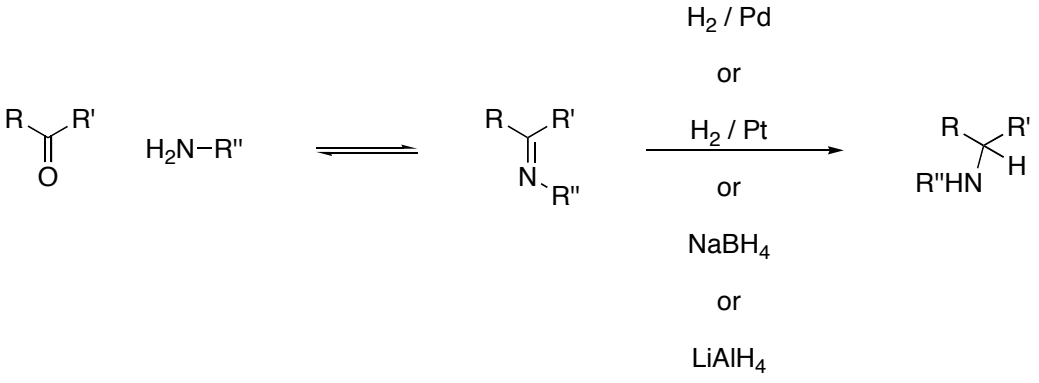
## Reductive Amination

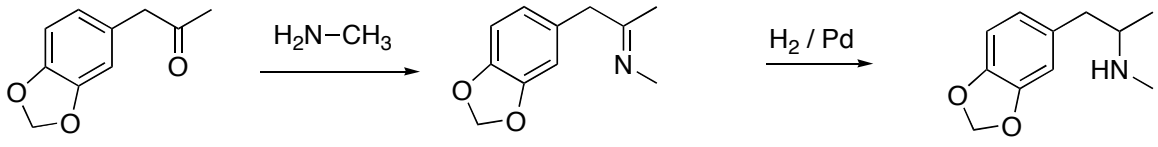
Amines can be synthesized in a single step by treatment of a ketone or aldehyde with ammonia or an amine in the presence of a reducing agent, a process called reductive amination.

Reductive amination takes place by the pathway shown below. The amine attacks the carbonyl and yields an imine by a nucleophilic addition reaction, then the imine is reduced by a reducing agent such as hydrogen gas and palladium ($H_2$/Pd), hydrogen gas and platinum ($H_2$/Pt), sodium borohydride ($NaBH_4$) followed by water or lithium aluminum hydride ($LiAlH_4$) followed by water to yield the amine.




imine

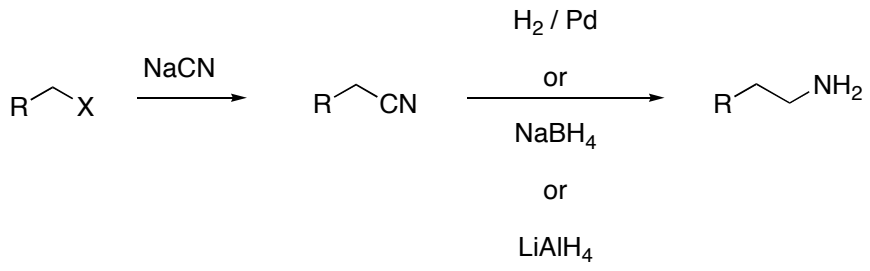
An example of this reaction is the formation of N-methyl methylenedioxyamphetamine (Ecstasy). Addition of methylamine to the ketone starting material yields the imine intermediate. This intermediate is then reduced with hydrogen gas and palladium to yield Ecstasy in racemic form (1:1 mixture of both stereoisomers). Only one enantiomer is known to be biologically active, whereas the biological activity of the other isomer is not known.




imine Ecstasy

**Reduction of Nitriles (Alkyl Cyanides)**

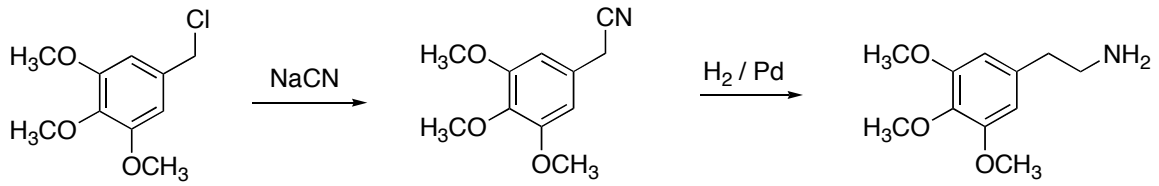
Primary amines can also be formed from the reduction of alkyl cyanides with a reducing agent. The reaction occurs by nucleophilic addition of hydride ion to the carbon of the polar nitrile bond, yielding an imine that undergoes further addition of a second equivalent of hydride to yield the primary amine. The nitrile can be formed from $S_N2$ displacement of an alkyl halide (X = Cl, Br, I) with sodium cyanide (NaCN) as shown below.




