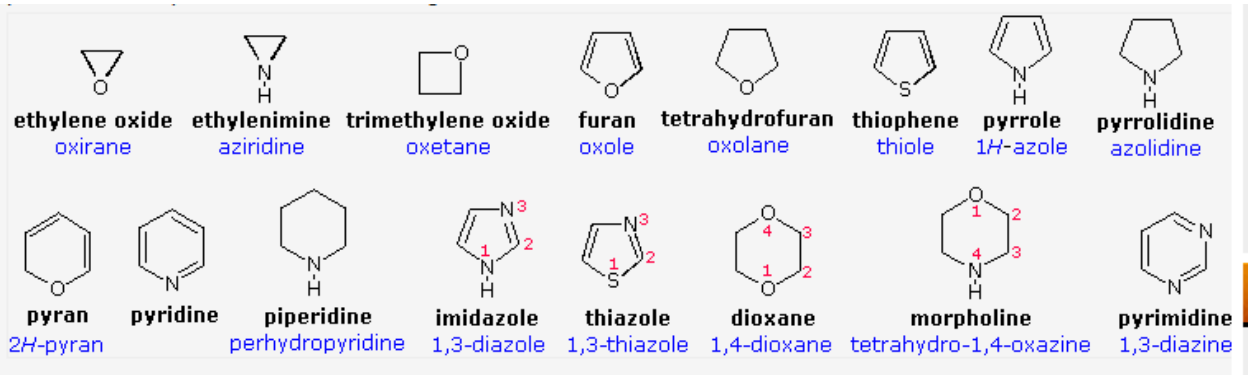
Heterocyclic Compounds

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most common heterocyclic elements), the permutations and combinations of such a replacement are numerous.

Nomenclature

Devising a systematic nomenclature system for heterocyclic compounds presented a formidable challenge, which has not been uniformly concluded. Many heterocycles, especially amines, were identified early on, and received trivial names which are still preferred. Some monocyclic compounds of this kind are shown in the following chart, with the common (trivial) name in bold and a systematic name based on the Hantzsch-Widman system given beneath it in blue. The rules for using this system will be given later. For most students, learning these common names will provide an adequate nomenclature background.



An easy to remember, but limited, nomenclature system makes use of an elemental prefix for the heteroatom followed by the appropriate carbocyclic name. A short list of some common prefixes is given in the following table, priority order increasing from right to left. Examples of this nomenclature are: ethylene oxide = oxacyclopropane, furan = oxacyclopenta-2,4-diene, pyridine = azabenzene, and morpholine = 1-oxa-4-azacyclohexane.

Element	oxygen	sulfur	selenium	nitrogen	phosphorous	silicon	boron
Valence	II	II	II	III	III	IV	III
Prefix	Oxa	Thia	Selena	Aza	Phospha	Sila	Bora

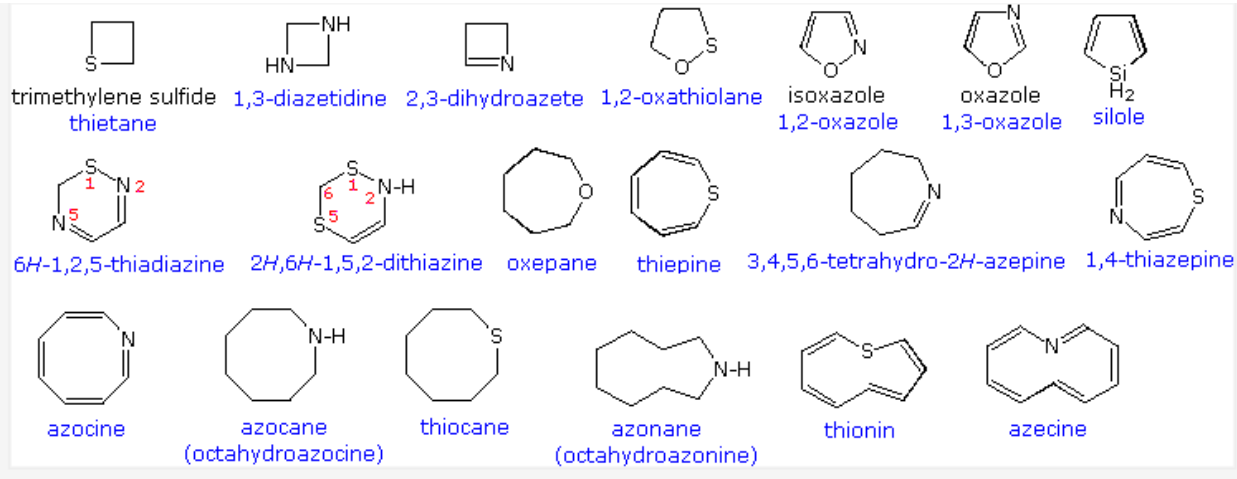
The **Hantzsch-Widman** system provides a more systematic method of naming heterocyclic compounds that is not dependent on prior carbocyclic names. It makes use of the same hetero atom prefix defined above (dropping the final "a"), followed by a suffix designating ring size and saturation. As outlined in the following table, each suffix consists of a ring size root (blue) and an ending intended to designate the degree of unsaturation in the ring. In this respect, it is important to recognize that the saturated suffix applies only to **completely saturated ring systems**, and the unsaturated suffix applies to rings incorporating **the maximum number of non-cumulated double bonds**. Systems having a lesser degree of unsaturation require an appropriate prefix, such as "dihydro"or "tetrahydro".

