Unit - IV (b)

Topic: Synthesis and Breakdown (1)

Purines and Pyrimidines:-

Introduction

DNA and RNA can be considered to be polymer of a simple unit called a 'nucleotide'.

Each nucleotide is made up of a base, a sugar and phosphoric acid.

If the phosphate is removed by hydrolysis, the residue consisting of a base and sugar is called a nucleoside.

The ~~Nucleotides~~ nucleosides can be further hydrolyzed to separate the base from the sugar.

Sugar -> The sugar moiety is

D-ribose in RNA

And

D-2, deoxyribose in DNA

They exist in the ring form as furanoside.

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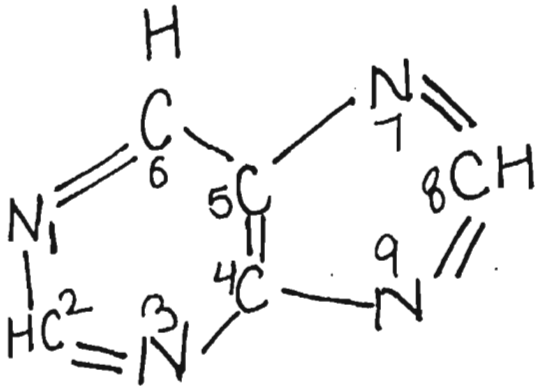
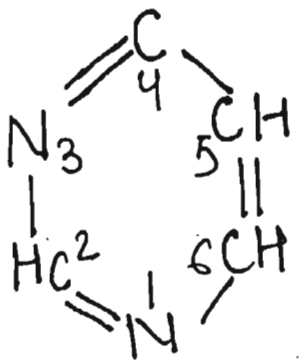


(Purine)

=> Bicyclic Structure
=> 4 => nitrogen (1, 3, 9)
=> 9 membered



(Pyrimidine)

-> Monocyclic Structure
-> 2 Nitrogen (1, 3)
-> 6 membered

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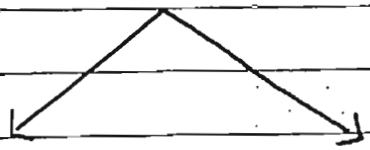
Base :-> Two types of bases are preser



Pyrimidine purine

Purines and Pyrimidnes

The nitrogen bases found in nucleotides (and therefore, nucleic acid) are aromati heterocyclic compounds.
Purines are numbered in the anticlock-wise direction.

Definition -> Purines and pyrimidnes are nitrogenous bases that make up the two different kind of nucleotide bases in DNA & RNA.

=> The two-carbon nitrogen ring bases are purines

=> The one-carbon nitrogen ring bases are ~~pyrimidin~~ pyrimidines.

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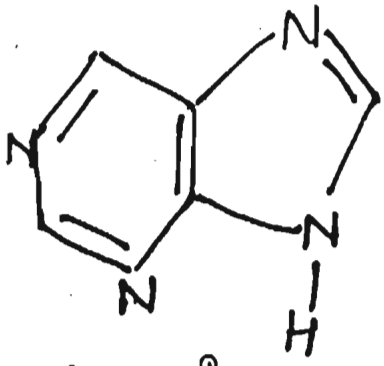
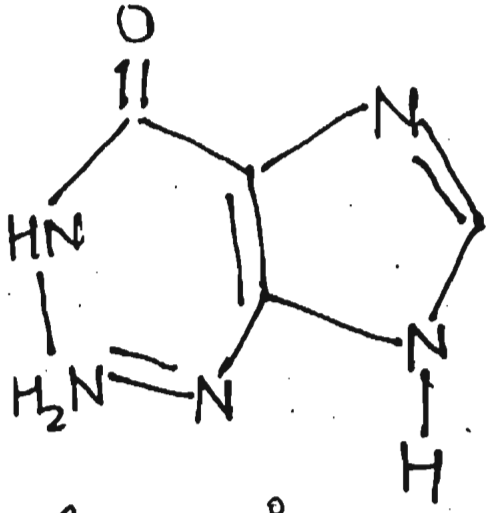
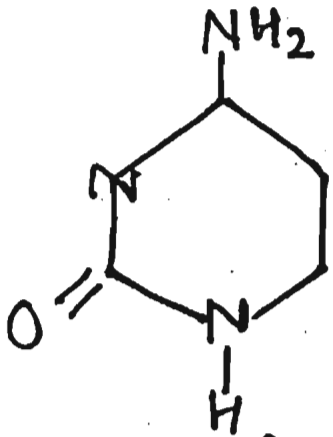


