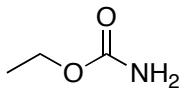
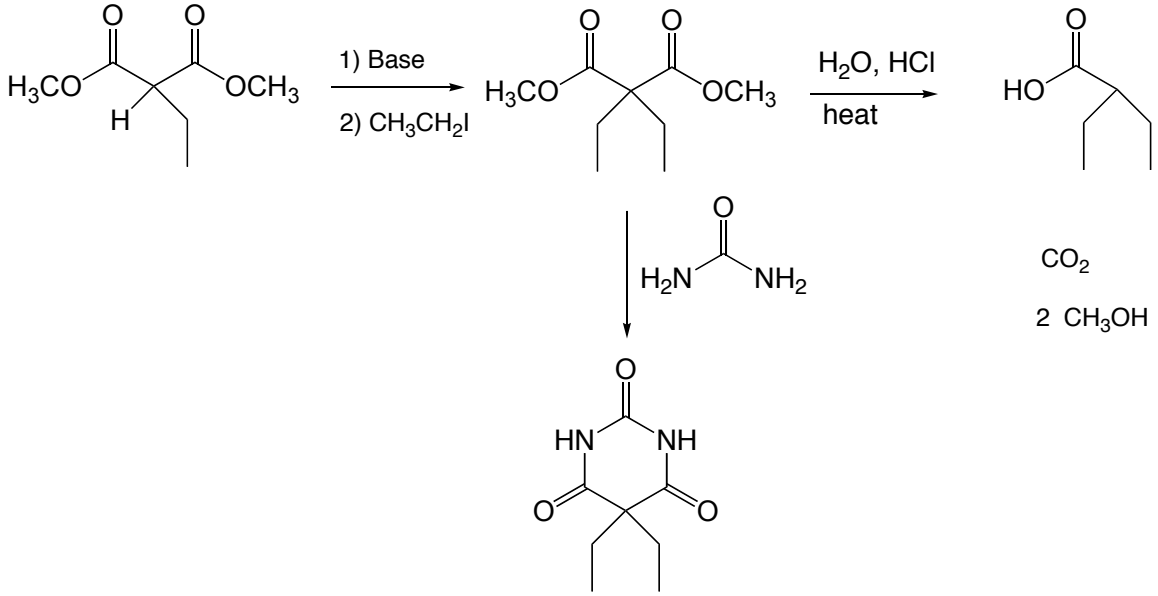
Note that another carbon dioxide derivative is a urethane. Some derivatives of these may be polymerized to form polyurethane.



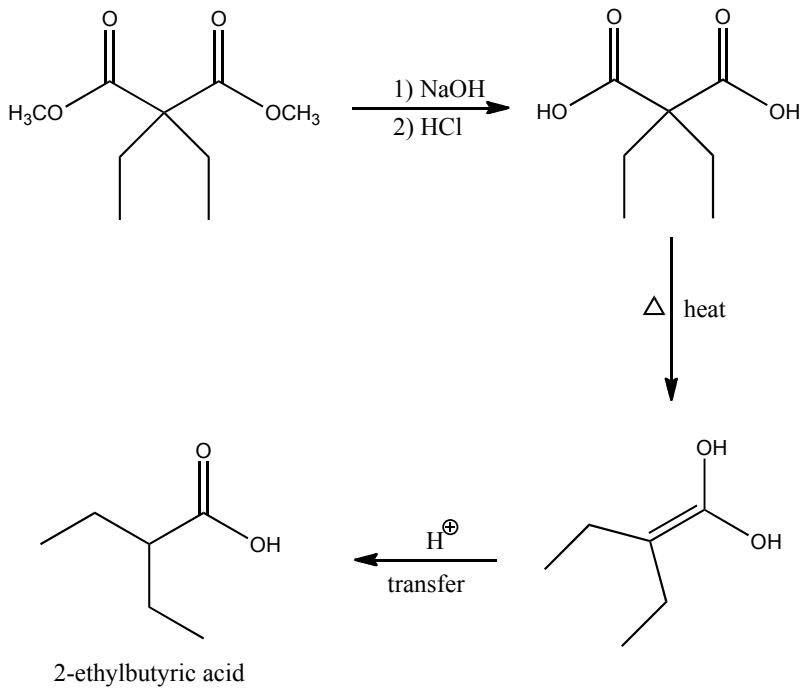
The alkylation product of dimethyl malonate shown last class can be alkylated again, as there is another alpha proton present.



The product from this reaction, dimethyl 2,2-diethylmalonate, can be used to perform other reactions as shown above.

