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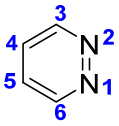
I.2. Diazine

They are two-nitrogen-containing heterocyclic compounds at the 1,2-, 1,3- and 1,4- positions commonly referred to as **pyridazine**, **pyrimidine** and **pyrazine**, respectively.

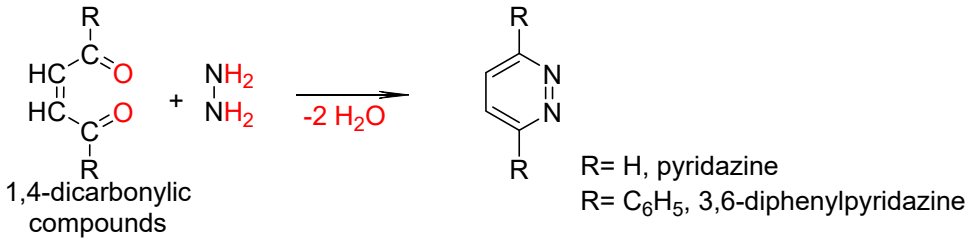
I.2.1. Pyridazine (1,2-diazine)



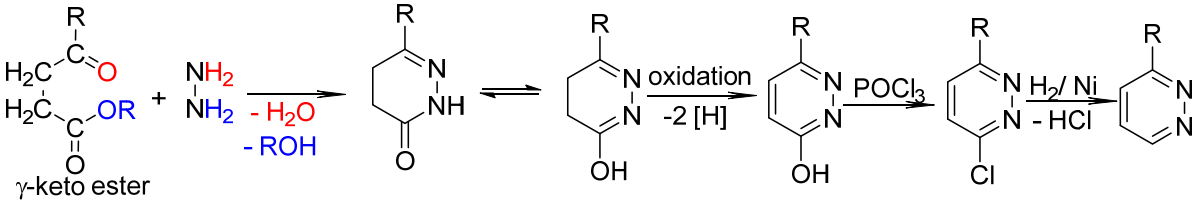
1,2-diazine
(pyridazine)

Synthetic methods:

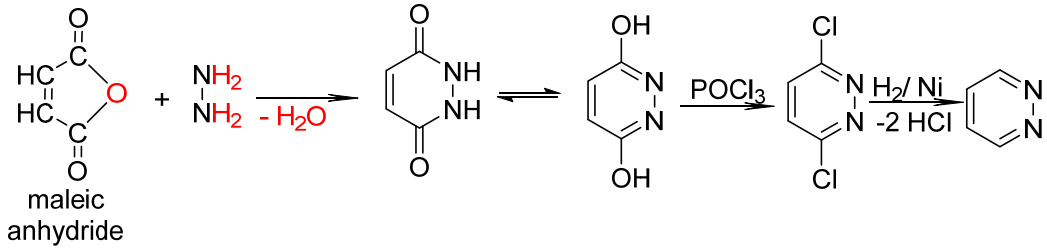
✓ Condensation of 1,4-dicarbonylic compounds (saturated or unsaturated) with hydrazine.



✓ Treatment of γ-keto esters with hydrazine.

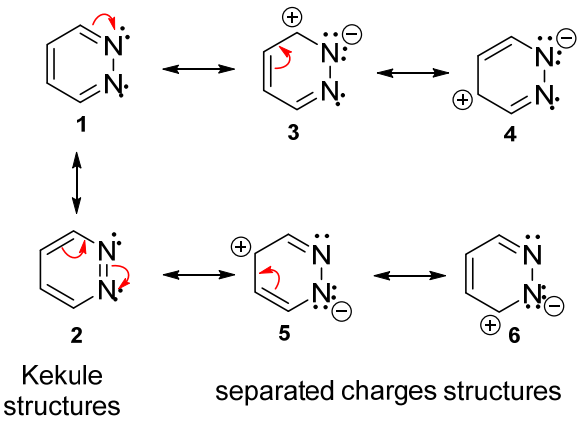


✓ Using maleic anhydride and hydrazine as starting material.



Structure and reactivity

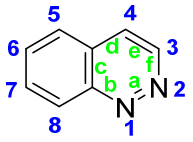
The presence of the nitrogen atoms in the pyridazine ring produces a general deactivation of the nucleus. Pyridazine may have two Kekule structures (**1** and **2**) and four separated-charges structures (**3-6**).



Separated charges structures explain the inertia of this compound over the electrophilic reactants.

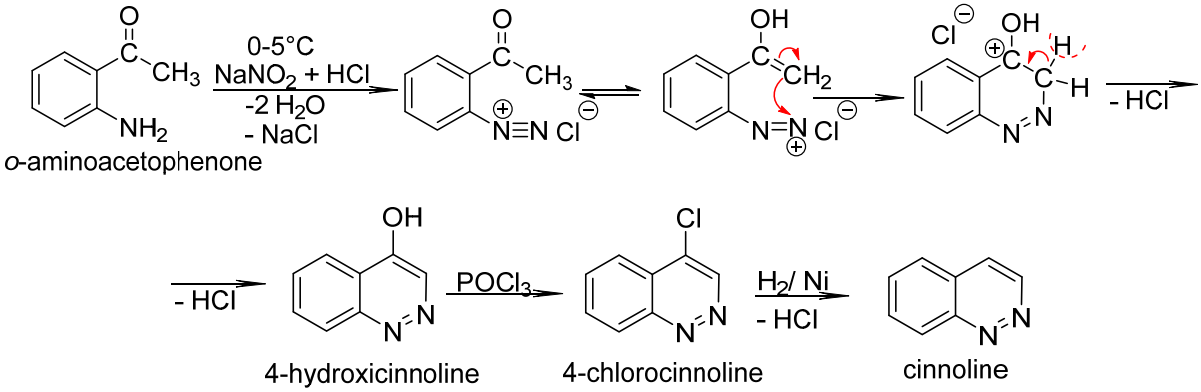
Pyridazine is also stable to oxidizing and reducing reactants. Pyridazine carboxylic acids are readily decarboxylated by heating to the melting point.

