with excess *p*-nitrophenylhydrazine (*412*) and with phenylhydrazine itself (*413*) to give a phenylhydrazone of the diethyl *N*-amino-substituted chelidamate (XII-253a, R = $COOC_2H_5$). Diacetylacetone (XII-253, R =



(XII-253) (XII-253a)

CH_3) (*412*) and dipropionylacetone (XII-253, R = C_2H_5) react in a similar fashion to give XII-253a (R = CH_3 and C_2H_5, respectively).

A variation of this method involves initial formation of the ketone derivative followed by ring closure with ammonia (XII-254).

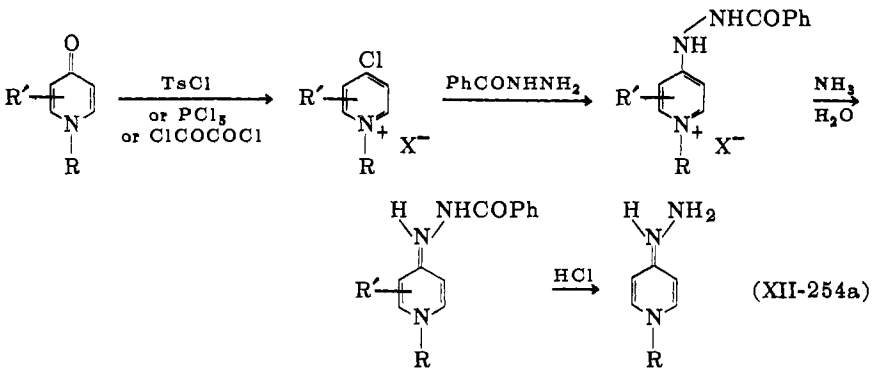


(XII-254)

This reaction gave the half ether when R = $NHCOCONH_2$ or $CONH_2$ (*415*), and the 2,6-dihydroxy compound when R = $NHCONH_2$ (*416*). The thiosemicarbazone did not give a pyridone derivative.

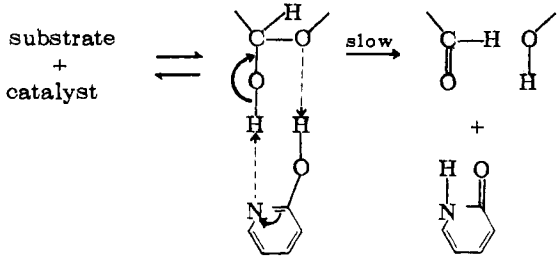
Several *N*- and nuclear-substituted 4(1*H*)-pyridones have been converted to benzoylhydrazones and hydrazones (*862*) by the sequence of steps shown (XII-254a). The hydrazone was oxidatively coupled with phenols (*863*) and aromatic amines (*864*) to give azo dyes.

The pyridinols form salts with acids and bases. Swain and Brown (*420*) have shown that this amphoteric property of 2-pyri-



(XII-254a)

dinol enables it to be used as a polyfunctional catalyst. It had previously been demonstrated (*421*) that simple polar displacement reactions of neutral substrates require simultaneous attack by both nucleophilic (*N*) and electrophilic (*E*) agents. 2-Pyridinol contains both *N* and *E* groups at an optimum distance for interaction with the reactive sites on the substrate, and should thus be a very effective catalyst, requiring only two species to orient themselves, rather than three when *N* and *E* are separate molecules. The reaction studied was the mutarotation of tetramethylglucose in benzene solution, for which the rate-controlling step is the hydrolysis of a hemiacetal bond. This reaction necessitates a concomitant attack of *N* on hydrogen and *E* on oxygen (XII-255). The proposed



(XII-255)

mechanism assigns the *N* function to the nitrogen and the *E* function to the hydroxyl group. It would have been just as satisfactory to employ the pyridone structure, which actually predominates, assigning the *N* function to the carbonyl oxygen and the *E* function to the N-H group. Although 2-pyridinol is one ten-thousandth as

strong a base as pyridine, and one hundredth as strong an acid as phenol, it is fifty times as effective a catalyst as an equimolar mixture of phenol and pyridine. Both 3- and 4-pyridinols are inferior polyfunctional catalysts because their *N* and *E* functions are too far apart to form the necessary complex with the substrate.

C. REACTIONS

A color test to distinguish the pyridinols from each other would be a valuable tool. The ferric chloride test is not definitive. The phosphomolybdic acid reagent of Folin and Denis (*422*) has been used to distinguish 3-pyridinol, which gives a blue coloration, from its 2- and 4-isomers, which give negative results (*423*). Recently it has been shown that 2,6-pyridinediol, 2,6-dihydroxyisonicotinic acid, 6-methoxy-2-pyridinol, and 6-amino-2-pyridinol all give positive tests with the Folin and Denis reagent (*424*). Therefore, the blue coloration is not specific for a hydroxyl group in the β-position. A negative test does, however, show the absence of a β-hydroxyl group. The best method for distinguishing the β- from the α- and γ-isomers is ultraviolet and infrared spectral analysis.

1. Involving O (or N)

a. Deoxygenation by Zinc

All three pyridinols and their alkyl derivatives undergo replacement of the hydroxyl by hydrogen when dry distilled with zinc dust in a hydrogen atmosphere. The yields, however, are poor, and consequently the reaction has limited synthetic value. Replacement of the OH by H is usually effected by the two-step sequence: OH $\rightarrow$ Cl $\rightarrow$ H. Some of the compounds that have been successfully distilled with zinc dust are listed in Table XII-18.

4,5,6-Trimethyl-2-pyridinol is deoxygenated in about 25% yield with iodine and red phosphorus in refluxing xylene (*827*).

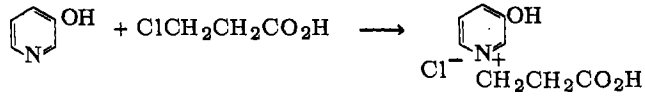
b. O- and N-Alkylation and Arylation

Although 3-pyridinols alkylate like phenols, the 2- and 4-isomers react quite differently. Thus, the potassium salt of 3-pyridinol with ethyl bromide in ethanol gives 3-ethoxypyridine. 3-Pyridinol with

TABLE XII-18. Compounds Reduced in Zinc Dust Distillation

Compound	Product	Ref.
3-Pyridinol	pyridine	426
3,3′,5,5′-Tetrahydroxy-2,2′-bipyridine	2,2′-bipyridine	425
4-Pyridinol	pyridine	427
5,6-Dimethyl-2-pyridinol	2,3-lutidine	53
4,5,6-Trimethyl-2-pyridinol	2,3,4-collidine	428
3,5-Diphenyl-4-pyridinol	3,5-diphenylpyridine	147
6-Hydroxypicolinic acid	pyridine	110

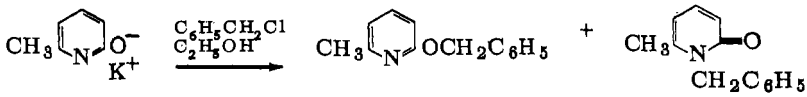
dimethyl sulfate in base gives a 92% yield of the methyl ether (*429*). With diazomethane, the same product is obtained (*409*). More recently 6-methyl-3-pyridinol was converted to the methyl ether (*317, 430*) with diazomethane in yields not in excess of 40%. (The need to maintain a solvent of high polarity partly accounts for the low yields.) Quaternary phenylammonium salts can be used as alkylating agents. Dimethyl 2-methyl-3-hydroxy-4,5-pyridinedicarboxylate was methylated and benzylated by heating the sodium salt in hot xylene under nitrogen with trimethylphenylammonium chloride and benzyldimethylphenylammonium chloride, respectively. The yields are 71 and 80% (*45*). 3-Pyridinol was itself benzylated in the same manner. 2-Iodo-3-pyridinol was methylated in 58% yield by pyrolysis of its trimethylammonium salt in dimethylformamide (*431*). *N*-Alkylation (*330*) occurs when 3-pyridinol is heated with 3-chloropropionic acid (XII-255a).



(XII-255a)

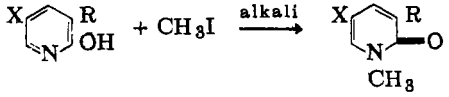
The alkylation of 2- and 4-pyridinols is complicated by the pyridinol-pyridone tautomerism. Under basic conditions *N*-alkylation predominates, a marked divergence from the *O*-alkylation of phenols. 2-Pyridinol was first *N*-alkylated by treatment with ethyl iodide in alkali (*408*). Räth (*432*) obtained yields of 30–85% by treating the potassium salt with ethyl, *n*- and *i*-propyl, *n*-butyl, *n*-

octyl, and benzyl halides. 5-Iodo-2-pyridinol was also *N*-alkylated with the same halides in alcoholic potassium hydroxide in comparable yields (*233*). Methylation has been effected in good yield with dimethyl sulfate (*432*). Both 4- and 6-methyl-2-pyridinol (XII-256)



(XII-256) 81% 16%

were *N*-methylated in yields of 75% by treating their potassium salts with dimethyl sulfate (*274*). This indicates that a methyl group in the 6 position does not offer any steric inhibition. However, when XII-256 is benzylated the yield of the *N*-benzyl derivative is 16%. The major product is the 2-benzyloxy-6-methylpyridine (*433*). The 16% yield is in contrast to the 50% yield of *N*-benzyl derivative obtained under the same conditions with 2-pyridinol. Evidently steric factors may affect the course of the reaction, since the electronic factors are the same. Several mono- and dihalo-2-pyridinols have been methylated with methyl iodide and alkali (XII-257). In these



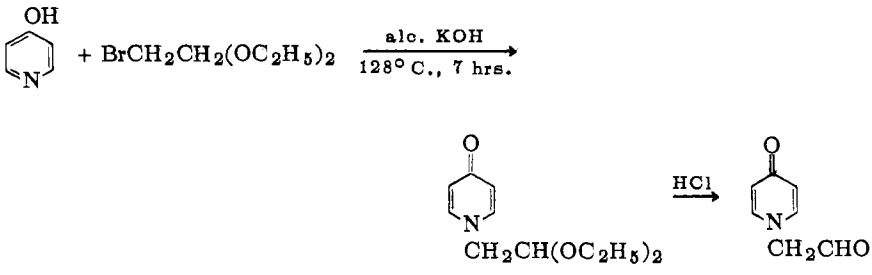
(XII-257)

X	R	Ref.
Cl	H	434
Br	H	434
Cl	Cl	434
Br	Br	434
I	I	434,104

cases the halogens are β-substituted and are stable to base. Several bifunctional halides have also been utilized for *N*-alkylations. Thus 2-pyridinol was heated with chloroacetic acid (*435*) to give the *N*-acetic acid derivative, whose structure was proved by decarboxylation to 1-methyl-2(1*H*)-pyridone. Similarly, the *N*-propionic acid is

formed when 2-pyridinol is heated with β-chloropropionic acid. As expected, the product is decomposed by heat or alkali to 2-pyridinol and acrylic acid. Bromopyruvic acid gives the expected condensation product in 78% yield without any basic catalyst (*450*). The sodium salts of 2-pyridinol and various *N*-substituted 2-hydroxynicotinamides react with several β-chloroethyldialkylamines to give the expected products (*436*). With β-chloroethylamine itself, 2-pyridinol is reported to give the *N*-vinyl derivative (*437*), although structure proof is lacking. Several 5- and 3,5-dihalo-2-pyridinols were condensed in alkali to give the *N*-acetic acid derivative (*438–440*); these are of interest as urographic *x*-ray contrast media. Alkali salts of α-pyridones have been alkylated with α- and β-haloalkylsulfonic acids in yields of 70–95%. Iodoalkylsulfonic acids give *N*- and also some *O*-substitution (*441*).

4-Pyridinols are also alkylated on nitrogen by alkyl halides or other alkylating reagents in base. Thus 1-methyl-4(1*H*)-pyridone is prepared from 4-pyridinol and methyl iodide in potassium hydroxide (*121*). The acetaldehyde (XII-258) is obtained in an over-all

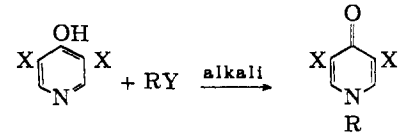


(XII-258)

yield of 55% from bromoacetal as shown. A similar series of reactions has been performed with 3-methoxy-4-pyridinol, to prepare the corresponding acetaldehyde, needed as a precursor in the synthesis of leucaenine (*442*). Several 3,5-dihalo-4-pyridinols have been alkylated as listed in Table XII-19. These compounds are of interest as potential gall bladder (*444*) and kidney (*445*) *x*-ray contrast agents.

Reactions with pyridinediols have been reported. Dimethyl sulfate in alkali methylates 3,4-pyridinediols at the nitrogen and the

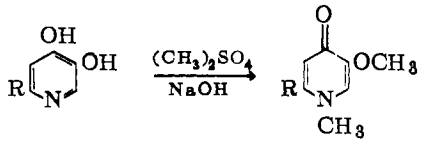
TABLE XII-19. *N*-Alkylation of 4-Pyridinols



(XII-259)

X	Substituent and position 2	6	RY	Ref.
I	H	H	$(CH_3)_2SO_4$	443
I	H	H	$ClCH_2COOH$	443,446
Cl	CO_2H	H	$(CH_3)_2SO_4$	443
I	CO_2H	H	$(CH_3)_2SO_4$	443
I	CO_2H	H	$ClCH_2COOH$	443
Br	CO_2H	H	$(CH_3)_2SO_4$	443
I	CO_2H	CO_2H	$(CH_3)_2SO_4$	443
I	CO_2CH_3	CO_2CH_3	$(CH_3)_2SO_4$	448
I	H	H	*p*-$ClCH_2C_6H_4CO_2Na$	447
I	H	H	*m*-$ClCH_2C_6H_4CO_2Na$	447
I	H	H	$CH_3CH_2CHBrCO_2H$	444
I	H	H	$CH_3(CH_2)_2CHBrCO_2H$	444
I	H	H	$CH_3(CH_2)_3CHBrCO_2H$	444
I	H	H	$(CH_3)_2CHCH_2CHBrCO_2H$	444
I	H	H	$CH_3(CH_2)_4CHBrCO_2H$	444
I	H	H	$(CH_3)_2CHCH_2CH_2CHBrCO_2H$	444
I	H	H	$CH_3(CH_2)_5CHBrCO_2H$	444
I	H	H	$CH_3(CH_2)_6CHBrCO_2H$	444
H	H	H	$Cl(CH_2)_2N(C_2H_5)_2$	209
H	H	H	$Br(CH_2)_2N(CH_3)_2$	209
H	H	H	$Br(CH_2)_3N(C_2H_5)_2$	209

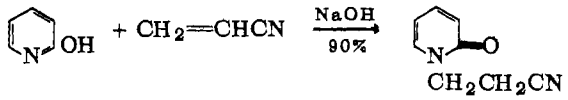
C_3 hydroxyl groups (XII-260). In contrast, 6-methyl-2,4-pyridinediol reacts with chloroacetic acid in alkali to give only the *N*-acetic acid (*465*).



(XII-260)

R = CH_3, COOH

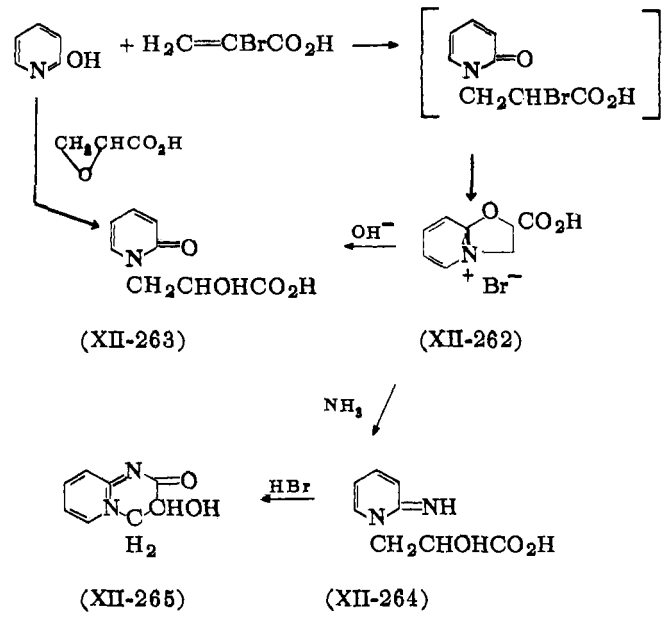
A novel variation of this *N*-alkylation reaction was devised by Adams and Jones (*449*). 2-Pyridinol reacted normally with acrylonitrile (XII-261) and with α-acetamidoacrylic acid. However, α-bromo-



(XII-261)

acrylic acid gave an unexpected product (XII-262), to which was originally assigned an incorrect structure. The correct structure, 2-carboxy-2,3-dihydroöxazolo-[2,3-a]-pyridinium bromide, given by Adams and Pachter (*451*) is probably explained by a cyclization of the expected adduct. XII-262 is also obtained with α,β-dibromopropionic acid. Treatment of XII-262 with hydroxide ion opens the oxazole ring giving XII-263, which is also obtained from 2-pyridinol and glycidic acid (*450*). (The opening of the oxide ring of glycidic acid in this reaction is another example of the versatility of 2-pyridinol as a nucleophile.) Ammonia causes ring-opening with the formation of the dihydroiminopyridinelactic acid (XII-264). This nucleophilic attack by ammonia on the pyridine ring carbon, rupturing the C-O bond, is unusual; the expected reaction would be attack on an oxazole ring carbon. The structure of the ring-closure product from XII-264 and HBr, a pyridopyrimidinone (XII-265) was established by analysis of the infrared and ultraviolet spectra. Thus the structures for XII-262, XII-263, and XII-264 were deemed to be unequivocal.

With electron-withdrawing groups ortho or para to the hydroxyl group, *N*-alkylation still predominates under alkaline conditions. 5-Nitro-2-pyridinol gives even higher yields of 1-substituted pyridones than 2-pyridinol itself (*452*) *e.g.*, 80% for the *N*-methylation of the potassium salt with methyl iodide. The *O*-methyl derivative is formed in only 0.8% yield. 3-Nitro-2-pyridinol undergoes quantitative methylation on nitrogen with dimethyl sulfate and potassium hydroxide (*237*). 3,5-Dibromo- and 3-nitro-5-chloro-2-pyridinol undergo *N*-methylation exclusively (*279*). Ethyl 6-hydroxynicotinate with methyl iodide in alkali gives a 70% yield of the 1-methyl derivative (*252*). However, when the dipotassium salt of the acid is heated in a sealed tube with *n*-propanol and *n*-propyl

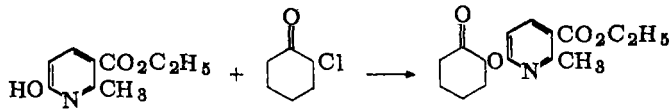


(XII-263) (XII-262)

(XII-265) (XII-264)

iodide, both *N*- and *O*-propylation occur (*453*). In view of the successful *N*-methylation of several nitro- and carboxyl-substituted 2-pyridinols, the report that 6-hydroxy-5-nitronicotinic acid was recovered unchanged after attempted methylation with methyl iodide or dimethyl sulfate in base (*279*) is very surprising.

In sharp contrast to these *N*-alkylations is the exclusive isolation of an *O*-alkylation product (XII-267) in fair yield from the base-catalyzed reaction of ethyl 2-methyl-6-hydroxynicotinate (XII-266)

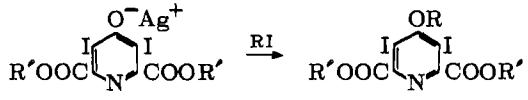


(XII-266) (XII-267)

with 2-chlorocyclohexanone (*244*). The structure of XII-267 was determined by infrared and ultraviolet spectral analysis. The only other example of the use of an α-halocarbonyl compound is the reaction of 2-pyridinol with chloroacetaldehyde to give the *N*-acetaldehyde (*450*). This reaction occurs in an acid medium, in which the

only nucleophilic site is the ring nitrogen. Although there is no explanation given in the report (*244*) for the unusual *O*-alkylation, one based on steric inhibition can be offered. The starting material (XII-266) is substituted in both the 2 and 6 positions, thus introducing an F-strain, and inhibiting nucleophilic attack by the ring nitrogen. The oxygen, however, is not encumbered by ortho groups, and it acts as the nucleophile. Electronic factors, therefore, may not be the sole criteria for predicting the course of the alkylation reaction. In base catalyzed alkylations, two side reactions are possible. When alcohols are solvents, they can etherify the halide, thus diminishing the yield. The halide can also undergo a base-catalyzed dehydrohalogenation. For this reason, tertiary halides cannot be used as alkylating agents.

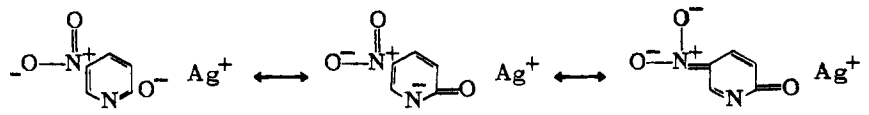
When silver salts replace the alkali metal salts, the proportion of *O*-alkylation increases. The silver salt of 2-pyridinol with ethyl iodide is converted into 2-ethoxypyridine only, but methyl iodide gives an equal mixture of the *O*- and *N*-methyl derivatives (*408*). Silver salts of dialkyl esters of diiodochelidamic acid (XII-268) have



(XII-268)

R = Me, Et, Pr, Bu, $PhCH_2$, allyl

been *O*-alkylated (*443*) in a xylene suspension with alkyl halides. According to another report (*448*), the occurrence of *O*- or *N*-methylation depends on temperature. Thus XII-268 (R = R′= CH_3) gives *O*-methylation at 110° C. but *N*-methylation at 160°. This effect is not explained by the authors, but might be due to *O*- to *N*-isomerization at the higher temperature. Unlike its small effect in alkylations of alkali salts, an electron-withdrawing group ortho or para to the hydroxyl group exerts a marked influence on the *O*- to *N*-isomer ratio given by silver salts; *N*-alkylation now predominates. The silver salt of 5-nitro-2-pyridinol (XII-269) with methyl iodide gives 60% *N*-methylation and 16% *O*-methylation (*233*). The



(XII-269)

structure of the *O*-methyl derivative was proved by synthesis from sodium methoxide and 2-iodo-5-nitropyridine. The success of *O*-alkylation depends on having sufficient negative charge on the oxygen atom. Since a *p*-nitro group diminishes this charge by resonance interaction, it decreases the yield. Reaction of XII-269 with ethyl iodide and benzyl iodide leads to *O*-alkylation products in yields of 34 and 22%, respectively (*233*). A comparable isomer ratio was obtained from the silver salt of 3-nitro-2-pyridinol and methyl iodide (*237*).

Recently, Kornblum (*452*) has promulgated a theory concerning the reaction of "ambident anions"—those having two nucleophilic sites—in which he compares and explains the reactions of their silver and alkali metal salts. Most of the work was done with the relatively simple nitrite ion, but the theory was generalized to include all other ambident ions, 2- and 4-pyridinols among them. In reactions with alkyl halides, silver salts differ from alkali salts by interacting with the halogen atom to increase the amount of carbonium ion character in the transition state. As the positive nature of the transition state (S_N1 type) increases, bond formation at the ambident anion atom having the higher electron density is preferred. Oxygen is more electronegative than nitrogen, and forms the covalent bond. The more stable the carbonium ion, the greater should be the preponderance of *O*-alkylation. The fact that the silver salt of 2-pyridinol gives a 50:50 mixture of both isomers with methyl iodide, but only the *O*-ethyl isomer with ethyl iodide, is explainable since the ethyl carbonium ion is more stable than the methyl. Polar solvents should favor the *O*-alkylation by solvating the carbonium ion in the transition state, and consequently, aid its formation by lowering the energy.

Alkali metal salts react by an S_N2 mechanism, and the preference is for bond formation with the atom less able to bear the nega-

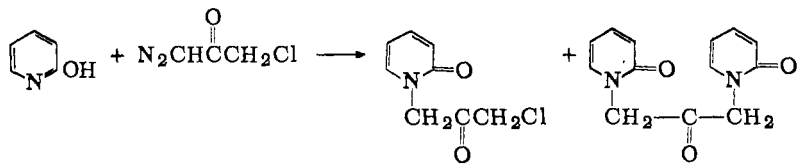
tive charge. Since N is less electronegative than O, the 2- and 4-pyridinol alkali metal salts are *N*-alkylated.

This is an excellent unifying theory, which, however, may be an oversimplification when applied to the pyridinols. As previously mentioned, substitution of groups on the pyridine ring at C_2 and C_6 may alter the course of the *N*-alkylation reaction by affecting the steric environment about the ring nitrogen. The complexity of the alkylation of 2-pyridinols is evidenced by recent findings on the course of the reaction of substituted benzyl halides with substituted 6-methyl-2-pyridinols, using alkali metals (*537*). The ratio of *N*- to *O*-alkylation depends on the electronic nature of the substituents on the pyridyl and phenyl rings, the size of the ortho substituent on the benzyl halide, the nature of the alcohol used, and even the nature of the metal used. The influence of the metal would imply the necessity of considering the role of ion pairs.

Even the position of the hydroxyl group affects the course of the reaction. As expected, the silver salt of 2-pyridinol reacts with phenacyl bromide to give the *O*-alkylated product, whereas the sodium salt undergoes mainly *N*-alkylation. In contrast, however, both salts of 4-pyridinol give mostly *N*-alkylation (*896*). Methyl iodide also reacts with the silver salt of 4-pyridinol to give the *N*- rather than the *O*-alkylated product.

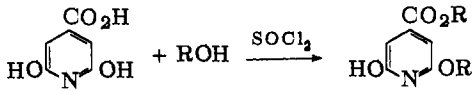
Several 2-pyridinols were converted to *N*-vinyl-2(1*H*)-pyridones by treatment with acetylene in dioxane containing potassium hydroxide (*898*).

2-Pyridinol reacts with chloracetyldiazomethane to give a mixture of 1-(3-chloroacetonyl)-2(1*H*)-pyridone (XII-269a) and 1,3-bis-(2-oxo-1,2-dihydro-1-pyridyl)-acetone (XII-269b). At higher temperatures XII-269b predominates (*899*).



(XII-269a) (XII-269b)

One instance of an acid-catalyzed etherification in the presence of thionyl chloride, inorganic oxygen acids, or organic sulfonic acids is cited (XII-270) (*464*). Only the mono-ethers are formed, and



(XII-270)

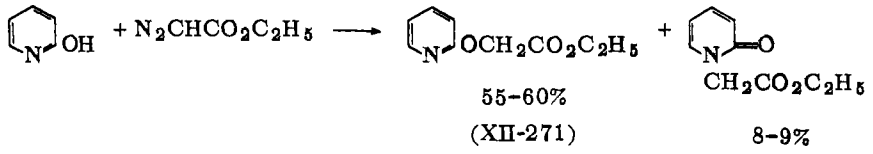
R = *n*-butyl, cyclohexyl, isoamyl

there are no reports in the literature of etherification of monohydroxypyridines under these conditions. Conceivably, the mechanism might first involve the esterification of an α-hydroxyl group and then displacement of the ester group by ROH. The presence of another hydroxyl group favors the reaction. The explanation of the replacement of only one hydroxyl group from a 2,6-diol is similar to that given for the replacement of the amino group from a 2,6-diamine (*306*) (p. 589).

Alkylation of 2- and 4-pyridinols with diazoalkanes usually leads to mixtures of *N*- and *O*-isomers. While 2-pyridinol and diazomethane give 2-methoxypyridine exclusively (*453,409*), 4-pyridinol gives some 4-methoxypyridine, but mostly 1-methyl-4(1*H*)-pyridone (*409*). It has been argued (*454*) that this variation indicates that the pyridone structure is much more important in 4-pyridinol than in 2-pyridinol, implying that the reaction can determine the position of the hydrogen. This is not a valid argument because it overlooks the mechanism of the reaction and the rates of reaction of the two tautomeric forms. Conceivably, the minor form can react faster than the major form and the rates thus control the yields of products. A similar argument was incorrectly used to establish the structure of saccharin (*455*). This argument is further discredited by the report that diazoethane and 4-pyridinol give the reverse isomer distribution from diazomethane, mostly 4-ethoxypyridine together with some *N*-ethyl isomer (*456*).

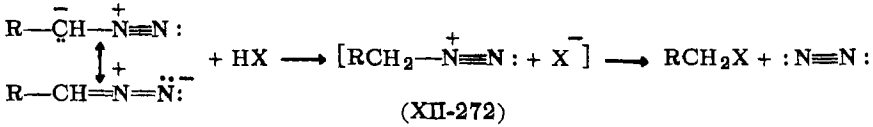
This difference in the behavior of 2- and 4-pyridinols is further evidenced by the observation that 6-ethyl-2-hydroxyisonicotinic acid gives the corresponding 2-methoxy ester (*457*), while 5-methoxy-4-hydroxypicolinic acid yields the *N*-methyl ester (*132*). With diazo-

ethane, 3,4-pyridinediol gives 3,4-diethoxypyridine (*458*); similarly 6-methyl-2,3-pyridinediol forms the dimethoxy derivative with diazomethane (*186*). Ethyl 2-pyridoxyacetate (XII-271) is obtained



as the chief product, together with a small amount of the isomeric pyridone, by reacting 2-pyridinol with ethyl diazoacetate. The yields are based on consumed 2-pyridinol, which amounts to only 26%. It has been reported that a 2-pyridinol, 2-hydroxy-6-methylnicotinic acid, esterified but failed to give either *N*- or *O*-methylation with diazomethane (*466*).

To account for the increased yield of *O*-alkylation with diazoalkanes, and the difference in *O*-:*N*-alkylation ratio when diazomethane and diazoethane are used, Kornblum's hypothesis concerning ambident anions may be applicable. It is postulated that the reaction of diazoalkanes with a compound HX, which contains a sufficiently acidic hydrogen, proceeds by addition of a proton to the diazoalkane to give an unstable alkyldiazonium salt (XII-272), which

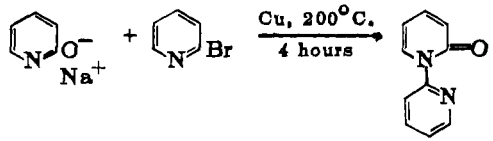


reacts with X^- to form alkylated X and nitrogen. Nitrogen has a large heat of formation, and its loss might begin to occur before the new C-X bond forms. A considerable carbonium ion character is imparted to the transition state, and the C-X covalency forms with the more electronegative atom, leading to *O*-alkylation. An increase in *O*-alkylation would be expected when diazoethane is used instead of diazomethane, because its carbonium ion is more stable. This discussion, however, does not adequately reconcile the marked difference in behavior of the 2- and 4-pyridinols. One possible difference between the diazoalkane and silver salt- alkyl halide re-

actions should be mentioned. When silver salts of anions are alkylated, all the ambident molecules are present as anions. In the diazoalkane reaction, the predominant species is the acid HX. Unless XII-272 exists as a caged ion-pair, and every reaction leading to alkylation occurs between the anion X^- and the cation $RCH_2N_2^+$, the HX itself would react with $RCH_2N_2^+$, and the "ambident anion" hypothesis need not apply. Until more is known concerning the mechanism of diazoalkane alkylation, all discussion is speculative.

Since the direct methods of *O*-alkylation of 2- and 4-pyridinols usually give mixtures, they are not reliable synthetic routes for obtaining alkoxy derivatives. The indirect methods of converting the hydroxy- to the chloropyridine, followed by treatment with the desired alkoxide, is preferred.

Arylation requires higher temperature and copper catalysis. Thus 1-phenyl-2(1*H*)-pyridone results from reacting the sodium salt of 2-pyridinol with iodobenzene and copper at elevated temperatures (*461*). Similarly, 2-bromopyridine gives 1-(2-pyridyl)-2(1*H*)-pyridone (XII-273) (*462*). While 2-pyridinol is *N*-arylated, the potassium salt



(XII-273)

of 3-pyridinol gives a 55% yield of 3-phenoxypyridine on treatment with bromobenzene and copper carbonate (*429*).

3-Pyridinol has been converted to the methyl ether with diazomethane below 0° C. (*900*).

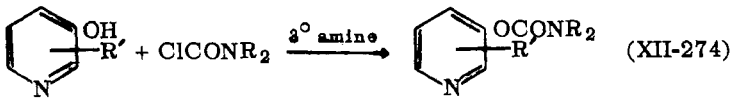
c. O- *and* N-*Acylation*

As expected, β-pyridinols undergo the normal reactions with various organic and inorganic acid derivatives to give esters.

3-Pyridinol reacts readily with acetic anhydride to give 3-acetoxypyridine (*425,429*) in 95% yield. Acylations with benzoyl chloride in 81% yield (*429*) and with diphenylacetyl chloride in 96% yield

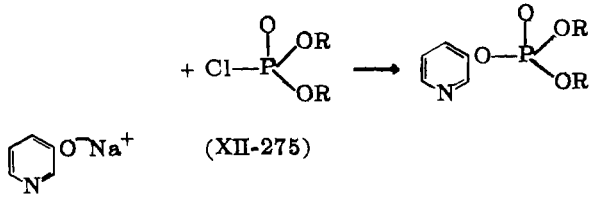
are reported (*510*). 2-Iodo-3-pyridinol was benzoylated (87%) with benzoyl chloride in benzene and trimethylamine (*431*).

Substituted 3-pyridinol carbamates and their *N*-alkylated derivatives were found to be capable of inhibiting cholinesterase. Several have been prepared by the action of carbamyl chlorides on β-pyridinols in the presence of a tertiary organic base such as triethylamine (*468*) or pyridine (*469*) (XII-274). In a few instances methyl (*468*)

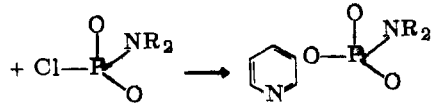


(XII-274)

and phenyl isocyanates (*470*) were used. Some carbamate esters are reported to be active against influenza virus (*470*). A sulfamate of 3-pyridinol was prepared using *N,N*-dimethylsulfamyl chloride (*468*). An ester of sulfanilic acid was prepared by fusing the sodium salt of 3-pyridinol with sulfanilyl fluoride (*471*). Phosphorylation (*472*) results when either the sodium or potassium salt of 3-pyridinol is treated with a dialkylphosphoryl chloride (XII-275) or *N,N*-dialkylphosphoramidechloridate (XII-276). These esters also show anti-cholinesterase activity.



(XII-275)



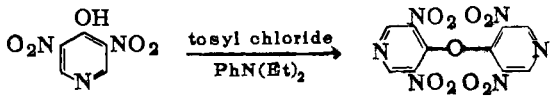
(XII-276)

R = C_2H_5, *i*-C_3H_7

Both the 2- and 4-pyridinols are acylated with difficulty, owing to the instability of the esters. In 1905, Meyer (*409*) accounted for the failure to acylate 2-pyridinol on a steric basis. However, twenty years later, the successful preparation of 2-acetoxypyridine was re-

ported (*473*) when acetyl chloride was added to anhydrous sodium 2-pyridinol. The previous failures were undoubtedly due to the presence of traces of water. Benzoylation succeeds under Schotten-Bauman conditions or with benzoic anhydride in ether (*474*). Likewise, *p*-nitrobenzoyl chloride in sodium hydroxide gives the corresponding 2-pyridyl ester (*473*). More recently (*467*) 2-pyridyl benzoate was prepared in 90% yield using benzoyl chloride in anhydrous pyridine; the sodium salt of 2-pyridinol gave 85% yields. 6-Methyl-2-pyridinol gives the 2-acetoxy derivative on being treated with acetic anhydride (*393*). A sulfonate was prepared (*467*) by heating *p*-nitrobenzenesulfonyl chloride with the sodium salt of 2-pyridinol.

Similarly, 4-pyridinol gives *O*-acetyl, *O*-benzoyl, and *O*-tosyl derivatives (*411*). It is imperative that the conditions be anhydrous (*526*). When 3,5-dinitro-4-pyridinol (XII-277) reacts with tosyl



(XII-277)

chloride, the dipyridyl ether results rather than the ester (*475*). It may be that the ester forms transiently and then, owing to the activation of the ortho nitro groups, undergoes displacement of the *p*-$CH_3C_6H_4SO_3$– group by the conjugate base of XII-277.

A few instances have been reported where nitrogen reacts rather than oxygen. Thus 3,5-diiodo-4-pyridinol (XII-278, R = H) and di-

(XII-278)

R = H, COOH

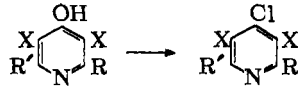
iodochelidamic acid (XII-278, R = COOH) react with chlorsulfonic acid to give the *N*-sulfate derivative (*443*). These are readily hydrolyzed by water, reforming XII-278. There is however, no ade-

quate proof of structure to exclude the possibility that the product is an *O*-sulfate.

d. Displacement by Halogen

A marked divergence in properties of both the 2- and 4-pyridinols from the 3-isomer is seen in the replacement of the hydroxyl group by halogen. The former compounds react smoothly with phosphorus halides and thionyl chloride, whereas the latter compound, like phenols, is unreactive. V. Pechmann and Baltzer (*408*) first reacted 2-pyridinol with phosphorus pentachloride in phosphorus oxychloride. Subsequently a large number of substituted 2-pyridinols were reacted. In a few instances the phosphorus halide is used alone. Neither the kind nor number of substituents influence the reaction. Amino- (*477*), nitro- (*235*), nitrocyano- (*28,63,480*), dinitro- (*247*), and nitrohalopyridinols (*240,247*) undergo displacement. However, as expected, carboxylic acids are converted to acid chlorides (*103,279*) and amides to nitriles (*479*).

4-Pyridinol is converted to the corresponding chloro compound with phosphorus trichloride (*121*) at 150° C. More recently this transformation was effected in 61% yield with phosphorus oxychloride in three hours on a steam bath. When the 4-hydroxy isomer is substituted in both the 3 and 5 positions, steric hindrance can be expected, and was in fact observed during the reactions of 3,5-dihalo-4-hydroxypicolinic acid (XII-279, R′= H, R = COOH) with



(XII-279)

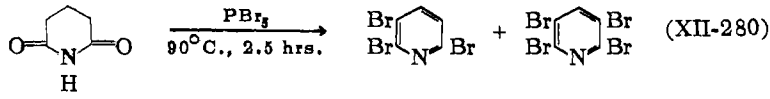
phosphorus pentachloride. In the case of the diiodo compound, the replacement of OH by Cl proceeded much less smoothly (*210*) although it was not prevented entirely. However, when X = I and R = CH_3, the reaction proceeds with a mixture of phosphorus trichloride and phosphorus oxychloride in 98% yield (*259*). Other 3,5-substituted 4-pyridinols were conveniently transformed in good yields with phosphorus oxychloride in the presence of secondary amines,

e.g., XII-279 (X = NO_2, R = Me, R′= H) (*371*) and XII-279, (X = Br or NO_2, R = R′= H) (*370*). Thionyl chloride gave a 95% conversion of the methyl ether of comenamic acid to the corresponding 4-chloro acid chloride (*483*).

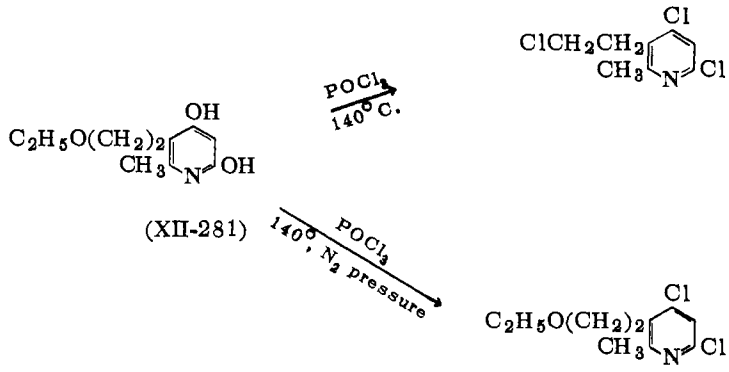
Robison in 1958 reported the use of phenylphosphonic dichloride, $C_6H_5POCl_2$, to replace α- and γ-hydroxy groups (*872*). This reagent has an advantage over phosphorus oxychloride in its higher boiling point, which obviates the need to perform sealed tube reactions which are hazardous, inconvenient, and limited in scale.

Replacement of OH by Br is effected by the phosphorus bromides. The 3-nitro, 3-nitro-5-bromo, 3-nitro-5-chloro (*390*), and 3-nitro-5-carboxy (*279*) derivatives of 2-pyridinol reacted in good yields with a mixture of phosphorus tribromide and bromine at 100° C. for about one day. 3-Nitro-2-pyridinol also reacts with phosphorus and bromine in toluene at 130° C. (*231*). In the preceding reactions the nitro and carboxyl groups sufficiently deactivate the ring towards electrophilic attack by bromine. In the absence of such electron-withdrawing groups, bromine could not be used. 5-Methyl-2-pyridinol reacts normally with phosphorus tribromide at elevated temperatures (*484*), while 3,5-dibromo-4-pyridinol (*374*), 3,5-dibromo-6-methyl-2-pyridinol, and 6-methyl-2-pyridinol (*485*) react with phosphorus oxybromide at elevated temperatures in fair yields. A number of nitro and bromo derivatives of 2-pyridinol and 6-methyl-2-pyridinol reacted normally in yields of 24–90%, on being heated for one hour at 180° with a mixture of phosphorus tribromide and phosphorus oxybromide (*486*).

In several instances ring bromination occurs during replacement of the OH group. When 4-pyridinol reacted with phosphorus penta- and oxybromide, a small quantity of 2,4,6-tribromopyridine was isolated (*487*). This product could not result from electrophilic bromination of 4-pyridinol, which would form the 3,4,5-tribromide instead. A small quantity of 2,5-dibromo-3-nitropyridine was isolated from the reaction of 3-nitro-2-pyridinol with a phosphorus tribromide-oxybromide mixture (*486*). Glutarimide reacts with phosphorus pentabromide to give a mixture of brominated pyridines (XII-280) (*488*). These correspond to the chlorinated products obtained with phosphorus pentachloride (*489*).



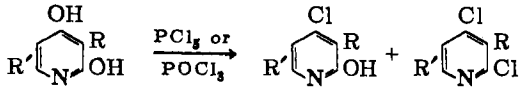
2,6-Diols were converted to the dichloro (*40,490,492,493*) and dibromo (*168*) compounds in yields ranging from 60–80%. Likewise, 2,4-pyridinediol (*492*) and its alkyl (*78,79*), nitro (*492*) and carbethoxy derivatives (*492*) react smoothly. When 4,6-dihydroxynicotinamides (*222,223*) react with phosphorus chlorides, the corresponding dihalonicotinonitriles are isolated. When 6-methyl-5(β-ethoxyethyl)2,4-pyridinediol (XII-281) is treated as shown, the ether is



cleaved or retained depending on the presence of nitrogen gas under pressure to suppress the action of hydrogen chloride (*392*).

In competitive reactions, it appears that the course of OH → Cl conversion is influenced by steric effects. Thus, treatment of 3-ethyl-4,5-dimethyl-2,6-pyridinediol with phosphorus oxychloride under mild conditions gave 6-chloro-4,5-dimethyl-3-ethyl-2-pyridinol, and not the 2-chloro-6-pyridinol; the OH group ortho to the methyl rather than the ethyl group reacted (*827*).

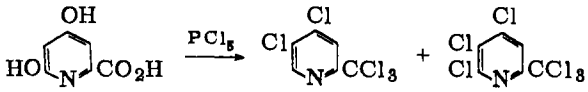
When a limited amount of the halogenating reagent is used, the opportunity is presented to study the relative susceptibility of the 2-, 6-, and 4-OH groups. In the few cases studied, the 4-OH group reacts preferentially. Thus 6-chloronorricinine (XII-281a, R = CN, R′= Cl) reacts as shown (*494*). 3-Nitro-6-methyl-2,4-pyridinediol (XII-281a, R = NO_2, R′= Me) with phosphorus oxychloride gives a similar



(XII-281a)

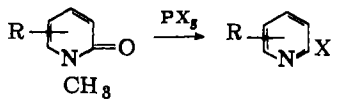
mixture (*495*). The structure of the monochloro compound was proved by reduction to the known 3-amino-6-methyl-2-pyridinol.

Treatment of 3,4-pyridinediol with phosphorus oxybromide gives only 4-bromo-3-pyridinol (*496*). Ost (*170*) reports isolating β,γ-dichloro compounds from the treatment of comenamic acid with phosphorus pentachloride in a sealed tube. This treatment, however, was severe enough to also convert the COOH group to the trichloromethyl group (XII-282).



(XII-282)

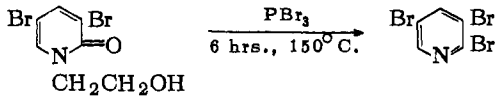
1-Methyl-2-pyridones (XII-283) undergo demethylation in addition to substitution of the oxygen by halogen. The parent com-



(XII-283)

pound (XII-283, R = H) has been successfully brominated and chlorinated (*498*) as have several halogenated derivatives (R = X) (*104, 248,497*). Nuclear halogenation can occur under severe conditions; XII-283 (R = H) at 200° C. gives 2,5-dichloropyridine (*499,501*). A γ-pyridone, 1-methyl-2,6-diphenyl-4(1*H*)-pyridone, yields 2,6-diphenyl-4-chloropyridine with phosphorus chlorides (*503*). The reaction of 2(1*H*)-pyridones having an *N*-substituent other than methyl is rare. The isolation in fair yield of 2,3,5-tribromopyridine after treating 1-(β-hydroxyethyl)-3,5-dibromo-2(1*H*)-pyridone (XII-284) with phosphorus tribromide is reported (*500*).

1-Methyl- and 1-phenyl-4(1*H*)-lutidones are converted to 1-methyl- and 1-phenyl-4-chlorolutidinium salts by phosphorus pentachloride

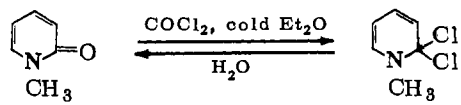


(XII-284)

and by benzenesulfonyl chloride (*862*). *N*-Alkylchelidamic acid, on treatment with thionyl chloride, is reported to undergo partial decarboxylative chlorination in addition to dealkylation and substitution of the oxygen function by chlorine (*901*). The *N*-methyl substrate with oxalyl chloride after a short time gives the diacid chloride of the 4-chloropyridinium salt, but after prolonged reaction, dealkylation occurs (*862*).

N-Methyl-5-methoxy-2-carboxy-4(1*H*)-pyridone with thionyl chloride gives 4,6-dichloro-5-methoxypicolinoyl chloride (*483*). A few substituted 1-phenyl-2(1*H*)-pyridones with phosphorus oxychloride give the respective 2-chloropyridinium salts and not the benzo[a]-quinolizinium salts (*902*).

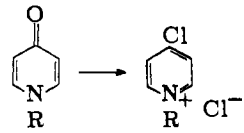
Phosgene dissolved in toluene can effect this change. In this manner Räth (*502*) converted several 5-substituted 1-methyl-2(1*H*)-pyridones. 1-Benzyl-5-chloro-2(1*H*)-pyridone reacts similarly (*502*). 1-Methyl-2(1*H*)-pyridone reacts easily with phosgene to give 2,2-dichloro-1-methyl-1,2-dihydropyridine (XII-285), which is very hy-



(XII-285)

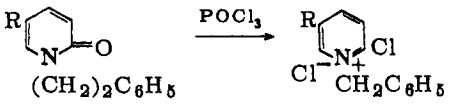
groscopic and readily regenerates the pyridone. Conceivably, in the aforementioned reactions, including those with phosphorus halides, compounds similar to XII-285 are intermediates which lose methyl chloride to give the chloropyridines.

Occasionally the reaction takes an alternate path to give chloropyridinium chlorides. Some 1-substituted 4(1*H*)-pyridones (XII-286) react in this manner. When R = CH_3, the reagent is a mixture of phosphorus halides at 130° C. and when R = C_6H_5, thionyl chloride is used for three hours at 140° C. 1-Phenethyl-5-ethyl-2(1*H*)-pyridone (XII-287, R = C_2H_5) with phosphorus oxychloride forms a



(XII-286)

R = CH_3 (*401*), C_6H_5 (*688*)



(XII-287)

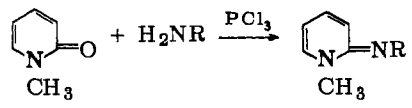
pyridinium salt (*357*). When XII-287 (R = COOH) is treated similarly, followed by alcohol and an iodide salt, the compound isolated is the ester of the 2-ethoxypyridinium iodide, which presumably arises from the intermediate chloro compound (*592*).

The conversion of pyridinols to halo compounds is also discussed in Chapter VI (pp. 326 ff.).

e. Miscellaneous Replacements

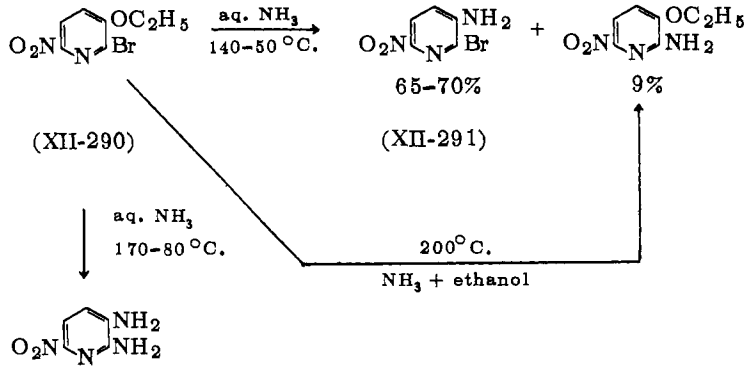
Thiation can be effectively accomplished with phosphorus pentasulfide by fusion (*324*) or in refluxing benzene (*411*), toluene (*507*), or pyridine, a superior solvent (*255,259*). 2-Pyridones (*255*), their 1-substituted derivatives (*504*), 4-pyridones (*259,324*) and their 1-substituted derivatives (*411,507*) have all been converted to sulfur analogs. When 5-iodo-2-pyridinol is heated with phosphorus pentasulfide, iodine is lost and 2-pyridinethiol is formed (*508*). If, however, the reaction is performed in refluxing pyridine, 5-iodo-2-pyridinethiol is obtained (*255*), indicating the greater reliability of this method. This reaction is further discussed in Chapter XV.

The oxygen function may also be replaced by nitrogen. 3-Methyl-4-pyridinol reacts with ammonia and copper at 200° C. to give 3-methyl-4-aminopyridine (*289*). 1-Methyl-2(1*H*)-pyridone reacts with primary amines in the presence of phosphorus trichloride (*256*) to give pyridonimines (XII-288). The amines utilized were aniline, *p*-phenetidine, β-naphthylamine, 2-aminopyridine, and *i*-amylamine.



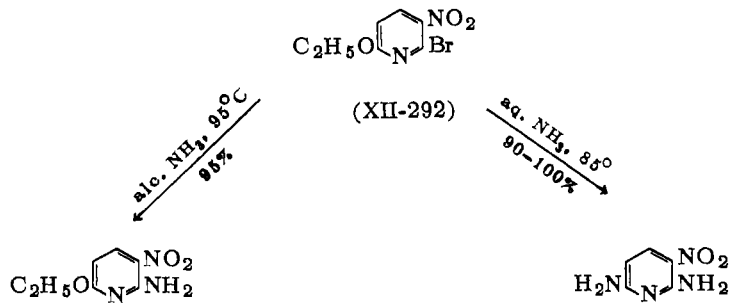
(XII-288)

Ether groups have been replaced by amino groups when activated by *o*-substituted nitro groups. Thus 3-nitro-4-methoxypyridine (XII-289) reacts with alkylamines (*505*) and *o*-toluidine (*239*). When 2-bromo-3-ethoxy-6-nitropyridine (XII-290) is heated with ammonia, a variety of products is obtained depending on conditions. At 140–150° C. a mixture is obtained in which either the ethoxy or bromo group is replaced. At 120° C. only XII-291 is obtained, the major

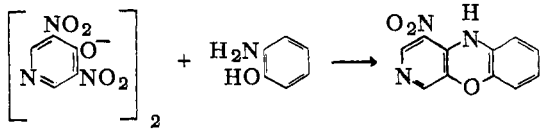


part of the starting material being recovered, whereas at 170–180° both groups are replaced. Ethanol retards the reaction; in its presence a temperature of 200° is required to introduce an amino group. Surprisingly, under these conditions the bromine is replaced. Increasing polarity of the solvent accelerates the replacement of the substituent para to the nitro group (*647*).

2-Bromo-6-ethoxy-3-nitropyridine (XII-292) undergoes displacement under much milder conditions (85° C.), since the bromo and ethoxy groups are activated by both the nitro group and the nuclear nitrogen. Again alcohol retards the displacement of the group para to the nitro group. Under the vigorous conditions used for XII-292, 2-nitro-3-ethoxypyridine gives a 65–70% yield of 2-nitro-3-aminopyridine with 9% of 2-amino-3-ethoxypyridine (*647*). A

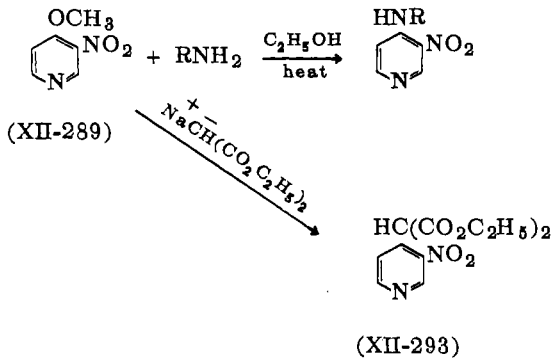


novel example of such a displacement (*475*) results in the formation of 5-nitro-3-azaphenoxazine (XII-294). A nitro group is displaced by



(XII-294)

the phenolic group to effect cyclization. Reaction of XII-289 with diethyl sodiomalonate also leads to replacement of the methoxy group to give XII-293 (*237,506*). Substituted malonic esters do not

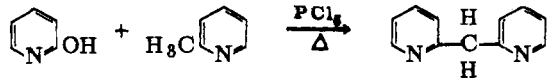


(XII-293)

R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *o*-MeC_6H_4

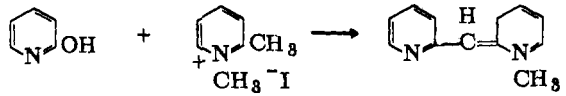
react (*237*). The marked reactivity of the methoxy group in XII-289 enables this stable compound to be used as a starting material in many reactions instead of the unstable corresponding halide.

Warming 2-pyridinol with 2-picoline in phosphorus pentachloride yields bis(2-pyridyl)methane (XII-295), while with 1-methyl-2-



(XII-295)

picolinium iodide, 1-methyl-2-[pyridyl-(2)-methylene]-1,2-dihydropyridine (XII-296) results (*509*). 2-Methylquinoline (quinaldine)



(XII-296)

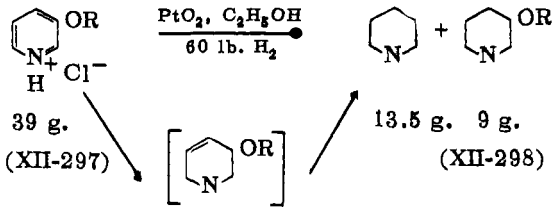
and 2-pyridinol give a similar product identical to the one obtained from 2-picoline and 2-quinolinol (carbostyril).

2. Involving the Nucleus

a. Reduction

All three isomeric pyridinols and 1-substituted 2- and 4-pyridones are reducible to piperidine derivatives. The reported results are occasionally contradictory, mainly because of the variation of conditions. The commonest methods are catalytic hydrogenation and sodium in alcohol.

Catalytic reduction of 3-pyridinol hydrochloride (XII-297, R = H) gives a mixture of 3-piperidinol (XII-298, R = H) and piperi-

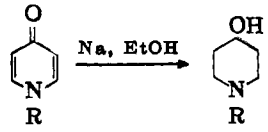


dine (*510*). Since 3-piperidinol resists further reduction under these conditions, the authors account for the formation of piperidine by proposing the formation of an intermediate allylic alcohol which

undergoes hydrogenolysis. Attempts to prepare substituted acetic acid esters of 1-alkyl-3-piperidinols as possible antispasmodics by reducing XII-297 (R = $COCHPh_2$) failed owing to the partial cleavage of the ester group (*510*). Pseudoconhydrine, 6-*n*-propyl-3-piperidinol, was synthesized in 96% yield by reducing 6-*n*-propyl-3-pyridinol with Adams catalyst in glacial acetic acid (*317*), and in 84% yield by reduction with sodium in ethanol (*297*). The catalytic reduction of 3-pyridinol (*511*) and 5-methyl-3-pyridinol (*516*) with nickel was reported.

4-Pyridinol was reduced with sodium and absolute ethanol by several experimenters (*512–514*), who obtained inadequate yields of 4-piperidinol and about 50% recovery of starting material. Reduction of 3,5-diphenyl-4-pyridinol with sodium in alcohol gave a poor yield of the 4-piperidinol (*147*). Catalytic reduction of 4-pyridinol has been unsuccessfully attempted under various conditions (*514*) although success was reported by the use of a large amount of platinum black (*512*). 2,6-Dimethyl-4-pyridinol was recently reduced in 60% yield with Raney nickel at 155° C. and 1400 p.s.i. in 5 hours (*93*).

1-Substituted 4-pyridones are reduced more easily than the 4-pyridinols, giving mainly *N*-substituted 4-piperidinols (XII-299).



(XII-299)

Yield	R
46%	CH_3 (*122, 515*), Ph (*130*)
65%	*p*-tolyl (*516*)
38%	2,4-dimethylphenyl (*516*)

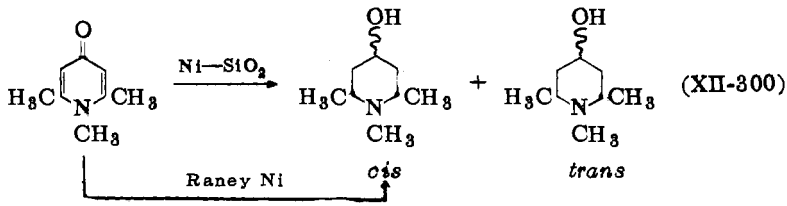
Most of the earlier workers used sodium and alcohol. Reduction of 1-(*p*-methoxyphenyl)chelidamic acid results in decarboxylation and the formation of XII-299 (R = *p*-methoxyphenyl) in 51% yield (*516*). However, electrolytic reduction preserves the carboxyl groups. Recently high pressure catalytic hydrogenation has been

studied (*93*); the findings are tabulated in Table XII-20. Copper chromite catalyst gives sharply reduced yields when converted to the "inactive red form." It should be noted that hydrogenolysis of the β-methoxy groups was not observed.