Alkyl halide (X=Cl, Br, I) nitrile primary amine

An example of this process is in the formation of mescaline. Mescaline or 3,4,5-trimethoxyphenethylamine is a psychedelic hallucinogenic drug. It is found peyote cactus (*Lophophora williamsii*), the San Pedro cactus (*Echinopsis pachanoi*), or the Peruvian Torch cactus (*Echinopsis peruviana*). It is also found in a number of other members of the Cactaceae. The effective human dosage is 200–400 milligrams (3.75 mg/kg), with the effects lasting for up to twelve hours. It is not physically addictive. Users typically experience visual hallucinations and altered states of consciousness, in some cases experienced as pleasurable and illuminating, but in others cases accompanied by feelings of intense fear and anxiety.

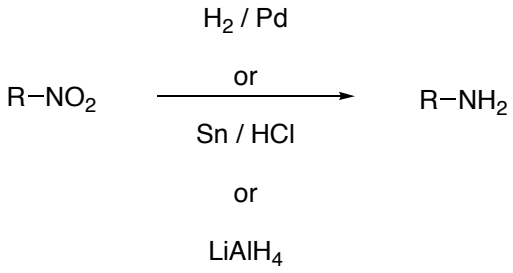
Addition of sodium cyanide to 3,4,5-trimethoxybenzyl chloride yields the nitrile, which is then reduced with hydrogen gas and palladium to yield mescaline. Since mescaline has no stereogenic centers, it is formed as only a single isomer.




3,4,5-trimethoxybenzyl chloride Mescaline

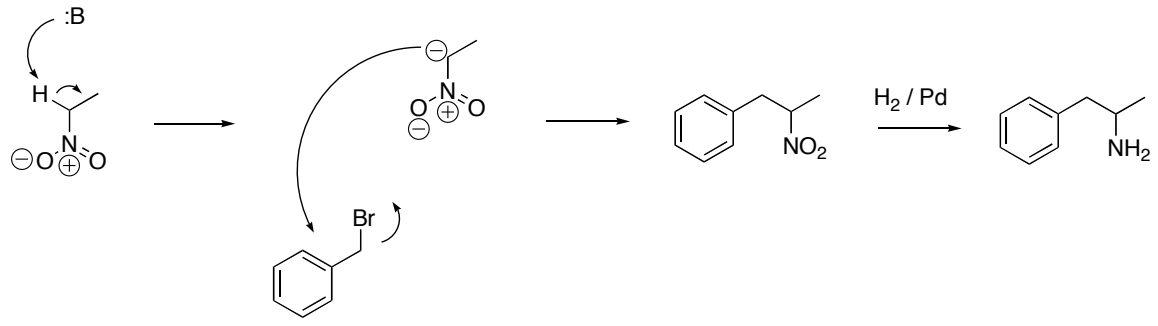
**Reduction of Nitro Groups to Amines**

Amines can be prepared by the reduction of a nitro group. The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum or palladium is clean but incompatible with the presence of other reducible groups such as double bonds. Lithium aluminum hydride followed by acid treatment is a useful method to obtain amines from nitro groups but incompatible with carbonyl groups present. Other methods involve the use of iron, zinc, or tin in acidic aqueous solutions.




nitro compound

An example is the preparation of amphetamine from benzyl bromide and nitroethane. Treatment of nitroethane with base removes the α-hydrogen to the nitro group forming an anion, which then displaces the bromine in an $S_N2$ type mechanism. The α-hydrogens are easily removed because the nitro group is similar in properties to a carbonyl group and is electron withdrawing making these hydrogen's acidic. Treatment of the resulting nitro compound with hydrogen gas and palladium then yields amphetamine.

