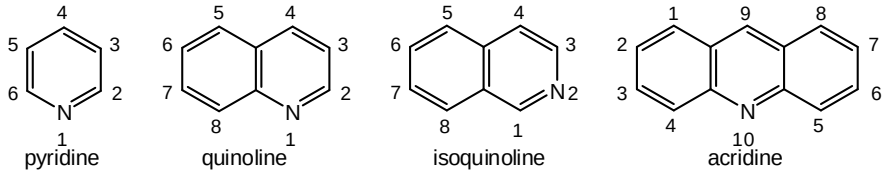
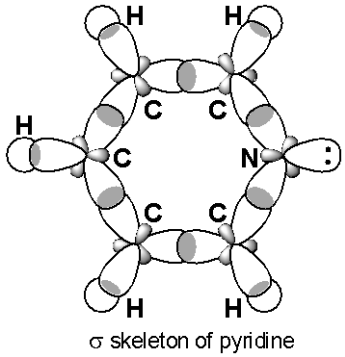
№ 37. SIX-MEMBERED HETEROCYCLES WITH ONE HETEROATOM. THE GROUP OF PYRIDINE.

The group of pyridine includes pyridine and its derivatives, as well as analogs with fused benzene rings. These rings share their connecting bonds. The term benzannulated compounds refers to derivatives of cyclic compounds, usually aromatic, which are fused to a benzene ring, e.g. quinoline, isoquinoline, acridine.

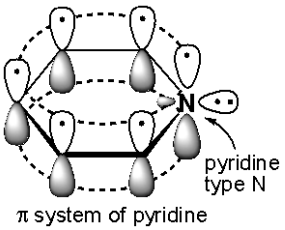


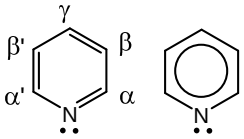
The numbering system in pyridine and quinoline begins from the nitrogen atom and proceeds counterclockwise. An allocation of positions in pyridine by letter of the Greek alphabet (α-γ) is used sometimes. Here α (*ortho*), β (*meta*) and γ (*para*) refer to the 2-, 3- and 4- position, respectively.

Pyridine is heteroaromatic analog of benzene in which nitrogen atom replaces one –CH= unit. Pyridine structure is similar to that of benzene – the molecule is planar hexagon. The pyridine nitrogen is in sp^2 hybrid state. Two of the hybrid orbitals form bonds to carbon. The third hybrid orbital is occupied by a lone pair that is not involved in the aromatic π-sextet. The aromatic system is completed by non-hybridized $2p_z$ orbitals on each of the five carbon atoms and the nitrogen atom. Each of these orbitals contains one electron and thus giving altogether 6 π electrons fulfilling Hückel's rule for (4n+2) electrons for an aromatic system.


σ skeleton of pyridine

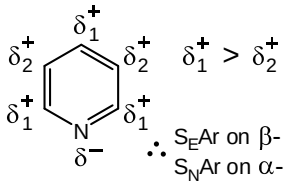
The shape of pyridine hybrid orbitals and 1s hydrogen orbitals forming the σ skeleton of the molecule is shown as viewed from the top. The π-sextet of pyridine is shown as viewed sideways.



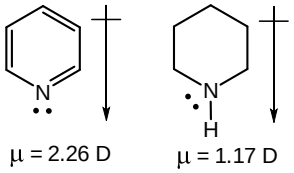


Pyridine is usually drawn using double bonds and hydrogens omitted but the circle can indicate better the delocalization pattern of π-electrons.

Pyridine exhibits all the characteristic properties of an aromatic compound. The stabilization (delocalization energy 113 kJ.mol^{-1}) leads to substitution by S_EAr mechanism rather to addition reactions. These reactions, however, are much more difficult than in benzene and even more difficult than in pyrrole. Due to the electronegative nature of nitrogen, relative to carbon, the total π electron density is decreased relatively to benzene, hence, pyridine is less reactive in S_NAr than benzene. Positions 2-, 4-, and 6- are with more decreased electron density, therefore electrophilic substitutions take place at 3- (β-). Many reactions that are characteristic of benzene proceed with pyridine either at more complicated conditions or/and with low yield. Owing to the decreased electron density in the aromatic system, electrophilic substitutions are suppressed in pyridine and its derivatives.

