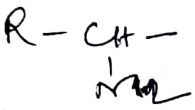
Biomolecules

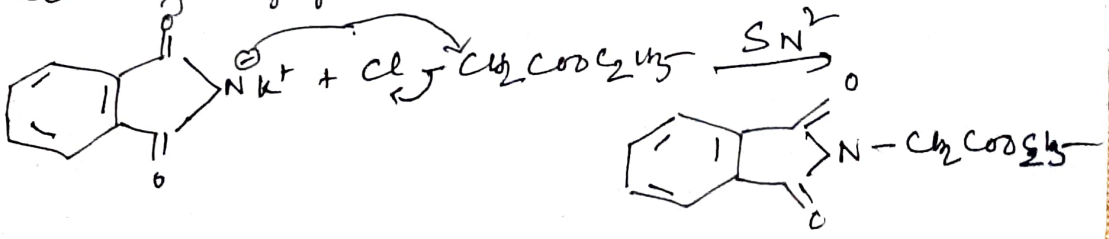
Amino acid – The term amino acid might mean any molecule that contains both an amino group and any type of acid group, however, the term is almost used to refer to an α-amino carboxylic acid. α-Amino acids are the units that comprise all proteins.

The general structure of the naturally-occurring α-amino acids is as follows

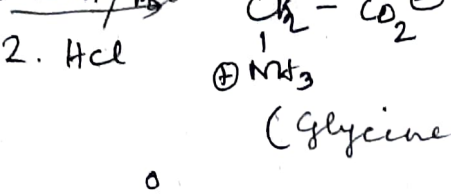


8. Discuss the following methods of amino acid synthesis. Give examples.
   a) Gabriel phthalimide synthesis
   b) Gabriel-malonic ester synthesis or N-Phthalimido malonic ester method.
   c) Acetamido malonic ester synthesis.

Answer a) Gabriel phthalimide synthesis: The method is a modification of Gabriel synthesis of primary amines. The potassium salt of phthalimide is treated with an α-halo ester. The resulting compound gives phthalic acid and the α-amino acid upon alkaline hydrolysis followed by acidification or by acid hydrolysis. The whole sequence may be examplified by the following synthesis of Glycine.

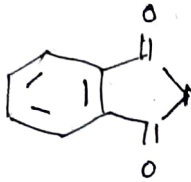


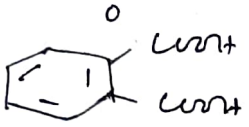
1 KOH/H_2O
2. HCl



(Glycine 85%)

Phthalic acid

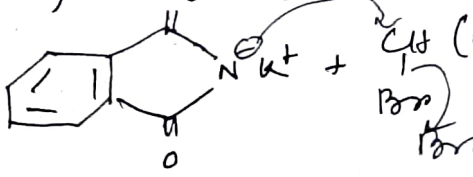




Glycine hydro Chloride (80%)

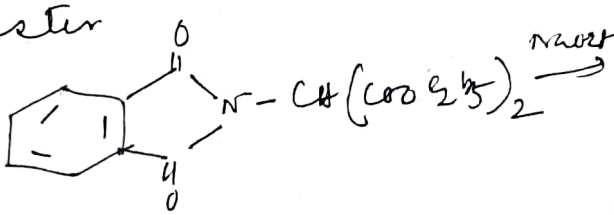
b) Gabriel-malonic ester synthesis or Phthalimido malonic ester method:

