Gábor Krajsovszky
Heterocyclic compounds

ISBN: 978-615-5722-01-1

Responsible editor: Gábor Krajsovszky
Publisher's reader: István Mándity
Translated by Péter Tétényi

Department of Organic Chemistry
Pharmaceutical Faculty
Semmelweis University
Budapest, 2018

Acknowledgements

**The editor wants to express many thanks
to Dr. István Mándity, who is Associate Professor and Director of Department of Organic Chemistry,
for the careful proofreading service of the current manuscript,
as well as to Dr. Péter Tétényi, who is Assistant Professor,
for the translation to English language.**

**Moreover, the editor renders many thanks to Mrs. Ferenc Juhász and Ms. Nikoletta Zlatzky
laboratory assistants for drawing material of the figures.**

**Dr. Gábor Krajsovszky
Associate Professor
Department of Organic Chemistry**

Literature used

Alan R. Katritzky, Charles W. Rees:
Comprehensive Heterocyclic Chemistry
Parts 2-3, 4-6, 7
Pergamon Press 1984
Oxford • New York • Toronto • Sydney • Paris • Frankfurt

T. Eicher, S. Hauptmann, A. Speicher:
The Chemistry of Heterocycles
Structure, Reactions, Syntheses, and Applications
Wiley-VCH GmbH 2003
Weinheim

E. Breitmaier, G. Jung:
Organische Chemie
Grundlagen, Stoffklassen, Reaktionen, Konzepte, Molekülstruktur
Georg Thieme Verlag 1978, 2005
Stuttgart • New York

Clauder Ottó:
Szerves kémia II/2. Egyetemi jegyzet
Semmelweis OTE Budapest, 1980

Bruckner Győző:
Szerves kémia III−1.
Tankönyvkiadó, Budapest, 1964

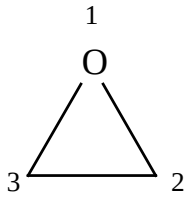
Természettudományi Lexikon – Harmadik kötet
Clauder Ottó: 'Heterociklusos vegyületek' címszó, 155-161.
Főszerkesztő: Erdey-Grúz Tibor
Akadémiai Kiadó, Budapest, 1966

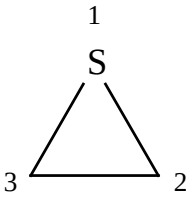
Szabó László:
Szerves kémia előadások - heterociklusos vegyületek
Semmelweis OTE Budapest, 1978-1996

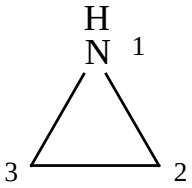
Three-, four- and five-membered heterocycles with one heteroatom and their derivatives

Three-membered heterocycles with one heteroatom and their derivatives

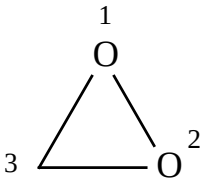
Nomenclature



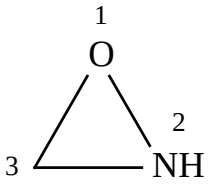




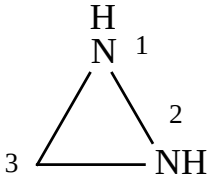
Hantzsch-Widman name	oxirane	thiirane	aziridine
Radicofunctional name	ethylene oxide	ethylene sulfide	ethylene imine
Replacement name	oxacyclopropane	thiacyclopropane	azacyclopropane



dioxirane

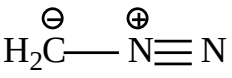


oxaziridine

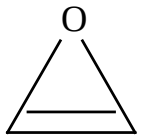


diaziridine

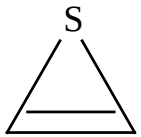
diazomethane



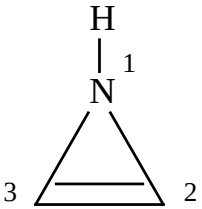
structural isomers



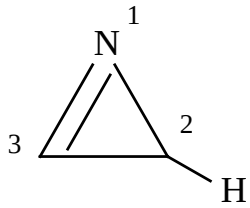
oxirene



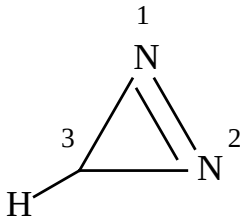
thiirene



1*H*-azirine
2-azirine



2*H*-azirine
1-azirine

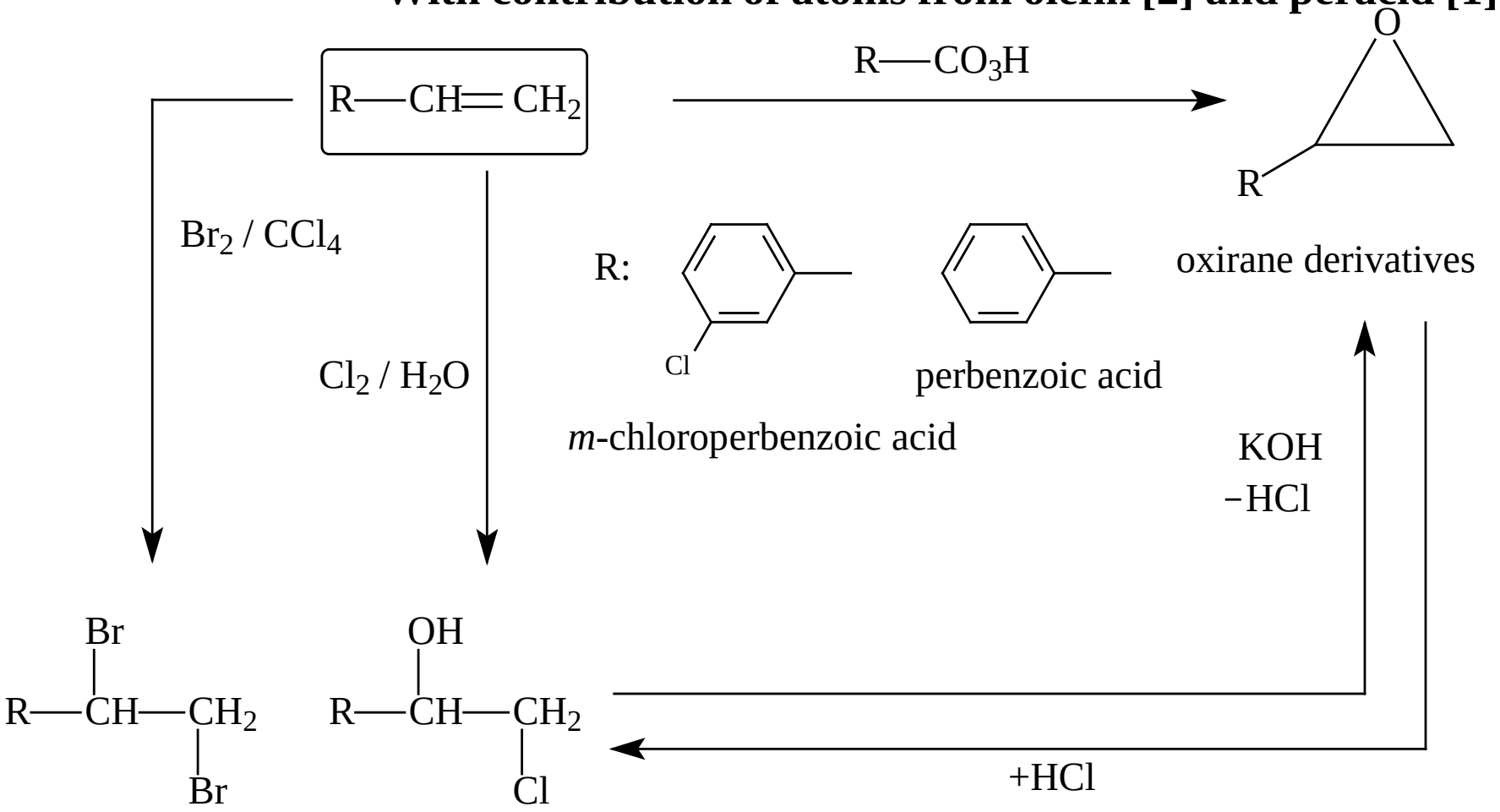


3*H*-diazirine

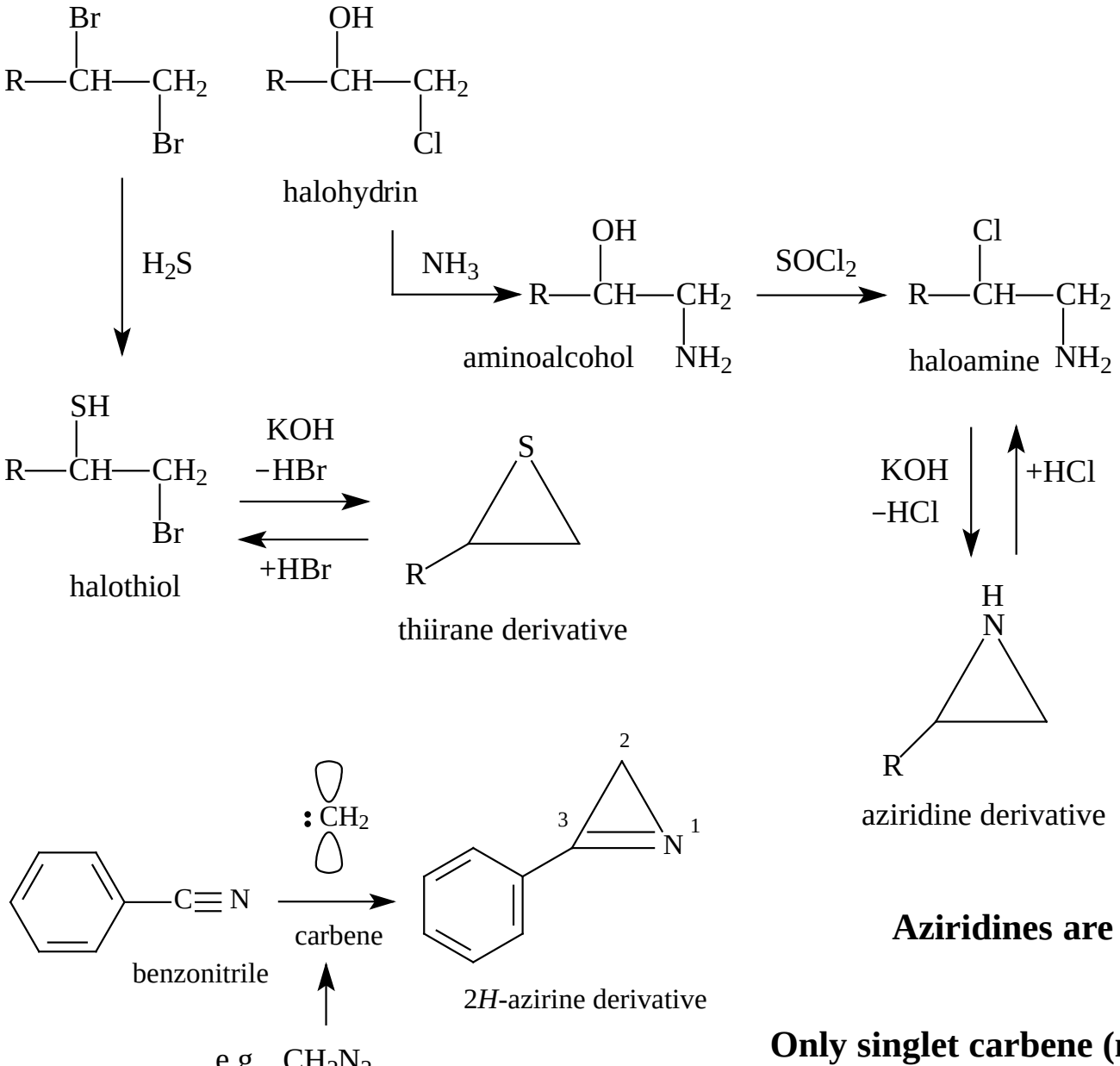
Preparation

[2+1] intermolecular ring closure

With contribution of atoms from olefin [2] and peracid [1]



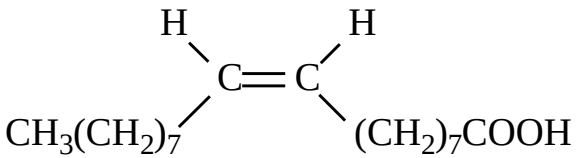
Ethylene oxide is used for gas sterilisation. It must be diluted with carbon dioxide, otherwise explosive mixture would be formed with air. Peracids are explosive, toxic compounds!



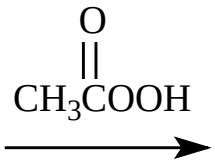
Aziridines are carcinogen compounds.

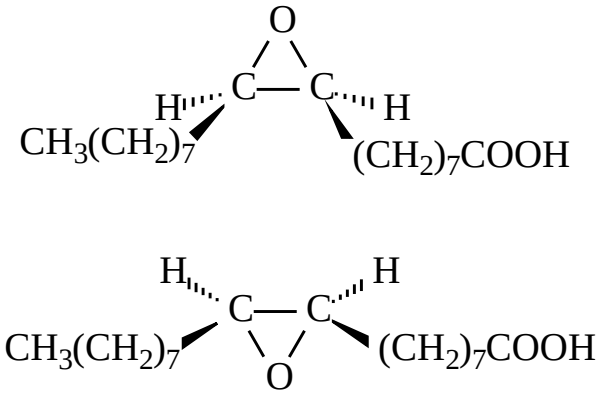
Only singlet carbene (not triplet) is suitable for the reaction.

Epoxidation with peracid without catalyst



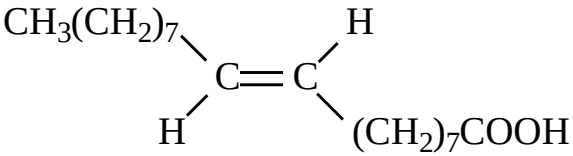
oleic acid



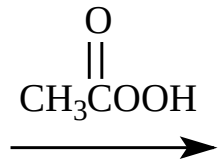


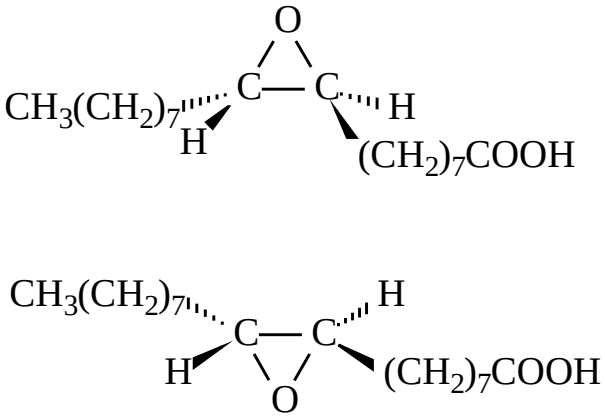
enantiomers

1:1



elaidinic acid



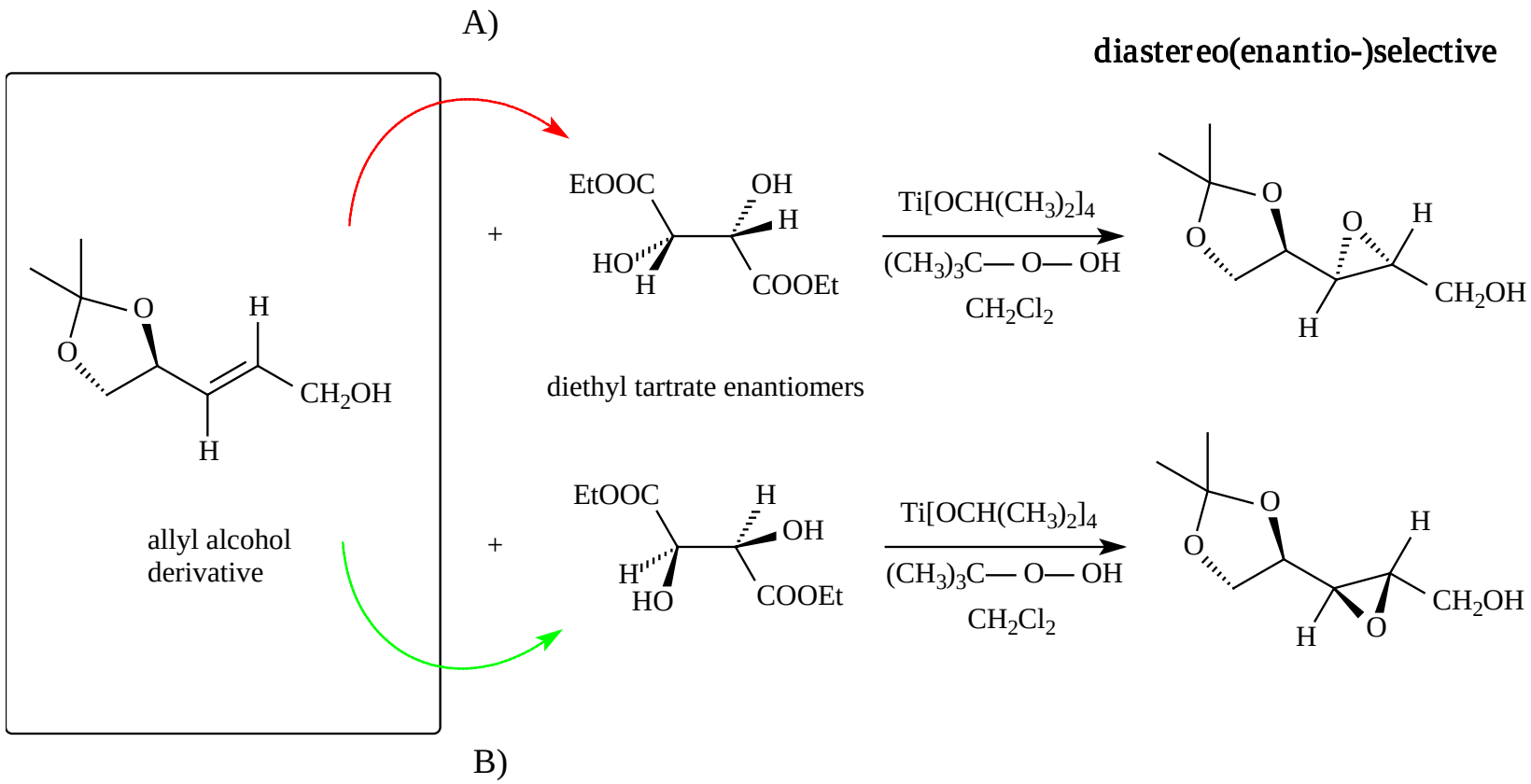


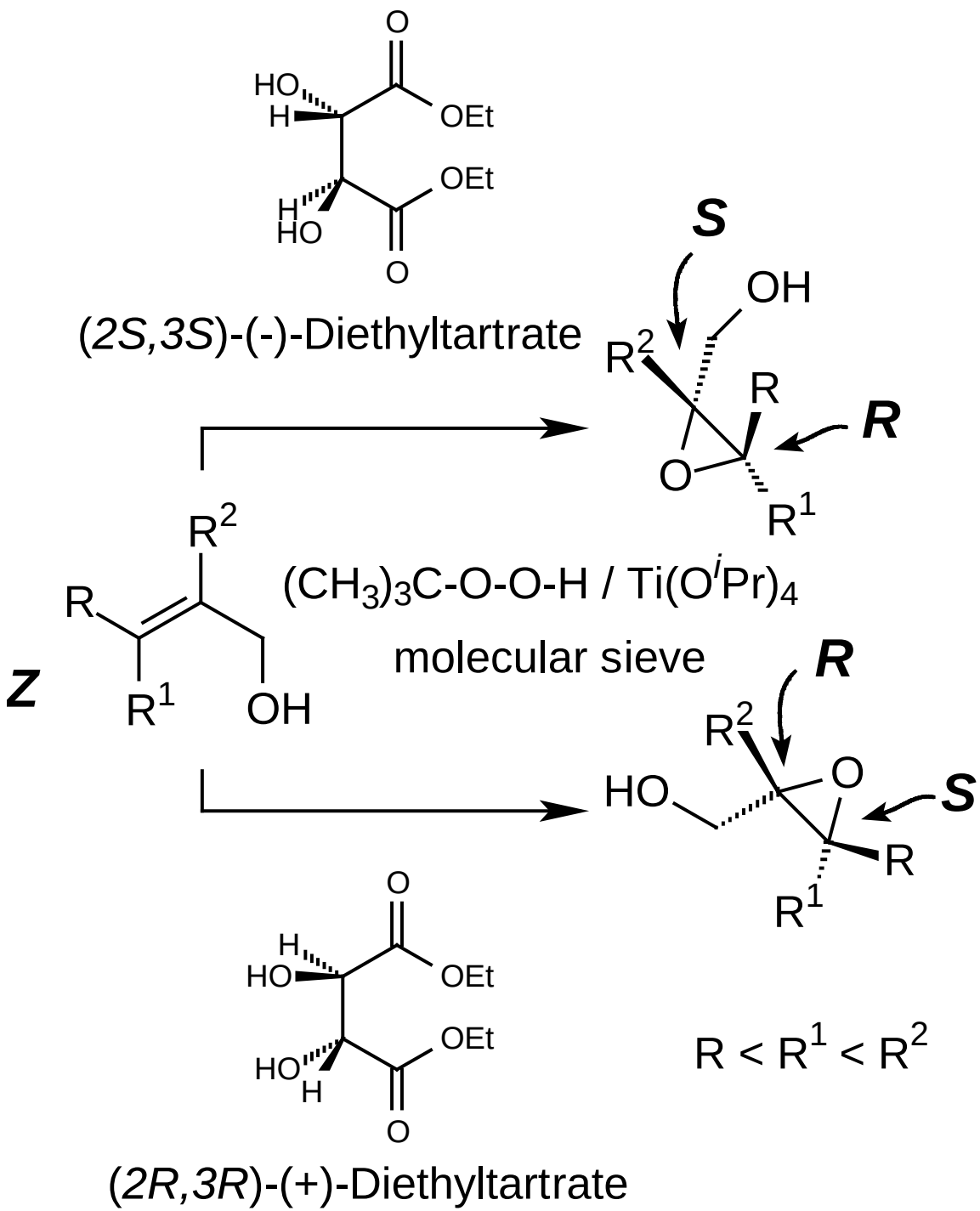
enantiomers

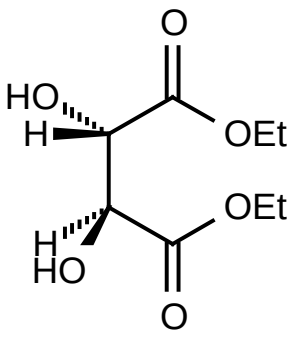
1:1

Asymmetric oxidation of alkenes
Sharpless epoxidation

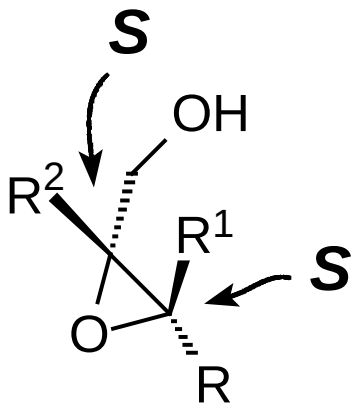
Knowles, Noyori, Sharpless *2001 Nobel-prize, Chemistry, chiral catalysis*

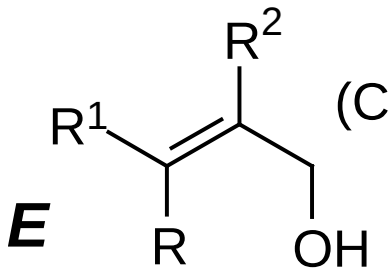



(2S,3S)-(-)-Diethyltartrate
S
R
Z
(CH3)3C-O-O-H / Ti(OiPr)4
molecular sieve
R < R1 < R2
(2R,3R)-(+)-Diethyltartrate



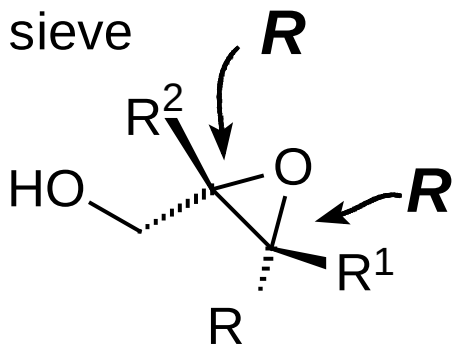
(*2S,3S*)-(-)-Diethyltartrate

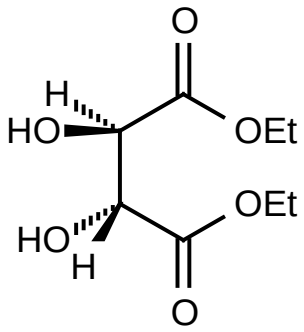




$(CH_3)_3C\text{-}O\text{-}O\text{-}H$ / $Ti(O^iPr)_4$

molecular sieve

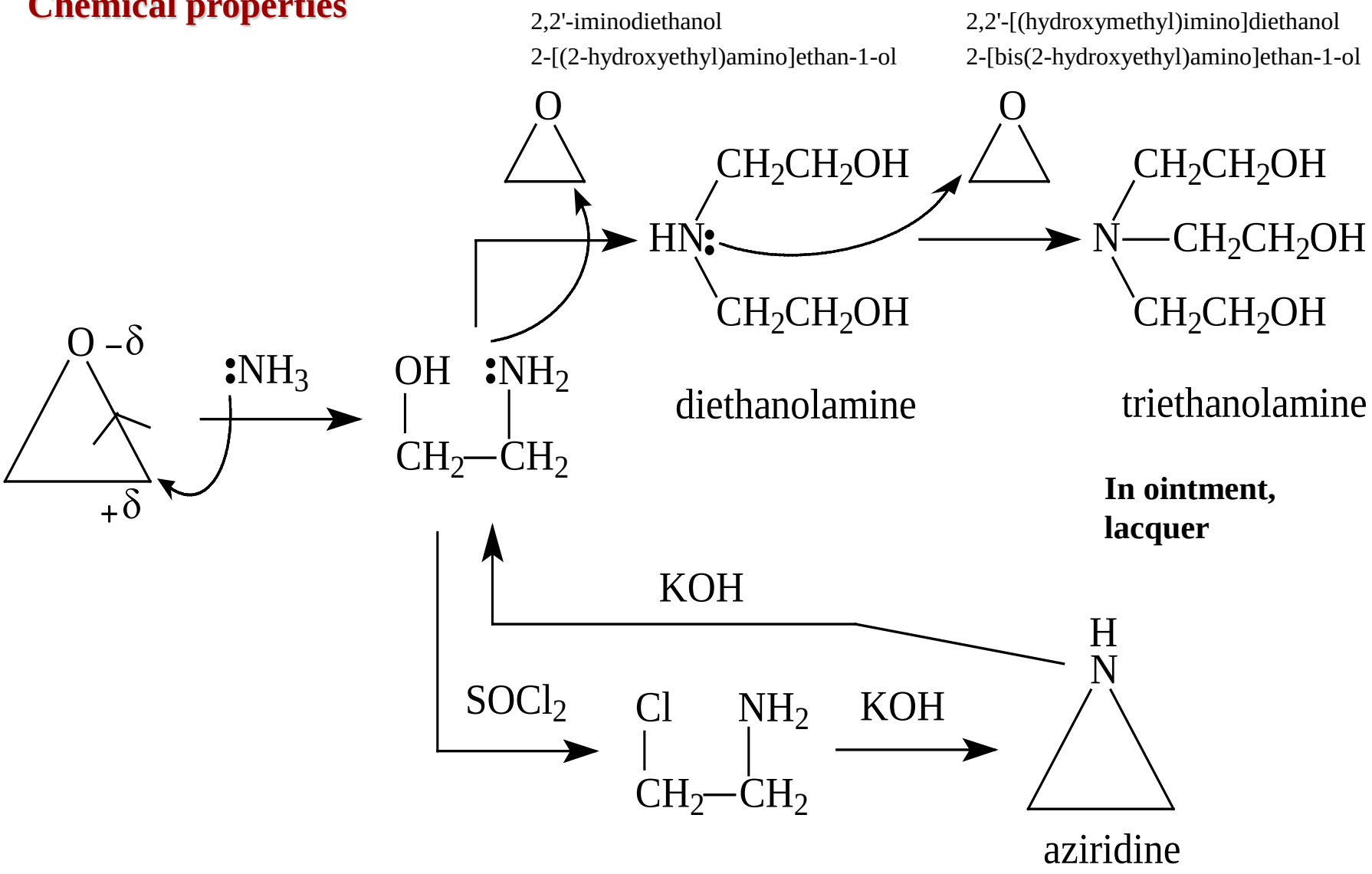




(*2R,3R*)-(+)-Diethyltartrate

$R < R^1 < R^2$

Chemical properties



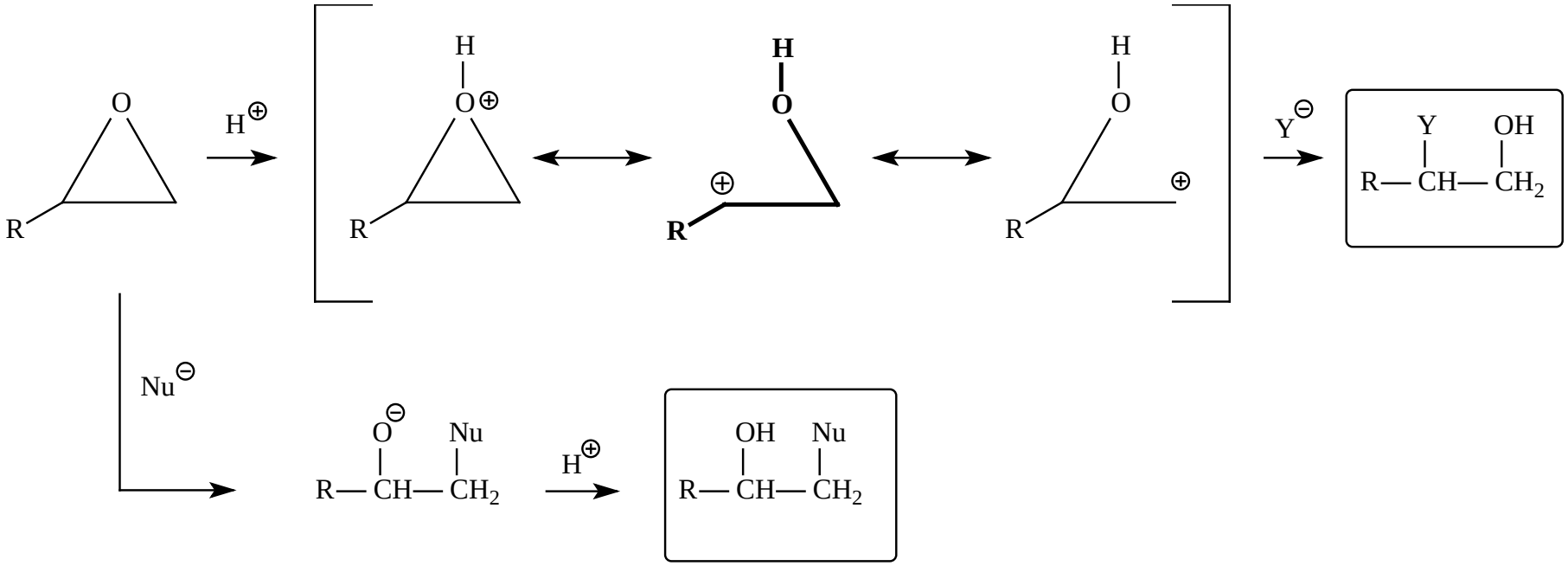
***Baeyer* strain is greater for 3-membered rings than for 4-membered ones. As a consequence of this ring opening, reactions are easier for the former ones.**

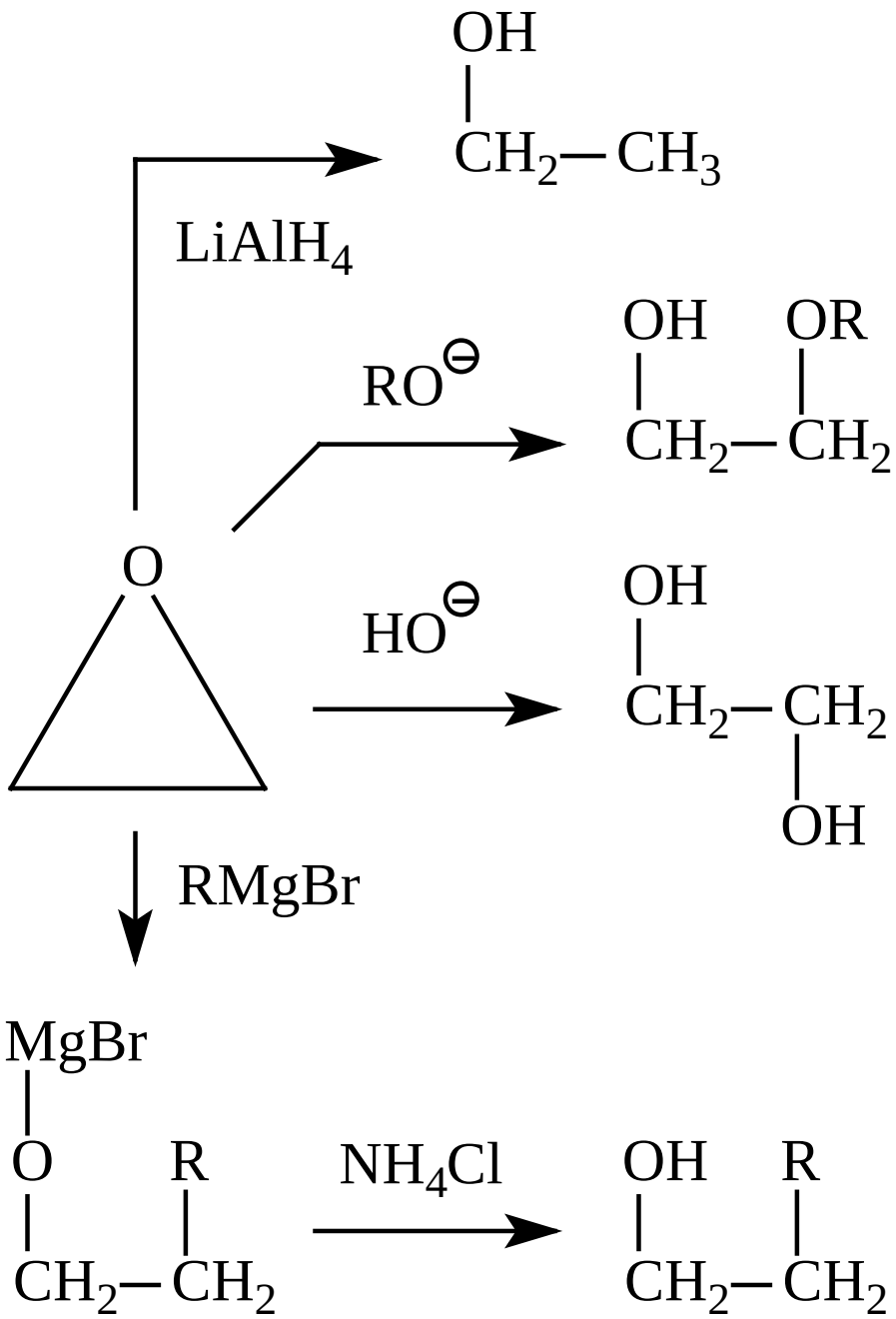
Ring opening – it may occur with acid or with base

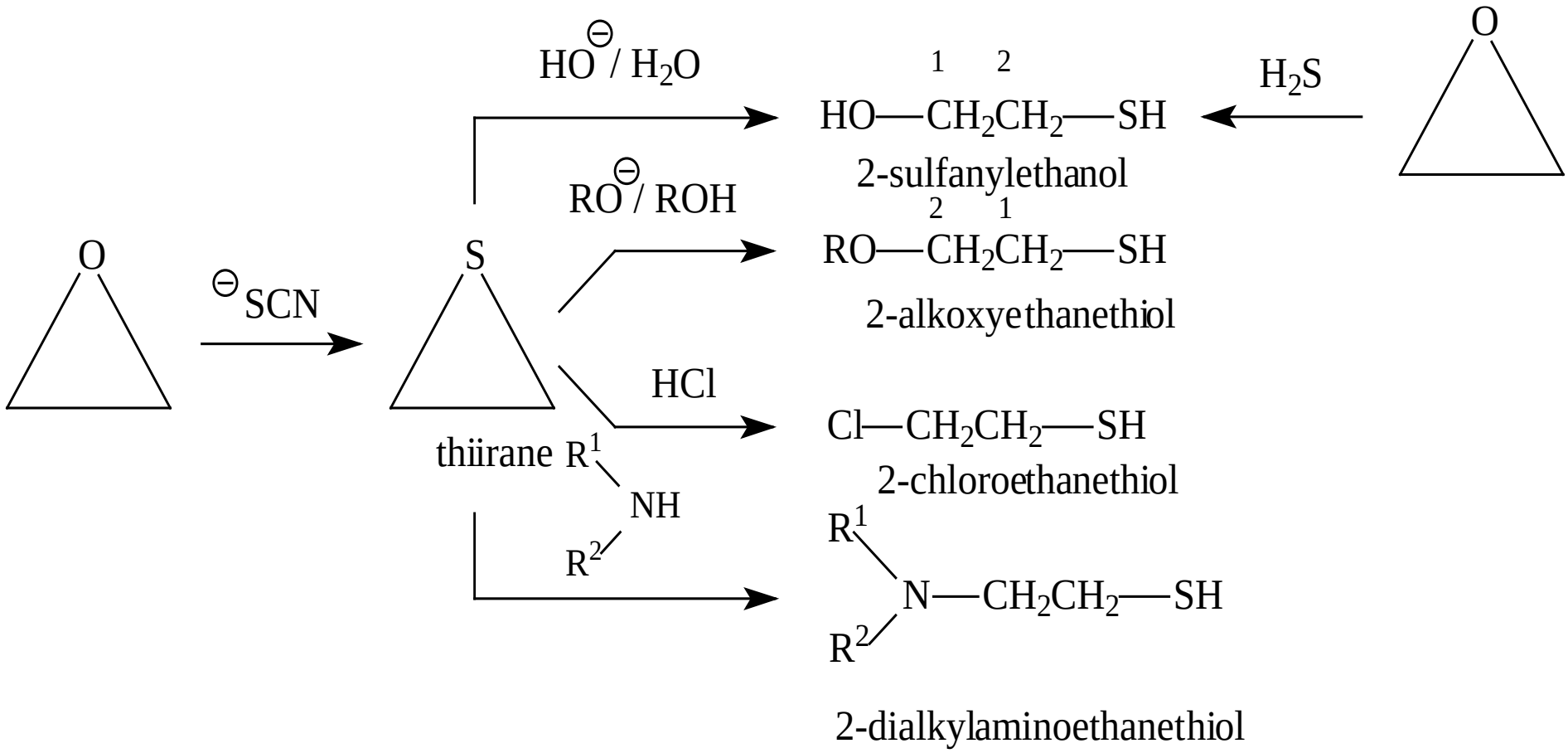
Different regiochemistry:

with acid: S_N1-like mechanism (alkyl cation of higher order is more stable)

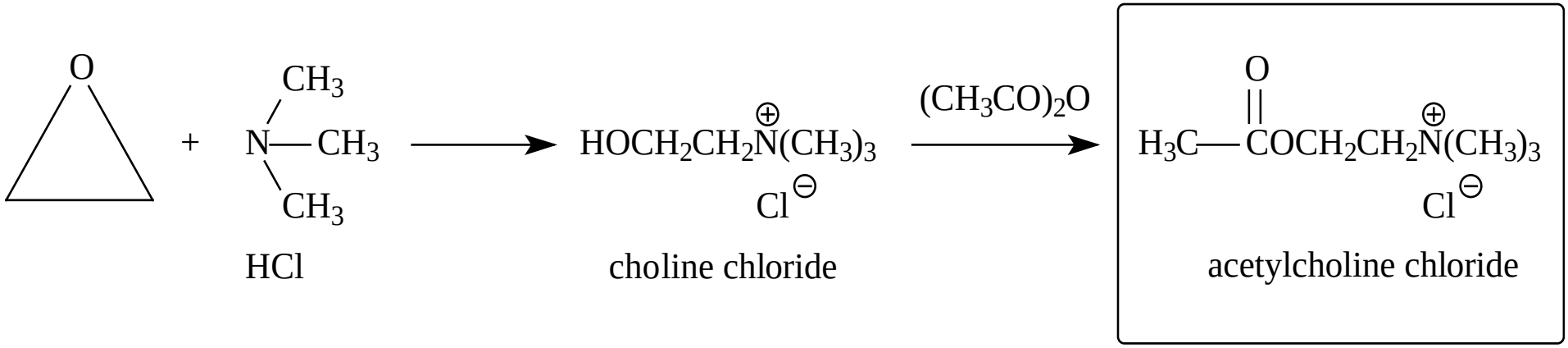
with base: S_N2 mechanism (for sterical reasons, the nucleophile attacks the carbon of lower order)



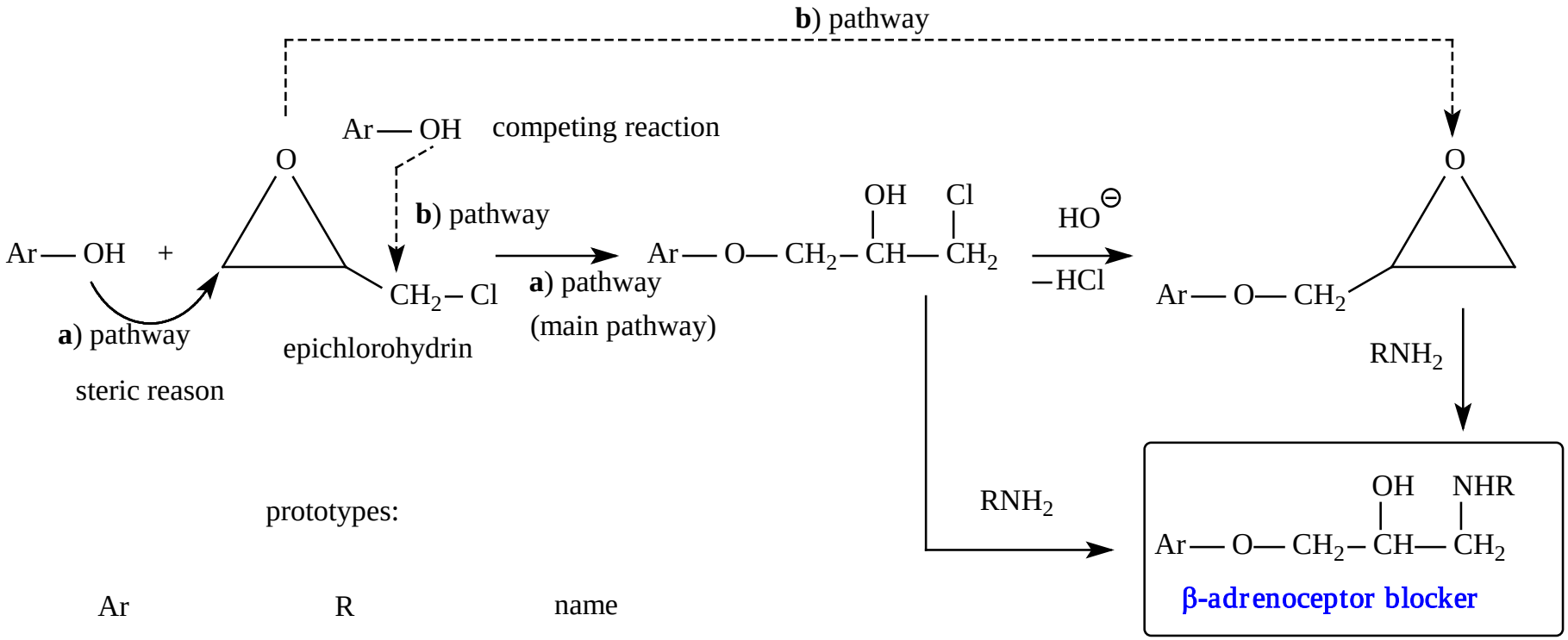

OH
CH2—CH3
LiAlH4
RO⊖
OH OR
CH2—CH2
O
HO⊖
OH
CH2—CH2
OH
RMgBr
MgBr
O R
CH2—CH2
NH4Cl
OH R
CH2—CH2


O
⊖SCN
S
thiirane
HO⊖ / H2O
RO⊖ / ROH
HCl
R1
NH
R2
1 2
HO—CH2CH2—SH
2-sulfanylethanol
2 1
RO—CH2CH2—SH
2-alkoxyethanethiol
Cl—CH2CH2—SH
2-chloroethanethiol
R1
N—CH2CH2—SH
R2
2-dialkylaminoethanethiol
H2S
O

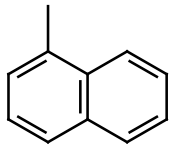
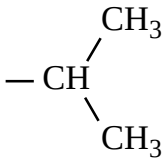
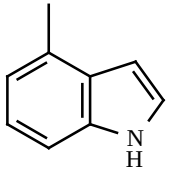
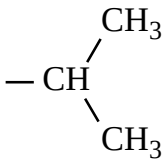
Some important derivatives



Acetylcholine: **neurotransmitter** of parasympathic nervous system
(it can be found in the parasympathic part of the vegetative nervous system and in the central nervous system)

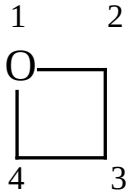
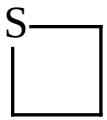
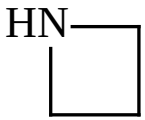


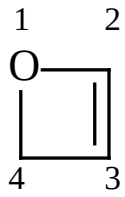
prototypes:

Ar	R	name
		propranolol
		pindolol

Four-membered heterocycles with one heteroatom and their derivatives

Nomenclature

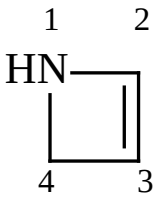
			
Hantzsch-Widman name	oxetane	thietane	azetidine
Radicofunctional name	trimethylene oxide	trimethylene sulfide	trimethylene imine
Replacement name	oxacyclobutane	thiacyclobutane	azacyclobutane



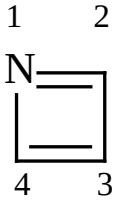
oxet(ene)

thiet(ene)

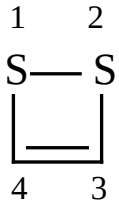
1-azetine



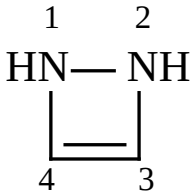
2-azetine



azet



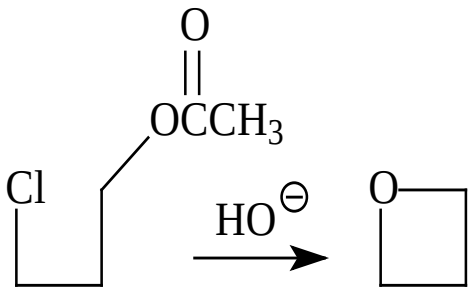
1,2-dithiet

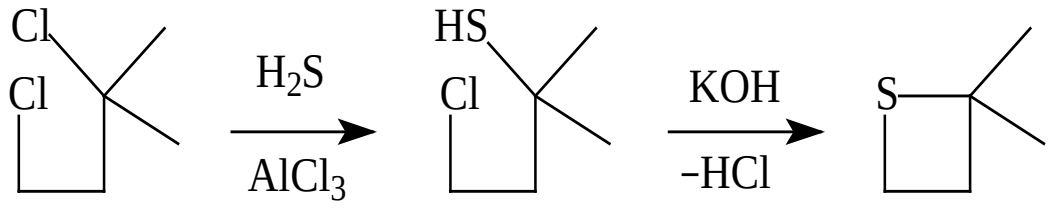


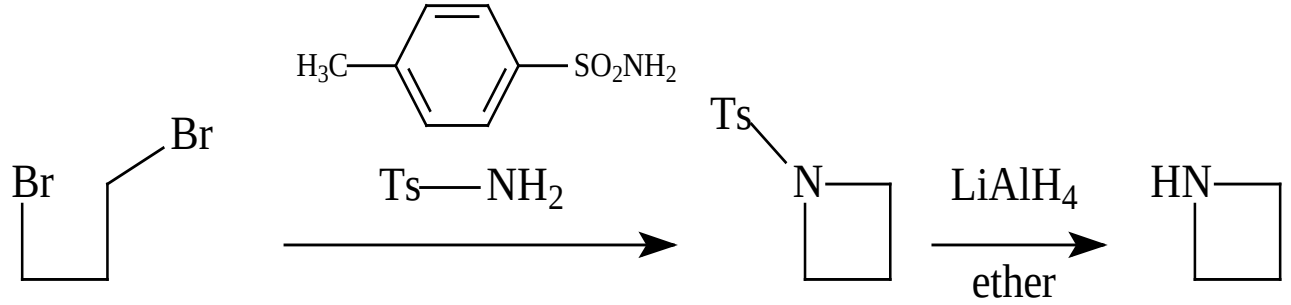
1,2-dihydro-1,2-diazet

Preparation

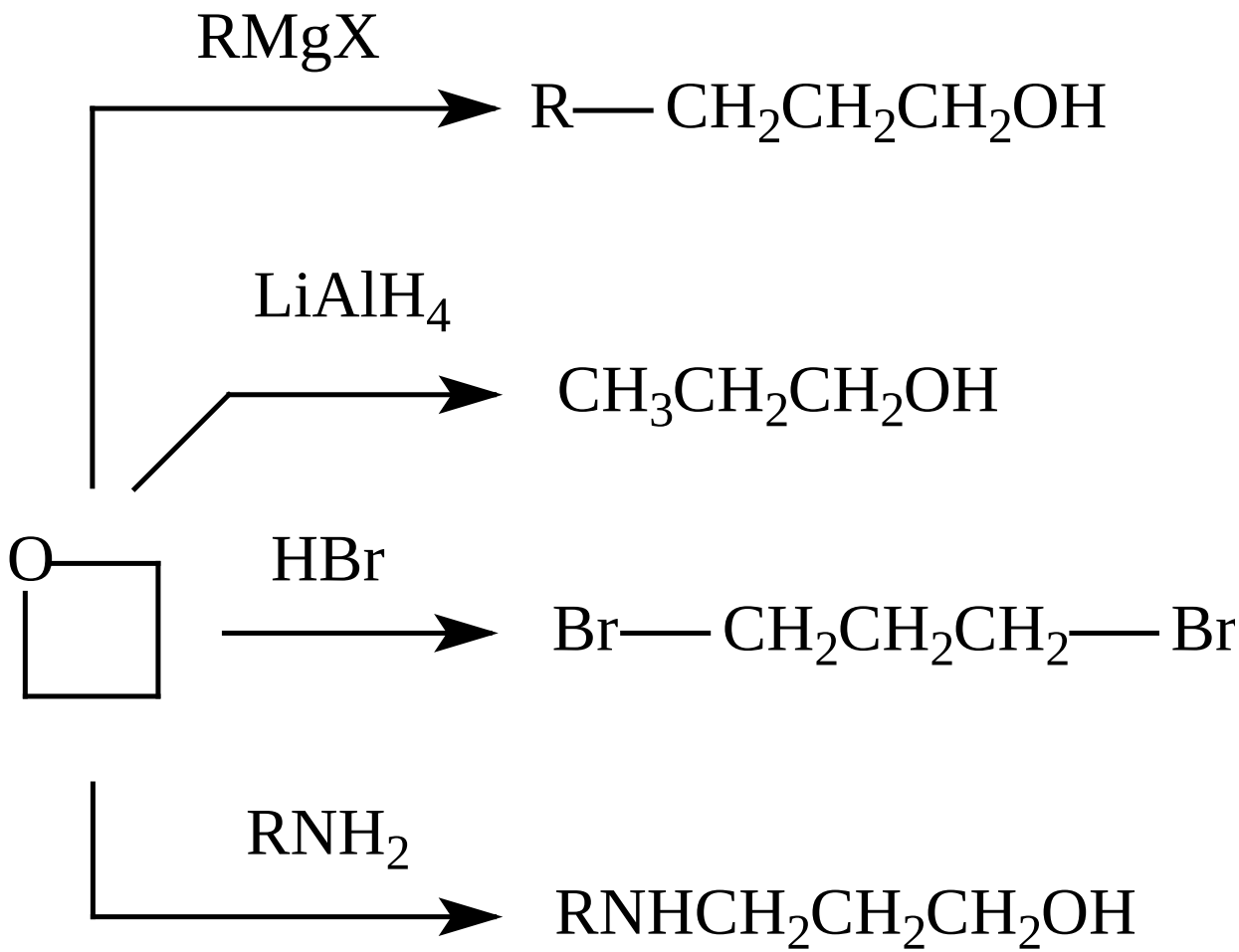
By intramolecular ring closure

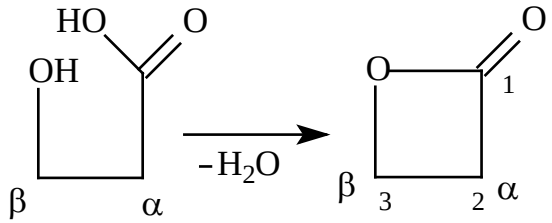






Chemical properties

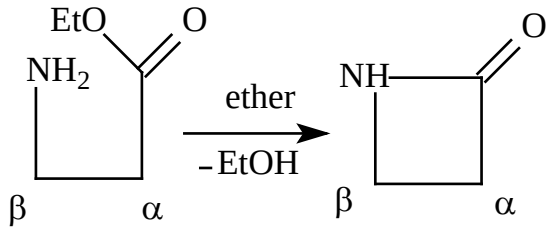




propano-3-lactone

β-propiolactone

cyclic ester

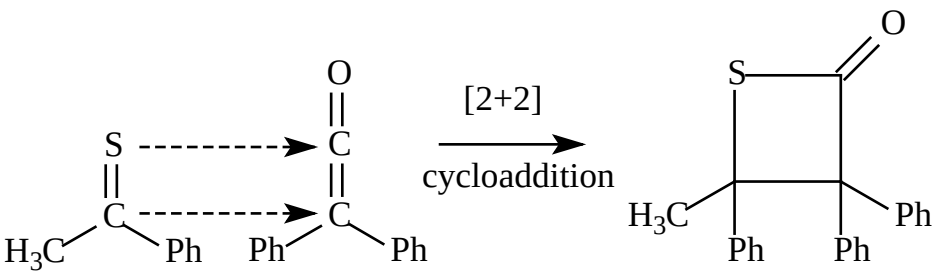


propano-3-lactam

β-propiolactam

cyclic amide

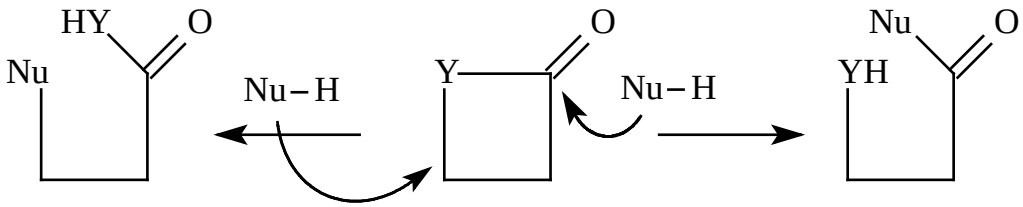
(antibiotics)



propano-3-thiolactone

β-propiothiolactone

cyclic thioester



Some important derivatives

β-Lactam antibiotics

- Penicillins
- Cephalosporins

Antibiotics: natural compounds produced either by microorganisms (e.g., fungi), or by a higher organism against other microorganisms (e.g., bacteria) to block the life and reproduction of the bacteria. Antibiotics are efficient in low concentration.

β-lactame ring of **penicillins** is sensitive to acids, bases, or penicillinase enzyme. Nowadays penicillins with broad therapeutic range also exist (see microbiology).

Cephalosporins (1948) makes the other main group of the β-lactame antibiotics. These are resistent to penicillinase enzyme.

The bacterium produces penicillinase/cephalosporinase enzyme in order to be resistent against the given penicillin/cephalosporin derivative. Thus, newer and newer penicillin/cephalosporin derivatives must be synthesized. Their total synthesis is possible, but it would be too expensive, thus new derivatives are produced by semisynthetic methods. The fermentation processes are combined by chemical methods (beginning of biotechnology).

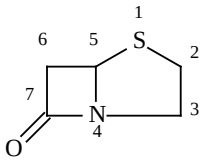
Clavulanic acid: inhibitor of the β-lactamase with low antibiotic effect. Clavulanic acid is produced by *Streptomyces clavurigeus* (the same fungus also produces penicillin as well as cephamycin).

Augmentin® contains amoxycillin and potassium clavulanate.

β -Lactam antibiotics

Basic skeletons

azetidine + thiazolidine

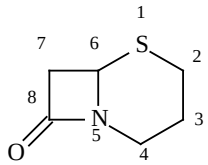


penam

lactam

Penicillium notatum

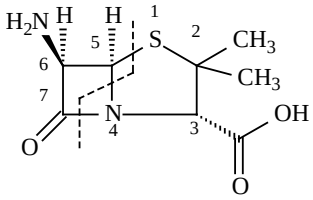
azetidine + [1,3]thiazidine



cepham

lactam

Cefalosporium acremonium



6-aminopenicillinic acid

6-APA

penicillinase enzyme

cleaves

penicillins "**-cillin**"

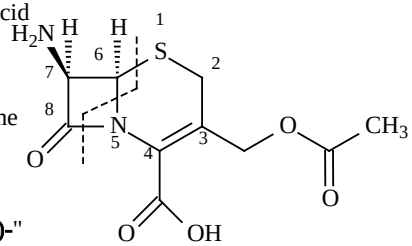
7-aminocephalosporinic acid

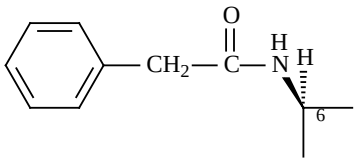
7-ACA

cephalosporinase enzyme

cleaves

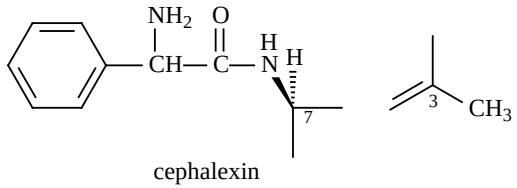
cephalosporins "**ceph(a)-**"



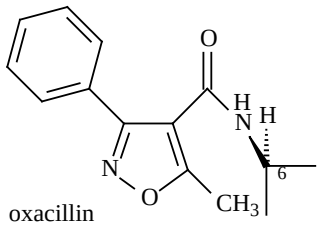


benzylpenicillin

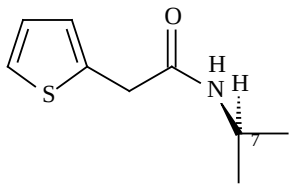
G-penicillin



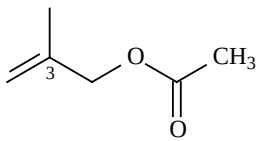
cephalexin

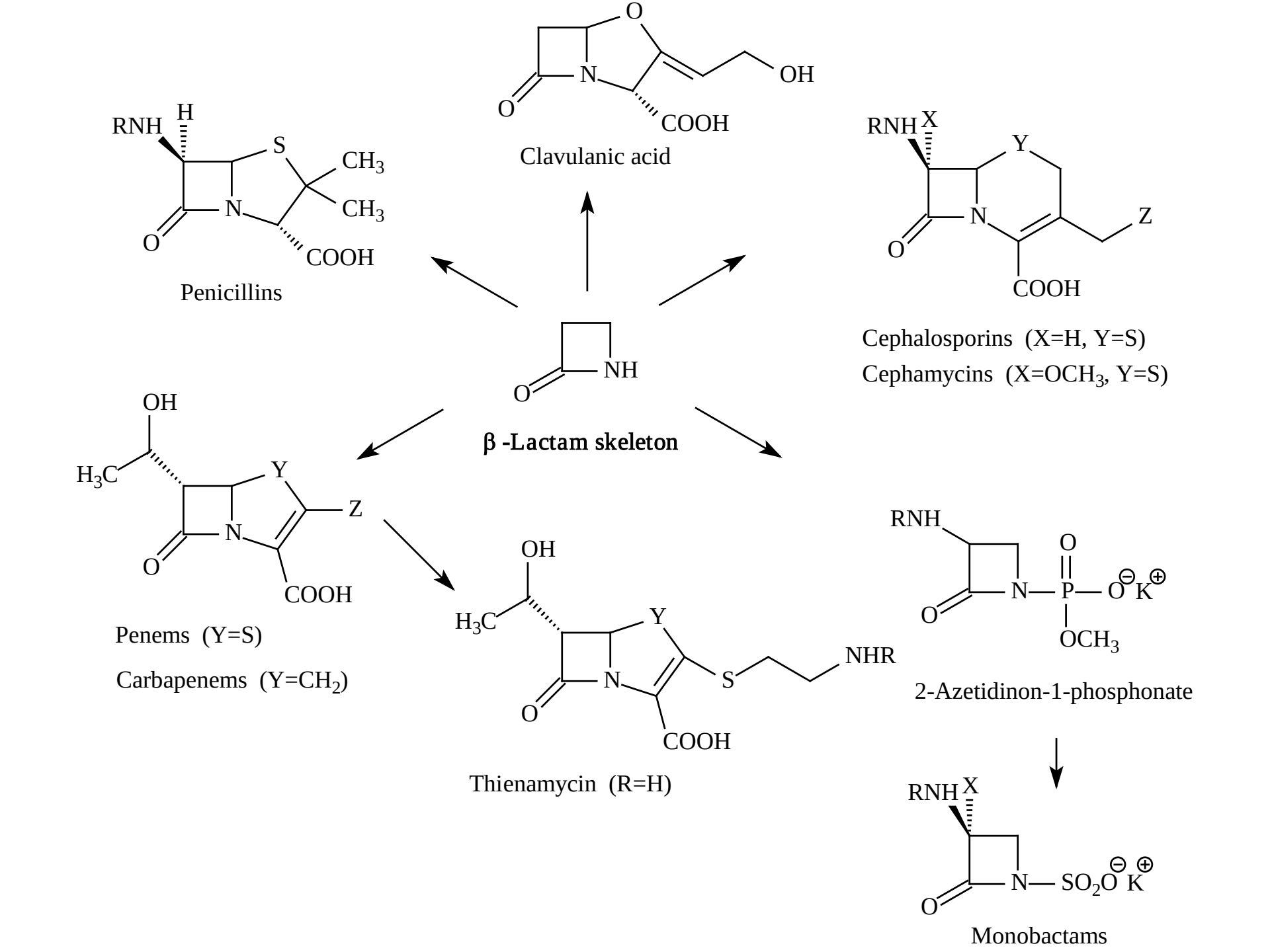


oxacillin



cephalotin

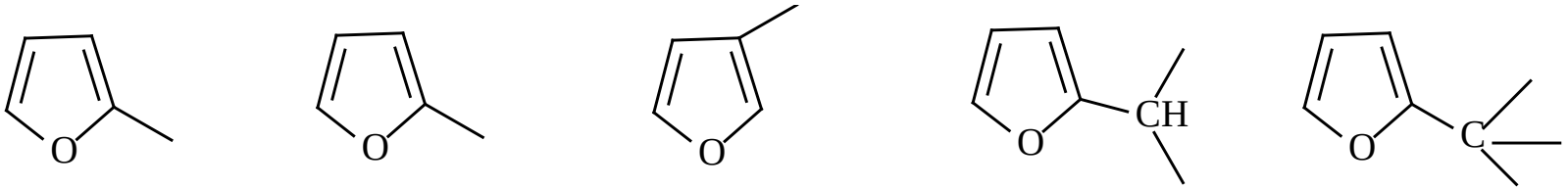



Clavulanic acid
Penicillins
Cephalosporins (X=H, Y=S)
Cephamycins (X=OCH3, Y=S)
β -Lactam skeleton
Penems (Y=S)
Carbapenems (Y=CH2)
Thienamycin (R=H)
2-Azetidinon-1-phosphonate
Monobactams

Five-membered heterocycles with one heteroatom and their derivatives with condensed ring systems

I/ Furan and its derivatives

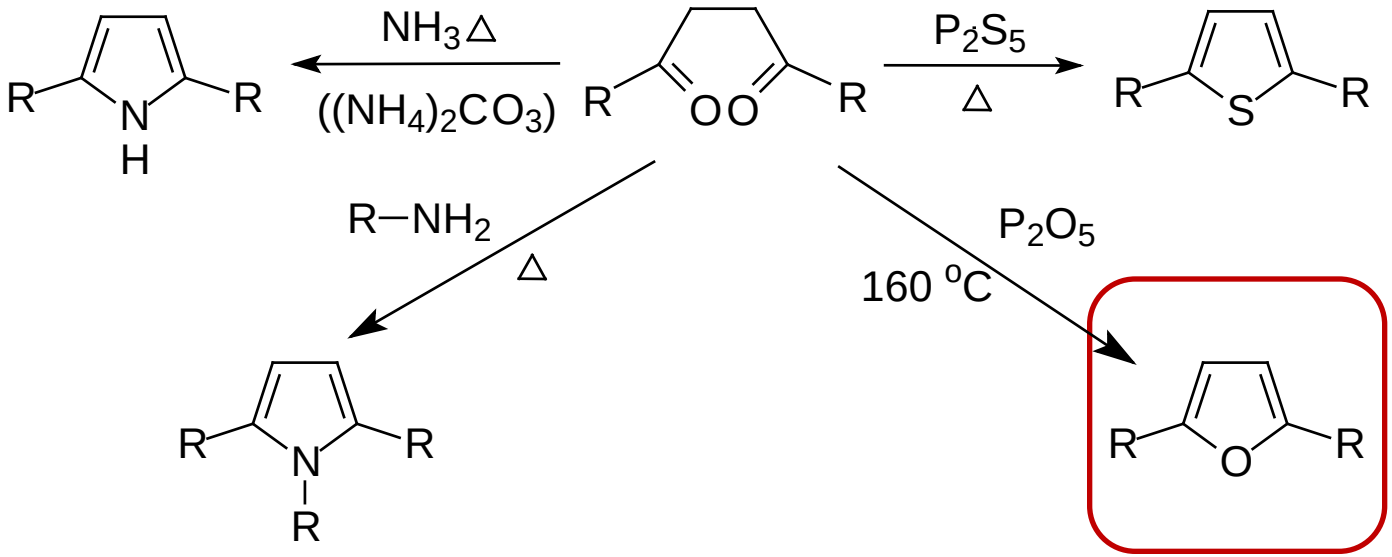
Nomenclature



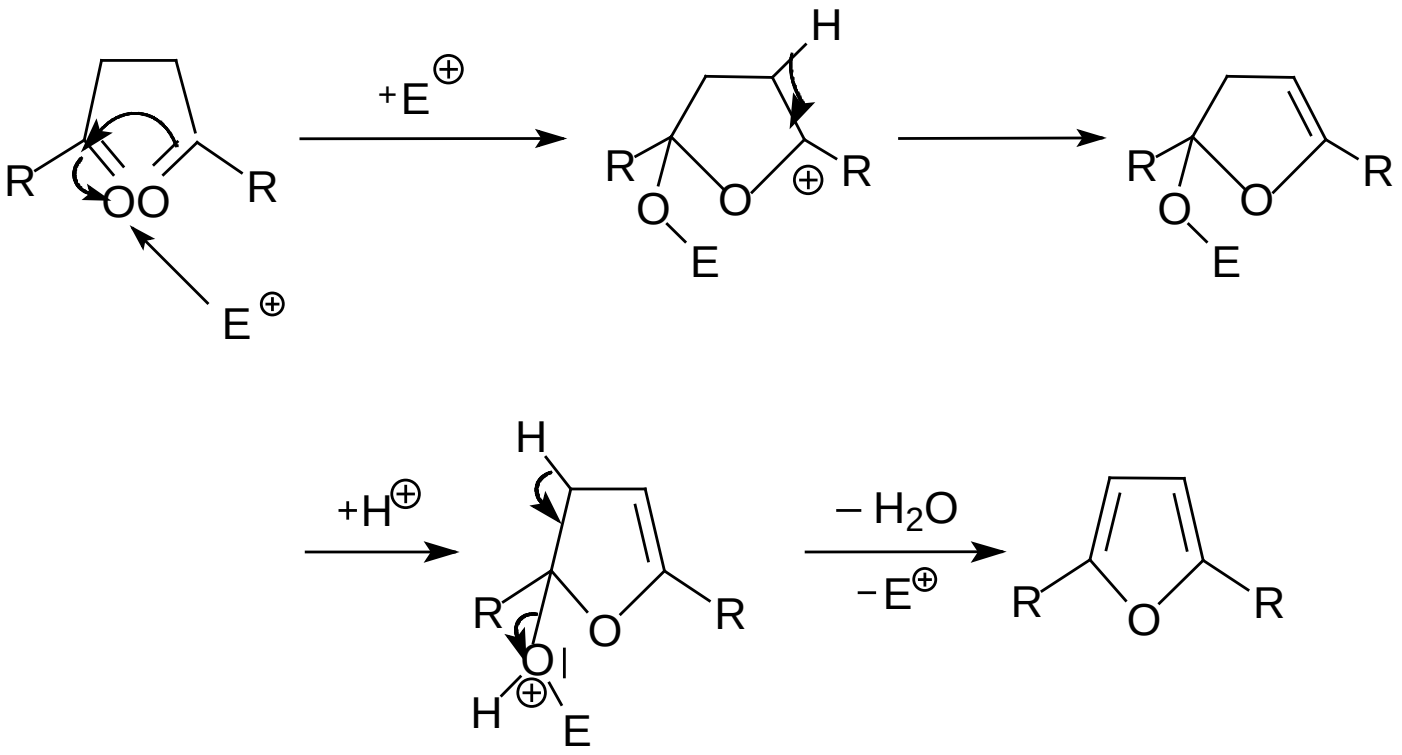
furan | α-furyl- | β-furyl- | α-furfurylidene- | α-furoyl-

Preparation

1/ By **Paal-Knorr** synthesis from dioxo compounds

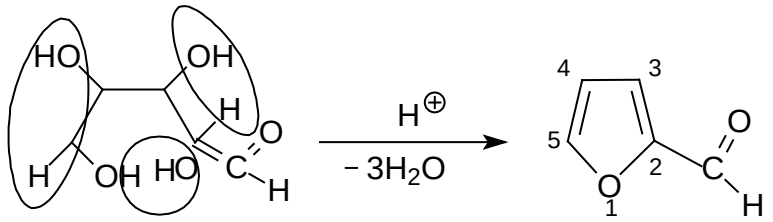


Its mechanism: $E^{\oplus}$: P_2O_5, $H^{\oplus}$



2/ From polyhydroxy oxocompound

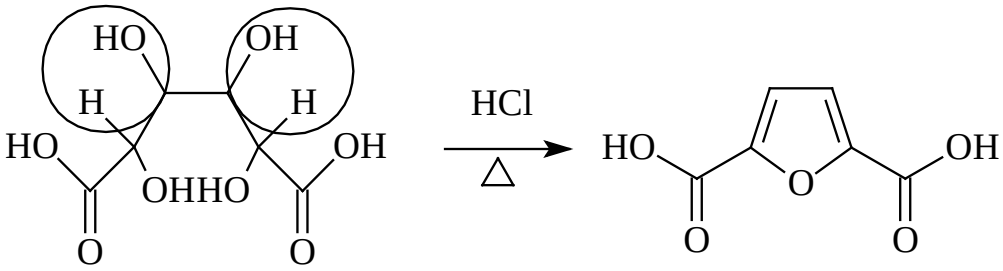
Found in wheat germ, corn germ



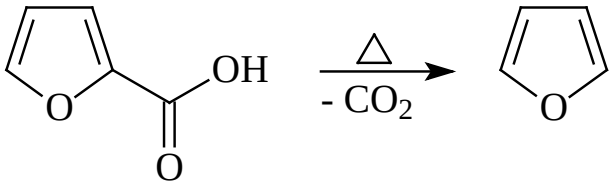
pentosane

furfural (furfurol)
furan-2-carboxaldehyde

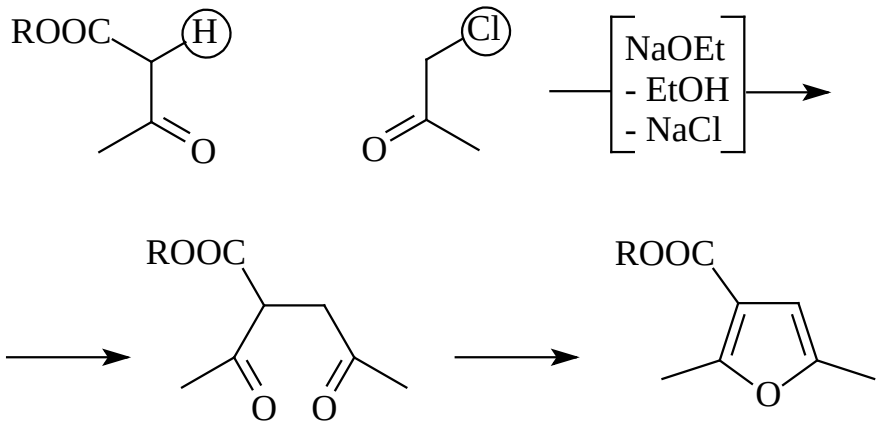
3/ From mucoic acid



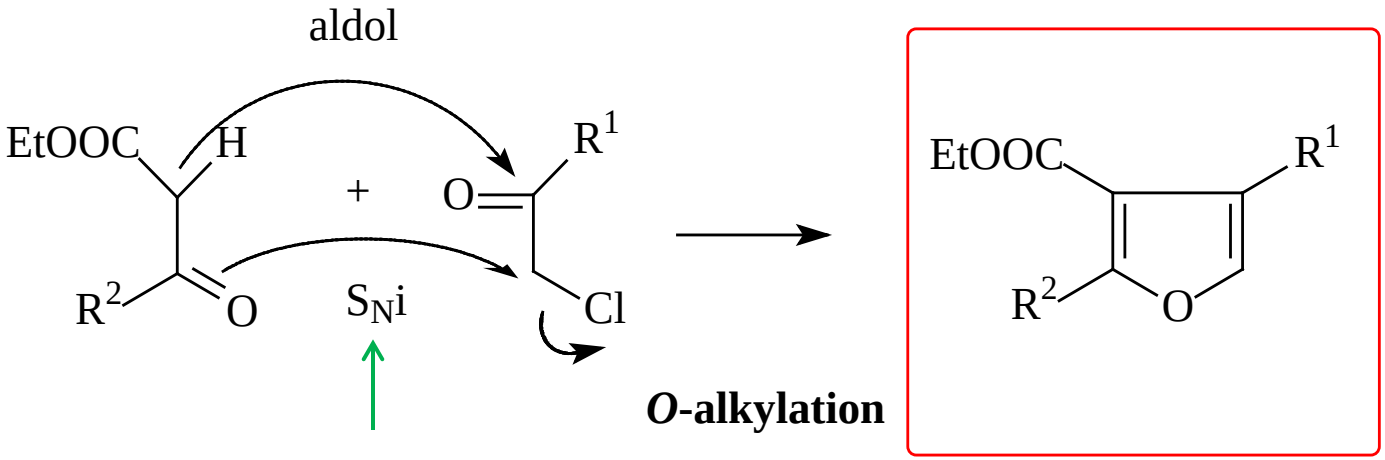
4/ By decarboxylation from dehydromucoic acid



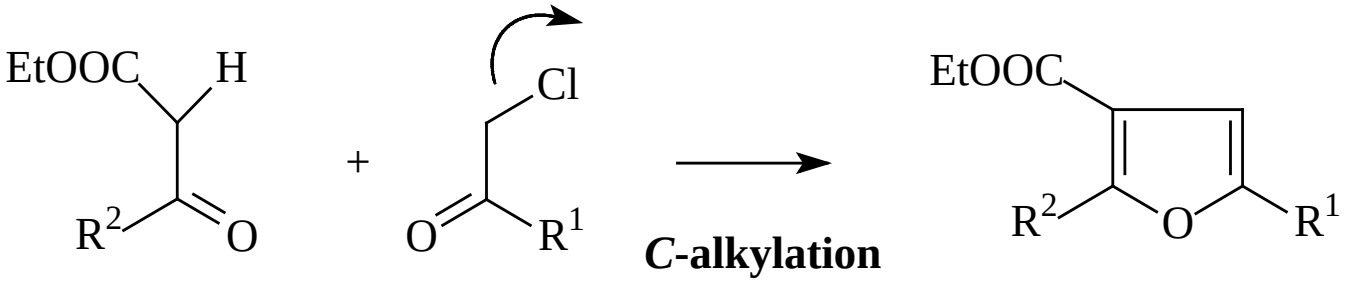
5/ By ring synthesis from β-oxoester and from α-chloroketone

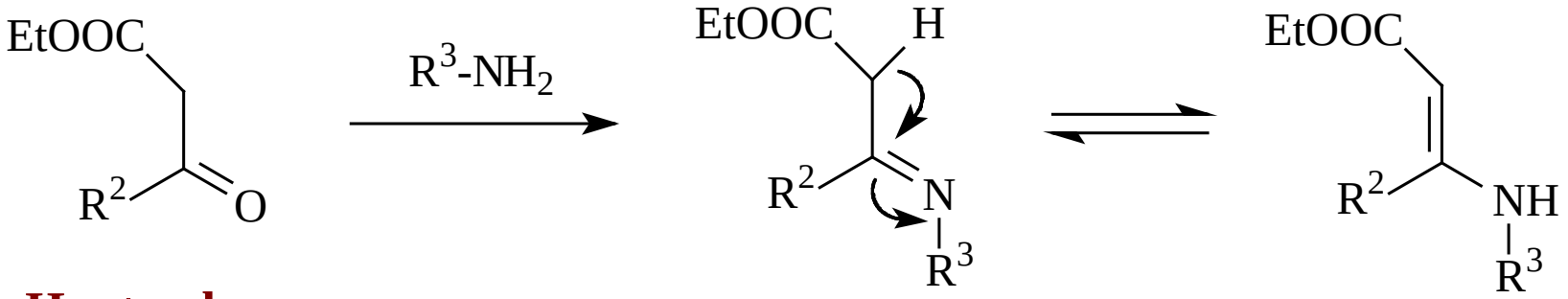


Feist-Benary

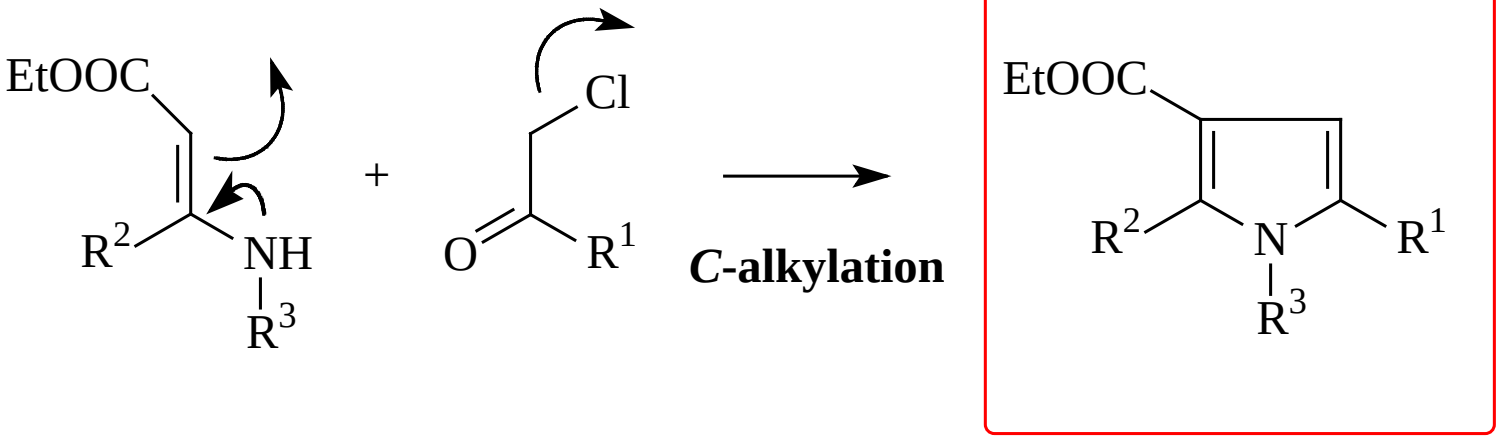


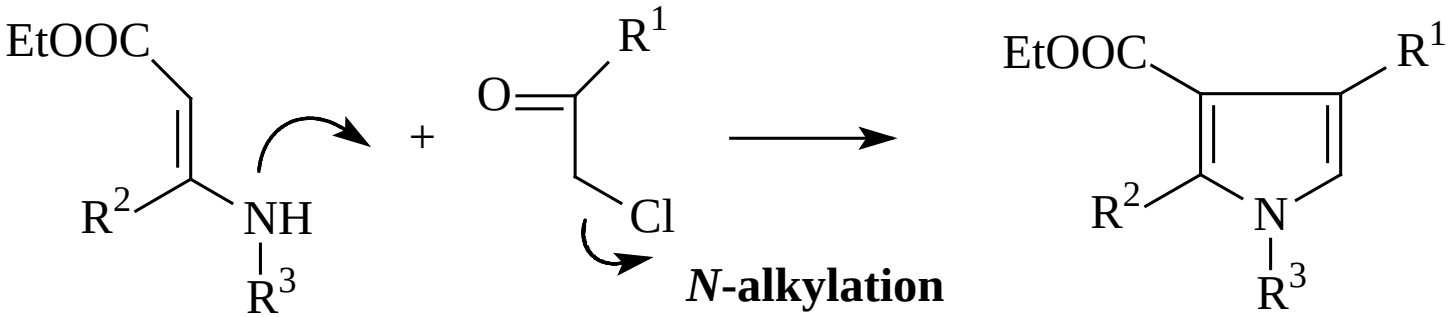
This can be the side reaction of *Hantzsch* reaction




EtOOC
R2
O
R3-NH2
EtOOC
H
R2
N
R3
EtOOC
R2
NH
R3

Hantzsch


EtOOC
R2
NH
R3
+
Cl
O
R1
C-alkylation
EtOOC
R2
N
R3
R1


EtOOC
R2
NH
R3
+
R1
O
Cl
N-alkylation
EtOOC
R1
R2
N
R3

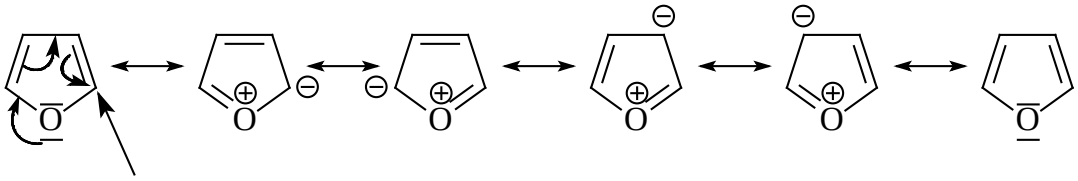
Physical properties

The parent compounds (furan, pyrrole, thiophene) are poorly soluble in water,
but imidazole and pyrazole are water-soluble due to hydrogene bridges

Their UV spectra are rather different from benzene
IR spectra: there are group vibrations
pyrrole has ν NH band at 3400-3300 cm^{-1} (sharp and strong band)

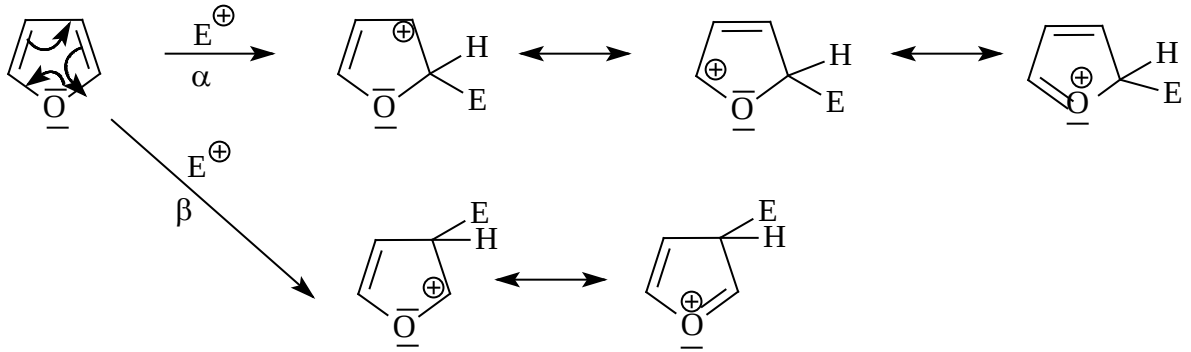
^{1}H NMR spectra: the signal of α H appears at lower δ value (more shielded), compared to the signal of β H (each within the usual aromatic range)
There are usual couplings typical for aromatic compounds.

Chemical properties



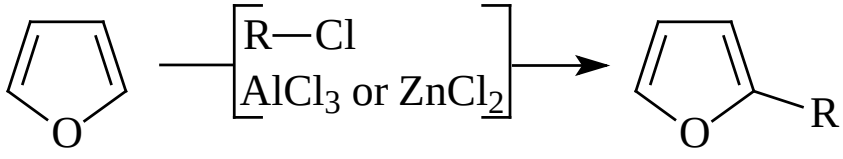
1/ S_EAr reactions

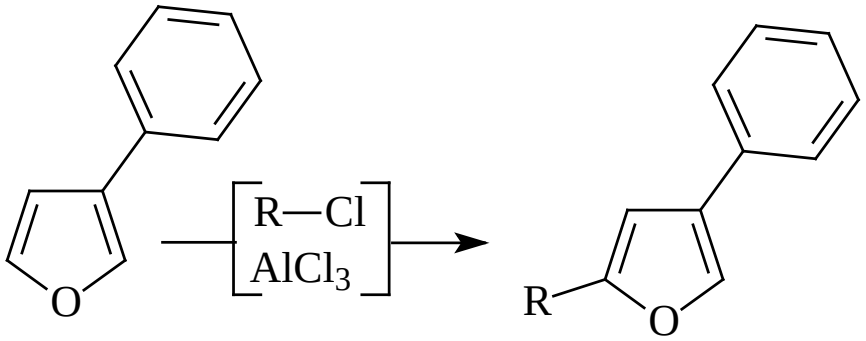
$E^{\oplus}$ attacks the α position ground state



α > β σ–complex is more stable, since more mesomeric structures can be written for it.