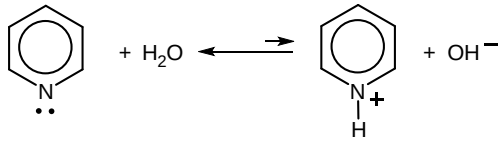


Physical properties. Pyridine is a colorless liquid with a distinctive, unpleasant fish-like odor. The pyridine ring occurs in many important compounds, including nicotinamides. Pyridine easily dissolves in water and harms both animals and plants in aquatic systems. The pyridine molecule is polar, more polar than the saturated, nonaromatic piperidine. This is a result of shifted electron density towards the nitrogen and contribution of polar structures as shown with δ^+ and δ^- signs, above.

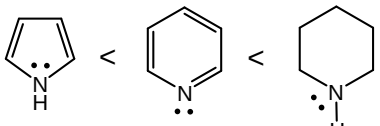


The presence of available lone pair in pyridine is the reason for its profound basic properties (pK_b = 8.75, conjugate acid pK_a = 5.25), in contrast to pyrrole. An aqueous solution of pyridine has pH slightly more than 7 because of excess hydroxide ions according to the equilibrium, although shifted to the left :

Pyridine is much weaker base than secondary amines. The reason for weaker basicity of pyridine *vs.* secondary and tertiary amines is the location of lone electron pair on sp^2 hybrid orbital. It is closer to the N nucleus (because of larger *s* character than sp^3 in

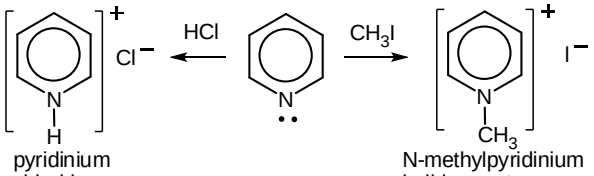


secondary amines) and electrons are not as available for protonation. In other words, the pyridine nitrogen holds its lone pair tighter than piperidine. The two adjacent CH_2 groups in piperidine donate electron density via positive inductive effect +I contributing to an increased basicity.



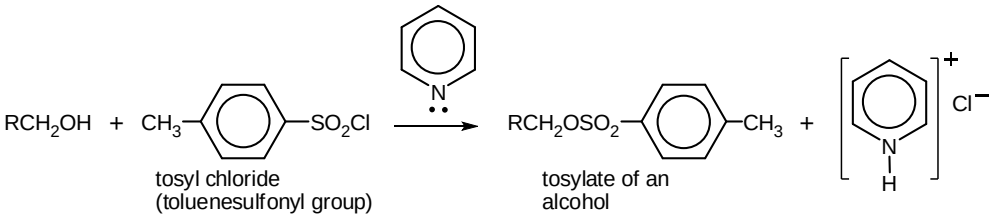
pyrrole $pK_B = 14$ | pyridine $pK_B = 8.8$ | piperidine $pK_B = 2.8$

Chemical properties. Pyridine forms **salts** (pyridinium salts) with strong acids. Pyridine is protonated by reaction with acids and forms a positively charged aromatic ion called pyridinium cation. The bond lengths and bond angles in pyridine and the pyridinium ion are almost identical. The additional proton is attached to nonbonding electron pair and has no effect on the aromatic sextet. One such salt, pyridinium chloro-chromate, PCC, is well soluble in organic solvents oxidizing agent.



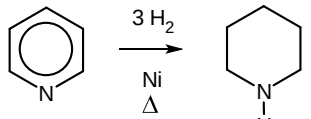
pyridinium chloride | N-methylpyridinium iodide; quaternary pyridinium salt

Pyridine is widely used as basic catalyst and scavenger of acids resulting in chemical reactions. This role is illustrated with the classical reaction of an alcohol with tosyl chloride that gives easily replaceable tosylate group (the hydroxyl is not good leaving group). The pyridine nitrogen can be **alkylated** by primary alkyl halides to quaternary pyridinium salts.



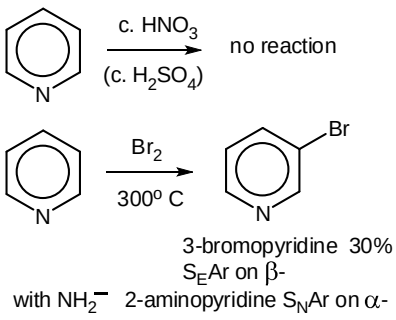
tosyl chloride (toluenesulfonyl group) | tosylate of an alcohol

Pyridine is not prone to hydrogenation although under harsher conditions and presence of catalyst can be hydrogenated to piperidine.



