Quinolines and isoquinolines

We move from benzo-fused pyrroles to benzo-fused pyridines and meet quinoline and isoquinoline. Isoquinolines will feature as benzylisoquinoline alkaloids in Chapter 51 and their synthesis will mostly be discussed there. In this section we shall concentrate on the quinolines.

Quinoline forms part of the structure of quinine, the malaria remedy found in cinchona bark and known since the time of the Incas. The quinoline in quinine has a 6-MeO substituent and a side chain attached to C4. In discussing the synthesis of quinolines, we will be particularly interested in this pattern. This is because the search for anti-malarial compounds continues and other quinolines with similar structures are among the available anti-malarial drugs.

We shall also be very interested in quinolones, analogous to pyridones, with carbonyl groups at positions 2 and 4 as these are useful antibiotics. A simple example is pefloxacin which has a typical 6-F and 7-piperazine substituents.

When we consider the synthesis of a quinoline, the obvious disconnections are, first, the C–N bond in the pyridine ring and, then, the C–C bond that joins the side chain to the benzene ring. We will need a three-carbon (C₃) synthon, electrophilic at both ends, which will yield two double bonds after incorporation. The obvious choice is a 1,3-dicarbonyl compound.

The choice of an aromatic amine is a good one as the NH₂ group reacts well with carbonyl compounds and it activates the ortho position to electrophilic attack. However, the dialdehyde is malonic dialdehyde, a compound that does not exist, so some alternative must be found. If the quinoline is substituted in the 2- and 4-positions this approach looks better.
The initially formed imine will tautomerize to a conjugated enamine and cyclization now occurs by electrophilic aromatic substitution.

The enamine will normally prefer to adopt the first configuration shown in which cyclization is not possible, and (perhaps for this reason or perhaps because it is difficult to predict which quinoline will be formed from an unsymmetrical 1,3-dicarbonyl compound) this has not proved a very important quinoline synthesis. We shall describe two more important variants on the same theme, one for quinolines and one for quinolones.

In the synthesis of pyridines it proved advantageous to make a dihydropyridine and oxidize it to a pyridine afterwards. The same idea works well in probably the most famous quinoline synthesis, the Skraup reaction. The diketone is replaced by an unsaturated carbonyl compound so that the quinoline is formed regiospecifically.

The first step is conjugate addition of the amine. Under acid catalysis the ketone now cyclizes in the way we have just described to give a dihydroquinoline after dehydration. Oxidation to the aromatic quinoline is an easy step accomplished by many possible oxidants.

Traditionally, the Skraup reaction was carried out by mixing everything together and letting it rip. A typical mixture to make a quinoline without substituents on the pyridine ring would be the aromatic amine, concentrated sulfuric acid, glycerol, and nitrobenzene all heated up in a large flask at over 100 °C with a wide condenser.

The glycerol was to provide acrolein (CH₂=CH-CHO) by dehydration, the nitrobenzene was to act as oxidant, and the wide condenser...? All too often Skraup reactions did let rip—with destructive results. A safer approach is to prepare the conjugate adduct first, cyclize it in acid solution, and then oxidize it with one of the reagents we described for pyridine synthesis, particularly quinones such as DDQ.
An important use of the traditional Skraup synthesis is to make 6-methoxy-8-nitroquinoline from an aromatic amine with only one free ortho position, glycerol, the usual concentrated sulfuric acid, and the oxidant arsenic pentoxide. Though the reported procedure uses 588 grams of As$_2$O$_5$, which might disconcert many chemists, it works well and the product can be turned into other quinolines by reduction of the nitro group, diazotization, and nucleophilic substitution (Chapter 23).

The more modern style of Skraup synthesis is used to make 8-quinolinol or ‘oxine’. ortho-Amino-phenol has only one free position ortho to the amino group and is very nucleophilic, so acrolein can be used in weak acid with only a trace of strong acid. Iron(III) is the oxidant with a bit of boric acid for luck, and the yield is excellent.

This compound is important because it forms unusually stable metal complexes with metal ions such as Mg(II) or Al(III). It is also used as a corrosion inhibitor on copper because it forms a stable layer of Cu(II) complex that prevents oxidation of the interior.

**Quinolones also come from anilines by cyclization to an ortho position**

The usual method for making quinolone antibiotics is possible because they all have a carboxylic acid in the 3-position. Disconnection suggests a rather unstable malonic ester derivative as starting material.

In fact, the enol ether of this compound is easily made from diethyl malonate and ethyl orthoformate [HC(OEt)$_3$]. The aromatic amine reacts with this compound by an addition–elimination sequence giving an enamine that cyclizes on heating. This time there is no worry about the geometry of the enamine.

For examples of quinolone antibiotics we can choose ofloxacin, whose synthesis is discussed in detail in Chapter 23, and rosoxacin whose synthesis is discussed overleaf. Both molecules contain the...
same quinolone carboxylic acid framework, outlined in black, with another heterocyclic system at position 7 and various other substituents here and there.

To make roxoxicin two heterocyclic systems must be constructed. Workers at the pharmaceutical company Sterling decided to build the pyridine in an ingenious version of the Hantzsch synthesis using acetylenic esters on 3-nitrobenzaldehyde. The ammonia was added as ammonium acetate. Oxidation with nitric acid made the pyridine, hydrolysis of the esters and decarboxylation removed the acid groups, and reduction with Fe(II) and HCl converted the nitro group into the amino group required for the quinolone synthesis.

Now the quinolone synthesis can be executed with the same reagents we used before and all that remains is ester hydrolysis and alkylation at nitrogen. Notice that the quinolone cyclization could in theory have occurred in two ways as the two positions ortho to the amino group are different. In practice cyclization occurs away from the pyridine ring as the alternative quinolone would be impossibly crowded.

Since quinolones, like pyridones, can be converted into chloro-compounds with POCl₃, they can be used in nucleophilic substitution reactions to build up more complex quinolines.

Because isoquinolines are dealt with in more detail in Chapter 51, we will give just one important synthesis here. It is a synthesis of a dihydroisoquinoline by what amounts to an intramolecular Vilsmeier reaction in which the electrophile is made from an amide and POCl₃. Since, to make the isoquinoline, two hydrogen atoms must be removed from carbon atoms it makes more sense to use a noble metal such as Pd(0) as the oxidizing agent rather than the reagents we used for pyridine synthesis.

More heteroatoms in fused rings mean more choice in synthesis

The imidazo-pyridazine ring system forms the basis for a number of drugs in human and animal medicine. The synthesis of this system uses chemistry discussed in Chapter 43 to build the pyridazine ring. There we established that it was easy to make dichloropyridazines and to displace the chlorine...