Medicinal Chemistry
Professor Dr. Harinath Chakrapani
Department of Chemistry
Indian Institute of Science Education and Research, Pune
Lecture 35
Drug Metabolism
Part II

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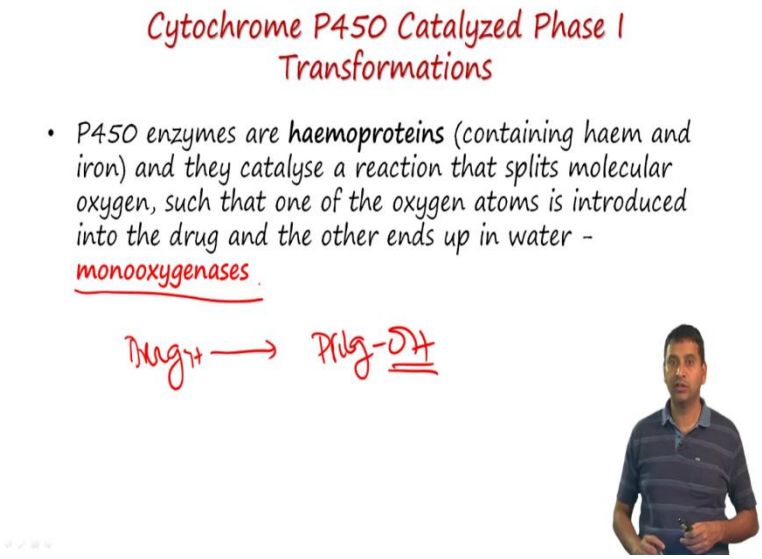

Right, so now let us look at a little bit in detail about P450 catalyzed transformations. So P450 are haemoproteins that is they contain haem and iron and we look at some of these details in the subsequent lectures. And they catalyze a reaction that splits molecular oxygen, we already saw that in the previous slide and one of the oxygen atoms is introduced to the drug. So the drug starts out as drug and ends up as, so you have a drug H and it ends up as drug OH. So this is the OH that is added and so these enzymes are known as monooxygenases okay.

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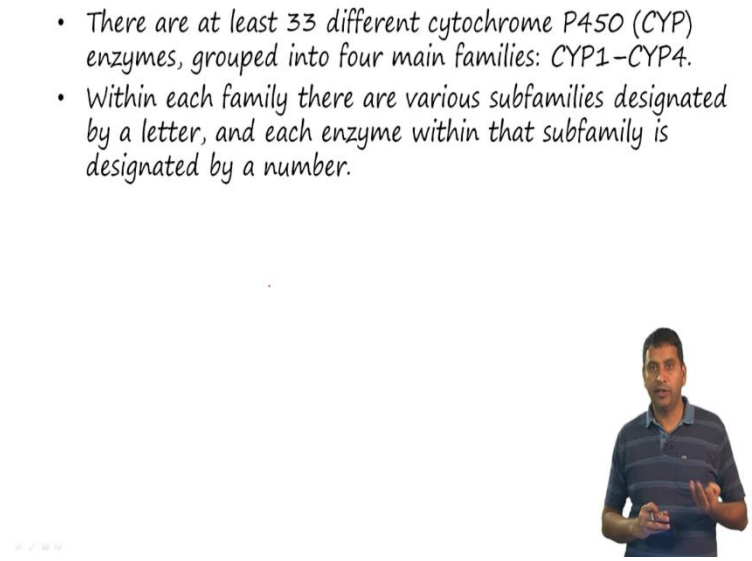

So there are 33 different types of cytochrome P450 and they are classified into 4 families that is CYP1 all the way to CYP4 and each of these families are again further divided and designated by letter. For example, you can have little CYP2A1 or CYP3A4 and so on and so forth, okay.

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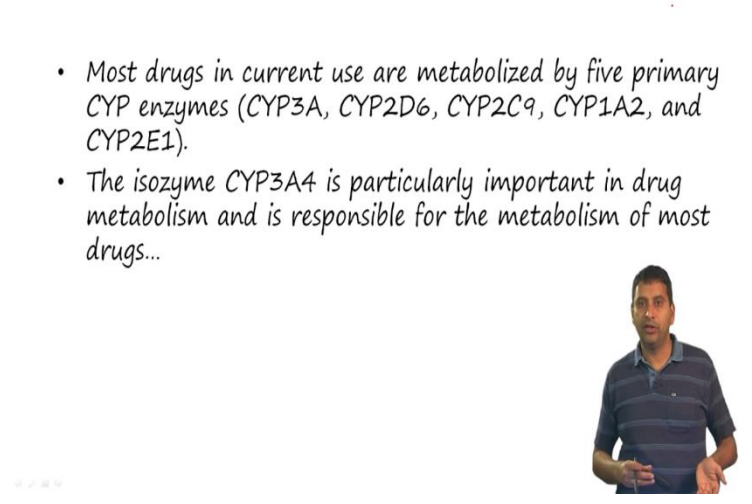

