

PYRIDINE AND ITS DERIVATIVES

In Four Parts

PART ONE

This is Part One of the fourteenth volume published in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

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PYRIDINE

and Its Derivatives

Part One

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The Chemistry of Heterocyclic Compounds

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

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

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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.

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ERWIN KLINGSBERG

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CHAPTER I

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BY R. A. BARNES
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A. GENERAL ASPECTS

1. Introduction

Of all the known heterocyclic systems, pyridine has perhaps the greatest importance, whether judged by the variety and interest of

its derivatives and their reactions or simply by the volume of literature devoted to them. Broadly speaking, the chemical properties of the pyridine system may be grouped into three categories:

(1) Properties roughly parallel to the benzene system, modified in some degree by the presence of the ring nitrogen. These include the typical electrophilic substitution reactions such as sulfonation and halogenation, which are more difficult than with benzene, and the radical reactions, which are rather similar. The behavior of most ring substituents also follows the pattern in the benzene series, with the greatest divergence observed in 2 and 4 substituted pyridines.

(2) Properties unusual for the benzene system. In this group are the various reactions in which the key step involves interaction of the pyridine ring system with a base or nucleophilic reagent, as in the amination by sodamide or the addition of organometallic compounds.

(3) Properties associated with the unshared electron pair on the ring nitrogen. The formation of salts, quaternary compounds, and *N*-oxides is of major interest, especially in the recent literature. The formation and subsequent transformations of these compounds have, of course, no analogies among benzene derivatives.

In view of this great wealth of chemical reactions, it is not surprising that the pyridine literature in recent years is growing faster than that of many other branches of organic chemistry. While the benzene literature still bulks far larger, the gap may well diminish in the near future.

Although there are a great many similarities between pyridine and benzene, the emphasis, particularly here in the first chapter, is on the differences, that is, the changes in behavior of the aromatic system which result from the presence of the nitrogen atom. In discussing the various reactions, an attempt has been made to formulate reaction mechanisms which are in harmony with the available data and which seem reasonable by analogy or because of similarity to more thoroughly studied examples from other systems. It is clearly recognized that as more experimental data accumulate, some of the generalizations which have been suggested will require revision.

2. Historical

Pyridine and its simple alkyl derivatives were undoubtedly obtained in a very impure state from the dry distillation of a variety of animal products as far back as the alchemistic period. However it was not until 1846 that investigations of the components of coal tar, which had been going on for several years, finally led to the isolation of the first pure substance of this series, which was named picoline (from *pix*, Latin for tar or pitch). This discovery was made by Anderson (1) in the course of experiments that proved pyrrole to be a constituent of coal tar. The similarity between picoline and some unidentified bases previously obtained from animal oil* led Anderson to extend his investigation to bone oil. From this source, after much laborious work, pyridine was first obtained in pure form (2). Its name was based, like "pyrrole," on its preparation by dry distillation (*pyros*, Greek for fire); the ending was chosen in harmony with the other organic bases, aniline and toluidine, which were known at the time.

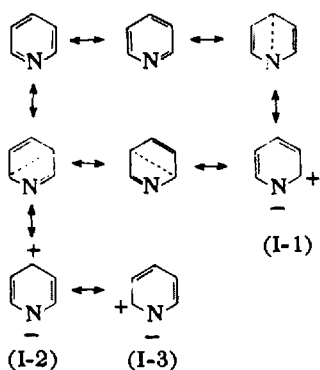
3. Structure

The structure for pyridine was proposed independently by Körner (3) and Dewar (4) and was apparently made largely by analogy with Kekulé's structure for benzene. Confirmation of this structure was obtained when pyridine was reduced with sodium and absolute ethanol to piperidine; the structure of piperidine in turn had been established by its synthesis from pentamethylenediamine. (5). This structure with three double bonds in the ring suffered from the same difficulty as the analogous structure for benzene, namely that it is not compatible with the lack of reactivity which characterizes these aromatic systems. Attempts to modify the structure followed the same lines as for benzene; centric (6), Ladenburg (7), and diagonal (8) structures were suggested and ultimately discarded.

It is impossible to write a "structure" in the classical sense which

* For a description of the work on crude bases obtained prior to the actual identification of pyridine see Calm and Bucka, *Die Chemie des Pyridins und Seiner Derivate*, Braunschweig, 1889-1891.

adequately characterizes an aromatic molecule, because the "aromatic electrons" (π electrons) cannot be localized in the neighborhood of any atoms or pairs of atoms. The most frequently used procedure for describing this situation is the valence bond or resonance approach, in which an aromatic molecule is characterized as a hybrid of various contributing resonance structures. More precisely, the true ψ function which completely describes the behavior of the π electrons of the aromatic system is assumed to be adequately approximated as a linear combination of the ψ functions of appropriately chosen contributing structures. Thus for pyridine there are two Kekulé and three Dewar structures, as for benzene, and three charged structures as well (I-1, I-2, I-3).



An alternate approach is to assume that the π electrons of the aromatic system are distributed in various "molecular orbitals" which extend over the whole system. These molecular orbitals have many of the properties of the atomic orbitals. Only two paired electrons can occupy each orbital, and when the lowest energy orbital is filled, the next two electrons are placed in the orbital of next higher energy. The energy of such orbitals could be calculated from the ψ function, which in this approach is usually assumed to be satisfactorily represented by a linear combination of the ψ functions of the atomic orbitals of the atoms of the aromatic system. For pyridine, therefore, the molecular orbitals are formed by a combination of the atomic orbitals of the five carbon atoms and the nitrogen atom of the ring. As in the case of benzene (9), the mole-

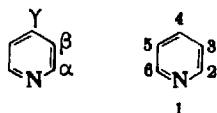
cular orbitals of pyridine can be visualized as continuous streamers extending around the ring, above and below its plane.

While the resonance approach is generally satisfactory for a strictly qualitative understanding, it cannot be used for even semi-quantitative estimations of the magnitude of charges, energies, etc., of pyridine or other unsaturated systems containing hetero-atoms. The basic difficulty is that there is no satisfactory method for determining the relative contribution of charged structures such as I-1, I-2, and I-3. This problem does not arise in the case of benzene because it is not necessary to include any charged structures in approximating the true ψ function.

To illustrate, the two approaches can be applied to the question of the electron density at the various positions of the pyridine nucleus. The resonance method predicts from a summation of all contributing structures that there will be a partial positive charge at the 2, 4, and 6 positions of pyridine and a net negative charge on the nitrogen (I-4). However, the magnitude of the charges cannot be estimated because these depend on the relative contributions of the charged structures, which are unknown. The conception that there are molecular orbitals for pyridine does not directly imply that the electrons are unevenly distributed among the atoms; however relatively simple calculations of the charge distributions in pyridine can be carried out (10). The magnitude of the charges varies somewhat with the parameters used for the calculations.



Formula I-5 gives the charges calculated from parameters chosen in such a way as to give reasonable agreement between calculated and observed dipole moments for a series of heterocyclic compounds (11).



4. Isomerism and Numbering

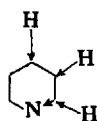
The nitrogen atom introduces an element of asymmetry into the aromatic system and there are, therefore, three possible positions for a single substituent and ten arrangements of two different substituents in the nucleus. For the monosubstituted pyridines the designation of positions by the Greek letters was used almost exclusively in the older literature and is still widely practiced. For di- and polysubstituted pyridines the numbering system with its obvious advantages has been almost universally adopted.

B. PHYSICAL PROPERTIES

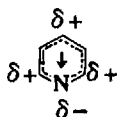
Since pyridine and benzene have essentially the same molecular size, shape, and weight, the differences in physical properties between the two may be attributed largely to the greater polarity of pyridine. This increase in polarity results from the presence of the electronegative nitrogen atom in the ring; the nitrogen atom is the center of negative charge and the positive charge is distributed over the rest of the ring.

1. Dipole Moments

The dipole moment, being a function of the magnitude of the charges in a molecule and the distance between them, can give some idea of the electron distribution, particularly in rigid molecules such as pyridine or its simple derivatives. Actually the observed dipole moment for an unsaturated system is the sum of a moment which results from unequal distribution of electrons in the σ bonds and a moment arising from unequal distribution of the π electrons. Thus the dipole moment of pyridine results from vector addition of the bond moments of the C—H and C—N bonds (I-6) plus a π moment (I-7) resulting from the excess of π electrons on the nitrogen; the σ moment for pyridine is calculated (II) to be 0.85 D and the observed moment, the sum of $\sigma + \pi$ moment, is 2.23 D . In practice it is frequently assumed that σ bond moments depend only on the nature of the two atoms and are independent of the π electron distribution or of substituents on either atom. Using this assumption it should be possible to calculate the charges produced by the π electrons from



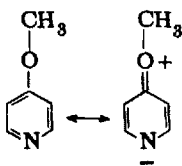
(I-6)



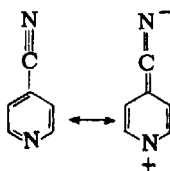
(I-7)

the dipole moment or the reverse. Attempts to correlate dipole moments for a number of heterocycles with charges calculated by the molecular orbital method have met with limited success (11).

It should be possible to tell whether a substituent on a pyridine ring interacts with the electrons of the pyridine ring by observing the dipole moment of the substituted pyridine. If there is no interaction, vector addition of the moment of the substituent and of pyridine should give a value identical with that experimentally measured; any electronic interactions will increase or decrease this value depending on the electron accepting or donating properties of the substituent. Comparison of the dipole moments of a series of 4-substituted pyridines with the corresponding benzene derivatives (98) indicates that electron-donating substituents interact with the pyridine nucleus (I-8) to a greater extent than with the benzene nucleus. Electron-attracting substituents interact only as much as with benzene if at all. This means that the pyridine nitrogen does not really act as a donor of π electrons; that is, structures such as I-9 make little contribution (99).



(I-8)



(I-9)

2. Melting Points

The melting point of an organic molecule is generally a function of the polarity and symmetry of the molecule. Pyridine is more polar but much less symmetrical than benzene; benzene melts at 5°

while pyridine melts at -38° . Almost all of the alkylpyridines are liquids at room temperature. Exceptions are 2,3,5,6-tetramethylpyridine, m.p. 71° (durene, 1,2,4,5-tetramethylbenzene, melts at 79°) and 3,5-di-*i*-propylpyridine, m.p. 46° . In this latter compound the symmetry is almost the same as in 1,3-di-*i*-propylbenzene (liquid); therefore, the greater polarity of the pyridine derivative is probably responsible for its higher melting point.

An examination of monosubstituted pyridines in which the substituent is amino, hydroxyl, carboxyl, or cyano indicates that for each substituent the melting points decrease in the order, 4-isomer, 3-isomer, and 2-isomer. This further illustrates the importance of the symmetry factor in determining how closely the molecules can pack together in a crystal lattice and hence how effectively the polar groups can interact.

3. Boiling Points

Boiling points are largely determined by molecular weight and by association of the molecules in the liquid. The molecular weight of benzene and pyridine are about equal; however, the greater association of pyridine, due to its greater polarity, is responsible for the higher boiling point, 115° (benzene boils at 80°). The presence of alkyl groups increases the boiling point, as in the benzene series. However a striking observation is that the isomers with an alkyl group adjacent to the nitrogen atom always boil lower than those with no substituent at either the 2 or 6 position. For example, 2-methyl- (b.p. 129°) and 2-ethylpyridine (b.p. 149°) both boil about 15° lower than the corresponding 3- or 4-isomer. Similarly, the dimethylpyridines with no α -substituent boil at $174 \pm 4^{\circ}$ and with one α -substituent at $159 \pm 2^{\circ}$ while 2,6-lutidine boils at 144° . The explanation for this phenomenon must be that a large part of the association of pyridine is due to interactions involving the nitrogen atom and that adjacent alkyl groups act as a steric block to such interactions. Thus, for 2,6-lutidine, the nitrogen atom is almost completely blocked and the degree of association of this compound is, therefore, fairly close to that of the corresponding benzene derivative, *m*-xylene (b.p. 139°).

4. Solubility

A third property in which pyridine differs from benzene and which is also directly due to the greater polarity of the heterocyclic system is solubility in water. For water solubility the presence of charged centers is not always sufficient, and hydrogen bonding is frequently the most important factor. The complete miscibility of pyridine and water is probably due to the excellent hydrogen bonding between pyridine and water molecules. The difficulty in preparing anhydrous pyridine, the hygroscopic nature of pyridine, and the existence of a constant boiling mixture of the approximate composition $C_5H_5N \cdot 3H_2O$ all attest to the tendency of pyridine to combine with water.

5. Spectroscopic Properties

The absorption of light by a pyridine derivative has been used, as for most kinds of organic compounds, to demonstrate the presence of certain structural features in the molecule and also for purposes of analysis and identification. The ultraviolet and infrared have been the most useful regions of the spectrum.

a. Ultraviolet

Absorption of a photon of light in the ultraviolet region results in an energy increase sufficient to cause an electronic transition. In a molecule such as pyridine, these transitions involve the shift of a π electron to a molecular orbital of higher energy.

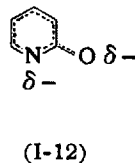
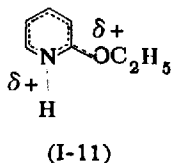
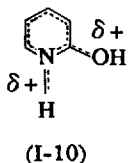
The shift of an electron from the highest energy bonding orbital to the lowest energy antibonding orbital is one of the important transitions in aromatic systems. The replacement of $-CH-$ by N in an aromatic system to yield pyridine, quinoline, acridine, etc. does not change the spectrum appreciably from that of the corresponding carbocyclic system (100). This observation is in accord with the molecular orbital calculations which show the energy levels of pyridine and benzene to have similar spacing. The principal maximum for pyridine is at 195 $m\mu$ (benzene 198 $m\mu$) and the center of the fine-structure bands is 250 $m\mu$ (benzene 255 $m\mu$).

The interactions of functional groups with the pyridine nucleus produces changes in the spectrum which are frequently similar to

those for the corresponding benzene derivatives. For example, the spectra of aniline and 3-aminopyridine are very similar (101). However, acetophenone and 3-pyridyl methyl ketone differ considerably (102,103).

The spectra of pyridines are of course modified by salt formation because the energy levels for the molecular orbitals are changed when the nitrogen atom takes on a positive charge.

An interesting example is 2(1*H*)-pyridone with three different spectra depending on the pH of the solution (104). In acid solution the spectrum resembles that of 2-ethoxypyridine in acid solution. In both of these molecules the aromatic system has an overall positive charge which is mostly at the nitrogen and oxygen atoms (I-10, I-11). In basic solution a proton may be lost to yield a negatively charged system (I-12). In a neutral solution the spectrum of uncharged 2(1*H*)-pyridone is found to be different from either I-10 or I-12.



b. Infrared

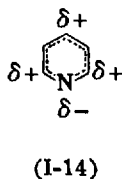
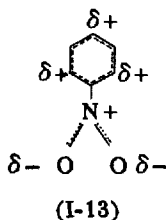
As yet the published data on the infrared spectra of pyridine derivatives are rather limited and it is difficult to make generalizations. Pyridine itself has been carefully studied (105-107) and its vibrational frequencies assigned with some certainty. The C—H stretching frequencies in the range 3020–3070 cm^{-1} as well as the C=C and C=N stretching frequencies at 1590–1660 cm^{-1} and near 1500 cm^{-1} are quite similar to the corresponding vibrations of benzene. The ring vibrations for pyridine are also similar to benzene but there are considerable differences in the C—H deformations, with those of pyridine occurring at lower frequencies. The important regions of the infrared spectrum for the latter two modes of vibration are near 1200 and 710 cm^{-1} and in the regions 1100–1000 and 900–650 cm^{-1} . Among the stronger absorption bands are

the out-of-plane C—H deformations, which depend on the number of adjacent hydrogens, *i.e.*, unsubstituted positions. Thus pyridine with five hydrogens has a band at 750 cm.^{-1} which corresponds to a monosubstituted benzene ($730\text{--}770\text{ cm.}^{-1}$ and $690\text{--}710\text{ cm.}^{-1}$). Similarly 2-, 3- and 4-picolines have bands in this region which parallel those of ortho, meta, and para disubstituted benzenes, respectively (107).

Raman spectral data also give information about the vibrational frequencies in a molecule, and although the technique for observing the weak Raman lines is rather tedious, some of the information obtained in this way cannot be derived from infrared absorption studies. Only a few pyridines have been studied (125, 126).

C. CHEMICAL REACTIVITY

It has been pointed out (19,20) that there are many analogies in reactivity between pyridine and nitrobenzene. This parallel behavior results from similarities in electron distribution; in both molecules π electrons are removed primarily from three positions on the ring by electronegative atoms (nitrogen and oxygen). If the extent of electron withdrawal is about equal, it would be anticipated that reactions at the ring carbons of these molecules would be very similar (I-13, I-14).



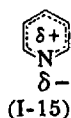
1. Theoretical Treatment of Aromatic Substitution Reactions

The replacement of a hydrogen atom by a substituent is the most characteristic and frequently the most important kind of reaction of aromatic systems. The questions as to the position which an entering group will take, if there are several choices, and the relative ease

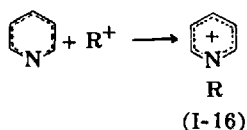
with which different nuclei will react with a given reagent have been fairly well worked out for the benzenoid aromatic systems.

Reagents are classified as electrophilic, nucleophilic, or radical depending on the nature of the fragment which actually attacks the aromatic nucleus. For benzene, electrophilic substitutions are most common, *i.e.*, by a positively charged fragment such as NO_2^+ . In contrast, nucleophilic reactions of the pyridine nucleus are relatively more important, for example amination by sodamide.

This general difference between pyridine and benzene is caused by the charge distribution in pyridine (I-15); more energy is re-



quired to bring the positive reagent within bonding distance of the positively charged carbons of the nucleus. This situation is made even worse by the basic nature of the nitrogen atom. The formation of pyridinium salt by interaction with either R^+ or H^+ (usually present in electrophilic reactions) means that a full positive charge is now distributed over the atoms of the ring (I-16), making substitution even more difficult.

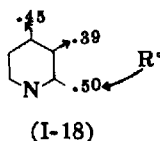
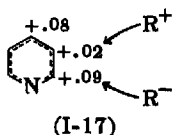


Although the positive charge hinders electrophilic substitution, it must, by the same mechanism, facilitate the approach of a negatively charged fragment in nucleophilic substitutions.

a. Static Approach

In the static approach the aromatic molecule in the ground state is examined and the relative charge at competing positions is estimated. The assumption is made that an electrophilic reagent will attack at the position of greatest electron density and a nucleo-

philic reagent at the position of lowest electron density (I-17). For free radical attack, the free valence* is calculated (13) (I-18), and it is assumed that a free radical will attack at the position of maximum free valence.

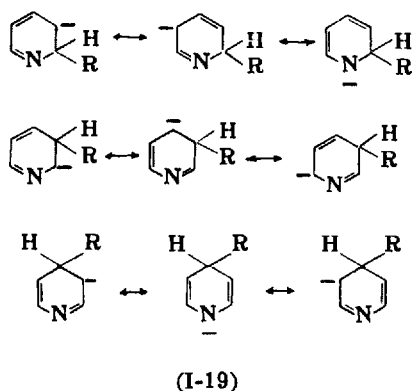


This procedure for predicting substitution frequently gives the correct answer, but in some instances it fails completely. The reason for these failures is that almost all substitutions are kinetically controlled processes in which the energy of activation is the important factor. Therefore the position which an entering substituent most frequently takes will be that one for which the energy requirement, in going from the initial state to the transition state, is the lowest. Thus in the ground state a certain position may have the greatest negative charge, but it does not necessarily follow that partial bond formation with a positive fragment will require the least energy at this position.

b. Activation Energy

While the activation energies may be determined by the usual kinetic studies, generally there are insufficient data available to be of much value for making generalizations or predictions about a given aromatic substitution. When considering the possible positions for attack by a reagent on an aromatic system such as that of pyridine, it is frequently possible to decide which transition state is lowest in energy by considering the important resonance structures for each state. Formulas I-19 give the important structures for nucleophilic attack at the 2, 3, and 4 positions of pyridine. There are three structures for each transition state; however for the 2 and

* Free valence is defined as the difference between the maximum bond number of a carbon atom ($N_{\max.} = 3 + \sqrt{3}$) and the actual bond number, which is the sum of the bond orders for all bonds the carbon atom in question makes with other atoms; see reference 9, p. 259.

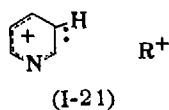
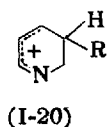


4 positions one structure has the negative charge on the more electronegative nitrogen atom. It may be concluded, therefore, that the transition state for nucleophilic substitution at the 2 and 4 positions is somewhat lower in energy than for the 3 position.

This method is useful only for comparing substitutions at different positions in the same molecule and also is of little value when there are stabilizing and destabilizing factors of uncertain magnitude in opposition.

c. Atom Localization Energy

Even with detailed knowledge of the structure of a transition state, calculation of energies of activation would be difficult. However an energy described as the "atom localization energy" (14) can be calculated rather easily by the molecular orbital method. This quantity, as the name suggests, is the amount of energy required to localize either zero, one, or two electrons (depending on the nature of the attacking reagent) at a given position. In effect, it is the energy required to go from the initial state to a sort of a "pseudo-transition state" in which the aromatic molecule is prepared to receive the reagent but yet is kept completely insulated from any interactions with the approaching reagent. A comparison of the true transition state (I-20) with the "localized state" (I-21) clearly



shows that in both there are the same number of π electrons distributed over the same atoms. A reasonable assumption, therefore, is that the atom localization energy differs from the true energy of activation by a constant factor for a given reaction. A comparison of these energy values should accurately predict the position of substitution in a given nucleus and even allow a comparison of reactivity of different heterocyclic systems as long as the same reaction is being considered for both systems and entropy effects are reasonably constant.

TABLE I-1. Atom Localization Energies

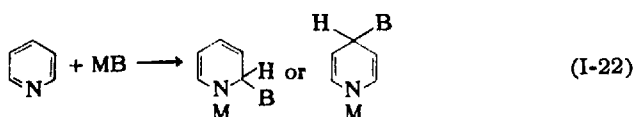
Position	Pyridine			Pyridinium ion		
	A_e	A_r	A_n	A_e	A_r	A_n
2	2.62	2.51	2.40	2.85	2.53	2.21
3	2.57	2.54	2.51	2.62	2.55	2.48
4	2.69	2.53	2.36	2.84	2.55	2.25

In Table I-1 are given the values (in terms of $-\beta$ which is about 17 kcal.) calculated (16) for the atomic localization energies A_e , A_r , and A_n for the three kinds of reagents. From this table it would be predicted that the activation energies would be lowest and hence substitution most rapid by electrophilic reagents at the 3 position, radical reagents at the 2 position, and nucleophilic reagents at the 4 position. In most electrophilic substitutions the pyridine molecule is probably present almost entirely as a pyridinium ion. To take this into account it is necessary only to recalculate the atomic localization energy, increasing the electronegativity of the nitrogen atom to account for the fact that it bears a positive charge. The last three columns in Table I-1 give values which have been calculated (16) in this way.

Table I-1 indicates that for radical substitution there would be little difference between the three positions and also that the value of A_r is very close to that of benzene ($A_e = A_r = A_n = 2.54$).

The atomic localization energies also predict that the 4 position will be most rapidly substituted by nucleophilic reagents but that the difference between the 2 and 4 positions is rather slight. In

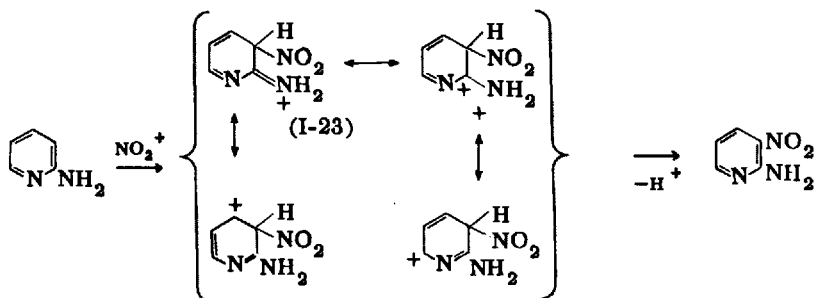
comparing experimental results with theory, a statistical factor of two must be used to account for the fact that there are two α -positions and a single γ -position. Another complicating factor in nucleophilic substitutions is that a stable intermediate may be formed in the reaction (I-22). If this were the case, then the yield of a given product may depend on the rate at which the intermediate can decompose to yield a substituted pyridine rather than on the energy of activation for formation of the intermediate.



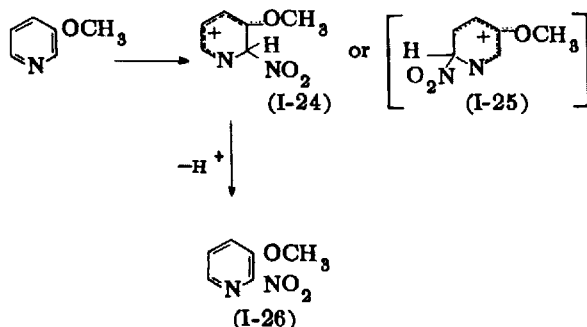
d. Effect of Substituents

In the pyridine series as in other aromatic systems, the course of substitution reactions can be greatly modified by substituents already present. Substituents are classified either as electron acceptors or electron donors, and in general the former are meta directing and the latter ortho-para directing. Some substituents, such as halogens and the nitroso group, are electron acceptors in the ground state of the molecule, but in the transition state can be electron donors and hence are ortho-para directing. The basic principle previously formulated (p. 14) that the position for which the transition state is lowest in energy is the one taken predominantly by the entering group, also applies to this situation provided that the reaction is not reversible.

(a) **Electron-Donating Substituents.** An electron-donating group such as hydroxyl or amino activates the positions ortho and para to it. The extra stability of the transition state for substitution at these positions may be visualized as resulting from the contribution of resonance structures such as I-23 which are not possible if the reagent were to enter a meta position. Since the 3 and 5 positions of pyridine itself are most readily attacked by electrophilic reagents, the effect of the amino group at the 2 position is to further activate these same positions. This same situation prevails when a hydroxyl or other electron-donating group is at the 4 position; that is, the 3 and 5 positions are activated toward electrophilic substitution.

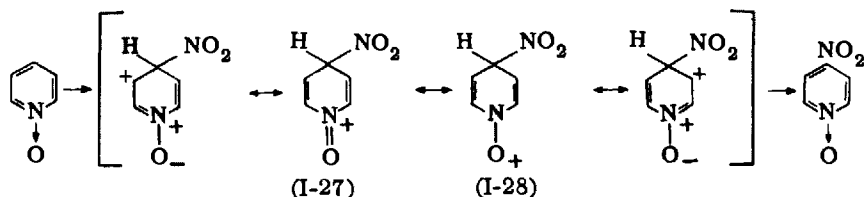


When the substituent is at the 3 position the orienting effect of the pyridine molecule and the substituent are in opposition. However, the major product is usually the one in which the new group enters position 2, indicating the predominating influence of the substituent already present. Qualitative inspection of the transition state reveals no reason why transition state I-24 should be lower in energy than I-25; molecular orbital calculations have not been applied to this situation. It is noteworthy that the electrophilic reagent does not react at the 4 position, which, although activated by the group at 3, is the least active position for pyridine itself (Table I-1); a second nitro group may be introduced at the 6 position of I-26.



(b) **Pyridine 1-Oxides.** Since the introduction of an electron-donating atom at one of the carbons of the pyridine nucleus activates certain positions to electrophilic substitution, it is not surprising that a similar effect should be observed when an oxygen atom is joined to the nitrogen atom. Pyridine 1-oxide reacts fairly

readily with nitric acid to yield 4-nitropyridine 1-oxide. The extra stabilization in the transition state may be due largely to structures such as I-27 and I-28.



There is some uncertainty about the parameters which should be used for molecular orbital calculations of the atom localization energies of pyridine 1-oxide (15,16). The values listed in Table I-2 were calculated (16) using parameters chosen in the same way as for pyridine itself (Table I-1).

These values predict that electrophilic and radical substitution for pyridine 1-oxide should be most rapid at the 2 position and nucleophilic substitution at the 4 position. The fact that nitration of pyridine 1-oxide actually takes place at the 4 position can be explained as a steric effect of the oxygen atom in blocking the adjacent 2 and 6 positions. The sulfonation of pyridine 1-oxide is about as difficult as with pyridine itself (18). In both reactions the sulfonic acid group enters the 3 position; this is in accord with the values in the tables if it is the salt rather than the free base which is reacting.

TABLE I-2. Atom Localization Energies^a

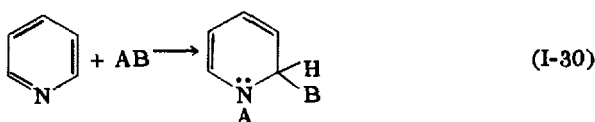
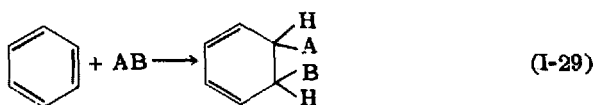
Position	Pyridine 1-oxide			Salt of pyridine 1-oxide		
	A_e	A_r	A_n	A_e	A_r	A_n
2	2.36	2.42	2.48	2.70	2.56	2.39
3	2.58	2.53	2.50	2.58	2.54	2.50
4	2.44	2.47	2.46	2.67	2.51	2.36

^aThe values for pyridine 1-oxide are determined using 0.75β as the resonance integral of the N—O bond while for the salt βNO is 0.5β .

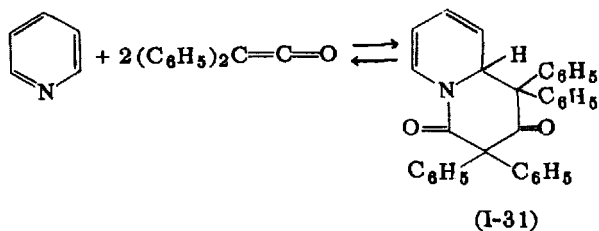
2. Additions to the Pyridine System

One of the features which distinguishes pyridine from benzene is the presence of a pair of unshared σ electrons on the nitrogen.

This situation gives to the pyridine molecule a facility for addition reactions which is not true of benzene. If a reagent AB were to add to the double bond of benzene an unsaturated (I-29) system having 4 π electrons distributed over four atoms remains. With pyridine, addition can take place to give an unsaturated system of 6 π electrons distributed over 5 atoms (I-30); in effect only the σ electrons on the nitrogen are required for bond formation with AB. Therefore the change in π -electron energy is much less when pyridine undergoes addition than benzene.

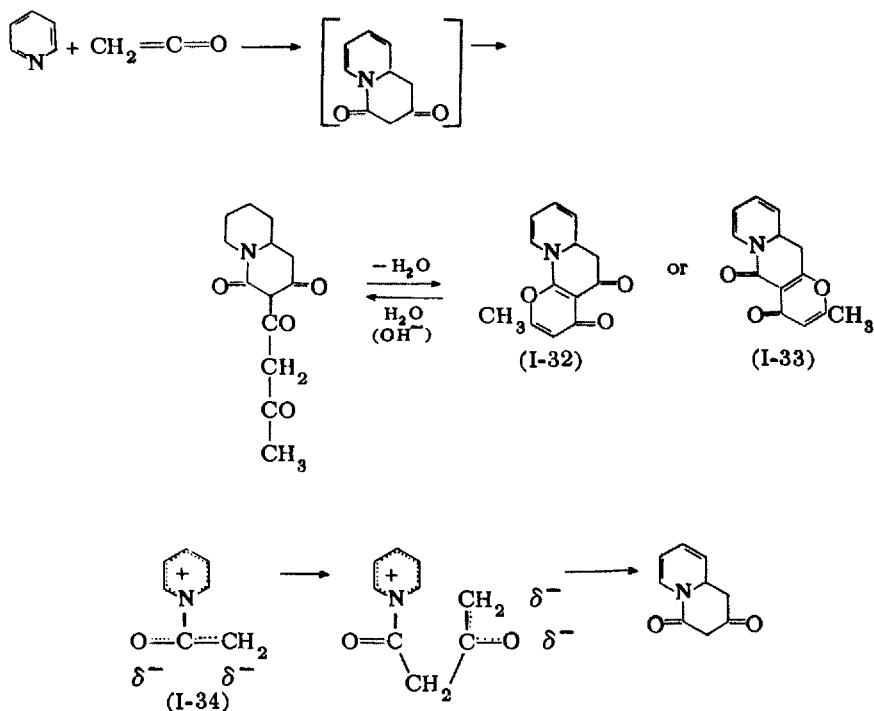


An example of such addition was reported by Staudinger (118) in his study of the chemistry of ketene. Adducts similar to I-31 are unstable and rather readily dissociate to the starting materials. With

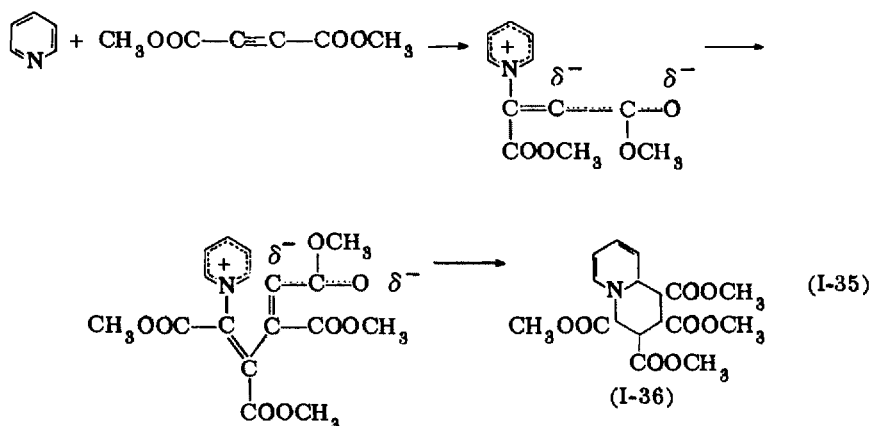


ketene itself a more stable product was isolated (119); however, its structure is not completely elucidated; both I-32 and I-33 are possibilities (120). This reaction most likely involves preliminary reactions of the electron-deficient carbonyl group of ketene with the σ electrons on the nitrogen atom to yield I-34 which reacts with a second mole of ketene.

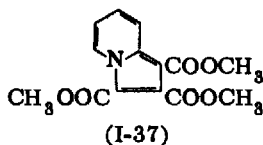
An interesting reaction between dimethyl acetylenedicarboxylate and pyridine, first described by Diels and Alder (121), is a



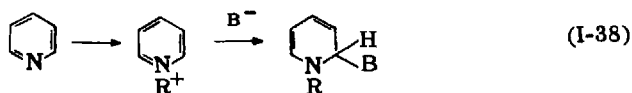
further example of addition to the pyridine ring. A mechanism (I-35) similar to that of the reaction with ketene seems logical (compare p. 32). Under various conditions these reactants yield other



products (123,124); for one of these, structure I-37 seems well established (122). It has been suggested (123) that a free radical process is involved in the formation of I-37. The conversion of I-36 to I-37, which can be effected by such diverse reagents as phenol, formic acid, and sodium dichromate in acetic acid, suggests that I-36 is formed by mechanism I-35 and is subsequently transformed to I-37 and to other products depending on experimental conditions.



Many reactions of pyridine which are discussed in other sections may be considered to be additions to the pyridine ring system. Among these are reactions with organometallic compounds (p. 50) and metals (p. 53). Many of the reactions of quaternary salts (pp. 33, 58) are in effect additions to the pyridine ring which are carried out in two steps (I-38).



3. Electrophilic Reactions

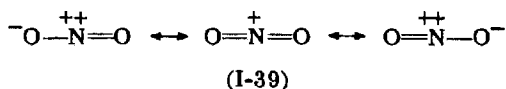
The previous discussion (pp. 12-15) emphasized the role of the pyridine nucleus in substitution reactions and the energy changes involved in forming bonds at the various positions with the reactive atom of a reagent. In order to compare the electrophilic reactions, one with the other, it is necessary to consider differences in the nature of the reagent.

It is readily apparent that the reagent with the greatest positive charge on the reactive atom should be most effective in forming a bond using two of the π electrons of the aromatic system. Table I-3 gives an estimate of the positive charge based on the various resonance structures for the electrophilic fragments; thus for NO_2^+ ,

TABLE I-3. Electrophilic Substitution

Reaction	Electrophilic fragment	Positive charge on bond-forming atom
Sulfonation	SO ₃ (or H ₂ SO ₄)	> 1
Nitration	NO ₂ ⁺	> 1
Bromination	Br ⁺	1
Mercururation	HgOAc ⁺	< 1
Friedel-Crafts	RCl · AlCl ₃	<< 1

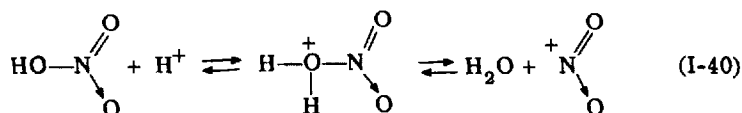
structures I-39 are important and the charge on the nitrogen atom must be larger than +1.



Since electrophilic reactions with the positively charged pyridine nucleus are rather slow, it is of practical importance to have the electron-seeking fragment present in high concentration. Another way to increase the reaction rate is to raise the temperature; therefore, it would be desirable for the electrophilic fragment to be stable at elevated temperatures.

Sulfonations may be carried out at 350° with a large excess of sulfuric acid or sulfur trioxide, both of which are stable. Thus all the factors are favorable and sulfonation is one of the more successful electrophilic reactions with pyridine itself (12). Lower yields of sulfonic acid are given by pyridine derivatives substituted by groups, such as alkyl groups, sensitive to the oxidizing and dehydrating action of the sulfuric acid (153). The sulfonation of 2,6-di-*t*-butylpyridine by sulfur trioxide proceeds with remarkable ease (23) probably because a pyridinium complex cannot form and substitution on the free base can take place.

The NO₂⁺ fragment necessary for nitrations results from reactions such as I-40, and its concentration in the nitrating mixture



cannot be increased beyond certain limits imposed by the equilibrium positions of the various reactions by which it is generated and transformed. Furthermore, as the temperature is raised to increase the reaction rate, free radical fragments begin to form at the expense of the ionic species. At 300° mainly 3-nitropyridine is formed, but at 450° 2-nitropyridine is reported to be the sole product (17).

The bromination of very reactive aromatic nuclei can be effected by a polarized bromine molecule, but it seems likely that complete ionization to yield Br^+ must take place before the pyridine ring can be attacked. There is the problem here also, as in the nitration, that, at temperatures above 300°, free radicals (in this case bromine atoms) are formed, and attack at the 2 position becomes of major importance.

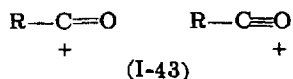
Mercuration can be effected by mercuric acetate at 155° to yield 3-pyridylmercuric acetate. At higher temperatures di- and polymercuration occurs (155). The introduction of the substituent into the 3 position makes it reasonably certain that the mercuration of pyridine, like that of many other aromatic nuclei, is an electrophilic reaction. The catalytic effect of water is undoubtedly exercised by promotion of ionization to yield HgOAc^+ which is necessary for electrophilic attack. The relatively mild reaction conditions strongly suggest that a mercury complex is involved in this reaction (see p. 41).

Although the Friedel-Crafts reaction is very useful in the benzenoid series, it is of no value for pyridine or its derivatives. The exact nature of the electrophilic fragment may vary depending on the reactivity of the aromatic nucleus being attacked. In some instances it may be a coordination complex (I-41) in which the carbon-halogen bond is broken only as the new carbon-carbon bond is formed (156) or it may be an ion pair (I-42) which separates as the aromatic nucleus approaches. Under certain conditions the free carbonium ion may be formed prior to reaction with the nucleus. The failure of the reaction with pyridine derivatives may be due to the fact that only the carbonium ion intermediate is capable of attacking the nucleus, but as the temperature is raised to permit the reaction to proceed at a finite rate, the carbonium ion begins to de-

compose in the presence of aluminum chloride to yield polymeric substances. Furthermore, pyridine forms a complex with aluminum chloride which may be less reactive than a pyridinium salt with a proton (see p. 40).



The Friedel-Crafts ketone synthesis is even more difficult because the carbon atom of the acylonium ion, I-43, is considerably less electrophilic than an ordinary carbonium ion in which the positive charge is usually distributed only by hyperconjugation.



4. Radical Reactions

Since radicals have a very wide range of stabilities, it is not surprising that relatively few are sufficiently reactive to attack the pyridine nucleus and yet are not so reactive that they are destroyed by side reactions shortly after being generated.

Aryl radicals as a group have been used most successfully for substitutions in the pyridine series. Among procedures available for generating aryl radicals are the decomposition of (a) diazonium hydroxides (the Gomberg reaction (108)), (b) acylarylnitrosamines (109), (c) 1-aryl-3,3-dimethyltriazenes (110), (d) arylazotriarylmethanes (111), (e) aroyl peroxides (72,112), (f) lead tetraarylcaboxylates (113), aryliodosarylcaboxylates (113) and (g) diaryliodonium halides (114). When a phenyl radical is generated by one of these methods in the presence of pyridine, a mixture of the three monophenylpyridines is produced.

Some of these mixtures have been analyzed and found to contain approximately 55% 2-phenylpyridine, 31% 3-phenylpyridine, and 15% 4-phenylpyridine (112,113). From these data the partial rate factors for attack of a phenyl radical on the pyridine molecule may be calculated: 2 position 1.69, 3 position 1.0, and 4 position 0.87. These values have been used, together with data on the rates of attack of trichloromethyl radicals on a series of polycyclic aro-

matic hydrocarbons (115), to determine a set of molecular orbital parameters for the nitrogen atom of pyridine. The rates of attack at the pyridine positions relative to a benzene position, calculated from the atom localization energies determined by these parameters, agree within 10% with the experimental rates (116). Thus there can be little doubt that these reactions are true radical substitutions in the pyridine nucleus.

Methyl radicals generated from acetyl peroxide react largely to form ethane and to abstract a hydrogen atom from the solvent; they can, however, attack any aromatic compounds which may be present. The extent of such attack, the "methyl affinity" (117) of various aromatic compounds relative to benzene, can be measured; pyridine has a methyl affinity of 3 based on the value unity for benzene. Since the products of methyl attack are formed in only small quantities, nothing is yet known of their nature. Because the methyl radical is much more reactive than a phenyl radical, it would be less selective and might react at all three pyridine positions with nearly the same rate.

In the section on electrophilic substitution (p. 22) it was pointed out that at high temperatures bromine atoms and nitro radicals are formed and react to yield mainly the 2-substituted pyridines; apparently these radicals are even more selective than phenyl radicals.

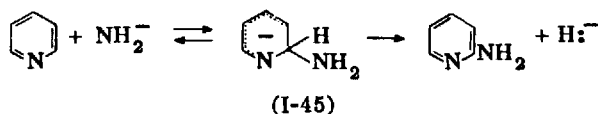
5. Nucleophilic Reactions

a. Chichibabin Reaction

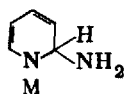
In electrophilic substitutions a positively charged fragment reacts with the aromatic system and a proton is lost. The analogous process for nucleophilic substitutions, the attack by a negatively charged reagent, with loss of a hydride ion, seldom if ever occurs. The Chichibabin amination of pyridine has frequently been regarded as an example of such a reaction (I-44). Since the hydride ion is a high energy fragment and the carbon-hydrogen bond energy



is greater than that of carbon-nitrogen bonds it seems probable that if the amide ion approached the pyridine molecule to form I-45, this entity would dissociate again rather than proceed to 2-aminopyridine.

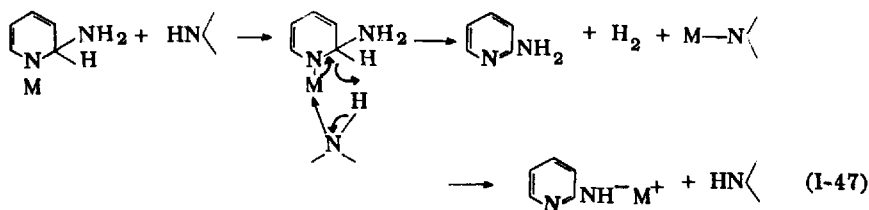


The reaction is usually carried out by heating a metal amide and pyridine at ca. 100–140°; hydrogen is evolved and the metal salt of 2-aminopyridine results. Bergstrom (59) has obtained evidence for the existence of an intermediate in the quinoline series; this, together with the fact that yields vary as the metal atom is changed, makes it seem likely that I-46 is an intermediate in the

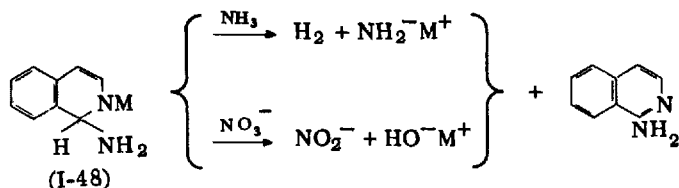


(I-46)

Chichibabin reaction. The transformation of I-46 to the observed products may take place in a bimolecular reaction (I-47). Accord-



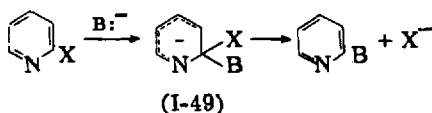
ing to this mechanism, ammonia, free aminopyridine, or perhaps even its monometal salt can serve as an acceptor for the hydride ion, with liberation of a hydrogen molecule. The experiments of Bergstrom in the isoquinoline series indicate that intermediate I-48 can be converted to 1-aminoisoquinoline with either the solvent, liquid ammonia, or nitrate ions acting as acceptor for the hydride ion.



The reaction of pyridine with potassium hydroxide is probably rather similar to the Chichibabin reaction, although the higher temperature (ca. 300°) necessary indicates that it is a more difficult reaction. It is interesting that 3-pyridinol will react at the same temperature as pyridine itself to yield 2,5-pyridinediol (50% yield). If this were a simple nucleophilic attack, the presence of an electron-donating substituent should make the reaction more difficult.

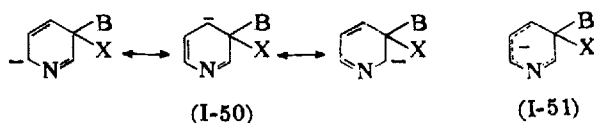
b. Displacement of Stable Ions

If the pyridine nucleus has substituents which are capable of existing as stable anions, the attack by nucleophilic reagents takes place readily and is extremely useful for synthesis of a great variety of pyridine derivatives. Such substituents as halogen, nitro, hydroxyl, amino, sulfonic acid, and sulfhydryl, when located at the 2 and 4 position, can all be replaced by a long list of bases and nucleophiles (see p. 63). The ease with which some of these reactions take place suggests that the energy required to bring together the base and the pyridine to yield I-49 is not large and that the main difference between these reactions and the Chichibabin reaction ($\text{X} = \text{H}$) is in the stability of the anion which must be eliminated to form the product.

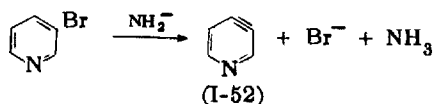


It is not possible to decide, a priori, whether I-49 is an intermediate or a transition state; perhaps as the nature of group X and B is changed, I-49 may shift from one to the other of the two possibilities. There are several examples in the benzenoid series in which an intermediate in a nucleophilic substitution has been isolated (58).

For substituents at the 3 position, nucleophilic displacement is much less readily accomplished because the nitrogen atom cannot facilitate the process by serving as a major site for the negative charges as is illustrated by the resonance structures I-50. However, the unsaturated system over which the negative charge is distributed does have the nitrogen atom as a member atom and hence the transition state (or intermediate) I-51 is more stable than in the benzene series. Thus, 3-bromopyridine reacts with sodium methoxide at 150° while bromobenzene is unreactive below about 250°.



From the reaction of 3-bromopyridine with sodioacetophenone in the presence of sodamide, using liquid ammonia as solvent, 4-phenacylpyridine and 4-aminopyridine were isolated (70). This reaction is believed to proceed by way of a "pyridyne" intermediate (I-52), which is analogous to the "benzyne" intermediate which has been suggested to explain similar transformations in the benzene series (71). It is somewhat surprising that the amide ion removed the proton at the 4 position to yield I-52, because the hydrogen at 2 would be expected to be more acidic; its loss would yield an isomeric pyridyne.



6. Pyridine as an Electron Donor

a. Basic Properties

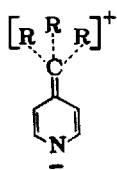
The strength of an organic base is usually considered to depend mainly on the electron density at the nitrogen atom. It is generally assumed that in pyridine the unshared electron pair is present in an sp^2 orbital having an axis in the plane of the ring. Therefore these electrons cannot be delocalized by interaction with the aromatic π

electrons. Since the π electron density is somewhat greater at the nitrogen than the carbon atoms, it might be predicted that the total electron density ($\pi + \sigma$ electrons) at the nitrogen should make pyridine at least as strong a base as the alkylamines (pK_b 3–5). Pyridine, with an ionization constant of 2.3×10^{-9} (pK_b 8.64), is very much less basic than expected.

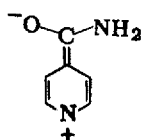
Wheland (21) has suggested that this lowered basicity is a manifestation of the general observation that atoms joined in multiple linkages have increased electronegativities (for example, the carbon atom of acetylene). Thus the electron density on the nitrogen atom of pyridine can be similar to that of the alkylamines but because of its increased electronegativity, the electrons are less available for bond formation with an acid.

(a) **Effect of Substituents.** The effect of substituents in the pyridine nucleus depends on whether the substituent is an electron acceptor or an electron donor. The basicity of the alkylpyridines has been studied by Brown and Mihm (22), who find that alkyl groups at the 2, 3, or 4 position increase the pK_a (ionization constant of the conjugate acid) by 0.5–0.8 units. With increasing size of the alkyl group at the 2 position, there is a slight decrease in base strength due to steric factors; however, there appear to be no steric effects in the reaction of 2,6-lutidine with a proton. 2,6-Di-*t*-butylpyridine, with very much bulkier groups around the nitrogen, is a much weaker base (pK_a 3.58) than either 2,6-lutidine or 2,6-di-*i*-propylpyridine (23); this indicates that the group in the 2 and 6 positions must be at least as large as *t*-butyl before there is much steric hindrance to reaction with a proton.

Alkyl groups could increase the electron density in the pyridine ring either by hyperconjugation or by the inductive effect. Since an alkyl group at the 4 position is somewhat more effective than at the 3 position, there must be some hyperconjugation (I-53) as well as inductive shift of the σ electrons toward the ring. The base strength does not change as the alkyl group at the 4 position is varied through the series, methyl, ethyl, *i*-propyl, *t*-butyl; this must mean that the sum of the hyperconjugative and inductive effects is about the same for these substituents.



(I-53)



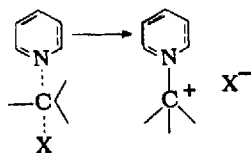
(I-54)

For electron-withdrawing substituents at the 3 and 4 positions there is a smaller difference in effect than would be expected if structure I-54 were important for pyridine bases; the pK_a values for the conjugate acids of nicotinamide and isonicotinamide are 4.77 and 4.90, respectively (24).

b. Quaternary Pyridinium Salts

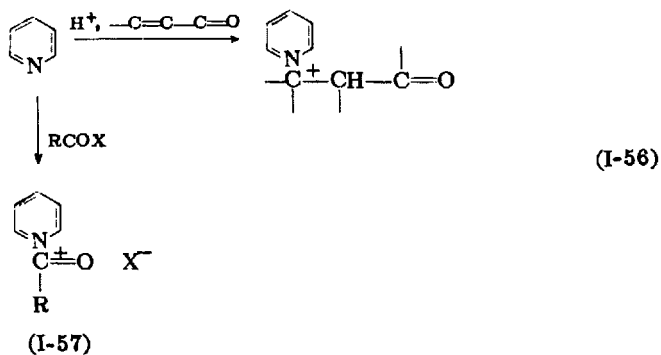
(a) **Formation.** The formation of pyridinium salts by a bimolecular displacement between a compound RX and a pyridine is a reaction which has been the subject of numerous investigations. The effects of the structure of R and X and the substituents on the pyridine ring are well understood (58,78). Cf. Chapter III.

Examination of the transition state (I-55) makes it clear that large groups around the carbon on which displacement is occurring, or bulky substituents at the 2 and 6 positions of pyridine, could make the reaction difficult. On the other hand, a group X which readily separates as a stable anion, or substituents on the pyridine ring which increase the basicity of the nitrogen, should assist the desired reaction.



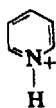
(I-55)

In what is essentially a Michael reaction (I-56), α,β -unsaturated acids or amines react with pyridines to yield pyridinium salts (see p. 21).

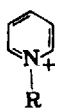


The reaction of an acid chloride or anhydride with a pyridine yields an *N*-acetylpyridinium salt (I-57).

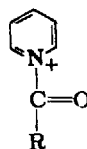
(b) **Reactions.** Aromatic substitutions in a pyridine nucleus which is in the salt form have been previously discussed (p. 16). Some differences in reactivity may exist between the three kinds of salts; the alkyl group on the nitrogen of (I-59) should act inductively as an electron donor by comparison with the hydrogen of (I-58). The carbonyl group of (I-60) is most effective in reducing the electron density of the pyridine ring; resonance structure (I-61) contributes in addition to those such as (I-62) which are also important for salts (I-58) and (I-59).



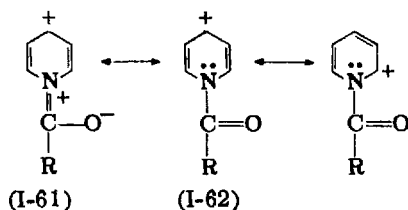
(I-58)



(I-59)



(I-60)

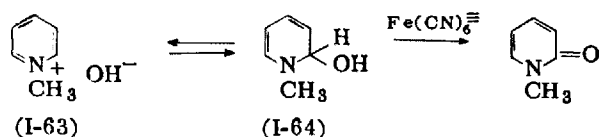


As the ability of the pyridine ring to undergo electrophilic attack is decreased, nucleophilic attack becomes easier (Table I-1). For an example showing that conversion of a pyridine to its proton salt increases the rate of nucleophilic substitution (see reference 16).

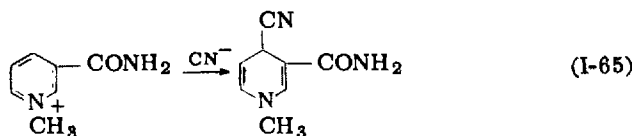
The greater reactivity of 1-alkyl and 1-arylpseudopyridinium salts toward nucleophilic reagents is manifested in a variety of reactions which are not possible with the free bases.

When a 1-alkylpyridinium salt is treated with a metal hydroxide one of the possible reactions is the formation of a "pseudo base" (I-64).

Conductometric investigations (80) indicate that there is very little if any of I-64 present in aqueous solution under normal laboratory conditions. If potassium ferricyanide is added to a solution of I-63, 1-methyl-2(1*H*)-pyridone is formed in good yield; I-64 must

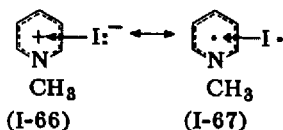


be an intermediate in this transformation. If I-64 were present in an aqueous solution one might expect the ring to open, converting the carbinolamine to a substance with free aldehyde and amine groups. This kind of reaction frequently occurs when quaternary salts are treated with bases (see p. 58). When cyanide ion is the base, 1-alkyldihydropyridines (I-65) have been isolated (81,82). The reduction of a pyridinium salt with a metal hydride is similar to reactions such as (I-65), with the relatively high-energy hydride ion acting as the nucleophilic reagent (p. 52).

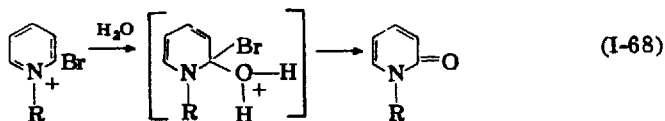


Observations of the ultraviolet spectrum of 1-methylpyridinium iodide solutions indicates that the iodide ion is also capable of reacting with the pyridinium ion (83,84) to yield a new species; this

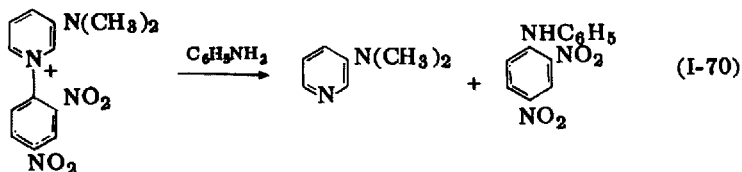
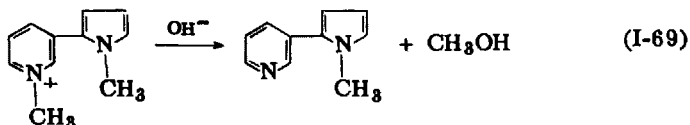
is believed to be a charge-transfer complex in which there is partial transfer of an electron from the iodide ion to the pyridine ring as is illustrated by contributing forms I-66 and I-67. It has also been suggested that charge-transfer complexes can be intermediates in addition to pyridinium rings (85); the experimental data which are available show that attack at the 4 position usually occurs with reactants which might be expected to form charge-transfer complexes and attack at the 2 position takes place with other reactants (see p. 12).

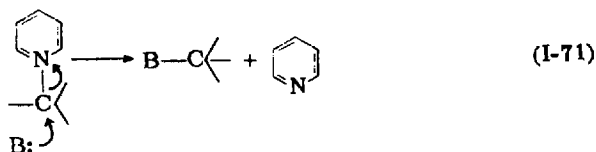


If the pyridinium salt has a substituent which can be eliminated as a stable anion, the reaction does not stop with addition but yields the aromatic substitution product (86,87) as in nucleophilic substitutions with pyridine bases. Equation I-68 shows that a base as weak as the water molecule can effect nucleophilic displacement of a substituent on a pyridinium ring.

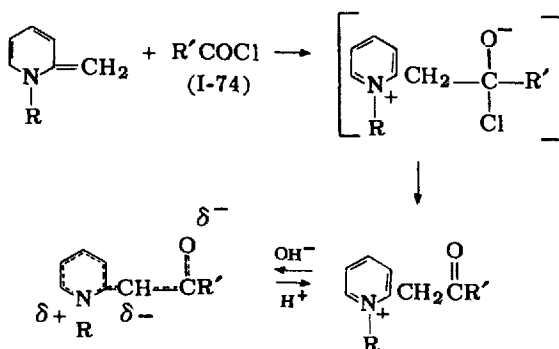
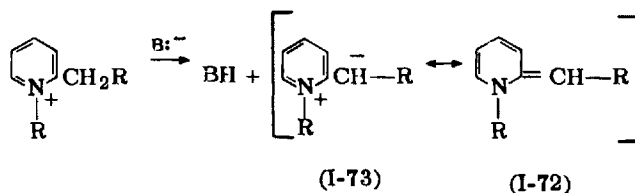


Another path for the reaction between a base and a 1-alkylpyridinium compound is displacement of the alkyl group (I-69). Aryl groups can also be displaced when warmed with a weak base such as aniline (I-70) (141). Reactions of this kind (I-71) are essentially the reverse of those by which pyridinium salts are usually formed.

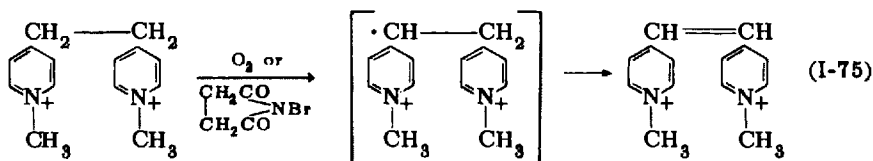




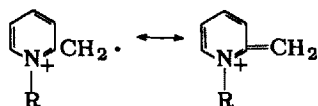
An alkyl group attached at the 2 or 4 position of the pyridinium ring can lose a proton to yield a neutral anhydro base (I-72). Anhydro bases are generally unstable substances because there is considerable negative charge (see resonance structure I-73) on the carbon atom; they are readily attacked by oxygen and a variety of reagents such as I-74 with electron-deficient centers.



Alkyl groups on a pyridinium ring may also be attacked by free radical reagents (I-75). The pyridinium ring can stabilize free radicals as well as carbanion intermediates, because the very electro-

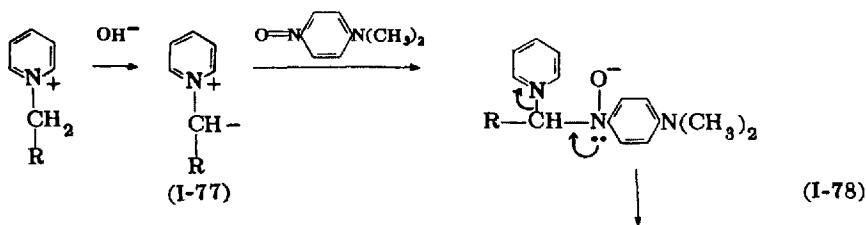


negative pyridinium nitrogen can accommodate more than its share of the seven (or eight for the carbanion) π electrons which are distributed over the seven atoms of the unsaturated system, I-76.

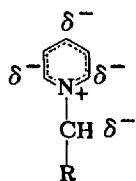
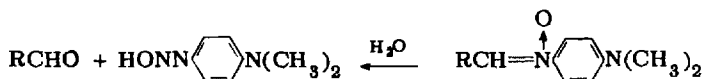


(I-76)

The pyridinium ring can also activate a methylene group attached to the ring nitrogens; thus the anion (I-77) is stabilized because the negative charge can be distributed over several atoms (I-79). A useful aldehyde synthesis (I-78) depends on the reaction of such a methylene group with an aromatic nitroso compound.



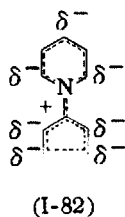
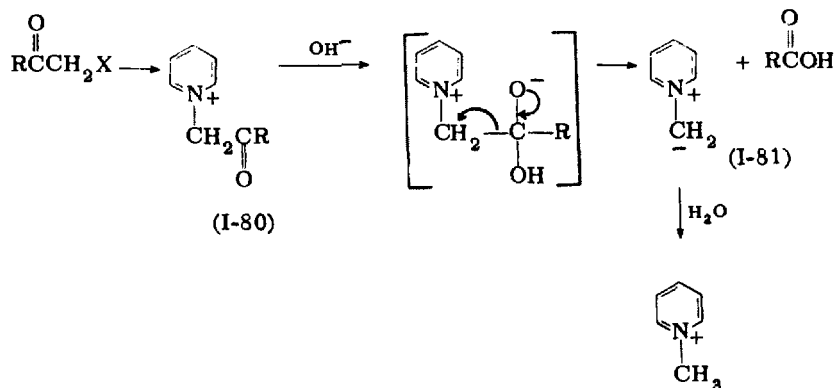
(I-78)



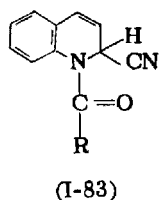
(I-79)

Another example of the ability of a pyridinium ring to stabilize a carbanion may be seen in the reaction of haloketones with pyridine and an alkali metal hydroxide. The cleavage of I-80 occurs so readily only because I-81 is a fairly stable carbanion. A stable substance (I-82) similar to I-81 has been isolated (88); the stability results from the fact that the negative charge is distributed over all

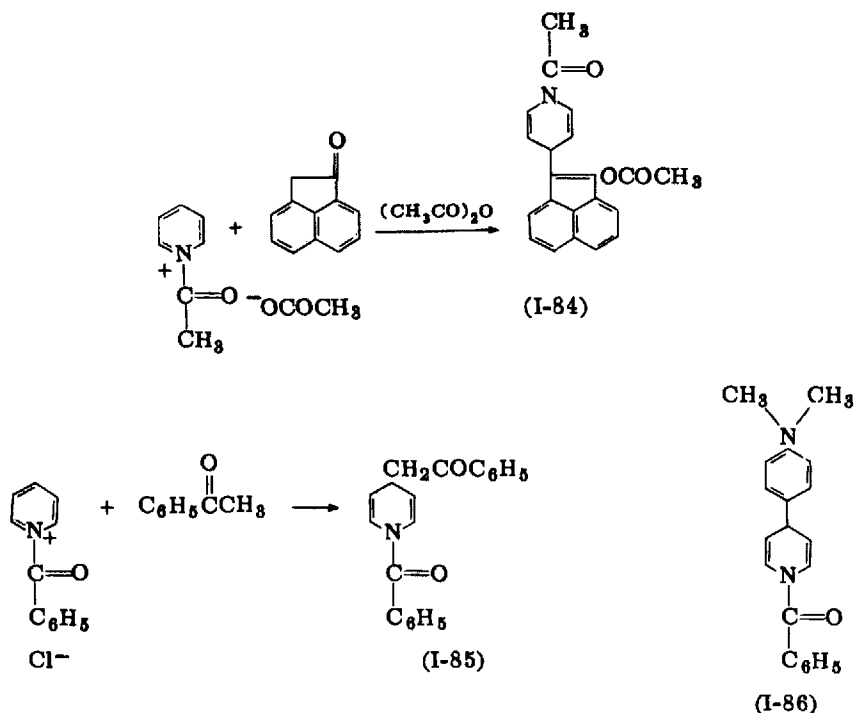
five carbons of the cyclopentadiene ring as well as the three carbons of the pyridinium ring.



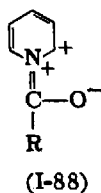
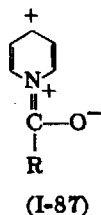
The effect of a 1-acyl group in increasing the positive charge on a pyridine ring would be expected to make the quaternary salts of this group most susceptible to attack by bases; many ring cleavage reactions (p. 57) are of this type. In the quinoline series the "Reissert Compounds" (I-83) are an important group of substances



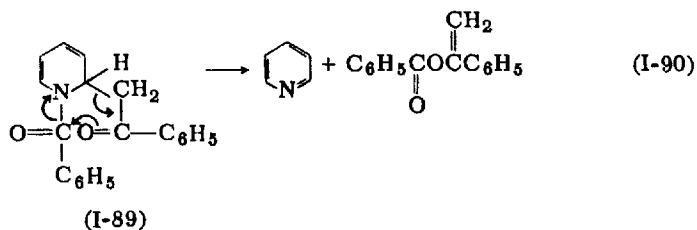
resulting from reaction of the cyanide ion with a 1-acylquinoline or isoquinoline (89). In the pyridine series, addition compounds have not been isolated from reaction with cyanide ion; however, acenaphthenone (90), acetophenone, and cyclohexanone (91) yield stable substances (I-84, I-85). Dimethylaniline can also act as a nucleophilic reagent to yield I-86.



In the 1-acylpyridinium ring the carbonyl group may remove electrons more effectively from the 4 position than from the 2 position; a comparison of resonance structure I-87 and I-88 suggests that I-87 should be more stable and hence make a larger contribution. The slightly greater positive charge at the 4 position as well as the steric effect of the acyl group on the 2 position may be sufficient to explain why only the 4-substituted 1,4-dihydropyridines have been obtained from 1-acylpyridines. An alternate explanation (91,92) in the reaction with acetophenone is that any 2-substituted

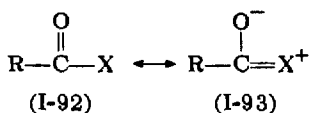
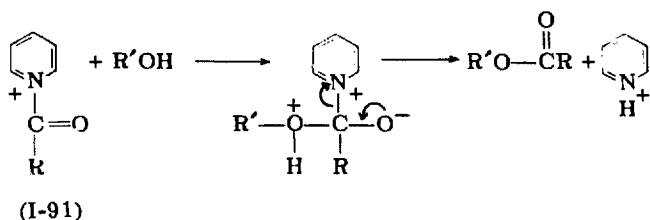


product (I-89) rapidly rearranges with elimination of pyridine. However the isolation of 1-benzyl-2-phenacyl-1,2-dihydroquinoline (92), which does not rearrange by a reaction similar to I-90, makes this scheme somewhat unlikely.



The use of pyridine as a catalyst in acylation reactions also involves reaction of a nucleophilic reagent with the 1-acylpyridinium ion. In these reactions the positive center on the carbonyl carbon, rather than the pyridine ring, is attacked by the electron donor.

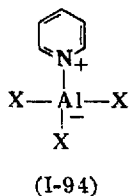
The reaction of a base such as the oxygen atom of an alcohol is faster with I-91 than with acid chlorides or anhydrides because in the latter cases the halogen or oxygen atom supply electrons to the carbon (I-93) while in I-91, the carbonyl is attached to the very electronegative pyridinium nitrogen and electrons can be supplied only rather inefficiently from the pyridine ring (structure I-87). Therefore the carbonyl carbon of I-91 is a much better electron acceptor than the carbonyl of I-92.



c. Pyridine Complexes with Metal Atoms

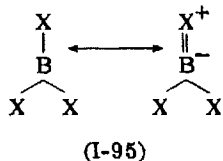
Nearly every metallic ion which forms hydrates or other coordination complexes in which the metal ion acts as an electron acceptor, has been observed to react with pyridine. There are rather limited data concerning the structural details for many of these complexes; the empirical formulas, solubility and physical appearance of the complexes are frequently all that is known. A few specific examples will illustrate some of the variations which are possible.

Aluminum salts can react to yield tetrahedral complexes in which the unshared sp^2 electrons of pyridine fill an sp^3 orbital of aluminum (60). The electron distribution in the aluminum-nitrogen bond depends considerably on the nature of the groups X (I-94). If the electronegativity of X is increased or the ionic character of the aluminum-X bond increased, the electrons of the nitrogen-aluminum bond shift toward the aluminum atom.



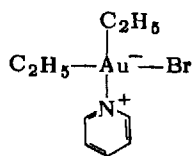
The complexes with beryllium, $\text{BeCl}_2 \cdot 2\text{C}_5\text{H}_5\text{N}$ (61), magnesium (62), and boron are similar to that of aluminum.

The formation of complexes from 2-substituted pyridines and boron trifluoride is sterically hindered as the size of the substituent increases (63). It has also been found that boron tribromide forms a more stable complex than the chloride, which in turn is more stable than the fluoride (64). The relative complexing ability of the boron atom is not determined by the inductive effect of the halogens but by the extent to which an unshared electron pair from the halogen can fill the unoccupied orbital of boron (I-95); the or-

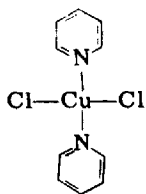


der of the halogens with respect to ability to form double bonds is $F > Cl > Br$.

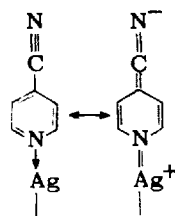
With the larger metallic ions in which d orbitals are available for bond formation, there are several possible configurations for the groups around the central atom. For example, the complex $(C_2H_5)_2AuBr \cdot C_5H_5N$ (65) has four dsp^2 bonds ($5d6s6p^2$) in a square configuration (I-96). The copper chloride complex (I-97) has been found to be coplanar (66) and therefore has a square rather than a tetrahedral configuration ($3d4s4p^2$ bonds). It is interesting to note that in I-97 the copper atom has an unshared $4p$ electron and it may be possible to have some additional π bonding involving overlap of this orbital with the π orbital of the nitrogen atom. This kind of π bonding in metal complexes was first suggested by Pauling (67) and has been used to explain the stability of dipyridyl complexes (68) and the relative stability of some silver complexes with 3- and 4-substituted pyridines (69). In the silver complexes the formation of a double bond must involve electrons in a $4d$ orbital of the silver atom. Thus, although nicotinonitrile and isonicotinonitrile are both weak bases, the latter gives a much more stable silver complex than the former, presumably because of some extra π bonding represented by structure I-98, which is not possible when the cyano group is at the 3 position.



(I-96)



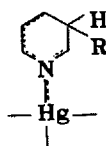
(I-97)



(I-98)

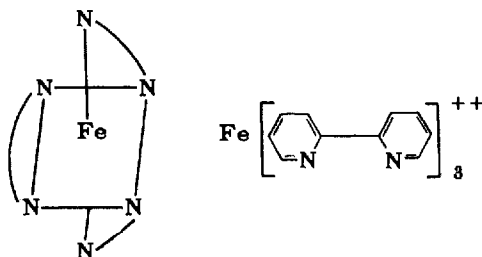
The section on electrophilic reactions (p. 24) discusses the catalytic effect of the mercury ion in the sulfonation of pyridine and also the rather mild conditions which are required for mercuration; both experiments suggest that a mercury complex is involved. Such a complex could facilitate substitution if a pair of electrons from a $5d$ orbital are available for stabilization of the transition state as in-

indicated by I-99. The effect of the mercury ion should be qualitatively similar to that of the hydroxyl group of pyridine 1-oxide salt. This assumes that the mercury complex has a tetrahedral configuration. However, even if the mercury complex has a square configuration like copper, with four $5d6s6p^2$ bonds, an electron pair would be available in the third $6p$ orbital for interaction with the pyridine ring.



(I-99)

Octahedral complexes are formed from reaction of cobaltic salts with pyridine. In such compounds as $\text{CoCl}_4 \cdot 2\text{C}_5\text{H}_5\text{N}$, cobalt forms bonds using 6 equivalent $3d^24s4p^3$ orbitals. One of the better known complexes of this type is that between ferrous iron and 2,2'-dipyridyl (I-100). A remarkable feature of this complex is its resistance to oxidation to the ferric state. This can be attributed, at least in part, to the fact that in the complex the $3d$, $4s$, and $4p$ orbitals of iron are just filled and oxidation would remove one electron to give a less stable complex.



(I-100)

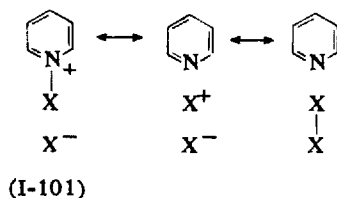
It is also possible to have octahedral complexes in which the bonds are largely ionic rather than covalent as in the dipyridyl complex. A salt of this kind, with the pyridinium ion as the cation, is

exemplified by $[\text{SbSl}_3\text{OEt}]^- [\text{HC}_5\text{H}_5\text{N}]^+$ (73); the bonds ($5s5p5d^2$) to antimony are probably rather ionic.

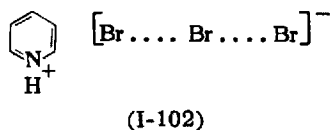
A complex between pyridine and chromium trioxide ($\text{CrO}_3 \cdot 2\text{C}_5\text{H}_5\text{N}$) has proved to be of considerable value as a selective oxidizing agent (74). It has been suggested that this crystalline complex has a dimeric or polymeric structure in which two of the oxygens are bonded to two chromium atoms. In this way the chromium atom forms bonds with six atoms rather than five indicated by the formula for the monomeric unit (75).

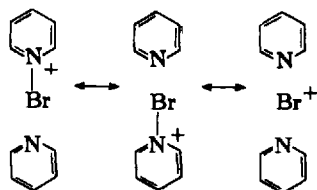
d. Other Pyridine Complexes

Pyridine and its derivatives react with a variety of substances having no metallic atom to yield complexes or addition compounds. The halogens and mixed halogens are examples of molecules which react to yield crystalline substances (154). These have the composition of 1-halopyridinium salts (I-101), but the very low conductivity observed for solutions of the iodochloride (93) suggests that I-101 is only one of the contributing structures and that this complex is something like the triiodide ion, with partially covalent bonds.



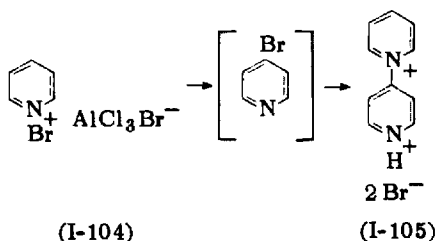
Pyridine perbromide is a rather stable complex which has been used for small scale brominations (76). This is probably a pyridinium salt (I-102). Some complexes involving two pyridine molecules, for example, $(\text{C}_5\text{H}_5\text{N})_2 \text{BrClO}_4$ (77), have also been prepared. This must be a salt with a perchlorate anion and a cation, $(\text{C}_5\text{H}_5\text{N})_2 \text{Br}^+$, in which the nitrogen atoms of both pyridine molecules may be bonded to the bromine (I-103).





(I-103)

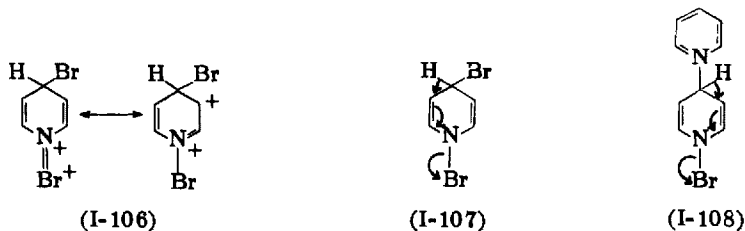
The formation of (I-105) from pyridine with bromine in the presence of aluminum chloride (94) may involve a pyridine complex (I-104). 4-Bromopyridine, if an intermediate, might result from (I-104) by either electrophilic or nucleophilic attack. Inspection



(I-104)

(I-105)

tion of the transition states for these two processes suggests that electrophilic attack via I-106 would be more difficult than nucleophilic attack to yield I-107. This latter substance could readily lose hydrogen bromide to yield 4-bromopyridine. It is also possible that 4-bromopyridine may not be an intermediate and that direct reaction of pyridine with I-104 can take place to yield I-108.

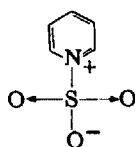


(I-106)

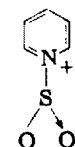
(I-107)

(I-108)

Both sulfur dioxide (95) and sulfur trioxide (96) form pyridine complexes; (I-109) has been used as a mild sulfonating agent for reactive molecules. The reaction of pyridine with thionyl chloride (I-111) (97) may also involve the formation of a complex (I-110)

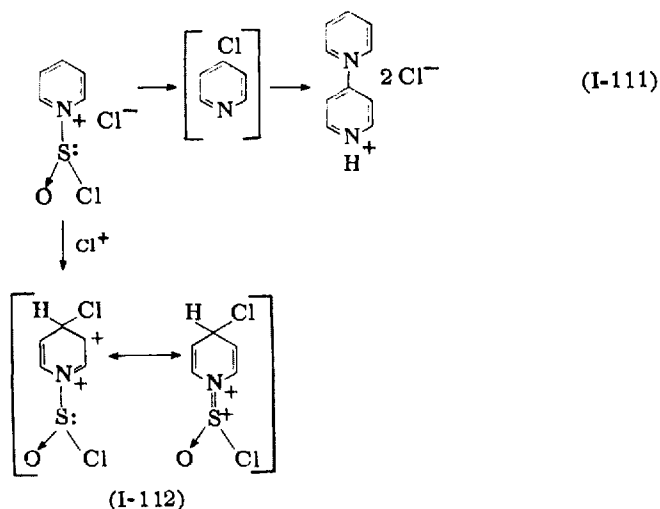


(I-109)



(I-110)

which modifies the reactivity of the pyridine nucleus. A complete mechanism for this transformation cannot be formulated without some knowledge of the fate of the rest of the thionyl chloride molecule.



The chlorination of picolinic acid at the 4 position by thionyl chloride is catalyzed by sulfur dioxide (98); this reaction is undoubtedly similar to that with pyridine itself, and may take place by way of a sulfur dioxide complex rather than one similar to I-110.

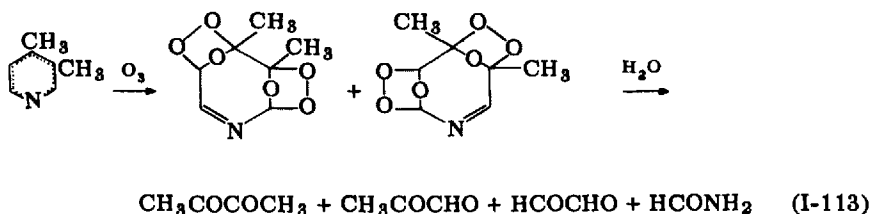
The chlorination by thionyl chloride of nicotinic acid at the 5 position and isonicotinic acid at the 3 position suggests that these reactions proceed by electrophilic attack. The carboxyl group would be expected to hinder such reactions but it is conceivable that a complex such as I-110 might stabilize the transition state sufficiently to allow electrophilic substitution to take place. Structure I-112 is somewhat analogous to the sulfur trioxide complex (I-109) with

adjacent positively charged sulfur and nitrogen atoms. In the case of the nicotinic and isonicotinic acids the observed orientation could result from the combined effects of the carboxyl group and the SOCl group linked to the nitrogen atom. If this interpretation is correct the effect of the SOCl group may be similar to that of the oxygen of pyridine 1-oxides or their proton salts (p. 19); it is not surprising that a sulfur atom should cause an effect similar to that of an oxygen atom.

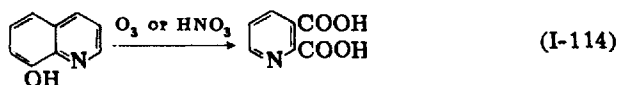
The complexes of pyridines with phenols are probably similar to picrates, with the electron-deficient pyridine ring acting in the same manner as picric acid.

7. Oxidation

Oxidizing agents can be considered as electron acceptors; therefore, it is not surprising that the pyridine ring of low electron density is comparatively resistant to oxidation. Potassium permanganate in sulfuric acid solution is one of the few reagents which oxidize pyridine to carbon dioxide; in this process the nitrogen atom gives mainly ammonia (25). Ozone also attacks pyridines, but more slowly than benzene, to yield diozonides (26) which hydrolyze as would be expected (I-113).

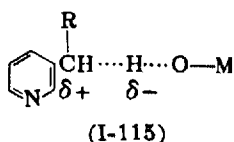


Alkyl groups or other ring systems joined to the pyridine nucleus are oxidized by a variety of reagents (I-114) to yield pyridine

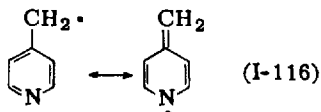


carboxylic acids (27). When an alkylpyridine is oxidized it seems likely that most of the oxidizing agents function as acceptors for hydride ions. The transfer of a hydride ion to the oxidizing agent

would generate a positive charge on the alkyl group (I-115). Since the 2 and 4 carbons of pyridine already bear a positive charge, alkyl groups at these positions should be more resistant to attack proceeding by this mechanism. The experimental facts indicate that ease of oxidation increases for alkyl groups in the order 4, 2, 3. These oxidations are discussed in detail in Chapter X.

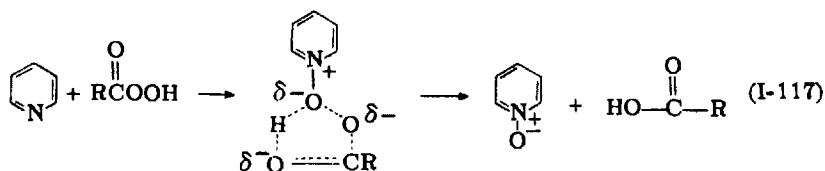


The oxidation under Willgerodt conditions (157) of 2- and 4-picolines but not 3-picoline suggest a different mechanism, perhaps involving a free radical intermediate (I-116) which would be most stable at the 2 and 4 positions.



An exception to the generalization that substituents are attacked more rapidly than the pyridine ring was first reported by Chichibabin (28): 2-phenylpyridine was oxidized by alkaline permanganate to yield mainly benzoic acid. In acid solution the pyridine nucleus was made more positive by salt formation and the benzene nucleus was preferentially attacked.

Since the nitrogen atom is the center of electron density it is not surprising that it should be attacked by reagents such as hydrogen peroxides and peracids (I-117).

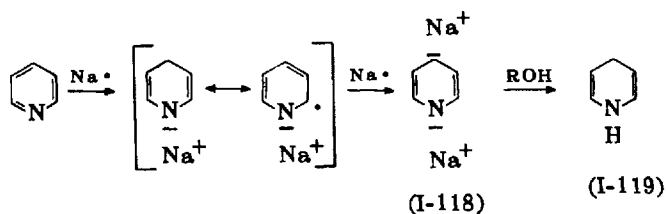


It may be that when the pyridine ring is attacked by oxidizing agents, a 1-oxide is first formed which increases the electron density in the ring and thus renders it more susceptible to further attack. Steric hindrance can also be important, since 2,6,8-trimethylquinoline does not form an oxide under the usual conditions (29), although 2,6-dimethylpyridine does react.

8. Reduction

a. Chemical Methods

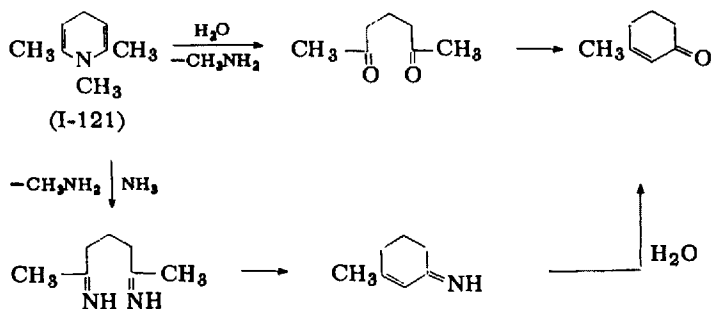
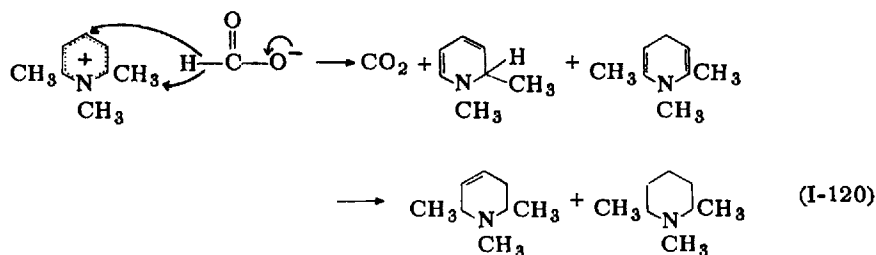
An aromatic ring which can act as an electron acceptor is easily reduced; for example, terephthalic acid can be reduced by sodium amalgam (30) while benzene cannot. Similarly pyridine is readily reduced by sodium and alcohol; tin and hydrochloric acid have also been used for certain pyridines. These reductions are generally believed to proceed by addition of the metal atom to the ring. The addition of the second metal atom probably takes place mainly at the 4 position, because the resulting intermediate, I-118, has the two negative centers separated by the greatest possible distance. Further reduction may proceed after isomerization of a double bond in the initially formed dihydropyridine (I-119). These reductions usually proceed all the way to the piperidine derivative, most likely because the intermediate di- and tetrahydro compounds are more readily attacked by the metal-acid combination than is the fully aromatic pyridine ring. Small amounts of a tetrahydropyridine have been isolated from some reductions (31) and in a few this is the major product (174).



If a carboxyl group is present in the ring, partial reduction is more successful; using aluminum amalgam in moist ether, Mumm and Beth (32) obtained some dihydropyridines.

An interesting partial reduction which occurs when quaternary pyridinium formates are heated has been investigated by Lukeš and co-workers (33) (I-120).

This reduction is apparently related to the Leuckart reaction, because in both transformations the reduction is accomplished by decomposition of the formate ion to carbon dioxide with release of a hydride ion which attacks the carbon atom of an unsaturated system having a carbon-nitrogen double bond. The exact nature of the intermediate is unknown. The cyclohexane derivatives which are formed along with the reduction products are believed to result from hydrolysis of an intermediate dihydropyridine (I-121). Cyclohexenones have also been obtained by Birch (34) in 12–30% yield when picoline, 2,6- and 2,4-lutidine and 2,4,6-collidine are treated with sodium and alcohol in liquid ammonia. In these experiments, cleavage of the intermediate I-121 must be brought about by ammonia.



Other partial reductions have been accomplished with sodium hydrosulfite (35) and sodium amalgam (36).

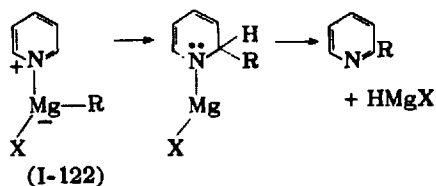
b. Catalytic Methods

Most of the catalysts which have been used for addition of hydrogen to multiple linkages have also been used for reduction of pyridines. Some difficulties in the reductions are occasioned by the fact that amines tend to be catalyst poisons, presumably because they are strongly adsorbed on the active surface. This difficulty may be overcome when platinum and palladium catalyst are used, by carrying out the reaction in an acidic aqueous or alcoholic solution. Under these conditions the amine is present largely as its salt and is less strongly adsorbed.

With nickel catalysts the solutions cannot be made acidic and a higher temperature is usually required, so that the rate of adsorption and desorption of the amines from the catalyst surface is fast enough to permit reduction to take place within a reasonable length of time. Thus, while benzene was reduced at 150° during one hour, pyridine required seven hours at 200° (37). It is interesting that 2,6- disubstituted pyridines are reduced more rapidly than pyridine itself or pyridines substituted in other positions. This effect undoubtedly indicates that the groups at the 2 and 6 positions decrease the ability of the nitrogen to bond with the catalyst; thus amines of this type are less effective as catalyst poisons.

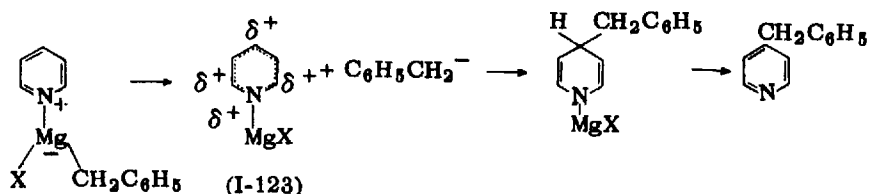
9. Reactions with Organometallic Compounds

Grignard reagents, the most common of the organometallic compounds, react with pyridine to give very low yields of 2-alkyl or 2-aryl pyridines (42,43). These reactions almost certainly proceed by preliminary complex formation of pyridine with the magnesium atom (I-122) followed by a shift of the alkyl group to the 2 position of the pyridine ring. This process is analogous to the reaction of Grignard reagents with carbonyl compounds.



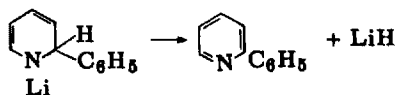
The main reason for the low yields is probably the difficulty in eliminating the elements of HMgX from I-122 to regenerate the completely aromatic system. Temperatures of about 150° are generally required to produce any of the alkylpyridine.

The reaction of benzylmagnesium chloride is somewhat unusual in that the major product is 4-benzylpyridine (44). This result would be expected if the primary complex ionized and the relatively stable (as compared to an alkyl carbanion) benzyl carbanion attacked I-123 at the sterically less hindered 4 position to a greater extent than at the 2 position.



Organolithium compounds are much more effective than the corresponding Grignard reagents for preparation of substituted pyridines. For example, *s*-butyllithium yields 2-*s*-butylpyridine in 58% yield at 100° , while *s*-butylmagnesium bromide at 150° produces only about 6% of the desired product (43).

Ziegler and Zeiser (158) first observed that equimolar amounts of pyridine and organolithium derivative reacted with evolution of heat and that further heating of the intermediate (I-124) converted it to lithium hydride and the 2-substituted pyridine. The initial reaction was not merely complex formation, because addition of water produced an unstable dihydropyridine, as would be expected of structure (I-124).

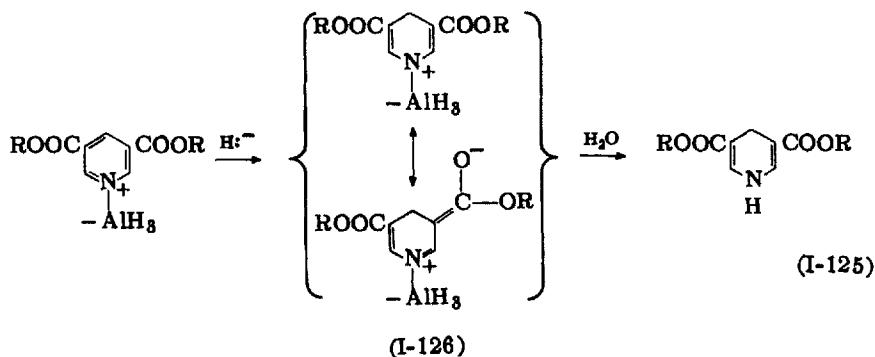


(I-124)

This reaction, which is further discussed in Chapter V, is probably a general one for alkali metal alkyls or aryls. Phenyl-

i-propylpotassium reacts almost instantaneously with pyridine to yield a colorless intermediate which could not be transformed to any recognizable products (158).

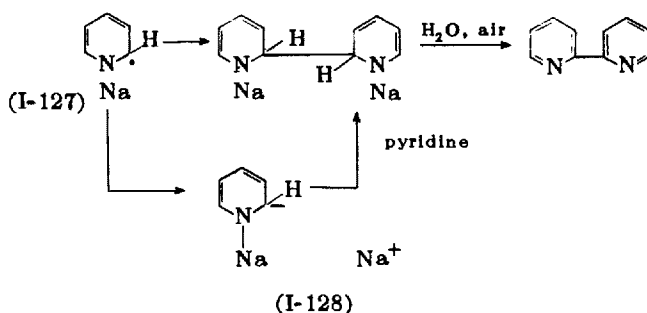
Lithium aluminum hydride can be classified with the organo-metallic compounds because of the similarity in the kinds of reactions it can produce. The nature of the substituents on a pyridine ring greatly influences the reaction which takes place. Pyridine itself can be reduced to piperidine in 10% yield by lithium aluminum hydride in refluxing dibutyl ether (159); under milder conditions an unstable dihydropyridine results (160). Pyridine diesters and dinitriles with the substituents in the 3 and 5 positions are reduced to dihydropyridines in preference to reduction of the substituent, while esters of monocarboxylic acids or the 3,4-dicarboxylic acid are reduced to carbinols without affecting the ring (161). The facile reduction of the 3,5-diester can be formulated as an addition to the pyridine ring system (I-125), with the ester groups reacting to stabilize the unsaturated system (I-126) remaining after attack by the hydride ion. Preliminary formation of a complex with the nitrogen atom is suggested because the 3,5-diester having methyl groups at the 2 and 6 positions does not react in this manner. The methyl groups, which cannot appreciably influence the 4 position, are believed to prevent the reaction by sterically inhibiting complex formation.



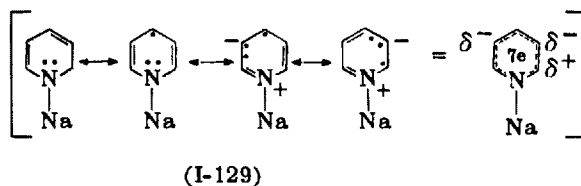
10. Reactions with Metals

The addition of metal atoms to pyridine was discussed briefly in connection with the reduction of pyridine. In the reduction process the metal-carbon bond of the organometallic intermediates is rapidly cleaved and the metal atom replaced by a hydrogen from the alcohol or other proton-donating solvent. In the absence of a proton donor a variety of other transformations may follow the preliminary reaction of a metal with a pyridine.

If sodium and dry pyridine are allowed to react at room temperature and the reaction mixture decomposed by addition of water, 2,2'-bipyridyl and 4,4'-bipyridyl result. These products must be formed either by coupling of two monosodium adducts (I-127) of pyridine or by addition of a disodium adduct (I-128) to pyridine. This latter process would be similar to the reaction of other organometallic compounds with pyridine (p. 50). However, the addition of most organometallic compounds to pyridine yields mainly the 2-substituted pyridine; in the present reaction 4,4'-bipyridyl is actually the major product.

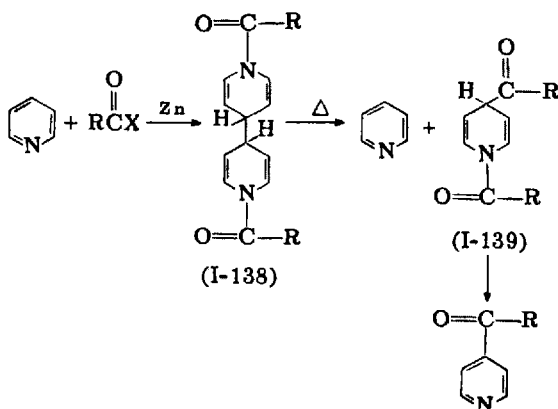


If the mono adduct has all seven unshared electrons in π orbitals (I-129), coupling could take place at either the 2 or 4 positions but would probably be more rapid at the unhindered 4 position. The fact that bipyridyls joined at the 3 position can be isolated at 100°

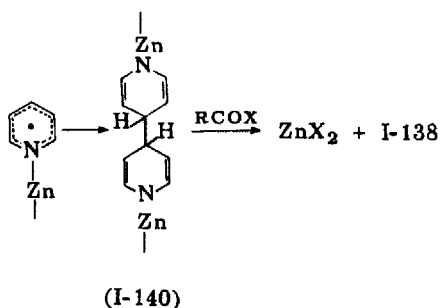


mainly the 2-pyridylcarbinol. The reaction is further discussed in Chapter XIII.

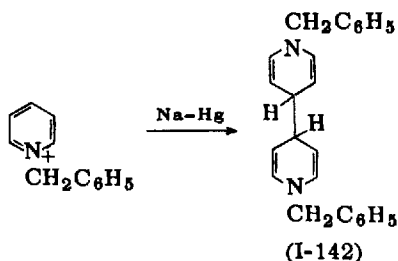
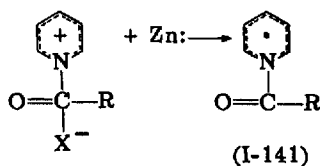
The reaction of pyridine with zinc and acid chlorides or anhydrides is sometimes useful for obtaining 4-substituted pyridines (133,135); the initial product, a tetrahydrobipyridyl (I-138), can be thermally converted to a 1,4-diacyl-1,4-dihydropyridine (I-139) and this to a 4-acylpyridine. It is possible that I-138 could be



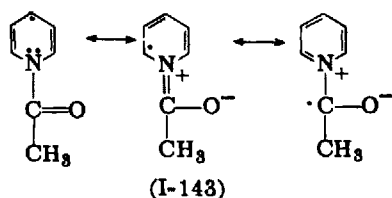
formed by an initial reaction of zinc and pyridine, as with the other metals, to yield I-140. Cleavage of the partly ionic zinc-nitrogen



bond by the acid anhydride (or chloride) then would yield I-138. An alternate possibility is that the zinc atom may not form a bond but merely donate an electron to a 1-acylpyridinium ion, producing radical (I-141); two such radicals then could couple at the 4 position



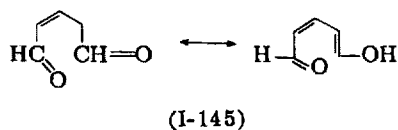
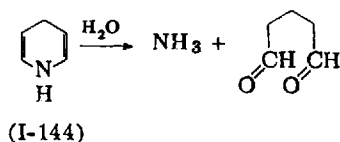
to yield I-138. The formation of a tetrahydrobipyridyl (I-142) by sodium-amalgam reduction of a 1-alkylpyridinium salt and the formation of dipiperidines in the electrolytic reduction of pyridine are reactions which most likely proceed by transfer of an electron to the pyridine ring. Actually all of the metal reactions may be considered to be of this type if it is assumed that the metal forms purely ionic (not covalent) bonds. Some evidence has been obtained (132) that (I-138, R = CH₃) dissociates merely on heating to yield a yellow diamagnetic substance which is believed to be the free radical I-141. The stability of this radical is best explained if it is assumed (as for I-129) that the unpaired electron is not localized in an *sp*³ orbital at the 2 or 4 position but is distributed over the unsaturated system which in this case should include the carbonyl group attached to nitrogen. Thus there are 9 electrons distributed over 8 atoms, two of which are the electronegative oxygen and nitrogen atoms. Resonance structures such as I-143 indicate the major sites for the unpaired electron.



11. Ring Cleavage Reactions

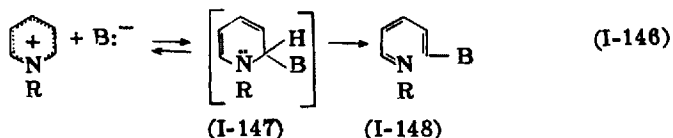
If pyridines are subjected to strongly reducing conditions ring cleavage takes place. High pressure catalytic hydrogenation usually causes some hydrogenolysis of carbon-oxygen and carbon-nitrogen bonds; the importance of this cleavage depends considerably on the temperature. For pyridine itself, hydrogenolysis has been reported to occur above 140° (130); at 250° in the presence of Raney nickel a complex mixture result from hydrogenolysis of the piperidine which is first formed (136). An excess of hydriodic acid at 300° also cleaves the C—N bonds to yield pentane (131) and ammonium iodide.

A peculiar cleavage occurs when pyridine is reduced with sodium and 95% rather than absolute ethanol; some glutaconic dialdehyde (I-145) can be isolated as the dioxime but polymers are also formed. Hydrolysis of an intermediate dihydropyridine (I-144) would lead to glutaric dialdehyde while glutaconic dialdehyde must be considered to be a hydrolysis product of pyridine itself. Since pyridine and water do not react under these conditions, a complex series of reactions must take place leading to I-145.

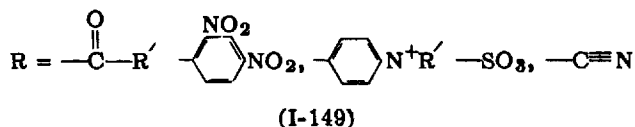


When pyridine is exposed to ultraviolet light in the presence of air and moisture it is converted to the ammonium salt of I-145 (139). This cannot be a simple hydrolysis facilitated by absorption of light energy, since oxygen is apparently necessary (140). It is a general reaction for substituted pyridines and will take place even with 2-alkylated pyridines which cannot be cleaved by the usual chemical methods.

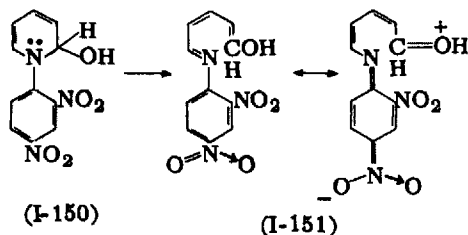
By far the most important cleavage reaction is that which takes place when a base reacts with a pyridinium compound. It is possi-



ble to carry out the reaction (I-146) with rather wide variations in the nature of R and B. Some generalizations can be made concerning the influence of the structure of R and of ring substituents on the reaction. Any group R which acts as an electron acceptor to reduce even further the electron density of the pyridine ring facilitates attack by the base. The groups which fall into this classification are listed (I-149). If I-147 is an intermediate formed reversi-

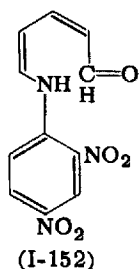


bly from the quaternary salt, the major function of R may be to stabilize the cleavage product by conjugation with the unsaturated system of I-148. For example (I-137) when hydroxide ion is the base which attacks the pyridine ring (I-150), an extended conjugated system results in which the π electrons from the olefinic double bonds are delocalized over the entire system. As would be expected, such substances are highly colored; I-151 is deep red.

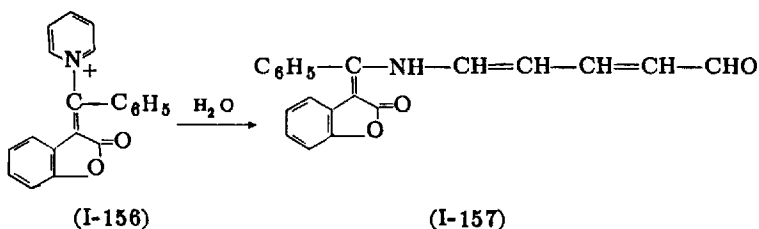
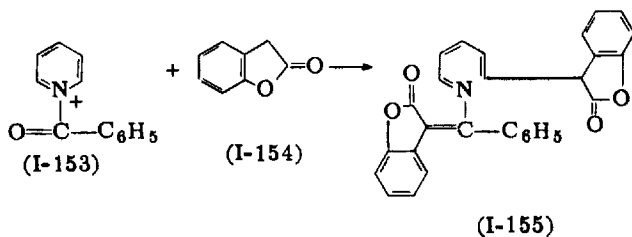


A tautomeric structure (I-152) with a terminal aldehyde rather than enol group, is also possible for this kind of cleavage product; it has not been established which of the two structures is correct or whether both are present.

With bases such as alcohols and amines the 1-acylpyridinium ring is not cleaved, but rather the carbonyl group is attacked to yield amides and esters (see p. 32). However an interesting cleavage



occurs when benzoyl chloride, pyridine, and a compound with a very reactive methylene group are mixed (138). Both ring cleavage and an aldol condensation between 2-coumaranone (I-154) and the benzoyl carbonyl group must take place, but it is difficult to decide in which order these processes occur. If ring cleavage is the first step, the carbanion from I-154 must be the attacking base. However, if the aldol condensation is first, (I-156) would be formed with elimination of a molecule of water. The water molecule might then act as the base to yield (I-157), which in a second aldol condensation would form the product (I-155). The coumaranone anion may also react directly with I-156 to yield I-155; ring cleavage by a carbanion must be possible in the reaction of 1-(2,4-dinitrophenyl)pyridinium chloride with coumaranone, because here no water is present or can be formed (138).



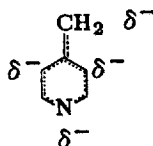
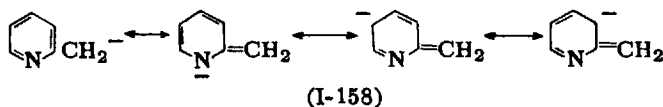
Electron-attracting groups on the pyridine ring might be expected to facilitate the cleavage process in the same way as the group R on the nitrogen. However, it is very difficult to prepare pyridinium salts from pyridines substituted in this way (141). The opposite effect by electron-releasing groups such as in 3-methyl, 3-methoxyl, and 3-acetaminopyridine is manifested in lower yields of cleavage product than from pyridine itself. Substituents such as 3-acetylamino, 3-hydroxyl, and 3-dimethylamino groups entirely prevent cleavage by aniline in ethanol.

Ring-opening reactions are discussed further in Chapter III.

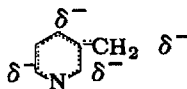
D. THE EFFECT OF THE PYRIDINE RING ON SUBSTITUENT GROUPS

1. Alkylpyridines

The hydrogen atoms of the methyl group in toluene are only weakly acidic; very strong bases are required to form the carbanion. The methyl hydrogens of 2- and 4-picoline are much more acidic. This effect can be explained by considering the nature of the anion which results when a proton is removed. In the case of these two molecules the anion is comparatively stable because a considerable part of the negative charge can be localized on the more electronegative nitrogen atom, as is illustrated by structures I-158 and I-159.



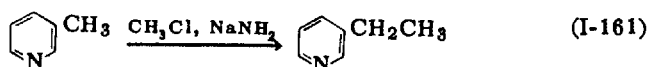
(I-159)



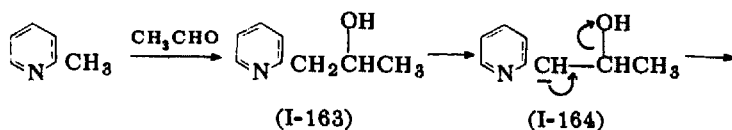
(I-160)

It is likely that even 3-picoline forms an anion (I-160) considerably more readily than toluene. For example, the alkylation of 3-

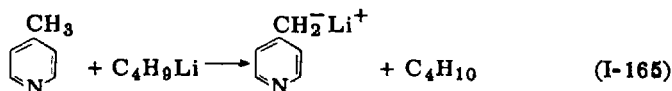
picoline may be accomplished by a reaction, I-161, in which sodamide is the base (38). Although no resonance structure can be written with negative charge on nitrogen atom, the molecular orbital concept would suggest that some of the negative charge of carbanion I-160 should be on the electronegative nitrogen atom.



Some of the very useful reactions for lengthening side-chain substituents at the 2 and 4 positions make use of the ready formation of these carbanions. For example, when α -picoline is treated with a base in the presence of a reactive carbonyl compound, an aldol condensation takes place (I-162). Depending on the nature of the carbonyl compound and the reaction conditions, the initial product (I-163) may dehydrate during the reaction. This process, too, may proceed by way of a carbanion intermediate (I-164). An acid catalyst such as zinc chloride is also effective for this kind of aldol condensation and subsequent dehydration.

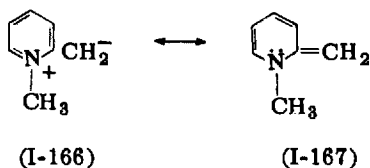


With a base such as phenyl- or butyllithium, the conversion to the lithium salt of the pyridine proceeds to completion (I-165). The picolylithium reacts with carbon dioxide, alkyl halides or sulfates, and carbonyl compounds.



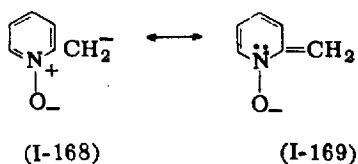
When the nitrogen atom is quaternized, thus increasing its electronegativity, the reactivity of the methyl groups is increased. When a proton is removed from the 2- or 4-methyl group of these

quaternary salts, anhydro bases (I-167) result. These anhydro bases react with carbonyl compounds in a manner similar to carbanions such as I-158 because there is appreciable negative charge on the carbon atom resulting from the contribution of structure I-166.



It has been reported (39) that the methyl group of 3-picoline reacts with carbonyl compounds when the nitrogen atom has been quaternized. However, it now seems likely that these results were due to the presence of 2- and 4-picolines as impurities in the 3-picoline (40).

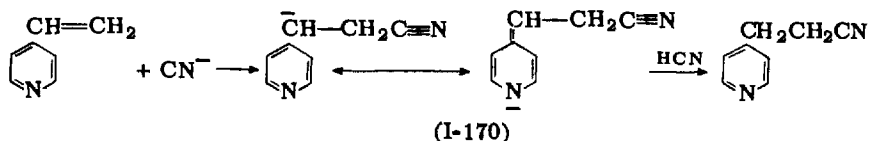
The fact that 2- and 4-picoline do not react with ethyl oxalate but the corresponding 1-oxides do, is evidence for activation of the methyl groups as in the formation of quaternary salts. This must mean that the oxygen atom, although it has unshared electrons in an orbital which may overlap with the *p*-orbital system of pyridine, can in fact aid the nitrogen atom in accepting a part of the negative charge of the carbanion (I-168). In resonance terminology, structure I-169 must make an important contribution to the carbanion.



In an interesting reaction of these picoline 1-oxides with acetic anhydride, the oxygen-nitrogen bond is broken and the methyl group converted to an acetoxymethyl group. A free radical mechanism was proposed to explain this result, but later experiments indicate that a nonradical process produces the major product (79).

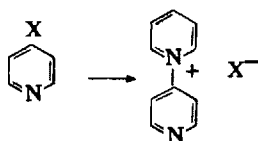
A side-chain double bond conjugated with the pyridine ring at the 2 or 4 position has quite different chemical properties from the double bond of styrene, and will add nucleophilic reagents such as

cyanide, malonate, or bisulfite ion (41). These reactions proceed readily because a stable carbanion (I-170) is the intermediate.

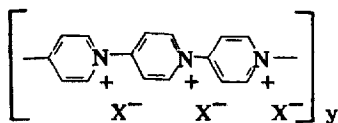


2. Halopyridines and Nitropyridines

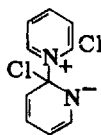
The effect of the pyridine ring in activating a halogen atom at the 2 and 4 positions is in striking contrast to the influence of a benzene ring on this substituent. While chlorobenzene is relatively unreactive toward basic reagents under normal laboratory conditions, 4-halopyridines are generally so unstable that they cannot be preserved for any length of time. If generated in the presence of pyridine they are converted to quaternary salts (I-171) which are readily isolated. This suggests that their instability results from polymerization to yield polypyridinium salts (I-172). The 2-halopyridine is more stable than the 4-isomer, probably because the halogen sterically inhibits interaction between the nitrogen atom of one molecule and the halogen of another. The intermediate (I-173) for dimerization of 2-chloropyridine seems less likely than the one (I-174) for the 4-isomer.



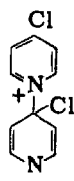
(I-171)



(I-172)



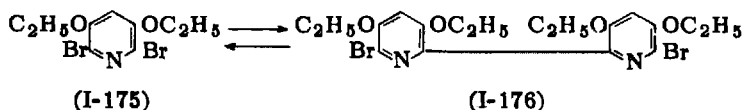
(I-173)



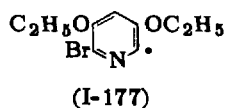
(I-174)

The displacement of halogens and similar substituents by bases was previously discussed in general terms (see p. 28). There are usually only slight differences in the rate of displacement of halogens from the 2 and 4 positions; 2,4-dichloropyridine reacts with ammonia to yield both 2-chloro-4-aminopyridine and 4-chloro-2-aminopyridine (142). The 3-halopyridines are much less reactive, although their displacement by a base is a practical route to the 3-substituted pyridines. 3-Methoxypyridine results from 3-bromopyridine by heating with sodium methoxide at 160° (143). Nitro groups increase the reactivity of ortho or para halogens on a pyridine ring as in the benzene series. For example, 3-nitro-4-chloropyridine is very readily hydrolyzed by water alone to 3-nitro-4-pyridinol, but does not polymerize, because of the lowered basicity of the pyridine nitrogen.

A remarkable reaction of 2,6-dibromo-3,5-diethoxypyridine (I-175) takes place in the presence of bromine and ferric bromide in



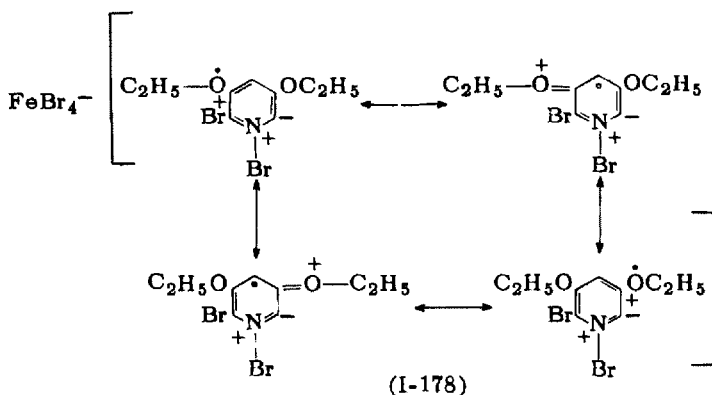
sunlight. The dependence of the reaction on sunlight, its reversibility, and the low values obtained in molecular weight determinations of (I-176) all suggest that a radical (I-177) may be formed either



by dissociation of I-176 or by homolytic cleavage of a carbon-bromine bond of I-175. A pyridyl radical of this kind would be stabilized by the two ethoxyl groups and perhaps may be present only as its 1-bromo salt (I-178).

Other reactions of halopyridines are normal; the formation of Grignard reagents from 2- and 3-bromopyridines, the Ullmann reaction with 2-bromopyridine, and the catalytic or chemical replacement by hydrogen are fairly similar to the corresponding reactions of benzenoid derivatives. Cf. Chapter VI.

The nitro group can be displaced as a nitrite ion and therefore



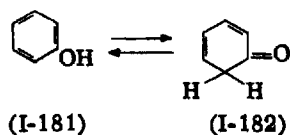
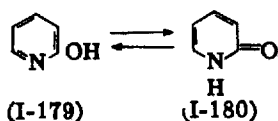
reacts much like halogen when at the 2 and 4 position of a pyridine. The recent availability of 4-nitropyridines by nitration of pyridine 1-oxides has made the displacement of this nitro group by bases an important method for obtaining 4-substituted pyridines.

The 3-nitropyridines which result from most nitration reactions are, like the 3-halopyridines, much less reactive than the 2- and 4-isomers. They behave as typical aromatic nitro compounds and may be reduced to amines, hydroxylamines, azo compounds, etc., by standard procedures. Cf. Chapter VIII.

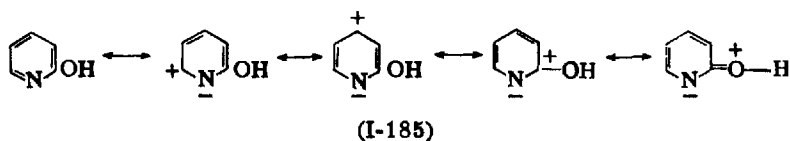
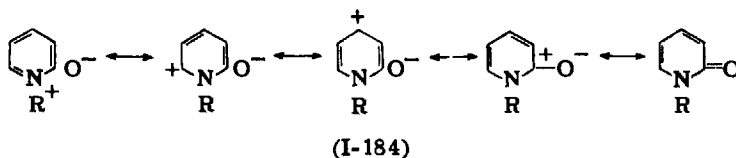
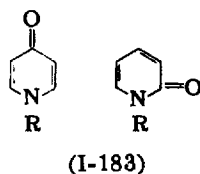
3. Pyridinols and Pyridones

a. Tautomerism

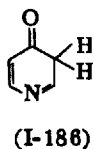
One of the unique properties of 2- and 4-pyridinols which distinguish them from phenols of the benzenoid series is the ease with which they are converted to the keto form. When a phenol is converted to the keto form (I-182), there is a considerable loss of resonance (delocalization) energy, since one carbon atom and 2 π electrons are removed from the unsaturated system of I-181, and furthermore the new unsaturated system (I-182) is noncyclic. However, when a proton moves to the nitrogen atom of 2- or 4-hydroxypyridine, the unshared σ electrons on the nitrogen are available for bond formation and the unsaturated system remains essentially unchanged, with eight π electrons distributed over seven atoms in both forms (I-179) and (I-180).



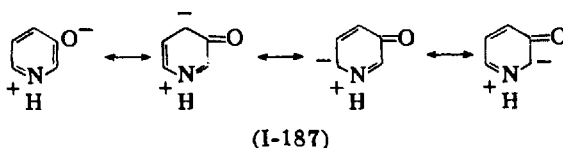
It is also clear from this description that 1-alkylpyridones (I-183) are just as aromatic as hydroxypyridines and accordingly it is not surprising that they behave normally in nitrations and other electrophilic substitutions. This is also apparent by comparing the resonance structures for a pyridone (I-184) and a pyridinol (I-185).



4-Pyridone is produced from 4-pyridinol by a shift of a proton to the nitrogen. Ketonization by a shift of the proton to carbon (I-186) would require considerable energy as in the benzene series.

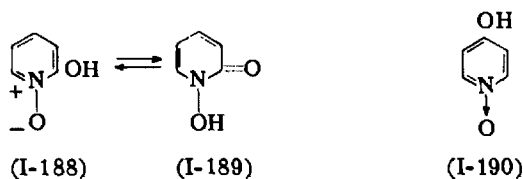


It is possible to transfer the hydrogen of 3-hydroxypyridine to the nitrogen atom; however, this cannot lead to a stable uncharged structure (I-187) as for 2- and 4-pyridinol.



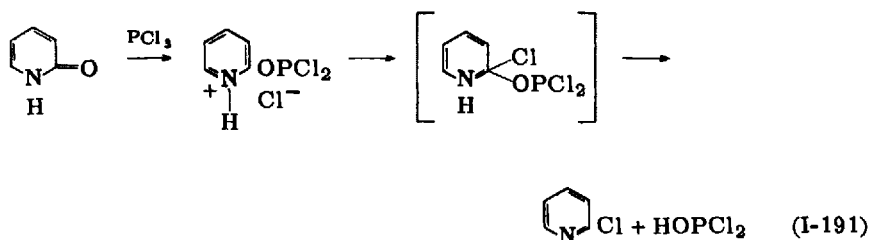
Since there is little energy difference between the two pyridones and their corresponding pyridinol, it might be possible under ordinary conditions to have one or the other of the two tautomers or a mixture of both. Actually there is a single crystalline substance rather than a mixture, and it has been shown from x-ray diffraction data to have the pyridone rather than the hydroxypyridine structure (53). Earlier work on the ultraviolet spectrum had indicated that the pyridone structure also predominates in neutral solution (54).