TABLE XII-20. Catalytic Hydrogenation of 4(1*H*)-Pyridones to 4- Piperidinols (*93*)

Substituents	Catalyst	Max. temp.	Init. pres., p.s.i.	Time, hrs.	Yield, %
1,2,6-Trimethyl	Raney Ni	125	1500	4	85
1,2,6-Trimethyl	Ni-SiO_2	125	1500	4	83
1,2,6-Trimethyl	Cu chromite	140	1600	4	80
1,2-Dimethyl-5-methoxy	Raney Ni	150	1500	4	87
1-Methyl-2-hydroxymethyl-5-methoxy	Raney Ni	155	1500	4	85
1-Methyl-2-hydroxymethyl-5-methoxy	Cu chromite	170	1500	4	49
1,2-Dimethyl-3-methoxy	Raney Ni	155	1500	5	60

The stereochemical course of these reactions is obscure. Hydrogenation of 1,2,6-trimethyl-4(1*H*)-pyridone gives different results (XII-300) depending on the catalyst; Raney nickel yields only the



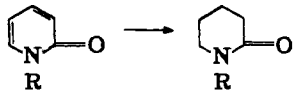
(XII-300)

cis isomer. The use of *cis* and *trans* refers to the 2- and 6-methyl groups since the configuration of the hydroxyl group is unknown. The stereochemistry of these molecules was determined by Mannich (*691*) who synthesized them and resolved the *trans* which is racemic but not the *cis* which is meso. All other 4-pyridinols in Table XII-20 gave but one isomer (*93*). Catalytic reduction of 1-methyl-4(1*H*)-pyridone with Raney nickel in methanol at 150° C. gave about a 70% yield of the expected 1-methyl-4-piperidinol with a small amount of 1-methylpiperidine (*517*).

In contrast to the behavior of the 3- and 4-pyridinols and pyridones, the 2-isomers give 2-piperidones on reduction (XII-301). Attempts at further reduction lead to ring cleavage and loss of the ring nitrogen. The fact that 2-piperidone is a δ-lactam and quite resistant to reduction accounts for its isolation; the next stage in reduction would be an unstable product having an OH and NH group on the same carbon. Cleavage would result with loss of ammonia.

Table XII-21 lists several 2-pyridones which have been reduced catalytically. This is the preferred method, and usually gives almost quantitative yields.

TABLE XII-21. Catalytic Hydrogenation of 2-Pyridones to 2-Piperidones



(XII-301)

R	Catalyst	Conditions	Ref.
H	$NiCO_3$-$CuCO_3$	200-35°	522
Me	Pt black	neutral or acid	518,521
Me	Ni	100°, 120 atm.	519
Me	Ni		520
Me	$NiCO_3$-$CuCO_3$	160-200°	522
Et	$NiCO_3$-$CuCO_3$	175-200°	522
n-Pr	$NiCO_3$-$CuCO_3$	180-240°	522
i-Pr	$NiCO_3$-$CuCO_3$	180-220°	522
n-Bu	$NiCO_3$-$CuCO_3$	185-210°	522
n-Oct	$NiCO_3$-$CuCO_3$	185-210°	522
$PhCH_2$	$NiCO_3$-$CuCO_3$	200-26°	522
CH_2CH_2OH	Raney Ni	sat. EtOH, R.T., 1 atm.	523
$CH_2CH(OH)CH_2OPr$	Raney Ni	sat. EtOH, R.T., 1 atm.	523
$CH_2CH(OH)CH_2OC_6H_{11}$	Raney Ni	sat. EtOH, R.T., 1 atm.	523
bis-$(CH_2)_n$ (n = 2 – 6)	Raney Ni	sat. EtOH, R.T., 1 atm.	343

1-Methyl-5-phenyl-2(1*H*)-pyridone was normally reduced in 93% yield by using a succession of catalysts: Adams' platinum, palladium, and Raney nickel (*350*). 1-Methyl- and 1-butyl-2(1*H*)-pyridones are quantitatively reduced with active platinum in forty-two hours to the deoxygenated 1-substituted piperidines (*524*).

1-Ethyl-2(1*H*)-pyridone with sodium amalgam undergoes ring rupture with loss of ethylamine (*521*), but 1-phenethyl-2(1*H*)-pyri-

done-5-carboxylic acid gives the normal piperidone product in 60% yield (*525*). Cavallito and Haskell (*526*) have made a comparative study of the hydrogenation of the isomeric pyridinols and their esters. In ethanol or dioxane at 25 and 55° C., 1–3 atm. hydrogen pressure with palladium sponge, 2-pyridinol is reduced to 2-piperidone while the 3- and 4-isomers are unchanged. Under the same conditions Adams' platinum and Raney nickel are ineffective.

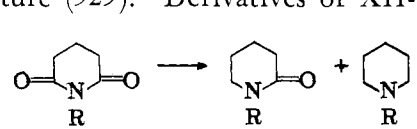
The benzoic and 2-naphthoic esters of 2-pyridinol hydrogenolyze rapidly to toluene (or 2-methylnaphthalene) and 2-pyridinol, which is then further reduced to 2-piperidone unless the reaction is stopped. The 4-pyridinol ester takes up only three mols of hydrogen to give toluene and 4-pyridinol. No reduction occurs with 3-pyridinol benzoate. The unusual hydrogenolysis to hydrocarbon under such mild conditions is attributed to the weakness of the ester bond which cleaves reductively to the pyridinol and the aldehyde, which is reducible to the hydrocarbon.

The tosyl derivatives gave different results (*527*). All three isomers absorbed one mole of hydrogen to yield the pyridine salt of *p*-toluenesulfonic acid. Further hydrogenation proceeded more slowly to give piperidinium salts, the 3 isomer proceeding most readily.

Lithium aluminum hydride reduction of 2-pyridinol was attempted unsuccessfully (*528*); an 8% yield of pyridine and 1.5% yield of piperidine resulted.

Ethers have also been reduced. Sodium and alcohol reduce 4-methoxypyridine mostly to piperidine (*512*). Hydrogenation of 2-methoxypyridine in methanolic hydrochloric acid with platinum black likewise gives piperidine.

Electrolytic reduction of *N*-methylglutarimides (XII-302, R = CH_3) gives a mixture (*529*). Derivatives of XII-302 were also re-



(XII-302)

duced with hydrogen over copper chromite at elevated temperatures and pressures to the corresponding oxygen-free piperidine (*530*).

b. Halogenation

Owing to the electron-withdrawing effect of the nuclear nitrogen, pyridine is inert toward electrophilic substitution. This deactivation is even more pronounced for pyridinium salts. However, since the OH and OR groups are strongly electron-releasing, the pyridinols and their ethers are easily substituted by electrophiles, although less readily than phenol. As expected, reaction occurs at carbon atoms ortho and para to the oxygen function. Halogenation is a typical example of such an electrophilic attack.

3-Pyridinol substitutes first at the 2 position. Bromination with an equivalent amount of bromine in pyridine (*496*), iodination with iodine and sodium carbonate (90% yield), and chlorination with hydrochloric acid and hydrogen peroxide (51% yield) (*380*), all give the 2-halo derivative. With excess iodine in potassium iodide, the 2,6-diiodo derivative is obtained (*867*).

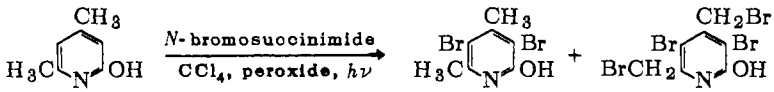
Since the 4- and 6-isomers are also likely products, an unequivocal structure proof is needed. This was achieved by independent synthesis of these two possibilities. The C_4 bromo compound was obtained by treating 3,4-pyridinediol with phosphorus oxybromide. The C_6 compound was synthesized from 2-amino-5-ethoxypyridine via 6-bromo-3-ethoxypyridine. Treating 2-nitro-3-ethoxypyridine with hydrobromic and acetic acids gives 2-bromo-3-pyridinol identical with the monobromination product of 3-pyridinol (*496*).

Iodination at 100° gives a 92% yield of a diiodo and a trace of triiodo derivative, both of unknown structure (*380*). Excess bromine water gives a tribromo derivative which is also obtained from both 2- and 6-bromo-3-pyridinol, thus proving that it is substituted at C_2 and C_6. Inasmuch as 5-bromo-3-pyridinol, under these conditions, itself takes up three atoms of bromine to give the 2,4,5,6-tetrabromo derivative, it is evident that the tribromo compound must be 2,4,6-tribromo-3-pyridinol. Two moles of bromine in pyridine gives 2,6-dibromo-3-pyridinol (*496*). Iodination of 5-methyl-3-pyridinol affords the 2,6-diiodo compound (*867*). Iodination of 3-hydroxypicolinic acid with iodine in an alkaline medium gave decarboxylation with the formation of 2,6-diiodo-3-pyridinol (*866*).

2-Pyridinol halogenates in the 3 and 5 positions. For example, iodine chloride in acid (*531*) or mild base (*532*) forms 3,5-diiodo-2-

pyridinol. Bromine water gives the corresponding dibromo compound (*533*), but in poor yield (*534*). On the other hand, chlorine in chloroform solution gives a mixture of 5-chloro- and 3,5-dichloro-2-pyridinols (*531*).

The structure proof of these halopyridinols is based mainly on conversion from the haloaminopyridines. 5-Iodo- (*218*), 5-bromo- (*272*) and 5-chloro-2-aminopyridines (*273*) each give the corresponding 5-halo-2-pyridinol on diazotization. Diazotization of 2-methoxy-5-aminopyridine followed by treatment with potassium iodide gives the same ether derived from 5-iodo-2-pyridinol. Hydrolysis of the known 2,5-dichloropyridine gives 5-chloro-2-pyridinol identical to the chlorination product of 2-pyridinol. 3,5-Dichloro-2-aminopyridine, obtainable either by ammonolysis of 2,3,5-trichloropyridine or Hofmann rearrangement of 3,5-dichloropicolinamide, gives 3,5-dichloro-2-pyridinol on diazotization (*692*). The dibromoamine reacts similarly (*272*). *N*-Bromosuccinimide reacts with 4,6-dimethyl-2-pyridinol to give a mixture of products showing both nuclear and side chain bromination (XII-303). When the quantity of benzoyl peroxide is reduced from 10 to 2.5 mole % and the ultraviolet light is omitted, the sole product is XII-304; this also results from reaction



49% (XII-304) 29% (XII-303)

with bromine in glacial acetic acid (*535*). These conditions are also used to brominate 2-hydroxy-4,6-dimethylnicotinonitrile (*535*) and -nicotinamide (*536*).

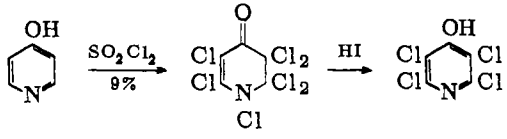
Deactivating substituents do not seriously impede the reaction. Thus 5-nitro-2-pyridinol is chlorinated and iodinated in the 3 position by potassium chlorate (*239*) and iodine chloride (*532*), respectively. 6-Hydroxypicolinic acid reacts with iodine in alkali followed by alternate acid-base treatment to give the 3,5-diiodo compound. Similarly 4-chloro-6-hydroxypicolinic acid is converted to the 3,4,5-trichloro derivative on chlorination in alkaline solution (*210*).

The reported absence of any 3-halo-2-pyridinols on halogenation seems strange. Recently, however, the 3- and 5-monobromo- and 3,5-dibromo-2-pyridinols were obtained by chromatographic analysis of the products resulting from bromination of 2-pyridinol in piperidine. The melting points of the 3- and 5-monobromo isomers were almost identical, but admixture gave a marked depression, and surprisingly, their ultraviolet spectra were appreciably different. Bromination in glacial acetic acid gave a greater preponderance of the 3,5-dibromo-2-pyridinol (*537*).

The reaction of 6-hydroxynicotinic acid with iodine-potassium iodide in aqueous ammonia to give 2,5-diiodo-6-hydroxynicotinic acid (*540*) is unusual because the 2-iodo group is not ortho or para to the hydroxyl group. In the absence of a rigorous structure proof the result is questionable.

4-Pyridinol is reported to halogenate with bromine water (*121*) and with iodine chloride in acid (*443*) to give the 3,5-dihalo derivative. The latter finding is challenged by Reitman (*541*) who failed to obtain the diiodo compound with iodine chloride in acid or iodine–potassium iodide but was successful with alkali. His results are confusing because he also asserts that iodide-iodate in acid serves as an iodinating reagent. Alternate acid and alkali treatment gives satisfactory yields (*327*). However, 2,6-dimethyl-4-pyridinol gives the expected 3,5-diiodo derivative in 98% yield with iodine chloride in hydrochloric acid at 100°C. (*259*).

4-Hydroxpicolinic acid was dihalogenated at the 3 and 5 positions with chlorine or iodine in alkali and with bromine water (*443*). 4-Hydroxy-2,6-pyridinedicarboxylic acid is iodinated quantitatively with iodine chloride in sodium bicarbonate (*259*). Exhaustive chlorination of 4-pyridinol with sulfuryl chloride gives a heptachloro-4-pyridone (XII-305). The same product is obtained from 4-pyridinol 1-oxide in 20–25% yields. Chemical or catalytic reduction of XII-305 gives the tetrachloro compound (XII-306). Each mole of XII-305



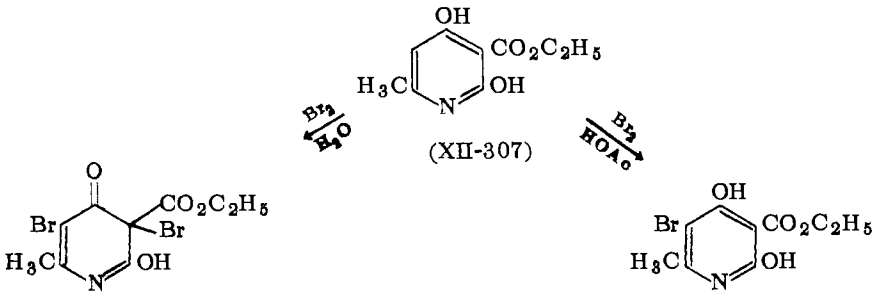
(XII-305) (XII-306)

liberates two moles of iodine from hydriodic acid; this provided a major clue to its structure (*228*).

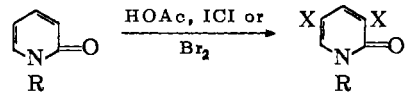
Ethers halogenate normally. Thus the expected dihalogenated product is obtained from 2,6-dibromo-4-methoxypyridine with bromine (*226*), or from 6- and 3-bromo-2-ethoxypyridine with hydrogen peroxide and hydrochloric acid (*266*). However, 4-chloro-2-ethoxypyridine with an excess of chlorine gas in acetic acid gives monochlorination; 4,5-dichloro-2-ethoxypyridine is isolated in 75–80% yield (*220*).

Polyhydroxypyridines and their ethers are also smoothly halogenated. Bromine water converts 2,4-pyridinediol to 3,5-dibromo-2,4-pyridinediol (*96*). Monobromination of 2,4-pyridinediol gives only the 3- and not the 5-bromo isomer (*492*). 3,5-Diethoxypyridine gives a dichloro and dibromo product (*542*) and 2,3,4-pyridinetriol gives a monobromo product (*170*), all of undetermined structure.

Ethyl 2,4-dihydroxy-6-methylnicotinate (XII-307) gives different products with varying conditions. Alkaline iodination gives the normal 5-iodo derivative (*543*).



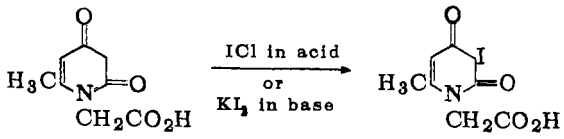
The aromaticity of the 1-substituted 2- and 4-pyridones is apparent since they undergo nuclear substitution. 1-Methyl-2-(1*H*)-pyridone is halogenated by chlorine (*337*), bromine (*544,337*), and iodine chloride in acetic acid (*545*) to give the 3,5-dihalo derivatives. Several other *N*-substituted 2-pyridones (XII-308) have been brominated and iodinated. Attempts to brominate XII-308 (R = $CH_2CH(OH)CH_2OR$) lead to unstable highly brominated compounds which have not been identified (*547*). The only example of monobromination occurs with XII-308 (R = 2-pyridyl) and one mole of bromine;



(XII-308)

R	X	Ref.
CH_2CO_2H	I	546
$(CH_2)_2SO_3H$	I	546
CH_2SO_3H	Br	546
$(CH_2)_2OH$	Br	547
$CH_2CH(OH)C_6H_5$	Br	547

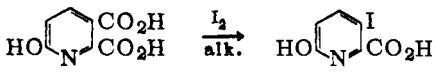
the 3-isomer is obtained in over 90% yield. Two moles give the 3,5-dibromo derivative (*375*). Both 1-methyl-3- and 5-bromo-2(1*H*)-pyridones react in glacial acetic acid with bromine to give the same 3,5-dibromo compound (*346*). Under the same conditions the 6-bromo isomer gives the 3,5,6-tribromo derivative (*497*). When the ring-opening reaction with cyanogen bromide was attempted with 1-methyl-5-nitro-2(1*H*)-pyridone, bromination occurred at C_3 (*233*). Iodination of a 2,4-dioxo compound (XII-309) reportedly gives the



(XII-309)

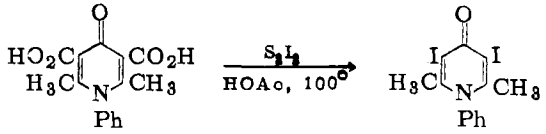
3-iodo derivative (*465*). Attempts to brominate *N*-alkyl-4(1*H*)-pyridones even with equimolar amounts of bromine result only in dibromination at C_3 and C_5 (*844*). In contrast, the corresponding pyrones do undergo monobromination.

Blocking groups such as COOH, AsO_3H, and NO_2 are replaced by halogen when they occupy a position ortho or para to the hydroxyl group. Thus 6-hydroxyquinolinic acid (XII-310) (*443*) and 6-hy-



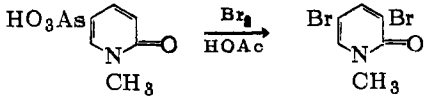
(XII-310)

droxy-5-nitronicotinic acid (*286*) both undergo replacement of the COOH group para to the OH group on iodination. Sulfur monoiodide can also effect iodination with decarboxylation (XII-311)



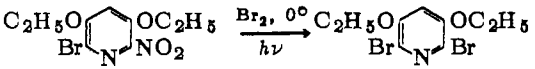
(XII-311)

(*550*). When 2-hydroxy-3-nitro-5-pyridinearsonic acid is heated with iodine–potassium iodide in sodium carbonate, 3-nitro-5-iodo-2-pyridinol is obtained in 91% yield (*548*). Bromination of 1-methyl-2-oxo-1,2-dihydropyridine-5-arsonic acid (XII-312) in acetic acid yields



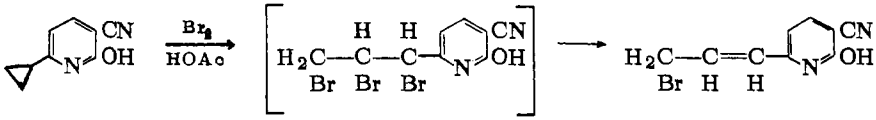
(XII-312)

the 3,5-dibromopyridone (*549*). Replacement of a nitro group is seen in the formation of 2,6-dibromo-3,5-diethoxypyridine from 2-bromo-3,5-diethoxy-6-nitropyridine (XII-313) (*425*).



(XII-313)

1-(Hydroxyphenyl)pyridones halogenate exclusively on the phenyl ring under competitive conditions (*550,125*). A unique result is the reaction of 2-hydroxy-6-cyclopropylnicotinonitrile (XII-314) with bromine in glacial acetic acid (*57*). The only evidence cited in support of structure XII-315 is molecular formula and probably ultra-



(XII-314) (XII-315)

violet spectral analysis; 2-vinyl- and 2-cyclopropylpyridines have markedly different ultraviolet spectra. Bromination of the three-

membered ring is assumed because analogs of XII-314 with other substituents in place of cyclopropyl do not brominate under the same conditions. A more rigorous structure proof of XII-315 is, however, needed.

c. Nitration

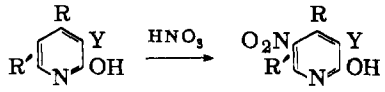
Like halogenation, nitration of 3-pyridinol occurs mainly in the ortho rather than the para position. To prevent oxidative destruction of the ring, the conditions should not be severe. Controlled nitration with nitric and sulfuric acid has been reported in the patent literature (*551,552*) to give mononitro derivatives of undetermined structure. The first careful study was made by Plazek and Rodewald (*553*) who obtained 2-nitro-3-pyridinol. The structure was proved by reduction to the aminohydroxy derivative, which condensed with picryl chloride to give a pyridyldinitrobenzoxazine. This reaction eliminates the 6-isomer as a possibility but not the 4-isomer. The latter was excluded by diazotizing the aminopyridinol and conversion to a compound which was shown to be the known 2,3-pyridinediol.

As would be expected, the ethers are more resistant to oxidation. Koenigs and co-workers (*207*) incorrectly ascribed the 6-nitro structure to the mononitro derivative obtained from 3-ethoxypyridine with concentrated sulfuric acid and fuming nitric acid at 100°C. The proof of structure was based on the incorrect 2,6-dihydroxy structure assigned to the alkaline fusion product of 3-pyridinol. Since this diol was later shown to be the 2,3-isomer (*380*), the nitro-group must be at the 2 position. Recently a yield of 75–80% was reported (*264*). Paper chromatographic analysis of the crude aminopyridinols formed from the nitropyridinols reveals only a trace of 6-substitution (*555*).

Although originally the 3-methyl ether was reported to undergo only dinitration (*207*) milder condition (5°C.) give a mononitro derivative, 2-nitro-3-methoxypyridine (*554*). More vigorous treatment gives 2,6-dinitro-3-methoxypyridine. The absence of 4-nitration seems to be general. Thus, 2-bromo-3-ethoxypyridine gives a good yield of 2-bromo-3-ethoxy-6-nitropyridine (*264*).

Early workers (*320*) attempted to protect the hydroxyl group by acetylation, but nitration of the acetate was difficult (*207*).

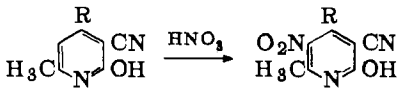
2-Pyridinol was first nitrated by Chichibabin and Schapiro (*557*) and later by Binz and Maier-Bode (*558*). The major product was 3-nitro accompanied by some 3,5-dinitro- and a trace of 5-nitro-2-pyridinol. Recently this work was repeated and the compounds reported by these authors were shown to be mixtures of the sodium salts of the 3- and 3,5-dinitro compounds (*279*). Nitration of 3- and 5-nitro-2-pyridinol gives the same 3,5-dinitro-2-pyridinol. The mononitration product is identical to the product obtained by diazotizing 3-nitro-2-aminopyridine (*277*). The preference for *o*-nitration is further seen in the formation of 3-nitro-6-methyl-2-pyridinol from 6-methyl-2-pyridinol in a mixture of glacial acetic acid and nitric acid (*495*). Contrary to this behavior, the ethers nitrate predominantly in the 5 position. Reactions have been carried out up to 100°C., in mixed acid or by adding the crystalline nitrate to concentrated sulfuric acid (*559*). The presence of a deactivating group does not impede nitration. Several 2-hydroxynicotinic acid derivatives have been successfully nitrated (XII-316). Improved results are given by fuming nitric acid in acetic anhydride (*247*).



(XII-316)

R	R′	Y	Ref.
CH_3	CH_3	CN	28,247
H	CH_3	CN	59
CH_3	CH_3	$CONH_2$	536
H	H	CO_2H	287

Successful nitration in the presence of two deactivating groups is seen in a stage of a Vitamin B_6 synthesis (XII-317).



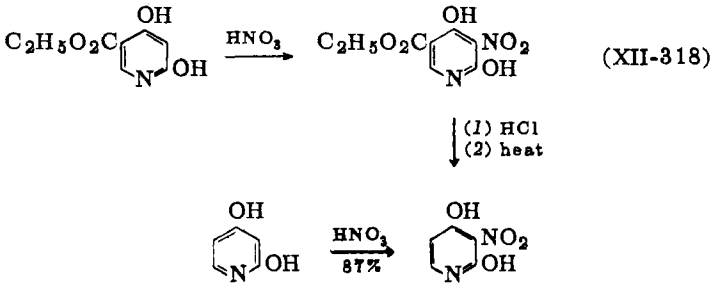
(XII-317)

R = CN (*479*), CO_2Et (*49,480*)

4-Pyridinol was first nitrated with fuming nitric and sulfuric acids to give a mixture of the 3-nitro- and 3,5-dinitro derivatives

(*560*). Under milder conditions good yields of the mononitro compound were obtained, whereas more severe conditions gave good yields of the dinitro derivative (*561,562*).

2,4-Diols are successfully nitrated under mild conditions to prevent oxidation. 2,4-Pyridinediol itself was warmed with nitric acid (d = 1.4) for a short time to give 3-nitro-2,4-pyridinediol. The proof of structure is shown (XII-318) (*563,492*). Excellent yields of the



(XII-318)

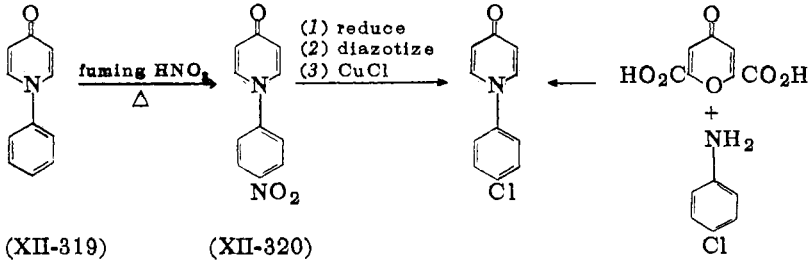
5-nitro derivative were obtained from ethyl 2,4-dihydroxy-6-methylnicotinate (*77,543*).

3,5-Diethoxypyridine gave the 2-nitro compound, which was converted under more vigorous conditions to 2,6-dinitro-3,5-diethoxypyridine (*564*). The structure of the mononitro compound was established by reducing it to the amine, which was also obtained from the known 2-bromo-3,5-diethoxypyridine and ammonia. The structure of the dinitro compound was established by treating it with hydrogen bromide in glacial acetic acid to give the known 2-bromo-3,5-diethoxy-6-nitropyridine (*565*). It was necessary to prove the structures because the mono- and dinitro products had the same melting point, which confused the early experimenters (*207*).

Again, the aromaticity of the 1-substituted pyridones is apparent since they undergo electrophilic nitration. Fischer and Chur (*337*) obtained a mononitro derivative from 1-methyl-2(1*H*)-pyridone in concentrated sulfuric and nitric acids, and a dinitro compound from 62% nitric acid in the absence of sulfuric acid. These were later shown to be the 3- and 3,5-dinitro compounds (*333,279*).

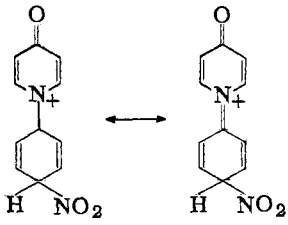
As would be expected, phenyl ethers nitrate exclusively in the benzene ring (*566,567*).

Nitration of 1-phenyl-4(1*H*)-pyridone (XII-319) affords 1-*p*-nitrophenyl-4(1*H*)-pyridone (XII-320). The structure was proved by con-



(XII-319) (XII-320)

verting the nitro compounds via the amine to the chloro compound which was independently synthesized (*129*). This result raises two important theoretical questions: (*1*) why does the pyridone ring direct para rather than meta? and (*2*) why is the phenyl ring more activated than the pyridone system? The ground state of XII-319 has considerable positive charge on nitrogen due to the appreciable contribution from the zwitterion resonance form. On this basis, one might predict a preponderance of meta substitution. In such analyses, however, it is also imperative to consider the transition state (in this case the intermediate). Thus, para substitution gives a resonance hybrid (XII-321) in which the positive charge is sub-



(XII-321)

stantially borne by the ring nitrogen. The pyridone system is clearly analogous to the nitroso group, of which it is a vinylog, and orients ortho, para with deactivation. A plausible answer to the second question is more obscure. The positive charge on the nitrogen (in the ground state) may deactivate the pyridone ring, of which it is an integral part, more than it does the phenyl group to which it is only an adjunct.

6-Hydroxynicotinic acid and its *N*-methyl derivative nitrate with decarboxylation to give 3,5-dinitro-2-pyridinol and 1-methyl-3,5-dinitro-2(1*H*)-pyridone, respectively. In both cases, less severe conditions give the expected mononitro compound (nitro group ortho to the oxygen function), with carboxylic acid group intact (*279*).

The nitration of pyridinols and their ethers is also discussed in Chapter VIII (pp. 474 ff.).

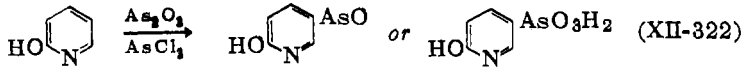
d. Miscellaneous Electrophilic Substitution

The literature on sulfonation is sparse, probably owing to the difficulty of the reaction. Plazek sulfonated 3-pyridinol with 100% sulfuric acid and vanadyl sulfate as a catalyst (*568*); the product is presumed to be the 3-hydroxypyridine-2-sulfonic acid (*569*). The 6-sulfo structure is eliminated as a possibility but there is no adequate proof that it is not the 4-sulfonic acid.

Sulfonation of 1-methyl-2(1*H*)-pyridone with chlorosulfonic acid gives the 5-sulfonic acid (80%) while oleum gives a mixture of the 5-sulfonic acid (50%) and 3,5-disulfonic acid (30%). Chlorosulfonic acid was also used to sulfonate 1-methyl-5-nitro-2(1*H*)-pyridone at C_3 and the corresponding *N*-acetic acid at C_5, both in good yields (*570*). No structure proofs are given. Dimethyl sulfate sulfonates 1-methyl-2(1*H*)-pyridone in the 5 position (*607,608*). Neither 2- nor 4-pyridinol has been sulfonated.

2-Pyridinol has been arsonated by fusion with arsenic acid to give mainly the 5- mixed with some 3-arsonic acid. The isomeric acids are separated on the basis of the difference in solubility of the monosodium salts in aqueous methanol. A short heating period (5 hours) favors the formation of the 5-isomer while long periods (24 hours) favor the 3-isomer (*571,572,606*). These results are reminiscent of the sulfonation of naphthalene and similarly indicate that the reaction is reversible, so that the products can be either kinetically or thermodynamically controlled. Fusion with arsenic acid at 210°C. converts 1-methyl-2(1*H*)-pyridone into the 3-arsonic acid (*572*). A series of other 1-substituted 2-pyridones has been arsonated at C_5 either by fusion or in a high boiling solvent such as tetralin (*573*). Reaction of 2-pyridinol with a mixture of arsenious oxide and chloride gives a product which can be reduced to the

5-arsenoso compound or oxidized to the arsonic acid (XII-322). The product obtained depends on the method of isolation (*cf.* Chapter XVI).



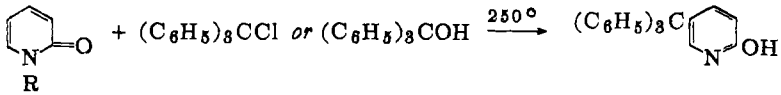
(XII-322)

Reaction of 2-pyridinol with mercuric acetate in methanol is reported to give a C_5 mercurated product (*575*).

The reaction has been more carefully observed using 2-, 3-, and 4-pyridinols (*869*). 2-Pyridinol with mercuric acetate in water gave the 3,5-dimercuriacetate, 3-pyridinol gave the 2-mercuriacetate, and 4-pyridinol gave the 3-mercuriacetate. The mercuriacetates were converted in the usual manner to the corresponding iodo compounds.

Diazonium salts couple with 2- and 3-pyridinols (*576*) and 2,6-pyridinediol (*98*) to give azo derivatives. The early workers did not determine the structure of the products. More recently 3-pyridinol was coupled in the 2 position with *p*-nitrobenzenediazonium chloride. Reduction of the azo compound gave 2-amino-3-pyridinol (*429*). 2,6-Dihydroxyisonicotinic acid (citrazinic acid) was quantitatively coupled with diazotized sulfanilamides (*577*) and with benzenediazonium chloride (*870*). 4-Methyl-2,6-pyridinediol gave the 3-phenylazo compound in 90% yield when reacted with benzenediazonium chloride (*578*). Pyridones such as 1-phenyl-4(1*H*)-pyridone do not couple with diazonium salts (*130*).

Failure to undergo the Friedel-Crafts reaction with acyl and aroyl halides was attributed to complexing of the catalysts, aluminum chloride and boron trifluoride, with the pyridinols and pyridones (*467*). It is also true, however, that this reaction is more sensitive to ring deactivation than the electrophilic substitutions previously discussed. A successful Friedel-Crafts type reaction was reported using triphenylchloromethane without a catalyst or triphenylcarbinol in the presence of a little sulfuric acid. Both 2-pyridinol and 1-methyl-2(1*H*)-pyridone give 5-triphenylmethyl-2-pyridinol (XII-323); the *N*-methyl group of the pyridone was lost. The position of the triphenylmethyl radical is assigned by analogy with other substitution reactions of 2-pyridinols. The authors assume that the

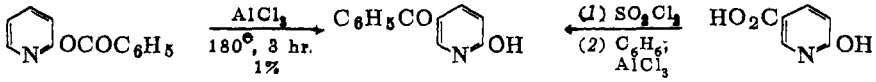


(XII-323)

R = H or CH_3

ease of formation and stability of the triphenylmethyl carbonium ion accounts for the ease of substitution. The reaction appears to be a general one inasmuch as trityl chloride reacts readily with 3-methyl-2-pyridinol, while diphenylxenylchloromethane or the corresponding carbinol reacts with 2-pyridinol and its 3-methyl homolog. Condensation with 6-methyl-2-pyridinol gives poor yields, probably because of steric hindrance. It is assumed that substitution occurs at C_3 since the product, unlike XII-323, cannot be converted to the chloropyridine and is insoluble in aqueous ethanolic sodium hydroxide, presumably because the hydroxyl group is sterically hindered (*467*) by the bulky group at C_3.

The Fries rearrangement of the *O*-benzoate of 2-pyridinol gave only a 1% yield of 5-benzoyl-2-pyridinol (XII-324). The structure



(XII-324)

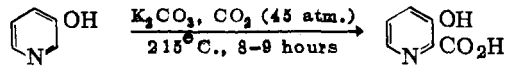
of XII-324 was proved by unequivocal synthesis from 6-hydroxynicotinic acid.

Nitrosation, another substitution reaction sensitive to deactivation by electron-withdrawing substituents, fails to occur with pyridinols.

e. Base-Catalyzed Substitution

Base converts pyridinols into resonating anions which have partial negative charge distributed to the ring carbons ortho and para to the hydroxyl group. These carbons can form covalent bonds with molecules containing electron-deficient carbons, *i.e.*, carbon

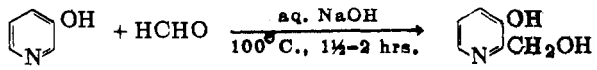
dioxide (Kolbe reaction) or formaldehyde (hydroxymethylation and Mannich reaction.). On the other hand, the Reimer-Tiemann reaction (displacement of halogen from chloroform by the phenol carbanion) is unsuccessful with the three isomeric pyridinols (*59,429, 580*). The sodium salt of 2-pyridinol, when autoclaved with carbon dioxide at 180–200°C., gave as the sole product 6-hydroxynicotinic acid, resulting from *p*-substitution (*579,104*). This result contrasts with the *o*-substitution in phenol. 3-Pyridinol, heated with anhydrous potassium carbonate and carbon dioxide, gave 3-hydroxypicolinic acid (XII-325). The sodium or potassium salt gave far inferior yields (*429*).



(XII-325)

5-Methyl-3-pyridinol undergoes the Kolbe reaction to give 5-methyl-3-hydroxypicolinic acid (*867*). However, if C_2 is blocked, as in 2-methyl-3-pyridinol, carbonation occurs at C_6 rather than at C_4 (*836*). This lack of reactivity at C_4, which is also observed in other base-catalyzed substitution reactions involving 3-pyridinols, has not been explained or even considered. On the surface, there is no reason for the marked difference in reactivity at the two ortho positions.

Hydroxymethylation of 3-pyridinol was effected by treatment with an alkaline aqueous solution of formaldehyde (XII-326). Sub-



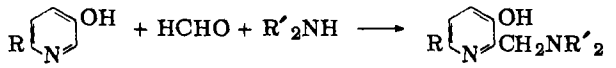
(XII-326)

(51%)

stitution at C_2 was demonstrated by oxidizing the product to 3-hydroxypicolinic acid (*294*). Repetition of this experiment led to the isolation of a disubstituted product in 20% yield which was characterized as the 2,6-derivative by conversion to 2,6-dimethyl-3-pyridinol (*584*). Similarly, 6-methyl (*581*) and 6-ω-carboxyheptyl-3-pyridinol (*582*) hydroxymethylate in the 2 position. Diols also

undergo the reaction; 2,4-dihydroxy-6-chloronicotinonitrile reacts with formaldehyde at C_5 (*494*).

The Mannich reaction was extended to 3-pyridinols in attempts to synthesize pyridoxine (*59*), its analogs (*318*), and antagonists (*585*). Brown and Miller (*318*) erroneously reported the formation of a 4-substituted product from the reaction of 2-methyl-3-pyridinol with formaldehyde and secondary amines. The same pyridinol reacted with formaldehyde and dimethylamine to give a product also erroneously alleged to be the C_4 product (*585*). The starting material has since been shown to be 6-methyl-3-pyridinol, substitution occurring at C_2 (XII-327) (*584*). Dialkylamines, alkarylamines, and



(XII-327)

R = H or CH_3

cyclic amines such as piperidine and morpholine have also been utilized.

When the 2 position is blocked the course of the reaction is obscure. Thus 2-methyl-5-hydroxymethyl-3-pyridinol is reported to resist the Mannich reaction (*59*). The reaction of authentic 2-methyl-3-pyridinol has not yet given well-defined products. There is also the possibility that reaction might occur at the methyl group, although this complication did not arise in the case of 6-methyl-3-pyridinol (*584*).

The reason that the aldehyde condensations do not occur with the 2- and 4-isomers is probably that they each have a resonance form with negative charge on nitrogen and the contribution from the carbanion forms is insufficient.

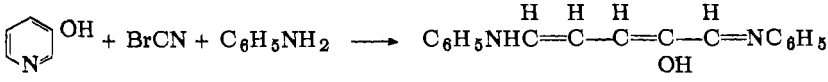
f. Anionic Substitution

Examples of such reactions are hydroxylation (see p. 612), amination, and arylation. 2-Pyridinol with sodamide in vaseline at 200–250° C. is reported to give 6-amino-2-pyridinol (*586*). The same reagent with 3,4-pyridinediol gives the 2-amino derivative in 40% yield (*587*). The sodium salt of 4-pyridinol, when heated with sodamide at 250° C. for three to six hours, is converted to 2,6-diamino-4-pyridinol (*885*).

When 3-methoxypyridine is refluxed in anhydrous ether with phenyllithium under nitrogen for seven hours, it is arylated at C_2; 3-methoxy-2-phenylpyridine is the sole product isolated (*886*). The authors attribute the lack of C_6 arylation to coordination of lithium with oxygen,—O : Li—C_6H_5.

g. Ring-Opening Reactions

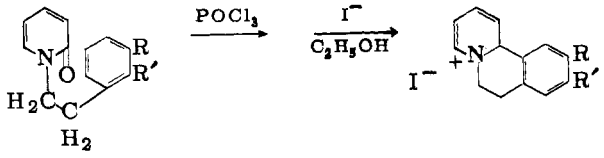
There are few instances of this type of reaction with pyridinols. One well-known example involves 3-pyridinol, aniline, and cyanogen bromide (XII-328) (*171*).



(XII-328)

h. Synthesis of Polycyclic Systems

The reaction of 1-phenethyl-2(1*H*)-pyridones (XII-329) with phosphorus oxychloride to form quinolizinium salts was originally developed by Sugasawa (*588*). The reaction is successful for XII-329 (R = R′ = H and -OCH_2O-) (*589*). The 3,4-dimethoxyphenethyl,

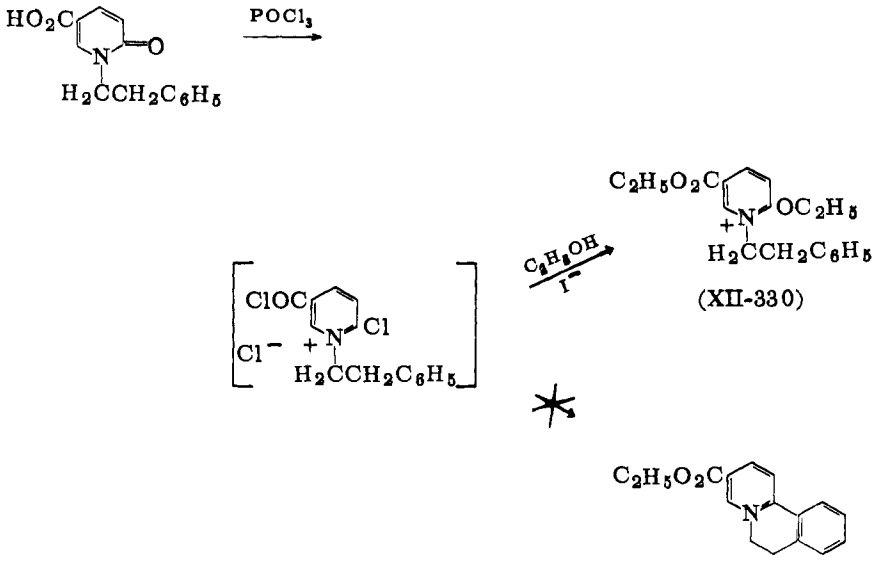


(XII-329)

6-methylphenethyl, 2-methoxyphenethyl, and 2,5-dimethoxyphenethyl, 6-methylphenethyl, 2-methoxyphenethyl, and 2,5-dimethoxyphenethyl pyridones also cyclize (*342*). The reaction is however not completely general. *o*-Methoxyphenethylpyridone does not cyclize (*342*). Although 1-(2-phenethyl)-2(1*H*)-pyridone undergoes cyclization (*341*), the 5-carboxy (*592*) and the 5-ethyl (*357*) derivatives do not.

It is assumed (*592*) that the intermediate in this reaction is the 2-chloropyridinium chloride. The deactivating effect of the 5-

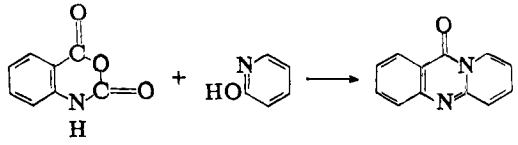
carboxy group toward displacement of C_2-chlorine can account for the failure to ring-close. Isolation of 1-phenethyl-6-ethoxy-3-carbethoxypyridinium iodide (XII-330) instead of the quinolizinium salt supports this assumption.



(XII-330)

The 2-(1-naphthyl)ethyl substituted pyridone cyclizes to give a naphthoquinolizinium iodide (*364*).

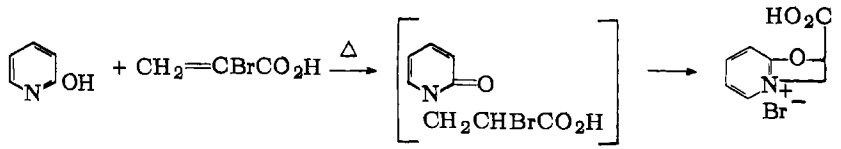
Pyracridone (XII-331) was synthesized from 2-pyridinol and isatoic anhydride (*593*).



(XII-331)

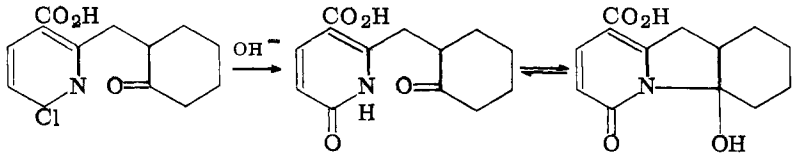
2-Pyridinol and α-bromoacrylic acid gave 2-carboxy-2,3-dihydrooxazolo[2,3-a]pyridinium bromide (XII-332) in 70% yield (*450,451*).

The alkaline hydrolysis of 2-(2′-oxocyclohexylmethyl)-6-chloronicotinic acid (XII-333) gave a substance in which the chlorine was replaced by the elements of OH. Since the infrared spectrum



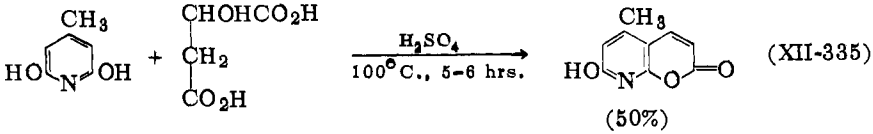
(XII-332)

showed hydroxyl absorption, structure XII-334 was assigned, representing a ring-closed tautomer of the 6-hydroxynicotinic acid.



(XII-333) (XII-334)

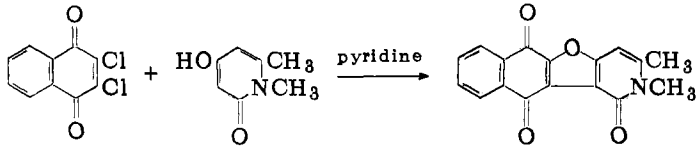
4-Methyl-2,6-pyridinediol and malic acid condense in the manner of the Pechmann coumarin synthesis (XII-335) (*594*).



(XII-335)

(50%)

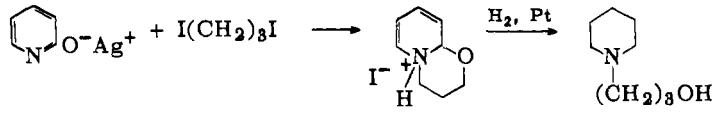
A quinoid derivative (XII-336) of naphtho(2,3,2′,3′)furan was prepared from 1,6-dimethyl-4-hydroxy-2(1*H*)-pyridone and 2,3-dichloro-1,4-naphthoquinone (*595*).



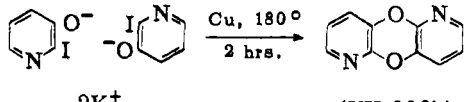
(XII-336)

The silver salt of 2-pyridinol reacts with trimethylene iodide to give 2,3-dihydro-4H-pyrid(2.1-b)-oxazinium iodide (XII-336a), catalytic reduction of which gives *N*-(3-hydroxypropyl)piperidine (*918*).

When the potassium salt of 2-iodo-3-pyridinol is heated with copper at 180° C., a fair yield of 1,6-diazadibenzo-*p*-dioxin (XII-336b) is produced (*869*).



(XII-336a)



(XII-336b)

D. *O*- AND *N*-SUBSTITUTION PRODUCTS

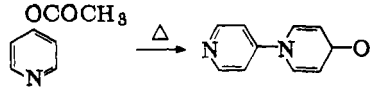
1. Properties

An *O*-alkyl derivative can be separated by steam distillation from the nonvolatile *N*-alkyl isomer. Recently chromatography was employed to give a more efficient separation, the *N*-alkyl compound being more readily absorbed on alumina than the *O*-alkyl. The latter also has the lower melting point.

Both isomers are stable compounds. The ethers isomerize under suitable conditions to the *N*-alkyl isomers, and also hydrolyze more readily than phenolic ethers.

Tables XII-27 to XII-30 (pp. 737 ff.) cover 2-pyridinol ethers; Tables XII-36 (pp. 783 ff.) and XII-38 (pp. 796 ff.) the 3 and 4 isomers, respectively. Tables XII-39 to XII-49 (pp. 801 ff.) cover *N*-substitution products.

Whereas the acylated 3-pyridinols (Table XII-35, pp. 781 f.) are relatively stable, the 2- and 4-isomers are very unstable; the aliphatic esters are sensitive even to traces of water. Esters of aromatic acids seem to be more stable than the aliphatic. Those of 4-pyridinol are the most unstable and are preparable only under anhydrous conditions (*526*); both the acetyl and tosyl derivatives yield 1-(4-pyridyl)-4(1*H*)-pyridone (XII-337) when heated (*507*). The same product is



(XII-337)

obtained when 4-pyridinol is refluxed with acetic anhydride. Inadequate structure proof makes the reported (*443,596*) preparation of

N-acyl derivatives doubtful. If formed, they are very easily hydrolyzed.

2. Reactions of Ethers

Aryl ethers can be cleaved by refluxing in strong acid or strong base. The mechanism of acid cleavage involves the formation of the ether onium salt followed by displacement on R of the pyridinol (XII-338). Basic cleavage involves concerted displacement on R of

$$\mathrm{ArOR} \xrightarrow{\mathrm{HX}} \mathrm{ArO\overset{H}{R}^{+}X^{-}} \longrightarrow \mathrm{RX + ArOH} \qquad \text{(XII-338)}$$

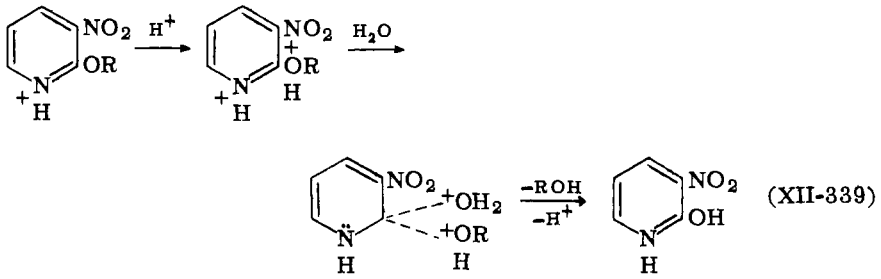
the aryloxide ion. In neither of these reaction paths is the Ar-O bond broken. In this respect the 3-pyridinol ethers are typical.

3-Alkoxypyridines have been cleaved by refluxing in hydrochloric acid (*266*), hydrobromic acid (*430*), a mixture of hydrobromic and glacial acetic acids (*207*), and hydriodic acid (*483*). 2-Pyridinol ethers are dealkylated in similar fashion; 2-propoxy in 42% hydrobromic acid (*449*), 2-*n*-butoxy in an ethereal solution of hydrogen chloride (*865*), and 2-alkoxy 5-substituted pyridines by heating the hydrochloride salt to 200° C. (*598,599*). An attempt to reduce 4,6-dimethyl-2-methoxynicotinonitrile in the presence of strong hydrochloric acid resulted in the formation of the 2-hydroxynitrile (*66*), which resisted hydrogenation. Acetic acid proved too weak an acid to effect hydrolysis. The cleavage of 2-phenoxypyridine in concentrated hydrochloric acid is interesting in view of the inertness of diphenyl ethers (*600*). The displacement may occur on the pyridine nucleus.

Both ether linkages hydrolyzed when 2,5-diethoxypyridine was heated in a concentrated aqueous solution of hydrobromic acid (*458*). When 2,4-dimethoxypyridine was heated with a 30% solution of hydrobromic acid in acetic acid for two hours at 85–90° C., only the 2-methoxy group hydrolyzed, giving 4-methoxy-2-pyridinol (*601*). On the other hand, 5-chloro-2,4-diethoxypyridine yields the 2,4-diol when heated at 160° C. for four hours in 25% aqueous hydrochloric acid (*220*).

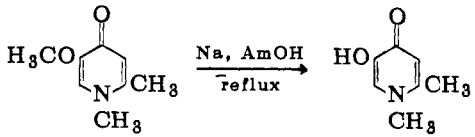
Bromination of 2,6-dibromo-4-methoxypyridine in a sealed tube yielded 2,3,5,6-tetrabromo-4-pyridinol; the ether was apparently cleaved by the hydrogen bromide formed in the reaction (*226*).

When a nitro group is present ortho or para to the alkoxy group, milder conditions are required. 2-Methoxy-3-nitropyridine is hydrolyzed with 0.5*N* acid in two hours on the steam bath (*237*). All attempts to hydrolyze the nitrile group of 2-ethoxy-5-nitronicotinonitrile resulted in hydrolysis of both the cyano and ethoxy groups to give the pyridinol (*63*). 3-Bromo-4-methoxy-5-nitropyridine is demethylated merely by cold methanolic hydrochloric acid (*506*). Since the alkoxy group of these nitroethers is readily displaced by amines and the malonate carbanion (see pp. 652 f.), these reactions undoubtedly proceed by a similar mechanism. Water can act as the nucleophile, displacing the alcohol as shown (XII-339).



(XII-339)

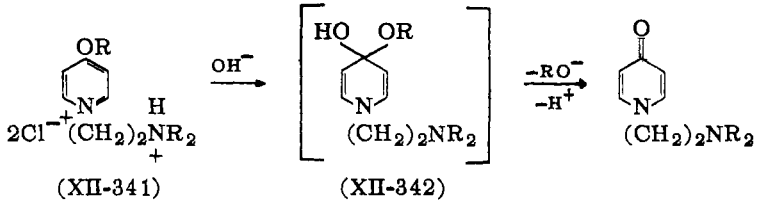
A basic cleavage was reported when 1,6-dimethyl-3-methoxy-4-(1*H*)-pyridone (XII-340) reacted with sodium amylate (*132*).



(XII-340)

The attempt (*209*) to oxidize *N*-dialkylaminoalkyl-4-alkoxy or aryloxy pyridinium halides (XII-341) to the 2-pyridone with alkaline potassium ferricyanide gave the 4-pyridone resulting from ether cleavage. It is postulated that reaction proceeds by hydroxide attack on C_4 giving the intermediate (XII-342), which loses the elements of alcohol.

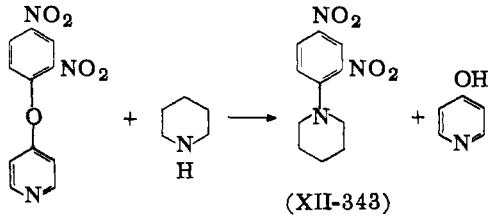
When 2-methoxy-4,6-dibromo-3-pyridinol was reduced catalytically in base, not only was the bromine replaced by hydrogen but the ether was cleaved as well (*496*).



(XII-341) (XII-342)

R = alkyl or aryl

A novel reaction was the formation of 1-(2,4-dinitrophenyl)-piperidine (XII-343) when 2,4-dinitrophenyl 4-pyridyl ether was



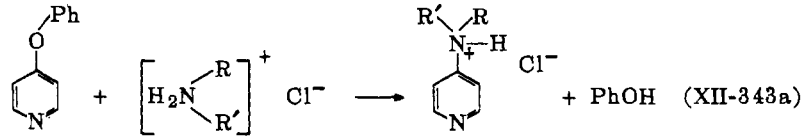
(XII-343)

treated with piperidine (*567*). In this instance the phenyl-oxygen bond was cleaved by displacement on the benzene ring, activated toward nucleophilic attack by the nitro group.

It is interesting to speculate as to the course of the cleavage if a nitro substituent were at C_3 of the pyridine ring.

Benzyl ethers are cleaved as expected by catalytic reduction (*45*).

A unique synthesis of 2- and 4-aminopyridines involves the displacement by amines of the phenoxy group (XII-343a) (*887,888*).



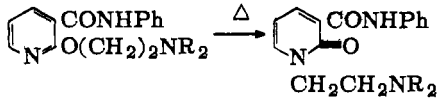
The reaction proceeds in good yields, in most cases over 70%, when the ether is heated with the amine hydrochloride at about 200° C. There is practically no reaction when the free bases are used. However, excellent yields are obtained from the methiodide of the pyridyl ether and the free amine. Evidently, the reaction is favored by a positive charge on the ring nitrogen which, in turn, is distributed

by resonance to C_2 and C_4 where the ether linkage is. Nucleophilic attack by the amine is promoted by electron deficiency. Neither 3-phenoxypyridine nor its methiodide reacts significantly, since C_3 is not sufficiently electron deficient. It is also noteworthy that 4-nitrodiphenyl ether does not react under the same conditions. Clearly, then, in this reaction, a 4-pyridinium group is more activating than a *p*-nitrophenyl group. The behavior of the phenoxy ethers is analogous to that of *N*-pyridyl-4-pyridinium chloride hydrochloride (*887*).

Alkoxy groups seem to stabilize diazonium salts. Thus, diazotized 4-amino-2-methoxypyridine underwent the Sandmeyer reaction to give the corresponding 4-substituted OH, I, Cl, Br, CN, and CNS derivatives (*889*).

3. O-N Rearrangements

The isomerization of ethers to *N*-alkyl derivatives would indicate that the latter are thermodynamically more stable. 1-Phenyl-2(1*H*)-pyridone was obtained when the isomeric ether was passed through a hot tube (*600*). This reaction can be used for preparative purposes (XII-343b) (*131*). The starting ethers were prepared from the chloro



(XII-343b)

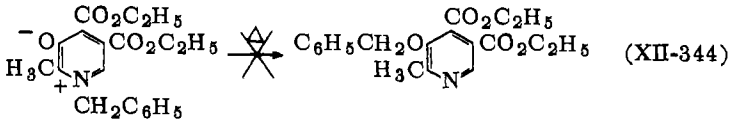
compounds. 2-Benzyloxypyridine was rearranged almost quantitatively to 1-benzyl-2(1*H*)-pyridone on heating for ten hours at 300° C. in a sealed tube *in vacuo* (*877*).

By means of a "crossover" experiment with a C^{13}-labeled starting material, the intermolecularity of the O-to-N rearrangement was unequivocally demonstrated. The reaction is catalyzed by benzoyl peroxide, which suggests a free radical chain reaction (*878*).

4-Pyridyl ethers likewise rearrange but the 3-ethers do not. 4-Methoxy-3-nitropyridine isomerizes at 180° C. (*506*). The vagaries of this reaction are apparent in the failure of the isomeric 6- (*506, 233*) and 2-methoxy-3-nitropyridines (*237*) to rearrange. It would be incorrect, however, to conclude that the rearrangement of the

C_4 ether is preferred to that of the C_2, since both 3-cyano (*222*) and 5-cyano-2,4-dimethoxypyridine (*223*), when heated at 130° C. for five hours with methyl iodide, rearrange to the 2- and not the 4-pyridone.

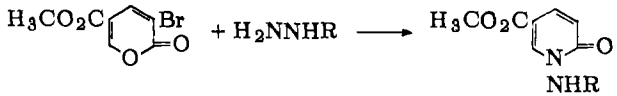
One reported attempt (*45*) to achieve intramolecular *O*-alkylation by thermal rearrangement of the *N*-alkyl isomer failed (XII-344).



(XII-344)

4. N-Amino Derivatives

One method for preparing these compounds is the reaction of hydrazine and its derivatives with pyrones. Bromocoumalic ester (XII-345) reacts in this manner with hydrazine and semicarbazide.



