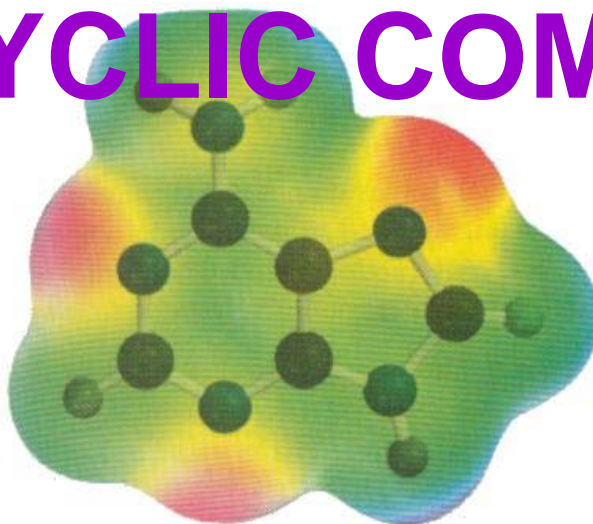


# CHAPTER 18

# HETEROCYCLIC COMPOUNDS



## 教学目的

1. 掌握呋喃、吡咯、噻吩、吡啶和喹啉及其衍生物的命名。
2. 掌握呋喃、吡咯、噻吩和吡啶的结构。
3. 掌握呋喃、吡咯、噻吩、吡啶和喹啉的化学性质。
4. 掌握喹啉的合成法。
5. 熟悉噻唑、咪唑、嘧啶、嘌呤的结构。
6. 了解生物碱。

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18.1 CLASSIFICATION AND NOMENCLATURE

18.2 FIVE-MEMBERED HETEROCYCLIC  
AROMATIC COMPOUNDS

18.3 SIX-MEMBERED HETEROCYCLIC  
COMPOUNDS

18.4 ALKALOID

习题课

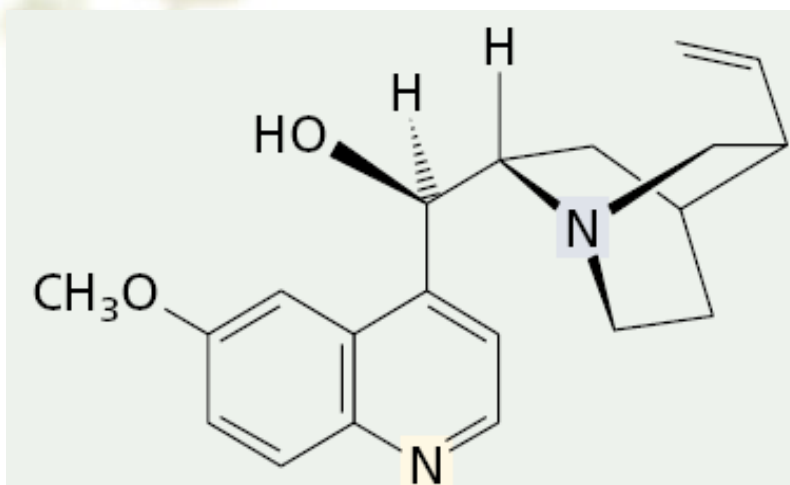
## Definition:

*Heterocyclic compounds* are cyclic compounds in which one or more ring atoms are not carbon (that is, *hetero* atoms).

Here, we shall consider only some of the more common systems in which the hetero atom is **N**, **O**, or **S**.

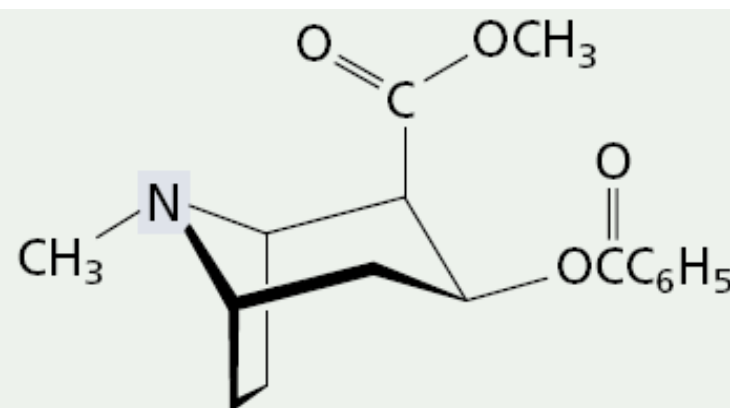
**Heterocyclic molecules are quite commonly encountered in nature.**

**Example 1:**



Quinine

(Alkaloid of cinchona bark used to treat malaria)



Cocaine

(A central nervous system stimulant obtained from the leaves of the coca plant.)

## Example 2:

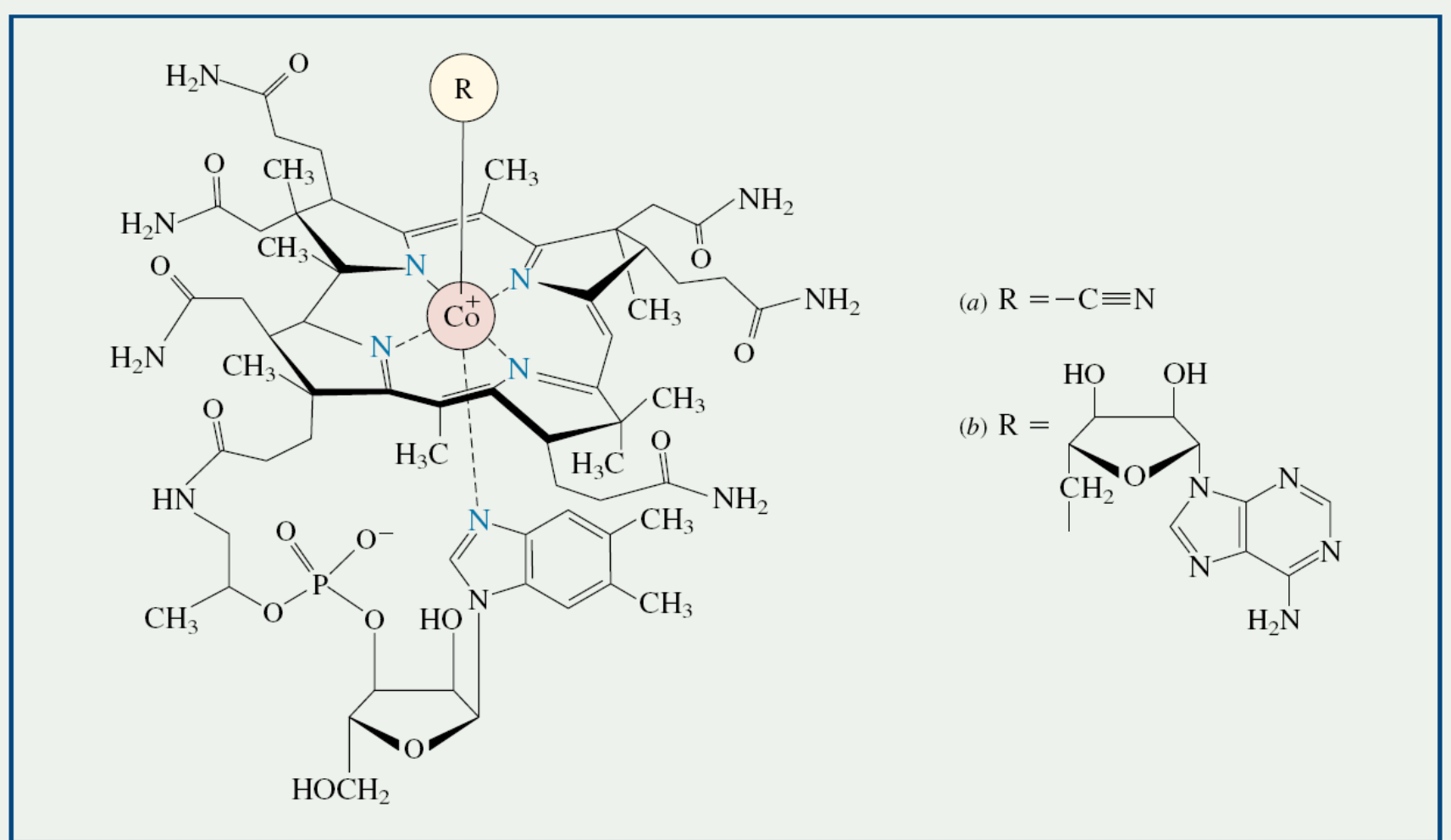
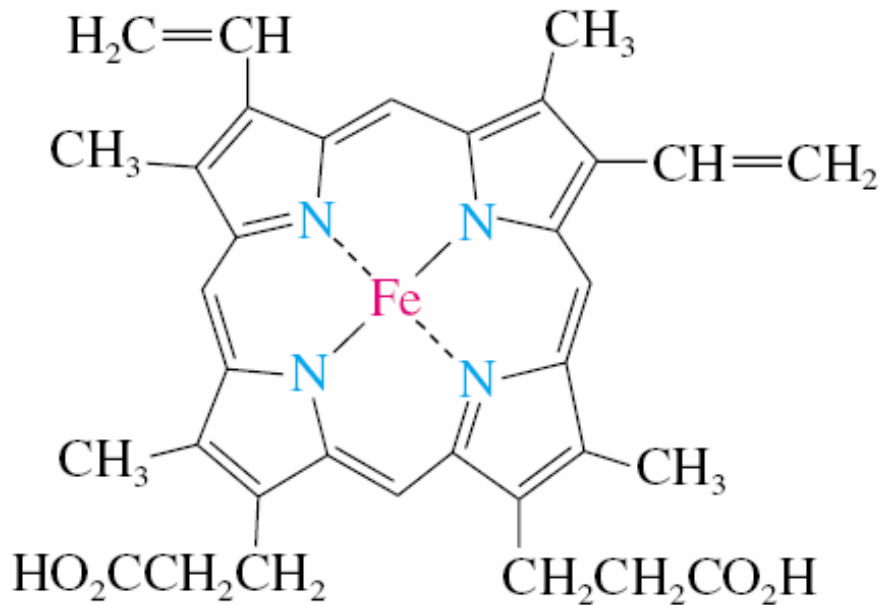
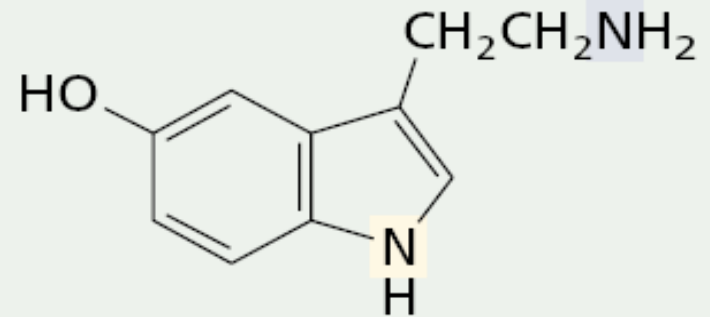


FIGURE 14.3 The structures of (a) vitamin B<sub>12</sub> and (b) coenzyme B<sub>12</sub>.

### Example 3:



**Heme**

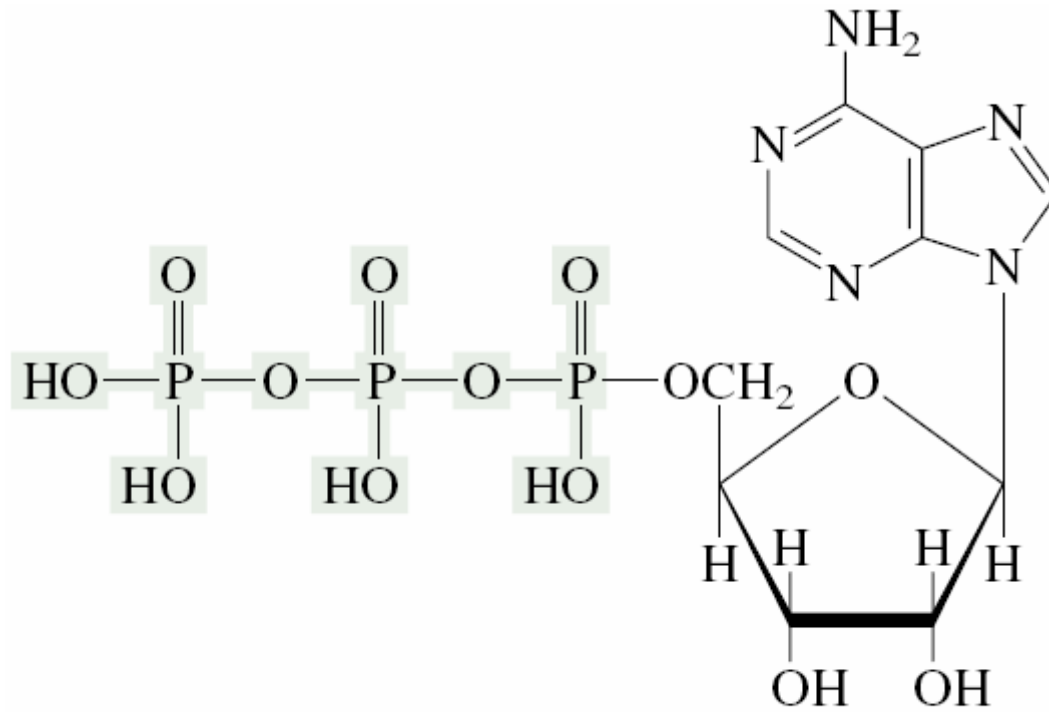


**Serotonin**

(A hormone synthesized in the pineal gland. Certain mental disorders are believed to be related to serotonin levels in the brain.)

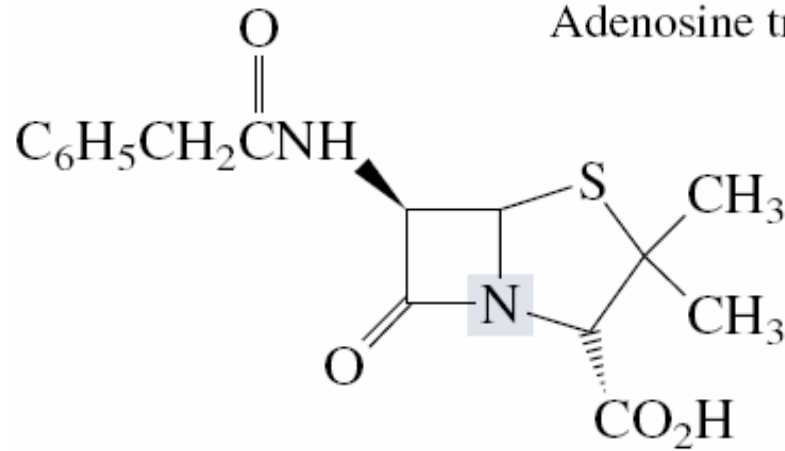


Example 4:



Example 5:

Adenosine triphosphate (ATP)



Penicillin G



# 18.1 CLASSIFICATION AND NOMENCLATURE

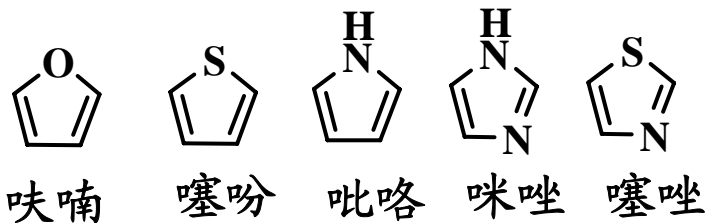
## 18.1.1 Classification

**Heterocycles are conveniently grouped into two classes, mono heterocycles and condensed heterocycles.**

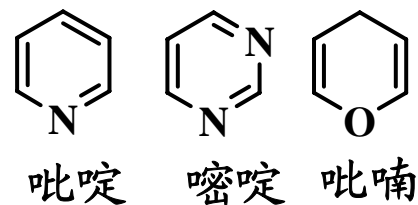
heterocycles

monoheterocycles

five-membered heterocycles

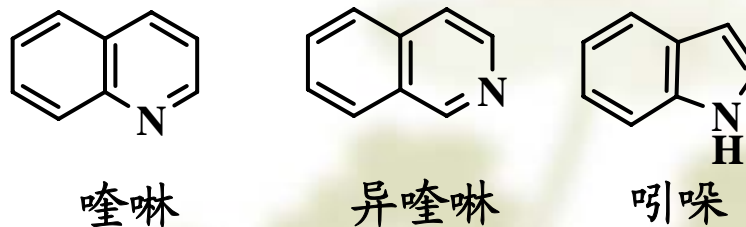


six-membered heterocycles

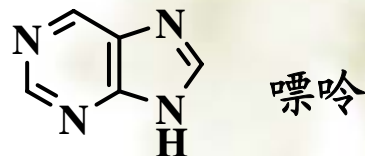


condensed heterocycles

benzo monoheterocycles



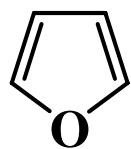
condensed with two or more monoheterocyclic rings



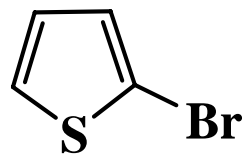
## 18.1.2 Nomenclature

- (1) 音译法：按英文名词音译，用带“口”旁的同音汉字表示；
- (2) 当母核上有取代基时，取代基位次从杂原子算起，用1, 2, 3... 编号；
- (3) 当母核上不止一个杂原子时按O, S, N顺序依次编号，杂原子的位次遵循最低系列原则。

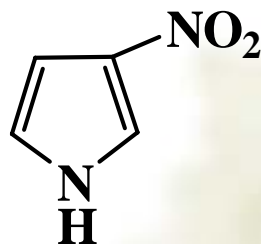
### Ex 1:



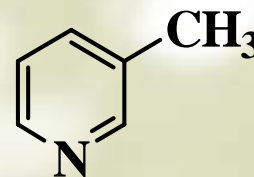
Furan



$\alpha$ -Bromothiophene

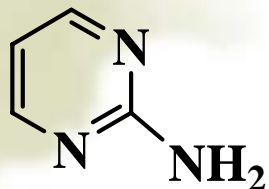


3-Nitro-pyrrole

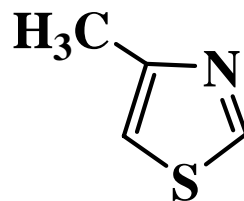


3-Methylpyridine

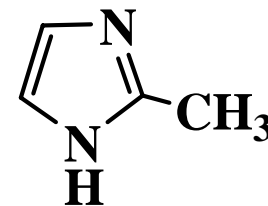
**Ex 2:**



**2-Aminopyrimidine**

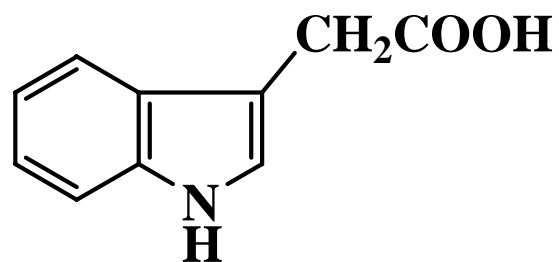


**4-Methylthiazole**

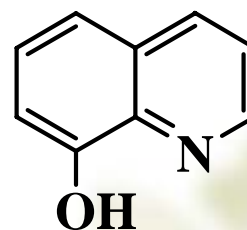


**2-Methylimidazole**

**Ex 3:**



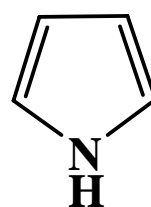
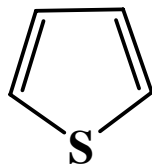
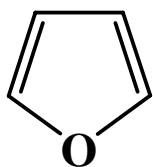
**2-(Indol-3-yl)acetic acid**



**Quinolin-8-ol**

[Contents](#)

## 18.2 FIVE-MEMBERED HETEROCYCLIC AROMATIC COMPOUNDS



**Furan**   **Thiophene**   **Pyrrole**  
(呋喃)   (噻吩)   (吡咯)

### 18.2.1 Structure

The structures of these three heterocycles would suggest that they have highly reactive diene character.