A similar problem exists with the pyridine 1-oxides; the hydroxyl derivatives could have either of two structures, I-188 or I-189. In this case also, spectroscopic data prove that the pyridone structure is present in aqueous solution (55). Calculations using the Hammett equation have been carried out to evaluate the constant for the equilibrium between 4-pyridinol 1-oxide and the tautomeric pyridone; structure I-190 is believed to be preferred (56). Molecular orbital calculations by a crude perturbation method suggest that (I-190) and (I-188) are the favored forms (57); however, this conclusion is in opposition to the spectroscopic evidence in favor of I-189.

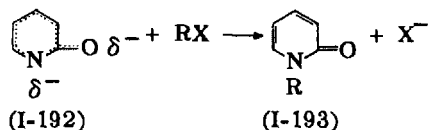


b. Reactions

In the benzene series the replacement of a phenolic hydroxyl group by a halogen atom is practical only for such exceptional cases as picric acid. However, 2- and 4-pyridinol react readily with phosphorus halides to yield the corresponding halopyridines. These reactions (I-191) are further examples of the effect of the pyridine ring in facilitating nucleophilic displacement at the 2 and 4 positions (see p. 63). The leaving group is undoubtedly an ion related to phosphorous acid (when phosphorus trichloride is used).



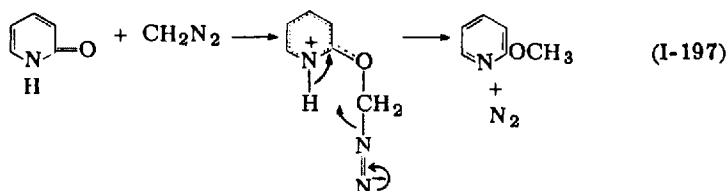
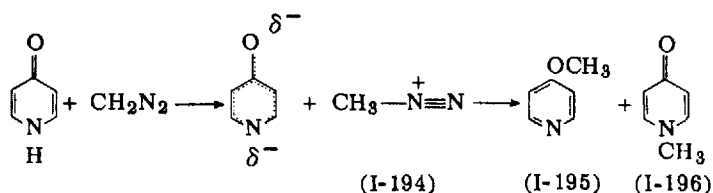
As would be expected from the discussion of tautomerism, either *O*-alkylation or *N*-alkylation of 2- and 4-pyridinols may be observed depending on conditions. Under strongly alkaline conditions, where the pyridinol is completely converted to the anion (I-192), the 1-alkylpyridone is nearly always the only product with alkyl halides and sulfates. Since both the oxygen and nitrogen atoms are negative centers in the anion, the formation of I-193 may be due to greater nucleophilicity (tendency to form a bond with carbon) of the nitrogen atom.



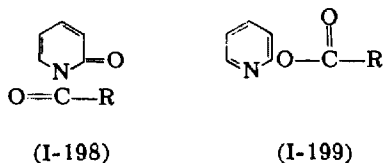
Both alkylation products are formed when the silver salt of 2-pyridinol reacts with methyl iodide (I-162). In this case the silver ion generates a carbonium ion which is unselective and reacts at both the nitrogen and oxygen atoms of the anion.

Alkylations with diazomethane are generally believed to proceed

by preliminary transfer of a proton to yield a methyldiazonium ion (I-194). The alkylation product can result either by unimolecular decomposition of I-194 to yield a methylcarbonium ion which then reacts with the anion, or in a bimolecular displacement with elimination of nitrogen taking place only as the anion begins to form a bond with the methyl group. The formation of both products (181) (I-195, I-196) from 4-pyridone suggests that, in this alkylation, the unimolecular mechanism is operating. The reaction of diazomethane with 2-pyridone (181) is unlike any of the other alkylations in that only the *O*-alkylated product, 2-methoxypyridine, is formed. A modified reaction path (I-197) with proton transfer as the second step may explain this observation.

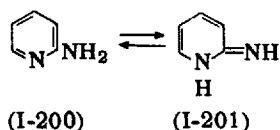


Acylation also might be expected to take place at either the nitrogen or oxygen atom; however, only the *O*-acyl derivatives have been reported (182). The product to be expected from *N*-acylation, I-198, is like an imide and may be unstable by comparison with the ester (I-199). These reactions are further discussed in Chapter XII.



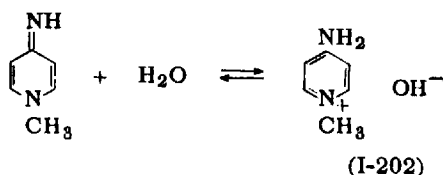
4. Aminopyridines

3-Aminopyridines are quite normal aromatic amines, but the same structural problem exists for the 2- and 4-isomers as in the hydroxypyridine series. The single substance which is obtained experimentally may have either an aminopyridine (I-200) or a pyridonimine (I-201) structure. The shift of a hydrogen from the amino group of compound I-200 to the ring nitrogen may be expected to occur rather readily for the same reasons advanced to explain the tautomerism of 2- and 4-pyridinol.

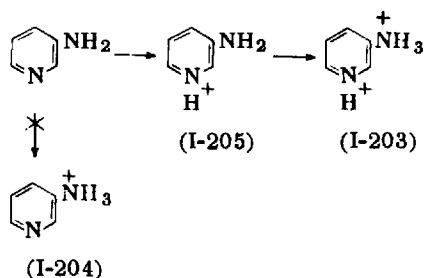


The most recent physical measurements, which include ultra-violet (144,147) and infrared spectrophotometrical (145) studies and measurement of dissociation constants (146), are in agreement that the amino form of both 2- and 4-aminopyridines is preferred and that there is no detectable amount of the pyridonimine form present in a variety of solvents. This is just the opposite of the situation with the hydroxypyridines. Since the same unsaturated system of 8 π electrons is present in both hydroxy- and aminopyridines the differences between the two are probably due to differences in electronegativity of oxygen and nitrogen atoms. In the conversion of hydroxypyridines to pyridones the electronegativity of the oxygen atom is increased and that of the nitrogen atom decreased, while the analogous change for aminopyridines would increase the electronegativity of the substituent nitrogen and decrease that of the ring nitrogen. The magnitude of these electronegativity differences must be such that the delocalization energy is slightly greater for the pyridone form where the side chain atom is oxygen and for the aminopyridine structure where the side chain atom is nitrogen.

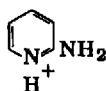
In connection with this problem it is interesting that 1,2-dihydro-2-imino-1-methylpyridine and 1,4-dihydro-4-imino-1-methylpyridine both react in water to form an appreciable amount of a pyridine (I-202) with an amino substituent (144).



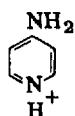
Since there are two nitrogen atoms in the aminopyridines it might be anticipated that they could be dibasic; this is observed with 3-aminopyridines. The formation of I-203 must be a stepwise process and it is of interest to decide whether I-204 or I-205 is the intermediate. In forming I-204 the proton reacts with the π electrons of the amino nitrogen and converts it to the tetrahedral state. This modifies the unsaturated system by removing the nitrogen and its two π electrons. To form I-205 only the σ electrons of the ring nitrogen are involved and the unsaturated system of eight π electrons distributed over seven atoms is unchanged. It is clear, therefore, that I-205 is much lower in energy than I-204 and is the preferred intermediate in the formation of I-203.



The 2- and 4-aminopyridines are considered to be monobasic, although ultraviolet spectral studies (148) indicate that a second proton may be accepted in concentrated acid solutions. The same reasoning used for 3-aminopyridines is applicable here and the salts must have structures I-206 and I-207. The addition of a proton to the amino nitrogen would have changed the ultraviolet spectrum to essentially that of pyridine just as the spectrum of aniline reverts to that of benzene in acid solution. Actually, the spectra of 2-, 3-, and 4-aminopyridine in dilute acid solution are quite different from pyridine (149), in agreement with structures I-205, I-206, and I-207.

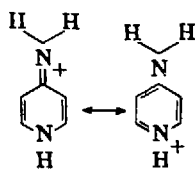


(I-206)

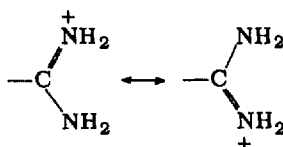


(I-207)

The great difficulty in adding a second proton to I-206 and I-207 is due to the fact that a considerable part of their positive charge is localized on the amino nitrogen (I-208), thus making it relatively difficult for a second proton to be added. This situation has been compared to the amidines which are also monobasic and in which the positive charge is distributed between two nitrogen atoms (I-209).

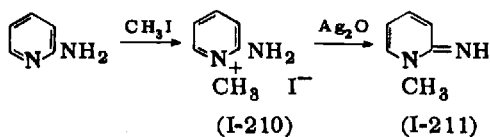


(I-208)



(I-209)

In reactions of aminopyridines with reagents having positive centers, the same principles which govern the reaction with a proton should apply. Therefore the reactions with alkyl halides should take place at the ring nitrogen; methyl iodide followed by silver oxide does yield 1,2-dihydro-2-imino-1-methylpyridine (I-211), indicating

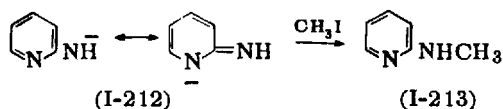


(I-210)

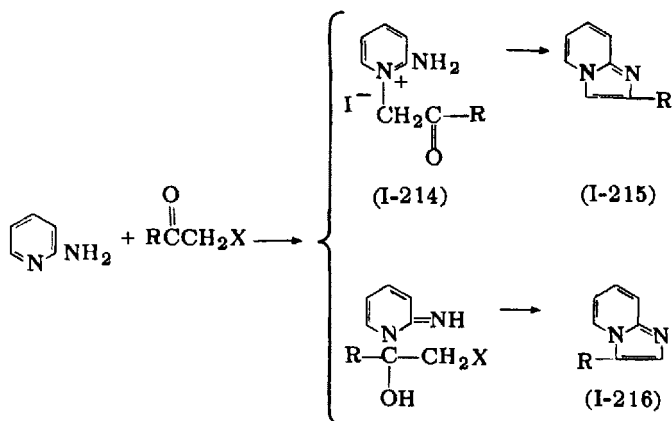
(I-211)

that I-210 is an intermediate. The isomeric 2-methylaminopyridine (I-213) can be prepared by methylating the anion (I-212), prepared by treating 2-aminopyridine with sodamide. The side chain nitrogen of I-212, unlike that in 2-aminopyridine itself, can react with methyl iodide and yet still have available a pair of π electrons for interaction with the pyridine ring.

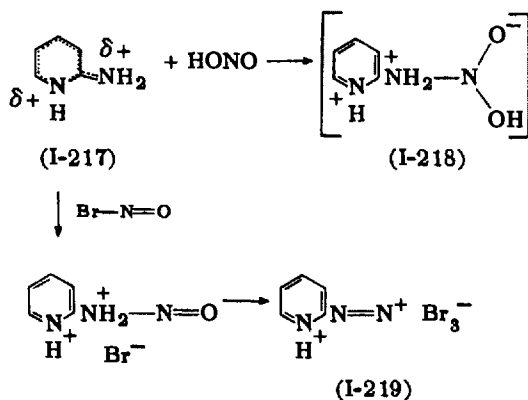
2-Haloketones, which have two positive centers, might react with 2-aminopyridine in either of two ways (152). The primary reaction



of the ring nitrogen with the halogenated carbon to yield intermediate I-214, which then is converted to I-215, seems more likely than the alternate path to I-216; pyridine itself reacts with α -haloketones to yield salts similar to I-214. Structure I-215 has generally been accepted, however, there is no independent evidence for it.



The diazotization of 3-aminopyridine proceeds normally by standard methods, while 2- and 4-aminopyridine can be converted to diazonium salts only with considerable difficulty. Since diazotization requires an acid solution, the salt of the aminopyridine is formed first and therefore reaction with nitrous acid, which requires that the amino group contribute an electron pair, is difficult. The formation of intermediate I-218 is similar to the addition of a second proton to the mono salt (I-217). Under ordinary diazotization conditions nucleophilic displacement of the amino group by water is an important reaction. However, a diazotization carried out in concentrated hydrobromic acid in the presence of bromine furnishes a good yield of 2-bromopyridine (150,151). Nitrosyl bromide may be the reagent involved in forming the diazonium salt, which is probably present as the tribromide (I-219).



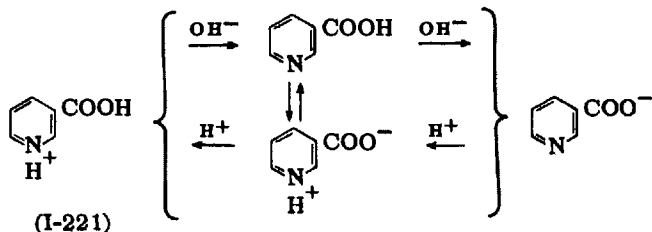
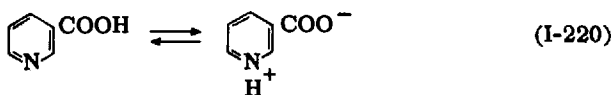
Aminopyridines are discussed further in Chapter IX.

5. Pyridinecarboxylic Acids

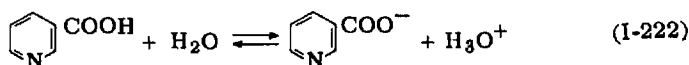
a. Acidity

Since the carboxyl groups of the three pyridine monocarboxylic acids are attached to a positively charged ring, the proton should be lost more readily than from benzoic acid. It is very difficult to test this experimentally because the pyridine acids have an internal base, the nitrogen atom, which can react with the proton.

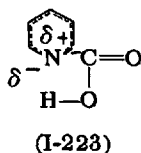
The two thermodynamic dissociation constants (pK_1 and pK_2 , Table IV) measured in the usual way (46-49) are for the loss of one and two protons from I-221. It is clear however, that these constants apply to the equilibrium mixture of the acid and its zwitterion.



In order to evaluate the equilibrium constant for the ionization of the pyridine acids (I-222) it is necessary to evaluate the constant



for equilibrium I-220. Green and Tong (50) have assumed that the equilibrium constant for the loss of a proton from the nitrogen atom of the acids is the same as for the corresponding methyl esters and in this way were able to calculate the desired equilibrium constant (K in Table I-4). This means that the pyridine acids are almost completely in the zwitterion form in aqueous solution. The last column in Table I-4 gives the pK_a (process I-222) values calculated using the values for K in the table. Thus all three pyridine acids are stronger than benzoic acid (pK_a 5.2); however, picolinic acid, which might be expected to be the strongest because the positive charge is largest at the 2 position of pyridine (see p. 6) is actually the weakest of the three acids. This suggests that the proximity of the nitrogen is playing some role in the acidity, and it is noteworthy that the carboxyl group can be oriented so that the proton is near the electronegative nitrogen atom (I-223). Perhaps



this accounts for the fact that it is less readily removed from its environment than in nicotinic and isonicotinic acids.

TABLE I-4. Dissociation Constants of Pyridinecarboxylic Acids

Acid	pK_1	pK_2	K	pK_a
Picolinic	1.01	5.32	15	4.12
Nicotinic	2.07	4.81	10	3.75
Isonicotinic	1.84	4.86	25	3.44

b. Decarboxylation

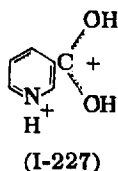
The presence of a positive center or an electron-accepting group facilitates decarboxylations, which proceed by way of the anion. This effect is observed because the positive center can stabilize the carbanion intermediate. The carbanions which result after loss of CO_2 from the zwitterion form of the pyridine acids (51) would have stabilities in the order $\text{I-224} > \text{I-225} > \text{I-226}$ if the charges were completely localized as indicated by the formulas. However, as in



pyridine itself, there is an unequal distribution of the π electrons, producing a positive charge mainly at the 2 and 4 positions (see p. 6) thus further increasing the stability of I-224 and making I-226 considerably more stable than I-225. The observed order of the three pyridine acids with respect to ease of decarboxylation, $2 > 4 > 3$, therefore is the same as that predicted from the relative stability of the carbanion intermediates.

c. Esterification

The conversion of pyridine acids to esters by reaction with an alcohol in the presence of an acid catalyst should be slower than for benzoic acids because the intermediate (I-227) has two positive charges and therefore is higher in energy than if the nitrogen atom were absent. However, the yield of the ester in most procedures is dependent on the position of the equilibrium in the esterification reaction rather than the rate; esters of all three acids may be readily prepared in yields of 90% (52).



d. Acid derivatives

Many of the reactions of the acid derivatives and the related pyridine aldehydes and ketones may be classified together as reactions in which a carbonyl group is attacked by a base or nucleophilic reagent. The rate of these reactions usually increases as the positive charge on the carbonyl carbon is increased. The positive pyridine ring, when directly joined to the carbonyl group, enhances the positive charge on the carbonyl carbon. The pyridine derivatives, therefore, react more rapidly than their benzene analogs. The effect is especially noticeable when carbonyl group is at the 2 or 4 position of the pyridine ring.

Pyridinecarboxylic acids and their derivatives are further discussed in Chapter X, aldehydes and ketones in Chapter XIV.

E. PARTIALLY HYDROGENATED PYRIDINES**1. Dihydropyridines***a. Structure*

The addition of two hydrogens to the pyridine ring could theoretically produce any or all of five possible isomers (I-228 to I-232).



(I-228)



(I-229)



(I-230)



(I-231)



(I-232)

Both the 1,2- and 1,4-dihydropyridines have unsaturated systems of six π electrons distributed over five atoms while the 2,3-, 3,4-, and 2,5-dihydropyridines have only 4 π electrons. In the 2,5-isomer these electrons are not even conjugated, but localized in two isolated double bonds. The unsaturated system of I-228 differs from I-229 only in having the nitrogen at the end rather than in the center of the five atoms; molecular orbital calculations indicate that the 1,2-dihydropyridine is only about 0.5 kilocalories more stable than the 1,4-isomer. Therefore the isomers may be arranged in order of decreasing stability: I-228 $\sim$ I-229, I-230 $\sim$ I-232, I-231. Substituents which can conjugate or interact strongly with the un-

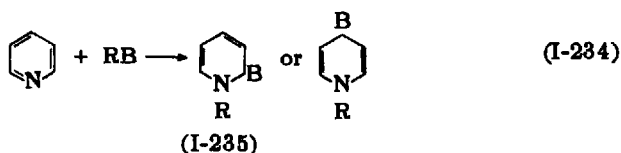
saturated system would be expected to change this order depending on their point of attachment.

Pyridones and 1-alkylpyridones are sometimes classified as dihydropyridines, but examination of their unsaturated systems (see p. 66) indicates that both 2- and 4-pyridones have complete cyclic systems of 8π electrons and are more properly considered as oxygen-substituted pyridines. This also applies to the aminopyridines and the tautomeric pyridonimines.

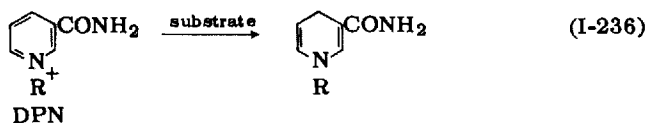
b. Preparation

There are two basic methods for preparing dihydropyridines; one is by addition of various reagents to a pyridine ring and the other is formation from aliphatic reagents as in the Hantzsch synthesis.

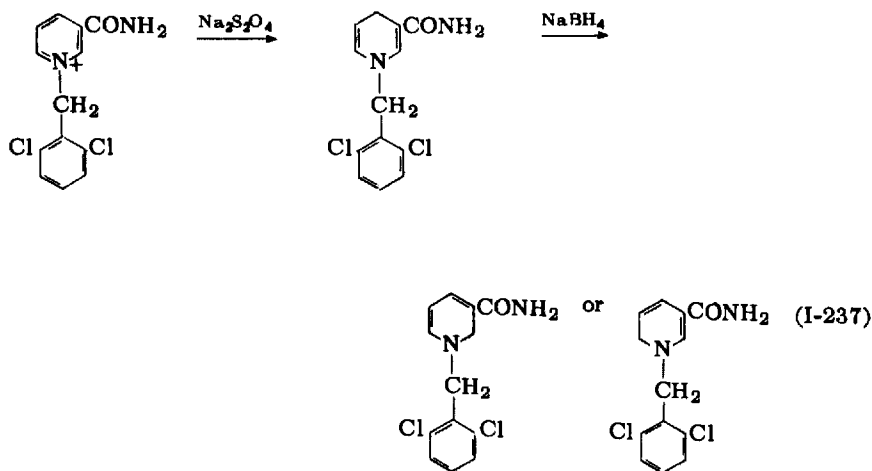
Most additions to the pyridine ring involve preliminary bond formation with the nitrogen atom and hence can produce either 1,2- or 1,4-dihydropyridines (I-234). When both R and B are large, repulsive forces between the two would be large in the 1,2-dihydropyridines (I-235). Even in a kinetically controlled process, the transition state is likely to resemble the product sufficiently so that the path leading to I-235 is unfavorable. For reductions of the pyridine system in which a hydrogen is added, there should be no appreciable steric factors and 1,2-addition products would be expected more frequently. The structures of such reduction products are difficult to establish and many of them are still in doubt; the question is also discussed in Chapter III.



The very important biological reduction of the coenzyme diphosphopyridine nucleotide (DPN) was for a number of years believed to yield a 1,2-dihydropyridine, but has now been proved to take place by direct transfer of a hydrogen atom (163) to the 4 position of the pyridine nucleus (35) (I-236). This kind of reduction

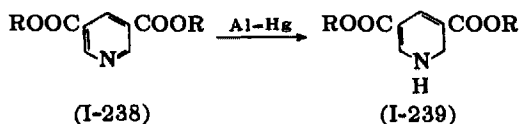


has been found to depend on the nature of the reducing agent; the quaternary salt from nicotinamide and 2,6-dichlorobenzyl chloride, yields different products with sodium hydrosulfite and with sodium borohydride (I-237). The observation that the *n*-propyl salt of nicotinamide produces the same dihydropyridine with either reducing agent (165) suggests that great care must be exercised in making generalizations and that the structure of the product in each different pyridine reduction may have to be determined separately.

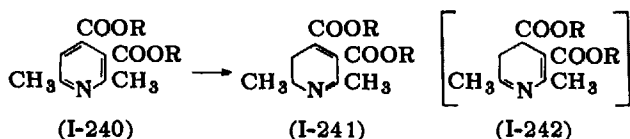


The chemistry of DPN is discussed further in Chapter III.

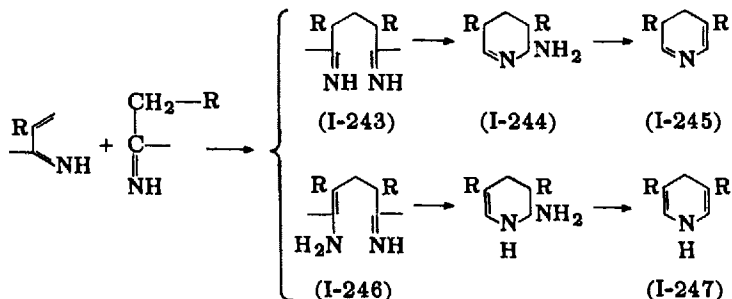
The influence of substituents is illustrated by some reductions of esters of pyridinedicarboxylic acids. When I-238 is reduced with aluminum amalgam, a dihydro derivative is produced which is different from the isomer (presumably 1,4-) obtained in a Hantzsch synthesis. The 1,2-isomer (I-239) is the only other one in which both carbalkoxyl groups are conjugated with the unsaturated system. The aluminum-amalgam reduction of I-240 is one of the few which is believed to produce other than a 1,2- or 1,4-dihydropyri-

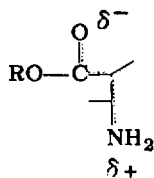


dine. The product is presumed to have a tertiary nitrogen since an acyl derivative cannot be formed; structure I-241 is preferred over the alternate I-242 because in the latter only one of the carbalkoxyl groups is conjugated with the unsaturated system.



Most of the many variations of the Hantzsch synthesis which lead to dihydropyridines may be considered to proceed by a Michael addition in which the carbonyl components are present largely as imines. The intermediate (I-243) could cyclize directly to yield the 3,4-dihydropyridine (I-245). However cyclization could equally well proceed through the tautomeric amino form (I-246) and this would be expected to produce the more stable 1,4-dihydropyridine (I-247). For most syntheses of this kind, R is a carbalkoxyl or similar group; this should favor tautomer I-246 because in this form the ester and amino group are a part of the same conjugated system (I-248). Even if cyclization were to yield some of the 3,4-isomer, it is likely that under the reaction conditions isomerization to the 1,4-product would occur. This would be expected particularly when the R groups are capable of conjugating with the unsaturated system.





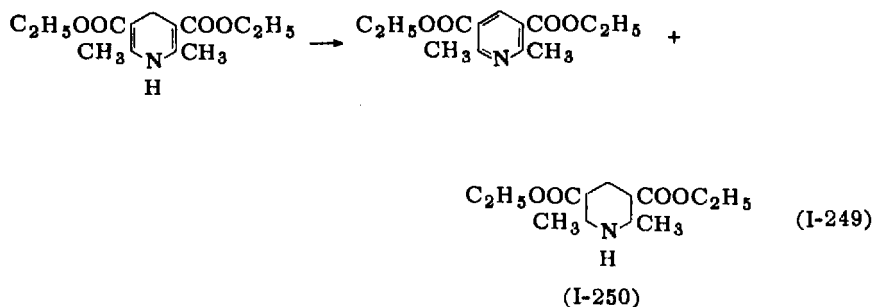
(I-248)

c. Reactions

The most important reaction of dihydropyridines is their oxidation to the corresponding pyridine. This process occurs readily; even contact with atmospheric oxygen frequently will be sufficient to bring about the transformation.

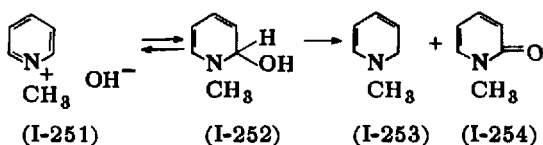
The ready oxidation of dihydropyridines is advantageous for synthesis of pyridines but it has made characterization and study of the properties of dihydropyridines rather difficult.

Chromic acid, iodine, and heating with palladium have been employed for aromatizing dihydropyridines which are stable in air. Sometimes excess aldehyde which is present in a Hantzsch synthesis will cause dehydrogenation during the reaction and no air or other oxidizing agent is required.

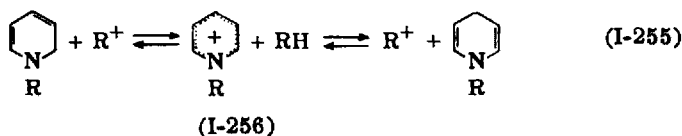


Dihydropyridines have also been observed to disproportionate I-249 in the presence of palladium or in hydrochloric acid solution (164). An interesting variation of this kind of disproportionation, first observed by Hofmann (166), was found to occur when a pyridine quaternary halide was heated with sodium hydroxide. A low yield of a dihydropyridine, presumed to be the 1,2-isomer (I-253)

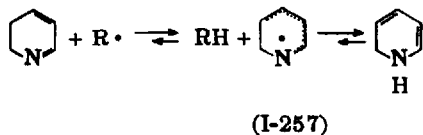
was formed. If it is indeed the pseudo base (I-252) which acts as the reducing agent, transferring a hydride ion to I-251, then I-254 should also be formed. Only polymeric substances which may result from the further action of sodium hydroxide on I-254 are actually isolated; in the quinoline series, however, both 1-methyl-2-(1*H*)-quinolone and tetrahydroquinoline can be isolated (167).



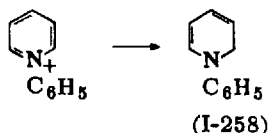
Another reaction, the isomerization of dihydropyridines, almost certainly takes place, but has not been the subject of detailed experimental study. A good deal of the uncertainty about structures of dihydropyridines revolves about the question of whether or not isomerization has occurred. Theoretically any reagent which can assist in the removal of a proton, hydrogen atom, or hydride ion may cause isomerization. Equation (I-255) illustrates isomerization of 1,2- and 1,4-dihydropyridines through a pyridinium ion intermediate (I-256). The isomerization of 2,3-, 2,5-, or 3,4-dihydro-



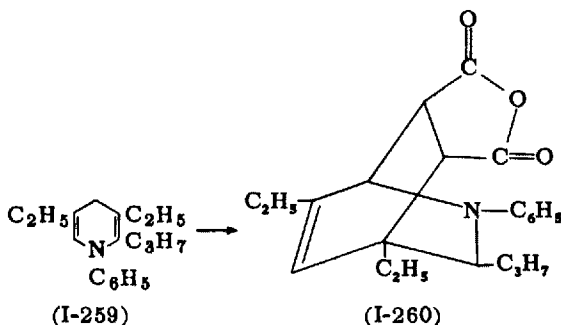
pyridines by a radical reagent would take place by way of intermediates such as I-257. If equilibrium is reached by processes such as these, the dihydropyridine finally isolated as the major product will be that one which is most stable for the particular set of substituents on the ring.



The Diels-Alder reaction would serve to differentiate 1,2- and 1,4-dihydropyridines if isomerization were not possible. The 1,2-dihydropyridine structure (I-258) was assigned to the reduction



product of 1-phenylpyridinium chloride because it reacted readily with maleic anhydride, although no characterizable product was isolated (168). A substituted 1-phenyldihydropyridine, believed to have the 1,4-structure (I-259) reacted only sluggishly with maleic anhydride (169) to yield a crystalline adduct (I-260). If structure I-259 is correct, isomerization must have occurred in the reaction mixture prior to the Diels-Alder reaction.

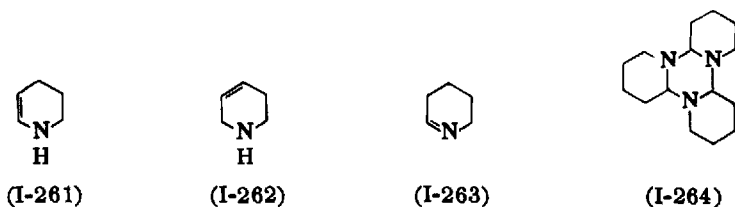


Hydrogenation of dihydropyridines to the tetrahydro and the completely reduced stages by both chemical and catalytic methods are quite normal reactions.

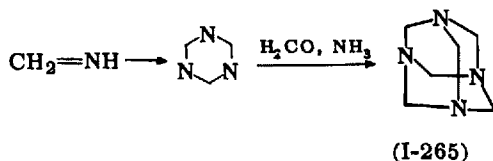
2. Tetrahydropyridines

a. Structure

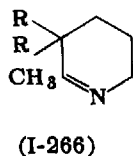
Only two, the 1,2,3,4-tetrahydropyridine (I-261) and the 1,2,3,6-tetrahydropyridine (I-262), of the three possible isomers of this series are readily available substances. The third isomer, I-263, is a very unstable substance and trimerizes almost immediately to I-264. Heating I-264 slowly in a vacuum reverses the polymerization to



yield monomeric I-263 in the vapor phase which trimerizes again when the vapors are cooled. Since I-263 is an aldimine it is not altogether surprising that it should react in this way. Hexamethylenetetramine (I-265) may result from ammonia by preliminary tri-



merization of an aldimine. Tetrahydropyridines with a carbon-nitrogen double bond, having three alkyl groups at the 2 and 3 positions (I-266) are stable, probably because they are ketimines rather than aldimines and also because the double bond cannot migrate.

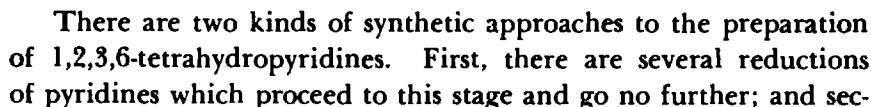


Isomers I-263 and I-261 are related as keto and enol forms of an aldehyde; however in the tetrahydropyridine series the enol-like structure (I-261) is more stable. Several reactions which might be expected to yield either I-261 or I-263 are found to produce only I-261.

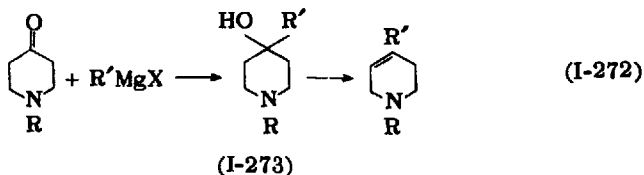
A comparison of the two stable isomers I-261 and I-262 suggests that the former should be more stable because the π electrons on the nitrogen can interact with those of the double bond (I-262). While this interaction lowers the total energy of the system as compared with I-262, the double bond becomes more susceptible to at-

b. Preparation

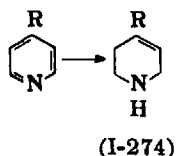
If a δ -aminoketone (I-268, $R' = H$) cyclizes, the carbinolamine which is first formed might dehydrate with formation of a carbon-nitrogen double bond as in noncyclic systems. However, the product is always the 1,2,3,4-tetrahydropyridine (I-270); this is, of course, the only isomer which can be formed if R' is an alkyl group. The aminoketones used in this synthesis are not isolated but generated by reaction of a bromoketone with ammonium or a primary amine (171,172). Another procedure for generating carbinolamines such as I-269 is by reaction of a tetrahydro-2-pyridone (I-271) with a Grignard reagent (173).



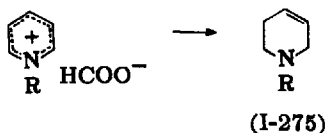
cond, elimination of a hydroxyl or related group bonded to the 4 position introduces a double bond in the expected position. The 4-hydroxypyridines (I-273) are usually produced by treating a tetrahydro-4-pyridone with an appropriate Grignard reagent (I-272).



The sodium-alcohol reduction of pyridine leads mainly to piperidine and only small amounts of 1,2,3,6-tetrahydropyridine are produced. With 4-alkyl substituted pyridines, however, the tetrahydro product having an isolated double bond (I-274) is not reduced fur-



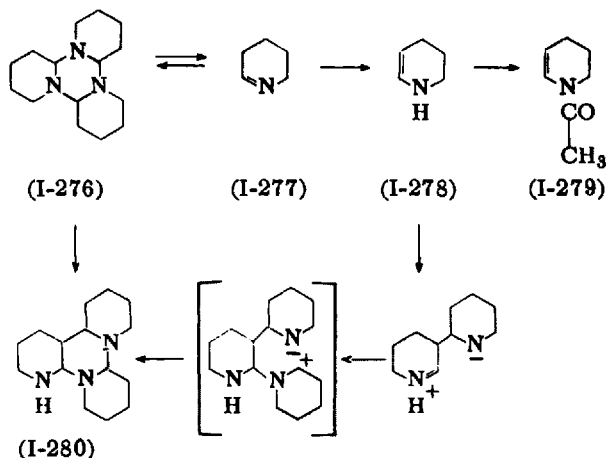
ther (174). The interesting reduction of quaternary pyridinium salts by formic acid has been discussed previously (p. 42). The tetrahydropyridine (I-275) is separated from the piperidine, which is also formed, by conversion to the dibromide; treatment of the dibromide with zinc regenerates the tetrahydropyridine.



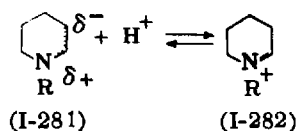
c. Reactions

The extremely ready trimerization of 2,3,4,5-tetrahydropyridine (I-277) has made it impossible to directly observe other reactions of this substance. However when the trimer (I-276) is heated with acetic anhydride, 1-acetyl-1,2,3,4-tetrahydropyridine (I-279) is formed (175). This may result by reversal to the monomer, which then

isomerizes and is acetylated. A similar process may account for the rearrangement of I-267 to I-280; the interaction of one molecule of I-278 with two molecules of I-277 would lead to the observed product (176).



Since 1,2,3,4-tetrahydropyridines are vinylamines, their reactions are quite different from the 1,2,3,6-isomer, in which the electrons of the double bond and nitrogen atom cannot interact. One manifestation of this interaction is the increased basicity of the molecule. The unshared electrons of the nitrogen, which in piperidine are available for bond formation with a proton, are delocalized as illustrated in formula I-281.

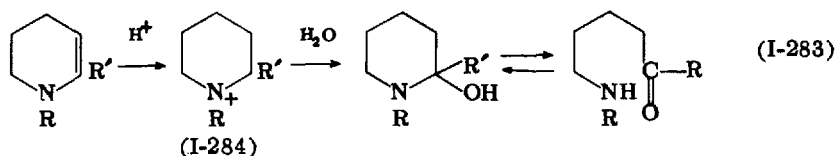


This effect should decrease the basicity of the nitrogen atom and it has been observed (178,179) that unsaturation in an amine generally does produce this result. When the nitrogen atom and double bond are separated by one or more saturated atoms, this must be due to dipole interactions. An explanation for the increased basicity of molecules such as I-281 is that the proton does not react at the nitrogen atom but at carbon 3 (178). The salt

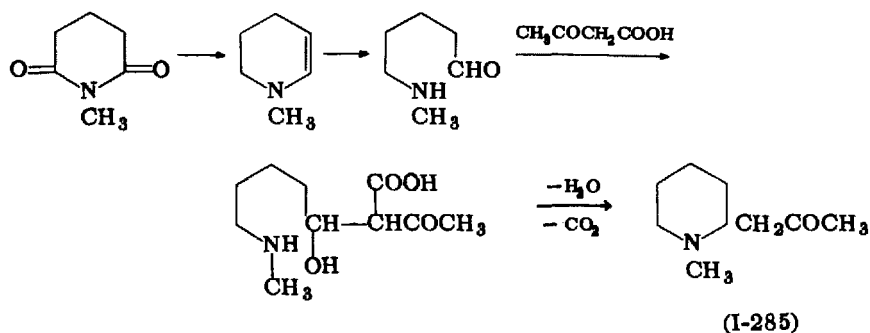
I-282 with a carbon-nitrogen double bond has resonance energy comparable to that of a carbonyl group and thus the energy change in going from the base to the salt is more favorable than for the corresponding piperidine. The infrared spectrum of salts of vinylamines has been interpreted as evidence in favor of I-282 as the correct structure (177).

The isomerization of I-277 to I-278 is probably acid catalyzed, and it may be that the same salt (I-282, R = H) results by addition of a proton to either one.

Vinyl ethers are readily hydrolyzed in aqueous acid and it is not surprising that the 1,2,3,4-tetrahydropyridines exhibit the same characteristic (I-283). Advantage was taken of this property to dem-



onstrate that in the electrolytic reduction of *N*-methylglutarimide some 1-methyl-1,2,3,4-tetrahydropyridine was formed. This unsaturated base, present in the mixture of products, reacted in an aqueous buffer to yield *N*-methyl-*i*-pelletierine (I-285). A salt (I-284, R' = CH₃), in which R is a phenyl group, was so readily hydrolyzed that attempts to liberate the free base always produced instead the amino ketone (180).



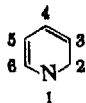
Hydrogenation of the double bond is a straightforward reaction for both 1,2,3,4- and 1,2,3,6-tetrahydropyridines. The other reac-

tions of the latter series of bases are those which are expected of an isolated double bond and a secondary or tertiary amine, with little influence of one functional group on the other.

Simple 1,2-dihydropyridines are given in Table I-5, 1,4-dihydropyridines in Table I-6, 1,2,3,4-tetrahydropyridines in Table I-7, 1,2,3,6-tetrahydropyridines in Table I-8, and 2,3,4,5-tetrahydropyridines in Table I-9. The tables follow the literature in the structure assignments, which, as has been pointed out, are not always rigorously established.

3. Tables *

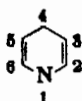
TABLE I-5. 1,2-Dihydropyridines



Substituents	B.p., °C./mm.	M.p., °C.	Derivatives; m.p., °C.	Ref.
1-CH ₃	129			166
1-C ₂ H ₅	148			166
1-CH ₂ CH ₂ CH(CH ₃) ₂	201-3		a	166
1-C ₆ H ₅		48-50		168
1-C ₆ H ₄ OCH ₃ (p)		82		168
1-C ₃ H ₇ , 2-C ₃ H ₇ , 3-C ₂ H ₅ , 5-C ₂ H ₅	120-21/12			183
1-C ₄ H ₉ , 2-C ₃ H ₇ , 3-C ₂ H ₅ , 5-C ₂ H ₅	132.5-133/12			183
1-CH ₂ C ₆ H ₅ , 2-C ₃ H ₇ , 3-C ₂ H ₅ , 5-C ₂ H ₅	118/12			183
2-CH ₃ , 2-CH ₃ , 4-CH ₃ , 6-CH ₃	50-51/12		b 154	184

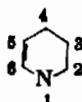
*Abbreviations in Tables I-5-1-9: a = chloroplatinate, b = picrate, c = chloroaurate, d = hydrochloride, e = perchlorate, f = mercurichloride, g = hydrochloride, h = benzenesulfonamide, i = methiodide, j = picrolonate, k = bisulfate.

TABLE I-6. 1,4-Dihydropyridines

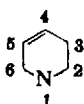


Substituents	B.p., °C./mm.	M.p., °C.	Derivatives; m.p., °C.	Ref.
2-CH ₃ , 4-CH ₃ , 6-CH ₃	165-66		a 200-10, c 52	185
2-C ₆ H ₅ , 4-C ₆ H ₅ , 6-C ₆ H ₅			b 155	186
1-C ₆ H ₅ , 2-C ₃ H ₇ , 3-C ₂ H ₅	125/.05			187
5-C ₂ H ₅				
2-C ₆ H ₅ , 4-C ₆ H ₅ , 4-C ₆ H ₅		235-36		188
6-C ₆ H ₅				

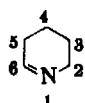
TABLE I-7. 1,2,3,4-Tetrahydropyridines



Substituents	B.p., °C./mm.	M.p., °C.	Derivatives; m.p., °C.	Ref.
6-CH ₃	131-32/716		a 194, b 120, c 145	171
6-C ₂ H ₅	149-51		a 179-81	189
6-C ₃ H ₇	173-74		a 192-95, c 79, d 143	190,191
6-CH(CH ₃) ₂	164-66		a 203, b 119, c 138	192
6-C ₄ H ₉	195-200		a 156	193
6-C ₆ H ₁₀	94.5-5/9		a 166, b 67, e 88.5	194
6-(CH ₂) ₃ CH:CH ₂	107/13			195
6-C ₆ H ₅	142-50/20		b 181.5, d 152, f 166	193
6-C ₆ H ₄ CH ₃ (p)	145/13		a 187, b 179, d 137.5	193
6-C ₆ H ₄ Cl(p)	165/13	54	a 192, b 178, d 215-17	193
1-CH ₃ , 6-CH ₃	145-46/720		a 200-205, b 160, c 180	171,196
1-C ₂ H ₅ , 6-CH ₃	163		a 199, f 213	172
1-C ₃ H ₇ , 6-CH ₃	184/768		a 180, c 59, f 64	172
1-CH ₃ , 6-C ₂ H ₅	58/10		a 213, c 131, e 237	196
1-CH ₃ , 6-C ₃ H ₇	73/10		b 170, c 80, e 130-33	197
1-CH ₃ , 6-C ₄ H ₉	85/12		a 182, b 144, e 143	196
1-CH ₃ , 6-C ₆ H ₁₀	114.5/10		a 126, e 136	196
1-CH ₃ , 6-C ₆ H ₅	139/20		b 133, e 146.5	196
1-CH ₃ , 6-CH ₂ C ₆ H ₅	169/25		b 151, e 135	196
1-CH ₃ , 6-C ₁₀ H ₇ (α)			b 140, e 135	196
5-CH ₃ , 6-CH ₃	154-57		a 160, b 155, c 147	198
1-CH ₃ , 5-CH ₃ , 6-CH ₃	165-67		b 152, c 158	199
2-C ₆ H ₅ , 4-C ₆ H ₅				
6-C ₆ H ₅		125.5		186
1-C ₆ H ₅ , 3-C ₂ H ₅				
5-C ₂ H ₅ , 6-C ₃ H ₇	115-20/0.2			187

TABLE I-8. 1,2,3,6-Tetrahydropyridines
 

Substituents	B.p., °C./mm.	M.p., °C.	Derivatives; m.p., °C.	Ref.
	117		a 188, c 142, d 191-93	200,201
1-CH ₃	112.5		b 202, g 160	202
1-C ₂ H ₅	57-59/43		b 169-71, e 66-68	177
1-C ₄ H ₉	72-74/20		b 106	204
1-C ₆ H ₅		45.5-46.5	b 145.5-46.5	203
4-C ₂ H ₅	158-58.5/749		h 50-52	174
4-C ₃ H ₇	178-79.5/742			174
4-C ₄ H ₉	196-97/741			174
1-CH ₃ , 2-CH ₃	132-32.5		b 227, g 223, i 288	205
1-CH ₃ , 4-C ₆ H ₅	128-32/12	33	d 250	206
1-CH ₃ , 4-C ₆ H ₄ OCH ₃ (o)	135/10			207
1-CH ₃ , 5-CH ₃	137-38		b 107, i 154	33
1-C ₂ H ₅ , 4-C ₆ H ₄ OCH ₃ (p)			d 198	207
1-CH ₃ , 2-CH ₃ , 6-CH ₃	149/744		b 229-31	208
1-CH ₃ , 4-CH ₃ , 5-C ₂ H ₅	75-85/20		j 191	209
2-CH ₃ , 2-CH ₃ , 6-CH ₃ , 6-CH ₃	146-47/740		c 176	210

 TABLE I-9. 2,3,4,5-Tetrahydropyridines
 

Substituents	B.p., °C./mm.	M.p., °C.	Derivatives; m.p., °C.	Ref.
2-CH ₃ , 3-CH ₃ , 3-C ₆ H ₅	80-83/0.5		j 151.5	211
2-CH ₃ , 3-C ₂ H ₅ , 3-C ₆ H ₅	94-95/0.5		b 128, d 148-50	211
2-CH ₃ , 3-C ₃ H ₇ , 3-C ₆ H ₅	112/1.0		j 135.5-37	211
2-CH ₃ , 3-C ₄ H ₉ , 3-C ₆ H ₅	118.5/0.5		j 121-23	211
2-CH ₃ , 3-C ₆ H ₅ , 3-C ₆ H ₅	128-30/0.5	106-07	d 207-209	211
2-CH ₃ , 3-C ₆ H ₅ , 3-CH ₂ C ₆ H ₅			b 174, d 218-20	211

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CHAPTER II

Synthetic and Natural Sources of the Pyridine Ring

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This chapter deals comprehensively with the preparation of pyridine compounds from non-pyridine sources. It is divided into two parts. The first considers naturally occurring materials, from which pyridines are obtained either directly or after degradation. The second part concerns chemical synthesis from non-pyridinoid compounds, both cyclic and acyclic.

The conversion of one pyridine compound to another is not discussed here, but rather in appropriate later chapters. Thus, the conversion of aminopyridines to pyridinols is treated at length in Chapter XII (pyridinols) and more briefly in Chapter IX (aminopyridines). By the same token the later chapters are brief in their treatment of nuclear synthesis, which is reserved for comprehensive review here. However, since nuclear synthesis is of special importance in the preparation of pyridinols, it is also discussed at some length in Chapter XII.

The scope of the present chapter extends to the preparation of dihydropyridines (including piperidinediones) but not tetrahydropyridines or piperidines. All preparative methods are considered except the biosynthetic. Literature coverage is essentially complete to the middle of 1956; important later papers are also covered.

PART I. PYRIDINES FROM NATURAL SOURCES

A rather small number of pyridine compounds are found in nature, principally among the enzymes and alkaloids. Others are obtained by degradation of complex natural materials such as coal, shale, and various alkaloids. Of these the only commercially important source is coal. The United States Tariff Commission reports 1.3 million gallons of pyridine crude bases as produced in the United States in 1956 by the carbonization of coal. The small group of pyridine bases recovered from this source have in turn led to countless derived products.

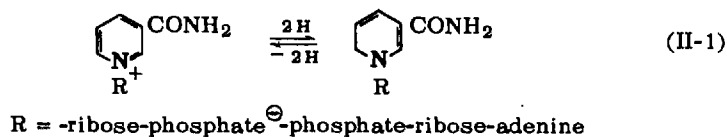
In the case of petroleum, at least some pyridine bases occur as such in the natural crude. Nevertheless, petroleum is considered along with other fuel deposits in the section on degradations.

A. PYRIDINES IN NATURE

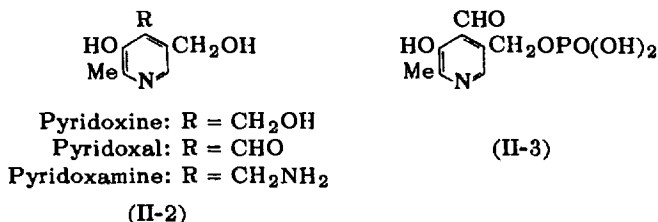
1. Pyridine Enzymes

The subject of the pyridine enzymes has been reviewed frequently (922,923). Such enzymes have been found in all animal and plant tissues so far examined, and are derived either from nicotinic acid or Vitamin B₆.

Nicotinic acid and its amide are converted almost entirely to Coenzyme I (Cozymase, diphosphopyridine nucleotide, DPN) and Coenzyme II (triphosphopyridine nucleotide, TPN) in living animal tissue; the disposition in plant tissue is not known with such certainty. The structure of DPN has been established as a combination of nicotinamide, ribose, phosphoric acid, and adenine in the scheme of II-1, about 35–45% being present in the reduced form; TPN has an additional phosphate group. The triphospho nucleotide is the less abundant of the two, but high concentrations of both are found in red blood cells, liver, and muscle, and of DPN in yeast. Both coenzymes combine with a variety of proteins, and thereby catalyze about forty different oxidation-reduction reactions in cells. Nicotinic acid may be extracted from most tissues after acid or alkaline hydrolysis; nicotinamide, after partial hydrolysis with dilute sulfuric acid. The coenzymes themselves have also been isolated: DPN (most commonly) from yeast in 95% purity, and TPN from liver in 92% purity. They are further discussed in Chapter III.



The B₆ vitamins comprise a group of three compounds (II-2) all of which are converted to pyridoxal phosphate (II-3) in tissue. The latter is itself the coenzyme, and the predominant form in most animal tissue; however pyridoxamine phosphate, which appears to be the form for storage, predominates in the liver and in yeast. The pyridoxal coenzyme participates in various cell reactions involving amino acids. Cf. Chapter XIII.



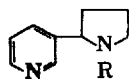
2. Tobacco Alkaloids

Few of the alkaloids are derived from the monocyclic aromatic pyridine system. These have been reviewed to 1950 by Marion (924). The most notable family within the group are the tobacco alkaloids (genus *Nicotiana*) which comprise a group of ten bases of known structure, oxygenated derivatives, and many others not yet identified. The designation "tobacco alkaloids" is for convenience only, since the principal bases occur in plants other than tobacco (Table II-1).

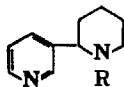
Commercial tobacco is prepared mainly from *Nicotiana tabacum*, and to a small extent from *N. rustica*. Two billion pounds were produced in the United States in 1953, over seven billion pounds on a world-wide basis (943). The tobacco is derived mostly from the leaf webs by a process of curing and aging; cigar tobaccos are then subjected to fermentation. Tobacco waste is further processed for extraction of the alkaloids, to be used as the insecticide, "nicotine sulfate." This is generally done by an alkaline steam distillation into sulfuric acid. Various methods for isolating tobacco alkaloids are given in Table II-2. The alkaloid content of cured tobacco varies widely; values ranging from 0.6% to 5% have been reported; 1-2% is commonest (941,939,583,940).

The pyridine bases which have been definitely identified are shown in II-4. Since most examinations were made on cured tobacco, there is no assurance as to their distribution or optical isomerism in the fresh plant. Compared to nicotine, the minor alkaloids occur in minute amounts. Their first separation was effected by tedious fractionation methods, largely through the efforts of Späth and co-workers. Since then paper chromatography has re-

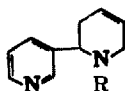
vealed up to twenty-seven pyridine compounds in various samples of tobacco, but most of these have not been identified (see also 952).



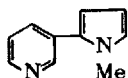
Nicotine, R = Me
Nornicotine, R = H



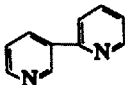
Anabasine, R = H
N-Methylanabasine, R = Me



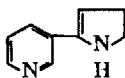
Anatabine, R = H
N-Methylanatabine, R = Me



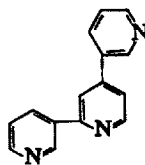
Nicotyrine



2,3'-Bipyridine



Myosmine



Nicotelline

(II-4)

By the method of Späth, nornicotine was extracted from crude nicotine by its greater solubility in acidic saturated brine (748,772). Then, after most of the nicotine was removed, the residue was fractionally extracted with acidic brine, yielding nicotyrine, *l*-N-methylanatabine, and *l*-N-methylanabasine (934). Other bases were obtained from a higher-boiling alkaloid fraction by fractional extraction with brine of increasing acid content. This furnished in turn *l*-anatabine (738), *dl*-anatabine, and *l*-anabasine (772); the last extract contained 2,3'-bipyridine (749).

Nicotelline was isolated in early work from the alkaloid fraction which was not volatile with steam (735-737). Myosmine was separated by paper chromatography (582,941), though its presence in the total alkaloid had been indicated by an analytical test (785). For the early history of the alkaloids, the determination of their struc-

tures, and their syntheses see reference 924; cf. also Chapter IX. Nicotelline has only recently been established as an authentic compound, first by oxidation to 2,4-pyridinedicarboxylic acid (868), and finally by synthesis (873,906).

The optical isomerism of the alkaloids has already been noted. It is of interest that nicotine is obtained only in the *l*-form and nornicotine as an optical mixture having a preponderance of *l*-form. An early report that nicotine occurs as a glucoside, tabacine, has been rejected on further evidence (612). Two additional glucosides since reported (932) also seem inadequately characterized. Probably nicotine occurs as a salt with an organic acid (612).

Besides these recognized bases, others were reported in the early literature but have since been disputed. Nicoteine (735-737) was shown to be a mixture of two bases, nornicotine (747) and anatabine (738). Isonicotine (737) has been identified as 2,3'-bipyridine (933). Nicotimine (735,736) and nicotoine (737) have not been found again since their first isolation, and there is some question as to their purity.

The relative proportions of the alkaloids is a matter of some complexity, since tobaccos differ widely depending on the plant strain, conditions of growth, and processing. The question is further obscured by the analytical methods, which often cannot distinguish closely related alkaloids (939). The paper chromatographic method seems capable of finding the most components with fair sensitivity (941). In general, commercial tobaccos fall into two groups according to whether they have a high or low proportion of nicotine. The most common varieties are high in nicotine, with this base constituting 80-98% of the total alkaloids (583,939). The chromatographic method detected nornicotine and anabasine as the most prominent minor alkaloids, and traces of myosmine, 2,3'-bipyridine, nicotine oxide, and nicotinic acid. An additional nine to seventeen compounds, probably all pyridines, were not identified (941,939). The second group of tobaccos has a low proportion of nicotine in the total alkaloids, and is represented by a few commercial varieties. Nornicotine is present in high proportion (583, 801), or may be the major alkaloid. By chromatography the fol-

lowing compounds were found in a typical specimen, in order of decreasing abundance (941,582,939): nornicotine, nicotine, anabasine, myosmine, nicotinic acid, nicotine oxide, 2,3'-bipyridine, and 3-pyridyl methyl ketone. An additional fourteen or more pyridines were not identified.

The oxygenated pyridines had previously been found only in tobacco after fermentation. In this process it has been noted that the nicotine content decreases by 30–95% of its initial value; at the same time the content of oxygenated products rises sharply. Thus nicotinic acid rises from less than 0.01% of tobacco weight to 0.2–0.4% (784,585,942); nicotine oxide increases ten-fold (941). It is possible that the oxygenated pyridines of ordinary (merely cured) tobacco also arise by enzymatic oxidation during the curing step (941).

When wild species of *Nicotiana* are considered, the variation in alkaloids is even greater. Of twenty-nine species examined (802) all had less total alkaloid than cultivated tobaccos; five had nornicotine (predominantly *l*) as the major alkaloid, four had *l*-nicotine (771,839), eighteen had significant proportions of both bases, and two species had *dl*-anabasine as the major alkaloid. These last were *N. debneyi* (939) and *N. glauca* (755,496). A process for the isolation of anabasine from *N. glauca* is given in Table II-2.

The significant tobacco alkaloids have also been found in plants other than tobacco (Table II-1). Of interest is *Anabasis aphylla* whose principal alkaloid, *l*-anabasine, was here first discovered (751, 752); a process for its extraction is given in Table II-2. *Duboisia hopwoodii* specimens generally contain both *l*-nicotine and nornicotine (827,860); while nicotine is usually the major component, the proportion is reversed in some cases (860), and there are specimens in which nicotine (847,860) or nornicotine (869,860,827,771) is the only alkaloid found. It is noteworthy that nornicotine occurs here in a preponderance of the *d*-form (766), in contrast to *Nicotiana* species. Similarly, *Duboisia myoporoides* contains both alkaloids (591). Various *Lycopodium* species and *Equisetum arvense*, which are botanically remote from *Nicotiana*, also contain nicotine, though in trace amounts.

TABLE II-1. Tobacco Alkaloids Identified in Tobaccos and Various Plants

Plant source	<i>l</i> -Nicotine	Nornicotine	Anabasine	<i>N</i> -Methyl-anabasine	Nicotyrine
1. U.S. tobacco, common varieties ^b	Major	Minor	Minor		
2. U.S. tobacco, occasional varieties ^c	Minor	Major	Minor		
3. Foreign tobaccos (17 varieties)	Major	None	None		
4. Brazilian tobacco	Major	Minor			Trace
5. Tobacco ^d	Major	Minor ^f	Trace ^g	Trace ^g	Trace
6. Tobacco ^d	Major				
7. Fermented tobacco	Minor	Minor	Minor		
8. <i>Nicotiana</i> wild species (various)	Major or minor	Minor or major ^f			
9. <i>Nicotiana glauca</i>			Major ^b		
10. <i>Nicotiana debneyi</i>			Major ^b		
11. <i>Duboisia hopwoodii</i> (various samples)	Major or minor	Minor or major ⁱ			
12. <i>Duboisia myoporoides</i>	Major	Minor			
13. <i>Anabasis aphylla</i>			Major ^g	Trace ^f	
14. <i>Withania somnifera</i>	Present				
15. <i>Asclepias syriaca</i>	Present				
16. <i>Lycopodium</i> species (various)	Trace				
17. <i>Equisetum arvense</i>	Trace				
18. <i>Sedum acre</i>	Trace ^k				

^aNicotinic acid, nicotine oxide, 3-pyridyl methyl ketone.^bFrom *Nicotiana tabacum* or *N. rustica*, cured.^cFrom *N. tabacum*, cured.^dUsed in isolation studies; apparently similar to common U.S. varieties.^e3-Pyridyl methyl ketone not found.^f*l*-Isomer in excess of *d*.

TABLE II-1 (Continued)

Anatabine	<i>l</i> -N-Methyl-anatabine	2,3'-Bi-pyridine	Nico-telline	Myosmine	Others ^a	Ref.
1.		Trace		Trace	Trace ^e	941,939, 801,583, 940,785
2.		Trace		Trace	Trace	941,939, 582,861 801
3.						553
4.						490,935
5.	Trace/	Trace	Trace			748,772, 934,738 749
6.			Trace			735-737
7.		Minor		Trace	Major ^l	585,942 784
8.						802,939 771,839
9.						755,496 802,1487
10.						939,802
11.						827,860 847,766, 771,869, 837,838
12.						591
13.						751,752, 486,936
14.						508
15.						814
16.						815,925 927-930
17.						815
18.						783

^a*l*-Isomer isolated.^b*dl*-Base found.^c*d*-Isomer in excess of *l* (see also 748).^dFinding (in 936) disputed in 926.^eReported absent in 872.^lAlso cotinine, *N*-methyl-2-(3-pyridyl)-5-pyrrolidone (951).

TABLE II-2. Isolation of Tobacco Alkaloids

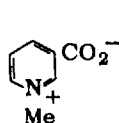
Source	Principal Steps	Ref.
Tobacco waste	Alk. steam distil., collect in H_2SO_4	1484
Tobacco	Alk. extract, counter-current with kerosene	1551
<i>Nicotiana rustica</i> plants	Expressed juice limed, counter-current with kerosene, re-extract with aq. H_2SO_4	953
Tobacco leaves	Alk. extract, re-extract with trichloroethylene, re-extract with aq. H_2SO_4	483
Tobacco, tobacco waste	Alk. extract, steam distil. into H_2SO_4 , neutralize, extract with pet. ether, ppte. as oxalate	1509,1523
Tobacco material	Alk. steam distil., with sudden changes of pressure	931
Tobacco leaves	Steam distil., ppt. with $HgCl_2$, recover base	488
Tobacco	Extr. with 20% NaOH, RT, 24 hrs. (recovery using 50% NaOH, or heating, is less)	492
<i>Nicotiana</i> plants (inc. <i>N. glauca</i>)	Extr. with aq. NH_3 and ethylene dichloride, counter-current with aq. $Al_2(SO_4)_3$, basify, counter-current with ethylene dichloride, distill	496,478
<i>Nicotiana</i> plants	Extr. with aq. $Al_2(SO_4)_3$	479
Tobacco leaves	Extr. with liq. NH_3 , remove NH_3 , treat with aq. $Ca(OH)_2$, then H_2SO_4 , filter	547
Tobacco material	Extr. with liq. NH_3 , remove NH_3 , extr. residue with trichloroethylene	506
<i>Anabasis aphylla</i> plant	Extr. with aq., absorb on silica gel or bentonite, desorb with aq. H_2SO_4 , or steam	486

3. Other Pyridine Alkaloids

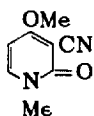
Trigonelline. Since trigonelline (II-5) was first discovered in 1885 in the seeds of *Trigonella foenum graecum* (174-176) it has been found in a diversity of other plants, such as coffee, soybean, and potatoes (see 924 for references), more recently in the fruit of

Quisqualis indica (481). The extraction of trigonelline from the sea urchin, *Echinarachnius mirabilis*, was said to be the first example of its occurrence in an animal (484); however, this compound is known to be present in the urine of certain mammals (922,923). Cf. Chapter III.

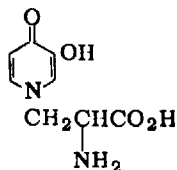
Ricinine. The alkaloid ricinine (II-6) was discovered in 1864 in the seeds of *Ricinus communis* (938), from which it has been isolated in various ways (299). A number of synthetic routes have been reported (243,1244,301,950). Cf. Chapter XII.



(II-5)



(II-6)



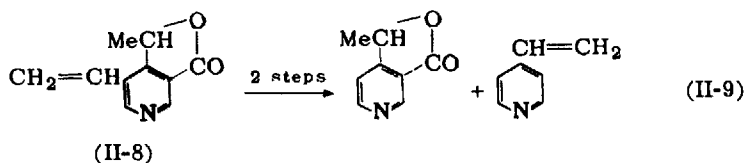
(II-7)

Mimosine (Leucaenine). The first isolation of mimosine (II-7) by Renz was from the shoots and stems of *Mimosa pudica* by crystallization of the sap (845). Subsequently Mascré obtained leucaenine (also called leucenol) from the seeds of *Leucaena glauca* by extraction with hot water (844). From preliminary work on the structure of mimosine (845,846) and considerably more on leucaenine (1391-1394,946-948), it was recognized that the two compounds were similar. However, early preparations of leucaenine were reported optically inactive (844,1391), while mimosine was levorotatory. Later preparations of the *Leucaena* alkaloid showed the same rotation as mimosine (944,945,1104), and indeed a re-examination of Mascré's original sample disclosed this same optical activity (539). The identity of the two alkaloids was finally established by X-ray diffraction (1456). The synthesis of mimosine (leucaenine) was effected from 3-methoxy-4-pyridone (1104). Cf. Chapter XII.

Fusarinic Acid. From culture media of the fungus *Fusarium heterosporium* was isolated fusarinic acid (1503), later found also in cultures of *F. lycopersici*, *F. vasinfectum* (1643), and *Gibberella fujikuroi* (1572,1643). This was shown to be 5-n-butylpicolinic acid,

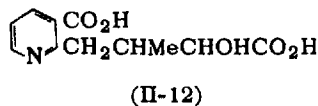
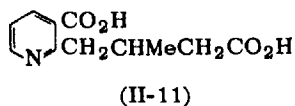
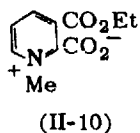
by decarboxylation to 3-*n*-butylpyridine (1504), and by synthesis of the natural product (1643).

Gentianine. The alkaloid gentianine (II-8) is found in *Gentiana kirilowi* (995) and *Dipsacus azureus* (997). Distillation with zinc dust gives pyridine, and the alkaloid has been oxidized to a carboxylic acid which on decarboxylation gives the products II-9 (996).



Miscellaneous Pyridines. 3-Methoxypyridine has been isolated from *Thermopsis rhombifolia* and *Equisetum arvense* (436). Pyridine itself was obtained by alkaline steam distillation of the foliage of *Aplopappus hartwegi* (937). The germinating spores of *Bacillus megatherium* excrete calcium dipicolinate; evidence of its occurrence in other members of the *Bacillus* group was also obtained (503,949). A fermentation auxin has been reported in sugar cane juice for which the betaine structure II-10, or its isomeric ester, has been proposed (1498).

The five ester alkaloids from *Tripterygium wilfordii* (1533–1535, 954) yield pyridine acids on hydrolysis. These alkaloids have a common polyhydroxy nucleus, $\text{C}_{15}\text{H}_{16}(\text{OH})_{10}$, of which most of the hydroxyl groups are bound by acetic, benzoic (or 3-furoic), and pyridinedicarboxylic acids. It is proposed that the pyridine acid of wilforine, wilforgine, and wilforzine is II-11, while that of wilfordine and wilfortrine is II-12. Both acids are oxidized to quinolinic, oxalic, and acetic acids, and give other reactions consistent with these structures (1532,954).



The isolation from musk of muscopyridine, $\text{C}_{16}\text{H}_{25}\text{N}$, has been reported; it is thought to be a 2,6-disubstituted pyridine since on

oxidation it yielded dipicolinic acid (1348). 1-Methylpyridinium hydroxide has been obtained from the shellfish, *Corbicula sandai* (1493), and the sea urchin, *Echinarachnius mirabilis* (484).

B. DEGRADATION OF NATURAL PRODUCTS

1. Coal

The plant life which became coal was laid down in a period ranging from one million to three hundred million years ago. This organic material was covered with stagnant water which excluded oxygen and so stopped the normal decay. The deposits were then overlaid and subjected to high temperatures and pressures which gradually increased the aromaticity of the organic matter. With allowances for differences in pressure and temperature, the age of the deposit determines the rank of the coal. Thus the young deposits are the low-ranking lignite and sub-bituminous, while the older are bituminous coal and anthracite.

About 1.1–1.6% of bituminous coal by weight is nitrogen, which probably came from plant protein, alkaloids, chlorophyll, and the like, though animal sources have been proposed. At least some of this nitrogen appears to be in the form of polycyclic, heterocyclic systems. The aromatic nature of such systems was shown typically by the controlled oxidation of coal to produce carboxylic acids which on decarboxylation yielded pyridine, phenylpyridines, quinoline, β -naphthoquinoline, and several carbocycles (662). The nature of coal and the technology of its carbonization have been reviewed. (1839–1841).

Coking is primarily a thermal cracking operation, though reforming may also occur. Coking is usually done at 900–1200°C. Lower temperatures (450–700°), which are little used in the U. S., produce a tar which is more aliphatic in nature, contains much less pyridine and picoline, but a large proportion of alkylpyridines and quinoline (635). Coking is done mostly in by-product ovens and only to a small extent in retorts. Bee-hive ovens are still used, but these do not recover the tar.

About 25–30% of the bituminous coal which is coked is driven off as a gas. Most of the nitrogen is evolved as ammonia. Cooling of this gas to 75–90°C. by a spray of “flushing liquor” (dilute am-

monia) condenses about 80% of the tar content as well as part of the ammonia. The remaining vapors are sent through a cooler which lowers the temperature to 25–35° and separates most of the remaining tar and additional ammonia. The remaining gas is reheated to 55–60° and passed through the saturator where dilute sulfuric acid extracts most of the residual bases. Further cooling and scrubbing of the gas may be done to remove a light oil containing small amounts of pyridine bases which are seldom recovered. The gas is now used for fuel. The above procedure is the commonest in the U. S.

Every ton of coal carbonized produces from 0.07 to 0.21 pound of pyridine bases; 40% of these bases, mostly higher boiling, are condensed in the tars, and the remainder, which is three-fourths pyridine itself, is found in the various ammonia liquors. These liquors are distilled and the distillate passed into the saturator containing sulfuric acid. Ammonium sulfate precipitates. The liquor from this step is run into a still and ammonia added to liberate the pyridine bases which are then distilled (491,505,550,1524,1566). The distillate separates into two phases. The pyridine layer is dried and fractionally distilled to give, for example, 69% pyridine, 7.5% picolines and 2,6-lutidine, 0.6% 2,4,6-collidine, and the remainder aniline and quinoline bases.

The tars, which were collected separately at the two stages or combined, are distilled to give light oil (boiling up to 200°C.), middle oil (200–250°), heavy oil (250–300°), anthracene oil (300–350°), and the residual pitch. The pyridine bases are normally recovered only from the middle oil. The oil is cooled to remove naphthalene, washed with 10% caustic to remove the tar acids, and then extracted twice with 15–30% sulfuric acid to remove the bases. These bases are then liberated with ammonia or caustic, dried (usually by distillation with benzene), and distilled.

In the distillation of any pyridine base mixture, pyridine (b.p. 115.3°) and 2-picoline (b.p. 128°) may be obtained in good purity. The next higher boiling fraction, the commercial "β-picoline" contains 2,6-lutidine (b.p. 143°), 3-picoline (b.p. 143.5°) and 4-picoline (b.p. 143.1°). These are not separable by distillation. Much of the literature on the separation of pyridine bases is concerned with this mixture.

Separation of bases has been done by both physical and chemical methods (see also Chapter V). The former consists of distillation of the bases or their salts, azeotropic distillation with aliphatic acids or phenols, counter-current extraction, and fractional freezing (Table II-3). All but the simple distillation give at least some separation of the " β -picoline" into its components.

Bases have often been separated through their formation of salts or complexes (Table II-4). Separation of bases in the early literature, usually done for identification purposes, was commonly accomplished by repeated recrystallization of salts with zinc chloride, mercuric chloride, picric acid, chloroplatinic acid, chloroauric acid, or other such reagent. The most important of these separations today is that of 2,6-lutidine from its mixture with 3- and 4-picolines by addition of urea.

Separation techniques have also been based on the chemical reactivity of 2- or 4-methyl groups with aldehydes, acid halides or anhydrides, ketene, active halogen compounds (organic or inorganic), or sulfur (Table II-5). These reagents have been used to obtain 3-picoline from commercial " β -picoline" by converting the 2,6-lutidine and 4-picoline to products of low vapor pressure. However, since destruction of large amounts of bases is uneconomical, such methods should be preceded by at least a preliminary separation by other methods. In a few cases oxidation has been used to give separation. In one case, oxidation with oxygen separated unchanged 3-picoline from the picoline-lutidine mixture, but generally the bases have all been oxidized to the carboxylic acids which were then separated.

Expectedly, several procedures use multiple operations based on two or more principles of separation (Table II-6). Typically, the separation of the bases in " β -picoline" would begin with the separation of 2,6-lutidine as a urea complex. The remaining bases would be partially separated into 3- and 4-picolines by azeotropic distillation with an aliphatic acid or phenol, and the 3-picoline would be purified by heating with a mixture of phthalic and acetic anhydrides.

Although a number of bases have been isolated from coal carbonization products, only a few are commercially available. Special grades of pyridine can be obtained, but the common purified grade

is the so-called "two degree" pyridine. Various crude pyridine fractions are available with boiling range up to 30°. 2-Picoline is also available as a high purity "two degree" grade as well as in several mixed picoline grades. The 3- and 4-picolines are usually sold as a mixture. Also available are 2,4-lutidine, 2,6-lutidine, and "mixed lutidines," as well as 2,4,6-collidine.

Many other bases have been identified in coal tar, including the six lutidines, all the collidines but the 3,4,5-isomer, the three tetramethylpyridines, 4-ethyl and 6-ethyl-2-picolines, and 2-phenylpyridine (575).

Early analytical methods often were based on isolation of the individual components and were not satisfactory. For binary mixtures, cloud point, clearing point, or ultraviolet spectrum analysis will suffice. Paper chromatography works well for qualitative analyses, and gas-liquid partition chromatography separates most bases, but fails on the important distinction between 3- and 4-picolines. Infrared analysis has been used with the most success (Table II-8).

TABLE II-3. Separation of Bases Involving Physical Methods

Bases	Method	Results	Ref.
Pyridine, 2-picoline	Gradual neutralization of base hydrochlorides during distillation	Poor separation	476
	Distillation	Separation	388
Pyridine, picolines, lutidines	Distillation	Separation	476
Pyridine homologs	Fractional freezing	Separation	396
3- and 4-Picoline	Distillation of hydrobromides	Separation	398
	Counter-current extraction, CHCl_3 vs. pH 4 buffer	Separation	463,519
	Counter-current extraction, hexane vs. H_2O	Separation in 90% purity	626
	Steam distillation with SO_2	3-picoline, 4-picoline (high purity)	618,1740

TABLE II-3 (Continued)

Bases	Method	Results	Ref.
3- and 4-Picoline, 2,6-lutidine	Distillation of hydrochlorides	Separation	398
3- and 4-Picoline, 2,6-lutidine	(1) Fractional crystallization of hydrochlorides from alc.	(1) 2,6-Lutidine ppt. (2) 3-Picoline (pure)	401
	(2) Distillation of more soluble salts		
	Distillation of CaCl_2 adduct	Separation	410
	Steam distillation with SO_2	Separation	1740
	Azeotrope with acetic acid	2,6-Lutidine (31% yield, 95% pure), 3-picoline (26% yield, 97% pure), 4-picoline (28% yield, 98% pure)	1099
	Steam distillation	Separation	389,390
	Azeotrope with phenols, halophenols, or cresols	Separation	392,393, 474
	Azeotrope with C_1 to C_8 acids	Separation	394,395
	Counter-current extraction with hexane and water	Separation in 90% purity	626
Tar base b.p. 140-50°	Azeotrope with acetic acid	Separation of bases	391
Tar base b.p. 157-58°	Distillation of hydrochlorides	2,4-Lutidine, 2,5-lutidine	397
Tar base b.p. 130-32° at 100 mm.	Distillation, 100 plate column	2,3,5,6-Tetramethylpyridine	1495
Tar base b.p. 135-35.2 at 100 mm.	Distillation, 100 plate column	2,3,4,6-Tetramethylpyridine	1507

TABLE II-4. Separation of Bases by Formation of Salts or Complexes

Bases	Method	Results	Ref.
Pyridine bases	Phosphate salts	Separation	402
Pyridine, 2-picoline	HClO ₄ (CAUTION: explosion noted)	Purified pyridine	471,472, 475,757
2- and 3-Picolines	Phthalic acid, alc. or ketone solvent	Fractional pre- cipitation	1474
3- and 4-Picolines	Salicylic acid, no solvent	4-Picoline ppt., 3- picoline 95% pure	1388
3- and 4-Picolines, 2,6-lutidine	Salicylic acid, toluene	4-Picoline and 2,6- lutidine ppt.; 3- picoline 85% pure	1388
	Urea	2,6-Lutidine ppt.	1512
	4-Hydroxybiphenyl, benzene, isooctane	Fractional ppt.	1389
	Benzoic acid, tolu- ene, gradual cooling	-10°: 2,6-lutidine ppt. >95% pure; -20°: 4-picoline ppt. >95% pure	1386
	Oxalic acid, recryst- allization of salt and distillation	Separation of pico- lines from lutidine	1307
3- and 4-Picolines, 2,6-lutidine	HCl, no solvent or hydrocarbon solvent	2,6-Lutidine 1st ppt., 4-picoline 2nd ppt.	399
	Oxalic acid, heat to equilibrium	4-Picoline ppt. high purity	834
	(1) ZnCl ₂	(1) Picolines ppt.	406
	(2) Ppt. from above with CaCl ₂	(2) 4-Picoline ppt.	
Tar base b.p. 137-45°	Aq., urea	2,6-Lutidine ppt.	413,414
Tar base b.p. 139.5-41°	Oxalic acid, alc.	3-Picoline, 4- picoline	1512
Tar base b.p. 140-42.5°	Phthalic acid	2,6-Lutidine ppt.	405
Tar base b.p. 140-45°	Aq., CuCl, boil, then cool	3-Picoline ppt. 75% yield (99% pure on dis- tillation)	562

TABLE II-4 (*Continued*)

Bases	Method	Results	Ref.
Tar base b.p. 140-48°	ZnCl ₂	Separation of picolines from 2,6-lutidine	1441
	Aq., CuSO ₄ , 70° cooled to 20°	3-Picoline 95% pure 66% recovery	1441
Tar bases b.p. 141-44°	HgCl ₂	2,6-Lutidine ppt.	1698
Tar bases b.p. 141-45°	HCl, 3- or 4-carbon alcohols	2,6-Lutidine 1st ppt., 4-picoline 2nd ppt.	549
	HgCl ₂ , HCl	2,6-Lutidine	1512
Tar bases b.p. 142-45°	HCl, fractional re- crystallization	2,6-Lutidine 1st ppt. 43% of prod- uct; 4-picoline 2nd ppt. 25.5% of prod- uct; liquor 3- and 4-picolines	1559
Lutidines	HCl, pet. ether	2,4-Lutidine ppt.	546
	Dry HCl	2,4-Lutidine 95% pure	1375
Tar bases b.p. 153-56°	HgCl ₂	2,4-Lutidine	1698
Tar base b.p. 159-63°	Aq., urea	2,3-Lutidine ppt.	412
Tar bases b.p. 160-65°	HgCl ₂ , HCl	2,5-Lutidine	1685
Tar bases b.p. 162-66°	HgCl ₂	2,5-Lutidine	1698
Tar bases b.p. 164-65°	HgCl ₂	3,4-Lutidine, 2,4,5-collidine	1676
Tar bases b.p. 165-70°	HgCl ₂	3,5-Lutidine	1685
Collidine bases	Aq., or anhydr. HCl (limited)	2,4,6-Collidine ppt.	400
Tar bases b.p. 170-80°	(1) Ac ₂ O (2) H ₂ Cr ₂ O ₇	(1) Aniline removed (2) 2,4,6-Collidine	1800
Tar bases b.p. 266-69°	ZnCl ₂ , HCl	2-Phenylpyridine 11.5% (remainder quinolines)	1401

TABLE II-5. Separation of Bases by Chemical Reactions

Bases	Method	Results	Ref.
3- and 4-Picoline	Phthalic anhydride, acetic anhydride, 160-80°	3-Picoline (pure)	416,417
Bases containing 3-picoline	2,4-Dinitrochloroben- zene	3-Picoline recovd.	423
3- and 4-Picolines, 2,6-lutidine	Halides, oxyhalides, or oxides of P or S	3-Picoline recovd.	419
	Ketene, acid catalyst	3-Picoline recovd.	421
	Benzaldehyde or furfuraldehyde	3-Picoline recovd.	422
	O ₂ , high temp., ox- ides of group V _A or VI _A	3-Picoline recovd.	424
	V ₂ O ₅ , MoO ₃ , Co ₂ O ₃ , 400°	Nicotinic acid (45% based on 3-picoline)	426
	KMnO ₄	Separation as acids	173
	S, heat	3-Picoline recovd.	427,1666
	Formaldehyde, R ₂ NH	3-Picoline recovd.	1387
Tar base b.p. 140-50°	Limited formaldehyde, 150-60°, 3 hrs.	3-Picoline, 2,6- lutidine recovd.	1744
Tar base b.p. 142-43°	Oxidation, V ₂ O ₅ , va- por phase	Isonicotinic acid	507
Tar base b.p. 142-45°	Limited formaldehyde, catalyst, reflux	3-Picoline, 2,6- lutidine recovd.	672
Lutidine fraction	HOAc, H ₂ O ₂	2,4-, 2,6-, and 3,4- Lutidine oxides	1511
Fractions contain- ing 2,4-lutidine	KMnO ₄	2,4-Pyridinedicar- boxylic acid	168-172

TABLE II-6. Separation of Bases by Multiple Methods

Bases	Conditions	Results	Ref.
3- and 4-Picolines, 2,6-lutidine	(1) Anhydr. HCl, cool	(1) 2,6-Lutidine ppt.	1475
	(2) Distillation of resulting liquor	(2) Sepn. of pico- lines	
	(1) ZnCl ₂ , steam distillation	(1) 2,6-Lutidine	1379
	(2) CaCl ₂ added to resulting residue	(2) 4-Picoline ppt.	
	(1) Urea	(1) 2,6-Lutidine ppt.	1587
	(2) Azeotrope liquor with phenol	(2) 3-Picoline (95% pure) 4-Picoline (90% pure)	
	(1) Alc. HCl	(1) 2,6-Lutidine ppt.	1602
	(2) Evaporation and sublimation of liquor	(2) 4-Picoline	
	(1) Urea	(1) 2,6-Lutidine ppt.	415
	(2) Phthalic anhy- dride, acetic an- hydride, 160-80°	(2) 3-Picoline (pure)	
	(1) Furfural or benz- aldehyde, 150°, 5 hrs.	3-Picoline recovd.	1665
	(2) Direct or steam distillation		
	(3) Steam strip with acid		

(continued)

TABLE II-6 (Continued)
Separation of Bases by Multiple Methods

Bases	Conditions	Results	Ref.
3- and 4-Picolines, 2,6-lutidine	(1) Urea, steam bath, 1 hr., then cool	(1) 2,6-Lutidine separates	556
	(2) Aq. CaCl_2 , 70°, then cool	(2) 4-Picoline separates	
	(3) S, ZnCl_2 , reflux 40 hrs.; repeat	(3) 3-Picoline remains	
	(4) Phthalic and acetic anhydrides, heat 4 hrs.	(5) Purified 3-picoline	
	(5) Azeotrope		
	(1) Urea	(1) 2,6-Lutidine ppt.	613
	(2) Azeotrope liquor with formic acid	(5) 3-Picoline	
	(3) Oxalic acid		
	(4) Steam distillation of salt		
	(5) Distillation		
	(1) Urea	(1) 2,6-Lutidine ppt.	1125
	(2) Azeotrope liquor with acetic acid	(4) 3-Picoline	
	(3) Distillation		
	(4) Fractional freezing		
Tar bases b.p. 142-44°	(1) <i>i</i> -PrOH, acidity with HCl	2,6-Lutidine	1562
	(2) Basify ppt. and distillation		
Tar bases b.p. 198-204°	(1) Separation of primary bases	(1) Primary bases	1142
	(2) Urea	(2) 2,3,5,6-Tetramethylpyridine, pyridane	
	(3) Decompose resulting ppt. and distillation	(3) 2,3,5,6- and 2,3,4,6-Tetramethylpyridines	

TABLE II-7. Purification of Bases

Base	Method	Ref.
Pyridine	Add $\text{Cu}(\text{ClO}_4)_2$, then sat. CuSO_4	411
	Distillation, 100 plate column	542
	HClO_4 (CAUTION: explosion noted ref. 472)	403,404, 472,475, 757,758
	Steam distillation from limited acid, followed by fractional distillation and freezing	1125
	Oxalic acid, acetone	723
	(1) KMnO_4 , then distillation	1735
	(2) Oxalic acid	
	(3) Recover and distillation	
Pyridine or homologs	(1) Distillation	678
	(2) Reflux with SeO_2	
	(3) Distillation from BaO	
	ZnCl_2 or HgCl_2	408
Picoline	(1) Aq. AgNO_3 , $(\text{NH}_4)_2\text{S}_2\text{O}_7$	411
	(2) Add. alkali and distillation ppt.	
2-Picoline	Recrystallization of oxalate followed by distillation	542
3-Picoline	Phthalic anhydride, acetic anhydride, then distillation; repeat until no color formed	416
	(1) Urea	1125
	(2) Liquor azeotroped with acetic acid	
	(3) Fractional freezing	
	Use of acid anhydride or chloride as above	417,418
	P or S halides, oxyhalides or oxides; heat	420
	O_2 in gas, catalyst, 350° , then distillation	425
	(1) S, ZnCl_2 , reflux, 40 hrs., then steam distillation	556
	(2) Phthalic and acetic anhydrides, heat	
2,6-Lutidine	(3) Azeotropic distillation	
	Repeated distillation and fractional freezing	542
	Ethyl 4-ethylbenzenesulfonate, reflux, then distillation	1499
	Repeated distillation and fractional freezing	542

(continued)

TABLE II-7 (*Continued*)
Purification of Bases

Base	Method	Ref.
2,6-Lutidine	(1) Precipitate with urea and recrystallization	1125
	(2) Regenerate base and distillation	
	(3) Fractional freezing	

TABLE II-8. Analytical Methods

Method	Applicability	Ref.
Paper chromatography	Separation of pyridine, quinoline, isoquinoline, and collidine	468
	Separation of crude pyridine oil into pyridine, 2-picoline, 2,6-lutidine, and s-collidine	469
Gas-liquid partition chromatography	Stationary phase of paraffin on kieselguhr; separation of most bases; 3- and 4-picoline not separated	518
Infrared spectrum	Detection of 2-ethylpyridine in commercial " β "-picoline, and pyridine	543
	Determination of 3- and 4-picoline, 2,6-lutidine, and 2-ethylpyridine (pyridine and 2-picoline do not interfere)	520
	Determination of commercial bases	542
	Analysis of higher boiling bases	1543
Ultraviolet spectrum	Determination of contents of commercial β -picoline (pyridine, 2-picoline, and 2-ethylpyridine interfere)	520
		1526
Cloud point in aq. NaCl	Good for binary mixtures only	777
		1095
Clearing temperatures of aq. perchlorates	Determination of pyridine in commercial samples	777

2. Petroleum

Petroleum is composed primarily of a wide variety of hydrocarbons ranging from methane to complex molecules which are paraffins, cycloparaffins (naphthenes), and aromatics. Petroleum deposits vary widely in their ratios of the three hydrocarbon types and in the amount of sulfur and nitrogen contained. The nitrogen content in Pennsylvania crude is as low as 0.008% but reaches 0.8% in some California deposits (805,1848). A review of petroleum acids and bases has been published recently (1848).

Much of the investigation of petroleum bases has been done on the kerosene fraction of California crude. In general, up to 85% of the bases are non-aromatic; of the aromatics, most are quinolines (433). The bases are removed from the kerosene by extraction with sulfur dioxide and then separated by fractional distillation, recrystallization of salts or complexes, partitioning of the hydrochlorides between water and chloroform (1849), and countercurrent fractional neutralization (1850). The kerosene fraction has yielded 3-picoline, 2,3- and 3,5-lutidine, 2,3,4- and 2,3,5-collidine, 5-ethyl-3-picoline (1848), 6-*i*-propyl-2,3-lutidine (1231), 6-*sec*-butyl-3,4-lutidine (1092), and 6-(2,2,6-trimethylcyclohexyl)-2,4-lutidine (1347). A large number of quinoline bases and non-aromatic bases are also present.

Work has also been done on cracked gas oil, which yielded a larger number of pyridines and fewer quinolines than did the straight run kerosene. The pyridines included all of the mono- and dimethyl pyridines, 2,3,4-, 2,3,6-, and 2,4,6-collidine, 4-ethylpyridine, the 4-, 5-, and 6-ethyl derivatives of 2-picoline, and 2-ethyl-4-picoline (432,433,1848).

It is not certain whether pyridine bases are formed during distillation of the petroleum; some at least have been shown to be present in the original crude. It has also been demonstrated that the total base content of the crude is unchanged by heating, but the effect on the character and proportions of the individual constituents is not known (1848).

Other bases have been isolated but not identified. For example, bases of ten, eleven, twelve, and thirteen carbons have been studied (1092,1219,1366,1222).

The origin of the bases in petroleum (or the base precursors) is not clear and could have been from either animal or vegetable sources. One proposal is that chlorophyll was degraded through a series of steps to alkylpyrroles which in turn gave pyridines (634). However, such a theory does not account for the formation of the trimethylcyclohexyllutidine or the quinoline bases.

3. Shale

The pyrolysis of oil shale (1844) gives an oil which resembles petroleum but is considerably richer in pyridine bases, and is exploited commercially for its hydrocarbon fractions.

Oil shale is a sedimentary rock, distributed throughout the world, which contains up to 33% organic matter (kerogen). It was probably formed at the bottom of stagnant pools by deposition of algae, spores, pollen grains, and fine plant debris interspersed with mineral matter (822). The source of its nitrogen is probably plant protein, with a lesser contribution by chlorophyll (822,824). Shales of different localities vary in yield of oil (usually below 50 gallons per ton) and in nitrogen content (from 0.2% to 3% on the weight of the kerogen, 822).

Oil shale industries were founded over a century ago in France and Scotland, and operate as well in other countries, including Australia, Estonia, Manchuria, Spain, Sweden, and the Union of South Africa. There is no such industry in the United States, but an intensive development program has been carried out by the U. S. Bureau of Mines since 1944. Though many of the states have oil shale deposits, the largest by far is the Green River Formation of Northwest Colorado, Utah, and Wyoming, whose richest bed, the Mahogany Ledge, yields over 25 gallons per ton. The reserves in Northwest Colorado alone are said to be 1.2 trillion barrels of oil (1843).

Retorting of the shale is carried out at about 900°F. (500°C.) either by external heating or by introduction of superheated steam or combustion gases into the bed of crushed shale. This, for Colorado shale, breaks down the kerogen to 66% volatile oil, 9% gas, and 25% residue fixed in the spent shale. The shale oil is similar to thermally cracked petroleum in containing paraffins, olefins, and

aromatic hydrocarbons; however, the non-hydrocarbon content (N, S, and O compounds) is higher, being 61% for Colorado oil, of which 60% are nitrogen compounds (1050). The oil is variously refined in different countries, but is usually distilled to give three or more volatile fractions; the low-boiling naphtha (light oil) is washed with caustic soda to remove tar acids (mainly phenols), and with dilute sulfuric acid to remove tar bases. The neutral fractions may be further treated, and redistilled to produce gasoline, Diesel oil, fuel oils, lubricating oil, and other hydrocarbon materials.

The composition of shale oil varies with the source of shale. Colorado oil is particularly high in nitrogen, with 1.6–2.0%, while a sample of Tennessee oil had 0.88% N, and ten foreign commercial samples had 0.11–0.90% (1063). The temperature of retorting is also significant, an increase giving a higher proportion of aromatics and a higher nitrogen content. Thus, at a retort temperature of 1500°F. Colorado oil was almost completely aromatic, and contained 3.1% nitrogen (544,1063).

Of the nitrogen in the shale (Colorado) about 50% remains in the spent shale, 28–36% goes into the oil, and 9.5–13% into the gas; with high-temperature retorting (rapid initial heating) a larger proportion appears in the oil (806). Most of the nitrogen is evolved as ammonia, the remainder as pyridine bases (principally), quinolines (1711,799), isoquinolines (799), pyrroles (504), benzonitrile and its homologs (504), and possibly other *N*-heterocycles (826).

The pyridine bases are found in the naphtha. The oil fraction boiling up to 200, or 300°C., or occasionally the whole crude, is treated for recovery of the bases, which are then repeatedly distilled to narrow fractions. Individual members are precipitated as mercuric chloride salts or picrates, with recrystallization where necessary. The bases are identified through derivatives and by oxidation to the pyridinecarboxylic acids. About twenty pyridine homologs have been identified in various oils, and are listed in Table II-9.

The earliest investigation of this kind was by Williams in 1854 who found several of the lower homologs; however, their purity and isomerism were then not known (803). Oils from various sources furnish similar bases, which may include pyridine in traces, picolines, lutidines, collidines, tetramethylpyridines, and ethylpico-

lines. A search of particular thoroughness was made on Colorado shale oil (200°C. cut) (504) and involved separation of the bases into ninety fractions by distillation, a rigorous identification of the components, and an estimation of their amounts from the distillation curve. Of the sixteen pyridines identified, *s*-collidine was the most abundant. Similar large numbers of pyridines were found in Scottish (1530) and Manchurian shale oil (1514,1344-1346), including in the latter case the uncommon 6,7-dihydro-5*H*-1-pyridine (1346), whose structure was later confirmed by synthesis (1221).

TABLE II-9. Pyridines Identified in Shale Oil

	Colorado shale		Scotland shale (refs. 1530, 1600, 1601)	Manchurian shale (refs. 1514, 1344-1346)	Russian shale (ref. 1075)
	Vol. % in naphtha ^a (ref. 504)	1500° F. retorting (ref. 544)			
Pyridine	Trace		X		X
2-Picoline	0.005 ^b	X	X	X	X
3-Picoline	0.01	X	X	X	X
4-Picoline	0.01	X	X	X	
2,3-Lutidine	0.02		X	X	
2,4-Lutidine	0.03	X	X	X	X
2,5-Lutidine			X	X	X
2,6-Lutidine	0.01		X	X	X
3,4-Lutidine	0.04		X	X	
3,5-Lutidine			X	X	
2,3,5-Colli- dine	0.16		X	X	
2,3,6-Colli- dine	0.04			X	
2,4,5-Colli- dine			X	X	
<i>s</i> -Collidine	0.71 ^b	X	X	X	
2,3,4,5-Tetra- methylpyridine				X	
2,3,4,6-Tetra- methylpyridine	0.08		X	X	
2,3,5,6-Tetra- methylpyridine			X		

TABLE II-9 (Continued)

	Colorado shale		Scotland shale (refs. 1530, 1600, 1601)	Manchurian shale (refs. 1514, 1344-1346)	Russian shale (ref. 1075)
	Vol. % in naphtha ^a (ref. 504)	1500° F. retorting (ref. 544)			
2-Ethylpyridine				X	
4-Ethyl-2-picoline	0.04		X	X	
5-Ethyl-2-picoline	X ^c				
6-Ethyl-2-picoline			X	X	
2-Ethyl-4-picoline	0.02				
6-Ethyl-2,3-lutidine				X?	
6-Ethyl-2,4-lutidine	0.45				
4-Ethyl-2,6-lutidine	0.17			X	
6,7-Dihydro-5H-1-pyridine				X	

^aPer cent base by volume in the shale oil fraction (200° C. cut).

^bIndicated or identified also in references 806, 1711, or 1842.

^cNot rigorously proved (1842).

4. Other Fuel Deposits

Lignite may be considered the lowest rank of coal, or an intermediate stage in the conversion of peat to coal by natural processes under heat and pressure. Of the 1.3 trillion metric tons probable reserve in the world, about 0.9 trillion are in the United States. The controlled high-pressure hydrogenation of lignite gave an oil from which pyridine bases were recovered (1586). These were obtained from the total oil by extraction with dilute sulfuric acid, fractional distillation of the bases and precipitation of the picrates. The following were identified: pyridine, the three picolines, all the lutidines but the 3,4, *s*-collidine, probably 2,4,5-collidine, 3-ethylpyridine, 4-ethylpyridine, 6-ethyl-2-picoline, 3-ethyl-4-picoline, 6,7-

dihydro-5*H*-1-pyridine (identified with a synthetic sample), and 5,6,7,8-tetrahydroquinoline. In addition quinoline, isoquinoline, and quinaldine were found.

The accumulation of plant debris at the bottom of lakes gives a mud, or sapropel, which is probably the precursor of oil shale (823). Pyrolysis of sapropel yields a tar which may be distilled, and the fractions boiling below 270°C. contain 8–9% pyridine bases (Latvian origin, 559). The bases from one source (U.S.S.R.) have been identified as follows: 3-picoline, 2,4-lutidine, 2,6-lutidine, *s*-collidine, 3-ethylpyridine, 4-ethyl-2-picoline, 6-ethyl-2-picoline, 3-ethyl-4-picoline, 2,4-diethylpyridine, and 2-butylpyridine (434).

Gilsonite is a form of natural asphalt (an asphaltite) which is essentially hydrocarbon in nature. It appears to be confined to one large deposit in Utah and Colorado. Pyrolysis of gilsonite from the Bonanza vein yields 55% oil, with a total estimated reserve of 110 million barrels. The commercial exploitation of this vein for gasoline, coke, and fuel gas has recently been started (1845). The oil fraction boiling between 60 and 150°C has been treated for recovery of the pyridines. Pyrroles and phenols were first removed by treatment with potassium metal, and the pyridine bases extracted with dilute phosphoric acid. Chromatographic separation then gave 4-picoline, 2,5-, 2,6-, 3,4-, and 3,5-lutidines, and 2,3,5-collidine (1230).

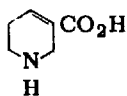
5. Alkaloids

The degradation of alkaloids containing hydropyridine or fused pyridine rings has sometimes yielded pyridine products, usually under drastic conditions and in very low yield. Such degradations have aided in the elucidation of alkaloid structures, and are treated more fully in reviews on alkaloids (1838). A number of examples are collected in Table II-10.

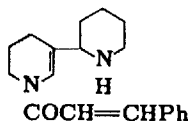
Either the alkaloid or an intermediate degradation product is converted to a pyridine by techniques such as the following: distillation with caustic potash, lime, soda-lime or barium hydroxide; distillation of the base or its hydrochloride with zinc dust; dehydrogenation at high temperature by means of a platinum or palladium catalyst, Raney nickel, silver acetate suspension, mercuric acetate,

mercuric chloride, selenium, or sulfur; oxidation by nitric acid or permanganate.

Piperidine and tetrahydropyridine alkaloids are dehydrogenated to pyridines. Thus coniine (2-propylpiperidine) gives 2-propylpyridine by various methods. The side-chain of pimidine (6-propenyl-2-pipecoline) becomes saturated, with palladium, and 6-propyl-2-picoline is formed (831). Zinc dust distillation of guvacine (II-13)

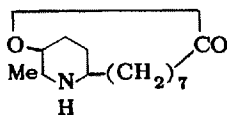


(II-13)



(II-14)

reduces the carboxyl group, to yield 3-picoline (956), and the isomeric baikiaine yields 2-picoline (495). Adenocarpine (II-14) (teidine, orensine, 1076,1078) is dehydrogenated with palladium to 2,3'-bipyridine (513). The analogous alkaloid, ammodendrine (II-14, acetyl for cinnamoyl) (1077) was first converted to 2,3'-bipiperidine, which was dehydrogenated by means of silver acetate (962). The alkaloid carpaine (II-15) (955) on palladium treatment undergoes hydrogenolysis of the lactone in forming II-16 (1561). But

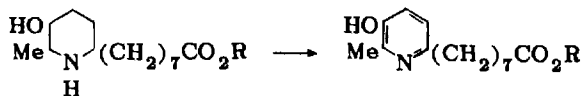


(II-15)



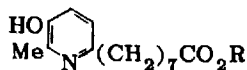
(II-16)

when the lactone ring is first opened, giving carpamic acid or ester (II-17), the product of dehydrogenation is carpyrinic acid or ester (II-18) (1578,1174).



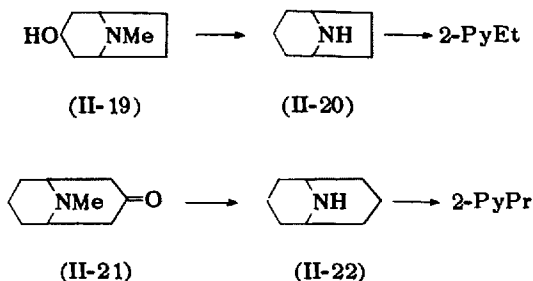
(II-17)

R = H, Et

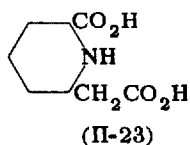


(II-18)

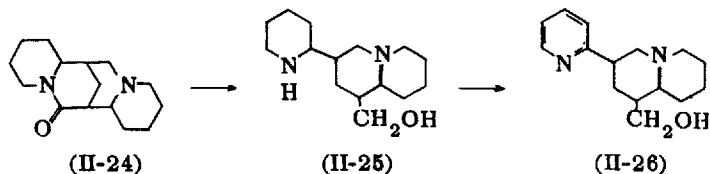
Alkaloids which contain a fused piperidine ring may be degraded with rupture of other rings. Thus tropine (II-19) is converted to 2-ethylpyridine through distillation of nortropine (II-20) hydrochloride with zinc (128). Similarly pseudopelletierine (II-21) going through granatane (II-22) gives 2-propylpyridine (957).



More commonly the polycyclic alkaloid is cleaved in preliminary steps to give a piperidine, which is then dehydrogenated. Thus pseudopelletierine (II-21) in an oxidative sequence was converted to granatic acid (II-23), which by dehydrogenation with mercuric

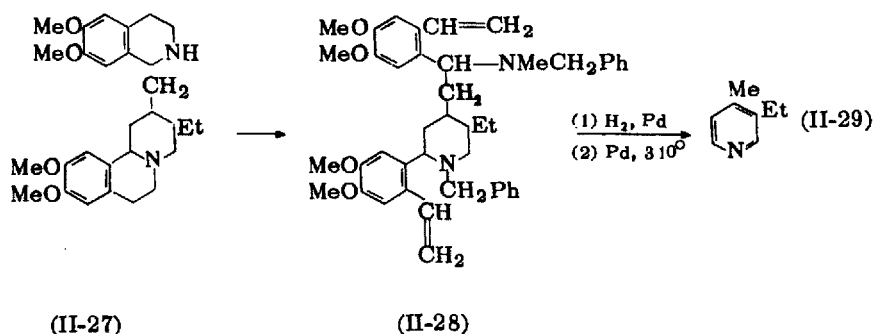


acetate and decarboxylation gave 2-picoline (958). In another instance, aphylline (II-24) was opened by hydrolytic or reductive means to a piperidinyquinolizine (II-25) which was dehydrogenated by palladium (II-26) (558).

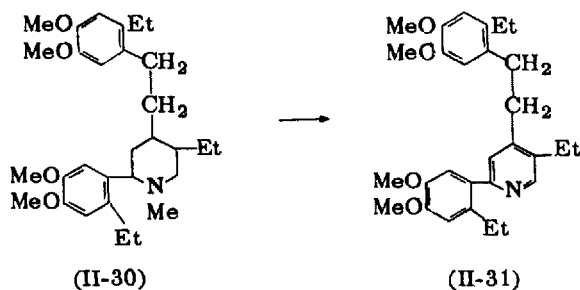


A Hofmann degradation was used to cleave two rings of emetine (II-27), performed on *N*-methylemetine dibenzyl iodide. The re-

sultant piperidine compound (II-28) was converted to 3-ethyl-4-picoline (II-29) (570). Alternatively, emetine was converted to the

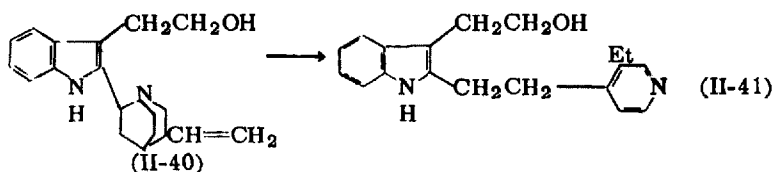


intermediate II-30; in this case dehydrogenation by palladium or silver acetate occurred with little loss of carbon, giving II-31 (1454, 990).

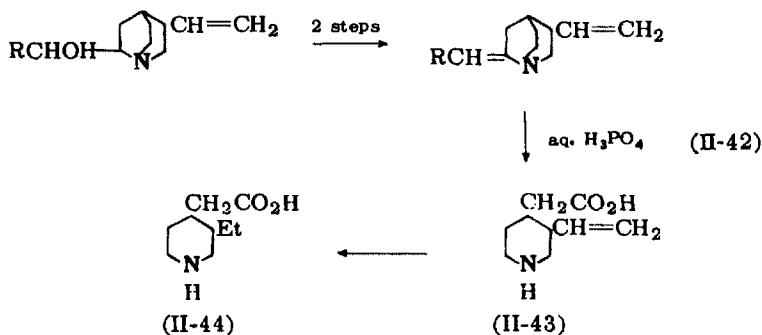


Cytisine (II-32) also was opened by Hofmann degradation¹, in either of two routes. In one case cytisine itself underwent two such degradations, with reduction of the unsaturates formed at each step. This eliminated the secondary amino nitrogen, and produced tetrahydrohemicytisylene (II-33), leading to II-34, either of which could be dehydrogenated to 2-propyl-3,5-lutidine (987). On the other hand the angular nitrogen could be eliminated by reduction and acetylation of cytisine prior to the Hofmann degradation (II-35); the resulting piperidine compound (II-36) was converted to 5-amyl-3-picoline (1215).

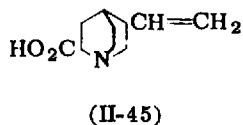
treated (494). The distillation of cinchonine with caustic potash gave other pyridine bases, namely 3-ethylpyridine and 3-ethyl-4-picoline (92,131,132). In the case of cinchonamine (II-40) the quinuclidine residue is cleaved, by palladium or selenium catalyst, with retention of all the carbon atoms (II-41) (154).

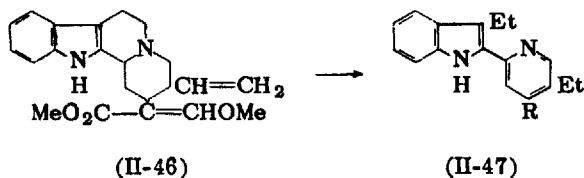


The quinuclidine ring has also been opened hydrolytically before effecting aromatization (II-42). The piperidine intermediate meroquinene (II-43) was dehydrogenated to 3-ethyl-4-picoline by heating with mercuric chloride (132,133) or to 3-ethylpyridine in a lime-zinc distillation (980), while cincholoipon (II-44) gave 3-ethylpyridine on distillation of its hydrochloride with zinc (979).

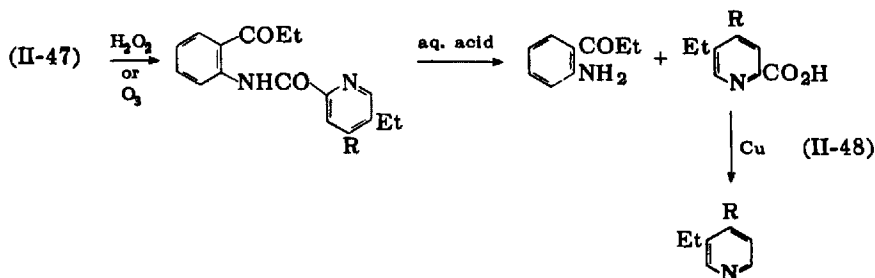


The quinuclidine nucleus was retained intact in the oxidation of quinamine with chromic acid, and the product (II-45) further degraded to vinylpyridine by a soda-lime distillation, or to 3-ethylpyridine with mercuric chloride (971).

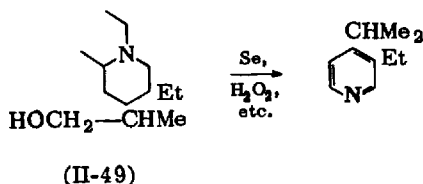




The selenium dehydrogenation of some indole alkaloids has been a valuable diagnostic of their structures. This technique often gives recognizable pyridine products with little or no loss of carbon content. Thus corynantheine (II-46) has given alstyrene (II-47, R = Et) and desethylalstyrene (R = H). The structure of each was proved by further degradation, as in II-48 (521,746,1438,498); desethyl-

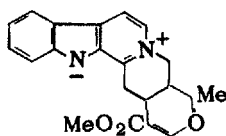


alstyrene has also been synthesized (724). The same degradative sequence applied to II-49 (an intermediate from dihydrocorynantheine) gave besides 3,4-diethylpyridine a lesser amount of 4-*i*-propyl-3-ethylpyridine (521,1546).

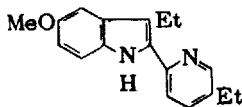


The formation of alstyrene is characteristic not only of corynantheine and its derivatives (746,765,1500), but also of alstonine (II-50), (731,725), its stereoisomers, and its hydro derivatives (726-732).

Similarly, aricine (cinchovatine) gives methoxydesethylalstyrine (II-51), (734), further degraded as in II-48 (654).

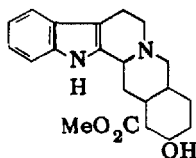


(II-50)

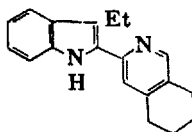


(II-51)

In a similar manner yohimbine (II-52) gives tetrabyrine (also called tetrahydroyobyryne and tetrahydroisoyobyryne) (II-53) among

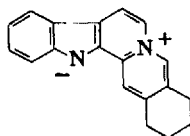


(II-52)



(II-53)

products of selenium dehydrogenation (852,853,1804). This is also obtained from yohimbine stereoisomers, (853,968), and from sempervirine (II-54) on treatment with Raney nickel (969,986). The

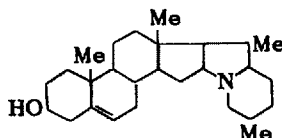


(II-54)

structure of tetrabyrine (II-53) was proved by oxidation to 2,4,5-pyridinetricarboxylic acid (1804) and by degradation in the manner of alstyrine (II-48) obtaining as the final products 2-aminopropiophenone and 5,6,7,8-tetrahydroquinaldinic acid (809).

The highly condensed alkaloids strychnine and brucine have been degraded by distillation with caustic potash (964,965), calcium oxide, or soda-lime (963), to give simple pyridine bases, namely, 3-picoline, 3-ethylpyridine, 4-ethylpyridine, and 3-ethyl-4-picoline. Similarly, aspidospermine is converted to 3,5-diethylpyridine by distillation of its desacetyl hydrochloride with zinc dust (1087).

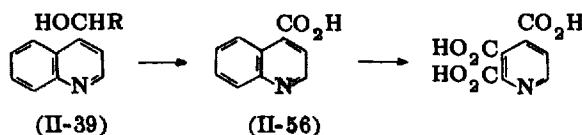
Selenium dehydrogenation of the solanum and veratrum alkaloids, exemplified by solanidine (II-55), gives simple pyridine deriva-



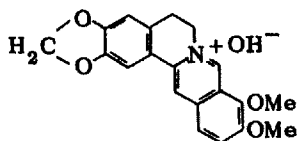
(II-55)

tives, most commonly 6-ethyl-3-picoline (989,1256). Other bases which have been obtained are pyridine (985), 2,5-lutidine (998), 3-picoline (999,1057-1059), 5-methyl-3-pyridinol (779,499) and, presumably, 2-ethyl-5-methyl-3-pyridinol (786,779) and 5-methyl-2-pyridinemethanol (1058).

Oxidative degradation of alkaloids to pyridine acids has also been practiced. Decarboxylation of a pyridine polycarboxylic acid may occur at the same time. Cinchonine (II-39) was early oxidized to 2,3,4-pyridinetricarboxylic, cinchomeric, or quinolinic acid by vigorous treatment with nitric acid, (147,181), or permanganate (151,157). Alternatively it was oxidized in stages, first to cinchoninic acid (II-56) by means of nitric or chromic acid, and this further to the pyridinetricarboxylic acid with permanganate (184-186,975,976). Similar transformations were effected with quinine.

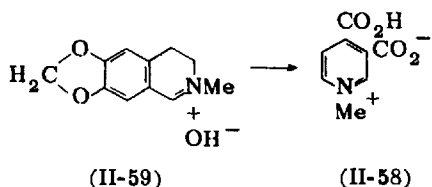


Isoquinoline alkaloids have likewise been oxidized. Berberine (II-57) gave 2,4,5-pyridinetricarboxylic acid (berberonic acid) with

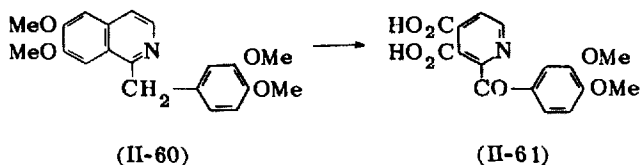


(II-57)

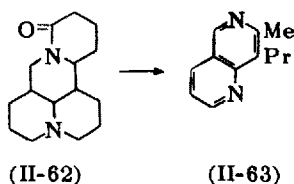
nitric acid (190,191). The alkaloid narcotine was converted to apophyllenic acid (II-58) as a minor product of oxidation by Wöhler in 1844 (993). More satisfactorily, narcotine was first degraded to cotarnine (II-59) by hydrolytic or oxidative cleavage, and this was



oxidized to apophyllenic acid using nitric acid (992,166). The oxidation of papaverine (II-60) with permanganate stopped at papaverinic acid (II-61) (991).



By a series of ring-openings, matrine (II-62) was converted to a naphthyridine (II-63), which was oxidized to quinolinic acid (998).



Harmine (II-64) with chromic acid gave harminic acid (II-65), which was further oxidized to isonicotinic acid by means of nitric acid at 200° (966,967).

