Organic Chemistry III

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

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

25. Heterocycles

Rings are made up solely of carbon, called **carbocycles**, while **heterocycles** contain heteroatoms such as oxygen, nitrogen, and sulfur in their rings.

The heteroatom often causes heterocyclic compounds to exhibit special chemical behavior. Most physiologically active compounds owe their biological properties to the presence of heteroatoms, mainly in the form of heterocycles.

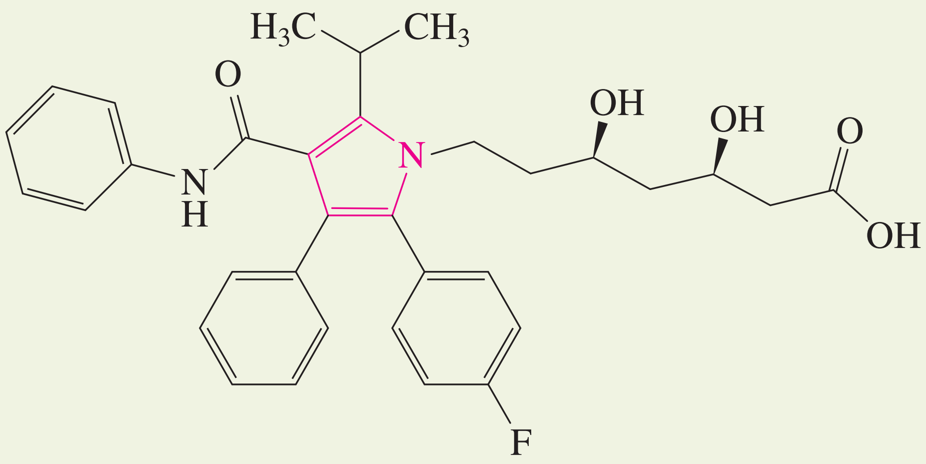
A majority of the known natural products are heterocyclic.

More than half the published chemical literature deals with such compounds.

The bases in DNA are heterocycles; so are many vitamins, such as B_1 (thiamine), B_2 (riboflavin), B_6 (pyridoxine), the spectacularly complex B_{12}, and vitamins C and E.

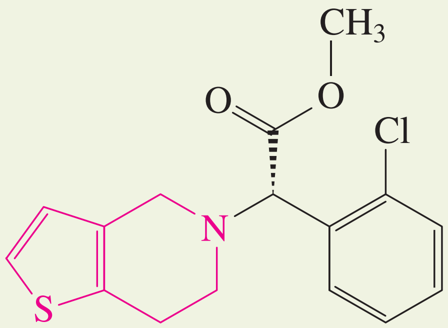
Table 25-1 Top Ten U.S. Prescription Drugs (Ranked by 2011 Sales) by Generic and, in Parentheses, Selected Brand Names[a]

1. Atorvastatin (Lipitor)



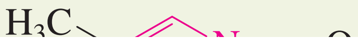
Cholesterol reducer

2. Clopidogrel (Plavix)

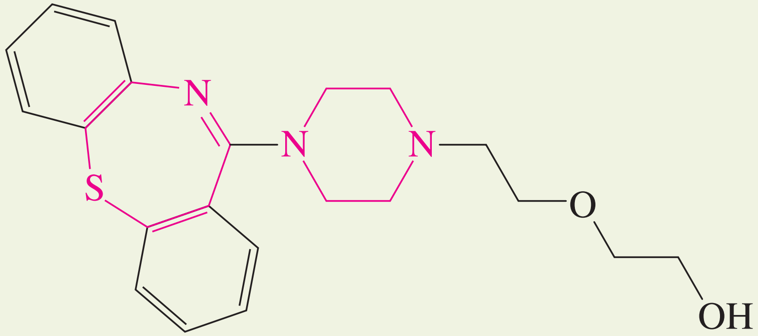


Antiplatelet agent

3. Esomeprazole (Nexium)

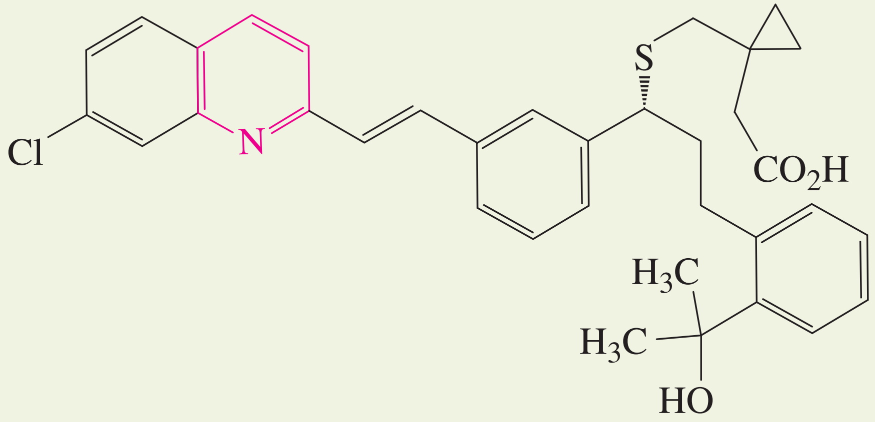


6. Quetiapine (Seroquel)



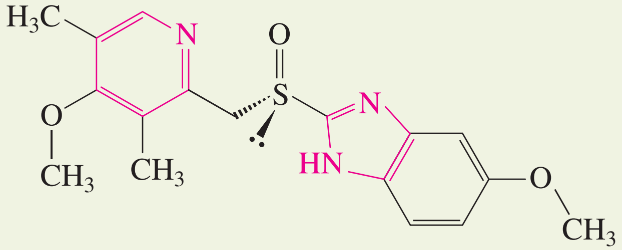
Antipsychotic

7. Montelukast (Singulair)



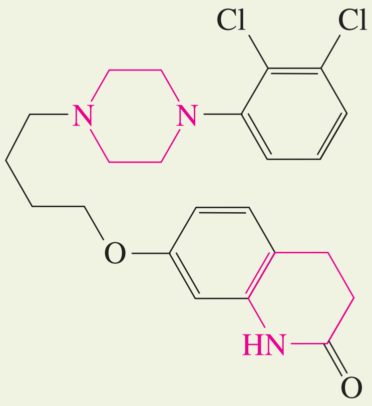
Antiasthmatic

3. Esomeprazole (Nexium)



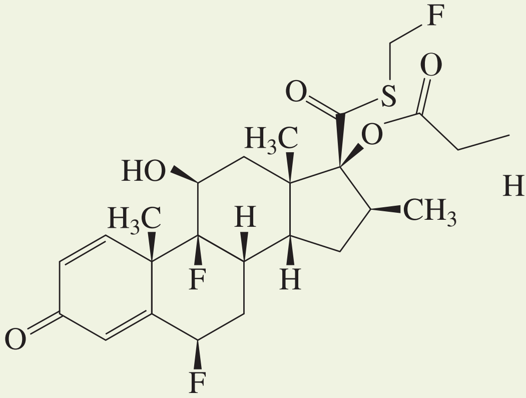
Stomach acid reducer

4. Aripiprazole (Abilify)

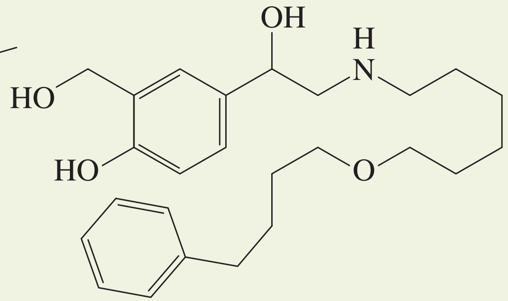


Antipsychotic

5. Fluticasone and salmeterol mixture (Advair Diskus)



Fluticasone

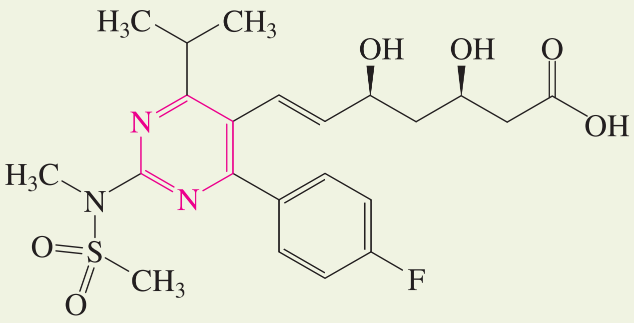


Salmeterol (Racemate)

