CARBOHYDRATES

Structural elucidation of glucose – Open chain structure of Glucose

1. Molecular formula of glucose is $C_6H_{12}O_6$
2. When treated with Acetic anhydride, glucose forms penta-acetyl derivative which indicates the presence of 5 –OH groups. As glucose is stable compound, the 5 –OH groups must be on 5 different Carbon atoms.

$$\underset{\text{Glucose}}{C_6H_{12}O_6 \equiv C_6H_7O(OH)_5} + 5.\ \begin{matrix}CH_3CO\\CH_3CO\end{matrix}\!>O \xrightarrow[-5CH_3COOH]{} \underset{\text{Penta acetyl derivative}}{C_6H_7O(O.COCH_3)_5}$$

3. On reduction with Conc HI and Red phosphorus, glucose gives 2-iodohexane and n-Hexane, This indicates that six Carbon atoms in glucose are present in a straight chain.

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \xrightarrow{HI/\text{Red P}} \underset{\text{n-Hexane}}{CH_3-(CH_2)_4-CH_3}$$

4.
a) Glucose reacts with HCN forms cyanohydrin
b) Glucose reacts with Hydroxylamine gives oxime
The above two reactions indicate that Glucose has Carbonyl group.

a) $C_5H_{12}O_5\}C=O + HCN \longrightarrow \ >C<^{CN}_{OH}$ (cyanohydrin)

b) $>C=O + H_2N-OH \xrightarrow[-H_2O]{} \ >C=N-OH$ (oxime)

5.
a) Glucose reacts with Tollens reagent gives silver mirror.
b) Glucose reacts with Fehling solution gives red ppt.
c) Glucose when oxidised with Bromine water gives gluconic acid.
The above reactions Confirms the presence of aldehyde (–CHO) group in glucose.

$$C_5H_{11}O_5-CHO \xrightarrow{Ag_2O} C_5H_{11}O_5-COOH + 2Ag$$
$$C_5H_{11}O_5-CHO \xrightarrow{2CuO} C_5H_{11}O_5-COOH + Cu_2O\downarrow \text{PPT}$$
$$C_5H_{11}O_5-CHO \xrightarrow[(O)]{Br_2/H_2O} C_5H_{11}O_5-COOH.$$

6. Glucose on oxidation with Conc HNO_3, gives a dicarboxylic acid, (Glucosaccharic acid) which contains 6 Carbon atoms. This reaction provides information that glucose has an aldehydic group (–CHO) at one end and a 1° Alcoholic group ($-CH_2-OH$) on the other end.

$$C_6H_{12}O_6 \equiv CHO-C_4H_8O_4-CH_2OH \xrightarrow{(O);\ Conc\ HNO_3} COOH-C_4H_8O_4-COOH$$

Glucose — Dicarboxylic acid

7. To arrange on middle Carbon atoms there are still 4 Hydrogen atoms and four hydroxyl groups. Glucose is stable compound hence each carbon atom contains only one Hydroxyl group and one Hydrogen atom.

Based on the facts discussed above, glucose was assigned the following straight chain structure. It is called straight chain poly-hydroxy aldehydic structure.

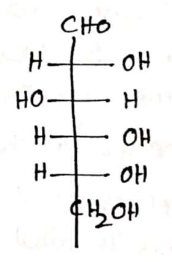
The proposed structure has *4 asymmetric Carbon atoms. The total number of optically active isomers were : 2^4 (4 = No. of chiral centers) = 16 out of 16 isomers 8 are dextro rotators and 8 are leavo isomers.

CHO
*CHOH
*CHOH
*CHOH
*CHOH
CH_2OH

Naturally occuring dextro rotatory glucose (+) glucose is one of the 16 stereoisomers.

Fischer represented the structure of D(+) Glucose with the cross formulation. The Horizontal lines project out towards the reader and vertical lines project behind the plane of the paper.

With the Cahn-Ingold-Prelog system of stereochemical designations, the open-chain form of D(+) Glucose is (2R,3S,4R,5R)-2,3,4,5,6-Pentahydroxy hexanal.



Anomers – Anomerisation In Glucose

Pyranose structure of Glucose

Haworth projections of Glucose

The open chain structure of glucose was converted to 6-membered cyclic structure. The cyclic forms of D(+) Glucose are hemiacetals formed by an intramolecular reaction of the $-OH$ group at C_5 with the aldehyde group. Cyclization creates a new stereogenic center at C_1, and this stereogenic centre explains how two cyclic forms are possible.

These two cyclic forms are diastereomers that differ only in the configuration at C_1.

In Carbohydrate chemistry diastereomers of this type are called anomers and C_1 Carbon is called Anomeric Carbon atom.

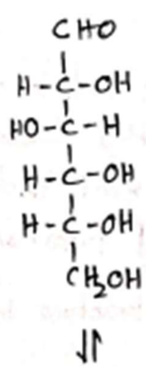
Each Glucose anomer is designated as α-Anomer (or) β-Anomer depending on the location of the $-OH$ group on C_1.

The α-anomer has the $-OH$ group trans to the $-CH_2OH$ group

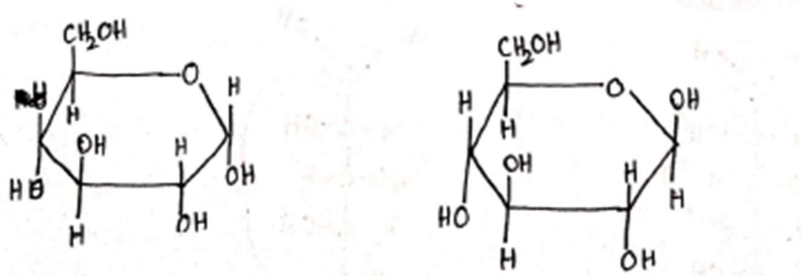
The β-anomer has the $-OH$ group cis to the $-CH_2OH$ group

α-Anomer is called α-(D)(+)-Glucopyranose.

β-Anomer is called β-D(+)-Glucopyranose.