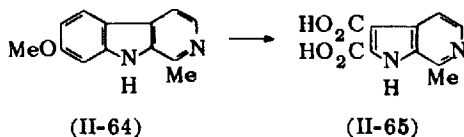


TABLE II-10. Degradation of Alkaloids to Pyridines

Alkaloid	Plant Source	Intermediate Degradation Product	Conversion to Pyridine	Pyridine Product	Ref.
PIPERIDINES AND TETRAHYDROPYRIDINES					
l-2,6-Dimethyl-piperidine Coniine	<i>Nanophyton erinaceum</i>		AgOAc, aq. AcOH, 18°	2,6-Lutidine	480
	<i>Conium maculatum</i>		Pd-C, 167°	2-PyPr	494
			Zn distn.	2-PyPr	100
			HCl salt, Zn distn.	2-PyPr	130,961
Pimidine	<i>Pinus sabiniana</i>		AgOAc, heat	2-PyPr	959
			Pd-C, 400-500°	6-Propyl-2-picoline	831
Ammodendrine	<i>Ammodendron conollyi</i>	2,3'-Bipiperidine	AgOAc, aq. AcOH, 180°	2,3'-Bipyridine	962,1077
Adenocarpine (teidine)	<i>Adenocarpus species</i>		Pd-C, 350°	2,3'-Bipyridine	513,1076, 1078
Conhydrine	<i>Conium maculatum</i>		Pd or Pt, then N ₂ O ₃	2-PyCOEt, 2-PyCHOHEt	960
Isopelletierine	<i>Punica granatum</i>		Pt, then N ₂ O ₃	2-PyCOEt	960
		Dihydroisopelletierine	Pd, then N ₂ O ₃	2-PyMe, 2-PyPr	960
Carpaine	<i>Carica papaya</i>		Pd-C, <i>p</i> -cymene reflux	8-(6-Methyl-2-pyridyl)-octanoic acid	1561
		Ethyl carpamate	Pd-C, <i>p</i> -cymene reflux	Ethyl carpynate ^a	1578,955

Pseudocarpaine	<i>Carica papaya</i>	Carpamic acid	Pd-C, <i>p</i> -cymene reflux	Carpynic acid ^a	1174
			Pd-C, <i>p</i> -cymene reflux	8-(6-Methyl-2-pyridyl)-octanoic acid	994
		Ethyl pseudo-carpamate	Pd-C, <i>p</i> -cymene reflux	Ethyl carpyrinat ^a	994
γ -Coniceine	<i>Conium maculatum</i>		HCl, salt, Zn dism.	2-PyPr	961
Baikiaine	<i>Baikiaea plurijuga</i>		Zn distn.	2-PyMe	495
Guvacine	<i>Areca catechu</i>		Zn distn.	3-PyMe	956
TROPANE AND POMEGRANATE ALKALOIDS					
Tropine	<i>Atropa belladonna</i>	Nortropine	HCl salt, Zn dism.	2-PyEt	128
Cocaine	<i>Erythroxylon</i> species	Ecgonine	CaO-Zn distn.	2-PyEt	129
Pseudopelletierine	<i>Punica granatum</i>	Granatanine	HCl salt, Zn dism.	2-PyPr	957
		Granatoline	HCl salt, Zn dism.	Pyridine	957
		Granatic acid	Hg(OAc) ₂ 160°, then Ba(OH) ₂ dism.	2-PyMe	958

(continued)

TABLE II-10 (Continued)
Degradation of Alkaloids to Pyridine

Alkaloid	Plant Source	Intermediate Degradation Product	Conversion to Pyridine	Pyridine Product	Ref.
QUINOLINES AND CINCHONA ALKALOIDS					
Cusparine	<i>Galipea officinalis</i>		Zn distn.	Pyridine	981
Cinchonine	<i>Cinchona, Remijia</i> species		Pd-C, 310°	4-Ethyl-3-picoline, 3,4-diethylpyridine	494
			KOH distn.	3-PyEt, 3-ethyl-4-picoline	92,131, 132,973
			HNO ₃	Cinchomeronic, quinolinic, 2,3,4-pyridinetricarboxylic acids	147,181
			KMnO ₄	2,3,4-Pyridinetricarboxylic acid	151,157
			H ₂ , Ni, 200°, 25 atm.	A Bz-tetrahydroquinoline	882
		Cinchoninic acid	KMnO ₄	2,3,4-Pyridinetricarboxylic acid	184,185, 186,975, 976
		Meroquinene	HgCl ₂ , aq. HCl, 240°	3-Ethyl-4-picoline	132,133
			CaO-Zn distn.	3-PyEt	980

Cinchonidine	Cinchona, <i>Remijia</i> species	Cincholoipon	HCl salt, Zn distn. Pd-C, 310° HNO ₃ KMnO ₄ Pd-C, 310° HNO ₃ KMnO ₄	3-PyEt 4-Ethyl-3-picoline, 3,4-diethylpyridine Cinchomeronic, quinolinic acids 2,3,4-Pyridinetri- carboxylic acid 4-Ethyl-3-picoline, 3,4-diethylpyridine Cinchomeronic acid 2,3,4-Pyridinetri- carboxylic acid 2,3,4-Pyridinetri- carboxylic acid 3-PyEt 4-Ethyl-3-picoline, 3,4-diethylpyridine 2,3,4-Pyridinetri- carboxylic acid 2,3,4-Pyridinetri- carboxylic acid	979 494 147 151 494 147, 148, 149, 150 151 187, 977, 978 980 494 151 187, 977, 978
Quinine	Cinchona, <i>Remijia</i> species	Quininic acid Meroquinene	KMnO ₄ CaO-Zn distn. Pd-C, 310° KMnO ₄ KMnO ₄		
Quinidine	Cinchona, <i>Remijia</i> species	Quininic acid	KMnO ₄		
Papaverine	<i>Papaver somniferum</i>	ISOQUINOLINE ALKALOIDS			
		Quininic acid	KMnO ₄	2-Veratroylcin- chomeronic acid	991

(continued)

TABLE II-10 (Continued)
Degradation of Alkaloids to Pyridine

Alkaloid	Plant Source	Intermediate Degradation Product	Conversion to Pyridine	Pyridine Product	Ref.
Narcotine	<i>Papaver somniferum</i>		MnO ₂ , H ₂ SO ₄	Apophyllenic acid (cinchomeronic N-methyl betaine)	993
Berberine	Wide distribution	Cotarnine	HNO ₃ HNO ₃	Apophyllenic acid 2,4,5-Pyridinetricarboxylic acid	992, 166 190, 191
LUPIN ALKALOIDS					
Lupinine	<i>Anabasis aphylla</i> , <i>Lupinus</i> species	2-Butyl-3-pipecoline	AgOAc, aq. HOAc, 180°	2-Butyl-3-picoline	1325, 982
Cytisine	Wide distribution	5-Amyl-3-pipecoline	Soda-lime distn. Pd, 190°	C ₉ Pyridine 5-Amyl-3-picoline	983 1215
Lupanine	<i>Lupinus</i> , <i>Cytisus</i> species	Tetrahydrohemicytisylen	Pd, 280°	2-Propyl-3,5-lutidine	987
Matrine	<i>Sophora</i> species	7-Methyl-8-propyl-1,6-naphthyridine	Zn distn.	2-PyEt	984
Aphylline, aphyllidine	<i>Anabasis aphylla</i>	Piperidinyl quinoline deriv. ^b	KMnO ₄ Pd, 190°	Quinolinic acid Pyridylquinoline deriv. ^b	988 558

IPECAC ALKALOIDS

Emetine	<i>P. sycoctria</i> species	Piperidine derivs. ^c Pd, 310° Piperidine derivs. ^d Pd-C, 270°	3-Ethyl-4-picoline 2-Aryl-4-β-aryl- ethyl-5-ethyl- pyridine ^d 2-Aryl-4-β-aryl- ethyl-5-ethyl- pyridine ^e	570 1454,990 1454,990

AgOAc, aq., 180°;
then heat dry

INDOLE ALKALOIDS

Alstonine	<i>Alstonia con-</i> <i>stricta</i>	Se, heat	Alstyrine ^e	731,725
Serpentine	<i>Rauwolfia</i> <i>serpentina</i>	Se, heat	Alstyrine	726
Serpentinine	<i>Rauwolfia</i> <i>serpentina</i>	Se, heat	Alstyrine	728
Mayumbine	<i>Pseudocinchona</i> <i>mayumbensis</i>	Se, heat	Alstyrine	729
δ-Yohimbine	<i>Pausinystalia</i> , <i>Corynanthe</i> species	Se, heat	Alstyrine	730
Akuammigine	<i>Picalima nitida</i>	Se, heat	Alstyrine	732
Corynantheine	<i>Pseudocinchona</i> <i>africana</i>	Se, 300°	Alstyrine, desethyl- alstyrine ^f	746,765, 1500,724, 812,1438, 725,498

(continued)

TABLE II-10 (Continued)
Degradation of Alkaloids to Pyridines

Alkaloid	Plant Source	Intermediate Degradation Product	Conversion to Pyridine	Pyridine Product	Ref.
Corynantheine (cont.)		Decarboxycorynantheine, corynantheal, d-corynantheic acid, corynantheane	Se, 300°	Alstyrine	746,765, 1500
		Corynantheane, dihydrocorynantheane	Pd-C, 290°	Alstyrine	746
Corynantheidine	<i>Pseudocinchona africana</i>		Se, 300°	Alstyrine	812
Dihydrocorynantheine	<i>Pausinystalia yohimba</i>	Tetrahydro-desmethoxycorynantheine alcohol	Se, 300°	Alstyrine and homolog ^g	521,1546
Aricine (cinchovatine)	<i>Cinchona pelletieriana</i>		Se, 300°	Methoxydesethylalstyrine ^b	654,734
Yohimbine	<i>Pausinystalia yohimba</i> and elsewhere		Se, 300°	Tetrabyrine ⁱ	1804,852, 853,809
Isoyohimbine	<i>Pausinystalia yohimba</i>		Se, heat	Tetrabyrine	853

Corynanthidine	<i>Pseudocinchona africana</i>	Se, heat	Tetrabyrine	968
Sempervitine	<i>Gelsemium sempervirens</i>	Raney Ni, boiling xylene	Tetrabyrine	969,986
Geissospermine	<i>Geissospermum vellosii</i>	Zn distn.	3-PyEt	970
Aspidospermine	<i>Aspidosperma quebracho</i> , <i>Vallesia glabra</i>	HCl salt, Zn distn.	3,5-Diethylpyridine	1087
Cinchonamine	<i>Cinchona</i> species	Desacetyl- aspidospermine		
Quinamine	<i>Cinchona</i> species	Se, 300°, or Pd-C, 240°	Dehydrocinchon- amine ^j	154
		3-Vinylquinclidine-Na salt, soda lime	3-Vinylpyridine	971
		6-carboxylic acid		
Harmane, harmaline	<i>Peganum harmala</i>	HgCl ₂ , HCl	3-PyEt	971
Strychnine	<i>Strychnos</i> species	HNO ₃ , 200°	Isonicotinic acid	966,967
		CaO distn.	3-PyMe, 3-PyEt	124,125, 126
		Soda lime distn.	3-PyMe	963
		KOH distn.	3-Ethyl-4-picoline	964,965
Brucine	<i>Strychnos</i> species	CaO distn.	3-PyMe, 3-PyEt	92,127
		KOH distn.	3-PyEt, 3-ethyl- 4-picoline, 4-PyEt	974
Melinonine-A	<i>Strychnos melinoniana</i>	Se, heat	Alstryne ^e	727

(continued)

TABLE II-10 (Continued)
Degradation of Alkaloids to Pyridines

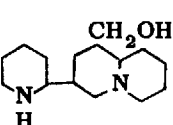
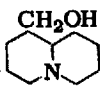
Alkaloid	Plant Source	Intermediate Degradation Product	Conversion to Pyridine	Pyridine Product	Ref.
SOLANUM AND VERATRUM ALKALOIDS					
Solanidine	<i>Solanum tuberosum</i>		Se, 320-40°	Pyridine	985
Solanocapsine	<i>Solanum pseudo-capsicum</i>		Se, 320°	6-Ethyl-3-picoline	989,1256
				6-Ethyl-3-picoline	1548,1547
Veratramine	<i>Veratrum viride</i> , <i>V. grandiflorum</i>		Se, 335°	5-Methyl-3-pyridinol	779,499
Jervine	<i>Veratrum</i> species		Se, 340°	6-Ethyl-3-picoline, 2-ethyl-5-methyl-3-pyridinol	786,779
				2,5-Lutidine, 6-ethyl-3-picoline	998
Protoveratrine	<i>V. album</i>		Se, 340°	6-Ethyl-3-picoline	1000
Rubijervine	<i>V. album</i>		Se, 340°	6-Ethyl-3-picoline	1030
Isorubijervine	<i>V. viride</i> , <i>V. album</i>		Se, 340°	6-Ethyl-3-picoline	999
Cevadine	<i>V. sabadilla</i>		Dry distn. or CaO distn.	3-PyMe	818,817
Cevadine, veratrine, veratridine	<i>V. sabadilla</i>	Cevine	Zn distn.	6-Ethyl-3-picoline	1057
			Se, 320°	3-PyMe, 6-ethyl-3-picoline	

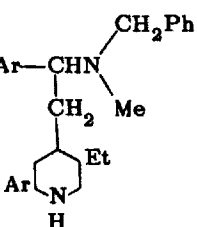
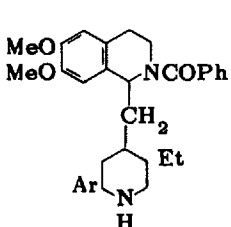
Protoveratridine, germerine, etc.	<i>Veratrum</i> species	Germin	Se, 345°	Same, and 5-methyl- 2-pyridine methanol 3-PyMe, 6-ethyl- 3-picoline	1058 1059
MISCELLANEOUS					
α-Longilobine	<i>Senecio longilobus</i>	α-Methyl-α'-ethyl- glutaric acid	Acid chloride, urea, fuse Pd, 290-310°	α-Methyl-α'-ethyl- glutarimide 3-Ethyl-4-picoline, 3-PyEt, 3,4- diethylpyridine	576 485, 528
Uncarine-A	<i>Uncaria</i> species		Soda lime dism.	3-Ethyl-2-picoline, 4-PyEt	1466
α-Obscurine	<i>Lycopodium</i> species		Pd-C, 290°	6-Methyl-2- pyridinol	568
Curarine I	Calabash curare, <i>Strychnos toxifera</i>	Norcurarine I	Zn distn.	3-PyEt	493
Toxiferine I	Calabash curare, <i>Strychnos toxifera</i>		Zn distn.	3-PyEt	493
Toxiferine II	Calabash curare, <i>Strychnos toxifera</i>		S, 240°	3-PyEt	1718
Nupharidine	<i>Nupharis japonicum</i>	Dihydro, tetrahy- drodesoxy- nupharidine	Pd, heat	2,5-Disubstituted pyridine	487, 552

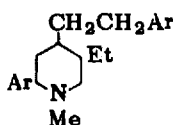
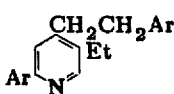
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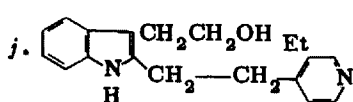
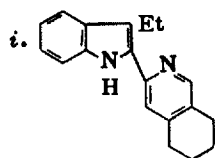
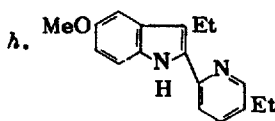
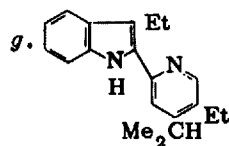
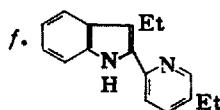
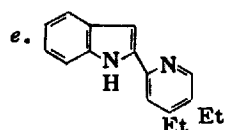
Notes to Table 10. Degradation of Alkaloids to Pyridines

a. Carpyrinic acid,  $(\text{CH}_2)_7\text{CO}_2\text{H}$

b. Intermediate is  ; product is 2-Py 

c.  or  (Ar = 2-ethyl-4,5-dimethoxyphenyl)

d. Intermediate is  ; product is  (see Note c)



6. Miscellaneous Natural Products

The pyrolysis of bones is practiced mainly for the manufacture of bone char (bone black, animal charcoal) (1847) for use in sugar refining. After removal of fat with boiling water or an organic solvent, the bone is retorted to yield 60–65% char, 20% fuel gas, 8% ammonia (as ammonium sulfate), 6% tar, and 3–5% oil. Most of the nitrogen appears in the tar, oil, and ammonia fractions.

Investigation of the bases in bone oil belongs to the earliest history of pyridine chemistry. Pyridine itself was here first discovered, and named, by Anderson in 1851 (788). He also isolated "picoline," "lutidine," and "collidine," (787–789), though their isomerism was not understood at the time. Later the lutidine fraction was shown to contain at least two isomers (2,5- and 2,4-) by oxidation to isocinchomeric and lutidinic acids, which were separated (168). An ethylpicoline was also found in the oil, perhaps equivalent to Anderson's "collidine," and was oxidized to lutidinic acid (1697). No further investigation of bone oil bases has since been reported. Recently the tar fraction has been examined, and, on distillation with steam, has yielded benzene and pyridine (1571).

It is evident that the pyridine nitrogen comes from the protein residue in the bone. However, protein materials alone do not give pyridines on pyrolysis, as shown for example for gelatin (1846) and silk (870). Presumably the residual bone fat, by way of acrolein, contributes to pyridine formation (1846). In a similar manner the condensate of casein with methylal (formed in aqueous acid) gave, on distillation with lime, pyridine, 2,6-lutidine, and isoquinolines; in the absence of methylal these bases were not formed (840,850). The analogous condensates of aminoacids with sugars were also pyrolyzed to pyridine bases (not characterized) (841,842).

The low temperature pyrolysis of cotton seed, in a medium of lubricating oil, gave a distillate yielding pyridine, the three picolines, 2,4-, 2,6-, and 3,5-lutidine, *s*-collidine, and 3-ethylpyridine (1802).

Soybean cake on dry distillation gave an oil containing 14.8% bases, including pyridine, 2-picoline, 2,4-lutidine, quinoline, and aniline (1464,482).

The distillation of sewage sludge produced an oil having 7.3% bases by volume, from which were isolated 5% pyridine, 18% "collidine," and 34% quinoline (1801).

The hydrolysis of algae by means of dilute sulfuric acid at 155–160° gave 3-pyridinol as one of the products (437).

PART II. PYRIDINES BY SYNTHETIC METHODS

A. FROM OTHER RING SYSTEMS

All preparations of pyridine compounds from cyclic materials are considered in this Section. Usually these involve the rearrangement of various ring compounds, such as pyrones, pyrans, pyrylium salts, furans, and pyrroles. However, we also consider the degradation of condensed pyridine compounds, such as quinolines and benzoquinolines, through oxidation (or reduction) of the benz rings. Finally, the dehydrogenation of hydropyridines is also included in this section. For convenience, the conversion of carbohydrates and furans to pyridines are considered together.

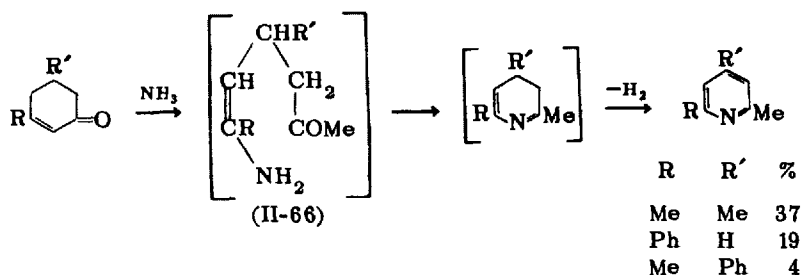
1. Carbocyclic Compounds

The preparation of pyridine derivatives from carbocyclic compounds is rarely of synthetic interest, for most of the products can be made in better yields by other methods.

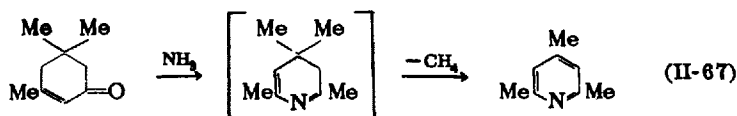
Cyclohexane Derivatives. Cyclohexanol, cyclohexanone, and cyclohexylamine react with excess ammonia and zinc chloride at 350° to produce 2-picoline, but cyclopentanone and cyclopentylamine do not give a pyridine product (1751). Since cyclohexylamine gave the best yield (40–50%), it may be an intermediate formed from the alcohol or ketone.

Cyclohexenones. Cyclohexenones produce pyridine derivatives in poor yields. It has been proposed that the reaction of these ketones with ammonia and ammonium chloride under pressure at 250° proceeds through a reverse aldol condensation to a ketone II-66 (1150). The isolation of 3-phenylcyclohexanol (3.8%) in the conversion of 3-phenyl-2-cyclohexenone to 6-phenyl-2-picoline suggests that some of the cyclohexenone is consumed in the oxidation

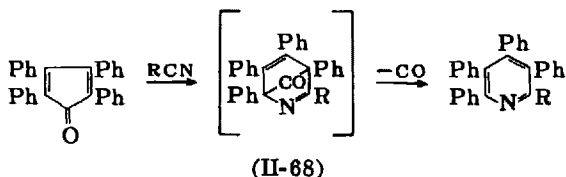
necessary for aromatization. In this respect, it is interesting that 2-methyl-5-*i*-propenyl-2-cyclohexenone (carvone) was converted in 6% yield to 2-ethyl-4-*i*-propenylpyridine, not to the *i*-propyl derivative (1150).



The reaction of ammonia and 3,5,5-trimethyl-2-cyclohexenone (isophorone) under pressure produced a 15% yield of *s*-collidine (probably as in II-67) along with other bases, but the reaction in the vapor phase produced only 3,5-dimethylaniline (377). Since isophorone may be considered an acetone condensation product, it is of interest to note that the vapor phase reaction of acetone and ammonia also produced *s*-collidine (p. 480).

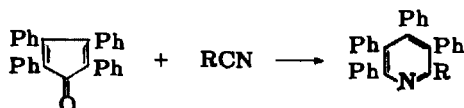


Tetraphenylcyclopentadienone. The condensation of tetraphenylcyclopentadienone and a phenyl or benzoyl cyanide produces a pyridine, often in good yield (Table II-11). This procedure, which offers uncommon products, apparently occurs by a Diels-Alder condensation to II-68, which gives a pyridine by elimination of carbon monoxide.



Benzene Derivatives. Benzene reacts with carbonyl azide, sulfonyl azide, carbazide, and hydrazoic acid to give low yields of pyridine and aniline. Toluene, *p*-xylene, and *p*-cymene give similar results (Table II-12).

TABLE II-11. Reactions of Tetraphenylcyclopentadienone with Nitriles



R	Conditions	Yield, %	Ref.
Ph	320–40°, 30–40 hrs.	74	1590
<i>p</i> -MeC ₆ H ₄	230–80°, 47 hrs.	60.5	1575
<i>p</i> -BrC ₆ H ₄	230°, 34 hrs.	86	1575
<i>m</i> -BrC ₆ H ₄	250–300°, 100 hrs.	52.3	1575
<i>p</i> -MeOC ₆ H ₄	250–70°, 36 hrs.	70.3	1575
COPh	250–70°, 13 hrs.	49.6	1575
	235°, 1 hr.	62	604
<i>p</i> -MeOC ₆ H ₄ CO	235°, 1 hr.	45	604

2. Furans

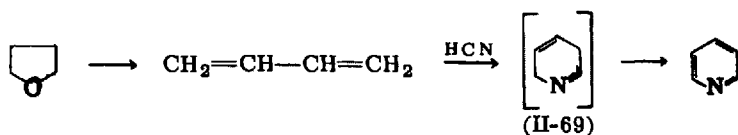
Furans and some of their dihydro and tetrahydro derivatives have been converted to pyridines by a variety of methods. Most often the furan derivative has a group in the 2 position to furnish the fifth carbon of the pyridine nucleus. The nitrogen for the pyridine ring may come from a 2-aminomethyl substituent, or by the addition of hydrogen cyanide, ammonia or its salts, or hydroxylamine. Liquid phase reactions are generally used, though reaction conditions vary widely with the nature of the furan.

Tetrahydrofurans. Tetrahydrofuran, which needs a fifth carbon to form pyridine, reacts with hydrogen cyanide in the vapor phase to produce pyridine and some β -vinylpropionitrile (378), though good yields are not reported. This reaction is similar to the 4-1 condensa-

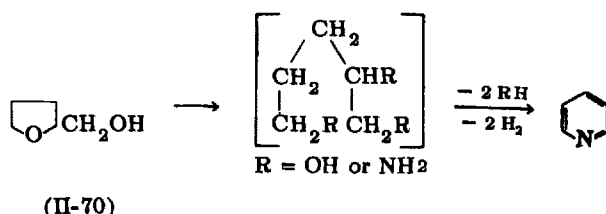
TABLE II-12. Reactions of Aromatic Hydrocarbons with Hydrazoic Acid Derivatives

Reactant	Conditions	Product	Ref.
Benzene	N_3CON_3 , heat, pressure; or	Pyridine	117-119,
	$\text{N}_3\text{SO}_2\text{N}_3$		1197,1198
	$(\text{NH}_2\text{NH})_2\text{CO}$, 150° , pressure	Pyridine, aniline	1193
Toluene	HN_3 , heat	Pyridine	1193
	N_3CON_3 , heat; or $(\text{NH}_2\text{NH})_2\text{CO}$, heat, pressure	4-Picoline	117-119,
		o-toluidine	1193,1198
<i>p</i> -Xylene	N_3CON_3 , 150° , pressure; or $(\text{NH}_2\text{NH})_2\text{CO}$	2,5-Lutidine	117-119,
		2,5-xylidine	1193,1198
<i>p</i> -Cymene	N_3CON_3 or $(\text{NH}_2\text{NH})_2\text{CO}$, pressure; $\text{N}_3\text{SO}_2\text{N}_3$, 180°	6- <i>i</i> -Propyl-	117,1193,
		3-picoline or	1197,1198
		5- <i>i</i> -propyl-2-picoline and 5- <i>i</i> -propyl-o-toluidine	

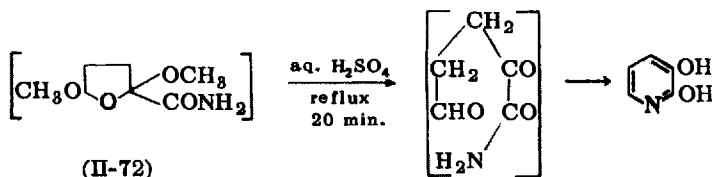
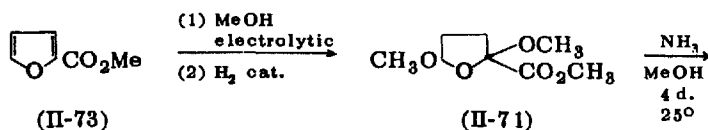
tion of butadiene and hydrogen cyanide (p. 346) which produces low yields of pyridine, and indeed, vapor phase dehydration of tetrahydrofuran does give butadiene. The vinylpropionitrile may be a by-product and not an intermediate, since the reaction of butadiene and hydrogen cyanide is probably a Diels-Alder condensation through II-69 which does not involve the shift of the cyanide hydrogen as does formation of vinylpropionitrile. 2,5-Dimethyltetrahydrofuran reacts with hydrogen cyanide to produce a lutidine (378).



2-Hydroxymethyltetrahydrofuran (II-70), which needs no additional carbon, combined with ammonia in the vapor phase at 500° over a reduced ammonium molybdate catalyst to give a 45% yield of pyridine (461). 2-Aminomethyltetrahydrofuran was also obtained, though whether this was a by-product or an intermediate in the formation of pyridine is not certain (663).

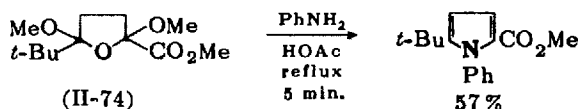


Treatment of 2-carbomethoxy-2,5-dimethoxytetrahydrofuran (II-71) with methanolic ammonia (which probably gave only the amide II-72) and then with hot, aqueous acid (which hydrolyzed the acetal and cyclized the open-chain intermediate) produced a 94% yield of 2,3-pyridinediol (595). The starting material can be made from methyl furoate (II-73) in 62% yield. This new method by Clauson-Kaas and co-workers, which has other variations in the dihydrofuran series, will probably find wider use shortly.



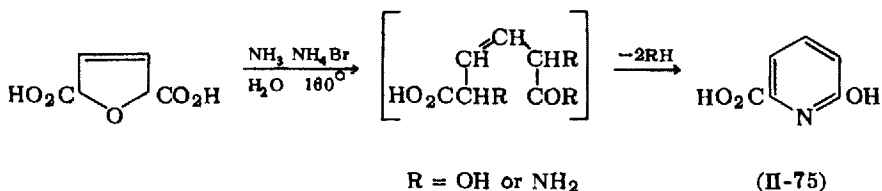
Aniline in acetic acid converted II-74, the 5-*t*-butyl derivative of II-71, to a pyrrole, not a pyridine (917). Apparently the ketals are hydrolyzed before any amide necessary for the formation of a pyri-

dinediol can be formed. The effect of aliphatic amines has not been reported.

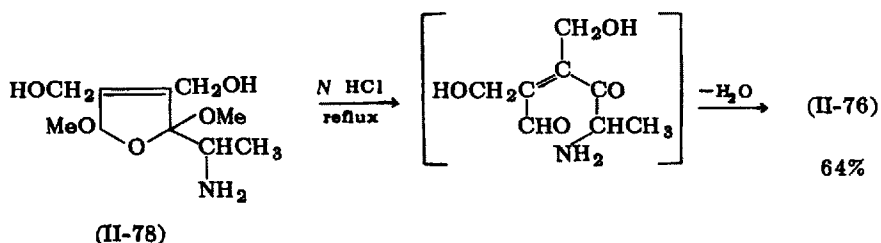
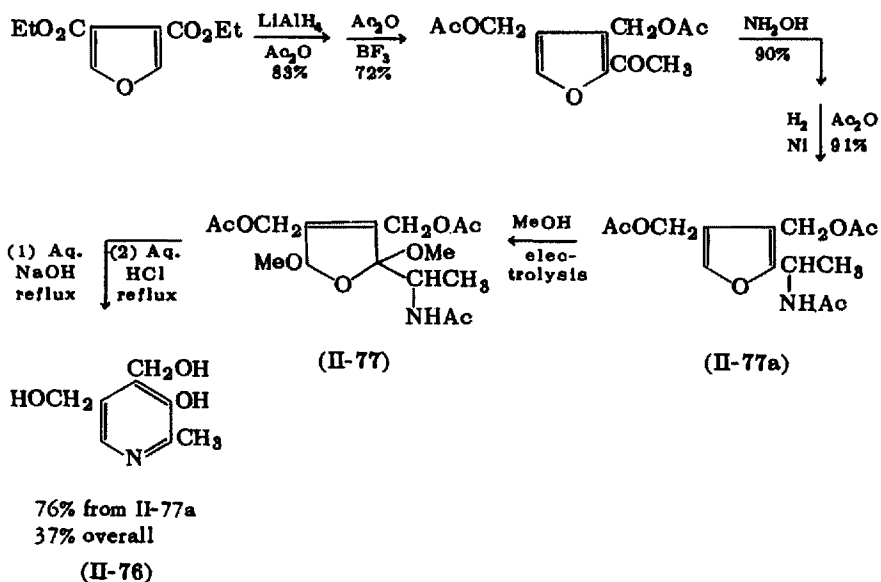


Dihydrofurans. Like tetrahydrofuran, dihydrofuran itself reacts with hydrogen cyanide in the vapor phase to give pyridine (378), but it is unlikely that high yields can be obtained. Perhaps vinylacetaldehyde or vinylacetylene is an intermediate.

Dihydrofurans which have a reactive group, such as carbonyl or aminomethyl, in the 2 position are of more general interest and can be used in the preparation of a variety of pyridinols (Tables II-14, 15). Thus the reaction of 2,5-dicarboxy-2,5-dihydrofuran with aqueous ammonia and ammonium bromide at 160° produced a 40% yield of 6-hydroxypicolinic acid (II-75) (245,446).

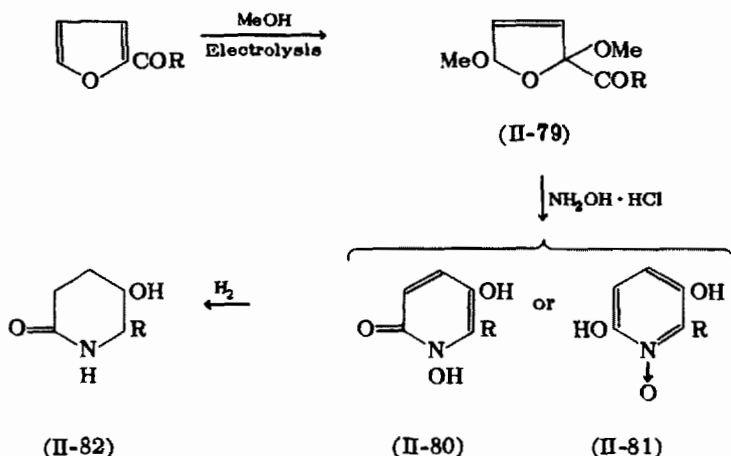


Clauson-Kaas and co-workers have introduced the use of substituted 2-aminomethyl-2,5-dimethoxy-2,5-dihydrofurans, which are readily hydrolyzed acetals, to form 3-pyridinols in good yields. This procedure, though not advantageous for the preparation of 3-pyridinol itself, is certainly one of the best available for the preparation of a less accessible 3-pyridinol such as pyridoxine (II-76), which can be obtained in this way from the ester of 3,4-furandicarboxylic acid (596). The key to the success of this method is the development of the electrolytic methoxylation of furans to give dimethoxydihydrofurans such as II-77. In the final step, the alkali treatment must be necessary only for the hydrolysis of the three acetyl groups, since II-78 was converted to pyridoxine by the action of normal hydrochloric acid (1820).

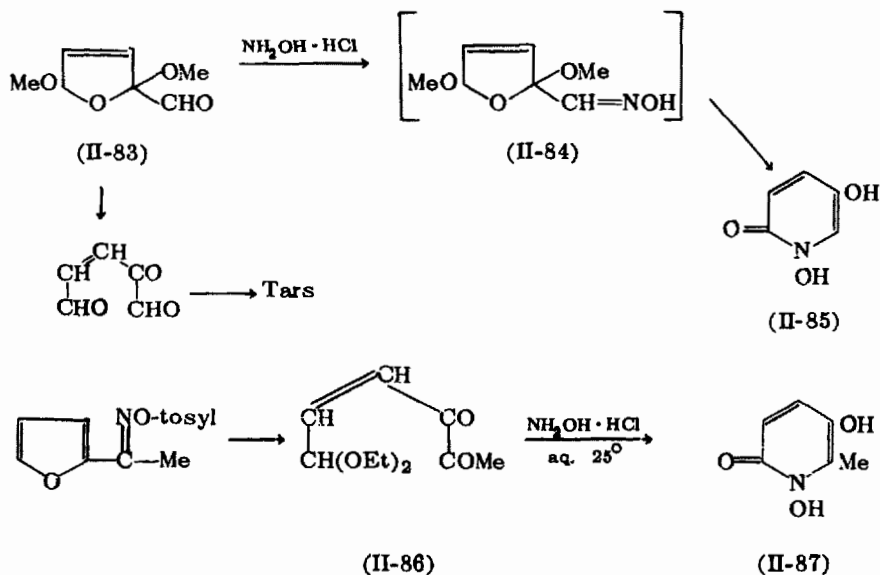


This interesting electrolytic methoxylation was also used by these chemists to convert 2-acylfurans to 2-acyl-2,5-dimethoxy-2,5-dihydrofurans. These ketones (II-79) upon standing with methanolic hydroxylamine hydrochloride, produced products which the authors thought were the *N*-hydroxypyridones II-80 (597,900) though the pyridinol oxide structures (II-81) were also considered possible (594). Other isomers were ruled out by hydrogenation of the product to the known II-82 (594,597).

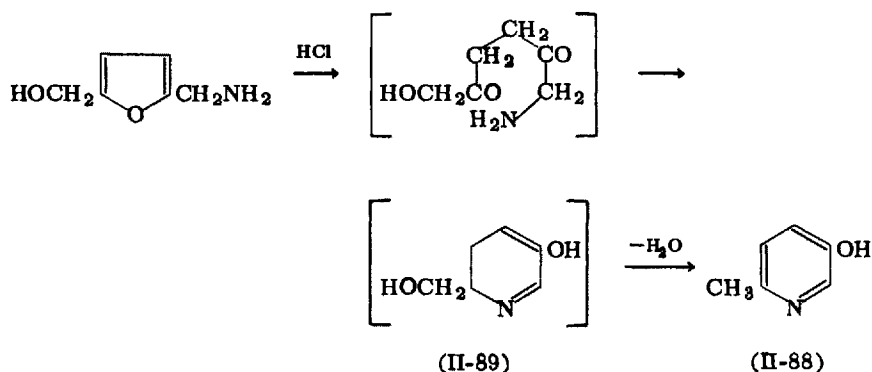
The methyl acetal of 2,5-dimethoxy-2,5-dihydrofurfural in its reaction with hydroxylamine hydrochloride gave tars, but the free



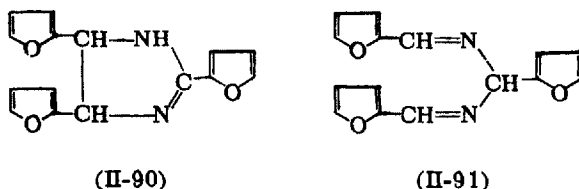
aldehyde II-83 gave II-85. It was proposed that the reaction proceeded through the intermediate II-84 (597). Apparently it is necessary to form the oxime before the dihydrofuran ring is opened by hydrolysis. The methyl ketone II-86 does react with hydroxylamine to give II-87 (594,598) but this molecule also has its aldehyde group protected as an acetal.



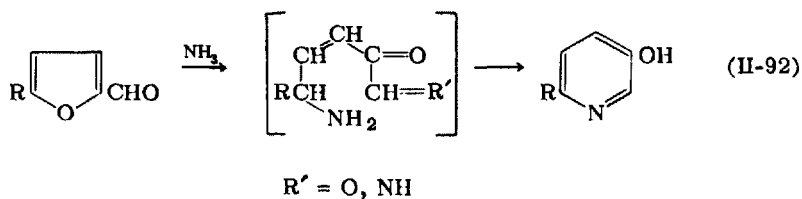
Furans. Furfuryl alcohol has not been reported to give a pyridine product; in fact it has been mentioned specifically that the alcohol and ammonia do not form such products in the vapor phase (1663,1738). Only one furfuryl alcohol derivative has been found to form a pyridine. Thus, treatment of 5-aminomethylfurfuryl alcohol with dilute hydrochloric acid produced 6-methyl-3-pyridinol (II-88) in 88% yield (884). Clearly, this reaction proceeds by cyclization through the aminomethyl group to give II-89 while the hydroxymethyl group is converted to a methyl group by dehydration.



Furfural and ammonia at 10° for four days produced only furfural (II-90) and hydrofuralamide (II-91) (1821); at higher tempera-

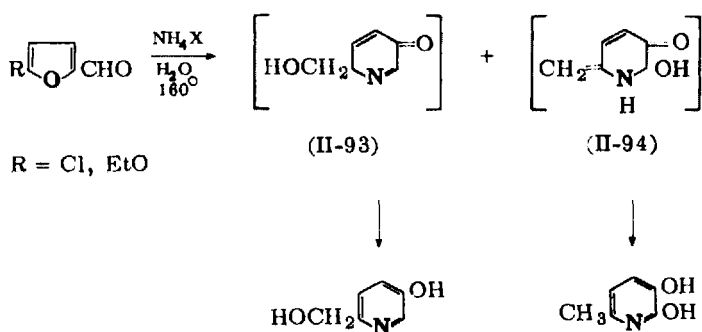


tures, furfural gave only tars and resins. However, 5-substituted furfural derivatives have produced 3-pyridinol derivatives by the reaction with aqueous ammonium salts at 160° (641,1206,1208). The reaction probably occurs by attack of ammonia on the 5 position, which is activated by the carbonyl group. The furan ring then opens and recycles to a pyridinol as in II-92. It has been said that



furfural does not readily give a pyridinol because of its tendency to form tars and because with ammonia it readily forms the aldimine, which does not polarize the furan ring as well as the carbonyl group (892).

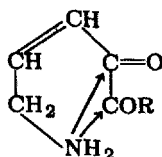
5-Chloromethylfurfural reacted with aqueous ammonium chloride at 165° to give 5-hydroxy-2-pyridinemethanol and 6-methyl-2,3-pyridinediol (1206). Here the chloromethyl group was hydrolyzed to the hydroxymethyl group. The 3-pyridinol was formed normally through II-93, but the diol was formed by elimination of water at the 6-hydroxymethyl group (II-94) rather than at the 2-carbon. 5-Ethoxymethylfurfural gave the same products.



Vapor phase reactions of furfural derivatives are rare, but it has been reported that furfural itself reacts with ammonia and hydrogen over a metal oxide catalyst (Pt, Co, Ni, or Cu) at 200° to give a mixture of piperidine and pyridine (1739).

2-Acylfurans and several 5-substituted derivatives, which do not give tars as readily as furfural, react with aqueous or alcoholic ammonia at 150–75° to give 3-pyridinols, often in 50–75% yields

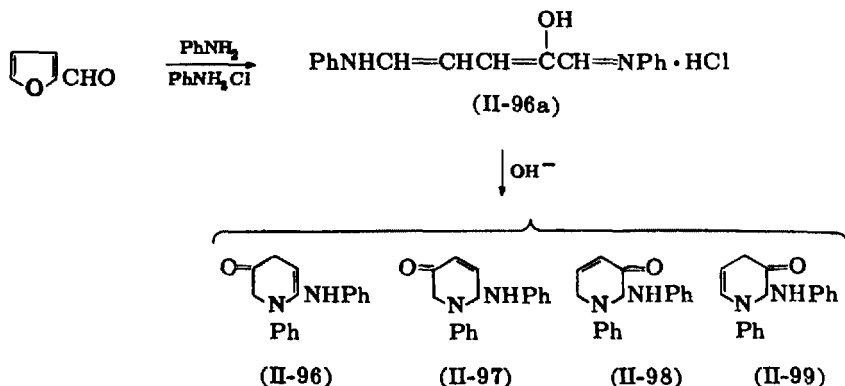
(Table II-16). This reaction is complicated by the formation of pyrroles, probably through such a common intermediate as II-95 (893). Alcohol as a solvent generally favors the formation of pyrroles (893), though pyridinols are sometimes obtained in good yields. Ammonium salts were often added to the reaction, but there does not seem to be good evidence that they are of value.



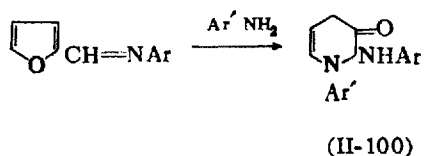
(II-95)

This preparative method from 2-acylfurans has one notable and disappointing failure; pyridoxine could not be made from 2-acetyl-3,4-bis(acetoxymethyl)furan or the bishydroxymethyl derivative by heating with aqueous or alcoholic ammonia, ammonium salts, or liquid ammonia and sodamide (819,1637,1638).

The reaction of furfural or its 5-chloro or nitro derivative with an aromatic amine and its hydrochloride yielded a product called a Stenhouse dye, which has been formulated as II-96a (464). Neutralization of this salt produced a pyridine derivative for which four structures may be proposed (II-96,97,98,99). Form II-99 is most favored since the infrared spectrum indicates a carbonyl with no

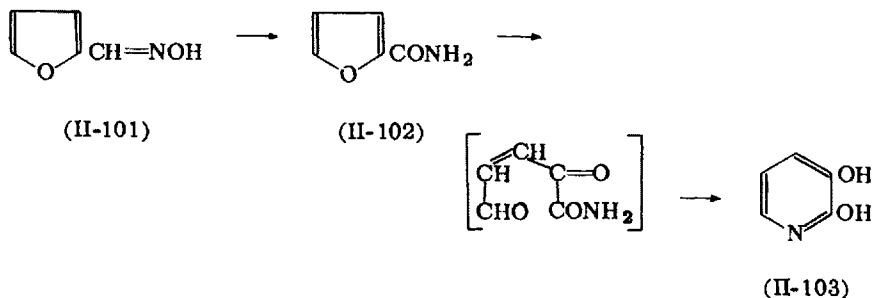


α,β -double bond, and the formation of only a monobenzylidene or furfurylidene derivative suggests that only one methylene group is alpha to the carbonyl (631). This product, II-99, may also be formed directly from furfural or its derivatives if no acid or acid salt is present (Table II-17). It has also been reported that a furfuraldimine of an aromatic amine reacted with a second aromatic amine to produce II-100; it was believed that the second amine contributed the 1-aryl group of the product (464). Aliphatic amines do not give these products.



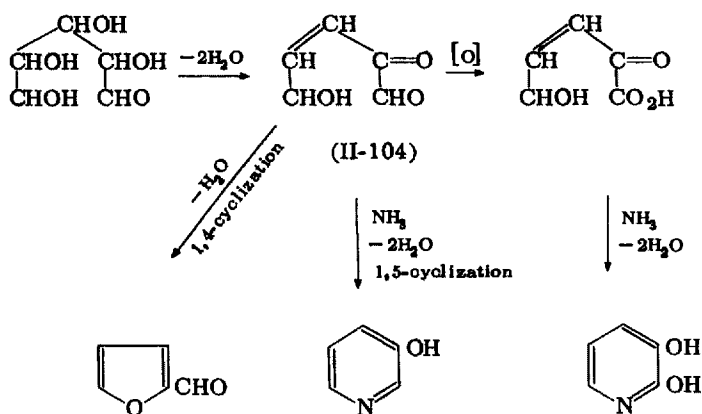
The Stenhouse dye from aniline and furfural, when heated in alcohol or acetic acid, produced 1-phenyl-3-hydroxypyridinium chloride in 37% yield (35,36,1133). The conversion by acid of the keto-tetrahydropyridine II-99 to 1-phenyl-3-hydroxypyridinium chloride has not been reported, though such a reaction appears logical.

Treatment of furfural with hydroxylamine hydrochloride or the salt of hydroxylaminedisulfonic acid at 160° produced 2,3-pyridinediol in low yield (Table II-19). Also believed that the aldoxime II-101 was converted to an amide II-102, which was hydrolyzed and cyclized to II-103. This mechanism was supported by the isolation of furoic acid from the reaction of furfural and the salt of hydroxylaminedisulfonic acid and by the conversion of furamide by acid at 160° to 2,3-pyridinediol in low yield (360).



Hydrazine sulfate at 150° converted furfural to 3-pyridinol and 2,3-pyridinediol (1207).

Carbohydrates. Carbohydrates are included at this point because they are a source of furans and 3-pyridinol. Yet this formation of pyridinols by the action of ammonium salts at 160° probably does not proceed through a furan derivative. More likely, the carbohydrate is converted to a common intermediate which, according to reaction conditions, gives one product or the other. Thus xylose, which has been converted to furfural in about 89% yield (895), has also given an unstated yield of 3-pyridinol and 2,3-pyridinediol (360) (Table II-20). The intermediate II-104, which has been proposed for the formation of furfural (894) may explain all the products. Similarly, hexoses, which give 5-hydroxymethylfurfural, produce three pyridinols through the intermediate II-105. The isolation of 5,6-dihydroxy-2-pyridinemethanol (II-106) and 6-methyl-3-pyridinol (1390,365) indicates that some of the hexose or the intermediate II-105 underwent a Cannizzaro reaction before cyclization. Probably the intermediate from xylose was also oxidized in a Cannizzaro reaction, but no pyridine product was obtained from the reduced portion.



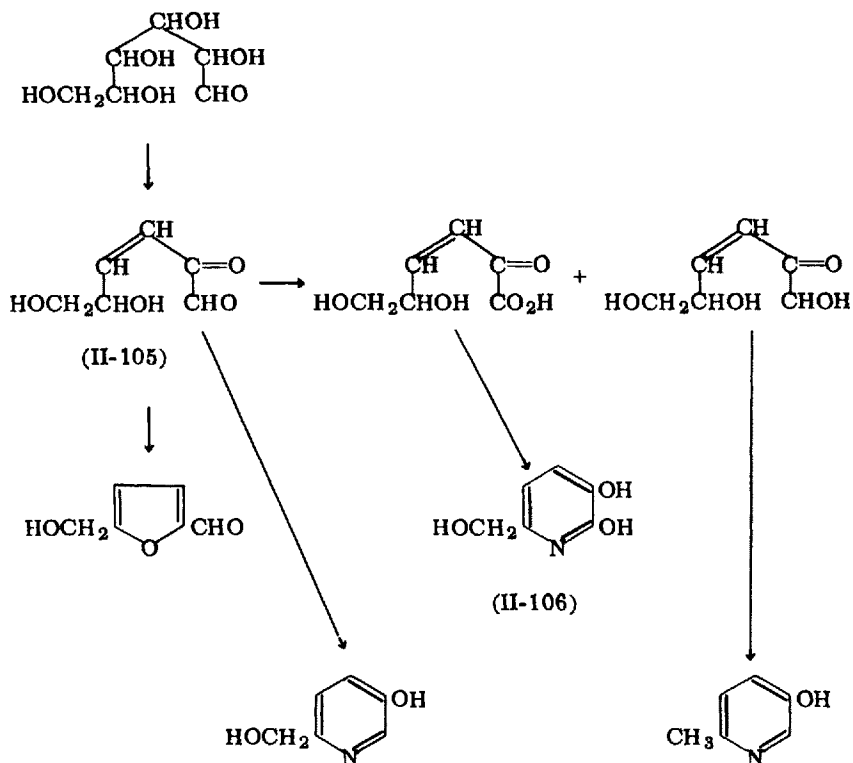


TABLE II-13. Formation of Pyridine Products from Dihydro and Tetrahydrofurans

Starting Material	Conditions	Product (Yield, %)	Ref.
Tetrahydrofuran	HCN, vapor phase, high temp.	Pyridine, $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{CN}$	378
2,5-Dimethyltetrahydrofuran	HCN, vapor phase, high temp.	A lutidine, $\text{CH}_3\text{CH}=\text{CHCH}_2\text{-CHMeCN}$	378

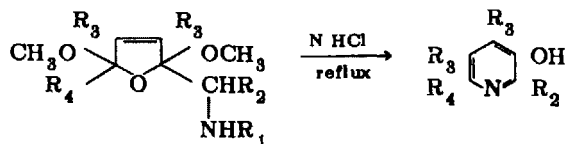
(continued)

TABLE II-13 (Continued)

Formation of Pyridine Products from Dihydro and Tetrahydrofurans

Starting Material	Conditions	Product (Yield, %)	Ref.
2-Hydroxymethyl-tetrahydrofuran	NH ₃ , 400°	Pyridine (3) piperidine (8)	1738
	NH ₃ , vapor phase, Cr ₂ O ₃ , Al ₂ O ₃ , 600°	Pyridine (26), 2-aminomethyltetrahydrofuran	1663
	NH ₃ , vapor phase, (H ₂ , reduced cat. of (NH ₄) ₂ MoO ₄ on alumina), 500°	Pyridine (45)	461
	NH ₃ , 400°		
2-Hydroxymethyl-5-methyltetrahydrofuran	NH ₃ , vapor phase, Cr ₂ O ₃ , Al ₂ O ₃ , 600°	2-Picoline (40)	461
	NH ₃ , vapor phase, (H ₂ , reduced cat. of (NH ₄) ₂ MoO ₄ on alumina) 500°		
2-Carbomethoxy-2,5-dimethoxytetrahydrofuran	(1) NH ₃ , methanol, 4d., 25° (2) Aq., H ₂ SO ₄ , reflux, 20 min.	2,3-Pyridinediol (94)	595
Dihydrofuran	HCN, vapor phase, high temp.	Pyridine	378
2,5-Dicarboxy-2,5-dihydrofuran	NH ₃ , Aq., NH ₄ Br, 160°, 12 hrs.	6-Hydroxypicolinic acid (40)	446, 245

TABLE II-14. Formation of 3-Pyridinols from 2-Aminomethyl-2,5-dimethoxy-2,5-dihydrofurans



R ₁	R ₂	R ₃	R ₄	Conditions	Yield, %	Ref.
H	H	H	H	30 min.	93	593
COCH ₃	H	H	H	30 min.	50	593
CO ₂ CH ₃	H	H	H	30 min.	76	593

TABLE II-14 (Continued)

R ₁	R ₂	R ₃	R ₄	Conditions	Yield, %	Ref.
CO (symmetrical urea)	H	H	H	30 min.	85 (from 2-amino-methyl-furan)	593
H	Me	H	H	Heat	95	593
CO ₂ CH ₃	Me	H	H	90 min.	72	593
CONH ₂	Me	H	H	90 min.	62	593
H	Me	CH ₂ OH	H	Reflux, then evaporate	64	1820
H	Me	CH ₂ OAc	H	(1) 3N NaOH, 21 hrs. (2) HCl, reflux, 20 min.	76 (as 4,5-bis-hydroxy-methyl deriv.)	596
H	H	H	<i>i</i> -Pr	15 min.	69	595
H	H	H	CH ₂ OH	20 min. reflux	74	884

TABLE II-15. Reaction of 2-Acyl-2,5-dimethoxy-2,5-dihydrofurans with Hydroxylamine



R	Conditions	Yield, %	Ref.
H	(1) NH ₂ OH, MeOH, 25°, 20 min. (2) Aq., HCl, 25°, 10 min.	69	597
H (as diacetate)	(1) NaOMe, MeOH, 15 min. (2) NH ₂ OH, MeOH, 25°, 20 min. (3) Aq., HCl, 25°, 10 min.	68	597
Me (as dimethyl ketal)	NH ₂ OH · HCl, aq., 15 min.	89	594, 597
<i>n</i> -Hexyl	NH ₂ OH · HCl, aq., MeOH, 17 hrs., stand	12	597, 900
Cyclohexyl	NH ₂ OH · HCl, MeOH, 17 hrs., stand	27	900
Ph	NH ₂ OH · HCl, aq., MeOH, 17 hrs., stand	27	597

TABLE II-16. Formation of 3-Pyridinols from 2-Acylfurans $R' \text{---} \text{COR}$ $\longrightarrow$ $R' \text{---} \text{C}_5\text{H}_4\text{OH}$

R	R'	Conditions	Yield	Ref.
H	Me	Aq., $(\text{NH}_4)_2\text{SO}_4$, 160°		1208
H	CH_2Ph	Aq., $(\text{NH}_4)_2\text{SO}_4$, 180° , 3 hrs.		641
H	CH_2Cl	Aq., NH_4Cl , 165° , 3 hrs.	R' is CH_2OH , also 6-methyl-2,3-pyridine-diol	1206
H	CH_2OEt	Aq., $(\text{NH}_4)_2\text{SO}_4$, 160° , 5 hrs.	R' is CH_2OH	1206
		Aq., NH_4Cl , 165° , 2 hrs.	R' is CH_2OH , also 6-methyl-2,3-pyridine-diol	1206
Me	H	$(\text{NH}_4)_2\text{SO}_4$, 160° , 2 hrs.		1481
		NH_3 , alc., $165\text{--}70^\circ$, 15-24 hrs.	5-10%	502, 1579
		NH_3 , aq., MeOH , 160° , 17 hrs.	47%	1563
		NH_3 , alc. or aq., NH_4Cl , 160° , 17-20 hrs.; or 205° , 2 hrs.	43-56%	1174, 1638, 1741
Me	Me	NH_3 , aq., MeOH , 160° , 17 hrs.	9%	1563
Me	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	NH_3 , aq., NH_4Cl , 170° , 15 hrs.	34% as amide	1174
Me	$(\text{CH}_2)_7\text{CO}_2\text{H}$	NH_3 , aq., NH_4Cl , 170° , 15 hrs.	45% as amide	1174
Me	$\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$	NH_3 , alc., NH_4Cl , 165°	48% as free acid	1174
Et	H	NH_3 , alc. or aq. MeOH , NH_4Cl , $160\text{--}200^\circ$, 10-20 hrs.	10-29%	502, 1144, 1563
		NH_3 , aq., NH_4Cl , 165° , 20 hrs.	60%	1174
Et	Me	NH_3 , alc., 170° , 15-24 hrs.	80%	502

Pr	H	NH ₃ , alc., 170°, 15-24 hrs.	74%	502
i-Pr	H	NH ₃ , alc., 170°, 15-24 hrs.	81%	502
Bu	H	NH ₃ , alc., 170°, 15-24 hrs., or 200°, 10 hrs.	52-78%	502, 1144
CHMeEt	H	NH ₃ , alc., 170°, 15-24 hrs.	60%	502
t-Bu	H	NH ₃ , alc., 170°, 15-24 hrs.	71%	502
C ₆ H ₁₁	H	NH ₃ , alc., NH ₄ Cl, 200°, 10 hrs.	55%	1144
CH ₃ Ph	H	NH ₃ , alc., NH ₄ Cl, 170°, 15-24 hrs., or 200°, 10 hrs.	5-26%	502, 1144
(CH ₃) ₇ CO ₂ H	Me	NH ₃ , aq., or alc., NH ₄ Cl, 165°, 15-20 hrs.	54-61% crude	1174
Ph	H	NH ₃ , aq., MeOH, 160°, 17-21 hrs. NH ₄ OAc, 250°, 10 hrs.	65%	603, 1563
p-MeC ₆ H ₄	H	NH ₃ , alc., NH ₄ Cl, 200°, 10 hrs.	59%	1115
p-ClC ₆ H ₄	H	NH ₃ , alc., NH ₄ Cl, 200°, 10 hrs.	47%	1115
3,4-Cl ₂ C ₆ H ₃	H	NH ₄ OAc, 250°, 10 hrs.	73%	1115
p-MeOC ₆ H ₄	H	NH ₄ OAc, 250°, 10 hrs.	76%	1115
m-MeOC ₆ H ₄	H	NH ₃ , alc., NH ₄ Cl, 200°, 10 hrs.	31-52%	1115, 1144
p-BuOC ₆ H ₄	H	NH ₃ , alc., NH ₄ Cl, 200°, 10 hrs.	41%	1144
3,4(MeO) ₂ C ₆ H ₃	H	NH ₃ , alc., NH ₄ Cl, 200°, 10 hrs.	54%	1144
2-Thienyl	H	NH ₃ , alc., NH ₄ Cl, 200°, 10 hrs.	43%	1144
3-(2-Methyl-4,5,6,7-tetra- hydro)indolyl	H	NH ₃ , alc., NH ₄ Cl, 200°	63%	1144
2-Carbazoly	H	NH ₃ , alc., NH ₄ Cl, 200°		1127
2-Dibenzofuranyl	H	NH ₃ , alc., NH ₄ Cl, 200°		1127

TABLE II-17. Reaction of Furfuraldehydes with Aromatic Amines



R	Ar	Conditions	Yield	Ref.
H	Ph	MeOH, reflux, 2 hrs.	9.2 %	631
H	Ph	(1) PhNH ₂ , Cl	20 %	1417
		(2) 3 N NaOH, shake with ether, 25°		
H	<i>p</i> -CH ₃ C ₆ H ₄	MeOH, reflux, 3 hrs.	23.3 %	631
H	<i>p</i> -CH ₃ C ₆ H ₄	(1) <i>p</i> -CH ₃ C ₆ H ₄ NH ₂ , Cl	15 %	1417
		(2) 3 N NaOH, shake with ether, 25°		
Cl	<i>p</i> -CH ₃ COC ₆ H ₄	Alc., excess 5-chlorofurfural	100 % (based on amine)	655
Cl	<i>p</i> -HO ₂ CC ₆ H ₄	Alc., cold, excess 5-chlorofurfural	104 % (based on amine)	655
Cl	<i>p</i> -EtO ₂ CC ₆ H ₄	Alc., cold, excess 5-chlorofurfural	86 % (based on amine)	655
Cl	<i>o</i> -HO ₂ CC ₆ H ₄	Aq., alc., cold, excess aldehyde	114 % (based on amine)	655
Cl	3,4-HO(HO ₂ C)-C ₆ H ₃	Aq., alc., cold, excess aldehyde	77 % (based on amine)	655
Cl	<i>p</i> -HO ₂ SC ₆ H ₄	Aq., alc., cold, several days, excess aldehyde	56 % (based on amine)	655
Cl	<i>p</i> -PhN ₂ C ₆ H ₄	MeOH		655
NO ₂	<i>o</i> -HO ₂ CC ₆ H ₄	Aldehyde diacetate, aq., H ₂ SO ₄ , MeOH, cold, several days	107 % (based on amine) 33 % (based on amine)	651
NO ₂	<i>o</i> -MeO ₂ CC ₆ H ₄	Aldehyde as diacetate, aq., H ₂ SO ₄ , MeOH, cold, several days	Excellent	651
H	<i>p</i> -NO ₂ C ₆ H ₄	Alc., heat		464
H	<i>m</i> -NO ₂ C ₆ H ₄	Alc., heat		464
H	<i>o</i> -NO ₂ C ₆ H ₄	Alc., heat		464

TABLE II-18. Reaction of Furfural with Two Aromatic Amines (464)

$\text{Furfural} \xrightarrow[\text{(2) Ar'NH}_2]{\text{(1) ArNH}_2} \text{Product}$	
Ar	Ar'
<i>p</i> -NO ₂ C ₆ H ₄	<i>m</i> -NO ₂ C ₆ H ₄
<i>p</i> -NO ₂ C ₆ H ₄	<i>p</i> -HOC ₆ H ₄
<i>p</i> -HOC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄
<i>p</i> -NO ₂ C ₆ H ₄	Ph
<i>p</i> -HOC ₆ H ₄	Ph

TABLE II-19. Miscellaneous Preparations of Pyridines from Furans

$\text{R} \quad \text{R}'$		Products		
R	R'	Conditions	Products	Ref.
CHO	H	NH ₂ OH · HCl, 160°, pressure	2,3-Pyridinediol ^a	1209
CHO	H	HON(SO ₃ Na) ₂ , 160°, 3 hrs.	2,3-Pyridinediol, succinic acid, pyromucic acid	360
CHO	H	HON(SO ₃ Na) ₂ , 160°	2,3-Pyridinediol ^a	1209
CHO	Me	NH ₂ OH · HCl, aq., 160°, 3 hrs.	6-Methylpyridine-2,3-diol	360
COCH ₃	H	NH ₂ OH · HCl, 160°	6-Methylpyridine-2,5-diol(?)	586
CHO	H	(N ₂ H ₄) ₂ · H ₂ SO ₄ , 152°	3-Pyridinol, 2,3-pyridine-diol ^a	1207
CHO	H	NH ₃ , H ₂ , over 200°, oxide of Pt, Ni, Co, or Cu	Pyridine and piperidine	1739
CHO	H	(1) PhNH ₂ , HCl, aq., alc., cold, 3 hrs. (2) Steam strip and evaporate (3) Alc., reflux, 30 min.	1-Phenyl-3-hydroxypyridinium chloride (37%)	35,36, 1133

(continued)

TABLE II-19 (*Continued*)

Miscellaneous Preparations of Pyridines from Furans

R	R'	Conditions	Products	Ref.
CONH ₂	H	HCl, 160°, 5 hrs.	2,3-Pyridinediol	360
CONH ₂	Me	H ₂ SO ₄ , 160°, 3 hrs.	6-Methylpyridine-2,3-diol	360
CH ₂ OH	CH ₂ NH ₂	0.6 N HCl, reflux, 15 hrs.	6-Methyl-3-pyridinol 88%	884

^aReported first as 2,5-diols.

TABLE II-20. Formation of Pyridinols from Carbohydrates

Carbohydrate	Conditions	Products	Ref.
Hexose	Ammonium salts	6-Methyl-2,3-pyridinediol	360
Hexose	NH ₃	6-Hydroxymethyl-3-pyridinol	1206
Hexoses	Ammonium salts, 160°	6-Methyl-3-pyridinol, 6-Methyl-2,3-pyridinediol 5-Hydroxy-2-pyridinemethanol	1390
Glucose	Ammonium salts, 165°, 3 hrs.	6-Methyl-3-pyridinol 6-Methyl-2,3-pyridinediol, 5-Hydroxy-2-pyridinemethanol	365
Sucrose	Ammonium salts, 165°, 3 hrs.	6-Methyl-3-pyridinol 6-Methyl-2,3-pyridinediol 5-Hydroxy-2-pyridinemethanol	365
Xylose	Ammonium salts	3-pyridinol, 2,3-pyridinediol	360

3. Pyrans

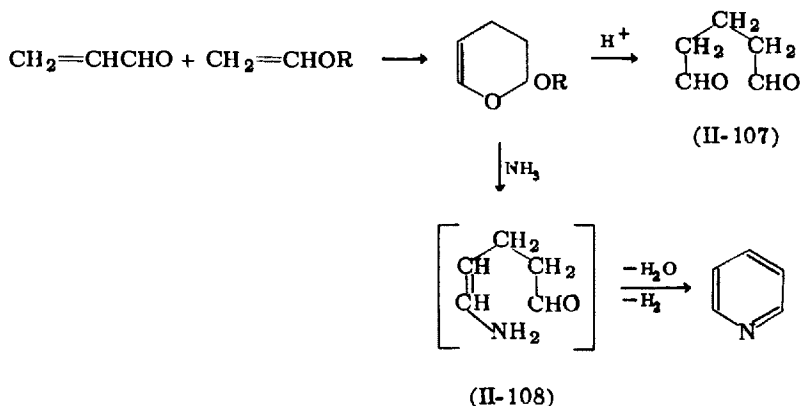
Pyridines have been prepared from tetrahydropyrans and dihydropyrans, but not from the pyrans themselves. Of these preparations, the commonest and most successful use the 2-alkoxy-3,4-dihydro-2*H*-pyrans. Ammonia converts several reduced pyrans to pyridines in the vapor phase at 275–400° over a metal oxide catalyst

such as alumina, but high yields are rare. 2-Alkoxy-3,4-dihydro-2*H*-pyrans also react with hot hydroxylamine hydrochloride to give pyridines (Tables II-21,22).

Reactions with Ammonia. Tetrahydropyran reacted with ammonia at 400° over alumina and produced a mixture of bases containing 16% piperidine and a small amount of pyridine (1738). Probably the reaction proceeded through dehydration of tetrahydropyran to an intermediate such as pentadiene which then cyclized with ammonia to give piperidine, which formed pyridine by dehydrogenation.

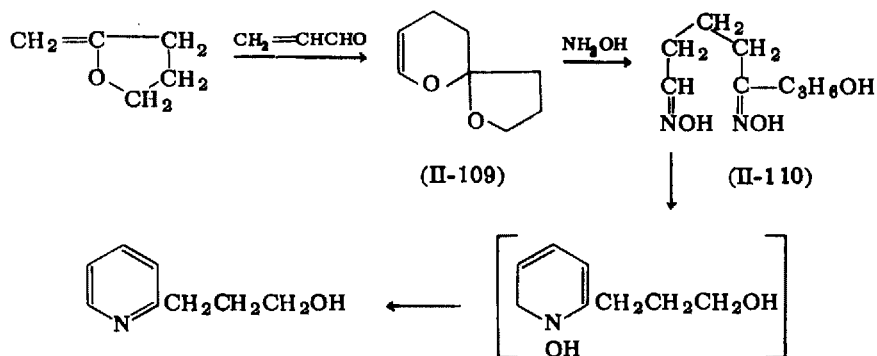
The interaction of ammonia with 3,4-dihydro-2*H*-pyran over a nickel on thoria catalyst at 365° produced a mixture of bases containing piperidine and pyridine (1549); no pyridine was produced over a chromia on alumina catalyst at 300–600° (1738).

Catalyzed vapor phase reactions of simple alkyl-2-alkoxy-3,4-dihydro-2*H*-pyrans in the presence of steam give pyridines in yields ranging from 31% for pyridine to 91.6% for 4-picoline (1823). These dihydropyrans, which may be prepared by addition of a vinyl ether to an α,β -unsaturated aldehyde, hydrolyze readily to the dialdehyde II-107. This hydrolysis of the cyclic acetal suggests that ammonia also opens the ring by attack at the 6-carbon (or possibly the 2-carbon) to give a dialdehyde derivative such as II-108 which can give a pyridine.

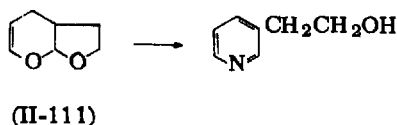


2-Alkoxy-3,4-dihydro-2*H*-pyran or its methyl derivatives may also be converted to pyridines in good yields by boiling with aqueous ammonium and cupric sulfate or ammonium and ferric chloride. The latter conditions also produce by-products of mono- and dichloropyridines or picolines. When 4-methyl-2-methoxy-3,4-dihydro-2*H*-pyran was first treated with chlorine at 0°, and then boiled with aqueous ammonium and ferric chloride a 52% yield of 3-chloro-4-picoline and a 3% yield of 3,5-dichloro-4-picoline were obtained (684).

Reactions with Hydroxylamine. Hot, aqueous hydroxylamine hydrochloride also converts 2-alkoxy-3,4-dihydro-2*H*-pyrans to pyridines. Unlike the reaction with ammonia, this uncommon reaction requires no dehydrogenation step to give the pyridine; the conditions are therefore relatively mild. Paul and Tchelitcheff found that the reaction of II-109 with excess hydroxylamine gave the dioxime II-110. This dioxime could be cyclized by hot, alcoholic



hydrogen chloride. Only the pyran II-111 could be directly converted to the pyridine by hot, aqueous acidic hydroxylamine (1168).



2-Acetoxy-3,4-dihydro-2*H*-pyran may also be converted to pyridine by the action of hydroxylamine hydrochloride, presumably by a very similar mechanism (1745).

TABLE II-21. Reactions of Pyran Derivatives with Ammonia

Pyran	Conditions	Products (Yields)	Ref.
Tetrahydropyran	Alumina, 400°	Piperidine (16%), pyridine (trace)	1738
	Copper on alumina, 350°	Bases containing pyridine	1549
3,4-Dihydro-2H-pyran	CrO ₃ on alumina, 300-600°	No pyridine	1738
	Nickel on alumina, 365°	Bases containing pyridine	1549
2-Methoxy-3,4-dihydro-2H-pyran	Silica and alumina, 400°; or alumina with trace Na ₂ SO ₄	Pyridine (29%)	459,1114
	Aq., NH ₄ Cl, FeCl ₃ , reflux	Pyridine (56%), chloropyridine (16%), 3,5-dichloropyridine (2%)	684
	(1) Cl ₂ , 0-5°	Chloropyridine (47%), 3,5-dichloropyridine (2.5%)	684
	(2) Aq., (NH ₄) ₂ SO ₄ , Fe ₂ (SO ₄), reflux	Pyridine (31.1%)	1823
2-Ethoxy-3,4-dihydro-2H-pyran	Steam, H ₂ , Cu(NO ₃) ₂ , Cr(NO ₃) ₃ , 275°	Pyridine (58%)	1823
2-(2'-ethoxyethoxy)-3,4-dihydro-2H-pyran	Steam, H ₂ , Cu(NO ₃) ₂ , Cr(NO ₃) ₃ , 275°	3-Picoline (83%)	1823
2-Ethoxy-3-methyl-3,4-dihydro-2H-pyran	Aq., NH ₄ Cl, FeCl ₃ , reflux	4-Picoline (35%), 3-chloro-4-picoline (21%), dichloro-4-picoline (1%)	684
2-Methoxy-4-methyl-3,4-dihydro-2H-pyran	(1) Cl ₂ , 0-5° (2) Aq., NH ₄ Cl, FeCl ₃ , reflux	3-Chloro-4-picoline (52%), 3,5-dichloro-4-picoline (3%)	684
2-Ethoxy-4-methyl-3,4-dihydro-2H-pyran	Steam, H ₂ , Cu(NO ₃) ₂ , Cr(NO ₃) ₃ , 275°	4-Picoline (91.5%)	1823
2-Ethoxy-5-methyl-3,4-dihydro-2H-pyran	Aq., (NH ₄) ₂ SO ₄ , CuSO ₄ , 1% H ₂ SO ₄ , reflux	3-Picoline (48%)	684

TABLE II-22. Reactions of Pyran Derivatives and Hydroxylamine

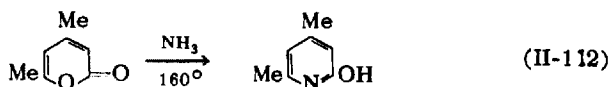
Pyran	Conditions	Product (Yields)	Ref.
2-Ethoxy-3,4-dihydro-2H-pyran	Aq., $\text{NH}_2\text{OH} \cdot \text{HCl}$, 120° , 3 hrs.	Pyridine (70-80%)	1745
2-Ethoxy-4-methyl-3,4-dihydro-2H-pyran	Aq., $\text{NH}_2\text{OH} \cdot \text{HCl}$, 120° , 3 hrs.	4-Picoline (58%)	1745
2-Ethoxy-5-methyl-3,4-dihydro-2H-pyran	Aq., $\text{NH}_2\text{OH} \cdot \text{HCl}$, 120° , 3 hrs.	3-Picoline (54%)	1745
2-Ethoxy-6-methyl-3,4-dihydro-2H-pyran	Aq., $\text{NH}_2\text{OH} \cdot \text{HCl}$, 120° , 3 hrs.	2-Picoline (45%)	1745
2-Ethoxy-4-ethyl-5-methyl-3,4-dihydro-2H-pyran	Aq., $\text{NH}_2\text{OH} \cdot \text{HCl}$, 120° , 3 hrs.	4-Ethyl-3-picoline (60%)	1745
2-Acetoxy-3,4-dihydro-2H-pyran	Aq., $\text{NH}_2\text{OH} \cdot \text{HCl}$, 120° , 3 hrs.	Pyridine (62%)	1745
4a,5,6,7a-Tetrahydro-4H-furo[2,3-b]pyran	Aq., $\text{NH}_2\text{OH} \cdot \text{HCl}$, reflux, 1 hr.	3-Pyridineethanol (33%)	1168
4a,5,6,7a-Tetrahydro-7a-methyl-4H-furo[2,3-b]-pyran	(1) Aq., excess NH_2OH , reflux (2) Alc., HCl , reflux	2-Methyl-3-pyridineethanol (21%)	1168
3,4,4a,8a-Tetrahydro-2H,5H-pyrano[2,3-b]pyran	(1) Aq., excess NH_2OH , reflux (2) Alc., HCl , reflux	3-Pyridinepropanol (24%)	1168
1,6-Dioxaspiro[4,5]dec-8-ene	(1) Aq., excess NH_2OH , reflux (2) Alc., HCl , reflux, 2 hrs.	2-Pyridinepropanol	1168

4. Pyrones

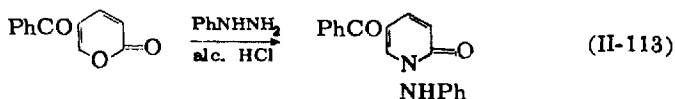
The conversion of pyrones to pyridones (pyridinols) has been studied for over seventy years. Many of these transformations have been reported in the literature, and will be found summarized in Tables II-23 to II-27. They generally proceed in satisfactory yields under mild conditions, and they often represent the preferred preparative method when the necessary pyrone is readily available. The preparation of pyrones has been reviewed (891) and will not be discussed here.

a. 2-Pyrones

The reaction with α -pyrones is usually carried out in aqueous or alcoholic solution at 100–160° in the presence of excess ammonia or amine. Pressure is usually used, but is not always necessary; thus 4,6-dimethyl-2-pyrone reacted in the molten state at 160° with a stream of gaseous ammonia (II-112) (1067). Acidic conditions have



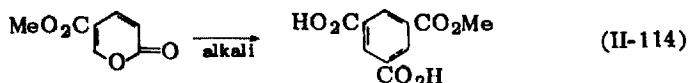
also been used, as in the reaction of phenethylamine with 6-carboxy-2-pyrone in refluxing acetic acid (1629), and the reaction of 5-benzoyl-2-pyrone with phenylhydrazine in alcoholic hydrogen chloride (II-113) (796).



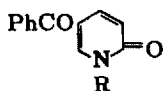
As might be expected, the more basic and less hindered amines give the best results. Though good comparative studies are rare, it appears that benzylamines react well, but α -substituted benzylamines do not. Aromatic amines are seldom used, while simple aliphatic amines give the best results.

As for the pyrone reactant, carbonyl or carbalkoxy groups in the 3 or 5 positions exert an activating effect sufficient in some cases to

permit the reaction to proceed at room temperature. The reaction with 5-carbomethoxy-2-pyrone may give trimesic acid mono ester II-114 as a by-product since aqueous alkali causes such a conversion. (1833).



In a few instances the reaction has been reported to fail, although the significance of these reports is not always clear. Thus it is stated that ammonia does (257) and does not (1732) react with 5-carbomethoxy-4,6-diphenyl-2-pyrone and 5-carbomethoxy-6-methyl-4-phenyl-2-pyrone to give the expected pyridinol. 5-Carbomethoxy-4,6-dimethyl-2-pyrone does not react with benzylamine, *p*-methoxybenzylamine, benzidine, phenethylamine, or 3,4-dimethoxyphenethylamine below 200°; above 200° benzylureas are obtained (1155). However, benzylamine and 3,4-dimethoxyphenethylamine react normally with 5-benzoyl-2-pyrone in refluxing aqueous alcohol to give II-115 (796).



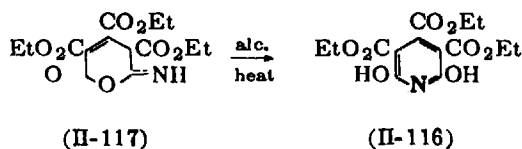
(II-115)

Hydrolysis of an ether linkage during the reaction is observed in the conversion of 6-carbomethoxy-4-ethoxy-2-pyrone to 6-carbomethoxy-2,4-pyridinediol (248).

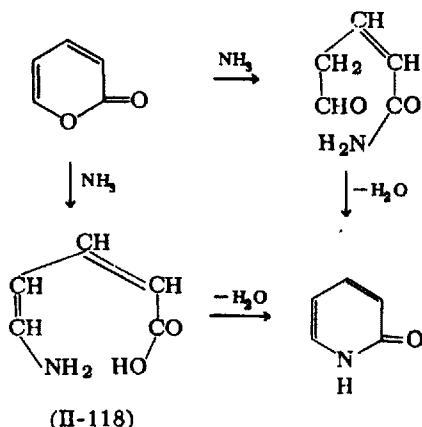
The conversion of dihydropyrone to dihydropyridinol is demonstrated by the reaction of 6-methyl 5,6-dihydro-2-pyrone with ammonia at 200° to give 6-methyl 5,6-dihydro-2-pyridinol (1204).

The pyridinediol II-116 is formed by isomerization when II-117 is heated in alcohol (1656); II-117 may be thought of as a pyrone, but it is more properly an anhydride.

The mechanism by which an α -pyrone is converted to a pyridinol



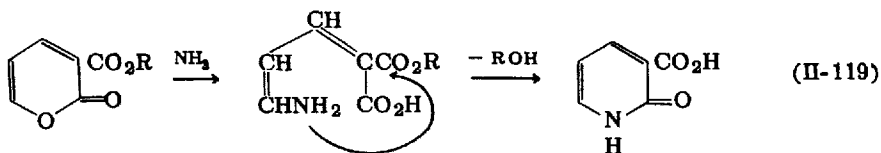
has been little investigated. Ammonia or the amine may initially attack the carbonyl carbon, as in the conversion of an ester to an amide or the 6-carbon atom as in the addition of ammonia to unsaturated carbonyl compounds (II-118). Both schemes postulate an open-chain intermediate.



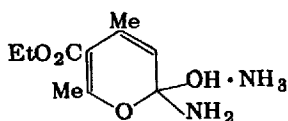
There is little evidence available that unequivocally favors one route over the other, although it should be noted that the effect of carbonyl groups in the 3 or 5 position, which facilitate the reaction, is perhaps better explained by intermediate II-118, since such groups would be expected by resonance interaction to promote nucleophilic attack at the 6-carbon but not at the 2-carbon.* Also α - and γ -pyrones

* The inactivity of 4,6-dimethyl-5-carbethoxypyrene toward amines can be explained by steric inhibition of coplanarity in the carbethoxy group, required for activation of the 6-carbon. However, Wiley attributes this inactivity to decreased electron density at the 2-carbon caused by the hyperconjugation of the methyl groups (1014).

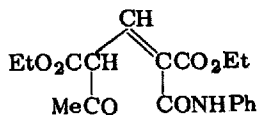
appear to be of the same order of reactivity, though the latter have no ester group; and the reaction of dehydracetic acid and ammonia (discussed at the end of this section) is best explained by an attack at the 6-carbon. It is also noteworthy that a 3-carbethoxy-pyrone may give the corresponding free acid, the 3-carboxy-pyridinol (1607,1610), which may decarboxylate under the reaction conditions (577,578,1358). Undoubtedly the reaction is not a simple hydrolysis, but rather cyclization of the open-chain intermediate through the 3-carbethoxy group (II-119). On the other hand a 5-carbethoxy group is stable (1607).



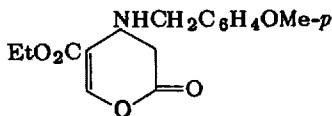
Some speculation is recorded in favor of attack at the 2-carbon. For example, the product from the mild treatment of 5-carbethoxy-4,6-dimethyl-2-pyrone with ammonia was assigned, without decisive evidence, the structure II-120 (658); and form II-121 was given to the intermediate from aniline and 3,5-dicarbomethoxy-6-methyl-2-pyrone (1607). Yet Wiley, Knabeschuh, Duckwall, and Smith, who obtained a similar product from *p*-methoxybenzylamine and 5-carbomethoxy-2-pyrone, stated that structure II-122 was possible. They also believed that the structure of the product was not of direct consequence since it did not appear to be an intermediate in the formation of the pyridone, at least in their case. The pyridone



(II-120)



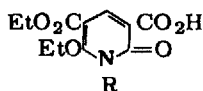
(II-121)



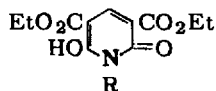
(II-122)

was obtained directly from the amine and pyrone in 45% yield, but from the possible intermediate in only 20% yield (1629).

3,5-Dicarbethoxy-6-ethoxy-2-pyrone, though once reported to react normally with ammonia (1627), has generally been found to react with ammonia (1610,1649,1654) or aniline (1651) with the loss of a mole of ethanol rather than water. The structures of the products remain speculative, though II-123 or II-124 are the most

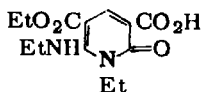


(II-123)

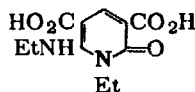


(II-124)

likely. This ethoxypyrone reacts with ethylamine under a variety of conditions giving products thought to be II-123, II-124, II-125, and II-126 (1652).



(II-125)



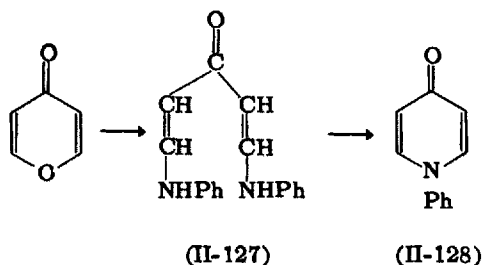
(II-126)

b. 4-Pyrones

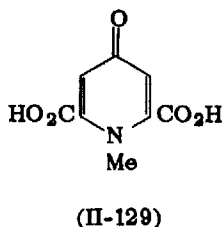
γ -Pyrones also react with ammonia and amines to give pyridinols. In general the γ -series has the same order of reactivity as the α -series, though no comparative study is available. Examination of Tables II-23 to II-26 shows also that the γ -series gives yields as high as or higher than the α -series.

For these reactions, alcohol and water are the commonest solvents. Alcohol would seem better for cases of low solubility, but though derivatives of 3-methoxy-4-pyrone react well in alcohol (1187), it is stated that these reactions are simpler and more satisfactory in water (1465). Yields are similar for both cases. Acetic acid has been used for such weak bases as 2,4-diiodoaniline (590). Strong alkali or acid may be used for difficult cases. For instance,

aniline converted γ -pyrone to an open-chain intermediate, II-127, but this could be cyclized to 1-phenyl-4(1*H*)-pyridone (II-128) by vacuum distillation or treatment with sodium hydroxide (1200) or hydrochloric acid (1056).



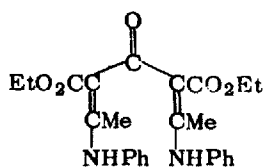
The presence of carboxy or carbalkoxy groups generally increases the reactivity and yields with the γ -pyrones. The more basic and less hindered amines can be expected to give generally higher yields (627). Accordingly, chelidonic acid (2,6-dicarboxy-4-pyrone) did not react well with *m*-nitroaniline and did not react at all with *o*-nitro or *p*-nitroaniline in 70% sulfuric acid or 50% potassium hydroxide (325); methylamine gave the expected pyridone II-129 in 89% yield (535). Although the sodium salt of glycine reacted with 2-methyl-5-methoxy-4-pyrone to give a 50% yield of the expected pyridone, glycine and its ester were unreactive (627).



Kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone) and ammonia at 100° for four hours gave a 30% yield of the expected pyridinol (627), though this reaction is also reported to be unproductive (1167, 1187). Certainly the results are poor compared to the methyl ether

(2-hydroxymethyl-5-methoxy-4-pyrone) and the dimethyl ether, which gave yields of 81% and 50% respectively when reacted with methylamine (627). The diacetyl derivative of kojic acid did not react with methylamine (1187).

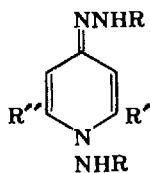
It was reported that 3,5-dicarbethoxy-2,6-dimethyl-4-pyrone and aniline reacted in acetic acid to give a good yield of II-130 but little of the expected pyridone, though the reaction with substituted anilines went normally (1158).



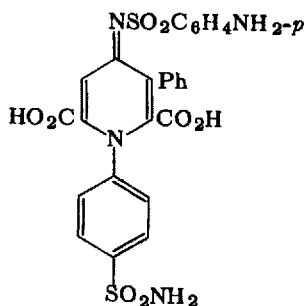
(II-130)

Decarboxylation sometimes accompanies the conversion to pyridinols. Although 2,6-dicarboxy-3-hydroxy-4-pyrone lost no carbon dioxide in its reaction with methylamine at 100° (1393), it lost the 2-carboxy group in its reaction with boiling, aqueous ammonia (1529,1641) and with methylamine, ethylamine, isopropylamine, and glycine at 230° (1290). Several examples in Tables II-25 and II-26 show that 2,6-dicarboxy-4-pyrone reacts with ammonia or amines with retention of the carboxyl groups below about 150°, but with loss of both carboxyl groups above that temperature.

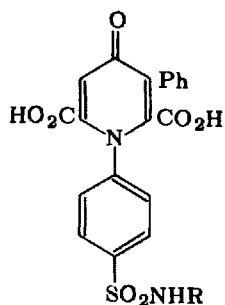
In a few cases, the carbonyl of the γ -pyrone also enters the reaction. With *p*-nitrophenylhydrazine, γ -pyrone and its 2-carboxy and 2,6-dicarboxy derivatives gave the pyridone hydrazone II-131. The *p*-nitrophenylhydrazone of the pyrone was not an intermediate since it does not react further with *p*-nitrophenylhydrazine (764). 3-Phenyl-2,6-dicarboxy-4-pyrone and sulfanilamide produced II-132; amide-substituted sulfanilamides gave normal products (II-133) (579). Arylbiguanides converted 2,6-dicarboxy-3-phenyl-4-pyrone to products such as II-134 (580).



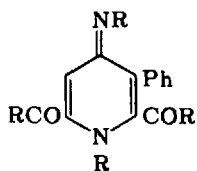
(II-131)



(II-132)

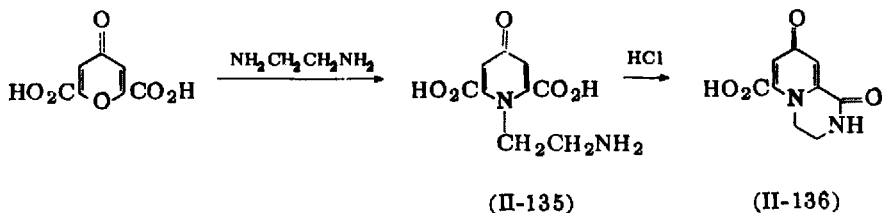


(II-133)



(II-134)

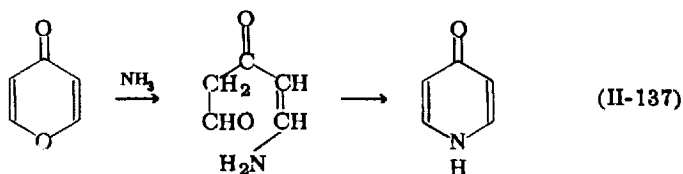
Ethylenediamine reacted with 2,6-dicarboxy-4-pyrone to give an unisolated intermediate (probably II-135) which was cyclized in hydrochloric acid to a product believed to be II-136 (1630). The



reaction of aniline with 2,6-dimethyl-3,5-dicarboxy-4-thiopyrone proceeded normally to give the thiopyridone (294).

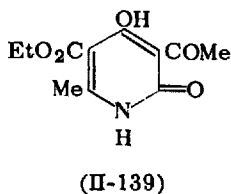
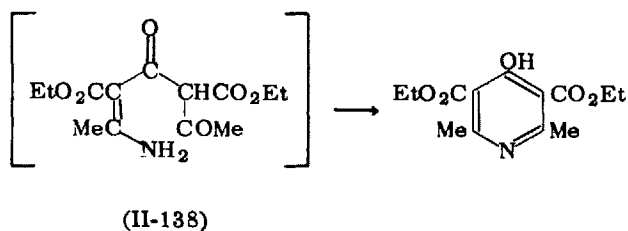
γ -Pyrone may be pictured as a vinylog of α -pyrone, or as the

inner ether of bis-hydroxymethyleneacetone. The amine or ammonia adds to an α,β -double bond and opens the ring as in II-137.



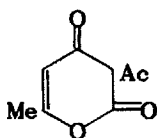
As with the α -pyrone, no direct proof for the mechanism is reported.

A carboxyl attached to the 2 position activates that position only by induction, but one in the 3 position can activate the 2 position by resonance interaction. This is consistent with the observation that the 3,5-dicarboxy-2,6-dimethyl-4-pyrone is more reactive than the 2,6-dicarbethoxy-4-pyrone and either one more reactive than γ -pyrone itself (590). The open-chain intermediate II-138 from 3,5-dicarbethoxy-2,6-dimethyl-4-pyrone cyclizes only through the acetyl group, as expected, and does not give any closure through the ester to II-139.

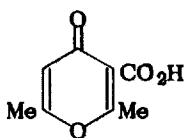


c. 2,4-Pyrandiones

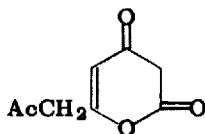
2,4-Pyrandiones, which have also been called pyronones, may also form pyridines. Probably the best known of these diones is dehydracetic acid (II-140). Other early proposed structures (II-141, II-142, and II-143), which account for most of the confusion in the early literature, were based to a large extent on the reaction with ammonia. Dehydracetic acid and ammonia at 130° formed 2,6-dimethyl-4-pyridinol (1604). Similar conditions have also given a 4:1 mixture of the above pyridinol and its 3-carboxy derivative (reported as 2-carboxymethyl-6-methyl-4-pyridinol, but shown later to be the 3-carboxy isomer) (1285). At steam bath temperatures only the carboxy derivative was obtained (1606).



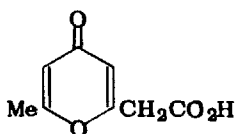
(II-140)



(II-141)



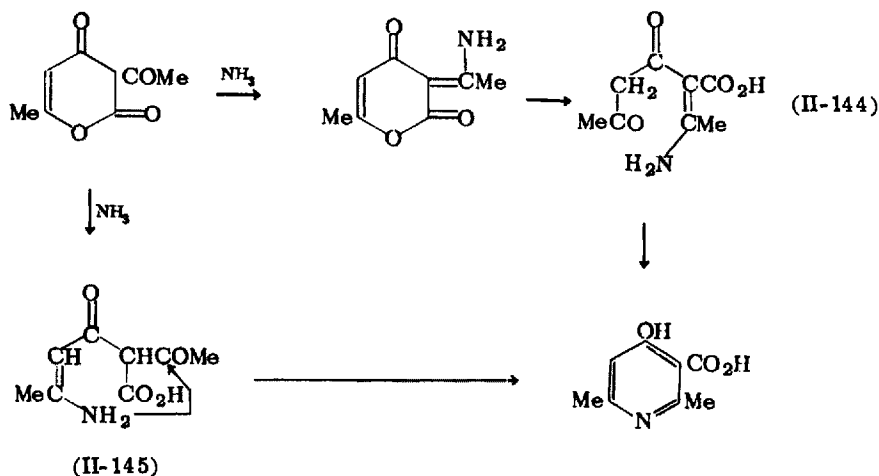
(II-142)



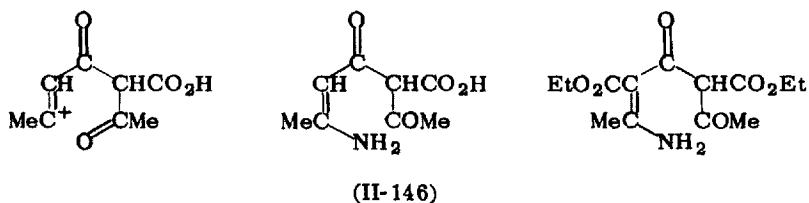
(II-143)

Though II-144 was proposed as a mechanism for this conversion (1073), it does not explain the initial opening of the pyrone ring. Attack of ammonia at the 6 position as in II-145 seems most likely. Attack at the 2 position would require a more complicated and less likely route. This likely attack at the 6 position also suggests a similar attack in the α -pyrone series.

Acid catalysis converts dehydracetic acid to 3-carboxy-2,6-dimethyl-4-pyrone (or the decarboxylated derivative at higher tem-

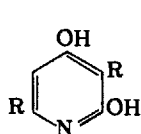


peratures). The probable mechanism for this rearrangement bears strong resemblance to that for the conversion to a pyridinol, and for the reaction of ammonia and 3,5-dicarbethoxy-2,6-dimethyl-4-pyrone; the proposed intermediates for these three reactions are given in II-146. In all cases, cyclization occurs through the ketone, not the ester.

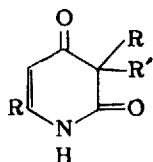


Although it has been reported that dehydrobenzoylacetic acid (3-benzoyl-6-phenyl-2,4-pyrandione) reacted with ammonia in analogy to dehydracetic acid to give 2,6-diphenyl-4-pyridinol (1079), this has been disputed, and the product was stated to be 3-benzoyl-6-phenyl-2,4-pyridinediol (1024,1081). While the evidence from the reaction with dehydracetic acid would favor the former, it is not conclusive since the carbonyl group would be less reactive in the benzoyl substituent than in the acetyl.

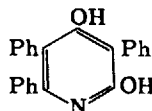
The 3,6-dialkyl and 3,3,6-trialkyl-2,4-pyrandiones with ammonia produced the expected II-147 and II-148 (1210), but 3-benzoyl-3,5,6-triphenyl-2,4-pyrandione was converted at 160° to II-149 (1216).



(II-147)



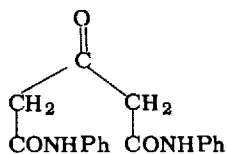
(II-148)



(II-149)

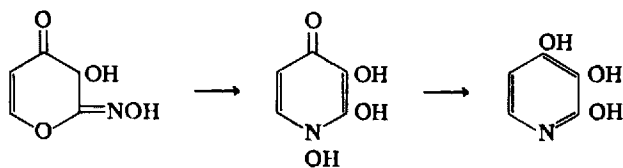
The action of alcoholic ammonia on 6-carbethoxy-4-ethoxy-2-pyrone, an enol ether of a pyronone, produced 6-carbethoxy-2,4-pyridinediol, not the 4-ethoxy derivative (248).

Aniline and 6-hydroxy-2,4-pyrandione formed an open-chain diamide II-150 which was cyclized by zinc chloride and heat to 2,6-dihydroxy-1-phenyl-4(1*H*)-pyridone (1205).



(II-150)

An unusual reaction was reported in which the oxime II-151, prepared from 3-hydroxy-4-pyrone and nitrous acid, was treated with sulfurous acid to give presumably 1,2,3-trihydroxy-4(1*H*)-pyridone (II-152). This was reduced with hydriodic acid to 2,3,4-pyridinetriol (47-49).



(II-151)

(II-152)

TABLE II-23. Formation of 2-Pyridinol from Ammonia and α -Pyrones

R_2	R_1	R_5	R_6	Conditions	Yield	Ref.
H	Me	H	Me	NH ₃ gas over molten pyrone, 160°		1067
H	H	H	Ph			1066
H	Me	Br ^a	Me	Aq., 100°		1658
H	H	CO ₂ H	H	Aq., boil	88%	796
H	H	<i>p</i> -MeC ₆ H ₄ COH	H	Aq., boil	86%	796
H	H	<i>p</i> -EtC ₆ H ₄ COH	H	Aq., boil	79%	796
H	H	<i>p</i> -ClC ₆ H ₄ COH	H	Aq., boil	80%	796
H	H	<i>p</i> -BrC ₆ H ₄ COH	H	Aq., boil	86%	796
H	H	CO ₂ H	H			271,1043, 1044
H	H	H	CO ₂ H	NH ₄ OAc, HOAc, Ac ₂ O, reflux, 2½ hrs.	40%	1807
H	H	CO ₂ Me	H			
H	H	Me	CO ₂ H	Aq., 25°, 18 hrs.	(Isolated as free acid by saponification)	251,440, 1808
H	H	Me	CO ₂ H	NH ₄ OAc, HOAc, reflux, 2 hrs.		1807
H	Me	CO ₂ H	Me			256
H	Me	CO ₂ Me	Me	MeOH		1067

(continued)

TABLE II-23 (Continued)
Formation of 2-Pyridinol-6-methyl-2-
pyridinol from Ammonia and α -Pyrones

R_3	R_4	R_5	R_6	Conditions	Yield	Ref.
CO_2Me	<i>i</i> -Pr	H	Me	MeOH	(4- <i>i</i> -Propyl-6-methyl-2-pyridinol)	578
CO_2Et	<i>i</i> -Pr	H	Me	MeOH	(4- <i>i</i> -Propyl-6-methyl-2-pyridinol, 45%)	578
H	Ph	CO_2alkyl	Me			257
CO_2Et	<i>i</i> -Pr	H	Ph	MeOH, 20 hrs.	(4- <i>i</i> -Propyl-6-phenyl-2-pyridinol, 30%)	577
CO_2Me	CH_3Ph	H	Ph	MeOH, 25°, 5 hrs.	(4-Benzyl-6-phenyl-2-pyridinol, 57%)	577
CO_2Me	Ph	H	Ph	Alc., 2 days	(Also 4,6-diphenyl-2-pyridinol)	1358
H	Ph	CO_2alkyl	Ph			257
CO_2Me	CH_3Ph	H	<i>p</i> - ClC_6H_4	MeOH		1218
CO_2Me	<i>o</i> - ClC_6H_4	H	Ph	MeOH, 1½ hrs.	(4- <i>o</i> -Chlorophenyl-6-phenyl-2-pyridinol, 50%)	443
CO_2Et	<i>o</i> - ClC_6H_4	Me	Ph	MeOH, 25°, 18 hrs.	(4- <i>o</i> -Chlorophenyl-5-methyl-6-phenyl-2-pyridinol also formed as byproduct)	577

Cl	H	CO ₂ Me	H	Aq.	253
Br	H	CO ₂ Me	H	Aq.	254
Br	Me	CO ₂ Et	Me	MeOH	439
H	CH ₂ CO ₂ H	CO ₂ H	CH ₂ CO ₂ H	Aq. or alc., 100°	1658
				(5-Carboxy-4-carboxy-methyl-6-methyl-2-pyridinol)	256
CO ₂ Et	H	CO ₂ Et	Me	Aq.	1607
				(5-Carbethoxy-3-carboxy-6-methyl-2-pyridinol)	
H	OEt	H	CO ₂ Et	Alc.	248
				(6-Carbethoxy-4-hydroxy-2-pyridinol)	
CO ₂ Et	H	CO ₂ Et	OEt	Aq.	1610, 1627
				(See pp. 180-181)	
H	H	2H ^b	H, Me ^b	Benzene	1654
				(See pp. 180-181)	
2H ^b	H, Ph ^b	H	Me	Aq., 200°	1204
				(6-Methyldihydro-2-pyridinol)	
				(6-Methyl-4-phenyl-dihydro-2-pyridinol)	1248

^aMay be 3-bromo-4,6-dimethyl-2-pyrone.^bThese are dihydropyrone.

TABLE II-24. Formation of 1-Substituted 2(1*H*)-Pyridones from Amines and α -Pyrones

$ \begin{array}{c} \text{R}_4 \\ \\ \text{R}_6 \text{---} \text{C}_5 \text{H}_4 \text{O} \text{---} \text{C}_6 \text{O} \\ \\ \text{R}_3 \end{array} \xrightarrow{\text{R}_1\text{NH}_2} \begin{array}{c} \text{R}_4 \\ \\ \text{R}_6 \text{---} \text{C}_5 \text{H}_3 \text{N} \text{---} \text{C}_6 \text{O} \\ \\ \text{R}_3 \end{array} $		R ₁		R ₂		R ₃		R ₄		R ₅		R ₆		Conditions	Yield, %	Ref.
Ph		H	H	H	H	H	H	H	H	Ph				Aq. alc., reflux	60	1066
Me		H	H	H	H	H	H	H	H	H				Aq. alc., reflux		796
CH ₂ CH ₂ (from ethylene diamine)		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	(The ethylene bis product)	796
CH ₂ Ph		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	35	796
CH ₂ CH ₂ Ph		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	65	796
CH ₂ CH ₂ [3,4-(MeO) ₂ C ₆ H ₃]		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	73	796
CH ₂ CH ₂ NEt ₂		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	68	796
3-Morpholino-1-propyl		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	67	796
4-NH ₂ C ₆ H ₄		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	55	796
OH		H	H	H	H	H	H	H	H	H				Hydroxylamine hydrochloride, alc., pyridine, heat	59	796
NH ₂		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	70	796
NHPh		H	H	H	H	H	H	H	H	H				Alc., trace HCl	30	796
Me		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	40	796
CH ₂ CH ₂ Ph		H	H	H	H	H	H	H	H	H				Aq. alc., reflux	34	796

NHPh	H	H	<i>p</i> -MeC ₆ H ₄ CO	H	Aq. alc., reflux	31	796
3-Morpholino-1-propyl	H	H	<i>p</i> -ClC ₆ H ₄ CO	H	Aq. alc., reflux	61	796
CH ₂ CH ₂ Ph	H	H	H	CO ₂ H	HOAc, reflux, 50 hrs.	37	1629
CH ₂ CH ₂ [3,4-(MeO) ₂ C ₆ H ₃]	H	H	H	CO ₂ H	HOAc, reflux, 50 hrs.	30	1629
Me	H	H	CO ₂ Me	H	(Isolated as free acid by saponification)	(Isolated as free acid by saponification)	251, 252
Me	H	H	CO ₂ Et	H	MeOH, HCl, 0°, 2 hrs.	(Ethyl 6-methoxynicotinate ?)	1199
CH ₂ CH=CH ₂	H	H	CO ₂ Me	H	Aq. or alc., 25°, 1 hr.	(Isolated as free acid by saponification)	1402, 1410
Cyclohexyl	H	H	CO ₂ Me	H	Aq., 25°, 1 hr.	(Isolated as free acid by saponification)	1402
CH ₂ Ph	H	H	CO ₂ Me	H	MeOH, 25°, 8 days	(Isolated as free acid by saponification) 45	1629
CHMePh	H	H	CO ₂ Me	H	MeOH, 25°, 8 days	(Isolated as free acid by saponification) 18	1629
CH ₂ CH ₂ Ph	H	H	CO ₂ Me	H	MeOH, 25°, 18 hrs.	44	1134
CHMeCH ₂ Ph	H	H	CO ₂ Me	H	MeOH, 25°, 18 hrs.	21.5	1134

(continued)

TABLE II-24 (Continued)
Formation of 1-Substituted 2(1H)-Pyridones from Amines and α -Pyrones

R_1	R_2	R_3	R_4	R_5	R_6	Conditions	Yield, %	Ref.
Ph	H	H	H	CO ₂ Me	H		(As free acid by saponification)	251
4-MeOC ₆ H ₄	H	H	H	CO ₂ Me	H	MeOH, 25°, 8 days	(Isolated as free acid by saponification) 81	1629
3,4-(MeO) ₂ C ₆ H ₃	H	H	H	CO ₂ Me	H	MeOH, 25°, 18 hrs.	69	1134
3,4-CH ₂ O ₂ C ₆ H ₃	H	H	H	CO ₂ Me	H	MeOH, 25°, 18 hrs.	33	1134
NHCONH ₂	Br	Br	H	CO ₂ Me	H	MeOH, 25°, 18 hrs.	40	1657
3,4-Dicarbethoxy-2,5-dimethyl-1-pyrryl	CO ₂ Et	CO ₂ Et	H	CO ₂ Me	H	HOAc, reflux, 6 hrs.	21.4	1657
Ph	CO ₂ Et	H	CO ₂ Et	Me	Me	(1) heat in aniline (2) boil intermediate in alcoholic KOH	(Isolated as free acid by saponification)	1607
Et	CO ₂ Et	H	CO ₂ Et	OEt	OEt	Aq.	(See pp. 180-181)	1652
Ph	CO ₂ Et	H	CO ₂ Et	OEt	OEt	Aq. or Aq. HOAc or ether	(See pp. 180-181)	1651

TABLE II-25. Formation of 4-Pyridinol from Ammonia and γ -Pyrones

R_2	R_3	R_4	R_5	R_6	Conditions	Yield, %	Ref.
Me	H	H		Me	Aq. 120°, 12 hrs.	(Isolated as 4-chloro derivative by use of PCl_5 and $POCl_3$) 75	1203
Me	Me	H		Me	Aq., 25°, 3 hrs.		1074, 1465
Et	H	H		Et	Aq., 140°, 4 hrs.		1074
Pr	H	H		Pr	Aq., 140°, 4 hrs.		1186
CH:CHPh	H	H		CH:CHPh	Alc., 180°, 10 hrs.	20	1186
Ph	H	H		H	Aq., evaporate to dryness		588
H	Ph	Ph		H	NH_4OAc , heat		1196
Me	COMe	H		Me	Aq., 75°, 1 hr., pressure		1195
Me	3,5-(NO_2) ₂ - C_6H_3CO	H		Me	Aq. alc., 25°, 18 hrs.	50 Crude	890
CO_2H	H	H		H	Aq., water bath	87-92	1733, 1641
CO_2H	H	H		CO_2H	Aq., water bath		769
					Aq.		270-272, 1052, 1055
					Aq., steam bath, 4 hrs.	32 Very pure	1334
					Aq., reflux, 5 hrs.; or evaporate to dryness twice		1518, 1644

(continued)

TABLE II-25 (Continued)
Formation of 4-Pyridinol-4-ones from Ammonia and γ -Pyrones

R_2	R_3	R_3	R_4	Conditions	Yield, %	Ref.
CO_2H	Ph	H	CO_2H	Aq., evaporate to dryness twice		864
CH:CHPh	CO_2H	CO_2H	CH:CHPh	Alc.	Excellent	698
				Aq., 100°, 10 hrs.	(2,6-Distyryl-4-pyridinol) 94.8	588
Me	CO_2Et	CO_2Et	Me	Alc., stand 3 days	90	275
				Alc.		276, 1071, 1285
Ph	CO_2Et	CO_2Et	Ph			1024, 1025, 1080
I	OH	H	I	Aq., reflux, 3 hrs.	25	554
CH_3OH	H	OH	H	Aq., heat (reflux or evaporation)	Low to 61	246, 247, 451, 1202, 1537, 1733
				Aq., 100°, 4 hrs., pressure	30	627
CH_3OH	H	OH	COCHOHMe	Aq., 105°, 3 hrs., pressure	Low	670
CO_2H	H	OH	Br	Aq., 150°, several hrs.	(2-Carboxy-4,5-dihydroxypyridine)	1734

CO ₂ H	OH	H	CO ₂ H	Aq., 5 hrs., reflux, or heat and evaporate	(2-Carboxy-4,5-dihydropyridine) low % to 56.2	1529, 1537, 1641
H	OMe	H	H	Aq., 100°, 2 hrs.	68-88	694, 1201, 1459
Me	OMe	H	H	Aq., water bath, 2 hrs.	Low	694
Me	H	OMe	H	Aq., 90°, 2 hrs., or 100°, several hrs., pressure		1451, 1332
CH ₂ OH	H	OMe	H	Aq., 90-100°, 2-3 hrs. (often with pressure)	75-100	1167, 1187, 1194, 1451, 1640
CH ₂ OMe	H	OMe	H	Aq., 90-100°, 3 hrs., pressure or evaporation		1167, 1332
CH ₂ NEt ₂	H	OMe	H	Aq., 100°, 6 hrs., pressure		627
CH ₂ NMe ₂ Cl	H	OMe	H	Aq., heat, 2 hrs., pressure		627
CO ₂ H	H	OMe	H	Aq., 90°, pressure		1167
H	OEt	H	H	Aq., water bath, 2 hrs.	Low	694
CH ₂ OH	H	OBu	H	Aq., water bath, 4 hrs., pressure	80.7	1641
CH ₂ OH	H	OCH ₂ CH:CH ₂	H	Aq., water bath, 2 hrs.	50	1834

TABLE II-26. Formation of 1-Substituted 4(1*H*)-Pyridones from Amines and γ -Pyrones

R_1	R_2	R_3	R_4	R_5	Conditions	Yield	Ref.
$CHPh_3$	H	H	H	H	Alc.	42.3%	1185
CH_2CHPh_3	H	H	H	H	Alc.	31%	1185
$CH_2CH_2CHPh_3$	H	H	H	H	Alc.	Impure	1185
$CH_2CHPhCH_2Ph$	H	H	H	H	Alc.	Impure	1185
$CH_2CH_2CO_2H$	H	H	H	H	105° , 4 hrs., pressure	81%	1104
$CH_2CH_2CO_2Et$	H	H	H	H	105° , 4 hrs., pressure	10% Isolated as free acid	1104
$CH_3CH_2NEt_2$	H	H	H	H	(1) acetic acid	85% (See p. 1200, 1056, 1337)	1192
Ph	H	H	H	H	(2) HCl or NaOEt or vac. distil	(See p. 182)	1200, 1337
<i>p</i> -MeC ₆ H ₄	H	H	H	H	(1) acetic acid	(See p. 182)	1200, 1337
					(2) HCl or NaOEt or vac. distil		
<i>p</i> -BrC ₆ H ₄	H	H	H	H	(1) acetic acid	(See p. 182)	1337
					(2) HCl or NaOEt or vac. distil		

m -NO ₂ C ₆ H ₄	H	H	H	(1) acetic acid (2) HCl or NaOEt or vac. distil	(See p. 182)	1200, 1337
p -MeOC ₆ H ₄	H	H	H	(1) acetic acid (2) HCl or NaOEt or vac. distil	(See p. 182)	1337
α -C ₁₀ H ₇	H	H	H	(1) acetic acid (2) HCl or NaOEt or vac. distil	(See p. 182)	1337
β -C ₁₀ H ₇	H	H	H	(1) acetic acid (2) HCl or NaOEt or vac. distil	(See p. 182)	1337
9-Fluorenyl	H	H	H	Alc.	42.3%	1185
Me	Me	H	Me	3 hrs., stand	88%	1465
Ph	Me	H	Me	Heat		1337
Me	H	p -MeC ₆ H ₄	H	MeOH, 160°, 14 hrs.	97%	1827
p -NO ₂ C ₆ H ₄ NH	CO ₂ H	H	H	HOAc, heat, 5 min.	(p -Nitrophenyl- hydrazone of 2-carboxy-1- (p -nitro-ani- lino)-4-pyri- done)	764
Me	CO ₂ H	H	H	Heat, 6 hrs.		1055,
				Aq., 90°, 3 hrs., pH 8		1644
				110°, 1 day, pres- sure	89%	798
						535

(continued)

TABLE II-26 (Continued)
Formation of 1-Substituted 4(1*H*)-Pyridones from Amines and γ -Pyrones

R_1	R_2	R_3	R_3	R_3	R_6	Conditions	Yield	Ref.
Et	CO_2H	H	H	H	CO_2H	Aq., 90°, 3 days, pH 8	64%	798
CH_2Ph	CO_2H	H	H	H	CO_2H	Alc.	84%	1185
$\text{CH}_2\text{CH}_2\text{CHPh}_2$	CO_2H	H	H	H	CO_2H	Alc.	79%	1185
$\text{CH}_2\text{CHPhCH}_2\text{Ph}$	CO_2H	H	H	H	CO_2H	Alc.	76.6%	1185
$\text{CH}_2\text{CO}_2\text{H}$	CO_2H	H	H	H	CO_2H	Aq., heat	66%	274, 1184
$p\text{-HO}_2\text{CC}_6\text{H}_4\text{-}$ CHCO_2H	CO_2H	H	H	H	CO_2H	Aq., heat	98%	1184
$p\text{-H}_2\text{O}_2\text{AsC}_6\text{H}_4\text{-}$ CHCO_2H	CO_2H	H	H	H	CO_2H	Aq., heat	90%	1184
$\text{CH}_2\text{CH}_2\text{NH}_2$	CO_2H	H	H	H	CO_2H	(1) Alc., reflux, 2 hrs. (2) Aq. HCl	(See p. 184)	1630
Ph	CO_2H	H	H	H	CO_2H	180° or 280°	(1-Phenyl- 4(1 <i>H</i>)-pyridone up to 90%)	273, 1052, 1055 1053, 1337

$p\text{-MeC}_6\text{H}_4$	CO_2H	H	H	CO_2H	Aq., reflux, 5 hrs.	Crude	273
					150°	85%	1053
					180°	(1-Tolyl-4(1H)-pyridone 100%)	1053
2,4-Me ₂ C ₆ H ₃	CO_2H	H	H	CO_2H	180°	(1-(2,4-Dimethyl-phenyl)-4(1H)-pyridone 65%)	1053
$p\text{-ClC}_6\text{H}_4$	CO_2H	H	H	CO_2H		(1- <i>p</i> -Chlorophenyl-4(1H)-pyridone)	325
$m\text{-NO}_2\text{C}_6\text{H}_4$	CO_2H	H	H	CO_2H		(1- <i>m</i> -Nitrophenyl-4-pyridone low %)	
$p\text{-CO}_2\text{HC}_6\text{H}_4$	CO_2H	H	H	CO_2H			274
$p\text{-NH}_2\text{SO}_2\text{C}_6\text{H}_4$	CO_2H	H	H	CO_2H	Aq., reflux, 2 hrs.	75% (See pp. 183-184)	1380
$o\text{-MeOC}_6\text{H}_4$	CO_2H	H	H	CO_2H	180°	(1- <i>o</i> -Methoxyphenyl-4(1H)-pyridone)	1053
$p\text{-EtOC}_6\text{H}_4$	CO_2H	H	H	CO_2H		(1- <i>p</i> -Ethoxyphenyl-4(1H)-pyridone)	325

(continued)

TABLE II-26 (Continued)
Formation of 1-Substituted 4(1H)-Pyridones from Amines and γ -Pyrones

R_1	R_2	R_3	R_4	R_5	Conditions	Yield	Ref.
p -AsO ₃ H ₃ C ₆ H ₄ , α -C ₁₀ H ₇	CO ₂ H	H	H	CO ₂ H	180°	(1- α -Naphthyl-4(1H)-pyridone)	274
	CO ₂ H	H	H	CO ₂ H			1053
p -NO ₂ C ₆ H ₄ NH	CO ₂ H	H	H	CO ₂ H	HOAc, heat, 5 min.	(p -Nitrophenyl-hydrazine of 2,6-dicarboxy-1- p -nitroanilino-4(1H)-pyridone)	764
Me	CH:CHPh	CO ₂ H	CO ₂ H	CH:CHPh	Aq., 100°, 6 hrs., pressure	(2,6-Distyryl-1-methyl-4(1H)-pyridone)	588
Me	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	72%	698, 864
CHMe ₂	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	59%	698, 864
CHMePr	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	45%	698, 864
CH ₂ CH ₂ CHMe ₂ CH ₂ CH ₂ NEt ₂	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	48%	864
	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	61%	698, 864
CH ₃ CH ₂ CH ₂ NEt ₂	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux	% Good	698

CHMe(CH ₃) ₂ NEt ₂	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	52%	864
Ph	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	72%	699, 865
<i>p</i> -NO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	63%	699, 865
<i>m</i> -NO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	55%	699, 865
<i>o</i> -NO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	57%	699, 865
<i>p</i> -ClC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	39%	699, 865
<i>o</i> -ClC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	35%	699, 865
<i>p</i> -MeC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	57%	699, 865
<i>m</i> -MeC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	57%	699, 865
<i>o</i> -MeC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ Hr.	51%	699, 865
<i>p</i> -CO ₂ HC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	68%	699, 865
<i>o</i> -CO ₂ HC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	81%	699, 865
<i>p</i> -MeOC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{3}{4}$ hr.	49%	699, 865

(continued)

TABLE II-26 (Continued)
Formation of 1-Substituted 4(1*H*)-Pyridones from Amines and γ -Pyrones

R_1	R_2	R_3	R_4	R_5	Conditions	Yield	Ref.
p -SO ₂ HC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Aq., alc., reflux, 1 hr.	62%	699, 865
m -SO ₂ HC ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Aq., alc., reflux, 1 hr.		699, 865
p -NH ₂ SO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Aq., reflux, 6 hrs.	1-(4-Sul- famyphenyl)- 2,6-dicarboxy- 3-phenyl-4- (4-aminoben- zenesulfon- imino)-1,4-di- hydropyridine 50%	579
p -(2-C ₆ H ₄ N)SO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, $\frac{1}{2}$ hr.	40%	579
p -(2-C ₆ H ₄ NS)- SO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H			579
p -(2-C ₆ H ₄ N ₂)- SO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	40%	579
p -(4-Me-2-C ₆ H ₂ N ₂)- SO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H		40%	579
p -(4,6-Me ₂ C ₆ H ₂ N ₂)- SO ₂ C ₆ H ₄	CO ₂ H	Ph	H	CO ₂ H			579
MeNHC(:NH)NH- C(:NH)	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	38% (See pp. 183-184)	580

PhNHC(:NH)NH-C(:NH)	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	39% (See pp. 183-184)	580
<i>p</i> -MeOC ₆ H ₄ NH-C(:NH)NHC(:NH)	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	44% (See pp. 183-184)	580
<i>p</i> -ClC ₆ H ₄ NH-C(:NH)NHC(:NH)	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	39% (See pp. 183-184)	580
<i>p</i> -MeC ₆ H ₄ NH-C(:NH)NHC(:NH)	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	47% (See pp. 183-184)	580
<i>p</i> -NO ₂ C ₆ H ₄ C(:NH)-NHC(:NH)	CO ₂ H	Ph	H	CO ₂ H	Alc., reflux, 1 hr.	37% (See pp. 183-184)	580
<i>p</i> -HOC ₆ H ₄	CO ₂ H	H	H	CO ₂ Et	70% HOAc, 100°, 20 min.		587
<i>p</i> -IC ₆ H ₄	CO ₂ Et	H	H	CO ₂ Et	50% HOAc, heat, 45 min.	32%	590
<i>p</i> -HOC ₆ H ₄	CO ₂ Et	H	H	CO ₂ Et	50% HOAc, heat, 25 min.		1158
<i>m</i> -HOC ₆ H ₄	CO ₂ Et	H	H	CO ₂ Et	50% HOAc, heat, 25 min.	48%	1158
3,5-(MeO) ₂ C ₆ H ₄	CO ₂ Et	H	H	CO ₂ Et			1158
<i>p</i> -AcNHC ₆ H ₄	CO ₂ Et	H	H	CO ₂ Et			1158
<i>p</i> -NH ₂ C ₆ H ₄	CO ₂ Et	H	H	CO ₂ Et		(The bis product)	1158
Me	Me	CO ₂ Et	CO ₂ Et	Me	HOAc, heat, short time	90%	275 276, 1071

(continued)

TABLE II-26 (Continued)
Formation of 1-Substituted 4(1*H*)-Pyridones from Amines and γ -Pyrones

R_1	R_2	R_3	R_3	R_3	R_4	Conditions	Yield	Ref.
Ph	Me	CO_2Et	CO_2Et	Me		HOAc, heat, short time		275, 276, 1071 1158
						HOAc, reflux, $\frac{1}{2}$ hr.	4% (2,6-Di-anilino-3,5-dicarbethoxy-2,5-hepta-diene-4-one major product)	
4- IC_6H_4	Me	CO_2Et	CO_2Et	Me		HOAc, water bath, $\frac{1}{2}$ hr.	70%	590
2,4- $\text{I}_2\text{C}_6\text{H}_3$	Me	CO_2Et	CO_2Et	Me		60% HOAc, water bath, 2 $\frac{1}{2}$ hrs.	26%	590
<i>p</i> - HOC_6H_4	Me	CO_2Et	CO_2Et	Me		50% HOAc, heat, 15 min.	97%	1158
<i>m</i> - HOC_6H_4	Me	CO_2Et	CO_2Et	Me		50% HOAc, heat	63%	1158
3,5- Me_2 -4-OH- C_6H_3	Me	CO_2Et	CO_2Et	Me				1158
<i>p</i> - AcNHC_6H_4	Me	CO_2Et	CO_2Et	Me				1158
<i>p</i> - $\text{NH}_2\text{C}_6\text{H}_4$	Me	CO_2Et	CO_2Et	Me			(The bis product) 73%	1158
Me	H	OH	H	H				324
Et	H	OH	H	H		230°	10%	1290
Br	H	OH	H	H		230°	26%	1290

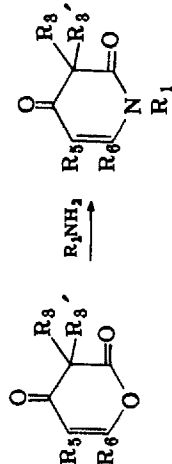
CH ₂ CH(OEt) ₂	H	OH	H	H	(1) Aq. steam bath (2) Stand	14%	1189
Me	CH ₂ OH	H	OH	H	Aq., boil	10%	1648
CH ₂ CH ₂ OH	CH ₂ OH	H	OH	H	230°	15.8%	627
Me	CO ₂ H	H	OH	H	Aq., 100°, 10 hrs.	44%	1290
Me	CO ₂ H	OH	H	CO ₂ H	230°	(1-Methyl-3- hydroxy-4(1H)- pyridone) 40%	1393
Et	CO ₂ H	OH	H	CO ₂ H	230°	(1-Ethyl-3- hydroxy-4(1H)- pyridone) 15%	1290
CHMe ₂	CO ₂ H	OH	H	CO ₂ H	230°	(1- <i>i</i> -Propyl-3- hydroxy-4(1H)- pyridone) 20%	1290
CH ₂ CO ₂ H	CO ₂ H	OH	H	CO ₂ H	230°	(1-Carboxy- methyl-3- hydroxy-4(1H)- pyridone) 47%	1290
Ph	OH	H	H	OH	ZnCl ₂ , boil	31%	1205
Me	H	OMe	H	H	Aq., 100°, 2 hrs.		1211
CH ₂ CH(OEt) ₂	H	OMe	H	H			1189
CH ₂ CH ₂ CO ₂ H	H	OMe	H	H	Aq., 105°, 4 hrs.	81%	1104
CH ₂ CH ₂ CO ₂ Et	H	OMe	H	H	Aq., 105°, 4 hrs.		1104
Me	Me	OMe	H	H	Aq., 25°, 3 hrs.	67%	1465

(continued)

TABLE II-26 (Continued)
Formation of 1-Substituted 4(1H)-Pyridones from Amines and γ -Pyrones

R ₁	R ₂	R ₃	R ₄	R ₅	Conditions	Yield	Ref.
Me	Me	H	OMe	H	Aq., 100°, sev. hrs., pressure		1332
Me	CH ₂ OH	H	OMe	H	MeOH, stand; or aq., 100°, 2 hrs.	71-81%	627, 1187, 1194, 1465
CH ₃ CH ₂ OH	Me	H	OMe	H	Reflux, 3 hrs.	58%	1451
CH ₃ CH ₂ OH	CH ₂ OH	H	OMe	H	Reflux, 1 hr.; or aq., reflux, 2 hrs.	40-76%	627, 1451
CH ₃ CO ₂ Na	Me	H	OMe	H	Aq., 115°, 24 hrs., pressure	53.5%	627
Me	CH ₂ OMe	H	OMe	H	MeOH, stand	50-80%	627, 1187
CH ₃ CO ₂ Na	CH ₂ OH	H	OMe	H	Aq., 120°, 10 hrs., pressure	18.3%	627
CH ₃ CO ₂ Et	CO ₂ H	H	OMe	H	Aq., 120°, 10 hrs., pressure	37.5%	1590
CH ₃ CH ₂ NEt ₂	CH ₂ OH	H	OMe	H	Aq., reflux, 2 hrs.	85%	627
Me	CH ₂ NEt ₂	H	OMe	H	60°, $\frac{1}{2}$ hr.		1167
Me	CH ₂ NMe ₂ Cl	H	OMe	H	MeOH, 2 hrs.		1167
CH ₃ CH ₂ NEt ₂	CO ₂ H	H	OMe	H	Aq., heat, 3 hrs.	75%	1590

TABLE II-27. Formation of Pyridinediones from Amines and 2,4-Pyrandiones

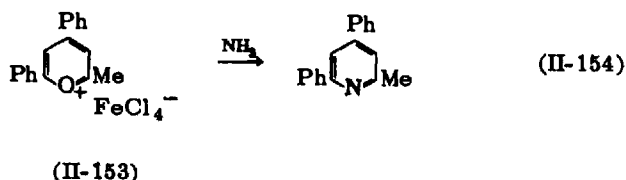


R ₁	R ₃	R _{3'}	R ₆	Conditions	Yield	Ref.
Me	Et	H	Me	Aq., steam bath, 4 hrs.	36%	1648
H	R	R	Me			1210
H	Ph	H	CH ₃ Ph	Aq., 100°, 11 hrs.; then 140°, 8 hrs.	80%	1805
H	Ac	H	Me	Aq., 100-30°	(See pp. 180-187)	69,70,71,72, 691,1604, 1605,1606
H	COPh	H	Ph		(See pp. 180-187)	1024,1079, 1080,1081
H	COPh	Ph	Ph	Aq., 160°, 3 hrs.	3,5,6-Triphenyl-2,4- pyridinediol 40%	1216
H	H	H	CO ₂ H	Aq., 120°, 18 hrs.	93.7%	915
H	OH	H	CO ₂ H	Aq.	63%	1202,1733

5. Pyrylium Salts

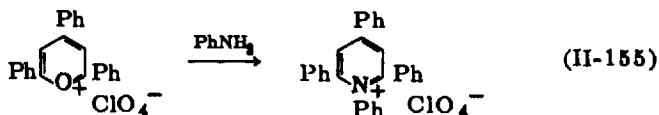
Pyrylium salts are converted to pyridine compounds by reaction with ammonia, primary amines, or hydrazines. This is a good preparative method since the yields are high and the starting materials readily obtained. However, the pyrylium salts available are limited almost exclusively to 2,4,6-trisubstituted ones, most commonly with two or three aryl substituents.