Antiasthmatic

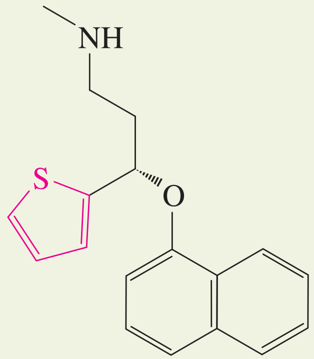
Antiasthmatic

8. Rosuvastatin (Crestor)



Cholesterol reducer

9. Duloxetine (Cymbalta)

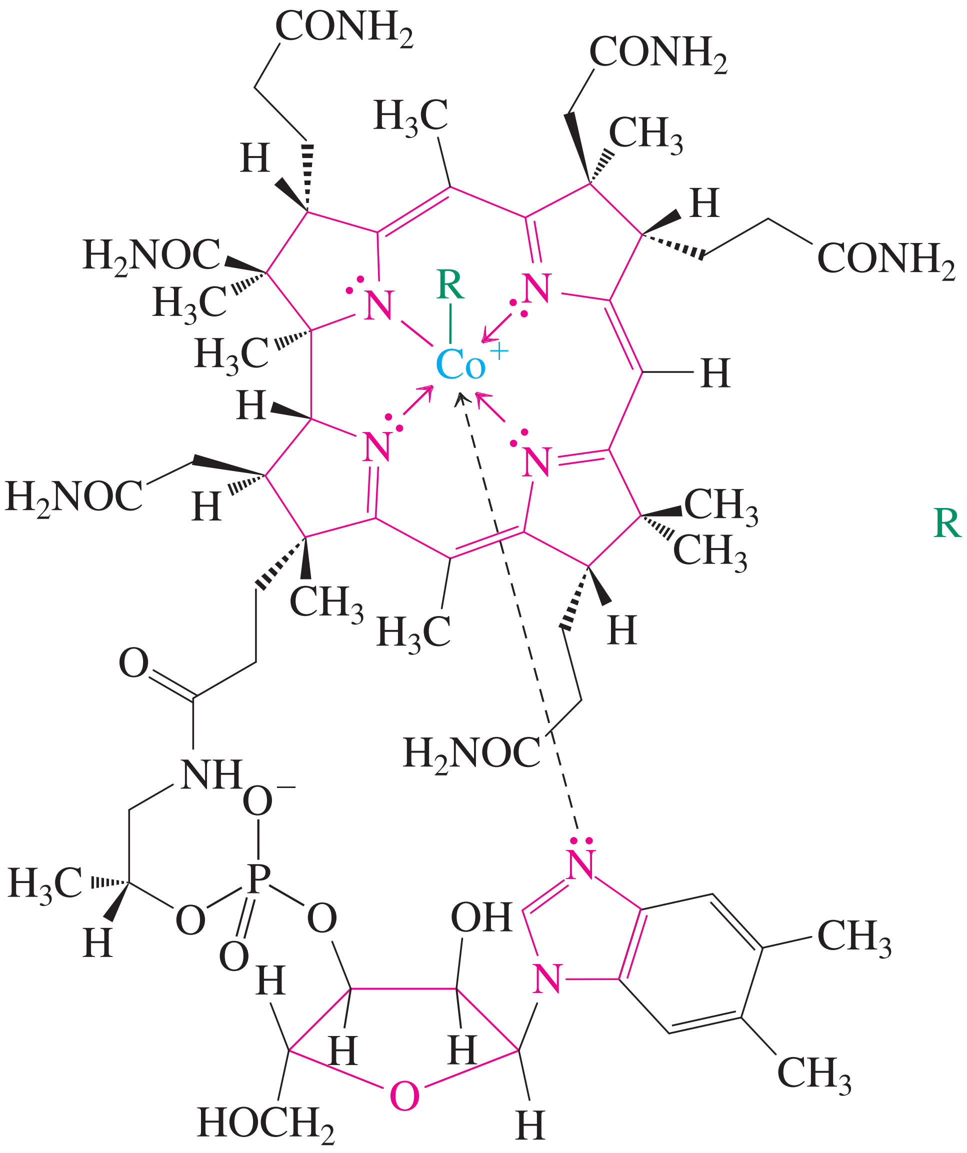


Antidepressant

10. Adalimumab (Humira)

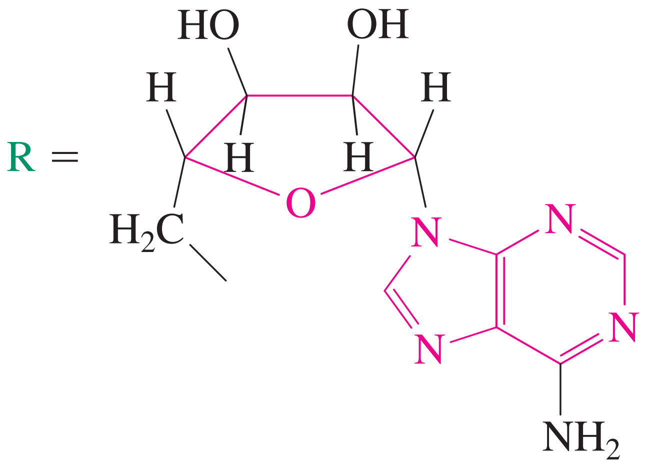
Monoclonal antibody

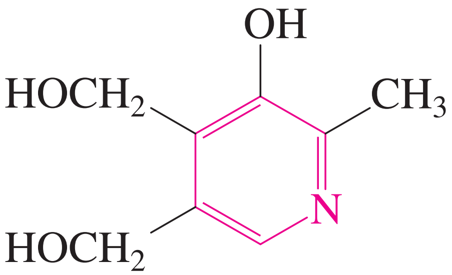
Antirheumatic



Vitamin B_{12}
(Cobalamin)

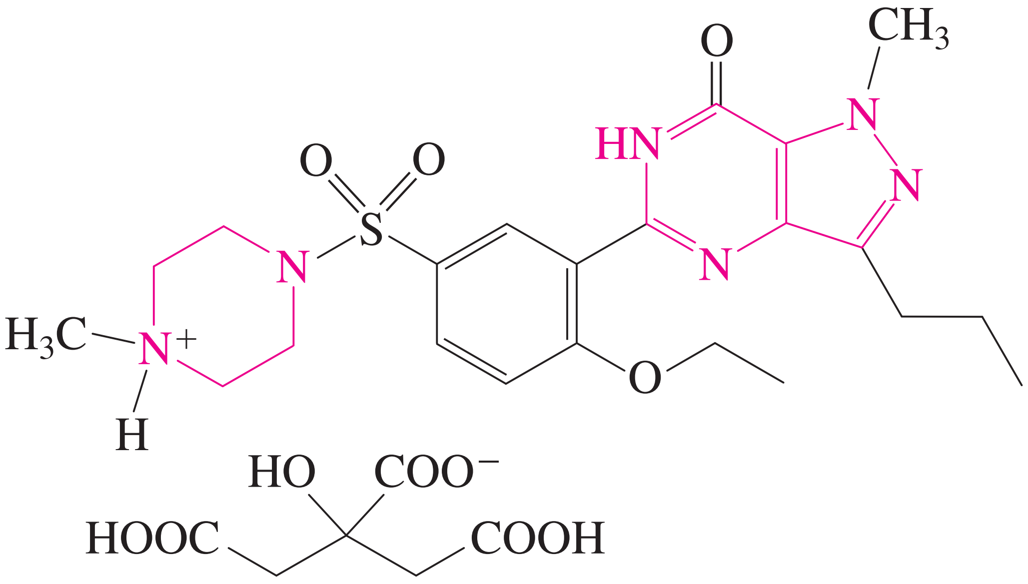
(Catalyzes biological rearrangements and methylations)