Most drugs currently in used are metabolized by 5 primary enzymes, so you can bring down those that large number down to pretty much 5 numbers, so that is CYP3A, 2D6, 2C9, 1A2 and 2E1 okay. This particular enzyme CYP3A4 is quite important in metabolism and it is responsible for metabolism of most drugs so therefore this is something that we should keep

in mind when we are designing a drug. So a drug can be easily tested with this enzyme to see how stable the drug is even during its discovery phase right.

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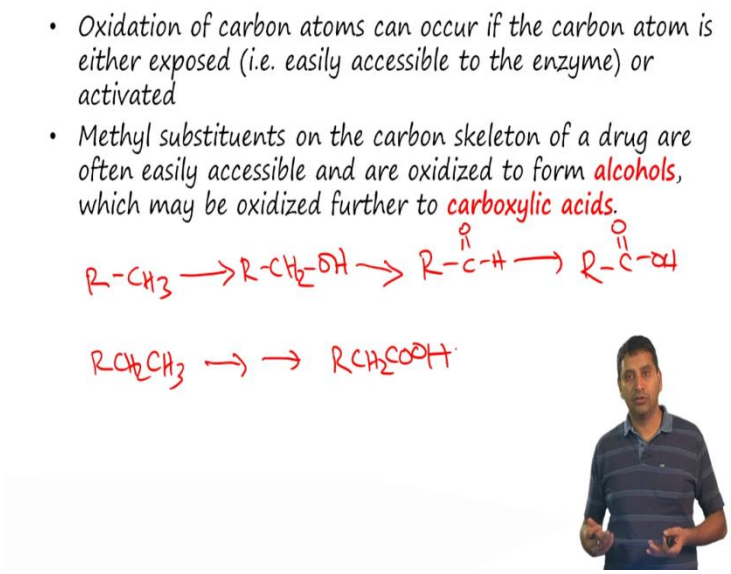

So oxidation of carbon atoms can occur if the carbon is exposed that is if it is easily accessible or if it is activated, right. So for example, methyl groups RCH_3 can undergo oxidation to form RCH_2OH, which then can be subsequently be oxidized again to Aldehyde which will undergo oxidation to form a carboxylic acid. So these are the sequence of reactions that can occur on a terminal or an exposed methyl group okay. It can also happen where you have RCH_2CH_3 that means you have a ethyl group which can get converted all the way to RCH_2COOH right. Eventually the product of oxidation is going to be carboxylic acids which are going to be soluble and they can be excreted through the urine.

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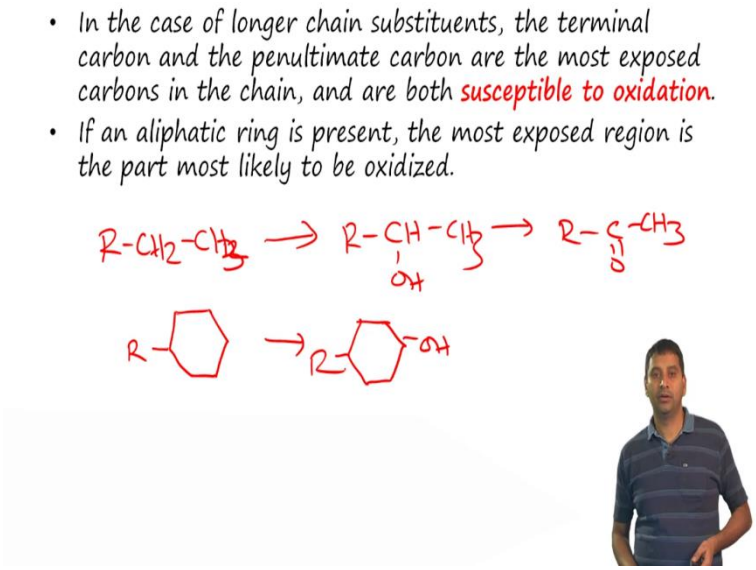

When you have longer chains, the terminal carbon and the penultimate carbon are the most exposed and they are both susceptible to oxidation. So we just look at the example of the terminal carbon, but now imagine that you can also have that you can have an internal carbon which can undergo oxidation. So let us say you have this molecule here, this can form $RCHOHCH_3$ which in turn can undergo oxidation again to form R - C double bar O – CH_3 so you are generating a ketone. In a cycling system such as an aliphatic ring, the most exposed region is more likely to be oxidized. If we have an example of cyclohexane ring, as shown here it can undergo oxidation to the corresponding alcohol okay.

