D. G. Palke.

Q. No. प्र. क्र.

Organic Synthesis via enolates.

B. Sc. III Sem - VI Chemistry XII

Introduction:

Active methylene compounds are those compounds which contain active methylene group in molecule. Active methylene group is the methylene group situated in between two electron withdrowing groups. H atoms of CH_2 group are becomes more acidic and reactive is termed as active methylene group.

$$\xi - CH_2 - \xi'$$

ξ and ξ' may be same or diff. electron withdrawing group.

e.g. $H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-O\xi H_5$ E.A.A. (A.A.E)

ethyl aceto acetate (Aceto acetic ester)

$N\equiv C-CH_2-\overset{O}{\overset{\|}{C}}-O\xi H_5$ cyano acetic ester.

$H_5\xi O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-O\xi H_5$ malonic ester.

Enolate- Enolate is an ion that formed by removal of H from active methylene group.

Q.No. प्र. क्र.

Organic Synthesis via Enolates

D.G. Palke.

B.Sc. III, Sem- VI

Active methylene group -

When methylene group ($-CH_2-$) is situated in between two electron withdrawing groups. H atoms of $-CH_2-$ group becomes more acidic and active is termed as active methylene ~~compounds~~ group. and compounds containing such $-CH_2-$ group are known as active methylene compounds.

$$Z_1 - CH_2 - Z'$$

Z and Z' may be same or diff. electron withdrawing groups, like $H_3C-\overset{O}{\overset{\|}{C}}-$, $-CN$, $H_5C_2O-\overset{O}{\overset{\|}{C}}-$

e.g. $H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$.

(E.A.A. or A.A.E.) ethyl aceto acetate or aceto acetic ester.

$N\equiv C-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$ cyano acetic ester.

$H_5C_2O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$ malonic ester.

Enolate - Enolate ion is an ion formed by removal of H proton from methylene ($-CH_2-$) gr.

$$H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow{C_2H_5O^{\ominus}Na^{\oplus}}$$

$$H_3C-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{C}H-\overset{O}{\overset{\|}{C}}-OC_2H_5 \longleftrightarrow H_3C-\overset{O^{\ominus}}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

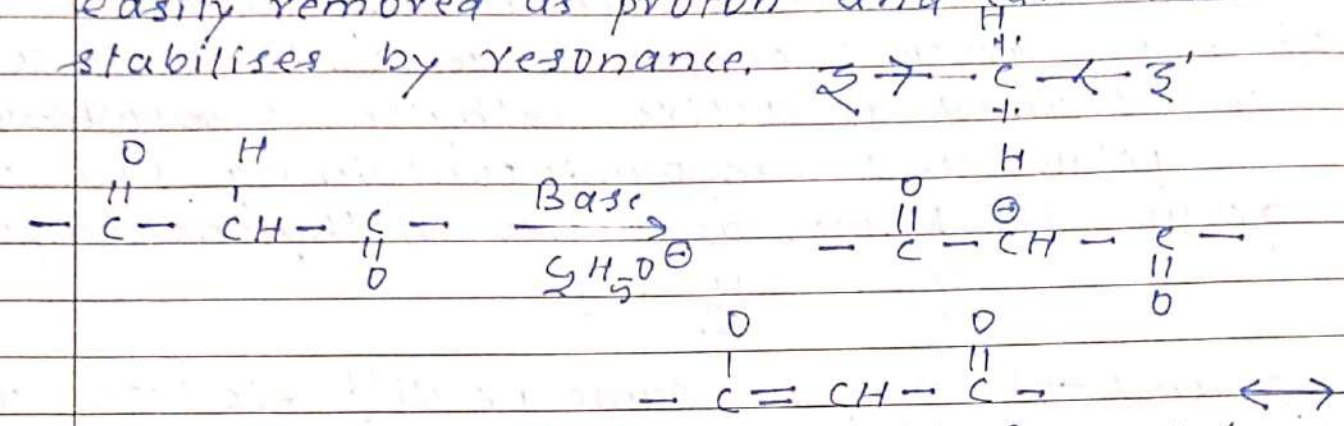
enolate.

Q.No. प्र. क्र.

(2)

Acidity of α-Hydrogen atom.-

In active methylene compound both electron withdrawing groups withdraws the electron from methylene group therefore −CH bond of $-CH_2-$ group becomes weaker in other word H atome easily removed as proton and carbanion ion stabilises by resonance.

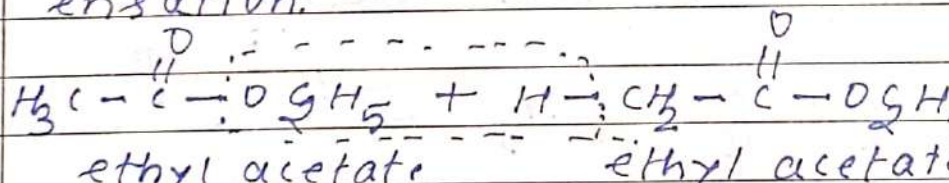


Resonance stabilised enolate

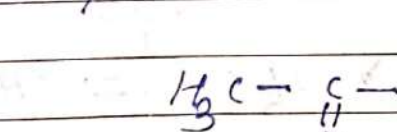
Hence in active methylene compound α-H are acidic.

* Preparation of ethyl aceto acetate by claisen condensation.

claisen condensation is the condensation of two ester molecules having ~~two~~ α-H atom in the presence of strong base like sod. ethoxide followed by protonation or acidification to yield β-keto ester is called as claisen condensation.



ethyl acetate ethyl acetate



ethyl aceto acetate.

Q.No. प्र. क्र.

Mechanism:- Mechanism of claisen condensation is proceed through following steps.

I) Dissociation of base C_2H_5ONa.

$$H_5C_2-O-Na \longrightarrow Na^+ + C_2H_5O^{\ominus}$$

ethoxide anion (base)

II) Abstraction of proton by base.

In this step ethoxide anion $C_2H_5O^-$ acts as strong base abstract proton from α- carbon atom ester molecule to form carbanion ion.

$$H_5C_2O^{\ominus} + H-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \longrightarrow C_2H_5OH + H_2C^{\ominus}-\overset{O}{\overset{\|}{C}}-OC_2H_5$$

carbanion.