Pyrylium salts have been prepared by various acid-catalyzed condensations. Benzylideneacetophenone and acetophenone, for example, give a 2,4,6-triphenylpyrylium salt; or acetic anhydride and two moles of acetophenone give a 2-methyl-4,6-diphenylpyrylium salt (II-153). They have also been made from 4-pyrones, by means of methylating agents (giving 4-methoxypyrylium salts), or Grignard reagents (giving 4-alkyl or 4-aryl derivatives).



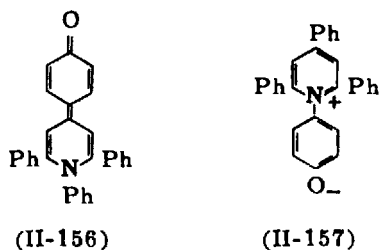
Ammonia converts pyrylium salts to pyridine bases (II-154) (121, 1705,517). The reaction, due originally to Baeyer (1596), and widely extended by Diltthey, is carried out in aqueous medium, sometimes in the presence of ammonium salts, or in absolute alcohol (Table II-28). One interesting application was the preparation of pyridine itself from pyrylium perchlorate by fusion with ammonium acetate (896); however, the yield was only 10%, and the starting material was derived from glutaconaldehyde, which is not readily available.

Primary amines convert pyrylium salts to pyridinium salts (II-155) (1284). Generally an excess of the amine is used, with mild

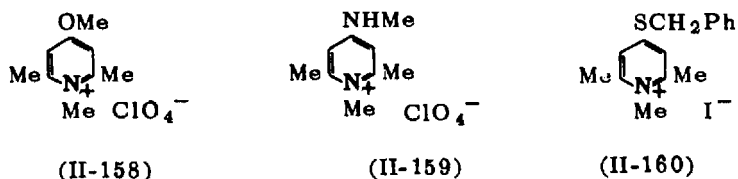


heating in the absence of solvent, or less frequently in an organic medium (Table II-29).

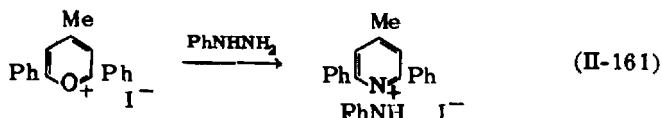
When a *p*-hydroxyphenyl group is present in the 4-position, the pyridinium salt on treatment with base forms a quinonoid compound (II-156), accompanied by a bathochromic change (1006,1034, 1035). When the hydroxyphenyl group is in the 1-position, on the other hand, basification produces a betaine (II-157) (904).



A 4-methoxy group may be replaced by the amine during pyridine formation. Thus, 2,6-dimethyl-4-methoxypyrylium perchlorate with one mole of methylamine gave the normal product (II-158), but with an excess gave II-159; (1203); it was also demonstrated that II-158 is convertible to II-159 (1636). A similar displacement of a 4-benzylthio group occurs, giving a mixture of the normal product (II-160) with II-159 (iodide) (1636).

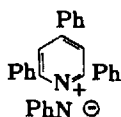


Arylhydrazines convert pyrylium salts to 1-arylamino-pyridinium compounds (II-161) (282), a reaction investigated mainly by Schneider (first report, reference 1007). A variety of arylhydrazines, as well as methylhydrazine, have been found to react with di- and triarylp-

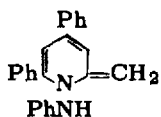


rylium compounds in refluxing benzene or other organic solvent (Table II-30).

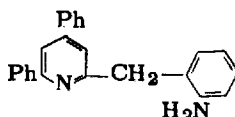
The 1-arylamino-pyridinium salts form anhydro bases on treatment with strong alkali. These have a dipolar structure (II-162), first assumed by Schneider and Riedel (899), and later supported on spectral evidence by Dimroth and co-workers, (898), who showed a hypsochromic shift with increasing dielectric constant of the solvent. When a 2- or 4-methyl group was present in the pyridinium salt, it was thought by Schneider, on the basis of chemical reactions, that the anhydro base was a tautomeric mixture containing some of the methylene base (II-163) (282,899). However, Dimroth and co-workers showed spectrally that it was a single substance, and dipolar in the same manner as II-162 (898).



(II-162)



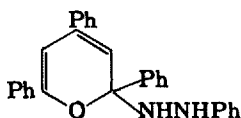
(II-163)



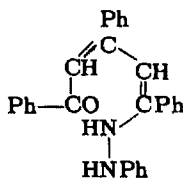
(II-164)

Further conversions to useful pyridines can be made. The anhydro base, II-162, can be converted to a good yield of 2,4,6-triphenylpyridine by reductive cleavage (914). Anhydro bases having a 2-methyl group rearrange in boiling alcohol to 2-*o*-aminobenzylpyridines (II-164) (914,899).

The reaction of pyrylium salts with arylhydrazines has sometimes given stable products containing oxygen. These have been assigned the 2-hydrazino-1,2-pyran structure (II-165) (282,283,898, 1650), but could as well be the open-chain tautomers (II-166), or mixtures of the two. Schneider and Müller (283) were able to con-

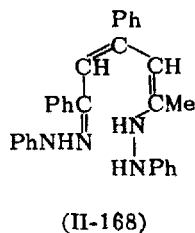
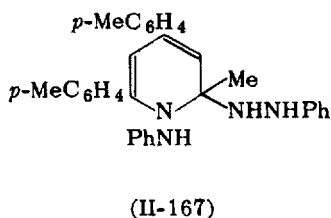


(II-165)



(II-166)

vert one such product into an isomer, different in chemical reactivity; but though they attempted to assign the ring structure to one and the open-chain structure to the other, the evidence was not conclusive, nor was the homogeneity of either product established. In all cases the oxygen-containing materials are converted to the 1-anilinopyridinium salts on treatment with hot glacial acetic acid, or to the anhydro pyridine base, in one case (283), on treatment with caustic or sodium ethoxide. For this reason it was assumed by Schneider and Müller that such compounds (either II-165 or II-166) are intermediates in the conversion of pyrylium salts to pyridines. Treatment of these "intermediates" with additional phenylhydrazine has given mixtures of new products for which both a ring structure (II-167) and open-chain structures (such as II-168) have been proposed, again on little evidence (283,1650).



The mechanism for the conversion of pyrylium salts to pyridines has not been established. No doubt the nucleophilic agent (ammonia, amine or hydrazine) attacks the 2 position (II-169), after which a proton is lost in concert with ring opening (II-170). The intermediate recycles in a different sense, by attack of the nitrogen on the carbonyl group. An equivalent of acid is liberated during the conversion, and this is of course available for catalysis of the last step.

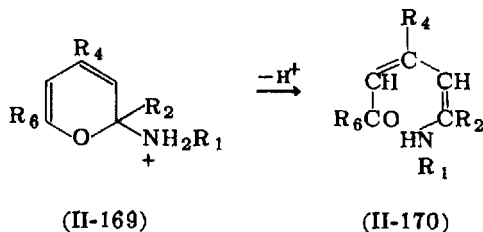
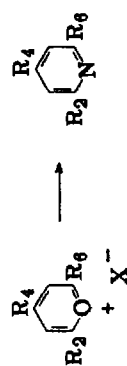
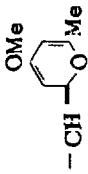


TABLE II-28. Reaction of Pyrylium Salts with Ammonia



R_3	R_4	R_6	X^-	Conditions	Yield, %	Ref.
H	H	H	ClO_4^-	NH_4OAc , fuse, 75° , 0.5 hr.	9.7	896
Me	Me	Me	ClO_4^-	Aq. NH_3 , warm		120,1650
				Aq. NH_3 , NH_4OAc , reflux 2 hrs.	77	1150
Me	Ph	Me	ClO_4^-	Aq. NH_3 , warm		120
Ph	Ph	Me	FeCl_4^-	Aq. NH_3 , RT overnight		121,122
				Aq. NH_3		517,1705
Ph	Ph	Ph	BF_4^-	NH_3		571
			FeCl_4^-	Aq. NaOAc ; then in MeOH , NH_3 , gas, reflux 2-3 hrs. ^a		121
<i>p</i> -Tolyl	Ph	Ph	FeCl_4^-	NH_3 , alc.		1037
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Me	ClO_4^-	NH_3 , alc., evaporate		1650
<i>p</i> -Tolyl	Ph	<i>p</i> -Tolyl	FeCl_4^-	NH_3 , alc.		1037
<i>p</i> -PhC ₆ H ₄	Ph	Ph	FeCl_4^-	NH_3 , alc.		1037
<i>p</i> -ClC ₆ H ₄	Ph	<i>p</i> -ClC ₆ H ₄	FeCl_4^-	NH_3 , alc.	100	1037
<i>p</i> -BrC ₆ H ₄	Ph	<i>p</i> -BrC ₆ H ₄	FeCl_4^-	NH_3 , alc., heat		1038
<i>m</i> -O ₂ NC ₆ H ₄	Ph	Ph	FeCl_4^-	NH_3 gas, alc.		1039
Ph	<i>m</i> -O ₂ NC ₆ H ₄	Ph	FeCl_4^-	NH_3 gas, alc.	80	1039
2-HO-4-Me-C ₆ H ₃	Ph	Ph	ClO_4^-	Aq. NH_3 , warm		1036

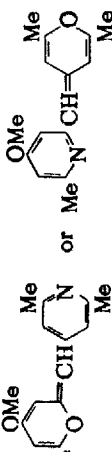
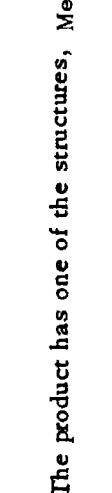
2-HO-4-Me- C ₆ H ₃	Ph	2-HOC ₆ H ₄	ClO ₄ ⁻	Aq. NH ₃	1036
<i>p</i> -Anisyl	Ph	Ph	FeCl ₄ ⁻	NH ₃ , alc.	1037
Ph	<i>o</i> -Anisyl	Ph	Br ⁻	NH ₃ , alc.	1191
Ph	<i>p</i> -Anisyl	Ph	FeCl ₄ ⁻	NH ₃ , alc.	1037
4-MeO-3-Me- C ₆ H ₃	Ph	Ph	FeCl ₄ ⁻	NH ₃ , alc., heat	1038
2-HO-4-Me- C ₆ H ₃	Ph	<i>p</i> -Anisyl	ClO ₄ ⁻	Aq. NH ₃ , heat	1036
<i>p</i> -Anisyl	<i>p</i> -Anisyl	Ph	FeCl ₄ ⁻	NH ₃ , alc.	1037
<i>p</i> -Anisyl	Ph	<i>p</i> -Anisyl	FeCl ₄ ⁻	NH ₃ , alc.	1037
2-HO-4-MeO- C ₆ H ₃	<i>p</i> -Anisyl	Ph	ClO ₄ ⁻	NH ₃	1036
2-HO-4-MeO- C ₆ H ₃	Ph	<i>p</i> -Anisyl	ClO ₄ ⁻	NH ₃ , alc., heat	1036
<i>p</i> -Anisyl	<i>p</i> -Anisyl	<i>p</i> -Anisyl	FeCl ₄ ⁻	NH ₃ , alc.	1037
2-HO-4-MeO- C ₆ H ₃	<i>p</i> -Anisyl	<i>p</i> -Anisyl	ClO ₄ ⁻	NH ₃ , alc.	1036
Ph	<i>p</i> -Me ₂ NC ₆ H ₄	Ph	Cl ⁻	NH ₃ , alc.	905
2-Naphthyl	Ph	Ph	FeCl ₄ ⁻	NH ₃ , alc.	1037
Me		Me	ClO ₄ ⁻	Aq. NH ₃ , 70°, 3 hrs.	^b 1203
Me	OMe	Me	ClO ₄ ⁻	Aq. NH ₃ , (NH ₄) ₂ CO ₃ , RT	87

(continued)

TABLE II-28 (Continued)
Reaction of Pyrylium Salts with Ammonia

R ₃	R ₄	R ₅	X ⁻	Conditions	Yield, %	Ref.
Me	OMe	Me	I ⁻	Aq. NH ₃ or (NH ₄) ₂ CO ₃		1596
Me	SMe	Me	I ⁻	Aq. NH ₃ , (NH ₄) ₂ CO ₃ , steam bath, 10 min.	85	1636, 1480
Me	SCH ₂ Ph	Me	I ⁻	Aq. NH ₃ , (NH ₄) ₂ CO ₃ , steam bath, 15 min.	75	1636, 1480
Me	SCH ₂ Ph	Me	ClO ₄ ⁻	Aq. NH ₃ , (NH ₄) ₂ CO ₃ , warm	c	1203
Me	N-Piperidino	Me	ClO ₄ ⁻	Aq. NH ₃ , (NH ₄) ₂ CO ₃ , MeOH, warm	75	1203
Me	N-Morpholino	Me	I ⁻	Aq. NH ₃ , (NH ₄) ₂ CO ₃ , steam bath, 0.5 hr.	94	1636
Pyrylium Salts Other Than 2,4,6-Trisubstituted						
2,3,4-Triphenyl-6-(p-bromophenyl)pyrylium tetrachloroferrate						
				NH ₃ , alc., heat		1038
2-Methyl-4,5-dimethoxypyrylium perchlorate (prepared <i>in situ</i> , used without purification)						
				(NH ₄) ₂ CO ₃ , aq., below 25°		1451

^aAqueous NaOAc gives the pyranol, which is isolated and further treated as indicated.

^bThe product has one of the structures,  or 

^cProduct isolated as picrate.

TABLE II-29. Reaction of Pyrylium Salts with Primary Amines

TABLE II-29. Reaction of Pyrylium Salts with Primary Amines

		$ \begin{array}{c} R_4 \\ \text{Pyrylium Ring} \\ R_2 \quad O^+ \quad R_6 \\ + \quad X^- \end{array} \xrightarrow{R_1NH_2} \begin{array}{c} R_4 \\ \text{Pyridine Ring} \\ R_2 \quad N \quad R_6 \\ R_1^+ \quad X^- \end{array} $		Yield, %	Ref.		
R ₂	R ₄	R ₆	X ⁻	R ₁	Conditions		
Me	Me	Me	ClO ₄ ⁻	Me	Aq., warm		120
Me	Me	Me	ClO ₄ ⁻	<i>p</i> -Tolyl	Alc., boil; HClO ₄	54	120
<i>p</i> -Me ₂ N- C ₆ H ₄ CH=CH	Me	<i>p</i> -Me ₂ N- C ₆ H ₄ CH=CH	ClO ₄ ⁻	Me			1510
<i>p</i> -Me ₂ N- C ₆ H ₄ CH=CH	Me	<i>p</i> -Me ₂ N- C ₆ H ₄ CH=CH	ClO ₄ ⁻	Et			1510
Me	Ph	Me	ClO ₄ ⁻	<i>p</i> -Tolyl	Alc., boil; HClO ₄	80	120
Styryl	Ph	CH=CHPh	ClO ₄ ⁻	Ph	Alc., heat 0.5 hr.		1510
<i>p</i> -MeO-	Ph	<i>p</i> -MeO-	ClO ₄ ⁻	Ph	Alc., heat 0.5 hr.		1510
C ₆ H ₄ CH=CH	Ph	C ₆ H ₄ CH=CH	ClO ₄ ⁻	Ph	Alc., heat 0.5 hr.		1510
3,4-CH ₂ O ₂ ⁻	Ph	3,4-CH ₂ O ₂ ⁻	ClO ₄ ⁻	Ph	Alc., heat 0.5 hr.		1510
C ₆ H ₄ CH=CH	Ph	C ₆ H ₄ CH=CH	ClO ₄ ⁻	Ph	Alc., heat 0.5 hr.		1510
<i>p</i> -Me ₂ N- C ₆ H ₄ CH=CH	Ph	<i>p</i> -Me ₂ N- C ₆ H ₄ CH=CH	ClO ₄ ⁻	Ph	Alc., heat 0.5 hr.		1510
<i>p</i> -Et ₂ N- C ₆ H ₄ CH=CH	Ph	<i>p</i> -Et ₂ N- C ₆ H ₄ CH=CH	ClO ₄ ⁻	Ph	Alc., heat 0.5 hr.		1510
Ph	Ph	Me	I ⁻	CH ₂ Ph		80	282
Ph	Ph	Me	I ⁻	Ph	Benzene, hot	100	282
<i>p</i> -Et ₂ N- C ₆ H ₄ CH=CH	Ph	Ph	ClO ₄ ⁻	Ph	Alc., heat 0.5 hr.		1510

(continued)

TABLE II-29 (Continued)
Reaction of Pyrylium Salts with Primary Amines

R_3	R_4	R_5	X^-	R_1	Conditions	Yield, %	Ref.
Ph	Ph	Ph	ClO_4^-	Ph	Water bath; then HClO_4 , MeOH	100	1284
Ph	Ph	Ph	ClO_4^-	<i>o</i> -Tolyl	Water bath; then HClO_4 , MeOH		1284
Ph	Ph	Ph	ClO_4^-	<i>p</i> -Tolyl	Water bath; then HClO_4 , MeOH		1284
Ph	Ph	Ph	I^-	<i>o</i> - HOC_6H_4	HClO_4 , MeOH KOAc, HOAc, reflux 10 min.; KI		904
Ph	Ph	Ph	I^-	<i>m</i> - HOC_6H_4	KOAc, HOAc, reflux 10 min.; KI		904
Ph	Ph	Ph	ClO_4^-	<i>p</i> - HOC_6H_4	MeOH, reflux; HClO_4		1284
Ph	Ph	Ph	I^-	<i>p</i> - HOC_6H_4	NaOAc, HOAc, reflux 10 min.; then aq. NaOH	^a	904
Ph	Ph	Ph	ClO_4^-	<i>o</i> -Anisyl	Water bath; then HClO_4 , MeOH		1284

Ph	Ph	Ph	I ⁻	<i>m</i> -Anisyl	Water bath 0.5 hr.; then aq. KI	904
Ph	Ph	Ph	ClO ₄ ⁻	<i>p</i> -Anisyl	Water bath; then HClO ₄ , MeOH	1284
Ph	Ph	Ph	I ⁻	<i>p</i> -Anisyl	HOAc, reflux 15 min.	1284
Ph	Ph	Ph	ClO ₄ ⁻	<i>p</i> -EtOC ₆ H ₄	Water bath; then HClO ₄ , MeOH	1284
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Me	ClO ₄ ⁻	CH ₂ Ph	Ether	1650
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Me	ClO ₄ ⁻	Ph	Ether	1650
<i>p</i> -HOC ₆ H ₄	Ph	Ph	Cl ⁻	<i>p</i> -H ₂ N- C ₆ H ₄	Alc.	1035
<i>p</i> -HOC ₆ H ₄	Ph	Ph	I ⁻	2-Naphthyl	Benzene, reflux	1034
Ph	<i>p</i> -HOC ₆ H ₄	Ph	Cl ⁻	Ph	Water bath	1006, 1034
Ph	<i>p</i> -HOC ₆ H ₄	Ph	Cl ⁻	<i>p</i> -Tolyl		1034
Ph	<i>p</i> -HOC ₆ H ₄	Ph	Br ⁻	<i>m</i> -O ₂ NC ₆ H ₄	150°, several hrs.	1035
Ph	<i>p</i> -HOC ₆ H ₄	Ph	Cl ⁻	<i>m</i> -H ₂ NC ₆ H ₄	Alc., reflux 2 hrs.; NH ₃	1035
Ph	<i>p</i> -HOC ₆ H ₄	Ph	Cl ⁻	<i>p</i> -H ₂ NC ₆ H ₄	Alc., reflux 1 hr.; NH ₃	1035
<i>p</i> -HOC ₆ H ₄	<i>p</i> -HOC ₆ H ₄	<i>p</i> -HOC ₆ H ₄	Br ⁻	Ph	Water bath 2 hrs.	1035

(continued)

TABLE II-29 (Continued)
 Reaction of Pyrylium Salts with Primary Amines

R_1	R_2	R_3	R_4	R_5	X^-	R_1	Conditions	Yield, %	Ref.
<i>p</i> -Anisyl		Ph		2-HO-4-MeOC ₆ H ₃	Picrate or ClO ₄ ⁻	Ph	Warm several hrs.		1036
2-HO-4-MeOC ₆ H ₃		<i>p</i> -Anisyl		Ph	ClO ₄ ⁻	Ph	Heat		1036
2-HO-4-MeOC ₆ H ₃		Ph		<i>p</i> -Anisyl	ClO ₄ ⁻	Ph	Water bath		1036
2-HO-4-MeOC ₆ H ₃		<i>p</i> -Anisyl		<i>p</i> -Anisyl	Picrate or ClO ₄ ⁻	Ph	Heat		1036
2-HO-4-MeOC ₆ H ₃		<i>p</i> -Anisyl		2-HO-4-MeOC ₆ H ₃	Picrate	Ph	Heat		1036
<i>p</i> -Me ₂ NC ₆ H ₄		Ph		Ph	ClO ₄ ⁻	Me	Alc., water bath 1 hr.		666
Ph		<i>p</i> -Me ₂ NC ₆ H ₄		Ph	ClO ₄ ⁻	Me	Alc., water bath 1 hr.		666
<i>p</i> -Me ₂ NC ₆ H ₄		<i>p</i> -Me ₂ NC ₆ H ₄		Ph	ClO ₄ ⁻	Me	Alc., water bath 1 hr.		666
<i>p</i> -Me ₂ NC ₆ H ₄		Ph		<i>p</i> -Me ₂ NC ₆ H ₄	ClO ₄ ⁻	Me	Alc., water bath 1 hr.		666
<i>p</i> -Me ₂ NC ₆ H ₄		<i>p</i> -Me ₂ NC ₆ H ₄		Ph	ClO ₄ ⁻	Me	Alc., water bath 1 hr.		666

Me	OMe	Me	I ⁻	Me	Alc., reflux 0.5 hr.	42	1636
					1 mole amine, alc., 80°, sealed, 0.5 hr.	19	1203
Me	OMe	Me	ClO ₄ ⁻	Me	Excess amine, MeOH, 70°, 15 min.	76 ^e	1203
					Excess amine, H ₂ CO ₃ , aq., warm 20 min.	f	1203
Me	OMe	Me	ClO ₄ ⁻	Ph	Excess amine, MeOH, reflux 1 hr.	g	1203
Me	SMe	Me	I ⁻	Me	Alc., reflux 0.5 hr.	81	1636
Me	SMe	Me	I ⁻	Ph	Alc., reflux 0.5 hr.	60	1636
Me	SCH ₂ Ph	Me	I ⁻	Me	Excess amine, aq. MeOH, reflux 15 min.	33 ^b	1636

(continued)

TABLE II-29 (Continued)
Reaction of Pyrylium Salts with Primary Amines

R ₁	R ₄	R ₆	X ⁻	R ₁	Conditions	Yield, %	Ref.
Me	SCH ₂ Ph	Me	I ⁻	CH ₂ Ph	1 mole amine, alc., reflux 0.5 hr.	80	1636
Me	Piperidino	Me	ClO ₄ ⁻	Me	Alc., 80°, sealed, 20 min.	60	1203
Me	Piperidino	Me	I ⁻	CH ₂ Ph	Alc., reflux 0.5 hr.	90	1636
Me	Morpholino	Me	I ⁻	CH ₂ Ph	Alc., reflux 0.5 hr.	97	1636

^aIsolated on the alkaline side as the betaine (see text).

^bProduct precipitated as the crude chloride, which was converted to the picrate and perchlorate salts.

^cIsolated on the alkaline side as the quinonoid compound (see text); also converted to the picrate.

^dIsolated as free base (quinonoid compound; see text); also converted to the chloride, bromide, and picrate.

^eProduct is 1,2,6-trimethyl-4-methylaminopyridinium perchlorate.

^fBy-product is the compound of Note e.

^gProduct is 1,2,6-trimethyl-4-anilinopyridinium perchlorate.

^hBy-product is 1,2,6-trimethyl-4-methylaminopyridinium iodide.

TABLE II-30. Reaction of Pyrylium Salts with Hydrazines

TABLE II-30. Reaction of Pyrylium Salts with Hydrazines

$ \begin{array}{c} \text{R}_4 \\ \\ \text{R}_2 \text{O} \text{---} \text{C} \text{---} \text{R}_6 \\ + \\ \text{X}^- \end{array} \xrightarrow{\text{R}_1\text{NH}_2} \begin{array}{c} \text{R}_4 \\ \\ \text{R}_2 \text{N} \text{---} \text{C} \text{---} \text{R}_6 \\ \\ \text{R}_1^+ \end{array} \text{X}^- $	R ₂	R ₄	R ₆	X ⁻	R ₁	Conditions	Yield, %	Ref.
Ph	Ph	Ph	Me	I ⁻	MeNH	Benzene, hot	70	282
Ph	Ph	Ph	Me	I ⁻	PhNH	Benzene, reflux		1007, 898
Ph	Ph	Ph	Me	Sulfo-	PhNH	Alc., RT	<i>b</i>	283
				acetate ^a				
Ph	Ph	Ph	Me	I ⁻	PhNMe	Alc., reflux	100	282
Ph	Ph	Ph	Me	I ⁻	Ph ₂ N	Alc., ether, steam bath 1 hr.	100	282
Ph	Ph	Ph	Me	I ⁻	<i>o</i> -Me-	Benzene, reflux		898
					C ₆ H ₄ NH			
Ph	Ph	Ph	Me	I ⁻	2,4-Cl ₂ -	Benzene, reflux; then conc. HCl	<i>c</i>	898
					C ₆ H ₃ NH			
Ph	Ph	Ph	Me	I ⁻	2,4,6-Cl ₃ -	Benzene, reflux		898
					C ₆ H ₂ NH			
Ph	Ph	Ph	Me	I ⁻	<i>p</i> -O ₂ N-	Benzene, reflux	60	898
					C ₆ H ₄ NH			
Ph	Ph	Ph	Me	I ⁻	2,4-(NO ₂) ₂ -	Benzene, reflux 40 min.	73	898
					C ₆ H ₃ NH			
Ph	Me	Ph	Ph	I ⁻	PhNH	Alc., HOAc, cool several hrs.	100	282, 898
Ph	Ph	Ph	Et	I ⁻	PhNH	Benzene, reflux		899, 898
Ph	Ph	Ph	Et	I ⁻	<i>p</i> -Me-	Benzene, reflux	70	899
					C ₆ H ₄ NH			

(continued)

(continued)

TABLE II-30 (Continued)
 Reaction of Pirylium Salts with Hydrazines

R ₃	R ₄	R ₆	X ⁻	R ₁	Conditions	Yield, %	Ref.
Ph	Ph	Et	I ⁻	<i>p</i> -Br-C ₆ H ₄ NH PhNH	Benzene, reflux		899
Ph	Ph	<i>i</i> -Pr	I ⁻	PhNH	HOAc, reflux; basify; ether, HClO ₄	7 ^d	898
Ph	Ph	<i>t</i> -Bu	I ⁻	PhNH	Alc., RT	^e	898
Ph	Ph	Ph	I ⁻	PhNH	Benzene, reflux	/	1007
					Benzene, heat; or alc. RT	^g	282
					Alc. RT	^b	898
Ph	Ph	Ph	I ⁻	PhNMe	Benzene, heat	100	282
<i>m</i> -Tolyl	<i>m</i> -Tolyl	Me	I ⁻	PhNH	Benzene, reflux	86	899
<i>m</i> -Tolyl	<i>m</i> -Tolyl	Me	I ⁻	<i>p</i> -MeC ₆ H ₄ NH	Benzene, reflux	93	899
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Me	I ⁻	PhNH	Benzene, reflux	90	899
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Me	ClO ₄ ⁻	PhNMe	Ether		1650
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Me	I ⁻	<i>m</i> -MeC ₆ H ₄ NH	Benzene, reflux	84	899
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Me	I ⁻	<i>p</i> -MeC ₆ H ₄ NH	Benzene, reflux		899
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Me	I ⁻	<i>p</i> -BrC ₆ H ₄ NH	Benzene, reflux	84	899
<i>p</i> -Tolyl	<i>p</i> -Tolyl	Et	I ⁻	PhNH	Benzene, reflux	92	899
<i>m</i> -ClC ₆ H ₄	<i>m</i> -ClC ₆ H ₄	Me	I ⁻	PhNH	Benzene, reflux	94	899

<i>m</i> -ClC ₆ H ₄	<i>m</i> -ClC ₆ H ₄	Me	I ⁻	<i>p</i> -MeC ₆ H ₄ NH	Benzene, reflux	95	899
<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	Me	I ⁻	PhNH	Benzene, reflux	93	899
<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	Me	I ⁻	<i>m</i> -MeC ₆ H ₄ NH	Benzene, reflux	95	899
<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	Me	I ⁻	<i>p</i> -MeC ₆ H ₄ NH	Benzene, reflux	89	899
<i>m</i> -BrC ₆ H ₄	<i>m</i> -BrC ₆ H ₄	Me	I ⁻	PhNH	Benzene, reflux	95	899
<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Me	I ⁻	PhNH	Benzene, reflux	88	899
<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Me	I ⁻	<i>p</i> -MeC ₆ H ₄ NH	Benzene, reflux	95	899
<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Me	I ⁻	<i>p</i> -BrC ₆ H ₄ NH	Benzene, reflux	93	899
<i>m</i> -O ₂ NC ₆ H ₄	<i>m</i> -O ₂ NC ₆ H ₄	Me	ClO ₄ ⁻	PhNH	Benzene, reflux	70	898
<i>p</i> -O ₂ NC ₆ H ₄	<i>p</i> -O ₂ NC ₆ H ₄	Me	ClO ₄ ⁻	PhNH	Benzene, reflux		898
<i>p</i> -Anisyl	<i>p</i> -Anisyl	Me	I ⁻	PhNH	Benzene, reflux 1 hr.	92	899
<i>p</i> -Anisyl	<i>p</i> -Anisyl	Me	I ⁻	<i>p</i> -MeC ₆ H ₄ NH	Benzene, reflux		899
<i>p</i> -Anisyl	<i>p</i> -Anisyl	Me	I ⁻	<i>p</i> -BrC ₆ H ₄ NH	Benzene, reflux		899
<i>p</i> -Anisyl	<i>p</i> -Anisyl	Me	I ⁻	<i>p</i> -O ₂ NC ₆ H ₄ NH	Benzene, reflux 1 hr.	61	898
<i>p</i> -Anisyl	<i>p</i> -Anisyl	Me	I ⁻	2,4-(NO ₂) ₂ -C ₆ H ₃ NH	Benzene, reflux	65	898

^aProbably MeCO₂SO₃⁻, formed from H₂SO₄ and Ac₂O during synthesis of the pyrylium salt.

^bProduct assumed to be a 2-hydrazino-1,2-pyran (see text), (65-85 % yield); this treated with boiling acetic acid, followed by aq. KI, gives the normal pyridinium iodide.

^cProduct obtained as the chloride.

^dProduct obtained as the perchlorate.

^eProduct assumed to be a 2-phenylhydrazino-1,2-pyran (see text) in 58 % yield; this was treated with HOAc at reflux, and the normal pyridinium product isolated as the perchlorate (12 % yield, last step).

^fProduct not characterized.

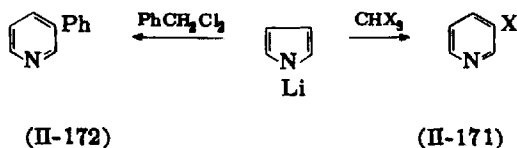
^gProduct assumed to be a 2-phenylhydrazino-1,2-pyran (see text); this with hot HOAc, then aq. NH₃, gave the betaine, 2,4,6-triphenyl-1-phenyliminopyridine, which could be converted to the normal pyridinium iodide.

^hThe 2-phenylhydrazino-1,2-pyran (90 % yield) was converted to the normal pyridinium iodide as in Note g.

6. Pyrroles

The formation of a pyridine from a pyrrole is of interest, not as a preparative method, for the yields are low and the products better obtained by other reactions, but as a rather unusual ring enlargement.

One form of this preparative method is the reaction of pyrrolyl-lithium and chloroform or bromoform to give a low yield of 3-chloropyridine (II-171) (Table II-31). Similarly, diiodomethane and pyrrolyl-lithium gave pyridine (1591), while benzal chloride and pyrrolyl-lithium produced 3-phenylpyridine (II-172) (1008,1136). Alexander, Herrick, and Roder investigated these reactions using pyrrolyl sodium, potassium, and lithium as well as pyrrole and sodium ethoxide; the lithium salt gave the best results (Table II-32).



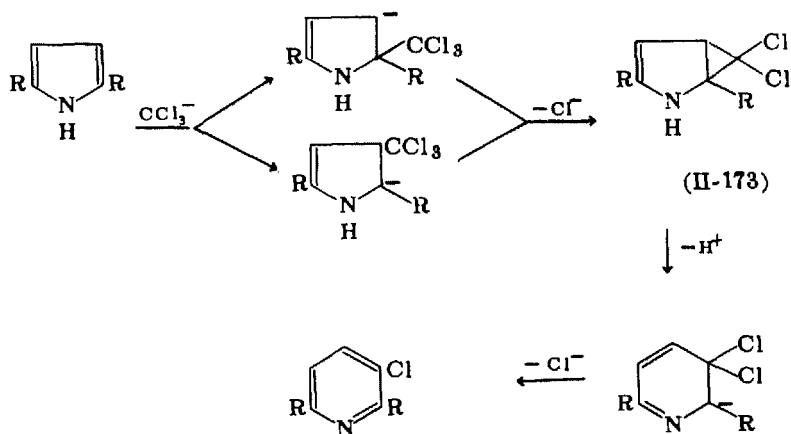
Pyrrole and chloroform also react in the vapor phase. Thus it has been reported that passage through a heated tube formed 3-chloropyridine in 33% yield with 2-chloropyridine in 2-5% yield as a by-product (1632).

Pyrolysis of *N*-methylpyrrole formed 2-methylpyrrole and a 10% yield of pyridine (857,1623). Pictet believed that 2-methylpyrrole was an intermediate in the formation of pyridine since pyrolysis of 2-methylpyrrole gave a 20% yield of pyridine (620,1009). Pyrolysis of *N*-carboxymethylpyrrole at 350° gave ethylene, carbon dioxide, and a 20-50% yield of pyridine (Table II-33) (1274).

Ordinarily, acidic conditions do not change pyrrole derivatives to pyridines, but treatment of 2,3,5-trimethylpyrrole with concentrated hydrochloric acid at 120° did give a low yield of a product thought to be a dihydro-2,6-lutidine (1624).

The new ring carbon atom must be in the 3-position, since chloroform and 2,5-dimethylpyrrole gave 3-chloro-2,6-lutidine (695) and

pyrolysis of *N*-benzylpyrrole gave a 16% yield of 3-phenylpyridine (1009). But it is uncertain whether the initial attack of chloroform on the pyrrole ring occurs at the 2 or 3 position. Attack at the 3-carbon is suggested by the isolation of 2,5-dimethyl-3-pyrrole-carboxaldehyde as a by-product from the reaction of 2,5-dimethylpyrrole and chloroform (709), and yet the Reimer-Tiemann reaction of pyrrole itself gives the 2-aldehyde. It has also been proposed that dichlorocarbene is the species which adds to the pyrrole double bond (1851). In any case, an intermediate such as II-173



would explain the results. Pyrolysis of 2-methylpyrrole may well go through some intermediate similar to II-174, though a free radical mechanism may be operating here.

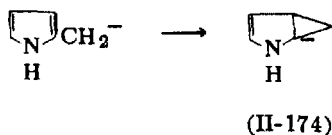


TABLE II-31. Reaction of Pyrroles with Halogen Compounds^a

R	R'	X	Conditions	Yield	Ref.
H	Cl	Cl	Pyrrylpotassium, ether, reflux, 2 hrs.	10%	1010
H	Cl	Cl	Hot glass tube, 550°	33% (Also 2-5% 2-chloro-pyridine)	1632
H	Br	Br	Pyrrylpotassium, ether, 2 hrs., reflux	10%	1007
H	H	I	Sodium methoxide, 200°	Very low	1591
H	Ph	Cl	Sodium ethoxide, 6 hrs., 170°		1008
Me	Cl	Cl	Sodium ethoxide, alc.		695
Me	Cl	Cl	KOH, aq., alc., reflux	(Also 2,5-dimethylpyrrole-3-carboxaldehyde)	709
Me	Br	Br	Sodium ethoxide, alc.		695

^aSee also Table II-32.

TABLE II-32. Effect of Catalyst on Yield in the Reaction of Pyrrole and Polyhalides (1136)

Polyhalide	Pyrryl-lithium, refluxing ether	Pyrryl-sodium, alc. sealed tube	Pyrryl-potassium, ether	NaOEt, refluxing alc.	Product
CHCl ₃	12.8%	1.6%	7.2%	3.8%	3-Chloropyridine
CHBr ₃	8.6%	<0.5%		2.5%	3-Bromopyridine
CHI ₃	0%	<0.5%		0%	Pyridine
PbCHCl ₂	1.3%	0.7%		0.5%	3-Phenylpyridine

TABLE II-33. Formation of Pyridines from Alkylpyrroles by Pyrolysis

Pyrrole derivative	Product (Yield)	Ref.
N-Alkyl	3-Alkylpyridines	142
N-Me	Pyridine (10%), also 2-methylpyrrole	857, 1623
N-CH ₂ Ph	3-Phenylpyridine (16%)	1009
N-CH ₂ CO ₂ Et	Pyridine (20-50%), also CO ₂ , C ₂ H ₄	1274
2-Me	Pyridine (20%)	620, 1009
2-Alkyl	3-Alkylpyridines	142

7. Hydropyridines

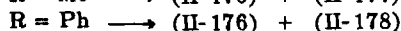
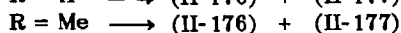
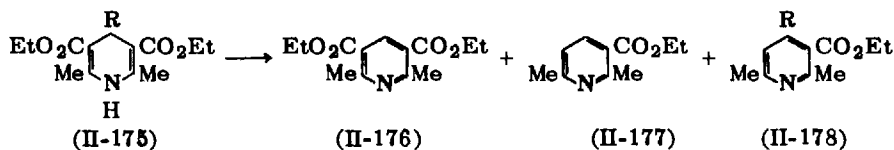
a. Dihydropyridines (and Piperidinediones)

Dihydropyridine Bases. The aromatization of dihydropyridines is more common than that of tetra- and hexahydropyridines, and is usually brought about by chemical oxidation rather than catalytic dehydrogenation. The majority of the dihydropyridines which have been prepared have an electron-withdrawing group in the 3 and 5 position and are usually thought to be the 1,4-dihydro tautomer (see Chapter I). Such dihydropyridines are formed most often in 3-2 and 2-1-2 condensations and in the cyclization of single molecules (*q.v.*).

Oxidation of the dihydro compounds, which is summarized in Table II-34, has been accomplished by nitric acid (often with sulfuric acid), nitrous acid, nitrogen trioxide, chromic oxide in acetic acid, potassium dichromate, sulfur, hydrogen peroxide, sulfuryl chloride, chloranil, and pyruvic acid. Excellent yields are usually reported. Heat alone has also been used, but it is not certain whether this caused loss of hydrogen or disproportionation.

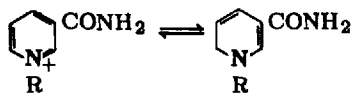
Disproportionation of dihydropyridines by heat, acid, palladium, or alcoholic ammonia produces mixtures of pyridines and reduced pyridines (Table II-35). The reduced portion of the product has been called the tetrahydropyridine in some cases and the piperidine in others, but rigorous proof is lacking. The best available proof comes from the palladium catalyzed disproportionation of ethyl 2-methyldihydronicotinate. The product of this reaction had an ultraviolet spectrum which agreed with that of a synthetic mixture of the pyridine and tetrahydropyridine derivatives (1756).

Distillation of II-175 to produce the products shown may have caused disproportionation in some cases, although none of the reduction products were isolated (704). It is also likely that some of these pyridines formed by simply splitting out methane or benzene, since these were found among the by-products, as well as carbon dioxide, carbon monoxide, ethanol, and ethylene.



An intramolecular oxidation-reduction was found in the case of 3,5-diacetyl-4-*o*-nitrophenyldihydro-2,6-lutidine, which under the influence of light was converted to the diacetyl-*o*-nitrosophenyllutidine (661).

N-Substituted pyridines and their dihydro derivatives are of biological interest. Coenzymes I and II have the structure II-179 (where R contains ribose, phosphate, and adenine residues) which is reduced reversibly to the 1,2- or 1,6-dihydro derivative (759). *N*-Substituted dihydropyridines are oxidized in some cases by such agents as silver nitrate, oxygen (in the presence of lactoflavine), sulfonated indigo, and potassium ferricyanide (Table II-34). The ease of oxidation of the dihydronicotinamide depends on the *N*-substituent; *N*-alkyl groups make the oxidation go more readily than does the *N*-glucosido group (759,762). *N*-Aryldihydropyridines having no carbamyl group are also oxidized by these reagents (760).



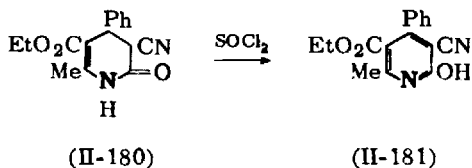
(II-179)

The 1,4-dihydro tautomers of the above compounds are also oxidized to the pyridinium products, but the reaction does not go as readily (763). Simple hydride transfer (at least formally) is suggested by the oxidation of 1-benzyl-1,4-dihydronicotinamide with

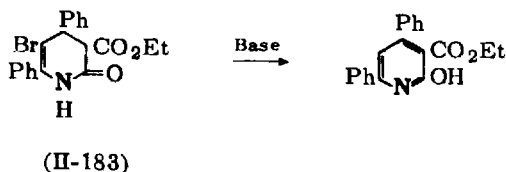
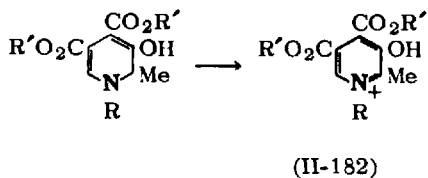
malachite green. When the dihydropyridine had a deuterio atom in the 4-position, the leuco-malachite green contained deuterium; it contained no deuterium when the 2- or 6-deuterated material was oxidized (669).

This subject is further discussed in Chapter III.

Dihydropyridinols and Diols. The oxidation of dihydro-2-pyridinols resembles that of dihydropyridines, and has been carried out with nitrous acid, amyl nitrite, ferricyanide, air, sulfuryl chloride, and bromine (Table II-36). Zinc at high temperature has been used to convert 6-methyl-4-phenyldihydro-2-pyridinol to 4-phenyl-2-picoline (1248). The conversion of II-180 to II-181 by thionyl

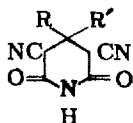


chloride has been reported (1119,1213,1233), and may involve a disproportionation. Sulfuryl chloride has been used to oxidize 1-alkyl-dihydro-3-pyridinols to the pyridinium salts II-182 (574) (Table II-130, p. 538). And finally, II-183 was reported to give the pyridinol by dehydrobromination with strong bases (1359).



Dihydro-2,6-pyridinediols (glutarimides) may be converted to pyridinediols (glutaconimides) by bromination followed by dehydrobromination. The treatment of glutarimides with phosphorus pentahalides gave polyhalopyridines (Table II-37).

The 3,5-dicyano-4,4-dialkylglutarimides (II-184) seem to be remarkably unstable. Guareschi found that they eliminated RH to give a 4-alkyldicyanoglutaconimide not only when heated but also at ordinary temperatures in water; however they were stable in strong aqueous acids or bases. Methane was eliminated with difficulty and therefore the 4,4-dimethyldicyanoglutarimide was quite stable (696,703,705).

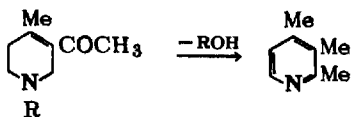


(II-184)

b. Tetrahydropyridines (and Piperidones)

The dehydrogenation of a tetrahydropyridine to a pyridine by chemical or catalytic methods, as expected, resembles that of piperidines (Table II-38). A tetrahydropyridine apparently gives better yields than the corresponding *N*-methyl derivative (921).

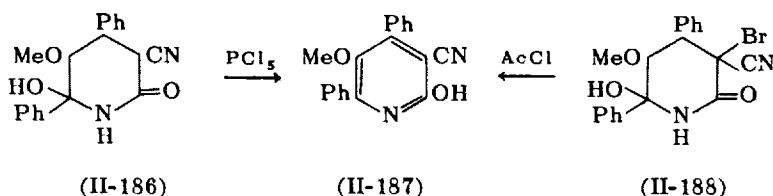
The conversion of a 3-acyl-1,2,5,6-tetrahydropyridine to a pyridine is similar to the conversion of acylpiperidines and acylpiperidinols. Although this reaction occurred in the presence of selenium, palladium, or hydrogen chloride (Table II-39), it did not take place when II-185 was distilled in the presence of sulfuric acid (444). This rearrangement proceeds by elimination of a molecule of an alcohol. An alcohol has not been isolated, but benzyl chloride was



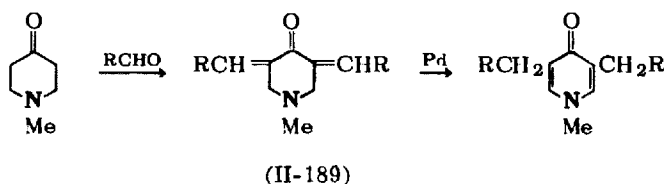
(II-185)

found in the rearrangement of an N-benzyl compound in the presence of hydrogen chloride (821).

2-Piperidone (δ -valerolactam) and the 1- and 6-methyl homologs, are changed to the corresponding pyridones by dehydrogenation over palladium at 240–70° (Table II-40). The hydroxypiperidone II-186 formed II-187 upon treatment with phosphorus pentachloride. This conversion went poorly with bromine in acetic acid and produced mostly II-188; however, hot acetyl chloride converted II-188 to II-187 (1261).



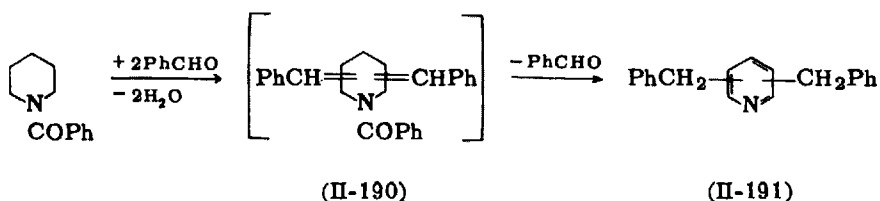
Rearrangement of the dibenzalpiperidone II-189 to the corresponding pyridone was effected by palladium in ethylene glycol at 195° (Table II-41).



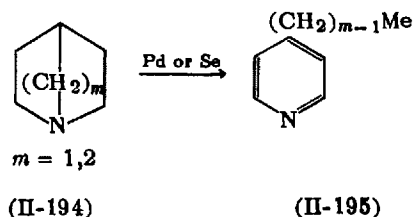
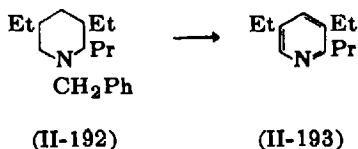
c. Piperidines

The conversion of a piperidine to a pyridine has been done both by catalytic and chemical dehydrogenation. The catalytic technique utilizes palladium or platinum on charcoal or asbestos at temperatures of 200–300°, and usually gives good yields (Table II-43). Other less common catalysts have been a mixture of titanium dioxide and alumina at 600° (1815) and nickel or nickel chromite at 350° (1090). Chemical dehydrogenation is less common. Selenium, zinc, and sulfur have been used at elevated temperatures.

Oxidation of piperidine and its *N*-acetyl derivative with bromine produced mixtures containing bromo and dibromo products (Table II-43). The reaction of *N*-benzoylpiperidine with benzaldehyde at 250° to produce a dibenzylpyridine (136) appears to be not a dehydrogenation, but formation of a dibenzal product II-190 which loses benzaldehyde and rearranges to the pyridine II-191.

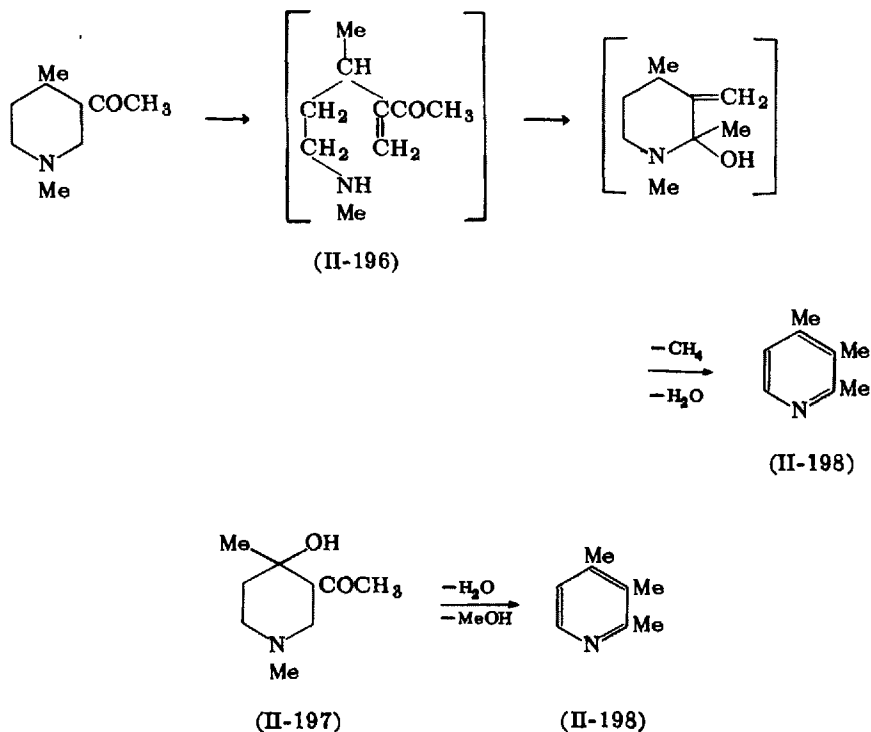


An *N*-alkyl group on piperidine is lost during aromatization. Thus the palladium dehydrogenation of II-192 gave a 62% yield of II-193 (1113); and in a related manner II-194 was converted to II-195 (1336). However, gem-disubstituted piperidines were essentially unchanged by palladium at 250° (607). As expected, 4-piperidinols also give pyridines by dehydrogenation with palladium, zinc, or sulfur Table (II-43).



The action of selenium on 3-acetyl-1-methylpiperidine at 300° does not proceed in the usual manner, but causes rearrangement to 2,3-pyridinediol (1214). Prelog and co-authors pointed out that a

3-acylpiperidine is a Mannich base and therefore ring opening to II-196 is not unexpected. Cyclization through the carbonyl group occurs and the resulting molecule forms the pyridine by loss of water and a hydrocarbon; no dehydrogenation occurs (1212). When a 4-hydroxy group is present as in II-197, heating with selenium also gives 2,3,4-collidine (1212). Stoichiometrically, this reaction involves the loss of one molecule each of water and an alcohol. Treat-



ment of II-197 with acetic anhydride and sulfuric acid followed by distillation at 180–200° also formed II-198 (444) (Table II-42).

H	Me	COME	2-NO ₂ -3-MeO-4-HO-C ₆ H ₃	Me	8N HNO ₃ , steam bath	I	1085
H	Me	COME	4-Quinolyl	Me	3-6N HNO ₃ , warm	I (100%)	1085
H	Me	CO ₂ Et	H	H	Dil. H ₂ SO ₄ , conc. HNO ₃	I (61%)	1756
H	Me	CO ₂ Et	Me	H	Dil. H ₂ SO ₄ , conc. HNO ₃	I (65%)	1756
H	Me	CO ₂ Et	Me	Me	HNO ₃	I	194
H	Me	CO ₂ Me	—CH ₂ OCH ₂ —	H	30% H ₂ O ₂	I	1814
H	Me	CO ₂ Et	4-Quinolyl	Me	Benzene, chloranil, reflux, 16 hrs.	I (94%)	1145
H	Me	CO ₂ Et	H	Me	K ₂ Cr ₂ O ₇ , Alc., N ₂ O ₃ , 2-6 hrs.	I	1145
						I (80%)	213
					20-25% HNO ₃	I (70-90%)	194, 213
					H ₂ SO ₄ , HNO ₃ , water bath, 10 min.	I (61%)	1756
					Alc., HNO ₂	I	231
					NH ₂ OH	I	220
					Pyruvic acid, 100°, 18 hrs.	I	669

(continued)

TABLE II-34 (Continued)
Oxidation of Dihydropyridines to Pyridines

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield)	Ref.
H	Me	CO ₂ Et	H	CO ₂ Et	Me	Distil	I (also ethyl 2,6-dimethyl-nicotinate)	704
H	Me	CO ₂ Et	Me	CO ₂ Et	Me	HNO ₃ HNO ₃ , H ₂ SO ₄ , heat	I I (65%)	194 1756
						HCl, Et ₂ O (air?)	I	194
						350°	Ethyl 2,6-dimethylnicotinate, diethyl ester of 2,6-dimethyl-3,5-pyridinedicarboxylic acid	704
H	Me	CO ₂ Et	(CH ₂) ₆ Me	CO ₂ Et	Me	5% alc. N ₂ O ₅	I	1589
H	Me	CO ₂ Et	CH ₂ Ph	CO ₂ Et	Me	Sulfur, 200°, 1/2 hr.	I (80%)	1089
H	Me	CO ₂ Et	Ph	CO ₂ Et	Me	HNO ₃ , dil H ₂ SO ₄ , heat 4 N HNO ₃	I (80%) I	1494 1129

H	Me	CO ₂ Et	p-Phenylene	CO ₂ Et	Me	4 N HNO ₃ , 100°, 3 hrs.	I (90%)	Diethyl 2,6-di- methyl-3,5- pyridinedi- carboxylate acid, ethyl 2,6-dimethyl- 4-phenyl- nicotinate	704
H	Ph	CO ₂ Et	Ph	CO ₂ Et	Me	Alc., nitrous fumes, cold	I		517
H	Ph	CO ₂ Et	Me	CO ₂ Et	Ph	HOAc, CrO ₃ Dil. HNO ₃ , water bath, 4 hrs.	I (53%) I		1713 524
H	Me	CO ₂ Et	o-NO ₂ C ₆ H ₄	CO ₂ Et	Me	1 N HNO ₃ , heat HOAc, CrO ₃ , heat, ¼ hr.	I I (90%)		1628 1163
H	Me	CO ₂ Et	m-AcOC ₆ H ₄	CO ₂ Et	Me	Benzene, chloranil, re- flux, 5 hrs.	I (82%)		1145
H	Me	CO ₂ Et	m-AcOC ₆ H ₄	CO ₂ Et	Me	HOAc, CrO ₃ , 100°, 10 min.	I (90%)		1429

(continued)

TABLE II-34 (Continued)
Oxidation of Dihydropyridines to Pyridines

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield)	Ref.
H	Me	CO ₂ Et	3-MeO-4-AcOC ₆ H ₃	CO ₂ Et	Me	HOAc, CrO ₃ , 100°, 10 min.	I (90%)	1429
H	Me	CO ₂ Et	4-Me ₃ PN ⁺ -C ₆ H ₄	CO ₂ Et	Me	8N HNO ₃ , steam bath	I (80%)	1085
H	Me	CO ₂ Et	1-Naphthyl	CO ₂ Et	Me	HOAc, CrO ₃ , 100°, 10 min.	I (85%)	1429
H	Me	CO ₂ Et	4-Quinolyl	CO ₂ Et	Me	4N HNO ₃	I	1129
CH ₃ Ph	H	CONH ₂	H	H	H	Alc., mala-chite green, 25°, 15 hrs.	II (25-75%)	669
Alkyl	H	CONH ₂	H	H	H	AgNO ₃ , cold	II	761, 763
R ^a	H	CONH ₂	H	H	H	K ₃ Fe(CN) ₆	II	761, 763
R ^b	H	CONH ₂	H	H	H	AgNO ₃ , warm	II	759
	H	CONH ₂	H	H	H	O ₂ , lactoflavin	II	759
						AgNO ₃	II	762
						I ₂ , NaHCO ₃	II	762
						o-(NO ₂) ₂ C ₆ H ₄	II	762
H	Me	CN	Ph	H	Ph	HOAc, CrO ₃ , 25°	I (70%)	515
H	Me	CN	o-ClC ₆ H ₄	H	Ph	HOAc, CrO ₃		524

H	Me	CN	Ph	CO ₂ Et	Me	Dil. HNO ₃ , water bath, 1/4 hr.	I	515
H	Me	CN	<i>o</i> -NO ₂ C ₆ H ₄	CO ₂ Et	Me	Aq. alc., HNO ₃ , water bath	I (85%)	1163
H	Me	CN	2-NO ₂ -4,5- CH ₃ O ₂ C ₆ H ₃	CO ₂ Et	Me	HOAc, CrO ₃ , heat, 1/4 hr.	I (85%)	1163
H	Me	CN	H	CN	Me	Alc. HNO ₃	I	1688
H	Me	CN	Me	CN	Me	Alc. HNO ₃	I	1688
H	Me	CN	CH ₃ CN	CN	Me	HOAc, NaNO ₂	I	1252
H	Ph	CN	CH ₃ Cl	CN	Ph	HNO ₃	I	1252
H	Me	CN	<i>o</i> -NO ₂ C ₆ H ₄	CN	Me	CrO ₃ , HOAc, heat	I (100%)	1164
H	Ph	CN	Ph	CN	Ph	Alc. HNO ₃	I	1688
H	OH ^c , <i>p</i> -MeOC ₆ H ₄	H	Ph	Ph	Br	AcCl	c	1250
Me	Me	OH	CO ₂ Et	CO ₂ Et	H	SO ₂ Cl ₂ , Cl ₂ , or Br ₂ , CCl ₄	II	574, 1370
CH ₃ Ph	Me	OH	CO ₂ Et	CO ₂ Et	H	SO ₂ Cl ₂ , Cl ₂ , or Br ₂ , CCl ₄	II	1370
						HCl, air or O ₂ , 1 day	II	1708
Alkyl	Alkyl	OH	CO ₂ Et	CO ₂ Et	Alkyl	Air or O ₂	II	1258

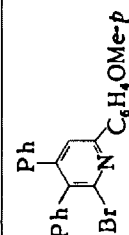
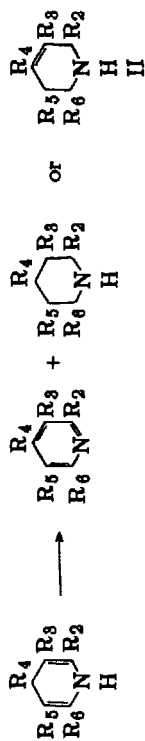
^aR = $\text{---CH}(\text{CHOH})_2\text{CHCH}_2\text{OH}$ ^bR = $\text{---CH}(\text{CHOH})_2\text{CHCH}_2\text{OH}$ ^c

TABLE II-35. Disproportionation of Dihydropyridines



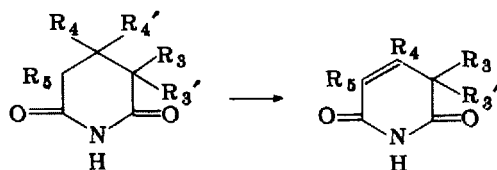
R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Reduced Product	Ref.
Me	CO ₂ Et	H	H	H	Pd-CaCO ₃ , N ₂ , 1 hr.	II	1756
Me	CO ₂ Et	Me	H	H	Pd-CaCO ₃ , N ₂ , 1 hr.	II	1756
Ph	H	CO ₂ NH ₄	H	Ph	270°	I (as free acid)	198
Me	CO ₂ Et	H	CO ₂ Et	Me	Pd, 115-310° (1) conc. HCl (2) soda	I I	1626 1673
Me	CO ₂ Et	Me	CO ₂ Et	Me	Et ₂ O, HCl	?	194
OH	CN	Ph	H	Ph	Alc., NH ₃ , 25°, 2 weeks	II	307,1327

TABLE II-36. Oxidation of Dihydro-2-pyridinols



R ₃	R ₄	R ₅	R ₆	Conditions	Yields	Ref.
H	Ph	H	Me	Zn distn.	(4-phenyl-2-picoline)	1248
Ph	Ph	H	<i>p</i> -MeOC ₆ H ₄	HOAc, BuNO ₂		1250
H	H	CO ₂ Et	Me	Pd, 260°, 4 hrs.	44%	628
CO ₂ Me	Ph	H	Ph	(1) Br ₂ , CHCl ₃	20%	1359
				(2) Alc., KOH or NaOMe		
CN	Ph	H	Alkyl	HOAc, HNO ₃ , 25°, 7 days		1327
CN	Ph	H	Ph	HNO ₃		307
CN	Ph	Br	Ph	HOAc, HNO ₃		307
				Alc., KOAc, or NaOMe	(4,6-diphenyl-2-hydroxy-nicotinonitrile)	307
CN	CH ₃ COPh	CO ₂ Et	Me	K ₃ Fe(CN) ₆	90%	1213, 1233
CN	Ph	CO ₂ Et	Me	SOCl ₂	70%	1119, 1213, 1233
CN	<i>p</i> -NO ₂ C ₆ H ₄	CO ₂ Et	Me	Alc. amyl nitrite, HCl, 60°, 10 min.		1233

TABLE II-37. Oxidation of Glutarimides to Glutaconimides



R_3	R_3'	R_4	R_4'	R_5	Conditions	Ref.
H	H	H	H	H	PBr_5 , 90° , $2\frac{1}{2}$ hrs. (produces 2,3,6-tri- and 2,3,5,6-tetra-bromopyridines)	337
Me	Me	H	H	H	(1) Br_2 light (2) Collidine, reflux	1177
Et	Et	H	H	H	(1) Br_2 light (2) Collidine, reflux	1177
H	H	Cyclo-pentyl	H	H	PCl_5 , warm (produces di- and trichloro products)	1219
Ph	Et	H	H	H	PCl_5 , warm (produces di- and trichloro products)	1177,1743
CN	H	Me	Me	CN	320°	703
CN	H	Me	Et	CN	320° , or stand in neutral water	705
CN	H	Et	Et	CN	Aq., NH_3 or $Mg(OH)_2$	697
CN	H	Pr	Et	CN	Aq., NH_3 or $Mg(OH)_2$	696
CN	H	Me	<i>i</i> -Bu	CN	Aq., NH_3 or $Mg(OH)_2$	696
CN	H	Me	<i>n</i> -Hexyl	CN	Aq. neutral solution	703
CN	H	Me	$(CH_2)_8Me$	CN	Aq.	696

TABLE II-38. Oxidation of Tetrahydropyridines to Pyridines

(1,2-, 1,4-, or 1,6-isomer)

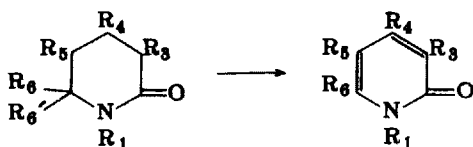
R ₁	R ₂	R ₃	R ₄	Conditions	Yield	Ref.
H	Me	Me	H	Pd-asbestos, 280°	90%	1357
				Zn, distil	20%	1357
Me	H	Et	Me	Se, 350°	42%	1212, 1338
Me	H	CHOHMe	Me	Se	(3-ethyl-4-picoline, high yield)	1212
^a	H	H	Me	Chromia, alumina, 475°		1831
H	H	H	Ph	Pd-alumina, PhNO ₂ , N ₂ , 135°, 6 hrs.	81%	1645
H	H	H	<i>p</i> -MeC ₆ H ₄	Pd-alumina, PhNO ₂ , 160°, ½ hr.	54%	921
Me	H	H	<i>p</i> -MeC ₆ H ₄	Pd-alumina, PhNO ₂ , 160°, ½ hr.	87%	921
H	H	H	<i>p</i> -Me ₂ CHC ₆ H ₄	Pd-alumina, PhNO ₂ , 160°, ½ hr.	75%	921
Me	H	H	<i>p</i> -Me ₂ CHC ₆ H ₄	Pd-alumina, PhNO ₂ , 160°, ½ hr.	56%	921
H	CO ₂ H	H	H	As amine hydrochloride, Zn, distil.	(2-picoline)	, 495

^aMixture of H, CH₃OH, -CH₂-.

TABLE II-39. Conversion of a 3-Acyltetrahydropyridine to a Pyridine

R	Conditions	Yield	Ref.
Me	Se, 300°	88%	1212
	Pd-C		1212
CH ₂ Ph	230-365°	34%	685
	3% HCl, 185-400°	48%	685
	As amine hydrochloride, 115-300°	65%	685

TABLE II-40. Conversion of 2-Piperidones to 2-Pyridones



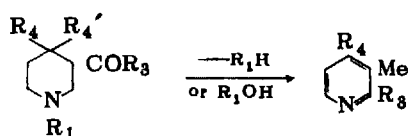
R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Yield	Ref.
H	H	H	H	H	H	Pd, 270°, 5 hrs.	60%	1232
H	H	H	H	Me	H	Pd, 270°, 5 hrs.		1232
Me	H	H	H	H	H	Pd, 240°, 5 hrs.		1232
H	CN	Ph	OMe	Ph	OH	PCl ₅		1261

TABLE II-41. Conversion of 3,5-Dibenzal-4-piperidones to 4-Pyridones (1631)



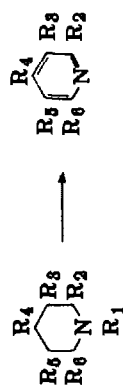
R	Conditions	Yield, %
Ph	Pd-C, ethylene glycol, 195°, ½ hr.	100
<i>p</i> -MeC ₆ H ₄	Pd-C, ethylene glycol, 195°, ½ hr.	92
<i>p</i> -Me ₂ CHC ₆ H ₄	Pd-C, ethylene glycol, 195°, ½ hr.	79
<i>p</i> -PhC ₆ H ₄	Pd-C, ethylene glycol, 195°, ½ hr.	77
<i>m</i> -NO ₂ C ₆ H ₄	Pd-C, ethylene glycol, 195°, ½ hr.	85
<i>p</i> -MeOC ₆ H ₄	Pd-C, ethylene glycol, 195°, ½ hr.	85
<i>p</i> -Me ₂ NC ₆ H ₄	Pd-C, ethylene glycol, 195°, ½ hr.	84

TABLE II-42. Conversion of 3-Acylpiperidines to Pyridines



R ₁	R ₂	R ₃	R ₄	Conditions	Yield, %	Ref.
Me	Me	H	H	Se, 300°, 8 hrs.	30	1214
Me	Me	Me	H	Se	50	1212
Me	Me	Me	OH	Se	17	1212
				(1) Ac ₂ O, H ₂ SO ₄ , 100°, 2½ hrs.		444
				(2) Distil., 178°		
Me	Ph	Ph	OH	(1) Ac ₂ O, H ₂ SO ₄ , 100°	30-35	444, 611
				(2) Distil., 180-95°		
Et	Ph	Ph	OH	(1) Ac ₂ O, H ₂ SO ₄ , 100°		444, 611
				(2) Distil., 185-200°, 0.9 mm.		

TABLE II-43. Dehydrogenation of Piperidines to Pyridines



R_1	R_2	R_3	R_4	R_5	R_6	Conditions	Yield	Ref.
H	H	H	H	H	H	Pd-C, 236°, 1½ hrs.	62%	1113
						Pd or Pd-asbestos, 250°		1581
						Pt or Pd on silica, H ₂ , 250°	96%	1824
						TiO ₂ , alumina, 600°, vac.		1815
						Ni or its chromite, 350°, 5 hrs.	48%	1090
						Br ₂ , 180°, 4 hrs.		1752
						The amine hydrochloride, aq., Br ₂ , heat, pressure	(Dibromopyridine low yield)	1064
						Conc. H ₂ SO ₄	(3,5-Dibromo-4-pyridinol?)	
							(Pyridine disulfonic acid)	289
Me	H	H	H	H	H	Pd-C, 250°		607
H	Me	H	H	H	H	Ni or its chromite, 350°, 5 hrs.	62%	1090
H	H	Me	H	H	H	Ni or its chromite, 350°, 5 hrs.	53%	1090

H	H	H	Me	H	H	Ni or its chromite, 350°, 5 hrs.	64%	1090
H	Me	H	H	Me	Me	Ni or its chromite, 250°, 5 hrs.	45%	1090
H	H	Et	H	H	H	Zn, amine · HCl, dist.l		134
Me	H	Et	H	H	H	Se, 350°, 8 hrs.	42%	1214
H	Me	H	H	Et	H	Pd-asbestos, 280°	90%	1357
H	Et	H	H	Me	H	The amine hydrochloride chloride, Zn, 300°, 5½ hrs.		1188
H	Pr	H	H	H	H	Pd-C, 167°, 5 hrs.	74%	494
H	H	Me	H	n-Amyl	H	Zn, amine · HCl, dist.l		100, 130, 135
CH ₂ Ph	Pr	Et	H	Et	H	Pd, 190°	47%	1215
H	Ph	H	H	H	H	Pd-C, 236°, 1½ hrs.	62%	1113
						Pt-asbestos, 330°, ½ hr.	50%	1602
H	H	Ph	H	Ph	H	Pd-C, 275°, ½ hr.	38%	1154
H	4-Piper- idyl	H	H	H	H	Pd-C, 300°, ½ hr.	(2,4-Dipyridyl)	630
H	H	H	4-Piper- idyl	H	H	Pd-C, 300°, ½ hr.	(4,4-Dipyridyl)	630
Me	H	CHOHMe	Me	H	H	Se	(6% 3-Ethyl-4- picoline)	1212

(continued)

TABLE II-43 (Continued)
 Dehydrogenation of Piperidines to Pyridines

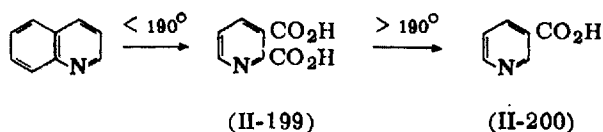
R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Yield	Ref.
COMe	H	H	H	H	H	Br ₂ (2 moles), heat	Pyridine (also bromo- and dibromopyridine)	1065
COPh	H	H	H	H	H	PhCHO, 250°, 6 hrs., pressure	(A dibenzylpyridine)	136
Me	H	Et	OH	Et	H	As amine hydrochloride, Pd, 280°, 2 hrs.	(3,5-Diethylpyridine 55%)	1087
						Pd-C, 330°, 10 hrs. Se, 350°, 30 hrs.	(4-Picoline) (4-Picoline)	1336 1336
						Pd-C, 330°, 10 hrs. Se, 350°, 30 hrs.	(4-Ethylpyridine) (4-Ethylpyridine)	1336 1336
Substituted piperidines							High	1639
Substituted piperidinols							(Pyridines, high %)	1639

8. Quinolines and Condensed Pyridines

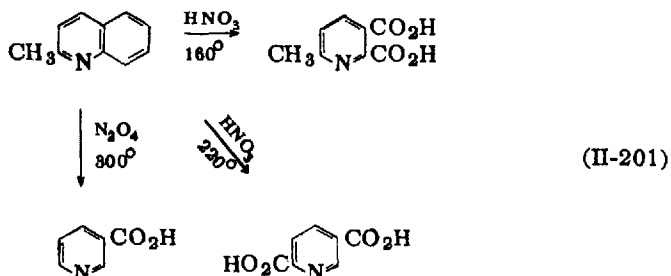
a. By Oxidation

The oxidation of quinoline, isoquinoline, and other polycycles which contain pyridine rings usually produces pyridine carboxylic acids. Nitric acid (often with a catalyst such as mercury or copper salts or selenium) and alkaline potassium permanganate are the commonest and most satisfactory oxidizing agents, though a wide variety of reagents have been used. Ozone (which gives aldehydes), nitrogen dioxide, nitrosyl chloride, and electrolysis have given good yields in some cases.

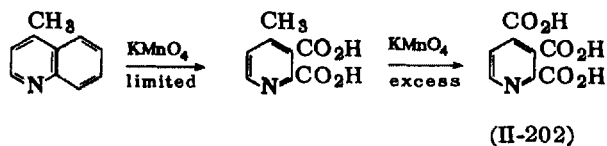
Generally, the oxidation of quinoline below 190° produces quinolinic acid (II-199) and above 190° produces nicotinic acid (II-200) (by decarboxylation of quinolinic acid) (Table II-44). Yields in either case are high. Oxidation with air and a stannic vanadate catalyst at 405° produced a 29% yield of pyridine (1567).



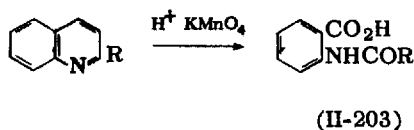
Oxidation of a quinoline containing alkyl groups in the benzo ring also produces quinolinic acid, but oxidation of a quinoline containing alkyl or phenyl groups in the pyrido ring is more complicated. Thus, the oxidation of 2-methylquinoline as given in II-201 produced 6-methylquinolinic acid, 2,5-pyridinedicarboxylic acid, or nicotinic acid depending on the conditions (Table II-45). A lim-



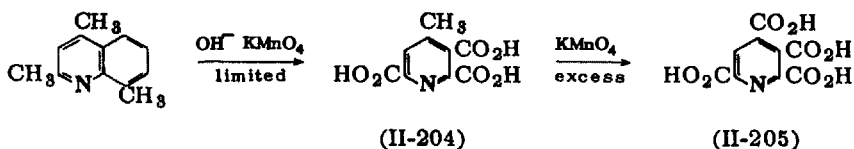
ited amount of alkaline permanganate oxidized 4-methylquinoline to 4-methylquinolinic acid, but excess permanganate produced the tricarboxylic acid (II-202) (202,692). However, acid permanganate



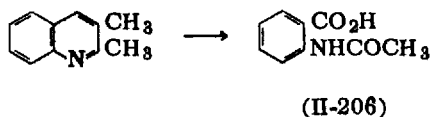
converted 2-methyl- and 2-phenylquinoline to acyl derivatives of anthranilic acid (II-203) (910). The oxidation of 3-methylquinoline



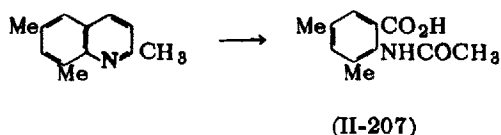
has been reported to give only oxalic acid, carbon dioxide, and ammonia (911). Though oxidation by alkaline permanganate converted 2,4,8-trimethylquinoline to 4-methyl-2,3,6-pyridine tricarboxylic acid (II-204) (or the tetracarboxylic acid (II-205) with excess re-



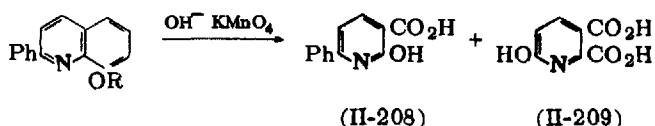
agent), 2,3-dimethylquinoline and 2,6,8-trimethylquinoline were oxidized to 2-acetamidobenzoic acid (II-206) and 2-acetamido-3,5-dimethylbenzoic acid (II-207) (1401).



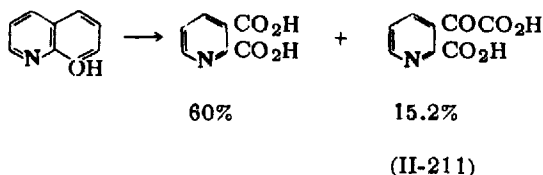
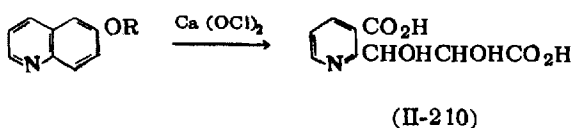
A quinoline with a hydroxyl, alkoxyl, or amino group in the benzo ring is readily oxidized, often to quinolinic acid, but also to



other products. Thus, 2-phenyl-8-hydroxyquinoline and its alkyl ethers were oxidized by alkaline permanganate to 6-phenyl-2-hydroxynicotinic acid (II-208) and 6-hydroxyquinolinic acid (II-209)



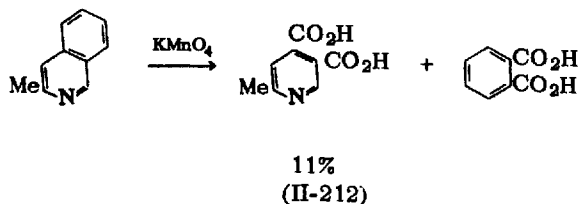
(249). Calcium hypochlorite oxidized 6-hydroxy- and 6-acetoxyquinoline to II-210 (1322,1323), and nitric acid at 25° converted 8-hydroxyquinoline to a 60% yield of quinolinic acid and 15.2% yield of II-211 (1748).



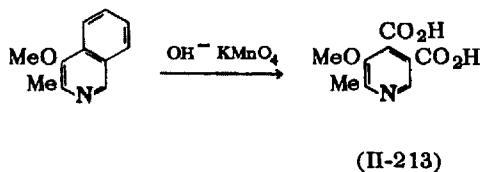
A hydroxyl group in the pyrido ring of quinoline renders that ring quite susceptible to oxidation; the oxidation products are isatin, benzoxazolones, and anthranilic acid derivatives (912).

Isoquinoline and its derivatives are also oxidized to pyridine-carboxylic acids (Table II-46), but the pyrido ring of isoquinoline is

more readily oxidized than that of quinoline. Thus 3-methylisoquinoline gave only an 11% yield of 6-methyl-3,4-pyridinedicarboxylic acid (II-212) along with phthalic acid (1482), and 5-nitro-, 5-iodo-, or 5-carboxyisoquinoline gave only the substituted phthalic acids (913). However, alkaline permanganate oxidation of 3-methyl-

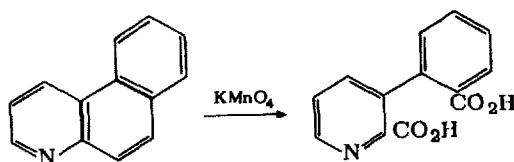


4-methoxyisoquinoline did give a low yield of 2-methyl-3-methoxy-4,5-pyridinedicarboxylic acid (II-213) (867,1674).

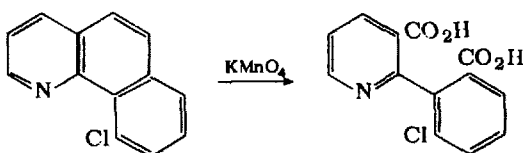


Polycyclic compounds containing pyrido rings are often oxidized by nitric acid or alkaline permanganate to pyridine acids (Table II-47). While in some cases the extra rings are removed by oxidation, benzo(*f*)- and benzo(*h*)quinolines usually give 2- and 3-phenylpyridine acids as in II-214. These oxidations are seldom of synthetic importance, but are often used as structure proofs.

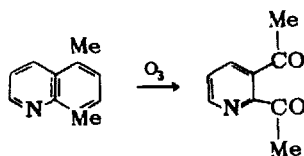
Ozonolysis of quinoline and isoquinoline produces pyridine aldehydes and ketones which are usually isolated as derivatives. If the ozonolysis is followed by oxidation with hydrogen peroxide, acids are formed (Tables II-45–II-47). Products from ozonolysis are those expected; quinoline which was quite inert to ozone, gave traces of 2,3-pyridinedicarboxaldehyde and 5,8-dimethylquinoline gave 2,3-diacetylpyridine (II-215). The yields from the ozonolysis are greatly affected by various substituents on quinoline. Thus 2,3-pyridinedicarboxaldehyde can be obtained from 8-hydroxyquino-



(II-214)



line in 92% yield and from 6-aminoquinoline in 65% yield, but from the 6-nitro and 6-fluoro derivatives in only poor yields. Isoquinoline upon oxidation by ozone and then hydrogen peroxide gave a 44.5% yield of 3,4-pyridinedicarboxylic acid and a 49.5% yield of phthalic acid (1440). Here again we see that the pyridine ring of isoquinoline is not inert to oxidation.



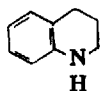
(II-215)

The preparation of pyridinecarboxylic acids by these oxidation reactions is also discussed in Chapter X.

b. By Reduction

Quinolines and isoquinolines may be hydrogenated in the benzene ring to give pyridine compounds. However, this partial reduction is not straightforward. Quinoline itself is reduced principally to

the 1,2,3,4-tetrahydro product (Py-tetrahydro) II-216, and only traces of the tetramethylenepyridine II-217 are found. Tsushima



Py-tetrahydroquinoline

(II-216)



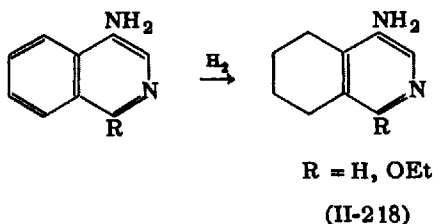
Bz-tetrahydroquinoline

(II-217)

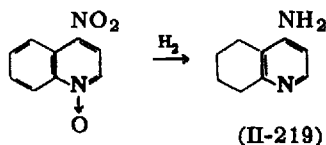
and Sudzuki (1837) showed that hydrogenation of quinoline over a nickel catalyst under a variety of conditions produced the Bz-tetrahydroquinoline in traces at best (Table II-48). Von Braun *et al.* investigated the hydrogenation of a number of quinoline derivatives (Table II-49). They found that alkyl groups in the pyrido ring increased the yield of Bz-tetrahydroquinoline formed until with three such groups (2,3,4-trimethylquinoline) the product was entirely the Bz-tetrahydro isomer.

Although it was reported that reduction of quinoline with phosphorus and hydriodic acid gave the Bz-tetrahydroquinoline, von Braun and Lempke found none of this product when they tried the reduction (882). Other methods of reduction have been investigated, but apparently have not given pyridines.

Isoquinoline and its derivatives are reduced only to the 1,2,3,4-tetrahydro products with the exception of the 4-amino derivatives which were hydrogenated to II-218 (673).



The hydrogenation of quinoline oxide derivatives has given Bz-tetrahydroquinolines. Thus 4-nitroquinoline oxide was reduced by hydrogen over nickel formate at 120° in a mixture of methanol, acetic acid, and sodium acetate to give a 70% yield of II-219. Simi-



larly, hydrogenation of 4-methoxyquinoline oxide with Raney nickel in methanol at 250° gave a 71% yield of 4-methoxy-5,6,7,8-tetrahydroquinoline (II-220) along with traces of II-221 and II-222 (565).

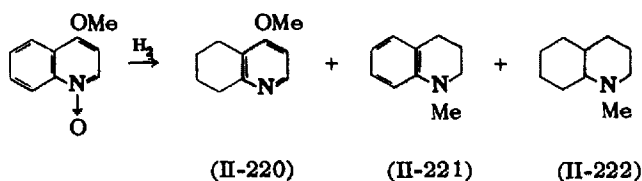


TABLE II-44. Oxidation of Quinoline

Conditions	Product (Yield)	Ref.
Alkaline KMnO_4	Quinolinic acid (55%)	154,155
Alkaline KMnO_4	Quinolinic acid	153,156,157, 158,636,693, 778,1498
93% H_2SO_4 , 70% HNO_3 , HgNO_3 , CuSO_4 , 150–60°	Quinolinic acid	1473
96% H_2SO_4 , vapor of 70% HNO_3 , 180°, 24 hrs.	Quinolinic acid	790
93% H_2SO_4 , 70% HNO_3 , 36% HCl , 150–70°, 6 hrs.	Quinolinic acid	1462
H_2SO_4 , H_2O_2 , CuSO_4 , 70°, 11 hrs.	Quinolinic acid (high yields)	159
Conc. H_2SO_4 , HClO_4 , Se or SeO_2 , 150–90°	Quinolinic acid	1522
Electricity, Pt electrode, V_2O_5 , H_2SO_4	Quinolinic acid (77%)	1439
Electricity, Pb anode (PbO_2 coated), H_2SO_4	Quinolinic acid	1471
(1) Ozone, HOAc , 25–35°, 2 days (2) 30% H_2O_2 , reflux, 2 hrs.	Quinolinic acid (trace)	1440

(continued)

TABLE II-44 (Continued)
Oxidation of Quinoline

Conditions	Product (Yield)	Ref.
93% H ₂ SO ₄ , 70% HNO ₃ , HgNO ₃ , CuSO ₄ , 215–25°	Nicotinic acid	1473
93% H ₂ SO ₄ , HNO ₃ , HgO, 300°	Nicotinic acid (88.4%)	1435
20% HNO ₃ , air, autoclave, 185– 95°, 4 hrs.	Nicotinic acid	681
93% H ₂ SO ₄ , HNO ₃ , Se, 270°, 3¼ hrs.	Nicotinic acid	1687
Conc. HNO ₃ (1) 130°, 5 hrs. (2) 150°, 5 hrs. (3) 180°, 5 hrs.	Nicotinic acid (32%)	1564
H ₂ SO ₄ , Se or SeO ₂ , heat	Nicotinic acid (65%)	643
93% H ₂ SO ₄ , 70% HNO ₃ , 36% HCl, 215–25°, 6 hrs.	Nicotinic acid	1462
Conc. H ₂ SO ₄ , HClO ₄ , Se or SeO ₂ , 320°	Nicotinic acid	1522
Conc. H ₂ SO ₄ , N ₂ O ₄ , SeO ₂ , 200° raise to 305°	Nicotinic acid (89.5%)	1470
(1) 95% H ₂ SO ₄ , Se, heat to 270° (2) Pass in NOCl, 75 min.	Nicotinic acid (85%)	659
Air, Sn(VO ₃) ₄ (also other vanadates), 400–600°	Pyridine (29%)	1567
Ozone, chloroform –25° to –35°	Pyridine-2,3-dicarbox- aldehyde (2.5%), glyoxal (12%)	667

TABLE II-45. Oxidation of Substituted Quinolines

Substituents	Conditions	Products (Yield)	Ref.
2-Me	96% H ₂ SO ₄ , 70% HNO ₃ , HgNO ₃ , CuSO ₄ , 150–60°	6-Methylquinolinic acid	1473
	96% H ₂ SO ₄ , 70% HNO ₃ , HgNO ₃ , CuSO ₄ , 215–25°	2,5-Pyridinedicarboxylic acid	1473
	60° Be. H ₂ SO ₄ , hydrogen halide, 295–315°	Nicotinic acid	1412
4-Me	Con. H ₂ SO ₄ , N ₂ O ₄ , SeO ₃ , 200° raised to 305° KMnO ₄ (limited)	Nicotinic acid (70%), 2,5-pyridinedicarboxylic acid 4-Methylquinolinic acid	1470 200,201, 202,692
2,3-Me ₂	KMnO ₄ (excess) Ozone, CHCl ₃ , –40°	2,3,4-Pyridinetricarboxylic acid 5,6-Dimethyl-2,3-pyridinedicarboxaldehyde, glyoxal, biacetyl (all as derivatives)	692 1463
5,8-Me ₂	Ozone, CHCl ₃ , –25° to –35°	2,3-Diacetylpyridine, glyoxal (as derivatives)	667,1463
6,8-Me ₂	KMnO ₄	Quinolinic acid	1401
6,7-Me ₂	Ozone, CHCl ₃ , –25° to –35°	2,3-Pyridinedicarboxaldehyde (2%), biacetyl (13%) (as derivatives)	667,1463

(continued)

TABLE II-45 (Continued)
Oxidation of Substituted Quinolines

Substituents	Conditions	Products (Yield)	Ref.
2,4,8-Me ₃	KMnO ₄ (limited)	4-Methyl-2,3,6-pyridine tricarboxylic acid	1401
	KMnO ₄ (excess)	2,3,4,6-Pyridinetetracarboxylic acid	1401
Bz-alkyl		Quinolinic acid	156
4-Ph	Aq., KMnO ₄ , boil, 6 hrs.	4-Phenylquinolinic acid (61%)	1585
2,2'-Biquinoline		6-Hydroxy-2,5-pyridinedicarboxylic acid	1044
4-Cl	KMnO ₄	4-Chloroquinolinic acid	243
6-F	(1) Ozone, HOAc, 25-35°, 2 d. (2) 30% H ₂ O ₂ , reflux, 2 hrs.	Quinolinic acid (15%)	1440
6-NO ₂	(1) Ozone, HOAc, 25-35°, 2 d. (2) 30% H ₂ O ₂ , reflux, 2 hrs.	Quinolinic acid (6%)	1440
8(?)>NO ₂	90% HNO ₃ , SO ₃ , SeO ₂ , 315-40°, 15 min.	Quinolinic acid	835
8-SO ₃ H	KMnO ₄ , base	Quinolinic acid (72%)	160
	Conc. H ₂ SO ₄ , MnO ₂ , 165-75°, 2 hrs.	Quinolinic acid	1686, 1399
	Electrolysis, 60-75°	Quinolinic acid	1372
3-CO ₂ H	KMnO ₄	2,3,5-Pyridinetricarboxylic acid	188, 189
4-CO ₂ H	KMnO ₄	2,3,4-Pyridinetricarboxylic acid	640
2,4-(CO ₂ H) ₂	K ₂ MnO ₄	2,3,4,6-Pyridinetetracarboxylic acid (75%)	640

6-OH	Ca(OCl) ₂ , cool	β-(3-Carboxy-2-pyridyl)glyceric acid	1322,1323
Bz-OH	HNO ₃ (1) 60% HNO ₃ , 60° (2) Concentrate and heat at 135°	Quinolinic acid (80-90%) Nicotinic acid (71%)	162 548
8-OH	HNO ₃ , heat usually water bath,	Quinolinic acid (50-100%)	161,441, 446,602, 615,1664
	HNO ₃ , stand, 18 hrs.	Quinolinic acid (60%), 2-carboxy-3-pyridylglyoxylic acid (15.2%)	1748
	(1) HNO ₃ , 27°, 1 hr. (2) distill off acid	Nicotinic acid (75.6%)	441
	KMnO ₄ , base	Quinolinic acid (43.5%)	160
	(1) Ozone, HOAc, 25-35°, 2 d. (2) 30% H ₂ O ₂ , reflux, 2 hrs.	Quinolinic acid (92%)	1440
2-P-8-OH	HNO ₃ (fuming), V ₂ O ₅	6-Propylquinolinic acid (41%), 6-propyl-3-carboxy-2-pyridinol	1430
2-P-h-8-OH	KMnO ₄	6-Phenyl-3-carboxy-2-pyridinol, 6-hydroxyquinolinic acid	249
2,4-P-h ₂ -7-OH	KMnO ₄ , KOH	4,6-Diphenylquinolinic acid	447
5,7-(NO ₂) ₂ -8-OH	72% HNO ₃ , boil, 18 hrs.	Quinolinic acid (65%), nicotinic acid	1446
	HNO ₃ , stand, 18 hrs.	Quinolinic acid (66%), 2-carboxy-3-pyridylglyoxylic acid (5%)	1748

(continued)

TABLE II-45 (Continued)
 Oxidation of Substituted Quinolines

Substituents	Conditions	Products (Yield)	Rev.
2,4-(CO ₂ H) ₂ -8-OH	Ozone	2,3,4,6-Pyridinetetracarboxylic acid (93%)	640
5-SCN-8-OH	HNO ₃ , several days	Quinolinic acid	1560
2-Ph-8-OMe	KMnO ₄	6-Phenyl-3-carboxy-2-pyridinol, 6-hydroxyquinolinic acid	249
2-Ph-6-OEt	KMnO ₄	6-Phenyl-3-carboxy-2-pyridinol, 6-hydroxyquinolinic acid	249
6-OAc	Ca(OC ₂ H ₅) ₂ , cool	β-(3-Carboxy-2-pyridyl)glyceric acid	1322,1323
6-NH ₂	(1) Ozone, HOAc, 25-35°, 2 d. (2) 30% H ₂ O ₂ , reflux, 2 hrs.	Quinolinic acid (65%)	1440
2-Ph-6-NH ₂	KMnO ₄	6-Phenyl-3-carboxy-2-pyridinol, 6-hydroxyquinolinic acid	249
6-F-8-NH ₂	(1) Ozone, HOAc, 25-35°, 2 hrs. (2) 30% H ₂ O ₂ , reflux, 2 hrs.	Quinolinic acid (44%)	1440
2-OMe-bz-NH ₂	KMnO ₄	6-Methoxyquinolinic acid	266
6-OMe-7-Br-8-NH ₂	KMnO ₄ , alkali, boil 2 hrs.	Quinolinic acid	1544
2-Me-3-alkoxy-4-CO ₂ H-x-NH ₂		6-Methyl-5-alkoxy-2,3,4-pyridine-tricarboxylic acid	1710

TABLE II-46. Oxidation of Isoquinoline and Derivatives

Substituent	Conditions	Product (Yields)	Ref.
None	93% H ₂ SO ₄ , 70% HNO ₃ , HgNO ₃ , CuSO ₄	3,4-Pyridinedicarboxylic acid	1473
	60° Be', H ₂ SO ₄ , hydrogen halide (e.g., HBr), 295-315°	3,4-Pyridinedicarboxylic acid	1412
	H ₂ SO ₄ , HClO ₄ , Se or SeO ₂ , 280°	3,4-Pyridinedicarboxylic acid	165
	(1) 95% H ₂ SO ₄ , Se, 270°	3,4-Pyridinedicarboxylic acid	1522
	(2) Pass in NOCl	3,4-Pyridinedicarboxylic acid (95.4%)	659
3-Me	(1) Ozone, HOAc, 25-35°, 2 d.	3,4-Pyridinedicarboxylic acid	1440
	(2) 30% H ₂ O ₂ , reflux, 2 hrs.	(44.5%), phthalic acid (49.5%)	
	KMnO ₄ , 90°, 2 hrs.	6-Methyl-3,4-pyridinedicarboxylic acid (11%), phthalic acid	1482
8-SO ₃ H	H ₂ SO ₄ , MnO ₂ , 175°	3,4-Pyridinedicarboxylic acid (55%)	1398
3-Me-4-OMe	KMnO ₄ , alkali	6-Methyl-5-methoxy-3,4-pyridine-dicarboxylic acid (low yield)	867, 1674

TABLE II-47. Oxidation of Other Condensed Pyridine Compounds

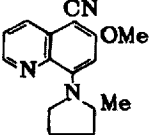
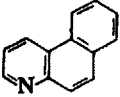
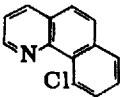
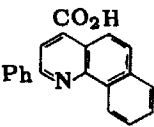
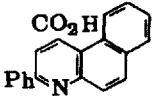
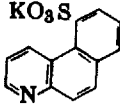
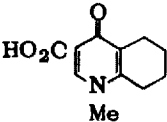
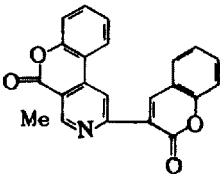
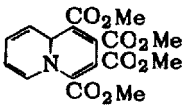
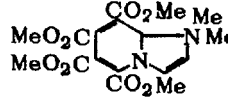
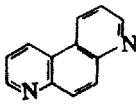
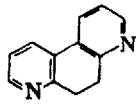
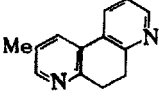
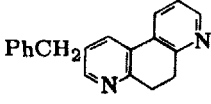
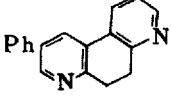
Heterocycle	Conditions	Product (Yield)	Ref.
	Aq., KMnO_4 , reflux, 8 hrs.	Quinolinic acid	1221
	Aq., KMnO_4 , K_2CO_3 , reflux, 8 hrs.	Quinolinic acid	535
	Alkaline KMnO_4	3-(2-Carboxyphenyl)-picolinic acid (21%)	564
	Aq., KMnO_4 , 100°	2-(Carboxy-6-chlorophenyl)nicotinic acid (38%)	1723
	KMnO_4	2-(2-Carboxyphenyl)-6-phenyl-3,4-pyridinedicarboxylic acid	1026, 1027
	KMnO_4 , warm	3-(2-Carboxyphenyl)-6-phenyl-2,4-pyridinedicarboxylic acid (74%)	1723
	Aq., KMnO_4 , room temp.	3-(2-Carboxy-6-sulfophenyl)-picolinic acid	1724
	68% HNO_3 , reflux, 14 hrs.	3,5-Dicarboxy-1-methyl-4-pyridone (12-25%), 3-carboxy-1-methyl-6-nitro-4-quinolone (50-60%)	1496

TABLE II-47 (Continued)

Heterocycle	Conditions	Product (Yield)	Ref.
	(1) 50% NaOH, 100°, several hrs. (2) KMnO ₄ , alkaline, 100°, 9 hrs.	2,3,4,6-Pyridine-tetracarboxylic acid	1461
	H ₂ O ₂ , HOAc	Picolinic acid oxide	1301, 1835
	Br ₂ , MeOH	Tetramethyl ester of 6-methyl-2,3,4,5-pyridinetetracarboxylic acid (65-80%)	1300
	Aq., KMnO ₄ , KOH, hot	2,2'-Dicarboxy-3,3'-dipyridyl	1016, 1694
	Aq., KMnO ₄ , KOH, heat, 1 hr.	2,2'-Dicarboxy-3,3'-dipyridyl (78%)	1582
	Aq., KMnO ₄ , KOH, heat, 1 hr.	2,2'-Dicarboxy-5-methyl-3,3'-dipyridyl (64%)	1582
	Aq., KMnO ₄ , KOH, heat, 1 hr.	2,2'-Dicarboxy-5-benzyl-3,3'-dipyridyl (62%)	1582
	Aq., KMnO ₄ , KOH, heat, 1 hr.	2,2'-Dicarboxy-5-phenyl-3,3'-dipyridyl (25%)	1582

(continued)

TABLE II-47 (Continued)

Oxidation of Other Condensed Pyridine Compounds

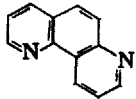
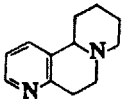
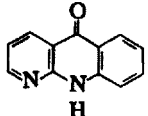
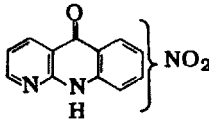
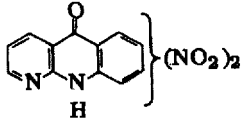
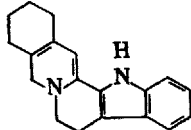
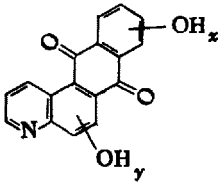
Heterocycle	Conditions	Product (Yield)	Ref.
	KMnO ₄	2,3'-Dicarboxy- 3,2'-dipyridyl	513, 1747
	Aq., KMnO ₄ , KOH, heat	2,3'-Dicarboxy- 3,2'-dipyridyl (80-85%)	1016, 1694
	Aq., KMnO ₄ , heat	Quinolinic acid (67%)	1568
 (?)	Aq., KMnO ₄ , KOH 25°, 1 hr.	 CO ₂ H NHCOCO ₂ H	1310
	KMnO ₄ , KOH, 35°, ½ hr.	2-Hydroxy-5-nitro- nicotinic acid	1310
	KMnO ₄	2-Amino-5-nitro- nicotinic acid, oxalic acid	1310
	Dil. HNO ₃ , boil	2,4,5-Pyridine- tricarboxylic acid	1804
	Dil. HNO ₃	Quinolinic acid (43-49%)	163,164

TABLE II-48. Hydrogenation of Quinoline over Nickel Catalyst (1837)

Temp., °C.	Pressure, atm.	Yield of Py-tetrahydro- quinoline, %	Yield of Bz-tetrahydro- quinoline, %	Yield of Decahydro- quinoline, %
70	70	71		
100	61	73	1	
210	70		1	62
270	61			52

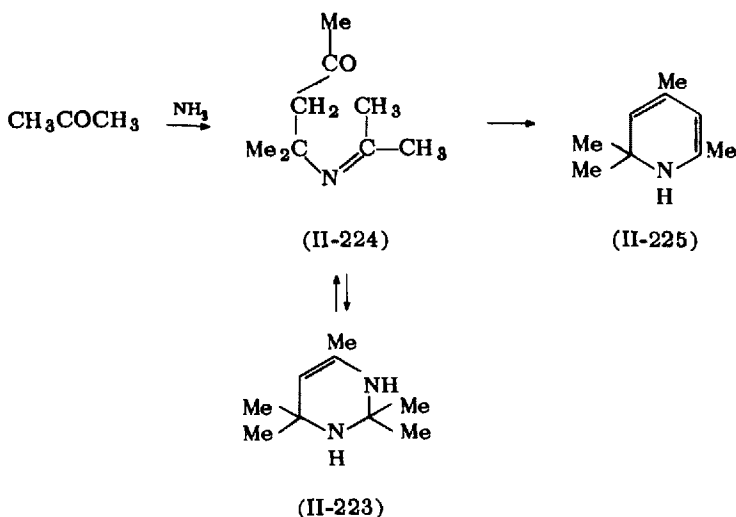
TABLE II-49. Reduction of Quinoline Derivatives by Hydrogen and Nickel (907-909)

Substituents	Temp., °C.	Yield of Py-tetra- hydroquinoline, %	Yield of Bz-tetra- hydroquinoline, %
2-Me	110-50	96	4
3-Me	190	66	33
4-Me	160	66	33
6-Me	120	90	
7-Me	150	100	
8-Me	120	97	
2,3-Me ₂	156	56	44
2,4-Me ₂	140	20	80
2,6-Me ₂	105	98	
2,3,4-Me ₃	155-60		100
2,4,5,8-Me ₄	160-70	96	4
3-Et	180-90		33
2-Pr	170	65	
3- <i>n</i> -Amyl	180-90	50	50
2-Me-4-Pr	170-80		84
2-Ph	150	100	
3-Ph	160	66	33
6-Cl	160	100	
6,7-Ethylenedioxy	180-90	90	
4-CO ₂ Et		Major prod.	
2,3-Me ₂ -4-CO ₂ Et	170	70	24
3-Me-2-Ph-CO ₂ Et		25	

9. Miscellaneous Heterocyclic Systems

Pentamethyltetrahydropyrimidine

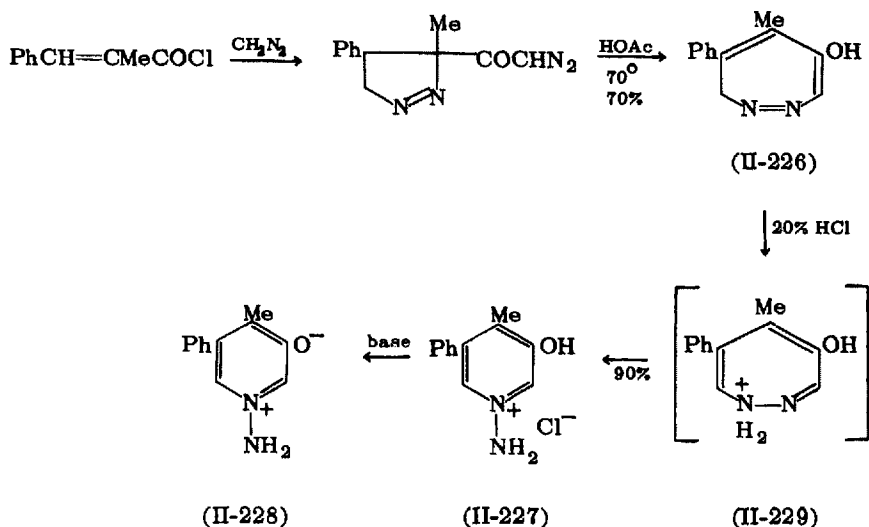
Acetonine, which is 2,2,4,4,6-pentamethyltetrahydropyrimidine (II-223) is formed from acetone and ammonia under mild conditions, probably through the intermediate II-224. The passage of acetonine over a catalyst of silica and alumina at 120° produced 2,2,4,6-tetramethyldihydropyridine (II-225) (745), again probably through intermediate II-224. This pyridine product may also be made directly from ammonia and acetone.



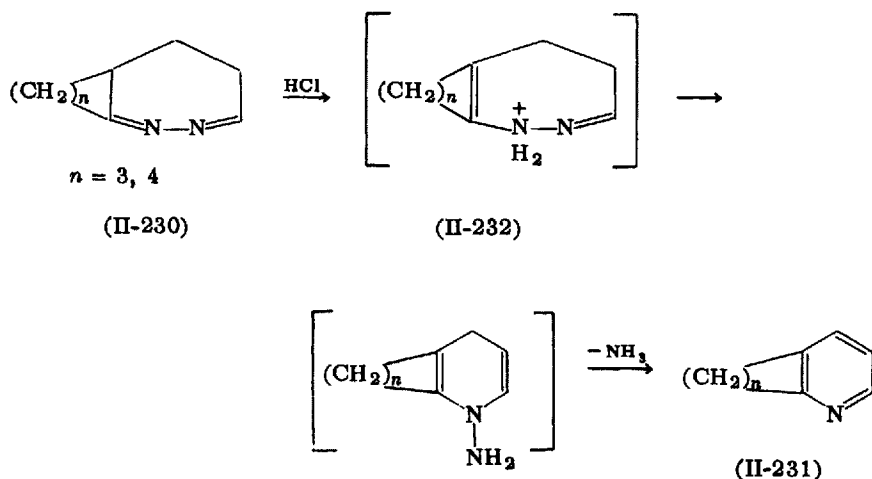
Diazepines

The diazepine II-226 was transformed by the action of hydrochloric acid to a 90% yield of 1-amino-3-hydroxy-4-methyl-5-phenylpyridinium chloride (II-227). This product was converted by the action of base into the inner salt II-228, and by the action of nitrous acid in methanol into 4-methyl-5-phenyl-3-pyridinol (671).

In contrast, the two dihydrodiazepines II-230 reacted in the presence of hydrogen chloride at 235° to give a 20% yield of the pyridines II-231 (1110). The difference in the products from the di-

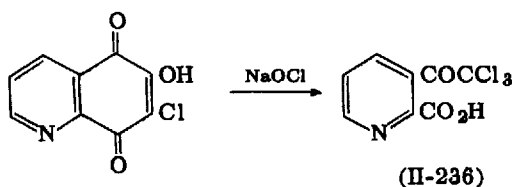
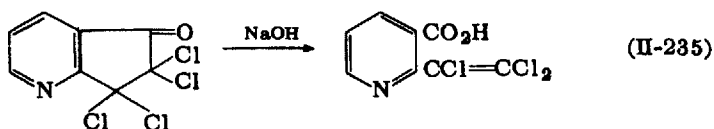
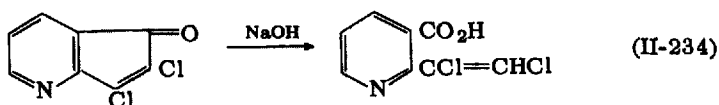
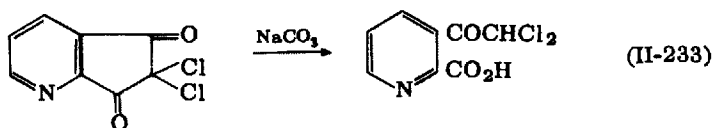


azepine and the dihydrodiazepine may be rationalized by the possible intermediates II-229 and II-232. Whereas the diazepine is converted to the 1-aminopyridinium salt, which is stable under such conditions, the dihydrodiazepine would isomerize to an aminodihydropyridine which under the reaction conditions would lose ammonia to give the more stable pyridine.

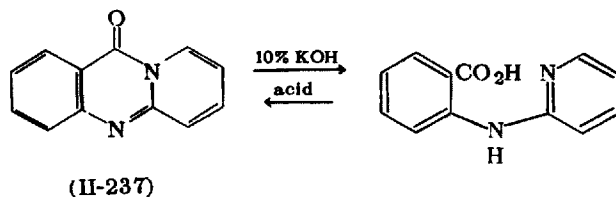


Pyridinone and Quinolinedione

Pyridinecarboxylic acids have been made from chloropyridinone derivatives by the action of alkali as in II-233 (1608), II-234, and II-235 (1609). The ring cleavage is brought about by a haloform-type reaction. A similar reaction is found in the hypochlorite oxidation of a quinolinedione to II-236 (1608).

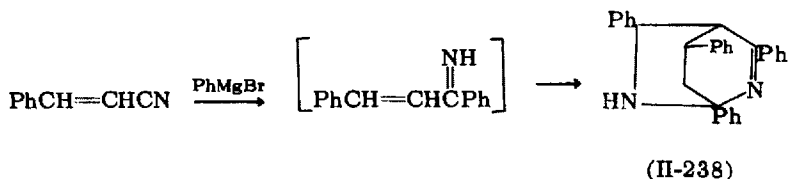
*Pyridoquinazolinone*

The preparation of 2-(2-carboxyanilino)pyridine from the pyridoquinazolinone II-237 by hydrolysis was done not for preparative purposes but as a structure proof. This conversion is reversed by acid (1822).

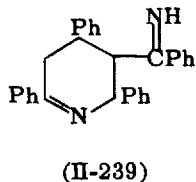


Styrylphenyl Ketimine Dimer

Piper and Wright reported that the reaction of cinnamionitrile and phenylmagnesium bromide gave a 40% yield of a styrylphenyl ketimine dimer thought to be II-238 (1131). This compound was



hydrolyzed in 81% yield to 3-benzoyl-2,4,6-triphenyltetrahydropyridine by the action of acid, was oxidized by bromine and alcohol to a 63% yield of dibromo-2,4,6-triphenylpyridine, and was converted at 300° to ammonia, toluene, and a 59% yield of 2,4,6-triphenylpyridine. While structure II-239 would also explain these reactions, it does not explain as well the reaction with sulfur at 190° which gave styrene and 2,4,6-triphenylpyrimidine. In contrast the reaction of 3-benzoyl-2,4,6-triphenyltetrahydropyridine (which is the keto form of II-239) and sulfur gave a 92% yield of 3-benzoyl-2,4,6-triphenylpyridine.



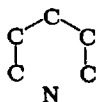
Oxidation of several heterocyclic compounds which contain pyrido rings produces substituted pyridines, but since such reactions

Chapter II

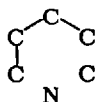
resemble the oxidation of quinolines, they have been discussed in that section (p. 251).

B. FROM ACYCLIC COMPOUNDS

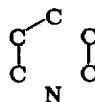
The synthesis of the pyridine ring from open-chain compounds takes so many interrelated forms, that any system of classification must be somewhat arbitrary. The system we have chosen is based on the size and arrangement of the carbon fragments which build the ring. In this way several well-defined classes emerge, as shown in the accompanying diagrams. Thus, all the carbons may be supplied as a *five-carbon chain* by a single molecule. A *4-1* condensation is the combination of two organic molecules which furnish four carbons and one carbon, respectively, to the ring. A *3-2* condensation is analogous. A *1-3-1* condensation requires three organic molecules, which furnish one carbon, three carbons, and one carbon, respectively, in that order. The *2-2-1* and *2-1-2* condensations differ only in the arrangement of the carbon fragments; since they often occur together it is advisable to read both sections con-



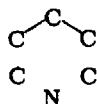
Cyclization of a
five-carbon chain



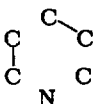
4-1 Condensation



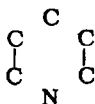
3-2 Condensation



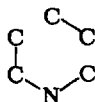
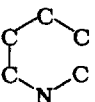
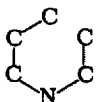
1-3-1 Condensation



2-2-1 Condensation



2-1-2 Condensation



Cyclizations not involving the ring nitrogen

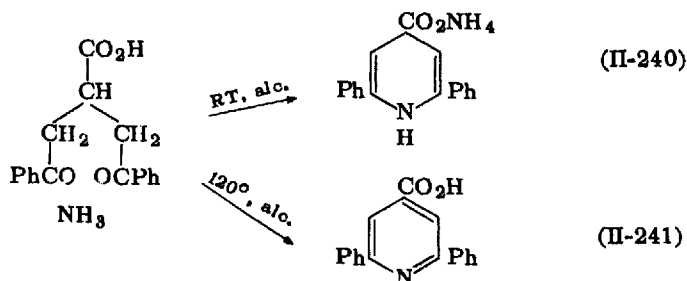
currently. In this system of classification, the source of the nitrogen is ignored. It is often attached at the end of a carbon fragment (e.g., imine or amide), but may be supplied separately, for example as ammonia or amine. In any case cyclization involves the formation of C-N bonds. There is also a class of synthesis in which the C-N bonds are initially present (as in disubstituted amines or *N*-substituted amides); cyclization then involves only the formation of C-C bonds; this is also illustrated in the diagrams.

1. Cyclization of a Five-Carbon Chain

a. 1,5-Dioxo Compounds and Derivatives

The cyclization of 1,5-diketones and 1,5-dialdehydes may be accomplished with ammonia, primary amines, hydrazines, or hydroxylamine, and leads either to pyridines or dihydropyridines depending on the reactants. The imines and oximes of the dioxo compounds may also be cyclized to similar products.

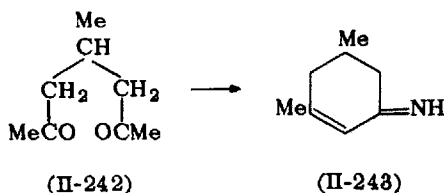
(a) **1,5-Dioxo Compounds and Their Acetals and Enol Ethers: (1) With Ammonia and Primary Amines.** Saturated 1,5-diketones and ammonia should normally give dihydropyridines, and these have been obtained under mild conditions, at room temperature in anhydrous solvents (II-240); at a higher temperature the aromatic pyridine was obtained (II-241) (198). Other conditions which have been used to cyclize saturated diketones are: ammonium acetate in acetic acid (1149), fusion with ammonium acetate (1713), aqueous ammonia and ammonium acetate at 250° (1165), formamide as the source of ammonia (448), and a mixture of ammonium formate and formamide (1149). In nearly all cases aromatic pyridines were the



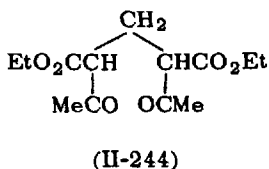
products. Primary aliphatic amines have also been used, and give 1-alkyl-1,4-dihydropyridines (Table II-50).

The saturated 1,5-diketones are often prepared by condensing one mole of an aldehyde with two moles of a methylenic or methyl ketone; thus II-244 comes from formaldehyde and acetoacetic ester. This leads to symmetrical pyridines, and the synthesis resembles the 2-1-2 condensation, in which the aldehyde, methylenic ketone, and ammonia are reacted directly (p. 500). A comparison made in one case showed the 1,5-diketone to give a somewhat higher yield than the simpler components (1165).

When the 1,5-diketone has terminal alkyl groups, cyclization to a cyclohexenone may preferentially occur. Thus II-242 with alcoholic ammonia gave the cyclohexenone imine (II-243) exclusively (87), and 3,7-nonadione gave 2-methyl-3-ethyl-2-cyclohexenone (328).



On the other hand II-244 gave the dihydropyridine in quantitative yield (239). Possibly the carbethoxy groups of II-244, by promoting ionization at the *alpha* carbons, effectively suppress ionization of the methyl groups; this eliminates methyl condensation and permits cyclization with ammonia.



When true pyridines are the products, their formation can be explained as disproportionation of the initial dihydropyridines under the influence of heat, acids, or bases to give both pyridines and products of higher hydrogen content. The latter have been isolated in several cases, and have been designated variously as

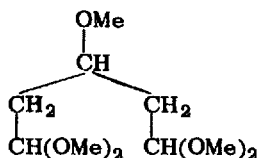
piperidines or tetrahydropyridines, without clear evidence for the distinction. The disproportionation of a dihydropyridine on long standing in alcoholic ammonia has been shown (307). Among 1,5-cyclizations, II-240 gave only the dihydropyridine, while II-241 (at the higher temperature) gave the pyridine and the corresponding piperidine, both of which were isolated (198). The cyclization of benzaldiacetophenone with ammonium acetate in refluxing acetic acid gave 2,4,6-triphenylpyridine and the piperidine (1149), while the imine of this diketone, cyclized in hot acetic acid, gave the tetrahydropyridine as co-product (371).

Aromatization by direct evolution of hydrogen has not been shown. But the evolution of ethane was fairly well demonstrated when benzaldiacetophenone was cyclized with ethylamine by heating at 130° for twenty hours; the product was then 2,4,6-triphenylpyridine (371).

The pyridine obtained from benzaldiacetophenone, ammonium formate, and formamide was accompanied by a piperidine in yield so high that disproportionation alone could not account for it. The investigators assumed that a Leuckart reaction also occurred, giving a 1,5-diaminopentane which cyclized to a piperidine (1149). Similarly, formamide itself was reported to give both pyridine and piperidine products in the same reaction (448).

Since glutaraldehydes are not readily available, it is not surprising that there are no reports of their cyclization with ammonia, except for a patent which describes excellent yields of pyridine and 4-picoline obtained in acid medium in the presence of ferric salts as oxidizing agents (Table II-50). In this case the glutaraldehydes were prepared by hydrolysis of 2-alkoxy-3,4-dihydro-2H-pyrans. The latter can react directly with ammonium and ferric salts to give the same products (684).

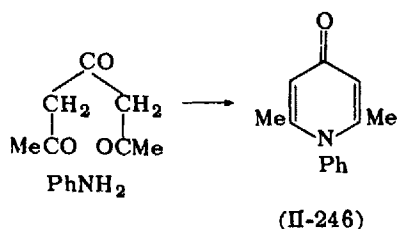
The cyclization of saturated 1,5-diacetals (II-245) with am-



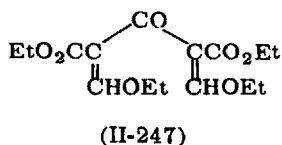
(II-245)

monium salts and ammonia has been reported (1818,1832). Since these contain also a β -alkoxy group, the complete elimination of alcohol gave pyridine itself (Table II-50).

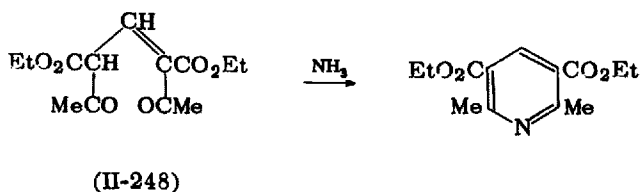
Diacetylacetone is the only 1,3,5-triketone which has been cyclized with ammonia or primary amines; the products are 4-pyridones (II-246) (355). A similar product was obtained from the 1,5-



dienol ether II-247, and ammonia (259). Since II-247 was prepared from acetonedicarboxylic ester and ethyl orthoformate *in situ* and used without purification, its conversion to a pyridine is in effect a 1-3-1 condensation (p. 473) (Table II-51).

