Organic Chemistry III

Mohammad Jafarzadeh

Faculty of Chemistry, Razi University

Organic Chemistry, *Structure and Function* **(7th edition)**

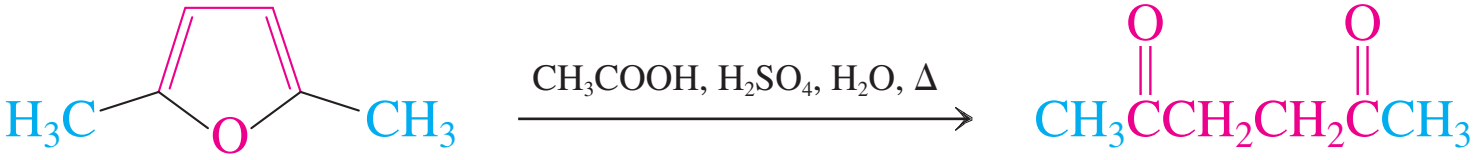
By *P. Vollhardt* and *N. Schore*, Elsevier, 2014

1-Hetero-2,4-cyclopentadienes can undergo ring opening and cycloaddition reactions

Furans can be hydrolyzed under mild conditions to γ-dicarbonyl compounds. The reaction is the reverse of the Paal-Knorr-type synthesis of furans.

Pyrrole polymerizes under these reaction conditions, whereas thiophene is stable.

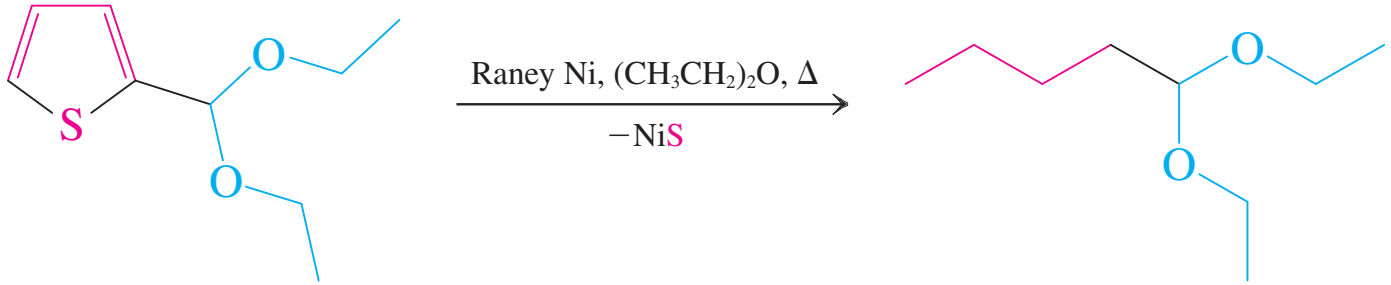
Hydrolysis of a Furan to a γ-Dicarbonyl Compound



90%

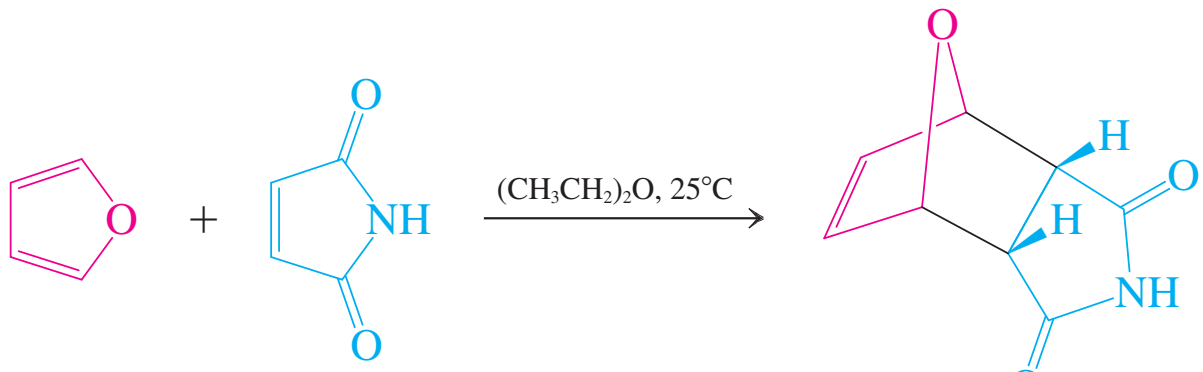
2,5-Hexanedione

Raney nickel desulfurization of thiophene derivatives results in sulfur-free acyclic saturated compounds.



50%

Being least aromatic, the π system of furan (but not of pyrrole or thiophene) possesses sufficient diene character to undergo Diels-Alder cycloadditions.



95%

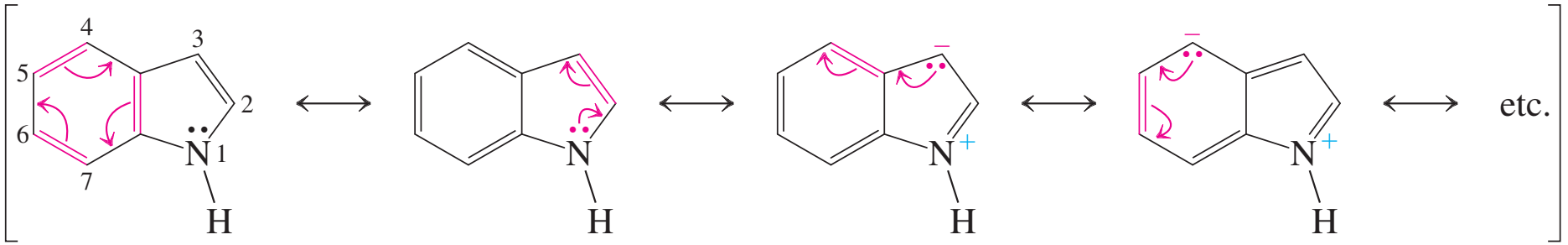
Indole is a benzopyrrole

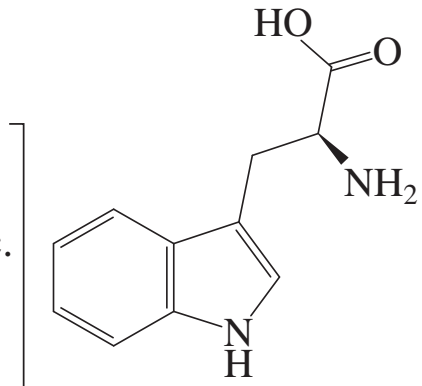
Indole is the most important *benzannulated* (fused-ring) derivative of the 1-hetero-2,4-cyclopentadienes. It forms part of many natural products, including the amino acid tryptophan.

Indole is related to pyrrole in the same way that naphthalene is related to benzene. Its electronic makeup is indicated by the various possible resonance forms that can be formulated for the molecule.

Although those resonance forms that disturb the cyclic six-π-electron system of the fused benzene ring are less important, they indicate the electron-donating effect of the heteroatom.

Resonance in Indole





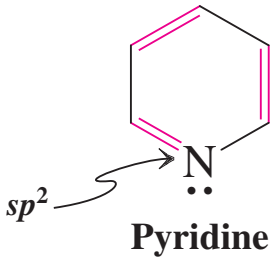
Tryptophan

25-5 STRUCTURE AND PREPARATION OF PYRIDINE: AN AZABENZENE

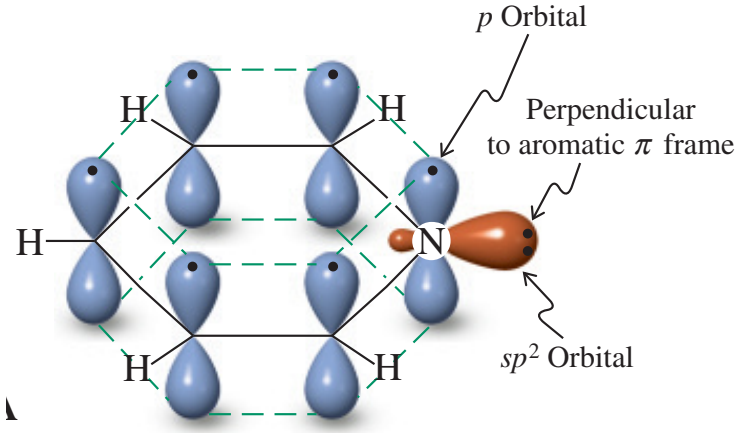
Pyridine can be regarded as a benzene derivative—an **azabenzene**—in which an sp^2-hybridized nitrogen atom replaces a CH unit. The pyridine ring is therefore aromatic, but its electronic structure is perturbed by the presence of the electronegative nitrogen atom.

