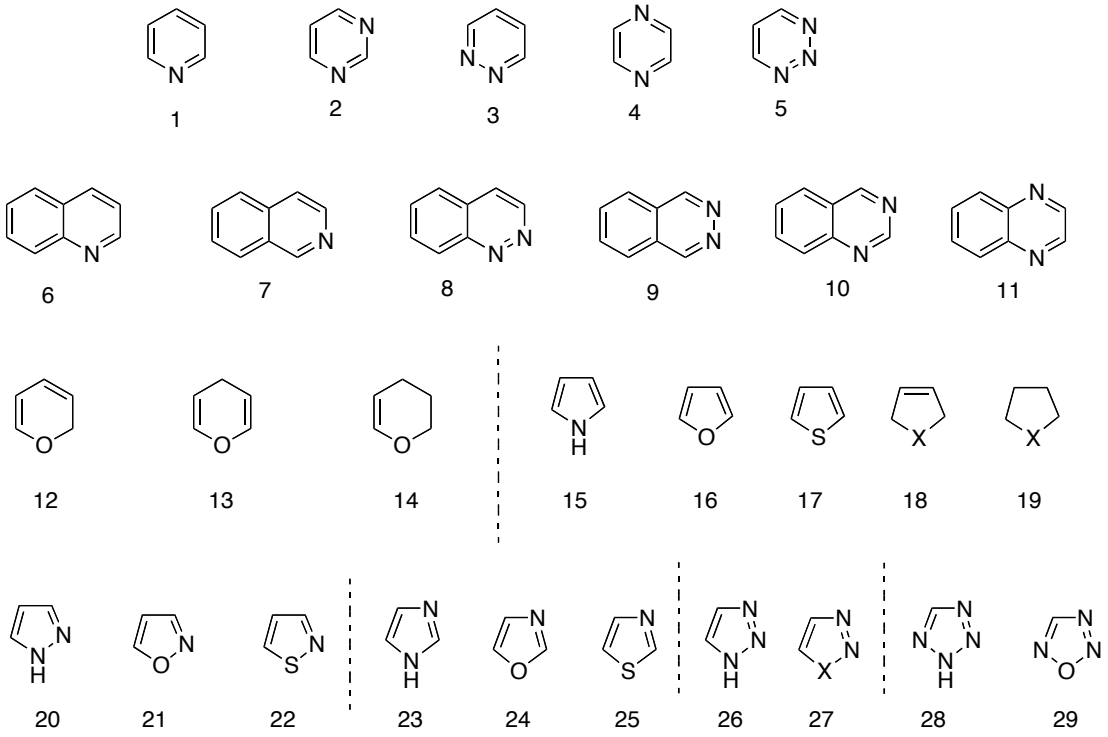
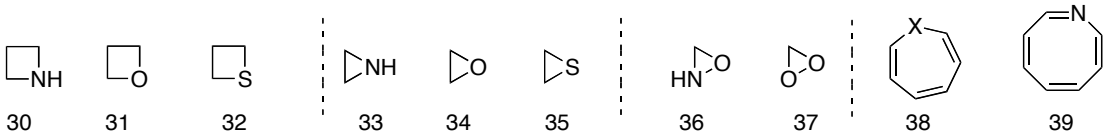
# Heterocyclic Chemistry – Monday Problem Session 18th Feb 2008

Heterocyclic chemistry plays a large part in the pharmaceutical industry, and as a result a good knowledge of the synthesis, reactivity and structure of various heterocycles is highly advantageous, especially when taking part in the interview process. Over the next few weeks we shall quickly brush-up on the basics (naming, nomenclature and structure), before delving into the core reactivity and synthesis of a few heterocycles, finally cumulating in a few blockbuster drug retrosynthetic analyses containing one or more heterocycles. Here goes….