III Attack of carbanion on carbonyl group:

In this step carbanion ion attack on carbonyl carbon of second molecule of ester to give 'A' intermediate compound which is converted to ethyl aceto acetate by removal of $-OC_2H_5$ group.

$$H_5C_2O-\overset{O}{\overset{\|}{C}}-CH_2^{\ominus} + O=C(-OC_2H_5)-CH_3 \longrightarrow$$

$$H_5C_2O-\overset{O}{\overset{\|}{C}}-CH_2-\underset{OC_2H_5}{\overset{O^-}{C}}-CH_3 \longrightarrow$$

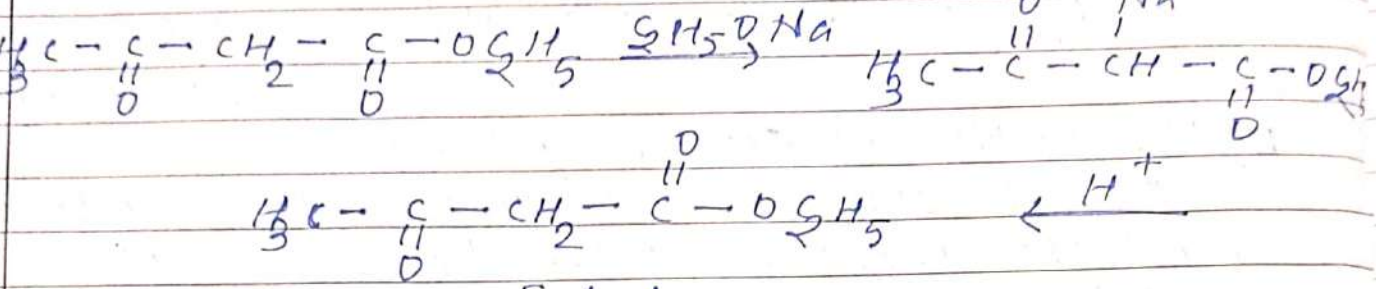
A

$$H_5C_2O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \quad \text{or}$$

$$H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \quad \text{E.A.A.}$$

Q.No. प्र. क्र.

Protonation: Since reaction is carried out in excess of C_2H_5ONa base then E.A.A. react with C_2H_5ONa to give sod. salt of E.A.A. therefore protonation is essential.



E.A.A.

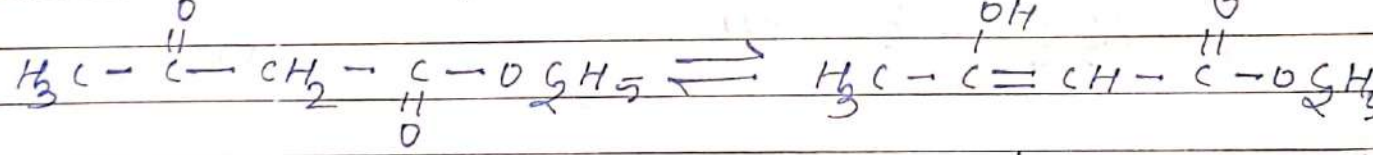
Keto-enol Tautomerism :-

Tautomerism is a special case of functional isomerism where isomers remains present together.

Def? Two isomeric forms of same compound having diff. functional groups which are continuously interconvertible and can exist a dynamic eqm are known as tautomers of each other and phenomenon is called as "tautomerism".

Other names of tautomerism - Desmotropism (desmo - bond, tropism - turn), Alleotropism, cryptomerism and merotrophy.

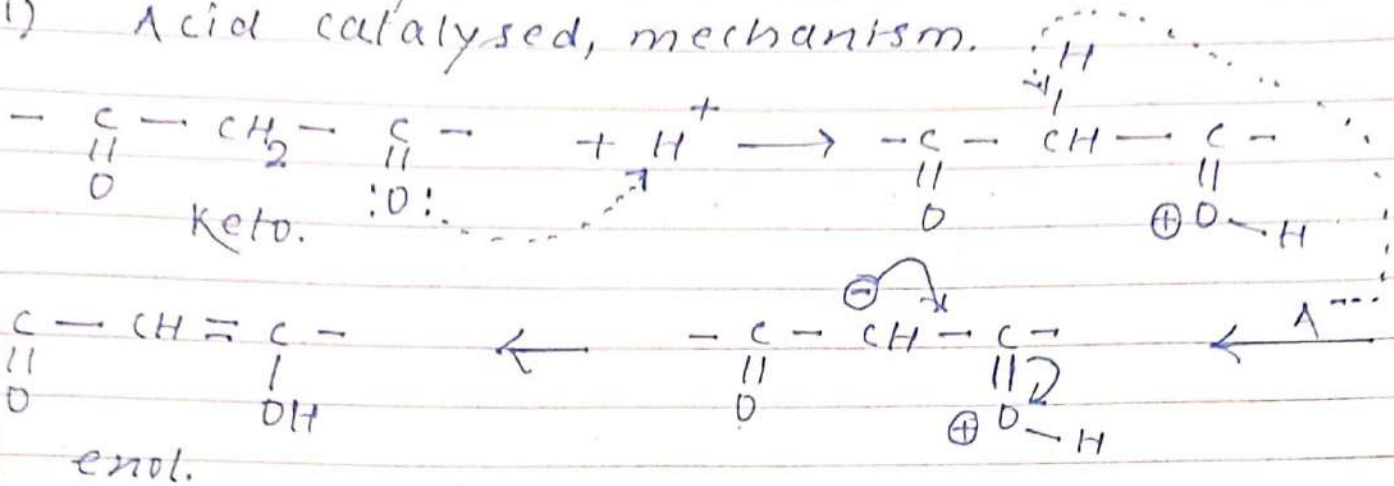
The best example of tautomerism is E.A.A. in which one isomer is keto form and another tautomer is enol form. Therefore it is also called as "Keto-enol tautomerism"