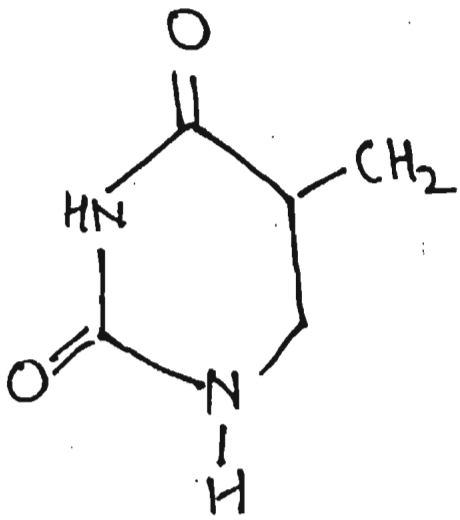
Adenine



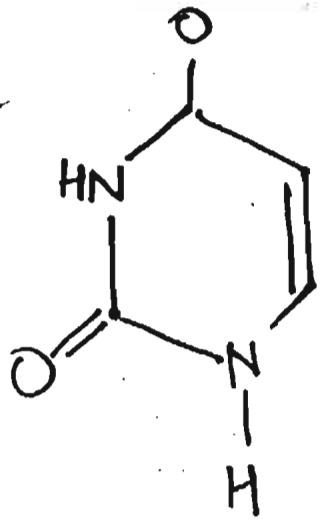
Guanine



Cytosine



Thymine



Uracil

Topic (5) Date

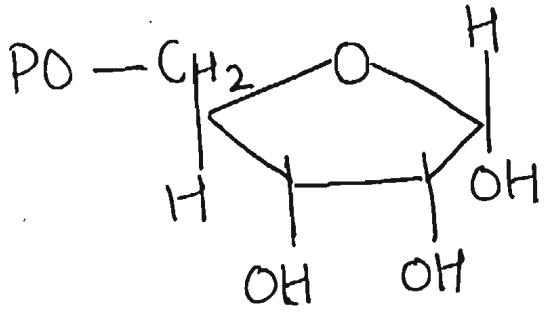
Types of pyrimidnes and purines

Pyrimidnes Bases

- Cytosine (2-oxy-4 amino-pyrimidine)
- Thymine (2,4-dioxy-5 methyl pyridimine)
- Uracil (2,4 dioxy pyrimidine)

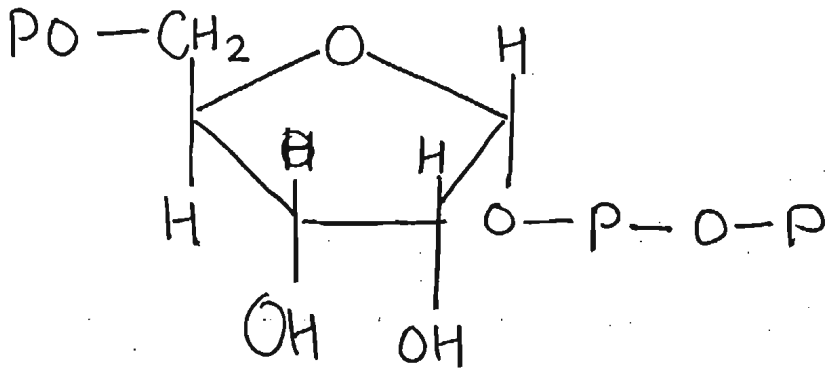
Purines Bases

- Adenine (6-aminopurine)
- Guanine (2-amino-6-oxypurine)



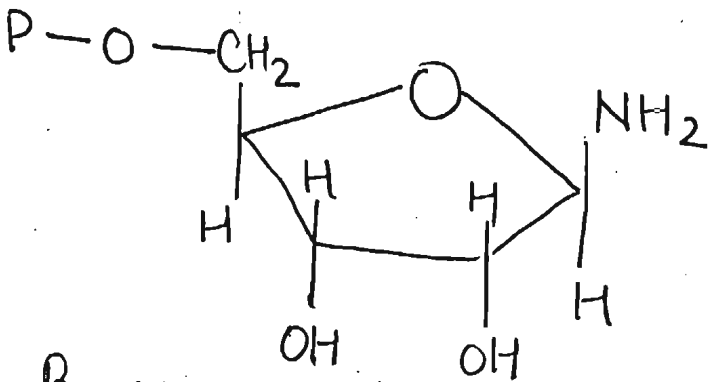
α D-Ribose-5-Phosphate

ATP → AMP ← PRPP Synthetase



5-Phosphoribosyl α pyrosphosph

Glutamine + H_2O → Glutamate + PPi ← PRPP Glutamyl amidotransferase



β-5-Phosphoribosylamine

Glycine + ATP → ADP + Pi ← Synthetase

Topic 7 Date

BIOSYNTHESIS OF PURINE

⇒ 1. Ribose 5 phosphate, produced in the hexose monophosphate shunt of CHO metabolism is the starting material for purine nucleotide synthesis it react with ATP to form phosphoribosyl pyrophosphate (PRPP).

⇒ 2. Glutamine transfers its amide nitrogen to PRPP to replace pyrophosphate and produce 5 phosphoribosylamine

The enzyme PRPP to replace Glutamyl amidotransferase is controlled by the feedback inhibition of nucleotide (imp) (AMP, GMP).
This reaction is the Commited step in purine nucleotide biosynthesis.

⇒3 Step i→ Phosphoribosylamine react with Glycine in the presence of ATP to form Glycinamide ribosyl 5-phosphate or glycinamide ribotide (GAR)

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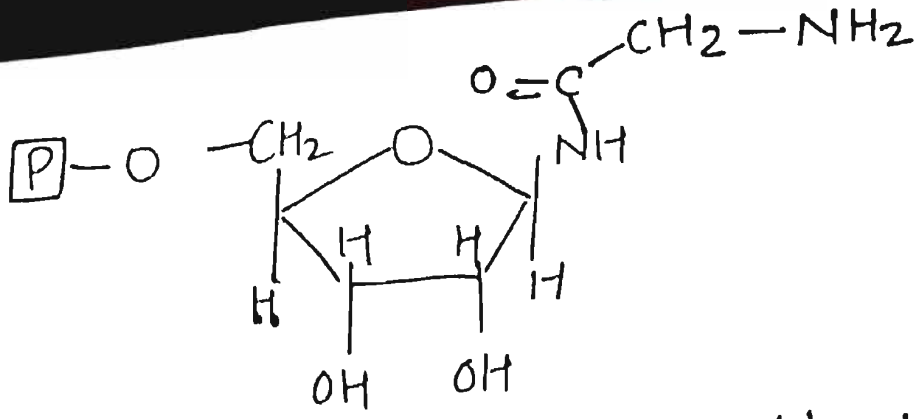
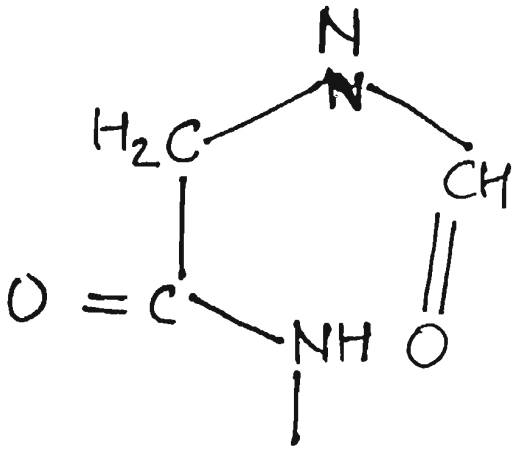


