NOVEL APPROACHES

TO THE

SYNTHESIS OF QUINOLINE DERIVATIVES

THESIS

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requirements for

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by

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ABSTRACT

The investigation has been concerned with the application of the Baylis-Hillman methodology to the synthesis of quinoline derivatives. An extensive range of novel Baylis-Hillman products has been prepared, typically in moderate to excellent yields, by condensing 2-nitrobenzaldehyde derivatives with various vinyl ketones and acrylic esters in the presence of diazabicyclo[2.2.2]octane (DABCO). Reduction of the nitro group in the Baylis-Hillman products was effected by catalytic hydrogenation in ethanol using a 10% palladium-on-carbon catalyst to afford quinoline, quinoline-*N*-oxide and quinolone derivatives. In all cases, it is apparent that cyclisation involves exclusive attack of nucleophilic nitrogen at the carbonyl centre, with acrylic ester derivatives affording quinolones and vinyl ketone derivatives affording quinolines and the corresponding quinoline-*N*-oxides. No products arising from a conjugate addition pathway were observed. The use of stannous chloride as an alternative reagent to effect reductive cyclisation of the Baylis-Hillman products has been explored, and found to favour the formation of 1,2-dihydroquinoline derivatives, with cyclisation occurring *via* a conjugate addition pathway. Isolation of the products, following work-up of the stannous chloride reactions, however, presented some difficulty. All compounds were characterised by spectroscopic (NMR and IR) and, where appropriate, elemental (high-resolution MS) analysis.

Interconversion of the quinoline and quinoline-*N*-oxide derivatives has been explored and finally achieved in quantitative yields. Reduction of 2,3-dimethylquinoline-*N*-oxide to the corresponding quinoline was effected using phosphorus tribromide in DMF, and the reverse transformation with *meta*-chloroperbenzoic acid (MCPBA) in $CHCl_3$. Application of these methods to *mixtures* of 2,3-dimethylquinoline and its *N*-oxide has afforded, selectively, *either* the quinoline derivative *or* the corresponding *N*-oxide.

CONTENTS

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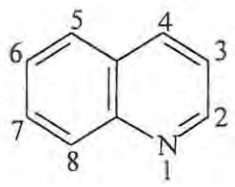
1. INTRODUCTION

1.1 STRUCTURE AND ISOLATION OF QUINOLINE

Quinoline (1-azanaphthalene or benzo[b]pyridine) **1** is one of the three possible azanaphthalenes, the other two being isoquinoline **2** and the quinolizium cation **3.** The bicyclic ring structure, first suggested by Korner,[1] was established on the basis of the constitution, syntheses and chemical properties of quinoline itself; the Friedlander synthesis and degradative oxidation and ring-opening reactions were particularly important in supporting this suggestion. The structure has also been confirmed by X-ray crystallographic analysis of derivatives and by various spectroscopic techniques.[1]



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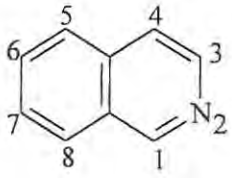

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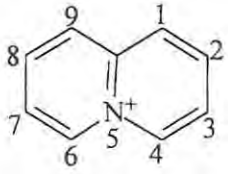
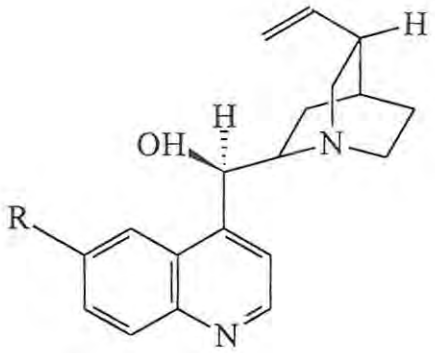


3

A large number of heterocyclic compounds have been found in nature, and their isolation and study have led to great advances in the field of heterocyclic chemistry. Quinolines form an important group of compounds in this field,[2] with many of the naturally occurring quinolines exhibiting significant biological activity. In 1834, Runge isolated crude quinoline from tar, the sample presumably also containing isoquinoline and alkyl derivatives of both bases.[1,3] Eight years

later,

Gerhardt[1] isolated quinoline from the alkaloids cinchonine **4** and quinine **5** by vigorous distillation in the presence of alkali. In fact, the name, quinoline, is derived from the word, quinine, which, in turn, is derived from *quina*, a Spanish version of a local South American name for the bark of quinine-containing *Cinchona* species.[4] Quinoline has also been obtained from tobacco by destructive distillation, from crude petroleum and shale oil and by direct synthesis.



4: R=H; cinchona
5: R=OMe; quinine

1.2 SYNTHESIS OF QUINOLINE DERIVATIVES

Numerous reactions have been used to prepare quinolines, and various approaches are possible. These differ according to which of the bonds (a) - (d) **(Figure 1)** completes the ring-closure and the method of introducing the missing carbons. The synthon types **7** - **10** represent the most common strategies. The first syntheses of quinolines were reported by Koenigs.[1] In one method, the vapours of ethylaniline, or other alkylanilines, were passed over heated litharge, while in a

second, the addition product of aniline and acrolein was heated. These syntheses were followed by those of Skraup[1,5] and of Doebner and von Miller.[1]

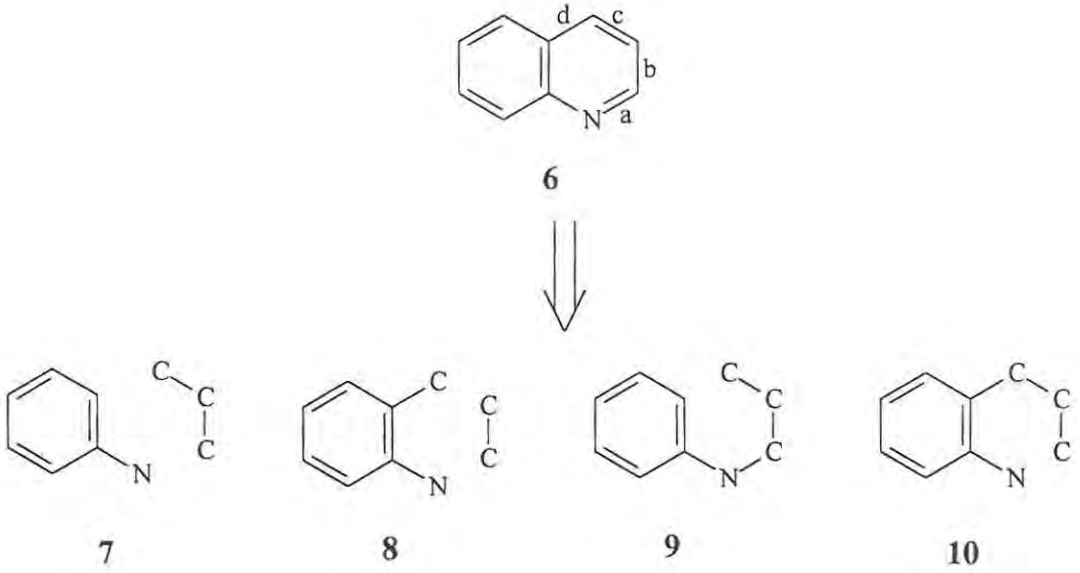
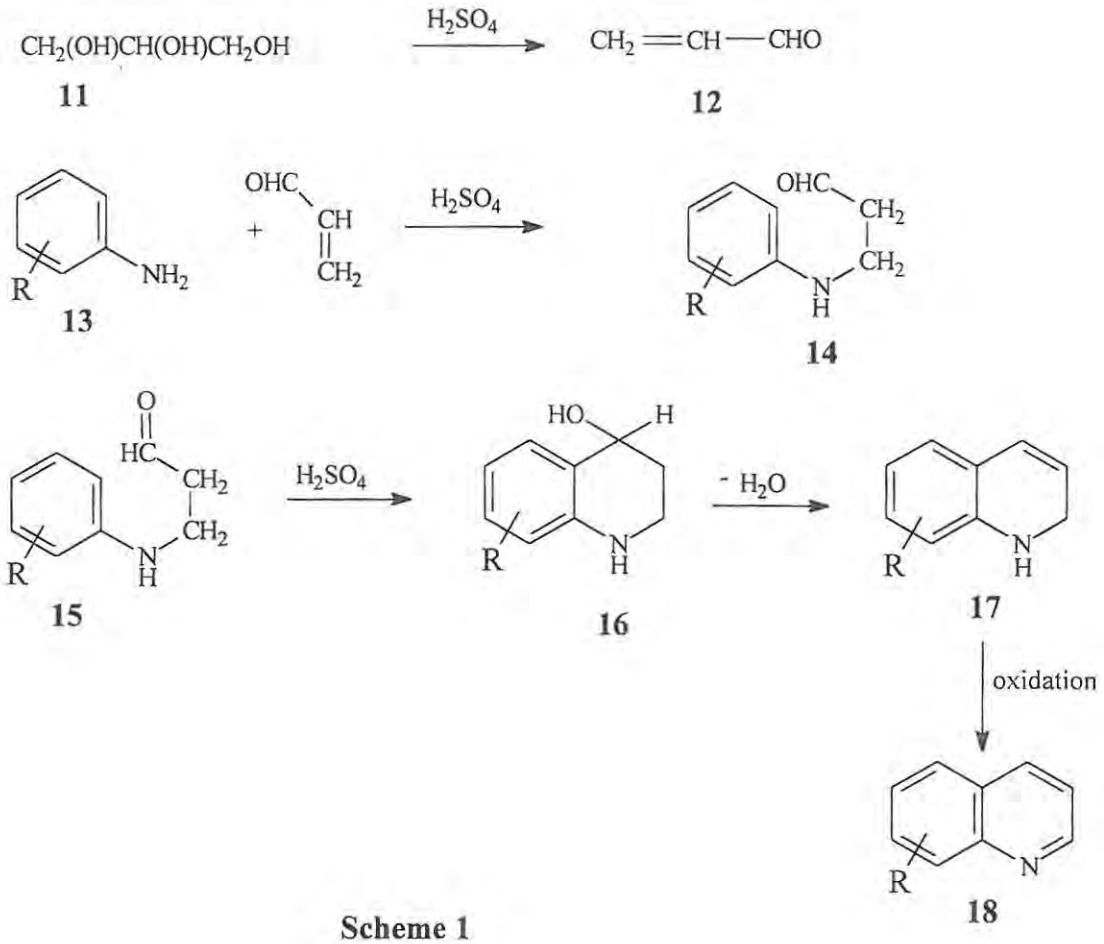


Figure 1. Common diconnections for the construction of quinolines

1.2.1. The Skraup Synthesis

The most widely used method for synthesising quinoline is the one developed by Skraup;[1,5] it can also be applied to the preparation of many quinoline derivatives. In this synthesis, a quinoline is produced when an aniline derivative with a vacant *ortho*-position is heated together with concentrated sulphuric acid, glycerol and a mild oxidizing agent. The initial stages of the reaction may be very vigorous and can be moderated by the inclusion of ferrous sulphate.[1] The reaction has been shown to proceed *via* acid-catalysed elimination of water from glycerol **11** to form

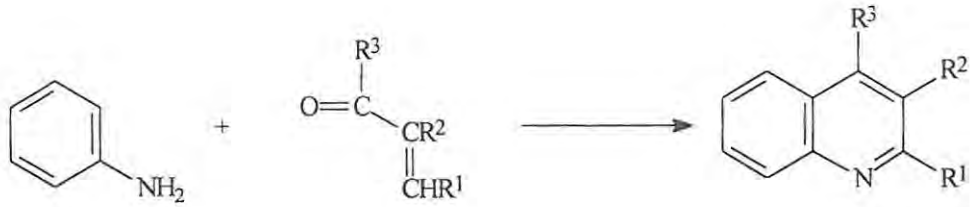
acrolein **12 (Scheme 1)**; conjugate addition of the aniline **13** to acrolein follows, resulting in the formation of an anilinopropanal intermediate **14**. Ring-closure then results from electrophilic attack by the carbonyl carbon at the ring position ortho to the amino group; subsequent dehydration gives the dihydroquinoline **17**, oxidation of which affords the quinoline product **18**.



Scheme 1

With glycerol **11** as the precursor for the key intermediate, acrolein **12**, the quinoline will contain no substituents in the heterocyclic ring but, if a substituted quinoline is required , glycerol may be replaced with pre-formed α,β-unsaturated carbonyl compounds **20** having the appropriate

substituents (**Scheme 2**).[1] Thus, crotonaldehyde **20a** gives 2-methylquinoline **21a,** and methyl vinyl ketone **20b** gives 4-methylquinoline **21b.**



19 **20** **21**

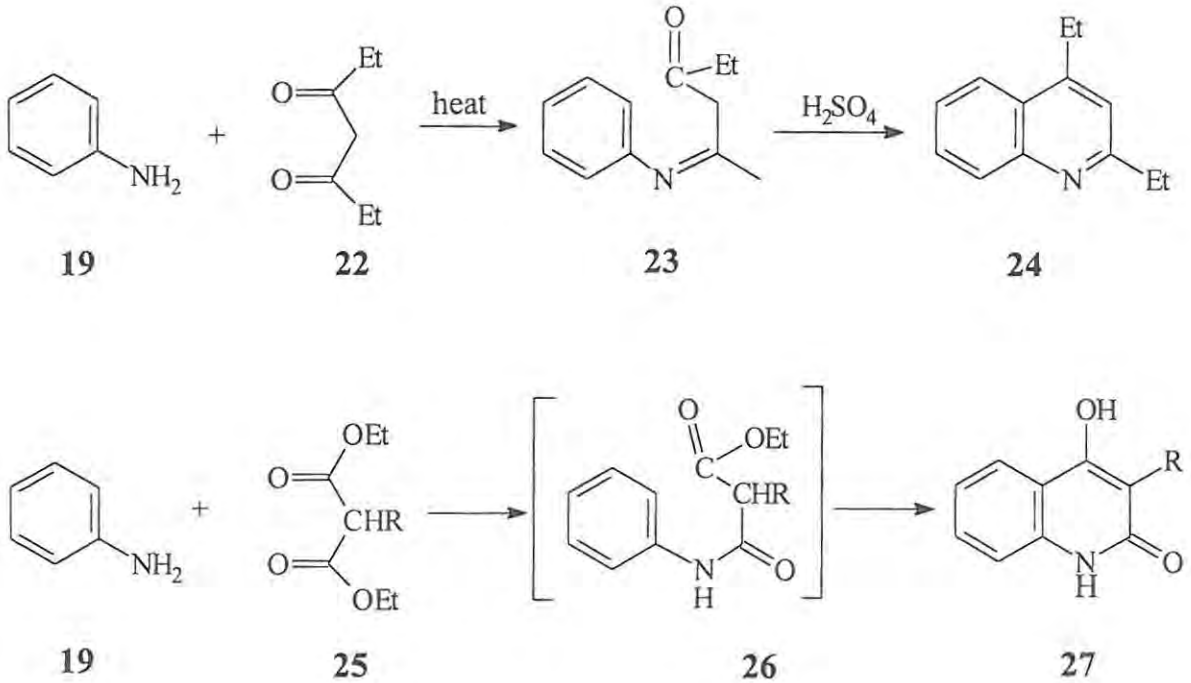
a: R^1=Me; R^2=R^3=H
b: R^1=R^2=H; R^3=Me

Scheme 2

Many attempts have been made to prepare quinoline directly from acrolein, but good yields were obtained only when acrolein vapour was passed into a mixture of aniline, sulphuric acid and an oxidizing agent. It appears that, under ordinary conditions, the acrolein is polymerized before it can combine with the aniline. Substituted anilines can be used to give quinoline derivatives with substituents in the carbocyclic ring.[1] Of course, anilines substituted at the ortho position have only one site for ring-closure and thus give 8-substituted quinolines. Symmetrical *para*-substituted anilines undergo ring-closure at either of the ortho positions to give 6-substituted quinolines, but *meta*-substituted anilines can give both 5- and 7-substituted quinolines. The Skraup synthesis cannot, however, be used on compounds which contain acid-labile substituents. Apart from this limitation, the Skraup synthesis is considered to be the best available method for the synthesis of quinolines unsubstituted on the heterocyclic ring.[4]

1.2.2. The Combes Synthesis

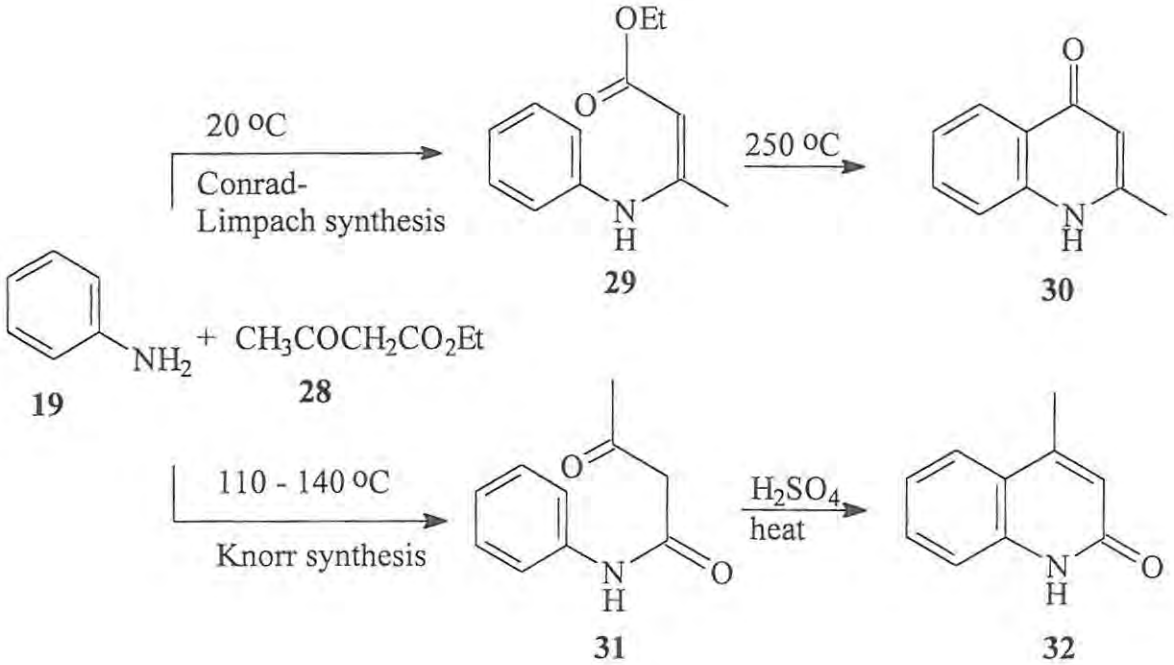
In this method, a 1,3-dicarbonyl compound is condensed with an arylamine to give a β-imino ketone, which can then be cyclized by treatment with concentrated acid.[4] The cyclization step involves electrophilic substitution by the *O*-protonated imino ketone followed by dehydration to give the quinoline. Thus, reaction of heptane-3,5-dione **22** with aniline **19** gives 2,4-diethylquinoline **24 (Scheme 3)**. When 2-substituted malonic esters **25** are reacted with an aromatic amine in diphenyl ether under nitrogen, 3-substituted 4-hydroxy-2-quinolones **27** are formed, the initial linking reaction, in this case, involving nucleophilic acyl substitution rather than nucleophilic addition at the carbonyl centre.



Scheme 3

1.2.3. The Conrad-Limpach and Knorr syntheses

Other reactions commonly used to prepare quinolines are the closely related Conrad-Limpach and Knorr syntheses. In these reactions, an aromatic amine is reacted with a β-keto-ester, such as ethyl acetoacetate, to give 2- or 4-quinolones, which can be readily converted to chloroquinolines with phosphoryl chloride and then reduced to quinolines.[1,3,4] The β-keto-ester **28** contains two different types of carbonyl group and, at low temperature (20 °C), the amino group condenses with the more reactive keto carbonyl (kinetic control) to give a β-aminoacrylic ester **29** which, on heating, cyclizes to give the 4-quinolone **30 (Scheme 4)**. At higher temperatures (110-140 °C), the more stable amide **31** is formed (thermodynamic control) after interaction of the arylamine with the ester group; the resulting anilide undergoes ring-closure on heating, alone or with

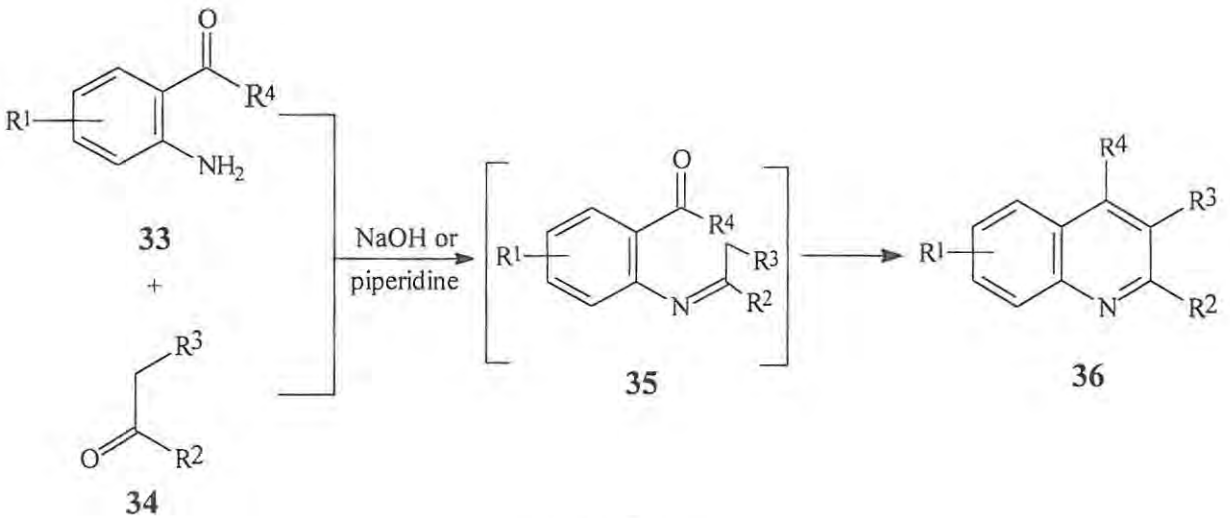


Scheme 4

sulphuric acid, to give the 2-quinolone **32**. The kinetically controlled process is known as the Conrad-Limpach synthesis, the thermodynamically controlled reaction as the Knorr synthesis.[4]

1.2.4. The Friedlander synthesis

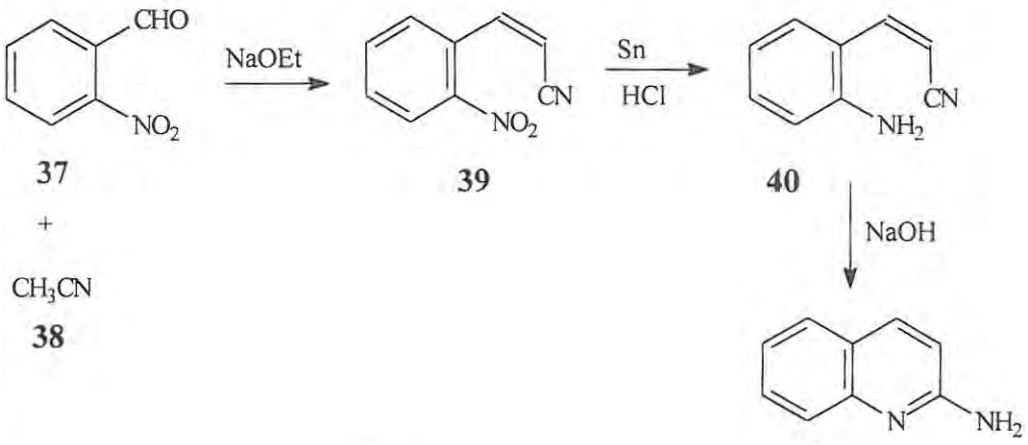
In the Friedlander synthesis, substituted quinolines **36** are formed by the condensation of *o*-aminobenzaldehydes or *o*-aminoacetophenones **33** with aldehydes, ketones and other compounds which contain an α-methylene group.[1] In this reaction **(Scheme 5)**, the first stage involves the base-catalysed formation of a Schiff base **35**; this is followed by ring-closure between carbons 3 and 4 of the quinoline ring by a Knoevenagel condensation.