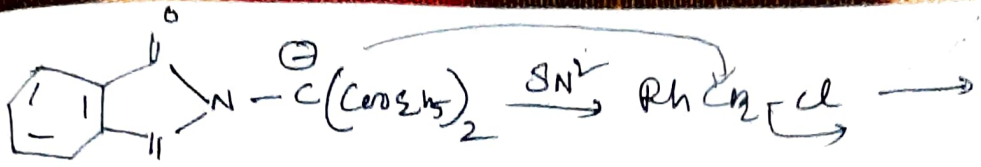
This is a variation of the malonic ester synthesis which is quite useful for synthesizing α-amino acids. The first important intermediate in this synthesis is N-Phthalimido malonic ester which is obtained by the action of potassium phthalimide on bromo malonic ester. This ester is converted, with base (Sodium ethoxide) to an anion that is resonance stabilised. The anion in turn, is treated with an alkyl halide to given an alkylated product. Vigorous hydrolysis of this alkylated product causes the hydrolysis of both ester groups and the phthalimido group. Under these condition the malonic acid derivative is decarboxylated to yield an α-amino acid. The sequence of various steps involved is illustrated by the synthesis of phenyl alanine.

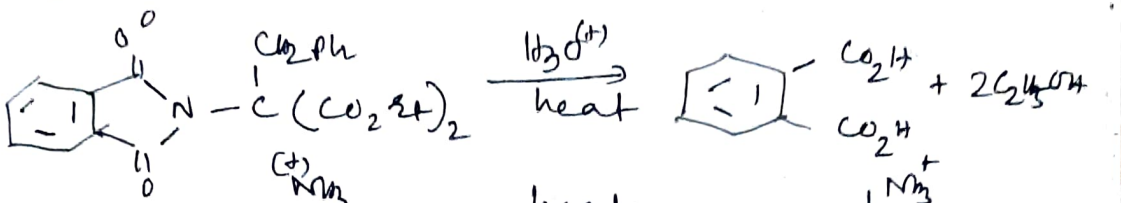


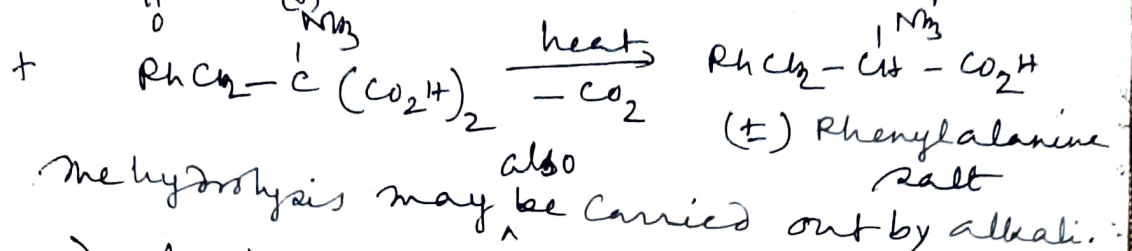
Potassium Phthalimide

Bromo malonic ester





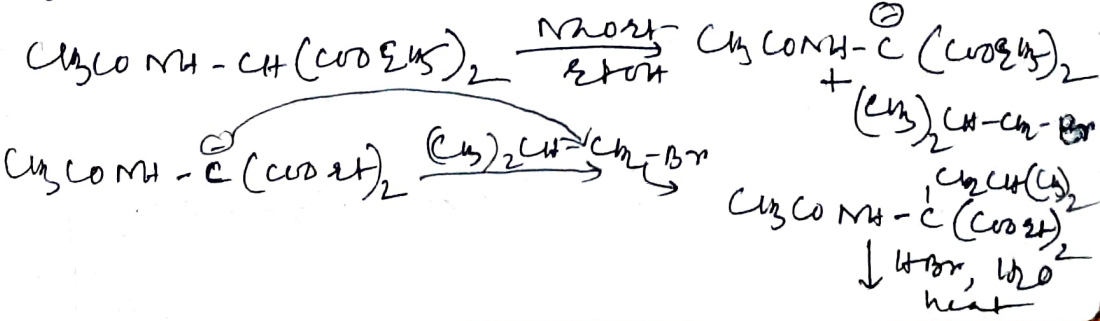




The hydrolysis may also be carried out by alkali.