**Addition Reactions**

However, like benzene, many of their chemical properties are not typical of dienes. They undergo **electrophilic substitution** rather than addition reactions.

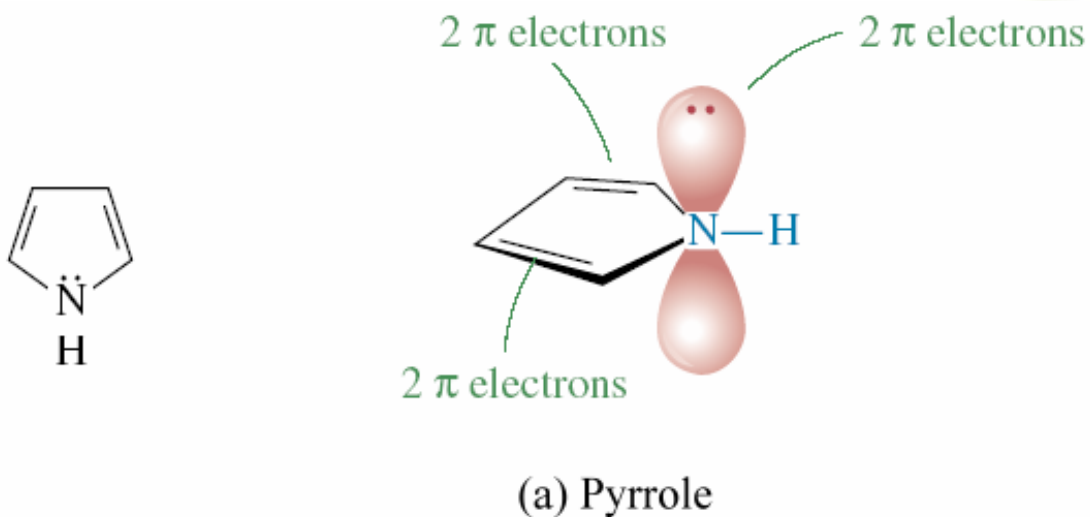
In short, these heterocycles have characteristics associated with **aromaticity** (芳香性).

*Why?*

***Hückel's Rule:*** The  $4n+2$   $\pi$  electron rule

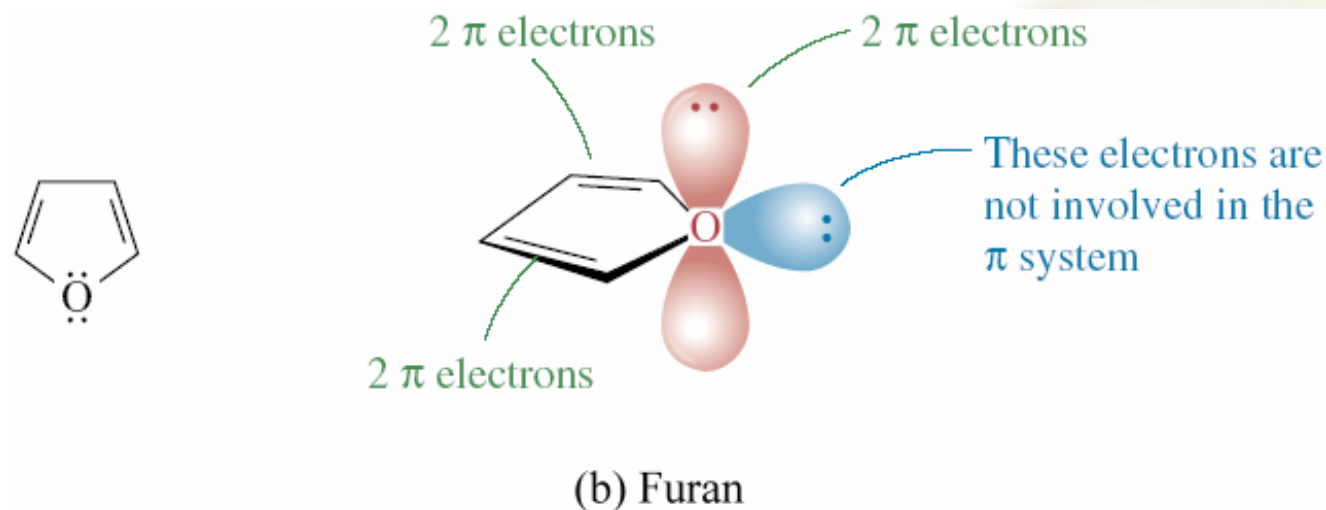
Planar monocyclic rings with 2, 6, 10, 14, ..., delocalized electrons should be aromatic.

In **pyrrole**, the nitrogen atom is  $sp^2$ -hybridized and the unshared pair of electrons occupies a  $p$  orbital. The pair belonging to nitrogen must be added to the four  $\pi$  electrons of the two double bonds in order to meet the six- $\pi$  electron requirement.

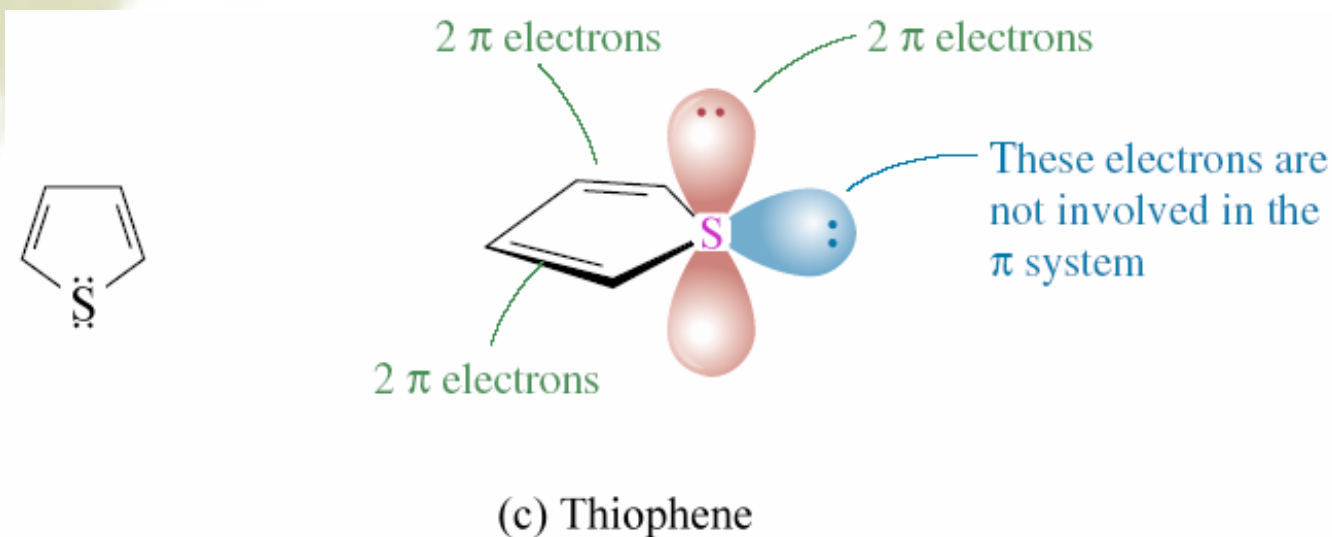




The oxygen in **furan** has two unshared electron pairs. One pair is like the pair in pyrrole, occupying a  $p$  orbital and contributing two electrons to complete the six- $\pi$  electron requirement for aromatic stabilization. The other electron pair in furan is an “extra” pair, not need to satisfy the  $4n + 2$  rule for aromaticity, and occupies an  $sp^2$ -hybridized orbital.



The bonding in **thiophene** is similar to that of furan.



**结构特点：**五中心六电子的富电子大 $\pi$ 体系，具有芳香性。

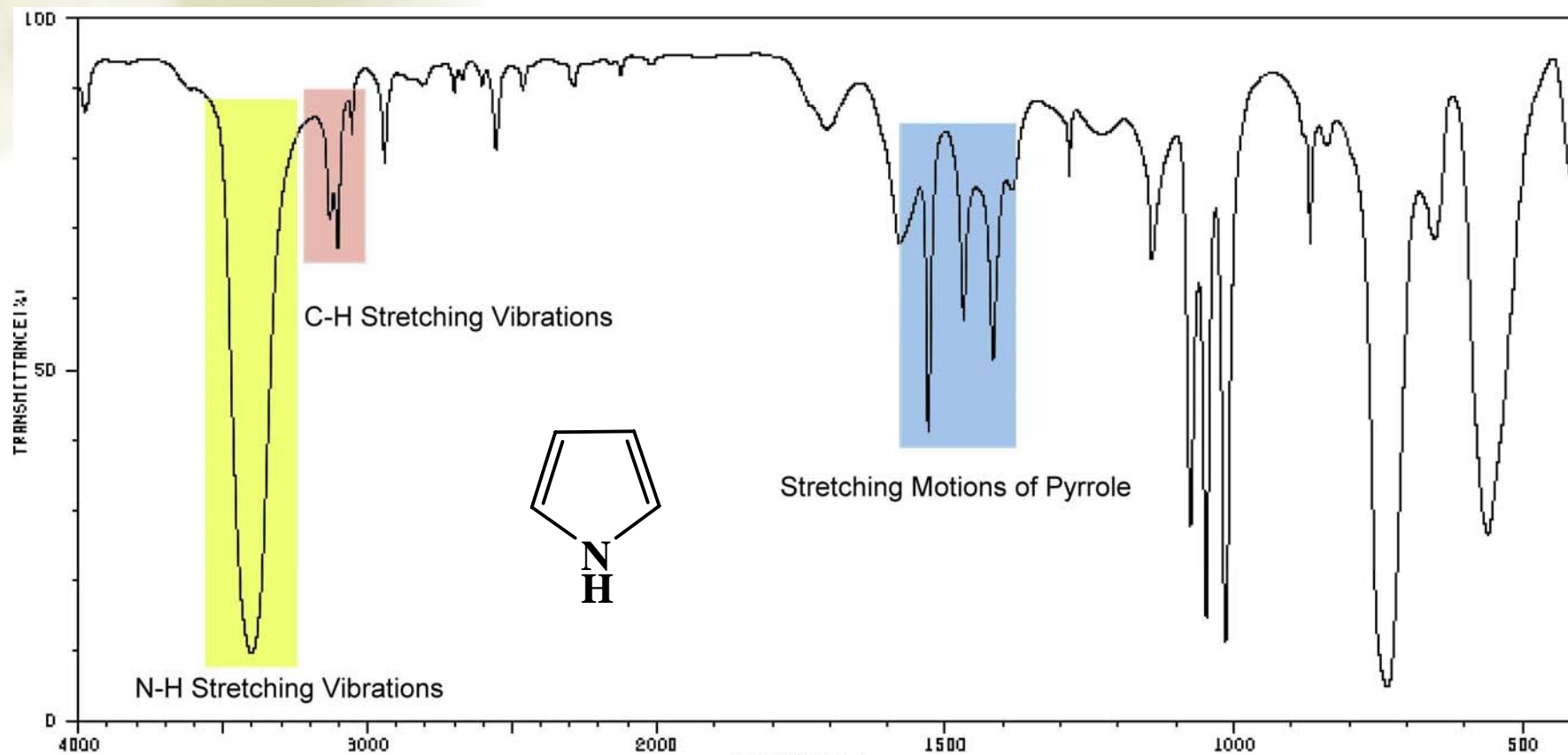
## 18.2.2 Physical Properties and Spectroscopy

### 18.2.2.1 Physical properties

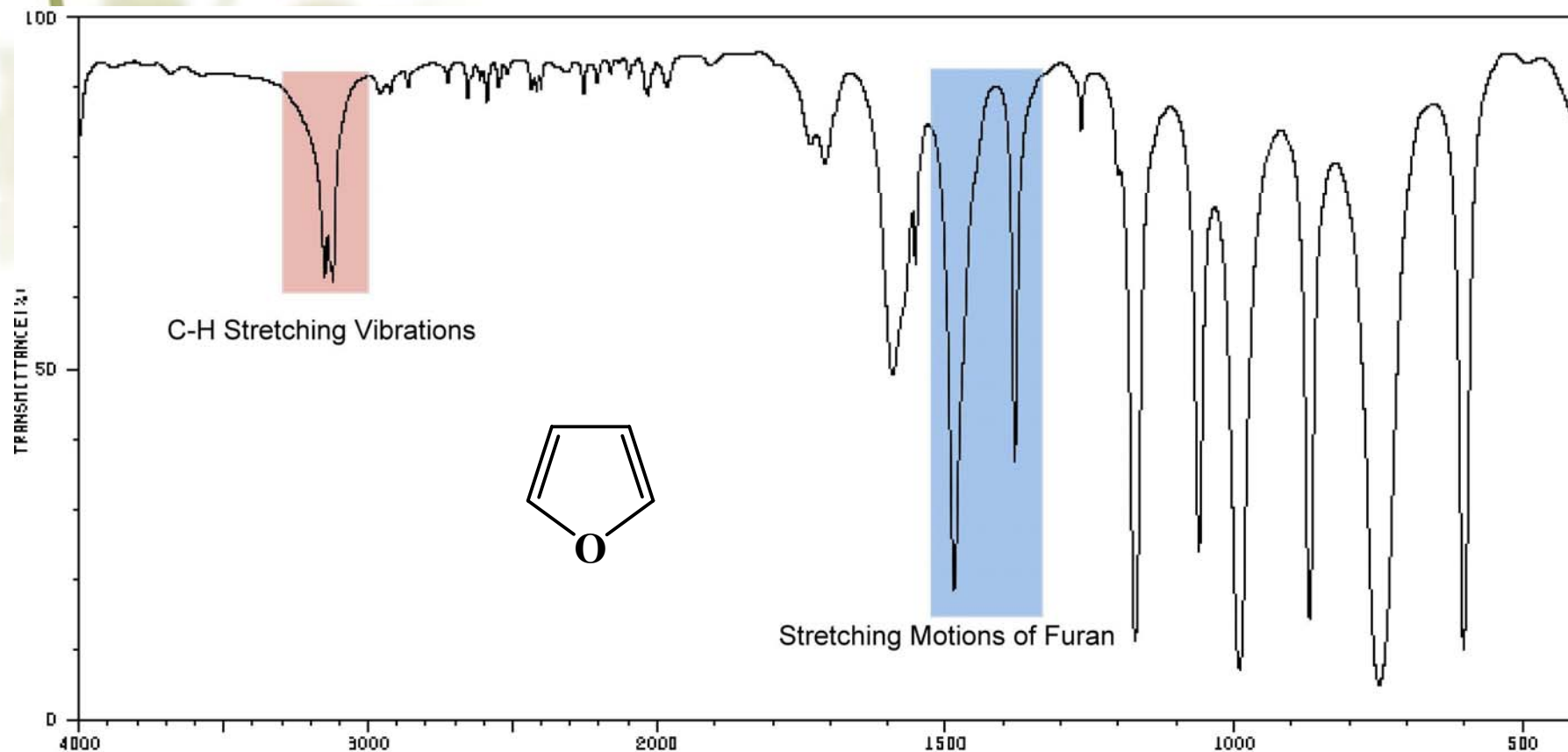
Heterocycles	Existence	Color, Odor	Identify
<b>Pyrrole</b>	煤焦油 骨焦油	无色液体 弱苯胺气味	松木片反应呈 <b>红色</b>
<b>Furan</b>	松木焦油	无色液体 氯仿气味	松木片反应呈 <b>绿色</b>
<b>Thiophene</b>	煤焦油	无色液体 特殊气味	在吲哚醌的硫酸中呈 <b>蓝色</b>

