Heterocyclic Chemistry

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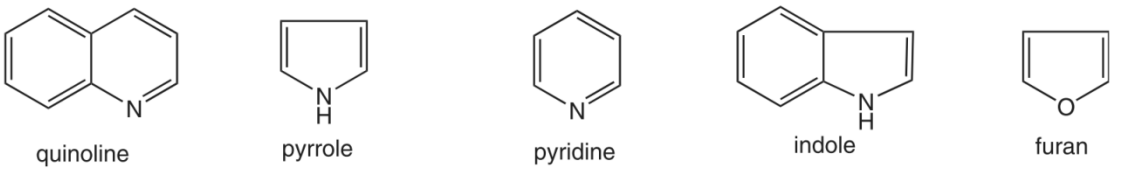
What are heterocyclic compounds?

Heterosubstituted rings are those in which one or more carbon atoms in a purely carbon-containing ring (known as a carbocyclic ring) is replaced by some other atom (referred to as a heteroatom). In practice, the most commonly found heteroatom is nitrogen, followed by oxygen and sulfur. However, many other atoms can form the stable covalent bonds necessary for ring construction and can lead to structures of considerable importance in contemporary heterocyclic chemistry. Of note are phosphorus, arsenic, antimony, silicon, selenium, tellurium, boron, and germanium. In rare cases, even elements generally considered to be metallic, such as tin and lead, can be incorporated in ring systems. In a 1983 report, the International Union of Pure and Applied Chemistry (IUPAC) recognized 15 elements coming from Groups II to IV of the Periodic System capable of forming cyclic structures with carbon atoms. The early heterocyclic compounds were isolated from natural sources; versatile synthetic procedures followed only after many years of research. Some examples of early compounds are as follows:

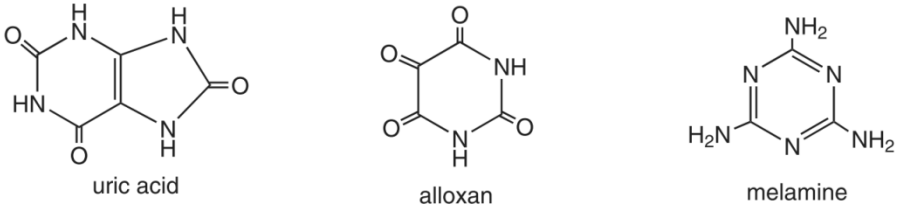
1. **Uric acid** (1776, by Scheele from human bladder stones)
2. **Alloxan** (1818, by Brugnatelli on oxidation of uric acid)
3. **Quinoline** (1834, by Runge from coal distillates, called coal tar)
4. **Melamine** (1834, by Liebig by synthesis)
5. **Pyrrole** (1834, by Runge in coal tar, but first purified by Anderson in 1858)
6. **Pyridine** (1849, by Anderson by pyrolysis of bones)
7. **Indole** (1866, by Baeyer from degradation of indigo)
8. **Furan** (1870, from wood and cellulose destructive distillation)

Some Early Heterocyclic Compounds of Natural Origins

A. Compounds That Are Parent Rings



B. Compounds With Functional Groups



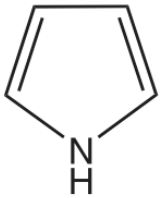
Nomenclature of Heterocyclic Compounds

The IUPAC allows the use of common names and the use of **The Hantzsch-Widman Nomenclature** for naming heterocyclic compounds. Some of the most common monocyclic heterocyclic compounds have been named below:

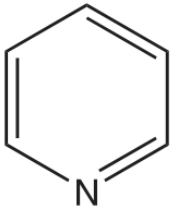
A. Nitrogen Heterocyclic Parents

azirine

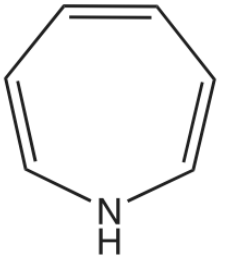
azete



azole
(pyrrole)



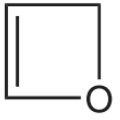
azine
(pyridine)



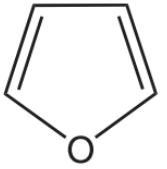
azepine

B. Oxygen Heterocyclic Parents

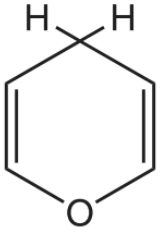
oxirene



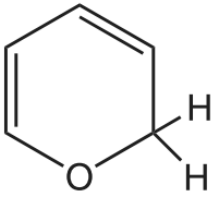
oxete



oxole
(furan)



γ-pyran
(1,4-pyran)

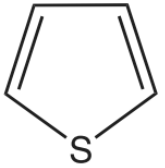


α-pyran
(1,2-pyran)

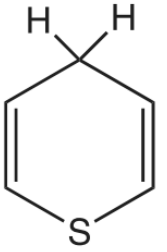
C. Sulfur Heterocyclic Parents

thiirene

thiete

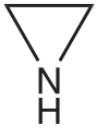


thiole
(thiophene)

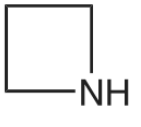


γ-thiopyran

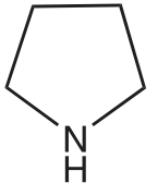
D. Some Saturated Rings



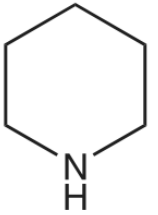
aziridine
(ethyleneimine)



azetidine

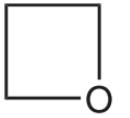


azolidine
(pyrrolidine)



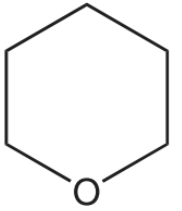
hexahydropyridine
(piperidine)

oxirane
(ethylene oxide)



oxetane

oxolane
(tetrahydrofuran)



oxane
(tetrahydropyran)

Nomenclature of Heterocyclic compounds: The Hantzsch-Widman System

The Hantzsch-Widman nomenclature is based on the following three criteria;

1. The prefix of the name is based on the type of the heteroatom
2. The stem of the name is based on the size of the ring
3. The suffix of the name is decided by the saturated or unsaturated nature of the ring.

According to this system heterocyles are named by combining appropriate prefix/prefixes with a stem from table given below. The letter "a" in the prefix is omitted wherever necessary.

Hantzsch-Widman Nomenclature

Type of Heteroatom (Prefix)		Ring Size (Stem)		Nature of the Ring (Suffix)		
				Saturated	Unsaturated	Saturated with "N"
Nitrogen	Aza-	3	-ir-	-irane	-irine	-iridine
Oxygen	Oxa-	4	-et-	-etane	-ete	-etidine
Sulphur	Thia-	5	-ol-	-olane	-ole	-olidine
Phosphorous	Phospha-	6	-in-	-inane	-ine	
Arsenic	Arsa-	7	-ep-	-epane	-epine	
Silicon	Sila-	8	-oc-	-ocane	-ocine	
Selenium	Selena-	9	-on-	-onane	-onine	
Boron	Bora-	10	-ec-	-ecane	-ecine	

Nomenclature of Heterocyclic compounds: The Hantzsch-Widman System

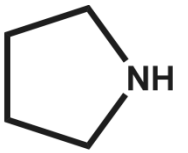
Miscellaneous points and exceptions

- For the prefix The "a" ending is dropped if the next syllable starts with a vowel. Thus "aza-irine" is properly written "azirine."

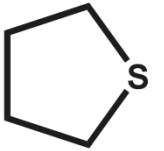
Oxa+irane= Oxirane

Thia+irane= Thiirane

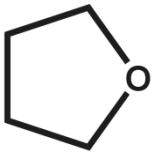
Oxa+etane=Oxetane



Aza+olidine= Azolidine



Thia+olane= Thiolane



Oxa+olane= Oxolane

- If fully saturated, the suffix is -ane for all ring sizes, except for Nitrogen containing systems, where suffixes -idine for rings of 3, 4, or 5 membered rings are used (shown in the table).

Aza+iridine= Aziridine

- The name oxane (not oxinane), is used for the 6-membered ring with Oxygen. Similar exceptions exist for P, As, and B containing rings as well.

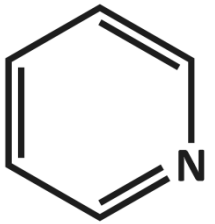
Nomenclature of Heterocyclic compounds: The Hantzsch-Widman System

Naming the systems with full/partial unsaturation

- The saturated suffix is applied only to completely saturated ring systems, and the unsaturated suffix applies to rings with the maximum number of non-cumulated double bonds which is regarded as the parent compound of the monocyclic systems of a given ring size.

Azirine

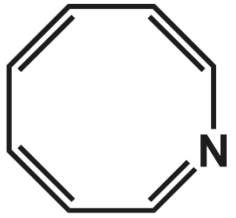
Oxirine



Azine

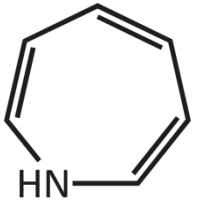
Pyridine

Azepine

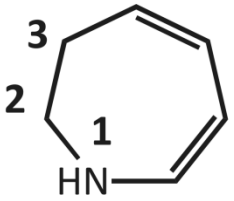


Azocine

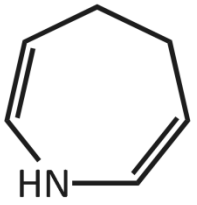
- Systems having a lesser degree of unsaturation require an appropriate prefix, such as "dihydro"or "tetrahydro" along with indicating the atom numbers with extra hydrogens.