I.2.2. Cinnoline (benzo-(c)pyridazine)



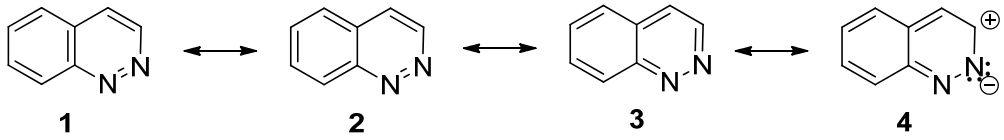
Synthetic methods:

✓ Cinnoline synthesis invokes formation of the pyridazine ring by the cyclization of a diazonium salt which contains an acyl group in *orto* position.



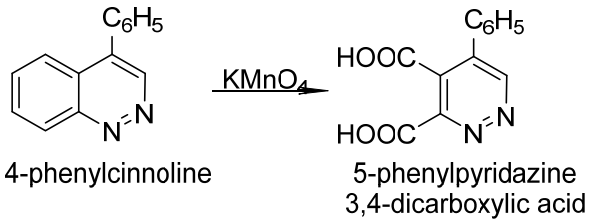
Structure and reactivity

➢ It has aromatic character and can be represented by the following limit structures:

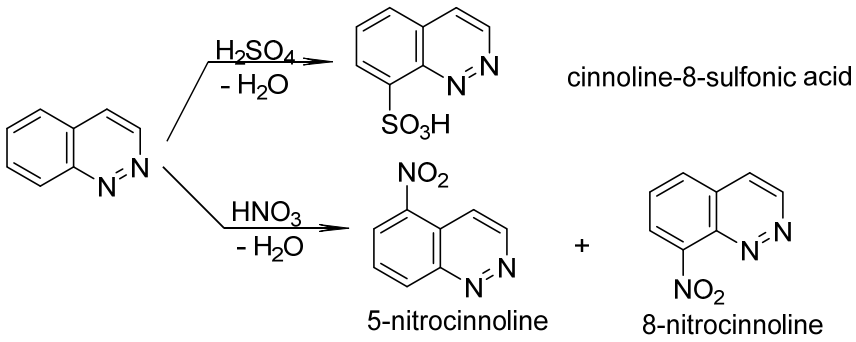


➢ Is a solid, poorly soluble in water, soluble in organic solvents.

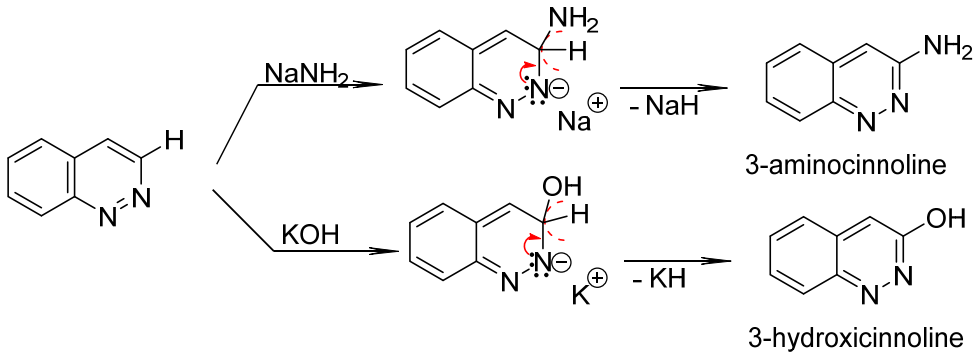
- The cinnoline pyridine nucleus is stable to the oxidants by degrading only the benzene nucleus. One example is the oxidation of 4-phenylcinnoline.



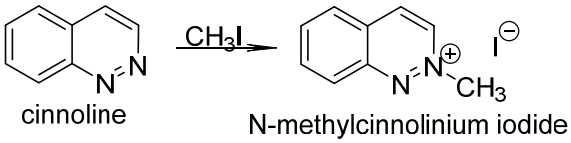
- *Electrophilic substituion* occurs in benzene ring, preferable in 5th and 8th positions. As an example, sulfonation and nitration reactions can be cited.



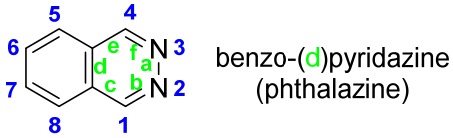
- *Nucleophilic substitution* occurs in pyridazine ring namely in 3th position.



- In reaction with alkyl halide quaternary salt is formed.

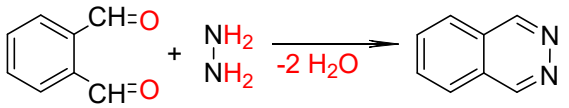


I.2.3. Phthalazine (benzo-(d)pyridazine)



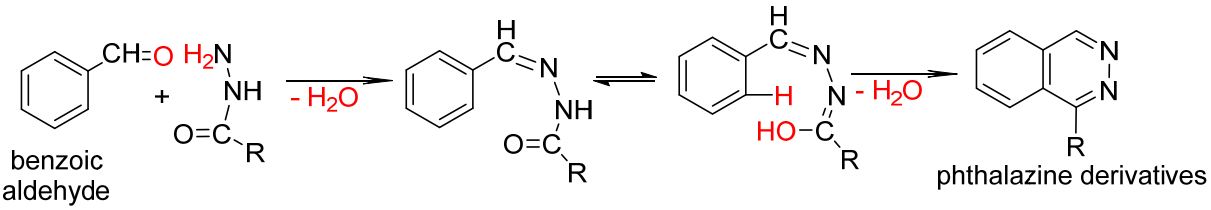
Synthetic methods:

✓ Phthalic aldehyde condensation with hydrazine.