## 18.2.2.2 Spectroscopy

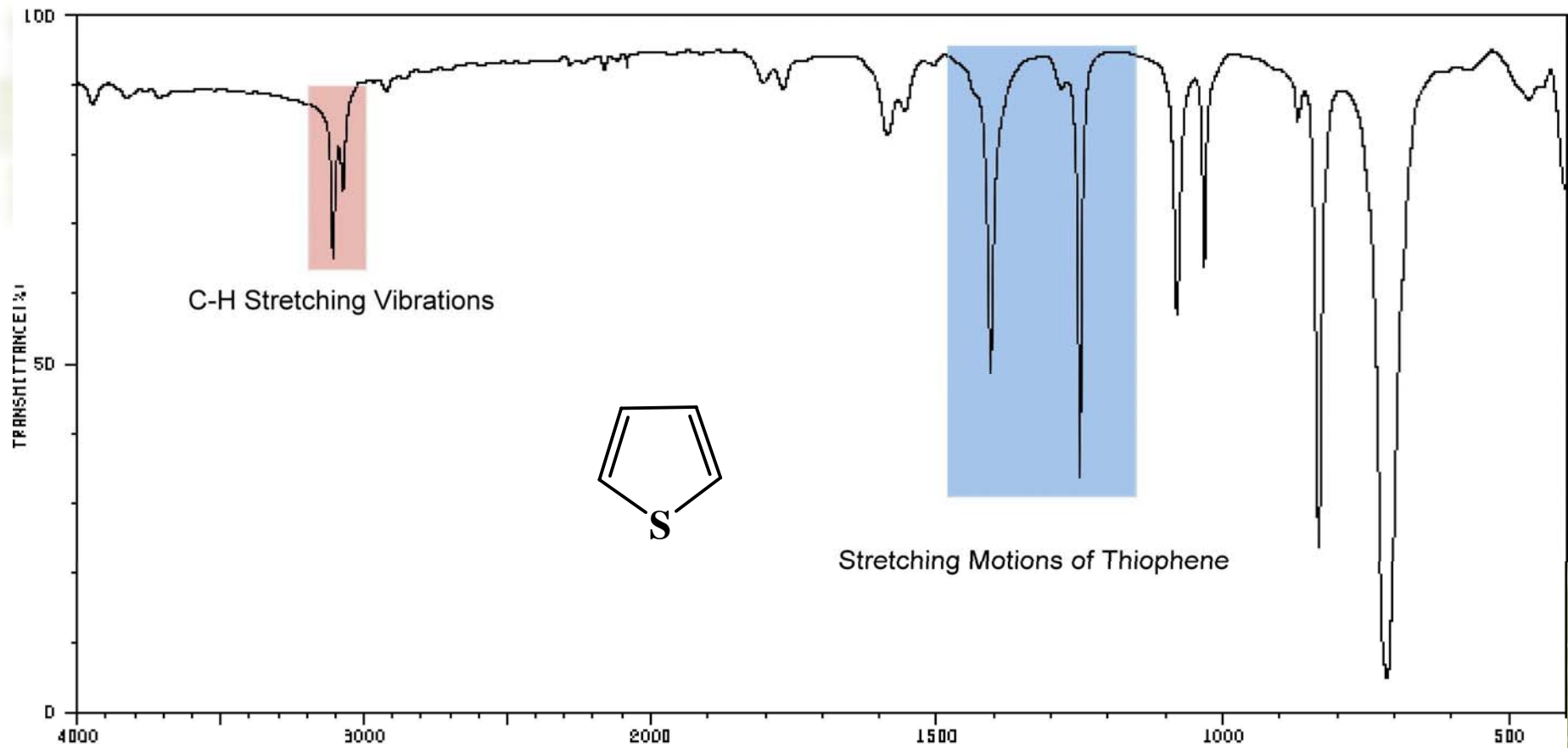
### 1. Infrared Spectra:



**Infrared Spectrum of Pyrrole**



**Infrared Spectrum of Furan**



**Infrared Spectrum of Thiophene**

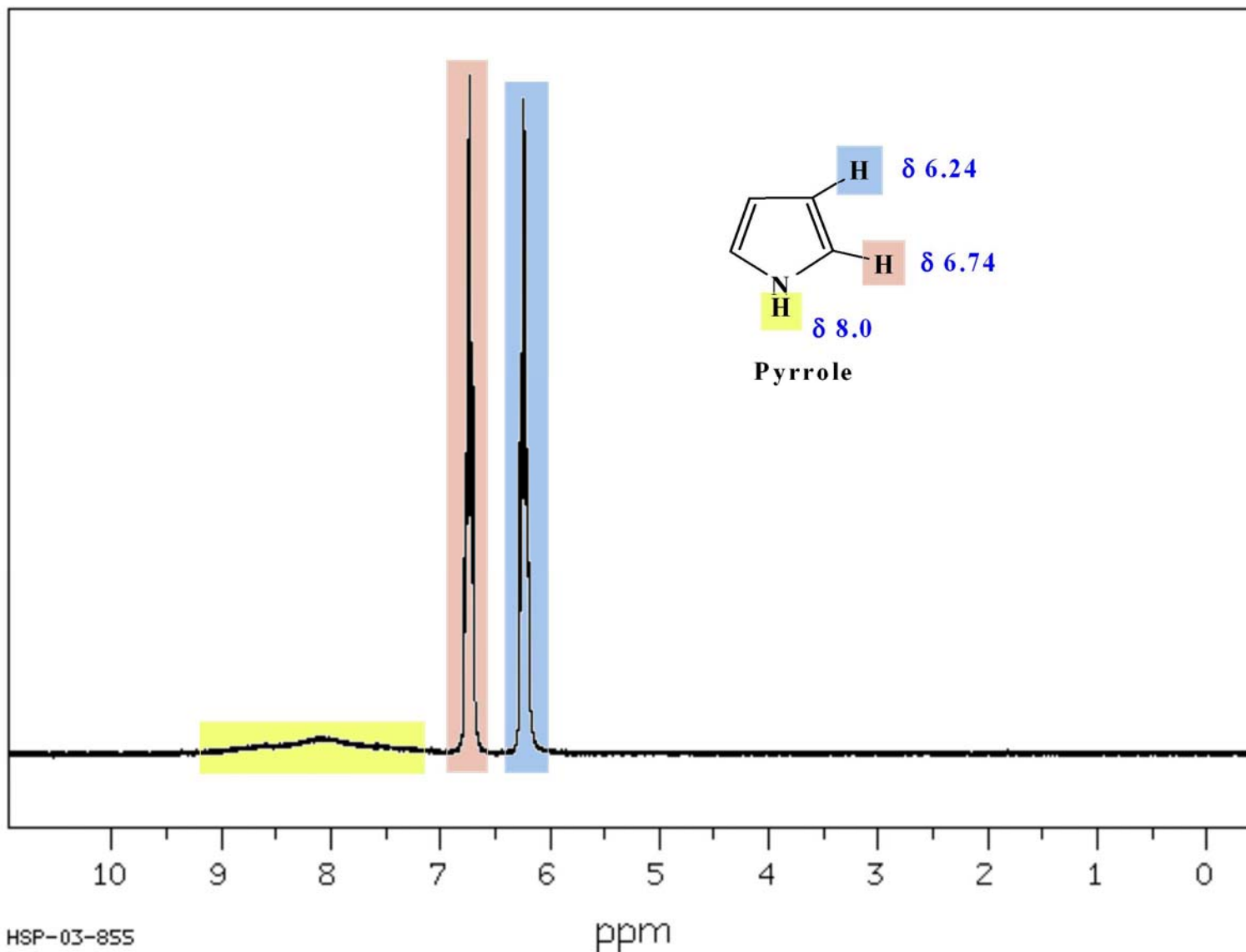
**Table 1. Infrared Absorption Frequencies of Furan, Thiophene and Pyrrole**

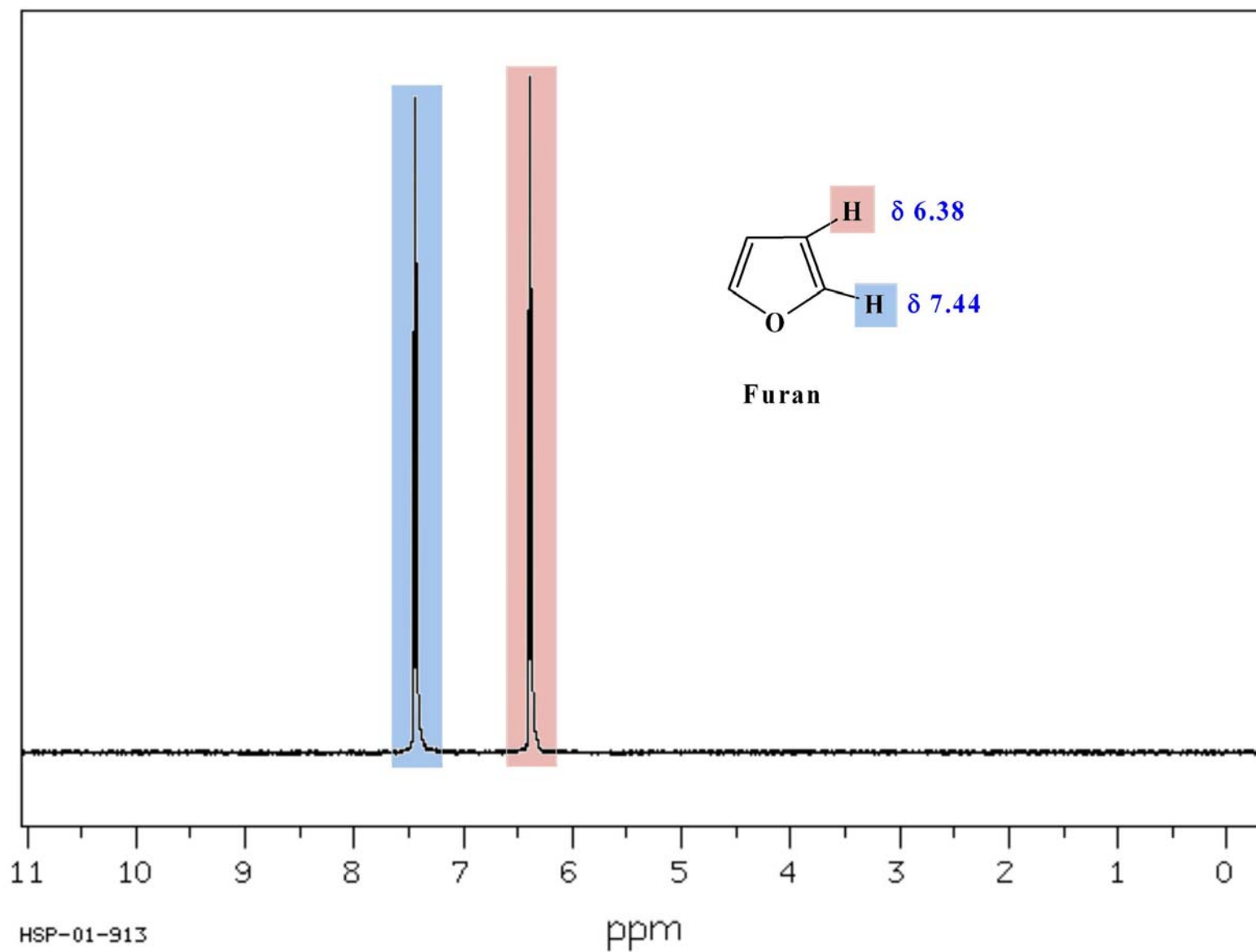
<b>Vibrations</b>	<b>Frequency, cm<sup>-1</sup></b>
<b>C-H stretching vibrations</b>	<b>3100-3003</b>
<b>Stretching motions of the heterocyclic ring (2-4 bands)</b>	<b>1600-1300</b>
<b>N-H stretching vibrations of pyrrole</b>	<b>3500-3200</b>

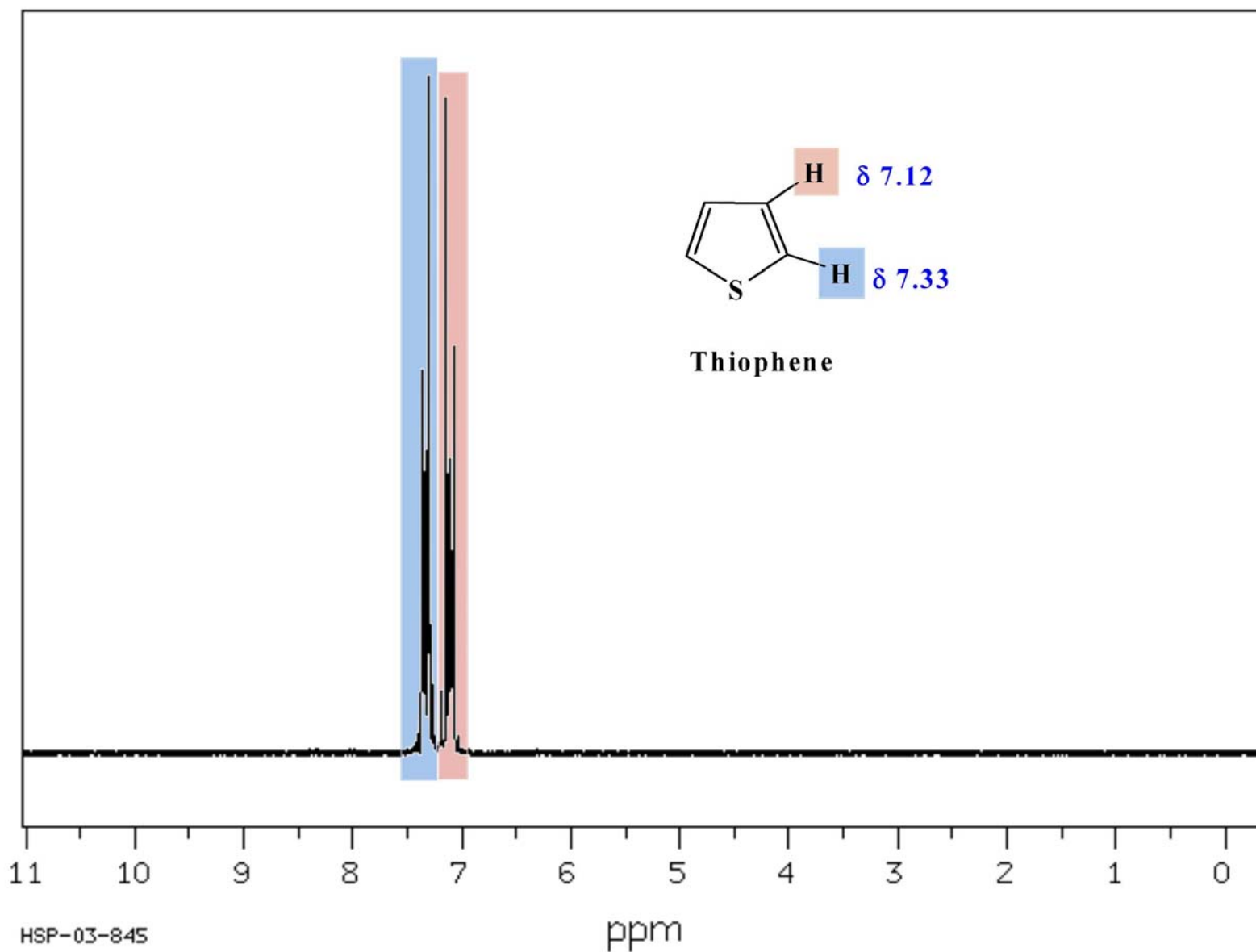
**\* Infrared absorption frequencies of benzene (cm<sup>-1</sup>): 3030, 1600-1450**



## 2. $^1\text{H}$ NMR Spectra: (ppm)







## 18.2.3 Chemical Properties

### 18.2.3.1 Electrophilic Substitution

Why?