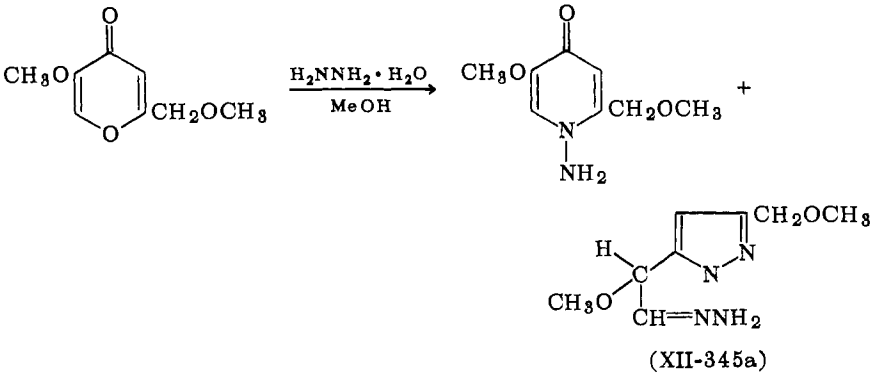
(XII-345)

R = H (*602*), $CONH_2$ (*603*)

5-Benzoyl-2-pyrone reacts with hydrazine and phenylhydrazine to give the corresponding *N*-amino and *N*-anilino derivatives. The *N*-amino compound had ultraviolet and infrared absorption bands characteristic of *N*-substituted 2-pyridones. The *N*-anilino derivative, however, showed significant variations in both types of spectra, which as yet have not been interpreted. This direct amination has been extended to 3-, 4-, 5-, and 6-methyl-2-pyridinols. The infrared spectra of these *N*-aminopyridones were reported, and several typical amino derivatives were prepared (*858*).

The dimethyl and monobenzyl ethers of kojic acid, as well as 2-methyl-5-benzyloxy-4-pyrone, have been converted into the *N*-aminopyridones (*838*) with hydrazine hydrate. Both ethers of kojic acid give as a minor by-product a pyrazole (XII-345a).

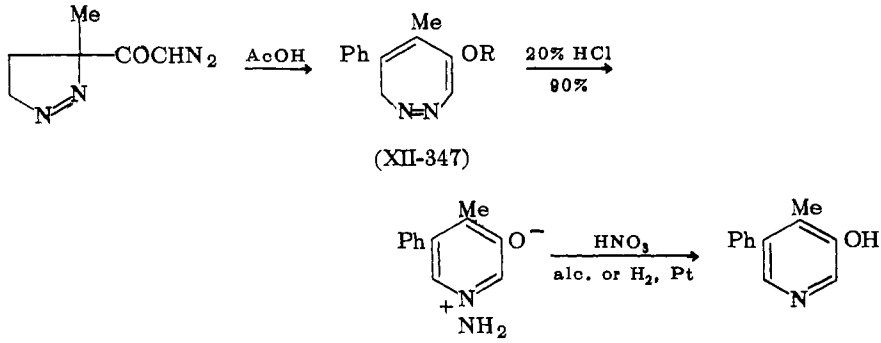
A chloramine solution reacts with the sodium salt of 2-pyridinol to give 1-amino-2(1*H*)-pyridone, which formed a salt with hydro-



(XII-345a)

chloric acid (*405*). Amines have also been prepared by ring closure methods using hydrazines.

The first synthesis of an *N*-amino-3-pyridinol betaine (XII-346) was by a series of reactions starting with 3-diazoacetyl-3-methyl-4-phenyl-Δ′-pyrazoline and proceeding via a diazepine (XII-347). The constitution of (XII-346) was established except for the position of the methyl and phenyl groups by quantitative deamination to XII-348, which was assigned a 3-pyridinol structure on the basis of



(XII-347)

(XII-346) (XII-348)

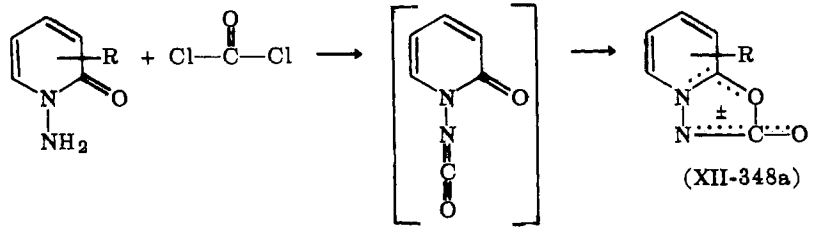
ferric chloride color, methylation and acetylation studies, ultraviolet spectrum, and dissociation constants. The ultraviolet spectrum of XII-346 was practically identical with that of 1-methyl-3-hydroxypyridinium chloride (*194*).

A mechanism for the rearrangement of the diazepine to the *N*-amino compound has been suggested (*839*).

The 4 and 5 positions of the methyl and phenyl groups were confirmed (*840*) by showing that the deaminated product of XII-346 is identical to 4-methyl-5-phenyl-3-pyridinol, obtained by an unequivocal independent synthesis.

Nitrous acid deaminates the *N*-amino compound, giving the parent pyridinol (*407,838,840*). The deamination of XII-346 has also been accomplished by catalytic hydrogenation (*839*). The amino group can be acylated, and reacts with benzaldehydes to give an azomethine-like compound (*838*). The ultraviolet spectra of several 1-amino compounds have been reported (*838*).

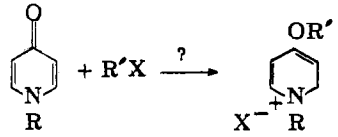
Treatment of 1-amino-2(1*H*)-pyridones with phosgene affords compounds with a new mesoionic ring system (XII-348a). The ring



is opened to give a urethane or a urea when treated with alcohols or amines (*859*).

5. Conversion of 1-Alkylpyridones to Pyridinium Compounds

A few such conversions were observed during reactions of pyridones with phosphorus halides (see p. 646). *Cf.* Chapter III, p. 20. Reaction with alkyl halide might be expected to transform pyridones to alkoxypyridinium salts. When this reaction was attempted (XII-349; R = C_6H_5), a product was obtained which regenerated the origi-



(XII-349)

nal pyridone with alkali (*130*). The structure of this methiodide is in doubt. Reaction of XII-349 (R = $CH_2CH_2NR''_2$) with alkyl

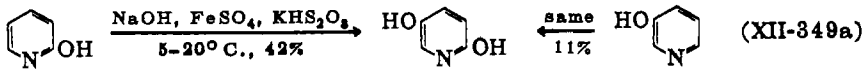
halides led to quaternization of the side chain nitrogen, but no pyridinium salts formed (*209*). It would seem therefore that the pyridone oxygen resists alkylation.

E. POLYHYDROXYPYRIDINES

1. Preparation

Polyhydroxypyridines are prepared for the most part by extensions of the methods already discussed (see pp. 510 ff.). The preparation of the six isomeric diols and their ethyl ethers has been reviewed by den Hertog, Wibaut, and co-workers (*458*). See Tables XII-50 and XII-51 (pp. 840 ff.).

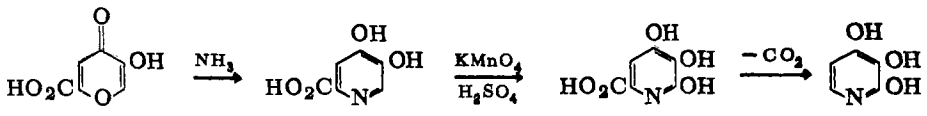
The Elbs peroxydisulfate hydroxylation reaction has been applied to both 2- and 3-pyridinols (*825*). In both cases the major product is 2,5-pyridinediol, which arises from hydroxylation in the para position (XII-349a). Small amounts of the ortho-hydroxylated



(XII-349a)

products are also isolated. This facile one-step synthesis of 2,5-pyridinediol, reported in 1958, displaces the lengthy older synthesis (*458,617*).

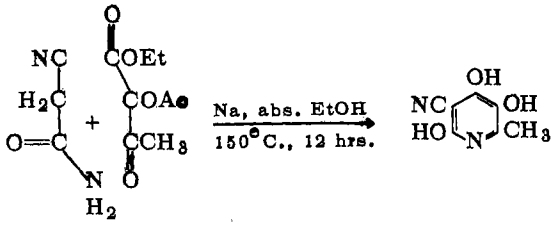
Only two of the six possible pyridinetriols are known. 2,3,4-Pyridinetriol was prepared by Ost (*170*) from pyromeconic acid and comenic acid (XII-350). This method is based on a unique oxida-



(XII-350)

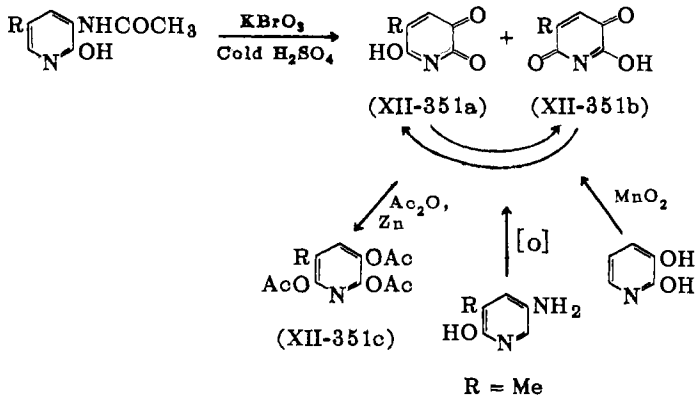
tive hydroxylation of a diol. The other known isomer, the 2,4,6-, has been prepared from various starting materials, including 4-amino-2,6-pyridinediol (*597*) and 6-chloro-2,4-dihydroxynicotinonitrile, which is obtained from cyanoacetyl chloride (*160*). Recently some methyl substituted 2,3,6-pyridinetriols were prepared by diazo

coupling with a 2,6-diol, reduction of the azo compound, and hydrolysis of the resulting amino group (*578*). Ring closure of cyanoacetamide and ethyl acetylacetoxyacetate with sodium ethoxide yields 2,4,5-trihydroxy-6-methylnicotinonitrile (XII-351) (*492*). See Table XII-52 (p. 855).



(XII-351)

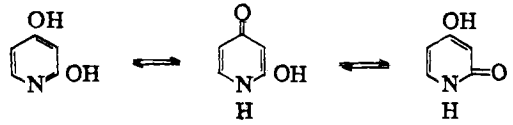
In 1881, the permanganate oxidation of 4,5-dihydroxypicolinic acid to 4,5,6-trihydroxypicolinic acid was reported (*880*). A recent study of the controlled oxidation of diols and of hydroxyacetamido derivatives has led to the preparation of hydroxyazaquinones (XII-351a,b) (*881*). The structure of the reaction product, an equilibrium mixture of an *ortho* and *para*-azaquinone, was proven by reductive acetylation to XII-351c with zinc and acetic anhydride. When R = CH_3, the isolated product was an azaquinhydrone.



2. Properties

The ultraviolet spectra of all the diols and their ethers in water and acid have been reported (*458*). The spectrum of the 2,4-diol

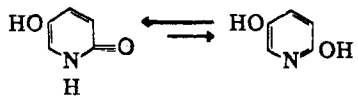
was compared with those of 1-methyl-4-methoxy-2(1*H*)-pyridone and 1-methyl-2-methoxy-4(1*H*)-pyridone to determine its predominant tautomeric structures (XII-352a–c). It appears that the principal



(XII-352a) (XII-352b) (XII-352c)

form in aqueous ethanol is XII-352c (*601*). The ultraviolet spectra in neutral and alkaline media were used to differentiate several hydroxypyridones. 3-Hydroxy-2- and -4-pyridones show pronounced bathochromic shifts of the principal maximum in alkaline medium while 4-hydroxy-2-pyridones and 2-hydroxy-4-pyridones exhibit hypsochromic shifts (*604*). This technique was useful in determining the structure of the diphenylketene-pyridine adduct (*605*).

The pK_a of 2,5-pyridinediol was shown to be 8.51 (*826*). Comparison with the pK_a's of 2-pyridinol (11.62) and of 3-pyridinol (8.72) shows that the pK_a of the 2,5-diol represents the ionization of the 5- rather than the 2-hydroxy group. It was previously shown (*398*) that 2-pyridinol exists mainly in the α-pyridone form, and the 2,5-pyridinediol (XII-352d) is expected to do the same. Since the pK_a's



(XII-352d)

of the 2,5-pyridinediol and 3-pyridinol are approximately the same, the conclusion is drawn that the α-pyridone grouping, NH—C=O, in XII-352d has an electronic effect of about the same magnitude as the N=C group; both are strongly electron attracting.

Color reactions with ferric chloride and Folin-Denis reagent are given by all six diols, except for the negative test given by the 2,4-isomer (*458*).

In an attempt to determine the major tautomeric form, a series of reactions was carried out with five different alkyl substituted 2,4-diols. Phenylhydrazine and hydroxylamine failed to react.

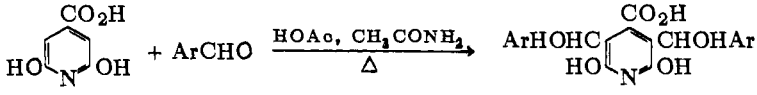
Acetic anhydride gave no diacetates, although benzoyl chloride in sodium hydroxide gave dibenzoates with two of the compounds. Diazomethane gave no diethers, while methyl iodide in sodium hydroxide gave only *N*-methylation. Attempts to locate the acetoxy group in the monoacetates were unsuccessful; they did not react with hydroxylamine or diazomethane, while phosphorus oxychloride in a sealed tube produced the dichloropyridine (*225*).

Unlike monohydroxypyridines, diols can be nitrosated; the 2,6-isomer gives a 3-nitroso derivative (*98*). They also give a positive Tollens test (*15,157*) as does the 2,3,4-triol. Like resorcinol, 2,6-pyridinediol gives a phthalein when heated with phthalic anhydride (*114*).

The 2,3,4-triol is comparable to its benzene analog, pyrogallol, in the ability of its basic solution to absorb oxygen rapidly from the air and the relative stability of its acid solution. The 2,4,6-triol is readily converted to the 4-amino-2,6-diol when heated with ammonia solution for a short time.

The 2,6-diols couple in the 3 position (*870*).

Wiley and Kraus (*583*) made a careful study of the reaction of a 2,6-diol (citrazinic acid) with aromatic aldehydes. The product that precipitates is the 3,5-disubstituted hydroxybenzyl derivative (XII-353). The monosubstituted product is soluble and reacts further even though equimolar quantities are used.



(XII-353)

The low temperature bromination in pyridine of 2,4-pyridinediol and its mono- and diethyl ethers has been studied (*868*). Except in the diethyl ether, the bromine atom occupies the 3 position; the diethyl ether brominates at the 5 position. The authors of this paper attribute the difference in behavior to the fact that whenever an OH group is present, the substrate exists mainly in the pyridone form. They then argue that the carbon atom between C=O and C—OR(H) is the most reactive one, and hence it is attacked. However, no reason is offered for this latter assumption. In the case of 2,4-di-

ethoxypyridine, there is no pyridone form and electrophilic substitution occurs at C_5 since it is less sterically hindered than C_3.

3. Leucenol (Leucaenine)

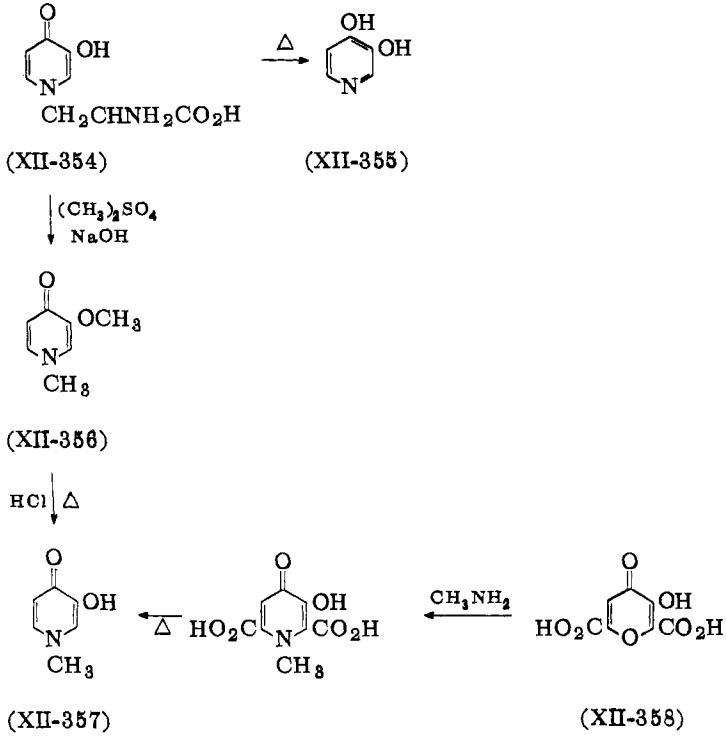
Elucidation of the structure (XII-354) of this alkaloid is mainly due to the efforts of the Dutch chemists, Wibaut, Bickel, and Kleipool, the American group of Roger Adams and his students, and the French chemist, Mascré. The alkaloid, $C_8H_{10}O_4N_2$ (*609*), is isolated from the seeds of *Leucaena glauca* Benth, a tropical plant, by extraction with 90% ethanol or methanol (*610,611*). There was much confusion about the melting point and optical rotation. As originally isolated, it was reported to be optically inactive (*610, 611*) with observed melting points of 291° C. (Maquenne block) and 240–245° C. (evacuated tube). Other methods of isolation gave samples with rotations of –9° (*609*) or –21° and m.p. 228–229° C. (*612*).

It was apparent that both the optically active and inactive modifications had the same structure and that varying amounts of racemization probably occurred during isolation, accounting as well for variations in melting point (*613*). The accepted value for the anhydrous racemic modification is 235–236° (dec.) while its hemihydrate decomposes at 227–228° C. The naturally occurring leucenol is obtained as white needles of m.p. 228–229° (dec.) and rotation –21° (water) and +10° (1% hydrochloric acid) (*615*). The observed melting point, however, varies with the apparatus used and the rapidity of heating (*614*). Leucenol is soluble in water, methanol, and ethanol, and is insoluble in other organic solvents. The ultraviolet (*137,611*) and infrared absorbtion spectra (*614,615*) have been determined. Crystalline salts with strong acids are known; hydrochloride (m.p. 174.5–175° C., dec.), hydrobromide (179.5°, dec.), hydroiodide (183–183.5°, dec.) and sulfate (143–143.5°, dec.) (*616*).

The presence of a phenolic hydroxyl group is demonstrated by positive ferric chloride and Folin reagent tests. The ninhydrin test shows the presence of an α-amino acid, while a van Slyke determination shows that the α-amino group accounts for half of the total nitrogen (*609,611*). Isolation of pyridine on zinc dust distillation (*609*) and the ultraviolet absorption spectrum indicated that leucenol was a pyridinol. The techniques that further clarified the structure

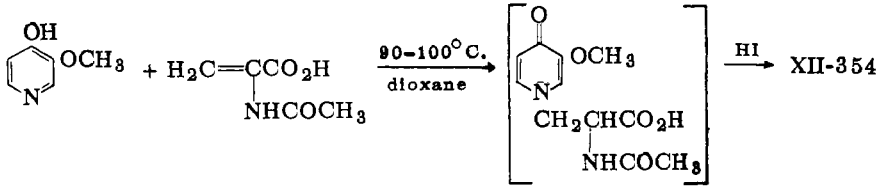
were pyrolysis (*611*) and degradative methylation (*609*). When XII-354 was pyrolyzed at a relatively low temperature, a product, $C_5H_5O_2N$ (XII-355), was obtained which seemed to be a pyridinediol. The relatively facile loss of the amino acid side chain indicated that it was not attached to carbon. The stability of XII-354 to hydriodic acid showed that the side chain was bound to nitrogen and not to oxygen. The pyrolysis product was originally considered to be 2,5-pyridinediol (*611*). Later, the 2,5-diol was synthesized (*617*) and proved different from the degradation product.

Contemporaneous with these pyrolytic studies was the degradative methylation of Bickel and Wibaut (*609*). Reaction with dimethyl sulfate in an alkaline medium produced a compound, $C_7H_{11}O_3N$ (XII-356), which gave a negative ferric chloride test. Permanganate oxidation gave methylamine, showing that XII-356 was an *N*-methyl compound. The hydrochloride of XII-356 lost methyl chloride when heated to give a compound, $C_6H_7O_2N$ (XII-357), which gave a positive ferric chloride test.



By independent synthesis from meconic acid (XII-358), XII-357 was shown to be 3-hydroxy-1-methyl-4(1*H*)-pyridone (*135*). XII-356 was identical with synthetic 3-methoxy-1-methyl-4(1*H*)-pyridone monohydrate prepared by heating an aqueous solution of 3-methoxy-4-pyrone with methylamine (*618*). On this basis, the diol (XII-355) must be the 3,4-derivative. Hence leucenol must have structure (XII-354).

The total synthesis of leucenol was effected by reacting 3-methoxy-4-pyridinol and α-acetamidoacrylic acid. The *N*-alkylated ether (XII-359) was hydrolyzed directly to (XII-354) with hydriodic acid

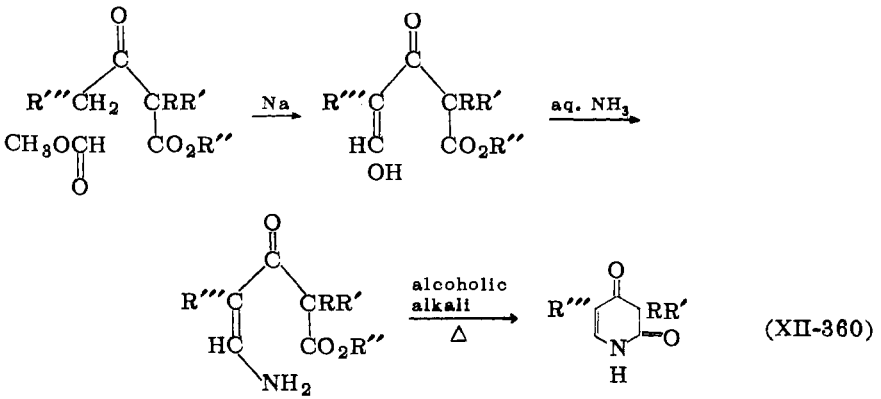


(XII-359)

(*615*). Mimosine isolated from *Mimosa pudica* Benth (*619*) was shown to be levorotatory leucenol (*137,611*).

4. Dioxo-3,3-dialkyltetrahydropyridines

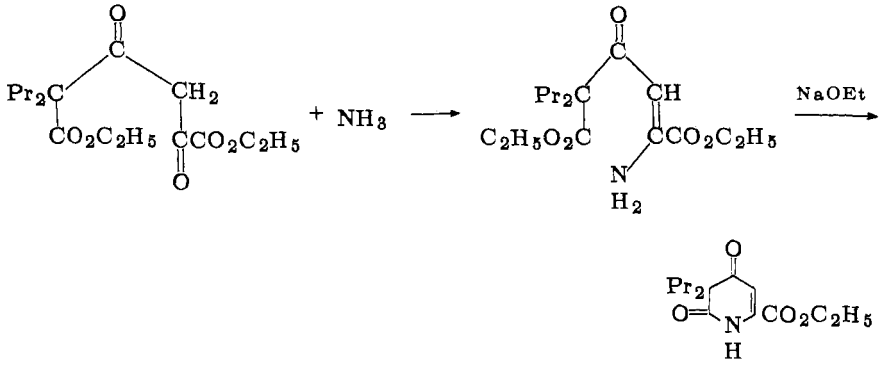
Schnider's report in 1936 (*32*) that 3,3-dialkyl-2,4-dioxotetrahydropyridines, which are barbiturate analogs, have soporific action, stimulated considerable interest in these compounds. They have been prepared from diketopyrones and pyridinediols and by ring-closure reactions. One cyclization method (XII-360) starts with



(XII-360)

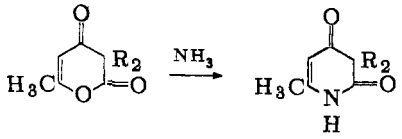
dialkylacylacetic esters (*32,33,624*). This procedure is restricted to lower molecular weight alkyl groups; unsaturated groups, as in diallylacetoacetic ester, prevent the condensation with methyl formate. This reaction was utilized to prepare 2,4-dioxo-3,3-diethyltetrahydropyridine tagged in the 6 position with C^{14} derived from labelled methyl formate. The isotopic compound was used to determine the absorption, tissue localization, and excretion patterns (*625*).

Another method starts with diethyl 2,2-dialkyl-3,5-dioxohexanedioate (*620*). The ring-closed carbethoxy compound (XII-361) can



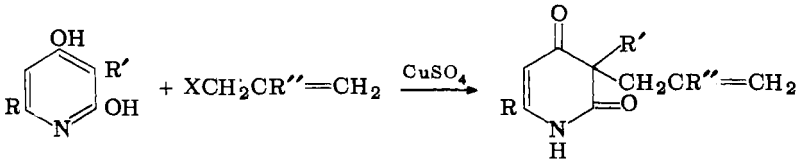
(XII-361)

be hydrolyzed to the free acid and then decarboxylated (*621*). Keto-δ-lactones (XII-362) are ammoniated to give the desired product



(XII-362)

(*622*). 2,4-Pyridinediol, its 6-methyl homolog, and their 3-monoalkyl derivatives are alkylated at C_3 by heating with allylic halides in aqueous alkali in the presence of copper or cupric salts (XII-363). This reaction emphasizes the tautomeric equilibrium which exists between 2,4-diols and the 2,4-diketo structures. The compound XII-363 (R = CH_3, R′ = allyl, R″ = H) is strongly soporific (*32,623*).



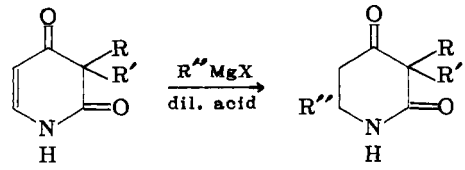
(XII-363)

R′ = H or alkyl

Halogenation by the usual methods (chlorine, bromine, or iodine monochloride in acetic acid) at low temperatures occurs at C_5 (*626*).

Reduction to the corresponding diketopiperidine has been effected catalytically with palladium black or Raney nickel in methanol. Allyl or other unsaturated groups at C_3 are also hydrogenated in the process (*627*). However, side-chain hydrogenation occurs without any nuclear reaction if a C_6 methyl is also present (*628*). A nearly quantitative electrolytic reduction of the 3,3-diethyl isomer was recently reported (*629*).

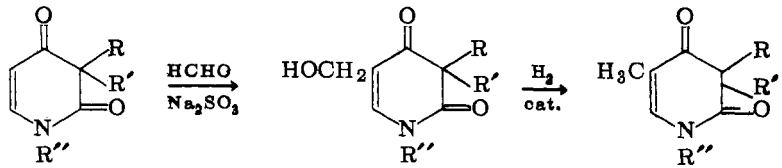
Grignard reagents add 1,4 to give the corresponding 6-substituted piperidine derivative (XII-364). The reaction is not sterically



(XII-364)

R″ = alkyl, aryl, or aralkyl

affected by a methyl substituent at C_5 or on the nitrogen (*630*). Hydroxymethylation occurs at C_5 on treatment with formalin and catalytic amounts of sodium sulfite. The methylol compound (XII-365) can be catalytically reduced to the C_5-methyl compound (*624*).



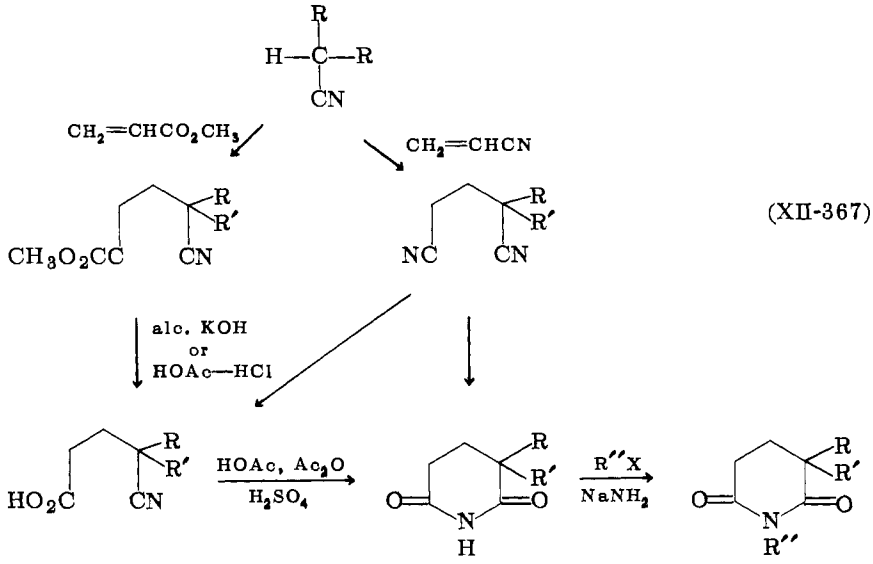
(XII-365)

R and R′ = alkyl, R″ = H or alkyl

These compounds exhibit an intense blue fluorescence in a strongly alkaline solution under ultraviolet light (*631*), which is related to the shift of keto-enol equilibrium toward the enol form in alkaline solution. This fluorescence can be quenched quantitatively and selectively by hydroxylamine in the presence of normal fluorescent constituents of urine. This property is utilized for rapid determination of Persedon (3,3-diethyl-2,4(1*H*,3*H*)-pyridinedione) and other 3,3-dialkyl derivatives (*632*). Persedon forms sharp-melting stable products with equimolar amounts of pyrazolone derivatives (*633*).

The pharmacology of 3,3-diethyl-2,4-diketotetrahydropyridine and the corresponding diketopiperidine has been discussed (*642*).

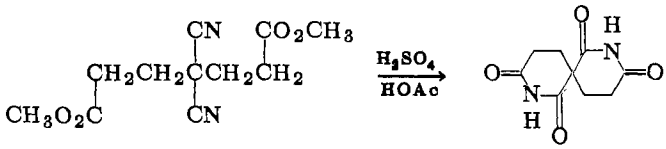
The 2,6-diketopiperidines (glutarimides) (XII-366) have useful physiological activity, anti-convulsant, mildly soporific, and parasympathicolytic. One of the most important is α-ethyl-α-phenylglutarimide (XII-366; R = C_2H_5, R′ = C_6H_5), whose trade name is Doriden. These compounds are conveniently prepared by cyclization of either the mononitrile or dinitrile of the properly substituted glutaric acid (XII-367).



(XII-367)

(XII-366)

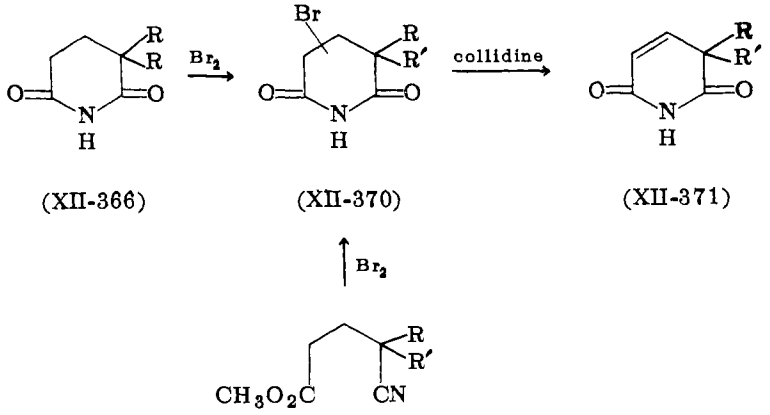
A wide variety of derivatives of type XII-366 have been prepared where either R or R′ are alkyl, aryl, heteroaryl, and dialkylaminoalkyl (*634,635*). 3-Diethylaminoethyl-3-phenyl-2,6-dioxopiperidine has an especially strong and specific parasympathicolytic action. The nuclear nitrogen is alkylated with the appropriate alkyl halide in the presence of sodamide in toluene at elevated temperatures (*635*). A novel adaptation of this reaction scheme leads to the formation of a diazaspiroundecane (XII-369) by ring closure of diethyl 4,4-dicyanopimelate (XII-368). Reaction of XII-369 with



(XII-368) (XII-369)

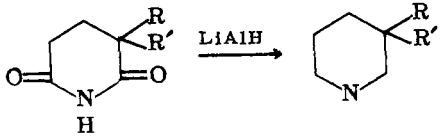
dialkylaminoalkyl halides in the presence of sodium ethoxide results in the alkylation of the two nitrogen atoms (*636*).

2,6-Dioxotetrahydropyridines (XII-371) can be prepared from the diketopiperidines by bromination and dehydrobromination. Without definite proof, the bromine is considered to be at C_5. When R = R′ = C_6H_5 the intermediate bromo product (XII-370) is prepared directly by brominating the open-chain cyanoester (*637*).



(XII-366) (XII-370) (XII-371)

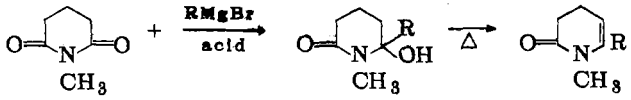
Both keto groups (XII-366) can be reduced with lithium aluminum hydride to give the corresponding piperidine (XII-372) (*634*).



(XII-366) (XII-372)

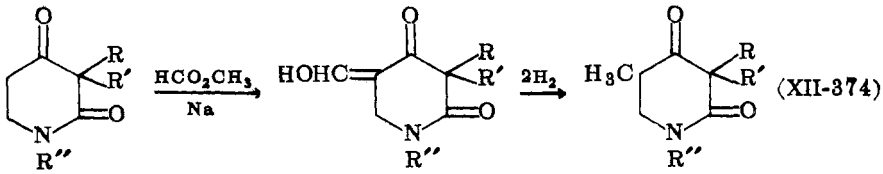
R = phenyl; R′ = $CH_2CH_2N(C_2H_5)_2$

N-substituted glutarimides react with Grignard reagents to give 6-alkyl-6-hydroxy-2-piperidones (XII-373), which dehydrate to dihydropyridones (*640*).



(XII-373)

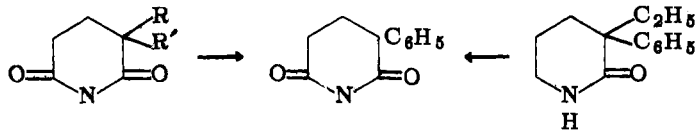
2,4-Diketo-3,3-dialkylpiperidines are methylated at C_5 by reduction of the 5-oxymethylene compound (XII-374) (*624*).



(XII-374)

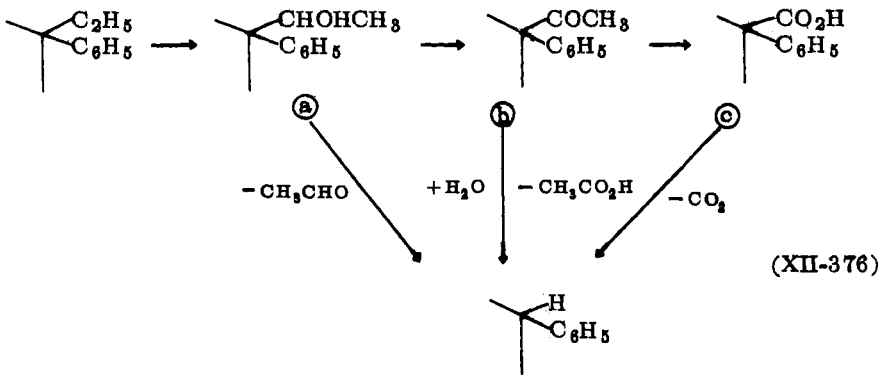
R,R′ = alkyl; R″ = H or alkyl

The metabolism of these diketopiperidines has been studied because of their therapeutic interest. Doriden (XII-366; R = C_2H_5, R′ = C_6H_5), an important soporific, was fed to dogs. A de-ethylated product, α-phenylglutarimide (XII-375) was isolated from the urine. The same product was obtained when 3-phenyl-3-ethyl-2-piperidone was fed (*639,641*). Elimination of the ethyl group is postulated to



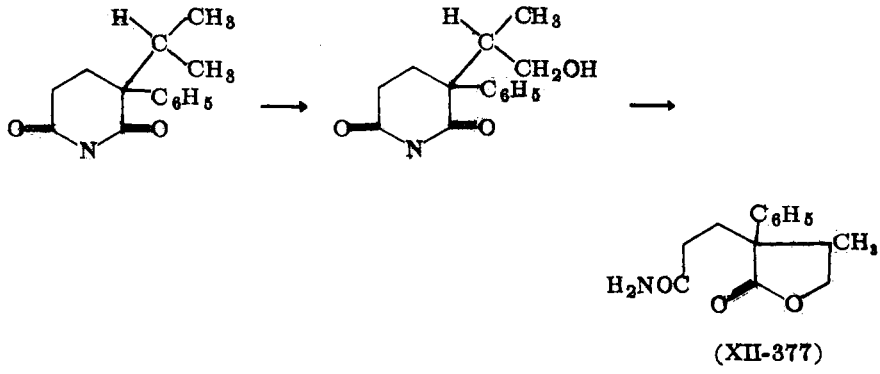
(XII-366) (XII-375)

proceed by several possible oxidative degradation routes (XII-376). To clarify the mechanism the methyl analog of Doriden (XII-366;



(XII-376)

R = CH_3, R′ = C_6H_5) was fed to dogs. Instead of dealkylation, dehydrogenation occurred to give (XII-371; R = CH_3, R′ = C_6H_5). The *i*-propyl analog was converted by biological hydroxylation of one of the methyl groups and intramolecular cyclization with simultaneous glutarimide ring fission to 3-phenyl-3-(β-carbamidoethyl)-4-methyltetrahydrofuranone-2 (XII-377) (*639*). The structure XII-377 is



(XII-377)

based on ultraviolet and infrared spectral data and biogenetical reasoning.

The metabolism of Doriden labeled with C^{14}, either in the ring or the side chain, has been investigated in the rat. Active carbon dioxide was detected after about five hours. Most of the activity (about 80%) was found in the urine, although some of this resulted from reabsorbtion of bile excreted material. Tissue localization after 15 hours was slight. Therefore the metabolism is fairly complete within a short time. The results seem to indicate that in the rat the ethyl side chain may not be lost (*638*).

For physical constants, see Tables XII-53 to XII-57 (pp. 856 ff.).

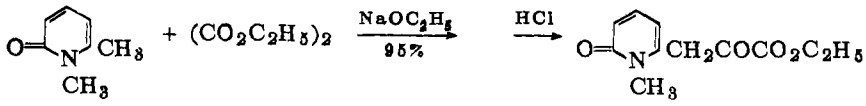
F. SUBSTITUTED PYRIDINOLS AND PYRIDONES

1. Alkyl and Aryl Derivatives

The most important methods for synthesizing these compounds are ring closures and transformation of pyrones. Where the corresponding amines, halides or sulfonic acids are available, these functional groups can be replaced by hydroxyl.

The pyridinols are stable toward oxidation, and their homologs can be conveniently oxidized in good yields to pyridinol carboxylic acids. Thus 2,6-dimethyl-4-pyridinol and its 3,5-diiodo derivative are oxidized with permanganate to the corresponding dicarboxylic acids (*259*).

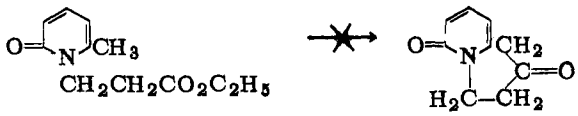
The reactivity of a C_6 and C_4 methyl substituent of 1-methyl-4(1*H*)-pyridone has been studied by Adams and Schrecker (*274*). 1,6-Dimethyl-2(1*H*)-pyridone undergoes condensation with ethyl oxalate in the presence of potassium or sodium ethoxide to form the salt of the pyruvic ester, from which the free ester (XII-378) was



(XII-378)

obtained by acidification. The same reaction proceeded at a somewhat slower rate and in lower yield (84%) with 1,4-dimethyl-2(1*H*)-pyridone.

The condensation of 1,6-dimethyl-2(1*H*)-pyridone with *m*-nitrobenzaldehyde gave only a 1% yield of the expected 6-(*m*-nitrostyryl) derivative. This result is in sharp contrast to the excellent yields obtained with 2-picoline. Unsuccessful attempts were made to effect intramolecular cyclization of ethyl 6-methyl-2-oxo-1(2*H*)-β-pyridinepropionate (XII-379). Apparently an α-methyl group is less reactive when the nucleus is oxygenated.



(XII-379)

2. Nitro Derivatives and Intermediate Reduction Products

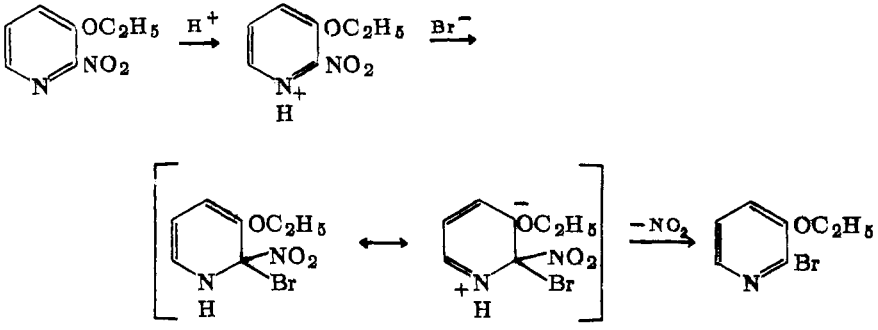
The nitropyridinols are usually prepared by direct nitration or from nitroaminopyridinols by diazotization or hydrolysis. There is one instance of a synthesis by cyclization: condensation of sodium nitromalonaldehyde with cyanoacetamide (*63*). The azo compounds are prepared by coupling with aromatic diazonium salts. The preparation of an azoxy compound is reported; 5-nitro-2-propoxypyridine gives a 37% yield of the 5-azoxy compound as sole product on catalytic reduction over palladium–calcium carbonate at room temperature. At 70° C. the amine forms in 70% yield (*229*).

As expected, *o*-and *p*-nitro groups enhance the acidity of the hydroxyl group. Thus 3,5-dinitro-2-pyridinol dissolves in sodium carbonate with evolution of carbon dioxide (*557*). The polynitropyridinols give red solutions in sodium hydroxide. Unexpected results were obtained in the reduction of 2,6-dinitro-3-methoxypyridine (*554*). Catalytic hydrogenation proceeded smoothly in glacial acetic acid and acetic anhydride to give a 60% yield of the corresponding diacetylamido derivative. However, in alcohol or alcoholic hydrogen chloride only highly colored compounds which could not be purified were obtained.

Although azo compounds are usually prepared by coupling reactions, they can also be formed as by-products in the reduction of nitro groups, especially in a basic medium. Reduction of 2-bromo-3-

ethoxy-6-nitropyridine in alkaline alcohol with a moderately active catalyst affords some 2,2′-azo-5,5′-diethoxypyridine (*264*).

A novel reaction of α-nitro-β-alkoxypyridines is the replacement of the nitro group by halogen. Koenigs, Gerdes, and Sirot (*207*) first reported the quantitative conversion of 2,6-dinitro-3,5-diethoxypyridine to 2,6-dibromo-3,5-diethoxypyridine by heating for three hours at 100° C. with a solution of hydrogen bromide in glacial acetic acid. 2-Nitro-3-ethoxypyridine, erroneously reported as the 6-nitro compound, was similarly converted in somewhat poorer yield (66%) at a slightly higher temperature (130° C.). This reaction has been more recently studied by den Hertog and his co-workers. Repetition of the reaction of 2,6-dinitro-3,5-diethoxypyridine gave replacement of only one nitro group, not both (*565*). The yield of 2-bromo-3-ethoxypyridine from the 2-nitro compound was increased to 85% (*264*). Using a 40% solution of hydrobromic acid in glacial acetic acid, 2-bromo-3-ethoxy-6-nitropyridine is converted to the 2,6-dibromo-3-ethoxypyridine (*496*). An unusual feature of this reaction is the absence of any cleavage of the ether group. A plausible reaction path would be protonation of the ring nitrogen followed by nucleophilic displacement of the nitro group by bromide ion. This mechanism assigns no useful role to the ethoxy group other than a stabilizing inductive effect in the intermediate (XII-380). It would

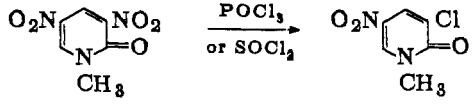


(XII-380)

be interesting to determine if the reaction proceeds in the absence of the ethoxy group. The absence of any acetoxy compound may be

due to the much smaller concentration of acetate ions as compared to bromide ions under the conditions of the reaction.

Replacement of a β-nitro group by chlorine has also been reported (*279*). Treatment of 1-methyl-3,5-dinitro-2(1*H*)-pyridone with phosphorus oxychloride-pentachloride or thionyl chloride gave a product $C_6H_5O_3N_2Cl$ (XII-381). By synthesis it was shown to be



(XII-381)

1-methyl-3-chloro-5-nitro-2(1*H*)-pyridone; the 5-chloro-3-nitro-isomer is different.

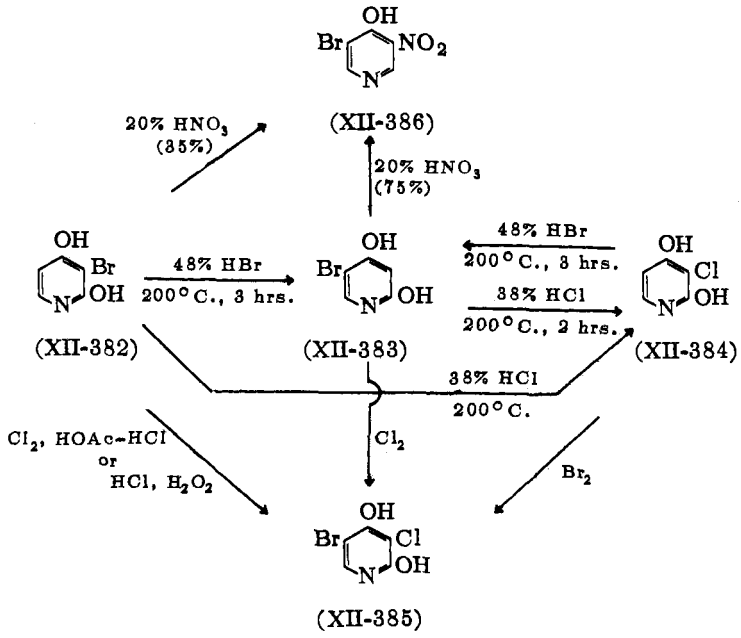
Nitro- and halopyridinols are covered in Tables XII-23 (p. 724), XII-32 (p. 769), and XII-37 (p. 790).

3. Halo Derivatives

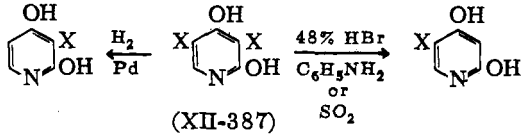
These compounds are chiefly prepared by halogenation of pyridinols, diazotization or hydrolysis of haloaminopyridines, and partial hydrolysis of polyhalopyridines.

An unusual series of rearrangement reactions is shown by the halogen derivatives of 2,4-pyridinediol (*643*). When 3-bromo-2,4-pyridinediol (XII-382) was heated with concentrated hydrobromic acid in a sealed tube, a 62% yield of 5-bromo-2,4-pyridinediol (XII-383) was obtained along with 10% of the starting material. Under similar conditions, XII-383 and concentrated hydrochloric acid give the 3-chloro-diol (XII-384) whose structure was established by conversion to 2,3,4-trichloropyridine with phosphorus oxychloride (*492*). Heating XII-384 with concentrated hydrobromic acid reforms XII-383 and heating XII-382 with concentrated hydrochloric acid forms XII-384. However, when XII-383 is heated with 48% hydrobromic acid it is slowly reduced to 2,4-pyridinediol. Both the 3- and 5-chloro-diols are unaffected by hydrochloric acid; the latter is also stable to hydrobromic acid. It would appear, therefore, that bromine migrates more easily than chlorine.

The first step in the migration is assumed to be the formation of 2,4-pyridinediol and halogen, followed by rehalogenation. To sub-



stantiate this hypothesis, the reactivity of 3,5-dihalo-2,4-pyridinediol (XII-387; X = Br or Cl) towards the reductive action of hydrobromic



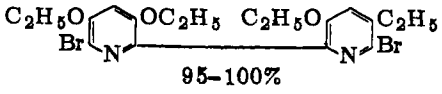
acid was studied (*646*). To prevent the reduced product from being rehalogenated, sulfur dioxide or aniline is added to remove the halogen as it forms. When XII-387 (X = Br or Cl) is so treated, only the halogen group at C_3 is removed. Surprisingly, however, catalytic reduction removes the C_5-halogen group (*646*). This mechanism cannot satisfactorily account for the conversion of XII-383 to XII-384 in hydrochloric acid. It would have to be demonstrated that chlorine can be formed when small amounts of bromine are heated in concentrated hydrochloric acid under the conditions of the migration. When XII-382 is chlorinated with hydrogen peroxide in con-

centrated hydrochloric acid (*644*) or chlorine in a mixture of hydrochloric and acetic acids (*645*), 5-bromo-3-chloro-2,4-pyridinediol (XII-385) is formed. This compound is also formed by brominating XII-384 or chlorinating XII-383. The structure of XII-385 was further established by partial reduction to XII-384 (*644*). It is noteworthy that the migration during chlorination proceeds at room temperature, conditions much milder than those needed for obtaining XII-383 from XII-382. From the fact that during the formation of XII-385 from XII-382 no dibromo- or dichloro- derivatives were formed, it is argued that the migration of the bromine atom is completely intramolecular.

Nitration of both XII-382 and XII-383 under relatively mild conditions gave the same product, 5-bromo-3-nitro-2,4-pyridinediol (XII-386). Its structure was established by conversion to the known 5-bromo-2,3,4-trichloropyridine via 5-bromo-2,4-dichloro-3-nitropyridine. As yet there is insufficient evidence to show whether the bromine migrates intramolecularly or if 3-nitro-2,4-pyridinediol, formed when a nitro group replaces the bromo group, is an intermediate (*645*).

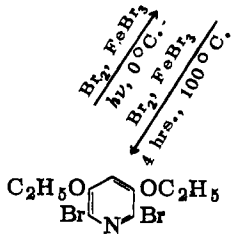
Some unique reactions of 2,6-dibromo-3,5-diethoxypyridine (XII-388) are reported by den Hertog and Mulder (*425*). Attempted bromination with bromine in glacial acetic acid failed. In the presence of ferric bromide, bipyridyl formation occurred at C_2 by bromine elimination. This reaction can be reversed at higher temperatures. The structure of XII-389 was established through conversion to 2,2′-bipyridyl by catalytic reduction of the bromine, acid cleavage of the ether linkages, and zinc dust reduction of the resulting hydroxyl groups. The bipyridyl (XII-389) is cleaved with a mixture of sulfuric and fuming nitric acids to yield, among other substances, 2-bromo-3,5-diethoxy-6-nitropyridine (XII-390). Treatment of XII-390 with bromine and ferric bromide re-formed XII-389. Since XII-388 is obtained when XII-390 is mixed with bromine without ferric bromide, XII-388 is assumed to be an intermediate in the formation of XII-389.

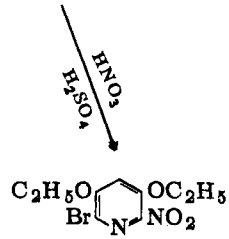
Several iodopyridinols and iodopyridones are used as X-ray contrast agents. The best-known ones are the sodium salt of 5-iodo-2-pyridinol (Selectan), 1-methyl-5-iodo-2(1*H*)-pyridone (Selectan-



95–100%

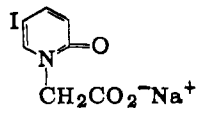
(XII-389)





(XII-388) (XII-390)

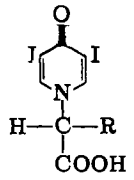
neutral), and the sodium salt of 5-iodo-2-oxo-1(2*H*)-pyridineacetic acid (Uroselectan, XII-391). An extensive review of their prepa-



(XII-391)

ration, physiological action, and pharmacology, is given by Maier-Bode and Altpeter (*648*). It is noteworthy that introduction of the *N*-acetic acid group in Uroselectan causes a marked drop in toxicity (*649*). Urinary excretion of Uroselectan was studied by radiological and chemical methods (*650*). Selectan has also been used in the preparation of vaccines for several cocci (*651*).

More recently several 3,5-diiodo-4(1*H*)-pyridones (XII-392) were prepared and tested as cholecystographic compounds (*444*) in the



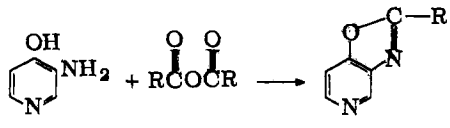
(XII-392)

form of their diethanolamine salts. The toxicity was found to increase with the length of R so that only those compounds containing seven or less carbons in the acid moiety were useful. These compounds were not absorbed when administered orally. The bromine atoms in 1-alkyl-3,5-dibromo-4(1*H*)-pyridones are reported to be inert toward alkali, and resist the formation of Grignard reagents even under forcing conditions (*844*).

4. Amino Derivatives

The chief methods of preparing these compounds and their ethers are (*a*) reduction of nitropyridinols; (*b*) reaction of haloaminopyridinols with alkoxides; (*c*) reaction of halopyridinols and their ethers with ammonia; and (*d*) ring closures (*155,477*). The few ring closures attempted lead to 4-amino or 6-amino-2-pyridones. 3-Amino derivatives have been prepared by the base-catalyzed condensation of cyanoacetamides and substituted acylamino β-diketones (*652*). The preparation of several aminoethoxypyridines was reported (*653*). Their monoacetyl derivatives showed marked antipyretic activity and 3-acetylamino-2-ethoxypyridine appeared to be even more potent than phenacetin. 4-Amino-2-pyridinol was prepared from 2-hydroxyisonicotinoyl azide (*253*) by warming in 50% acetic acid.

The preparation of oxazolopyridines by heating *o*-aminopyridinols with acids and acid derivatives, *viz.*, amides, nitriles, esters, and chlorides, proceeds less readily than in the benzene series, as demonstrated (*654*) with 3-amino-4-pyridinol (XII-393). When it was refluxed with a variety of aliphatic and aromatic anhydrides, it gave moderately good yields of the desired oxazolopyridines (XII-394)

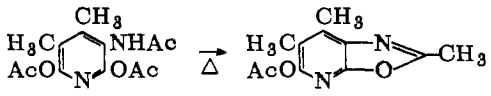


(XII-393) (XII-394)

R = alkyl, aryl

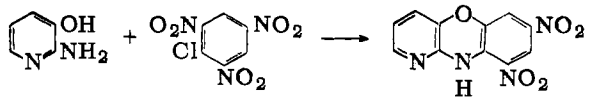
(*654*). The parent compound XII-394 (R = H) could not be synthesized from the diformyl derivative of XII-393. Distillation of the triacetyl derivative of 3,4-dimethyl-5-amino-2,6-pyridinediol (XII-

395) gave an oxazolopyridine characterized by its ultraviolet and infrared spectra (*578*).



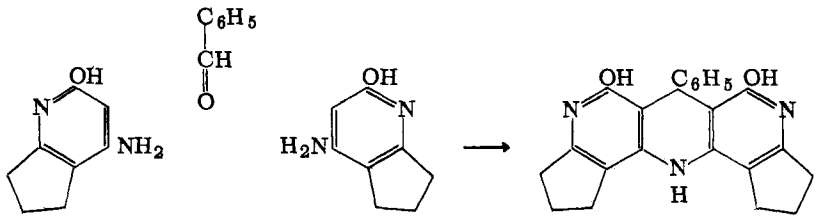
(XII-395)

Another cyclization involving an *o*-aminopyridinol was the condensation of 2-amino-3-pyridinol and picryl chloride to form a pyridobenzoxazine (XII-396) (*553*). A few cyclizations of *m*-aminopyri-



(XII-396)

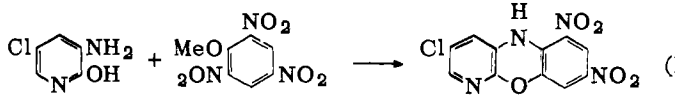
dinols and their ethers have been reported. In each case the hydroxyl or alkoxyl group serves to activate the ring towards attack by an electrophilic carbon. 4-Amino-2-hydroxy-6,7-dihydropyrindine (XII-397) reacts with benzaldehyde to give a dipyridopyridine derivative (XII-398) (*156*).



(XII-397) (XII-398)

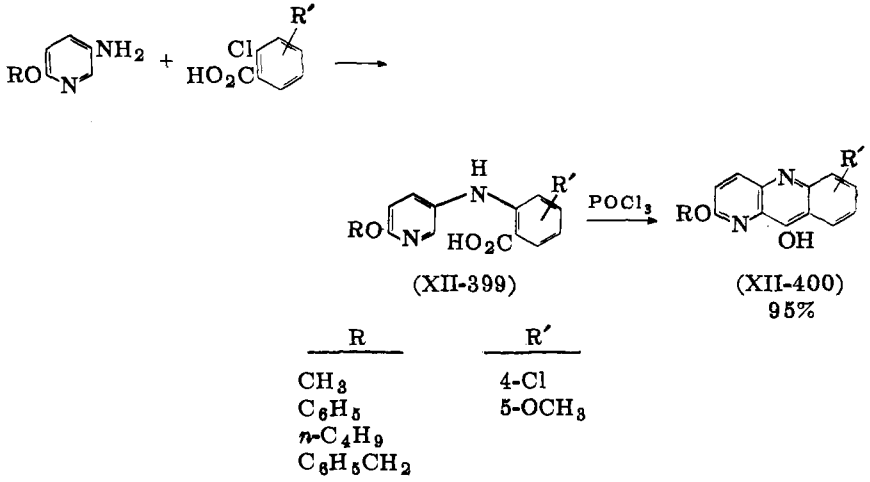
A 3-amino-2-pyridinol reacted with 2,4,6-trinitroanisole to give a pyridobenzoxazine (XII-398a) (*897*).

5-Amino-2-alkoxypyridines are arylated with chlorobenzoic acids in the presence of anhydrous potassium carbonate, copper oxide,



(XII-398a)

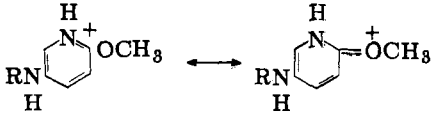
and amyl alcohol (solvent) to form pyridylaminobenzoic acids (XII-399) which are cyclodehydrated by phosphorus oxychloride to the corresponding 1,10-diazaanthracene (XII-400). That cyclization oc-



(XII-399) (XII-400)
95%

R	R'
CH_3	4-Cl
C_6H_5	5-OCH_3
n-C_4H_9	
$C_6H_5CH_2$	

curred on C_6 and not C_4 of the pyridine ring was demonstrated by synthesizing XII-400 by an unequivocal alternate route. Ring-closure did not occur unless an alkoxy group was present at C_2. Such a group cannot directly affect the electron density at C_6. The authors attribute to it an indirect influence, whereby it counteracts the electron-withdrawing effect of the protonated ring nitrogen (XII-401), thus facilitating electrophilic substitution at C_6 (*655*).