Ring Size	3	4	5	6	7	8	9	10
Suffix								
Unsaturated	**ir**ene	**et**e	**ol**e	**in**e	**ep**ine	**oc**ine	**on**ine	**ec**ine
Saturated	**ir**ane	**et**ane	**ol**ane	**in**ane	**ep**ane	**oc**ane	**on**ane	**ec**ane

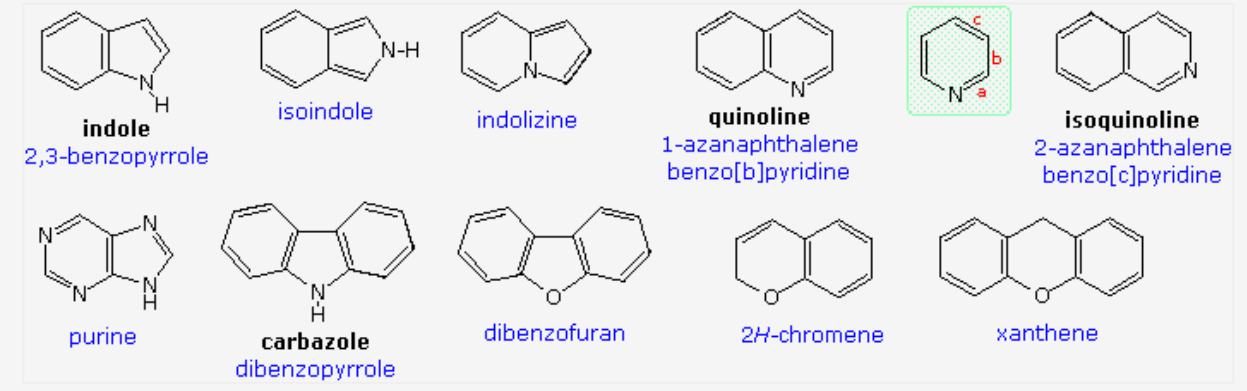
Despite the general systematic structure of the Hantzsch-Widman system, several exceptions and modifications have been incorporated to accommodate conflicts with prior usage. Some examples are:

- The terminal "e" in the suffix is optional though recommended.
- Saturated 3, 4 & 5-membered nitrogen heterocycles should use respectively the traditional "iridine", "etidine" & "olidine" suffix.
- Unsaturated nitrogen 3-membered heterocycles may use the traditional "irine" suffix.
- Consistent use of "etine" and "oline" as a suffix for 4 & 5-membered unsaturated heterocycles is prevented by their former use for similar sized nitrogen heterocycles.
- Established use of oxine, azine and silane for other compounds or functions prohibits their use for pyran, pyridine and silacyclohexane respectively.

Examples of these nomenclature rules are written in blue, both in the previous diagram and that shown below. Note that when a maximally unsaturated ring includes a saturated atom, its location may be designated by a "#*H* " prefix to avoid ambiguity, as in pyran and pyrrole above and several examples below. When numbering a ring with more than one heteroatom, the highest priority atom is #1 and continues in the direction that gives the next priority atom the lowest number.



All the previous examples have been monocyclic compounds. Polycyclic compounds incorporating one or more heterocyclic rings are well known. A few of these are shown in the following diagram. As before, common names are in black and systematic names in blue. The two quinolines illustrate another nuance of heterocyclic nomenclature. Thus, the location of a fused ring may be indicated by a lowercase letter which designates the edge of the heterocyclic ring involved in the fusion, as shown by the pyridine ring in the green shaded box.



Heterocyclic rings are found in many naturally occurring compounds. Most notably, they compose the core structures of mono and polysaccharides, and the four DNA bases that establish the genetic code. By clicking on the above diagram some other examples of heterocyclic natural products will be displayed.