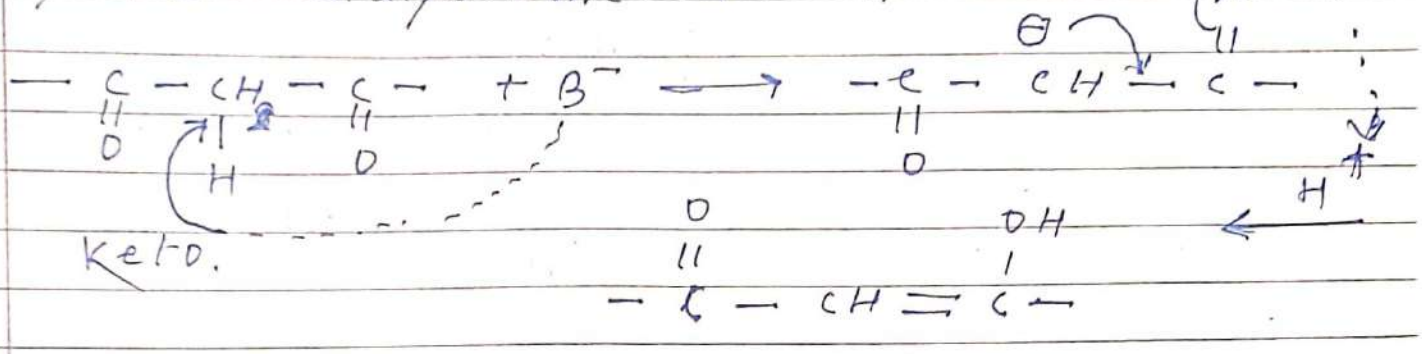
Keto form (92.5%) enol form (7.5%)

Mechanism of tautomerism:

i) Acid catalysed, mechanism.



ii) Base catalysed mechanism:

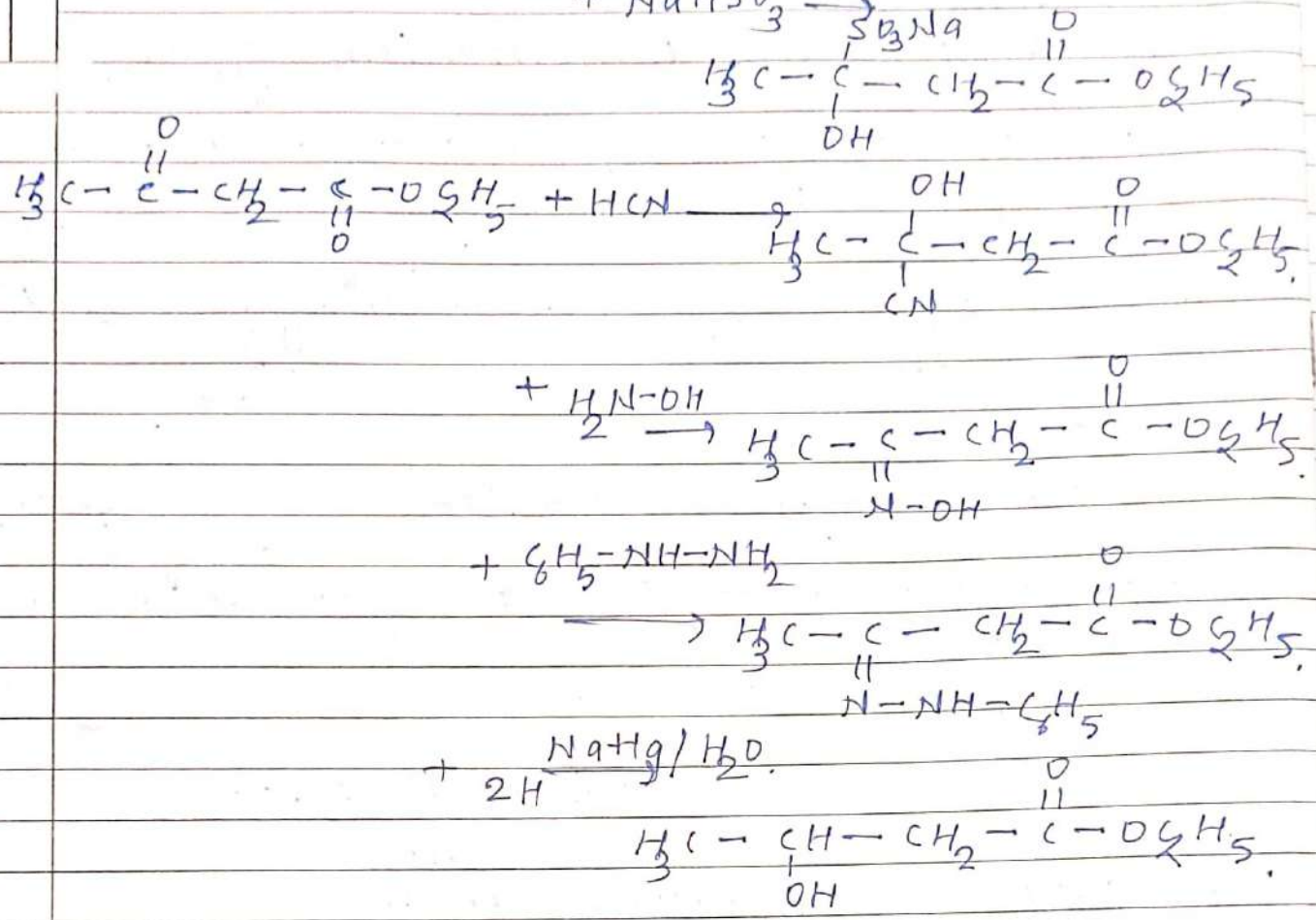


– Evidences supporting keto form

1) E.A.A. form bisulphite addition product with $NaHSO_3$.
2) E.A.A. form cyanohydrin with HCN.
3) E.A.A. undergoes condensation reaction with hydroxyl amine (CH_2N-OH) gives oxime.
4) E.A.A. undergoes condensation with phenyl hydrazine to form hydrazone derivative.
5) E.A.A. reduced to secondary alcohol by $Na-Hg/H_2O$

all these reactions indicate the presence of keto group in E.A.A.

Q.No. प्र. क्र.

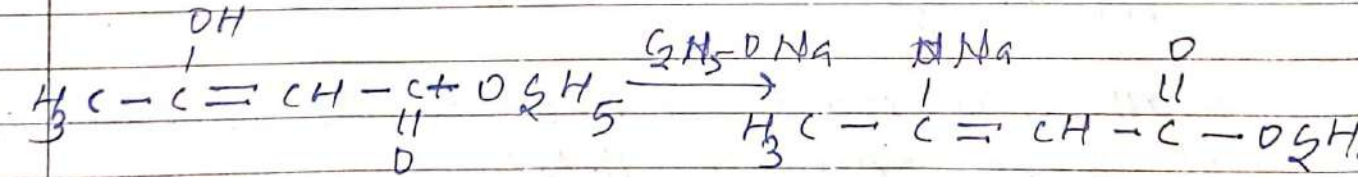


- Evidences of enol group.