Pyridine contains an sp^2-hybridized nitrogen atom like that in an imine. In contrast to pyrrole, only one electron in the *p* orbital completes the aromatic π-electron arrangement of the aromatic ring; as in the phenyl anion, the lone electron pair is located in one of the sp^2 hybrid atomic orbitals in the molecular plane.

In pyridine, the nitrogen does not donate excess electron density to the remainder of the molecule. Quite the contrary: Because nitrogen is more electronegative than carbon, it withdraws electron density from the ring, both inductively and by resonance.

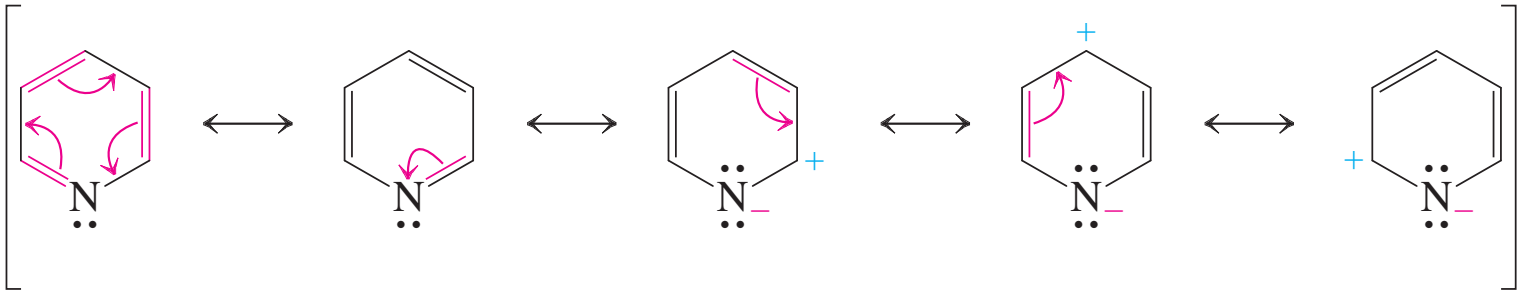


Pyridine

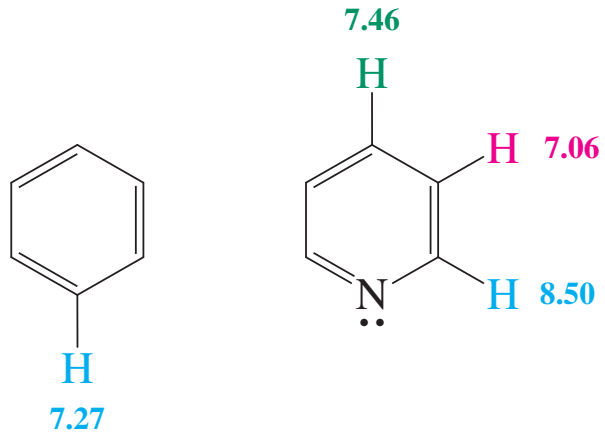


Aromatic delocalization in pyridine is evident in the ^{1}H NMR spectrum, which reveals the presence of a ring current. The electron-withdrawing capability of the nitrogen is manifest in larger chemical shifts (more deshielding) at C2 and C4, as expected from the resonance picture.

Resonance in Pyridine

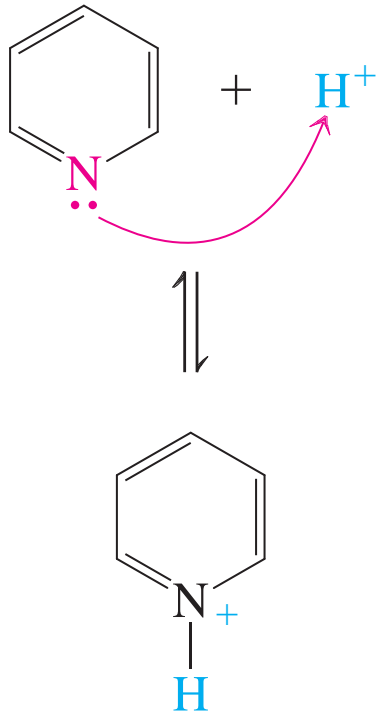


^{1}H NMR Chemical Shifts (ppm) in Pyridine and Benzene



Because the lone pair on nitrogen is not tied up by conjugation (as it is in pyrrole), pyridine is a weak base. Compared with alkanamines (pK_a of ammonium salts < 10), the pyridinium ion has a low pK_a, because the nitrogen is sp^2 and not sp^3 hybridized (the effect of hybridization on acidity).

Pyridine Is a Weak Base

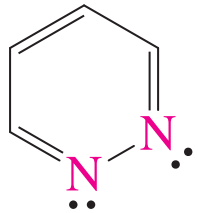


Pyridinium ion
pK_a = 5.29

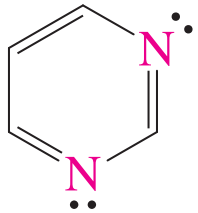
Pyridine is the simplest azabenzene. Some of its higher aza analogs are shown here.

They behave like pyridine but show the increasing effect of aza substitution—in particular, increasing electron deficiency.

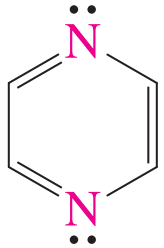
Minute quantities of several 1,4-diazabenzene (pyrazine) derivatives are responsible for the characteristic odors of many vegetables. One drop of 2-methoxy-3-(1-methylethyl)-1,4-diazabenzene (2-isopropyl-3-methoxypyrazine) in a large swimming pool would be more than adequate to give the entire pool the odor of raw potatoes.



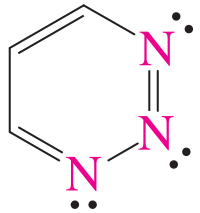
1,2-Diazabenzene (Pyridazine)



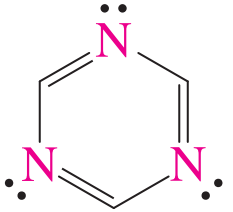
1,3-Diazabenzene (Pyrimidine)



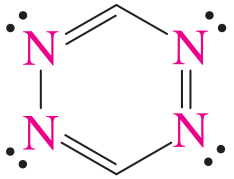
1,4-Diazabenzene (Pyrazine)



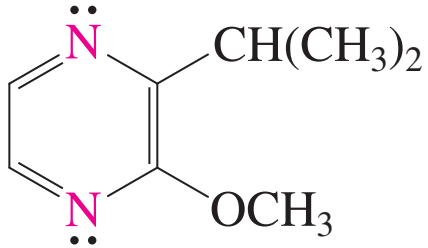
1,2,3-Triazabenzene (1,2,3-Triazine)



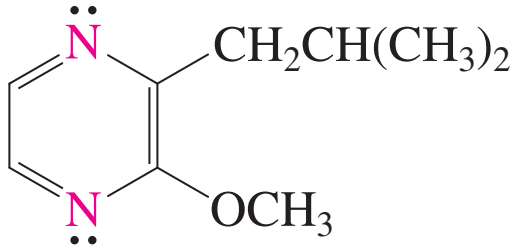
1,3,5-Triazabenzene (1,3,5-Triazine)



1,2,4,5-Tetraazabenzene (1,2,4,5-Tetrazine)



2-Methoxy-3-(1-methylethyl)-1,4-diazabenzene (Potatoes)



2-Methoxy-3-(2-methylpropyl)-1,4-diazabenzene (Green peppers)