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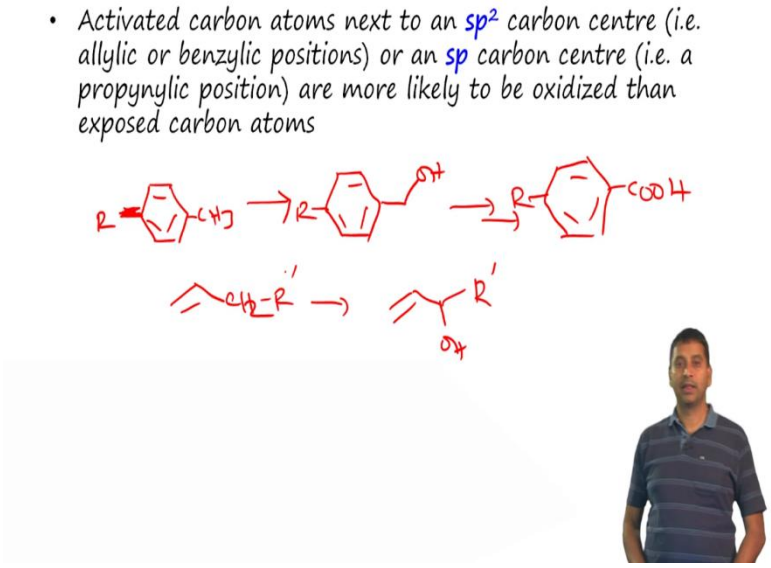

Uh You can also have sp2 centres and these sp2 centres are like allylic or benzylic positions uh can be susceptible to oxidation and they are more likely or if they are next to an sp carbon centre, so let us first look at the case of sp2 carbon Centre. So you have a benzene ring which has a methyl group on it and you have some other functional groups on the left hand side and what can happen is this undergoes oxidation to give you the corresponding benzylic alcohol which then can undergo steps of oxidation to give you correspondingly the benzoic acid okay. So this is a fairly straightforward for us to understand, it is also possible that you have in olefin such as this, there is an allylic position which can undergo oxidation to give you R prime okay.

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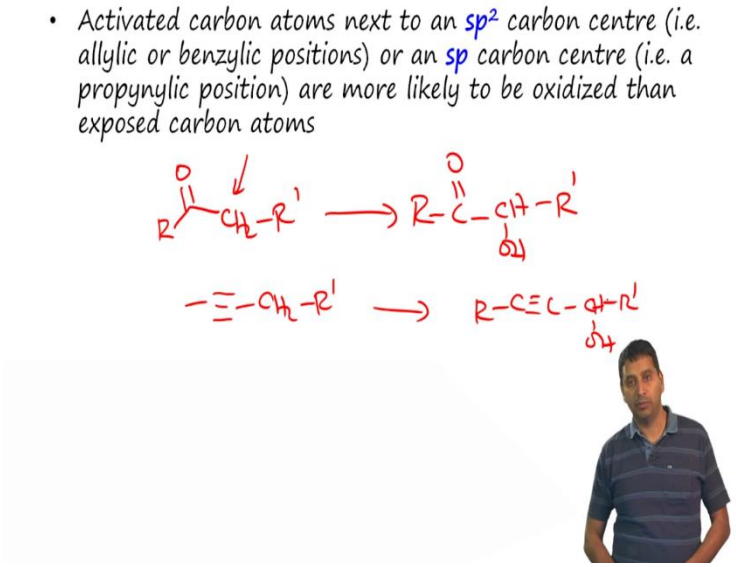

And you can also have oxidation next to the ketone so for example, you have R - C double bond OCH_2R prime, now this position here is quite susceptible to oxidation and so you can have R - C double bond O - CH - OH - R prime right. And as I mentioned earlier you can also have similarly the sp carbon which is basically a carbon - carbon double bond which will form CH_2R prime can undergo oxidation to R - C triple bond C - C - OH - R prime okay. So these are the major reactions that one could expect with in the case of sp2 or sp carbons.

