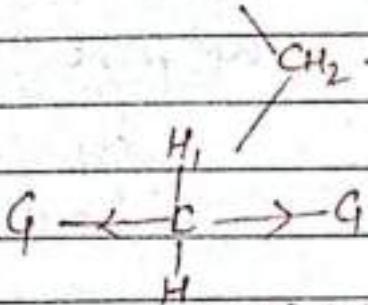
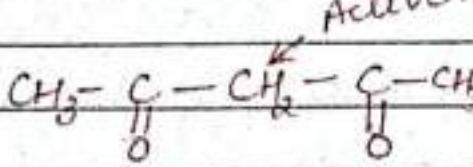
Active Methylene Compounds

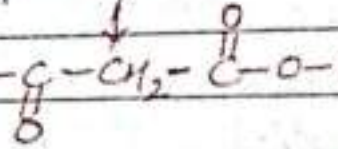
Hydrogens in methane do not exhibit acidic character. However when two hydrogens are replaced by electron withdrawing groups the rest of hydrogen become acidic in nature.



Active methylene groups

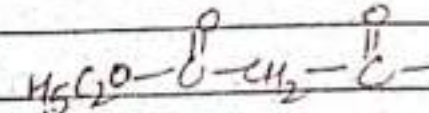


Pentane-2,4 dione
Acetyl acetone



Ethyl acetoacetate
(Acetoacetic ester)

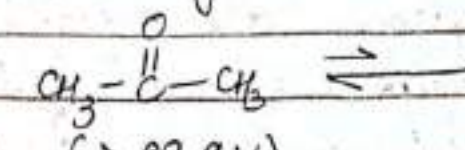
* The class of compounds which contain a methylene group ($-CH_2-$) directly bonded to two electron withdrawing groups such as $-COCH_3$, $-COOC_2H_5$, $-N$ are called Active methylene compounds.
This is because the $-CH_2-$ group in them is acidic and reactive.



Diethyl malonate
(Malonic ester)

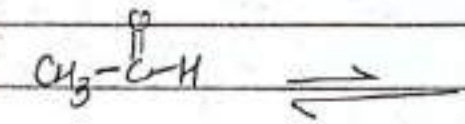
* Enolisation:-
The phenomenon of enolisation is exhibited by compounds containing methylene gp $>CH_2$ or a methyne group $>CH-$ adjacent to a carbonyl gp.

The presence of one Carbonyl group does not always give rise to appreciable amount of enol form
Ex- acetaldehyde and acetone



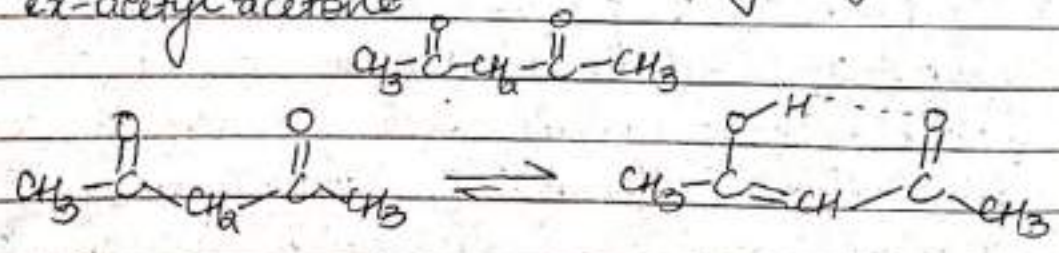
(> 99.9%) (< 0.1%)

Keto form enol form



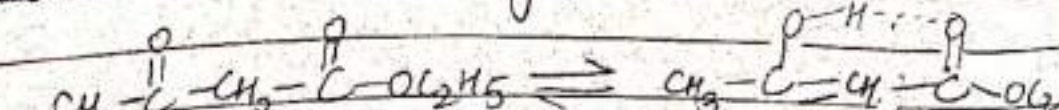
Keto enol

In Simple aldehyde and Ketones the amount of enolic form is negligibly small
If the Compound contains a methylene or methyne group attached to two Carbonyl groups the percentage of enol form is usually high
ex-acetyl acetone



24% 76%

If the enolic form is stabilized by intramolecular H-bonding (Chelation) such as in 1,3 dicarbonyl Compounds. The amount of enolic form is much greater than in acetaldehyde and Ketone

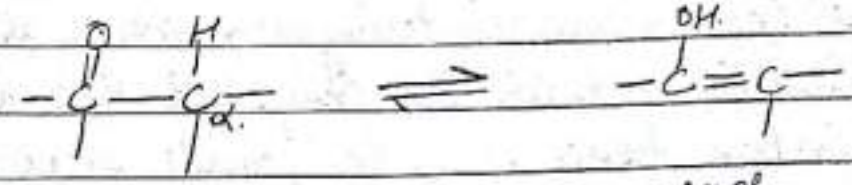


93% 7%

DATE

The amount of enolic form is higher in acetylacetone than in acetoacetic ester, This is due to the reason that Keto group is much better electron withdrawing group than ester group.

* There are two forms of same Compound which arise due to migration of a hydrogen atom. The two forms are readily interconvertible and exist in dynamic equilibrium with each other. This phenomenon is known as tautomerism.



or

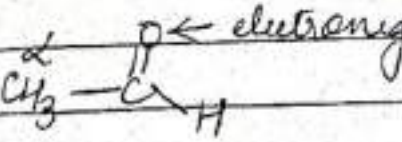
* It arises due to 1,3 migration of a hydrogen atom from one polyvalent atom to other within the same molecule. Isomers thus obtained which exist in dynamic equilibrium with each other are called tautomers and the phenomenon is called tautomerism.

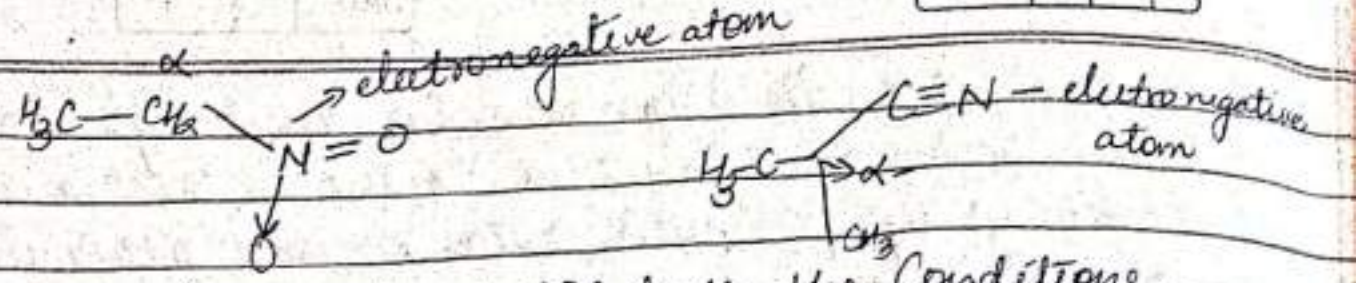
Structural requirement for tautomerism

(1) Compound should have electronegative atom bonded with multiple bond (i.e N & O).