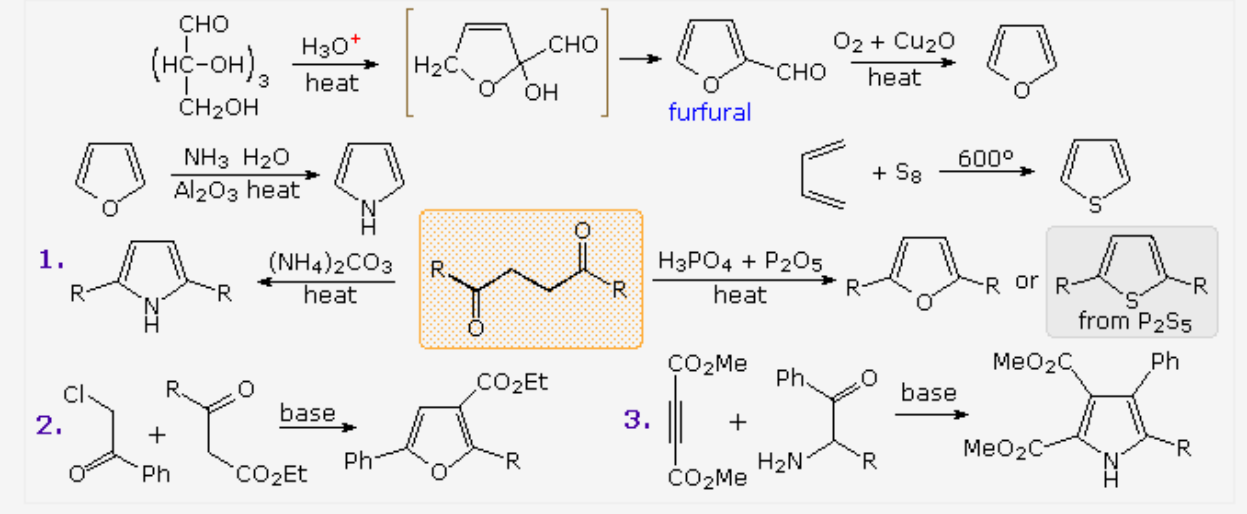
Preparation and Reactions

Five-Membered Rings

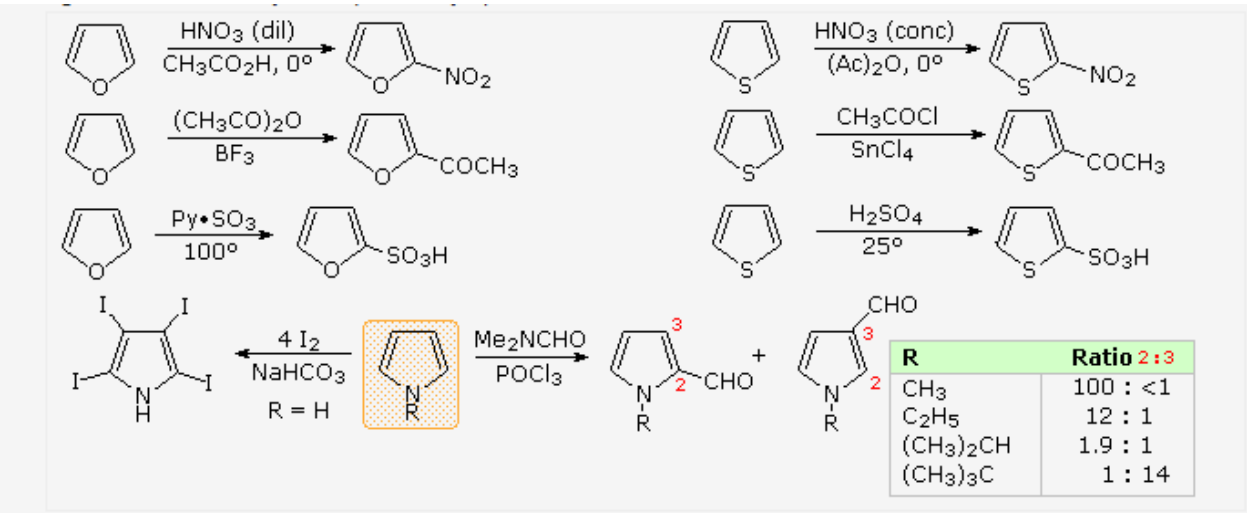
Preparation

Commercial preparation of furan proceeds by way of the aldehyde, furfural, which in turn is generated from pentose containing raw materials like corncobs, as shown in the uppermost equation below. Similar preparations of pyrrole and thiophene are depicted in the second row equations. Equation 1 in the third row illustrates a general preparation of substituted furans, pyrroles and thiophenes from 1,4-dicarbonyl compounds, known as the Paal-Knorr synthesis.

Many other procedures leading to substituted heterocycles of this kind have been devised. Two of these are shown in reactions 2 and 3. Furan is reduced to tetrahydrofuran by palladium-catalyzed hydrogenation. This cyclic ether is not only a valuable solvent, but it is readily converted to 1,4-dihalobutanes or 4-haloalkylsulfonates, which may be used to prepare pyrrolidine and thiolane.
Dipolar cycloaddition reactions often lead to more complex five-membered heterocycles.

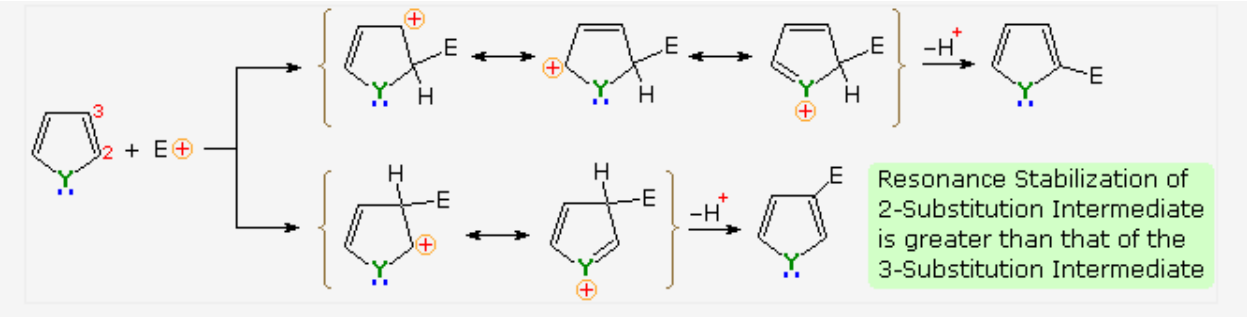


Reactions



There is a clear preference for substitution at the 2-position (α) of the ring, especially for furan and thiophene. Reactions of pyrrole require careful evaluation, since N-protonation destroys its aromatic character. Indeed, N-substitution of this 2º-amine is often carried out prior to subsequent reactions. For example, pyrrole reacts with acetic anhydride or acetyl chloride and triethyl amine to give N-acetylpyrrole. An explanation for the general α-selectivity of these substitution reactions is apparent from the mechanism outlined below. The intermediate formed by electrophile attack at C-2 is stabilized by charge delocalization to a greater degree than the intermediate from C-3

attack. From the Hammond postulate we may then infer that the activation energy for substitution at the former position is less than the latter substitution.

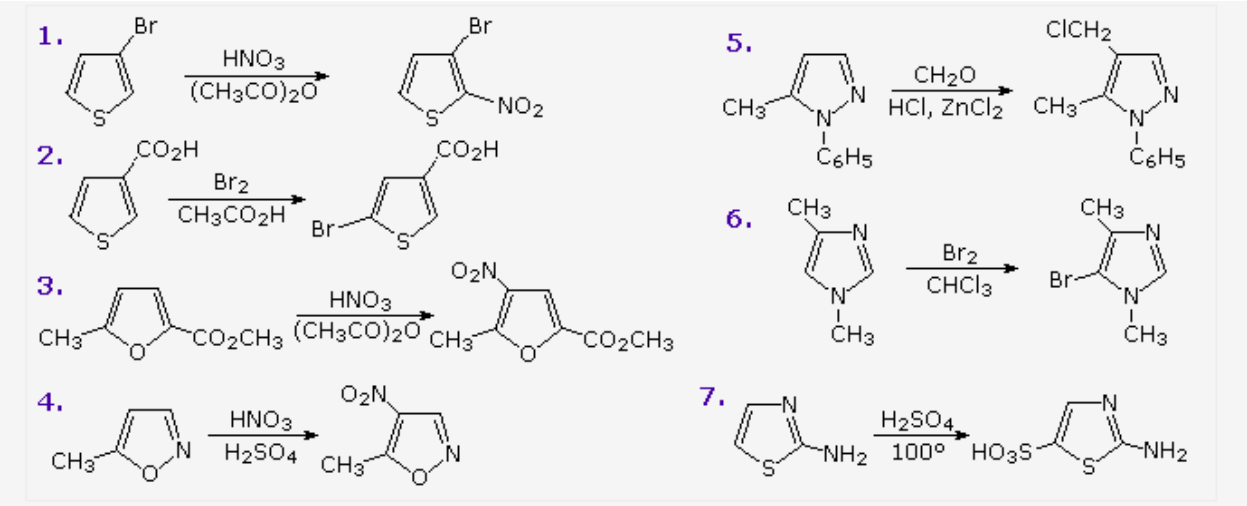


Functional substituents influence the substitution reactions of these heterocycles in much the same fashion as they do for benzene.

