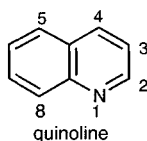
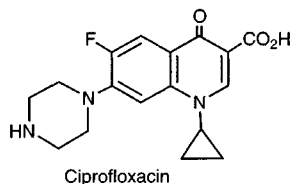
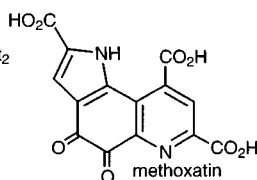
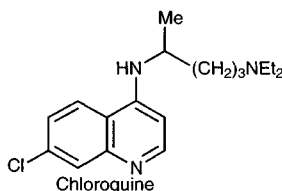
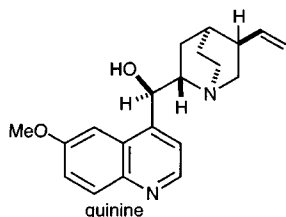


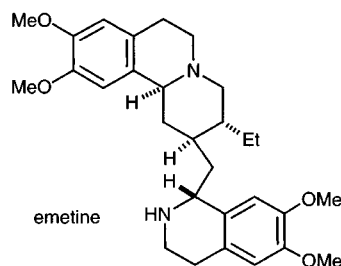
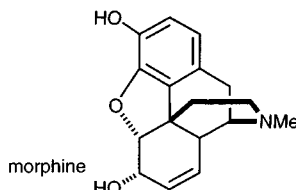
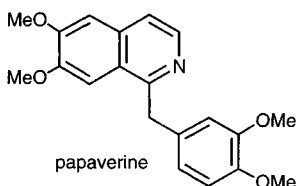
## 6 Quinolines and isoquinolines: reactions and synthesis



Quinoline and isoquinoline are stable; the former is a high-boiling liquid the latter a low-melting solid, each with a sweetish odour. Both bases have been known for a long time: quinoline was first isolated from coal tar in 1834, isoquinoline from the same source in 1885. Shortly after the isolation of quinoline from coal tar it was also recognised as a pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine, from which the name quinoline is derived; the word quinine, in turn, derives from *quina*, a Spanish version of a local South American name for the bark of quinine-containing *Cinchona* species. Several synthetic antimalarial drugs are based on the quinoline nucleus, chloroquine is an example. Ciprofloxacin is one of several 4-quinolone-based antibiotics in use.

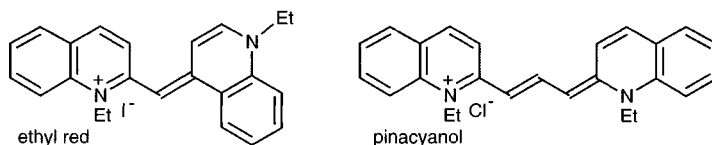


Quinolines play a relatively minor role in fundamental metabolism, methoxatin, an enzyme cofactor of methylotrophic bacteria, being one of the small number of examples. There are also comparatively few quinoline-containing secondary metabolites, in contrast to isoquinoline, which occurs, mainly at the 1,2,3,4-tetrahydro-level, in a large number of alkaloids – the opium poppy alkaloids papaverine and, in more-elaborated form, morphine are examples.<sup>1</sup> Emetine, with two tetrahydroisoquinoline units, is a medicinally important amoebicide.



Quinoline compounds provided the first photographic film sensitizers: the cyanine dye<sup>2</sup> ethyl red extended photography from the blue into the green and then in 1904,

with pinacyanol, into the red. Subsequently, thousands of sensitizing dyes have been made and tested and quinoline-based dyes replaced by other, more efficient systems.



## 6.1 Reactions with electrophilic reagents

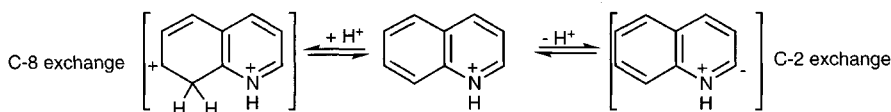
### 6.1.1 Addition to nitrogen

All the reactions noted in this category for pyridine (section 5.1.1), which involve donation of the nitrogen lone pair to electrophiles, also occur with quinoline and isoquinoline and little further comment is necessary, for example the respective  $pK_a$  values, 4.94 and 5.4, show them to be of similar basicity to pyridine. Each, like pyridine, forms *N*-oxides and quaternary salts.

### 6.1.2 Substitution at carbon

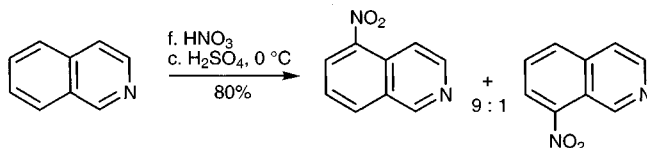
#### 6.1.2.1 Proton exchange

Benzene ring *C*-protonation, and thence exchange, *via N*-protonated quinoline, requires strong sulfuric acid and occurs fastest at C-8, then at C-5 and C-6; comparable exchange in isoquinoline takes place somewhat faster at C-5 than at C-8.<sup>3</sup> At lower acid strengths each system undergoes exchange  $\alpha$  to nitrogen, at C-2 for quinoline and C-1 for isoquinoline. These processes involve a zwitterion produced by deprotonation of the *N*-protonated heterocycle.



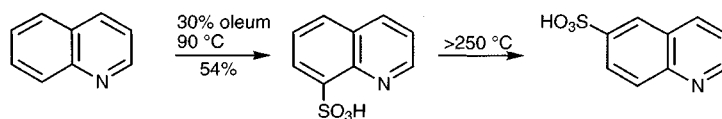
#### 6.1.2.2 Nitration (see also 6.3.1.2)

The positional selectivity for proton exchange is partly mirrored in nitrations, quinoline gives approximately equal amounts of 5- and 8-nitroquinolines whereas isoquinoline produces almost exclusively the 5-nitro-isomer;<sup>4</sup> mechanistically the substitutions involve nitronium ion attack on the *N*-protonated heterocycles.



#### 6.1.2.3 Sulfonation

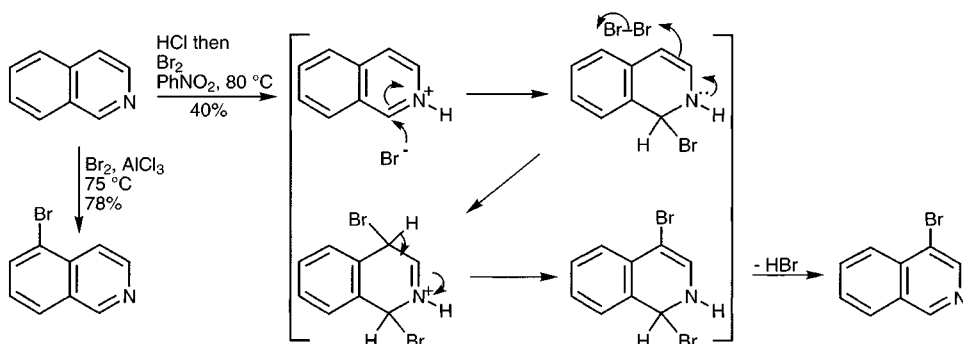
Sulfonation of quinoline gives largely the 8-sulfonic acid whereas isoquinoline affords the 5-acid.<sup>5</sup> Reactions at higher temperatures produce other isomers, under thermodynamic control, for example both quinoline 8-sulfonic acid and quinoline 5-sulfonic acid are isomerised to the 6-acid.<sup>6</sup>



#### 6.1.2.4 Halogenation

Ring substitution of quinoline and isoquinoline by halogens is rather complex, products depending on the conditions used.<sup>7</sup> In concentrated sulfuric acid quinoline gives a mixture of 5- and 8-bromo-derivatives; comparably, isoquinoline is efficiently converted into the 5-bromo derivative in the presence of aluminium chloride;<sup>8</sup> both processes involve halogen attack on a salt.

Introduction of halogen to the hetero-rings occurs under remarkably mild conditions in which the nitrogen lone pair initiates a sequence by interaction with an electrophile. Thus treatment of quinoline and isoquinoline hydrochlorides with bromine produces 3-bromoquinoline and 4-bromoisoquinoline respectively as illustrated below for the latter.<sup>9</sup>



#### 6.1.2.5 Acylation and alkylation

There are no generally useful processes for the introduction of carbon substituents by electrophilic substitution of quinolines or isoquinolines except for a few examples in which a ring has a strong electron-releasing substituent.

### 6.2 Reactions with oxidising agents

It requires vigorous conditions to degrade a ring in quinoline and isoquinoline: examples of attack at both rings are known, though degradation of the benzene ring, generating pyridine diacids, should be considered usual;<sup>10</sup> ozonolysis can be employed to produce pyridine dialdehydes,<sup>11</sup> or after subsequent hydrogen peroxide treatment, diacids.<sup>12</sup> Electrolytic oxidation of quinoline is the optimal way to convert quinoline to pyridine-2,3-dicarboxylic acid ('quinolinic acid')<sup>13</sup>; alkaline potassium permanganate converts isoquinoline into a mixture of pyridine-3,4-dicarboxylic acid ('cinchomeric acid') and phthalic acid.<sup>14</sup>

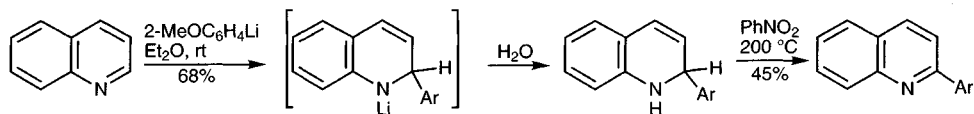
### 6.3 Reactions with nucleophilic reagents

#### 6.3.1 Nucleophilic substitution with hydride transfer

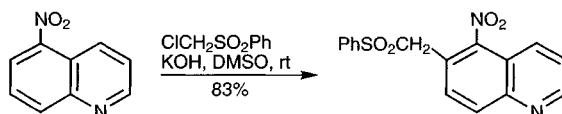
Reactions of this type occur fastest at C-2 in quinoline and at C-1 in isoquinolines.