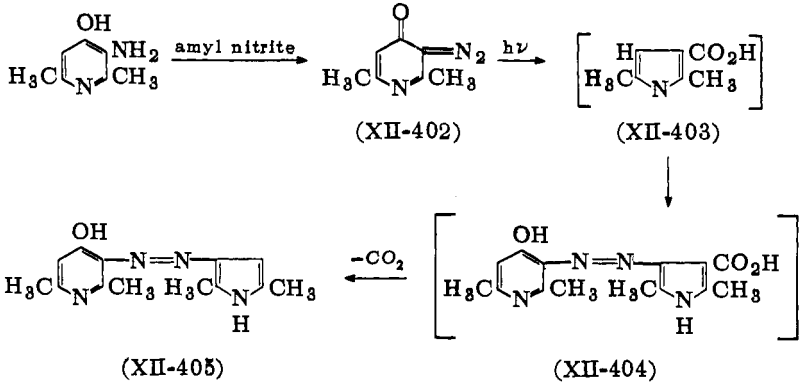
(XII-401)

Studies have been made of selective acylation. When 6-amino-2-pyridinol sulfate is suspended in pyridine and treated with one equivalent of *p*-acetamidobenzenesulfonyl chloride, condensation proceeds mainly on oxygen; a small amount of disulfonylation occurred (*656*). Likewise, XII-397 is tosylated in sodium hydroxide on oxygen (49%) and nitrogen (12%). *p*-Nitrobenzoyl chloride re-

acts with XII-397 on oxygen in base but on nitrogen in glacial acetic acid (*156*). These results are explainable in terms of the relative nucleophilicities of *N* and *O*. In base the oxide ion, the predominant species, is more nucleophilic than the amino group, whereas in glacial acetic acid the amino group is more nucleophilic than the intact hydroxyl group.

Ring contraction occurs when the diazonium salt of 2,6-dimethyl-3-amino-4-pyridinol is exposed to light. The product isolated in small yield is a pyridineazopyrrole (XII-405). The acid (XII-404) cannot be isolated since it loses carbon dioxide very readily.

The structure of XII-405 was confirmed by coupling XII-402 with XII-403 synthesized by an alternate method (*657*).



The reactivity of a side-chain amine can be affected by the presence of an oxygen function on the ring. Thus 3-aminomethyl-6-methyl-2-pyridinol (XII-406) gave a red amorphous solid rather than the expected 3-hydroxymethyl analog (*466*).

(XII-406)

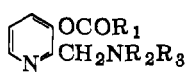
Since both the amino and hydroxyl groups are electron-releasing, they facilitate electrophilic substitution. For example, nitrosation, which fails with pyridinols, does occur with aminopyridinols. 6-Amino-2-pyridinol reacts with nitrous acid in the cold to give a

poor yield of impure compound assumed to be the 3-nitroso derivative (*307*). The structure was not determined and the product could just as well have been the 5-nitroso derivative or a mixture of the two isomers. Nitrosation, coupling, nitration, and halogenation of XII-397 occur easily at C_3 (*156*). In this compound, the 5 position is blocked, and consequently it is incorrect to generalize that C_3 is more susceptible to attack than C_5.

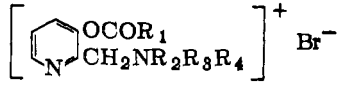
A few aminopyridinols were prepared and compared as to color with ferric chloride, dichloroquinonechloroimide test (*658*) color on coupling with diazotized 2,5-diaminopyridine, and R_f values (butanol-petroleum) (*555*).

Alkoxyaminopyridines have been extensively studied as antituberculosis agents. Feinstone (*659*) first reported the specific *in vitro* tuberculostatic effect of 2-butoxy-5-aminopyridine. The formaldehyde-bisulfite adduct was the least toxic of the derivatives studied. Variations in structure indicate: (*a*) isosteres also have activity; (*b*) 4 to 6 is the optimum number of atoms in the alkoxy group; (*c*) cyclic, aryl, aralkyl, heterocyclic, and branched-chain alkyl substitution in the alkoxy group and nuclear substitution all diminish activity; (*d*) replacing the alkoxy group by an alkyl group does not seriously impair activity; (*e*) the amino group is essential; and (*f*) hydroxyalkyl and diethylaminoalkyl derivatives have no activity (*661a*). The 2-alkoxy-5-aminopyridines were synthesized from 2-chloro-5-nitropyridine by interaction with the appropriate sodium alkoxide or phenoxide. The nitro ethers were then reduced with iron and acetic acid in aqueous methanol. In a few cases (*t*-butyl and dipropylcarbinyl) the nitro ethers exploded during vacuum distillation (*230*). Twenty-five N^5-derivatives of 2-butoxy-5-aminopyridine were prepared (*662*), and many of them had *in vitro* activity comparable to, but not higher than, the parent compound. In more recent *in vivo* studies, 2-butoxy-5-aminopyridine sodium formaldehyde bisulfite proved ineffective in the treatment of experimental tuberculosis in mice and guinea pigs (*660*).

A series of 24 esters of 3-pyridinol containing an aminolkyl substituent at C_2 have been prepared in the form of the tertiary (XII-407) and quaternary salts (XII-408). Several members of both series exhibit marked parasympathomimetic and anti-curare activity (*469*).



(XII-407)



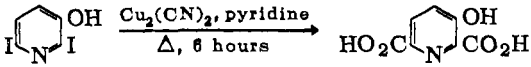
(XII-408)

The most potent compounds of type XII-407 are those in which R_1 = dimethylamino and R_2 and R_3 = methyl or ethyl. In series XII-408, the best compounds again have R_1 = dimethylamino and R_2, R_3, and R_4 = CH_3, C_2H_5, *n*- and *i*-C_3H_7, and *n*-C_4H_9. Although the active compounds compared favorably to "Prostigmin," they were not superior. Physical constants of aminopyridinols are given in Tables XII-24 (p. 726), XII-33 (p. 772), and XII-37 (p. 790).

5. Carboxylic Acids and Derivatives

The usual methods for synthesizing the hydroxy acids are: (*a*) transformation of pyronecarboxylic acids; (*b*) ring closures, usually giving esters and nitriles; (*c*) from amino acids; and (*d*) Kolbe reaction.

3-Hydroxypyridine-2,6-dicarboxylic acid was prepared from the corresponding diiodo compound using cuprous cyanide (XII-409) (*721*).



(XII-409)

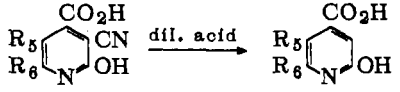
Since many of the ring closure methods for the synthesis of pyridinols give hydroxyesters and nitriles, the removal of the acid function is an important synthetic step. The most important group of hydroxy acids obtained by cyclization are the 5- and 5,6-substituted-2-hydroxynicotinic acids. The presence of the hydroxyl group facilitates decarboxylation. Heating to temperatures of about 300°C. (*52, 56,68,69,285*), distillation over copper (*53*), and heating in the presence of quinoline and copper catalyst at about 300°C. (*82,244*) have all been utilized. Catalysis by hydrochloric (*60,80*) or sulfuric (*428*) acid permit lower temperatures (150–160°C.) to be used. Alkyl-substituted 4-hydroxynicotinic acids, where the two functional groups are ortho, also lose carbon dioxide when heated over the melting point (*151*). The two functions (OH and CO_2H) need not be ortho; 3-methyl-6-hydroxypicolinic acid reacts at 300°C. in the

presence of copper (*661*) and 4-hydroxypyridine-2,6-dicarboxylic acid loses both carboxylic acid groups at 200–260°C. (*324*). However, 6-ethyl-2-hydroxyisonicotinic acid resists reaction even with soda lime or copper (*457*).

The removal of the nitrile group from 2-hydroxy-5-phenyl-6-aminonicotinonitrile with 1 : 1 concentrated hydrobromic and glacial acetic acids was slow (21 hours). The amide was obtained when the reaction time was curtailed (*477*).

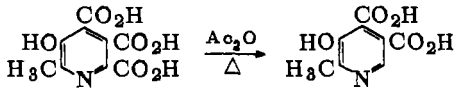
The presence of a second hydroxyl group facilitates the loss of carbon dioxide. The esters of several 2,4-dihydroxynicotinic acids were decarboxylated during hydrolysis with dilute hydrochloric acid (*78,79,543*).

In the hydrolysis of substituted 2-hydroxy-3-cyanoisonicotinic acids (XII-410) carbon dioxide is more readily lost ortho than meta



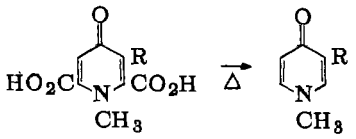
(XII-410)

to the hydroxyl group (*100,457*). In an interesting competitive study, 6-methyl-5-hydroxy-2,3,4-pyridinetricarboxylic acid (XII-411) lost the para-carboxyl group (*299*).



(XII-411)

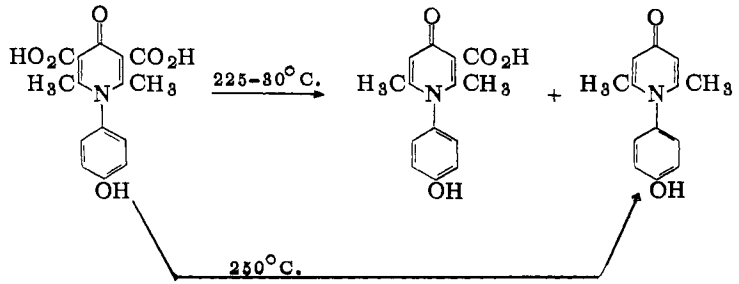
Pyridones react fairly readily. 1-Methyl and 1-methyl-3-hydroxychelidamic acids lose both carboxylic acid groups when vacuum-pyrolyzed (XII-412). A stepwise decarboxylation of a 4(1*H*)-



(XII-412)

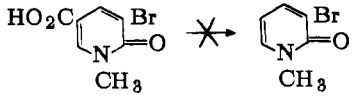
R = H (*122*), OH (*135*)

pyridone-3,5-dicarboxylic acid (XII-413) was achieved (*126*) by vacuum pyrolysis with pure copper bronze. Starting material was recovered at 190°C.



(XII-413)

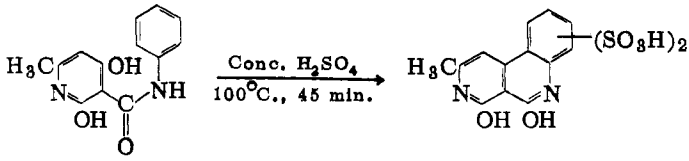
Unwanted side reactions occasionally occur. Pyrolysis of 1-methyl-3-bromo-2(1*H*)-pyridone-5-carboxylic acid (XII-414) in the



(XII-414)

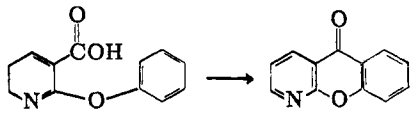
presence of copper or under reduced pressure evolved carbon dioxide but did not give the desired 1-methyl-3-bromo-2(1*H*)-pyridone. Possibly at elevated temperatures reaction occurs at the brominated position (*346*).

A few cyclizations of derivatives of pyridinol carboxylic acids have been reported (*662a*). The anilide of 2,4-dihydroxy-6-methylnicotinic acid (XII-415) cyclizes on the phenyl ring in hot concentrated sulfuric acid to give a pyridoquinoline compound.



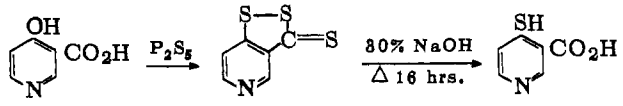
(XII-415)

Cyclodehydration of 2-phenoxynicotinic acid with phosphorus oxychloride gave a poor yield of 9-oxa-1-aza-anthrone (XII-416) (*663*).



(XII-416)

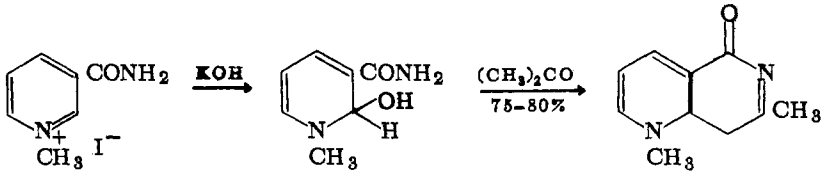
An unexpected reaction occurred when 4-hydroxynicotinic acid was refluxed with a mixture of phosphorus pentasulfide and pyridine. A 48% yield of a product $C_6H_6NS_3$ (XII-417) was obtained. The product was remarkably stable to hydrolysis, being recovered after boiling for one hour with 20% sodium hydroxide or for four hours with concentrated hydrochloric acid. Refluxing for 16 hours in 30% sodium hydroxide gave 4-mercaptonicotinic acid (XII-418).



(XII-417) (XII-418)

On the basis of the analysis and the formation of XII-418, the structure XII-417 is assigned (*664*). *Cf.* Chapter XV.

When the methiodide of nicotinamide is treated with potassium hydroxide in acetone, hydroxylation occurs at the 2 position and the intermediate condenses with acetone to form a compound isolated as the hydrochloride, which is assigned the structure XII-419 (*672*).



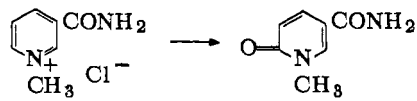
(XII-419)

The yield was measured by decrease in amide nitrogen, determined by ammonia evolution on hydrolysis (*667*). More evidence as to the structure of XII-419 would be desirable. Competitive methylation of pyridinol carboxylic acids with diazomethane favors the carboxylic acid group, as typified by 6-methyl-2-hydroxynicotinic acid (*245*).

Various pyridinol- and pyridonecarboxylic acids have been tested for physiological activity. 2-Alkoxy- and 2,6-dialkoxyisonicotinic acids and derivatives were tested as local anesthetics. The 2,6-dialkoxy compounds were more active than the monoalkoxy compounds and the amides more than the esters. The activity increases to a maximum at butoxy and then declines at pentoxy. The β-diethylaminoethyl amides of the dipropoxy and dibutoxy compounds were four to six times stronger than cocaine or novocaine (*206*). A large number of 1-substituted 2(1*H*)-pyridone-3-carboxylic acids have been prepared (*436,665*) and reported to be antiparasitic agents.

Sodium 1-(β-mercuri-γ-methoxypropyl)-2(1*H*)-pyridone-5-carboxylate is a mercurial diuretic (*686*). Its activity has been assayed in combination with theophylline in different animal species (*687*).

Knox and Grossman reported isolating 1,6-dihydro-1-methyl-6-oxonicotinamide (XII-420) from an enzymatic oxidation (*668,669*) of the methochloride of nicotinamide (XII-421). The same metabolite



(XII-421) (XII-420)

(XII-420) was isolated from urine of humans who ingested XII-421 (*670*). Ingestion by humans of nicotinamide itself gave rise to XII-420 in the urine. Humans excrete large amounts of this metabolite, rats and goats small amounts, and calves none at all (*671*).

Acid hydrolysis of the polypeptide Factor S, a component of Staphylomycin, an antibiotic very active against gram-positive bacteria, has yielded among several products, 3-hydroxypicolinic acid. This acid is linked to the amino group of threonine (*903*).

The structure of hydroxypyridinecarboxylic acids has been investigated by Albert (*826*). He determined the pK_a of 6-hydroxynicotinic acid to be 3.82. This value is equal to the pK_a of nicotinic acid in the carboxylic acid form rather than in the zwitterion form (pK_a 4.81). The conclusion is reached that 6-hydroxynicotinic acid does not exist in a zwitterion form. Hence, once again the

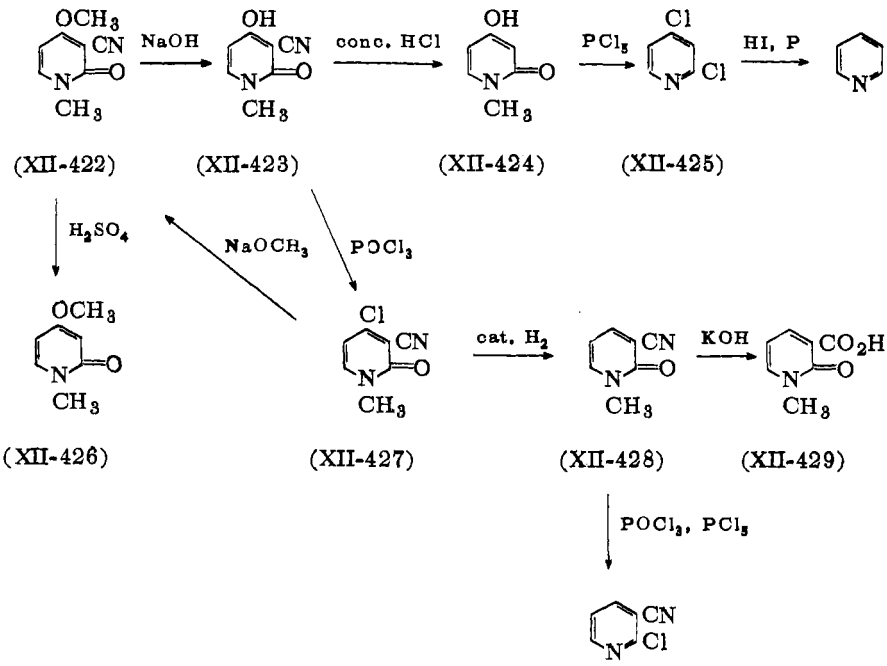
—NH—C=O and N=C— groups are found to be qualitatively and quantitatively similar.

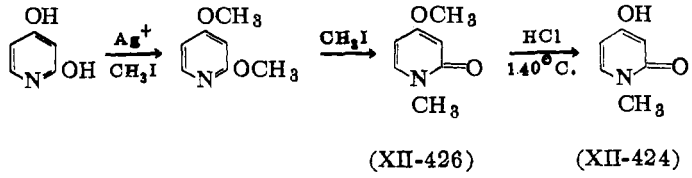
Physical constants of the isomeric pyridinolcarboxylic acids are given in Tables XII-25 (p. 728), XII-34 (p. 778), and XII-37 (p. 790).

6. Ricinine

This alkaloid was isolated by Tuson in 1864 from the oil of the castor bean, *Ricinus communis L.* (*673*). It has since been extracted from the leaves (*674*) and is present to the extent of about 1% in the entire plant. It is toxic and is effective against codling-moth larvae (*675*). The alkaloid is a neutral, optically inactive white crystalline solid, m.p. 201.5°C. (*673*) and has molecular formula $C_8H_8O_2N_2$ (*676*). Various color tests are described by Marion (*678*). The major contribution towards the elucidation of the structure of ricinine was made by Späth and his co-workers Koller and Tschelnitz.

Zinc dust distillation gave pyridine (*679*). Saponification with sodium hydroxide gave methanol and an acid, $C_7H_6O_2N_2$, called ricininic acid (XII-423) (*676*), thought to arise by hydrolysis of an ester. Concentrated hydrochloric acid at 150°C. decomposes XII-423 to carbon dioxide, ammonium chloride, and a base, $C_6H_7O_2N$ (XII-424), isolated as its hydrochloride. The red coloration with ferric chloride indicated that XII-424 was a pyridinol (*677*). Treatment of XII-424 with phosphorus pentachloride substitutes two chlorine atoms for two oxygen functions and removes a methyl group to give $C_5H_3NCl_2$ (XII-425), which gave pyridine when heated with hydrochloric acid and red phosphorus. To explain these transformations, XII-424 was regarded as a 1-methylhydroxypyridone. The position of the two oxygen functions was established by synthesizing XII-424 from 2,4-pyridinol by methylation, O-N rearrangement of methyl, and hydrolysis. Identification of XII-424 as 1-methyl-4-hydroxy-2(1*H*)-pyridone was an important step in the structure proof (*680*). Assignment of the structure for XII-426 was based on tenuous arguments: color reactions and boiling point comparisons with 2- and 4-pyridones. This methoxy compound was identical with the compound obtained when ricinine was refluxed



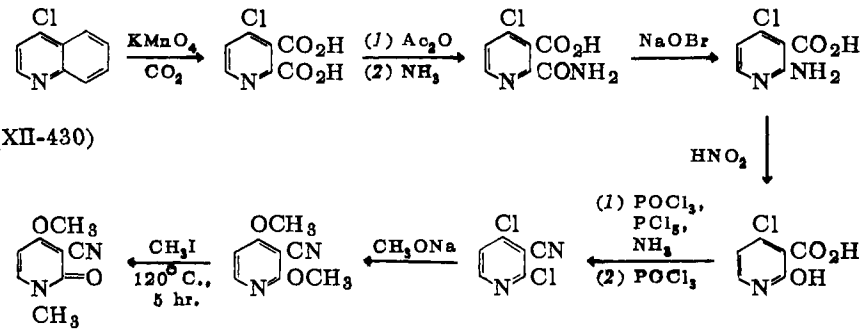


with sulfuric acid, establishing the fact that ricinine itself has a methoxyl group. The acidity of ricininic acid (XII-423) is therefore due to a hydroxyl rather than a carboxyl group. Ricininic acid can be reconverted to ricinine by reaction with phosphorus oxychloride to give a chloro compound (XII-427) which is treated with sodium methoxide. This conversion confirms the presence of a methoxyl group in the parent alkaloid (*681*).

The position of the two oxygen groups and the remaining features of the structure were revealed by a second degradative path.

Catalytic reduction of XII-427 gave ricinidine, or desmethoxyricinine, $C_7H_6ON_2$ (XII-428). Warming XII-428 with potassium hydroxide gave ammonia and 1-methyl-2(1*H*)-pyridone-3-carboxylic acid (XII-429) (see above). Under controlled conditions the amide can be isolated. The carboxylic acid (XII-429) was synthesized by an unequivocal route. That ricinidine (XII-428) is 1-methyl-3-cyano-2(1*H*)-pyridone is further confirmed by conversion to 2-chloronicotinonitrile on treatment with phosphorus pentachloride. These data establish the fact that ricinine is a 3-cyano-2-pyridone and hence is 3-cyano-4-methoxy-1-methyl-2(1*H*)-pyridone (XII-422).

The structure of ricinine has been confirmed by Späth and Koller (*222,682*) and later workers by unequivocal syntheses. The original synthesis (*222*), carried out in 1932, starts with the oxidation of 4-chloroquinoline (XII-430). The last step is equivocal since the 4- rather than the 2-methoxy group could also rearrange. Incidentally, the rearrangement of O to N did not occur merely on heating, even at 300°C. Another Späth and Koller synthesis (*682*) starts with ethyl 2,4-dihydroxy-6-methylnicotinate and proceeds to XII-431, which is similarly converted to XII-422. The authenticity



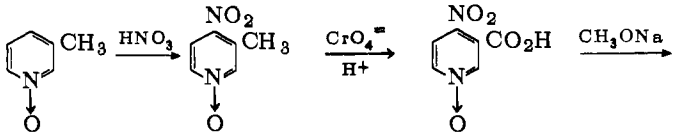
of synthetic XII-422 is confirmed by mixed melting point (197°) and preparation of a mercuric chloride complex (m.p. 203–204°C.).

Reitman (*683*) reported a synthesis from 3-nitro-4-pyridinol via 4-chloro- to 4-methoxy-3-nitropyridinol. The 3-nitro group is reduced to 3-amino, which is replaced by a cyano group. Methylation

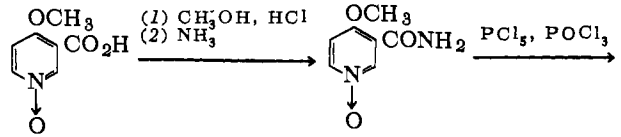
of the ring nitrogen is followed by pyridone formation with potassium ferricyanide to give XII-422.

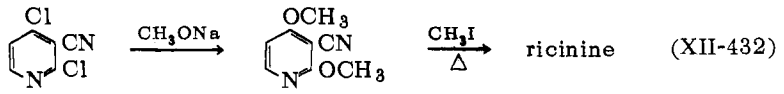
A much shorter synthesis starts with 6-chloronorricinine, 6-chloro-2,4-dihydroxynicotinonitrile, formed by the spontaneous polymerization of cyanoacetyl chloride (see p. 000) (*159*). The disodium salt of this compound is reacted with dimethyl sulfate and the resulting product is reductively dechlorinated with zinc and sulfuric acid, yielding ricininic acid (XII-423) (*684*). The conversion of XII-423 to ricinine via the chloro compound (XII-427) has been described.

The fifth and most recent synthesis, described by Taylor and Crovetti (*685*) in 1956, utilizes 3-picoline 1-oxide as starting material. The successive steps leading to the intermediate (XII-431) are shown (XII-432). The oxidative formation of XII-433 had to be



(XII-433)



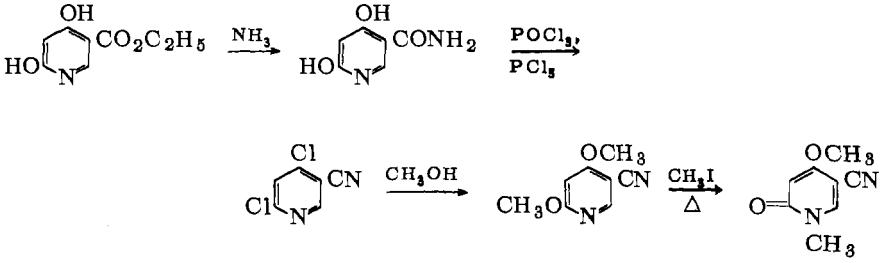


(XII-432)

(XII-431)

performed under carefully controlled acidic conditions to prevent decomposition. However, displacement of its nitro group was facile because of its combined activation by the carboxyl and *N*-oxide functions. Surprisingly, the step leading to loss of the *N*-oxide group did not form any isomeric 4,6-dichloronicotinonitrile.

The structural isomer of ricinine, 5-cyano-4-methoxy-1-methyl-2(1*H*)-pyridone (XII-434) has been prepared for comparison pur-

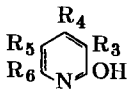


(XII-434)

poses (*223*). It is noteworthy that the O-N isomerization occurs more readily than the analogous conversion of XII-431 to ricinine.

G. TABLES

The rest of this chapter consists of tables of the physical properties of the pyridinols and pyridones and their substitution products and derivatives.

TABLE XII-22. Alkyl and Aryl 2-Pyridinols 

R_3	R_4	R_5	R_6	M.p., °C.	B.p., °C.	Derivatives	Ref.
				106–7	280–81	picrate, m.p. 170–71°	266,376,382,408, 865
						K salt·H_2O, m.p. 274–76°	522
						mercuric chloride, m.p. 196–97°	722
						Na salt·2 H_2O	376
						p-tosyl, m.p. 53°	527
						acetyl, b.p. 110–12°/10 mm.	473
						benzoyl, b.p. 183–86°/ 30 mm.; m.p. 47°	467,474,526
						benzoyl chloroplatinate, m.p. 186° (dec.)	474
						p-nitrobenzoyl, m.p. 115–16°	473
						p-nitrobenzenesulfonyl, m.p. 157–60°	467
						β-naphthoyl, m.p. 116°	526
						3,4,5-tribenzyloxybenzoyl, m.p. 116°	526
						p-benzyloxybenzoyl, m.p. 123–25°	526

Me				140			269,874
	Me			130	307–9	monohydrate, m.p. 65°	268,274
		Me		182–83			484,874
			Me	163–65			393
				159			69,82,244,274, 382,485,538
						picrate, m.p. 159–50°	270,377
						Na salt, m.p. 290°	274
						acetyl, b.p. 118°/0.4 mm.	393
Et							795
			Et	205–6			62
			n-Pr	88–89			54,68
			i-Pr	129–30			68
			i-Bu	102–3			55
			cyclo-Pr	165–66			57
			n-Am	40–41			68
			Ph	197			285,708
		Ph_3C		365–68			467
			CH_2CH_2Ph	152			53
	CH=CHPh			238–39			274
Me			Me			$\frac{1}{2}H_2O$, m.p. 138–39°	157
	Me		Me	179–80		hydrochloride, m.p. 127–28°	27,50,288
						picrate, m.p. 157°	50

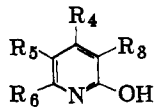
(*continued*)

TABLE XII-22. Alkyl and Aryl 2-Pyridinols (*continued*)

R_3	R_4	R_5	R_6	M.p., °C.	B.p., °C.	Derivative	Ref.
Et			Me	100–1		picrate, m.p. 152°	271
	Me		Et	144			41
	Et		Et	61–62			27
		Me	Me	208–9			52,53
		Me	Et	141			42
	i-Pr		Me	112.5–13.5			389
		Me	*n*-Bu	88–90			56
	Me		Ph	182–83			27,41,42,81, 285,707
	Ph		Me	209			25,41,67,81, 113,824
	Me		*p*-MeC_6H_4	183			50,707
	Ph		Et	165			25,67
	i-Pr		Ph	127–28.5			389
	Ph		Ph	208			18,25,42,67
	Ph		*p*-MeC_6H_4	226–38			25,27,67
	p-MeC_6H_4		Ph	237–39			27
	Ph		*p*-$NO_2C_6H_4$	275–76			67
$(Ph)_3C$			Me	314–17			467
	CH_2Ph		Ph	195–98			389
		—$(CH_2)_3$—		187–88		picrate, m.p. 164°	60
		—$(CH_2)_{13}$—		189–90			80
	Me	Me	Me	252			428

	Me	Et	Me	150	41
	Me	Me	Ph	166	797
	Ph	Me	Ph	227–29; 263–64	42,51
Ph	Ph		Ph	263	20
Ph	Ph		*p*-$MeOC_6H_4$	249	22
p-$NO_2C_6H_4$	Ph		Ph	311–12	21
		—$(CH_2)_5$—		194–94.5	829
Ph	Me		Me	215–18	824
Me	Ph		Me	155–57	824
	Ph	Ph	Me	264–66	824
Ph	Me	Ph	Me	295–97	824,831
Me	Ph	Ph	Me	299–302	824
Me	3-Py	Ph	Me	310–12	824
Ph	Me	Ph	Ph	308–11	831
Ph	Me	Ph	CH_2Ph	218–20.5	831
Ph	Et	Ph	Me	268–71	831
Ph	Et	Ph	Ph	270–73	831
Ph	Et	Ph	CH_2Ph	260–63	831
Ph	Ph	Ph	CH_3	303–5	831
Ph	Ph	Ph	Ph	271–73	831
Ph	Ph	Ph	CH_2Ph	298–300	831
Ph	CH_2Ph	Ph	Ph	292–94	831
Ph	CH_2Ph	Ph	CH_2Ph	262–64	831
Me	Me	Me		76–78	827
Ph	Me	keto	keto	160–61	842

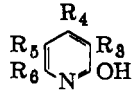
TABLE XII-23. Halo and Nitro 2-Pyridinols



R_3	R_4	R_5	R_6	M.p., °C.	Derivatives	Ref.
				HALO		
Cl				163, 180		273,865
	Cl			184		275
		Cl		163		273
					benzoyl, m.p. 95°; *p*-nitrobenzoyl, m.p. 142-43°	315
			Cl	128.5-29		266,865
		Br		177-78		272
				162-66		346
			Br	123		216,254
I				182		558
				170		233
	I			195		275
		I		192		218,233,549, 689
		Br	Me	204		274
	Cl		CH=CHPh	234-35		258
		$(CH_2)_2Br$		258		52
Cl	Cl			227-28		228
Cl		Cl		177-78		273
	Cl	Cl		231 (dec.)		220
	Cl		Cl	151		257
Br		Br		207-208		272,314
I		I		261-62, 265		272,286,869
				268-69		104,438
Br	Me		Me	228-29		535
	Me	Br	Me	240-41		535
	Ph	Br	Ph	278		18
Br		Br	Me	254-55		274,485
Cl	Cl	Cl				807
Cl		Cl	Cl	174-75		261
Br	Me	Br	Me	236-37		535
Br	CH_2Br	Br	CH_2Br	154-56		535

TABLE XII-23 (*continued*)

R_3	R_4	R_5	R_6	M.p., °C.	Derivatives	Ref.
				NITRO		
NO_2				224		277,310,557, 884
					Na salt, m.p. 303° (dec.)	557
		NO_2		186–88		63,237,251, 266,310
NO_2	Me			234–35		280
NO_2		Me		251–53.5		280,698
Me		NO_2		228.5–29.5		280,304
NO_2			Me	223–24		235,280,281
				245		495
	Me	NO_2		186–88		280,655
		NO_2	Me	234–36		235,236,280, 281,655
NO_2		NO_2		175	Na salt, m.p. 289–90°	279,909,910
	Me	NO_2	Me	251		247
Ph	Me	NO_2		250–53		842
				HALO AND NITRO		
Cl		NO_2		198		239,279
NO_2		Cl		235		240,278,279
NO_2		Br		245–47		486
				237–38		278
Br		NO_2		221–23, 212		486,911
NO_2		I		247–48		272,286,548
I		NO_2		203		532
NO_2	Cl		Me	215–16		495
Br		NO_2	Me	262–64		281,486
NO_2		Br	Me	221–23		486
Br	Me	NO_2	Me	273		247

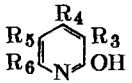
TABLE XII-24. Amino 2-Pyridinols 

R_3	R_4	R_5	R_6	M.p., °C.	Derivatives	Ref.
NH_2					hydrochloride	558
					picrate, m.p. 214°	495
	NH_2			219–21		253
		NH_2			acetyl, m.p. 232–33°	385
					dibenzoyl, m.p. 214°	759
					sulfanilamido, m.p. 243–44°(dec.)	716
			NH_2	214		305,308
					monoacetyl, m.p. 213°	308
					diacetyl, m.p. 162–63°	308
					picrate, m.p. 191°	555
					N-*p*-aminobenzenesulfonyl, 239–40°	656
					O-*p*-aminobenzenesulfonyl, m.p. 148°	656
					O,*N*-di(*p*-acetamidobenzenesulfonyl), m.p. 222°	656
NH_2		Me		119–20	*N*-acetyl, m.p. 253	280,881
NH_2			Me		picrate, m.p. 222–25°	495
	NH_2		Me			156
		Ph	NH_2	235–37		477
CH_2NH_2			Me		dihydrochloride, m.p. 236–37°	245
	NH_2	Me	Et	288		158
	NH_2	Ph	CH_2Ph	245–46		158
	NH_2	—$(CH_2)_3$—		323	*N*-acetyl, m.p. 314°	156
					diacetyl, m.p. 232°	156
					O-*p*-nitrobenzoyl, m.p. 203°	156
					N-*p*-nitrobenzoyl, m.p. 218–19°	156
					O-tosyl, m.p. 167°	156
					N-tosyl, m.p. 168°	156
	NH_2	—$(CH_2)_4$—		130		156

TABLE XII-24 (*continued*)

R_3	R_4	R_5	R_6	M.p., °C.	Derivatives	Ref.
CH_2NH_2	Me		Me		hydrochloride, m.p. 310–12 °(dec.)	66
					hydrobromide, m.p. 305 °(dec.)	66
					picrate, m.p. 223–24 °	66
					benzoyl, m.p. 210–11 °	747
Me	NH_2	Ph	Ph	214–15		158
Ph	NH_2	Me	Et	224–25		158
Me	NH_2	—$(CH_2)_3$—		287		156
—CH_2[a]—	NH_2	—$(CH_2)_3$—		360	monoacetyl, m.p. >360°	156
NH_2	NH_2		Me	255	picrate, m.p. 232 °	495
NH_2	NH_2	—$(CH_2)_3$—		286–87		156
					picrate, m.p. 221 °	495
					dihydrochloride, m.p. 198 °	595
CH_2NH_2	Me	NH_2	Me	323–24		536
NH_2		Br		182–84		732
					hydrochloride, m.p. 220 °(dec.)	278
					N-acetyl, m.p. 230 °	278
NH_2		I			hydrochloride, m.p. 218 °(dec.)	548
I		I	NH_2		Na salt, m.p. 182 ° (dec.)	728
Cl	NH_2	—$(CH_2)_3$—		324	acetyl, m.p. 324 °	156
Br	NH_2	—$(CH_2)_3$—		204–5 (dec.)		156
NO_2	NH_2			315–16		495
NO_2	NH_2		Me	270		495
NO	NH_2	—$(CH_2)_3$—		260 (dec.)		156
Me		NH_2		247 °		881

[a]Symmetrical bis compound.

TABLE XII-25. 2-Pyridinol Carboxylic Acids 

R_3	R_4	R_5	R_6	M.p., °C.	Derivatives	Ref.
COOH				255		69,222,283 287,663
					Et ester, m.p. 139°	69
					amide, m.p. 266–67°	69
					anilide, m.p. 261°	69
	COOH			318–25 (dec.)	Me ester, m.p. 209–12°	253
					hydrazide, m.p. 256–58° (dec.)	
					azide, m.p. 140° (dec.)	
		COOH		302		104,252,286 579
					Me ester, m.p. 164°	798
					Et ester, m.p. 150°	252
					N-ethylamide, m.p. 205–6°	737
			COOH	280		110,172
CH_2CH_2COOH				86		799
COOH			Me	228		68,69,285
					Me ester, m.p. 184–85°	245
COOH			Et	300–2		25,67
COOH			$-(CH_2)_5-$	245–48		829
COOH			*n*-Pr	160		54,68
					Et ester, m.p. 91–92°	58
COOH			*i*-Pr	185–86		68

COOH			*i*-Bu	170–71		55
COOH			*n*-Am	108–109		68
COOH			cyclo-Pr	248–50 (dec.)		57
COOH			Ph	287–88		291
				304 (dec.)		191,285
COOH			$(CH_2)_2Ph$	211–12		53
$(CH_2)_2COOH$	Me			214		594
	COOH		Me	314	Me ester, m.p. 228°	41
					hydrazide, m.p. 147–48°	100
	COOH		Et	308		457
	COOH		Ph	350		27,50
	Me		CH_2COOH	190–91		70
					Et ester, m.p. 165°	106
		Me	COOH	290–300 (dec.)		110
		COOH	Me	252		24
				ca. 325 (dec.)	Et ester, m.p. 207–9°	244
COOH	Me		Me	257–58		66,74,285, 580
					Me ester, m.p. 182–83°	66
					hydrazide, m.p. 239–40°	580
					phenylsulfonhydrazide, m.p. ca. 285° (dec.)	580

(*continued*)

TABLE XII-25. 2-Pyridinol Carboxylic Acids (*continued*)

R_3	R_4	R_5	R_6	M.p. °C.	Derivatives	Ref.
					Et ester, m.p. 136°	74
					amide, m.p. 224°	27,74
COOH		Me	Me	310–12 (dec.)		52,53,285
Me		COOH	Me	300–5		801
	Me	COOH	Me	256–58		802
					monohydrate, m.p. 300°	786,802
					Et ester, m.p. 137°	71
COOH		Me	Et	287–88		42
Et		COOH	Me	305		801
Pr		COOH	Me			801
COOH		Me	*n*-Bu	211–13		56
COOH	Me		Ph	278	Et ester, m.p. 163°	285
					amide, m.p. 286–87°	81
COOH	Ph		Ph			107
					Me ester, m.p. 253°	18
COOH	Ph		*p*-ClC_6H_4	262	Me ester, m.p. 196°	18
COOH	CH_2Ph		*p*-ClC_6H_4		Et ester, m.p. 210°	109
	Ph	COOH	Ph		Et ester, m.p. 210°	113
COOH		—$(CH_2)_3$—		276 (dec.)		60
COOH	Me	Me	Me			803
COOH	Et	Me	Ph	240–42		389
Ph	Me	COOH			amide, m.p. 350–520	840
COOH	Ph	Me	Ph	270–71		51

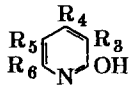
COOH			COOH	287–89		191
				303–305	Me ester, m.p. 252°	192
					Et ester, m.p. 206°	192
		COOH	COOH		di-Me ester, m.p. 158°	723
					anhydride, m.p. 245°	723
					anhydride acetyl, m.p. 109°	723
					imide, m.p. 334°	723
					imide acetyl, m.p. 257°	723
					cyclic hydrazide, m.p. 400° (dec.)	723
COOH	COOH		Me	222 (dec.)	di-Me ester, m.p. 173–75°	714
COOH		COOH	Me	305	mono-Et ester, m.p. 225°	82
					di-Et ester, m.p. 205°	82
					monohydrate, m.p. 303°	42
	Me	COOH	COOH	252–53		800
	CH_2COOH	COOH	Me	200–201 (dec.)		113,802
COOH	Me	COOH	Me	232		288
COOH		Cl		220		222
Cl		COOH		305 (dec.)		243
Br		COOH		296	Me ester, m.p. 221–22°	804
	Cl		COOH	> 300 (dec.)		257
	COOH		Cl		Me ester, m.p. 189–90°	805
Br		COOH	Me		Et ester, m.p. 226–27°	244
Cl	Cl		COOH	284 (dec.)		257

(*continued*)

TABLE XII-25. 2-Pyridinol Carboxylic Acids (*continued*)

R_3	R_4	R_5	R_6	M.p., °C.	Derivatives	Ref.
I		COOH	I	242–49 (dec.)		540
I		I	COOH	272		443
CH_2CH_2COOH	Me		Cl	204–6		594
COOH	Me	Br	Me		amide, m.p. 325° (dec.)	536
COOH	Ph	Br	Ph	270 (dec.)	Me ester, m.p. 238–40°	18
Cl	Cl	Cl	COOH	238 (dec.)	Me ester, m.p. 212–14°	210
Cl		COOH	COOH	228	di-Me ester, m.p. 163°	723
					cyclic hydrazide, m.p. 380–400° (dec.)	723
Br		COOH	COOH	229	di-Me ester, m.p. 182°	723
					cyclic hydrazide, m.p. 400–50° (dec.)	723

I		COOH	COOH	235	di-Me ester, m.p. 216°	723
					cyclic hydrazide, m.p. 420–50° (dec.)	723
NO_2		COOH		278 (dec.)		279,286
					Et ester, m.p. 165–67°	279
					Me ester, m.p. 206°	279
COOH		NO_2		265		193
				250–51		63,287
COOH		NO_2	Me	268		245
COOH	Me	NO_2	Me	225	amide, m.p. 292°	247
NO_2	Me	COOH	Me	260	Et ester, m.p. 215°	806
	COOH		NH_2			805
	Me	COOH	NH_2		amide, m.p. 250°	913

TABLE XII-26. Cyano and Alkoxy 2-Pyridinols 

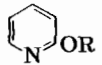
R_3	R_4	R_5	R_6	M.p., °C.	Derivatives	Ref.
				CYANO		
CN				225–26		69,494
					piperidine salt, m.p. 197°	69
		CN		252–53		252
CN			Me	295		59,69
				276–78		68
					piperidine salt, m.p. 192°	69
CN			*n*-Pr	153		54,58,68
CN			*i*-Pr	203–4		68
CN			*i*-Bu	149–50		55
CN			*n*-Am	95–96		68
CN			cyclo-Pr	239–40	monobromo, m.p. 221–22°	57
CN			CH_2CH_2Ph	198 (dec.)		53
CN	Me		Me	289		27,28,41,861
CN	Me		Et	240–41		41
CN	Et		Et	186		27
CN	Me		Ph	310		27,41,42,64,81
CN	Ph		Me	275–76		25,42,67,81
CN	Et		Ph	240 (dec.)		41
CN	Ph		Et	267–68		25,41,67
CN	Ph		Ph	318–20		19,25,27,42,67
CN	Ph		*p*-MeC_6H_4	267–68		25,26,67

CN	p-MeC_6H_4		Ph	311–12		27
CN	Ph		p-$NO_2C_6H_4$	332–33		67
CN		Me	Me	270		53,55
CN		Me	n-Bu	196–97		56
CN			$-(CH_2)_{13}-$	210–11		80
CN			$-(CH_2)_5-$	247–50		829
CN	Me	Me	Me	304–5		428
CN	Ph	Me	Ph	295–98		42,51
CN	CN		Me	241–43		479,695,822
CN		I				252
CN	Me	Cl	Me	279–80		84
CN	Me	Br	Me	259–60		535
CN	Ph	Br	Ph	303–6		19
CN		NO_2		265–66		63
CN		NO_2	Me	253–54(dec.)		59
CN	Me	NO_2	Me	268(dec.)		247,861
CN	CN	NO_2	Me	242–44		479,695
CN		Ph	NH_2	320(dec.)	amide, m.p. 279–81°	477
CN	Me	Ph	NH_2	346(dec.)		477
CN	COOH		Me		Et ester, m.p. 218–19°	49,480
					Me ester, m.p. 229–33° (dec.)	912
					amide, m.p. > 300° (dec.)	479,695
					hydroxamic acid m.p. > 250°	740
CN	COOH		Pr		Et ester, m.p. 153–55°	58
CN	Ph	COOH	Me		Et ester, m.p. 238°	383
CN	p-$NO_2C_6H_4$	COOH	Me		Et ester, m.p. 232°	383

(*continued*)

TABLE XII-26. Cyano and Alkoxy 2-Pyridinols (*continued*)

R_3	R_4	R_5	R_6	M.p. °C.	Derivatives	Ref.
CN	COOH		—$(CH_2)_4$—		Et ester, m.p. 214–15°	42
CN	COOH	NO_2	Me		Et ester, m.p. 193°	49, 480
CN	CN	Me	Et	226–30		822
CN	CN		Ph	> 300		822
CN	CN		*p*-$CH_3OC_6H_4$	> 300		822
CN	CN	Ph	Ph	266–68		822
CN	CN		*t*-Bu	226–28		822
CN	Me	Ph	NH_2	346		840
				ALKOXY		
	OMe			165–66	picrate, m.p. 184–85°	601
	OEt			168		361, 868
			OMe	105–6		609
	Me		OMe	170–71		578
	OEt	Cl		210		220
	$NHNHCOCONH_2$		OEt	274		415
	COOH		OEt		Et ester, m.p. 67°	464
	COOH		*O*-*n*-Bu	205	Bu ester, m.p. 60–61°	464
	COOH		*O*-*i*-Am	258 (dec.)	*i*-Am ester, m.p. 82°	464
	COOH		*O*-cyclohexyl	223	cyclohexyl ester, m.p. 97°	464
Br	OEt			181–82		868
CN	Ph	OMe	Ph	318–20 (dec.)		23

TABLE XII-27. 2-Pyridinol Ethers 

R	Physical properties	Derivative	Ref.
Me	b.p. 142–44°	mercurichloride, m.p. 199–202°	408,409,453,521
Et	b.p. 160–61°		703
	b.p. 155–56°		263,408,808
		hydrochloride, m.p. 90–91°	703
		mercurichloride, m.p. 152–53°	703
		m.p. 141–42°	808
n-Pr	b.p. 179–82°	picrate, m.p. 116.5–18°	449,907
i-Pr		picrate, m.p. 136–37°	696
n-Bu	b.p. 65–66°/4 mm.		865
n-Hexyl	b.p. 73°/2 mm.		908
n-Heptyl	b.p. 83°/2 mm.		908
i-Octyl	b.p. 85°/2 mm.		908
i-Cyclohexyl	b.p. 65°/2 mm.		908
$CH_2CH_2NEt_2$	b.p. 98–100°/2 mm.	hydrochloride, m.p. 135°	738
CH_2COOH	m.p. 111.5–12.5°		459
		Et ester, b.p. 96–97°/4 mm.	204,459
		amide, m.p. 63–64°	459
$CH_2COOCH_2CH_2NEt_2$	b.p. 103–5°/0.14 mm.	dihydrochloride, m.p. 94–96°	204
$CH_2COO(CH_2)_3NEt_2$	b.p. 114–15°/0.2 mm.		204
CH(Me)COOEt	b.p. 113–15°/8 mm.		204
$CHMeCOOCH_2CH_2NEt_2$	b.p. 121–23°/1 mm.		204
$CHMeCOO(CH_2)_2NEt_2$	b.p. 122–23°/0.4 mm.		204

(*continued*)

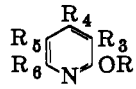
TABLE XII-27. 2-Pyridinol Ethers (*continued*)

R	Physical properties	Derivatives	Ref.
Ph	m.p. 42–44°	picrate, m.p. 104.5–5.5°	227
	m.p. 46–48°; b.p. 227°	chloroplatinate, m.p. 175–77°	302
	b.p. 134–35°/11 mm.		203
o-C_6H_4OMe	m.p. 91–92°	hydrochloride, m.p. 158–59°	204
m-C_6H_4OMe	b.p. 133–35°/1 mm.	hydrochloride, m.p. 136–39°	204
p-C_6H_4OMe	b.p. 152–53°/3 mm.	hydrochloride, m.p. 160–62°	204
p-C_6H_4OEt	m.p. 45–45.5°; b.p. 110–11°/0.14 mm.		204
p-$C_6H_4OCH_2Ph$	m.p. 72.5–73.0°		204
p-C_6H_4Br	b.p. 122–23°/1 mm.	hydrochloride, m.p. 151–52°	204
p-$C_6H_4NO_2$	m.p. 79–81°		566
o-$C_6H_4NO_2$	m.p. 59–61°		566
m-$C_6H_4NO_2$	m.p. 100–1°		566
o-C_6H_4COOH	m.p. 117–18°	Et ester, m.p. 67–68°	204
m-C_6H_4COOH	m.p. 125–26°	Et ester, b.p. 143–44°/1 mm.	204
p-C_6H_4COOH	m.p. 174°	Et ester, m.p. 64–65°	204
o-$C_6H_4COOCH_2CH_2NEt_2$	b.p. 170–71°/1 mm.		204
o-$C_6H_4COO(CH_2)_2NEt_2$	b.p. 179–80°/1 mm.		
m-$C_6H_4COOCH_2CH_2NEt_2$	b.p. 169–70°/1 mm.	dihydrochloride, m.p. 110–12°	204
m-$C_6H_4COO(CH_2)_3NEt_2$	b.p. 174–75°/1 mm.	dihydrochloride, m.p. 129–30°	204
p-$C_6H_4COOCH_2CH_2NEt_2$	b.p. 184.5–85.5°/1 mm.	dihydrochloride, m.p. 141–42°	204
p-$C_6H_4COO(CH_2)_3NEt_2$	b.p. 187–89°/1 mm.	dihydrochloride, m.p. 161–64°	204

$C_{10}H_6COOH(2',3')$	m.p. 149–50°	Et ester, m.p. 96–97°	204
$C_{10}H_6COOCH_2CH_2NEt_2(2',3')$		hydrochloride, m.p. 139–40°	204
$C_{10}H_6COO(CH_2)_3NEt_2(2',3')$		hydrochloride, m.p. 150–51°	204
o-cresyl	b.p. 156–58°/21 mm.		203
p-cresyl	b.p. 171–72°/22 mm.		203
m-cresyl	b.p. 164–66°/20 mm.		203
carvacryl	b.p. 133–34°/2 mm.		203
m-C_6H_4[a]	m.p. 154–56°; b.p. 183–85°/3 mm.		203
CH_2COPh	m.p. 84°		896
allyl	b.p. 30–35°/1.5 mm.	picrate, m.p. 105.5–6.5°	907
2-Py	m.p. 49–50°	picrate, m.p. 124–25°	851
		monomercurichloride, m.p. 125–28°	851
		dimercurichloride, m.p. 175–77°	851
3-Py	m.p. 30–32°	picrate, m.p. 162–64°	851
		mercurichloride, m.p. 153–55°	851
CH_2Ph	b.p. 162–64°/20 mm.		203
	b.p. 134–35°/2 mm.		205
$CHPh_2$	m.p. 57–58°		204
$3,4\text{-}(MeO)_2C_6H_3CH_2$	m.p. 58–59°		204
CHPhCOOH	m.p. 115°	Et ester, b.p. 135–37°/1 mm.	204
$CHPhCOOCH_2CH_2NEt_2$		hydrochloride, m.p. 110.5–12°	204
$CHPhCOO(CH_2)_3NEt_2$		hydrochloride	204

[a]Bis substituted.

TABLE XII-28. Alkyl, Aryl, Halo, and Nitro 2-Pyridinol Ethers



R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
CH_2Ph		Me			b.p. 142-45°/5 mm.	picrate, m.p. 140-41°	720
CH_2Ph				Me	m.p. 45-46[1]		433
					m.p. 51-52°; b.p. 166-67°/20 mm.		538
CH_2COOEt				Me	b.p. 132°/15 mm.		274
n-Bu	Ph	Ph		Ph	m.p. 94°		20
Et		Cl				picrate, m.p. 130-31°	220
Me			I		b.p. 231°, 109-10°/15 mm.	picrate, m.p. 147°	218,233
							218
						HCl salt m.p. 145-50°(dec.)	233
Et			Br		m.p. 34-35°		264
CH_2Ph			Br		m.p. 56-58°	picrate, m.p. 107-9°	720
Et				Br	b.p. 218-19°		216
Ph				Br	m.p. 86.5-87.5°		227
Et	Cl		Cl		m.p. 31°		533
Et	Br		Br		m.p. 29-30°		264
Et		Cl	Cl		m.p. 56-57°		220
Ph		Br		Br	m.p. 41.5-42.5°		227
Et	Cl		Cl	Br	m.p. 46-47°		266
Me	NO_2				m.p. 57-59°		237
Et	NO_2				m.p. 20°		809
2,4-$Cl_2C_6H_3$	NO_2				m.p. 92-94°		232
Me			NO_2		m.p. 109°		218,230, 233,234, 322,617
Et			NO_2		m.p. 91-92°		230,233, 277,322

TABLE XII-28 (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
n-Pr			NO_2		b.p. 102-5°/3 mm.		230
i-Pr			NO_2		m.p. 92°		231
Allyl			NO_2		m.p. 48-50°		230,231
n-Bu			NO_2		b.p. 147-48°/12 mm.		230,559 741
i-Bu			NO_2		b.p. 125-26°/1.5 mm.		230
s-Bu			NO_2		b.p. 121-25°/7 mm.		230
n-Amyl			NO_2		b.p. 108-11°/0.8 mm.		230
i-Amyl			NO_2		m.p. 107-8°		230
3-*n*-Amyl			NO_2		b.p. 150-60°/1.5 mm.		230
n-Hexyl			NO_2		b.p. 125-35°/1.5 mm.		230
n-Heptyl			NO_2		b.p. 130-40°/1 mm.		230
n-Octyl			NO_2		b.p. 175-77°/1.5 mm.		230
n-Decyl			NO_2		m.p. 42-43°		230
CH_2CH_2Cl			NO_2		m.p. 131-32°		712
$CH_2CH_2NEt_2$			NO_2		m.p. 37-38°		230
					b.p. 170°/3 mm.		712
CH_2CH_2OH			NO_2		m.p. 114-15°		230,712
CH_2CH_2OMe			NO_2		m.p. 66-67°		230
					b.p. 160-65°/12 mm.		559
CH_2CH_2OEt			NO_2		m.p. 43-44°		230
$CH_2CH_2OC_4H_9$-*n*			NO_2		m.p. 26-27°; b.p. 130-38°/0.2 mm.		230
Ethoxyethoxyethyl			NO_2		m.p. 42-43°		230
CH_2CH_2OPh			NO_2		m.p. 90-91°		230-705
$CH_2CH_2OCH_2Ph$			NO_2		b.p. 189-91°/1 mm.		230
Ph			NO_2		m.p. 93-94°		105,230
o-MeC_6H_4			NO_2		m.p. 69-71°		230

(*continued*)

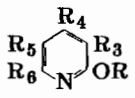
TABLE XII-28. Alkyl, Aryl, Halo, and Nitro 2-Pyridinol Ethers (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
o-ClC_6H_4			NO_2		m.p. 75-77°		232
m-ClC_6H_4			NO_2		m.p. 86-88°		232
p-ClC_6H_4			NO_2		m.p. 93-95°		232
2,4-$Cl_2C_6H_3$			NO_2		m.p. 93-95°		232
2,5-$Cl_2C_6H_3$			NO_2		m.p. 88-90°		232
2,6-$Cl_2C_6H_3$			NO_2		m.p. 111-13°		232
3,4-$Cl_2C_6H_3$			NO_2		m.p. 102-4°		232
3,5-$Cl_2C_6H_3$			NO_2		m.p. 129-30°		232
2,3,4-$Cl_3C_6H_2$			NO_2		m.p. 145-47°		232
2,3,6-$Cl_3C_6H_2$			NO_2		m.p. 134-35°		232
2,4,5-$Cl_3C_6H_2$			NO_2		m.p. 118-20°		232
2,4,6-$Cl_3C_6H_2$			NO_2		m.p. 107-8°		232
3,4,5-$Cl_3C_6H_2$			NO_2		m.p. 183-84°		232
o-$C_6H_4NO_2$			NO_2		m.p. 135°		705
p-$C_6H_4NO_2$			NO_2		m.p. 98-99°		230,463
3,4-Cl_2-3-$NO_2C_6H_2$			NO_2		m.p. 127-28°		232
p-$C_6H_4NH_2$			NO_2		m.p. 156-57°	acetyl, m.p. 179-80°	230,566 566
β-Naphthyl			NO_2		m.p. 95-96°		230
CH_2Ph			NO_2		m.p. 107-8°		230,233
3-Py			NO_2		m.p. 92-94°		230
2-Pyridylethyl			NO_2		m.p. 114-16°		230
Tetrahydrofurfuryl			NO_2		m.p. 94-95°		230
Cyclohexyl			NO_2		b.p. 145-52°/2.5 mm.		230
Me		Me	NO_2		m.p. 82-84°		655
Me			NO_2	Me	m.p. 64-65°		235
					m.p. 70-72°		655
p-ClC_6H_4				Me	m.p. 91-92°		236
2,5-$Cl_2C_6H_3$			NO_2	Me	m.p. 100-1°		236
2,4,5-$Cl_3Cl_6H_2$			NO_2	Me	m.p. 116-18°		236
p-$NO_2C_6H_4$			NO_2	Me	m.p. 104-6°		236
Me		Me	NO_2	Me	m.p. 60°		264
Me	NO_2	Me_2	NO_2	Me	m.p. 66°		247

TABLE XII-28 (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	NO_2		Cl		m.p. 89–92°		240
Me	Cl		NO_2		m.p. 63–64°		239
Me	Br		NO_2		m.p. 89°		506
Et	Cl		NO_2		m.p. 71°		239,737
Ph	NO_2		Cl		m.p. 84–85°		240
p-ClC_6H_4	NO_2		Cl				240
2,5-$Cl_2C_6H_3$	NO_2		Cl		m.p. 120–21°		240
o-$NO_2C_6H_4$	NO_2		Cl		m.p. 141–42°		240
p-$NO_2C_6H_4$	NO_2		Cl		m.p. 105–6°		240
Ph	Cl		NO_2		m.p. 90°		239
o-$NO_2C_6H_4$	Cl		NO_2		m.p. 96–98°		239
m-$NO_2C_6H_4$	Cl		NO_2		m.p. 115–16°		239
p-$NO_2C_6H_4$	Cl		NO_2		m.p. 114–16°		239
m-ClC_6H_4	Cl		NO_2		m.p. 69–70°		239
p-ClC_6H_4	Cl		NO_2		m.p. 103–5°		239
2,5-$Cl_2C_6H_3$	Cl		NO_2				239
2,4,5-Cl_3-C_6H_2	Cl		NO_2				239
Et			NO_2	Br	m.p. 83–84°		647
Me	Br	Me	NO_2	Me	m.p. 90°		264
Pr			azoxy[a]		m.p. 97–98°		229
n-Hexyl				*n*-Bu	b.p. 72°/ 0.5 mm.		908
n-Heptyl				*n*-Amyl	b.p. 85°/ 0.5 mm.		908
n-Amyl				*i*-Hexyl	b.p. 98°/ 0.5 mm.		908
n-Amyl				*n*-Nonyl	b.p. 130°/ 0.5 mm.		908
n-Bu	Cl				b.p. 75°/ 2 mm.		865

[a]Bis substituted.