1. The Name Game:



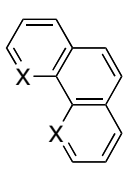

2. Some slightly trickier ones (O = ‘oxa’, S = ‘thia’ and N =’aza’):



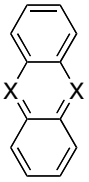

N.B. You might find the Hantzsch-Widman stem suffixes nomenclature useful.

| Ring Size | Maximally unsaturated | One Double Bond | Saturated |
|---|---|---|---|
| 3 | -irene, -irine (N) | - | -irane, -iridine (N) |
| 4 | -ete | -etene, -etine (N) | -etane, -etidine (N) |
| 5 | -ole | -olene, -oline (N) | olane, -olidine (N) |
| 6 | -ine | - | -ane, -inane (N) |
| 7 | -epine | - | -epane |
| 8 | -ocine | - | -ocane |
| 9 | -onine | - | -onane |
| 10 | -ecine | - | -ecane |

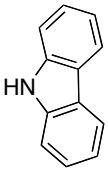
3. Work out the IUPAC fused heterocycle nomenclature (Also the name of the compounds where X =C)



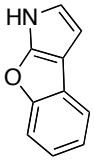

40



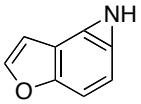

41



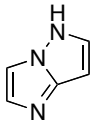

42



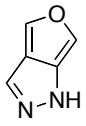

43




44




45

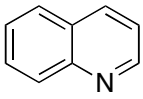



46

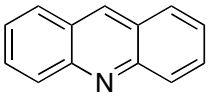
Reactivity of Pyridine Derivatives

4. Why do benzo-fused pyridines react more readily with nucleophiles? Propose where nucleophilic and electrophilic attack occurs on pyridones **50** and **51**, and *N*-oxide **52**.

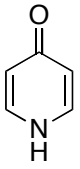

47



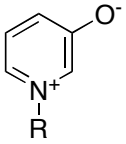

48



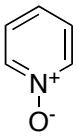

49




50




51




52

5. Try and estimate the pKa of compounds **2**-**5** and give a rational of the order described given that the pKa of pyridine (**1**) is 5.2.

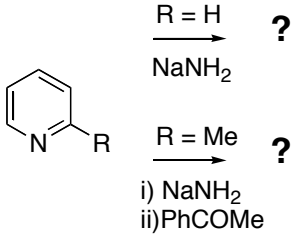
6. Try and explain the trends in the effect of substituents on the basicity (*i.e.* pKa) of pyridine – the table shows the ΔpKa

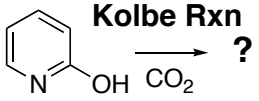
| | Me | Ph | $NH_2$ | OMe | Cl | $NO_2$ |
|---|---|---|---|---|---|---|
| 2-Substituted | 0.8 | 0.1 | 1.7 | - 1.9 | - 4.5 | - 7.8 |
| 3-Substituted | 0.5 | - 0.4 | 0.9 | - 0.3 | - 2.4 | - 4.4 |
| 4-Substituted | 0.8 | 0.3 | 4.0 | 1.4 | - 1.4 | - 3.6 |

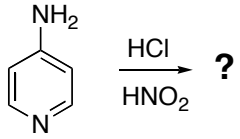
7. How do you form a pyridine-*N*-oxide and give an example of its reactivity with a nucleophile? How does this differ from nucleophilic substitution with pyridine?

8. Acetic anhydride and phosphorus oxychloride are the reagents for two classical transformations using pyridine-*N*-oxide; provide the mechanisms.