### 6.3.1.1 Alkylation and arylation

The immediate products of addition of alkyl and aryl Grignard reagents and alkyl- and aryllithiums are dihydroquinolines and -isoquinolines and can be characterised as such, but can be oxidised to afford the C-substituted, rearomatised heterocycle; illustrated below is a 2-arylation of quinoline.<sup>15</sup>



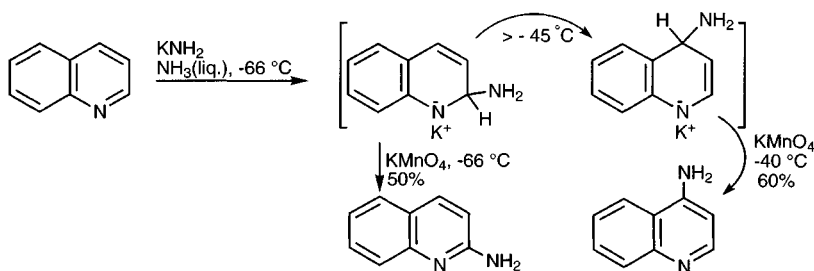
Vicarious nucleophilic substitution (section 2.3.3) allows the introduction of substituents into nitroquinolines: cyanomethyl and phenylsulfonylmethyl groups, for example, can be introduced *ortho* to the nitro group, in 5-nitroquinolines at C-6 and in 6-nitroquinolines at C-5.<sup>16</sup>



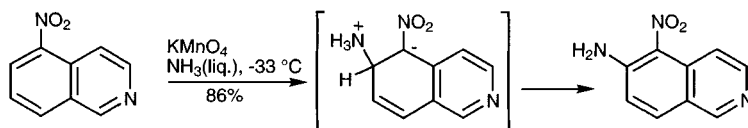
There are considerable possibilities inherent in addition of organolithiums to osmium complexes of quinoline for the synthesis of 5-substituted quinolines.<sup>17</sup>

### 6.3.1.2 Amination and nitration

Sodium amide reacts rapidly and completely with quinoline and isoquinoline, even at  $-45^{\circ}\text{C}$ , to give dihydro-adducts with initial amide attack at C-2 (main) and C-4 (minor) in quinoline and C-1 in isoquinoline. The quinoline 2-adduct rearranges to the more stable 4-aminated adduct at higher temperatures.<sup>18</sup> Oxidative trapping of the quinoline adducts provides 2- or 4-aminoquinoline;<sup>19</sup> isoquinoline reacts with potassium amide in liquid ammonia at room temperature to give 1-aminoisoquinoline.<sup>20</sup>

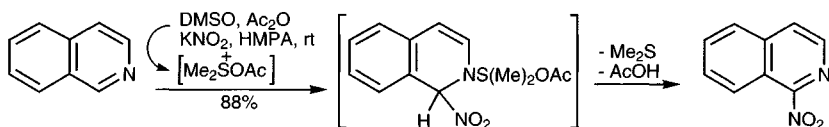


Oxidative aminations are possible at other quinoline and isoquinoline positions, even on the benzene ring, providing a nitro group is present to promote the nucleophilic addition.<sup>21</sup>



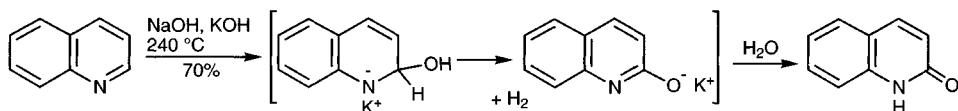
The introduction of a nitro group at C-1 in isoquinolines can be achieved using a mixture of potassium nitrite, dimethylsulfoxide and acetic anhydride.<sup>22</sup> The key step

is the nucleophilic addition of nitrite to the heterocycle previously quaternised by reaction through nitrogen with a complex of dimethylsulfoxide and the anhydride.



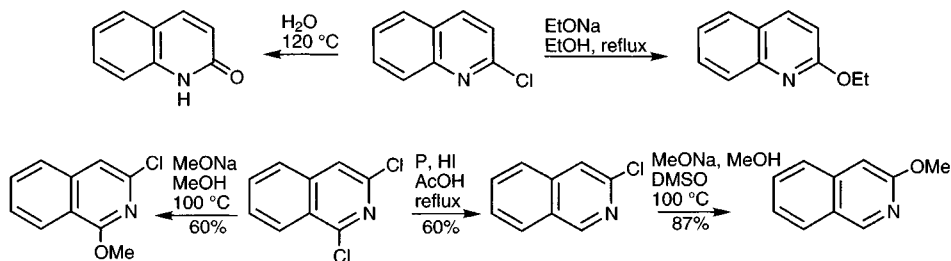
### 6.3.1.3 Hydroxylation

Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen.<sup>23</sup> 2-Quinolone ('carbostyryl') and 1-isoquinolone ('isocarbostyryl') are the isolated products.

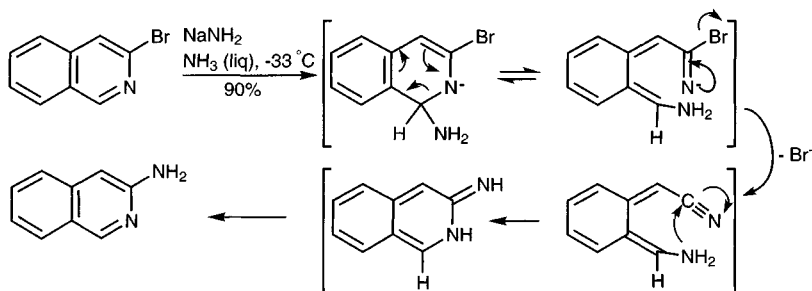


### 6.3.2 Nucleophilic substitution with displacement of halide

The main principle here is that halogen on the homocyclic rings of quinoline and isoquinoline, and at the quinoline-3- and the isoquinoline 4-positions behave as would halobenzenes. In contrast, 2- and 4-haloquinolines and 1-haloisoquinolines have the same susceptibility as  $\alpha$ - and  $\gamma$ -halopyridines (see section 5.3.2). 3-Haloisoquinolines are intermediate in their reactivity to nucleophiles.<sup>24</sup>



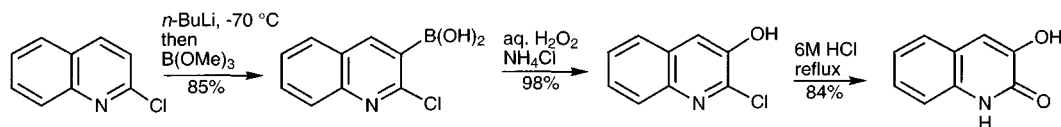
An apparent exception to the relative unreactivity of 3-haloisoquinolines is provided by the reaction of 3-bromoisoquinoline with sodium amide. Here, a different mechanism, known by the acronym ANRORC (Addition of Nucleophile, Ring Opening and Ring Closure), leads to the product, apparently of direct displacement, but in which a switching of the ring nitrogen, to become the substituent nitrogen, has occurred.<sup>25</sup>



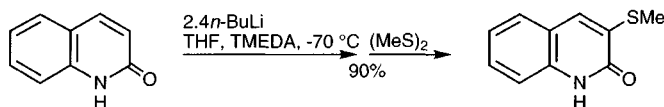
## 6.4 Reactions with bases

### 6.4.1 Deprotonation of C-hydrogen

Direct lithiation, i.e. C-deprotonation of quinolines<sup>26</sup> requires an adjacent substituent such as chlorine, fluorine, or alkoxy – probably the first ever strong base C-deprotonation of a six-membered heterocycle was the 3-lithiation of 2-ethoxyquinoline.<sup>27</sup> Both 4- and 2-dimethylaminocarbonyloxyquinolines lithiate at C-3. 4-Pivaloylaminoquinoline lithiates at the *peri* position, C-5. 3-Substituted quinolines lithiate at C-4, not at C-2.



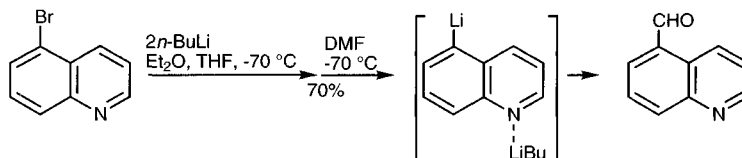
2-Lithiation of 1-substituted 4-quinolones<sup>28</sup> and 3-lithiation of 2-quinolone<sup>29</sup> provides derivatives with the usual nucleophilic propensity, as illustrated below.



## 6.5 Reactions of C-metallated quinolines and isoquinolines

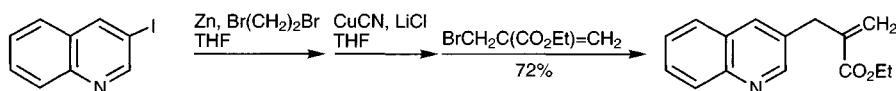
### 6.5.1 Lithium derivatives

The preparation of lithioquinolines and -isoquinolines *via* metal-halogen exchange is complicated by competing nucleophilic addition. Low temperatures do allow metal-halogen exchange at both pyridine<sup>30</sup> and benzene ring positions<sup>31</sup> in quinolines, and the isoquinoline-1-<sup>30</sup> and 4-positions,<sup>32</sup> subsequent reaction with electrophiles generating C-substituted products. It seems that for benzene ring lithiation two mol equivalents of butyllithium are necessary to allow one butyllithium to associate with the ring nitrogen as suggested below.