Scheme 5

The disadvantage of this method is that aminobenzaldehydes are bifunctional and prone to self

condensation. This problem may be controlled either by use of the Pfitzinger modification (see **section 1.2.5**) or by use of the less reactive nitro compounds in place of the amines.[1] Under the latter conditions, the Knoevenagel condensation occurs first, and ring-closure to the nitrogen can be achieved by reduction of the nitro group. This is illustrated by the formation of 2-aminoquinoline **41** from *o*-nitrobenzaldehyde **37** and acetonitrile **38 (Scheme 6)**



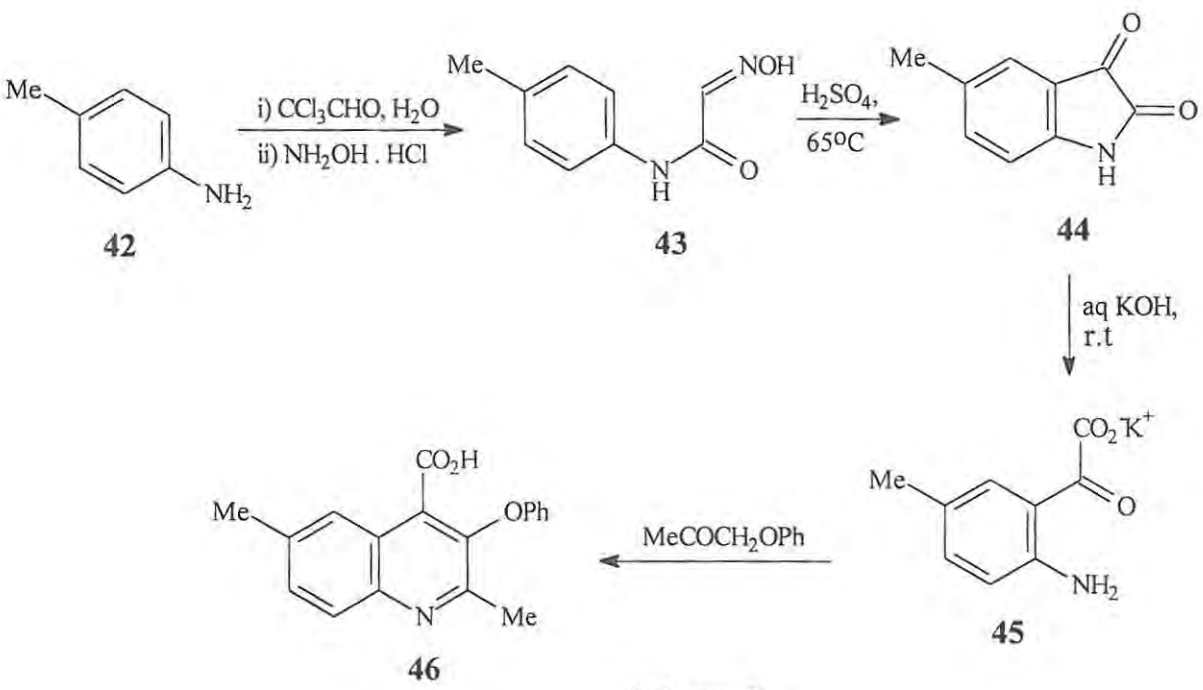
37 + CH_3CN **38** → **39** → **40** → **41**

Scheme 6

1.2.5. The Pfitzinger Synthesis

The *ortho*-aminobenzaldehydes required for the Friedlander synthesis are often not easy to obtain, and this modification makes use of substituted isatinic acid (*o*-aminobenzoylformic acid) derivatives **45 (Scheme 7)**, which are formed by alkaline cleavage of the isatin lactam ring. Condensation with a keto-methylene moiety, or its oxime, gives a quinoline-4-carboxylic acid,

such as compound **46**.[1] Many such compounds have been prepared for transformation into derivatives for pharmacological testing as antimalarials.[4] If the 4-carboxyl group is not required, it can readily be eliminated by pyrolysis with calcium oxide or copper powder.

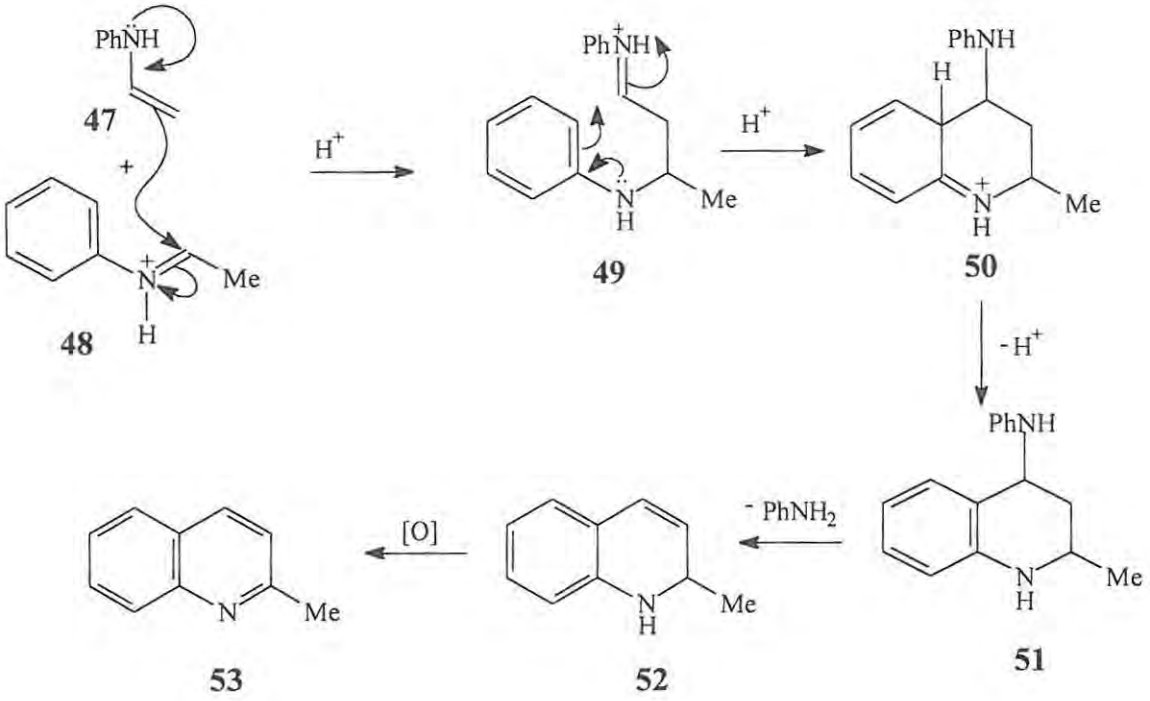


42 **43** **44** **45** **46**

Scheme 7

1.2.6. The Doebner-von Miller synthesis

The Doebner-von Miller synthesis is closely related to that of Skraup, and involves heating a primary aromatic amine with an aldehyde in the presence of an acid; however, no oxidizing agent is used. The pioneers of this reaction used ethylene glycol (from which acetaldehyde can be



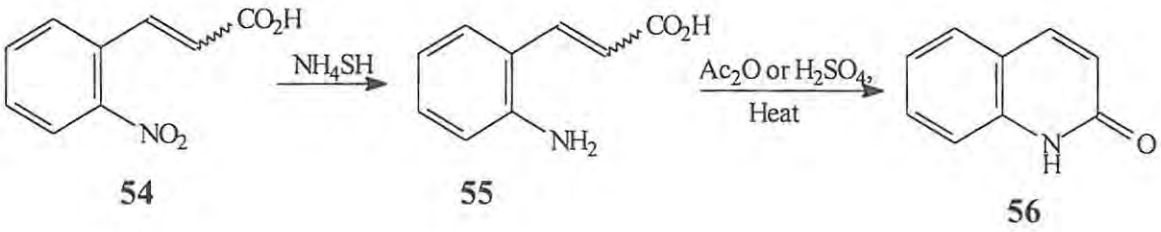
Scheme 8

formed by the elimination of water), but other aldehyde precursors, such as paraldehyde or acetals, may be used in place of the aldehyde itself.[1] The condensing agent typically used is zinc chloride, and it has been proposed that the quinoline system **53** is formed as a result of the self-condesation of two molecules of the Schiff base, obtained by condensation of the aromatic amine and the aldehyde (**Scheme 8**); the nucleophilic species is depicted as the tautomer **47** and the electrophile as the ketimine **48**.

1.2.7. Cyclisation of *o*-amino derivatives of cinnamic acid

Ortho-amino *allo*-cinnamic acid derivatives readily undergo ring closure to give 2-quinolones. The *o*-amino *trans*-cinnamic acid derivatives (obtained by reduction of the corresponding nitro

compounds), on treatment with acetic anhydride or sulphuric acid, give bimolecular anhydrides, which rearrange to the *cis*-isomer on heating; subsequent cyclisation gives the 2-quinolones **56 (Scheme 9)**. Claret[1] cites this reaction as one of the earliest syntheses of the quinoline ring system.

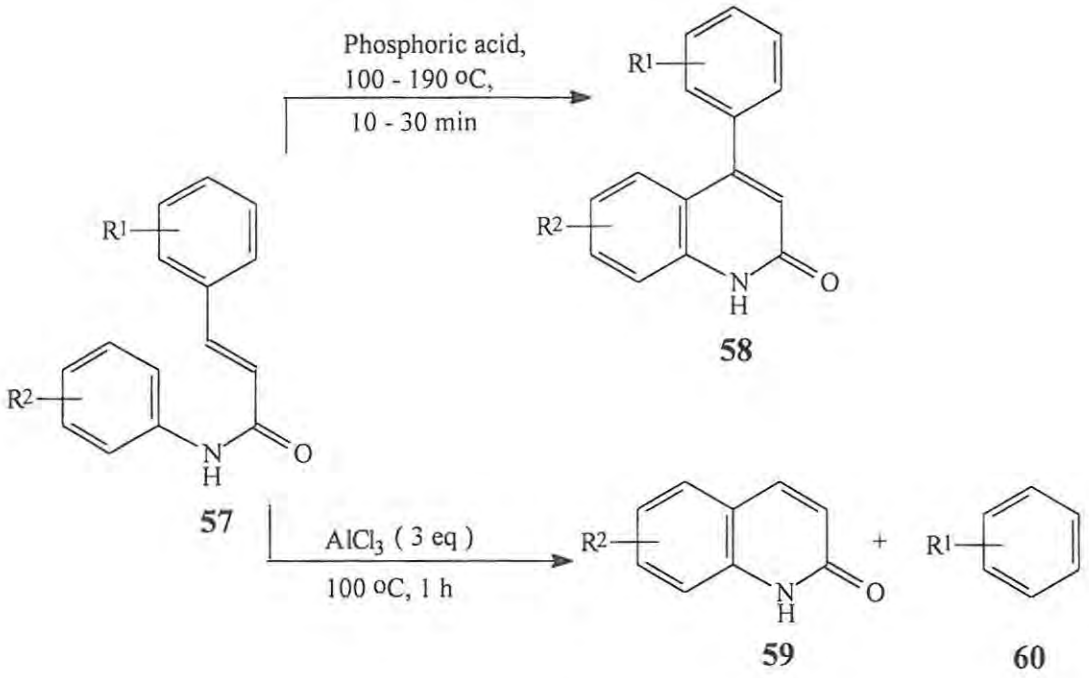


54 **55** **56**

Scheme 9

1.2.8. Cyclisation of cinnamanilides

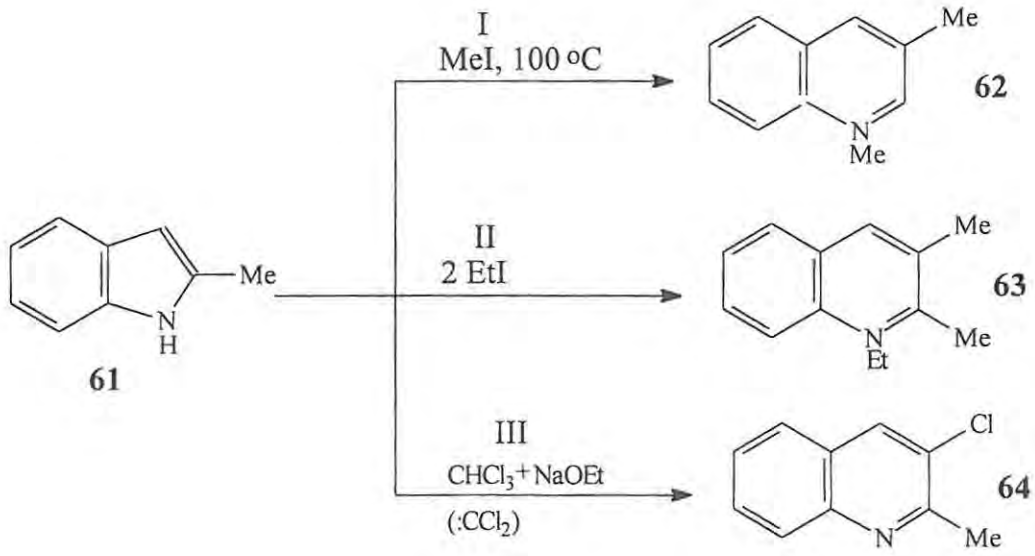
When heated with polyphosphoric acid, cinnamanilides **57** afford 4-aryl-3,4-dihydro-2-quinolones **58 (Scheme 10)**. The reaction is successful with a variety of *para*-substituents (R^1) in the 4-aryl ring, but *ortho*-substituents hinder ring-closure. Electron-withdrawing groups in the benzannulated ring may also prevent ring closure, while strongly electron-releasing groups may cause loss of the aryl group if the reaction temperature is not kept as low as possible.[1] When aluminium chloride is used as a catalyst, 2-quinolones **59** are, in fact, formed with elimination of the aryl group.



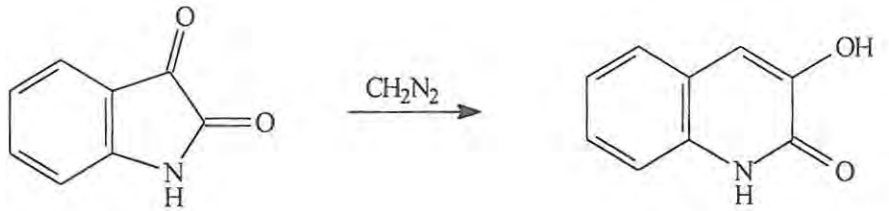
Scheme 10

1.2.9. Ring-enlargement methods

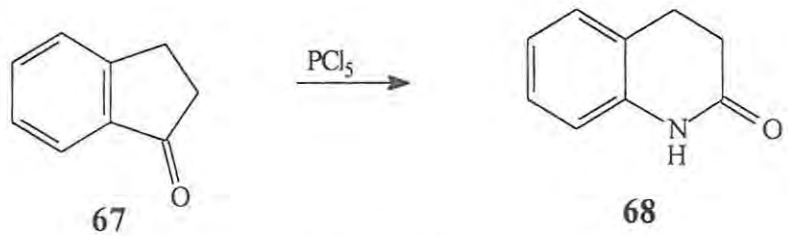
The quinoline derivatives **62 - 64** can be prepared from the indole **61** by ring-enlargement using alkyl halides (routes I and II) or dichlorocarbene (route III) **(Scheme 11)**.[1] The hydroxyquinolone **66 (Scheme 12)** can be obtained by treating isatin **65** with diazomethane, while the oxime of indan-1-one **67** undergoes a Beckmann rearrangement to give 3,4-dihydro-2-quinolone **68 (Scheme 13)**.



Scheme 11



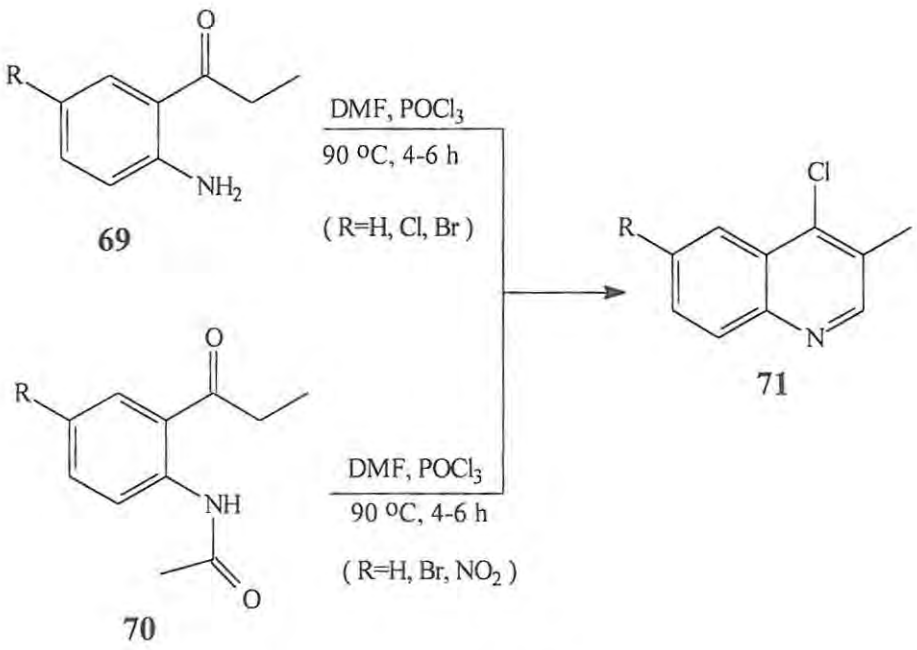
Scheme 12



Scheme 13

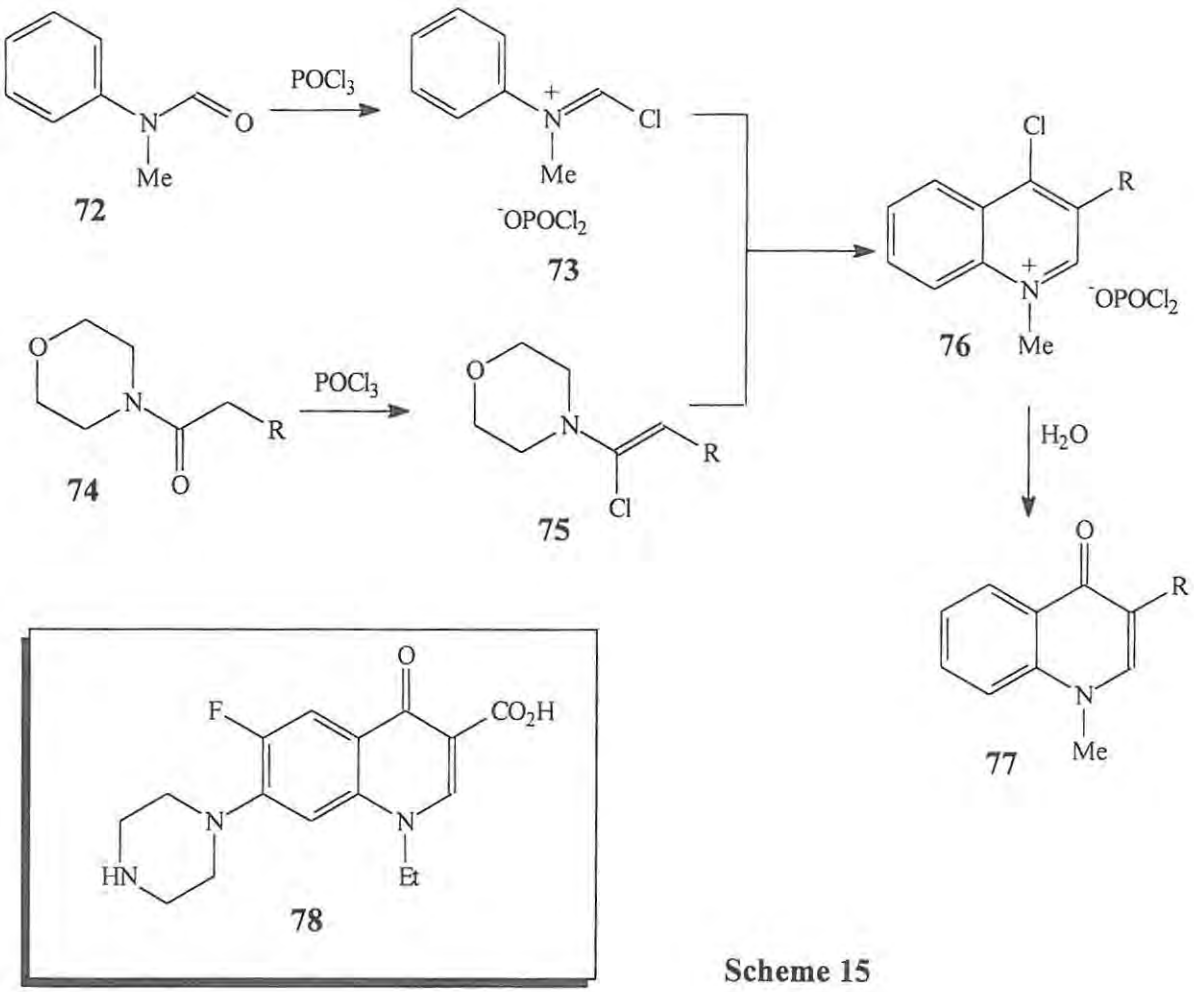
1.2.10. Miscellaneous Syntheses

Perumal *et al.*[6] have reported the synthesis of various 6-substituted 4-chloro-3-methylquinolines **71** from 1-(2-aminophenyl)propanones using a Vilsmeier reagent **(Scheme 14).** They also extended the scope of the reaction by introducing an acetyl group on to the nitrogen atom of the substrate to obtain similar products, and observed a remarkable improvement in the yield of the product - a result attributed to the susceptibility of the free amino group to undergo *N*-formylation, thus interfering with the cyclization step.