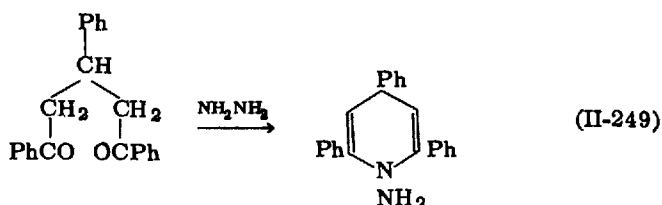


Unsaturated 1,5-diketones and dialdehydes should cyclize with ammonia to aromatic pyridines. Unfortunately the starting materials are not as accessible as saturated diketones, and few such cases are reported (Table II-52). The 1,5-diketone II-248 was cyclized in aqueous ammonia (216). Glutaconaldehydes are particularly difficult to obtain. In the earliest such preparation, in 1889, Hantzsch obtained α -chloroglutaconaldehyde by the reaction of phenol with chlorine and alkali, and cyclized it to 3-chloropyridine by heating its sodium salt in aqueous ammonium acetate (1012). Glutaconaldehyde itself is obtained from pyridine by various methods of ring-opening, and has in turn been halogenated to α -bromo and α -iodoglutaconaldehyde. All of these have been re-cyclized to pyridines by the Hantzsch method (1,1011).

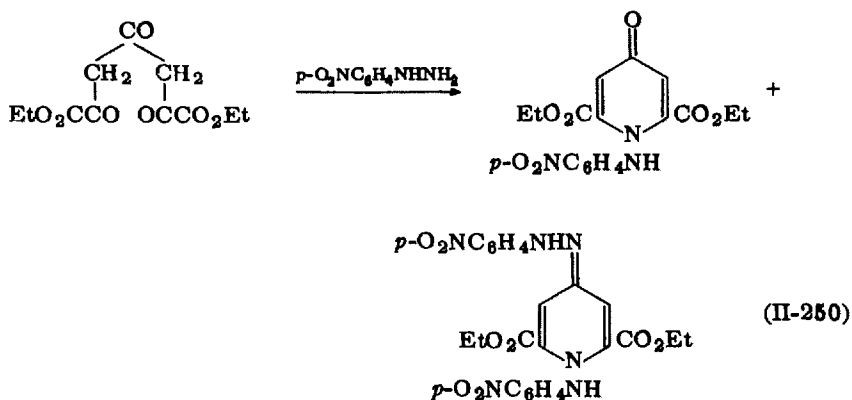


The cyclization of 1,5-dioxo compounds could proceed through formation of the monoimine or diimine; derivatives of both kinds have been cyclized, under basic, acid, or neutral conditions (see p. 279).

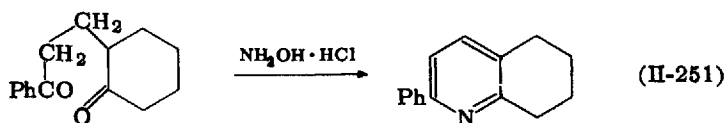
(2) *With Hydrazines.* Hydrazine hydrate has been reacted with a few 1,5-diketones, giving 1-amino-1,4-dihydropyridines (II-249) (371) (Table II-50).



The use of arylhydrazines has been limited to 1,3,5-triketones (Table II-51), in which case both a 1-arylamino-4-pyridone and its arylhydrazone may be obtained (II-250) (764). In general either type of product can be made to predominate by choice of the solvent, time, and amount of reagent.

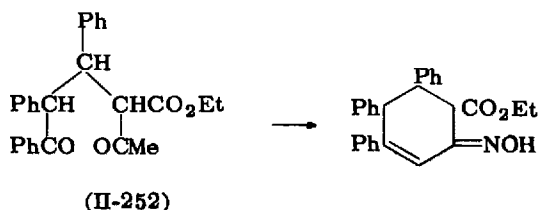


(3) *With Hydroxylamine.* Hydroxylamine reacts with saturated 1,5-diketones to produce high yields of the aromatic pyridines in one step (II-251) (1110). The method, as originated by Knoevenagel (239), uses hydroxylammonium chloride (three moles) in alcohol or aqueous alcohol, and temperatures above 120° in a sealed tube. But an equal yield has been obtained at reflux temperature in longer time (1019) (Table II-53).

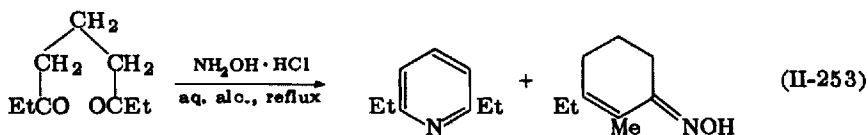


Acid medium is essential, since free hydroxylamine base (with one exception) gave only the mono or dioxime of the 1,5-diketone (1019,1699,1700,1701,1703). This may in turn be cyclized to a pyridine by treatment with anhydrous acid (see below).

When the 1,5-diketone has a terminal alkyl group, cyclization to a cyclohexenone is a competing reaction. Thus, Knoevenagel found that II-252 gave the cyclohexenone oxime exclusively on treatment



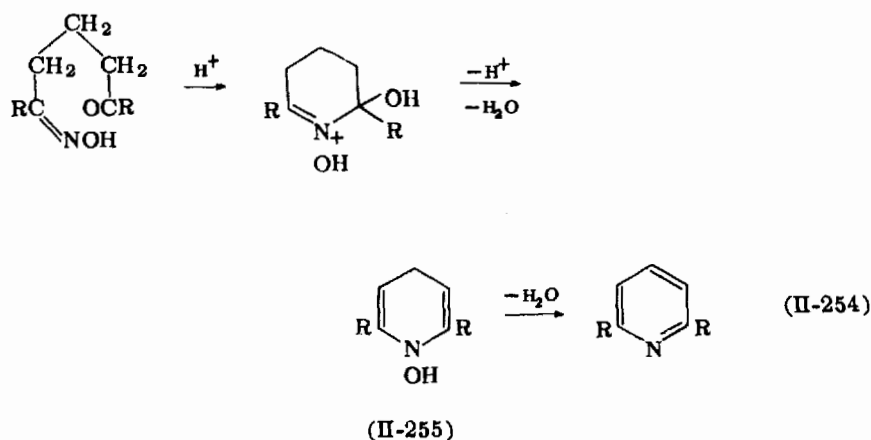
with hydroxylammonium chloride, or with hydrogen chloride, in alcohol (239). On the other hand, the pyridine base was the major product from 3,7-nonadione (II-253), and the by-product could be further minimized by cyclizing the diketone dioxime (328).



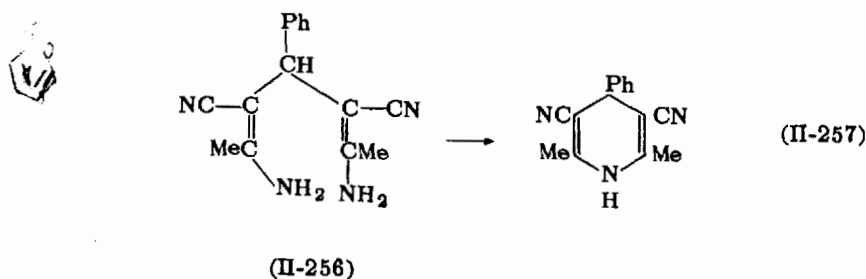
The cyclization of a glutaraldehyde with hydroxylamine salts is rare, only the conversion of β -methylglutaraldehyde to 4-picoline

appearing in the literature (1745). The aldehyde was prepared by hydrolysis of 2-ethoxy-4-methyl-3,4-dihydro-2H-pyran, which may also be converted directly to the pyridine by treatment with hydroxylammonium chloride (1168,1745).

The mechanism of pyridine formation by hydroxylamine has not been elucidated. One may suppose that it proceeds as in II-254 through a 1-hydroxydihydropyridine (II-255), which then loses water, all steps being acid-catalyzed. A similar mechanism starting with the dioxime may be written.



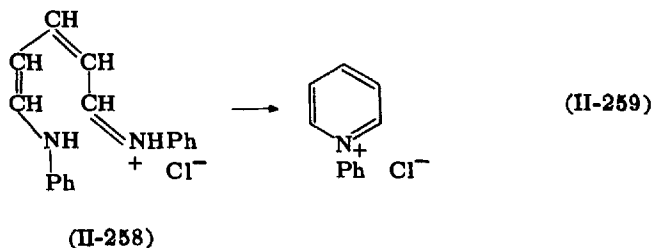
(b) **Imines of 1,5-Dioxo Compounds.** The imine derivatives of saturated 1,5-diketones have rarely been cyclized (Table II-54), since it is more convenient to cyclize the free diketones themselves with ammonia or amines. Diimines like II-256, however, readily available from an aromatic aldehyde and two moles of β -amino-crotononitrile, have been cyclized by acid agents (II-257) (1613).



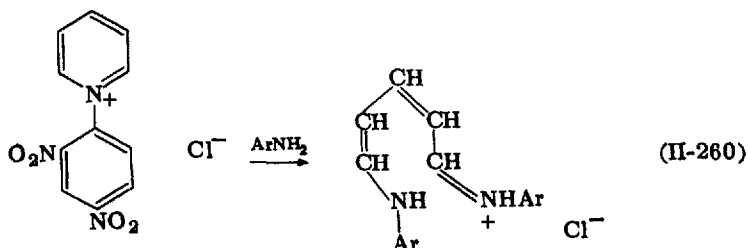
The monoimine of benzaldiacetophenone has been cyclized by acids or bases, or by heat alone, giving 2,4,6-triphenylpyridine (371). The product must have arisen by disproportionation of an initial dihydropyridine, since in one experiment some of the tetrahydropyridine was also isolated. There was no advantage over cyclizing benzaldiacetophenone itself with alcoholic ammonia.

The 1,5-dianil of β -oxoglutaraldehyde (obtained from 4-pyrone and aniline) was converted to 1-phenyl-4(1*H*)-pyridone by means of acid, base, or heat (1056).

In contrast, many imine derivatives of glutaconaldehydes have been cyclized, mainly the dianil acid salts (II-258); these close the ring on heating alone, or in a solvent, or more commonly on heating in the presence of strong acid. The products are 1-arylpyridinium salts (II-259) (2) (Table II-55). Although the starting dianils are themselves prepared by cleavage of a pyridine, this is a very convenient method for preparing otherwise inaccessible 1-arylpyridinium salts.

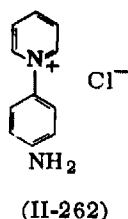
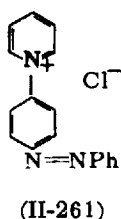


The starting dianils are obtained from suitable quaternary salts of pyridine, most often from 2,4-dinitrophenylpyridinium chloride, by treatment with an aromatic primary amine in hot alcohol (II-260) (606,621,862,874). Other quaternary salts which have been

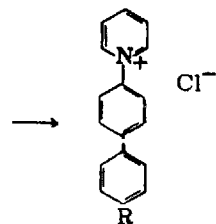
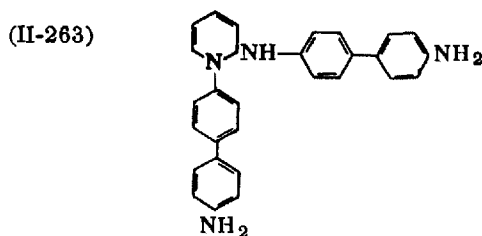
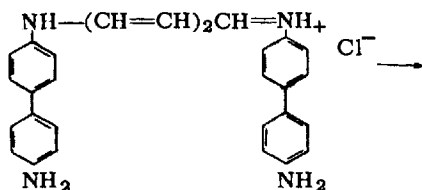


used are derived from pyridine and 2,4-dinitro-1,5-dichlorobenzene (9), cyanogen bromide (11,35,36,1015), or diphenyloxalimidyl chloride (10). The dianils of α -hydroxyglutaconaldehyde may also be prepared by an independent method, from furfural, an aromatic amine, and an acid (35,36).

The method has been extended to the preparation of pyridinium salts having rather complex 1-aryl substituents, by using the appropriate dianil, derived for example from xenylamine (621), 4-aminoazobenzene (II-261) (862), or *p*-phenylenediamine (II-262)

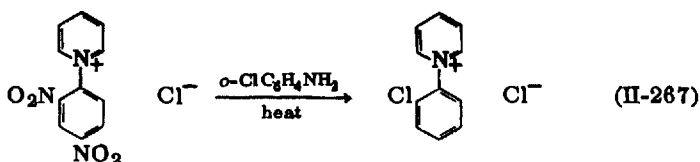


(874). The dianil of benzidine (II-263), however, when subjected to heat or alcoholic hydrogen chloride, cyclized to a product which was very likely II-264 (621). Further treatment of II-264 with hot concentrated hydrochloric acid then gave the normal pyridinium salt (II-265) (874); or diazotization and heating gave II-266 (621).

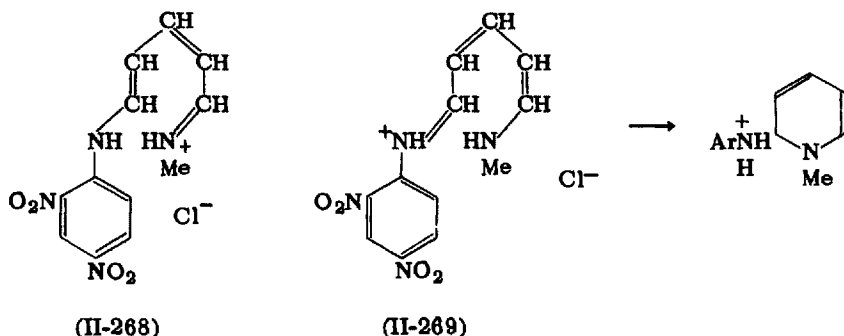


The cyclization of glutaconic dianils has been effected by means of bromine, which results in bromination of the 1-aryl substituent (2,4). The dianils of α -haloglutaconaldehydes (1011,1015) and of α -hydroxyglutaconaldehyde (35,36) have also been cyclized.

In some cases conversion to a pyridinium salt was effected without isolation of the intermediate dianils. Rather, 2,4-dinitrophenylpyridinium chloride itself was treated with the aromatic amine (or with methylamine) to form the new pyridinium salt in one step (II-267) (2) (Table II-56).

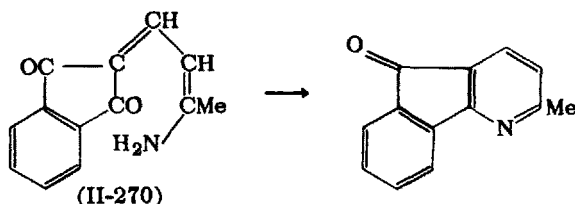


It may be assumed that cyclization of a dianil salt proceeds by attack of the tertiary amino group on the opposite aldimine residue which is already polarized by the presence of a proton. When an unsymmetrical diimine like II-268 is used (obtained from an *aliphatic* amine and dinitrophenylpyridinium chloride) its reactive form should be II-269 since the *aliphatic* nitrogen is the more nucleophilic. Accordingly the product is a 1-alkylpyridinium salt, and 2,4-dinitroaniline is ejected (7).

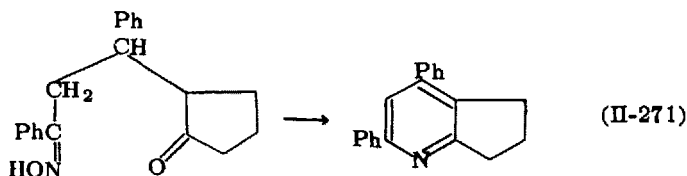


A *monoanil*, the 2,4-dinitroanil of glutaconaldehyde, was cyclized by means of hydrogen chloride in acetic acid. This represented merely a reversal of the ring-opening, since in this case the anil was prepared by hydrolysis of 2,4-dinitrophenylpyridinium chloride in

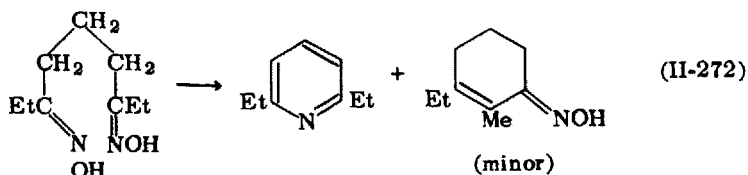
aqueous carbonate (2). The monoimine of an unsaturated 1,5-diketone (II-270) has been converted to the corresponding pyridine by heating in acetic acid (1714) (Table II-55).



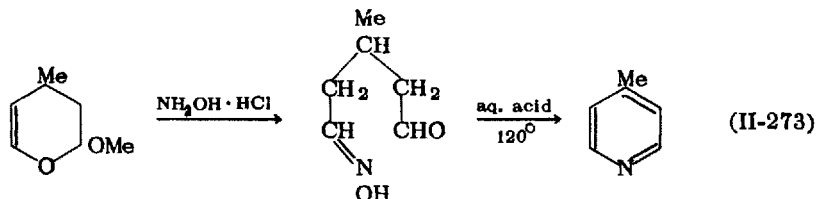
(c) **Oximes of 1,5-Dioxo Compounds.** The mono and dioximes of saturated 1,5-diketones and dialdehydes are cyclized to pyridine bases by acid agents (II-271, position of oxime function not established) (1699) (Table II-57). Usually hydrogen chloride in an anhydrous solvent is used.



The oximes have been prepared from 1,5-diketones by the use of hydroxylamine base; depending on the quantity of reagent a mono or dioxime is obtained (1019,1699,1700,1701,1703). When an acidic reagent is used (hydroxylamine salt) direct cyclization to the pyridine occurs (see above). There is no advantage in preparing the oxime except when the diketone has a terminal alkyl group. In that case the acid agent promotes competing cyclization to a cyclohexenone, while the oxime gives a higher yield of pyridine (II-272) (328).



The use of oximes is also convenient in the case of glutaraldehydes, which are not readily accessible. According to a patent (794) these oximes are prepared from glutaraldehyde precursors, the 2-alkoxy-3,4-dihydro-2*H*-pyrans, by mild treatment with hydroxylammonium chloride (II-273). However, it is also possible to convert

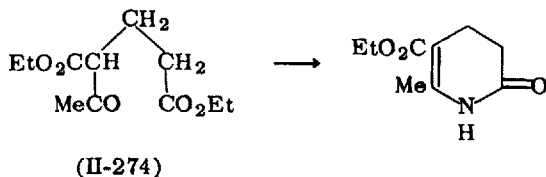


the precursors directly to pyridines by more vigorous treatment with the reagent (1168,1745).

b. 5-Oxocarboxylic Acids and Derivatives

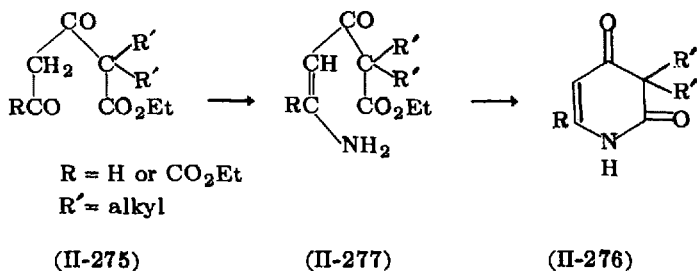
A variety of 5-ketoacid and 5-aldehydoacid derivatives are cyclized to pyridinols or dihydropyridinols. These include the oxoesters, amides and nitriles and 5-iminoesters; ammonia supplies the ring nitrogen unless this element is already present.

(a) *5-Oxocarboxylic Acids and Esters and Their Oxo Derivatives* (Table II-58). The cyclization of γ -benzoylbutyric acid was effected by the passage of ammonia for a long time at 160–70°, giving 6-phenyl-3,4-dihydro-2-pyridinol (332). In contrast, α -acetylglutaric ester (II-274) reacted under milder conditions, with alcoholic am-

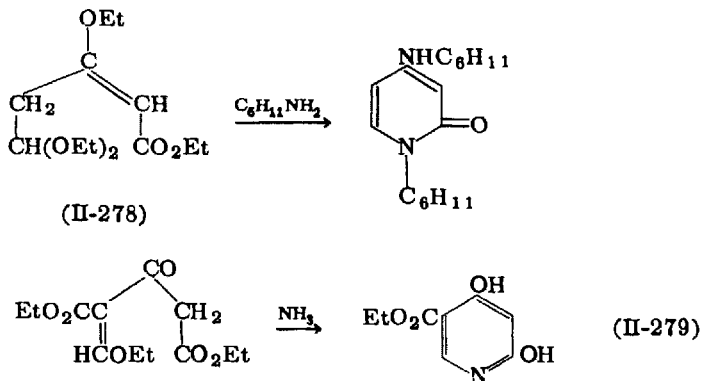


monia (1726) or ammonium acetate in benzene (629). It will be noted in II-274 that the keto group is active in ring formation (reacts with ammonia) in preference to the second carboxy group, because of the greater polarization of keto carbonyl; this is general throughout pyridine synthesis.

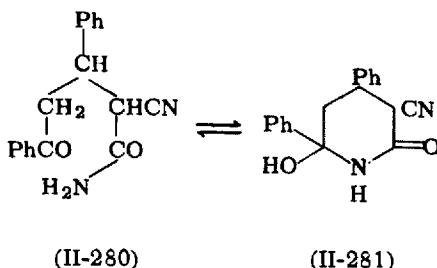
The synthesis has been applied to a series of 3,5-dioxoesters (II-275), reported largely in the patent literature (reviewed in references 1239 and 625). While vigorous treatment with ammonia (150° in methanol) gave II-276 directly, gentle warming in a solvent gave only the imine derivative (II-277). This was cyclized *in situ*, or after isolation, by addition of a strong base, such as sodium ethoxide. The difficult cyclization with ammonia, in contrast to II-274, may perhaps be a steric effect of the *gem*-dialkyl group, which hinders attack of the imine on carbethoxy. The use of strong base then creates the more nucleophilic enamine anion. The cyclization of II-277 has also been effected with boron trifluoride-acid mixtures (1449).



A 1,5-acetal-ester (II-278) has been converted to a pyridone by means of cyclohexylamine; replacement of the enol ether group by amine occurred at the same time (1742). Similarly, an enol ether group in the 5 position may participate in ring formation (II-279) (259,820).

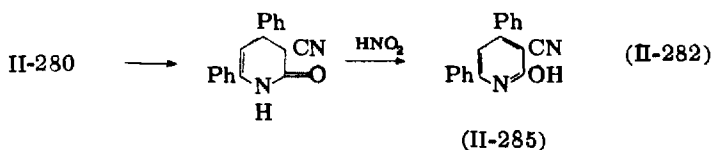


(b) **5-Oxocarboxamides.** It is not certain whether saturated 5-ketoamides have the open-chain (II-280) or ring form (II-281). Several investigators have preferred II-281 on feeble chemical evidence,



such as the failure of ketonic reactions and the difficult hydrolysis of the amide (1327,1261). A mixture of ring-chain tautomers may well be present (332). Ketoamides having a cyano substituent are prepared from an unsaturated ketone (*e.g.*, benzalacetophenone) and cyanoacetamide. When the ring structure (II-281) has been assigned, the cases are treated under 3-2 condensations (p. 443). Otherwise they are considered here.

Saturated 5-ketoamides are converted to dihydropyridinols by heat alone or by acid agents such as acetyl chloride, sulfuric acid or hydrogen chloride (II-282) (307) (Table II-59). It is significant that the carbamoyl group participates in ring closure in preference to the cyano group though the latter has the more nucleophilic nitrogen.

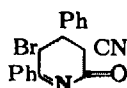


This is because the amide nitrogen is more favorably situated in proximity to the carbonyl group; ring closure may involve a simple prototropic shift to II-281, as we have indicated.

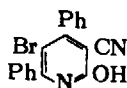
Strong basic agents should also effect conversion to dihydropyridinols. This has not been reported, but may be inferred from the preparation of the ketoamides (*e.g.*, II-280), which is carried out with weak, organic bases, or a trace of sodium alkoxide. When an

equivalent of the latter is used the dihydropyridinol is obtained directly (3-2 condensation, p. 443).

When bromine was the cyclizing agent, II-280 was converted to a bromine-containing substance assumed to be II-283, since on oxidation with nitrous acid it gave a bromopyridinol (assigned structure II-284). Elimination of hydrogen bromide from II-283, by heat or strong base, gave the normal pyridinol (II-285) (307).

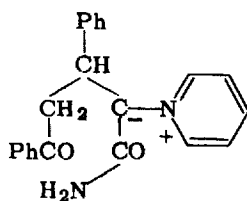
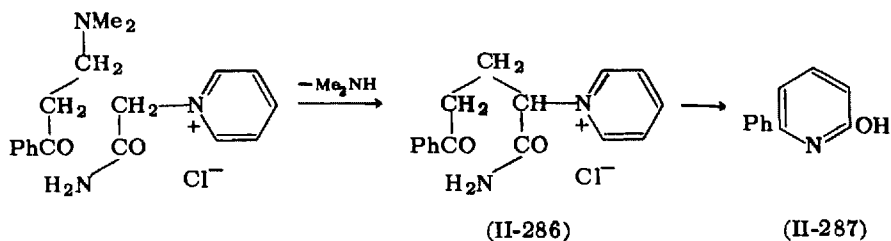


(II-283)



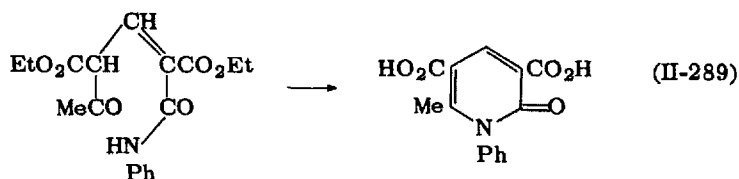
(II-284)

The unusual ketoamide II-286 was prepared by reacting the Mannich base of acetophenone with 1-carbamoylmethylpyridinium chloride. This ketoamide gave a pyridinol directly on heating (II-287), with elimination of pyridinium chloride, no separate oxidation step being required. Similarly, the ketoamide II-288, prepared from benzalacetophenone and the same pyridinium reagent, gave 4,6-diphenyl-2-pyridinol on heating or on treatment with acid (906).

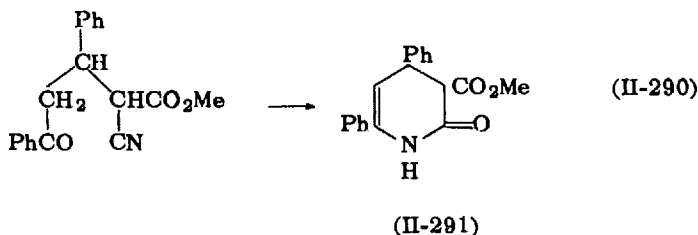


(II-288)

An example of an *unsaturated* 5-ketoamide is reported which closed to a 1-phenylpyridone (II-289); since alcoholic potassium hydroxide was used, at reflux, the carbethoxy groups were hydrolyzed in the process (1607).



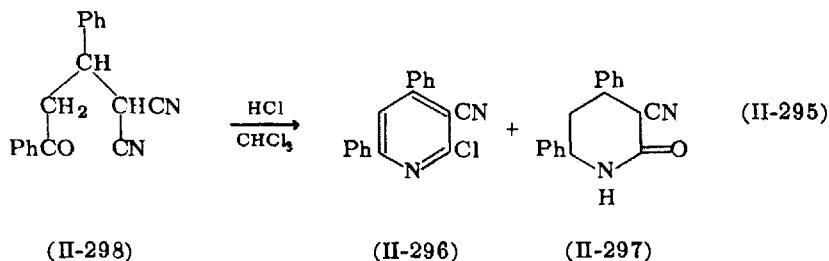
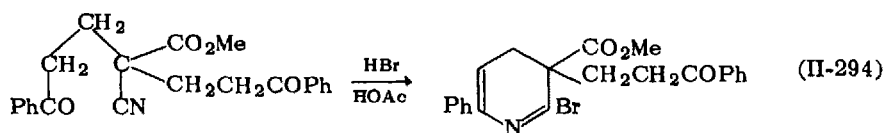
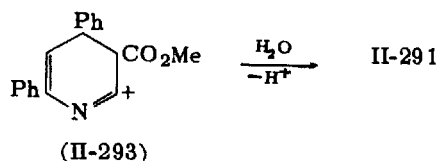
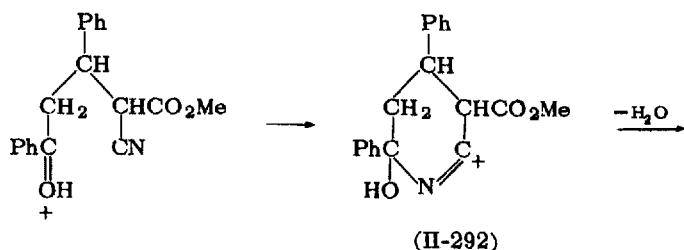
(c) **5-Oxonitriles.** The cyclization of saturated 5-ketonitriles proceeds under acid conditions and gives dihydropyridinol as the normal products (II-290) (1359). Hydrogen halides in acetic acid,



chloroform or carbon tetrachloride are common media; hydrochloric, sulfuric, and other acids have also been used; the reaction usually occurs at room temperature in a short time (Table II-60).

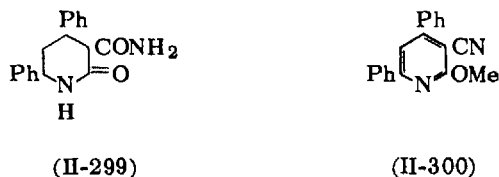
The cyano nitrogen acts as the nucleophile to close the ring (II-292). Water is eliminated in the next step and re-enters at the positive carbon of II-293 to form the dihydropyridinol. As an alternative mechanism, hydrolysis of the nitrile to an amide, which cyclizes, cannot be ruled out. This is true at least in concentrated sulfuric acid, where such hydrolysis is known to occur readily (330).

Anomalous reactions have been reported. The cyclization II-294 (333) no doubt proceeds with entrance of bromide instead of water at the positive carbon. Similarly, in II-295 (307), a 2-chloropyridine is reported; that it is an aromatic pyridine can be explained by a disproportionation of the initial dihydropyridine to give II-296 and higher hydrogenated products, of which II-297 was isolated.

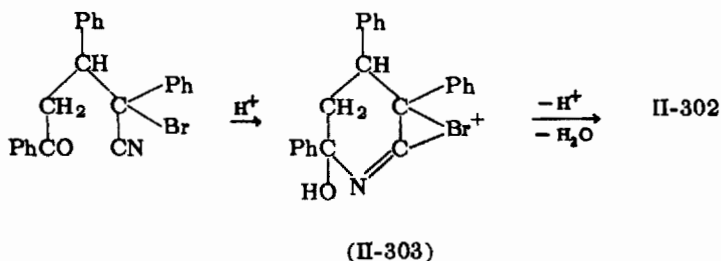
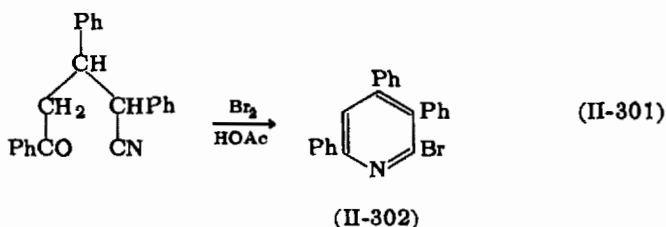


The reaction of II-298 with hydrogen bromide in chloroform was said to give the 2-bromopyridine and II-299 (307).

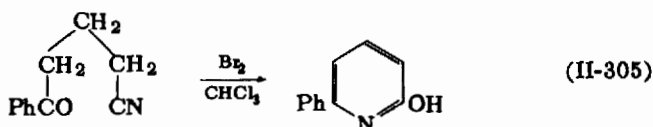
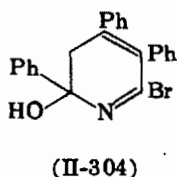
The cyclization of II-298 was also accomplished in basic medium, using potassium hydroxide in an alcohol. Entrance of alkoxide ion at the positive carbon, and disproportionation, then gave a 2-alkoxy-pyridine (II-300) (307).



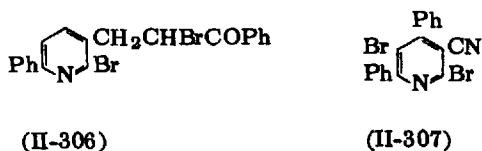
Bromine in acetic acid or chloroform cyclizes 5-ketonitriles to 2-bromopyridines as the typical products (II-301) (331). The reaction probably proceeds by bromination on the α -carbon, and through a cyclic bromonium intermediate (II-303). A minor



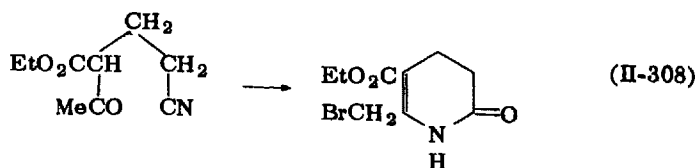
amount of a co-product, thought to be II-304, was obtained in chloroform; this could be dehydrated to II-302 with acid or basic agents (331,1250). In the absence of an α -substituent, which activates bromination, only the pyridinol was obtained, in low yield (II-305) (332), by an ordinary acid-catalyzed cyclization, and *subsequent* oxidation.



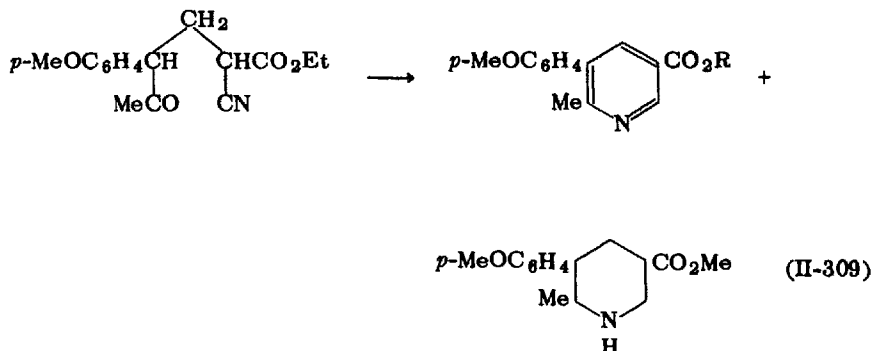
A second atom of bromine enters the molecule in some cases, though its position has not been well established. Thus, bis-(β -benzoyl-ethyl)acetonitrile gave only a dibromo product, perhaps II-306 (333), while II-307 was considered to be the product in an-



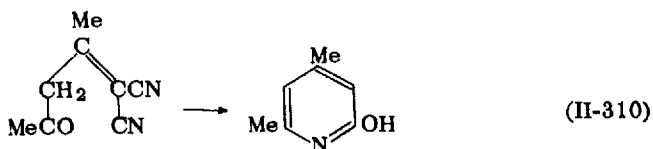
other instance (307). In II-308 the *first* bromine entered an unusual position, there being no activating group alpha to the cyano (1141).



The uncommon *reductive* cyclization of a β -ketonitrile has been effected, though in low yield, by using hydrogen and Raney nickel in methanol under pressure (II-309). It was thought that reduction of the nitrile to an aldimine occurred first; cyclization produced a dihydropyridine; and disproportionation of the latter accounted for both products (1540).



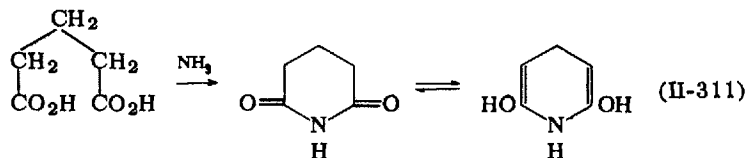
An example of an *unsaturated 5-ketonitrile*, cyclized to a pyridinol, has been reported (II-310) (1489). Since the medium was 50%



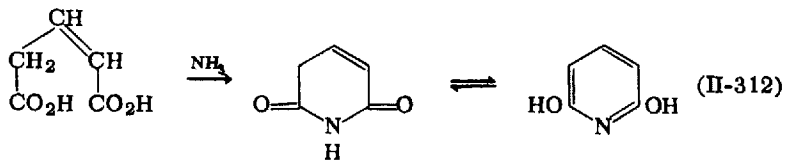
sulfuric acid at reflux, the second cyano group was lost through hydrolysis at the same time. It is not unlikely that under such vigorous conditions the first cyano group is converted to carbamoyl, which is the effective cyclizing agent.

c. 1,5-Dicarboxylic Acids and Derivatives

A 1,5-dicarboxylic acid, its anhydride, or its ester is cyclized with ammonia to its imide. Usually the 1,5-acid-amide, acid-nitrile, or dinitrile is cyclized by acid to the same imide which would be obtained from the free acid. Cyclization of glutaric acids or their derivatives produces dihydro-2,6-pyridinediols (glutarimides) (II-311), and of β -ketoglutaric acids produces the corresponding β -keto-



imides. Glutaconic acids, β -hydroxyglutaric acids, and derivatives of these two types give 2,6-pyridinediols (glutaconimides) (II-312).

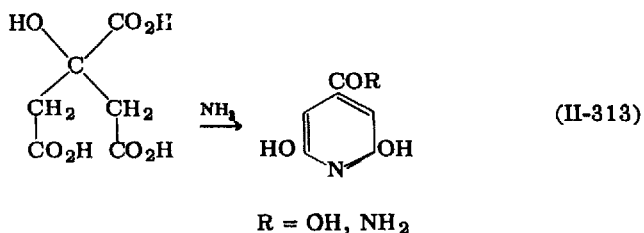


(a) 1,5-Diacids or Anhydrides. The heating of a glutaric acid with

ammonia or an amine produces a glutarimide. This simple reaction has been run in water, alcohol, or aromatic solvent, or without solvent; urea and formamide have also been used as sources of ammonia. Yields are usually good with ammonia or strongly basic and unhindered amines (Table II-61).

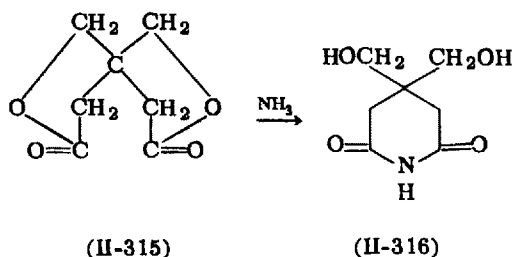
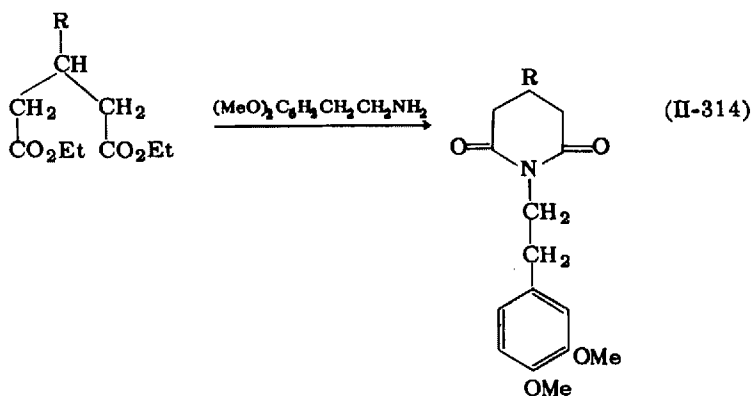
Glutaric anhydrides, often used in place of the free acids, form imides by heating with urea or fusion in a stream of ammonia or amine vapor (Table II-62). The yields are excellent, and, though a comparative study has not been made, appear higher than those from the corresponding free acids. The anhydride may be prepared simply by heating the acid in acetyl chloride or acetic anhydride, and used without purification (600,782,1220,1222,1223).

Certain other acids give fully aromatic 2,6-pyridinediols. Thus, the thermal cyclization of citric acid with ammonia is accompanied by the loss of three molecules of water to form citrazinic acid or under certain conditions citrazinamide (II-313) (Table II-63). The anhydride of citric acid has also been used (1577). Glutamic acid was converted to glutaconimide by the action of sulfuric acid, (1731), perhaps by deamination to glutaconic acid.

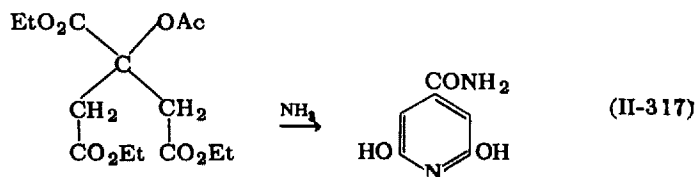


More commonly, a glutaconimide is prepared from an ammonia or amine salt of glutaconic acid by heating at 150–200° or by slow distillation. Reported yields are fair to good (Table II-64).

(b) **1,5-Diesters.** A few reactions involving esters of glutaric acids have been reported. Thus, the diethyl esters of β -ethyl- and β -propylglutaric acids have given the 3,4-dimethoxyphenethylimide (II-314) in poor yield along with the diamide (1570), and the bis-lactone II-315 was converted by alcoholic ammonia to the imide II-316 (652).

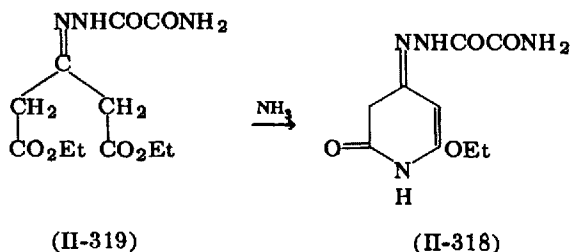


The di- or triester of citric acid when heated with ammonia has given a glutaconimide in fairly good yield (Table II-63). The 4-carboxy or carbethoxy group is sometimes converted to the carbamyl group. The acetate of the triester gave citrazinamide (2,6-dihydroxy-isonicotinamide) (II-317) upon standing with ammonia (263,767).



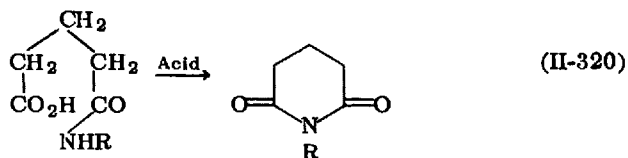
Diethyl β -ketoglutarate and aniline gave a product thought to be *N*-phenylketoglutarimide (1725). Similarly, the semicarbazone of the ester with ammonia gave the semicarbazone of the ketoimide (1238). However, II-318 was believed to be the product of the re-

action of the diester II-319 and ammonia (1237), which would be unusual.



Diesters of glutaric acids react with aqueous or alcoholic ammonia to give 2,6-pyridinediols, occasionally in good yield. The reaction is usually carried out at 100–50° for several hours or at room temperature for several days. Side chain esters are usually converted to amides (Table II-64).

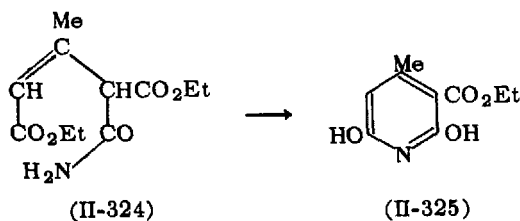
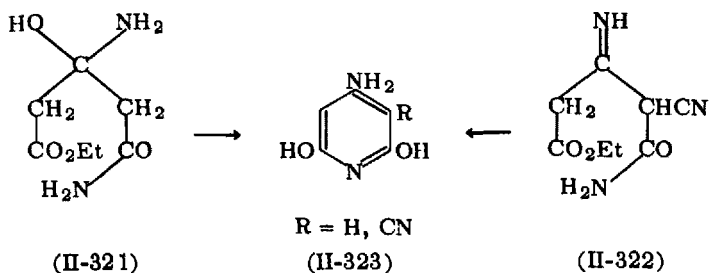
(c) **1,5-Amide-Acids and Amide-Esters.** The monoamide or anilide of a glutaric acid (II-320) may be cyclized to an imide by hot acidic



reagents such as acetyl chloride, acetic anhydride, or concentrated hydrochloric acid. Though the yields of this reaction are often good or excellent (Table II-61), the monoamides are usually prepared from the anhydrides, and this reaction is then in fact a two-step preparation from the anhydride or a three-step synthesis from the free acid.

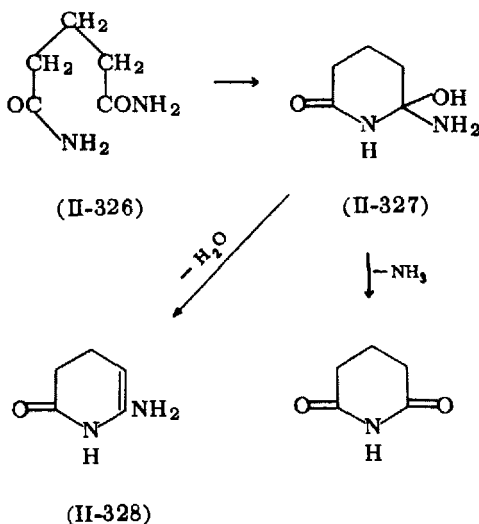
The monoamide of glutaric acid was converted to the imide by dilute sulfuric acid at 135°, and the monitoluidides were cyclized by heat (Table II-64).

The amide-ester of a β -ketoglutaric acid as the ammonia addition compound II-321 or the imine II-322 was changed by hot sodium carbonate to a 4-amino-2,6-pyridinediol II-323 (Table II-65). The amide-ester of a glutaric acid II-324 formed the imide II-325 at 190° (1611). The use of amide esters appears to have no advantages and is not common.



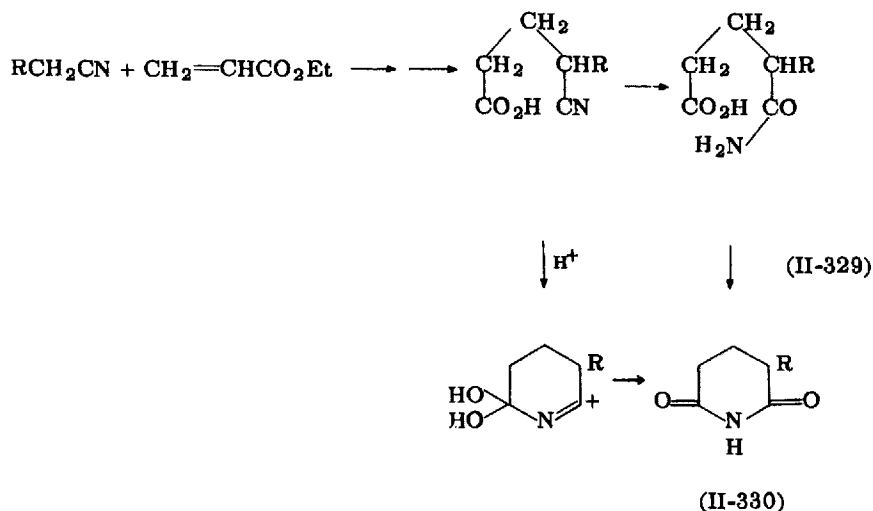
(d) **1,5-Diamides.** A few diamides of glutaric, β -hydroxyglutaric, and glutaconic acids have been changed to the imides by heat or acid (Tables II-61,63,64), but again, despite good yields, the method is seldom employed, since the diamides are rarely as easily available as the free acids which give the same results.

Although β -hydroxyglutaramide usually gives 2,6-pyridinediol, its reaction with phosphorus pentachloride produced 2-amino-3,4,5,6-



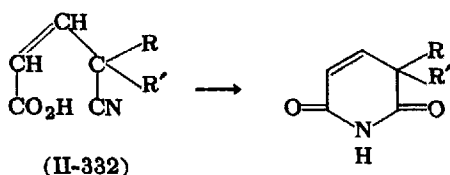
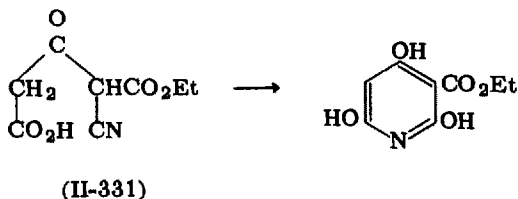
tetrachloropyridine (1040–1042). In the normal reaction, the nitrogen of one amide group attacks the carbonyl of the other (II-326). In the presence of phosphorus pentachloride, the intermediate II-327 may lose water rather than ammonia and thus give the amine. However, it is just as likely that one or both of the amide groups are first dehydrated to nitriles which then account for the amine II-328; cyclizations of nitriles to aminopyridines are known (p. 391). The chlorination is expected, since the action of phosphorus pentachloride on glutarimide produces polychloropyridines.

(e) **1,5-Nitrile-Acids.** Mononitriles of glutaric acid and its derivatives are good sources of glutarimides; unlike some dicarboxylic acid derivatives that are available mainly from the free acid, the acid-nitrile may be made by other methods typified by II-329 (522). The cyclization of these acid-nitriles is done in acidic medium such



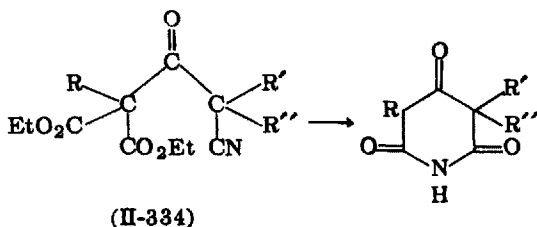
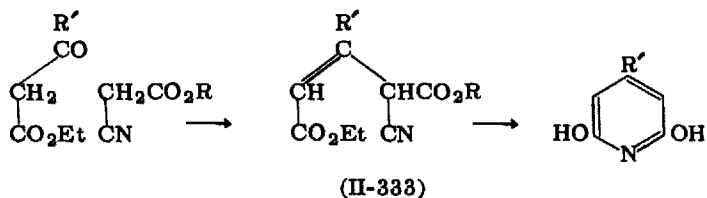
as hydrochloric acid, sulfuric acid, or mixtures of acetic acid and anhydride with sulfuric acid or stannic chloride (Table II-66). The mechanism of cyclization to II-330 appears to be straightforward.

The β -ketoacid II-331 was cyclized at 145–170° to the trihydroxynicotinic ester. The corresponding imine gave ethyl 4-amino-2,6-dihydroxynicotinate (1617). As expected, the γ -cyanocrotonic acids II-332 were cyclized by acid to glutaconimides (Table II-67).



(f) **1,5-Nitrile-Esters.** The ester-nitriles are converted to the imides in the same manner as the acid-nitriles. The γ -cyanobutyrate and their β -keto derivatives have been used infrequently (Tables II-66,68,69), the γ -cyanocrotonates more often (Table II-67).

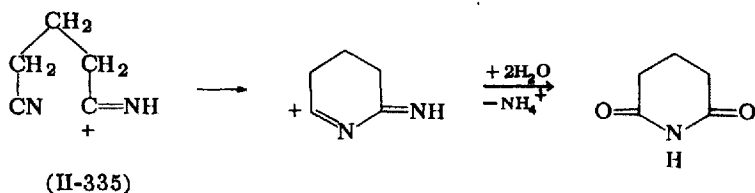
In some cases, the nitrile is hydrolyzed to an amide or carboxyl group as a side-reaction. The carbethoxy substituent of II-333 and



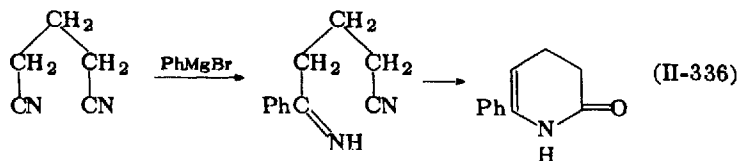
II-334 may be lost during cyclization. Compounds such as II-333 are accessible from cyanoacetic ester.

(g) **1,5-Dinitriles.** The dinitriles of glutaric acid are cyclized by mineral acids to the glutarimides (Table II-70). The reaction may

involve attack of the nitrile-nitrogen on the carbon of a protonated nitrile II-335. However, the reaction might also proceed by hydrolysis of one or both nitriles to amides.



Uniquely, the reaction of glutaronitrile with phenylmagnesium bromide (II-336) produced 6-phenyldihydro-2-pyridinol (332). The first step of the reaction would form a 1,5-iminonitrile. The next step resembles the cyclization of a 1,5-ketonitrile which, however, is usually acid catalyzed.

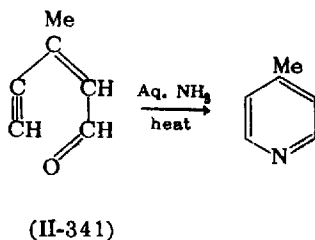
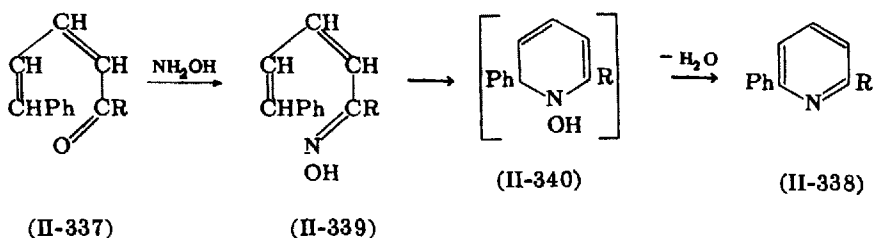


Glutacononitriles give glutaconimides, but only a few examples have been reported (Table II-71).

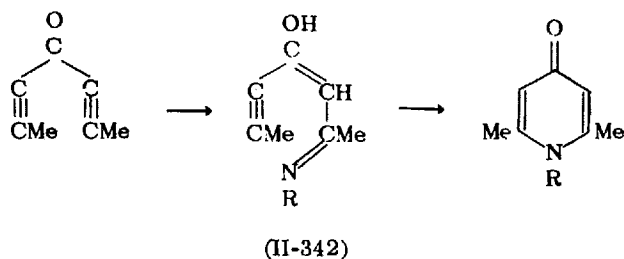
d. Compounds Having Terminal Unsaturation

This small group of reactions may be divided into two types. The first involves cyclization through one unsaturated group and a carbonyl group as found in 2,4-pentadienones. The second type utilizes the two triple bonds which occur in 1,4-pentadiyne-3-ones.

Cinnamaldehyde condenses with a methyl ketone such as acetone or acetophenone to give the dienone II-337. The oxime of the ketone is cyclized by heat or distillation to the pyridine II-338. The yields from II-339 were 25–30% (Table II-72). These cyclizations would be expected to proceed through a 1-hydroxy-dihydropyridine (II-340). Similarly, 3-methyl-2-pentene-4-ynal (II-341) was cyclized with hot, aqueous, alcoholic ammonia or ammonium carbonate to 4-picoline in 10–15% yield (1426).



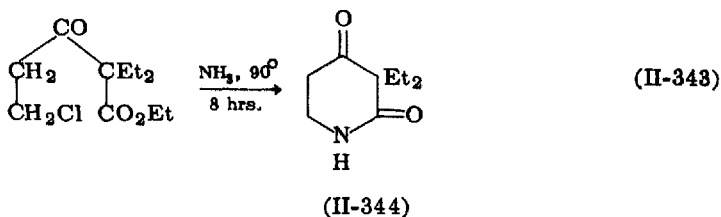
The cyclization of a 1,4-pentadiyne-3-one with ammonia or an amine gives 4-pyridones (Table II-73). This reaction may be carried out by simply heating the reactants at $150\text{--}200^\circ$ or by first warming the reactants to produce an intermediate II-342 or its tautomer and then heating the intermediate to the higher temperature. The diyne has nearly always been 2,5-heptadiyne-4-one or 1,5-diphenyl-1,4-pentadiyne-3-one. The reaction has been reported for a wide variety of aliphatic and aromatic amines.



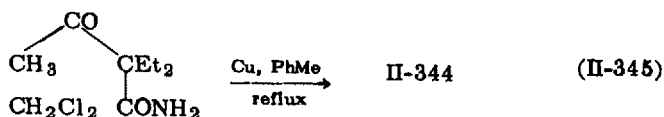
The passage of divinylacetylene and ammonia over a catalyst of lead and cadmium on alumina at $325\text{--}370^\circ$ produced 2-picoline and benzene (382).

e. Miscellaneous 1,5-Bifunctional Compounds

The cyclization of a 5-chloroester in aqueous alcoholic ammonia in 70% yield has been reported in a patent (II-343) (1541). The



starting material was prepared by chloromethylation of α, α -diethylacetoacetic ester; both steps could be effected simultaneously by a 4-1 condensation (p. 353) (II-345) (1542).



The *N*-acyl derivative of a 5-aminoketone (II-346) has been cyclized under reductive conditions. In an inert solvent (alcohol, Methyl Cellosolve, low pressure for twenty hours) hydrogenolysis of the carbobenzoxy group occurs as well as elimination of methanol, to give a dihydropyridine in 49% yield (II-347). When the reaction is carried out in acid medium, hydrogenolysis of both the carbobenzoxy and methoxy groups occurs, and a tetrahydropyridine is the product (1528).

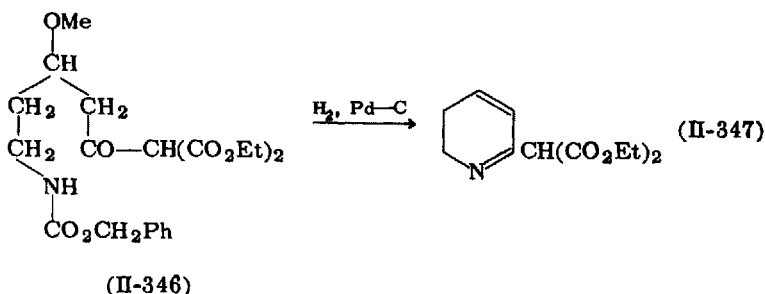
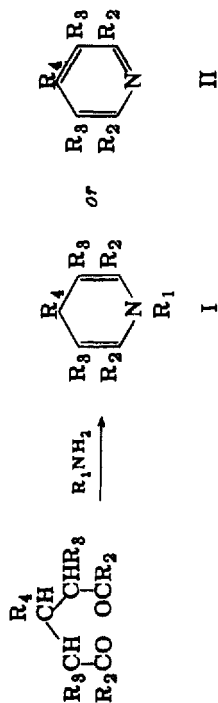


TABLE II-50. Reaction of Saturated 1,5-Dioxo Compounds with Ammonia, Primary Amines, or Hydrazine



R ₂	R ₃	R ₄	R ₁	Conditions	Product (Yield)	Ref.
H	H	H	H	(NH ₄) ₂ SO ₄ , aq. H ₂ SO ₄ , Fe ₂ (SO ₄) ₃ , reflux 2 hrs.	II (82%)	684
H	H	Me	H	(NH ₄) ₂ SO ₄ , aq. Fe ₂ (SO ₄) ₃ , reflux	II (91%)	684
				NH ₄ Cl, aq. HCl, FeCl ₃ , reflux 2-3 hrs.	II + Chloro + dichloropyridine	684
Me	H	Me	NH ₂	NH ₂ NH ₂ · H ₂ O, 4 hrs.	I	87
Ph	H	H	H	HCONH ₂ (as NH ₃ source)	II + 2,6-Diphenyl-piperidine + formyl deriv.	448
Ph	H	Ph	H	Anhyd. NH ₃ , abs. alc., ice bath 1 hr., RT overnight	II (85%) ^a	371
				NH ₃ , NH ₄ OAc, aq. 250°, pressure	II (42%)	1165
				NH ₄ OAc, HOAc, reflux	II + 2,4,6-Tri-phenylpiperidine · HCl	1149

				HCO ₂ NH ₄ , HCONH ₂ , 180-85°, 5 hrs.	II Picrate (31%) + 2,4,6-triphenyl-piperidine·HCl (47%)	1149
				HCONH ₂ (as NH ₃ source)	II + 2,4,6-Tri-phenylpiperidine	448
				Et Anhyd. amine, 130°, 20 hrs., sealed	II (68%) + Ethane	371
				CH ₃ CH ₂ NH ₂ Amine·H ₂ O, 140-150°, 10 hrs., sealed	I (90%)	371
				NH ₂ NH ₂ ·H ₂ O, 130°, 10 hrs., sealed	I (94%)	371
				NH ₃ , NH ₄ OAc, aq., 250°, pressure	II (18%)	1165
				NH ₃ , NH ₄ OAc, aq., 250°, pressure	II (51%)	1165
				Anhyd. NH ₃ , alc.-CHCl ₃ , RT 24 hrs.	I (58%) ^b	371
				Me Anhyd. amine, MeOH, RT	I (88%)	371
				Et Anhyd. amine, alc.-CHCl ₃ , RT 40 d.	I (65%)	371
				CH ₃ CH ₂ NH ₂ Amine·H ₂ O, 165-70°, 8 hrs., sealed	I (100%)	371
				H NH ₃ , NH ₄ OAc, aq., 250°, pressure	II (38%)	1165
				H HCO ₂ NH ₄ , HCONH ₂ , 180-85°, 5 hrs.	II (35%) + The pi-peridine·HCl (45%)	1149
				(MeO) ₃ C ₆ H ₃		
Me	COMe	H		Anhyd. NH ₃ , ether	I ^c	298
Ph	H	CO ₂ H		Anhyd. NH ₃ , alc., RT 1-2 d.	I ^d	198

(continued)

TABLE II-50 (Continued)
Reaction of Saturated 1,5-Dioxo Compounds with Ammonia, Primary Amines, or Hydrazine

R ₂	R ₃	R ₄	R ₁	Conditions	Product (Yield)	Ref.
Ph	H	CO ₂ H, CO ₂ H ^e	H	Anhyd. NH ₃ , alc., 120°, sealed	II + the piperidine II ^e	198 198
Me	CO ₂ Et	H	H	Anhyd. NH ₃ , alc., cold, 48 hrs. Anhyd. NH ₃ , alc., RT 2 d./ HCONH ₂ (as NH ₃ source)	I (100%) I ^f II	239 213 448
Me	CO ₂ Et	Me	H	Anhyd. NH ₃ , alc., cold, 48 hrs. Anhyd. NH ₃ , alc., RT, several da. NH ₄ OAc, 170°, 5 hrs.	I I (36%) I (63%) ^g	239 1521 1713
Ph	CO ₂ Et	H	H	HCONH ₂ (as NH ₃ source)	I	448
H ^b	H	OMe	H	NH ₄ OAc, 120°, then anhyd. NH ₃ , 145°	<i>h</i>	1818
H ⁱ	H	OEt	H	NH ₄ Cl, H ₂ SO ₄ , aq., reflux 1 hr., then NH ₃ gas 1 hr.	<i>i</i>	1832

^aBy-product, monoimine of the diketone.

^bProduct was converted to II by heating at 190°, or HOAc on water bath.

^cThe unpurified product oxidized to II with HNO₃ in alc.

^dAs the ammonium salt; heated at 270° it is converted to II (free acid).

^eStarting material is diphenacylmalonic acid; product is 2,6-diphenylisonicotinic acid with the corresponding piperidine as by-product.

^fStarting material used without purification; product oxidized to II with N₂O₃, alc., or dil. HNO₃.

^gProduct oxidized to II with CrO₃.

^hStarting material is the diacetal, (MeO)₂CHCH₂CH(OMe)CH₂CH(OMe); product is pyridine (91% yield).

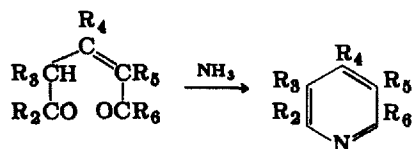
ⁱStarting material is the diacetal, (EtO)₂CHCH₂CH(OEt)CH₂CH(OEt); product is pyridine (54% yield).

TABLE II-51. Reaction of 1,3,5-Trioxo Compounds with Ammonia, Primary Amines, or Hydrazines

$ \begin{array}{c} \text{R}_3\text{CH} \\ \\ \text{CO} \\ \\ \text{R}_2\text{CO} \quad \text{O} \quad \text{CHR}_3 \\ \quad \\ \text{R}_2\text{CO} \quad \text{O} \quad \text{CHR}_3 \end{array} \xrightarrow{\text{R}_1\text{NH}_2} $			Conditions	Yield, (%)	Ref.
R ₂	R ₃	R ₁			
Me	H	H	NH ₃ , water bath	100	1073
Me	H	Me	Aq., evap. to dryness	80	355
Me	H	CH ₂ Ph	Aq., reflux 30 min.	75	355
Me	H	CH ₂ CH ₂ OH	Aq., evap. to dryness		355
Me	H	Ph	Benzene, reflux 2 hrs.	64	355
Me	H	2-Naphthyl	Xylene, reflux 25 hrs., separating aq.	50	355
Me	H	<i>p</i> -O ₂ NC ₆ H ₄ NH	1 Mole hydrazine, alc., 10 min.		764
			2 Moles hydrazine, HOAc, 10 min.	^a	764
Et	H	<i>p</i> -O ₂ NC ₆ H ₄ NH		^b	338
CO ₂ Et	H	PhNH	Alc., water bath 4 hrs.	^c	780,1328
CO ₂ Et	H	<i>p</i> -O ₂ NC ₆ H ₄ NH	1 Mole hydrazine, alc., reflux less than 1 hr.	^d	764
			1 Mole hydrazine, alc., reflux 1 hr.	^e	764
H/	CO ₂ Et	H	NH ₃ , alc.		259

^aThe *p*-nitrophenylhydrazine of the 4-pyridone is obtained.^bThe 4-pyridone and its *p*-nitrophenylhydrazine are variously reported as the products.^cThe phenylhydrazine of the 4-pyridone is obtained.^dThe 4-pyridone and a lesser amount of its *p*-nitrophenylhydrazine are obtained.^eThe *p*-nitrophenylhydrazine is the major product, with a lesser amount of the 4-pyridone./The dienol ether, EtOCH=C(CO₂Et)COC(CO₂Et)=CHOEt, used without purification.

TABLE II-52. Reaction of Unsaturated 1,5-Dioxo Compounds with Ammonia



R ₃	R ₅	R ₄	R ₂	R ₆	Conditions	Ref.
H	H	H	H	H	Na salt of dialdehyde, NH ₄ OAc, aq., steam distil	1
H	Cl	H	H	H	Na salt of dialdehyde, NH ₄ OAc, aq., steam distil	1012,1013
H	Br	H	H	H	Na salt of dialdehyde, NH ₄ OAc, aq., steam distil	1011
H	I	H	H	H	Na salt of dialdehyde, NH ₄ OAc, aq., steam distil	1011
Me	COMe	H	COMe	Me	NH ₃ , aq., RT 2-3 d.	216,217
Me	CO ₂ Et	H	CO ₂ Et	Me	NH ₄ OAc, HOAc, reflux	216,217

TABLE II-53. Reaction of Saturated 1,5-Dioxo Compounds with Hydroxylamine

$ \begin{array}{c} R_4 \\ \\ R_3CH-CH(R_5) \\ \quad \\ R_2CO \quad OCR_6 \end{array} \xrightarrow{NH_2OH \cdot HCl} \begin{array}{c} R_4 \\ \\ R_3-CH=CH-R_5 \\ \quad \\ R_2 \quad R_6 \end{array} $					
R ₂	R ₃	R ₄	R ₅	R ₆	Ref.
H	H	Me	H	H	1745
Et	H	H	H	Et	328
-(CH ₂) ₄ -		H	-(CH ₂) ₃ -	Alc., heat	74
-(CH ₂) ₄ -		H	-(CH ₂) ₄ -	Alc., heat	95
Ph	H	H	-(CH ₂) ₃ -	Alc., heat	80
Ph	H	H	-(CH ₂) ₄ -	Alc., heat	94
Ph	H	Ph	-(CH ₂) ₃ -	Alc., 120-30°, 4 hrs.	1699
Ph	H	Ph	-(CH ₂) ₃ -	Alc., reflux 10 min.	1700
Ph	H	Ph	-(CH ₂) ₂ CHMeCH ₂ - Ph	Alc., reflux 6 hrs.	1019, 1020
Ph	Ph	Ph	H	Alc., 150°, sealed	1019
Ph	Ph	Ph	H	Aq. alc., 140-50°, 4 hrs., sealed	239
Ph	Ph	H	Ph	Alc., 170°, 6 hrs., sealed	1021
Ph	Ph	Ph	Ph	Aq. alc., 150°	284
Ph	H	<i>p</i> -ClC ₆ H ₄	H	Alc., 160°, 6 hrs., sealed	1165
Ph	H	<i>p</i> -MeOC ₆ H ₄	-(CH ₂) ₃ -	Alc. ^a	1701

(continued)

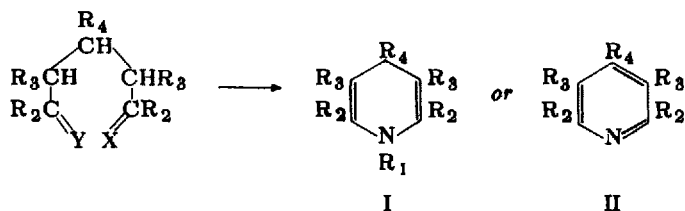
TABLE II-53 (Continued)
Reaction of Saturated 1,5-Dioxo Compounds with Hydroxylamine

R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Yield, %	Ref.
Ph	H	<i>p</i> -MeOC ₆ H ₄	-(CH ₂) ₂ CHMeCH ₂ -	Ph	Alc., reflux 3 hrs.		1704
Ph	H	<i>p</i> -MeOC ₆ H ₄	H	Ph	Alc., 160°, 6 hrs., sealed	62	1165
Ph	H	3,4-CH ₂ O ₂ -	-(CH ₂) ₃ -		Alc., warm	80	1701
Ph	H	C ₆ H ₅ 3,4-CH ₂ O ₂ -	-(CH ₂) ₂ CHMeCH ₂ -		Alc., water bath, 0.5 hr.		1703
2-Py	H	Ph	H	2-Py	Alc., 160°, 5 hrs., sealed	8	1153
Ph	CO ₂ Et	Ph	CO ₂ Et	Ph	Aq. alc., 120-30°, 4 hrs., sealed ^b		239
					Aq. alc., 120-30°, 6 hrs., sealed	46	524

^aThe reaction also succeeds with hydroxylamine base in alc.

^bHydroxylamine base specified, probably in error in view of context.

TABLE II-54. Cyclization of Imines of Saturated 1,5-Dioxo Compounds.

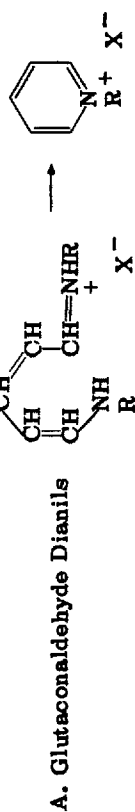


X	Y	R ₂	R ₃	R ₄	R ₁	Conditions	Product (Yield)	Ref.
NH	O	Ph	H	Ph	H	HOAc, water bath, 15 min.	II (48%) ^a	371
						Heat above 120°	II (64%)	371
						Aq. NaOH, 100°, 2 hrs.	II	371
						Picric acid, alc., water bath, 15 min.	I Picrate	371
NH	NH	Me	CN	Ph	H	Conc. HCl, H ₂ SO ₄ , or Ac ₂ O	I	1613
NH	NH	Me	CN	<i>p</i> -MeOC ₆ H ₄	H	Ac ₂ O	I	1613
NPh	NPh	H	H	O ^b	Ph	Dil. HCl, long boil	^b	1056
						NaOEt, heat	^b	1056
						Distill <i>in vacuo</i>	^b	1056

^aBy-product, 2,4,6-triphenyl-tetrahydropyridine.

^bThe dianil of a trioxo compound was used, *i. e.*, PhN=CHCH₂COCH₂-CH=NPh; product was 1-phenyl-4(1H)pyridone.

TABLE II-55. Cyclization of Imines of Unsaturated 1,5-Dioxo Compounds



R	X ⁻	Conditions	Yield	Ref.
Ph	Cl ⁻	Conc. HCl, alc., heat 100°, long time	70	2
		Br ₂ , MeOH, ice bath	<i>a</i>	2
		100°, long time		2
		150°		2
<i>p</i> -MeC ₆ H ₄	Cl ⁻	Heat to 135°	<i>b</i>	621
<i>p</i> -PhC ₆ H ₄	Cl ⁻	HCl, alc., heat 8 hrs.	<i>b</i>	621
4'-Nitrobiphenyl	Cl ⁻	160-80°	<i>b</i>	621,874
4'-Aminobiphenyl	Cl ⁻	PhNO ₂ , heat	90	621,874
<i>m</i> -ClC ₆ H ₄	Br ⁻	Br ₂ , HOAc or MeOH	<i>c</i>	4
	Br ⁻	Conc. HCl, alc., heat	70	4
<i>p</i> -ClC ₆ H ₄	Cl ⁻	Br ₂ , MeOH, ice bath	<i>d</i>	2
		Conc. HCl, MeOH, heat 0.5 hr.	<i>e</i>	2
<i>m</i> -O ₂ NC ₆ H ₄	Cl ⁻	Dil. HCl, heat		606
2,4-(NO ₂) ₂ C ₆ H ₃ ; Me ^e	Cl ⁻	Conc. HCl, reflux; then aq. FeCl ₃ , 182°	90 ^f	7
<i>p</i> -MeOC ₆ H ₄	Cl ⁻	128-33°	60	760
<i>m</i> -H ₂ NC ₆ H ₄	Cl ⁻	Aq., heat	53	874
<i>p</i> -H ₂ NC ₆ H ₄	Cl ⁻	PyH, reflux 1 hr.	<i>g</i>	874
<i>p</i> -Me ₂ NC ₆ H ₄	Cl ⁻	220°	<i>g</i>	874
Bis-dianils ^g	Cl ⁻			874

<i>p</i> -AcNHC ₆ H ₄	Cl ⁻	Heat above m.p.			874
<i>p</i> -PhN=NC ₆ H ₄	Cl ⁻	PyH, heat			862
		Aq., reflux			862
		125-28°, 15-20 min.			862

B. Dianils of Substituted Glutaconaldehydes

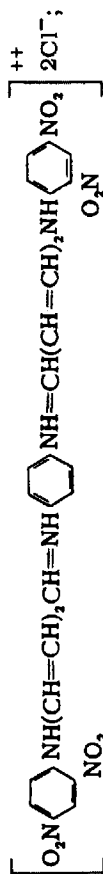
$$\begin{array}{c}
 \text{CHO} \\
 | \\
 \text{CH} \\
 | \\
 \text{CH}(\text{R}_1) - \text{CH}(\text{R}_3) - \text{CH} = \text{CH} - \text{CHO} \\
 \text{HN} \quad \text{NHR}_1 \\
 \text{R}_1
 \end{array}
 \longrightarrow
 \begin{array}{c}
 \text{Pyridine ring} \\
 \text{with } \text{R}_3 \text{ at position 3 and } \text{R}_1^+ \text{X}^- \text{ at position 1}
 \end{array}$$

R ₃	R ₁	X ⁻	Conditions	Ref.
Cl	Ph	Cl ⁻	Conc. HCl, alc., reflux HCl, MeOH	1015, 1011 6
Br	Ph	Br ⁻	HBr, alc.; product isolated as iodide	1011
I	Ph	I ^{-b}	Aq. alc., heat	1011
OH	Ph	Cl ⁻	Alc. or aq. HOAc, heat long	35
OH	Ph	Br ⁻	Alc. or aq. HOAc, heat long	35
OH	<i>p</i> -MeC ₆ H ₄	Cl ⁻	HCl, alc.; product obtained as chloride	36
OH	<i>p</i> -ClC ₆ H ₄	Cl ⁻	Alc. or aq. HOAc, heat long	35
			HCl, alc.	36

(continued)

TABLE II-55 (Continued)

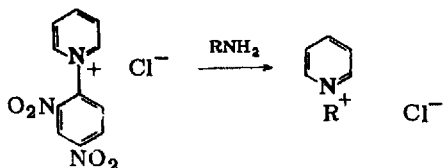
C. Monoimines							Ref.
R ₃	R ₄	R ₅	R ₆	R ₁	Conditions		
H	H		H	2,4-(NO ₂) ₂ C ₆ H ₃	HCl, HOAc	2	
Me				H	Conc. HOAc, reflux; product is free pyridine base	1714	

^aProduct is a (tribromophenyl)pyridinium perbromide.^bSee text.^cProduct is 2,4,6-tribromo-3-chlorophenylpyridinium perbromide.^dProduct is a dibromo-4-chlorophenylpyridinium perbromide.^eA mixed diimine salt used, *i.e.*, 2,4-(NO₂)₂C₆H₃NH(CH=CH)₂CH=NHMe + Cl⁻; product is 1-methylpyridinium chloride.^fAs the tetrachloroferrate, converted to the chloride by aq. Na₂CO₃.^gStarting material is the bis-glutaconic dianil salt, *i.e.*,

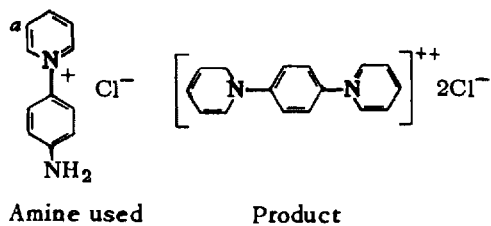
product is 4-aminophenylpyridinium chloride.

^bThe dianil dihydroiodide was used.

TABLE II-56. Conversion of 2,4-Dinitrophenylpyridinium Chloride to Other Pyridinium Compounds



R	Conditions	Yield	Ref.
Me	Aq., RT 24 hrs.		7
Ph	Alc., water bath, long time	60	2
<i>o</i> -ClC ₆ H ₄	Heat on water bath	60	2
<i>p</i> -ClC ₆ H ₄	Alc., water bath, long time	60	2
<i>p</i> -O ₂ NC ₆ H ₄	Alc., heat		606
<i>p</i> -(1-Py)C ₆ H ₄ ⁺ Cl ⁻ ^a	Alc., water bath 5 min.	60 ^a	874



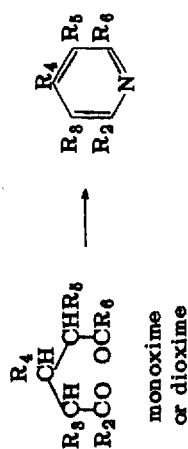


TABLE II-57. Cyclization of Oximes of Saturated 1,5-Dioxo Compounds

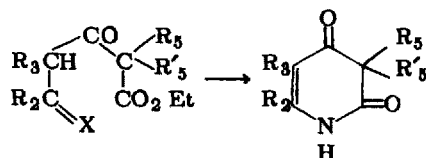
Oxime	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Yield	Ref.
Di	H	H	H	H	H	H	Oxime to aq. HCl at boil over 2 hrs.	56	794,1745
Di	Me	H	H	H	H	H	Aq. HCl, reflux 2 hrs.	21	794,1745
Mono	H	Me	H	H	H	H	18% aq. HCl, warm	20	1240
Mono	H	H	Me	H	H	H	30% aq. H ₃ PO ₄ , reflux		794
Di	Et	H	H	H	H	H	Aq. acid, 120°, 2 hrs.		794
Mono	Ph	H	Ph	H	Et	Et	Aq. acid, 120°, 2 hrs.	62	794,1745
Mono	Ph	H	Ph	H	-(CH ₂) ₃ -	-(CH ₂) ₂ CHMeCH ₂ -	HCl, alc., reflux	60	328
Mono	Ph	H	Ph	H	-(CH ₂) ₂ CHMeCH ₂ -	Ph	HCl, benzene, RT		1699
Mono	Ph	H	Ph	H	-(CH ₂) ₃ -	Ph	HCl, benzene		1700
Mono	Ph	H	Ph	H	-(CH ₂) ₃ -	Ph	HCl, alc., RT		239
Di	Ph	H	Ph	H	-(CH ₂) ₃ -	Ph	HCl, benzene		1701
Mono	Ph	H	Ph	H	-(CH ₂) ₃ -	Ph	HCl, benzene		1701
Mono	Ph	H	Ph	H	-(CH ₂) ₃ -	Ph	HCl, benzene		1703

TABLE II-58. Cyclization of 5-Oxoacids, 5-Oxoesters, and Their Oxo Derivatives



R ₂	R ₃	X	R ₁	Conditions	Yield, %	Ref.
Ph	H	H	H	NH ₃ , gas, 160–70°, 9 hrs.		332
Me	CO ₂ Et	Et	H	NH ₃ , alc., cold, 24 hrs.		1726
				NH ₄ OAc, HOAc, benzene, reflux 4 hrs.	76	629
Me	CO ₂ Et	Et	Ph	PhNH ₂		1726

B. 3,5-Dioxoesters and Imine Derivatives



R ₂	R ₃	R ₅	R' ₅	X	Conditions	Ref.
H	H	Me	Me	NH	NaOMe, MeOH, Me ₂ SO ₄ ^a	1442
H	H	Et	Et	NH	NaOMe, MeOH, heat ^b	1124
					NaOEt, alc., reflux 0.5 hr.	367–369, 1810
					NaOEt, alc., 80°, 0.5 hr. (87% yield)	1432
					KOH, aq. alc., 50°, 15 min.	367–369, 1810
					BF ₃ , conc. HCl, 180°	1449
					BF ₃ , oleum, 80°	1449
H	H	Pr	Pr	O	NH ₃ , alc., warm; add NaOEt, reflux 0.5 hr.	367–369

(continued)

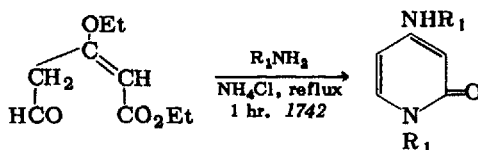
TABLE II-58 (Continued)

Cyclization of 5-Oxoacids, 5-Oxoesters, and Their Oxo Derivatives

B. 3,5-Dioxoesters and Imine Derivatives

R ₂	R ₃	R ₃	R' ₃	X	Conditions	Ref.
H	H	<i>i</i> -Pr	Pr	O	NH ₃ , MeOH, boil; add KOH, reflux, 0.5 hr.	367-369
H	H	C ₃ H ₅	C ₃ H ₅	O	NH ₃ , MeOH, 150°, 6 hrs. sealed	367-369
H	H	Bu	Et	O	NH ₃ , alc., 50-60°, 0.5 hr.; add NaOEt	367-369
H	H	Bu	Pr	O	NH ₃ , alc., boil; add NaOEt, distil	367-369
H	H	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	O	NH ₃ , alc., 50-60°, 0.5 hr.; add NaOEt	367-369
H ^c	CO ₂ Et ^c H	H	H	O	NH ₃ , aq., exotherm, 1 hr.	259,820
CO ₂ Et	H	Et	Et	NH	NaOMe, MeOH, reflux 0.5 hr.	339,1811
CO ₂ Et	H	Pr	Me	NH	NaOEt, alc., reflux 0.5 hr.	339
CO ₂ Et	H	Pr	Pr	NH	NaOEt, alc., reflux 0.5 hr.	339,340
CO ₂ Et	H	C ₃ H ₅	C ₃ H ₅	NH	NaOEt, alc., reflux 0.5 hr.	339

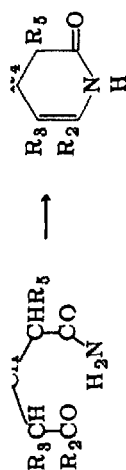
C. Derivatives of Unsaturated 5-Oxoesters



Aldehyde Derivative	R ₁	Yield, %
Ethyl acetal	Cyclohexyl	
Enol methyl ether	CH ₂ Ph	66

^aProduct is the *N*-methyl derivative.^bStarting material is labelled at the δ -carbon with C¹⁴; used without purification.^cStarting material is the enol ether, EtOCH=C(CO₂Et)COCH₂CO₂Et.

TABLE II-59. Cyclization of 5-Oxoamides



R ₂	R ₃	R ₄	R ₅	Conditions	Yield, %	Ref.
Ph	H	H	H	Heat		332
Ph	H	H	1-C ₂ H ₅ N ⁺ Cl ^{-a}	AcCl, reflux 0.5 hr.		332
Ph	H	Ph	⁺ NC ₃ H ₃ ^b	Heat above m.p.	43 ^a	906
				Heat	42-46 ^b	906
				HOAc, MeOH	85 ^b	906
Me ^c	CO ₂ Et ^c	H ^c	CO ₂ Et ^c	KOH, alc., boil short time		1607
Ph	H	Ph	CN	AcCl, RT		330
				AcCl, PhNMe ₃ , RT 5 da.		330
				HCl or H ₃ Br, CHCl ₃	100 ^d	307
				3I ₂ , KOAc, CHCl ₃	^e	307
				Br ₂ , HOAc	^e	307
Me	CO ₂ Et	CH ₂ OPh	CN	MeSO ₃ H, HOAc, RT 0.5 hr.		1118, 341, 342, 343
Me	CO ₂ Et	Ph	CN	Conc. H ₂ SO ₄ , HOAc, RT 10 min.	100	1118, 341, 342, 343, 1406
Me	CO ₂ Et	<i>p</i> -O ₂ NC ₆ H ₄	CN	Conc. H ₂ SO ₄ , HOAc, RT 10 min.	100	1118, 341, 342, 343
H ^f	H ^f	O ^f	Et ₃ Et ^f	BF ₃ , P ₂ O ₅ (or ZnCl ₂ or AlCl ₃), heat		1449

^aStarting material is PhCOCH₂CH₂CH(CONH₂)—NC₃H₃⁺Cl⁻; products are 6-phenyl-2-pyridinol and pyridinium chloride.

^bStarting material is the betaine, PhCOCH₂CHPhC⁻—⁺NC₃H₃; products are 4,6-diphenyl-2-pyridinol and pyridine.

^cStarting material is the unsaturated 5-ketoanilide, MeCOCH(CO₂Et)CH=C(CO₂Et)CONHPh; product is 6-methyl-1-phenyl-2-oxo-1,2-dihydropyridine-3,5-dicarboxylic acid.

^dProduct with nitrous acid gives the pyridinol (50% yield).

^eProduct contains an atom of bromine (see text); further treatment with KOAc in alc., or NaOMe, or by heating, gives 4,6-diphenyl-2-pyridinol.

^fStarting material is HOCH=CHCOCHEt₂CONH₂; product is the corresponding 2,4-dione.

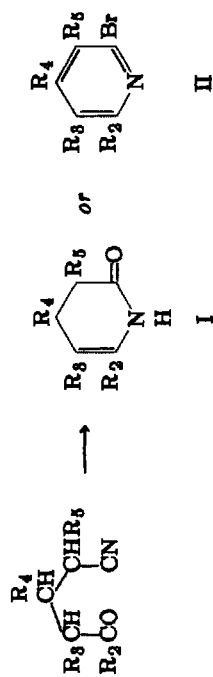


TABLE II-60. Cyclization of 5-Ketonitriles

R_2	R_3	R_4	R_5	Conditions	Product (Yield, %)	Ref.
Me	H	H	H	$HCl, CHCl_3, 1.5 \text{ hr.}$	I	1141
Ph	H	H	H	$Br_2, CHCl_3$	6-phenyl-2-pyridinol (low)	332
Ph	H	H	CH_3CH_2COPh	Conc. H_2SO_4 , RT	I (70)	333
				$Br_2, HOAc$	a	333
Ph	H	Ph	Ph	$HBr, HOAc$, RT 2 da.	I (90) ^b	331
				$Br_2, HOAc$, heat	II (89)	331
				$Br_2, CHCl_3$	II ^c	331
Ph	H	Ph	$p-O_2NC_6H_4$	$HBr, HOAc$	I (92) ^b	330
				$Br_2, HOAc$	II	330
$p-MeOC_6H_4$	H	Ph	Ph	$HBr, HOAc$, RT 4 da.	I (91) ^b	1250
				$Br_2, CHCl_3$	II (80) ^d	1250
Ph	H	Ph	CO_2Me	HBr, CCl_4 , few min.	I (95) ^b	1359
				$Br_2, HOAc$, heat	II	1359
$p-ClC_6H_4$	H	Ph	CO_2Me	$HBr, CHCl_3$	I (90) ^b	1359
				$Br_2, HOAc$, heat	II	1359
Ph	H	H	CO_2Me , CH_3CH_2COPh ^e	$HBr, HOAc$, 4 hrs.	e	333

Me	CO ₂ Et	H	H	Conc. HCl, 0-5°, 20 min.	I (86)	I (86)	1141
				90% H ₂ SO ₄	I (84)	I (84)	1141
				HCl, CHCl ₃ , 1 hr.	I (74)	I (74)	1141
				Br ₂		<i>f</i>	1141
Me	<i>p</i> -MeOC ₆ H ₄	H	CO ₂ Et	H ₂ , Raney Ni, MeOH, 115°, 100 atm., 20 hrs.		<i>g</i>	1540
Me ^b	H ^b	Me ^b	CN ^b	50% H ₂ SO ₄ , reflux 6 hrs.		<i>b</i>	1489
Me	CO ₂ Et	<i>i</i> -Pr	CN	Fuming aq. HBr, alc., 50-60°	I		1118, 341, 342, 343
				HCl, alc., 30°	I		1396
Me	CO ₂ Et	CH ₂ OPh	CN	20 min.	I		1118, 341, 342, 343, 1407
				5% alc. HCl, 60°	I		1397
				10 min.	I		
				MeSO ₃ H, HOAc,	I		
Me	CO ₂ Et	Ph	CN	0.5 hr.	I (100)		1118, 341, 342, 343, 1396
				HCl, alc., 20-30°	I (100)		
				20 min.		<i>i</i>	307
Ph	H	Ph	CN	HCl, CHCl ₃			
				HBr, CHCl ₃	II (30)		307
					+ 2-oxo-4,6-diphenyl-nipecotinamide (25)		

(continued)

TABLE II-60 (Continued)
Cyclization of 5-Ketonitriles

R ₃	R ₂	R ₁	Conditions	Product (% Yield)	Ref.
			Br ₂ , KOAc	2,5-dibromo-4,6-diphenylnicotinonitrile	307
			KOH, MeOH aq., RT 24 hrs.	2-methoxy-4,6-diphenylnicotinonitrile	307
			KOH, alc.	2-ethoxy-4,6-diphenylnicotinonitrile	307

^aProduct assumed to be 6-phenyl-2-bromo-3-(β -benzoyl- β -bromoethyl)pyridine.

^bProduct converted to the pyridinol.

^cCo-product is 2,4,5-triphenyl-6-bromo-2-hydroxy-2,3-dihydropyridine in lesser yield.

^dCo-product is 2-*p*-anisyl-4,5-diphenyl-6-bromo-2-hydroxy-2,3-dihydropyridine in 10% yield.

^eStarting material is di-substituted on the α -carbon; product is methyl 6-phenyl-2-bromo-3- β -benzoylethyl-3,4-dihydropyridine.

^fProduct assumed to be 6-bromomethyl-5-carbethoxy-3,4-dihydro-2-pyridinol (48% yield); also, I is converted to this compound on treatment with Br₂, CHCl₃.

^gProducts are 6-methyl-5-*p*-anisylnicotinic acid (12% yield after saponification of the crude ester), and methyl 6-methyl-5-*p*-anisylnicotinate (25% yield).

^hThe unsaturated 5-ketonitrile, MeCOCH₂CMe=C(CN)₂, was used; product was 4,6-dimethyl-2-pyridinol.

ⁱProducts are 2-chloro-4,6-diphenylnicotinonitrile (30% yield) and 2-oxo-4,6-diphenylnicotinonitrile (15% yield).

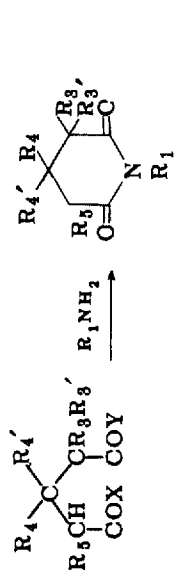


TABLE II-61. Preparation of Glutarimides from Glutaric Acids

X	Y	R ₃	R ₃ '	R ₄	R ₄ '	R ₅	R ₁	Conditions	Yield	Ref.
OH	OH	H	H	H	H	H	H	Aq. NH ₃ , heat		501
								NH ₃ salt, 180-280°	84%	711,1169
								Formamide, 160-170°		466
								4 hrs.		
								SO ₂ (NH ₂) ₂ , pyridine, steam bath, 3 hrs.	75%	465
OH	OH	H	H	H	H	H	Me	MeNH ₂ salt, distil		642 1321
								MeNH ₂ salt, distil	86.5%	715

(continued)

TABLE II-61 (Continued)
Preparation of Glutarimides from Glutaric Acids

X	Y	R ₃	R ₃ '	R ₄	R ₄ '	R ₅	R ₁	Conditions	Yield	Ref.
OH	OH	H	H	H	H	H	<i>i</i> -Pr	<i>i</i> -PrNH ₂ , 260°, 10 hrs. sealed tube; or 175°, 5 hrs.	20-26%	1497
OH	OH	H	H	H	H	H	Bu	BuNH ₂ , 175°, 5 hrs.	25%	1497
OH	OH	H	H	H	H	H	<i>o</i> -MeC ₆ H ₄	<i>o</i> -Toluidine, boiling xylene, 6 hrs.	11%	1497
OH	OH	H	H	H	H	H	<i>p</i> -MeC ₆ H ₄	<i>p</i> -Toluidine, 290°, 10 hrs.	6%	1497
OH	OH	H	H	H	H	H	2-Py	2-Aminopyri- dine, boil- ing xylene, 6 hrs.		1497
OH	OH	H	H	H	H	H	(See amine in condi- tions)	10b-(3-Amino- propyl)-1,2, 3-10b-tetra- hydrofluo- ranthene, 245°		1517

OH	OH	Me	H	H	H	Et	H	Urea, 160° Aq. NH ₃ , 220°, 4 hrs.	65% Crude 69%	576 616
OH	OH	H	H	Me	Et	H	H			
OH	OH	H	H	Me	Et	H	Me	Aq. MeNH ₂ NH ₃ , heat to 220°	58% 93%	589 1219
OH	OH	H	H	Cyclopentyl	H	H	H			
OH	OH	(CH ₂) ₄ - CO ₂ H	H	H	H	H	Me	Aq. MeNH ₂ , 25° sev. da., then 210°, 6 hrs.	(Side chain carboxyl converted to amide)	674
OH	OH	H	H	CH ₃ CO ₂ H	CH ₃ CO ₂ H	H	H	NH ₃ salt, 210°	59% (A 4,4- spiro product) 76% ^c	1728 633
OH	OH	^c	H	H	H	^c	H	NH ₃ salt, 300°		
OH	OH	Ph	Ph	H	H	H	H	Current of NH ₃ , 190°		1720
OH	OH	NH ₃	H	H	H	H	H	Conc. H ₂ SO ₄ (Gluracon- imide)		1731
OEt	OEt	H	H	Et	H	H	R ^b	3,4-dimeth- oxyphen- ethylamine, 210°, 3½ hrs.	Poor (also bis-amide)	1570

(continued)

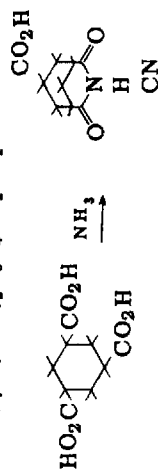
TABLE II-61 (Continued)
Preparation of Glutarimides from Glutaric Acids

X	Y	R ₃	R ₃ '	R ₄	R ₄ '	R ₅	R ₁	Conditions	Yield	Ref.
OEt	OEt	H	H	Pr	H	H	R ^b	3,4-dimethoxyphenethylamine, 210°, 3½ hrs.	Poor (also bis-amide)	1570
OH	NH ₂	H	H	H	H	H	H	215°, 3 hrs.	84%	501
OH	NHR ^a	Me	Me	H	H	H	R ^a	NaOAc, Ac ₂ O, reflux 6 hrs.	55% ^a	1565
OH	NHR ^b	H	H	Pr	H	H	R ^b	Ac ₂ O, water bath, ½ hr.	16%	1570
OH	NHR ^b	H	H	CH ₂ CONHR ^b	H	H	R ^b	Ac ₂ O, pyridine, heat, 1 hr.	75%	560
OH	NH ₂	Ph	Me	H	H	H	H	200°, 42 hrs.		534
OH	NHPh	Ph	Me	H	H	H	Ph	Conc. HCl, heat briefly		538
OH	NH ₂	Ph	Et	H	H	H	H	AcCl, heat, 45 min.	80%	538
OH	NHPh	Ph	Et	H	H	H	Ph	HOAc, H ₂ SO ₄ , heat, short time		610
OH	NHPh	Ph	Et	H	H	H	Ph	AcCl, heat, 45 min.	80%	682
OH	NHPh	Ph	Et	H	H	H	Ph			538

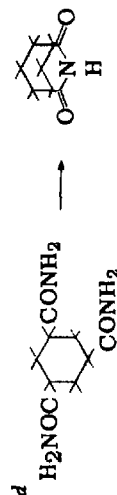
OH	NH ₂	Ph	Pr	H	H	H	Conc. HCl, heat briefly	538
OH	NHPh	Ph	Pr	H	H	Ph	AcCl, heat, 45 min.	538
OH	NHPh	Ph	CH ₂ Ph	H	H	Ph	AcCl, heat, 45 min.	538
OH	NHPh	Ph	Ph	H	H	Ph	AcCl	537
OH	NH ₂	CO ₂ H	H	-(CH ₂) ₃ -	CO ₂ H	H	Heat	1599 (Loss of CO ₂) ^e
OH	^e	Ph	Ph	H	H	H	HOAc, H ₂ SO ₄ , 70°	645
NH ₂	NH ₂	cyclo- pentyl	H	H	H	H	Distill	1223
NHPh	NHPh	H	H	CH ₂ CONHPh	CH ₂ CO NHPh	Ph	310°	1728 72% (A 4,4- spiro product) 78% ^d
NH ₂	NH ₂	^d	H	H	H	^d	285°, 6 hrs.	663

^aR represents the bis-amide from dianthranisylene, product is also a bis-amide.

^bR is 3,4-(MeO)₂C₆H₄CH₂CH₂



^eA thioamide which gives a thioimide.



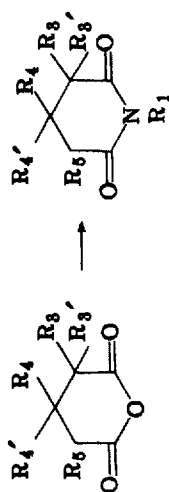
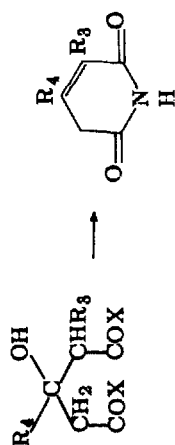


TABLE II-62. Preparation of Glutarimides from Glutaric Anhydrides

R ₃	R ₃ '	R ₄	R ₄ '	R ₅	R ₅ '	R ₆	R ₆ '	Conditions	Yield, %	Ref.
Me	H	H	H	H	H	H	H	NH ₃ , 120° ½ hr., then 200°	82	1220
Me	Me	H	H	H	H	H	H	NH ₃ , stream, 180–200°	80	600,782
Me	H	H	H	Me	H	H	H	NH ₃ , 120° ½ hr., then 200°	34	1220
								NH ₃ , stream, 180°	87	600
H	H	Me	Me	H	H	H	H	NH ₃ , stream, 180–200°	77	600,811
								Urea, 200°	78	810
H	H	Me	Me	Me	H	Me	Me	MeNH ₂ passed into melt, 200°, 1 hr.	83	811
H	H	Me	Me	Me	H	Et	Et	EtNH ₂ passed into melt, 200°, 1 hr.	73	811
H	H	Me	Me	Me	H	Bu	Bu	BuNH ₂ passed into melt, 200°, 45 min.	69	811
Me	H	Me	Me	Me	H	H	H	NH ₃ , stream, 180°		600
Me	H	H	H	Et	Et	H	H	NH ₃		1222
								Urea, 200°, ¼ hr.		1696
H	H	Et	Me	H	H	H	H	Urea, 200°	79	810
								NH ₃ passed into melt, 200°, 1 ½ hr.	82	811

H	H	Et	Me	H	Me	MeNH ₂ passed into melt, 200°, 1 hr.	64	811
H	H	Et	Me	H	Et	EtNH ₂ passed into melt, 200°, 1 hr.	70	811
H	H	Et	Me	H	Bu	BuNH ₂ passed into melt, 200°, 45 min.	65	811
H	H	Pr	Me	H	H	Urea, 200°	55	810
						NH ₃ passed into melt, 200°, 1½ hr.	55	811
H	H	Pr	Me	H	Me	MeNH ₂ passed into melt, 200°, 1 hr.	74	811
H	H	Pr	Me	H	Et	EtNH ₂ passed into melt, 200°, 1 hr.	67	811
H	H	Pr	Me	H	Bu	BuNH ₂ passed into melt, 200°, 45 min.	73	811
Me	H	H	H	n-Amyl	H	Urea, 200°, ¼ hr.		1696
Me	Me	H	H	n-Amyl	H	Urea, 200°, ¼ hr.		1696
C ₁₂ H ₁₃	H	H	H	H	H	Aq. alc., NH ₃ , distill to 250°, hold at 250°, 20 min.	65	541
H	H	cyclopentyl	H	H	H	NH ₃ , 230°, ¼ hr.	65	1223
cyclopentyl	H	H	H	Me	H	NH ₃ , Et ₂ O	71	1222
Ph	H	H	H	Ph	H	(NH ₄) ₂ CO ₃ , 165°, ½ hr.	71	1154

TABLE II-63. Cyclization of β -Hydroxyglutaric Acid Derivatives

X	R ₃	R ₄	Conditions	Yields	Ref.
OH	H	CO ₂ H	(1) Toluenesulfonic acid, MeOH, reflux, 2½ hrs. (2) Aq. NH ₃ , 130°, 2 hrs. Urea	35%	1830,836
			Aq., NH ₃ , 140°, 18 hrs.	65%, 43% Conv.	1369
			Aq., NH ₃ , 165–200°	(β -Carbamylglutaconimide 50–60%)	854
			Urea, 150°	(β -Carbamylglutaconimide 60–70%)	1829
OMe	H	CO ₂ Me	(1) Aq. NH ₃ , evaporate to dryness (2) 73% H ₂ SO ₄ , 130°, 15 min.	39.8%	1819
			Aq., NH ₃ , 145°, 4 hrs.	62%	1819
OEt	H	CO ₂ H	NH ₃		1369
OEt	H	CO ₂ Et ^a	NH ₃ , 25°, several days	(β -Carbamylglutaconimide)	263,767
NH ₂	H	H	Conc. H ₂ SO ₄ , 130° PCl ₅ , heat	(2-Amino-3,4,5,6-tetrachloro-pyridine)	1046,1731 1040,1041, 1042,
NH ₂	H	CONH ₂	(1) Na ₂ CO ₃ , glycol, 140° (2) 5N NaOH, heat	80%	1295 1825
O ^b	H	CO ₂ H	75% H ₂ SO ₄ , 130° Aq., NH ₃ , 135°, 5 hrs.	(β -Carboxyglutaconimide, 26%) 56%	261,262 1577

^a Acetate of triethyl citrate used.^b 4-Carboxy-4-hydroxyglutaric anhydride.

TABLE II-64. Cyclization of Glutaconic Acids, Esters, or Amides

TABLE II-64. Cyclization of Glutaconic Acids, Esters, or Amides

The reaction scheme shows the cyclization of a substituted glutaric acid derivative to a substituted pyridine-2,5-dione. The starting material is a glutaric acid derivative with substituents R₁, R₂, R₃, R₄, R₅, and R₆. The product is a pyridine-2,5-dione with substituents R₁, R₂, R₃, R₄, R₅, and R₆.

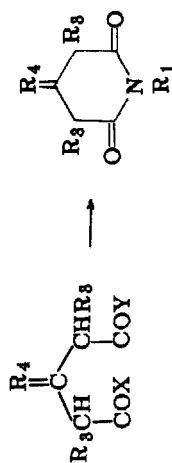
X	Y	R ₃	R ₄	R ₅	R ₁	Conditions	Yield, %	Ref.
OH	OH	H	Me	H	Ph	Aniline, 150°, 2 hrs.	35	863
OH	OH	H	Me	H	<i>o</i> -MeC ₆ H ₄	<i>o</i> -Toluidine, 150°, 2 hrs.	25	863
OH	OH	H	Me	H	<i>p</i> -MeC ₆ H ₄	<i>p</i> -Toluidine, 150°, 2 hrs.	30	863
OH	OH	H	Me	H	2,6-Me ₂ C ₆ H ₃	2,6-Xylydine, 150°, 2 hrs.	60	863
OH	OH	H	Me	H	<i>m</i> -ClC ₆ H ₄	<i>m</i> -Chloroaniline, 150°, 2 hrs.	30	863
OH	OH	H	Me	H	<i>p</i> -ClC ₆ H ₄	<i>p</i> -Chloroaniline, 150°, 2 hrs.	45	863
OH	OH	H	Me	H	<i>o</i> -NO ₂ C ₆ H ₄	<i>o</i> -Nitroaniline, 150°, 2 hrs.	25	863
OH	OH	H	Me	H	2,5-(MeO) ₂ C ₆ H ₃	2,5-Dimethoxyaniline, 150°, 2 hrs.	50	863
OH	OH	H	Me	H	<i>p</i> -Me ₂ NC ₆ H ₄	<i>p</i> -Dimethylaminoaniline, 150°, 2 hrs.	25	863
					<i>p</i> -Et ₂ NC ₆ H ₄	<i>p</i> -Dimethylaminoaniline, benzene, reflux, 18 hrs.	10	863
OH	OH	H	Me	H		<i>p</i> -Diethylaminoaniline, 150°, 2 hrs.	20	863
OH	OH	H	Me	H	H	NH ₃ , distil		1611
OH	OH	H	Me	H	H	NH ₃ salt, distil		1611

(continued)

TABLE II-64 (Continued)
 Cyclization of Glutaconic Acids, Esters, or Amides

X	Y	R ₃	R ₄	R ₅	R ₁	Conditions	Yield, %	Ref.
OH	OH	H	Me	H	Me	(1) Alc., MeNH ₂ , 220° (2) Vac. distil	18	1635
OH	OH	Me	Me	H	OCH ₂ Ph	PhCH ₂ ONH ₂ , xylene, reflux, 45 min.	good	1635
OH	OH	H	Me	Me	H	NH ₃ salt, distil		1611
OH	OH	Me	Me	Me	H	NH ₃ salt, distil		1611
OH	OH	Et	Me	H	H	NH ₃ salt, distil		1611
OH	OH	H	<i>i</i> -Pr	H	H	NH ₃		1235
OH	OH	H	3-Me-4- MeOC ₂ H ₅	H	H	NH ₃ salt, distil red. press.		334
OH	OH	H	5-Me-2- MeOC ₂ H ₅	H	H	NH ₃ salt, distil red. press.		336
OH	OH	H	<i>p</i> -HOC ₂ H ₄	H	H	NH ₃ salt, distil red. press.		334
OH	OH	CO ₂ Et	H	CO ₂ Et	H	Formamide, heat		279
OEt	OEt	H	H	Me	H	Aq. NH ₃ , 100°, sealed tube, sev. hrs.		689
OEt	OEt	H	H	Et	H	Aq. NH ₃ , 100°, sealed tube, sev. hrs.		689
OEt	OEt	H	H	CH ₂ Ph	H	Aq. NH ₃ , 100°, sealed tube, 3 d.		688
OEt	OEt	H	CH ₂ CO ₂ Et	H	H	Alc. NH ₃	(4-Car- bamyl- methyl deriv.)	329

OMe	OMe	Ph	H	H	H	Alc. NH ₃ , 130°, 4 hrs.	43	1112
OEt	OEt	H	Ph	H	H	Aq. NH ₃ , 100°, sealed tube, 2 d.	78	1732
OEt	OEt	H	Ph	CH ₂ Ph	H	Aq. NH ₃ , 150°, 6 d.	poor	1732
OEt	OEt	<i>p</i> -ClC ₆ H ₄	H	H	H	Alc. NH ₃ , 130°, 4 hrs.	44	1112
OEt	OEt	H	CO ₂ Et	H	H	NH ₃ , 25°, 3 d.	(4-Carbamyl-deriv.)	264, 265
OEt	OEt	H	Ph	CO ₂ Et	H	Alc. NH ₃ , 100°, sev. d.	78	1732
OEt	OEt	CO ₂ Et	CO ₂ Et	H	H	Aq. NH ₃ , 5 d.		768
OEt	OEt	CO ₂ Et	H	CO ₂ Et	H	Aq. NH ₃ , 25°, 2 wks.	Poor (3,5-dicar-bamyl deriv.)	687
OH	NH ₂	H	H	H	H	Dil. H ₂ SO ₄ , 135°		1046
<i>o</i> -Me-C ₆ H ₄ NH	OH	H	Me	H	<i>o</i> -MeC ₆ H ₄	175°, 20 min.		863
<i>p</i> -Me-C ₆ H ₄ NH	OH	H	Me	H	<i>p</i> -MeC ₆ H ₄	175°, 20 min.		863
<i>p</i> -Cl-C ₆ H ₄ NH	OH	H	Me	H	<i>p</i> -ClC ₆ H ₄	175°, 20 min.		863
NH ₂	OEt	H	Me	CO ₂ Et	H	190°		1611
NH ₂	NH ₂	H	H	H	H	Conc. H ₂ SO ₄	78	1732
						Dil. H ₂ SO ₄ , 135°		1046

TABLE II-65. Cyclization of β -Ketoglutaric Acid Derivatives

X	Y	R ₁	R ₂	R ₃	R ₄	R ₅	Conditions	Yields	Ref.
OE _t	OE _t	H	O	H	Ph	PhNH ₂			1725
OE _t	OE _t	H	NNHCOCONH ₂	H	H	Aq. NH ₃		2-OEt	1237
OE _t	OE _t	H	NNHCONH ₂	H	H	Aq. NH ₃ , stand 15 hrs.			1238
NH ₂	ONH ₂	Me	O	H	H	Aq., Na ₂ CO ₃ , N ₂ , reflux, 20 min.		86%	919
						4N HCl, reflux, 15 min.		90%	919
						140°, no solvent		(β -Amino- α , α -dimethyl glutaraconimide)	919
NH ₂	OE _t	H	O ^a	H	H	Na ₂ CO ₃ , reflux, 10 min.		(β -Amino-glutaraconimide, 40%)	1051, 1052, 1061
NH ₂	OE _t	CN	NH	H	H	Na ₂ CO ₃ , reflux, 1 hr.			1617

^aGiven as 4-amino-4-hydroxyglutaric acid (an ammonia addition product).

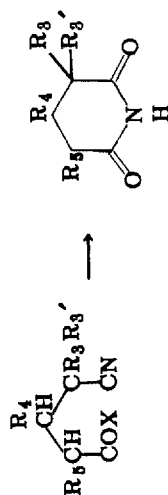


TABLE II-66. Cyclization of Glutaric Mononitriles

X	R ₃	R ₃ '	R ₄	R ₅	Conditions	Yield	Ref.
OH	Me	H	H	Me, Me ^a	20% HCl, 25°, 12 hrs., then reflux, ½ hr.	62%	600
OH	Ph	Me	H	H	85% H ₂ SO ₄ , warm, short time	(Only acidamide)	538
OH	Ph	Et	H	H	Conc. HCl, heat, 1 min.	Imide (also acid- amide)	538
OH	Ph		H	H	85% H ₂ SO ₄ , warm, short time	30% (Also 70% acid-amide)	500, 538
OH	Ph		H	H	HOAc, H ₂ SO ₄ , 100°, 10 min.		610, 682, 523
OH	Ph	Pr	H	H	Conc. HCl, heat, 1 min.	Imide (also acid- amide)	500, 538
OH	Ph		H	H	85% H ₂ SO ₄ , warm, short time	Only acid-amide	538
OH	Ph	<i>i</i> -Pr	H	H	HOAc, H ₂ SO ₄ , 100°, 10 min.		523, 610, 682
OH	Ph	<i>i</i> -Bu	H	H	HOAc, H ₂ SO ₄ , 100°, 10 min.		610, 523
OH	Ph	Amyl	H	H	HOAc, H ₂ SO ₄ , 100°, 10 min.		610, 523

(continued)

TABLE II-66 (Continued)
Cyclization of Glutaric Mononitriles

X	R ₂	R ₁ '	R ₁	R ₂	Conditions	Yield	Ref.
OH	Ph	isoamyl	H	H	HOAc, H ₂ SO ₄ , 100°, 10 min.		610,523
OH	Ph	cyclohexyl	H	H	HOAc, Ac ₂ O, SnCl ₄ , 110°, 10 min.		523
OH	Ph	CH ₂ Ph	H	H	85% H ₂ SO ₄ , warm, short time		500,538
OH	Ph	CH ₂ CH ₂ NMe ₂	H	H	HOAc, Ac ₂ O, H ₂ SO ₄ , 100°, 10-15 min.		522,617
					HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.		617
OH	Ph	OH ₂ CH ₂ NEt ₂	H	H	Ac ₂ O, reflux 2 hrs.		522
					HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, ¼ hr.		617
					HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.		617
OH	Ph	CH ₂ CHMe-NMe ₂	H	H	HOAc, H ₂ SO ₄ , 100°, 5 min.		522
					HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, ¼ hr.		617
					HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.		617
OH	Ph	(CH ₂) ₃ NEt ₂	H	H	HOAc, Ac ₂ O, H ₂ SO ₄ , 100-120°, 15 min.		522,617

OH	Ph	3-(1-piperidyl)H propyl	H	HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.	617
				HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, ¼ hr.	617
				HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.	617
OH	Ph	2-(N-cyclo- heptyl- N-methyl- amino)- ethyl	H	Ac ₂ O, reflux, 6 hrs.	522
				HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, 15 min.	617
				HOAc, Ac ₂ O, SnCl ₄ , water bath 10 min.	617
OH	Ph	Ph	H	80% H ₂ SO ₄ , 25°	776
				80% H ₂ SO ₄ , warm, short time	537
				HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, ¼ hr.	617
OH	p-ClC ₆ H ₄	CH ₃ CH ₂ NMe ₂	H	HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.	617
OH	p-ClC ₆ H ₄	CH ₃ CH ₂ NEt ₂	H	HOAc, H ₂ SO ₄ , 120°, 10 min.	522
OH	p-ClC ₆ H ₄	Ph	H	HOAc, Ac ₂ O, SnCl ₄ , 110°, 10 min.	523

(continued)

TABLE II-66 (Continued)
Cyclization of Glutaric Mononitriles

X	R ₁	R ₂ '	R ₃	R ₄	Conditions	Yield	Ref.
OH	<i>m</i> -MeOC ₆ H ₄	CH ₃ CH ₂ NMe ₂	H	H	HOAc, H ₂ SO ₄ , 100°; ½ hr.		522
					HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, ¼ hr.		617
					HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.		617
OH	<i>m</i> -MeOC ₆ H ₄	CH ₃ CH ₂ NEt ₂	H	H	HOAc, H ₂ SO ₄ , 110°; 10 min.		522
					HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, ¼ hr.		617
					HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.		617
OH	2-thenyl	CH ₃ CH ₂ NEt ₂	H	H	HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, ¼ hr.		617
					HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.		617
OH	2-thenyl	Ph	H	H	Ac ₂ O, reflux, 12 hrs.		522
OH	3-pyridyl	CH ₃ CH ₂ NMe ₂	H	H	HOAc, H ₂ SO ₄		523
					HOAc, Ac ₂ O, H ₂ SO ₄ , water bath, ¼ hr.		617
					HOAc, Ac ₂ O, SnCl ₄ , water bath, 10 min.		617
OH	2-pyridyl	Ph	H	H	HOAc, Ac ₂ O, SnCl ₄ , 110°, 20 min.		523

OH	2-pyridyl	<i>p</i> -ClC ₆ H ₄	H	H	HOAc, Ac ₂ O, SnCl ₄ , 110°, 10 min.	523	
OEt	H	H	H	(CH ₃) ₃ CO ₂ Et	(1) Aq. Na ₂ CO ₃ (2) Heat dried product of (1)	573	
OMe	Ph	Me	H	H	HOAc, H ₂ SO ₄ , reflux, 4 hrs.	682	
OEt	Ph	Ph	H	H	80% H ₂ SO ₄ , warm, short time	Low (mostly acy- clic ester-amide)	537
					80% H ₂ SO ₄ , 25°	Good	776
					Br ₂ , 130°, light, 2½ hrs.	(A monobromo product)	1177
OMe	<i>p</i> -ClC ₆ H ₄	Et	H	H	HOAc, H ₂ SO ₄ , reflux, 3 hrs.	682	
OMe	CO ₂ Me	H	CH ₃ CO ₂ Me	H	Conc. HCl, 25°, 1 hr.	(4-Carboxymethyl- glutarimide)	916
OMe	spiro ^b	^b	H	H	HOAc, H ₂ SO ₄ , 120°, ¼ hr.	90% ^b	1178

^aStarting material is γ -cyano- α , α -dimethylvaleric acid; product is that expected.

^bBis-Carbomethoxymethylmalononitrile gives a spiro product

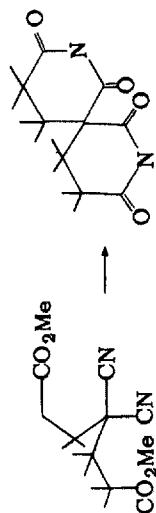
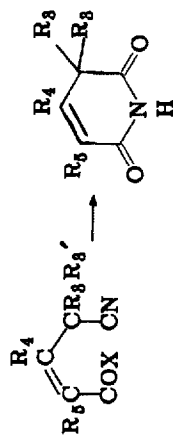


TABLE II-67. Cyclization of 4-Cyanocrotonic Acids or Esters



X	R ₃	R ₂	R ₁	R ₅	Conditions	Yield	Ref.
OH	Ph	Et	H	H	HOAc, H ₂ SO ₄ , (NH ₄) ₂ CO ₃ , 80–100°, 4 hrs.		1743
OH	Ph	CH ₂ CH ₂ NEt ₂	H	H	HOAc, H ₂ SO ₄ , (NH ₄) ₂ CO ₃ , 80–100°, 4 hrs.		1743
OH	Ph	Ph	H	H	HOAc, H ₂ SO ₄ , (NH ₄) ₂ CO ₃ , 80–100°, 4 hrs.		1743
OEt	Me	H	Me	Me	Alc., H ₂ SO ₄ , heat, 3 hrs. Alc., H ₂ SO ₄ , heat, longer period	^a	1611 1611
OEt	CH ₂ CH ₂ OPh	H	CH ₃ CO ₂ Et	H	Conc. HCl, reflux, 12 hrs.	Very good (hy- drolysis of side-chain ester)	1262
OEt	Ph	Et	H	H	HOAc, H ₂ SO ₄ , reflux, 4 hrs.		1177
OEt	Ph	CH ₂ CH ₂ NEt ₂	H	H	HOAc, H ₂ SO ₄ , water bath, ½ hr.		1177
OEt	Ph	Ph	H	H	HOAc, H ₂ SO ₄ , 110°, 10 min.		1177

OEt	CO ₂ Et	H	Me	H	Conc. H ₂ SO ₄ Conc. HCl, until solution Conc. HCl, 12 hrs.	(Loss of 3-car- bethoxy) 77% (Loss of 3- carbethoxy)	1611 1611 1611
					Conc. HCl, reflux, 4 hrs.		609
					Alc., KOH	(Loss of 3-car- bethoxy)	1611
OEt	CO ₂ Et	Me	Me	H	HCl, reflux	(Loss of 3-car- bethoxy)	1611
					MeOH, KOH, reflux, 5 hrs.	(Loss of 3-car- bethoxy)	1611
OEt	CO ₂ Et	H	Me	Me	HCl, reflux	Trace (loss of 3- carbethoxy, also 75% of acyclic diacid)	1611
OEt	CO ₂ Et	Me	Me	Me	HCl, reflux	(Loss of 3-car- bethoxy)	1611, 1730
OEt	CO ₂ Et	Et	Me	H	MeOH, KOH	(Loss of 3-car- bethoxy)	1611
OEt	CO ₂ Et	H	Me	Et	Conc. H ₂ SO ₄ , 12 hrs. MeOH, KOH	(Loss of 3-car- bethoxy)	1611 1611

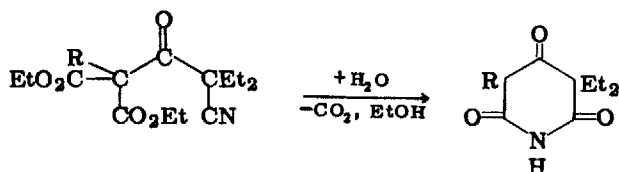
(continued)

TABLE II-67 (Continued)
Cyclization of β -Cyanomethylacrylic Acids or Esters

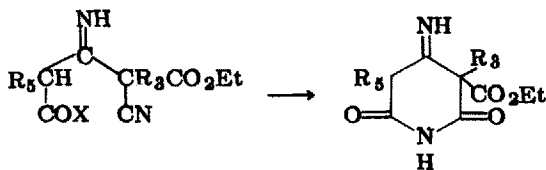
X	R ₃	R ₃ '	R ₄	R ₅	Conditions	Yield	Ref.
OEt	CO ₂ Me	H	-CH ₂ CH ₂ CH ₂ -		Conc. HCl, reflux, 10 hrs.	23% (Loss of 3-carbomethoxy, also 39% of 2-carboxy-1-cyclopentenyl-acetic acid)	649
OEt	CO ₂ Et	H	-CH ₂ CH ₂ CH ₂ -		Conc. H ₂ SO ₄ , overnight; or conc. HCl, reflux 2½ hrs.	Low	1277
					Conc. HCl, reflux, 10 hrs.	30% (Loss of 3-carbomethoxy, also 46% of 2-carboxy-1-cyclopentenyl-acetic acid)	649
OEt	CO ₂ Et	Me	-CH ₂ CH ₂ CH ₂ -		MeOH, KOH, reflux, 24 hrs.	Low (loss of 3-carbomethoxy)	1277
OEt	CO ₂ Et	Et	-CH ₂ CH ₂ CH ₂ -		MeOH, KOH, reflux, 24 hrs.	Poor (loss of 3-carbomethoxy)	1277
OEt	CO ₂ Et	H	-CH ₂ CH ₂ CH ₂ CH ₂ -		Aq. MeOH, KOH, reflux, 3 hrs.	Good (loss of 3-carbomethoxy)	1094
					MeOH, KOH, reflux, 24 hrs.	Poor (loss of 3-carbomethoxy)	1277
					Conc. H ₂ SO ₄ , 18 hrs.; or HCl, reflux, 2½ hrs.	Poor	1277

OEt	CO ₂ Et	CH ₃ CH ₂ OPh	Me	H	HCl, reflux, 12 hrs.	20% (Loss of 3-carbethoxy)	1276
OEt	CO ₂ Et	H	CO ₂ Et	H	Conc. H ₂ SO ₄ MeOH, KOH, boil	2,6-Dihydroxy-isonicotinic acid	1615 1615
OEt	CO ₂ Et	Me	CO ₂ Et	H	Conc. H ₂ SO ₄ MeOH, KOH	No reaction 2,6-Dihydroxy-3-methyliso-nicotinic acid	1615 1615
OEt	CO ₂ Et	H	CO ₂ Et	Me	Conc. H ₂ SO ₄		1615
OEt	CO ₂ Et	Me	CO ₂ Et	Me	Conc. H ₂ SO ₄ MeOH, KOH	No reaction 2,6-Dihydroxy-3,5-dimethyl-isonicotinic acid	1615 1615

^aProduct not certain; thought to be 6-ethoxy-3,4,5-trimethyl-2-pyridinol.