Pyridines are made by condensation reactions

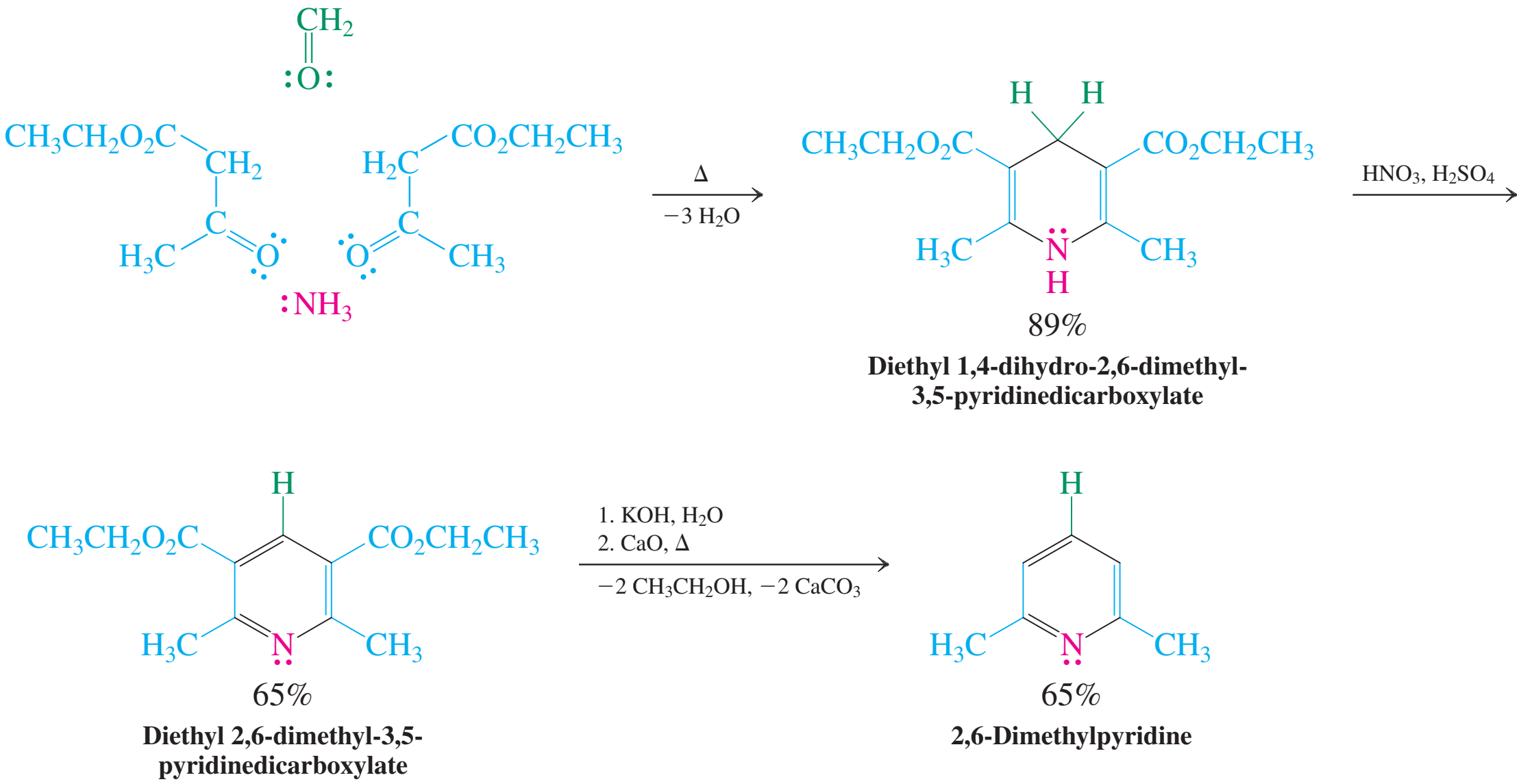
Pyridine and simple alkylpyridines are obtained from coal tar. Many of the more highly substituted pyridines are in turn made by both electrophilic and nucleophilic substitution of the simpler derivatives.

Pyridines can be made by condensation reactions of acyclic starting materials such as carbonyl compounds with ammonia. The most general of these methods is the **Hantzsch pyridine synthesis.**

In this reaction, two molecules of a β-dicarbonyl compound, an aldehyde, and ammonia combine in several steps to give a substituted dihydropyridine, which is readily oxidized by nitric acid to the aromatic system.

When the β-dicarbonyl compound is a 3-ketoester, the resulting product is a 3,5-pyridinedicarboxylic ester. Hydrolysis followed by pyrolysis of the calcium salt of the acid causes decarboxylation.

Hantzsch Synthesis of 2,6-Dimethylpyridine

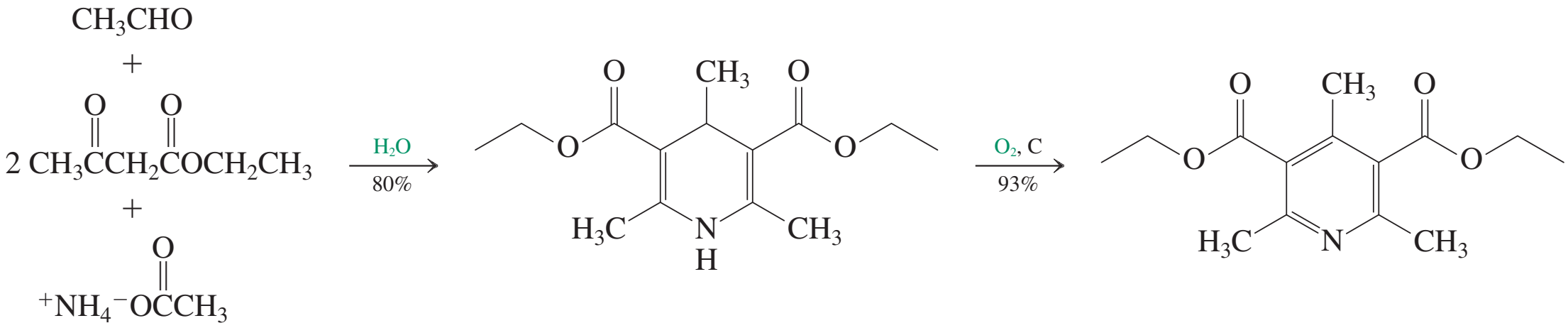


The first step of the Hantzsch pyridine synthesis is an example of a four-component reaction: Four molecules combine in a specific fashion to form a single product.

Multicomponent reactions (MCR) of this type, in which water is the only by-product, are by their very nature atom economical and hence “green”.

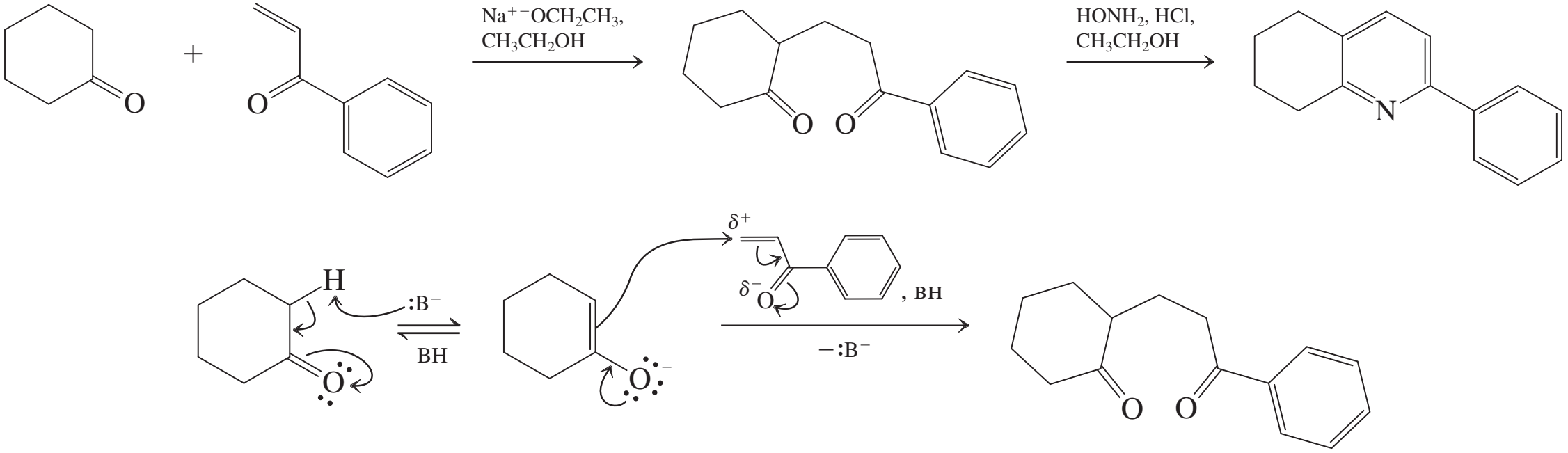
Even more environmentally friendly is the use of water as a solvent and, in the aromatization step to the substituted pyridine, simply oxygen in the presence of activated carbon (a form of highly porous carbon derived from charcoal).