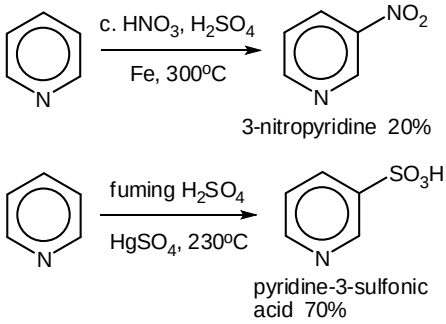
pyridine | piperidine

Electrophilic aromatic substitution (S_EAr) reactions proceed with difficulty. Pyridine resists S_EAr not only because of electron withdrawing effect of the nitrogen atom but because in acidic conditions (Friedel-Crafts, nitration) the nitrogen is protonated or engaged in complex as a Lewis acid.



with NH_2^- 2-aminopyridine S_NAr on α- | 3-bromopyridine 30% S_EAr on β-

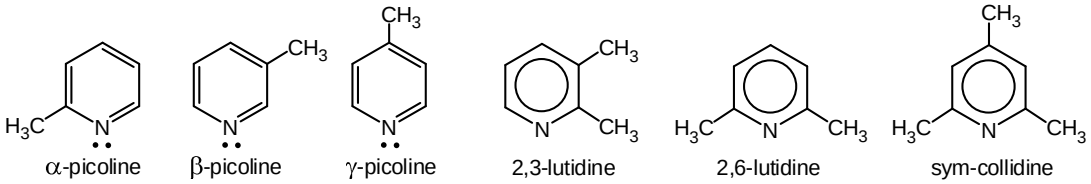
The nitration of pyridine in similar condition applied to benzene fails completely. The bromination which proceeds well with benzene, requires harsh conditions and the yield is low. Nitration and sulfonation of pyridine can be conducted at high temperatures to overcome the resistance to S_EAr reactions. Just for comparison, the electron rich furan is nitrated with dilute HNO_3 at 0^oC and pyrrole reacts with iodine to tetraiodopyrrole.



3-nitropyridine 20% | pyridine-3-sulfonic acid 70%

In contrast to benzene, pyridine efficiently reacts in several nucleophilic substitutions. The reason for this is relatively lower electron density of the carbon atoms of the ring. Amide anion is used as a nucleophile yielding 2-aminopyridine in rare for other aromatic systems replacement of hydride ion.

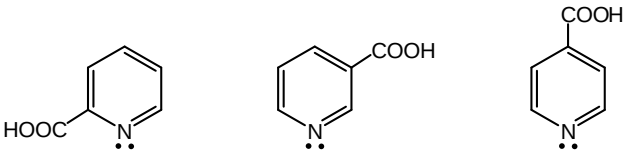
Pyridine derivatives. The methylpyridines are called picolines, and the dimethylpyridines - lutidines. The 2,4,6-trimethylpyridine has trivial name *sym*-collidine (symmetrical).



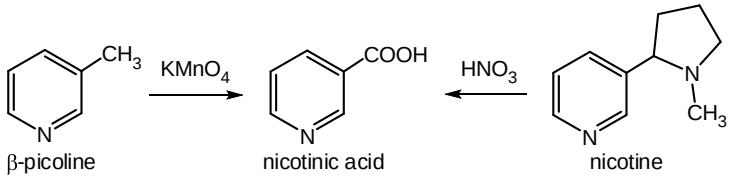
α-picoline | β-picoline | γ-picoline | 2,3-lutidine | 2,6-lutidine | sym-collidine

Pyridine itself and alkylpyridines are produced from coal tar. Some of them are used in industrial syntheses as starting materials.

Pyridine carboxylic acids and their derivatives. All three positional isomers of a pyridine carboxylic acid have trivial names. The pyridine nitrogen is not strong enough base to form zwitterionic structures. Nicotinic acid can be obtained by oxidation of methyl group on β-picoline or by oxidation of nicotine. Nicotine is an alkaloid found in particularly large percentage in tobacco leaves. The alkaloid has strong physiological effect on central nervous system

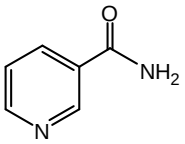


picolinic acid pyridine-2-carboxylic acid | nicotinic acid pyridine-3-carboxylic acid | isonicotinic acid pyridine-4-carboxylic acid