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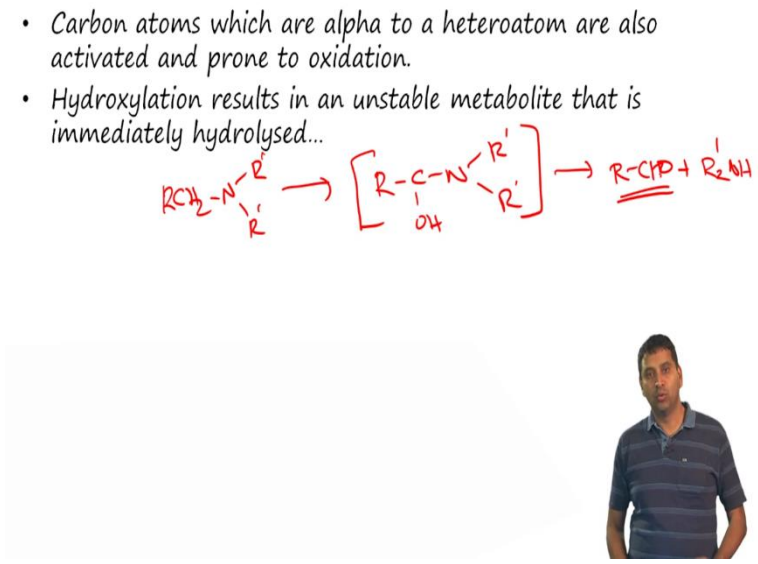

Now when the carbons which have an alpha which are alpha 2 hetero atom are also activated and they are also more prone to oxidation. So the example that we are going to look at is RCH_2- NRR, this can undergo oxidation this central is quite uh susceptible to oxidation and so you have CH - OH right so let us say you put a prime over here and this is going to be the product of oxidation. But this product is not very stable okay and this is going to further undergo hydrolysis to form an aldehyde and amine, in this case it will form a secondary amine, so the product of this oxidation is actually an aldehyde. Now you can actually extrapolate this to other heteroatoms as well and you can look at for example, an ether.

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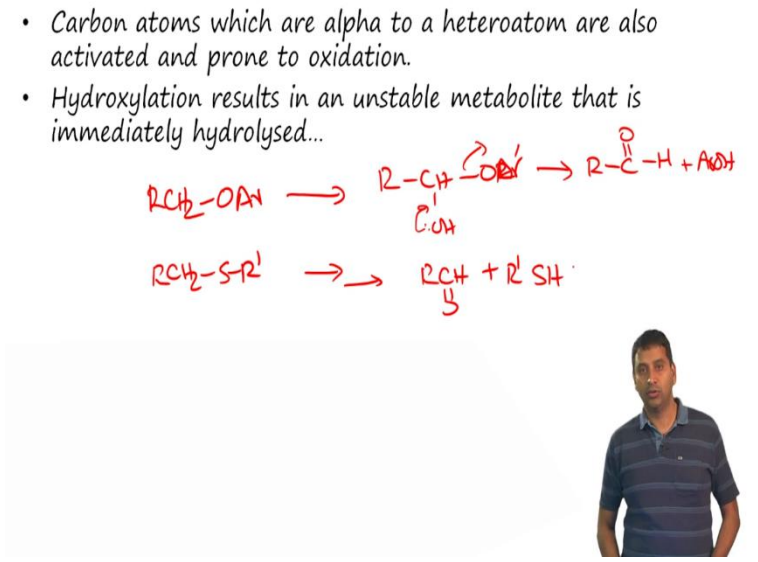

So you have RCH_2OAr which can undergo oxidation to give you RCHOHOR, now this is quite unstable you can push electrons, take over the alkoxide, it will form R - C double bond O - H so we have looked at Ar here so we will stick to the same convention + ArOH okay. So these are again possible similarly, you can do the same thing with uh thiols right, you have ethers which can again collapse to give you the corresponding aldehyde and and a thiol. So for example, you have RCH_2SR prime, I am not going to draw the arrows, you are going to form RCHO + R prime SH okay, so this is the other way in which we can do this metabolism.

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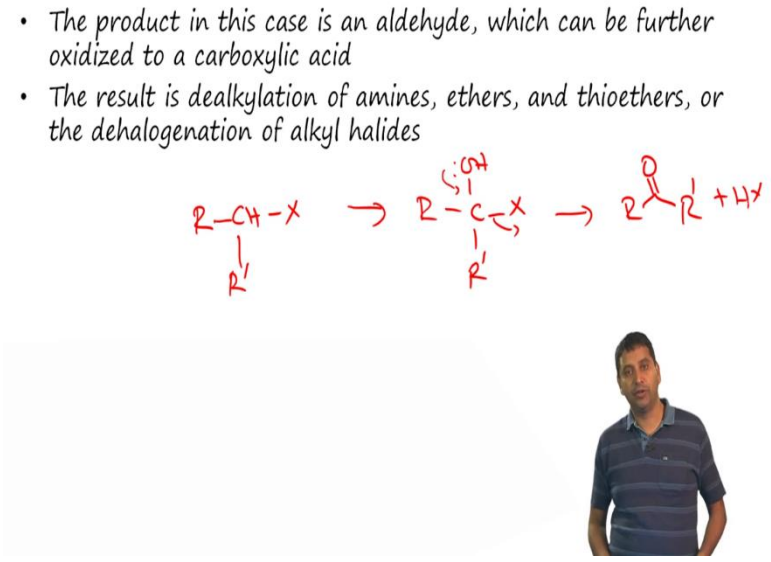