Dimethyl 2,2-diethylmalonate can be treated with base or acid and water to form a dicarboxylic acid (hydrolysis), which can react further upon heating to lose carbon dioxide, as shown in the figure below.

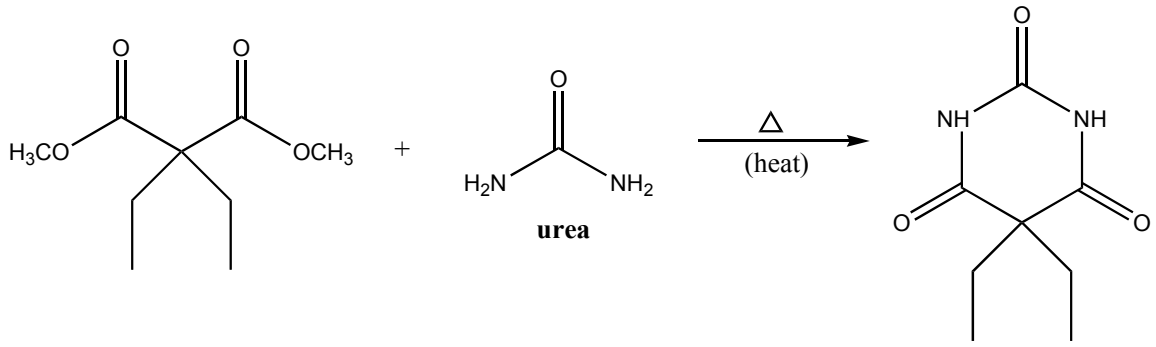
Alternately, dimethyl 2,2-diethylmalonate can react with urea to form barbital (diethyl barbiturate).



2-ethylbutyric acid

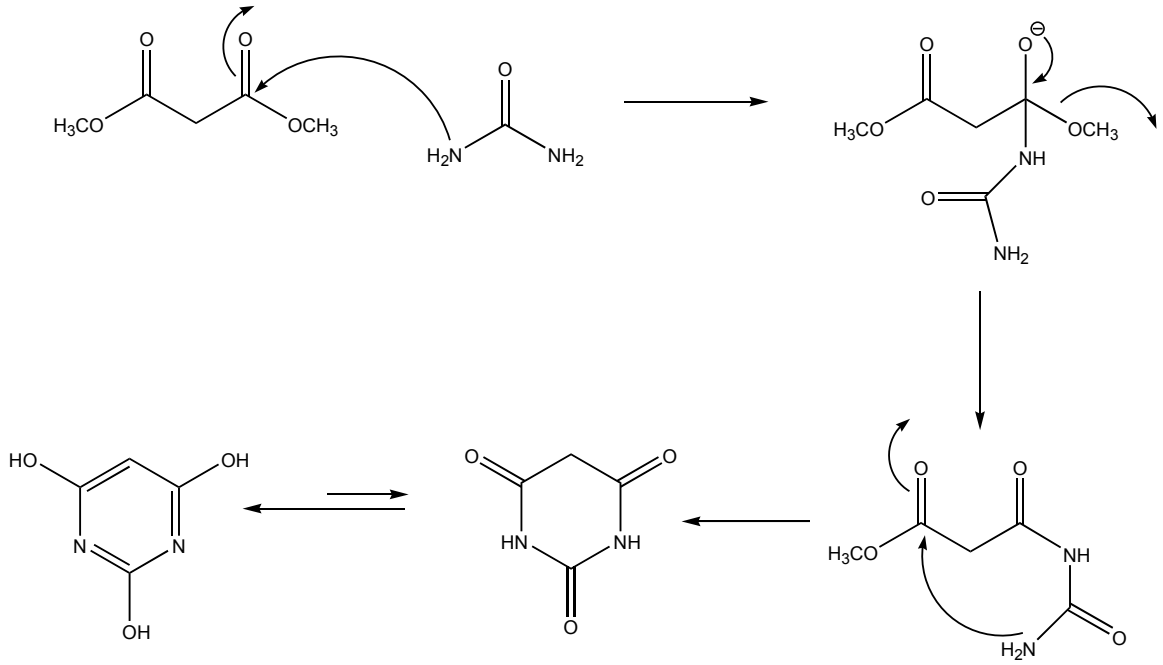
Upon heating (denoted by the triangle), the dicarboxylic acid loses one of its carboxylic groups (CO_2). This process is called decarboxylation. The product from this step is an enol. Upon treating with acid, we get a substituted acetic acid, specifically 2-ethylbutyric acid as the product.