Scheme 14

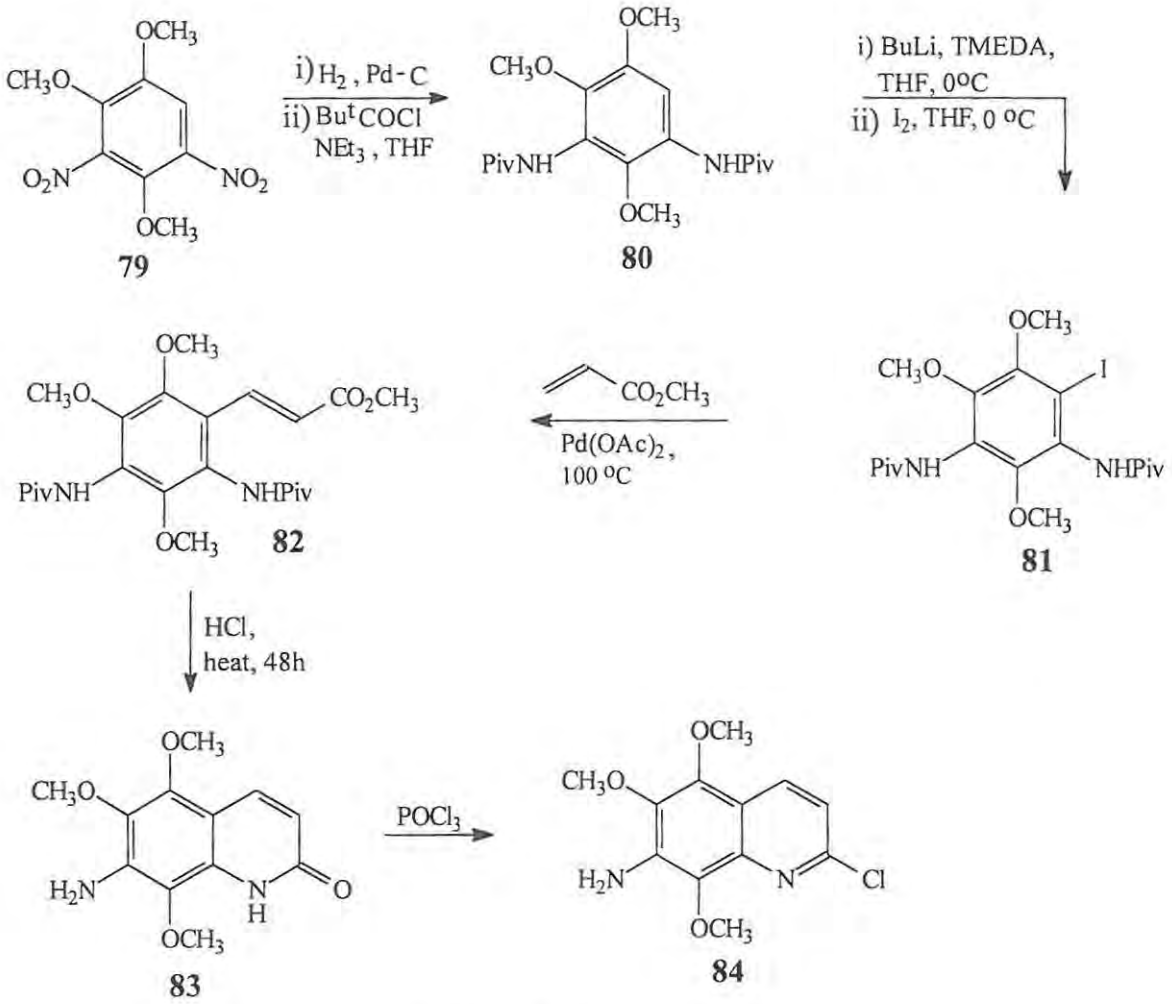
The reaction of *N*-methylformanilides **72** with *N*-alkylmorpholides **74** in the presence of excess phosphorous oxychloride has been shown to give 4-chloro-*N*-alkylquinolinium salts **76** and, hence, 1-alkyl-4-quinolones **77** **(Scheme 15)**.[7,8] The *N*-alkylmorpholide is converted, *in situ*, to a chloroenamine **75**, which then adds to an iminium salt **73**, generated from the *N*-alkylformanilide. This methodology has been adapted to provide a short and efficient route to norfloxacin **78** and related antibiotics.[7,8,9]



Scheme 15

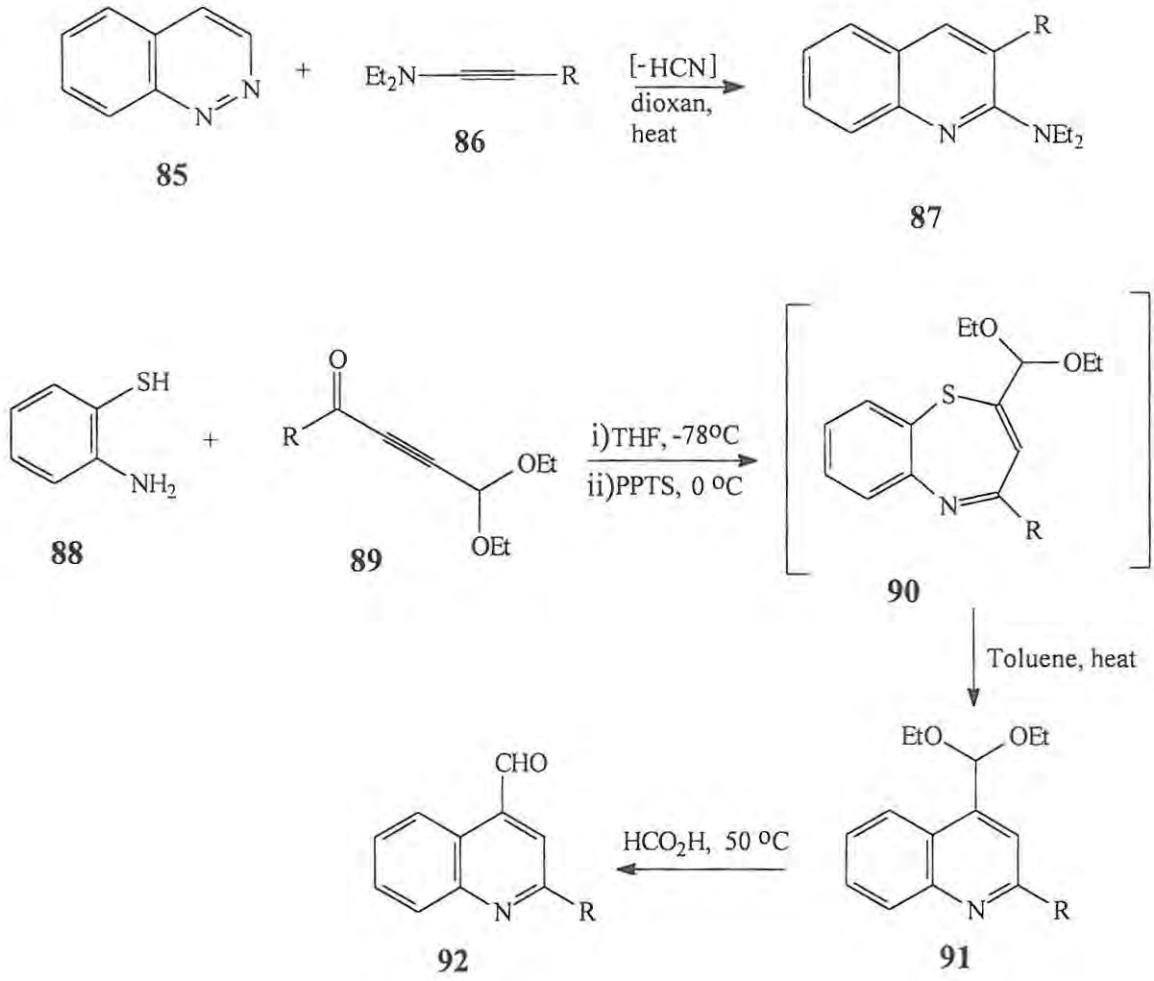
Organometallic methodology has been applied in a synthesis of the 2-chloroquinoline derivative **84 (Scheme 16)**, for which 1,2,4-trimethoxy-3,5-dinitrobenzene **79** was used as starting material.[9] Catalytic hydrogenation of the dinitro compound **79** afforded, quantitatively, 3,5-diamino-1,2,4-trimethoxybenzene, which was transformed into the dipivaloylamino derivative **80** by treatment with pivaloyl chloride. Metallation of the diamide **80** with butyllithium at 0 °C, followed by reaction with iodine, afforded the iodo derivative **81**. A Heck reaction with methyl acrylate, in the presence of a catalytic quantity (3%) of palladium diacetate at 100 °C in a sealed tube, gave the *trans*-cinnamate ester **82**, the somewhat drastic conditions being necessary due to steric hindrance at the nucleophilic centre. Cyclisation of the *ortho*-aminocinnamate derivative **82** was carried out in acidic medium and, finally, chlorination of the quinolone **83** with $POCl_3$ afforded the 2-chloroquinoline **84**.[10]

Two unusual methods of synthesising quinolines are illustrated in **Scheme 17**. In the first, cinnoline **85** reacts with ynamides **86** in boiling dioxan with elimination of hydrogen cyanide, to give the diethylamino derivative **87.**[7,11] In the second, access to 2,4-disubstituted quinolines of types **91** and **92** has been achieved starting from 2-aminothiophenol **88** and acetylenic acetals **89** to yield various substituted benzo[*b*][1,4]thiazepine intermediates of type **90**. Subsequent sulfur extrusion in refluxing toluene led to the 2,4-disubstituted quinoline acetals **91**, which may be hydrolysed to the corresponding 2-substituted quinoline-4-carbaldehydes **92**. The unstable benzothiazepines **90** can be isolated, but extrude sulphur when heated.[7,12,13]



Scheme 16

Quinoline derivatives, both naturally occuring and synthetic, have been reported to exhibit a wide spectrum of biological activities, including bactericidal, antitumour, antimalarial[14-19] and anti-inflammatory.[6,20-22] The following sections will focus on quinolines as antimalarials **(1.3)**, antibacterials **(1.4)** and HIV-1 integrase inhibitors **(1.5)**.

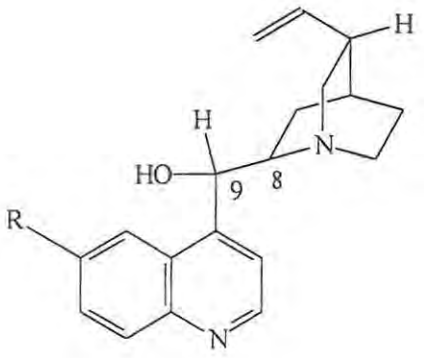

85
86
[-HCN]
dioxan,
heat
87
88
89
i)THF, -78°C
ii)PPTS, 0 °C
90
Toluene, heat
91
HCO2H, 50 °C
92

Scheme 17

1.3 QUINOLINE ANTIMALARIALS

1.3.1 Cinchona Alkaloids

Despite major campaigns to eliminate malaria, the disease is still one of the most significant health problems in many parts of the world.[23] The earliest of the antimalarials was quinine, an alkaloid which was first extracted from the bark of the cinchona tree in 1600 and which is still in use.[4] South American Indians, as mentioned earlier **(Section 1.1)**, recognized the fever-reducing properties of cinchona bark, and crude cinchona extracts were introduced into Europe in the seventeenth century. The four major cinchona alkaloids (quinine, quinidine, cinchonine and cinchonidine; **Figure 2**) are all quinolinemethanol derivatives which bear a substituted quinuclidine ring system.[24] Quinine is the most abundant alkaloid present in extracts of cinchona bark - to the extent of about 5 %. Although all four alkaloids show antimalarial activity, their C-9 epimers are inactive.[24] Any modification of the secondary alcohol function at C-9, through oxidation, esterification or other processes, diminishes activity and, while the quinuclidine portion is not necessary for activity, the



R	
OMe	quinine (8*S*, 9*R*)
OMe	quinidine (8*R*, 9*S*)
H	cinchonine (8*R*,9*S*)
H	cinchonidine (8*S*, 9*R*)

Figure 2

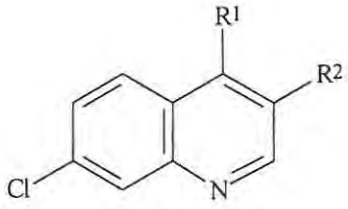
presence of a tertiary alkylamine attached to C-9 is important. These structural requirements formed the basis for the design of synthetic antimalarials,[24] and the quinolinemethanol moiety was targeted in the development of new drugs.

The cinchona alkaloids act on the erythrocytic merozoites;[24] they do not effect a radical cure from the disease but they do decrease symptoms. A major drawback to the use of these alkaloids is the wide spectrum of side-effects, including skin allergies, deafness, vertigo and slight mental depression. Despite these short-comings, the cinchona alkaloids are still used extensively in some parts of the world where the economics of large-scale drug delivery is problematic. Quinine is the drug of choice for chloroquine resistant *Plasmodium falciparum*, and it is interesting to note that resistance to quinine has not developed as readily as it has to the synthetic antimalarial agents.[24]

1.3.2 4-Aminoquinoline Derivatives

The diminished supply of cinchona bark during World War II led to a search for synthetic antimalarial agents. Research efforts centred on modification of the quinine structure and , as a result, the 4-aminoquinoline antimalarials were developed, examples of which are illustrated in **Figure 3** . These drugs are active against the erythrocytic forms of all malarial parasites and thus provide a clinical cure.[24] However, they do not prevent the disease, and they are not active against the liver-infected forms.[24] For all types of human malaria susceptible to treatment by 4-aminoquinolines, chloroquine **93a** or amodiaquine **93c** have long been the drugs of choice for both chemotherapy and supressive chemoprophylaxis.[25] The 4-aminoquinolines, in general, and

chloroquine, in particular, have been very effective in treating the erythrocytic forms of *P. vivax* and *P. falciparum,* being more potent erythrocytic schizontocides than quinine or the 9-aminoacridines.[24] A consideration of structure-activity relationships has revealed that the side-chain length, the presence of a 7-chloro substituent and the introduction of a terminal hydroxyl group [as in hydroxychloroquine **93b**] are critical for reducing toxicity and increasing plasma concentration of the drug. Incorporation of an aromatic ring in the side chain of chloroquine, as in amodiaquine **93c**, produces a compound of reduced activity and toxicity. The toxicity of these compounds tends



93 a-d

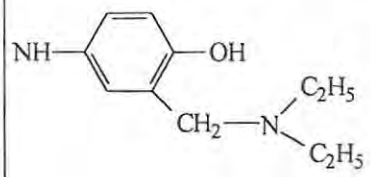
	R1	R2	
a	$NHCH(CH_3)(CH_2)_3-N(C_2H_5)_2$	H	chloroquine
b	$NHCH(CH_3)(CH_2)_3-N(C_2H_5)(CH_2CH_2OH)$	H	hydroxychloroquin
c		CH_3	amodiaquine
d	$NHCH(CH_3)(CH_2)_3-N(C_2H_5)_2$	CH_3	sontoquine

Figure 3. Selected 4-Aminoquinoline derivatives

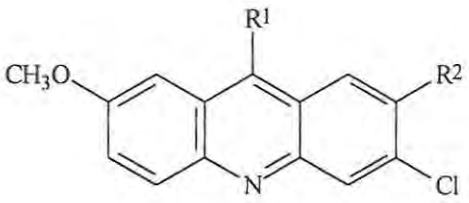
to be low, but large doses may affect hearing and vision.[24] Hydroxychloroquine **93b** is, of course, but one of the large series of 4-aminoquinolines with antimalarial activity, and it has been used in malaria therapy since 1955 as an alternative to, or in combination with, chloroquine.[26]

"Although hydroxychloroquine was developed primarily as an antimalarial agent, it possesses other pharmacological properties as well.[28] Its anti-inflammatory activity is well known, and it has been useful in the treatment of rheumatoid arthritis and in systemic lupus erythematosus". Its application in the treatment of photo-allergic reactions is also established. Tonnesen *et al.*[26] found that hydroxychloroquine also shows substantial binding to plasma proteins as well as to metabolically active tissues including the liver, spleen, lung and adrenal glands, where it accumulates, with long-term administration, reaching concentrations of 6000-8000 times the plasma level. It is also deposited in the epidermis in considerable amounts (at levels 100-200 times the plasma concentration). Furthermore, hydroxychloroquine accumulates in melanin-rich areas of the body and is retained in the iris and choroid of the eye.[26] Several side-effects are associated with the use of hydroxychloroquine **93b**; the drug has been reported to cause changes in skin-pigmentation and bleaching of the hair while, with long-term usage, it is likely to affect the cornea and retina of the eye.[25, 26]

1.3.3. Acridine Derivatives

Ehrlich's early observation that methylene blue had some antimalarial activity led to the discovery of such activity in several acridine derivatives (**94a-c; Figure 4**).[24] These agents act as

schizonticides but, as a class, are less effective than the 4-aminoquinolines. A side-effect of their use in therapy is yellow pigmentation of the skin and a yellow colouration of the urine. Acridine derivatives are, in fact, extremely toxic and have been largely replaced by the 4-aminoquinolines.



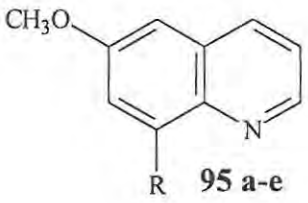
94 a-c

	R1	R2	
a	$NHCH_9CH_3)(CH_2)_3-N(C_2H_5)_2$	H	9-aminoacridine
b	$NH(CH_2)_4-N(C_2H_5)_2$	H	acriquine
c	$NHCH_9CH_3)(CH_2)_3-N(C_2H_5)_2$	NH_2	3-aminoacridine

Figure 4. Some acridine derivatives

1.3.4. 8-Aminoquinoline Derivatives

These synthetic compounds reflect a more pronounced departure from the quinine structure. The 8-aminoquinoline, primaquine (**95a**; **Figure 5**), is the only drug now in general use that is effective against the persistent tissue stages of relapsing malarias and thus able to effect a radical cure.[25] Unlike the 4-aminoquinolines, the 8-aminoquinolines are active against pre- or exoerythrocytic activity, but do not show gametocidal activity. The presence of a 6-methoxy group and a 4- to 6-carbon chain appear to provide the best activity.[24] The extent of substitution of the terminal amine moiety is not as critical as in the 4-aminoquinolines, and the drug of choice, primaquine, is a primary amine.[24]



95 a-e

	R	
a	$NHCH(CH_3(CH_2)_3NH_2$	primaquine
b	$NHCH(CH_3)(CH_2)_3-N(C_2H_5)(C_2H_5)$	pamaquine
c	$NH(CH_2)_3CH(CH_3)-N(C_2H_5)(C_2H_5)$	quinocide
d	$NH(CH_2)_5NH-CH(CH_3)(CH_3)$	pentaquine
e	$NHCH(CH_3)(CH_2)_3NH-CH(CH_3)(CH_3)$	isopentaquin

Figure 5. Examples of 8-aminoquinoline derivatives

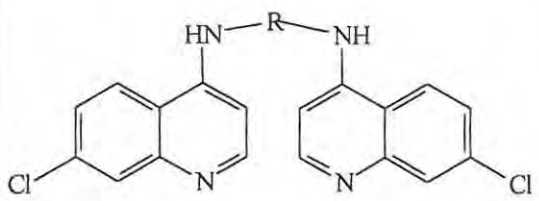
However, primaquine is far from being an ideal drug; the 8-aminoquinolines appear, in general, to be more toxic than the 4-aminoquinolines, producing side-effects which include gastric disturbance and leakopenia.[24] The primary toxicity of primaquine is manifested as methemoglobinemia and as hemolytic anemia in persons with a genetic deficiency of the enzyme, glucose-6-phosphate dehydrogenase.[24, 25] Unfortunately, this abnormality occurs, primarily, in areas of the world where malaria is endemic and, hence, the use of primaquine in such areas is not without risk. However, primaquine is still used in combination with chloroquine **93a** to effect radical cures of *P. vivax,* and is the only drug currently available for the radical treatment of relapsing vivax or ovale malaria. [24,27]

1.3.5. Other Antimalarials

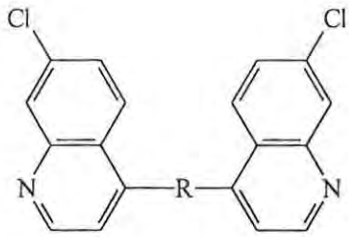
Several bisquinolines, such as piperaquine, had been observed to possess notable activity against chloroquine-resistant malaria and, consequently, Vennerstrom and co-workers [28] prepared a series of thirteen *N,N*-bis-(7-chloroquinolin-4-yl)alkanediamines **(96a-l; Figure 6)**. Not only were these bisquinolines generally found to be active against chloroquine-resistant malaria but, relative to chloroquine, they also exhibited:- a significantly lower resistance index; greater potency; a longer duration of action; and reduced toxicity. Maximum activity was observed for bisquinolines with a connecting bridge (R) of only two carbon atoms, the decreased conformational mobility appearing to increase activity.

Vennerstrom *et al.*[29] extended their study by preparing a further series of eleven *N,N*-bis(7-

chloroquinolin-4-yl)heteroalkanediamine analogues **(97 a-j)** to examine the effects of incorporating oxygen or nitrogen atoms into the bisquinoline bridge on antimalarial activity and the inhibition of hematin polymerisation. On balance, the incorporation of nitrogen or oxygen atoms failed to improve antimalarial activity, the exceptions being the ether-bridged analogues **(97 b-d)** for which *in vivo* antimalarial efficacy was enhanced. Decreased *in vivo* antimalarial activity was especially evident for the bisquinolines **(97 e-h)**, and it was suggested that the presence of the central bridging nitrogen probably allows rapid, metabolic *N*-dealkylation, which would convert these bisquinolines to monoquinolines and, thus, offer no advantages over chloroquine and other monoquinolines. [29]



96 a-l



97 a-j

	R
a	$(CH_2)_2$
b	$CH_2CH(CH_3)$
c	*trans*-1,2-cyclohexyl
d	$(CH_2)_3$
e	$(CH_2)_4$
f	$(CH_2)_5$
g	$(CH_2)_3CH(CH_3)CH_2$
h	$(CH_2)_6$
i	$(CH_2)_7$
j	$(CH_2)_8$
k	$(CH_2)_9$
l	$(CH_2)_{10}$

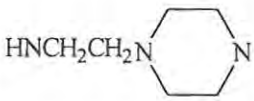
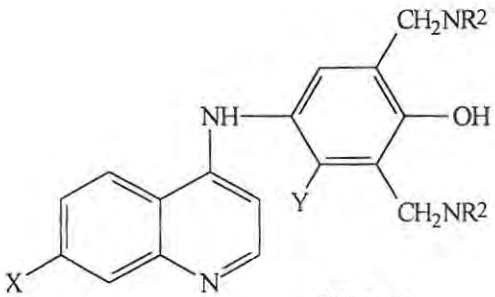
	R
a	$HN(CH_2)_2O(CH_2)_2NH$
b	$HN(CH_2)_2O(CH_2)_2O(CH_2)NH$
c	$HN(CH_2)_3O(CH_2)_4O(CH_2)NH$
d	$HN(CH_2)_3O(CH_2)_2O(CH_2)_2O(CH_2)_3NH$
e	$HN(CH_2)_2NH(CH_2)_2NH$
f	$HN(CH_2)_3NH(CH_2)_2NH$
g	$HN(CH_2)_3NH(CH_2)_3NH$
h	$HN(CH_2)_3NCH_3(CH_2)_3NH$
i	$HN(CH_2)_6NH(CH_2)_6NH$
j	

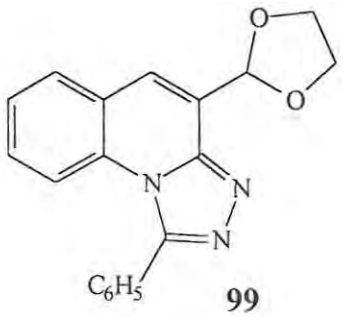
Figure 6. Examples of bisquinoline derivatives

Riechmann and co-workers [30] have recently discovered that the four quinoline Mannich base

derivatives **(98 a-d)** possess marked and prolonged antimalarial activity, while triazoloquinolines, such as **99**, have been shown to exhibit antibacterial, anti-allergic, antidepressant and anti-arrythmic effects.[14]



98 a-d

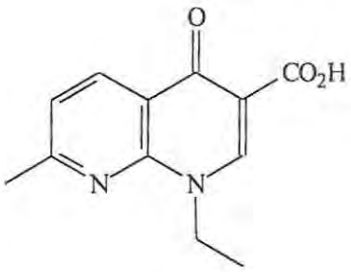


99

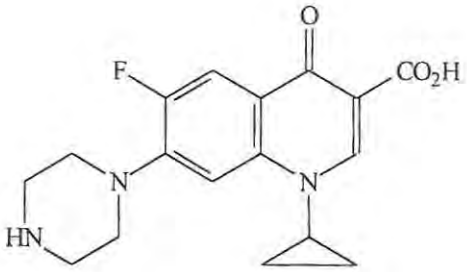
	X	Y	NR2
a	CF_3	H	pyrrolidinyl
b	CF_3	H	piperidinyl
c	CF_3	H	4-methylpiperazinyl
d	Cl	Me	piperidinyl

