

A warm welcome to all the viewers of this video, this online lecture series is brought to you by director of Higher Education, Government of Goa under the initiative. DISHTAVO. Dr. Mira Parmekar, assistant professor in chemistry at St. Xavier's College- Mapusa, and today I'll be talking on the module for the TY students, Which comes in the paper CHC 107. That is organic chemistry, in the section A and the module is from Unit 2, that is Alkaloids, named - Structure, Elucidation and Synthesis of Papaverine. And I'll be doing the part 3 of this module. The outline of the presentation, we will be introducing the topic, then will go slightly in the background to revise what has been already covered in the module 1 and 2 of this particular topic then will do the final structure elucidation of the last part that is remaining, will infer what is obtained from the structural elucidation of all the fragments. Then, once the structure is confirmed, will go for the synthesis and then finally Summarize. The learning outcomes, Students do check at the end of the module. You should be able to fulfill all the outcomes that are listed here. That is, to understand the given structure

of the alkaloid. Analyzed this structure. Co-relate the various strategies which are used to give the proper structure of the molecule, And imply the same and analyze unknown molecules.

So to start with Papaverine, it is a benzyl isoquinoline alkaloid which is also called mesotina, or carespan, this compound does not contain any asymmetric carbon, so it is optically inactive. Likewise, many of the alkaloids. The structure was established by Goldschmiedt and others somewhere in the year 83 to 88 and the first synthesis of this particular alkaloid was reported by Pictet and Gams in the year 1909. Now why do we need to study this?

It has to have some importance. This alkaloid has many medicinal importance. It is an antispasmodic which is used primarily in the treatment of visceral spasm, an vasospasm..

It works by dilating blood vessels, thereby lowering the blood pressure and allowing more blood to flow through arteries and vein. And mostly the one form which is used is the hydrochloride salt of this particular molecule. For the medicinal use. So if you have.

understood this. OK, let's go to the background. Whatever we have studied in the part 1 and Part 2 of the module. So, so far what

we know is the molecular formula. Molecular formula is $C_{20}H_{21}O_4N$. Then we also know the nitrogen which is present here. OK, it is a tertiary nitrogen that is confirmed. We also know the functionality of Oxygen. All the oxygens which are present in this molecule. They are 4 methoxy groups that is O-Me. And when this molecule is reacted with cold diluted $KMnO_4$, this molecule resulted in an secondary alcohol, which gave us a ketone which basically told us the molecule has a methylene Group. That is connecting Group present in the structure. Also when the molecule was treated with hot, concentrated $KMnO_4$ there were four fragments formed from this molecule the structure of three of them have been already confirmed in the first 2 modules. That is veratric acid Pyridine- 2,3,4-tricarboxylic acid and meta-hemipinic acid. So this has been already covered. If you want to revise go to module 1 and 2 will come to the last part of this structure. Starting part is already done. The last part 6,7-Dimethoxyisoquinoline-1-carboxylic acid. This was the last fraction which resulted on oxidation with concentrated $KMnO_4$. Now this molecule was known to have One carboxylic acid and.

Two methoxy groups. This two information was available, So what was done was the researchers, They took the molecule and subjected to KMnO_4 oxidation and they found that the molecule gives a pyridine derivative which is having three carboxylic groups in 2, 3 and 4 position that told us that whatever this molecule is, that molecule contains a pyridine nucleus which is tri substituted OK.

Further, the same molecule when dehydrated with calcium oxide, it lost the molecule of CO_2 and gave the isoquinoline nucleus which has the two dimethoxy group in this particular position. So this also confirmed that the molecule doesn't have only pyridine nucleus, but it has a isoquinoline nucleus with two methoxy groups. This molecule, when further oxidized, KMnO_4 .