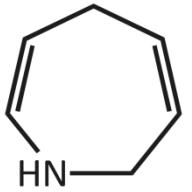
Azepine



2,3-Dihydroazepine



4,5-Dihydroazepine



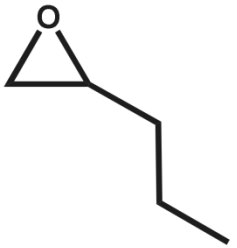
2,5-Dihydroazepine

- Saturated 3, 4 & 5-membered nitrogen heterocycles should use respectively the traditional "iridine", "etidine" & "olidine" suffix.

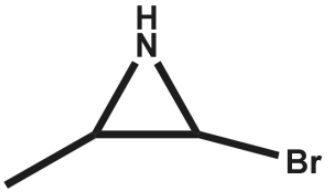
Nomenclature of Heterocyclic compounds: The Hantzsch-Widman System

Naming the systems with substituents

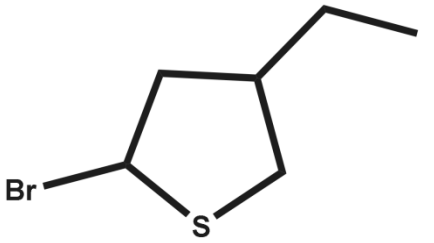
- The heteroatom is always given the number 1 priority and the substituents around the chain are numbered so as to have the lowest number for the substituents.



2-Propyloxirane

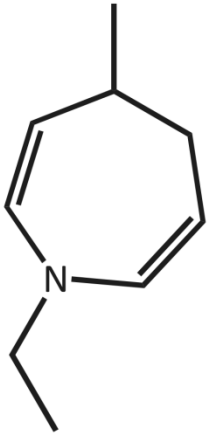


2-Bromo-3-methylaziridine

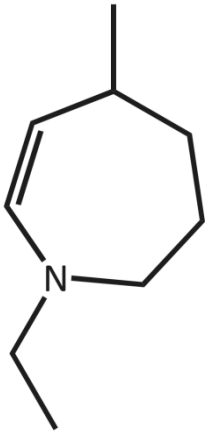


2-Bromo-4-ethylthiolane

- For partially saturated monocyclic systems with substituents, the priority (lower number) is given to saturated atoms



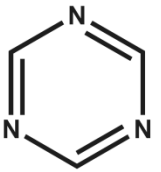
1-Ethyl-4-methyl-4,5-dihydroazepine



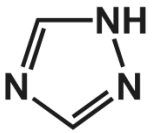
1-Ethyl-5-methyl-2,3,4,5-tetrahydroazepine

Nomenclature of Heterocyclic Rings With More Than One Heteroatom

When two or more similar atoms are present in a ring it is dealt with by adding the prefixes 'di-', 'tri', etc.



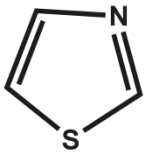
1,3,5-Triazine



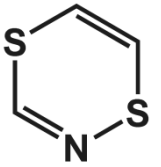
1,2,4 - Triazole

When more than one type of heteroatoms are present in the ring, then the heterocycle is named by combining the appropriate prefixes for each atom in order of their preference, O > S > Se > N > P.

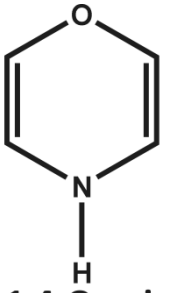
Oxaziridine



1,3-Thiazole
(Thiazole)

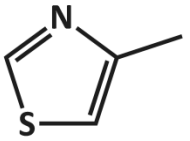


1,4,2 - Dithiazine

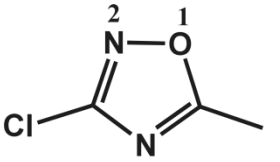


1,4-Oxazine

The ring is numbered from the atom of preference in such a way so as to give the smallest possible number to the other hetero atoms in the ring. As a result the position of the substituent plays no part in determining how the ring is numbered in such compounds.



4-Methyl-1,3-thiazole



3-chloro-5-methyl-1,2,4-oxadiazole

Nomenclature of Heterocyclic Rings With More Than One Heteroatom

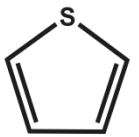
Punctuation is important as well?

- A comma separates the numbers and a dash separates the numbers from the heteroatom prefixes.
- A slight modification is used when two vowels adjoin; one is deleted, as in the listing for "oxaaza," which becomes simply "oxaza."
- As for monohetero systems, substituents on the ring are listed alphabetically with a ring atom number for each (not grouped together).

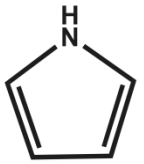
For more on the nomenclature, refer "Fundamentals of Heterocyclic Chemistry" by J. D. Quin and J. Tyrell

Common Names

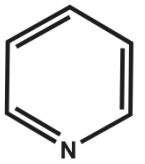
Furan



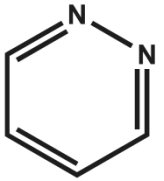
Thiophene



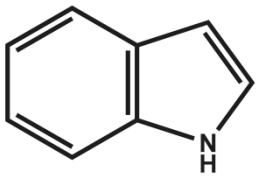
Pyrrole



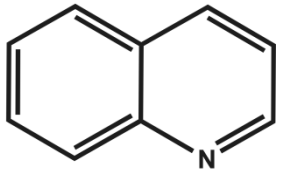
Pyridine



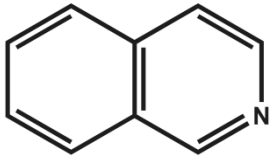
Pyridazine



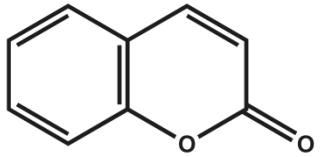
Indole



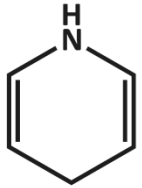
Quinoline



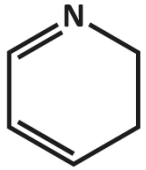
Isoquinoline



Coumarin



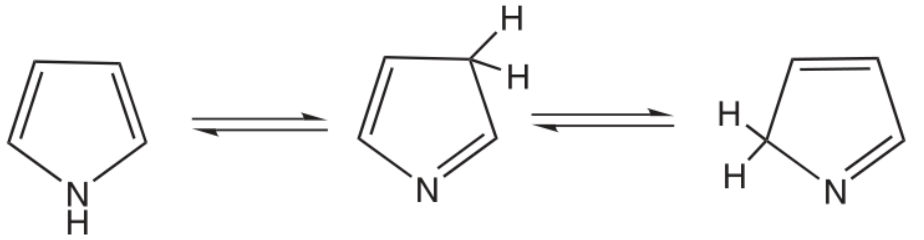
1,4-Dihydropyridine



2,3-Dihydropyridine

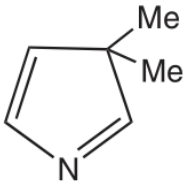
Handling the Extra Hydrogen

Due to the possibility of isomerism in some heterocycles, there is a problem in giving a single name for all the isomers. Consider the case oh pyroll; There are actually two additional isomeric forms that result from apparent 1,3-shifts of hydrogen starting from the familiar structure we have already observed. This is referred to as the "extra-hydrogen" problem, and the naming of the isomers is handled by simply adding a prefix that indicates the number of the ring atom that possesses the hydrogen, thus, 1H, 2H, and 3H. In the case of pyrrole, there is no stability to the isomers when the extra hydrogen is on carbon, although the double-bond structure can be stabilized by proper substitutions of the hydrogens. When these unstable forms are created in a synthesis, they immediately rearrange to the form with H on nitrogen. This is properly known as 1H-pyrrole, but the convention is followed that the 1H designation is dropped if H appears on the heteroatom.



1H-pyrrole 3H-pyrrole 2H-pyrrole

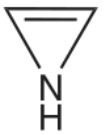
An example of a stabilized 3H-pyrrole is shown as follows:



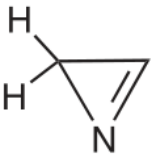
3,3-dimethyl-3H-pyrrole

Handling the Extra Hydrogen

The extra-hydrogen problem can occur in any ring system of nitrogen containing an odd number of ring atoms but not of course with an even number because there is no H to relocate (as in pyridine). For example, it is known in the azirine system.

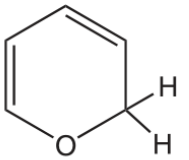


1H-azirine

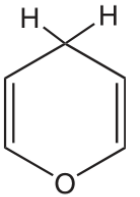


2H-azirine

The extra-hydrogen problem can also appear in odd-numbered rings containing other heteroatoms, phosphorus for example, and in some oxygen cycles, as in the pyrans (and the related thiopyrans). Note here the use of Greek letters to imply the location of the extra hydrogen, using the convention that the carbon next to the heteroatom is designated the alpha position.