1.4. QUINOLONE ANTIBACTERIALS

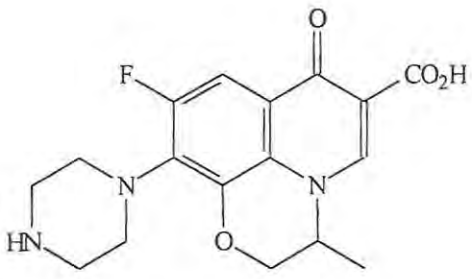
Fluoroquinolone antimicrobial agents were introduced into the chemotherapy of infections in the early 1960's during the search for improved antimalarial agents. At the time, little work was done to chemically modify these compounds, and it was only in the 1980's that significant advances were made with this group of drugs.[31] The currently available fluoroquinolones, which include ciprofloxacin **101** and ofloxacin **102**, provide major advances over the use of the original DNA gyrase inhibitor, nalidixic acid **100**. Norfloxacin **103** shows little binding to gyrase or DNA alone, but significant amounts of the drug bind to the gyrase-DNA complex. Ciprofloxacin **101** is used worldwide to treat a broad variety of bacterial infections, including those in the urinary tract,



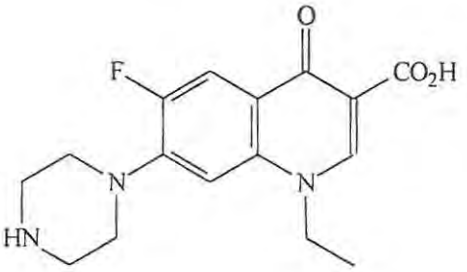
Nalidixic Acid **100**



Ciprofloxacin **101**



Ofloxacin **102**



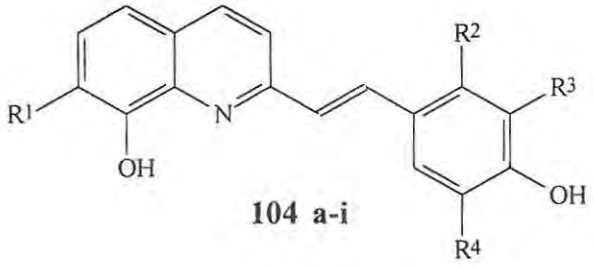
Norfloxacin **103**

respiratory system and skin and soft tissue, as well as those involving sexually transmitted diseases.[32] While ciprofloxacin is the most effective of the currently available fluoroquinolones, it has a number of limitations which have provided an impetus for the search for new analogues. Ciprofloxacin has relatively low intrinsic potency against many Gram-positive organisms, including *Streptococus pneumoniae*, and is not very potent against the anaerobic organisms which are commonly encountered in intra-abdominal infections.[32] Based on their mechanism of action on the bacteria-specific DNA gyrase, the quinolones may be classified as DNA-directed drugs of comparatively low toxicity.[33]

1.5. STYRYLQUINOLINE DERIVATIVES AS HIV-1 INTEGRASE INHIBITORS

New, potential HIV-1 integrase inhibitors have been designed, in which a quinoline substructure is linked, by means of an ethylenic spacer, to an aryl nucleus possessing various dihydroxy substitution patterns.[34] Although the most active compounds contain the catechol structure, this moiety is not essential for activity since the most potent analogue **104i (Figure 7)** lacks this group, thus implicating a different pharmacophore. The most promising styrylquinolines inhibit HIV-1integrase *in vitro* at micromolar or submicromolar concentrations and block HIV replication in CEM cells, with no significant cellular toxicity in a 5-day period.[34] These new styrylquinolines may provide lead compounds for the development of novel antiretroviral agents for AIDS therapy, based upon the inhibition of HIV-1 integrase. They might also be used to elucidate the mechanism of inhibition of this enzyme, *e.g.* they could serve as candidates for co-recrystallization studies with HIV-1 integrase.[34]

Styrylquinolines, in general, and 2-(*p*-dimethylaminostyryl)quinolines and their quaternary iodides, in particular, have been the subject of extensive screening for tumour inhibiting properties, and for bactericidal and fungicidal properties.[1]



104 a-i

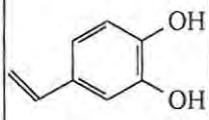
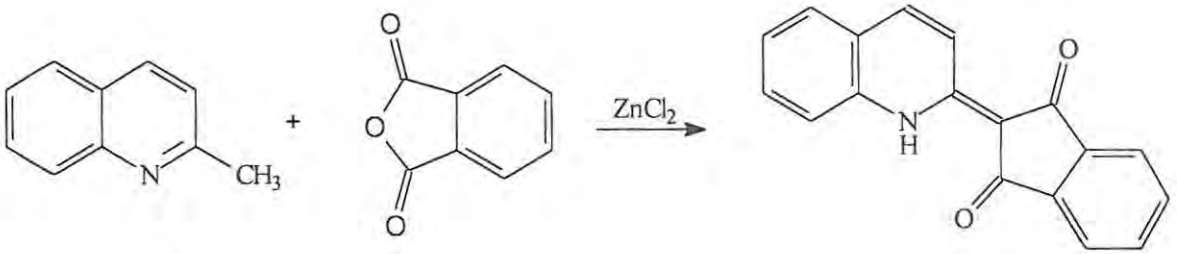
	R1	R2	R3	R4
a	H	H	OH	H
b		H	OH	H
c	CO_2H	OH	H	H
d	CN	H	OH	H
e	CO_2H	H	OH	H
f	CO_2Na	H	OH	H
g	CO_2H	H	OH	OH
h	CO_2Na	H	OH	OH
i	CO_2H	H	CO_2H	H

Figure 7. Examples of Styrylquinoline derivative:

1.6 QUINOLINE DYES

Although many commercially valuable dyestuffs contain fused quinoline rings, quinoline yellow (quinophthalone) **107** is the only simple quinoline derivative to find such use, and it is readily obtained by the condensation of quinaldine **105** and phthalic anhydride **106 (Scheme 18)**.[1]

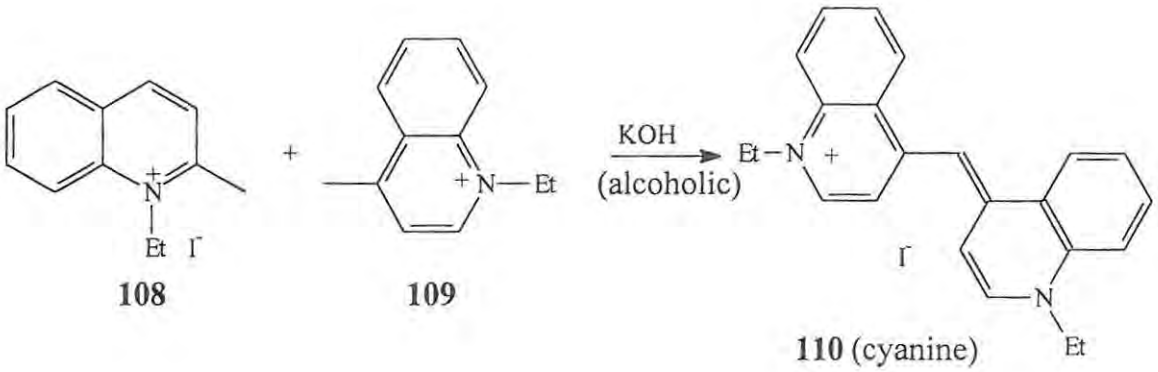


105 **106** **107**

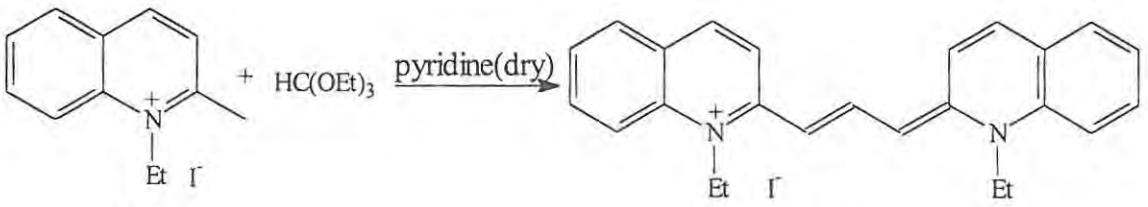
Scheme 18

The cyanines (*e.g.* **110** and **112**; **Scheme 19**) are an important group of dyes used for improving the colour sensitivity of photographic emulsions. They are useless as fabric dyestuffs owing to their instability to light but, in 1875, Vogel found that they could sensitize photographic emulsions to green light.[3] The reason for this is that they contain one of the few organic structures capable of absorbing light in the visible and infrared regions and transferring the energy to a photographic emulsion as a 'latent image' of activated silver halide crystals. In this way, the sensitivity of a silver bromide emulsion can be extended from its natural position in the ultraviolet and blue regions of the spectrum to the green , red and near-infrared regions. With suitable combinations of these dyes the sensitivity can be balanced throughout the visible spectrum to give

'panchromatic' emulsions. The dye, cyanine **110** (a green sensitizer), is formed by base-catalyzed condensation of the quaternary ethiodides of 2-methylquinoline **108** and 4-methylquinoline **109**; the dye, pinacyanol **112** (a red sensitizer), is formed similarly from 1-ethyl-2-methylquinolinium iodide **111** and ethyl orthoformate **(Scheme 19)**.



108 **109** **110** (cyanine)



111 **112** (pinacyanol)

Scheme 19

1.6 AIMS OF THE PRESENT INVESTIGATION

Previous work in our laboratories has demonstrated the potential of the Baylis-Hillman reaction in the construction of heterocyclic systems. Thus, pyridine-2-carbaldehyde-derived Baylis-Hillman products have been used as precursors for the synthesis of indolizine derivatives[35, 36] in a reaction which involves the thermal cyclisation of the acetylated Baylis-Hillman products. The Baylis-Hillman reaction has also been used to access oxygen-containing heterocycles, *viz.*, chromenes, coumarins and numerous derivatives thereof.[37-43] In cognate studies, attention has been given to the chemoselective formation of chromene and coumarin systems. Extension of the general methodology to the synthesis of quinoline derivatives was initiated at Rhodes by Familoni,[44] and the present investigation was undertaken to extend, and further explore, applications of the Baylis-Hillman reaction in the synthesis of quinoline derivatives. Specific objectives in this study have included the following.

1. The synthesis of a range of Baylis-Hillman products, derived from various 2-nitrobenzaldehyde derivatives and activated alkenes.
2. Optimisation of the reaction conditions for the catalytic reduction and cyclisation of these Baylis-Hillman products to quinoline derivatives.
3. An investigation of the use of stannous chloride as an alternative reagent for the reductive cyclisation of the Baylis-Hillman products.
4. The development of convenient methods for the interconversion of the quinoline derivatives and their *N*-oxides isolated from some of the above reactions.

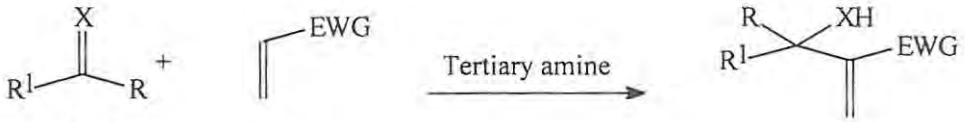
2. DISCUSSION

In the discussion which follows, attention will be given to the preparation of Baylis-Hillman products as quinoline precursors **(Section 2.1)** and their reduction to quinoline derivatives:- i) *via* catalytic hydrogenation with palladium-on-carbon as catalyst **(Section 2.2.1)** and ii) using stannous chloride **(Section 2.2.2)**. Finally, the interconversion of the quinoline derivatives and their *N*-oxides will be considered in **Section 2.3.**

2.1 PREPARATION OF BAYLIS-HILLMAN PRODUCTS

Carbon-carbon bond formation is one of the most fundamental reactions in organic chemistry, and the development of efficient and selective methods for the construction of these bonds is an exciting and challenging endeavour. The Baylis-Hillman reaction permits the formation of such carbon-carbon bonds between the α-position of an activated alkene and a carbon electrophile containing an electron-deficient sp^2 carbon atom; the reaction proceeds in the presence of a suitable catalyst (typically, a tertiary amine) and affords multifunctional products **(Scheme 20)**.[42,43] In the most recent review of this reaction, [45] it has been called the Morita-Baylis-Hillman reaction in recognition of early contributions by Morita.[46] The most commonly employed activated alkenes are acrylic esters, but a number of other systems[47] couple with aldehydes to give the analogous Baylis-Hillman products. Examples of these include methyl vinyl ketone and other vinyl ketones, acrylonitrile, diethyl vinylphosphonate, phenyl vinyl

sulfone and acrolein.[42,48] The reaction thus involves three components, *viz.*, an electrophile, an activated alkene and, typically, a tertiary amine catalyst. There are various catalysts that can be used but, in this project, 1,4-diazabicyclooctane (DABCO) was used exclusively.

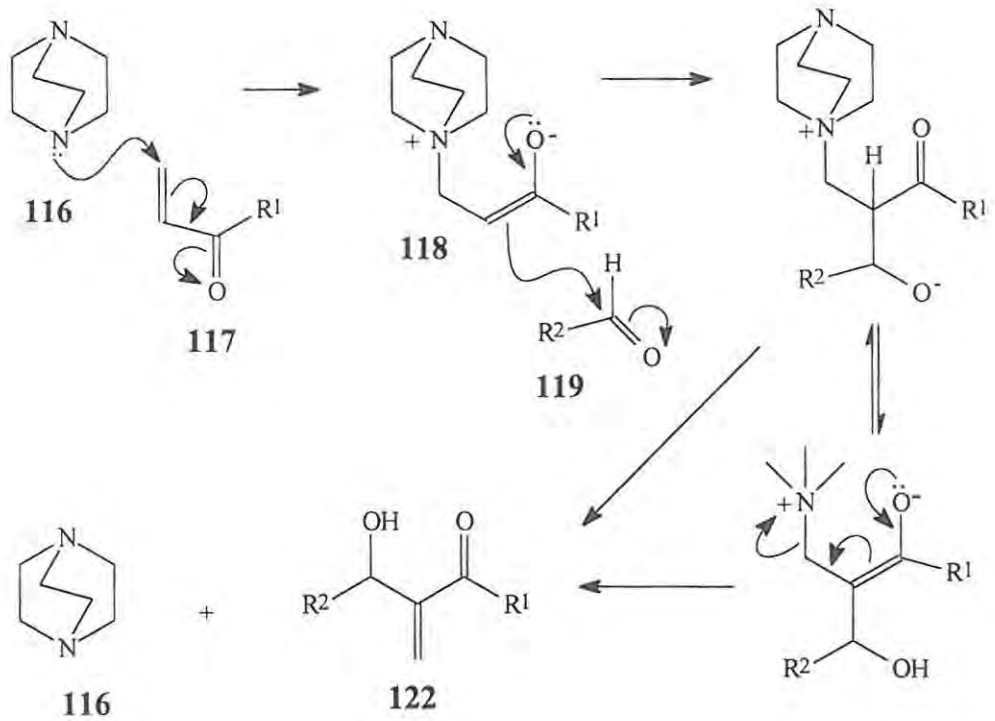


113 **114** **115**

EWG = Electron Withdrawing Group

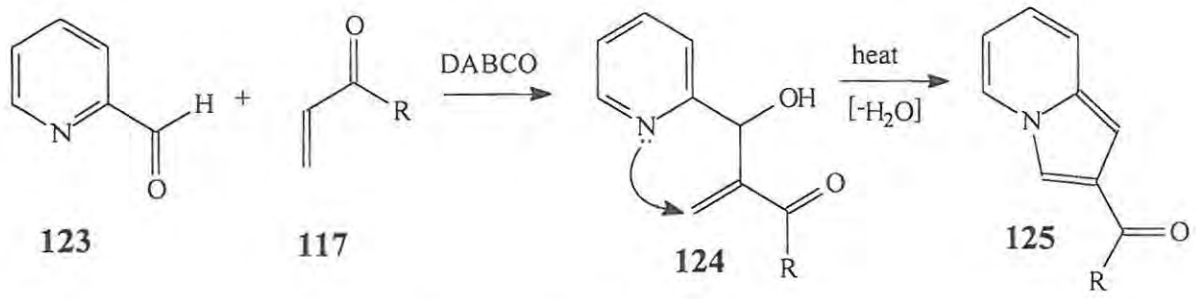
Scheme 20

Mechanistic studies [42] have indicated that the reaction proceeds as illustrated in **Scheme 21**. The reaction is initiated by conjugate addition of the nucleophilic catalyst (*e.g.* DABCO **116**) to the activated alkene **117** resulting in the formation of a zwitterionic enolate **118**, which subsequently attacks the aldehyde **119** (in a nucleophilic addition step) to produce the zwitterionic adduct **120**, which undergoes elimination to afford the final Baylis-Hillman product **122** and release the catalyst, DABCO. Recent computational studies[49] suggest that the elimination proceeds *via* an E1cB mechanism involving formation of the intermediate enolate anion **121**.

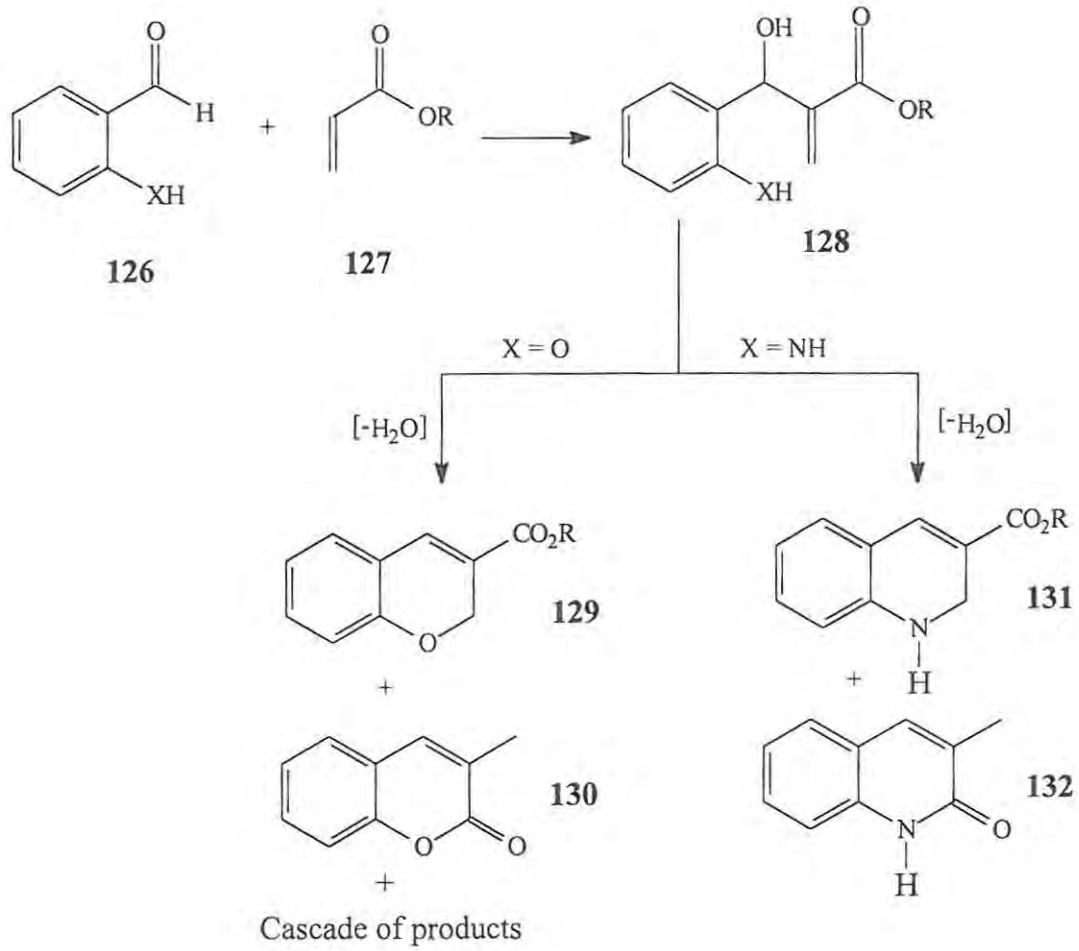


Scheme 21

In research conducted in our laboratories, Bode and Kaye [35,36] have demonstrated applications of the Baylis-Hillman reaction in the synthesis of substituted indolizines **125** from pyridine-2-carbaldehydes **123 (Scheme 22)**, and in analogous reactions of salicylaldehydes, Kaye and Robinson [37,39] have uncovered a cascade of transformations involving the formation of chromene **129** and coumarin **130** derivatives **(Scheme 23)**. The chromenes result from conjugate addition of the nucleophilic phenolic oxygen (X=O) to the double bond of the Baylis-Hillman product **128**, whereas the coumarins result from nucleophilic attack on the carbonyl carbon. In view of these observations, the use of 2-aminobenzaldehydes **128** (X=NH) as electrophiles in Baylis-Hillman reactions was expected to result in the corresponding quinoline derivatives **131** and **132** **(Scheme 23)**

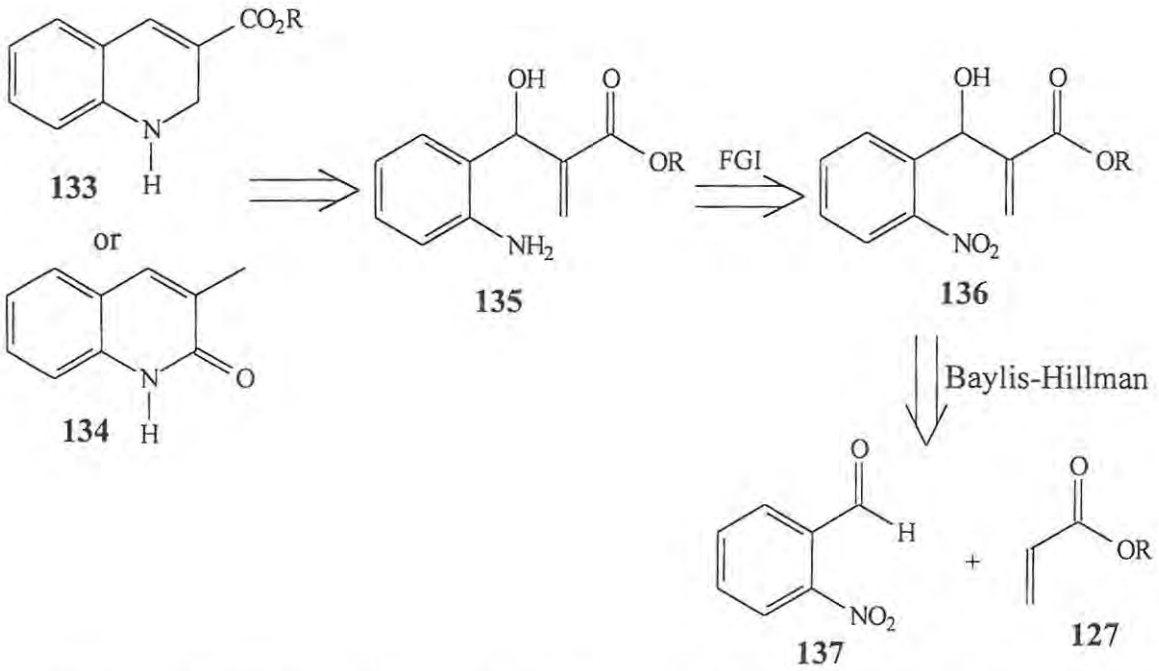


Scheme 22



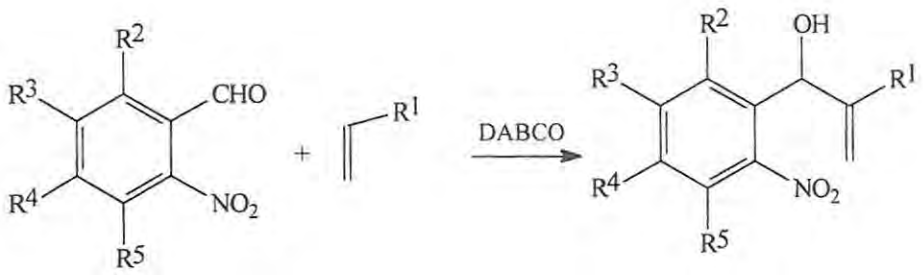
Scheme 23

As mentioned earlier **(Section 1.2)**, numerous quinoline syntheses have been developed and, in one of them, the Friedlander synthesis, 2-aminobenzaldehyde is used as a precursor. The disadvantage of the Friedlander methodology, however, is the relative inaccessibility of the substituted 2-aminobenzaldehydes which are required for the construction of substituted quinolines. Furthermore, aldehyde electrophilicity is one of the over-riding factors in the Baylis-Hillman reaction and 2-nitrobenzaldehydes were expected to be more electrophilic than 2-aminobenzaldehydes. Consequently, a method was planned wherein 2-nitrobenzaldehyde is used as the substrate and reductive cyclisation of the resulting Baylis-Hillman product **136** affords the target quinoline *via* the 2-amino synthon **135 (Scheme 23a)**. The investigation was begun in our laboratories by Familoni[44] and, in the present study, this work has been extended, and some of the results have already been published.[44]



Scheme 23a: Retrosynthetic analysis for expected quinoline derivatives

A range of Baylis-Hillman products **140 a-p** were synthesised as quinoline precursors by reacting a series of 2-nitrobenzaldehyde derivatives **138** with activated alkenes **139** in the presence of DABCO **(Scheme 24)**. ^{1}H NMR spectroscopy and thin layer chromatography of the crude reaction mixtures revealed the formation of the complex mixtures of products.