Dimethyl 2,2-diethylmalonate can also be used as a synthetic precursor for drugs.



Barbital

Barbital (or diethyl barbiturate) belongs to a class of drugs called barbiturates. It is a sleeping pill used widely in the 1950's. However, it is also addictive. The mechanism of a similar reaction is shown below with dimethyl malonate as the starting material (for simplicity, the loss and gain of protons on nitrogen is not shown):



barbituric acid

In this reaction, the product is barbituric acid, which is biologically inactive.

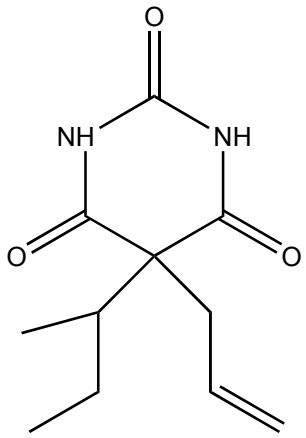
It is in equilibrium with its enol form, which is favoured.

Why is it favoured?

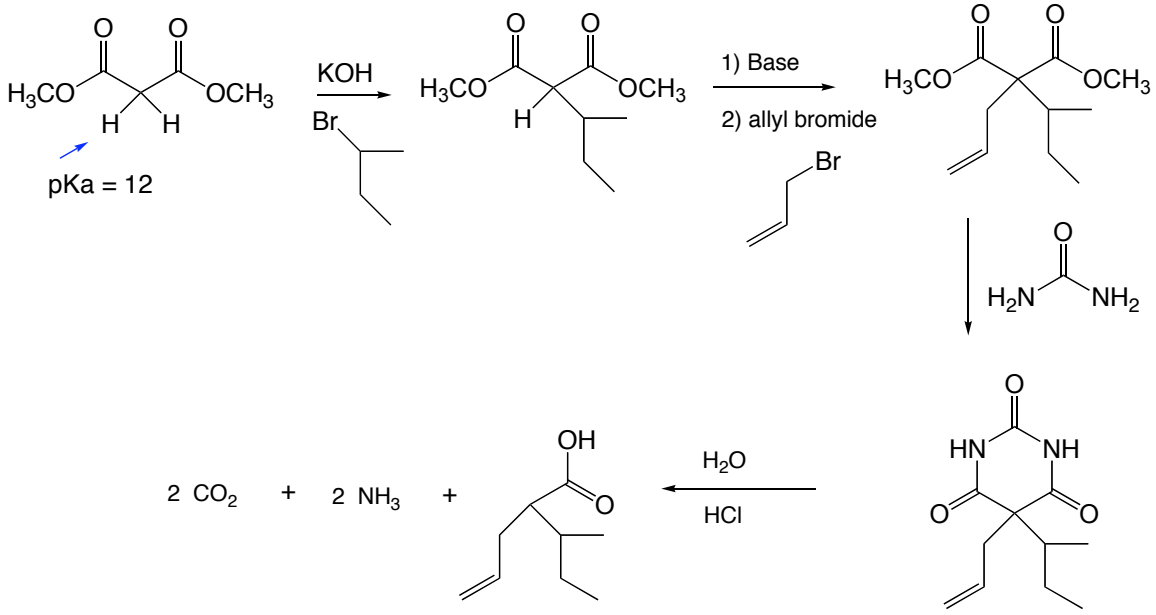
The enol form is more stable since it is aromatic (aromatic stabilization).

When alkylation is performed on barbituric acid, only alkylation on the oxygen was observed since the compound likes to stay in the enol form. Therefore, the alkylation of malonate must occur before cyclization with urea.

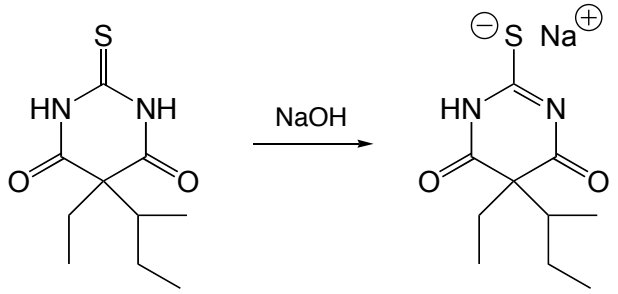
Another example of this class of compounds is seconal.