TABLE XII-29. Amino 2-Pyridinol Ethers 

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	NH_2				m.p. 68°; b.p. 116–18°/13 mm.	acetyl, m.p. 163°	380
Et	NH_2					picrate, m.p. 136–37°	653
						acetyl, m.p. 79°	653
2,4-$Cl_2C_6H_3$	NH_2					hydrochloride, m.p. 97–99°	232
Bu	2-(*N*-methylpyrrolidyl)					picrate, m.p. 124–26°	696
$CH_2CH_2NEt_2$	2-(*N*-methylpyrrolidyl)						696
$CH_2C(Me)_2NH_2$	2-(*N*-methylpyrrolidyl)					hydrochloride, m.p. 239° (dec.)	696
Ph	2-(*N*-methylpyrrolidyl)						696
CH_2Ph	2-(*N*-methylpyrrolidyl)						696

Me	NH_2	m.p. 92°	picrate, m.p. 170.5–2.8°	748
Et	NH_2	m.p. 88–89°		653,220
			picrate, m.p. 161–62°	653
			acetyl, m.p. 105°	653
Me	NH_2	m.p. 135–36°		233,218
		b.p. 135°/14 mm.		617,655, 229,232
			acetyl, m.p. 185°	810
			monopicrate, m.p. 160°	617
			dipicrate, m.p. 128°	617
Me	$NHCONH_2$	m.p. 185°		760
Me	2-COOH-5-ClC_6H_3NH	m.p. 208°		655
Me	*p*-$MeOC_6H_4NH$	m.p. 190–92°		655
Me	*p*-$NH_2C_6H_4SO_2NH$	m.p. 176–77°	acetyl, m.p. 194–95°	729

(*continued*)

TABLE XII-29. Amino 2-Pyridinol Ethers (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Et			NH_2		m.p. 67°; b.p. 123–24°		229,230
						acetyl, m.p. 122°	647,752, 277
						sulfanilamide, m.p. 207–8°	716
						propionyl, m.p. 95–96°	752
						butyryl, m.p. 91–92°	752
						benzoyl, m.p. 132–33°	
						or m.p. 152–53.	752
Et			NHCOCHOHMe		m.p. 111°		752
						acetyl, m.p. 101–2°	757
Et			$NHCOCH_2NEt_2$		m.p. 42–43°		752

Et	$NHCONH_2$	m.p. 95°		760
Et	NHCHOHPh	m.p. 128–29°	acetyl, m.p. 121–22°	757
Et	N=CMeNMePh	b.p. 170–72°/–0.075 mm.	picrate, m.p. 168–69°	755
Et	NHCMe=N(*p*-C_6H_4OEt)	m.p. 106°		754
Et	glucosylamine			811
n-Pr	NH_2	b.p. 145–47°/18 mm.		229
		b.p. 124–30°/1.3 mm.		230
			propionyl	752
i-Pr	NH_2	m.p. 77°		231
Allyl	NH_2	b.p. 112–16°/1.8 mm.		230,231
Allyl	glucosylamine	m.p. 156–57°		
n-Bu	NH_2	b.p. 156°/16 mm.		811 229

(*continued*)

TABLE XII-29. Amino 2-Pyridinol Ethers (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
					b.p. 146–47°/12 mm.		230,741
					b.p. 128–30°/2 mm.		655
						acetyl, m.p. 86°	662,752
						butyryl, m.p. 69–71°	662
						succinoyl, m.p. 148–49°	662
						p-aminobenzoyl, m.p. 144–46°	662
						p-tosyl, m.p. 73–75°	662
						sulfanilamido, m.p. 139–40°	662

			acetylsulfanilamido, m.p. 173–74°	662
n-Bu	NHC_4H_9	m.p. 51–52°; b.p. 155–56°/2.7 mm.		662
n-Bu	$N(CH_3)_2$	m.p. 73–75°; b.p. 205–6°/0.15 mm.		662
n-Bu	$NHCH_2CH_2OH$	b.p. 178–81°/3 mm.		662
n-Bu	$NHCH_2SO_2Na$	dec.		662
n-Bu	$NHCH_2SO_3Na$	dec.		662
n-Bu	$NHCH(CH_3)SO_3Na$	dec.		662
n-Bu	$N{=}CHC_6H_5$	m.p. 53.5–54.5°		662
n-Bu	$NHC_6H_{11}O_5$	m.p. 137–37.5°		655,66
n-Bu	$NHC_6H_{12}O_5(SO_3Na)$	dec.		662
n-Bu	$NHCOC_6H_4COOH$-*o*	m.p. 159–59.5°		662

(*continued*)

TABLE XII-29. Amino 2-Pyridinol Ethers (*continued*)

R	R_3	R_4	R_5	R_6	Physcial properties	Derivatives	Ref.
n-Bu			phthalimide		m.p. 164–64.5°		662
n-Bu			$NHCONH_2$		m.p. 153–54°		662
n-Bu			NHCONHPh		m.p. 142–44°		662
n-Bu			NHCSNHPh		m.p. 123.5–24°		662
n-Bu			$NHC{=}NH[(NH_2)]_2 \cdot H_2CO_3$		dec.		662
			$NHCH_2COOH$		m.p. 125–26°		662
n-Bu			$NHSO_3Na$		dec.		662
n-Bu			$NH(2\text{-}COOH\text{-}5\text{-}ClC_6H_3)$		m.p. 208°		665
n-Bu			glucosylamine		m.p. 137°		655
i-Bu			NH_2		b.p. 147–51°/15 mm.		230
s-Bu			NH_2		b.p. 117–28°		230
n-Am			NH_2		b.p. 117–20°		230
i-Am			NH_2		b.p. 100–7°		230

i-Am	glucosylamine	m.p. 124°	811
3-*n*-Am	NH_2	b.p. 126–28°/5 mm.	230
n-Hexyl	NH_2	b.p. 132–35°/1 mm.	230
n-Hexyl	glucosylamine	m.p. 132°	230
n-Heptyl	NH_2	b.p. 134–42°/1.5 mm.	230
n-Octyl	NH_2	b.p. 149–52°/1.5 mm.	230
n-Decyl	NH_2	b.p. 175–76°/1 mm.	230
$CH_2CH_2NEt_2$	NH_2		230,712
CH_2CH_2OH	NH_2	b.p. 147–57°/0.2 mm.; m.p. 64–68°	230
CH_2CH_2OMe	NH_2	b.p. 119–22°/0.2 mm.	230

(*continued*)

TABLE XII-29. Amino 2-Pyridinol Ethers (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
CH_2CH_2OMe			glucosylamine		m.p. 128–30°		811
CH_2CH_2OEt			NH_2		b.p. 137–38°/1 mm.		230
CH_2CH_2OBu-*n*			NH_2		b.p. 147–53°/0.3 mm.		230
CH_2CH_2OPh			NH_2		b.p. 187–90°/2 mm.		230
$CH_2CH_2OCH_2Ph$			NH_2		b.p. 168–74°/0.6 mm.		230
Ethoxy-ethoxyethyl			NH_2		b.p. 168–69°/1.5 mm.		230
Ph			NH_2		m.p. 70–72°		705,655
					b.p. 170–75°/1.7 mm.		230

Ph	2-COOH-5-ClC_6H_3NH	m.p. 186–88°		655
Ph	$NHCH_2CH_2NEt_2$	b.p. 202°/1 mm.		705
Ph	$NHCHMe(CH_2)_3NEt_2$	b.p. 213°/1 mm.		705
o-MeC_6H_4	NH_2	b.p. 155–60°/1.5 mm.		230
β-Naphthyl	NH_2	m.p. 91–93°		230
o-ClC_6H_4	NH_2		hydrochloride, m.p. 211–12°	232
m-ClC_6H_4	NH_2		hydrochloride, m.p. 182–84°	232
p-ClC_6H_4	NH_2		hydrochloride, m.p. 90–92°	232
2,4-$Cl_2C_6H_3$	NH_2		hydrochloride, m.p. 114–15°	232
2,5-$Cl_2C_6H_3$	NH_2		hydrochloride, m.p. 101–3°	232

(*continued*)

TABLE XII-29. Amino 2-Pyridinol Ethers (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
2,6-$Cl_2C_6H_3$			NH_2			hydrochloride, m.p. 127-29°	232
3,4-$Cl_2C_6H_3$			NH_2			hydrochloride, m.p. 79-81°	232
3,5-$Cl_2C_6H_3$			NH_2			hydrochloride, m.p. 90-92°	232
2,3,6-$Cl_3C_6H_2$			NH_2			hydrochloride, m.p. 99-101°	232
2,4,5-$Cl_3C_6H_2$			NH_2			hydrochloride, m.p. 93-94°	232
2,4,6-$Cl_3C_6H_2$			NH_2			hydrochloride, m.p. 119-21°	232
3,4,5-$Cl_3C_6H_2$			NH_2			hydrochloride, m.p. 107-9°	232
2-Cl-4-$NH_2C_6H_3$			NH_2			hydrochloride, m.p. 173-75°	232

p-$NO_2C_6H_4$	NH_2	m.p. 114–16°		566,230
			acetyl, m.p. 138–39°	566
p-$NH_2C_6H_4$	NH_2	m.p. 127–29°		566,230
			dihydrochloride · ½ H_2O, m.p. 250° (dec.)	463
			diacetyl, m.p. 185–87°	566
o-$NH_2C_6H_4$	NH_2	b.p. 211°/1 mm.		705
o-$C_6H_4NH(CH_2)_2NEt_2$	$NHCH_2CH_2NEt_2$	b.p. 249°/1 mm.		705
CH_2Ph	NH_2	m.p. 46–48°		655
		b.p. 170–74°/2.5 mm.		230
CH_2Ph	2-$COOHC_6H_4NH$	m.p. 178–80°		655
CH_2Ph	2-COOH-5-ClC_6H_3NH	m.p. 188–90°		655

(*continued*)

TABLE XII-29. Amino 2-Pyridinol Ethers (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
CH_2Ph			2-COOH-4-ClC_6H_3NH		m.p. 222°		655
2-Pyridyl			NH_2		m.p. 104–5°		230
2-Pyridylethyl			NH_2			dihydrochloride, m.p. 187–89°	230
Tetrahydrofurfuryl			NH_2		b.p. 164–66°/2 mm.		230
Cyclohexyl			NH_2		b.p. 146–54°/3 mm.		230
Cyclohexyl			NHCOCHOHMe		m.p. 155–56°		752
Me			CH_2NH_2			hydrochloride, m.p. 216–18°	386
Me			CH_2NH_2			hydrochloride, m.p. 216–18°	386
n-Bu			CH_2NH_2			dihydrochloride, m.p. 228°	386

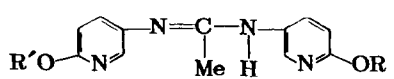
(–)-Menthoxy		2-(*N*-methylpyrrolidyl)			picrate, m.p. 118°	696
Me			NH_2	b.p. 118–20°/21 mm.	picrate, m.p. 213–14°	609
Me			$NHSO_2C_6H_4NH_2$	m.p. 145–48°	acetyl, m.p. 170–71°	729 216
Et			NH_2	b.p. 238°	picrate, m.p. 224° acetyl, m.p. 136–37°	653 653,216
Et			1-Py	b.p. 170°/22 mm.	picrate, m.p. 121–22°	142,276
$CH_2CH_2NEt_2$			NH_2	b.p. 133–35°/4 mm.	m.p. 157–59°	728
Me	Me	NH_2		m.p. 97°		655
Me	Me	2-COOH-5-ClC_6H_3NH		m.p. 250–52°		655
Me		NH_2	Me	b.p. 97°/1 mm	acetyl, m.p. 130–31°	655

(*continued*)

TABLE XII-29. Amino 2-Pyridinol Ethers (*continued*)

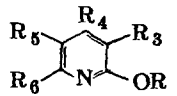
R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me			2-COOH-5-ClC_6H_3NH		m.p. 228–30°		655
Ph			NH_2	Me	m.p. 112–14°		236
p-ClC_6H_4			NH_2	Me	m.p. 77–78°		236
2,5-$Cl_2C_6H_3$			NH_2	Me	m.p. 225°		236
Me	CH_2NH_2	Me		Me	b.p. 88–92°/0.5 mm.	picrate, m.p. 231°	747
Ph	NH_2		Cl		m.p. 131–32°		240
2,5-$Cl_2C_6H_3$	NH_2		Cl		m.p. 128–31°		240
p-$NH_2C_6H_4$	NH_2		Cl		m.p. 204°		240
Ph	Cl		NH_2		m.p. 127–28°		239
o-$NH_2C_6H_4$	Cl		NH_2		m.p. 137–39°		239
m-$NH_2C_6H_4$	Cl		NH_2		m.p. 163–65°		239

p-$NH_2C_6H_4$	Cl	NH_2		m.p. 119–20°		239
m-ClC_6H_4	Cl	NH_2		m.p. 80–83°		239
p-ClC_6H_4	Cl	NH_2		m.p. 95–97°		239
2,5-$Cl_2C_6H_3$	Cl	NH_2		m.p. 140–42°		239
2,4,5-$Cl_3C_6H_2$	Cl	NH_2		m.p. 128–32°		239
Et		NH_2	Cl	m.p. 94–95°	picrate, m.p. 118–19°	647
Et		NH_2	Br	m.p. 75°	acetyl, m.p. 128–29°	647



R	R′	Physical properties	Derivatives	Ref.
Et	*n*-Bu	m.p. 91–92°		754
n-Bu	*n*-Bu	m.p. 63–65°	hydrochloride, m.p. 209–10°	754
Et	*n*-Bu	b.p. 210–15°/0.025 mm.		754

TABLE XII-30. Ethers of 2-Pyridinol Carboxylic Acids and Nitriles



R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	COOH					amide, m.p. 130–31°	685
Ph	COOH				m.p. 179–80°		663
$CH_2CH_2NH_2$	CONHPh					hydrochloride, m.p. 203°	738
$CH_2CH_2NMe_2$	CONHPh					hydrochloride, m.p. 204°	738,242
$CH_2CH_2NEt_2$	CONHEt					hydrochloride, m.p. 142°	242
$CH_2CH_2NEt_2$	CONHPh					hydrochloride, m.p. 172°	738,242
$CH_2CH_2NEt_2$	CONEtPh					hydrochloride, m.p. 142°	738
$CH_2CH_2NEt_2$	$COO(CH_2)_2NEt_2$					dihydrochloride, m.p. 180°	738
$CH_2CH_2NEt_2$	$CONH(CH_2)_2NEt_2$					dihydrochloride, m.p. 195°	242,738
$CH_2CH_2NEt_2$	$CONEt_2$					hydrochloride, m.p. 184°	738
$CH_2CH_2NEt_2$	$CONHC_6H_4OEt$-*p*				m.p. 63°	hydrochloride, m.p. 163°	738

$CH_2CH_2N(n\text{-}Bu)_2$	CONHPh				hydrochloride, m.p. 123°	738,242
Piperidylethyl	CONHPh				hydrochloride, m.p. 198°	738,242
$(CH_2)_2NH(CH_2)_2OH$	CONHPh				picrate, m.p. 206–8°	738
$—(CH_2)_2NH(CH_2)_2—$ [a]	COOH				benzamide, m.p. 133°	738
Me		COOH			Me ester, m.p. 33–35°	724,100
					hydrazide, m.p. 136–37°	217
Et		COOH			Me ester, b.p. 107–10°/13 mm.	100
					hydrazide, m.p. 152°	217
n-Pr		COOH		m.p. 126–27°	acid chloride, b.p. 117–18°/30 mm.	206
n-Bu		COOH		m.p. 124°	acid chloride, b.p. 127°/10 mm.	206
Me			COOH	m.p. 173°		812
					Et ester, m.p. 71°	119

(*continued*)

TABLE XII-30. Ethers of 2-Pyridinol Carboxylic Acids and Nitriles (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Et			COOH		m.p. 183°		813
n-Pr			COOH		m.p. 116–17°		453
n-Bu			COOH			amide, m.p. 150–51°	241
						N-Et amide, m.p. 78–79°	737
$(CH_2)_2NEt_2$			COOH			anilide, m.p. 76–77°	738
Me			C=NH(NH_2)			hydrochloride, m.p. 278–80°	386
						benzoyl, m.p. 253°	386
						acetyl, m.p. 246–48°	386
n-Bu			C=NH(NH_2)			hydrochloride, H_2O, m.p. 95°	386
						benzoyl, m.p. 228°	386
Me		COOMe		Et		picrate, m.p. 133–35°	206
Et		COOH		Me		Et ester, b.p. 104–5°/2.5 mm.	244

2-Ketocyclohexyl			COOEt	Me	m.p. 100–1°		244
Me	COOMe	Me		Me	m.p. 57–58°		66
Me			COOH	COOH	m.p. 140° (dec.)		814
Me		COOH		Cl		Me ester, m.p. 102–4°	100
						hydrazide, m.p. 196°	217
Et		COOH		Cl	m.p. 163–65°	Me ester	100
						hydrazide, m.p. 192°	217
n-Pr		COOH		Cl		hydrazide, m.p. 152°	217
Allyl		COOH		Cl		hydrazide, m.p. 126–30°	100
						acid chloride, b.p. 93°/0.8 mm.	100
i-Pr		COOH		Cl		hydrazide, m.p. 171°	217
n-Bu		COOH		Cl		hydrazide, m.p. 159°	217
i-Am		COOH		Cl		hydrazide, m.p. 138°	217
Ph		COOH		Cl		hydrazide, m.p. 171°	217

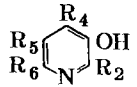
(*continued*)

TABLE XII-30. Ethers of 2-Pyridinol Carboxylic Acids and Nitriles (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me			Cl	COOH	m.p. 98–100°		655
Me			NH_2	COOH		acetyl, m.p. 186–88°	655
Me			NHC_6H_4-(*p*-OMe)	COOH	m.p. 108–9°		655
Me	CN				m.p. 75–77°		685
Me			CN		m.p. 94°		386
n-Bu			CN		m.p. 24°; b.p. 140–50°/15 mm.		386
Me	CN			Me	m.p. 81°; b.p. 184°/5 mm.		245

Me	CN	Me		Me	m.p. 93.5–95.0°	746,747
Me	CN	Ph		Ph	m.p. 70–72°	19
Et	CN	Ph		Ph	m.p. 112°	19
Me	CN		Me	Me	b.p. 141–42°/12 mm.	746
Et	CN		NO_2		m.p. 62.5–63.0°	63
Me	CN		NO_2	Me	m.p. 63°	247
Me	CN	Me	NO_2	Me	m.p. 84°	247
Et	CN	Me	NO_2	Me	m.p. 46°	247
Me	CN	—$(CH_2)_3$—			m.p. 114°	830
Me	CN	—$(CH_2)_4$—			m.p. 106°	830
Me	CN	—$(CH_2)_5$—			m.p. 82–84°	830

[a]Symmetrical bis compound.

TABLE XII-31. Alkyl and Aryl 3-Pyridinols 

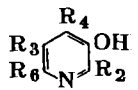
R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
				m.p. 129°	oxalate, m.p. 115°	320,426
Me				m.p. 168.6–68.8°		176,174,581, 584,179, 914
					picrate, m.p. 201.6–1.8°	176,174,836
					hydrochloride, m.p. 225–27°	179
					hydrobromide, m.p. 195–97°	584
					chloroplatinate, m.p. 160–63°	176
	Me			m.p. 118–20°		316,850,867
					acetyl, b.p. 97–98°/4.5 mm.	850
					butyryl, b.p. 109–10°/2.5 mm.	850
					butyryl picrate, m.p. 111–14°	850
					picrate, m.p. 203–5°	867
					mercurichloride, m.p. 156.5–58.0°	867
					mononitro, m.p. 90–92°	551
		Me		m.p. 136–37°		319,867
				m.p. 134–36°; b.p. 153°/5 mm.	picrate, m.p. 187–88°	102,867
					mercurichloride, m.p. 167.5–69.0°	867
					acetyl, m.p. 147.5–49.0°	867
			Me	m.p. 167–69°	acetyl picrate, m.p. 146–47°	430,317,281, 290
					dimethyl carbamate, b.p. 98°/0.45 mm.	468
					picrate, m.p. 203°	700

Et			m.p. 134.6–35.2°	picrate, m.p. 171.7–72.3°	176,174
Pr			m.p. 133–35°		176
		Pr	m.p. 93.0–93.5°		317,297
				p-ClC_6H_4 methyl carbamate, b.p. 182–85°/2.5 mm.	468
i-Pr			m.p. 191–92°		176
		i-Pr	m.p. 155–57°		181
n-Bu			m.p. 127–29°		176
s-Bu			m.p. 157–59°		176
		s-Bu	m.p. 96–98°	3,5-dinitro, m.p. 133–35°	237
t-Bu			m.p. 199–201°		176
C_6H_5			m.p. 206–7.5°		174,173,886
				picrate, m.p. 201.0–1.4°	174
p-$CH_3C_6H_4$			m.p. 199–200°		173
p-$(CH_3O)C_6H_4$			m.p. 186°		173
p-ClC_6H_4			m.p. 225–26°		173
3,4-$Cl_2C_6H_3$			m.p. 249–50°		173
CH_2Ph			m.p. 189–91°		176
3-Dibenzofuranyl			m.p. 233°		175
2-Carbazolyl			m.p. 249–50°		175
3-(2-Methylindolyl)			m.p. 221°		175
Me	Me		m.p. 144–46°	picrate, m.p. 242–43°	730
				dimethyl carbamate, b.p. 78–79°/0.15 mm.	468

(*continued*)

TABLE XII-31. Alkyl and Aryl 3-Pyridinols (*continued*)

R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me			Me	m.p. 209°		174,584,292
					picrate, m.p. 204.5–4.9°	174
					hydrobromide, m.p. 183–85°	584
Me		Et		m.p. 170–73°		316
					mononitro, m.p. 163–65°	551
Et			Me	m.p. 170–72°		176
Me	Me	Me		m.p. 178°	hydrochloride, m.p. 216°	713
					dimethyl carbamate, b.p. 109–12°/0.5 mm.	468
Me	Me		Me	m.p. 137°	dimethyl carbamate, b.p. 92–93°/0.2 mm.	292,468
	—$(CH_2)_6$—			m.p. 198–200°		857
	Me	Ph		m.p. 197–98°		839
					p-tosyl, m.p. 71–72°	840
					p-tosyl picrate, m.p. 170–71°	840
					acetate, m.p. 147°	840
		Me	cyclo-hexyl	m.p. 223–25°		840

TABLE XII-32. Halo, Nitro, and Alkoxy 3-Pyridinols 

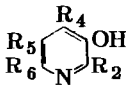
R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Cl				m.p. 166–67°		431,266,380,468
					benzoyl, m.p. 53–55°	431
					hydrochloride, m.p. 208° (dec.)	207
					acetyl	431
					dimethyl carbamate, m.p. 99–100°	468
Br				m.p. 186.5–87.0°	hydrobromide, 360° (dec.)	264
	Br			m.p. 123.5–24.0°		496
		Br		m.p. 166.5–67.5°		496,291
			Br	m.p. 135.5–36.5°		496
I				m.p. 195–96°		558,429,380,869
					benzoyl, m.p. 90–91°	431
					methyl carbamate, m.p. 111.0–14.5°	468
					dimethyl carbamate, b.p. 114°/0.5 mm.	468
CH_2Br					hydrobromide, m.p. 186–88°	584,294
Cl			Me	m.p. 194–96°		281

(*continued*)

TABLE XII-32. Halo, Nitro, and Alkoxy 3-Pyridinols (*continued*)

R_2	R_4	R_5	R_6	Physical Properties	Derivatives	Ref.
Me			Cl	m.p. 208°		281
CH_2Br			Me		hydrobromide, m.p. 224°	581
Br			Br	m.p. 162–63°		496
CH_2Br			CH_2Br		hydrobromide, m.p. 188–90°	584
	Br		Br (?)	m.p. 190–91°		496
I			I	m.p. 200–1°	acetyl, m.p. 120.5–21.5°	721
I		(I ?)		m.p. 194–96°		380
					dimethyl carbamate, m.p. 90.5–92.0°	468
I		Me	I	m.p. 217–18.5°		867
Me	Me	CH_2Cl			hydrochloride, m.p. 220–25° (dec.)	745
Br	Br		Br	m.p. 90.5–91.0°	hydrazine salt, m.p. 179.0–79.5°	496

Br	Br	Br	Br	m.p. 146.5–47.5°		496
NO_2				m.p. 67–68°		553,555
					dimethyl carbamate, m.p. 189–92°	468
OMe				m.p. 68°		380,468
				m.p. 65.0–65.5°	picrate, m.p. 155.5–56.0°	609
					dimethyl carbamate, m.p. 58°	468
			OMe	m.p. 81°		617
OMe	Br		Br	m.p. 86–87°		496
			—N=$NC_6H_4NO_2$-*p*	m.p. 231–32°		842
—N=$NC_6H_4NO_2$-*p*				m.p. 234–35°		842
—N=$NC_6H_4NO_2$-*p*	Me	Ph		m.p. 230–35°		842
	Me	Ph	—N=$NC_6H_4NO_2$-*p*	m.p. 261–69° (dec.)		842

TABLE XII-33. Amino 3-Pyridinols 

R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
NH_2				m.p. 169–70°		553
					picrate, m.p. 257°	555,429
					N-benzoyl, m.p. 95–96°	842
					N-benzoyl picrate, m.p. 237–38°	842
					N,N,O-tribenzoyl, m.p. 169–70	842
		NH_2		m.p. 158–60°		291
CH_2NHMe					dihydrochloride, m.p. 226–30°	584
					dimethylamide · 2HCl, m.p. 140–41°	469
CH_2NMe_2				m.p. 56–59°		584
				b.p. 95–96°/ 8 mm.	dihydrochloride, m.p. 178–86°	584
					dimethylamide · HCl, m.p. 128–30°	469
					dimethylamide · 2HCl, m.p. 164–67°	469
					di(*i*-Pr)amide · 2HCl, m.p. 116–18°	469

$CH_2NMe_3^+Br^-$		dimethylamide, m.p. 175–77°	469
		(p-BrC_6H_4)methylamide, m.p. 176–78°	469
		(p-MeC_6H_4)methylamide, m.p. 153–55°	469
		di(i-Pr)amide, m.p. 173–75°	469
		acetyl, m.p. 166–67°	469
		benzoyl, m.p. 191–93°	469
		diphenyl acetyl, m.p. 186–87°	469
CH_2NEt_2	b.p. 85–92°/ 1 mm.	dihydrochloride, m.p. 195–97°	
		methylbromide, m.p. 132–33°(dec.)	584
		dimethyl amide · 2HCl, m.p. 117–19°	469
		phenylmethylamide · 2HCl, m.p. 142–44°	469
$CH_2NEt_2Me^+Br^-$		dimethylamide, m.p. 141–43°	469
$CH_2NEt_3^+Br^-$		dimethylamide, m.p. 166–69°	469
$CH_2N(n\text{-}Pr)_2$	b.p. 103–5°/ 1 mm.	dihydrochloride, m.p. 164–68°	584

(*continued*)

TABLE XII-33. Amino 3-Pyridinols (*continued*)

R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
$CH_2N(n\text{-}Pr)_2Me^+ Br^-$					dimethylamide, m.p. 110–13°	469
$CH_2N(i\text{-}Pr)_2$				b.p. 98–101°/ 1.2 mm.	dihydrochloride, m.p. 173–76°	469
			NH_2	m.p. 116–17°	hydrochloride, m.p. 125–26°	842
					picrate, m.p. 225–27°	842
					N-benzoyl, m.p. 181–82°	842
					N,O-dibenzoyl, m.p. 180–82°	842
					N,N,O-tribenzoyl, m.p. 179–83°	842
$CH_2N(i\text{-}Pr)_2Me^+ Br^-$					dimethylamide, m.p. 159–61°	469
$CH_2N(n\text{-}Bu)_2$				b.p. 112–114°/ 1.4 mm.		584
$CH_2N(n\text{-}Bu)_2Me^+ Br^-$					dimethylamide, m.p. 154–55°	469
CH_2NMePh				m.p. 136–38°		584
					dihydrochloride, m.p. 135–37°	469
CH_2NHCH_2Ph					dihydrochloride, m.p. 236–41°	469

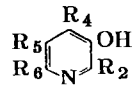
$CH_2N(Me)CH_2Ph$			b.p. 135–37°/ 0.7 mm.	dihydrochloride, m.p. 210–12°	584
				dimethylamide, m.p. 167–69°	469
$CH_2N(CH_2Ph)_2Me^+Br^-$				dimethylamide, m.p. 177–79°	469
$CH_2N(Ph)CH_2CH_2NMe_2$				dihydrochloride, m.p. 185–87°	469
$CH_2N(Ph)CH_2CH_2NEt_2Me^+Br^-$				dimethylamide, m.p. 172–74°	469
Piperidinomethyl ($CH_2NC_5H_{10}$)			b.p. 151–56°/ 14 mm.	dihydrochloride, m.p. 201–3°	584,469
				dimethylamide · 2HCl, m.p. 111–13°	469
$CH_2NC_5H_{10}(Me)^+Br^-$				dimethylamide, m.p. 156–57°	469
Morpholinomethyl			b.p. 163–67/ 12 mm.	dihydrochloride, m.p. 206–11°	584
Me	CH_2NH_2			hydrochloride, m.p. 268–70° (dec.)	59
				benzoyl, m.p. 242–43°	59
				N-acetyl-*O*-benzoyl, m.p. 141–42°	59
Me		CH_2NEt_2	m.p. 139–41°	acetyl, b.p. 111–15°/1.4 mm.	584

(*continued*)

TABLE XII-33. Amino 3-Pyridinols

R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
CH_2NHMe			Me		dihydrochloride, m.p. 226–30°	584
CH_2NMe_2			Me	b.p. 121–25°/ 13 mm.	dihydrochloride, m.p. 202–6°	584
				b.p. 75–76°/ 0.5 mm.	monohydrochloride, m.p. 223–24°	585
CH_2NEt_2			Me	b.p. 100.0–.5°/3 mm.	dihydrochloride, m.p. 211.0–11.5°	318
$CH_2N(n\text{-}Bu)_2$			Me	b.p. 134–36°/ 3 mm.		318
CH_2NMeCH_2Ph			Me	b.p. 157–60°/ 2.7 mm.	dihydrochloride, m.p. 196–98°	584
Piperidinomethyl			Me	b.p. 145–47°/ 7 mm.	dihydrochloride, m.p. 250–52° (dec.)	318
Me	Me	CH_2NMeCH_2-CH_2Cl			dihydrochloride, m.p. 211–14° (dec.)	745
Me	Me	CH_2NEtCH_2-CH_2OH			dihydrochloride, m.p. 220–223 (dec.)	745
Me	Me	$CH_2N(CH_2$-CH_2Cl_2			dihydrochloride, m.p. 201–40° (dec.)	745

Me	Me	$CH_2N(CH_2CH_2OH)_2$			dihydrochloride, m.p. 183–87°	745
Me	CH_2NH_2	CH_2NH_2			trihydrochloride · $3H_2O$, m.p. > 280° (dec.)	45
Ph	CH_2NH_2	CH_2NH_2			trihydrochloride, m.p. 198° (dec.)	47
					trihydrobromide	47
CH_2PH	CH_2NH_2	CH_2NH_2			trihydrobromide · $2H_2O$,	46
NH_2	Me	Ph		m.p. 210° (dec.)	picrate, m.p. 260° (dec.)	842
					N-benzoyl picrate, m.p. 213°	842
					N,O-dibenzoyl, m.p. 195–96°	842
					N,N,O-tribenzoyl, m.p. 182°	842
NO	Me	Ph	NH_2	m.p. 72–80°		842
	Me	Ph	NH_2	m.p. 190–95° (dec.)	*N*-benzoyl, m.p. 216–17°	842
					N,O-dibenzoyl, m.p. 199–200°	842

TABLE XII-34. 3-Pyridinol Carboxylic Acids and Derivatives 

R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
COOH				m.p. 215°		294,905
					mercurichloride, m.p. > 220° (dec.)	429
					picrate, m.p. 158.5–62°	429
					Me ester, m. p. 73–74°	294,429
					Et ester, b.p. 124°/15 mm.	429
					amide, m.p. 193–94°	906
	COOH			m.p. 312° (dec.)		295,243,764
					Me ester, m.p. 78.5–80.5°	296
					acetyl, m.p. 226° (dec.)	296
		COOH		m.p. 299° (dec.)		284
			COOH	m.p. 269–70° (dec.)		321
				m.p. 258–59°		765,700,915
					Me ester, m.p. 191–92°	483
					Me ester, m.p. 71.5–73.0°	721
$(CH_2)_2COOH$				m.p. 189–91°		177
$(CH_2)_7COOH$				m.p. 87–89°		177
COOH			Me	m.p. 228° (dec.)		581
		COOH	Me		Et ester, m.p. 163–64.5°	298
Me			$(CH_2)_2COOH$		Et ester, m.p. 70–72°	177

					Et ester · hydrochloride, m.p. 156–58°	177
					amide hydrochloride, m.p. 232–35° (dec.)	177
Me			COOH	m.p. 246–47° (dec.)		836
COOH		Me		m.p. 230–30.5°		837
$(CH_2)_3COOH$			Me	m.p. 174–76°		177
Me			$(CH_2)_7COOH$	m.p. 110–11°	Et ester, m.p. 80–82°	177,836
					hydrochloride, m.p. 88–89°	177
					amide hydrochloride, m.p. 96–98°	177
					Me ester, m.p. 125–26°	836
$(CH_2)_7COOH$			Me	m.p. 76–78°	Et ester, m.p. 51–53°	177
					Et ester hydrochloride, m.p. 112–14°	177
COOH			COOH	m.p. 222° (dec.), remelt 250°		721
	COOH	COOH		m.p. 243–44° (dec.)	monohydrate, m.p. 237–38°	293
Me	COOH	COOH		m.p. 258–59°		49
					monomethyl ester	912
					diamide, m.p. > 250° (dec.)	45
					diethyl ester · hydrochloride, m.p. 144–45°	45

(*continued*)

TABLE XII-34. 3-Pyridinol Carboxylic Acids and Derivatives (*continued*)

R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	COOMe	COOMe		m.p. 138–40°	hydrochloride, m.p. 165–68°	45
					tosyl, m.p. 99–100°	45
i-Pr	COOMe	COOMe		m.p. 68°	$PhCH_2Cl$, m.p. 146° (dec.)	47
i-Bu	COOMe	COOMe			$PhCH_2Cl$, m.p. 130° (dec.)	47
Ph	COOMe	COOMe		m.p. 244°	$PhCH_2Cl$, m.p. 165°	47
CH_2Ph	COOH	COOH		m.p. 241°	dimethyl ester · hydrochloride, m.p. 148–50° (dec.)	46
Me		COOH	COOH		dimethyl ester, m.p. 157.0–57.5°	391
Me	COOH	CH_2NH_2		m.p. 340–60° (dec.)	lactum, m.p. 360° (dec.)	300
Me	COOH	COOH	COOH	m.p. 204–6° (dec.)		299
Me	CN	CH_2Cl		m.p. 167–68°		694
Me	Me	CN	Cl		acetyl, m.p. 46–47°	84
Me	COOH	COOH	Cl	m.p. 215–16° (dec.)		912

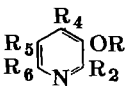
TABLE XII-35. 3-Pyridinol Esters 

R	Physical properties	Derivatives	Ref.
MeCO	b.p. 43–44°/0.21 mm.		468
	b.p. 92°/9 mm.	picrate, m.p. 155.5–57.0°	429
		mercurichloride, m.p. 148.9°	429
PhCO	m.p. 50.0–50.5°		429,526
		picrate, m.p. 152–53°	429
		mercurichloride, m.p. 168–70°	429
3,4,5-$(HO)_3$-C_6H_2CO	m.p. 180–85°		526
3,4,5-$(PhCH_2O)_3$-C_6H_2CO	m.p. 120°		526
Ph_2CHCO	b.p. 188–90°/0.5 mm.	hydrochloride, m.p. 151–52°	510
		methiodide, m.p. 126–28°	510
MeNHCO			468
Me_2NCO	b.p. 90°/0.25 mm.		468,470
		hydrochloride, m.p. 89°	751
Et_2NCO	b.p. 82–84°/0.1 mm.		468
PhNHCO	m.p. 43–45°		470
$PhCH_2N(Me)CO$	b.p. 152–54°/0.3 mm.		468
$(PhCH_2)_2NCO$	b.p. 182–85°/0.15 mm.		468
p-ClC_6H_4NMeCO	b.p. 186–88°/2 mm.		468
Ph_2NCO	m.p. 112–14°		468
Pyrrolidyl-CO	m.p. 64–66°		468
Morpholinyl-CO	m.p. 71–73°		468
p-$NH_2C_6H_4SO_2$	m.p. 178.5–79.0°		471
p-$MeC_6H_4SO_2$	m.p. 80°		365,527
	b.p. 170–72°/6 mm.		365
Me_2NSO_2	b.p. 116.5–118°/1 mm.		468
$PO(OEt)_2$	b.p. 82°/5.8×10^{-6} mm.		472

(*continued*)

TABLE XII-35. 3-Pyridinol Esters (*continued*)

R	Physical properties	Derivatives	Ref.
$PO(O\text{-}i\text{-}Pr)_2$	b.p. 84°/1.5 × 10^{-4} mm.		472
$PO(OEt)NEt_2$	b.p. 87°/4 × 10^{-3} mm.		472
$PO(Et)NEt_2$	b.p. 98°/2.8 × 10^{-4} mm.		472

TABLE XII-36. Ethers of 3-Pyridinol and Its Substitution Products 

R	R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
CH_3					b.p. 178–79°		409,207,429, 900
						mercurichloride, m.p. 110–11°	429
						chloroplatinate, m.p. 182°	409,900
						m.p. 269°	207
						hydrochloride, m.p. 160–61°	900
						picrate, m.p. 136–39°	900
						mercurichloride, m.p. 193–95°	900
Et					b.p. 78–80°/15 mm.		264
					b.p. 200°		213,426
						chloroplatinate, m.p. 192°	213
Ph					b.p. 147–49°/17 mm.		203
						hydrochloride, m.p. 95–97°	429

(continued)

TABLE XII-36.. Ethers of 3-Pyridinol (*continued*)

R	R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
						picrate, m.p. m.p. 130–32°	567,429
						mercurichloride, m.p. 76–77.5°	429
p-$NO_2C_6H_4$					m.p. 108–10°		567
2,4-$(NO_2)_2C_6H_3$					m.p. 129–32°		567
$PhCH_2$					b.p. 114°/0.6 mm.	picrate, m.p. 118–20°	45
Me				Me	b.p. 188–89°; 43–45°/1 mm.	picrate, m.p. 138–40°	317,430
Me	Ph				b.p. 110–12°/0.34 mm.	picrate, m.p. 153.5–55°	886
Me		Me	Ph		m.p. 152–55°	picrate, m.p. 136–37°	841
Me		Me			m.p. 149.5–50.5°		867
Me				*n*-Pr	b.p. 60–61°/0.7 mm.	picrate, m.p. 113–14°	317
Et				Me	b.p. 83°/9 mm.	picrate, m.p. 137–39°	430
Et				styryl	m.p. 70–72°	picrate, m.p. 215–17°	430
Me	I				m.p. 56–57°	hydrochloride, m.p. 154–55° (dec.)	431

					benzyl iodide, m.p. 175–76° (dec.)	431
Me		Br		m.p. 32–33°	picrate, m.p. 159–60°	215
Me			Br	b.p. 113°/59 mm.		267
Et	Br			b.p. 257–59°(dec.)		207
					hydrobromide, m.p. 185° (dec.)	207,264
Et		Br		b.p. 119–20°/20 mm.	picrate, m.p. 153–54°	214
Et			Br	m.p. 49–49.5°		458
				b.p. 107°/33 mm.		267
i-Pr			Br	b.p. 11–13°/28 mm.		267
n-Bu			Br	b.p. 113–14°/35 mm.		267
Me			$(CH_2)_6Cl$	b.p. 154°/2.5 mm.		582
Me	I		I	m.p. 100–1°		721
Et	I		I	m.p. 96–98°		303
Et	Cl	Br	Cl	m.p. 77–78°		266
Et	Br	Br	Br	m.p. 86–87°		266
Me	NO_2			m.p. 74–74.5°		215,554
Et	NO_2			m.p. 31–32°		207,264,555
Me	NO_2		NO_2	m.p. 114–15°		554
Me	NO_2	Br		m.p. 111.5–12.0°		215
Et	Br		NO_2	m.p. 112.5–13.5°		264

(*continued*)

TABLE XII-36. Ethers of 3-Pyridinol (*continued*)

R	R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	NO_2		Br	NO_2	m.p. 103.5-4.5°		215
Et				azo[a]	m.p. 187.5°		264
Me		NH_2			m.p. 94.5-95.5°	picrate, m.p. 201-3°	748
						acetyl, m.p. 128-29°	748
Et	NH_2				m.p. 84.5-85.5°		653,207
						acetyl, m.p. 73.5-75.5°	653
						picrate, m.p. 235-36°	653
						sulfanilamide, m.p. 198-200°	716
Et	NH_2					acetyl, m.p. 112.5-13.5°	653
						picrate, m.p. 194-95°	653
2,4-$(NO_2)_2C_6H_3I$					m.p. 143-44°		869
Et			NH_2		m.p. 22-23°	acetyl, m.p. 143-43.5°	214
					b.p. 159-62°/18 mm.	picrate, m.p. 189-90°	214
Et				NH_2	m.p. 50-50.5°		264

						hydrochloride, m.p. 143–45°	842
						acetyl, m.p. 113–14°	264,653,842
						picrate, m.p. 239–40°	264,653,842
Me	NH_2			NH_2		diacetyl, m.p. 173.5–74.5°	554
Me	Me	CH_2NH_2	CH_2NH_2			trihydrochloride, $\frac{1}{2}H_2O$, m.p. 200° (dec.)	45
						trihydrobromide, ca. 280° (dec.)	45
Me	CH_2Ph	CH_2NH_2	CH_2NH_2			trihydrochloride · H_2O, m.p. 193°	46
Me	NH_2		Br		m.p. 84.5–85°	acetyl, m.p. 113.5–4.5°	215
						picrate, m.p. 235–36°	215
Me		Cl		NH_2	m.p. 99–100°		744
Et	NH_2		Br		m.p. 96.5–97.0°		215
Me				COOH		Et ester, m.p. 33–34°	915
Et	NH_2			NO_2	m.p. 162.5–63.0°		647
Me	COOH			Me	m.p. 104°		581

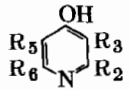
(continued)

TABLE XII-36. Ethers of 3-Pyridinol (*continued*)

R	R_2	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	Me	COOH	COOH		m.p. 213–15°		756,701,188
						anhydride, m.p. 67°	711,701,188
						imide, m.p. 238–41°	711
						diamide, m.p. 210° (dec.)	47,711
						dimethyl ester, m.p. 40–41°; b.p. 114–16°/ 0.5 mm.	45,711
Me	Ph	COOH	COOH			diamide, m.p. 224° (dec.)	47
Me	CH_2Ph	COOH	COOH			diamide, m.p. 194°/(dec.)	46
CH_2Ph	Me	COOH	COOH			dimethyl ester, m.p. 68°	45
						diethyl ester, m.p. 48–49°	45

						diamide, m.p. 194° (dec.)	45
CH_2Ph	CH_2Ph	COOH	COOH			dimethyl ester, m.p. 78°	46 188
Me	Me	COOH	COOH	COOH	m.p. 205–15° (dec.)		
Me	Me			COOH	m.p. 172–74°		836
Me	Me			$(CH_2)_7COOH$		hydrochloride, m.p. 134–36°	830
Me		Cl		COOH	m.p. 209°		483,149
						acid chloride	483
						Me ester, m.p. 166–67°	483,149
						Et ester, m.p. 140°, 149°	149,915
						amide, m.p. 207–8°	149
Me	Me	CN	CN		m.p. 78°		45
Me	Ph	CN	CN		m.p. 128°		47
Me	CH_2Ph	CN	CN		m.p. 64°		46
CH_2Ph	Me	CN	CN		m.p. 96°		45

[a]Symmetrical.

TABLE XII-37. 4-Pyridinols 

R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
				ALKYL AND ARYL		
				m.p. 148°		766,243,326,325, 507
					p-tosyl, m.p. > 70° (dec.)	527
					acetyl, m.p. 140–50°	507
					nitrate, m.p. 190°	
					benzoyl, m.p. 81°	526,507
					monohydrate, m.p. 65–66°	325
					oxalate, m.p. 218–19°	369
					picrate, m.p. 238–39°	369
					picrate, m.p. 375°	324
	Me			m.p. 97–98°	picrate, m.p. 206–7°	289
Ph					½ hydrate, m.p. 155°	148
					chloroplatinate, m.p. 213°	154
Me		Me		m.p. 225°		259,768,769,770, 154,151,93, 871
					hydrochloride, m.p. 225°	259
					picrate, m.p. 219–20°	
					chloroplatinate, m.p. 230–31°	
					benzoyl, m.p. 61–65°	871
					benzoyl picrate, m.p. 194–95°	871
					phenylacetyl, b.p. 121–32°/	871

					diphenylacetyl, b.p. 164–67°/0.2 mm.	871
Et			Et	m.p. 65–66°	hydrochloride, m.p. 76–78°	146
					chloroplatinate, m.p. 203° (dec.)	146
n-Pr			*n*-Pr	m.p. 85–88°	monohydrate, m.p. 62°	146
				b.p. 210–15°/12 mm.	hydrochloride, m.p. 96–98°	146
					chloroplatinate, m.p. 204°	146
Me			Ph	m.p. 177–78°	picrate, m.p. 194–95°	777,788,819
Ph			Ph	m.p. 176–78°		771,154,819
					chloroplatinate, m.p. 218–21°	771
Me			*p*-ClC_6H_4	m.p. 236–37°		819
Ph			*p*-ClC_6H_4	m.p. 208–13°		819
Ph			*p*-$CH_3OC_6H_4$	m.p. 219–22°		819
—$(CH_2)_3$—			*p*-$CH_3OC_6H_4$	m.p. > 300°		819
t-Bu			*t*-Bu	m.p. 170.5–72°	chloroaurate, m.p. 199–201°	860
	Ph	Ph		m.p. 376° (dec.)		147
Me	Me		Me	m.p. 185–92°	chloroplatinate, m.p. 205°	770
				HALO		
	I			m.p. 303°		558
	Cl	Cl				767
	Br	Br		m.p. 370° (dec.)		370,121,766,767
	I	I		m.p. 321° (dec.)	acetyl, m.p. 245° (dec.)	443
					sulfate ester, m.p. 183° (dec.)	443
Me	I	I		m.p. 231–32°		260
Me	Br	Br	Me			768,769

(*continued*)

TABLE XII-37. 4-Pyridinols (*continued*)

R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
Me	I	I	Me	m.p. 259–61°		259
Cl	Cl	Cl	Cl	m.p. 232–33°		228
Br	Br	Br	Br	m.p. 258–59°		226
	NO_2			m.p. 284° (dec.)		309,560,562,917
Me	NO_2		Me			776
	NO_2	NO_2			monohydrate, m.p. 325°	560,370,917
Me	NO_2	NO_2		m.p. 269° (dec.)		371
	Br	NO_2				238
	NO_2	I		m.p. 310° (dec.)		761
Me	NO_2	NO_2	Me	m.p. 324–25° (dec.)		916
				AMINO		
	NH_2				dihydrochloride, m.p. 228–30°	761
					monoacetyl, m.p. 213–14°	654
					chloroplatinate	562
	NH_2	Br		m.p. 190° (dec.)		558
	NH_2	NO_2				562
Me	NH_2		Me	m.p. 238.5°	diazonium hydrochloride, m.p. 200–2°	657
	NH_2	NH_2			di-*p*-$AcNHC_6H_4SO_2$, m.p. 284° (dec.)	917
Me	NH_2	NH_2	Me		di-*p*-$AcNHC_6H_4SO_2$, m.p. 303–4°	917
NH_2			NH_2	m.p. 191° (dec.)	nitrate, m.p. 260–61°	885
					sulfate, m.p. 277.5°	885
					picrate, m.p. 242° (dec.)	885
					mercurichloride, m.p. 214°	885

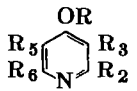
NH_2	N_2Ph		NH_2	m.p. 225.5–27°		885
				CARBOXY		
COOH				m.p. 257–58° (dec.)		210,243,141
					Et ester, m.p. 124–26°	141
					hydrazide, m.p. 220–21° (dec.)	141
	COOH			m.p. 250° (dec.)		772
Me	COOH				Et ester, m.p. 64°	82
Me			COOH	m.p. 295°		739
Me	COOH		Me	m.p. 158–59° (dec.)	Et ester, m.p. 161–62°	151
Ph	COOH		Ph	m.p. 243–45°		771
COOH			COOH	m.p. 251–55°		259,767,427
COOH	NO_2	NO_2	Me	m.p. 264–65° (dec.)		916
					dimethyl ester, m.p. 125°	409
					diethyl ester, m.p. 80–81°	767
	COOH	COOH		m.p. 315°	diethyl ester, m.p. 251°	96
Me	COOH	COOH			diethyl ester, m.p. 156–57°	82
					diamide, m.p. 321° (dec.)	82
COOH	Ph		COOH	m.p. 210–15°		143
Me	COOH	COOH	Me		monoethyl ester, m.p. 181–84°	151
				m.p. 267° (dec.)	diethyl ester, m.p. 221°	768
Ph	COOH	COOH	Ph	m.p. 258° (dec.)	diethyl ester, m.p. 195°	773
COOH	COOH	COOH	COOH		tetraethyl ester, m.p. 229°	774
COOH	Cl	Cl		m.p. > 300°		443
COOH	Br	Br		m.p. > 300°		443
COOH	I	I		m.p. 250° (dec.)		443

(*continued*)

TABLE XII-37. 4-Pyridinols (*continued*)

R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
COOH	Cl	Cl	COOH		diethyl ester, m.p. 96°	443
COOH	Br	Br	COOH		diethyl ester, m.p. 108°	443
COOH	I	I	COOH	m.p. 235–38°		259
					diacid chloride, m.p. 149°	443
					dimethyl ester, m.p. 173°	443
					diethyl ester, m.p. 169°	443
					dibenzyl ester, m.p. 200° (dec.)	443
					sulfate ester, m.p. 210° (dec.)	443
				CYANO		
Cyano						
Me	CN		Me	no m.p. up to 280°		777
Ph	CN		Me	m.p. 244°		777
				ALKOXY		
OMe				m.p. 133.5–34.0°	picrate, m.p. 203–4°	601,889
	OMe			m.p. 180.5–81.5°	trihydrate, m.p. 119°	735
	OMe		Me	m.p. 115°	picrate, m.p. 205–6°	149
OEt		Cl		m.p. 201.5–2.0°		220

OMe		$NHCO_2Et$		1.5 hydrate, m.p. 115–20°	141
	OMe	CH_2NEt_2		dipicrate, m.p. 188°	744
				methiodide, m.p. 204°	744
	OMe	COOH	m.p. 265°		483
			m.p. 249.50° (dec.)	amide, m.p. 178°	149,709
				Et ester, m.p. 145–46°	141,744
				hydrazide · 1.5 hydrate, m.p. 213–14°	141
				azide, m.p. 130–32° (dec.)	141
				nitrate, m.p. 236–37°	132
				picrate, m.p. 225° (dec.)	132
	OMe	COOMe	m.p. 134°	picrate, m.p. 205–7°	132
	OMe	COOH		Et ester, m.p. 118°	409
OEt	Bu		m.p. 251–53°	nitrate, m.p. 235–38°	915
			m.p. 119°		868
	n-BuO	COOH	m.p. 245–46° (dec.)	nitrate, m.p. 132–33° (dec.)	141
				Et ester, m.p. 85–86°	141
				hydrazide, m.p. 179–81° (dec.)	141

TABLE XII-38. 4-Pyridinol Ethers 

R	R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
Me					b.p. 190°	picrate, m.p. 175°	369,203
						hydrochloride, m.p. 163–64°	369
Et					b.p. 200–2°		742,739,368
						chloroplatinate, m.p. 215°	368
n-Bu					b.p. 129–31°/25 mm.		203
Ph					m.p. 44–46°; b.p. 277–79°, 134–36°/10 mm.		208,325,203, 368,227, 742
						chloroplatinate, m.p. 159–62°	325
						chloroplatinate, m.p. 196–97°	208,325
						hydrochloride, m.p. 177–78°	208,325
						picrate, m.p. 171.5–72.0°	227
o-MeC_6H_4					b.p. 161–62°/19 mm.		325,203
m-MeC_6H_4					b.p. 124–26°/4 mm.		203
p-MeC_6H_4					b.p. 166–67°/22 mm.		203

p-$NO_2C_6H_4$					m.p. 79–81°	methiodide, m.p. 207–9°	567
2,4-$(NO_2)_2C_6H_3$					m.p. 92.0–94.5°	methiodide, m.p. 156°	567
p-$NH_2C_6H_4$					m.p. 160–62°		567
CH_2Ph					m.p. 55–56°; b.p. 155–60°/4 mm.	picrate, m.p. 150–51°	731
4-Py					m.p. 177–78°	picrate, m.p. 198°	411
3,5-Dinitro-4-pyridyl					m.p. 288°		475
Me	Me			Me	b.p. 203°	picrate, m.p. 125–30°	775,871
Et	Me			Me	b.p. 217°	picrate, m.p. 114°	775,871
					b.p. 107–8°/19 mm.		151
Me		Cl			b.p. 83–84°/3 mm.		506
Et		Cl				picrate, m.p. 159.5–60°	492
						picrolonate, m.p. 202–3°	492
p-$NH_2C_6H_4$	Me	I		Me	m.p. 268°		219
Me	Br			Br	m.p. 136–37°		226
Ph	Br			Br	m.p. 84.5–85.5°		227
Ph	Me	I	I	Me	m.p. 138°		219
p-$NO_2C_6H_4$	Me	I	I	Me	m.p. 236–38°	hydrochloride, m.p. 234–36°	219
p-$NH_2C_6H_4$	Me	I	I	Me	m.p. 236–37°	hydrochloride, m.p. 234–38°	219
Me		NO_2			m.p. 73°; b.p. 127°/1 mm.		506,683,862

(*continued*)

TABLE XII-38. 4-Pyridinol Ethers (*continued*)

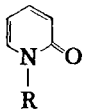
R	R_2	R_3	R_4	R_6	Physical properties	Derivatives	Ref.
Et		NO_2			m.p. 49–50°		238,653,561
						hydrochloride, m.p. 160°	238
						chloroplatinate, m.p. 246–48° (dec.)	238
CH_2CH_2Cl		NO_2			m.p. 70–71°		712
CH_2CH_2OH		NO_2			m.p. 112–13°		712
Et	Me	NO_2	Me		m.p. 99°		739
Me		Br	NO_2		m.p. 39–40°		506
Et	NH_2				m.p. 119–20°	acetyl, m.p. 142.5–43.5°	653
						picrate, m.p. 230.0–30.5°	653
Me		NH_2					683
Et		NH_2			m.p. 65.5–66.0°	acetyl, m.p. 78.5–79°	653
						picrate, m.p. 176.5–77.0°	653
Et	Me	NH_2		Me	m.p. 62; b.p. 267°		739
Et		NH_2		Cl	m.p. 73°	picrate, m.p. 197°	238
						chloroplatinate, m.p. > 280 (dec.)	238
Me	COOH					hydrazide, m.p. 152–54°	211
Et	Me	COOH		Me	m.p. 200–1°		73
Et	COOH			COOH	m.p. 182–84°		901
						diacid chloride, m.p. 77–78°	901
						diamide, m.p. 289°	901
						dianilide, m.p. 258–59°	901

Me	Ph	COOH	COOH	Ph	m.p. 240°	diethyl ester, m.p. 229–30°	773
Me	COOH	I	I	COOH	m.p. 176° (dec.)		443,448
						dimethyl ester, m.p. (ca.) 125°	448
						diethyl ester, m.p. 100–1°	443
Et	COOH	I	I	COOH	m.p. 174° (dec.)	dimethyl ester, m.p. 131°	443,448
n-Pr	COOH	I	I	COOH	m.p. 156° (dec.)	dimethyl ester, m.p. 89°	443,448
n-Bu	COOH	I	I	COOH	m.p. 145° (dec.)	dimethyl ester, m.p. 82°	443
allyl	COOH	I	I	COOH	m.p. 143–44° (dec.)	dimethyl ester, m.p. 98°	443
CH_2Ph	COOH	I	I	COOH	m.p. 167° (dec.)	dimethyl ester, m.p. 120°	443
Me		CN			m.p. 124°		683
Me	Me	NH_2	CN	Cl	m.p. 130–31°		59
Me	COOH			COOH	m.p. 222–24°	diacid chloride, m.p. 97–99°	901
						diamide, m.p. > 300°	901
						dianilide, m.p. 275–77°	901
Et	*t*-Bu				b.p. 115–16°/15 mm.	picrate, m.p. 121–22°	860
Et	*t*-Bu			*t*-Bu	b.p. 141–42°/21 mm.	chloroaurate, m.p. 193–94°	860
i-Pr	Me			Me	b.p. 131°/50 mm.	picrate, m.p. 146°	871
i-Bu	Me			Me	b.p. 116°/13 mm.	picrate, m.p. 141°	871
$(CH_2)_2NEt_2$	Me			Me	b.p. 136°/5 mm.	picrate, m.p. 168°	871
CH_2Ph	Me			Me	b.p. 129°/0.2 mm.	picrate, m.p. 210°	871

(*continued*)

TABLE XII-38. 4-Pyridinol Ethers (*continued*)

R	R_2	R_3	R_5	R_6	Physical Properties	Derivatives	Ref.
Ph	Me			Me	b.p. 112°/2 mm.	picrate, m.p. 186°	871
o-MeC_6H_4	Me			Me	b.p. 156°/13 mm.	picrate, m.p. 165°	871
m-MeC_6H_4	Me			Me	b.p. 165°/22 mm.	picrate, m.p. 196°	871
p-MeC_6H_4	Me			Me	b.p. 140°/7 mm.	picrate, m.p. 147°	871
o-$MeO_2CC_6H_4$	Me			Me	b.p. 250°/5 mm.		870
p-$NH_2C_6H_4$	Me	NO_2	NO_2	Me	m.p. 217–8°		916
p-$MeOC_6H_4$	Me	NO_2	NO_2	Me	m.p. 103–4°		916
p-$PhCH_2OC_6H_4$	Me	NO_2	NO_2	Me	m.p. 146–7°		916
p-MeC_6H_4	Me	NO_2	NO_2	Me	m.p. 124–5°		916
C_6H_5	Me	NO_2	NO_2	Me	m.p. 134–5°		916
p-$NO_2C_6H_4$	Me	NO_2	NO_2	Me	m.p. 152–3°		916
2,4-Di-$NO_2C_6H_3$	Me	NO_2	NO_2	Me	m.p. 153–4°		916
p-C_6H_4	Me	NO_2	NO_2	Me	m.p. 258–9°		916

TABLE XII-39. 1-Substituted 2(1*H*)-Pyridones 

R	Physical properties	Derivatives	Ref.
Me	m.p. 30°		432
	b.p. 122–24°/11 mm.		338,334,336
		hydrochloride, m.p. 166°	337
		hydrobromide, m.p. 174°	337
		picrate, m.p. 144–45°	382
		chloroplatinate, m.p. 141°	337
		mercurichloride, m.p. 127°	274
		picrolonate, m.p. 120°	337
		chloroaurate, m.p. 145–46°	453
		styphnate, m.p. 162°	337
Et	b.p. 249–51°, 139°/12 mm.	mercurichloride, m.p. 112–13°	432,335
n-Pr	b.p. 263–64°, 139°/12 mm.		522
		picrate, m.p. 95.5–96.5°	907
i-Pr	b.p. 145–50°/15 mm.		522
n-Bu	b.p. 148°/10 mm.		522,339
i-Bu	b.p. 264–65°		335
i-Am	b.p. 283–84°		335
n-Octyl	b.p. 189°/12 mm.		432
n-Dodecyl		picrate, m.p. 96–97°	332
Vinyl	m.p. 73–78°		437
		picrate, m.p. 91–92.5°	897

(continued)

TABLE XII-39. 1-Substituted 2(1*H*)-Pyridones

R	Physical properties	Derivatives	Ref.
Allyl	b.p. 88.5–91.5°/1.5 mm.	picrate, m.p. 104.5–5.5°	907
—$(CH_2)_2$—[a]	m.p. 183°	dipicrate, m.p. 170° (dec.)	343
—$(CH_2)_3$—[a]	m.p. 132°	dipicrate, m.p. 146°	343
—$(CH_2)_4$—[a]	m.p. 133°; b.p. 282–85°	dipicrate, m.p. 209° (dec.)	343
—$(CH_2)_5$—[a]	m.p. 93°; b.p. 280–83°	dipicrate, m.p. 174° (dec.)	343
CH_2CH_2Cl	m.p. 69°		436,710
$CH_2CH_2NH_2$		hydrobromide, m.p. 203°	436
		hydrochloride, m.p. 183°	436
		phthalamide, m.p. 135–37°	436
		phthalimide, m.p. 205°	436
$CH_2CH_2NMe_2$		dihydrochloride, m.p. 255°	436
CH_2CH_2NHEt		dihydrochloride, m.p. 183°	436
$CH_2CH_2NEt_2$	b.p. 127°/1 mm.	hydrochloride, m.p. 148°	436,131
		hydrate, m.p. 74°	436
$CH_2CH_2N(n\text{-}Pr)_2$	b.p. 147°/2 mm.		436
$CH_2CH_2N(n\text{-}Bu)_2$	b.p. 163–65°/2 mm.		436
$CH_2CH_2N(i\text{-}Am)_2$	b.p. 180–83°/3 mm.		436
$CH_2CH_2N(CH_2CH{=}CH_2)_2$		hydrochloride, m.p. 129°	436
piperidylethyl		hydrochloride, m.p. 204°	436
$(CH_2)_3NH_2$		hydrochloride, m.p. 181–82°	436
		phthalimide, m.p. 225°	436
CH_2COOH	m.p. 222°		435,330,681
		Me ester, m.p. 45°	435
		Et ester, b.p. 142–47°/4 mm.	449
		amide, m.p. 233–34°	459,435

CH_2CH_2COOH	m.p. 176–78°		449
		hydrochloride, m.p. 96°	330
$CH_2CHCOOH$[a]	m.p. 151°		450
CH_2CHNH_2COOH	m.p. 236° (dec.)	*N*-acetyl, m.p. 199° (dec.)	450
CH_2CH_2CN	m.p. 93–94°		449
CH_2CH_2OH	m.p. 100°; b.p. 185°/9 mm.		331
	m.p. 85° and 94°[b]		436,706
		picrate, m.p. 103°	753
		chloroplatinate, m.p. 205° (dec.)	753
		chloroaurate · 2EtOH, m.p. 92°	753
		benzoyl, m.p. 118°	753
		phenyl urethane, m.p. 132°	753
$CH_2CHOHCH_2OEt$	b.p. 186°/14 mm.	phenyl urethane, m.p. 117°	344b
$CH_2CHOHCH_2O(n\text{-Pr})$	b.p. 200°/17 mm.	phenyl urethane, m.p. 115°	344b
$CH_2CHOHCH_2O(n\text{-Bu})$	b.p. 195–97°/12 mm.	phenyl urethane, m.p. 98°	344b
$CH_2CHOHCH_2O(i\text{-Am})$	b.p. 211–13°/12 mm.	phenyl urethane, m.p. 126°	344b
$—CH_2CH_2OCH_2CH_2—$[a]	m.p. 158°; b.p. 172–76°/25 mm.	dipicrolonate, m.p. 258°	340
$CH_2CHOHCOOH$	m.p. 168–72°		450;451
CH_2CHO		hydrochloride, m.p. 139–40°	450
		oxime, m.p. 78–79°	450
		semicarbazone, m.p. 155–56°	450
CH_2SO_3Na			441

(continued)

TABLE XII-39. 1-Substituted 2(1*H*)-Pyridones (*continued*)

R	Physical properties	Derivatives	Ref.
Ph	m.p. 127°		600,129
		hydrochloride, m.p. 192°	129
		nitrate, m.p. 88°	129
		perchlorate, m.p. 164°	129
		picrate, m.p. 193°	129
		mercurichloride, m.p. 118°	129
p-ClC_6H_4	m.p. 105°		129
m-$NO_2C_6H_4$	m.p. 210°	perchlorate, m.p. 176°	129
		picrate, m.p. 175°	129
p-$NO_2C_6H_4$	m.p. 202°	*nitrate*, m.p. 146°	129,896
	m.p. 188°		896
		perchlorate, m.p. 245°	129
		picrate, m.p. 190–92°	129
p-$NH_2C_6H_4$	m.p. 260–70° (dec.)		129
p-HOC_6H_4	m.p. ca. 200° (dec.)		129
p-$EtOC_6H_4$	m.p. 154–56°	perchlorate, m.p. 195°	129
CH_2Ph	m.p. 75°		334,522,311
		mercurichloride, m.p. 124°	334
CH_2CH_2Ph	m.p. 87°		589
	m.p. 105–6°		364,341
2-$MeOC_6H_4CH_2CH_2$	m.p. 250° *or* m.p. 130–31°		342
2-Me-4,5-$(MeO)_2C_6H_2CH_2CH_2$			342
3,4-$(CH_2O_2)C_6H_3CH_2CH_2$	m.p. 148°		589

α-$C_{10}H_7CHMe$	m.p. 72°		364
$CH_2CHOHPh$	m.p. 127°		344a
CH_2COPh	m.p. 154–55°	perchlorate, m.p. 131°	249,896
2-Py	m.p. 55°		462
	m.p. 48°	picrate, m.p. 117–18°	539
		mercurichloride, m.p. 172–73°	539
5-Methyl-2-pyridyl	m.p. 94°		375
3-Methyl-2-pyridyl	m.p. 108°		375
4-Methyl-2-pyridyl	m.p. 114°		375
6-Methyl-2-pyridyl	m.p. 42°		375
2-Quinolyl	m.p. 147.5°	picrate, m.p. 167.5°	462
NH_2	m.p. 64–66°	hydrochloride, m.p. 175–77°	405,858
		N-acetyl, m.p. 157–58°	858
		N-benzoyl, m.p. 198–99.5°	858
		N-carbobenzoxy, m.p. 132.5–34°	858
NHCONHPh	m.p. 232°		858
N=CHPh	m.p. 88–89°		858
$CHCOCH_2Cl$	m.p. 131–32°		899
2,4-$(NO_2)_2C_6H_3$	m.p. 166°		896
o-$NO_2C_6H_4$			896
o-$NH_2C_6H_4$		dihydrochloride, m.p. 190°	896
$NHCONH_2$	m.p. 197–98°		859
$NHCONMe_2$	m.p. 187–88.5°		859
$NHCONEt_2$	m.p. 126–27°		859
—NHCNH—[a] (‖ O)	m.p. 199–201°		859

(continued)

TABLE XII-39. 1-Substituted 2(1*H*)-Pyridones

R	Physical properties	Derivatives	Ref.
NHCOOH	m.p. 213–14.5 °	methyl ester, m.p. 151–52 °	859
		ethyl ester, m.p. 122–23 °	858,859
		propyl ester, m.p. 100–1 °	859
		butyl ester, m.p. 81–81.5 °	859
		cyclohexyl ester, m.p. 134–36 °	859
4-Py	m.p. 158–60 °	picrate, m.p. 175–76 °	851
		mercurichloride, m.p. 240–44 °	851

[a]Di-2(1*H*)-pyridone.
[b]Dimorphic.