138 **139** **140 a-p**

	R^1	R^2	R^3	R^4	R^5
a	CO_2Me	H	H	H	H
b	CO_2Et	H	H	H	H
c	COMe	H	H	H	H
d	CN	H	H	H	H
e	SO_2Ph	H	H	H	H
f	SO_3Ph	H	H	H	H
g	COH	H	H	H	H
h	COEt	H	H	H	H
i	CO_2Me	H	OMe	OMe	H
j	COMe	H	OH	H	H
k	CO_2Me	H	H	NO_2	H
l	CO_2Me	H	Cl	H	H
m	COMe	H	$-OCH_2O-$		H
n	COEt	Cl	H	H	H
o	COEt	H	H	H	OMe
p	COEt	NO_2	H	H	H

Scheme 24

Yields for these reactions ranged between 7 and 63 % **(Table 1;** p.47), with acrolein giving the

lowest yield. Reaction times were between one and five weeks and the mole ratio of the reactants was:- aldehyde: activated alkene: DABCO ::1:1:0.05. The Baylis-Hillman products **140 a-p** were fully characterised by spectroscopic (NMR and IR) and elemental (high resolution MS) anlysis. Representative ^{1}H, COSY and HMQC NMR spectra are illustrated for methyl 3-hydroxy-2-methylene-3-(2,4-dinitrophenyl)propanoate **140k** in **Figures 8-10**. Various structural features are clearly evident in the ^{1}H NMR spectrum of this compound. Thus, the methoxy and hydroxyl groups resonate at 3.75 and 3.46 ppm respectively, while the vinyl proton signals at *ca* 5.7 and 6.3 ppm are characteristic of this class of compounds. Coupling is observed between the hydroxyl proton and the vicinal proton - an interaction clearly apparent in the COSY spectrum **(Figure 9)**. The number of carbon atoms in the compound corresponds exactly with the number of C-13 signals in the ^{13}C NMR spectrum (two of the signals almost coincide but, on expansion of the spectrum, are clearly evident at 127.6 and 127.7 ppm), and the correlations between these carbons and the protons in compound **140k** are confirmed by the HMQC data **(Figure 10)**.

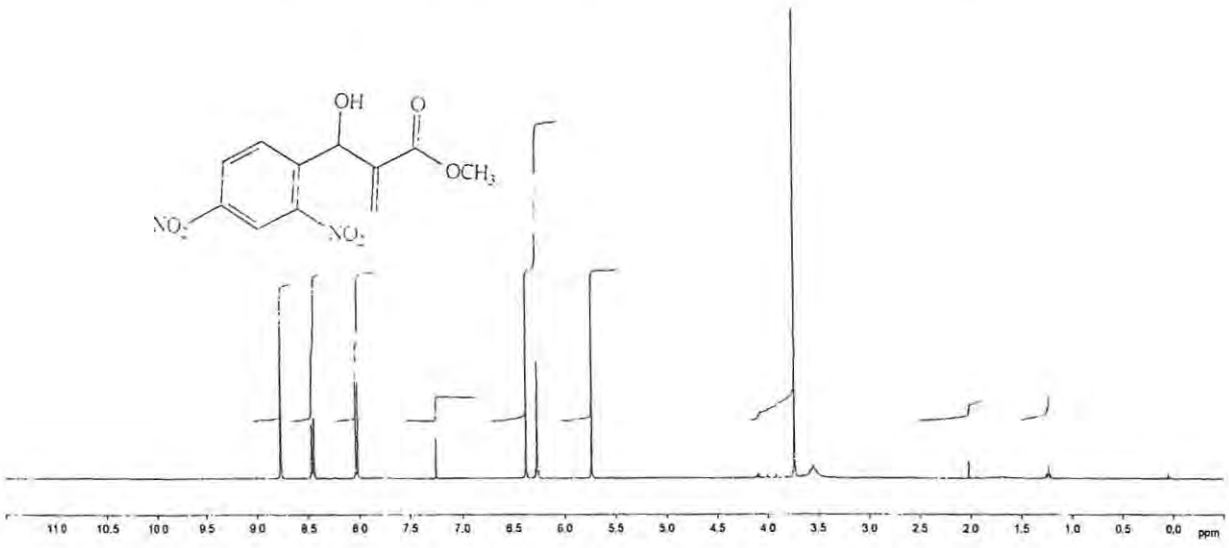


Figure 8: 400 MHz ^{1}H NMR spectrum of Baylis-Hillman product **140 k** in $CDCl_3$

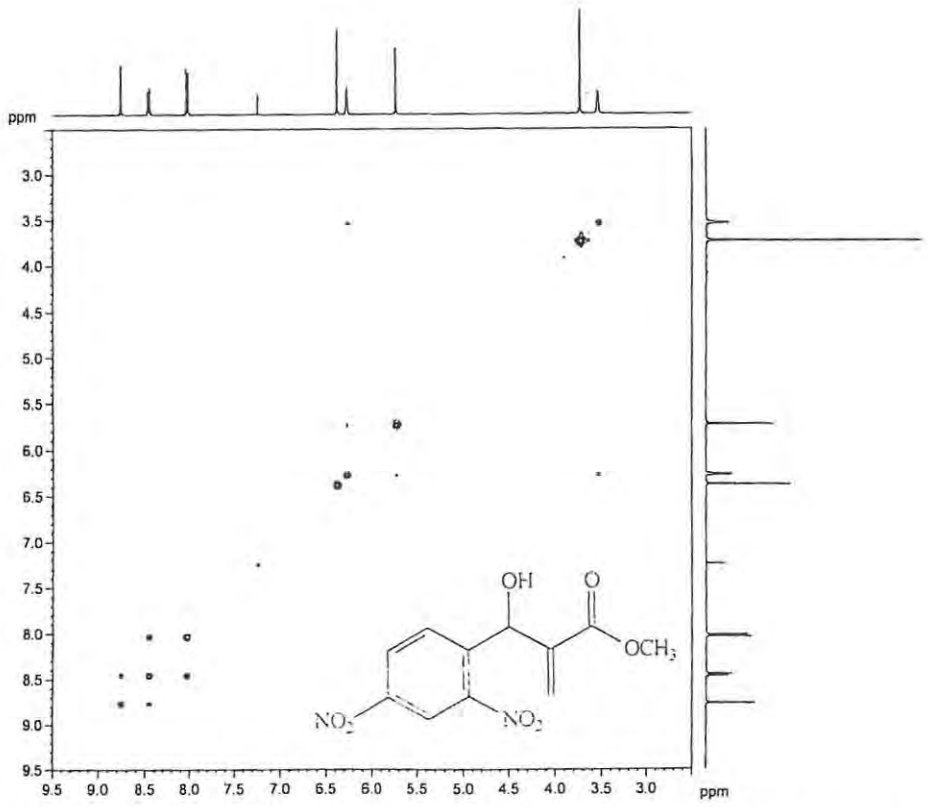


Figure 9. 400 MHz COSY spectrum of the Baylis-Hillman product **140k** in $CDCl_3$

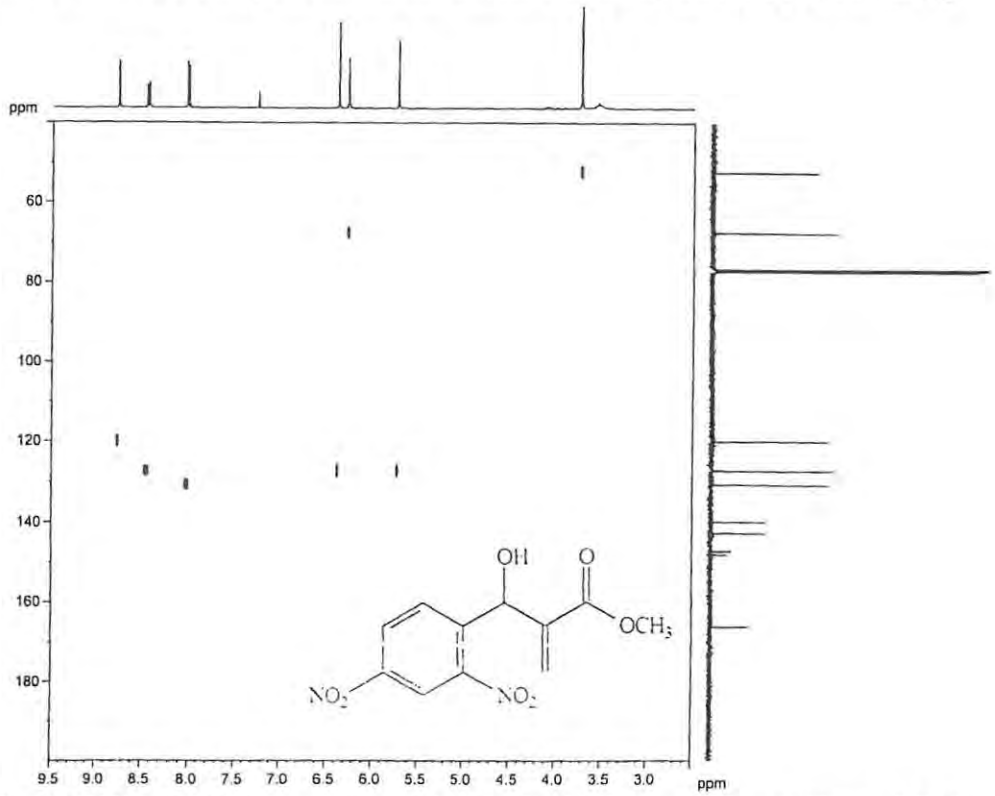
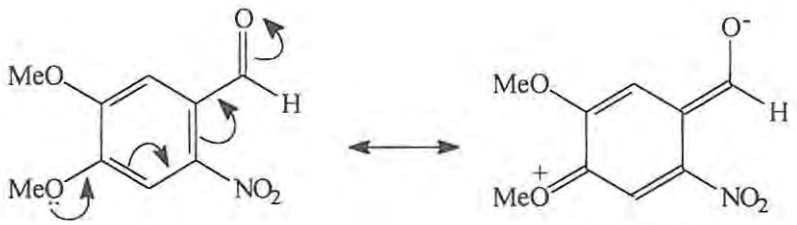


Figure 10. 400 MHz HMQC spectrum of the Baylis-Hillman product **140k** in $CDCl_3$

2-Nitrobenzaldehyde derivatives which contain other, electron-releasing substituents are expected to show reduced reactivity in the Baylis-Hillman reaction due to the decreased electrophilicity of the aldehyde function. Thus, delocalisation of lone pair electrons from the *para*-methoxy group should decrease the reactivity of the dimethoxy analogue **138i** (reflected by the canonical structures **141** and **142**; **Figure 11**) and this is presumably reflected in the low yield observed for this substrate (14 %). The apparently sluggish reactivity of the dinitro analogue **138k**, however, was surprising, given the presence of the additional electron-withdrawing substituent. From the results obtained for these reactions, vinyl ketones and α,β-unsaturated carboxylic esters generally appear to exhibit greater conversion efficiencies than the other vinyl systems examined.

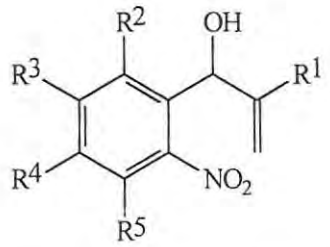


141 **142**

Figure 11: Delocalisation of lone-pair electrons in the dimethoxy substrate **138i**

Optimisation studies were undertaken to improve the yields of the Baylis-Hillman products, and several reaction variables, such as the concentration of the reagents, the catalyst and the reaction time were examined. After many attempts to establish the optimum molar ratio of reactants , the best results were obtained with an aldehyde: activated alkene: DABCO mole ratio of 1: 1.5: 0.05. Having the aldehyde as the limiting reagent and increasing the mole ratio of the activated alkene proved particularly effective, since the use of equimolar ratios of these two components always resulted in the recovery of unreacted aldehyde. The improved yields obtained for selected reactions is evident from a comparison of the data in **Tables 1** and **2**. Excellent yields were obtained for four of the products **140b**, **c**, **k** and **o**; the reaction of 2-chloro-6-nitrobenzaldehyde **138n** with ethyl vinyl ketone, however, gave a disappointing yield of the 5-chloro analogue **140n**, while 2,6-dinitrobenzaldehyde failed to react under these conditions. The lack of reactivity of 2,6-dinitrobenzaldehyde may be attributed to steric hindrance about the carbonyl group by the bulky nitro group, which inhibits nucleophilic attack at the carbonyl centre.

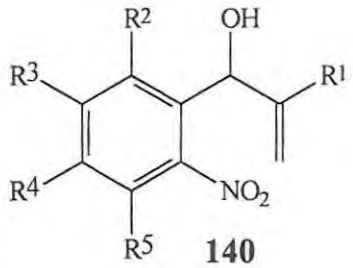
Table 1. Yields for the Baylis-Hillman products **140 a-m**



Compd.	R^1	R^2	R^3	R^4	R^5	Yield† / %
140a	CO_2Me	H	H	H	H	57
140b	CO_2Et	H	H	H	H	46
140c	COMe	H	H	H	H	47
140d	CN	H	H	H	H	44
140e	SO_2Ph	H	H	H	H	32
140f	SO_3Ph	H	H	H	H	27
140g	COH	H	H	H	H	7
140h	COEt	H	H	H	H	63
140i	CO_2Me	H	OMe	OMe	H	14
140j	COMe	H	OH	H	H	22
140k	CO_2Et	H	H	NO_2	H	26
140l	CO_2Me	H	Cl	H	H	52
140m	COMe	H	$-OCH_2O-$		H	33

† Yields given in this table and elsewhere are for chromatographed products

Table 2. Yields for selected Baylis-Hillman products **140** following optimisation studies

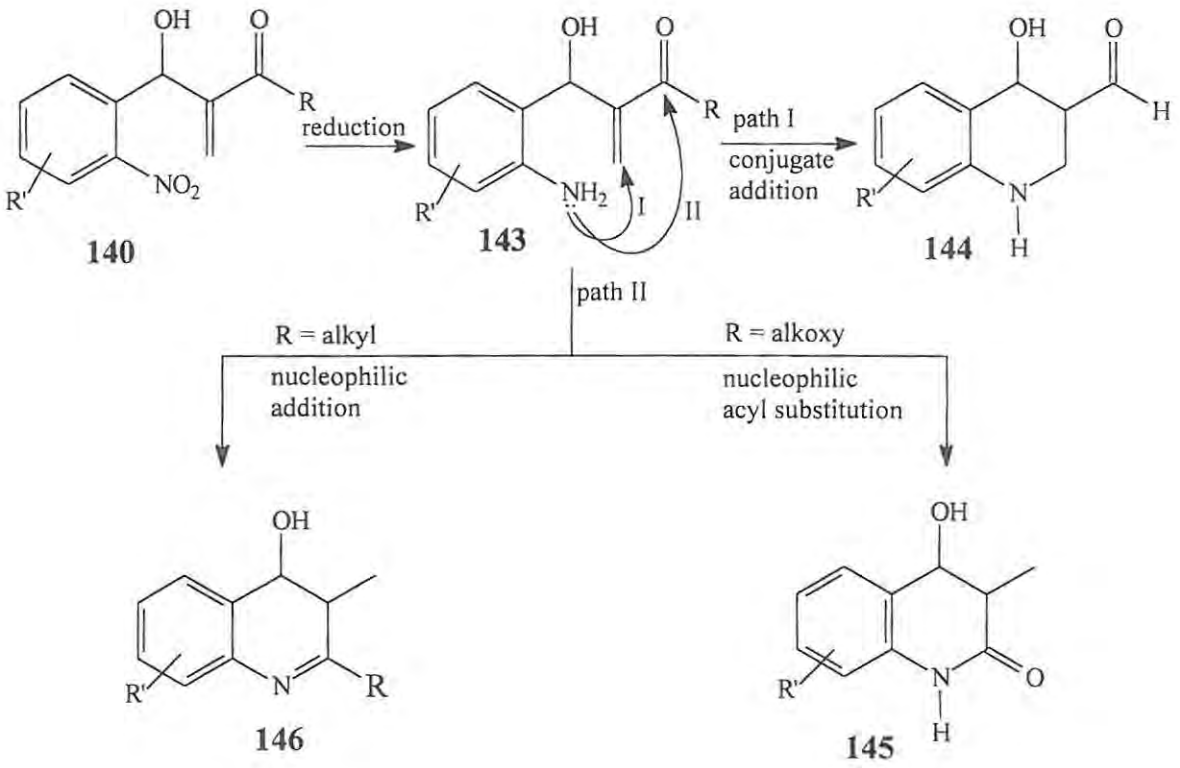


140

Compd.	R^1	R^2	R^3	R^4	R^5	Yield / %
140b	CO_2Et	H	H	H	H	95
140c	COMe	H	H	H	H	60
140k	CO_2Me	H	H	NO_2	H	92
140n	COEt	Cl	H	H	H	25
140o	COEt	~~Cl~~	H	H	OMe	89
140p	COEt	NO_2	H	H	H	0

2.2 REDUCTIVE CYCLIZATION OF THE BAYLIS-HILLMAN PRODUCTS

The next step in the synthesis of the quinoline derivatives involved reduction of the *ortho*-nitro group to generate the nucleophilic *ortho*-amino group required for cyclisation. Initially, the reduction was effected by catalytic hydrogenation; subsequently, attention was given to the use of stannous chloride as the reducing agent. It was, of course, recognised that cyclisation of the *ortho*-amino derivative could, in principle, involve:-



Scheme 25: Possible cyclisation pathways for the*o*-amino derivatives

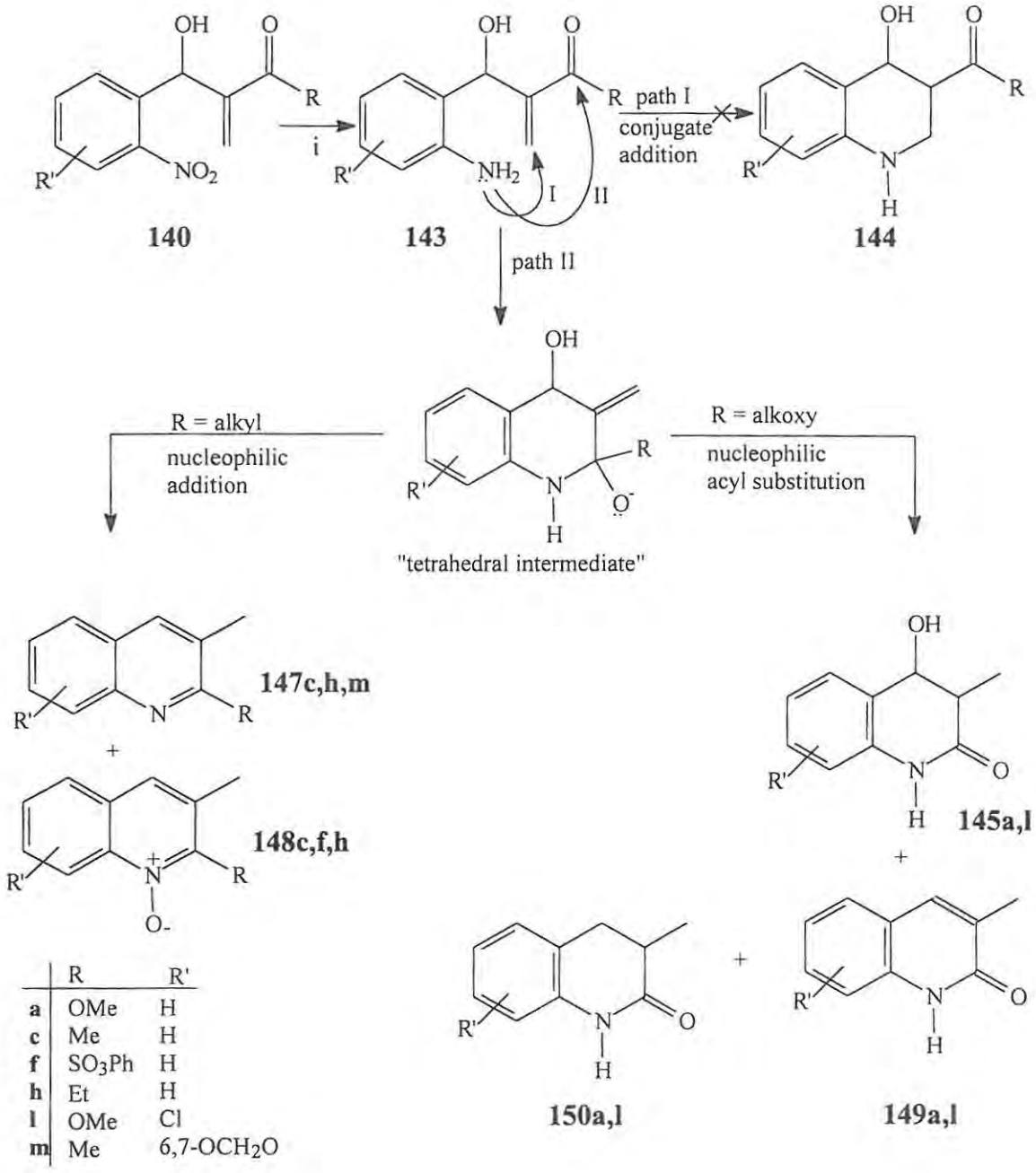
(i) conjugate addition to the α,β-unsaturated carbonyl system, following path I **(Scheme 25)**

and/or

(ii) nucleophilic attack at the carbonyl carbon, following path II, with the vinyl ketones (R= alkyl) undergoing nucleophilic addition and the esters (R=alkoxy) undergoing acyl substitution. Subsequent dehydration of the primary cyclisation products **144, 145** and **146** would then afford the corresponding, unsaturated derivatives.