Friedel-Crafts alkylation

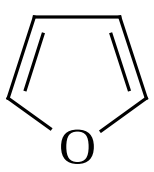




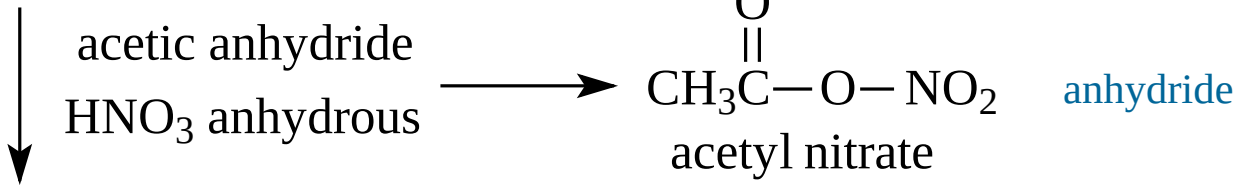
previous explanation: furan is a superaromatic compound, since the aromatic reactions take place much easier, than of benzene

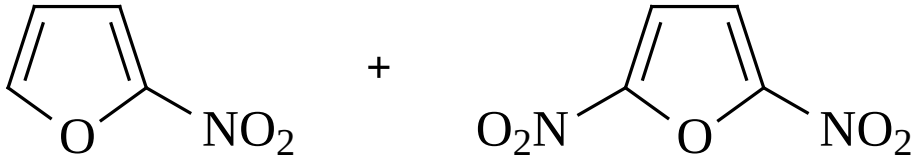
current explanation: furan is much less aromatic, than benzene, since its reaction is energetically much easier, than of benzene

Nitration



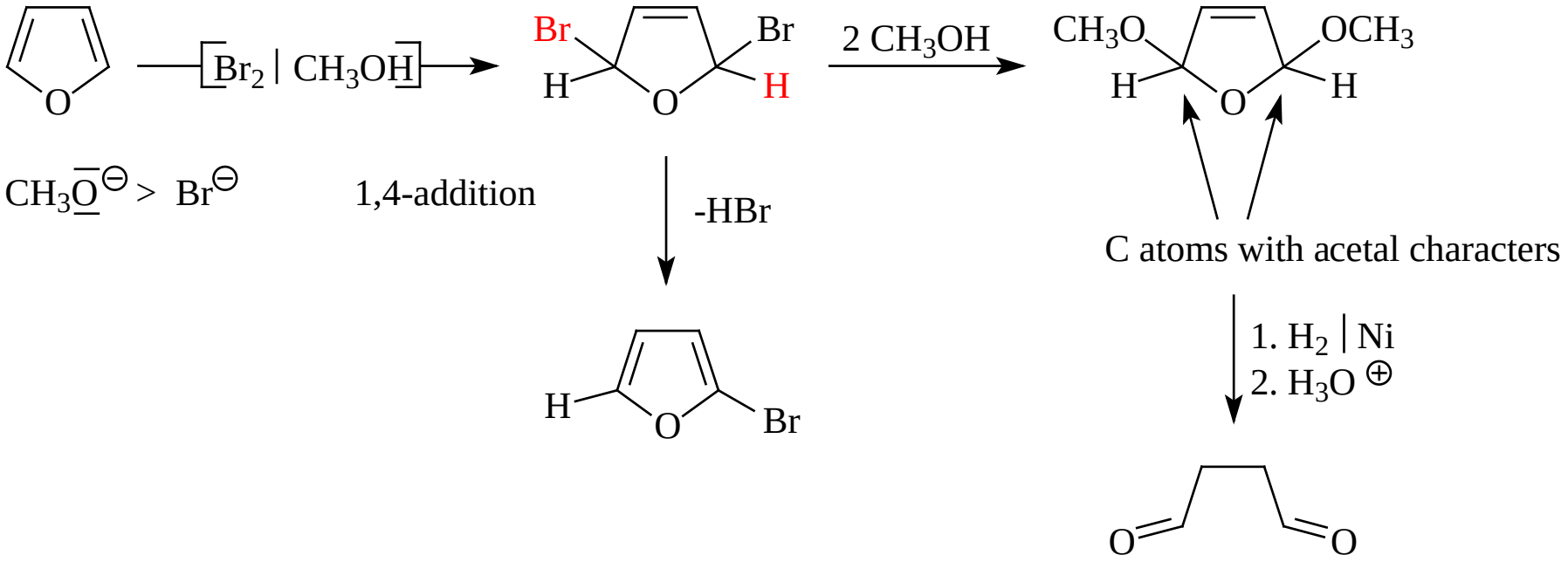
cc. HNO_3 is destroying the ring



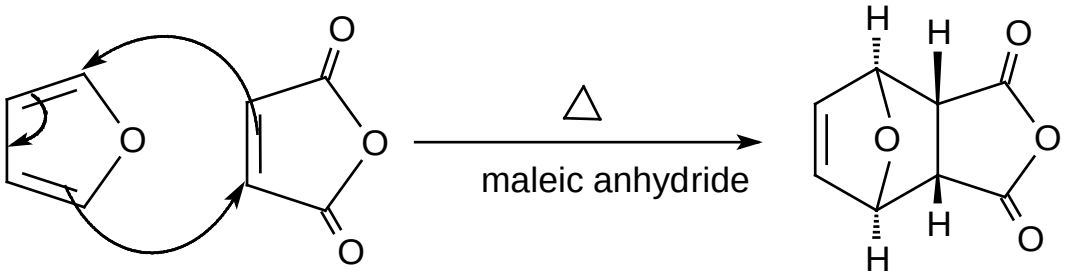


2/ Addition reactions

1,4-addition

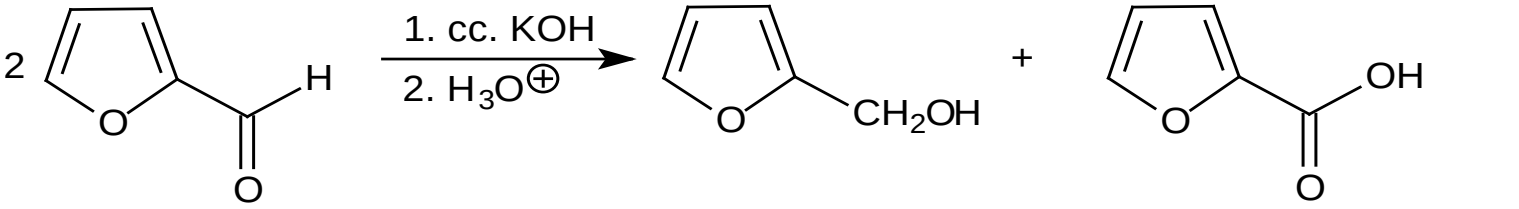


Diels-Alder reaction



3/ Other reactions

Cannizzaro reaction

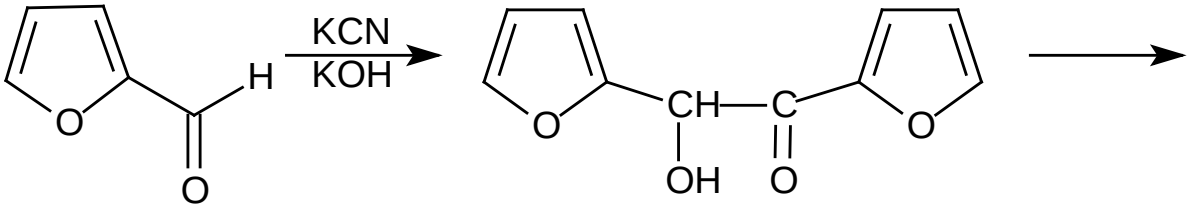


furfural
(furfurol)

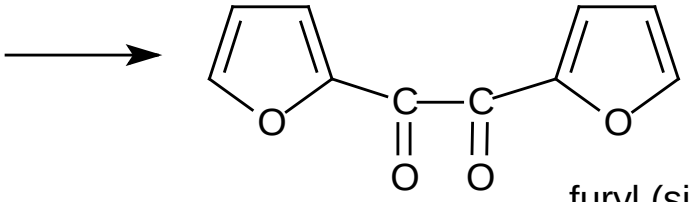
furfurylalcohol

furan-2-carboxylic acid

Acyloin condensation

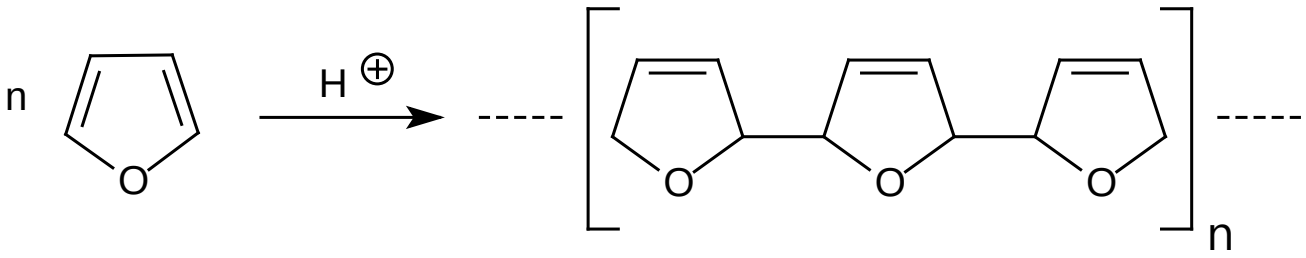


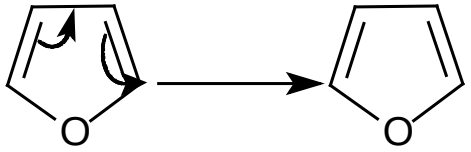
furoin
(similar to benzoin)



furyl (similar to benzyl)

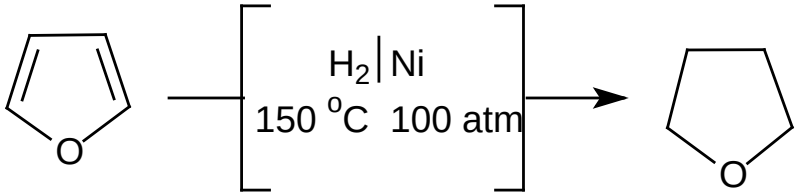
Polymerisation





1,4-addition
addition polymerisation

Reduction

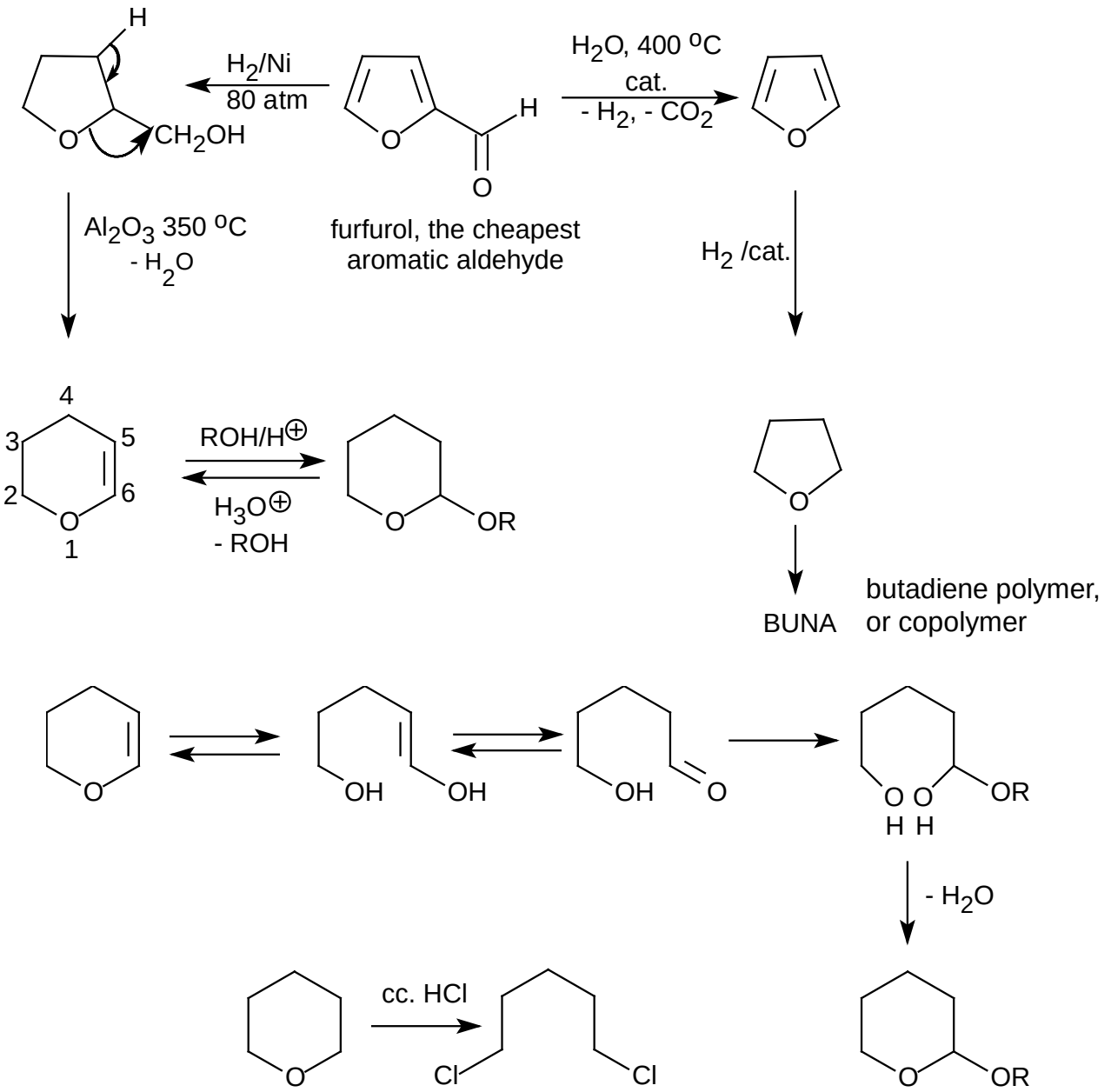


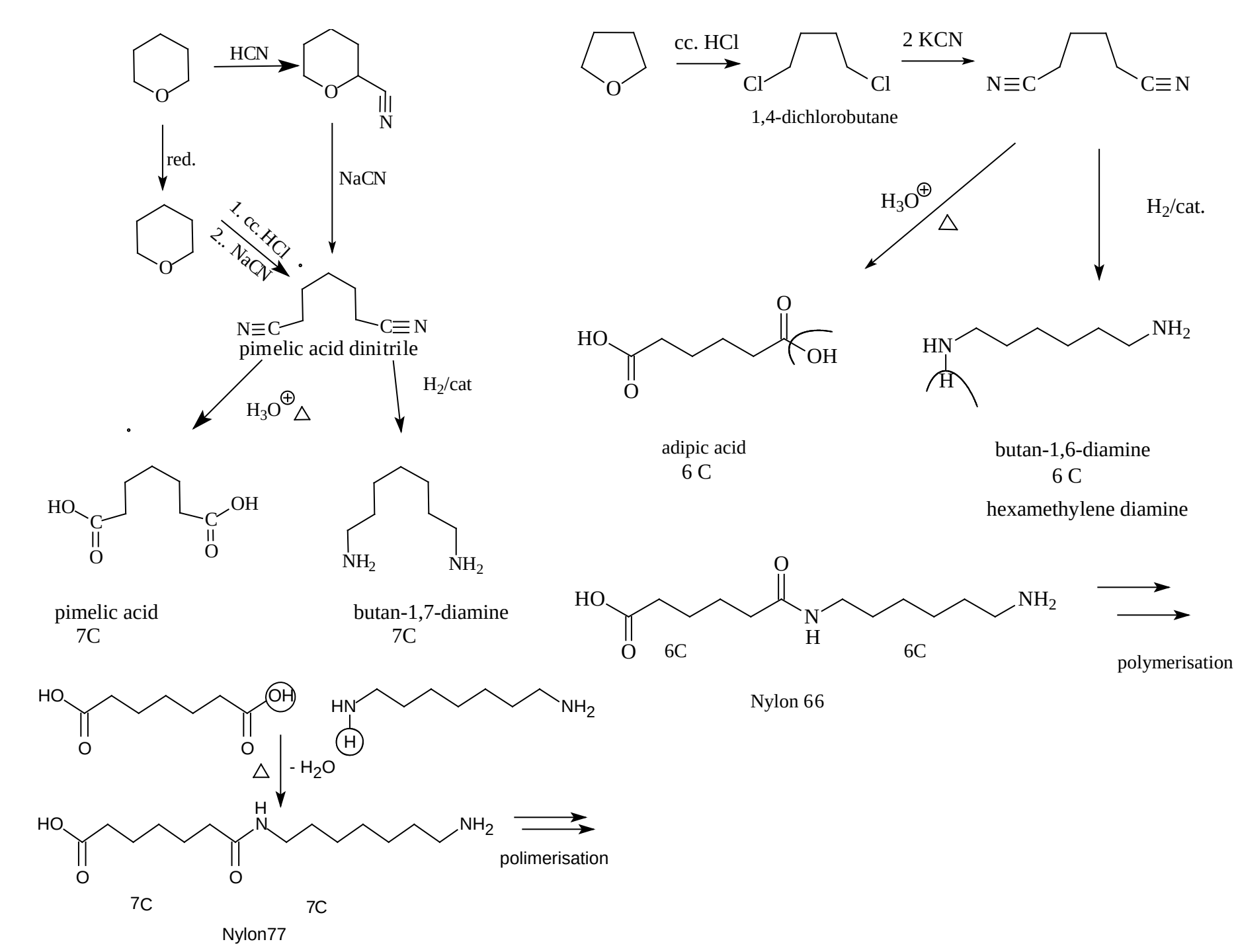
THF

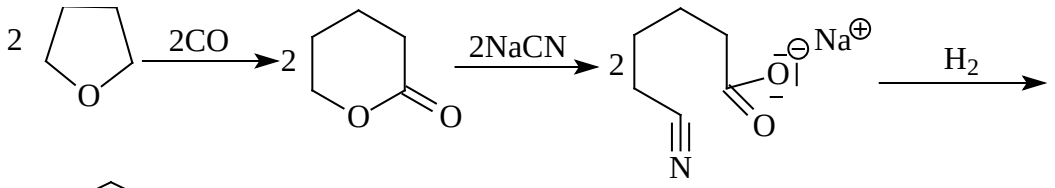
tetrahydrofuran

butan-1,4-diol
(for preparation of diolefins by Reppe synthesis)

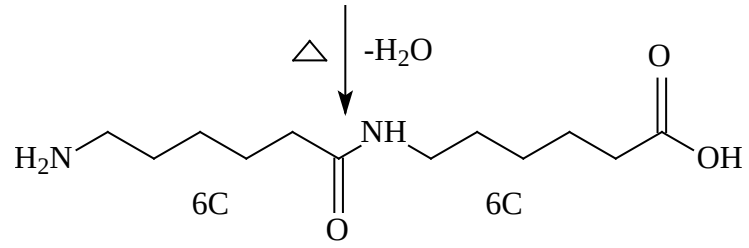
More important derivatives



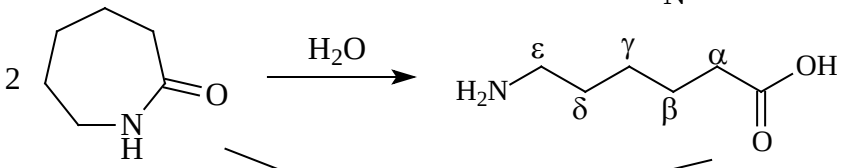

HCN
red.
NaCN
1. cc. HCl
2.. NaCN
N≡C
C≡N
pimelic acid dinitrile
H3O⊕ △
H2/cat
HO
OH
O
pimelic acid
7C
NH2
butan-1,7-diamine
7C
cc. HCl
Cl
1,4-dichlorobutane
2 KCN
H3O⊕ △
H2/cat.
adipic acid
6 C
HN
H
butan-1,6-diamine
6 C
hexamethylene diamine
6C
Nylon 66
polymerisation
- H2O
7C
Nylon77
polimerisation



ε-caprolactam + ε-aminocaproic acid



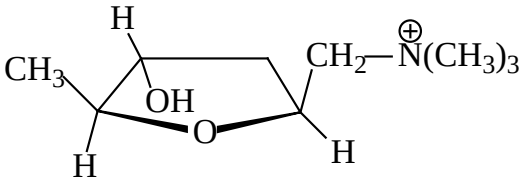
Nylon 6



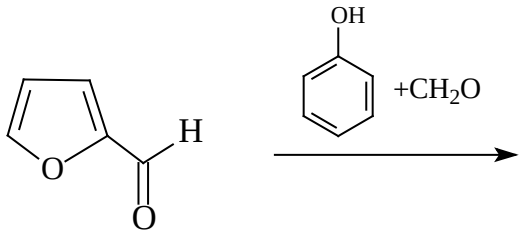
ε-amino-
caproic acid

ε-caprolactam

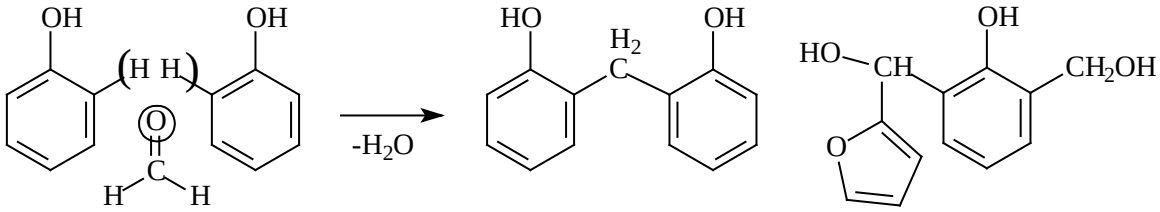
Nylon 6

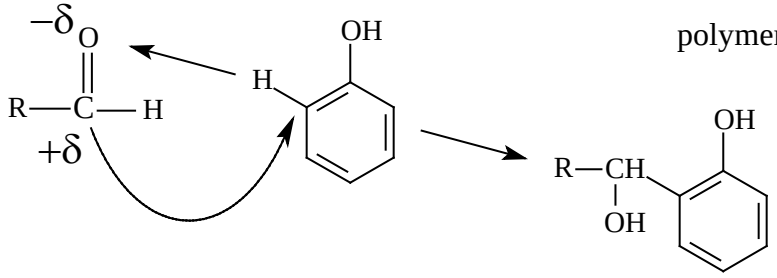


(+)-2*S*,3*R*,5*S*
Muscarin
alkaloid of
Amanita muscaria



polymer plastics

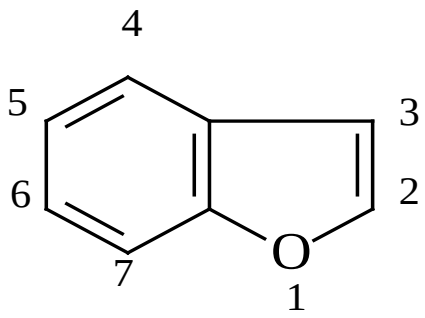




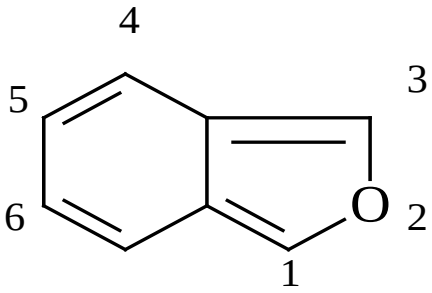
polymerisation chances

II/ Furan derivatives with condensed rings

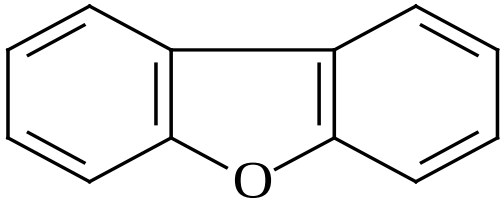
Nomenclature



benzo[*b*]furan
coumarone

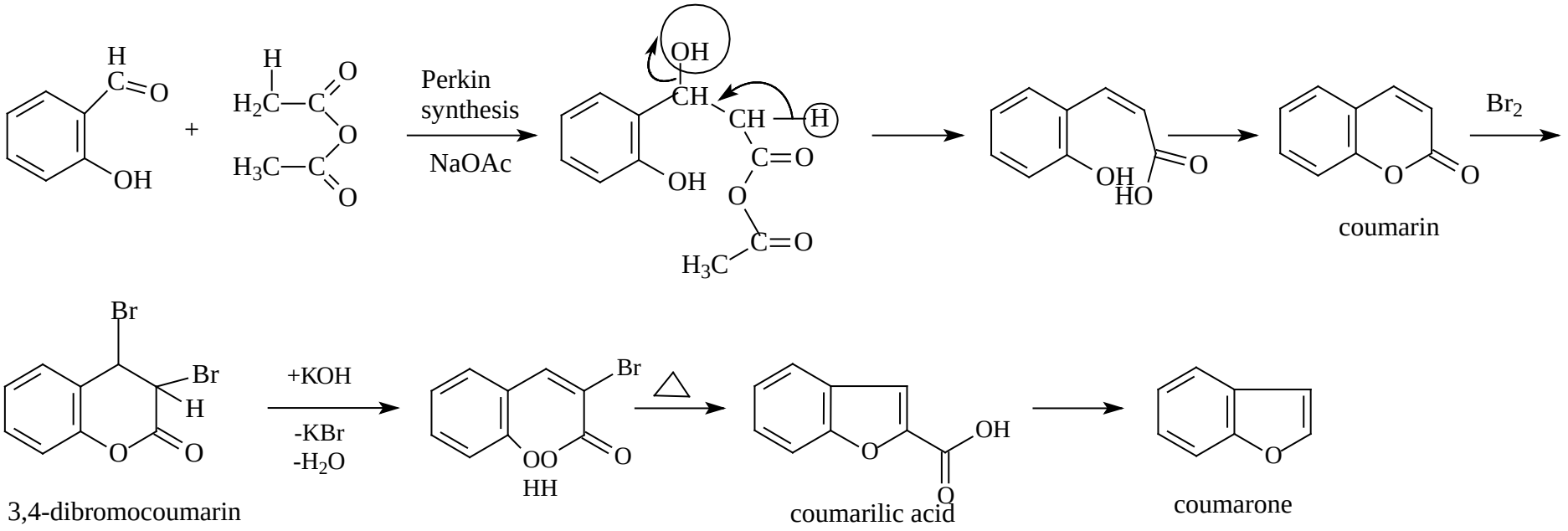


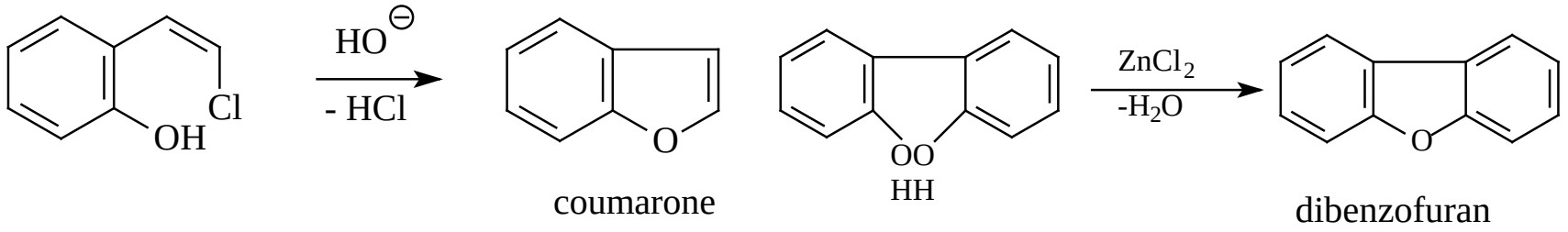
benzo[*c*]furan
isocoumarone
(derivatives of it
are known only)

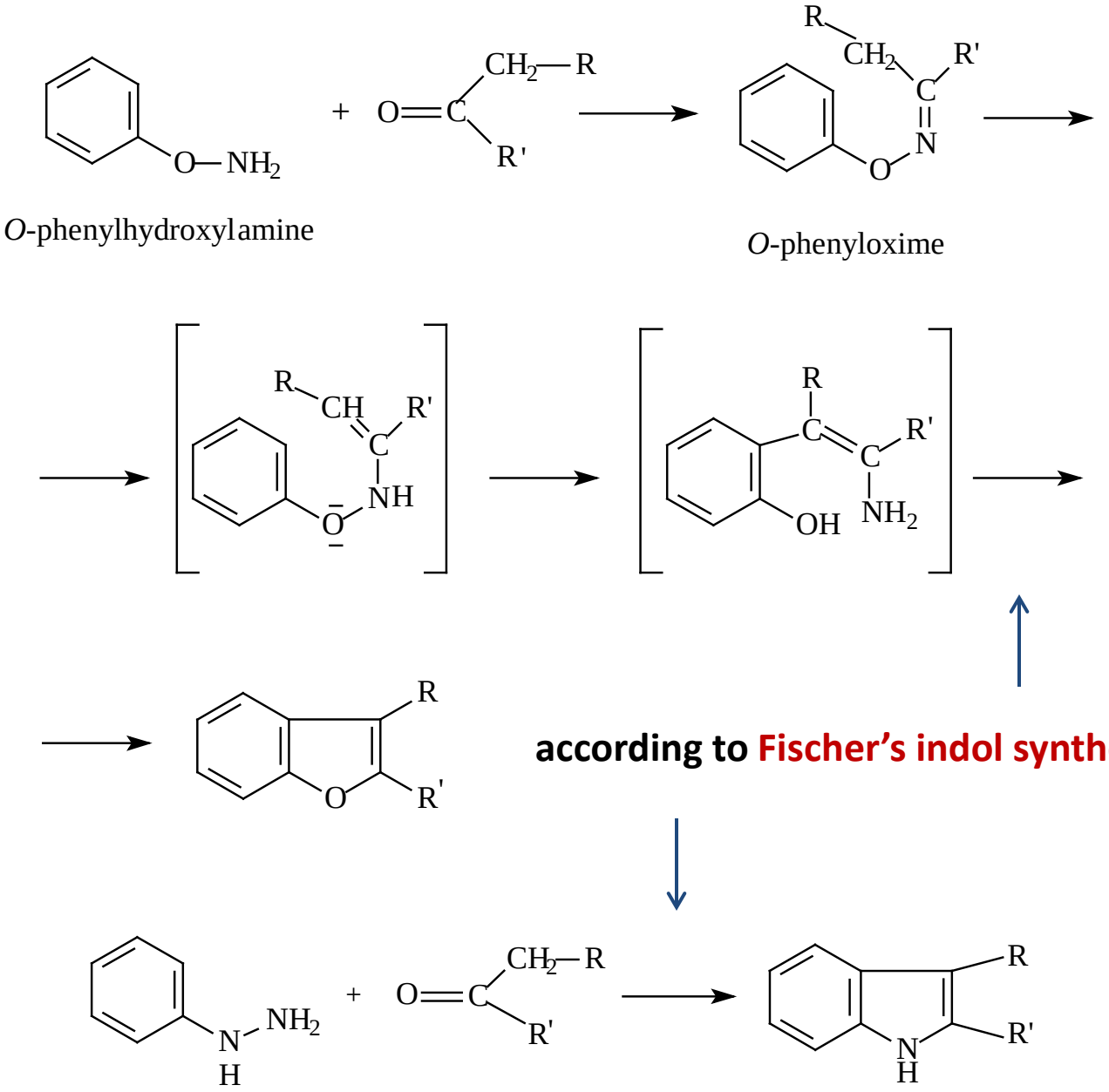


dibenzofuran
diphenylene oxide

Preparations

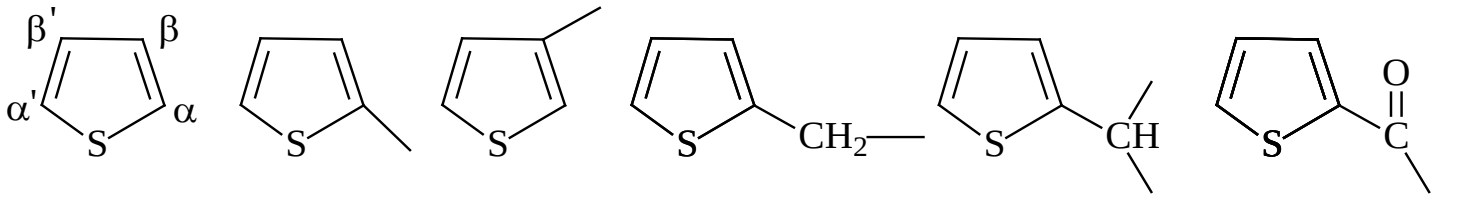





O-phenylhydroxylamine
O-phenyloxime
according to Fischer's indol synthesis

III/ Thiophene and its derivatives

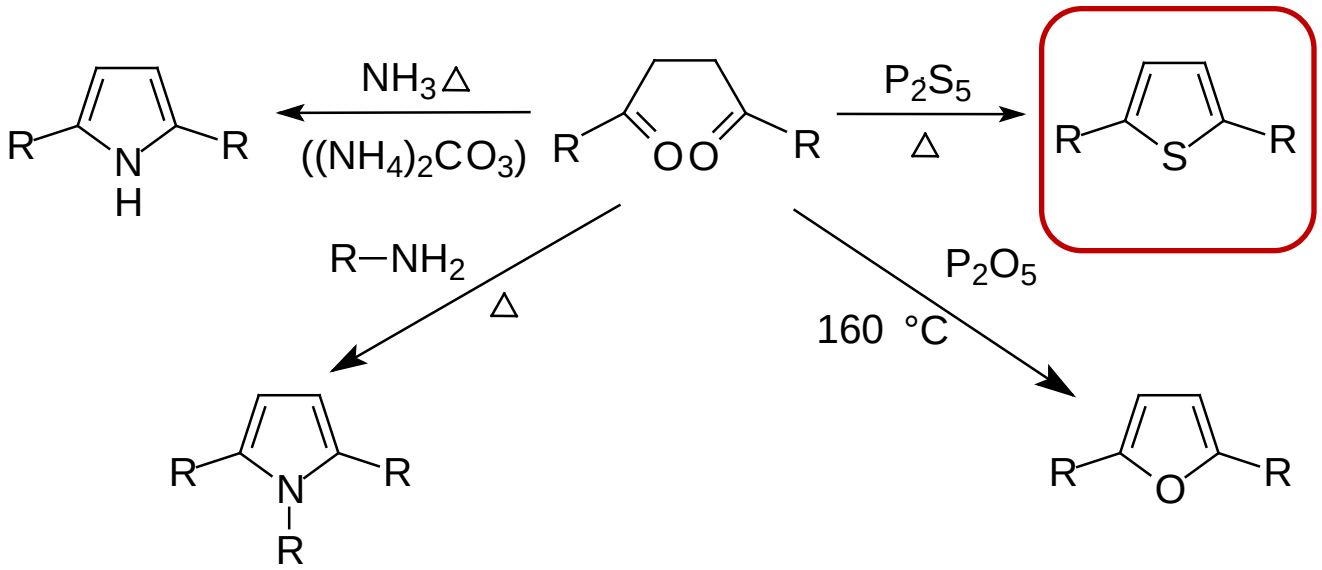
Nomenclature



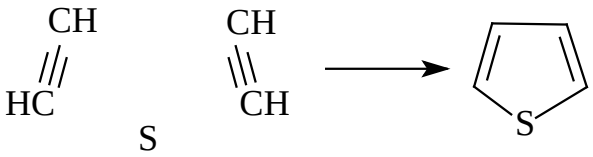
thiophene α–thienyl- 2-thienyl β–thienyl- 3-thienyl thenyl- 2-thenal α-thenal 2-thenoil- α-thenoil-

Preparations

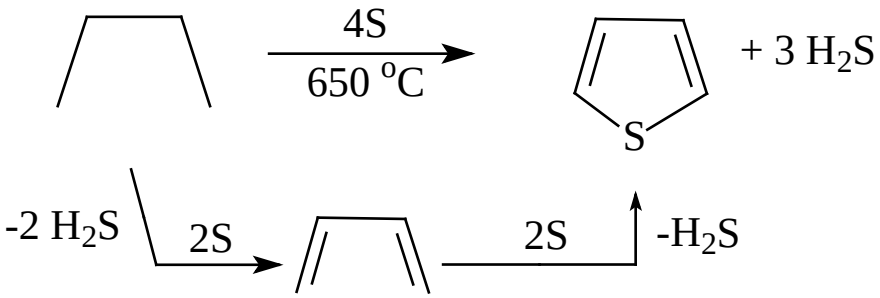
1/ By **Paal-Knorr** synthesis from dioxo compounds



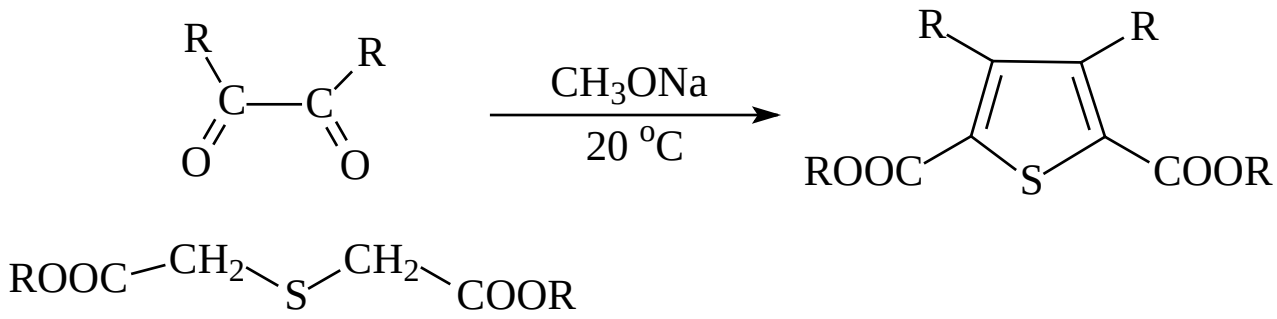
2/ From acetylene



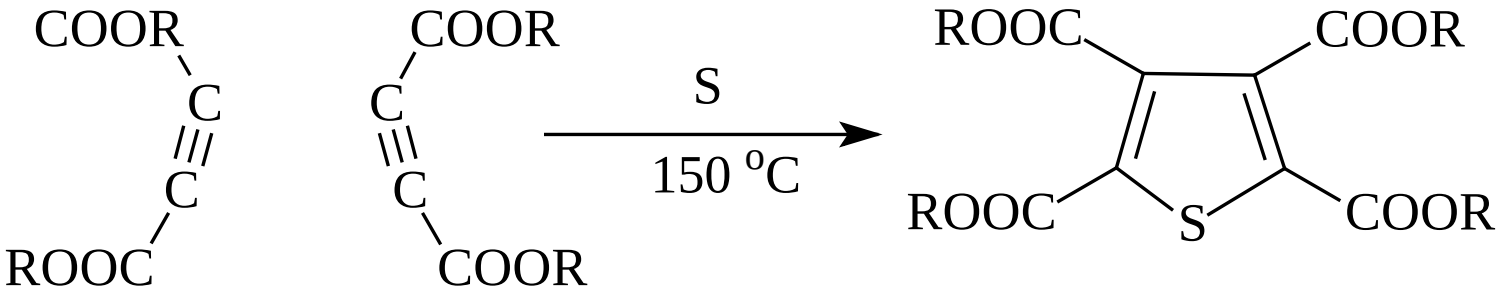
3/ By dehydrogenation, then by ring closure



4/ According to Hinsberg

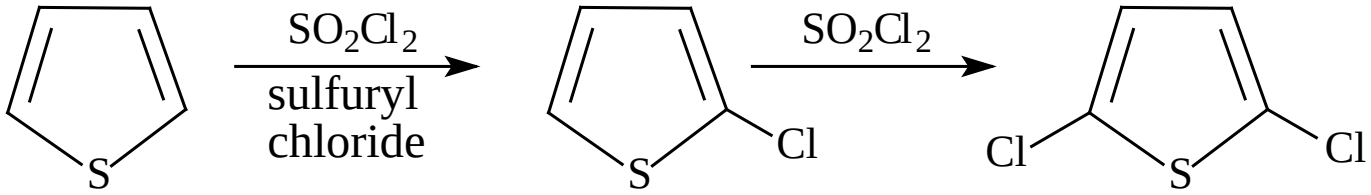


5/ From dialkyl acetylenedicarboxylate

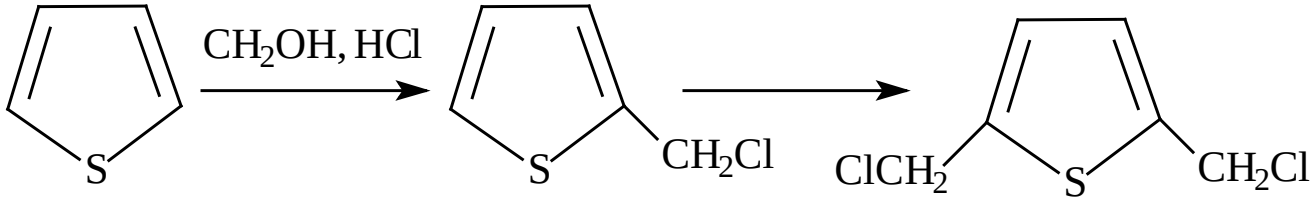


Chemical properties

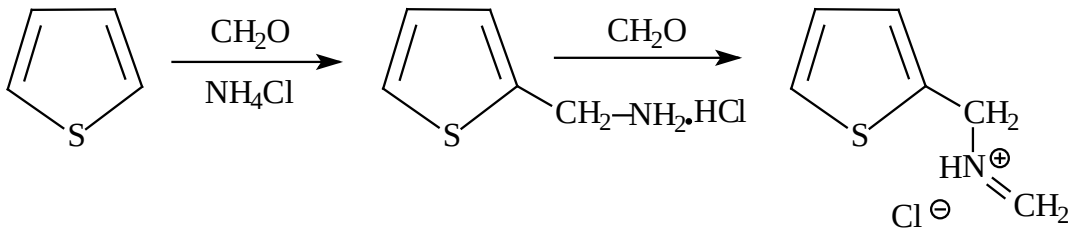
1/ By halogenation



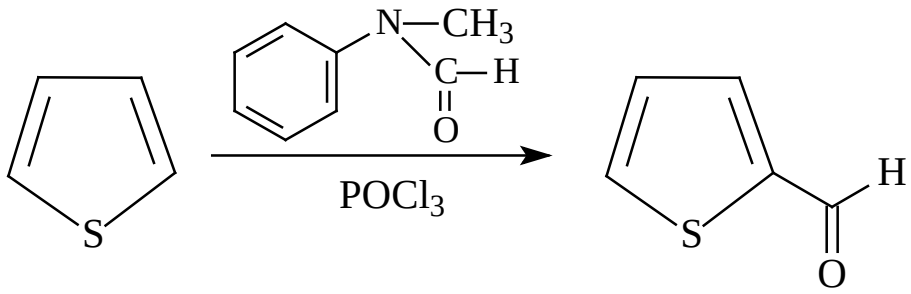
2/ By chloromethylation



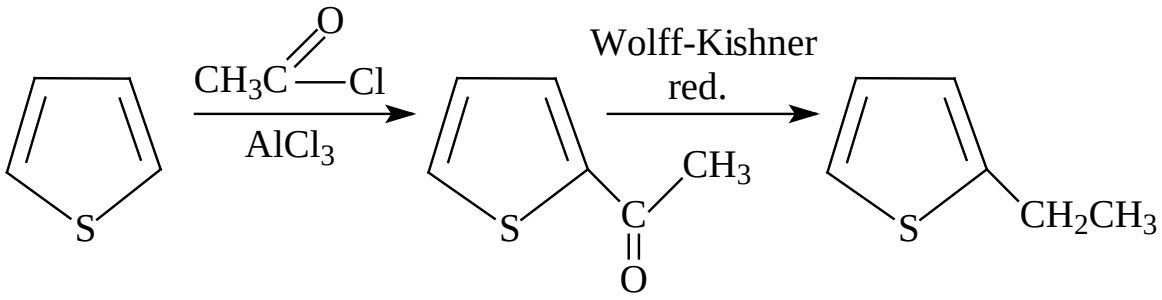
3/ By Mannich reaction



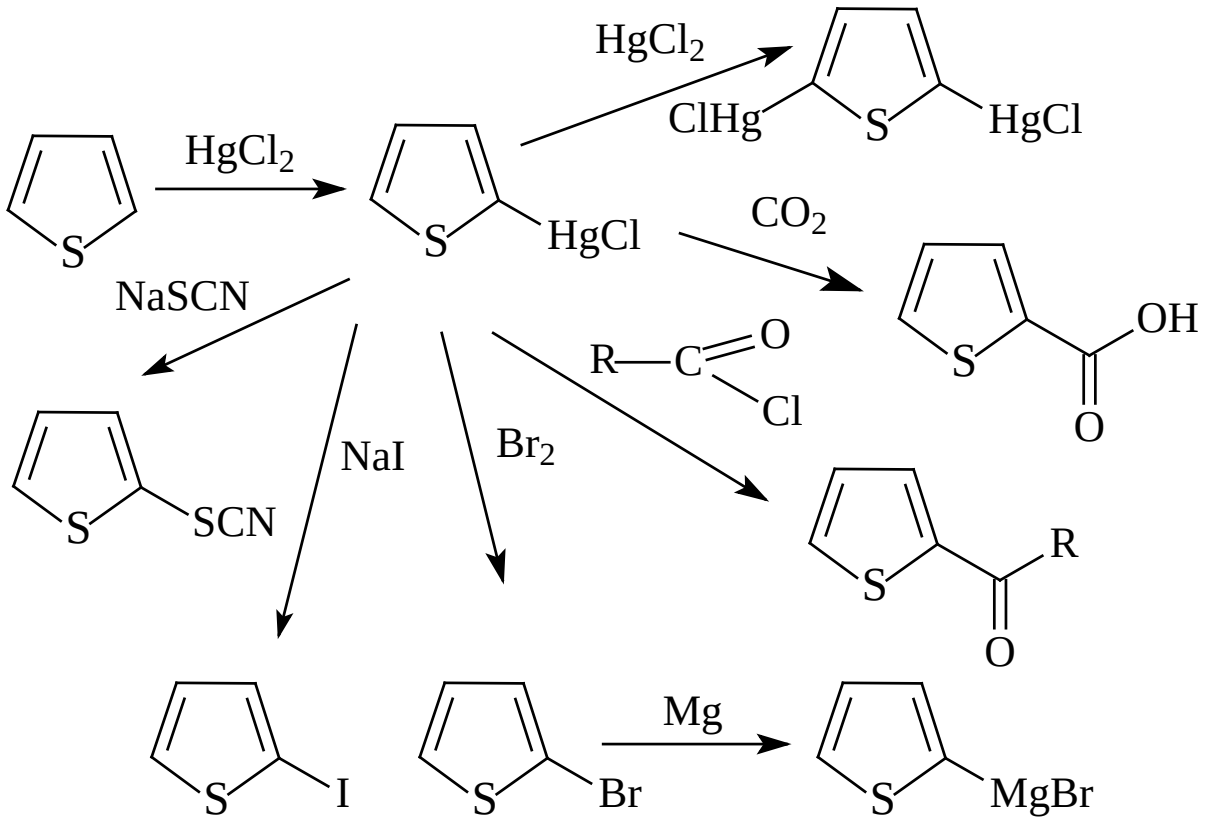
4/ By Vilsmeier formylation



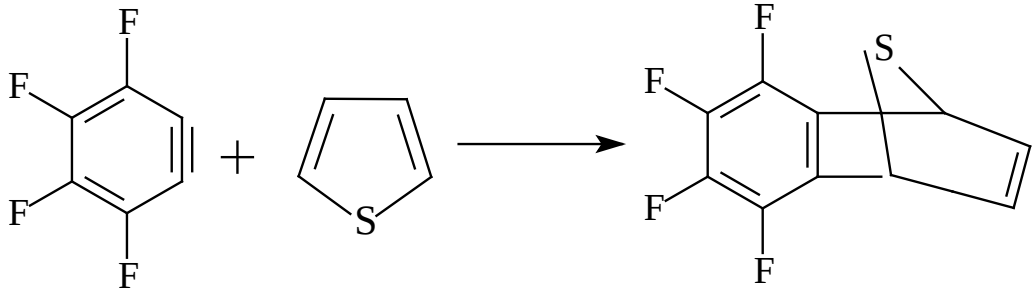
5/ By Friedel-Crafts acylation



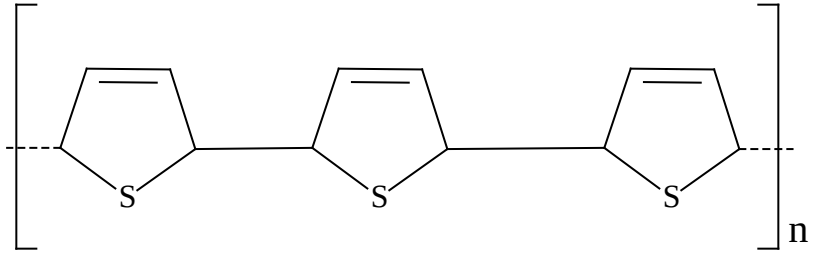
6/ Transformation to mercury derivatives



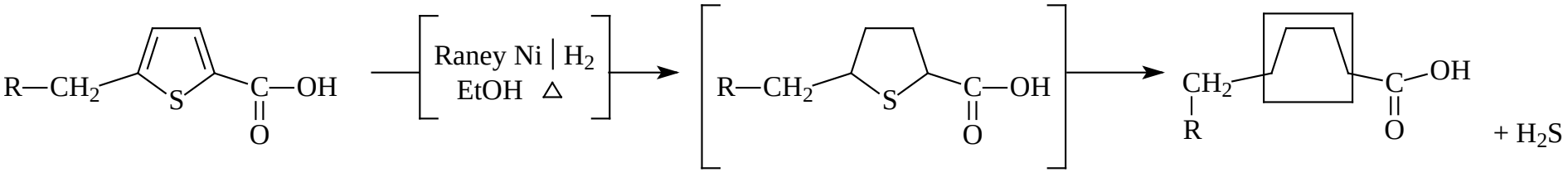
7/ By Diels-Alder (addition) reaction



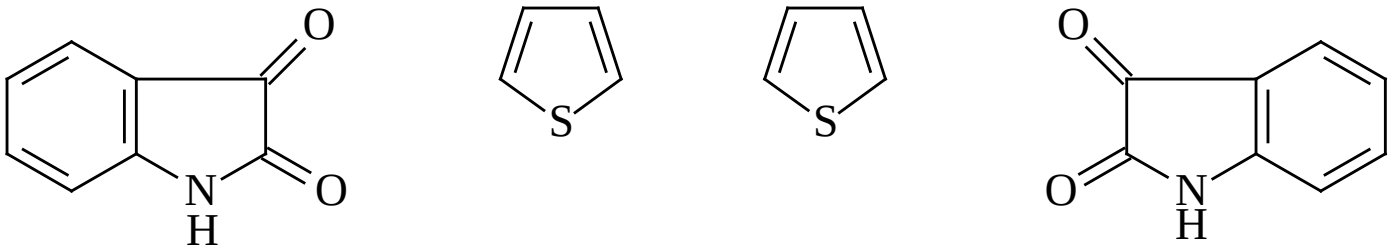
8/ By polymerisation



9/ By hydrogenation

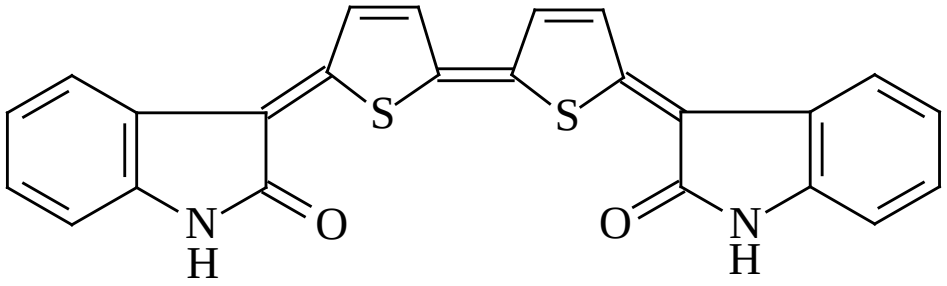


10/ By indophenin reaction



isatin

HCl

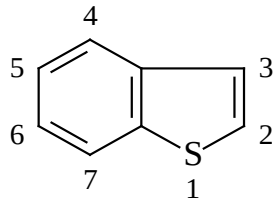


indophenin

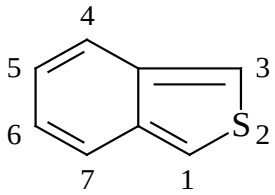
compound with blue colour

IV/ Thiophene derivatives with condensed ring system

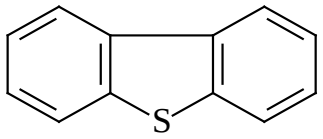
Nomenclature



thionaphthene
benzo[*b*]thiophene

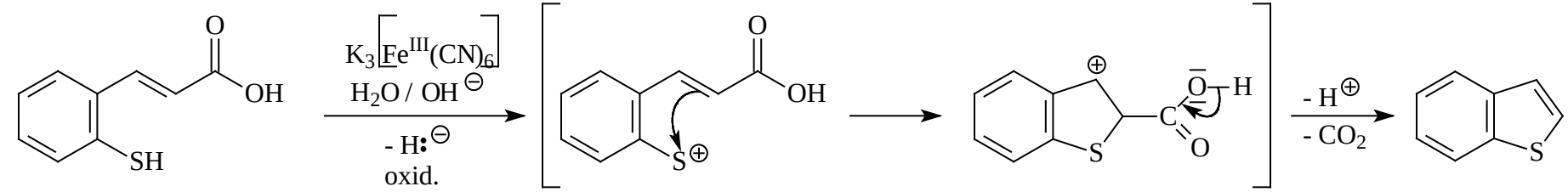


iso-benzothiophene
benzo[*c*]thiophene
isonaphthene

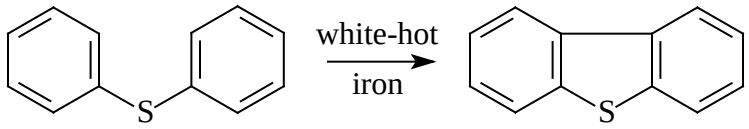


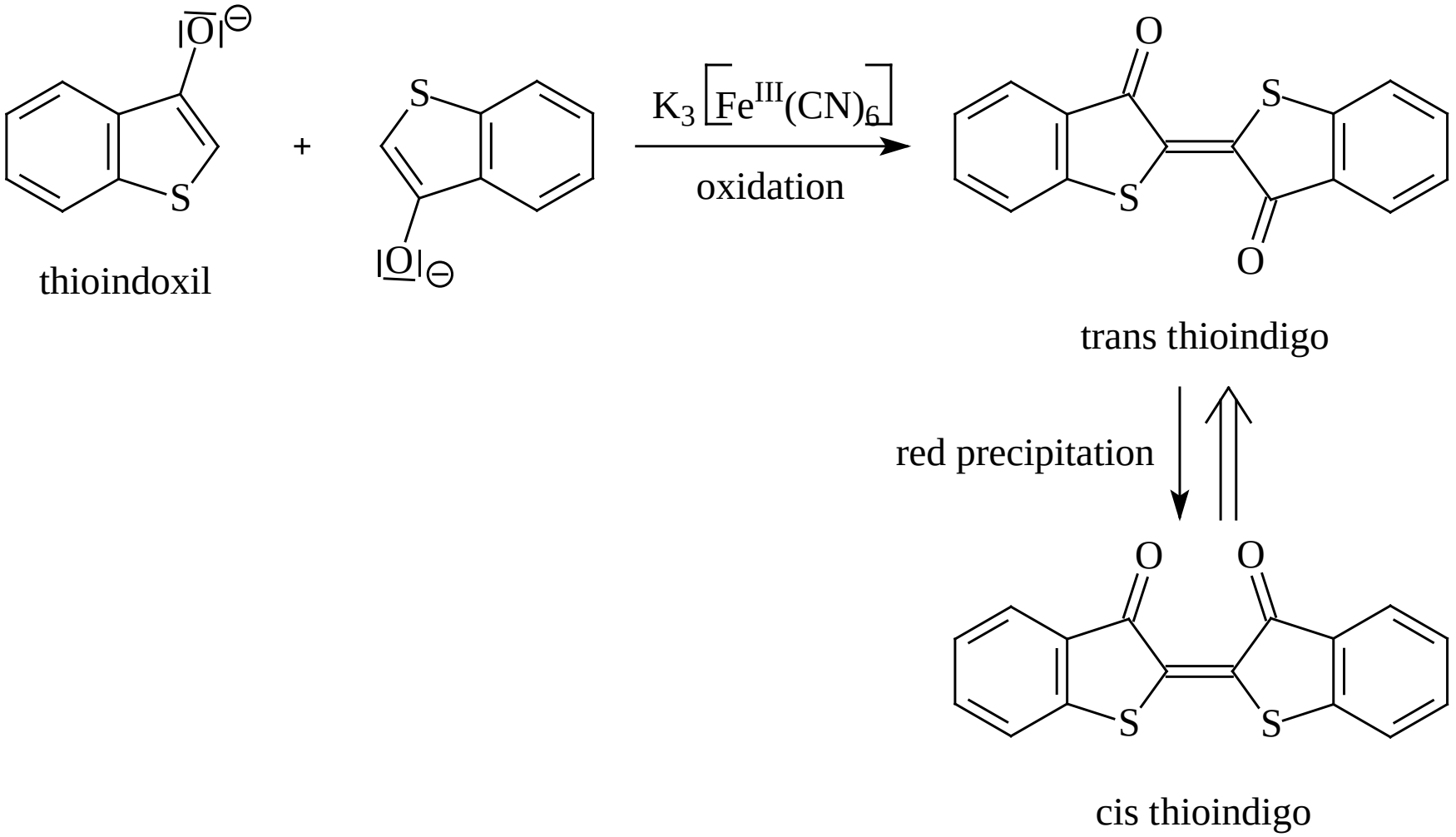
dibenzothiophene

Preparations

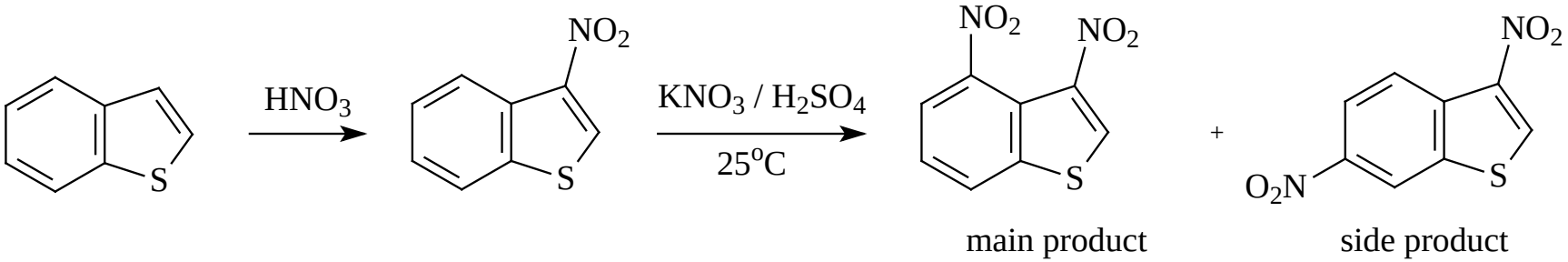


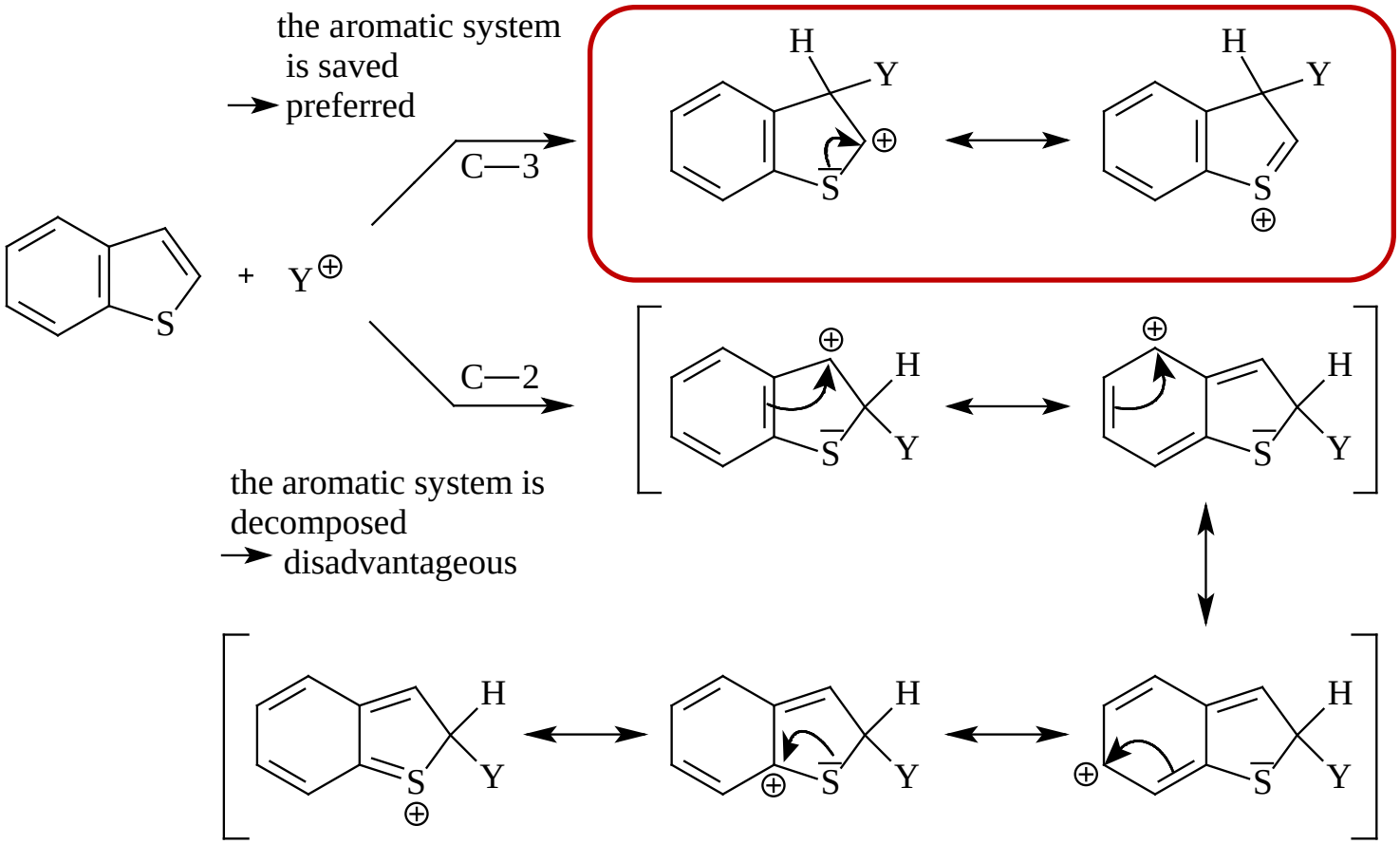
mercaptocinnamic acid




thioindoxil
+
$K_3[Fe^{III}(CN)_6]$
oxidation
trans thioindigo
red precipitation
cis thioindigo

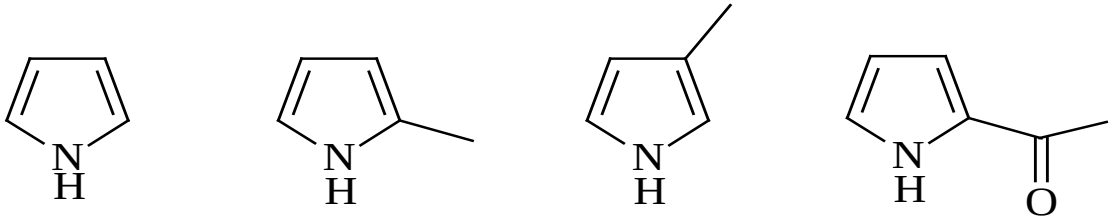
Chemical properties





V/ Pyrrole and its derivatives

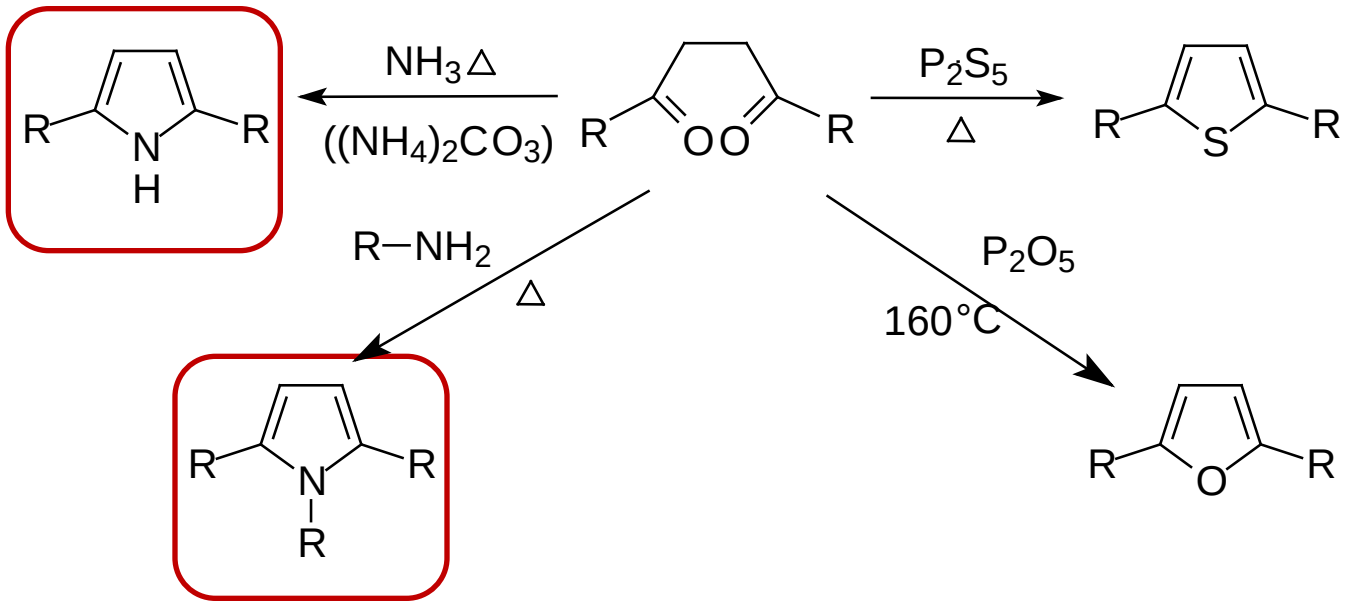
Nomenclature



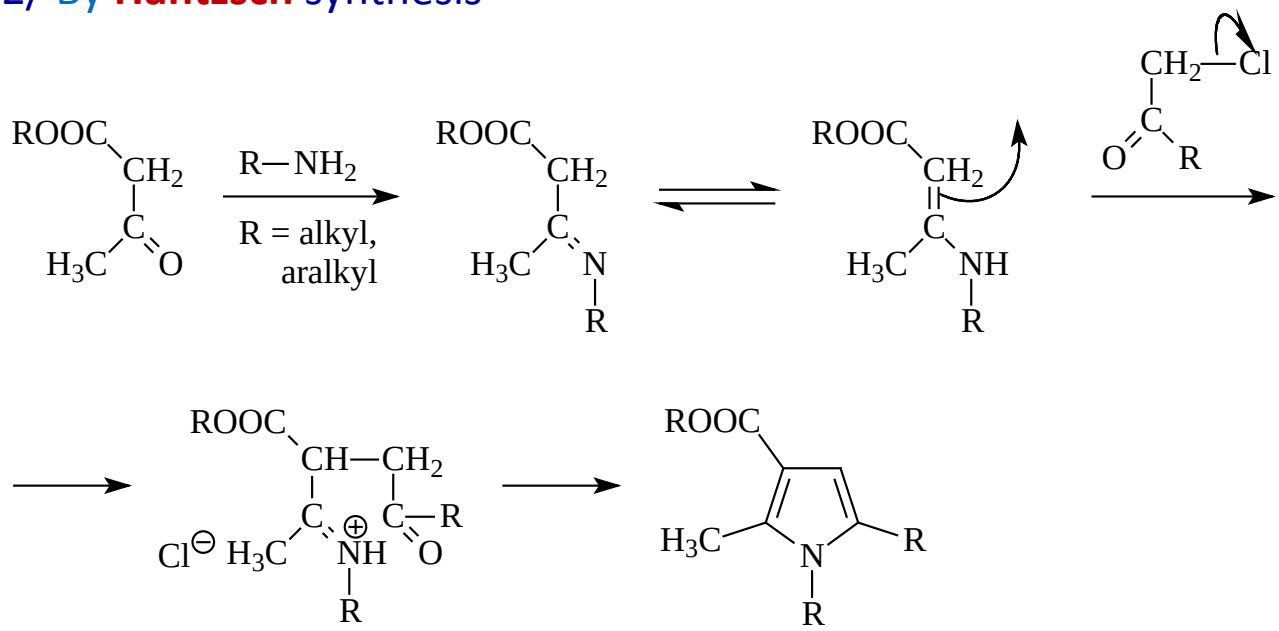
pyrrole α-pyrryl- β-pyrryl- α-pyrroyl-

Preparations

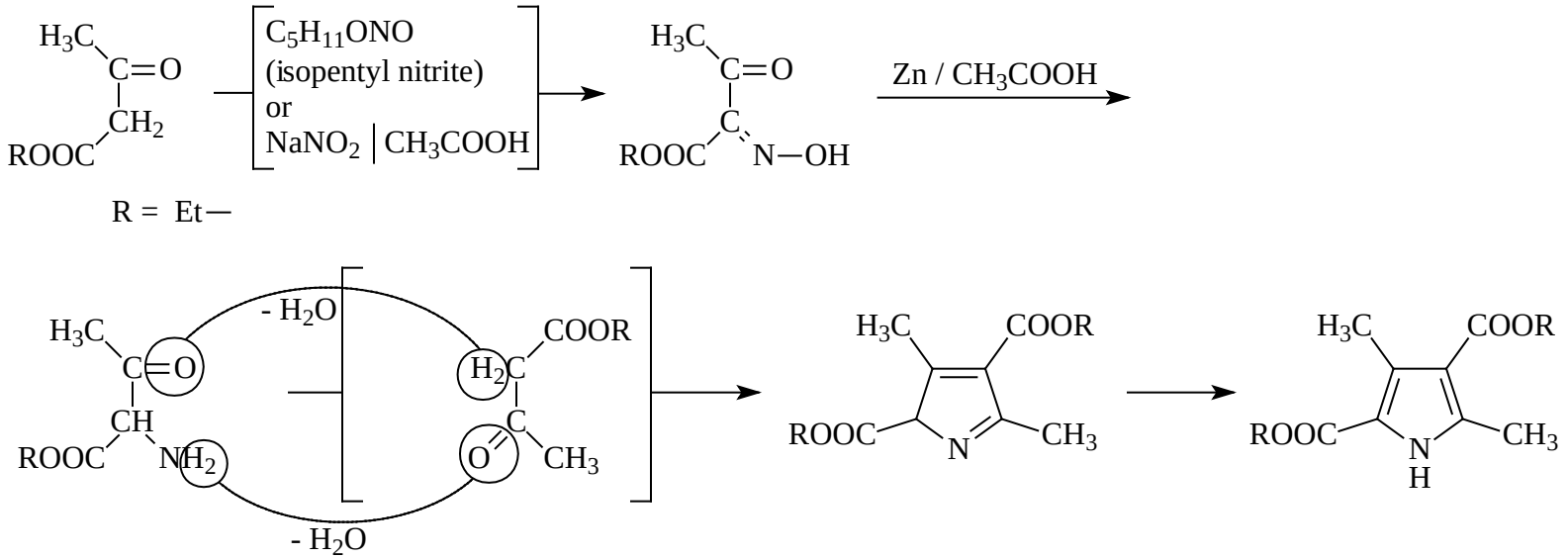
1/ By **Paal-Knorr** synthesis from dioxo compounds

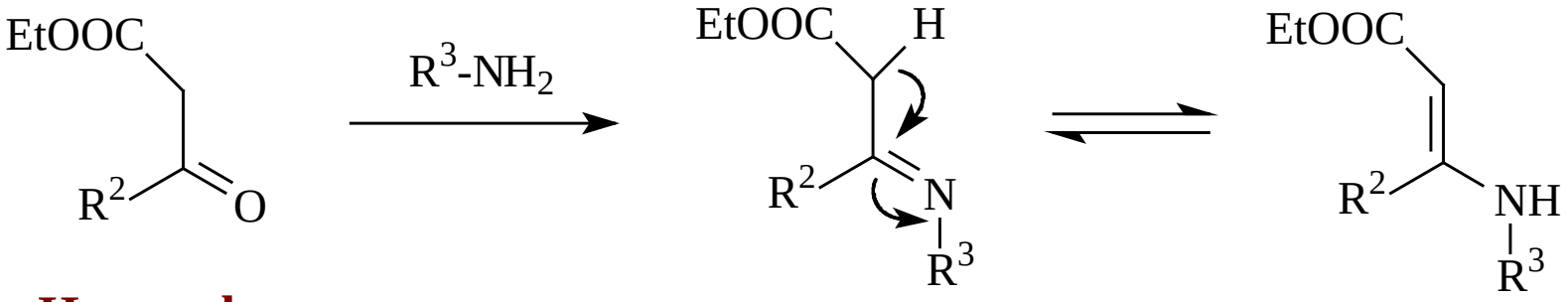


2/ By **Hantzsch** synthesis

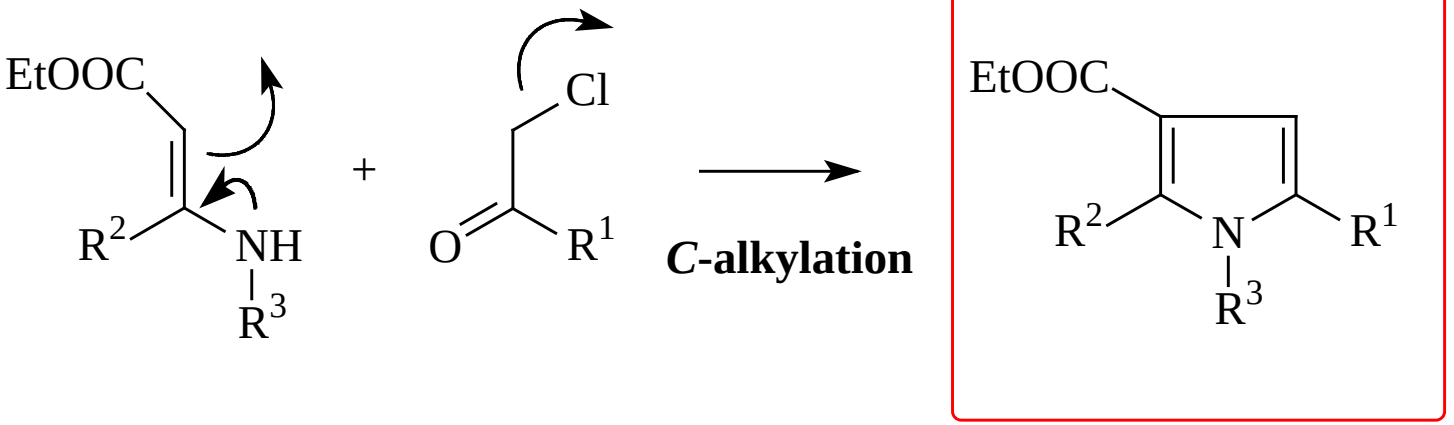


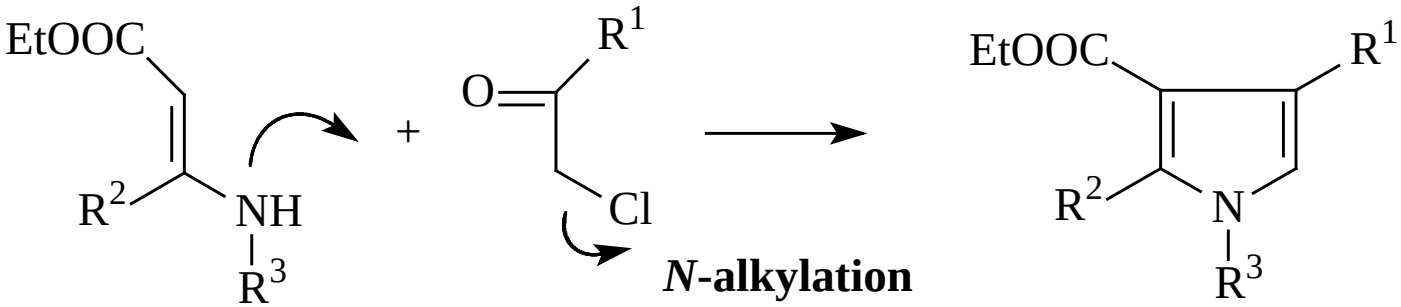
3/ By **Knorr** synthesis



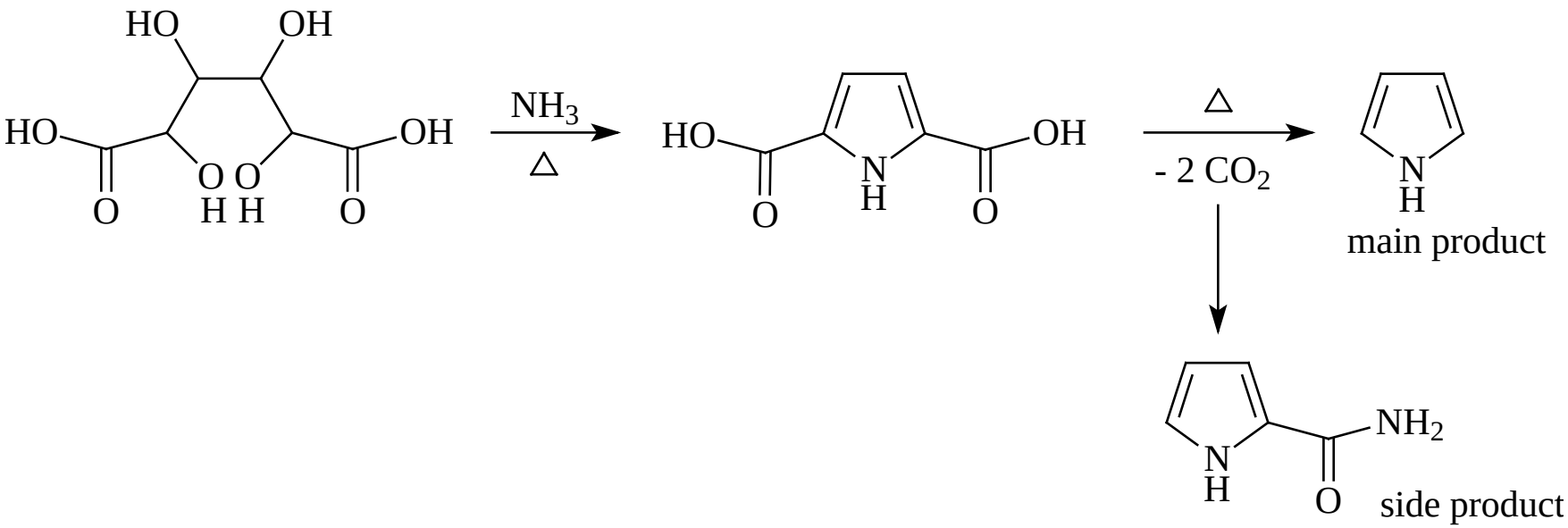

EtOOC
R2
O
R3-NH2
EtOOC
H
R2
N
R3
EtOOC
R2
NH
R3

Hantzsch

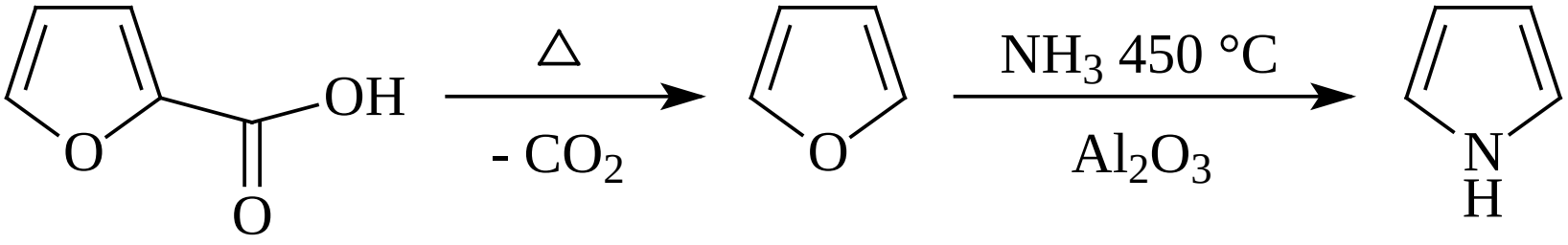

EtOOC
R2
NH
R3
+
Cl
O
R1
C-alkylation
EtOOC
R2
N
R1
R3


EtOOC
R2
NH
R3
+
R1
O
Cl
N-alkylation
EtOOC
R1
R2
N
R3

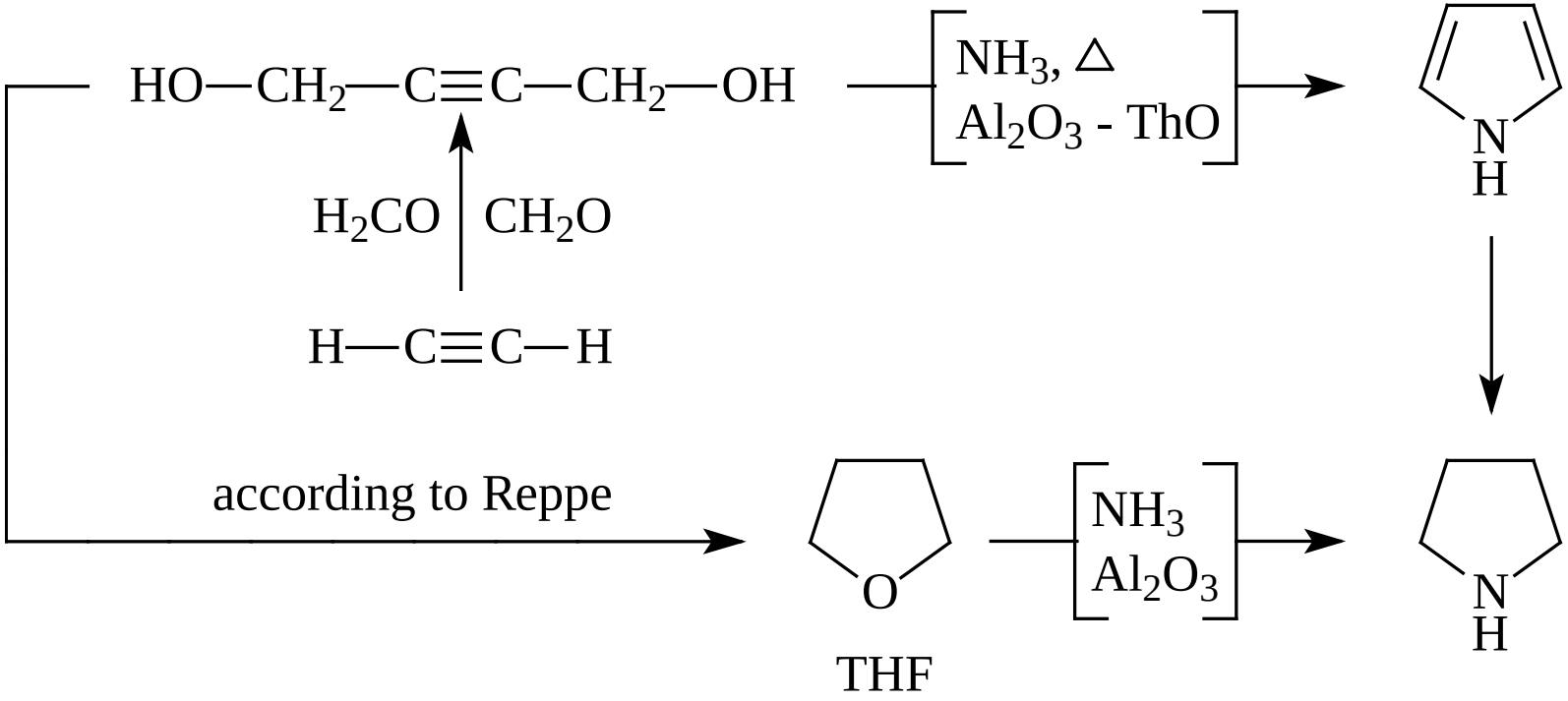
4/ By pyrolysis of ammonium mucoate



5/ From dehydromucoic acid through furan



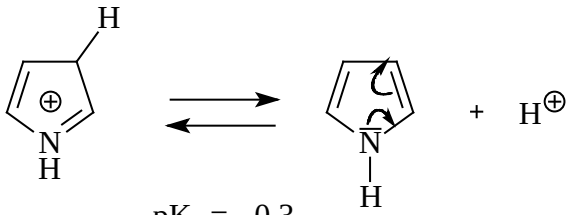
6/ According to **Reppe,** **from** butyn-1,4-diol



Chemical properties

1/ Acid-base properties

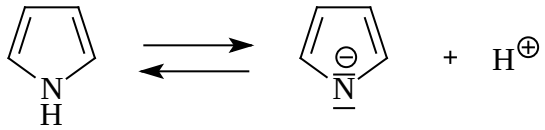
a/ pyrrole, as base



$pK_a = - 0.3$

Absorption of a proton is an addition process (not S_EAr)
Protonation takes place at the C-2, not at the N
Protonation ceases the aromatic system, resulting in a conjugated diene with much higher reactivity.
For this reason, pyrrole is sensitive to acids

b/ pyrrole, as acid



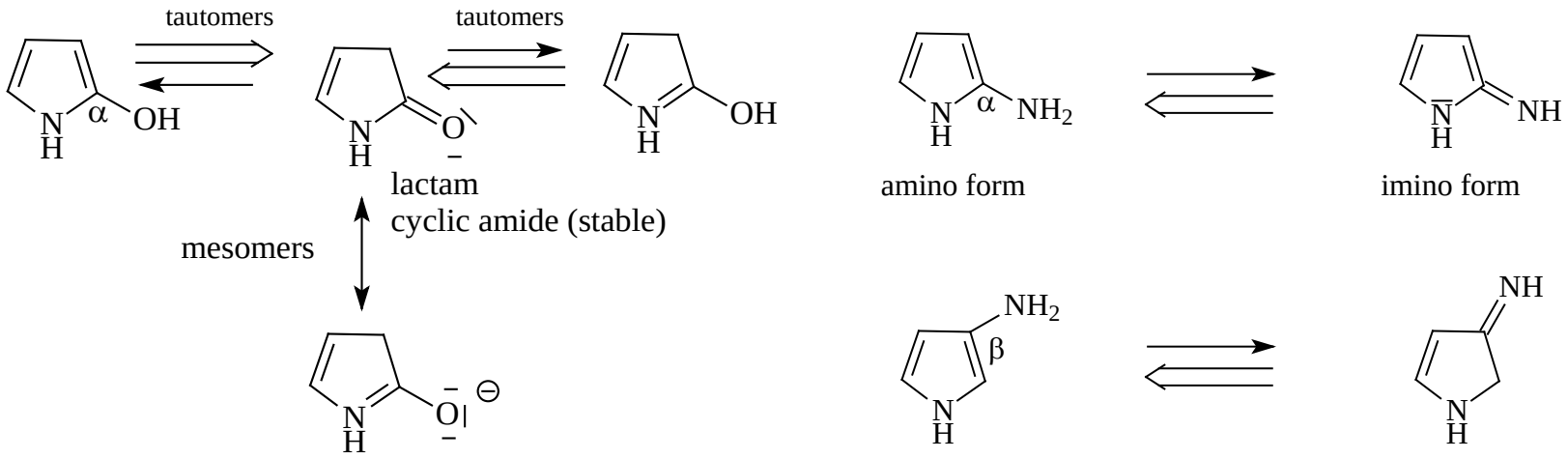
$pK_a \sim 15$
(pK_a water = 15.6)

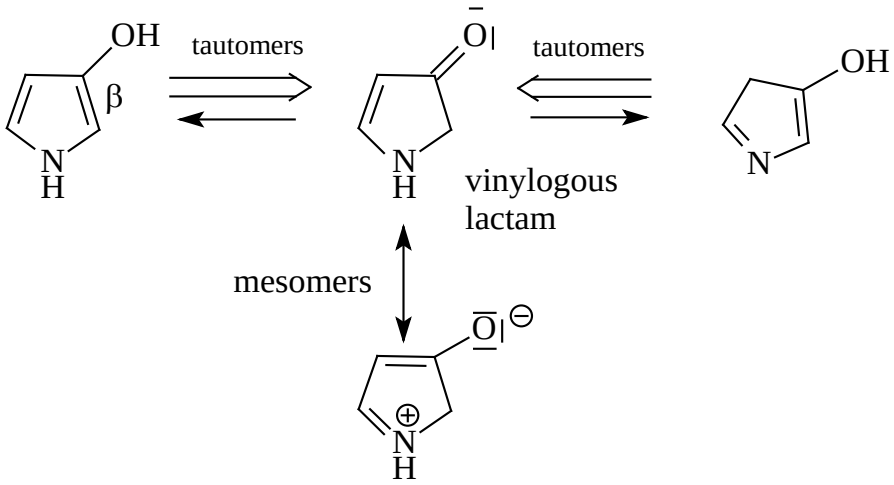
Pyrrole is a weak acid – and an amphotheric compound
Furan, pyrrole, thiophene are stable against bases

2/ Tautomerism

Tautomerism of hydroxy- and amino-derivatives

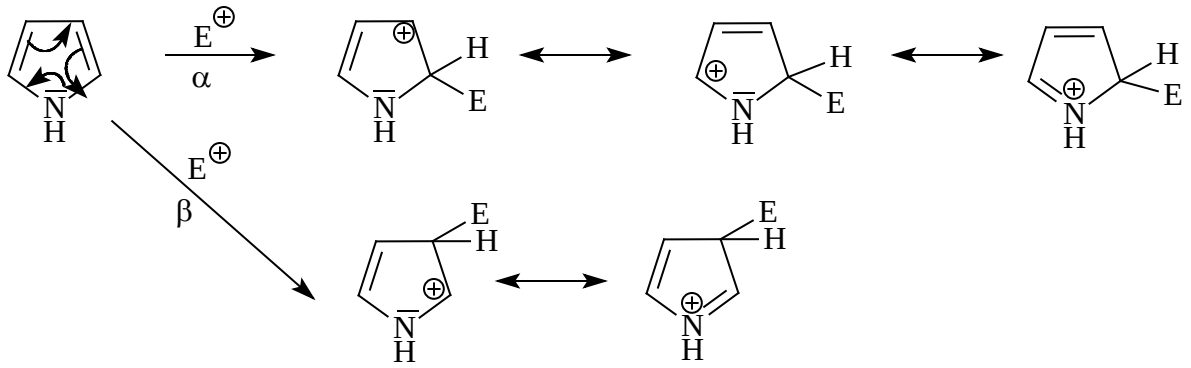
The hydroxy compounds exist mostly in oxo forms, the amino compounds in amino forms (→ can be diazotised)





3/ S_EAr reactions

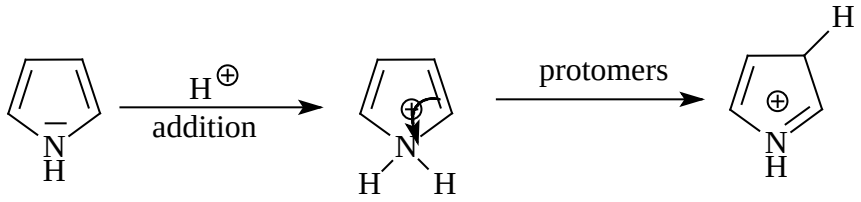
Take place in two steps, with much greater reaction rate, compared to of benzene



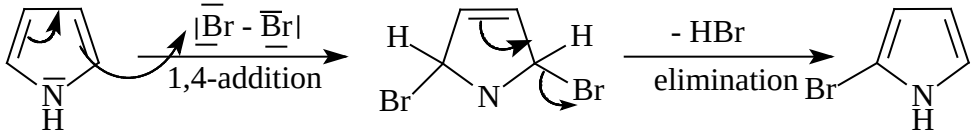
α > β σ–complex is more stable, since more mesomeric structures can be written for it.

If attack happen to β position $E^{\oplus} = H^{\oplus}$ ⟶ protonation reaction takes place.
Otherwise the electrophilic reagent attacks the β position, if the α position is occupied.

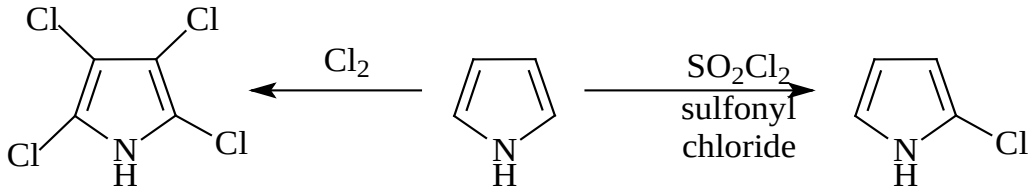
Protonation



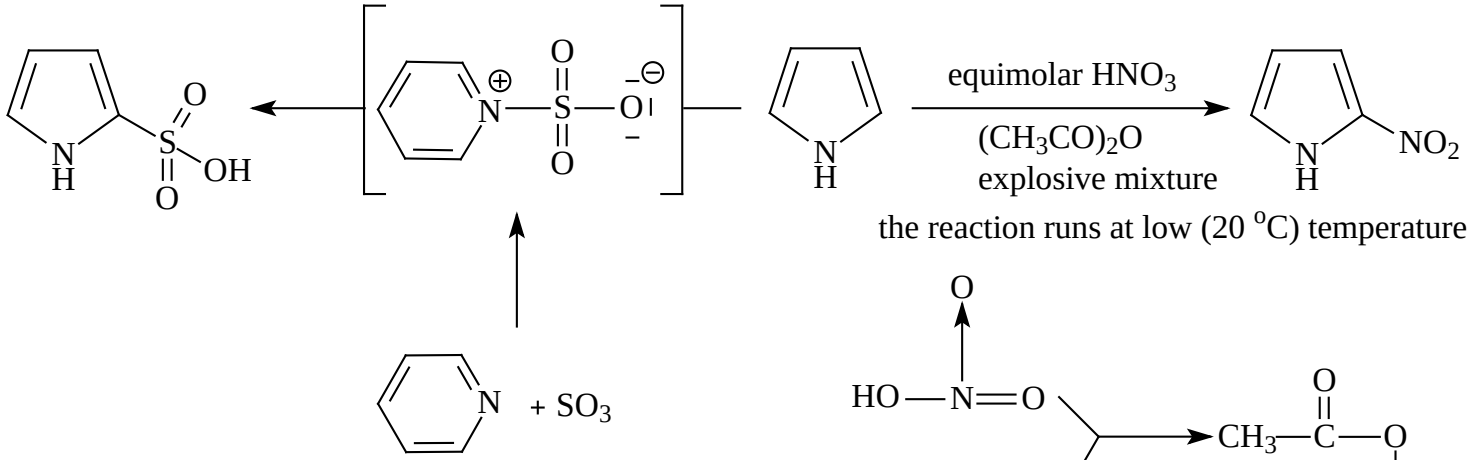
By bromination



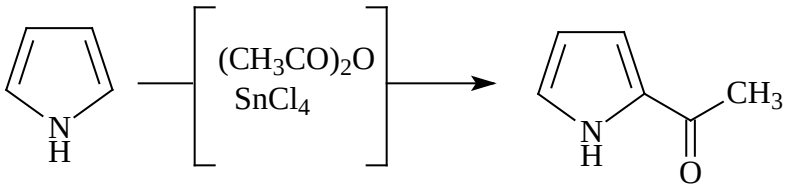
By chlorination



By nitration, sulfonation

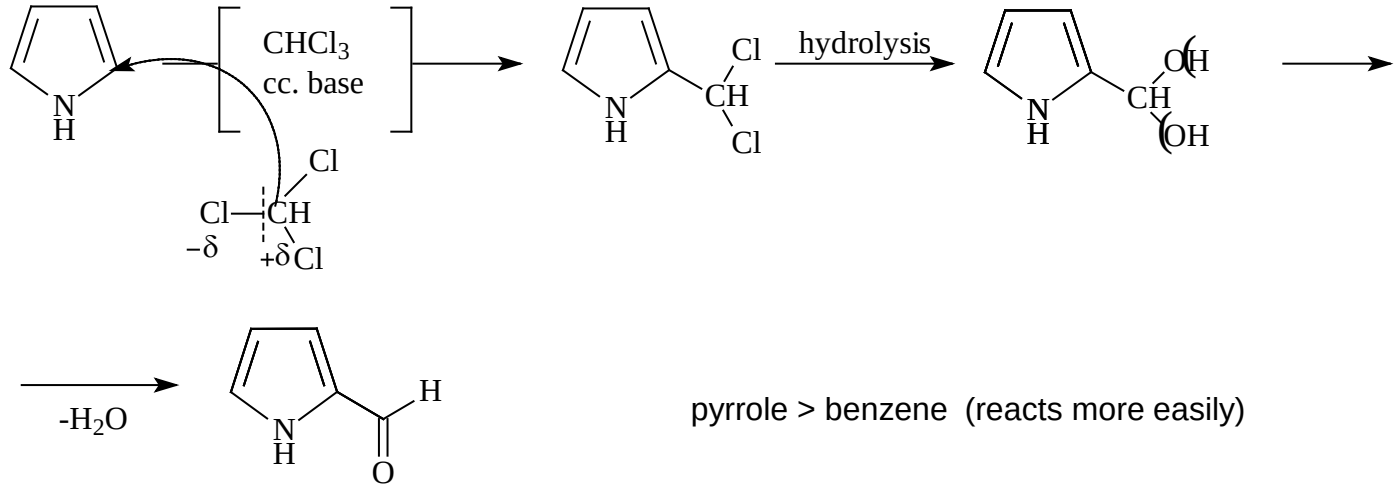


By Friedel-Crafts acylation



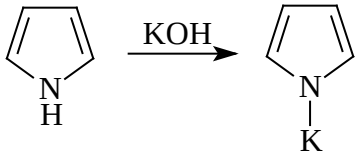
pyrrole > benzene ($SnCl_4$ < $AlCl_3$ both are electrophilic catalyst, but the latter is much more powerful, therefore the latter is not used for the acylation of pyrrole, since the reaction would be too vigorous

By Reimer-Thiemann reaction

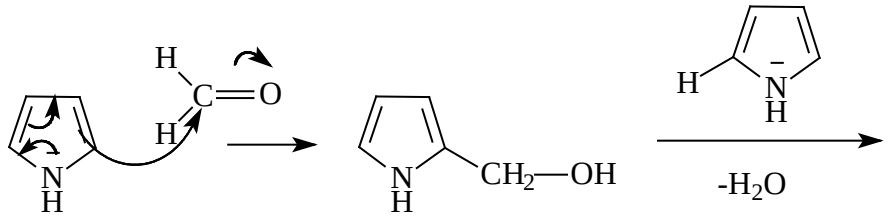


pyrrole > benzene (reacts more easily)

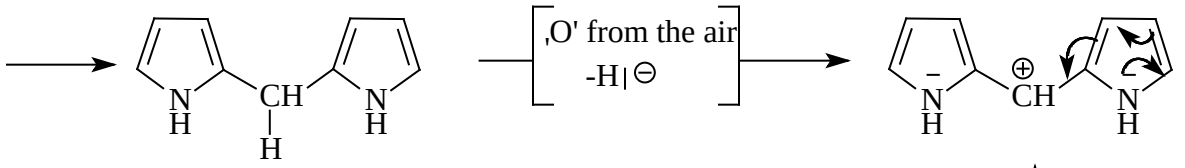
At first, *N*-potassium salt is formed due to cc. KOH



Formation of dipyrrylmethane

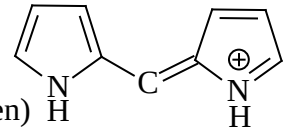


analogous process to the formation of phenol resins

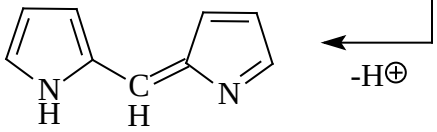


dipyrrylmethane

(many mesomeric structures can be written)



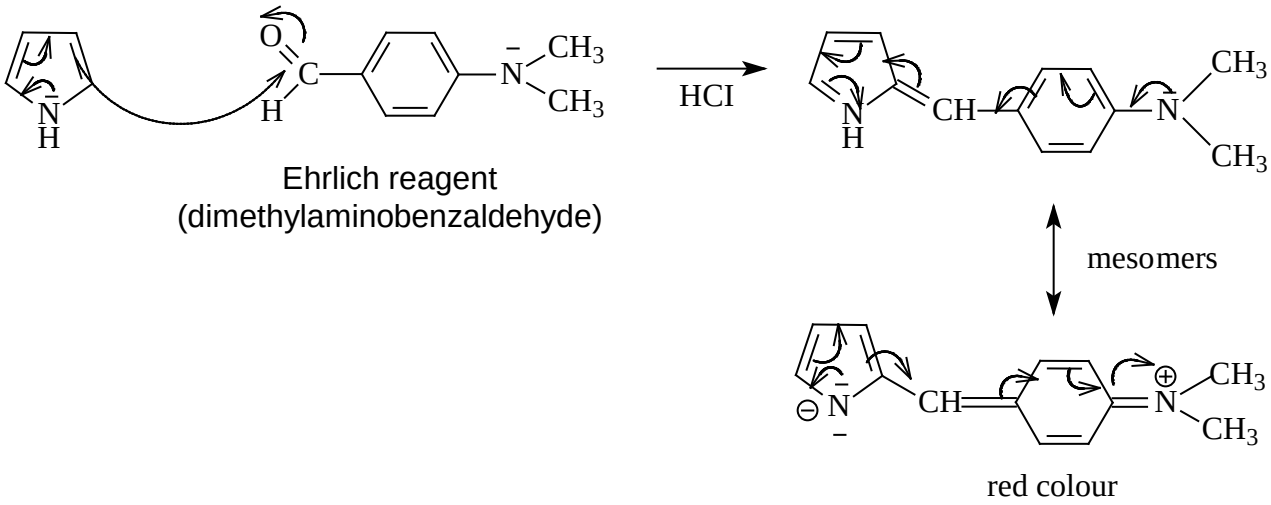
conjugate acid of dipyrrylmethene



dipyrrylmethene

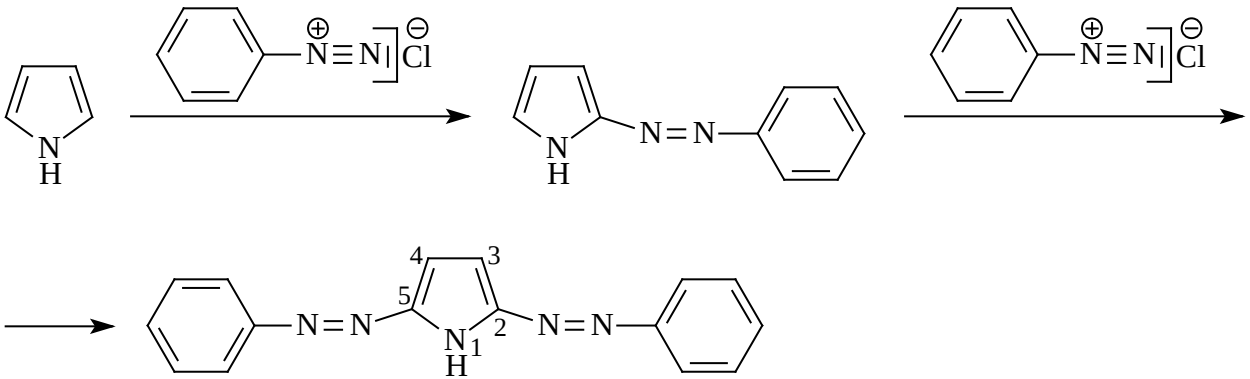
there are 4 pyrrole rings in the synthetic intermediates of compounds with porphin ring system

By Fischer-Orth reaction



Ehrlich reagent
(dimethylaminobenzaldehyde)

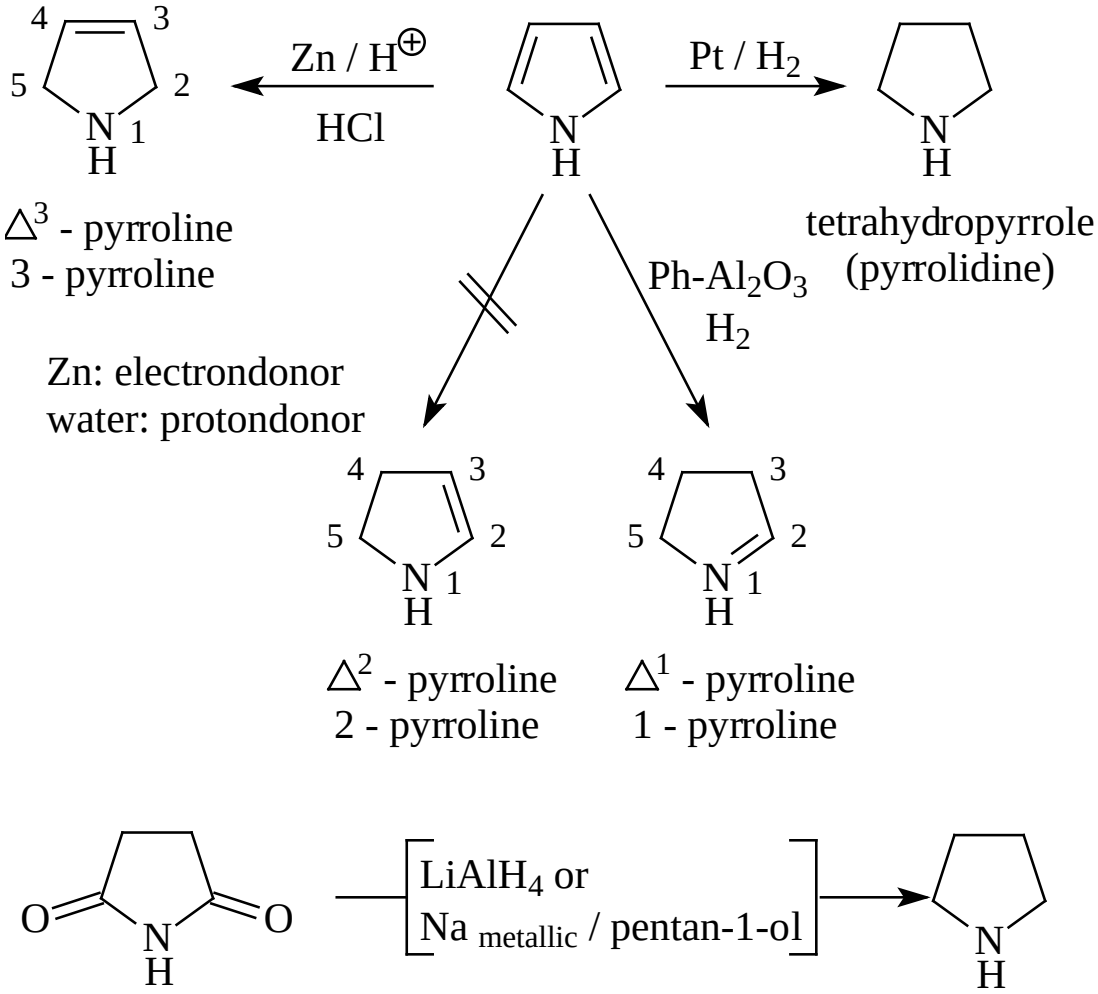
By Fischer-Bartholomäus reaction



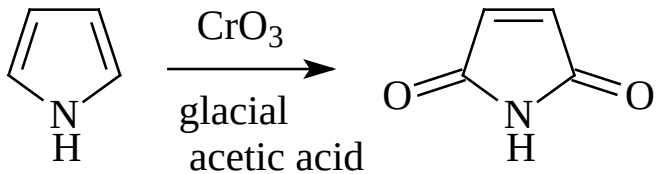
2,5-bis(phenylazo)pyrrole

4/ Transformation to heteroalkene-, or heteroalkane derivatives

By reduction reactions

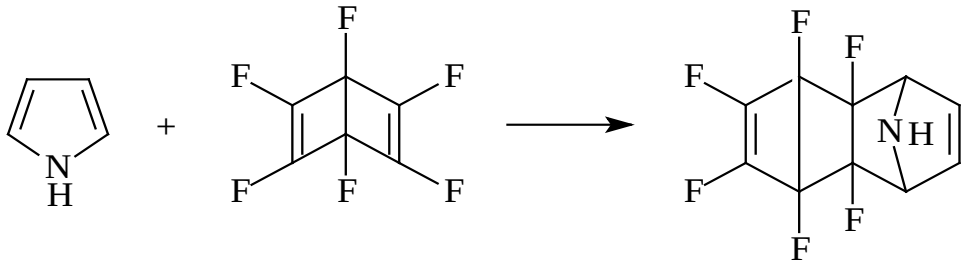


By oxidation reaction



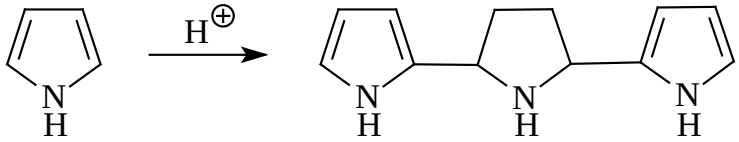
maleic acid imide

By Diels-Alder reaction



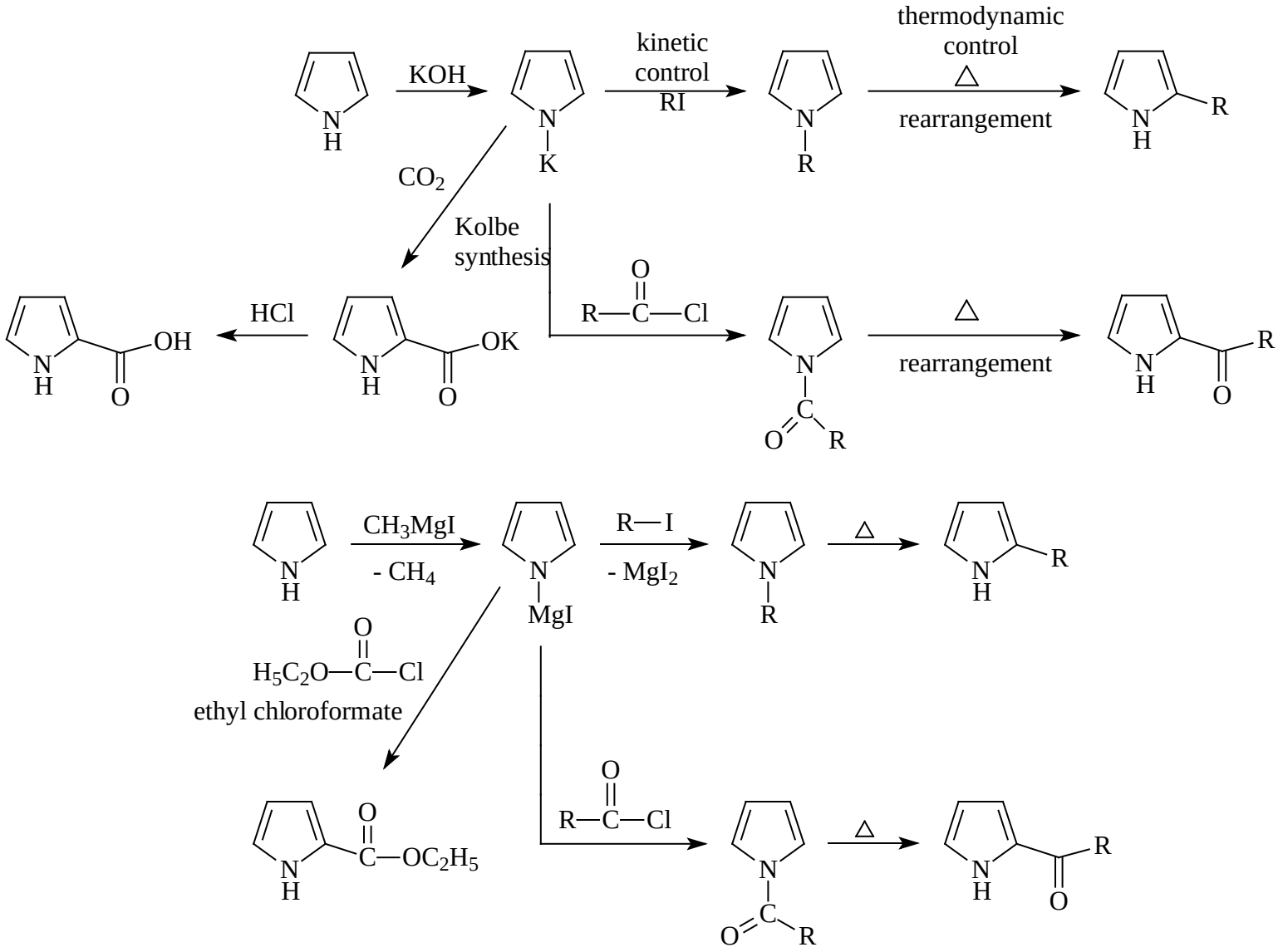
there is no reaction with pyrrole, but there is formation of adduct with hexafluoro-Dewar-benzene

By polymerisation



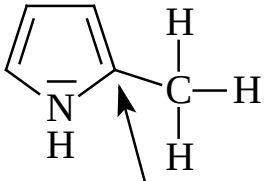
5/ Amphotheric properties of pyrrole

Metal derivatives and their transformations

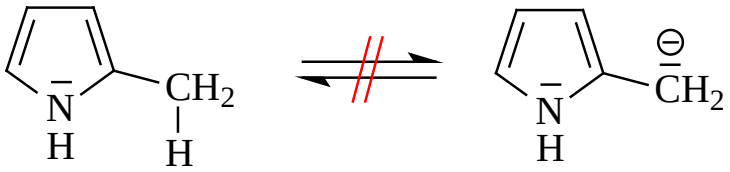


Pyrrole does not react by nucleophilic substitution reactions

The H at α-metil group is not active (the C-H bond is stable due to π electron excess)

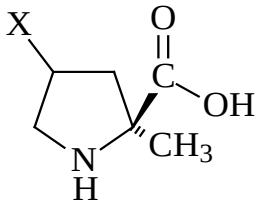


electron rich C-atom

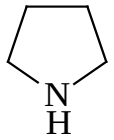


More important derivatives

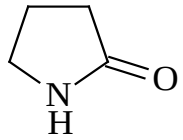
a/ monocyclic pyrrole derivatives



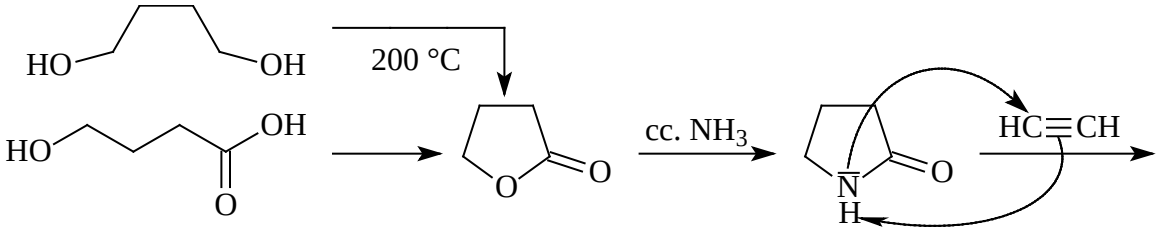
X = H proline
= OH hydroxyproline



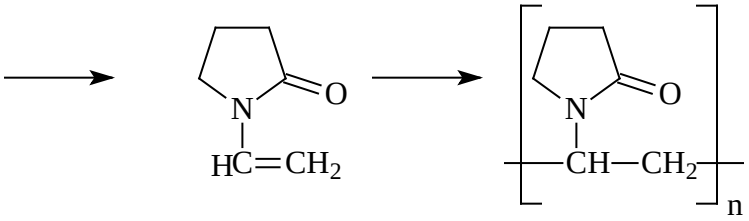
pyrrolidine



pyrrolidone

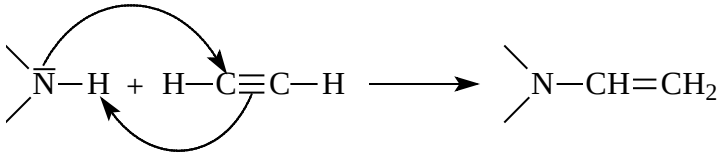


butyric acid butyrolactone



vinylpyrrolidone

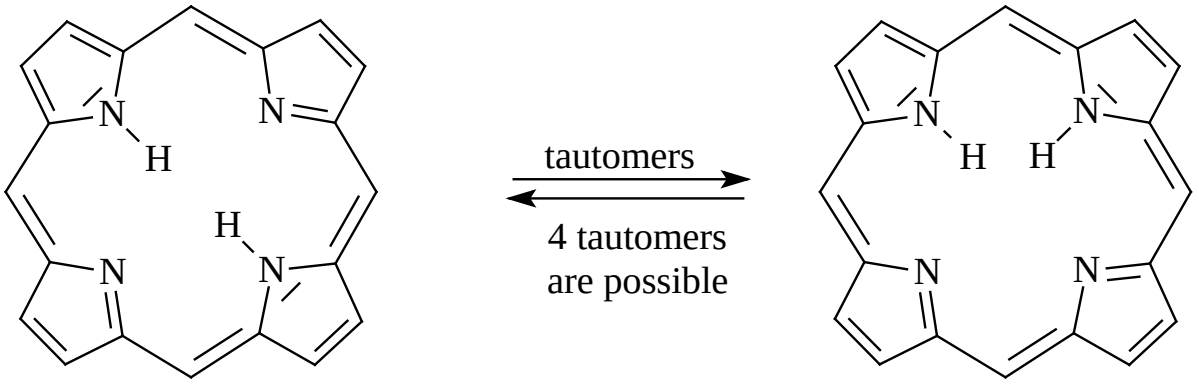
polyvinyl-pyrrolidone
MW 5 - 10 thousand



X-H addition to acetylene

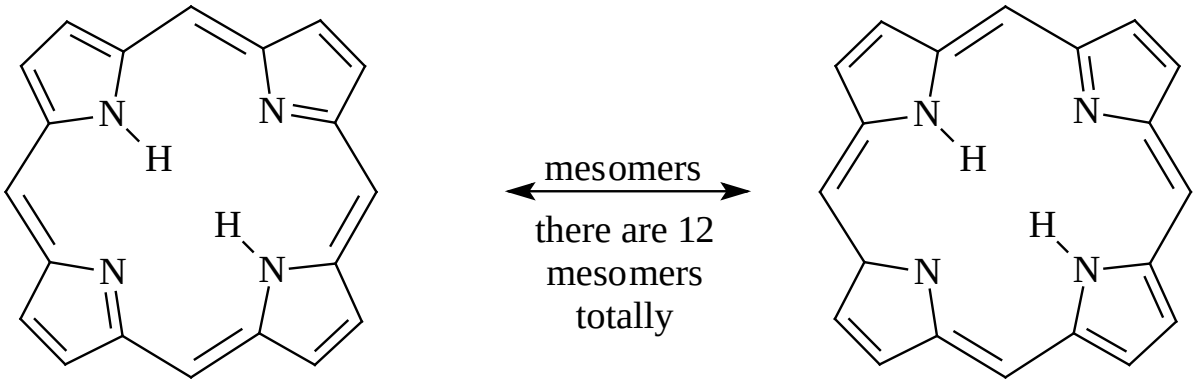
b/ compounds with porphin skeletone

Porphin



- bonds in aromatic system 4 n + 2 n = 4
- alkene bonds (double bonds) 18 π electrons

The Fe, Mg, Co salts of porphin can be found in nature.
Very stable, what is necessary for it purposes. Mp: 300 °C, red crystals



The tautomer forms can be also described by mesomers.
Each tautomer may have many mesomers.