TABLE II-68. Cyclization of β -Ketoglutaric Mononitriles

R	Conditions (920)	Yield, %
H	HOAc, 85% H ₂ SO ₄ , 90°, 2½ hrs.	78
Me	HOAc, 85% H ₂ SO ₄ , 90–100°, 4 hrs.	75
Et	HOAc, 85% H ₂ SO ₄ , 90°, 2½ hrs.	53
Bu	HOAc, 85% H ₂ SO ₄ , 100°, 4 hrs.	56
Ph	HOAc, 85% H ₂ SO ₄ , 100°, 4 hrs.	32

TABLE II-69. Cyclization of β -Iminoglutaric Mononitriles

X	R ₁	R ₂	Conditions (617)	Yields
OH	H ^a	H	145–70°	^a
OH	H	H	145°, 10 min.	
OEt	H	H	Conc. H ₂ SO ₄ , cold Conc. HCl, boil, 6 hrs., then evap.	High 2,4,6-pyridine- triol
OEt	H	Me	Conc. H ₂ SO ₄ , 10 min.	
OEt	H	Et	Conc. H ₂ SO ₄ , 12 hrs.	
OEt	Me	Me	Conc. H ₂ SO ₄ , 5 hrs.	
NH ₂	H	H	Conc. H ₂ SO ₄ , cold	

^a β -Keto derivative, not the imine.

TABLE II-70. Cyclization of Glutaronitriles

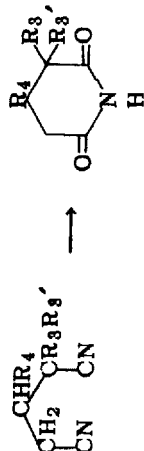
				Yield	Ref.
R ₃	R ₃ '	R ₄	Conditions		
H	H	Cyclopentyl	Conc. HCl, 100°, 4½ hrs.	Good (crude)	1219
H	H	(4,4-oxy-dimethylene)	(1) Alc. ether, HCl, cold 24 hrs. (2) Dil. HCl, reflux	(4-Chloromethyl-4-hydroxymethyl-glutarimide)	652
Ph	Me	H	75% H ₂ SO ₄ , 100°, 6 hrs.	45%	534
Ph	CH=CH ₂	H	HOAc, 78% H ₂ SO ₄ , 125°, 1 hr.	Near 100%	883
Ph	1-Cyclo-hexenyl	H	HOAc, H ₂ SO ₄ , 100°, 10 min.		523
Ph	(CH ₂) ₄ NEt ₂	H	HOAc, H ₂ SO ₄ , 130°, 10 min.		522
1-C ₁₀ H ₇	CH ₃ CH ₂ NEt ₂	H	HOAc, conc. HCl, reflux, 6 hrs.		522
3-pyridyl	Et	H			610
3-pyridyl	CH ₃ CH ₂ NMe ₂	H	HOAc, H ₂ SO ₄ , 135°, 10 min.		522

TABLE II-71. Miscellaneous Intramolecular 1,5-Cyclizations

Reactant	Conditions	Product	Ref.
Diethyl α,γ -dicyanoglutaconate	Alc., heat	3,5-Dicarbethoxy- β -glutaconimide	277,278
	Dil. HCl	3,5-Dicarbethoxy- β -glutaconimide	280
Sodium salt of diethyl β -carbethoxy- α,γ -dicyanoglutaconate	(1) Acid (2) Alc. reflux	3,4,5-tricarbethoxy- β -glutaconimide	1656
Mixture of β -methylglutacononitrile and isomers	HCl	4-methylglutaconimide (also β -methylglutaconic acid)	338
The bis-lactone of β , β -bis-hydroxymethylglutaric acid	Alc., NH ₃ , pressure	4,4-bis-hydroxymethylglutarimide	652
Glutaronitrile and phenylmagnesium bromide		6-phenyldihydro-2-pyridinol	332

TABLE II-72. Cyclization of the Oximes of 2,4-Pentadienones and Derivatives

R ₂	R ₅	R ₆	Yield, %	Ref.
Me	H	Ph	25	116,599,1292
Me	Me	Ph		1023
C ₉ H ₁₉	H	Ph		137
Ph	H	Ph	30	116,1292
Ph	Me	Ph		1023
<i>p</i> -MeC ₆ H ₄	H	Ph		1032
Ph	H	<i>p</i> -MeC ₆ H ₄		1032
<i>p</i> -MeC ₆ H ₄	H	<i>p</i> -MeC ₆ H ₄		1032
<i>p</i> -MeOC ₆ H ₄	H	Ph		137

TABLE II-73. Cyclization of 1,4-Pentadiyne-3-ones with Primary Amines

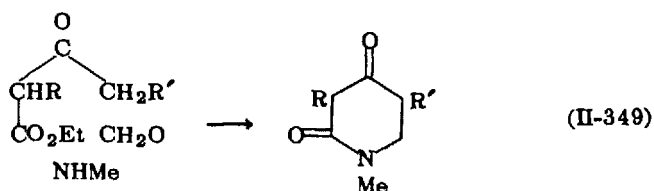
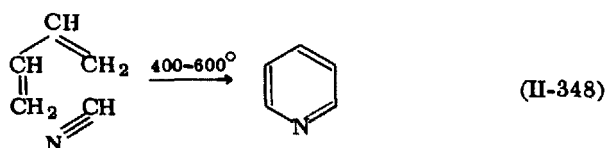
R ₁	R ₂	R ₆	Ref.
Ph	H	Me	497
H	Me	Me	1171,1236,1385
Me	Me	Me	1171,1236,1385
Pr ^a	Me	Me	1171
CH ₂ C≡CH	Me	Me	714
CH ₂ CO ₂ Et	Me	Me	675
Ph	Me	Me	1171,1236,1385
<i>p</i> -MeC ₆ H ₄ ^b	Me	Me	1171,1385
Ph	Me	Ph	1170
H	Ph	Ph	1171,1385
Me	Ph	Ph	1171,1385
Et ^a	Ph	Ph	1171
Ph ^b	Ph	Ph	1171,1271,1385

^a A list is given of many aliphatic amines which may participate in this reaction.

^b A list is given of many aromatic amines which may participate in this reaction.

2. 4-1 Condensation

The formation of pyridines by a 4-1 condensation may be divided easily into two classes. In the first class, dienes condense with simple nitriles in the vapor phase to give low yields of pyridine derivatives as in II-348. In the second class, certain derivatives of

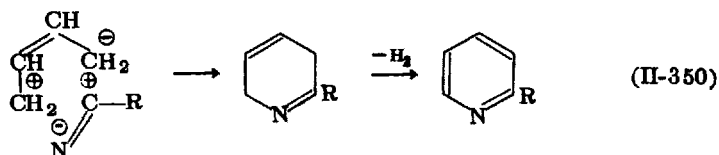


acetoacetic ester condense at moderate temperatures with an amine and formaldehyde, ethyl formate, or ethyl orthoformate as in II-349.

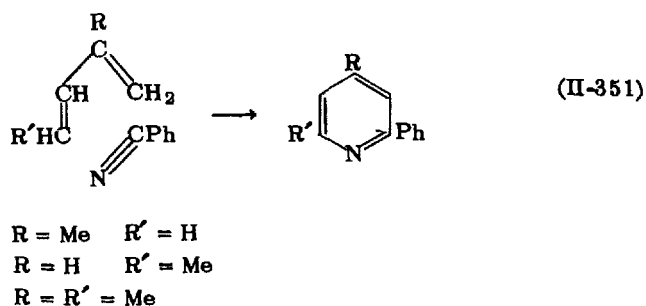
a. Diene Compounds with Nitriles

Butadiene, its methyl and dimethyl homologs, and chloroprene react with hydrogen cyanide and simple nitriles at 400–600° to give pyridine products (Table II-74). Though this reaction is thermodynamically favorable (1101,1181,1717) it occurs with only low conversion of starting materials and generally in poor yield. A catalyst of alumina or chromia on alumina increased the rate of reaction, but it did not increase the yield significantly.

The diene-nitrile condensation, which was found to be second order by Hawkins and Janz (1183), was thought by Janz and Wait to be a Diels-Alder condensation as in II-350 (1179). Whether the final step is a simple loss of hydrogen or some more complicated oxidation step is not certain.



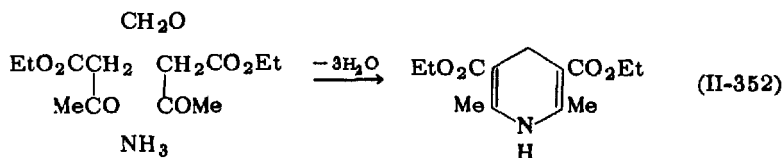
The reaction of methylbutadiene (isoprene), 1,3-pentadiene, and 2-methyl-1,3-pentadiene with a nitrile gives only the expected isomer as illustrated by the reactions of benzonitrile in II-351. However, the reaction of dimethylbutadiene with benzonitrile produced 2-phenyl-4-picoline, not the expected 6-phenyl-3,4-lutidine (1633). It is not certain whether the product from cyanogen and chloroprene was the 4-chloro- or 5-chloro-2-picolinonitrile or a mixture, since all of these have been indicated (Table II-74).



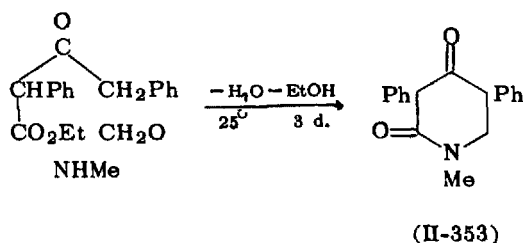
Condensation of dienes with nitriles gives a variety of by-products. Butadiene and acetonitrile gave aniline (1558), while butadiene and propionitrile produced aniline, ethylbenzene, and vinylcyclohexene (1557,1558). Acrylonitrile and butadiene gave not only vinylpyridine, but also propionitrile and cyanocyclohexene (Table II-74). As expected, the condensation of cyanogen with butadiene gave both 2-picolinonitrile and 2,2'-bipyridine (1097, 1467).

b. β -Ketoesters with Orthoformic Ester or Formaldehyde

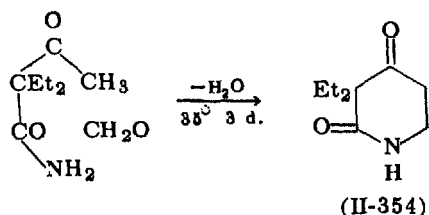
Acetoacetic ester reacts with formaldehyde and an amine by a 2-1-2 condensation as in II-352 (section 6, p. 500). However, if the



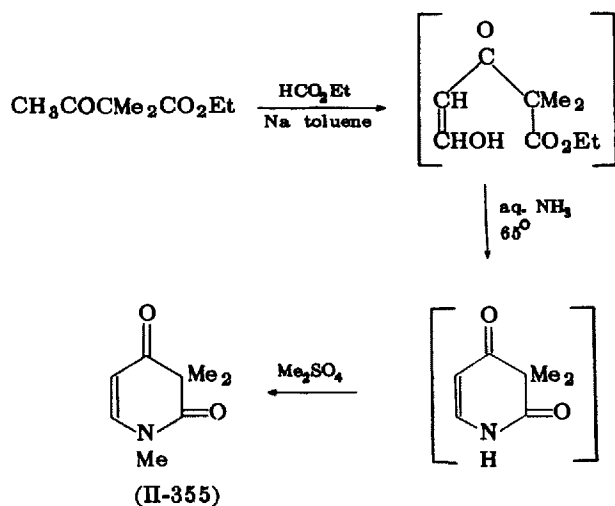
methylene group of the ketoester is substituted, different reactions take place. Ethyl α,γ -diphenylacetoacetate condensed with formaldehyde and methylamine to give a 78% yield of II-353 (1486). Simi-



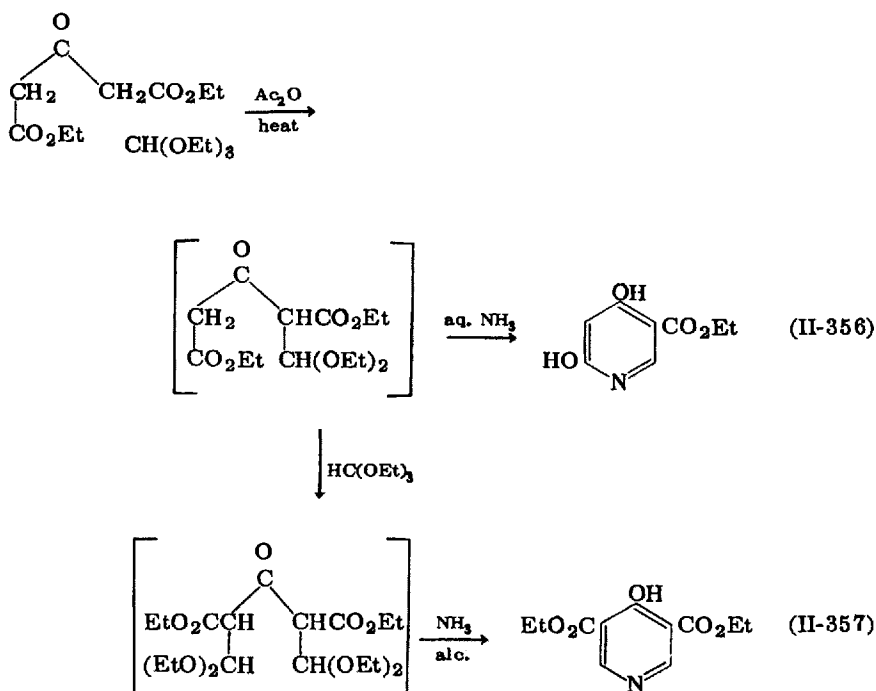
larly, α,α -diethylacetoacetamide and formaldehyde produced an 80.7% yield of the piperidinedione II-354 (1432).



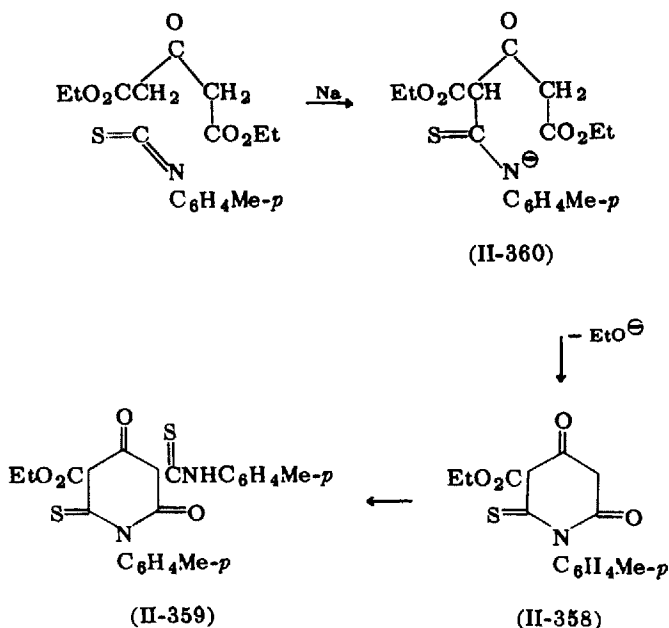
Since formaldehyde produced a dihydropyridine derivative (the piperidinedione), ethyl formate should give a pyridine derivative. This approach has been used indirectly by first condensing ethyl formate and α,α -dimethylacetoacetate in the presence of sodium, and then reacting this intermediate with ammonia. The product II-355 was isolated as the 1-methyl derivative (1442). The condensation (II-356) of diethyl β -ketoglutarate first with one equivalent



of ethyl orthoformate and then with ammonia gave a 4-1 condensation; but the condensation (II-357) of this glutarate with two equivalents of ethyl orthoformate and ammonia gave a 1-3-1 condensation (259).



Diethyl β -ketoglutarate condensed with one or two equivalents of *p*-tolyl isothiocyanate in the presence of sodium to give II-358 and II-359 (363). In either event, the key to the reaction would be the attack of an anion of the keto ester on the carbon of the isothiocyanate (II-360).

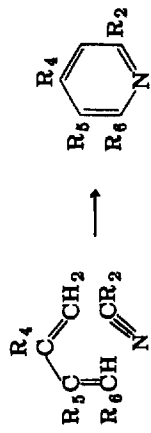


Miscellaneous. The reaction of hydrogen cyanide with 1,4-butanediol or 3-buten-1-ol gave some pyridine (379,380). Perhaps the first step is a dehydration to butadiene, whose reaction with nitriles has already been discussed.

Pyridine bases were produced in low yield by the reaction of butadiene and propane with ammonia under pressure at 640° (1492).

The vapor phase reaction of crotonaldehyde, methanol, and ammonia over a cadmium chromate catalyst was reported to give pyridine in unstated yield (619). It is not known whether the methanol is first converted to formaldehyde, methylamine, or some other intermediate.

TABLE II-74. Vapor Phase Reaction of Dienes with Nitriles

						
R ₁	R ₂	R ₃	R ₄	Conditions	Yield	Ref.
H		H	H	400–600°, Al ₂ O ₃ with or without Cr ₂ O ₃	Low	1101, 1468, 1633, 1717
Me		H	H	400–600°, no catalyst, or Al ₂ O ₃ , or SnCl ₄ on Al ₂ O ₃	Low	462, 1101, 1179, 1468, 1633, 1717
Et		H	H	420–600°, Cr ₂ O ₃ on Al ₂ O ₃	Low (also aniline, ethylbenzene, vinylcyclohexene)	1557, 1558, 1633
CH=CH ₂		H	H	400–430°, Al ₂ O ₃ , or Cr ₂ O ₃ on Al ₂ O ₃	Low (also propionitrile, cyclohexene)	1180, 1182, 1633
Ph		H	H	400°, Al ₂ O ₃ , or 400–600° with no catalyst	13.6% Conversion with 24% yield	1101, 1181, 1468, 1515, 1633, 1717, 1757
CF ₃		H	H	475°	Low conversion with good yield	1647
CN		H	H	400–600°, no catalyst, or 400°, Cr ₂ O ₃ on Al ₂ O ₃	Low	1101, 1183, 1468, 1633, 1647, 1717
Ph		H	Me	480°, no catalyst, or 270°, pressure 400°, Al ₂ O ₃	18% (Also 2,2'-bipyridine) 28% Conversion with 9% yield	1097, 1467, 1633

(continued)

TABLE II-74 (Continued)
Vapor Phase Reaction of Dienes with Nitriles

R ₄	R ₄	R ₃	R ₂	Conditions	Yield	Ref.
Me	Me	H	H	400°, Al ₂ O ₃	5%	1179, 1633
Ph	Me	H	H	400°, Al ₂ O ₃	12% conversion with 63% yield	1633
CN	Me	H	H	Heat	18%	1467
				400°, Al ₂ O ₃		1098, 1633
Me	Me	H	Me	400°, Al ₂ O ₃	1%	1179, 1633
Ph	Me	H	Me	400°, Al ₂ O ₃	28% conversion with 26% yield	1633
CN	Me	H	Me	400°, Al ₂ O ₃	61%	1098, 1467, 1633
Ph	Me	Me	H	400°, Al ₂ O ₃	(2-Phenyl-4-picoline) 12% con- version with 53% yield	1633
CN	Cl	H	H	Heat	(5-Chloropicolinonitrile)	1098
				400°, Al ₂ O ₃	(4- and 5-Chloropicolinonitrile)	1633
				Heat	(4- or 5-Chloropicolinonitrile)	1467
H	^a			High temperature	(Pyridine)	380
H	^b			High temperature	Pyridine (also 4-pentenitrile, 379 3-butene-1-ol, tetrahydrofuran)	
None	H	H	H	Propane, NH ₃ , Ni, 640°, pressure	(Pyridine bases), low yield	1492

^a3-Buten-1-ol.

^b1,4-Butanediol.

TABLE II-75. 4-1 Condensations of β -Ketoacid Derivatives

Reactants	Conditions	Products (Yields)	Ref.
$\text{MeCOCEt}_2\text{CO}_2\text{Et}$, CH_2O , NH_3	(1) ZnCl_2 , HCl , 8 hr. (2) Alc., NH_3 , 90° , 8 hr.	3,3-Diethyl-2,4-piperidinedione (70%)	1541
$\text{PhCH}_2\text{COCHPhCO}_2\text{Et}$, CH_2O , MeNH_2	Alc., 25° , 3 days	3,5-Diphenyl-1-methyl-2,4-piperidinedione (78%)	1486
$\text{MeCOCEt}_2\text{CONH}_2$, CH_3Cl_2	(1) Toluene, Cu, reflux, 6 hr. (2) evap., vac.	3,3-Diethyl-2,4-piperidinedione (70%)	1542
$\text{MeCOCEt}_2\text{CONH}_2$, CH_3O	Aq., 35° , 3 days	3,3-Diethyl-2,4-piperidinedione (80.7%)	1432
$\text{MeCOCMe}_2\text{CO}_2\text{Et}$, HCO_2Et , NH_3	(1) Na, toluene, 8° , 20 hrs. (2) Aq., NH_3 , 65° , 1 hr. (3) NaOMe , Me_2SO	1,3,3-Trimethyl-2,4-pyridine-dione	1442
$\text{CO}(\text{CH}_3\text{CO}_2\text{Et})_2$, $p\text{-MeC}_6\text{H}_4\text{NCS}$ (1:1 ratio)	Na, ether	5-Carbethoxy-4-hydroxy-6-mercapto-1- p -tolyl-2(1H)-pyridone (28%)	363
$\text{CO}(\text{CH}_3\text{CO}_2\text{Et})_2$, MeNCS (1:2 ratio)	Na, ether	5-Carbethoxy-4-hydroxy-6-mercapto-1-methyl-3-methylthiocarbamyl-2(1H)-pyridone	1255
$\text{CO}(\text{CH}_3\text{CO}_2\text{Et})_2$, $p\text{-MeC}_6\text{H}_4\text{NCS}$ (1:2 ratio)	Na, ether	5-Carbethoxy-4-hydroxy-6-mercapto-1- p -tolyl-3- p -tolylthiocarbamyl-2(1H)-pyridone (20.4%)	363

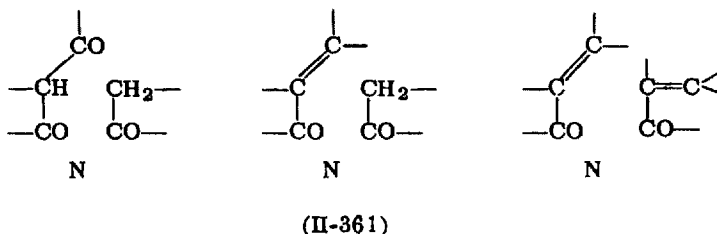
(continued)

TABLE II-75 (Continued)
4-1 Condensations of β -Ketoacid Derivatives

Reactants	Conditions	Products (Yields)	Ref.
CO(CH ₃ CO ₂ Et) ₂ , HC(OEt) ₂ (1:1 ratio)	(1) Ac ₂ O	5-Carbethoxy-2,4-pyridinediol, hydroxytrimesic acid, triethyl ester	259
	(2) Aq., NH ₃ , heat, 1 hr.		
	(1) Ac ₂ O, 130°, 1 hr.	5-Carbethoxy-2,4-pyridinediol (60%), hydroxytrimesic acid, triethyl ester	820
	(2) Aq., NH ₃ , 1 hr. stand		

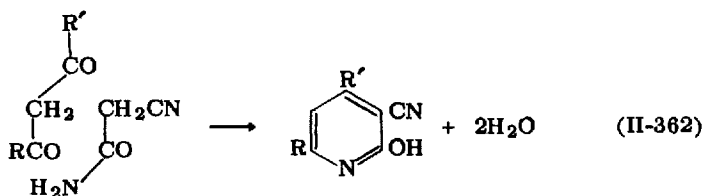
3. 3-2 Condensation

Combination of a three-carbon with a two-carbon fragment is the most common method of forming the pyridine ring. The variations of such 3-2 condensations are numerous, and three general schemes are shown in II-361.



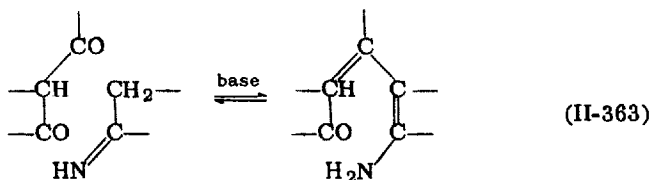
a. 1,3-Dicarbonyl Compounds and Derivatives with Methylenic Compounds

This method is illustrated in II-362. A variety of compounds may serve as three-carbon donors, such as β -ketoaldehydes, 1,3-di-

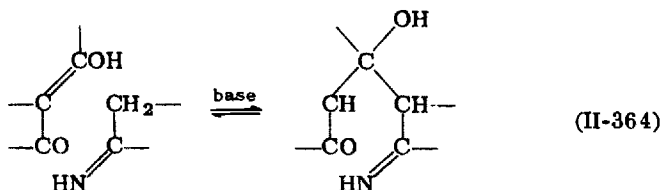


ketones, and β -ketoesters, and also their functional derivatives, such as acetals, enol ethers, imine derivatives, and the β -ketonitriles. The two-carbon donor may be a methylenic ketone, ketimine, ester, amide, or nitrile. If nitrogen is not already present it is supplied as ammonia or as a primary amine. It can be seen that many compounds can play either role. Thus β -aminocrotonic ester acts as a three-carbon donor (β -iminoester) in some condensations, and as a two-carbon donor (methylenic ester) in others. The chemistry of 1,3-dicarbonyl compounds and their derivatives has been reviewed elsewhere (878,879).

The common mechanism of these condensations involves *first* a Knoevenagel reaction between the methylene group and the *most active* carbonyl group present (II-363), followed by cyclization. By

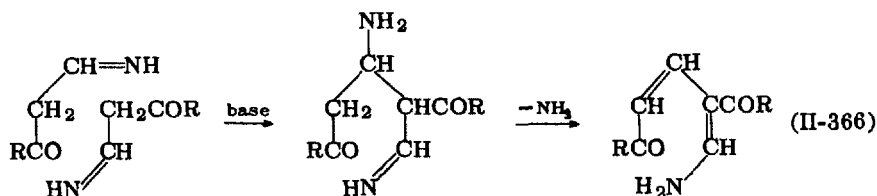
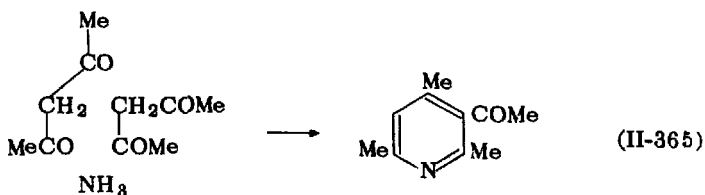


this sequence it is the most active carbonyl group which becomes C₄ of the pyridine ring. Illustrations of the mechanism—and exceptions—will be given as they arise. It is also possible to consider the first step as a Michael-type addition of the methylenic compound on the enolic double bond (II-364). This question has not been settled, but the product is the same by either route.

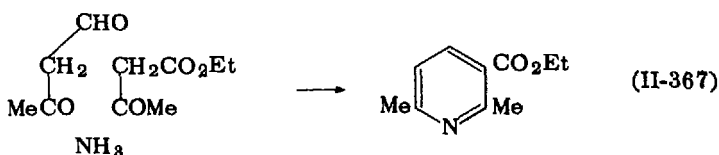


For the subsequent discussion this type of synthesis has been subdivided according to the nature of the *three-carbon donor*, considered in the following order: (1) 1,3-dioxo compounds (malon-aldehydes, β -ketoaldehydes, 1,3-diketones) and their acetals; (2) enol ethers of (1); (3) enol esters of (1); (4) β -chlorovinyl ketones; (5) imine derivatives of (1); (6) β -oxoesters and their enol ethers; (7) imine derivatives of β -oxoesters; (8) β -ketoamides and acid chlorides; (9) β -oxonitriles and their enol ethers and imine derivatives; and (10) malonic acid derivatives.

(a) **1,3-Dioxo Compounds and Their Acetals:** (1) *With Methylenic Ketones and Aldehydes.* The simplest example of a 3-2 synthesis is the reaction of two moles of a 1,3-diketone or β -ketoaldehyde with ammonia (II-365) (1109). No doubt the imine is first formed, the more polar carbonyl group becoming aminated and forming C₄ of the pyridine (II-366). β -Ketoaldehydes give low yields, with side

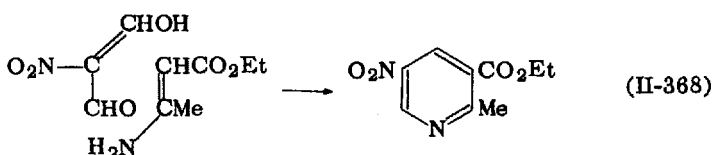


reactions to 1,3,5-triacylbenzenes (296) and imino-bis-vinyl ketones, $\text{NH}(\text{CH}=\text{CHCOR})_2$ (296,1249). Only one reaction of two different carbonyl compounds is reported; the yield of the mixed condensation product was low (II-367) (1592,1646) (Table II-76).



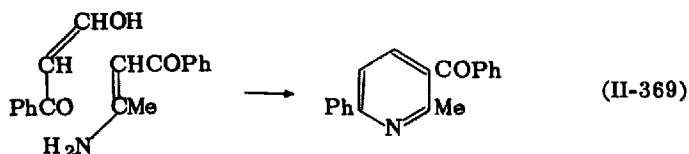
(2) *With Methylenic Ketimines.* It is more common to react the dioxo compound with a methylenic ketimine, that is, an "enamine compound" such as β -aminocrotonic ester. These reactions are exothermic and are usually run without added catalyst or solvent. The enamine compound in its polarized form, $^+\text{H}_2\text{N}=\text{CMeCH}-\text{CO}_2\text{Et}$, must add directly to the carbonyl group (Tables II-77 and II-78).

The reaction of nitromalonaldehyde, as the sodium salt, with β -aminocrotonic ester in water at 50° , goes in fair yield (II-368),

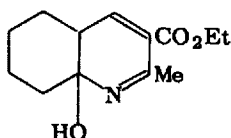


and is one of the few cases where a nitropyridine is formed directly from acyclic materials (1148).

β -Ketoaldehydes react initially through their aldehyde group (the more polarized carbonyl function), which thus becomes C₄ (II-369) (1288). At ice-bath temperature an intermediate (presumably

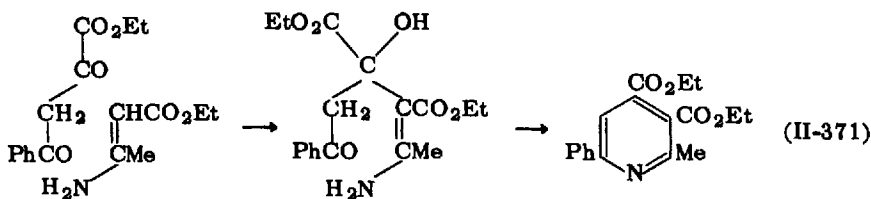


II-370) was isolated in one case, which then formed the pyridine on heating (888).



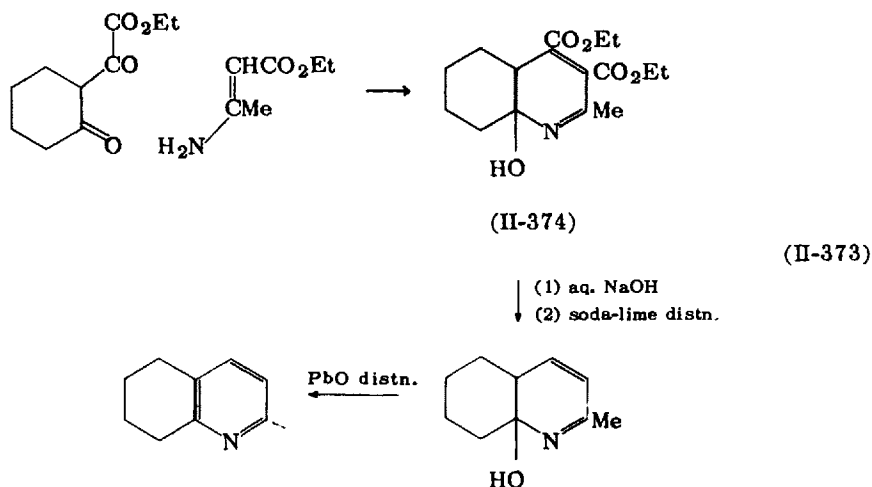
(II-370)

Acylpyruvic esters with enamines give 4-pyridinecarboxylic esters (II-371) (199,733); the α -keto group, being the more polarized by the adjacent carboxy group, enters first into reaction and contributes C₄. Here the initial condensation is sufficiently vigorous to require cooling, but to complete the dehydration and cyclization steps heating is necessary, sometimes up to 130°. Alternatively the reaction may be performed in ether in the presence of anhydrous sodium sulfate, in which case all steps are completed. An intermediate isolated in the cold was believed to be II-372, though two different melting points have been reported (199,733).

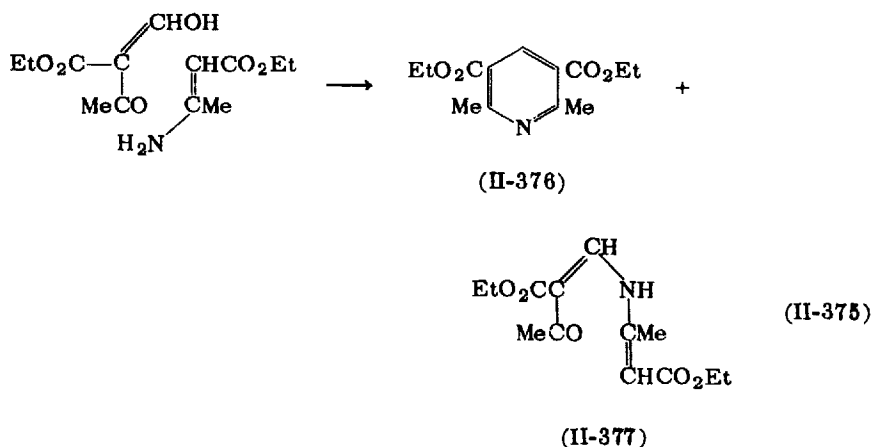


(II-372)

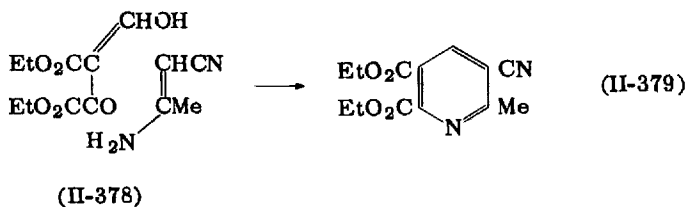
Reaction of 2-oxalylcyclohexanones with enamines (II-373) has likewise given intermediates, to which structures such as II-374 have been assigned. In this case the elements of water remained bound throughout vigorous alkaline treatments which stripped off the carbethoxy groups; dehydration was finally effected by distillation over lead oxide (888).



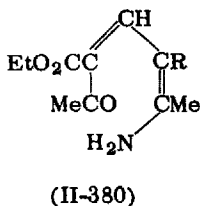
The reaction of *tricarboxyl* compounds, containing an aldehyde function, with enamine compounds is apt to be complicated (II-375) (566). Besides the normal product (II-376) in 30% yield, there is obtained a 25% yield of an iminodiacrylic ester (II-377) formed



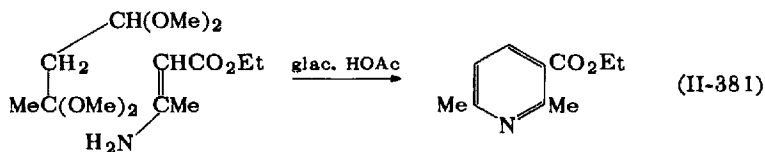
by nucleophilic attack of the *nitrogen* on the aldehyde group. This acid-catalyzed addition proceeds under the influence of the acidic tricarbonyl compound itself. As the acidity of the latter is further increased, in II-378, this becomes the exclusive reaction, and no pyridine is formed with most enamine compounds *e.g.*, with β -aminocrotonic ester (572). Even II-378, however, reacts with β -aminocrotononitrile to give a pyridine (II-379), in 38% yield, perhaps because the cyano group, as a powerful electron sink, deactivates the amino nitrogen as a nucleophile. The high acidity of II-378 is still evident in its ability to catalyze the hydrolysis of the enamine to ammonia, and a by-product of reaction II-379 is therefore the ammonium salt of II-378, in 37% yield. It is of interest that when the acidity of these tricarbonyl compounds is eliminated by forming the enol ethers, reaction with enamines gives normal pyridines in high yield (p. 372).



A further question presented by tricarbonyl compounds concerns the ring-closure. When a ketonic and an ester carbonyl are both available for this purpose, as in II-380, it is the former which cyclizes since it has the more electrophilic carbon. This preference is common to all pyridine syntheses where pertinent.

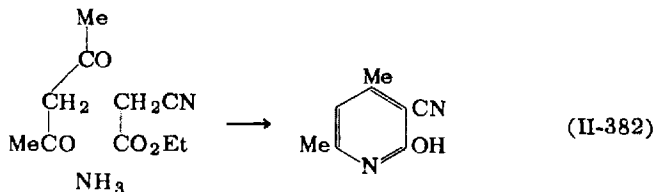


A ketal-acetal may replace a β -ketoaldehyde in reactions with enamine compounds (II-381) (1573). This avoids trimerization of

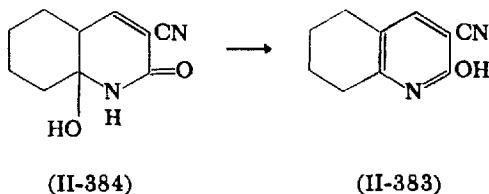


the ketoaldehyde to a 1,3,5-triacylbenzene. Probably the enamine attacks the acetal group directly, displacing methoxide; the acetal, with a more electrophilic carbon, would react before the ketal, and become C₄ of the pyridine ring.

(3) *With Methylenic Esters.* The condensation of 1,3-diketones, ethyl cyanoacetate, and ammonia or amines is one form of the *Guarreschi Synthesis* (II-382) (706). It is usually run in aqueous or alcoholic ammonia (or amine solution) at room temperature, or with gentle warming, but temperatures up to 250° in a sealed vessel have been used (876) (Table II-79). Under all conditions both components react rapidly with ammonia to form the diketone imine and cyanoacetamide, which are no doubt the condensing species.

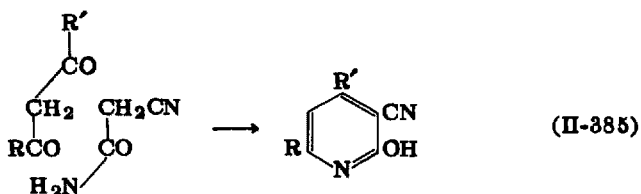


From benzoylacetone a mixture of isomeric pyridinols was obtained (306), showing that both keto groups are reactive in the initial condensation. 2-Hydroxymethylenecyclohexanone gave only one pyridinol (II-383), indicating that the formyl group is by far the more reactive of the carbonyls. In the latter case isolation of an intermediate (II-384) was also reported (1353), to be discussed in the next section.

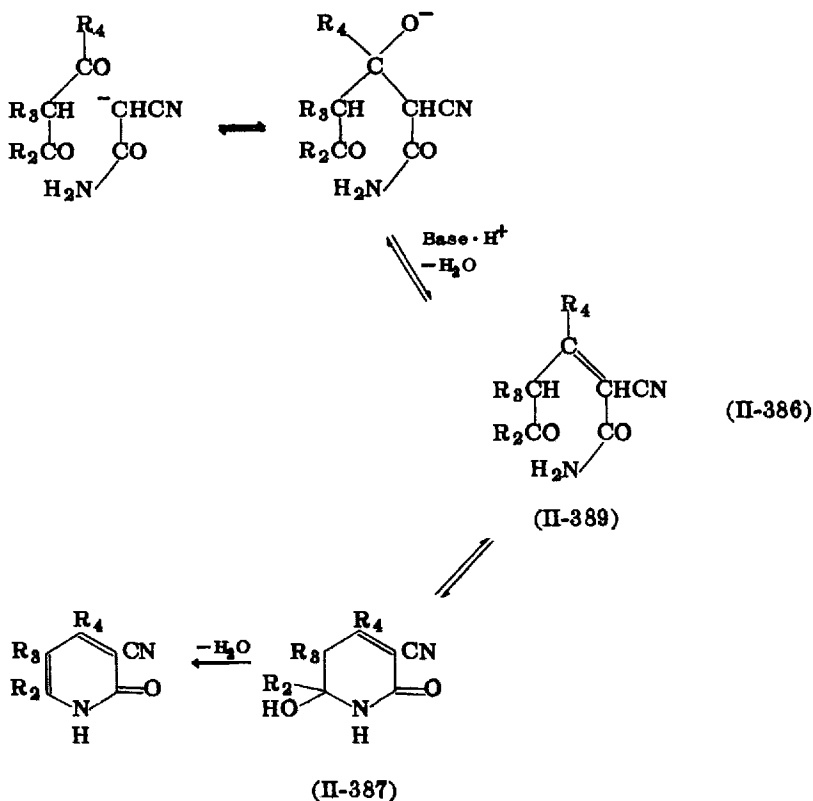


In the absence of ammonia an "abnormal" reaction occurs with cyanoacetic ester which involves cyclization through the cyano group. Such condensations are considered elsewhere (p. 368).

(4) *With Methylenic Amides.* The condensation of 1,3-dicarbonyl compounds with cyanoacetamide is by far the most common synthesis of pyridines from acyclic components (II-385). It has been applied to numerous 1,3-dioxo compounds, and proceeds under mild conditions in good to excellent yields. In some cases malonamide or *N*-methylcyanoacetamide has served as the methylenic amide. Usually piperidine or diethylamine is the catalyst, in alcoholic medium, but piperidine acetate, sodium ethoxide, anhydrous potassium carbonate, ammonia, and aqueous alkali have also been used, in a suitable solvent, or the sodium salt of cyanoacetamide has itself been reacted in benzene. A report of comparative yields from ethyl acetylpyruvate showed for piperidine, 15%; sodium ethoxide, 65%; and potassium carbonate in acetone, 82% (1427) (Tables II-80 and II-81).



The course of the reaction may be deduced from the pyridinol isomers obtained (II-386). If the first step is a Knoevenagel condensation as shown, it is the more polarized keto group which reacts, accepting attack by the cyanoacetamide anion; it therefore supplies C₄ of the pyridine ring. It is of interest that this step proceeds with small concentrations of the reactive species. The dioxo compound is by far a stronger acid than cyanoacetamide; under basic conditions, therefore, only small concentrations of unionized dioxo and ionized cyanoacetamide are available. The dioxo compound plays the acceptor role, however, since its carbonyl group is more polarized than the amide. Quite likely self-condensation of the dioxo compound also occurs, but this is reversible, while pyridinol formation is irreversible in its last step.

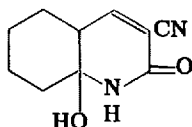


The yield of pyridinol has been shown to be pH-dependent. Thus the yield from acetylacetone and cyanoacetamide in aqueous buffers goes through a maximum of 74% at pH 9.1 (1520). This is no doubt a composite effect which only in part arises from the equilibrium of the first step.

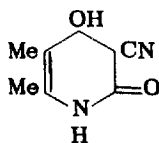
The initial condensation may also be considered as a Michael-type addition of cyanoacetamide to the double bond of the enol species (p. 356), in which case the basis for preference between the two possible enolic species is not at all clear. A good deal of the early literature was concerned with the question of whether the condensation was indeed Knoevenagel or Michael in nature (309,314, 664,1353,1354,1361). No firm evidence was advanced, however.

As regards the cyclization step, intermediates have occasionally been isolated for which structures II-387 have been assumed. These

were obtained from the reaction of cyanoacetamide, under piperidine catalysis, with the 2-hydroxymethylene derivatives of cyclohexanone (giving II-388) (1353), cyclopentanone (1221), cyclopentadecanone (1340), and indanone (516). All were converted to pyridinols by vigorous acid treatment, usually with hydrolysis or loss of the cyano group. The structures II-387 have not been well established, nor adequately distinguished from the open-chain isomers II-389. Indeed it is likely that a tautomeric mixture of these ring-chain forms is the true composition. A somewhat different structure (II-390) was preferred in another case, on the basis of ease of acetylation (1362). It correct this would imply that cyclization can occur before the first dehydration step, a point which is by no means settled.



(II-388)



(II-390)

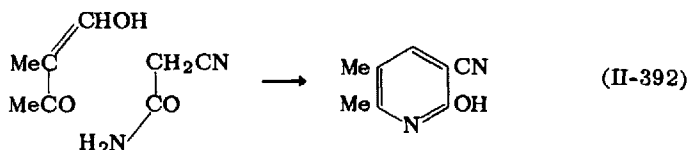
The variety of 1,3-dioxo compounds which have been reacted with cyanoacetamide will now be considered.

Nitromalonaldehyde gives a nitropyridinol (II-391) in 93% yield, a rare example of the preparation of a nitropyridine from acyclic materials (1229).



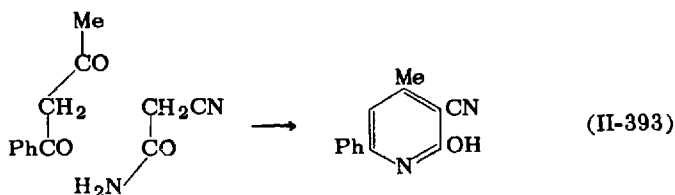
(II-391)

β -Ketoaldehydes (II-392) are preferably handled as the sodium salts, added to an aqueous solution of piperidine acetate. This gives a higher yield than the addition of the free enol to piperidine (compare reference 1103 with 1362), in which case considerable amounts of 1,3,5-triacylbenzene may be formed (1361). As usual the aldehyde group condenses before the ketone and supplies C_4 to the pyridine ring.



The β -ketoaldehydes are prepared from ketones by formylation with ethyl formate and sodium. When the ketone is unsymmetrical the position of formylation has been determined by proving the structure of the pyridinol obtained with cyanoacetamide. Thus methyl ethyl ketone has been shown to formylate on the methylene group (781,1362); methyl propyl ketone on the methyl, with some methylene formylation (1111,1469); methyl *i*-butyl ketone on the methyl (1103); methyl phenethyl ketone on the methyl (354); and ethyl butyl ketone on the methylene of the shorter alkyl (1083).

When 1,3-diketones react with cyanoacetamide the more polar carbonyl reacts first and becomes C_4 . Thus benzoylacetone gives the 4-methylpyridinol (II-393) and a much smaller amount of the

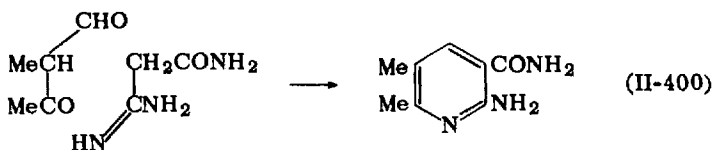
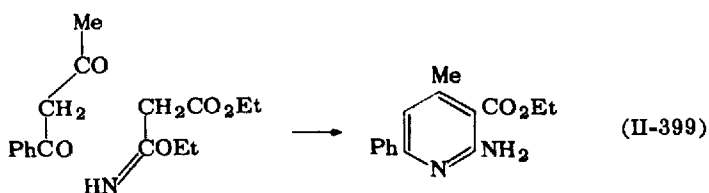


isomeric 4-phenyl-6-methyl-2-pyridinol (309); in the case of *p*-toluylacetone the isomer amounts to 10% of the yield (314). When the symmetry is greater, as in *p*- $\text{MeC}_6\text{H}_4\text{COCH}_2\text{COPh}$, the two isomers are formed in more nearly equal amounts (310). In the diketone $\text{MeCOCH}_2\text{COCH}_2\text{OR}$, a type which has often been used, the alkoxy group exerts an inductive effect on the nearer carbonyl, favoring formation of the 4-alkoxymethylpyridinol (II-394). The structure of II-394 has been proved by conversion to the 3,4-lactone (II-395) (357). A small amount of the 6-alkoxymethyl isomer is formed at the same time (584,1234). 2-Acetylcyclohexanone has also given two isomers, whose yields and structures were not reported (664).

with reference 1091). The derivatives react in the same sense as the ketoaldehydes themselves; that is, the acetal group, as the more polarized, reacts first and enters the C₄ position. It is likely that condensation and cyclization occur by direct displacement of alkoxide ions.

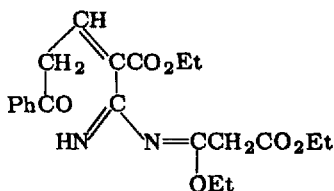
The use of *N*-methylcyanoacetamide in condensations with dioxo compounds gives, as expected, the 1-methylpyridones (309,314). On the other hand α -methylcyanoacetamide should not give a pyridine, nor did it with acetylacetone (1354). 2-Acetylcyclohexanone, however, was said to give the same pyridinol with α -methylcyanoacetamide as with cyanoacetamide (664), a reaction which is quite unusual since it involves elimination of methanol.

(5) *With Methylenic Imidates and Amidines.* 1,3-Dioxo compounds have been condensed with an imide (iminoether) or an amidine (II-399, II-400) (1172). In either case one obtains a 2-aminopyridine, a product not often formed from acyclic components. The imide is reacted without solvent or added catalyst; the amidine hydrochloride may be added to the sodium salt of the dicarbonyl compound in alcohol, with or without addition of a basic catalyst (Table II-82).



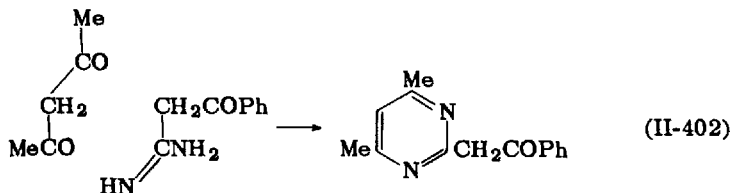
In the imide reaction the 2-amino group apparently arises from a second mole of imino-ether which attacks the first imide group at some stage. Thus, Dornow and Neuse (1172) isolated an inter-

mediate thought to be II-401, since on warming in alcohol it liberated malonic ester.



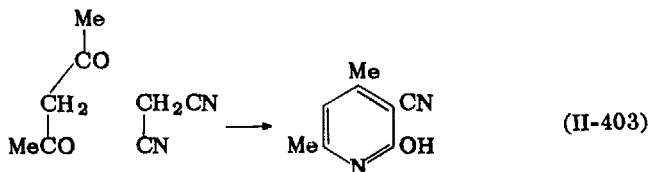
(II-401)

Ethyl benzoylacetimide and benzoylacetimidine give pyrimidines rather than pyridines (II-402); the imide is thought to disproportionate first to form ester and amidine, and the latter cyclizes.



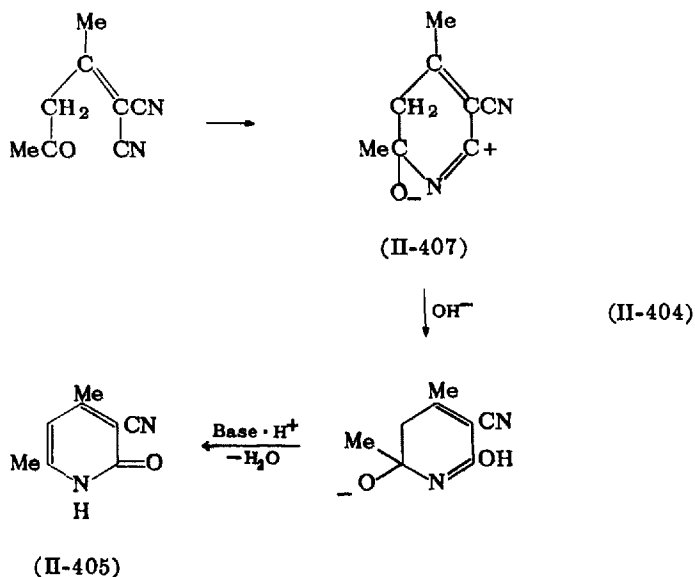
(II-402)

(6) *With Methylenic Nitriles.* 1,3-Dioxo compounds have been condensed with malononitrile or cyanoacetic ester in a few instances in which the cyano group has supplied the ring nitrogen (II-403) (310) (Table II-83). The reaction, catalyzed by organic bases, gives pyridinols, which means that water eliminated in the primary condensation must re-enter at a later stage. The cyano group acts as a nucleophile (II-404).

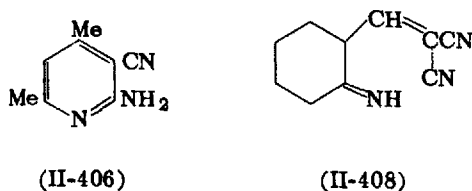


(II-403)

This reaction with malononitrile (II-403) occurs also when a small amount of ammonia is the catalyst (348). However, in the

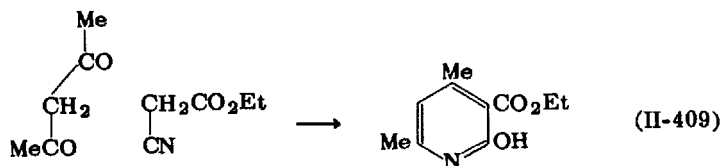


presence of excess ammonia in methanol various products are reported, depending on the order of addition (876). With all reagents present initially, the product is the pyridinol (II-405) as before. If the diketone and ammonia are allowed to react first, before addition of malononitrile, a significant yield of the 2-aminopyridine (II-406) is also obtained, such being the exclusive product in the case of 2-hydroxymethylenecyclohexanone. We may interpret this as attack of ammonia in place of hydroxyl at the positive carbon of II-407, though it is not clear why the order of addition should matter. Dornow and Neuse assumed that the imine of the dioxo compound was first formed and condensed through an intermediate such as II-408; the imino nitrogen was then the nucleophile in cyclization. This explanation holds if the *di*-imine is first formed: a *mono*-imine

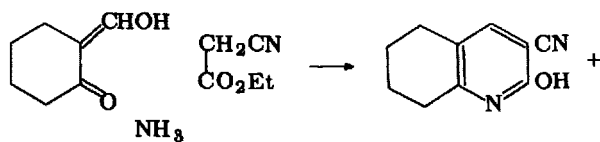


would be of the aldehydic variety (aminomethylenecyclohexanone) and would lose ammonia again during the primary condensation. A patent (1268) on the condensation of a diketone imine with malononitrile reports only the pyridinol product.

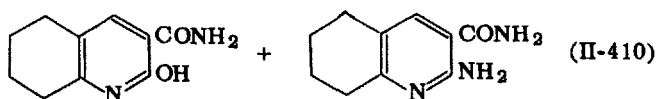
When ethyl cyanoacetate is the methylene component, cyclization may again occur through the cyano group, provided ammonia is absent (organic base as catalyst) (II-409) (1159,460), or present in small amount (876). If ammonia is added subsequently the carboxy group is converted to carbamoyl (458,1418). However when a large excess of ammonia is present initially, the cyanoacetic ester is rapidly converted to cyanoacetamide, and this undergoes its



normal condensation to a cyanopyridinol (p. 362). In one instance three different products were isolated by Dornow and Neuse (876) from the reaction of ethyl cyanoacetate, 2-hydroxymethylenecyclohexanone, and excess ammonia, in aqueous methanol for eight days (II-410). The hydroxynitrile (II-411) (30–40% yield) arose from the usual conversion to cyanoacetamide, with ring closure by



(II-411)

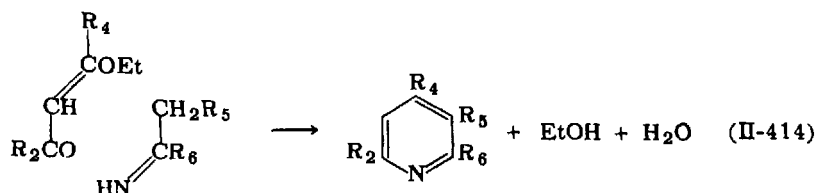


(II-412)

(II-413)

the *carbamoyl* group. The hydroxyamide (II-412) (15%) involved ring-closure by the *nitrile* group of ethyl cyanoacetate, with amidation occurring later. Finally, the aminoamide (II-413) (10–15%) also involved cyclization through the nitrile, with entrance of *ammonia* at the appropriate stage (as in II-406).

(b) **Enol Ethers of 1,3-Dioxo Compounds and Their Acetals.** Enol ethers may be used in place of the free dioxo compounds in condensations with methylene components (II-414). Since the double bond is now fixed, reaction can only be by Michael-type addition; no hydrolysis to the free dioxo compound is possible under the anhydrous conditions employed. That reaction does indeed occur at the double bond and not at the remaining carbonyl group can be demonstrated from the nature of the pyridine isomers obtained.

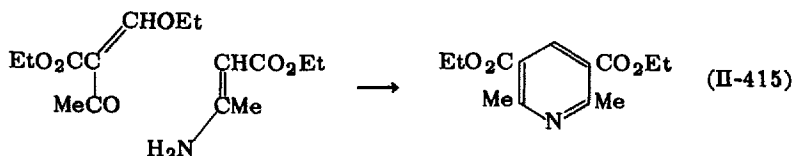


The enol ethers have been prepared by reaction of the dioxo compounds with an alcohol in the presence of an acid catalyst and ethyl orthoformate (Claisen method). However one cannot predict which enolic form will become etherified; thus, benzoylacetone forms $\text{PhCOCH}=\text{CMeOEt}$ (through its more enolic carbonyl), (309), while ethyl acetylpyruvate forms $\text{MeC(OEt)}=\text{CHCOCO}_2\text{Et}$ (through its less enolic carbonyl) (1427). In the latter case the structure of the pyridine was used to prove the structure of the enol ether, and Michael addition was assumed. An unequivocal preparation is from an α,β -dibromoketone by treatment with alcoholic potassium hydroxide; this gave $\text{PhC(OEt)}=\text{CHCOMe}$, isomeric with the ether above (309).

The enol ethers were first used in studies of mechanism, as models for the dioxo compounds with fixed double bonds. Though their value for this purpose was dubious they do have certain

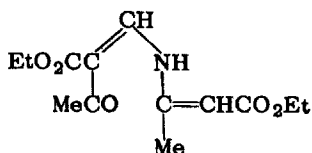
practical advantages. They give single pyridine products where the dioxo compounds may give mixtures of isomers (310). They can be used to "reverse the activity" of a 1,3-dioxo compound; thus benzoylacetone gives one pyridine isomer while its appropriate ether gives another (309). Finally they are convenient stable forms of the enolic aldehydes; malonaldehyde in particular is best handled as its enol ether acetal, $\text{EtOCH}=\text{CHCH}(\text{OEt})_2$.

(I) *With Methylenic Ketimines.* The enol ethers react with enamine compounds, such as β -aminocrotonic ester, without catalyst (II-415) (566), though occasionally sodium ethoxide or glacial acetic

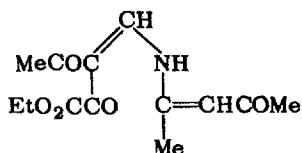


acid has been used. The yields by all three methods were the same in one case (566), but in another sodium ethoxide failed, while acetic acid was effective (516) (Tables II-84 and II-85). We may assume that under basic conditions the nucleophilic species is the carbanion of the methylene compound, while under neutral or acid conditions it is the unionized, but polarized, enamine itself, $^+\text{H}_2\text{N}=\text{CMeCH}-\text{CO}_2\text{Et}$.

A by-product which may be formed under neutral conditions is a substituted divinylamine (II-416). This appears in 8% yield in reaction II-415, but is a significant product in another case (II-417).



(II-416)

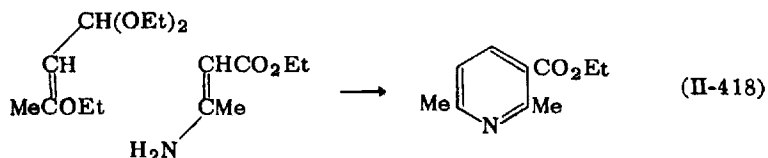


(II-417)

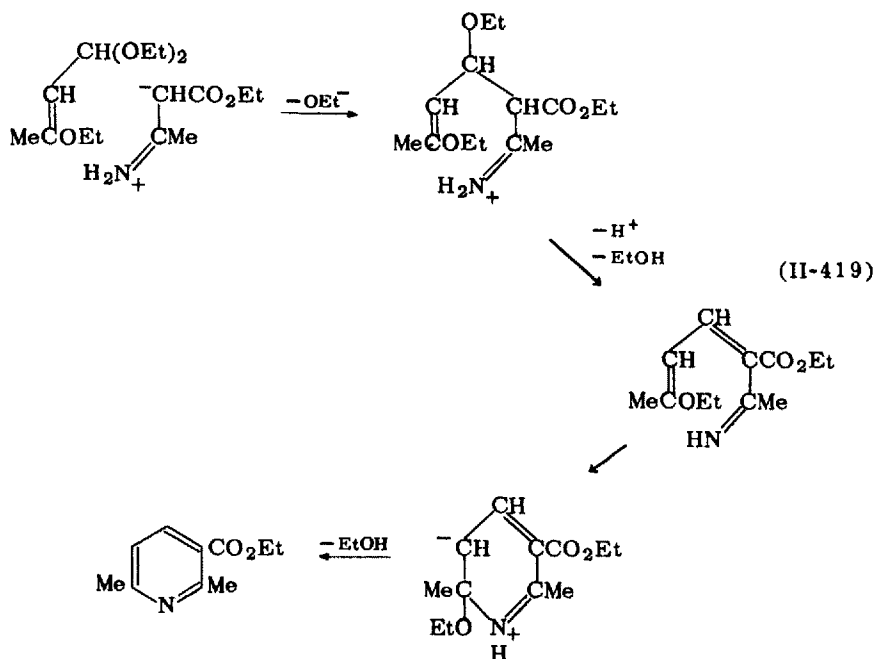
Such compounds arise from attack of the *nitrogen* on the enolic carbon. It will be recalled that when the corresponding hydroxymethylene compounds were used instead of the ethers, such divinylamines were often the exclusive products (p. 359).

An important class of enol ethers are the enol ether acetals, spe-

cifically, β -ethoxyacrolein diethyl acetal, $\text{CH}(\text{OEt})=\text{CHCH}(\text{OEt})_2$, which is in effect a stabilized form of malonaldehyde, and its homolog, β -ethoxycrotonaldehyde diethyl acetal, $\text{MeC}(\text{OEt})=\text{CHCH}(\text{OEt})_2$. These condense in an opposite sense from other enol ethers (II-418)



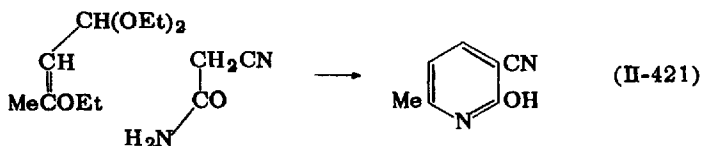
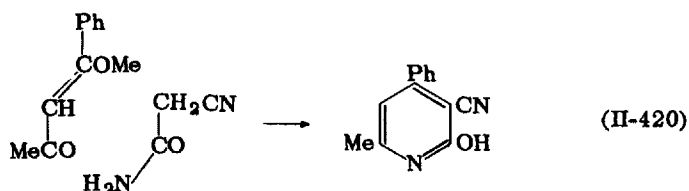
(359), i.e., the *acetal* carbon reacts with the methylene group, and so becomes C_4 of the pyridine ring. This exceptional behavior is perhaps explained by the fact that the acetal group can exert only an inductive effect, and thus activates the olefinic bond less than a conjugated free carbonyl group. Accordingly acetal reaction occurs in preference to Michael-type addition. The reaction proceeds without added catalyst, no doubt by displacement of ethoxide ion (II-419); β -elimination of a second ethoxide ion occurs at the elevated



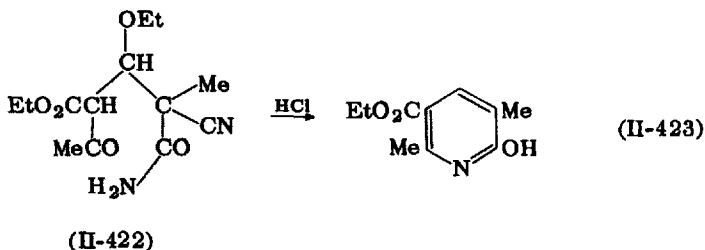
temperature. It is, of course, possible that the *first* step is the attack of nitrogen on the enolic carbon. However this could not explain the analogous condensation with cyanoacetamide (see next section), where under basic conditions the nucleophilic agent can only be a carbanion.

(2) *With Methylenic Esters and Amides.* One example has been reported of the condensation of an enol ether (ethoxymethyleneacetoacetic ester) with ethyl cyanoacetate in excess ammonia (1353) (Table II-86). The product is identical with that given by cyanoacetamide (see below).

Enol ethers react with cyanoacetamide in the presence of a basic catalyst, which may be piperidine, diethylamine, sodium ethoxide or potassium carbonate (Table II-86). The primary attack is on the enolic carbon (II-420) (309), except in the case of enol ether acetals where it is on the acetal carbon (II-421) (356).

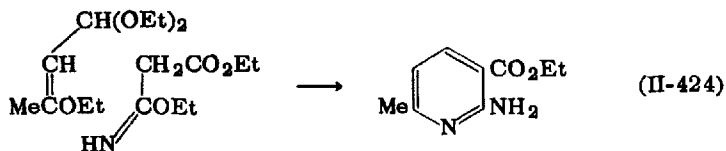


When α -methylcyanoacetamide was a reactant, an intermediate, presumably II-422, was isolated (141). This could be cyclized to the pyridinol by heating in acid, with loss of the cyano group (II-423).

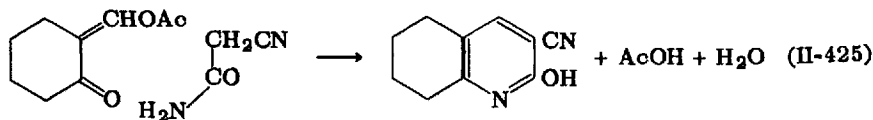


The intermediate, which still retains an ethoxy group, lends support to the idea that the first step in enol ether condensations is addition to the double bond.

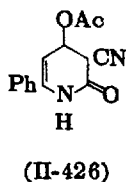
(3) *With Methylenic Imidates and Amidines.* Enol ether acetals, $RC(OEt)=CHCH(OEt)_2$ have been condensed with a methylenic imidate (II-424) (1254), and with a methylenic amidine (1423) (Table II-87). As usual the acetal group is the primary target of condensation, and becomes C₄ of the pyridine. The product is a 2-aminopyridine, whether one starts from the amidine or the imidate (imino-ether). In the latter case, a second mole of imidate is required to supply the 2-amino group (p. 367).



(c) *Enol Acetates of 1,3-Dioxo Compounds.* Enol acetates have occasionally been used in reactions with cyanoacetamide in the presence of sodium ethoxide (II-425) (1353) (Table II-86). There is



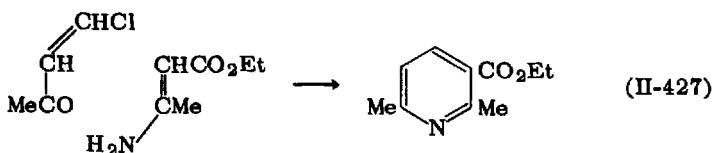
no synthetic advantage over the use of the dioxo compounds themselves, this early work having been done for the study of mechanisms. In two cases, the acetoxy group was retained in the product as isolated (II-426) (1361); aqueous alkali then gave the pyridinol. If



this structure is correct, it indicates that cyclization can occur immediately after the primary condensation, and before loss of acetic acid (or water, or alcohol, in analogous condensations).

(d) **β -Chlorovinyl Ketones.** The β -chlorovinyl ketones, $\text{RCOCH}=\text{CHCl}$, may be considered as enolic derivatives of β -ketoaldehydes, and as such enter into analogous condensations (Table II-88). They have been prepared in good yield by the condensation of acid chlorides, RCOCl , with acetylene in the presence of aluminum chloride.

The chlorovinyl ketones react with acetoacetic ester and acetylacetone in excess ammonia (624,1479), and also with β -aminocrotonic ester (II-427) (624) and other enamine compounds



(1816) without catalyst or solvent; the yields are usually good. It may be presumed that the mechanism is the same as for the enol ethers, except that a chloride ion is ejected after initial condensation on the double bond.

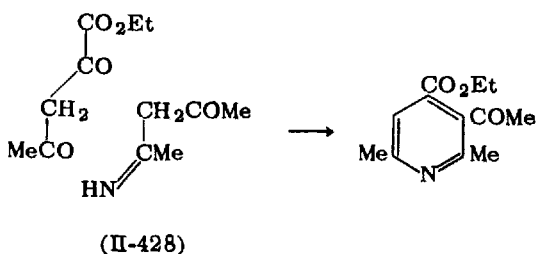
(e) **Imines of 1,3-Dioxo Compounds.** The imine derivatives of 1,3-dioxo compounds, *e.g.*, acetylacetoneimine, may be condensed with suitable methylenic compounds to give pyridines. Here the imine derivative acts as the *three-carbon* component in a 3-2 synthesis. We have already seen how such compounds, and other "enamine compounds," are used as *two-carbon* components.

The imine derivatives (enamines) are commonly prepared by ammonolysis of the dioxo compounds, preferably under anhydrous conditions. The more polarized carbonyl group is converted to the imine. They have also been prepared from enol ethers, β -chlorovinyl ketones, and acetylenic ketones by reaction with ammonia, and by special methods.

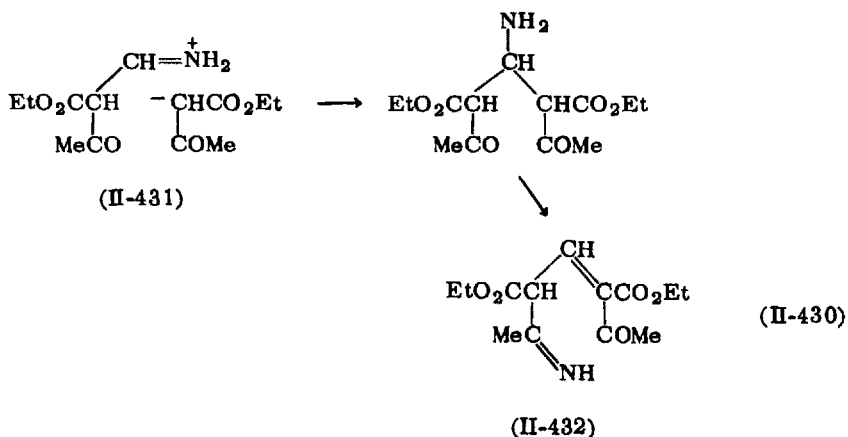
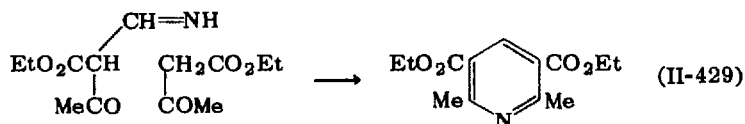
The mechanism of these enamine condensations is often obscure, and two types of product are observed, depending on whether the aminated carbon or the carbonyl carbon unites with the methylene group of the other reactant.

(1) *With Methylenic Ketones.* The imines of 1,3-diketones have been encountered as two-carbon components when the other re-

actant had a highly polarized carbonyl group (p. 357). Thus in II-428 the α -keto group is highly active and is the *acceptor* in the initial condensation.



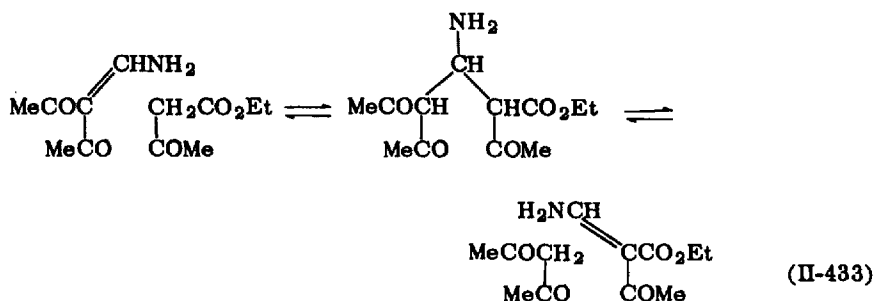
On the other hand β -ketoaldehydes act as three-carbon components (Table II-89) with acetoacetic ester (II-429) (1428). The reaction proceeds, in low yield, without solvent or catalyst, at 160° , and may follow the path II-430. We may assume that the aldimine first abstracts a proton from acetoacetic ester, becoming an aldiminium group (II-431), and that this group is more highly polarized than the carbonyl groups of acetoacetic ester; it is therefore the acceptor in the initial condensation. When this step is complete



ammonia is eliminated thermally, but must re-enter at a new position, forming a new imine (II-432) which closes the ring.

The same reaction occurs with cyclohexanone or acetone in place of acetoacetic ester, but in the case of acetone the yield is very low indeed.

A side reaction with aminomethylene compounds appears to involve a reversal of the primary condensation step. This is of consequence when two dissimilar reactants are used (II-433); the main product is then the symmetrical pyridine (II-434), only a small yield

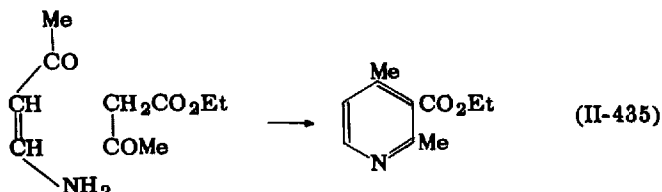


of the normal product being obtained. Henecka assumed that II-434 arose by hydrolysis of the initial aminomethylene compound to formamide, which then recombined with two moles of acetoacetic ester. A separate experiment showed that formamide did react with acetoacetic ester to give II-434 (1428); however, the yield was extremely low.

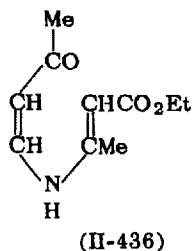


(II-434)

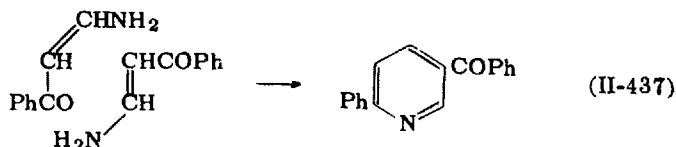
An entirely different reaction was observed when acetyl-acetalimine was condensed with acetoacetic ester (II-435) (624).



Here the aminomethylene group assumed the C₆ position in the pyridine ring. The starting material differs from previous aldimines (as in II-429) in the absence of an electron-withdrawing group from the α position. The mechanism of this reversed orientation is obscure. It may be that the keto group of acetylacetalimine is more electrophilic than the aldimine and reacts first with acetoacetic ester. On the other hand it is possible that primary attack is by the *nitrogen* on the keto group of acetoacetic ester, giving an intermediate II-436; the nitrogen would be more nucleophilic in the absence of an electron-withdrawing group from the α position.



(2) *With Methylenic Aldimines.* The self-condensation of a β -ketoaldehyde is reported in one case (II-437) (605), carried out under

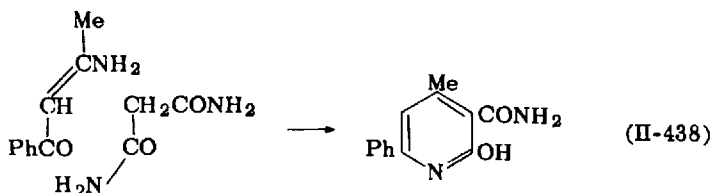


acid catalysis (sulfuric acid in aqueous acetone); the electrophilic species is presumably the conjugate acid of the aldimine (Table II-89).

(3) *With Methylenic Esters, Amides, and Nitriles.* The imine derivatives of dioxo compounds have been used as three-carbon components with malonic ester, cyanoacetic ester, malonamide, cyanoacetamide, and malononitrile. The reactions have been run with sodium ethoxide as catalyst, with organic bases, or in the absence of a catalyst (Table II-90).

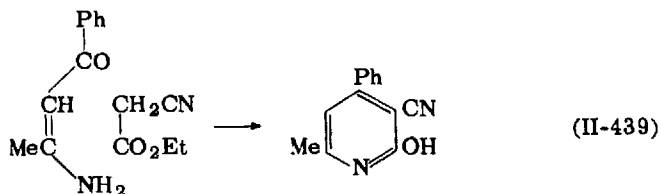
Though the products are all 2-pyridinols, an examination shows that at least three different mechanisms may operate, depending on the malonic acid derivative used.

With methylenic amides, namely, malonamide (372) and cyanoacetamide (1364,314,1361), the reaction follows a "normal" course in which the aminated carbon of the enamine compound becomes C₄ of the pyridine ring (II-438). The reactions are carried out without catalyst at temperatures of 125–185°. Probably the initial condensation is between the ketimine and methylene groups.



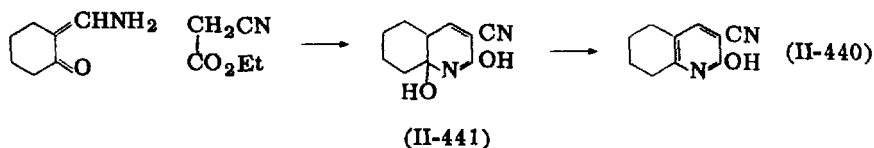
Some question arises as to which component contributes its nitrogen to the ring. Moir (1068) observed that when an *N*-methylamide was used, a 1-methylpyridone was obtained, whereas an *N*-methylimine gave the unalkylated pyridinol. This indicates that the ring nitrogen comes from the amide. However, Basu (372) found that whichever *N*-methyl derivative was used a mixture of the two products was obtained (ratios not stated). This indicates that both components can furnish nitrogen to the ring, and that the ammonia or methylamine eliminated in the primary condensation returns to a new position and participates to some extent in closing the ring.

When the methylene component was cyanoacetic ester, a different mode of condensation was observed by Basu (372) in the presence of sodium ethoxide (II-439). This may arise by attack of

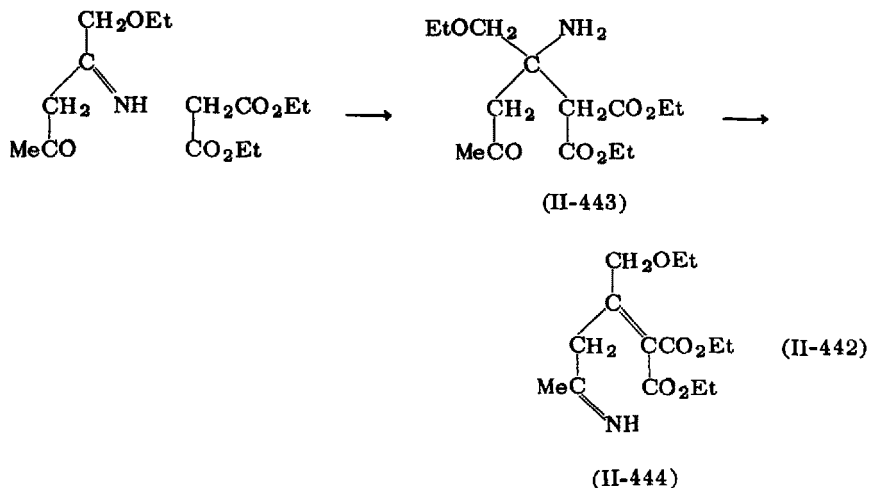


the imine group on the ester as a first step. The reason for the variable behavior of the same enamine compound in II-438 and II-439 is not clear, but the ester group would be more susceptible to nucleophilic attack than the amide. Moreover, in the presence of strong base the nucleophilic agent could be the anion, $\text{PhCO}-\text{CH}=\text{CMeNH}^-$. The situation is complicated by the results of Sen-Gupta (1353), who, using an organic base as catalyst, observed a

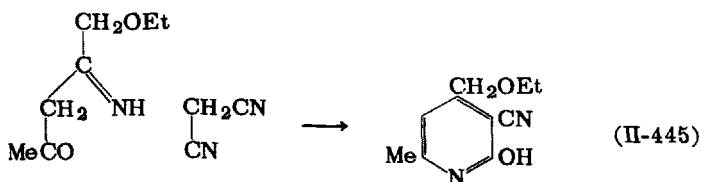
“normal” condensation with cyanoacetic ester (II-440). Here an intermediate, thought to be II-441, was isolated, which in acetic acid at 210° lost water to give the pyridinol.



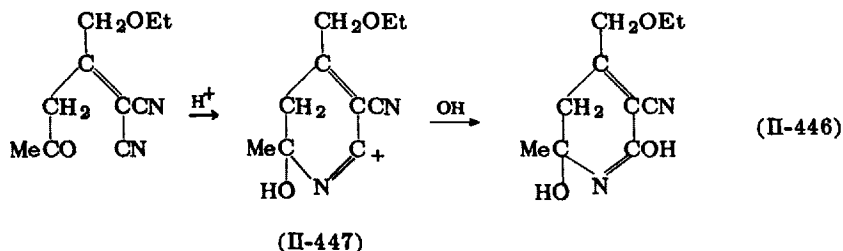
When malonic ester is the methylene component, with sodium ethoxide as catalyst, the orientation is again normal (II-442). Like all “normal” condensations, it requires the transfer of ammonia from its initial position to the final (II-443 and II-444). This reaction is described in the patent literature (1268,347,351), where the structure of the starting material is given incorrectly as $\text{EtOCH}_2\text{COCH}_2\text{-C(=NH)Me}$.



When the methylene component is malononitrile, then, according to patents (1268,1593), the orientation is normal (II-445), but a



third mechanism must be operating. The reaction proceeds at low temperature in water or alcohol, without added catalyst. Since the product is again a pyridinol one must assume that the *cyano* group initiates cyclization by nucleophilic attack on the carbonyl (II-446); hydroxyl ion then enters at the appropriate stage (II-447). If during



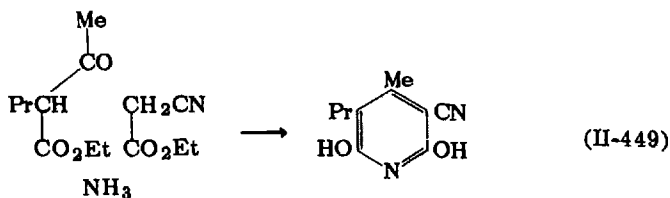
cyclization cyano were the acceptor, a 2-aminopyridine would result. Such a product (II-448) was indeed observed by Dornow and Neuse (876), when the imine of the diketone was prepared *in situ* (p. 369).



(II-448)

(f) β -Oxoesters and Their Enol Ethers. β -Ketoesters react as three-carbon components with methylene compounds which have less active carbonyl groups, commonly with ethyl cyanoacetate or cyanoacetamide.

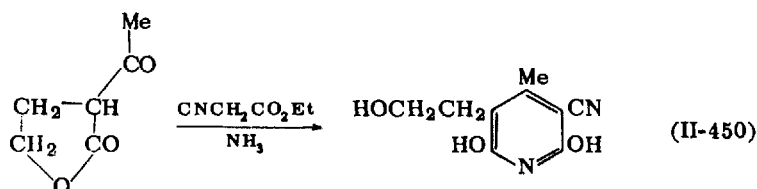
The reaction of β -ketoesters, cyanoacetic ester, and ammonia (or amines) was early investigated by Guareschi (II-449) (138,719). It is



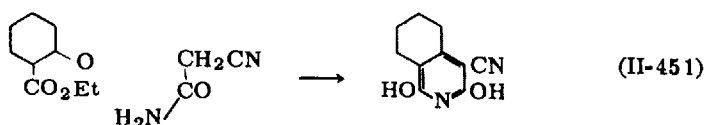
usually run in water at room temperature, but also in anhydrous methanol or without a solvent at temperatures up to 200° (876) (Table II-92). Since the keto group is the strongest electrophile present, it is the acceptor in the initial condensation, and the

products are 2,6-pyridinediols. Guareschi believed the condensing species to be the β -ketoamide and cyanoacetamide, formed *in situ*, since by substituting either of these compounds, or both, he obtained the same pyridine. Under the conditions some β -iminoester (*e.g.*, β -aminocrotonic ester) would also be formed *in situ* (881) but is not a likely reactant; its condensation with cyanoacetamide has been reported only under severe conditions (1364).

The condensation of a β -ketolactone with cyanoacetic ester and ammonia has also been reported (II-450) (856).

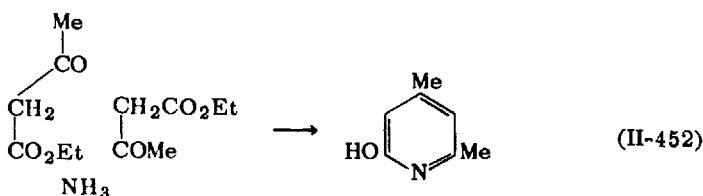


More commonly β -ketoesters are condensed with cyanoacetamide directly, using piperidine or sodium ethoxide as the catalyst (II-451) (1364). A variety of β -ketoesters and a β -ketolactone have been so reacted (Table II-93). When α -acetylacetoacetic ester is em-

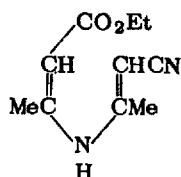
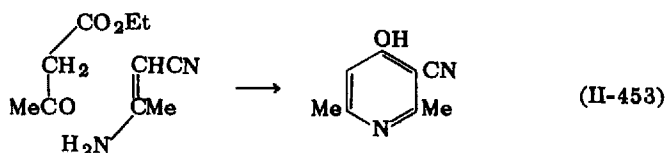


ployed, an acetyl group is lost by saponification, giving the same product as acetoacetic ester itself (1364).

Acetoacetic ester has served as both components in a 3-2 synthesis; its self-condensation in ammonia at 150° occurs with loss of a carbethoxy group (II-452) (1068) (Table II-91).



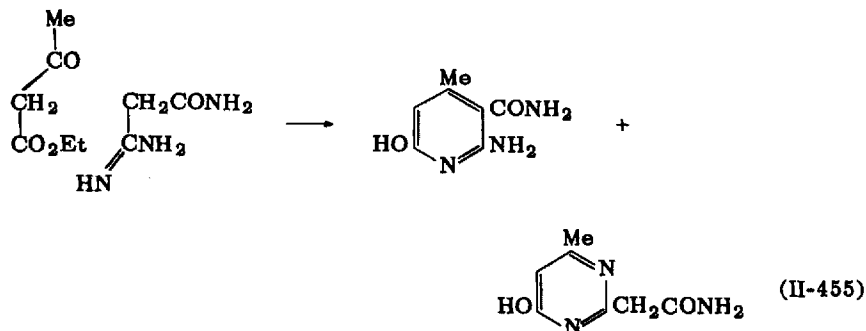
Acetoacetic ester has also been condensed with several methylenic ketimines (Table II-91), for example with diacetonitrile in the presence of piperidine (II-453) (1688,303,304). Here the reaction follows an "abnormal" course, and the product is a 4-pyridinol. We



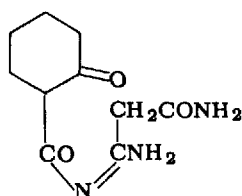
(II-454)

must assume that the first step is attack by amino nitrogen on the keto group, giving II-454, which cyclizes by a Claisen condensation.

Finally, acetoacetic ester has been reacted with a methylenic amidine (II-455), and a methylenic imidate, $\text{EtO}_2\text{CCH}_2\text{C}(=\text{NH})\text{OEt}$ (877) (Table II-94). As usual with these reagents, the product



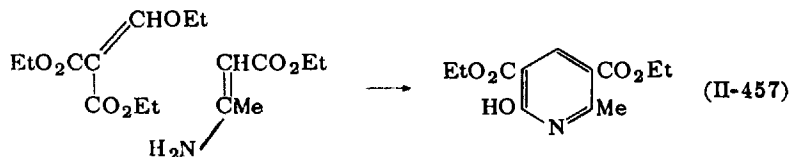
is a 2-aminopyridine, in low yield; in the case of the imidate a second mole of reagent is required to furnish the additional nitrogen (p. 367). With amidines a competing reaction is the formation of pyrimidines, which is indeed the major reaction of II-455, while benzoylacetamidine leads to pyrimidines exclusively (1172). An intermediate isolated in one case was thought to be II-456 on elementary analysis, and was converted to the expected 6-amino-2-



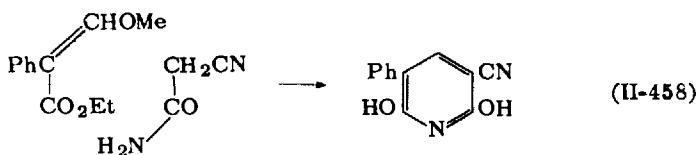
(II-456)

pyridinol by warming in glacial acetic acid. Such intermediates involve reaction of the ester group before the keto group, and would seem to be less likely than the Knoevenagel intermediates which we have been assuming in the general case.

The enol ethers of β -oxoesters have occasionally been used, in reaction with β -aminocrotonic ester (no added catalyst) (II-457) (362), or with cyanoacetamide (sodium ethoxide) (II-458) (1112). Presumably the methylenic compound first adds to the olefinic bond, with subsequent elimination of alcohol (Table II-95).

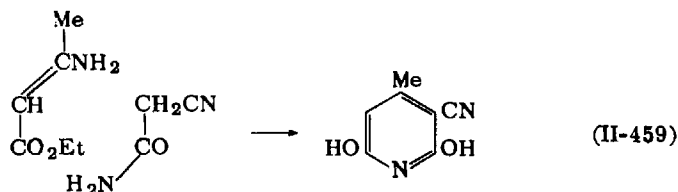


(II-457)



(II-458)

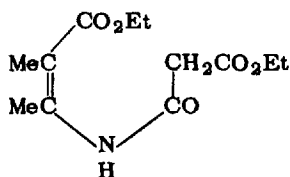
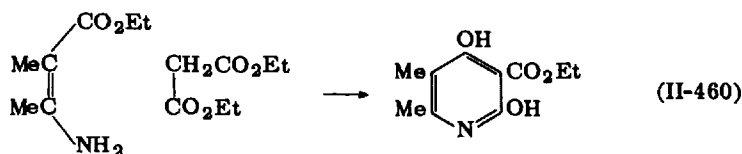
(g) **Imines of β -Oxoesters.** The imine derivatives of β -ketoesters and β -formylesters (*e.g.*, β -aminocrotonic ester) may be used as three-carbon components in 3-2 syntheses. Their reaction is "normal" with cyanoacetamide (II-459) (1364), that is, the first step is a con-



(II-459)

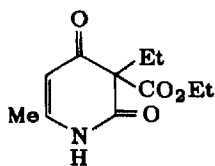
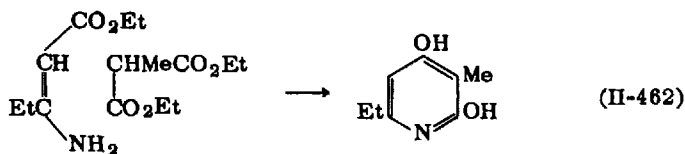
condensation between the ketimine group (or its conjugate acid) and the methylene group of cyanoacetamide, with elimination of ammonia. The products are 2,6-pyridinediols (Table II-97).

With other methylene components, however, a different mode of condensation is followed, and the mechanism is more obscure. Thus with malonic ester and sodium ethoxide catalyst, 2,4-pyridinediols are obtained (II-460) (344). Probably the first step is attack by the



(II-461)

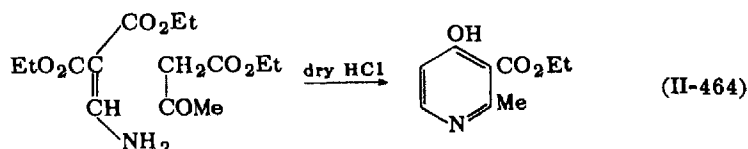
imine on the ester carbon (II-461); a Claisen condensation then closes the ring. However the reverse sequence of steps cannot be ruled out. The use of α -methylmalonic ester results in the loss of a carbethoxy group (II-462) (1256), and from α -ethylmalonic ester the



(II-463)

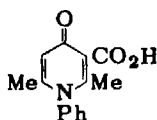
appropriate intermediate (II-463) was isolated, which lost its carbethoxy group on treatment with caustic soda (Table II-96).

A similar "abnormal" mode of condensation is observed when aminomethylenemalononic ester is reacted with acetoacetic ester (II-464) (362); under acid catalysis a carbethoxy group is lost; under

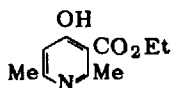


basic catalysis both are retained. Quite analogous is the reaction of β -anilinoacronic ester with acetoacetic ester, catalyzed by zinc chloride at high temperature, to give II-465 (Table II-98).

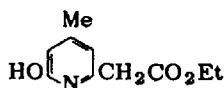
β -Aminocrotonic ester can undergo various self-condensations, assuming both roles in 3-2 syntheses. Depending on how they are carried out, both normal and abnormal condensations are observed (Table II-99). The destructive distillation of β -aminocrotonic ester gave 2-ethoxy-4,6-lutidine (690). Distillation *in vacuo* gave a small



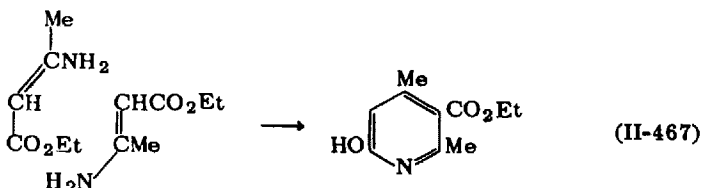
(II-465)



(II-466)

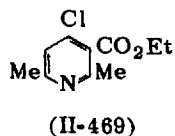


(II-468)

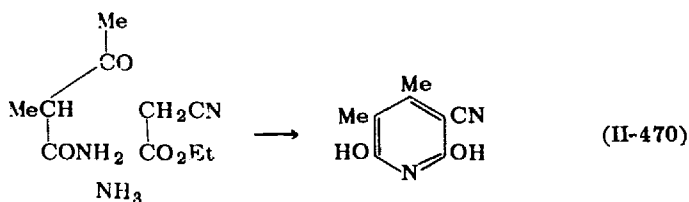


yield of II-466, which could be converted to 2,6-lutidine (255,686). An isomeric product was obtained in 40% yield by heating the hydrochloride of β -aminocrotonic ester at 120° (II-467) (1603,255), and its structure was proved by conversion to 4,6-dimethyl-2-pyridinol (1067). By heating equal moles of the hydrochloride and the free base, this product was again obtained together with a 33% yield of still another isomer, assumed to be II-468 since it could also

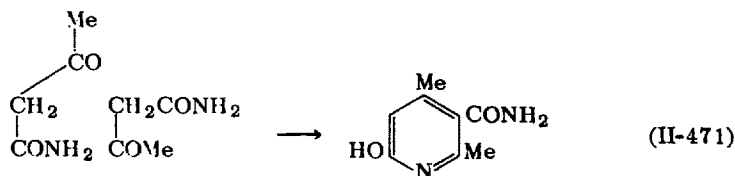
be degraded to 4,6-dimethyl-2-pyridinol (255,1603,1067). The formation of II-468 is unique in that it requires the two-carbon component to furnish its methyl group rather than its methylene to the pyridine ring. Finally, the self-condensation of β -aminocrotonic ester in phosphorus oxychloride gives a 4-chloropyridine (II-469) in 70% yield (241,242,1398,1595).



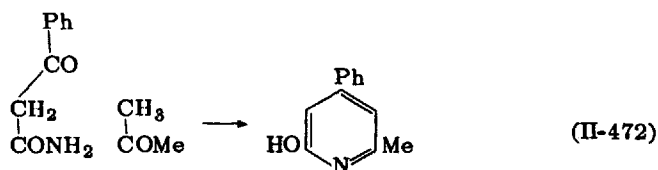
(h) **β -Ketoamides and β -Ketoacid Chlorides.** β -Ketoamides have been condensed as three-carbon components with cyanoacetic ester or cyanoacetamide in ammonia to give 2,6-pyridinediols (II-470) (344). Although the pure ketoamide has occasionally been used, it is more common to prepare it *in situ* by reacting the β -ketoester with concentrated aqueous ammonia (or amine), and filtering off the by-product, the β -aminoacrylic ester, which precipitates. The yields in the condensation are excellent (Table II-101).



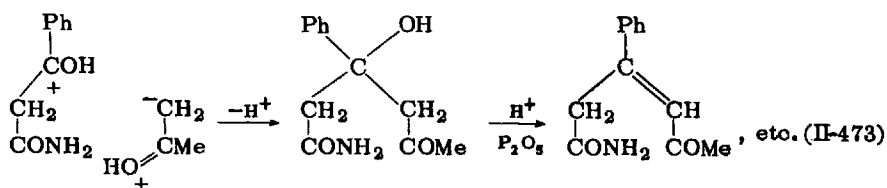
The self-condensation of acetoacetamide, on heating, has been reported (II-471) (881) (Table II-100).



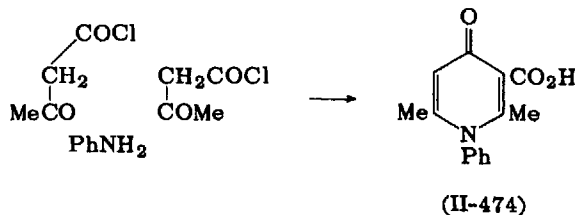
β -Ketoamides also react with acetone (II-472), (901) and with benzyl methyl ketone (886) to give 2-pyridinols (Table II-100). The syntheses are unusual not only in the "unactivated" ketones em-



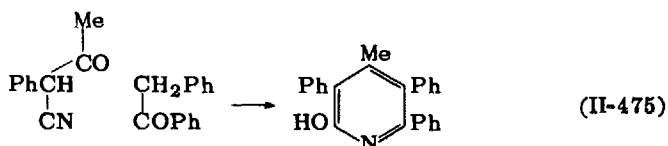
ployed, but also in the use of the acid catalysts, polyphosphoric acid, and concentrated sulfuric acid in acetic acid, respectively, which serve also as dehydrating agents (II-473).

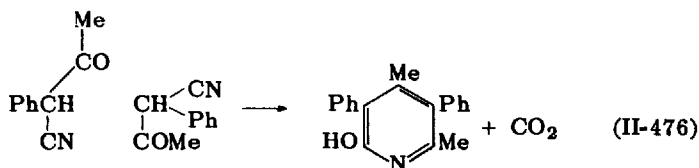


Acetoacetyl chloride readily undergoes self-condensation in the presence of aniline, the product said to be II-474 (361) (Table II-100).



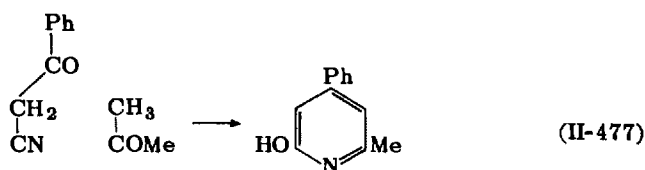
(i) **β -Oxonitriles and Their Enol Ethers and Imine Derivatives.** *β -Ketonitriles* have not been condensed with the common activated methylenic compounds, but rather with simple ketones, under acid catalysis, to give pyridinols (Table II-102). A number of α -phenyl- β -ketonitriles have been so reacted with benzyl ketones by heating with sulfuric acid, with or without acetic acid as solvent (II-475) (886). In the absence of a second component, in acetic acid medium, the β -ketonitrile undergoes *self*-condensation, with loss of a cyano



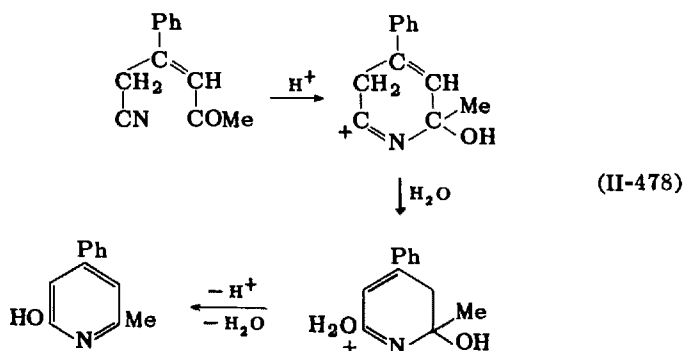


group (II-476). Such self-condensation may also occur as a side-reaction even when the benzyl ketone is present, as in the reaction of α -phenylbenzoylacetone nitrile with benzyl methyl ketone.

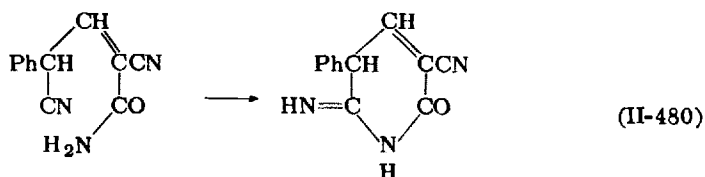
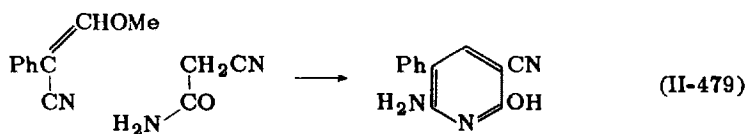
In analogous fashion, β -ketonitriles react with acetone, cyclohexanone, and benzyl methyl ketone in polyphosphoric acid (II-477) (901), and the self-condensation II-476 proceeds in this medium as well.



These acid-catalyzed condensations may well proceed through the β -ketoamide, whose formation from the β -ketonitrile has been demonstrated under the conditions. In that case the mechanism would be as in II-473. However, since the yield from the nitrile is higher than from the amide, a more direct mechanism would seem more likely (II-478). This involves nucleophilic attack by the nitrile group to close the ring; solvation of the carbonium ion then leads to a pyridinol.

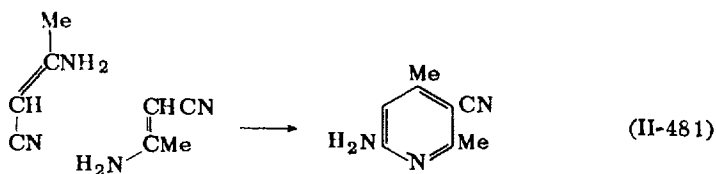


The *enol ethers* of β -oxonitriles have been reacted with cyanoacetamide, using sodium ethoxide as catalyst (II-479) (1112); the products are 6-amino-2-pyridinols in good yield (Table II-103). As usual we may assume a Michael-type addition to the enolic double



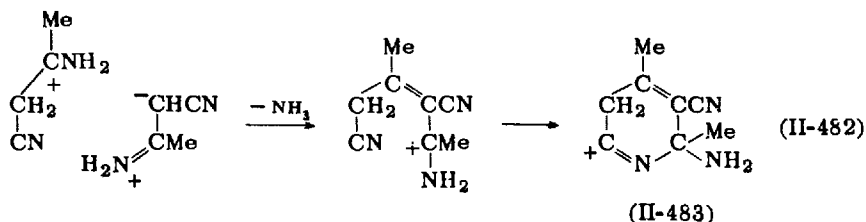
bond, with elimination of alcohol. Then, accounting for the 6-amino group, the ring is closed by attack of the carbamoyl group on the nitrile (II-480).

The *imine derivatives of β -ketonitriles (β -aminoacrylonitriles)* have been used as three-carbon components only in self-condensations (Table II-104). Thus, the self-condensation of diacetonitrile (β -aminocrotononitrile) proceeds at high temperatures without catalyst, or in the presence of organic acids, with or without a solvent (II-481) (303,1068,1688,1806). The products are 2-aminopyridines

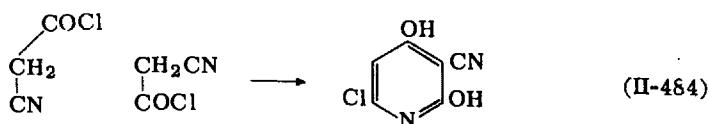


when water is rigorously excluded, otherwise they are 2-pyridinols; a 2-ethoxypyridine has also been reported in certain instances.

The normal mechanism of ketimine condensations is apparently followed (II-482). To explain the variable products we may assume that ring-closure is by nucleophilic attack of the nitrile on the remaining ketimine group. The resulting carbonium ion (II-483) is attacked by ammonia, water, or alcohol, as the case may be.



(j) **Malonic Acid Derivatives.** Malonic acid derivatives do not ordinarily act as three-carbon components in 3-2 syntheses. An exception is the self-condensation of cyanoacetyl chloride, which proceeds in 60% yield merely on storing the fresh compound for several days, with mild cooling (II-484) (301,302,713,1242). The prob-



able mechanism is shown in II-485 and employs the cyano group as a nucleophilic agent.

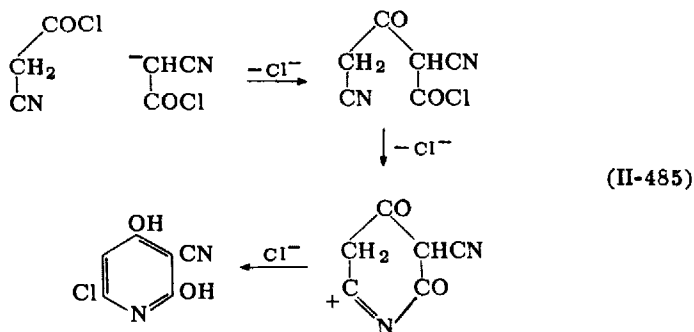
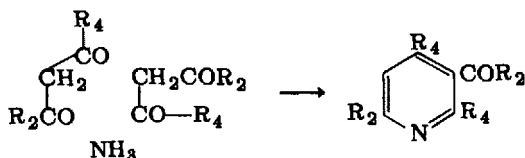


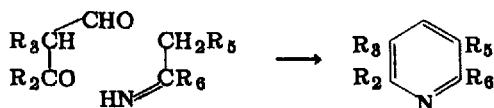
TABLE II-76. Self-Condensation of 1,3-Dioxo Compounds^a

R ₂	R ₄	Conditions	Yield, %	Ref.
Me	H	Na salt, NH ₄ OAc, HOAc, ether, 25°, 2 d.	40	296,297
Me	Me	NH ₄ OAc, water bath, 3-5 d. NH ₄ salt, NH ₃ , heat	75	1109 346
Et ^b	H ^b	Na salt, NH ₄ OAc, HOAc, ether, 25°, 2 d.		1270
Pr	H	Na salt, NH ₄ OAc, HOAc, ether, 25°, 2 d.		1249
CH=Me ₂	H	Na salt, NH ₄ OAc, HOAc, ether, 25°, 2 d.		1249
Ph	H	NH ₄ OAc, HOAc, ether, RT, 3 d.	40	296,297
CO ₂ H ^c	Me ^c	NH ₄ salt, heat dry	^c	208

^aOne example of the condensation of a β-ketoaldehyde with a *different* methylenic ketone has been reported (1592): Acetylacetaldehyde (Na salt) was condensed with ethyl acetoacetate and NH₄OAc in alc., at reflux, 4 hrs., to give ethyl 2,6-dimethylnicotinate (20% yield).

^bCrude formylation product of MeCOEt used, containing only very small amount of EtCOCH₂CHO.

^cProduct reported as 3-acetyl-4-methylpyridine-2,6-dicarboxylic acid; structure not proved.

TABLE II-77. Condensation of Malonaldehydes and β -Ketoaldehydes and Their Acetals with Methylenic Ketimines

R ₂	R ₃	R ₅	R ₆	Conditions	Yield, %	Ref.
Et	Me	COMe	Me		44	1288
	-(CH ₂) ₄ -	COMe	Me	Water bath, 8 hrs.		887
	-CH ₂ CHMe(CH ₂) ₂ -	COMe	Me			887
	-(CH ₂) ₂ CHMeCH ₂ -	COMe	Me			887
Ph	H	COMe	Me			1288
<i>p</i> -Tolyl	H	COMe	Me			1288
	-(CH ₂) ₄ -	COPh	Me	Alc., reflux, 12 hrs.		887
	-CH ₂ CHMe(CH ₂) ₂ -	COPh	Me	Alc., reflux, 16 hrs.		1707
	-(CH ₂) ₂ CHMeCH ₂ -	COPh	Me			887
Ph	H	COPh	Me			1288
<i>p</i> -Tolyl	H	COPh	Me			1288,366
Me ^a	H ^a	CO ₂ Et	Me	HOAc, 50-60°, 3 hrs.	35	1573
Me	Me	CO ₂ Et	Me		40	366
Et	Me	CO ₂ Et	Me			1253
	-(CH ₂) ₃ -	CO ₂ Et	Me	Water bath, 12 hrs.		888
	-(CH ₂) ₄ -	CO ₂ Et	Me	Steam bath, 8 hrs.		1707
				Ice cold 2-3 d., separating aq.	^b	888
				Ice cold 2-3 d., separating aq.	40 ^b	889

TABLE II-77 (Continued)

R ₂	R ₃	R ₅	R ₆	Conditions	Yield, %	Ref.
	-CHMe(CH ₂) ₃ -	CO ₂ Et	Me	Water bath, 10 hrs.	40	887
	-CH ₂ CHMe(CH ₂) ₂ -	CO ₂ Et	Me	Steam bath, 8 hrs.		1707
	-CH ₂ (CHMe) ₂ CH ₂ -	CO ₂ Et	Me	Water bath, 8 hrs.	33	887
Ph	H	CO ₂ Et	Me	Ether		193
Ph	Me	CO ₂ Et	Me		50	366,1288
<i>p</i> -Tolyl	H	CO ₂ Et	Me			366
H	NO ₂	CO ₂ Et	Me	Na salt, aq., 50°	35	1148
Me	CO ₂ Et	CO ₂ Et	Me	RT, 12 d.	30 ^c	566
	-(CH ₂) ₄ -	CN	Me	Water bath, 7 hrs.		887
CO ₂ Et	CO ₂ Et	CN	Me	Ether, 0.5 hrs.	38 ^d	572

^aKetal-acetal used, MeC(OMe)₂CH₂(OMe)₂.

^bThe intermediate, ethyl 6-hydroxy-2-methyl-5,6-tetramethyleno-5,6-dihydronicotinate was isolated, which, heated above m.p., gave the product in yield indicated.

^cBy-product, MeCOC(CO₂Et)=CHNHCMe=CHCO₂Et, in 25% yield.

^dBy-product, NH₄ salt of initial β-ketoaldehyde, in 37% yield.

TABLE II-78. Condensation of 1,3-Diketones with Methylenic Ketimines

$ \begin{array}{c} R_4 \\ \\ R_3CH-CO \\ \quad \\ R_2CO \quad CH_2R_5 \\ \quad \quad \\ \quad \quad OR_6 \\ \quad \quad \\ \quad \quad HN \end{array} \longrightarrow \begin{array}{c} R_4 \\ \\ R_3 \quad R_5 \\ \diagdown \quad / \\ \text{C} \\ / \quad \backslash \\ R_2 \quad R_6 \end{array} $						Ref.	
R_4	R_3	R_4	R_5	R_6	Conditions	Yield, %	Ref.
Me	H	Me	COMe	Me	ZnCl ₂ , 150–60°, 4 hrs. Long heating	77	1409 346
Me	H	CO ₂ Et	COMe	Me	Cold, 2 hrs., distil	65	199
Ph	H	CO ₂ Et	COMe	Me	RT, 4 d.	22	733
Me	H	CO ₂ Et	COPh	Me	RT, 4d.	60	199
Me	H	CO ₂ Me	CO ₂ Me	Me	Ether, anhyd. Na ₂ SO ₄ , cold 4 d., distil		1333
Me	H	CO ₂ Et	CO ₂ Me	Me	Ice bath overnight, warm, then in ether, anhyd. Na ₂ SO ₄ , 3 d.	75	1333
Me	H	CO ₂ Me	CO ₂ Et	Me	Ether, anhyd. Na ₂ SO ₄ , cold, 4 d., distil	60	1333
Me	H	CO ₂ Et	CO ₂ Et	Me	Ice bath overnight, then water bath	90	199
					Ether, anhyd. Na ₂ SO ₄ , ice bath, 24 hrs.	90	199
Et	H	CO ₂ Et	CO ₂ Et	Me	Ether, 15 hrs.	100 ^a	743
Pr ^b	H ^b	CO ₂ Et ^b	CO ₂ Et	Me	Cold overnight, then heat	80	199
					Cold overnight, then heat	89 ^b	199

<i>i</i> -Pr ^b	H ^b	CO ₂ Et ^b	CO ₂ Et	Me	Cold overnight, then heat	90 ^b	199
<i>t</i> -Bu	H	CO ₂ Et	CO ₂ Et	Me	Cold overnight, then heat	64 ^c	199
	-(CH ₂) ₄ -	CO ₂ Et	CO ₂ Et	Me	RT, 1 wk.	^c	888
	-CHMe(CH ₂) ₃ -	CO ₂ Et	CO ₂ Et	Me	RT, 10 d.	^d	888
	-CH ₂ CHMe(CH ₂) ₂ -	CO ₂ Et	CO ₂ Et	Me	RT, 14 d.	^d	888
	-(CH ₂) ₂ CHMeCH ₂ -	CO ₂ Et	CO ₂ Et	Me	RT, 15 d.	^d	888
Ph	H	CO ₂ Et	CO ₂ Et	Me	Alc., cold, 18 hrs., then heat	90	199
					Ether, 0°, 24 hrs., RT, 24 hrs., 130°, 1 hr.	40	733
					Fuse at 30°; RT, 24 hrs.; 130°	42	733

^aIsolated as the dicarboxylic acid after hydrolysis of crude ester with KOH.

^bStructures of starting diketone and product not rigorously proved.

^cProduct was ethyl 6-hydroxy-2-methyl-5,6-tetramethyleno-5,6-dihydrocinchononate (36% yield); this was converted in several steps to 5,6,7,8-tetrahydroquinoline.

^dProduct as in Note c, but not further converted.

TABLE II-79. Condensation of 1,3-Dioxo Compounds with Cyanoacetic Ester

$ \begin{array}{c} R_4 \\ \\ R_3CH-CO \\ \\ R_2CO \\ \\ R_1NH_2 \end{array} \xrightarrow{\quad} \begin{array}{c} R_4 \\ \\ R_3 \\ \\ R_2 \\ \\ N \\ \\ R_1 \end{array} \begin{array}{c} CN \\ O \\ \backslash \\ / \end{array} $					Yield, %	Ref.
R ₁	R ₂	R ₃	R ₄	Conditions		
H	Me	H	Me	Aq. Aq. alc., reflux; or MeOH, 100–200°; or NH ₄ SCN, 120–70°	up to 85	706 876
Me	Me	H	Me	Aq.		706
H	Me	Me	Me	Aq.		706, 140, 75
Me	Me	Me	Me	Aq.		706
Et	Me	H	Me	Aq.		706
Pr	Me	H	Me	Aq.		706
H	<i>n</i> -Hexyl	H	Me	Aq.	^a	706
H	–(CH ₂) ₄ –	H	H	Alc., 35–40°, 2 d. MeOH, reflux 5 hrs.	^b	1353
				Alc., 250°, 6 hrs., sealed	70	876
				Aq. MeOH, 20°, 8 d.	^c	876
				Aq.	^d	876
H	Ph	H	Me	Aq. Aq. alc., reflux; or MeOH, 100–200°; or NH ₄ SCN, 120–70°	^e	306
					20–60	876
H	Me	H	CH ₂ OMe			855

H	Me	OAc	Me	Reactants (except NH ₃) with piperidine in alc., 24 hrs.; then aq. NH ₃ , 2 d.	g	1418, 458

^aMixture of isomers of unknown composition.

^bProduct is 6-hydroxy-5,6-tetramethyleno-2-oxo-1,2,5,6-tetrahydronicotinonitrile (26% yield), which is HOAc at 210° gives the pyridinol.

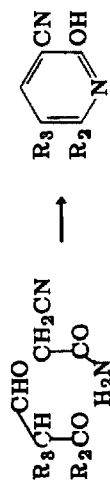
^cOnly 2 moles NH₃ used; product is 2-hydroxy-5,6,7,8-tetrahydroquinoline-3-carboxamide (see text).

^dObtain normal product (30-40% yield), the product of Note c. (15% yield), and 2-amino-5,6,7,8-tetrahydroquinoline-3-carboxamide (10-15% yield) (see text).

^eObtain mixture of isomers (4-methyl-6-phenyl-, and 6-methyl-4-phenyl-2-hydroxy-nicotinonitrile).

^fDiketone converted to imine by aq. NH₃ in benzene; aqueous layer (containing imine) treated with cyanacetic ester overnight.

^gObtain 5-acetoxy-4,6-dimethyl-2-hydroxynicotinamide (structure not proved).

