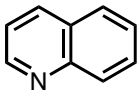
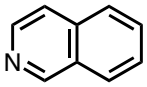
Chapter 6

Quinolines and isoquinolines: Reactions and synthesis

Pyridine

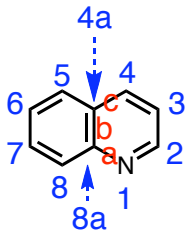


Quinoline

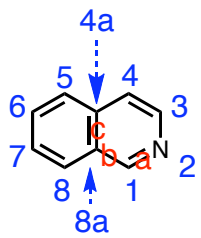


Isoquinoline

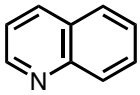
Quinolines and isoquinolines: Benzo condensed pyridines



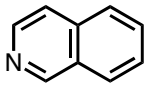
Quinoline
Benzo[b]pyridine
(1-azanaphtalene)



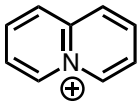
Isoquinoline
Benzo[c]pyridine
(2-azanaphtalene)



Quinoline



Isoquinoline



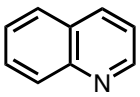
Quinolizinium cations

chapt. 25

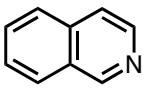
Reaction with electrophiles

Protonation on N

pKa 5.2

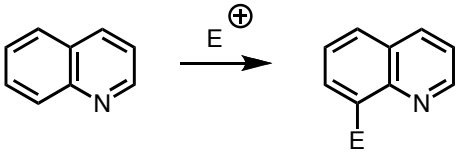


pKa 4.9

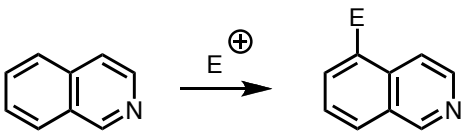


pKa 5.5

Electrophilic Ar subst

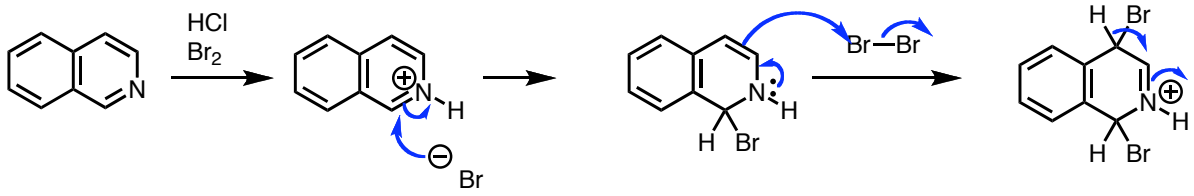


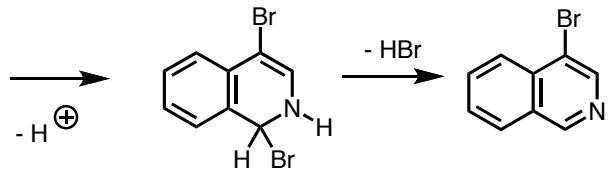