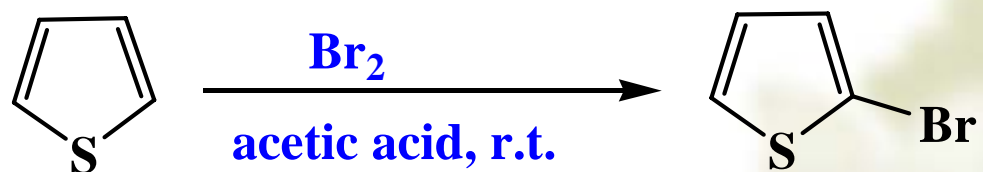
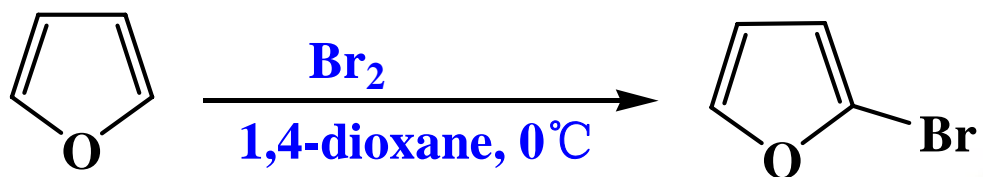
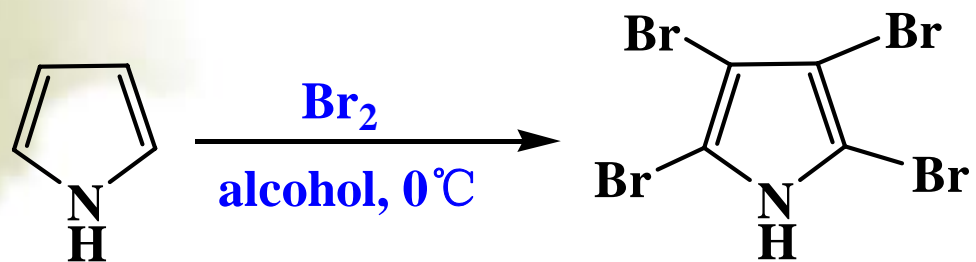
The order of reactivity:

Pyrrole > Furan > Thiophene >> Benzene

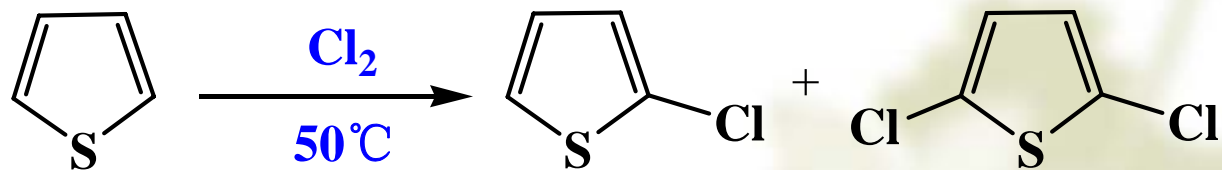
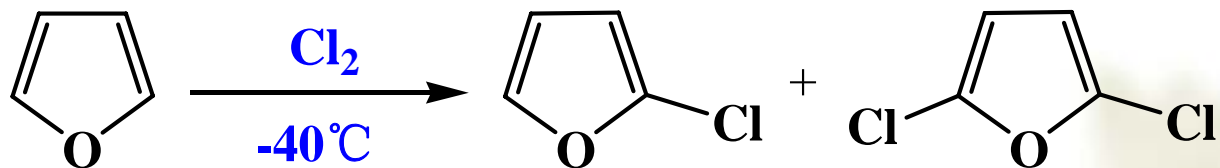
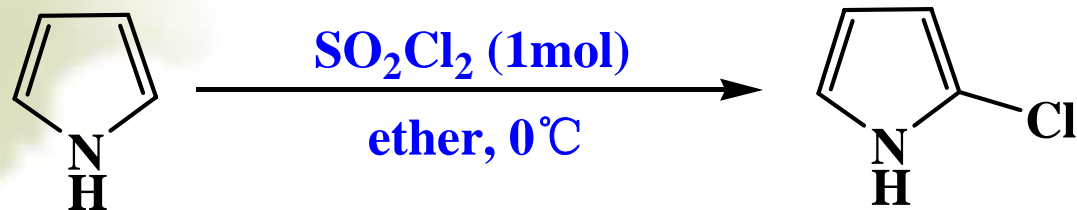
五中心六电子的大π体系

六中心六电子的大π体系

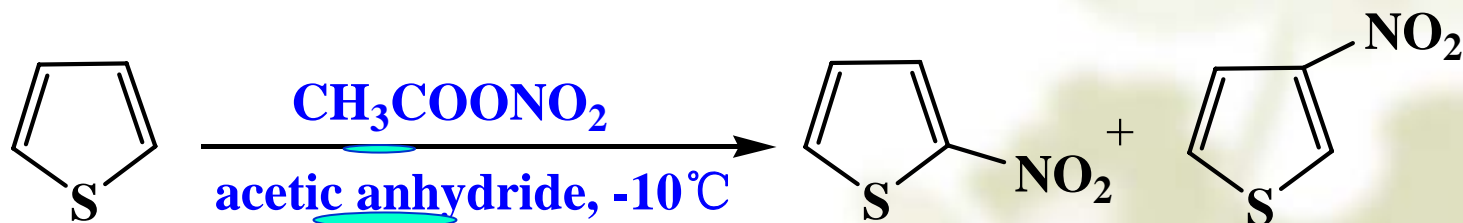
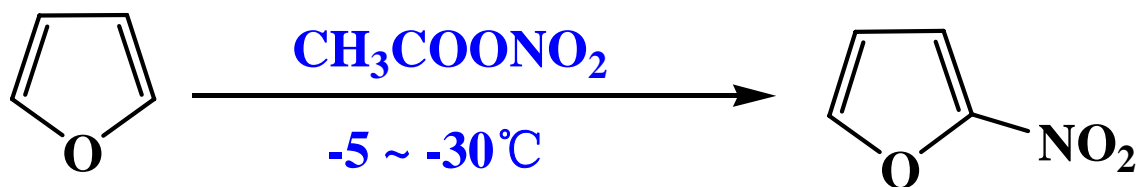
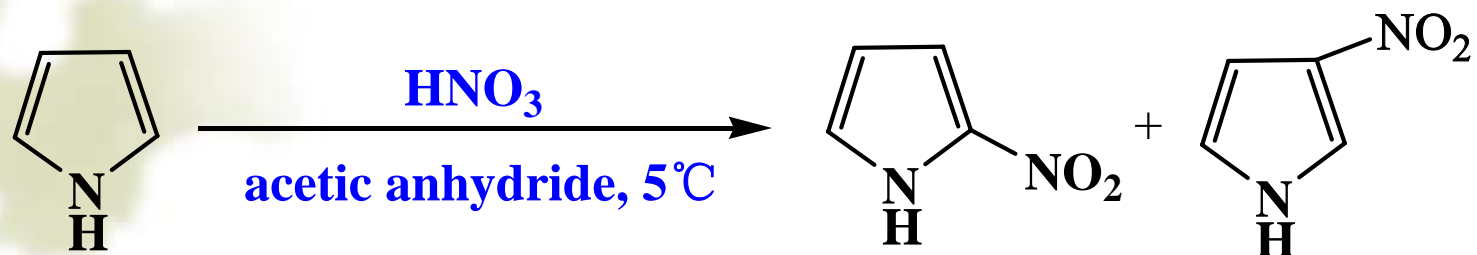
# 1. Bromination Reaction:



## 2. Chlorination Reaction:



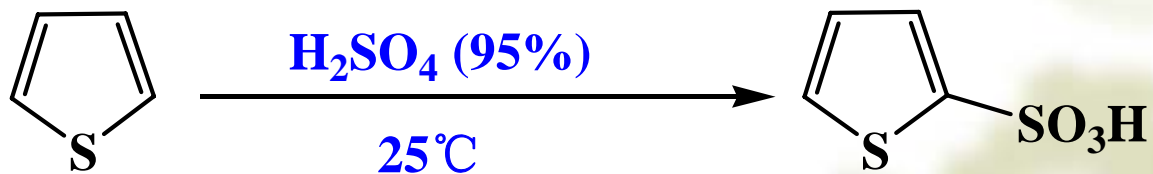
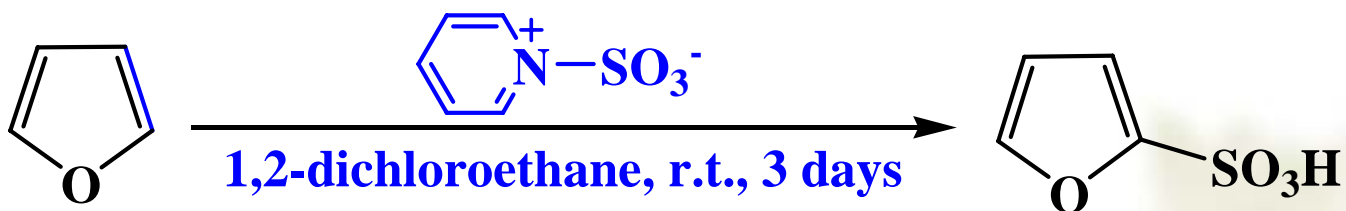
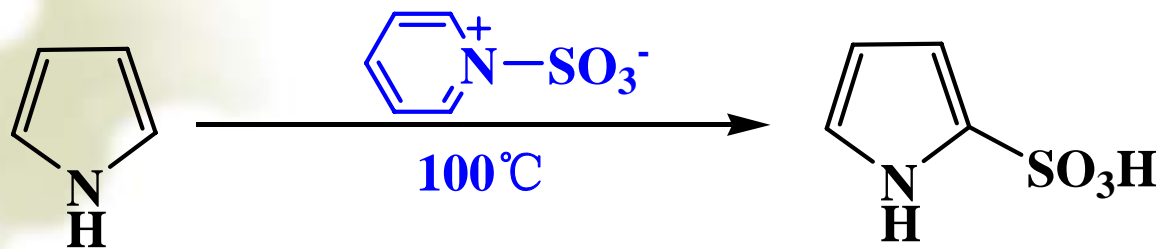
### 3. Nitration Reaction:



较温和的硝化剂，现制现用

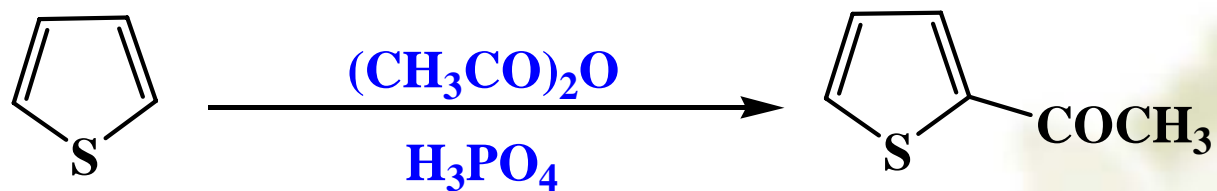
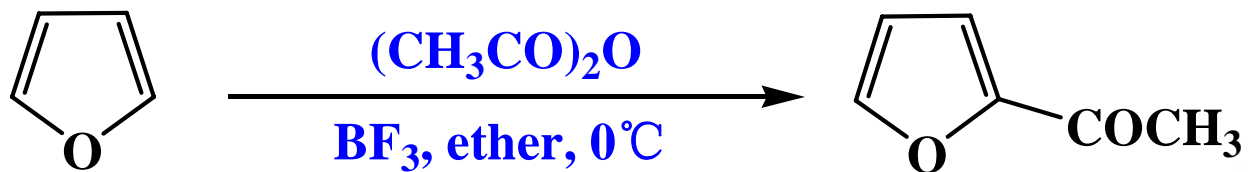
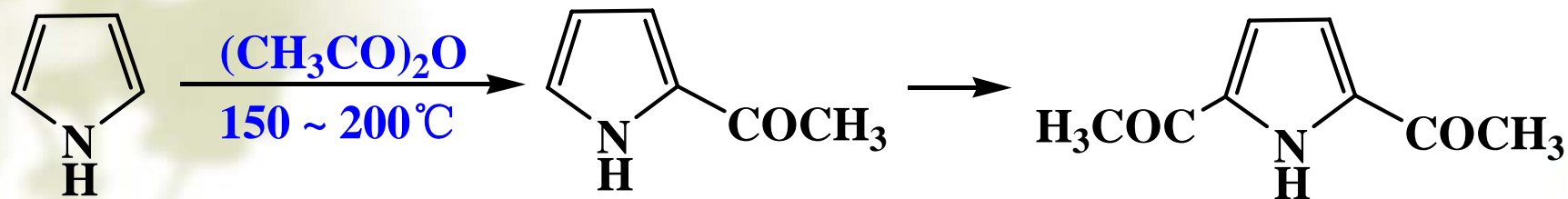


## 4. Sulfonation Reaction:



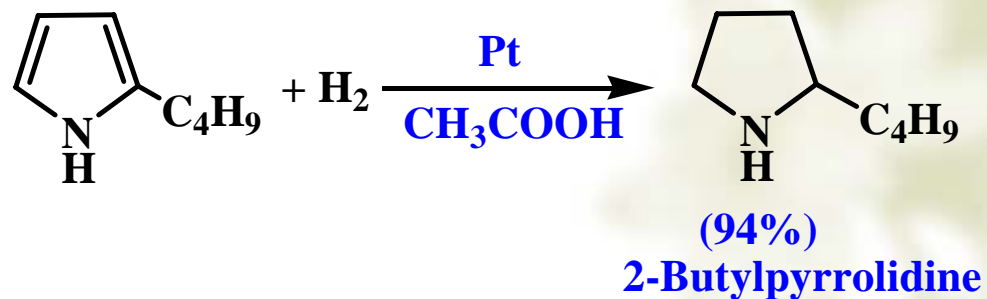
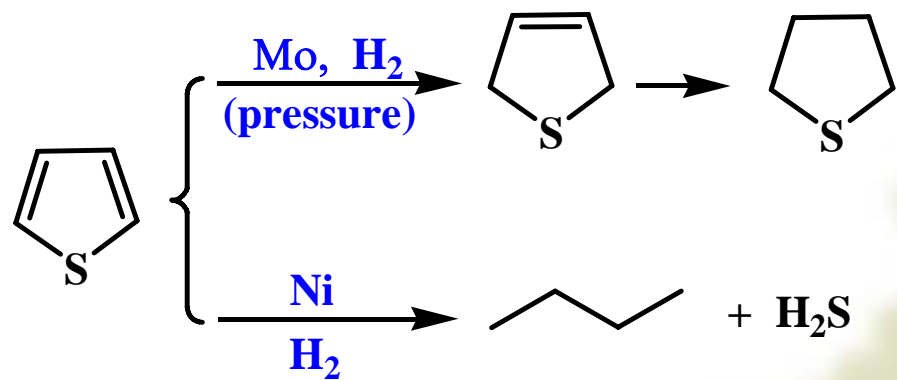
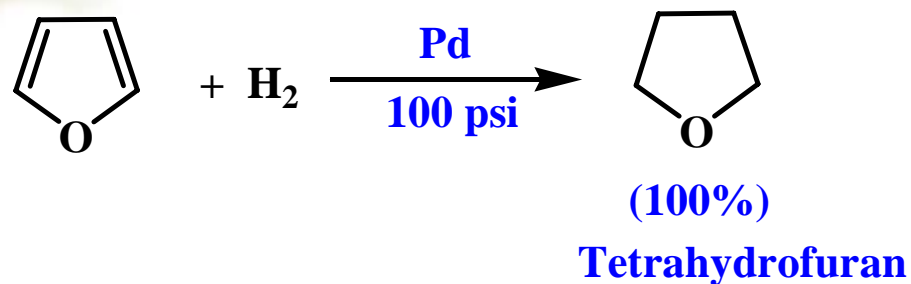
**Q:** How to separate thiophene from benzene?

## 5. Acetylation:

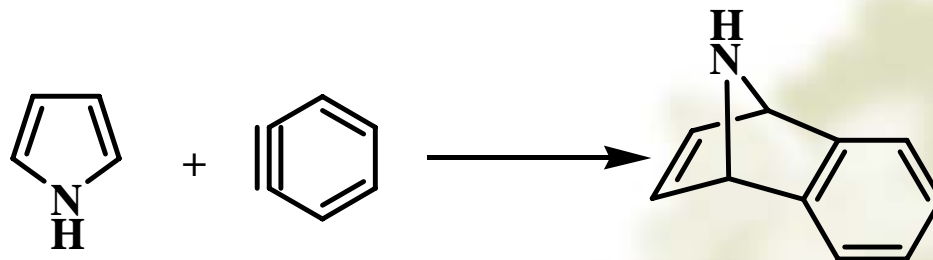
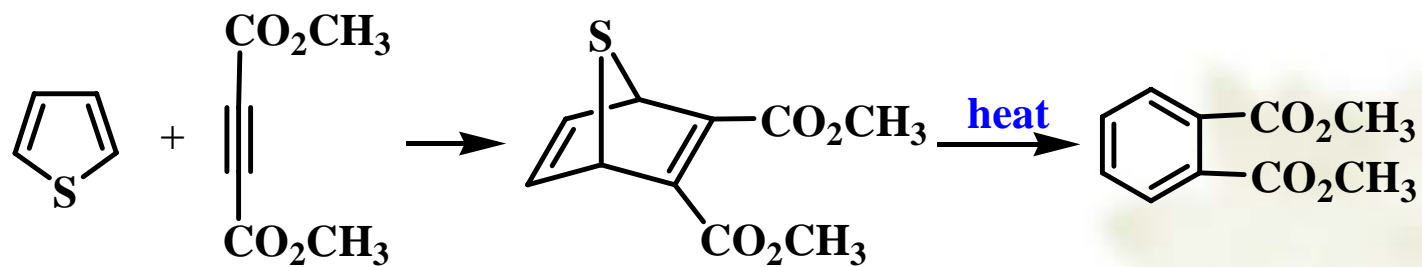
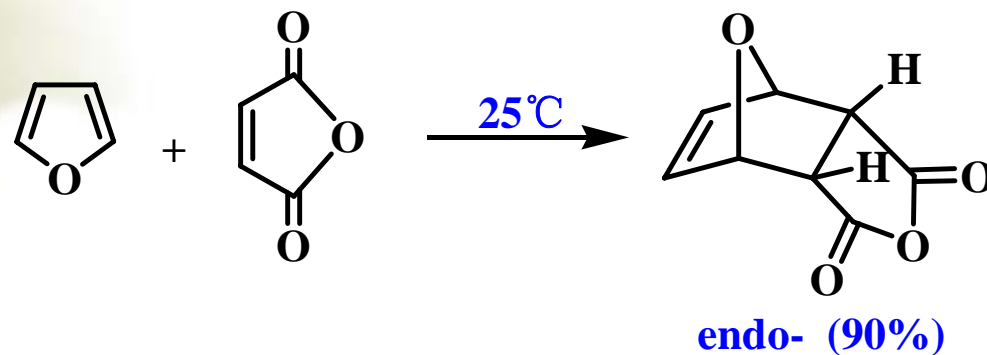