Fischer projection Formula



HAWORTH FORMULA

α-Anomer

α-D-(+) Glucopyranose

β-Anomer

β-D-(+) Glucopyranose

Epimers – Epimerisation

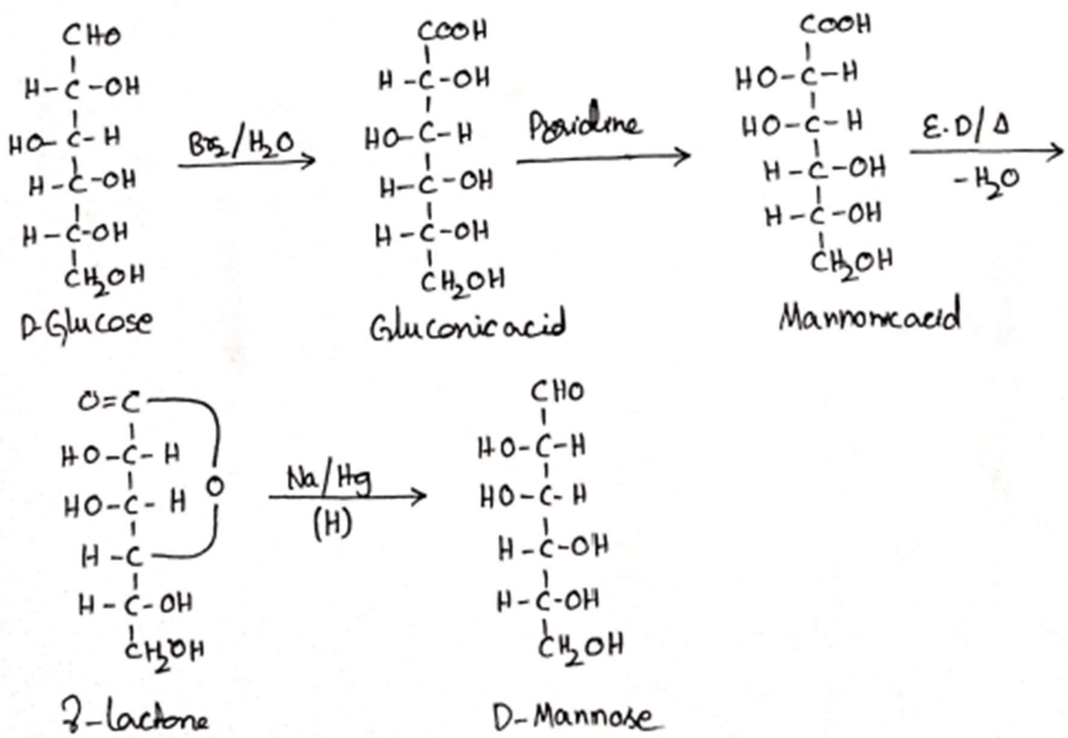
An epimer is one of a pair of diastereomers. The two epimers have opposite configuration at only one stereogenic center out of at least two. Here, The aldoses which differ in their configuration at only one stereogenic center are called epimers.

Example : 1. D-Glucose & D-Mannose (Differ at C_2)
2. D-Glucose & D-Galactose (Differ at C_4)

The process of conversion of one epimer into another is known as epimerisation.

Example : Conversion of D-Glucose to D-Mannose

1. Glucose on oxidation with Br_2/H_2O forms Gluconic acid.
2. It is treated with pyridine solution forms Mannonic acid
3. Mannonic acid on heating loses a water molecule forms γ-lactone
4. γ-lactone is reduced with Na/Hg forms D-Mannose.



Mutarotation in Glucose

α-(D)(+) Glucopyranose and β-(D)(+) Glucopyranose comes from the experiments in which both α & β forms have been isolated. When the optical rotations of these two forms are measured, they found to be significantly different.

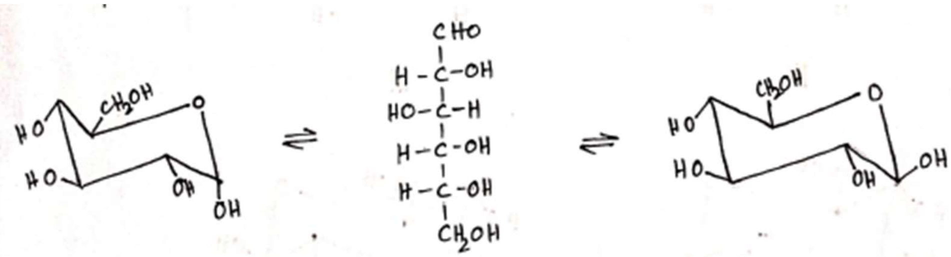
When the aqueous solution of either form is allowed to stand, its rotation changes.

The specific rotation of one form decreases and the rotation of other increases, untill both solutions show the same value.

Experimental studies reveals that, A solution of α-Glucose has an initial specific rotation of +112° but ultimately, the specific rotation of this solution falls to +52.7° and a solution of β-Glucose has an initial specific rotation of +19° but slowly the specific rotation of this solution raises to +52.7°.

The change in optical rotation of an optically active compounds is known as mutarotation.

explanation for mutarotation lies in the existence of an equilibrium b/w the open chain form and α & β forms of Glucose.



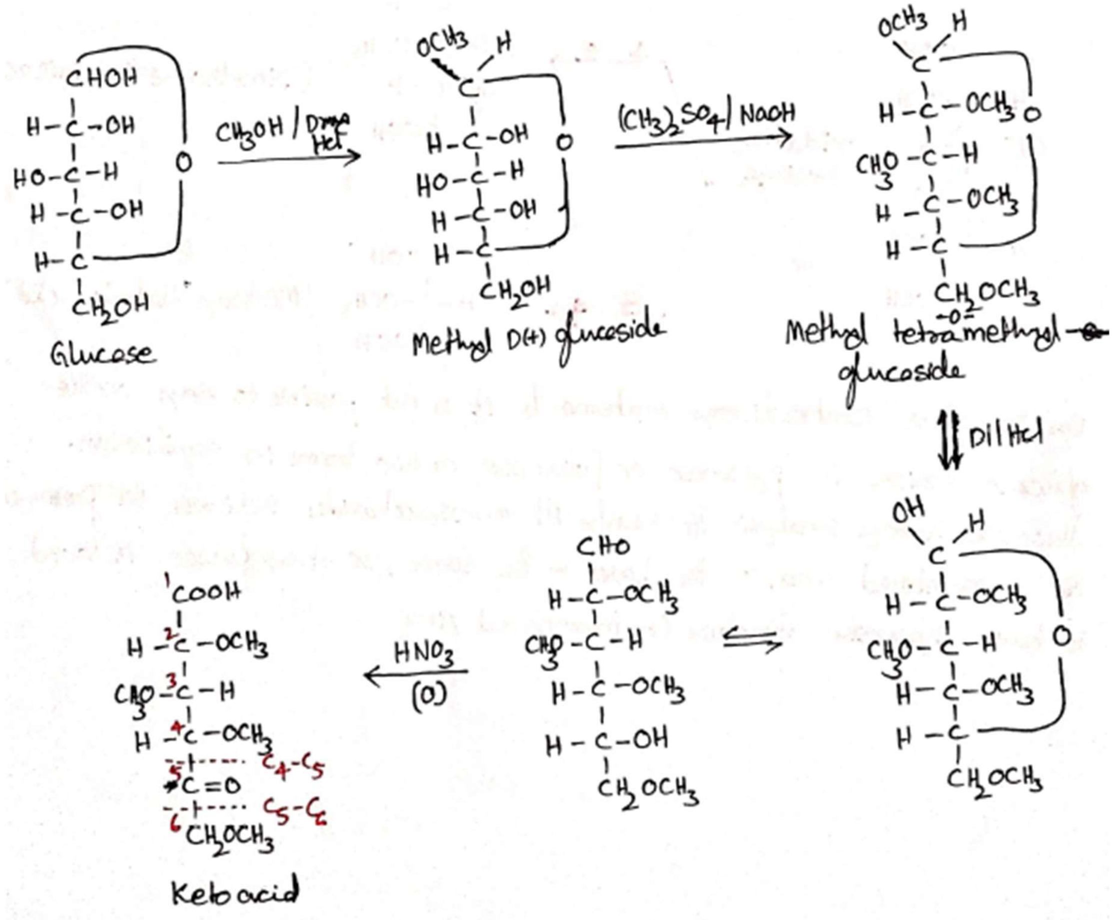
α-D-Glucopyranose $(\alpha)_D^{25} = +112°$ | open chain form of D(+) Glucose | β-D(+) Glucopyranose $(\alpha)_D^{25} = +19°$