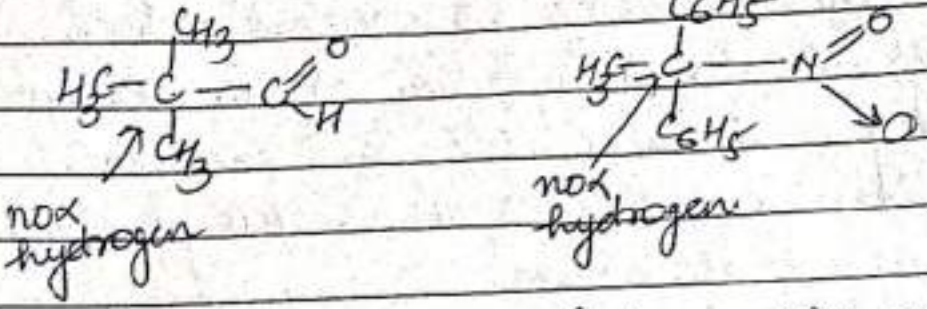
(2) Compound should have atleast one acidic hydrogen present on α-Carbon of the molecule.

If is two Condition are fulfilled the Compound will show tautomerism



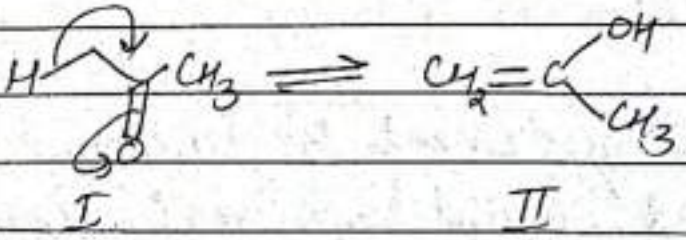


These Compounds fulfill both the Conditions, hence these will show tautomerism.



In these Compounds electronegative atom is bonded with multiple bond but Compound has no hydrogen on α-Carbon hence these Compounds will not show tautomerism.

Cause of tautomers :- Migration of acidic hydrogen from α-Carbon to electronegative atom which is bonded with multiple bond is the Cause of tautomers & this phenomenon is known as tautomerism.



I II

(1) Both (I) & (II) are isomers known as Tautomers
(2) Tautomers are always in equilibrium state
(3) Number of σ & π electrons in both tautomers are always same
(4) Tautomerism is a chemical phenomenon which takes place only in liquid state

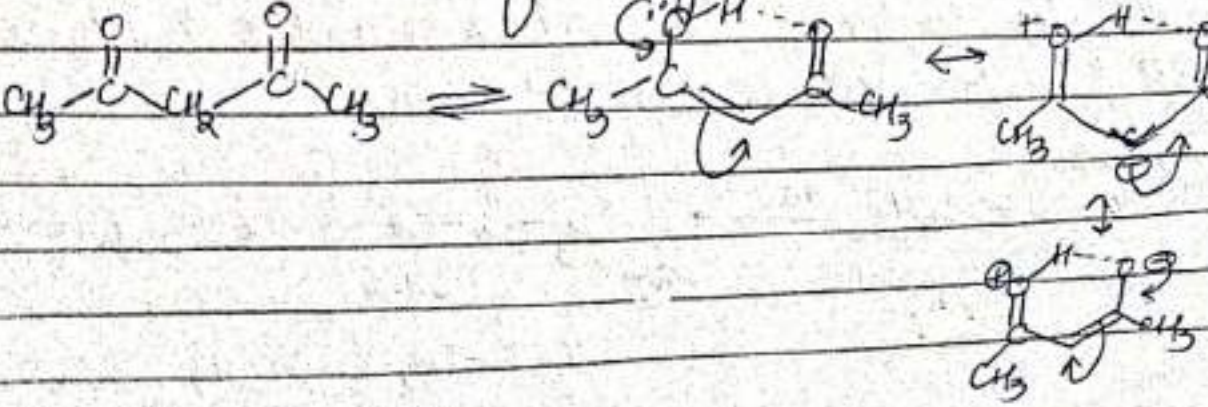
(5) Tautomerism is catalysed by acid as well as base.
(6) Tautomers are always functional isomers.

Enolisation in the following order
$CH_3COCH_3 < CH_3COCH_2COOC_2H_5 < C_6H_5COCH_2COOC_2H_5$
$< CH_3COCH_2COCH_3 < CH_3COCH_2CHO$

The Conversion of a keto form into an enol form is known as enolisation and the enolisation of a Compound has been found to depend upon various factors such as structural factors, temperature and nature of solvent.

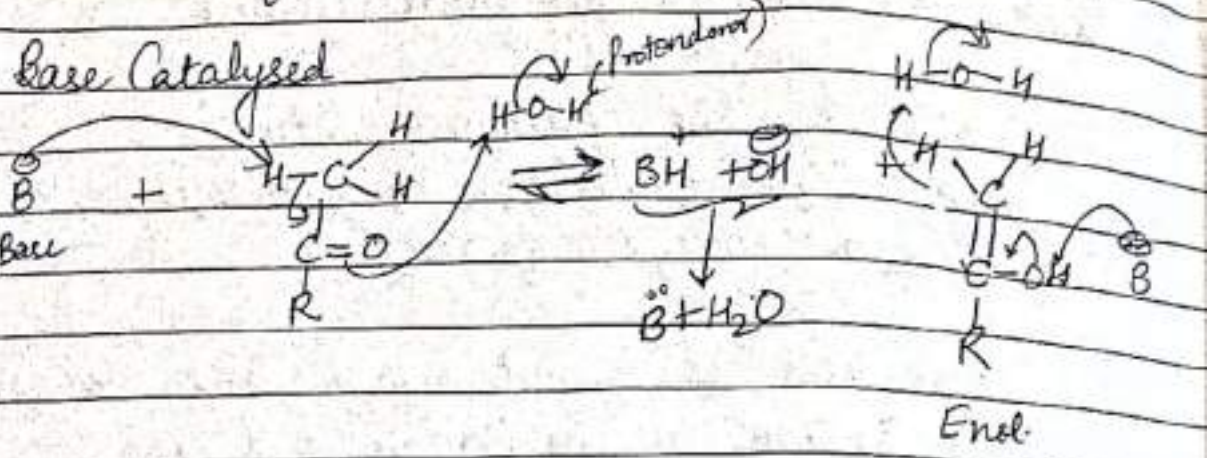
* Ketonic form predominates in the simple mono Carbonyl Compounds like acetaldehyde, acetone & Cyclohexanone. This is due to the greater bond strength of C=O (X=0.365 KJ/mole) present in keto form than the Carbon-Carbon double bond (C=C, 250 KJ/mole) present in enolic.