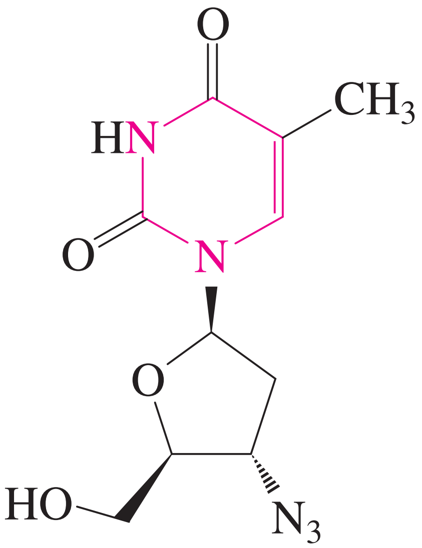


Pyridoxine, vitamin B_6

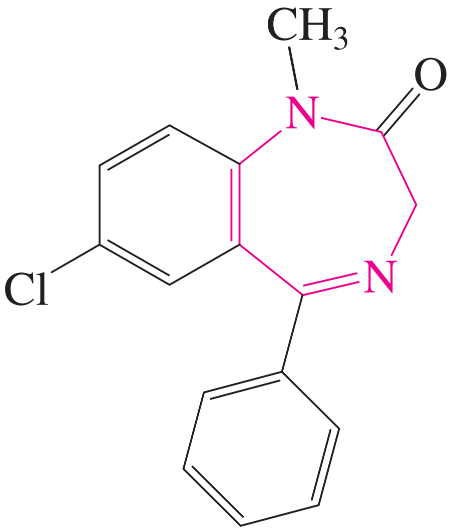
(Enzyme cofactor vitamin with multiple functions)



Sildenafil citrate
(Viagra)
(Treats erectile dysfunction; see also Worked Example 25-29)



Zidovudine
(AZT)
(Antiviral AIDS drug, see Real Life 26-3)



Diazepam
(Valium)
(Tranquilizer)

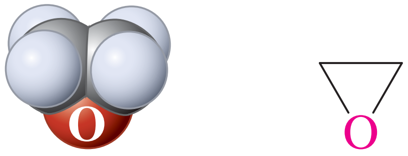
25-1 NAMING THE HETEROCYCLES

There are several competing systems for naming heterocycles, which is sometimes confusing. We shall adhere to the simplest system.

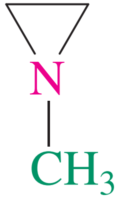
We regard saturated heterocycles as derivatives of the related carbocycles and use a prefix to denote the presence and identity of the heteroatom: **aza-** for nitrogen, **oxa-** for oxygen, **thia-** for sulfur, **phospha-** for phosphorus, and so forth.

Other widely used names will be given in parentheses.

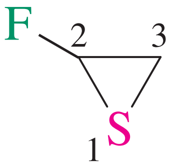
The location of substituents is indicated by numbering the ring atoms, starting with the heteroatom.



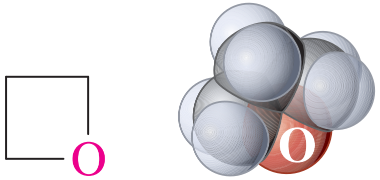
Oxacyclopropane
(Oxirane, ethylene oxide)



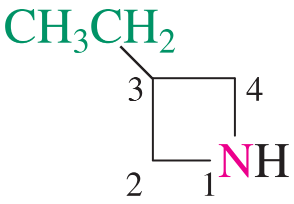
***N*-Methylazacyclopropane**
(*N*-Methylaziridine)



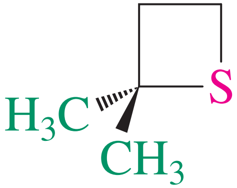
2-Fluorothiacyclopropane
(2-Fluorothiirane)



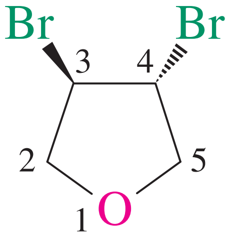
Oxacyclobutane
(Oxetane)



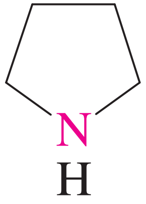
3-Ethylazacyclobutane
(3-Ethylazetidine)



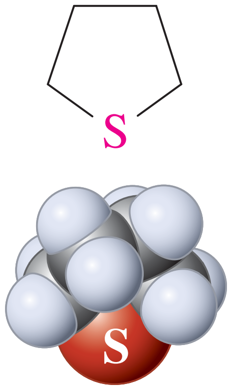
2,2-Dimethylthiacyclobutane
(2,2-Dimethylthietane)



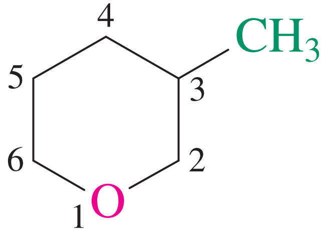
***trans*-3,4-Dibromooxacyclopentane**
(*trans*-3,4-Dibromotetrahydrofuran)



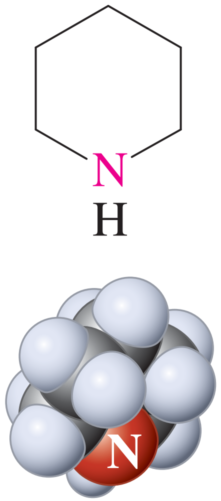
Azacyclopentane
(Pyrrolidine)



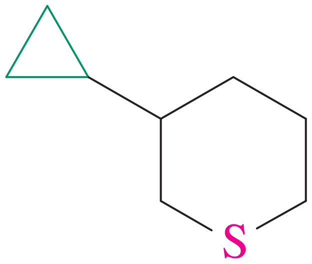
Thiacyclopentane
(Tetrahydrothiophene)



3-Methyloxacyclohexane
(3-Methyltetrahydropyran)

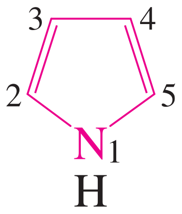


Azacyclohexane
(Piperidine)

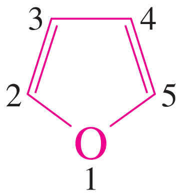


3-Cyclopropylthiacyclohexane
(3-Cyclopropyltetrahydrothiopyran)

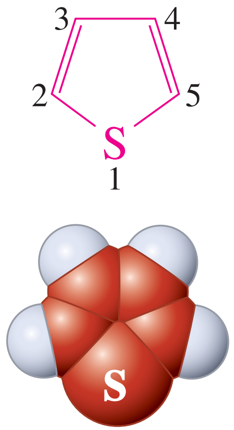
The common names of unsaturated heterocycles are so firmly entrenched in the literature that we shall use them here.



