Welcome students

In this session I'll be discussing unit IV, that is Chemistry of Heterocyclic Compounds. Module name is Electrophilic Substitution on C5/C8 positions in Quinoline and Isoquinoline and Module number is 30.

Outline of the module:
In this module, we will be discussing, structures of quinoline and isoquinoline, electrophilic substitution reactions of quinoline and isoquinoline, mechanism of electrophilic substitution reactions at different carbons in quinoline and isoquinoline, some examples of electrophilic substitution reactions in quinoline and isoquinoline and summary and then references.

Learning outcomes:
At the end of this module, the students will be able to:
Understand the electrophilic substitution reaction and its mechanism in quinoline and isoquinoline
Identify the favoured carbons or positions of quinoline and isoquinoline in electrophilic substitution reactions
Explain the reasons for the selective product formation in electrophilic substitution reactions in quinoline, and isoquinoline and also predict the major product of electrophilic substitution reactions in quinoline and isoquinoline.
So, first of all, we should know the structures of quinoline and isoquinoline. Here I have shown the structure of quinoline and in another box I have shown structure of isoquinoline. So these two compounds are bicyclic heterocyclic compounds which are having nitrogen heteroatom as a part of the ring. However, these two compounds are different from each other with respect to the position of this nitrogen atom. If you see the numbering, the numbering starts from nitrogen in quinoline and this nitrogen is given as number 1 followed by the carbons in the same ring, that is carbon 2, 3 and 4, directly the carbon 5, 6, 7 & 8 are numbered and the junction carbons are numbered is 4a and 8a. In the same way, when it comes to isoquinoline, carbon is numbered as 1 and nitrogen is numbered as 2 because the order has to be in a particular direction and then the carbons 3 and 4 are numbered of the same ring followed by carbons 5, 6, 7, 8 of the other ring and the junction carbons are numbered as 4a and 8a.
So let us see the favored electrophilic carbons or positions in quinoline.
Quinoline structure can be assumed as if it is a combination of two rings, that is, one is benzene ring which I have marked in blue color and the other ring is pyridine ring which I have marked in red color. So when electrophilic attack takes place, first the nitrogen lone pair will attack on the electrophile, as a result, the electrophilic addition at nitrogen takes place, which makes the pyridine ring electron deficient because the nitrogen will carry a + charge. As a result, the benzene ring becomes more electron rich than the pyridine ring and hence the electrophilic substitution occurs in benzene ring. But there are four positions in benzene ring where the electrophilic substitution can occur, out of which selectively the position 5 and position 8, the electrophilic substitution takes place. However, the other two positions, the electrophilic substitution is not preferred.

The same thing is applicable for isoquinoline. Isoquinoline also can be assumed as a combination of pyridine ring with the benzene ring and when electrophilic attack takes place, firstly the nitrogen lone pair

will pick up the electrophile and will get positively charged, making the pyridine ring electron deficient. As a result, benzene ring will undergo preferably the electrophilic substitution reaction and out of the four positions again carbon 5 and carbon 8 will undergo electrophilic substitution reaction. So on carrying out electrophilic substitution reaction, quinoline gives a mixture of 5-substituted quinoline product and 8-substituted quinoline product. In the same way, isoquinoline also undergoes reaction with electrophile to give a mixture of 5-substituted isoquinoline product and 8-substituted isoquinoline product.