## 18.2.3.2 Addition Reaction

### 1. Hydrogenation

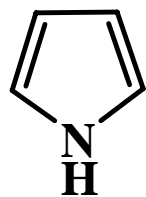


## 2. Diels-Alder Reaction

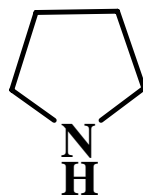


### 18.2.3.3 Acidity and Basicity of Pyrrole

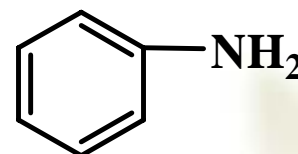
Because the unshared electron pair of nitrogen in pyrrole ring is a part of the aromatic sextet, it is not available for donation to a proton. Thus, in aqueous solution, pyrrole is not appreciably basic.



$$K_b = 2.5 \times 10^{-14}$$

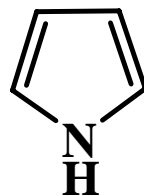


$$K_b = 2 \times 10^{-4}$$

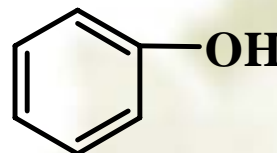


$$K_b = 3.8 \times 10^{-10}$$

Weak acidity:

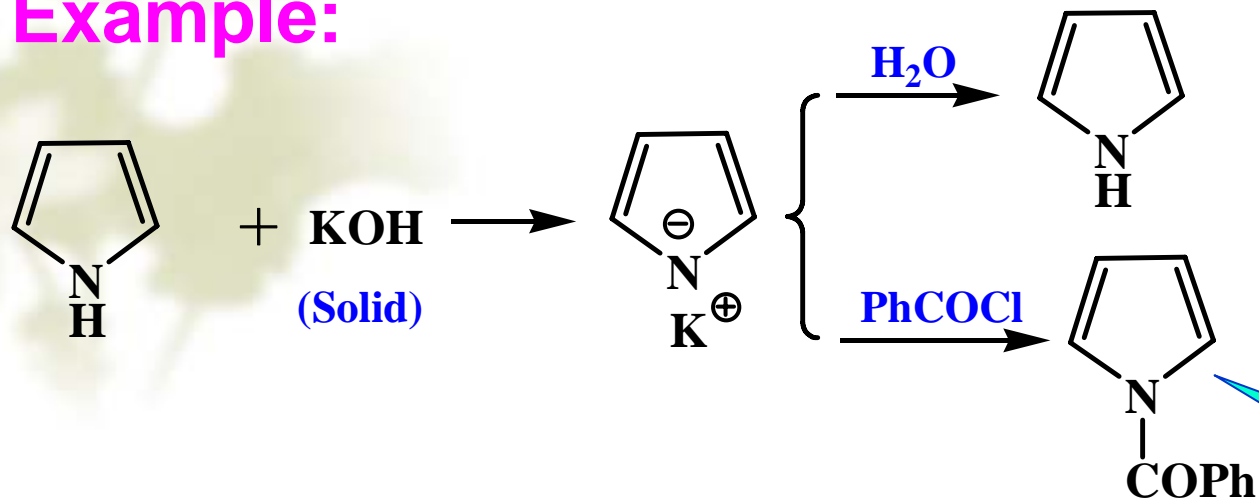


$$K_a = 10^{-15}$$

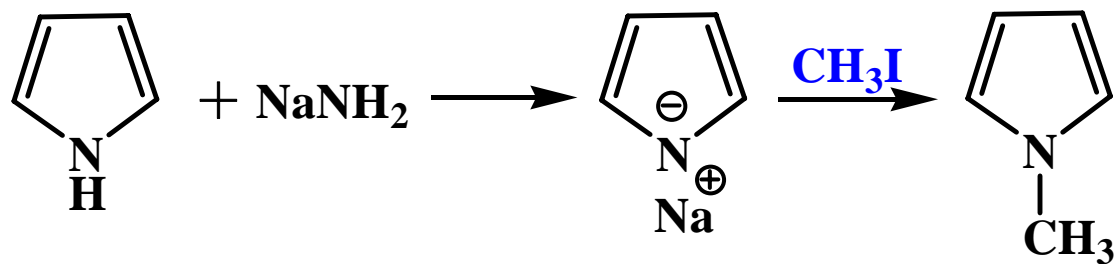


$$K_a = 1.3 \times 10^{-10}$$

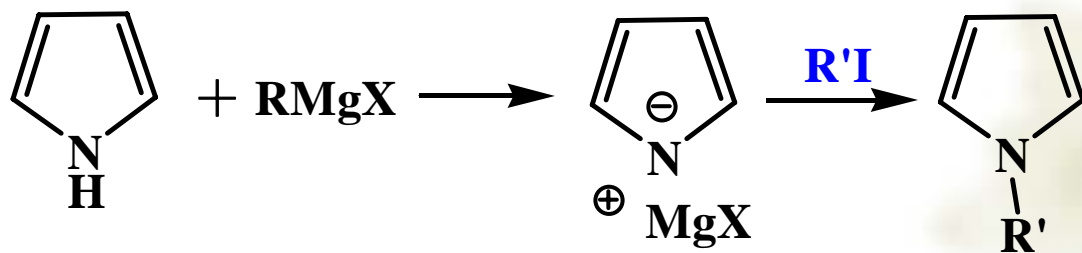
Example:



**N-Acylation**

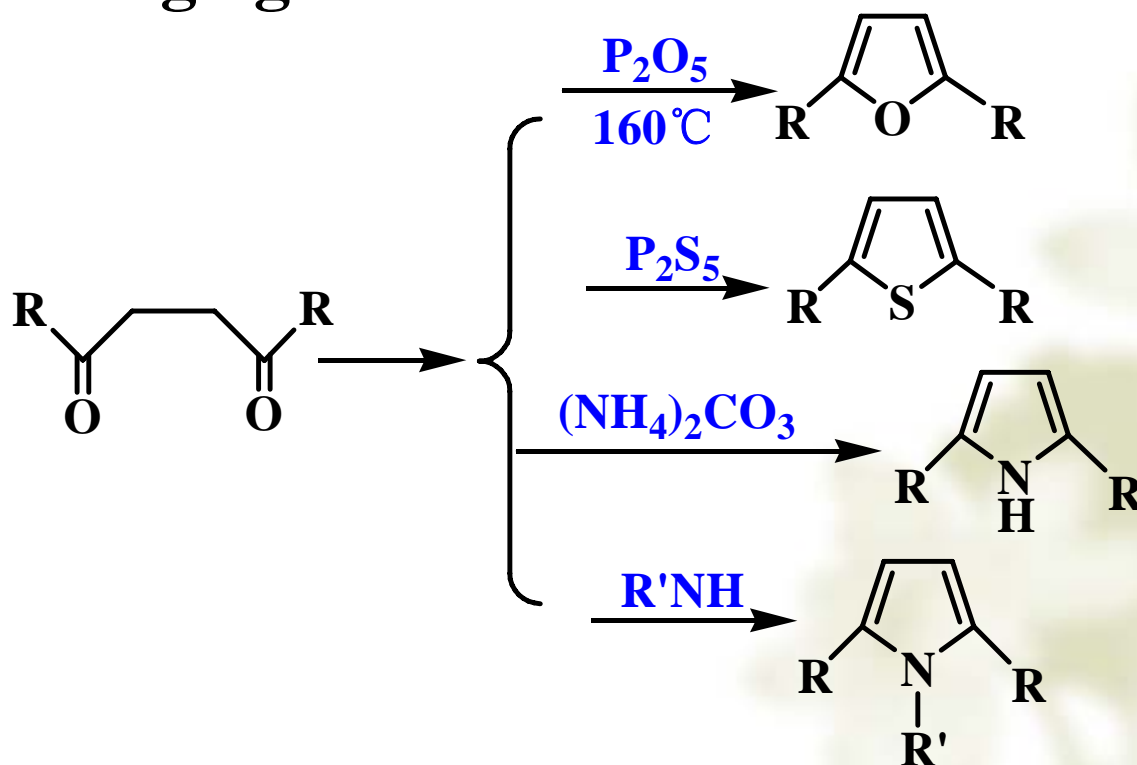


**N-Alkylation**

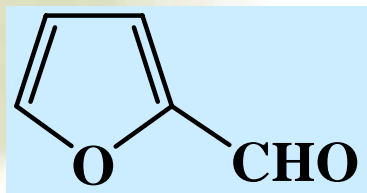


## 18.2.4 Synthesis of the three five-membered heterocyclic compounds

The most general is the **Paal-Knorr** synthesis, in which a 1,4-dicarbonyl compound is heated with a dehydrating agent.



## 18.2.5 Furfural (Furan- $\alpha$ -carbaldehyde)



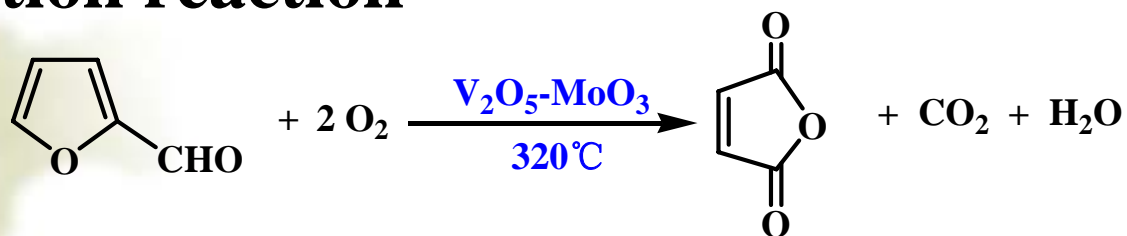
**Colorless liquid, turn yellow or brown in the air.**

**Aldehyde without  $\alpha$ -H atom**

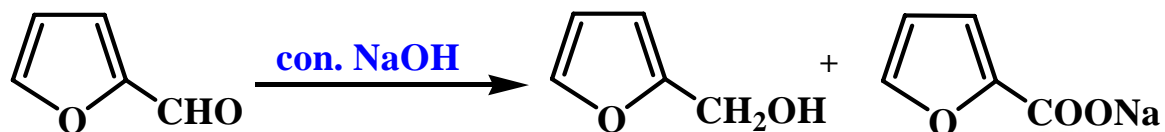
- **Preparation**  
industrial product, wet distillation
- **Properties and application**  
good solvent;  
yield furyl alcohol by catalytic hydrogenation,  
which is the monomer of alcohol-furfural resin.



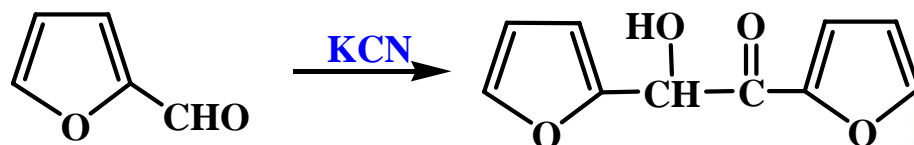
➤ Oxidation reaction



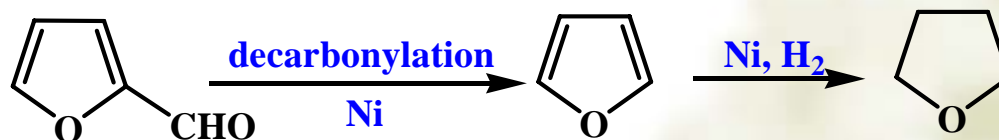
➤ Disproportionation reaction (歧化)



➤ Benzoic condensation



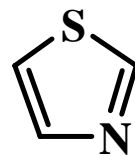
➤ Preparation of tetrahydrofuran



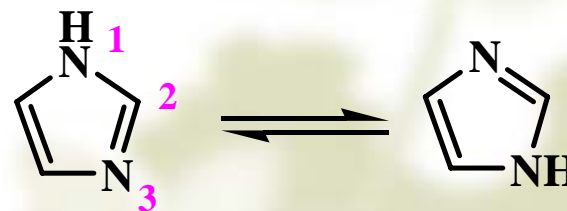
## 18.2.6 Thiazole, Imidazole and Indole

A large group of heterocyclic aromatic compounds are related to pyrrole by replacement of one of the ring carbons  $\beta$  to nitrogen by a second heteroatom. Compounds of this type are called *azoles*.

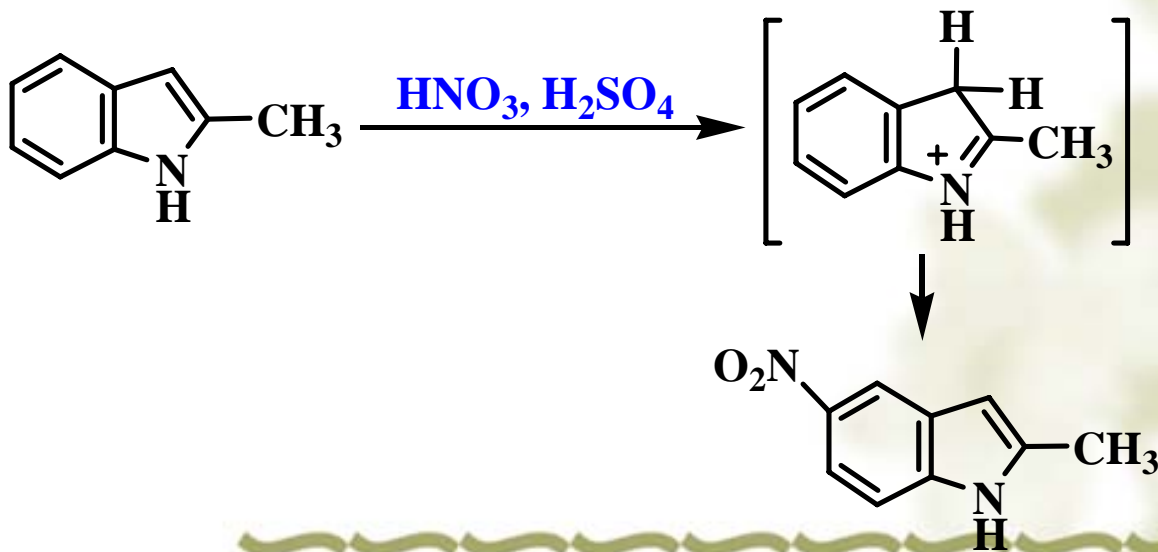
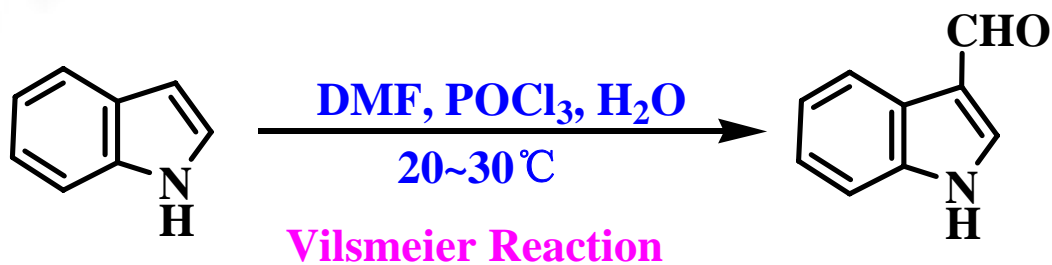
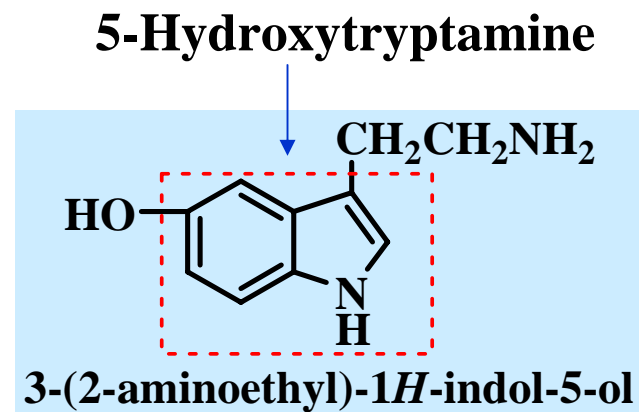
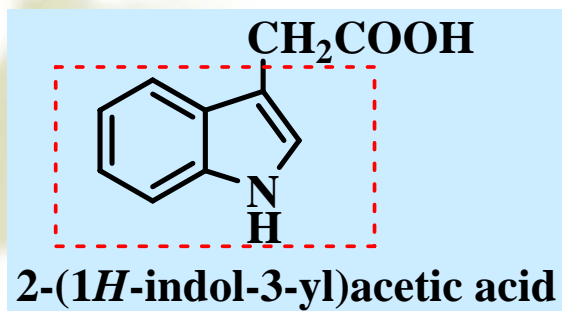
1. Thiazole: colorless **liquid**