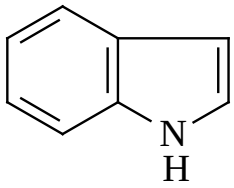
Vitamin B_{12} (cyanocobalamin)

Preparation of it was carried out from liver, from mud of canals, or by fermentation (Streptomyces griseus)
Structure determination was executed by X-ray analysis (Dorothy-Crowfort Hodgkin)
Synthesis of it was carried out by Robert Burns Woodward (Harvard University) and Albert Eschenmoser (ETH Zürich)
Vitamin B_{12} has been isolated from mud of canals by Richter Pharmaceutical Works (Budapest, Hungary) since Years 1950s. Woodward synthesized chlorophyll by total synthesis in 1965, while Woodward and Eschenmoser in cooperation prepared Vitamin B_{12} in 1972-73.
Vitamin B_{12} has important role in biological methylation. It is the antidote of Anemia perniciosa (pernicious anemia). Its appearence is in deep red needles. Liver extracts were useful in this disease.
It was the first macromolecule, which structure was elucidated by X-ray analysis. There is delocalisation in Vitamin B_{12}, but it is neither a cyclic delocalised system, nor aromatic system. The current Vitamin B_{12} extract is of not synthetic origin.

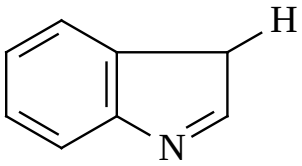
The question is the following: how did these compounds appear in nature and why not other compounds were prepared by biosynthesis. There are building blocks for living organisms – hem, or chlorophyll were prepared at rather low stage of evolution. Usually the most symmetric structure is set – the rest is prepared, but disorderness has always greater probability $\rightarrow$ enthropy is increasing by having the least symmetry elements. It is selected by molecular evolution and does the job perfectly. The role of cobalt in Vitamin B_{12}: it depends on ring size. Woodward's report on it is a complete chemical thriller.

VI/ Pyrrole derivatives with condensed ring systems

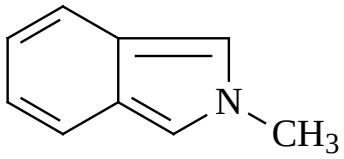
Nomenclature



1*H*-indole
benzo[*b*]pyrrole

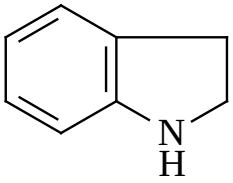


3*H*-indole
benzo[*b*]pyrrole
(indolenine)

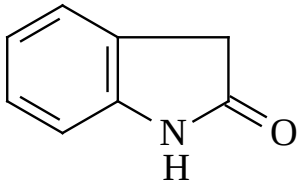


N-methylisoindole
(isoindole does not exist)

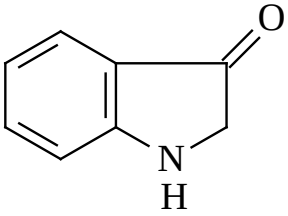
benzo[*c*]pyrrole



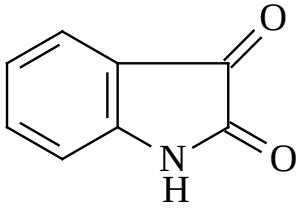
indoline



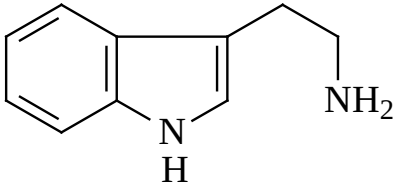
oxindole



indoxil

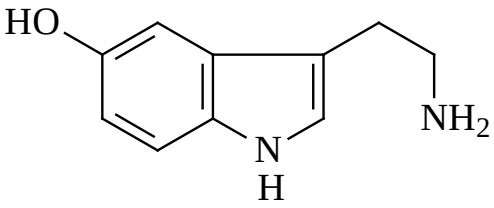


isatin



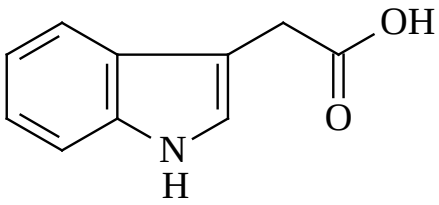
tryptamine

takes place in the
biosynthesis of indolealkaloids



serotonine

5-hydroxytryptamine
important for brain work

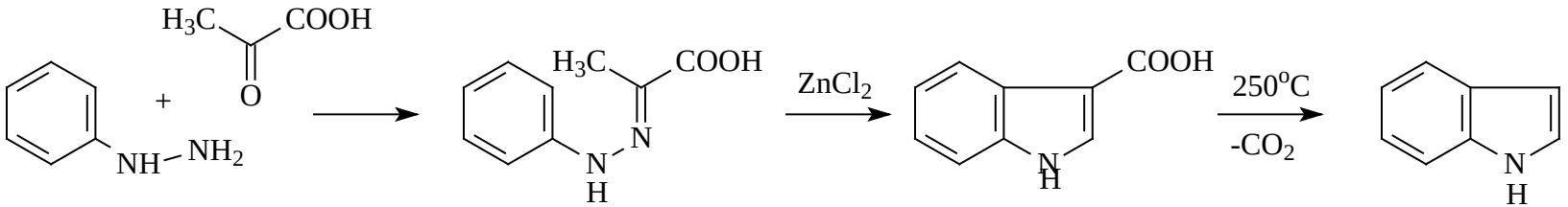


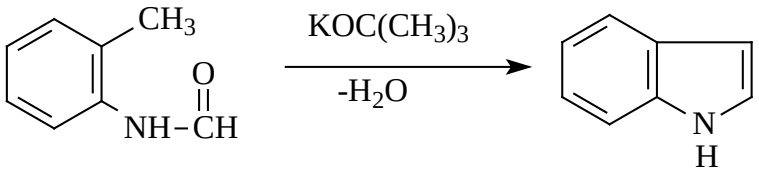
3-indolylacetic acid

heteroauxin
plant growing
hormone

Preparations

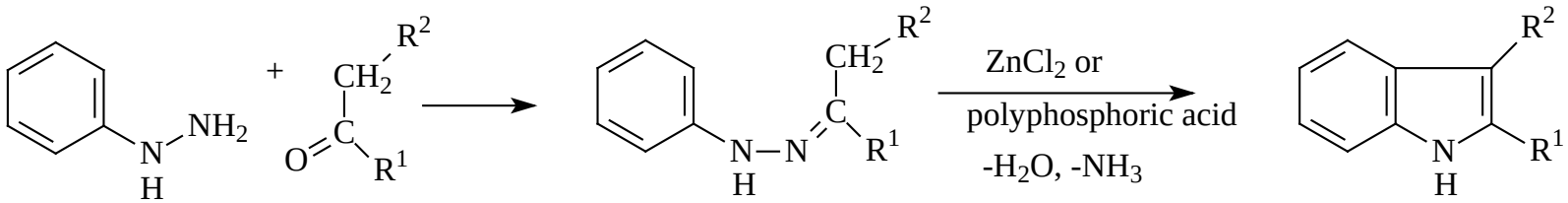
1/ Preparation of indole

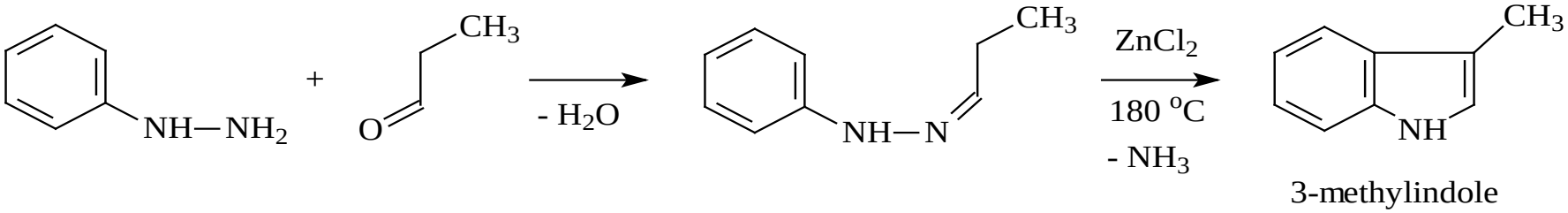




2/ Preparation of indole derivatives

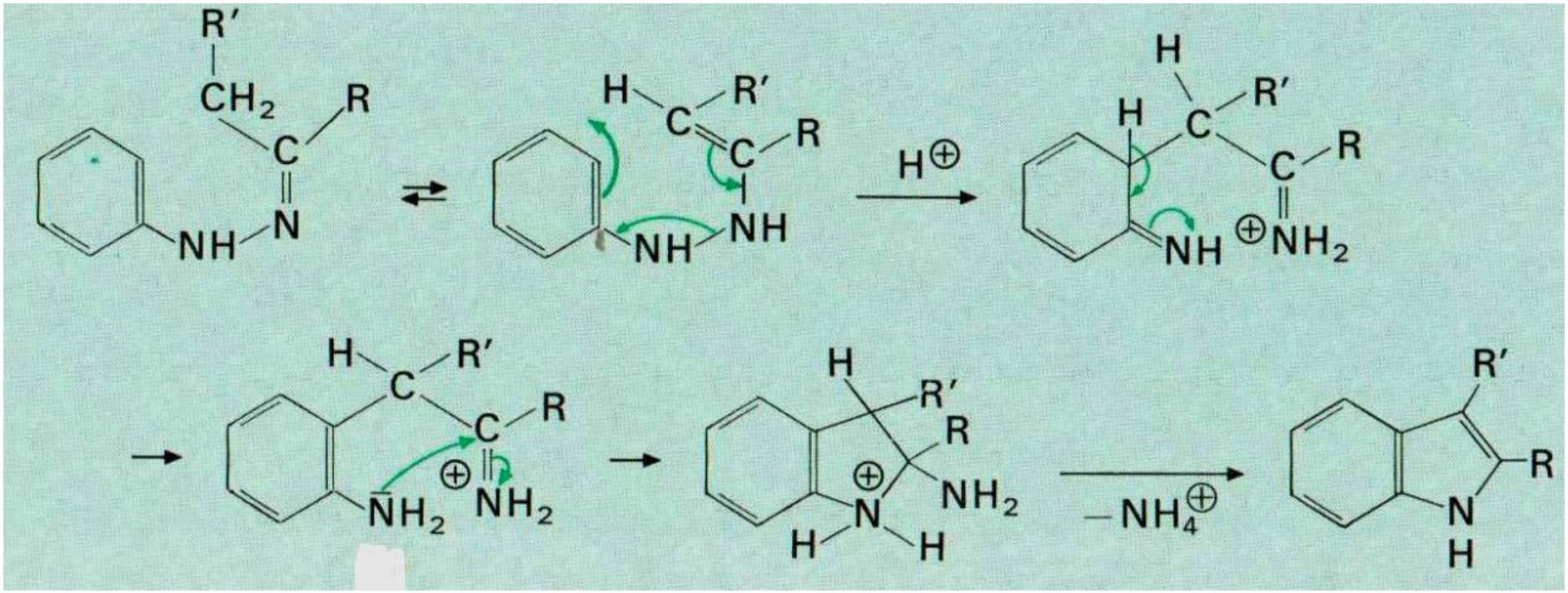
a/ **Fischer's** indole synthesis

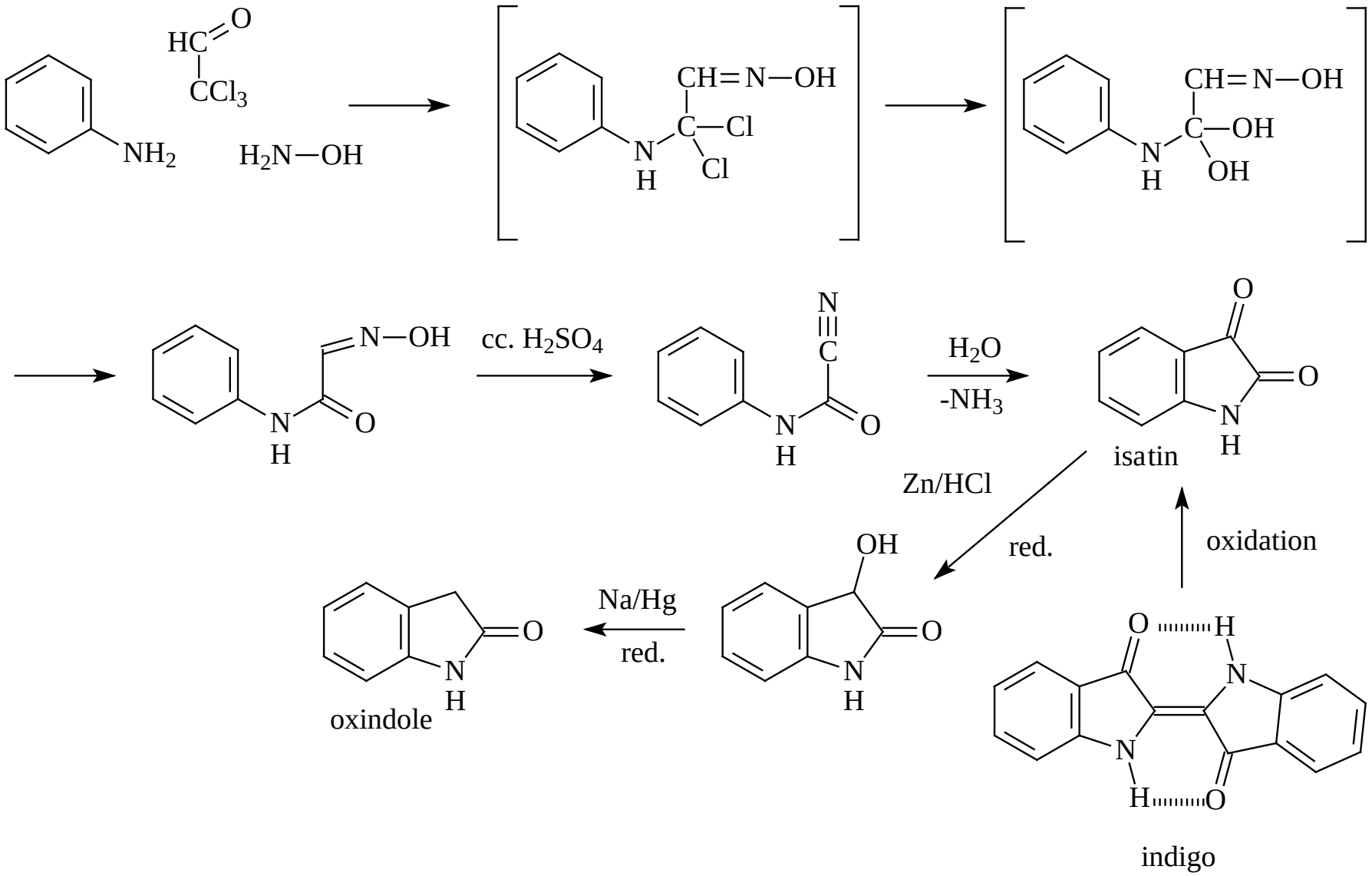




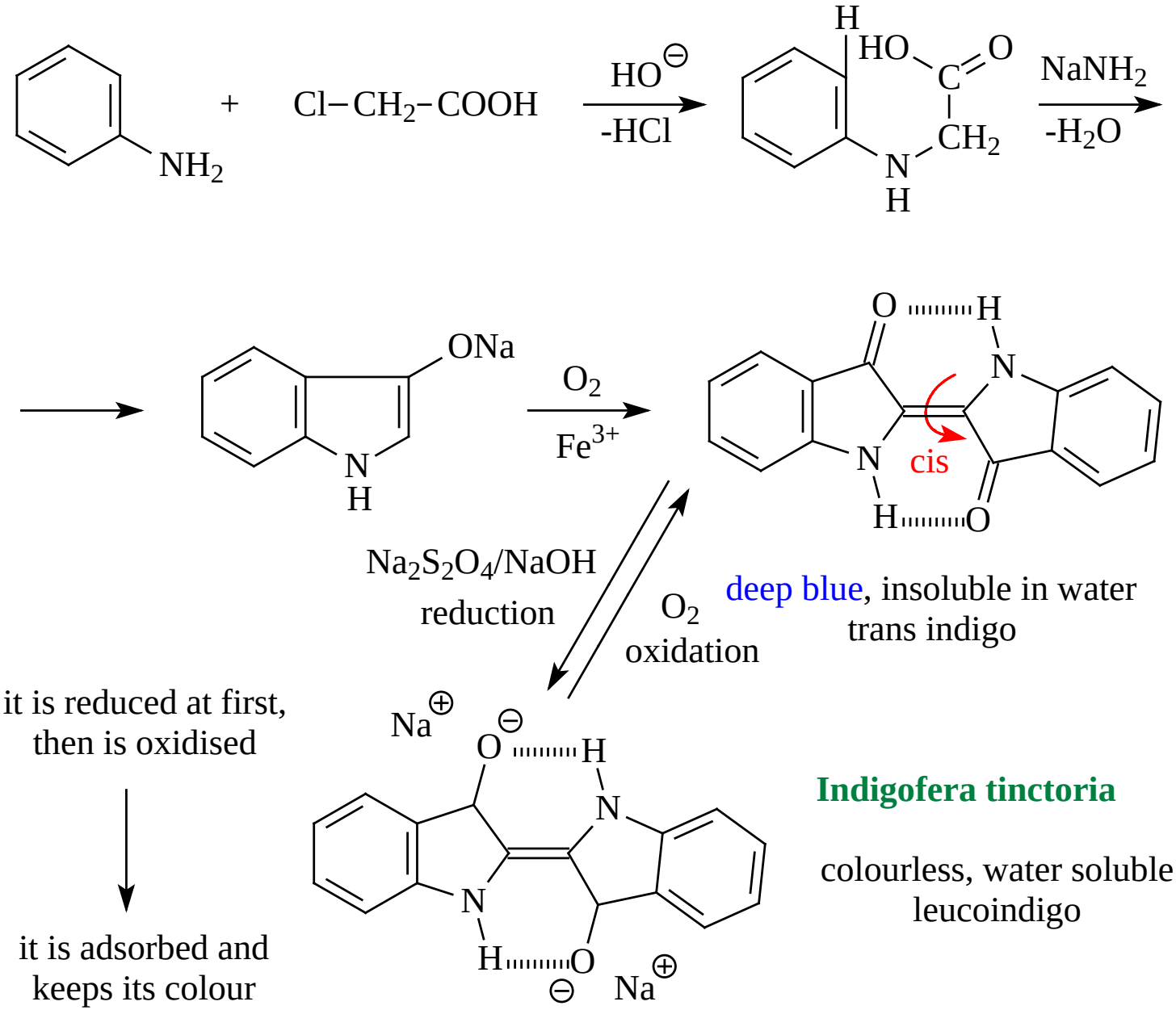
3-methylindole

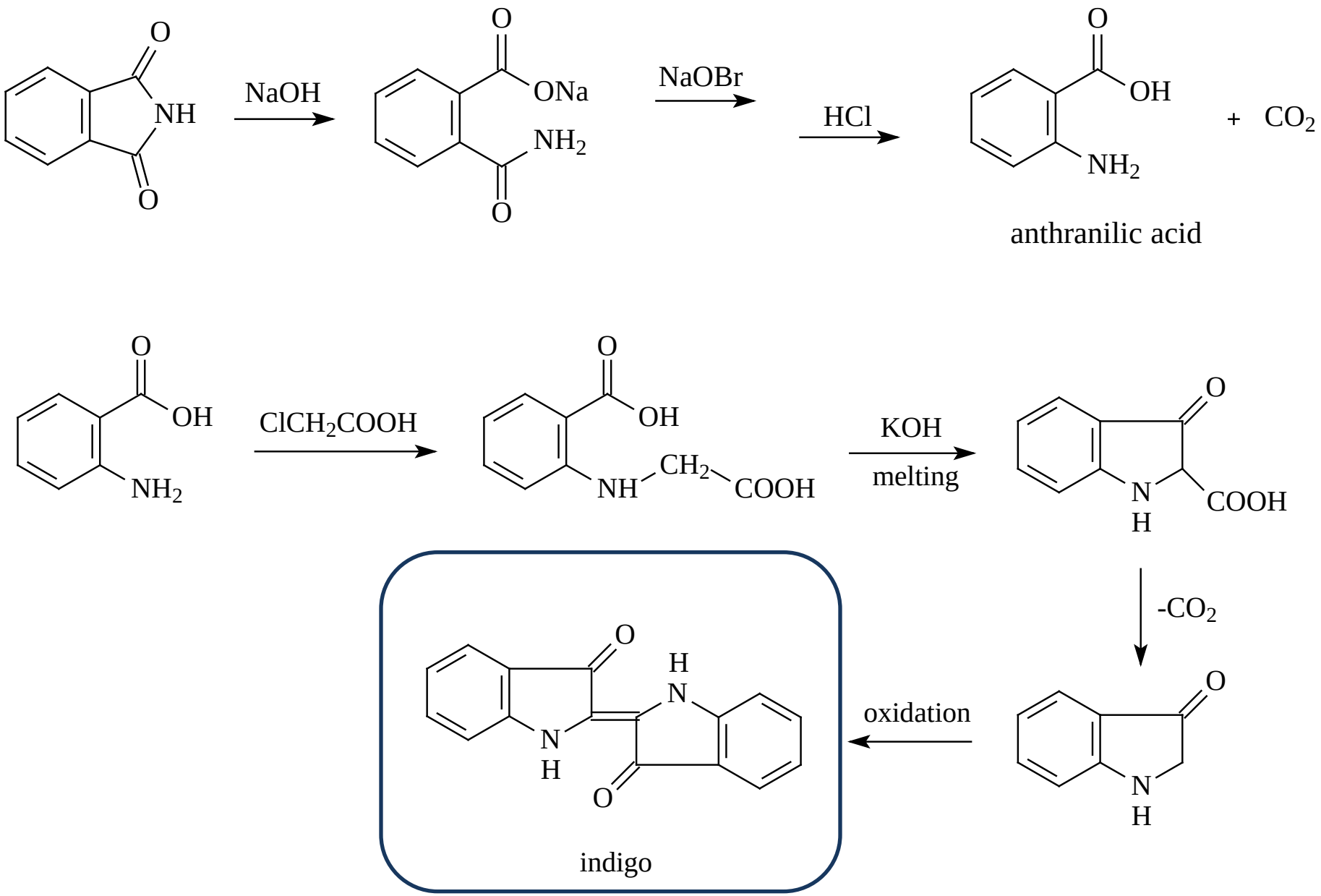
Mechanism of the Fischer's indole synthesis

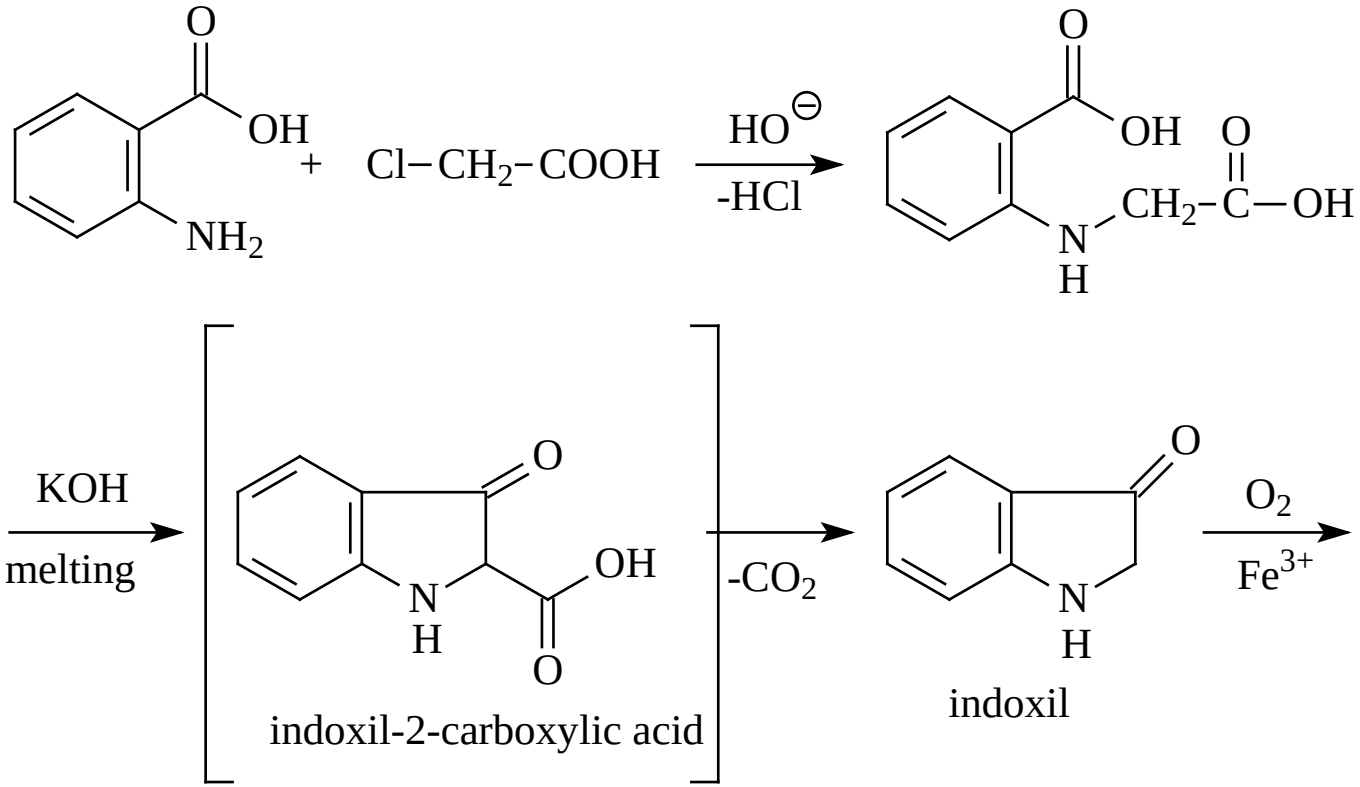



HC=O
CCl3
NH2
H2N—OH
CH=N—OH
C—Cl
Cl
N
H
CH=N—OH
C—OH
OH
N—OH
O
cc. H2SO4
N
C
H2O
-NH3
isatin
Zn/HCl
red.
oxidation
OH
Na/Hg
red.
oxindole
indigo

b/ **Heumann's** indigo synthesis

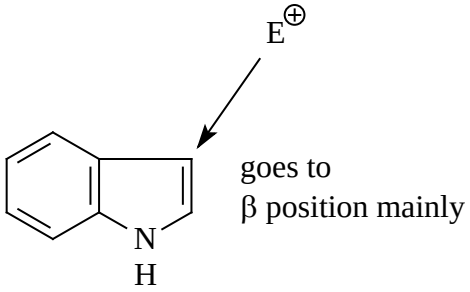



O
NH
O
NaOH
O
ONa
NH2
O
NaOBr
HCl
O
OH
NH2
+ CO2
anthranilic acid
O
OH
NH2
ClCH2COOH
O
OH
NH
CH2
COOH
KOH
melting
O
N
H
COOH
-CO2
O
N
H
oxidation
O
H
N
N
H
O
indigo


O
OH
NH2
+
Cl−CH2−COOH
HO⊖
-HCl
O
OH
O
CH2−C−OH
N
H
KOH
melting
O
OH
N
H
O
indoxil-2-carboxylic acid
-CO2
O
N
H
indoxil
O2
Fe3+
O
H
N
N
H
O
indigo
oxidation
O
N
H
O
isatin

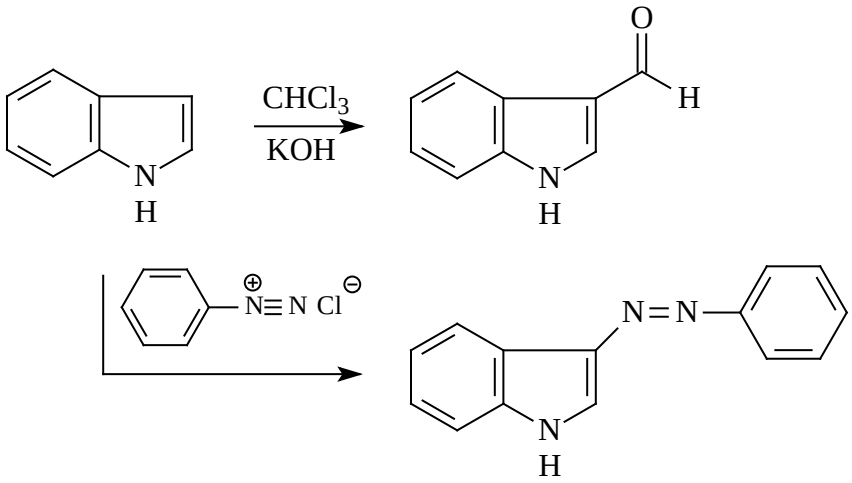
Chemical properties

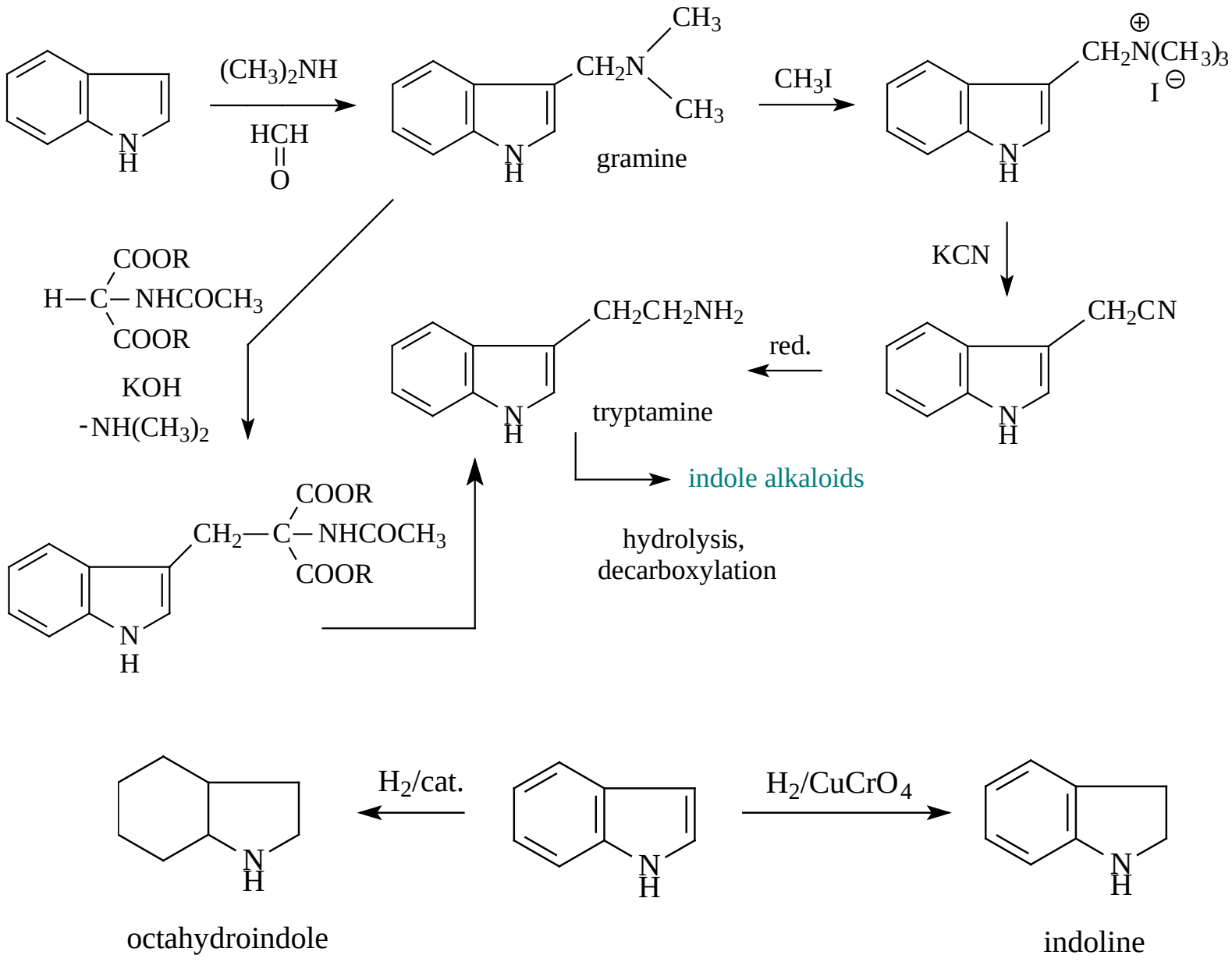
1/ S_EAr reactions

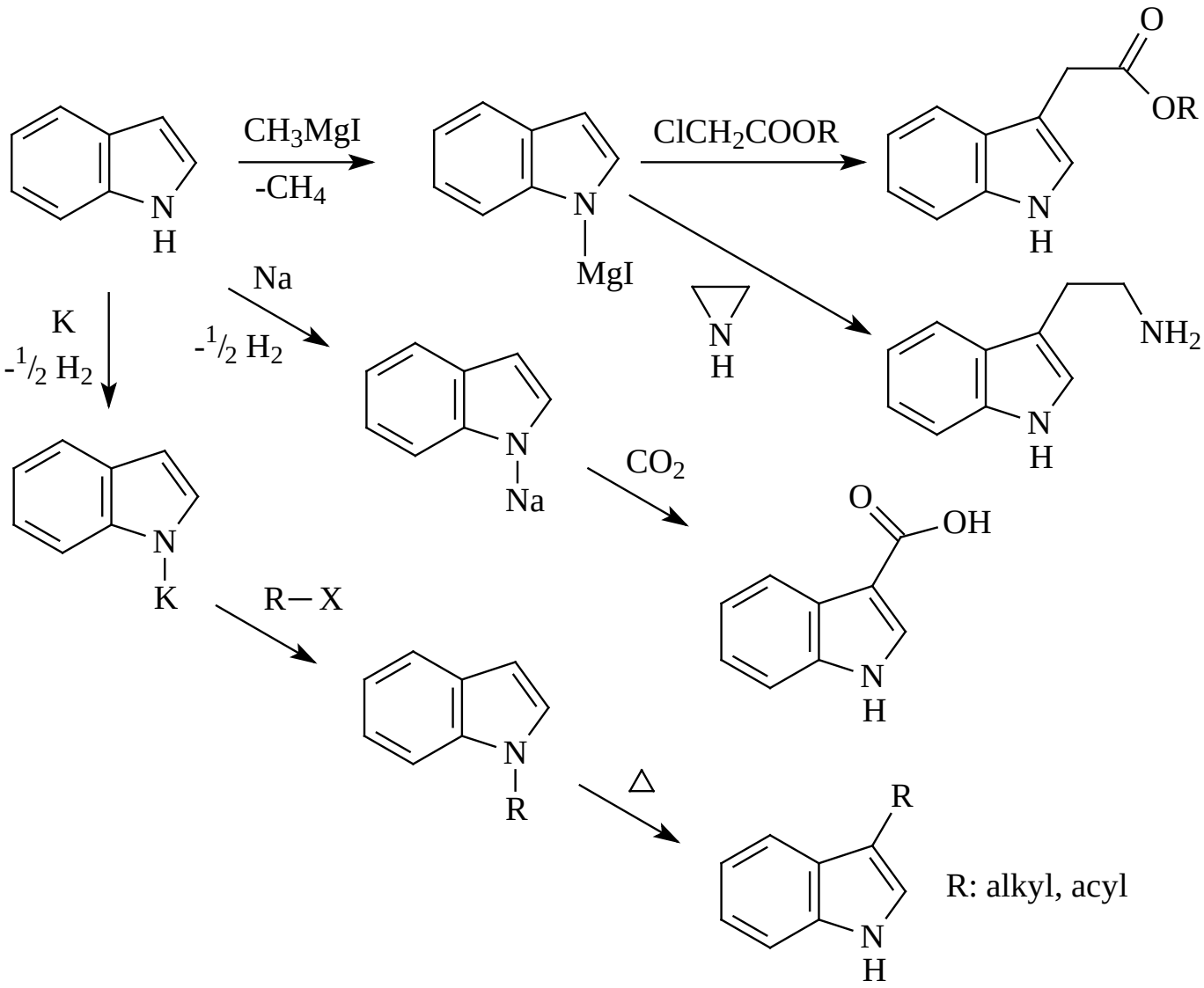


halogenation
nitration
sulfonation
alkylation
acylation

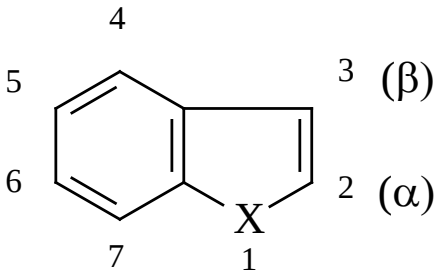
2/ Other reactions




(CH3)2NH
HCH
O
gramine
CH3I
KCN
red.
tryptamine
indole alkaloids
hydrolysis,
decarboxylation
KOH
-NH(CH3)2
H2/cat.
H2/CuCrO4
octahydroindole
indoline

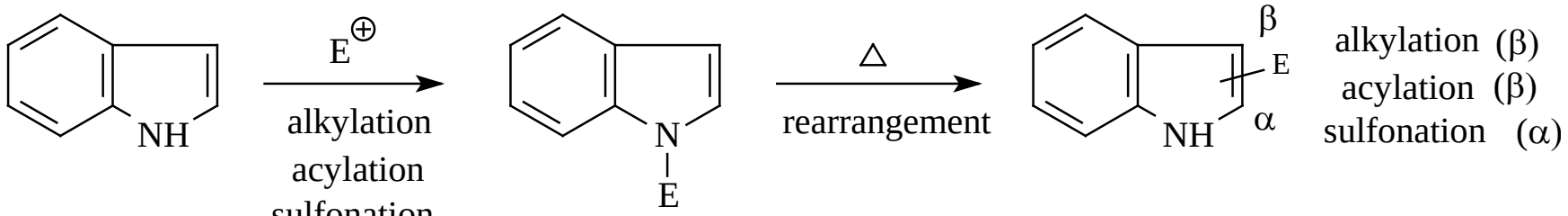

CH3MgI
-CH4
ClCH2COOR
O
OR
N
H
MgI
Na
K
-1/2 H2
-1/2 H2
NH2
CO2
OH
R—X
R
△
R: alkyl, acyl

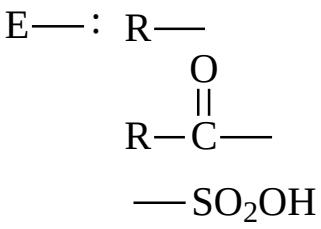
Benzocondensed systems with five-membered heterocycle

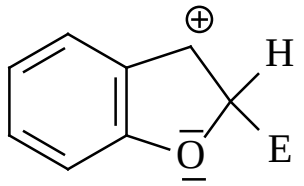


S_EAr

X:			
NH	1*H*-indole	β	(α)
O	coumarone	α	
S	thiocoumarone	β	(α)

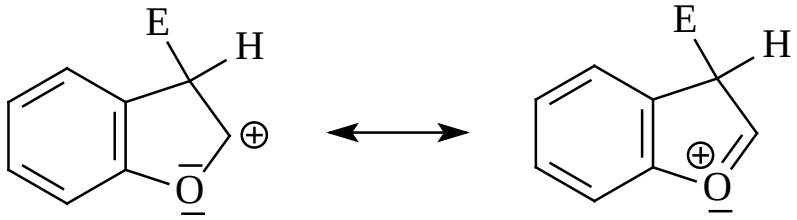




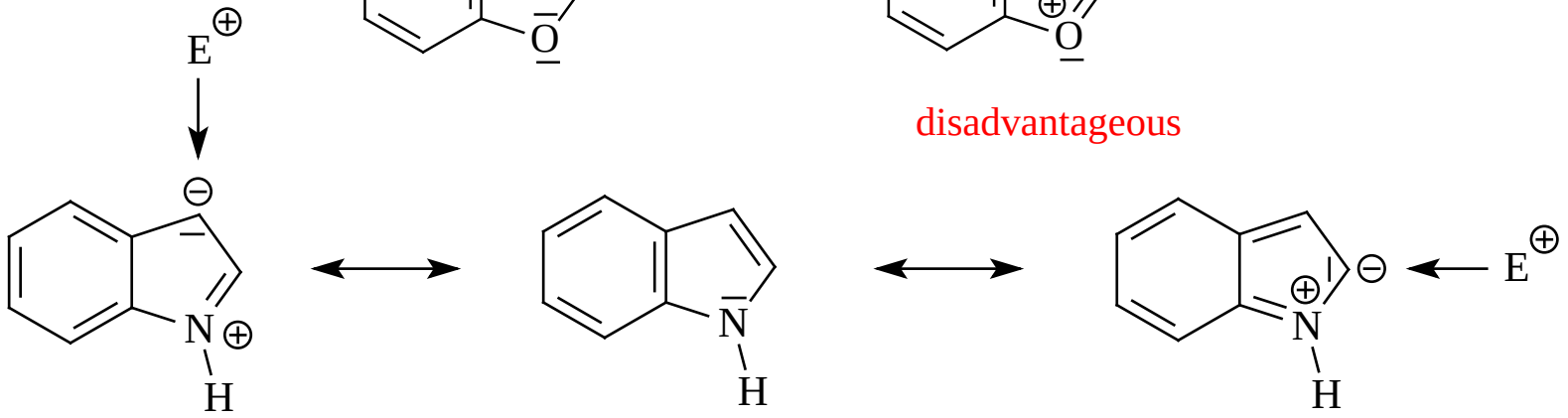


coumarone

advantageous



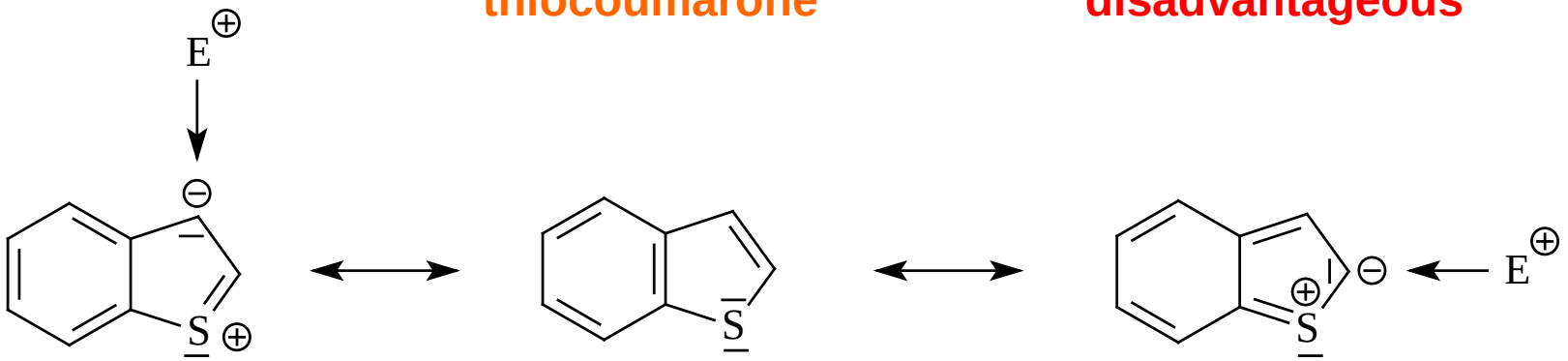
disadvantageous



aromatic
advantageous

1*H*-indole and
thiocoumarone

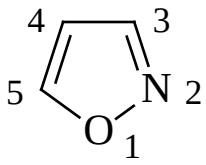
nonaromatic
disadvantageous



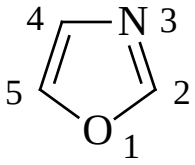
Five-membered heterocycles with two or more heteroatoms and their derivatives with condensed ring systems

Compounds with two heteroatoms

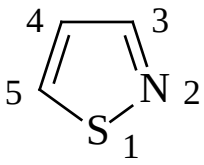
Nomenclature



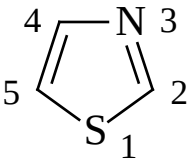
isoxazole
1,2-oxazole



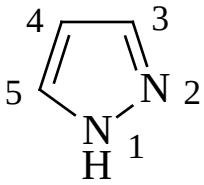
oxazole
1,3-oxazole



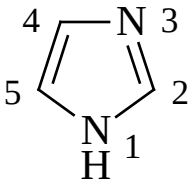
isothiazole
1,2-thiazole



thiazole
1,3-thiazole



pyrazole
1,2-diazole



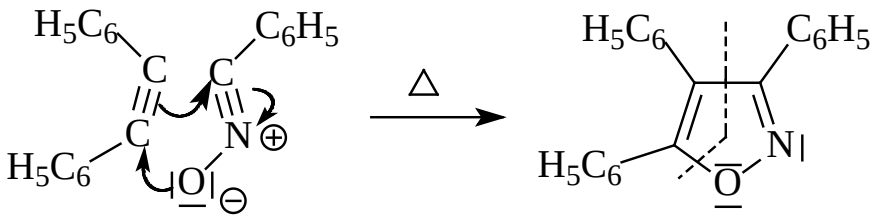
imidazole
1,3-diazole

Introduction of another nitrogen → the pyrrole-like properties are shifted to the pyridine-like properties, e.g., at basicity, water solubility.

I/ Isoxazole and its derivatives

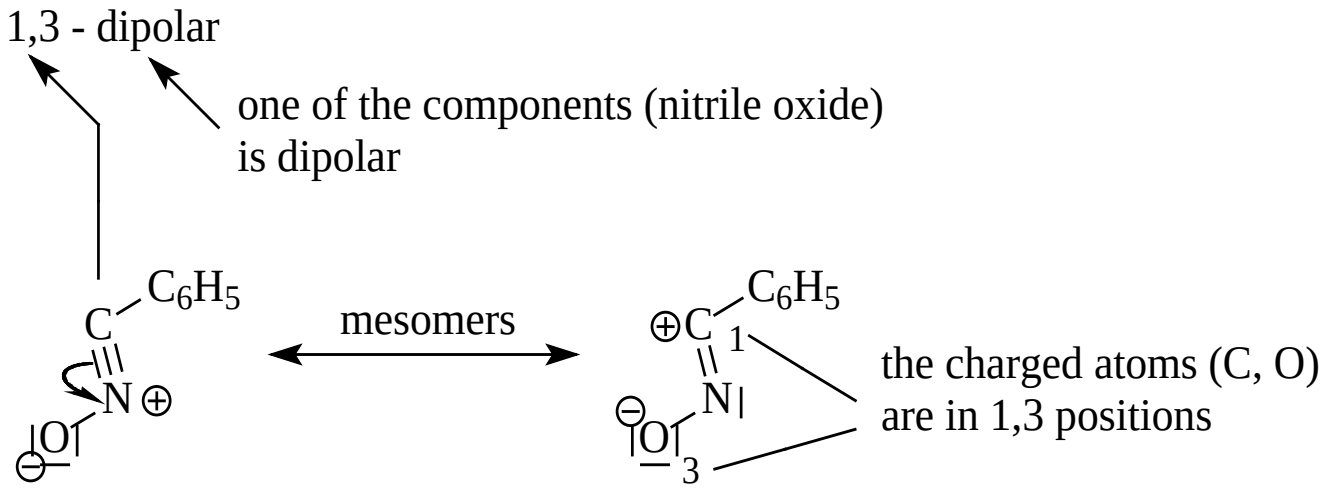
Preparations

1/ By 1,3-dipolar cycloaddition (**Huisgen**)

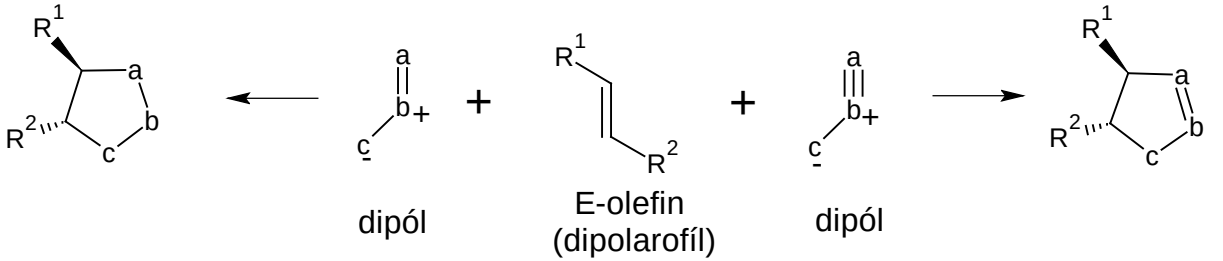


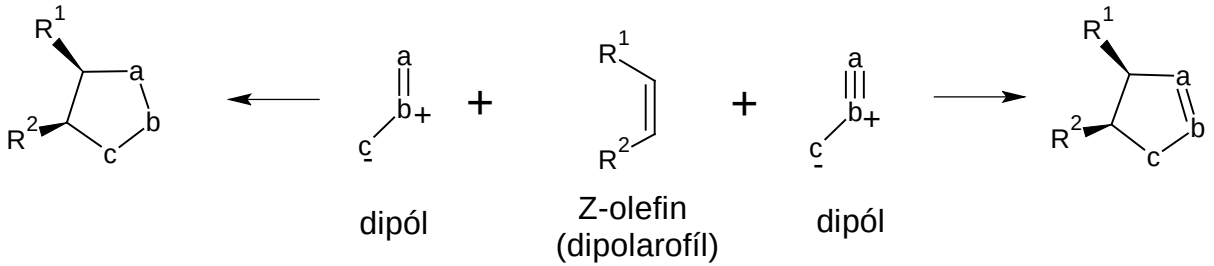
nitrile oxide

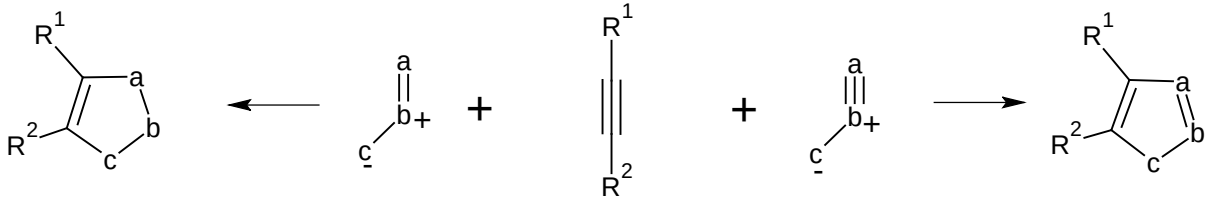
It takes place by 4n+2 electrons, n=1
→suprafacial reaction, 1,3-dipolar cycloaddition, in one step through a cyclic transition state

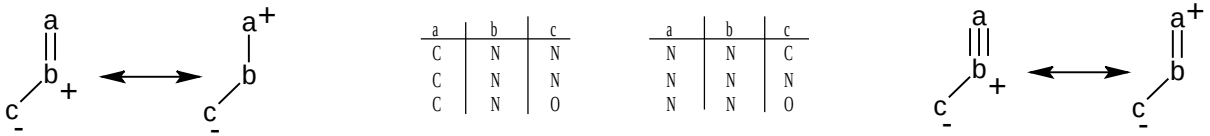


By 1,3-dipolar cycloaddition









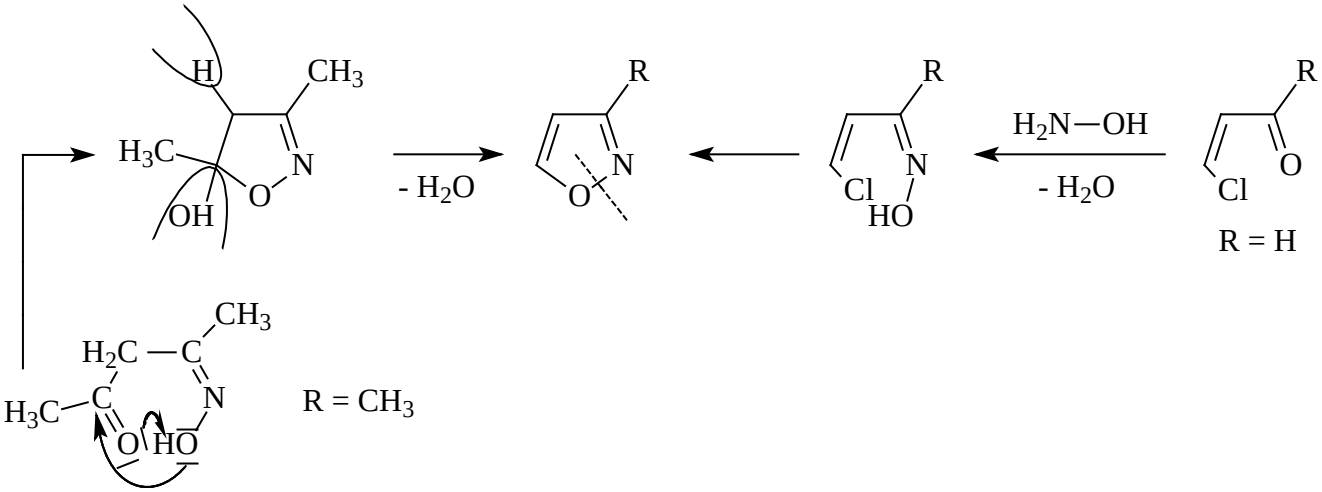
a	b	c
C	N	N
C	N	N
C	N	O

a	b	c
N	N	C
N	N	N
N	N	O

R. Huisgen, *Angew. Chem.* **75** (1963) 604-637. 742-754.

A. Padwa, *1,3-Dipolar Cycloaddition Chemistry*. Vol. 1-2. John Wiley and Sons 1984.

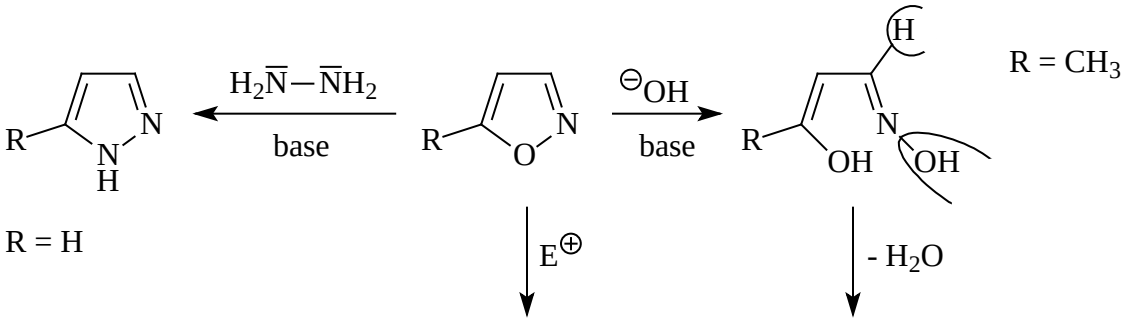
2/ By other ring syntheses



Chemical properties

1/ It is sensitive to bases, resulting in ring opening

It is relatively stable against acids

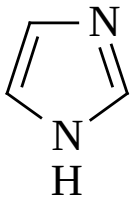


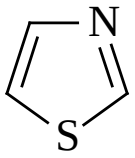
2/ S_EAr reactions

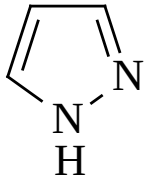
E: Br^+, NO_2^+, HSO_3^+

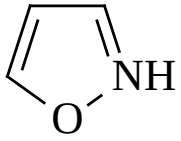
3/ Basic strength in aqueous solution

pK_a values for the conjugated acids of the bases



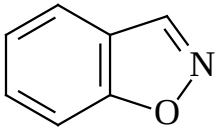




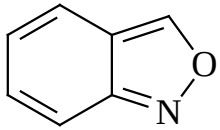


pK_a values	7.0	2.5	2.5	1.3
basicity	Imidazole >>	Thiazole $\underline{\geq}$	Pyrazole >	Isoxazole

More important derivatives

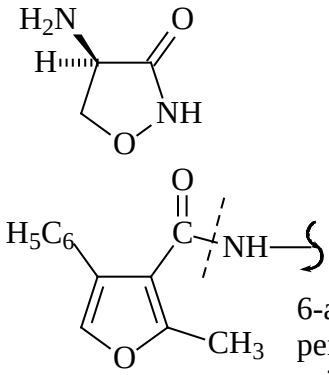


benzisoxazole
benzo[*d*]isoxazole

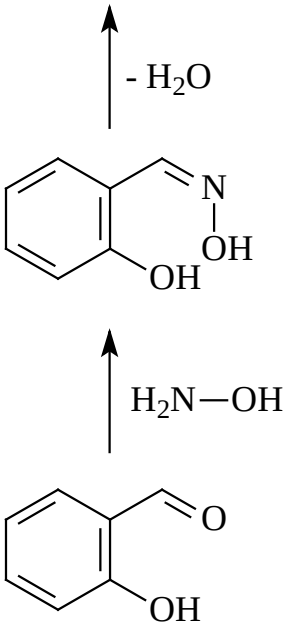


anthranil
benzo[*c*]isoxazole

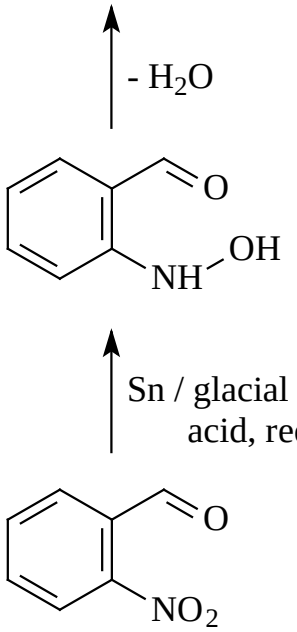
Oxamycin antibiotic
Oxacillin semisynthetic penicillin



6-amino-penicillanic acid fragment



salicylaldehyde

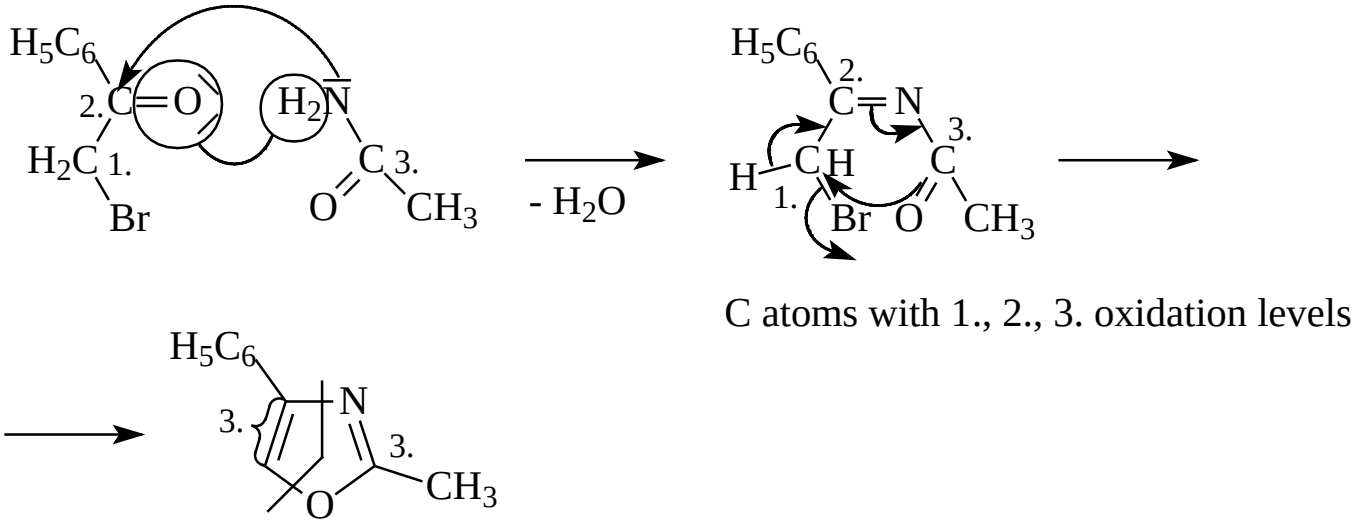


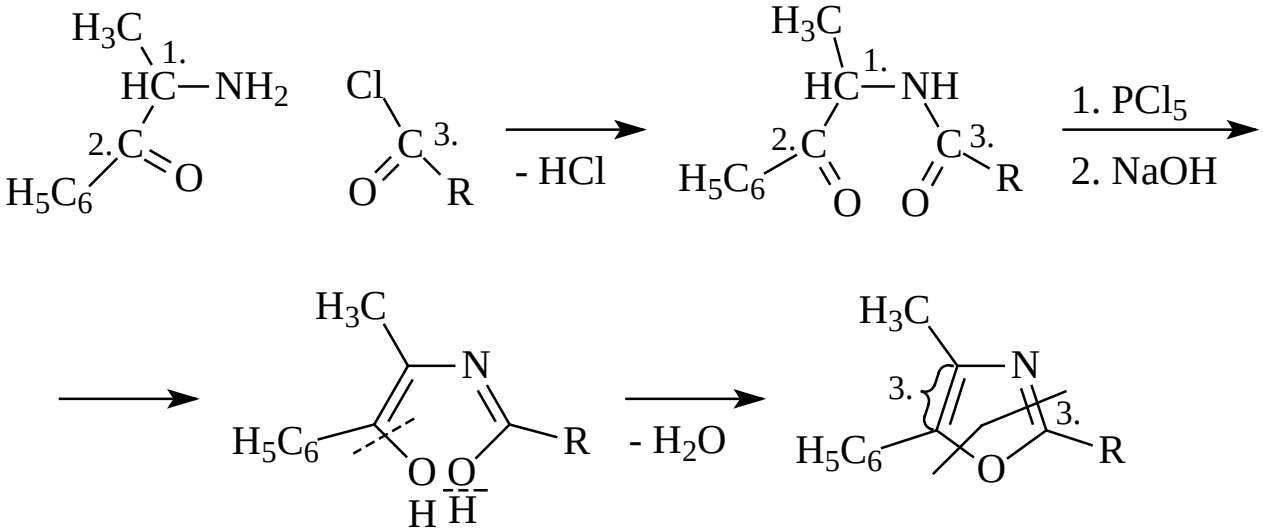
Penicillin: was prepared from *Penicillium notatum* fungus (Fleming, 1929) at first by fermentation method. It was the first antibiotic compound: 6-amino-penicillanic acid. Some microorganisms are preparing it by cleavage of the acyl group. This is useful for preparation of other semisynthetic derivatives

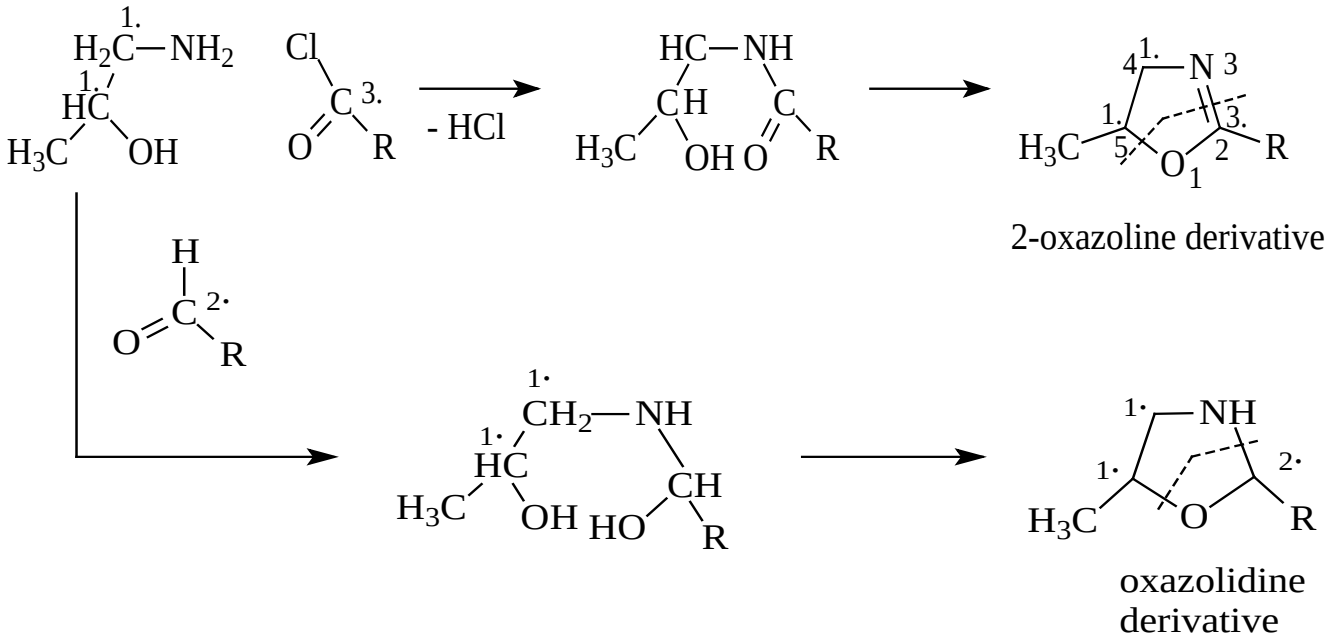
II/ Oxazole and its derivatives

Preparations

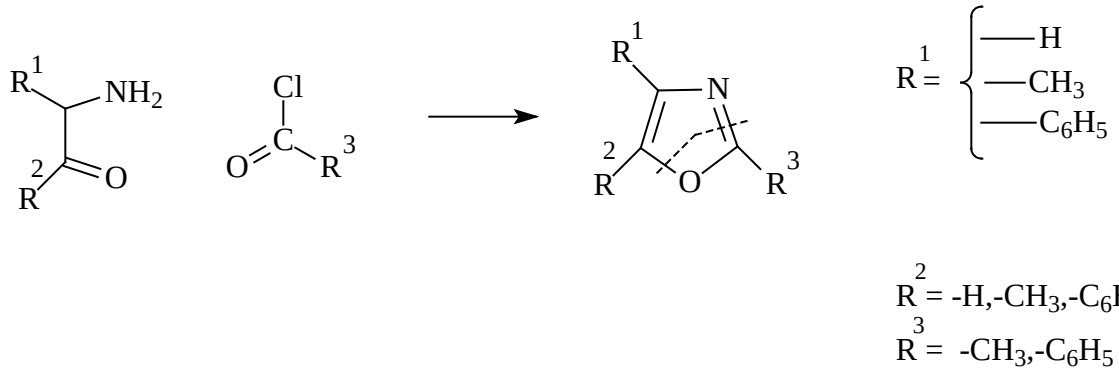
1/ From 1,2-bifunctional compounds

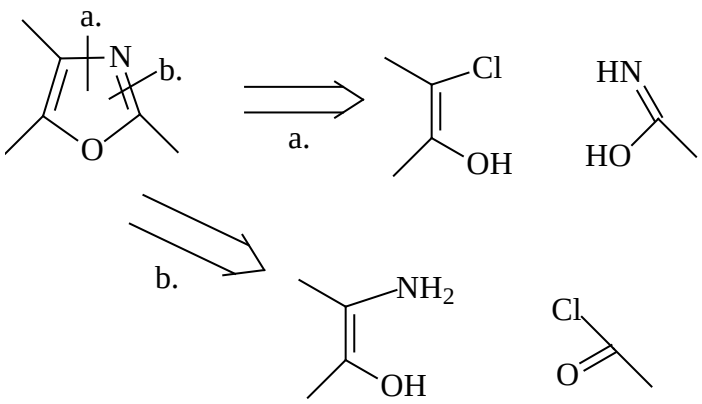


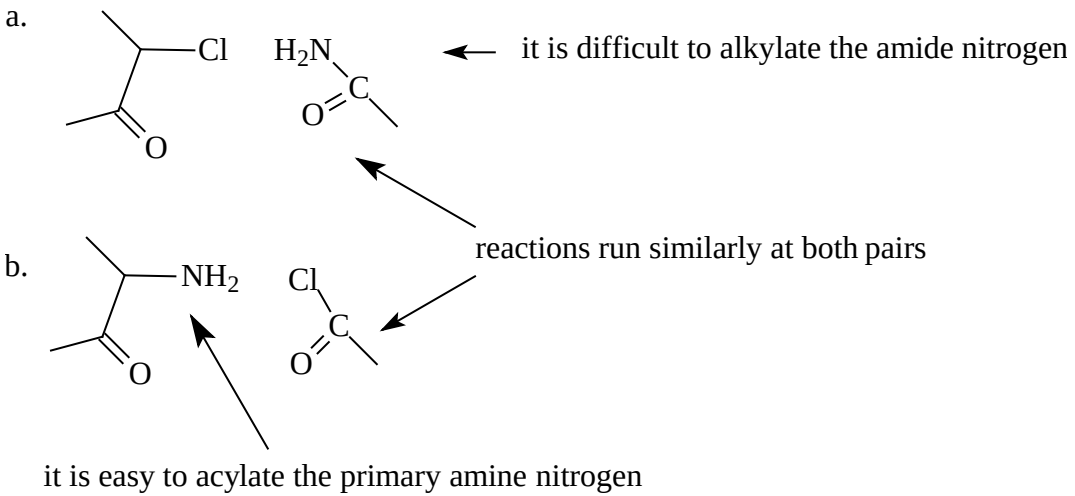




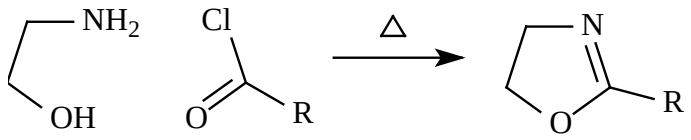
More generally:

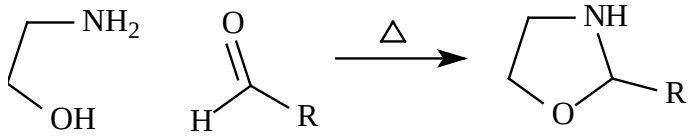


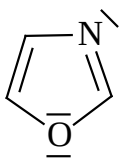




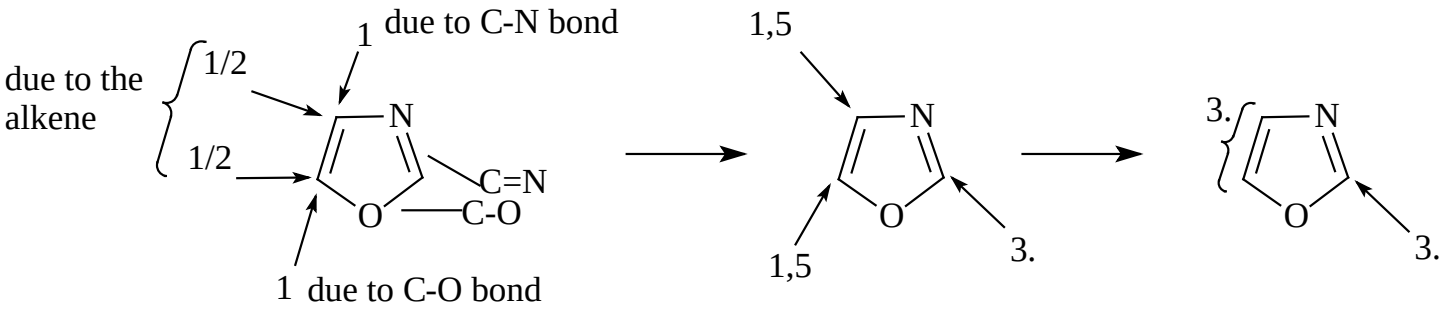
Differences in saturation of the products can be reached by selection of the proper oxidation level of the starting materials.

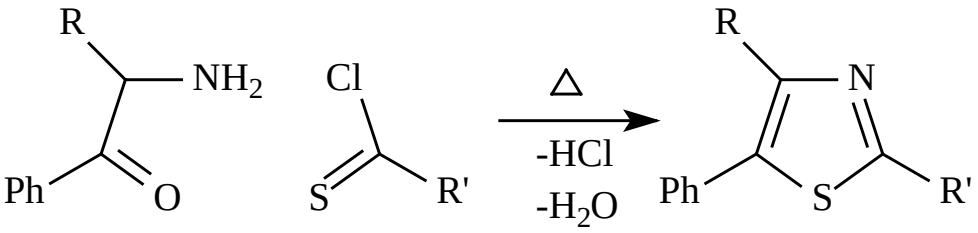




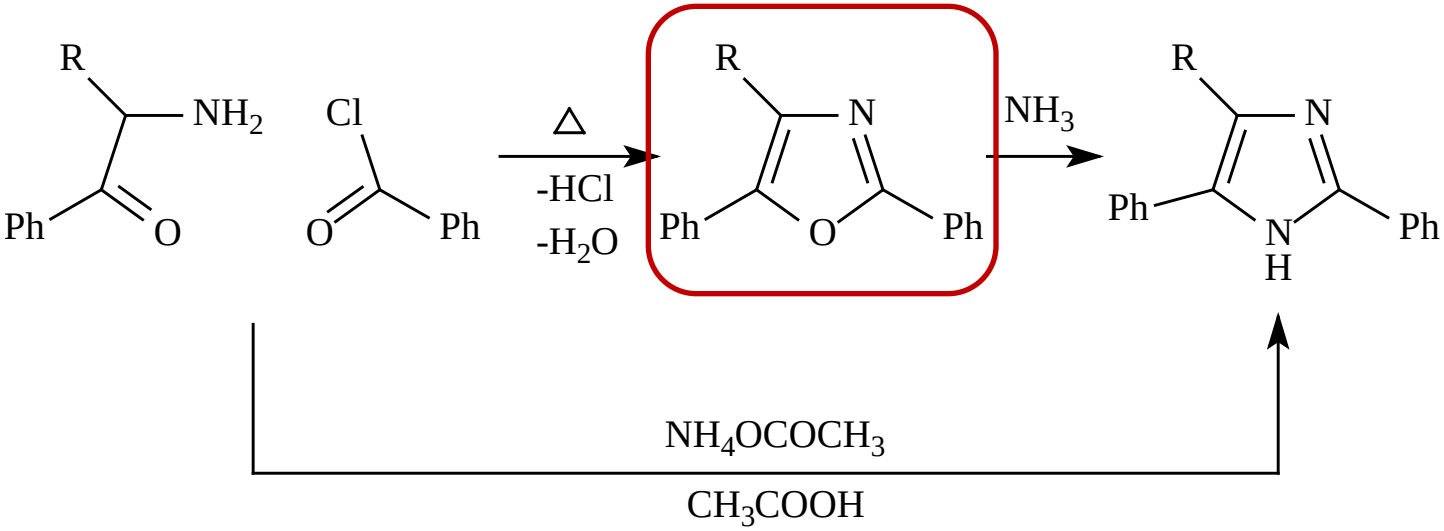


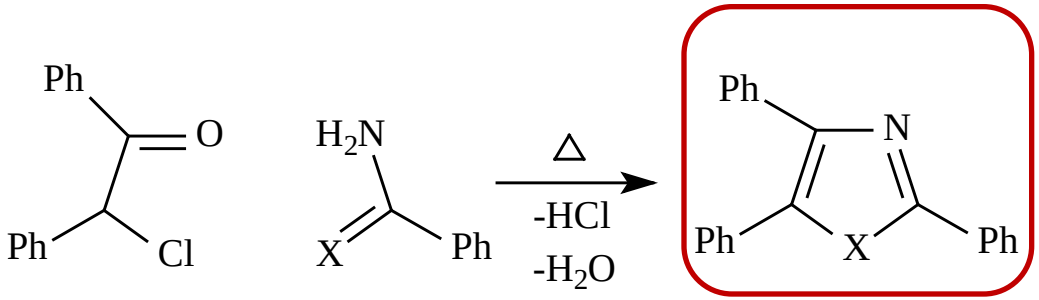
6 π-electrons
the nonbonding electron pair of *O*
takes part in the formation of an aromatic sextet





R': Alkyl, NH_2

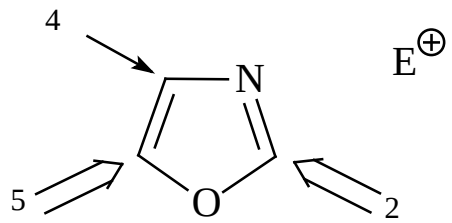




X: O, S, NH

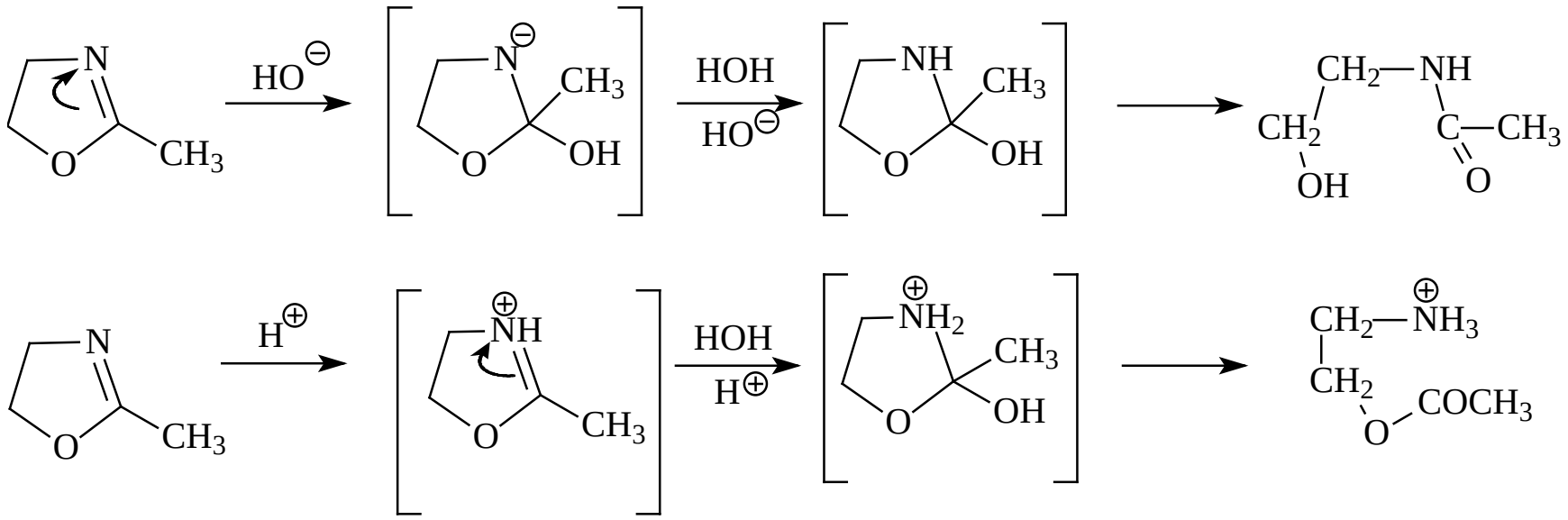
Chemical properties

1/ S_EAr reactions

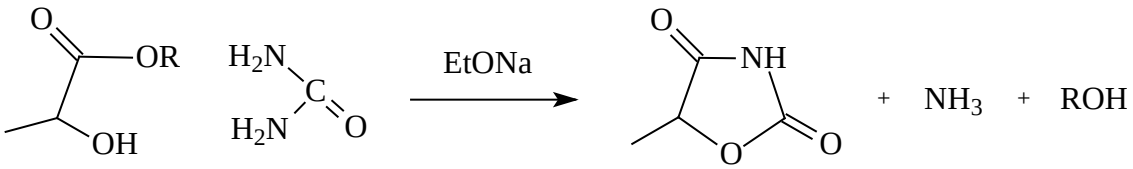


One of the most stable derivatives of 2-oxazoline is 2-methyloxazoline. This compound has an interesting feature, since mechanism of acyl migration (Bruckner, at ephedrine or alkaloids with tropane skeletone), as well as the ring opening due to bases or acids can be easily demonstrated.