### 6.5.2 Zinc derivatives

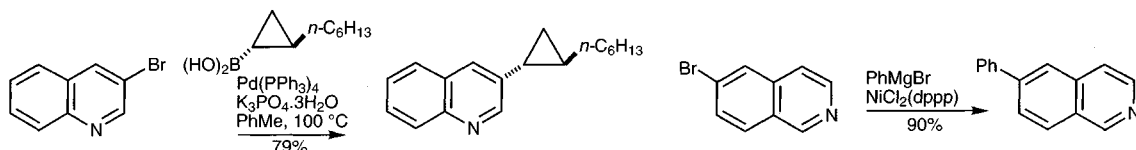
Direct formation of quinoliny zinc reagents is illustrated below.<sup>33</sup>



### 6.5.3 Palladium- and nickel-catalysed reactions

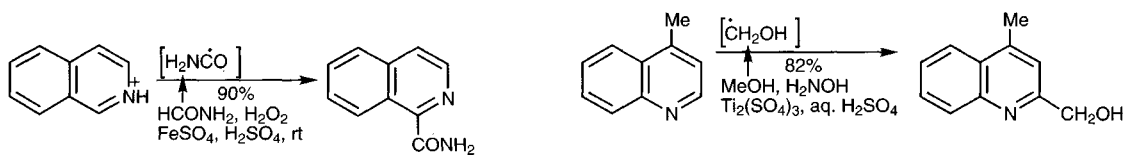
The coupling of various haloquinolines and -isoquinolines has been effected with palladium<sup>34</sup> or nickel reagents<sup>35</sup> – a couple of examples are shown below. Even chlorine, at the quinoline 2-position, will take part in such processes.<sup>36</sup> A nice

distinction is made between chlorine at the isoquinoline 1- and 3-positions: 1,3-dichloroisoquinoline couples only at the 1-position with arylboronic acids using palladium catalysis (*cf.* section 6.3.2).<sup>37</sup>



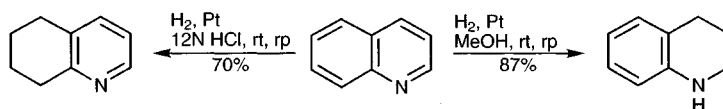
## 6.6 Reactions with radical reagents

Phenyl radicals generated by the decomposition of dibenzoyl peroxide attack quinoline and isoquinoline with formation of mixtures of all the isomeric phenyl-substituted products. Much more discriminating substitutions can be achieved with more nucleophilic radicals in acid solution (*cf.* section 2.4.1).

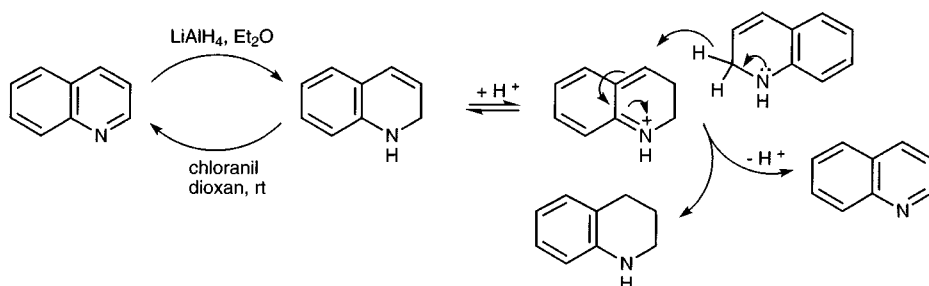


## 6.7 Reactions with reducing agents

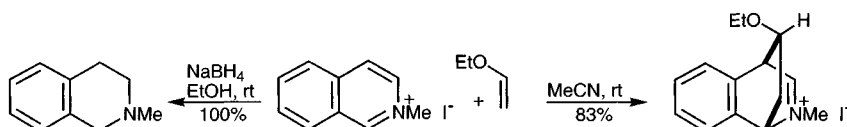
Selective reduction of either the pyridine or the benzene rings in quinolines and isoquinoline can be achieved: the heterocyclic ring is reduced to the tetrahydro level by sodium cyanoborohydride in acid solution,<sup>38</sup> by sodium borohydride in the presence of nickel(II) chloride,<sup>39</sup> by zinc borohydride,<sup>40</sup> or, traditionally, by room temperature and room pressure catalytic hydrogenation in methanol. However, in strong acid solution it is the benzene ring which is selectively saturated;<sup>41</sup> longer reaction times can then lead to decahydro-derivatives.



Lithium in liquid ammonia conditions can produce 1,4-dihydroquinoline<sup>42</sup> and 3,4-dihydroisoquinoline<sup>43</sup> under certain conditions. Conversely, lithium aluminium hydride reduces generating 1,2-dihydroquinoline<sup>44</sup> and 1,2-dihydroisoquinoline.<sup>45</sup> These dihydro-heterocycles<sup>46</sup> can be easily oxidised back to the fully aromatic systems, or disproportionate,<sup>47</sup> especially in acid solution, to give a mixture of tetrahydro- and rearomatised compounds as shown below. Stable dihydro derivatives can be obtained by trapping following reduction, as a urethane by reaction with a chloroformate.<sup>48</sup>



Quaternary salts of quinoline and isoquinoline are particularly easily reduced in the heterocyclic ring, either catalytically or with a borohydride in protic solution.



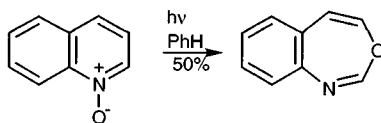
1-Methylquinolinium iodide is reduced by tributylstannane to give mainly the 1,2-dihydro-isomer, which isomerises at room temperature to the 1,4-dihydro-isomer; reduction with this reagent but with concurrent irradiation, produced exclusively 1,4-dihydro-1-methylquinoline, quantitatively.<sup>49</sup>

## 6.8 Electrocyclic reactions (ground state)

The tendency for relatively easy nucleophilic addition to the pyridinium ring in isoquinolinium salts is echoed in the cycloaddition (shown above) of electron-rich dienophiles such as ethoxyethene, which is reversed on refluxing in acetonitrile.<sup>50</sup> The comparable reaction of 4-oxygenated 2-arylisquinolinium salts is a neat method for the synthesis of heavily functionalised tetralins.<sup>51</sup>

## 6.9 Photochemical reactions

Of a comparatively small range of photochemical reactions described for quinolines and isoquinolines perhaps the most intriguing are some hetero-ring rearrangements of quaternary derivatives, which can be illustrated by the ring expansions of their *N*-oxides.<sup>52</sup> As with 2-pyridones, 2-quinolones undergo 2 + 2 photo-dimerisation.<sup>53</sup>

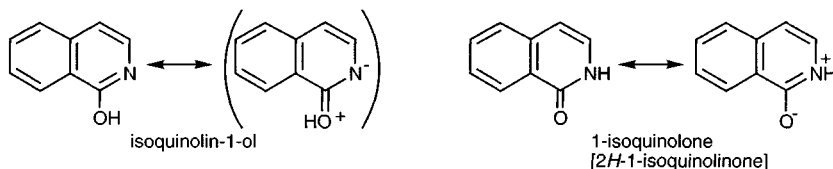


## 6.10 Oxyquinolines and -isoquinolines

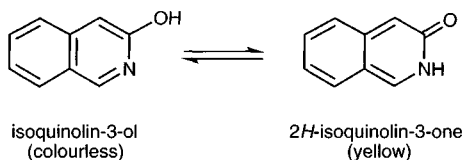
Quinolinols and isoquinolinols in which the oxygen is at any position other than 2- and 4- for quinolines and 1- and 3- for isoquinolines are true phenols i.e. have an hydroxyl group, though they exist in equilibrium with variable concentrations of zwitterionic structures with the nitrogen protonated and the oxygen deprotonated. They show the typical reactivity of naphthols.<sup>54</sup> 8-Quinolinol has long been used in

analysis as a chelating agent, especially for Zn(II), Mg(II), and Al(III) cations; the Cu(II) chelate is used as a fungicide.

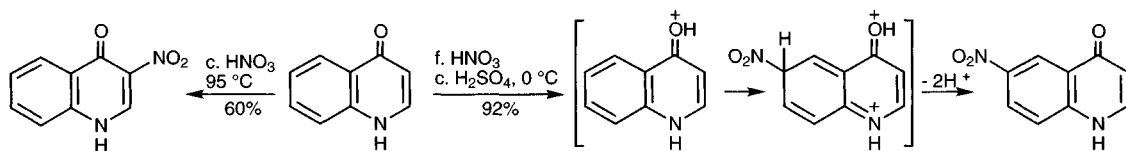
2-Quinolone (strictly 2(1*H*)-quinolinone) and 4-quinolone and 1-isoquinolone are completely in the carbonyl tautomeric form<sup>55</sup> for all practical purposes – the hydroxyl tautomers lack a favourable polarised resonance contribution, as illustrated below for 1-isoquinolone. There is considerable interest in quinolones as antibacterial agents.<sup>56</sup>



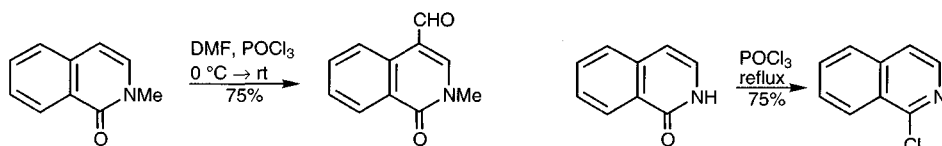
In 3-oxy-isoquinoline there is an interesting and instructive situation: here the two tautomers are of comparable stability. 3-Isoquinolinol is dominant in dry ether solution, 3-isoquinolone is dominant in aqueous solution. A colourless ether solution of 3-isoquinolinol turns yellow on addition of a little methanol because of the production of some of the carbonyl tautomer. The similar stabilities is the consequence of the balancing of two opposing tendencies: the presence of an amide unit in 3-isoquinolone forces the benzene ring into a less favoured quinoid structure, conversely, the complete benzene ring in isoquinolinol necessarily means loss of the amide unit and its contribution to stability. One may contrast this with 1-isoquinolone which has an amide, as well as a complete benzene, unit.<sup>57</sup>



The position of electrophilic substitution of quinolones and isoquinolones depends upon the *pH* of the reaction medium. Each type protonates on carbonyl oxygen so reactions in strongly acidic media involve attack on this cation: the contrast can be illustrated by the nitration of 4-quinolone at different acid strengths.<sup>58</sup> The balance between benzene ring and unprotonated heterocyclic ring selectivity is small, for example 2-quinolone chlorinates preferentially, as a neutral molecule, at C-6, and only secondly at C-3.