2. Imidazole: colorless **solid**

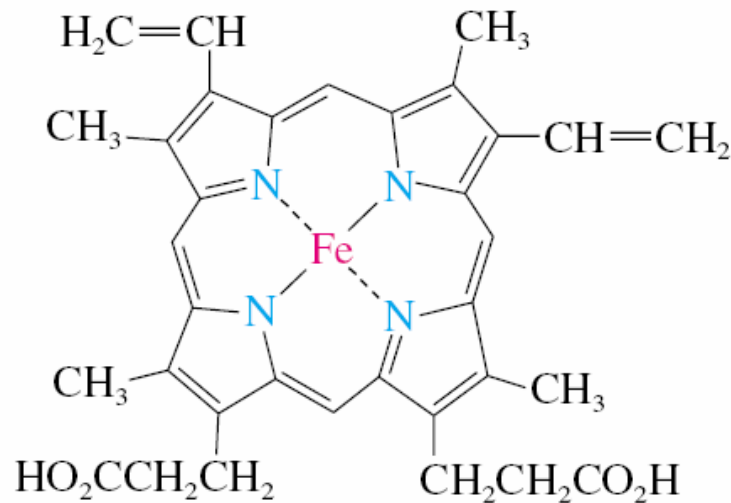
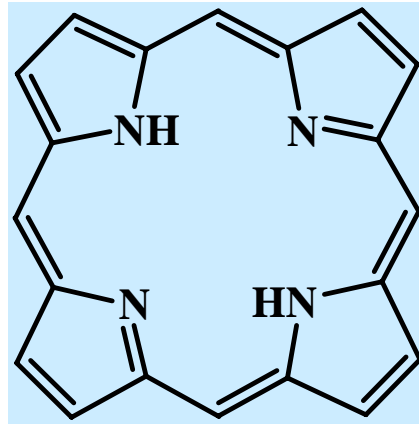


### 3. Indole:



## 18.2.7 卟啉化合物

四个吡咯环和四个次甲基交替相连组成的大环叫做卟吩。



血红素，叶绿素，维生素 $\text{B}_{12}$ 都是卟啉化合物。

**Heme**

Contents

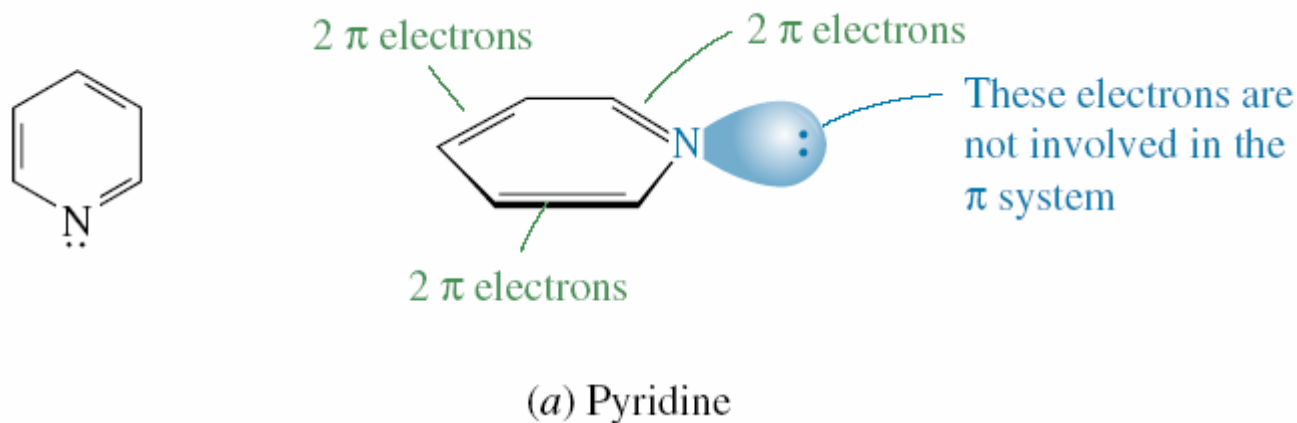
## 18.3 SIX-MEMBERED HETEROCYCLIC COMPOUNDS

### 18.3.1 Pyridine

**colorless liquid with peculiar odour;  
soluble in ether, alcohol and water in all proportions.**

#### 1. Structure and Preparation

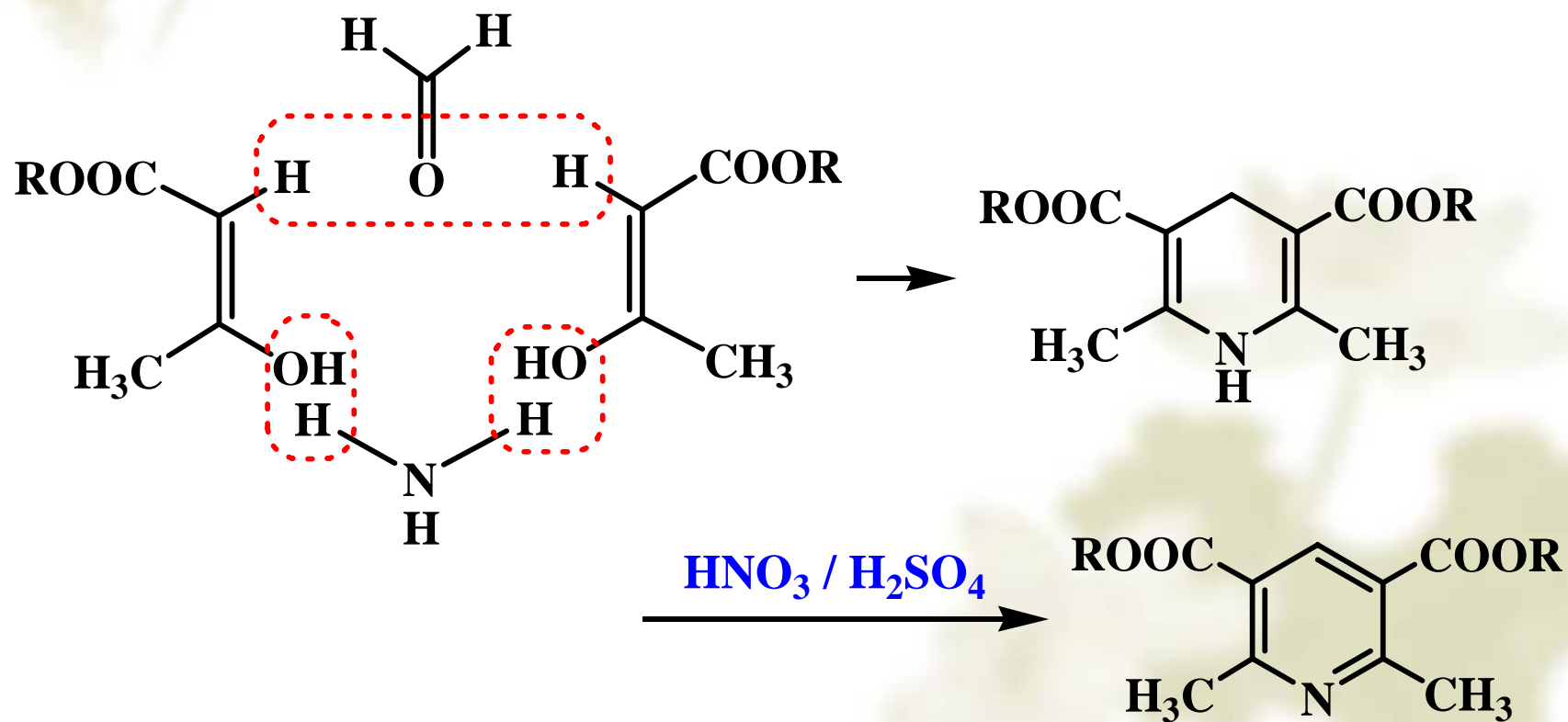
Pyridine is simply a benzene ring in which a nitrogen atom has replaced a CH group. The nitrogen is  $sp^2$ -hybridized, and the three double bonds of the ring contribute the necessary six  $\pi$  electrons to make pyridine a heterocyclic aromatic compound. The unshared electron pair of nitrogen occupies an  $sp^2$  orbital in the plane of the ring, not a  $p$  orbital aligned with the  $\pi$  system.



**Commercial production: aminolysis of furyl alcohol**

**Important synthetic method in laboratory: Hantzsch**

**Pyridine synthesis**





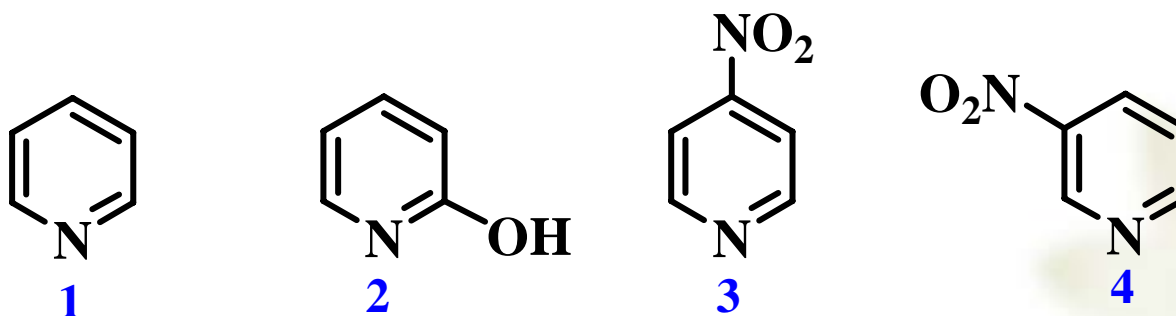
## **2. Basicity and Nucleophilic Properties**

**Pyridine, like pyrrole, is weak base, but it is much more basic than pyrrole. When pyridine is protonated, its unshared pair is used to bond to a proton and, since the unshared pair is not involved in the system, the aromatic character of the ring is little affected.**



当吡啶及其同系物的环上有吸电子取代基后，其碱性会减弱，特别是2, 4, 6位上的取代。

**Ex:** Rank the order of basicity of the following compounds.

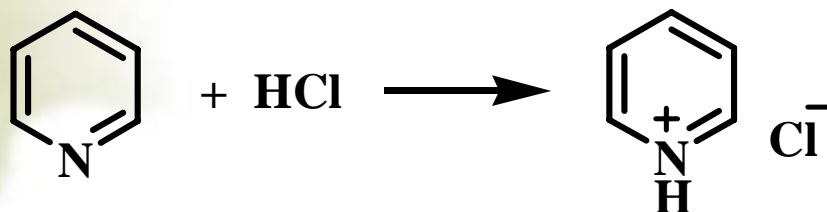


**Sample solution:**



Pyridine can react with strong acids to give salts.

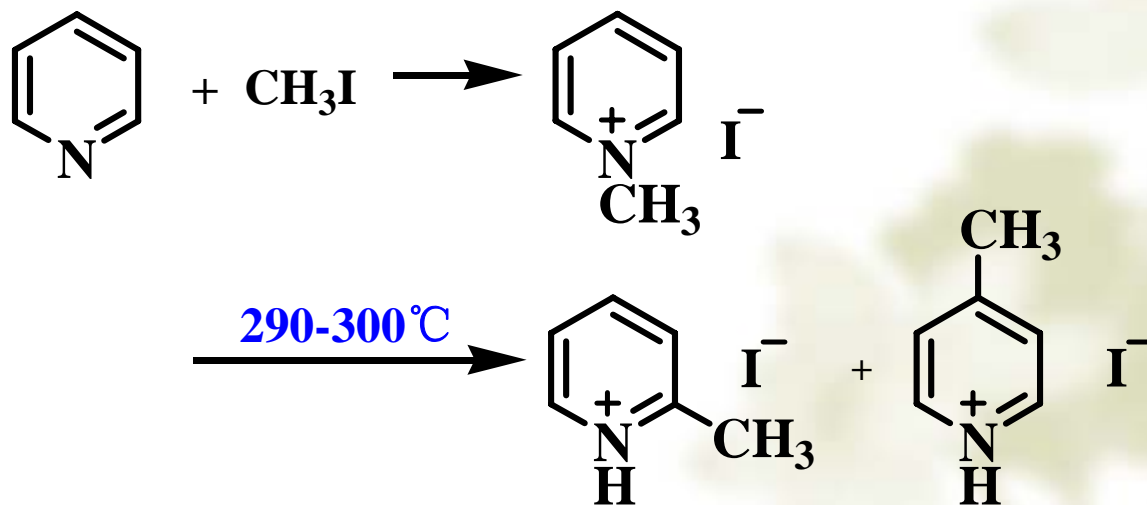
Ex:



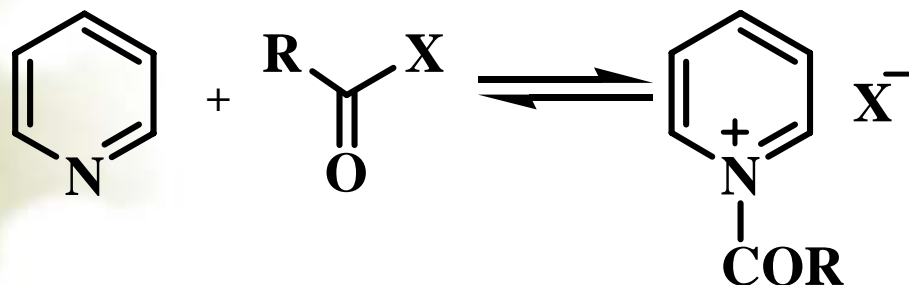
Quaternary ammonium salt

Pyridine can react with alkyl halides as nucleophile to yield quaternary ammonium salts.

Ex:



Ex:

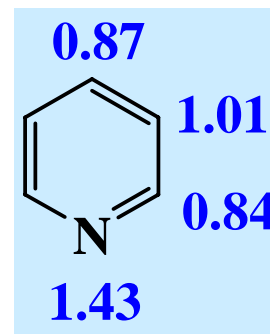


吡啶能与许多Lewis酸生成络合物。如：吡啶和三氧化硫生成的络合物可用于对酸灵敏的化合物，如：呋喃，吡咯的磺化。

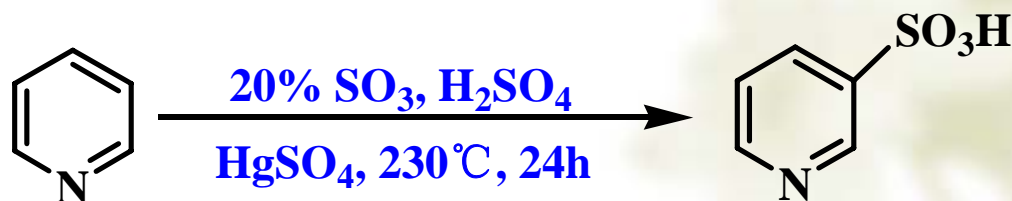
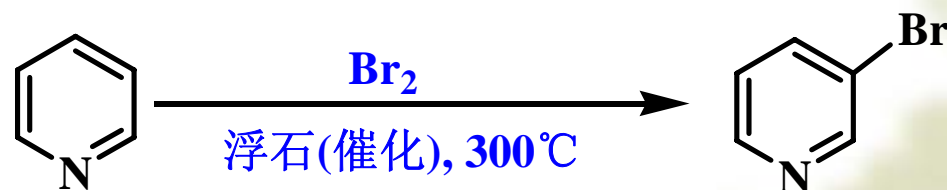
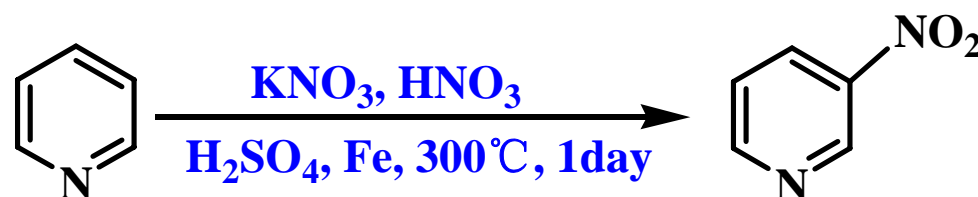
**注意：**吡啶的弱碱性和亲核性都是由N原子表现出来的。

### 3. Electrophilic Substitution

吡啶环上氮原子吸电子，所以吡啶环属于缺电子的芳杂环，亲电取代反应较苯难进行，如和硝基苯相似，不起傅-克反应。

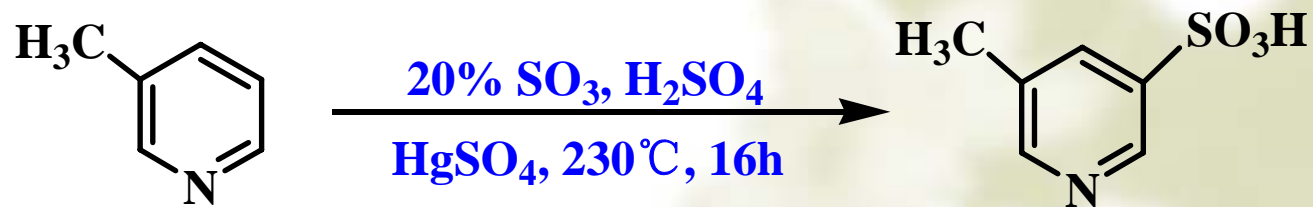
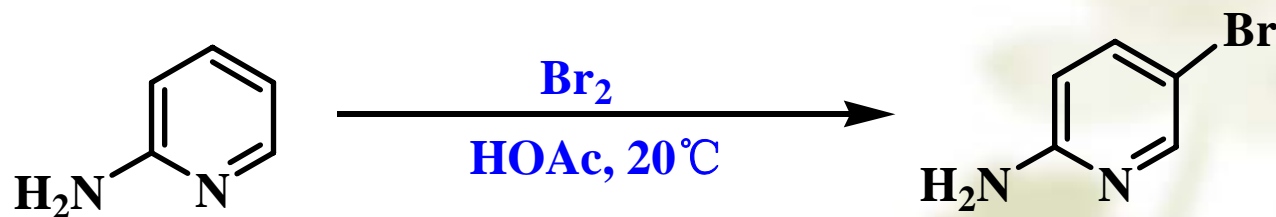
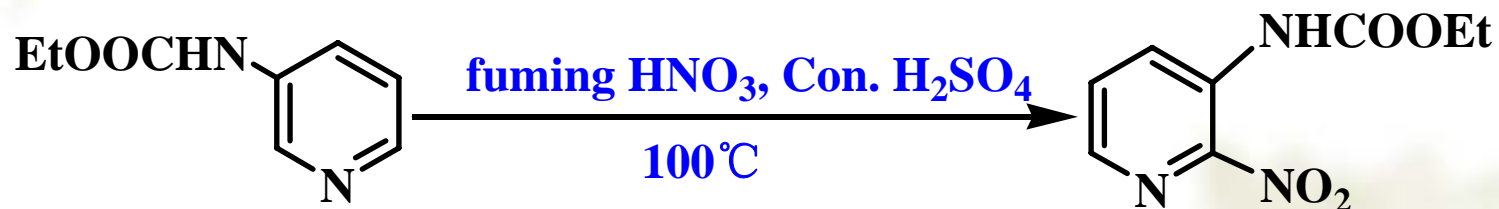