1) E.A.A. forms sod. salt when react with C_2H_5ONa.

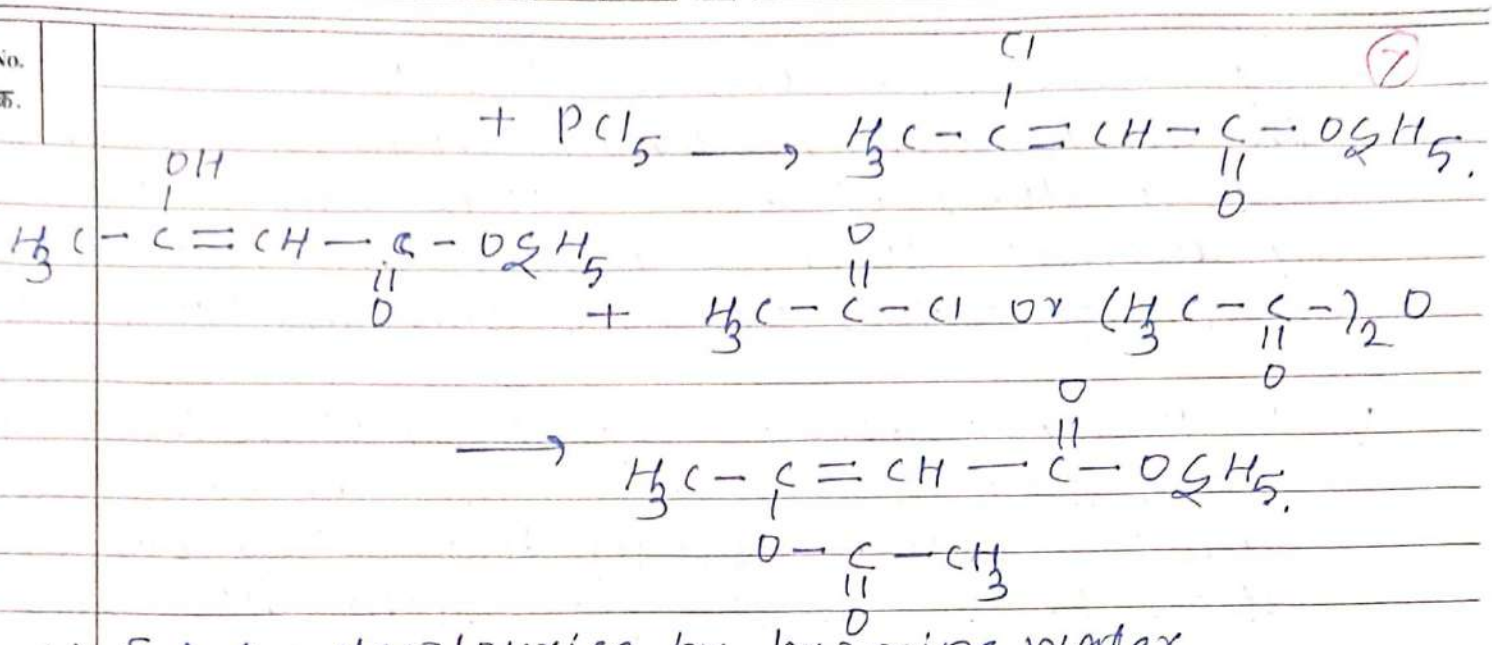
2) E.A.A. form acetyl derivative when react with either acetyl chloride or acetic anhydride.

3) E.A.A. can be halogenated or chlorinated by the action of PCl_5, PCl_3 or $SOCl_2$.

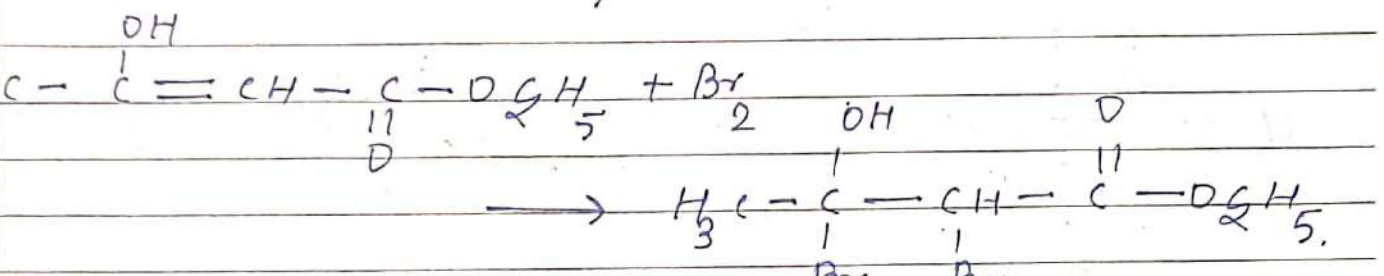


Q.No. प्र. क्र.

(7)



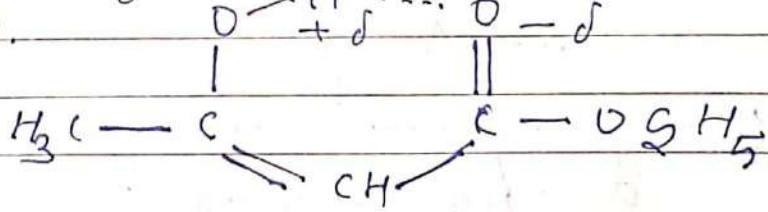
4) E.A.A. decolourise by bromine water.



5) E.A.A. also give violet colouration with $FeCl_3$. All these observation indicate the presence of enol group.

Isolation: In 1911 Knorr succided to separate keto form, He cooled the solution of E.A.A. in petroleum ether to -78°C temp. the colourless crystalline solid which do not give violet colouration with $FeCl_3$.

In 1920 K.H. Meyer separated enol form by fractional distilation in quartz flask, enol form distilled out first due intramolecular hydrogen bonding.