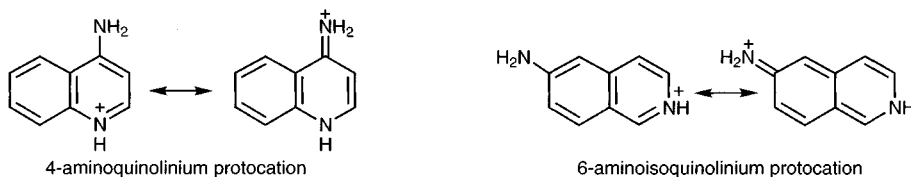
Strong acid-catalysed H-exchange of 2-quinolone proceeds fastest at C-6 and C-8; of 1-isoquinolone at C-4, then 5–7.<sup>59</sup> This is echoed in various electrophilic substitutions, for example formylation.<sup>60</sup>



The carbonyl tautomers deprotonate at N–H generating ambident anions which can react at either oxygen or nitrogen depending on the exact conditions. They are converted, as with the pyridones, into haloquinolines and -isoquinolines<sup>61</sup> by reaction with phosphorus halides; the quinolinols and isoquinolinols do not react in this way.

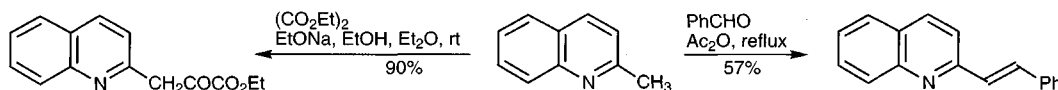
### 6.11 Aminoquinolines and -isoquinolines

Aminoquinolines and -isoquinolines exist as amino tautomers and all protonate on ring nitrogen. Only 4-aminoquinoline shows appreciably enhanced basicity ( $\text{p}K_a$  9.2); the most basic aminoisoquinoline is the 6-isomer ( $\text{p}K_a$  7.2), indeed this is the most basic of all the benzene-ring-substituted aminoquinolines and aminoisoquinolines.

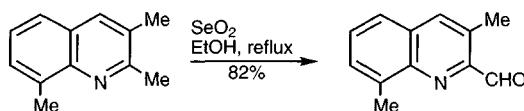


### 6.12 Alkylquinolines and -isoquinolines

The particular acidity of the protons of pyridine  $\alpha$ - and  $\gamma$ -alkyl groups is echoed by quinoline-2-<sup>62</sup> and 4-alkyl groups and by alkyl at the isoquinoline 1-position, but to a much lesser extent by alkyl at isoquinoline C-3. Condensation reactions with alkyl groups at these activated positions can be achieved in either basic or acidic media; the key nucleophilic species in the latter cases is probably an enamine,<sup>63</sup> or enamide,<sup>64</sup> and in the former, a side-chain carbanion.<sup>65</sup>



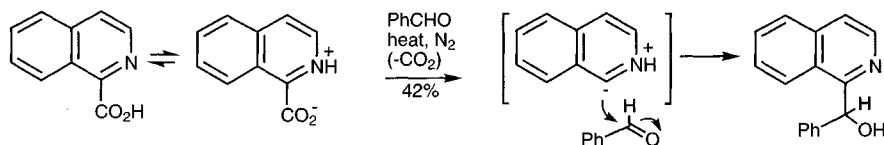
The selectivity is nicely illustrated by the selective oxidation of the 2-methyl in the example below.<sup>66</sup>



### 6.13 Quinoline and isoquinoline carboxylic acids and esters

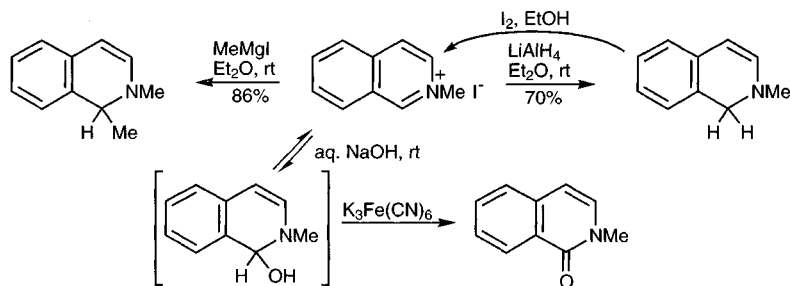
There is little to differentiate these derivatives from straightforward aromatic acids and esters save for the easy decarboxylation of quinoline-2- and isoquinoline-1-acids, via an ylide which can be trapped with aldehydes as electrophiles – the Hammick reaction.<sup>67</sup> Loss of carbon dioxide from *N*-methylquinolinium-2- and -isoquinoli-

nium-1-acids, and trapping of resulting ylides, can be achieved with stronger heating.<sup>68</sup>

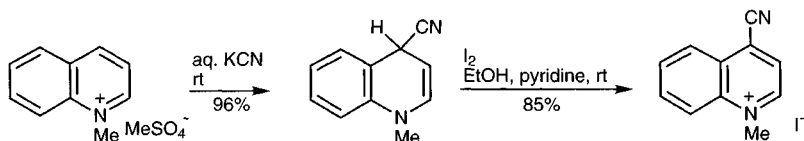


## 6.14 Quaternary quinolinium and isoquinolinium salts

The predominant property of these salts is the ease with which nucleophiles add to the quinolinium-2- and the isoquinolinium-1-positions. Hydroxide, hydride<sup>69</sup> and organometallic nucleophiles all add with facility, though the resulting dihydroaromatic products require careful handling if they are not to disproportionate (see also section 6.7) or be oxidised.<sup>70</sup>

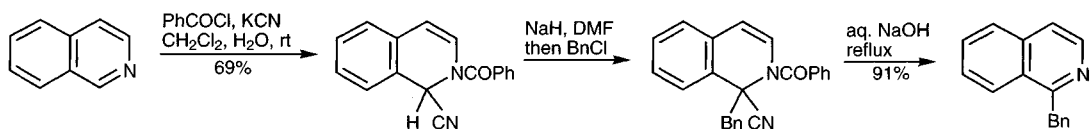


The position of fastest addition to quinolinium salts is C-2, but with reversible reactions, a thermodynamic adduct with the addend at C-4 and the residual double bond in conjugation with the nitrogen, can be obtained.<sup>71</sup> Sonication even allows the addition of ketone enolates, at C-2 of quinolinium salts.<sup>72</sup>



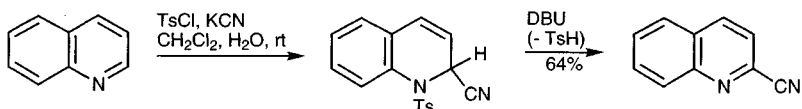
Treatment of quinoline and isoquinoline with sodium borohydride in a mixture of acetic acid and acetic anhydride gives good yields of *N*-acetyl-1,2-dihydro-derivatives.<sup>73</sup>

The long known Reissert reaction involves the kinetic trapping by cyanide of an *N*<sup>+</sup>-acylquinolinium or -isoquinolinium salt; in the classical process<sup>74</sup> the acylating agent is benzoyl chloride. Reissert compounds<sup>75</sup> are usually prepared using a dichloromethane/water two-phase medium; recent improvements include utilising phase-transfer catalysts with ultrasound<sup>76</sup> or crown ether catalysis.<sup>77</sup>

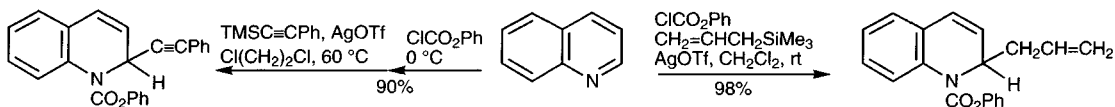


Reissert compounds have utility in a number of ways: deprotonation, alkylation and removal of acyl and cyanide groups leads to the corresponding substituted

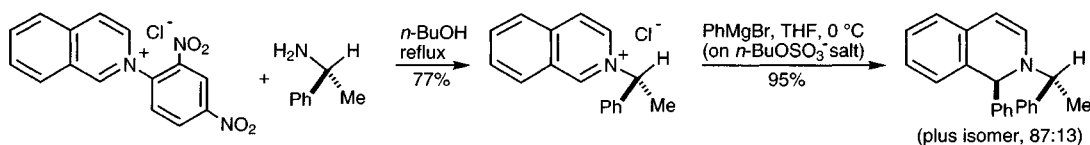
heterocycles. *N*-Sulfonyl analogues of Reissert adducts easily eliminate arylsulfinate, thus providing a method for the introduction of a cyano group.<sup>78</sup>



Allylsilanes will also trap *N*-acylisoquinolinium<sup>79</sup> and *N*-acylquinolinium<sup>80</sup> salts, and silyl alkynes will add,<sup>81</sup> also with silver ion catalysis.