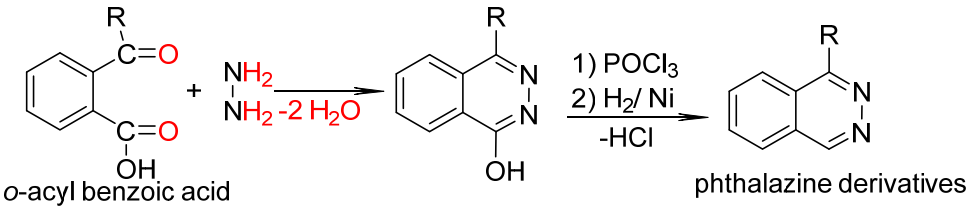
o-phthalic aldehyde phthalazine

✓ Condensation of an aromatic aldehyde with the hydrazide of a carboxylic acid.



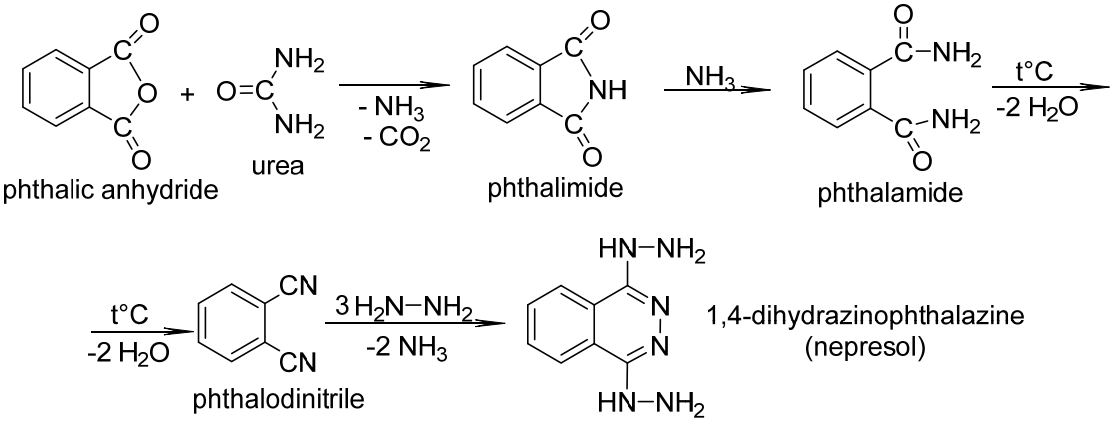
benzoic aldehyde phthalazine derivatives

✓ From *o*-acyl benzoic acid and hydrazine.



o-acyl benzoic acid phthalazine derivatives

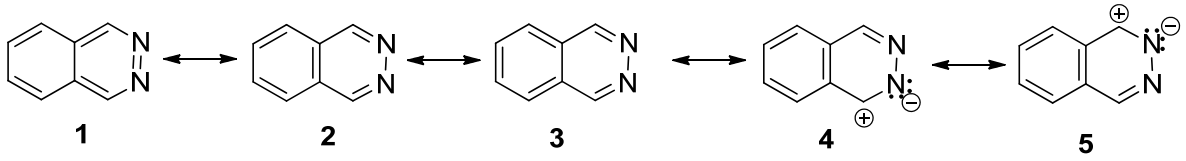
✓ A phthalazine derivative, nepresol (an antihypertensive drug), is obtained using as starting products phthalic anhydride and urea thus:



phthalic anhydride phthalimide phthalamide

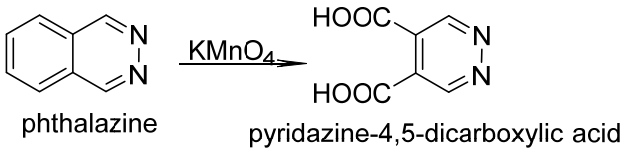
Structure and reactivity

➢ It has aromatic character and can be represented by the following limit structures:

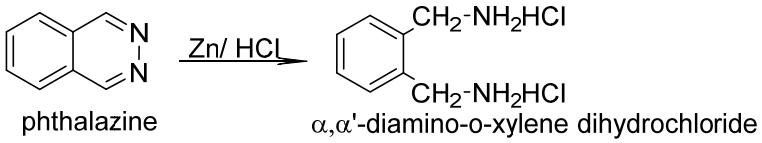


➢ Is a slightly water and organic solvents soluble crystalline product. Forms salts with strong acids.

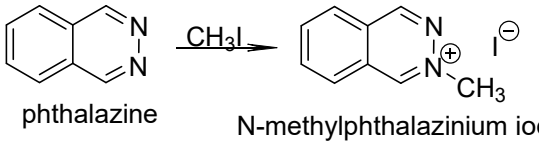
- The pyridazine nucleus of phthalazine is resistant to the action of $KMnO_4$ by degrading only the benzene nucleus.



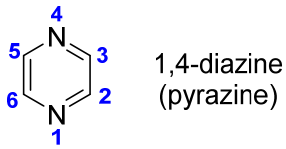
- Reduction with Zn and HCl degrades the pyridazine nucleus resulting in α,α'-diamino-o-xylene dihydrochloride.



- In reaction with alkyl halide quaternary salt is formed.