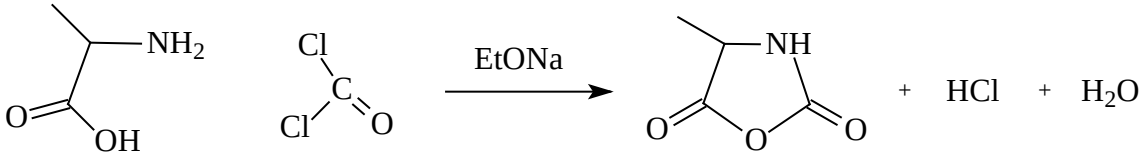
2/ Sensitivity against bases and acids



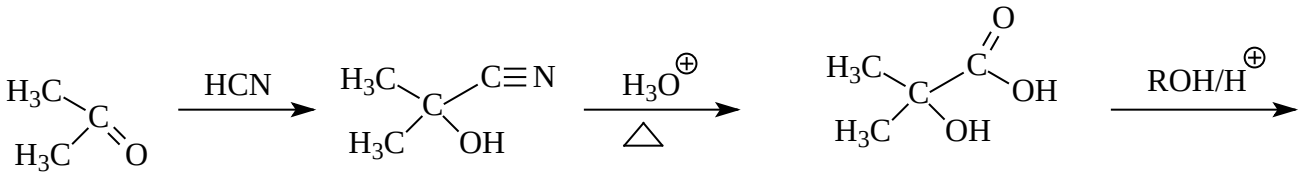
More important derivatives



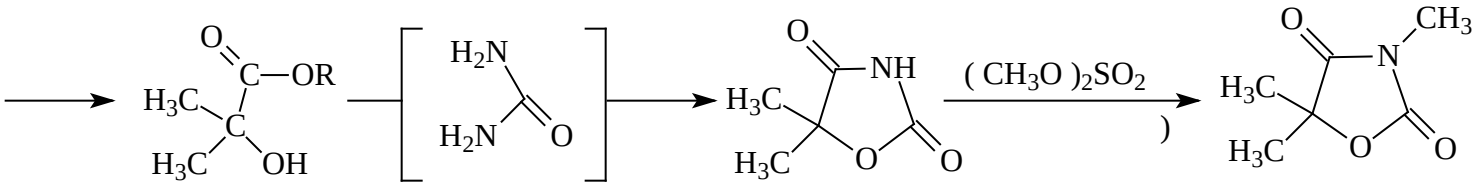
2,4-oxazolidindione



2,5-oxazolidindione

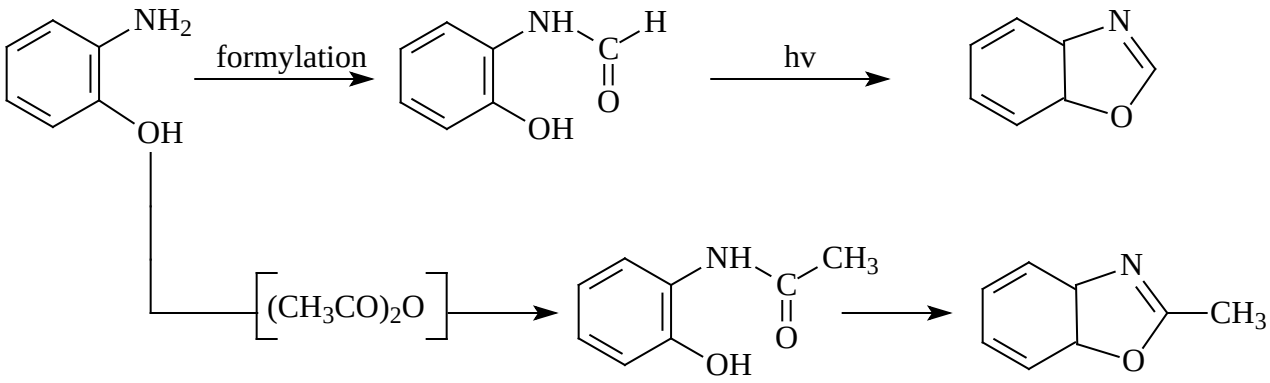


aceton-cyanhidrine



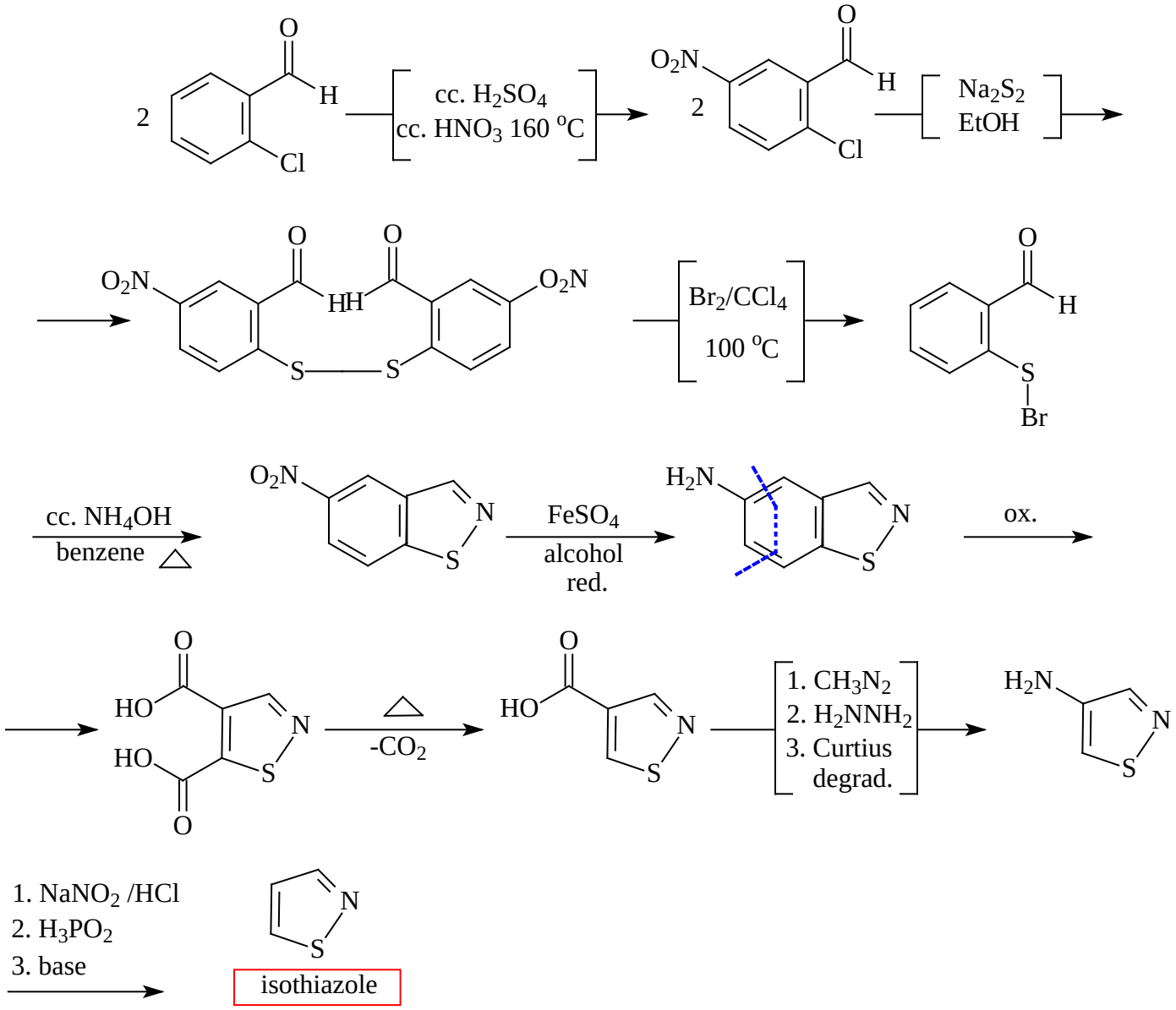
Ptimal

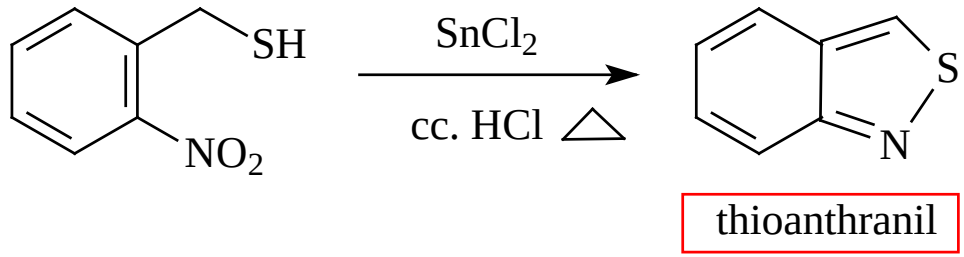
Drug of the ‚petit mal' form of epilepsy



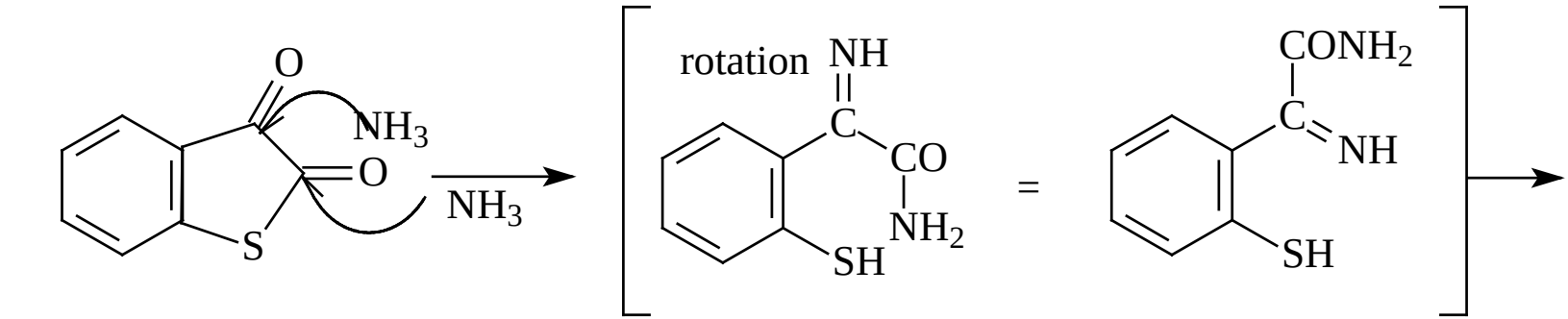
blocks maturation of rye mould

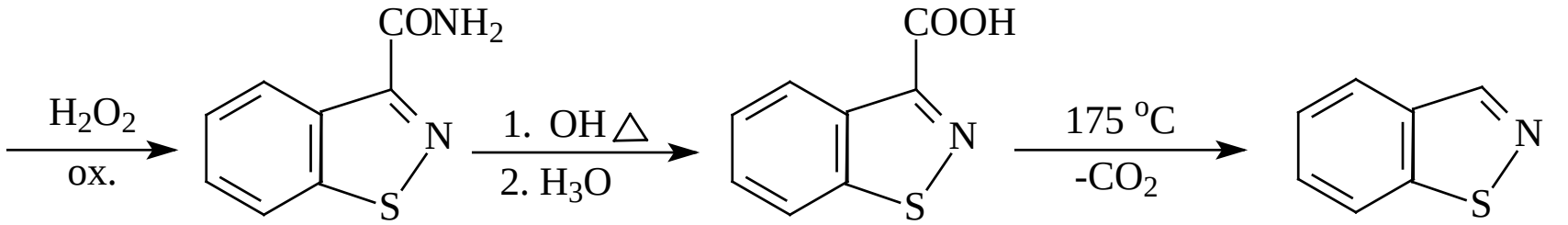
III/ Isothiazole and its derivatives





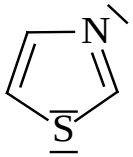
thioanthranil





benzisothiazole

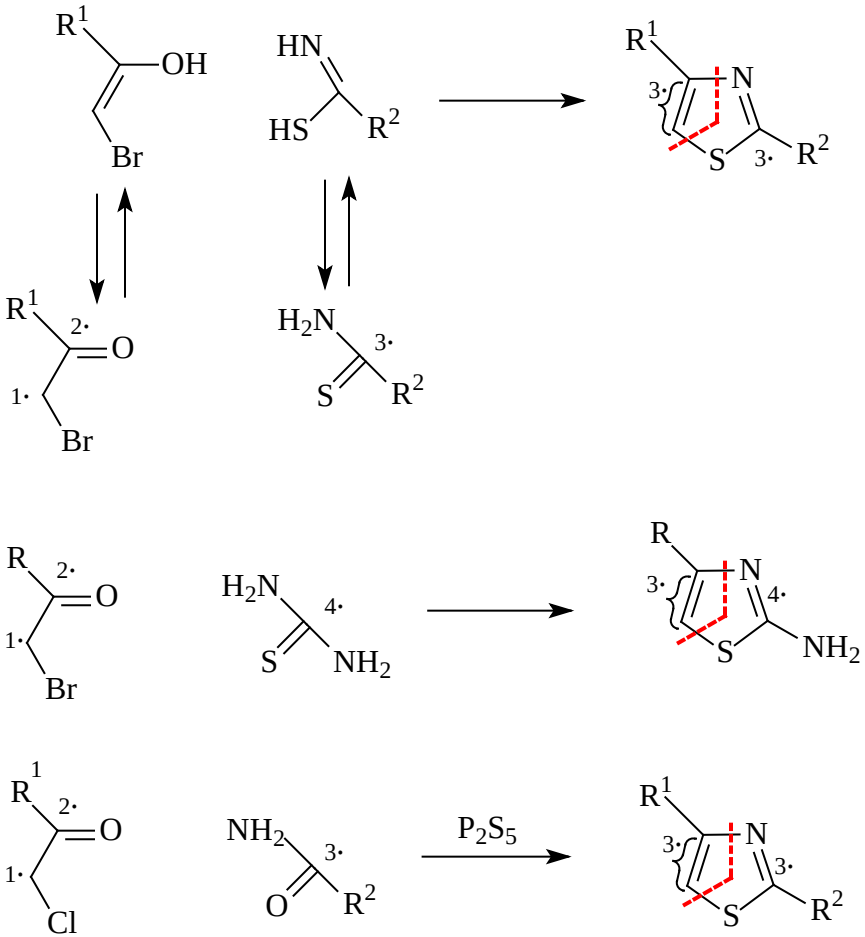
IV/ Thiazole and its derivatives



6 π electrons

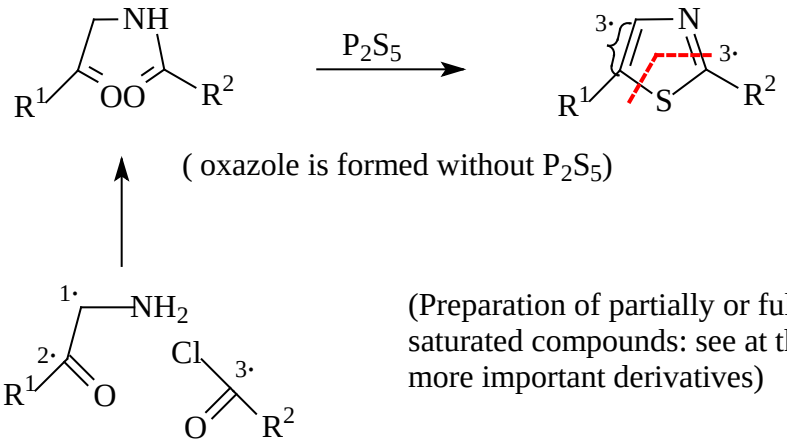
(similar to oxazole)

1/ Hantzsch synthesis



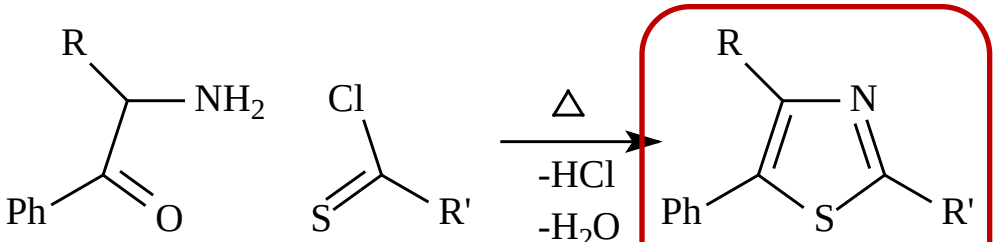
(oxazole is formed without P_2S_5)

2/ Gabriel's preparation

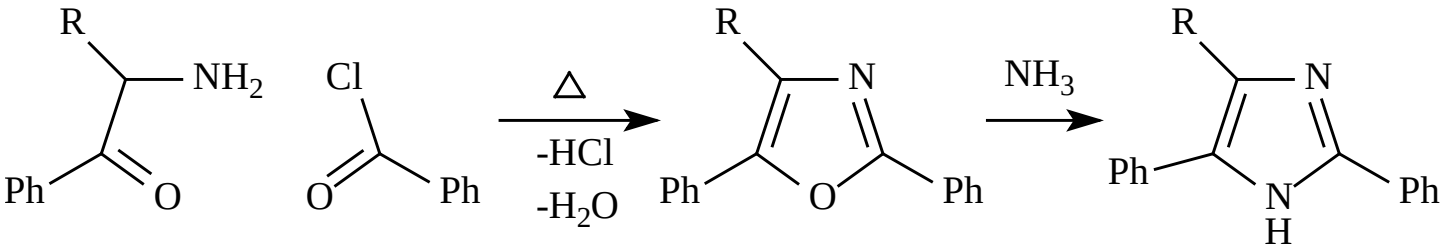


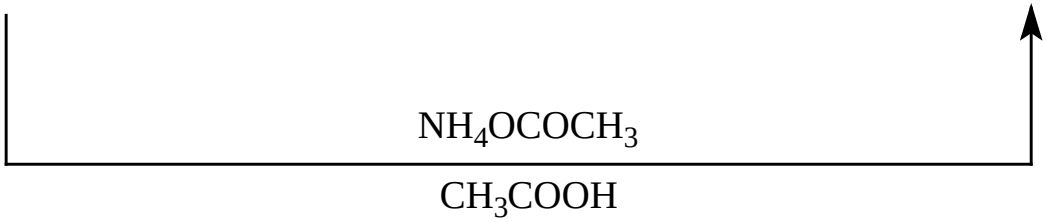
(oxazole is formed without P_2S_5)

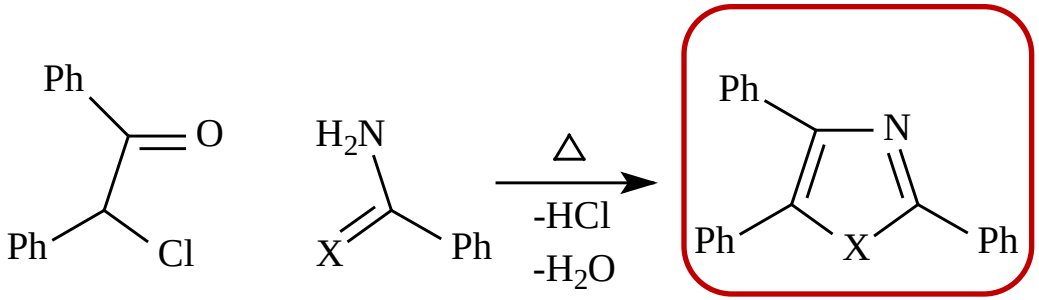
(Preparation of partially or fully saturated compounds: see at the more important derivatives)



R': Alkyl, NH_2



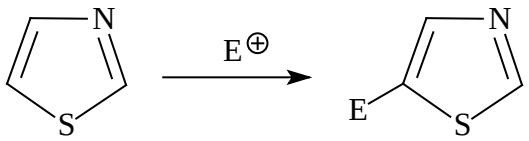


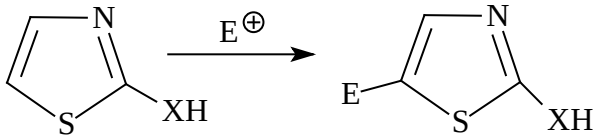


X: O, S, NH

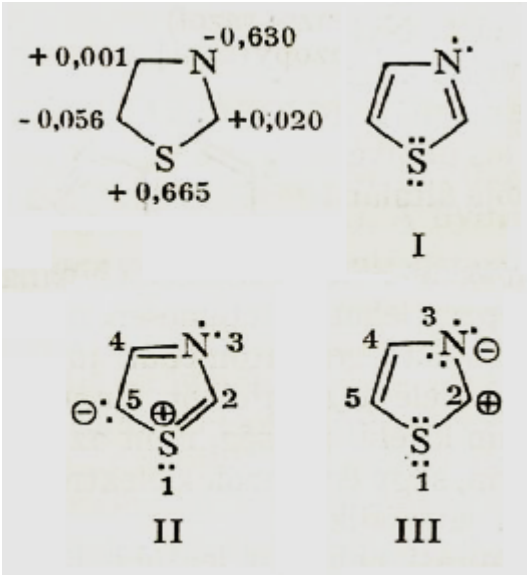
Chemical properties

1/ S_EAr reactions

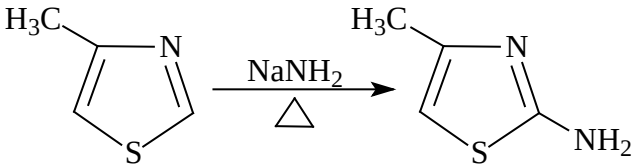




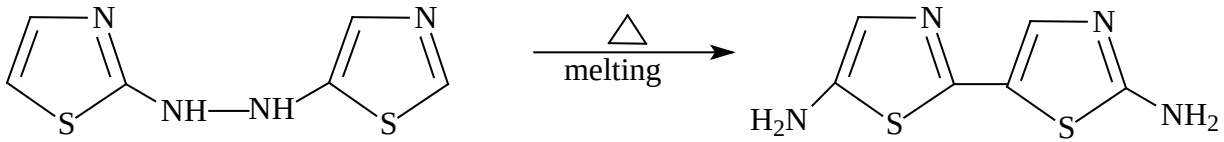
X=O, NH

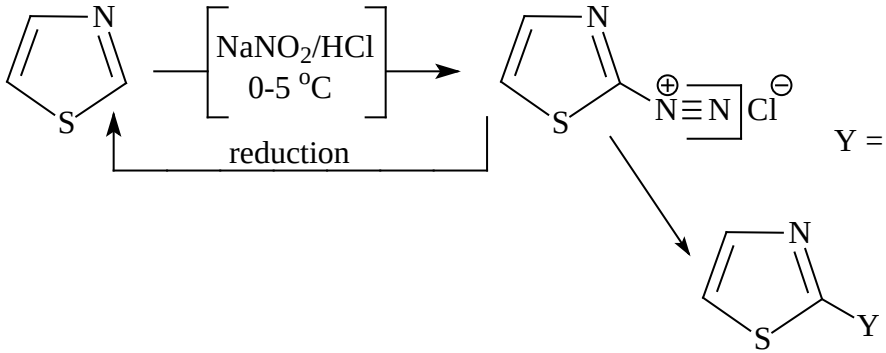


2/ S_NAr reactions



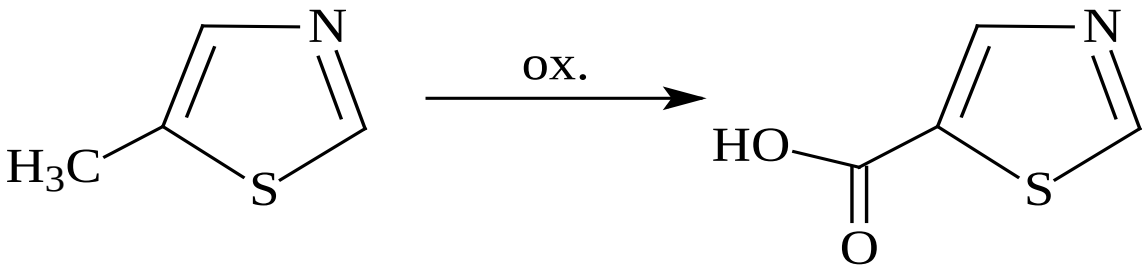
pyridine-like property





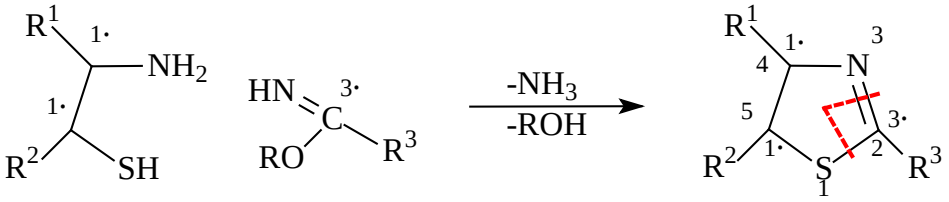
Y = halogene, hydroxy, etc.
(see reactions of (aromatic) diazonium compounds)

3/ By oxidation

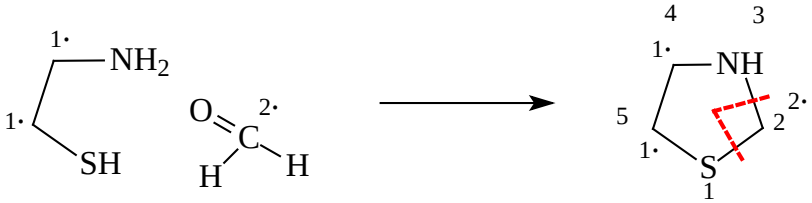


thiazole ring is resistant to oxidation

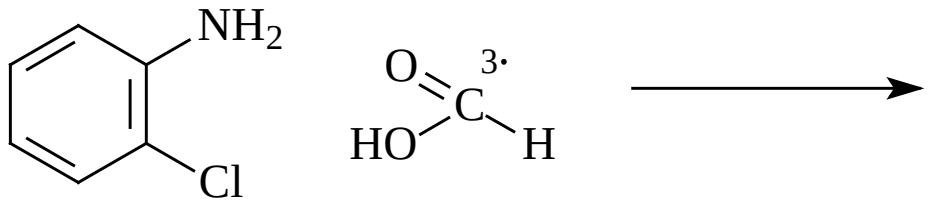
More important derivatives



2-thiazoline derivative

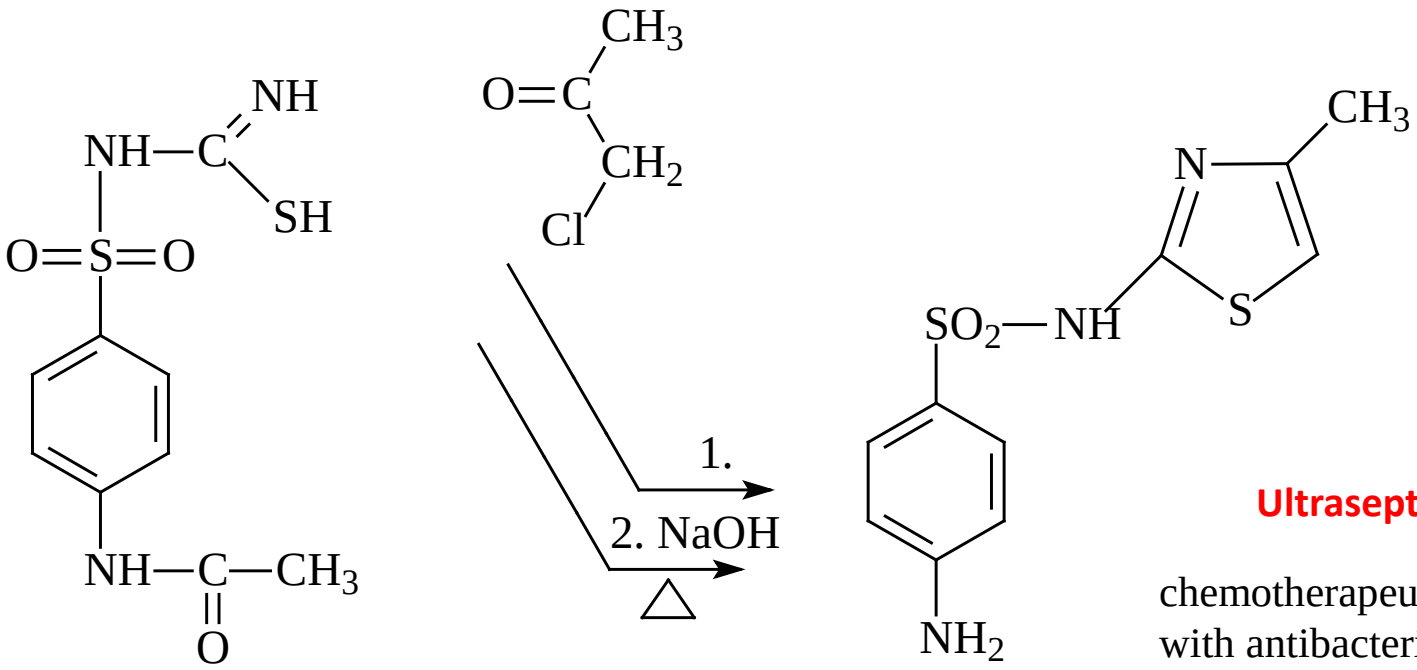


thiazolidine



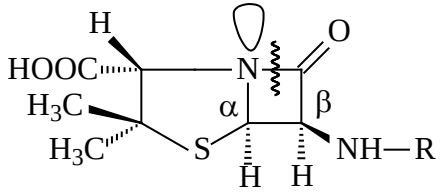
benzo[*d*]thiazole

benzo[*d*][1,3]thiazole



Ultraseptyl

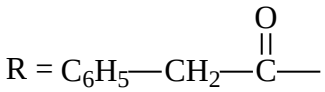
chemotherapeutic agent
with antibacterial effect



penam skeletone

(condensed ring system of thiazolidine and azetidine monocycles)

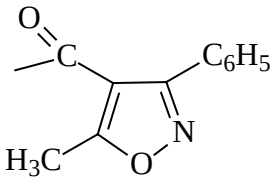
R = H **6-aminopenicillanic acid** (6-APA)



benzylpenicillin

Penicillin G

R =



Oxacillin (see at isothiazoles)

B lactam ring is unstable group, sensitive to acids, to bases, as well as to penicillinase enzyme. They are inhibitors of synthesis of cell walls. If a microorganism produces penicillinase, then it will be resistant to the given penicillin derivative ⟶ other derivative must be prepared. Previously, penicillin derivatives were prepared from ferment solution, adding phenylacetic acid to it, generating benzylpenicillin. Benzylpenicillin + enzyme ⟶ 6-APA +R-COCl ⟶ many thousands penicillin derivatives.

Source: Penicillium notatum, P. crysogenum bacteria. Antibiotics are more uniform compounds, than vitamins.

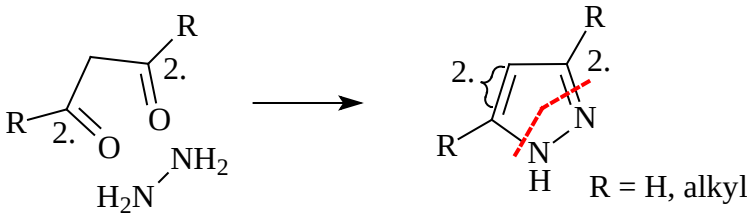
Antibiotics are natural compounds, produced by some microorganisms against other microorganisms, blocking the latter. Fleming observed extinction spots, thus he had hard earned the Nobel Prize.

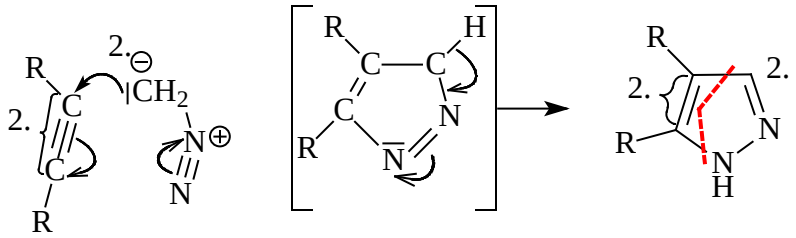
Currently penicillin derivatives are prepared by semisynthesis methods: 6-APA is made to be produced by bacteria. This was one of the first trials of biotechnology.

V/ Pyrazole and its derivatives

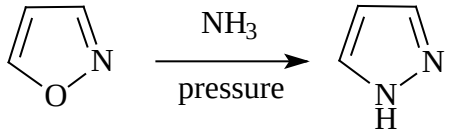
Preparations

1/ By 1,3-dipolar cycloaddition (**Huisgen**)





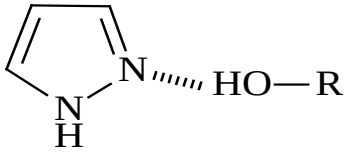
2/ By isosteric replacement from isoxazole



Chemical properties

1/ Acid-base properties

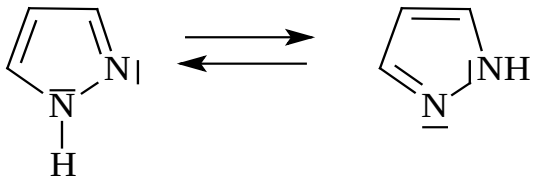
Introduction of a nitrogene shifts the pyrrole-like properties to the pyridine-like properties.



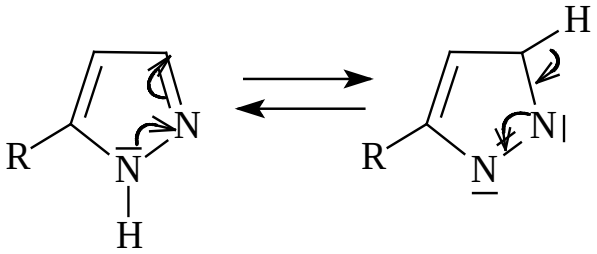
makes a H-bridge

weak base $pK_a = 2.5$
(pyrrole< pyrazole< imidazole< pyridine)
very weak acid $pK_a = 14$
(it is amphotheric compound)

2/ Tautomerism

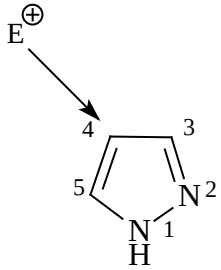


virtual tautomerism
(equivalent tautomerism)
the two tautomers can not be distinguished from each other

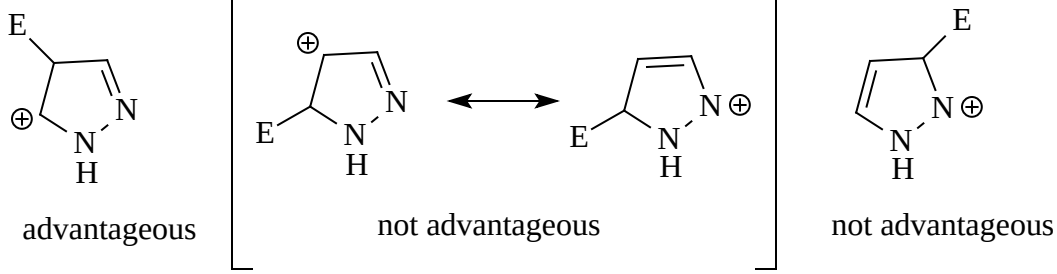


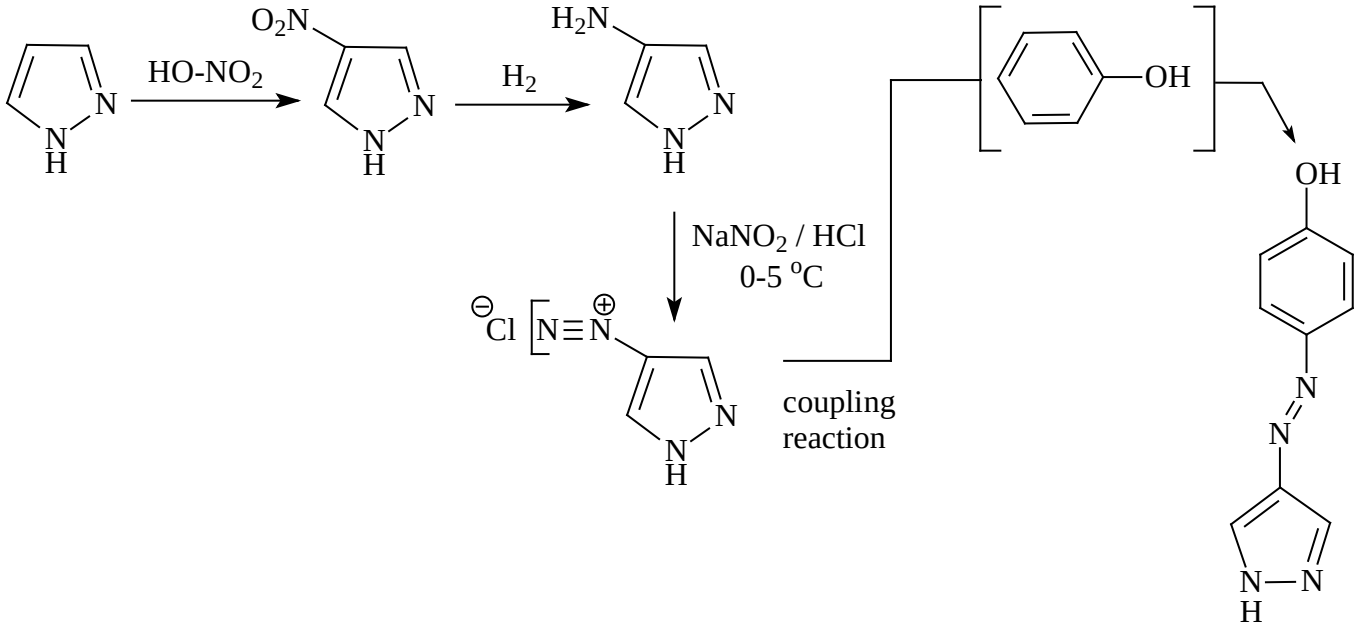
real tautomerism - if a R group (alkyl group) is attached to the ring, the tautomer is fixed. The indicated H is migrating - it can be marked by isotope or substituent

3/ S_EAr reactions

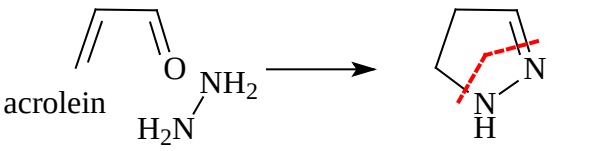


substitution on the C-4:
bromination, nitration, sulfonation

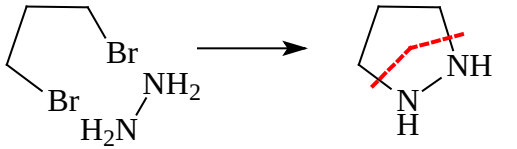




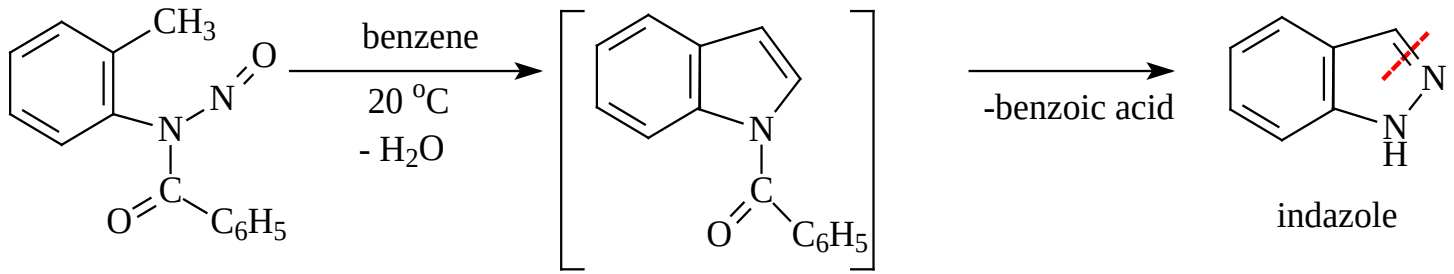
More important derivatives



2-pyrazoline

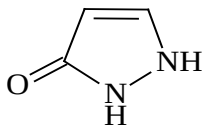


pyrazolidine

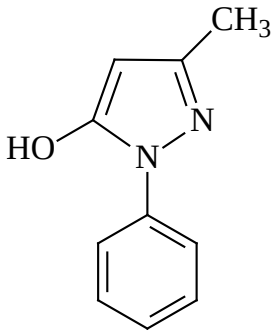


indazole

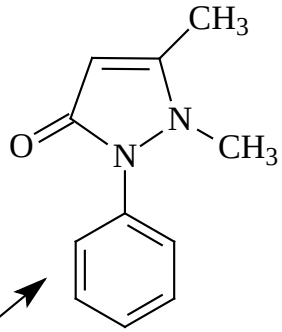
N-benzoyl-*N*-nitrozotoluidine



pyrazol-3-one



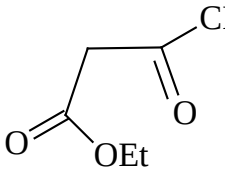
tautomerism



$(CH_3O)_2SO_2$

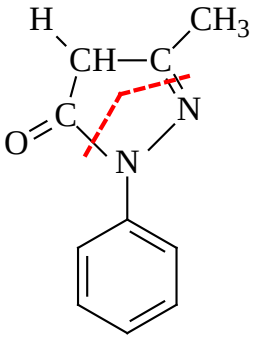
antipyrin

fever- and pain-killer compound

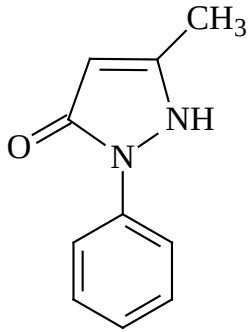


- H_2O

NaOEt

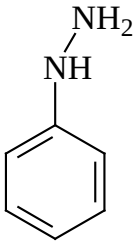


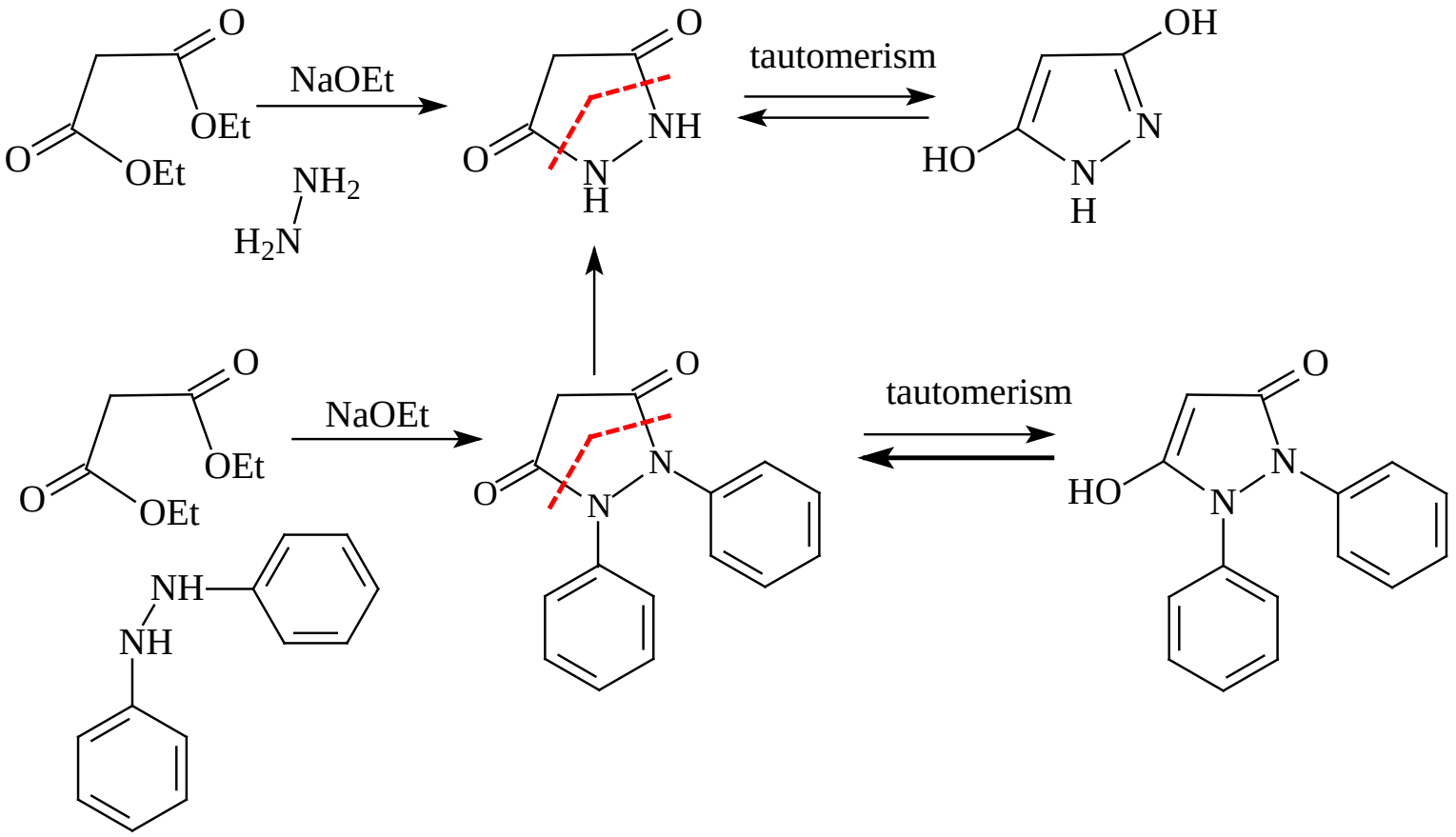
tautomerism

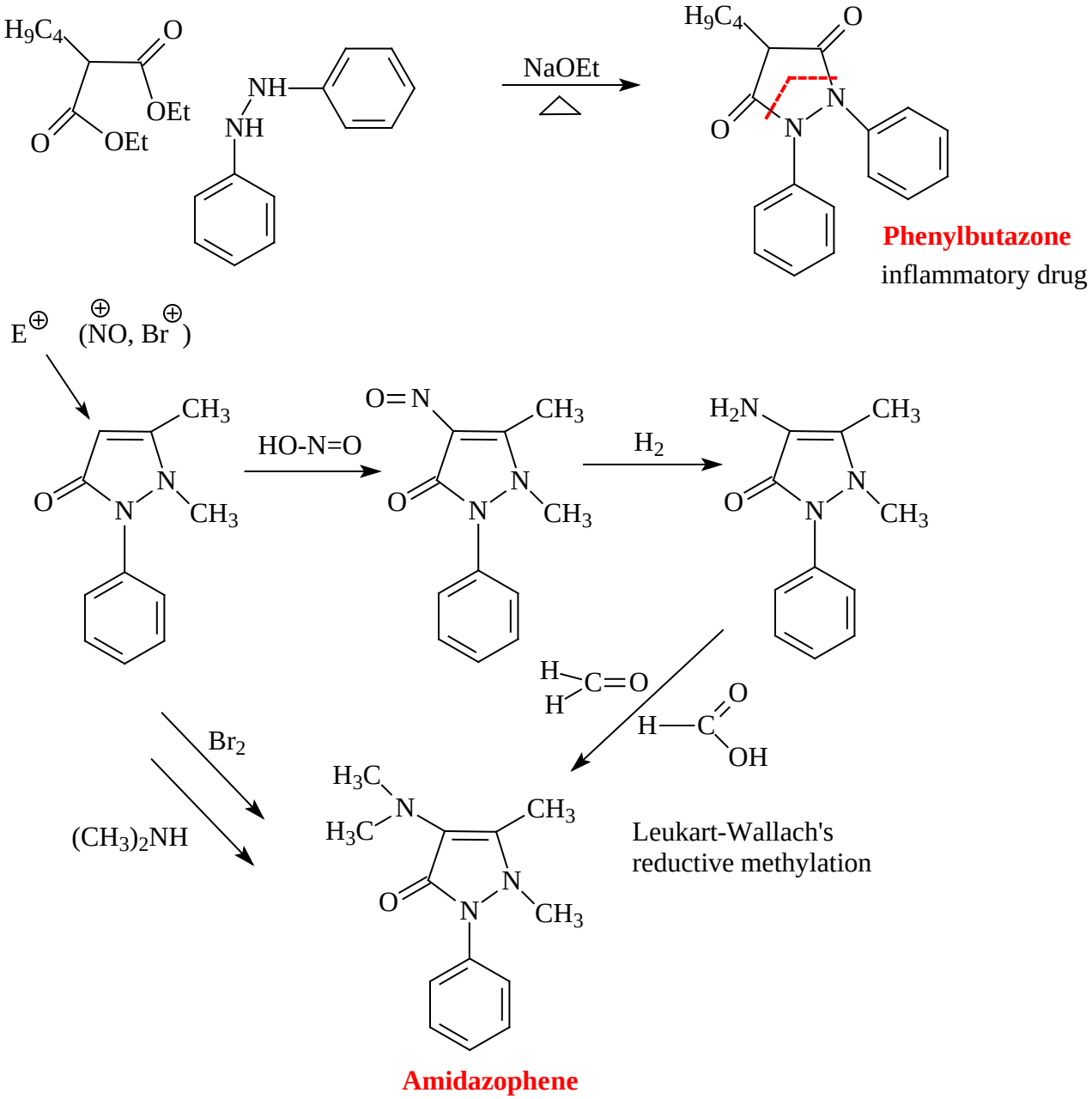


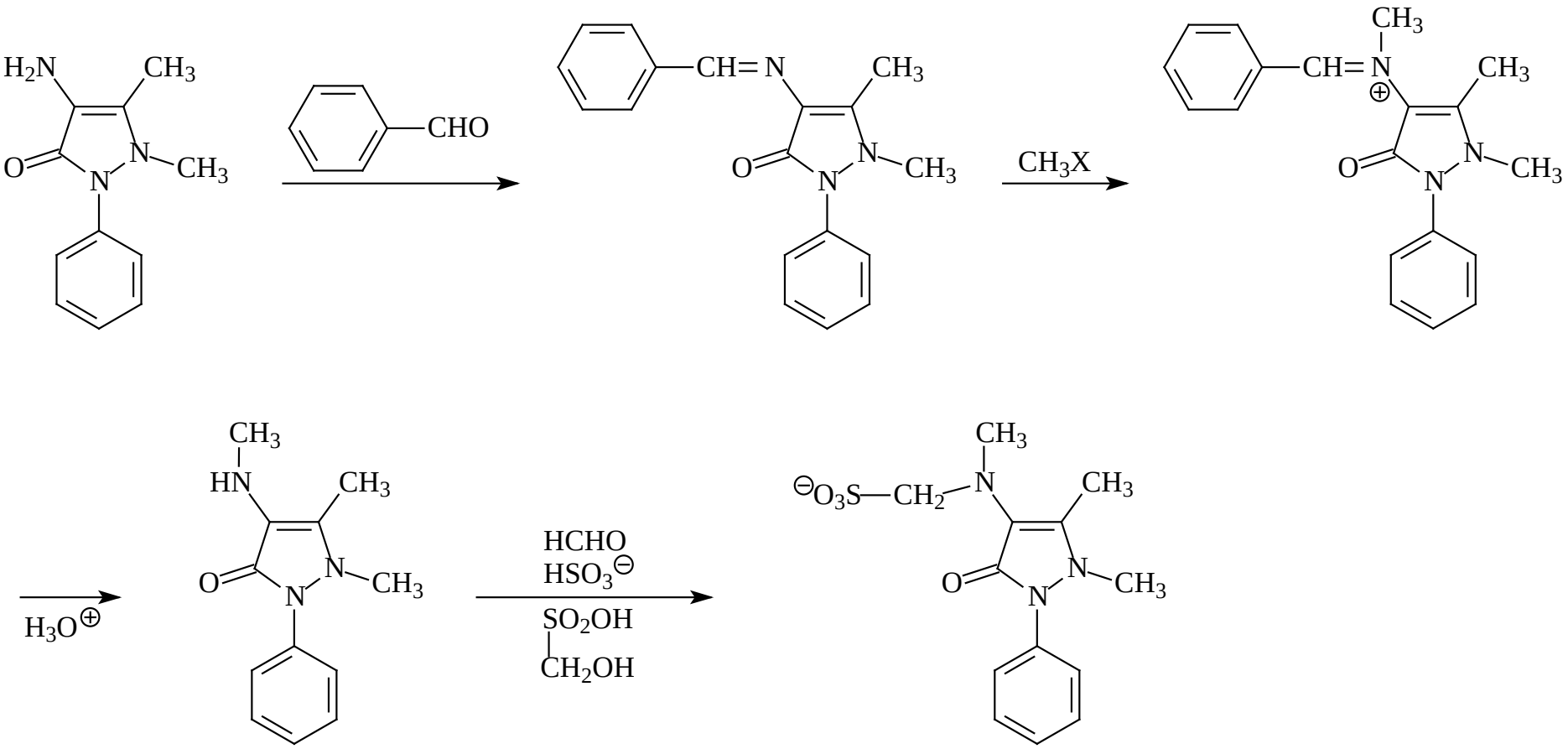
norantipyrin

- EtOH




O
OEt
O
OEt
NaOEt
NH2
H2N
O
NH
O
N
H
tautomerism
OH
N
HO
N
H
O
OEt
O
OEt
NaOEt
NH
NH
O
N
O
N
tautomerism
O
N
HO
N


NaOEt
Phenylbutazone
inflammatory drug
HO-N=O
H2
Br2
(CH3)2NH
Leukart-Wallach's
reductive methylation
Amidazophene

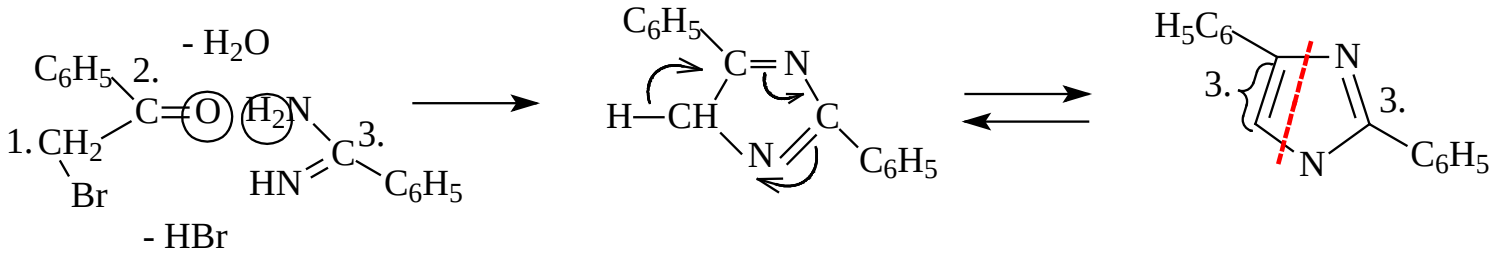


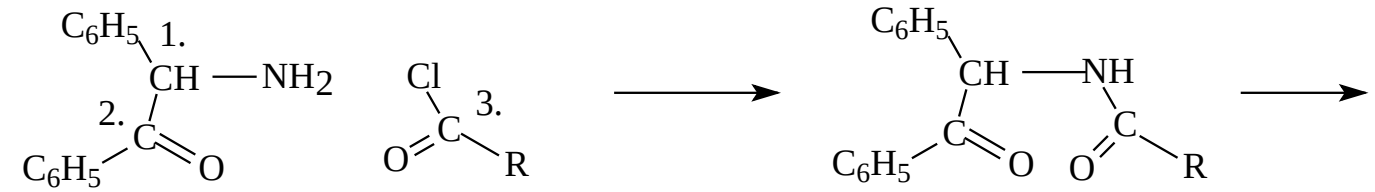
Methamisole

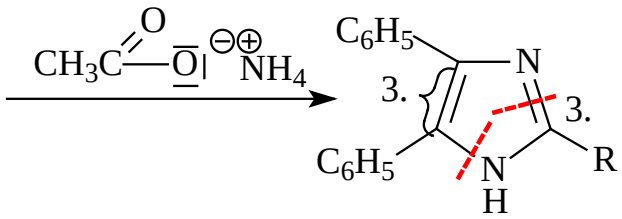
VI/ Imidazole and its derivatives

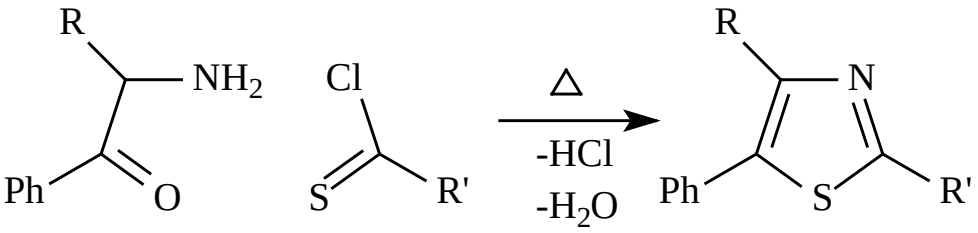
Preparations

1/ From 1,2-bifunctional compounds

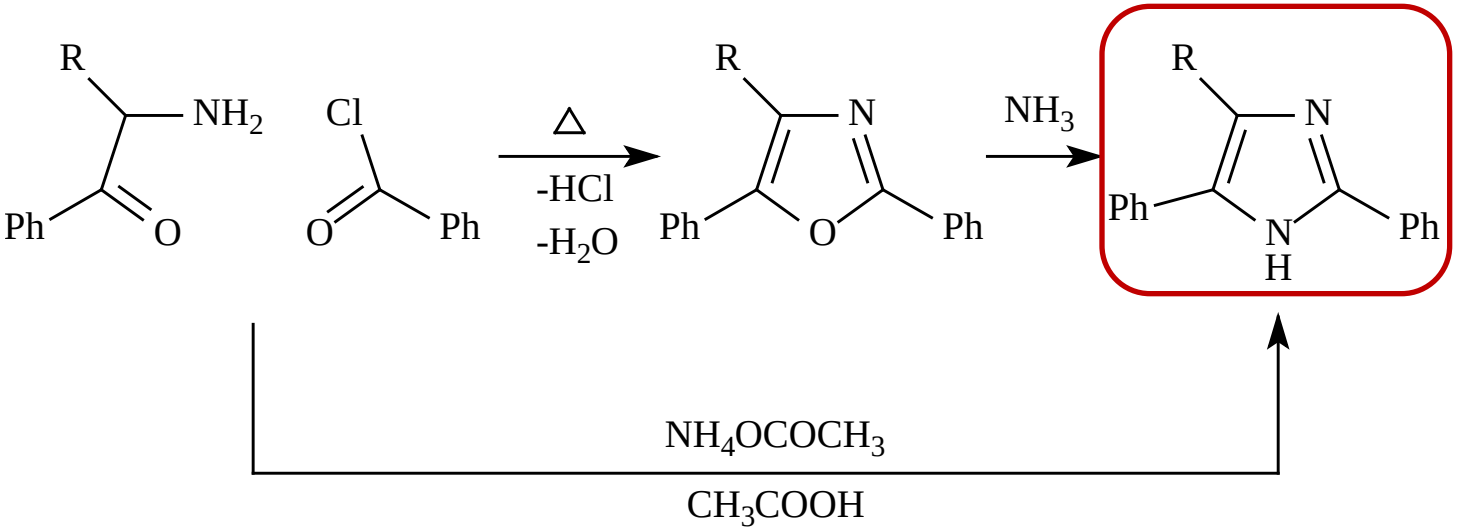


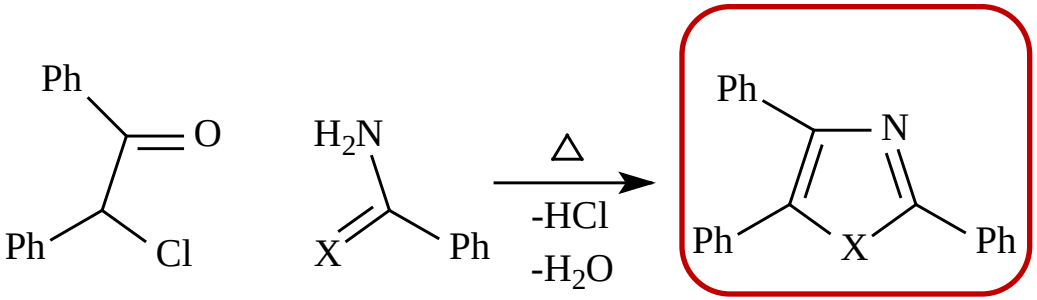




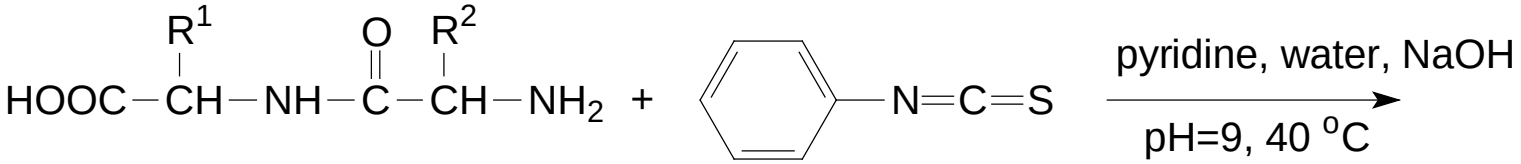


R': Alkyl, NH_2

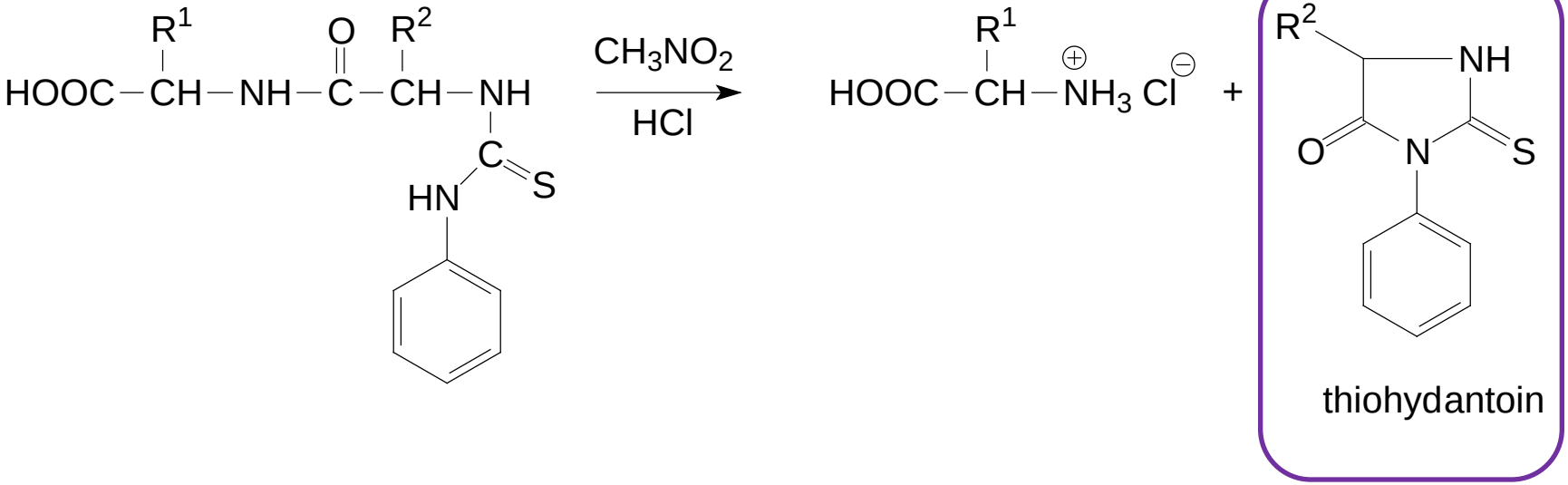




X: O, S, NH



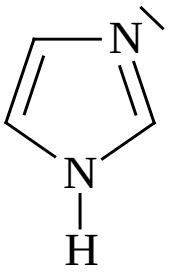
R^1, R^2: alkyl groups



Edman sequencing of peptides

Chemical properties

1/ Acid-base properties

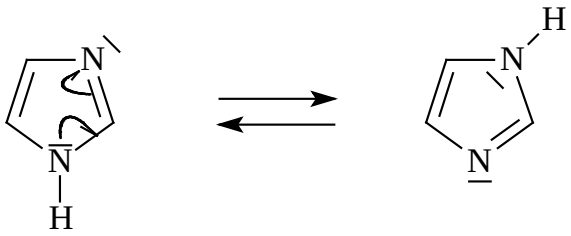


pKa 7.2

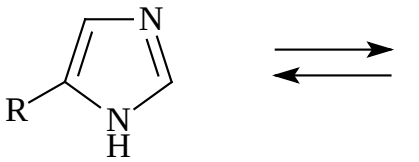
amphotheric compound

pKa 14.5

2/ Tautomerism

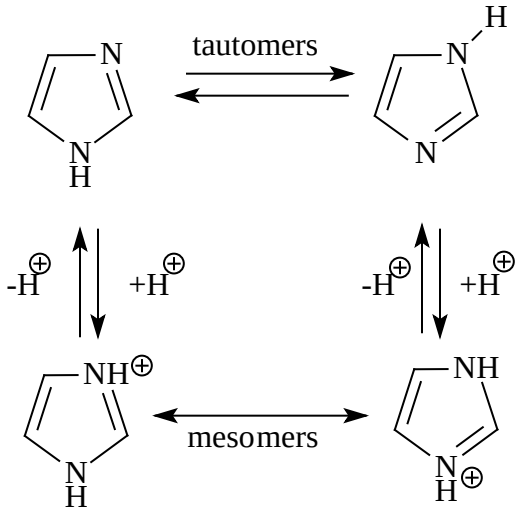


virtual tautomerism

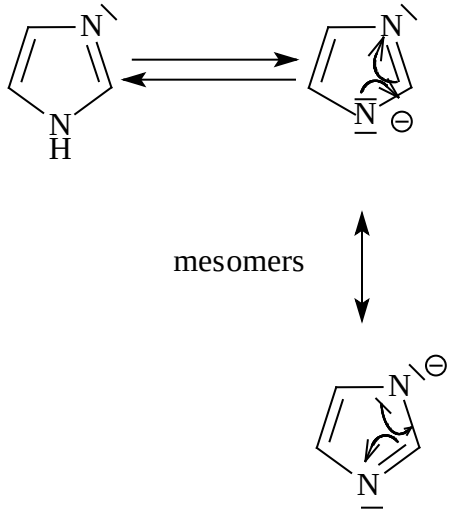


real tautomerism

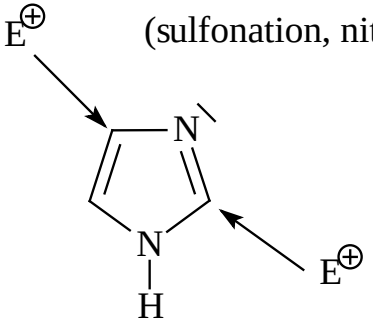
as base



as acid



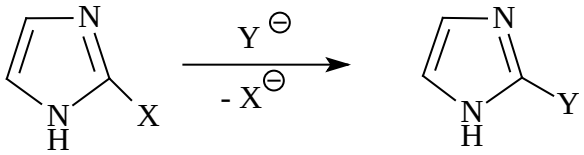
3/ By S_EAr reactions



(sulfonation, nitration, coupling with diazonium salt)

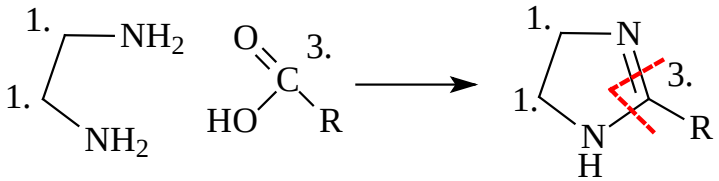
(methylation, formylation by *N*-methyl formamide derivative)

4/ By S_NAr reactions



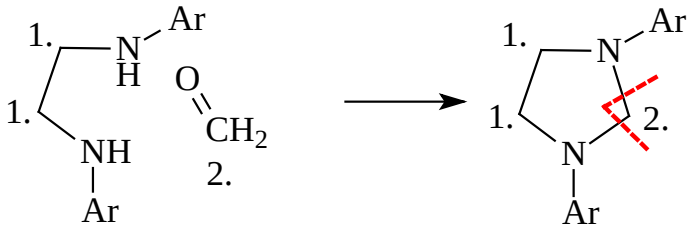
X =Cl, Br

More important derivatives

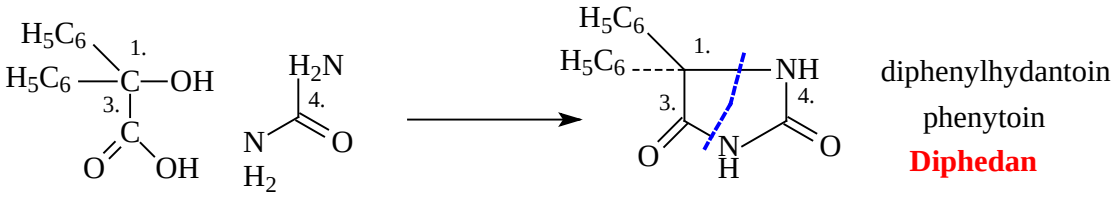


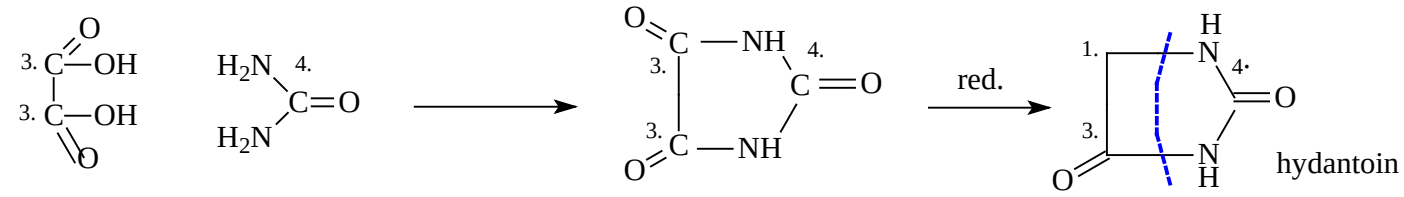
R = H, alkyl

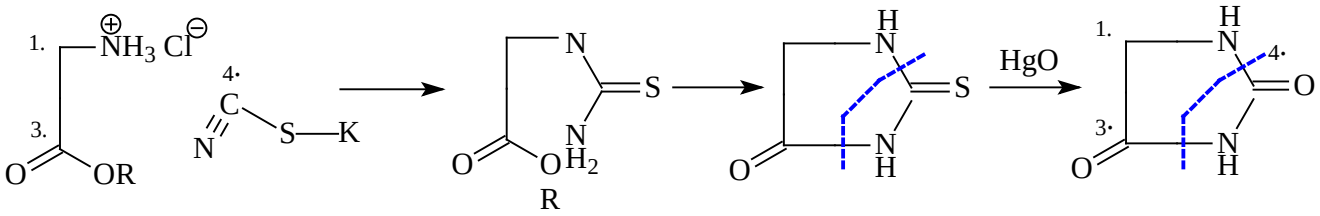
2-imidazoline derivative

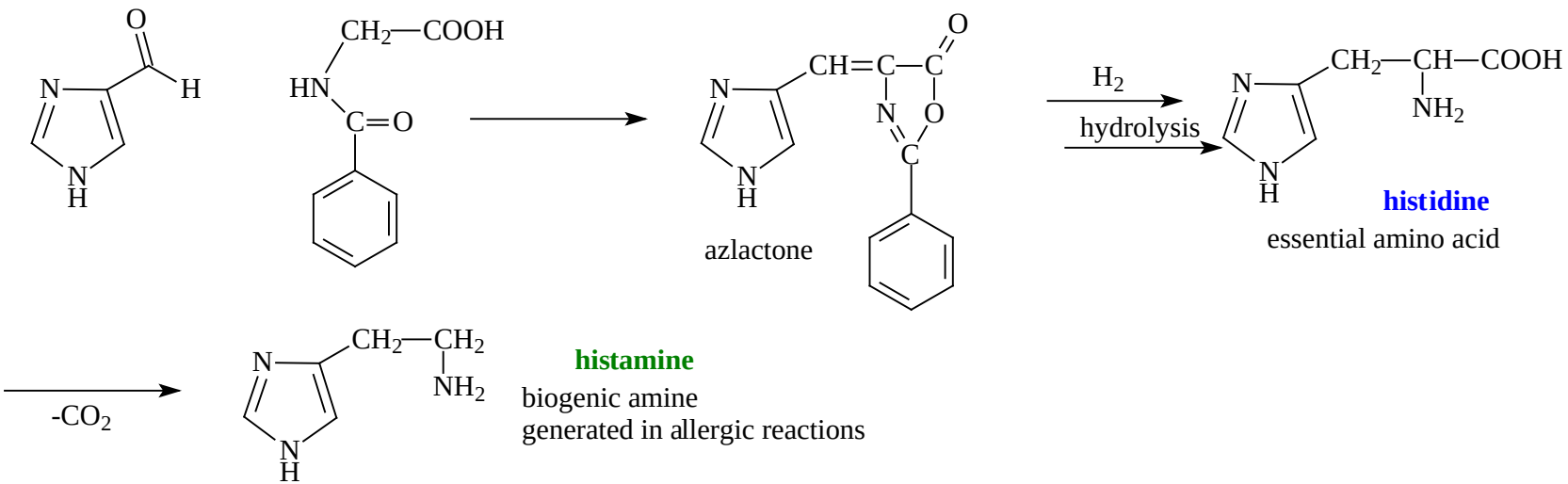


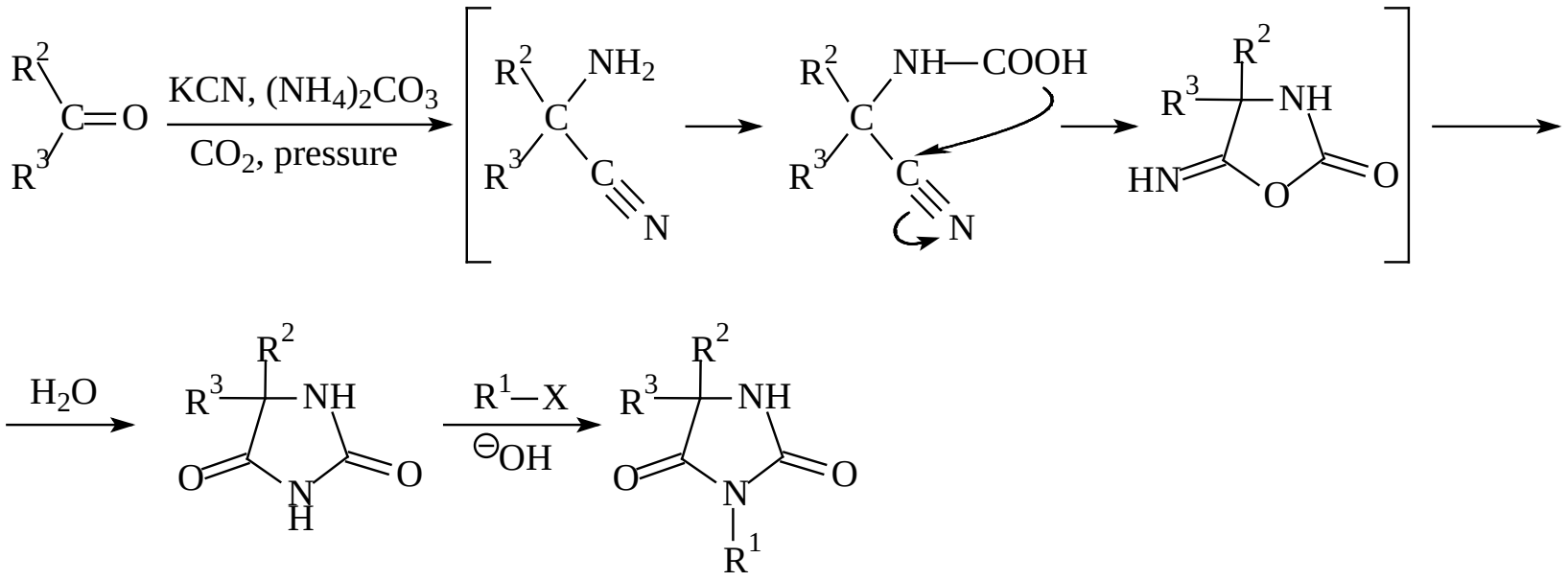
imidazolidine derivative

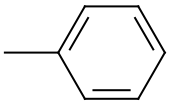
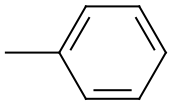
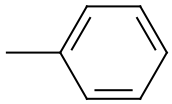

diphenylglycolic acid
diphenylhydantoin
phenytoin
Diphedan

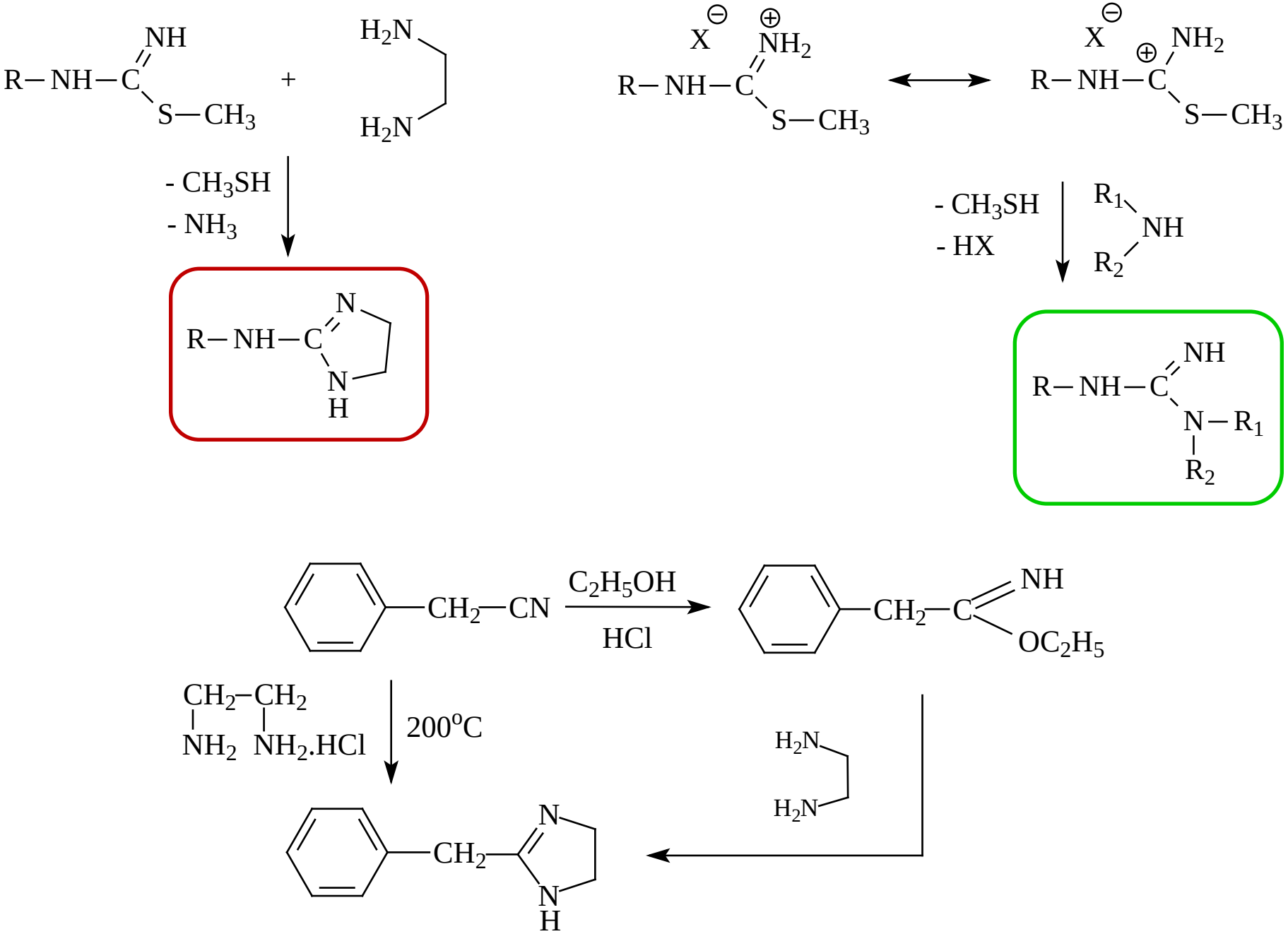

red.
parabanic acid
hydantoin

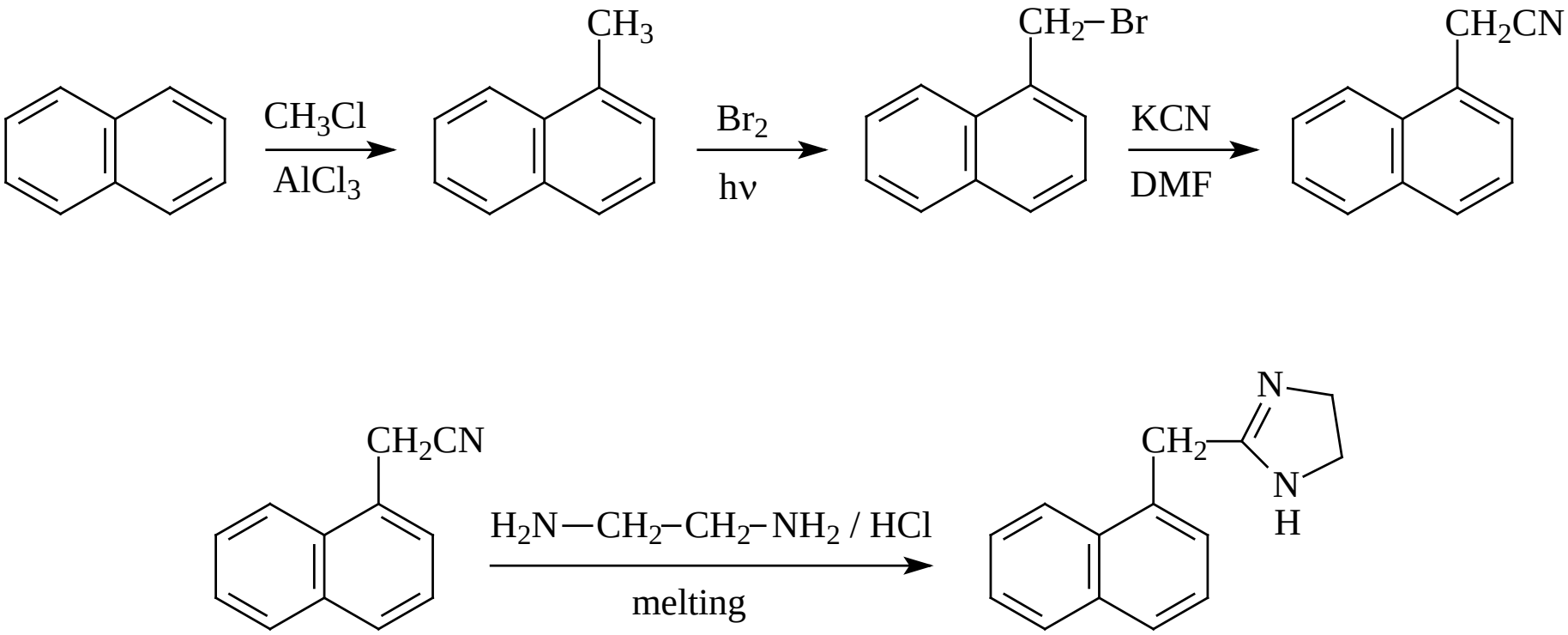

HgO
R


azlactone
histidine
essential amino acid
histamine
biogenic amine
generated in allergic reactions

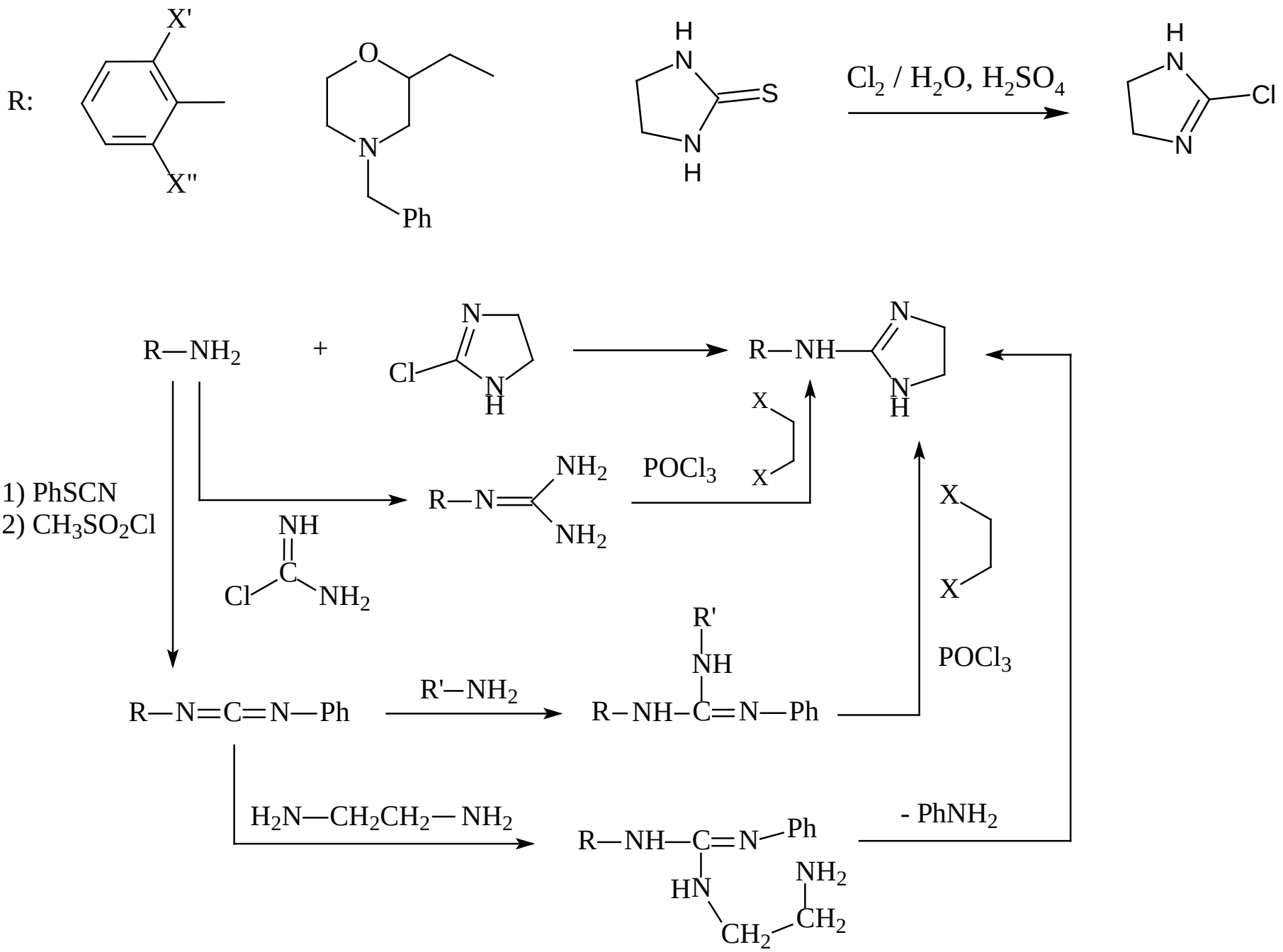


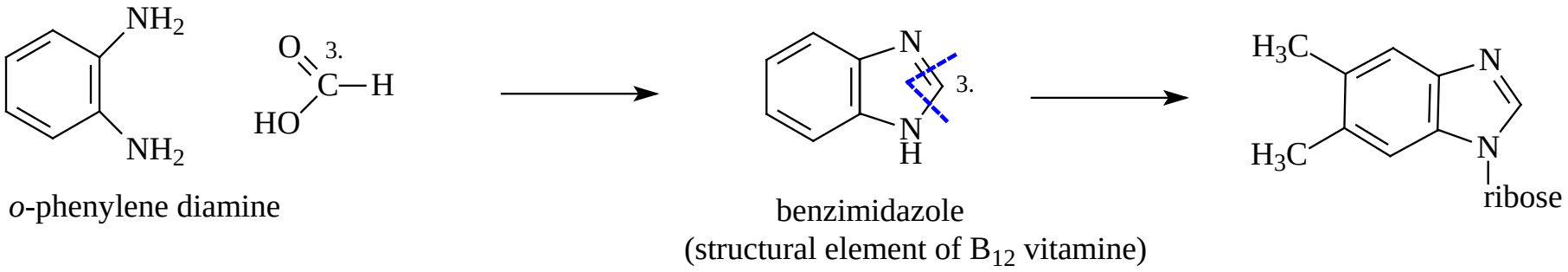
	R^1	R^2	R^3
Phenytoin	—H		
Diphedan antiepilepticum			
Mephenytoin	—CH_3	—C_2H_5	
Sacerno antiepilepticum			


R—NH—C(=NH)—S—CH3 + H2N—CH2—CH2—NH2
- CH3SH
- NH3
R—NH—C(=N—CH2—CH2—NH)
X⊖ ⊕NH2
R—NH—C(=NH2)—S—CH3
- CH3SH
- HX
R1 R2 NH
R—NH—C(=NH)—N(R1)(R2)
C2H5OH
HCl
CH2—CN
CH2—C(=NH)—OC2H5
CH2—CH2
NH2 NH2.HCl
200°C
H2N—CH2—CH2—NH2
tolazoline sympatholytic



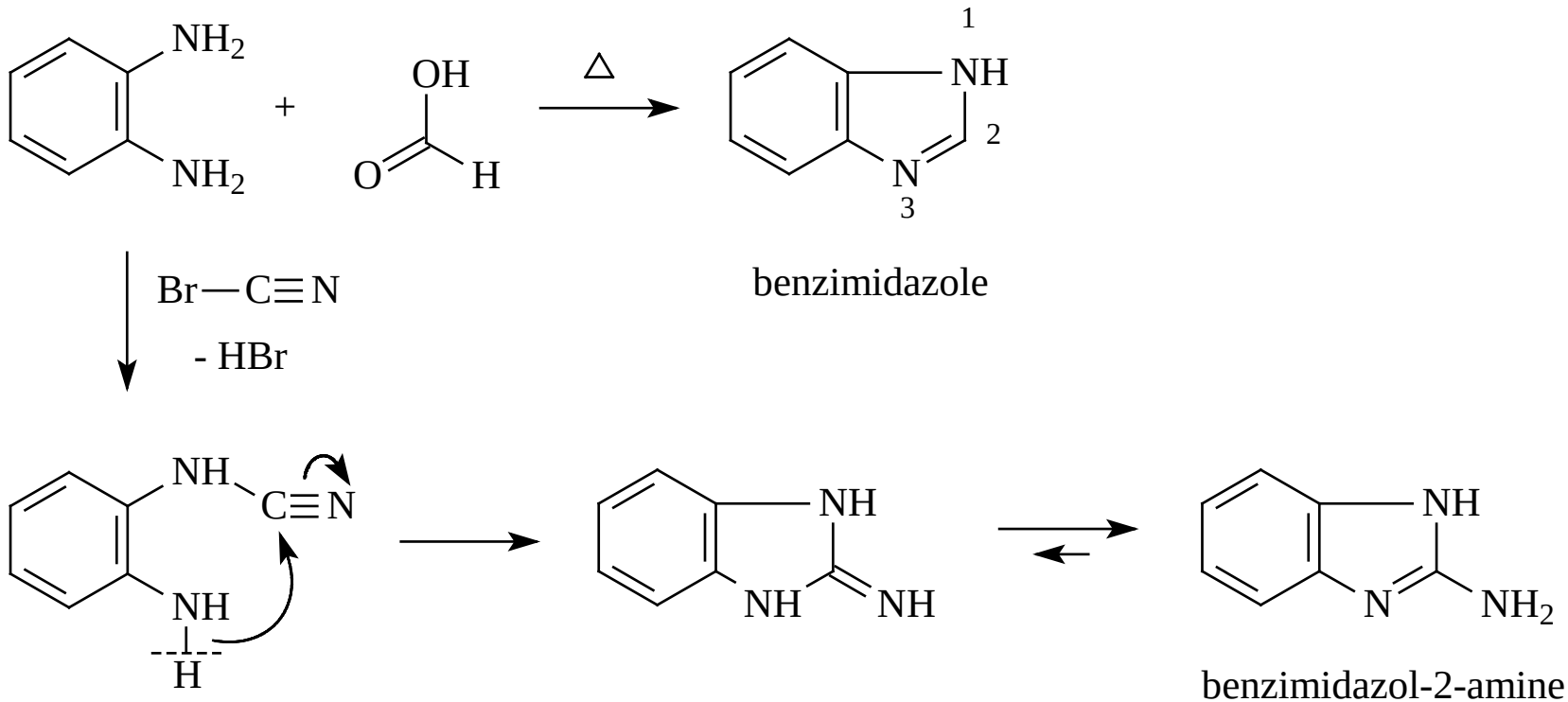
Naphazoline


R:
X'
X''
O
N
Ph
H
N
S
N
H
Cl2 / H2O, H2SO4
H
N
Cl
N
R—NH2
+
N
Cl
N
H
R—NH
N
N
H
X
X
1) PhSCN
2) CH3SO2Cl
NH2
R—N
NH2
POCl3
NH
C
Cl
NH2
X
X
R'
NH
POCl3
R—N=C=N—Ph
R'—NH2
R—NH—C=N—Ph
H2N—CH2CH2—NH2
R—NH—C=N
Ph
HN
NH2
CH2
CH2
- PhNH2



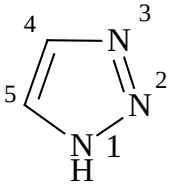
o-phenylene diamine

benzimidazole
(structural element of B_{12} vitamine)

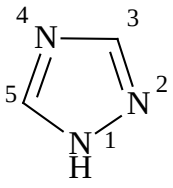


Monocyclic compounds with more than two heteroatoms

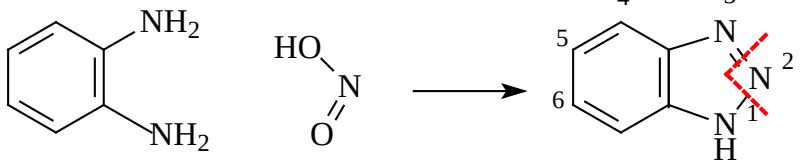
I/ Triazoles and its derivatives



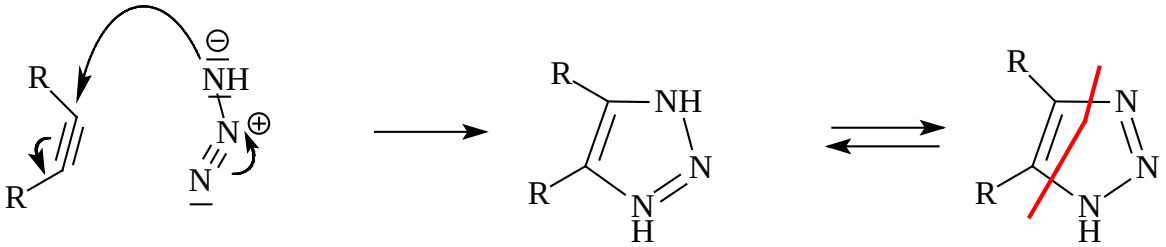
1,2,3-triazole



1,2,4-triazole

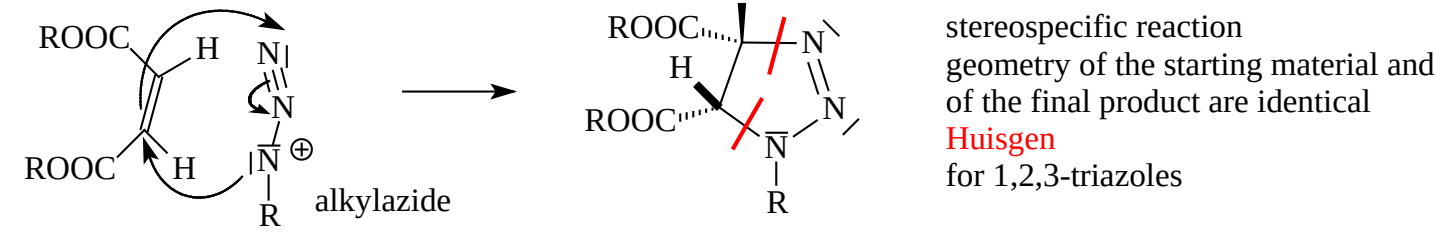


1,2,3-benzotriazole



acetylene derivative

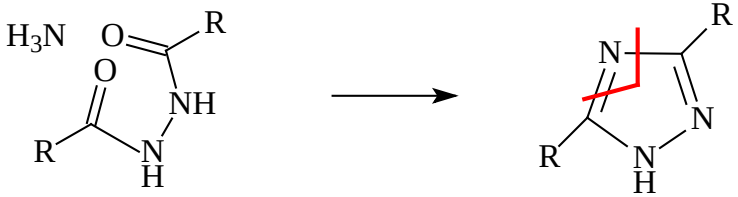
azoimide



dialkyl maleate

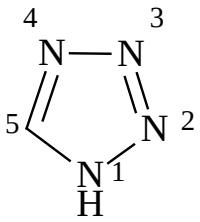
alkylazide

stereospecific reaction
geometry of the starting material and of the final product are identical
Huisgen
for 1,2,3-triazoles

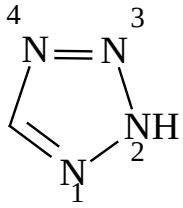


1,2,4-triazoles

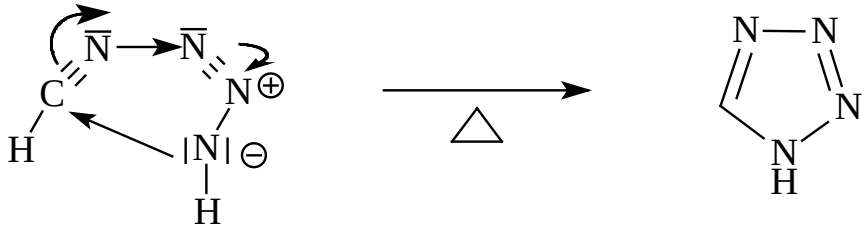
II/ Tetrazole and its derivatives

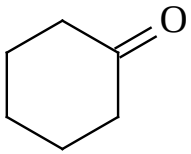


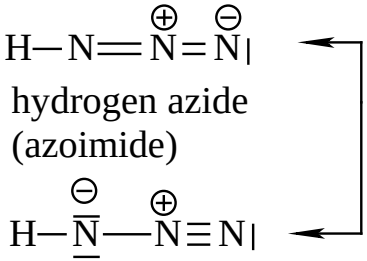
1*H*-tetrazole

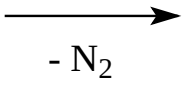


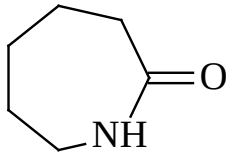
2*H*-tetrazole

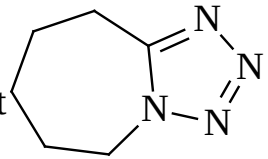








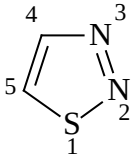




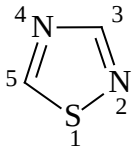
Pentetrazol
analeptic agent

1,5-pentamethylenetetrazole

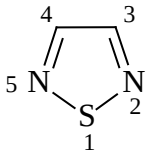
III/ Thiadiazole and its derivatives



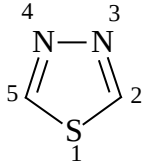
1,2,3-thiadiazole



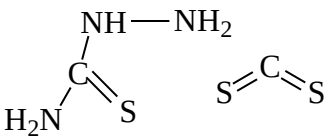
1,2,4-thiadiazole



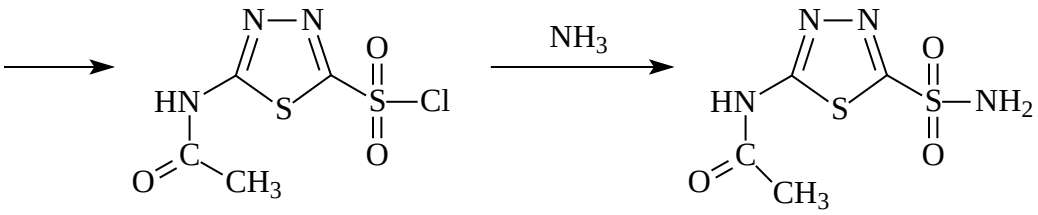
1,2,5-thiadiazole



1,3,4-thiadiazole

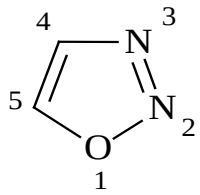


thiosemicarbazide

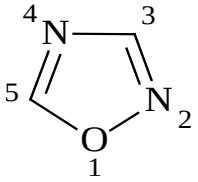


Fonurit
Diamox
diuretic compound
with carboanhydrase blocking effect

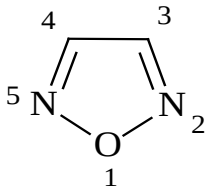
IV/ Oxadiazole and its derivatives



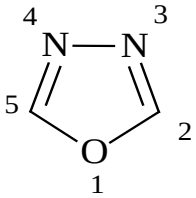
1,2,3-oxadiazole



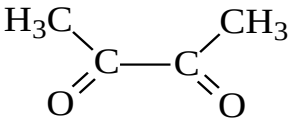
1,2,4-oxadiazole
(azoxime)



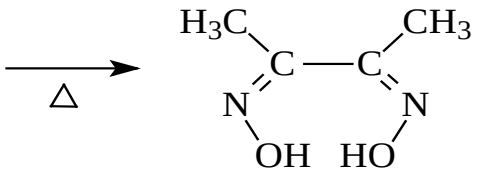
1,2,5-oxadiazole
(furazane)



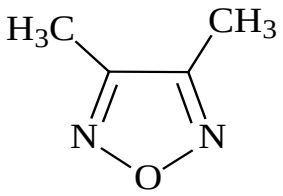
1,3,4-oxadiazole

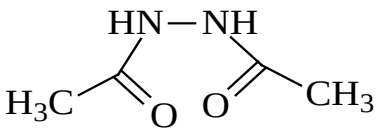


+ 2 $H_2N—OH$

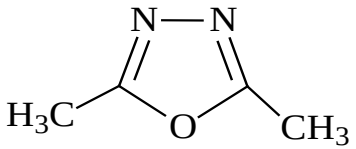


dimethyl glyoxime

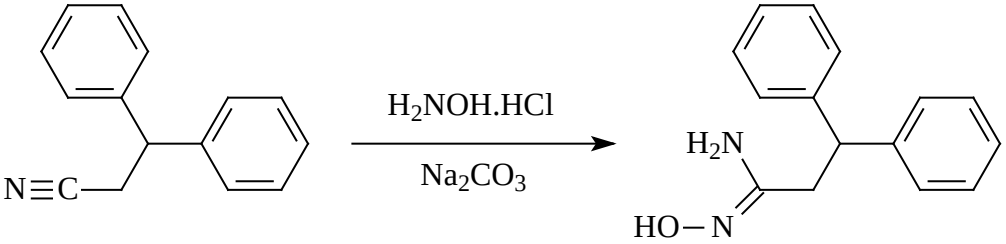


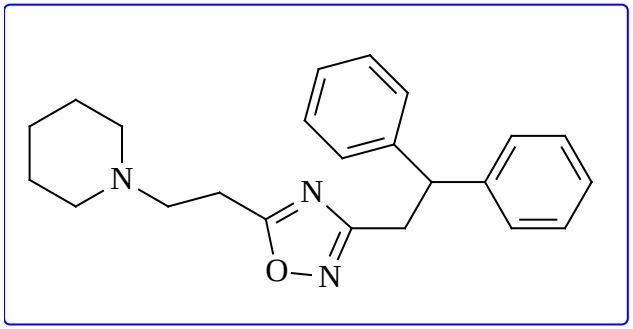


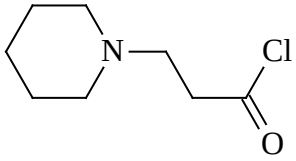
symmetric diacyl
hydrazine



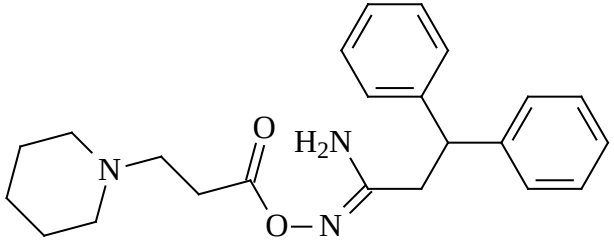
Prenoxdiazine





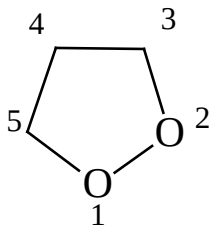


Libexin

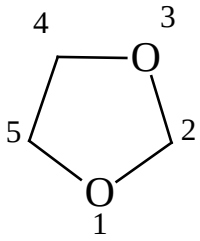


Less frequent heterocyclic rings and ring systems

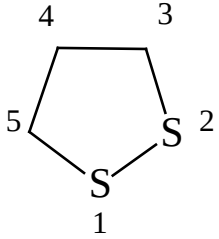
I/ Dioxolanes and dithiolanes



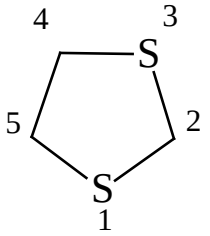
1,2-dioxolane



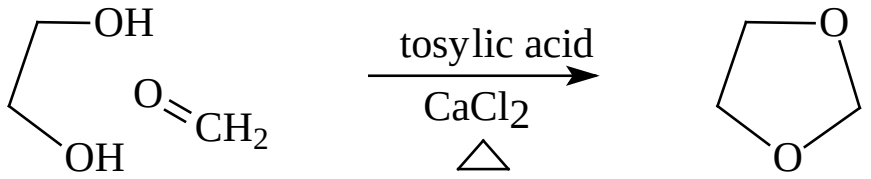
1,3-dioxolane

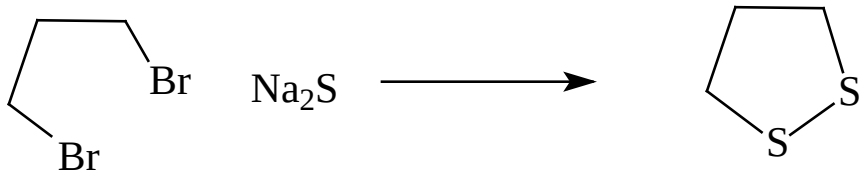


1,2-dithiolane

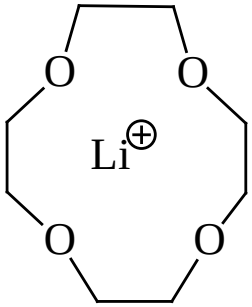


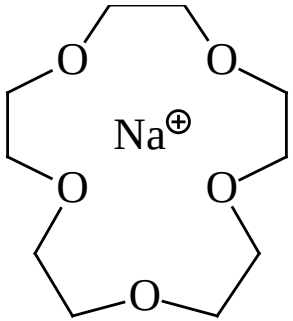
1,3-dithiolane

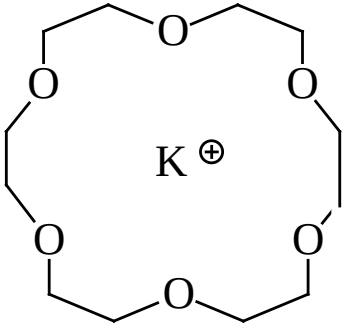




II/ Crown ethers and cryptands







[4] crown [12]

number of heteroatoms

number of elements of the skeletone

[5] crown [15]

[6] crown [18]

Crown ether with O atoms: cyclic polyether

Crown ether with S, P, N atoms: cryptands

C.J. Pedersen, J.M. Lehn and D.J. Cram
1987 Chemical Nobel Prize

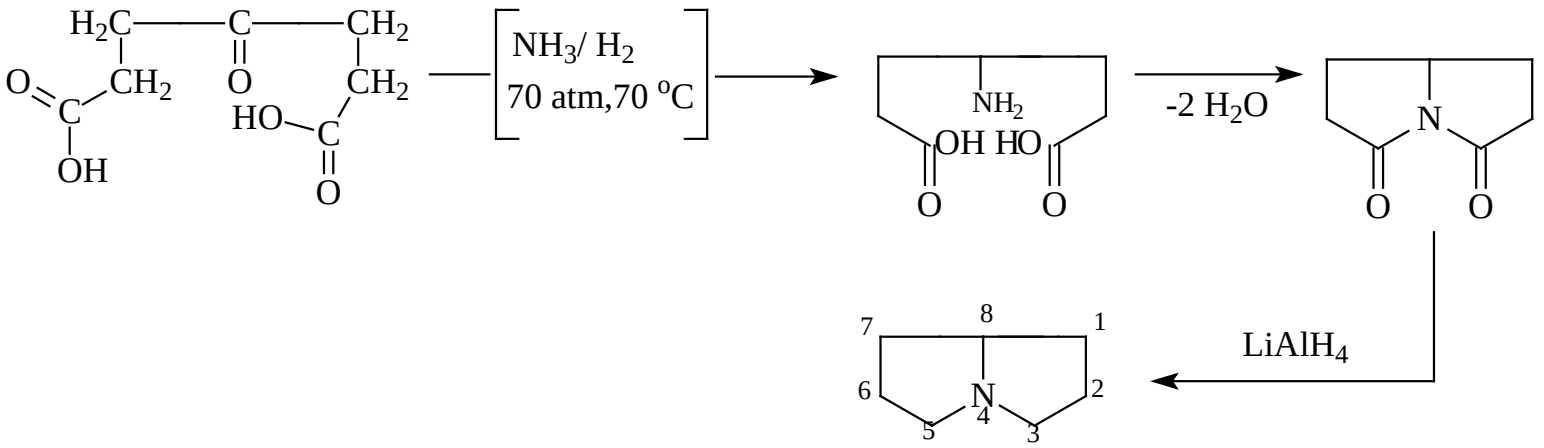
Crown ethers

C. J. Pedersen discovered these cyclic polyethers with many oxygen atoms in 1967. Their curiosity is that they are able to form insoluble complex with various metal cations, e.g., Li, Na, K, depending on the inner diameter of the ring, resulting in removal of these cations by filtration. This discovery had great importance from organic chemical point of views. Large-scale preparation of crown ethers was carried out by industry. There are crown ethers with 4, 5 and 6 oxygen atoms.