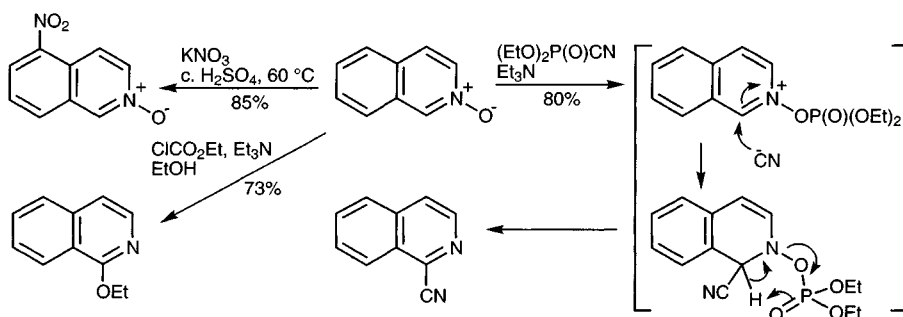
The Zincke salt of isoquinoline<sup>82</sup> is easily transformed into chiral isoquinolinium salts on reaction with chiral amines.<sup>83</sup> Nucleophilic addition of Grignard reagents to these salts shows good stereoselectivity.<sup>84</sup>



## 6.15 Quinoline and isoquinoline *N*-oxides

*N*-Oxide chemistry in these bicyclic systems largely parallels the processes described for pyridine *N*-oxide, with the additional possibility of benzene ring electrophilic substitution, for example mixed acid nitration of quinoline *N*-oxide takes place at C-5 and C-8 *via* the *O*-protonated species, but at C-4 at lower acid strength;<sup>85</sup> nitration of isoquinoline *N*-oxide takes place at C-5.<sup>86</sup>

Diethyl cyanophosphonate converts quinoline and isoquinoline *N*-oxides into the 1- and 2-cyano heterocycles in high yields in a process which must have *O*-phosphorylation as a first step, and in which the elimination of diethylphosphate may proceed *via* a cyclic transition state;<sup>87</sup> trimethylsilyl cyanide and diazabicycloundecene effect the same transformation.<sup>88</sup> Chloroformates and an alcohol convert the *N*-oxides into ethers, as illustrated below for isoquinoline *N*-oxide.<sup>89</sup>



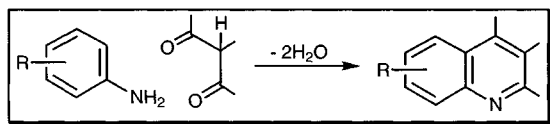
## 6.16 Synthesis of quinolines and isoquinolines

### 6.16.1 Ring syntheses

Three of the more generally important approaches to quinoline and three to isoquinoline compounds from non-heterocyclic precursors, are summarised in this section.

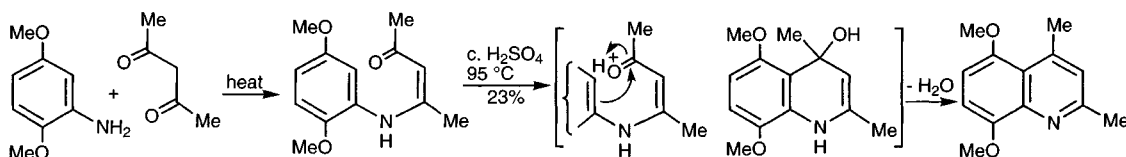
#### 6.16.1.1 Quinolines from arylamines and 1,3-dicarbonyl compounds

Anilines react with 1,3-dicarbonyl compounds to give intermediates which can be cyclised with acid.

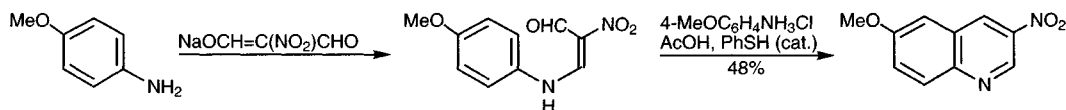


#### The Combes synthesis

Condensation of a 1,3-dicarbonyl compound with an arylamine gives a high yield of a  $\beta$ -amino-enone, which can then be cyclised with concentrated acid.<sup>90</sup> Mechanistically, the cyclisation step can be viewed as an electrophilic substitution by the *O*-protonated amino-enone, as shown, followed by loss of water to give the aromatic quinoline.

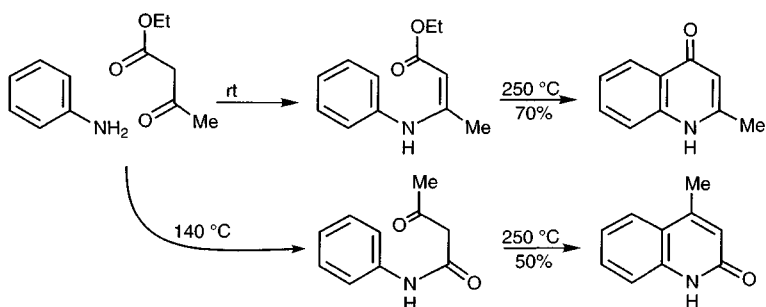


An example of this approach which provides 4-unsubstituted 3-nitroquinolines, is shown below.<sup>91</sup>

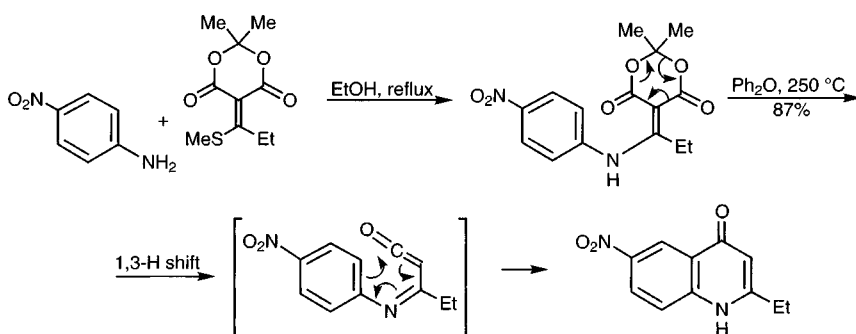


#### The Conrad–Limpach–Knorr synthesis

This closely related synthesis uses  $\beta$ -ketoesters and leads to quinolones.<sup>92</sup> Anilines and  $\beta$ -ketoesters can react at lower temperatures to give the kinetic product, a  $\beta$ -aminoacrylate, cyclisation of which gives a 4-quinolone. At higher temperatures,  $\beta$ -ketoester anilides are formed and cyclisation of these affords 2-quinolones.  $\beta$ -Aminoacrylates, for cyclisation to 4-quinolones, are also available *via* the addition of anilines to acetylenic esters<sup>93</sup> or by reaction with diethyl ethoxymethylenemalonate ( $\text{EtOCH}=\text{C}(\text{CO}_2\text{Et})_2 \rightarrow \text{ArNHCH}=\text{C}(\text{CO}_2\text{Et})_2$ ).<sup>94</sup>

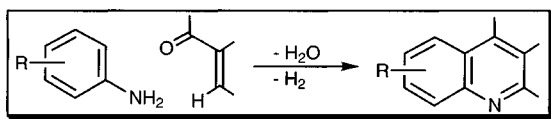


Cyclisations where the benzene ring carries an electron-withdrawing group can be effected using the variant shown below – the substrate is simply heated strongly – the mechanism of ring closure probably does not involve electrophilic attack on the benzene ring but rather is better viewed as the electrocyclic cyclisation of a 1,3,5-3-azatriene.<sup>95</sup>



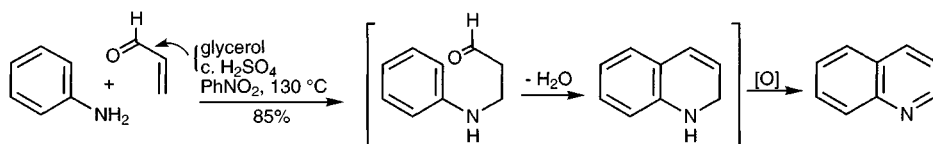
#### 6.16.1.2 Quinolines from arylamines and $\alpha,\beta$ -unsaturated carbonyl compounds

Arylamines react with an  $\alpha,\beta$ -unsaturated carbonyl compound in the presence of an oxidising agent to give quinolines. When glycerol is used as an *in situ* source of acrolein, quinolines carrying no substituents on the heterocyclic ring are produced.

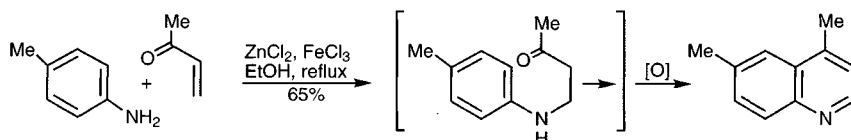


#### The Skraup synthesis<sup>96</sup>

In this extraordinary reaction, quinoline is produced when aniline, concentrated sulfuric acid, glycerol and a mild oxidising agent are heated together.<sup>97</sup> The reaction has been shown to proceed by dehydration of the glycerol to acrolein to which aniline then adds in a conjugate fashion. Acid-catalysed cyclisation produces a 1,2-dihydroquinoline finally dehydrogenated by the oxidising agent – the corresponding nitrobenzene or arsenic acid have been used classically, though with the inclusion of a little sodium iodide, the sulfuric acid can serve as oxidant.<sup>12</sup> The Skraup synthesis is the best for the ring synthesis of quinolines unsubstituted on the hetero-ring.<sup>98</sup>



The use of substituted carbonyl components confirms the mechanism, showing that interaction of the aniline amino group with the carbonyl group is not the first step.