Indeed, once one understands the ortho-para and meta-directing character of these substituents, their directing influence on heterocyclic ring substitution is not difficult to predict.

The following diagram shows seven such reactions. Reactions 1 & 2 are 3-substituted thiophenes, the first by an electron donating substituent and the second by an electron withdrawing group. The third reaction has two substituents of different types in the 2 and 5-positions.

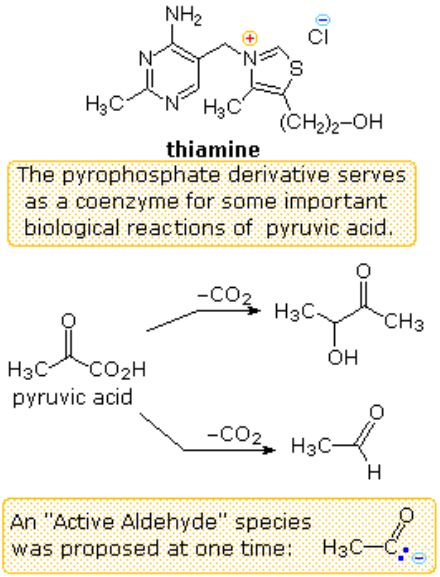
Finally, examples 4 through 7 illustrate reactions of 1,2- and 1,3-oxazole, thiazole and diazole. Note that the basicity of the sp^2-hybridized nitrogen in the diazoles is over a million times greater than that of the apparent sp^3-hybridized nitrogen, the electron pair of which is part of the aromatic electron sextet.

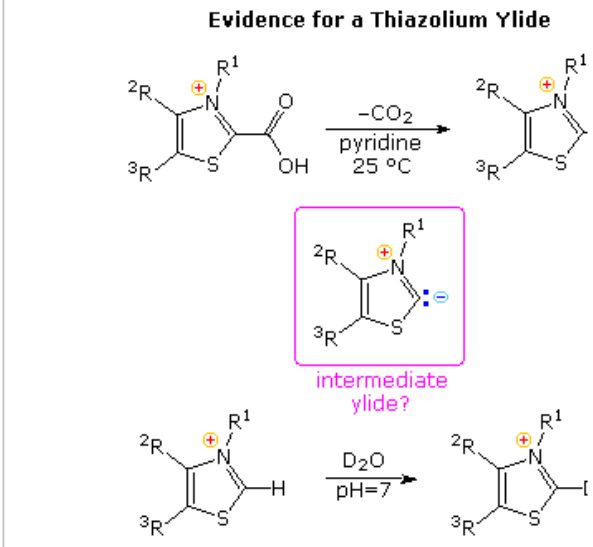


Other possible reactions are suggested by the structural features of these heterocycles. For example, furan could be considered an enol ether and pyrrole an enamine.

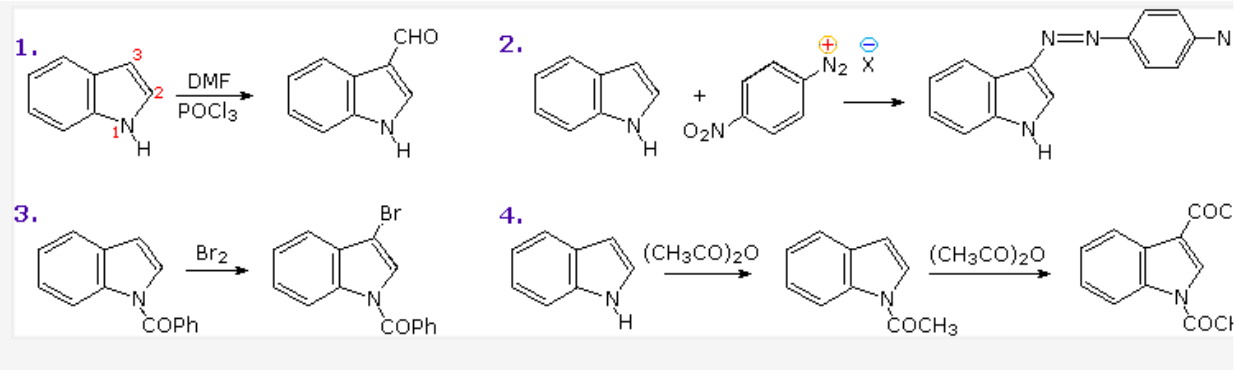
Such functions are known to undergo acid-catalyzed hydrolysis to carbonyl compounds and alcohols or amines.

Since these compounds are also heteroatom substituted dienes, we might anticipate Diels-Alder cycloaddition reactions with appropriate dienophiles.





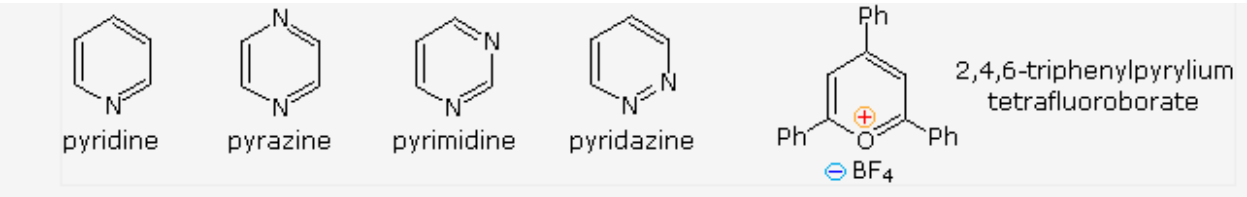
The most important condensed ring system related to these heterocycles is indole. Some electrophilic substitution reactions of indole are shown in the following diagram. Whether the indole nitrogen is substituted or not, the favored site of attack is C-3 of the heterocyclic ring. Bonding of the electrophile at that position permits stabilization of the onium-intermediate by the nitrogen without disruption of the benzene aromaticity.