Major isomers shown

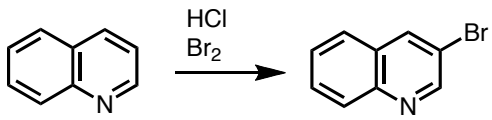


Benzene more electron rich than pyridine

Halogenation in the pyridine ring

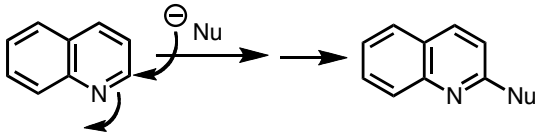




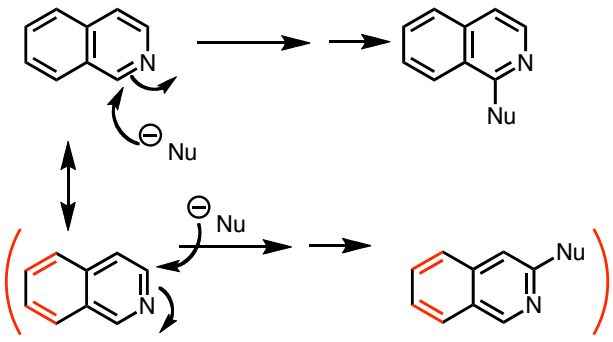


Reaction with nucleophiles

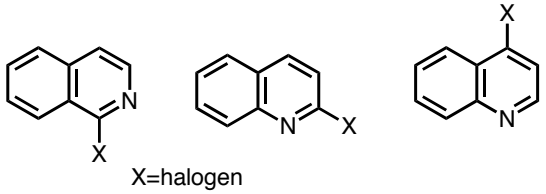
Exchange of H



c.f. react α to N in pyridines

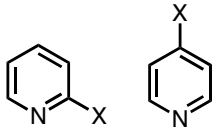


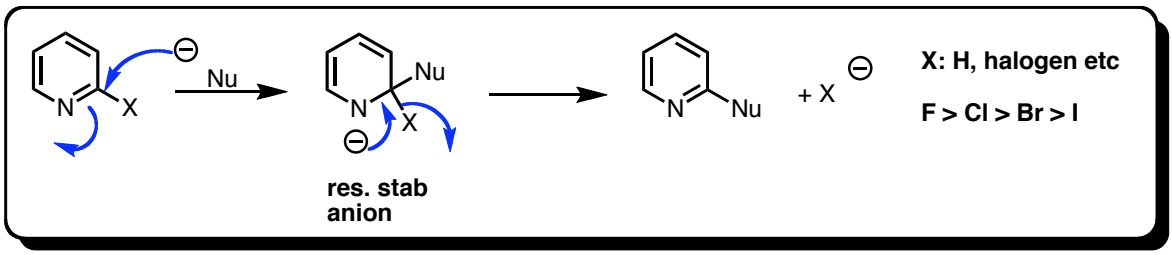
Exchange of halogen etc.



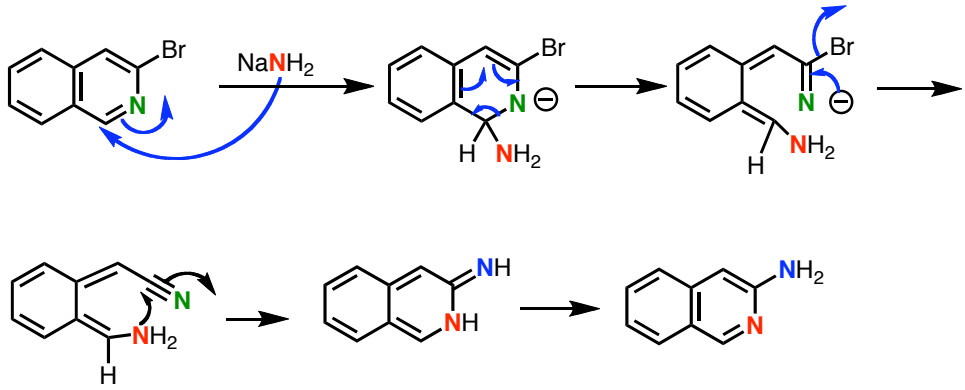
X=halogen

Reactivity towards Nu as





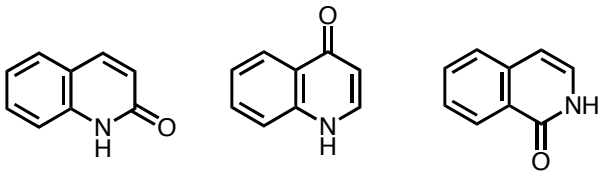
ANRORC (Add. of Nu., Ring Opening and Ring Closure)



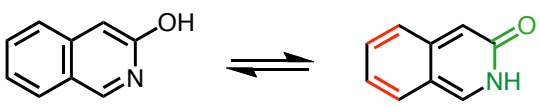
Oxy- and Aminoderivatives - Tautomeri

-All - isomers amino (not imino)

-"One"-Isomers:



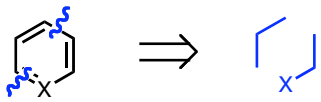
Tautomeric Mixt.:

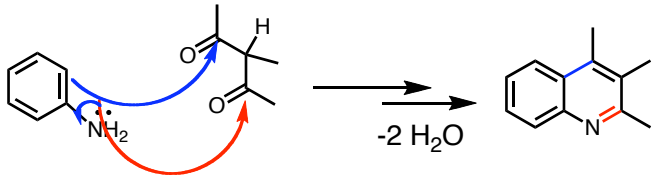


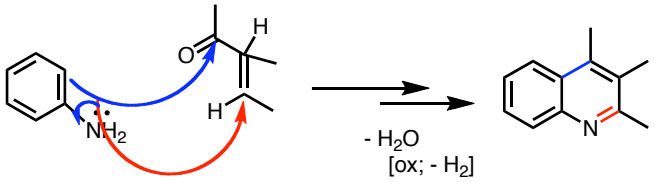
Quinoid struct.: Negative
Amide: Positive, c.f. pyridine