Glycinamide ribosyl 5-phosphate

N10-formyl THF → THF

formyltransferase

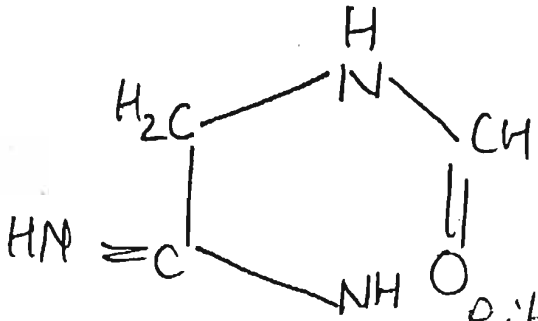


Ribose 5-P

Formylglycinamide ribosyl 5-phosp

Glutamine + ATP → Glutamate + ADP + Pi

synthetase



Ribose 5-P

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4→ Step - 4

N^{10} - Formyl tetrahydrofolate donates the formyl group and the product formed is Formylglucinamide ribosyl 5 - phosphate.

Step-5 → Glutamine transfers the second amido amino group to produce formylglycinamidine ribosyl 5- phosphate.

6. The Step-6 → The imidazole ring of the purine is closed in an ATP dependent reaction to yield 5- aminoimidazole ribosyl 5 - phosphate.

Step - 7 → Incorporation of CO_2 (Carboxy-lation) occurs to yield aminoimidazole carboxylate ribosyl 5 - phosphate.

This reaction does not require the Vitamin biotin and ATP which is the case with most of the carboxlation reactions.

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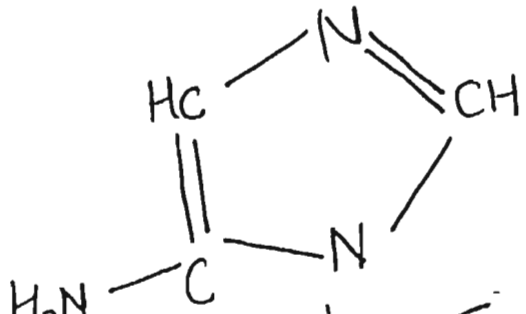
Formylglycineamidine ribosyl-5-phosph

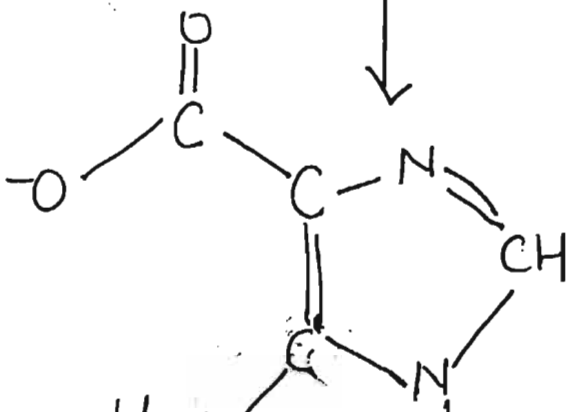
ATP → ADP + Pi + H2O (Synthetase)



Ribose 5-P

5-Aminomidazole ribosyl 5-phosphate

CO_2 → (Carboxylase)



Ribose 5-P

5-Aminoimidazole carboxylate ribosyl 5-pho

Aspartate + ATP → ADP + Pi (Synthetase)

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Step-8 Aspartate condenses with the product in reaction 7 to form aminoimidazole 4-Succinyl carboxamide ribosyl 5-phosphate.

Step-9 Adenosuccinate lyase cleaves off fumarate and only the amino groups of aspartate is retained to yield aminoimidazole 4-Carboxamide ribosyl 5-phosphate.

Step-10 N^{10}-formyl tetrahydrofolate donates a one-carbon moiety to produce formaminoimidazole 4-carboxamide ribosyl 5-phosphate with this reaction, all the carbon and nitrogen atoms of purine ring are contributed by the respective sources.

