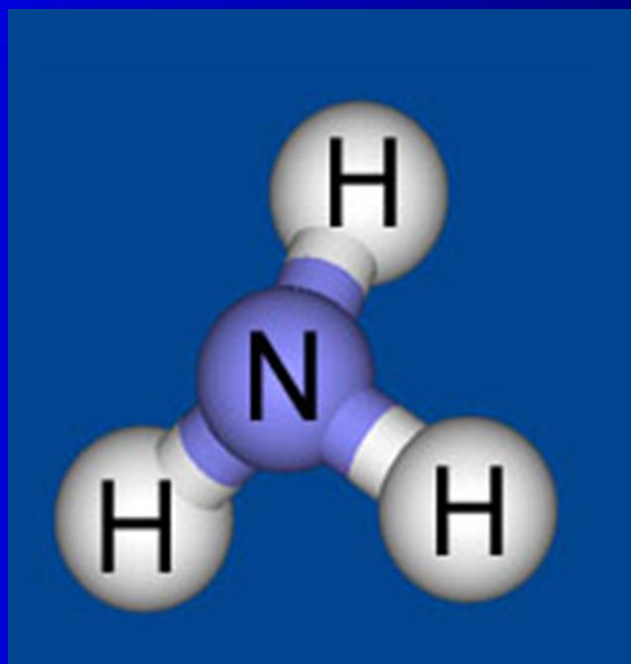


Lecture 23

Amines



Michael Reaction

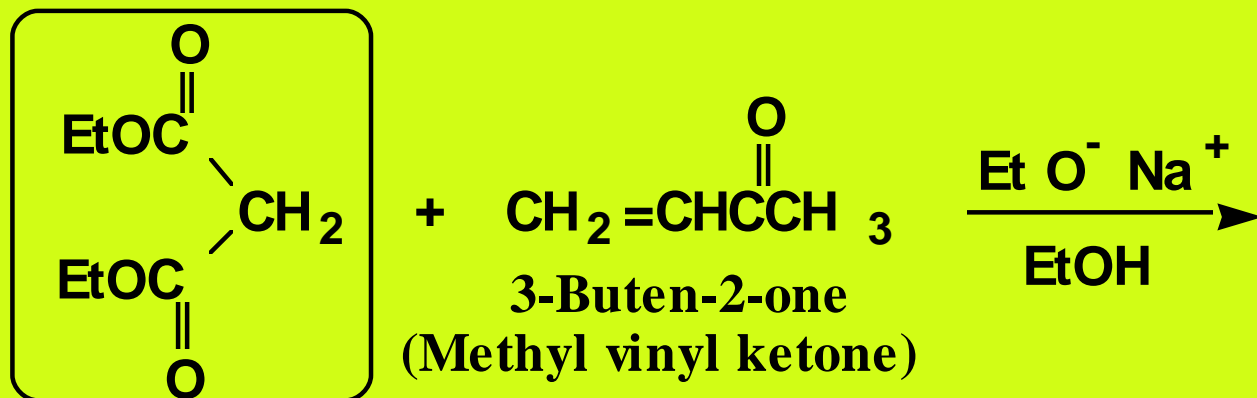
- **Michael reaction:** conjugate addition of an enolate anion to an α,β -unsaturated carbonyl compound!!
- **Following a**
 - in the first
 - in the second
- **An excellent**