Application of crown ethers may take place in organic chemistry by dissolution of a crown ether in aprotic solvent, then adding potassium, or sodium salts to it, the crown ether makes complex with the cation, and precipitated. There is a highly reactive anion in the solution after filtration. E.g., potassium permanganate becomes soluble in benzene after treating it with crown ether, then this apolar solution of permanganate anion is used as strong oxidating agent. Similarly potassium cyanide, potassium fluoride, potassium nitrite, potassium iodide can be dissolved apolar solvents. Reduction by sodium borohydride can be carried out in aromatic solvents, if crown ether was added. E.g., dehydration of an O-tosylate runs for 42 hours at usual conditions, while the yield is only 9 %. The same compound has dehydration in the presence of crown ether within 1 hour with yield of 70 %. Many such kind of applications can be found in the literature.

Pedersen, then Jean Mary Lehn were working with such crown ethers in 1965. They prepared ethers with greater ring size → crown ethers. The oxygen atoms are arranged in the structure in order to make noble gas configuration with the proper cations. The counter anion is attached from outside. $KMnO_4$ is insoluble in benzene. However, adding some crown ether to the suspension, – e.g., [18] crown [6] – colour of benzene turns to be of violet, showing dissolution of $KMnO_4$. The crown ether can solvate $K^{\oplus}$, while permanganate ion is attached to this complex in form of ion pair, from in front of the ring or from behind the ring. Permanganate ion is naked, there is only electrostatic attachment of ions. Therefore, the oxidating behaviour of permanganate ion is remained. KOH can be dissolved in apolar solvents by a crown ether. Hydroxide anion is naked, its nucleophilic power is remained in S_N reactions. The only condition of dissolution of the reagent is that the cation must make stable complex, while the anion is naked. The similar dissolution happens in dipolar aprotic solvents. The naked anions are of much more nucleophilic, than any solvated anions. Such kind of dissolutions are called as solid-liquid transfer. Liquid-liquid transfer: see PTC reactions (phase transfer catalysis).

III/ Pyrrolizidine

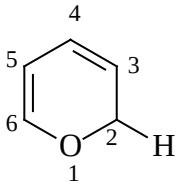


pyrrolizidine
(in alkaloids)

Six-membered heterocyclic compounds with one heteroatom and their derivatives with condensed ring system

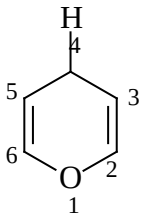
I/ Pyrane and its derivatives

Nomenclature



2*H*-pyrane

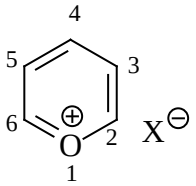
α-pyrane



4*H*-pyrane

γ-pyrane

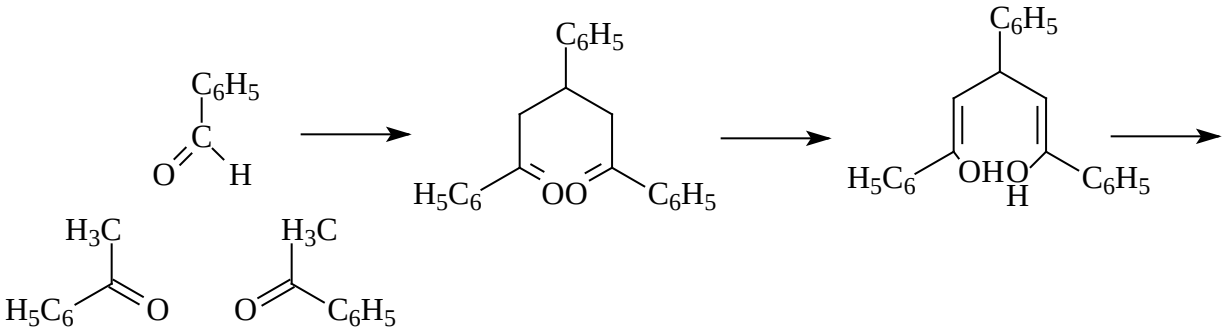
these are not stable compounds



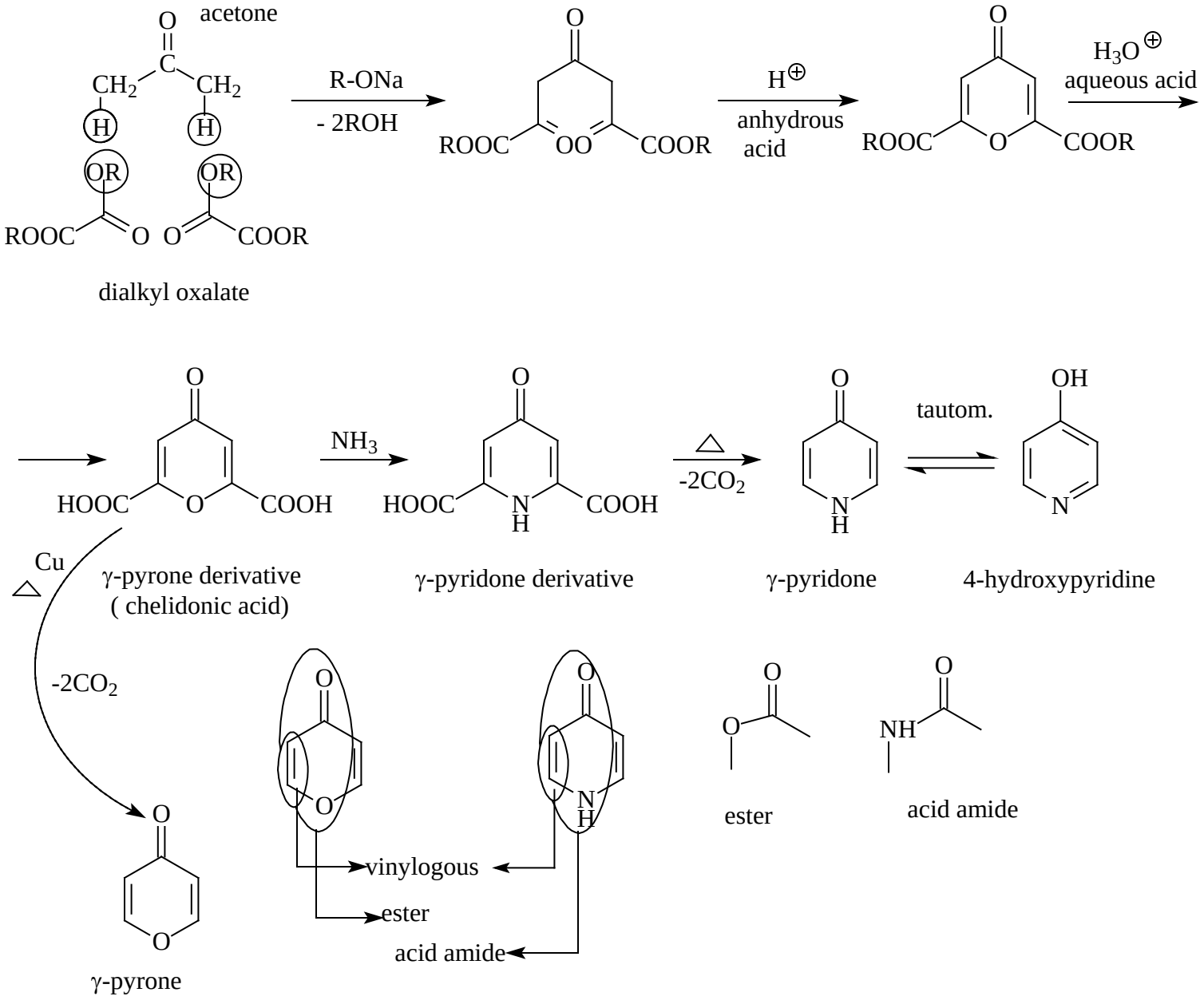
pyrilium salt

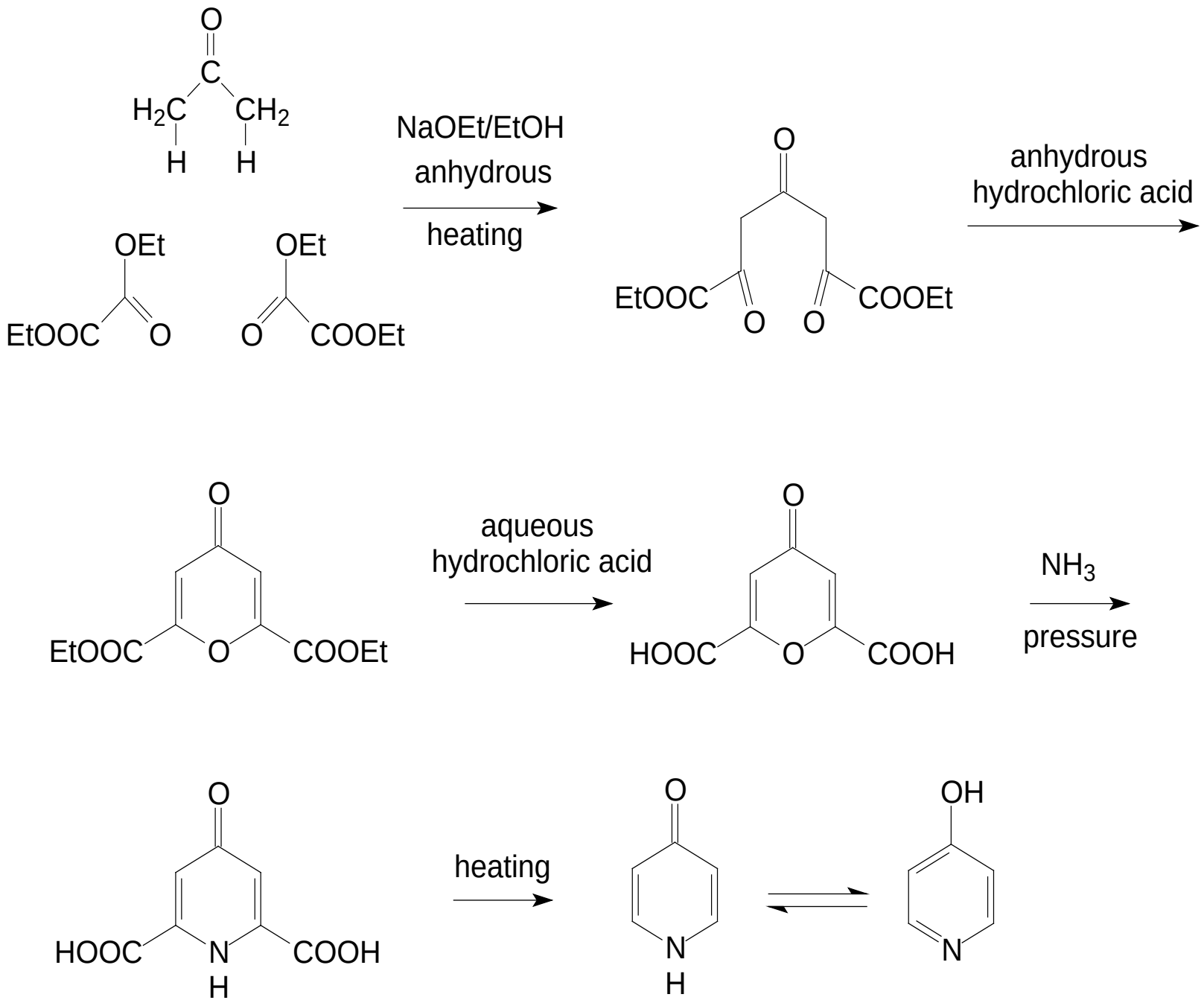
the benzopyrilium salts are stable compounds

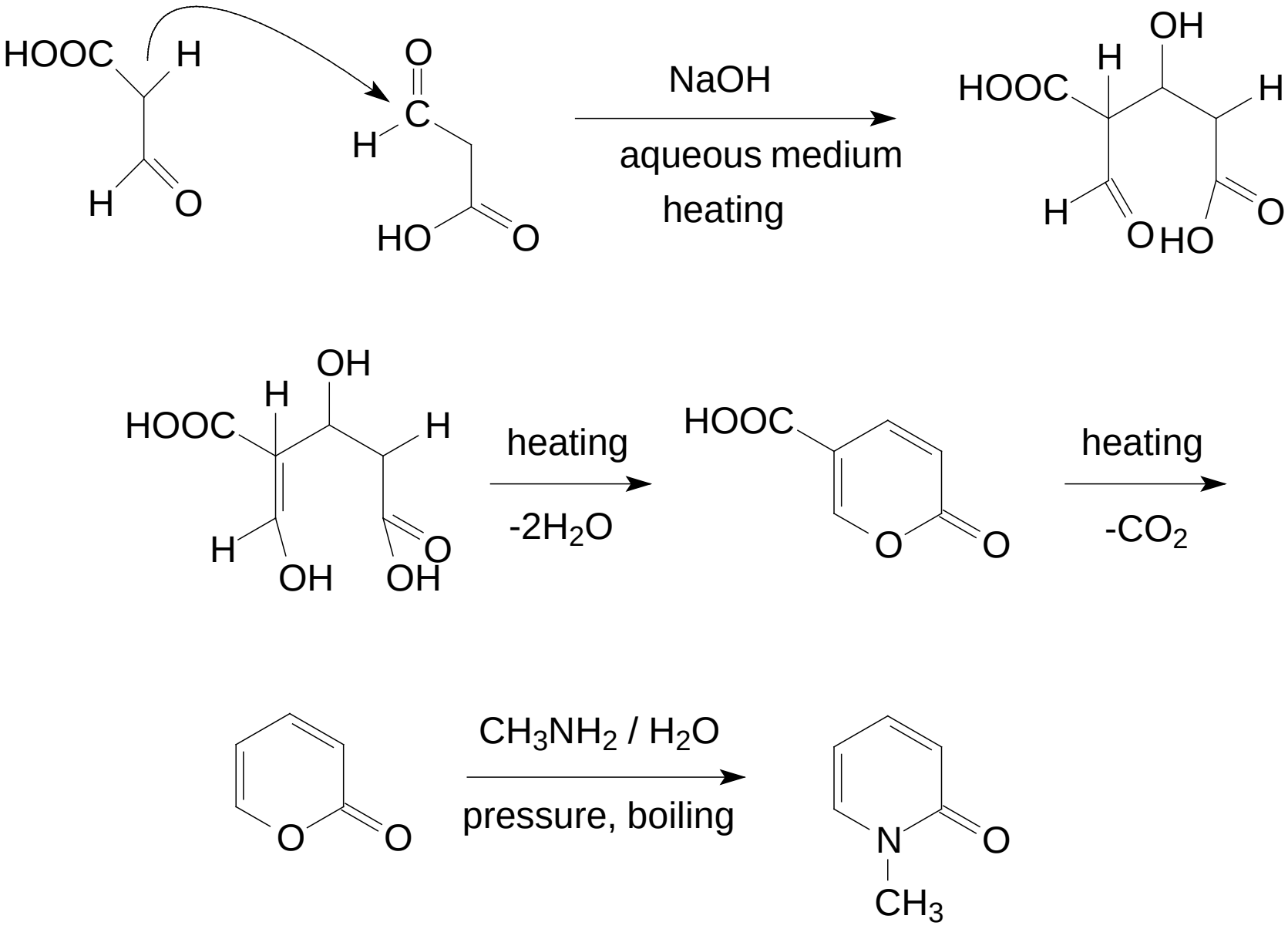
Preparations



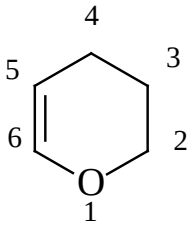
pyrilium salt


acetone
R-ONa
- 2ROH
H⊕
anhydrous acid
H3O⊕
aqueous acid
dialkyl oxalate
NH3
-2CO2
tautom.
Cu
γ-pyrone derivative
(chelidonic acid)
γ-pyridone derivative
γ-pyridone
4-hydroxypyridine
-2CO2
γ-pyrone
vinylogous
ester
acid amide
ester
acid amide

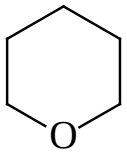

O
C
H2C
CH2
H
H
OEt
EtOOC
O
OEt
O
COOEt
NaOEt/EtOH
anhydrous
heating
O
EtOOC
O
O
COOEt
anhydrous
hydrochloric acid
O
EtOOC
O
COOEt
aqueous
hydrochloric acid
O
HOOC
O
COOH
NH3
pressure
O
HOOC
N
H
COOH
heating
O
N
H
OH
N


HOOC
H
H
O
O
C
H
HO
O
NaOH
aqueous medium
heating
OH
H
HOOC
H
H
O
HO
O
OH
H
HOOC
H
H
OH
OH
O
heating
-2H2O
HOOC
O
O
heating
-CO2
O
O
CH3NH2 / H2O
pressure, boiling
N
O
CH3

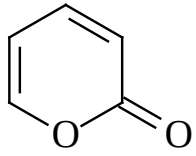
More important derivatives



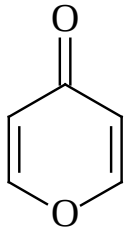
3,4-dihydro-
-2*H*-pyran



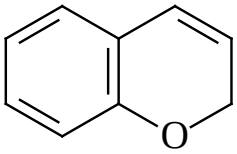
tetrahydro
-pyran



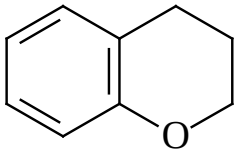
2*H*-pyran–2-one
α-pyrone



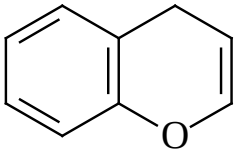
4*H*-pyran–4-one
γ-pyrone



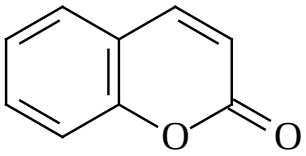
α-chromen
2*H*-chromen (stable)



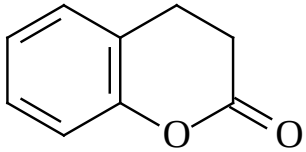
chroman



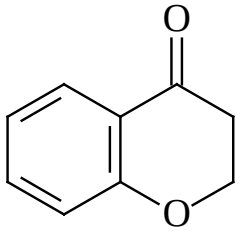
γ-chromen
4*H*-chromen (unstable)



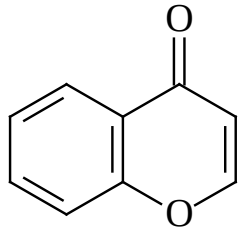
2*H*-chromen-2-one
α-chromone
coumarin



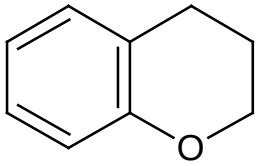
α-chromanone



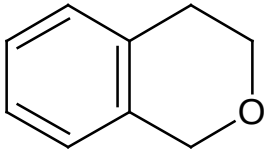
γ-chromanone



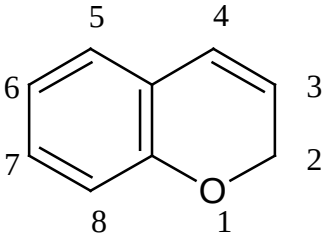
4*H*-chromen-4-one
γ-chromone



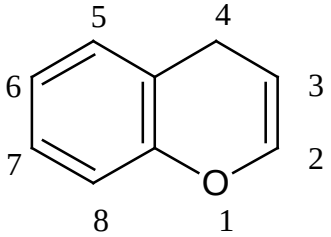
chroman



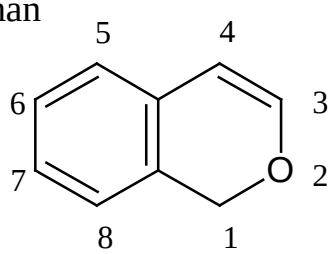
isochroman



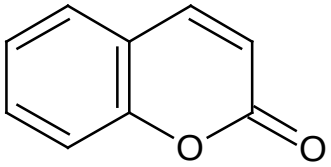
2*H*-chromen



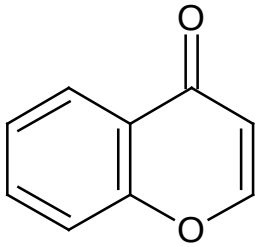
4*H*-chromen



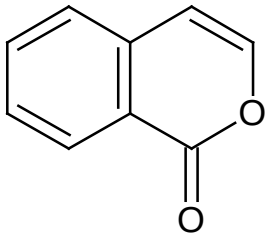
isochromen



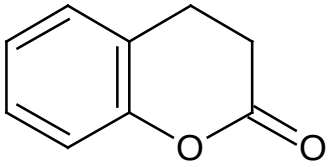
coumarin



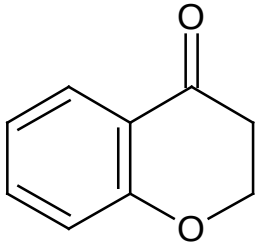
chromone



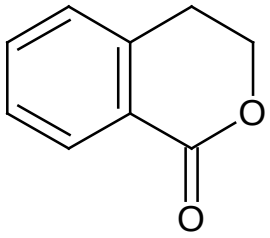
isocoumarin



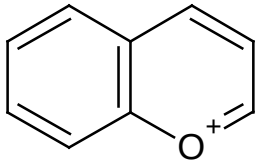
2-chromanone
(dihydrocoumarin)



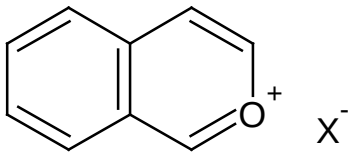
4-chromanone
(dihydrochromone)



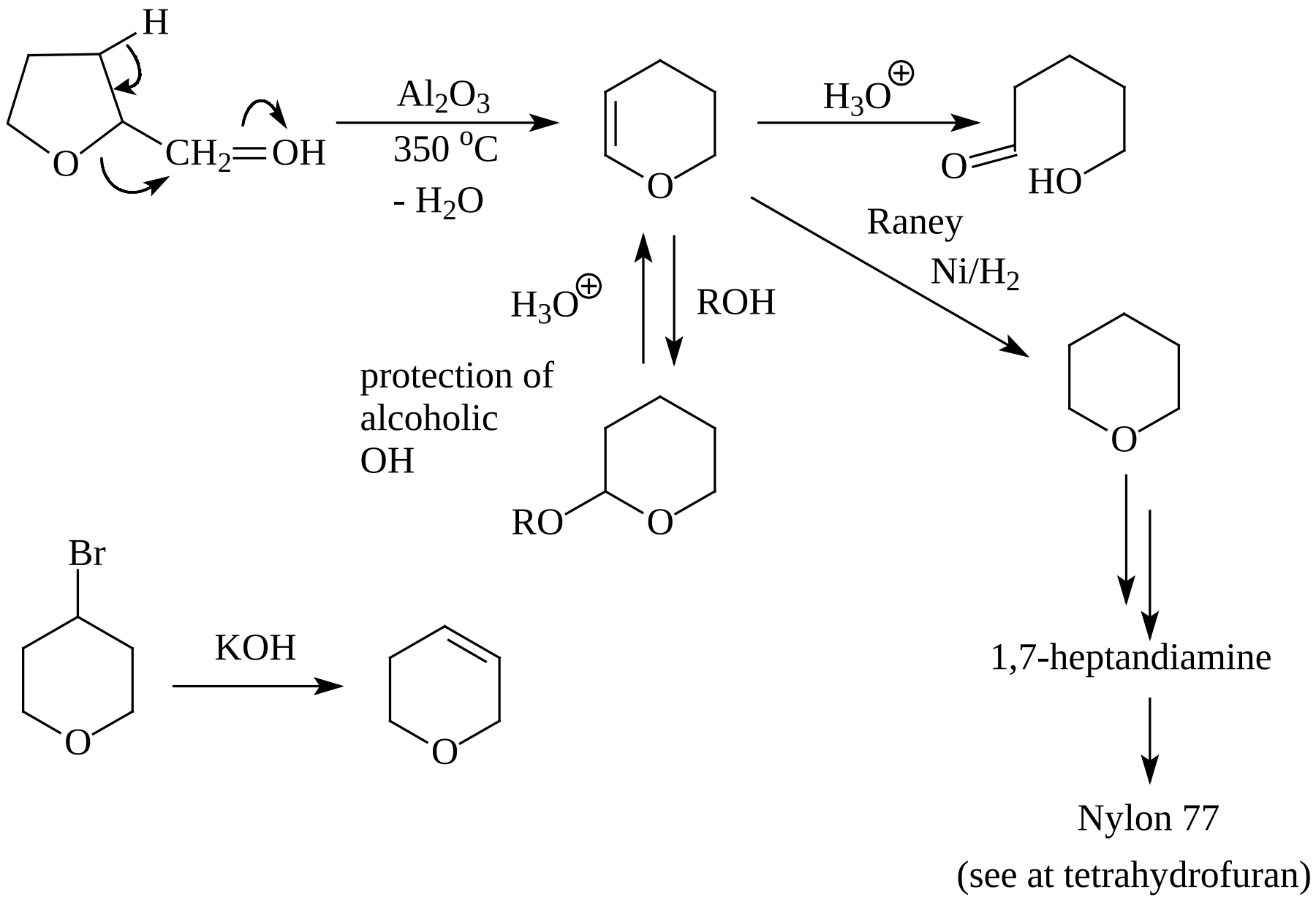
isochromanone
(dihydroisocoumarin)

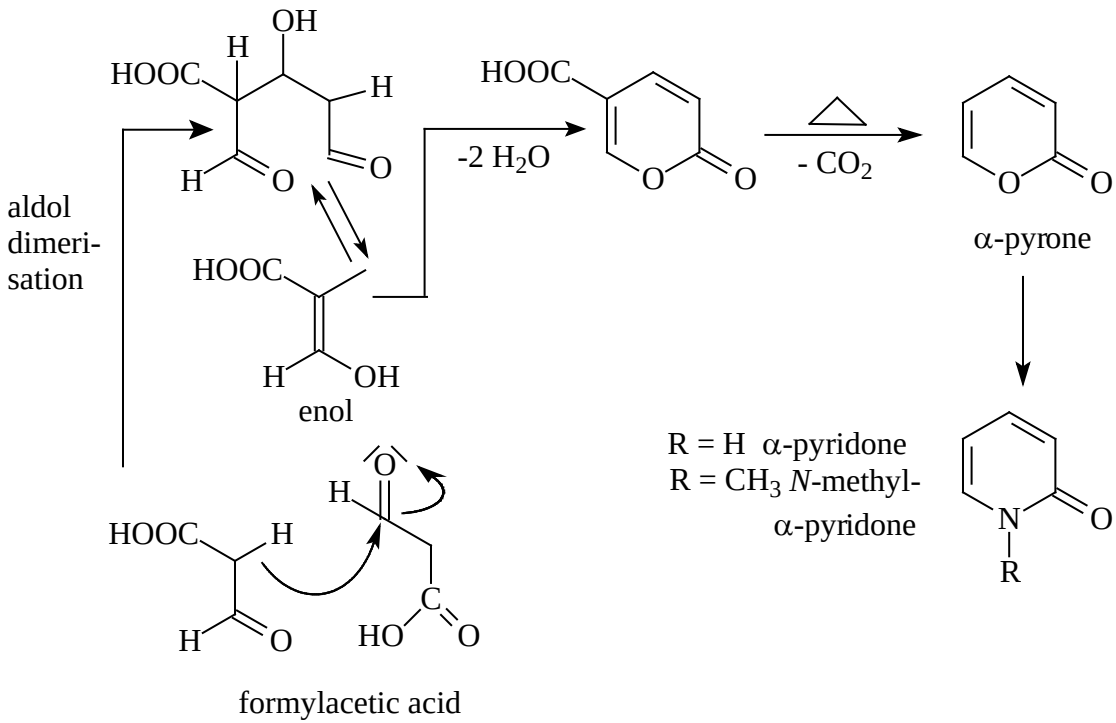


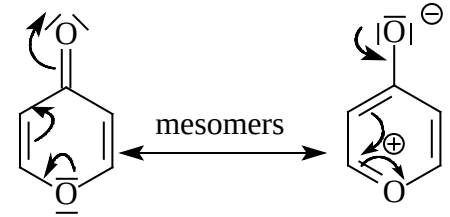
chromilium salt
(benzopyrilium salt)



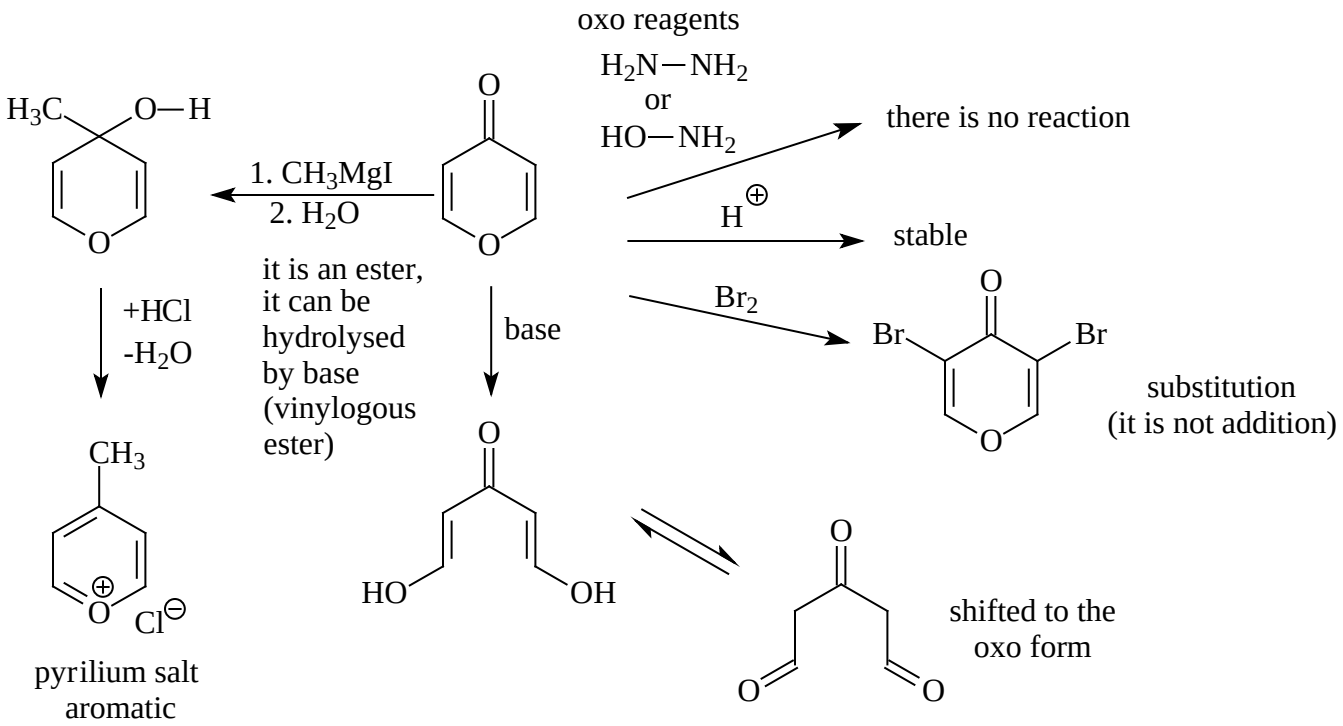
isobenzopyrilium salt


H
O
CH2=OH
Al2O3
350 oC
- H2O
O
H3O⊕
O
HO
Raney
Ni/H2
H3O⊕
ROH
protection of
alcoholic
OH
RO
O
O
1,7-heptandiamine
Nylon 77
(see at tetrahydrofuran)
Br
O
KOH
O





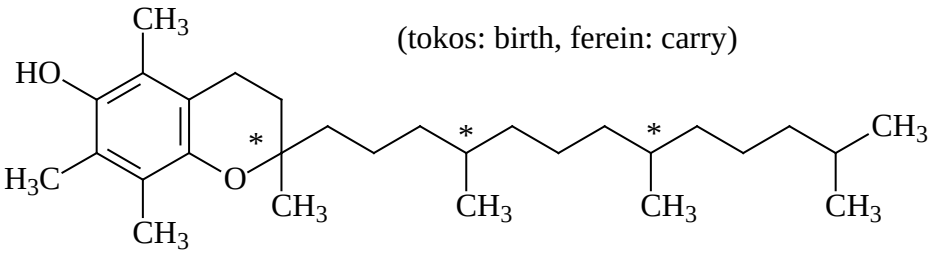
It is a double vinylogous lactone
Both mesomers contribute to the real structure


oxo reagents
H2N—NH2
or
HO—NH2
there is no reaction
1. CH3MgI
2. H2O
H⊕
stable
Br2
substitution
(it is not addition)
+HCl
-H2O
it is an ester,
it can be
hydrolysed
by base
(vinylogous
ester)
base
pyrilium salt
aromatic
shifted to the
oxo form

Vitamin E
α-Tocopherol

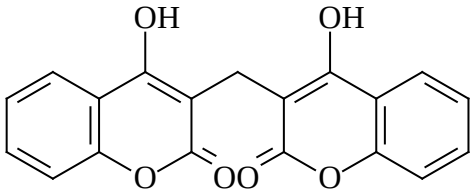
it can be isolated from
wheat germ oil
it participates in
keeping pregnancy

(tokos: birth, ferein: carry)



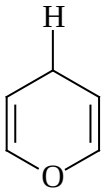
Coumarin - its hydroxy derivatives occur in glycoside form in nature

dicoumarol
an anticoagulant
(its antidote is Vitamin K)

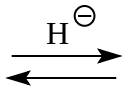


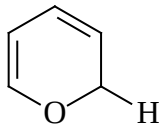
tautomers

these differ from each
other in the position of a
H ($H^{\ominus}$ anion) and of
a double bond



4*H*-pyran



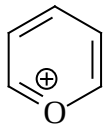


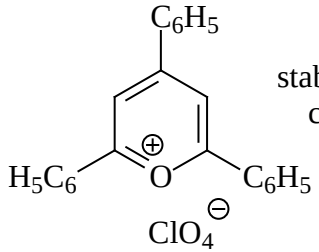
2*H*-pyran

(difference lays at oxo-enol taumerism
in differences in mobile $H^{\oplus}$ as well as
position of a double bond)

- $H^{\ominus}$
oxidation

not existing





stable aromatic
compound

Anthocyanines

These derivatives are compounds with conjugated double bonds (conjugated: 2*H*-pyran, or isolated: 4*H*-pyran) (heterocyclic alkenes). The compounds are reactive ones with high energy content.

Anthocyanines are glycosides $\xrightarrow{\text{hydrolysis}}$ anthocyanidine (aglycon) + sugar component

Flavinium salts: coloured materials of plants with glycoside type (flower petals, fruits, strawberry, pelargonium, red poppy, black grape, bluebonnet, chrysanthemum): these might be red, purple, violet, blue

α-Chromene derivatives are polyhydroxy compounds with 5 hydroxy groups. Its derivatives occur in the nature only, e.g., methyl ether, acetyl derivative, or with free hydroxy groups.

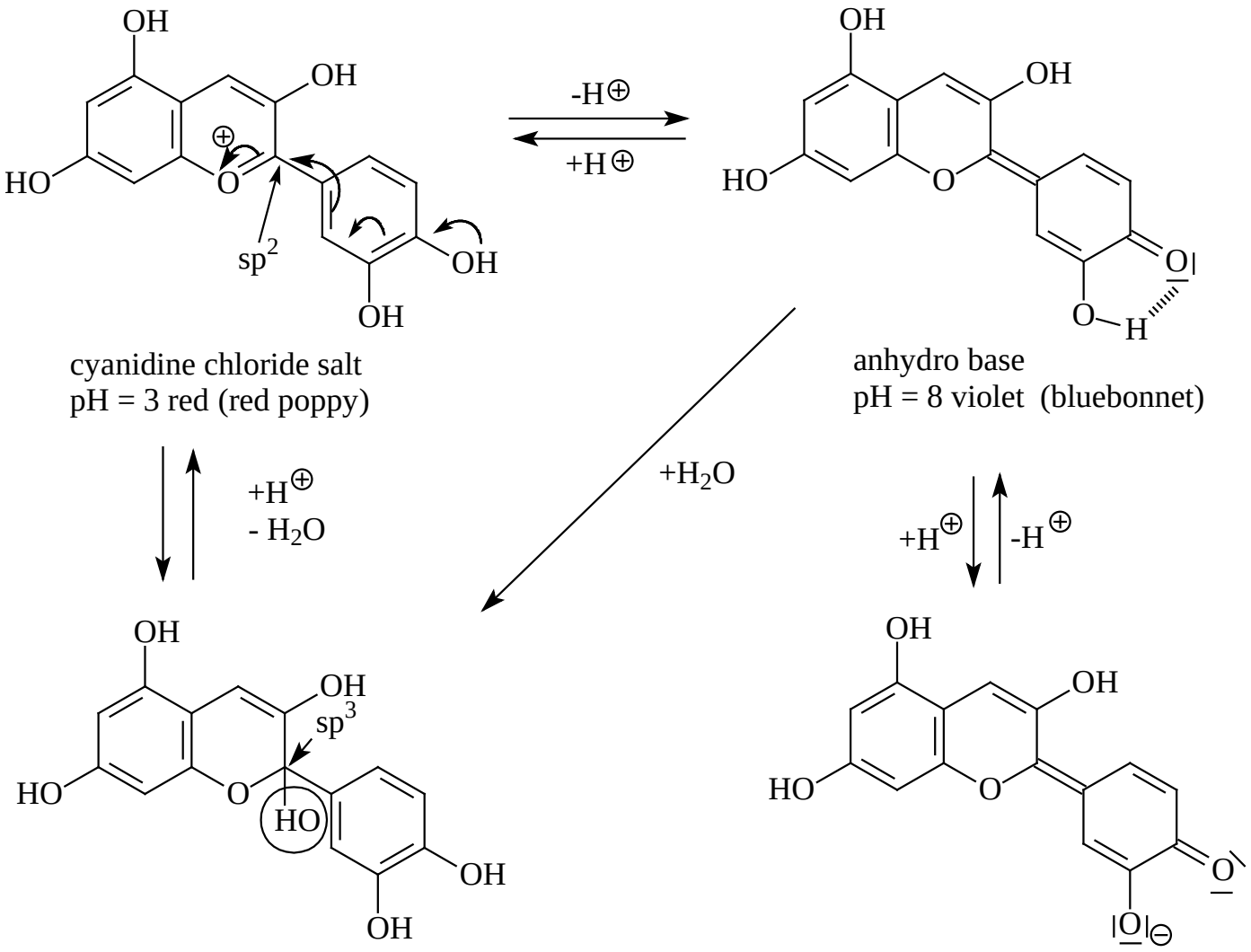
The glycoside structure is the remnant of molecular phylogenesis, representing its carbohydrate origine.

Cyanin (greek) – blue

The actual colour depends on pH of cells as well as on depth of layers, since coloured components do not move freely within the cells, these form layers. Blue colour of bluebonnet and red colour of red poppy comes from the same molecule.

Colour depends on:

1. pH value
2. number of hydroxy groups
3. the actual form of hydroxy group (free, methyl ether, glycoside)
4. position of glycoside group

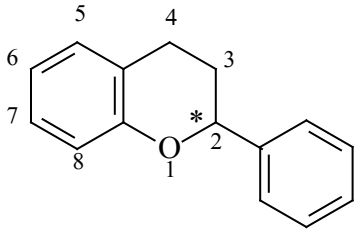


These differ in the number and positions of hydroxy groups, in quality and position of the sugar components.
Source of red colour can be carotenoids (red pepper), while other carotenoids are yellow.
White colour of flower petals come from the colourless air, but from not a coloured material.
There is sp^2 conjugated system in cyanidine chloride, where the pyrilium salt is the auxochrome component.
Appearence of a sp^3 carbon separates the two chromophores, resulting in no absorbance in the coloured range.

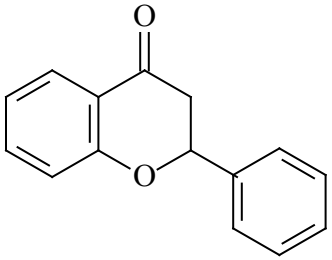
Flavonoids

Yellow colour of yellow plants (flavus – yellow)
γ-chromene derivatives

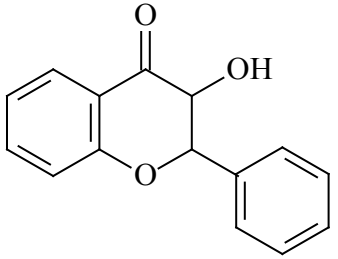
Colour of tulips and other plants by springtime. There can be 4 types of hydroxy derivatives (free, methyl ether, acetoxy derivative or glycoside), similarly to the anthocyanines.



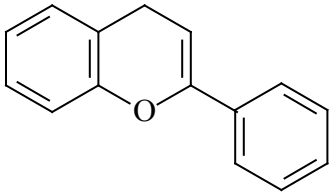
2–phenylchromane
flavane



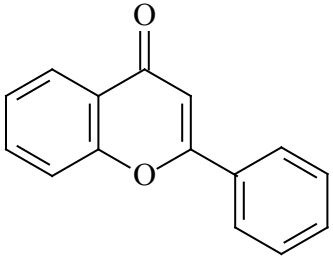
flavanone



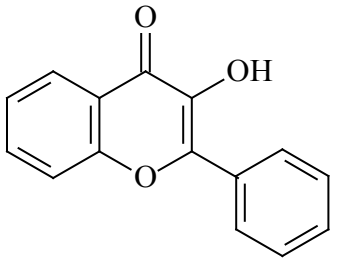
flavanonol



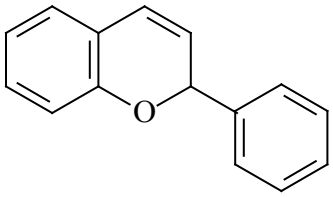
2- phenyl-4*H*-chromene
flavene



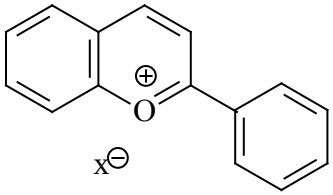
flavone



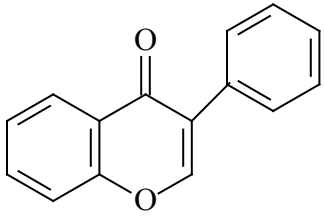
flavonol



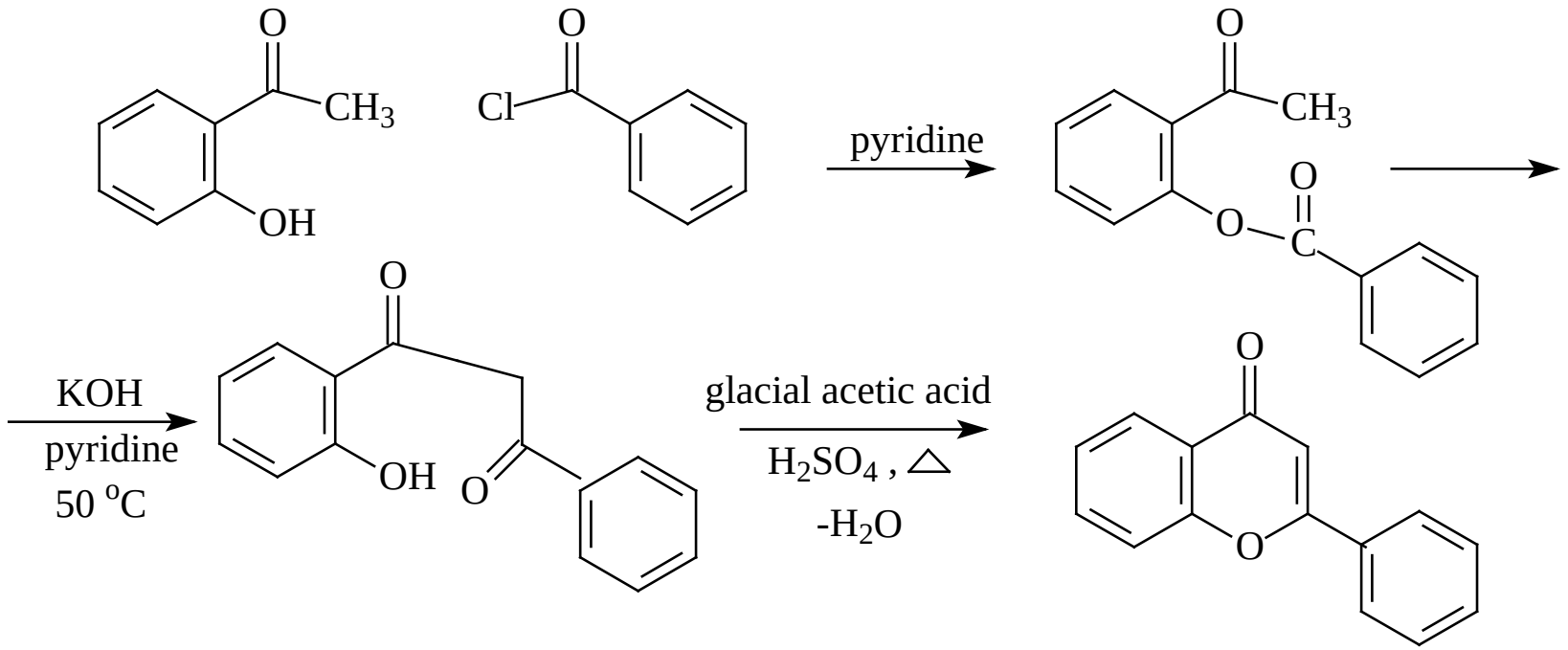
2-phenyl-2*H*-chromene

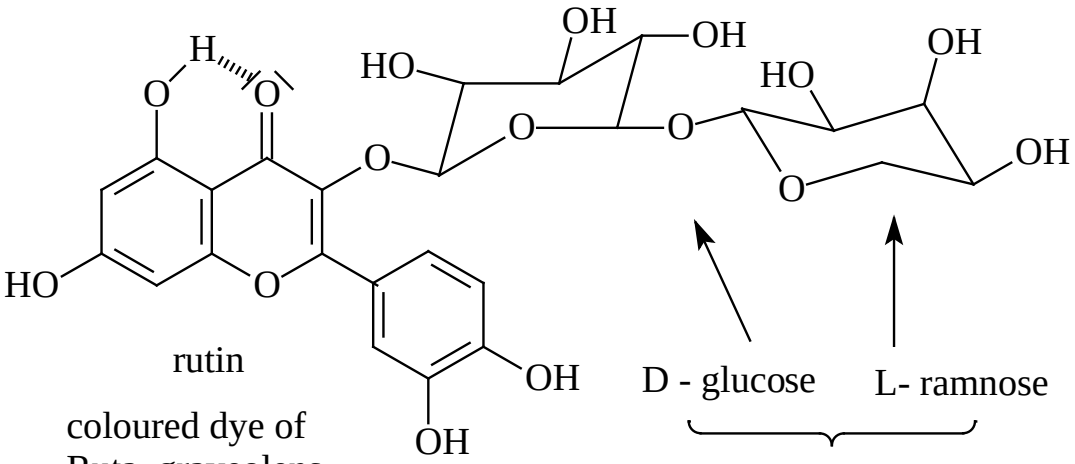


flavinium salt



isoflavone

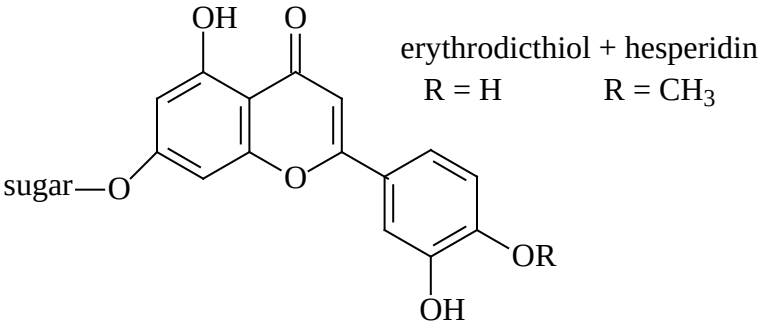




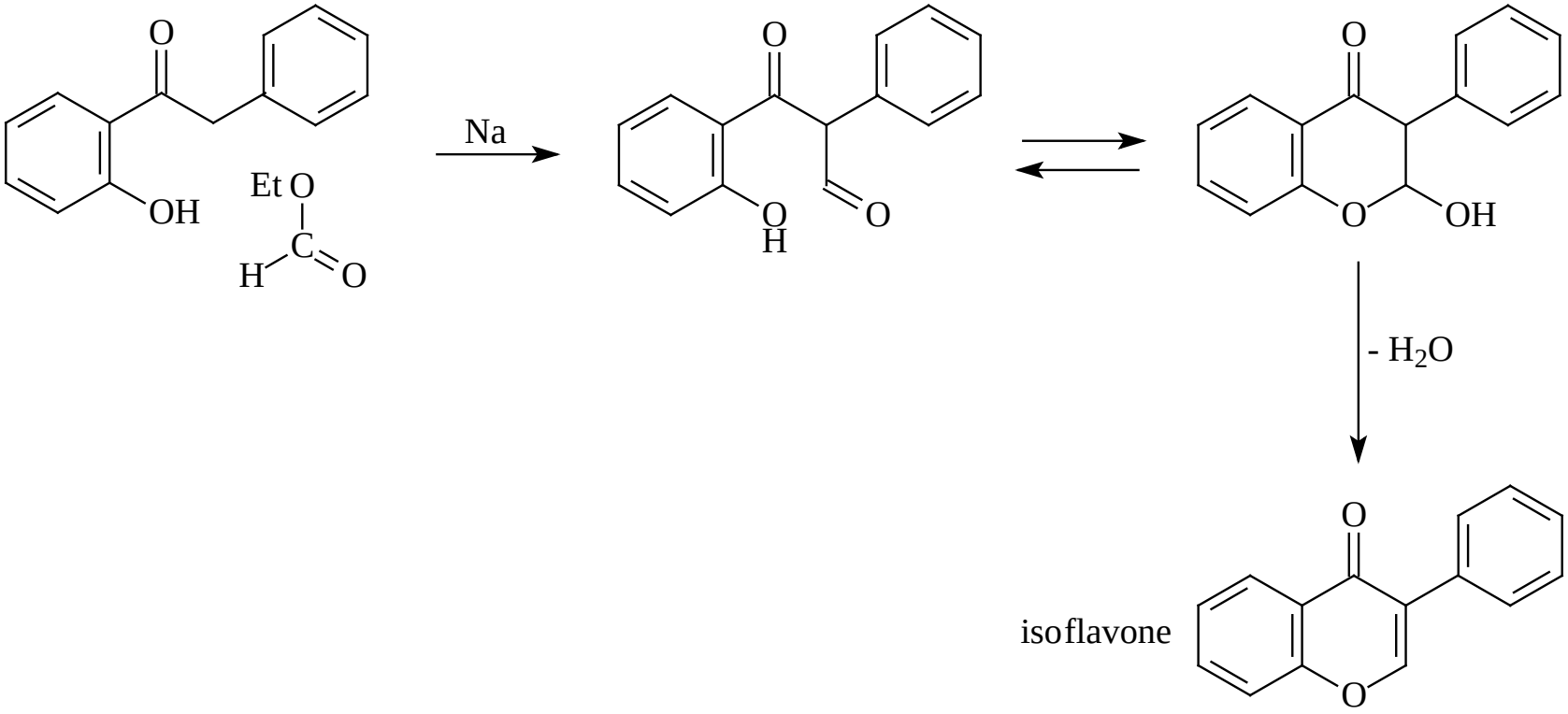
Prof. Géza Zemplén
Technical University at Budapest :
he was a flavonoid
researcher

flavanol type

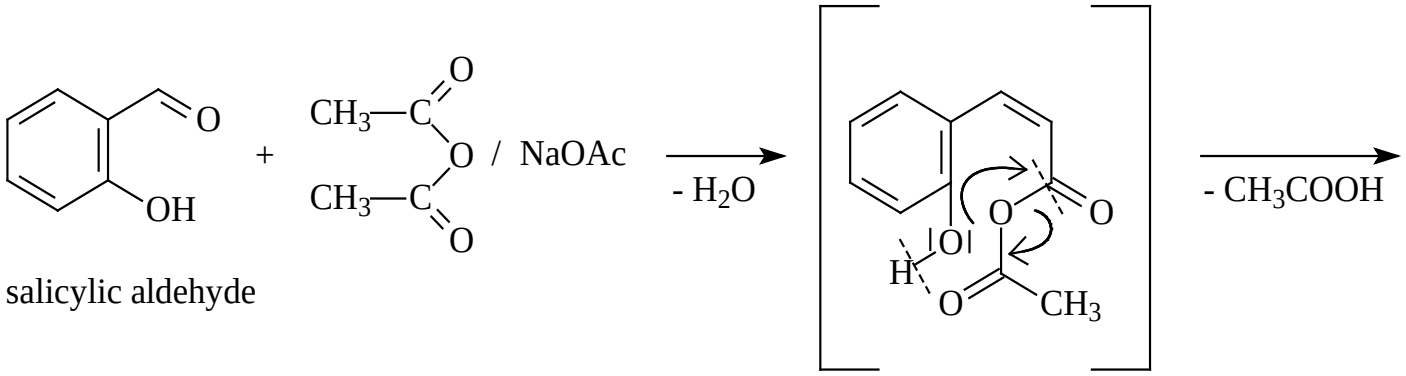
Vitamine P: discovered by Szent-Györgyi, Rusznyák, Bruchner
It decreases permeability of capillaries, increasing their resistance.



erythrodicthiol + hesperidin
R = H R = CH_3

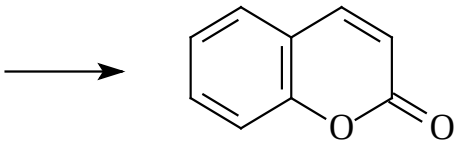


isoflavone

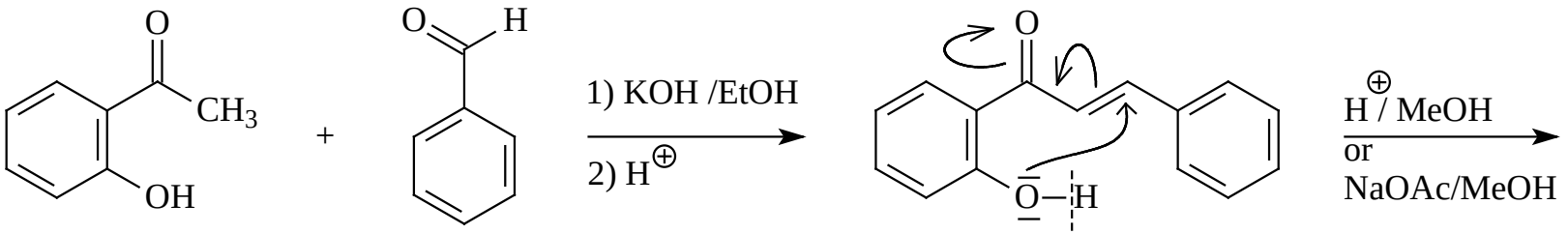


salicylic aldehyde

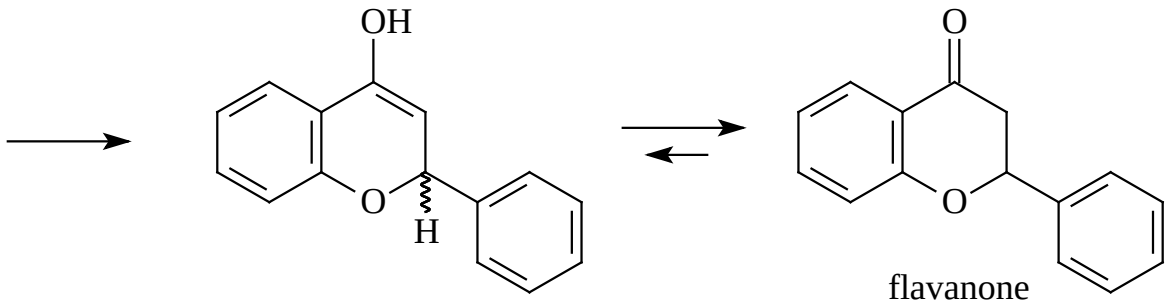
Perkin-synthesis



coumarin

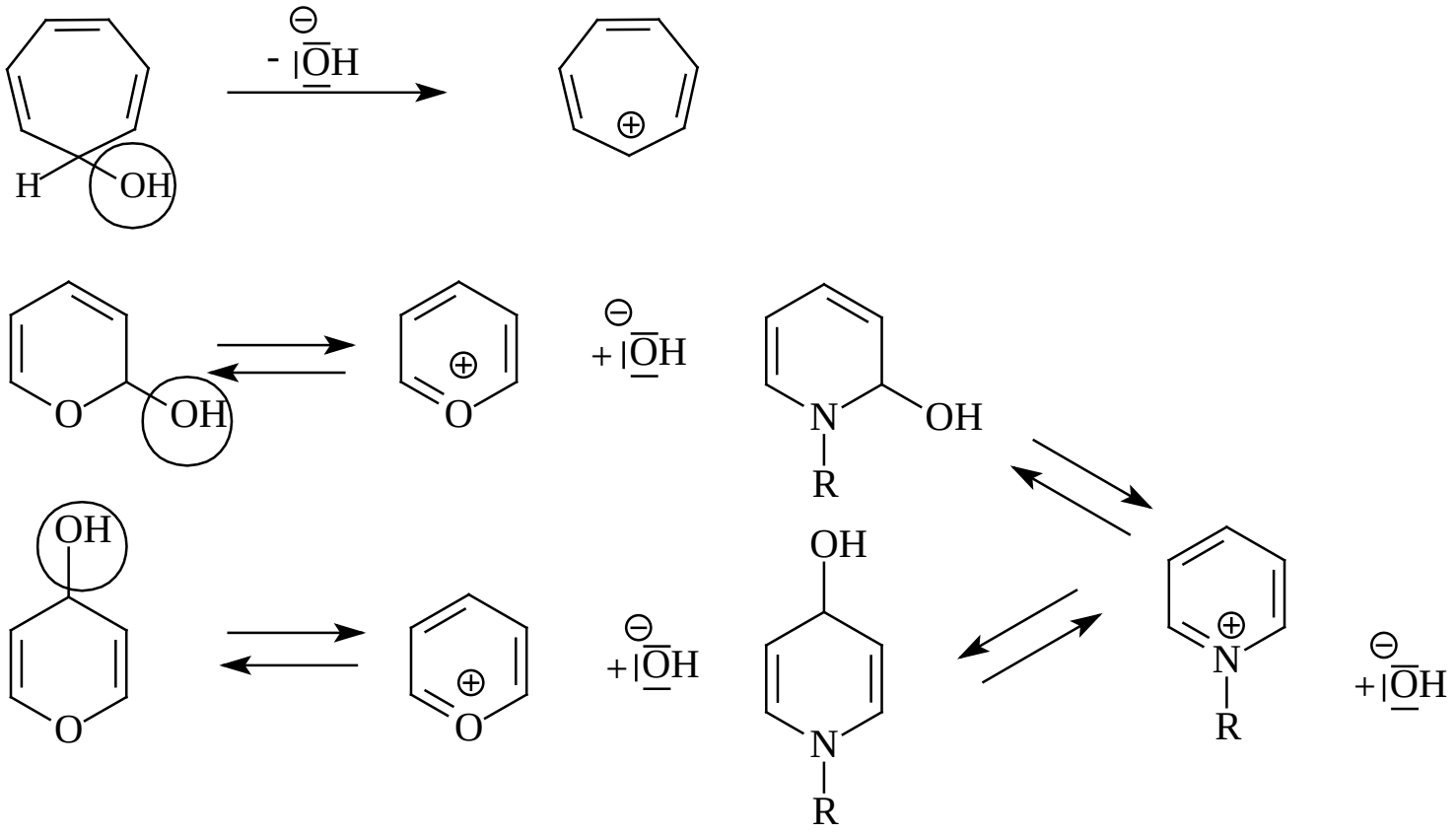


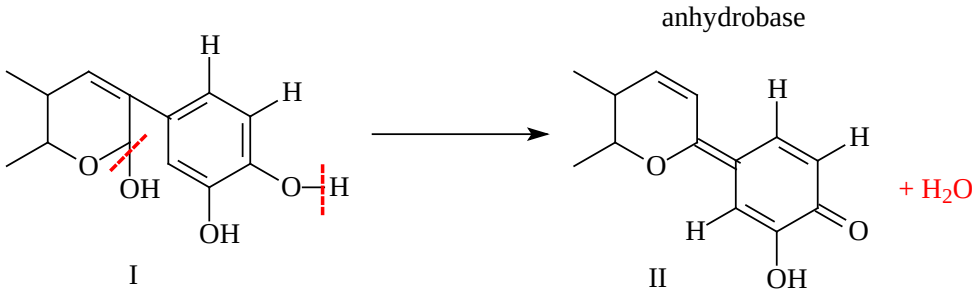
hydroxychalcone



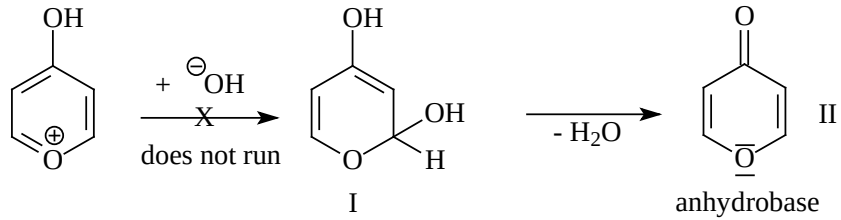
flavanone

Anthocyanines: α-chromene derivatives
Flavonoids: γ-chromene derivatives
Anhydrobases: compounds forming salts with acids without generating water (see the examples on the previous slides)
Pseudobases: some secondary carbons with OH can dissociate to hydroxy, similarly to the effect of bases ⟶ pseudobases

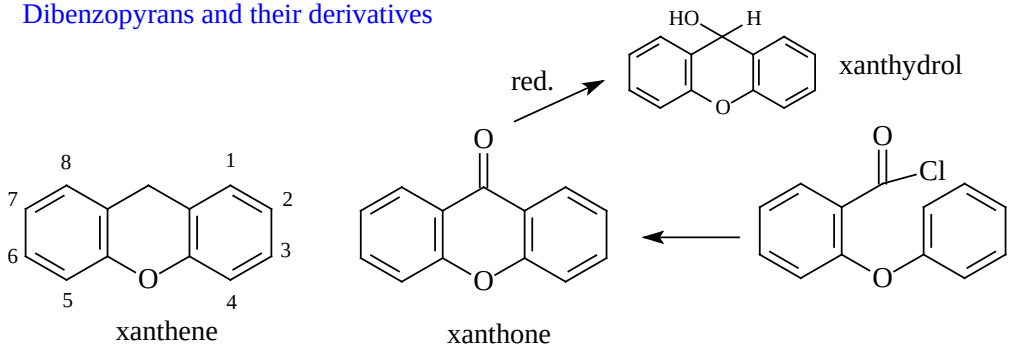


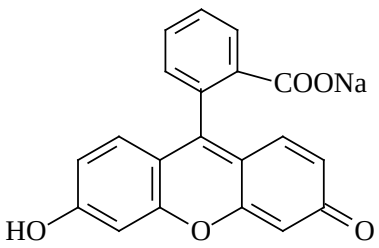


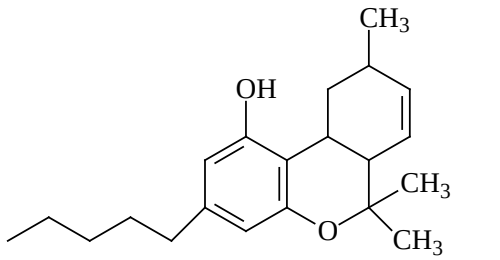
compound II is an anhydrobase, since it contains one water molecule less, than compound I



Dibenzopyrans and their derivatives

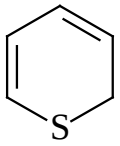




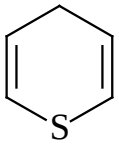


II/ Thiapyran and its derivatives

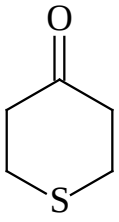
Structure



α-thiapyran

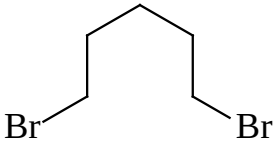


γ-thiapyran

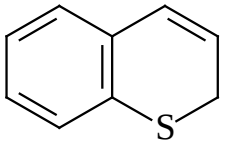


tetrahydrothiapyrone

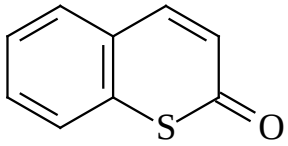
Preparation



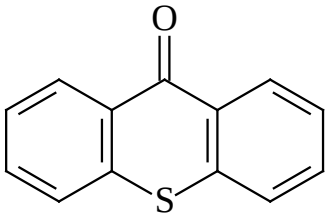
tetrahydrothiapyran



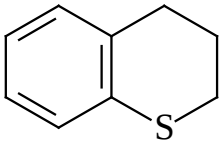
α-thiachromene



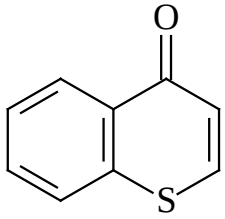
thiacoumarin



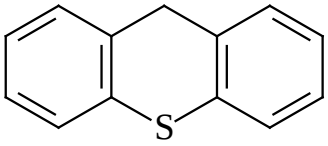
thiaxanthone



thiachroman



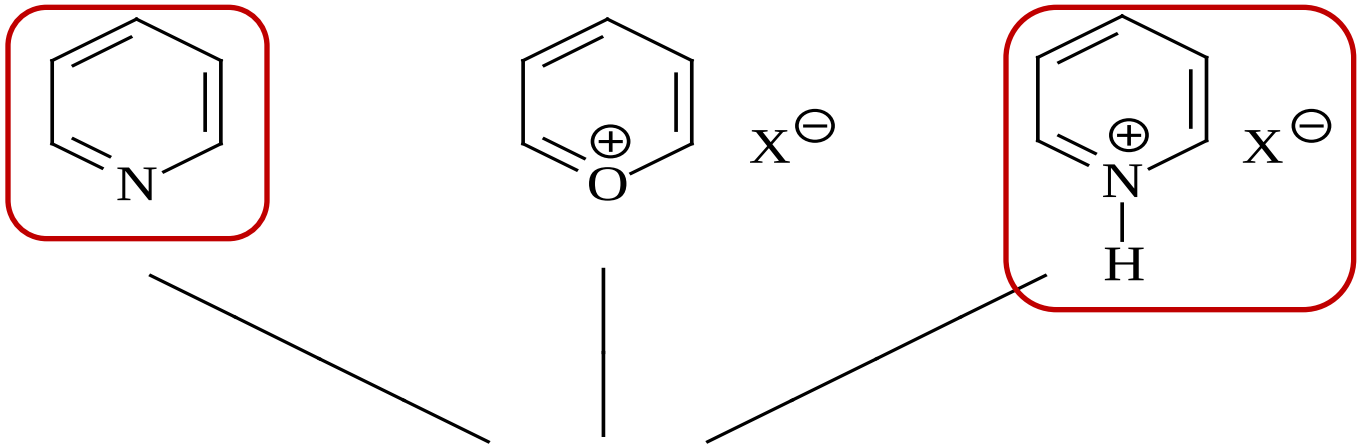
γ-thiachromone



thiaxanthene

III/ Pyridine and its derivatives

Structure



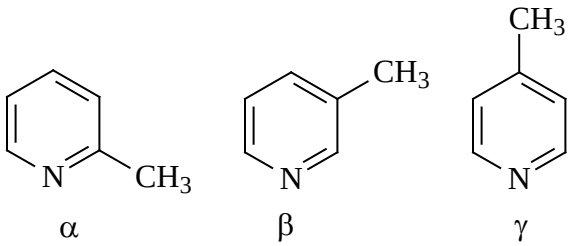
aromatic compounds with π - electron deficiency

Preparations

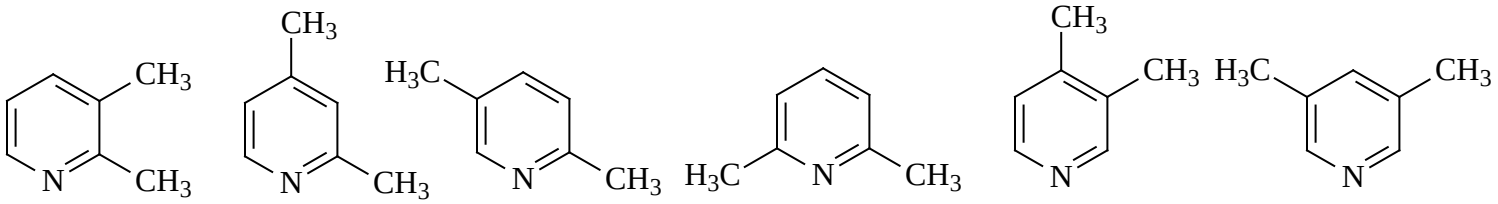
1/ Isolation from coal tar

Homologues of pyridine are isolated from coal tar
Homologues of pyridine with 1 methyl groups are called as picolines
Homologues of pyridine with 2 methyl groups are called as lutidines
Homologues of pyridine with 3 methyl groups are called as collidines
Homologues of pyridine with 4 methyl groups are called as parvolines

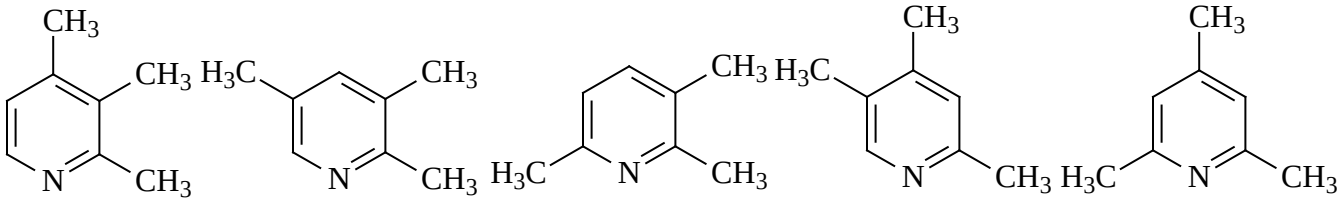
picolines:



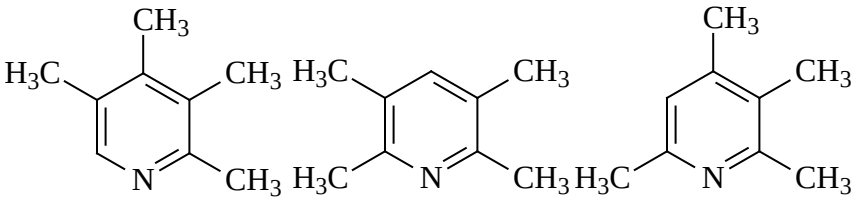
lutidines:



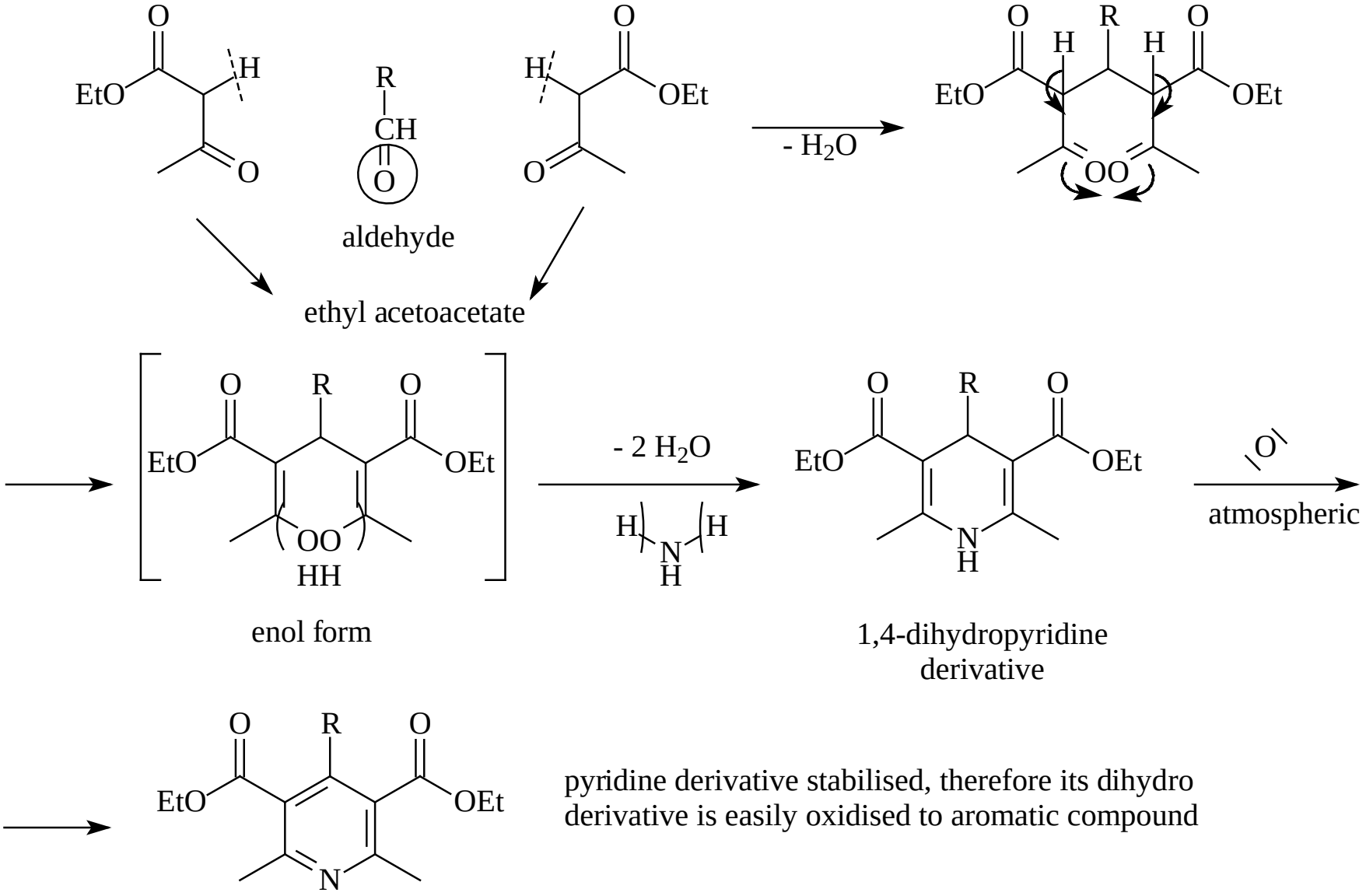
collidines:



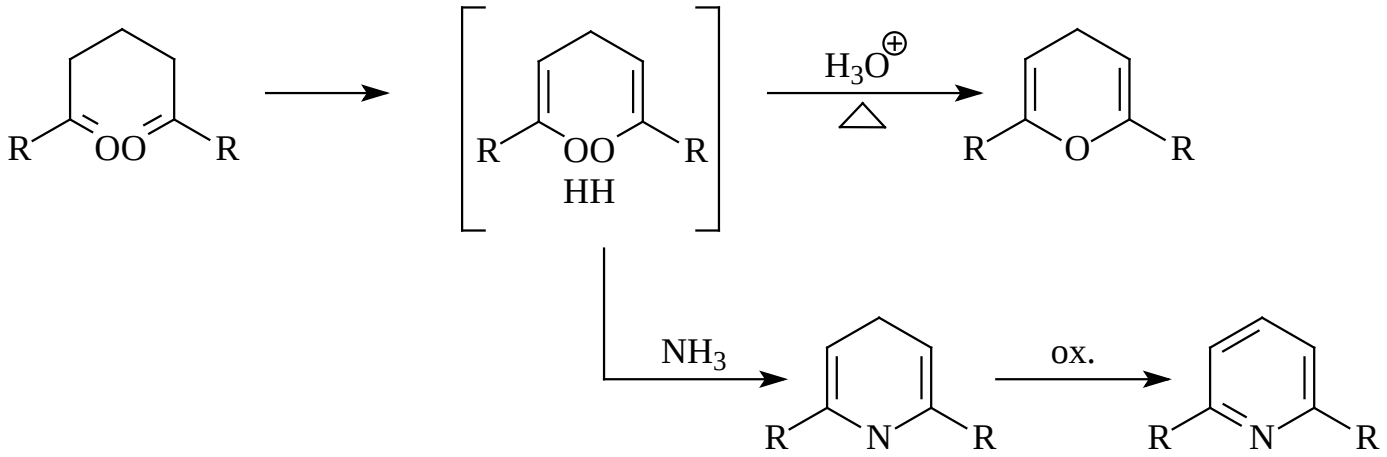
parvolines:



2/ **Hantzsch** synthesis



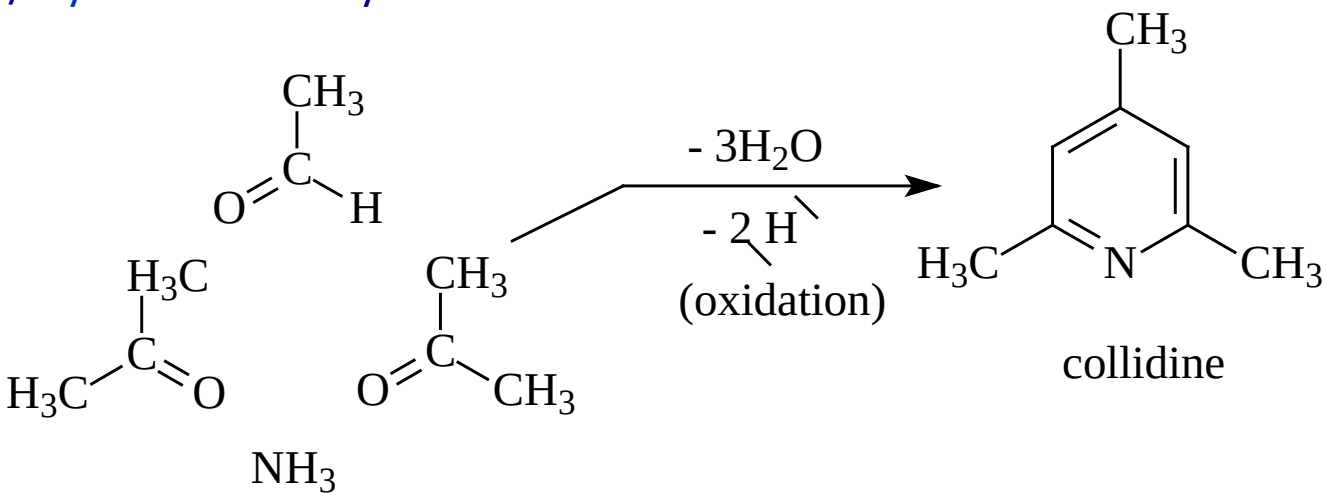
3/ From 1,5-dioxo compounds



4/ By isosteric exchange

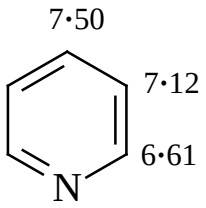
see at pyran and its derivatives

5/ By **Chichibabin** synthesis

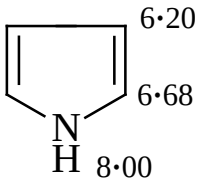


Physical properties

The parent compounds have high solubility in water
Their UV spectra are similar to of benzene.
There are group vibrations in their IR spectra: pyridine counts to monosubstituted benzene, in respect to the fingerprint region of 700-900 cm^{-1}
Their NMR spectra:



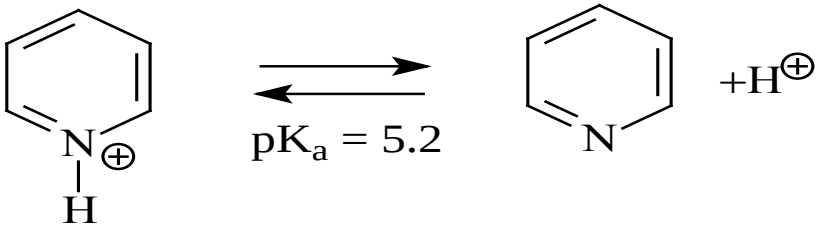
compare to:



Chemical properties

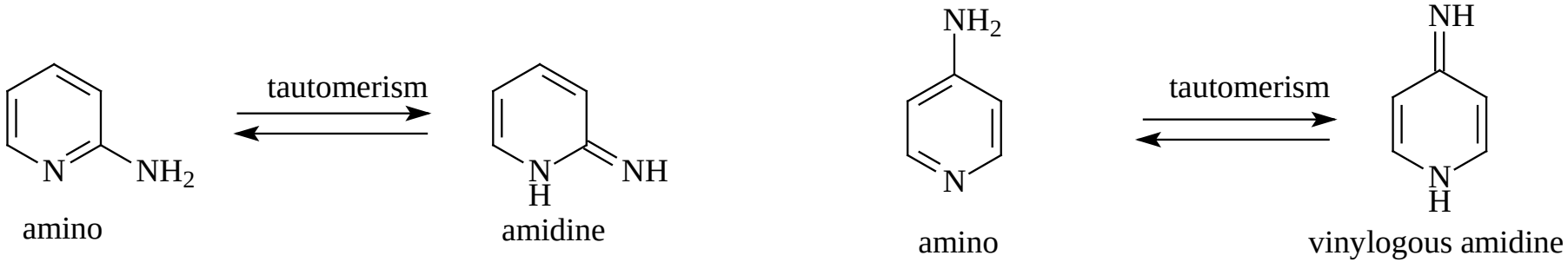
1/ Acid-base properties

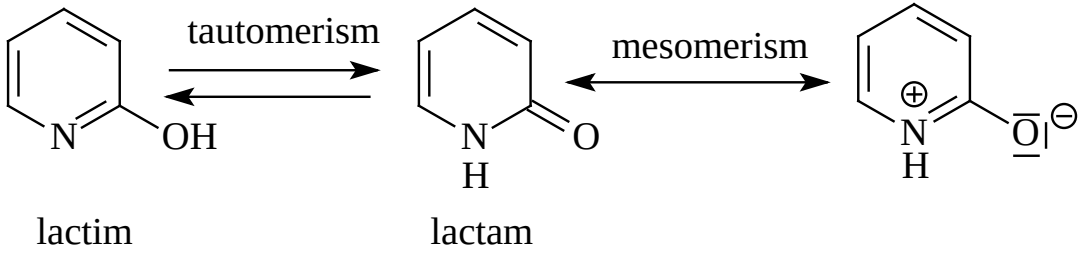
The compounds are stable against acids (salt formation), while are somewhat labile to bases (hydrolysis), except for pyridine. Base sensitivity increases by the number of heteroatoms. Pyridine is of basic property – introduction a second N decreases basicity.

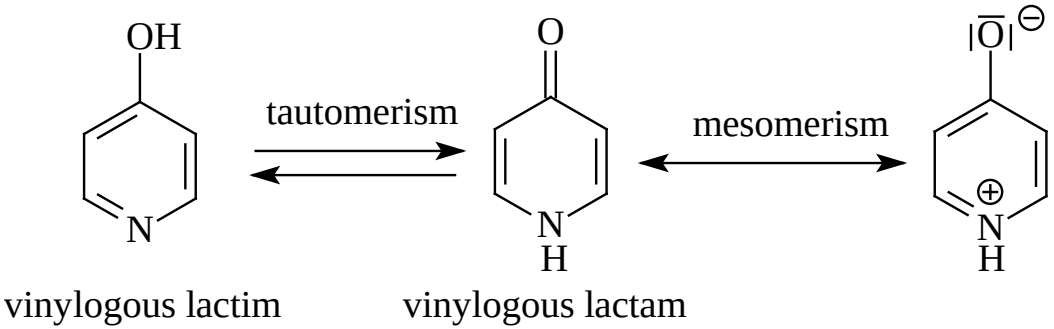


2/ Tautomerism

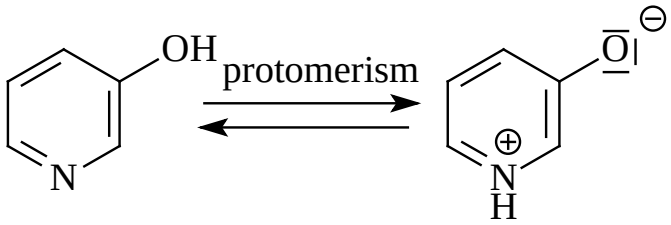
This is function of solvent, of pH, of structure, and of functional group(s)

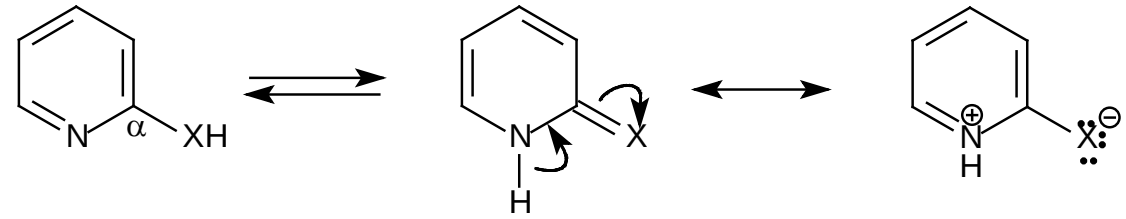


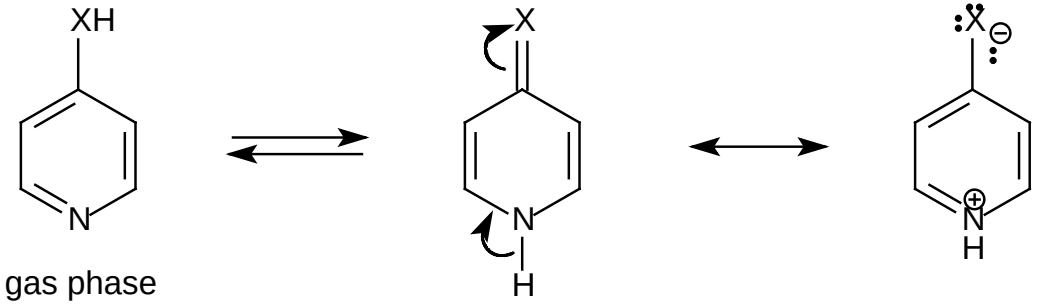




there is no tauto-merism

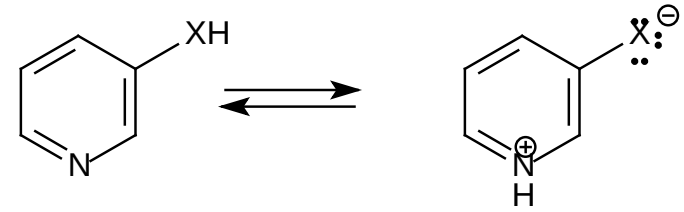






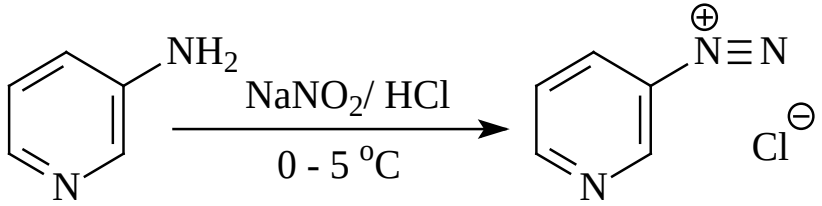
gas phase

in polar solvents



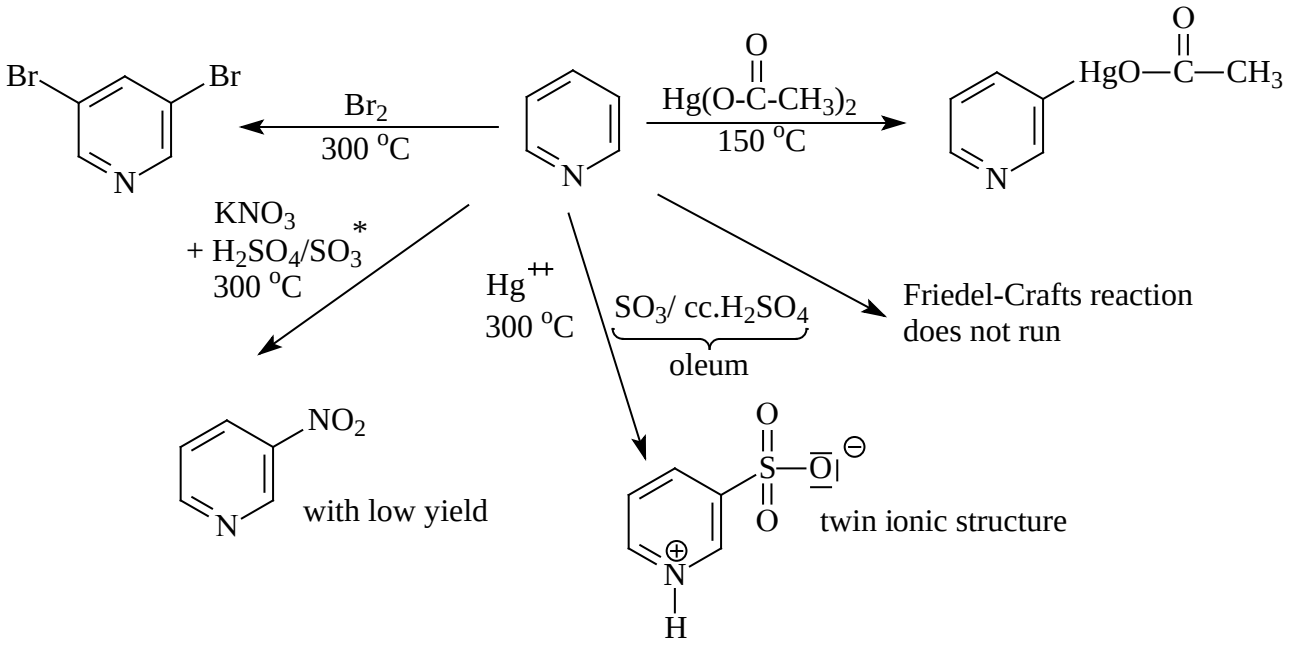
X = O, S, NH

in water only;
50% ratio of it



Diazotization if the amino group is possible, proving that the equilibrium is shifted to the amino form **in highly acidic conditions**. The 2- or 4-diazonium derivatives can be decomposed easily, while the 3-diazonium derivative is stable.

3/ S_EAr reactions It takes place with difficulties, and into β position only



* Sulfur trioxide absorbs the water generated in the reaction. KNO_3 is less volatile, than HNO_3. HNO_3 is generated in the reaction mixture.

Pyridinium ion withdraw electrons from ring carbons even more.

Pyridine reacts in S_EAr reactions with difficulties due to two reasons:

a) electron density is decreased in α- or in γ-positions especially, the least in β-position

b) Protonation of the N atom (NH^+) increases electronegativity of N, thus withdrawing electrons from the ring carbons even more.

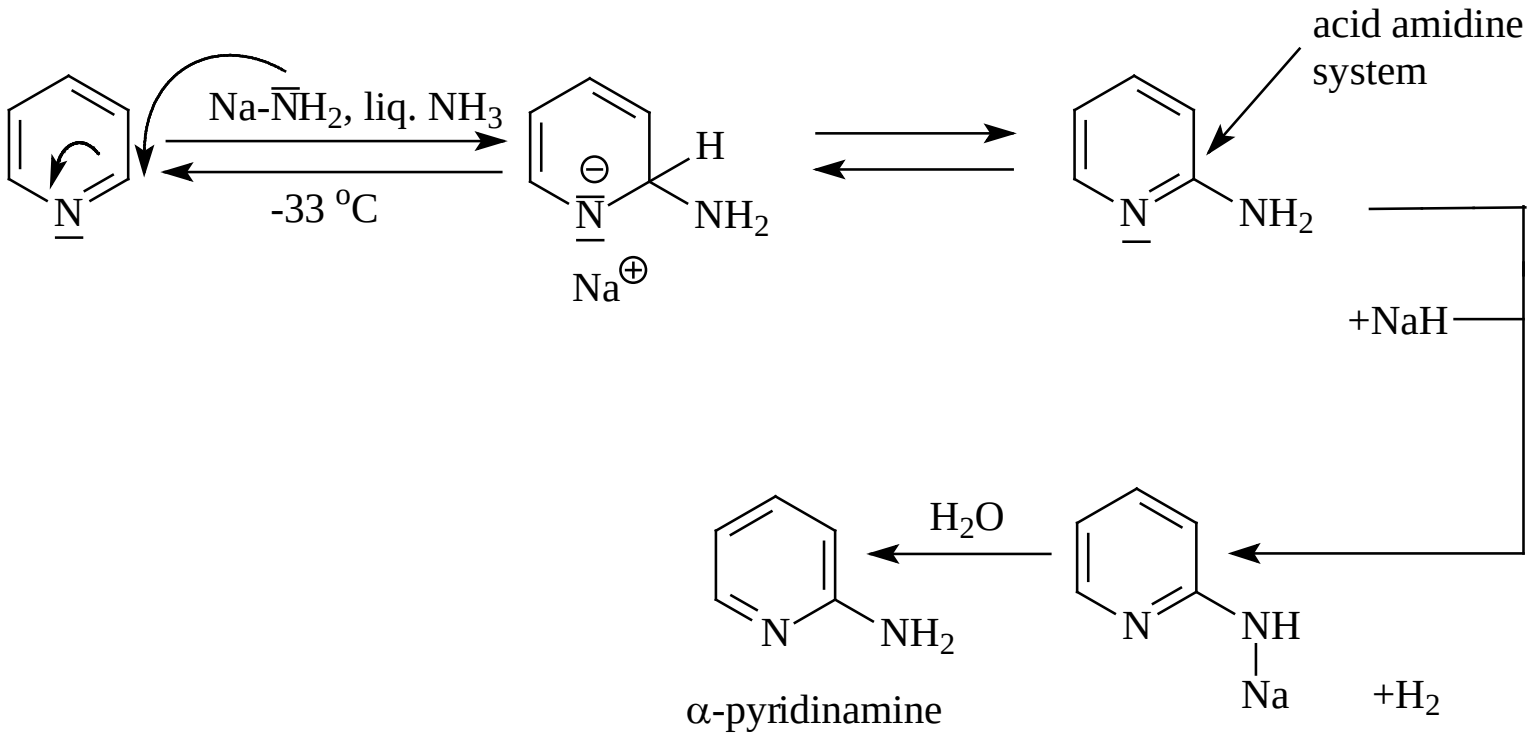
4/ S_NAr reactions

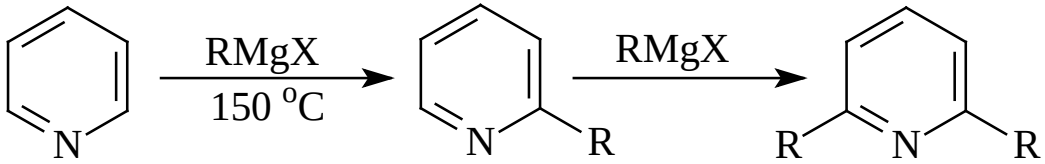
It takes place in α- and γ-positions mainly due to the lower electron density in these positions

NaH is deprotonating the amidine NH_2, resulting in H_2.