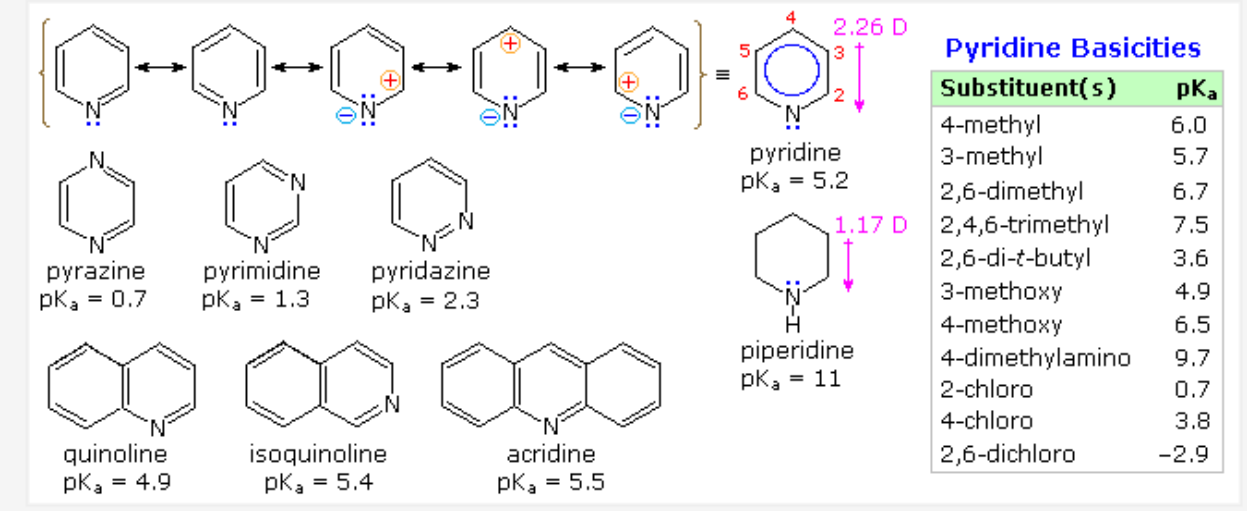


Six-Membered Rings

Properties

The chemical reactivity of the saturated members of this class of heterocycles: tetrahydropyran, thiane and piperidine, resemble that of acyclic ethers, sulfides, and 2º-amines, and will not be described here. 1,3-Dioxanes and dithianes are cyclic acetals and thioacetals. These units are commonly used as protective groups for aldehydes and ketones, as well as synthetic intermediates, and may be hydrolyzed by the action of aqueous acid. The reactivity of partially unsaturated compounds depends on the relationship of the double bond and the heteroatom (*e.g.* 3,4-dihydro-2H-pyran is an enol ether).
Fully unsaturated six-membered nitrogen heterocycles, such as pyridine, pyrazine, pyrimidine and pyridazine, have stable aromatic rings. Oxygen and sulfur analogs are necessarily positively charged, as in the case of 2,4,6-triphenylpyrylium tetrafluoroborate.





Pyridine Basicities

Substituent(s)	pK_a
4-methyl	6.0
3-methyl	5.7
2,6-dimethyl	6.7
2,4,6-trimethyl	7.5
2,6-di-*t*-butyl	3.6
3-methoxy	4.9
4-methoxy	6.5
4-dimethylamino	9.7
2-chloro	0.7
4-chloro	3.8
2,6-dichloro	–2.9

Electrophilic Substitution of Pyridine

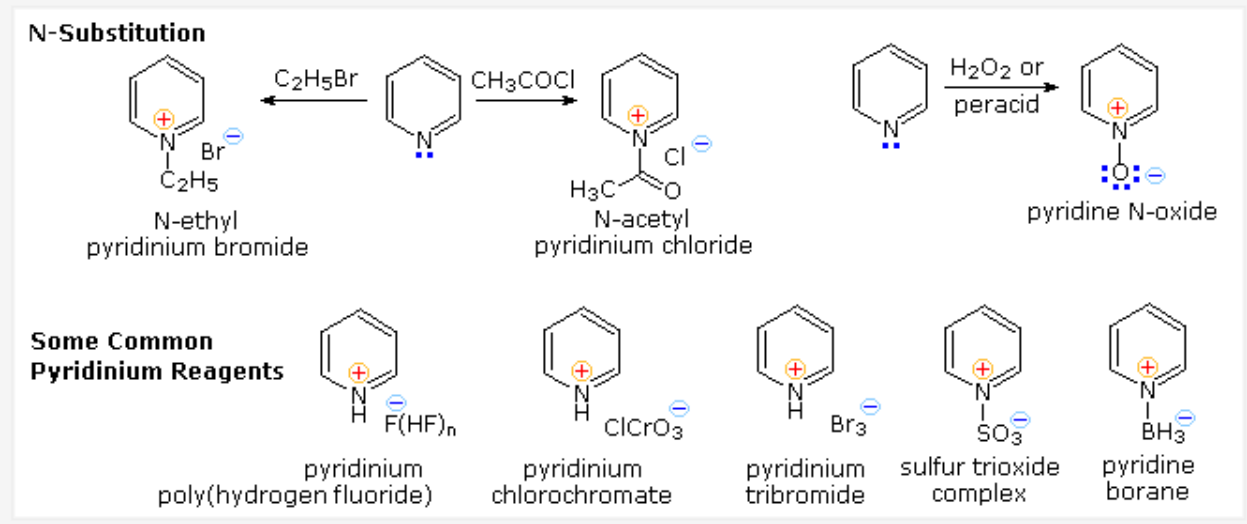
Pyridine is a modest base (pK_a=5.2). Since the basic unshared electron pair is not part of the aromatic sextet, as in pyrrole, pyridinium species produced by N-substitution retain the aromaticity of pyridine.