on of malonic ester
of acetoacetic ester
yl compounds

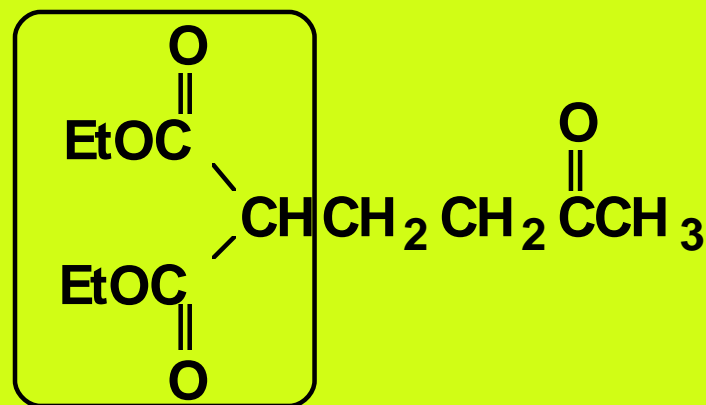


Michael Reaction

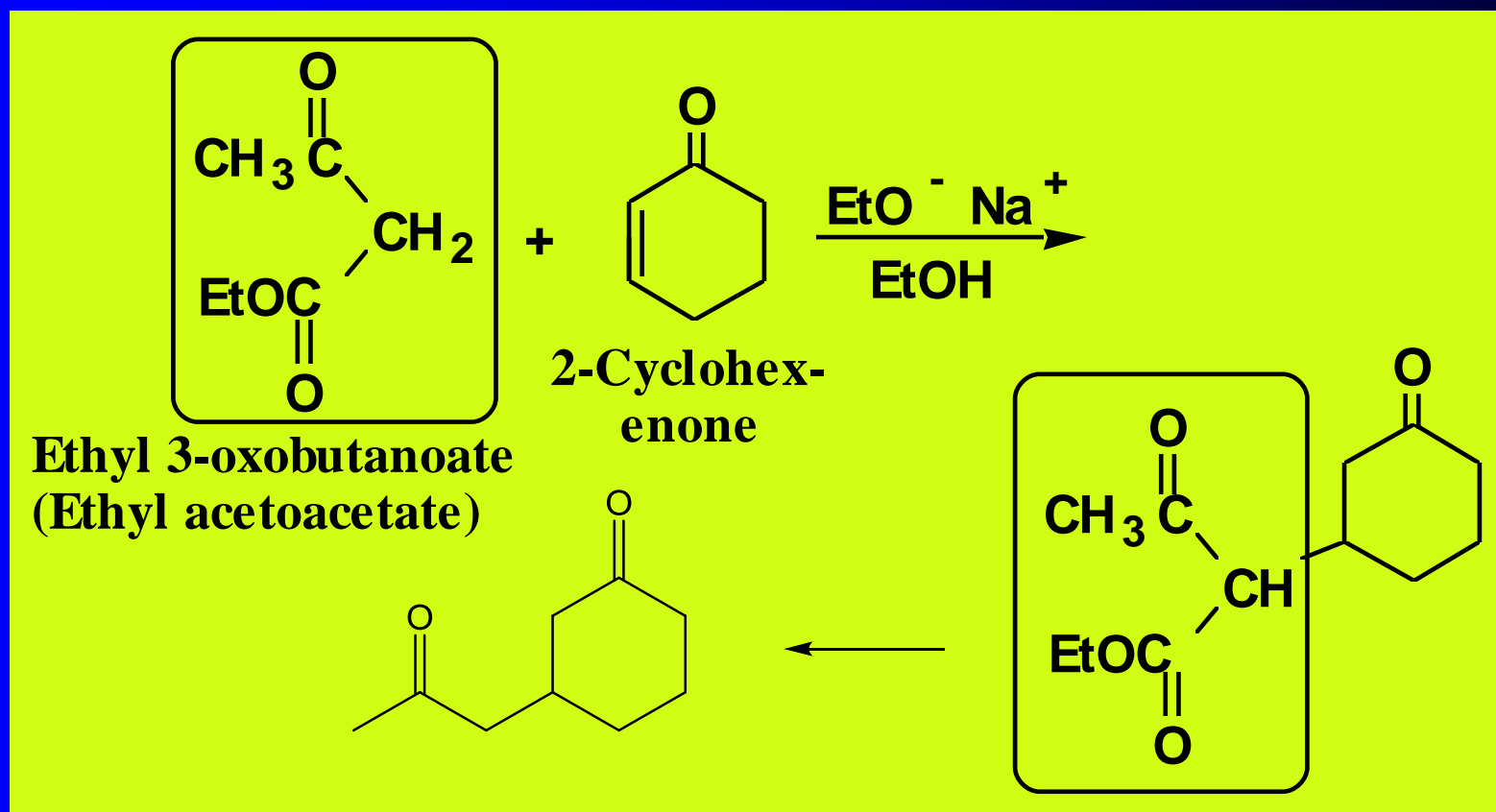


**Diethyl propanedioate
(Diethyl malonate)**

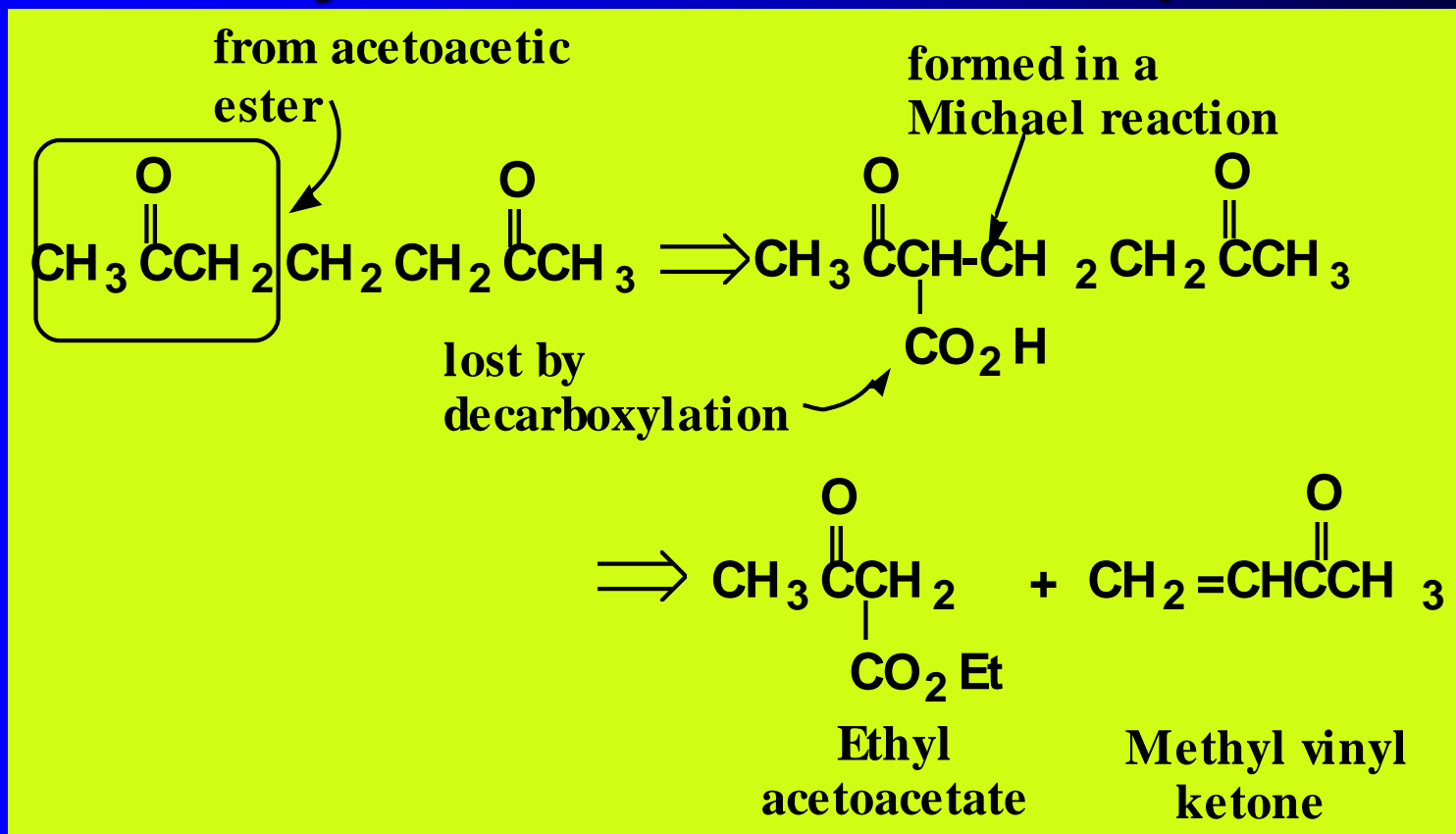
**3-Buten-2-one
(Methyl vinyl ketone)**



Michael Reaction



Retro-synthesis of 2,6-Heptadione

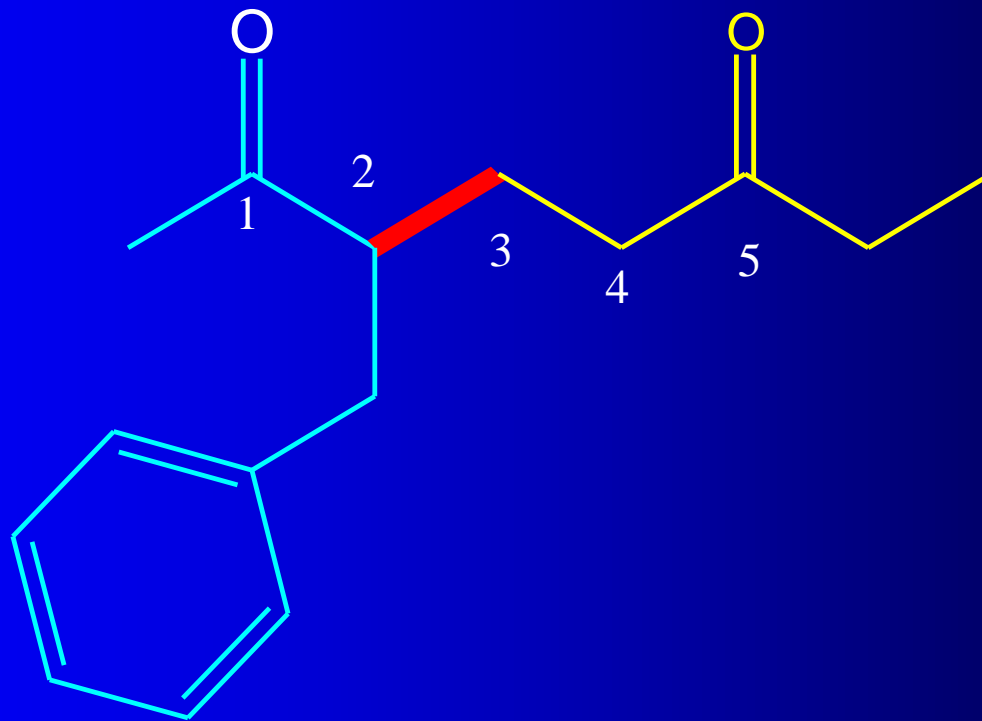


Always gives a 1,5-dicarbonyl product



Michael Addition

- The Michael reaction is a useful method for forming carbon-carbon bonds....1,5 dicarbonyls

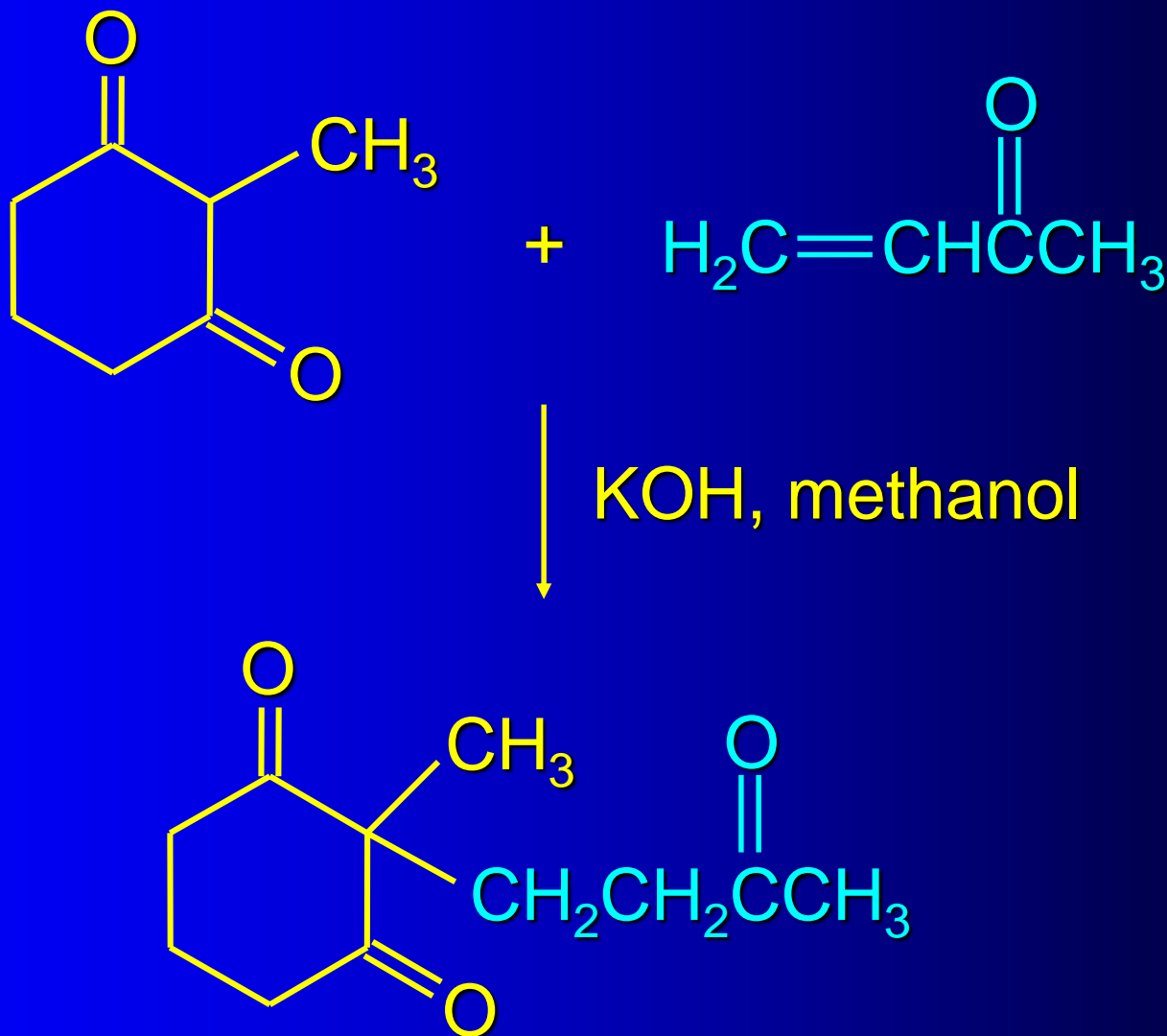


Michael Addition

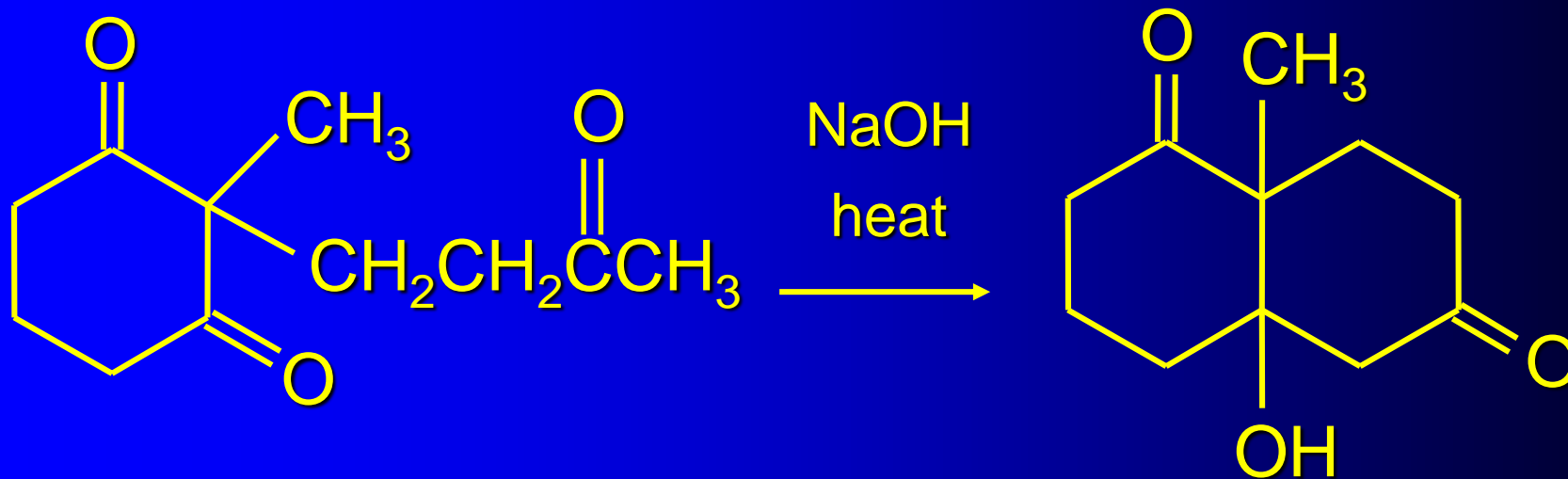
- It is also useful in that the product of the reaction can undergo an intramolecular aldol condensation to form a six-membered ring. One such application is called the Robinson annulation.
- This reaction enabled the first synthesis of steroids