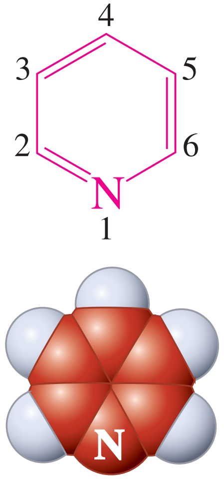
Pyrrole



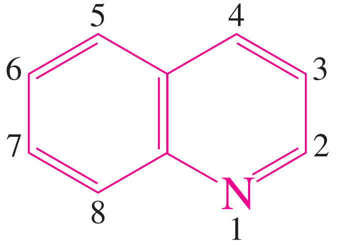
Furan



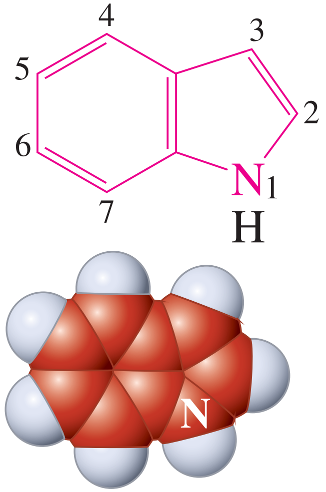
Thiophene



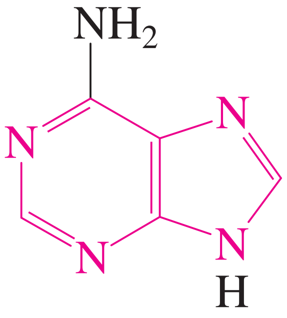
Pyridine



Quinoline



Indole



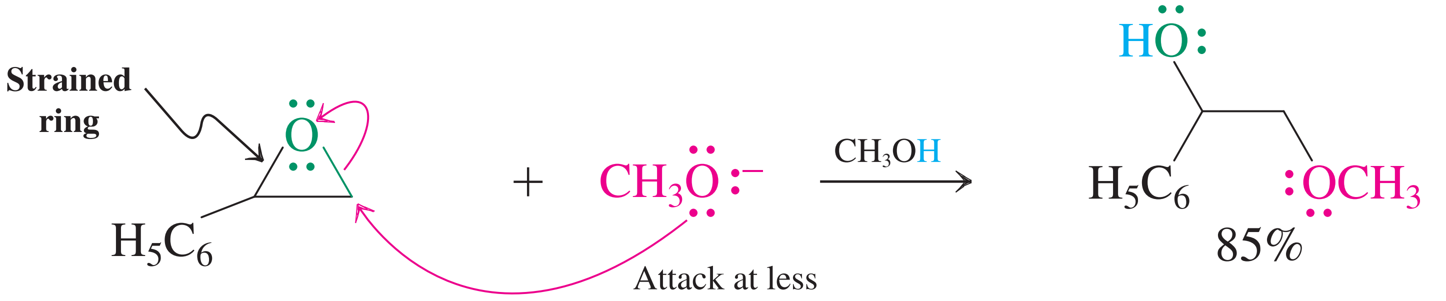
Adenine

(See Section 26-9)

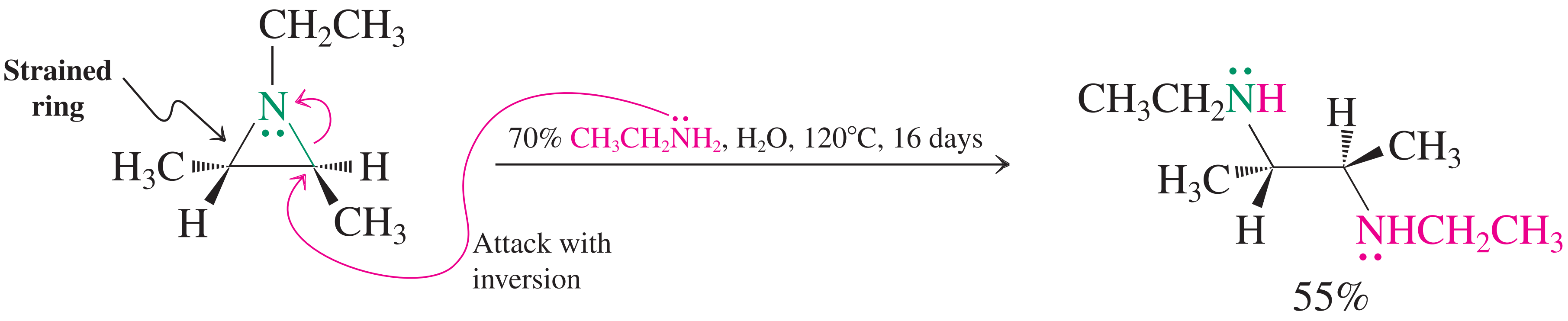
25-2 NONAROMATIC HETEROCYCLES

Ring strain allows the three- and four-membered heterocycles to undergo nucleophilic ring opening readily. In contrast, the larger, unstrained systems are relatively inert to attack.

Under basic conditions, the ring opening process gives rise to inversion at the less substituted center.



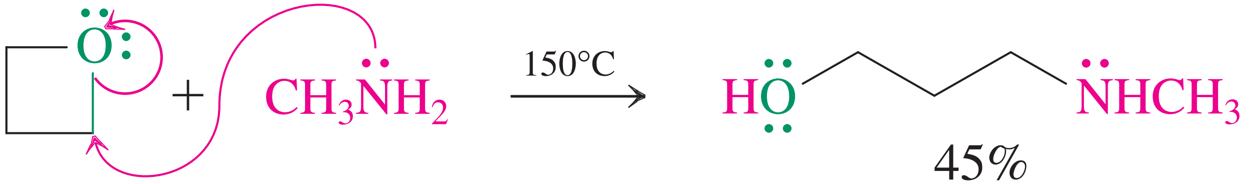
2-Phenyloxacyclopropane **2-Methoxy-1-phenylethanol**



***N*-Ethyl-(2*S*,3*S*)-*trans*-2,3-dimethylazacyclopropane**

***meso*-*N*,*N*′-Diethyl-2,3-butanediamine**

The four-membered heterocycloalkanes undergo ring opening, but more stringent reaction conditions are usually required.



***N*-Methyl-3-amino-1-propanol**

The β-lactam antibiotic penicillin functions through related ring-opening processes.

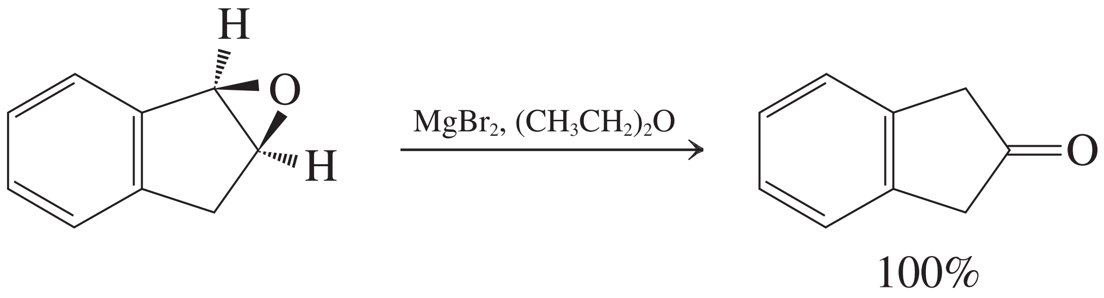
Heterocyclopentanes and heterocyclohexanes are relatively unreactive

The unstrained heterocycles are relatively inert. Oxacyclopentane (tetrahydrofuran, THF) is used as a solvent.

However, the heteroatoms in aza- and thiacycloalkanes allow for characteristic transformations. In general, ring opening occurs by conversion of the heteroatom into a good leaving group.

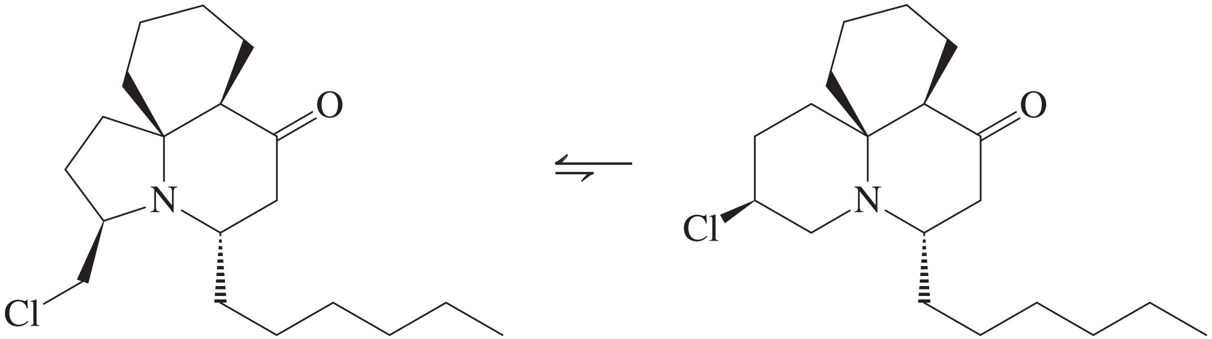
Exercise 25-2

Explain the following result by a mechanism. (**Caution:** This is not an oxidation. **Hints:** Calculate the molecular formulas of starting material and product. Try a ring opening catalyzed by the Lewis acid and consider the options available to the resulting intermediate.)