2.2.1 Catalytic hydrogenation

When selected Baylis-Hillman products **140a-m** were hydrogenated at atmospheric pressure, using a 10% palladium-on-carbon catalyst, no compounds arising from conjugate addition (path I; **Scheme 25**) were, in fact, isolated. The conjugate addition pathway (path I) would have afforded the tetrahydroquinolines **144** (and their dehydrated derivatives), and the ^{1}H NMR spectra for such compounds would clearly indicate the presence of the 3-substituent (RC=O), while the ^{13}C NMR spectra would exhibit a carbonyl signal at *ca.* 170 ppm. No products with such NMR characteristics were isolated, and it became apparent that regioselective cyclisation involving attack at the carbonyl carbon (path II) was favoured. For the esters (R= alkoxy; **Scheme 26**) it became clear that cyclisation involved nucleophilic acyl substitution to afford products of type **145**, **149** and **150**, while the vinyl ketones (R=alkyl) gave rise to condensation products of type **147** and **148** *via* nucleophilic addition at the carbonyl centre.



	R	R'
a	OMe	H
c	Me	H
f	SO_3Ph	H
h	Et	H
l	OMe	Cl
m	Me	6,7-OCH_2O

Scheme 26. Reagents and conditions: i) H_2, Pd-C, r.t

2.2.1.1 Nucleophilic acyl substitution

From spectroscopic analysis it was evident that reductive cyclisation of the Baylis-Hillman esters proceeds *via* the nucleophilic acyl substitution pathway to give, in addition to the initial 4-hydroxy quinolones **145**, the quinolones **149** and their hydrogenated derivatives **150 (Scheme 26; Table 3)**.

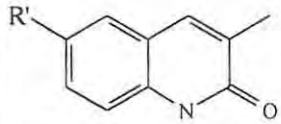
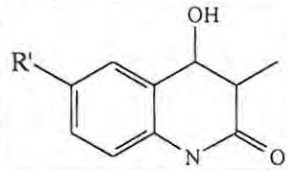
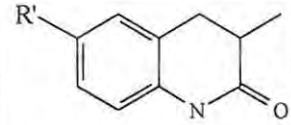
Structure	Compd.	R'	Yield / %
	**149a**	H	15
	149l	Cl	11
	**145a**	H	18
	145l	Cl	9
	**150a**	H	41
	150l	Cl	24

Table 3. Yields for the nucleophilic substitution reactions (Path II; Scheme 25)

The formation of these products can be rationalised in terms of the mechanism outlined in **Scheme 26**. Thus, after the nitro group has been reduced, the resulting, nucleophilic amino group attacks the carbonyl carbon to give the "tetrahedral intermediate". Loss of the alkoxide leaving group then affords the diastereomeric 4-hydroxy quinolones **145**, and subsequent dehydration and

reduction of the resulting endocyclic double bond then leads to products **149** and **150**. The dehydration step has been demonstrated previously by Familoni,[42] who treated the diastereomeric system **145** (R=H) with *p*-toluenesulfonic acid in refluxing toluene to obtain the conjugated, achiral 3-methylquinolone **149**; (R= H). The structural differences between the substrates **140** and the products **145**, **149** and **150** are clearly evident in their ^{1}H NMR spectra. **Figures 12a** and **b** illustrate the differences between compounds **140a** and **150a**. Thus, the characteristic vinylic signals of the Baylis-Hillman product between 5.5 and 6.5 ppm and the methoxy singlet at 3.75 ppm are clearly absent in the spectrum of compound **150**. The spectrum of the tetrahydroquinoline **150a**, reveals a methyl doublet at 1.25 ppm and the methine and methylene multiplets between 2.5 and 3.05 ppm.

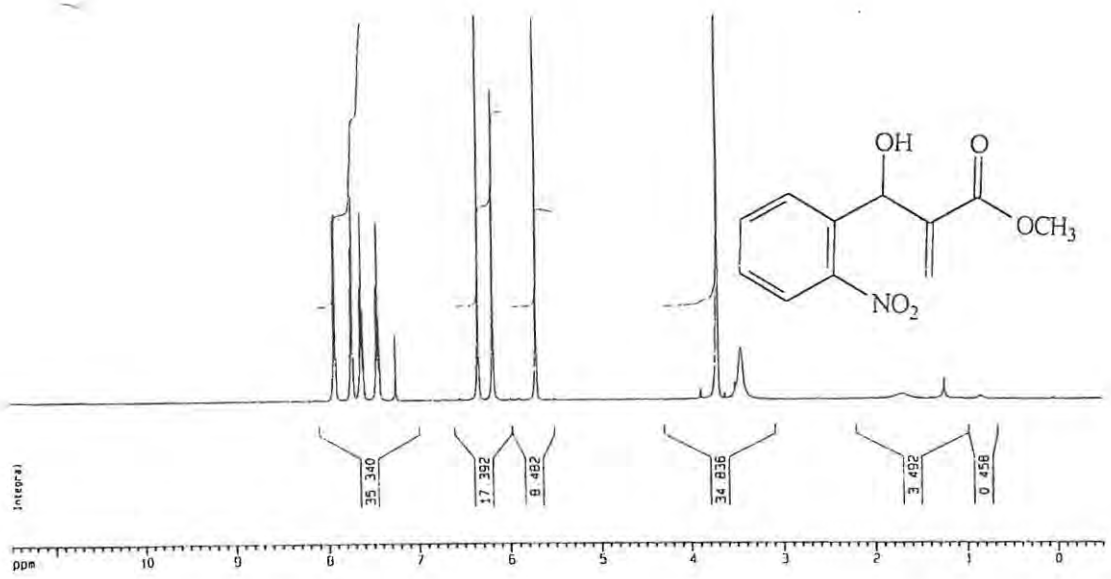


Figure 12a. 400 MHz ^{1}H NMR spectrum of th Baylis-Hillman product **140a** in $CDCl_3$

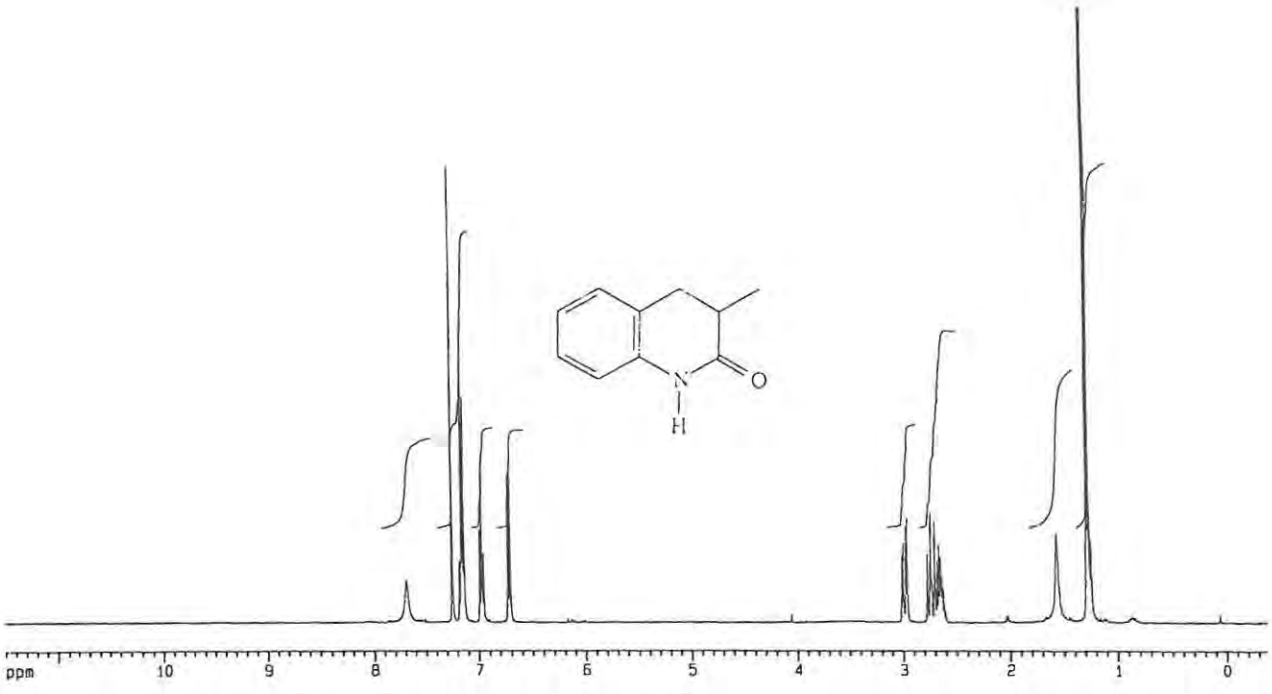


Figure 12b. 400 MHz ^{1}H NMR spectrum of the tetrahydroquinoline **150a** in $CDCl_3$

2.2.1.2 The nucleophilic addition pathway

In the case of the vinyl ketone derivatives **140** (R=alkyl), reduction of the nitro group and nucleophilic attack of the resulting amino group at the carbonyl carbon gives the "tetrahedral" intermediate (**Scheme 26;** R=alkyl). Protonation and elimination of two molecules of water then gives the aromatic quinolines **147**, which were fully characterised by spectroscopic (^{1}H, ^{13}C, HMQC and COSY NMR and IR) and elemental (high resolution MS) analysis. The COSY and HETCOR NMR spectra for compound **147h** (R =CH_2CH_3) are illustrated in **Figures 13** and **14.** The COSY spectrum clearly shows the coupling between CH_2 and CH_3 protons, while the HETCOR spectrum shows the expected correlation between the carbons and the protons.

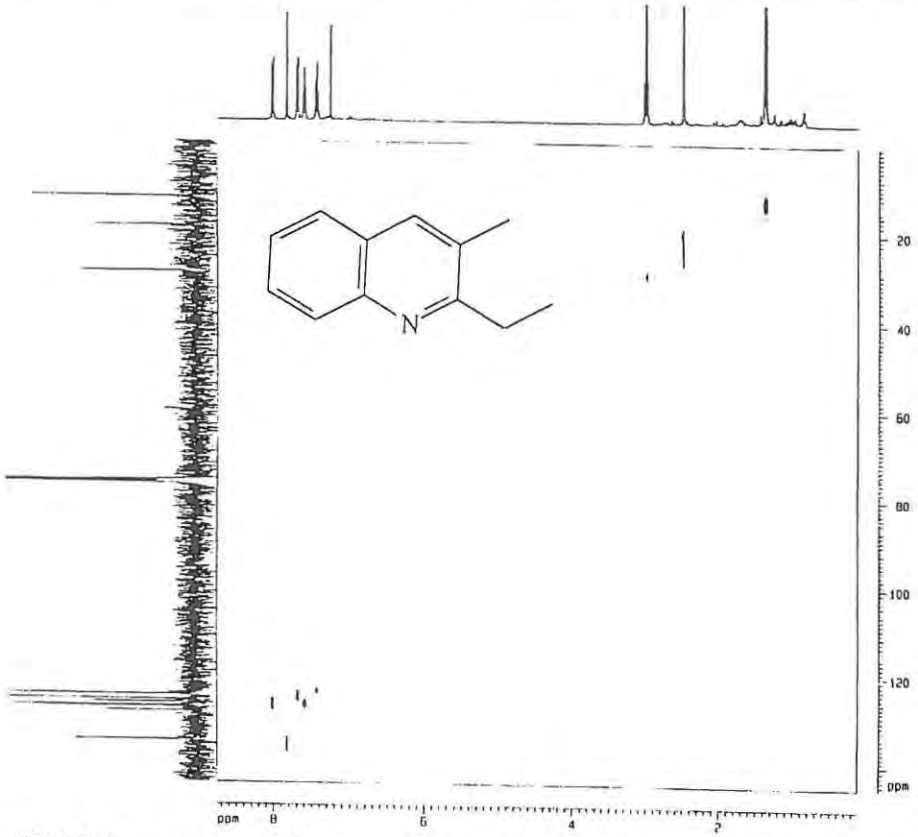


Figure 13. HMQC spectrum of the quinoline derivative **147h** in $CDCl_3$.

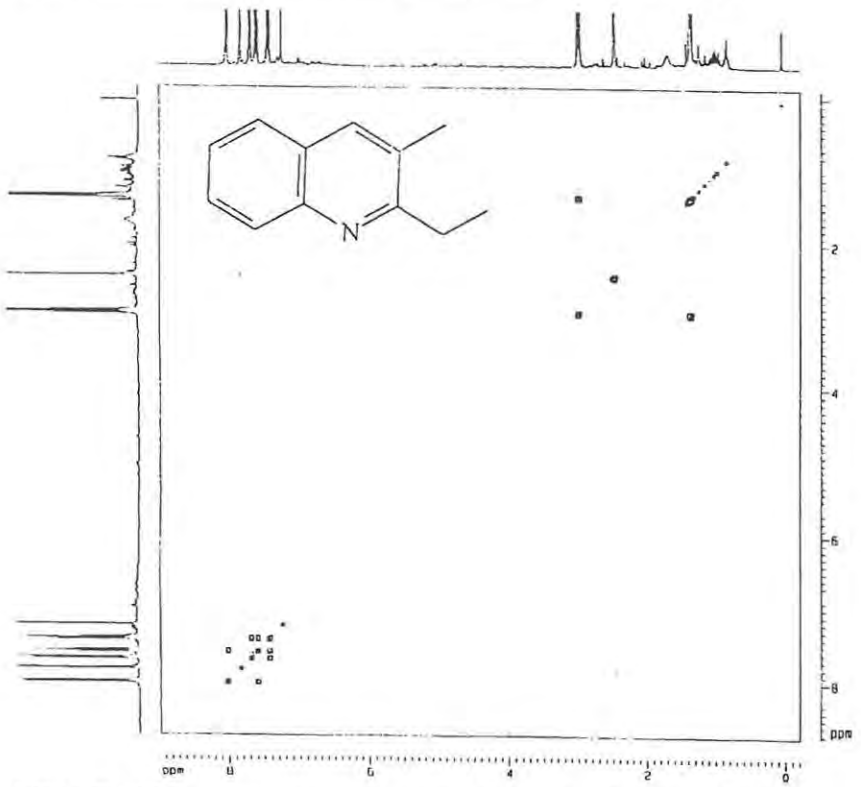


Figure 14. 400 MHz COSY spectrum of quinoline derivative **147h** in $CDCl_3$.

This pathway, in fact, typically afforded two products, the quinoline **147** and its *N*-oxide **148** **(Scheme 26)**. The isolation of *N*-oxides from these reactions was initially confusing, since the *N*-oxides **148** have very similar ^{1}H and ^{13}C NMR spectra to the corresponding quinoline derivatives **147**, and in EI mass spectrometry, ready loss of an oxygen atom from the *N*-oxide affords the quinoline radical cation, which was initially viewed as the molecular ion rather than as a fragment. In the apparent absence of any published data, the NMR spectra could not be used to establish unambiguously which compound was which. The *N*-oxides were finally characterised by high resolution FAB mass spectrometry (which confirmed the presence of an oxygen atom) and by the presence of the IR N-O absorption band at *ca.* 1271 cm^{-1}. The ^{1}H NMR spectra of the quinoline **147h** and quinoline *N*-oxide **148h** are illustrated in **Figure 15.** The 8-H nucleus in the quinoline *N*-oxide is deshielded by the positively charged nitrogen atom and,

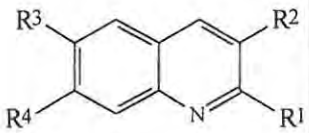
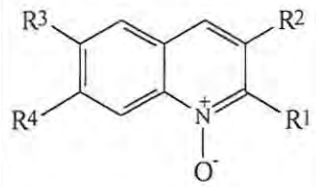
Structure	Compd.	R1	R2	R3	R4	Yield / %
	**147h**	Et	Me	H	H	34
	147c	Me	Me	H	H	20
	147m	Me	Me	-OCH_2O-		26
	**148f**	H	SO_3Ph	H	H	5
	148c	Et	Me	H	H	39
	148h	Me	Me	H	H	52

Table 4. Quinolines and quinoline *N*-oxides obtained *via* the nucleophilic addition pathway

hence, resonates downfield (at *ca.* 8.7 ppm) of the corresponding nucleus (at *ca.* 8.0 ppm) in the quinoline derivative. The quinolines and corresponding *N*-oxides obtained in the present study are detailed in **Table 4**.

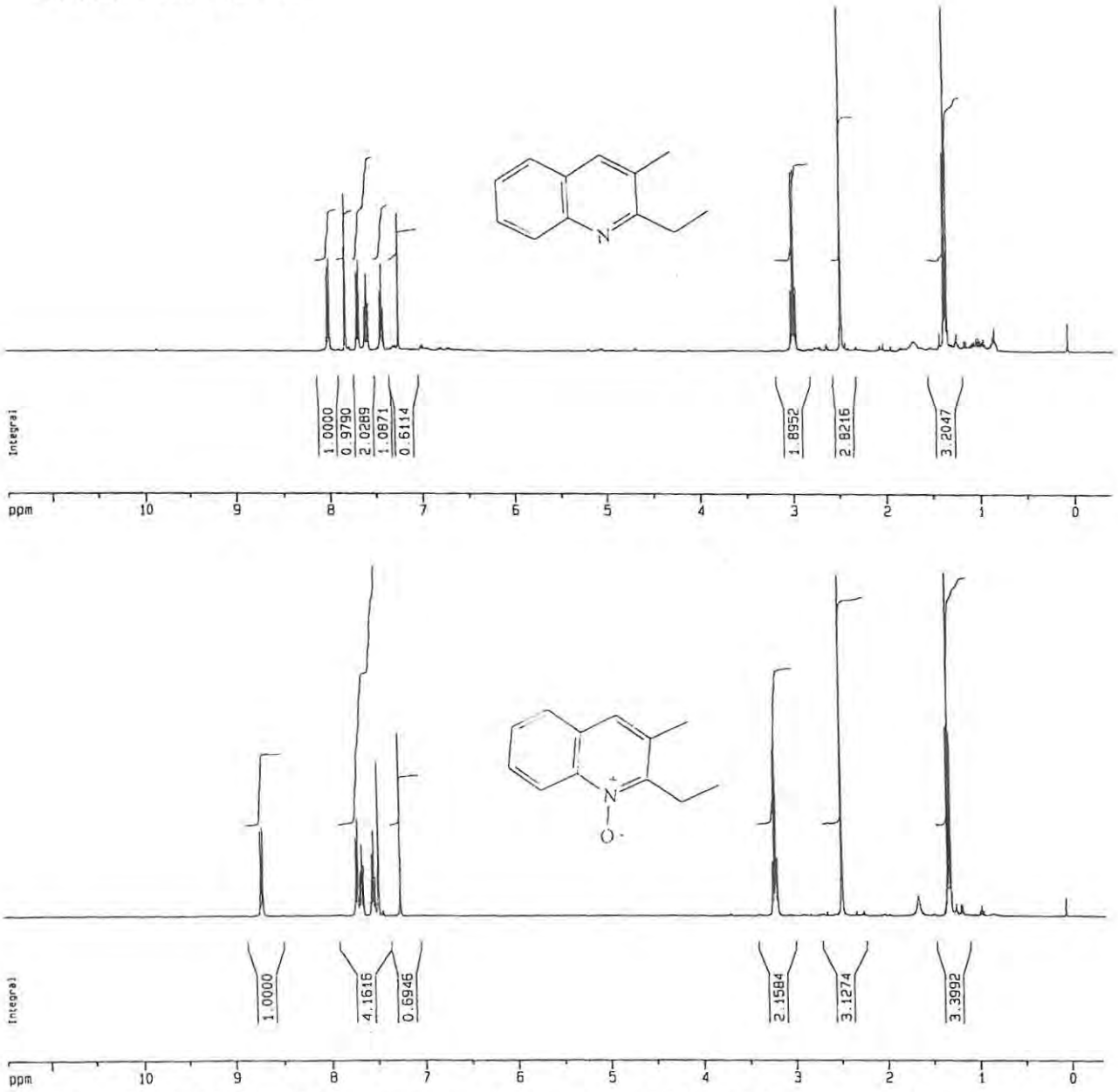
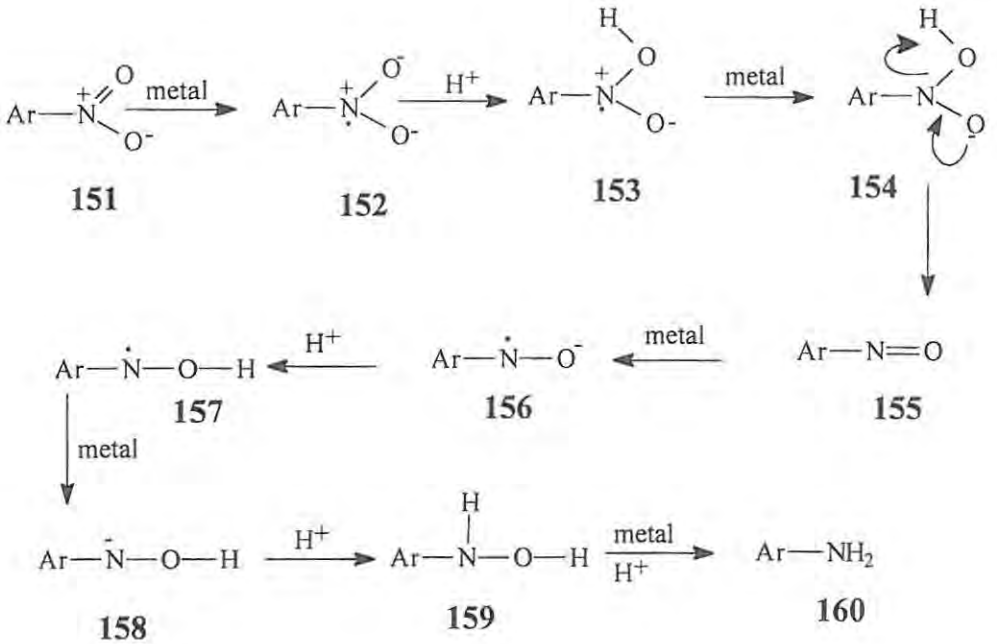


Figure 15. 400 MHz ^{1}H NMR spectra of the quinoline **147h** and the corresponding quinoline *N*-oxide **148h** in $CDCl_3$

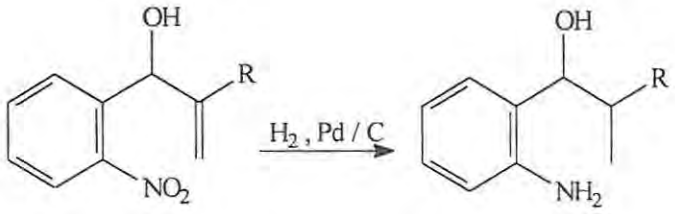
Formation of the quinoline *N*-oxides **148** is attributed to cyclisation of an incompletely reduced nitro species. Illustrated below is the generally accepted mechanism for the reduction of the nitro group **(Scheme 27)**,[50] and it is apparent that either of the intermediates **158 or 159** could, in principle, act as a nucleophile, attacking the carbonyl carbon before reduction to the amino group is complete. The fact that quinoline *N*-oxides were always isolated in higher yields than the corresponding quinolines is consistent with relatively rapid cyclisation prior to complete formation of the amino group.

In two of the cases examined, reduction of the Baylis-Hillman products ,*viz.*, the nitrile **140d** and the sulfone **140e**, afforded the corresponding acyclic derivatives **161d** and **161e** respectively, **(Scheme 28)**.



Scheme 27

These products arise from reduction of the double bond, and it seems that cyclisation involving conjugate addition at the acrylonitrile or vinyl sulfonyl moieties is not favoured. The formation of these acyclic compounds was evident from their proton and carbon-13 NMR spectra. The compounds are produced as diastereomeric mixtures due to the presence of two stereocentres, with resultant doubling of proton and carbon-13 NMR signals.