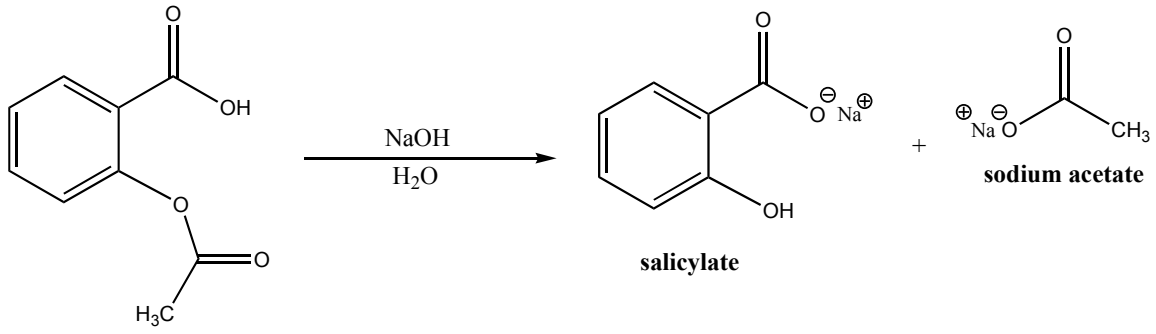
Think about how this could be synthesized:



A derivative of barbiturates is sodium pentothal, sometimes used as a truth serum.



Here's an example reviewing some chemistry of carboxylic acid derivatives:

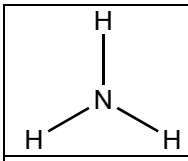
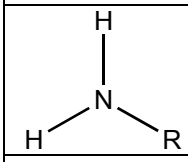
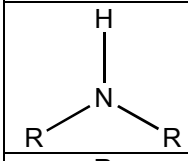
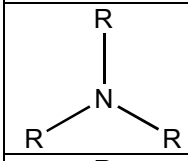
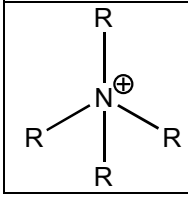


Aspirin or *acetylsalicylic acid* is a drug, often used as an analgesic (against minor pains and aches), antipyretic (against fever), and anti-inflammatory. It has also an anticoagulant ("blood-thinning") effect and is used in long-term low-doses to prevent heart attacks.

Aspirin has ester and carboxylic acid functional groups. When treated with a base such as NaOH, the first thing occurs is the deprotonation of the carboxylic acid to form a salt. The ester of aspirin also reacts and gives alcohol as product. The other product is sodium acetate. One thing to keep in mind is that the singly bonded oxygen, nitrogen or halogen is what always breaks away from the parent carbonyl.

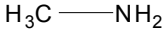
Lecture Outline 5 - Amines

Nomenclature:

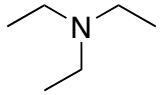
	Ammonia (simplest amine)
	Primary amine
	Secondary amine
	Tertiary amine
	Quaternary ammonium salt

For simple amines, name the alkyl group (R), and add amine at the end of the nomenclature. Secondary and tertiary amines in which R groups are all the same are simpled named as di- or trialkylamines. Amines bearing different R groups are named by ordering the groups alphabetically.

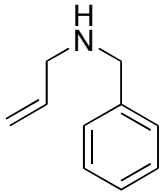
Examples:



Methylamine

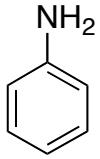


Triethylamine

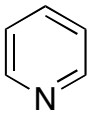


Allylbenzylamine

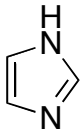
You should know these three structures:



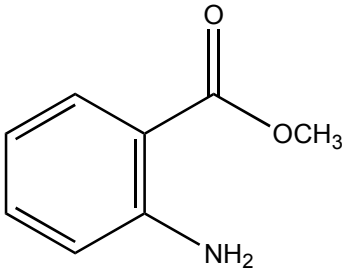
Aniline



Pyridine

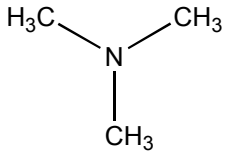


Imidazole

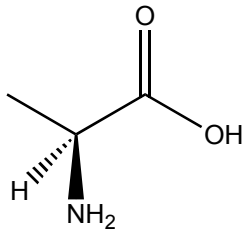


Methyl 2-aminobenzoate. It has the flavour of grapes, and also repels geese.

Note that the ester group takes priority as parent structure, rather than the amine. Then you count around the ring to give the lowest substitution number. In this case, C2 is where the amine is substituted.