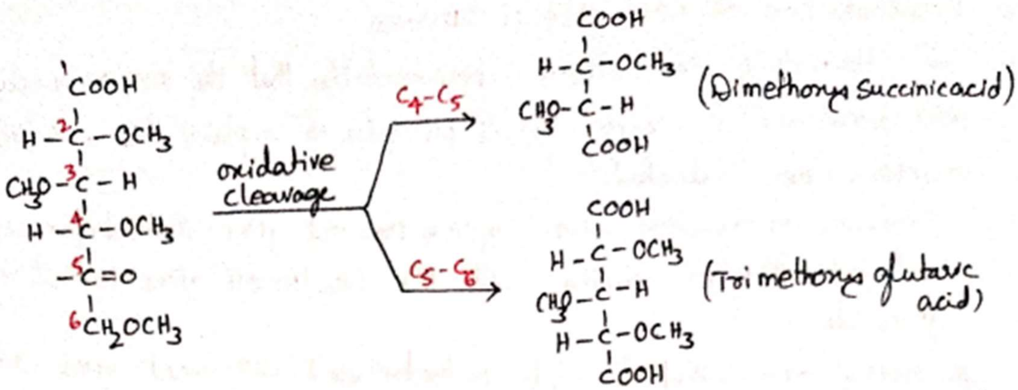
The Concentration of open chain st of glucose in solution at equilibrium is very small, whose concentration is neglected. At equilibrium the percentage of α-anomer is 36% and β-anomer is 64%, which shows that greater stability for β-anomer. This is expected on the basis of its having only equitorial groups.

Determination of ring size of glucose

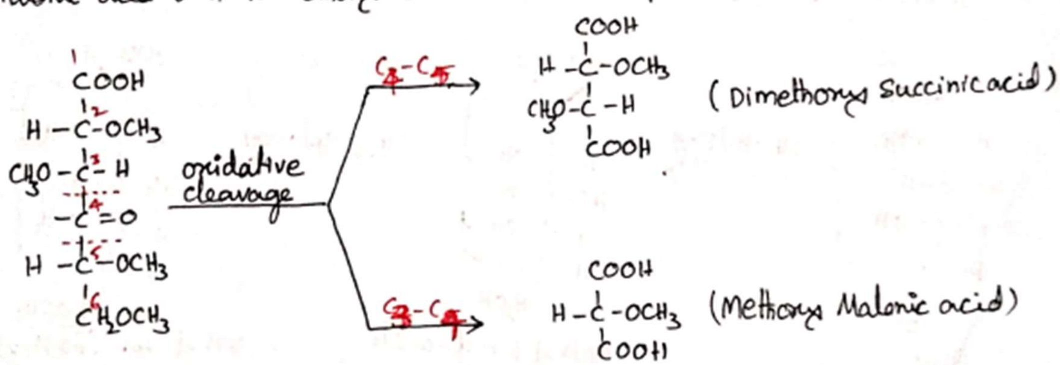
Haworth & Hirst shown experimentally that the ring in glucose and glucosides is six-membered. In order to explain this a series of reactions were conducted.

1. Glucose on reaction with CH_3OH & Dry HCl gives Methyl glucoside.
2. methyl glucoside on reaction with $(CH_3)_2SO_4/NaOH$ gives Methyl tetramethyl glucoside
3. Methyl tetramethyl glucoside is hydrolysed with acid gives Tetramethyl glucose
4. It is then oxidised with HNO_3 to form Intermediate Keto acid. which undergo oxidative cleavage at C_4-C_5 and C_5-C_6 gives Dimethoxy succinic acid and Trimethoxy glutaric acid respectively.





with an assumption that if the ring size of glucose is 5-membered and the above series of reactions were conducted. In the last step keto acid undergo oxidative cleavage at C_3-C_4 and C_4-C_5 gives methoxy malonic acid and Dimethoxy succinic acid respectively.



By the above contradictory statements it is not possible to say whether glucose exists in pyranose or furanose or two forms in equilibrium. However X-ray analysis of nearly all monosaccharides indicates the presence of 6-membered ring, on the basis of the same, α-D(+)glucose is found to have pyranose structure (6-membered ring).

Conformational structures of Glucose

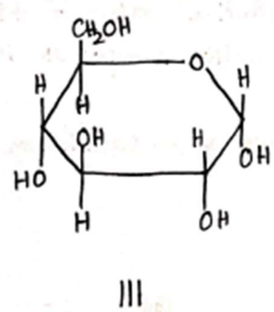
Haworth along with Hirst demonstrated the cyclic form of glucose consisting of 6-membered ring.

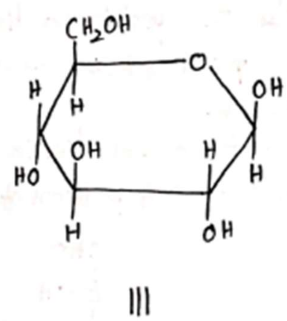
The cyclic forms of D(+) Glucose are hemiacetals formed by an intramolecular reaction of the -OH group at C_5 with the aldehyde group. Cyclization creates a new stereogenic center at C_1, which is responsible for two isomers (Anomers).

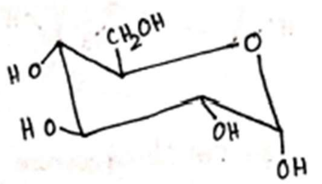
Anomers are the diastereomers that differ in the configuration at C_1

α- Anomer is called α- D(+) Glucopyranose which has the -OH group trans to the $-CH_2OH$ group.

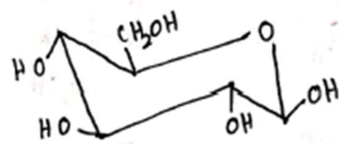
β- Anomer is called β- D(+) Glucopyranose which has the -OH group cis to the $-CH_2OH$ group.