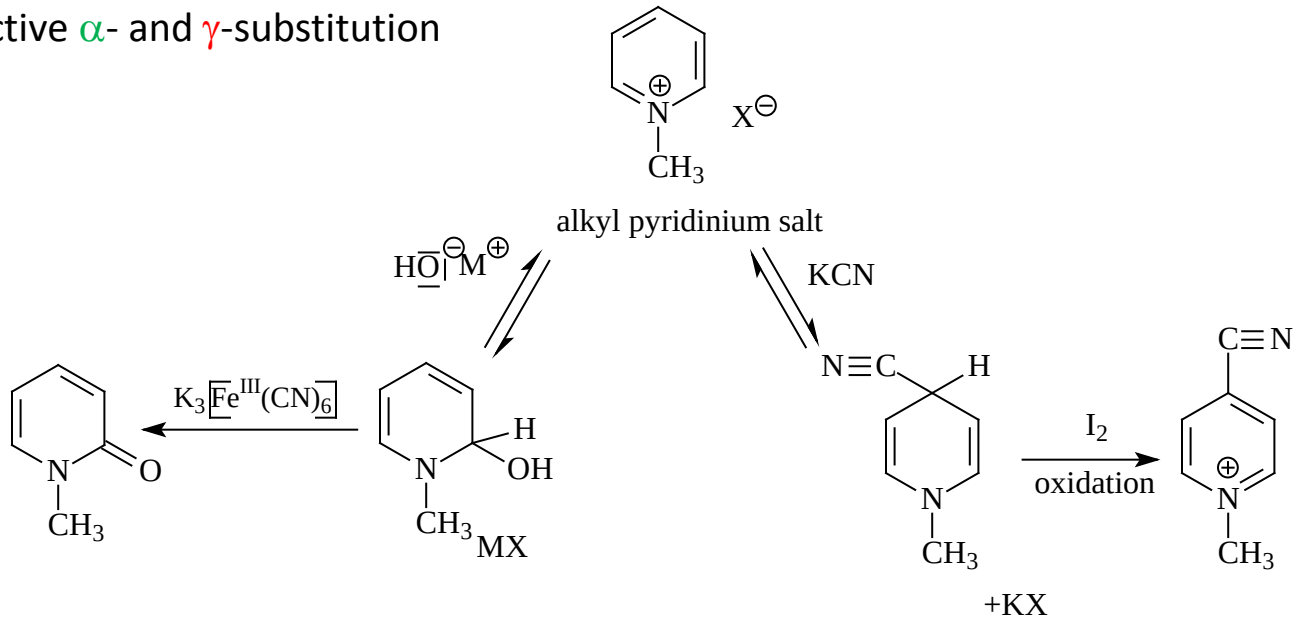
The reaction becomes irreversible, since H^- is the leaving group, and it reacts with the proton source NaH.

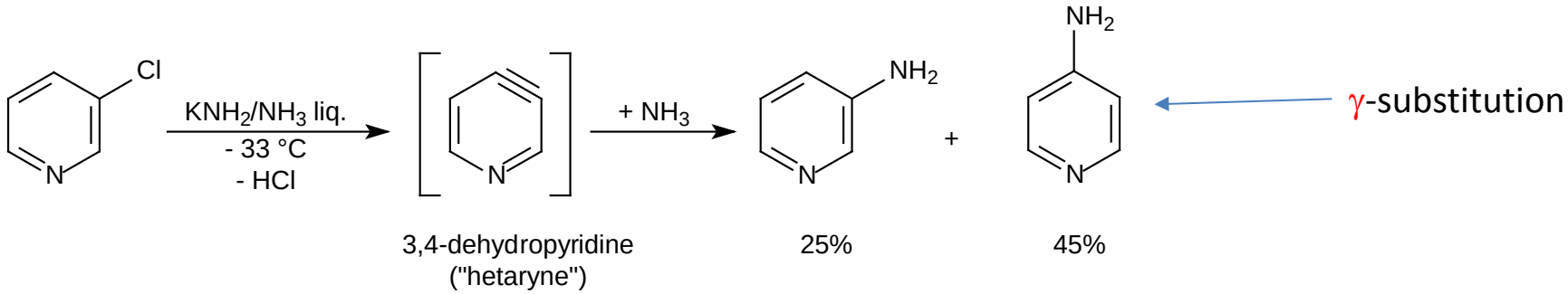
α-substitution:

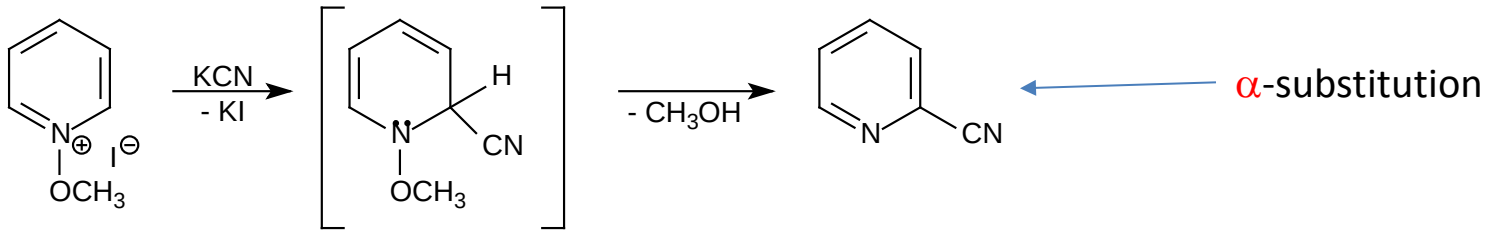




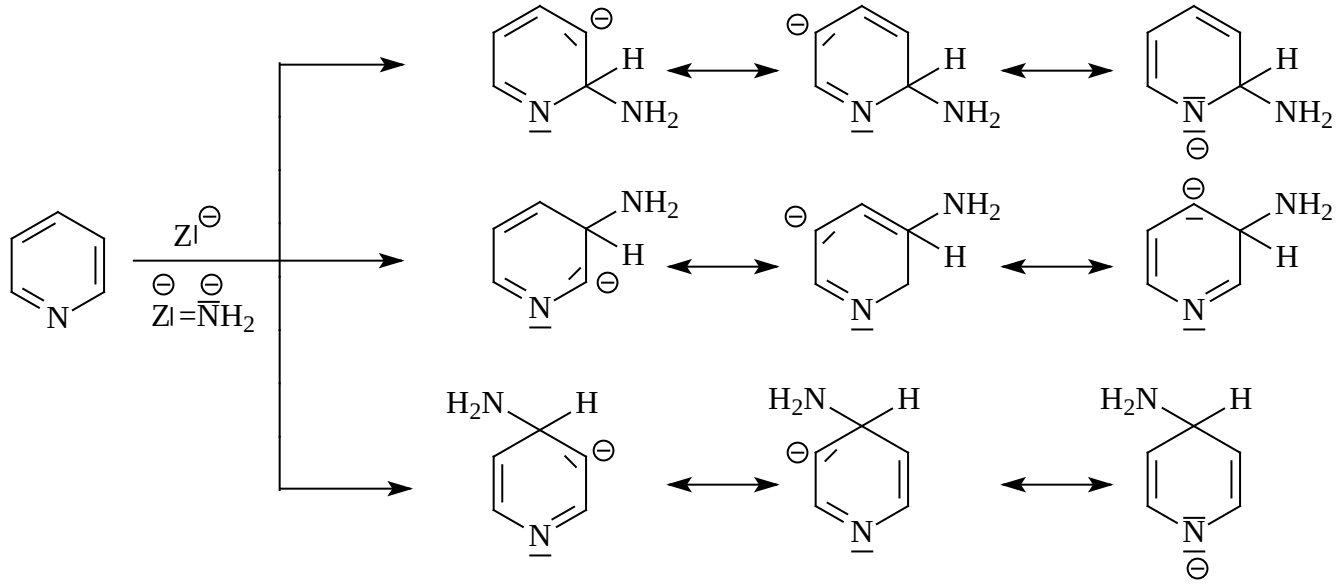
Regioselective α- and γ-substitution



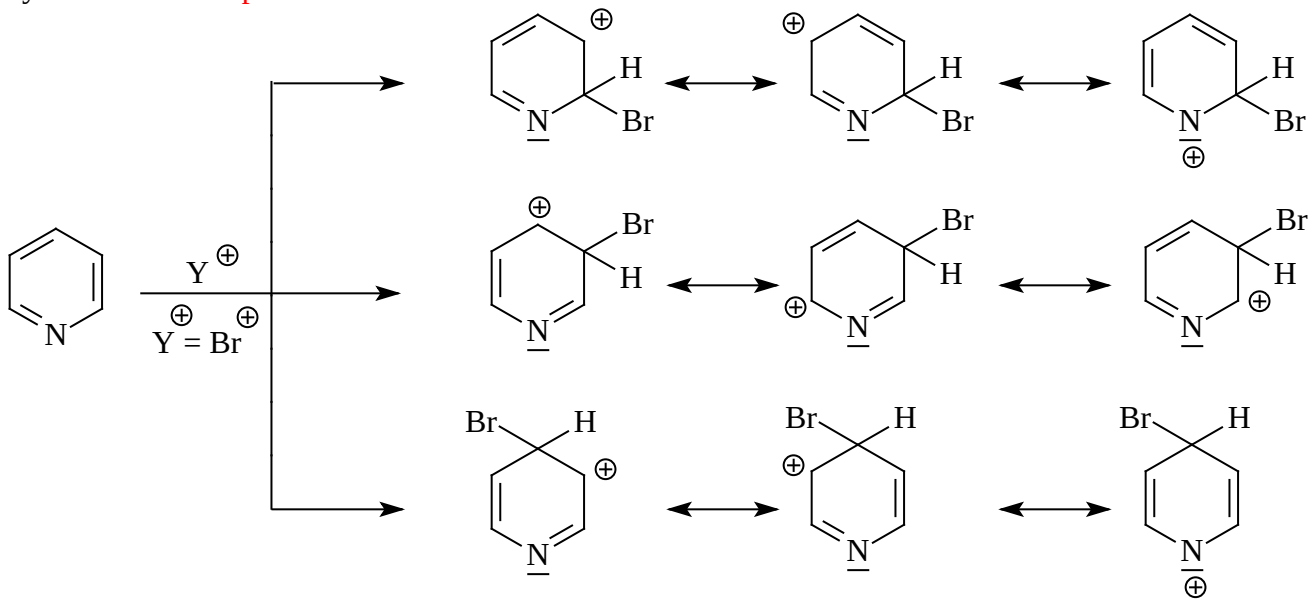




Pyridine in nucleophilic reactions



Pyridine in electrophilic reactions



In ground state

There are lower electron densities in α- and γ-positions

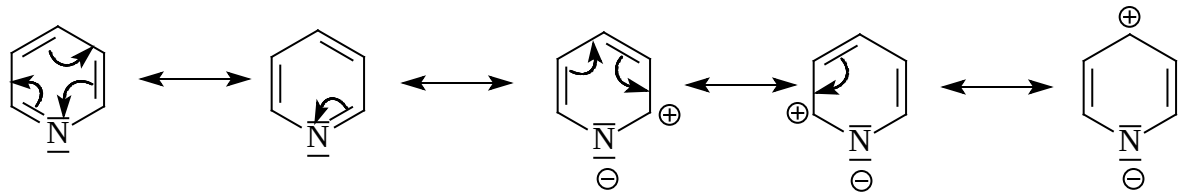
In nucleophilic reactions

The ring N causes –Iα>-Iγ, the β carbon does not react. The negative charge in the intermediate can appear on the N, as well.

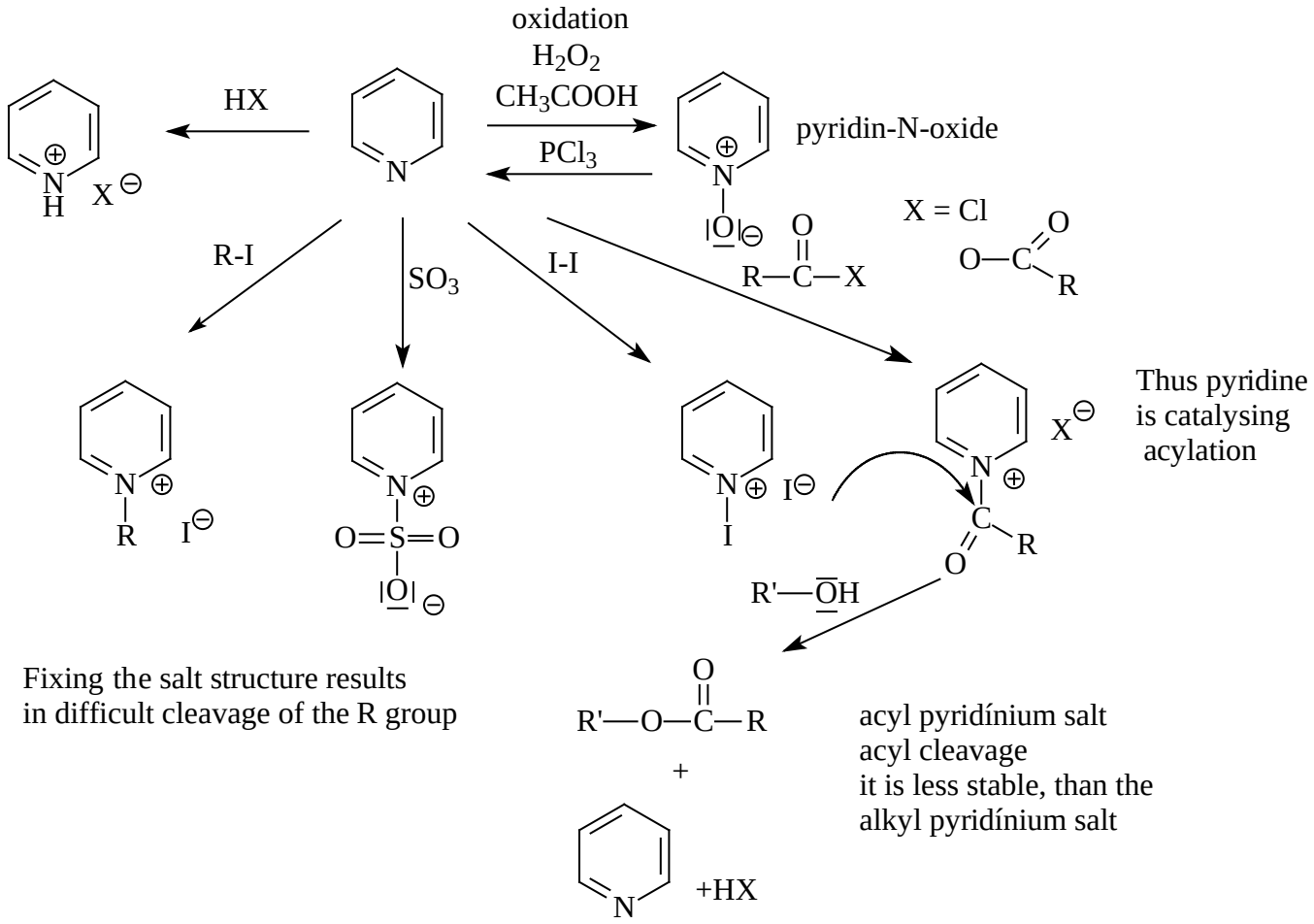
In electrophilic reactions

The relatively highest electron density is found on the β ring carbon, since there is no positive charge on the N, and moreover, there is no positive charge in any mesomers if β-substitution takes place.

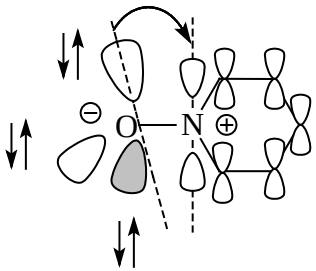
Pyridine in ground state



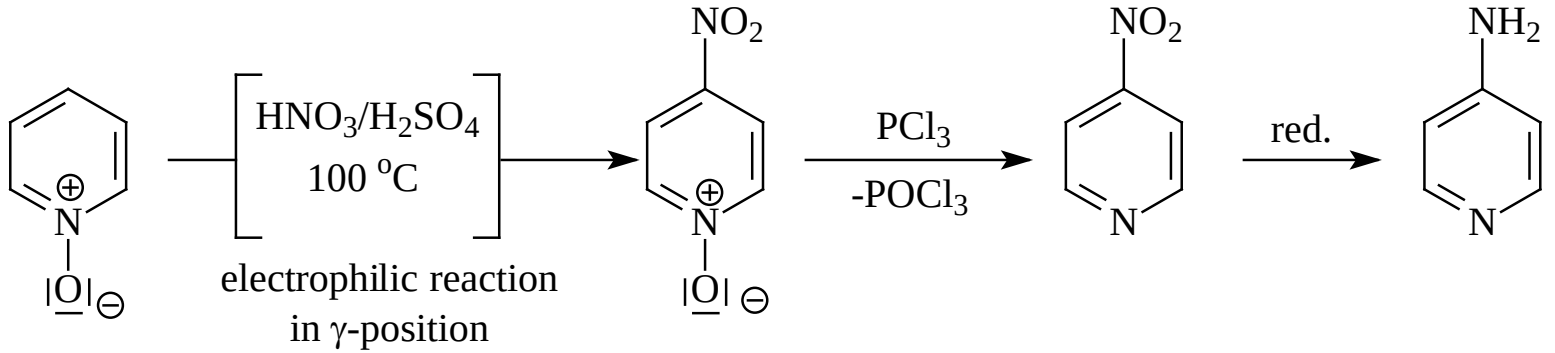
5/ Reactions at a lone pair of electrons



Reactions of pyridin-N-oxide

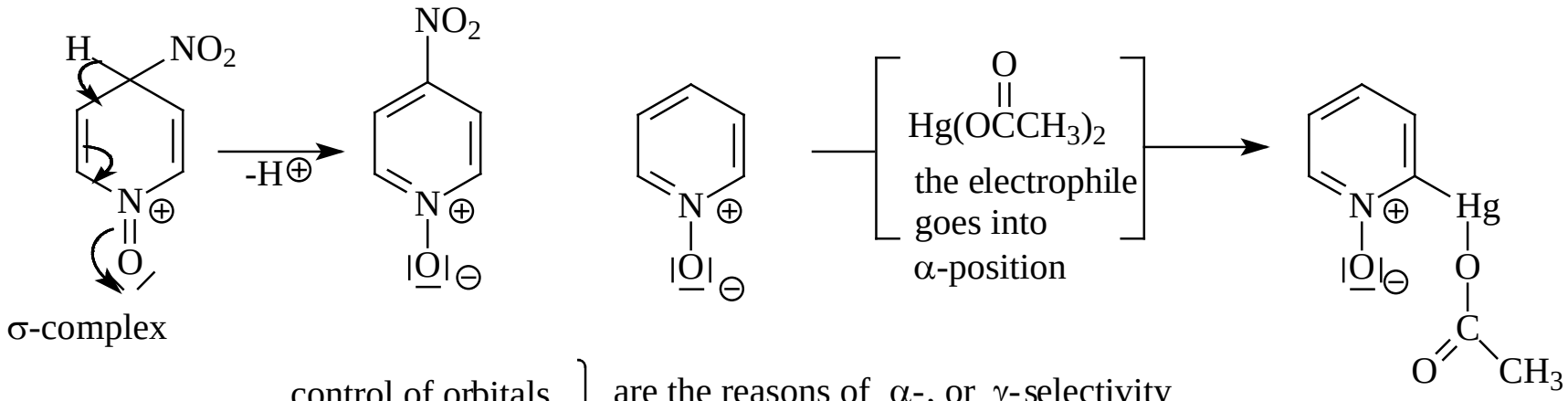


One of the nonbonding orbitals of oxygen can be coplanar (in the same plane) to the combining p AO-s of the ring atom. Thus, the +M effect of the oxygen is overcompensating the -I effect of the nitrogen, resulting in electron richness in α- és γ- positions of the ring. One electron is excited to the LUMO orbital. Size of delocalisation is increased.

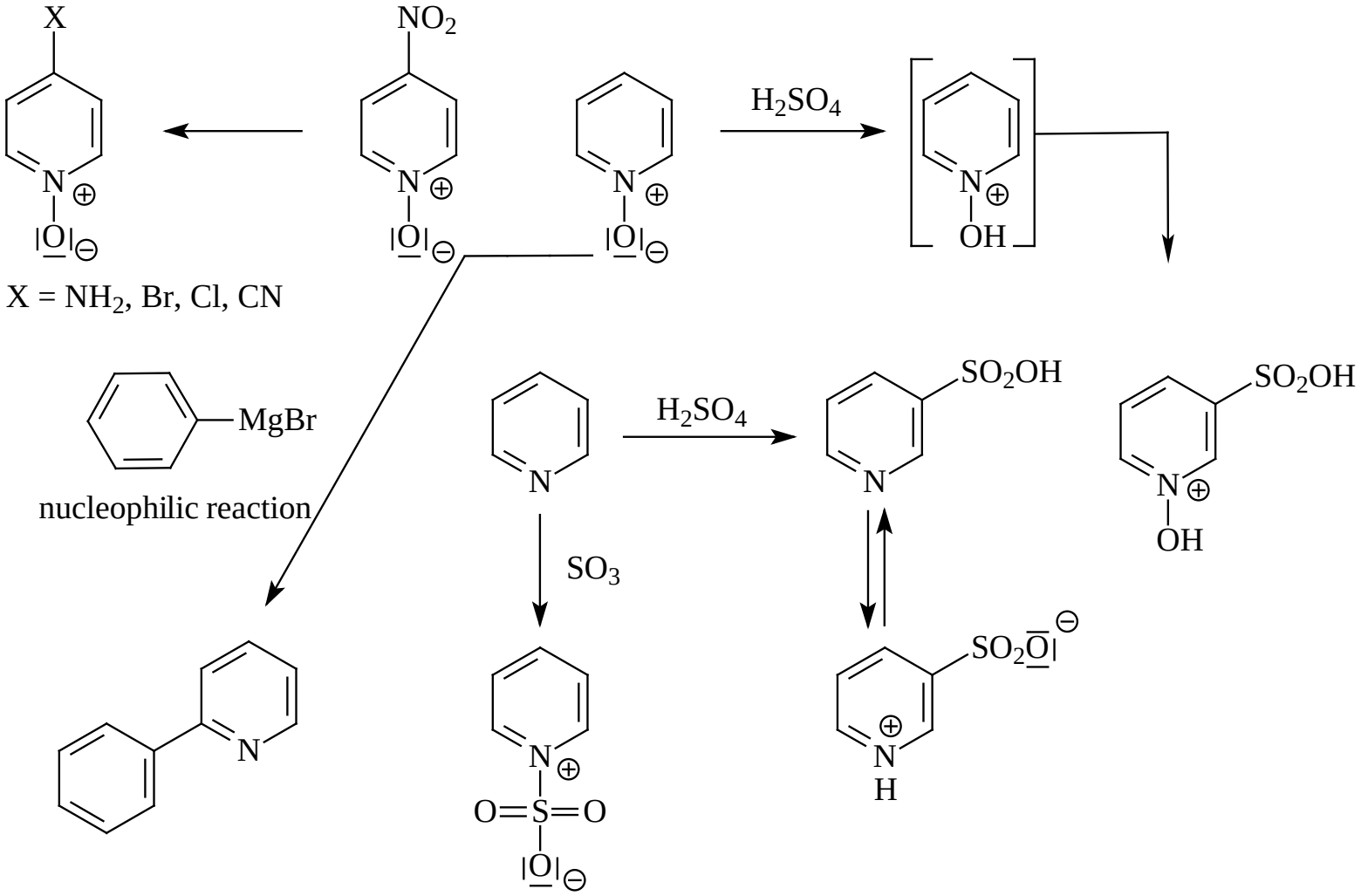


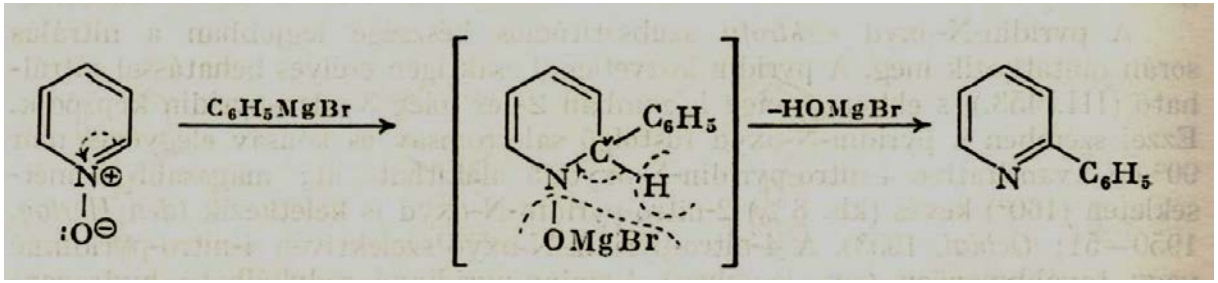
Not at 300 ^{o}C-on, like for pyridine

$\triangle$t = 200 ^{o}C ⟶ the difference in reactivities is 10^{8} times



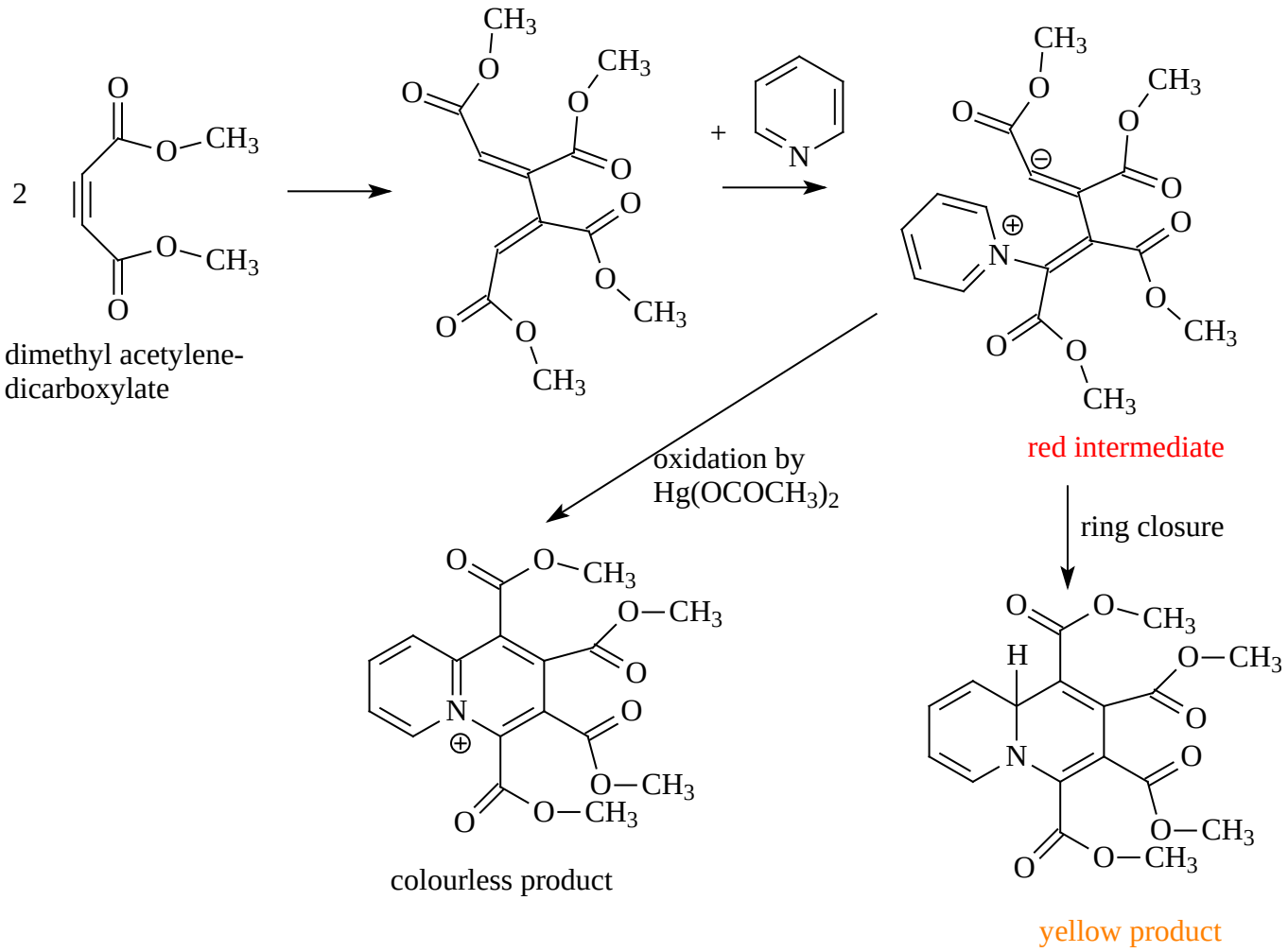
control of orbitals
control of charges
} are the reasons of α-, or γ-selectivity


X
NO2
H2SO4
OH
X = NH2, Br, Cl, CN
MgBr
nucleophilic reaction
SO2OH
SO3
SO2OH
OH
SO2O
H
O=S=O

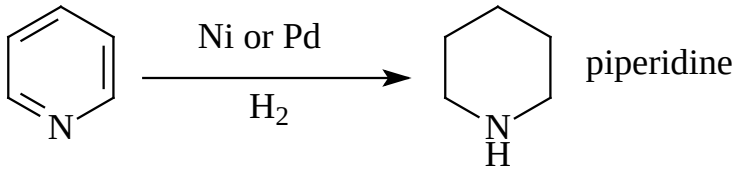

C6H5MgBr
C6H5
C
H
OMgBr
–HOMgBr
C6H5

6/ Addition reactions

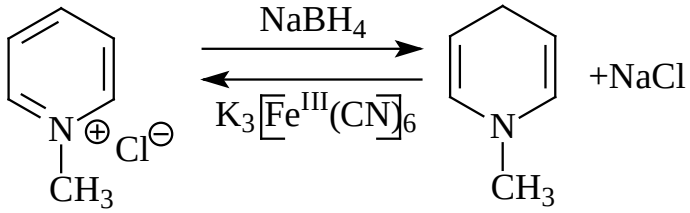
The Diels-Alder reaction has a very complex mechanism with pyridine, the reaction is not concerted (asynchronous) and the final product is formed by aromatic stabilization of the previous, coloured intermediate.

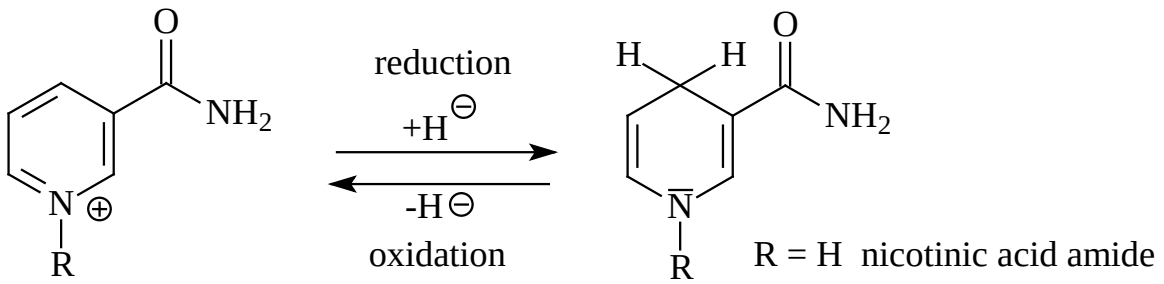


7/ Reduction



Reduction is the easiest, if the compound has strong electron absence.





This system can be reduced even more easily, since it has stronger electron absence ⟶ reduction takes place in α- or in γ-positions

It is a biochemical H-transfer agent, main ingredient of coenzymes NAD, NADH

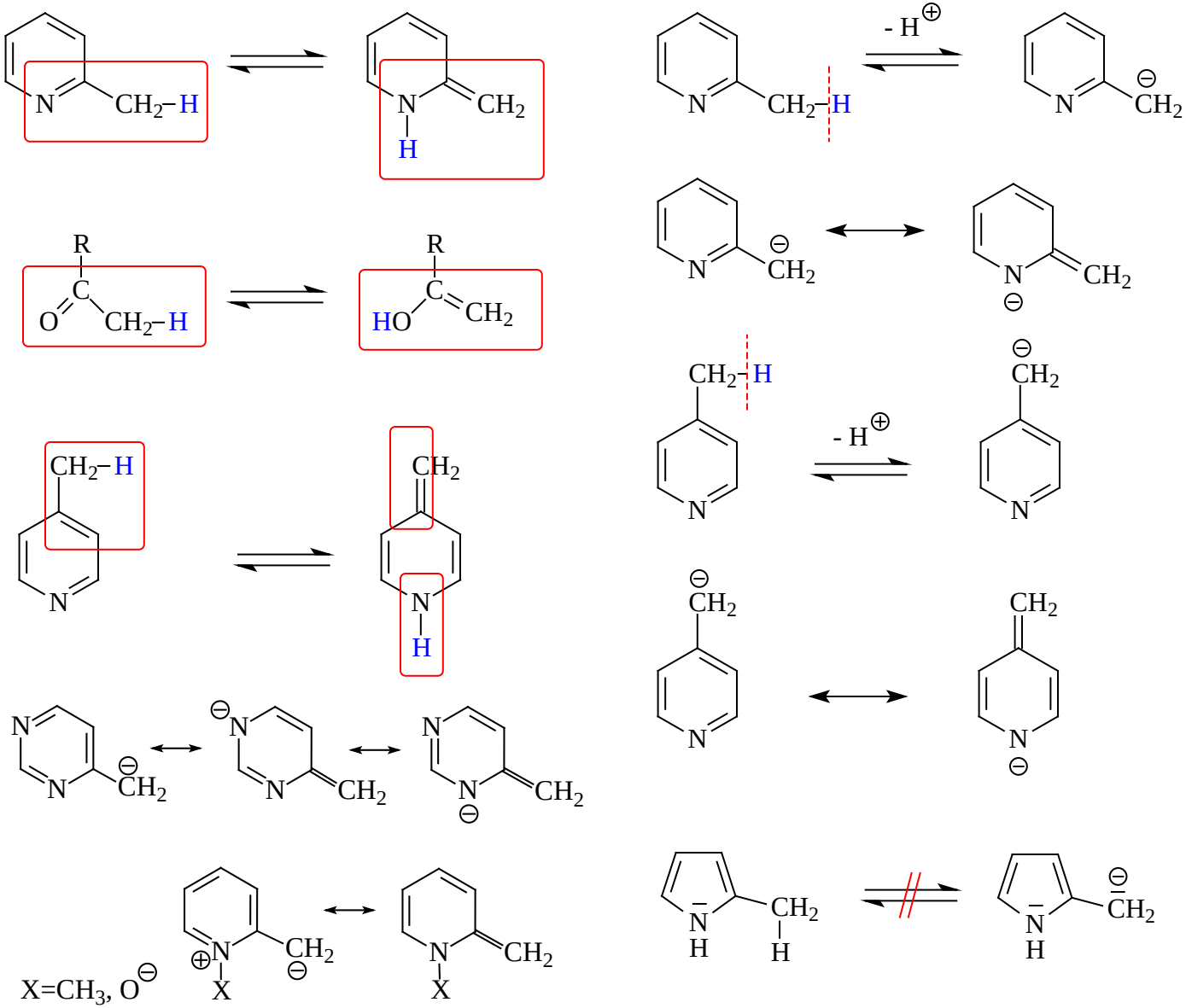
8/ Oxidation

The stronger the electron absence, the more difficult is the oxidation.
There is no ring opening for pyridine by oxidation.
Formation of N-oxide is possible from pyridine.

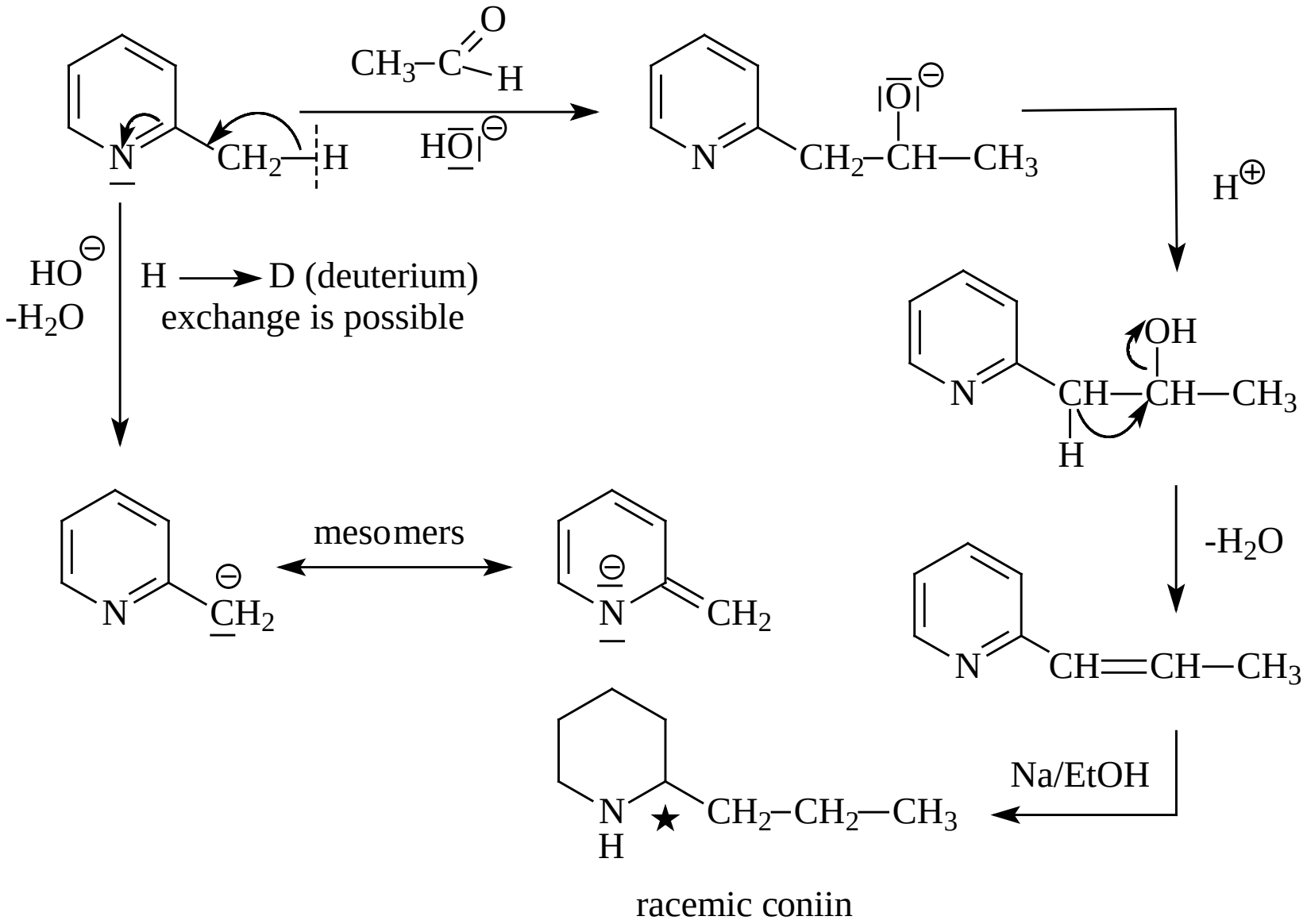
9/ Polymerisation

It does not run, in the contrary of five-membered heterocycles.

There is active H at α- and γ-methyl groups
for heterocycles with π-electron deficiency

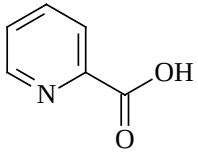


10/ Reactions of the active C-H group

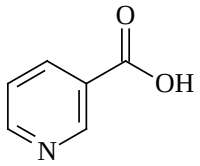


More important derivatives

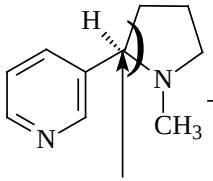
nicotine: the very poisonous alkaloid of tobacco (Nicotiana tabacum)



2-picolinic acid

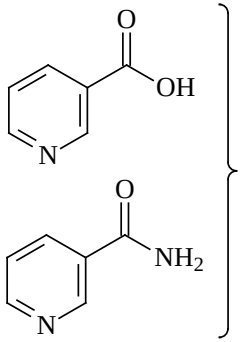


nicotinic acid

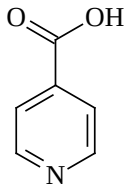


it is oxidised at this carbon

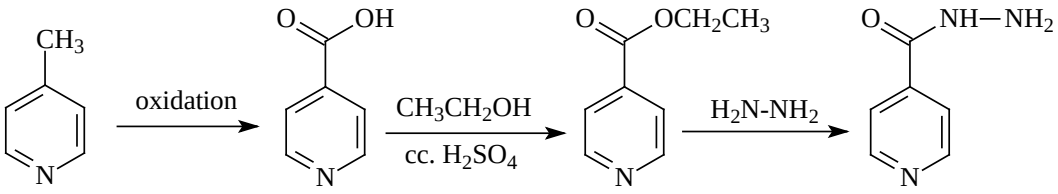
cc. HNO_3



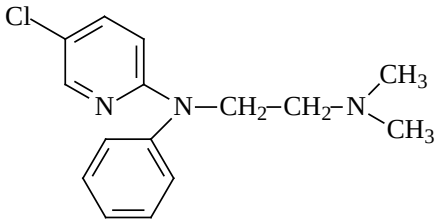
coenzyme complex belonging to the vitamin B group



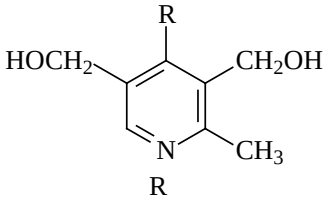
isonicotinic acid



isonicotinic acid hydrazide, INH
first drug of tuberculosis, 1952



chloropyramine (Synopen)
an antihistaminic drug

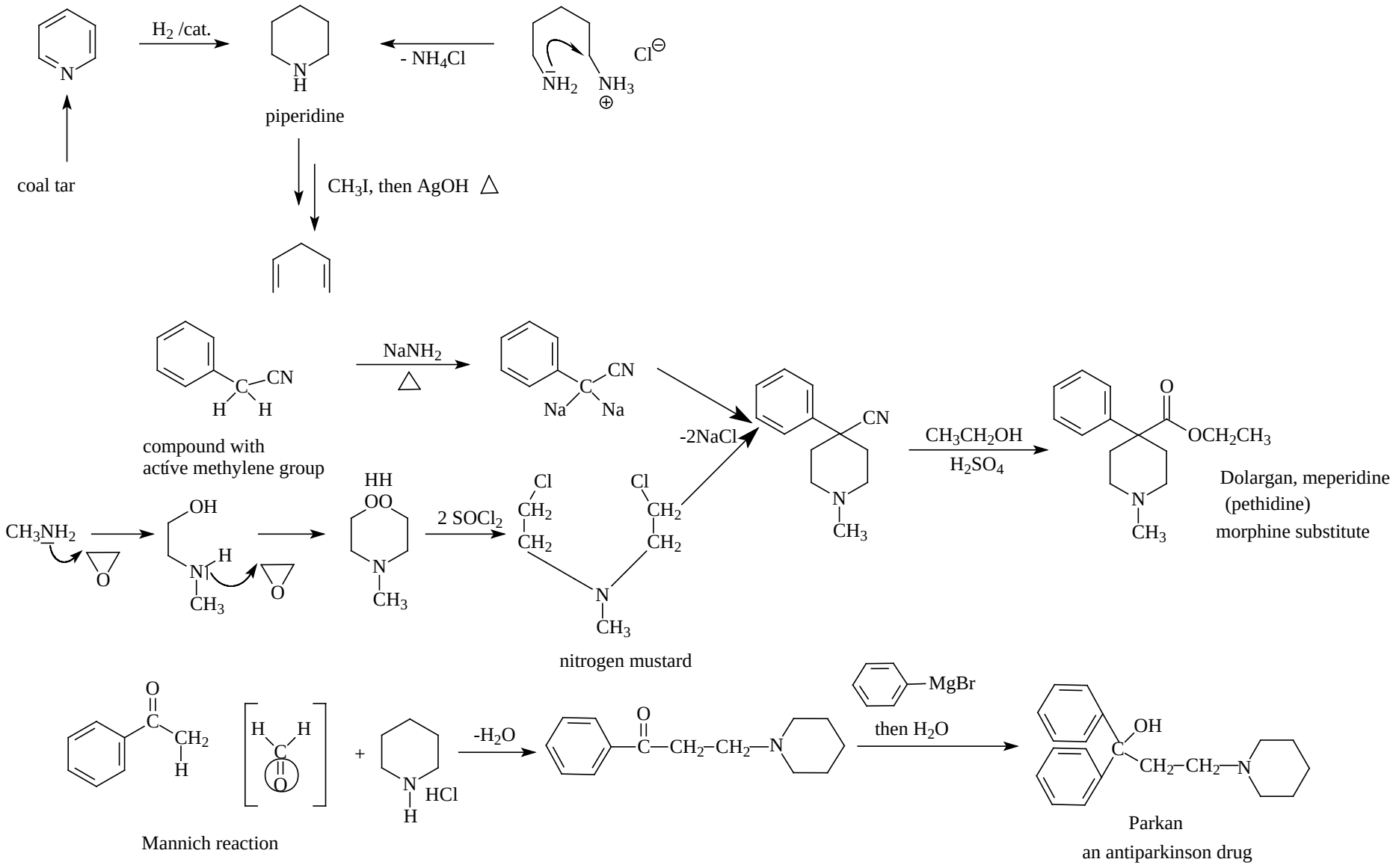


pyridoxine -CH_2OH
(pyridoxol vitamin B_6)

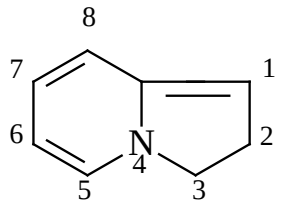
pyridoxal —C(=O)H

pyridoxamine —CH_2–NH_2

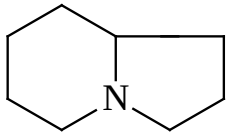
their phosphate ester is used in coenzymes of transaminating and of redoxy reactions


H2 /cat.
- NH4Cl
Cl⊖
piperidine
coal tar
CH3I, then AgOH △
NaNH2
△
compound with
actíve methylene group
-2NaCl
CH3CH2OH
H2SO4
Dolargan, meperidine
(pethidine)
morphine substitute
CH3NH2
2 SOCl2
nitrogen mustard
-H2O
MgBr
then H2O
Mannich reaction
Parkan
an antiparkinson drug

Indolizine, indolizidine

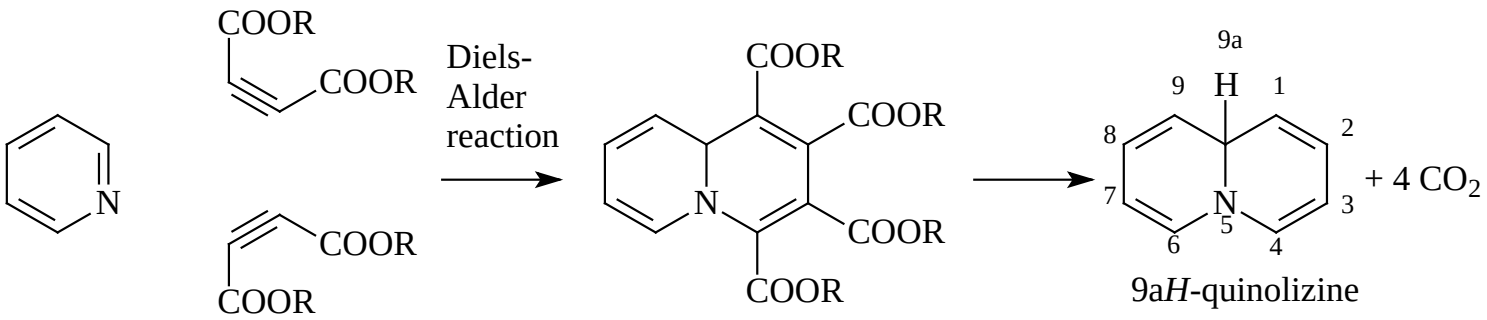


indolizine



indolizidine
(in alkaloids)

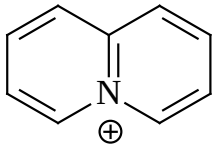
Quinolizine, quinolizidine



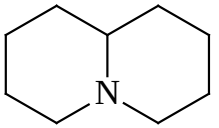
dialkyl acetylenedicarboxylate

9a*H*-quinolizine

H_2

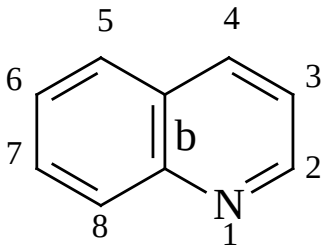


quinolizinium salt

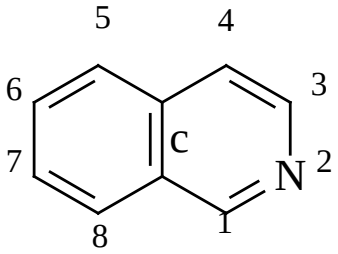


quinolizidine
(in alkaloids)

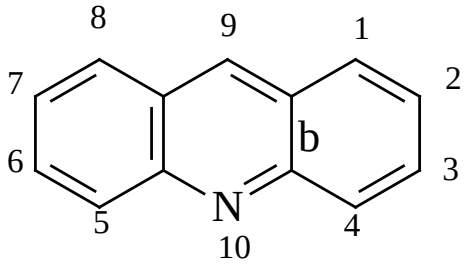
The benzocondensed derivatives of pyridine



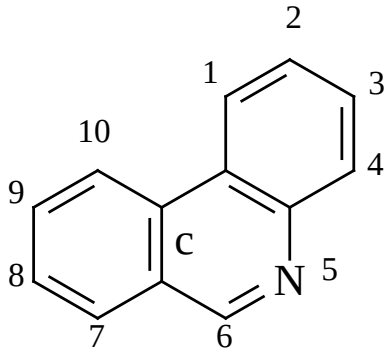
quinoline
benzo[*b*]pyridine



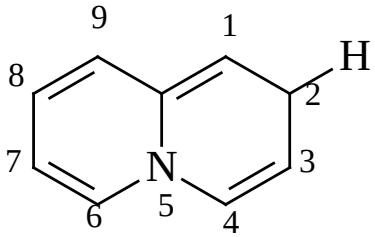
isoquinoline
benzo[*c*]pyridine



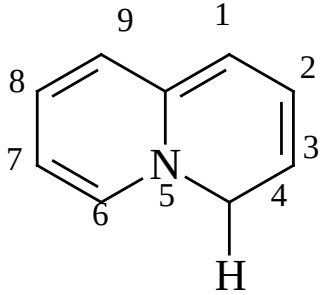
acridine
benzo[*b*]quinoline



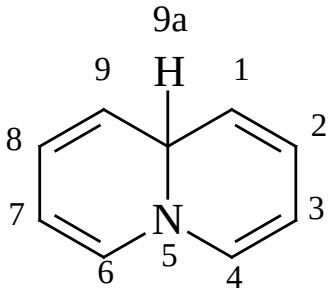
phenanthridine
benzo[*c*]quinoline



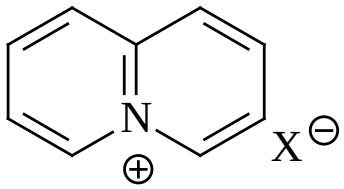
2*H*-quinolizine



4*H*-quinolizine



9a*H*-quinolizine

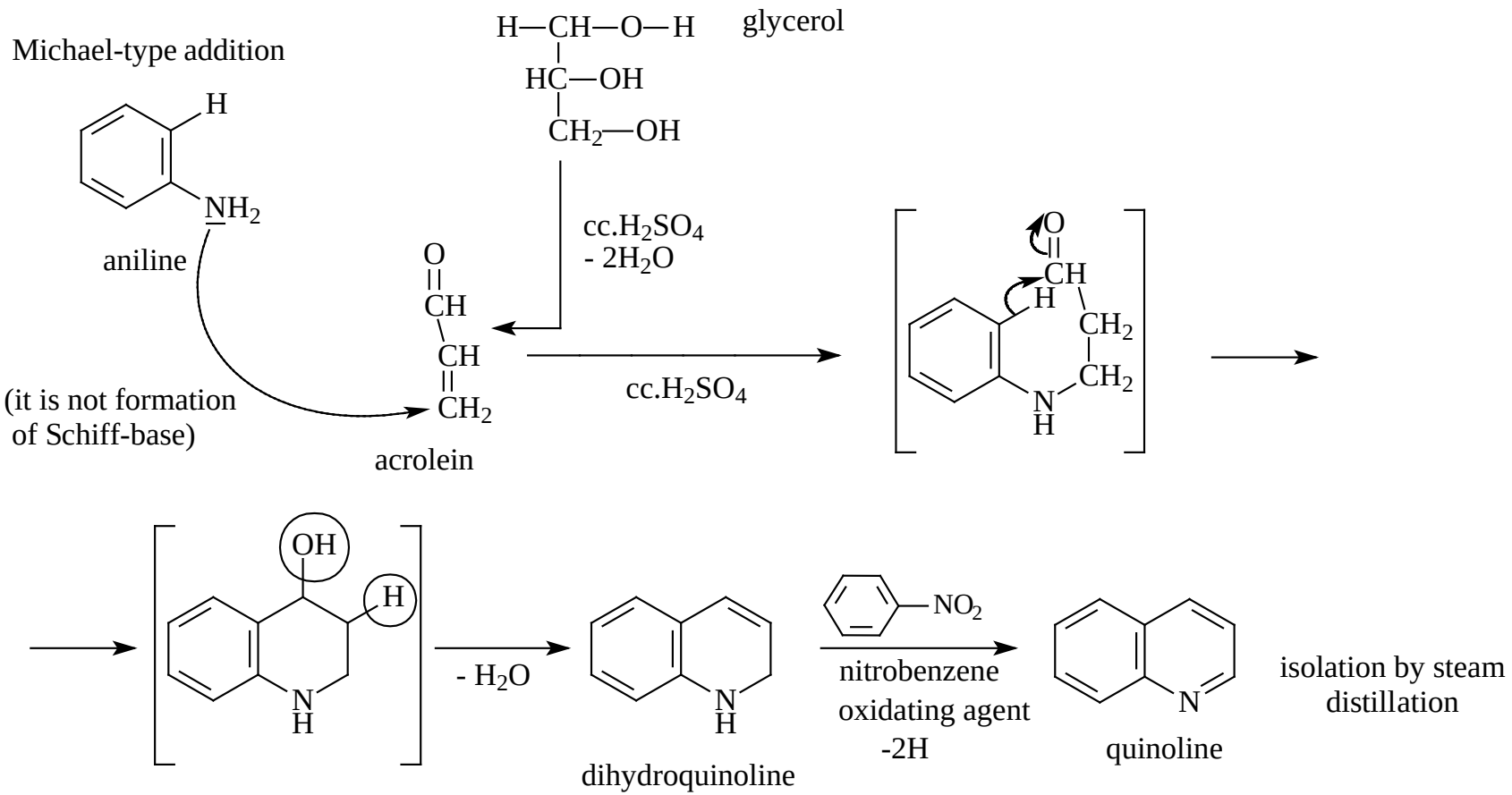


dehydroquinolizinium salt

Quinoline

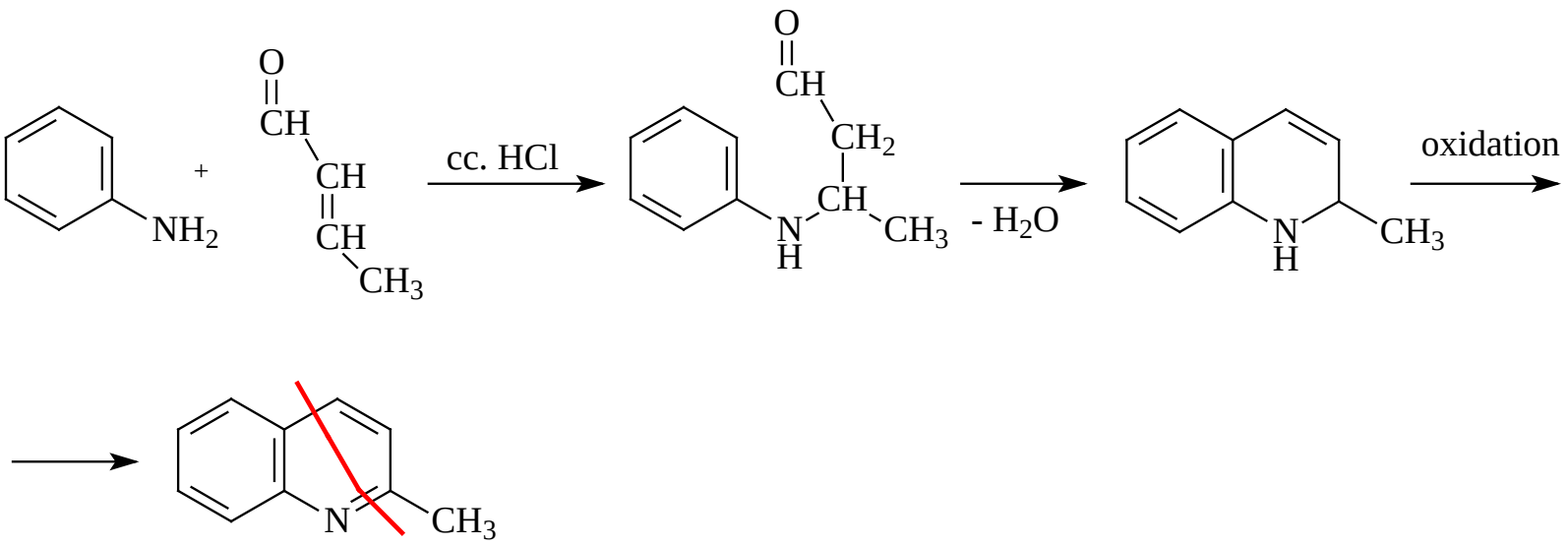
Preparations

1/ By **Skraup** synthesis



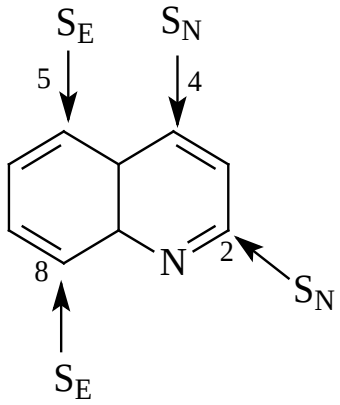
isolation of quinoline may take place from coal tar

2/ By **Döbner-Müller** process



Chemical properties

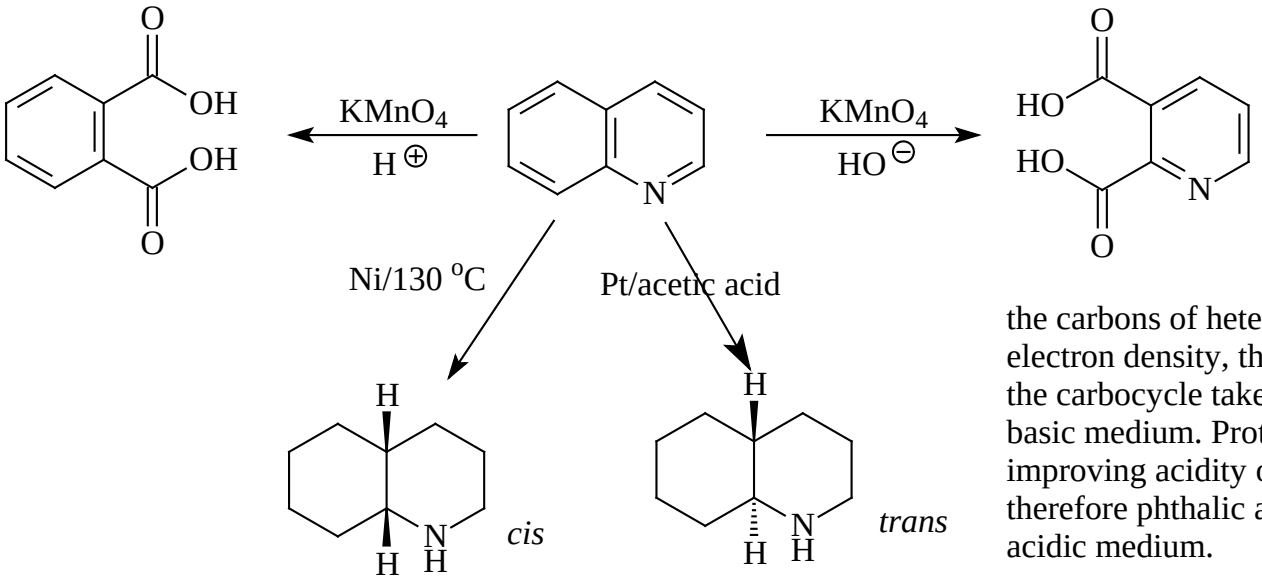
These are similar to of pyridine:
S_E reaction takes place at the carbocycle, in position 5, or 8
S_N reaction takes place at the heterocycle, in position 2, or 4



bromination
nitration
sulfonation
S_E Ar

1/ Oxidation

oxidation: the carbocycle is oxidized in basic medium, while the heterocycle is oxidized in acidic medium

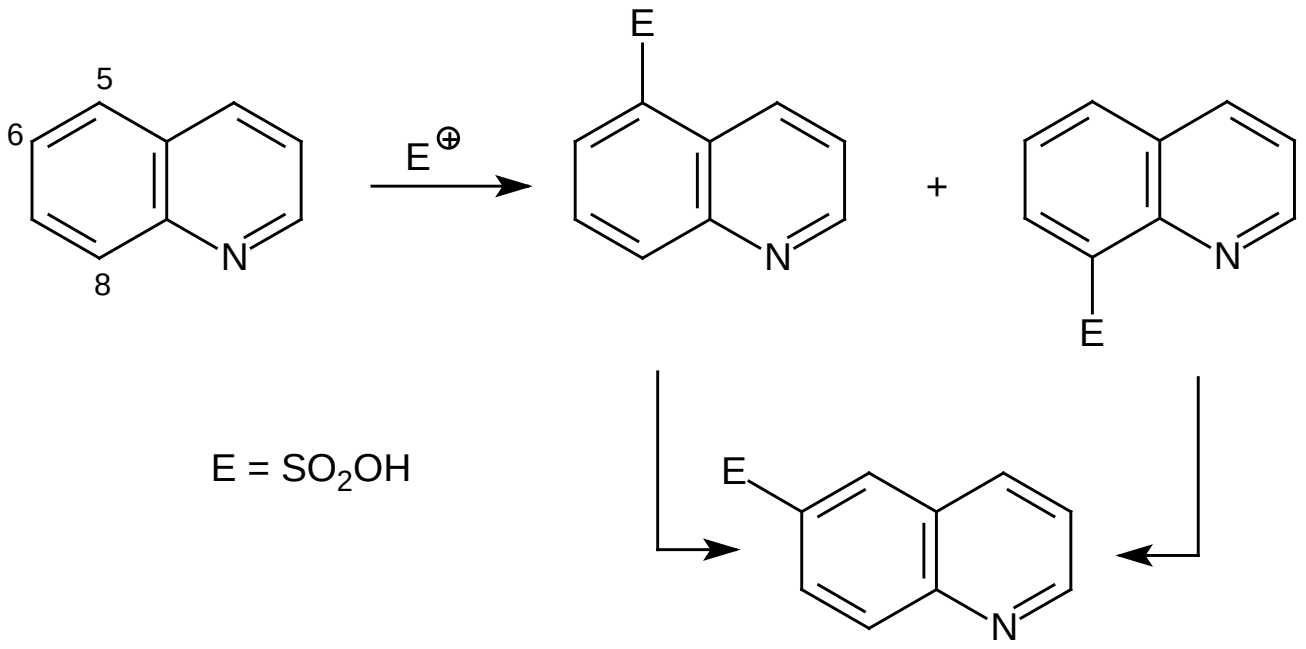


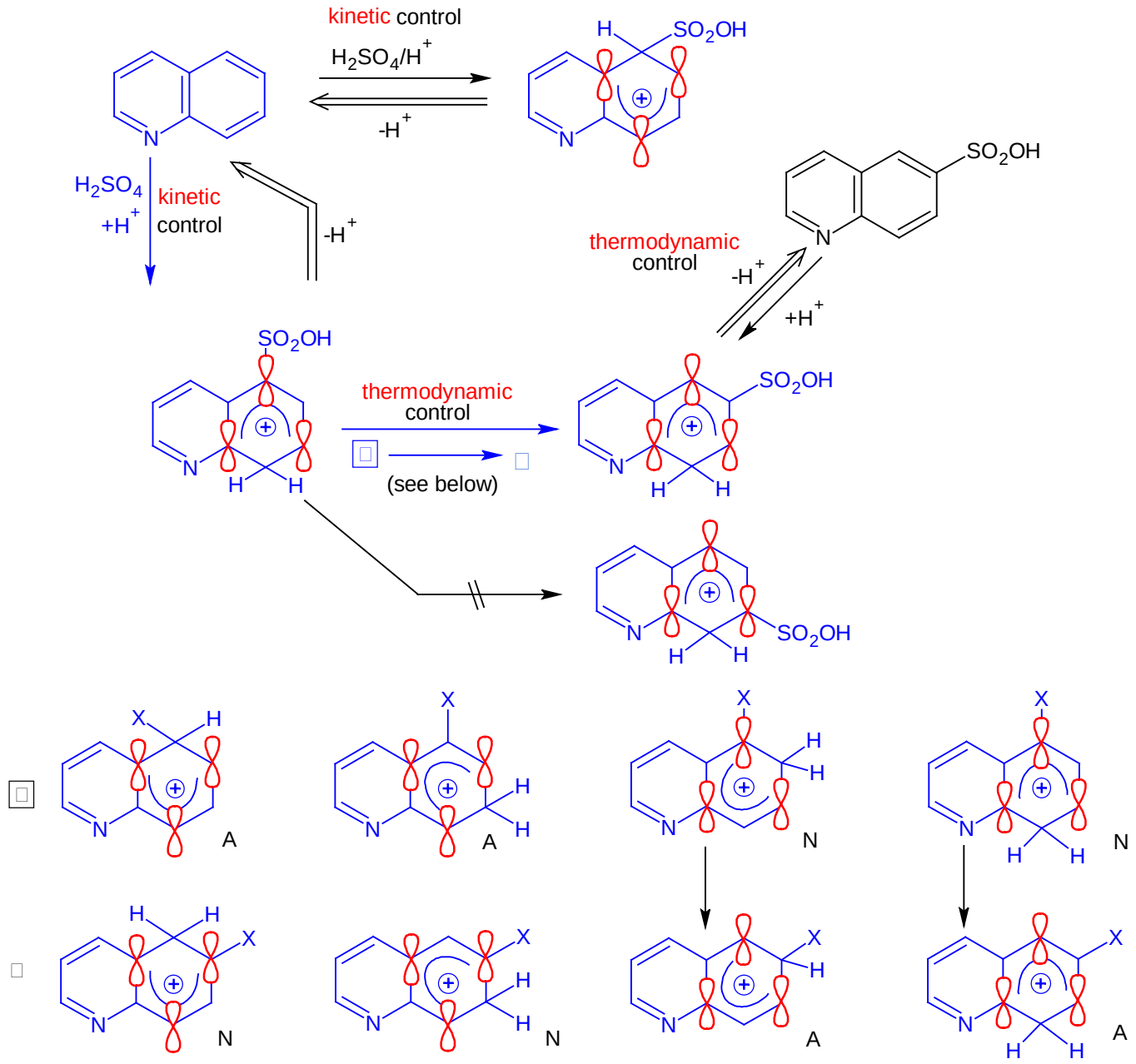
2/ Reduction

the carbons of heterocycle have low electron density, therefore oxidation of the carbocycle takes place in neutral/ basic medium. Protonation of the N helps improving acidity of the heterocycle, therefore phthalic acid is prepared in acidic medium.

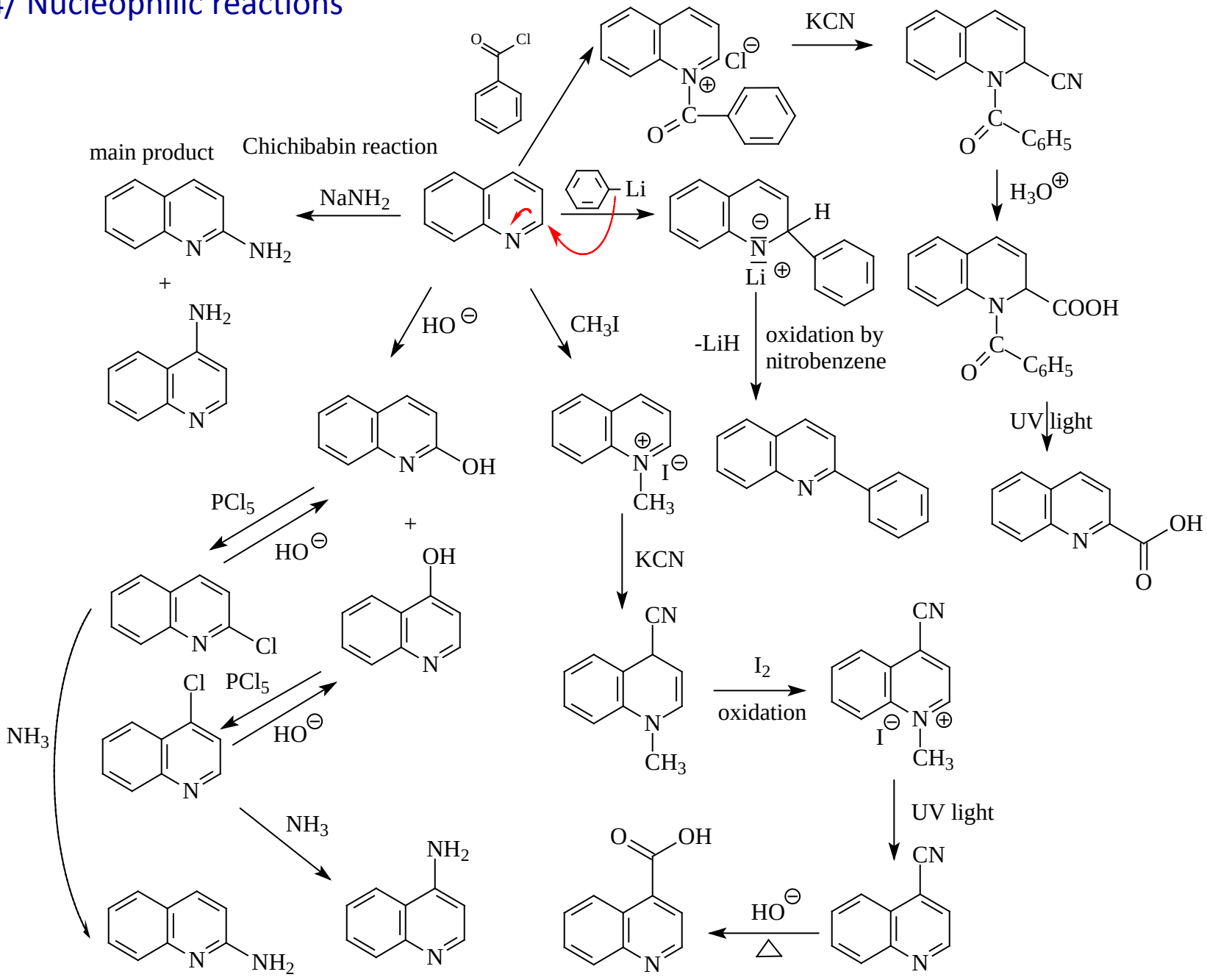
reduction: depends on catalyst and solvent

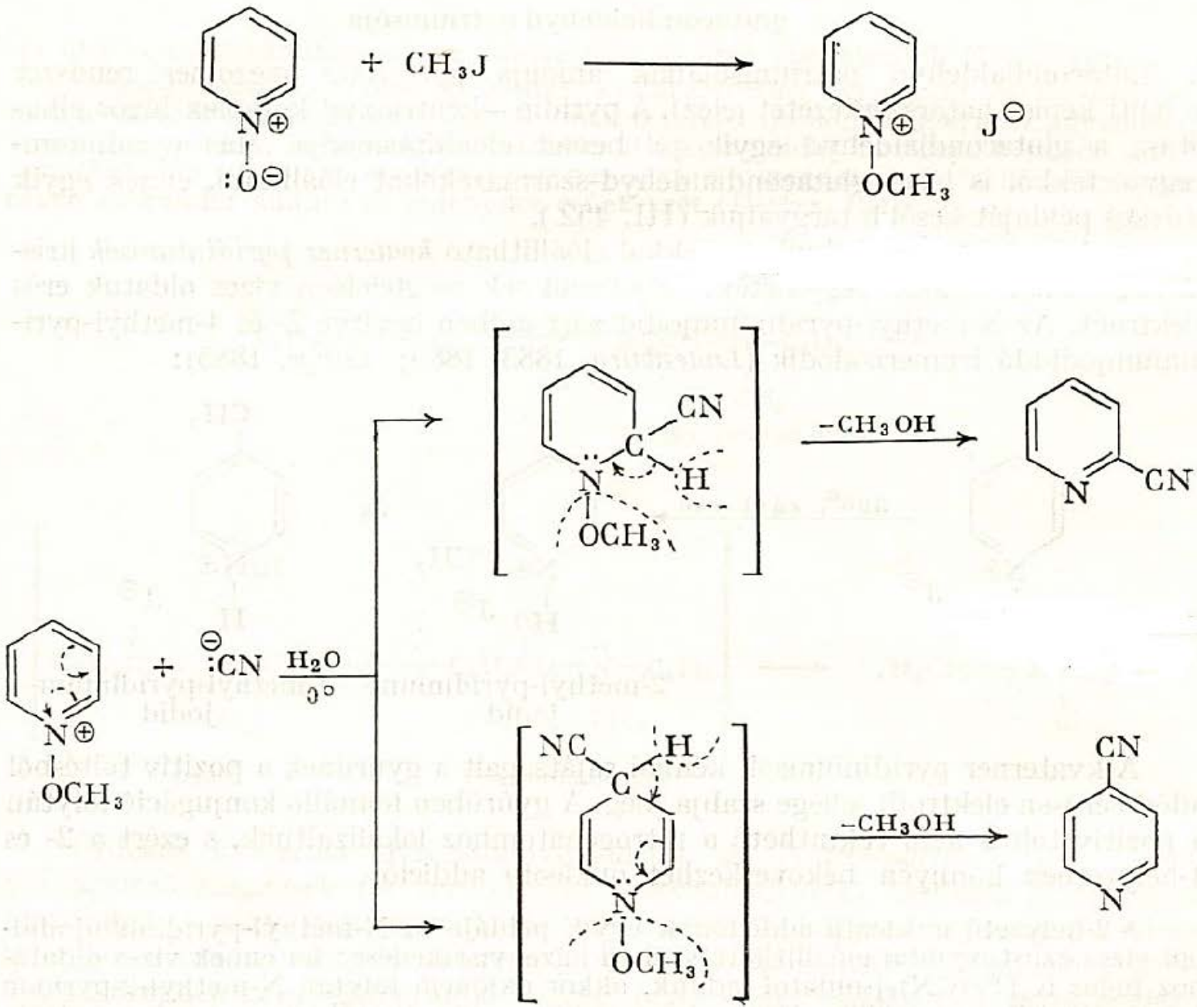
3/ Electrophilic reactions



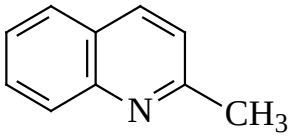

kinetic control
H_2SO_4/H^+
$-H^+$
H_2SO_4
$+H^+$
kinetic
control
$-H^+$
thermodynamic
control
$-H^+$
$+H^+$
thermodynamic
control
(see below)
SO_2OH
A
A
N
N
N
N
A
A
A: advantageous
N: not preferred

4/ Nucleophilic reactions

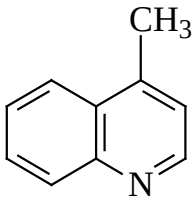



+ CH3J
J⊖
OCH3
CN
C
H
N
OCH3
−CH3OH
CN
+ ⊖:CN
H2O
0°
NC
H
C
N
OCH3
−CH3OH
CN
N

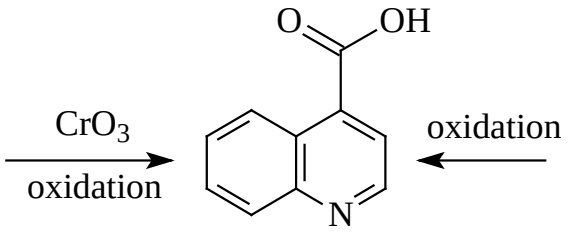
More important derivatives



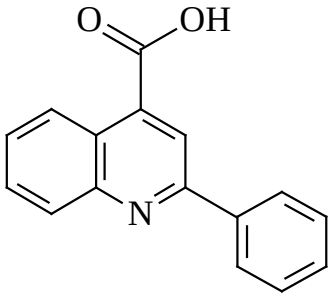
quinaldine



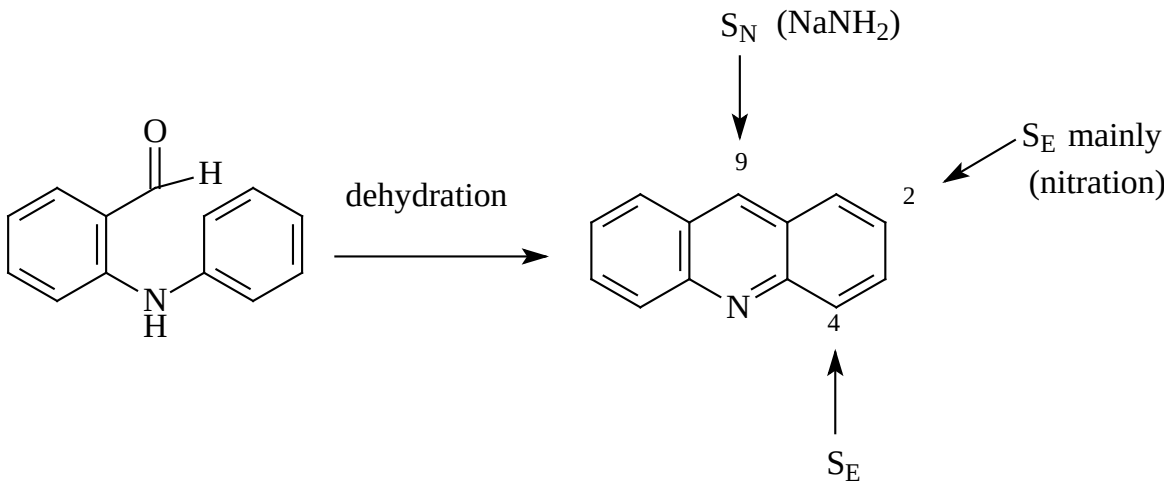
lepidine



cinchonine

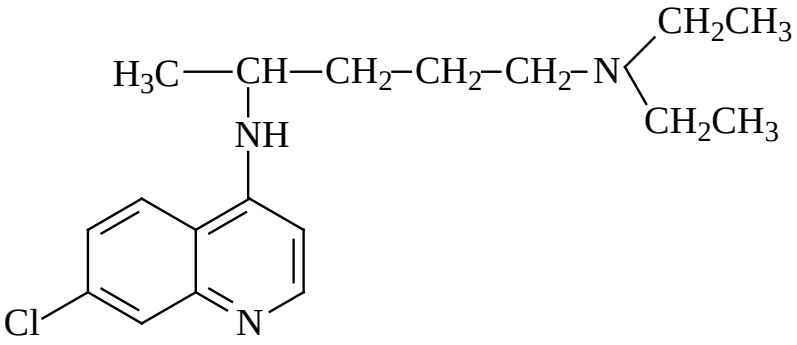


Atophen (aciphenoquinoline)
drug against gout and joint diseases

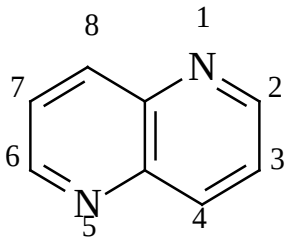


drugs and dyes with acridine skeletone

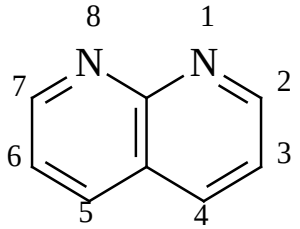
Plasmochin (Chloroquin): against malaria. There were many patients infected with malaria during the II. World War in Japan, due to the tropical climate. There was international cooperation for drugs against malaria: 100 thousand compounds were tested during 3 years, and 11 compounds became drugs.



Plasmochin

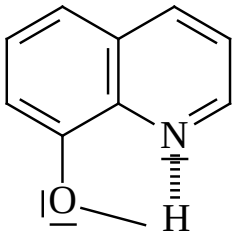


1,5-naphthiridine
pyrido[3,2-*b*]pyridine



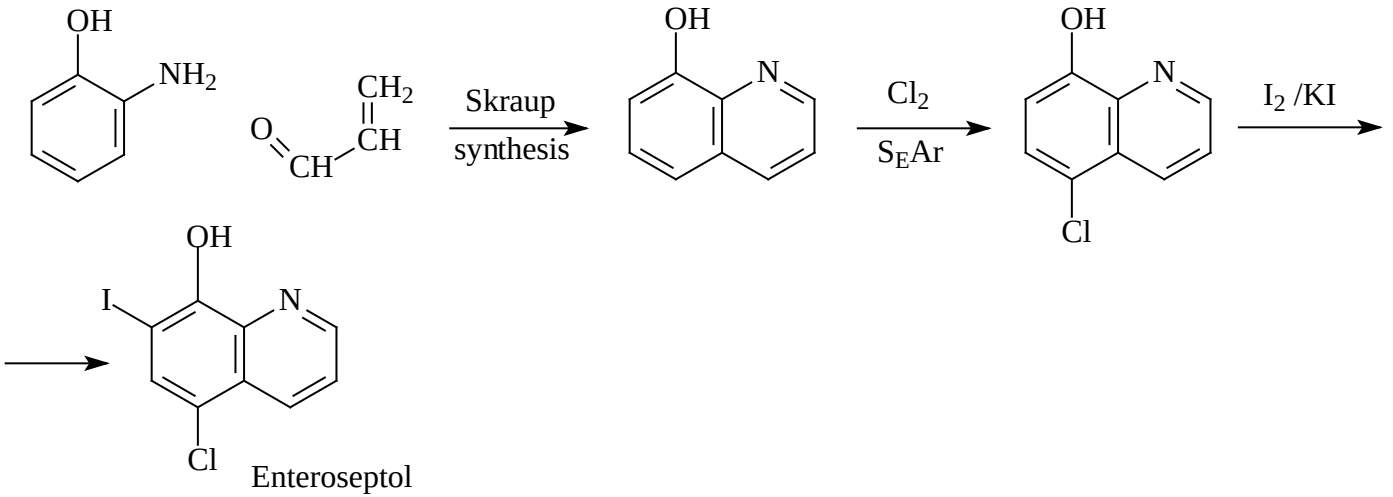
1,8-naphthiridine
pyrido[2,3-*b*]pyridine

8-Hydroxyquinoline (Chinosan)

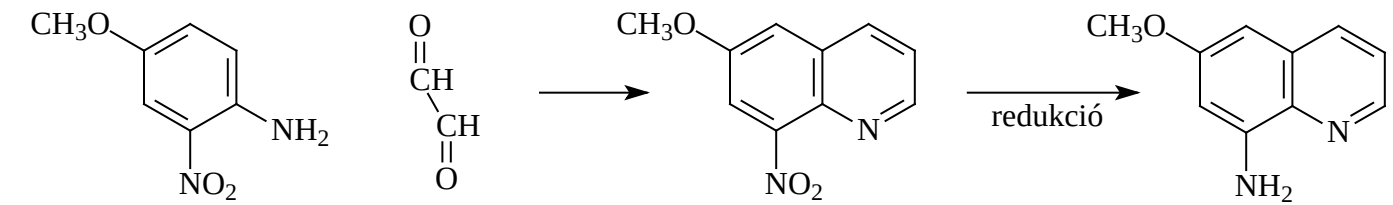


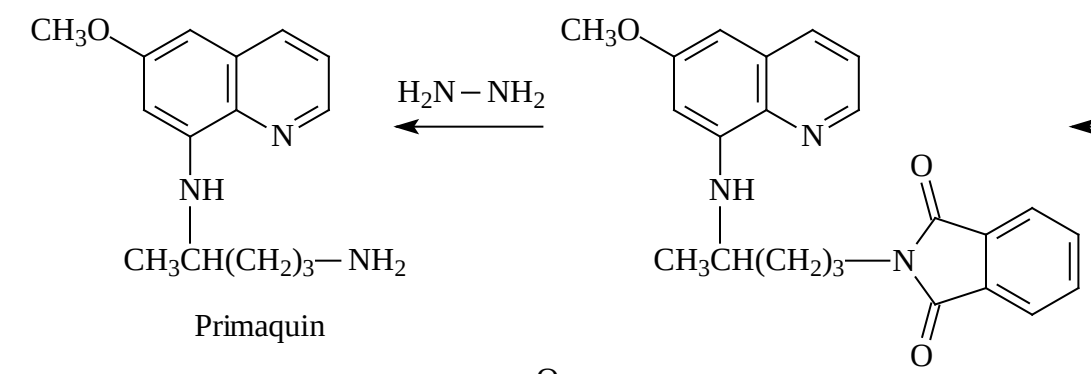
H ⟶ Al, Fe
makes insoluble complexes with heavy metals
(see analytical chemistry)

alkaloids with quinoline skeletone (see alkaloids)

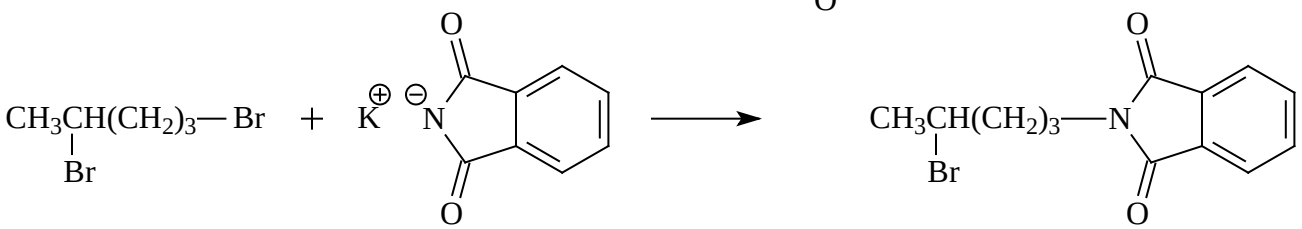


Enteroseptol

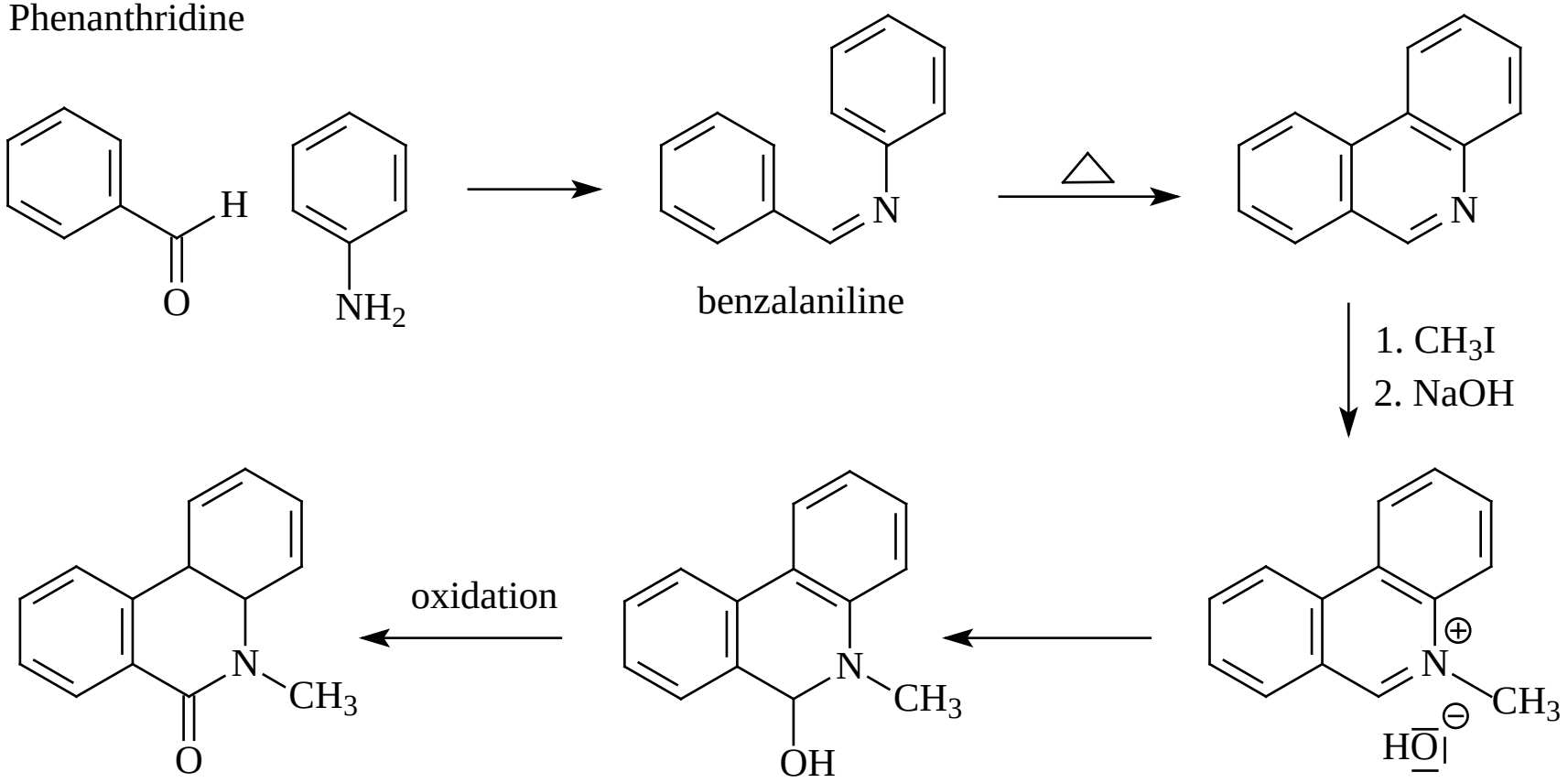




Primaquin



Phenanthridine



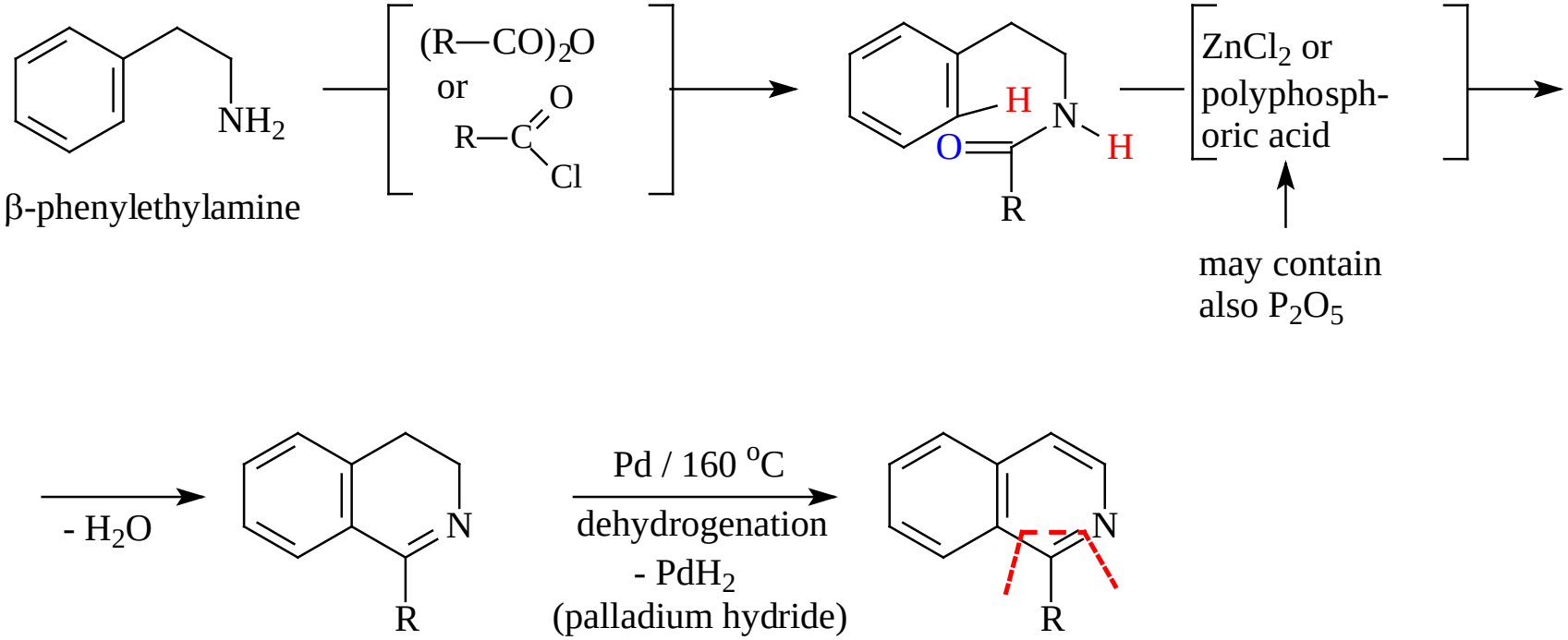
drugs with trypanocidal activity

Isoquinoline

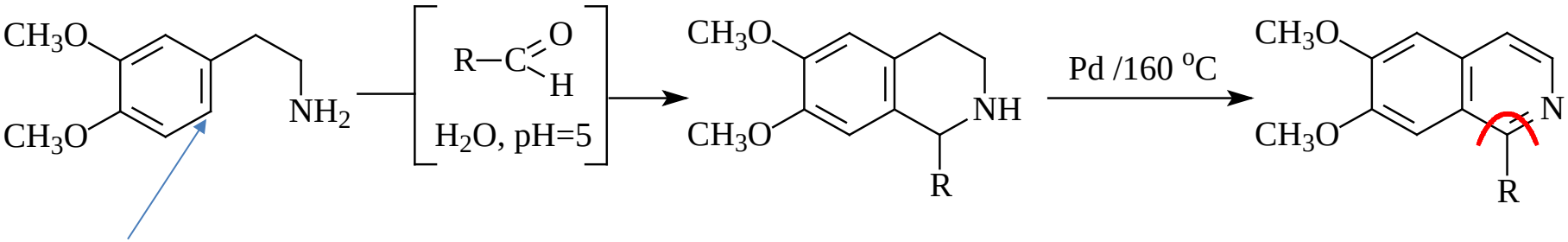
Origin of it is from coal tar.

Preparations

1/ **Bischler-Napieralski** synthesis

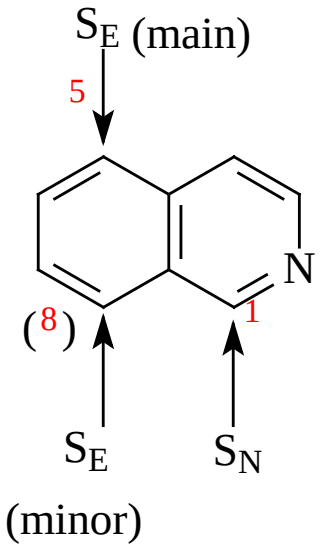


2/ By **Pictet-Spengler** synthesis



Position 6 is activated by the methoxy groups, similarly to the biosynthesis.

Chemical properties



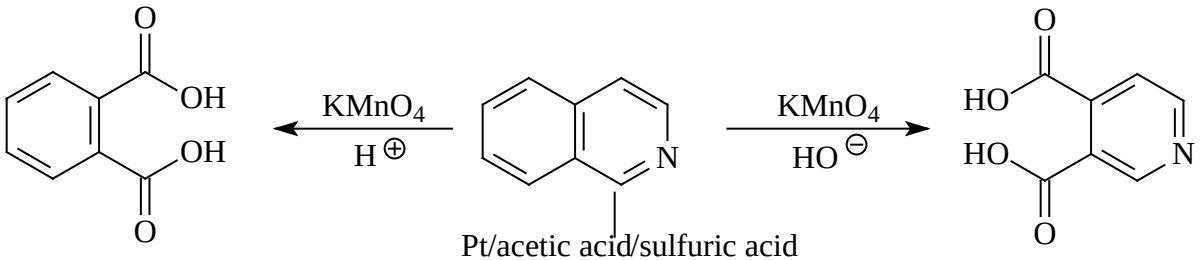
The chemical properties are similar to of pyridine

S_E the carbocycle reacts mainly - bromination, nitration, sulfonation

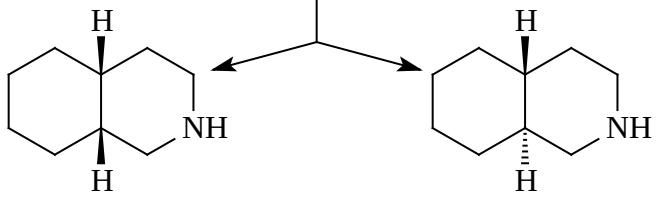
S_N the heterocycle reacts in position C-1

1/ By oxidation

The carbons of heterocycle have low electron density, therefore oxidation of the carbocycle takes place in neutral / basic medium. Protonation of the N helps improving acidity of the heterocycle, therefore phthalic acid is prepared in acidic medium.