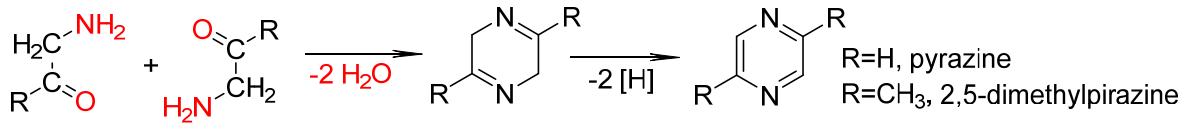


I.2.4. Pyrazine (1,4-diazine)



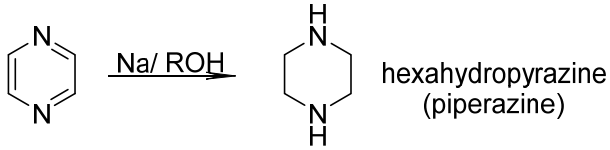
Synthetic methods:

✓ Pyrazine and its derivatives are obtained by selfcondensation of α-aminoaldehydes or α-aminoketones in alkaline solution and in the presence of $CuSO_4$ as catalyst.



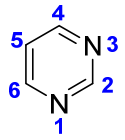
Structure and reactivity

- It is a solid substance with a slight odor of pyridine and has a basic character.
- By reduction with Na and alcohol it is converted to piperazine, a drug used in the treatment of gout, and its citrate is used as an antiparasitic drug in veterinary medicine.



➢ Piperazine is a strong base comparable to secondary aliphatic amines.

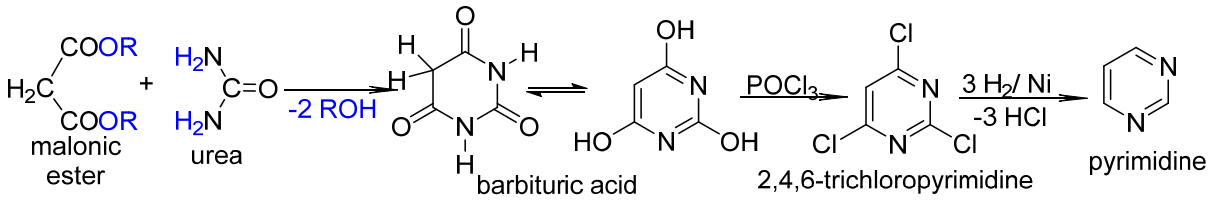
I.2.5. Pyrimidine (1,3-diazine)



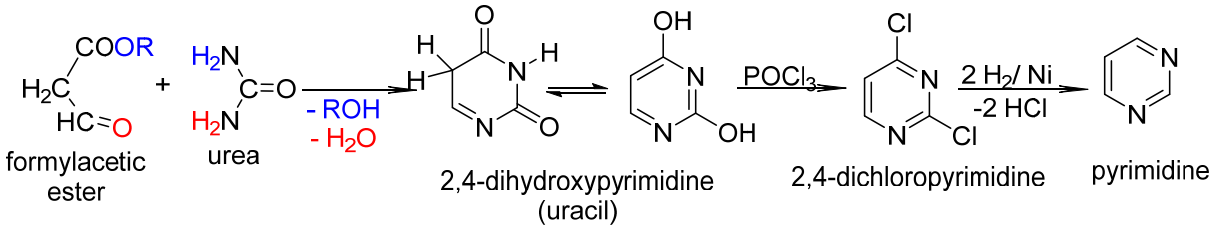
1,3-diazine
(pyrimidine)

Synthetic methods:

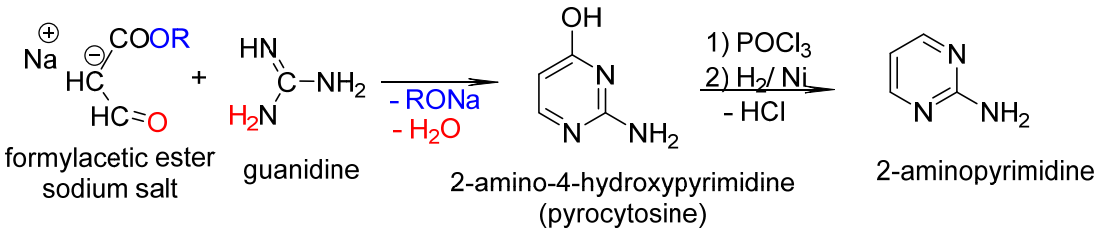
✓ Condensation of urea with malonic ester in ethanolic solution and in the presence of sodium ethoxide.



✓ Condensation of urea with formylacetic ester.

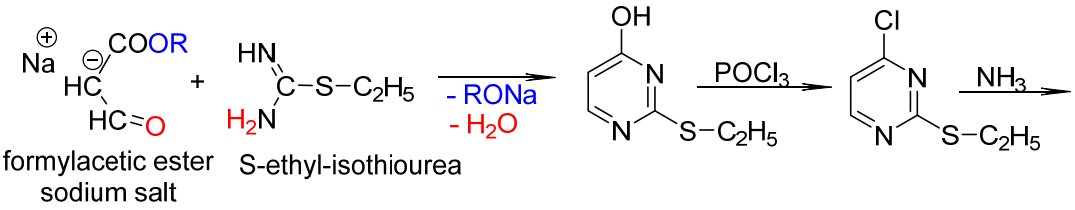


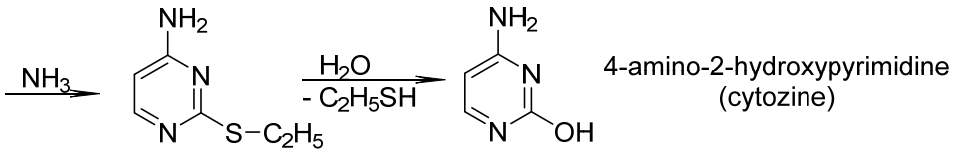
✓ Condensation of guanidine with formylacetic ester sodium salt.