c) Acetamidomalonic ester synthesis: This widely used method for preparing α-amino acids is a variation of the malonic ester synthesis. The malonic ester derivative which is used in this synthesis is acetamido malonic ester or diethyl acetamido malonate in which a protected amino group is already in place. This compound is treated with sodium ethoxide in ethanol to form the enolate ion, which is then alkylated with an alkyl halide. The resulting compound is then heated with aqueous HCl or HBr. This causes the acetamido and the ester groups to undergo hydrolysis to yield a malonic acid derivative which decarboxylates under the reaction condition to gives an α-amino acid derivative which decarboxylates under the reaction conditions to give an α-amino acid

The following sequence shows the synthesis of leucine by this method.



$CH_3COOH + 2C_2H_5OH + \left[{}^{+}NH_3 - {}^{1}C(CH_2CH(CH_3)_2)(COOH)_2 \right] \xrightarrow[-CO_2]{heat}$

$(CH_3)_2CH-CH_2-{}^{1}CH(^{+}NH_3)-COOH$

(±) - Leucine (salt)

The hydrolysis (Step-3) may also be carried out by alkali.

The synthesis of acetamido malonic ester is out lined below:

$CH_2(COOC_2H_5)_2 \xrightarrow{HNO_2} [ON=CH(COOC_2H_5)_2] \longrightarrow$

$OH-N=CH(COOC_2H_5)_2 \xrightarrow[Ac_2O]{H_2/Pt} CH_3CONH(COOC_2H_5)_2$

Q) Show how Gabriel-malonic ester synthesis could be used to make

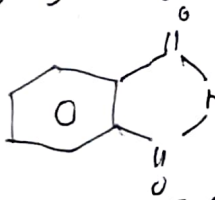
a) (D,L) - Valine (b) (D,L) - aspartic acid

(c) (D,L) - glutamic acid (d) (D,L) - leucine

(e) (D,L) - methionine (f) (D,L) - proline

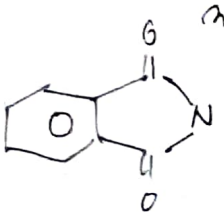
(g) (D,L) - cysteine and (±) cystine.

Ans a)



$+HC(COOC_2H_5)_2 \xrightarrow[2.\ (CH_3)_2CHBr]{1.\ NaOEt}$

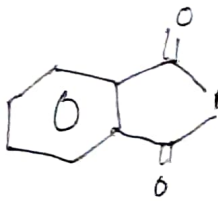
N - Phthalimido malonic ester



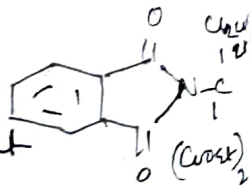
$\xrightarrow[2.\ OH^{\ominus}/H_2O]{1.\ H_3O^{+}/heat} (CH_3)_2CH-CH(^{+}NH_3)-COO^{(-)}$

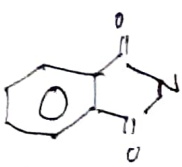
(D,L) - Valine

b)



$\xrightarrow[2.\ BrCH_2COOEt]{1.\ NaOEt}$

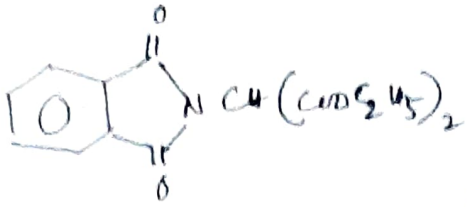




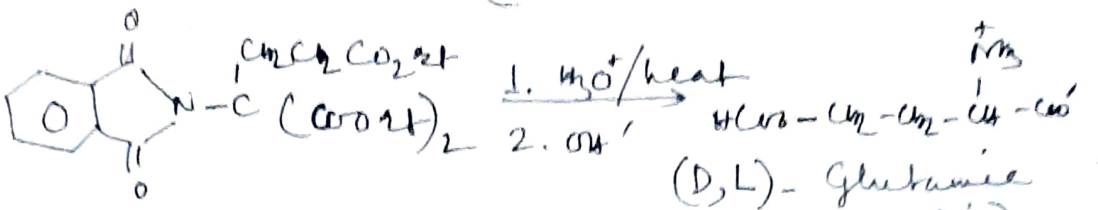
$\xrightarrow[2.\ OH^{\ominus}/NaO]{1)\ H_3O^{+}/Heat} COOH-CH_2-CH(^{+}NH_3)-COO^{\ominus}$