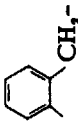
TABLE II-80. Condensation of Malonaldehydes and β -Ketoaldehydes and Their Acetals with Cyanoacetamide

R_3	R_1	Conditions	Yield, %	Ref.
Me	H	Na deriv., piperidine · HOAc, aq., reflux 2 hrs.	55-62	540
		Na deriv., piperidine · HOAc, aq., reflux 2 hrs.	68	1091
Me ^a	H ^a	Piperidine · HOAc, aq., reflux 12-15 hrs.	75	525
Me ^b	H ^b	Piperidine · HOAc, aq., reflux 1-2 hrs.	79	1573
Me	Me	Piperidine, 90% alc., reflux 4 hrs.	42	354
		Na deriv., piperidine · HOAc, aq., reflux 2 hrs.	56	1103
		Piperidine, aq. alc., cold 0.5 hrs., RT, 2-3 d.	40	1361, 1362
		NaOEt, alc., RT, 1 d.	40	1361, 1362
		Piperidine, alc., reflux 2 hrs., cold overnight	c	1362
Et	Me	Et ₃ NH, 1.5 hrs.		1353
Pr	H	Piperidine · HOAc, aq., reflux 3 hrs.	37	1111
		Na deriv., piperidine · HOAc, aq., reflux 2.5 hrs.	51	1469
Pr ^a	H ^a	Piperidine · HOAc, aq., reflux 12-15 hrs.	64	525
i-Pr ^a	H ^a	Piperidine · HOAc, aq., reflux 12-15 hrs.	77	525
Bu	Me	Na deriv., piperidine · HOAc, aq., reflux 3 hrs.	50	1083
i-Bu	H	Na deriv., piperidine · HOAc, reflux 2 hrs.	83	1103
Am ^a	H ^a	Piperidine · HOAc, aq., reflux 12-15 hrs.	68	525
Cyclo- propyl	H	Na deriv., piperidine · HOAc, aq., reflux 2 hrs.	53	1715

$-(CH_2)_3-$	Na deriv., piperidine · HOAc, aq., reflux 2 hrs.	<i>d</i>	880
$-(CH_2)_4-$	Piperidine, aq. alc., 40°, several d.		1221
	Piperidine or Et ₃ NH, aq. alc., 35°, 2 d.	<i>e</i>	1353
	Piperidine or Et ₃ NH, aq. alc., 35°, 2 d.	66	882
	Na deriv., piperidine · HOAc, aq. reflux 2 hrs.		880
$-CHMe(CH_2)_3-$	Piperidine or Et ₃ NH	<i>f</i>	1353
$-CH_2CHMe(CH_2)_2-$	Piperidine or Et ₃ NH		1353
	NH ₃ , alc., 35-40°, 2 d.	<i>g</i>	1353
$-(CH_2)_2CHMeCH_2-$	Piperidine or Et ₃ NH		1353
	NH ₃ , alc.	<i>g</i>	1353
$-CH(CH_2)_2CHMe-$ <i>i</i> -Pr	Piperidine or Et ₃ NH, alc.	20	1353
$-(CH_2)_5-$	Piperidine · HOAc, aq., reflux 2.5 hrs.	47	880
$-(CH_2)_3-$	Piperidine, aq. alc., 35-45°, 1 d.	<i>f</i>	1340
CH_2CH_2Ph H	Piperidine, 90% alc., reflux 4 hrs.	47	354
Ph H	Piperidine, aq. alc., cold 0.5 hrs.; RT, 2-3 d.	25 ^b	1361
	NaOEt, alc., RT, 1 d.	40	1361
	Na deriv., piperidine, aq., 1-2 d.	60	1361
Ph Me	Piperidine, aq. alc., cold 0.5 hr.; RT, 2-3 d.	75-80	1361
<i>p</i> -Tolyl H	Piperidine, aq. alc., cold 0.5 hr.; RT, 2-3 d.	50 ⁱ	1361
	NaOEt, alc., RT, 1 d.	80	1361
H NO ₂	Na deriv., piperidine, aq., 1-2 d.		1361
	Na deriv., Triton B, aq., 30°, 20 min.	93	1229

(continued)

TABLE II-80 (Continued)
Condensation of Malonaldehydes and β -Ketoaldehydes and Their Acetals with Cyanoacetamide

R_2	R_1	Conditions	Yield, %	Ref.
Me	$\text{CH}_3\text{CH}_2\text{OEt}$	Piperidine-HOAc, alc., reflux 5-6 hrs.; RT, 3 d.	2	1362
		Piperidine, aq. alc., 50-55°, 26 d.	12 ^j	516

^aUsed $\text{R}_1\text{COCH}_2\text{CH(OMe)}_2$.

^bUsed $\text{MeC(OMe)}_2\text{CH}_2\text{CH(OMe)}_2$.

^cProduct assumed to be 5,6-dimethyl-4-hydroxy-2-oxo-1,2,3,4-tetrahydronicotinonitrile (23% yield), which with conc. HCl after 3 hrs. reflux was converted to 5,6-dimethyl-2-hydroxynicotinic acid.

^dProduct assumed to be 6-hydroxy-5,6-trimethyleno-2-oxo-1,2,5,6-tetrahydronicotinonitrile, which with conc. HCl at 120-30° for 2 hrs. gave 2-hydroxy-5,6-trimethylenonicotinic acid (50% yield).

^eProduct analogous to that of Note *d*. (65% yield); this in HOAc at 210° gave the normal product.

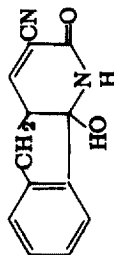
^fProduct analogous to that of Note *d*. in addition to normal product.

^gProduct analogous to that of Note *d*.

^hBy-product, 1,3,5-tribenzoylbenzene (50% yield).

ⁱBy-product, 1,3,5-tris(*p*-tolyl)benzene (10% yield).

^jProduct assumed to be



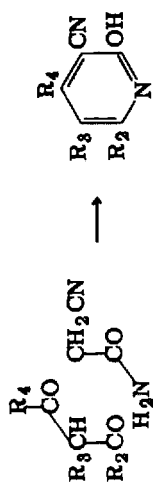


TABLE II-81. Condensation of 1,3-Diketones with Methylenic Amides

R ₁	R ₂	R ₃	R ₄	Conditions	Yield, %	Ref.
Me	H		Me	Piperidine, heat	87	1161, 1538
				Piperidine, heat		1382
				Et ₃ NH, alc.		1354
				NaOEt, alc.		309
				Na deriv. of cyanoacetamide, benzene, RT, overnight		309
				Phosphate buffer, aq., pH 9, 25°, 1 d.	74	1520
				K ₂ CO ₃ , aq., pH 8.5-9, 25°, 1 d.	94-98	1520
				Et ₃ NH, alc.	60 ^a	310
				Piperidine, alc.	^b	309
				Na deriv. of methylene amide ^b , benzene, RT, overnight	^b	309
Me	Me		Me	Piperidine, alc., RT, overnight	74	1212
				Piperidine, alc.	75	309
				Piperidine, alc.; or NaOEt, alc.	^b	309
Et	H		Me	Et ₃ NH, alc., 50°, then RT, 1 d.		1354
Me	Et		Me	Et ₃ NH, alc., 50°, then RT, 1 d.	90	1087
				Et ₃ NH, alc., 50°, then RT, 1 d.		1354

(continued)

TABLE II-81 (Continued)
Condensation of 1,3-Diketones with Methylene Amides

R_2	R_3	R_4	Conditions	Yield, %	Ref.
Et	H	Et	Et ₃ NH, alc., 50° 2 h., RT, overnight	90	310
	-(CH ₂) ₄ -	Me	Piperidine, alc., 60°, RT, overnight; or NaOEt, alc., RT, overnight	94 ^c	664
	-CHMe(CH ₂) ₃ -	Me	Piperidine or NaOEt	52 ^d	664
	-CH ₂ CHMe(CH ₂) ₂ -	Me	Piperidine	84 ^e	664
	-(CH ₂) ₂ CHMeCH ₂ -	Me	Piperidine	^e	664
Ph	H	Me	Piperidine	^e	664
		Me	Et ₃ NH, aq. alc.		309
		Me	Et ₃ NH, alc., 50°, RT, 1 d.		1354
Ph	H	Et	Et ₃ NH, alc., 50°, RT, 1 d.		1354
Ph	H	Ph	Piperidine, alc.	40	309
			Et ₃ NH, alc., RT, overnight	55-70	310
			NaOEt, alc., 60°, 24 hrs.	18-20	310
Ph	Me	Ph	Piperidine, alc., reflux 12 hrs.	40	444
			Et ₃ NH, aq. alc., reflux 12 hrs.		309
<i>p</i> -Tolyl	H	Me	Et ₃ NH, alc., 60°, 10 min.	80	314
			Et ₃ NH, alc.	^b	314
<i>p</i> -Tolyl	H	Ph	Et ₃ NH, alc., RT, 7-10 d.	34 ^f	310
Me	Cl	Me	Piperidine, warm 30 min.		458,1418

Me	H	CH ₃ OMe	Piperidine	358,1265
			Piperidine, cold, 12 hrs.	92 ^g
			Piperidine, cold, 12 hrs.	584
			Piperidine, cold, 12 hrs.	85
			Piperidine, cold, 12 hrs.	1616
			Piperidine, alc.	1234
i-Bu	H	CH ₃ OMe	Piperidine, alc.	632
Am	H	CH ₃ OMe	Piperidine, alc.	632
CH ₃ OMe	H	CH ₃ OMe	Piperidine · HOAc, aq., reflux 2 hrs.	1126
Me	H	CH ₃ OEt	Piperidine, alc.	59
			Piperidine, alc.	81
			Piperidine, alc.	75 ^b
			Piperidine	1234
			Piperidine, 95% alc.	1376
			NaOEt, alc., reflux 0.5 hrs.	353
			Na salt of diketone	1472
			Piperidine, alc., reflux 3 hrs.	601
			Piperidine, alc.	100 ^b
			Piperidine, alc.	50 ^a
Et	H	CH ₃ OEt	Piperidine, alc., heat, then RT	460
Me	H	CH ₃ OPr	Piperidine	1424
Me	H	CH ₃ OCH ₂ Ph	Piperidine, alc., RT, several hrs., then 50°	1265
Me	H	CH ₃ OPh	Piperidine	1234
Me	CH ₂ CH ₂ OAc	Me		1265
Me	CH ₂ NHCOPh	Me	Piperidine, alc., reflux 45 min.	1371
Me	CH ₂ NHCOPh	CH ₃ OEt	Piperidine, alc., reflux 45 min.	1425,1267
Me	H	CO ₂ Me	Et ₃ NH, alc., RT, 24 hrs.	1425,1267
				897

(continued)

TABLE II-81 (Continued)
Condensation of 1,3-Diketones with Methylene Amides

R_3	R_2	R_4	Conditions	Yield, %	Ref.
Me	H	CO ₂ Et	Piperidine, aq. alc., heat 6 hrs.	15	1427
			NaOEt, alc., 65°, 6 hrs.	65	1427
			K ₂ CO ₃ , Me ₂ CO, 6 hrs.	82	1427
			Et ₃ NH, alc., 50°, 0.5 hrs.	46	1550
			Et ₃ NH, alc.	41	1709
			Et ₃ NH, alc., 50°, RT, 1 d.	1354, 897	
			Na cyanoacetamide, benzene, RT, overnight	309	
			Piperidine, benzene	309	
			Na salt of diketone, Na, benzene, steam bath, 5 hrs.	897	
			150°, 3 hrs.		
			Et ₃ NH, alc., RT, 24 hrs.	^b	897
			Piperidine, 60°, 0.5 hrs., cold overnight	59	1356
			Piperidine, aq. alc., water bath 24 hrs.	48 ^f	1469
Et	H	CO ₂ Et	K ₂ CO ₃ , Me ₂ CO, reflux 8-14 hrs.	70 ^f	665
Pr	H	CO ₂ Et	K ₂ CO ₃ , Me ₂ CO, reflux 8-14 hrs.	65 ^f	665
<i>i</i> -Pr	H	CO ₂ Et	K ₂ CO ₃ , Me ₂ CO, reflux 8-14 hrs.	70	665
<i>i</i> -Bu	H	CO ₂ Et	Piperidine, alc., 60°, 2 hrs.; RT, overnight	52	309
<i>t</i> -Bu	H	CO ₂ Et	NaOEt/alc., RT, 18 hrs.	50	665
	-(CH ₂) ₄ -		Et ₃ NH, alc.		314
Ph	H	CO ₂ Et	Piperidine, alc., 60°, then RT	60	665

Me	H	CONH ₂	Et ₃ NH, alc., overnight	73	1400
Me	OAc	Me	Piperidine, alc., warm 30 min.		458,1418
Me	OAc	CH ₃ OMe	Piperidine, alc., warm 30 min.		458,1418
Me	NHAc	Me	Piperidine, alc., reflux 45 min.		1425,1267
Me	NHAc	CH ₃ OEt	Piperidine, alc., reflux 45 min.		1425,1267

^aUsed malonamide instead of cyanoacetamide, obtaining the nicotinamide product instead of the nicotinonitrile.

^bUsed *N*-methylcyanoacetamide instead of cyanoacetamide, obtaining the *N*-methylpyridone.

^cObtained mixture of isomers.

^dUsed α -methylcyanoacetamide; obtained mixture of same products as in Note c (loss of α -methyl group).

^eProduct not characterized as to isomer content.

^fAlso obtained 6-phenyl-4-*p*-tolyl-2-hydroxynicotinonitrile (17% yield).

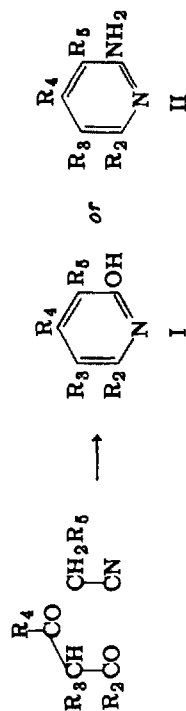
^gAlso obtained isomer in 7% yield.

^hAlso obtained isomer in 15% yield.

ⁱProduct said to be the 4-hydroxymethyl compound.

^jStructures of starting acylpyruvic ester and product not rigorously proved.

TABLE II-83. Condensation of 1,3-Dioxo Compounds with Methylenic Nitriles



R ₂	R ₃	R ₄	R ₅	Conditions	Products, Yield	Ref.
Me	H	Me	CO ₂ Et	Et ₃ NH, cold overnight, heat 12 hrs.	I	1159
-(CH ₂) ₄ -		H	CO ₂ Et	2 moles NH ₃ , alc., 250°, 6 h., sealed	a	876
				Excess NH ₃ , aq. MeOH, 20°, 8 d.	b	876
Me	H	CH ₃ OEt	CO ₂ Et	Piperidine, alc., reflux 3 hrs.	I 40%	460
Me	H	H	CN	Na salt of ketoaldehyde	I	450
Me	Me	H	CN	NH ₃ and ketoaldehyde reacted in MeOH; add nitrile, cool several hrs., RT overnight	I 20%, II 42-48%	876
Me	H	Me	CN	NH ₃ and ketoaldehyde reacted in MeOH; add nitrile, cool 12 hrs.	I 35-40%, II 24%	876
				Piperidine, alc.; or small amt. alc. NH ₃	I	348
-(CH ₂) ₄ -		H	CN	Et ₃ NH, cold overnight	I 77%	310
				NH ₃ and ketoaldehyde reacted in MeOH; add nitrile, RT, 2 d.	II 22-25%	876
Ph	H	Me	CN	Et ₃ NH, alc., RT overnight	I 58%	310

(continued)

TABLE II-83 (Continued)
Condensation of 1,3-Dioxo Compounds with Methylene Nitriles

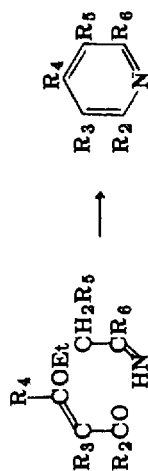
R ₃	R ₅	R ₄	R ₂	Conditions	Products, Yield	Ref.
Me	H	CH ₃ OEt	CN	Piperidine, alc. Diketone and NH ₄ Cl in aq., 45-50°, 1 hr.; add nitrile, 60°, 2 hrs.	I I	348 1268
Me	OAc	Me	CO ₂ Et	Piperidine, alc., reflux 1 hr., RT, 24 hrs.; add NH ₃ , RT, 2 d.	c	458, 1418

^aObtained 2-hydroxy-5,6,7,8-tetrahydroquinoline-3-carboxamide (55% yield).

^bObtained product of Note a (15% yield), the 2-amino analog of that (10-15% yield), and 2-hydroxy-3-cyano-5,6,7,8-tetrahydroquinoline (30-40% yield) (see text).

^cObtained 5-acetoxy-2-hydroxy-4,6-dimethylnicotinamide.

TABLE II-84. Condensation of Enol Ethers of 1,3-Dioxo Compounds with Methylene Ketimines



R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Yield, %	Ref.
CO ₂ Et	CO ₂ Et	COMe	H		Me	Ether	27 ^a	566
Me	CO ₂ Et	CO ₂ Et	H		Me	Steam bath, several hrs.	42 ^b	566
CF ₃	CO ₂ Et	CO ₂ Et	H		Me	Ether	83	566
CO ₂ Et	CO ₂ Et	CO ₂ Et	H		Me	Ether or benzene	65-70	566
CO ₂ Et	COMe	COMe	H		Me	Ether	83	566
CO ₂ Et	COMe	COMe	CO ₂ Et		Me	40-60°, 15 min.; steam bath 1 hr.	35	1135
CO ₂ Et	CO ₂ Et	CO ₂ Et	H		Me	Ether; water bath 0.5 hr.	86	566
CO ₂ Et	CO ₂ Et	COMe	CO ₂ Et		Me	Let stand 1 hr.; 60-70° 2 hrs.	69	648
						40-60°, 15 min.; steam bath 1 hr.	69	1135
						40-60°, 15 min.; steam bath 1 hr.	65	1135
CO ₂ Et	CO ₂ Et	CO ₂ Et	CO ₂ Et		Me	Ether	69	566
CO ₂ Et	CO ₂ Et	CONHPh	H		Me	NaOEt, alc., RT overnight	30	447
Ph	H	CN	Ph		Ph		63	1116
CF ₃	CO ₂ Et	CN	H		Me		19 ^c	516
Me	CO ₂ Et	CN	H		Ph	HOAc, water bath, 3.5 hrs.		516
Ph	CO ₂ Et	CN	H		Ph	HOAc, water bath, 8 hrs.		516
CO ₂ Et	COMe	CN	H		Me	Ether	47	566

(continued)

TABLE II-84 (Continued)
Condensation of Enol Ethers of 1,3-Dioxo Compounds with Methylene Ketimines

R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Yield, %	Ref.
CO ₂ Et	CO ₂ Et	H	CN	Me	Ether, RT; steam bath 0.5 hr. HOAc	70	566
					NaOEt, alc.	72	566
CO ₂ Et	CO ₂ Et	H	CN	Ph	HOAc, water bath, 1.5 hrs. ^d	70	566
CO ₂ Et	CO ₂ Et	CO ₂ Et	CN	Me	40-60°, 15 min.; steam bath 1 hr.	55	516
					40-60°, 15 min.; steam bath 1 hr.	71	1135
						75	1813

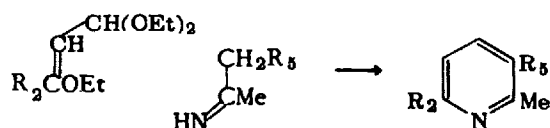
^aBy-product, EtO₂CCOC(COMe)=CHNHCMe=CHCOMe (24% yield).

^bBy-products, MeCOC(CO₂Et)=CHNHCMe=CHCO₂Et (8% yield), and ethyl 5-acetyl-6-hydroxy-2-methyl-nicotinate.

^cBy-product, MeCOC(CO₂Et)=CHNHCPh=CHCN.

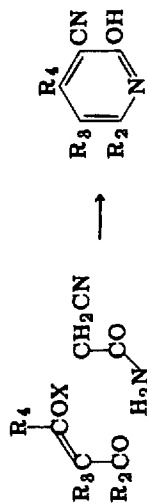
^dNo product obtained with NaOEt in alc.

TABLE II-85. Condensation of Enol Ether Acetals with Methylenic Ketimines



R_2	R_5	Conditions	Yield, %	Ref.
H	COMe	Steam bath, several d. 110°, 24 hrs.	25 90-95	1253 1422,442
Me	COMe	Water bath, 4 d.	30-40	359
H	COPh	Steam bath, several d.	5	1253
Me	COPh	Water bath, 8 d.	40	359
H	CO ₂ Et	Steam bath, several d. Reflux 24 hrs.	30 98	1253 1419
Me	CO ₂ Et	Water bath, 4 d.	40	359
H	CN	Steam bath, several d.	43	1253
Me	CN	Water bath, 5 d.	35	359

TABLE II-86. Condensation of Enol Ethers and Acetates of 1,3-Dioxo Compounds with Methylene Amides and Esters



R ₃	R ₃	R ₄	X	Conditions	Yield, %	Ref.
H ^e	H ^e	H ^e	Et ^e	Piperidine, alc.	25	356
H/	H/	Me/	Et/	Secondary amine	35/	352
				Piperidine, alc.	/	356
				Secondary amine		352
Ph	-(CH ₂) ₄ -	H	Ac	NaOEt, alc., overnight	a	1353
Ph	H	H	Ac	NaOEt, alc.		1361
	H	Me	Et	NaOEt, alc., RT, 2 d.; or Et ₃ NH, aq. alc., water bath 45 min.	84	309
Me	H	Ph	Me	NaOEt, alc., RT, 3 d.	30	309
Ph	H	Ph	Et	NaOEt, alc., RT, 3 d.	75	310

<i>p</i> -Tolyl	H	H	Ac	NaOEt, alc.	^a	1361
<i>p</i> -Tolyl	H	Me	Et	Et ₃ NH, alc.	100	314
<i>p</i> -Tolyl	H	Ph	Me	Et ₃ NH, alc., RT		310
Ph	H	<i>p</i> -Anisyl	Me	Et ₃ NH, alc.		314
Me	COMe	H	Et	NaOEt, alc., RT, 12 hrs.	^b	1353
CO ₂ Et	H	Me	Et	K ₂ CO ₃ , Me ₂ CO, reflux 14 hrs.	73	1427
Me	CO ₂ Et	H	Et	NaOEt, alc., RT, several hrs. ^c	7	267
				NaOEt, alc., heat, several hrs. ^c	^c	141
				Cyanoacetic ester ^d , aq. NH ₃ , RT, 3 d.		1353

^aObtained the 4-acetoxy-2-oxo-6-aryl-2,3,4,5-tetrahydronicotinonitrile, which with aqueous NaOH gave the normal product.

^bStructure uncertain.

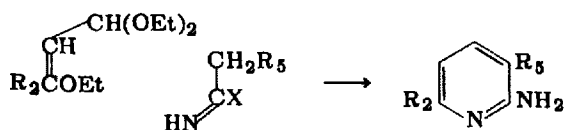
^cUsed α -methylcyanoacetamide instead of cyanoacetamide; obtained an adduct which, heated with aq. HCl, gave ethyl 6-hydroxy-2,5-dimethylnicotinate (loss of CN group).

^dUsed ethyl cyanoacetate instead of cyanoacetamide.

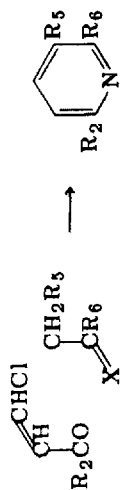
^eThe enol ether acetal used, CH(OEt)=CHCH(OEt)₂.

The enol ether acetal used, MeC(OEt)=CHCH(OEt)₂. The orientation is different than in type equation; product is 6-methyl-2-hydroxynicotinonitrile.

TABLE II-87. Condensation of Enol Ether Acetals with a Methylenic Imidate or Amidine

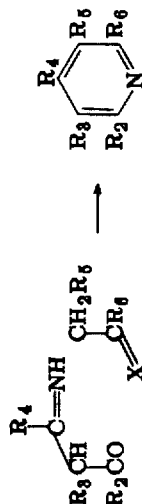


X	R ₂	R ₅	Conditions	Yield, %	Ref.
OEt	H	CO ₂ Et	Water bath, 16 hrs.	18	1254
OEt	Me	CO ₂ Et	Water bath, 16 hrs.		1254
NH ₂	H	CONH ₂	NaOH, alc., RT	25	1423

TABLE II-88. Condensation of β -Chlorovinyl Ketones with Methylenic Ketones, Ketimines and Aldimines

R_2	R_3	R_6	X	Conditions	Yield, %	Ref.
Me	COMe	H	NH	RT, 2 d.; 20% H_2SO_4 , reflux	51	1816
Me	COMe	Me	O	NH_3 , alc., RT, 1 hr.; steam bath 4 hrs.	50	624
Et	COEt	H	NH	RT, 2 d.; 20% H_2SO_4 , reflux	80	1816
Pr	COPr	H	NH	RT, 2 d.; 20% H_2SO_4 , reflux	41	1816
Am	COAm	H	NH	RT, 2 d.; 20% H_2SO_4 , reflux	14	1816
Me	CO ₂ Et	Me	O	NH_3 , alc., 25°, 1 hr.; reflux 5 hrs.	56	1479
Me	CO ₂ Et	Me	NH	RT, 1 hr.; steam bath 4 hrs.	75	624
CH_3Cl	CO ₂ Et	Me	NH	RT, 1 hr.; steam bath 4 hrs.	41	624
Pr	CO ₂ Et	Me	O	NH_3 , alc., RT, 1 hr.; steam bath 4 hrs.	62	624
<i>i</i> -Bu	CO ₂ Et	Me	O	NH_3 , alc., RT, 1 hr.; steam bath 4 hrs.	61	624
Am	CO ₂ Et	Me	O	NH_3 , alc., RT, 1 hr.; steam bath 4 hrs.	46	624

TABLE II-89. Condensation of Imines of 1,3-Dioxo Compounds with Methylenic (and Methyl) Ketones and Aldimines



R ₂	R ₃	R ₄	R ₅	R ₆	X	Conditions	Yield, %	Ref.
Ph	H	H	COPh	H	NH	H ₂ SO ₄ , aq. Me ₂ CO, RT, 1.5 hrs.		605
Me	CO ₂ Et	H	H	Me	O	180–190°, 24 hrs.	8	1428
Me	H	H	CO ₂ Et	Me	O	Reflux 5 hrs.	14 ^b	624
Me	CO ₂ Et	H	-(CH ₂) ₄ -		O	150–160°, 24 hrs.	29	1428
Me	COMe	H	CO ₂ Et	Me	O	160°, 36 hrs.	^a	1428
Me	CO ₂ Et	H	CO ₂ Et	Me	O	160°, 24 hrs.	31	1428

^aVery small yield; major product was ethyl 2,6-lutidine-3,5-dicarboxylate.

^bOrientation is different than in type equation; product is ethyl 2,4-dimethylnicotinate.

TABLE II-90. Condensation of Imines of 1,3-Dioxo Compounds with Methylenic Esters, Amides and Nitriles

R ₃	R ₅	R ₄	R ₃	X	Conditions	Yield, %	Ref.
Me	H	Me	CO ₂ Et	OEt	NaOEt	65	250
Me ^a	H ^a	CH ₃ OEt ^a	CO ₂ Et	OEt	NaOEt, alc., reflux 5 hrs.		351, 347, 1268
Me ^a	H ^a	CH ₃ OEt ^a	CONH ₂	NH ₃	180-85°, 3 hrs.		1594, 1268
Ph	H	Me	CONH ₂	NH ₃	175-80°, 1 hr.		372
Me	H	Me	CN	OEt			707
Me ^b	H ^b	Me ^b	CN	NH ₃			1068
Me	H	Me	CN	NHMe		c	1068
Me	Me	Me	CN	NH ₃	150°, 0.5 hr.		1364
-(CH ₃) ₄ -	Me	H	CN	OEt	Et ₃ NH or piperidine, alc.	d	1353
Ph	Me	H	CN	NH ₃	Heat; or NaOEt, alc.	75-80	1361
Ph	H	Me	CN	NH ₃	150°, 0.5 hr.		1364
Ph ^b	H ^b	Me ^b	CN	NH ₃	125°	e	372
Ph	H	Me	CN	NHMe	150°, 0.5 hr.	e	372

(continued)

TABLE II-90 (Continued)
Condensation of Imines of 1,3-Dioxo Compounds with Methylenic Esters, Amides and Nitriles

R ₂	R ₃	R ₄	R ₅	X	Conditions	Yield, %	Ref.
Ph	H	Me	CN	OEt	NaOEt, alc., reflux 3 hrs. NaOEt, alc., reflux 6 hrs.; RT overnight	/ 20/	372 901
<i>p</i> -Tolyl	H	H	CN	NH ₂	Heat; or NaOEt, alc.	60-65	1361
<i>p</i> -Tolyl	H	Me	CN	NH ₂			314
Me ^a	H ^a	CH ₂ OEt ^a	CN	NH ₂	140-50°, 1.5-2 hrs. 140-50°, 1.5-2 hrs. in PhOMe		1268 1395
Me ^a	H ^a	CH ₂ OEt ^a			Malononitrile, aq. or alc., 50-60°, 4 hrs.		1268, 1593

^aPatents designate imine as MeC(=NH)CH₂COCH₂OEt; probably incorrect.

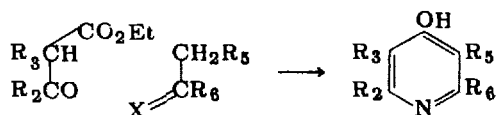
^bThe methylimine used, R₂COCH₂C(=NMe)Me; a pyridinol obtained (*i.e.*, not an *N*-methylpyridone).

^cProduct was the *N*-methylpyridone.

^dIntermediate isolated, 6-hydroxy-5,6-tetramethylene-2-oxo-1,2,5,6-tetrahydronicotinonitrile; this in acetic acid at 210° gave the product.

^eObtained a mixture of the pyridinol and the corresponding *N*-methylpyridone.

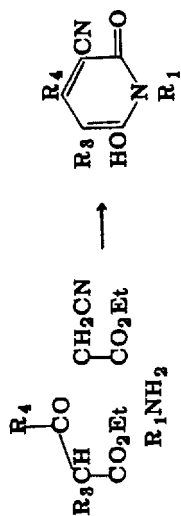
^fOrientation different than in type equation; product is 6-methyl-4-phenyl-1-2-hydroxynicotinonitrile.

TABLE II-91. Condensation of β -Ketoesters with Methylenic Ketones and Ketimines

R ₂	R ₃	R ₅	R ₆	X	Conditions	Product, Yield	Ref.
Me	H	CO ₂ Et	Me	NPh	ZnCl ₂ , 180–90°	20 ^a	258
Me	H	CO ₂ Et	Me	O	NH ₃ , 150°, 2 hrs	^b	1068
Me	H	CN	Me	NH	Small amt. pyridine (!)		303
					Piperidine		1688
Me	H	CN	Ph	NH	HCl gas		303,304,
							1688

^aProduct was 3-carboxy-2,6-dimethyl-1-phenyl-4(1*H*)pyridone.

^bProduct was 4,6-dimethyl-2-pyridinol.

TABLE II-92. Condensation of β -Ketoesters with Cyanoacetic Ester

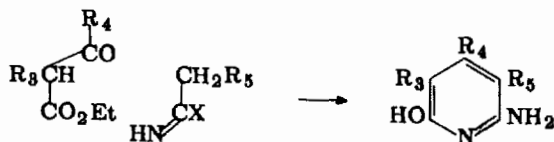
R_1	R_3	R_4	Conditions	Yield, %	Ref.
H	H	Me	Aq.		138
			Aq. alc., reflux, 1-5 hrs.	85-90	876
			Absolute MeOH, 100-200°, 6-24 hrs.	80-95	876
			NH ₃ gas, NH ₄ SCN, 120-70°, 5-12 hrs.	80-90	876
Me	H	Me	Aq.		138
Me	Me	Me	Aq.		138
Et	H	Me	Aq.		138
H	Pr	Me	Aq.		719
Allyl	H	Me	Aq.		138
H	Allyl	Me	Aq., RT, 2-3 d.		719
H	Bu	Me	Aq., RT, 2-3 d.		719
H	<i>i</i> -Bu	Me	Aq., RT, 2-3 d.		719
H	CH ₂ Ph	Me	Aq.	low	719
H	H	Ph	Aq.		719, 138
H	CH ₂ CH ₂ OH	Me	Aq., 12-15 d.		719
H	CH ₂ CO ₂ Et	Me	Aq., 2-3 d.		719
H	2-(2-Hydroxyethyl)- acetoacetic acid, γ -lactone		Aq., RT, 2 wks.	65 ^a	856

^aProduct was 5-(2-hydroxyethyl)-4-methyl-2,6-dihydroxynicotinonitrile, as NH₄ salt.

TABLE II-93. Condensation of β -Ketoesters with Methylenic Amides

R_3	R_4	Conditions	Yield, %	Ref.
H	Me	Piperidine, aq. alc., overnight		1364
$-(CH_3)_3-$		Piperidine, aq. alc., 50°, 3 d.	38	1349
$-(CH_3)_4-$		Piperidine, alc.; or NaOEt, alc.		1364, 664
CH_3CH_2OEt	Me	Malonamide ^a , piperidine, alc.	^a	372
COMe	Me	Aq. NH ₃	35	1257
	Me	Piperidine, aq. alc., overnight	^b	1364
		<i>N</i> -Methylcyanoacetamide, ^c piperidine, alc., 2 d.	^c	1364
H	CO ₂ Et	Piperidine, MeOH	36	1263
H	CH ₃ CO ₂ Et	Piperidine, MeOH	32	1263
H	CH ₃ CH ₂ CO ₂ Et	Piperidine, MeOH	37	1263
OAc	Me	NaOEt, alc., 150°, 12 hrs., sealed		1418, 458
2-(2-Hydroxyethyl)-		Aq. NH ₃	52 ^e	1257
acetoacetic acid,		Aq. NH ₃ , RT, 8 d.	70 ^e	856
γ -lactone		Aq. NH ₃ , RT, overnight	73 ^e	849
		Piperidine, alc., 40°, 3 d.	50 ^e	856

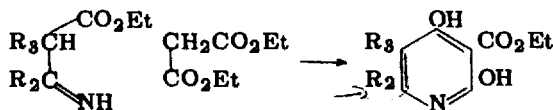
^aMalonamide used in place of cyanoacetamide; product is the nicotinamide instead of the nicotinonitrile.^bProduct was 4-methyl-2,6-dihydroxynicotinonitrile (loss of an acetyl group).^c*N*-Methylcyanoacetamide used in place of cyanoacetamide; product was 6-hydroxy-1,4-dimethyl-3-cyano-2-(1*H*)pyridone (loss of an acetyl group).^dProduct said to be 6-methyl-2,4,5-trihydroxynicotinonitrile; the isomeric 4-methyl-2,5,6-trihydroxynicotinonitrile is more likely.^eProduct is 2,6-dihydroxy-4-methyl-5-(2-hydroxyethyl)nicotinonitrile.

TABLE II-94. Condensation of β -Ketoesters with Methylene Imidate or Amidine

R_3	R_4	R_5	X	Conditions	Yield, %	Ref.
H	Me	CO_2Et	OEt	MeOH, reflux 8 hrs.	25-30	877
H	Me	$CONH_2$	NH_2	Piperidine, aq. alc., RT, 24-hrs.	27-30 ^a	877
$-(CH_2)_4-$		$CONH_2$	NH_2	Aq. alc., cold, 2 hrs.	^b	877

^aAdditional product, 2-(4-hydroxy-6-methyl-2-pyrimidinyl)acetamide (55-60% yield).

^bProduct was 2-[N'-(2-oxocyclohexanecarbonyl)amidino]acetamide (90-97% yield), which on warming in acetic acid gave the aminopyridinol (100% yield).

TABLE II-96. Condensation of Imines of β -Ketoesters with Methylenic Esters

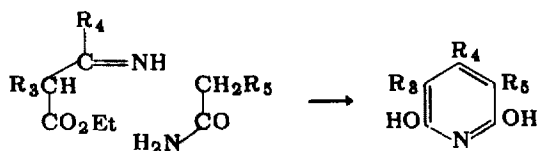
R ₂	R ₃	Conditions	Yield, %	Ref.
Me	H	NaOEt, alc.		1239, 1244
		NaOEt, alc., 140–50°, 7–9 hrs.		260
		NaOEt, alc., 140–50°, 5 hrs.	17	1458
		NaOEt, alc., RT, 1 d.	13–38	1457
		NaOEt, alc., steam bath, 17 hrs.	13	1458
		NaOEt, alc., reflux 13 hrs.	42	557
		NaOAm, AmOH, reflux 4 hrs.	43 ^a	1458
Me	Me	NaOEt, alc., 150°	60	344
Me	Et	NaOEt, alc., 150°	60	344
Me	Pr	NaOEt, alc.		1086
Me	Bu	NaOEt, alc.		1086
	–(CH ₂) ₃ –	NaOEt, alc., 110°, 30 hrs.	77	1343
	–(CH ₂) ₄ –	NaOEt, alc., 110°, 30 hrs.	72	1343
	–(CH ₂) ₅ –	NaOEt, alc., 110°, 30 hrs.	40	1339
	–(CH ₂) ₁₁ –	NaOEt, alc., 110–20°, 45 hrs.	57	1340
Me	CH ₂ CH ₂ OEt	NaOEt, alc., 150°, 8 hrs.	62	1352
Me	H	Ethyl α -methylmalonate, NaOEt, alc.	^b	1256
Et	H	Ethyl α -methylmalonate, NaOEt, alc.	53 ^c	1256
Me	H	Ethyl α -methylmalonate, NaOEt, alc.	^d	1239

^aR₃ of product is CO₂Am.

^bProduct was 3,6-dimethyl-2,4-pyridinediol (loss of CO₂Et group).

^cProduct was 3-methyl-6-ethyl-2,4-pyridinediol (loss of CO₂Et group).

^dProduct was ethyl 3-ethyl-6-methyl-2-hydroxy-4-oxo-3,4-dihydronicotinate, which on treatment with aqueous sodium hydroxide gave 6-methyl-3-ethyl-2,4-pyridinediol.

TABLE II-97. Condensation of Imines of β -Ketoesters with Methylenic Amides

R ₃	R ₄	R ₅	Conditions	Ref.
H	Me	CONH ₂	Piperidine, alc., RT, 4 d.; or heat 1 hr.	372
-(CH ₂) ₄ -		CONH ₂	190°, several hrs.	372
H	Me	CN	130°, 15 min.	1364
-(CH ₂) ₄ -		CN	120°, 25 min.	1364

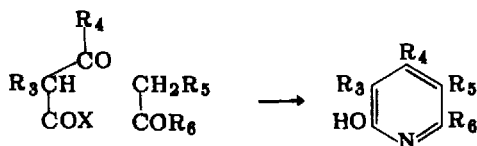
TABLE II-98. Condensations of Imines of β -Oxoesters with Ethyl Acetoacetate

Imine	Conditions	Product	Ref.
Ethyl β -anilinocrotonate	ZnCl ₂ , 180–90°	1-Phenyl-3-carboxy-2,6-dimethyl-4(1H) pyridone (20% yield)	258
Ethyl 2-aminomethylene-malonate	Dry HCl, RT, 3 d.	Ethyl 2-methyl-4-hydroxy-nicotinate	362
	Sodio acetoacetic ester, benzene, water bath, 5 hrs.	Ethyl 2-methyl-4-hydroxy-pyridine-3,5-dicarboxylate (assumed)	362

TABLE II-99. Self-Condensation of Ethyl β -Aminocrotonate^a

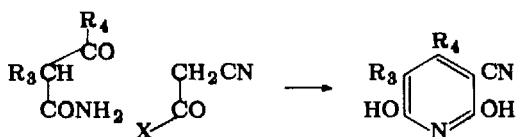
Conditions	Products (Yield)	Ref.
Destructive distillation, atm. press., 200-360°	2-Ethoxy-4,6-dimethylpyridine	690
Distilled <i>in vacuo</i>	Ethyl 4-hydroxy-2,6-dimethylnicotinate	686,224,255
Hydrochloride heated at 120°	Ethyl 6-hydroxy-2,4-dimethylnicotinate (40%)	1603,255,1067
Hydrochloride (1 mole) and free base (1 mole) heated at 120°	Ethyl 6-hydroxy-4-methyl-2-pyridylacetate (assumed, 33%); ethyl 6-hydroxy-2,4-di- methylnicotinate (7%)	1603,255,1067
POCl ₃	Ethyl 4-chloro-2,6-dimethylnicotinate (42%)	241,242
POCl ₃ , benzene, short warming	Ethyl 4-chloro-2,6-dimethylnicotinate (34%)	1595
POCl ₃ , 100°	Ethyl 4-chloro-2,6-dimethylnicotinate (70%)	1398

^aThe self-condensation of ethyl β -arylaminoacrylates has also been reported (364): $\text{RNHCH}=\text{CHCO}_2\text{Et}$ heated *in vacuo* below m.p. gave an intermediate, presumably $\text{RN}(\text{CH}=\text{CHCO}_2\text{Et})_2$, which without isolation, in alc. KOH, gave the 1-aryl-4-oxo-1,4-dihydronicotinic acid ($\text{R} = \text{Ph}$ or 2-naphthyl).

TABLE II-100. Condensation of β -Ketoamides and β -Ketoacid Chlorides with Methylenic (and Methyl) Ketones

X	R ₃	R ₄	R ₅	R ₆	Conditions	Yield, %	Ref.
NH ₂	H	Ph	H	Me	Polyphosphoric acid, RT; steam bath, 0.5 hr.; 130–40°, 0.5 hr.	60	901
NH ₂	Ph	Me	H	Me	Polyphosphoric acid, RT; steam bath, 0.5 hr.; 130–40°, 0.5 hr.	18	901
NH ₂	Me	Ph	H	Me	Polyphosphoric acid, RT; steam bath, 0.5 hr.; 130–40°, 0.5 hr.	38	901
NH ₂	Ph	Me	Ph	Me	Conc. H ₂ SO ₄ , HOAc, heat 2 hrs.	57	886
Cl	H	Me	COCl	Me	PhNH ₂ , RT	^a	361
NH ₂	H	Me	CONH ₂	Me	Heat		881

^aProduct of self-condensation of acetoacetyl chloride in presence of aniline, 1-phenyl-3-carboxy-2,6-dimethyl-4(1*H*)pyridone.

TABLE II-101. Condensation of β -Ketoamides with Cyanoacetic Ester and Cyanoacetamide

R ₃	R ₄	X	Conditions	Yield, %	Ref.
Me	Me	OE _t	Aq. NH ₃		138
			Aq. NH ₃ ^a	90	344
Et	Me	OE _t	Aq. NH ₃ , RT		138
			Aq. NH ₃ , RT, 14 d. ^a	85	139
Me	Et	OE _t	Aq. NH ₃ , several d. ^a		1672
Me ^b	Et ^b	OE _t	Aq. MeNH ₂ ^b	^c	1672
Pr	Me	NH ₂	Aq. NH ₃		719

^aThe β -ketoamide prepared *in situ* from the corresponding β -ketoester and aqueous NH₃.

^bThe *N*-methyl β -ketoamide was used, prepared *in situ* from the ketoester and MeNH₂.

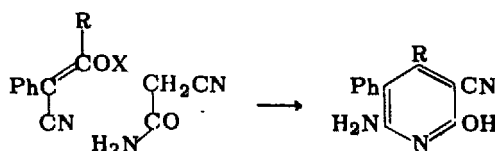
^cProduct is the *N*-methyl hydroxypyridone.

TABLE II-102. Condensation of β -Ketonitriles with Methylene (and Methyl) Ketones

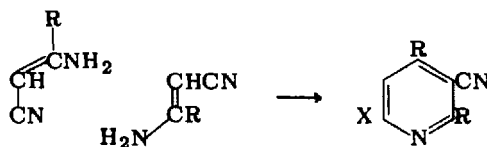
$ \begin{array}{c} \text{R}_4 \\ \\ \text{R}_3\text{CH}-\text{C}-\text{CH}_2\text{R}_5 \\ \quad \\ \text{CN} \quad \text{COR}_6 \end{array} \longrightarrow \begin{array}{c} \text{R}_4 \\ \\ \text{R}_3-\text{C}_6\text{H}_3-\text{N} \\ \quad \quad \\ \text{HO} \quad \text{R}_5 \quad \text{R}_6 \end{array} $						
R ₃	R ₄	R ₅	R ₆	Conditions	Yield, %	Ref.
H	Ph	H	Me	Polyphosphoric acid, RT; steam bath 0.5 hr.; 130-40°, 0.5 hr.	68	901
Ph	Me	H	Me	Polyphosphoric acid; steam bath 20 min.; 125°, 15 min.	29	901
Me	Ph	H	Me	Polyphosphoric acid, RT; steam bath 0.5 hr.; 130-40°, 0.5 hr.	43	901
H	Ph	-(CH ₂) ₄ -		Polyphosphoric acid, RT; steam bath 0.5 hr.; 130-40°, 0.5 hr.	53	901
Ph	Et	Me	CH ₂ Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	46 ^a	886
				Conc. H ₂ SO ₄ , HOAc, heat	^b	886
H	Ph	H	Ph	Polyphosphoric acid, RT; steam bath 0.5 hr.; 130-40°, 0.5 hr.	5	901
H	Ph	Ph	Me	Polyphosphoric acid, RT; steam bath 0.5 hr.; 130-40°, 0.5 hr.	63	901
Ph	Me	Ph	Me	Polyphosphoric acid, RT; steam bath 0.5 hr.; 130-40°, 0.5 hr.	58	901
				Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	56	886

Me	Ph	Ph	Me	Polyphosphoric acid, RT; steam bath 0.5 hr.; 130-40°, 0.5 hr.	60	901
Ph	Et	Ph	Me	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	27	886
Ph	Me	Ph	CH ₃ Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	28	886
Ph	Et	Ph	CH ₃ Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	27	886
Ph	CH ₃ Ph	Ph	CH ₃ Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	12	886
Ph	Ph	Ph	Me	Conc. H ₂ SO ₄ , HOAc, heat	10	886
				Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	44	886
				Conc. H ₂ SO ₄ , HOAc, heat	27 ^c	886
Ph	Me	Ph	Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	53	886
Ph	Et	Ph	Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	34	886
Ph	CH ₃ Ph	Ph	Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	26	886
Ph	Ph	Ph	CH ₃ Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	24	886
Ph	Ph	Ph	Ph	Conc. H ₂ SO ₄ , 80-120°, 6 hrs.	50	886
Me	3-Py	Ph	Me	Polyphosphoric acid, RT; steam bath 0.5 hr.; 130-40°, 0.5 hr.	34	901
Ph	Me	Ph, CN ^d	Me ^d	Polyphosphoric acid, 140-50°, 0.5 hr.	55 ^d	901
				Conc. H ₂ SO ₄ , HOAc, heat 1 hr.	70 ^d	886
Ph	Ph	Ph, CN ^e	Ph ^e	Conc. H ₂ SO ₄ , HOAc, heat	15 ^e	886

^aMixture with the isomeric product, 4,6-diethyl-3,5-diphenyl-2-pyridinol.^bBy-product, 2-methyl-6-ethyl-5-phenyl-4-hydroxypyrimidine.^cBy-product, 3,4,5,6-tetraphenyl-2-pyridinol.^dUsed α -phenylacetone (i. e., in self-condensation); product was 4,6-dimethyl-3,5-diphenyl-2-pyridinol.^eUsed α -phenylbenzoylacetonitrile (i. e., in self-condensation); product was 3,4,5,6-tetraphenyl-2-pyridinol.

TABLE II-103. Condensation of Enol Ethers of β -Oxonitriles with Cyanoacetamide

R	X	Conditions	Yield, %	Ref.
H	Me	NaOEt, alc., reflux 2 hr.	78	1112
H	<i>i</i> -Bu	NaOEt, alc., N ₂ , reflux 6 hr.	81	1112
Me	<i>i</i> -Bu	NaOEt, alc., reflux 3 hr.	32	1112

TABLE II-104. Self-Condensation of Imines of β -Ketonitriles

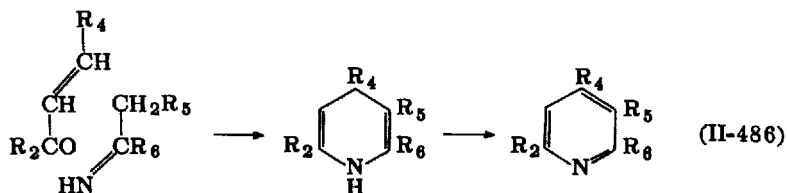
R	Conditions	X	Yield, %	Ref.
Me	ZnCl ₂ -NH ₃	NH ₂		1068
	Aq. benzene	OH	< 8	1068
	Dry ethylene bromide	NH ₂		303
	Moist ethylene bromide	OH		303
	Ethylene bromide, 70% alc., heat 5 hrs.	OH		1688
	Cyanoacetic acid, dry, 140°	NH ₂		1806
	Cyanoacetic acid, moist, 140°	OH		1806
Ph	Glycolic acid, alc.	OEt		1806
	Glycolic acid, alc., 150°, sealed	^a		1806
	Me ₂ C(OH)CO ₂ H, alc., heat	OH		1806
	Oxalic acid, alc., 170°	OH		1806
<i>p</i> -Tolyl	Succinic acid, alc., 150°	OH ^b		1806

^aA mixture obtained, X = OEt and X = NH₂.

^bWith by-product, X = NH₂.

*b. α,β -Unsaturated Carbonyl Compounds with
Methylenic Compounds*

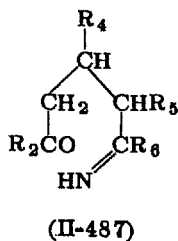
A second type of 3-2 condensation is the combination of an α,β -unsaturated carbonyl compound with an active methylenic (or methyl) compound. The nitrogen is attached to either component, but may be supplied separately as ammonia. An example is II-486.



The products are typically dihydropyridines, which are isolated and oxidized to pyridines. But often the dihydro stage is not found, the pyridine product being obtained directly.

As three-carbon donors one may use α,β -olefinic aldehydes, ketones, esters, or amides, or acetylenic ketones. The two-carbon component may be acetaldehyde, a methyl ketone, a methylenic ketone, a methylenic ketimine (*e.g.*, β -aminocrotonic ester), or a methylenic ester or amide.

The two reactants most likely undergo Michael addition as the first step, giving II-487, which then cyclizes. The dihydro products



are usually considered, without evidence, to have the 1,4-dihydro structure.

The oxidation step when necessary may be accomplished, often in good yield, with nitrous acid, bromine, nitric acid, chromic acid, or hydrogen peroxide.

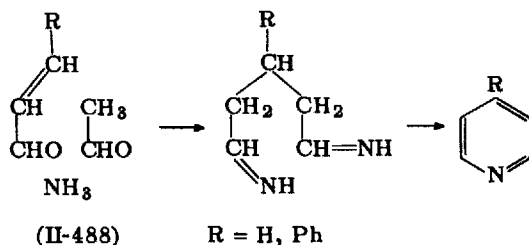
Where the pyridine is isolated directly, the mechanism of oxida-

tion has rarely been elucidated. It probably occurs by disproportionation of dihydropyridine to pyridine and tetrahydropyridine. While the latter has not been isolated from a 3-2 reaction, such disproportionations are known to occur under the conditions often employed (p. 229). The yields are at least consistent with the disproportionation theory; when true pyridines are obtained the yields are uniformly low, while yields of dihydropyridines are often high.

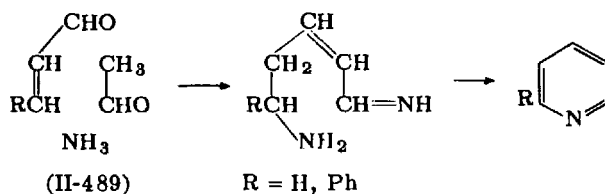
It is also possible for the unsaturated reactant to serve as hydrogen acceptor. Thus α -styrylcynoacetic ester in a 3-2 condensation gave α -phenethylcyanoacetamide as a by-product along with a pyridine (1251). Finally, oxidation by air or dehydrogenation over a catalyst at high temperature may explain some cases of pyridine formation.

(a) **With Aldehydes and Ketones.** Reactions of unsaturated carbonyl compounds with aldehydes and ketones are run at high temperatures, often in the vapor phase, and give low yields of mixtures of pyridines (Table II-105).

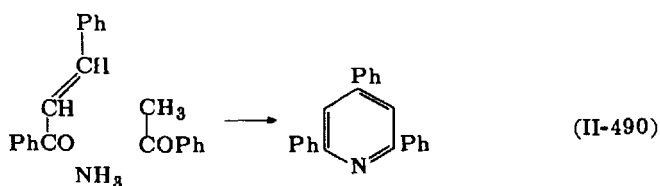
The simplest example is the condensation of acrolein, acetaldehyde, and ammonia, over aluminum oxide at 300°, from which Chichibabin and Oparina (1316) obtained pyridine itself in 2.5% yield as the picrate. This can arise from two orientations of the starting materials, II-488 and II-489. By-products in this case were 2-picoline, formed from acetaldehyde and ammonia (2-2-1 synthesis), and 3-picoline, from acrolein and ammonia. In a similar manner, a mixture of cinnamaldehyde, acetaldehyde, and ammonia gave both 4-phenylpyridine (15% yield) by route II-488, and 2-phenylpyridine (3%) by route II-489.



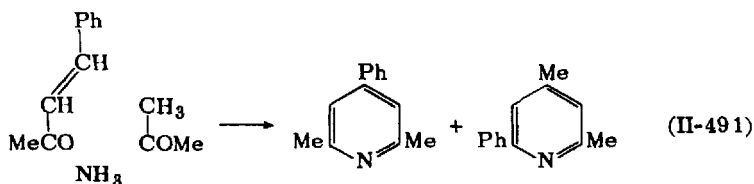
These two modes of condensation are also encountered in liquid-phase reactions. Frank and Seven (1165) consensed a number of



unsaturated ketones with acetophenone or phenyl benzyl ketone at 250° in aqueous ammonia under pressure, using ammonium acetate as catalyst. Their highest yield was 39%, for reaction II-490, where

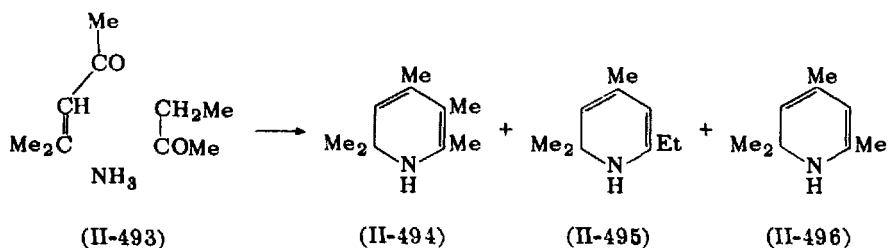


the mode of condensation is ambiguous. However, benzalacetone showed both orientations in reaction with acetone (II-491), in equal but very low yields. The same reactants in the vapor phase gave only II-492 (1001).



(II-492)

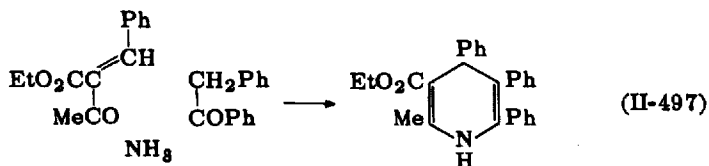
With mesityl oxide only orientation II-493 was observed, the reaction proceeding even at 100° in aqueous caustic (455,1477). Products II-494 and II-495 arise from the two possible arrangements



of methyl ethyl ketone; product II-496 arises by cleavage of mesityl oxide to acetone, which then undergoes a similar condensation with more mesityl oxide.

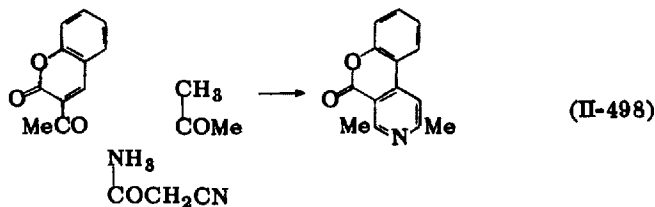
For either route (II-488 or II-489) it seems likely that ammonia reacts first, in II-488 by forming imines, in II-489 by adding to the olefinic bond. The addition product with mesityl oxide is the stable diacetoneamine, $\text{Me}_2\text{C}(\text{NH}_2)\text{CH}_2\text{COMe}$.

When the two components are more highly activated (II-497), their condensation proceeds at room temperature in a solvent, and

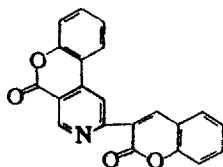


the dihydro stage is isolated (239). Of the two carbonyl groups in the unsaturated compound, the keto is more polarized than the ester; accordingly it is the one which reacts with ammonia and enters the ring.

A special application of 3-2 condensation was the use of 3-acetyl-coumarins as unsaturated components (1461) (Table II-106). These reacted with acetone, acetophenone, and cyclohexanone at high temperatures to give fair yields of pyridines (II-498). Cyanoacetamide, which was also present, served as the source of nitrogen, but took no other part in the reactions. The 3-acetylcoumarin was also used



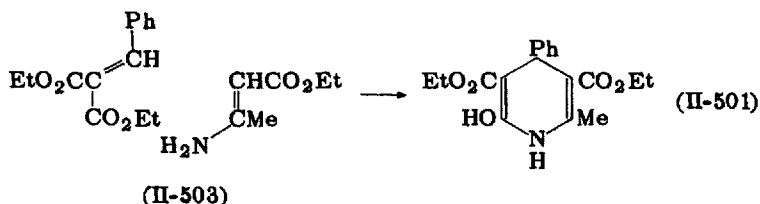
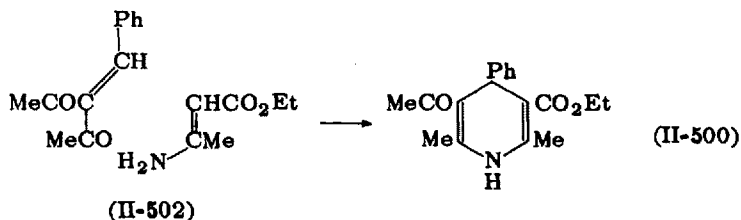
as a two-carbon component, its self-condensation yielding II-499; ammonium formate and various other compounds served as nitrogen donors, but alcoholic ammonia was ineffectual.



(II-499)

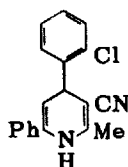
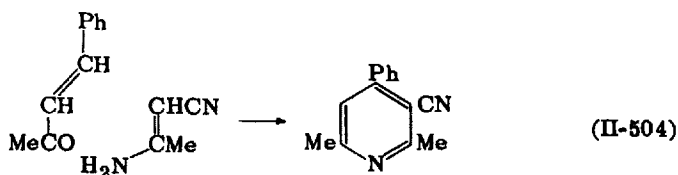
(b) **With Methylenic Ketimines.** Unsaturated carbonyl compounds have been condensed frequently with ketimines having active methylene groups, *i.e.*, the so-called enamine compounds, such as β -amino-crotonic ester or acetylacetonimine. The reaction proceeds to various stages, giving the pyridine, dihydropyridine, or a still earlier stage, depending on the catalyst used (Tables II-107 and II-108).

Under neutral conditions, the reactants heated without solvent or added catalyst, the dihydro stage is reached. Unsaturated ketones give dihydropyridines (II-500) (195), and unsaturated esters give dihydropyridinol II-501) (1712). In the absence of a catalyst we may assume that the enamine compound itself in its polarized form, $^+H_2N=CMeCH-CO_2Et$, attacks the double bond to give the Michael adduct. It is of interest that all known examples of such neutral condensation deal with highly activated double bonds, in which there are two electron-withdrawing groups on the α -carbon (II-502, II-503). Similarly, an electron-withdrawing group on the β -carbon also favors condensation; thus in II-500 a *m*-nitro substituent



on the phenyl ring leads to 80% yield, while a *p*-dimethylamino group gives 35% (1128).

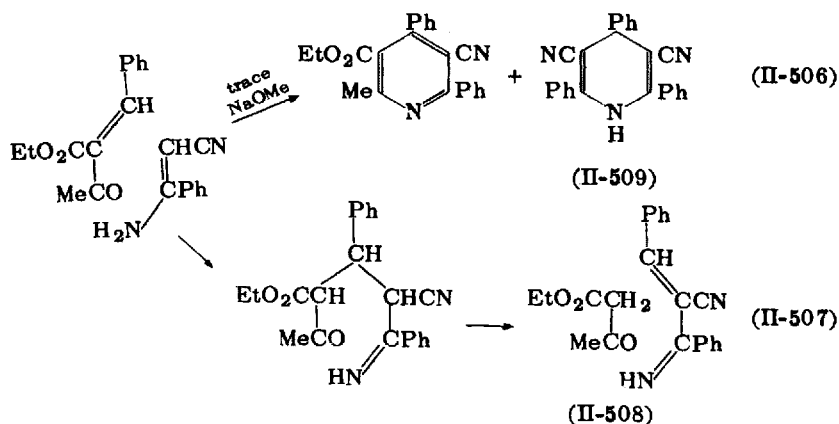
In the presence of sodium alkoxides unsaturated carbonyl compounds react with enamines as far as the pyridine stage. That is, unsaturated ketones give pyridine bases (II-504) (515) and unsaturated esters give pyridinols. An exception is the dihydro product



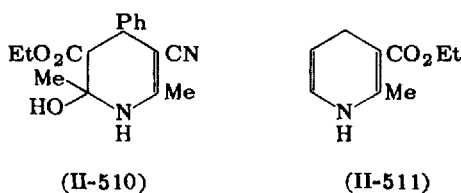
(II-505)

II-505 containing an *o*-chlorophenyl group in the 4 position; the *m*- and *p*-chloro products are pyridines; the *o*-methoxy and *o*-ethoxy products are mixtures of both types (524). It would appear that oxidative attack on the dihydro intermediate occurs in the 4 position, where it is subject to steric interference; apparently, also, it is favored by base. An interesting side-reaction in one instance (II-506) (885) seems to involve a reversal of the Michael condensation (II-507); the new unsaturated compound (II-508) thus formed condenses with β -aminocinnamionitrile to give the symmetrical by-product II-509.

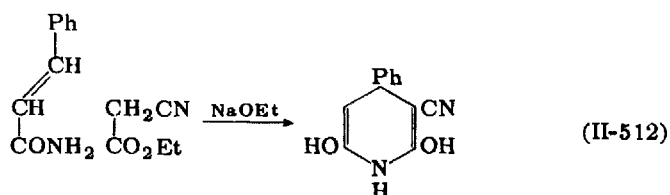
Organic bases have been used infrequently in the condensation of unsaturated carbonyl compounds with enamines. In one case (diethylamine as catalyst) the product was assumed to be II-510, though its distinction from the isomeric Michael adduct was not made clear; dehydration to the dihydropyridine base was effected on heating or treatment with acetic anhydride (515). In the condensation of acrolein with β -aminocrotonic ester (piperidine as catalyst)

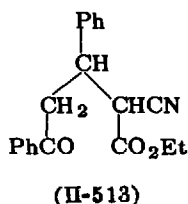


three states of oxidation were recognized among the products. The dihydropyridine II-511 was isolated in 57% yield, the true pyridine in 15% yield, and the tetrahydropyridine was detected by its ultra-violet spectrum (1756). This supports the idea that disproportionation can account for the aromatic pyridines formed in 3-2 condensations.

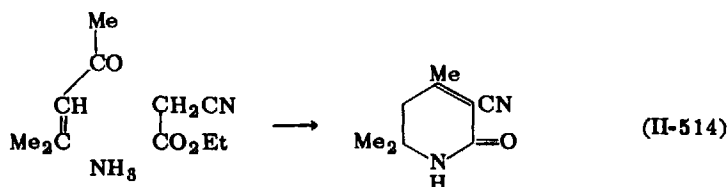


(c) **With Methylenic Esters.** α,β -Unsaturated carbonyl compounds have occasionally been reacted with cyanoacetic ester (Tables II-109 and II-110). Unsaturated amides gave the normal dihydropyridines (II-512) (1355), the carbamoyl group serving to close the ring. Benzalacetophenone and cyanoacetic ester, in the presence of a trace

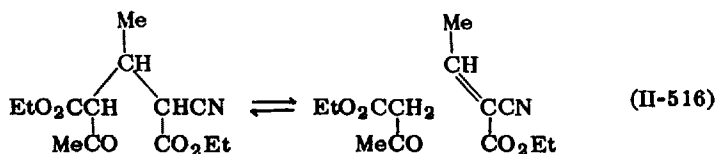
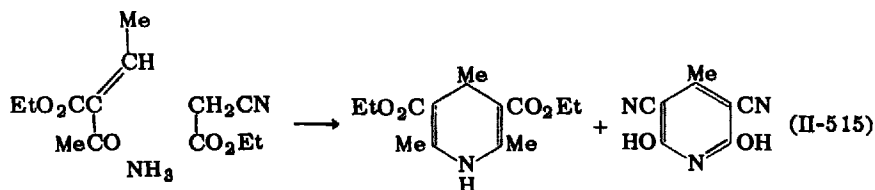




of sodium methoxide, gave the open-chain adduct (II-513) (447, 1359), which could be cyclized through the *ciano* group on treatment with acid agents (p. 288). A different course was taken by mesityl oxide in its reaction with cyanoacetic ester and ammonia (II-514) (710). Probably ammonia first adds to the double bond, forming diacetonamine, which condenses further in the only sense possible.

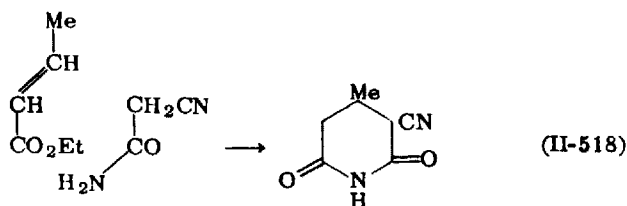
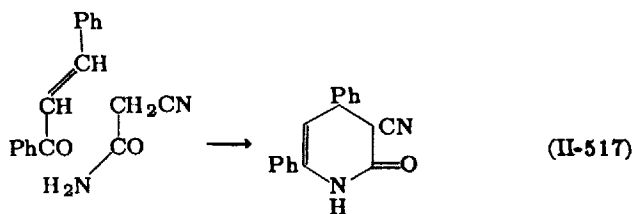


α -Ethylideneacetoacetic ester did not give the expected product with cyanoacetic ester and ammonia but only symmetrical products (II-515) (700). These probably arise from a reversal of the Michael condensation (II-516), which liberates two new components for other 3-2 combinations.

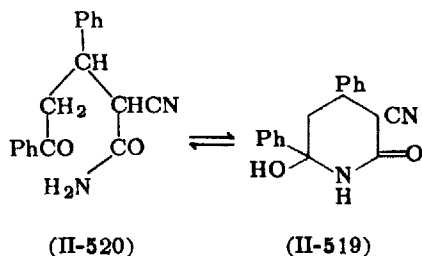


(d) **With Methylenic Amides.** A variety of α,β -unsaturated carbonyl compounds have been condensed with cyanoacetamide under basic catalysis, the product being obtained at various stages (Tables II-109 and II-110).

With one equivalent of sodium ethoxide, the dihydropyridine stage was reported; unsaturated ketones gave dihydropyridinols (II-517) (1327), and unsaturated esters gave glutarimides (II-518) (1355). A small amount of the pyridine might be obtained at the same time; thus, ethylideneacetophenone gave the dihydropyridinol in 80% and the pyridinol in 10% yield (1360).

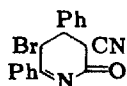


With organic bases as catalysts (piperidine or diethylamine) the condensation of unsaturated ketones and cyanoacetamide stops at an earlier stage. The products have been assigned structures such as II-519, based on chemical reactivity (1327,322), but have not been

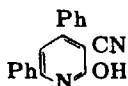


adequately distinguished from the open-chain isomers (II-520), and may well be tautomeric mixtures of the two. Dehydration by hydrogen chloride, phosphorus trichloride, or sodium ethoxide converts them to the dihydropyridinols.

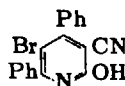
Similar intermediates were obtained by using sodium methoxide in trace amounts (307), and the products furthermore aromatized by means of bromine. Thus the intermediate (II-519 or II-520) gave a bromo derivative thought to be II-521, which could either eliminate hydrogen bromide to give a pyridinol (II-522), or be oxidized to a bromopyridinol (presumably II-523). In analogous fashion (1261) α -methoxybenzalacetophenone gave an intermediate



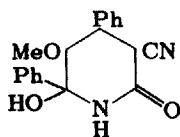
(II-521)



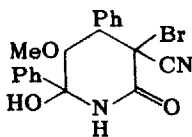
(II-522)



(II-523)



(II-524)



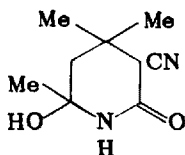
(II-525)



(II-526)

assumed to be II-524, which was dehydrated to a dihydropyridinol, or brominated to II-525 (assumed); the latter in turn gave a pyridinol (II-526).

Like other unsaturated ketones, mesityl oxide condensed with cyanoacetamide in the normal sense and gave the same product (assigned structure II-527) with piperidine or an equivalent of sodium



(II-527)

ethoxide (1360). This was dehydrated to the dihydropyridinol, which, as expected, could not be oxidized to a pyridinol.

A synthetic method which requires no separate oxidation step, and proceeds in high yield, is the condensation of an unsaturated ketone or aldehyde with carbamoylmethylpyridinium chloride (II-528) (906). The Michael adduct, a betaine (II-529), was isolated in one case; more commonly it was treated *in situ* with acetic acid, giving the pyridinol directly, with simultaneous formation of pyridinium chloride (II-530).

α,β -Acetylenic ketones have also been condensed with cyanoacetamide. In this case, of course, no dihydro stage is observed, the products being pyridinols (II-531) (305). Acetylenic aryl ketones gave higher yields than acetylenic alkyl ketones; sodium ethoxide as catalyst gave higher yields than piperidine (Table II-111).

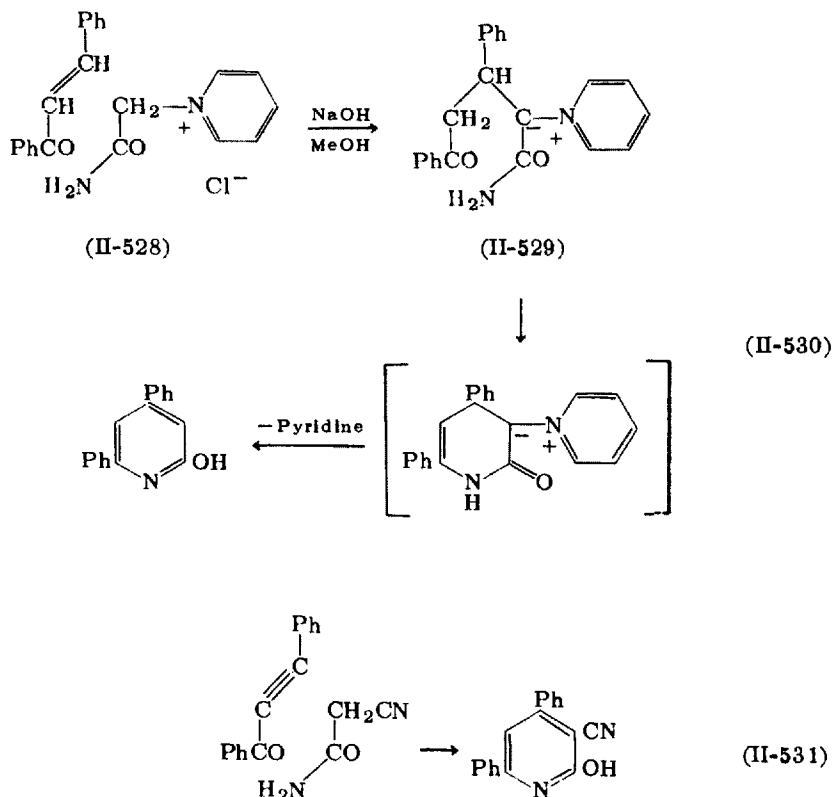
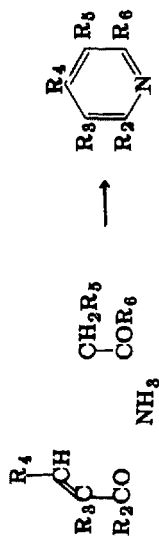


TABLE II-105. Condensation of α , β -Unsaturated Aldehydes and Ketones with Methylene Aldehydes and Ketones



R_1	R_2	R_3	R_4	R_5	R_6	Conditions	Yield, %	Ref.
H	H	H	H	H	H	NH_3 , Al_2O_3 , 370–80°	2.5 ^a	1316
Me ^b	H ^b	Me	Me, Me ^b	Me	Me	NH_3 , 25% aq. NaOH, 100°, 2 hrs.	^b	455, 1477
H	Me	Me	Et	Me	H	NH_3 , alc., 200°	^c	742
H	H	H	Ph	H	H	NH_3 , Al_2O_3 , 310°	11–19 ^d	1001, 77
Me	H	H	Ph	H	Me	NH_3 , Al_2O_3 , 310°	16	1001, 77
						Aq. NH_3 , NH_4OAc , 250°, 3 hr., pressure	4 ^e	1165

Ph	H	Ph	H	Ph	Aq. NH ₃ , NH ₄ OAc, 250°, 3 hr., pressure	39	1165
Ph	Ph	Ph	Ph	Ph	Aq. NH ₃ , NHOAc, 250°, 3 hr., pressure	8	1165
Ph	H	<i>p</i> -ClC ₆ H ₄	H	Ph	Aq. NH ₃ , NH ₄ OAc, 250°, 3 hr., pressure	32	1165
Ph	H	<i>m</i> -Anisyl	H	Ph	Aq. NH ₃ , NH ₄ OAc, 250°, 3 hr., pressure	18	1165
Ph	H	<i>p</i> -Anisyl	H	Ph	Aq. NH ₃ , NH ₄ OAc, 250°, 3 hr., pressure	11	1165
Me	CO ₂ Et	Ph	Ph	Ph	Alc. NH ₃ , 1 d.	/	239

^aAs picrate; by-products, 2-picoline and 3-picoline, as picrates.

^bUsed mesityl oxide; orientation different from type equation; obtained a mixture of 2,2,4,5,6-pentamethyl-1,2-dihydropyridine and 6-ethyl-2,2,4-trimethyl-1,2-dihydropyridine (11% yield), and also 2,2,4,6-tetramethyl-1,2-dihydropyridine (13% yield).

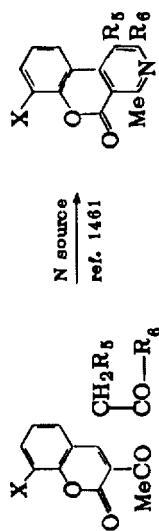
^cProduct identified as a "C₆-pyridine."

^dBy-product, 2-phenylpyridine (1-4% yield).

^eOther products, 2,4-dimethyl-6-phenylpyridine (5% yield), and a methyl-phenyl-styrylpyridine (1% yield).

^fProduct was ethyl 2-methyl-4,5,6-triphenylnicotinate.

TABLE II-106. Condensation of 3-Acetylcoumarins with Methyl (or Methylene) Ketones



R_4	R_5	X	N Source	Conditions	Yield, %
H	Me	H	Cyanoacetamide	175–180°, 4 hr.	32
H	Me	OMe	Cyanoacetamide	175–180°, 6 hr.	42
H	Et	H	Cyanoacetamide	175–180°, 4 hr.	37
$-(CH_2)_4-$	Ph	H	Cyanoacetamide	175–180°, 4 hr. ^a	21
H ^b	3-Coumarinyl ^b	H ^b	Cyanoacetamide	175–180°, 4 hr.	52
			Malonamide	165°, 15 min.	49
			Formamide	165°, 15 min.	11
			NH ₄ formate	165°, 15 min.	47
			Urea	165°, 15 min.	47
H ^b	8-Methoxy-3-coumarinyl ^b	OMe ^b	Cyanoacetamide	205°, 15 min.	64

^aAn intermediate was isolated, which, in aq. HCl at boil, 12 hr., gave the product in over-all yield indicated.^bI.e., the self-condensation of the 3-acetylcoumarin.

TABLE II-107. Condensation of α , β -Unsaturated Aldehydes and Ketones with Methylene Ketimines

R_1	R_3	R_4	R_5	R_6	I II III
					Product (Yield) Product Further Converted (Yield) Ref.
Me	COMe	Me	COMe	Me	II II 195
Me	COMe	Me	COMe ^a	Me ^a	II^a II^a 195
Me	COMe	Ph	COMe	Me	II II 195
Me	COMe	<i>o</i> -O ₂ NPh	COMe	Me	II (32%) II (32%) 1164
Ph	COMe	Ph	<i>p</i> -MeC ₆ H ₄ CO CO ₂ Et	Me	II II 1364
H	H	H	H	Me	II (57%), I (15%) II (57%), I (15%) 1756
H	H	Me	CO ₂ Et	Me	II (75%) II (75%) 1756

(continued)

TABLE II-107 (Continued)
Condensation of α,β -Unsaturated Aldehydes and Ketones with Methylenic Ketimines

R_2	R_3	R_4	R_5	R_6	Conditions	Product (Yield)	Product Further Converted (Yield)	Ref.
Me	CO_2Et	Me	COMe	H	Cold over- night; water bath several hr.	II (26%)	w. HNO_3 to I (82%)	1428
Me	CO_2Et	Me	COMe	Me	Water bath, long time	II		196
Me	CO_2Et	Ph	COMe	Me	Water bath, 1-2 hr.	II	w. dil. HNO_3 to I (low)	195
Me	COMe	Ph	CO_2Et	Me	Water bath, 1-2 hr.	II		195
Me	COMe	$o\text{-O}_2\text{NC}_6\text{H}_4$	CO_2Et	Me	Water bath, 2 d.	II (42%)	w. CrO_3 to I	1164
Me	COMe	$m\text{-O}_2\text{NC}_6\text{H}_4$	CO_2Et	Me	Steam bath, 16 hr.	II (66%)		1145
Me	COMe	$p\text{-Me}_2\text{NC}_6\text{H}_4$	CO_2Et	Me	Steam bath, 16 hr.	II (80%)		1128
Me	COMe	$p\text{-Me}_2\text{NC}_6\text{H}_4$	CO_2Et	Me	Steam bath, 16 hr.	II (35%)		1128

Me	CO ₂ Et	Me	CO ₂ Et	Me	Exotherm. II	w. HNO ₂ to I	196
Me	CO ₂ Et	Me	CO ₂ Et	Me	Exotherm. II (81%)	w. HNO ₂ to I	196
Ph	CO ₂ Et	Ph	CO ₂ Et	Me	Et ₂ NH, alc., 50-60°, 3 d.	w. Ac ₂ O or PCl ₃ to II w. N ₂ O ₃ to I	517, 515
Ph	CO ₂ Et	m-O ₂ NC ₆ H ₄	CO ₂ Et	Me	Steam bath, 16 hr.		1128
Me	H	Ph	CN	Me	NaOEt, alc., I reflux, 5 hr.		515
Ph	H	Ph	CN	Me	NaOEt, alc., I water bath		303, 1688
Ph	H	CH=CHPh		Ph	NaOEt, alc., I water bath		515, 517
Ph	H	Ph	CN	Ph	NaOEt, alc., I water bath		303, 1688
p-Tolyl	H	Ph	CN	Me	NaOEt, alc., I		303
-(CH ₂) ₄ -	Ph	Ph	CN	p-Tolyl	Trace I		1455
					NaOMe, RT 2 wks.; reflux 4 hr.		

(continued)

TABLE II-107 (Continued)
Condensation of α,β -Unsaturated Aldehydes and Ketones with Methylenic Ketimines

R_2	R_3	R_4	R_5	R_6	Conditions	Product (Yield)	Product Further Converted (Yield)	Ref.
Ph	H	$\text{CH}=\text{CHPh}$	CN	<i>p</i> -Tolyl	NaOEt, alc., water bath	I		303,1688
Ph	H	Ph	CN	<i>p</i> -Tolyl	NaOEt, alc., water bath	I		303,1688
Ph	H	<i>o</i> -ClC ₆ H ₄	CN	Me	NaOEt, alc.	II	w. CrO ₃ , or dil. HNO ₃ , to I	524
Ph	H	<i>m</i> -ClC ₆ H ₄	CN	Me	NaOEt, alc., reflux 4 hr.	I (30%)		524
Ph	H	<i>p</i> -ClC ₆ H ₄	CN	Me	NaOEt, alc., reflux 2 hr.	I (35%)		524
Ph	H	<i>o</i> -Anisyl	CN	Me	NaOEt, alc., reflux 2 hr.	I + II	II w. CrO ₃ , or HNO ₃ , to I	524
Ph	H	<i>p</i> -Anisyl	CN	Me	NaOEt, alc., water bath	I		303,1688
Ph	H	<i>p</i> -Anisyl	CN	Ph	NaOEt, alc., water bath	I		303,1688
Ph	H	<i>p</i> -Anisyl	CN	<i>p</i> -tolyl	NaOEt, alc., water bath	I		303,1688

Ph	H	o-EtOC ₆ H ₄	CN	Me	NaOEt, alc., I + II reflux 2 hr.	II w. CrO ₃ or HNO ₃ to I	524
Ph	H	3,4-Methylene- dioxyphenyl	CN	Me	NaOEt, alc., I water bath		303,1688
Ph	H	3,4-Methylene- dioxyphenyl	CN	Ph	NaOEt, alc. I		303
Ph	H	3,4-Methylene- dioxyphenyl	CN	p-Tolyl	NaOEt, alc., I water bath		303,1688
Me	COMe	o-O ₂ NC ₆ H ₄	CN	Me	Water bath, II 2 d.	w. CrO ₃ to I	1164
Me	COMe	2-MeO-5-NO ₂ - C ₆ H ₃	CN	Me	Fuse	w. CrO ₃ to I	1525
Me	CO ₂ Et	Ph	CN	Me	Et ₂ NH, alc., III 40°, 48 hr.	on heating, (88%) or w. Ac ₂ O to II; w. HNO ₃ to I	515
Me	CO ₂ Et	Ph	CN	Ph	Trace NaOMe, MeOH, RT 2 wks.; water bath		885

(continued)

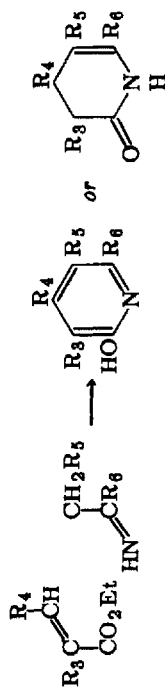
TABLE II-107 (Continued)
Condensation of α,β -Unsaturated Aldehydes and Ketones with Methylenic Ketimines

R_2	R_3	R_4	R_5	R_6	Conditions	Product (Yield)	Product Further Converted (Yield)	Ref.
Me	CO_2Et	Ph	CN	<i>p</i> -Tolyl	Trace NaOMe, MeOH, RT 2 wks.; water bath	I		885
Me	CO_2Et	Ph	CN	<i>p</i> -Anisyl	Trace NaOMe, MeOH, RT 2 wks.; water bath	I		885

^aThe *N*-methylimine was used, giving the *N*-methyl derivative of the type product.

^bBy-product, 2,4,6-triphenyl-1,4-dihydropyridine-3,5-dicarbonitrile.

TABLE II-108. Condensation of α,β -Unsaturated Esters with Methylenic Ketimines



I				II		
R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield)	Ref.
CO ₂ Et	Me	CO ₂ Et	Me	130-50°, 40 mm., 9 hr. RT, 10 d.	II II (70-90%)	1712 1619
CO ₂ Et	Ph	CO ₂ Et	Me	140-60°, 7 hr. 130-50°, 40 mm., 9 hr. 130-50°, 18 hr.; 150-70°, 9 hr.	II II (82%) II (75%) II ^a	1248 1619 1712 1712
CO ₂ Et	<i>p</i> - <i>i</i> -Pr-C ₆ H ₄	CO ₂ Et	Me	140-55°, 12 hr.	^b	1619
CO ₂ Et	Ph	CN	<i>p</i> -Tolyl	Trace NaOMe, MeOH, RT, 2 wks.; reflux 4 hr.	I	1455
CO ₂ Et	Ph	CN	<i>p</i> -Anisyl	Trace NaOMe, MeOH, RT, 2 wks.; reflux 4 hr.	I	1455
CN	Ph	CN	Ph	Et ₃ NH, alc., RT, 2 d.	^c	885
CN	Ph	CN	<i>p</i> -Tolyl	NaOEt, alc., reflux 2 hr.	I	885
CN	Ph	CN	<i>p</i> -Anisyl	NaOEt, alc., reflux 2 hr.	I	885

^aBy-products: (1) Derivative of II in which $R_3 = \text{CONHCMe}=\text{CHCO}_2\text{Et}$; (2) Derivative of II in which R_3 or $R_4 = \text{H}$; (3) a quinoline.

^b Product is derivative of II in which $R_1 = \text{CONHMe} \equiv \text{CHCO}_2\text{Et}$.

Report not clear on nature of product.

TABLE II-109. Condensation of α , β -Unsaturated Ketones with Methylenic Amides and Esters

					Ref.		
R ₂	R ₃	R ₄	R ₅	Conditions	Product (Yield)	Product Further Converted	Ref.
Me	H	Me	CN	NaOEt, alc., 2 d.	II	w. HNO ₃ to I	1360
Me ^a	H ^a	Me, Me ^a	CN	Piperidine, alc., 3 d.	III	dehydrated to II	1360
Me ^b	H ^b	Me, Me ^a	CN	NaOEt, alc., or piperidine, alc.	III ^a	w. HCl in CCl ₄ to II ^a	1360
Me ^b	H ^b	Me, Me ^b		<i>Ethyl cyanoacetate</i> , NH ₃	<i>b</i>		710
Me ^b	H ^b	Me, Me ^b		<i>Ethyl cyanoacetate</i> , MeNH ₂	<i>b</i>		710
Me	-(CH ₂) ₄ -		CN	NaOEt, alc.	II (60%)		1360
Ph	H	Me	CN	Piperidine, alc.	II (50%)		1360
				NaOEt, alc., 2 d.	II (80%); I (10%)	II w. HNO ₃ to I	1360
Me	H	Ph	CN	Piperidine, alc., 3 d.	III		1360
				NaOEt, alc., 3-4 d.	II (65%)	w. HNO ₃ to I	1327
				Piperidine or Et ₃ NH, 40-50°, 2-3 wks.	III 60%	w. Ac ₂ O or HCl to II	1327

Et	H	Ph	CN	NaOEt, alc., 2 d. Piperidine or Et ₃ NH, 40-50°, 1-2 wks. NaOEt, alc. Et ₃ NH, alc., warm 3 hr. Trace NaOMe, MeOH	II (60%) III (45%) I III III ^c	w. HNO ₂ to I w. Ac ₂ O or HCl to II	1327 1327
	-(CH ₂) ₄ -	Ph	CN				1455 1455
Ph	H	Ph	CN			w. HCl or HBr to II w. Br ₂ and base to I II w. HNO ₂ to I w. HNO ₂ to I	307 1327
				NaOEt equiv., alc., RT, 2 d. Piperidine or Et ₃ NH, alc., 45-50°, 1 wk. NaOEt, alc., 2 d.	II (87%) III (75%) II (80%); I (10%)	w. Ac ₂ O or HCl to II	1327 1327 1360
p-Tolyl	H	Me	CN			II w. HNO ₂ to I	1360
				Piperidine, alc., 3 d. NaOEt, alc., RT, 2 d. Piperidine or Et ₃ NH, alc., 40-50°, 3-4 d. Na deriv. of cyanoacetamide	III II (90%) III (75%) II	w. HNO ₂ to I w. Ac ₂ O or HCl to II	1360 1327 1327
Ph	H	p-Anisyl	CN			w. HNO ₂ to I	314
Me	CO ₂ Et	Ph	CN	Et ₃ NH, alc., overnighr	III (68%)	w. PCl ₃ to II	322

(continued)

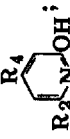
TABLE II-109 (Continued)
Condensation of α,β -Unsaturated Ketones with Methylene Amides and Esters

R ₂	R ₃	R ₄	R ₁	Conditions	Product (Yield)	Product Further Converted	Ref.
Ph	OMe	Ph	CN	Trace NaOMe, MeOH	III (55-60%)	w. PCl ₅ or AlCl ₃ to I w. HCl to II w. Br ₂ and AcCl to I	1261 906
H	H	Ph	1-Py ⁺ Cl ^{-d}	NaOH, aq. MeOH, 10 min.; add HOAc, heat	47% ^d		906
Me	H	Ph	1-Py ⁺ Cl ^{-d}	NaOH, aq. MeOH, 10 min.; add HOAc, heat	60% ^d		906
Ph	H	Ph	1-Py ⁺ Cl ^{-d}	NaOH, aq. MeOH, 10 min.; add HOAc, heat	82% ^d		906
3-Py	H	3-Py	1-Py ⁺ Cl ^{-d}	NaOH, MeOH, RT, 30 min.; add HOAc	80% ^d		906, 873
Ph	H	Ph	1-Py ⁺ Cl ^{-e}	Me ₂ NH, aq. MeOH, reflux 0.5 hr.; to dryness; residue at 205°, 7 min.	57% ^e		906

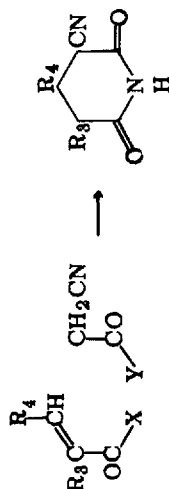
^aMesityl oxide used; products III and II were the 4,4-dimethyl compounds.

^bMesityl oxide used; the orientation was different from the type equation; product was 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydronicotinonitrile (or its 1-methyl derivative).

^cProduct reported as the open-chain adduct; but Barat (1327) assigned cyclic structure III.

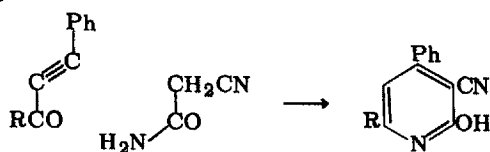
^dThe methylenic amide was 1-carbamoylmethylpyridinium chloride; product was  co-product, pyridinium chloride.

^eThe methylenic amide was N-methylcarbamoylmethylpyridinium chloride; product was as in Note d, N-methylpyridone.

TABLE II-110. Condensation of α,β -Unsaturated Esters (or Amides) with Cyanoacetamide (or Cyanoacetic Ester)

R_3	R_4	X	Y	Conditions	Yield, %	Ref.
H	H	OEt	NH ₂	NaOEt, alc., RT, 1 wk.		1355
H	Me	OEt	NH ₂	NaOEt, alc., RT, 1 wk.		1355
H	Ph	OEt	NH ₂	NaOEt, alc., RT, 1 wk.		1355
H	Ph	NH ₂	OEt	NaOEt, alc., RT, 1 wk.		1355
H	<i>p</i> -O ₂ NC ₆ H ₄	OEt	NH ₂	NaOEt, alc., RT, 1 wk.		1355
H	<i>p</i> -O ₂ NC ₆ H ₄	NH ₂	OEt	NaOEt, alc., RT, 1 wk.		1355
CO ₂ Et	Ph	OEt	NH ₂	Et ₃ NH, RT, 3 d.	82	1455
				NaOEt, alc., overnight	^a	1455
CN	Ph	OEt	NH ₂	Et ₃ NH, alc., RT, overnight	59	322

^aReported to be the pyridinediol, 2,6-dihydroxy-4-phenyl-5-carbethoxynicotinonitrile.

TABLE II-111. Condensation of α,β -Acetylenic Ketones with Cyanoacetamide

R	Conditions	Yield, %	Ref.
Me	NaOEt, alc., RT, 1 d.	40-50	305
Et	Na cyanoacetamide, alc., RT, 12 hr.		1354
	NaOEt, alc., RT, 1 d.	40	305
	Et ₃ NH or piperidine, aq. alc., RT		305
Ph	NaOEt, alc., RT, 1 d.	75	305
	Piperidine, aq. alc., RT, 1 wk.	40-50	305
	N-methylcyanoacetamide	^a	305
<i>p</i> -Tolyl	NaOEt, alc., RT, 1 d.	78	305
	N-methylcyanoacetamide	^a	305
<i>p</i> -O ₂ NC ₆ H ₄	NaOEt, alc., RT, 1 d.	75	305

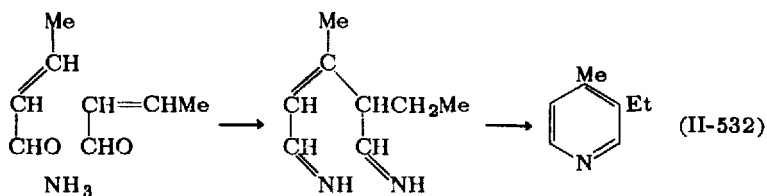
^aProduct is the 1-methyl-2(1*H*)pyridone.

c. Self-Condensation of α,β -Unsaturated Aldehydes or Ketones with Ammonia

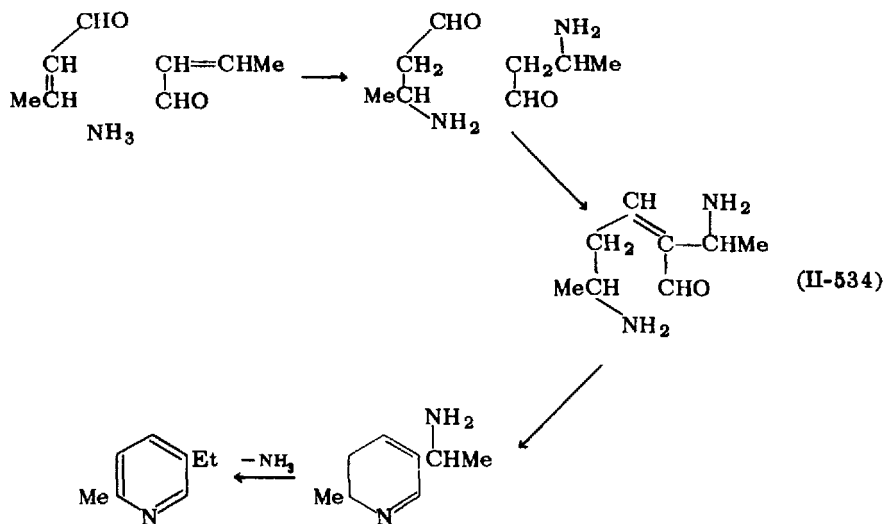
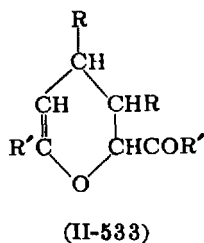
A third type of 3-2 synthesis, of limited scope, is the reaction of two moles of an unsaturated aldehyde or ketone with ammonia. This is carried out either in the vapor phase or in solution at high temperature, and generally gives mixtures of pyridine bases in low yield (Table II-112).

The reaction of crotonaldehyde with ammonia in the vapor phase was effected by Chichibabin, over alumina at 340° (73) or kaolin above 385° (676,677,722). The main product was 3-ethyl-4-picoline in low yield, with lesser amounts of 5-ethyl-2-picoline, 2-picoline, 4-picoline, and higher homologs. On the other hand crotonaldehyde with aqueous ammonia in the liquid phase, at 250° under pressure, and ammonium acetate as catalyst, gave a higher yield (18%) of pyridine base which was exclusively 5-ethyl-2-picoline (1165).

Apparently two different modes of condensation are involved in the two media. The main vapor-phase reaction goes according to



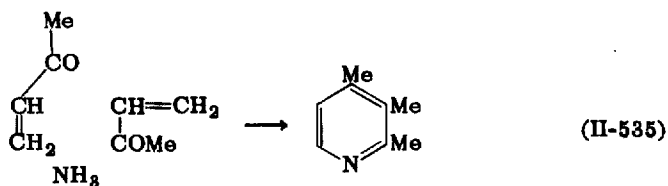
II-532, which is the dimerization of an olefin; polymerization in the same sense would account for the predominance of resin. Probably ammonia enters before the dimerization step, since it has been shown that in the absence of ammonia (or catalyst) dimerization occurs by 1,4-addition (II-533) (902,903). In the liquid phase the reaction scheme is II-534, in which ammonia saturates the double bond as a first step, and aldol condensation follows. The picolines formed in



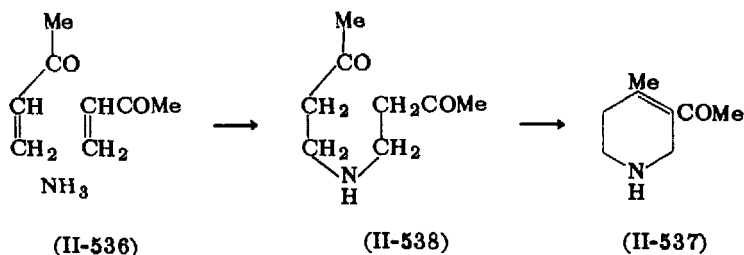
the vapor reaction probably arise by cleavage of crotonaldehyde to acetaldehyde, which forms 2-picoline by a 2-2-1 condensation, and 4-picoline by a 3-2 condensation (crotonaldehyde and acetaldehyde).

In a similar fashion acrolein and ammonia reacting at 350° over aluminum phosphate, in benzene vapor as a diluent, gave a 56% yield of 3-picoline and 1% of pyridine. The presence of a diluent was necessary to prevent polymerization, though other diluents and catalysts could be used (1122,1809). The reaction of acrolein in the liquid phase gave only polymer (1165). Glycerol has been substituted for acrolein in various experiments (Table II-113). In early work glycerol was heated with ammonium phosphate (91,92,93), ammonium sulfate (90), or a mixture of phosphorus pentoxide and acetamide (85,88). In a modern experiment glycerol was heated with aqueous ammonia vapors at 300–400° over alumina, but gave only a 6% yield of 3-picoline (374). Similarly, allyl alcohol, which may also be a precursor of acrolein, was heated with ammonia over cadmium phosphate or tungstate (620) or over an alumina-copper catalyst (526,531,1690,1691), giving in the latter case a 20% yield of 3-picoline. The formation of 3-picoline from acrolein can occur by either mechanism II-532 or II-534 though the former seems more likely, as the one which operates in the vapor phase. Among the by-products variously reported are pyridine (1809,92) and 2-picoline (92,93), which probably arise by cleavage of acrolein to formaldehyde and acetaldehyde; then pyridine is formed from acrolein and acetaldehyde (3-2 condensation) and 2-picoline from acetaldehyde alone (2-2-1 condensation).

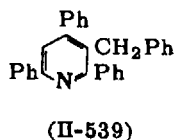
The reaction of methyl vinyl ketone with ammonia was run in the liquid phase under the same conditions as for crotonaldehyde, and gave a 12% yield of 2,3,4-collidine (II-535) (1165). The mechanism is probably analogous (II-534).



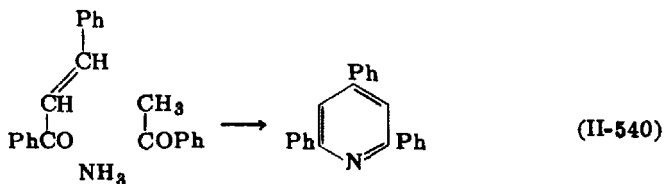
Methyl vinyl ketone can also react in a sense we have not yet considered (II-536). When treated with aqueous ammonia at room temperature it gave an oil of undetermined nature which in dilute hydrochloric acid at 120° yielded the tetrahydropyridine II-537 (656); the intermediate II-538 is assumed.



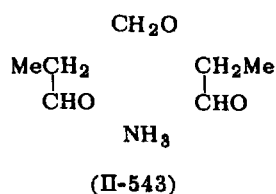
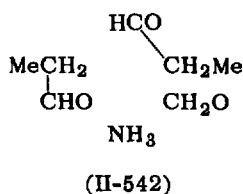
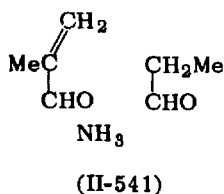
Finally, an unsaturated ketone may in its main reaction cleave by a reverse-aldol process. This leads to simpler pyridines than normally expected. Thus benzalacetophenone in aqueous ammonia at 250°, in the presence of ammonium acetate, gave none of the expected II-539, but rather a 42% yield of 2,4,6-triphenylpyridine.



This must have arisen by cleavage of benzalacetophenone to acetophenone, followed by a new 3-2 combination (II-540). Ethylideneacetone behaved similarly (1165). α -Methylacrolein underwent such a dealdolization in the vapor phase, when heated with ammonia above 325° over a boron phosphate catalyst (1501). The product,

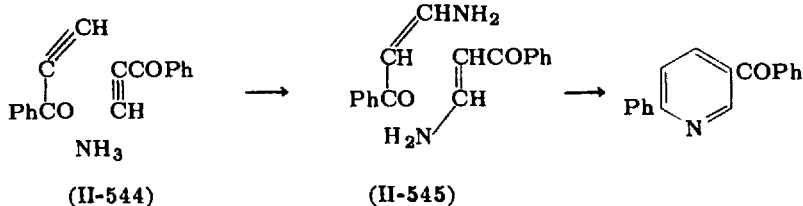


3,5-lutidine, could have been formed *via* propionaldehyde and formaldehyde by any of the combinations II-541, II-542, or II-543.



Acetals and β -ethoxyacetals have been used in place of unsaturated aldehydes in the liquid-phase reaction with ammonia, *e.g.*, 1,1,3-triethoxybutane for crotonaldehyde (1165). These are considered later (p. 470).

Acetylenic ketones and ammonia give pyridines under milder conditions than olefinic ketones, in refluxing alcohol (1505, 1506, 1269), and by a different mode of combination (II-544). No doubt



ammonia first adds to the triple bond, forming enamine compounds (II-545), which condense in the recognized manner of such compounds (p. 379).

TABLE II-112. Self-Condensation of α , β -Unsaturated Aldehydes or Ketones

Unsat'd Carbonyl Compound	Conditions	Products (Yields)	Ref.
Acrolein	NH ₃ , addn. compound, distil	3-Picoline (v. small)	1659,89
	NH ₃ , AlPO ₄ , 350°, aq. vapor	3-Picoline (51%)	1122,1809
	NH ₃ , AlPO ₄ , 350°; benzene or MeOH	3-Picoline (56%), pyridine (1%)	1122,1809
	NH ₃ , catalyst (Al ₂ O ₃ ; silica gel; Na ₂ SiO ₃ -silica; or ThO ₂ -silica), 350°, benzene	3-Picoline	1122,1809
α -Methylacrolein	NH ₃ , addn. compound, NH ₃ , Al ₂ O ₃ , MeOH, 350°	None	1122,1809
	NH ₃ , BPO ₄ , 325-70°	3,5-Lutidine	1501
	do.	3,5-Diethylpyridine	1501
	NH ₃ , Al ₂ O ₃ , 340°	3-Et-4-picoline (7.5%); 5-Et-2-picoline (v. small); 2-picoline; 4-picoline	73
α -Ethylacrolein	NH ₃ , kaolin, 385-96°	3-Et-4-picoline (mainly); 5-Et-2-picoline;	676,677
		2-propenylpyridine;	
		4-Pr-Py; 2-Pr-Py	
		5-Et-2-picoline (18%)	
Crotonaldehyde	NH ₃ , aq., NH ₄ OAc, 250°, 3 h., pressure		1165

(continued)

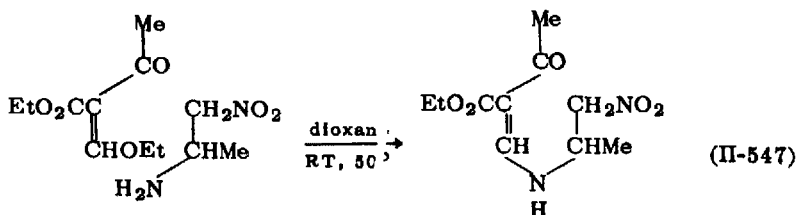
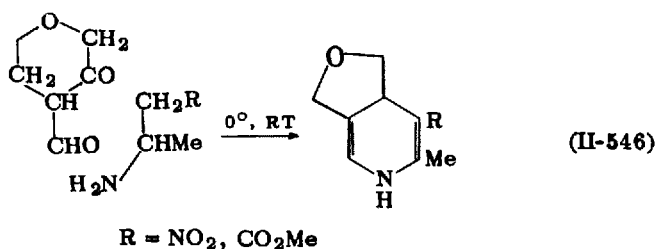
TABLE II-112 (Continued)
Self-Condensation of α,β -Unsaturated Aldehydes or Ketones

Unsat'd Carbonyl Compound	Conditions	Products (Yields)	Ref.
Methyl vinyl ketone	NH ₃ , aq., NH ₄ OAc, 250°, 3 hr., pressure NH ₃ (0.5 mole), aq., 20°, 0.5 hr.; the oil treated w. dil. HCl, 120-40°, 4 hr.	2,3,4-Collidine (12%) 3-Acetyl-1,2,5,6-tetrahydro-4-picoline (mainly); 2,3,4-collidine	1165 656
2-Thienyl ethynyl ketone	As above; the oil treated w. NaOH, or HCl-FeCl ₃ , (NH ₄) ₂ CO ₃ , aq. alc., reflux 2.5 hr.	2,3,4-Collidine 6-(2-Thienyl)-3-thienylpyridine	656 1505
3-Methyl-2-thienyl ethynyl ketone	(NH ₄) ₂ CO ₃ , aq. alc., reflux 2.5 hr.	6-(3-Methyl-2-thienyl)-3-thienylpyridine (89%)	1505
Phenyl ethynyl ketone	(NH ₄) ₂ CO ₃ , aq. alc., reflux 2 hr. NH ₄ OAc, HOAc, RT 3 d	6-Phenyl-3-benzoylpyridine (29%) 6-Phenyl-3-benzoylpyridine (20%)	1506 1269

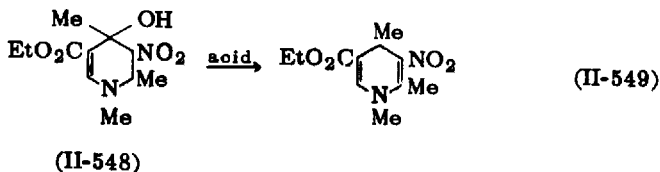
d. Miscellaneous 3-2 Condensations

Besides the three main types of 3-2 condensation there are numerous variants which have occasionally been reported. In general these are characterized by a lower state of oxidation of the starting materials.

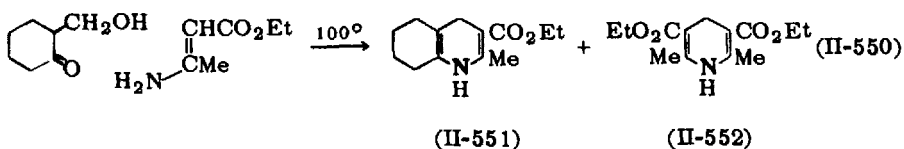
β -Ketoaldehyde (or its Enol Ether) with a Methylenic Amine. The condensation II-546 of the β -ketoaldehyde with primary amines proceeded on mixing, without added catalyst (1814). Use of an



enol ether gave an open-chain adduct which could not be cyclized by acidic or basic agents (II-547); the same enol ether with the corresponding *N*-methylamine gave a cyclic product (II-548) directly, which could be dehydrated to a dihydropyridine (II-549) (532).

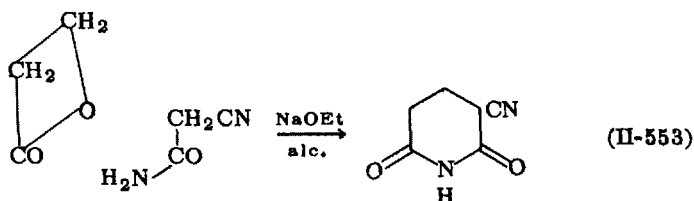


β -Hydroxyketone with β -Aminocrotonic Ester. In this reaction (II-550) the 3-2 product (II-551) was the minor one (20% yield); it was converted by boiling hydrochloric acid to the aromatic pyridine

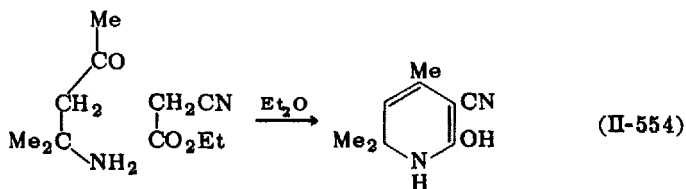


(tetrahydroquinoline), no doubt by disproportionation, with saponification of the ester. The major product (II-552, 50% yield) probably arose by cleavage of the hydroxyketone to formaldehyde, and a subsequent 2-1-2 condensation (formaldehyde with β -aminocrotonic ester) (889).

β -Lactone with Cyanoacetamide. The reaction II-553 proceeded in 12% yield (1485); the lactone is perhaps converted to an α,β -unsaturated ester which undergoes a normal condensation with cyanoacetamide.

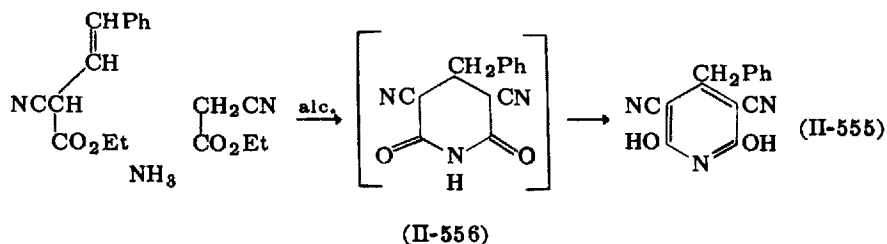


β -Aminoketone with Cyanoacetic Ester. The starting material, diacetonamine, is prepared from mesityl oxide and ammonia. The product of reaction II-554 is therefore the same as obtained from mesityl oxide, ammonia, and cyanoacetic ester (p. 442) (710).

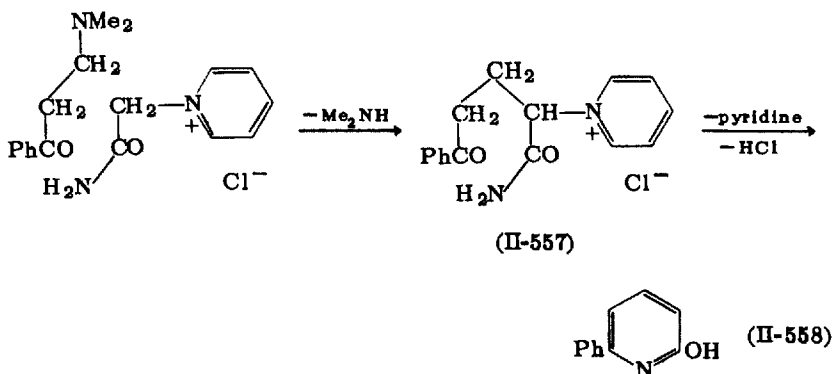


β,γ -Unsaturated Ester with Cyanoacetic Ester. The starting material, α -styrylcynoacetic ester, was shown to be a β,γ -unsaturated compound by a variety of chemical reactions. Nevertheless, in pyridine synthesis (II-555) it behaved like an α,β -unsaturated ester (1251), giving the product in 55% yield. Simultaneously, a 48% yield of $\text{PhCH}_2\text{CH}_2\text{CH}(\text{CN})\text{CONH}_2$ was formed, showing that oxi-

ation of the primary product (II-556, a dihydropyridine) occurred by reduction of the unsaturated starting material.

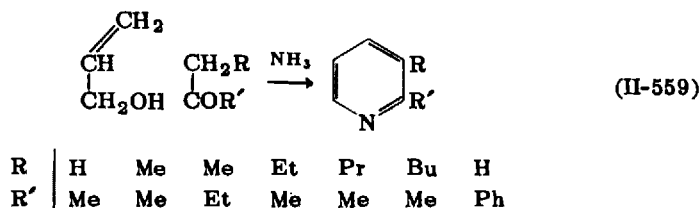


Mannich Base with Methylenic Amide. The reaction to II-557 occurred on warming in methanol without added catalyst. Presumably the Mannich base abstracts a proton from the methylenic amide, and during the primary condensation dimethylamine is displaced. The adduct II-557 has been isolated, or cyclized in the crude stage (II-558) by heat alone or by treatment with acetic acid in formamide; over-all yield, 50–56%; pyridinium chloride is simultaneously formed. A similar condensation was run using 2-dimethylaminomethylcyclohexanone as the Mannich base; yield, 22–29% (906).



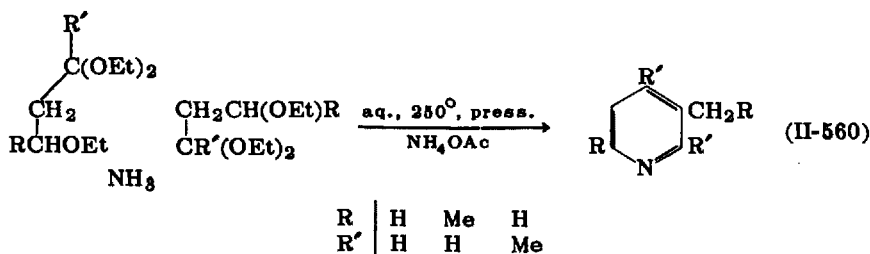
Three-Carbon Compounds with Acetylene. Acrolein, or allyl alcohol, heated with acetylene and ammonia over a cadmium tungstate or cadmium chromate catalyst was reported to give pyridine (619). Allylamine behaved similarly over cadmium phosphate and required no ammonia (620).

Allyl Alcohol with Methylenic (or Methyl) Ketones. Allyl alcohol has been reacted with various ketones and ammonia at temperatures above 350° , over catalysts of cadmium phosphate supported on clays (II-559); yields of pyridine bases ranging from 15% to 30% were reported (832,833). The by-products, 3-picoline and 3,5-lutidine, are formed by the reaction of allyl alcohol alone with ammonia (next Section).

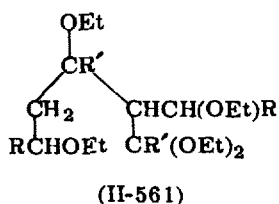


Three-Carbon Compounds with Ammonia. A number of three-carbon compounds resemble acrolein in reacting with ammonia at high temperatures to give 3-picoline (p. 462) (Table II-113). Glycerol no doubt forms acrolein initially. 1,2,3-Tribromopropane (89) may form acrolein imine, by reaction with ammonia and loss of hydrogen bromide. Allyl alcohol or allylamine reacts with ammonia over a contact catalyst, and may undergo dehydrogenation first to acrolein or acrolein imine, or the cyclization product may be dehydrogenated as a last step. The formation of 3,5-lutidine as a by-product may be explained by cleavage of allyl alcohol (or allylamine) to formaldehyde, and isomerization to propionaldehyde (or propionaldimine); the new intermediates then undergo a 2-2 condensation.

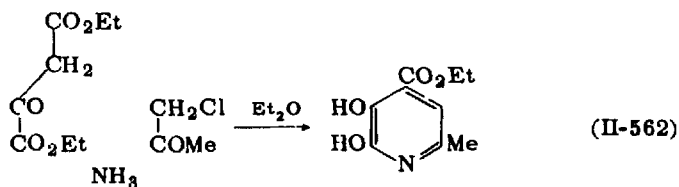
Unsaturated Acetals and β -Ethoxyacetals (or Ketals) with Ammonia. In place of an α,β -unsaturated aldehyde (page 460) one may use its acetal or a β -ethoxyacetal in the reaction with aqueous ammonia (II-560) (1165). Under the conditions used acrolein itself or



acrolein diethyl acetal gave only tars, while 1,1,3-triethoxypropane gave a 20% yield of 3-picoline. Crotonaldehyde and its diethyl acetal gave about the same yield (18–19%) of 5-ethyl-2-picoline, while 1,1,3-triethoxybutane gave 46%. Similarly the replacement of methyl vinyl ketone by 1,3,3-triethoxybutane raised the yield of 2,3,4-collidine from 12% to 20%. Though the investigators proposed gradual release of the unsaturated aldehyde (or ketone) in the reaction medium, it is also likely that direct condensation occurs with displacement of ethoxide ions. Thus the first intermediate would be II-561, and further displacements would occur by attack of ammonia, ring-closure, and elimination of ethanol.



Oxalacetic Ester with Chloroacetone. The condensation II-562 is an unusual 3-2 synthesis in that the *three*-carbon component sup-



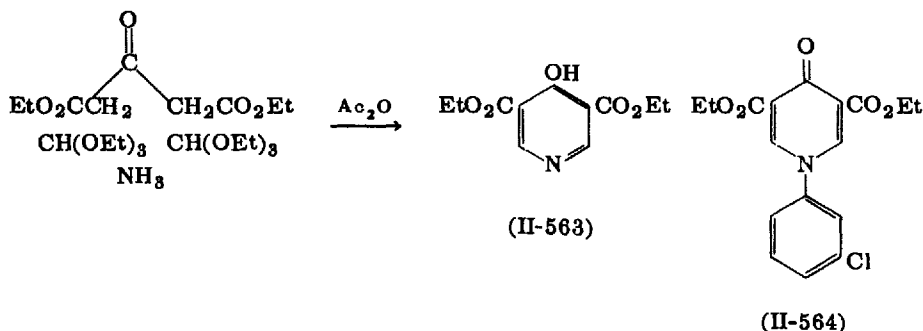
plies the active methylene group, and the product is a 2,3-pyridinediol (360,1675).

TABLE II-113. Pyrolysis of Three-Carbon Compounds to 3-Picoline

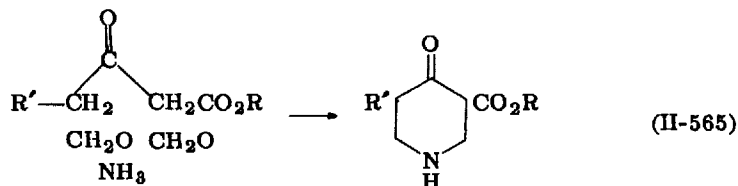
Three-Carbon Compound	Conditions	Yield, 3-Picoline	By-products	Ref.
Glycerol	Acetamide, P_2O_5 , heat 40–50 hr.	28–30% (?)		86, 88
	$(NH_4)_3PO_4$, heat, 6–8 hr.	V. small	Pyridine, 3-Et-Py, 3-Pr-Py, 2-Et-Py, 2-Pr-Py, 2-picoline	92, 91
	$(NH_4)_3PO_4$, P_2O_5 , reflux 50 hr.	Mixed bases (containing 80% 3-picoline and 2-picoline)		93
	$(NH_4)_2SO_4$ (or phosphate), 200–230°, 2–3 hr.	V. small		90
	NH_3 , aq., Al_2O_3 , 325°, 12 hr.	6%	None	374
1,2,3-Tribromopropane	Urea, MeOH, Al_2O_3 , 375°, 8 hr.	2%	None	374
	NH_3 , alc., 120°, 8 hr.;	V. small		89
	250°, 3 d.			
Allyl alcohol	NH_3 , N_2 , Al_2O_3 -Cu, 400°	12–20%		531, 526, 1690, 1691
	NH_3 , $Cd_3(PO_4)_2$ or $CdWO_4$ on Fuller's earth, 350– 400°	Mainly	3,5-Lutidine	620
Allylamine	NH_3 , $Cd_3(PO_4)_2$ or $CdWO_4$ on Fuller's earth, 350–400°	Mainly	3,5-Lutidine	620

4. 1-3-1 Condensation

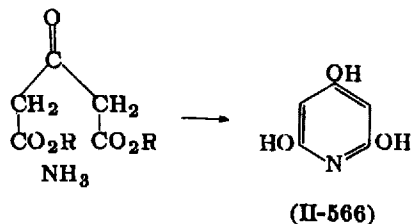
The 1-3-1 condensation is not well known and is limited to few examples. One mole of diethyl β -ketoglutarate was condensed with two moles of ethyl orthoformate by heating in acetic anhydride, and this intermediate was heated in alcoholic ammonia to give the ester of 4-hydroxy-3,5-pyridinedicarboxylic acid (II-563) (259). This reaction has been run with *m*-chloroaniline in place of the ammonia by heating a mixture of the reactants at 160° to give II-564 (1266).