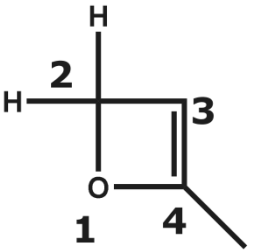


2H-pyran
(α-pyran)

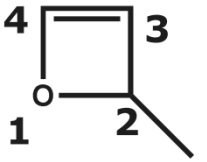


4H-pyran
(γ-pyran)

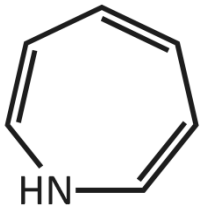
Handling the Extra Hydrogen



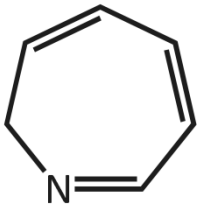
4-Methyl-*2H*-oxete



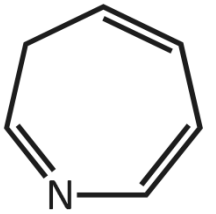
2-Methyl-*2H*-oxete



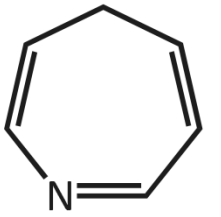
Azepine



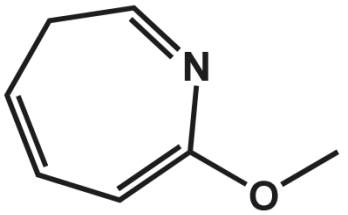
2*H*-Azepine



3*H*-Azepine

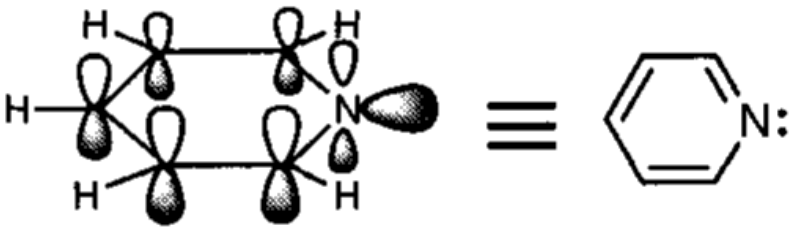


4*H*-Azepine



7-Methoxy-3*H*-azepine

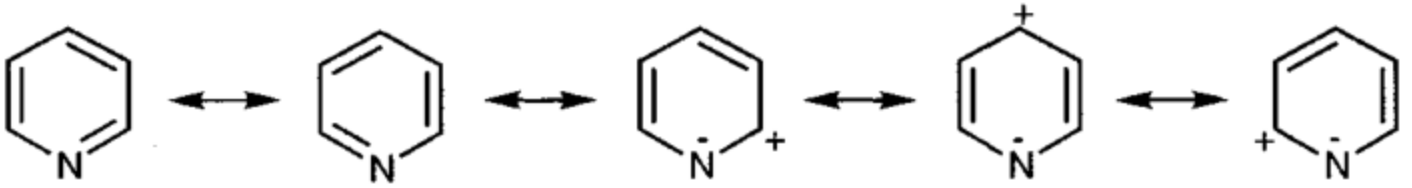
Pyridine



The structure of pyridine is completely analogous to that of benzene, being related by replacement of CH by N. The key differences are;

1. The departure from perfectly regular hexagonal geometry caused by the presence of the hetero atom, in particular the shorter carbon-nitrogen bonds
2. The replacement of a hydrogen in the plane of the ring with an unshaired electron pair, likewise in the plane of the ring, located in an sp^2 hybrid orbital, and not at all involved in the aromatic π-electron sextet; it is this nitrogen lone pair which is responsible for the basic properties of pyridines.
3. A strong permanent dipole, traceable to the greater electronegativity of the nitrogen compared with carbon.

Electronegative nitrogen causes inductive polarisation, mainly in the σ-bond framework, and additionally, stabilises those polarised canonical structures in which nitrogen is negatively charged. The polarised contributors imply a permanent polarisation of the π -electron system as well.



Pyridine

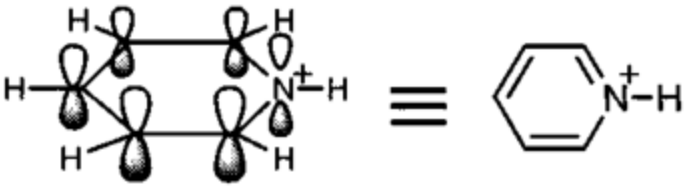
Since the inductive and mesomeric effects work in the same sense in pyridine, there results a permanent dipole towards the nitrogen atom. It also means that there are fractional positive charges on the carbons of the ring, located mainly on the α- and γ-positions. It is because of this general electron-deficiency at carbon that pyridine and similar heterocycles are referred to as 'electron-poor', or sometimes 'π-deficient.

Further a comparison with the dipole moment of piperidine,(in which the dipole moment is due wholly to the induced polarisation of the α-skeleton), gives an idea of the additional polarisation associated with distortion of the π-electron system.

Pyridine

Pyridinium ion

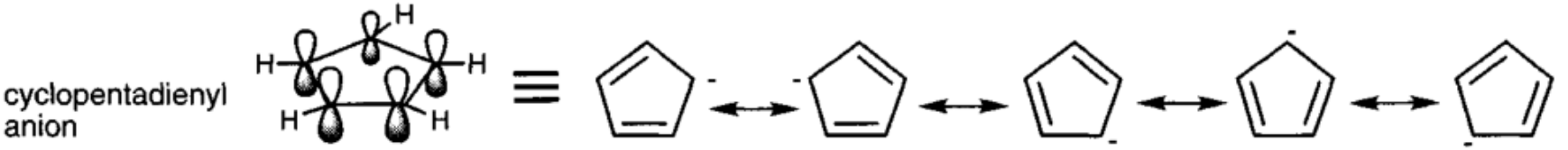
Electrophilic addition to the pyridine nitrogen generates pyridinium ions, the simplest being 1H-pyridinium formed by addition of a proton. 1H-Pyridinium is actually isoelectronic with benzene, the only difference being the nuclear charge of nitrogen, which makes the system, as a whole, positively charged. Thus pyridinium cations are still aromatic with the system of six p orbitals required to generate the aromatic molecular orbitals is still present, though the formal positive charge on the nitrogen atom severely distorts the π -system, making the α - and γ -carbons in these cations carry fractional positive charges which are higher than in pyridine, with a consequence for their reactivity towards nucleophiles. Electron density at the pyridinium β-carbons is also reduced relative to these carbons in pyridines.



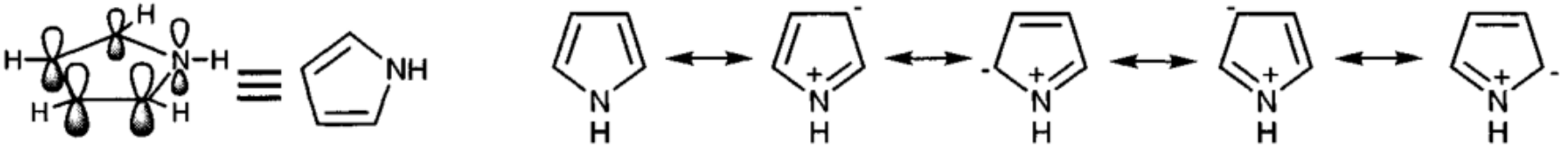
1*H*-pyridinium cation

Pyrrole

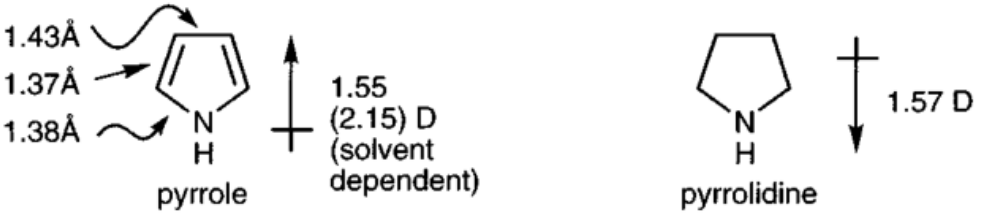
Cyclopentadiene, with a pKa of about 14, is much more acidic than a simple diene, just because the resulting anion is resonance stabilised.



Pyrrole is isoelectronic with the cyclopentadienyl anion, but is electrically neutral because of the higher nuclear charge on nitrogen. The other consequence of the presence of nitrogen in the ring is the loss of radial symmetry, so that pyrrole does not have five equivalent canonical forms: it has one with no charge separation, and two pairs of equivalent forms in which there is charge separation, indicating electron density drift away from the nitrogen.