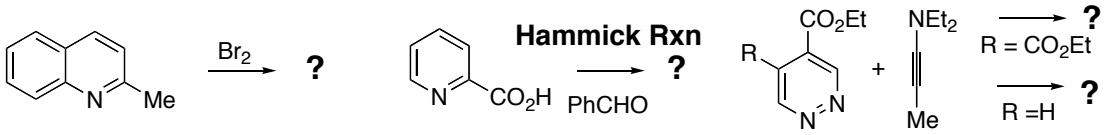
9. What are the products of the following reactions (and give the mechanism):

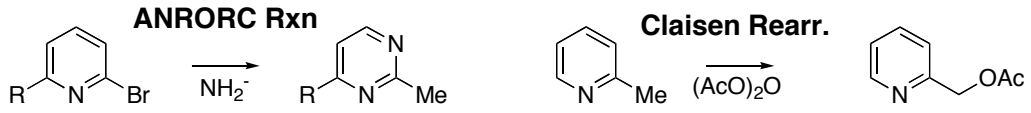


10. And finally a few toughies:



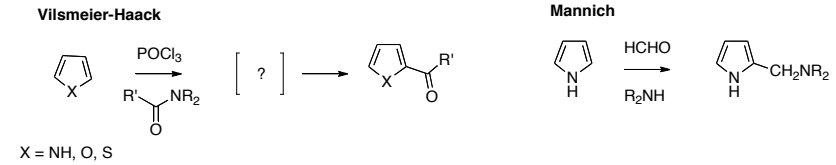

## Heterocyclic Chemistry – Monday Problem Session 25th Feb 2008

Carrying on from last weeks master class we're now going to focus on 5-membered ring heterocycles, and there's even some homework to do for the problem class next week…but more of that later. For now:

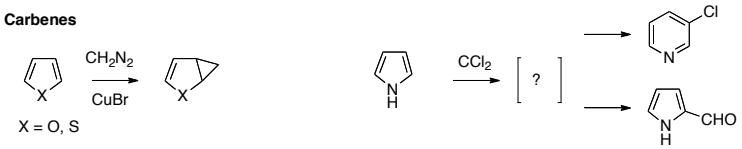
1. Below is a table of $pK_a$ data for a few 5-membered heterocycles. Try and glean some trends from the information below:

| Heterocycle | Substituent | $pK_a$ | Position of protonation |
|---|---|---|---|
| Pyrrole | | - 3.8 | 2 |
| | 1-methyl | - 2.9 | 2 |
| | 2-methyl | - 0.2 | 2 |
| | 3-methyl | - 1.0 | 2 |
| Indole | | - 3.6 | 3 |
| | 1-methyl | - 2.3 | 3 |
| | 2-methyl | - 0.3 | 3 |
| | 3-methyl | - 4.6 | 3 |
| Pyrrole | 2,5-Di$^t$butyl | -1.01 | 2 |
| Furan | | - 10.01 | 2 |
| Thiophene | | - 10.16 | 2 |

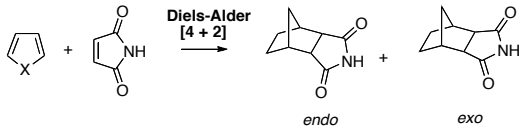
2. Reactivity of 5-membered rings: Propose the mechanisms for the two classical reactions (N.B. Only pyrrole derivatives undergo Mannich type reactions)




3. Now some carbene chemistry. How would you generate the two carbenes in the example below? Propose the mechanism and why does cyclopropanation of pyrrole generate the 2-substituted pyrrole solely?




4. Furan and *N*-substituted pyrroles are good substrates for the Diels-Alder reaction. What makes the *endo* adduct kinetically favourable and the *exo* adduct thermodynamically favourable?




5. More pKa's: This time of 5-membered heterocycles containing 2-heteroatoms. Say what you see…

| Ring Systems | X = NH | X = NMe | X= O | X = S |
|---|---|---|---|---|
|  | 2.52 | 2.06 | -2.97 | -0.51 |
|  | 6.95 | 7.33 | 0.8 | 2.53 |
|  | 1.17 | 1.25 | | |
|  | 1.31 | 0.42 | - 4.7 | |
|  | 5.53 | 5.57 | -0.13 | 1.2 |