140 **161**

	R	Yield / %
d	CN	37
e	SO_2Ph	31

Scheme 28

The IR spectrum of compound **161d** clearly shows the CN stretching band at 2244 cm^{-1} **(Figure 16)**. The ^1H NMR spectra of the substrate **140d** and product **161d** are illustrated in **Figure 17**; the disappearance of the substrate vinyl proton signals between 5.8 and 6.3 ppm and the appearance of the (doubled) methyl signal in the product spectrum clearly confirms the proposed transformation. The acyclic products (**161d** and **161e**) were fully characterised.

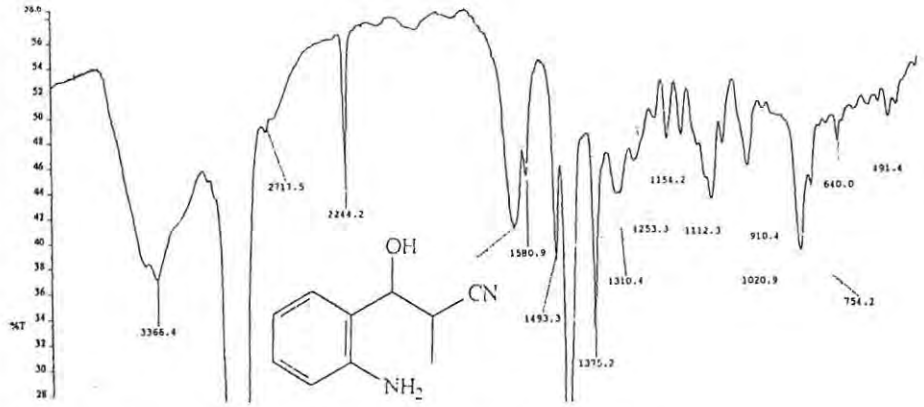


Figure 16. The IR spectrum of compound **161d** in nujol

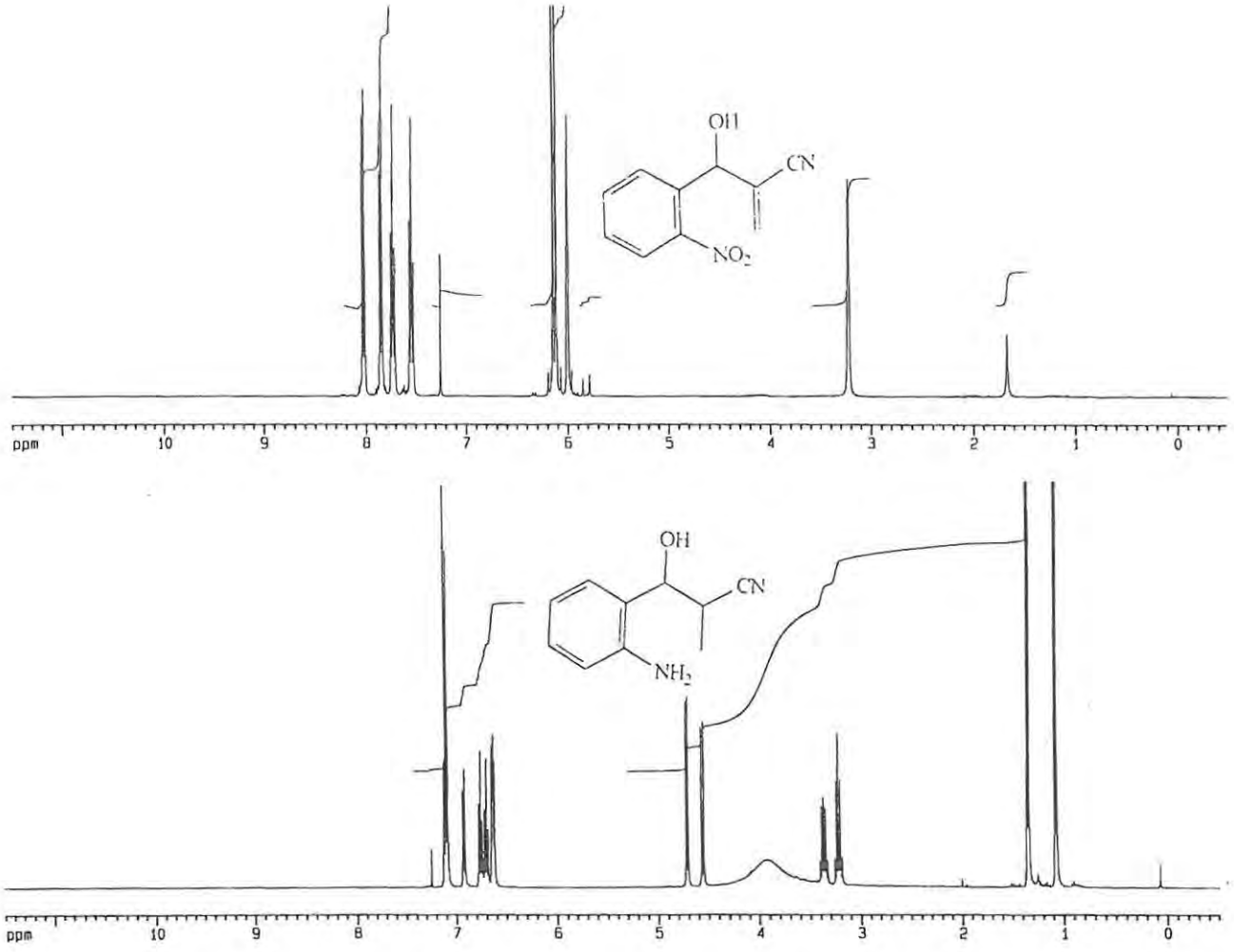
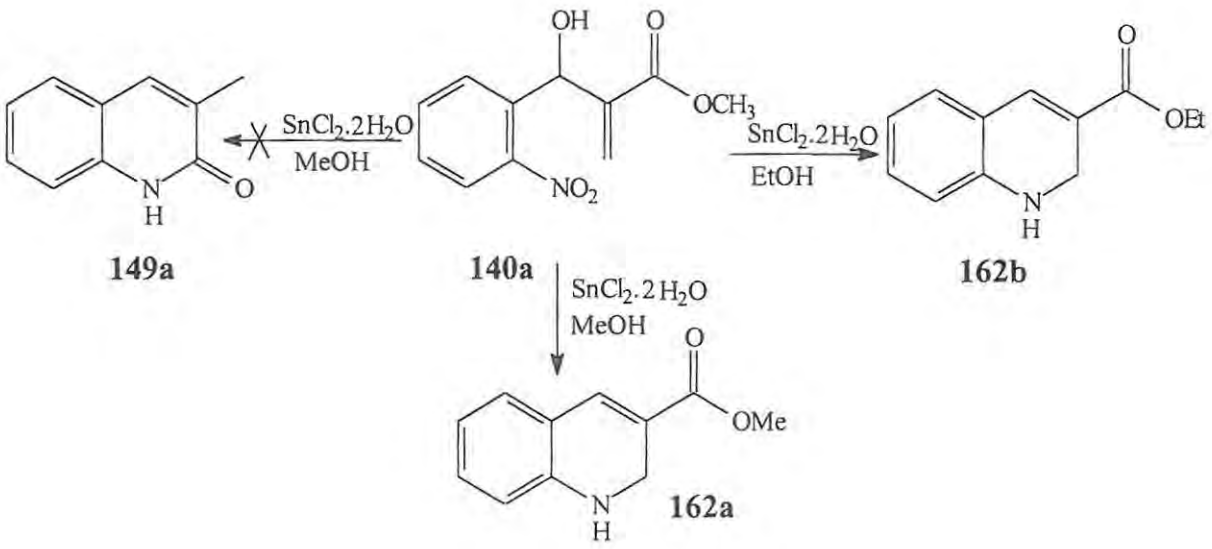


Figure 17. 400MHz ^{1}H NMR spectra of the Baylis-Hillman product **140d** and its reduced derivative **161d** in $CDCl_3$.

2.2.2 Reduction with Stannous Chloride

The reduction of aryl nitro groups may be achieved with a variety of reagent systems[51-53], and it was decided to explore the use of stannous chloride as an alternative reducing agent.[54] Ethanol is typically used as the solvent with this reagent, but when the reaction was applied to the reduction of the methyl ester **140a**, two unexpected observations were made. Firstly, cyclisation appeared to favour conjugate addition to afford the dihydroquinoline (**Scheme 29**) rather than the nucleophilic acyl substitution pathway observed on catalytic hydrogenation of the same substrate; subsequent extension of the reaction to other Baylis-Hillman products revealed that regioselective cyclisation to 3-substituted dihydroquinolines was, in fact, general. Secondly, $SnCl_2$ reduction of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** in *ethanol* afforded the *ethyl* ester **162b**, and it was clear that stannous chloride was acting as a Lewis acid, catalysing transesterification of the methyl ester in the presence of ethanol. The ethyl ester **162b** was fully



Scheme 29

characterised using IR, MS and NMR spectroscopic techniques. The COSY spectrum **(Figure 18)** clearly reveals the coupling between the methyl (triplet at δ 1.30 ppm) and methylene (quartet at δ 3.60 ppm) nuclei of the ethyl group. To avoid transesterification, methanol was used as the solvent instead of ethanol, and the methyl ester **162a** was obtained in 50% yield.

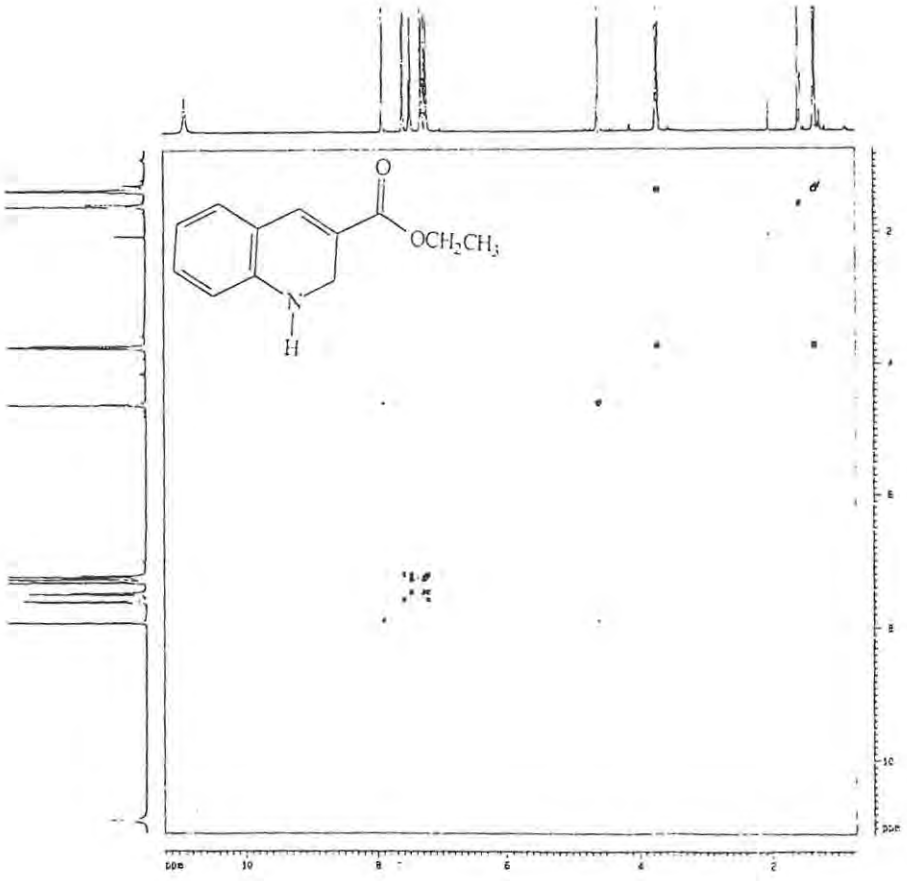
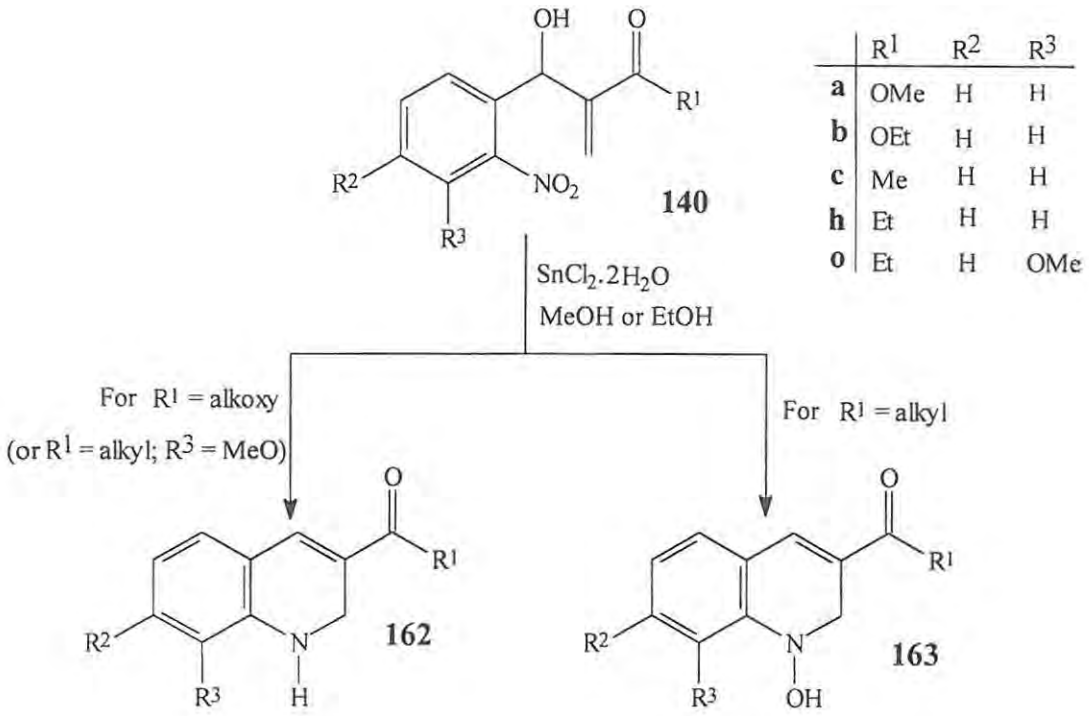


Figure 18: 400 MHz COSY spectrum of the methyl ester **174**

A third, unexpected observation was made when the reaction was extended to other substrates. Baylis-Hillman esters gave rise to the corresponding 1,2-dihydroquinolines whereas the ketone

analogues gave the *N*-hydroxy analogues **163** (**Scheme 30**). The presence of an extra oxygen atom (and, hence, the *N*-hydroxy moiety) in these latter compounds was confirmed by FAB MS analysis. In the case of the Baylis-Hillman ketone **140c**, however, the presence of the methoxy group at C-8 appears to inhibit formation of the *N*-hydroxy product, and the corresponding 1,2-dihydroquinoline **162o** was isolated. To our knowledge, all of the 1,2-dihydroquinoline derivatives synthesised in this project are new. An ethyl dihydroquinoline-3-carboxylate derivative has been reported by Blicke *et al.*,[55] but there is some ambiguity as to the position



	R1	R2	R3
a	OMe	H	H
b	OEt	H	H
c	Me	H	H
h	Et	H	H
o	Et	H	OMe

	R1	R2	R3
a	OMe	H	H
b	OEt	H	H
o	Et	H	OMe

	R1	R2	R3
c	Me	H	H
h	Et	H	H

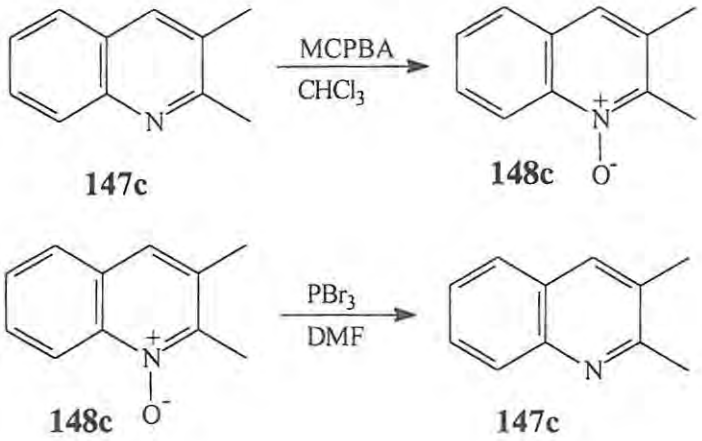
Scheme 30

of the double bond; the authors suggest probable formation of the dihydro isomer.

In the ^{13}C NMR spectrum of compound **162a**, the methylene signal overlaps the solvent ($CHCl_3$) signal at *ca.* 77.0 ppm but its presence is confirmed by the DEPT spectrum; in the ^{13}C NMR spectra of the analogous compounds **162b** and **162o**, the methylene nuclei resonate at *ca.* 77.5 ppm. Yields for these reactions ranged between 14 and 54 %. It is quite possible that the conversion efficiences were, in fact, higher, but considerable difficulty was encountered in attempting to extract the product from the emulsions which formed when the reaction mixtures were added to ice.

2.3. INTERCONVERSION OF QUINOLINE DERIVATIVES AND THEIR *N*-OXIDES

The reduction of *N*-oxides has been achieved using ammonium formate as a catalytic hydrogen transfer agent,[56] but recent work[57] has shown that phosphorus tribromide is a better reducing agent. *m*-Chloroperbenzoic acid (MCPBA), on the other hand, has been found to be an effective oxidising agent for converting amines to their *N*-oxides.[58] Consequently, the use of PBr_3 or MCPBA was investigated for the selective formation of *either* the free quinoline derivatives *or* their *N*-oxides respectively. Following some exploratory studies, 2,3-dimethylquinoline **147c**, isolated from reductive cyclisation of the Baylis-Hillman product **140c** using catalytic hydrogenation, was oxidized with MCPBA in $CHCl_3$ to afford the quinoline *N*-oxide **148c** in good yield (78 %) **(Scheme 31)**. In the reverse transformation, 2,3-dimethylquinoline *N*-oxide **148c**, was reduced with PBr_3 in DMF to afford 2,3-dimethylquinoline **147c** in 76 % yield.



Scheme 31

The ^{1}H NMR spectra of the quinoline **147c** and its *N*-oxide **148c** are illustrated in **Figure 19**.The quinoline derivative **147c** exhibits two methyl signals between δ 2 and 3 ppm, while the 4-H nucleus resonates as a singlet at δ 7.7 ppm. The quinoline *N*-oxide **148c** exhibits similar chemical shifts except in the aromatic region where the deshielded 8-H nucleus resonates as a doublet downfield (at *ca.* 8.7 ppm) of the corresponding proton (at *ca.* 8 ppm) in the spectrum of the quinoline derivative **147c**. As mentioned earlier, this deshielding is due to the positive charge on the nearby nitrogen atom.

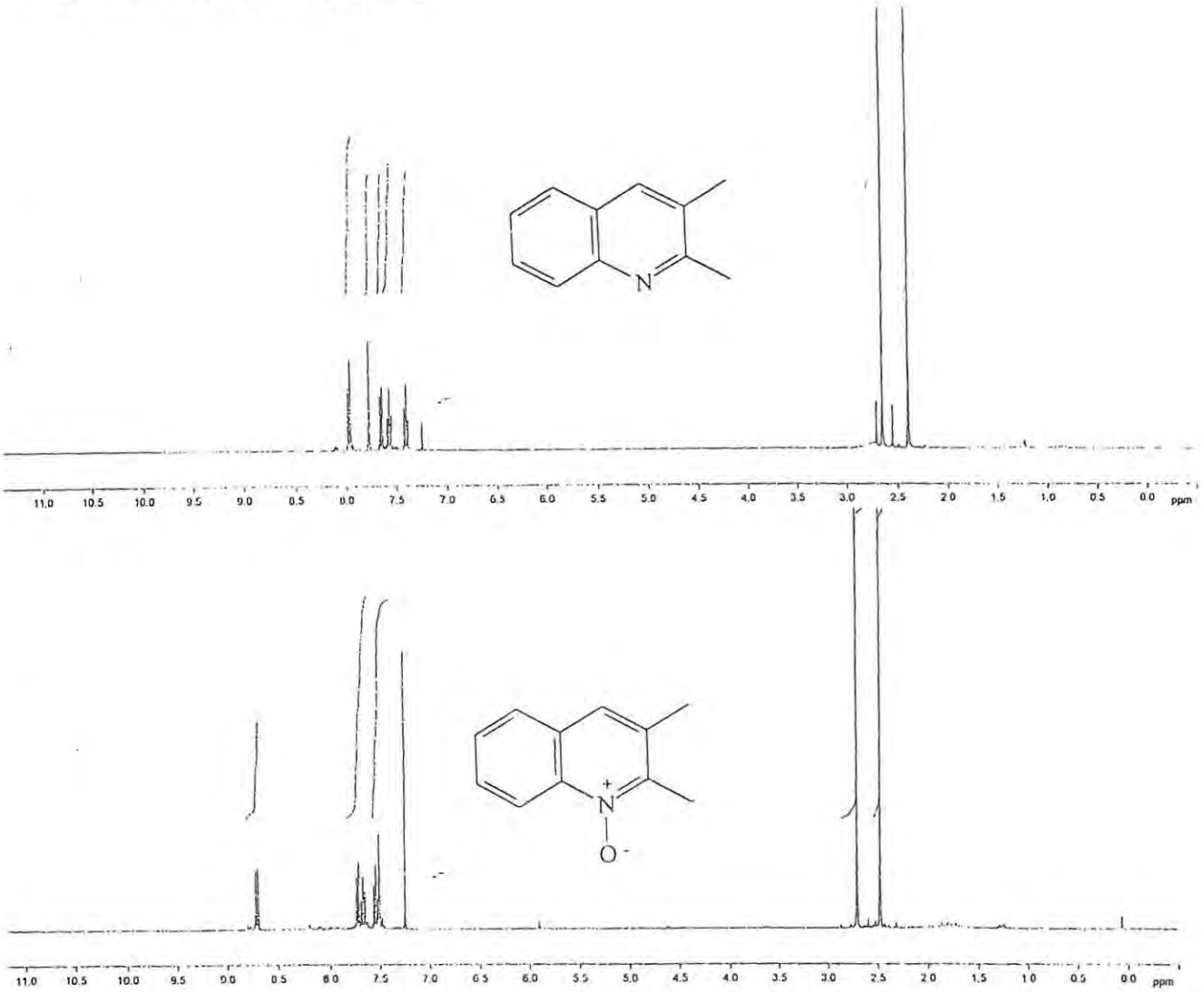
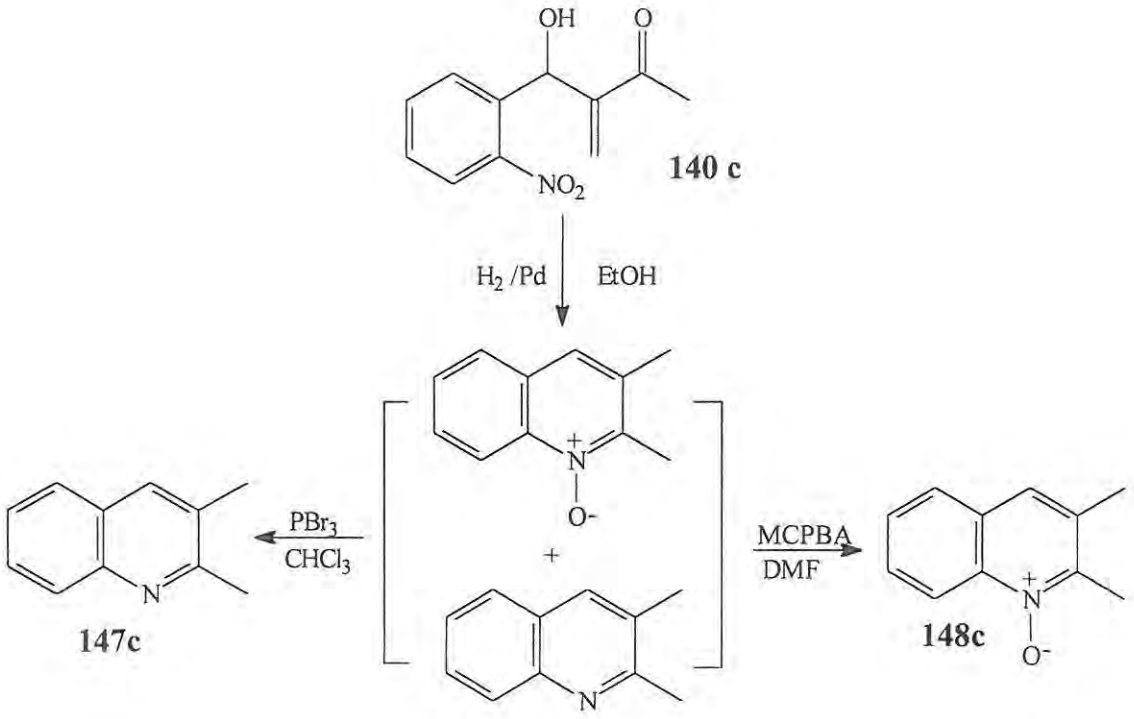


Figure 19: ^{1}H NMR of quinoline **147c** and quinoline N-oxide **148c** in $CDCl_3$

To avoid having unnecessary steps, it was decided to explore i) reduction and ii) oxidation of a *mixture* of the quinoline derivative **147c** and its *N*-oxide **148c** to demonstrate "one-pot" formation of *either* the quinoline *or* the quinoline *N*-oxide. Thus, a mixture (1:1.63 molar ratio) of the quinoline **147c** and the quinoline *N*-oxide **148c** (obtained *via* catalytic reduction of the Baylis-Hillman product **140c**) was divided into two portions. One portion of the mixture was reduced with PBr_3 and, since only the *N*-oxide is susceptible to reduction, the quinoline **147c** was the only product isolated from the reaction mixture **(Scheme 32)**. The other portion was oxidized using MCPBA as an oxidising agent and,in this case, oxidation of the quinoline present in the mixture appeared to occur quantitatively, permiting isolation of the *N*-oxide **148c** as the sole product.