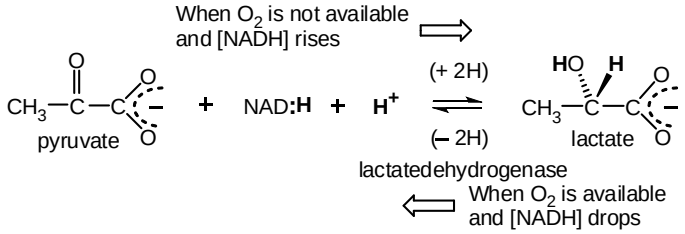
β-picoline | nicotinic acid | nicotine

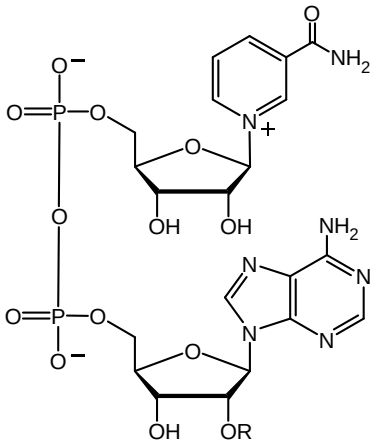
Nicotinic acid is present in small amounts in living cells. In biochemistry, nicotinic acid is known also as **niacin** (**ni**cotinic **ac**id + vitam**in**), which is called vitamin B_3. Therefore nicotinic acid is an essential human nutrient. Severe deficiency of niacin in the diet causes the disease pellagra. Pellagra is characterized by diarrhea, dermatitis (red skin lesions) and dementia, and eventually death, if left untreated. Pellagra can be common in people who obtain most of their food energy from maize (often called "corn", the only grain low in niacin), notably South America where maize is a widely used as food. Niacin is found in variety of foods including liver, chicken, beef, fish, cereal, peanuts and is also synthesized from tryptophan, which is found in meat, dairy and eggs.



nicotinamide

Niacin is converted to **nicotinamide** (other form of vitamin B_3) and then to NAD^+/ NADH and $NADP^+$/ NADPH, which play essential metabolic roles in living cells. Nicotinamide is a water-soluble vitamin and is part of the vitamin B group. Other forms of vitamin B_3 as nicotinic acid include the corresponding amide, nicotinamide ("niacinamide"), where the carboxyl group has been replaced by a carboxamide group ($CONH_2$), as well as more complex amides and a variety of esters. The terms niacin, nicotinamide, and vitamin B_3 are often used interchangeably to refer to any member of this family of compounds, since they have the same biochemical activity. In cells, niacin is incorporated into **nicotinamide adenine dinucleotide (NAD)** and **nicotinamide adenine dinucleotide phosphate (NADP)**, although the pathways for nicotinamide and nicotinic acid are very similar. NAD^+ and $NADP^+$ are coenzymes in a wide variety of enzymatic oxidation-reduction reactions. The reduced form NADH provides hydride ion which along with a proton are the reducing equivalents in biosynthetic reactions, for instance lactate from pyruvate. NADH is a reducing agent, NAD^+ is oxidizing agent.

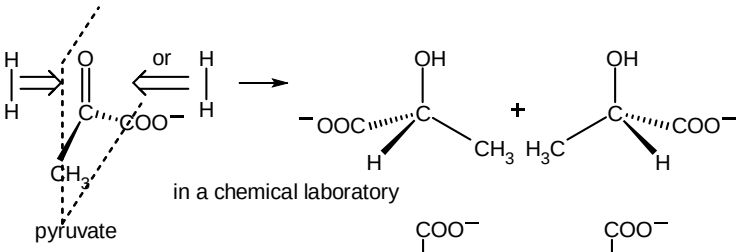


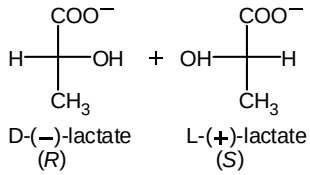


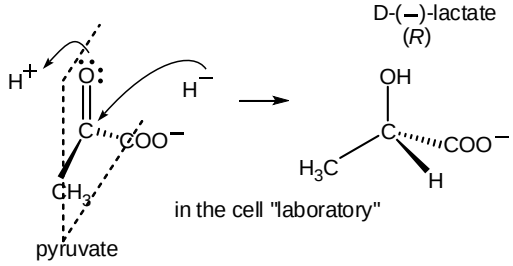
R = H NAD Nicotinamide adenine dinucleotide
R = OPO_2H NADP

The NAD(P)-dependent L-lactate dehydrogenase in humans is found in skeletal muscle.