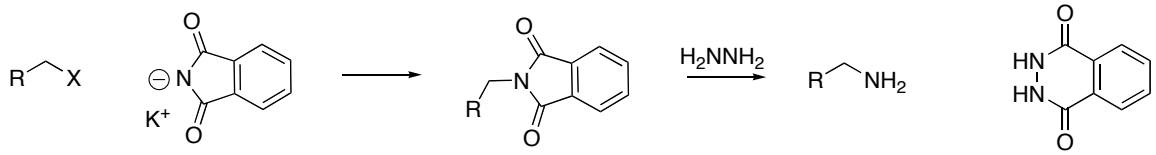



nitroethane benzyl bromide Amphetamine

Amphetamine, also known as speed, is a synthetic stimulant that has been used to suppress the appetite, control weight, and treat disorders including narcolepsy and attention-deficit hyperactivity disorder. It is also used recreationally and for performance enhancement (these uses are illegal in most countries).

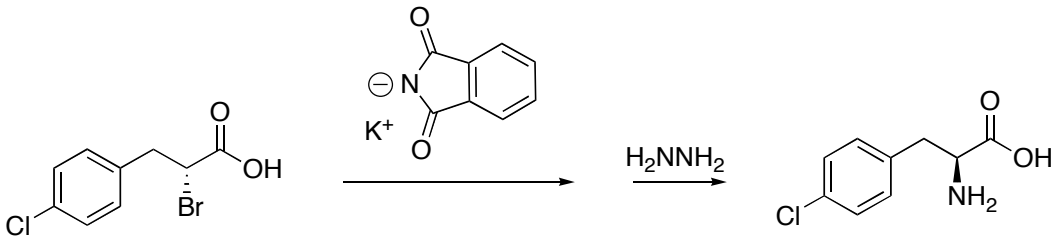
**Gabriel Synthesis**

The Gabriel amine synthesis uses phthalimide alkylation in preparing a primary amine from an alkyl halide (where X=Cl, Br, I). Imides (-CONHCO-) are similar to ethyl acetoacetate in that the NH hydrogen is flanked by two carbonyl groups. Thus, imides are deprotonated by such bases as KOH, and the resultant anions are readily alkylated. Reaction with hydrazine ($H_2NNH_2$) of the N-alkylated imide then yields a primary amine product along with a byproduct that is similar to luminol (seen in demo).




potassium phthalimide N-alkylated imide primary amine

An example is the preparation of p-chlorophenylalanine from the chirally pure brominated starting material in the (S) configuration. The phthalimide displaces the bromine in an $S_N2$ mechanism, which is then followed by hydrazine treatment, yielding ( R )-p-chlorophenylalanine as shown below. P-chlorophenylalanine is an unnatural amino acid, which was found to be an aphrodisiac (sexual stimulant).

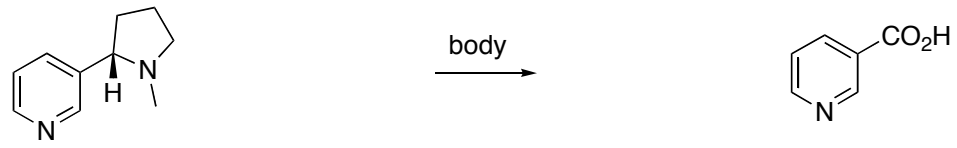



p-chlorophenylalanine

**Alkaloids**

Alkaloids are nitrogen-containing substances from plant sources. The study of alkaloids provided much of the growth in organic chemistry in the nineteenth century and remains today a fascinating area of research. Many alkaloids have pronounced biological properties, and many pharmaceutical agents used today are derived from naturally occurring amines. Morphine (as shown previously) and related alkaloids from the opium poppy, for example, are used from pain relief. In the next section, we will look at some important and well-known alkaloids from various sources of plant material from the Solanaceae plant family (includes peppers, tobacco, potato, and tomato) including nicotine, solanine, and atropine.