As shown below, N-alkylation and N-acylation products may be prepared as stable crystalline solids in the absence of water or other reactive nucleophiles. The N-acyl salts may serve as acyl transfer agents for the preparation of esters and amides. Because of the stability of the pyridinium cation, it has been used as a moderating component in complexes with a number of reactive inorganic compounds.

Several examples of these stable and easily handled reagents are shown at the bottom of the diagram. The poly(hydrogen fluoride) salt is a convenient source of HF for addition to alkenes and

conversion of alcohols to alkyl fluorides, pyridinium chlorochromate (PCC) and its related dichromate analog are versatile oxidation agents and the tribromide salt is a convenient source of bromine.

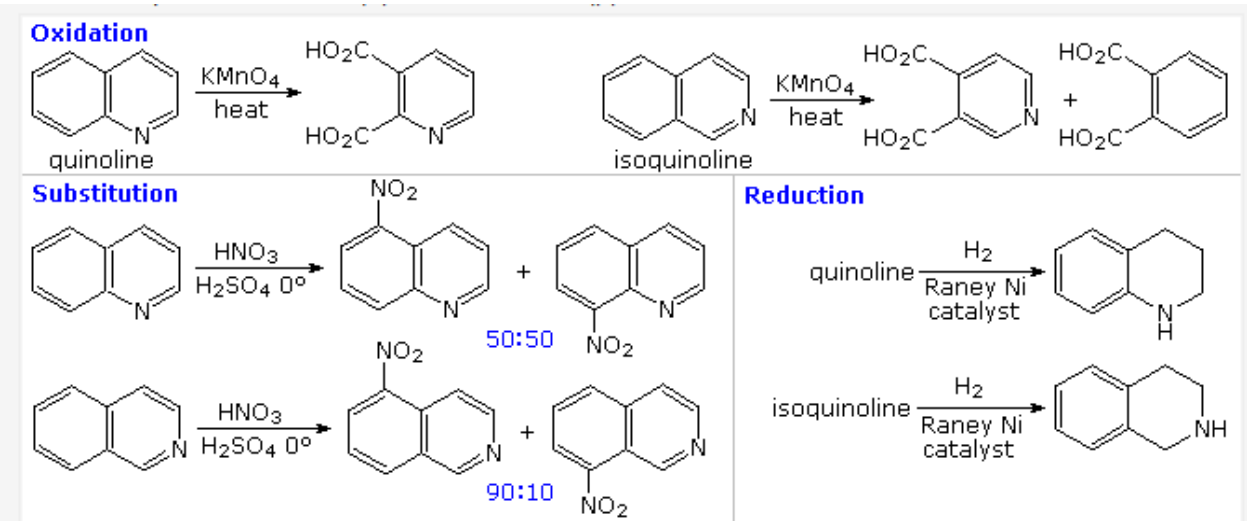
Similarly, the reactive compounds sulfur trioxide and diborane are conveniently and safely handled as pyridine complexes.Amine oxide derivatives of 3º-amines and pyridine are readily prepared by oxidation with peracids or peroxides, as shown by the upper right equation. Reduction back to the amine can usually be achieved by treatment with zinc (or other reactive metals) in dilute acid.



From the previous resonance description of pyridine, we expect this aromatic amine to undergo electrophilic substitution reactions far less easily than does benzene.

The fused ring heterocycles quinoline and isoquinoline provide additional evidence for the stability of the pyridine ring. Vigorous permanganate oxidation of quinoline results in predominant attack on the benzene ring; isoquinoline yields products from cleavage of both rings. Note that naphthalene is oxidized to phthalic acid in a similar manner.

By contrast, the heterocyclic ring in both compounds undergoes preferential catalytic hydrogenation to yield tetrahydroproducts. Electrophilic nitration, halogenation and sulfonation generally take place at C-5 and C-8 of the benzene ring, in agreement with the preceding description of similar pyridine reactions and the kinetically favored substitution of naphthalene at C-1 (α) rather than C-2 (β).

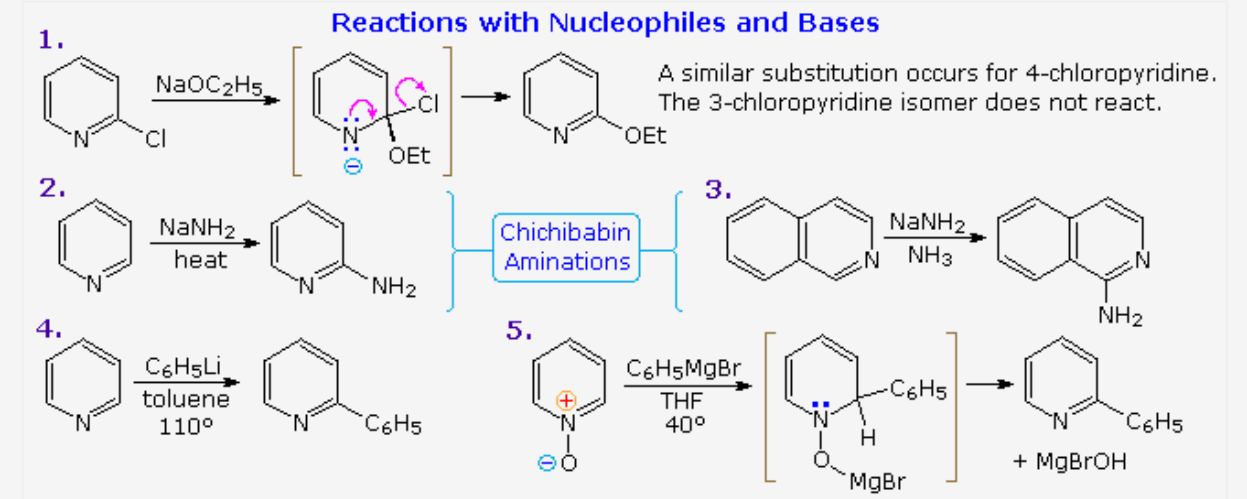


Other Reactions of Pyridine

Thanks to the nitrogen in the ring, pyridine compounds undergo nucleophilic substitution reactions more easily than equivalent benzene derivatives.