The Robinson Annellation: 1. Michael addition



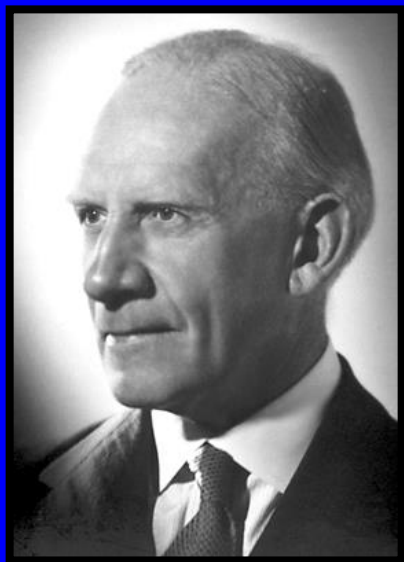
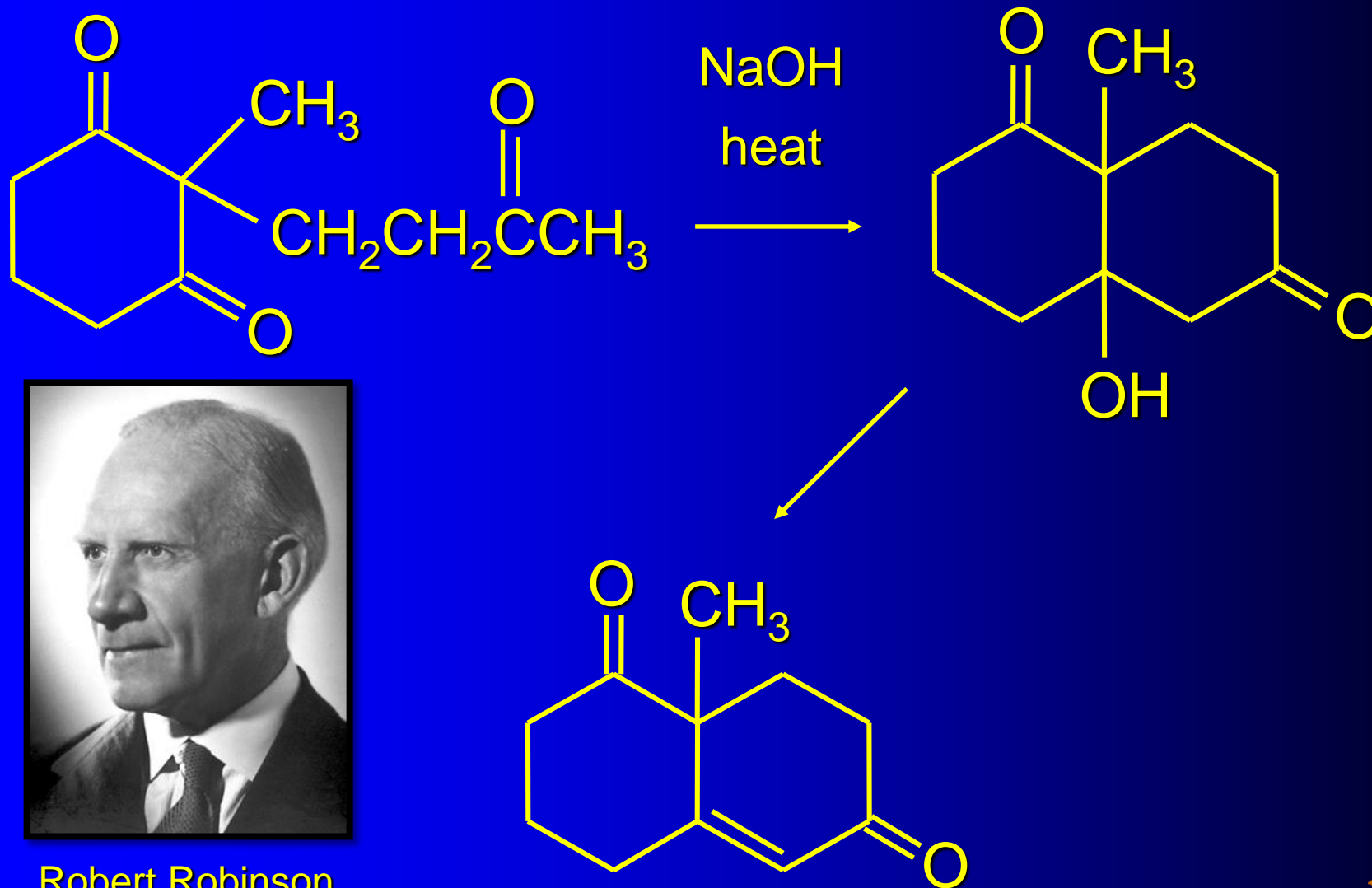
Robinson annelation: 2. aldol condensation



not isolated;
dehydrates under
reaction conditions



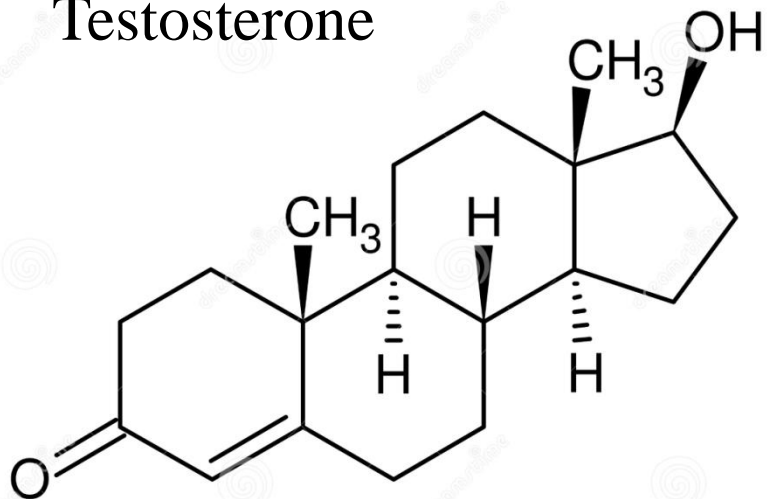
Robinson annelation: 3. elimination



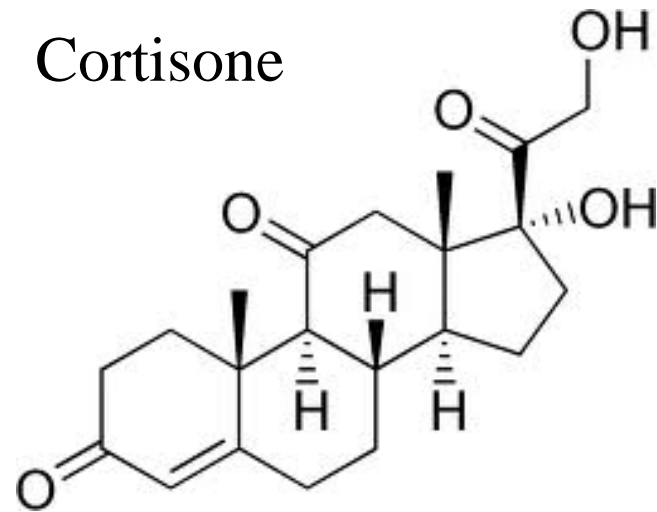
Robert Robinson
Nobel 1947



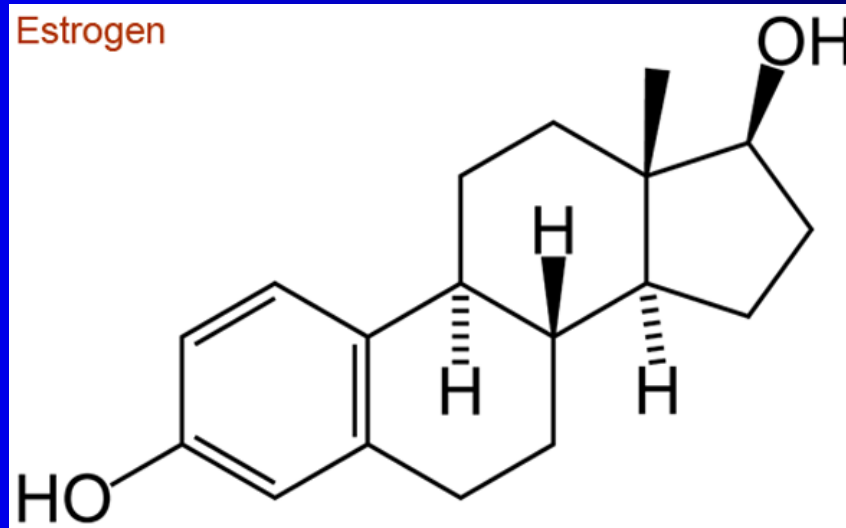
Testosterone



Cortisone



Estrogen



The Signature Page

Claisen Condensation: β -ketoesters

Dieckmann: Cyclic β -ketoesters

Aldol: α , β -unsaturated aldehydes and ketones

Acetoacetic ester synthesis: decorated acetones

Malonic ester synthesis: decorated acetic acids

Michael Reaction: 1-5 dicarbonyl compounds

Grignard Reaction: Alcohols

Wittig Reaction: Alkenes. ..., etc



The Diels-Alder Reaction



Otto Paul Hermann Diels
1876-1954



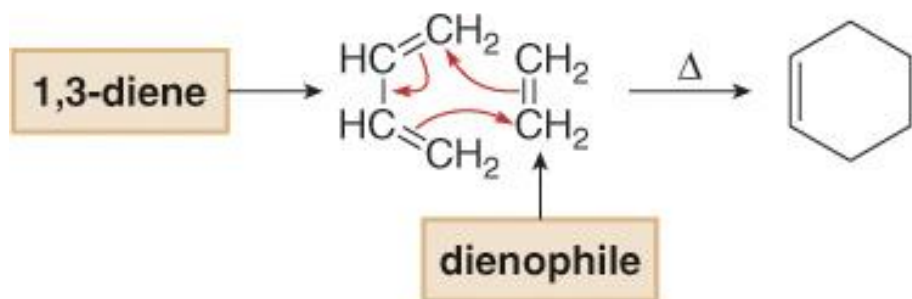
Kurt Alder
1902-1958



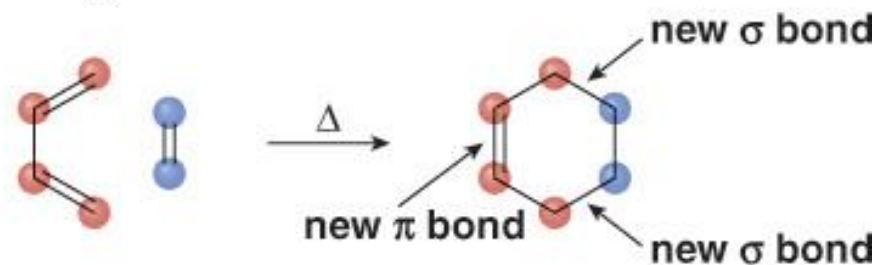
Diels-Alder Reaction:

- **The Diels-Alder reaction** is an addition reaction between a 1,3-diene and an alkene (called a **dienophile**), that forms a new six-membered ring.

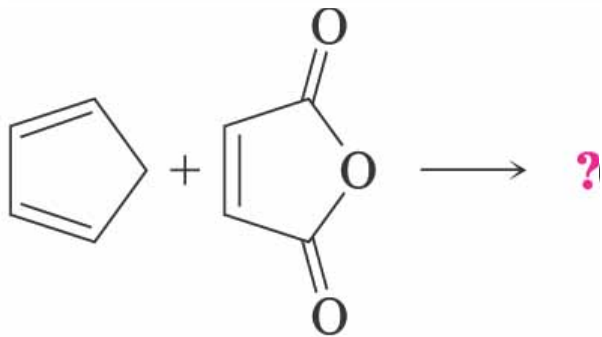
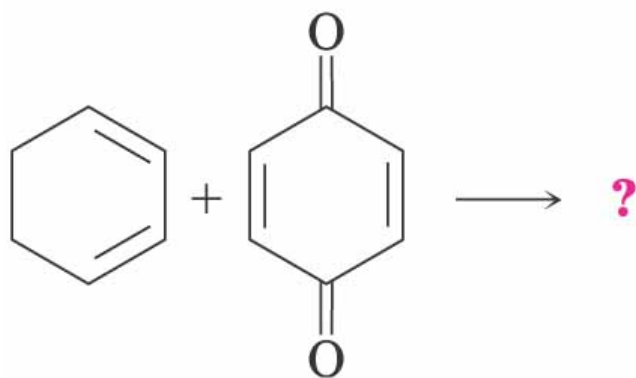
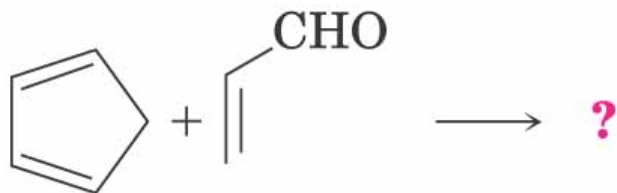
General Diels-Alder reaction



Or, emphasizing how the two components fit together:



Predict the products



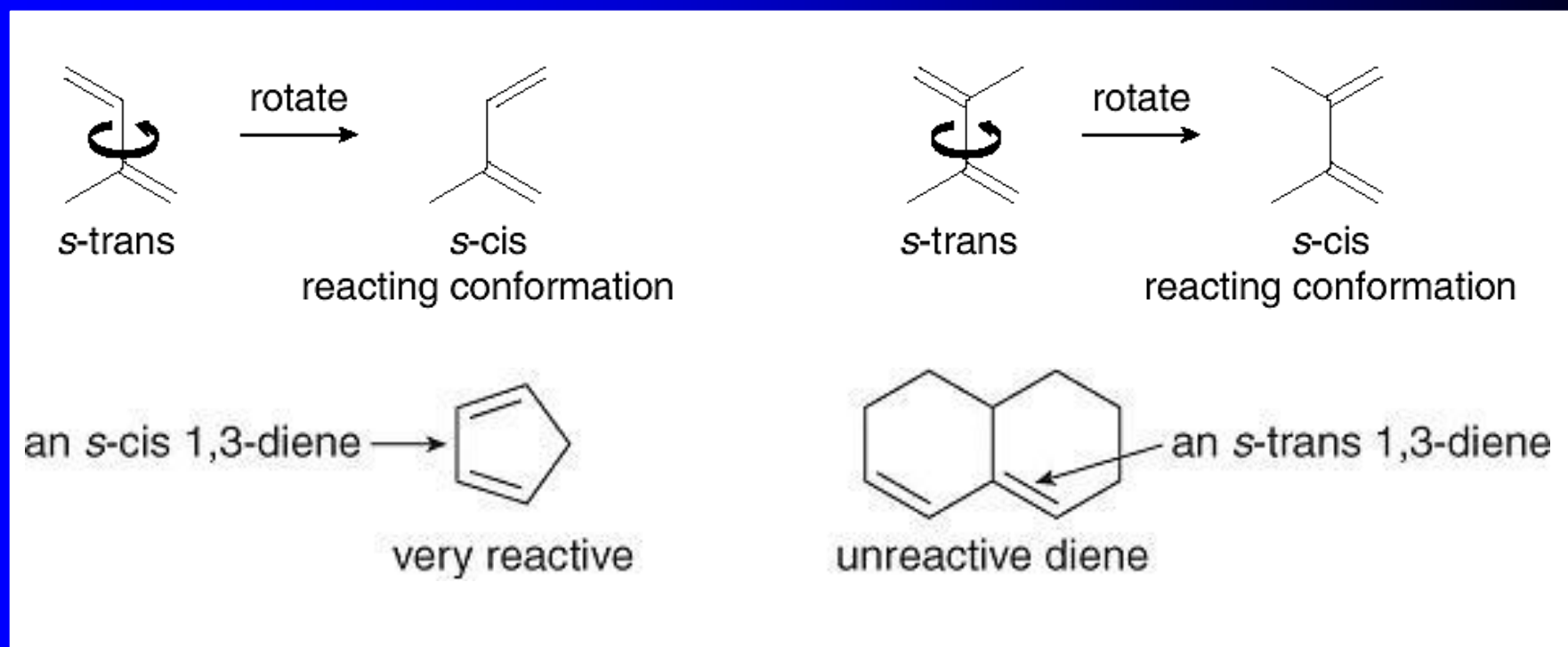
All Diels-Alder reactions:

1. are initiated by heat; that is, the Diels-Alder reaction is a thermal reaction.
2. form new six-membered rings.
3. involve breaking three π bonds and making two new σ bonds and one new π bond.
4. are **concerted**; that is, all bonds are broken and new bonds formed in a single step.



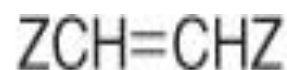
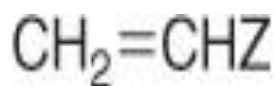
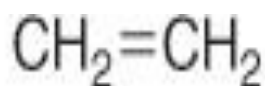
4 Rules that govern the Diels-Alder reaction

1. The diene can react only from the *s-cis* conformation.

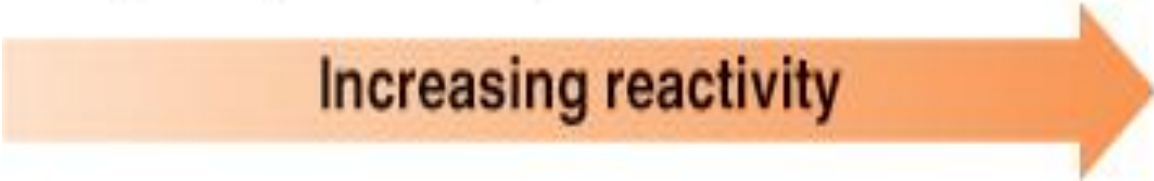


2. Electron-withdrawing substituents in the dienophile increase the reaction rate.

- The conjugated diene acts as a nucleophile and the dienophile acts as an electrophile.
- Electron-withdrawing groups make the dienophile more reactive
- If Z is an electron-withdrawing group, then the reactivity of the dienophile increases as follows:

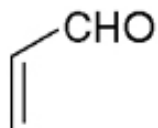


Increasing reactivity

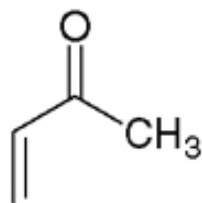


Common dienophiles

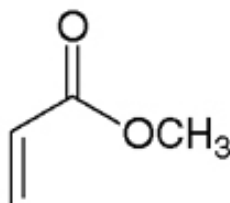
The carbonyl group is electron-withdrawing and activates dienophiles



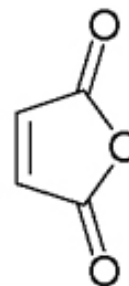
acrolein



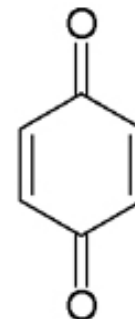
methyl vinyl
ketone



methyl acrylate



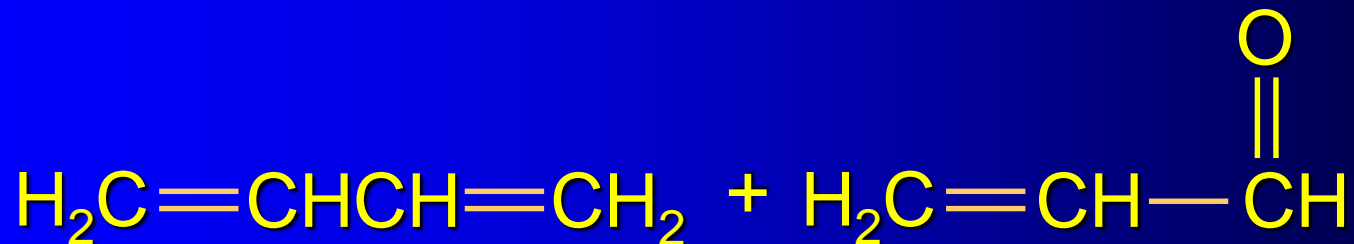
maleic anhydride



benzoquinone

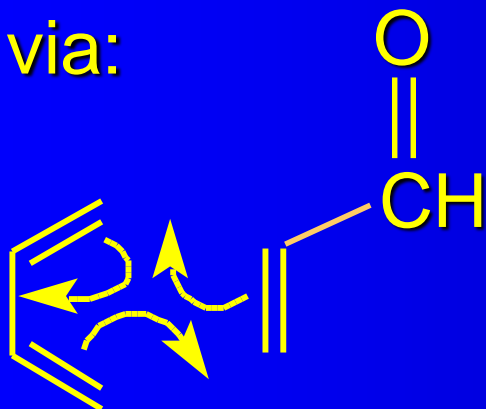


Example



benzene \downarrow 100°C

via:

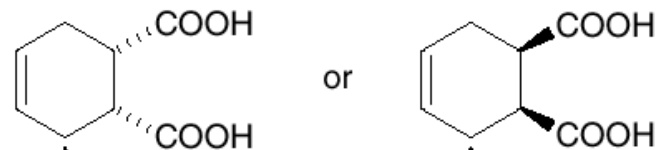
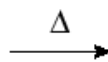
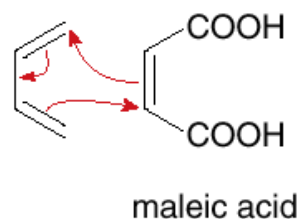


(100%)



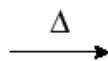
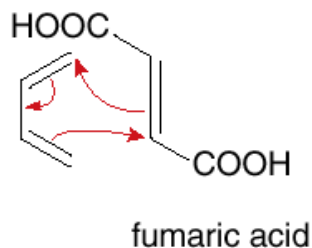
3. The stereochemistry of the dienophile is retained.

cis dienophile



cis product

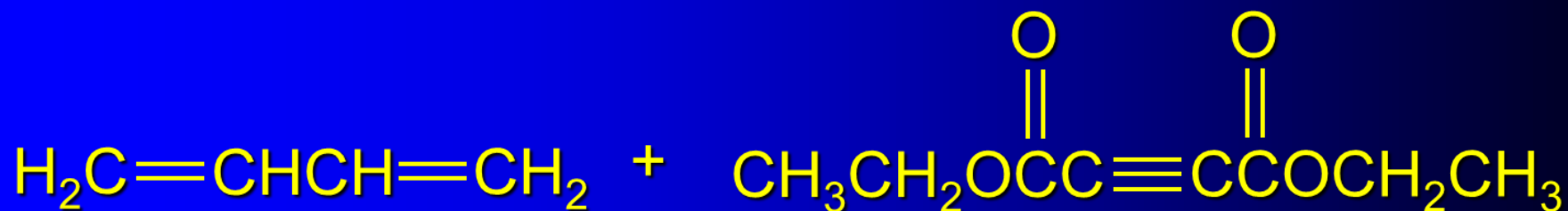
trans dienophile



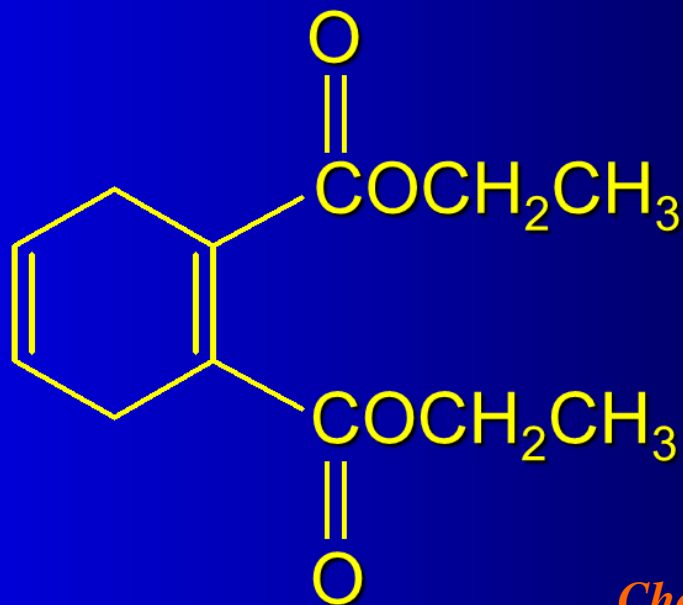
trans product



Acetylenic Dienophile



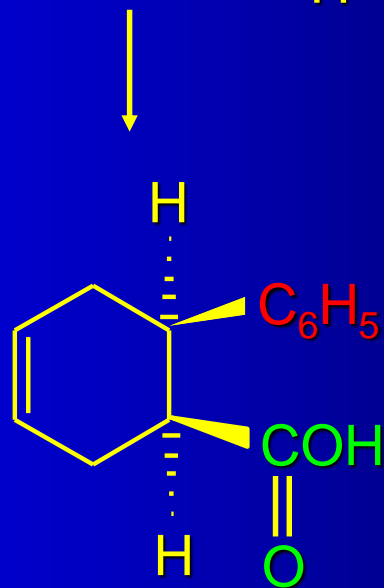
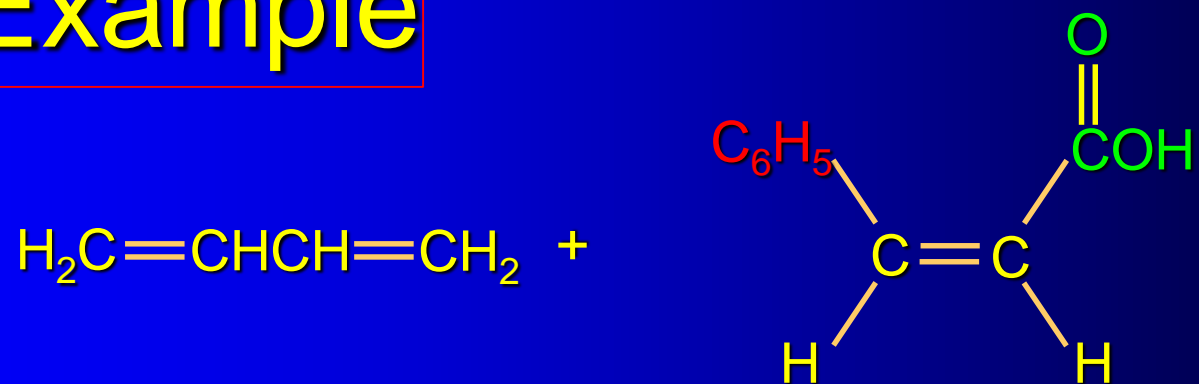
benzene \downarrow 100°C