α-D(+) Glucopyranose



β- D(+) Glucopyranose

X-ray analysis reveals that the actual conformations of the rings are the chair forms represented by the above conformational formulas.

It is interesting to note that in β- D(+) Glucopyranose, all the bulky substituents i.e -OH and $-CH_2OH$ are equitorial

In α- D(+) Glucopyranose, Bulky substituent i.e -OH on C_1 is axial and the rest of the bulky substituents are equitorial.

Structural Elucidation of Fructos
OR
Open chain structure of Fructo:

1. Molecular formula of Fructose is $C_6H_{12}O_6$

2. When treated with Acetic anhydride, Fructose forms penta-acetyl derivative which indicates the presence of 5-OH groups. As Fructose is stable compound the 5-OH groups must be on 5-different carbon atoms.

$$C_6H_{12}O_6 \equiv C_6H_7O(OH)_5 + 5.\ \begin{matrix} CH_3-CO \\ CH_3-CO \end{matrix}\!\!>O \xrightarrow[-5CH_3COOH]{} C_6H_7O(O.COCH_3)_5$$

Penta acetyl derivative

3.
a) Fructose reacts with HCN forms cyanohydrin
b) Fructose reacts with Hydroxylamine gives oxime.
The above two reactions indicate that Fructose has carbonyl group

a) $>C=O + HCN \longrightarrow >C<^{CN}_{OH}$ (cyanohydrin)

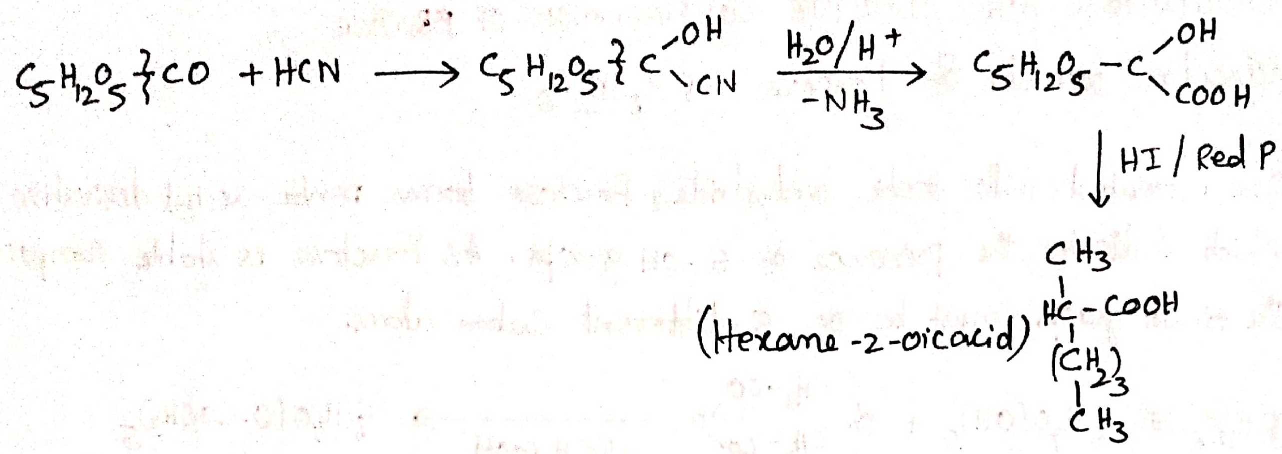
b) $>C=O + H_2N-OH \xrightarrow[-H_2O]{} >C=N-OH$ (oxime)

4.
a) Fructose doesnot oxidises with Bromine water [(O) / Br_2/H_2O]
b) Fructose on oxidation with Conc HNO_3 gives Formic acid, Trihydroxy glutaric acid, Glycolic acid and Tartaric acid. This confirms the presence of Ketonic group in Fructose.

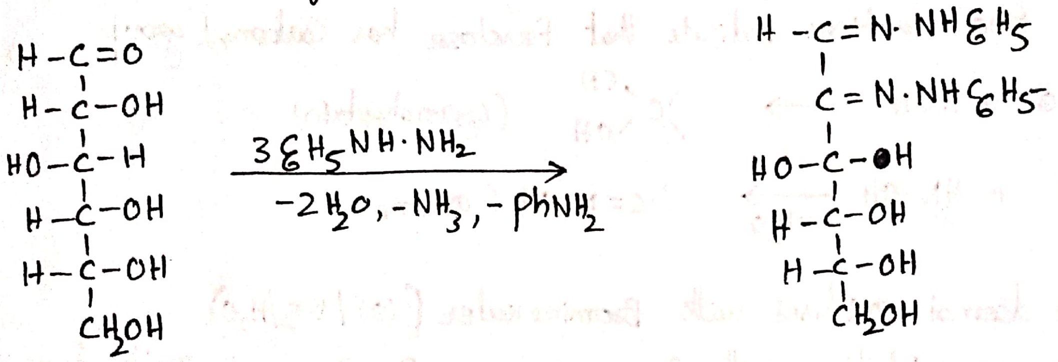
$$C_6H_{12}O_6 \xrightarrow{(O);\ Conc\ HNO_3} HCOOH + COOH-CHOH-CHOH-CHOH-COOH + CH_2OH-COOH + COOH-CHOH-CHOH-COOH$$

Formic acid; Trihydroxy glutaric acid; Glycolic acid; Tartaric acid

5. Fructose reacts with HCN, forms fructose cyanohydrin. On hydrolysis and reduction with HI and Red P, forms Hexane-2-oicacid. This reaction confirms the presence of Keto group on 2nd carbon atom.

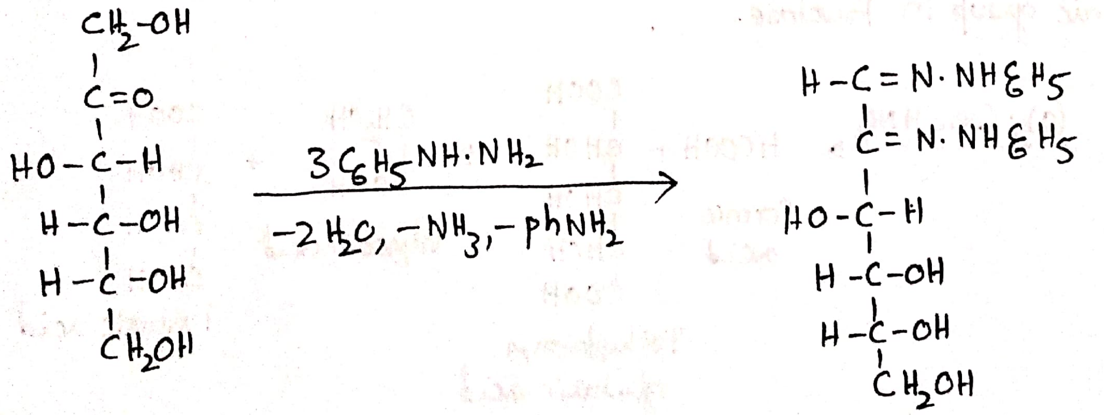


6. Glucose & Fructose reacts with phenyl hydrazine forms same osazone In this reaction C_1 & C_2 are involved. It states that the glucose & fructose have same configuration on C_3, C_4, C_5 & C_6 atoms.