(D,L) - Aspartic acid.

c)

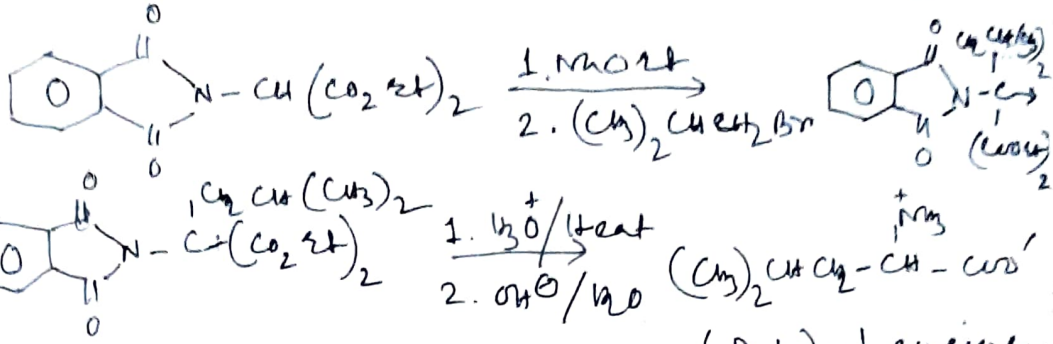


(Michael addition)



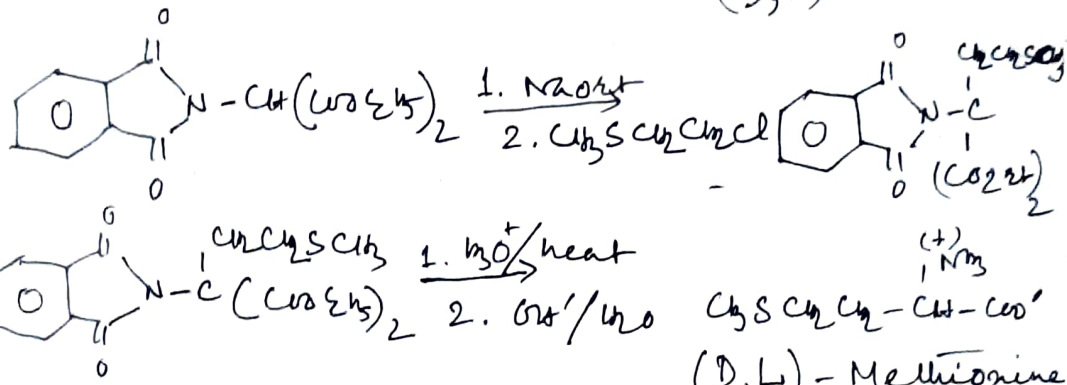
(D,L)- Glutamic acid.

d)