TABLE XII-40. Alkyl and Aryl Derivatives of 2(1*H*)-Pyridones 

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	Me				b.p. 86–88°/1.5 mm.	hydrochloride, m.p. 120–21°	346
Me	Et				b.p. 122–23°/11 mm.	picrate, m.p. 60–62°	351
Et	Me				b.p. 95–96°/2.5 mm.		346
3,4-(CH_2O_2)-$C_6H_3CH_2CH_2$	Et				m.p. 82–83°		719
Me		Me			m.p. 59°	hydrochloride, m.p. 173–74°	274
					b.p. 110°/1 mm.	picrate, m.p. 168–69°	274
Me			Me		m.p. 36.8°; b.p. 109–11°/1.7 mm.	hydrochloride, m.p. 160°	346
Me			Et			picrate	351
Me			Ph		m.p. 73–74°; b.p. 167–69°/2 mm.	picrate, m.p. 131–33°	350
Et			Me		b.p. 104–6°/1.7 mm.		346
CH_2COOH			CPh_3		m.p. 264–66°		467
CH_2CH_2Ph			Et		m.p. 52–54°		357
CH_2CH_2Ph			Ph			picrate, m.p. 132–34°	350
Me				Me	m.p. 56.5–58.0°	hydrochloride, m.p. 202–3°	274
						picrate, m.p. 134–36°	274
Me				*n*-Am			274
Me				CH_2CH_2Ph	m.p. 95.5–96.5°		274

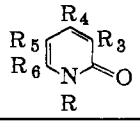
(*continued*)

TABLE XII-40. Alkyl and Aryl Derivatives of 2 (1*H*)-Pyridones (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me				*m*-nitrostyryl	m.p. 216–18°		274
CH_2COOH				Me	m.p. 229° (dec.)	Et ester, m.p. 81–82°	274
CH_2CH_2COOH				Me	m.p. 165–66°		274
CH_2CH_2CN				Me	m.p. 109–10°		274
$CH_2CH_2SO_3Na$				Me			441
Ph				Ph	m.p. 144–46°		115
CH_2Ph				Me	m.p. 110–12°		433
CH_2CH_2Ph				Me	m.p. 108°		364
Me		Me		Me	m.p. 90–92°		355
Me		Ph		Me	m.p. 112°		815
Me		furfuryl		Me	m.p. 153.5°		758
NH_2	Me				m.p. 95–96°	*N*-acetyl, m.p. 124.5°	858
						N-dibenzoyl, m.p. 136–37°	858
NH_2		Me			m.p. 77–79°	*N*-acetyl, m.p. 171°	858
						N-dibenzoyl, m.p. 151°	858
NH_2			Me		m.p. 100–1.5°	*N*-acetyl, m.p. 156–57°	858
						N-dibenzoyl, m.p. 161.5–63.5°	858
NH_2				Me	m.p. 70–71.5°	*N*-acetyl, m.p. 140.5–41°	858
						N-dibenzoyl, m.p. 147–48.5°	858

NH_2		Me		Me	m.p. 90–90.5°	*N*-benzoyl, m.p. 234–34.5°	858
$NHCONH_2$				Me	m.p. 197–98°		859
—NHCONH[a]				Me	m.p. 190.5–91.5°		859
NHCOOH				Me		Me ester, m.p. 173–74°	859
						Et ester, m.p. 164.5–167°	859
$NHCONH_2$			Me		m.p. 211–12.5°		859
—NHCONH—[a]			Me		m.p. 193–95°		859
NHCOOH			Me			Me ester, m.p. 163–63.5°	859
						Et ester, m.p. 162°	859
$NHCONH_2$		Me			m.p. 211–12°		859
—NHCONH—[a]		Me			m.p. 225.5–26.0°		859
NHCOOH		Me				Me ester, m.p. 180–80.5°	859
						Et ester, m.p. 125–26°	859
$NHCONH_2$	Me				m.p. 215–16°		859
—NHCONH—[a]	Me				m.p. 205–5.5°		859
NHCOOH	Me					Me ester, m.p. 164–64.5°	859
						Et ester, m.p. 156–57.5°	859
$NHCONH_2$		Me		Me	m.p. 216.5–17.0°		859
—NHCONH—[a]		Me		Me	m.p. 168.5–169°		859
NHCOOH		Me		Me		Me ester, m.p. 157–58°	859
						Et ester, m.p. 123–23.5°	859

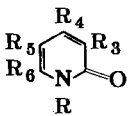
[a]Di-2(1*H*)-pyridone.

TABLE XII-41. Halo 2(1*H*)-Pyridones 

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	Cl				m.p. 44-45°		434
Me	Br				m.p. 62-63°; b.p. 126-31°/1.6 mm.		346
					m.p. 53°		434
Me	I				m.p. 66-67°		558
CH_2COOH	I				m.p. 215° (dec.)		558
2-Py	Br				m.p. 129°		375
Me			Cl		m.p. 44-45°		434
Me			Br		m.p. 53; b.p. 157°/12 mm.		434
Me			I		m.p. 73-74°	hydrochloride, m.p. 130° (dec.)	233
							233
					b.p. 182-85°/ 12 mm.		233
Et			I		m.p. 75-76°		233
					b.p. 180-85°/ 22 mm.		233
n-Pr			I		b.p. 185-88°/ 15 mm.	hydrochloride, m.p. 112° (dec.)	233
i-Pr			I		m.p. 110-11°		233
n-Bu			I		b.p. 185°/12 mm.	hydrochloride, m.p. 125° (dec.)	233
n-Octyl			I		b.p. 221-22°/ 12 mm.	hydrochloride, m.p. 85° (dec.)	233
CH_2COOH			Br		m.p. 237-38°		440
CH_2COOH			I		m.p. 240°		440,689
						Et ester, m.p. 113-14°	689
CH_2SO_3Na			I				441
CH_2Ph			I		m.p. 100-1°		233

TABLE XII-41 (*continued*)

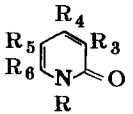
R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
2-Py			Cl		m.p. 124–25°	mercurichloride, m.p. 193°	539
2-Py			Br		m.p. 134°		375
Me				Br	m.p. 105°		248
Me	Cl		Cl		m.p. 142°		434,337
Me	Br		Br		m.p. 182°		314,549, 346,434
Me	I		I		m.p. 227°		434,545
Et	Br		Br		m.p. 109°; b.p. 124°/9 mm.		544
CH_2COOH	Br		Br		m.p. 240–41°		440
CH_2COOH	I		I		m.p. 248° (dec.)		438,440
					m.p. 236°		546
						Et ester, m.p. 150°	697,438
CH_2COOH	Br		I		m.p. 244–45°		440
CH_2CH_2COOH	Br		Br		m.p. 182°		450
CH_2CH_2OH	Br		Br		m.p. 168.5°	benzoyl, m.p. 107°	547
CH_2SO_3H	Br		Br				546
CH_2SO_3Na	I		I				441
$CH_2CH_2SO_3H$	I		I				546
$CH_2CHOHPh$	Br		Br		m.p. 166°		547
2-Py	Br		Br		m.p. 158°		375
Me	Br		Br	Br	m.p. 151°		497
Me	Br	Me	Br	Me	m.p. 173°		355
Ph			Cl		m.p. 122–23°		845
Ph			Br		m.p. 114–15°		845
Ph			I		m.p. 119–21°		845
Ph		Cl			m.p. 101–30°		845

TABLE XII-42. Nitro and Amino 2(1*H*)-Pyridones 

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	NO_2				m.p. 175–76°		237,333
Me			NO_2		m.p. 175°		233
Et			NO_2		m.p. 142–43°		233,333,337
n-Pr			NO_2		m.p. 76–77°		233
i-Pr			NO_2		m.p. 86–90°		233
n-Bu			NO_2		m.p. 46–47°		233
$CH_2CH_2SO_3Na$			NO_2				441
CH_2Ph			NO_2		m.p. 105–6°		233
5-Nitro-2-pyridyl			NO_2		m.p. 167°		463
Me	NO_2		NO_2		m.p. 178°		279
Me	NO_2		Cl		m.p. 126°		279
Me	Cl		NO_2		m.p. 115°		279
Me	Br		NO_2		m.p. 124–25°		233
Et	*N*-methyl-2-pyrrolidyl				m.p. 110°		353

n-Pr	*N*-methyl-2-pyrrolidyl		m.p. 95–96°		353
n-Bu	*N*-methyl-2-pyrrolidyl		b.p. 155–60°/ 2 mm.		353
Me		NH_2	m.p. 125–26° (dec.)		233
CH_2Ph		NH_2	m.p. 155–60°		688
$(CH_2)_2Ph$		*N*-methyl-2-pyrrolidyl	b.p. 198–203°/ 0.02 mm.	methiodide m.p. 91–92°	354
3,4-$(CH_2O_2)C_6H_3CH_2CH_2$		*N*-methyl-2-pyrrolidyl	b.p. 230–35°/ 0.05 mm.		354
$(CH_2)_2Ph$		$NHCOOCH_2Ph$	m.p. 134°		845
Ph		$NHCOOCH_2PH$	m.p. 144–45°		845
Ph		NH_2		hydrochloride, m.p. 166–69°	845
				$HCl·H_2O$, m.p. 203–5° (dec.)	845
Ph		NO_2	m.p. 155–58°		845

TABLE XII-43. 2(1*H*)-Pyridone Carboxylic Acids and Nitriles



R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
Me	COOH				m.p. 183°		348
						Et ester, m.p. 74°	252
						amide, m.p. 219–20°	346,681, 348
$CH_2CH_2NMe_2$	CONHPh					hydrochloride, m.p. 218°	436,242
$(CH_2)_2NEt_2$	CONHEt					hydrochloride, m.p. 102°	242
$(CH_2)_2NEt_2$	$CONH(CH_2)_2$-NEt_2					dihydrochloride, m.p. 83°	436,242
$CH_2CH_2NEt_2$	CONHPh				b.p. 205°/ 0.03 mm.	hydrochloride, m.p. 195°	242,436
$(CH_2)_2NEt_2$	$CONHC_6H_4$-OEt-*p*					hydrochloride, m.p. 221°	436
$(CH_2)_2NEt_2$	CON(Et)Ph					hydrochloride, m.p. 102°	436
$(CH_2)_2N(n\text{-Bu})_2$	CONHPh					hydrochloride, m.p. 181°	436,242
piperidylethyl	CONHPh					hydrochloride, m.p. 215°	436,242

Me	CH_2COOH		m.p. 184°		274
Me		COOH	m.p. 238°	Et ester, m.p. 72.0–73.5°	348,848
				Me ester, m.p. 139°	812,848
				amide, m.p. 210°	346,347, 348
n-Pr		COOH	m.p. 141–42°	*n*-Pr ester, b.p. 147–49°/4 mm.	453
				chloroaurate, m.p. 181–82°	453
$CH_2CH_2NEt_2$		COOH		anilide, m.p. 102°	436
Ph		COOH	m.p. 275–80°		817
CH_2Ph		COOH	m.p. 206–8°	hydrazide, m.p. 177–78°	116
			m.p. 199–200°	benzylurethan, m.p. 101–3°	688
CHMePh		COOH	m.p. 192–94°		116
			m.p. 207–8°		592

(continued)

TABLE XII-43. 2 (1*H*)-Pyridone Carboxylic Acids and Nitriles

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
p-$MeOC_6H_4CH_2$			COOH		m.p. 198–99°		116
Me		COOH			m.p. 254°	acid chloride	847
						Et ester, m.p. 89°	847
						acid hydrazide, m.p. 258–60°	847
						amide, m.p. 234–36°	847
$(CH_2)_2Ph$		COOH			m.p. > 260°	Et ester, m.p. 102–4°	845
						acid hydrazide, m.p. 190–93° (dec.)	845
$(CH_2)_2Ph$			COOH			Et ester, m.p. 55–56°	845
						acid hydrazide $HCl \cdot H_2O$, m.p. 252°	845
$PhCH_2CH_2$			COOH		m.p. 189°		592,525, 702
p-$MeC_6H_4CH_2CH_2$			COOH		m.p. 180–81°		116

$3,4\text{-}(MeO)_2C_6H_3CH_2CH_2$		COOH		m.p. 207.5–9.0°		592
$3,4(CH_2O_2)C_6H_3CH_2CH_2$		COOH		m.p. 230–31°		592
Me			COOH	m.p. 247–48°		681,274
Me			CH_2COOH	m.p. 188° (dec.)	Me ester, m.p. 102°	274
					Et ester, m.p. 100–1°	274
Me			CH(*n*-Bu)COOH		Et ester, b.p. 159–60°/2 mm.	274
Me			$CH(CH_2Ph)$-COOH	m.p. 155° (dec.)	Et ester, m.p. 104–5°	274
CH_2Ph			CH_2COOH	m.p. 167°	Et ester, m.p. 78–79°	538
CH_2CH_2Ph			COOH	m.p. 192–93°		116
$3,4\text{-}(MeO)_2C_6H_3CH_2CH_2$			COOH	m.p. 218°		116
$CH_2{=}CHCH_2$	COOEt	COOH	CH_2COOEt	m.p. 130–33°		108
CH_2CH_2Cl	COOEt	COOH	CH_2COOEt	m.p. 115°		108

(continued)

TABLE XII-43. 2(1*H*)- Pyridone Carboxylic Acids and Nitriles (*continued*)

R	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
CH_2CH_2OH	COOEt		COOH	CH_2COOEt	m.p. 109°	ethanolamine salt, m.p. 189°	108
Me	COOH		Br			Me ester, m.p. 290°	346
Me	I		I	COOH	m.p. 194° (dec.)		443
Me	NO_2		COOH		m.p. 217–22°	Me ester, m.p. 147–49°	279
						Et ester, m.p. 124°	279
Me	CN				m.p. 139°		681
Me				CH_2CN	m.p. 95.5–96.5°		274
Me				$CH(CH_2Ph)CN$	m.p. 132°		274
Me	CN	Me		Ph	m.p. 266°		81
Me	CN	Ph		Me	m.p. 146°		67
Me	CN	Ph		Et	m.p. 158°		67
Me	CN	Ph		Ph	m.p. 175°		67

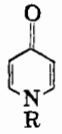
Me	CN	Ph	p-MeC_6H_4	m.p. 136–38°	67
Me	CN	Ph	p-$NO_2C_6H_4$	m.p. 322–34°	67
Me	CN	Cl		m.p. 159°	681
4-Antipyryl	CN	Me	Me	m.p. 244.5–46.5°	855
NHPh	CN	Me	Me	m.p. 213.5–15°	855
Phenacetylamine ($NHCOCH_2Ph$)	CN	Me	Me	m.p. 223.5–25°	855
—NH-tosyl	CN	Me	Me	m.p. 255–56.5°	855
—NHCONH—[a]	CN	Me	Me	m.p. 310–13°	855
—$NHCOCH_2CONH$	CN	Me	Me	m.p. 276–78°	855
Ph	CN	Me	Me	m.p. 261–62.5°	855
Ph		CN		m.p. 144–46°	855

[a]Di-2(1*H*)-pyridone.

TABLE XII-44. Hydroxy and Alkoxy 2(1*H*)-Pyridones 

R_1	R_3	R_4	R_5	R_6	Physical Properties	Derivatives	Ref.
Me	OH				m.p. 130–31°		609
Me		OH			m.p. 171–72°	picrate, m.p. 155–56°	601,223,680,361
Me				OH	m.p. 162–63°		609
Me		OMe			m.p. 113–14°	picrate, m.p. 154–55°	601,680
						picrolonate, m.p. 126.5° (dec.)	601,680
Me		OEt			m.p. 131–32°		361
Me		OH		Me	m.pl 225–26° (dec.)		150
Et		OH		Me	m.p. 198° (dec.)		150
n-Pr		OH		Me			162
Cyclohexyl		OH		Me	m.p. 108°		150
$CH_2CH_2NMe_2$		OH		Me			162
$CH_2CH_2NEt_2$		OH		Me			162
CH_2COOH		OH		Me	m.p. 270° (dec.)		465
CH_2CH_2OH		OH		Me			162
p-$Me_2NC_6H_4$		OH		Me	m.p. 270–75° (dec.)		150
CH_2Ph		OH		Me			162
Me		OH		Et			162
$CH_2CH_2NH_2$		OH		Et			162
Me		OH		Ph			162
Me		Me		OMe	m.p. 92°		578
Me	Et	OH		Me	m.p. 238–40.5°		604

Me	Me	Me		OMe	m.p. 119–20 °		578
Me		Me	Me	OMe	m.p. 85–7 °		578
CH_2COOH	I	OH		Me	m.p. 226 ° (dec.)	ethanolamine salt, m.p. 190–91 ° (dec.)	465
						Na salt, m.p. > 230 ° (dec.)	465
Me	CN	MeO			m.p. 200–2 °		685
						mercurichloride, m.p. 203–4 °	222,682
Me	CN	EtO			m.p. 138–39 °	mercurichloride, m.p. 129–30 °	750
Me	CN	*n*-PrO			m.p. 123–24 °	mercurichloride, m.p. 129–30 °	750
Me	CN	*i*-PrO			m.p. 130–31 °	mercurichloride, m.p. 115–16 °	750
Me	CN	*n*-BuO			m.p. 112–13 °		750
Me	CN	*n*-AmO			m.p. 130–31 °		750
Me		MeO	CN		m.p. 241–42 °		223
Me	CN	OH		Cl	m.p. 249 ° (dec.)		750
Ph		OH			m.p. 202–4 °		845
Ph		Me		OH	m.p. 164 °		835
$2\text{-}MeC_6H_4$		Me		OH	m.p. 121 °		835
$4\text{-}MeC_6H_4$		Me		OH	m.p. 163 °		835
$2,6\text{-}Me_2C_6H_3$		Me		OH	m.p. 228 °		835
$2,5\text{-}(MeO)_2C_6H_3$		Me		OH	m.p. 149 °		835
$3\text{-}ClC_6H_4$		Me		OH	m.p. 151 °		835
$4\text{-}ClC_6H_4$		Me		OH	m.p. 178 °		835
$2\text{-}NO_2C_6H_4$		Me		OH	m.p. 170 °		835
$4\text{-}Me_2NC_6H_4$		Me		OH	m.p. 233 °		835
$4\text{-}Et_2NC_6H_4$		Me		OH	m.p. 182 °		835

TABLE XII-45. 1-Substituted 4(1*H*)-Pyridones 

R	Physical properties	Derivatives	Ref.
Me			122
	m.p. 86°		693
	m.p. 92–94°	mercurichloride, m.p. 177°	328
	b.p. 223–24°/15 mm.		680
	b.p. 94°/5 mm.	picrate, m.p. 186–87°	387
		N-benzoylhydrazone, m.p. 261–63°	862
		hydrazone · 2HCl, m.p. 269–71°	862
Et		picrate, m.p. 197–98°	369
		dibromide, m.p. 209°	369
$CH_2CH_2NMe_2$	b.p. 201–40°/1 mm.	dihydrochloride, m.p. 264–65°	209
		methiodide, m.p. 239–41°	209
		allyl bromide, m.p. 179–81°	209
		benzyl chloride, m.p. 201–2°	209
$CH_2CH_2NEt_2$	b.p. 175°/0.03 mm.		738,242
	b.p. 224–47°/2 mm.	dihydrochloride, m.p. 190–91°	209
		methiodide, m.p. 198–99°	209
		allyl bromide, m.p. 198.5–201°	209
CH_2CH_2COOH		hydrochloride, m.p. 196°	330
		Et ester, m.p. 182–83°	615
CH_2CHNH_2-COOH	m.p. 170–72° (dec.)		615
CH_2CH_2CN	m.p. 109–11°		615
$CH_2CH(OEt)_2$		hydrate, m.p. 87–89°	442
		picrate, m.p. 137–39°	442
CH_2CHO		picrate, m.p. 182°	442
		semicarbazone, m.p. 208° (dec.)	442

TABLE XII-45 (*continued*)

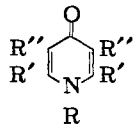
R	Physical properties	Derivatives	Ref.
Ph	m.p. 116°	picrate, m.p. 190°	130
		methiodide, m.p. 146°	130
	m.p. 125°	hydrochloride, m.p. > 330°	123
		dihydrate, m.p. 105°	123
	m.p. 131–32°	*N*-benzoylhydrazone, m.p. 258–60°	862
		hydrazone · 2HCl, m.p. 131–40°	862
		chloroplatinate, m.p. 208° (dec.)	123
		chloroaurate, m.p. 122–23°	123
o-MeC_6H_4	m.p. 148°	hydrochloride, m.p. 131°	123
m-MeC_6H_4	m.p. 133–34°	hydrochloride, m.p. 92–93°	123
		chloroplatinate, m.p. 205° (dec.)	123
		chloroaurate, m.p. 122–23°	123
p-MeC_6H_4	m.p. 142–43°	hydrochloride, m.p. 208° (dec.)	123
		dihydrate, m.p. 78°, 66–67°	123,862
		chloroplatinate, m.p. 205° (dec.)	123
		chloroaurate, m.p. 178°	123
		N-benzoylhydrazone, m.p. 264–66°	862
		hydrazone · 2HCl, m.p. 184–87°	862
2,4-$Me_2C_6H_3$		hydrate, m.p. 90°	123
p-$MeOC_6H_4$	m.p. 110–11°		44
	m.p. 185–86°	hydrate hydrochloride, m.p. 159–61°	516
$CHPh_2$	m.p. 170°		124
CH_2CHPh_2	m.p. 159–60°		124
9-Fluorenyl	m.p. 177°		124
α-Naphthyl	m.p. 173°		123

(*continued*)

TABLE XII-45. 1-Substituted 4(1*H*)-Pyridones *(continued)*

R	Physical properties	Derivatives	Refs.
4-Py		dipicrate · H_2O, m.p. 202°	324
		chloroaurate, m.p. 226°	324
		methiodide, m.p. 238°	203
		ethiodide · H_2O, m.p. 134–35°	203
3-Bromo-4-pyridyl	m.p. 243–44°		778
4-$NO_2C_6H_4$	m.p. 202°	*N*-benzoylhydrazone, m.p. 283–84°	862,129
		hydrazone · 2HCl, m.p. 239°	862
4-$Me_2NC_6H_4$	m.p. 191°	*N*-benzoylhydrazone, m.p. 270–72°	862
		hydrazone · 3HCl, m.p. 170–73°	862
p-ClC_6H_4	m.p. 159°	*N*-benzoylhydrazone, m.p. 291–93°	862,129
		hydrazone · HCl, m.p. 245–48°	862
CH_2COPh	m.p. 238° (dec.)		896
CH_2Ph	m.p. 109–11°		895
2-Py	m.p. 164–65°	picrate, m.p. 185–86°	851
		mercurichloride, m.p. 183–84°	851
2-(3-BrPy)	m.p. 173–75°		851

TABLE XII-46. Alkyl and Aryl Derivatives of 4(1*H*)-Pyridones



R	M.p., °C.	Derivatives	Ref.
	R′ = Me; R″ = H		
Me	244		17,93,768, 862,844
		$3H_2O$, m.p. 110°	768
		picrate, m.p. 196°	844
		N-benzoylhydrazone	862
		hydrazone · 2HCl	862
n-Pr	157		17
i-Pr			17
n-Bu	109		17
i-Bu	119		17
n-Am	143		17
i-Am	130		17
n-Hexyl	107		17
n-Heptyl	136		17
$CH_2C(Et)_2(CH_2)_3CH_3$			17
Allyl	132		17
Propargyl	227		17
CH_2COOEt	187		17
Ph	197		16,17,768, 862,844
		HCl, m.p. 295°	862
		N-benzoylhydrazone, m.p. 294°	862
CH_2Ph	199		17
CHMePh			17
o-MeC_6H_4	167		17
m-MeC_6H_4	170		17
p-MeC_6H_4	201		17

(continued)

TABLE XII-46. Alkyl and Aryl Derivatives of 4(1*H*)-Pyridones (*continued*)

R	M.p., °C.	Derivatives	Ref.
2,4,6-$Me_3C_6H_2$	228		17
α-Naphthyl	195		17
β-Naphthyl	221		17
o-ClC_6H_4	147		17
m-ClC_6H_4	241		16
p-ClC_6H_4	248		17
o-$MeOC_6H_4$	156		17
p-$MeOC_6H_4$	199		17
o-$EtOC_6H_4$	146		17
m-$EtOC_6H_4$	141		17
p-$EtOC_6H_4$	193		17
o-BrC_6H_4	196		17
m-BrC_6H_4	225		17
p-BrC_6H_4	231		17
p-IC_6H_4	320		17
p-PhC_6H_4	235		17
2,4-$Cl_2C_6H_3$	209		17
2,5-$Cl_2C_6H_3$	203		17
o-$NO_2C_6H_4$			17
m-$NO_2C_6H_4$	226		17
p-$NO_2C_6H_4$	230		17
3,5-$Br_2C_6H_3$	289		17
p-$Me_2NC_6H_4$	210		17
p-$MeCOC_6H_4$	219		17
p-$NHCOMeC_6H_4$	312		17
2-NO_2-4-MeC_6H_3			17
3-NO_2-2-MeC_6H_3	240		17
o-$COOMeC_6H_4$	179		17
o-HOC_6H_4	>360		17
p-HOC_6H_4	>360		17
$CH_2CH_2C_6H_5$	175		17
p-$(BrCH_2)C_6H_4$	201		17
CH_2CH_2[a]	360		17
m-C_6H_4[a]	360		17
p-C_6H_4	400		17

TABLE XII-46 (*continued*)

R	M.p., °C.	Derivatives	Ref.
	R′ = Et; R″ = H		
p-$NO_2C_6H_4NH$	78	chloroplatinate, m.p. 198	414
		p-nitrophenylhydrazone m. 164	414
Et	72	picrate, m.p. 191°	844
	R′ = Ph; R″ = H		
Me	187	picrate, m.p. 220°	844,819
		N-benzoylhydrazone, m.p. 307–10° (dec.)	862
		hydrazone · 2HCl, m.p. 130–34°	862
Et		picrate, m.p. 200°	17,844
n-Pr			17
i-Pr	178		17
Propargyl	154		17
n-Bu			17
i-Bu			17
n-Am			17
i-Am			17
n-Hexyl			17
n-Heptyl			17
Ph	280		17
CH_2CH_2Ph	258		17
o-MeC_6H_4	223		17
m-MeC_6H_4	255		17
p-MeC_6H_4	295		17
2,4,6-$Me_3C_6H_2$	233		17
α-Napthyl	287		17
β-Naphthyl	260		17
o-ClC_6H_4	255		17
m-ClC_6H_4	264		17
p-ClC_6H_4	304		17
o-$MeOC_6H_4$	213		17
p-$MeOC_6H_4$	260		17

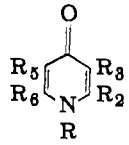
(*continued*)

TABLE XII-46. Alkyl and Aryl Derivatives of 4(1*H*)-Pyridones (*continued*)

R	M.p., °C.	Derivatives	Ref.
m-$EtOC_6H_4$	194		17
p-$EtOC_6H_4$	248		17
o-BrC_6H_4	266		17
m-BrC_6H_4	262		17
p-BrC_6H_4	286		17
p-IC_6H_4	287		17
p-PhC_6H_4	234		17
m-$NO_2C_6H_4$	302		17
3,5-$Br_2C_6H_3$	271		17
2-Me-5-$NO_2C_6H_3$	277		17
o-HOC_6H_4	360		17
m-HOC_6H_4	360		17
p-HOC_6H_4	d400		126
p-$NH_2C_6H_4$	315		17
p-C_6H_4[a]	400		17
	R′ = H; R = Me		
R″			
$PhCH_2$	167–8		384
p-$MeC_6H_4CH_2$	231–4		384
m-$NO_2C_6H_4CH_2$	251–2		384
p-$MeOC_6H_4CH_2$	202		384
p-*iso*-$PrC_6H_4CH_2$	215–7		384
p-$Me_2NC_6H_4CH_2$	215–7		384
p-$PhC_6H_4CH_2$	243		384

[a]Bis-pyridone.

TABLE XII-47. Halo, Nitro, and Amino 4(1*H*)-Pyridones



R	Physical properties	Derivatives	Ref.
	$R_3 = R_5 = Br$; $R_2 = R_6 = H$		
Me	m.p. 143–44°		370
		N-benzoylhydrazone, m.p. 183–85°	862
CH_2COOH	m.p. 261° (dec.)		718
3,5-Dibromo-4-pyridyl	no m.p. >300°		443
	$R_3 = R_5 = I$; $R_2 = R_6 = H$		
Me	m.p. 214–15°		443,541
allyl	m.p. 171–72°		541
CH_2CH_2Cl	m.p. 180°		541
CH_2CH_2Br	m.p. 189°		541
$CH_2CH_2NEt_2$	m.p. 85°		718
$CH_2CH_2NEt_3^+MeSO_4^-$	m.p. 215°		541
CH_2COOH	m.p. 246° (dec.)		541,443
		amide, m.p. 275°	541
		n-Bu ester, m.p. 194°	717
		i-Pr ester, m.p. 215°	717
		octadecenyl ester, m.p. 115°	717
CHEtCOOH	m.p. 168.4–69°		444
CHPrCOOH	m.p. 194–97°		444
CH(*n*-Bu)COOH	m.p. 205–7°		444
CH(*i*-Bu)COOH	m.p. 185.4–86.2°		444
CH(*n*-Am)COOH	m.p. 202.5–4.5°		444

(continued)

TABLE XII-47. Halo, Nitro, and Amino 4(1*H*)-Pyridones (*continued*)

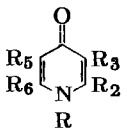
R	Physical properties	Derivatives	Ref.
CH(*n*-hexyl)COOH	m.p. 176.2–77°		444
CH(*n*-heptyl)COOH	m.p. 132–33°		444
CH(*n*-octyl)COOH	m.p. 124.5–26.5°		444
CH_2CH_2OH	m.p. 260°		541
$CH_2CHOHCH_2OH$	m.p. 161°		541
CH_2SO_3H		salts	541
$CH_2CH_2SO_3H$		Na, K, Ba salts	541
$CH_2(o\text{-}COOHC_6H_4)$	m.p. 295–300° (dec.)		447
$CH_2(m\text{-}COOHC_6H_4)$	m.p. 285–89° (dec.)		447
$CH_2(p\text{-}COOHC_6H_4)$	m.p. 295–300° (dec.)		447
3,5-Diiodo-4-pyridyl	no. m.p. > 300°		443

R	R_2	R_3	R_5	R_6			
CH_2COOH	Me	I	I		m.p. 231–32° (dec.)		260
Ph	Me	I	I	Me	m.p. 257–58°		550
Me		NO_2			m.p. 233°		506,683
						N-benzoylhydrazone, m.p. 265–66°	862
						hydrazone·HCl, m.p. 236–37°	862
CH_2COOH		NO_2			m.p. 268–69°	*n*-octyl ester, m.p. 135°	761
CH_2COOH		NO_2	I		m.p. 252–54°	NH_4^+ salt, m.p. 225–28°	761
						diethanolamine salt, m.p. 156–58°	761
						Et ester, m.p. 122°	761
						n-octyl ester, m.p. 105–7°	761
Me		NH_2				hydrochloride, m.p. m.p. 130–33°	761

TABLE XII-47 (*continued*)

R	R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
CH_2COOH		NH_2			m.p. 242–45°		761
						hydrazone · 2HCl, m.p. 232°	862
CH_2COOH		NH_2	I			hydrochloride, m.p. 216–18°	761
						diazonium chloride, m.p. 141–43°	761

TABLE XII-48. 4(1*H*)-Pyridone Carboxylic Acids



R	R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
m-OHC_6H_4	COOH					m.p. 197°	550
						Et ester, m.p. 176–77°	550
p-OHC_6H_4	COOH				m.p. 226–27°	Et ester, m.p. 225–27° (dec.)	550
4-OH-3,5-$I_2C_6H_2$	COOH				m.p. 213–14°		550
3-OH-2,4,6-I_3C_6H	COOH				m.p. 203–4° (dec.)		550
Ph		COOH			m.p. 263–64°		43
p-$MeOC_6H_4$		COOH			m.p. 252°	acid chloride, m.p. 143–44°	44
						Et ester, m.p. 88°	44
						amide, m.p. 225–26°	44
						diethyl amide, m.p. 118–19°	44
β-Naphthyl		COOH			m.p. 252–53; 306–7°[a]		43
6-Quinolyl		COOH			m.p. 353° (dec.)	acid chloride, m.p. 262–63°	43
						Et ester, m.p. 116–17°	43
						diethyl amide, m.p. 155–56°	43

Ph	Me	COOH	Me	m.p. 267–68° (dec.)	Me ester, m.p. 209°	76
p-OHC_6H_4	Me	COOH	Me	m.p. 277–78° (dec.)		126
Me	COOH		COOH			541,122
					diethyl ester *N*-benzoylhydrazone, m.p. 173–74°	862
CH_2COOH	COOH		COOH	m.p. 228° (dec.)		127
Ph	COOH		COOH		diethyl ester · H_2O, m.p. 65–66°	411
					monoethyl ester, m.p. 159° (dec.)	411
p-MeC_6H_4	COOH		COOH	m.p. 192° (dec.)	diethyl ester, m.p. 65–66°	411,507
p-IC_6H_4	COOH		COOH	m.p. 189–90°	diethyl ester, m.p. 165–66°	125
2,4-$I_2C_6H_3$	COOH		COOH	m.p. 226° (dec.)		125
p-$COOHC_6H_4$	COOH		COOH	m.p. 188° (dec.)		127
m-OHC_6H_4	COOH		COOH	m.p. 194° (dec.)	diethyl ester, m.p. 175–76°	126
p-OHC_6H_4	COOH		COOH	m.p. 198°	diethyl ester, m.p. 185°	126
4-OH-3,5-$I_2C_6H_2$	COOH		COOH	m.p. 225–30° (dec.)		125
3-OH-2,4,6-I_3C_6H	COOH		COOH	m.p. 190–200°		125
p-$AsO_3H_2C_6H_4$	COOH		COOH	m.p. 210°		127
p-C_6H_4[b]	COOH		COOH	m.p. 400° (dec.)	tetraethyl ester, m.p. 239–40°	126
$CHPh_2$	COOH		COOH	m.p. 210° (dec.)		124

(continued)

TABLE XII-48. 4(1*H*)-Pyridone Carboxylic Acids (*continued*)

R	R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
$(CH_2)_2CHPh_2$	COOH			COOH	m.p. 220° (dec.)		124
$CH_2CHPhCH_2Ph$	COOH			COOH	m.p. 210° (dec.)		124
NHPh	COOEt			COOEt		phenylhydrazone	413
p-$NO_2C_6H_4NH$	COOEt			COOEt	m.p. 146°	*p*-nitrophenylhydrazone, m.p. 210°	210,412
m-ClC_6H_4		COOH	COOH			diethyl ester, m.p. 198–99°	97
Me	COOH	Ph		COOH	m.p. 160°		143
i-Pr	COOH	Ph		COOH	m.p. 154°		143
sec-Am	COOH	Ph		COOH	m.p. 145°		143
i-Am	COOH	Ph		COOH	m.p. 162°		143
$CH_2CH_2NEt_2$	COOH	Ph		COOH		hydrochloride, m.p. 147°	143
$CHMe(CH_2)_3NEt_2$	COOH	Ph		COOH	m.p. 172°		143
Ph	COOH	Ph		COOH	m.p. 171°		144
o-$NO_2C_6H_4$	COOH	Ph		COOH	m.p. 168°		144
m-$NO_2C_6H_4$	COOH	Ph		COOH	m.p. 145°		144
p-$NO_2C_6H_4$	COOH	Ph		COOH	m.p. 195°		144
o-ClC_6H_4	COOH	Ph		COOH	m.p. 173°		144
p-ClC_6H_4	COOH	Ph		COOH	m.p. 187°		144
o-MeC_6H_4	COOH	Ph		COOH	m.p. 122°		144
m-MeC_6H_4	COOH	Ph		COOH	m.p. 127°		144
p-MeC_6H_4	COOH	Ph		COOH	m.p. 195°		144
o-COOH-C_6H_4	COOH	Ph		COOH	m.p. 225°		144
p-COOH-C_6H_4	COOH	Ph		COOH	m.p. 250°		144
p-MeO-C_6H_4	COOH	Ph		COOH	m.p. 165°		144

p-SO_3H-C_6H_4	COOH	Ph		COOH	m.p. 152°		144
m-SO_3H-C_6H_4	COOH	Ph		COOH	m.p. 145°		144
p-(2-pyridylamino-sulfonyl C_6H_4	COOH	Ph		COOH	m.p. 142°		145
2-thiazolyl	COOH	Ph		COOH	m.p. 92°		145
2-pyrimidyl	COOH	Ph		COOH	m.p. 242°		145
4,6-Me_2-2-pyrimidyl	COOH	Ph		COOH	m.p. 120°		145
p-I-C_6H_4	Me	COOH	COOH	Me	m.p. 253° (dec.)	diethyl ester, m.p. 234°	125
Me	Me	COOH	COOH	Me		diethyl ester, m.p. 193°	862
2,4-$I_2C_6H_3$	Me	COOH	COOH	Me	m.p. 223–24°	diethyl ester, m.p. 208°	125
p-$NH_2C_6H_4$	Me	COOH	COOH	Me	m.p. 240° (dec.)	*N*-acetyl diethyl ester, m.p. 273°	126
p-HOC_6H_4	Me	COOH	COOH	Me	m.p. 246° (dec.)	diethyl ester, (dec.) 259–60°	126
m-HOC_6H_4	Me	COOH	COOH	Me	m.p. 249–50° (dec.)	diethyl ester, m.p. 241°	126
4-HO-3,5-$(MeO)_2C_6H_2$	Me	COOH	COOH	Me	m.p. 258° (dec.)	diethyl ester, m.p. 265° (dec.)	126
4-HO-3,5-$I_2C_6H_2$	Me	COOH	COOH	Me	m.p. 238–39° (dec.)		125
3-HO-2,4,6-I_3C_6H	Me	COOH	COOH	Me	m.p. 250–52° (dec.)		125
p-C_6H_4[b]	Me	COOH	COOH	Me	m.p. > 300°	diethyl ester	126
Me	COOH	Cl	Cl		m.p. 166°		443

(continued)

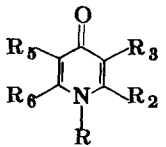
TABLE XII-48. 4(1*H*)-Pyridone Carboxylic Acids (*continued*)

R	R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
Me	COOH	Br	Br		m.p. 170° (dec.)		443
Me	COOH	I	I		m.p. 159° (dec.)		443
CH_2COOH	COOH	I	I		m.p. 223°		443
Ph	Me	COOH	I	Me	m.p. 250–51° (dec.)		550
Me	COOH	I	I	COOH	m.p. 175°		448,541
						dimethyl ester, m.p. 195–96°	448
						diethyl ester, m.p. 112.5°	448
						dipropyl ester, m.p. 74–75°	443
4-OH-3,5-$Br_2C_6H_2$	COOH	Br	Br	COOH	m.p. 347° (dec.)		550
3-OH-2,6-$Br_2C_6H_2$	COOH	Br	Br	COOH	m.p. 160–74°		550
Me	Ph			*p*-MeO-C_6H_4		picrate, m.p. 164°	844
Et	Ph			*p*-MeO-C_6H_4		picrate, m.p. 199°	844
Me	Me	Br	Br	Me	m.p. 308°		844
Et	Me	Br	Br	Me	m.p. 248°		844
Me	Ph	Br	Br	Ph	m.p. 313°		844
Et	Ph	Br	Br	Ph	m.p. 285°		844

[a]Two forms.

[b]Bis substituted.

TABLE XII-49. Hydroxy and Alkoxy 4(1*H*)-Pyridones



R	R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
Me	OMe				m.p. 141–43°	picrate, m.p. 198°	737
Me		OH			m.p. 227–28° (dec.)		618,609
						hydrochloride, m.p. 185.5° (dec.)	609
						picrate, m.p. 227°	609
						picrolonate, m.p. 236°	609
Et		OH			m.p. 168.5–70°		618,136
						picrate, m.p. 182–84°	136
						m.p. 169.5–71.7°	618
n-Pr		OH			m.p. 182.5–84.0°		136
i-Pr		OH			m.p. 209°		136
$CH_2CH(NH_2)COOH$		OH			m.p. 235–36° [a]		615
					m.p. 228–29° [b]		615
					m.p. 291°		611
						L-Me ester dihydrochloride, m.p. 180–81°	611
						rac-½H_2O, m.p. 227–28° (dec.)	615

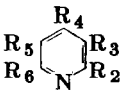
(*continued*)

TABLE XII-49. Hydroxy and Alkoxy 4(1*H*)-Pyridones

R	R_2	R_3	R_5	R_6	Physical properties	Derivatives	Ref.
CH_2CHO		OH				*p*-nitrophenylhydrazone, m.p. 220–22°	136
						DNPH, m.p. 223.5–25.0°	136
						semicarbazone, m.p. 208–9°	136
						ethyl acetal, m.p. 145–46° (dec.)	138
Me		OMe			m.p. 91–92°		628,734
						picrate, m.p. 215–16°	618
Et		OMe			m.p. 100–1°	hydrochloride m.p. 150–51°	618
$CH_2CH(OEt)_2$		OMe			m.p. 113–14°		136
						picrate, m.p. 158–59°	138
CH_2CHO		OMe				*p*-nitrophenylhydrazone, m.p. 215.5–17.0°	136
						semicarbazone, m.p. 188°	442
Me	Me	OMe				hydrate, m.p. 79–80°	93

Me	Me	OMe			trihydrate, m.p. 98°	93,149
					picrate, m.p. 208–10°	149
Me		OH	Me	m.p. 273–74°	hydrochloride, m.p. 236–38° (dec.)	132
Me		OMe	Me	m.p. 150°	trihydrate, m.p. 95°	132
					hydrochloride, m.p. 216–17°	132
					picrate, m.p. 208°	132
Me		OMe	CH_2NEt_2	m.p. 177°	methiodide, m.p. 221° (dec.)	744
					tetrahydrate, m.p. 208°	149
Me		OH	COOH	m.p. 224–25°		136
Et		OH	COOH	m.p. 210°		136
i-Pr		OH	COOH	m.p. 196–97°		136
CH_2COOH		OH	COOH		$\frac{1}{2}H_2O$, m.p. 225.5–27.0°	136
					Ba salt, m.p. 340°	136
					dimethyl ester, m.p. 188–89°	136
					diethyl ester, m.p. 195–96°	136

[a]Racemic.
[b]Natural.