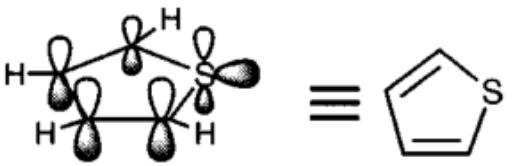


Resonance leads, then, to the establishment of partial negative charges on the carbons and a partial positive charge on the nitrogen. Of course the inductive effect of the nitrogen is, as usual, towards the hetero atom and away from carbon, so that the electronic distribution in pyrrole is a balance of two opposing effects, of which the mesomeric effect is probably the more significant. The lengths of the bonds in pyrrole are in accord with this exposition, thus the 3,4-bond is very much longer than the 2,3-/4,5-bonds, but appreciably shorter than a normal single bond betwen sp^2 hybridised carbons, in accord with contributions from the polarised structures. It is most important to recognize that the nitrogen lone pair in pyrrole forms partof the aromatic six-electron system

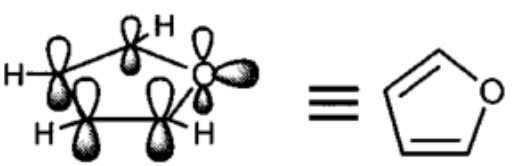


Thiophene and Furan

The structures of thiophene and furan are closely analogous to pyrrole, except that the NH is replaced by S and O respectively. A consequence is that the hetero atom in each has one lone pair as part of the aromatic sextet, as in pyrrole, but also has a second lone pair which is not involved, and is located in an sp^2 hybrid orbital in the plane of the ring.

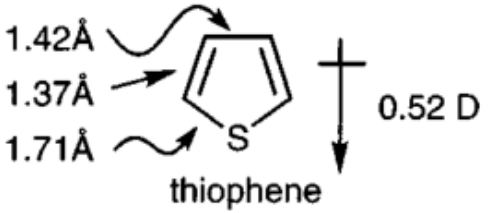


thiophene

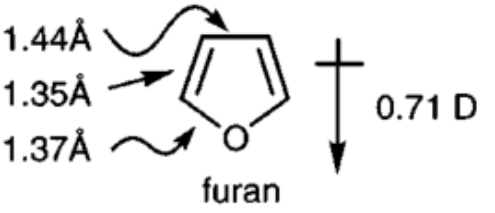


furan

Canonical forms exactly analogous to those (above) for pyrrole can be written for each, but the higher electronegativity of both sulfur and oxygen means that the polarised forms, with positive charges on the hetero atoms, make a smaller contribution. The decreased mesomeric electron drift away from the hetero atoms is insufficient, in these two cases, to overcome the inductive polarisation towards the hetero atom (the dipole moments of tetrahydrothiophene and tetrahydrofuran, 1.87D and 1.68D, respectively, both towards the hetero atom, are in any case larger) and the net effect is to give dipoles directed towards the hetero atoms in thiophene and furan.



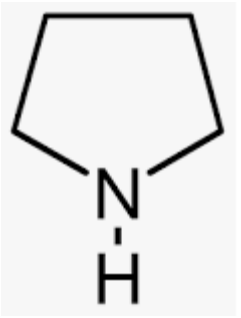
thiophene

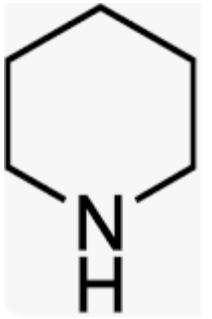


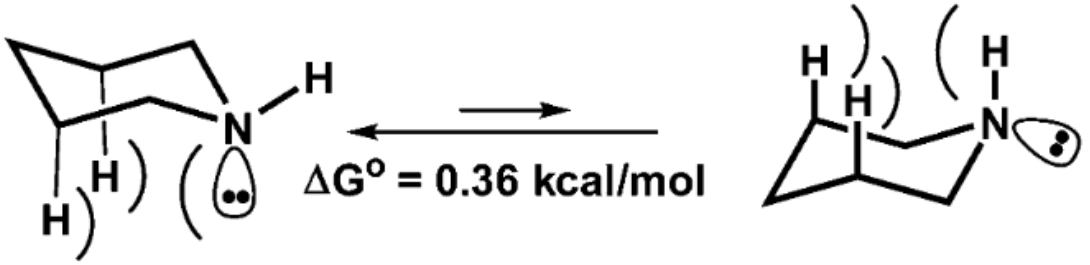
furan

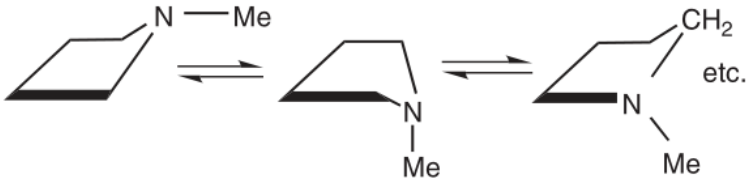
The larger bonding radius of sulfur is one of the influences making thiophene more stable (more aromatic) than pyrrole or furan -the bonding angles are larger and angle strain is somewhat relieved.

Saturated Heterocycles: Pyrrolidine and Piperidine

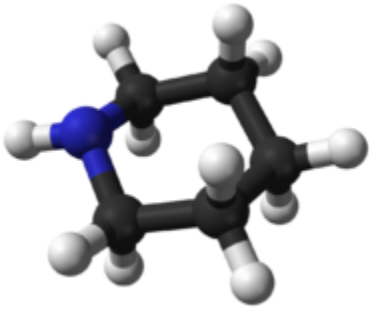




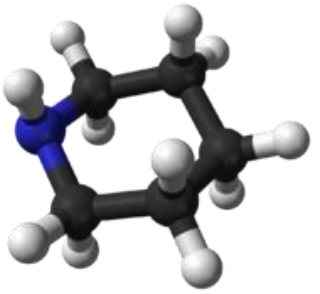




Conformational equilibrium for N-methylpyrrolidine

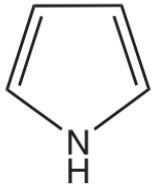


Equatorial



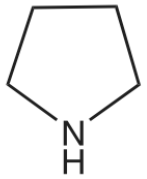
Axial

Basicity comparison: Pyrrole, Pyrrolidine, Pyridine, Piperidine



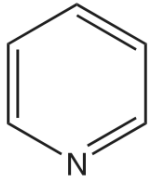
azole
(pyrrole)

Aromatic with the lone pair on N delocalized and a part of the pi-system. Least basic among the four.



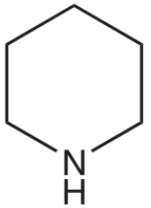
azolidine
(pyrrolidine)

Alicyclic molecule with a non-planar structure (Look at the conformational analysis of cyclopentane). Lone pair on the N-atom is always available for attack by an acid and hence more basic than Pyrrole.



azine
(pyridine)

Aromatic, but the lone pair on the N-atom is in the plane of the ring and not a part of the aromatic pi-system. Lone pair is in an sp2 hybridized orbital and hence less basic than Piperidine