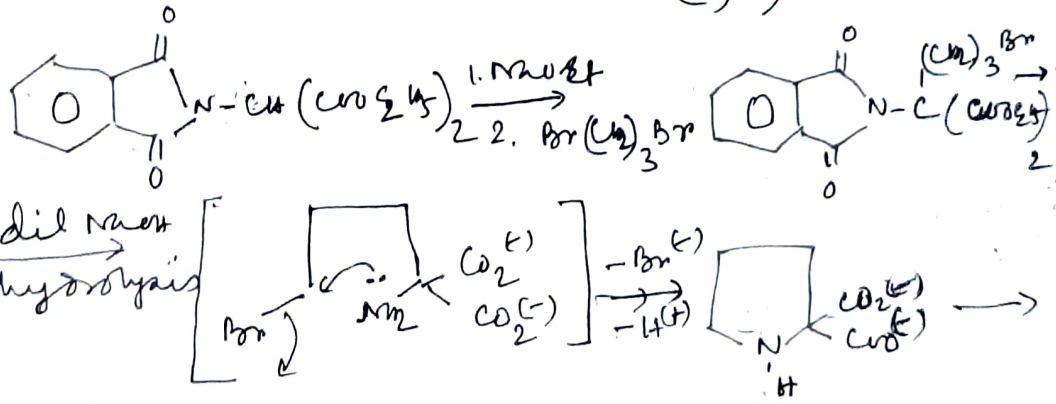
(D,L)- Leucine.

e)



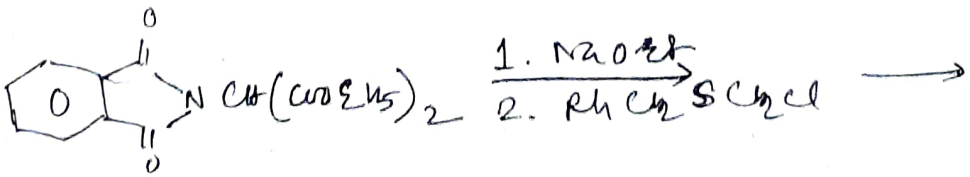
(D,L)- Methionine

f)

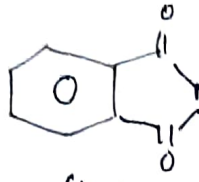


(D,L)- Proline

g)



q)



$\xrightarrow[2.\ HCl]{1.\ NH_3}$ $NH_2-CH(CH_2SCH_2Ph)-COOH$

$NH_2-CH(CH_2SCH_2Ph)-COOH \xrightarrow{Na/NH_3(l)} NH_2-CH(CH_2SH)-COOH \xrightarrow{O_2(air)}$ (D, L) - cystine

$NH_2-CH(COOH)-CH_2S-S-CH_2-CH(COOH)-NH_2$

± cystine

Synthesis of $PhCH_2SCH_2Cl$:-

$PhCH_2SH + HCHO + HCl \rightarrow [PhCH_2SCH_2OH] \xrightarrow{HCl} PhCH_2SCH_2Cl$.

Q. What is Streeker synthesis for the preparation of α-amino acids? What problem arises in application of this method for the synthesis of lysine?

Ans:- Streeker synthesis is a general method for the synthesis of α-amino acids. The treatment of an aldehyde with ammonium chloride and potassium cyanide produces a α-amino nitrile, which gives an α-amino acid when hydrolysed with dilute acid.

$RCH=O + NH_4Cl + KCN \rightarrow R-CH(NH_2)-CN \xrightarrow{HCl,\ H_2O}$

$R-CH(NH_2)-COOH$

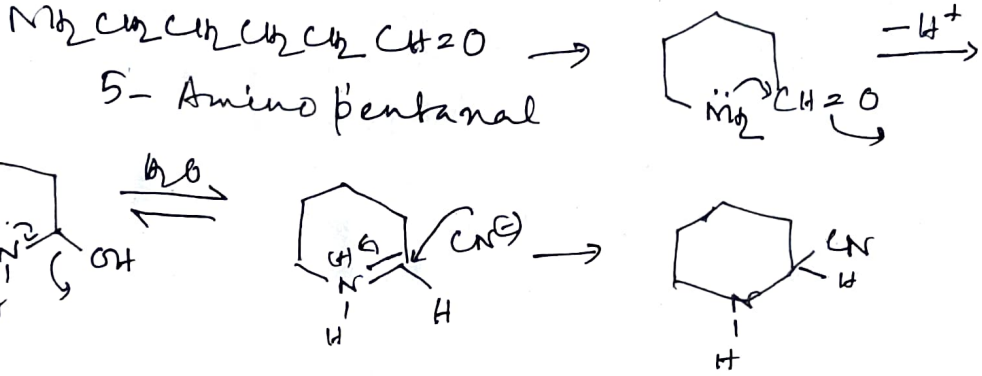
α-amino acid.