(98%)



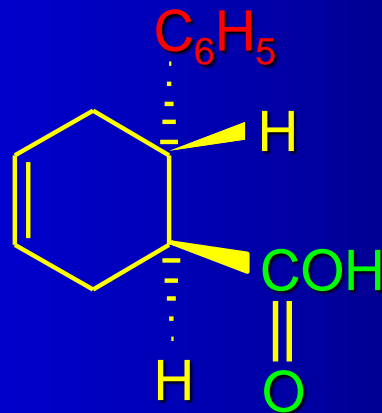
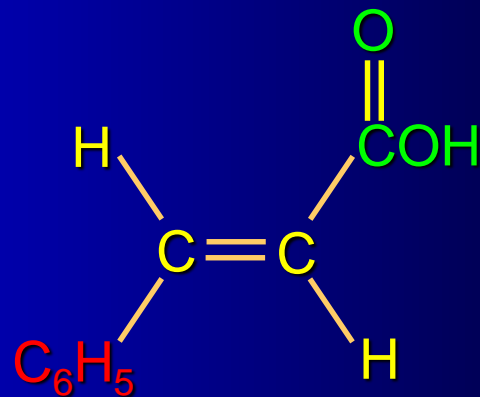
Example



only product

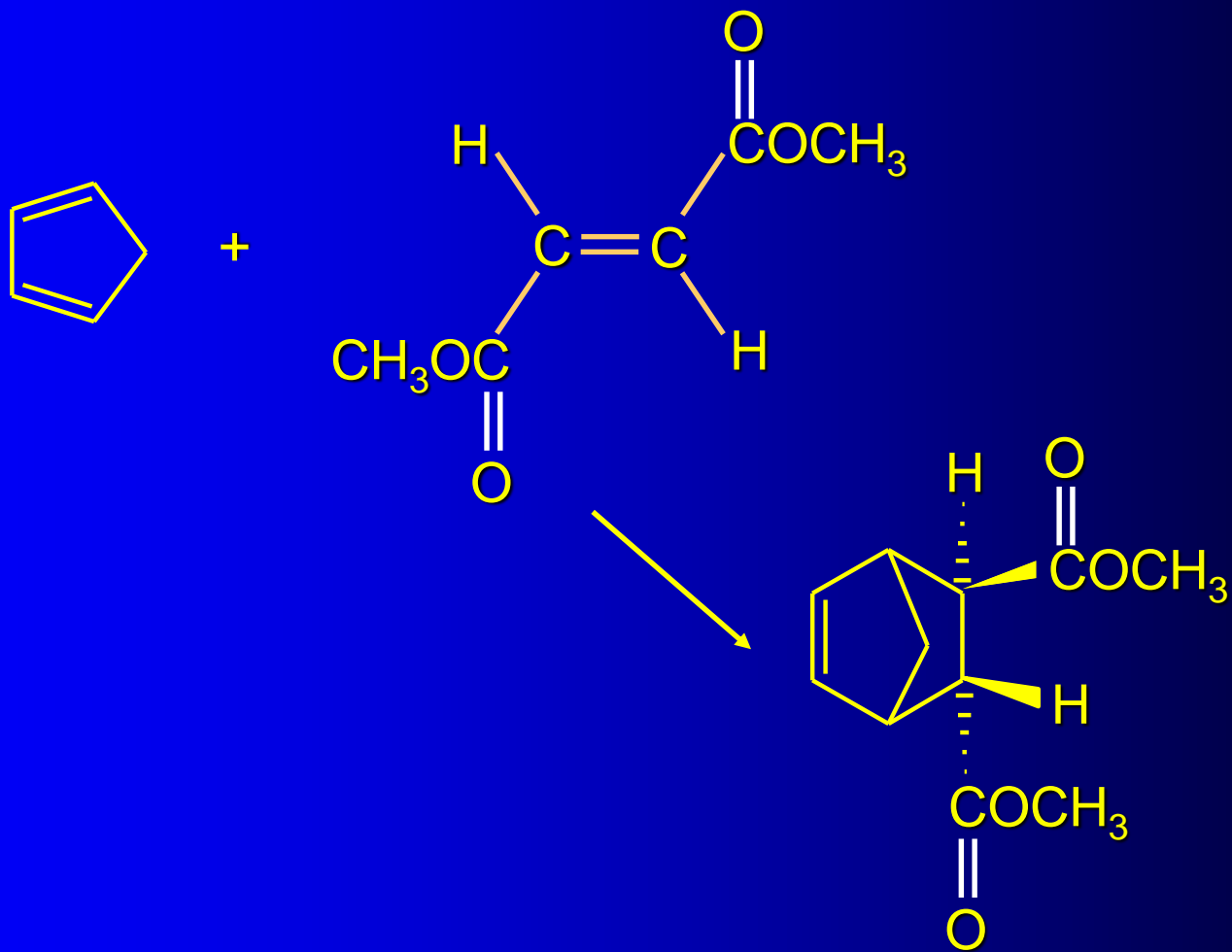


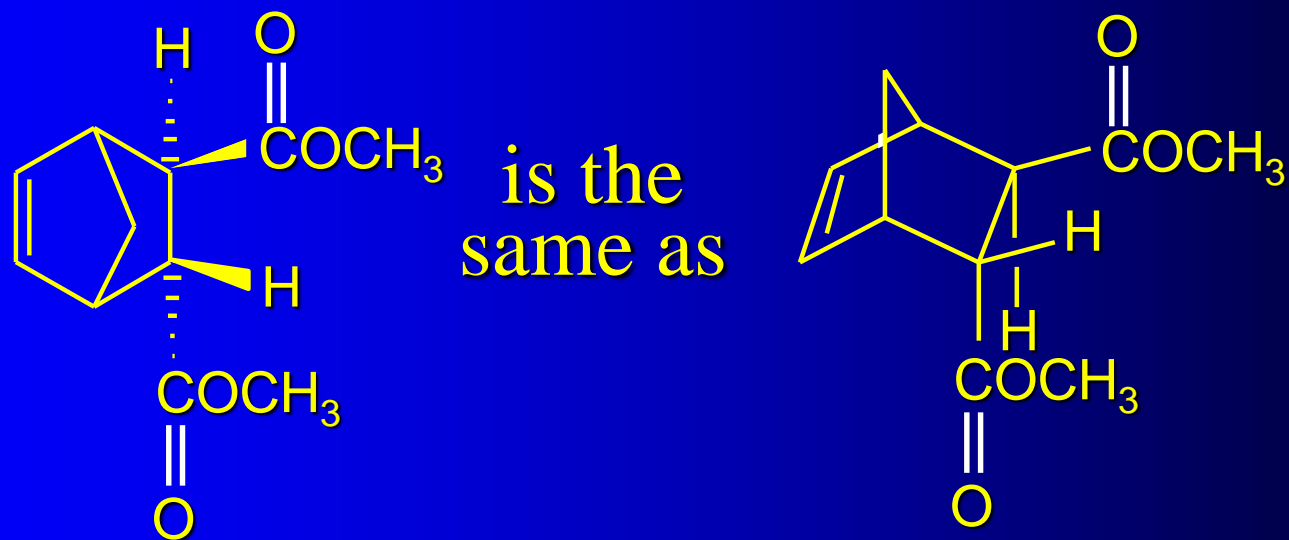
Example



only product





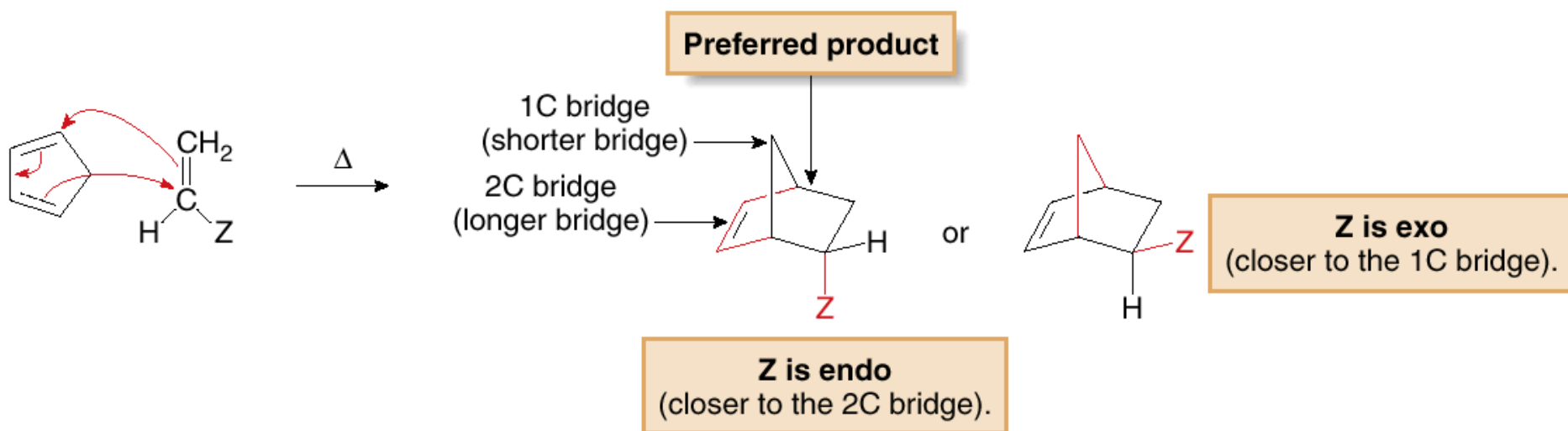


4. When endo and exo products are possible, the endo product is preferred.

endo and exo indicate the orientation of Z.

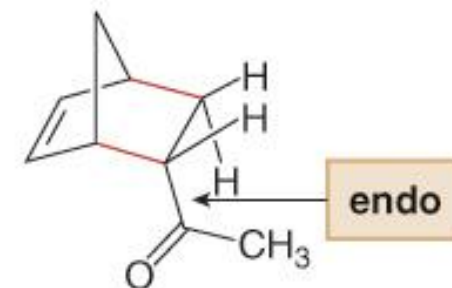
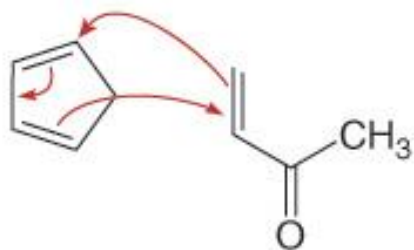
endo = on the side of the big bridge

exo = on the side of the small bridge

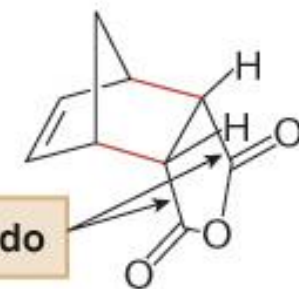
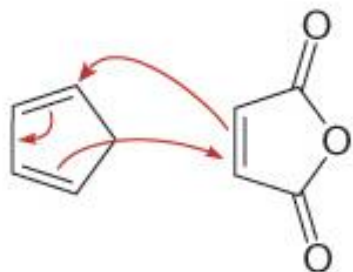


The endo product is preferred!