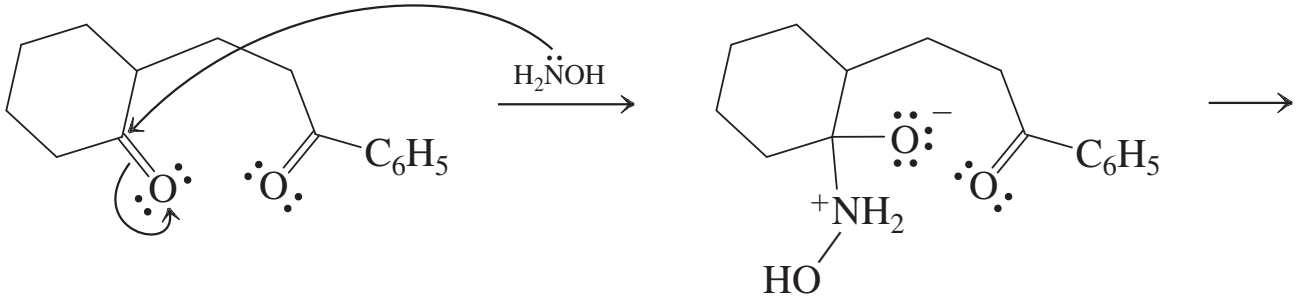
A “Super Green” Hantzsch Pyridine Synthesis

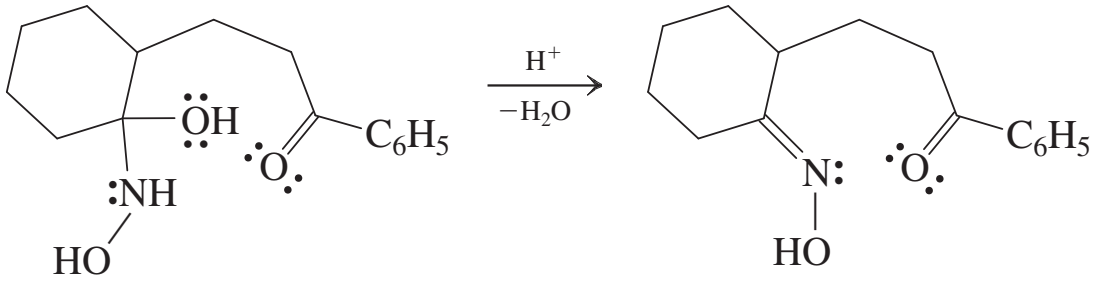


Solved Exercise 25-19

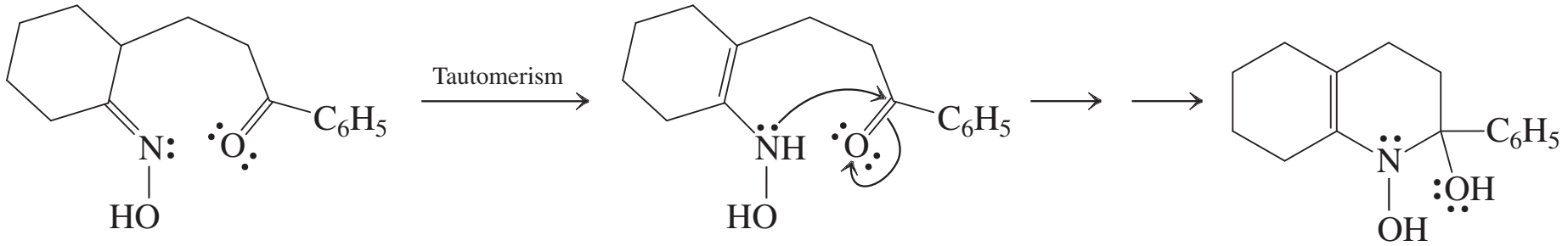
The Hantzsch synthesis of pyridines features 1,4-dihydropyridines in the first step. A variant of the method uses hydroxylamine, which can be regarded as an oxidized version of ammonia. With this reagent, pyridines are formed directly from 1,5-dicarbonyl compounds, in turn readily made by Michael additions of enolates to α,β-unsaturated aldehydes and ketones. Formulate the mechanisms of the two steps in the pyridine synthesis shown.



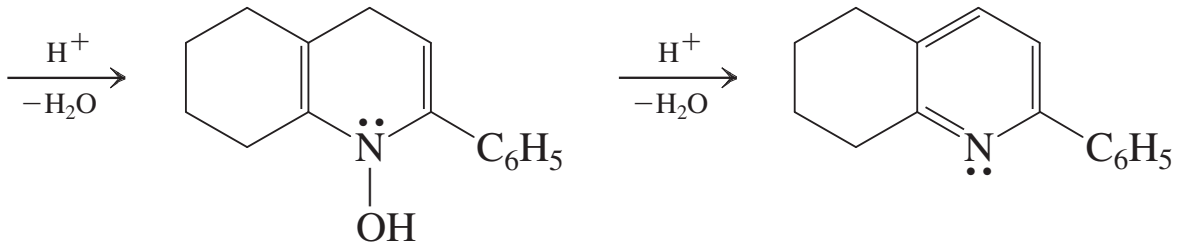




Hemiaminal **Oxime**



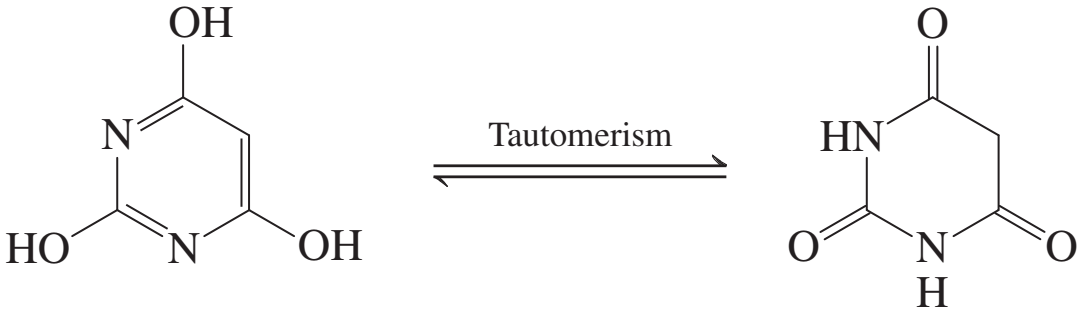
Oxime **Enamine** **Intramolecular hemiaminal**



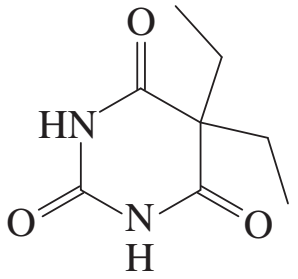
Exercise 25-21

1,3-Diazabenzene-2,4,6-triol prefers the triketo tautomeric form by about 29 kcal mol^{-1}. It is commonly known as barbituric acid (pK_a = 7.4) and constitutes the basic frame of a group of sedatives and sleep inducers called barbiturates: veronal and phenobarbital.