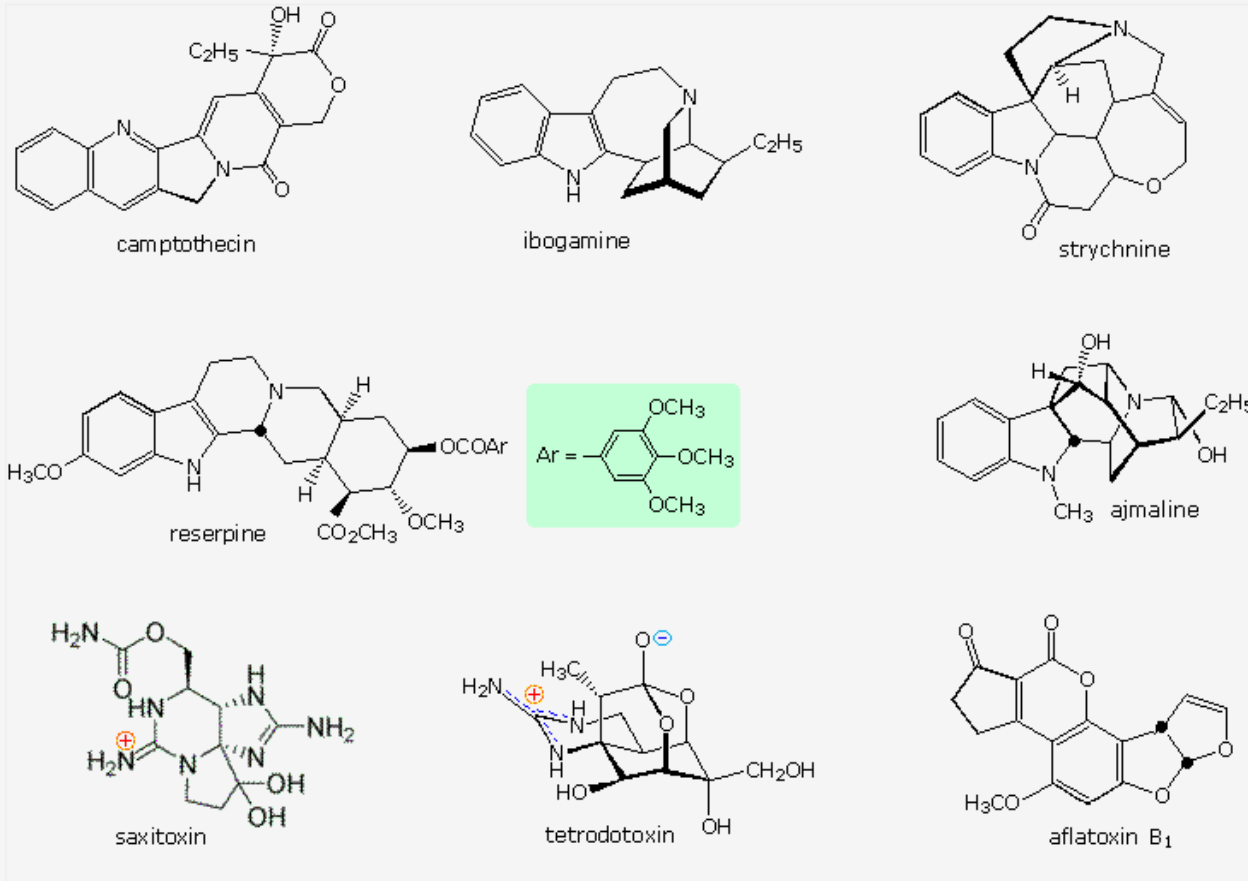
In the following diagram, reaction 1 illustrates displacement of a 2-chloro substituent by ethoxide anion. The addition-elimination mechanism shown for this reaction is helped by nitrogen's ability to support a negative charge. A similar intermediate may be written for substitution of a 4-halopyridine, but substitution at the 3-position is prohibited by the the failure to create an intermediate of this kind.

The two Chichibabin aminations in reactions 2 and 3 are remarkable in that the leaving anion is hydride (or an equivalent). Hydrogen is often evolved in the course of these reactions. In accord with this mechanism, quinoline is aminated at both C-2 and C-4. Addition of strong nucleophiles to N-oxide derivatives of pyridine proceed more rapidly than to pyridine itself, as demonstrated by reactions 4 and 5. The dihydro-pyridine intermediate easily loses water or its equivalent by elimination of the –OM substituent on nitrogen.