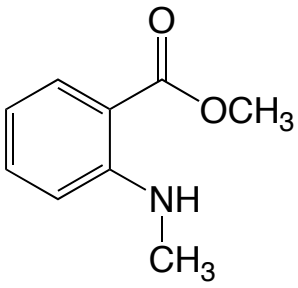


Trimethylamine

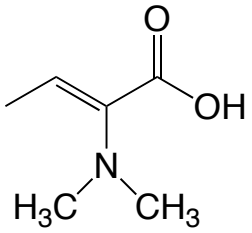


The structure shown above is an α-amino acid, named L-alanine. It is a major constituent of spider silk.

The systematic name for alanine is **(S)-2-aminopropanoic acid**.



Methyl 2-(N-methylamino)benzoate

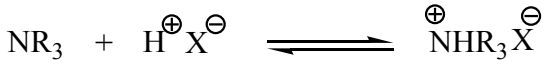


2-(N,N-dimethylamino)-2Z-butenoic acid

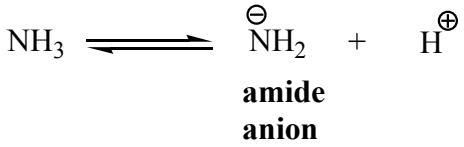
<u>Properties of Amines</u>

Amines are polar, and therefore have higher boiling point than hydrocarbons of similar molecular weight. Small amines tend to be water soluble, while larger amines containing more carbons are usually soluble in acid.

Amines have a lone pair and are both nucleophiles and bases, so they will react with acids such as a hydrogen halide to form salts

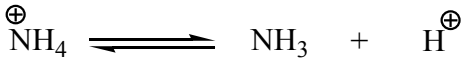


The pKa for ammonia is about 36.



$K_a = [NH_2][H+]/[NH_3] = 10^{-36}$

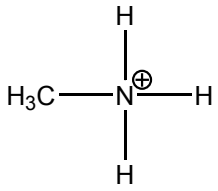
The pKa for an ammonium ion is about 9.4.



$K_a = [NH_3][H+]/[NH_4] = 10^{-9.4}$

In biology, the acidity of pKa of an amine may be mentioned, but usually they are referring to the ammonium ion and not the amine itself.

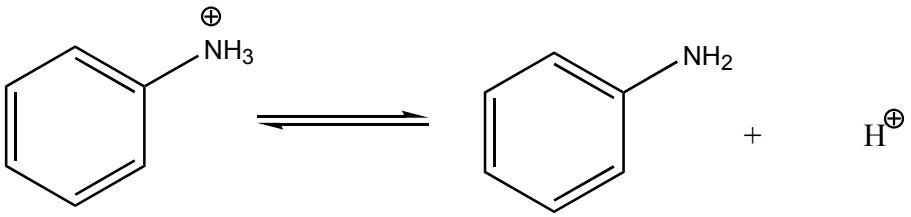
The pKa of protonated methylamine is around 10.5.



Is this more or less acidic than ammonium ion?
It is less acidic. Higher pKa means less acidity (more basic).

Why is methylamine less acidic than ammonium?
Because the alkyl group donates electron density to the nitrogen (inductive donation), which stabilizes the positive charge on nitrogen. Ammonium has only hydrogens on it. H is less electron donating than an alkyl group, therefore the positive charge is less stabilized.

Example:

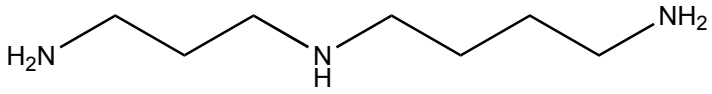


The pKa of protonated aniline is 4.6.

Is this more or less acidic than methylamine?
It is more acidic since the pKa is lower. The increased acidity means it is more likely to give away its proton.

Why?
Because the nitrogen lone pair in aniline is conjugated into the aromatic ring (resonance stabilization).

Example:

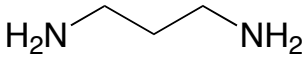


spermidine

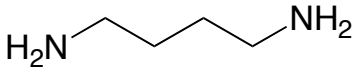
Spermidine is a polyamine isolated from seminal fluid in males but occurs in all cells. It reacts with acetic acid that is present in females.

Which amine is protonated first?
The secondary amine in the middle, since it is the most basic nitrogen (2 alkyl groups donate negative charge through the inductive effect to nitrogen).

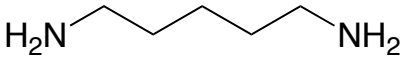
Example of diamines:



1,3-diaminopropane



1,4-diaminobutane
(putrescine)



1,5-diaminopentane
(cadaverine)

Some of these diamines occur in rotting meat, warning you not to eat it.