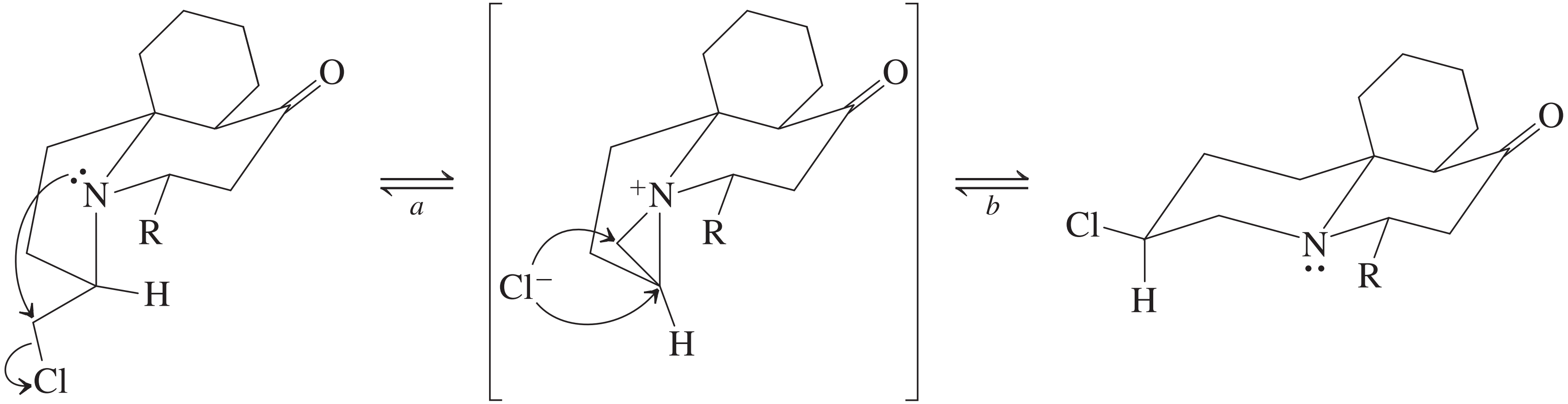


Solved Exercise 25-4

Isomeric cylindricines A and B, isolated in 1993, are the two main alkaloids present in extracts from the Australian marine plant *Clavelina cylindrica*. The two compounds equilibrate to a 3:2 mixture. Formulate a mechanism for this process. (**Hint:** Check Exercise 9-25.)



Cylindricine A **Cylindricine B**



Cylindricine A **A** **Cylindricine B**

25-3 STRUCTURES AND PROPERTIES OF AROMATIC HETEROCYCLOPENTADIENES

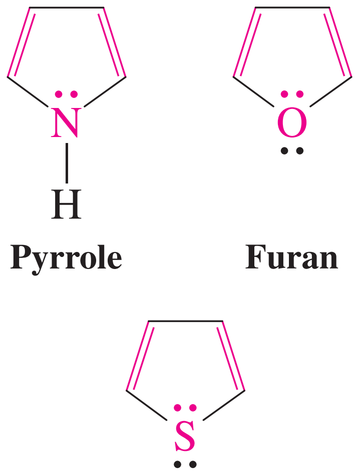
Pyrrole, furan, and **thiophene** are 1-hetero-2,4-cyclopentadienes. Each contains a butadiene unit bridged by an sp^2-hybridized heteroatom bearing lone electron pairs.

These systems contain delocalized π electrons in an aromatic six-electron framework.

The electronic structure of the three heterocycles pyrrole, furan, and thiophene is similar to that of the aromatic cyclopentadienyl anion.

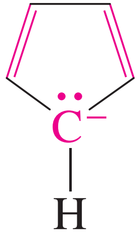
This anion may be viewed as a butadiene bridged by a negatively charged carbon whose electron pair is delocalized over the other four carbons.

Aromatic Heterocyclopentadienes



Pyrrole **Furan**

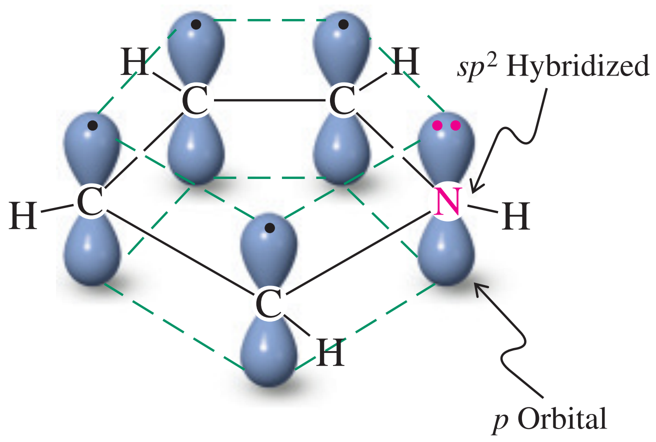
Thiophene



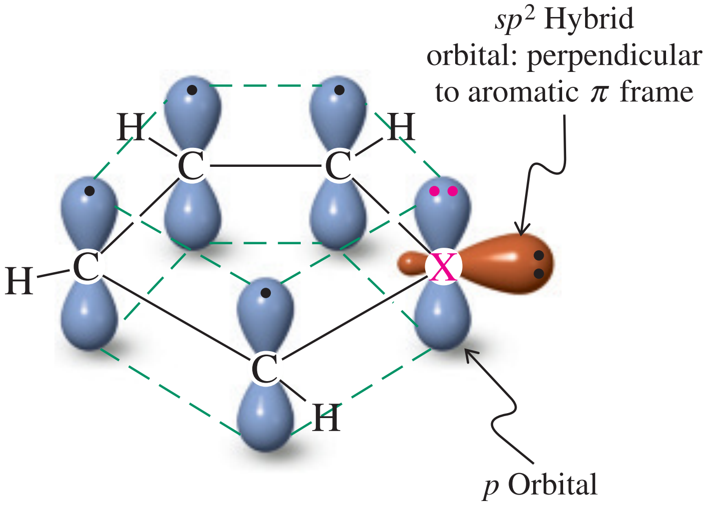
Cyclopentadienyl anion

The heterocyclics contain a neutral atom bearing lone electron pairs. One of these pairs is similarly delocalized, furnishing the two electrons needed to satisfy the 4*n*+2 rule.

To maximize overlap, the heteroatoms are hybridized *sp*², the delocalized electron pair is in *p* orbital. In pyrrole, the *sp*²-hybridized nitrogen bears a hydrogen substituent in the plane of the molecule. For furan and thiophene, the second lone electron pair is placed into one of the *sp*² hybrid orbitals, in the plane and therefore with no opportunity to achieve overlap.



Pyrrole



Furan (X = O)
Thiophene (X = S)

Pyrrole, furan, and thiophene exhibit properties of typical of aromatic compounds, such as unusual stability, deshielded protons in the ^{1}H NMR spectra (due to the presence of ring currents), and the ability to undergo electrophilic aromatic substitution.

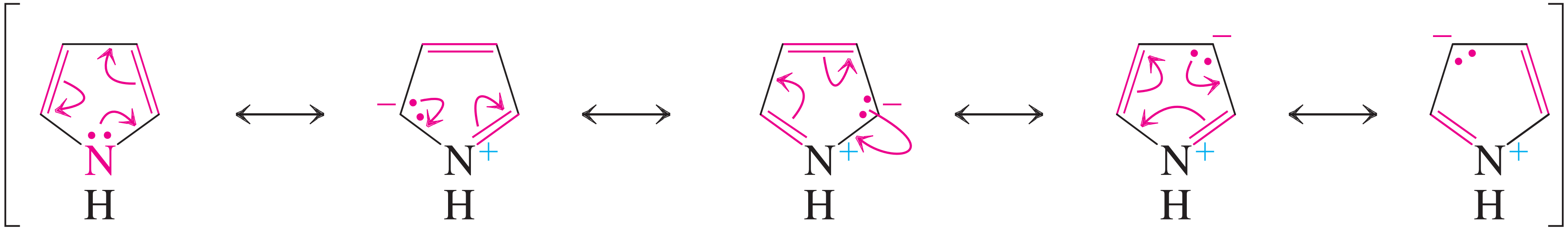
The delocalization of the lone pair in the 1-hetero-2,4-cyclopentadienes can be described by charge-separated resonance forms, as shown for pyrrole.