* Enolic form predominates in β-diketones due to intramolecular hydrogen bonding and resonance. Intramolecular hydrogen bonding stabilizes enol form by 7 Kcal/mole and Resonance stabilizes enol form by 15 Kcal/mole. Thus enol form is more stable than keto form by 22 Kcal/mole in 1,3-diketone

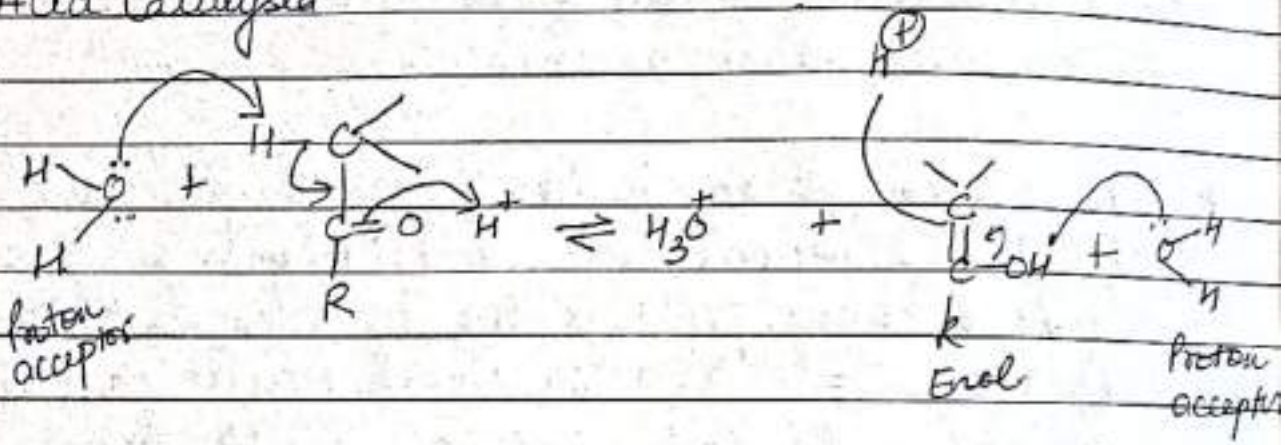


Mechanism of Tautomerism

① Base Catalysed



② Acid Catalysed



Ethyl acetoacetate (EAA)

Ethylacetoacetate is also called Acetoacetic ester
IUPAC - Ethyl-3-oxobutanoate
EAA - A keto ester formed by the reaction between two molecules of ester containing α-hydrogen atom

Claisen Condensation

It involves base-catalysed condensation of two ester molecules to form an alcohol and a β-keto ester.
Ethyl acetoacetate is a β-keto ester.

$$2\,CH_3-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow{NaOEt} \left[CH_3-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{|}{C}}-\overset{O}{\overset{\|}{C}}-OC_2H_5\right] + C_2H_5OH$$

$$\downarrow HCl$$

$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

(76%)

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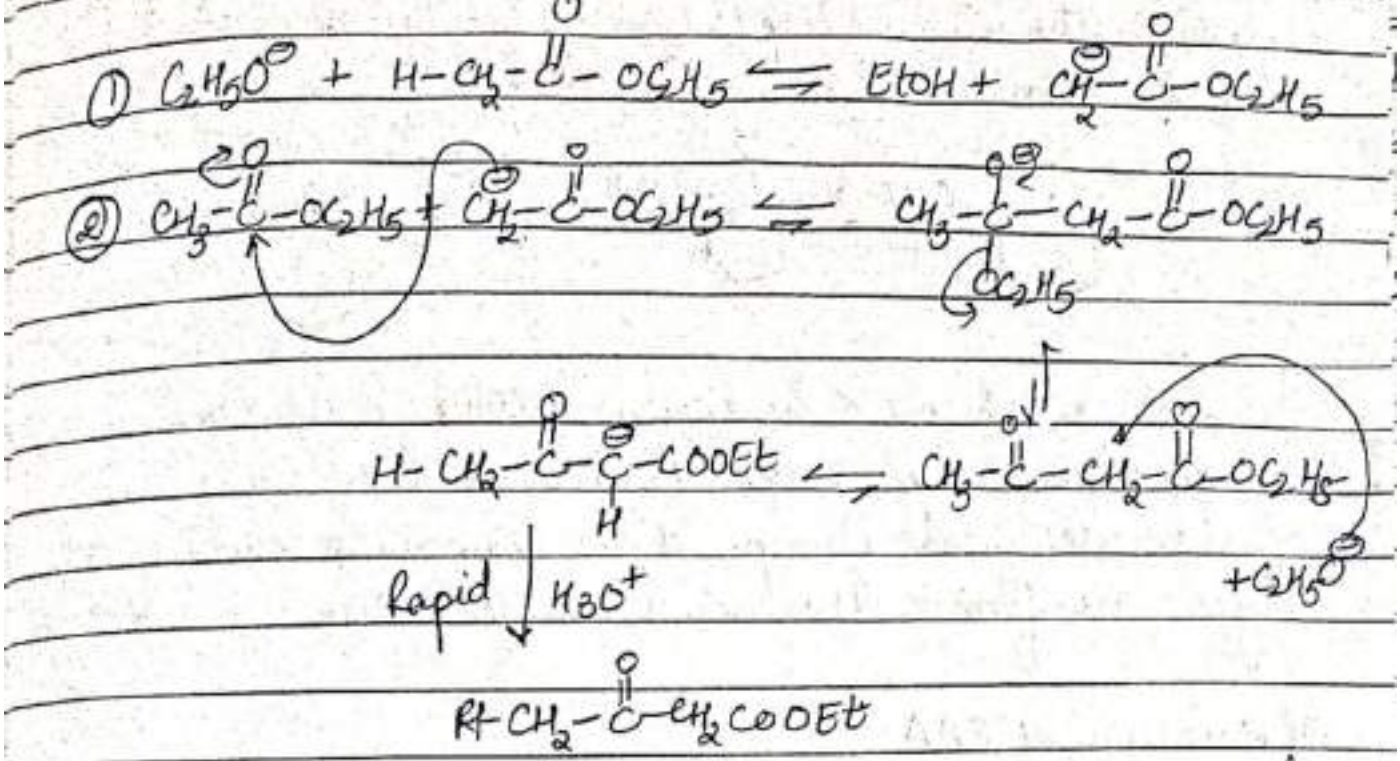
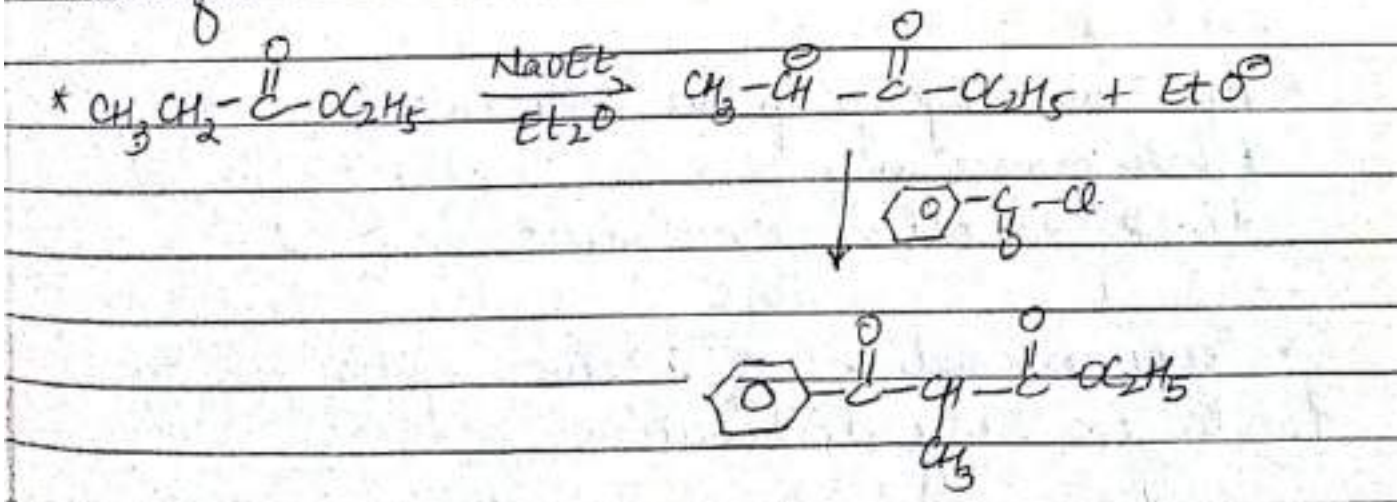
Mechanism:-