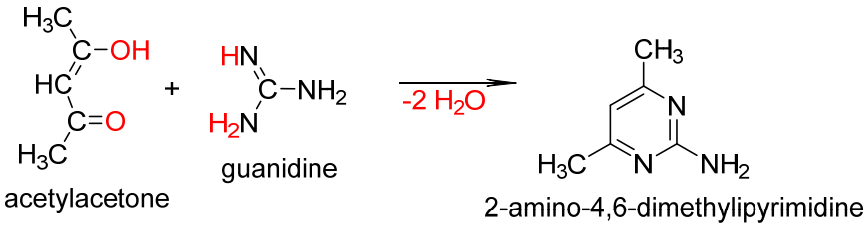
2-Aminopyrimidine is a raw material in the synthesis of sulfadiazine (a sulfamide).

✓ Condensation of S-ethyl-isothiourea with formylacetic ester sodium salt.



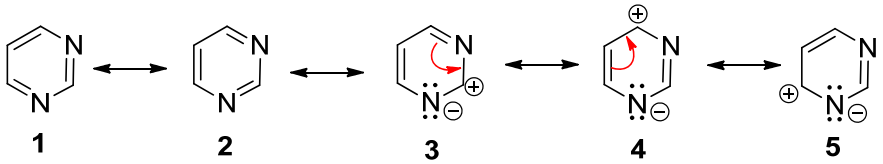


✓ Condensation of guanidine with acetylacetone.

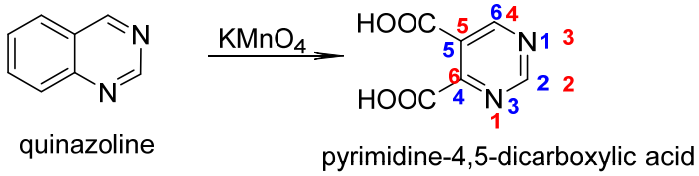


Structure and reactivity

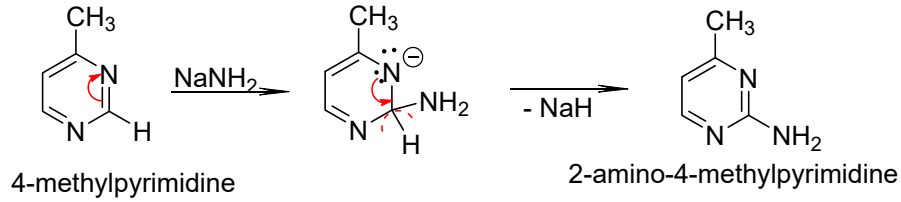
- Due to the electronegative nature of the nitrogen atoms causes a general decrease in the electron density of the CH groups in the pyrimidine nucleus and a more pronounced decrease in the positions 2,4 and 6 as it results from the following structures representing the distribution of electrons in this system..



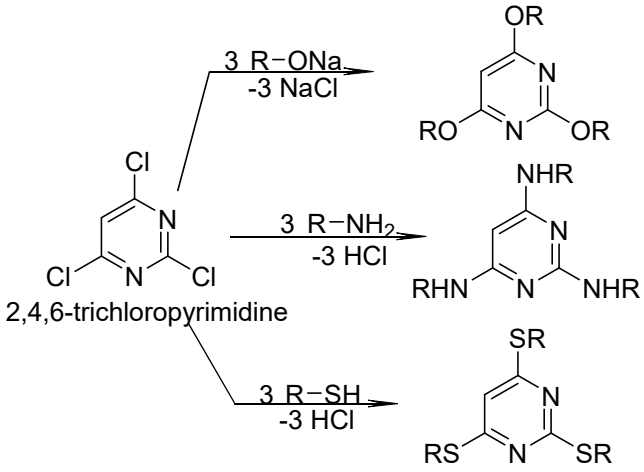
- It is a solid, slightly water-soluble product with a basic character.
- The aromatic character of pyrimidine is manifested by its high resistance to $KMnO_4$. For example, oxidation of the quinazoline (benzo-(d)pyrimidine) degrades only the benzene nucleus, the pyrimidine nucleus remaining intact.



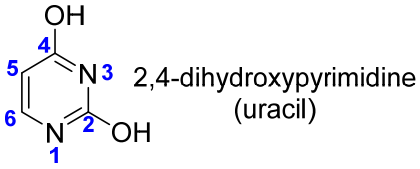
- Simple derivatives of pyrimidine (substituted with alkyl, aryl, halogen, nitro, etc.) have aromatic character and chemical properties similar to pyridine (see pyridine).
- The aromatic character of pyrimidine decreases as OH or NH_2 groups are introduced at 2nd, 4th and 6th positions. Such compounds, such as uracil and barbituric acid, are sensitive to electrophilic reactants.
- Pyrimidine and especially its alkylated derivatives are sensitive to nucleophilic derivatives. One example is the application of the Cicibabin reaction to 4-methylpyrimidine.



- The substituents from 2nd, 4th and 6th positions are more reactive than those from 5th position. Thus, for example, the replacement of the chlorine in 2nd, 4th and 6th positions by nucleophilic substituents allows the introduction of such groups as alkoxy, amino, mercapto, etc.

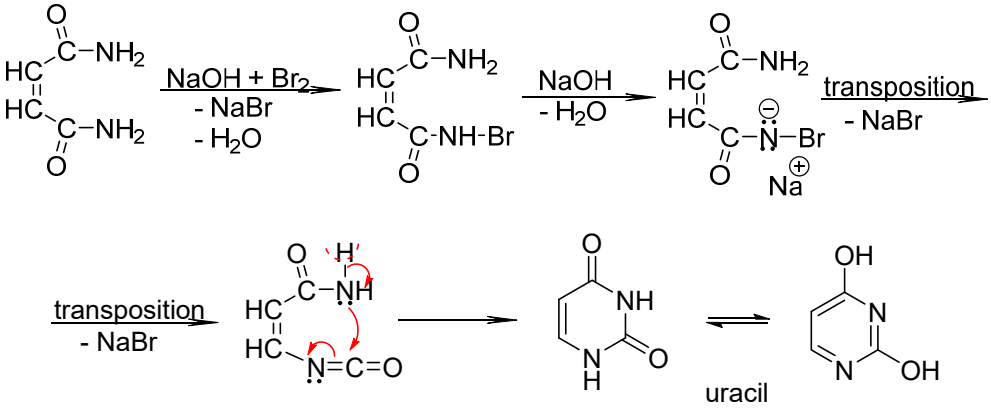


I.2.6. Uracil (2,4-dihydroxypyrimidine)