So the product in all these cases is an aldehyde okay, so we have already looked at that aldehyde can undergo oxidation to produce the corresponding carboxylic acid okay. And the result of this whole process is dealkylation of amines, ethers or thioethers, and we have not looked at it, but dehalogenation of alkyl halides can also occur. So the way in which dehalogenation of alkyl halide occurs is in the following way; RCHXR prime which can undergo oxidation to give you better RCOHXR prime and now you can push arrows in the following manner to give you R - C double bond O - R prime + HX okay, so dehalogenation of alkyl halides is also possible to give you the corresponding ketone.

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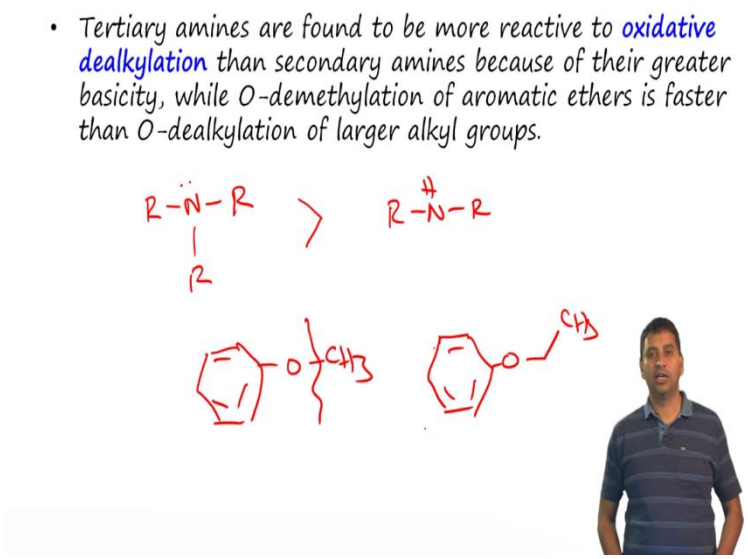

Tertiary amines are found to be more reactive oxidative dealkylation than secondary amines okay, so I am not going to spend a lot of time on this but we already know that basicity plays an important role, so tertiary amine are these which are definitely more reactive than the corresponding secondary amine and so on, right. While O-demethylation of aromatic ethers is faster than O-dealkylation of larger alkyl groups. So if you look at it, O-demethylation that is breaking here is much faster than O-dealkylation, so if we compare this with the same O - dealkylation with a ethyl group, this is slower than that of methyl group.

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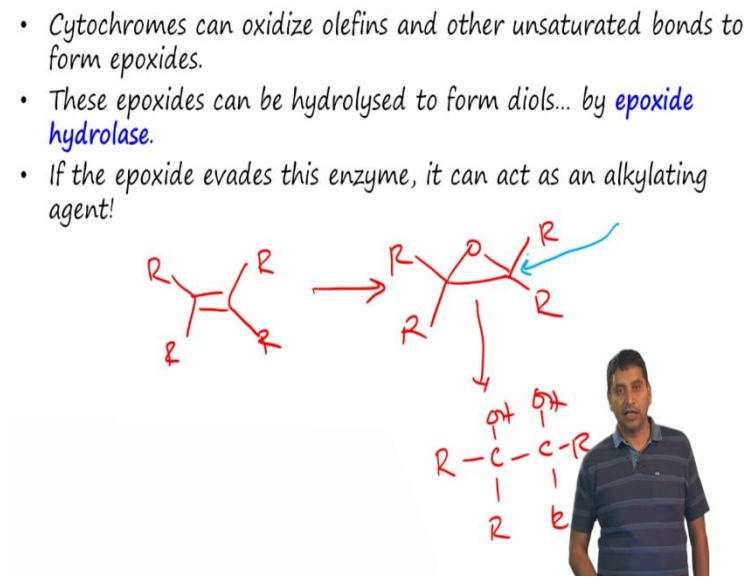

So cytochromes can also oxidize olefins and other unsaturated bonds to form the epoxides okay. So let us look at what the reaction is, so you have R, let us say we have a olefin like this. In the presence of cytochrome P450 this can actually undergo epoxidation to form this kind of molecule okay. Now there is an enzyme called as epoxide hydrolase, which opens up this epoxide and forms RCOHCOHR okay this is not indicative of stereochemistry here but this is the product that is formed which is a diol. But if the epoxide evades this enzyme right, so that means if the reaction does not happen quickly enough then this center is a very good center for attack by nucleophile, so what can happen is that this ends up into an alkylating agent.