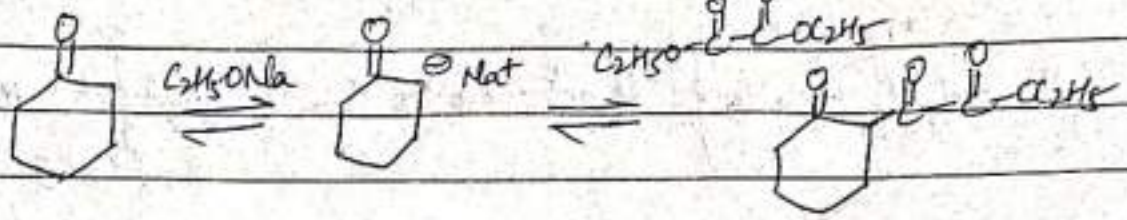


*Addition of acid quenches the reaction by neutralising the base & promoting the Claisen Condensation product. The β-ketoester product exist as an equi mix of its keto & enol forms.



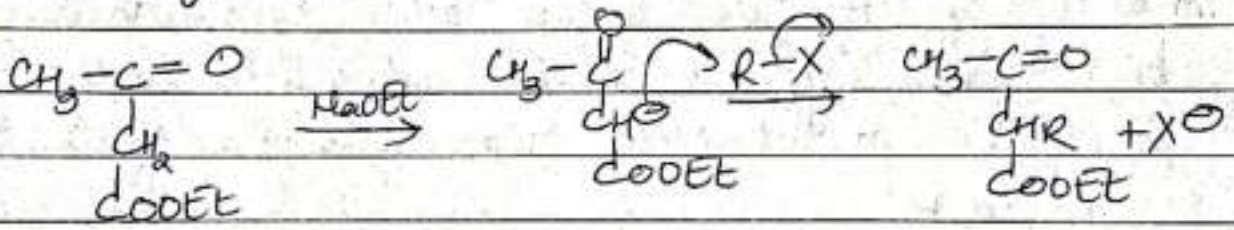
*Ethylacetoacetate is a Colorless, pleasent Smelling liq bp-181°C. Sparingly soluble in water but miscible with most Organic solvents. It is readily reduced by Na-Hg or Catalytically to β-hydroxybutyric ester

* Enolate anions derived from ketones also react with esters in nucleophilic substitution reactions that resembles Claisen Condensation



* Esters with no α-hydrogen atoms will Condense only one way with Compounds Containing an active methylene Group. Three important esters of this type are formic, benzoic & oxalic esters.

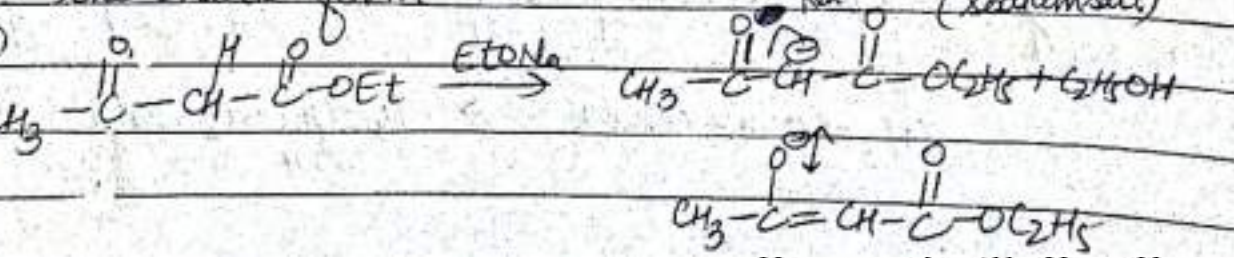
Alkylation of EAA



* After one alkyl group has been introduced the whole process may then be repeated to give the dialkylderivative of acetoacetic ester.

* Secondary halide gives lower yields and tertiary halides give only elimination.