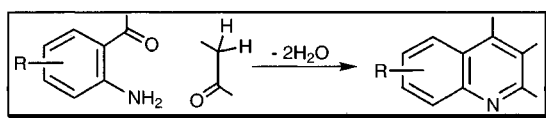
Skraup syntheses sometimes become very vigorous and care must be taken to control their potential violence; preforming the Michael adduct and using an alternative oxidant (*p*-chloranil was the best) has been shown to be advantageous in terms of yield and as a better means for controlling the reaction.<sup>99</sup>

### Orientation of ring closure in Skraup syntheses

In principle, *meta*-substituted arylamines could give rise to both 5- and 7-substituted quinolines. In practice, electron-donating substituents direct ring closure *para*, thus producing 7-substituted quinolines; *meta*-halo-arylamines produce mainly the 7-halo isomer. Arylamines with a strong electron-withdrawing *meta* substituent give rise mainly to the 5-substituted quinoline.

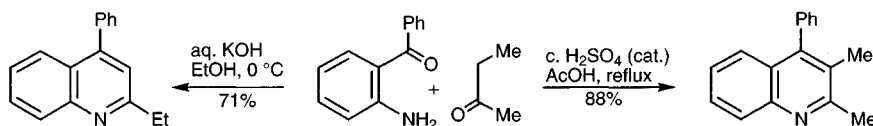
#### 6.16.1.3 Quinolines from *ortho*-acylarylamines and carbonyl compounds

*ortho*-Acylarylamines react with ketones having an  $\alpha$ -methylene to give quinolines.

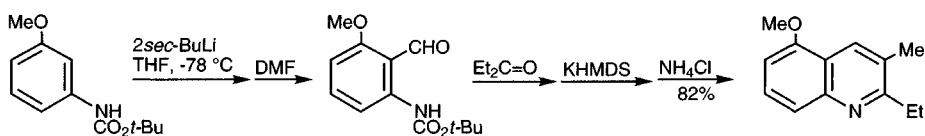


### The Friedländer synthesis<sup>100</sup>

*ortho*-Acylarylamines<sup>101</sup> condense with a ketone or aldehyde (which must contain an  $\alpha$ -methylene group) by base or acid catalysis to yield quinolines. The orientation of condensation depends on the orientation of enolate or enol formation.<sup>102</sup> The use of an oxime ether, as synthon for the  $\alpha$ -methylene ketone, has been shown to be advantageous.<sup>103</sup>

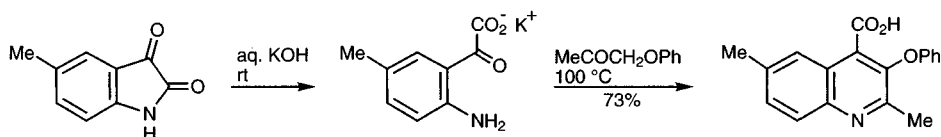


The potential of *ortho*,*N*-dilithiated *N*-protected arylamines for the preparation of *ortho*-acylarylamines starting components has been described,<sup>104</sup> and this idea taken further to provide a one-pot modification as illustrated below.



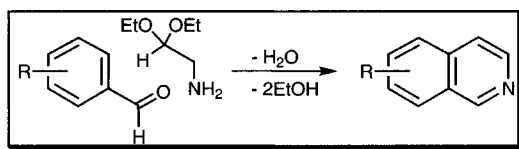
### The Pfitzinger synthesis

*ortho*-Aminoaraldehydes are sometimes difficult of access; in this modification, isatins (sections 17.14.3 and 17.17.4), which are easy to synthesise, are hydrolysed to *ortho*-aminoarylglyoxylates, which react with ketones affording quinoline-4-carboxylic acids.<sup>105</sup> The carboxylic acid group can be removed, if required, by pyrolysis with calcium oxide.



#### 6.16.1.4 Isoquinolines from arylaldehydes and aminoacetal

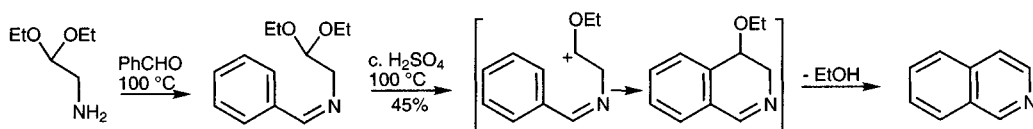
Aromatic aldehydes react with aminoacetal (2,2-diethoxyethanamine) to generate imines which can be cyclised with acid to isoquinolines carrying no substituents on the heterocyclic ring.



### The Pomeranz-Fritsch synthesis

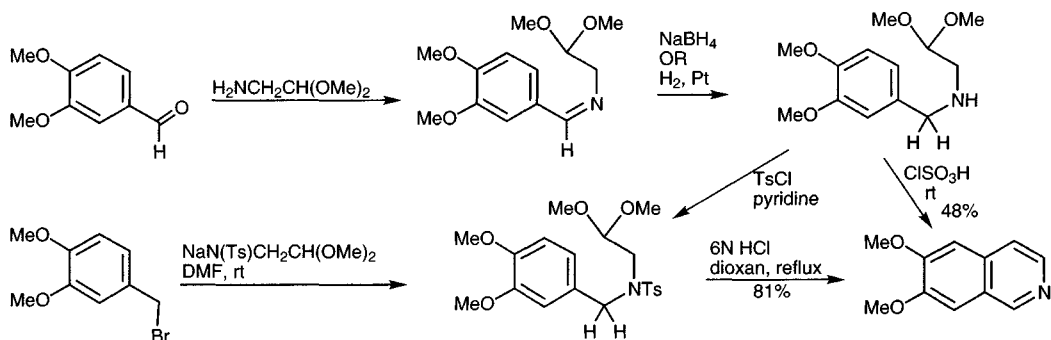
The Pomeranz-Fritsch synthesis<sup>106</sup> is normally carried out in two stages. Firstly, an aryl aldehyde is condensed with aminoacetal to form an aryl aldimine. This stage proceeds in high yield under mild conditions. Secondly the aldimine is cyclised by treatment with strong acid; hydrolysis of the imine competes and reduces the efficiency of this step and for this reason trifluoroacetic acid with boron trifluoride is a useful reagent.<sup>107</sup>

The second step is similar to those in the Combes and Skraup syntheses, in that the acid initially protonates, causing elimination of ethanol and the production of a species which can attack the aromatic ring as an electrophile. Final elimination of a second mole of alcohol completes the process.

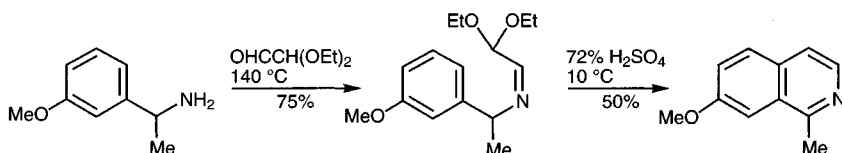


The electrophilic nature of the cyclisation step explains why the process works best for araldimines carrying electron-donating substituents (especially when these are oriented *para* to the point of closure leading to 7-substituted isoquinolines) and least well for systems deactivated by electron-withdrawing groups.

The problem of imine hydrolysis can be avoided by cyclising at a lower oxidation level, with tosyl on nitrogen for subsequent elimination as toluenesulfonic acid. The ring closure substrates can be obtained by reduction and tosylation of imine condensation products<sup>108</sup> or by benzylating the sodium salt of 2-tosylaminoethanal acetal.<sup>109</sup> Alternatively, a benzylic alcohol can be reacted with *N*-sulfonyl-aminoacetals in a Mitsunobu reaction.<sup>110</sup> Cyclisation of benzylaminoethanal acetals using chlorosulfonic acid gives the aromatic isoquinoline directly.<sup>111</sup>

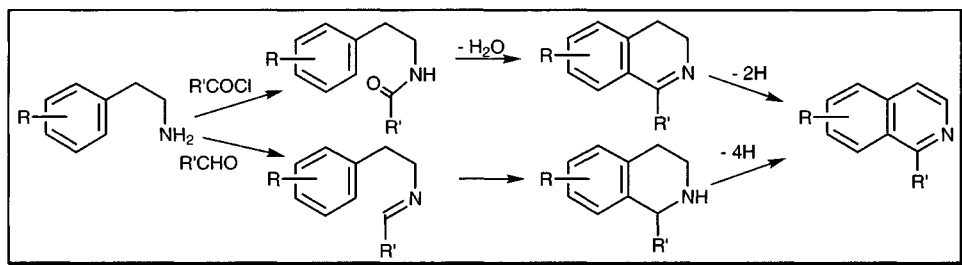


Isoquinolines substituted at C-1 are not easily formed by the standard Pomeranz-Fritsch procedure. The first step would require formation of a ketimine from aminoacetal and a aromatic ketone, which would proceed much less well than for an aryl aldehyde. A variation, which overcomes this difficulty, has a benzylamine condensing with glyoxal diethyl acetal; the resulting, isomeric imine, can be cyclised with acid.<sup>112</sup>



#### 6.16.1.5 Isoquinolines from arylethanamides

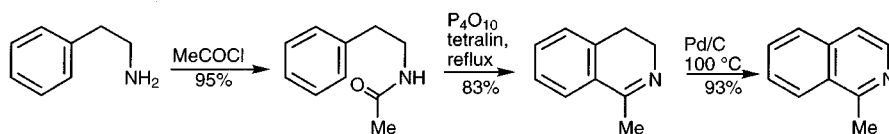
The amide or imine from reaction of 2-arylethanamines with an acid derivative or with an aldehyde, can be ring-closed to a 3,4-dihydro- or 1,2,3,4-tetrahydroisoquinoline respectively. Subsequent dehydrogenation produces the aromatic heterocycle.