Examples of endo addition



preferred product



two bonds endo

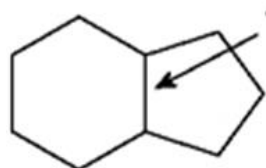
preferred product

[new σ bonds in red]



Some nomenclature

A fused bicyclic system



This C–C bond is **shared** by both rings.

- One bond is shared by two rings.
- The shared C's are adjacent.

A bridged bicyclic system

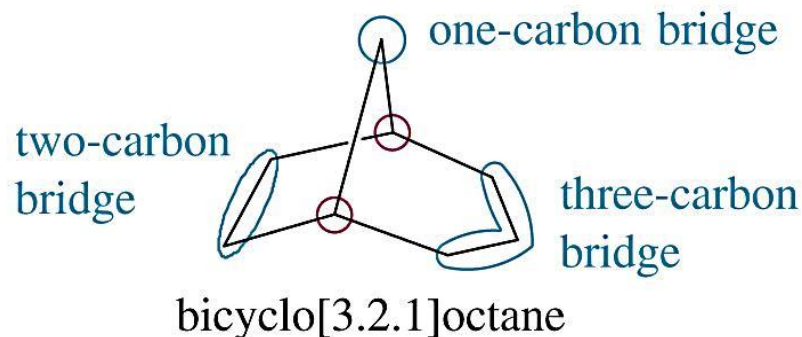
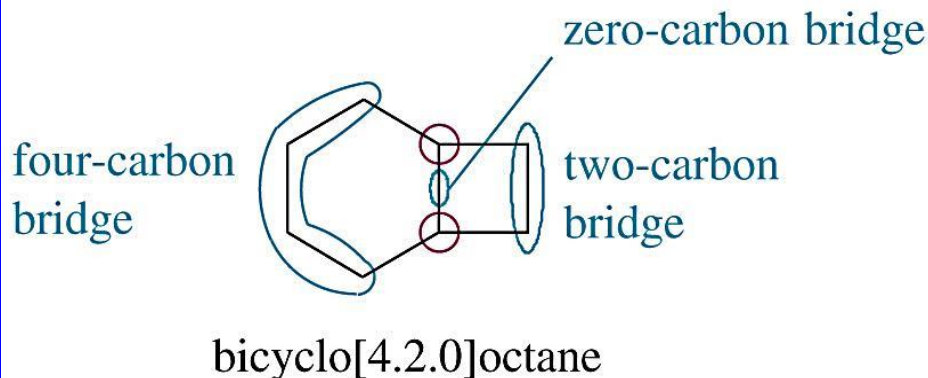


These C's are **shared** by two rings.

- Two non-adjacent atoms are shared by both rings.



Nomenclature of Bicyclic Systems



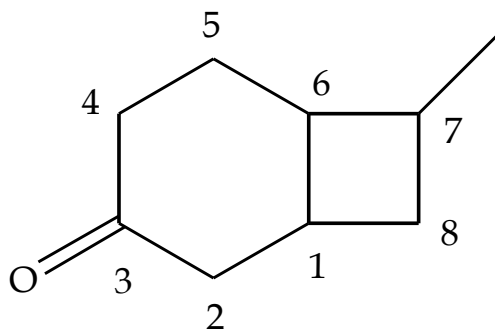
Bicyclo [#.#.#]alkane

Where # is the number of carbons on the bridges (in decreasing order) and the alkane name includes all the carbons in the compound.



Nomenclature of Bicyclic Systems

Numbering begins at a bridgehead, goes around the **largest** ring first, to give the lowest number to any functionality on the ring.

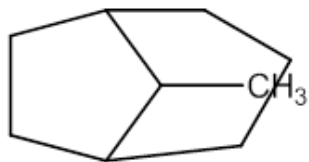


7-Methyl-bicyclo[4.2.0]octan-3-one

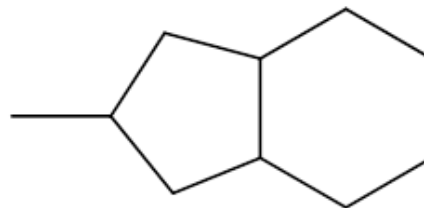


Some nomenclature

- If substituents are present, number the bridge ring system beginning at on bridge-head, proceeding first along the longest bridge to the other bridge-head. The shortest bridge is named last



8-methylbicyclo[3.2.1]octane

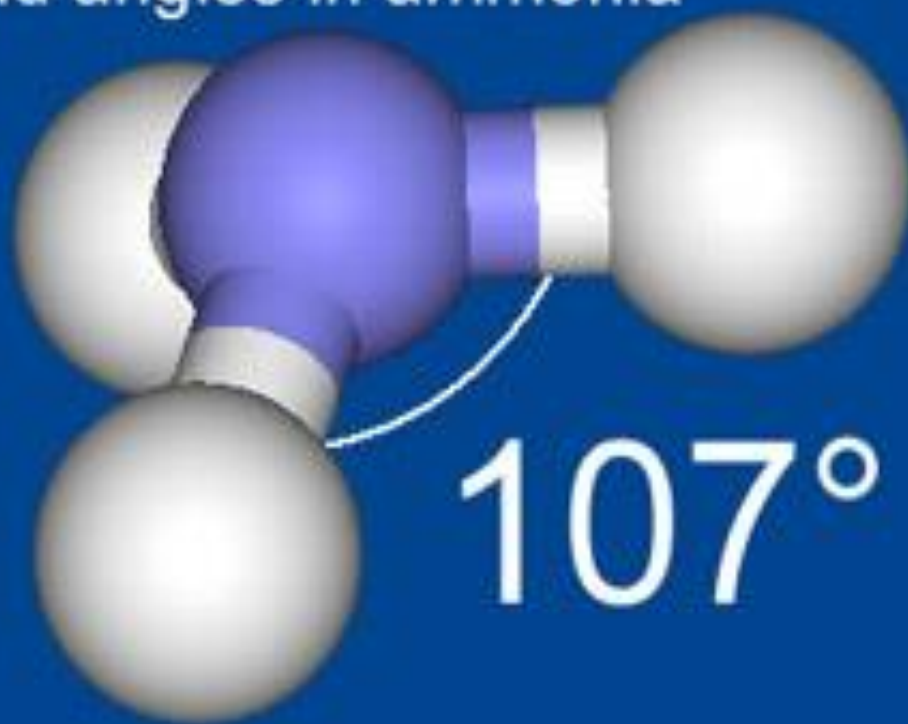
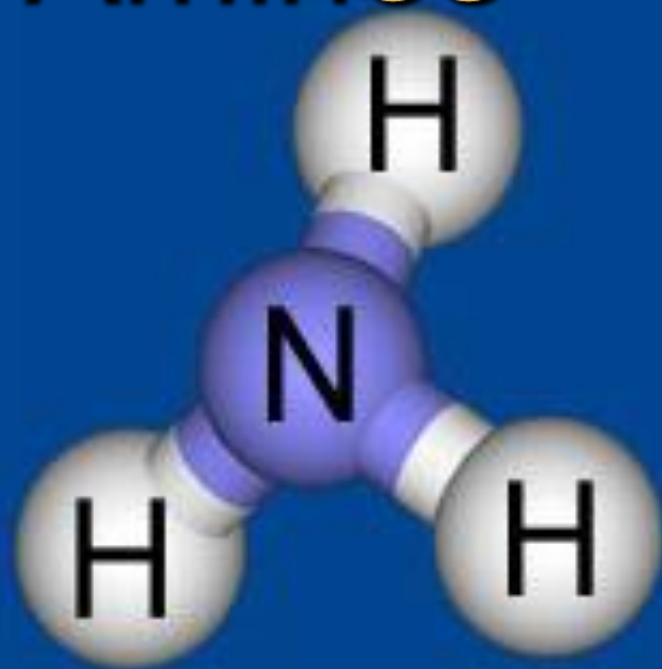


8-methylbicyclo[4.3.0]nonane



Amines

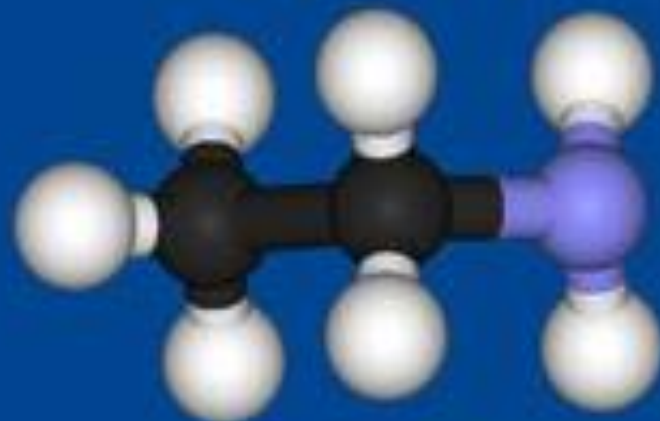
Bond angles in ammonia



Ammonia



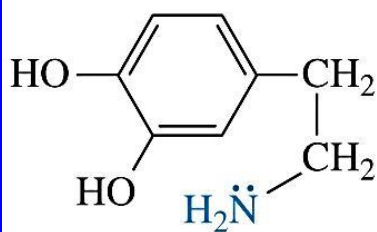
Methylamine



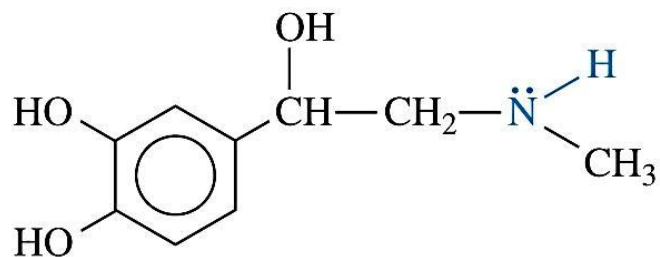
Ethylamine

Amines

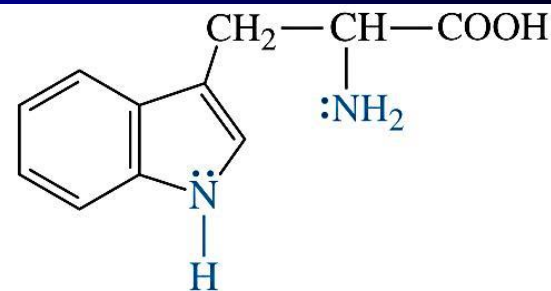
- Organic derivatives of ammonia.
- Many are biologically active.