* EAA when treated with Sodium ethoxide, acetoacetic ester forms Sodioacetic ester. i.e the Sodium derivative of the enolic form.



* Acetoacetic ester and its alkyl derivatives can undergo two types of hydrolysis with KOH.

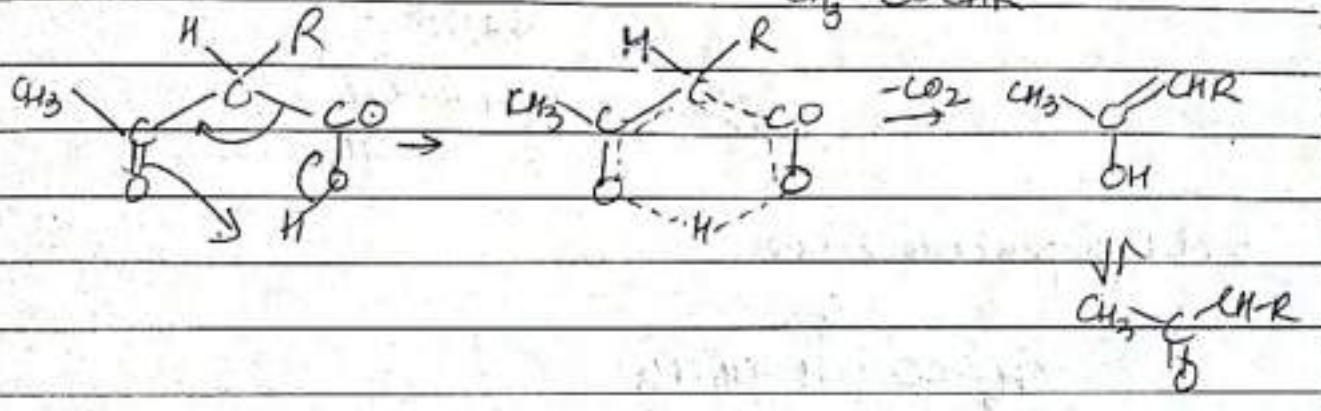
(a) Ketonic hydrolysis

Ketonic hydrolysis, so called because a ketone is chief product, is carried out by boiling with dilaq. or ethanolic KOH solution & usually followed by dil H_2SO_4 (acidification).

$$CH_3-\underset{R}{CO}CH-CO_2C_2H_5 \xrightarrow[2)H_2SO_4]{1)KOH} [CH_3-\underset{k}{CO}CH-COOH]$$

$$\downarrow -CO_2$$

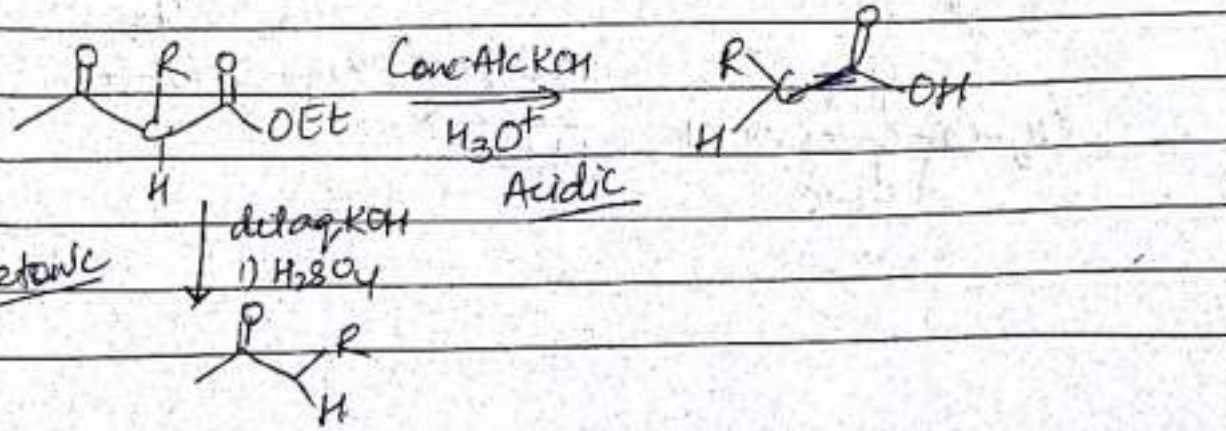
$$CH_3-COCHR$$



(b) Acidic hydrolysis

Acid hydrolysis so called because an acid is the chief product, is carried out by boiling with Conc. Ethanolic KOH solution.

$$CH_3-CO-CH_2-COOEt + 2KOH \longrightarrow CH_3CO_2K + CH_3CO_2K + C_2H_5OH$$



* Alkyl groups are introduced one at a time, better to introduce the larger group before the smaller effect (steric effect)

Butanone ($CH_3\overset{O}{\overset{\|}{C}}CH_2-CH_3$)

$$CH_3-CO-CH_2-CO_2Et \xrightarrow{EtONa} \left[CH_3-CO\overset{\ominus}{C}H-CO_2Et\right] + CH_3I$$

$$\downarrow$$

$$CH_3-CO-\underset{CH_3}{\underset{|}{CH}}-CO_2Et$$

$$\downarrow \text{1) dil aq KOH}$$
$$\text{2) } H^+$$

$$CH_3-CO-\underset{CH_3}{\underset{|}{CH}}$$

3 Methyl pentane-2-one

$$CH_3-CO-\underset{CH_3}{\underset{|}{CH}}-CH_2CH_3$$

$$CH_3-CO-CH_2-COOEt \xrightarrow{EtONa} CH_3CO-\overset{\ominus}{C}H-COOEt$$

$$\downarrow C_2H_5I$$

$$CH_3-CO-\underset{C_2H_5}{\underset{|}{\overset{\ominus}{C}}}-COOEt \xleftarrow{EtONa} CH_3-CO-\underset{C_2H_5}{\underset{|}{CH}}-COOEt$$

$$\downarrow CH_3I$$

$$CH_3-CO-\underset{C_2H_5}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-COOEt \xrightarrow[\text{2) } H_3O^+]{\text{1) dil aq KOH}} CH_3-CO-\underset{C_2H_5}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-H$$

n- Butyric Acid

$CH_3CH_2CH_2COOH$

$CH_3COCH_2COOEt \xrightarrow{NaOEt} CH_3CO\overset{\ominus}{C}H-COOEt \xrightarrow{EtI} CH_3-CO-CH(C_2H_5)-COOEt$