TABLE XII-50. Pyridinediols 

R_2	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
OH				OH	m.p. 184–85°	hydrate, m.p. 203.5–4.0°	458
						diacetyl, m.p. 69°	306
							306
OH	Me			OH	m.p. 190–91°		3
							578,13,81
OH		Me		OH	m.p. 190–96°	hydrochloride · H_2O, m.p. 217–19°	578
						hydrochloride · $2H_2O$, m.p. 222–24°	578
						diacetyl, m.p. 62°	578
OH	Et			OH	m.p. 175°		3
		Pr		OH	m.p. 225–27°		85,37,780
OH		*i*-Pr		OH	m.p. 213–14°		37
OH		*n*-hexyl		OH	m.p. 175–80°		85,191
OH	Ph			OH	m.p. 214°		477
OH		Ph		OH	m.p. 256–57°		85,4,780
OH		*m*-MeC_6H_4		OH	m.p. 255–57°		85,780
OH		*p*-(*i*-Pr)C_6H_4		OH	m.p. 240°		85,780
OH	*p*-ClC_6H_4			OH	m.p. 216–17°		477
						tribenzoyl, m.p. 177°	7
OH		*p*-HOC_6H_4		OH	m.p. 257°	isonitroso, m.p. 194°	7
						sulfate, m.p. 320–30°	7
						dibenzoyl, m.p. 163°	7

OH		*p*-$CH_3OC_6H_4$		OH	m.p. 248°	isonitroso, m.p. 201°	7
						sulfate, m.p. 310–15°	7
						dibenzoyl, m.p. 173°	7
OH		3-Me-4-CH_3O-C_6H_3		OH	m.p. 252°	isonitroso, m.p. 217°	7
						sulfate, m.p. 320°	7
						dibenzoyl, m.p. 134°	8
OH		5-Me-2-CH_3O-C_6H_3		OH	m.p. 200°		2
OH	CH_2Ph			OH	m.p. 184°		40,578,85, 12
OH	Me	Me		OH	m.p. 188–90°	diacetyl, b.p. 136–40°/1 mm.	578
						hydrochloride·H_2O, m.p. 93–94°	578
							85,780
OH	Me	Et		OH	m.p. 200°		85,12,780, 26
OH	Et	Me		OH	m.p. 175°	hydrobromide, m.p. 165°	26
OH	*n*-Pr	Me		OH	m.p. 154–55°		85
OH	CH_2Ph	Me		OH	m.p. 176, 156–57°		85,780,781
OH		—$(CH_2)_3$—		OH	m.p. 264, 258°		690,15
OH	Me	Me	Me	OH	m.p. 180°		12,827

(continued)

TABLE XII-50. Pyridinediols (*continued*)

R_2	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
OH	Me	—$(CH_2)_3$—		OH	m.p. 252°	hydrochloride, m.p. 200°	15
OH	Et	—$(CH_2)_3$—		OH	m.p. 203–4°		30
OH	NO_2			OH			98
OH	N=NPh	Me		OH	m.p. 251–52°		578
OH	Me	Me	N=NPh	OH	m.p. 255–56°		578
OH		NHNHPh		OH	m.p. 232°		415
OH		NHNH-$CONH_2$		OH	m.p. 165–67°	NH_4^+ salt, m.p. 144°	416
OH		NH_2		OH			5
OH	NH_2	Me		OH		triacetyl, m.p. 177–78°	578
						N,*N*-diacetyl *O*,*O*′-diacetyl, m.p. 142–43°	578
OH	Me	Me	NH_2	OH		triacetyl, m.p. 197–98°	578
						N,*N*-diacetyl *O*,*O*′-diacetyl, m.p. 96–97°	578
OH	COOH			OH	m.p. 197–98°	Et ester	14,4a
OH		COOH		OH	m.p. > 300° (dec.)		168,10,11, 114
						Me ester, m.p. 220°	
						hydrazide, m.p. 202–5°	699
						hydrazide·H_2O, m.p. 215–20° (dec.)	726
OH		CH_2COOH		OH		amide, m.p. 228°	6

OH		CH_2CH_2COOH		OH	m.p. 268–69°		38
OH	COOH	Me		OH		Et ester, m.p. 218°	12,36
						amide, m.p. 198° (dec.)	81
OH	Me	COOH		OH			782
OH	COOH	Ph		OH	m.p. 285°		783
OH	*p*-ClC_6H_4	COOH		OH		amide, m.p. 280° (dec.)	477
OH	COOH	Me	Me	OH		Et ester, m.p. 187°	12,36
OH	Me	COOH	Me	OH			782
OH	COOH	Me	Et	OH		Et ester, m.p. 134°	85,12
OH	COOH	COOH		OH		diethyl ester, m.p. 161–62°	782,784
OH	COOH		COOH	OH		diethyl ester, m.p. 201–2°	14,98,14a
OH	COOH	Me	COOH	OH		2.5 H_2O, m.p. 250–52°	92
OH	COOH	COOH	Me	OH		Et ester, m.p. 173°	782
OH	COOH	Et	COOH	OH			785
OH	COOH	*n*-Pr	COOH	OH			780
OH	COOH	*i*-Pr	COOH	OH			85
OH	COOH	Ph	COOH	OH			85
OH	COOH	Me	CH_2COOH	OH			794
OH	NO	COOH		OH			786
OH	N=NC_6H_4-SO_2NH_2	COOH		OH	m.p. 278° (dec.)		577
OH	NO_2	COOH	NO_2	OH			787
OH	Me	Me	CN	OH		NH_4^+ salt, m.p. 343° (dec.)	40
OH	Et	Me	CN	OH		NH_4^+ salt, m.p. 315°	26
OH	CN	Et	CN	OH			785
OH	CN	*n*-Pr	CN	OH			780

(continued)

TABLE XII-50. Pyridinediols (*continued*)

R_2	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
OH	CN	*i*-Pr	CN	OH	m.p. 231°		89,85
OH	CN	*i*-Bu	CN	OH	m.p. 239°		89
OH	CN	Ph	CN	OH	m.p. 234–35°		85
OH	CN	Me		OH	m.p. 315–20° (dec.)		821
OH	—N=NPh	COOH		OH		Me ester, m.p. 223–25°	870
						Et ester, m.p. 260°	870
OH	NH_2	COOH		OH		Me ester, m.p. 192–93°	870
						Et ester, m.p. 206–8°	870
OH	N_2^+	COOH		OH	m.p. 250°	Me ester, m.p. 172–74°	870
						Et ester, m.p. 162–64° (dec.)	870
OH	Et	Me	Me	OH		monohydrate, m.p. 106°	827
OH	Et	Me	Et	OH	b.p. 115–20°/0.3 mm.		827
OH	COOH	CH_2COOH		OH		diethyl ester, m.p. 176.5°	883
OH	Ph	Me	CN	OH	m.p. 295–96°		853
OH	Ph	Me			m.p. 220–22°		853
OH	CN	CH_2Ph	CN	OH	m.p. 279°	NH_4^+ salt, m.p. 320° (dec.)	112
OH	CN	COOEt		OH	m.p. 120–50°	piperidine salt, m.p. 180–81°	38
OH	CN	CH_2COOH		OH		Et ester, m.p. 239°	38
OH	CN	CH_2CH_2COOH		OH		Et ester, m.p. 247°	38

OH	CN	Me	CH_2COOH	OH			794
					m.p. 271–72°		96,458,380
OH		OH		Me	m.p. 331°		35
						monoacetyl, m.p. 194–96°	225
						monobenzoyl, m.p. 197–98°	225
OH		OH		Et			162
OH		OH		*n*-Bu			162
				Ph	m.p. 315–18°		150
OH	Me	OH		Me	m.p. 276.5°		78
OH	Me	OH		Et	m.p. 238°		78
OH		OH	Me	Me	m.p. > 350°		40
						monobenzoyl, m.p. 233°	225
						dibenzoyl, m.p. 109–10°	225
						monomethyl ether, m.p. 172–73°	225
OH		OH	Et	Me	m.p. 330°		40
						monobenzoyl, m.p. 194–96°	225
						monomethyl ether, m.p. 202–3°	225
OH		OH	*n*-Pr	Me	m.p. 330–32° (dec.)		789
						monoacetyl, m.p. 158–59°	225
						monomethyl ether, m.p. 183–84°	225

(continued)

TABLE XII-50. Pyridinediols (*continued*)

R_2	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
OH		OH	*n*-Bu	Me	m.p. 348–50° (dec.)		789
						monoacetyl, m.p. 153–54°	225
						monobenzoyl, m.p. 152–53°	225
						monomethyl ether, m.p. 160–61°	225
OH		OH	—$(CH_2)_3$—		m.p. 305° (dec.)		78
					m.p. > 380°	diacetyl, m.p. 92°	156
OH		OH	—$(CH_2)_4$—		m.p. > 310° (dec.)		78
OH		OH	—$(CH_2)_5$—				79
OH	Ph	OH	Ph	Ph	m.p. 288–89°	diacetyl, m.p. 143–44°	165
OH	Ph	OH	Ph	CH_2Ph	m.p. 260°		
OH	Cl	OH			m.p. 310° (dec.)		492,646
OH	Br	OH			m.p. 263°		220
OH		OH	Cl		m.p. 273–74° (dec.)		220
OH		OH	Br		m.p. 226.5–27.5°		492
OH		OH		Cl	m.p. 234°		494
OH		OH	I	Me	m.p. 193–95°		543

OH	Cl	OH	Cl		m.p. 298–303 °		645
OH	Cl	OH	Br		m.p. 252–54 ° (dec.)		644,645
OH	Br	OH	Cl		m.p. 258–59 d.		220
OH	Br	OH	Br		m.p. 245		778,96
OH	NO_2	OH			m.p. 266		563
OH		OH	NO_2	Me		hydrazide, m.p. 238 °	543
OH	NO_2	OH	Br		m.p. 248 ° (dec.)		645
OH	NO	OH	—$(CH_2)_3$—		m.p. ca. 250 (dec.)		156
OH	COOH	OH			m.p. 182 (dec.)		684
OH		OH	COOH		m.p. 310		96,790
						diethyl ester, m.p. 213 ° (dec.)	96
						monobromo, m.p. 225 ° (dec.)	96
						amide, m.p. 353 ° (dec.)	223
OH		OH	COOH			Et ester, m.p. 198–200 °	163
OH	COOH	OH		Me		Et ester, m.p. 208–10 °	682,35,543
						n-amyl ester, m.p. 146–47 °	77
						amide, m.p. 280–81 ° (dec.)	77,682
						anilide, m.p. 279–80 °	662
OH	COOH	OH	Me	Me		Et ester, m.p. 222 °	40

(continued)

TABLE XII-50. Pyridinediols (*continued*)

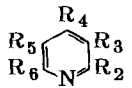
R_2	R_3	R_4	R_5	R_6	Physical	Derivatives	Ref.
OH	COOH	OH	Et	Me		Et ester, m.p. 196–97 °	40
OH	COOH	OH	*n*-Pr	Me		Et ester, m.p. 192–93 °	789
OH	COOH	OH	*n*-Bu	Me		Et ester, m.p. 182–84 °	789
OH	COOH	OH	—$(CH_2)_5$—			Et ester, m.p. 213 °	79
OH	COOH	OH	—$(CH_2)_{13}$—			Et ester, m.p. 280–300 ° (dec.)	80
OH		OH	COOH	COOH	m.p. 263		187
OH	Cl	OH	COOH			Et ester, m.p. 257–58 °	492
OH	COOH	OH		Cl	m.p. 226	Et ester, m.p. 154 °	494
OH	COOH	OH	Br	Me	m.p. 265 (dec.)	Et ester, m.p. 249–50 °	543
OH	COOH	OH	I	Me	m.p. 220 (dec.)	Et ester, m.p. 238 ° (dec.)	543
OH	Br	OH	COOH	COOH	m.p. 240		187
OH	NO_2	OH	COOH		m.p. 253	Et ester, m.p. 236–37 °	563
OH	COOH	OH	NO_2	Me		Et ester, m.p. 253 ° (dec.)	77
						n-Am ester, m.p. 201–2 °	77
						amide, m.p. 307–9 °	77
OH	COOH	OH	NH_2	Me		dihydroiodide, m.p. 260 ° (dec.)	77
						n-Am ester, m.p. 154 °	77
OH	CN	OH		Cl	m.p. > 190 ° (dec.)		159

OH	CN	OH	NO_2	Me	m.p. 253° (dec.)		77
OH	CN	OH		NH-NH_2	m.p. > 260° (dec.)		494
OH	*n*-Bu	OH		Me	m.p. 280–85° (dec.)		854
OH	OH				m.p. 247–48°		458,186, 181,207
						hydrochloride, m.p. 154°	207
						monoacetyl, m.p. 155°	380
						chloroplatinate $\cdot H_2O$, m.p. 130°	207
OH	OH			Me	m.p. 202–3°		3,186,700
OH	OH			COOH	m.p. 236–37°		186
OH	OH	COOH	Me (5 or 6)			dihydrate, m.p. 255°	792
OH	OH	Me	COOH	Me		Et ester, m.p. 118°	793
OH			OH		m.p. 248°	monobenzoate, m.p. 187–89°	617,458,842
						diacetyl, m.p. 68°	842,458
OH	Ph	Me	OH		m.p. 250–60°		842
OH	$CONH_2$	Me	OH	Me		monoacetyl-(5), m.p. 345–46°	84
OH	CN	Me	OH	Me		monoacetyl-(5), m.p. 313°	84
OH			OH	NO	m.p. 210° (dec.)		842

(continued)

TABLE XII-50. Pyridinediols (*continued*)

R_2	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
OH			OH	NH_2		2,3-dibenzoyl, m.p. 243–44°	842
	OH	OH			m.p. 240–41°	diacetyl, m.p. 139–40°	458,611
					m.p. 255°		587,170
						monoacetyl (3?), m.p. 145.5–46.5°	735
	OH	OH		Me	m.p. 280° (dec.)		149
NH_2	OH	OH			m.p. 295°		587
COOH	OH	OH			m.p. 260–62°	Et ester, m.p. 204–5°	134
						diethyl amide, m.p. 159°	134
	OH	OH		COOH	m.p. 265–70° (dec.)		140,149, 409,170
						Et ester, m.p. 202–4°	140
						Et ester·H_2O, m.p. 205°	141
						hydrazide, m.p. 265–70° (dec.)	141
	OH		OH		m.p. 252–53 (dec.)		458
Cl	OH		OH	Cl	m.p. 195°		565

TABLE XII-51. Pyridinediol Ethers 

R_2	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
				2,3-DIOL ETHERS			
OEt	OEt				b.p. 215–17°		207
						dibromo, m.p. 69–70°	458
OMe	OMe			Me		picrate, m.p. 121–22°	186
OMe	OMe			COOH	m.p. 175°		186
				2,4-DIOL ETHERS			
OMe		OMe				picrolonate, m.p. 152–53°	226,680,221
						picrate, m.p. 162–64°	601
OEt		OEt				picrate, m.p. 139.5–40.0°	458
						picrolonate, m.p. 158°	458
OPh		OPh			m.p. 87.5–88.5°	picrate, m.p. 140–41°	227
OEt		OEt	Cl		m.p. 56.5–57.0°		220
OPh		OPh		Br	m.p. 87–88°		227
OMe	CN	OMe			m.p. 146.5–47.5°		685,222,682
OMe		OMe	CN		m.p. 154.7–55.7°		223
OMe	CN	OMe		COOH	m.p. 205–6°		682
OEt	Br	OEt			m.p. 55–55.5°		868
OEt		OEt	Br		m.p. 71–72°		868

(continued)

TABLE XII-51. Pyridinediol Ethers (*continued*)

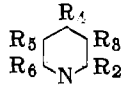
R_2	R_3	R_4	R_5	R_6	Physical Properties	Derivatives	Ref.
			2,5-DIOL ETHERS				
OEt		OEt				picrate, m.p. 118–19°	458
						picrolonate, m.p. 139°	458
			2,6-DIOL ETHERS				
OEt			OEt		m.p. 21.5°		216
OPh			OPh		m.p. 60–61°		227
OMe	Me		OMe		m.p. 33°		578
OMe	Me	Me	OMe		m.p. 26–27; b.p. 61–62°/0.9 mm.		578
OPh	Br		OPh		m.p. 93.5–94.5°		227
OEt	Br	Br	OEt		m.p. 72–73°		458
OMe	COOH		OMe		m.p. 224°	Et ester, b.p. 263–67°	217
						hydrazide, m.p. 170°	727,217,100
OEt	COOH		OEt		m.p. 100–1°		206,217
						acid chloride, b.p. 118–20°/1 mm.	206
						Et ester, b.p. 283–86°	217
						hydrazide, m.p. 128.5–32.0°	217,100,137
OPr	COOH		OPr		m.p. 97°	hydrazide, m.p. 94°	217
					m.p. 91°	acid chloride, b.p. 122–24°/1.4 mm.	206
						Et ester, b.p. 153–55°/5 mm.	217

O(*i*-Pr)		COOH		O(*i*-Pr)	m.p. 131°	Et ester, b.p. 144–46°/7 mm.	217
						hydrazide, m.p. 141°	217
O(*n*-Bu)		COOH		O(*n*-Bu)	m.p. 74°	acid chloride, b.p. 154–55°/1.6 mm.	206
					m.p. 78°	Et ester, b.p. 173–74°/1 mm.	217
						hydrazide, m.p. 96–98°	100,217
O(*i*-Am)		COOH		O(*i*-Am)	m.p. 81°	Et ester, b.p. 175–77°/1 mm.	217
					m.p. 72–73°	acid chloride, b.p. 158–60°/1 mm.	206
						hydrazide, m.p. 75°	217
OPh		COOH		OPh	m.p. 183°	Et ester, b.p. 225–27°/2 mm.	217
						hydrazide, m.p. 155°	217
				3,4-DIOL ETHERS			
	OMe	OMe				picrate, m.p. 173–74°.	736
	OEt	OEt				picrate, m.p. 169–70°	458
						picrolonate, m.p. 212–13°	458
				3,5-DIOL ETHERS			
	OMe		OMe		b.p. 66–68°/0.2 mm.	picrate, m.p. 146–47°	215
	OEt		OEt			picrate, m.p. 124.5–25.5°	458
						picrolonate, m.p. 153°	458
						mercurichloride, m.p. 104.5–6.0°	273
						dichloride	692
						dibromide, m.p. 141–42°	692
Me	OEt	Me	OEt	Me	b.p. 217–19°		763
Br	OEt		OEt		m.p. 75–76°		565

(*continued*)

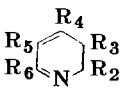
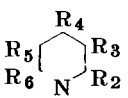
TABLE XII-51. Pyridinediol Ethers (*continued*)

R_2	R_3	R_4	R_5	R_6	Physical Properties	Derivatives	Ref.
Br	OEt	OEt	Br		m.p. 138–39°		565,425
NO_2	OMe	OMe			m.p. 115.5–16.5°		215
NO_2	OEt	OEt			m.p. 117.5–18.5°		564
NO_2	OEt	OEt	NO_2		m.p. 120°		564,207
Br	OEt	OEt	NO_2		m.p. 164.5–65.5°		565
NH_2	OMe	OMe			m.p. 69–70°	picrate, m.p. 236.0–36.5°	215
NH_2	OEt	OEt			m.p. 81–82°	acetyl, m.p. 111–12°	743,564
NH_2	OEt	OEt	NH_2		m.p. 60° (dec.)		207
NH_2	OEt	OEt	Br		m.p. 129–30°	acetyl, m.p. 135.5–36.5°	565
COOH	OEt	OEt			m.p. 132–33°		565
COOH	OEt	OEt	COOH		m.p. 161–62° (dec.)		565
COOH	OEt	OEt	Br		m.p. 163–64°		565
CN	OEt	OEt			m.p. 105–6°		565
CN	OEt	OEt	Br		m.p. 164–65°		565

TABLE XII-52. Pyridinetriols and Their Ethers 

R_2	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
OH	OH	OH				monobromide	170
OH		OH		OH	m.p. 220–30° (dec.)		5,597
OH	OH	OH		Me	m.p. 263–65°	diacetyl, m.p. 247°	818
OH	OH	Me		OH		dihydrohydrochloride, m.p. 82–83°	578
						triacetyl, b.p. 170–74°/0.9 mm.	578
OH	Me	OH		OH	m.p. 240°		5*a*
OH	Et	OH		OH	m.p. 245°		5*a*
OH	OH	OH		COOH			140
OH	Me	Me	OH	OH		hydrochloride, m.p. 98–100°	578
						triacetyl, b.p. 175–77°/0.9 mm.	578
OH	Me	OH	Me	OH			5*a*
OH	CN	OH	OH	Me	m.p. 330°		84
OEt	OEt		OEt		m.p. 30.5–31.5°		565
OMe		OMe		OMe	m.p. 48.5–49.5°		226,492
OPh		OPh		OPh	m.p. 79–79.5°		227
OMe	Cl	OMe	Cl	OMe	m.p. 95.5–96°		492
OEt	OEt		OEt	OEt	m.p. 52.5–53.0°		565
OH	OH			OH		triacetyl, m.p. 159°	881
OH	OH	Me	Ph	OH		triacetyl, m.p. 106–7°	881

TABLE XII-53. Dihydropyridinols and Dihydropyridones

R_2	R_3	R_4	R_5	R_6	Physical properties	Derivatives	Ref.
							
OH, Ph		Ph	Ph	Br	m.p. 100°	benzoyl, m.p. 137°	20
OH, *p*-MeC_6H_4		Ph	Ph	Br	m.p. 119°		22
OH	COOH	Ph		Ph		amide, m.p. 166°	19
OH	CN	Ph		Ph	m.p. 200°		21,19
OH	CN	Ph	Br	Ph	m.p. 178–81°		19
OH,	—$(CH_2)_3$—		COOH	OH	m.p. > 310°		60
OH,	—$(CH_2)_{13}$—		CN	OH	m.p. 247–48°		30
							
OH				Me	m.p. 234–36°		24
OH		Ph		Ph	m.p. 130°		18

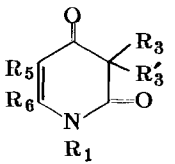
OH	Ph	Ph	Ph		m.p. 173°		20
OH	p-$NO_2C_6H_4$	Ph		Ph	m.p. 236°		21
OH	Ph	Ph		p-$MeOC_6H_4$	m.p. 199°		22
OH			COOEt	CH_2Br	m.p. 120–21°		244
OH			COOEt	$CH_2NC_5H_5{}^+Br^-$	m.p. 181–82°		244
OH			COOEt	CH_2(1-carbethoxy-2-ketocyclohexyl)	b.p. 100–20°/0.001 mm.		244
OH	CN	Ph		Ph	m.p. 219–20°		21
OH	CN	i-Pr	COOEt	Me			90
OH	CN	Pr	COOEt	Me	m.p. 141°		90
OH	CN	p-$NO_2C_6H_4$	COOEt	Me	m.p. 129°		90
OH	CN,Br	CH_2OPh	COOEt	Me	m.p. 152°		90
Keto	CN, Br	Ph	Br	Ph	m.p. 195° (dec.)		19
OH			cyclopentyl	OH	m.p. 131°		31
OH	CN	OH	Me	Me	m.p. 347° (dec.)	4-acetyl, m.p. 283–85° (dec.)	53
				(?) Dihydro			
Me	OCH_2Ph	COOEt	COOEt		m.p. 102–4°		45

(continued)

TABLE XII-53. Dihydropyridinols and Dihydropyridones (*continued*)

R_1	R_2	R_3	R_4	R_5	R_6	Physical properties	Ref.
							
Me	keto				Me	b.p. 96–98°/9 mm.	640
Me	keto				Et	b.p. 108–11°/11 mm.	640
Me	keto				*n*-Pr	b.p. 116°/10 mm.	640
Me	keto				*n*-Bu	b.p. 134°/8 mm.	640
Me	keto				*n*-Am	b.p. 145°/9.5 mm.	640
Me	keto				*n*-Hex	b.p. 158°/8 mm.	640
Cl	Cl_2	Cl_2	keto	Cl	Cl	m.p. 96–97°	228

TABLE XII-54. 2,4-Diketo-3,3-dialkyltetrahydropyridines



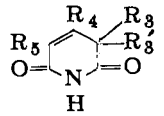
R_1	R_3	R_3'	R_5	R_6	Physical properties	Derivatives	Ref.
	Et	Et			m.p. 90–91°		625
	n-Pr	*n*-Pr			m.p. 92–93°		33
	i-Pr	*n*-Pr			m.p. 131–32°		33
	i-Pr	allyl			m.p. 86–87°		623
	allyl	allyl			m.p. 81–82°		33
	Et	*n*-Bu			m.p. 86°		33
	n-Pr	*n*-Bu			m.p. 101–2°		33
	n-hexyl	*n*-hexyl			m.p. 125°		33
	n-Pr	$CH_2CBr{=}CH_2$			m.p. 123–24°		623
Me	Et	Et			m.p. 74–75°		733
					b.p. 152–54°/4 mm.		733
Me	*n*-Pr	*n*-Pr			m.p. 61–62°		33
					b.p. 162–64°/14 mm.		733
Et	Et	Et			b.p. 148–50°/14 mm.		733
	Et	Et	Me		m.p. 140–41°		624
	n-Pr	*n*-Pr	Me		m.p. 68°		624
	n-Pr	*n*-Pr		Me	m.p. 104°		628,623

(*continued*)

TABLE XII-54. 2,4-Diketo-3,3-dialkyltetrahydropyridines (*continued*)

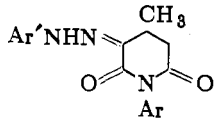
R_1	R_3	R_3'	R_5	R_6	Physical properties	Derivatives	Ref.
	n-Pr	allyl		Me	m.p. 73–74°		623
	allyl	allyl		Me	m.p. 84–85°		623
	Et	methallyl		Me	m.p. 100–1°		623
	allyl	methallyl		Me	m.p. 144–45°		623
	n-hexyl	allyl		Me	m.p. 152–53°		623
	Et	Et	Cl		m.p. 116–17°		626
	Et	Et	Br		m.p. 111-12°		626
	Et	Et	I		m.p. 117–118°		626
	n-Pr	*n*-Pr	Cl		m.p. 74–75°		626
	n-Pr	*n*-Bu	Br		m.p. 88–89°		626
	Et	Et		COOH	m.p. 145–46°	Et ester, m.p. 80–81°	34
	Me	Pr		COOH	m.p. 144–45°	Et ester, m.p. 84–85°	34
	allyl	allyl		COOH	m.p. 148–50°	Et ester, b.p. 202–3°/14 mm.	34
	Pr	Pr		COOH	m.p. 110–1°		34
						Et ester, m.p. 64–65°	620,34
Me	Et	Et	Me		m.p. 68°		624
Allyl	allyl	allyl		Me	b.p. 183–86°/14 mm.		733
Me	Et	Et	Br		m.p. 80–81°		626
	n-Pr	*n*-Pr	Br	Me	m.p. 141–42°		626
	n-Pr	*n*-Pr	Br	Me	m.p. 141–42°		626
	n-Pr	*n*-Pr	I	Me	m.p. 127–28°		626
	Br	COOH	Br	Me		Et ester, m.p. 168–69°	543
Me	*n*-Pr	*n*-Pr	Br	Me	m.p. 86–87°		626

TABLE XII-55. 2,6-Diketo-3,3-dialkyltetrahydropyridines



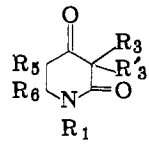
R_3	R'_3	R_4	R_5	Physical properties	Derivatives	Ref.
Me	Me			m.p. 125–27°		637
Et	Et			m.p. 90–92°		637
Ph	Ph			m.p. 163–65°		637
Ph	Ph			m.p. 170–72°		637
$(CH_2)_2N(Et)_2$	Ph				hydrochloride, m.p. 225–27°	637
Et	COOEt	—$(CH_2)_3$—		m.p. 112°		30

TABLE XII-55a. 1-Aryl-1,2,5,6-tetrahydro-2,6-diketo-4-methyl-5-arylhydrazonopyridines



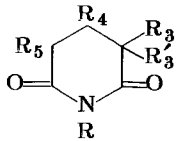
Ar	Ar′	M.p., °C.	Ref.
Ph	4-ClC_6H_4	239	835
Ph	2,6-$Me_2C_6H_3$	192	835
Ph	1,4-C_6H_4	242	835
Ph	1-naphthyl	302	835
Ph	2-naphthyl	254	835
4-MeC_6H_4	4-$MeOC_6H_4$	221	835
4-$MeOC_6H_4$	4-ClC_6H_4	241	835
4-$MeOC_6H_4$	2,6-$Me_2C_6H_3$	204	835
2,6-$Me_2C_6H_3$	Ph	82	835
2,6-$Me_2C_6H_3$	2-$MeOC_6H_4$	213	835
2,6-$Me_2C_6H_3$	4-$MeOC_6H_4$	169	835
2,6-$Me_2C_6H_3$	2,5-$(MeO)_2C_6H_3$	210	835
2,6-$Me_2C_6H_3$	4-$Me_2NC_6H_4$	190	835
2,6-$Me_2C_6H_3$	4-$Et_2NC_6H_4$	149	835
2,6-$Me_2C_6H_3$	4-ClC_6H_4	200	835
4-ClC_6H_4	4-$MeOC_6H_4$	249	835
2,5-$(MeO)_2C_6H_3$	4-ClC_6H_4	208	835

TABLE XII-56. 2,4-Diketo-3,3-dialkylpiperidines



R_1	R_3	R'_3	R_5	R_6	Physical properties	Ref.
	Et	Et			m.p. 104°	625, 629
	Me	Me	Me		m.p. 110–11°	624
	Me	Et	Me		m.p. 97–99°	624
	Et	Et	Me		m.p. 72–73°	625
					m.p. 75–76°	624
	Pr	Pr	Me		m.p. 107°	624
	Me	Me		*i*-Pr	m.p. 151–52°	630
	Et	Et		Me	m.p. 92–93°	630
	Et	Et		Et	m.p. 72°	630
	Et	Et		*i*-Pr	m.p. 100°	630
	Et	Et		*n*-Bu	m.p. 50–51°	630
	n-Pr	*n*-Pr		Me	m.p. 97–98°	630
	Et	Et		allyl	m.p. 151–52°	630
	Me	Me		Ph	m.p. 168°	630
	Me	Et		Ph	m.p. 123–24°	630
	Et	Et		Ph	m.p. 104°	630
	Et	Et		CH_2Ph	m.p. 129°	630
	Et	Et		CH_2CH_2Ph	m.p. 99–110°	630
	Et	Et		$(CH_2)_4OMe$	m.p. 41°	630
Me	Me	Me	Me		b.p. 138°/12 mm.	624
Me	Me	Et	Me		b.p. 163°/20 mm.	624
Me	Et	Et	Me		m.p. 97°	624
Me	Et	Et		Me	b.p. 143°/10.0 mm.	630
Me	Et	Et		*i*-Pr	b.p. 91°/0.01 mm.	630
Me	Et	Et		Ph	b.p. 143°/0.04 mm.	630
	Et	Et	Me	Me	m.p. 69–70°	630
	n-Pr	*n*-Pr	Me	Me	m.p. 96°	630

TABLE XII-57. 2,6-Diketo-3,3-dialkylpiperidines



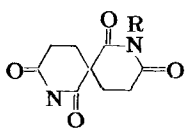
R	R_3	R_3'	R_4	R_5	Physical properties	Derivatives	Ref.
	Me	Me				monobromo (5?), m.p. 140–41°	637
	Et	Et				monobromo (5?), m.p. 106–8°	637
	Me	Ph			m.p. 100–4°		639
	Et	Ph			m.p. 82–86°		635,638
						monobromo (5?), m.p. 165–67°	637
	i-Pr	Ph			m.p. 115–18°		635
	i-Bu	Ph			m.p. 78–81°		635
	n-Am	Ph			m.p. 43–45°; b.p. 181–86°/0.3 mm.		635
	i-Am	Ph			m.p. 65–68°		635
	cyclohexyl	Ph			m.p. 140–44°		635
	1-cyclohex-enyl	Ph			m.p. 167–70°		635
	$CH(Me)CH_2$-OH	Ph			m.p. 128–30°		639
	Ph	Ph				monobromo (5?), m.p. 185–87°	637

(*continued*)

TABLE XII-57. 2,6-Diketo 3,3-dialkylpiperidines (*continued*)

R	R_3	R_3'	R_4	R_5	Physical properties	Derivatives	Ref.
	p-ClC_6H_4	Ph			m.p. 155–57°		635
	2-Py	Ph			m.p. 182–84°		635
	2-Py	*p*-ClC_6H_4			m.p. 185–87°		635
	2-thienyl	Ph			m.p. 185–90°		635
	Ph	$CH_2CH_2NMe_2$			m.p. 138–40°	hydrochloride, m.p. 220–25°	634
						methiodide, m.p. 217–20°	634
	Ph	$CH_2CH_2NEt_2$			m.p. 118–20°	hydrochloride, m.p. 72–75°	634
						methiodide, m.p. 200–2°	634
	Ph	$(CH_2)_3NEt_2$			b.p. 198–205°/0.2 mm.	hydrochloride, m.p. 187–90°	634
	Ph	$CH_2CHMeNMe_2$			m.p. 170–72°	hydrochloride, m.p. 245–49°	634
	Ph	$(CH_2)_3N(CH_2)_5$			b.p. 198–204°/0.2 mm.	hydrochloride, m.p. 110–13°	634
	Ph	$(CH_2)_2NMeCH(CH_2)_6$			m.p. 97–98°	hydrochloride, m.p. 231–37°	634
	m-$MeOC_6H_4$	$CH_2CH_2NMe_2$			m.p. 158–60°	hydrochloride, m.p. 212–14°	634
	m-$MeOC_6H_4$	$CH_2CH_2NEt_2$			m.p. 118–20°	hydrochloride, m.p. 188–90°	634
	p-ClC_6H_4	$CH_2CH_2NEt_2$			m.p. 136–41°	hydrochloride, m.p. 187–89°	634

NMe_2	α-naphthyl	$CH_2CH_2NEt_2$	m.p. 164.0–64.5°	hydrochloride, m.p. 232–34°	634
	2-thienyl	$CH_2CH_2NEt_2$	m.p. 116–23°	hydrochloride, m.p. 149–51°	634
	3-Py	$CH_2CH_2NMe_2$	m.p. 105–7°	hydrochloride, m.p. 150–56°	634
Me	Et	Ph	b.p. 138–42°/0.4 mm.		635
n-Pr	Et	Ph	b.p. 119–22°/0.05 mm.		635
CH_2Ph	Et	Ph	m.p. 48–52°; b.p. 173–76°/0.07 mm.		635
$(CH_2)_2NEt_2$	Et	Ph	b.p. 148–53°/0.1 mm.		635
$(CH_2)_2NEt_2$	$(CH_2)_2NEt_2$	Ph	b.p. 184–89°/0.05 mm.		634
$(CH_2)_3NEt_2$	$(CH_2)_3NEt_2$	Ph	b.p. 218–27°/0.03 mm.	diethiodide, m.p. 155–58°	634
$(CH_2)_2NMe$-$CH(CH_2)_6$	$(CH_2)_2NMe$-$CH(CH_2)_6$	Ph	b.p. 252–62°/0.15 mm.	dimethiodide, m.p. 233–35°	634



R	Physical properties	Derivatives	Ref.
H	m.p. 268–70°		636
$(CH_2)_2NEt_2$	b.p. 236–42°/0.07 mm.	methiodide, m.p. 78–80° (dec.)	636
$(CH_2)_3NEt_2$	b.p. 234–36°/0.05 mm.	methylbromide,	636
$(CH_2)_3$ piperidyl	b.p. 283–86°/0.07 mm.	methiodide, m.p. 122–24° (dec.)	636

TABLE XII-58. Hydroxy and Alkoxy Bipyridyls

Compound	Physical properties	Derivatives	Ref.
6,6′-Dichloro-3,3′,5,5′-tetrahydroxy-2,2′-dipyridyl	m.p. 295° (dec.)		425
3,3′,5,5′-Tetraethoxy-2,2′-dipyridyl	m.p. 138–39°	dipicrate, m.p. 136–37°	425
6,6′-Dibromo-3,3′,5,5′-tetraethoxy-2,2′-dipyridyl	m.p. 220.5–21.5°		425
3,3′,5,5′,6,6′-Hexaethoxy-2,2′-dipyridyl	m.p. 126.5–27°		425
6,6′-Dihydroxy-3,3′-dipyridyl	m.p. 366–68°		749

G. BIBLIOGRAPHY

1. Thorpe, *J. Chem. Soc.*, **87**, 1669 (1905).
2. Ruhemann, *ibid.*, **63**, 259 (1893).
3. Ruhemann, *ibid.*, **63**, 874 (1893).
4. Ruhemann, *ibid.*, **75**, 249 (1899).
4a. Guthzeit, *Ber.*, **32**, 779 (1899).
5. Niementowski and Sucharda, *J. prakt. Chem.*, **94**, (2) 193 (1916).
5a. Baron, Remfry, and Thorpe, *J. Chem. Soc.*, **87**, 1730 (1905).
6. Ingold and Nickoles, *ibid.*, **122**, 1638 (1922).
7. Dixit, *J. Indian Chem. Soc.*, **8**, 787 (1931).
8. Limaye and Goyate, *J. Univ. Bombay*, **3**, 135 (1934); *C.A.*, **26**, 3496[5] (1932).
9. U.S. patent 2,185,243, Boese, (Jan. 2, 1940); *C.A.*, **34**, 2863[7] (1940).
9a. Feist, *Ann.*, **257**, 253 (1890).
10. Levelt and Wibaut, *Rec. trav. chim.*, **48**, 466 (1929).
11. Behrmann and Hofmann, *Ber.*, **17**, 2681 (1884).
11a. Bland and Thorpe, *J. Chem. Soc.*, **101**, 889 (1912).
12. Rogerson and Thorpe, *ibid.*, **87**, 1685 (1905).
12a. Adams, Van Duuren, and Braun, *J. Am. Chem. Soc.*, **74**, 5608 (1952).
13. Mooradian and Cloke, *ibid.*, **68**, 785 (1946).
14. Errera, *Ber.*, **31**, 1241 (1898).
14a. Ruhemann and Browning, *J. Chem. Soc.*, **73**, 284 (1898).
15. Kon and Nanjii, *ibid.*, **1932**, 2426.
16. Chauvelier, *Compt. rend.*, **212**, 793 (1941); **226**, 677 (1948).
17. Chauvelier, *Bull. soc. chim. France*, **1954**, 734.
18. Kohler, Graustein, and Merrill, *J. Am. Chem. Soc.*, **44**, 2536 (1922).
19. Kohler and Souther, *ibid.*, **44**, 2903 (1922).

20. Kohler and Allen, *ibid.*, **46**, 1522 (1924).
21. Allen, *ibid.*, **47**, 1733 (1925).
22. Allen, *ibid.*, **49**, 1112 (1927).
23. Allen and Scarrow, *Can. J. Research*, **11**, 395 (1934).
24. Albertson, *J. Am. Chem. Soc.*, **74**, 3816 (1952).
25. Barat, *J. Indian Chem. Soc.*, **7**, 321 (1930).
26. Ruzicka and Fornasir, *Helv. Chim. Acta*, **2**, 338 (1918).
27. Basu, *J. Indian Chem. Soc.*, **7**, 815 (1930).
28. Van Wagtendonk and Wibaut, *Rec. trav. chim.*, **61**, 728 (1942).
29. British patent 4,553,097, Bergel and Cohen (May 7, 1943); *C.A.*, **38**, 4271 (1944).
30. Prelog and Metzler, *Helv. Chim. Acta*, **29**, 1163 (1946).
31. Lochte, Thomas, and Truitt, *J. Am. Chem. Soc.*, **66**, 550 (1944).
32. Schnider, *Festschrift Emil Barell*, **1936**, 195; *C.A.*, **31**, 2607[6] (1937).
33. U.S. patent 2,090,068, Preiswerk and Schnider, (Aug. 17, 1937); German patent 634,284 (Aug. 25, 1936); *C.A.*, **31**, 2191 (1933).
34. German patent 668,489 (Dec. 5, 1938); *C.A.*, **33**, 2150[4] (1939).
35. Knoevenagel and Fries, *Ber.*, **31**, 761 (1898); *Ann.*, **281**, 25 (1894); Knoevenagel and Ruschaupt, *Ber.*, **31**, 1025 (1898).
36. Guareschi, *Chem. Zentr.*, **1**, 601 (1896).
37. Ranganathan, *J. Indian Chem. Soc.*, **16**, 67 (1939).
38. Stevens and Beutel, *J. Am. Chem. Soc.*, **65**, 449 (1943).
39. Stevens, Beutel, and Chamberlin, *ibid.*, **64**, 1093 (1942).
40. Wibaut and Kooyman, *Rec. trav. chim.*, **63**, 231 (1944).
41. Bardhan, *J. Chem. Soc.*, **1929**, 2223.
42. Sen Gupta, *ibid.*, **107**, 1347 (1915).
43. Rubtsov, *J. Gen. Chem. U.S.S.R.*, **9**, 1524 (1939); *C.A.*, **34**, 2845[4] (1940).
44. Rubtsov, *ibid.*, **7**, 1885 (1937); *C.A.*, **32**, 5261 (1938).
45. Cohen, Haworth, and Hughes, *J. Chem. Soc.*, **1952**, 4374.
46. Cohen and Silk, *ibid.*, **1952**, 4386.
47. Davoll and Kipping, *ibid.*, **1953**, 1395.
48. Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 1245 3307 (1939).
49. Itiba and Emoto, *Sci. Papers, Inst. Phys. Chem. Research (Tokyo)*, **38**, 347. (1940); *C.A.*, **35**, 6960[3] (1941).
50. Basu, *J. Indian Chem. Soc.*, **8**, 119 (1931).
51. Plati and Wenner, *J. Org. Chem.*, **15**, 1165 (1950).
52. Tracy and Elderfield, *ibid.*, **6**, 63, (1941).
53. Joshi, Kaushal, and Deshapande, *J. Indian Chem. Soc.*, **18**, 479 (1941).
54. Mariella and Stanfield, *J. Am. Chem. Soc.*, **73**, 1368 (1951).
55. Mariella, *ibid.*, **69**, 2670 (1947).
56. Mariella and Kvinge, *ibid.*, **70**, 3126 (1948).
57. Mariella, Peterson, and Ferris, *ibid.*, **70**, 1494 (1948).
58. Gruber and Schlögl, *Monatsh.*, **81**, 83 (1950).
59. Perez-Medina, Mariella, and McElvain, *J. Am. Chem. Soc.*, **69**, 2574 (1947).

60. Thompson, *ibid.*, **53**, 3160 (1931).
61. Prelog and Geyer, *Helv. Chim. Acta*, **28**, 1677 (1945).
62. Barat, *J. Indian Chem. Soc.*, **8**, 801 (1931).
63. Fanta and Stein, *J. Am. Chem. Soc.*, **77**, 1045 (1955).
64. Troccoli, *Ann. Chim. appl.*, **21**, 41 (1931); *C.A.*, **25**, 2999[8] (1931).
65. Simonsen and Nayak, *J. Chem. Soc.*, 792 (1915).
66. Mariella and Belcher, *J. Am. Chem. Soc.*, **73**, 2616 (1951).
67. Barat, *J. Indian Chem. Soc.*, **7**, 851 (1930).
68. Kochetwa, *Doklady Akad. Nauk. S.S.S.R.*, **84**, 289 (1952).
69. Dornow, *Ber.*, **73**, 153 (1940).
70. Collie, *Ann.*, **226**, 294 (1884).
71. Collie, *Ber.*, **20**, 445 (1887).
72. Michaelis and von Arend, *Ber.*, **34**, 2283 (1901).
73. Michaelis and Hanisch, *ibid.*, **35**, 3156 (1902).
74. Knoevenagel and Cremer, *ibid.*, **35**, 2390 (1902).
75. Rabe, *ibid.*, **45**, 2170 (1912).
76. Kondo and Nakajima, *ibid.*, **65**, 791 (1932).
77. Bruce and Perez-Medina, *J. Am. Chem. Soc.*, **69**, 2571 (1947).
78. Prelog and Szpilfogel, *Helv. Chim. Acta*, **25**, 1306 (1942).
79. Prelog and Hinden, *ibid.*, **27**, 1854 (1944).
80. Prelog and Geyer, *ibid.*, **28**, 1680 (1945).
81. Basu, *J. Indian Chem. Soc.*, **12**, 299 (1935).
82. Ochiai and Ito, *Ber.*, **74**, 1111 (1941).
83. Golides, *J. prakt. Chem.*, **123**, 169 (1929).
84. U.S. patent 2,523,612, Coover and Bowman (Sept. 26, 1950); *C.A.*, **45**, 2030*d* (1951).
85. Gibson and Simonsen, *J. Chem. Soc.*, **1929**, 1074.
86. Guareschi, *Chem. Zentr.*, **1897, I**, 903, 927.
87. Palit, *J. Indian Chem. Soc.*, **14**, 219 (1937).
88. Day and Thorpe, *J. Chem. Soc.*, **117**, 1465 (1920).
89. Curtis, Day, and Kimmins, *ibid.*, **123**, 3131 (1923).
90. U.S. patent 2,334,490, Hoffer (Nov. 16, 1943); *C.A.*, **38**, 2664[8] (1944).
91. Guareschi, *Gazz. chim. ital.*, **48**, (2), 83 (1918).
92. Guareschi, *Chem. Zentr.*, **1901, I**, 577.
93. Campbell, Ackerman, and Campbell, *J. Org. Chem.*, **15**, 337 (1950).
94. Thole and Thorpe, *J. Chem. Soc.*, **99**, 422 (1911).
95. Wood and Thorpe, *ibid.*, **103**, 1586 (1913).
96. Errera, *Ber.*, **31**, 1682 (1898).
97. Snyder and Jones, *J. Am. Chem. Soc.*, **68**, 1253 (1946).
98. Gotterman and Skita, *Ber.*, **49**, 494 (1916).
99. Hurd and Kelso, *J. Am. Chem. Soc.*, **62**, 1548 (1940).
100. Isler, Gutmann, Straub, Fust, Bohni, and Studer, *Helv. Chim. Acta*, **38**, 1033 (1955).
101. Den Hertog, *Rec. trav. chim.*, **65**, 129 (1946).
102. U.S. patent 2,557,076, Chitwood; *C.A.*, **46**, 145 (1952).

103. Von Pechmann and Welsh, *Ber.*, **17**, 2384 (1884).
104. Caldwell, Tyson, and Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).
105. Hers and Rittenberg, *J. Biol. Chem.*, **186**, 429 (1950).
106. Von Anschütz, Bendix, and Kerp, *Ann.*, **259**, 148 (1890).
107. Kohler, *J. Am. Chem. Soc.*, **44**, 384 (1922).
108. Mitra, *J. Indian Chem. Soc.*, **15**, 455 (1938).
109. Kohler and Smith, *J. Am. Chem. Soc.*, **44**, 624 (1922).
110. Fried and Elderfield, *J. Org. Chem.*, **6**, 566 (1941).
111. Dimroth, *Ber.*, **35**, 2882 (1902).
112. Linstead and Williams, *J. Chem. Soc.*, **1926**, 2735.
113. Ruhemann, *ibid.*, **75**, 411 (1899).
114. Ruhemann, *Ber.*, **20**, 3366 (1887).
115. Leben, *ibid.*, **29**, 1673 (1896).
116. Wiley, Beasley, and Knabeschuh, *J. Am. Chem. Soc.*, **76**, 311 (1954).
117. Wiley, Knabeschuh, Duckwall, and Smith, *ibid.*, **76**, 625 (1954).
118. Wiley, Hart, Davis, and Smith, *ibid.*, **76**, 4931 (1954).
119. Ruzicka, *Helv. Chim. Acta*, **4**, 486 (1921).
120. Robinson and Thornley, *J. Chem. Soc.*, 2169 (1924).
121. Haitinger and Lieben, *Monatsh.*, **6**, 279 (1885).
122. Toomey and Riegel, *J. Org. Chem.*, **17**, 1492 (1952).
123. Smirnoff, *Helv. Chim. Acta*, **4**, 599 (1921).
124. Freeman, Ringk, and Spoerri, *J. Am. Chem. Soc.*, **69**, 858 (1947).
125. Hebky, *Forsch. für Pharmazie & Biochemie*, **16**, 348 (1951).
126. Ettel and Hebky, *Collection Czechoslov. Chem. Communs.*, **15**, 639 (1950).
127. German patent 554,950, Dohrn and Diedrich (June 30, 1932); *C.A.*, **26**, 5970[8] (1932).
128. Schwab, *J. Am. Chem. Soc.*, **76**, 1189 (1954).
129. Vorländer, *Ber.*, **58**, 1893 (1925).
130. Borsche and Bonacker, *ibid.*, **54**, 2678 (1921).
131. British patent 355,017 (1930); *C.A.*, **26**, 5574[8] (1932).
132. Armit and Nolan, *J. Chem. Soc.*, **1931**, 3023.
133. Ost and Meyer, *Monatsh.*, **26**, 1311 (1905).
134. Belonosov, *Zhur. Priklad. Khim.*, **24**, 113 (1951); *C.A.*, **46**, 11209[9] (1952).
135. Wibaut and Kleipool, *Rec. trav. chim.*, **66**, 24 (1947).
136. Kleipool and Wibaut, *ibid.*, **69**, 1041 (1950).
137. Kostermans, *ibid.*, **66**, 93 (1947).
138. Kleipool and Wibaut, *ibid.*, **66**, 459 (1947).
139. Adams and Johnson, *J. Am. Chem. Soc.*, **71**, 705 (1949).
140. Garkusha, *J. Gen. Chem. U.S.S.R.*, **16**, 2025 (1946); *C.A.*, **42**, 566a (1948).
141. Heyns and Vogelsang, *Ber.*, **87**, 1440 (1954).
142. Hebký, Rádek, and Urban, *Chem. listy*, **46**, 736 (1952); *C.A.*, **47**, 11187b–g (1953).
143. Neelakantan, Iyer, and Guha, *J. Indian Inst. Sci.*, **31A**, 51 (1949); *C.A.*, **47**, 5492a (1953).
144. Neelakantan, Iyer, and Guha, *ibid.*, **31A**, 57 (1949); *C.A.*, **47**, 5492f (1953).

145. Neelakantan, Iyer, and Guha, *ibid.*, **29**, 61 (1952).
146. Desaphande, *ibid.*, **9**, 303 (1932).
147. Benary and Bitter, *Ber.*, **61**, 1057 (1928).
148. Borsche and Peter, *Ann.*, **453**, 148 (1927).
149. Yabuta, *J. Chem. Soc.*, 575 (1924).
150. Arndt, Eistert, Scholz, and Aron, *Ber.*, **69**, 2373 (1936).
151. Rassweiler and Adams, *J. Am. Chem. Soc.*, **46**, 2785 (1924).
152. Haitinger, *Monatsh.*, **6**, 103 (1885).
153. Perkin, *J. Chem. Soc.*, **51**, 484 (1887).
154. Feist, *Ann.*, **257**, 253 (1890).
155. U.S. patent 2,333,493, Rigby (Nov. 2, 1943); *C.A.*, **38**, 2507[8] (1944).
156. Schroeder and Rigby, *J. Am. Chem. Soc.*, **71**, 2205 (1949).
157. Errera, *Ber.*, **31**, 1241 (1898); **34**, 3691 (1901).
158. Reynolds, Humphlett, Swamer, and Hauser, *J. Org. Chem.*, **16**, 165 (1951).
159. Schroeter and Seidler, *J. prakt. Chem.*, **105**, 165 (1932).
160. Schroeter, *Ber.*, **65**, 432 (1932).
161. Collie, *J. Chem. Soc.*, **59**, 179 (1891).
162. U.S. patent 2,431,190, Morgan (Nov. 18, 1947); *C.A.*, **42**, 2198b (1948).
163. Wislicenus and Schollkopf, *J. prakt. Chem.*, **95**, 269 (1917).
164. Kaushal, *J. Indian Chem. Soc.*, **20**, 127 (1943).
165. Adickes and Meister, *Ber.*, **68**, 2191 (1935).
166. Kuhn and Jerchel, *ibid.*, **76**, 413 (1943).
167. Pickard and Lochte, *J. Am. Chem. Soc.*, **69**, 14 (1947).
168. Abe, Kitagawa, and Ishimura, *J. Pharm. Soc., Japan,* **73**, 969 (1953).
169. Baeyer, *Ber.*, **43**, 2338 (1910).
170. Ost, *J. prakt. Chem.*, **19**, 203 (1879); **23**, 441 (1881); **27**, 257 (1883).
171. Zincke and Muhlhausen, *Ber.*, **38**, 3824 (1905).
172. Fischer, Hess, and Stahlschmidt, *ibid.*, **45**, 2456 (1912).
173. Leditschke, *ibid.*, **85**, 202 (1952).
174. U.S. patent 2,636,882, Dunlop and Swadesh (Apr. 1953).
175. Leditschke, *Ber.*, **86**, 612 (1953).
176. Gruber, *Can. J. Chem.*, **31**, 564 (1953).
177. Gruber, *Ber.*, **88**, 178 (1955).
179. Clauson-Kaas, Elming, and Tyle, *Acta Chem. Scand.*, **9** (1), (1955).
180. Nielsen, Elming, and Clauson-Kaas, *ibid.*, **9** (9), (1955).
181. Clauson-Kaas and Nedenskov, *ibid.*, **9** (14), (1955).
182. Elming and Clauson-Kaas, *ibid.*, **9** (23), (1955).
183. Nielsen, Elming, and Clauson-Kaas, *ibid.*, **9** (30), (1955).
184. Aso, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **18**, 171 (1939), *C.A.*, **34**, 3782[6] (1940).
185. Aso, *J. Agr. Chem. Soc. Japan,* **15**, 629 (1939).
186. Aso, *ibid.*, **16**, 253 (1940).
187. Meyer and Heimann, *Compt. rend.*, **203**, 264 (1936).
188. U.S. patent 2,345,633, Salzer and Henecke (April 1944); *C.A.*, **38**, 4621 (1944).

189. Itiba and Miti, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **36**, 173, (1939).
190. Kuhn, Westphal, Wendt, and Westphal, *Naturwissenschaften*, **27**, 469 (1939).
191. Swiss patent 76,149 (Nov. 1917); *C.A.*, **12**, 1107[1] (1918).
192. Ueda, *J. Pharm. Soc. Japan*, **57**, 654 (1937).
193. Räth, *Ann.*, **486**, 284 (1931).
194. Moore, *J. Am. Chem. Soc.*, **77**, 3417 (1955).
195. Aso, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **18**, 182 (1939), *C.A.*, **34**, 3273 (1940).
196. Aso, *ibid.*, **18**, 177 (1937); *C.A.*, **34**, 3273[5] (1940).
197. Aso, *ibid.*, **18**, 180 (1939).
198. Williams, Kaufmann, and Mosher, *J. Org. Chem.*, **20**, 1139 (1955).
199. Kornfeld, *ibid.*, **20**, 1135 (1955).
200. Nedenskov, Elming, Nielsen, and Clauson-Kaas, *Acta Chem. Scand.*, **9**, 17 (1955).
201. British patent 288,628, Räth (April 14, 1927); *C.A.*, **23**, 607[2] (1929).
202. Swiss patent 146,546 (August 10, 1929); *C.A.*, **26**, 257 (1932).
203. Renshaw and Conn, *J. Am. Chem. Soc.*, **59**, 297 (1937).
204. Hill and McGraw, *J. Org. Chem.*, **14**, 783 (1949).
205. U.S. patent 2,540,218, Shaw (Feb. 6, 1951); *C.A.*, **45**, 6224 (1951).
206. Büchi, Labhart, and Ragaz, *Helv. Chim. Acta*, **30**, 507 (1949).
207. Koenigs, Gerdes, and Sirot, *Ber.*, **61**, 1022 (1928).
208. Koenigs and Neumann, *ibid.*, **48**, 956 (1915).
209. Shinkai and Parks, *J. Am. Pharm. Assoc.*, **39**, 283 (1950).
210. Graf, *J. prakt. Chem.*, **148**, 13 (1937).
211. Mosher and Look, *J. Org. Chem.*, **20**, 283 (1955).
212. Maier-Bode, *Ber.*, **69**, 1534 (1936).
213. Weidel and Blau, *Monatsh.*, **6**, 651 (1885).
214. Den Hertog, Falter, and Vander Linde, *Rec. trav. chim.*, **67**, 377 (1948).
215. Den Hertog, Van Ammers, and Schukking, private communication.
216. Den Hertog and Wibaut, *Rec. trav. chim.*, **55**, 122 (1936).
217. Okajima and Seki, *J. Pharm. Soc. Japan*, **73**, 845 (1953); *C.A.*, **48**, 10021g (1954).
218. Magidson and Menschikoff, *Ber.*, **58**, 113 (1925).
219. Fujimoto, *Pharm. Bull. (Tokyo)*, **4**, 1 (1956).
220. Kolder and den Hertog, *Rec. trav. chim.*, **72**, 285 (1953).
221. Den Hertog and Overhoff, *ibid.*, **69**, 468 (1950).
222. Späth and Koller, *Ber.*, **56**, 2454 (1923).
223. Taylor, Crovetti, and Loux, *J. Am. Chem. Soc.*, **77**, 5445 (1955).
224. Itai, *J. Pharm. Soc. Japan*, **65**, 70 (1945); *C.A.*, **45**, 8525i (1951).
225. Woodburn and Hellman, *Rec. trav. chim.*, **70**, 813 (1951).
226. Den Hertog, *ibid.*, **67**, 381 (1948).
227. Den Hertog and de Jonge, *ibid.*, **67**, 385 (1948).
228. Den Hertog, Maas, Kolder, and Combé, *ibid.*, **74**, 59 (1955).

229. Binz and Schickh, *Ber.*, **68**, 315 (1935).
230. Friedman, Braitberg, Tolstoouhov, and Tisza, *J. Am. Chem. Soc.*, **69**, 1204 (1947).
231. Shibasaki, *J. Pharm. Soc. Japan*, **71**, 662 (1951); *C.A.*, **46**, 8109h (1952).
232. Shibasaki, *ibid.*, **71**, 786 (1951); *C.A.*, **46**, 8090h (1952).
233. Räth, *Ann.*, **484**, 56 (1930).
234. Gruber, *Can. J. Chem.*, **31**, 1020 (1953).
235. Baumgarten and Chien-fan Su, *J. Am. Chem. Soc.*, **74**, 3828 (1952).
236. Takahashi, Shipasaki, Hamada, and Okuda, *J. Pharm. Soc. Japan*, **72**, 434, (1952); *C.A.*, **47**, 6404d (1953).
237. Gruber, *Can. J. Chem.*, **31**, 1181 (1953).
238. Koenings and Felter, *Ber.*, **57**, 1187 (1924).
239. Takahashi and Shibasaki, *J. Pharm. Soc. Japan*, **72**, 378 (1952); *C.A.*, **47**, 6403d (1953).
240. Shibasaki, *ibid.*, **72**, 431 (1952); *C.A.*, **47**, 6404a (1953).
241. Kushner, Dalalian, Cassell, Sanjurjo, McKenzie, and Subbarow, *J. Org. Chem.*, **13**, 834 (1948).
242. British patent 355,017 (1930); *C.A.*, **26**, 5574[8] (1932).
243. Meyer and Graf, *Ber.*, **61**, 2202 (1928).
244. Ramirez and Paul, *J. Org. Chem.*, **19**, 183 (1954).
245. Mariella and Havlik, *J. Am. Chem. Soc.*, **74**, 1915 (1952).
246. Brown, *J. Chem. Soc.*, **1956**, 1248.
247. Mariella, Callahan, and Jibril, *J. Org. Chem.*, **20**, 1721 (1955).
248. Wibaut, Speakman, and von Wagtendonk, *Rec. trav. chim.*, **58**, 100 (1939).
249. Kröhnke and Heffe, *Ber.*, **70**, 864 (1937).
250. Bradlow and Vanderwerf, *J. Org. Chem.*, **14**, 509 (1949).
251. U.S. patent 1,778,784, Räth (Oct. 21, 1930); *C.A.*, **25**, 116[8] (1931).
252. Räth and Schiffman, *Ann.*, **487**, 127 (1931).
253. Bäumler, Sorkin, and Erlenmeyer, *Helv. Chim. Acta*, **34**, 496 (1951).
254. Wibaut, Haagman, and van Dijk, *Rec. trav. chim.*, **59**, 202 (1940).
255. Klingsberg and Papa, *J. Am. Chem. Soc.*, **73**, 4988 (1951).
256. Haack, German patent 595,361 (1934); *C.A.*, **28**, 4069[9] (1934).
257. Graf, *J. prakt. Chem.*, **133**, 36 (1932).
258. Koller, *Ber.*, **60**, 1920 (1927).
259. Ochiai and Fujimoto, *Pharm. Bull. (Tokyo)*, **2**, 131 (1954).
260. Ochiai, Fujimoto, and Ichimura, *ibid.*, **2**, 137 (1954).
261. Ishikawa, *J. Pharm. Soc. Japan*, **65**, 6 (1945); *C.A.*, **45**, 8527h (1951).
262. Katada, *ibid.*, **67**, 56 (1947); *C.A.*, **45**, 9564 (1951).
263. Katada, *ibid.*, **67**, 59 (1947); *C.A.*, **45**, 9564 (1951).
264. Den Hertog, Jouwersma, van de Wal, and Willebrands-Schogt, *Rec. trav. chim.*, **68**, 4 (1949).
265. Blanksma, *ibid.*, **27**, 42 (1908).
266. Den Hertog and de Bruyn, *ibid.*, **70**, 182 (1951).
267. Shibasaki, *J. Pharm. Soc. Japan*, **72**, 3814 (1952); *C.A.*, **47**, 6403d (1953).

268. Seide, *Ber.*, **57**, 791 (1924).
269. Chichibabin, *ibid.*, **57**, 1802 (1924).
270. Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 534 (1918); *Chem. Zentr.*, **1923, III,** 1022.
271. Chichibabin and Widonowa, *ibid.*, **53**, 238 (1921); *Chem. Zentr.*, **1923, III,** 1025.
272. Chichibabin and Tjashelowa, *ibid.*, **50**, 483 (1918); *Chem. Zentr.*, **1923, III,** 1021.
273. Chichibabin and Jegerow, *ibid.*, **60**, 683 (1928); *C.A.*, **23**, 2182[4] (1929).
274. Adams and Schrecker, *J. Am. Chem. Soc.*, **71**, 1186 (1949).
275. Graf, *Ber.*, **64**, 21 (1931).
276. Den Hertog and Wibaut, *Rec. trav. chim.*, **55**, 122 (1936).
277. Chichibabin and Bylinkin, *J. Russ. Phys. Chem. Soc.*, **50**, 471 (1918); *Chem. Zentr.*, **1923, III,** 1020.
278. Takahashi, Sarkashi, Goto, and Shirmamura, *J. Pharm. Soc. Japan*, **64,** (No. 8A), 7, (1944).
279. Berrie, Newbold, and Spring, *J. Chem. Soc.*, **1951,** 2590.
280. Lappin and Slezak, *J. Am. Chem. Soc.*, **72,** 2806 (1950).
281. Parker and Shive, *ibid.*, **69,** 63 (1947).
282. Phillips, *J. Chem. Soc.*, **1941,** 9.
283. Chichibabin and Woroshtzow, *Ber.*, **66,** 364 (1933).
284. Graf, *J. prakt. Chem.*, **136,** 244 (1933).
285. Dornow and Neuse, *Ber.*, **84,** 296 (1951).
286. Räth and Prange, *Ann.*, **467,** 1 (1928).
287. Carboni, *Gazz. chim. ital.*, **83,** 637 (1953).
288. Kirpal and Reimann, *Monatsh.*, **38,** 249 (1917).
289. Clemo and Swan, *J. Chem. Soc.*, **1948,** 198.
290. Graf, *J. prakt. Chem.*, **133,** 19 (1932).
291. Marcinkow and Plazek, *Roczniki Chem.*, **16,** 136 (1936); *C.A.*, **31,** 2216[3] (1937).
292. Plazek, *Ber.*, **72,** 577 (1939).
293. Reed and Shive, *J. Am. Chem. Soc.*, **68,** 2740 (1946).
294. Urbanski, *J. Chem. Soc.*, **1946,** 1104.
295. Blanchard, Dearborn, Lasagna, and Buhle, *Bull. Johns Hopkins Hosp.*, **91,** 330 (1952); *C.A.*, **47,** 10536b (1953).
296. Fox, *J. Org. Chem.*, **17,** 547 (1952).
297. Gruber and Schlögl, *Monatsh.*, **80,** 499 (1949).
298. Fanta, *J. Am. Chem. Soc.*, **75,** 737 (1953).
299. Jones, *ibid.*, **73,** 5610 (1951).
300. Velluz and Amiard, *Bull. soc. chim. France*, **1947,** 136.
301. British patent 588,806, Hindley and Low (June 3, 1947);*C.A.*, **41,** 6893b (1947).
302. Chichibabin, *J. Russ. Phys. Chem. Soc.*, **50,** 502 (1918); *Chem. Zentr.*, **1923, III,** 1021.

303. Rodewald and Plazek, *Roczniki Chem.*, **16**, 130 (1936); *C.A.*, **30**, 1166 (1936).
304. Hawkins and Roe, *J. Org. Chem.*, **14**, 328 (1949).
305. U.S. patent 1,863,676, Tisza and Joos (June 21, 1932); *C.A.*, **26**, 4347[9] (1932).
306. Titov and Levin, *J. Gen. Chem. U.S.S.R.*, **11**, 9 (1941); *C.A.*, **35**, 5501[5] (1941).
307. Titov, *ibid.*, **8**, 1483 (1939); *Chem. Zentr.*, **10**, 4209 (1939).
308. Seide and Titov, *Ber.*, **69**, 1884 (1936).
309. Koenigs, Mielda, and Gurlt, *Ber.*, **57**, 1179 (1924).
310. Chichibabin and Kirssanow, *ibid.*, **61**, 1223 (1928).
311. Goldfarb and Smorgonskii, *J. Gen. Chem. U.S.S.R.*, **12**, 255 (1942); *C.A.*, **37**, 3094[4] (1943).
312. Chichibabin and Kirssanow, *Ber.*, **60**, 2433 (1927).
313. Räth and Prange, *ibid.*, **58**, 1208 (1925).
314. Chichibabin and Kirssanow, *ibid.*, **61**, 1236 (1928).
315. Kabachnik, *J. Gen. Chem. U.S.S.R.*, **7**, 1749 (1937); *C.A.*, **32**, 560[4] (1938).
316. U.S. patent 1,880,645, Wulff (Oct. 4, 1932); German patent 541,681 (1931); British patent 335,818 (1929); French patent 685,583 (1929); Swiss patent 147,793 (1929); *Fried.*, **17**, 2437; *C.A.*, **27**, 513[8] (1933).
317. Marion and Cockburn, *J. Am. Chem. Soc.*, **71**, 3402 (1949).
318. Brown and Miller, *J. Org. Chem.*, **11**, 388 (1946).
319. Jacobs and Sato, *J. Biol. Chem.*, **191**, 71 (1951).
320. Weidel and Murmann, *Monatsh.*, **16**, 749 (1895).
321. Duesel and Scudi, *J. Am. Chem. Soc.*, **71**, 1866 (1949).
322. Mangini and Colonna, *Gazz. chim. ital.*, **73**, 313 (1943).
323. British patent 591,896, Tyrer (Sept. 2, 1947); *C.A.*, **42**, 926f (1948).
324. King and Ware, *J. Chem. Soc.*, **1939**, 873.
325. Koenigs and Greiner, *Ber.*, **64**, 1049 (1931).
326. Bak and Christensen, *Acta Chem. Scand.*, **8**, 390 (1954).
327. Baker and Briggs, *J. Soc. Chem. Ind. (London)*, **62**, 189 (1943).
328. Chichibabin and Ossetrowa, *Ber.*, **58**, 1708 (1925).
329. Chichibabin, DRP, **489**, 184; *Chem. Zentr.*, **1930, I**, 2012.
330. Kirpal and Wojnar, *Ber.*, **71**, 1261 (1938).
331. Knunjanz, *ibid.*, **68**, 397 (1935).
332. Sharp, *J. Chem. Soc.*, 1855 (1939).
333a. Chichibabin and Konowalowa, *Ber.*, **58**, 1712 (1925).
333b. Chichibabin and Konowalowa, *ibid.*, **59**, 2055 (1926).
334. Chichibabin and Konowalowa, *J. Russ. Phys. Chem. Soc.*, **53**, 193 (1921); *Chem. Zentr.*, **1923, III**, 1023.
335a. Decker, *Ber.*, **25**, 443 (1892).
335b. Decker, *J. prakt. Chem.*, **47**, 28 (1893).
335c. *Ibid.*, **84**, 425 (1911).
336. Fargher and Furness, *J. Chem. Soc.*, **107**, 690 (1915).