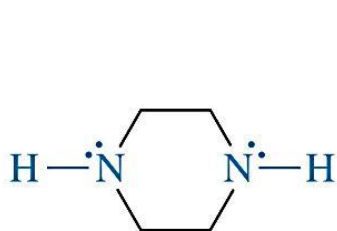
dopamine
a neurotransmitter



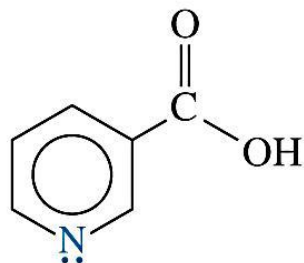
epinephrine
an adrenal hormone



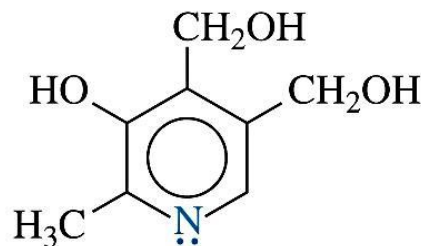
L-tryptophan
an amino acid



piperazine
kills intestinal worms



nicotinic acid
niacin, a vitamin

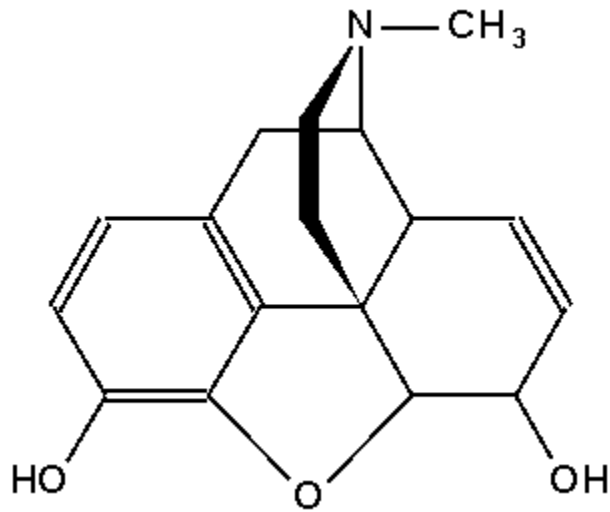


pyridoxine
vitamin B₆

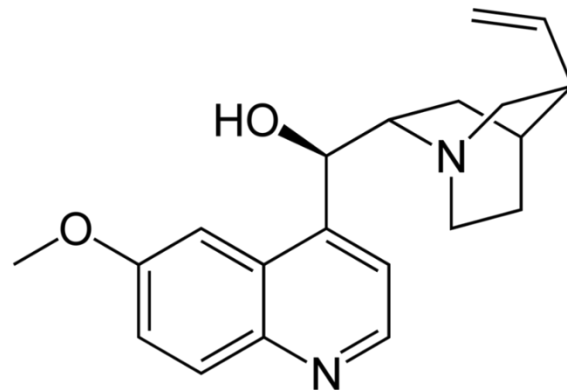


histamine
dilates blood vessels

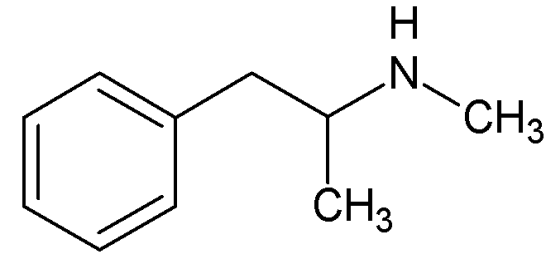
Biologically active amines



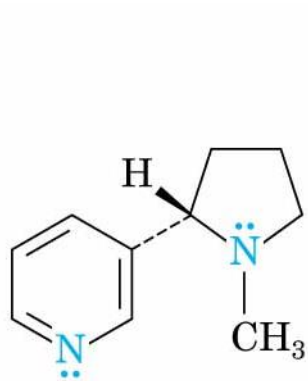
Morphine



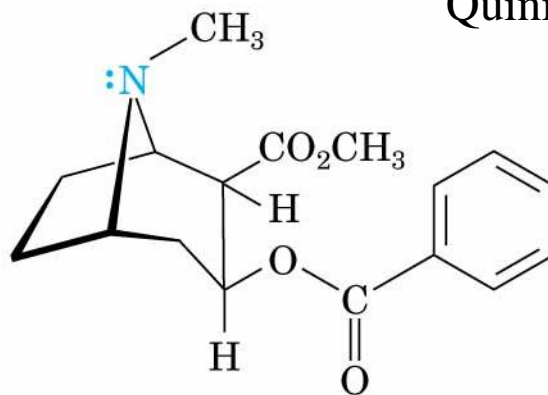
Quinine



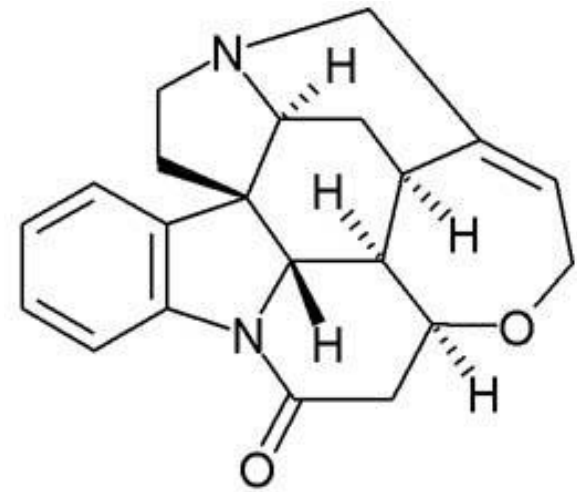
Methamphetamine



Nicotine

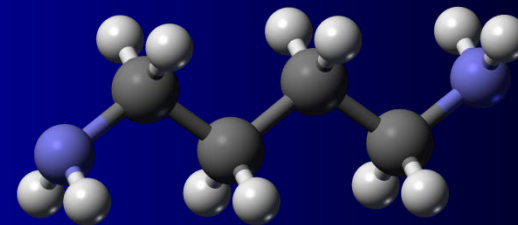


Cocaine

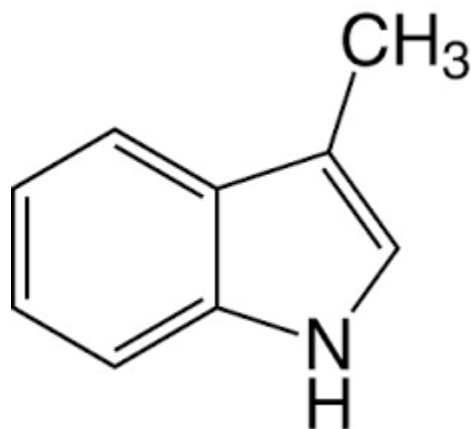
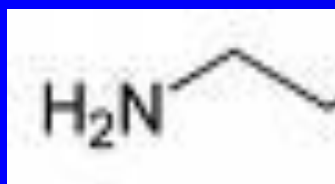


Strychnine

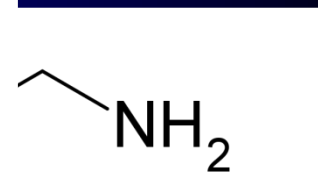
AMINES



- Tend to have foul odors (two of the amines produced in decaying flesh have suggestive names -



Skatol



- Essential
 - Occur in
 - Essential
 - processes
- o acids
- synthetic

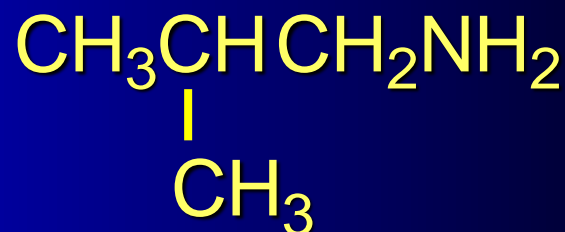


Nomenclature of Amines

- **IUPAC name** – Remove final “e” of longest alkane group and replace by “amine”. The name is one word.



1-butanamine

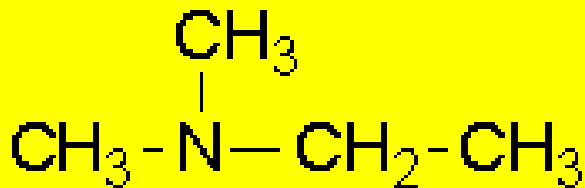


2-methylpropanamine



IUPAC Nomenclature of secondary and tertiary Amines

- Find the longest chain bonded to the nitrogen
- Final “e” is replaced with “amine”
- Number the carbon to which nitrogen is bonded
- Number any substituents on the alkyl chain
- Use italicized *N*- for each additional substituent(s) on the nitrogen



N,N-dimethylethanamine



IUPAC Names

- Name is based on longest carbon chain.
- -e of alkane is replaced with -*amine*.
- Substituents on nitrogen have *N*- prefix.



N,N-dimethyl-3-hexanamine

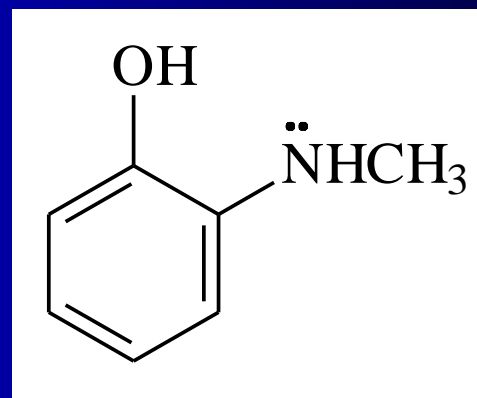


Amine as Substituent

- On a molecule with a higher priority functional group, the amine is named as a substituent. The substituent name is amino.



γ -aminobutyric acid or
4-aminobutanoic acid



2-methylaminophenol



Basicity of Amines

1. Alkylamines are slightly stronger bases than ammonia.
2. Alkylamines differ very little in basicity.



Basicity of Amines in Aqueous Solution

•Amine	Conj. Acid	pK _a
•NH ₃	NH ₄ ⁺	9.3
•CH ₃ CH ₂ NH ₂	CH ₃ CH ₂ NH ₃ ⁺	10.8
•(CH ₃ CH ₂) ₂ NH	(CH ₃ CH ₂) ₂ NH ₂ ⁺	11.1
•(CH ₃ CH ₂) ₃ N	(CH ₃ CH ₂) ₃ NH ⁺	10.8

Notice that the difference separating a primary, secondary, and tertiary amine is only 0.3 pK units.

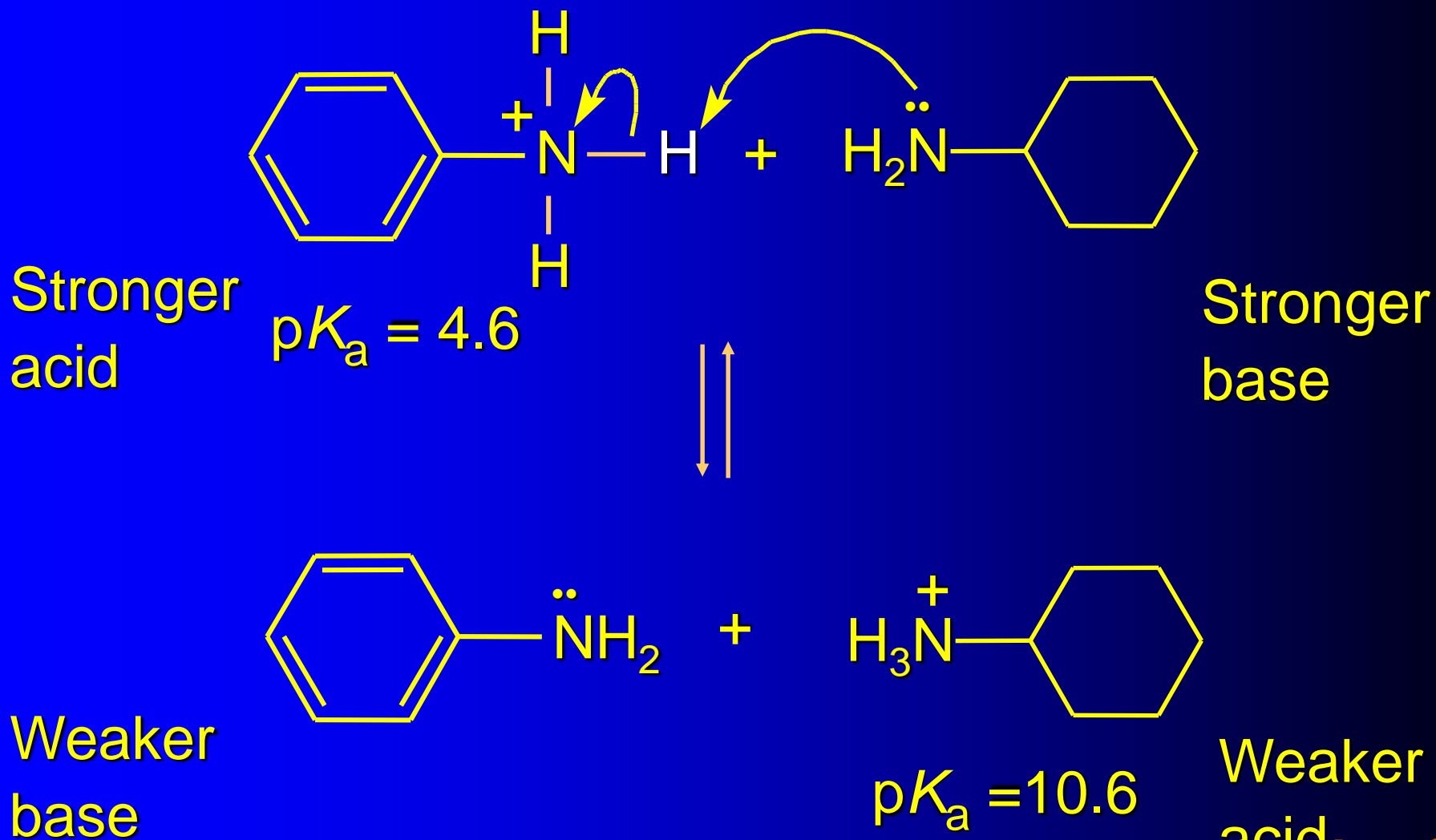


Effect of Structure on Basicity

1. Alkylamines are slightly stronger bases than ammonia.
2. Alkylamines differ very little in basicity.
3. Arylamines are much weaker bases than ammonia.