$\downarrow$ 1) Conc AlcKOH, 2) H^+

$CH_3CH_2CH_2COOH$

α- Methyl n-valeric Acid

$CH_3-CH_2-CH_2-CH(CH_3)-COOH$

$CH_3-COCH_2COOC_2H_5 \xrightarrow{NaOEt} CH_3CO\overset{\ominus}{C}H-C(=O)-OEt \xrightarrow{CH_3CH_2CH_2I} CH_3-CO-CH(CH_2CH_2CH_3)-C(=O)-OEt$

$\downarrow$ 1) NaOEt, 2) CH_3I

$CH_3-CO-C(CH_3)(CH_2CH_2CH_3)-COOEt \xrightarrow[2)\ H^+]{1)\ Conc\ AlcKOH} CH_3-CH(CH_2CH_2CH_3)-COOH$

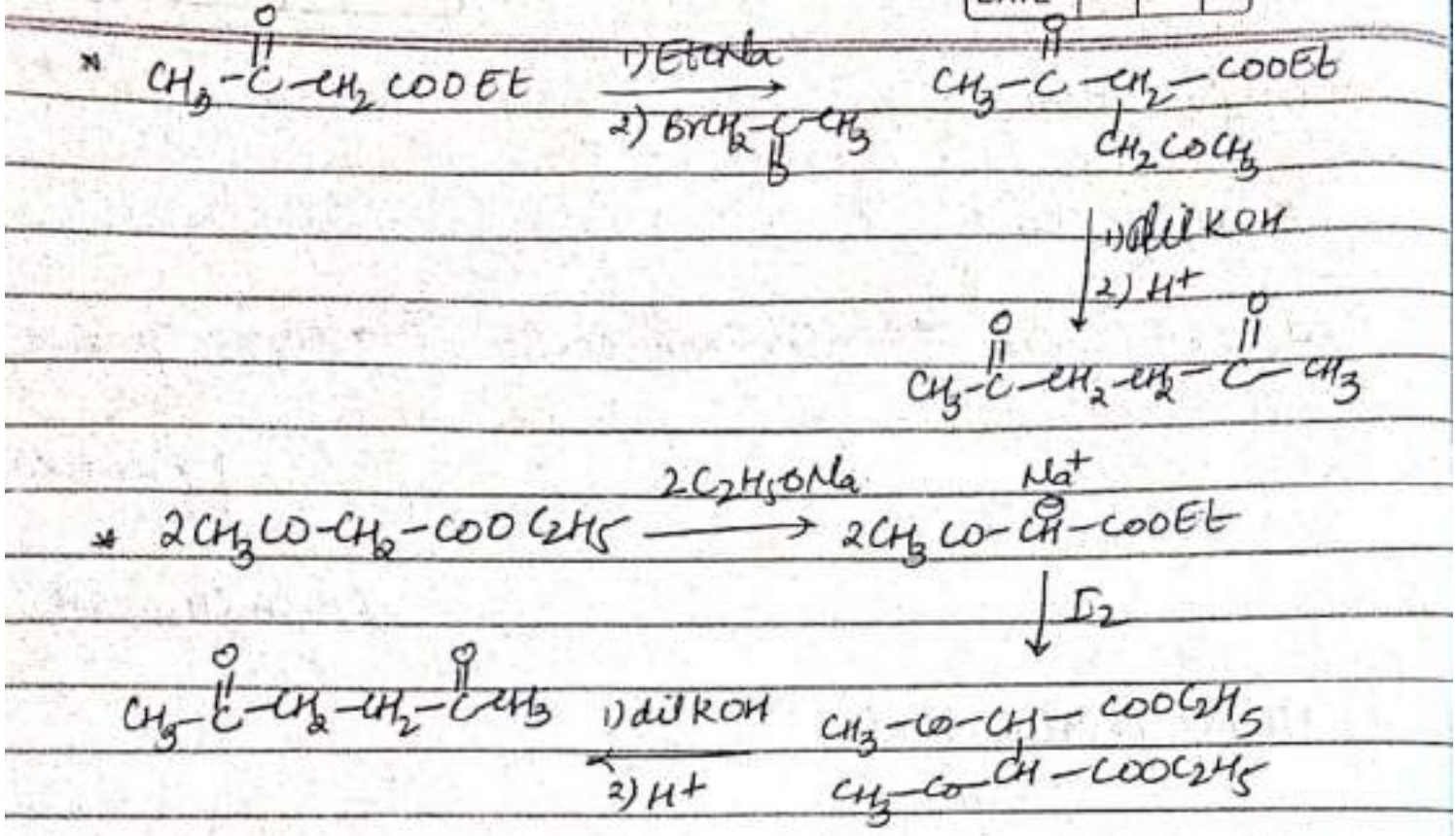
1,3 diketones

In the Synthesis of 1,3 diketones the halogen Compound is an acid Chloride

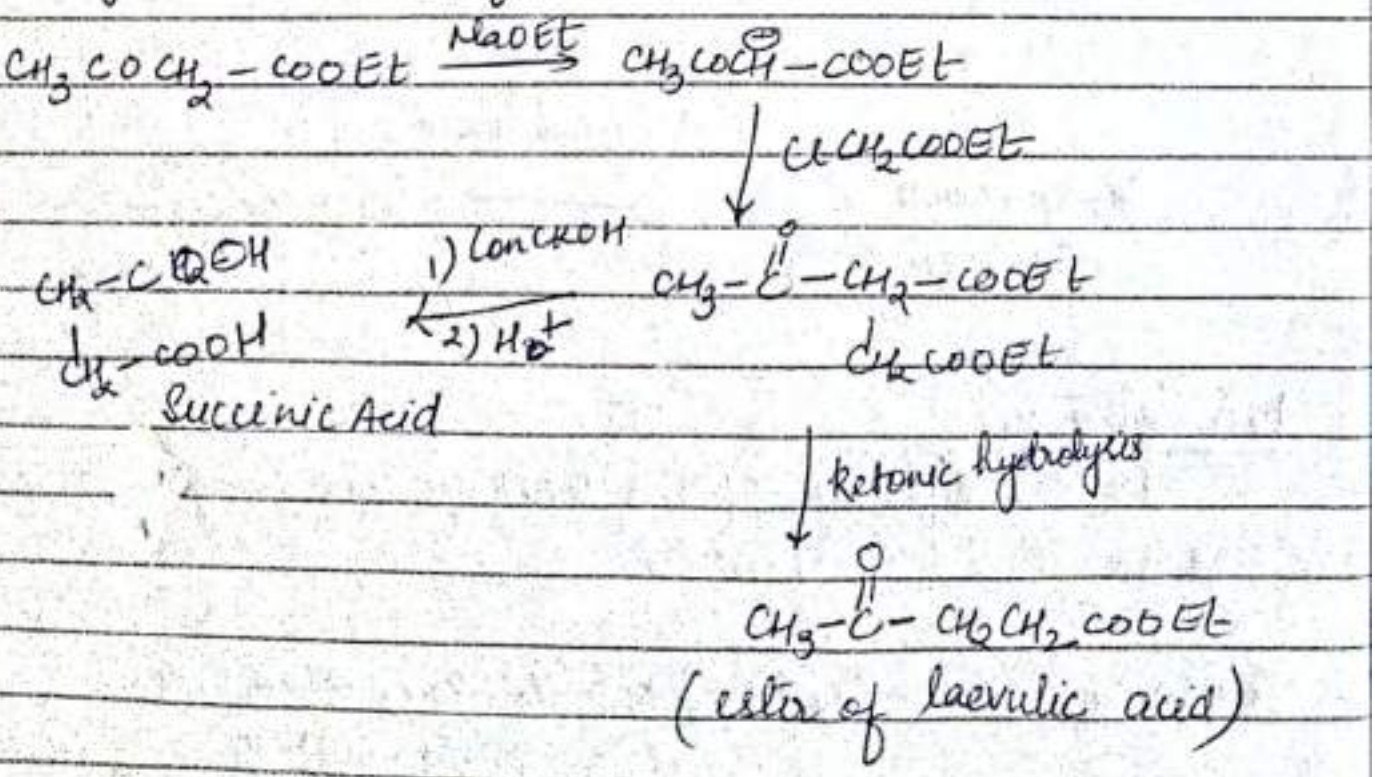
$CH_3CO\cdot CH_2CO_2Et + CH_3COCl \xrightarrow{Mg} (CH_3\cdot CO_2)_2CH\cdot CO_2C_2H_5$