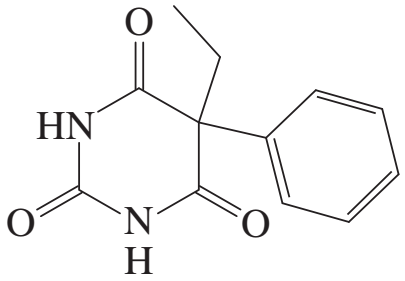
Propose a synthesis of veronal from diethyl propanedioate (malonic ester) and urea.



Barbituric acid



Veronal



Phenobarbital

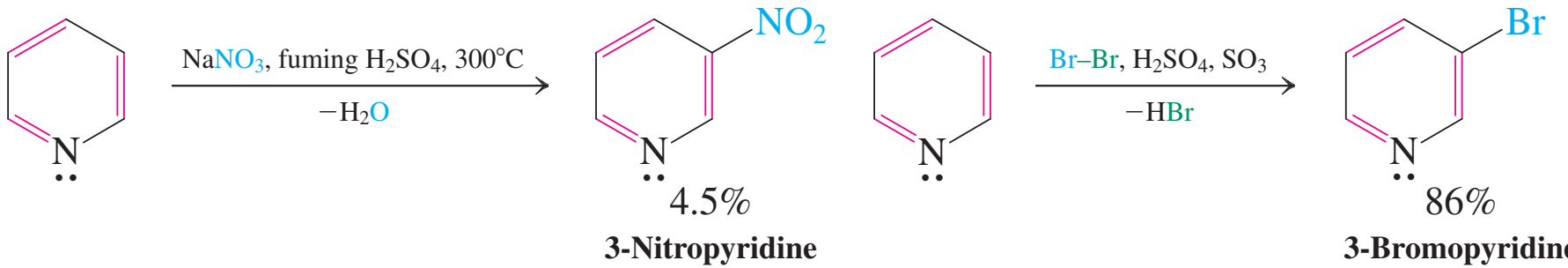
25-6 REACTIONS OF PYRIDINE

The reactivity of pyridine derives from its dual nature as both an aromatic molecule and a cyclic imine. Both electrophilic and nucleophilic substitution processes may occur, leading to a variety of substituted derivatives.

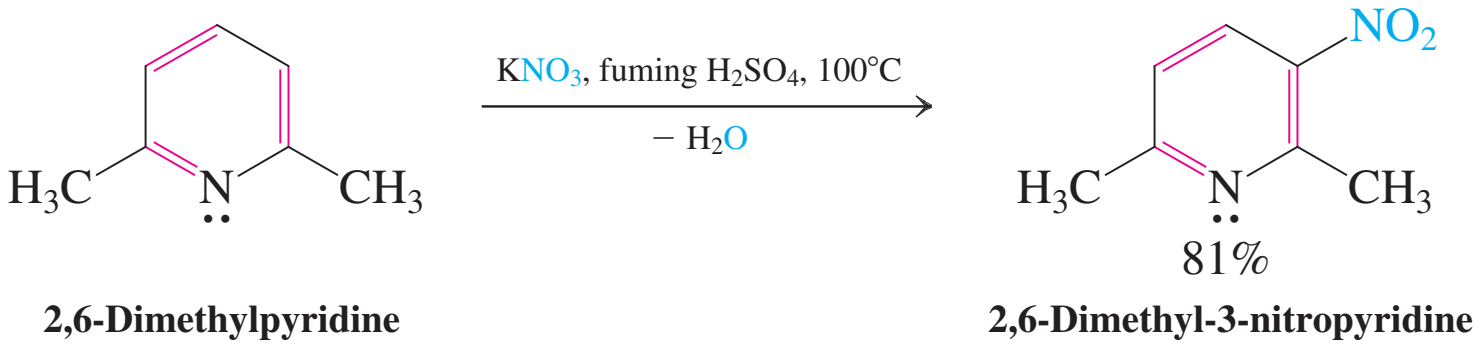
Pyridine undergoes electrophilic aromatic substitution only under extreme conditions

Because the pyridine ring is electron poor, the system undergoes electrophilic aromatic substitution only with great difficulty, several orders of magnitude more slowly than benzene, and at C3.

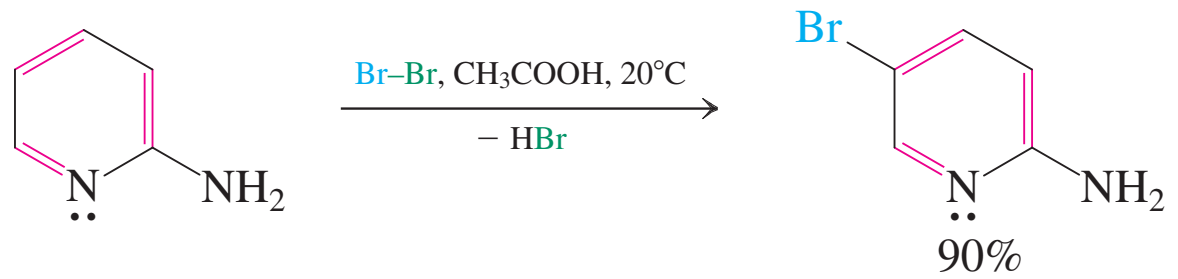
Electrophilic Aromatic Substitution of Pyridine



Activating substituents allow for milder conditions or improved yields.



2,6-Dimethylpyridine **2,6-Dimethyl-3-nitropyridine**



2-Aminopyridine **2-Amino-5-bromopyridine**

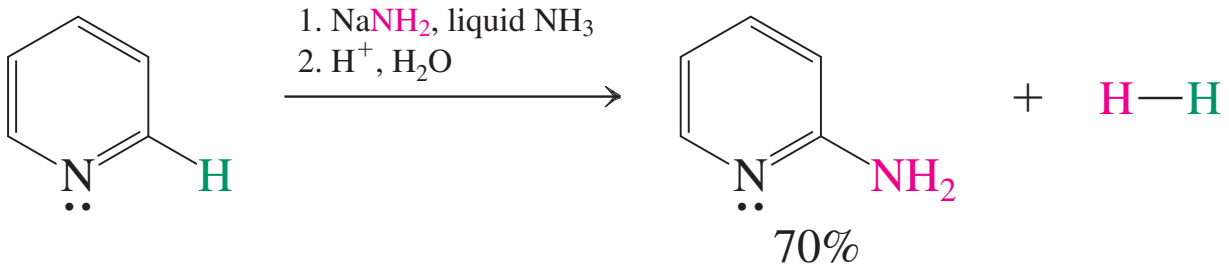
Pyridine undergoes relatively easy nucleophilic substitution

Because the pyridine ring is relatively electron deficient, it undergoes nucleophilic substitution much more readily than does benzene.

Attack at C2 and C4 is preferred because it leads to intermediates in which the negative charge is on the nitrogen.

An example of nucleophilic substitution of pyridine is the **Chichibabin reaction,** in which the heterocycle is converted into 2-aminopyridine by treatment with sodium amide in liquid ammonia.