Step-11 The final reaction catalysed by cyclohydrolase leads to ring closure with an elimination of water molecules.
The product obtained is inosine monophosphate (IMP)

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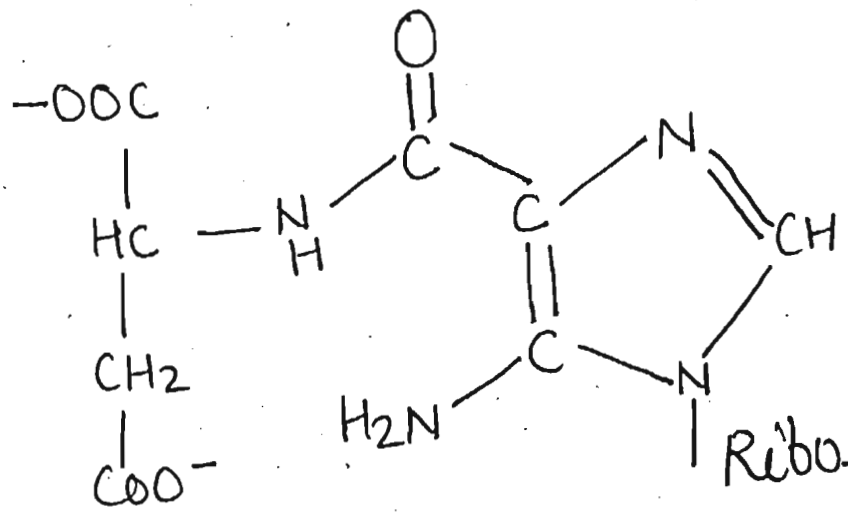
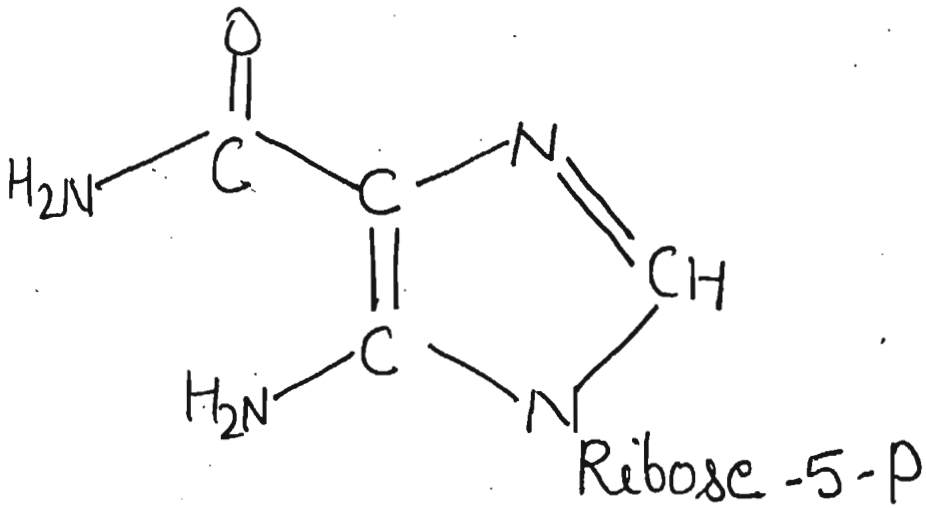


5- Aminoimidazole 4- Succinyl carboxam ribosyl 5- phosphate

Fumarate ← | Adenosuccinate lyase



5 - Aminoimidazole 4- carboxamide ribosyl 5- phosphate

N^{10}- formyl TH7 → TH7 | formyltransferase

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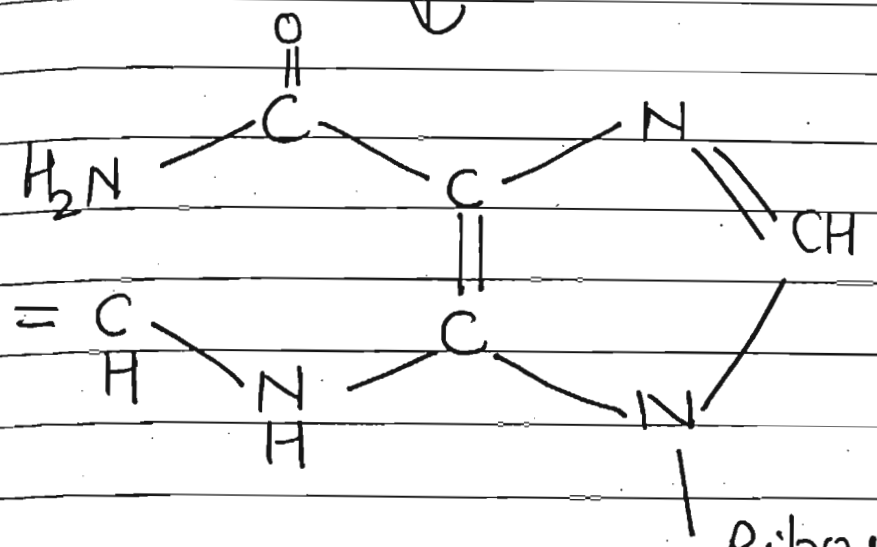
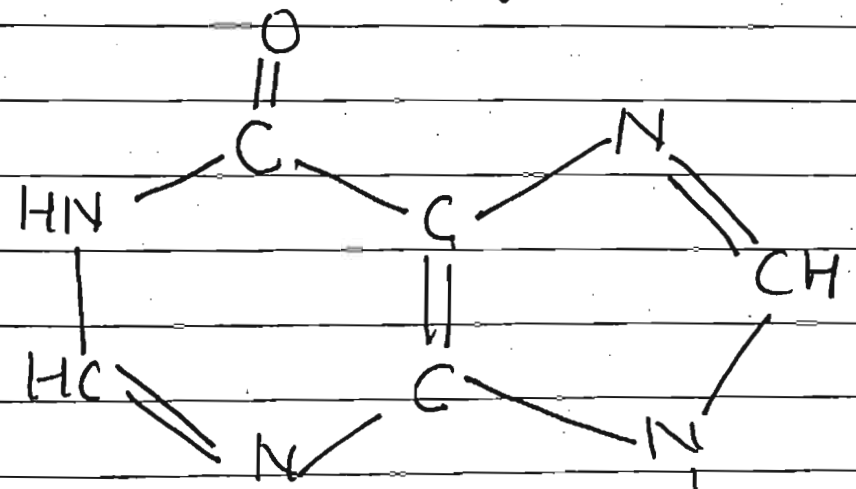