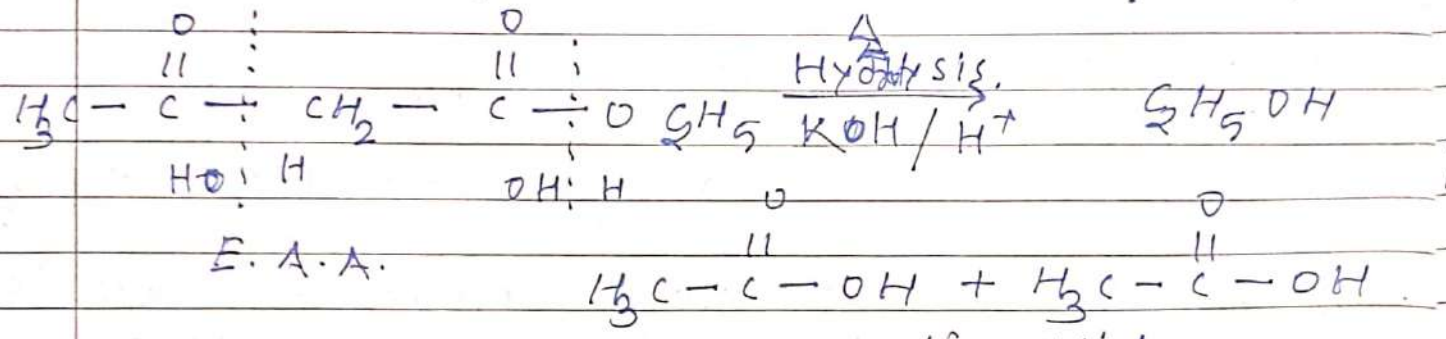


Q.No. प्र. क्र.

Synthetic Applications of E.A.A. (8)

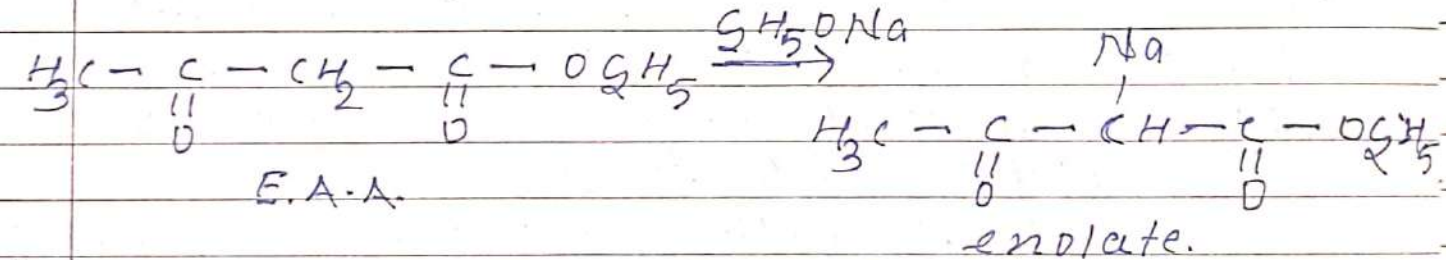
In E.A.A. active methylene group is present and H atoms of $-CH_2-$ group can be replaced by another atoms or groups. Therefore we can synthesize various organic compound from E.A.A.

1) Acidic hydrolysis - (synthesis of acetic acid) When E.A.A. heated with conc. aq. or alcoholic alkali (KOH or NaOH) followed by protonation so as to give carboxylic acid (acetic acid) is called acidic hydrolysis.

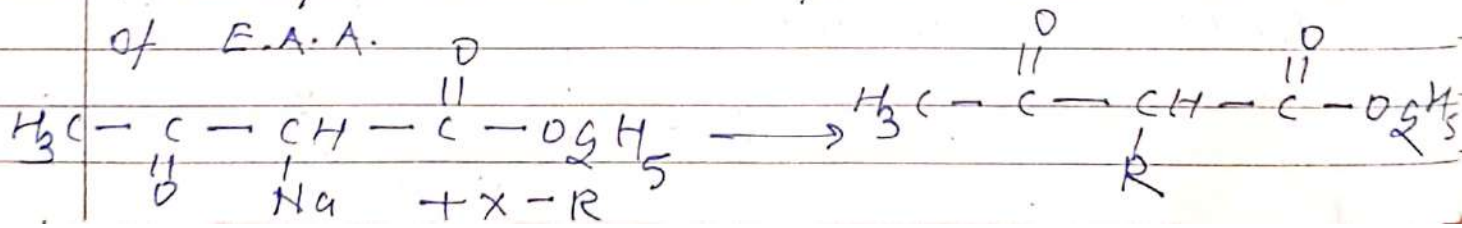


2) Synthesis of mono (sub.) carboxylic acid.

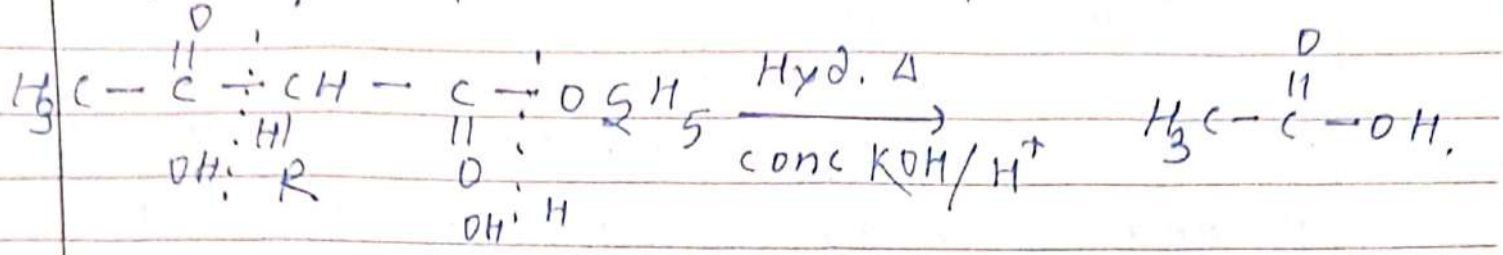
i) Formation of enolate by the action of C_2H_5ONa.



ii) Alkylation - Formation of mono alkyl derivative by the action alkyl halide on sod. salt of E.A.A.



2) Mono alkyl derivative of E.A.A. on acidic hydrolysis produces carboxylic acid.