Glucose

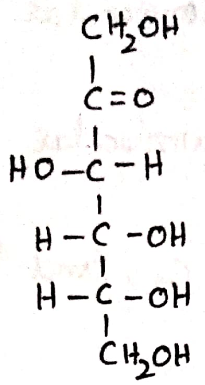
Glucosazone



Fructose

Fructosazone

Based on the above reactions, the open chain structure of fructose is



Furanose and Pyranose structures of Fructose

The open chain structure of fructose was converted to 5-membered and 6-membered cyclic structure.

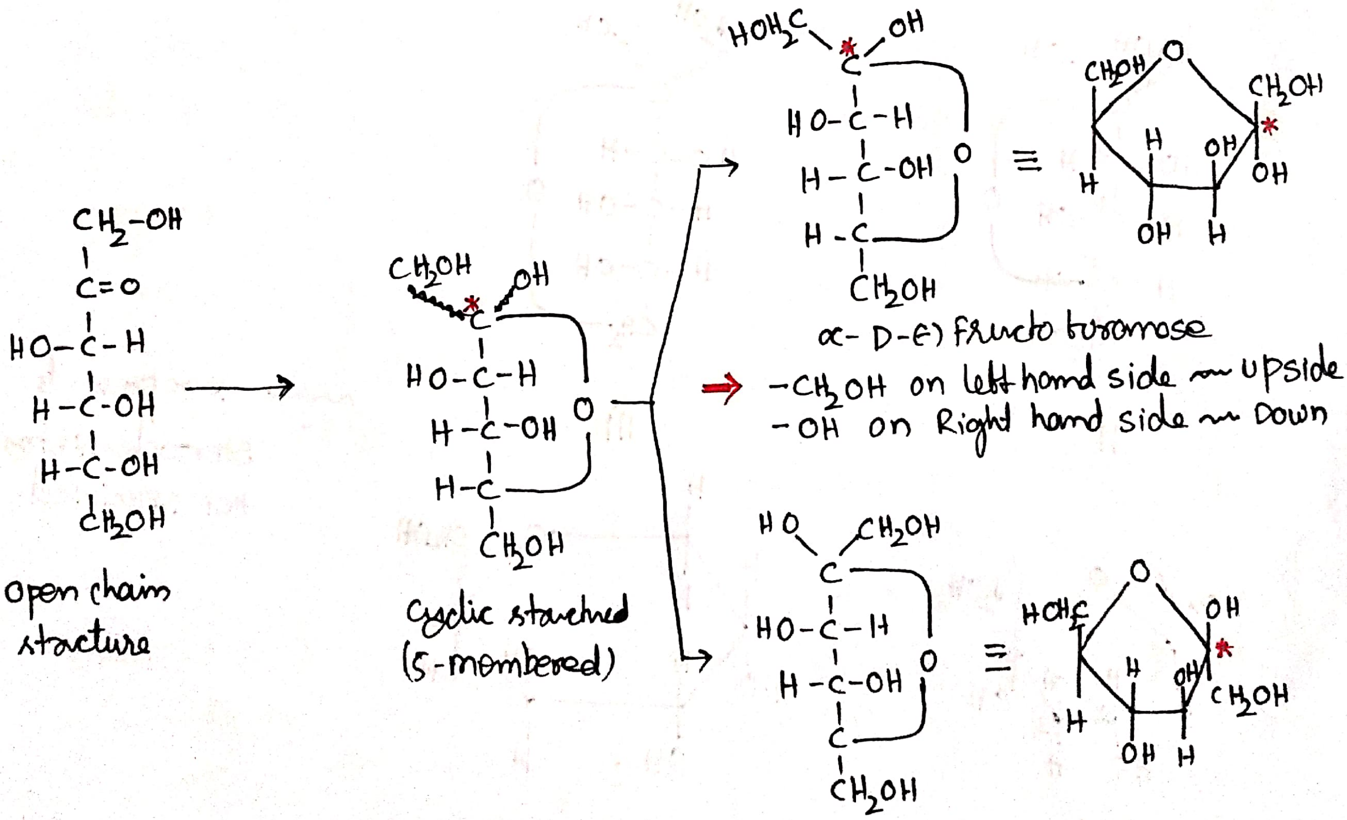
5-membered cyclic structure is formed by an intramolecular reaction of the -OH group at C_5 with the ketonic group.

6 membered cyclic structure is formed by an intramolecular reaction of the -OH group at C_6 with the ketonic group.

Cyclization creates a new stereogenic center at C_2, (and this stereogenic center explains)

5-membered cyclic structure
- → α-Anomer – α-(D)(-) Fructofuranose
- → β-Anomer – β-(D)(-) Fructofuranose

6-membered cyclic structure
- → α-Anomer – α-D(-) Fructopyranose
- → β-Anomer – β-D(-) Fructopyranose