Ex:



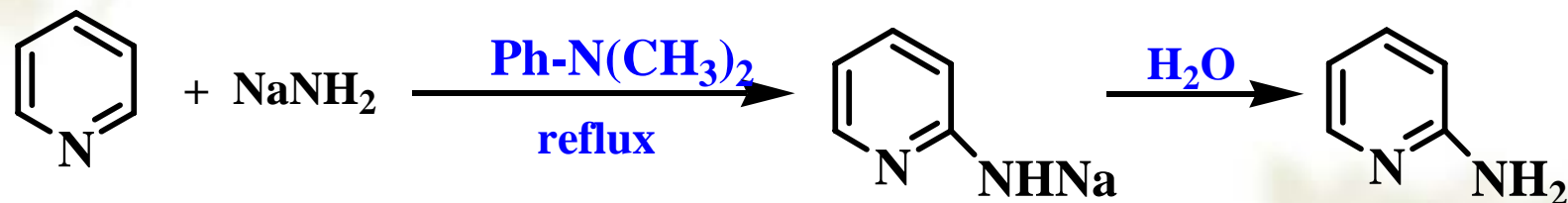
如果在环上有烷氧基，烷基，氨基等给电子基团时可以帮助于亲电取代反应的进行，但反应活性仍低于相应的苯系化合物。

Ex:

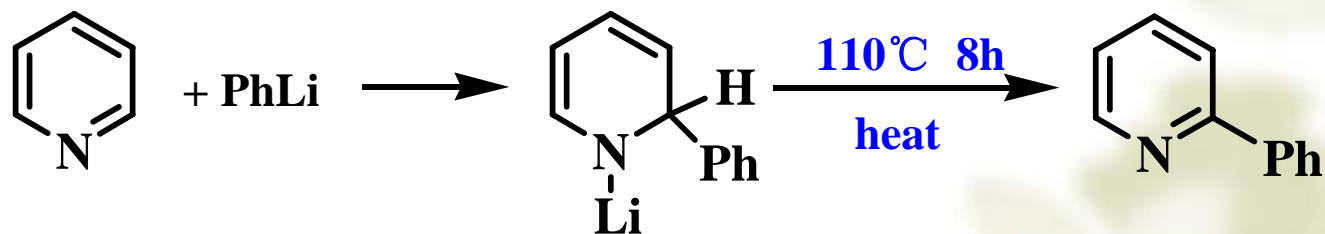


## 4. Nucleophilic Substitution

由于环上氮原子的邻对位电子出现的几率密度低，易进行亲核取代。



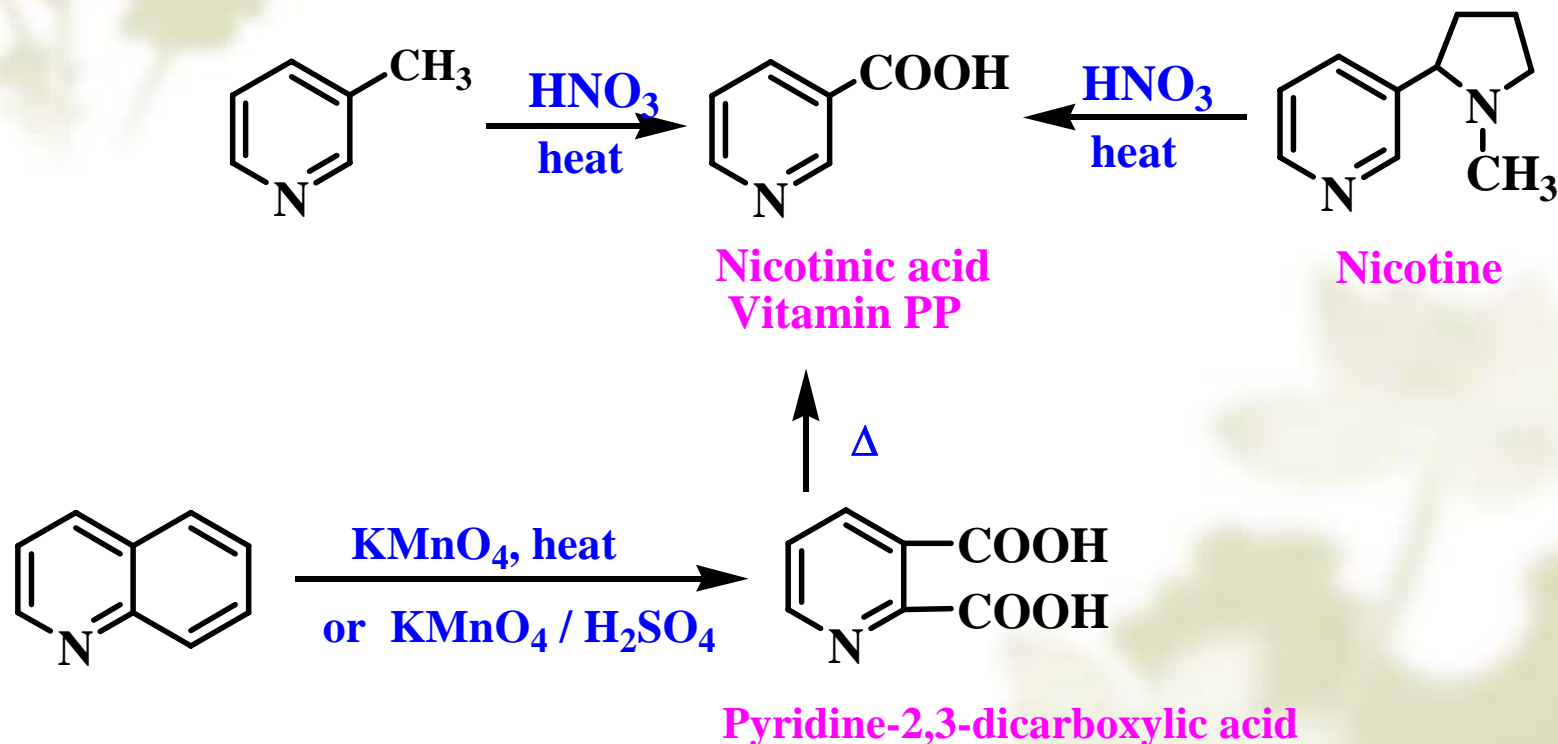
### ChiChibabin Reaction



### 1,2- Additive product

## 5. Oxidation

Pyridines are rather resistant to oxidation, and are more stable than benzene in the acidic oxidants.



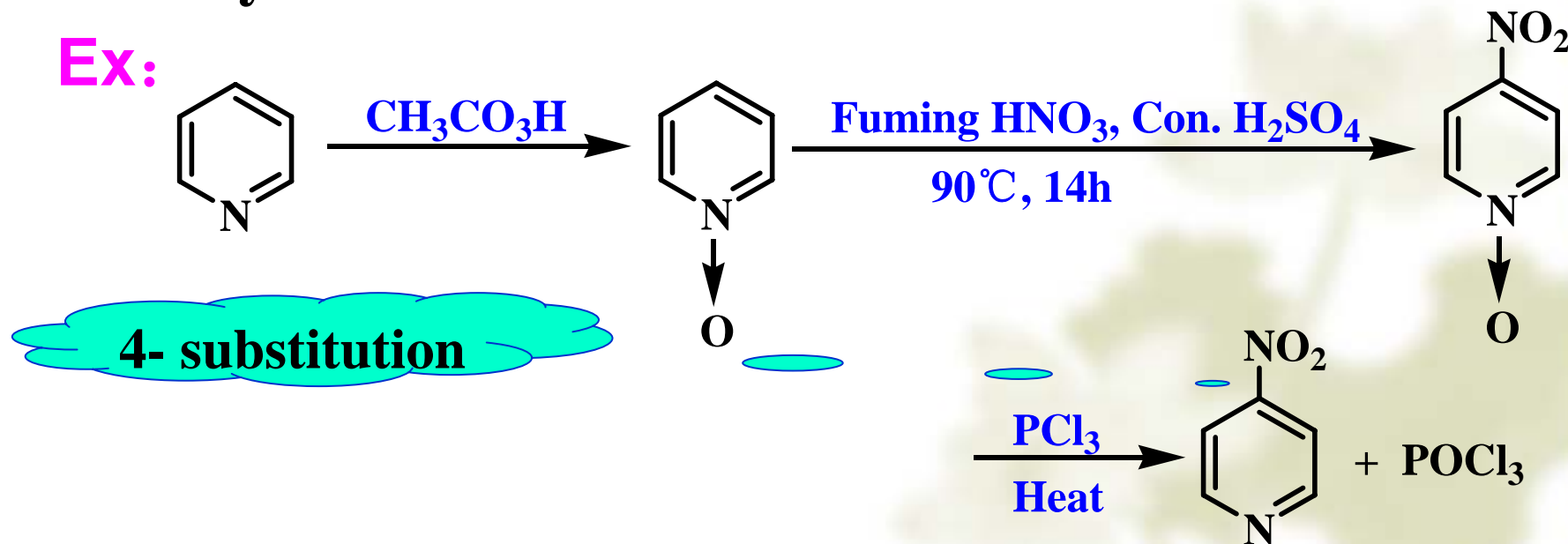
Nicotine is used as an agricultural insecticide but is also toxic to man; the fatal dose is about 40 mg.



Because of its resistance to oxidation, pyridine is commonly used as a solvent for chromium trioxide oxidations (Sarrett procedure).

However, under the proper conditions, the nitrogen is oxidized to the N-oxide, as are other tertiary amines.

Ex:

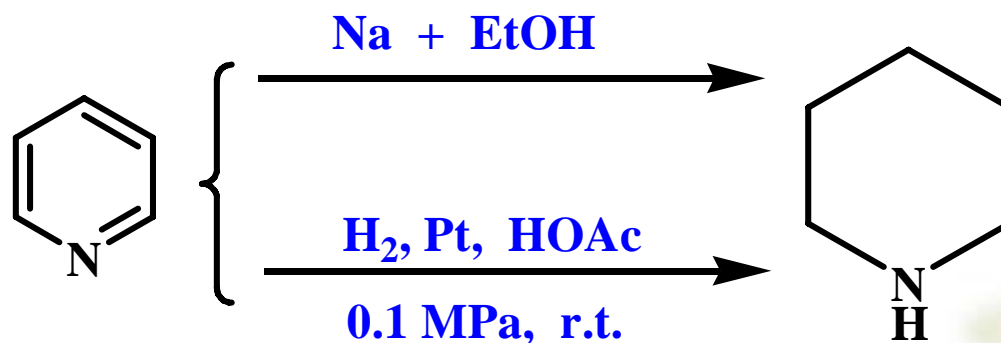




## 6. Reduction

Pridines are active to reductant than that of benzene.

Ex:



## **Review of Pyridine:**

**Aromaticity**

**Basicity**

**Nucleophilicity**

**Aromatic Electrophilic Substitution** ← 3, 5位

**Aromatic Nucleophilic Substitution** ← 2, 4位

**Chichibabin Reaction**

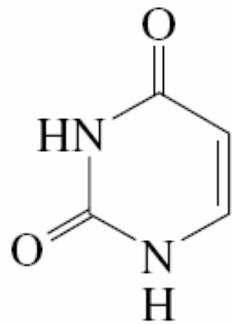
**Acidity of  $\alpha$ -methylpyridine**

**Synthesis of Pyridine**

## 18.3.2 Pyrimidine

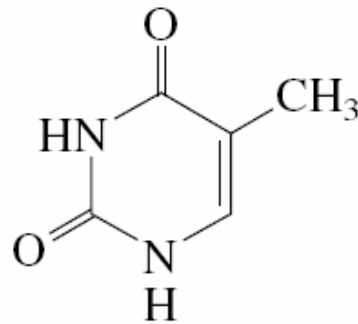
嘧啶碱性比吡啶弱得多，亲电取代较吡啶困难，亲核取代较吡啶容易得多。

在核酸的含氮碱基中有三种含嘧啶环。



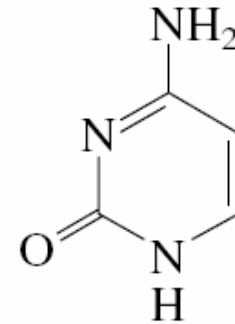
Uracil  
(occurs in RNA)

尿嘧啶



Thymine  
(occurs in DNA)

胸腺嘧啶

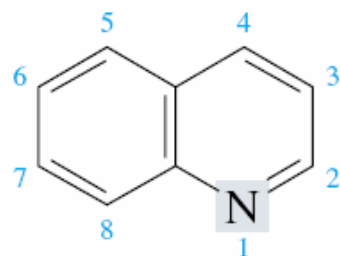


Cytosine  
(occurs in both RNA and DNA)

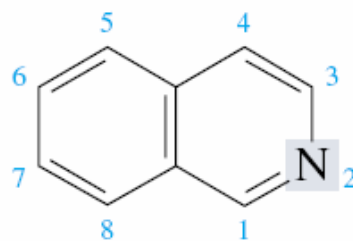
胞嘧啶

### 18.3.3 Quinoline and Isoquinoline

A benzene ring and a pyridine ring, for example, can share a common side in two different ways. One way gives a compound called *quinoline*; the other gives *isoquinoline*.



Quinoline



Isoquinoline

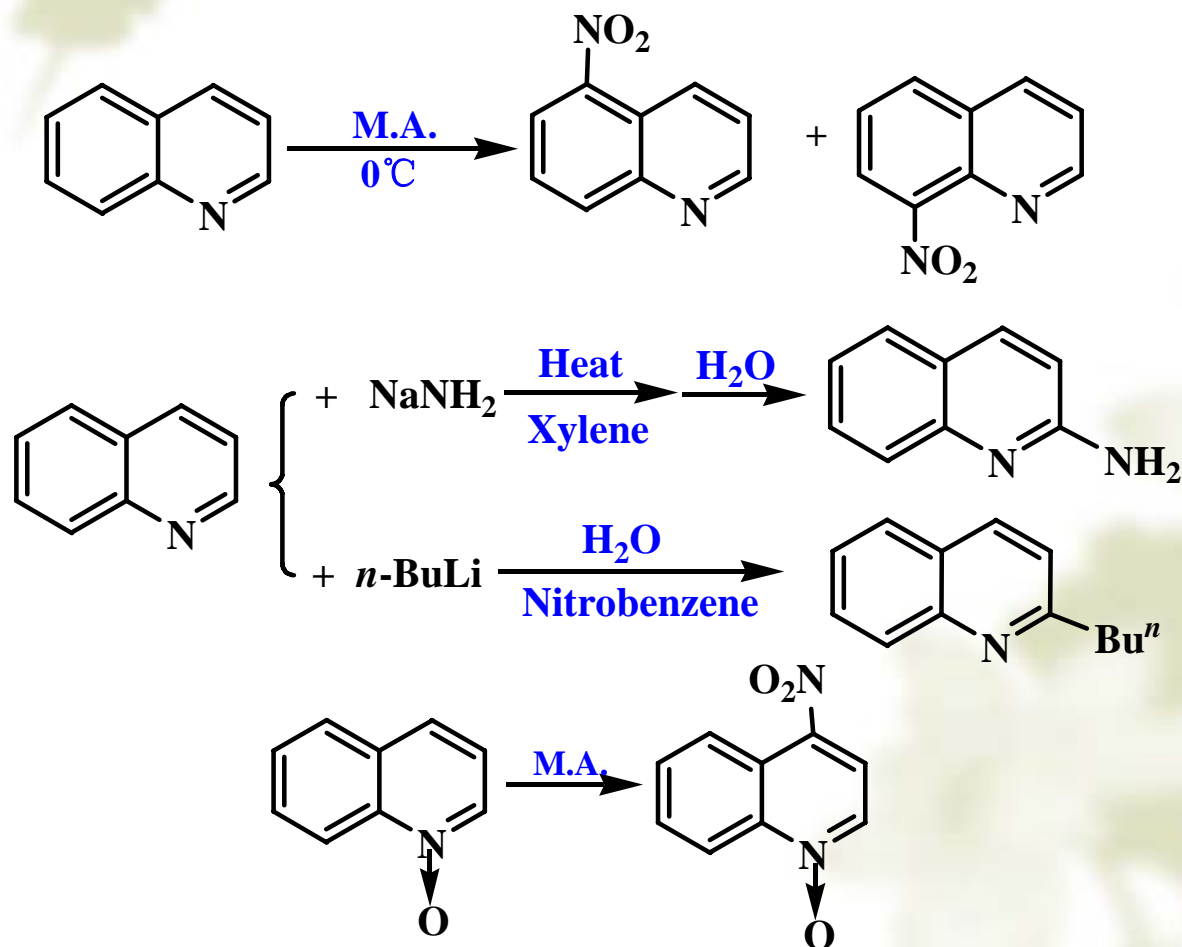
Alkaloids based on the quinoline and isoquinoline skeleton are widespread in the plant kingdom.