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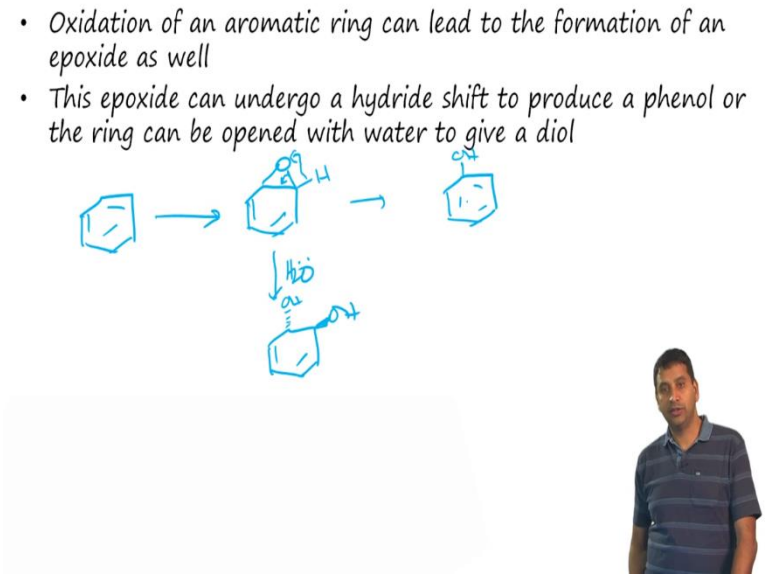

Oxidation of aromatic ring can also happen and hence we have a couple of possibilities here, so let us draw out a benzene ring. So this reacts with cytochrome P450 and produces the corresponding epoxide, let us say this carbon bond undergoes epoxidation. Now the straightforward way to do this is if we add water across the epoxide, you are going to get the corresponding diol and so let us say the attacks happened from the top, the other oxygen ends up in the bottom and rest of the molecule remains the same. But it is also possible that you have a hydride shift that can occur so you can think about the hydride shift like this and it gives you the corresponding phenol right. So these are the 2 possibilities that can really happen and if we have a subsequent on the *para*-position that is over here you typically favour the formation of the *para*-alcohol right.

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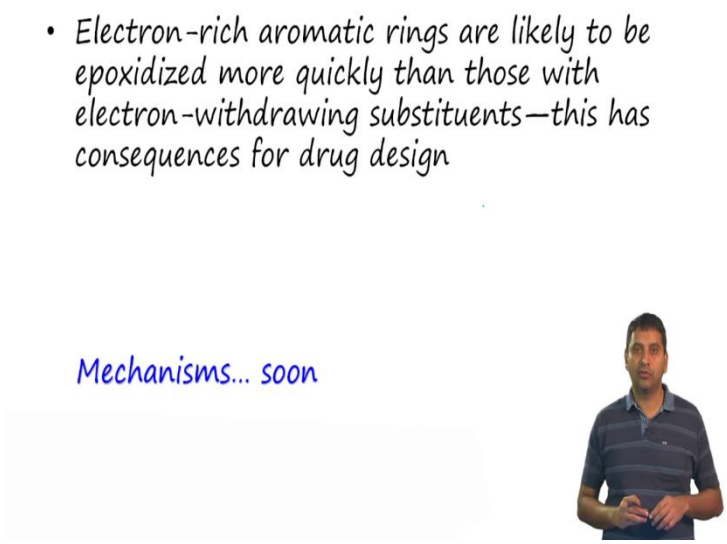

And electron rich aromatic rings are likely to be epoxidized more quickly than the one with electron-withdrawing groups on it and we look at some of the mechanisms of these oxidations very soon but we have to keep this in mind because we have to factor this while we are designing a drug okay.