Synthesis - Quinolines

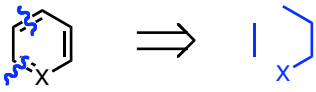
Chapt. 3
Strategy b, 6-membered rings

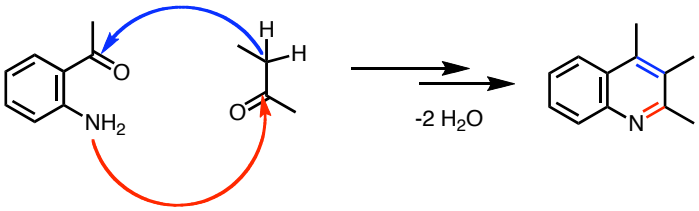






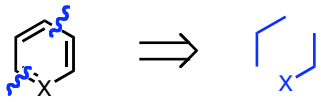
"New" strategy

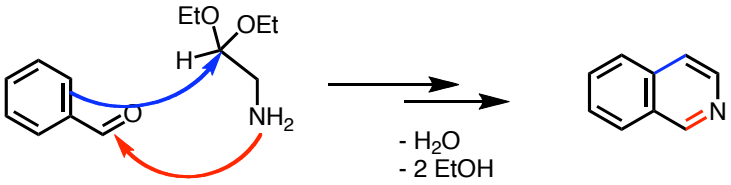




Synthesis - Isoquinolines

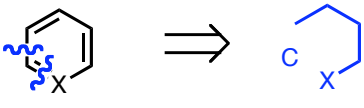
Chapt. 3
Strategy b, 6-membered rings

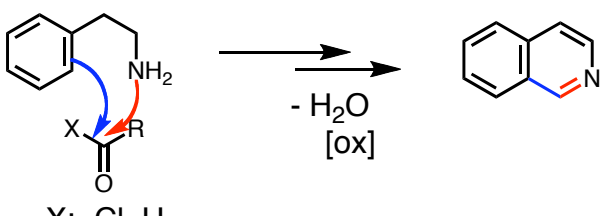




"Blue bonds" formed by FC type react.

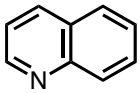
"New" strategy



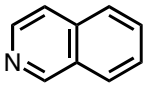


X: -Cl, H

Alkaloid natural products



Quinoline

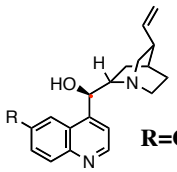


Isoquinoline

- **Largets class of secondary metabolites, >6500 compds known**
- **Contains N, most compds basic (alkaline), often heterocyclic**
- **Often highly toxic**
- **Found in certain higher plants (seldom in bacteria)**
- **Little is known regarding why alkaloids are produced**
- **Biosynthesis from amino acids**

Quinoline alkaloids

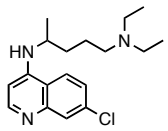
Cinchona pubescens (Kinatre) from South America



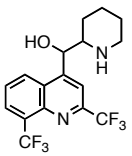
R=OMe: Quinine (Cinchonidine epimer at C-9)

R=H: Quinidine (Cinchonine epimer at C-9)

Quinidine: Antiarytmic
Quinine: Antimalaria



Chloroquine



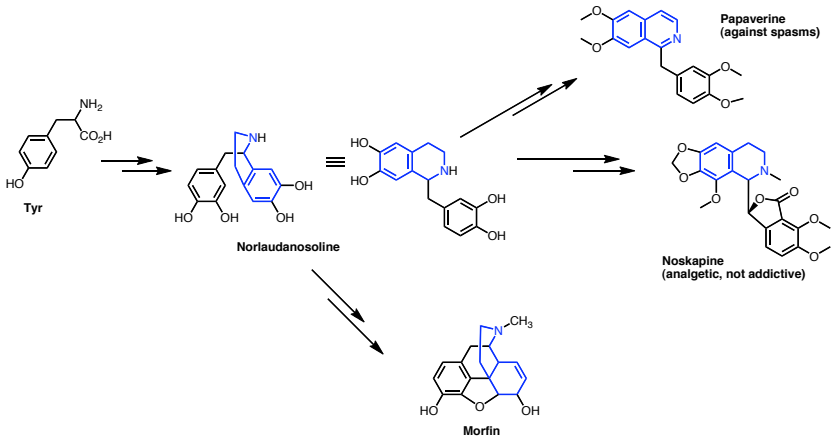
Mefloquine

Dihydroquini(di)ne and der.

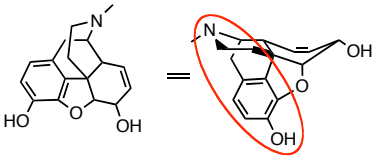
Chiral ligands

Asym. dihydroxylation (Sharpless)

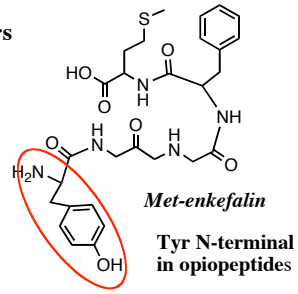
Isoquinoline alkaloids



Morfinanalogs, binds to opiopeptide (endorfin / enkefalin) reseptors



Morfin



Met-enkefalin

Tyr N-terminal in opiopeptides