**Quinoline:** an oily liquid;  
soluble in many organic solvents;  
high boiling point;  
weak base.

**Basicity:** 脂肪胺 > 氨 > 芳香胺  
氨 > 异喹啉 > 吡啶 > 喹啉 > 吡咯

# 1. Substitution Reaction

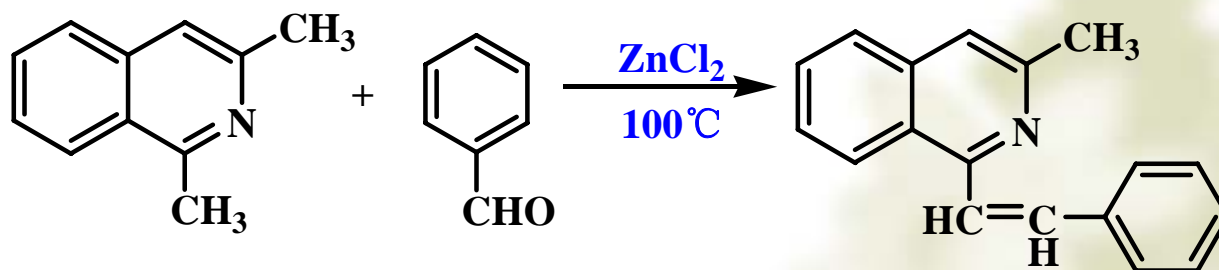
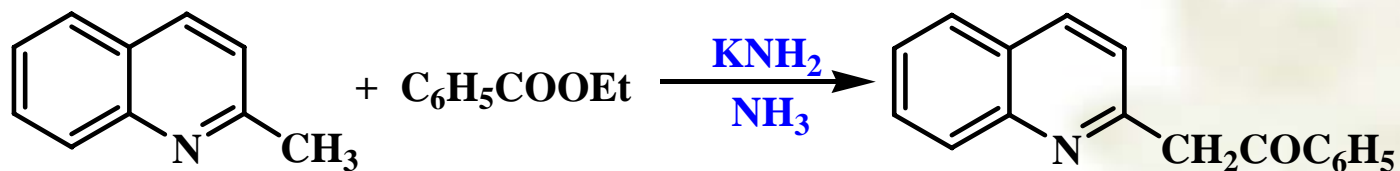
亲电取代主要发生在苯环的**5或8**位，而亲核取代主要在吡啶环的**2或4**位。



## 2. Acidity of $\alpha$ -Alkylquinolines

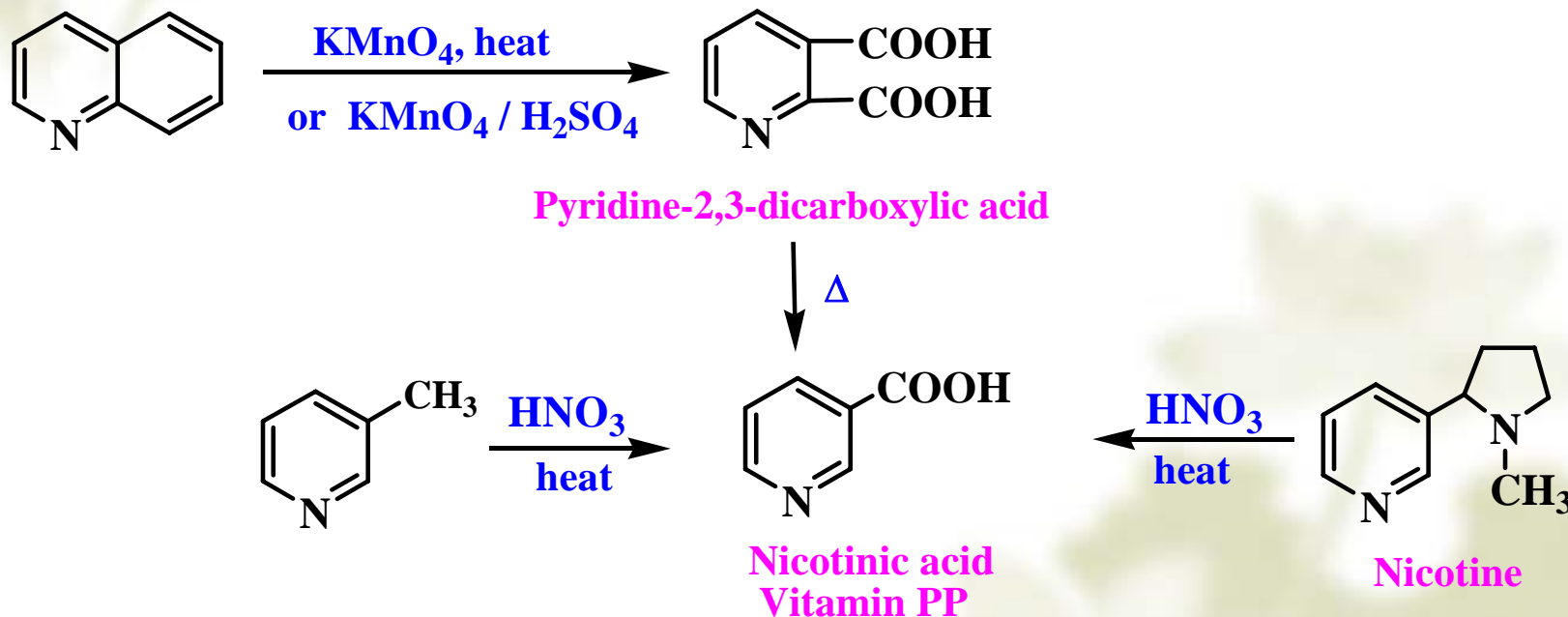
As with 2- and 4- alkylpyridines, 2- and 4-alkylquinolines and 1-alkylisoquinolines have  $\alpha$ -hydrogens that are significantly acidic and enter into base-catalyzed reactions.

Ex:



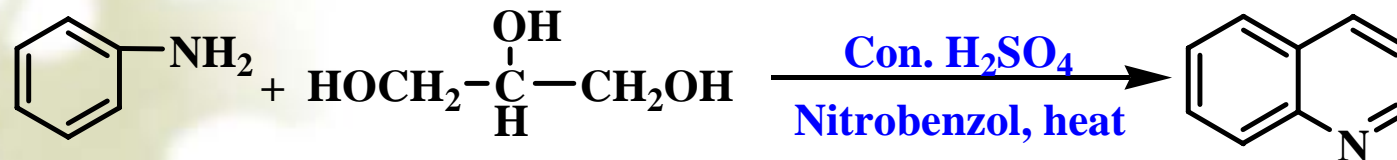
### 3. Oxidation

Pyridines are rather resistant to oxidation, and are more stable than benzene in the acidic oxidants.

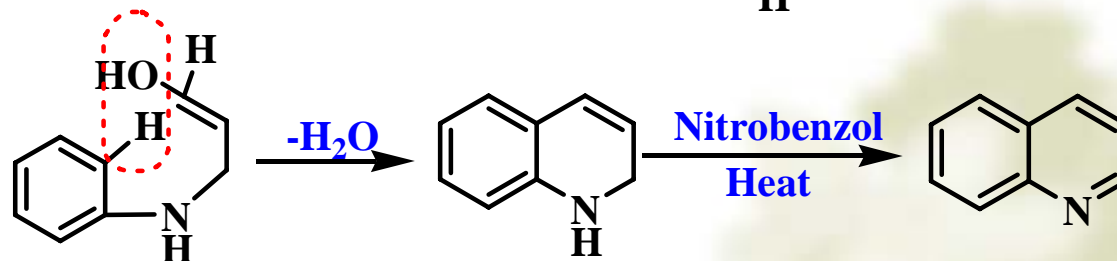
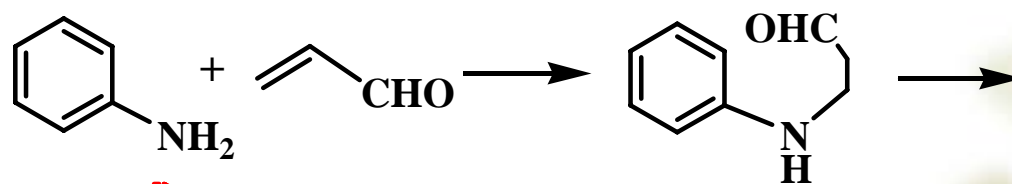
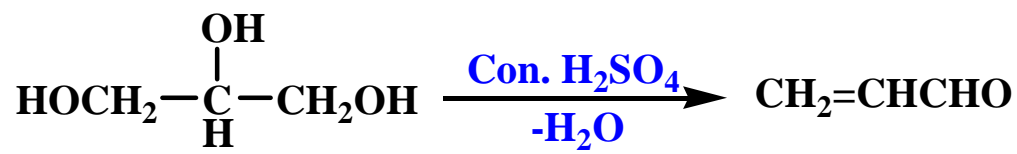




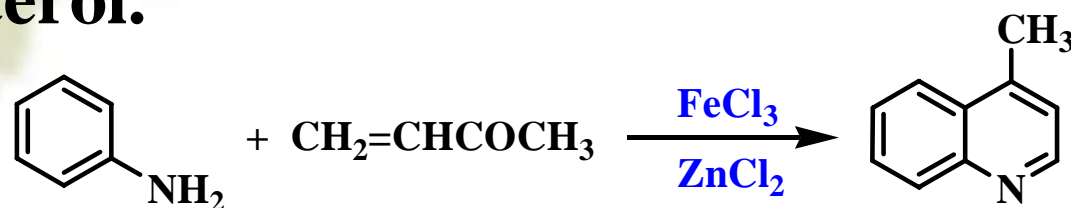
## 4. Synthesis: Skraup Reaction



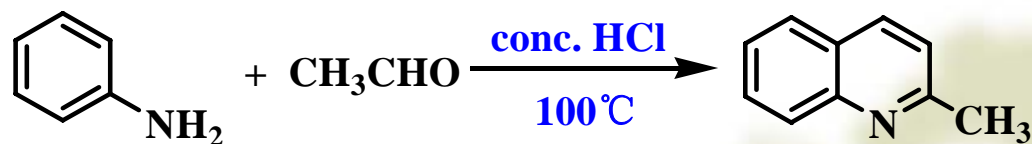
### Mechanism:



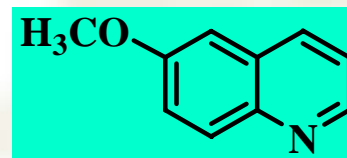
Identical results are obtained if an  $\alpha, \beta$ -unsaturated ketone or aldehyde is substituted for the glycerol.



If a saturated aldehyde is used, an initial aldol condensation occurs to give an  $\alpha, \beta$ -unsaturated aldehyde which engages in the normal condensation .

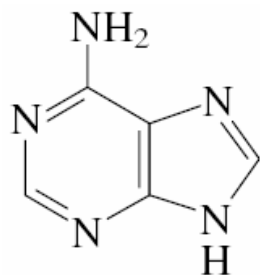


**Problem:** How to prepare ?

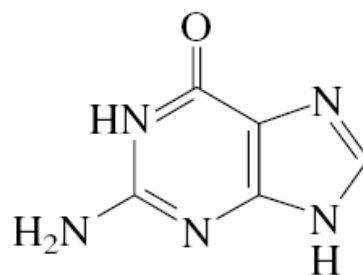


## 18.3.4 Purine

Adenine and guanine are the principal purines of both DNA and RNA.

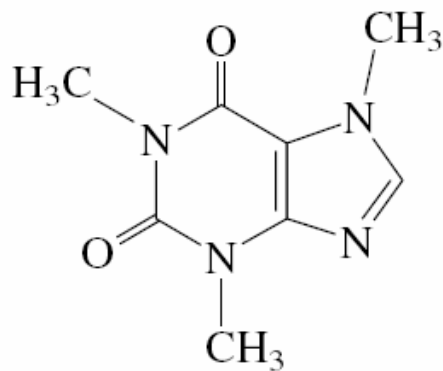


Adenine

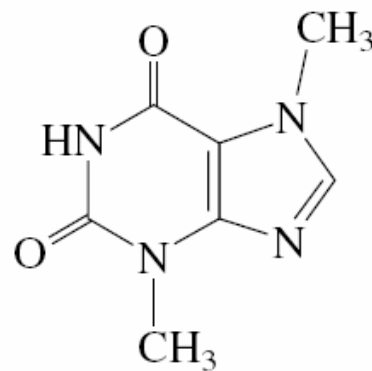


Guanine

Tea contains both caffeine and theobromine (可可碱).



Caffeine

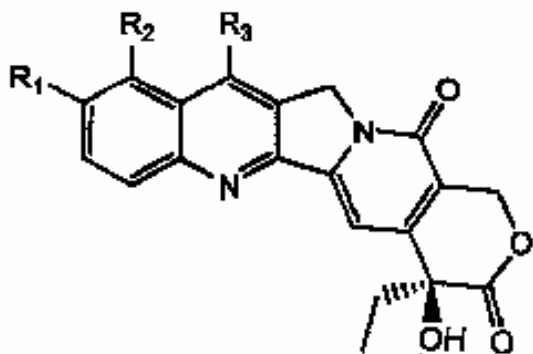


Theobromine

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## 18.4 Alkaloid

生物碱是一类存在于植物体内（偶尔亦在动物体内发现），对人体和动物有强烈生理作用的含氮碱性有机化合物。多数是含氮杂环。



1. CPT

$R_1=R_2=R_3=H$

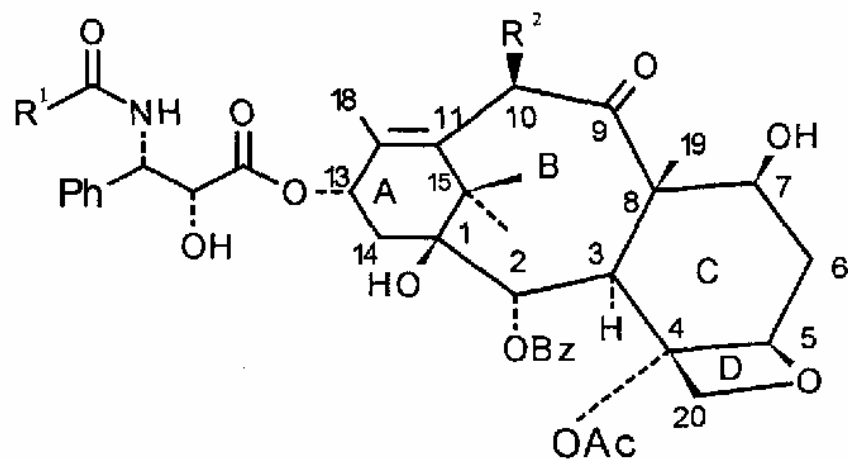
2. Irinotecan

$R_1 = \text{piperazine ring with } NCO^- \text{ group}, R_2=H, R_3=Et$

3. Topotecan

$R_1=OH, R_2=CH_2N(CH_3)_2, R_3=H$

喜树碱



1 : Taxol,  $R^1=Ph, R^2=OAc$

2 : Taxotere,  $R^1=t-BuO, R^2=OH$

紫杉醇

生物碱在植物体内常与有机酸结合而存在，也有和无机酸结合的。一般情况下，生物碱在植物中含量很低，当然也有特别高的，如：金鸡纳和黄连。



DATANG.NET

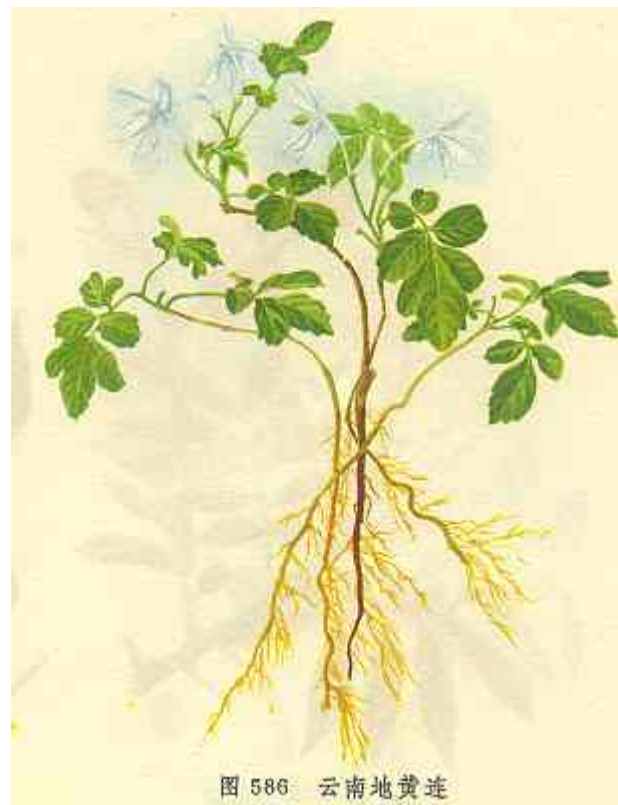


图 586 云南地黄连

### 18.4.1 一般性质

无色固体结晶（黄连素为黄色，烟碱为液体），有苦味，分子有手性碳，具有旋光作用。

**沉淀反应：**最灵敏的是碘化汞钾和碘化铋钾。  
检查中草药中生物碱的存在。

**颜色反应：**浓酸试剂（1% 钒酸铵的浓硫酸，1% 钼酸钠的浓硫酸，浓硝酸）

### 18.4.2 提取方法

植物细粉中的生物碱  $\xrightarrow{\text{酸}}$  生物碱成盐溶于水  $\longrightarrow$  浓缩  
 $\xrightarrow{\text{碱}}$  游离生物碱  $\xrightarrow{\text{有机溶剂}}$  结晶生物碱

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