Give meta hemapinic acid. These two structures basically were confirmed from the earlier fragments, so if all this thing had to be true, the structure of 6,7-dimethoxy isoquinoline 1- carboxylic acid had to be this. Which on treating with KMnO_4 it will undergo cleavage. Here you get COOH COOH and this is already there. On treatment with Calcium oxide this molecule loses carbon dioxide which gives you the Iso.

quinoline nucleus, which further with KMnO_4 , there will be a cleavage. Here you get meta hemipinic acid. So the structure of 6,7-Dimethoxyisoquinoline-1-carboxylic acid was confirmed. So now we had the structure of Papaverine in two fragments. The two fragments were fragment A and fragment B. OK these two fragment basically have to combine. this fragment has 12 carbons. This segment has 9 carbons. So if I combine 9 and 12 where. I get 21 carbon, but what was known about Papaverine? In actual the Papaverine molecule has 20 carbons. So how to solve this mystery? The only way we can solve this mystery is if we consider this C_a carbon and this C_b carbon the same. Then we all have the structure. This is what we get and this carbon is nothing but the methylene carbon which was confirmed earlier. So this gives us the total structure of the molecule.

Up over in Marin, Papaverine has a molecular formula.

$\text{C}_{20}\text{H}_{21}\text{O}_4\text{N}$ If this has to be true, now how to confirm this structure? To confirm the structure, we have to synthesize it.

the simplest way is you synthesize the molecule. Then you take the molecule which is synthesized and compare the properties of the synthesized with the naturally occurring and see the properties are matching. Then we say the molecule.

Is molecule in consideration. So we go about the synthesis of Papaverine

OK, which is 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy

isoquinoline, which is the IUPAC name of the molecule. Now many

synthesis which are reported for this molecule. We will go about

simplest of them wherein we start with a very readily

available starting material. That is Veratrole which

is 1,2-dimethoxybenzene.

Now this molecule when treated with formaldehyde in presence of

HCl, we get the expected product that is the carbonyl

carbon is introduced onto the ring. You get 3,4-dimethoxy

benzyl chloride. So once this is treated with KCN, this chlorine

molecule or chloride will be replaced for the cyanide, giving

you 2-(3,4-dimethoxy phenyl) acetonitrile. Well, which is this

molecule? This molecule has

special importance. If this molecule we treat under two

different conditions, we get two intermediates and these

intermediates can condense together to give the main

structure of this molecule Papaverine. So in one set we

take the molecule and subject to reduction reaction using Raney

Ni catalyst and we get homoveratryl amine wherein the

cyanide is reduced to $\text{CH}_2\text{-NH}_2$. In the second set we take

the same molecule and subject to

hydrolysis. But in this CN will be converted to amide CONH₂,

which on treatment with PCl₅ will give you the corresponding

acid chloride. So you get homoveratryl chloride in the next

step. Both this intermediate are subjected to a famous name

reaction that is Bischler-Napieralski, wherein it is a

condensation reaction. So you will lose a molecule of HCl

from the amine and chloride. From here to give a condensed adduct

where in this.

Big molecule, which form basically the skeleton of the

Papaverine molecule will be formed. Once this molecule is

formed. The further step is simple. You treated with a

dehydrating agent like P₂O₅, and enolise the molecule. So this

Will go in tautomeric form wherein

OH will be formed here and this hydrogen here will be lost with

this OH and H accounting for one water molecule. The whole

molecule will cyclise

We're almost there, but this

is the dihydro Papaverine molecule. In the last step, We

take this molecule and it is oxidized using Palladium on

asbestos at a higher temperature. Where in this bond which is a

single bond is dehydrogenated to give a double bond wherein the Papaverine molecule is formed. This simple synthesis was given by Bide and Wilkinson.

In the year 1945. So in summary what we have learned building on the knowledge of part 1 and Part 2 of this module we added to that by doing the structure elucidation of 6,7-dimethoxyisoquinoline-1-carboxylic acid, to which then further we did the final structure confirmation by adding up the fragments and synthesizing the molecule by the Biden and Wilkinson synthesis. Overall, this is the synthesis you take veratrole, Convert it to 3,4-dimethoxy benzylchloride, which on treatment with KCN will give you this characteristic intermediate which under two different reaction sets gives you homoveratryl amine and homoveratryl chloride which can be also be called homoveratroyl chloride, there many names for this. This when subjected to Bischer-Napieralski will undergo condensation and then further enolisation will give the Dihydro Papaverine molecule Which on oxidation gives the final Papaverine. For reference, you can refer to I.L. Finar. There are two volumes for this volume 2 you can refer and there are many

editions. This is the third edition. The latest is 5th
edition, I think 2014 you can refer to these and this
video also will be helpful. Thank you so much.