Ribose 5-p

5-formaminoimidazole 4-carboxam-
-die ribosyl 5-phosphate

H_2O ← cyclohydrolase



Ribose 5-p

Inosine Monophosphate

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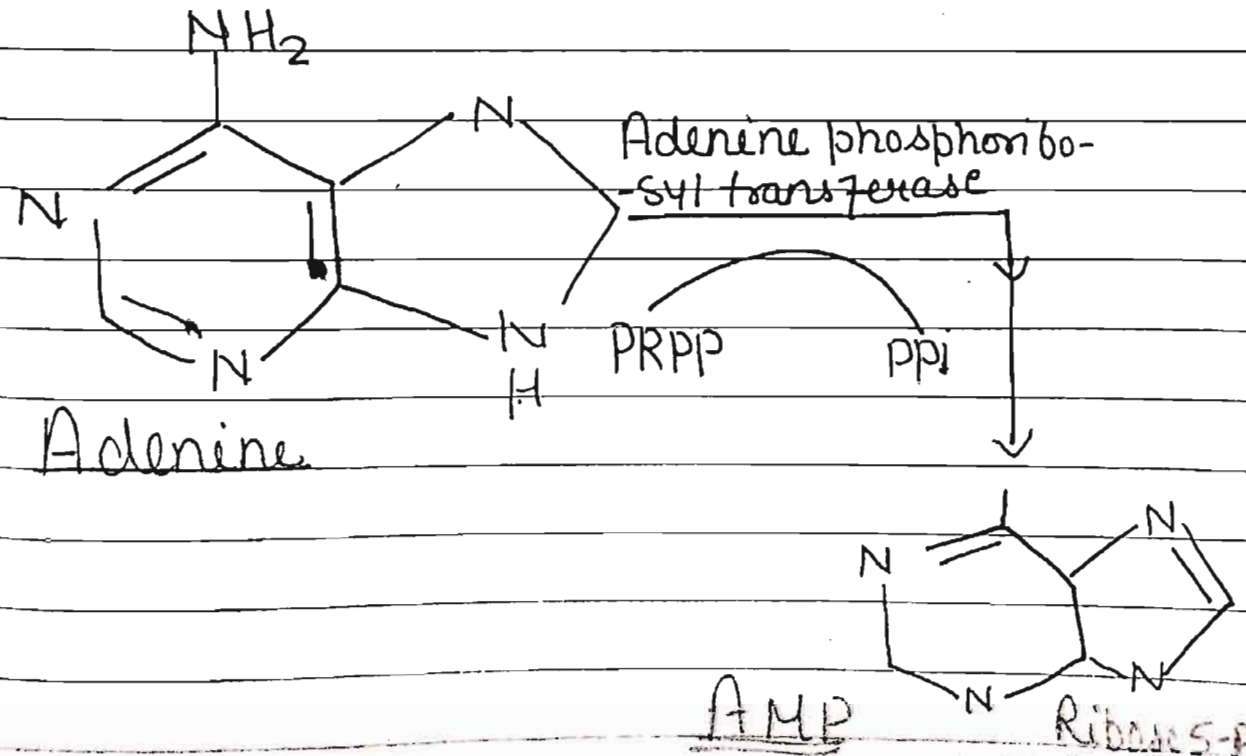
Salvage Pathway for Purine

The free purines (adenine, guanine & hypoxanthine) are formed in the normal turnover of nucleic Acid (particularly RNA), and also obtained from the dietary sources.

The purines can be directly converted to the corresponding nucleotides. and this process known as salvage pathway.

Adenine phosphoribosyl transferase catalyses the formation of AMP from Adenine.