There are four dipolar forms in which a positive charge is placed on the heteroatom and a negative charge successively on each of the carbons.

It is suggested that the heteroatom should be relatively electron poor and the carbons relatively electron rich.

The nitrogen in pyrrole is less electron rich than that in its saturated counterpart azacyclopentane, whereas the diene portion in pyrrole is more electron rich than that in 1,3-cyclopentadiene.

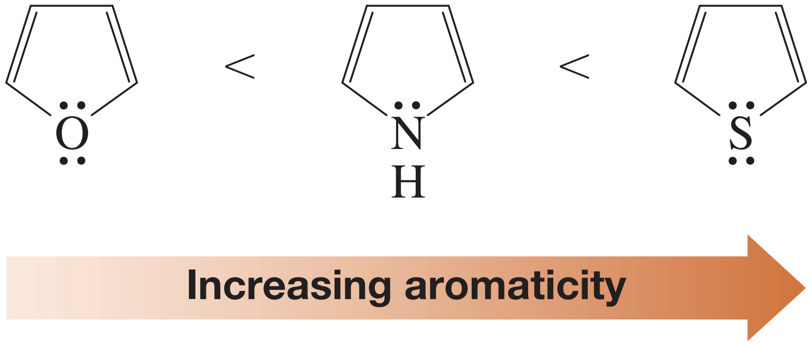
Resonance Forms of Pyrrole



The extent of aromaticity in these systems depends on the relative ability of the heteroatom to donate its lone electron pair, in turn described by its respective electronegativity.

Consequently, the aromatic character increases from furan to pyrrole to thiophene, a trend that is reflected in relative reactivity and stability.

Aromaticity in Heterocyclopentadienes

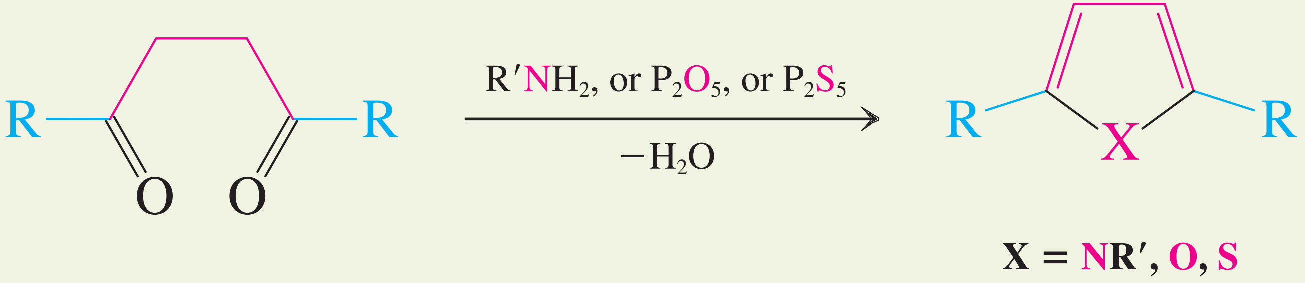


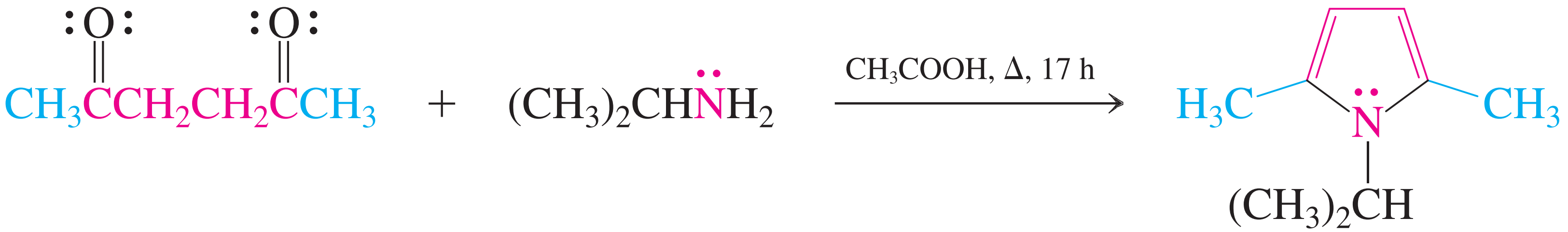
Pyrroles, furans, and thiophenes are prepared from γ-dicarbonyl compounds

Syntheses of the heterocyclopentadienes use a variety of cyclization strategies. A general approach is the **Paal-Knorr synthesis**.

The target molecule is made from an enolizable γ-dicarbonyl compound that is treated with an amine derivative (for pyrroles) or P_2O_5 (for furans) or P_2S_5 (for thiophenes).

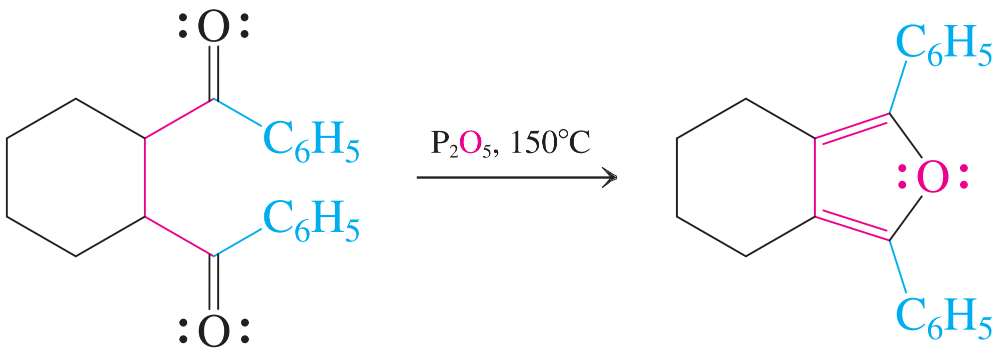
Cyclization of a γ-Dicarbonyl Compound to a 1-Hetero-2,4-cyclopentadiene



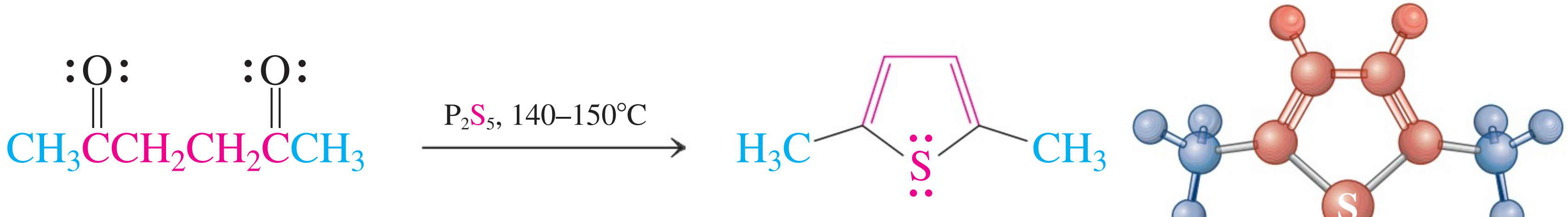


70%

N-(1-Methylethyl)-
2,5-dimethylpyrrole



62%



60%

2,5-Dimethylthiophene

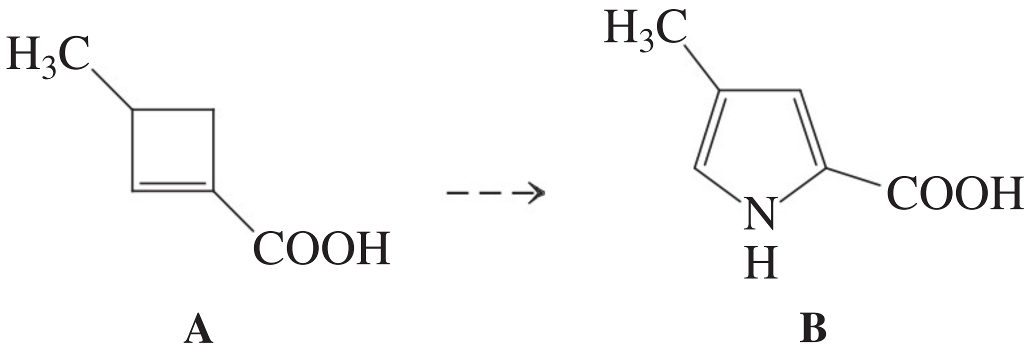
Exercise 25-8

Azacyclopentane and pyrrole are both polar molecules. However, the dipole vectors in the two molecules point in opposite directions. What is the sense of direction of this vector in each structure? Explain your answer.