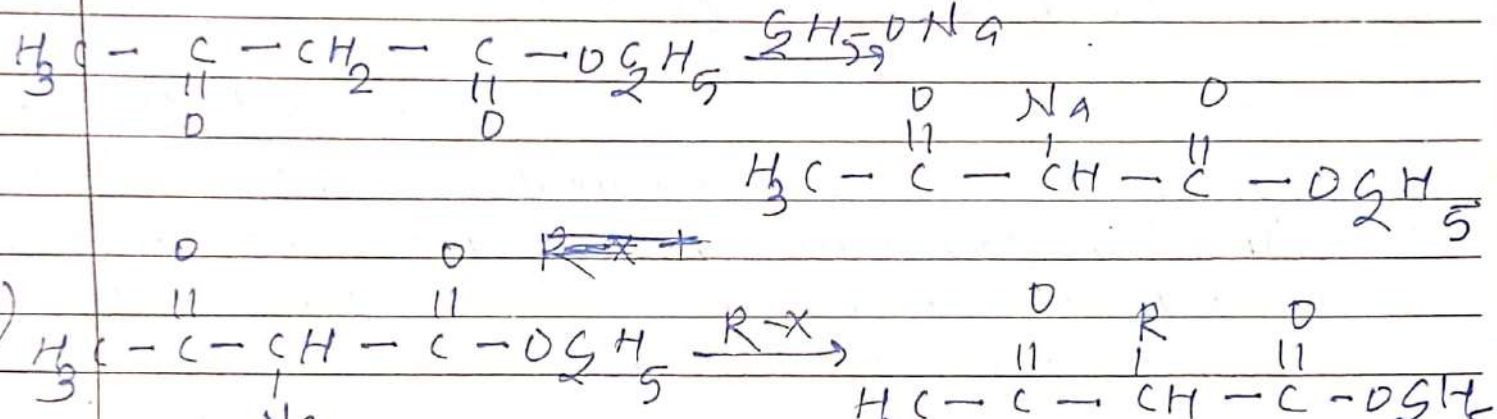
$$R-CH_2-COOH + C_2H_5OH$$

sub. acid.

$R = CH_3$ - Propanoic acid.

$R = C_2H_5$ - Butanoic acid.

3) Disubstituted carboxylic acid. –



Q.No. प्र. क्र.

4) $H_3C-\overset{O}{\overset{\|}{C}}-\underset{OH}{\underset{|}{\overset{R'}{\overset{|}{C}}}}-\underset{OH}{\underset{|}{\overset{H}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[KOH/H^+]{\Delta\ Hyd.} H_3C-\overset{O}{\overset{\|}{C}}-OH$

$$R-\underset{R'}{\underset{|}{CH}}-COOH + C_2H_5OH.$$

R and R' may be same or diff. alkyl group

R and R' = CH_3

$$\text{then acid} = H_3C-\underset{CH_3}{\underset{|}{CH}}-COOH$$

2-methyl propanoic acid

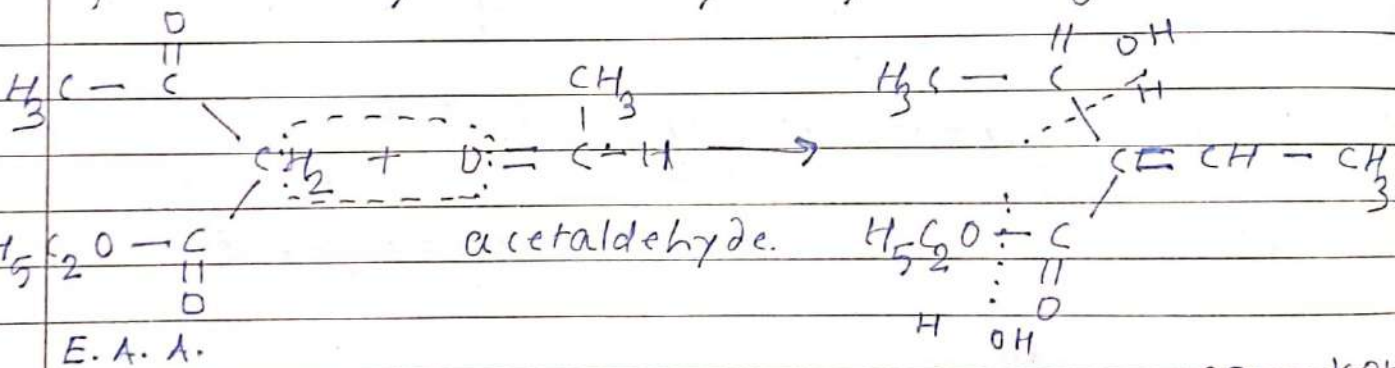
$R = CH_3$, $R' = C_2H_5$,

$$\text{then acid} = H_3C-CH_2-\underset{CH_3}{\underset{|}{CH}}-COOH$$

2-methyl butanoic acid.

4) Synthesis of α-β unsaturated acid.

Unsaturated carboxylic acid can be synthesized by the condensation of aldehyde with E.A.A. followed by acidic hydrolysis.