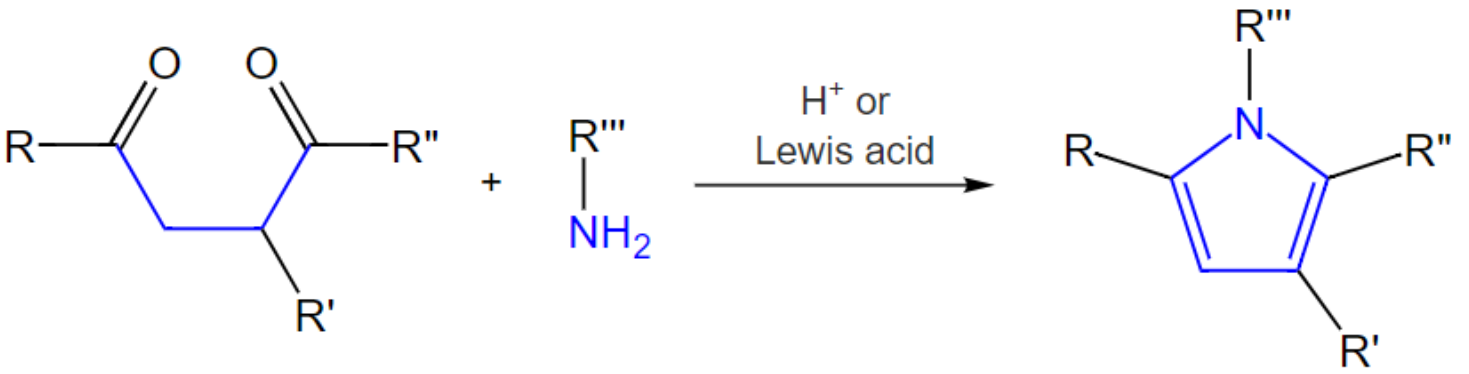


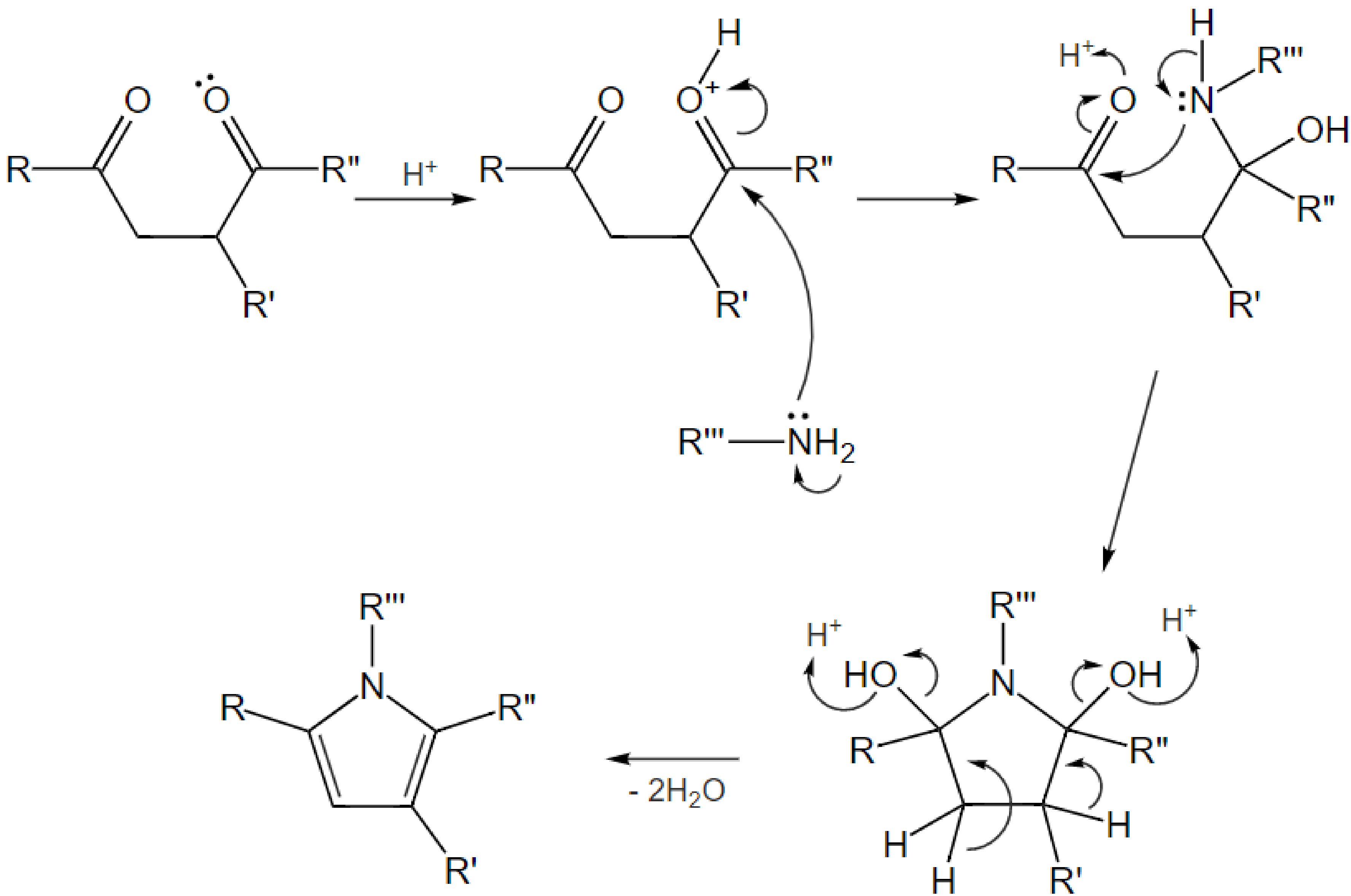
hexahydropyridine
(piperidine)

Alicyclic molecule with a non-planar structure (boat and chair conformations like cyclohexane). Lone pair on the N-atom is present in an sp3 hybridized orbital and is always available for attack by an acid. More basic among the four.

Paal Knorr Synthesis

It is a classical reaction to prepare substituted pyrroles in a single step from amines. The Paal–Knorr method makes use of a 1,4-di-carbonyl compound (aldehyde or ketone) in reaction with primary amines or ammonia. Many pyrroles have been made by this general process. Alkyl and some other substituents are allowed on the dicarbonyl chain. Diketones, dialdehydes, and ketoalde- hydes all serve as reactants. Primary amines give rise to 1-alkylpyrroles.



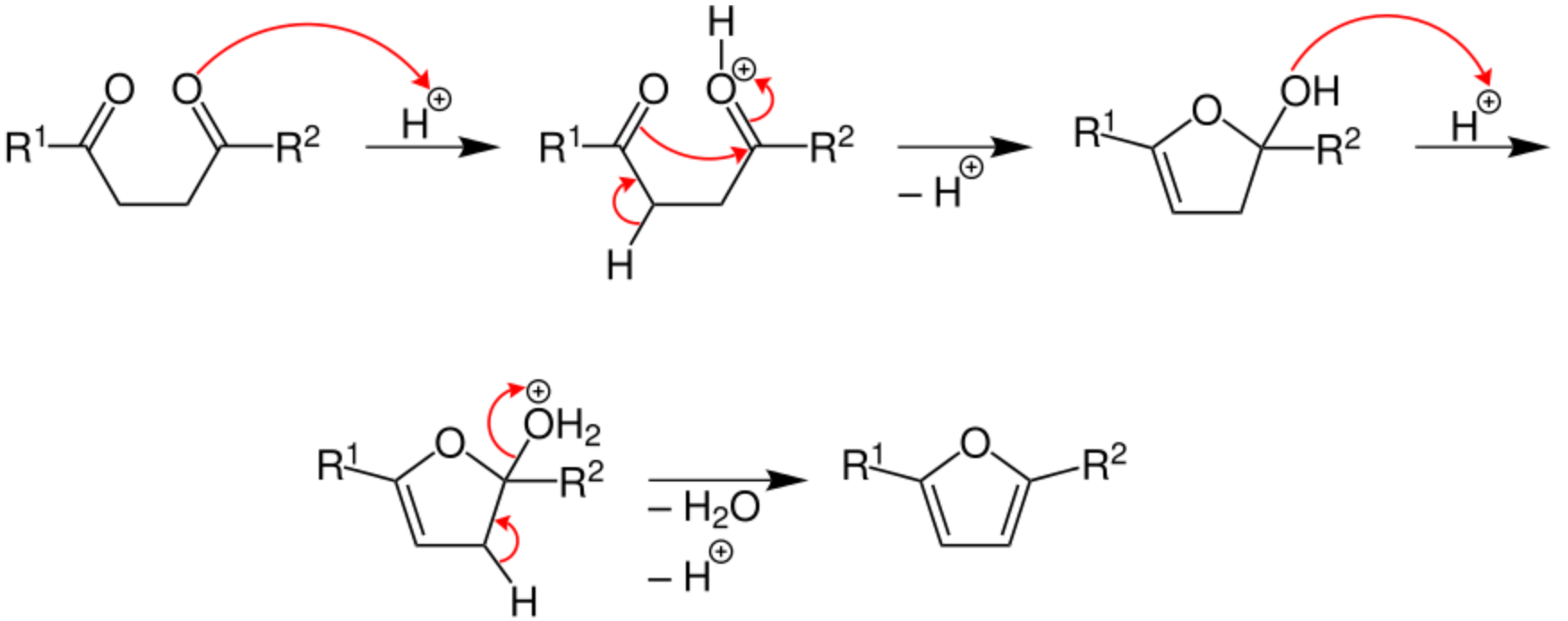


H+
- 2H2O

Paal Knorr Synthesis

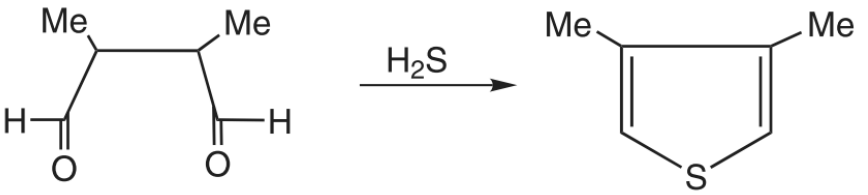
This reaction can also be used to synthesize substituted Furans and Thiophenes if suitable reagents in place of the amines are used.

Paal-Knor Furan Synthesis: The acid catalyzed furan synthesis proceeds by protonation of one carbonyl which is attacked by the forming enol of the other carbonyl. Dehydration of the hemiacetal gives the resultant furan.