Exercise 25-10

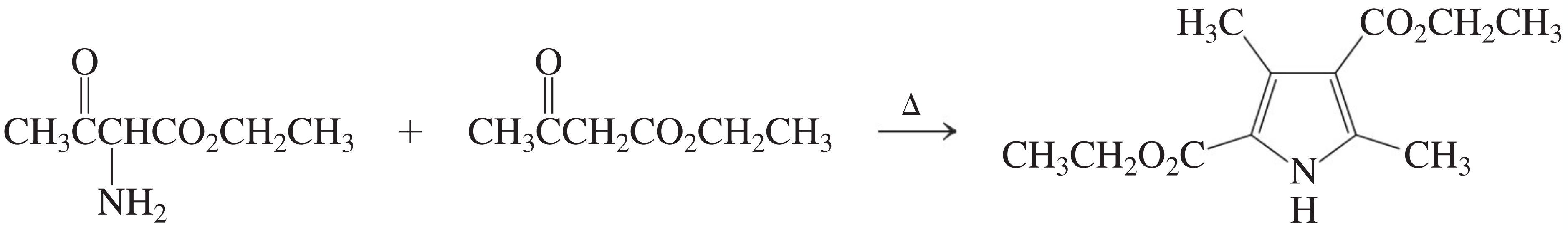
4-Methylpyrrole-2-carboxylic acid (compound B) is the trail pheromone of the ant species *Atta texana*. A third of a milligram has been estimated to be sufficient to mark a path around Earth, and each ant carries only 3.3 ng (10^{-9} g).

Propose a synthesis starting from 3-methylcyclobutene-1-carboxylic acid (compound A). (**Hint:** What dione is the retrosynthetic precursor to compound B, and how can you make it from compound A?)



Exercise 25-11

The following equation is an example of another synthesis of pyrroles. Write a mechanism for this transformation. (**Hint:** Refer to Section 17-9.)



Ethyl 2-amino-3-oxobutanoate **Ethyl 3-oxobutanoate** **Diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate**

25-4 REACTIONS OF THE AROMATIC HETEROCYCLOPENTADIENES

The reactivity of pyrrole, furan, and thiophene and their derivatives is governed largely by their aromaticity and is based on the chemistry of benzene.

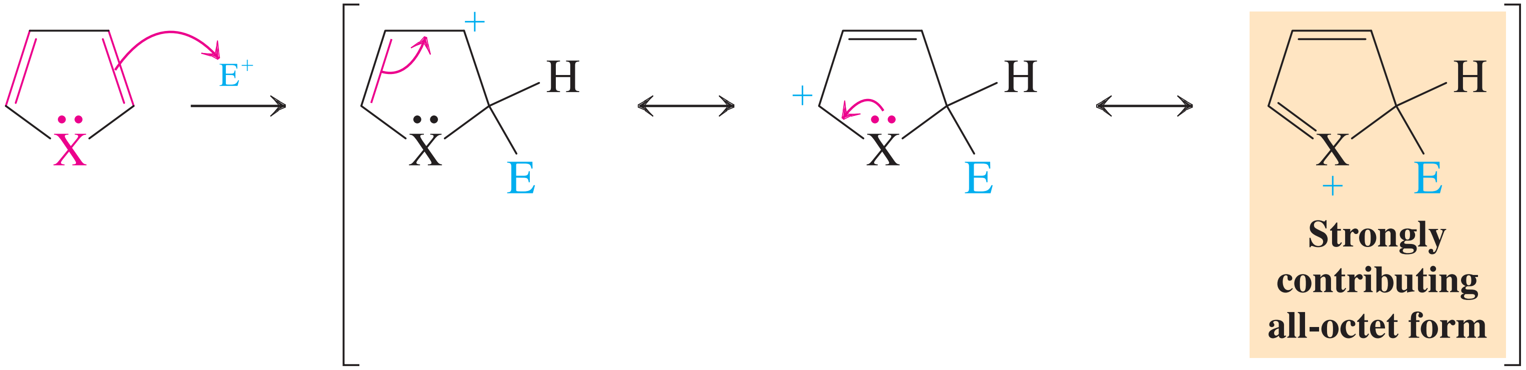
Pyrroles, furans, and thiophenes undergo electrophilic aromatic substitution

There are two sites of possible attack, at C2 and at C3. Which one should be more reactive?

An answer can be found by the same procedure used to predict the regioselectivity of electrophilic aromatic substitution of substituted benzenes: enumeration of all the possible resonance forms for the two modes of reaction.

Consequences of Electrophilic Attack at C2 and C3 in the Aromatic Heterocyclopentadienes

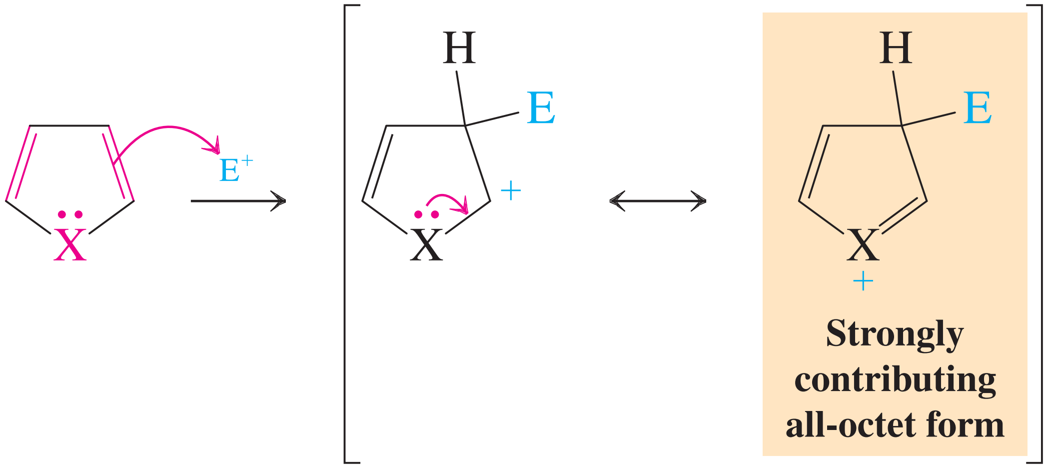
Attack at C2



Strongly contributing all-octet form

Three resonance forms

Attack at C3

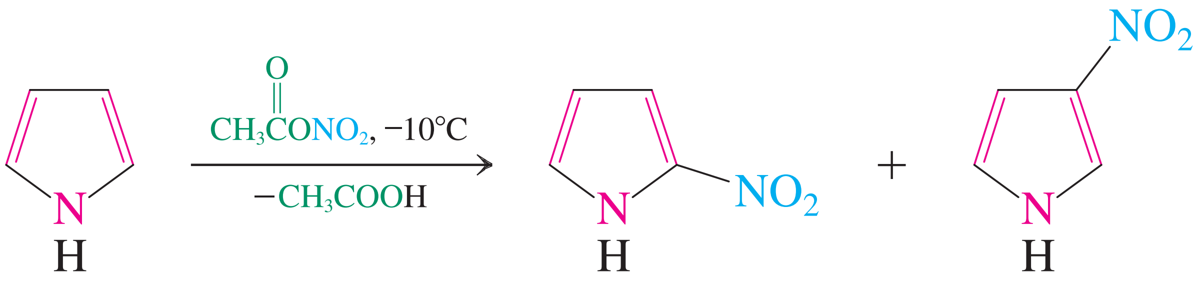


Strongly contributing all-octet form

Two resonance forms

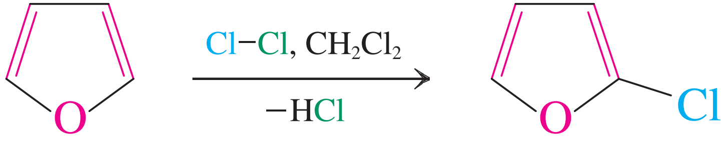
Both modes benefit from the presence of the resonance-contributing heteroatom, but attack at C2 leads to an intermediate with an additional resonance form, thus indicating this position to be the preferred site of substitution.