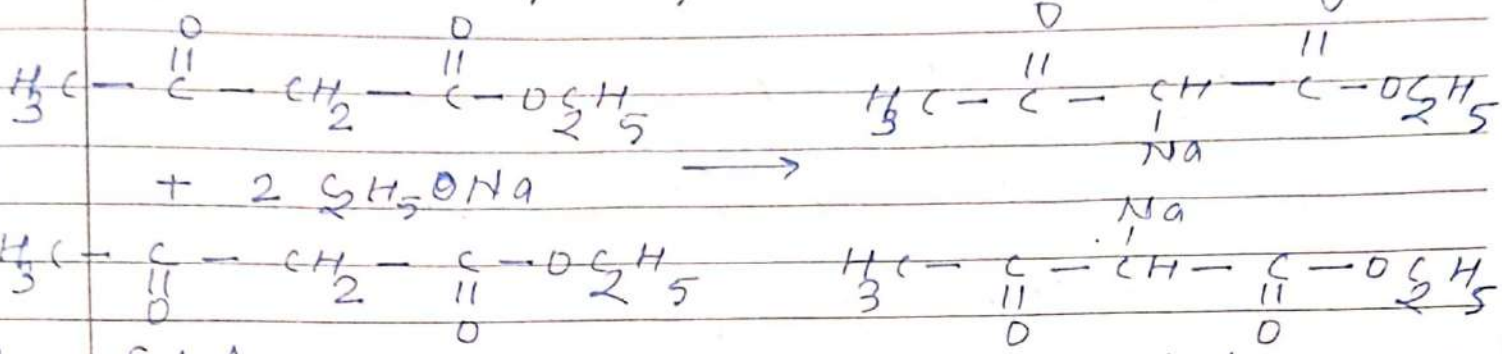


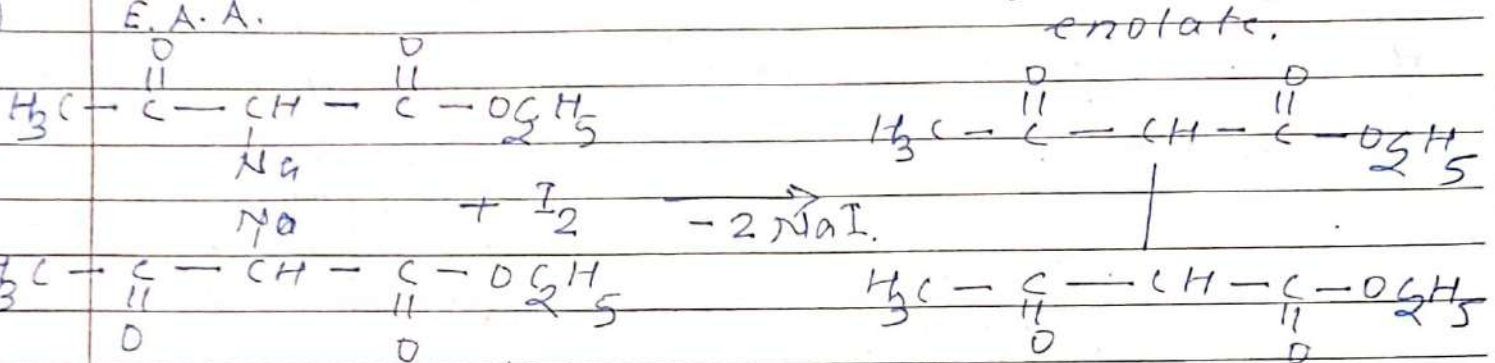
$$H_3C-COOH + C_2H_5OH + H_3C-CH=CH-COOH \xleftarrow[\Delta\ Hyd.]{conc.KOH}$$

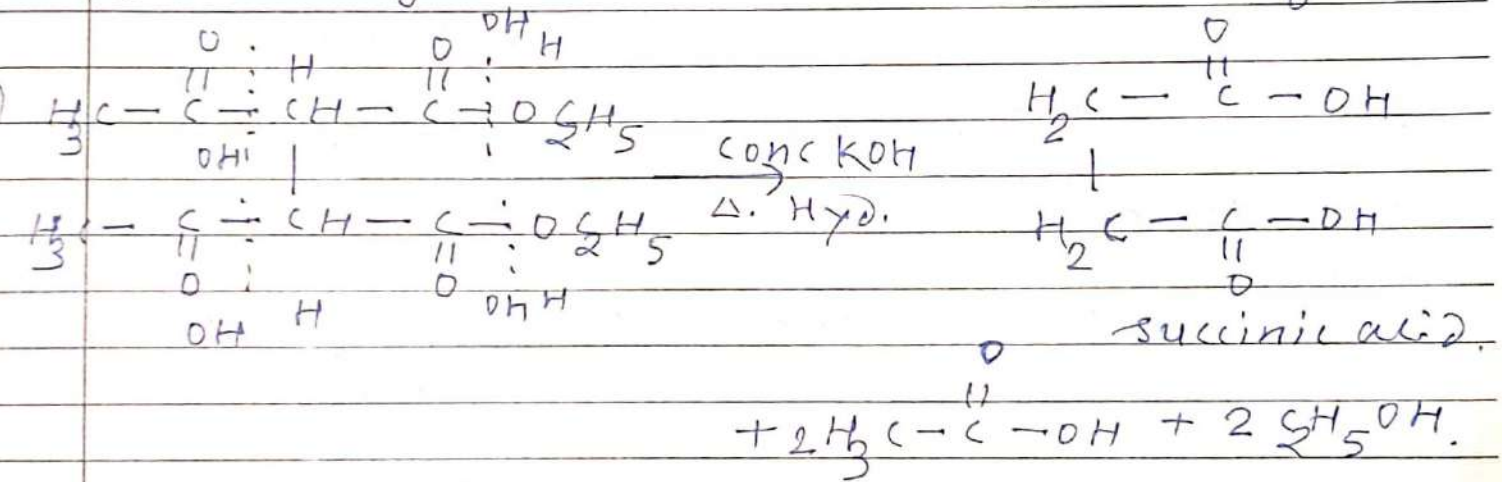
2-butenoic acid.

5) Synthesis of dicarboxylic acid. (Succinic acid)
Succinic acid can be obtained from E.A.A. by following steps.

i) Formation of enolate
ii) Action of I_2
iii) Acidic hydrolysis.



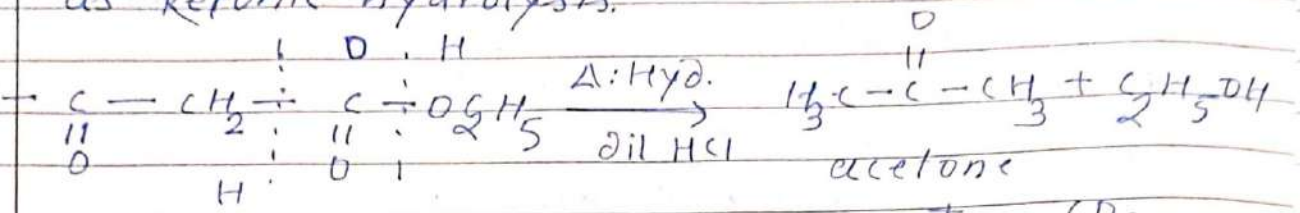




6) Ketonic Hydrolysis. (Synthesis of acetone).
When E.A.A. heated with dil HCl or dil KOH. followed by protonation the net result is ketone, i.e hydrolysis of E.A.A. by heating with

Q.No. प्र. क्र.

dil acid/ alkali so as to give ketone is called as ketonic hydrolysis.