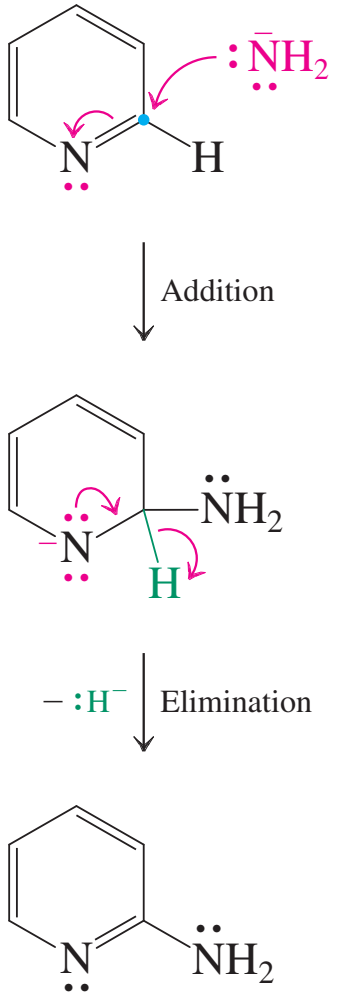
Chichibabin Reaction



70%

2-Aminopyridine

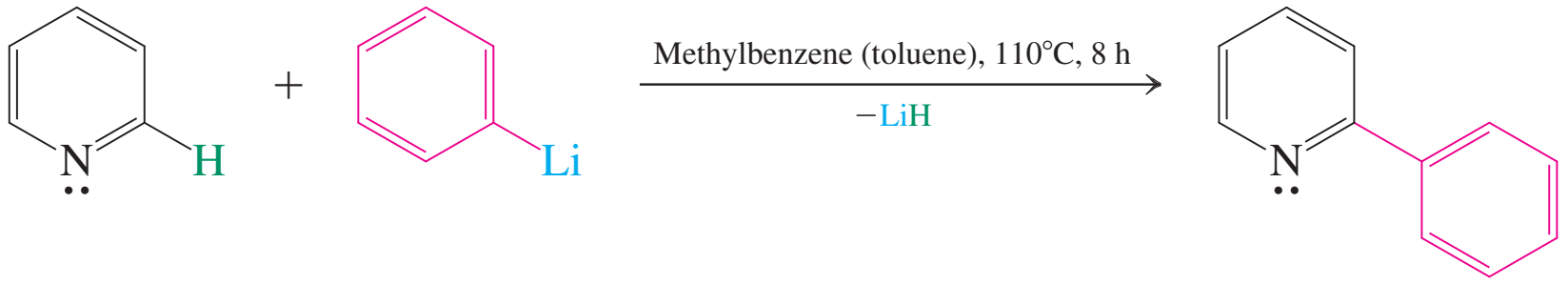
Mechanism of the Chichibabin Reaction



This reaction proceeds by the addition–elimination mechanism. The first step is attack by $^{-}NH_2$ at C2, a process that resembles 1,2-addition to an imine function. Expulsion of a hydride ion, H^{-}, from C2 is followed by deprotonation of the amine nitrogen to give H_2 and a resonance-stabilized 2-pyridineamide ion. Protonation by aqueous work-up furnishes the final product.

Note the contrast with *electrophilic* substitutions, which include *proton* loss, not expulsion of hydride as a leaving group.

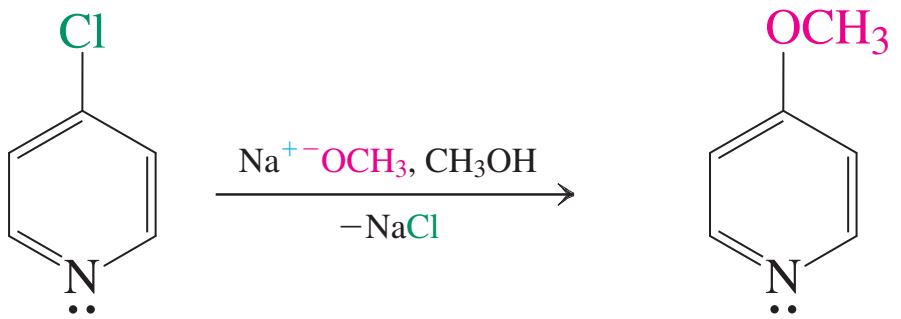
Transformations related to the Chichibabin reaction take place when pyridines are treated with Grignard or organolithium reagents.



49%

2-Phenylpyridine

In most nucleophilic substitutions of pyridines, halides are leaving groups, the 2- and 4-halopyridines being particularly reactive.



75%

4-Methoxypyridine

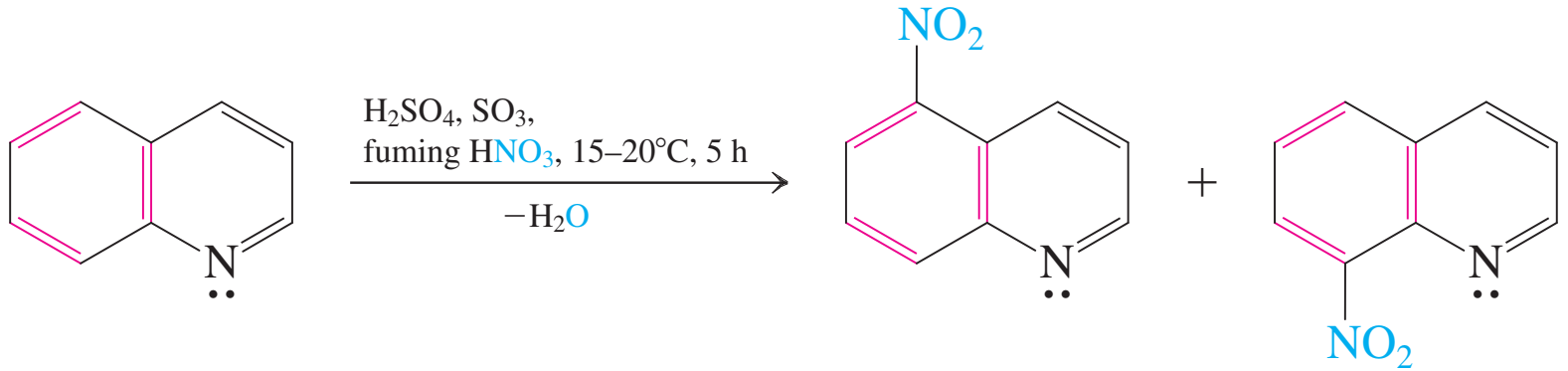
25-7 QUINOLINE AND ISOQUINOLINE: THE BENZOPYRIDINES

The fusion of a benzene ring to pyridine in either of two ways, giving **quinoline** and **isoquinoline** (1- and 2-azanaphthalene).

Both are liquids with high boiling points. Many of their derivatives are found in nature or have been synthesized in the search for physiological activity. Like pyridine, quinoline and isoquinoline are readily available from coal tar.

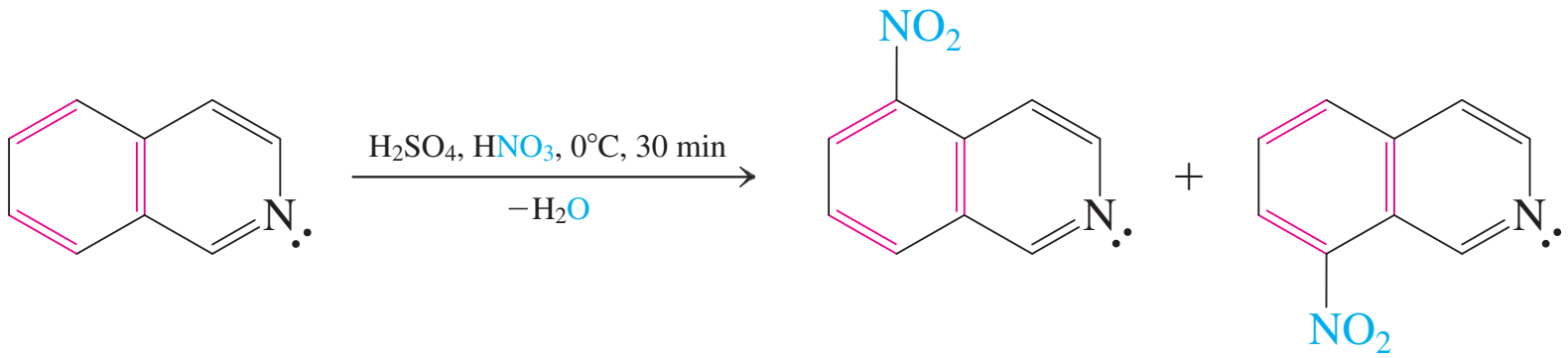
As might be expected, because pyridine is electron poor compared with benzene, electrophilic substitutions on quinoline and isoquinoline take place at the *benzene* ring.

As with naphthalene, substitution at the carbons next to the ring fusion predominates.