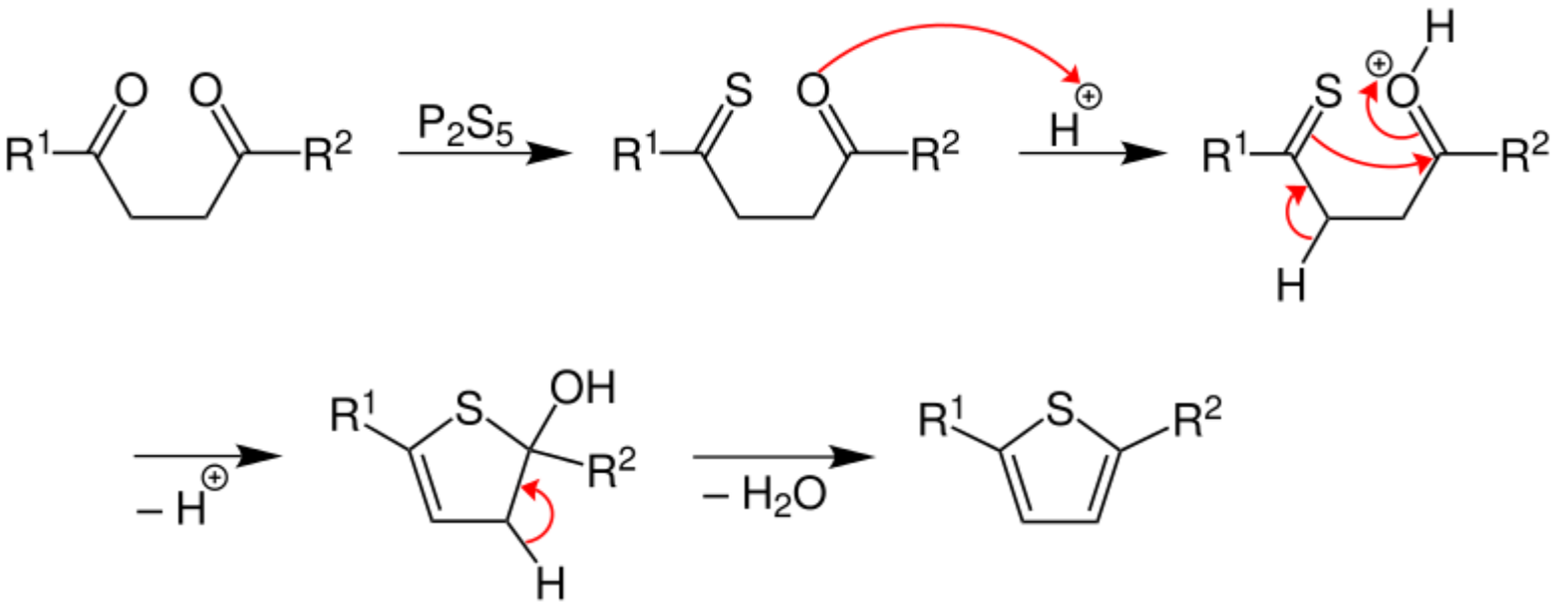


Paal Knorr Synthesis

Hydrogen sulfide can replace ammonia in the Paal–Knorr process and provide a synthesis of the thiophene ring.



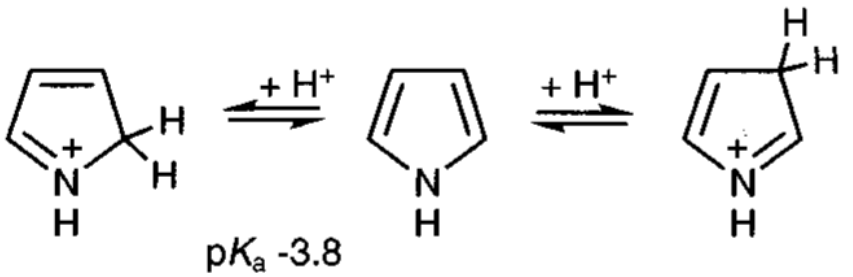
The mechanism is very similar to the furan synthesis. Alternatively the initial diketone may be converted to a thioketone with a sulfurizing agent, which then undergoes the same mechanism as the furan synthesis.



Electrophilic Substitution Reactions of Pyrrole

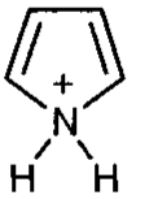
Whereas pyrroles are resistant to nucleophilic addition and substitution, they are very susceptible to attack by electrophilic reagents and react almost exclusively by substitution.

Protonation: In solution, reversible proton addition occurs at all positions. . In the gas phase, mild acids protonate pyrrole only on carbon and with a larger proton affinity at C-2 than at C-3.

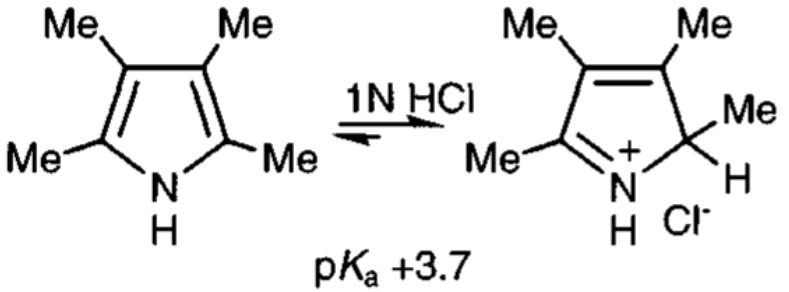


2*H*-pyrrolium cation (stablest)

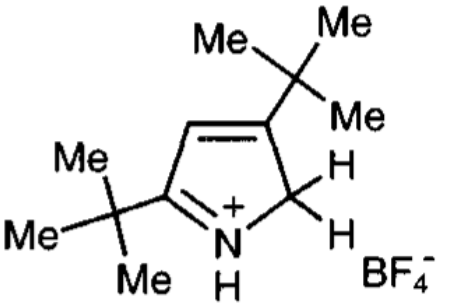
3*H*-pyrrolium cation



1*H*-pyrrolium cation (least stable)

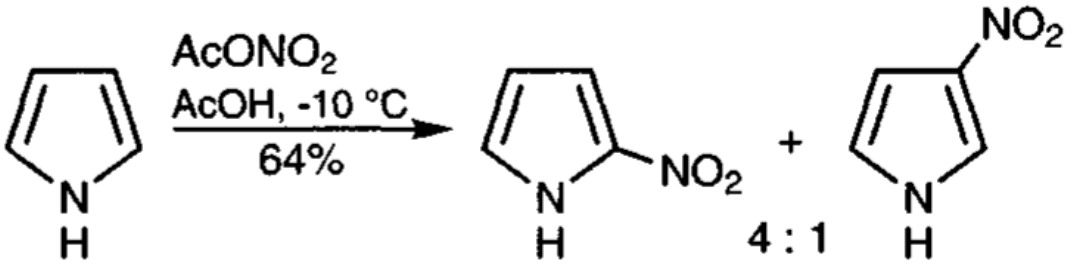


stable, crystalline salt of 2,4-di-*t*-butylpyrrole



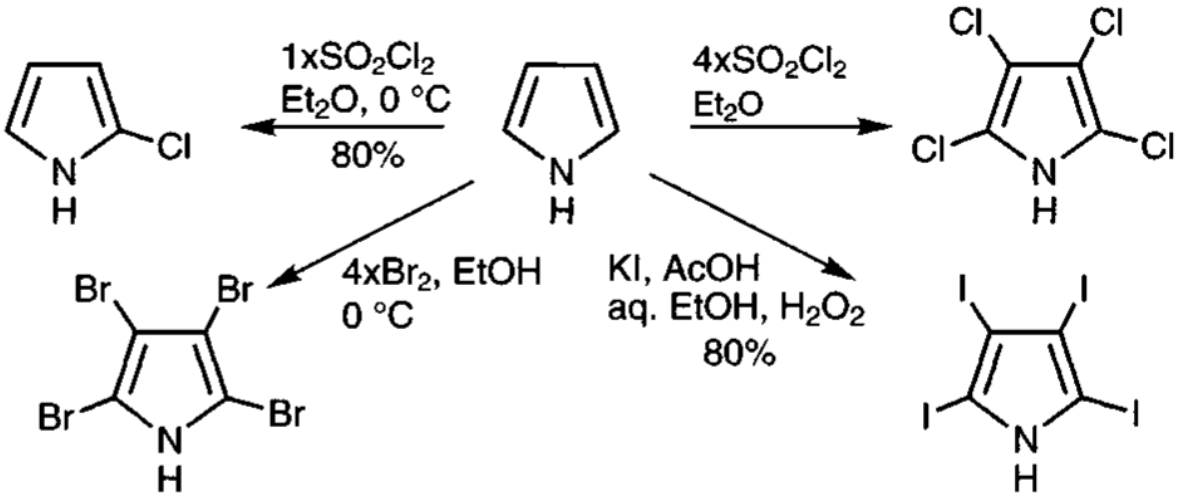
Electrophilic Substitution Reactions of Pyrrole

Nitration: Nitrating mixtures suitable for benzenoid compounds cause complete decomposition of pyrrole, but reaction occurs smoothly with acetyl nitrate at low temperature, giving mainly 2-nitropyrrole. This nitrating agent is formed by mixing fuming nitric acid with acetic anhydride to form acetyl nitrate and acetic acid, thus removing the strong mineral acid. In the nitration of pyrrole with this reagent it has been shown that C-2 is 1.3×10^5 and C-3 is 3×10^4 times more reactive than benzene.

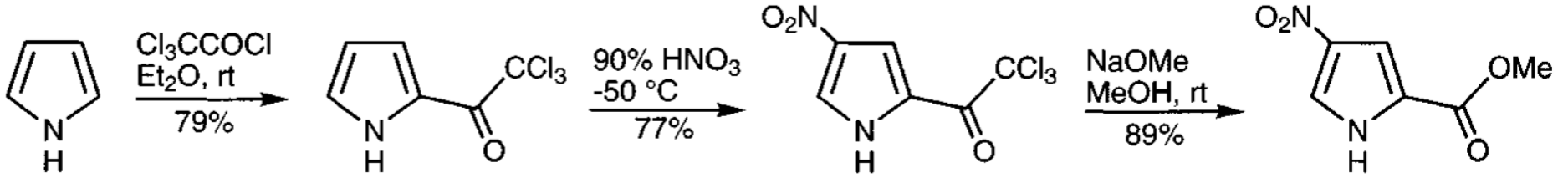


Electrophilic Substitution Reactions of Pyrrole

Halogenation: Pyrrole halogenates so readily that unless controlled conditions are used, stable tetrahalopyrroles are the only isolable products.