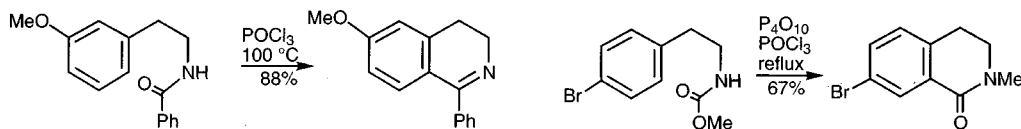
#### The Bischler-Napieralski synthesis<sup>113</sup>

In the classical process, a 2-arylethanamine reacts with a carboxylic acid chloride or anhydride to form an amide, which can be cyclised, with loss of water, to a 3,4-

dihydroisoquinoline, then readily dehydrogenated to the isoquinoline using palladium, sulfur, or diphenyl disulfide. Common cyclisation agents are phosphorus pentaoxide, phosphoryl chloride and phosphorus pentachloride. The electrophilic intermediate is very probably an imino chloride,<sup>114</sup> or imino phosphate; the former have been isolated and treated with Lewis acids when they are converted into isonitrilium salts, which cyclise efficiently to 3,4-dihydroisoquinolines.<sup>115</sup>



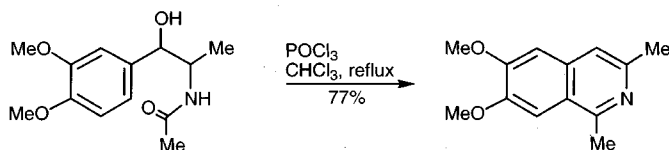
Here, once again, the cyclising step involves electrophilic attack on the aromatic ring so the method works best for activated rings, and *meta*-substituted substrates give exclusively 6-substituted isoquinolines.



Urethanes can be cyclised to 1-isoquinolones using trifluoromethanesulfonic anhydride and 4-dimethylaminopyridine; it may be that this reagent combination is well suited to the standard formation of 3,4-dihydroisoquinolines too.<sup>116</sup> The cyclisation of urethanes with a combination of phosphorus pentaoxide and phosphoryl chloride is not restricted to substrates with activated benzene rings.<sup>117</sup>

### Pictet-Gams modification

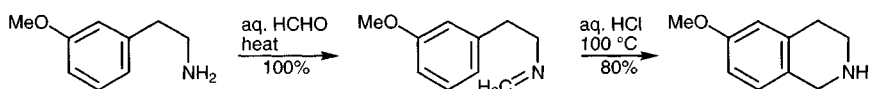
By conducting the Bischler-Napieralski sequence with a potentially unsaturated aryloethanamine, a fully aromatic isoquinoline can be obtained directly. The amide of a  $\beta$ -methoxy- or  $\beta$ -hydroxy- $\beta$ -aryloethanamine is heated with the usual type of cyclisation catalyst. It is not clear whether dehydration to an unsaturated amide or to an oxazolidine<sup>118</sup> is an initial stage in the overall sequence.



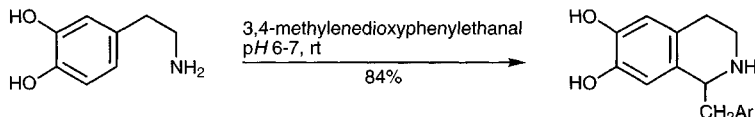
#### 6.16.1.6 Isoquinolines from activated aryloethanamines and aldehydes

##### The Pictet-Spengler synthesis<sup>119</sup>

Aryloethanamines react with aldehydes easily and in good yields to give imines. 1,2,3,4-Tetrahydroisoquinolines result from their cyclisation with acid catalysis. Note that the lower oxidation level imine, *versus* amide, leads to a tetrahydro- not a dihydroisoquinoline. After protonation of the imine, a Mannich-type electrophile is generated; since these are intrinsically less electrophilic than the intermediates in Bischler-Napieralski closure, a strong activating substituent must be present, and appropriately sited on the aromatic ring, for efficient ring closure.



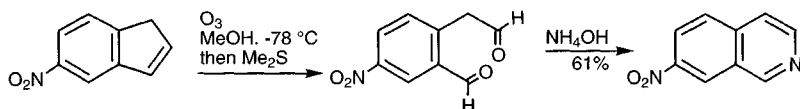
Highly activated hydroxylated aromatic rings permit Pictet-Spengler ring closure under very mild, 'physiological' conditions.<sup>120</sup>



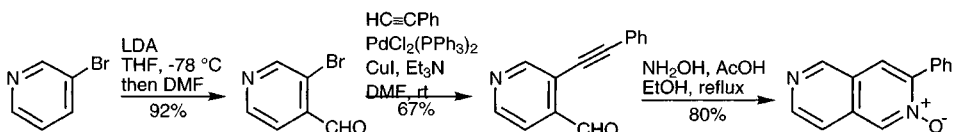
Routine dehydrogenation easily converts the tetrahydroisoquinolines produced by this route into fully aromatic species. Perhaps of more interest is their selective conversion into 3,4-dihydroisoquinolines using potassium permanganate and a crown ether.<sup>121</sup>

### 6.16.1.7 Newer methods

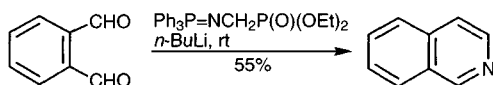
A number of recently described routes take rather different approaches to the synthesis of quinolines and isoquinolines, for example ozonolyses of indenenes, as shown below provides homophthalaldehydes which are at exactly the right oxidation level for aromatic pyridine ring closure with ammonia.<sup>122</sup> Another method for the generation of equivalent species depends on the side-chain lithiation of *ortho*-methylarylaldehyde cyclohexylamine imines, then acylation with a Weinreb amide.<sup>123</sup>



A route<sup>124</sup> in which a synthon for such a dialdehyde is central depends on *ortho* lithiation of an aryl bromide for conversion to *ortho* bromoaryl aldehyde, then palladium-catalysed replacement of the halide with an alkyne, subsequent reaction with ammonia producing the isoquinoline. The sequence below shows how this type of approach can be used to produce naphthyridine mono-*N*-oxides by reaction of the alkynyl-aldehyde with hydroxylamine instead of ammonia.<sup>125</sup>

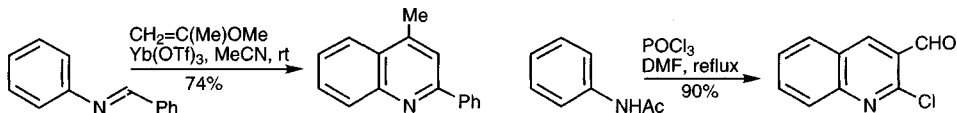


An isoquinoline ring disconnection, with considerable potential, could not be brought to practical fruition until a 1,2-monoazabisylide was synthesised; it involves Wittig and aza-Wittig condensations on phthalic dicarboxaldehyde to generate isoquinoline.<sup>126</sup>

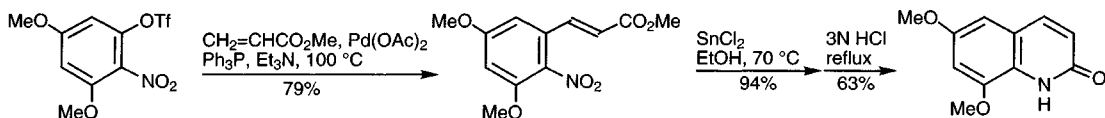


Some routes have been described which involve the formation of two C–C bonds in the same pot to produce quinolines and isoquinolines. For the production of 2-arylquinolines a Schiff base is reacted with an enol ether in presence of ytterbium(III) triflate.<sup>127</sup> 2-Chloro-3-formylquinolines result from a practically simple process

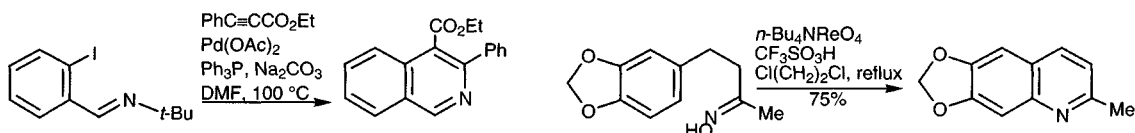
involving the interaction of acetanilide with phosphoryl chloride and dimethylformamide,<sup>128</sup> and for the synthesis of isoquinolines, an arylacetate is treated with a nitrile and trifluoromethanesulfonic anhydride.<sup>129</sup>



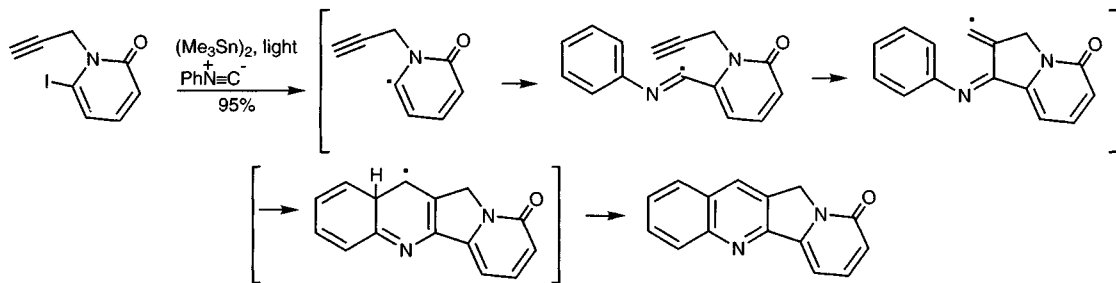
In a 2-quinolone synthesis<sup>130</sup> a *trans* cinnamate must isomerise during the ring closing process.