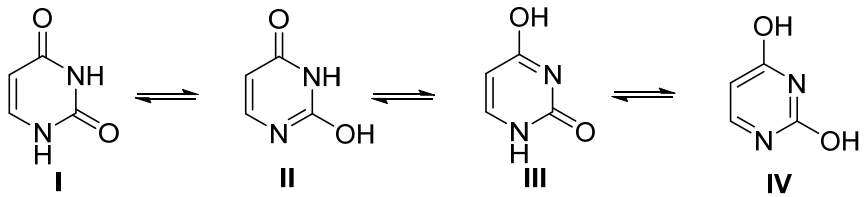
Synthetic methods:

- ✓ Condensation of urea with formyl ester (see pyrimidine synthesis).
- ✓ Hoffmann degradation of a maleic acid diamide.

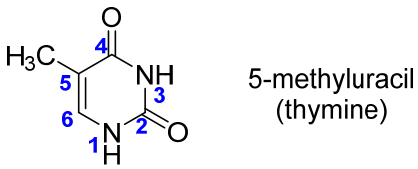


- Uracil is an important component of nucleic acids.

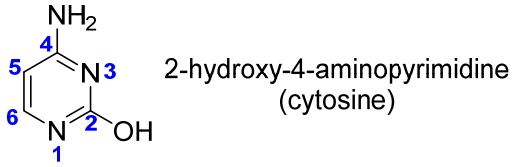
- Uracil may present several tautomeric forms by "***lactam-lactime***" type represented by **I-IV** formula:



- Uracil is a colorless crystalline compound, soluble in water and organic solvents.
- A uracil derivative is **thymine**, a component of nucleic acids.



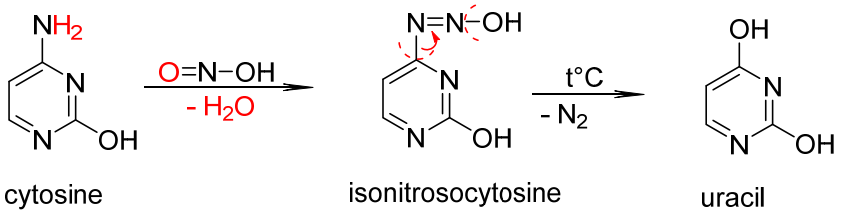
I.2.7. Cytosine (2-hydroxy-4-aminopyrimidine)



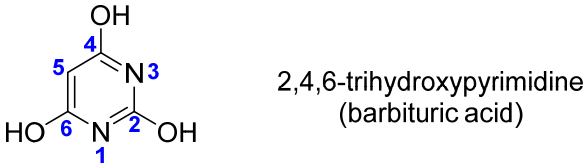
✓ It is prepared by condensing S-ethyl-isothiourea with formylacetic ester sodium salt (see synthesis of pyrimidine).

✓ It is a solid product, soluble in organic solvents, is a component of nucleic acids.

✓ By treatment with nitrous acid cytosine is transformed in uracil.

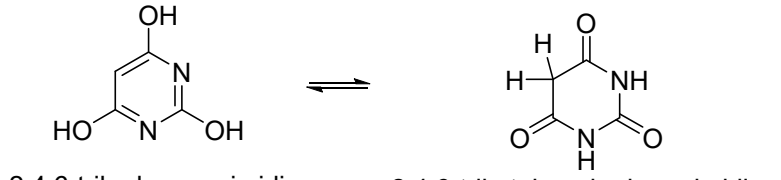


I.2.8. Barbituric acid (2,4,6-trihydroxypyrimidine)



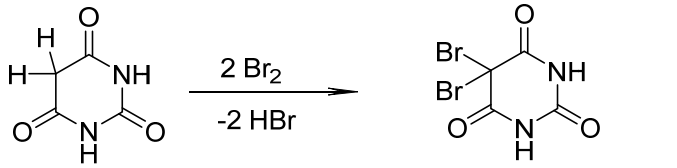
✓ Is prepared by condensation of urea with malonic ester in ethanolic solution and in the presence of sodium ethoxide (see pyrimidine synthesis).

✓ May present two tautomeric forms:



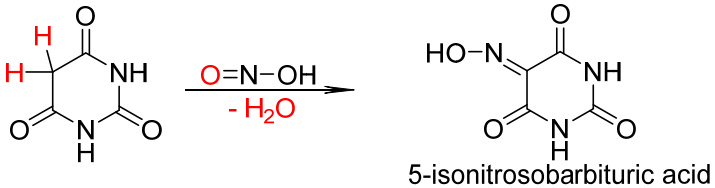
2,4,6-trihydroxypyrimidine 2,4,6-triketohexahydropyrimidine

- ✓ It is a solid, colorless, insoluble product in cold water, soluble in hot water.
- ✓ Barbituric acid is suitable for electrophilic substitution; the substituent always enters in 5th position.
- ✓ Halogenation with bromine affords 5,5-dibromobarbituric acid.



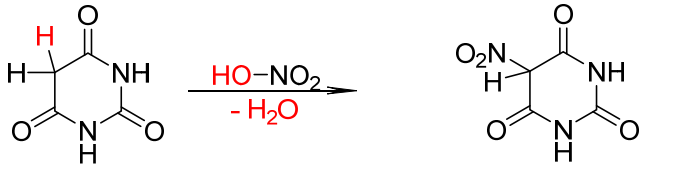
5,5-dibromobarbituric acid

- ✓ With nitrous acid, 5-isonitrosobarbituric acid is formed.