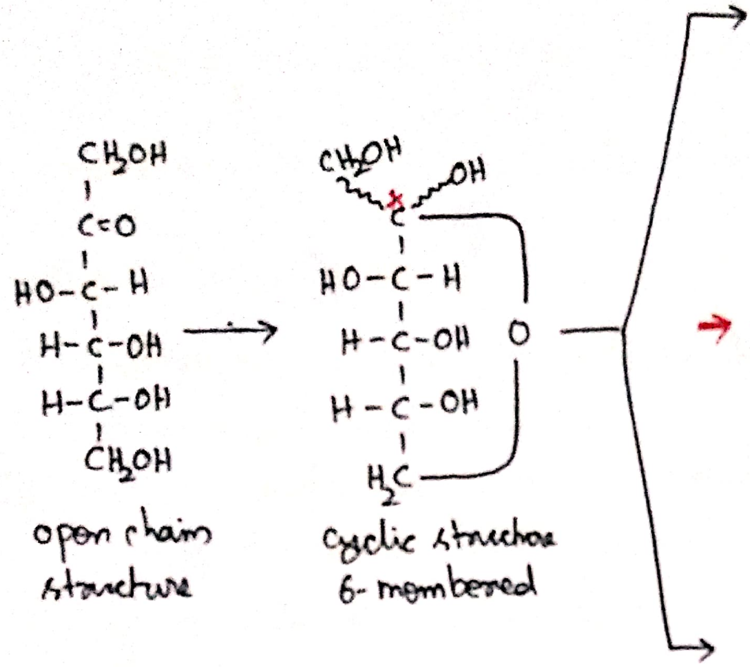


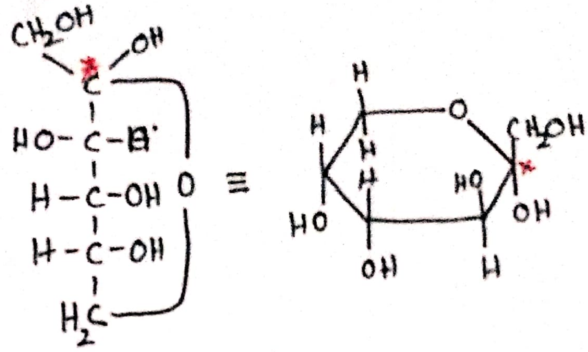
α-D-(-) Fructofuranose

→ -CH_2OH on left hand side ~ upside
-OH on Right hand side ~ Down

β-D(-) Fructofuranose

→ -CH_2OH on Right hand side ~ Down
-OH on left hand side ~ upwards

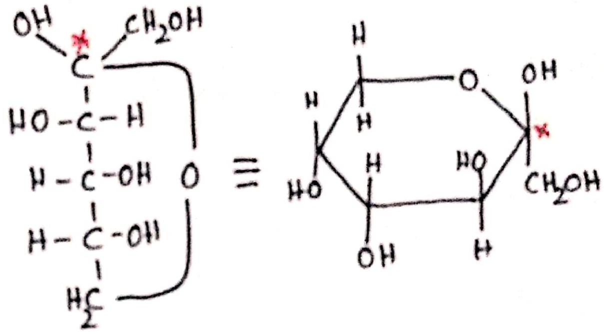




α- D(-) Fructo pyranose

→ $-CH_2OH$ on left hand side ~ upwards

$-OH$ on Right hand side ~ down



β- D(-) Fructopyranose

→ $-CH_2OH$ on right hand side ~ down

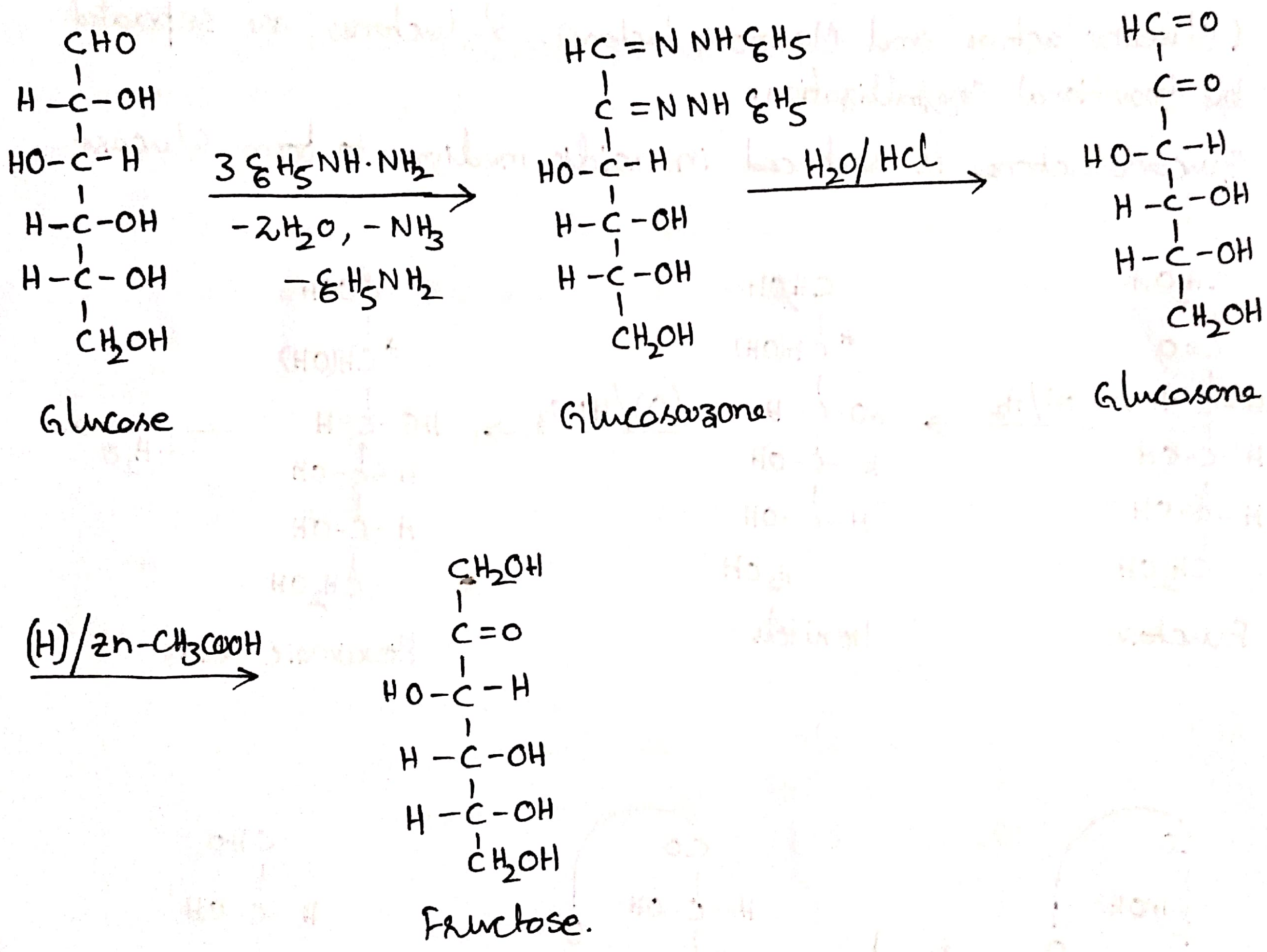
$-OH$ on left hand side ~ upwards

CONVERSION OF ADLOHEXOSE TO KETOHEXOSE

OR

CONVERSION OF GLUCOSE TO FRUCTOSE

1. Glucose is warmed with excess of phenyl hydrazine to form Glucosazone.
2. Glucosazone is hydrolysed with Conc HCl to give Glucosone
3. Glucosone is reduced with Zn/CH_3COOH gives Fructose.