However, because C3 also is activated to electrophilic attack, mixtures of products can form, depending on conditions, substrates, and electrophiles.

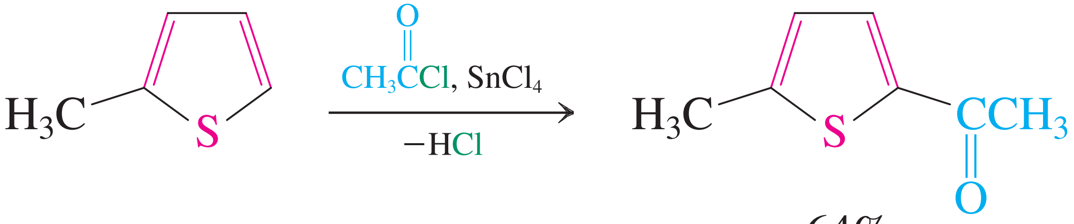


50% **2-Nitropyrrole**

13% **3-Nitropyrrole**



64%
2-Chlorofuran



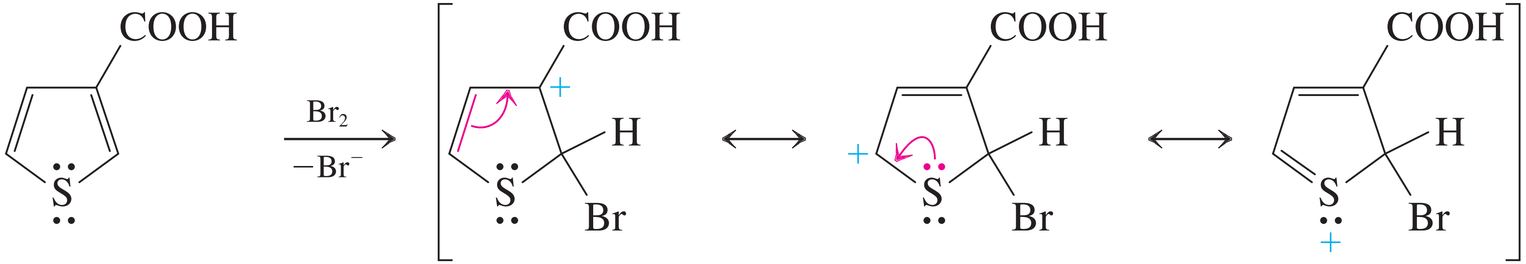
64%
2-Acetyl-5-methylthiophene

Solved Exercise 25-12

The monobromination of thiophene-3-carboxylic acid gives only one product. What is its structure, and why is it the only product formed?

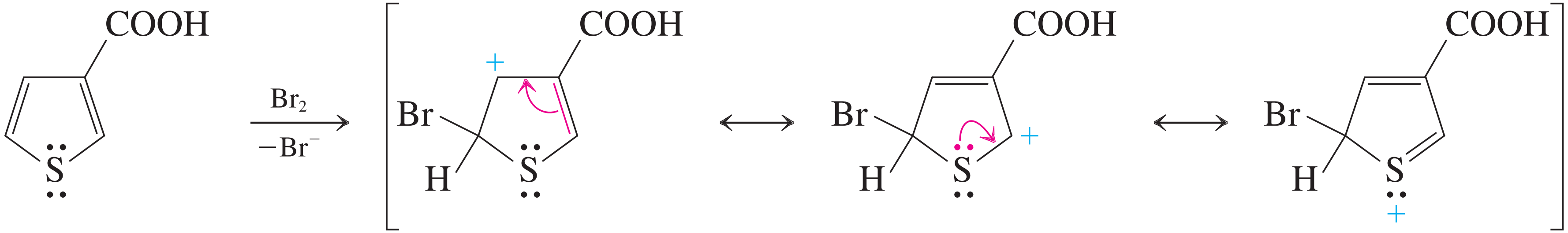
Solution

- Attack at C2



A

- Attack at C5



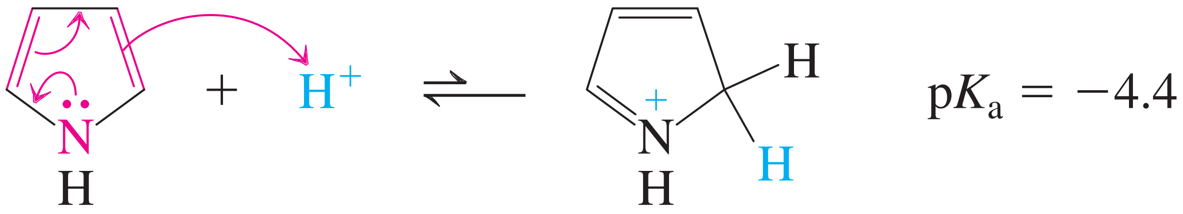
The relative reactivity of benzene and the three heterocycles in electrophilic substitutions is the result of contributions from the aromaticity of the respective rings and the stabilization of the intermediate cations.

It increases in the order benzene ≪ thiophene < furan < pyrrole.

Pyrrole is extremely nonbasic compared to ordinary amines, because the lone electron pair on nitrogen is tied up by conjugation.

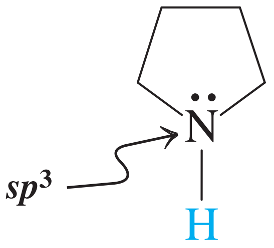
Very strong acid is required to effect protonation, and it takes place on C2, not on the nitrogen.

The Protonation of Pyrrole Occurs on Carbon



Pyrroles are not only very nonbasic, they are, in fact, relatively acidic. Thus, while azacyclopentane has a pK_a = 35 (normal for an amine), the corresponding value for pyrrole is 16.5!

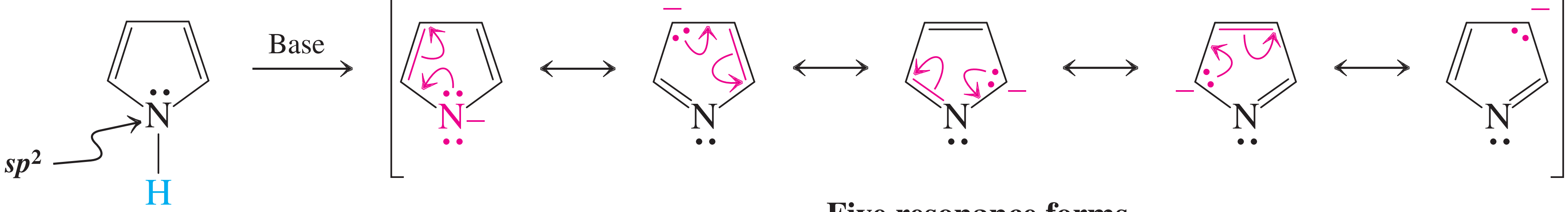
The reasons for this increase in acidity are the change in hybridization from *sp*^{3} to *sp*^{2} and the delocalization of the negative charge (as in cyclopentadienyl anion).



pK_a = 35

Azacyclopentane

Pyrrole Is Relatively Acidic



pK_a = 16.5

Five resonance forms