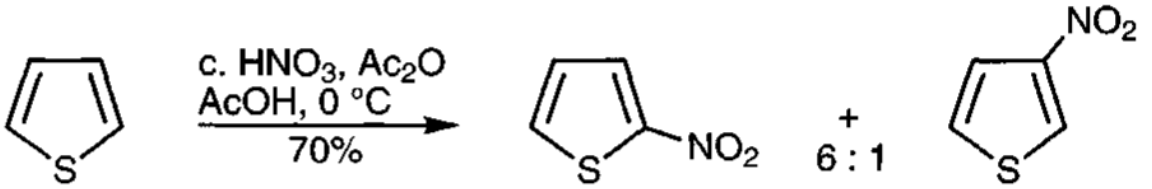


Acylation: Direct acetylation of pyrrole with acetic anhydride at 200°C leads to 2-acetylpyrrole as main product together with some 3-acetylpyrrole, but no N-acetylpyrrole.

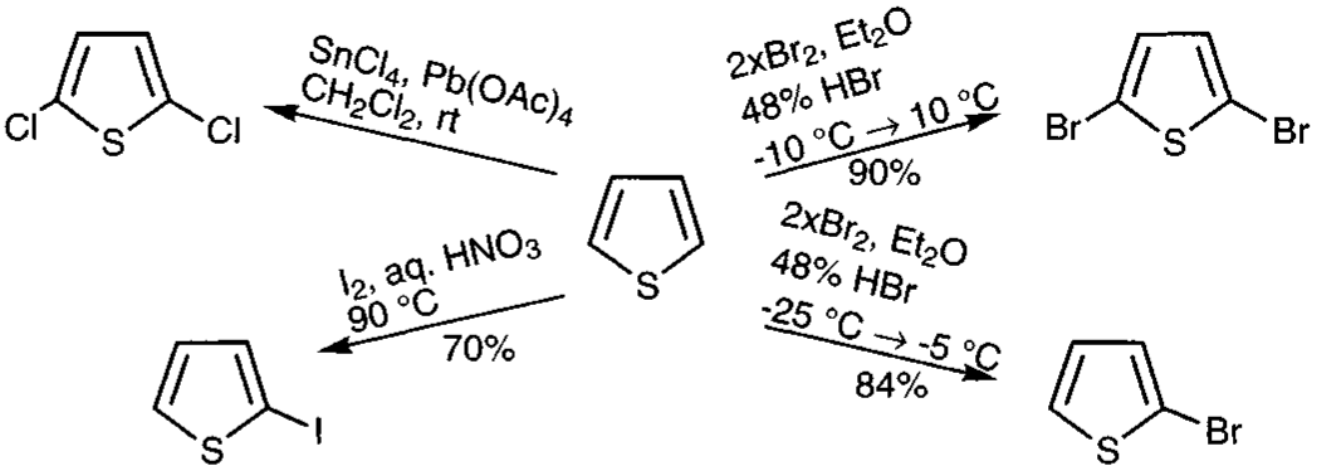


Electrophilic Substitution Reactions of Thiophene

Nitration: Nitration of thiophene needs to be conducted in the absence of nitrous acid which can lead to an explosive reaction the use of acetyl nitrate or nitronium tetrafluoroborate are satisfactory. Invariably the major 2-nitro-product is accompanied by approximately 10% of the 3-isomer



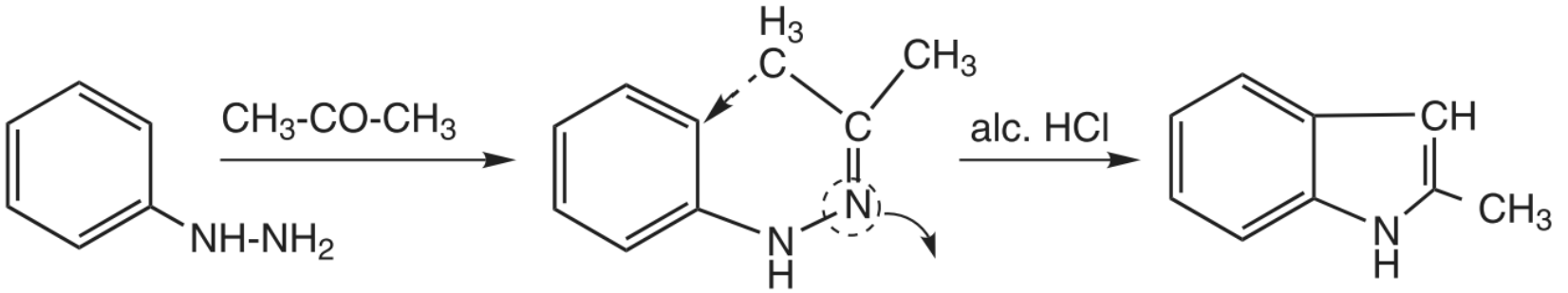
Halogenation: Halogenation of thiophene occurs very readily at room temperature and is rapid even at -30°C in the dark, halogenation occurs easily.



For more on the electrophilic substitution reactions of Pyrrole, Thiophene, Furan and other heterocycles, refer to the book "**Heterocyclic Chemistry by J. A. Joule and K. Mills**".
Soft copy is available at my website: https://sites.google.com/view/irshadium/for-students/books?authuser=0

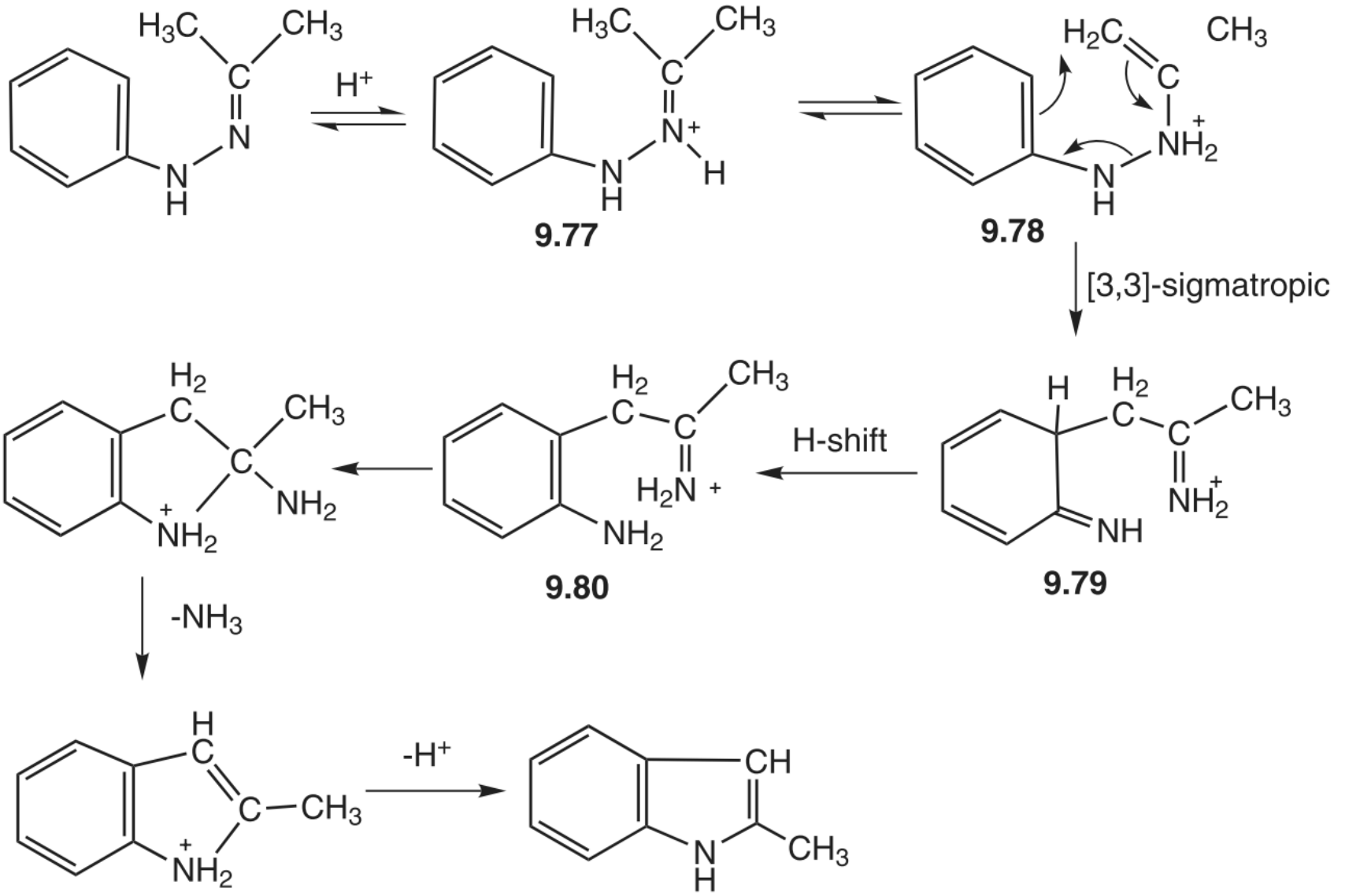
Fischer-Indole Synthesis

Because of its biological importance, numerous methods have been developed for the synthesis of indoles. The most important of these is that devised by Emil Fischer in 1883. It is still of great value in the synthesis of complex indoles. The Fischer synthesis is simple and begins by making phenyl hydrazones of aldehydes or ketones by reaction with phenylhydrazine, which was also discovered by Fischer. The hydrazone is heated with a protic [alcoholic HCl or polyphosphoric acid] or a Lewis acid ($ZnCl_2$, BF_3, etc.), and the indole ring is formed. Many indoles have been made by this process, but there are some restrictions. The ketone from which the phenylhydrazone is to be made must have at least one CH_3 or CH_2 group on the carbonyl group. The phenyl group may have electron-releasing substituents, but electron-withdrawing groups deactivate the ring and in general cannot be tolerated. The synthesis fails with acetaldehyde as starting material, and thus indole itself cannot be prepared by the acid-catalyzed method.