$\downarrow$ 1) dil KOH, 2) H^+

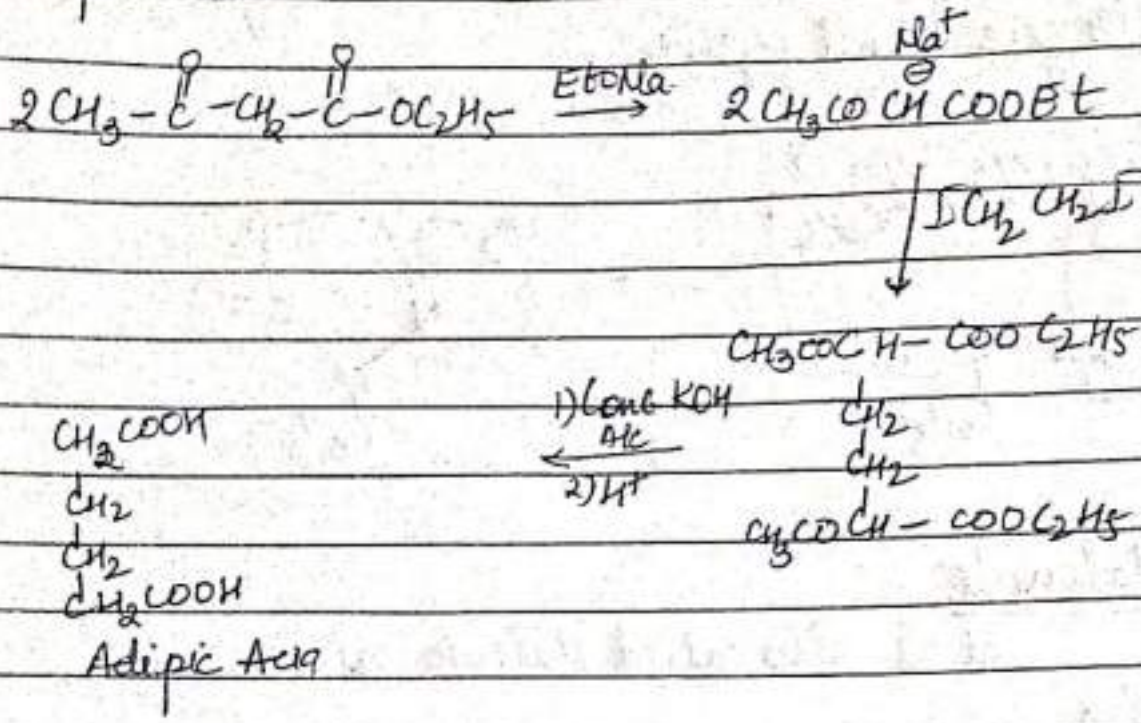
$CH_3-C(=O)-CH_2-C(=O)-CH_3$



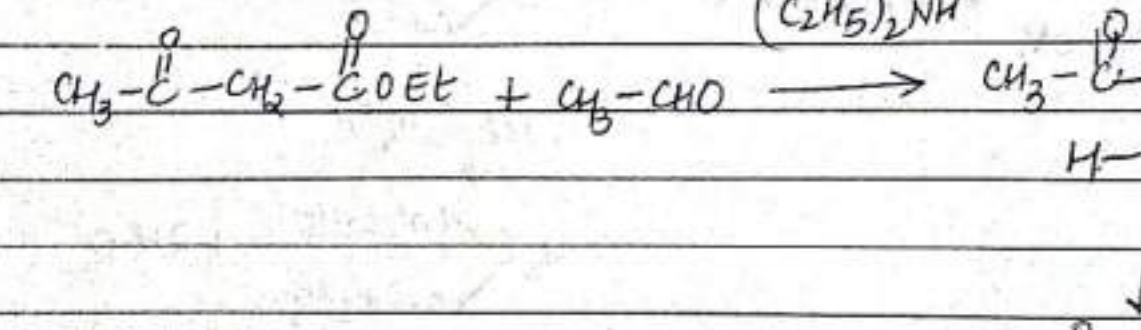
Dicarboxylic acid :- Dicarboxylic acid may be prepared by interaction of Sodioacetic ester and a halogen derivative of an ester