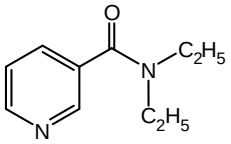
There is a fundamental difference between a chemical and a biochemical reaction. When hydrogenation of pyruvate is performed in chemical laboratory using hydrogen gas and a catalyst the result is a mixture of the two enantiomers of lactate. The mixture contains equal amounts of the enantiomers and such 1:1 mixtures are called racemates. Most biochemical reactions result in single enantiomer. Such reactions are enantiospecific and enantioselective! For instance, the reduction of pyruvate on lactate dehydrogenase using NADH gives only L-(+)-lactate, because the substrate binding to enzyme active center effectively blocks one side of the flat carbonyl group from approaching hydride from NADH. The hydride transfer occurs only from one side of the carbonyl plane. The same is true for the reversed reaction. The abstraction, removal of hydrogen (as a hydride) is possible only from one side of the L-lactate molecule.

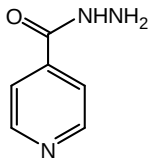




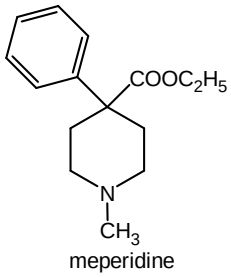


Coramine (Nikethamide, N,N-diethylnicotine amide) is a stimulant which mainly affects the respiratory cycle. It has non-specific analeptic properties (a central nervous system stimulant). The substance is banned as illegal in sports.



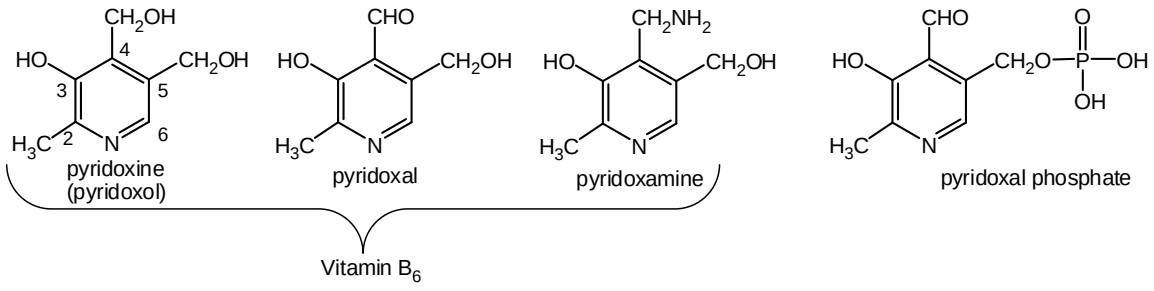


Isoniazid (hydrazide of isonicotinic acid) is the first-line antituberculosis medication in prevention and treatment (1950s). Isoniazid is never used on its own to treat active tuberculosis because microbial resistance quickly develops. The mechanism of tuberculostatic action involves formation of an isonicotinic acyl-NADH complex which inhibits the synthesis of component of mycobacterial cell wall.



Meperidine (Demerol) is a piperidine derivative. It is synthetic opioid, analgesic drug with the same action as morphine. The substance is widely prescribed as an effective narcotic. The structure does not have chiral center and the molecule is achiral.

Vitamin B_6. Vitamin B_6 combines three forms that occur in natural sources – pyridoxol, pyridoxal, and pyridoxamine. The difference between them is the nature of the substituent at position C(4) in pyridine core. These compounds are water soluble and easily utilized in mamaliam organism. Most people get their supply of pyridoxine vitamin from either milk or meat products. Plants do not contain the vitamin. Pyridoxal phosphate is the physiologically active form where benzylic type alcohol is acylated with phosphoric acid to phosphate ester. Pyridoxal phosphate is a cofactor in many reactions of amino acid metabolism such as decarboxylation, transamination, enzymatic steps in metabolism of tryptofan, sulfur- and hydroxy-containing amino acids. All forms of vitamin B_6 are converted to pyridoxal phosphate in the body.



Quinine is a natural alkaloid (from tree bark) with a quinoline ring. The compound possesses antipyretic (fever-reducing), antimalarial, analgesic (painkilling), and anti-inflammatory properties and a very bitter taste. Quinine was the first effective treatment for malaria caused by *Plasmodium falciparum*. It remained the antimalarial drug of choice until the 1940s but is still used today to treat the disease in certain critical situations. Quinine is added in small amount in tonic water. That is why the carbonated drink fluoresces under UV light due to quinine. Gin and tonic cocktail originated from the need to take better tasting quinine.