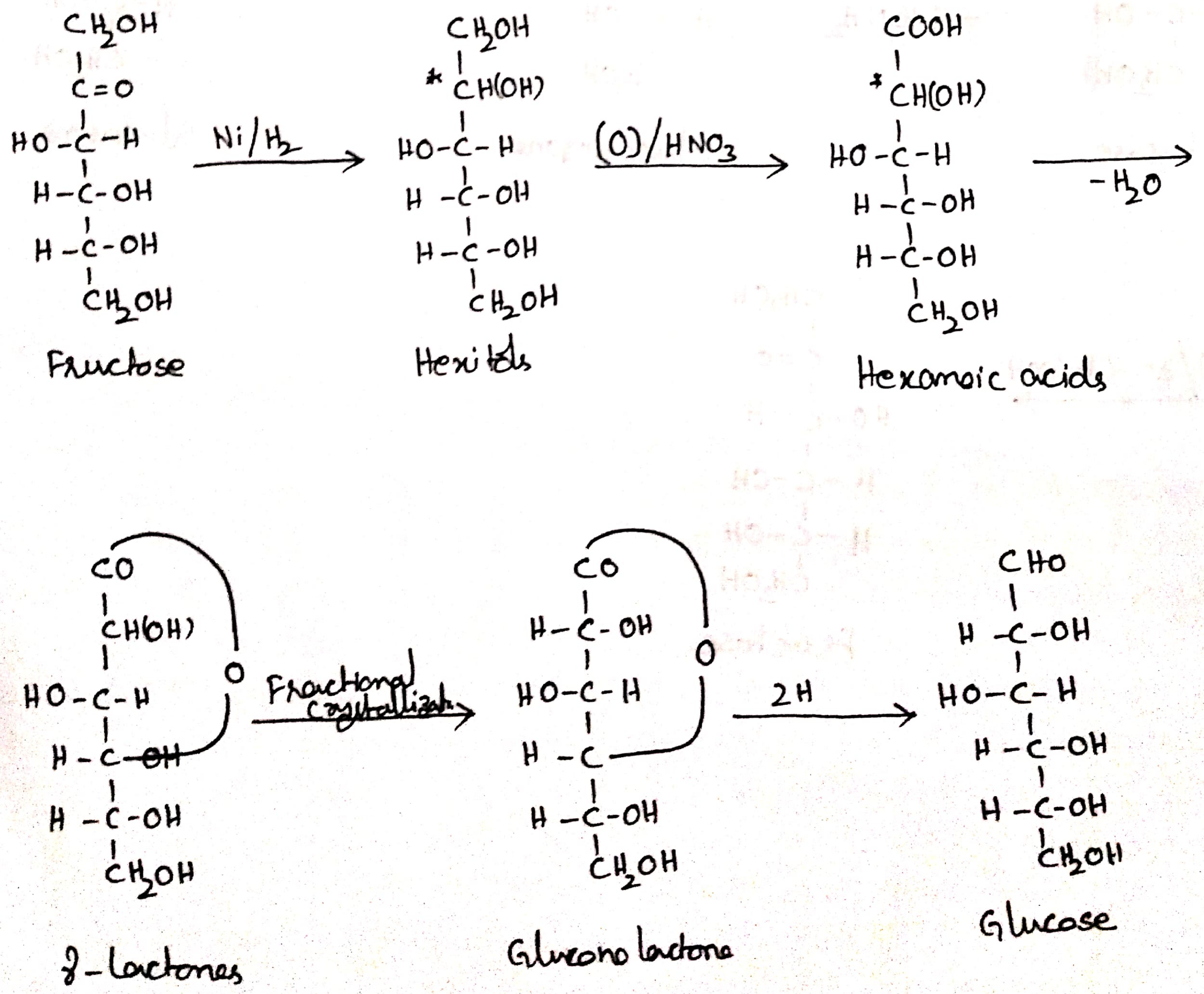


CONVERSION OF KETOHEXOSE TO ALDOHEXOSE

(OR)

CONVERSION OF FRUCTOSE TO GLUCOSE

1. Fructose is Catalytically reduced to give a mixture of sorbitol and mannitol (Hexitols)
2. The mixture of Hexitols is oxidised with HNO_3 to form a mixture of Hexanoic acid (Gluconoic acid and Mannonic acid).
3. These acids immediatly lose a molecule of water forming δ-lactone (Glucono lactone and Mannono lactone). δ-lactones are seperated by fractional crystallization.
4. Glucono lactone is reduced in acidic medium to form Glucose



CONVERSION OF ALDOPENTOSE TO ALDOHEXOSE

(OR)

CONVERSION OF ARABINOSE TO GLUCOSE

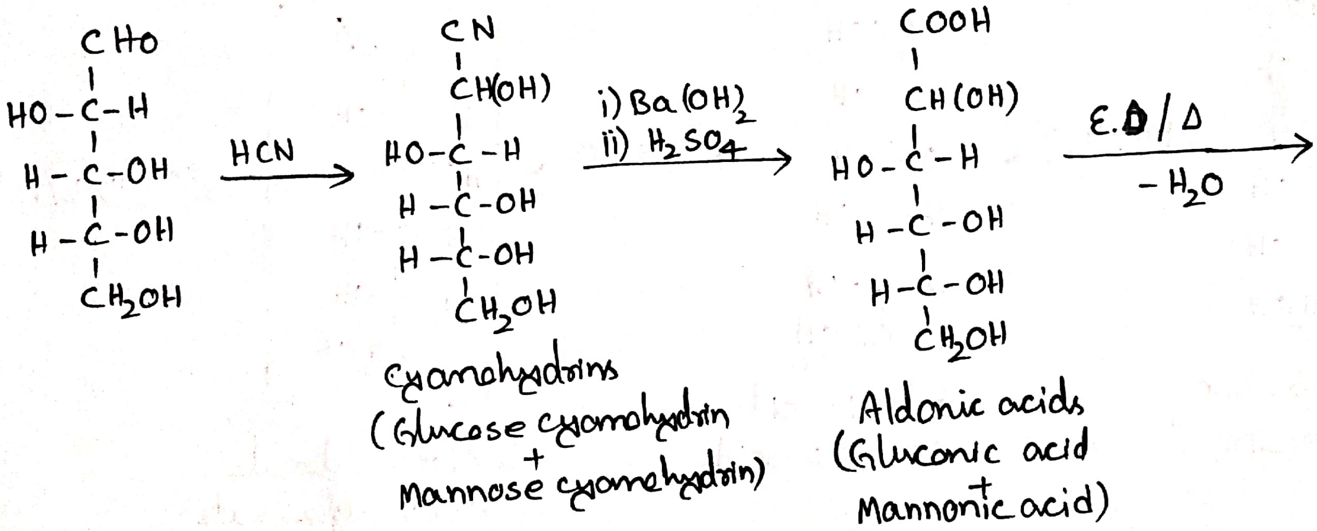
(OR)