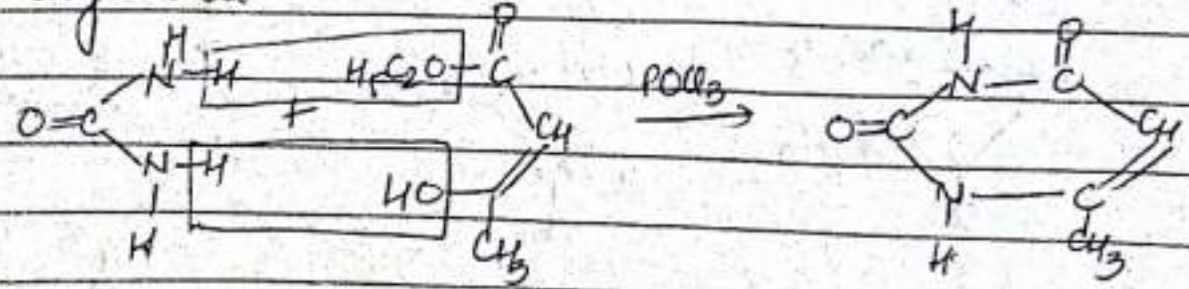
Adipic Acid



Crotonic Acid

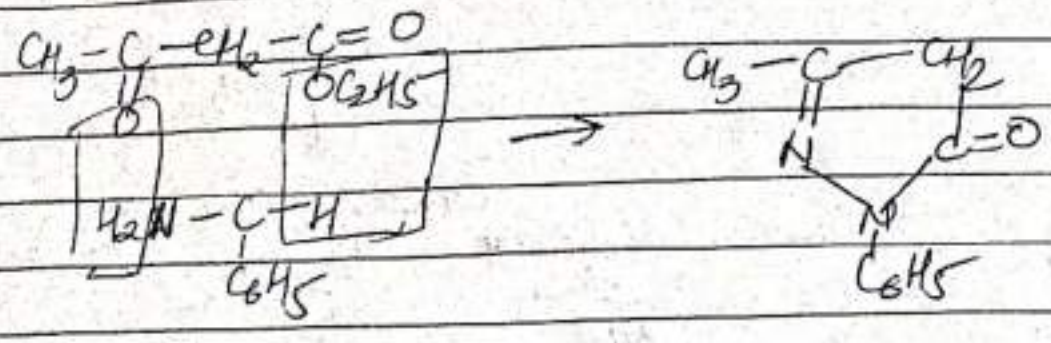


4-Methyl Uracil



Ethylacetoacetate (in its enol form) reacts with urea in the presence of $POCl_3$ to give 4-methyl Uracil

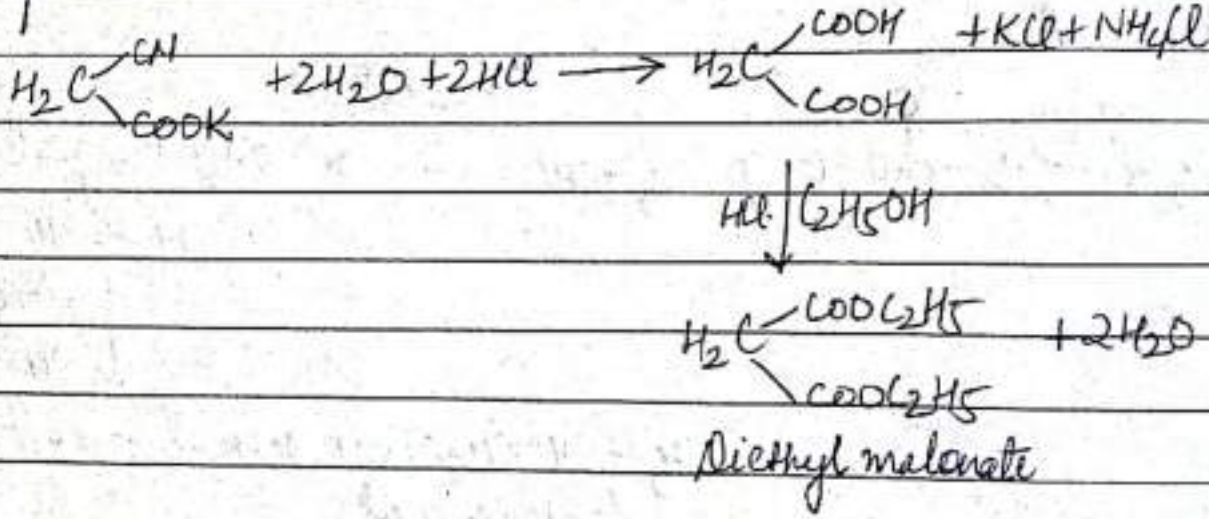
Antipyrine :- Ethylacetoacetate reacts with Phenyl hydrazene to give anti pyrine



Diethyl Malonate

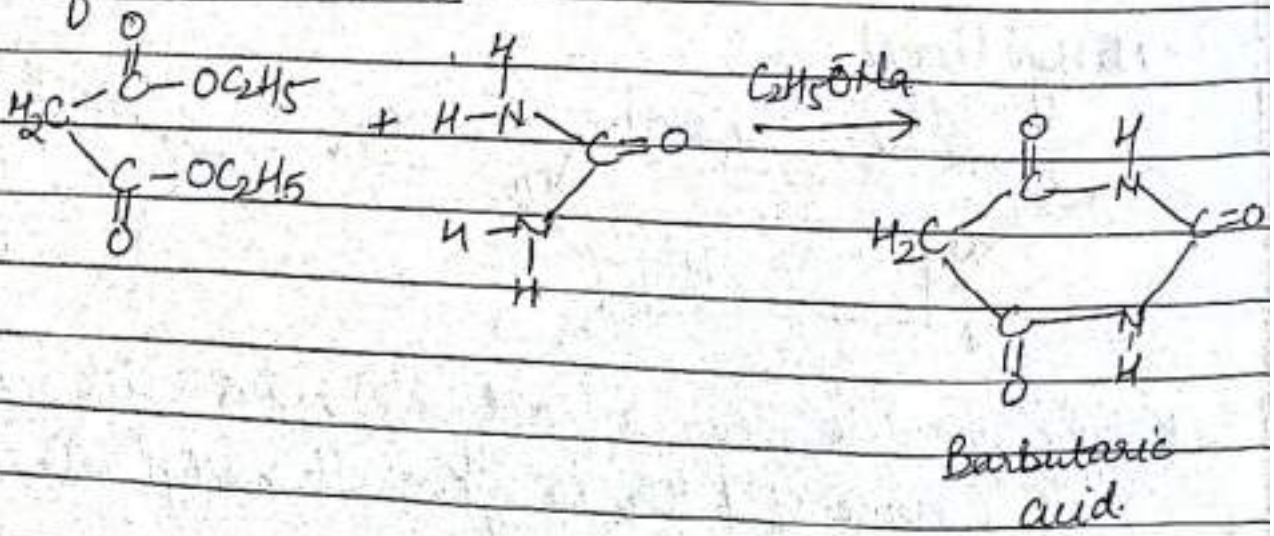
It is also called Malonic ester

Preparation



Diethyl malonate

Synthesis of Barbituric Acid



Barbituric acid