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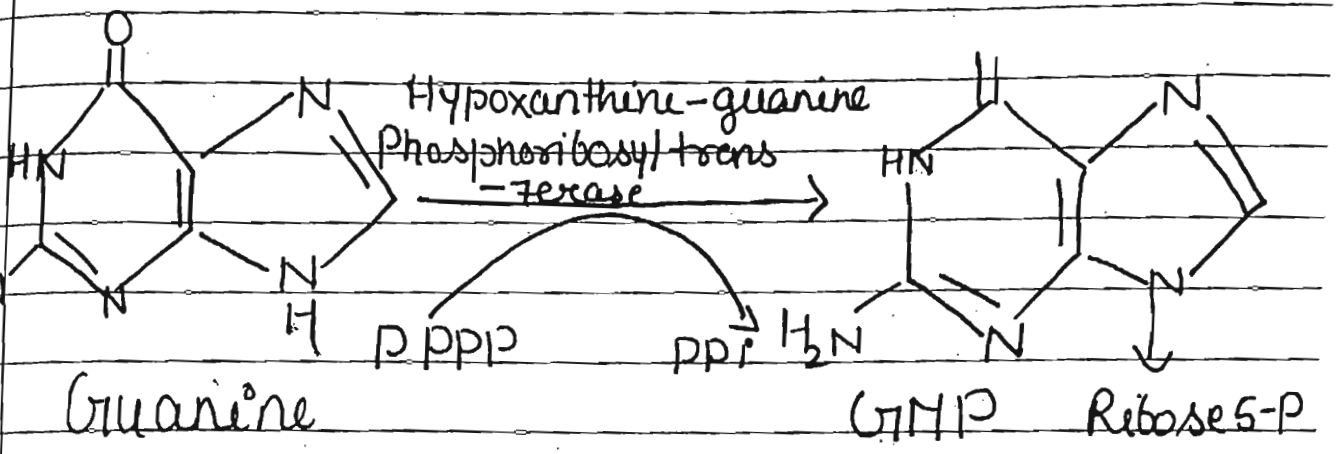
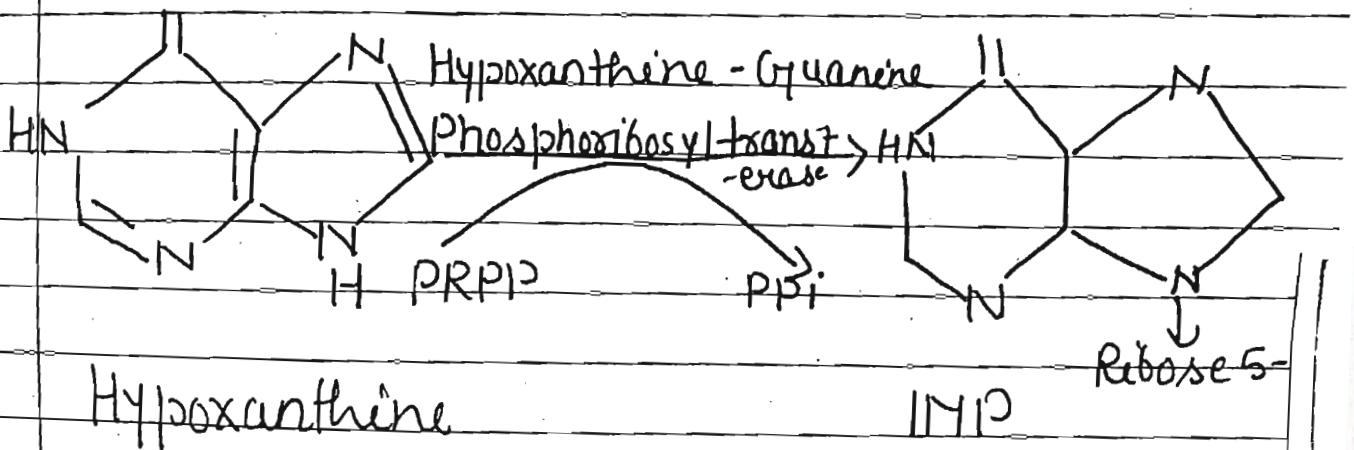
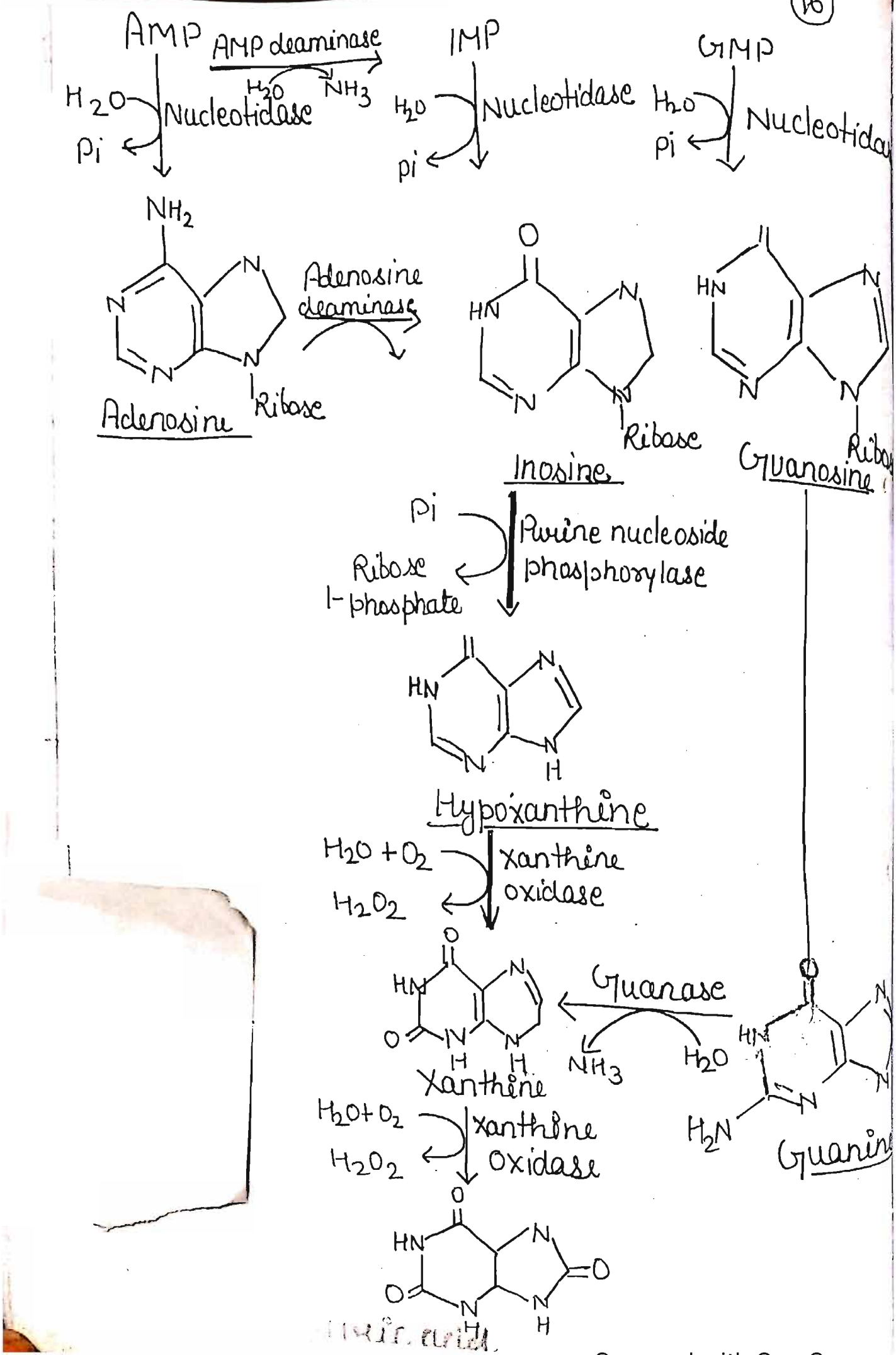
Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) converts guanine and hypoxanthine, respectively, to GMP and IMP.