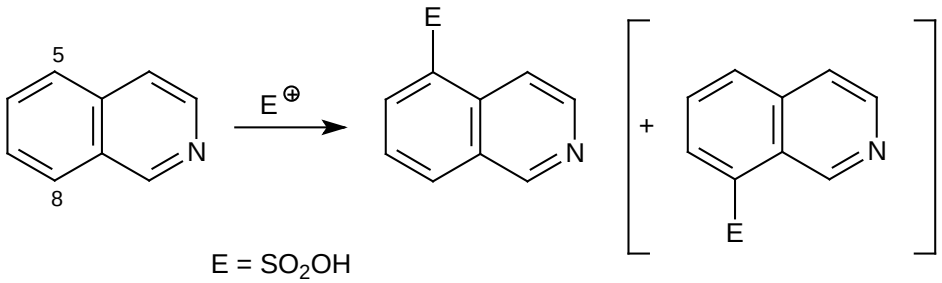
2/ By reduction



cis : *trans*

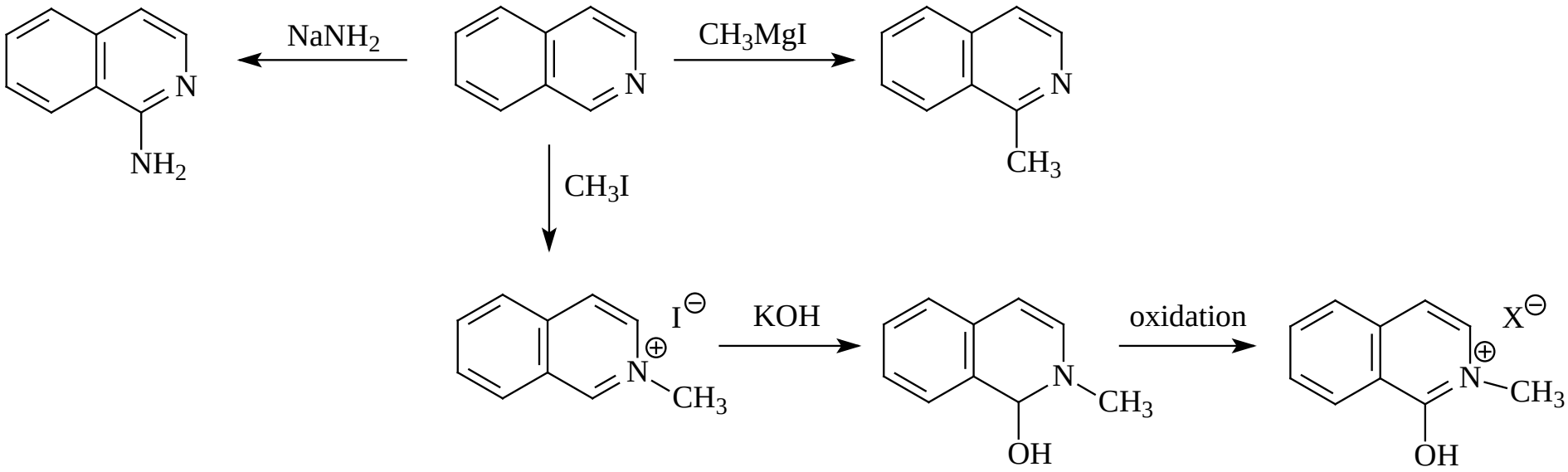
4 : 1

3/ By electrophilic reactions

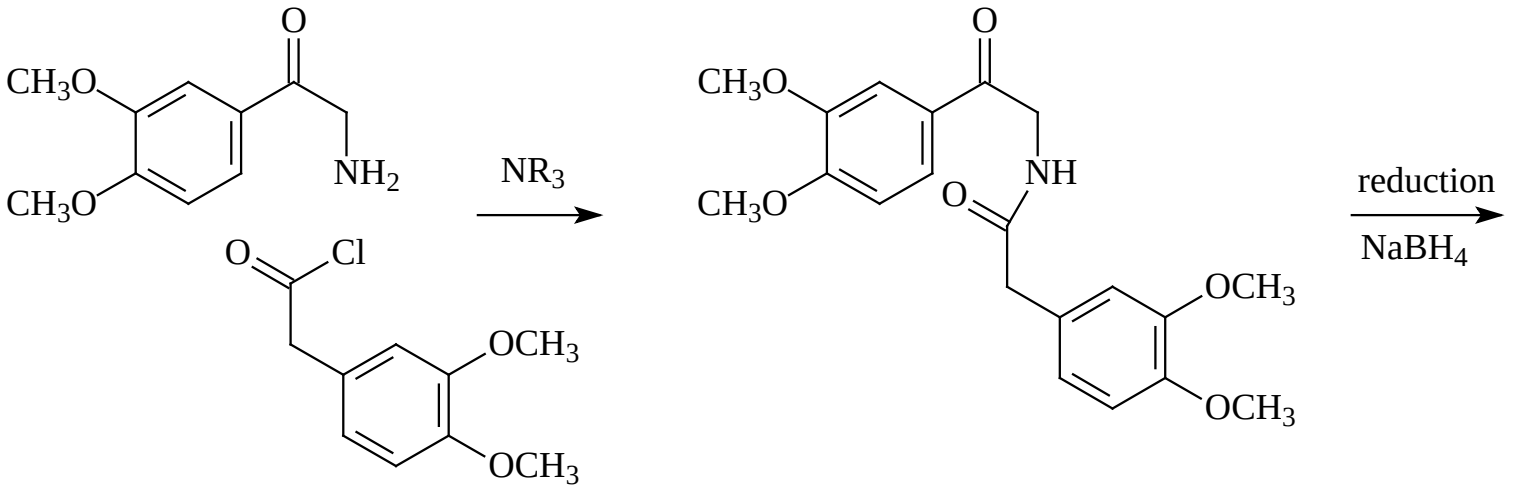


E = SO_2OH

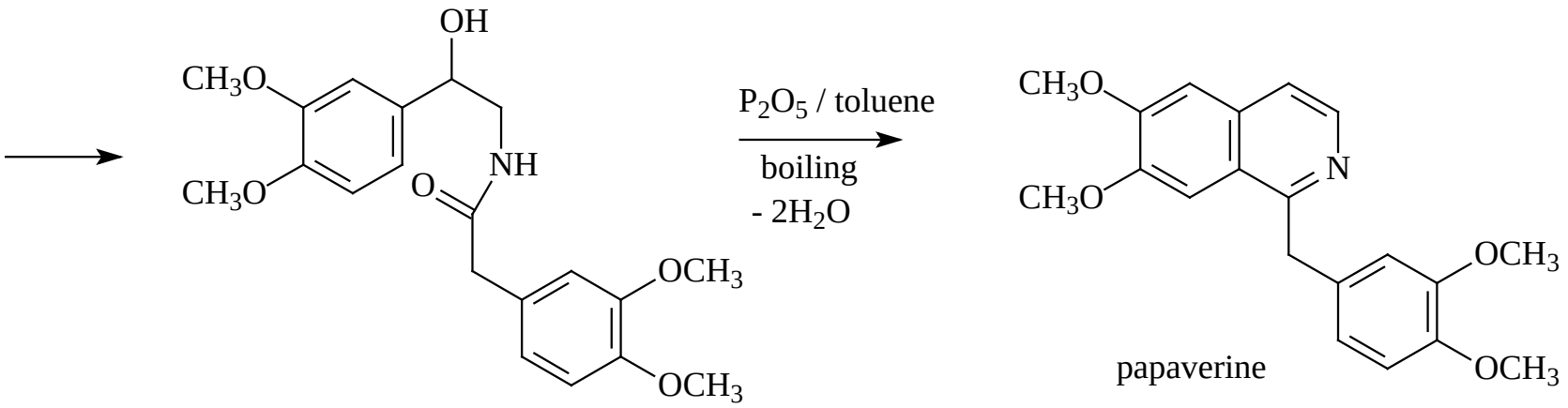
4/ By nucleophilic reactions



More important derivatives



By Zoltán Földi CHINOIN industrial synthesis



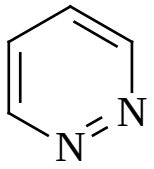
papaverine

muscle relaxant drug

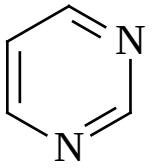
Six-membered heterocyclic compounds with two or more heteroatoms and their derivatives with condensed ring system

Compounds with two nitrogens

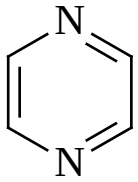
I/ Azines and its derivatives



pyridazine
1,2-diazine



pyrimidine
1,3-diazine

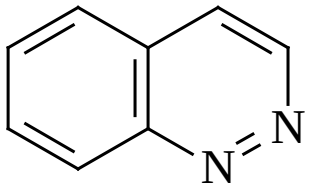


pyrazine
1,4-diazine

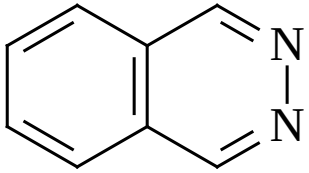
Similar heteroaromatic compounds with oxygens or sulfur atoms are not important, their partial or fullly saturated derivatives only. Introduction of the second nitrogen makes the derivative with even more π-electron deficient.

Pyridazine and its derivatives

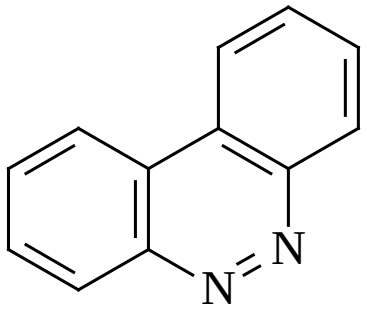
Structure



cinnoline



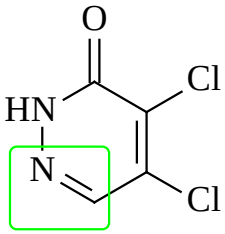
phthalazine



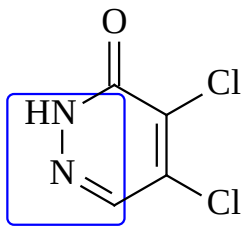
benzo[*c*]cinnoline

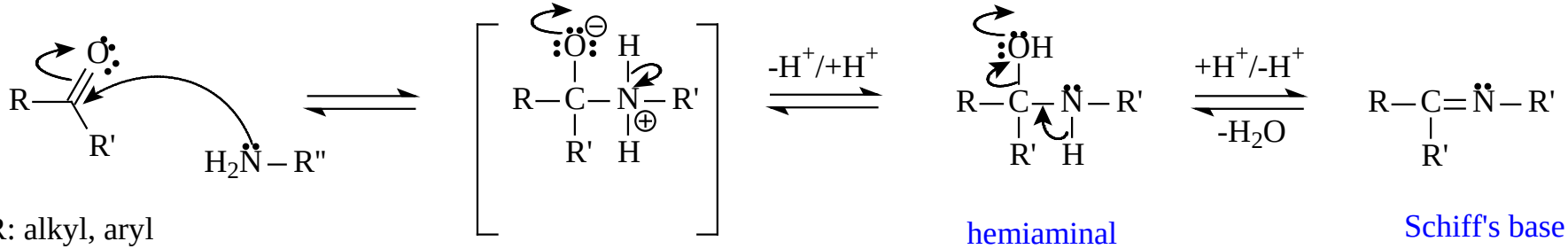
Preparations

Schiff's base structural unit



Hydrazone structural unit

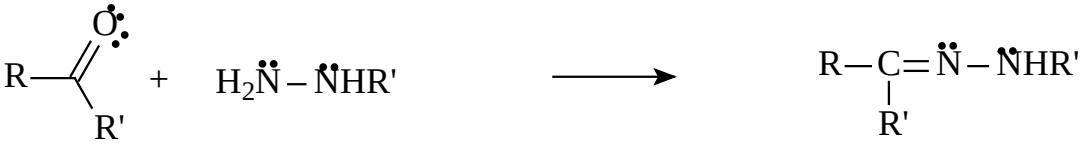




R: alkyl, aryl
R': alkyl, aryl, H
R": alkyl, aryl

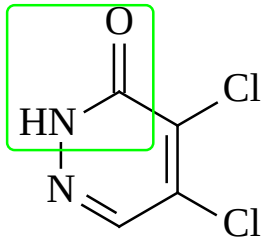
hemiaminal

Schiff's base
(N-substituted imine)

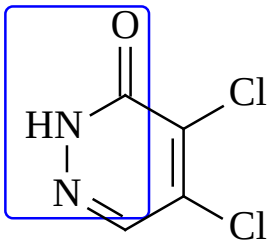


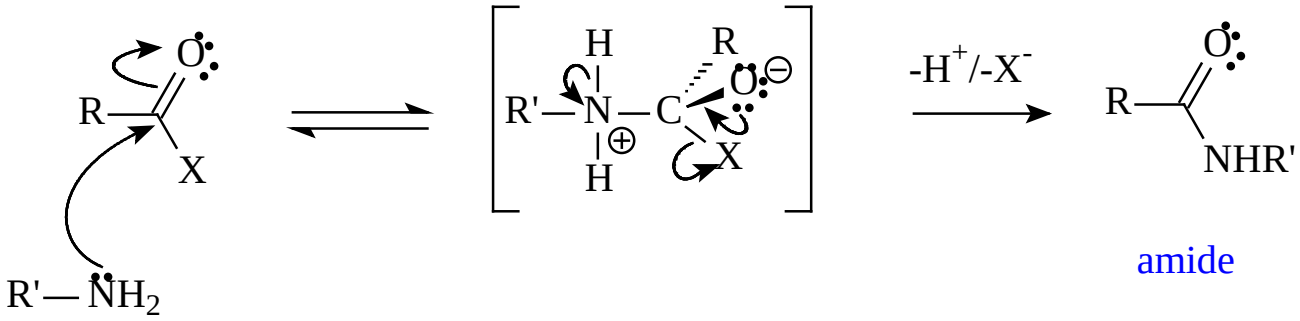
hydrazone

Amide structural unit



Hydrazide structural unit



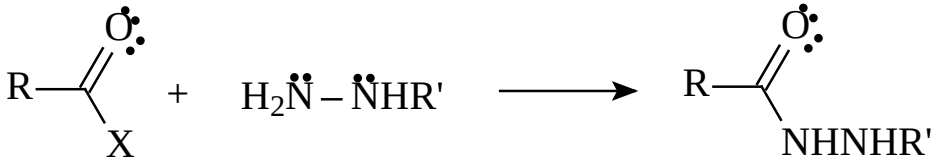


amide

R: alkyl, aryl

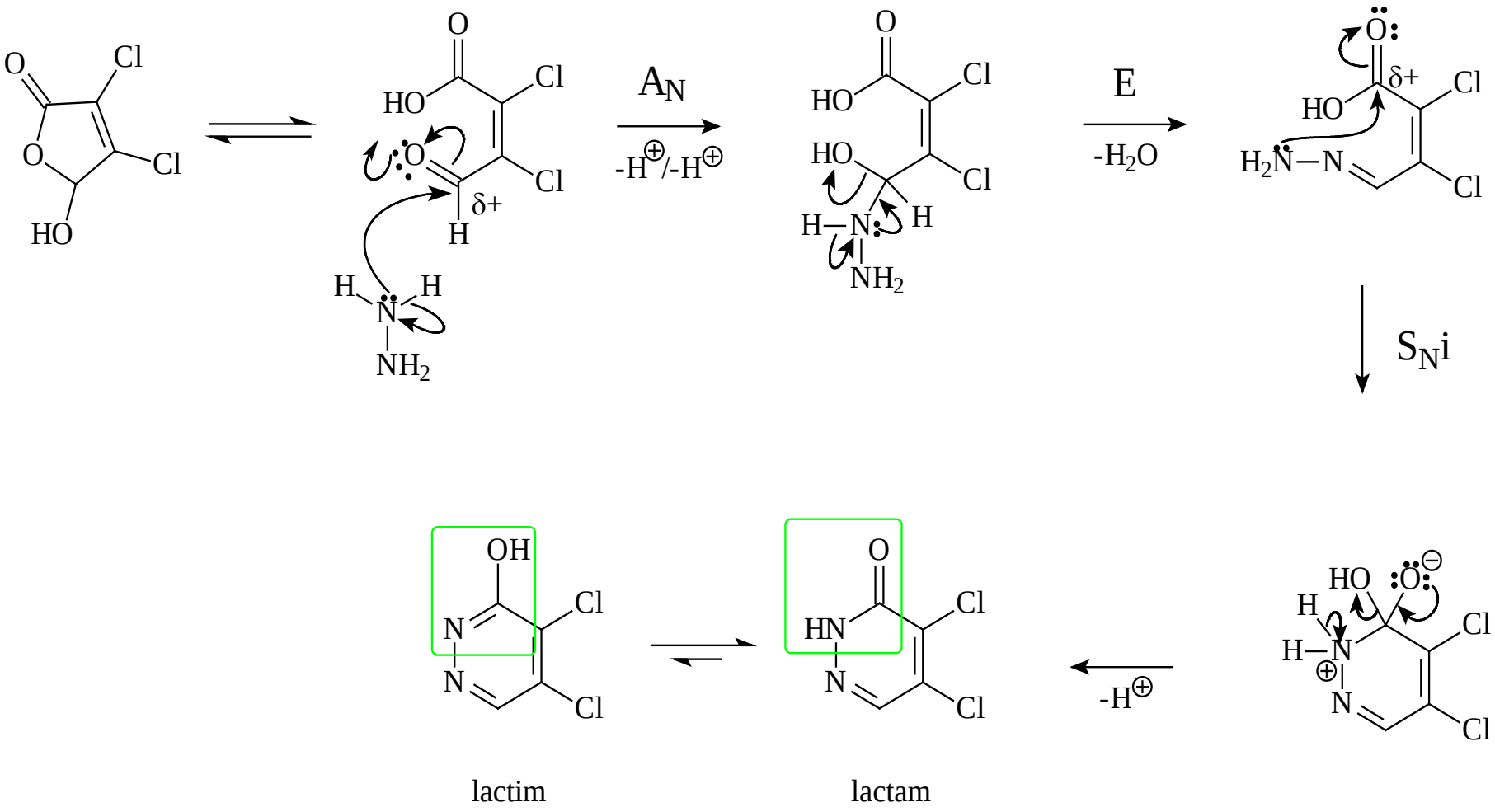
R': alkyl, aryl,

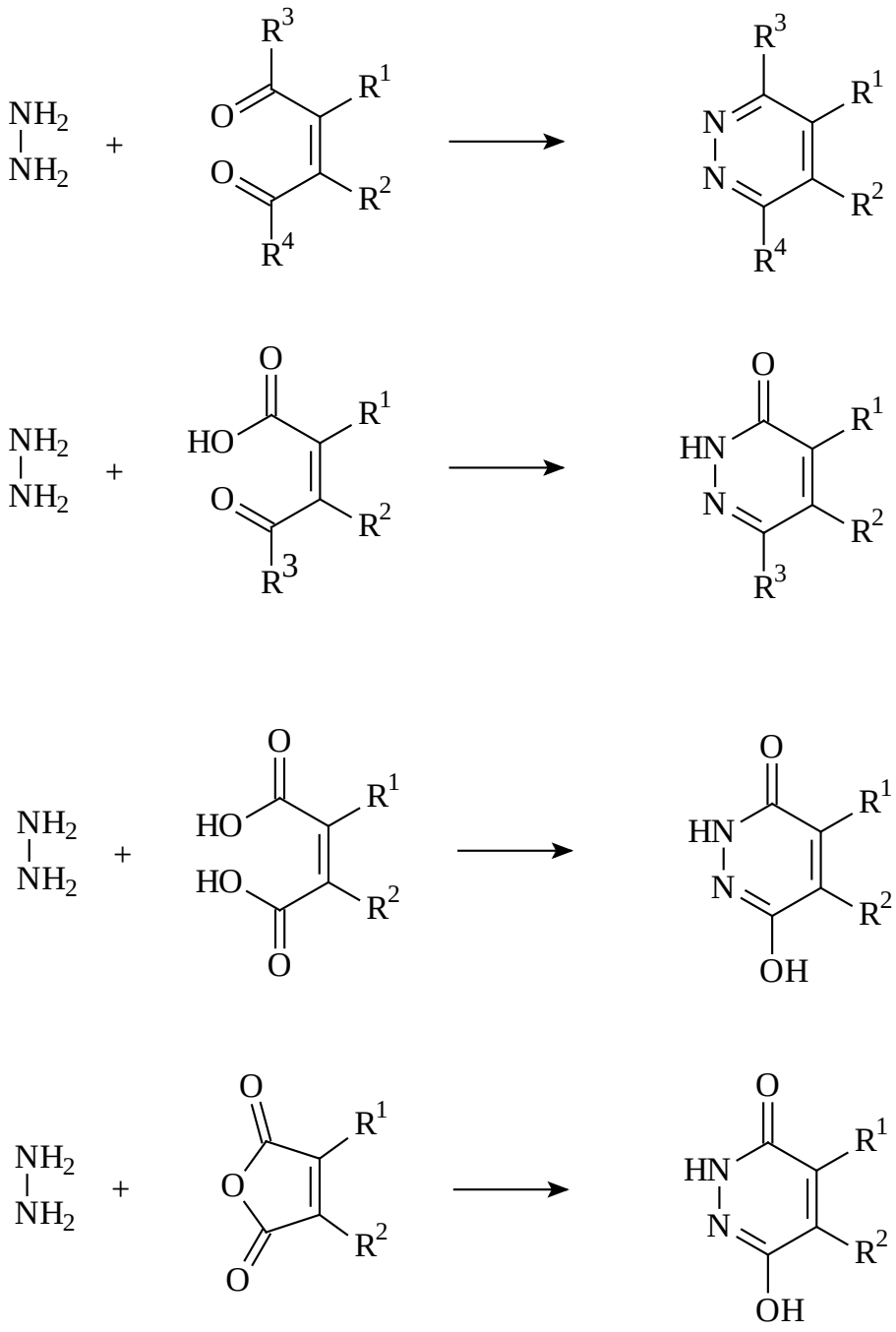
X: halogen, $OC(=O)-R$

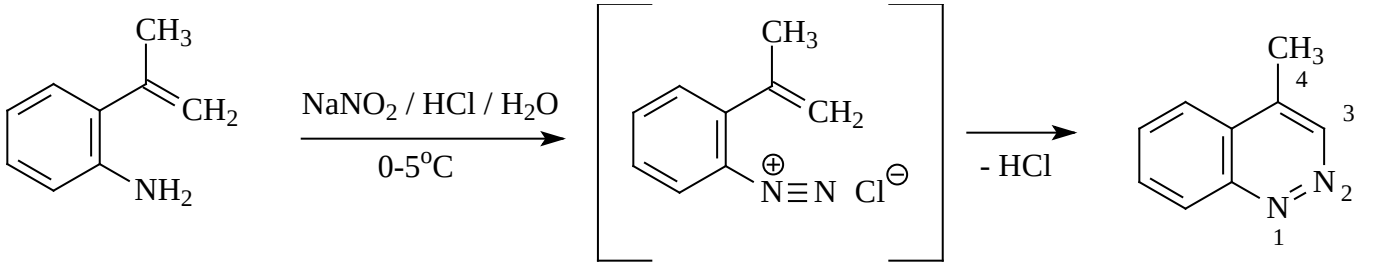


hydrazide

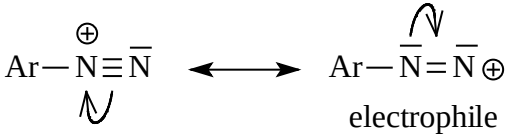
Mechanism



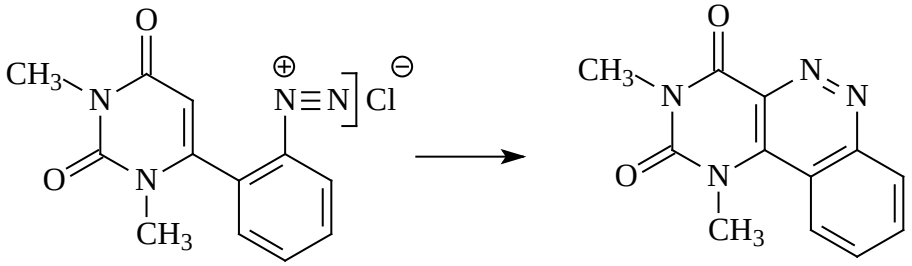




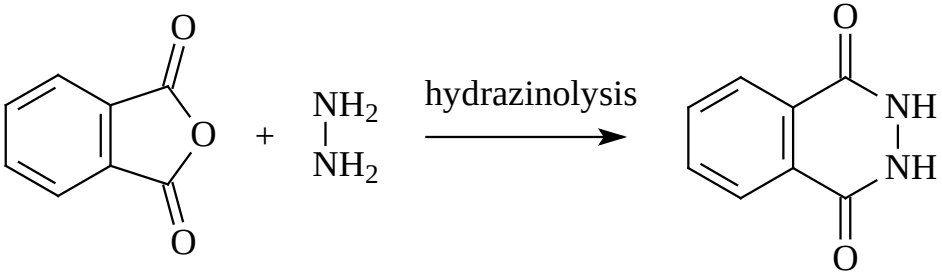
4-methylcinnoline



electrophile

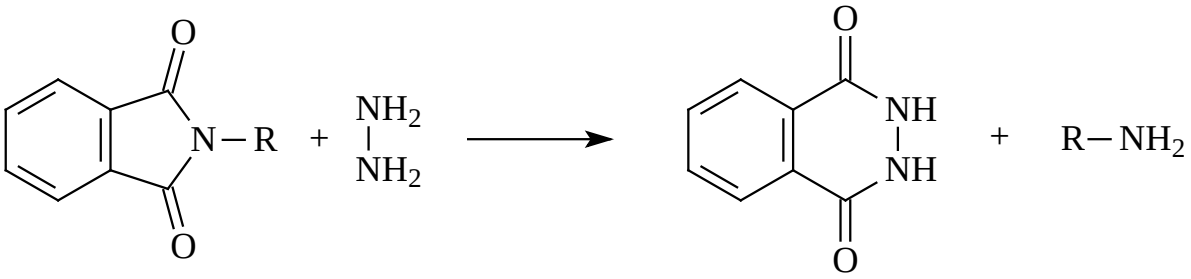


pyrimido[5,4-*c*]cinnoline ring system



phthalic anhydride

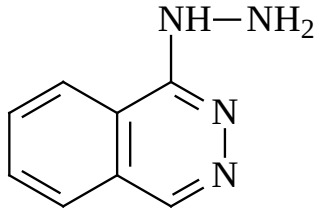
phthalic acid hydrazide



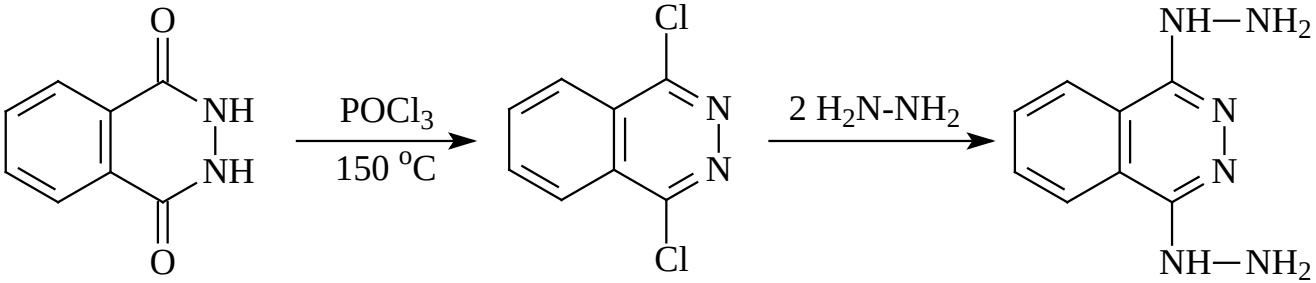
N-alkylphthalimide

phthalic acid hydrazide

There are many drugs with phthalazine ring system:



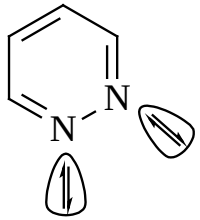
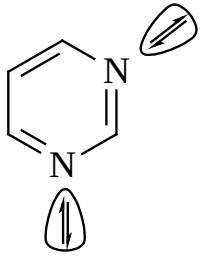
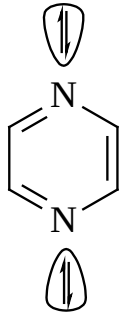
Aprezolin
renal dilatator

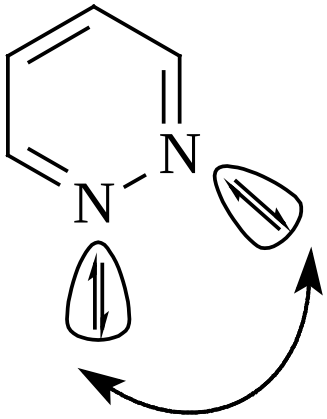


Nepresor
decreasing blood pressure

Basic strength in aqueous solution

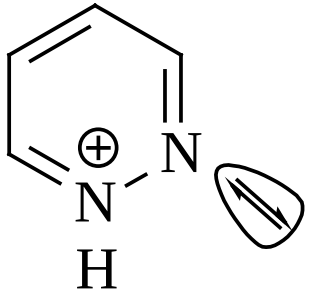
pK_a values for the conjugated acids of the bases

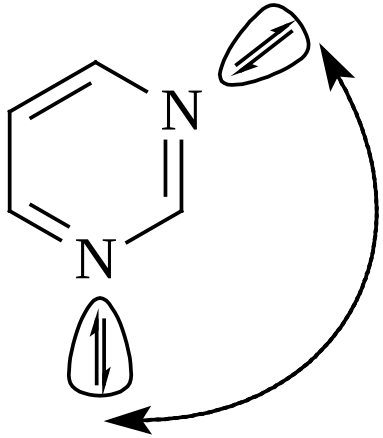
	strong repulsion		medium repulsion		weak repulsion
					
pK_a values	2.3		1.3		0.7
basicity	pyridazine	>	pyrimidine	>	pyrazine



strong repulsion

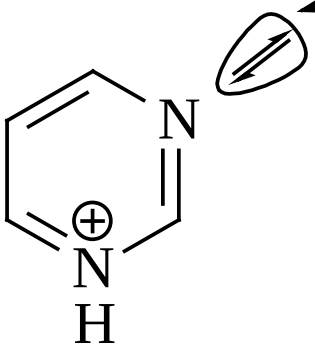
high
energy
released

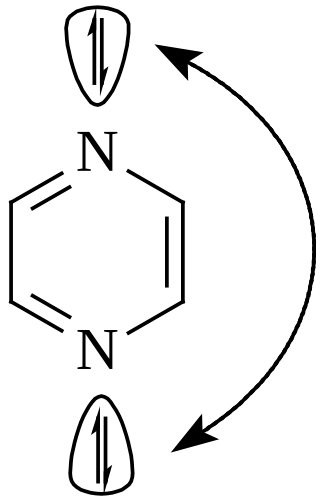




medium repulsion

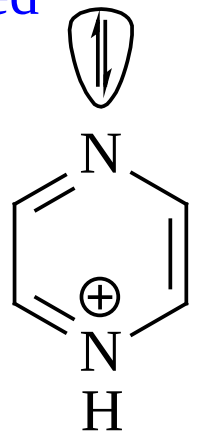
medium
energy
released





weak repulsion

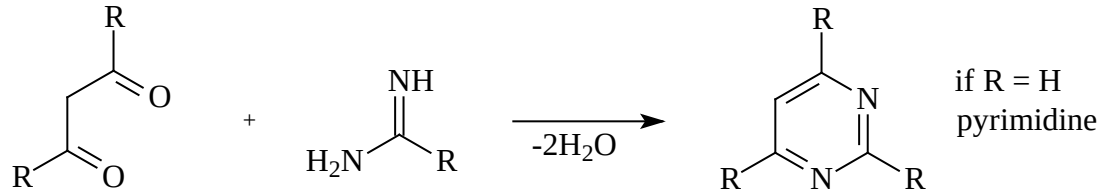
little
energy
released



Pyrimidine and its derivatives

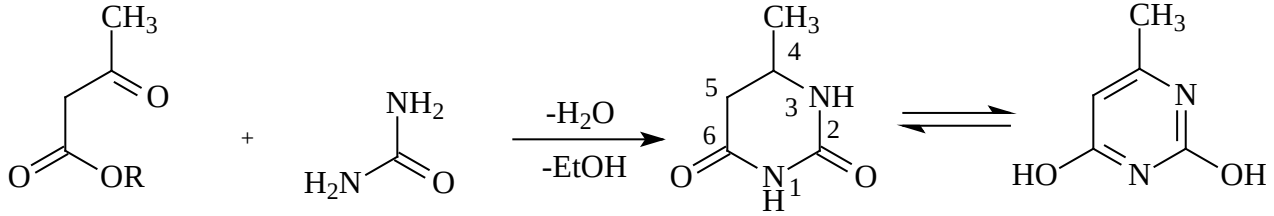
Preparations

1.

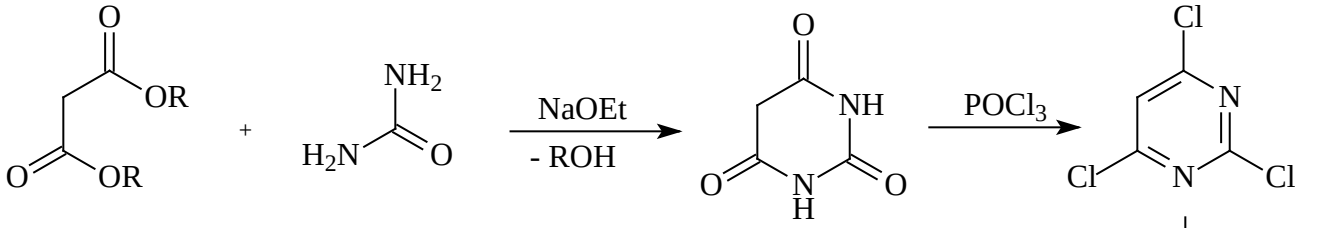


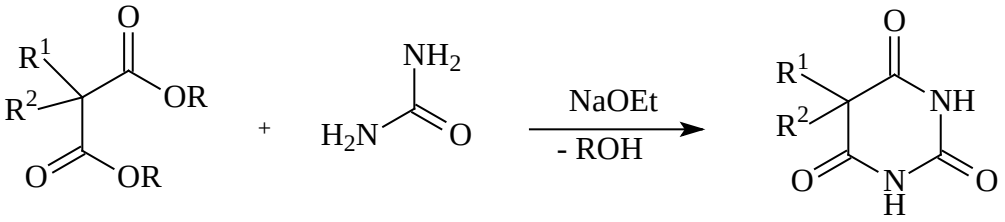
if R = H
pyrimidine

2.



3.

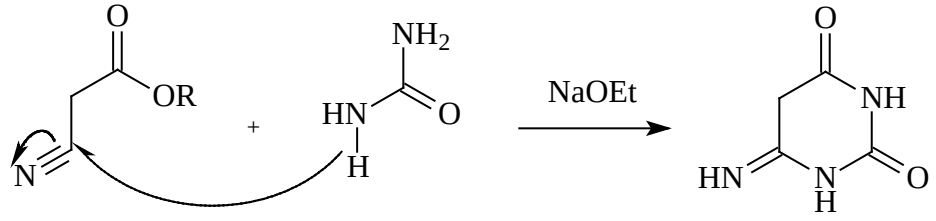




barbituric acid
derivative

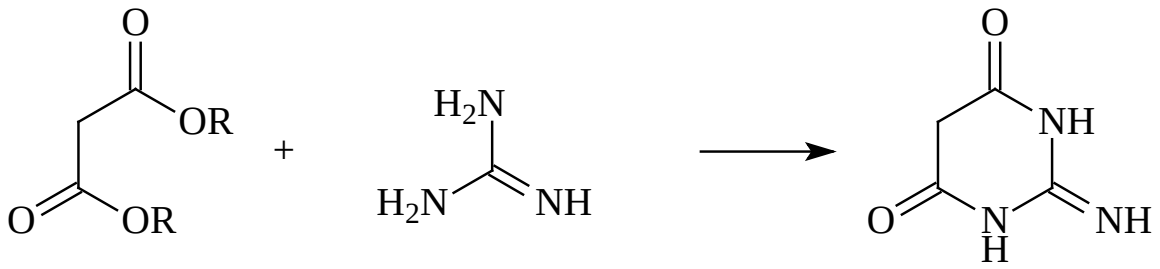
pyrimidine

4.

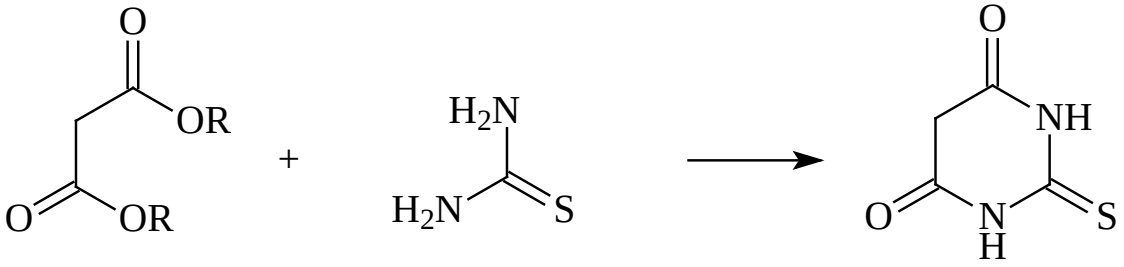


addition step

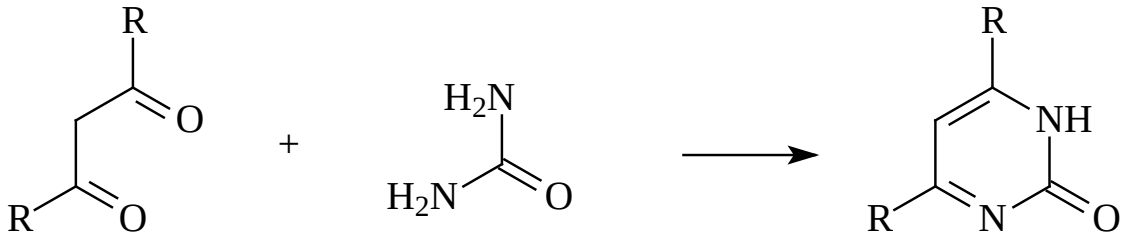
5.



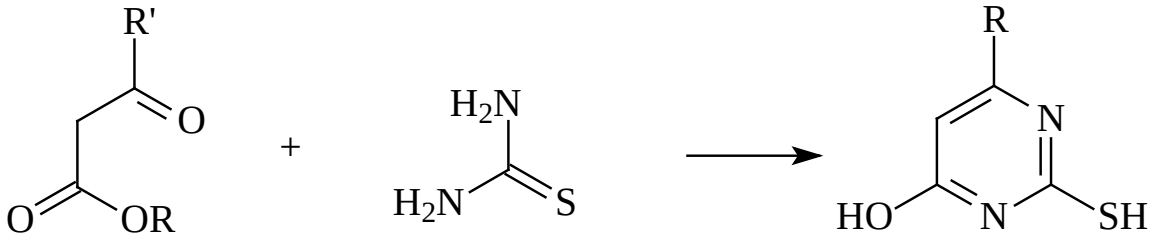
6.



7.

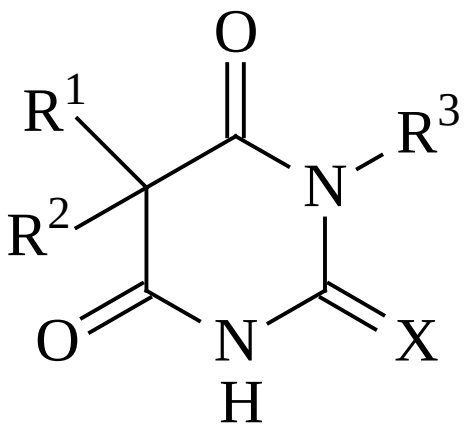


8.



R' = CH_3

Basethyrin
hyperthyreotic
compound



Barbituric acid derivatives

The barbiturate name is improper, can be applied for salts only. Uses are against insomnia (usually not for surgical uses).
Barbituric acid itself is without effects.

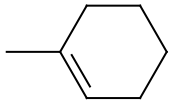
long
medium
short
ultrashort
} The efficient period depends on the excretion

	R^1	R^2	R^3	X
Amobarbital	C_2H_5	$CH_2CH_2CH(CH_3)_2$	H	O

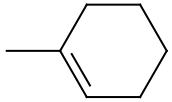
Dorlotyn (narcotic, with medium length)

Butobarbital	C_2H_5	$CH_2CH_2CH_2CH_3$	H	O

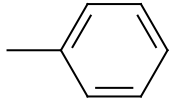
Etoval (narcotic, long)

Cyclobarbital	C_2H_5		H	O

Hypnoval (narcotic, medium)

Hexobarbital	CH_3		CH_3	O

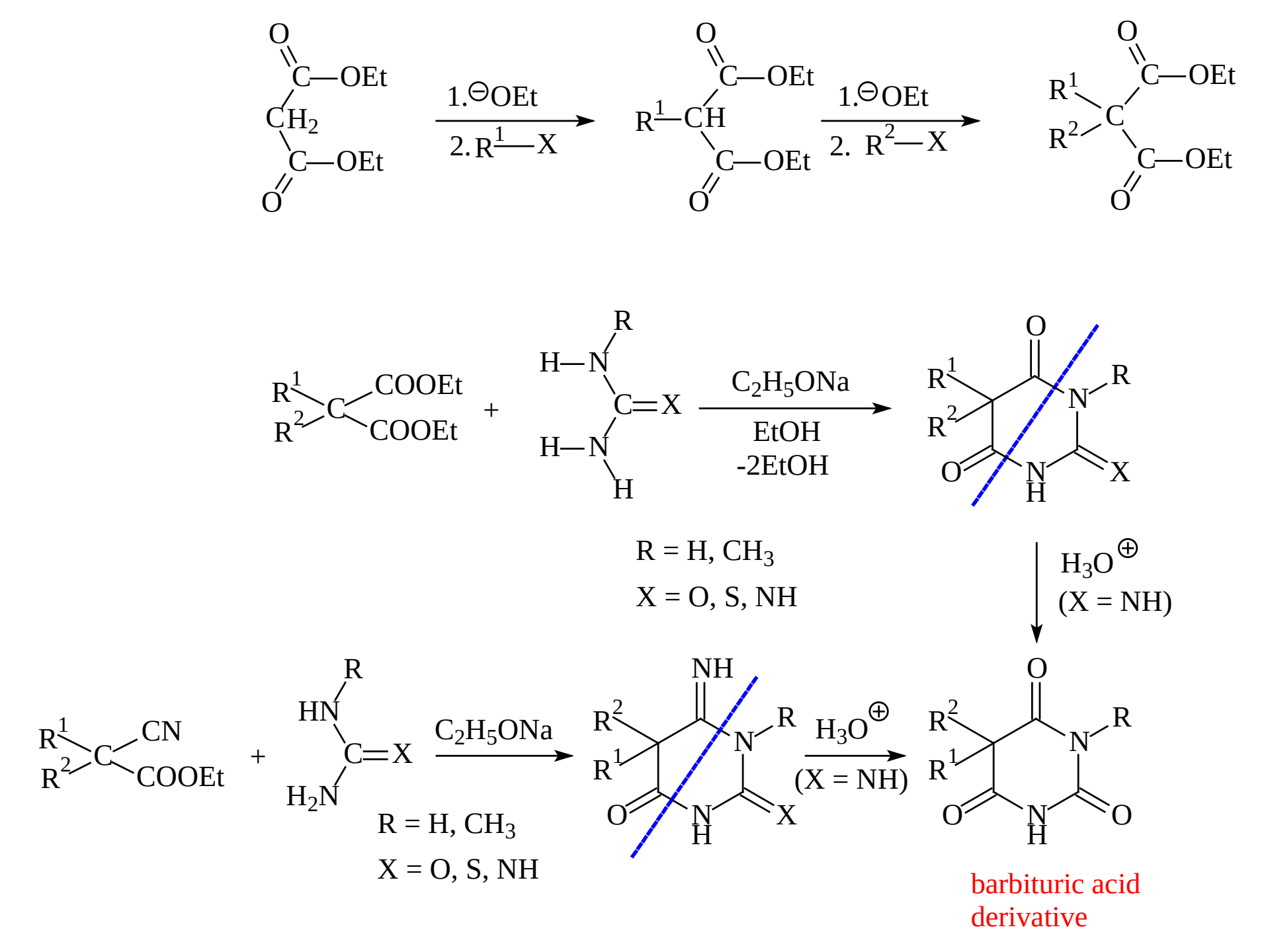
Novopan (parapulmonar narcotic agent)

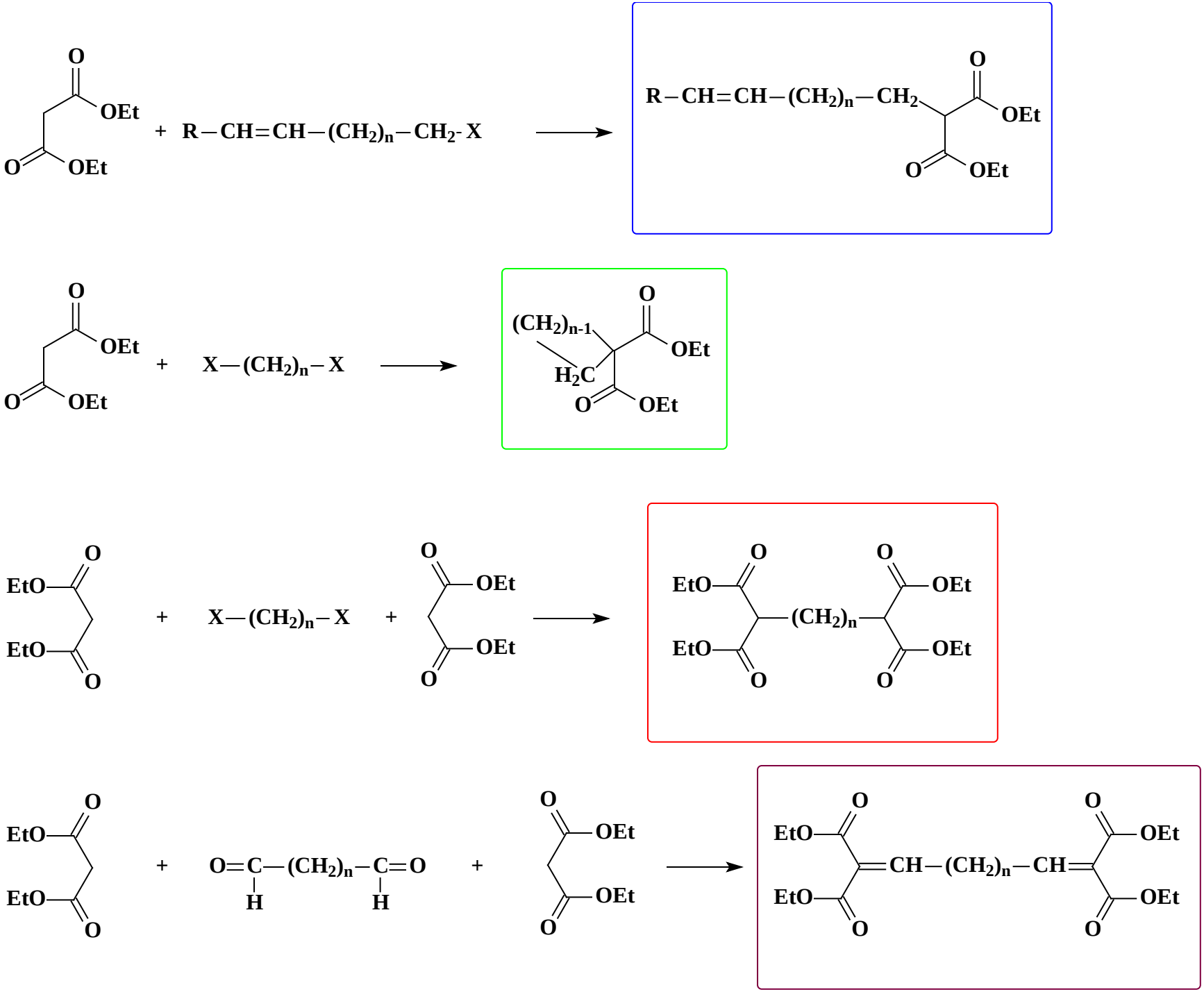
Phenobarbital	C_2H_5		H	O

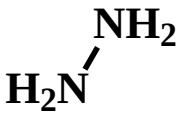
Sevenal (narcotic, long, antiepileptic agent)

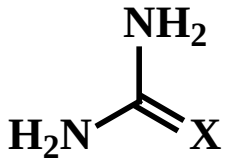
Inactin	C_2H_5	$CH(CH_2{-}CH_3)(CH_3)$	H	S

Venobarbital (parapulmonar narcotic agent)

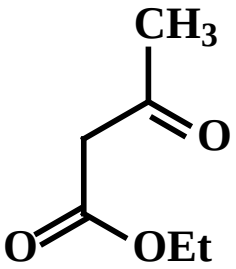

1. ⊖OEt
2. R1—X
1. ⊖OEt
2. R2—X
C2H5ONa
EtOH
-2EtOH
R = H, CH3
X = O, S, NH
H3O⊕
(X = NH)
C2H5ONa
R = H, CH3
X = O, S, NH
H3O⊕
(X = NH)
barbituric acid
derivative

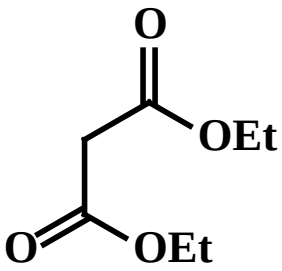

O
OEt
O
OEt
+ R–CH=CH–(CH2)n–CH2- X
R–CH=CH–(CH2)n–CH2
O
OEt
O
OEt
O
OEt
O
OEt
+ X–(CH2)n–X
(CH2)n-1
H2C
O
OEt
O
OEt
EtO
O
EtO
O
+ X–(CH2)n–X +
O
OEt
O
OEt
EtO
O
EtO
O
(CH2)n
O
OEt
O
OEt
EtO
O
EtO
O
+
O=C–(CH2)n–C=O
H
H
+
O
OEt
O
OEt
EtO
O
EtO
O
CH–(CH2)n–CH
O
OEt
O
OEt

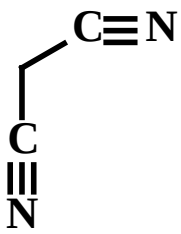

NH2
H2N

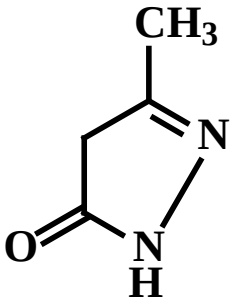

NH2
H2N
X

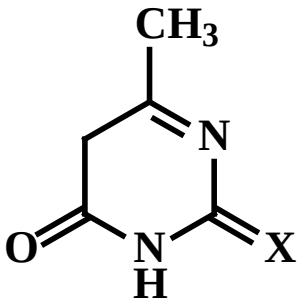
X: O, S, NH

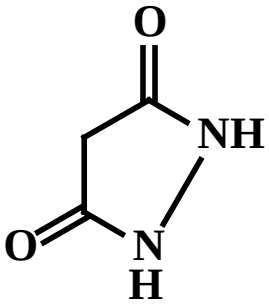

CH3
O
O
OEt

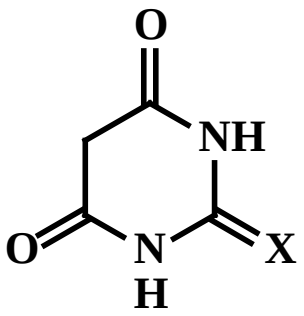

O
OEt
O
OEt

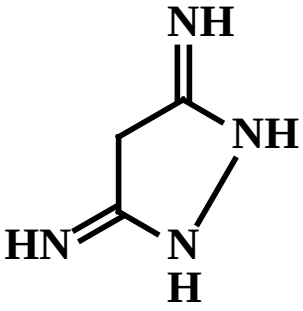

C≡N
C≡N

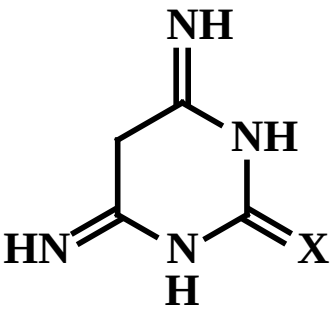

CH3
N
O
N
H


CH3
N
O
N
H
X

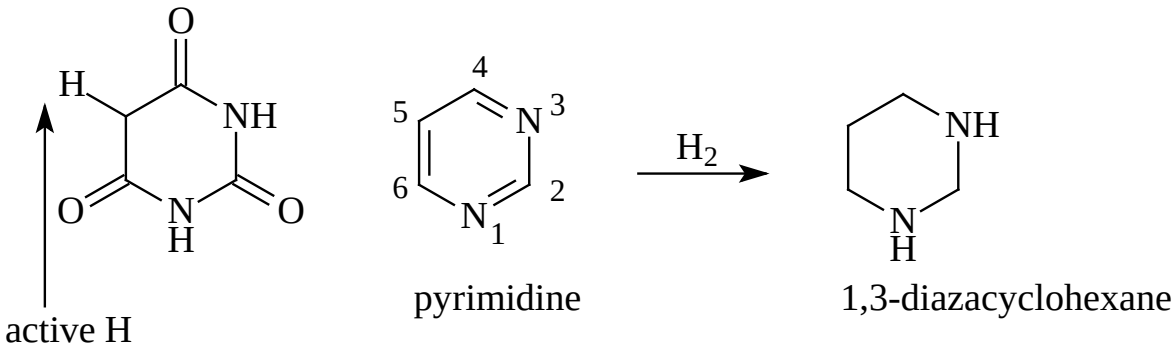

O
NH
O
N
H


O
NH
O
N
H
X

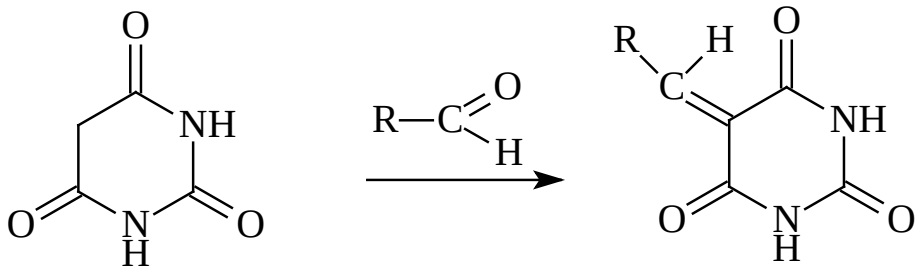

NH
NH
HN
N
H


NH
NH
HN
N
H
X

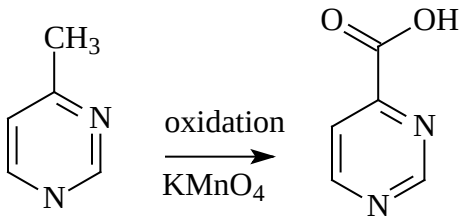
Chemical properties



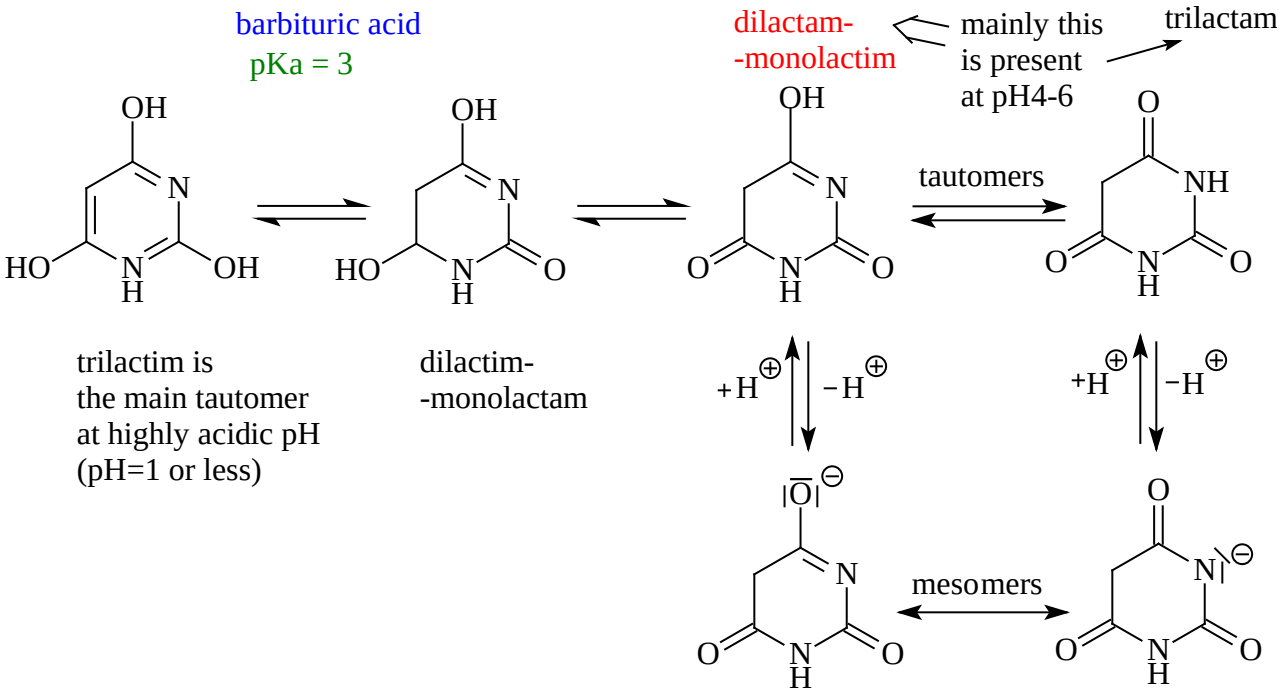
1. Pyrimidine is a weak base, pKa =1.3
It is able to participate in nucleophilic reactions:
OH→Cl; Cl →H
2. Electrophilic reactions do not run.
3. Centre No 5 is the most reactive, it is an active methylene group in barbituric acid. But it is impossible to run alkylation or arylation in centre No 5 of barbituric acid after ring closure, since the alkyl or aryl group attacks the heteroatoms only.

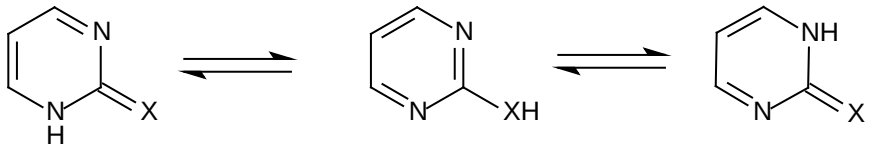


4. Resists oxidation: the substituents are oxidised only



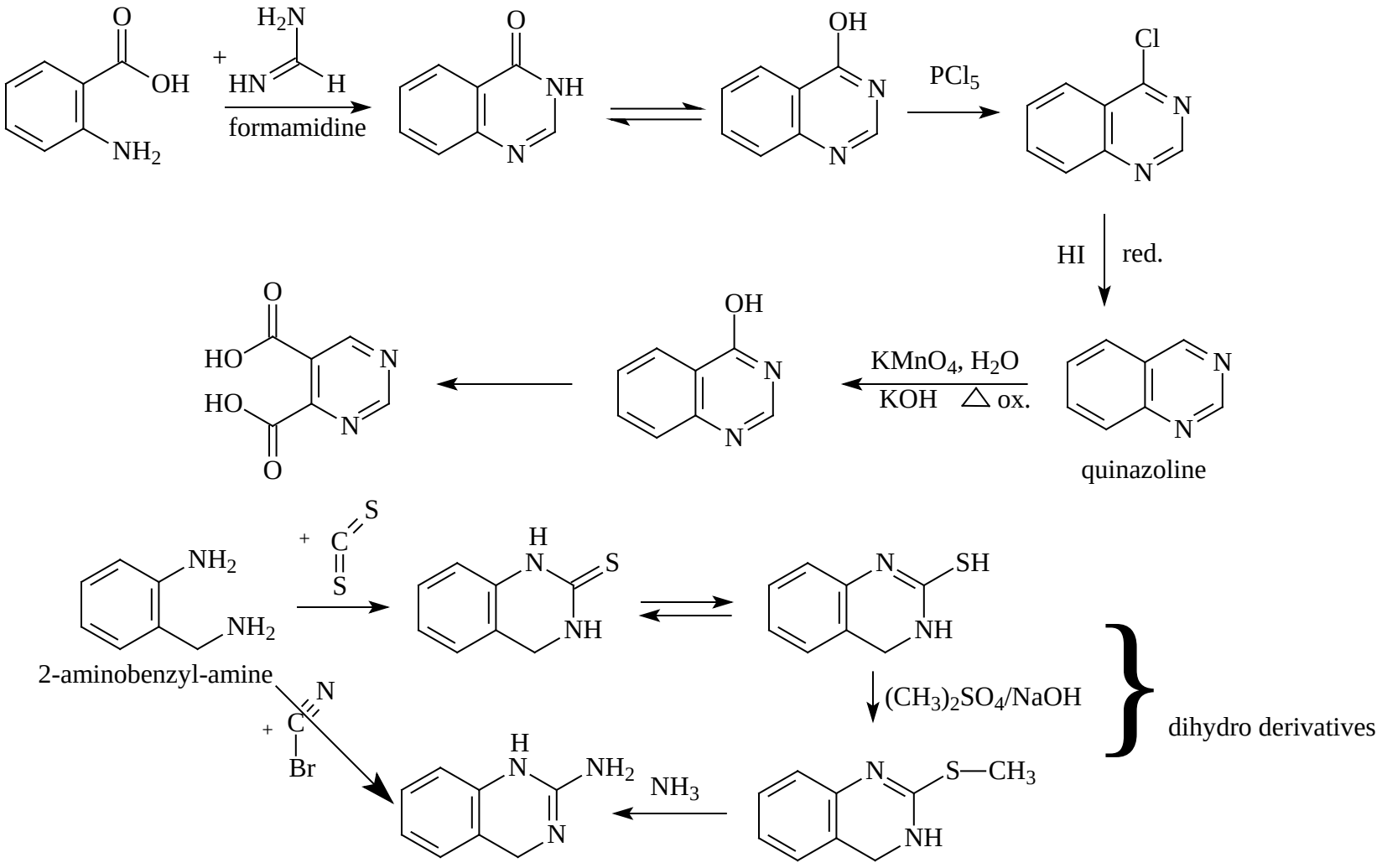
5. There is tautomerism at hydroxy- and at aminoderivatives, e.g.,

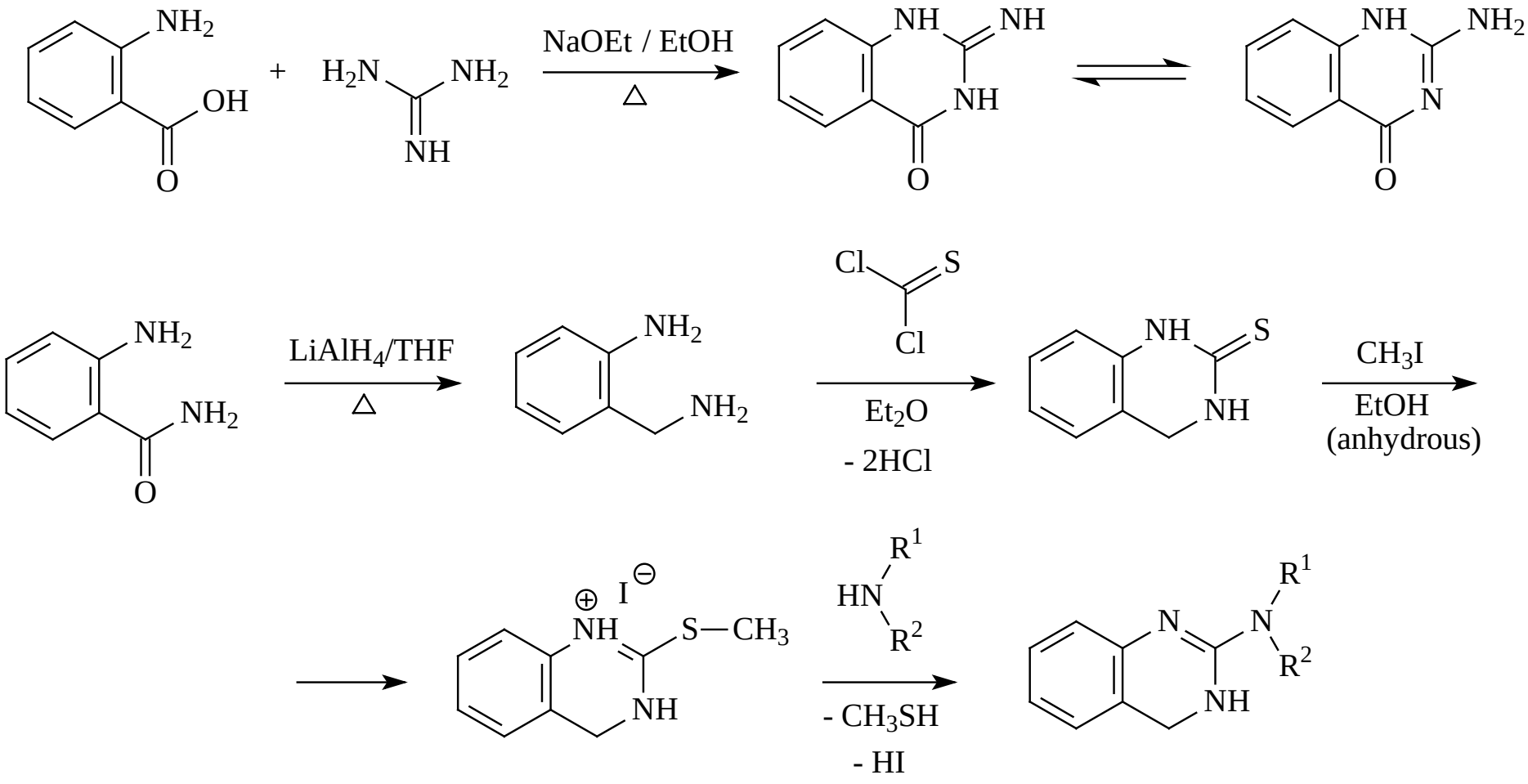




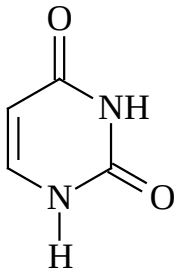
The tautomeric equilibrium depends on temperature and solvent strongly.
Rate of N-alkylation is higher, than rate of O-alkylation.
Usually more than one tautomer are present in crystalline form, the actual main tautomer depends on the isolation conditions.

Benzocondensed derivatives of pyrimidine

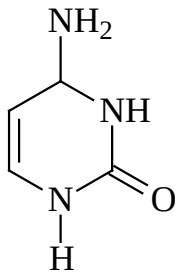



NH2
OH
O
+
H2N
NH2
NH
NaOEt / EtOH
△
NH
NH
NH
O
NH
NH2
N
O
NH2
NH2
O
LiAlH4/THF
△
NH2
NH2
Cl
S
Cl
Et2O
- 2HCl
NH
S
NH
CH3I
EtOH
(anhydrous)
I
NH
S—CH3
NH
R1
HN
R2
- CH3SH
- HI
N
N
R1
R2
NH

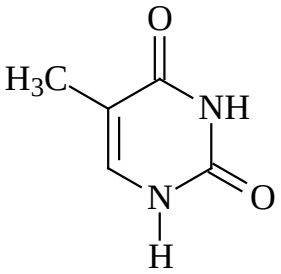
More important derivatives



uracil
RNA



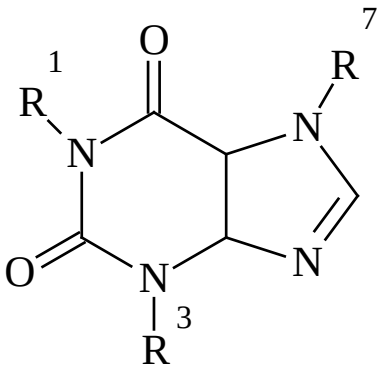
cytosine
RNA
DNA



thymine
DNA

pyrimidine bases

7*H*-purine derivatives

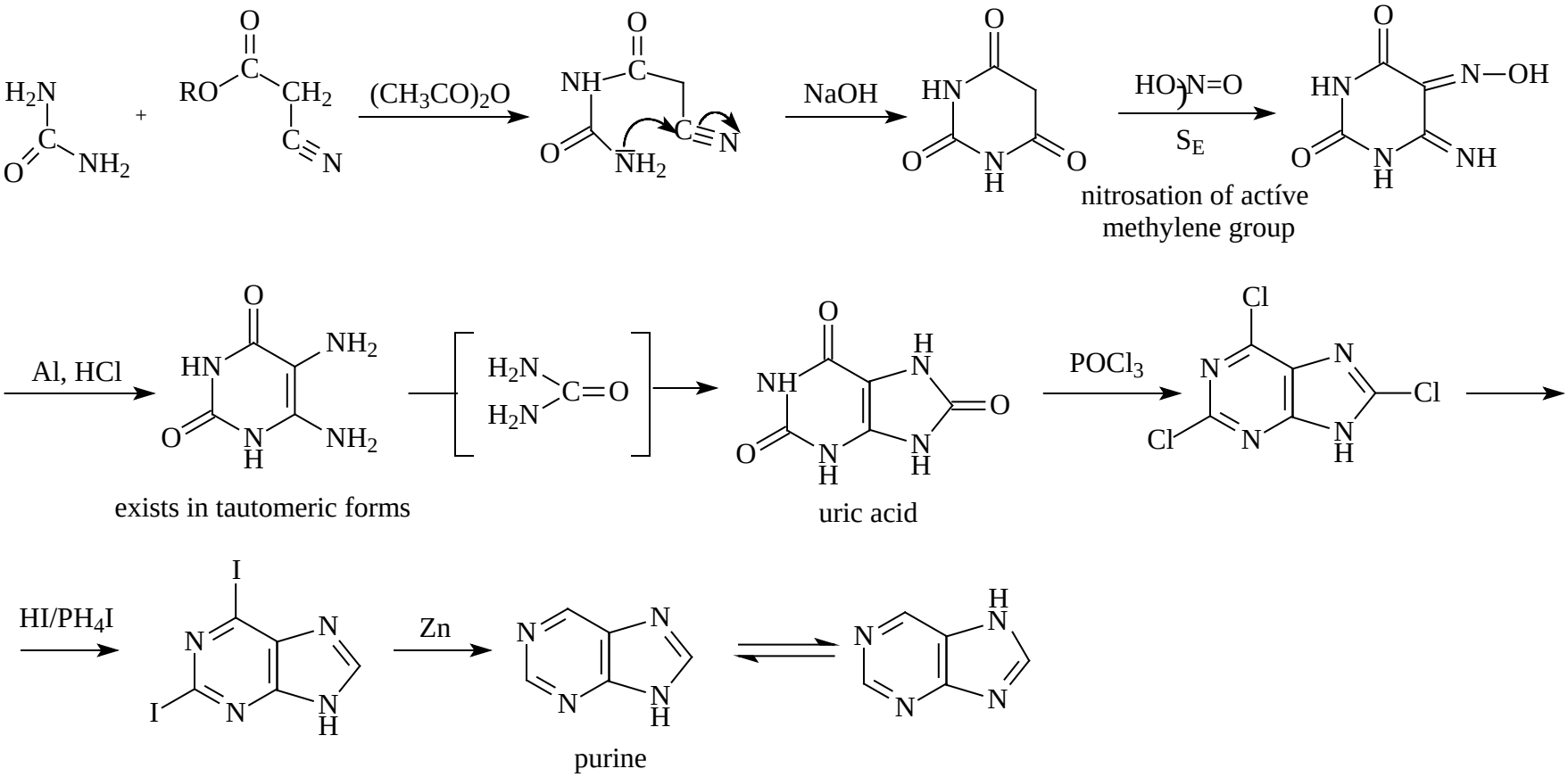


	R^1	R^2	R^3	
xanthine	H	H	H	
theophylline	CH_3	CH_3	H	in Chinese tea
theobromine	H	CH_3	CH_3	in cocoa beans
caffeine	CH_3	CH_3	CH_3	in coffee beans

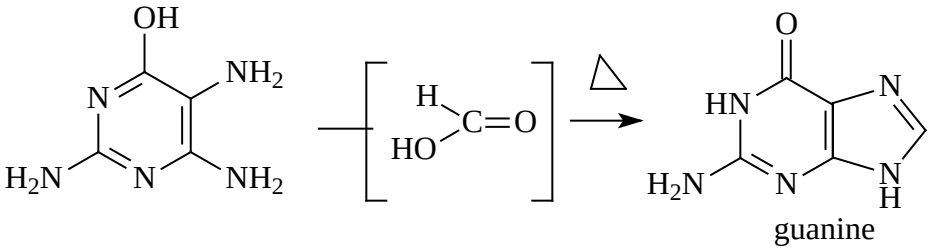
Each compound can be found in all of these plants, but the main component is characteristic.
They have diuretic effect.

Synthesis of uric acid and of purine

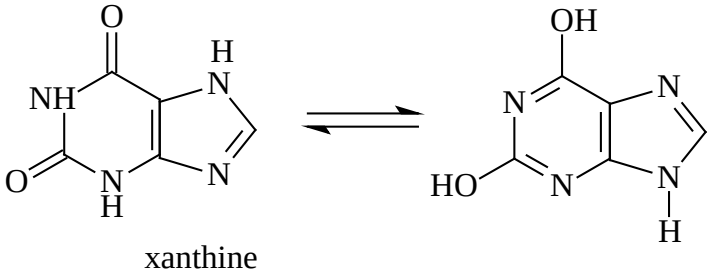
These are compounds isolated in the XVIII. Century (Scheele, 1776). The following synthetic method for purine was introduced by E. Fischer (1898):



Another synthesis of a purine derivative is Traube's method (1900):



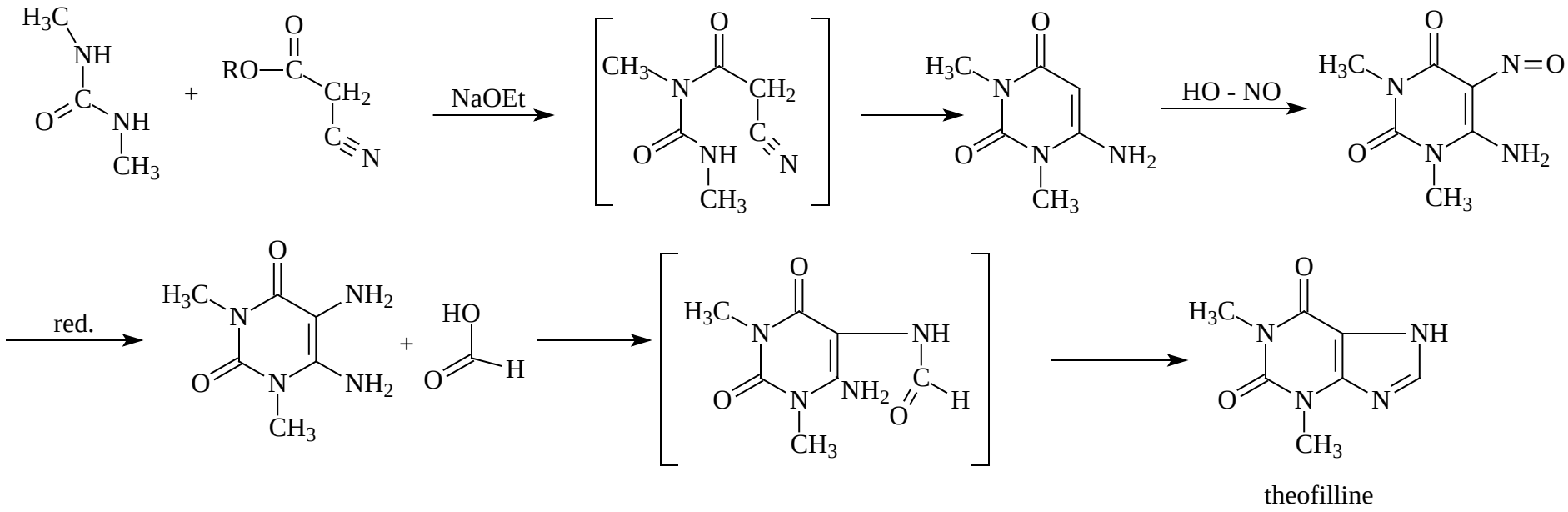
guanine



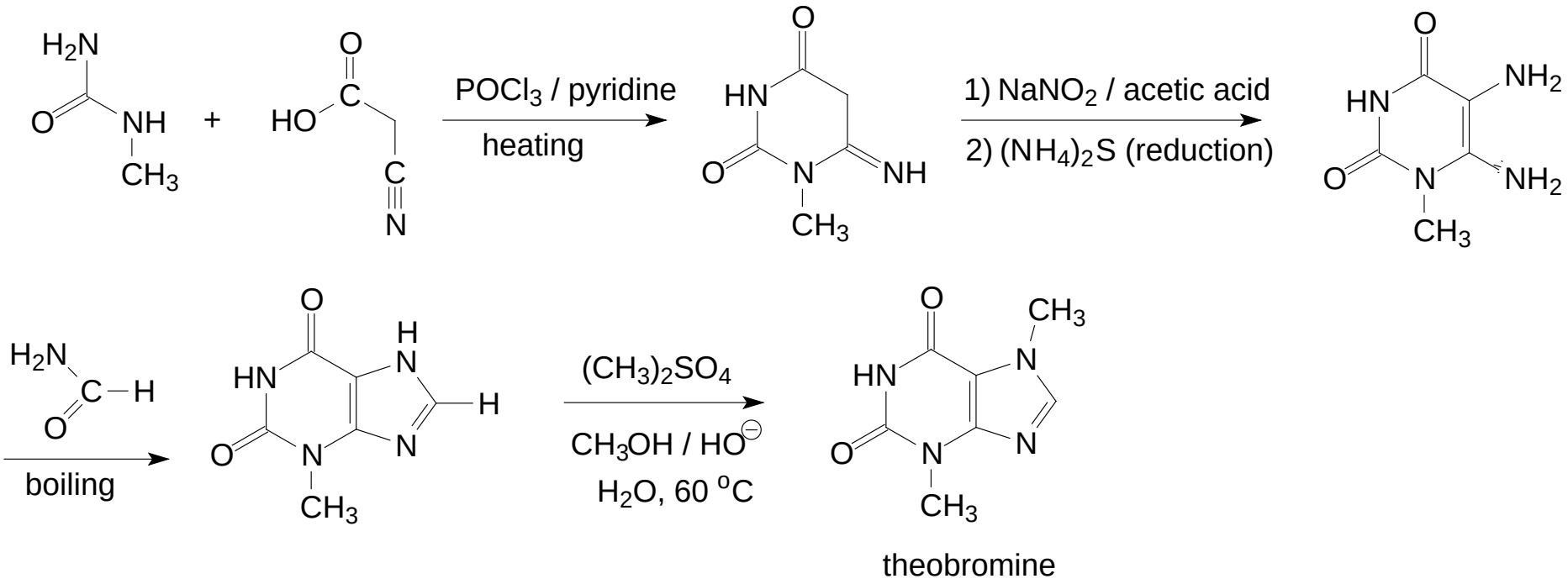
xanthine

Compounds with **purine ring** system

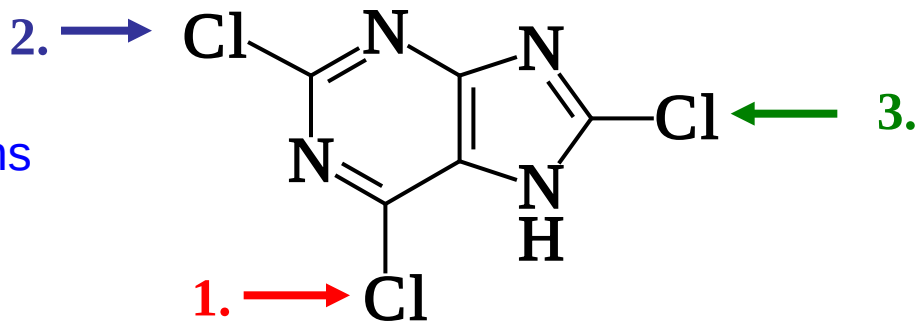
Synthesis of theofilline (Traube synthesis)



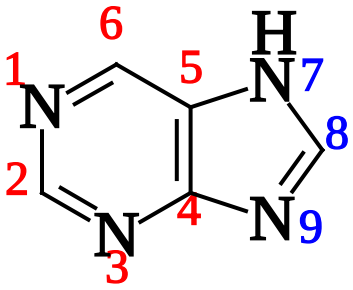
Synthesis of theobromine (Traube synthesis)

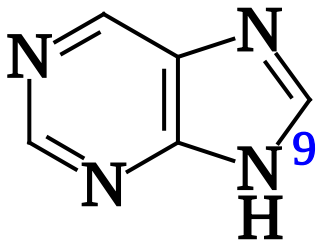


theobromine



S_N reactions





(7*H*)-9*H*-imidazo[4,5-*d*]pirimidin
(unusual, biogenetic numbering)

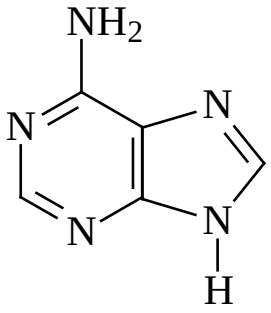
Purine

More important derivatives:

- **guanine**
- **adenine**
- **xanthine**
- **theofilline**
- **theobromine**
- **caffeine**

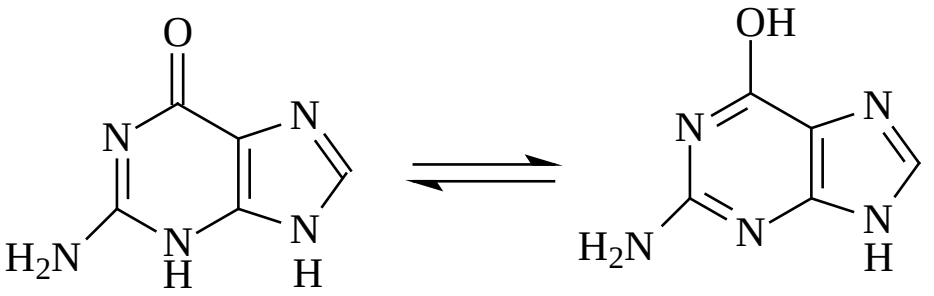
9*H*-purine derivatives

purine bases



adenine

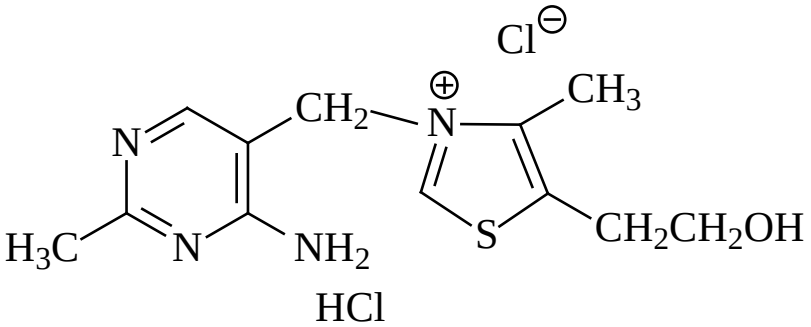
RNS
DNS



guanine

RNS
DNS

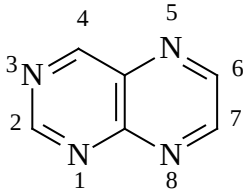
Vitamin B_1 Thiamine, aneurine



Eykmann (1896); absence of it may cause disease beri-beri.
It was isolated at first by Funk from rice bran. Peeled rice may cause beri-beri.

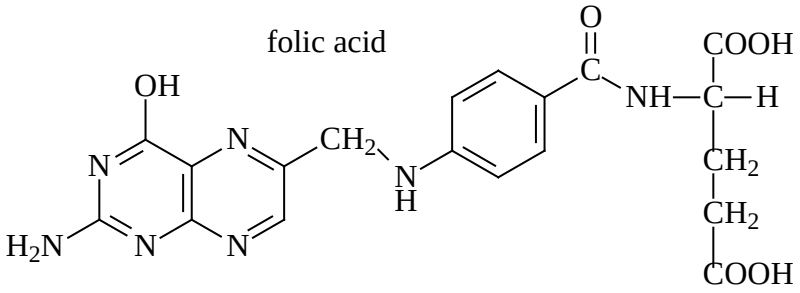
It gives positive thiochrome reaction

Pteridine and its derivatives



pteridine

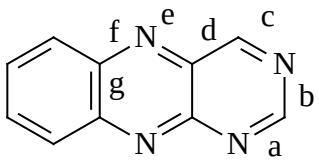
folic acid



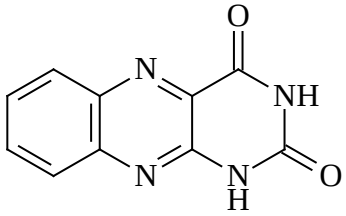
pterine part — p-aminobenzoic acid — L-glutaminic acid

pteroyl group

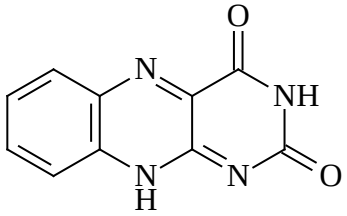
Folic acid is an important vitamin: its N-formyl derivative builds the C_1 unit in biosyntheses



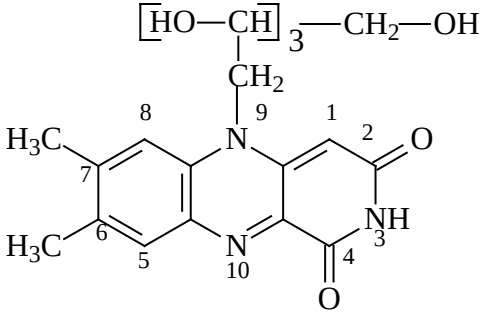
benzo[*g*]pteridine



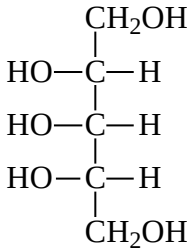
alloxazine



isoalloxazine



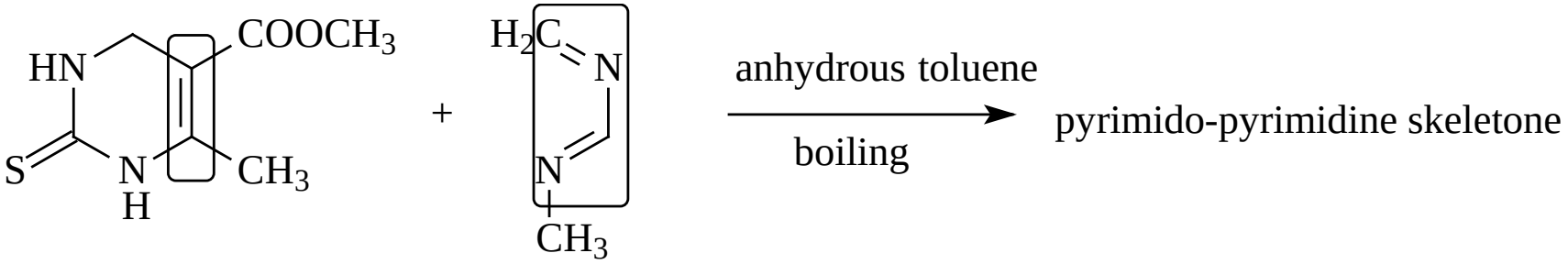
Vitamin B_2



ribitol

take place by prosthetic groups of enzymes
(flavoproteide enzymes, e.g., FAD)

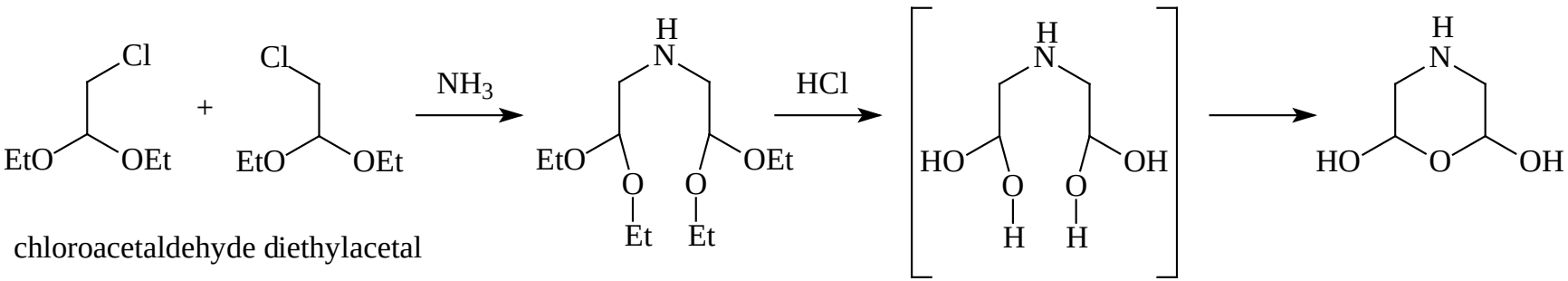
Compounds with **pyrimido-pyrimidine ring** system



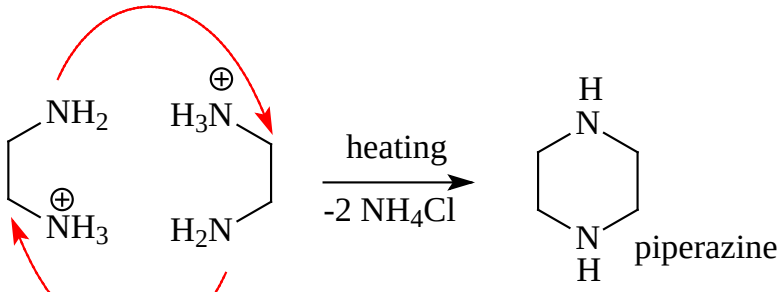
regioisomers

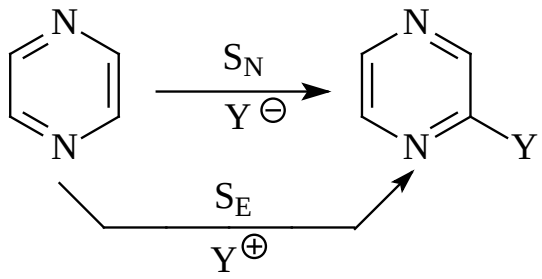
regioisomers

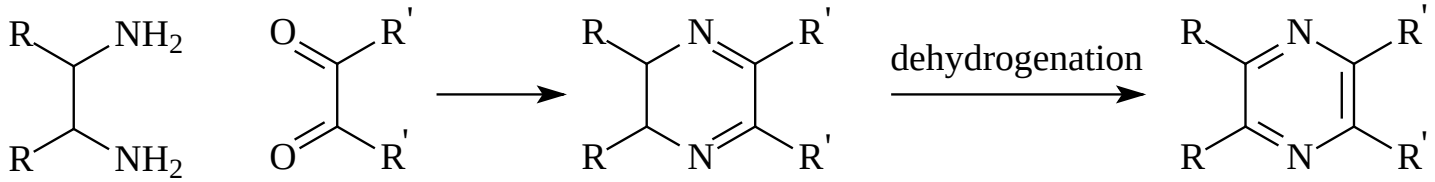
Pyrazine and its derivatives



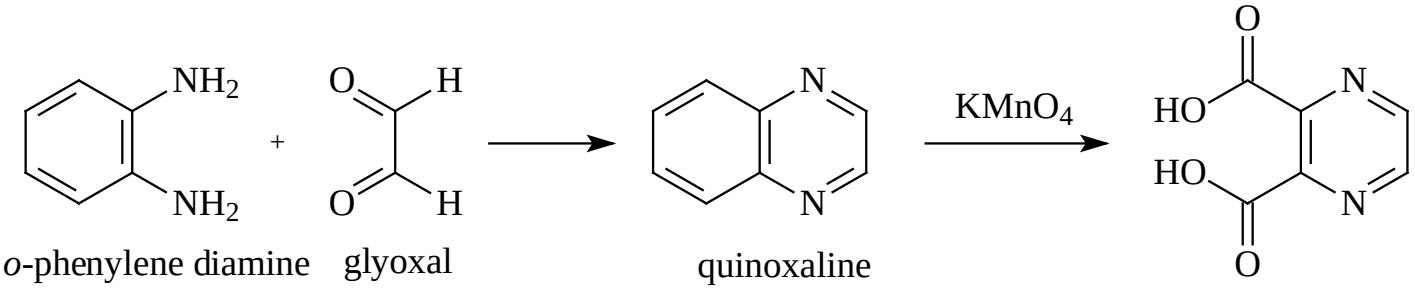
chloroacetaldehyde diethylacetal



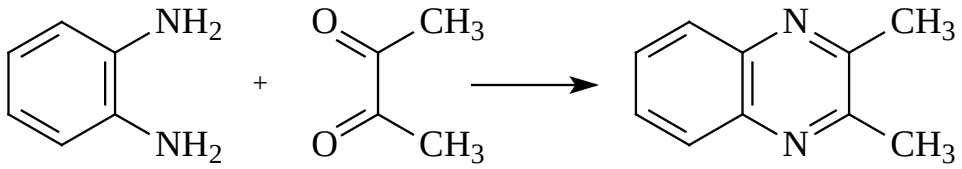




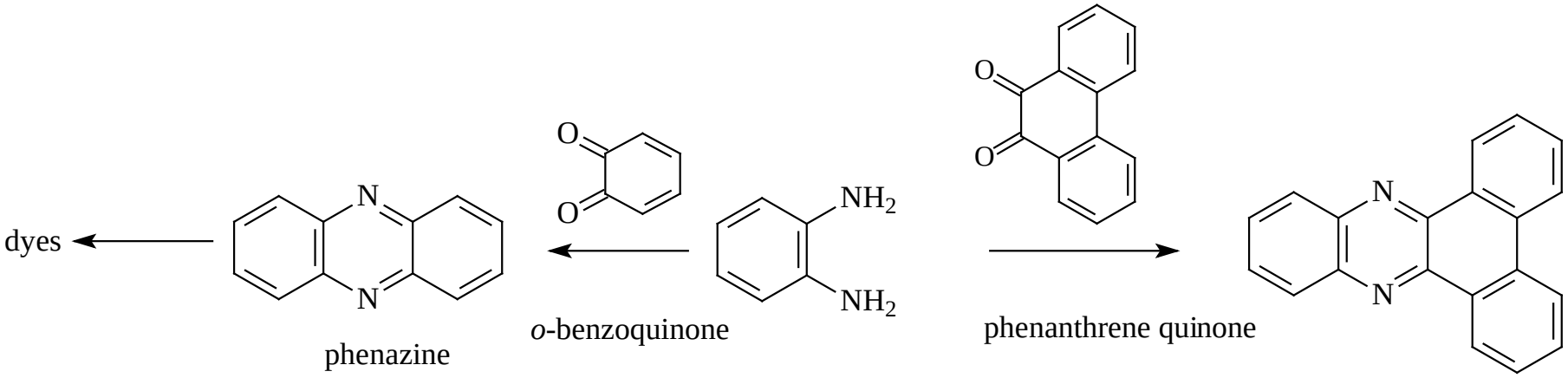
Benzocondensed derivatives of pyrazine



o-phenylene diamine glyoxal quinoxaline



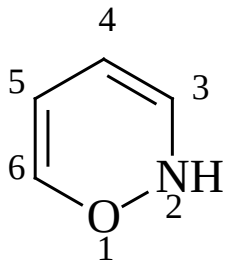
o-phenylene diamine dimethylglyoxal 2,3-dimethylquinoxaline



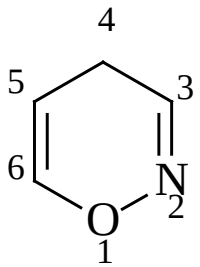
phenazine *o*-benzoquinone phenanthrene quinone dibenzophenazine

Compounds with two different heteroatoms

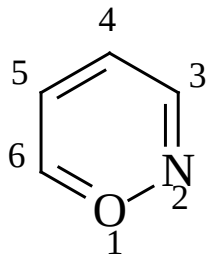
I/ Oxazine and its derivatives



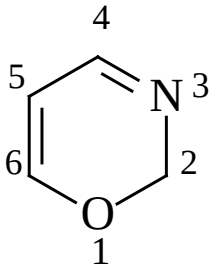
2*H*-1,2-oxazine



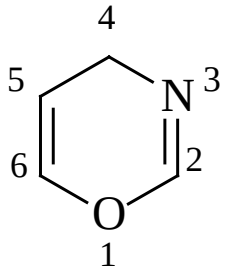
4*H*-1,2-oxazine



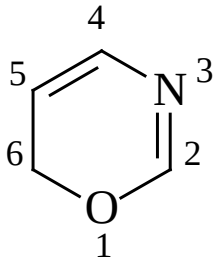
6*H*-1,2-oxazine



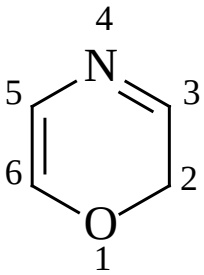
2*H*-1,3-oxazine



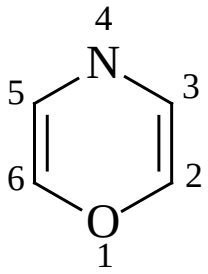
4*H*-1,3-oxazine



6*H*-1,3-oxazine

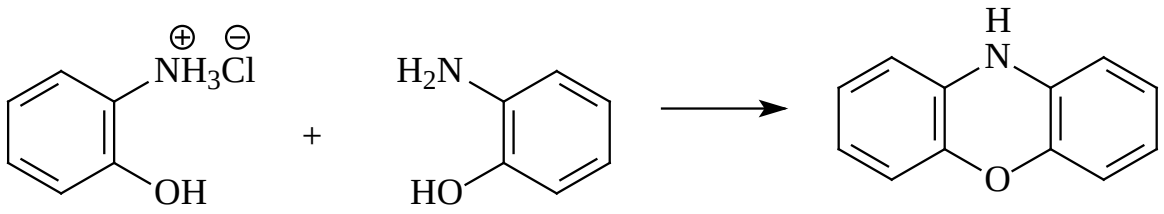


2*H*-1,4-oxazine

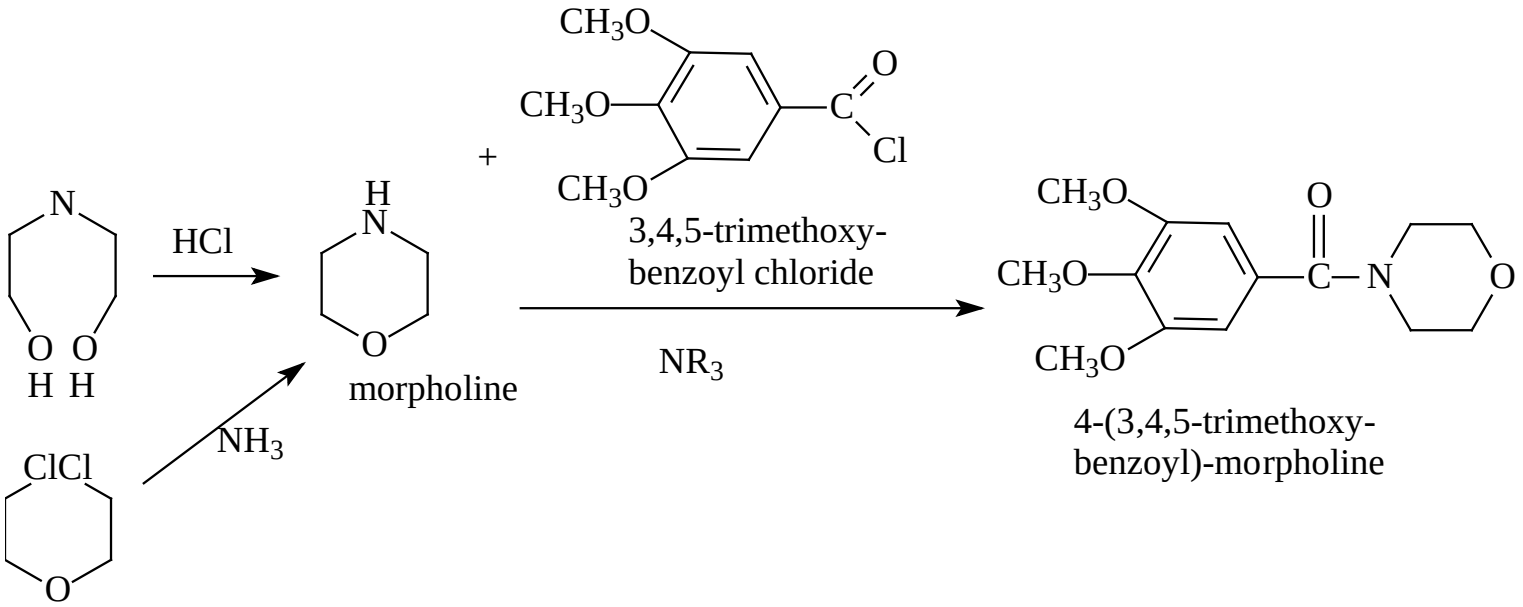


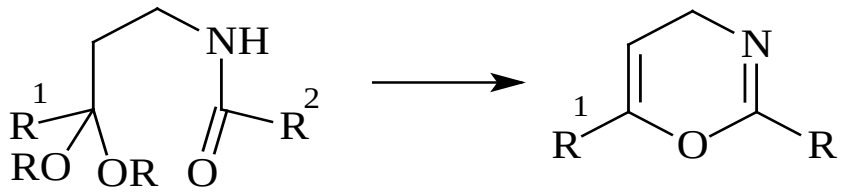
4*H*-1,4-oxazine

Further derivatives: benzocondensed derivatives
partially saturated derivatives



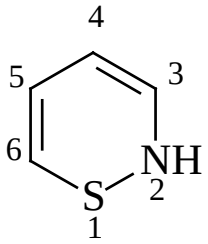
dibenzo-1,4-oxazine
phenoxazine



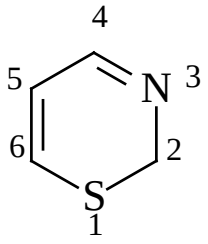


acetals of β-acetyl-
aminoketones

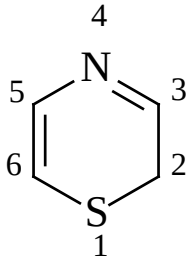
II/ Thiazine and its derivatives



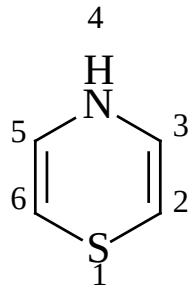
2*H*-1,2-thiazine



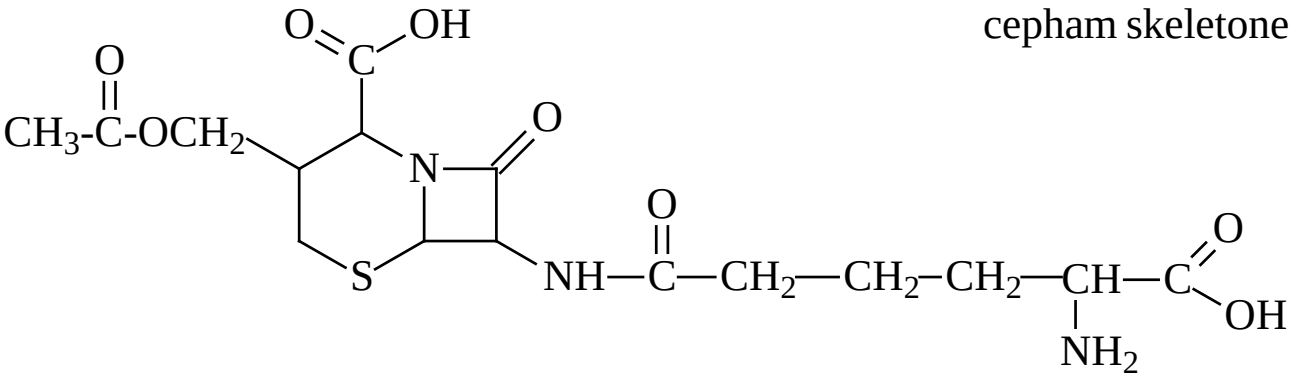
2*H*-1,3-thiazine



2*H*-1,4-thiazine



4*H*-1,4-thiazine



cepham skeletone

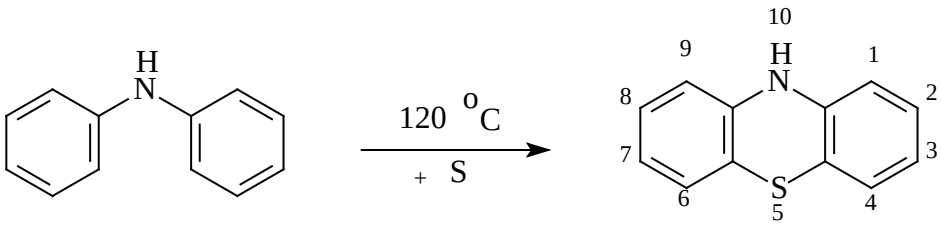
-NH_2

7- amino-cephalosporanic acid

Cephalosporin C antibiotic drug

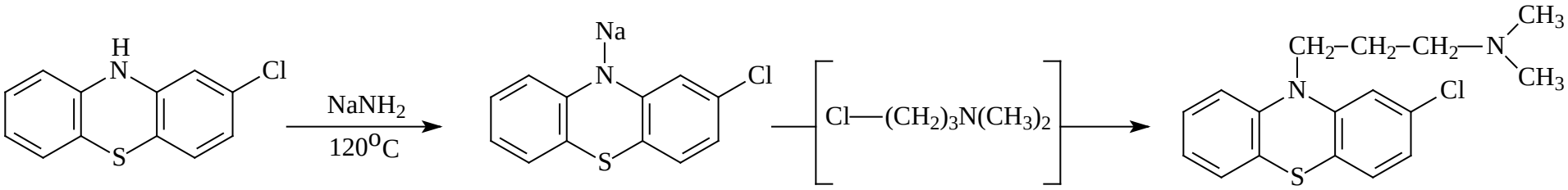
Cephalosporium fungi species

Antibiotics: microorganisms (fungi) are producing against other microorganisms (bacteria)



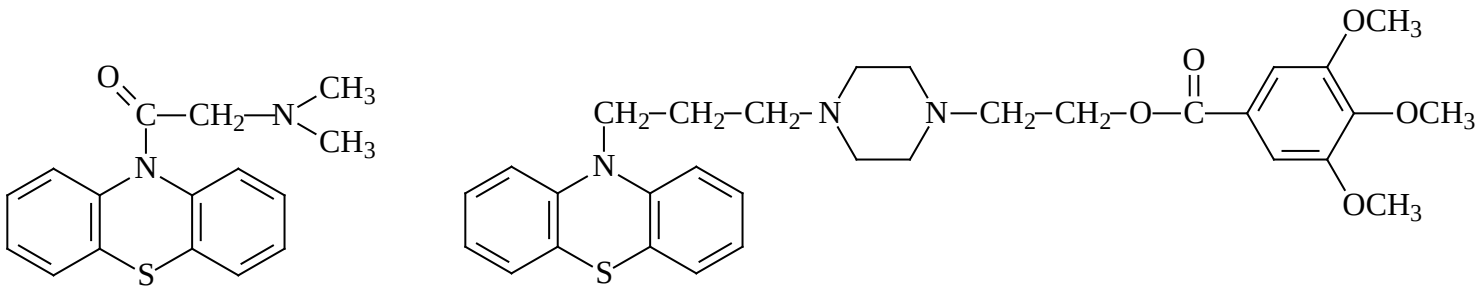
phenothiazine

many important drugs have phenothiazine ring system (neuroleptics, anthelmintic agents)



chloropromazin (Hibernal, Largactil, Plegomazin)

neuroleptic drug



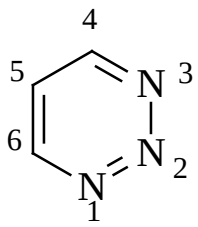
Ahistan (antihistaminic agent)
prepared at first by O. Clauder

Frenolon (original Hungarian drug)
neuroleptic drug

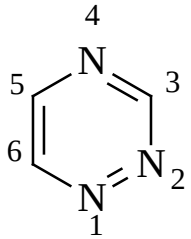
There are phenothiazine dyes (methylen blue), and other benzocondensed derivatives.