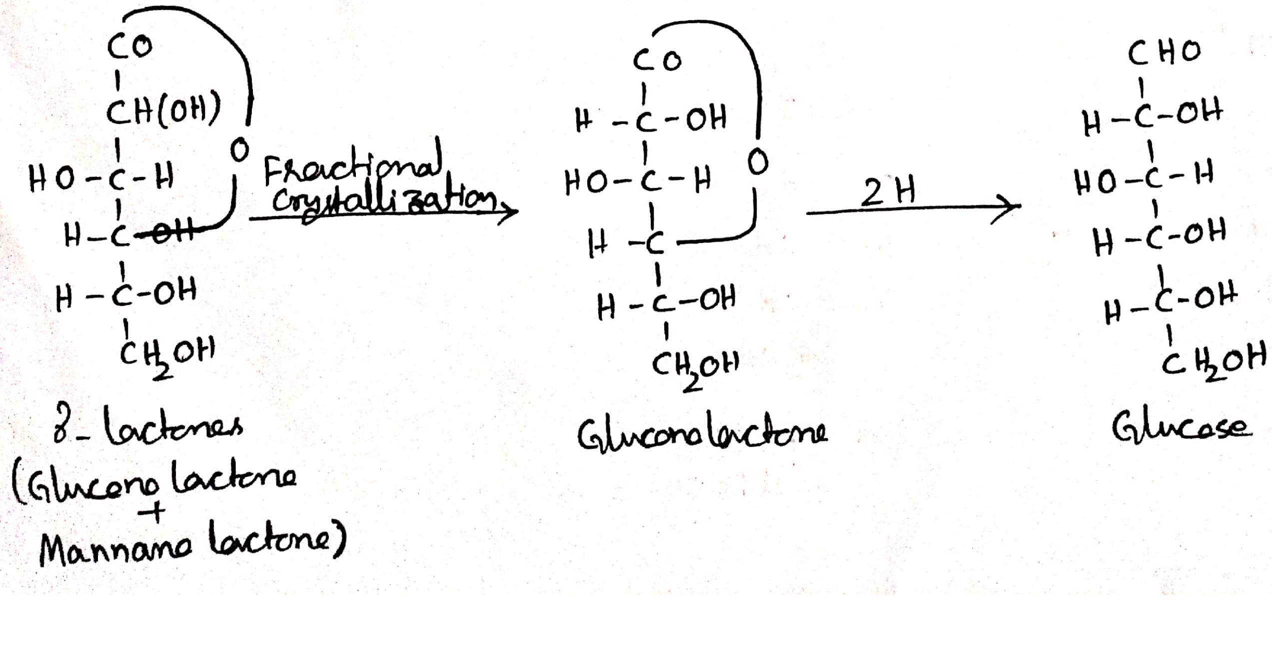
CONVERSION OF AN ALDOSE TO NEXT HIGHER ALDOSE

(OR)

KILIANI'S SYNTHESIS

1. The Aldopentose (Arabinose) reacts with Hydrogen cyanide (HCN), forms a mixture of two stereoisomeric cyanohydrins.
2. The mixture of cyanohydrins are hydrolysed with $Ba(OH)_2$ give a mixture of Aldonic acids.
3. The mixture of aldonic acids are evaporated to dryness, gives a mixture of γ- lactones. Which are then separated by fractional crystallization
4. Gluconolactone is reduced in acidic medium gives Aldohexose (Glucose)





CONVERSION OF ALDOHEXOSE TO ADLOPENTOSE

(OR)

CONVERSION OF GLUCOSE TO ARABINOSE

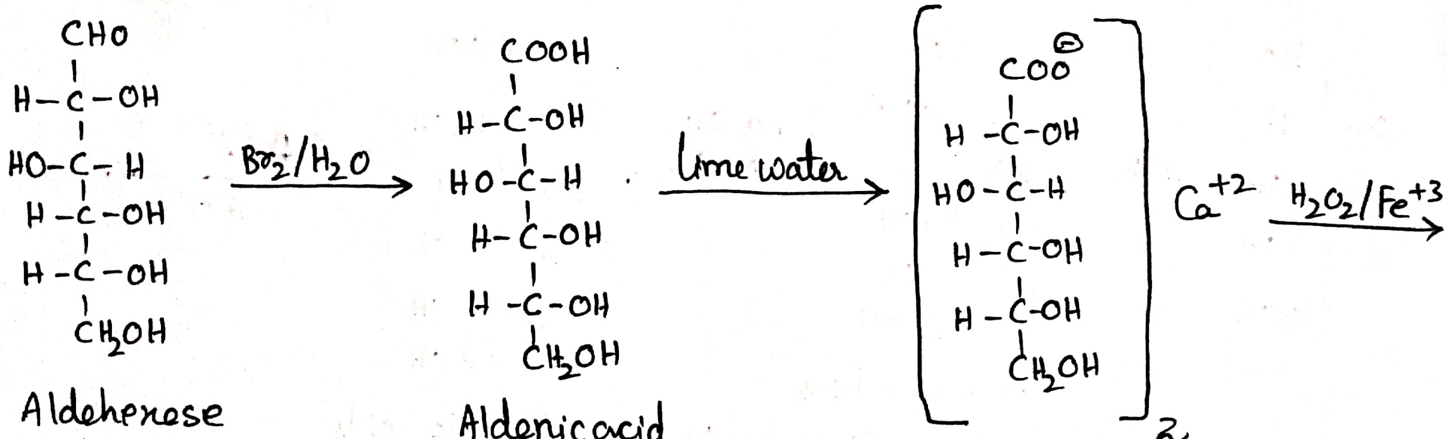
(OR)

CONVERSION OF AN ALDOSE TO NEXT LOWER ALDOSE

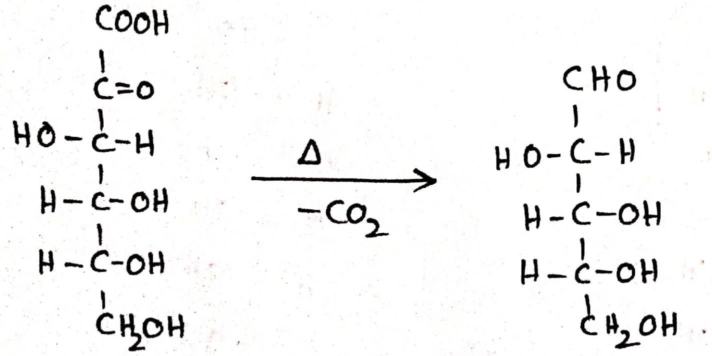
(OR)

RUFF'S DEGRADATION

1. Aldohexose (Glucose) is oxidised with Bromine water to form aldonic acid (Gluconic acid)
2. Aldonic acid (Gluconic acid is treated with lime water to form Calcium aldonate (Calcium gluconate)
3. Calcium aldonate (calcium gluconate) is oxidised with Fenton's reagent (H_2O_2 + Ferrous salt) to form keto acid.
4. Keto acid is readily decarboxylated to the next lower aldose (Arabinose)



Aldohexose (Glucose) — Aldonic acid (Gluconic acid) — Calcium aldonate (Calcium gluconate)



Keto acid — Aldopentose (Arabinose)