Decreased basicity of arylamines



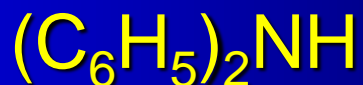
Decreased basicity of arylamines

- Increasing delocalization makes diphenylamine a weaker base than aniline, and triphenylamine a weaker base than diphenylamine.

pK_a of conjugate acid



4.6



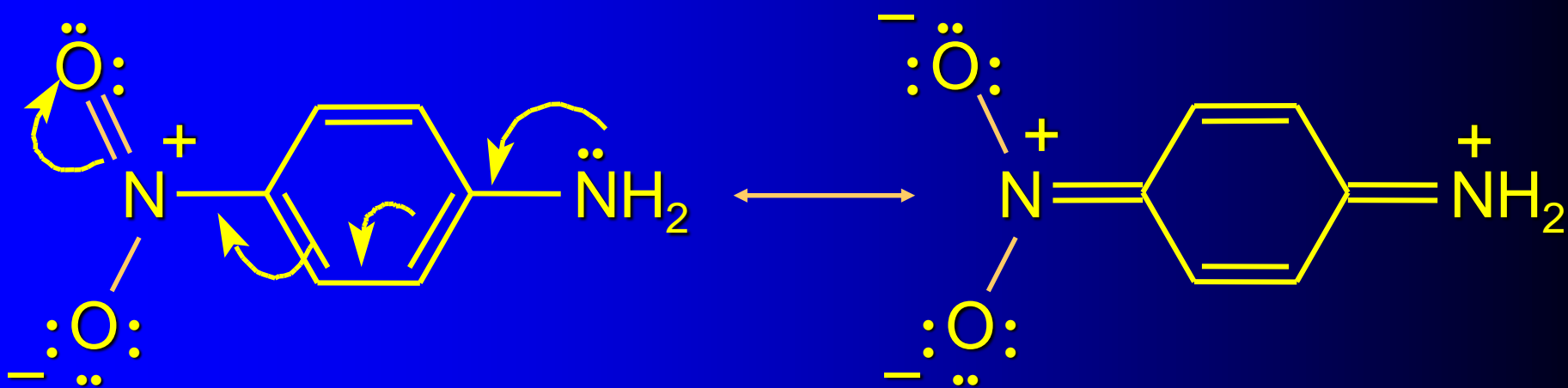
0.8



~-5



p-Nitroaniline



- Lone pair on amine nitrogen is conjugated with *p*-nitro group—more delocalized than in aniline itself. Delocalization lost on protonation.

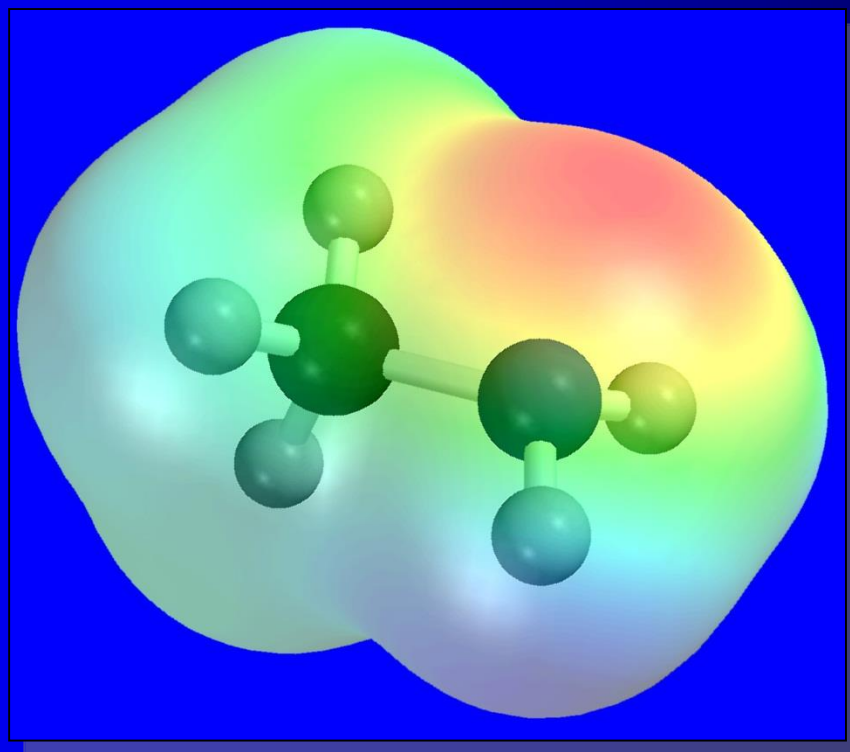


Effect is Cumulative

- Aniline is 3800 times more basic than *p*-nitroaniline.
- Aniline is ~1,000,000,000 times more basic than 2,4-dinitroaniline.

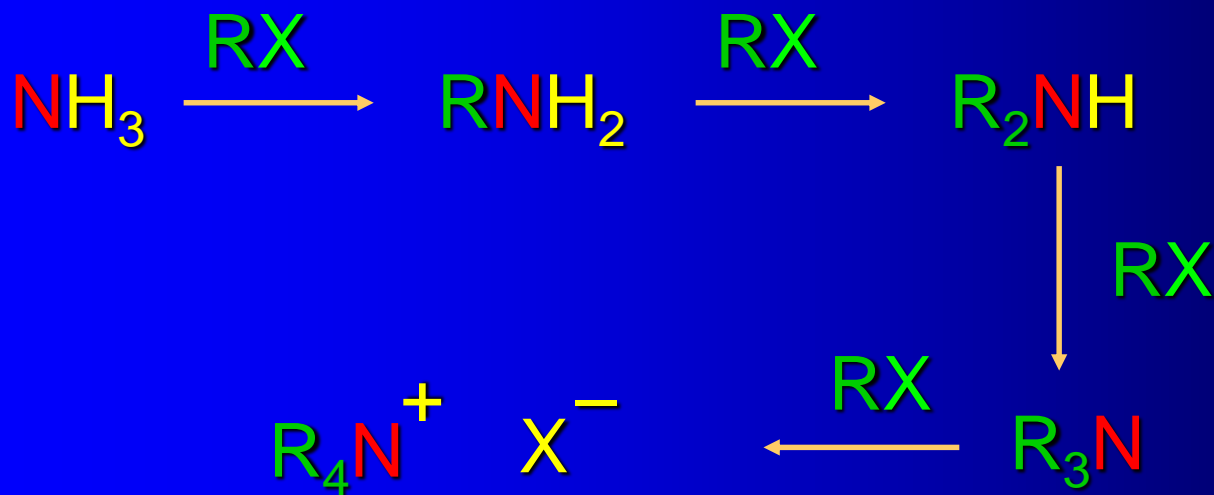


Synthesis of Amines

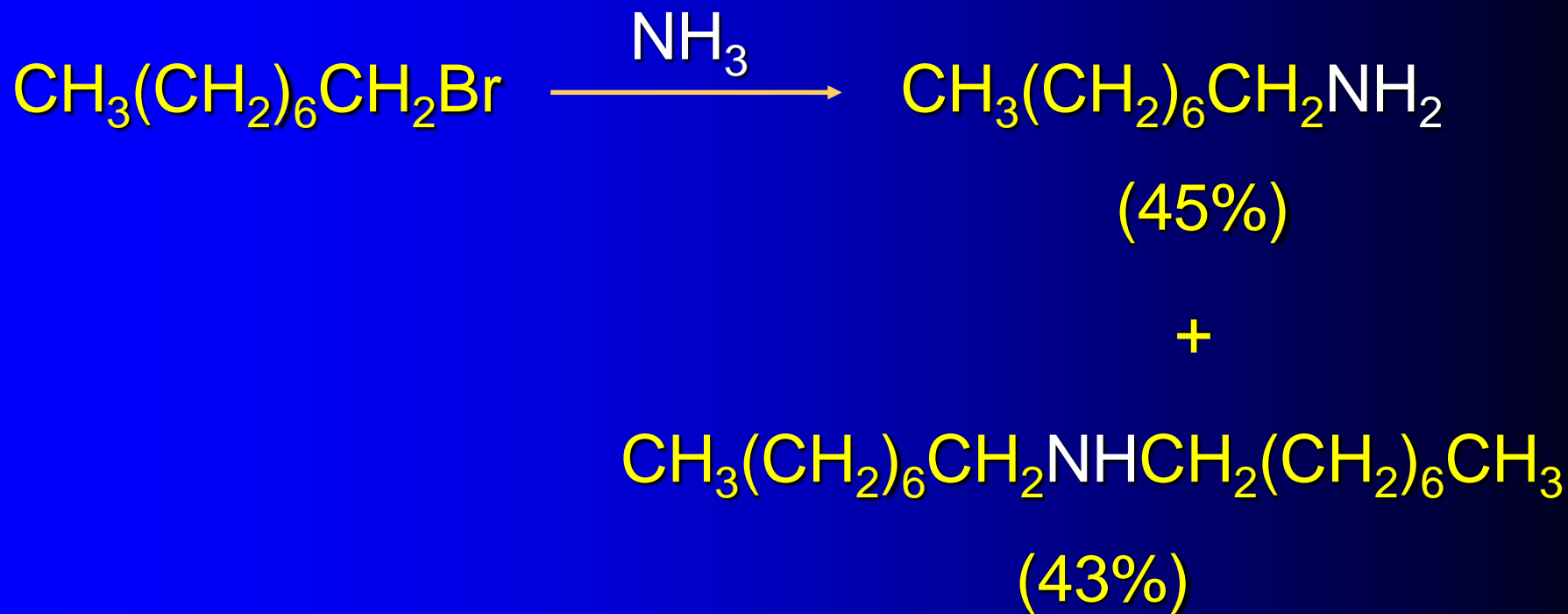


Alkylation of Ammonia

This method doesn't work well in practice. Usually gives a mixture of primary, secondary, and tertiary amines, plus the quaternary salt.



Example



- As octylamine is formed, it competes with ammonia for the remaining 1-bromooctane. Reaction of octylamine with 1-bromooctane gives *N,N*-dioctylamine.