The mechanism of the formation of the α-amino nitrile may be a nucleophile addition of HCN to an imine formed by the reaction between an aldehyde and NH_3

$NH_4Cl + KCN \rightarrow NH_3 + HCN + KCl$

For the preparation of lysine using streeker

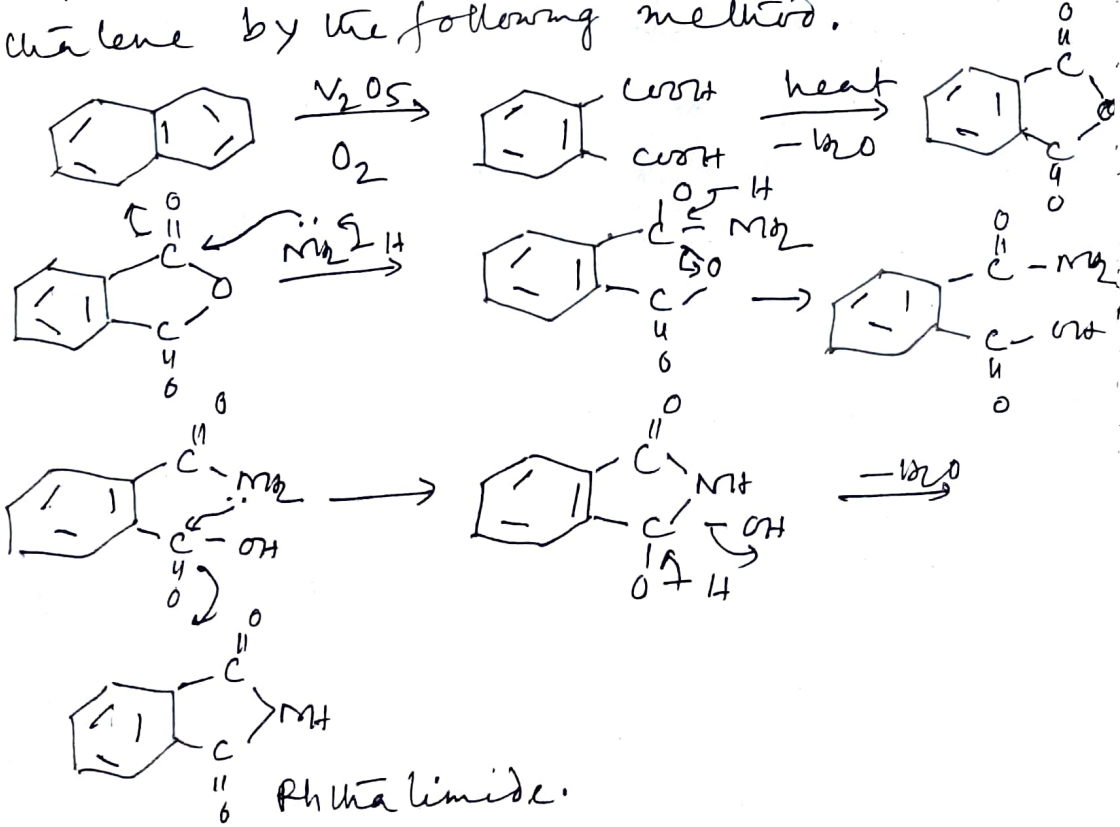
Synthesis, we need an aldehyde like $NH_2-(CH_2)_4-CHO$ and the preparation of that compound in stable form is difficult because it readily forms a six-membered nitrogenous heterocyclic by intramolecular reaction. This is followed by reaction with cyanide ion to form 2-Cyanopiperidine. The course of this reaction is shown below.