35% 43%

Quinoline **5-Nitroquinoline** **8-Nitroquinoline**

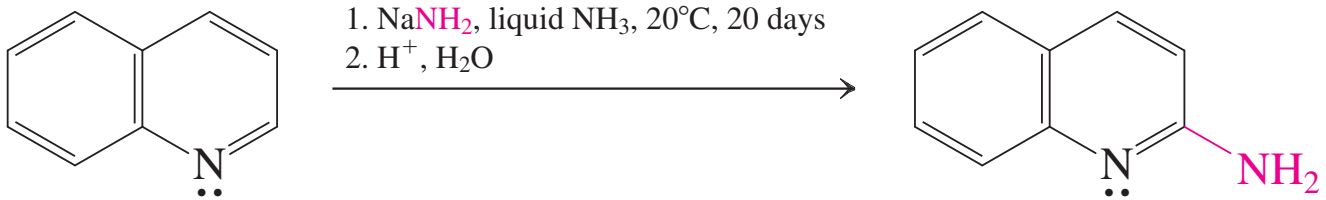


72% 8%

Isoquinoline **5-Nitroisoquinoline** **8-Nitroisoquinoline**

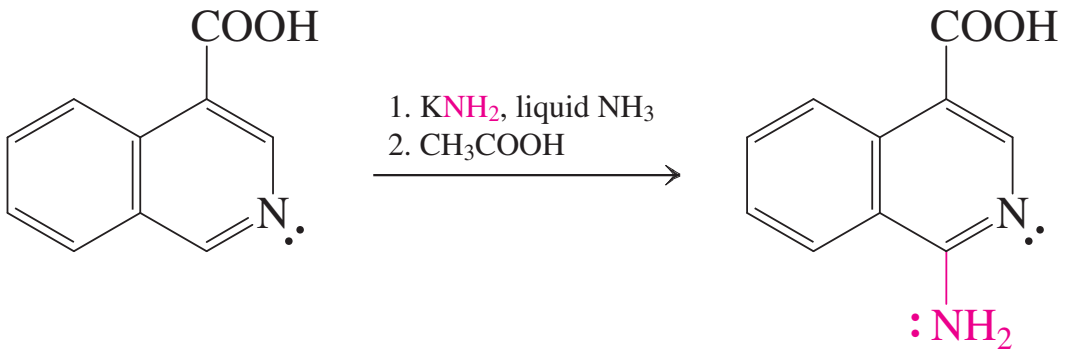
In contrast to electrophiles, nucleophiles prefer reaction at the electron-poor *pyridine* nucleus. These reactions are quite analogous to those with pyridine.

Chichibabin Reaction of Quinoline and Isoquinoline



80%

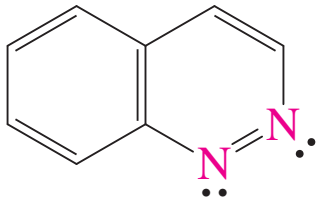
2-Aminoquinoline



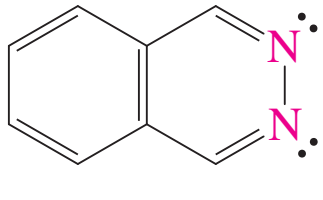
71%

1-Aminoisoquinoline-4-carboxylic acid

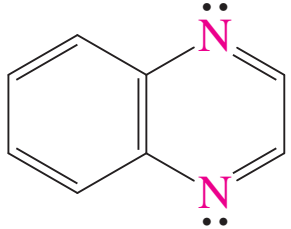
The following structures are representative of higher aza analogs of naphthalene.



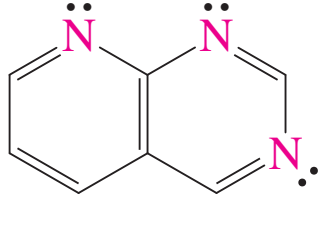
1,2-Diazanaphthalene (Cinnoline)



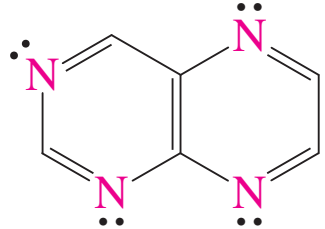
2,3-Diazanaphthalene (Phthalazine)



1,4-Diazanaphthalene (Quinoxaline)



1,3,8-Triazanaphthalene (Pyrido[2,3-*d*]pyrimidine)

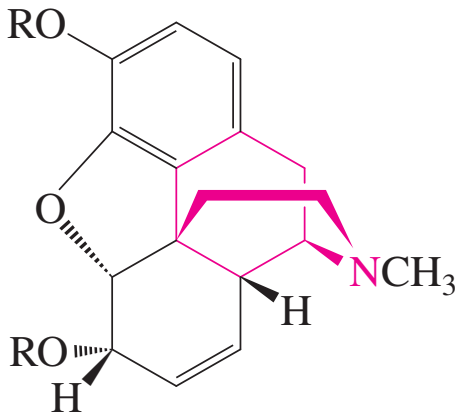


1,3,5,8-Tetraazanaphthalene (Pteridine)

25-8 ALKALOIDS: NITROGEN HETEROCYCLES IN NATURE

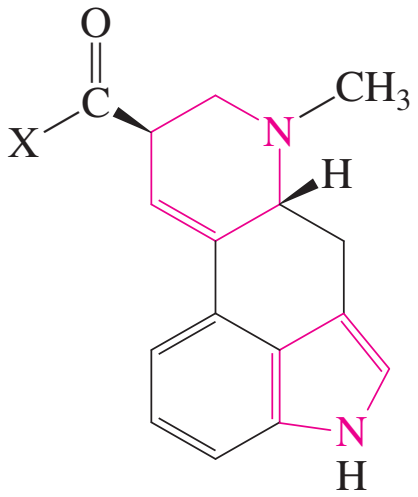
The **alkaloids** are bitter-tasting, natural nitrogen-containing compounds found particularly in plants. The name is derived from their characteristic basic properties (alkali-like), which are induced by the lone electron pair of nitrogen.

As with acyclic amines, the (Lewis) basic nature of the alkaloids, in conjunction with their particular three-dimensional architecture, gives rise to often potent physiological activity.

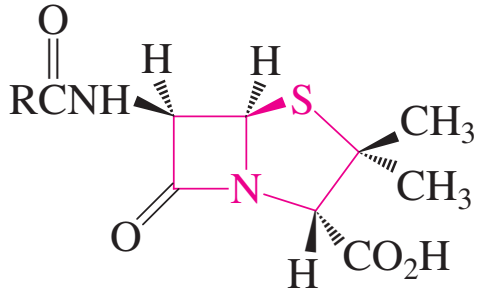


Morphine (R = H)

Heroin (R = CH_3C(=O)–)