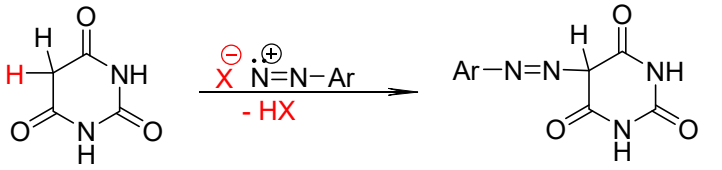
5-isonitrosobarbituric acid
(violuric acid)

- ✓ With concentrated nitric acid is transformed in 5-nitrobarbituric acid.



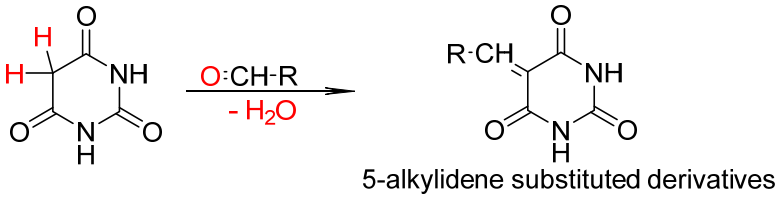
5-nitrobarbituric acid

- ✓ With diazonium salts, coresponding 5-azoderivatives are formed.



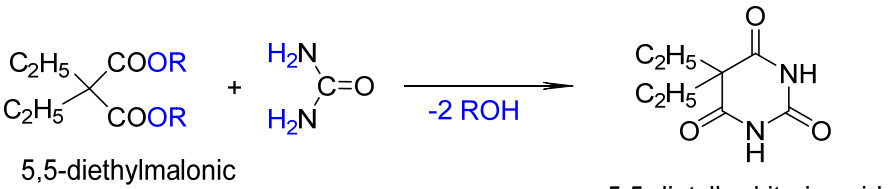
5-azoderivatives

- ✓ With aliphatic aldehydes leads to 5-alkylidene substituted derivatives.



5-alkylidene substituted derivatives

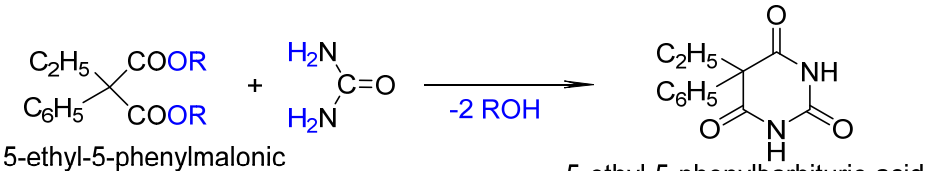
✓ Some 5,5-disubstituted barbituric acid derivatives are hypnotic and sedative drugs. These are obtained by condensation of urea with malonic ester previously disubstituted with alkyl, aryl, cycloalkyl, etc. groups.



5,5-diethylmalonic acid ester

5,5-dietylbarbituric acid (veronal; barbital)

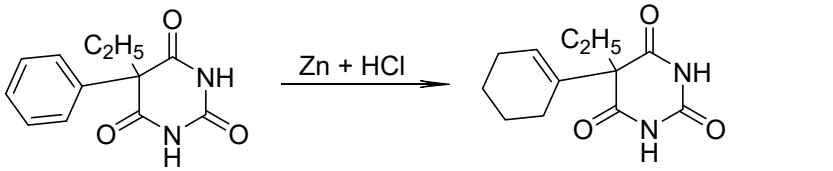
✓ If the ethyl-phenylmalonic acid ester is used, 5-ethyl-5-phenylbutyric acid is formed.



5-ethyl-5-phenylmalonic ester acid

5-ethyl-5-phenylbarbituric acid (luminal; phenobarbital)

✓ By phenobarbital reduction result cyclobarbital.

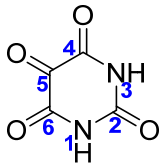


phenobarbital

5-ethyl-5-cyclohexenylbarbituric acid (cyclobarbital)

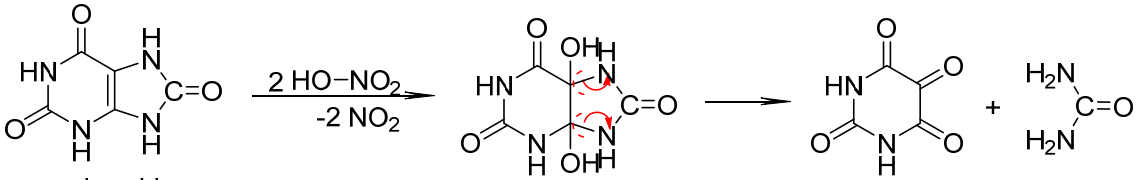
These drugs are hypnotic, sedative and anticonvulsant; they cause a deep sleep that occurs half an hour after administration for 4-12 hours.

I.2.9. Alloxan (tetraketo-hexahydropyrimidine)



tetraketo-hexahydropyrimidine (alloxan)

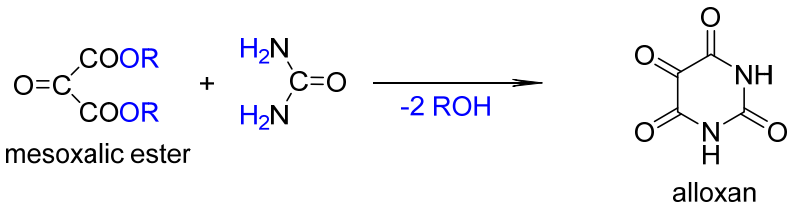
✓ Uric acid oxidation with nitric acid, lead to alloxan.