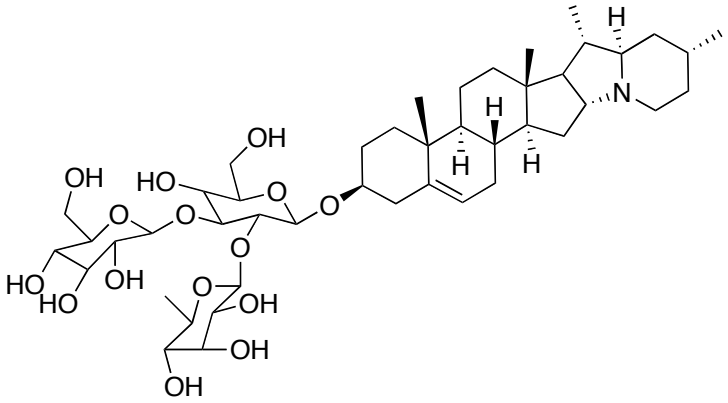
Nicotine is found naturally in tobacco and is shown below. It constitutes 0.3 to 5% of the tobacco plant by dry weight. It is a potent nerve poison and is included in many insecticides. In lower concentrations, the substance is a stimulant and is one of the main factors leading to the habit-forming qualities of tobacco smoking. Nicotine seems to provide both a stimulant and a depressant effect, and it is likely that the effect it has at any time is determined by the mood of the user, the environment and the circumstances of use. The body converts nicotine into nicotinic acid or better known as niacin. Niacin, also known as vitamin B3, is a water-soluble vitamin whose derivatives such as NADH, NAD, NAD+, and NADP play essential roles in energy metabolism in the living cell and DNA repair. Severe lack of niacin causes the deficiency disease pellagra, whereas a mild deficiency slows down the metabolism, which in turn decreases cold tolerance and is a potential contributing factor towards obesity.




Nicotine

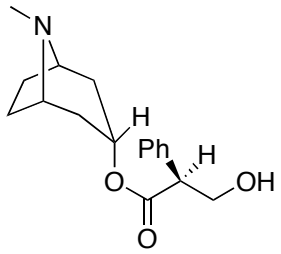
Nicotinic acid

Solanine (shown below) is a glycoalkaloid (contains a steroidal alkaloid linked to a sugar) poison found primarily in the green parts of potato (stems,leaves) and greening potatoes. It is very toxic even in small quantities. Studies suggest that 2-5 mg/kg body weight can cause toxic symptoms and a dosage of 3-6 mg/kg body weight can be fatal. Solanine has both fungicidal and pesticidal properties, and it is one of the plant's natural defenses. A few people fall ill or die each year from eating green potatoes, which is attributed to the consumption of solanine. Potatoes naturally produce solanine as a defense mechanism against insects, disease, and predators.




Solanine

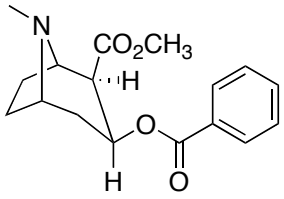
Atropine is a tropane alkaloid extracted from the deadly nightshade (*Atropa belladonna*) and other plants of the family Solanaceae. It is a secondary metabolite of these plants and serves as a drug with a wide variety of effects. Being potentially deadly, it derives its name from Atropos, one of the three Fates who, according to Greek mythology, cut the thread of life. In the Renaissance times, women used the juice of the berries of *Atropa belladonna* to enlarge the pupils of their eyes, for cosmetic reasons; "belladonna" is Italian for "beautiful lady".




Atropine

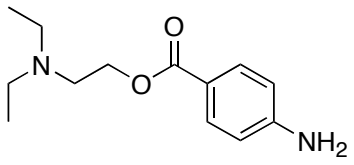
Generally, atropine lowers the "rest and digest" activity of all muscles and glands regulated by the parasympathetic nervous system. This occurs because atropine is a competitive antagonist of the acetylcholine receptors (Acetylcholine is the neurotransmitter used by the parasympathetic nervous system). Therefore, it may cause swallowing difficulties and reduced secretions. The racemic form is isolated from *Hyoscyamus* species known as henbane and from *Datura* species (e.g. *D. stramonium*), many of which have trumpet shaped flowers.

Cocaine is a crystalline tropane alkaloid that is obtained from the leaves of the coca plant (*Erythroxylum coca*). This is not in the *Solanaceae* family, but rather is in family *Erythroxylaceae*. It is a stimulant of the central nervous system and an appetite suppressant, creating what has been described as a euphoric sense of happiness and increased energy. Though most often used recreationally for this effect, cocaine is also a topical anesthetic that was used in eye and throat surgery in the 19th and early 20th centuries. Cocaine is addictive, especially in free base form (e.g. Crack).

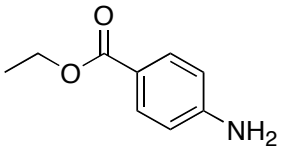



Cocaine

The addictive properties of cocaine hindered its use as an anasthetic. Derivatives were synthesized to isolate the anasthetic properties from the addictive properties. Novocain and Benzocaine are non-addictive, local anesthetics commonly used in dentistry and as a topical pain reliever respectively.




Novocaine




Benzocaine