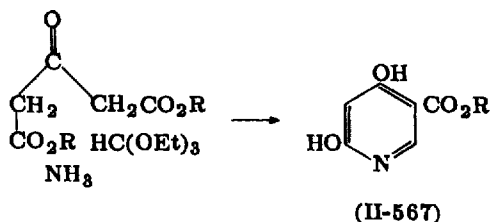


The 1-3-1 condensation is also known in the preparation of 4-piperidones from β -ketoesters, formaldehyde and ammonia as in II-565 (800,1335,1341).



It should be noted that diethyl β -ketoglutarate and ammonia condense to give II-566; the ketoglutarate, ethyl orthoformate, and ammonia also condense to give II-567.



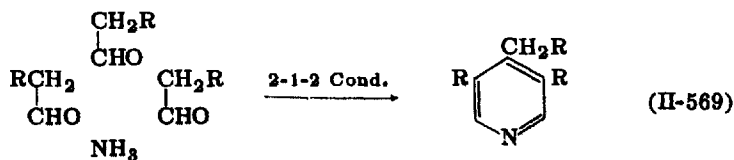
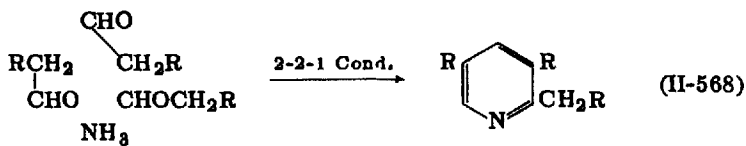


5. 2-2-1 Condensation

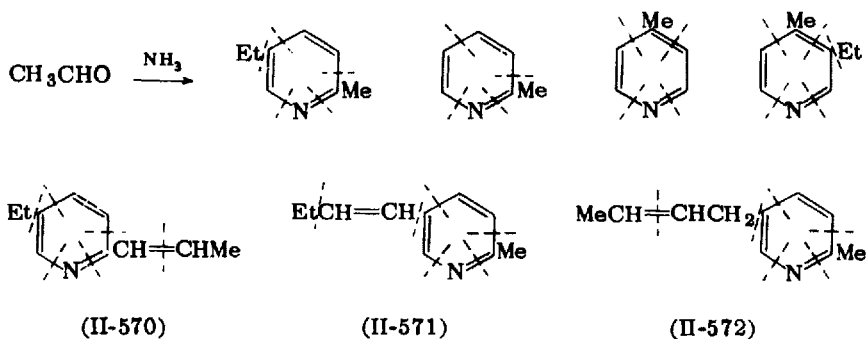
a. Aldehydes with Ammonia or Amines

In 1860, Hübner and Geuther heated acrolein with ammonia and obtained a basic, oily product, a pyridine (1659); soon the reaction of ammonia with several simple aldehydes was reported. It became apparent that these reaction products were mixtures of several pyridines formed in definite patterns. Since then, two procedures have been developed: reaction in the liquid phase (under pressure) at 150–250°, and reaction in the vapor phase (atmospheric pressure) at 300–500°. In general, the two methods give the same mixture of products, but in different proportions (Table II-114).

Aldehydes and ammonia condense by two different routes, II-568 and II-569. These routes will be called 2-2-1 and 2-1-2 condensations to indicate whether the aldehyde which contributes only one carbon atom forms the 2- and 4-carbon of the pyridine. This section will deal primarily with the reaction of a single aldehyde or its derivative with ammonia or an amine, since this favors 2-2-1 condensation. Reactions of mixtures of aldehydes and ketones tend to give more 2-1-2 condensation and will be dealt with more fully in the following section.



(a) **Liquid Phase Reactions.** (1) *With Ammonia.* For the reaction of aldehydes with ammonia, water and alcohol have been the common solvents, though aqueous and glacial acetic acid and benzene have also been used. The reaction, usually of one to four hours' duration, has most often been conducted at 150–250°, though 500° has been used with good results (1569). The commonest reaction is that of acetaldehyde with ammonia which gives mainly 5-ethyl-2-picoline with lesser amounts of 2-picoline, 4-picoline, and 3-ethyl-4-picoline, and, as shown by Graf, Langer and Haumeder, traces of II-570, II-571, and II-572 (1368). The formation of the major product by the condensation of four aldehyde molecules is found only with acetaldehyde. Other aldehydes furnish no more than three molecules toward formation of pyridines.

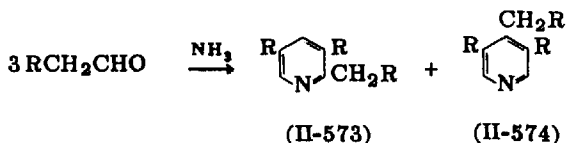


Ammonium salts greatly facilitate the reaction. Though the acetate is the commonest salt, the fluoride is reported to give better yields (1569). Several fluorine containing compounds such as ammonium bifluoride, sulfur hexafluoride, sulfuryl fluoride, and sulfonyl fluorides have been patented, and the synergistic effect of metal phosphates has been claimed (1826, 1828). Cobalt chloride has been reported as a good catalyst (679). Though basic catalysts (aside from ammonia itself) are uncommon, sodium hydroxide has been used to condense acetone and ammonia to form 2,2,4,6-tetramethyl-dihydropyridine (663), and propionaldehyde and calcium amide gave a 12% yield of 2-ethyl-3,5-lutidine (1618).

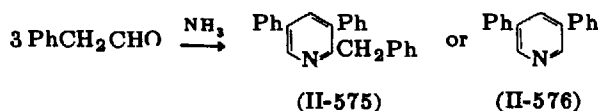
Frank *et al.* showed that in the presence of ammonium acetate, as the ratio of ammonia to acetaldehyde went from 1.17 to 3.7 to 10.7 the yield of 5-ethyl-2-picoline rose from 31% to 57% to 70%

(1088). This favorable excess of ammonia has also been maintained by the gradual addition of acetaldehyde throughout the course of the reaction (614).

A few other simple aldehydes have also been used. Reactions of ammonia with butyraldehyde, isovaleraldehyde, and *n*-caproaldehyde gave the expected products II-573 and II-574 (1618), but with



propionaldehyde, 3,5-lutidine was produced as well as the expected 2- and 4-ethyl derivatives (1315). Eliel, McBride and Kaufmann found that though the reaction of phenylacetaldehyde and ammonia once gave 2-benzyl-3,5-diphenylpyridine (II-575, the expected product), subsequent experiments gave only a 13% yield of 3,5-diphenylpyridine (II-576) and an 11.6% yield of toluene. 3,4-Dimethoxyphenylacetaldehyde gave similar results (1154).



Liquid phase reactions of acrolein and crotonaldehyde, which are complicated by reactive double bonds, have been investigated, but isolation of a pyridine product has been rare. Crotonaldehyde or its acetal react with ammonia to give 5-ethyl-2-picoline in 18–19% yield (1165), and α -methyl- β -ethylacrolein has produced a pyridine base mixture (742,638). Obviously, crotonaldehyde did not form a pyridine by the generalizations given for saturated aldehydes, but by a 3-2 condensation (II-577), as discussed in section B,A3 (p. 460).

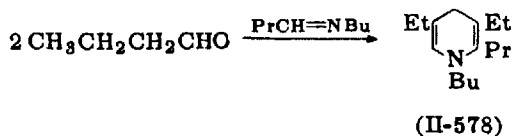


(2) *With Amines, Imines, or Amides.* Though the reaction of acetaldehyde and aldehydeammonia at 220° was reported to give a 58% yield of 5-ethyl-2-picoline (99,100), low yields are usually ob-

tained, probably because of the lack of excess ammonia or a catalyst such as ammonium acetate.

Acetaldehyde and acetamide gave a low yield of 2-picoline, but the reaction with formamide and thioformamide did not produce a pyridine (775). Since the reaction of propionaldehyde and acetamide with phosphorus pentoxide produced 2-ethyl-3,5-lutidine, the expected 2-2-1 product (88), the amide appears to act only as a source of ammonia.

Aldehydes react with simple amines or their corresponding aldimines to give *N*-substituted products. Thus butyraldehyde and its butylimine were converted in refluxing benzene to a 70% yield of 1-butyl-2-propyl-3,5-diethyldihydropyridine (II-578) (680), while the



less reactive anil gave only a 32% yield of 1-phenyl-2-propyl-3,5-diethyldihydropyridine along with 42% of the anil of α -ethyl- β -propylacrolein (1113). Reaction of butyraldehyde with aniline in acetic acid was reported to give at 100° 1-phenyl-2-propyl-3,5-diethyldihydropyridine (1448), but to give at reflux the corresponding 1-phenylpyridinium salt (1460). Butyraldehyde benzylimine did not react with crotonaldehyde to give a pyridine, and, more surprisingly, acetaldehyde with its ethylimine produced only tars (1113).

(b) **Vapor Phase Reactions.** The vapor phase reaction of aldehydes and ammonia, often called the *Chichibabin* reaction, also produces pyridines. Though thermal condensations have been done without catalysts, the best procedures have used a heated tube packed with a catalyst such as an oxide or a phosphate of a tri- or tetravalent metal at temperatures of 250–500°. Often a diluent or sweep of nitrogen or steam has been employed. A good example of the vapor phase technique is found in the reaction of acetaldehyde with ammonia at 450° over a catalyst composed of 82% silica, 15% alumina, and 3% thorium; this produced a 34% yield of 2-picoline, a 32% yield of 4-picoline, a 10% yield of 5-ethyl-2-picoline, and a 3% yield of 3-ethyl-4-picoline (644). Here the yield of products from the 2-2-1

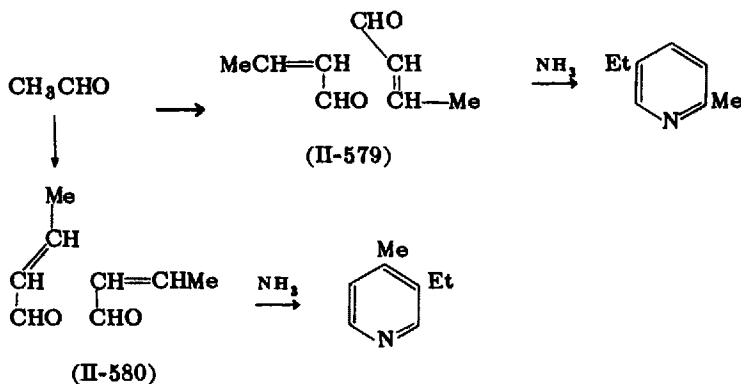
condensation was only slightly higher than from the 2-1-2 combination and 5-ethyl-2-picoline was only about 12% of the pyridine products. In the liquid phase the condensation was almost exclusively 2-2-1 and 5-ethyl-2-picoline was about 90% of the product.

Use of aldehyde-ammonia complexes is rare, and use of aldimines in the vapor phase has not been reported. The acrolein-ammonia complex produced only tars (1122).

As with liquid phase reactions, an anomaly was noted with the reaction of propionaldehyde and ammonia, which gave 3,5-lutidine as well as its expected 2- and 4-ethyl derivative (69-72), while butyraldehyde gave 3,5-diethylpyridine as well as its 2-propyl derivative (452).

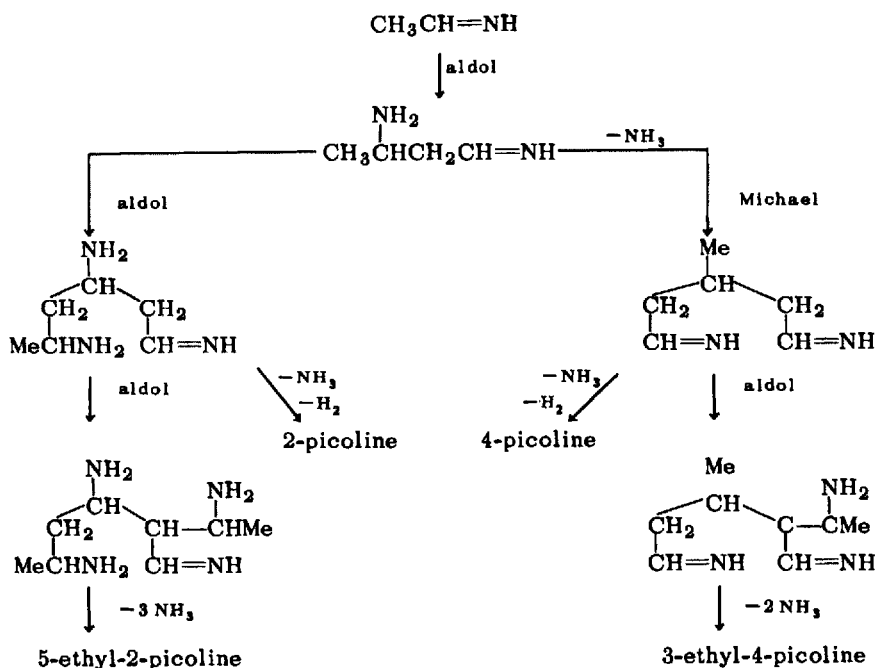
Aldehydes with α,β -double bonds react primarily by the 3-2 condensation and do not follow the generalizations given for the simple aldehydes. Thus the vapor phase reaction of acrolein and ammonia gave 3-picoline, in 57% yield (1122), yet crotonaldehyde does not react simply, but gives 2- and 4-picolines, 5-ethyl-2-picoline, 3-ethyl-4-picoline, and traces of other alkylpyridines (677); α -methylacrolein gave only 3,5-lutidine (1501).

(c) **Mechanism of Reaction.** A definite mechanism for the reactions of aldehydes and ammonia has not been established. Dürkopff and Schlaugk (102) proposed that acetaldehyde first formed crotonaldehyde which dimerized head-to-tail (II-579), but Chichibabin pointed out that under comparable conditions in the liquid phase acetaldehyde gave better yields of 5-ethyl-2-picoline than did crotonaldehyde. He proposed that in the vapor phase, the crotonaldehyde formed from acetaldehyde dimerized (II-580) to form the



3-ethyl-4-picoline fraction (676). A discussion of the possible mechanism of condensation of unsaturated aldehydes is given in Section B,3 (p. 460).

A mechanism which explains all of the products from acetaldehyde would be somewhat like II-581. Two separate and simultaneous routes are assumed, depending on whether the condensations are all of the aldol type, or whether one Michael condensation occurs. Michael condensation is favored when unsaturated chains are produced by the elimination of ammonia. When saturated chains are present (retention of ammonia), only aldol condensations can occur. The Michael route (2-1-2 condensation) accounts for 4-picoline and 3-ethyl-4-picoline, according to whether three or four moles of acetaldehyde participate. The aldol route (2-2-1 condensation) accounts for 2-picoline and 5-ethyl-2-picoline. In the liquid phase, where ammonia is in excess, deamination is suppressed, which favors 2-2-1, and particularly 5-ethyl-2-picoline. In the vapor phase, deamination is enhanced; the 2-1-2 route is therefore more promi-

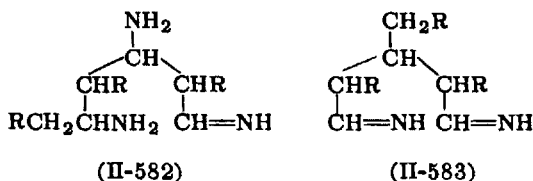


(II-581)

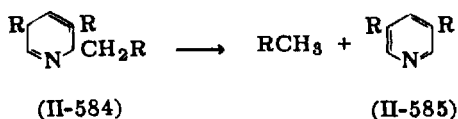
nent, and in the 2-2-1 route 2-picoline is favored over 5-ethyl-2-picoline.

Of the products from saturated aldehydes, only the two ethylpicolines from acetaldehyde can aromatize by loss of water. All others must be oxidized (or dehydrogenated).

The condensation of larger aldehydes would begin in the same manner, but at the intermediates II-582 and II-583 steric hindrance



would block entry of a fourth molecule. The anomaly whereby an aldehyde such as propionaldehyde produces a product such as 3,5-lutidine in addition to the normal products is explained by aromatization by loss of ethane rather than hydrogen to give II-585. The reaction of ammonia, phenylacetaldehyde, and isobutyraldehyde

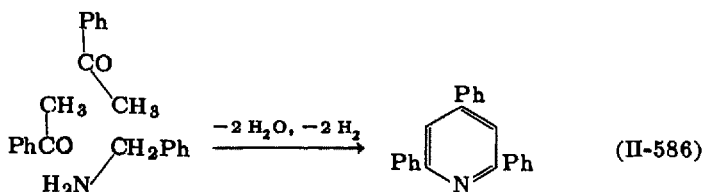


produces more 3,5-diphenylpyridine than does the reaction of ammonia, phenylacetaldehyde, and acetaldehyde, for propane is more readily eliminated than methane in the aromatization of II-584 (797).

b. Ketones with Ammonia

Few ketones have been combined with ammonia to give pyridine products (Table II-115). These reactions, which do not give good yields require more drastic conditions than those with aldehydes, and catalysts such as phosphorus pentoxide, zinc chloride, and sodium hydroxide have been used. The mechanism of reaction must be similar to that for aldehydes. Since the reaction of acetone may be made to give either 2,2,4,6-tetramethyldihydropyridine or 2,4,6-collidine, the aromatization must be by loss of a methyl group.

In an unusual variation the reaction (II-586) of acetophenone



and benzylamine in the presence of zinc chloride produced 2,4,6-triphenylpyridine (1020,1022).*

c. Alcohols with Ammonia

The reaction of ammonia with ethanol, butanol, ethylene glycol, glycerine, and allyl alcohol produces substituted pyridines (Table II-116). In general, the product is that which would be obtained from the corresponding aldehyde, but the alcohol gives low yields and would rarely be used. Glycerine is probably converted to acrolein, which gives 3-picoline. The other alcohols may also proceed through the aldehydes, or through the corresponding amine or ethylene derivative.

d. Acetylene with Ammonia

Since aldehydes react with ammonia to give pyridines, acetylene would also seem a logical starting material, and indeed, the patent literature shows that much effort has been expended to develop a commercial process using acetylene. For example, it reacts with aqueous ammonia under pressure in the presence of cobalt chloride at 140° to give a 75% yield of 5-ethyl-2-picoline (1583) (Table II-117). Acetaldehyde, a possible intermediate in the process, gives very similar results.

Pyridines may also be formed from acetylene and ammonia in the vapor phase over catalysts similar to those used with aldehydes (Table II-118). In general, most reports mention 2-picoline, 4-picoline, 3-ethyl-4-picoline, and 5-ethyl-2-picoline as products; the same products are formed by acetaldehyde and ammonia. Yet several early workers stated that the vapor phase reaction of acetylene and

* Note added in proof: This is actually a 2-1-2 condensation, as shown by Amoros-Marín and Carlin, *J. Am. Chem. Soc.*, **81**, 733 (1959).

ammonia produced traces of pyridine itself, and a patent (58) asserted that a two-stage process using first a catalyst of finely divided cadmium and then one of nickel would produce good yields of pyridine.

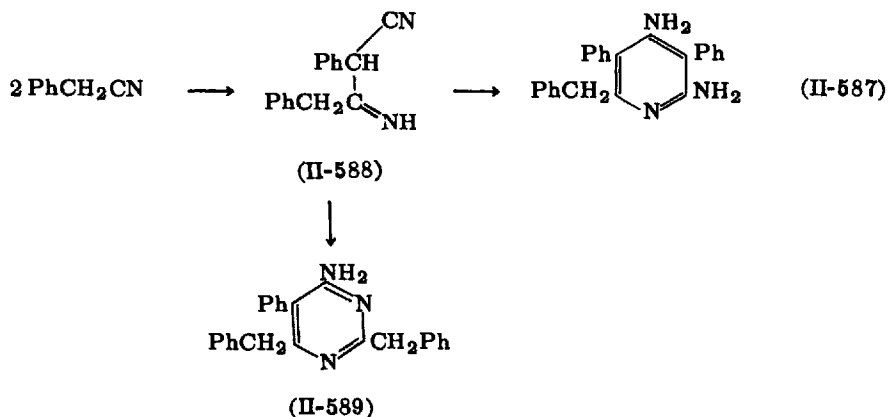
Under certain conditions, the reaction of ammonia and acetylene gave mostly non-pyridinoid products. Thus at 400° with a catalyst of alumina, chromia, and zinc oxide, there was produced an 85.9% yield of acetonitrile along with hydrogen, ethylene, hydrocarbons, 2,5-diethyl-3,6-dimethylpyrazine, 2,5-dihydroxypiperazine, 4-methyl-3-ethylquinoline, and several substituted pyridines (1491). The pyridine products were likely formed from intermediates such as acetaldimine or vinylacetylene rather than from a nitrile since the condensation of acetylene, ammonia, and hydrogen cyanide produced little or no pyridine (38,40-42). The reaction of nitriles with acetylene in the presence of potassium at 180° gave pyrimidines, though with benzonitrile, a 2% yield of 2-phenylpyridine was also found (456,1130).

Pyridine and some of its derivatives may be obtained from the reaction of acetylene and ammonia with methanol (551,1749), formaldehyde, acrolein, or allyl alcohol (619), but the reported yields are discouraging (Table II-119).

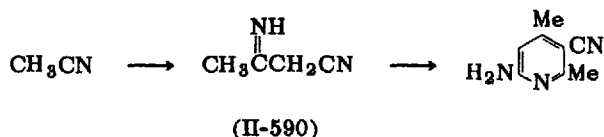
e. Nitriles

The self-condensation of phenylacetonitrile in the presence of equimolar diisopropylaminomagnesium bromide under carefully controlled conditions gave a 25% yield of 2-benzyl-4,6-diamino-3,5-diphenylpyridine (438). A similar condensation had been observed earlier, with diethyl zinc as the catalyst (828,871). The probable course of reaction (II-587) may be inferred from the isolation of the phenylacetonitrile dimer (II-588) (828) and 4-amino-2,6-dibenzyl-5-phenylpyrimidine (II-589) (438).

Attempts to perform the above reaction with other nitriles having α -methylene groups have been made, but not successfully. The self-condensation of acetonitrile in the presence of a Grignard reagent, followed by treatment with water, was reported to give impure 6-amino-3-cyano-2,4-lutidine and 5-cyano-4,6-dimethyl-2-pyridinol (1246). Formation of a pyridine from acetonitrile by the action



of a Grignard reagent as a base should pass through diacetonitrile (II-590). Yet the product reported from the reaction of diaceto-



nitrile and ammonia, which was also called 6-amino-3-cyano-2,4-lutidine, had a different melting point than that from acetonitrile (304).

f. Miscellaneous

As shown in Table II-120, gem-dihalides, ethylene, allylamine, styrene oxide, and ethylene oxide have all been used as starting materials with ammonia for the formation of pyridine bases, but with limited success. Though ethylene oxide has been reported as reacting with ammonia over alumina at 400–500° to give a 16–19% yield of pyridine itself (1576), other publications mention only pyridine bases with an even number of carbon atoms. As from acetylene, it seems that the formation of pyridine itself is difficult at best. Whatever the product, it may have been formed through an ethanolamine intermediate, since that amine, when passed with ammonia over alumina, gave acetaldehyde and amines (1516), and these are known to form pyridine bases. Why such bases were not found in the ethanolamine reaction itself is not clear.

TABLE II-114. Reactions of Aldehydes with Ammonia or Amines

Aldehyde	Amine	Conditions	Product (Yield)	Ref.
MeCHO (parald.)	NH ₃	Aq., NH ₄ F, 500°, 3 hrs.	5-Ethyl-2-picoline (64.9%)	1569
		Aq., KHF ₂ , 7.9-fold excess NH ₃ , 250°	5-Ethyl-2-picoline (70.4%) picolines 2.5%	679
		Aq., NH ₄ OAc, 500°, 3 hrs.	5-Ethyl-2-picoline (51.4%)	1569
		Aq., NH ₄ OAc, 225-265°, 10 min. (continuous process)	5-Ethyl-2-picoline (70%)	1812
		Aq., NH ₄ OAc, 180°, 8 hrs.	5-Ethyl-2-picoline (36%), traces of 2- and 4-picoline, 3-ethyl-4-picoline, 3-ethyl-6-propenylpyridine, 5-(1-butene-1-yl)-2-picoline, 5-(2-butene-1-yl)-2-picoline	1368
		Aq., NH ₄ OAc, 8 to 10-fold excess NH ₃ , 200-250°, 1 hr.	5-Ethyl-2-picoline (60-70%)	445, 1088
		Aq., NH ₄ OAc, 250° HOAc	5-Ethyl-2-picoline (59.5%) 5-Ethyl-2-picoline (major product)	1165 106, 107, 795, 1272
		Liquid phase	5-Ethyl-2-picoline (major product)	102, 103, 104, 808, 1678, 1680
		Liquid phase, NH ₄ salt, catalyst	5-Ethyl-2-picoline (major product)	105, 106, 614, 677, 795, 1681

MeCHO (acetal)	NH ₃	Aq., NH ₄ OAc, 250°	5-Ethyl-2-picoline (57.5%)	1165
MeCHO	NH ₃	CoCl ₂ , 230°, 1 hr.	5-Ethyl-2-picoline (60%)	623
		Aq., NH ₄ OAc, 250°	5-Ethyl-2-picoline (34%)	1165
MeCHO (aldehyde-ammonia)	NH ₃	Aq., or alc., 130-220°	5-Ethyl-2-picoline (major product)	95, 98, 99, 100, 101, 1314
MeCHO	NH ₃	Vapor phase, 1% alumina on silica, 500°	2-Picoline (20.4%), 4-Picoline (17.6%)	457
		Vapor phase, Ni, Zn on thoria, H ₂ diluent, 280°	Pyridine bases	58
		Vapor phase, 82% silica, 15% alumina, 3% thoria, 450°	2-Picoline (34%), 4-picoline (32%), 5-ethyl-2-picoline (10%), 3-ethyl-4-picoline (3%)	644
		Vapor phase	2- and 4-Picoline, 5-ethyl-2-picoline, 3-ethyl-4-picoline, 4-propylpyridine, 2-propylpyridine, 2-propenylpyridine	69, 70, 71, 72, 79, 677, 741, 1311, 1313, 1452, 1576, 1692
MeCHO	NH ₃ (from MeCONH ₂)	280°	2-Picoline	775, 1612
		P ₂ O ₅ , 160°, 20 hrs.	5-Ethyl-2-picoline, 3-ethyl-4-picoline	88
EtCHO	NH ₃	320°	2-Ethyl-3,5-lutidine (18%), 4-ethyl-3,5-lutidine (7%), 3,5-lutidine (8%)	1315
		200°, sev. days	A C ₆ pyridine	637
		Ca (NH ₃) ₂ , $\frac{1}{2}$ hr., distill	2-Ethyl-3,5-lutidine (12%)	1618

(continued)

TABLE II-114 (Continued)
Reactions of Aldehydes with Ammonia or Amines

Aldehyde	Amine	Conditions	Product (Yield)	Ref.
EtCHO (as aldehyde-ammonia)	NH ₃	230°, sev. days	2-Ethyl-3,5-lutidine	111,112,742
EtCHO	NH ₃	Vapor phase, Cu, Zn, 350°	EtCN (77%), 2-ethyl-3,5-lutidine	1373
EtCHO	NH ₃ (from MeCONH ₂)	Vapor phase	2-Ethyl-3,5-lutidine, 4-ethyl-3,5-lutidine, 3,5-lutidine	69,70,71,72,741
PrCHO	NH ₃	P ₂ O ₅ , 190°	2-Ethyl-3,5-lutidine	88
PrCHO	NH ₃	Alc., 150°, 50 hrs.	2-Propyl-3,5-diethylpyridine (40%)	114
PrCHO (as aldehyde-ammonia)	NH ₃	Ca (NH ₃) ₂ , $\frac{1}{2}$ hr., distil	2-Propyl-3,5-diethylpyridine (30%)	1618
PrCHO (as imine)	PrNH ₂ (as amine)	160°, 24 hrs.	2-Propyl-3,5-diethylpyridine (42%), 3,5-diethyl-2-(2-ethyl-3-hydroxypentyl)pyridine	373
PrCHO (as imine)	BuNH ₂ (as imine)	Benzene (azeotropic removal of water) 1 hr.	1,2-Dipropyl-3,5-diethyl-dihydropyridine (66%)	680,1113
PrCHO (as imine)	BuNH ₂ (as imine)	Benzene (azeotropic removal of water) 1 hr.	1-Butyl-3,5-diethyl-2-propyldihydropyridine (70%)	680,1113,1421
PrCHO (as imine)	PhCH ₂ NH ₂ (as imine)	Benzene or alc., reflux, 2 hrs.	1-Benzyl-3,5-diethyl-2-propyldihydropyridine (37%)	680,1113

PrCHO	PhNH ₂	HOAc, 40-100°	3,5-Diethyl-1-phenyl-2-propyldihydropyridine	1448
		HOAc, reflux, 5 hrs.	3,5-Diethyl-1-phenyl-2-propyldihydropyridine	1460
PrCHO	NH ₃	Vapor phase, silica, 330°	3,5-Diethyl-2-propylpyridine, 3,5-diethylpyridine	452
i-BuCHO	NH ₃		3,5-Diisopropyl-2-iso-butylpyridine	114
		Vapor phase, alumina	3,5-Diisopropyl-4-iso-butylpyridine, 3,5-diisopropylpyridine	78
		Vapor phase, alumina, 370°	3,5-Diisopropyl-2-iso-butylpyridine, (26%), traces of 3,5-diisopropyl-4-iso-butylpyridine, 3,5-diisopropylpyridine	1318
AmCHO PhCH ₂ CHO	NH ₃ NH ₃	Ca (NH ₄) ₂ , $\frac{1}{2}$ hr., distil 230°, 6 hrs.	3,5-Diamyl-2-hexylpyridine (?) 3,5-Diphenylpyridine (13%), toluene (11.6%)	1618 1154
3,4-(MeO) ₂ C ₆ H ₃ -CH ₂ CHO	NH ₃	Alc., reflux, 1 hr.	3,5-bis-(3,4-Dimethoxyphenyl)pyridine (10%)	1154
		MeOH, 230°, 6 hrs.	2-(3,4-Dimethoxybenzyl)-3,5-bis-(3,4-dimethoxyphenyl)pyridine, 3,5-bis-(3,4-dimethoxyphenyl)pyridine	1154

(continued)

TABLE II-114 (Continued)
Reactions of Aldehydes with Ammonia or Amines

Aldehyde	Amine	Conditions	Product (Yield)	Ref.
3,4-(MeO) ₂ C ₆ H ₃ -CH ₂ CHO	MeNH ₂	Alc., reflux, 1 hr.	3,5-bis-(3,4-Dimethoxyphenyl)-1-methylpyridinium salt	1154
MeCH(OH)CH ₂ CHO (as aldehyde-ammonia)	NH ₃	Distill in NH ₃ stream	A collidine	1677
CH ₂ :CHCHO	NH ₃	Distill with ammonia Vapor phase, BPO ₄ , 360°, or AlPO ₄ , 350°, benzene or steam diluent	3-Picoline 3-Picoline (50-57%), pyridine (trace)	89 1122,1476, 1809
CH ₂ :CHCHO (as aldehyde-ammonia)	NH ₃		3-Picoline	89
MeCH:CHCHO	NH ₃	Aq., NH ₄ OAc, 250° 200°	5-Ethyl-2-picoline (18%) 5-Ethyl-2-picoline (low) (mostly non-pyridines)	1165 677
		Vapor phase Vapor phase, glass tube, 390°	Pyridine bases 2-Picoline, 4-picoline, 5-ethyl-2-picoline, 3-ethyl-4-picoline, 4-propylpyridine, 2-propylpyridine, 2-propenylpyridine	619,918 676,677

MeCh : CHCHO (as acetal)	NH ₃	Vapor phase, alumina, 340°	3-Ethyl-4-picoline (7.5%)	73
CH ₃ : CMeCHO	NH ₃	Aq., NH ₄ OAc, 250°	5-ethyl-2-picoline (2%)	1165
			5-Ethyl-2-picoline (19%)	
CH ₃ : CEtCHO	NH ₃	Vapor phase, BPO ₄ , 325- 70°	3,5-Lutidine	1501
		Vapor phase, BPO ₄ , 325- 70°	3,5-Diethylpyridine	1501
EtCH : CMeCHO	NH ₃	Alc., 200°, 42 hrs.	C ₉ , C ₆ , and C ₁₂ Pyridines	638,742
MeCH : CHCO ₂ H ^a	NH ₃	CaCl ₂ · (NH ₃) ₂ , 230°	5-Ethyl-2-picoline	1684

^aForms acetaldehyde first.

TABLE II-115. Reactions of Ammonia and Ketones

Ketone	NH ₃ Source	Conditions	Product (Yield)	Ref.
MeCOMe	NH ₃	CaCl ₂ , NH ₄ Cl, 190°, 3 hrs.	2,2,4,6-Tetramethyldihydropyridine (22%)	663
		Aq., NaOH or soda lime, 120°, 3 hrs.	2,2,4,6-Tetramethyldihydropyridine	663,455
MeCOMe	Urea	NH ₄ Cl, 265°, 2 d.	2,4,6-Collidine (low)	108
MeCOMe	NH ₃	ZnCl ₂ , 140°, 3 d.	2,4,6-Collidine	108
MeCOMe	MeCONH ₂	Vapor phase, Cd ₃ (PO ₄) ₂ and ZnO, 400°	2,4,6-Collidine (low)	620
		Benzene (azeotrope to remove water); or 250°, no solvent	2,4,6-Collidine (low)	775,1612
Isophorone	NH ₃	Vapor phase, iron tube, Porocel, 500°	2,4,6-Collidine	377
PhCOMe	NH ₃	P ₂ O ₅ , boil	2,4,6-Triphenylpyridine	1028,1029
PhCOMe	PhCONH ₂	No solvent, 275°	2,4,6-Triphenylpyridine (low)	775,1612
CH ₃ :CHCOMe	NH ₃	(1) 20°, 1.5 hrs. (2) Aq., HCl, 140°, 4 hrs.	2,3,4-Collidine (low), 3-acetyl-4-methyltetrahydro- pyridine	656
CH ₃ :CHCOMe	NH ₃	(1) 20°, 1.5 hrs. (2) Alkali; or FeCl ₃ and HCl	2,3,4-Collidine	656
MeCOCO ₂ H	NH ₃	Aq., alc., saturate with NH ₃ for 2 hrs. or boil	6-Methyl-2,4-pyridinedicarboxylic acid (31%)	203,204, 205,206, 207,1574
Me ₂ C=CHCO ₂ H ^a	NH ₃	CaCl ₂ · (NH ₃) ₂ , 230°	s-Collidine	1684

^aForms acetone first.

TABLE II-116. Reaction of Alcohols

Conditions	Product (Yield)	Ref.
Ethanol, ammonia, hot tube,	Some pyridine bases	80
Ethanol, ammonia, vapor phase, iron tube, Zn, Al, Th or Si oxides	Pyridine bases	68,385
Ethylene glycol, ammonia, vapor phase, alumina, 400°	2-Picoline, 4-picoline, no pyridine	449
Ethanolamine, ammonia, vapor phase, alumina, 400-50°	Acetaldehyde, amines, no pyridines	1516
Allyl alcohol, ammonia, vapor phase, Cd ₃ (PO ₄) ₂ , or tungstate, 350-400°	3-Picoline major product, 3,5-lutidine	620
Allyl alcohol, ammonia, nitrogen, vapor phase, alumina containing Cu, 400°	3-Picoline (20%)	526,531
Allylamine, ammonia, vapor phase, Cd ₃ (PO ₄) ₂ on Fuller's earth, 350-400°	3-Picoline (major product), 3,5-lutidine	620
Glycerine, ammonium phosphate, heat	Pyridine, 3-picoline, 3-ethylpyridine, 3-propylpyridine	90,91,92
Glycerine, ammonium phosphate, P ₄ O ₁₀	3-Picoline major product, 2-picoline	93
Glycerine, ammonia, water, vapor phase, alumina, 400°	3-Picoline (6%)	374
n-Butyl alcohol, ammonia, vapor phase, silica, 330°	Pyridine bases	452
Methanol, acetaldehyde, vapor phase, Cd tungstate or chromate	Pyridine	619
Methanol, crotonaldehyde, vapor phase, Cd tungstate	Pyridine	619

(continued)

TABLE II-116 (Continued)
Reaction of Alcohols

Conditions	Product (Yield)	Ref.
Allyl alcohol, acetone, vapor phase, $\text{Cd}_3(\text{PO}_4)_2$ on clay, 350–400°	2-Picoline (20–30%)	832
Allyl alcohol, methyl ethyl ketone, vapor phase, $\text{Cd}_3(\text{PO}_4)_2$, 350–400°	2,3-Luxidine (24%)	832, 833
Allyl alcohol, methyl propyl ketone, vapor phase, $\text{Cd}_3(\text{PO}_4)_2$ on clay, 350–425°	3-Ethyl-2-picoline (16%)	832, 833
Allyl alcohol, methyl <i>n</i> -propyl ketone, vapor phase, $\text{Cd}_3(\text{PO}_4)_2$ on clay, 375–425°	3-Propyl-2-picoline (15%)	833
Allyl alcohol, methyl <i>n</i> -butyl ketone, vapor phase, $\text{Cd}_3(\text{PO}_4)_2$ on clay, 375–425°	3-Buryl-2-picoline (18%)	833
Allyl alcohol, diethyl ketone, vapor phase, $\text{Cd}_3(\text{PO}_4)_2$ on clay, 350–400°	2-ethyl-3-picoline (20–30%)	832
Allyl alcohol, acetophenone, vapor phase, $\text{Cd}_3(\text{PO}_4)_2$ on clay, 350–400°	2-phenylpyridine (20–30%)	832
Glycerine, acetamide, heat	3-Picoline	85, 86, 87, 88

TABLE II-117. Reaction of Acetylene and Ammonia under Pressure

Conditions	Product (Yield)	Ref.
Aq., NH_3 , HOAc, 190°	5-Ethyl-2-picoline	527
Aq., MeCHO, CdI_2 , 180° , 1 hr.	5-Ethyl-2-picoline (60%)	530
Aq., nickel biacetyl, CoCl_2 (or nickel or titanium chloride), 140°	5-Ethyl-2-picoline (75%)	1583
Oxides or carbides of Fe, Cr, W, U, or Al; 250°	Mostly picolines	79
CdO on clay, 320° , 45 hrs.	2-Picoline, 4-picoline, 5-ethyl-2-picoline, 2,3,6-collidine, 3-ethyl-4-picoline, acetonitrile	381
ZnCl_2 , 180°	A trimethylpyridine	383
Aq., NH_3 , NH_4OAc , 200° , 3 hrs.	2-Picoline, 5-ethyl-2-picoline	454

TABLE II-118. Vapor Phase Reaction of Ammonia and Acetylene

Conditions	Product (Yield)	Ref.
Al_2O_3 , 400–25°	2-Picoline, 4-picoline, 5-ethyl-2-picoline, β -collidine, pyrrole	327, 1317
Al_2O_3 , ZnO or chromium oxide, hydrogen, 400°	Acetonitrile (86%), 2-picoline, 4-picoline, 4-ethyl-2-picoline, 2,4-lutidine, 2,5-lutidine, s-collidine	1491
Bauxite, 380°	Pyridines, pyrrole, acetonitrile	43
Reduced Bauxite	Pyridines, pyrrole, acetonitrile	1754
Oxides of Al, Cr, Fe, Zn, Ni, Ti, Th or Si on kaolin; also use of AlPO_4 , 300°	2-Picoline, collidines, pyrrole, hydrogen acetaldehyde-ammonia	1620
ZnO or ThO on alumina or silica, 350°	Pyridine bases and acetonitrile	1753
CdCrO_4 (or the molybdate, tungstate, or vanadate) on silica, alumina, or clay, 250–350°	Pyridine bases (mostly picolines) (79%) acetonitrile, ethylamine	1437
$\text{Cd}_3(\text{PO}_4)_2$ (or chromate, tungstate, or vanadate) on Fuller's earth, 350–425°	2-Picoline, 4-picoline, 2,3,6-collidine	551
CdO on Fuller's earth	2-Picoline and other bases	1662
ZrO_2 (no water) 400–500°	Acetonitrile (99%), traces of pyridine bases	1736

Hydrates of oxides of Cu, Cr or Fe	Pyridine bases	44
ThO ₂ and ZrO ₂ (or ThO ₂ , ZnO and SiO ₂)	Pyridine bases	61,62,63,64
U ₃ O ₈ , 350-400°	Pyridine bases	650
Palladium oxide on kaolin 300°	A pyridine base	657
Partially reduced metal oxides	Pyridine bases	46,47
Silicates, iron oxides, or limonite	Pyridine bases	45
Basic zinc carbonate on kaolin, 400°	Acetonitrile (91%), pyridine bases (less than 1%)	510
Cd ₃ (PO ₄) ₂ on Fuller's earth, 300°	2-Picoline	511
ZnCl ₂ or FeCl ₃ on pumice or asbestos, 280-350°	2-Picoline, 4-picoline, higher boiling bases	384
ZnCl ₂ (or CdCl ₂ , PbCl ₂ , FeCl ₃ , SnCl ₄), 470°	Acetonitrile, pyridine traces	1737
Two stage: Cd metal on silicic acid, 350°, nickel metal, 250°	Pyridine, bases	58
SiO ₂ , CdHPO ₄ , 300°	Bases (51.3%)	1817
Cd metal on silica, 320°	Pyridine bases (mostly picolines) (80%)	1755
Pd, Cd, Bi, or Au metal on oxides of Al, Zn or Si, 300-500°	Pyridine bases	1750
Hot tube	Pyridine, traces	37,38,40,41
		42

TABLE II-119. Vapor Phase Reaction of Acetylene, Ammonia and a Third Component

Conditions	Product (Yield)	Ref.
Methanol, ZnHPO_4 on clay, 380-400°	Acetonitrile (25%), pyridine (15%), picolines, lutidines	1749
Methanol, $\text{Cd}(\text{NO}_3)_2$ on a carrier, 400°	Picolines (34.8%), pyridine (9.6%)	1539
Methanol, Cd phosphate, chromate, tungstate or vanadate on Fuller's earth 350-425°	Pyridine (24%), 3-picoline, 3,5-lutidine	551,619
Allyl alcohol, Cd tungstate or chromate	Pyridine	619
Allylamine, $\text{Cd}_3(\text{PO}_4)_2$ on Fuller's earth	Pyridine	620
Formaldehyde, Cd tungstate or chromate	Pyridine	619
Paraldehyde	Pyridine bases	66
Aldol	Pyridine bases	66
Crotonaldehyde	Pyridine bases	66
Acrolein, Cd tungstate or chromate	Pyridine	619
Acetone, $\text{Cd}_3(\text{PO}_4)_2$ on Fuller's earth, 400°	Mostly 2,4,6-collidine	66,620
HCN, hydrogen	Pyridine traces	40,41,42
HCN, hot tube of metal or porcelain	No pyridine	38
Acetonitrile, potassium, 8 hrs., pressure, 180°	2,4-Dimethylpyrimidine, no pyridine	1130
Propionitrile, potassium, 8 hrs., pressure, 180°	An aminocollidine (12.5%), a pyrimidine (10%)	1130
α -Methylpropionitrile, potassium, 8 hrs., pressure, 180°	2,4-Dimethylpyrimidine, no pyridine	1130
Benzonitrile, potassium, 8 hrs., pressure, 180°	2-Phenylpyridine (2%), 2,4-diphenylpyrimidine	1130,456
MeNH_2 , Diatonite, ZnCl_2	Pyridine	65

TABLE II-120. Reactions of Olefins, Epoxides, and Halides

Conditions	Product (Yield)	Ref.
Ethylene, methyl amine, water, pressure, ZnO, Cr ₂ O ₃ , 350°	Alkylpyridines	59
Ethylene oxide, ammonia, vapor phase, alumina, 400-50°	Pyridine (16-19%)	1576
Ethylene oxide, ammonia, vapor phase, alumina, 400-50°	Pyridine bases, pyrrole, ethanol	1531
Ethylene oxide, ammonia, vapor phase, alumina, 450°	Pyridine (poor yields)	376,1516
Ethylene oxide, ammonia, vapor phase, alumina, 400°	2-Picoline, 4-picoline, <i>no</i> pyridine	449
Ethylene oxide, ammonia, vapor phase, alumina and MgO, 400°	2-Picoline, 5-ethyl-2-picoline	512
Methyl vinyl ether, ammonia, aqueous NH ₄ F-HF, pressure, 6 hrs., 260°	5-Ethyl-2-picoline	647
1,1-Dichloroethane, ammonia, alcohol, pressure, 160°	5-Ethyl-2-picoline	96,97
1,1-Dichloroethane, ethylamine, pressure, 180°	A C ₈ Pyridine	1682
1,1-Dichloroethane, ammonia, acetaldehyde, pressure, 9 hrs., 160°	5-Ethyl-2-picoline	97
1,1-Dibromoethane, ammonia, alcohol, pressure, 10 hrs., 140°	A C ₈ Pyridine	1683
Styrene oxide, ammonia, vapor phase, alumina, 500°	Pyridine (traces), a methylphenylpyridine	555
Propylene oxide, vapor phase, alumina, 400-500°	3,5-Lutidine, bases	1576
Allylamine, NH ₃ , vapor phase, Cd ₃ (PO ₄) ₂ on Fuller's earth, 350-400°	3-Picoline (major product) 3,5-lutidine	620

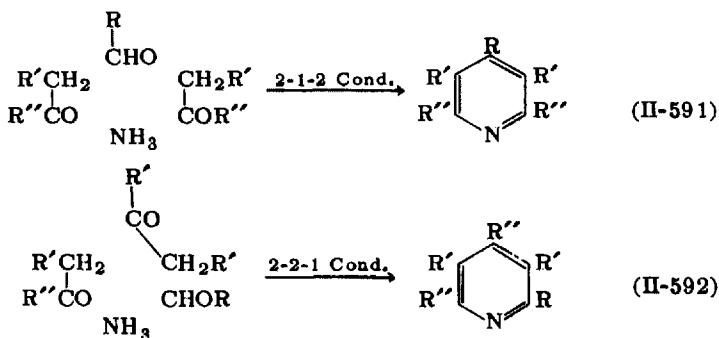
6. 2-1-2 Condensation

The reaction of an aldehyde with ammonia and a second aldehyde or ketone produces a pyridine or its dihydro derivative (Tables II-121 through II-125). Ammonia and unactivated aldehydes or ketones react under pressure at 150–250° or in the vapor phase over a catalyst at 200–300° to give pyridines. The reaction of ammonia and an aldehyde with an activated ketone such as ethyl acetoacetate proceeds in alcohol at only 25–75° and produces dihydropyridines.

Less common is the reaction of an aldehyde or ketone with ammonia and ethyl cyanoacetate to produce pyridinediols or their dihydro derivatives. Cyanoacetamide reacts with aldehydes or ketones without ammonia to give a mixture of pyridine products.

a. Mixtures of Aldehydes and Ketones with Ammonia

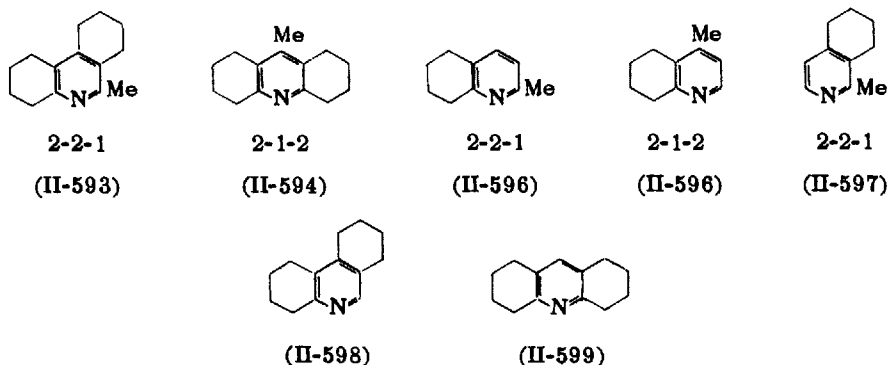
The condensation of an aldehyde and ammonia with a second aldehyde or a ketone may occur in two reaction patterns, II-591 and II-592. Whether the reaction goes by one of these routes or by both depends upon the nature of the R groups of II-591 and II-592 and



the conditions used in condensation. The 2-1-2 condensation is favored in the vapor phase and by the use of two different carbonyl reactants, while the 2-2-1 condensation (discussed in the previous section) is favored in the liquid phase and by the use of a single aldehyde.

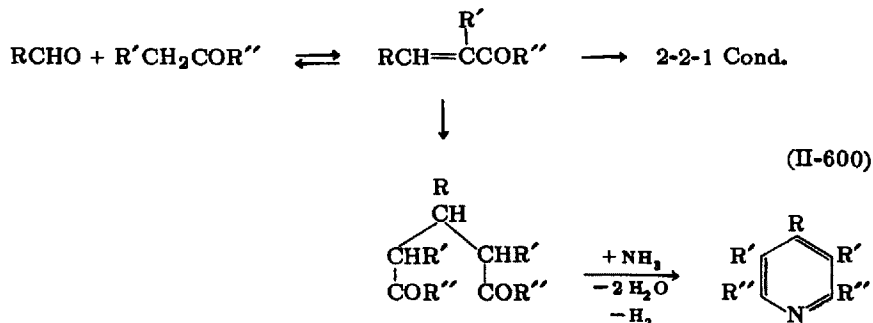
Chichibabin pointed out that reaction of ammonia and two different aldehydes having α -methylene groups could produce twelve products (773). The reaction of an aldehyde and a ketone can give only five products; thus acetaldehyde, cyclohexanone, and am-

monia under pressure produced a 47% yield of II-593 and II-594 (predominantly II-593) and a 10% yield of a mixture of II-595, II-596, and II-597 (773). This same reaction in the vapor phase over alumina gave II-596 with small amounts of II-594 and II-595, but no II-593 or II-597 (774). Formaldehyde, cyclohexanone, and ammonia in the liquid phase gave a 34% yield of octahydrophenanthridine (II-598) and a 6% yield of octahydroacridine (II-599), the only possible products (773).



Though the vapor phase reaction of ammonia with a mixture of formaldehyde, acetone, and methyl ethyl ketone formed 2,3,6-collidine and 2,3,5,6-tetramethylpyridine (75), the use of more than two carbonyl compounds is generally complex and therefore rare.

Weiss proposed that the 2-1-2 condensation proceeded as in II-600 (1152). The formation of the unsaturated ketone in the first step was thought to be reversible since the reaction of benzalacetophenone and ammonia produced 2,4,6-triphenylpyridine but



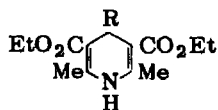
none of the 3-benzyl derivative (1165). (The former product was thought to come from the condensation of acetophenone and benzalacetophenone, while the latter was that expected from a self-condensation of benzalacetophenone.) The steps which lead to the 2-2-1 condensation are available to simple aldehydes, but not to ketones with their greater steric hindrance and lesser carbonyl reactivity.

Simple aldehydes and ketones without activating groups require mildly forcing conditions and produce the fully aromatic pyridines; accordingly, acetophenone, benzaldehyde, and ammonia in refluxing acetic acid gave a 68% yield of 2,4,6-triphenylpyridine and a 25% yield of β -phenylpropio-phenone (1152). Since no hydrogen was found, even in a closed system, it was assumed that the propio-phenone was formed as benzalacetophenone oxidized the dihydro-pyridine to the fully aromatic product.

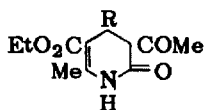
b. Aldehydes or Ketones with Active Methylenic Compounds

(a) **With Methylenic Ketones.** Condensation of ammonia and an aldehyde with an active methylenic ketone (*The Hantzsch Synthesis*) such as ethyl acetoacetate requires only mild conditions and produces a dihydropyridine (II-601). The isolation of a dihydropyridine might be attributed to the mildness of the reaction conditions, but the activating groups on the original ketone (carbethoxy or cyano) may also play a role. Perhaps such substituted dihydropyridines are more resistant to mild oxidizing agents, or perhaps a suitable oxidizing agent is not present in these cases. These dihydro products, which are usually written without evidence as the 1,4-form, are readily oxidized by reagents such as nitric acid.

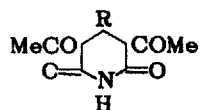
It is interesting that to date only II-601 has been found in the reaction of ethyl acetoacetate with an aldehyde and ammonia. Perhaps a trace of II-602, or even of II-603, is formed though not yet identified. The ketone carbonyl would be expected to react in



(II-601)

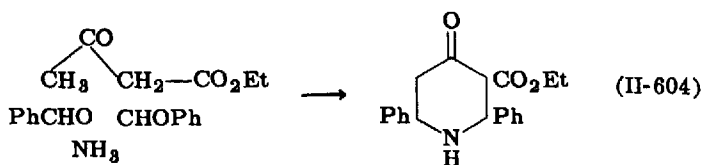


(II-602)



(II-603)

preference to, but not necessarily to the exclusion of, the ester group, for aqueous ammonia and ethyl acetoacetate give acetoacetamide as well as ethyl β -aminocrotonate (881). In a few cases ethyl acetoacetate, ammonia, and certain benzaldehydes have combined to give piperidones in a rare 1-3-1 condensation shown in II-604 (800) (Sect. B,4, page 473).



Note that the 2-1-2 condensation becomes in its second step a 3-2 condensation which in turn becomes the ring-closure of a five-carbon chain. The 2-1-2 condensation is preferred for simpler, symmetrical pyridines; the other two reactions are better for unsymmetrical or more complex pyridine derivatives, but they require less available starting materials.

Haley and Maitland demonstrated the effect of pH on the yield in the reaction of acetaldehyde, ethyl acetoacetate, and ammonia (II-605) (1520). That the optimum condition was weakly basic suggests that while the aldol and Michael condensations are base catalyzed, a proton donor must also be available in the over-all reaction. A similar study was also made with acetylacetone.

Reaction of Acetaldehyde, Ethyl Acetoacetate, and Ammonia

pH	5.5	6.0	7.1	7.5	8.5	10.0
Yield	0%	3%	18%	33%	43%	21%

(II-605)

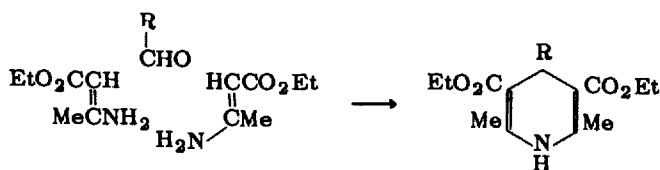
The effect of substituents on benzaldehyde in its reaction with ethyl acetoacetate and ammonia is given in II-606 (1628). The yields here vary generally with the positive character of the carbonyl carbon of the benzaldehyde. Groups which by induction or resonance tend to increase the electron density also lower the yield and vice versa. In several cases, the effect of two or three substituents on benzaldehyde has produced yields which were predictable from the effect of single groups (316,317).

Yield in the Reaction of a Benzaldehyde with Ammonia and
Ethyl Acetoacetate

Position	Substituent				
	H	Cl	Me	MeO	NO ₂
Ortho	74%	62%	9%	57%	62%
Meta	...	76%	57%	75%	88%
Para	...	73%	37%	64%	64%

(II-606)

For its reaction with aldehydes and ketones, free ammonia may be replaced by an aldehyde-ammonia complex, but with no apparent advantage. The ammonia may also be supplied in combination with a ketone. Thus an aldehyde and ethyl β -aminocrotonate give II-607. But the real advantage of this method is in the use of such



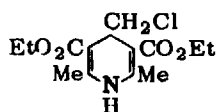
(II-607)

compounds as β -aminocrotononitrile (acetonitrile dimer) which is more accessible than β -ketobutyronitrile. Conditions for cyclization may be different in such cases. For example, benzaldehyde and β -aminocrotononitrile in alcohol gave only the benzylidene derivative, but this could be cyclized to the dihydropyridine by acid (1613).

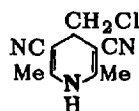
Stoichiometrically only one of the two ketone molecules need be an ammonia derivative, and in fact, such a procedure has been used (Table II-123). This method has no advantage in the preparation of symmetrical products and has not been reported as a route to unsymmetrical ones. Probably the attempt to react an aldehyde and a ketone with the imine of a different ketone would produce mostly the symmetrical product using only the more reactive compound.

Formamide has been used as a source of ammonia in a reaction with formaldehyde and ethyl acetoacetate (448).

α,β -Dichloroethyl ethyl ether acted as an aldehyde in its reaction with ethyl β -aminocrotonate which gave a good yield of II-608 (227, 228, 1245). Similarly, bis- α,β -dichloroethyl ether and β -aminocrotononitrile produced II-609 (1252).



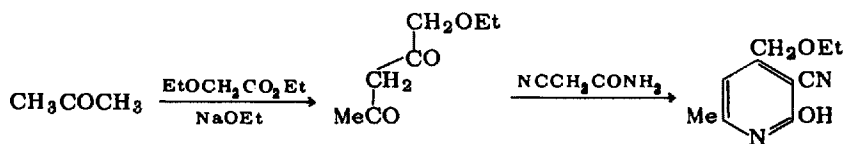
(II-608)



(II-609)

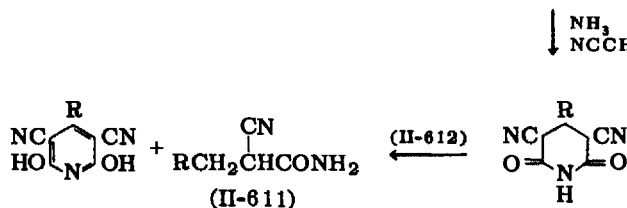
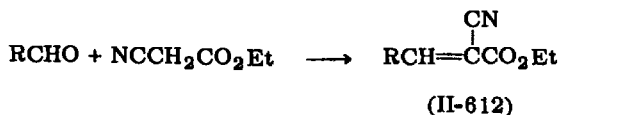
Meyer found that ketones reacted with β -aminocrotononitrile and formed 4,4-disubstituted dihydropyridines (Table II-125). Since the ketones are less reactive than aldehydes, the condensations were run in alcoholic hydrogen chloride.

The reaction of ethyl acetoacetate with an acid derivative rather than an aldehyde would be expected to give a pyridine rather than a dihydro derivative; and indeed, the reaction with formamide, which was also the ammonia source, produced 3,5-dicarbethoxy-2,6-lutidine, but in only 3% yield (1428). This variation is more successful as it becomes the 3-2 condensation as shown by the successive reaction, without isolation of intermediates, of acetone with ethyl ethoxyacetate and cyanoacetamide as shown in II-610 (1472).

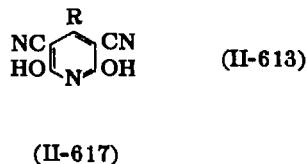
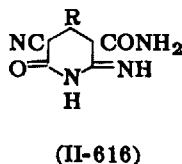
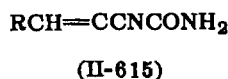
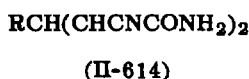


(II-610)

(b) **With Methylenic Esters and Amides.** Ethyl cyanoacetate condenses with an aldehyde and aqueous ammonia (Table II-126) to form not a dihydropyridine (a glutarimide), but a pyridine (a glutaconimide). The isolation of a cyanopropionamide (II-611) suggests that the dihydro intermediate was oxidized by the cyanoacrylic ester (II-612) (708).

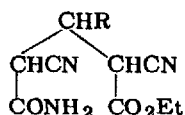


The reaction of an aldehyde with cyanoacetamide (Table II-126) is more complicated and gives four products (II-613). Generally, aliphatic aldehydes produced II-614 with traces of II-616 (cyclization through one nitrile and one amide group) and II-617 (cyclization through two amide groups), while aromatic aldehydes gave II-615 (1241,1286). However, the reaction of cyanoacetamide with benzaldehyde in alcoholic potassium hydroxide formed a 46% yield of II-617 and a 38% yield of α -cyano- β -phenylpropionamide. The



latter was probably formed from with simultaneous oxidation of the dihydropyridine intermediate (1286). It was reported that isobutyraldehyde gave a 30% yield of II-616 and a trace of II-617 (1241) and, in contradiction, a "good" yield of II-617 (1287). Obviously, the reaction of ethyl cyanoacetate does not proceed through cyanoacetamide, but probably goes by way of II-618 which would not be found in the cyanoacetamide reaction.

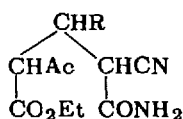
The reaction of aldehydes with a mixture of ammonia, ethyl acetoacetate, and ethyl cyanoacetate is expectedly complex and gives the products shown in II-619 (720). It has also been reported that



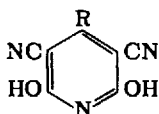
(II-618)

benzaldehyde produced II-625 rather than II-622 (322). The unsymmetrical product is not easily obtained, for even the reaction of ethyl cyanoacetate, ethyl α -ethylideneacetoacetate, and ammonia gave symmetrical products II-621 and II-623 but little or none of II-622 (700,1670).

Products from Condensation of an Aldehyde,
Ethyl Acetoacetate, and Ethyl Cyanoacetate



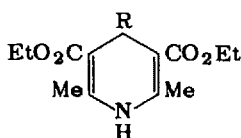
(II-620)



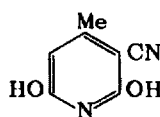
(II-621)



(II-622)



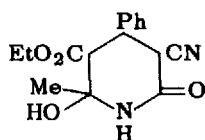
(II-623)



(II-624)

Aldehyde:	PrCHO	EtCHO	MeCHO	PhCHO	H ₂ CO
Products:	II-620	II-620	II-620	II-622	II-621
	II-621	II-621	II-621	II-620	II-620
	II-624	II-622 (?)	II-623		(trace)

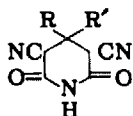
(II-619)



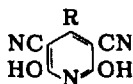
(II-625)

A further variation is the reaction of ethyl cyanoacetate with ketones rather than aldehydes (Table II-127). Guareschi showed

that in the absence of water the product was a dihydropyridine II-626, but in the presence of water a hydrocarbon was often eliminated to give a pyridine II-627 (323,696,697,700); yet the dihydropyridine II-626 was stable in alkali or acid (705). Guareschi also



(II-626)



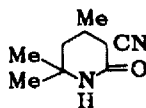
(II-627)

noted that a ketone with one phenyl or long alkyl group reacted well, but that a ketone with two such groups or with a tertiary carbon next to the carbonyl reacted poorly if at all. Methane was never eliminated (696).

Though one molecule of acetone can react with two of ethyl cyanoacetate in the presence of ammonia and gives II-628, the ratio of reactants may be reversed to give a 2-2-1 condensation as in II-629 (707,710,1671).

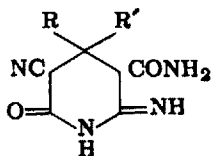


(II-628)

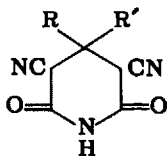


(II-629)

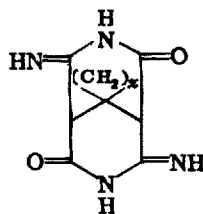
The condensation of cyanoacetamide with ketones gave mostly II-630 with a little II-631. This reaction proceeds with cyclohexanone but not with its 2-methyl or 2,4-dimethyl derivative (1597-1599). While the product from cyclohexanone (II-631) could be converted to II-632 by sodium ethoxide, cyclopentanone with a piperidine catalyst gave this directly (1599).



(II-630)



(II-631)



(II-632)

TABLE II-121. Miscellaneous Reactions of Two or More Carbonyl Compounds with Ammonia^a

Carbonyl Compounds	Conditions	Product (Yield)	Ref.
H ₃ CO, MeCHO	180°, 8 hrs.	2-Picoline (50%), 5-ethyl-2-picoline (25%)	94,795, 1679
	Vapor phase	Pyridine and derivatives	69,70, 71,72
	Vapor phase, alumina, silica, 425°	60% of bases, pyridine and 3-picoline	592,646
	Vapor phase alumina, silica, 200-400°	Pyridine (21.6%), 3-picoline	918
H ₃ CO, EtCOME	Vapor phase, alumina, copper tube	2,3,5,6-Tetramethylpyridine	1420
H ₃ CO, Cyclohexanone	Aq., NH ₄ OAc, 180°, 11 hrs.	Octahydrophenanthridine (34%)	773
H ₃ C(OEt) ₃ , MeCHO	Vapor phase, alumina, 380°	Octahydroacridine (6%) Pyridine, 2-picoline, 3-picoline, 4- picoline (low yields)	1316
H ₃ C(OEt) ₃ , EtCHO	Vapor phase, alumina, 380°	3,5-Lutidine and other bases	75,76
MeCHO, EtCHO (latter as aldehyde-ammonia)	Heat	A C ₉ base	113

(continued)

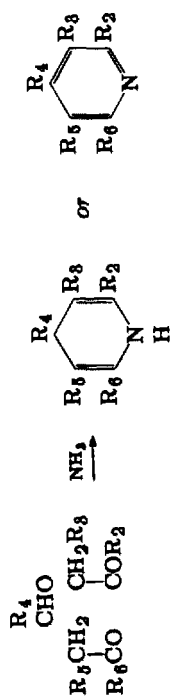
TABLE II-121 (Continued)
Miscellaneous Reactions of Two or More Carbonyl Compounds with Ammonia^a

Carbonyl Compounds	Conditions	Product (Yield)	Ref.
MeCHO, Cyclopentanone	NH ₄ OAc, 200°, 10 hrs.	5-Ethyl-2-picoline, 	773
MeCHO, Cyclohexanone	Aq., NH ₄ OAc, 180°, 11 hrs. Vapor phase, alumina, 370-400°	traces of other bases (See p. 499) 4-Methyl-5,6,7,8-tetrahydroquinoline	773 774
MeCHO, PhCHO	Vapor phase	4-Phenylpyridine	77
MeCHO, PhCH ₂ CHO	Alc., 230°, 6 hrs.	3,5-Diphenylpyridine, 3,5-diphenyl-2-picoline, 5-phenyl-2-picoline	797
MeCHO, CH ₂ :CHCHO	Vapor phase	3-Ethyl-4-picoline	73,74
MeCHO, MeCOMe	Vapor phase, alumina, 380°	Pyridine, 2-picoline, 3-picoline	1316
MeCHO (as aldehyde-ammonia), MeCOMe	NH ₄ OAc, 180°, 8 hrs. Heat, 10 hrs.	2,4,6-Collidine 2,4,6-Collidine	94,1679 1109
EtCHO, PhCH ₂ CHO	Alc., 230°, 6 hrs.	3,5-Diphenylpyridine, 2-ethyl-3,5-diphenylpyridine, 2-ethyl-5-phenyl-3-picoline, 2-benzyl-3,5-diphenylpyridine, 5-phenyl-3-picoline	797

EtCHO, EtCH:CMcCHO	Alc., 200°	A C ₆ pyridine	742
<i>i</i> -PrCHO, PhCH ₂ CHO	Alc., 230°, 6 hrs.	3,5-Diphenylpyridine, 2-benzyl-3,5-diphenylpyridine, 3,5-diphenyl-2-isopropylpyridine	797
PhCHO, PhCH ₂ CHO	Alc., 230°, 6 hrs.	3,5-Diphenylpyridine, 2,3,5-triphenylpyridine, unknown pyridine	797
PhCOMe, PhCH ₂ NH ₂	ZnCl ₂ , heat	2,4,6-Triphenylpyridine	1020, 1022
Me ₂ C:CHCOMe, EtCOMe	Aq., alkali, 100°	2,2,4,5,6-Pentamethyldihydropyridine, 2,2,4-trimethyl-6-ethyldihydropyridine	455
MeCOMe, NCCH ₂ CO ₂ Et		3-Cyano-4,6,6-trimethyldihydro-2-pyridinol	707, 710, 1671
H ₂ CO, MeCOMe, MeCOEt	Vapor phase, alumina, 350°	2,3,6-Collidine, 2,3,5,6-tetramethylpyridine	75

^aSee also Table II-122.

TABLE II-122. 2-1-2 Condensations of Oxo Compounds with Ammonia



R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield, %)		Ref.
						I	II	
H	H	H	H	H	Vapor phase, alumina silica, 360°	II (18), 2-Picoline (6), 3-picoline (16)	II (18), 2-Picoline (6), 3-picoline (16)	592 (see Table II-121)
Me	H	Me	H	H	Vapor phase, alumina, 350°	II (Traces of others)	II (Traces of others)	75
Me	H	H	H	Me	Vapor phase, alumina, 350°	II, 2,4-Lutidine	II, 2,4-Lutidine	75
H	Me	H	Me	H	Aq., 250°, 6 hrs.	II (16), 2-Ethyl-3,5- lutidine (trace)	II (16), 2-Ethyl-3,5- lutidine (trace)	514
H	Me	H (as acetal)	Me	H	Vapor phase, alumina, copper tube, 350°	II (18), 3-Picoline and pyridine traces	II (18), 3-Picoline and pyridine traces	1001,326

Me	Me	Me	H	H	Vapor phase, alumina, 350°	II, Other bases	75
Me	Me	H	H	Me	Vapor phase, alumina, 350°	II, 2,3,5,6-tetra- methylpyridine	75
Me	H	Me	H	Me	NH ₄ OAc, 180°, 8 hrs.	II	795
Me	Me	H	Me	Me	Vapor phase, alumina	II	110
					Vapor phase, alumina, 350°	II	75,1420
H	H	Ph	H	H	Vapor phase, alumina, 310°	II (11), 2-phenylpyr- idine, 6-phenyl- 2,4-lutidine	77,1001
Me	H	Ph	H	Me	Vapor phase, alumina, 310°	II (13%)	77,1001
CMe ₃	H	Ph	H	CMe ₃	NH ₄ OAc, 250°, 3 hrs.	?	1165
Ph	H	H	H	Ph	NH ₄ OAc, heat	II, 2,4-Diphenylpyr- idine	658
Ph	H	Ph	H	Ph	NH ₄ OAc, 250°, 3 hrs.	II (36)	1165
					NH ₄ OAc, HOAc, reflux, 1 hr.	II (68)	1152
Ph	Ph	Ph	Ph	Ph	NH ₄ OAc, 250°, 3 hrs.	II (20)	1165
					NH ₄ OAc, MeCONH ₂ , re- flux, 2 hrs.	II (30)	1152
Ph	H	p-ClC ₆ H ₄	H	Ph	NH ₄ OAc, 3 hrs.	II (18)	1165
Ph	H	p-MeOC ₆ H ₄	H	Ph	NH ₄ OAc, 250°, 3 hrs.	II (16)	1165
					NH ₄ OAc, HOAc, reflux, 1 hr.	II (68)	1152

(continued)

TABLE II-122 (Continued)
2-1-2 Condensations of Oxo Compounds with Ammonia

R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield, %)	Ref.
Ph	H	<i>o</i> -MeOC ₆ H ₄	H	Ph	NH ₄ OAc, HOAc, reflux, 1 hr.	II (60)	1152
Ph	H	3,4-CH ₂ O ₂ C	H	Ph	NH ₄ OAc, HOAc, reflux, 1 hr.	II (68)	1152
Ph	Ph	3,4-CH ₂ O ₂ C C ₆ H ₅	Ph	Ph	NH ₄ OAc, MeCONH ₂ , re- flux, 2 hrs.	II (24)	1152
Ph	H	Me ₂ NC ₆ H ₄	H	Ph	NH ₄ OAc, HOAc, reflux, 1 hr.	II (64)	1152
3-Py	H	Ph	H	3-Py	Aq., NH ₄ OAc, 250°	II (32)	1153
2-Py	H	Ph	H	2-Py	250°, 3 hrs.	II (17)	1536
3-Py	Ph	Ph	Ph	3-Py	Aq., NH ₄ OAc, 250°	II (32)	1153
Ph	2-Py	Ph	2-Py	Ph	Aq., NH ₄ OAc, 250°	II (5)	1153
3-Py	H	3-Py	H	3-Py	Aq., NH ₄ OAc, 250°	II (32)	1153
3-Py	2-Py	3-Py	2-Py	3-Py	Aq., NH ₄ OAc, 250°	II (5)	1153
4-Me-2- C ₆ H ₃ N	H	Ph	H	4-Me-2- C ₆ H ₃ N	Aq., excess NH ₃ , NH ₄ - OAc, 250°, 5 hrs., pressure	II (18)	875
4-Et-2- C ₆ H ₃ N	H	Ph	H	4-Et-2- C ₆ H ₃ N	Aq., excess NH ₃ , NH ₄ - OAc, 250°, 5 hrs., pressure	II (16)	875
4-Ph-2- C ₆ H ₃ N	H	Ph	H	4-Ph-2- C ₆ H ₃ N	Aq., excess NH ₃ , NH ₄ - OAc, 250°, 5 hrs., pressure	II (21)	875

6-Ph-2- C ₅ H ₃ N	H	Ph	H	6-Ph-2- C ₅ H ₃ N	Aq., excess NH ₃ , NH ₄ - OAc, 250°, 5 hrs., pressure	II (17)	875
2-Quinolyl	H	Ph	H	2-Quinolyl	Aq., excess NH ₃ , NH ₄ - OAc, 250°, 5 hrs., pressure	II (18)	875
Me	COMe	H	COMe	Me	Formamide as NH ₃ , source	I	448
Me	COMe	Me	COMe	Me	10% (NH ₄) ₂ CO ₃ , 25°, 4 days	I (51)	1520
Me	COMe	Ph	COMe	Me	Aq., alc., steam bath, 3 hrs.	I (32)	1128
Me	COMe	<i>p</i> -NO ₂ C ₆ H ₄	COMe	Me	Aq., alc., steam bath, 3/4 hr.	I	1145
Me	COMe	<i>m</i> -HO ₂ C ₆ H ₄	COMe	Me	Aq., alc., steam bath, 3 hrs.	I (50)	1128
Me	COMe	<i>o</i> -NO ₂ C ₆ H ₄	COMe	Me	Aq., alc., steam bath, 3/4 hr.	I (23)	1145
Me	CO ₂ Et	Me	H	H	100°	II (25)	192
Me	CO ₂ Me	Me	CO ₂ Me	Me	Aldehyde-ammonia	I	221
Me	CO ₂ Me	Ph	CO ₂ Me	Me	Aq., alc., heat	I (63)	1085
Me	CO ₂ Me	<i>m</i> -NO ₂ C ₆ H ₄	CO ₂ Me	Me	Aq., MeOH, heat	I (75)	1085
Me	CO ₂ Me	<i>p</i> -Me ₂ N- C ₆ H ₄	CO ₂ Me	Me	Aq., MeOH, heat, 7 hrs.	I (61)	1085
Me	CO ₂ Me	<i>p</i> -Et ₂ NC ₆ H ₄	CO ₂ Me	Me	Aq., MeOH, heat	I (53)	1085

(continued)

TABLE II-122 (Continued)
2-1-2 Condensations of Oxo Compounds with Ammonia

R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield, %)	Ref.
Me	CO ₂ Et	H	CO ₂ Et	Me	Alc., heat, 1 hr.; or stand, sev. days Aq., alc.; (1) 25°, 12 hrs., (2) heat, $\frac{1}{2}$ hr. Hexamethylene tetra- mine, ZnCl ₂ , 2 hrs., sealed tube Formamide as NH ₃ source	I I (63-89) I (90-95) I II	704,1129, 1145 800,1291, 1292 211,212, 1673 215 448
Me	CO ₂ Et	H (as form- amide	CO ₂ Et	Me	Formamide as source of NH ₃ and 4-carbon	II (3)	1428
Me	CO ₂ Et	Me	CO ₂ Et	Me	NH ₄ OAc, HOAc, reflux, $\frac{1}{2}$ hr. Aldehyde-ammonia; (1) 110°, 3 min. (2) 2N HCl, warm Formamide as NH ₃ source	I (15) I	800 194,219 448

Me	CO ₂ Et	Et	CO ₂ Et	Me	I	214
Me	CO ₂ Et	Pr	CO ₂ Et	Me	I (89)	321
Me	CO ₂ Et	<i>i</i> -Pr	CO ₂ Et	Me	I	214
Me	CO ₂ Et	<i>i</i> -Bu	CO ₂ Et	Me	I (75)	320
Me	CO ₂ Et	(CH ₂) ₃ Me	CO ₂ Et	Me	I	214, 229
Me	CO ₂ Et	(CH ₂) ₁₄ Me	CO ₂ Et	Me	I	214
Me	CO ₂ Et	CH ₂ Ph	CO ₂ Et	Me	I	229, 318, 1589
Me	CO ₂ Et	CH:CHPh	CO ₂ Et	Me	I	313
Me	CO ₂ Et	Ph	CO ₂ Et	Me	I (71)	1089
Me	CO ₂ Et				I	230
Me	CO ₂ Et				I	232, 704, 1085, 1129, 1331
					I (74)	1628
					I	448
Me	CO ₂ Et	<i>p</i> -MeC ₆ H ₄	CO ₂ Et	Me	I (37)	1628
Me	CO ₂ Et	<i>m</i> -MeC ₆ H ₄	CO ₂ Et	Me	I (57)	1628
Me	CO ₂ Et	<i>o</i> -MeC ₆ H ₄	CO ₂ Et	Me	I (9)	1628

(continued)

TABLE II-122 (Continued)
2-1-2 Condensations of Oxo Compounds with Ammonia

R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield, %)	Ref.
Me	CO ₂ Et	2,4-Me ₂ - C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (33)	1628
Me	CO ₂ Et	2,5-Me ₂ - C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (44)	1628
Me	CO ₂ Et	3,4-Me ₂ - C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (35)	1628
Me	CO ₂ Et	2,4,6-Me ₃ - C ₆ H ₂	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (none)	1628
Me	CO ₂ Et	p-ClC ₆ H ₄	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (69)	316,1628
Me	CO ₂ Et	m-ClC ₆ H ₄	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (76)	316,1628
Me	CO ₂ Et	o-ClC ₆ H ₄	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (62)	316,1628
Me	CO ₂ Et	p-NO ₂ C ₆ H ₄	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (64)	1145,1628
Me	CO ₂ Et	m-NO ₂ C ₆ H ₄	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (88)	1085,1628
Me	CO ₂ Et	o-NO ₂ C ₆ H ₄	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (62)	1145,1628
Me	CO ₂ Et	4-Me-3,5- (NO ₂) ₂ - C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (68)	1628

Me	CO ₂ Et	2,4,6-Me ₃ - 3,5- (NO ₂) ₂ - C ₆	CO ₂ Et	Me	I (less than 1)	1628
Me	CO ₂ Et	<i>p</i> -HOC ₆ H ₄ C ₆	CO ₂ Et	Me	I (49-68)	235,316, 1138,1628
Me	CO ₂ Et	<i>m</i> -HOC ₆ H ₄	CO ₂ Et	Me	I (67)	316,1628
Me	CO ₂ Et	<i>o</i> -HOC ₆ H ₄	CO ₂ Et	Me	I (Poor)	316,1628
Me	CO ₂ Et	2-HO- 5-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	I (14)	315
Me	CO ₂ Et	3-HO- 4-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	I (57)	315
Me	CO ₂ Et	5-HO- 2-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	I (51) (Mixture of I and 2-aryl-4,6-di- methyl-3,5-pyri- dinedicarbox- ylic acid, di- ethyl ester)	315
Me	CO ₂ Et	4-HO- 3-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	I (61)	315
Me	CO ₂ Et	<i>p</i> -MeO- C ₆ H ₄	CO ₂ Et	Me	I (65)	235,316, 1145,1628

(continued)

TABLE II-122 (Continued)
2-1-2 Condensations of Oxo Compounds with Ammonia

R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield, %)	Ref.
Me	CO ₂ Et	<i>m</i> -MeO- C ₆ H ₄	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (33-75)	316, 1628
Me	CO ₂ Et	<i>o</i> -MeO- C ₆ H ₄	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (48-57)	316, 1628
Me	CO ₂ Et	2-MeO-5- NO ₂ C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (77)	315
Me	CO ₂ Et	3-MeO- 2-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (51)	315
Me	CO ₂ Et	3-MeO- 4-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (69)	315
Me	CO ₂ Et	5-MeO- 2-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (64)	315
Me	CO ₂ Et	4-MeO- 3-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	Alc.; (1) 25°, 18 hrs. (2) heat, 7 hrs.	I (77)	315
Me	CO ₂ Et	3-MeO-2,- 6-(NO ₂) ₂ - C ₆ H ₃	CO ₂ Et	Me		No product	315

Me	CO ₂ Et	3-HO- 4-MeO- C ₆ H ₃	CO ₂ Et	Me	I (73)	317
Me	CO ₂ Et	4-HO- 3-MeO- C ₆ H ₃	CO ₂ Et	Me	I (74)	317
Me	CO ₂ Et	3-HO- 4-MeO- 5-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	I (76)	317
Me	CO ₂ Et	4-HO- 3-MeO- 2-NO ₂ - C ₆ H ₃	CO ₂ Et	Me	I (72)	317
Me	CO ₂ Et	2,6-(NO ₂) ₂ - 3-HO- 4-MeO- C ₆ H ₃	CO ₂ Et	Me	No product	317
Me	CO ₂ Et	3,4-(MeO) ₂ - C ₆ H ₃	CO ₂ Et	Me	I (76)	317
Me	CO ₂ Et	2-Cl-3,4- (MeO) ₂ - C ₆ H ₃	CO ₂ Et	Me	I (67)	317
Me	CO ₂ Et	2-Br-3,4- (MeO) ₂ - C ₆ H ₃	CO ₂ Et	Me	I (70)	317

(continued)

TABLE II-122 (Continued)
2-1-2 Condensations of Oxo Compounds with Ammonia

R ₂	R ₃	R ₄	R ₅	R ₆	Conditions	Product (Yield, %)	Ref.
Me	CO ₂ Et	3,4-(MeO) ₂ -2-NO ₂ - C ₆ H ₃	CO ₂ Et	Me		I	317
Me	CO ₂ Et	4,5-(MeO) ₂ -3-NO ₂ - C ₆ H ₃	CO ₂ Et	Me		I (70)	317
Me	CO ₂ Et	4,5-(MeO) ₂ -2-NO ₂ - C ₆ H ₃	CO ₂ Et	Me		I (68)	317
Me	CO ₂ Et	3,4-CH ₃ O- C ₆ H ₃	CO ₂ Et	Me	Alc.	I	311
Me	CO ₂ Et	p-Me ₂ N- C ₆ H ₄	CO ₂ Et	Me	Aq., MeOH, heat, 7 hrs.	I (53)	308,1085
Me	CO ₂ Et	3-Br-4-Me ₂ N- C ₆ H ₄	CO ₂ Et	Me		I (80)	312
Me	CO ₂ Et	4-Me ₂ N-3-NO ₂ - C ₆ H ₃	CO ₂ Et	Me		I (70)	312
Me	CO ₂ Et	p-Et ₂ N- C ₆ H ₄	CO ₂ Et	Me	Aq., MeOH, heat	I (50)	1085

Me	CO ₂ Et	2-C ₄ H ₉ O	CO ₂ Et	Me	Aq., alc.	I	231,238
Me	CO ₂ Et	3-Quinolyl	CO ₂ Et	Me	Alc., 100°, 7 hrs.	I (79)	319
Me	CO ₂ Et	4-Quinolyl	CO ₂ Et	Me	Alc., 100°, 7 hrs.	I	1129
Me	CO ₂ Et	5-Quinolyl	CO ₂ Et	Me	Alc., 100°, 7 hrs.	I (52)	319
Me	CO ₂ Et	8-Quinolyl	CO ₂ Et	Me	Alc., 100°, 7 hrs.	I (27)	319
Me	CO ₂ Bu	<i>m</i> -NO ₂ - C ₆ H ₄	CO ₂ Bu	Me	Aq., MeOH, heat	I (68)	1085
Me	CO ₂ alkyl	4-Quinolyl	CO ₂ alkyl	Me	Heat	I	1719
Ph	CO ₂ Et	Me	CO ₂ Et	Me	Aldehyde-ammonia, re- flux, 12 hrs.	I (8.2)	524
Me	CO ₂ Et	<i>p</i> -HOC ₆ H ₄	CO ₂ Et	Me	Aniline (no NH ₃) alc., 25°	3,5-Dicarbomethoxy- 2,6-dimethyl-4- (<i>p</i> -hydroxyphenyl)- 1-phenylidihydro- pyridine	235

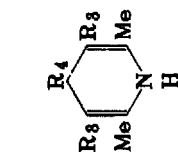


TABLE II-123. Reactions of an Aldehyde and a Ketone with a Ketimine

R ₃	R ₄	Conditions	Product (Yield)	Ref.
COMe	4-HO-3-MeO- 2-NO ₂ C ₆ H ₃	Aq., alc., water bath, 2 days	(21%)	1164
CO ₂ Et	Ph	Aq., alc.	(77%)	1494
CO ₂ Et	<i>m</i> -HOC ₆ H ₄	Ac ₂ O, ½ hr.	(Hydroxy group acetylated in reaction)	1436
CO ₂ Et	<i>p</i> -Me ₂ NC ₆ H ₄	(1) Water bath, 8 hrs.	(22%)	308
CO ₂ Et	1-C ₁₀ H ₇	(2) Ac ₂ O, reflux		1429
CO ₂ alkyl	4-Quinolyl	Heat		1085, 1719

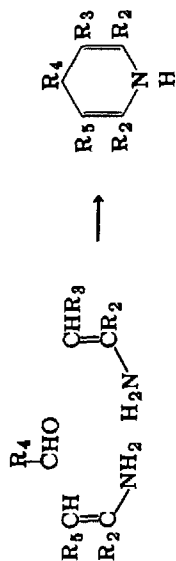


TABLE II-124. Reactions of Aldehydes with Ketimines

R ₁	R ₃	R ₄	R ₅	Conditions	Yield	Ref.
Me	COPh	CH ₂ Cl	COPh	EtOCHClCH ₂ Cl as aldehyde		1245
Me	CO ₂ Et	<i>m</i> -NO ₂ C ₆ H ₄	CO ₂ Et	100°, 5 hrs.	80%	319
Me	CO ₂ Et	<i>p</i> -NO ₂ C ₆ H ₄	CO ₂ Et	Steam bath, 6 hrs.	56%	319
Me	CO ₂ Et	<i>p</i> -CHOC ₆ H ₄ (terephthalaldehyde)	CO ₂ Et	Steam bath, 3 hrs.	28% (The bis product)	1137
Me	CO ₂ Et	2-Quinolyl	CO ₂ Et	Heat	35%	319
Me	CO ₂ Et	4-Quinolyl	CO ₂ Et	Heat	32%	319
Me	CO ₂ Et	6-Quinolyl	CO ₂ Et	Heat	53%	319
Me	CO ₂ Et	CH ₂ Cl	CO ₂ Et	EtOCHClCH ₂ Cl as aldehyde		1245
Me	CO ₂ alkyl	4-Quinolyl	CO ₂ alkyl	Heat		1085, 1719
Me	CO ₂ Et	<i>o</i> -NO ₂ C ₆ H ₄	CN	Alc., reflux, 80 hrs.	22%	1163
Me	CO ₂ Et	4-HO-3-MeOC ₆ H ₃	CN	(1) Alc., reflux, 50 hrs. (2) Ac ₂ O, heat		1163

(continued)

TABLE II-124 (Continued)
Reactions of Aldehydes with Ketimines

R_2	R_3	R_4	R_5	Conditions	Yield	Ref.
Me	CO_2Et	4-HO-3-MeO-2- $\text{NO}_2\text{C}_6\text{H}_3$	CN	(1) Alc., reflux, 50 hrs. (2) Ac_2O , heat	68% (As acetate of 4-aryl group)	1163
Me	CO_2Et	3,4-(MeO) $_2$ - C_6H_3	CN	(1) Alc., reflux, 50 hrs. (2) Ac_2O , heat	36%	1163
Me	CO_2Et	4,5-Methylenedioxy-2- $\text{NO}_2\text{C}_6\text{H}_3$	CN	(1) Alc., reflux, 50 hrs. (2) Ac_2O , heat	18%	1163
Me	CN	H	CN	HOAc (may use hexamethylene tetramine)		303,1688, 1068
Me	CN	Me	CN	Alc., HCl (may use aldehyde-ammonia)		303,1068, 1688
Me	CN	Ph	CN	HOAc, or other acid		1613,1688, 1614
Me	CN	o- $\text{NO}_2\text{C}_6\text{H}_4$	CN	HOAc, reflux, $\frac{1}{4}$ hr.	88%	1164,1614
Me	CN	2,4-(NO_2) $_2$ - C_6H_3	CN	HOAc, reflux, $\frac{1}{4}$ hr.	100%	1164
Me	CN	Terephthalaldehyde	CN	HOAc, water bath, 1 hr.	good (Bis product)	524
Me	CN	Isophthalaldehyde	CN	HOAc, water bath, 1 hr.	82% (Bis product)	524

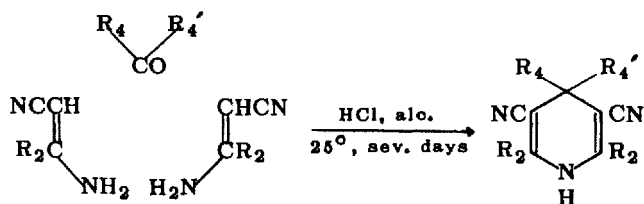
Me	CN	Phthalaldehyde	CN	HOAc, water bath, 1 hr.	18% (Bis product)	524
Me	CN	o-HOC ₆ H ₄	CN	HOAc, reflux, ½ hr.		1613, 1614
Me	CN	p-MeOC ₆ H ₄	CN	(1) Alc. or benzene (2) HCl, H ₂ SO ₄ , or Ac ₂ O		1613
Me	CN	4-HO-3-MeO-2-NO ₂ C ₆ H ₃	CN	HOAc, reflux, ¼ hr.	70%	1164
Me	CN	CH ₂ Cl	CN	(CH ₂ ClCHCl) ₂ O as aldehyde, aq., sev. hrs.	45%	1252
Ph	CN	H	CN	Hexamethylene tetramine, alc., HCl		1688
Ph	CN	Me	CN	Alc., HCl	70%	1688, 1716
Ph	CN	Ph	CN	Alc., HCl		303, 1068, 1688
Ph	CN	o-NO ₂ C ₆ H ₄	CN	HOAc, reflux, 1 hr. or alc. HCl	High yield	1164, 1688
Ph	CN	2,4-(NO ₂) ₂ -C ₆ H ₃	CN	HOAc, reflux 1 hr.	45%	1164
Ph	CN	p-HOC ₆ H ₄	CN	HOAc		1260
Ph	CN	m-HOC ₆ H ₄	CN	HOAc		1260
Ph	CN	4-HO-3-MeO-2-NO ₂ C ₆ H ₃	CN	HOAc, reflux, 1 hr.	70%	1164

(continued)

TABLE II-124 (Continued)
Reactions of Aldehydes with Ketimines

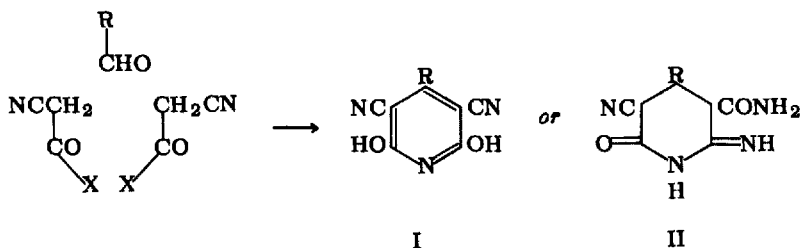
R ₂	R ₃	R ₄	R ₅	Conditions	Yield	Ref.
Ph	CN	CH ₃ Cl	CN	(CH ₂ ClCHCl) ₂ O as aldehyde		1252
<i>p</i> -MeC ₆ H ₄	CN	<i>p</i> -HOC ₆ H ₄	CN	HOAc		1260
<i>p</i> -MeC ₆ H ₄	CN	<i>m</i> -HOC ₆ H ₄	CN	HOAc		1260
<i>p</i> -MeC ₆ H ₄	CN	<i>o</i> -HOC ₆ H ₄	CN	HOAc		1260
<i>p</i> -ClC ₆ H ₄	CN	Ph	CN	Alc., HCl		1716
<i>m</i> -ClC ₆ H ₄	CN	Ph	CN	Alc., HCl		1716
<i>o</i> -ClC ₆ H ₄	CN	Ph	CN	Alc., HCl		1716
<i>p</i> -MeOC ₆ H ₄	CN	<i>p</i> -HOC ₆ H ₄	CN	HOAc		1260
<i>p</i> -MeOC ₆ H ₄	CN	<i>m</i> -HOC ₆ H ₄	CN	HOAc		1260
<i>o</i> -MeOC ₆ H ₄	CN	Me	CN	HOAc reflux 1 hr.		1525
<i>o</i> -MeOC ₆ H ₄	CN	Ph	CN	HOAc reflux 1 hr.	High	1525
2-MeO-5- NO ₂ C ₆ H ₃	CN	Me	CN	HOAc reflux 1 hr.	High	1525
2,4-(MeO) ₂ - C ₆ H ₃	CN	Me	CN	HOAc reflux 1 hr.	80%	1525
2,4-(MeO) ₂ - 5-NO ₂ C ₆ H ₃	CN	Me	CN	HOAc reflux 1 hr.	80%	1525
3,6-(MeO) ₂ - 2-NO ₂ C ₆ H ₃	CN	Me	CN	HOAc reflux 1 hr.	62%	1525
<i>p</i> -EtOC ₆ H ₄	CN	Ph	CN	Alc. HCl		1716

TABLE II-125. Reactions of Ketones with Ketimines



R ₂	R ₄	R ₄ '	Yield, %	Ref.
Me	Me	Me	70	1716
Me	Me	Et	67	1716
Me	Me	Pr	58.5	1716
Me	Me	CH ₂ Ph	52.5	1716
Me	Et	Et	34	1716
Me	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ - (cyclohexanone)		80	1716
Ph	Me	Me	87	1716
Ph	Me	Et	74	1716
Ph	Me	Pr	68	1716
Ph	Me	Bu	61	1716
Ph	Me	CH ₂ Ph	53.5	1716
Ph	Me	Ph	16.5	1716
Ph	Et	Et	23.2	1716
Ph	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ - (cyclohexanone)		78.5	1716
<i>p</i> -MeC ₆ H ₄	Me	Me	83.5	1716
<i>p</i> -MeC ₆ H ₄	Me	Et	87	1716
<i>p</i> -MeC ₆ H ₄	Me	Pr	85	1716
<i>p</i> -MeC ₆ H ₄	Me	CH ₂ Ph	84.5	1716
<i>p</i> -MeC ₆ H ₄	Et	Et	71	1716
<i>p</i> -MeC ₆ H ₄	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ - (cyclohexanone)		88.5	1716

TABLE II-126. Reactions of Aldehydes with Cyanoacetic Acid Derivatives



X	R	Conditions	Product (Yield)	Ref.
OEt	Me	NH ₃	I	1670
OEt	Et	Aq., NH ₃ , stand	I	718
OEt	Pr	Aq., NH ₃ , stand, 1 d.	I	708,717
OEt	<i>i</i> -Pr	Aq., NH ₃ , stand	I	718
OEt	<i>i</i> -Bu	Aq., NH ₃ , stand	I	718
OEt	(CH ₂) ₅ Me	Aq., NH ₃ , stand	I	718
OEt	Ph	Aq., or anhydrous	I	702,717
OEt	<i>m</i> -MeC ₆ H ₄	NH ₃ Aq., NH ₃ , 25°, 2-3 d.	I (30%)	717,718
OEt	<i>p</i> -isoPrC ₆ H ₄	Aq., NH ₃ , 25°, 2-3 d.	I	717,718
OEt	<i>p</i> -MeOC ₆ H ₄	Aq., NH ₃	I	702,708
OEt	2-C ₄ H ₃ O	Aq., or anhydrous	I	702
NH ₂	Me	NH ₃ Aq., KOH, 3 hrs.	I, II (Traces)	1286
NH ₂	Et	Aq., KOH, 3 hrs. (no NH ₃)	II (Trace)	1286
NH ₂	Pr	Aq., KOH, 3 hrs. (no NH ₃)	II (Trace)	1286
NH ₂	<i>i</i> -Pr	Aq., Et ₃ NH, sev. hrs.	I, II (Traces)	1241
NH ₂	<i>i</i> -Pr		I (Good)	1287
NH ₂	<i>i</i> -Bu	Aq., alc.	II (30%) I (Trace)	1241
NH ₂	(CH ₂) ₅ Me	Aq., alc.	II (1-2%)	1241
NH ₂	CH ₂ CH ₂ OMe	Aq., piperidine, 20°, 7 d.	II (15.9%)	536
NH ₂	Ph	Aq., KOH, 2 hrs.	PhCH: C(CN)- CONH ₂ only	1286
NH ₂	Ph	Aq., alc., KOH, 40°, 3 d.	I (46%)	1286

TABLE II-127 (Continued)
Reactions of Ketones with Cyanoacetic Acid Derivatives

X	R	R'	R''	Conditions	Product (Yield)	Ref.
OEt	Me	Me	CH ₂ Ph	Alc.	1-Benzyl-3-Cyano-4,6,6-trimethyl-5,6-dihydro-1H-pyridone	710
OEt	Me	Et	H	Alc.	I	696
				Anhydrous	I	705
				Alc., NH ₃ , cold, 2 d.	I (56-64%)	589,810
				Anhydrous	II (HCN, ethane)	1669
OEt	Me	Et	Me	Alc.	I	696
OEt	Me	Et	Et	Alc.	I	696
OEt	Me	Et	CH ₂ CH:CH ₂	Alc.	I	696
OEt	Me	Pr	H	Aq.	II (HCN, C ₃ H ₈)	1671
				Alc.	I (70%)	701,810
				Alc.	I	696
OEt	Me	Pr	Me	Alc.	I (19%)	701,1599
OEt	Me	<i>i</i> -Pr	H	Aq., or alc.	I	1671
OEt	Me	Bu	H	Aq.	II (Butane)	696
				Alc.	I	696
				Alc.	I	696
				Alc.	I	696
				Alc.	I (Low)	1599
				Alc.	I	703
				Aq.	II (HCN, hexane)	1671
OEt	Me	Bu	Me			
OEt	Me	<i>i</i> -Pr	H			
OEt	Me	CHMeEt	H			
OEt	Me	(CH ₃) ₂ Me	H			

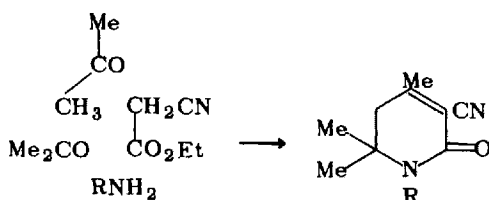
OEt	Me	(CH ₂) ₃ CHMe ₂	H	Alc.	I	696
OEt	Me	CH ₂ CH ₂ CH : CMe ₂	H	Alc.	I	696
OEt	Me	(CH ₂) ₄ Me	H	Alc.	I	696
OEt	Me	CH ₂ Ph	H	Alc.	I (75%)	323,1599
OEt	Me	CH ₂ Ph	Me	Alc.	I	696
OEt	Me	CH ₂ CH ₂ Ph	H	Alc.	I	323,696
OEt	Me	CH : CHPh	H	Alc.	I	696
OEt	Me	Ph	H	Alc.	I	696
OEt	Et	Et	H	Alc., 25°, 2 d.	I (37%)	697,1693
OEt	Et	Pr	H	Alc.	I	696
OEt	Et	CH ₂ Ph	H	Alc.	I (19-32%)	323,1599
OEt	Et	CH ₂ CH ₂ Ph	H	Alc., followed by HCl	I (17.6%)	323
OEt	Pr	Pr	H	Alc.	I	696
OEt	Pr	CH ₂ Ph	H	Alc., followed by HCl	I (11.3%)	323
OEt	i-Pr	CH ₂ Ph	H	Alc., followed by HCl	I	323
OEt	i-Bu	CH ₂ Ph	H	Alc., followed by HCl	I (low)	323
OEt	-CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentanone)		H	Alc.	I (50%)	1599
OEt	-CHMeCH ₂ CH ₂ CH ₂ -		H	Alc., 40°, 2 d.	I (Low)	1599
OEt	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -		H	Alc.	I	721
OEt	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -	Me		Alc.	I	712
OEt	-CHMeCH ₂ CH ₂ CH ₂ CH ₂ -		H	Alc.	I (Low)	712,1599

(continued)

TABLE II-127 (Continued)
Reactions of Ketones with Cyanoacetic Acid Derivatives

X	R	R'	R''	Conditions	Product (Yield)	Ref.
OEt	-CHMeCH ₂ CH ₂ CH ₂ CH ₂ -	Me		Alc.	I	712
OEt	-CH ₂ CHMeCH ₂ CH ₂ CH ₂ -	H		Alc.	I	721
OEt	-CH ₂ CH ₂ CHMeCH ₂ CH ₂ -	H		Alc., 25°, several hrs.	I	712
OEt	-CH ₂ CH ₂ CHMeCH ₂ CH ₂ -	Me		Alc.	I	712
OEt	-CHMeCH ₂ CHMeCH ₂ CH ₂ -	H		Alc.	I	1599
OEt	-CHMeCH ₂ CH ₂ CMe ₂ CH ₂ -	H		Alc., 40°, 2 d.	I	1599
NH ₂	Me	Me	H (no NH ₃)	Aq., KOH, or piperidine, 25°, 1 d.	III (93%)	1597
NH ₂	Me	Et	H (no NH ₃)	Aq., KOH, or piperidine, 25°, 1 d.	III (57%)	1597
NH ₂	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -		H (no NH ₃)	Aq., KOH, or piperidine, 25°, 1 d.	III (87%)	1597

TABLE II-128. Reaction of Acetone, Ethyl Cyanoacetate, and an Amine



Amine	Ref.
NH ₃ (anhydrous)	707
MeNH ₂	710
NH ₂ CH ₂ CH ₂ NH ₂ (gives the bis product)	707
PhCH ₂ NH ₂	710
C ₁₀ H ₁₇ NH ₂ (Camphylamine)	707

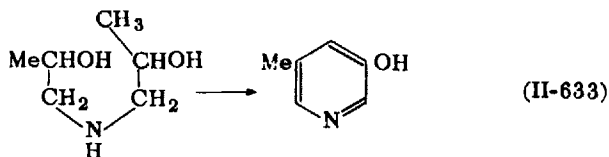
7. Cyclization Not Involving the Ring Nitrogen

The large majority of pyridine preparations from acyclic materials require the formation of at least one carbon-nitrogen bond. A small number of acyclic compounds which contain the necessary carbon-nitrogen skeleton may be cyclized by the formation of only carbon-carbon bonds. With one exception, these compounds are secondary or tertiary amines or *N*-substituted amides.

a. Cyclization of Secondary and Tertiary Amines

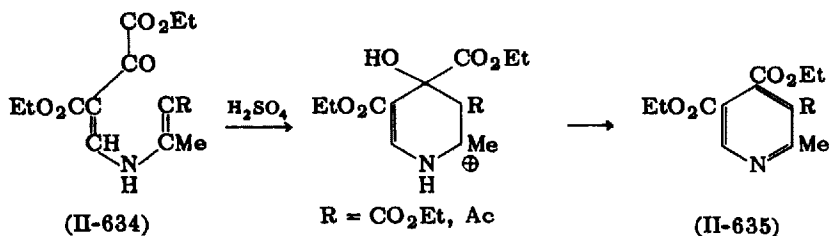
The simplest amine to cyclize to a pyridine is allylethylamine, which in the vapor phase over lead oxide at 500° produced low yields of pyridine and pyrrole (67). The initial product was probably piperidine which oxidized to pyridine under the strenuous conditions.

More successful is the vapor phase reaction of bis- β -hydroxypropylamine over metal catalysts at 350° which is reported to give a 45% yield of 5-methyl-3-pyridinol (II-633) (1478). It is probable



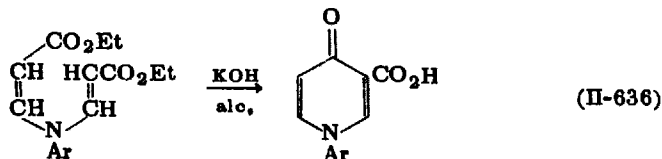
that neither diallylamine, nor a piperidinol, is an intermediate, for these would be expected to give 3-picoline. A more likely intermediate is imino-bis-acetone.

A more useful approach involves the cyclization of secondary or tertiary amines through a carbonyl group. Accordingly, the sulfuric acid-catalyzed cyclization of the amine II-634 gave the pyridine II-635 in fairly good yields (Table II-129). In working up the reaction mixture, dilution with alcohol instead of water obviated the problem of partial ester hydrolysis (572,683). Cyclization of II-634

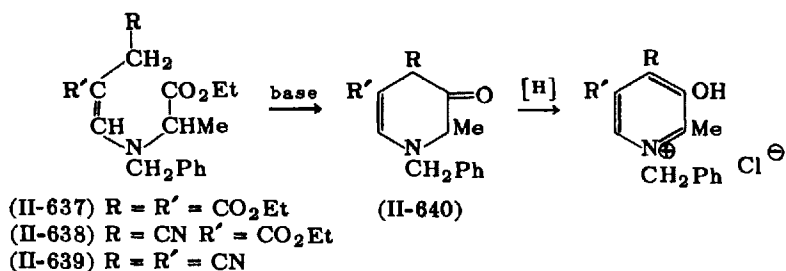


was not brought about by heat, anhydrous hydrogen chloride, boron trifluoride, or phosphoric acid (572).

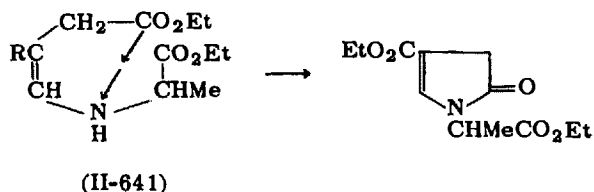
A similar condensation which utilizes an ester rather than a ketone carbonyl (II-636) is brought about by alcoholic potassium hydroxide, which also saponifies the ester group (364,370).



Cyclization may also occur at a carbonyl beta to the nitrogen, as shown in the tertiary amine II-637. This reaction, which is catalyzed by sodium, sodamide, or sodium methoxide (Table II-130), gives a dihydropyridine II-640 which is readily oxidized by sulfuryl chloride or air to the fully aromatic product. Though II-637 gave the pyridinium product in good yield, II-638 gave only a low yield and II-639 did not cyclize (1156). The products, which are 1-benzylpyridinium salts, may be debenzylated by hydrogen to the corresponding pyridine (574,792,1156,1157).

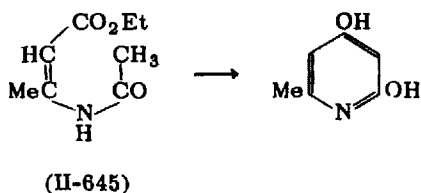
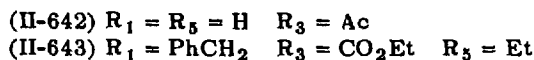
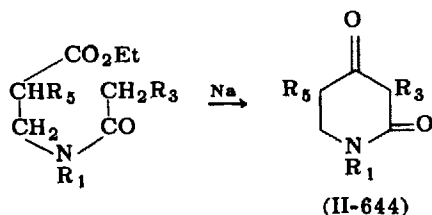


The above method converted a secondary γ -aminoester II-641 to a pyrrole rather than a pyridine (574,1156,1434).

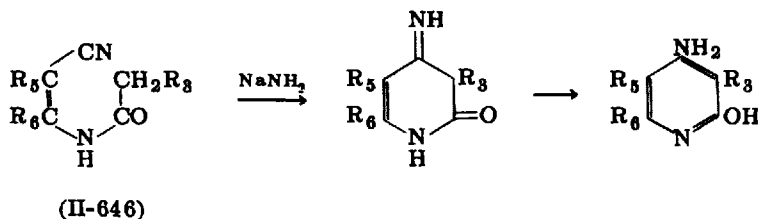


b. Cyclization of *N*-Substituted Amides

Amides which have been cyclized to pyridines have with one exception required the participation of the acyl group, which usually furnished an active methylene group for a Claisen-type condensation. Thus II-642 (1634) and II-643 (622) were cyclized by sodium or sodium ethoxide to II-644. When the starting material was an amide of an aminoacrylic ester as in II-645, the product was a pyridinediol (1082).

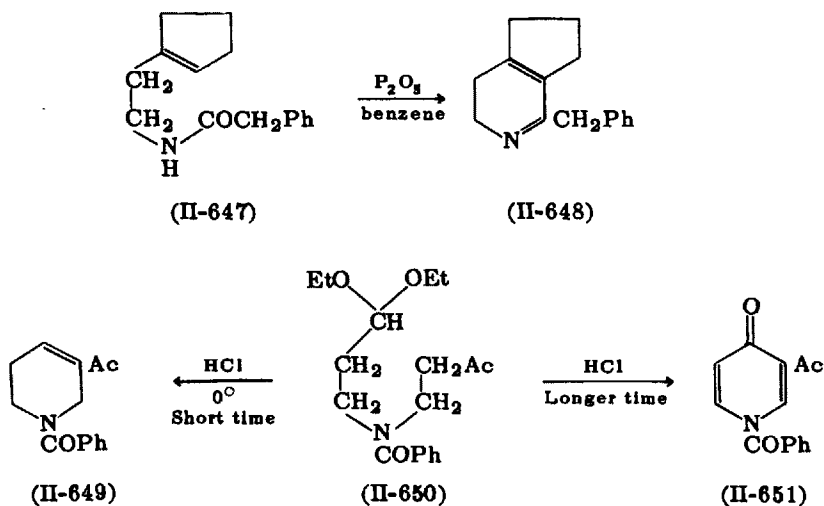


Somewhat more common is the sodamide-catalyzed condensation of a β -acylamidoacrylonitrile (II-646), which usually proceeds in good yields (Table II-131). Although this method is limited in scope, it is unusual in that the products are 4-aminopyridines. The reaction appears to be a straightforward attack of a carbanion on the nitrile group.



The involvement of the carbonyl of the amide in cyclization is singular. Thus, the ring closure of the amide II-647 by phosphorus pentoxide in boiling benzene produced the dihydropyridine II-648 in good yield (649). This synthesis resembles the Bischler-Napieralski synthesis of dihydroisoquinolines, though in this instance the double bond attacked is isolated rather than a part of an aromatic system.

Another interesting reaction is that of the amide II-650, which in cold hydrochloric acid for a short period gave the amide of the tetrahydropyridine II-649, but gave in a longer period a polymeric material and a low yield of a product which might be II-651 (345).



c. Cyclization of Two Molecules

A single patent furnishes all the known examples of this reaction (608), which is essentially the condensation of the methylimine of pyruvonnitrile with 1,4-dihydroxybutanone in the presence of piperidine (II-652). Various other starting materials are mentioned, such as butynediol and tetrahydrofuran-3-one.

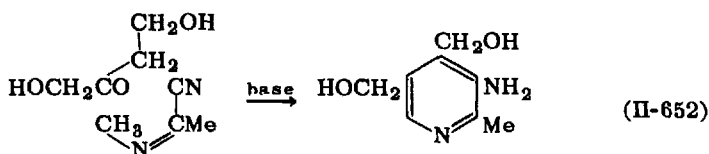
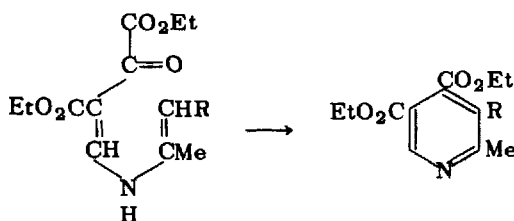


TABLE II-129. Cyclization of Divinyl Amines

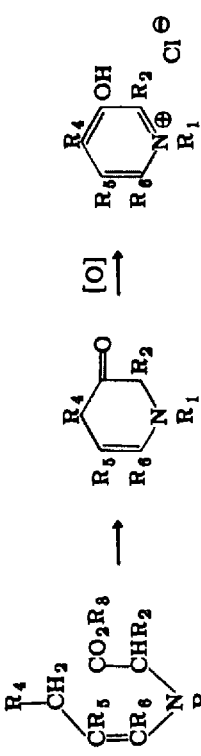


R	Conditions	Yield	Ref.
Ac	H ₂ SO ₄	(Partial hydrolysis)	668
	H ₂ SO ₄ 97%, 25°, 2 hrs.	^a	683
	H ₂ SO ₄ 97%, 25°, 2 hrs.	9% (Also product with hydrolysis of one ester 70%, with hydrolysis of both esters 5%)	572,848
CO ₂ Me	H ₂ SO ₄ 97%, 25°, 1 hr.	41% (Also product with hydrolysis of one ester 20%)	572
CO ₂ Et	H ₂ SO ₄ 97%, 25°, 1 hr.	61% (Also product with hydrolysis of one ester 12%)	572

^aDrown in alcohol to get diester.

Drown in ice to get 80% yield stated to be the 4-carboxy-5-carbethoxy product.

TABLE II-130. Cyclization of N-Vinylglycine Derivatives

						Yield,		Ref.		
R ₃	R ₂	R ₁	R ₄	R ₅	R ₆	Conditions to I	Yield		Conditions to II	%
CH ₂ Ph	Me	Me	CO ₂ Me	CO ₂ Me	H	Na, benzene NaNH ₂ , benzene, N ₂ , water bath		Alc., HCl, air SO ₂ Cl ₂	70	1264 792
						Na, benzene, N ₂ , heat, 1 hr.		SO ₂ Cl ₂		1156
						NaOEt, benzene, N ₂		SO ₂ Cl ₂	62	1156
						Na, NaOMe, MeOH, reflux, 1 hr.		Aq. HCl, air or O ₂ , 24 hrs.		1708

Me	Me	Et	CO ₂ Et	CO ₂ Et	H	Na, benzene Na, NaOMe, or NaNH ₂	Alc., HCl, air SO ₂ Cl ₂	1264 574
						Na, benzene, N ₂ , heat, 1 hr.	^a Alc., HCl	45
	CH ₃ Ph	Me	Et	CO ₂ Et	H	Na, NaOMe, or NaNH ₂	SO ₂ Cl ₂	574
	CH ₃ Ph	CH ₂ Ph	Me	CO ₂ Me	H	NaOMe, MeOH, N ₂ , reflux, 75 min.	^a SO ₂ Cl ₂	79
	CH ₃ Ph	<i>i</i> -Pr	Me	CO ₂ Me	H	Na, benzene, N ₂ , reflux, 1 hr.	^a SO ₂ Cl ₂ , 25°, 2 hrs.	62
	CH ₃ Ph	<i>i</i> -Bu	Me	CO ₂ Me	H	Na, benzene, N ₂ , reflux, 1 hr.	^a SO ₂ Cl ₂ , 25°, 2 hrs.	34
	CH ₃ Ph	Ph	Me	CO ₂ Me	H	Na, benzene, N ₂ , reflux, 1 hr.	^a SO ₂ Cl ₂ , 25°, 2 hrs.	64
	alkyl or aryl	alkyl or aryl	alkyl	CO ₂ -alkyl	alkyl or alkali metal or base H		Alc., HCl, air	1258
	CH ₂ Ph	Me	Et	CN	CO ₂ Et	Na, benzene	Poor	1156

^aConverted to II without isolation.

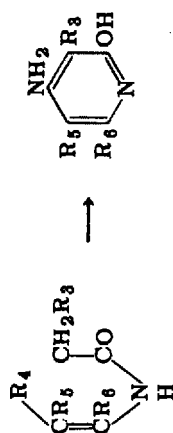


TABLE II-131. Cyclizations of N-Vinylamides

R ₃	R ₄	R ₅	R ₆	Conditions	Yield	Ref.
H	CO ₂ Et	H	Me	Na, toluene	^a	1082
H	CN	H	Me	NaNH ₂	poor	349
H	CN	Me	Et	NaNH ₂ , dioxane, reflux, 3 hrs.	73%	438
Ph	CN	Me	Et	NaNH ₂ , dioxane, reflux, 3 hrs.	90%	438
H	CN	Ph	CH ₃ Ph	NaNH ₂ , dioxane, reflux, 3 hrs.	86%	438
Me	CN	Ph	CH ₃ Ph	NaNH ₂ , dioxane, reflux, 3 hrs.	82%	438
H	CN	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	NaNH ₂ , NH ₃ , 3½ hrs.	96%	349,1084
Me	CN	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	NaNH ₂ , NH ₃ , 3½ hrs.	97%	349,1084
Cl	CN	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	NaNH ₂ , NH ₃ , 3½ hrs.	92%	349,1084
Ac	CN	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	NaNH ₂ , NH ₃ , 3½ hrs.	85%	349,1084
-CH ₃ -	CN	-CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ -	NaNH ₂ , NH ₃ , 3½ hrs.		349
H	CN	-CH ₂ CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ CH ₂ -	NaNH ₂ , NH ₃ , 3½ hrs.	93%	349,1084
H	CN	-CH:CHCH:CH-	-CH:CHCH:CH-	NaNH ₂ , NH ₃ , 3½ hrs.	93%	1084

^a 4-Hydroxy rather than 4-amino.

TABLE II-132. Miscellaneous Cyclizations Involving Carbon-Carbon Bond Formation

Reactants	Conditions	Product (Yield)	Ref.
Ethylallylamine	Lead oxide, 400–500°, vapor phase	Pyridine (low), pyrrole (poor), (NH ₄) ₂ CO ₃	67
β-Hydroxyethyl-β-hydroxypropylamine	Cu, Ni, and Cr, H ₂ , 350°, vapor phase	3-Pyridinol (10%)	1478
bis-β-Hydroxypropylamine	Cu, Ni, and Cr, H ₂ , 350°, vapor phase	5-Methyl-3-pyridinol (45%)	1478
$ \begin{array}{c} \text{CO}_2\text{Et} \\ \\ \text{CH} \\ \\ \text{CH} \\ \\ \text{N} \\ \\ \text{6-quinolyl} \end{array} $	Alc. KOH	3-Carboxy-1-(6-quinolyl)-4(1H)-pyridone	364
$ \begin{array}{c} \text{CO}_2\text{Et} \\ \\ \text{CH} \\ \\ \text{CH} \\ \\ \text{N} \\ \\ \text{p-anisyl} \end{array} $	Alc. KOH, heat	1-p-Anisyl-3-carboxy-4(1H)-pyridone	370

(continued)

TABLE II-132 (Continued)
Miscellaneous Cyclizations Involving Carbon-Carbon Bond Formation

Reactants	Conditions	Product (Yield)	Ref.
$ \begin{array}{c} \text{CO}_2\text{Et} \\ \\ \text{CH}_2 \\ \\ \text{CH}_2 \\ \\ \text{CH} \\ \\ \text{CO} \\ \\ \text{CH}_2 \\ \\ \text{N} \\ \\ \text{H} \end{array} $	NaOEt, EtOH, benzene, reflux, 2 hrs.	2-Acetyl-2,4-piperidine- dione (poor)	1634
$ \begin{array}{c} \text{CO}_2\text{Et} \\ \\ \text{CH} \\ \\ \text{CH}_2 \\ \\ \text{CH} \\ \\ \text{CO} \\ \\ \text{CH}_2 \\ \\ \text{N} \\ \\ \text{CH}_2\text{Ph} \end{array} $	Na, xylene, reflux	1-Benzyl-3-carbethoxy- 5-ethyl-2,4-piperidine- dione	622

 1,4-Dihydroxybutanone, with the methylimine of pyruvonnitrile	P₂O₅, benzene, reflux, 1 hr.	2-Benzyl-3,4-trimethylene- dihydropyridine (78% crude) 649
3-Amino-4,5-bis-hydroxy- methyl-2-picoline 608		
3-Amino-4,5-oxymethylene- 2-picoline 608	Piperidinium acetate or LiNEtPh, 25-100°	
3-Amino-4,5-bis-hydroxy- methyl-2-picoline 608	Hg(OAc)₂, piperidinium acetate, 25-100°	

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