337. Fischer and Chur, *J. prakt. Chem.*, **93**, 363 (1916).
338. Prill and McElvain, *Org. Syntheses, Coll. Vol. II*, 419 (1943).
339. Ochiai, Tsuda, and Yokoyama, *Ber.*, **68**, 2295 (1935).
340. Rohmann and Zietan, *ibid.*, **71**, 296 (1938).
341. Sugasawa, Akahoshi, and Suzuki, *J. Pharm. Soc. Japan*, **72**, 1273 (1952); *C.A.*, **47**, 10539g (1953).
342. Sugasawa and Shigehara, *Ber.*, **74**, 459 (1941).
343. Gautier and Renault, *Rec. trav. chim.*, **69**, 421 (1950).
344a. Gautier, *Compt. rend.*, **198**, 1430 (1934).
344b. Gautier, *ibid.*, **203**, 794 (1936).
345. Taylor and Baker, *Sidgwick's Organic Chemistry of Nitrogen*, Oxford Univ. Press, London, 1942, p. 524.
346. Bradlow and Vanderwerf, *J. Org. Chem.*, **16**, 73 (1951).
347. Huff, *J. Biol. Chem.*, **171**, 639 (1947).
348. Holman and Wiegand, *Biochem. J.*, **43**, 423 (1948).
349. Knox and Grossman, *J. Biol. Chem.*, **168**, 363 (1947).
350. Sugasawa and Kirisawa, *Pharm. Bull. (Tokyo)*, **3**, 187 (1955).
351. Sugasawa and Kirisawa, *ibid.*, **4**, 139 (1956).
352. Sugasawa and Kirisawa, *ibid.*, **3**, 190 (1955).
353. Karrer and Takahashi, *Helv. Chim. Acta*, **9**, 458 (1926).
354. Sugasawa and Tatsuno, *J. Pharm. Soc. Japan*, **72**, 248 (1952).
355. Mumm and Hingst, *Ber.*, **56**, 2301 (1923).
356. Mumm and Petzold, *Ann.*, **536**, 1 (1938).
357. Berson and Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956).
358. Meislich and Psihas, private communication.
359. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947).
360. Boekelheide and Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).
361. Sgarashi, *Japan*, 7672 (1951), Dec. 14.
363. Berson and Cohen, *J. Am. Chem. Soc.*, **77**, 1281 (1955).
364. Govindachari and Thyagarajan, *Proc. Indian Acad. Sci.*, **39A**, 232 (1954); *C.A.*, **49**, 9653g (1955).
365. Murakami and Matsumura, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **70**, 393 (1949); *C.A.*, **45**, 4698e (1951).
366. Matsumura, *ibid.*, **74**, 446 (1953).
367. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).
368. Ochiai and Katada, *J. Pharm. Soc. Japan*, **63**, 265 (1943); *C.A.*, **45**, 5152h (1951).
369. Ishii, *ibid.*, **71**, 1092 (1951); *C.A.*, **46**, 5046b (1952).
370. Ochiai and Futaki, *ibid.*, **72**, 274 (1952); *C.A.*, **47**, 6416i, 6417a (1953).
371. Ochiai, Suzuki, and Futaki, *ibid.*, **74**, 666 (1954); *C.A.*, **48**, 10746c (1954).
372. Katada, Hamamoto, and Tone, *ibid.*, **72**, 1427 (1952); *C.A.*, **47**, 8071a (1953).
373. Ochiai, Katada, and Naito, *ibid.*, **63**, 210 (1943); *C.A.*, **45**, 5154i (1951).
374. Den Hertog and Combé, *Rec. trav. chim.*, **70**, 581 (1951).

375. Ramirez and von Ostwalden, *Chem. & Ind. (London)*, **1957,** 46.
376. Chichibabin, *Ber.,* **56,** 1879 (1923).
377. Chichibabin, *Chem. Zentr.,* **1925, I,** 1567; DRP 406, 208.
378. Koenings and Koerner, *Ber.,* **16,** 2152 (1883).
379. Kudernatsch, *Monatsh,* **18,** 613 (1897).
380. v. Schickh, Binz, and Schulz, *Ber.,* **69,** 2593 (1936); German patent 657,778 (March 29, 1938).
381. Fischer, Yoshioka, and Hartmann, *Z. physiol. Chem.,* **212,** 146 (1932).
382. Späth and Galinovsky, *Ber.,* **69,** 2059 (1936).
383. U.S. patent 2,400,045, Hoffer (May 7, 1946); British patent 552,419 (April 7, 1943); German patent 730,910 (Dec. 24, 1942).
384. Leonard and Locke, *J. Am. Chem. Soc.,* **77,** 1852 (1955).
385. Caldwell and Kornfeld, *ibid.,* **64,** 1695 (1942).
386. Forrest and Walker, *J. Chem. Soc.,* **1948,** 1939.
387. Ishii, *Japan,* 3986 (1952), Oct. 2.
388. Lewis, Kinsey, and Johnson, *J. Am. Chem. Soc.,* **78,** 4294 (1956).
389. Smith and Kelly, *ibid.,* **74,** 330 (1952).
390. Berrie, Newbold, and Spring, *J. Chem. Soc.,* **1952,** 2042.
391. Jones, *J. Am. Chem. Soc.,* **74,** 1489 (1952).
392. Wilson and Harris, *ibid.,* **73,** 2388 (1951).
393. Kobayashi and Furukawa, *Pharm. Bull. (Tokyo),* **1,** 347 (1953); *C.A.,* **49,** 10948e (1955).
394. Mathes, Sauermilch, and Klein, *Ber.,* **84,** 452 (1951).
395. Shaw, *J. Am. Chem. Soc.,* **71,** 67 (1949).
396. Specker and Gawrosch, *Ber.,* **75,** 1338 (1942).
397. Metzler and Snell, *J. Am. Chem. Soc.,* **77,** 2431 (1955).
398. Albert and Phillips, *J. Chem. Soc.,* **1956,** 262.
399. Sensi and Gallo, *Ann. Chim. (Rome),* **44,** 232 (1954); *C.A.,* **49,** 14757g (1955).
400. Pullman and Pullman, *Les Theories Electroniques de la Chimie Organique,* Masson, Ed. 1952 (Paris), p. 116.
401. Fischer and Demeler, *Ber.,* **32,** 1307 (1899).
402. Ramirez and Paul, *J. Am. Chem. Soc.,* **77,** 1035 (1955).
403. Wiley and Slaymaker, *ibid.,* **78,** 2393 (1956).
404. Penfold, *Acta Cryst.,* **6,** 591 (1953).
405. Hoegerle and Erlenmeyer, *Helv. Chim. Acta,* **39,** 1203 (1956).
406. Ramirez and Paul, *J. Am. Chem. Soc.,* **77,** 3337 (1955).
407. Wiley and Slaymaker, *ibid.,* **78,** 2393 (1956).
408. Von Pechmann and Baltzer, *Ber.,* **24,** 3150 (1891).
409. Meyer, *Monatsh.,* **26,** 1311, 1314 (1905).
410. Berson, *J. Am. Chem. Soc.,* **75,** 3521 (1953).
411. Arndt and Kalischek, *Ber.,* **63,** 587 (1930).
412. Bedekar, Kaushal, and Deshapande, *J. Indian Chem. Soc.,* **12,** 465 (1935).
413. Koenigs and Gurlt, *Ber.,* **69,** 358 (1936).

414. Deshapande, Dingankar, and Kopil, *J. Indian Chem. Soc.*, **11**, 595 (1934).
415. Jacini, *Gazz. chim. ital.*, **68**, 592 (1938); *C.A.*, **33**, 3763 (1939).
416. Jacini, *ibid.*, **67**, 715 (1937); *C.A.*, **32**, 4527[9] (1938).
417. Albert and Hampton, *J. Chem. Soc.*, **1954**, 505.
418. Stiller, Kerestezy, and Stevens, *J. Am. Chem. Soc.*, **61**, 1237 (1939).
419. Ross, *J. Chem. Soc.*, **1951**, 1374.
420. Swain and Brown, *J. Am. Chem. Soc.*, **74**, 2538 (1952).
421. Swain and Brown, *ibid.*, **74**, 2534 (1952).
422. Folin and Denis, *J. Biol. Chem.*, **12**, 239 (1912).
423. Kuhn and Wendt, *Ber.*, **72**, 305 (1939).
424. Kleipool and Wibaut, *Rec. trav. chim.*, **69**, 59 (1950).
425. Den Hertog and Mulder, *ibid.*, **68**, 433 (1949).
426. Fischer and Renouf, *Ber.*, **17**, 764, 1896 (1884).
427. Lieben and Haitinger, *ibid.*, **16**, 1261 (1883).
428. Oparina, *ibid.*, **64**, 569 (1931).
429. Halina, Bojarska-Dahlig, and Tadeusy Urbanki, *C.A.*, **48**, 1337i (1954).
430. Gruber and Schlögl, *Monatsh.*, **81**, 473 (1950).
431. Baker and McEvoy, *J. Org. Chem.*, **20**, 118 (1955).
432. Räth, *Ann.*, **489**, 107 (1931).
433. Leonard and Boyer, *J. Am. Chem. Soc.*, **72**, 2980 (1950).
434. Räth, *Ann.*, **486**, 71 (1931).
435. Kirpal, *Ber.*, **57**, 1954 (1924).
436. U.S. patent 1,941,312, Miescher and Urech (Dec. 26, 1933); German patent 551,029 (Mar. 21, 1930); *C.A.*, **26**, 4343[9] (1932).
437. Takahashi and Kawashima, *J. Pharm. Soc. Japan*, **63**, 546 (1943); *C.A.*, **45**, 619f (1951).
438. Sugii and Shindo, *ibid.*, **51**, 416 (1931); *C.A.*, **25**, 4549[2] (1931).
439. Slack, *J. Soc. Chem. Ind.*, **64**, 188 (1945).
440. U.S. patent 1,870,203, Räth (Aug. 2, 1932); *C.A.*, **26**, 5312 (1932).
441. German patent 544,620, Allardt and Schickh (Feb. 4, 1932); *Friedl.*, **18**, 2780; *C.A.*, **26**, 3519[6] (1932).
442. Bickel, *J. Am. Chem. Soc.*, **70**, 328 (1948).
443. Dohrn and Diedrich, *Ann.*, **494**, 284 (1932).
444. Archer, Hoppe, Lewis, and Haskell, *J. Am. Pharm. Assn.*, **40**, 143 (1951).
445. Maier-Bode and Altpeter, "Das Pyridin und seine Derivate," Wilhelm Knapp Verlag, Halle, 1934, p. 138-41. (Photo-lithoprint reproduced by Edwards Bros., Ann Arbor, Mich., 1943.)
446. Baker and Briggs, *J. Soc. Chem. Ind.*, **62**, 189 (1948).
447. Swedish patent 137,579, Ferno and Linderot (Oct. 14, 1951); *C.A.*, **48**, 1444i (1954).
448. Herold, Jirat, and Zubenko, *Časopis Českoslov Lékárnictva*, **16**, 210 (1936); *C.A.*, **33**, 6313[9] (1939).
449. Adams and Jones, *J. Am. Chem. Soc.*, **69**, 1803 (1947).
450. Adams and Jones, *ibid.*, **71**, 3826 (1949).

451. Adams and Pachter, *ibid.*, **74,** 4906 (1952).
452. Kornblum, Smiley, Blackwood, and Iffland, *J. Am. Chem. Soc.,* **77,** 6269 (1955).
453. El'kina and Shemyakin, *J. Gen. Chem. U.S.S.R.,* **13,** 164 (1943); *C.A.,* **38,** 1504[5] (1944).
453a. von Pechmann, *Ber.,* **28,** 1624 (1895).
454. Mosher in Elderfield, editor, *Heterocyclic Compounds,* Wiley, New York, 1950, Vol. I, p. 535.
455. Wheland, *Advanced Organic Chemistry,* 2nd ed., Wiley, New York, 1949, p. 619.
456. Peratoner and Azzarello, *Atti accad. nazl. Lincei, Rend.,* [5] **15, I,** 141 (1886).
457. Tracy and Elderfield, *J. Org. Chem.,* **6,** 70 (1941).
458. Den Hertog, Wibaut, Schepman, and Van der Wal, *Rec. trav. chim.,* **69,** 700 (1950).
459. Maas, de Graaff, and den Hertog, *ibid.,* **74,** 175 (1955).
460. Eistert, *Newer Methods of Preparative Organic Chemistry,* Interscience, New York-London, 1948, p. 518.
461. Chichibabin and Jeletzki, *Ber.,* **57,** 1158 (1924).
462. Takeda and Hamamoto, *J. Pharm. Soc. Japan,* **73,** 1158 (1953).
463. Takahashi, Tsubaki, and Yajima, *ibid.,* **62,** 486 (1942).
464. U.S. patent 2,190,444, Dohrn and Nahme (Feb. 13, 1940); British patent 490,073 (Aug. 9, 1938); *C.A.,* **34,** 4234[9] (1940).
465. U.S. patent 2,212,187, Schnider (Aug. 20, 1940); Swiss patent 212,521 (Mar. 3, 1941); *C.A.,* **35,** 4665 (1941).
466. Mariella and Havlik, *J. Am. Chem. Soc.,* **74,** 1915 (1952).
467. Adams, Hine, and Campbell, *ibid.,* **71,** 387 (1949).
468. Wuest and Sakal, *ibid.,* **73,** 1210 (1951).
469. Stempel and Aeschlimann, *ibid.,* **74,** 3323 (1952).
470. Ueda, Takahashi, Toyoshima, and Ose, *Pharm. Bull. (Tokyo),* **1,** 371 (1953).
471. Jensen, Hansen, Jorgensen, and Schmith, *Dansk Tidsskr. Farm.,* **18,** 201 (1944); *C.A.,* **40,** 1466 (1946).
472. Andrews, Atherton, Bergel, and Morrison, *J. Chem. Soc.,* **1954,** 1638.
473. Chichibabin and Szokow, *Ber.,* **58,** 2650 (1925).
474. Chichibabin and Oparina, *J. Russ. Phys. Chem. Soc.,* **56,** 153 (1925); *Chem. Zentr.,* **1926, I,** 938.
475. Petrow and Saper, *J. Chem. Soc.,* **1946,** 588.
476. Dunlop and Peters, *The Furans,* Reinhold, New York, 1953, p. 667.
477. Chase and Walker, *J. Chem. Soc.,* **1953,** 3548.
478. Yamamoto, *J. Pharm. Soc. Japan,* **71,** 662 (1951).
479. Mowat, Pilgrim, and Carlson, *J. Am. Chem. Soc.,* **65,** 954 (1943).
480. Scott, Norris, Heuser, and Bruce, *ibid.,* **67,** 157 (1945).
481. Fischer, Hess, and Stahlschmidt, *Ber.,* **45,** 2456 (1912).

482. Rubtsov and Klimko, *J. Gen. Chem. U.S.S.R.*, **16**, 1860 (1946); *C.A.*, **41**, 6245c (1947).
483. Heyns and Vogelsang, *Ber.*, **87**, 13 (1954).
484. Case, *J. Am. Chem. Soc.*, **68**, 2574 (1946).
485. Willink and Wibaut, *Rec. trav. chim.*, **53**, 416 (1934).
486. Brown and Burke, *J. Am. Chem. Soc.*, **77**, 6053 (1955).
487. Wibaut, Overhoff, and Geldof, *Rec. trav. chim.*, **54**, 807 (1935).
488. Den Hertog and Farenhorst, *ibid.*, **67**, 380 (1948).
489. Crouch and Lochte, *J. Am. Chem., Soc.*, **65**, 270 (1943).
490. Guthzeit and Laska, *J. prakt. Chem.*, **58**, 403 (1898).
492. Den Hertog, Schogt, de Bruyn, and de Klerk, *Rec. trav. chim.*, **69**, 673 (1950).
493. Rabe, *J. prakt. Chem.*, **151**, 71 (1938).
494. Schroeter and Finck, *Ber.*, **71**, 671 (1938).
495. Salemink and van der Want, *Rec. trav. chim.*, **68**, 1013 (1949).
496. Den Hertog, Schepman, de Bruyn, and Thysse, *ibid.*, **69**, 1281 (1950).
497. Wibaut and van Wagtendouk, *ibid.*, **60**, 22 (1941).
498. Fischer, *Ber.*, **31**, 611 (1898).
499. Fischer, *ibid.*, **32**, 1303 (1899).
500. Gautier, *Compt. rend.*, **208**, 816 (1939).
501. Steinhauser and Diepolder, *J. prakt. chem.*, **93**, 387 (1916).
502. Räth, *Ann.*, **486**, 71 (1931).
503. Petrenko-Kretschenko and Schöttle, *J. prakt. chem.*, **85**, 1 (1912).
504. Renault, *Compt. rend.*, **232**, 77 (1951).
505. Weidenhagen and Train, *Ber.*, **75**, 1936 (1942).
506. Bremer, *Ann.*, **529**, 290 (1937).
507. Arndt, *Ber.*, **65**, 92 (1932).
508. Räth, *Ann.*, **487**, 105 (1931).
509. Moir, *J. Chem. soc.*, **127**, 2341 (0000).
510. Biel, Friedman, Leiser, and Sprengler, *J. Am. Chem. Soc.*, **74**, 1485 (1952).
511. German patent 571,227, Nicodemus and Wulff (Apr. 7, 1933); *C.A.*, **27**, 4253 (1933).
511a. German patent 568,759, Nicodemus and Wulff (Oct. 27, 1929); *C.A.*, **27**, 2694 (1933).
512. Emmert and Dorn, *Ber.*, **48**, 687 (1915).
513. Koenigs and Neumann, *ibid.*, **48**, 961 (1915).
514. Renshaw and Conn, *J. Am. Chem. Soc.*, **60**, 745 (1938).
515. Riegel and Reinhard, *ibid.*, **48**, 1334 (1926).
516. Hahn, Cerkovnikov, and Prelog, *Helv. Chim. Acta*, **26**, 1132 (1943).
517. Ishii, *J. Pharm. Soc. Japan*, **71**, 1097 (1951).
518. Ruzicka, *Helv. Chim. Acta*, **4**, 474 (1921).
519. Covert, Connor, and Adkins, *J. Am. Chem. Soc.*, **54**, 1658 (1932).
520. Prill and McElvain, *ibid.*, **55**, 1238 (1933).
521. Grave, *ibid.*, **46**, 1460, 1466 (1924).

522. Räth, *Ann.*, **489**, 107 (1931).
523. Gautier, *Compt rend.*, **205**, 614 (1937).
524. Galinovsky and Stern, *Ber.*, **77B**, 132 (1944).
525. Sugasawa, Sakurai, and Okayama, *J. Pharm. Soc. Japan*, **62**, 77 (1942); *C.A.*, **45**, 2955b (1951).
526. Cavallito and Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).
527. Cavallito and Haskell, *ibid.*, **66**, 1927 (1944).
528. DeMayo and Rigby, *Nature*, **166**, 1075 (1950).
529. Lukeš and Smetackova, *Collection Czechoslov. Chem. Communs.*, **5**, 61 (1933); *Chem. Zentr.*, **1933, I**, 2802.
530. Paden and Adkins, *J. Am. Chem., Soc.*, **58**, 2487 (1936).
531. U.S. patent 1,706,775, Dohrn and Dirksen (Mar. 26, 1929); *C.A.*, **23**, 2189^{5} (1929).
532. German patent 513,293, Kochendoerfer; *C.A.*, **25**, 1263^{2} (1931).
533. Koenigs and Geigy, *Ber.*, **17**, 1832 (1884).
534. von Ammers and den Hertog, *Rec. trav. chim.*, **75**, 1259 (1956).
535. Mariella and Belcher, *J. Am. Chem. Soc.*, **74**, 1916 (1952).
536. U.S. patent 2,516,673, Bruce (July 25, 1950); *C.A.*, **45**, 670*h* (1950).
537. Ramirez, private communication.
538. Adams and Miyano, *J. Am. Chem. Soc.*, **76**, 3168 (1954).
539. DeVilliers and den Hertog, *Rec. trav. chim.*, **75**, 1303 (1956).
540. Burger and Bailey, *J. Am. Chem. Soc.*, **68**, 520 (1946).
541. German patent 579,224, Reitmann (June 22, 1933); *C.A.*, **27**, 4880^{5} (1933).
542. Sell, *J. Chem. Soc.*, **93**, 1997 (1908).
543. Klosa, *Arch. Pharm.*, **285**, 453 (1952).
544. Babcock and Fuson, *J. Am. Chem. Soc.*, **55**, 2946 (1933).
545. German patent 500,915, Dohrn and Thiele (June 5, 1930); *C.A.*, **24**, 4793^{5} (1930).
546. German patent 563,131, Allardt and von Schickh (Oct. 31, 1932); *C.A.*, **27**, 1002^{7} (1932).
547. Gautier, *Compt. rend.*, **208**, 816 (1939).
548. Binz, Räth, and Urbschat, *Ann.*, **475**, 136 (1929).
549. Binz, Räth, and Maier-Bode, *ibid.*, **478**, 22 (1930).
550. Hebky and Radek, *Chem. Listy*, **46**, 637 (1952); *C.A.*, **47**, 8070c (1953); *C.A.*, **28**, 4073^{4} (1934).
551. U.S. patent 1,957,089, Wulff (May 1, 1934); French patent 705,113 (Nov. 4, 1930); *C.A.*, **24**, (1930).
552. U.S. patent 1,889,303, Wulff (Nov. 29, 1932); *C.A.*, **27**, 1366^{3} (1933).
553. Plazek and Rodewald, *Roczniki Chem.*, **16**, 502 (1936); *C.A.*, **31**, 3918^{9} (1937).
554. Bernstein, Stearns, Shaw, and Lott, *J. Am. Chem. Soc.*, **69**, 1151 (1947).
555. Bray, Neale, and Thorpe, *Biochem. J.*, **46**, 506 (1950).
557. Chichibabin and Schapiro, *J. Russ. Phys. Chem. Soc.*, **53**, 233 (1921).
558. Binz and Maier-Bode, *Angew. Chem.*, **49**, 486 (1936).
559. German patent 568,549, Haack (Jan. 5, 1933); *C.A.*, **27**, 2697^{9} (1933).

560. Koenigs and Freter, *Ber.*, **57**, 1189 (1924).
561. Koenigs and Fulde, *ibid.*, **60**, 2107 (1927).
562. Crowe, *J. Chem. Soc.*, **127**, 2028 (1925).
563. Kögl, Van der Want, and Salemink, *Rec. trav. chim.*, **67**, 29 (1948).
564. Den Hertog and von Weeren, *ibid.*, **67**, 980 (1948).
565. Den Hertog and Mulder, *ibid.*, **67**, 957 (1948).
566. Takahashi and Shibasaki, *J. Pharm. Soc. Japan*, **72**, 1137 (1952); *C.A.*, **47**, 7497*h* (1953).
567. Takahashi and Shibasaki, *Pharm. Bull. (Tokyo)*, **1**, 70 (1953); *C.A.*, **49**; 12459*h* (1955).
568. Plazek, *Roczniki Chem.*, **16**, 403 (1936); *C.A.*, **31**, 1808[5] (1937).
569. Plazek, *ibid.*, **17**, 97 (1937); *C.A.*, **31**, 4669[2] (1937).
570. German patent 601,896, Schickh (Aug. 27, 1934); *C.A.*, **28**, 7267[2] (1934).
571. Binz, Räth, and Maier-Bode, *Ann.*, **478**, 22 (1930).
572. Binz, Räth, and Maier-Bode, *ibid.*, **487**, 119 (1931).
573. German patent 544,361, Binz and Räth (Mar. 8, 1927); *C.A.*, **26**, 3519[8] (1932).
574. German patent, 525,090, Binz and Räth (Apr. 30, 1931); *C.A.*, **25**, 4012 (1927).
575. Austrian patent 112,128, Weickel, (1929).
576. Mills and Widdows, *J. Chem. Soc.*, **93**, 1372 (1908).
577. Swiss patent 217,079, Cilag (Jan. 16, 1942); *C.A.*, **42**, 6992*e* (1948).
578. Ames, Bowman, and Grey, *J. Chem. Soc.*, **1953**, 3008.
579. Chichibabin and Kirssanow, *Ber.*, **57**, 1161 (1924).
580. Geissman, Schlatter, Webb, and Roberts, *J. Org. Chem.*, **11**, 741 (1946).
581. Urbanski, *J. Chem. Soc.*, **1947**, 132.
582. Govindachari, Narasimhan, and Rajadurai, *Chem. and Ind.*, **1956**, 53.
583. Wiley and Kraus, *J. Org. Chem.*, **21**, 757 (1956).
584. Stempel and Buzzi, *J. Am. Chem. Soc.*, **71**, 2969 (1949).
585. Martin, Avakian and Moss, *J. Biol. Chem.*, **174**, 495 (1948).
586. German patent 374,291, Chichibabin (1923); *Chem. Zentr.*, **1923, IV**, 725.
587. Belonosov, *Zhur. Priklad. Khim.*, **22**, 1103 (1949); *C.A.*, **45**, 5650*h* (1951).
588. Sugasawa, *Ber.*, **71**, 1860 (1938).
589. Sugasawa and Sugimoto, *ibid.*, **72**, 977, 980 (1939).
592. Wiley, Smith, and Knabeschuh, *J. Am. Chem. Soc.*, **75**, 4482 (1953).
593. Späth and Kuffner, *Ber.*, **71**, 1657 (1938).
594. Robinson and Watt, *J. Chem. Soc.*, **1934**, 1536.
595. Eistert, *Ber.*, **80**, 47 (1947).
596. German patent 556,142, Dohrn and Diedrich (July 14, 1932); *C.A.*, **26**, 5579[4] (1932).
597. Stokes and von Pechmann, *Ber.*, **19**, 2694 (1886).
598. German patent 596,728, Haack (May 9, 1934); *C.A.*, **28**, 5083[3] (1934).
599. German patent 597,974, Haack and Rost (May 9, 1934); *C.A.*, **28**, 7268[9] (1934).
600. Chichibabin and Jeletzky, *Ber.*, **57**, 1158 (1924).

601. Den Hertog and Buurman, *Rec. trav. chim.*, **75**, 257 (1956).
602. von Pechmann and Mills, *Ber.*, **37**, 3836 (1904).
603. Bulow and Filchner, *ibid.*, **41**, 3281 (1908).
604. Berson, Jones, and O'Callaghan, *J. Am. Chem. Soc.*, **78**, 622 (1956).
605. Berson and Jones, *ibid.*, **78**, 1625 (1956).
606. Ref. 445, p. 181.
607. German patent 597,452, Haack (May 24, 1934); *C.A.*, **28**, 5083[6] (1934).
608. Naegeli, Kundig, and Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938).
609. Bickel and Wibaut, *Rec. trav. chim.*, **65**, 65 (1946).
610. Mascré, *Compt. rend.*, **204**, 890 (1937).
611. Adams, Cristol, Anderson, and Albert, *J. Am. Chem. Soc.*, **67**, 89 (1945).
612. Kostermans, *Rec. trav. chim.*, **65**, 319 (1946).
613. Wibaut, *ibid.*, **65**, 392 (1946).
614. Wibaut and Schuhmacher, *ibid.*, **71**, 1017 (1952).
615. Adams and Johnson, *J. Am. Chem. Soc.*, **71**, 705 (1949).
616. Bickel, *ibid.*, **70**, 326 (1948).
617. Adams and Govindachari, *ibid.*, **69**, 1806 (1947).
618. Bickel, *ibid.*, **69**, 1801 (1947).
619. Renz, *Z. physiol. Chem.*, **244**, 153 (1936).
620. Swiss patent 212,566 (March 17, 1941); German patent 668,489; *C.A.*, **36**, 3633[1] (1942).
621. Swiss patent 187,826.
622. U.S. patent 2,137,192, Schnider (Nov. 15, 1938); *C.A.*, **33**, 1448[2] (1939); also Swiss patent 199,181 (Dec. 1, 1938).
623. U.S. patent 2,090,237, Schnider (Aug. 17, 1937); *C.A.*, **31**, 7069[5] (1937).
624. Schnider, Frick, and Lutz, *Experientia*, **10**, 135 (1954).
625. Bernhard, Brubacher, and Lutz, *Helv. Chim. Acta*, **37**, 1839 (1954).
626. German patent 650,049 (Sept. 9, 1937); *C.A.*, **32**, 1280[7] (1938).
627. German patent 637,875 (Nov. 5, 1936); *C.A.*, **31**, 5381[1] (1937).
628. German patent 638,532 (Nov. 17, 1936); *C.A.*, **31**, 3209[2] (1937).
629. Ito and Nagawa, *Japan*, 1132 (1950), Mar. 31; *C.A.*, **47**, 2216*g* (1953).
630. Lutz and Schnider, *Helv. Chim. Acta*, **39**, 81 (1956).
631. Kubi and Schmid, *ibid.*, **28**, 213 (1945).
632. Hirschberg, Greenberg, deRitter, and Rubin, *J. Am. Pharm. Assoc.*, **37**, 288 (1948).
633. German patent 639,712 (Dec. 11, 1936); *C.A.*, **31**, 4061[1] (1937).
634. Tagmann, Sury, and Hoffmann, *Helv. Chim. Acta*, **35**, 1235 (1952).
635. Tagmann, Sury, and Hoffmann, *ibid.*, **35**, 1541 (1952).
636. Sury and Hoffmann, *ibid.*, **36**, 1815 (1953).
637. Urech, Tagmann, Sury, and Hoffmann, *ibid.*, **36**, 1809 (1936).
638. Bernhard, Just, Vuilleumier, and Brubacher, *ibid.*, **39**, 596 (1956).
639. Kebrle and Hoffmann, *ibid.*, **39**, 767 (1956).
640. Lukeš and Gorocholinskij, *Collection Czechoslov. Chem. Communs.*, **8**, 223 (1936); *C.A.*, **30**, 5989[8] (1936).

641. Kebrle and Hoffmann, *Experientia,* **12,** 21 (1956).
642. Koppanyi, Herwick, Linegar, and Foster, *Arch. intern. pharmacodynamie,* **64,** 123 (1940); *C.A.,* **34,** 5937[4] (1940).
643. Den Hertog, *Rec. trav. chim.,* **64,** 85 (1945).
644. Den Hertog and Schogt, *ibid.,* **70,** 353 (1951).
645. Kolder and den Hertog, *ibid.,* **72,** 853 (1953).
646. Den Hertog, Combé, and Kolder, *ibid.,* **73,** 1 (1954).
647. Den Hertog and Jouwersma, *ibid.,* **72,** 125 (1953).
648. Ref. 445 p. 137-140.
649. Binz, Räth, and Junkmann, *Biochem. Z.,* **227,** 200 (1930).
650. Dellepiane, *Arch. intern. pharmacodynamie,* **40,** 1 (1931); *C.A.,* **25,** 5209[9] (1931).
651. German patent 535,676, Räth (Sept. 24, 1931); *C.A.,* **26,** 1068[1] (1932).
652. U.S. patent 2,372,690, Stiller (April 3, 1945).
653. Bijesma and den Hertog, *Rec. trav. chim.,* **75,** 1187 (1956).
654. Fraser and Tittensor, *J. Chem. Soc.,* **1956,** 1781.
655. Besly and Goldberg, *ibid.,* **1954,** 2448.
656. Phillips, *ibid.,* **1941,** 291.
657. Süs, Glos, Möller, and Eberhardt, *Ann.,* **583,** 150 (1953).
658. Gibbs, *J. Biol. Chem.,* **72,** 649 (1931).
659. Feinstone, *Proc. Soc. Exptl. Biol. Med.,* **63,** 153 (1946).
660. Duca, Williams, and Scudi, *J. Am. Chem. Soc.,* **67,** 159 (1948).
661. Case, *ibid.,* **63,** 2574 (1946).
661a. Feinstone, Friedman, Rothlauf, Kelly, and Williams, *J. Pharmacol. Exptl. Therap.,* **89,** 153 (1947).
662. Friedman, Braitberg, Tolstoouhov, and Tisza, *J. Am. Chem. Soc.,* **69,** 1795 (1947).
662a. Das Gupta and Ghosh, *J. Indian Chem. Soc.,* **18,** 120 (1941); *C.A.,* **36,** 4749 (1942).
663. Mann and Turnbull, *J. Chem. Soc.,* **1951,** 761.
664. Katz, Schroeder, and Cohen, *J. Org. Chem.,* **19,** 711 (1954).
665. U.S. patent 1,881,236, Miescher and Urech (Oct. 4, 1933); *C.A.,* **27,** 1096 (1933).
666. Ciusa and Nebbia, *Gazz. chim. ital.,* **80,** 518 (1950); *C.A.,* **45,** 6636*d* (1951).
667. Huff, *J. Biol. Chem.,* **167,** 151 (1947).
668. Knox, *ibid.,* **163,** 699 (1946).
669. Knox and Grossman, *ibid.,* **166,** 391 (1946).
670. Knox and Grossman, *ibid.,* **168,** 363 (1947).
671. Pearson, Perlzweig, and Rosen, *Arch. Biochem.,* **22,** 191 (1949).
672. Huff, *J. Biol. Chem.,* **167,** 151 (1947).
673. Tuson, *J. Chem. Soc.,* **17,** 195 (1864).
674. Subba Rao, *Proc. Indian Acad. Sci.,* **32,** 123 (1945); *C.A.,* **39,** 5361[3] (1945).
675. Siegler, Schechter, and Haller, *J. Econ. Entomol.,* **37,** 416 (1944); *C.A.,* **39,** 4714[3] (1945).

676. Maquenne and Philippe, *Compt. rend.*, **138**, 506 (1904).
677. Maquenne and Philippe, *ibid.*, **139**, 840 (1904).
678. Marion in Manske and Holmes, eds., *The Alkaloids*, Academic Press, New York, 1950, Vol. I, p. 206.
679. Winterstein, Keller, and Weinhagen, *Arch. Pharm.*, **255**, 513 (1917).
680. Späth and Tschelnitz, *Monatsh.*, **42**, 251 (1921).
681. Späth and Koller, *Ber.*, **56**, 880 (1923).
682. Späth and Koller, *ibid.*, **58**, 2124 (1925).
683. Reitman, *Med. u. Chem. Abhandl. med.-chem. Forschungsstätten, I. G. Farbenind.*, **2**, 384 (1934); *C.A.*, **29**, 4359[8] (1935).
684. Schroeter, Seidler, Salzbacher, and Kanitz, *Ber.*, **65**, 432 (1932).
685. Taylor and Crovetti, *J. Am. Chem. Soc.*, **78**, 214 (1956).
686. Hunt, Walter, and Fosbinder, *J. Am. Pharm. Assoc.*, **31**, 278 (1942).
687. Cahen, *ibid.*, **36**, 139 (1947).
688. Sugasawa, Akahashi, Toda, and Tomisawa, *J. Pharm. Soc. Japan*, **72**, 192 (1952).
689. Sugii, Shimoya, and Shindo, *ibid.*, **50**, 727 (1930).
690. Prelog and Metzler, *Helv. Chim. Acta*, **29**, 1170 (1946).
691. Mannich, *Arch. Pharm.*, **272**, 323 (1934).
692. Sell, *J. Chem. Soc.*, **93**, 2001 (1908).
693. Ruzicka and Fornasir, *Helv. Chim. Acta*, **3**, 811 (1920).
694. U.S. patent 2,583,774, Heyl; *C.A.*, **47**, 2217*d* (1953).
695. British patent 567,611 (Feb. 23, 1945); *C.A.*, **41**, 2755*b* (1947).
696. U.S. patent 2,315,314, Burger (Mar. 30, 1943); *C.A.*, **37**, 5556[4] (1943).
697. Klingsberg and Papa, *J. Am. Chem. Soc.*, **71**, 2373 (1949).
698. Childress and McKee, *ibid.*, **73**, 3504 (1951).
699. Carrara *et al.*, *Gazz. chim. ital.*, **82**, 652 (1952); *C.A.*, **48**, 6424*g* (1954).
700. Aso, *J. Agr. Soc. Japan*, **16**, 249 (1940); *C.A.*, **34**, 6278[6] (1940).
701. German patent 702,829, Westphal and Andersag (Jan. 23, 1941); *C.A.*, **36**, 873[1] (1942).
702. Sugasawa, Sakurai, and Okayama, *Proc. Imp. Acad. (Tokyo)*, **16**, 225 (1940); *C.A.*, **34**, 6940[7] (1940).
703. Walter and McElvain, *J. Am. Chem. Soc.*, **57**, 1891 (1935).
704. Sculley and Hamilton, *ibid.*, **75**, 3400 (1953).
705. German patent 550,327, Putzer and Schonhofer (Apr. 21, 1932); *C.A.*, **26**, 4062.
706. Shephard, Bratton, and Blanchard, *J. Am. Chem. Soc.*, **64**, 2532 (1942).
707. Barat, *J. Indian Chem. Soc.*, **8**, 699 (1931).
708. Allen and Ball, *J. Am. Chem. Soc.*, **59**, 686 (1937).
709. Yabuta and Kambe, *J. Agr. Chem. Soc., Japan*, **6**, 516 (1930); *C.A.*, **26**, 1931[8] (1932).
710. Gautier, *Compt. rend.*, **212**, 164 (1941), *C.A.*, **36**, 4741,2 (1942).
711. Ichiba, Michi, and Emoto, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **39**, 126 (1941); *C.A.*, **41**, 6246e (1947).

712. Bremer, *Ann.*, **521** 286 (1936).
713. Harris, *J. Am. Chem. Soc.*, **62**, 3203 (1940).
714. U.S. patent 2,431,463, Carlson and Pilgrim (Nov. 25, 1947); *C.A.*, **42**, 1393*b* (1948).
715. German patent 506,425, Räth (Aug. 21, 1930); *C.A.*, **25**, 1036[6] (1931).
716. Roblin and Winnek, *J. Am. Chem. Soc.*, **62**, 1999 (1940).
717. British patent 517,382, Branscombe (Jan. 29, 1940); *C.A.*, **35**, 7124[3] (1941).
718. U.S. patent 2,064,944, Reitmann and Hecht (Dec. 22, 1936); *C.A.*, **31**, 817[2] (1937).
719. Sugasawa and Tatsuno, *Pharm. Bull. (Tokyo)*, **3**, 193 (1954).
720. Lott and Shaw, *J. Am. Chem. Soc.*, **71**, 70 (1949).
721. Bojarska-Dahlig and Swirska, *Roczniki Chem.*, **27**, 258 (1953); *C.A.*, **49**, 10287*b* (1956).
722. Newbold and Spring, *J. Chem. Soc.*, **1948**, 1864.
723. Gleu and Wackernagel, *J. prakt. Chem.*, **148**, 72 (1937).
724. Shimizu, Naito, Ohta, Suzuki, Kasahara, Murai, and Asano, *J. Pharm. Soc. Japan*, **72**, 1639 (1952).
726. Beyerman and Bontekoe, *Rec. trav. chim.*, **72**, 262 (1953).
727. McMillan, Leonard, Meltzer, and King, *J. Am. Pharm. Assoc. Sci. Ed.*, **42**, 457 (1953).
728. Bernstein, Stearns, Dexter, and Lott, *J. Am. Chem. Soc.*, **69**, 1147 (1947).
729. Bernstein, Pribyl, Losee, and Lott, *ibid.*, **69**, 1158 (1947).
730. Furukawa, *Pharm. Bull. (Tokyo)*, **3**, 413 (1955).
731. Shaw, *J. Am. Chem. Soc.*, **71**, 67 (1949).
732. Yamamoto and Takahashi, *J. Pharm. Soc. Japan*, **71**, 169 (1951).
733. German patent 637,385, Hoffmann-LaRoche (Oct. 27, 1936); *C.A.*, **31**, 817[6] (1937).
734. Adams, Jones, and Johnson, *J. Am. Chem. Soc.*, **69**, 1810 (1947).
735. Bickel, *ibid.*, **69**, 1805 (1947).
736. Kleipool and Wibaut, *Rec. trav. chim.*, **69**, 37 (1950).
737. German patent 597,974, Haack and Rost (June 2, 1934); *C.A.*, **28**, 7268[9] (1934).
738. U.S. patent 1,881,236, Miescher and Urech (Oct. 4, 1932); *C.A.*, **27**, 1096 (1933).
739. Collie and Bishop, *J. Chem. Soc.*, **127**, 962 (1925).
740. Gardner, Wenis, and Smith, *J. Am. Chem. Soc.*, **73**, 5455 (1951).
741. Yamamoto, *J. Pharm. Soc. Japan*, **72**, 1017 (1952); *C.A.*, **46**, 10285*h* (1952).
742. Katada, *ibid.*, **67**, 53 (1947); *C.A.*, **45**, 9536g (1951).
743. Den Hertog, Henkins, and Dilz, *Rec. trav. chim.*, **72**, 296 (1953).
744. Ettel and Hebký, *Collection Czechoslov. Chem. Communs.*, **15**, 356 (1950); *C.A.*, **45**, 3847*c* (1951).
744a. Ettel and Hebký, *ibid.*, **15**, 639 (1950); *C.A.*, **46**, 504*g* (1952).
745. Wilson and Tishler, *J. Am. Chem. Soc.*, **73**, 3635 (1951).
746. Mariella and Leech, *ibid.*, **71**, 331 (1949).

747. Sculley and Hamilton, *ibid.*, **75**, 3400 (1953).
748. Den Hertog and Von Ammers, *Rec. trav. chim.*, **74**, 1160 (1955).
749. Brydowna and Wiszniewski, *Roczniki Chem.*, **15**, 378 (1935).
750. German patent 515,991, Schroeter (Dec. 24, 1930); *Friedl.*, **17**, 2447; *C.A.*, **25**, 2441[6] (1931).
751. Stevens and Beutel, *J. Am. Chem. Soc.*, **63**, 308 (1941).
752. French patent 769,688 (Aug. 31, 1934); *C.A.*, **29**, 1435[8] (1935).
753. Gautier, *Compt. rend.*, **196**, 1124 (1933).
754. German patent 596,730, Haack (May 9, 1934); *Friedl.*, **21**, 520; *C.A.*, **28**, 5182[3] (1934).
755. German patent 599,385, Haack (June 30, 1934); *Friedl.*, **21**, 522; *C.A.*, **29**, 816 (1935).
756. U.S. patent 2,390,593, Keresztesy and Stevens (Dec. 11, 1945); *C.A.*, **40**, 1636[8] (1946).
757. German patent 607,662, Räth and Haack (Jan. 4, 1935); *Friedl.*, **21**, 527; *C.A.*, **29**, 4026[2] (1935).
758. Mumm, *Ann.*, **443**, 272 (1925).
759. German patent 586,879, Maier-Bode; *Chem. Zentr.*, **1934, I**, 129.
760. Pieroni, *Atti. accad. nazl. Lencei. Rend.* [6] **5**, 303 (1927).
761. Bojarska-Dahlig, *Roczniki Chem.*, **29**, 119 (1955); *C.A.*, **50**, 11643d (1956).
762. Fischer and Renouf, *Ber.*, **17**, 1896 (1884).
763. Pfeiffer, *ibid.*, **20**, 1343 (1887).
764. Kirpal, *Monatsh.*, **23**, 929 (1902).
765. Beilmann, *J. prakt. Chem.*, **29**, 7 (1884).
766. Haitinger and Lieben, *Monatsh.*, **5**, 339 (1884).
767. Lerch, *ibid.*, **5**, 367 (1884).
768. Conrad and Guthzeit, *Ber.*, **20**, 154 (1887).
769. Marckwald, *ibid.*, **27**, 1317 (1894).
770. Philippi and Seka, *ibid.*, **54**, 1089 (1921).
771. Petrenko-Kritschenko and Schottle, *ibid.*, **44**, 2826 (1911).
772. Kirpal, *Monatsh.*, **23**, 239 (1902).
773. Petrenko-Kritschenko, *Ber.*, **42**, 2020, 3683 (1909).
774. Peratoner and Strazzie, *Gazz. chim. ital.*, **21**, 304 (1891).
775. Conrad and Eckhardt, *Ber.*, **22**, 73 (1889).
776. Hall and Collie, *J. Chem. Soc.*, **73**, 237 (1898).
777. Meyer, *J. prakt. Chem.*, **10**, 560 (1904).
778. Den Hertog, *Rec. trav. chim.*, **64**, 85 (1945).
779. Aso, Matsuda, and Shuna, *Tôhoku, J. Agr. Research*, **2**, 53 (1952); *C.A.*, **47**, 9972f (1953).
780. Guareschi, *Chem. Zentr.*, **1902, II**, 700; **1907, I**, 459.
781. Kon and Nanjii, *J. Chem. Soc.* **1931**, 560.
782. Rogerson and Thorpe, *ibid.*, **89**, 643 (1906).
783. Ruhemann, *ibid.*, **75**, 414 (1899).
784. Ruhemann and Stapleton, *ibid.*, **77**, 239 (1900).

785. Plano, *Chem. Zentr.*, **1901**, I, 582.
786. Sell and Jackson, *J. Chem. Soc.*, **75**, 508 (1899).
787. Sell and Easterfield, *ibid.*, **65**, 831 (1894).
788. Ruhemann, *ibid.*, **93**, 1294 (1908).
789. Woodburn and Hellmann, *J. Am. Chem. Soc.*, **70**, 2294 (1948).
790. Meyer and Heimann, *Compt. rend.*, **204**, 1204 (1937).
791. Wedekind, *Ann.*, **378**, 271 (1911).
792. Feist, *Ber.*, **35**, 1553 (1902).
793. Feist, *ibid.*, **26**, 757 (1893).
794. Guareschi, *Chem. Zentr.*, **1905, II**, 684.
795. Hall and Sprinkle, *J. Am. Chem. Soc.*, **54**, 3469 (1932).
797. Bossi, *Gazz. chim. ital.*, **29**, 1 (1899).
798. Meyer, *Monatsh.*, **22**, 440 (1901).
799. Einhorn, *Ann.*, **265**, 212 (1891).
800. Besthorn and Byvanck, *Ber.*, **31**, 802 (1898).
801. Errera and Labati,' *Chem. Zentr.*, **1903, II**, 1283.
802. Nieme and von Pechmann, *Ann.*, **261**, 190 (1890).
803. Guareschi, *Chem. Zentr.*, **1899, I**, 289.
804. von Pechmann, *Ber.*, **17**, 2396 (1884).
805. Sell and Dootson, *J. Chem. Soc.*, **77**, 233 (1900).
806. Collie and Tickle, *Chem. Zentr.*, **1898, I**, 848.
807. Sell and Dootson, *J. Chem. Soc.*, **77**, 771 (1900).
808. Chichibabin and Rjasanzew, *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915); *Chem. Zentr.*, **1916, II**, 228.
809. German patent 543,288, Dohrn and Diedrich (Apr. 2, 1932).
810. Pieroni, *Atti reale accad. Lincei.* [6], **5**, 305 (1927).
811. U.S. patent 2,426,012, Friedman and Braitberg (Aug. 19, 1947); *C.A.*, **42**, 225d (1948).
812. Meyer, *Monatsh.*, **28**, 47 (1907).
813. Reissert, *Ber.*, **28**, 119 (1895).
814. Feer and Koenigs, *ibid.*, **18**, 2394 (1885).
815. Hantzsch, *ibid.*, **17**, 2903 (1884).
817. von Pechmann and Welsh, *ibid.*, **17**, 2384 (1884).
818. Hess, *ibid.*, **32**, 1986 (1899).
819. Light and Hauser, *J. Org. Chem.*, **25**, 538 (1959).
820. Bobbitt and Scola, *ibid.*, **25**, 560 (1959).
821. Hope, *J. Chem. Soc.*, **121**, 2216 (1922).
822. Dickinson, *J. Am. Chem. Soc.*, **82**, 4367 (1960).
823. Middleton, Heckert, Little, and Krespan, *J. Am. Chem. Soc.*, **80**, 2783 (1958).
824. Hauser and Eby, *J. Am. Chem. Soc.*, **79**, 728 (1957).
825. Behrman and Pitt, *ibid.*, **80**, 3717 (1958).
826. Albert, *J. Chem. Soc.*, 1020 (1960).
827. Bailey and Brunskill, *J. Chem. Soc.*, 2554 (1959).

828. Sugisawa and Aso, *Chem. and Ind.,* 887 (1958).
829. Godar and Mariella, *J. Am. Chem. Soc.,* **79,** 1402 (1957).
830. Godar and Mariella, *J. Org. Chem.,* **25,** 557 (1960).
831. Wajon and Arens, *Rec. trav. chem.,* **76,** 65 (1957).
832. Wajon and Arens, *ibid.,* **76,** 79 (1957).
833. Baizer, Dub, Gister, and Steinberg, *J. Am. Pharm. Assoc.,* **45,** 478 (1956).
834. De Malde and Alneri, *Chimica e industria,* **38,** 473 (1956); *C.A.,* **51,** 408*e* (1957).
835. Wiley and de Silva, *J. Am. Chem. Soc.,* **78,** 4683 (1956).
836. Rapaport and Volcheck, *ibid.,* **78,** 2451 (1956).
837. Wuest, Bigot, de Boer, van der Wal, and Wibaut, *Rec. trav. chem.,* **78,** 226 (1959).
838. Thomas and Marxer, *Helv. Chim. Acta,* **43,** 469 (1960).
839. Moore and Binkert, *J. Am. Chem. Soc.,* **81,** 6029 (1959).
840. Moore and Puschner, *ibid.,* **81,** 6041 (1959).
841. Moore and Binkert, *ibid.,* **81,** 6045 (1959).
842. Moore and Marascia, *ibid.,* **81,** 6049 (1959).
843. Taylor and Driscoll, *ibid.,* **82,** 3141 (1960).
844. Elkaschef and Nosseir, *J. Am. Chem. Soc.,* **82,** 4344 (1960).
845. Tomisawa, *Yakugaku Zasshi,* **79,** 1173 (1959); *C.A.,* **54,** 3417*h* (1960).
846. Tomisawa, *ibid.,* **79,** 1167 (1959); *C.A.,* **54,** 3416*g* (1960).
847. Fronk and Mosher, *J. Org. Chem.,* **24,** 196 (1959).
848. Peterson, *ibid.,* **25,** 565 (1960).
849. Traynelis and Martello, *J. Am. Chem. Soc.,* **80,** 6590 (1958).
850. Traynelis and Martello, *ibid.,* **82,** 2744 (1960).
850a. Boekelheide and Harrington, *Chem. and Ind.,* 1423 (1955).
851. de Villiers and den Hertog, *Rec. trav. chim.,* **76,** 647 (1957).
852. Boyer and Morgan, *J. Am. Chem. Soc.,* **82,** 4748 (1960).
853. Chatterjea and Prasad, *Chem. Ber.,* **93,** 1740 (1960).
854. Schreiber and Adam, *ibid.,* **93,** 1848 (1960).
855. Ried and Schleimer, *Ann.,* **626,** 106 (1959).
856. Sugasawa and Kirisawa, *Chem. and Pharm. Bull. (Tokyo),* **6,** 615 (1958).
857. Biermann, Büchi, and Walker, *J. Am. Chem. Soc.,* **79,** 5558 (1957).
858. Hoegerle, *Helv. Chim. Acta,* **41,** 539 (1958).
859. Hoegerle, *ibid.,* **41,** 548 (1958).
860. van der Plas and den Hertog, *Tetrahedron Letters,* **1,** 13 (1960).
861. Wibaut, Uhlenbroek, Kooyman, and Kettenes, *Rec. trav. chim.,* **79,** 481 (1960).
862. Hünig and Kobrich, *Ann.,* **617,** 181 (1958).
863. Hünig and Kobrich, *ibid.,* **617,** 203 (1958).
864. Hünig and Kobrich, *ibid.,* **617,** 216 (1958).
865. Cava and Bhattacharya, *J. Org. Chem.,* **23,** 1287 (1958).
866. Bojarska-Dahlig, *Roczniki Chem.,* **30,** 315 (1956).
867. Bojarska-Dahlig, *ibid.,* **30,** 475 (1956).

868. Kolder and den Hertog, *Rec. trav. chim.*, **79,** 474 (1960).
869. Takahashi and Yoneda, *Chem. and Pharm. Bull. (Tokyo)*, **6,** 611 (1958); *C.A.*, **54,** 14246*b* (1960).
870. Papanastassiou, McMillan, Czebotar, and Bardos, *J. Am. Chem. Soc.*, **81,** 6056 (1959).
871. Kato and Hamaguchi, *Yakugaku Zasshi*, **77,** 222 (1957); *C.A.*, **51,** 11342*i* (1957).
872. Robison, *J. Am. Chem. Soc.*, **80,** 5481 (1958).
873. Lukeš and Kuthan, *Collection Czechoslov. Chem. Communs.*, **25,** 2173 (1960).
874. Bain and Saxton, *Chem. and Ind.*, 402 (1960).
875. Kato, Ogawa, and Ohta, *ibid.*, 1300 (1960).
876. Dimroth, *Angew. Chem.*, **72,** 331 (1960).
877. Hanson, Nelsen, and Kintner, *Proc. S. Dakota Acad. Sci.*, **38,** 256; *C.A.*, **54,** 19670*e* (1960).
878. Wiberg, Shryne, and Kintner, *J. Am. Chem. Soc.*, **79,** 3160 (1957).
879. Light and Hauser, *J. Org. Chem.*, **25,** 538 (1960).
880. Reibstein, *Ber.*, **14,** 2692 (1881).
881. Boyer and Kruger, *J. Am. Chem. Soc.*, **79,** 3552 (1957).
882. den Hertog, van der Plas, and Buurman, *Rec. trav. chim.*, **77,** 963 (1958).
883. Ferrier and Campbell, *J. Chem. Soc.*, 3513 (1960).
884. Taylor and Driscoll, *J. Org. Chem.*, **25,** 1716 (1960).
885. Bojarska-Dahlig and Nantka-Namirski, *Roczniki Chem.*, **30,** 461 (1956); *C.A.*, **51,** 14722*e* (1957).
886. Abramovitch and Notation, *Can. J. Chem.*, **38,** 1445 (1960).
887. Jerchel and Jakob, *Chem. Ber.*, **91,** 1266 (1958).
888. Vompe, Monitch, Turitsyna, and Ivanova, *Tetrahedron*, **2,** 361 (1958).
889. Talik and Plazek, *Roczniki Chem.*, **33,** 1343 (1959); *C.A.*, **54,** 13123*e* (1960).
890. Jones, Katritzky, and Lagowski, *Chem. and Ind.*, 870 (1960).
891. Spinner, *J. Chem. Soc.*, 1226 (1960).
892. Spinner, *ibid.*, 1232 (1960).
893. Katritzky and Jones, *Proc. Chem. Soc.*, 313 (1960).
894. Katritzky, *Quart. Revs.*, **13,** 353 (1959).
895. Katritzky and Jones, *J. Chem. Soc.*, 2947 (1960).
896. Takahashi and Yoneda, *Chem. Pharm. Bull.*, **6,** 365 (1958); *C.A.*, **53,** 8143*e* (1959).
897. Takahashi and Yoneda, *ibid.*, **6,** 46 (1958); *C.A.*, **53,** 8143*d* (1959).
898. Mikhant'ev and Federov, *Izvest. Vysshykh Ucheb. Zavedenii, Khim. i Khim. Tekhnol.*, **2,** No. 3, 390 (1959); *C.A.*, **54,** 4565*i* (1960).
899. Winterfeld and Michael, *Chem. Ber.*, **93,** 61 (1960).
900. Prins, *Rec. trav. chim.*, **76,** 58 (1957).
901. Markees, *J. Org. Chem.*, **23,** 1030 (1958).
902. Ban, Yonemitsu, Oishi, Yokoyama, and Nakagawa, *Chem. and Pharm. Bull. (Tokyo)*, **7,** 609 (1959); *C.A.*, **54,** 14242*i* (1960).

903. Vanderhaeghe and Parmentier, *J. Am. Chem. Soc.*, **82,** 4414 (1960).
904. Lukeš and Fábryová, *Collection Czechoslov. Chem. Communs.*, **25,** 1618 (1960).
905. Habib and Rees, *J. Chem. Soc.*, 3371 (1960).
906. Arnold, Johnson, and Mauger, *ibid.*, 4466 (1958).
907. Mikhant'ev, Fedorov, Kucherova, and Potapova, *Zhur. Obshcheĭ Khim.*, **29,** 1874 (1959); *C.A.*, **54,** 8808 (1960).
908. Furst and Feustel, *Chem. Tech. (Berlin)*, **10,** 693 (1958); *C.A.*, **53,** 18951*b* (1959).
909. Takahashi and Yoneda, *Chem. Pharm. Bull. (Tokyo)*, **6,** 442 (1958); *C.A.*, **53,** 2229*b* (1959).
910. Kozlowska and Plazek, *Roczniki Chem.*, **33,** 831 (1959); *C.A.*, **54,** 3410 (1960).
911. Finger and Starr, *J. Am. Chem. Soc.*, **81,** 2674 (1959).
912. Blackwood, Hess, Larrabee, and Pilgrim, *ibid.*, **80,** 6244 (1958).
913. Dornow and Siebrecht, *Chem. Ber.*, **93,** 1106 (1960).
914. Sugisawa and Aso, *Chem. and Ind.*, 887 (1958).
915. Beyerman, *Rec. trav. chim.*, **77,** 249 (1958).
916. Fujimoto, *Pharm. Bull. (Japan)*, **4,** 77 (1956); *C.A.*, **51,** 5069*g* (1957).
917. Fujimoto, *ibid.*, **4,** 340 (1956); *C.A.*, **51,** 9607 (1957).
918. Winterfeld and Michael, *Chem. Ber.*, **93,** 61 (1960).

SUBJECT INDEX

Italicized page numbers refer to tables; individual compounds from tables are not indexed.

D

E

I

J

K

L

M

N

O

P

Q

R

S

T

V

W