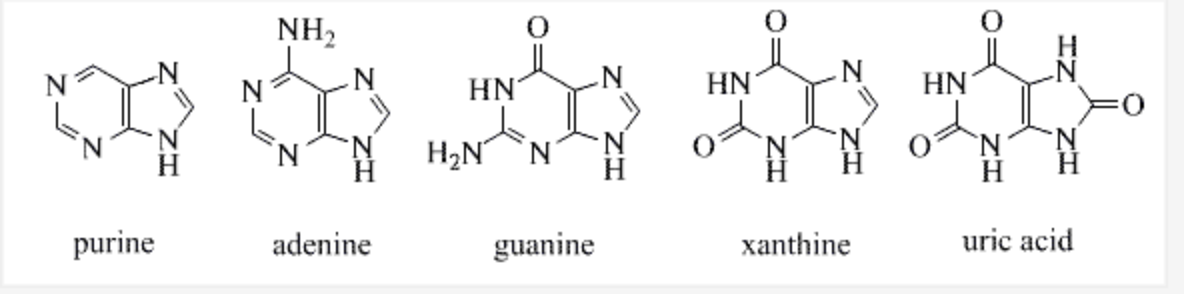
Some Polycyclic Heterocycles

Heterocyclic structures are found in many natural products. Examples of some nitrogen compounds, known as alkaloids because of their basic properties. Some other examples are displayed in the following diagram. Camptothecin is a quinoline alkaloid which inhibits the DNA enzyme topoisomerase I. Reserpine is an indole alkaloid, which has been used for the control of high blood pressure and the treatment of psychotic behavior. Ajmaline and strychnine are also indole alkaloids, the former being an antiarrhythmic agent and latter an extremely toxic pesticide. The neurotoxins saxitoxin and tetrodotoxin both have marine origins and are characterized by guanidiniun moieties. Aflatoxin B_1 is a non-nitrogenous carcinogenic compound produced by the Aspergillus fungus.



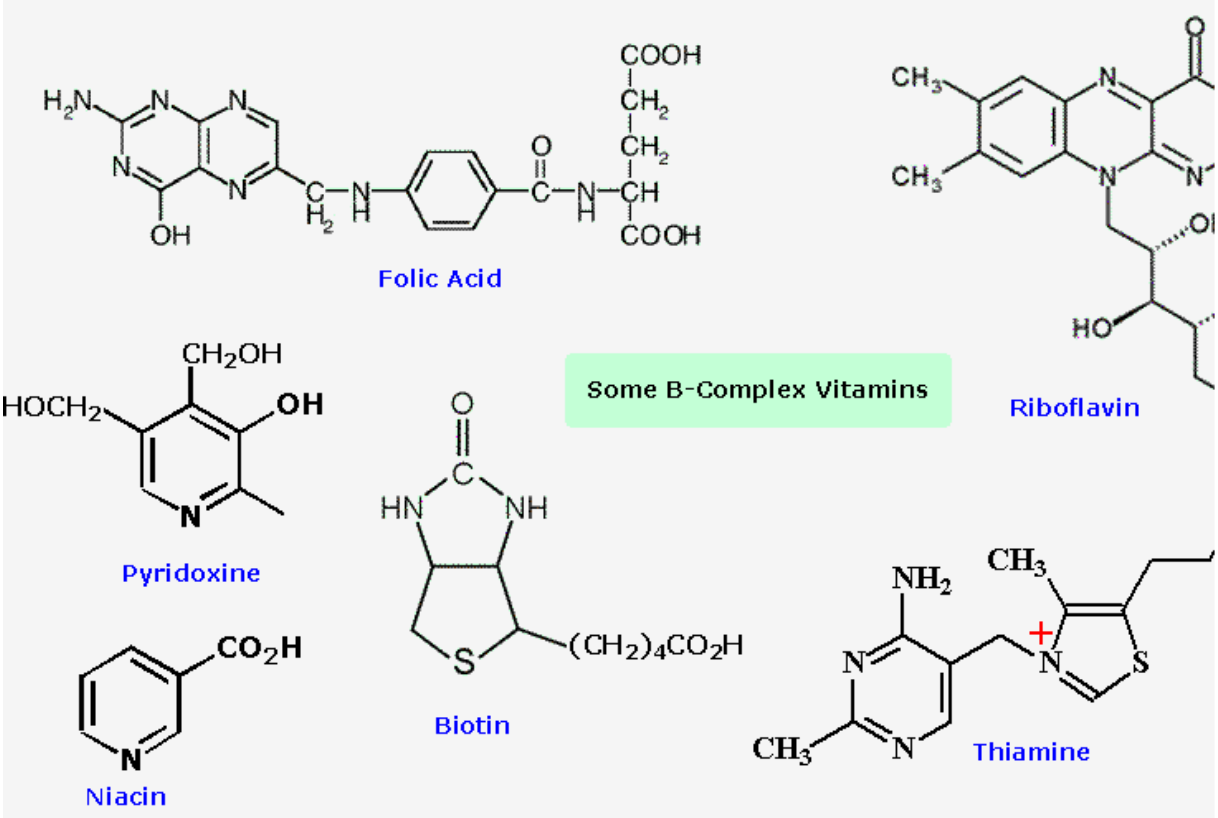
Porphyrin is an important cyclic tertrapyrrole that is the core structure of heme and chlorophyll.

Derivatives of the simple fused ring heterocycle purine constitute an especially important and abundant family of natural products. The amino compounds adenine and guanine are two of the complementary bases that are essential components of DNA. Structures for these compounds are shown in the following diagram. Xanthine and uric acid are products of the metabolic oxidation of purines. Uric acid is normally excreted in the urine; an excess serum accumulation of uric acid may lead to an arthritic condition known as gout.



Caffeine, the best known of these, is a bitter, crystalline alkaloid. It is found in varying quantities, along with additional alkaloids such as the cardiac stimulants theophylline and theobromine in the beans, leaves, and fruit of certain plants. Drinks containing caffeine, such as coffee, tea and some soft drinks are arguably the world's most widely consumed beverages. Caffeine is a central nervous system stimulant, serving to ward off drowsiness and restore alertness. Paraxantheine is the chief metabolite of caffeine in the body.

Sulfur heterocycles are found in nature, but to a lesser degree than their nitrogen and oxygen analogs. Two members of the B-vitamin complex, biotin and thiamine, incorporate such heterocyclic moieties. These are shown together with other heterocyclic B-vitamins in the following diagram.



Terthienyl is an interesting thiophene trimer found in the roots of marigolds, where it provides nemicidal activity. Studies have shown that UV irradiation of terthienyl produces a general phototoxicity for many organisms. Polymers incorporating thiophene units and fused systems

such as dithienothiophene have interesting electromagnetic properties, and show promise as organic metal-like conductors and photovoltaic materials. The charge transfer complex formed by tetrathiofulvalene and tetracyanoquinodimethane has one of the highest electrical conductivities reported for an organic solid.