Phosphoribosyl pyrophosphate (PRPP) is the donor of ribose 5-phosphate in the salvage pathway.



Topic 17 Date

Degradation of Purine Nucleo-tides

The end product of purine metabolism in humans is uric acid.

Step-I => The nucleotide monophosphate (AMP, GMP, IMP) are converted to their respective nucleoside form (adenosine, inosine, and guanosine) by the action of nucleotidase.

Step-II -> The amino group, either from AMP as adenosine can be removed to produce IMP or inosine respectively.

Step-III

Inosine and guasine are, respectively, converted to hypoxanthine and guanine (purine bases) by purine nucleoside phosphorylase.

Adenosine is not degraded by this enzyme, hence it has to be converted to inosine.

Step-4 => Guanine undergoes deamination by guanase to form xanthine.

Step-5 => Xanthine oxidase is an important enzyme that converts hypoxanthine to xanthine, and xanthine to uric acid.

This enzyme contains FAD, molybdenum and iron, and is exclusively found in liver and small intestine.
Xanthine oxidase liberates H_2O_2 which is harmful to the tissue.

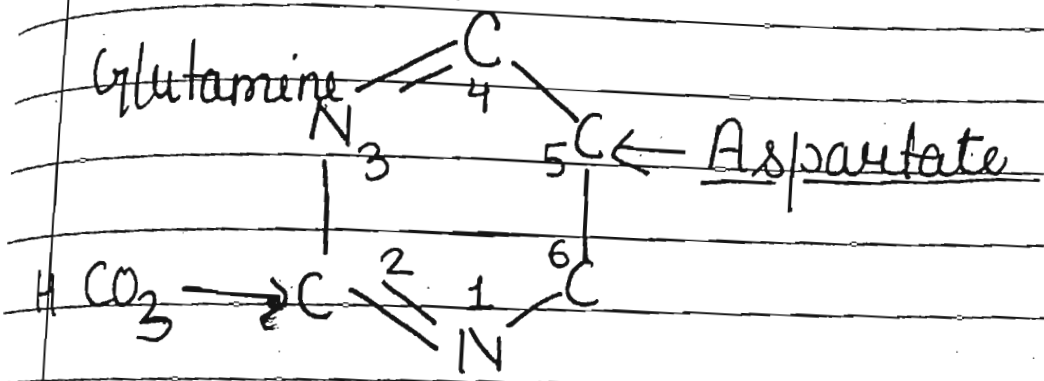
Uric acid (2,6,8-trioxypurine) is the final excretory product of purine metabolism in humans.

Topic 19 Date

BIOSYNTHESIS OF PYRIMIDINE

The synthesis of Pyrimidines is a much simpler process compared to that of purines

Aspartate, Glutamine and CO_2 contribute to atoms in the formation of pyrimidine ring.



Pyrimidine ring is first synthesized and then attached to ribose 5-phosphate

Isotopic labeling experiments have shown that atoms N_1, C_4, and C_6 of the pyrimidine ring are all derived from aspartic acid C_2 arises from HCO_3, and N_3 is contributed by Glutamine.

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Metabolic Pathway

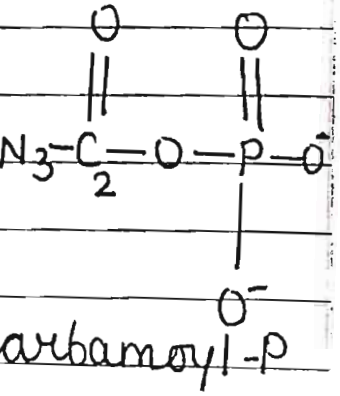
STEP-1: Synthesis of Carbamoyl phosphate

The first reaction of pyrimedine biosynthesis is the synthesis of carbamoyl phosphate from bicarbonate ion and the amide nitrogen of Glutamine by the cytosolic enzyme Carbamoyl phosphate Synthetase II (CPSII). This reaction is unusual in that it does not use biotin and Consumes two molecule of ATP:

One provides a phosphate group and the other energizes the reaction.