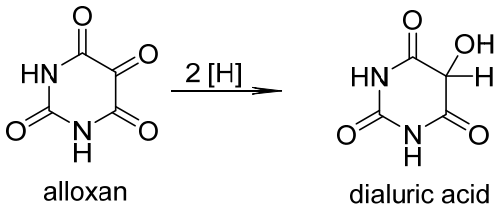
uric acid

alloxan

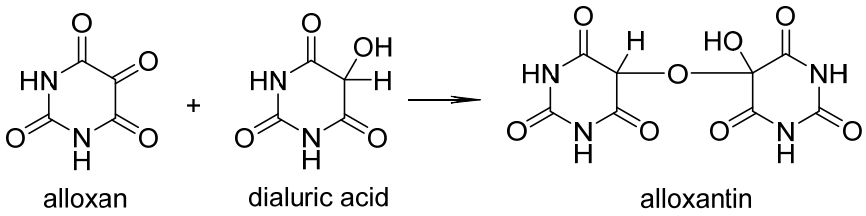
✓ It is prepared by condensation of the urea with a mesoxalic ester.



- ✓ In the anhydrous state they are in the form of yellowish-green crystals, which in the presence of water become colorless.
- ✓ By energetic hydrogenation passes into dialuric acid.



- ✓ By soft reduction (ammonium sulfide), alloxantin – a molecular combination between alloxan and dialuric acid is formed.

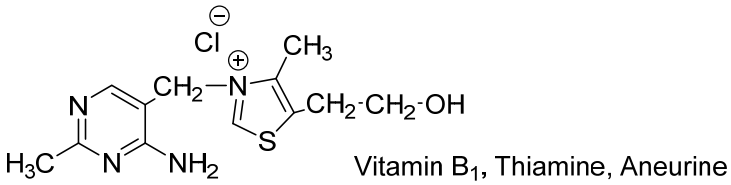


Treatment of alloxantin with ammonia results in the murexide, an orange red product. The reaction is used to determine uric acid in the body (see purine - uric acid).

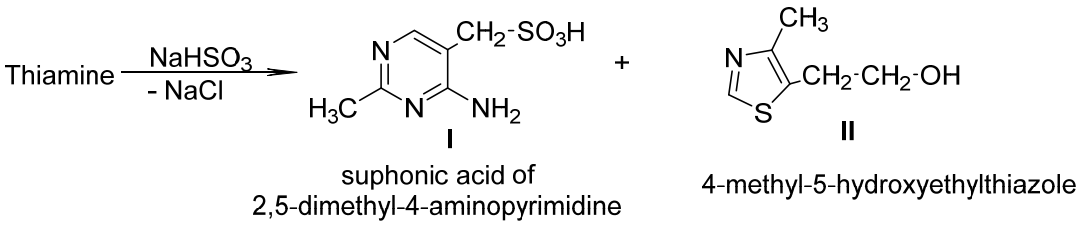
I.2.10. Thiamine (Vitamin B_1, Aneurine)

It is found in large quantities in rice bran and beer yeast. In lower concentration is found in green plants and animal tissues.

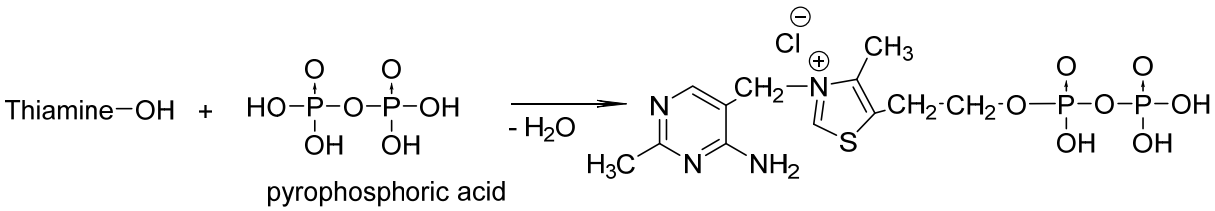
Thiamine is a quaternary thiazole salt of the following formula::



The vitamin B_1 structure was determined by heating with sodium hydrogen sulphite which cleaves the molecule into 2,5-dimethyl-4-aminopyrimidine (**I**) and 4-methyl-5-hydroxyethylthiazole (**II**).

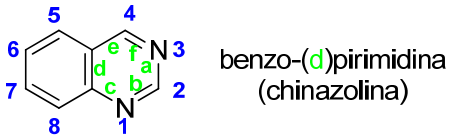


Vitamin B_1 is an important precursor for the production of the coenzyme called cocarboxylase. This is the thiamine ester with pyrophosphoric acid in the primary alcohol group.

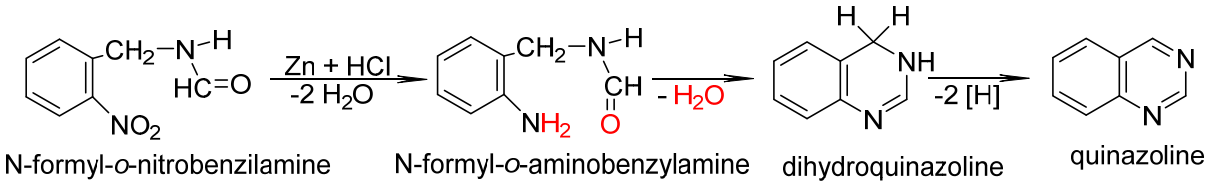


Cocarboxylase occurs in the decarboxylation of pyruvic acid in the body. The lack of vitamin B1 in food leads to the accumulation of pyruvic acid and to the occurrence of "**beribery**" disease (it stains the tears in yellow and especially the eyes). This disease is common in the East Asian population, which feeds mainly on husked rice.

I.2.11.Quinazoline (benzo-(d)pyrimidine)



✓ Is obtained starting from N-formyl-*o*-nitrobenzylamine thus:



✓ It is a solid product, soluble in organic solvents, it is a base and forms quaternary salts with alkyl halides.