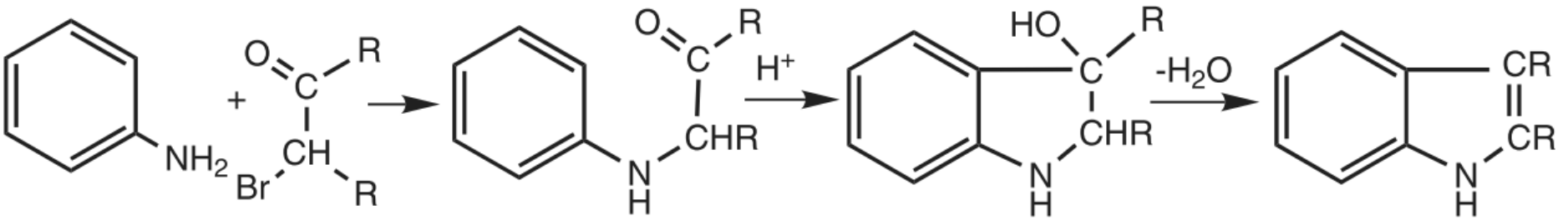
Fischer-Indole Synthesis

Mechanism



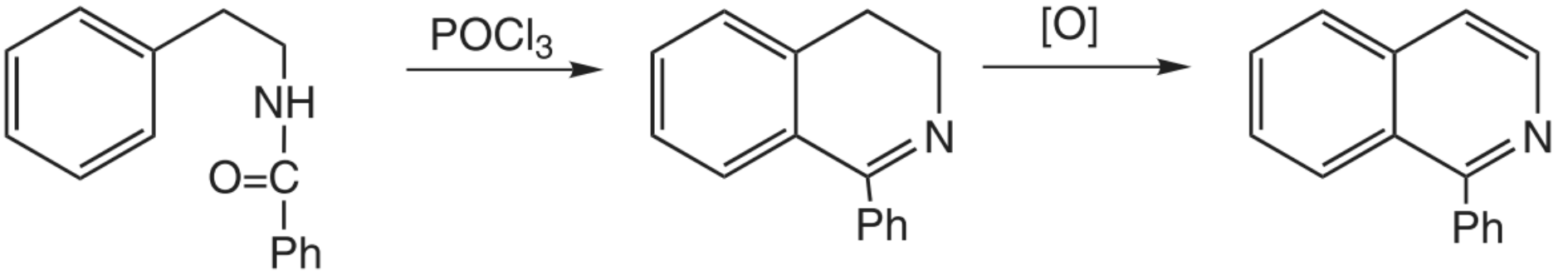
Bischler synthesis of Indoles

Among other classic but useful indole syntheses are those of Bischler (1892) and Madelung (1912). In the Bischler synthesis, an aniline derivative is alkylated by an alpha-haloketone. Heating the resulting product effects the electrophilic attack of the carbonyl group on the benzene ring; the loss of water from the product gives the indole structure



Bishlier-Napierlaski synthesis of isoquinolines

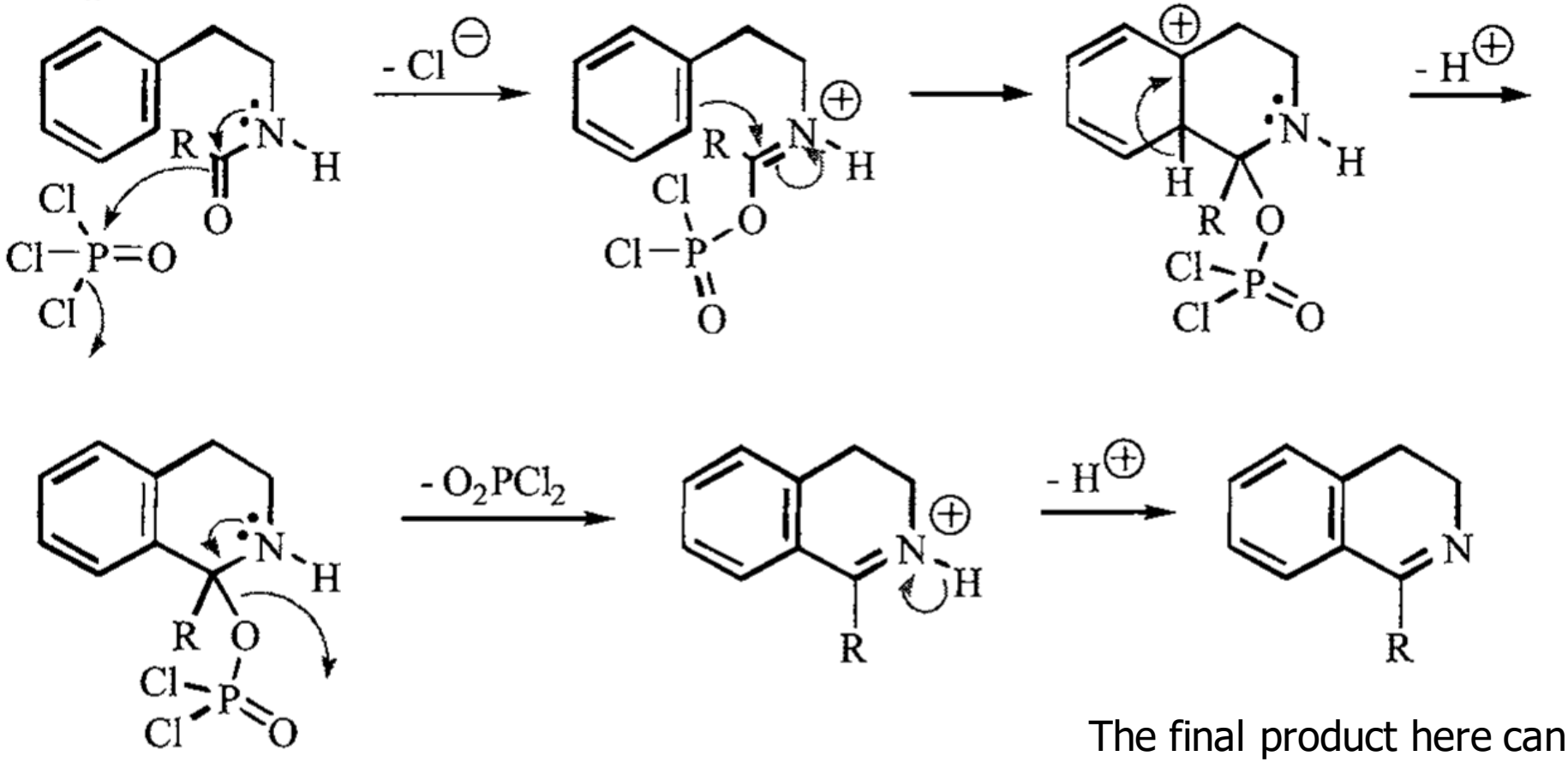
Many procedures have been developed for the synthesis of quinolines because of the prominence of the ring system in natural products and pharmaceuticals. Bischler-Napieralski synthesis that was reported in 1893. With some modifications, it is still of great value today for the synthesis of isoquinolines. The process is simple and involves the reaction of an acyl derivative (an amide) of a 2-arylethylamine with phosphorus oxychloride or phosphorus pentoxide. The product is a dihydroisoquinoline, which is easily oxidized to the iso-quinoline.



Bishlier-Napierlaski synthesis of isoquinolines

Mechanism

Proposed Mechanism:



The final product here can be oxidised to isoquinoline

References

1. Fundamentals of Heterocyclic Chemistry, L. D. Quin and J. A. Tyrell, 2010, John Wiley & Sons, Inc.
2. Heterocyclic Chemistry by J. A. joules and K. Mills
3. https://www2.chemistry.msu.edu/faculty/reusch/virttxtjml/heterocy.htm
4. https://profiles.uonbi.ac.ke/sderese/files/upc_213-nomenclature_of_heterocyclic_compounds_0.pdf