Step-I

$$HCO_3^- + \text{Glutamine} + 2\,ATP + H_2O \xrightarrow{CPSII} \underset{\text{Glutamate}}{} + 2\,ADP + P$$



Carbamoyl-P

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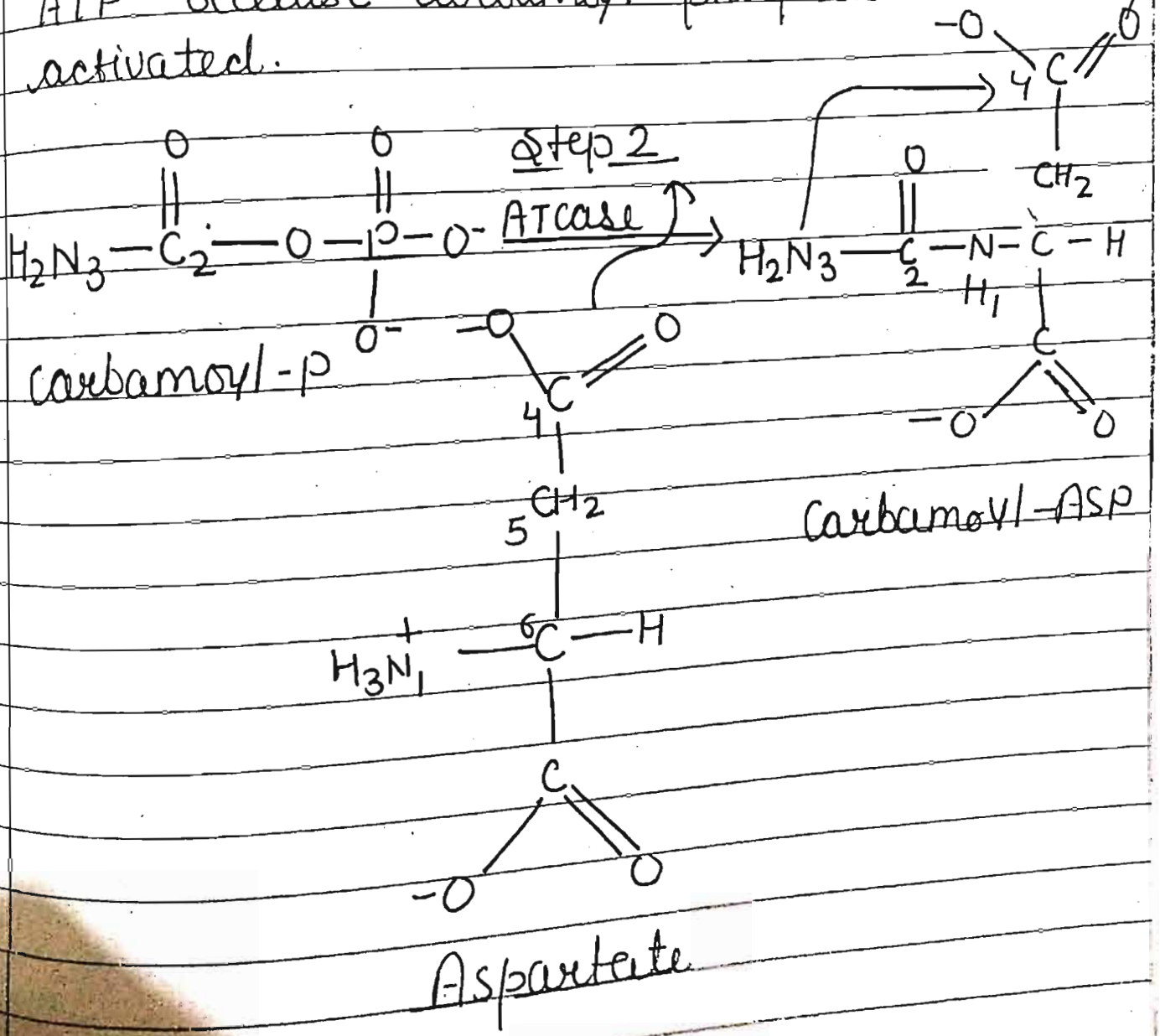
STEP 2:- Synthesis of carbamoyl Aspar-tate

Condensation of carbamoyl phosphate with aspartate to form carbamoyl aspartate is catalyzed by aspartate transcarbamylase (ATcase)

This reaction occurs without need of ATP because carbamoyl phosphate intrinsically activated.



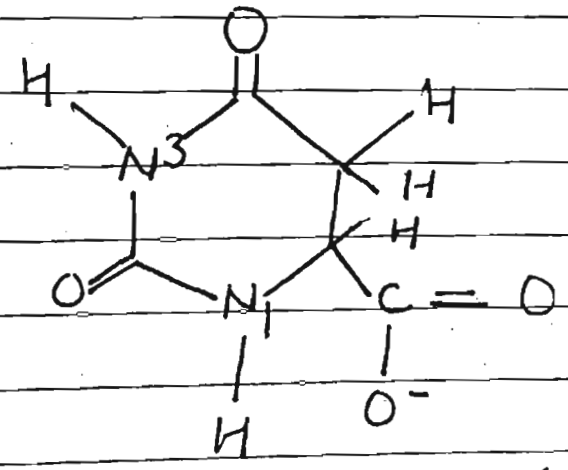
Step-3:- Ring Closure to form dihydro-orotate.

The third reaction of pathway forms the pyrimidine ring yielding dihydroorotate in an intramolecular condensation catalysed by the zinc metalloenzyme dihydroorotase.

Step-3

Carbamoyl-Asp

Dihydroorotase, OH^-



Dihydroorotate (DHO)

Step 4:- Oxidation of dihydroorotate

The hydro orotate irreversibly oxidized to orotate by the enzyme Dihydro orotate Dehydrogenase.

The Eukaryotic enzyme, which contains FMN and non-heme iron, is located on the outer surface of the inner mitochondrial membrane where quinines supply its oxidizing power.

Dihydro orotate + Quinone → Orotate + Reduced Quinone

Step-5 Decarboxylation to form UMP

The final reaction of the pathway is the decarboxylation of OMP by the OMP decarboxylase to form UMP this is an unusual reaction in that it requires no cofactors.

$$OMP \rightarrow UMP + CO_2$$

End.