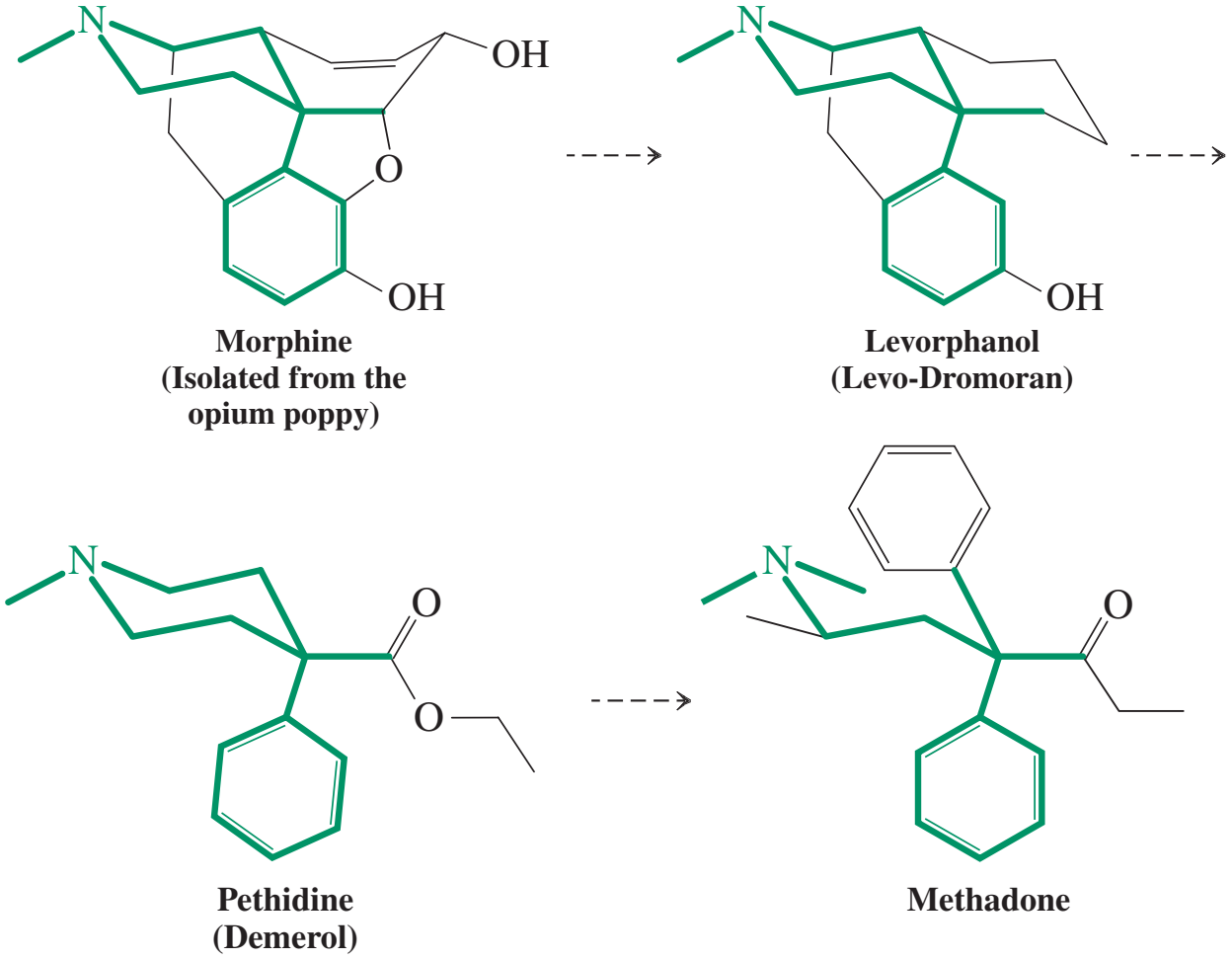
Lysergic acid (X = OH)
Lysergic acid diethylamide, LSD
[X = $(CH_3CH_2)_2N$]



Penicillin

Medicinal chemists strive to strip down the structures of complex natural drugs to identify the minimal requirements for activity: the pharmacophore. For morphine this approach has yielded hundreds of simpler analogs with a varying pharmacological spectrum.

The Pharmacophore of Morphine



Morphine (Isolated from the opium poppy)

Levorphanol (Levo-Dromoran)

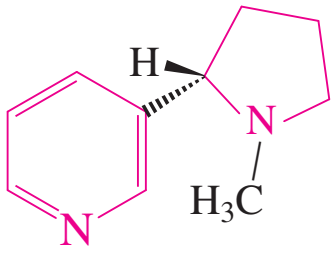
Pethidine (Demerol)

Methadone

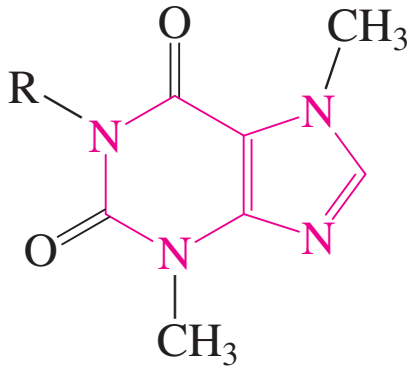
Nicotine, present in dried tobacco leaves in 2–8% concentration, is the stimulating ingredient in cigarettes and other tobacco products. Even more stimulating than nicotine are caffeine and theobromine, present in coffee and tea or cocoa (chocolate), respectively.

Perhaps the most dangerous stimulant is cocaine, extracted from the leaves of the coca shrub. Cocaine is shipped and sold in the form of the water-soluble hydrochloride salt ("street cocaine"), which may be ingested through the nasal passages by "snorting" or orally and intravenously.

There are severe physical and psychological side effects of the drug, such as brain seizures, respiratory collapse, heart attack, paranoia, and depression. Moreover, it functions as a very effective topical anesthetic in eye operations.

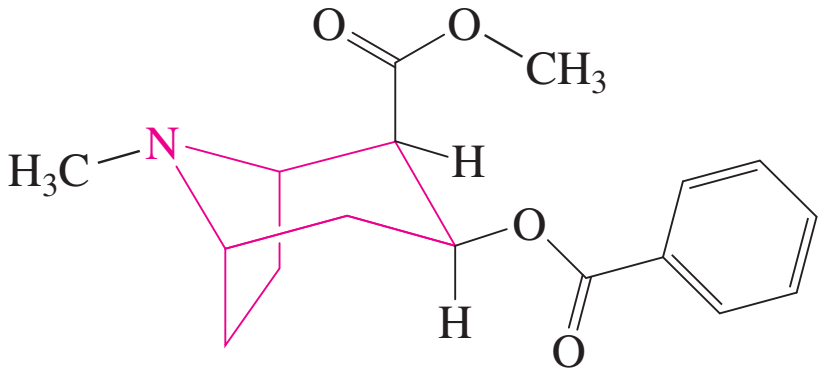


Nicotine



Caffeine (R = CH_3)

Theobromine (R = H)

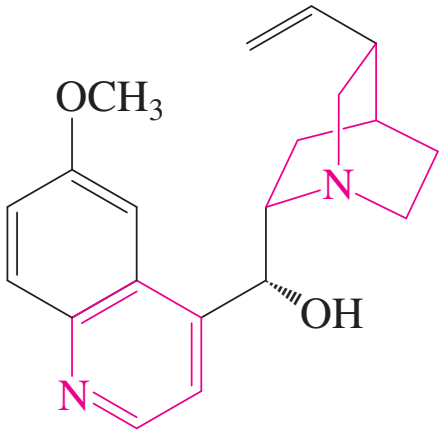


Cocaine

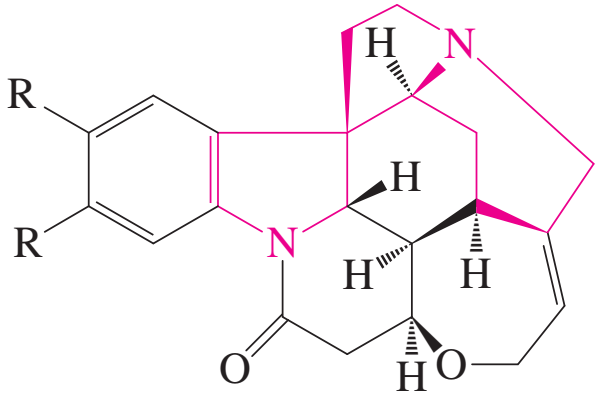
Quinine, isolated from cinchona bark (as much as 8% concentration), is the oldest known effective antimalarial agent.

Strychnine is a powerful poison (the lethal dose in animals is about 5–8 mg kg^{-1}).

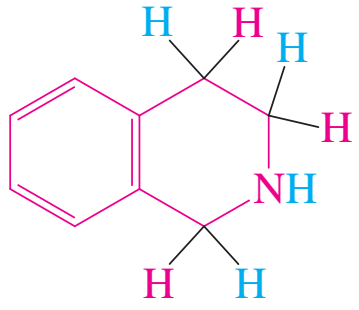
The isoquinoline and 1,2,3,4-tetrahydroisoquinoline nuclei are abundant among the alkaloids, and their derivatives are physiologically active, for example, as hallucinogens, central nervous system agents (depressants and stimulants), and hypotensives.



Quinine



Strychnine (R=H)
Brucine (R=CH_3O)



1,2,3,4-Tetrahydroisoquinoline