Compounds with *three* heteroatoms

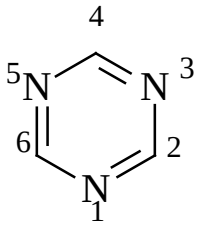
I/ Triazines



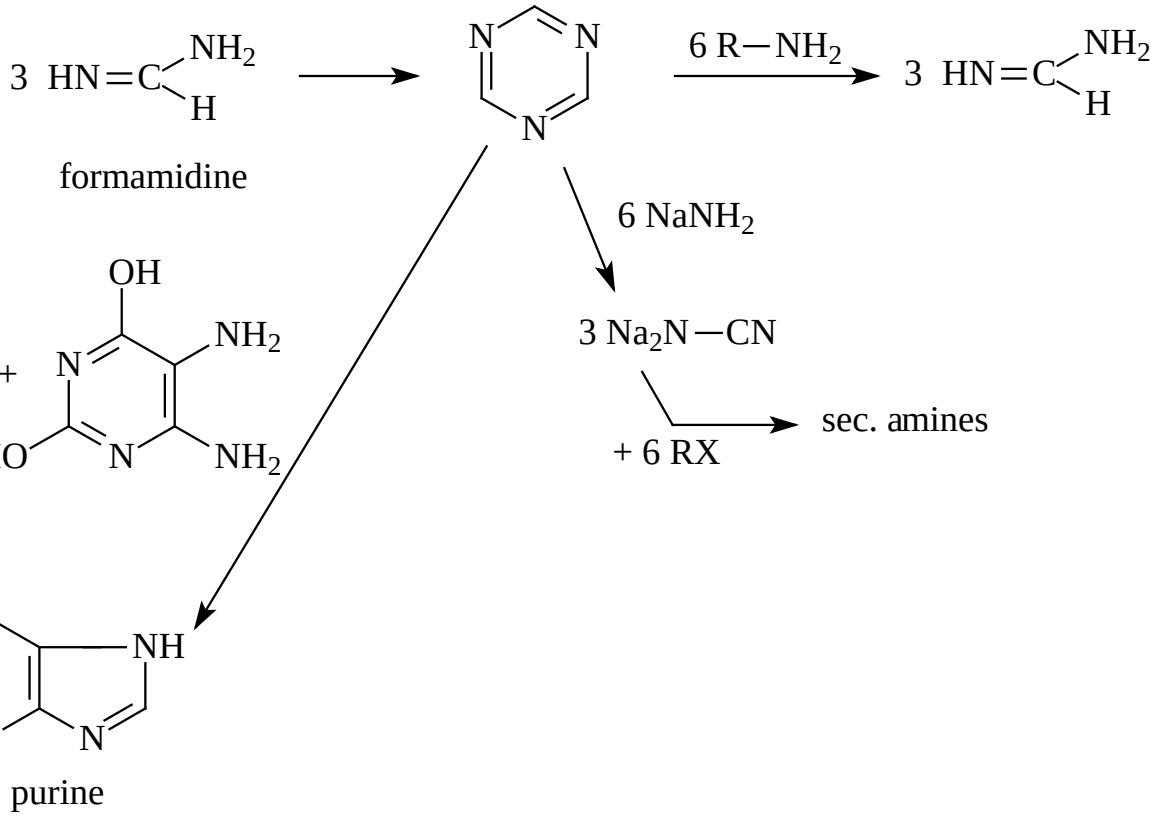
1,2,3-triazine
(vicinal)

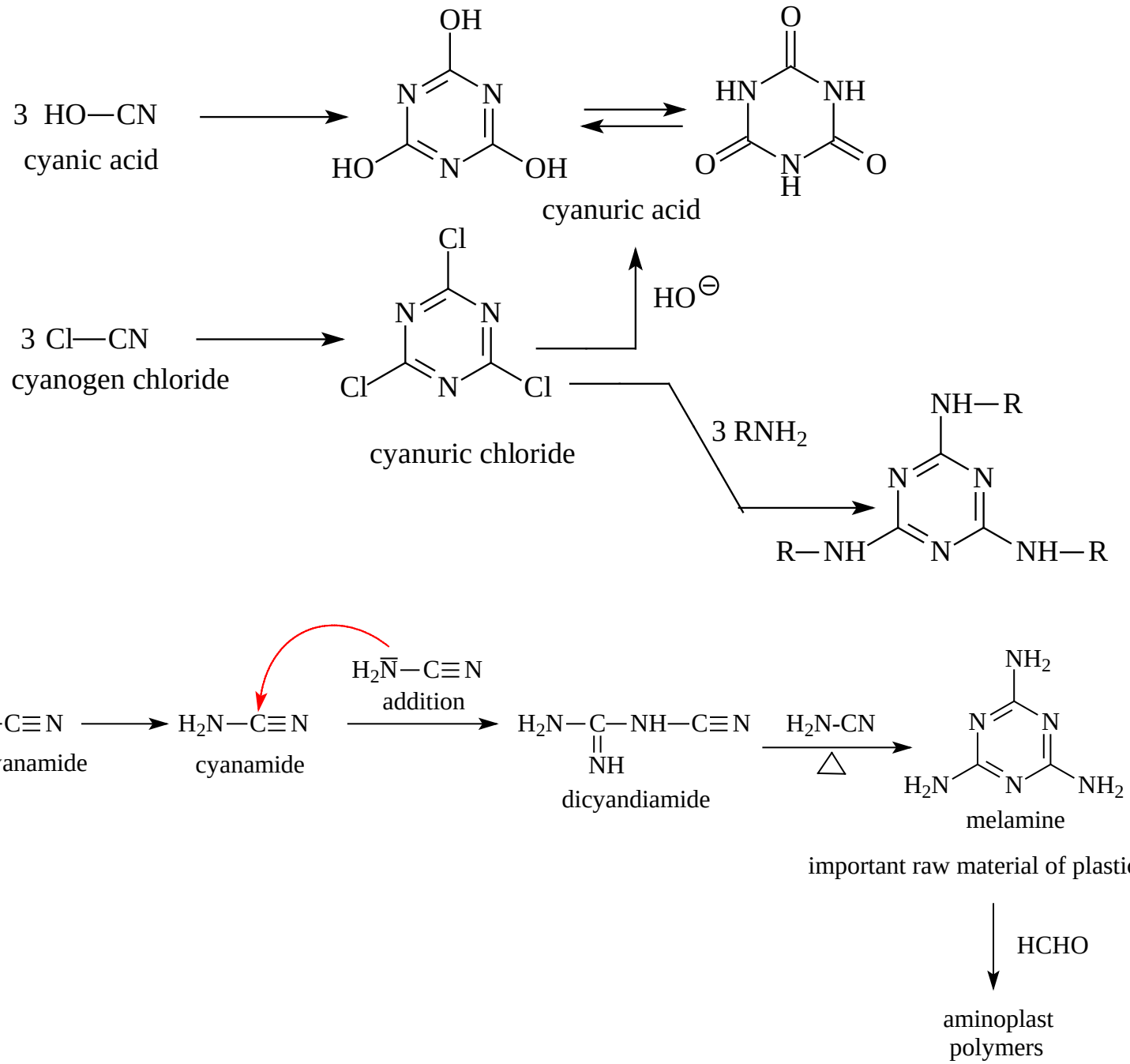


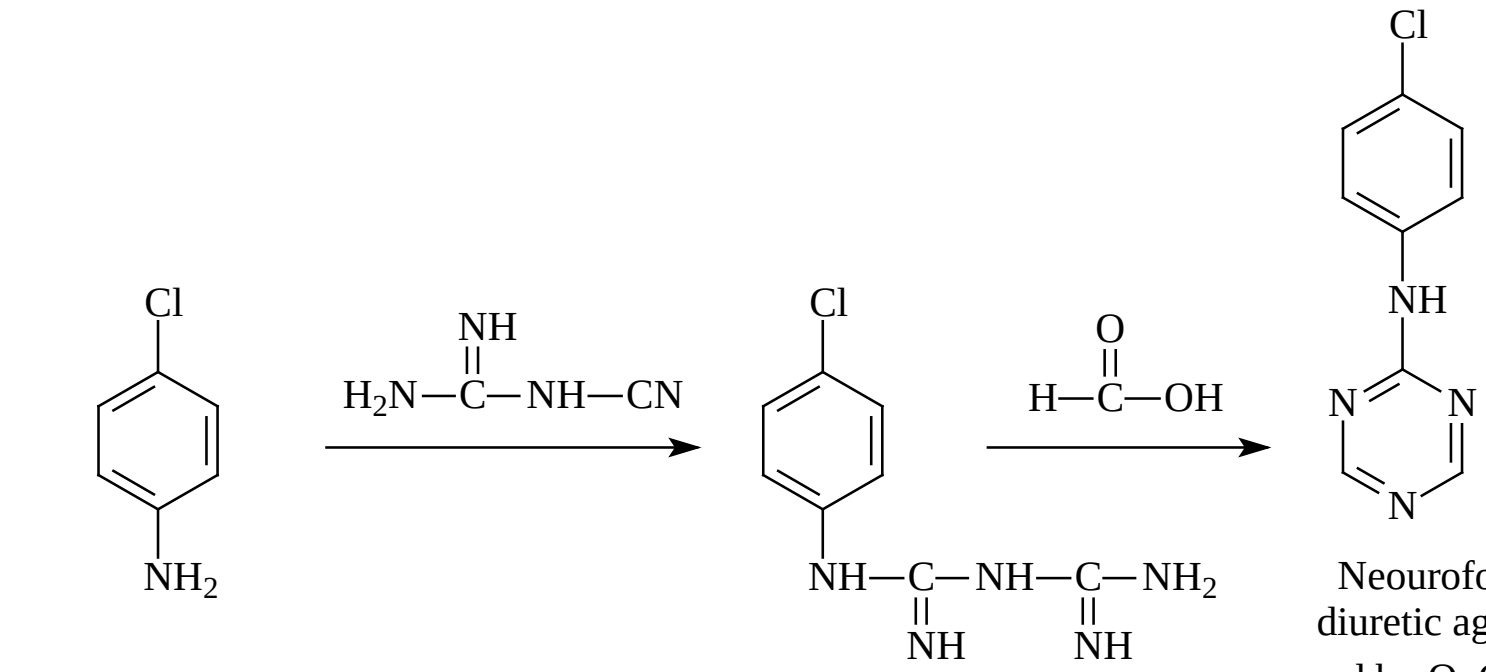
1,2,4-triazine
(asymmetric)



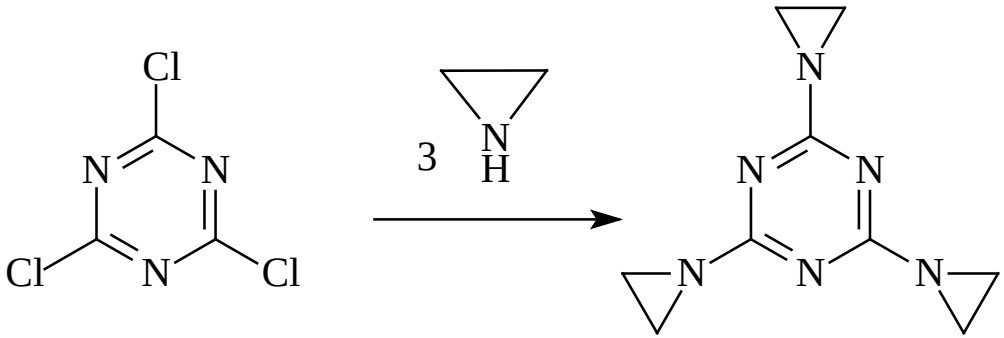
1,3,5-triazine / sym-triazine
(symmetric)




3 HO—CN
cyanic acid
cyanuric acid
3 Cl—CN
cyanogen chloride
cyanuric chloride
3 RNH2
addition
Ca═N—C≡N
calcium cyanamide
H2N—C≡N
cyanamide
H2N—C—NH—C≡N
NH
dicyandiamide
H2N-CN
melamine
important raw material of plastic industry
HCHO
aminoplast
polymers

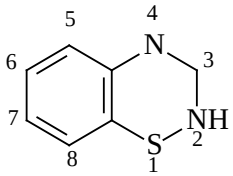


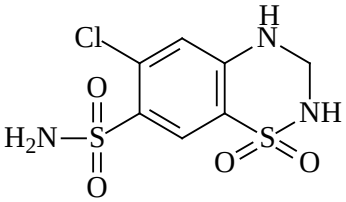
Neourofort
diuretic agent
prepared by O. Clauder at first



triethylenemelamine
against leukaemia, leucosarcoma
[2,4,6-tris(aziridin-1-yl)]-1,3,5-triazine

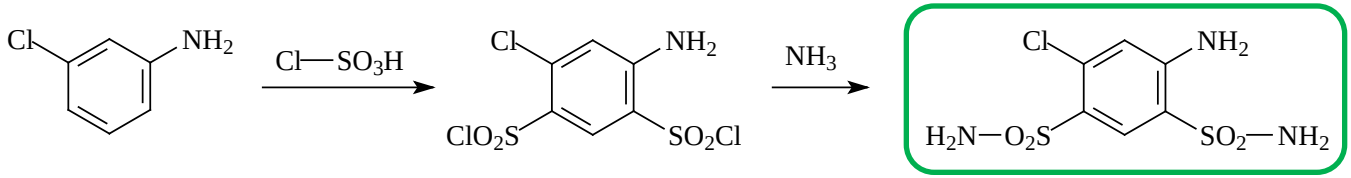
II/ Thiadiazines

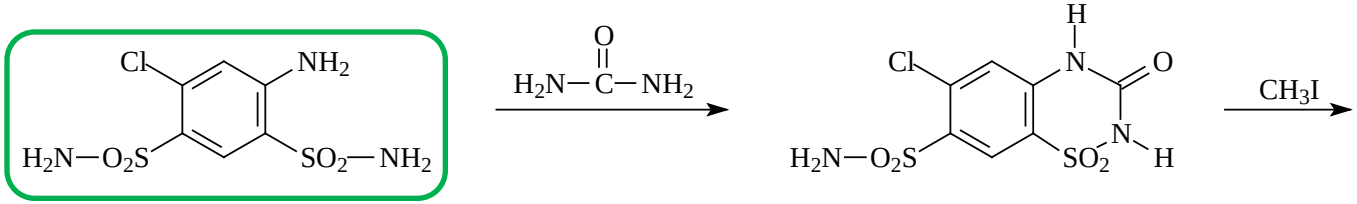


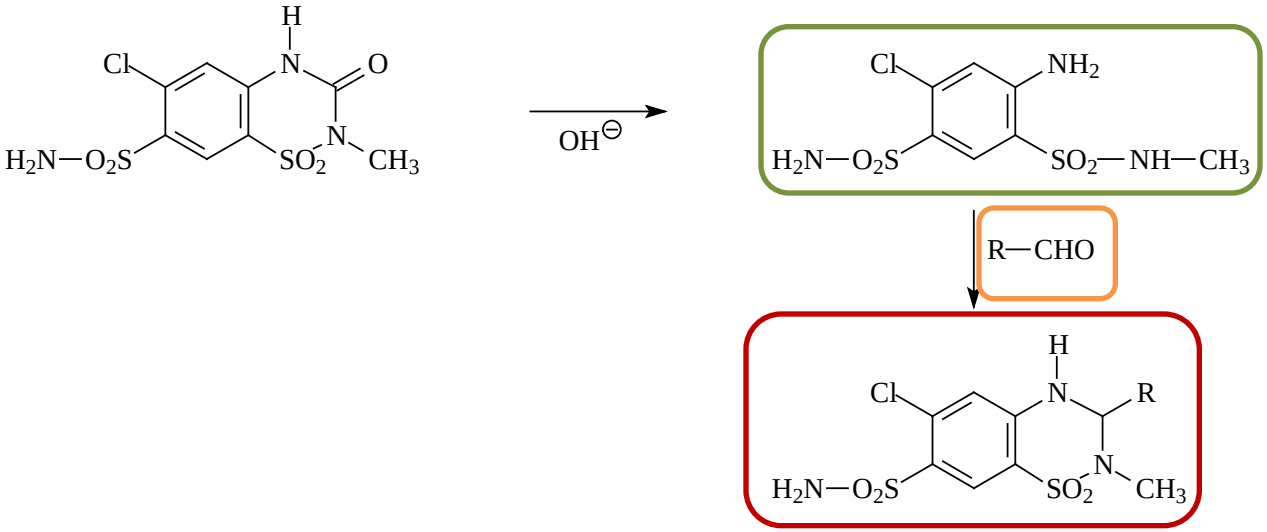


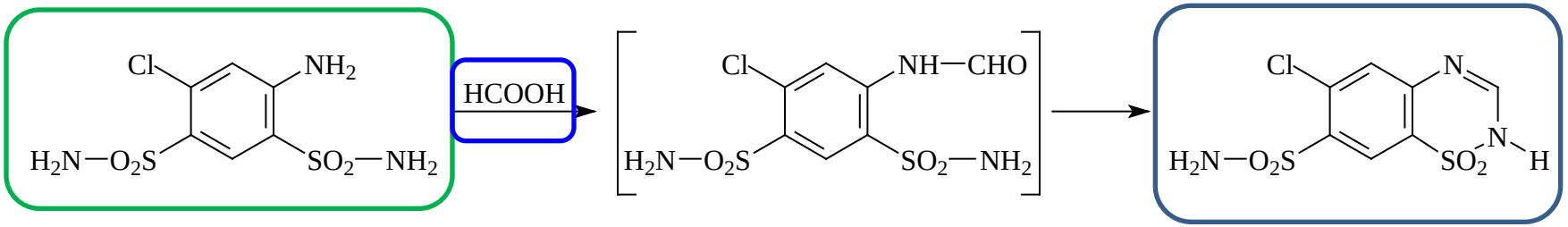
hydrochlorothiazide
diuretic agent

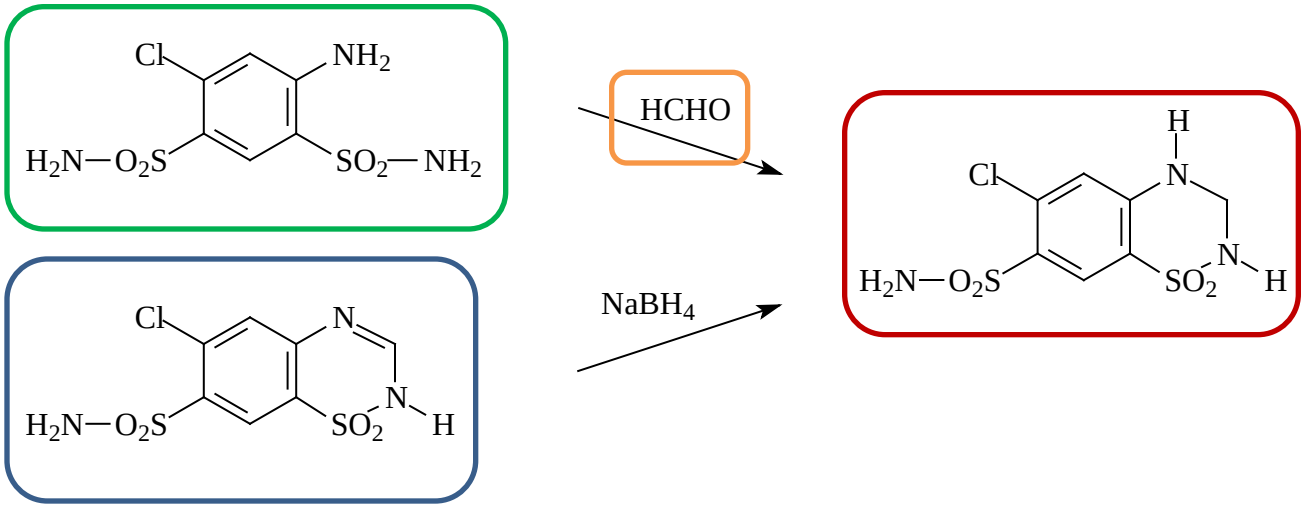
2*H*-1,2,4-benzo[*e*]thiadiazine





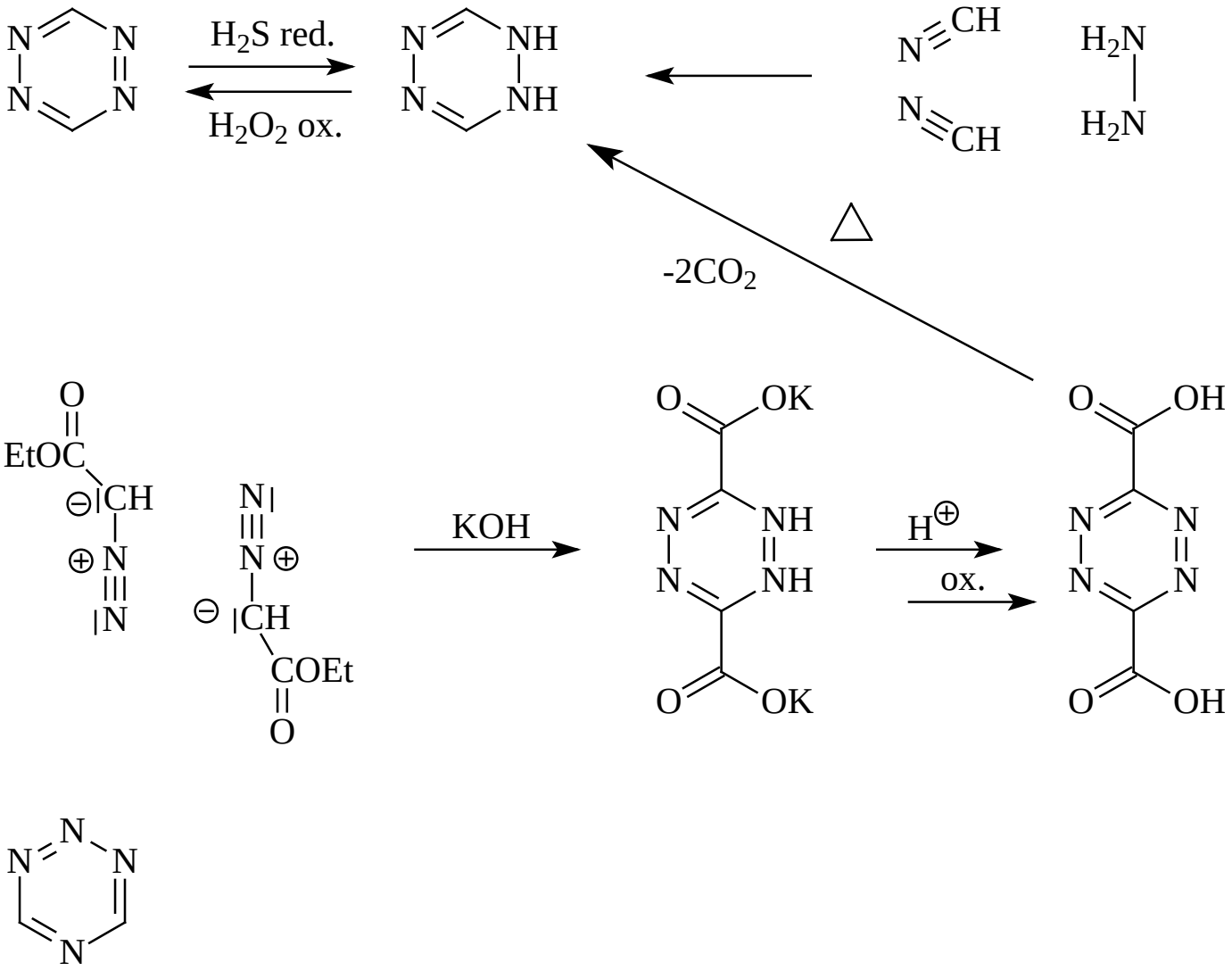



Cl
NH2
H2N—O2S
SO2—NH2
HCOOH
NH—CHO
N
H


Cl
NH2
H2N—O2S
SO2—NH2
HCHO
NaBH4
N
H

Compounds with *four* heteroatoms

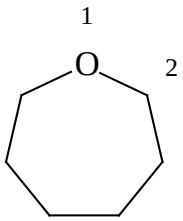
I/ Tetrazines



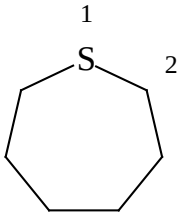
Heterocyclic compounds with seven- and eight-membered rings and their derivatives

Heterocyclic compounds with seven-membered rings

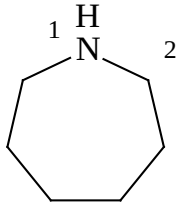
Nomenclature, some important derivatives



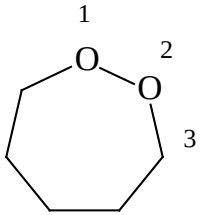
oxepane



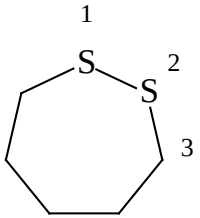
thiepane



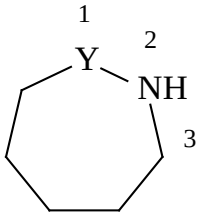
azepane



1,2-dioxepane

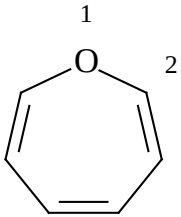


1,2-dithiepane

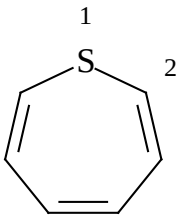


Y=O 1,2-oxazepane

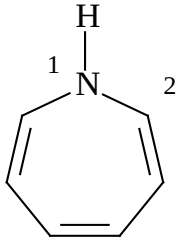
Y=S 1,2-thiazepane



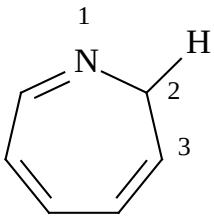
oxepine



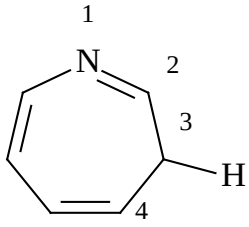
thiepine



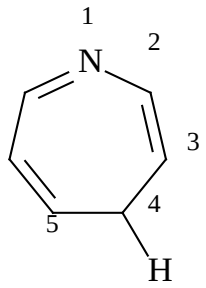
1*H*-azepine



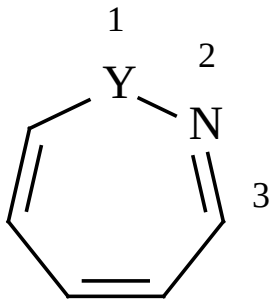
2*H*-azepine



3*H*-azepine

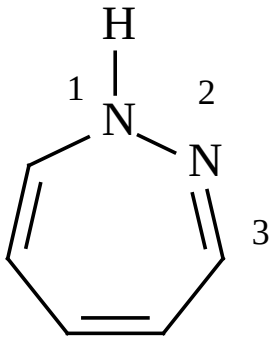


4*H*-azepine

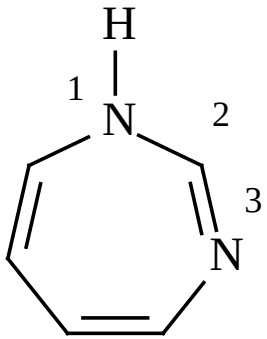


Y=O 1,2-oxazepine

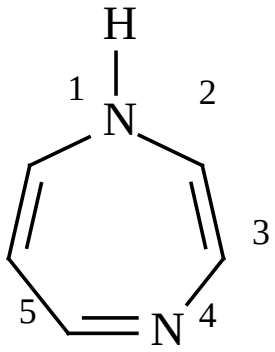
Y=S 1,2-thiazepine



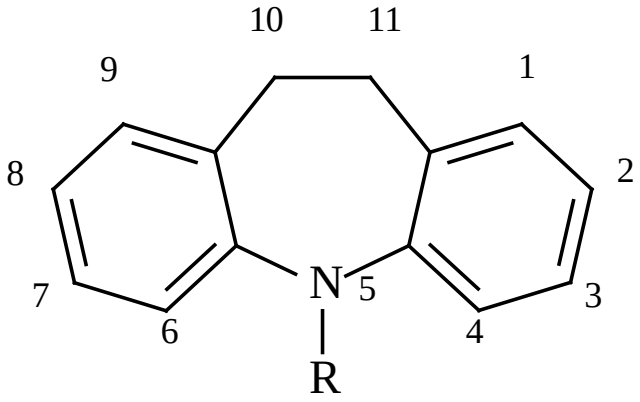
1*H*-1,2-diazepine



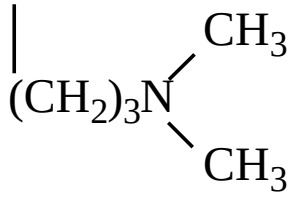
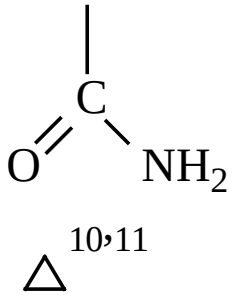
1*H*-1,3-diazepine



1*H*-1,4-diazepine

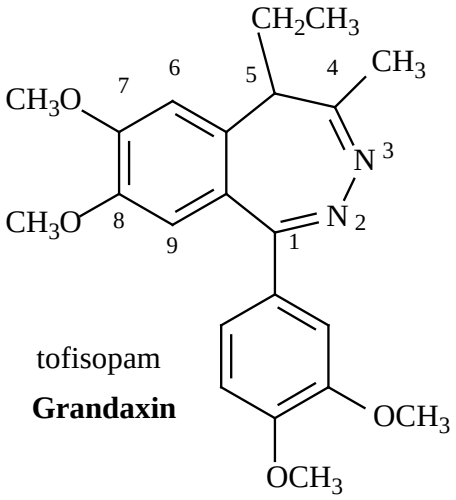


dibenzoazepine
derivatives

R	Name
	imipramin **antidepressant**
	carbamazepine **antiepileptics**

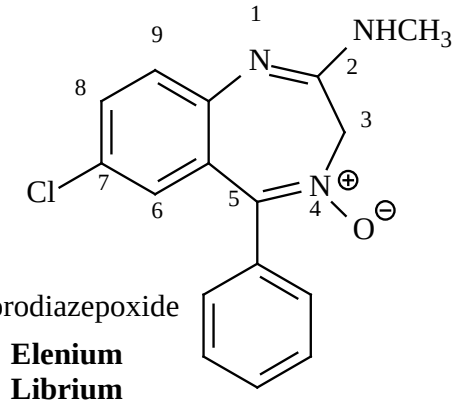
Benzodiazepine derivatives

Sedatohypnotica



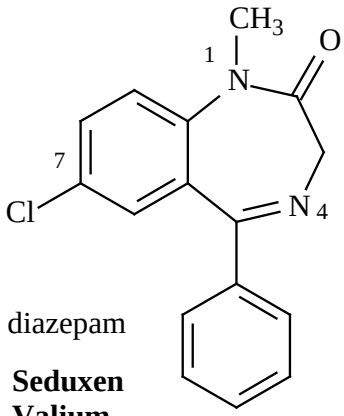
tofisopam

Grandaxin



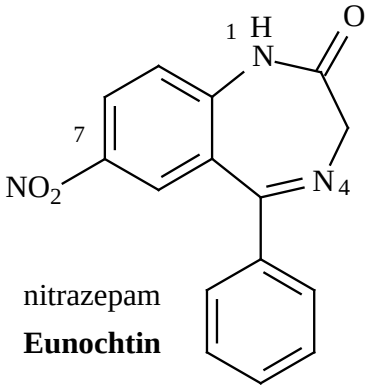
chlorodiazepoxide

Elenium
Librium



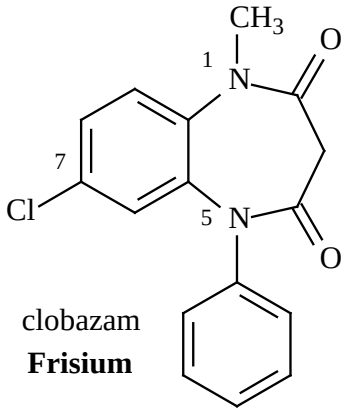
diazepam

Seduxen
Valium



nitrazepam

Eunochtin

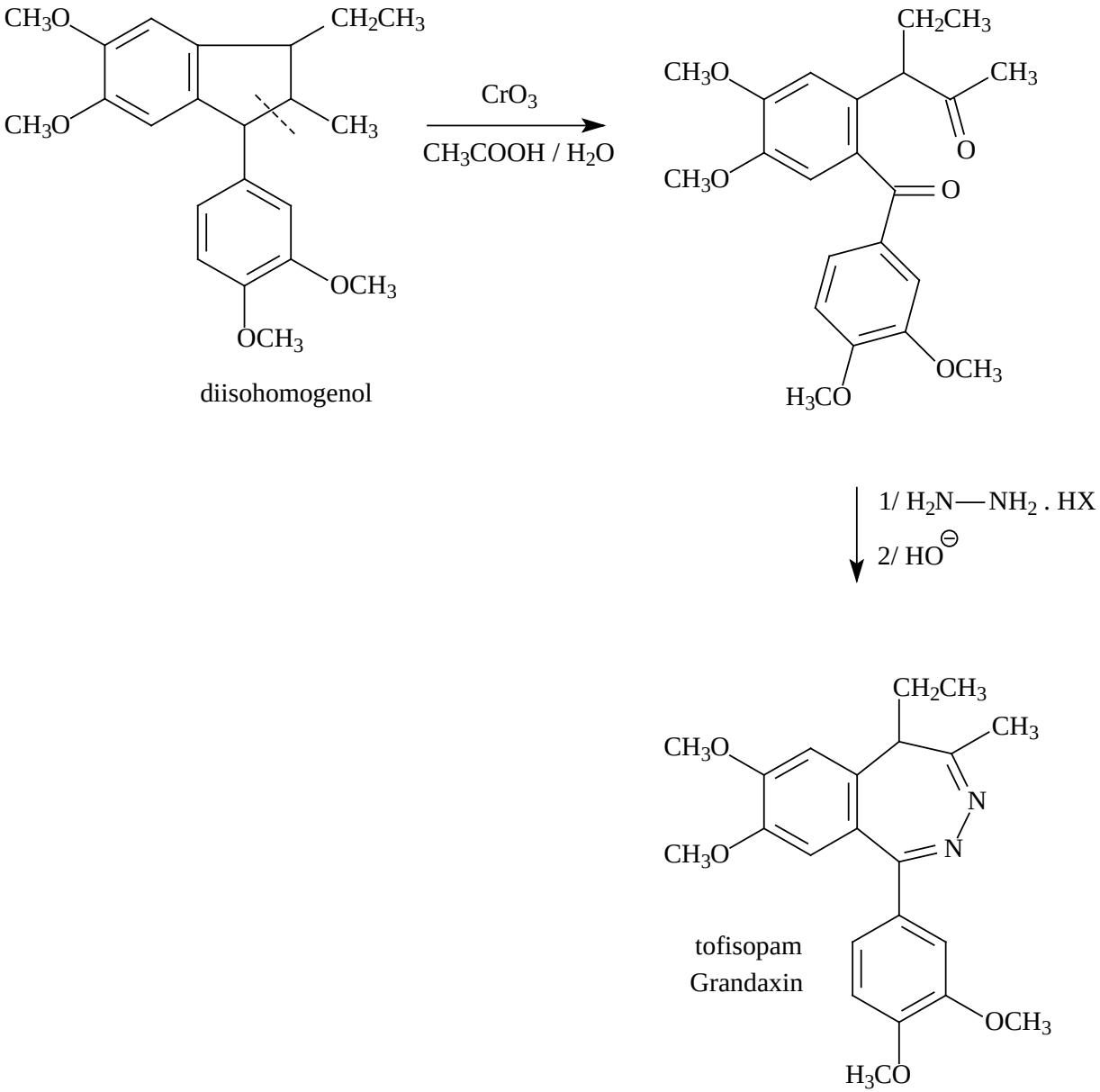


clobazam

Frisium

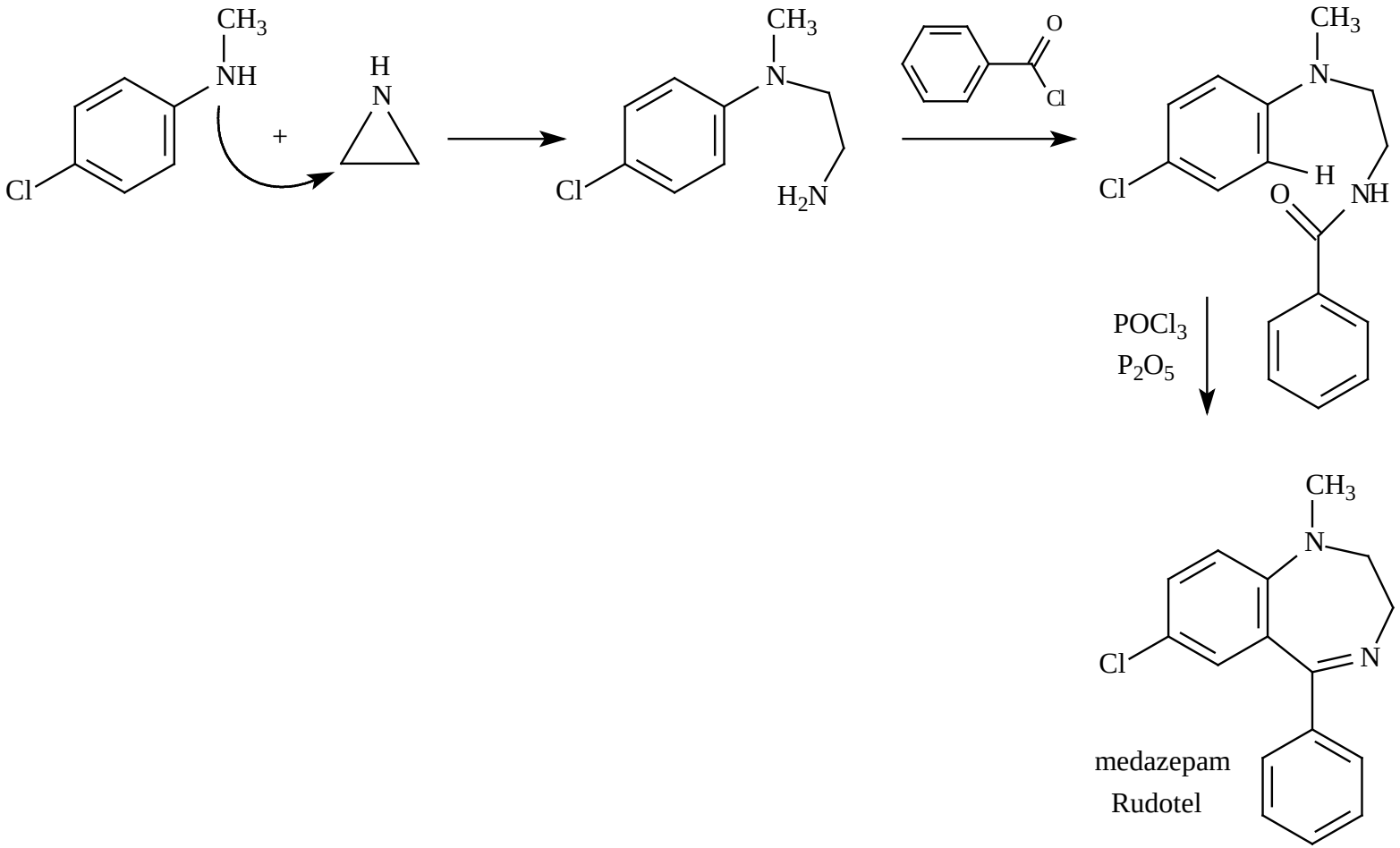
Grandaxin: anxiolitics free from sedative side-effects (e.g., it can be administered before driving) (J. Kőrösi at GYKI, EGYT, 1966. Hungarian patent)

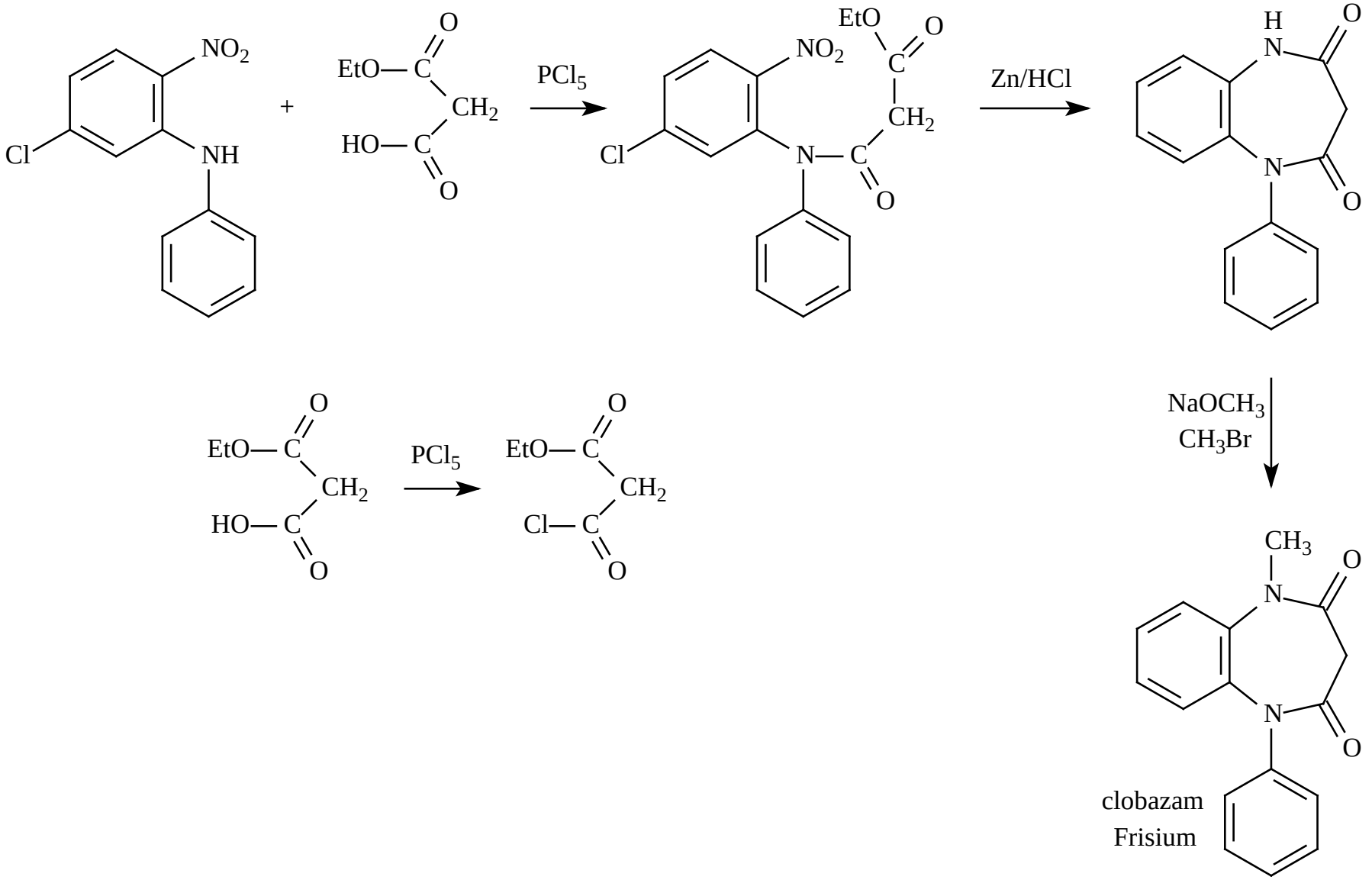
Preparation

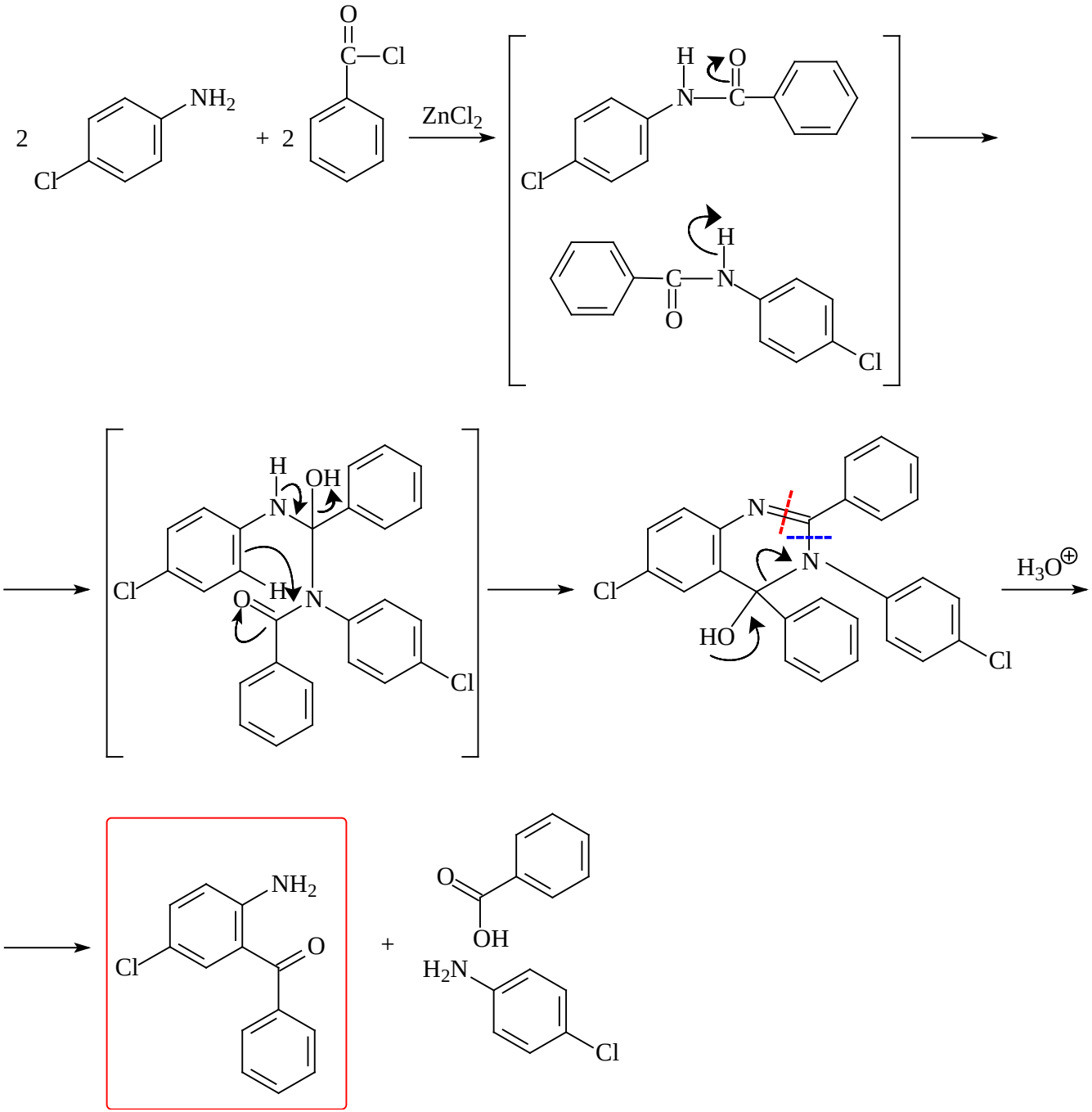


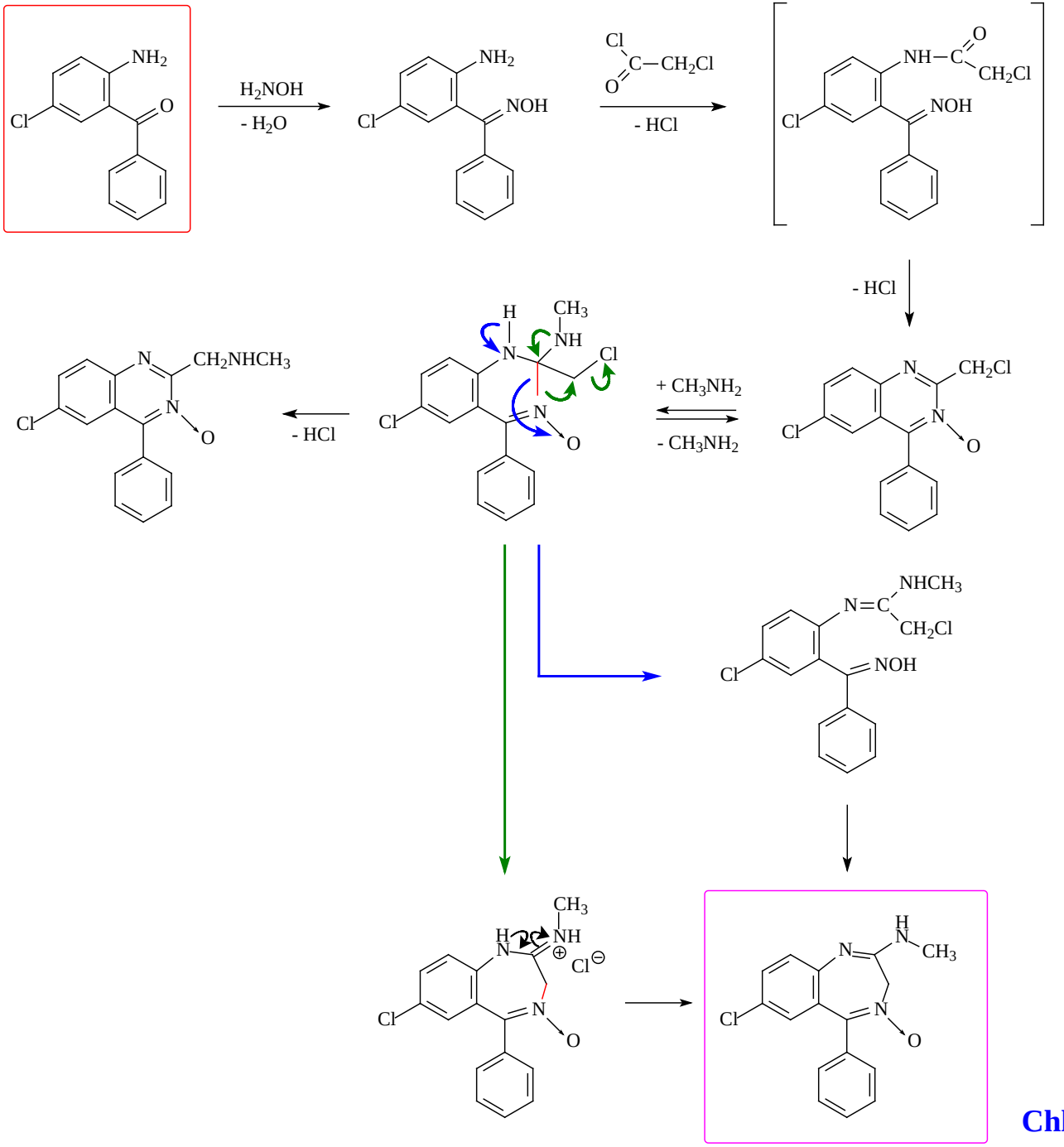
diisohomogenol

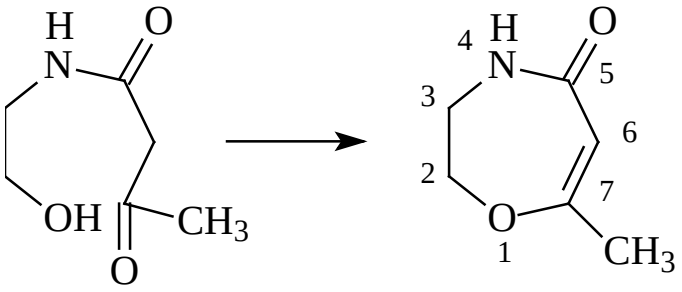
tofisopam
Grandaxin


CH3
NH
Cl
+
H
N
CH3
N
Cl
H2N
O
Cl
CH3
N
Cl
H
O
NH
POCl3
P2O5
CH3
N
Cl
N
medazepam
Rudotel

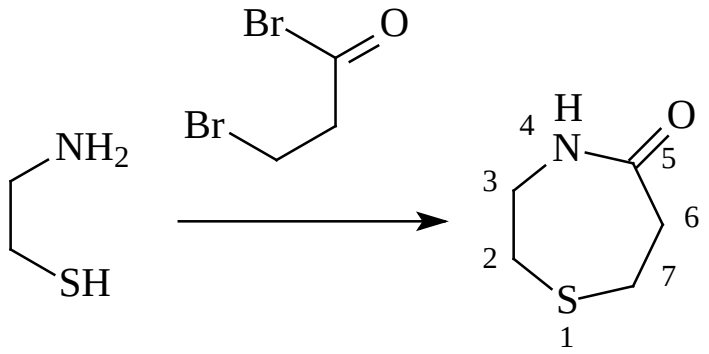

NO2
Cl
NH
+
EtO
C
O
CH2
HO
PCl5
Zn/HCl
H
N
NaOCH3
CH3Br
CH3
clobazam
Frisium


2
NH2
Cl
+ 2
O
C
Cl
ZnCl2
H
N
O
C
Cl
H
C
N
O
Cl
H
OH
N
Cl
H
N
O
Cl
N
N
Cl
HO
Cl
H3O⊕
NH2
Cl
O
+
O
OH
H2N
Cl

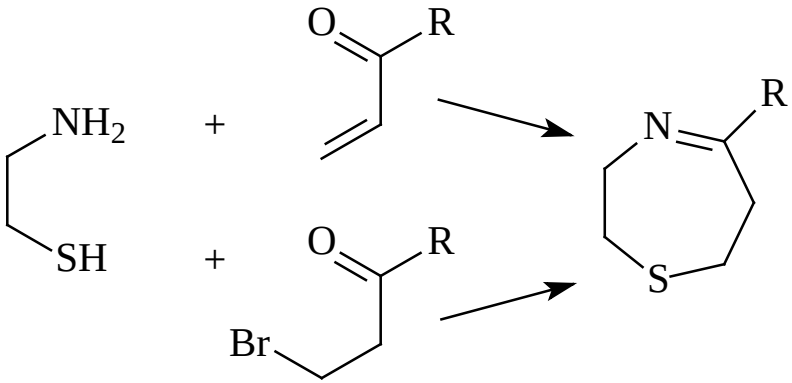

NH2
Cl
O
H2NOH
- H2O
NOH
Cl
C—CH2Cl
- HCl
NH—C
CH2Cl
- HCl
H
CH3
NH
N
Cl
+ CH3NH2
- CH3NH2
CH2NHCH3
- HCl
CH2Cl
NHCH3
N=C
CH2Cl
NOH
Cl⊖
Chlordiazepoxide

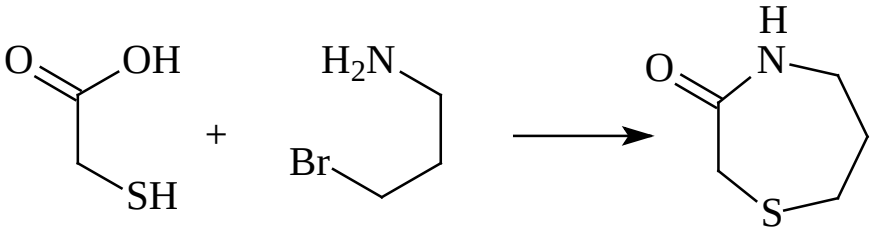


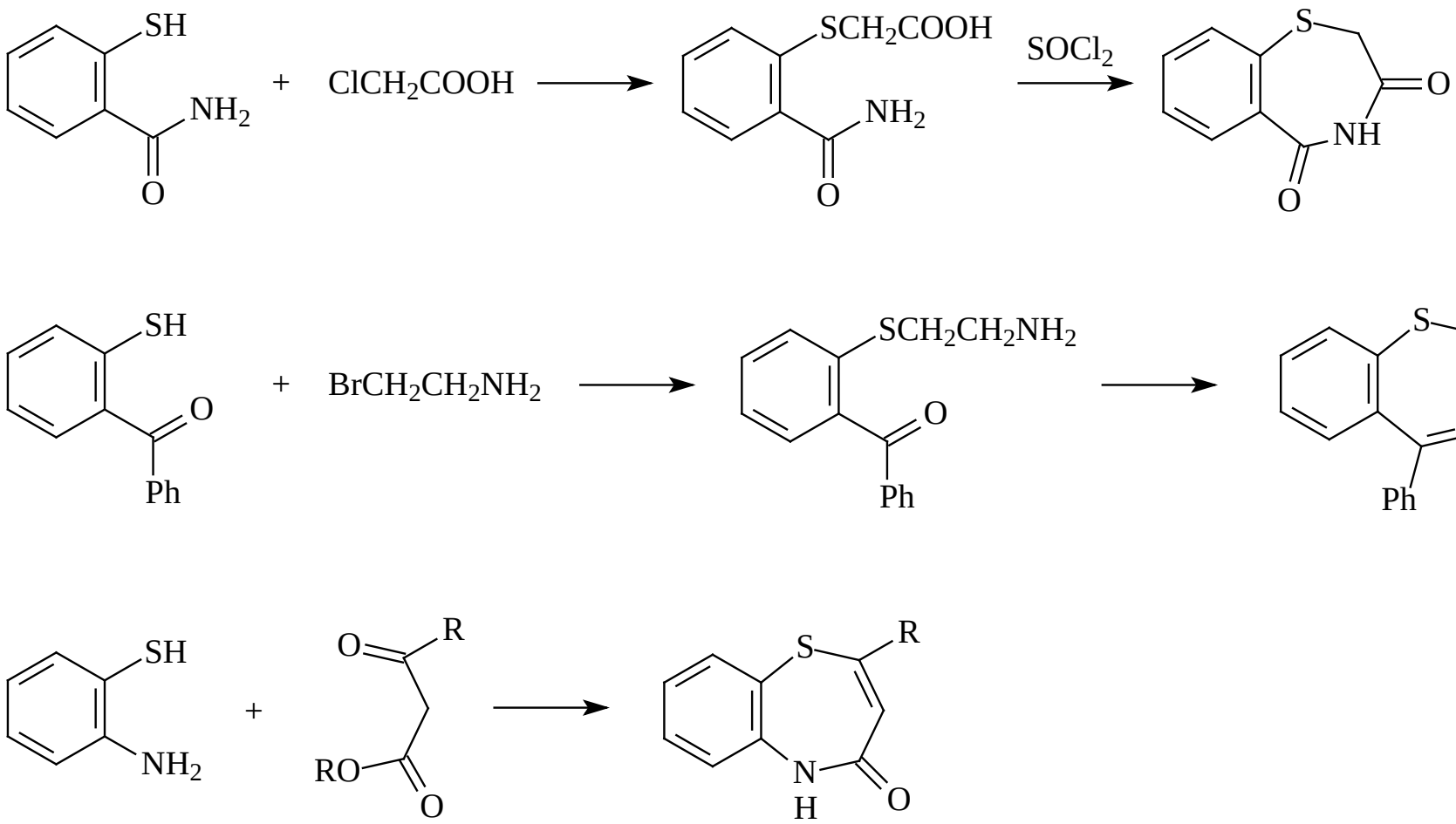
1,4-oxazepine derivative

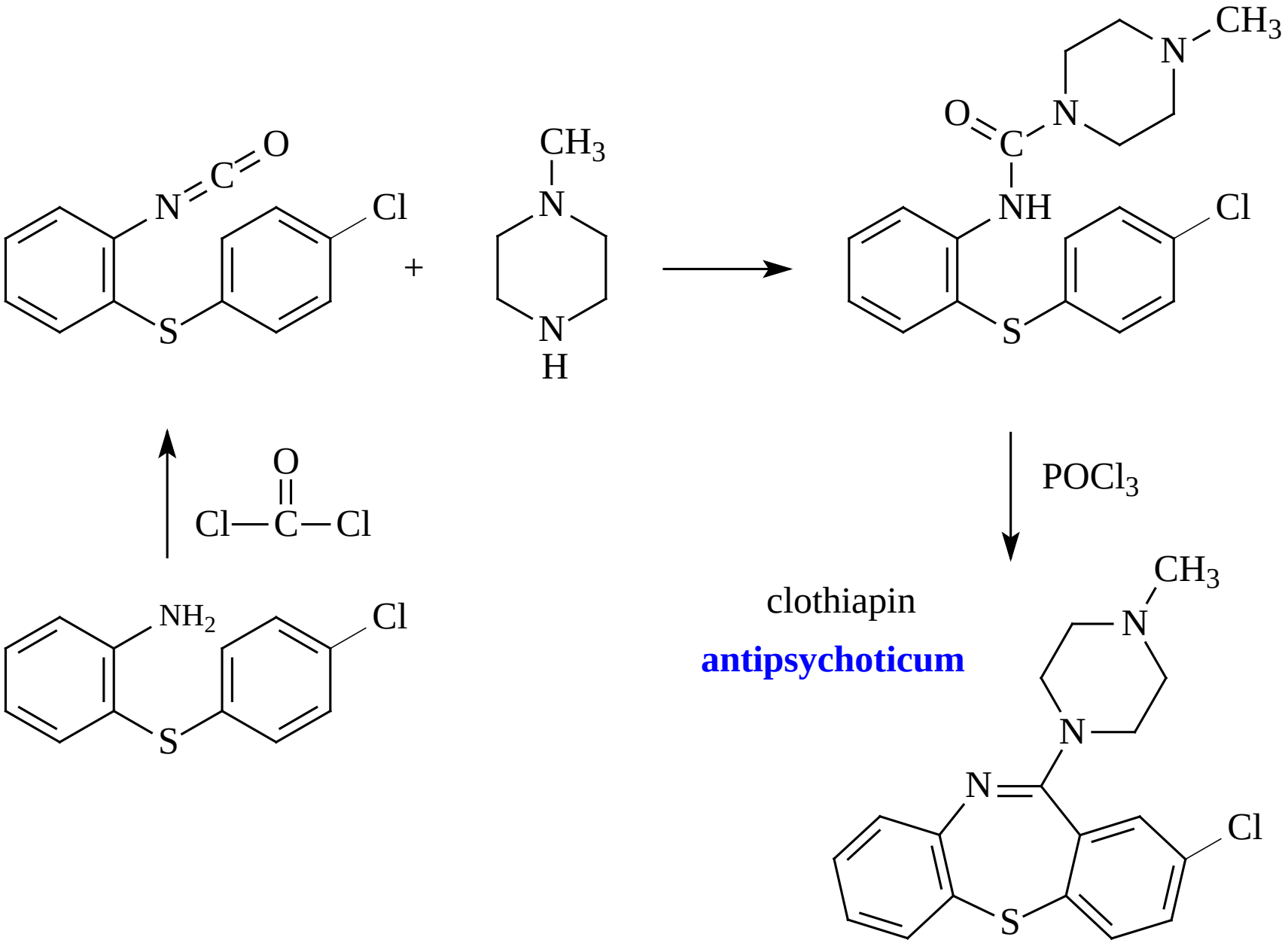


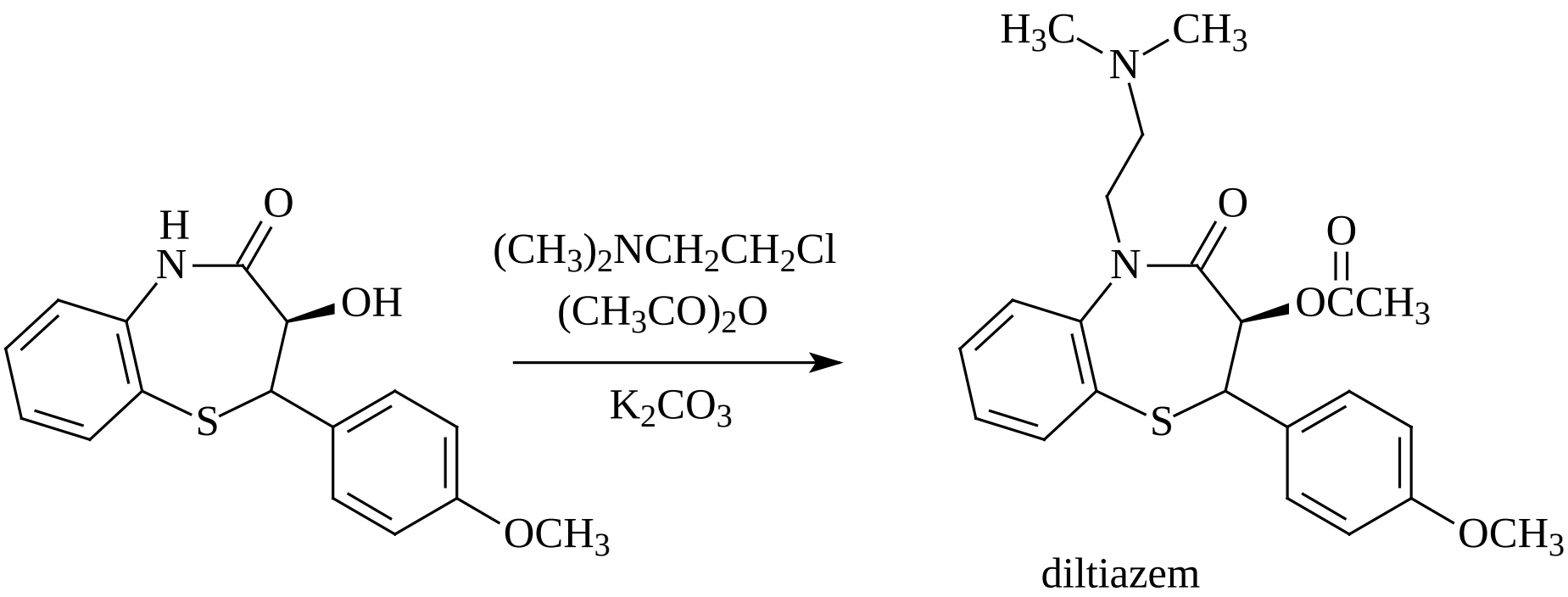
1,4-thiazepine derivative






SH
NH2
O
+
ClCH2COOH
SCH2COOH
NH2
O
SOCl2
S
O
NH
O
SH
O
Ph
+
BrCH2CH2NH2
SCH2CH2NH2
O
Ph
S
N
Ph
SH
NH2
+
O
R
RO
O
S
R
N
H
O


O
C
N
Cl
S
+
CH3
N
N
H
CH3
N
O
C
N
NH
Cl
S
POCl3
O
Cl
C
Cl
NH2
Cl
S
clothiapin
antipsychoticum
CH3
N
N
N
Cl
S



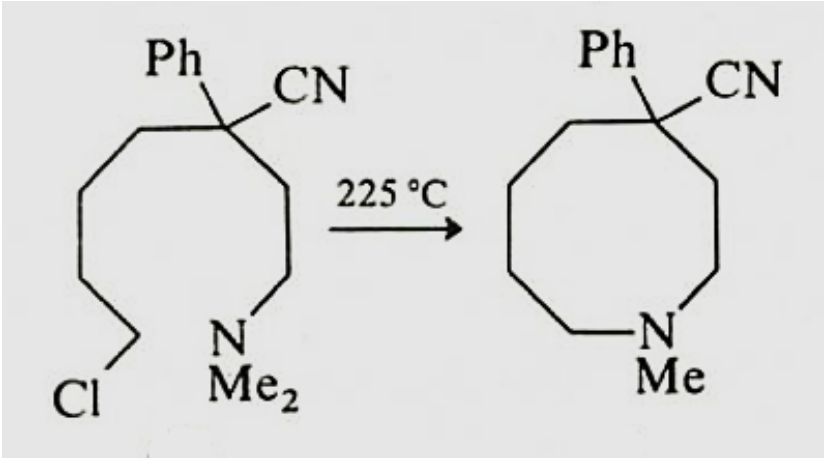
diltiazem

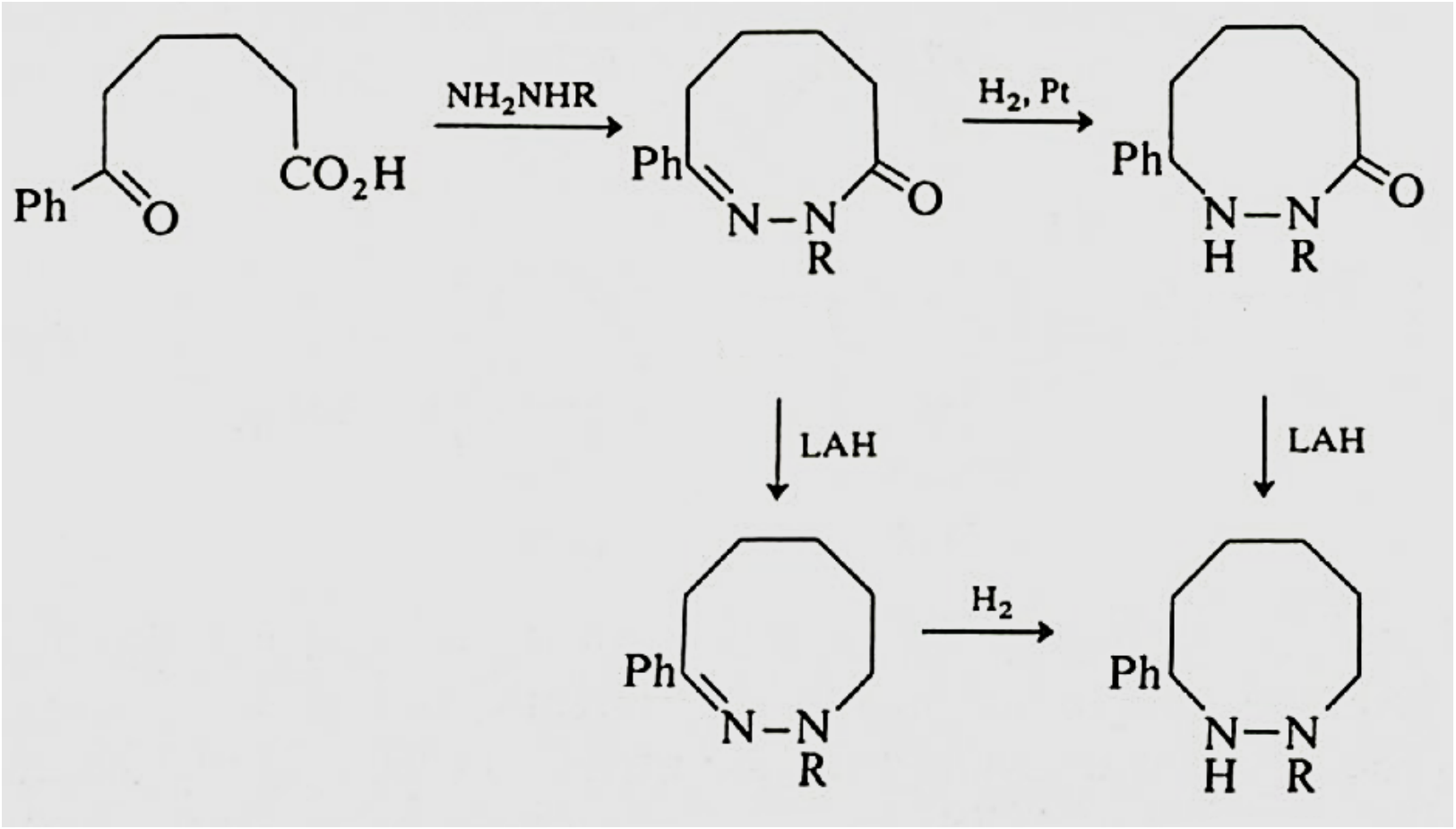
antihypertensive agent

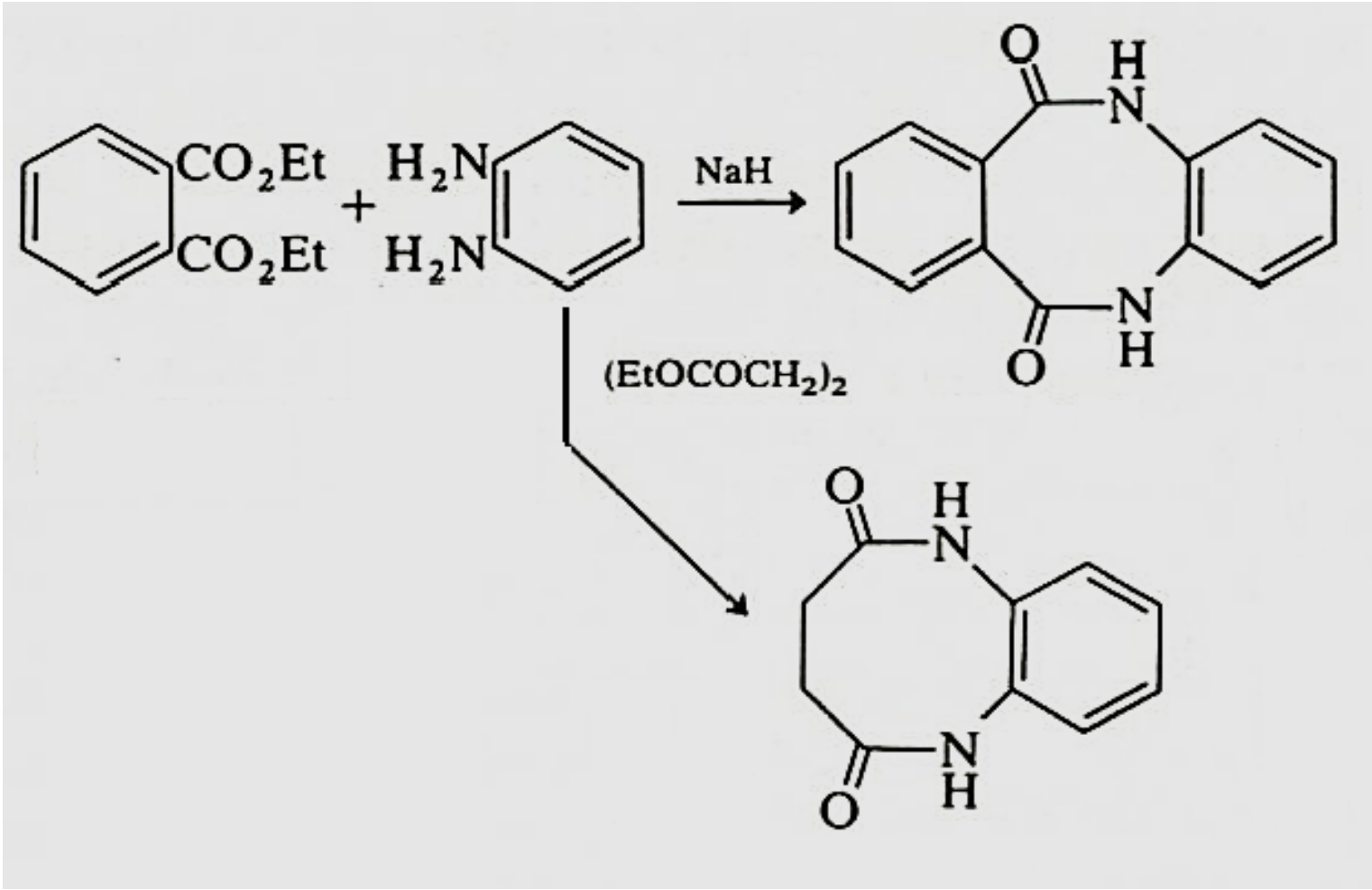
for treatment of heart disease and antiarrhythmics

Heterocyclic compounds with eight-membered rings

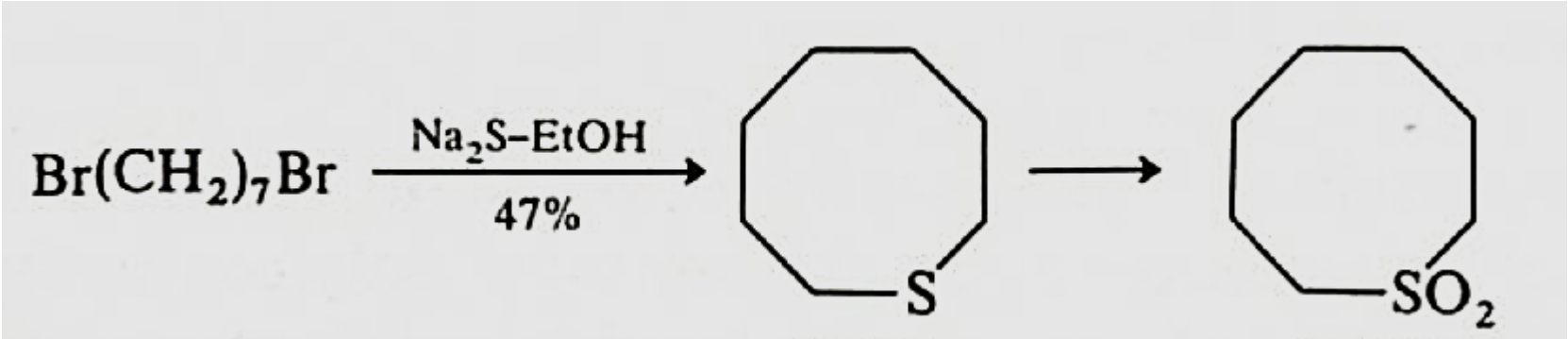
Azocane / **Diazocane** derivatives

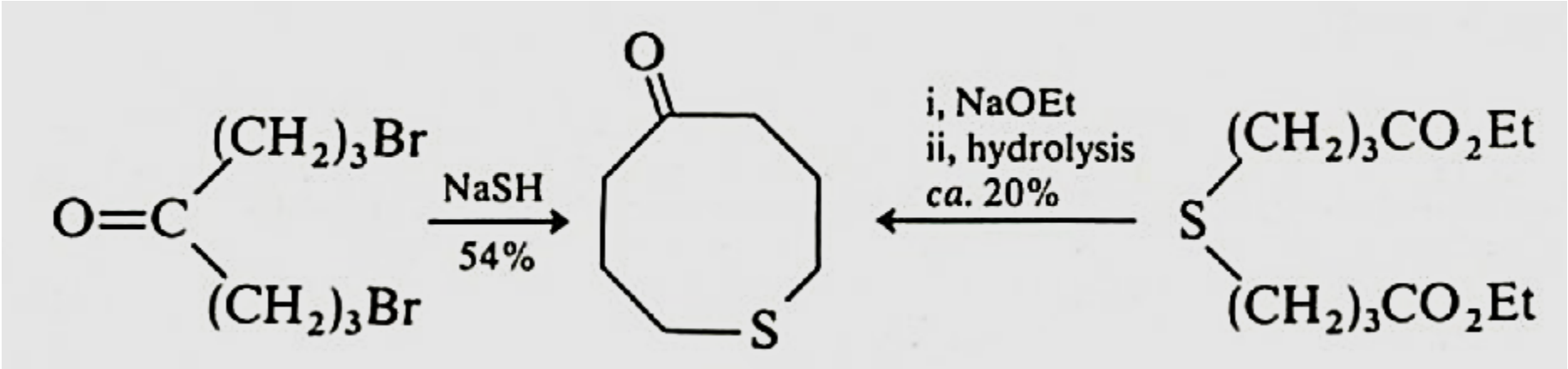


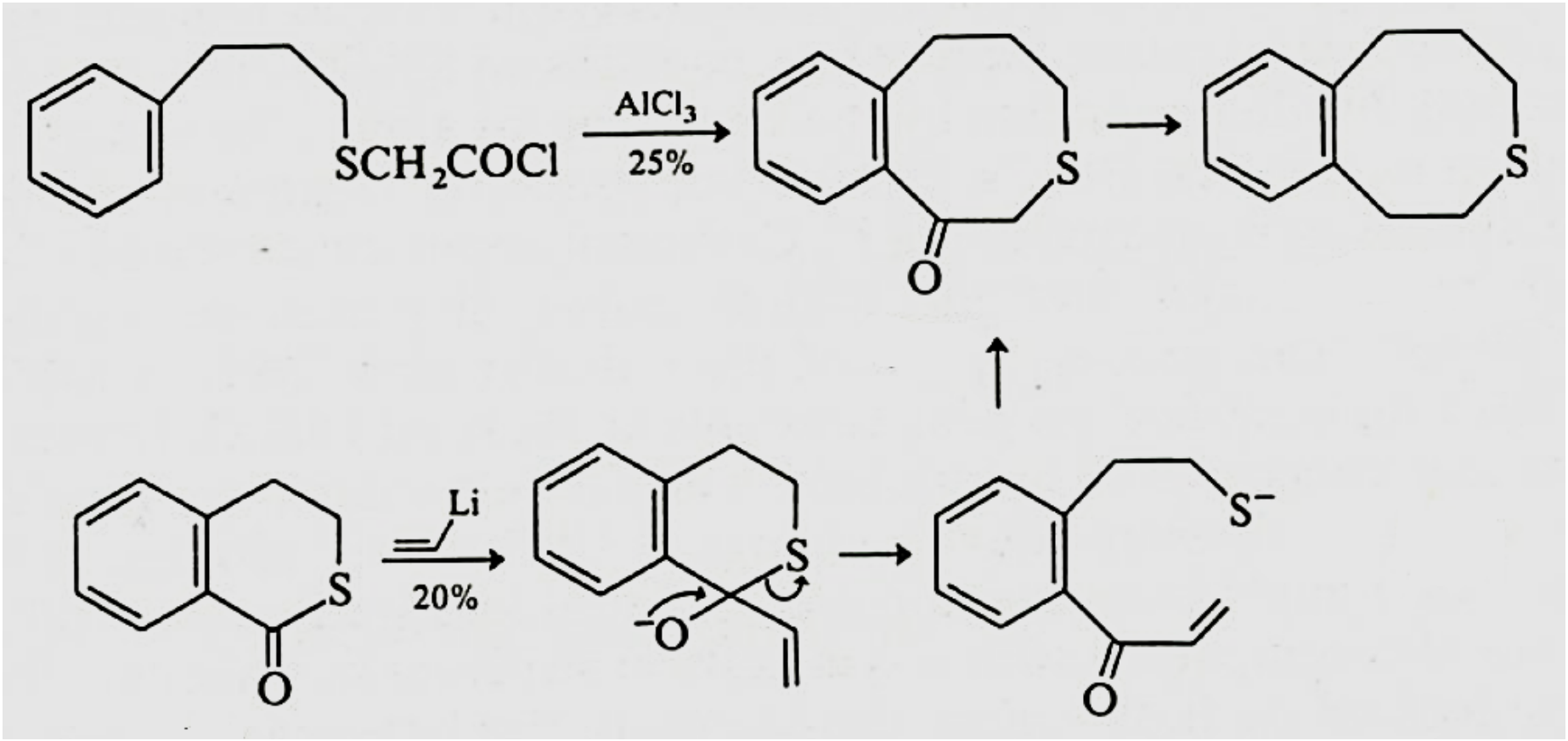


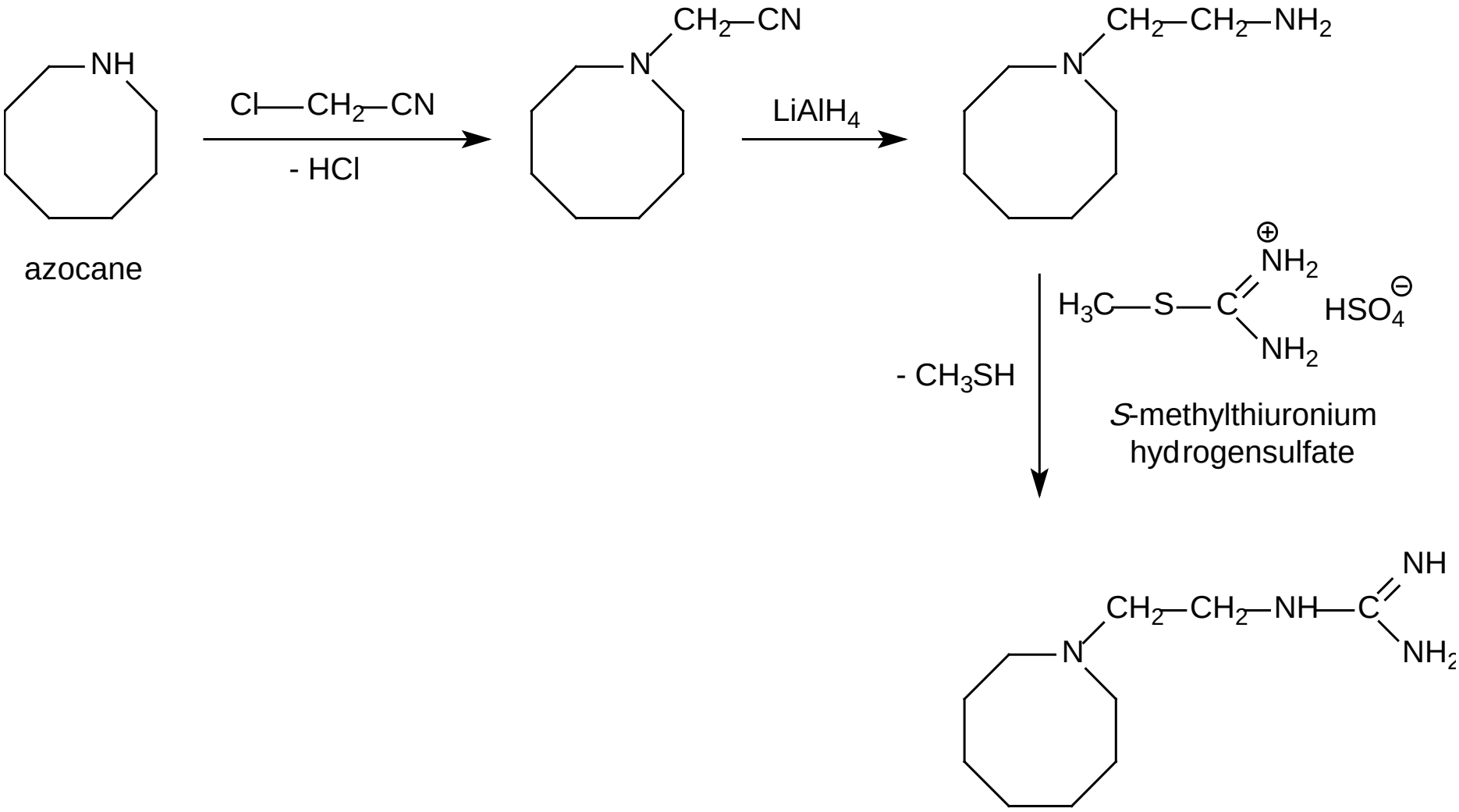

CO2Et
CO2Et
+
H2N
H2N
NaH
O
H
N
N
H
O
(EtOCOCH2)2
O
H
N
N
H
O

Thiocane derivatives






SCH2COCl
AlCl3
25%
S
O
S
S
O
Li
20%
S
O
S
O
S−
O



blood pressure reducing (antihypertensive) agent