2- Cyano piperidine.

Q How Phthalimide can be prepared?

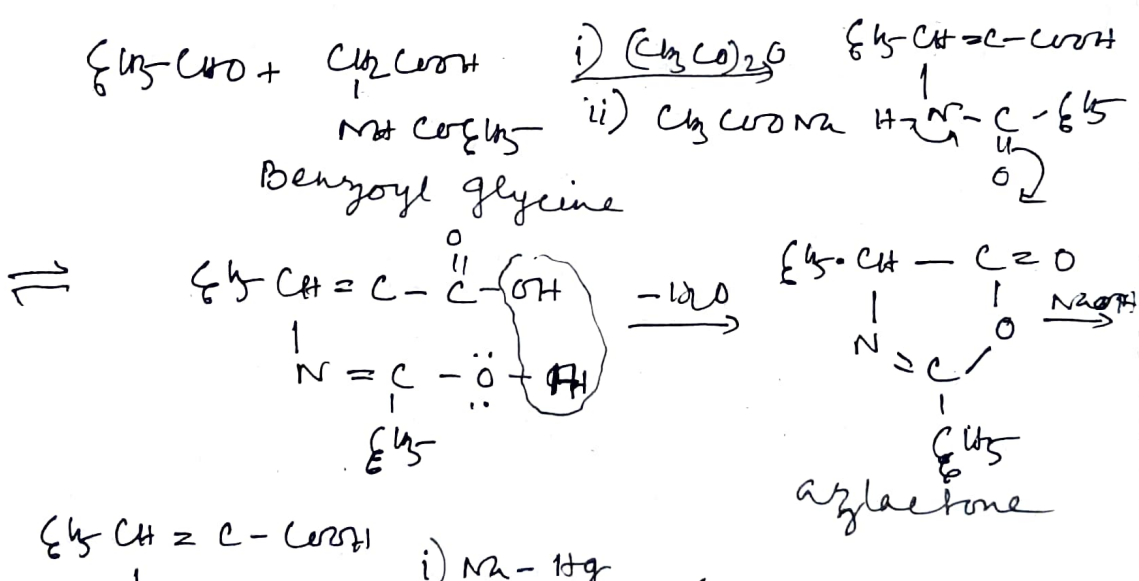
Ans:- Phthalimide can be prepared from Naphthalene by the following method.

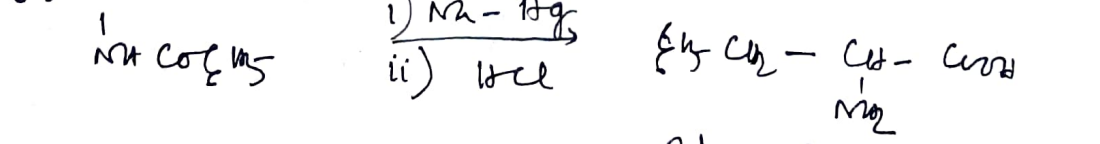


Phthalimide.

Q. What is Erlenmeyer 'azlactone' synthesis? How would you use this method to synthesise phenylalanine. Is this synthesis is stereo specific?

Ans:- An aromatic aldehyde reacts with benzoyl glycine (Hippuric acid) to form azlactone, a five membered cyclic ester containing nitrogen in the ring. When azlactone is warmed with dilute Sodiumhydroxide, an open chain compound is formed. This open-chain compound gives amino acid by reduction followed by hydrolysis with dilute acid. Synthesis of phenylalanine is shown below.





Benzoyl derivative of glycine is used to activate the methylene group of glycine so that it can readily condense with less reactive aromatic aldehyde.
The synthesis is not stereo specific and we will always get a racemic mixture in case of synthesis of a chiral amino acid.