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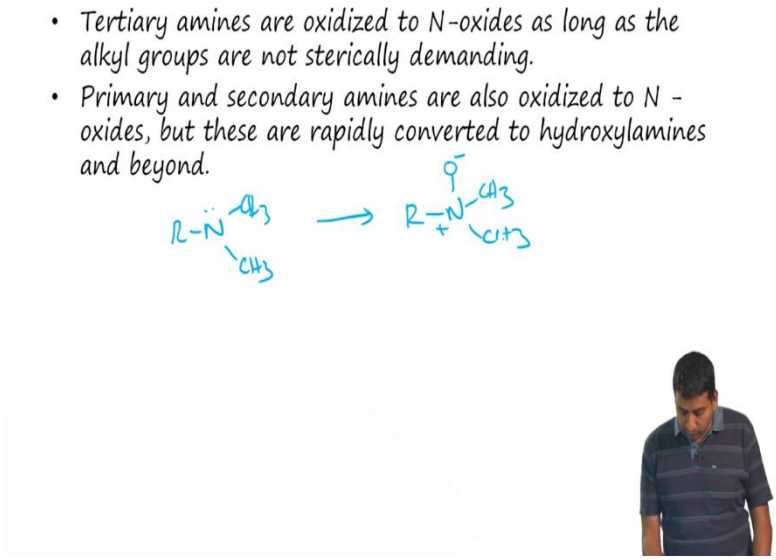

Tertiary amines that we looked that can also be oxidized uh to $_N$-oxides okay as long as the alkyl groups are not hysterically demanding, right. So the reaction that we are looking at here is RN and let us take the example of methyl groups CH_3 is going to get oxidised over here to form RNO minus - CH_3CH_3 these are known as *N*-oxides. And primary and secondary amine saw also oxidize to N-oxides but these rapidly converts to hydroxylamine and beyond.

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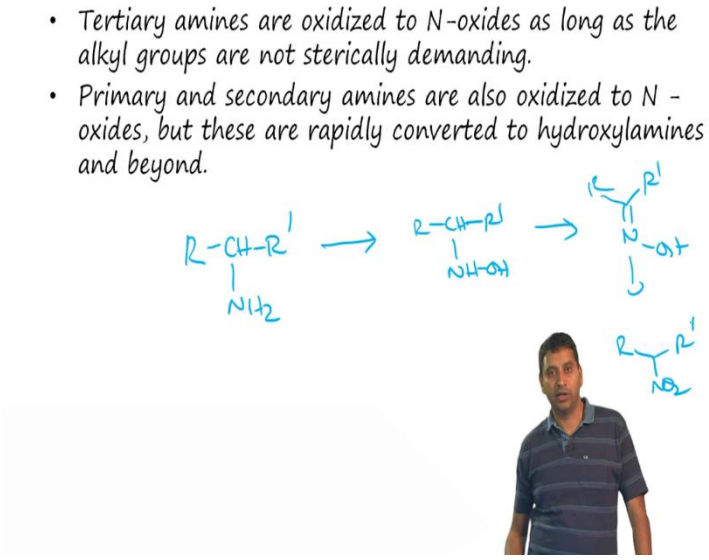

So the reaction that we are looking at here is RCHR prime and let us do, now this can undergo oxidation to form RCHR prime NHOH, right and this can actually form what is known amine by further oxidation and it will give you R prime - R double bond NOH, it can form a hydroxylamine for example, which can subsequently get converted to a nitro group, okay so this can also be at the terminal carbon can be attached to the amine and you will correspondingly form the terminal carbon with a nitro group.

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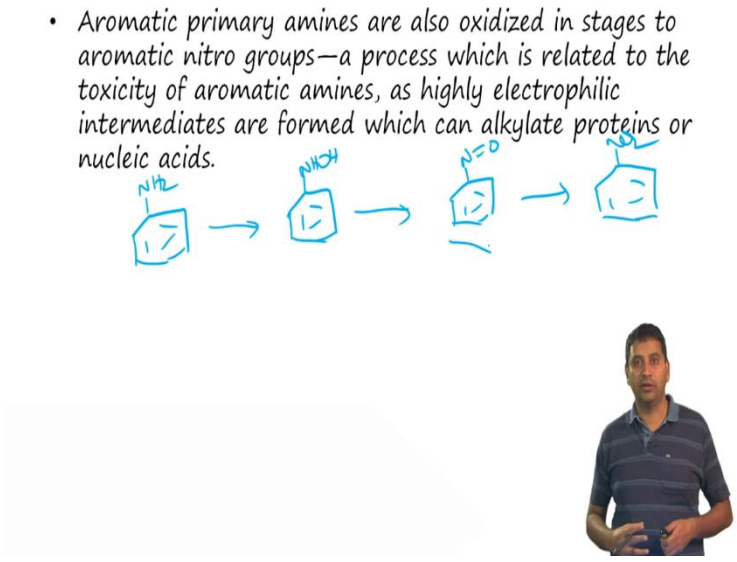

Aromatic amine are also oxidized to in stages and so we will look at if you have and aromatic amine such as aniline this can further get oxidized to form OH, which can then give you correspondingly the nitroso group which will then form finally the nitro group okay. So some

of these intermediates such as nitroso benzene is actually quite electrophilic and they can alkylate proteins or nucleic acids, so anilines are something that can be potentially quite toxic to incorporate in a drug.