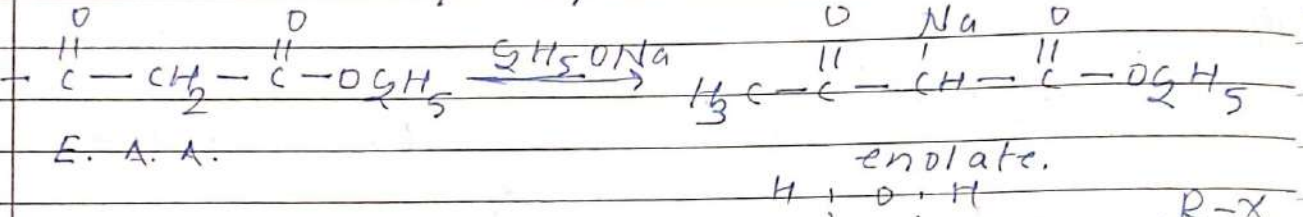
E.A.A.

7) Synthesis of 2-ketone -

i) Formation of enolate

ii) Alkylation by action of alkyl halide

iii) Ketonic hydrolysis.



$H_3C-C(=O)-CH_2-R + CO_2 + C_2H_5OH$.

2- Ketone

R = CH_3, Ketone $H_3C-C(=O)-CH_2-CH_3$

2-butanone

R = C_2H_5, Ketone $H_3C-C(=O)-CH_2-CH_2-CH_3$

2- pentanone.

Q.No. 8) Synthesis of 3-alkyl sub. ketone.

i) Enolisation and alkylation.

ii) Enolisation and alkylation.

iii) Ketonic hydrolysis.

i) $H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[ii)\ R-X]{i)\ C_2H_5ONa} H_3C-\overset{O}{\overset{\|}{C}}-\underset{R}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-OC_2H_5$

ii) $H_3C-\overset{O}{\overset{\|}{C}}-\underset{R}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[b)\ R'-X]{a)\ C_2H_5ONa} H_3C-\overset{O}{\overset{\|}{C}}-\underset{R'}{\underset{|}{\overset{R}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}-OC_2H_5$

iii) $H_3C-\overset{O}{\overset{\|}{C}}-\underset{R'}{\underset{|}{\overset{R}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[dil.\ HCl]{\Delta\ Hyd.} C_2H_5OH + CO_2$

$$H_3C-\overset{O}{\overset{\|}{C}}-\underset{R'}{\overset{R}{\underset{|}{CH}}}$$

$R = R' = CH_3$ then Ketone

$$H_3C-\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\underset{|}{CH}}-CH_3$$

3-methyl-2-butanone

$R = CH_3$ & $R' = C_2H_5$ the ketone

$$= H_3C-\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\underset{|}{CH}}-CH_2-CH_3$$

3-methyl-2-pentanone.

Q.No. प्र. क्र. 9) Synthesis of diketone (4)

From E.A.A. diketone can be synthesised by the action of alkanoyl halide on enolate followed by ketonic hydrolysis.

i) $H_3C-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow{C_2H_5ONa} H_3C-\overset{O}{\overset{\|}{C}}-\underset{Na}{CH}-\overset{O}{\overset{\|}{C}}-OC_2H_5$

ii) $H_3C-\overset{O}{\overset{\|}{C}}-\underset{Na}{CH}-\overset{O}{\overset{\|}{C}}-OC_2H_5 + Cl-\overset{O}{\overset{\|}{C}}-CH_3 \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-\underset{\underset{CH_3}{|}}{\overset{C=O}{|}}-\overset{O}{\overset{\|}{C}}-OC_2H_5$

iii) $H_3C-\overset{O}{\overset{\|}{C}}-\underset{O=C-CH_3}{\overset{H}{|}}-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[-H_2O,\ -HCl]{Acid\ hyd.} H_3C-\overset{O}{\overset{\|}{C}}-\underset{2}{CH_2}-\overset{O}{\overset{\|}{C}}-\underset{3}{CH_3}$

2,4-pentandione

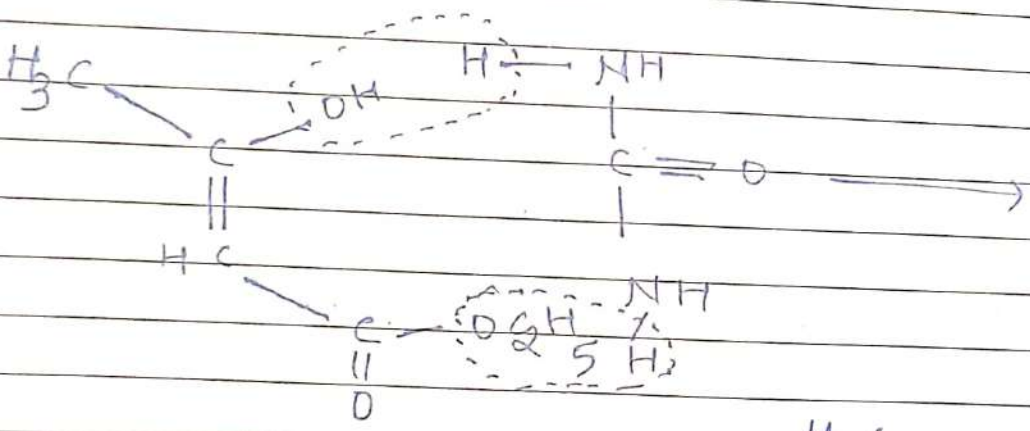
$+ CO_2 + C_2H_5OH$

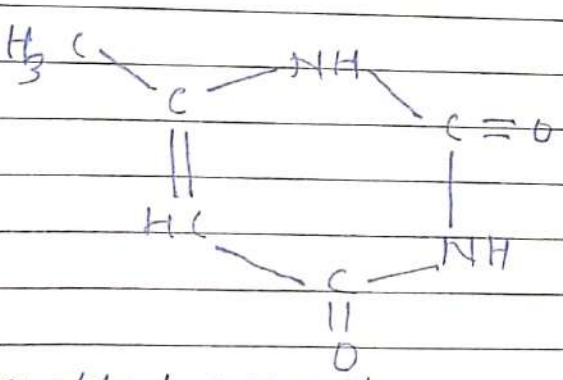
10) Synthesis of Heterocyclic compound.

Synthesis of 4-methyl uracil.

From E.A.A. 4-methyl uracil is obtained by the action of urea on enolic form of E.A.A.

15





4-methyl uracil.