Now we have to see why only these two positions, that is, C5 and C8 are preferred when it comes to electrophilic substitution reaction in quinoline. This can be explained from the mechanism. Here, when the electrophile is added to quinoline, first obviously the nitrogen lone pair will pick up the electrophile, making the aromatic ring that is pyridine ring less reactive, hence the further attack by carbon 5 and 6 double bond occurs on this electrophile to give this intermediate I. This intermediate can be further we can write another resonating structure for this by delocalizing the bond, as a result, the + charge comes on carbon 8. So we can write two resonating structures for this intermediate, hence it is more stable and finally the loss of this Hydrogen and the loss of this electrophile from the nitrogen gives us 5-substituted quinoline product. In the same way, when the electrophilic substitution takes place at C8 position in quinoline, firstly nitrogen lone pair will pick up the electrophile, and then the electrophilic attack at 8-position takes place, which gives intermediate I which can be written further by delocalising the double bond and hence + charge goes on carbon 5. Hence we get two resonating structures for this intermediate, which makes it more stable. As a result, finally, the loss of H+ ion gives us 8-substituted quinoline product. So both these attacks at C5 and C8 positions, they involve the delocalization of positive charge and hence they are favoured. But, then why the substitution reaction at C6 position and C7 position is not favoured, can also be explained with the help of mechanism. So here is the mechanism. Nitrogen lone pair will first attack on the electrophile and then the electrophilic attack at carbon 6 will give us this intermediate which is now less stable because we cannot write another resonating structure for it. If we write another resonating structure, it will disturb the aromaticity of the pyridine ring. As a result, we can say that the positive charge is localized in this intermediate, hence it is less stable, and finally the loss of H+ ion and the loss of electrophile from nitrogen gives us 6-substituted quinoline product. In the same way, when the electrophilic substitution occurs at C7 in quinoline, the same mechanism is followed and we can have only this one resonating structure which is less stable, because we cannot write another stable resonating structure for this. As a result, finally, the loss of H+ ion, we get this 7-substituted quinoline product. Now, since both these C6 and C7 positions when the electrophilic substitution occurs at these two positions, it does not involve delocalization of positive charge and there is localization of positive charge. Hence these two attacks are not favoured.

Now with respect to quinoline we have seen, same thing applies for isoquinoline. So here we will see first the electrophilic substitution reaction at C5 position. In this again the nitrogen lone pair will first attack on this electrophile and followed by the introduction of electrophile at 5-position, which gives this canonical structure I of the intermediate. We can write another canonical structure for this same intermediate. As a result, we have now two resonating structures and which makes this intermediate more stable. Finally, the loss of hydrogen, and electrophile from nitrogen, gives us 5-substituted isoquinoline product. Similarly, when the electrophilic attacks occur at a position, we can write these two resonating structures, which

makes it more stable and the loss of H+ ion and electrophile from nitrogen, will result in the formation of this 8-substituted isoquinoline product. So both the attacks at C5 and C8 positions of isoquinoline involves the delocalization of positive charge, hence they are favoured. Then the attack at 6 position is not favoured because it involves this only one intermediate. The same thing is applicable when the electrophilic attack takes place at C7 position. Hence both these attacks involve less stable intermediate and as a result these two attacks C6 and C7 positions are not favoured because they involve localization of positive charge and there is no delocalization of positive charge in the intermediate.

Finally we will have a look at 2 examples of electrophilic substitution reactions in quinoline and isoquinoline. One is nitration, in which the quinoline gives 2 products, that is 5-nitroquinoline and 8-nitroquinoline in 1:1 ratio. In the same way, isoquinoline when treated with fuming HNO3 and concentrated H2SO4 at zero degree centigrade, gives a mixture of 5-nitroquinoline and 8-nitroquinoline in 9:1 ratio. So this shows that 5-nitroquinoline is a major product. When it comes to sulfonation, quinoline when treated with 30% oleum at 90 degree centigrade, gives quinoline-8-sulfonic acid as the kinetic product, which on heating at 250 degree centigrade isomerizes to more stable quinoline-6-sulfonic acid product. Similarly, isoquinoline when treated with 30% oleum at 90 degree centigrade, first gives isoquinoline-5-sulfonic acid product, which further on heating at 250 degree centigrade, isomerizes to more stable isoquinoline-6-sulfonic acid product.

So in summary, we have seen quinoline and isoquinoline undergoes electrophilic substitution reaction at C5 and C8 positions and not at C6 and C7 positions. We have seen the mechanism for the electrophilic substitution reactions at C5, C6, C7 and C8 positions in both the compounds that is quinoline and isoquinoline. We have also seen from the mechanism that, electrophilic substitution reactions in quinoline and isoquinoline is preferred at C5 and C8 positions because it involves the delocalization of positive charge whereas the C6 and C7 positions are not preferred because they do not involve the delocalization of positive charge. And at the end, we have seen some examples of electrophilic substitution reactions, such as nitration and sulfonation of quinoline and isoquinoline.

These are the references to be referred for this module.

Thank you.