*ortho*-Iodoaraldehyde imines react directly with alkynes, using palladium(0) catalysis, generating isoquinolines in which the original nitrogen substituent has been lost.<sup>131</sup> An unusual quinoline synthesis has a bond making between the aromatic ring and the nitrogen of the future heterocycle as a key step. Reaction of alkyl 2-arylethylketone oximes with tetra-*n*-butylammonium perrhenate produces quinolines; depending on the aromatic substituents the mechanism involves either direct cyclising attack *ortho*, or *ipso* attack followed by rearrangement.<sup>132</sup>



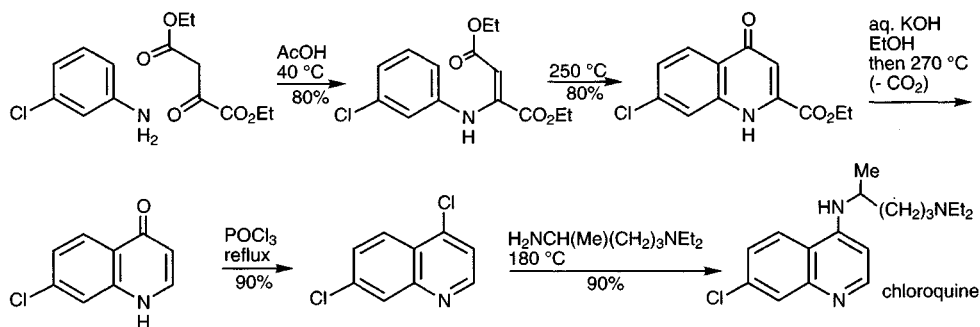
A radical-based quinoline ring synthesis was developed<sup>133</sup> with the total synthesis<sup>134</sup> of the anti-cancer alkaloid camptothecin in mind. The sequence<sup>135</sup> below shows the construction of the ring skeleton of camptothecin and suggests a mechanism for the process.



## 6.16.2 Examples of notable syntheses of quinoline and isoquinoline compounds

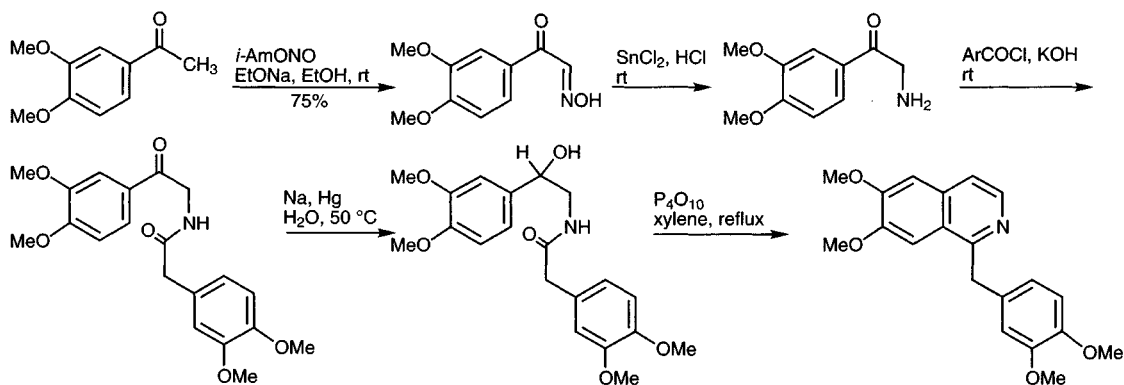
### 6.16.2.1 Chloroquine<sup>136</sup>

Chloroquine is a synthetic antimalarial.



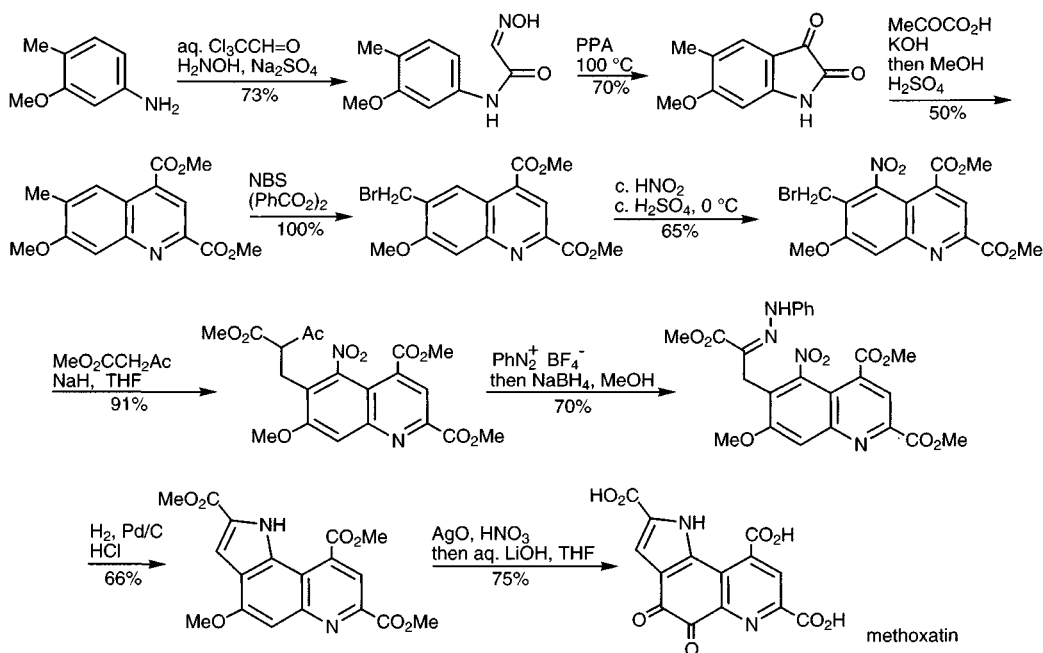
### 6.16.2.2 Papaverine<sup>137</sup>

Papaverine is an alkaloid from opium; it is a smooth muscle relaxant and thus useful as a coronary vasodilator – the synthesis illustrates the Pictet-Gams variation.



### 6.16.2.3 Methoxatin<sup>138</sup>

Methoxatin is an enzyme cofactor of bacteria which metabolise methanol. This total synthesis is a particularly instructive one since it includes an isatin synthesis (section 17.17.4), a quinoline synthesis, and an indole synthesis.



## Exercises for chapter 6

### Straightforward revision exercises (consult chapters 4 and 6)

- At which positions do quinoline and isoquinoline undergo nitration? Why these positions?
- At which positions do quinoline and isoquinoline react most readily with nucleophiles? Why these positions?
- At which positions do quinoline and isoquinoline react most readily with radical reagents?
- How might one selectively reduce the heterocyclic ring of quinoline or isoquinoline?
- How could one convert 4-methylquinoline into 4-ethylquinoline?
- How could one convert (i) isoquinoline into 2-methyl-1-isoquinolone; (ii) quinoline into 2-cyanoquinoline?
- What reactants would combine to produce 6-methoxy-2,4-diethylquinoline?
- What ring synthesis method would be suitable for converting 4-methoxyaniline into 6-methoxyquinoline?
- How could one prepare 2-ethyl-3-methylquinoline-4-carboxylic acid from aniline (see also 17.17.4)?
- What ring synthesis method would be suitable for the preparation of 6-methoxyisoquinoline?
- How could 2-(4-methoxyphenyl)ethanamine be converted into 7-methoxy-1-phenylisoquinoline?

### More advanced exercises

1. Predict the structures of the high yield mono-nitration products (i)  $C_{16}H_{12}N_2O_2$  from 1-benzylisoquinoline (ii)  $C_{10}H_8N_2O_3$  from 6-methoxyquinoline, (iii)  $C_{10}H_8N_2O_3$  from 7-methoxyisoquinoline.
2. Write a sequence to rationalise the conversion of quinoline into 3-bromoquinoline by reaction with  $Br_2$  in  $CCl_4$ /pyridine.
3. Suggest a structure for product  $C_{16}H_{16}ClNO_4$  from 1,3-dichloroisoquinoline and  $NaCH(CO_2Et)_2$ .
4. Deduce a structure for the product,  $C_{15}H_{18}N_2OS$  formed on treatment of 2-*t*-BuCONH-quinoline successively with 3 x *n*-BuLi then dimethyl disulfide.
5. Write a sequence of mechanistic steps to explain the conversion of 2-methylisoquinolinium iodide into 2-methyl-1,2,3,4-tetrahydroisoquinoline with sodium borohydride in ethanol.
6. Draw the most stable tautomer of 3-oxyquinoline, and of 1-, 4- and 8-oxyisoquinolines.
7. Suggest a mechanistic sequence to rationalise the formation of methyl 2-methylquinoline-3-carboxylate from the reaction of aniline with methyl acetoacetate ( $\rightarrow C_{11}H_{13}NO_2$ ) and then this with DMF/ $POCl_3$ .
8. Deduce the structure of the product quinolones: (i)  $C_{12}H_{11}NO_4$  resulting from reaction of 2-methoxyaniline with dimethyl acetylenedicarboxylate then heating at 250 °C; (ii)  $C_{10}H_6ClNO_3$  from 3-chloroaniline and diethyl ethoxymethylenemalonate ( $EtOCH=C(CO_2Et)_2$ ) then heating at 250 °C, then heating with aq. NaOH.
9. Deduce structures for the quinolines produced from the following combinations: (i)  $C_{16}H_{11}NO_2$  from isatin/NaOH then acetophenone; (ii)  $C_{10}H_7NO_3$  from isatin/KOH then 3-chloropyruvic acid; (iii)  $C_{10}H_7NO_3$  from *N*-acetyl isatin and NaOH.
10. Deduce structures for the heterocyclic products from the following combinations: (i)  $C_{11}H_7N_3O_2$  from 2-aminobenzaldehyde and barbituric acid (section 7.10); (ii)  $C_{14}H_{11}NO_6$  from 4,5-methylenedioxy-2-aminobenzaldehyde and dimethyl acetylenedicarboxylate; (iii)  $C_{14}H_{11}NS$  from 2-aminoacetophenone and 2-acetylthiophen; (iv)  $C_{21}H_{19}NO$  from 2-aminobenzophenone and dimesityl oxide; (v)  $C_{15}H_{12}N_2O_2S$  from 2-aminopyridine-3-aldehyde and 1-phenylsulfonylacetone; (vi)  $C_{15}H_{11}N_3$  from 4-amino-pyrimidine-5-aldehyde and  $\alpha$ -tetralone.

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