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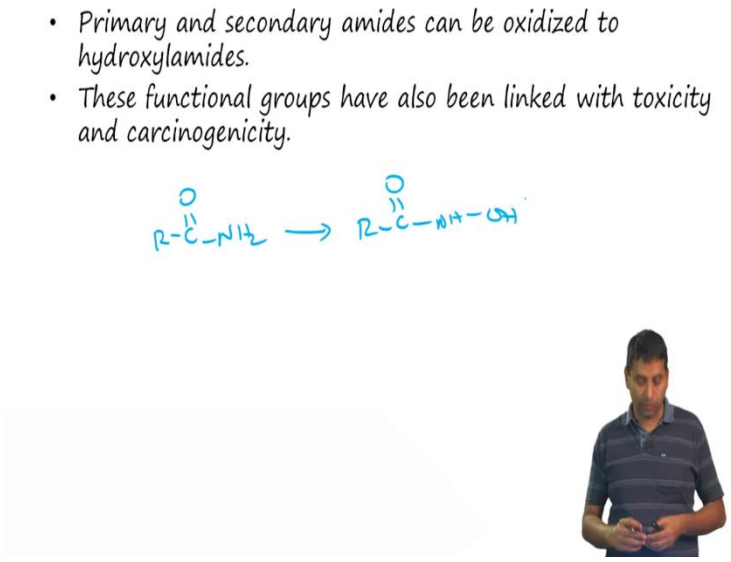

Primary and secondary amides can also be oxidized to the corresponding hydroxylamides. So when you have R - C double bond O – NH_2, this can also undergo oxidation to form R – C double bond O NH – OH, and these are some functional groups that have been associated with uh toxicity and carcinogenicity and so one needs to understand whether an amide that is going to be formed has a propensity to form this kind of intermediate or not okay. You can also have secondary amides R – C double bond O – NH R prime which can then undergo oxidation to give you R - C double bond O – N - OH, this R prime is intact, right so this is also possible. And so this is something to keep in mind if you are going to have an amide as a functional group in your drug.

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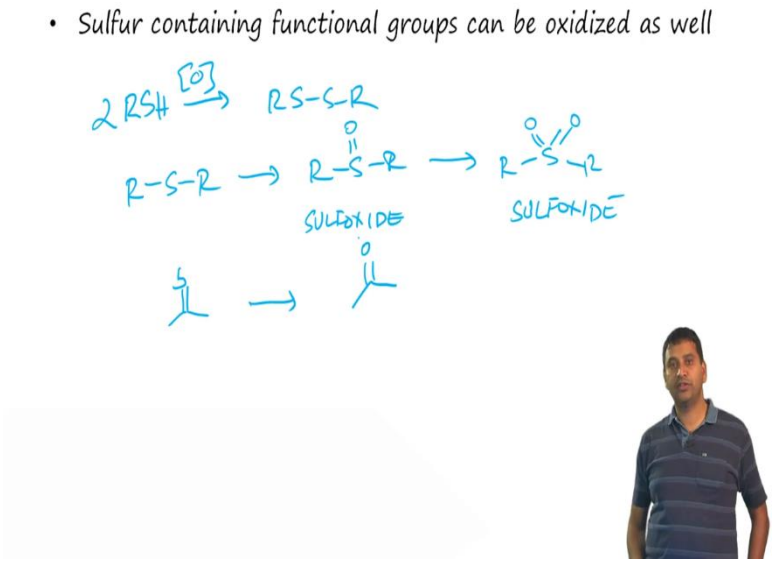

Sulfur containing functional groups can also be oxidized, so let us say you have a thiol, we have already looked at this, this can undergo oxidation to give you RSSR which is basically a disulphide. You can also have a thio-ether which can give you RS double bond O which is a sulfoxide right, which can then subsequently be oxidized further to form R double bond O - R, which is basically a sulfoxide okay so all these are possible. If your drug has a thiocarbonyl compounds such as this, then you can also have oxidation, you can have desulfuration to give you a ketone, so these are some of the fates that we can expect of sulfur containing compounds.