Scheme 32

This approach clearly solves the problem of selectivity in this reaction. When the synthesis of quinolines is required, PBr_3 can be added to the mixture after the catalyst has been filtered off, and any quinoline *N*-oxide present will be reduced to the quinoline. On the other hand, MCPBA may be added to the reaction mixture (after removal of the catalyst) when the quinoline *N*-oxide is required.

2.5. CONCLUSION

During the course of this research, a range of Baylis-Hillman products has been successfully prepared from 2-nitrobenzaldehyde derivatives and various activated alkenes. Reductive cyclisation *via* catalytic hydrogenation has been shown to afford, depending on the nature of the Baylis-Hillman product, either quinoline, quinoline *N*-oxide or quinolone derivatives, and the structures of these products have been established unambiguously using NMR, high resolution MS and, in some cases, FAB MS spectroscopy. Attention has been given to optimising the yields in these reactions, and the use of stannous chloride as an alternative reagent to effect reductive cyclisation has been explored. Use of this reagent, however, resulted in the unexpected formation of different products, *viz.*, 1,2-dihydroquinoline derivatives, arising from cyclisation *via* conjugate addition. In contrast, under catalytic hydrogenation conditions, cyclisation involves nucleophilic attack at the carbonyl carbon resulting in condensation or acyl substitution. The different modes of attack thus provide scope for the chemoselective synthesis of quinoline, quinoline *N*-oxide and quinolone derivatives, on one hand, and the synthesis of 1,2-dihydroquinoline derivatives on the other, the chemoselectivity being determined by the appropriate choice of substrate and reducing system.

Methods for effecting the efficient interconversion of the quinoline and quinoline *N*-oxide derivatives have been successfully optimised; reduction of the *N*-oxide to the quinoline was achieved using PBr_3 and the reverse transformation with MCPBA. Finally, the methods were successfully applied to *mixtures* of the quinoline derivative and its *N*-oxide.

It is apparent that the objectives of this investigation have been successfully addressed and the results have opened novel, efficient and chemoselective approaches to a very important class of heterocyclic compounds.

Possibilities for future research in this area include:-

i, the use of other reducing systems to effect reductive cyclisation of the initial Baylis-Hillman products;

ii, detailed investigation of the mechanistic basis of the observed regioselectivities; and

iii, elaboration of the quinoline derivatives to pharmacologically active systems and, in particular, quinoline-based antimalarials.

EXPERIMENTAL

3.1. GENERAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. NMR spectra were run on a Bruker AMX400 spectrometer, and chemical shifts (δ) are expressed in parts per million (ppm). NMR samples were, in most cases, dissolved in $CDCl_3$. Spectra recorded in $CDCl_3$ were calibrated using the solvent signal at 7.25 for ^1H and 77.0 for ^{13}C. IR spectra were recorded on a Perkin-Elmer Spectrum2000 FT-IR spectrometer. Low resolution mass spectra were obtained on a Finnegan Mat GCQ mass spectrometer and high resolution mass spectra on a Kratos MS 80RF mass spectrometer (Cape Technikon Mass Spectrometry Unit).

Flash chromatography [59,60] was carried out using Merck silica gel 60 [particle size 0.040 - 0.063 mm (230 - 400 mesh)] and preparative layer chromatography (PLC) was achieved using Merck silica gel 60 PF_{254}. Thin layer chromatography (TLC) was performed using precoated Merck silica gel F_{254} plates, visualisation of the components being achieved by exposure to iodine or inspection under UV light. Methanol was dried under dry N_2 using the procedure described by Perrin and Armarego. [61]

3.2 SYNTHETIC PROCEDURES

3.2.1. Preparation of Baylis-Hillman products

Methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a**

A solution of 2-nitrobenzaldehyde (10g, 66 mmol), methyl acrylate (5.9g, 68 mmol) and DABCO (0.354g, 3.16mmol) in chloroform (3 ml) was stirred at room temperature for 5 days.¶ The crude mixture was purified by flash chromatography [on silica; elution with hexane-EtOAc (3:1)] to afford, as a pale green oil, methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** (8.96g, 54 %) (Found M^+- H_2O: 219.05329. Calc for $C_{11}H_{11}NO_5$: *M*-H_2O, 219.05316); ν_{max} (nujol)/cm^{-1} 3444 (OH) and 1710 (C=O); δ_H (400 MHz; $CDCl_3$) 3.45 (1H, br s, OH), 3.83 (3H, s, CH_3), 5.71 and 6.34 (2H, 2 x s, C=CH_2), 6.18 (1H, s, C*H*OH), 7.45 (1H, t, Ar-H), 7.63 (1H, t, Ar-H), 7.73 (1H, d, Ar-H) and 7.91 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 52.1 (OCH_3), 67.5 (CHOH), 124.5 (C=*C*H_2), 126.4 (*C*=CH_2), 128.6 (C-3'), 128.8 (C-6'), 133.4 (C-4'), 136.1 (C-1'), 140.7 (C-5'), 148.2 (C-2') and 166.4 (C=O); *m/z* 219 (*M*$^+$- H_2O, 11 %) and 77 (100).

¶ The reaction was generally monitored by TLC analysis and, when necessary, stirring was continued for a longer period.

Ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140b**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2-nitrobenzaldehyde (2.0 g, 13 mmol), ethyl acrylate (1.37 g, 13.7 mmol) and DABCO (0.071 g, 0.63 mmol). Work-up and flash chromatography [on silica; elution with hexane-EtOAc (3:1)] gave, as a pale green oil, ethyl 2-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140b** (1.53g, 46 %) (Found M^+-H_2O: 233.07069. Calc for $C_{12}H_{13}NO_5$: *M*-H_2O, 233.06881); ν_{max} (nujol)/cm^{-1} 3423 (OH) and1708 (C=O); δ_H (400MHz; $CDCl_3$) 1.21 (3H, t, CH_3), 3.39 (1H, d, OH), 4.22 (2H, m, CH_2), 5.72 and 6.36 (2H, 2xs, $C=CH_2$), 6.17 (1H, d, C*H*OH), 7.47 (1H, t, Ar-H), 7.63 (1H, t, Ar-H), 7.74 (1H, d, Ar-H) and 8.13 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 13.7 (CH_3), 61.0 (CH_2), 66.9 (CHOH), 123.5 ($C=CH_2$), 125.8 ($C=CH_2$), 128.4 (C-3'), 129.0 (C-6'), 133.2 (C-4'), 136.2 (C-5'), 141.1 (C-1'), 148.1 (C-2') and 165.7 (C=O); *m/z* 233 (M^+- H_2O, 14 %) and 77 (100).

4-Hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **140c**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2-nitrobenzaldehyde (5.0 g, 33 mmol), methyl vinyl ketone (2.4 g, 34 mmol) and DABCO (0.18 g, 1.6 mmol). Work-up and flash chromatography [on silica; elution with hexane-EtOAc (3:1)] gave, as pale brown crystals, 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **140c** (4.2 g, 57 %), m.p. 133-136 °C (Found M^+-H_2O: 203.05776. Calc for $C_{11}H_{11}NO_4$:*M*-H_2O, 203.06607); ν_{max}/cm^{-1} (nujol) 1703 (C=O); δ_H (400 MHz; $CDCl_3$) 2.35(3H,

s, CH_3), 3.53(1H, br s, OH), 5.77 and 6.15 (2H, 2xs, C=CH_2), 6.20 (1H, s, C*H*OH), 7.45 (1H, t, Ar-H), 7.65 (1H, t, Ar-H), 7.75 (1H, d, Ar-H) and 7.95 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 26.0 (CH_3), 67.4 (CHOH), 124.6 (C=H_2), 126.5 (C=CH_2), 128.5 (C-4'), 128.8 (C-5'), 133.5 (C-1'), 136.4 (C-3'), 148.0 (C-2'), 148.8 (C-6') and 199.8 (C=O); *m/z* 203 (M^+-H_2O, 2 %) and 161 (100).

3-Hydroxy-2-methylene-3-(2-nitrophenyl)propanenitrile **140d**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2-nitrobenzaldehyde (10.0 g, 66 mmol), acrylonitrile (3.52 g, 66 mmol) and DABCO (0.37 g, 3.3 mmol). Work-up and flash chromatography [on silica ; elution with hexane-EtOAc (3:1)] gave, as pale yellow crystals, 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanenitrile **140d** (5.2 g, 38 %), m.p. 41 - 44 °C (Found M^+-H_2O: 186.04305. Calc. for $C_{10}H_8N_2O_3$: *M*-H_2O, 186.04293); ν_{max} / cm^{-1} (nujol) 3396 (OH) and 2226 (CN); δ_H (400 MHz; $CDCl_3$) 3.32 (1H, br s, OH), 6.00 (IH, s, C*H*OH), 6.12 and 6.15 (2H, 2xs, C=CH_2), 7.70 (1H, t, Ar-H), 7.75 (1H, t, Ar-H), 7.83 (1H, d, Ar-H) and 8.02 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 69.1 (CHOH), 116.5 (C=*C*H_2), 124.2 (C-1'), 125.1 (*C*=CH_2), 129.1 (C-3'), 129.7 (C-6'), 132.1 (C-5'), 134.3 (C-4'), 134.4 (C-2') and 147.9 (CN); *m*/z 186 (M^+- H_2O, 11 %) and 77 (100).

1-(2-nitrophenyl)-2-(phenylsulfonyl)-2-propenol **140e**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2-nitrobenzaldehyde (1.66 g, 11 mmol), phenyl

vinyl sulfone (1.8 g, 11 mmol) and DABCO (0.11 g, 1.0 mmol). Work-up and flash chromatography [on silica; elution with hexane-EtOAc (2:1)] gave, as pale yellow crystals, *1-(2-nitrophenyl)-2-(phenylsulfonyl)-2-propenol* **140e** (1.1 g, 32 %), m.p. 85-88 °C (Found M^+-NO_2: 273.05699. $C_{15}H_{13}NO_5S$ requires *M*-NO_2, 273.05854); ν_{max}/ cm^{-1} (nujol) 3476 (OH) and 1516 (NO_2); δ_H (400 MHz; $CDCl_3$) 3.99 (1H, s, OH), 5.65 and 6.50 (2H, 2xs, C=CH_2), 6.05 (1H, s, C*H*OH), 7.47(1H, m, Ar-H), 7.54 (2H, m, Ar-H), 7.62 (2H, m, Ar-H), 7.82(2H, d, Ar-H) and 7.89 (2H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 67.4 (CHOH), 124.6 (C=*C*H_2), 124.9 (*C*=CH_2), 128.1, 128.4, 129.2, 129.5, 129.7, 133.6, 133.9 and 138.3 (Ar-C), 147.4 (C-NO_2) and 151.0 (Ar-C); *m/z* 273 (*M*$^+$-NO_2, 4.8 %) and 160 (100).

Phenyl 3-hydroxy-3-(2-nitrophenyl)propene-2-sulfonate **150f**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2-nitrobenzaldehyde (2.1 g, 14 mmol), phenyl vinyl- sulfonate (2.5 g, 14 mmol) and DABCO (0.11 g, 1 mmol) . Work-up and flash chromatography [on silica gel; elution with hexane-EtOAC (2:1)] gave, as a pale brown oil, *phenyl 3-hydroxy-3-(2-nitrophenyl)propene-2-sulfonate* **140f** (1.2 g, 27 %) (Found M^+: 335.04546. $C_{15}H_{13}NO_6S$ requires *M*, 335.0 4636); ν_{max} /cm^{-1} (nujol) 3476 (OH) and 1522 (NO_2); δ_H (400 MHz; $CDCl_3$) 3.82 (1H, br s, OH), 5.83 and 6.26 (2H, 2xs, C=CH_2), 6.44 (1H, s, C*H*OH), 7.32 (1H, m, Ar-H), 7.41 (2H, m, Ar-H), 7.49 (2H, m, Ar-H), 7.55 (1H, t, Ar-H), 7.75 (1H, t, Ar-H), 7.91 (1H, d, Ar-H) and 8.07(1H, d, Ar-H); δ_C (400 MHz; $CDCl_3$) 67.5 (CHOH), 122.1 (C=*C*H_2), 127.3 (*C*=CH_2), 128.8, 129.5, 130.1, 131.9, 133.8 , 134.1, 144.8, 146.4, 147.9 and 149.3 (Ar-C); *m/z* 335 (*M*$^+$, 8 %)

and 94 (100).

3-Hydroxy-2-methylene-3-(2-nitrophenyl)propanal **150g**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2-nitrobenzaldehyde (5.0 g, 33 mmol), acrolein (1.9 g, 34 mmol) and DABCO (0.2 g, 2 mmol). Work-up and flash chromatography [on silica ; elution with hexane-$CHCl_3$(1:3)] gave, as a brown oil, *3-hydroxy-2-methylene-3-(2-nitrophenyl)propanal* **140g** (0.42 g, 7.0 %) (Found M- NO_2:129.60351. $C_{10}H_9NO_4$ requires *M*-NO_2, 129.6039); ν_{max}/cm^{-1} (nujol) 3463 (OH) and 1675 (C=O); δ_H (400 MHz; $CDCl_3$) 3.63 (1H, br s, OH), 4.86 and 5.76 (2 H, 2x s, C=CH_2), 5.51 (1H, s, C*H*OH), 7.51 (1H, t, Ar-H), 7.78 (1H, t, Ar-H), 7.95 (1H, d, Ar-H), 8.10 (1H, d, Ar-H) and 10.39 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 62.9 (CHOH), 122.4 (C=*C*H_2), 124.1 (*C*=CH_2), 128.6 (C-4'), 129.6 (C-5'), 134.0 (C-3'), 135.8 (C-2'), 140.5 (C-1'), 143.2 (C-6') and 191.2 (CHO); *m/z* 129 (M^+- NO_2, 6.4 %) and 65 (100).

1-Hydroxy-2-methylene-1-(2-nitrophenyl)pentan-3-one **150h**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2-nitrobenzaldehyde (5.0 g, 33 mmol), ethyl vinyl ketone (2.8 g, 33 mmol) and DABCO (0.19 g, 1.7 mmol). Work-up and flash chromatography [on silica; elution with hexane-EtOAc (2:1)] gave, as a pale brown oil, *1-hydroxy-2-methylene-1-(2-*

nitrophenyl)pentan-3-one **140h** (4.79 g, 62 %) (Found: M^+-NO_2: 189.09051. $C_{12}H_{13}NO_4$ requires *M*-NO_2,189.09155); ν_{max} (nujol)/cm^{-1} 3396 (OH) and 1675 (C= O); δ_H (400 MHz; $CDCl_3$) 1.11 (3H, t, CH_3), 2.75 (2H, q, CH_2), 3.73 (1H, br s, OH), 5.71 and 6.23 (2H, 2xs, C=CH_2), 6.13 (1H, s, C*H*OH), 7.45 (1H, t, Ar-H), 7.64 (1H, t, Ar-H), 7.81 (1H, d, Ar-H) and 7.98 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 8.0 (CH_3), 30.9 (CH_2), 67.6 (CHOH), 124.1 (C=*C*H_2), 124.5 (*C*=CH_2), 128.9 (C-3'), 129.1 (C-6'), 133.6 (C-4'), 136,5 (C-5'), 148.0 (C-1'), 148.4 (C-2') and 202.6 (C=O); *m/z* 189 (*M*$^+$,9 %) and 57 (100).

Methyl 3-(4,5-dimethoxy-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate **140i** ✓

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 4,5-dimethoxy-2-nitrobenzaldehyde (3.0 g, 14 mmol), methyl acrylate (1.2 g, 14.2 mmol) and DABCO (0.08 g, 0.7 mmol). Work-up and flash chromatography [on silica gel; elution with hexane-$CHCl_3$ (1:3)] gave, as a brownish oil, m*ethyl 3-(4,5-dimethoxy-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate* **140i** (0.58 g, 14 %) (Found M^+: 297.08578. $C_{13}H_{15}NO_7$ requires *M*, 297.08485); ν_{max} /cm^{-1} (nujol) 3489 (OH) and 1708 (C=O); δ_H (400MHz; $CDCl_3$) 3.47 (1H, br s, OH), 3.76 (3H, s, OCH_3). 3.94(3H, overlapping s, OCH_3), 3.96 (3H, overlapping s, OCH_3), 5.55 and 6.27 (2H, 2xs, C=CH_2), 6.29 (1H, overlapping s, C*H*OH), 7.24 (1H, s, Ar-H) and 7.62 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 52.3 (OCH_3), 56.7 (CHOH), 66.6 (OCH_3), 67.6 (OCH_3), 107.6 (C=*C*H_2), 110.0 (*C*=CH_2), 125.9 (C-2'), 131.4 (C-3'), 139.9 (C-1'), 141.4 (C-6'), 147.8 (C-4'), 153.2 (C-5') and 166.6 (C=O) ; *m/z* 297 (*M*$^+$, 26 %) and 192 (100).

4-Hydroxy-4-(2-hydroxy-6-nitrophenyl)-3-methylenebutan-2-one **140j**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl) propanoate **140a** was followed, using 6-hydroxy-2-nitrobenzaldehyde (3.0 g, 18 mmol), methyl vinyl ketone (1.3 g, 18 mmol) and DABCO (0.10 g, 0.90 mmol). Work-up and flash chromatography [on silica ; elution with hexane-EtOAc (1:2)] gave, as yellow crystals, *4-Hydroxy-4-(2-hydroxy-6-nitrophenyl)-3-methylenebutan-2-one* **140j** (0.95 g, 22 %), m.p. 133 - 136 °C (Found M^+-NO_2: 191.07123. $C_{11}H_{11}NO_5$ requires *M*-NO_2,191.07221); ν_{max} (nujol)/cm^{-1} 3356 (OH) and 1675 (C=O); δ_H (400MHz; CD_3OD) 2.35 (3H, s, CH_3), 4.87 (1H, br s, OH), 5.65 and 6.36 (2H, 2xs, $C=CH_2$), 6.17 (1H, s, C*H*OH), 6.20 (1H, br s, ArOH), 6.80 (1H, dd, Ar-H), 7.22 (1H, d, Ar-H) and 8.01 (1H, d, Ar-H); δ_C (100 MHz; CD_3OD) 26.1 (CH_3), 66.9 (CHOH), 115.4 ($C=CH_2$), 116.0 ($C=CH_2$), 126.1 (C-3'), 129.0 (C-4'), 140.7 (C-1'), 143.2 (C-5'), 152.0 (C-6'), 164.1 (C-2') and 220.4 (C=O); *m/z* 191 (M^+-NO_2,100%).

Methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-methylenepropanoate **140k**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2,4-dinitrobenzaldehyde (3.0 g, 15 mmol), methyl acrylate (3.0 g, 35 mmol) and DABCO (0.09 g, 0.8 mmol). Work-up and flash chromatography [on silica; elution with hexane-EtOAc-$CHCl_3$ (1:2:1)] gave, as pale green crystals, *methyl 3-(2,4-*

dinitrophenyl)-3-hydroxy-2-methylenepropanoate **140k** (1.5 g, 25 %), m.p 82 - 85 °C (Found M^+-H_2O: 264.03844. $C_{11}H_{10}N_2O_7$ requires *M*-H_2O, 264.038824); ν_{max} /cm^{-1} (nujol) 3436 (OH) and 1701 (C=O); δ_H (400 MHz; $CDCl_3$) 3.46 (1H, d, OH), 3.75 (3H, s, OCH_3), 5.74 and 6.39 (2H, 2xs, $C=CH_2$), 6.29 (1H, d, C*H*OH), 8.04 (1H, d, Ar-H), 8.45 (1H, d, Ar-H) and 8.78 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 52.8 (OCH_3), 68.1 (CHOH), 117.7 (C-3'), 127.6 (*C*=CH_2), 127.7 (C=*C*H_2), 131.1 (C-5'), 140.3 (C-6'), 143.1 (C-1'), 147.7 (C-2'), 148.6 (C-4') and 166.4 (C=O); *m/z* 264 (*M*$^+$-H_2O, 40%) and 59 (100).

Methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate **140l**

The procedure described for the synthesis of methyl 3-hydroxy-2methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 5-chloro-2-nitrobenzaldehyde (3.0 g, 16 mmol), methyl acrylate (1.38 g, 16 mmol) and DABCO (0.09 g, 1.0 mmol). Work-up and flash chromatography [on silica; elution with hexane-chloroform (1:3)] gave, as a brownish oil, *methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate* **140l** (2.25 g, 51 %) (Found M^+-CH_3O: 240.00666. $C_{11}H_{10}O_5NCl$ requires *M*-CH_3O, 240.00636); ν_{max}(nujol)/cm^{-1} 3465 (OH) and 1714 (C=O); δ_H (400MHz; $CDCl_3$) 3.38 (1H, d, OH), 3.75 (3H, s, OCH_3), 5.58 and 6.35 (2H, 2xs, $C=CH_2$), 6.22 (1H, d, C*H*OH), 7.43 (1H, d, Ar-H), 7.76 (1H, s, Ar-H) and 7.94 (1H, d, Ar-H); δ_C (400 MHz; CDCl3) 52.3 (OCH_3), 67.5 (CHOH), 126.2 and 126.7 ($C=CH_2$), 128.8 (C-3'), 129.2 (C-6'), 138.3 (C-2'), 140.3 (C-1'), 140.4 (C-4'), 145.1 (C-5') and 166.3 (C=O); *m/z* 240 (*M*$^+$-CH_3O, 5 %) and 225 (100).

4-Hydroxy-3-methylene-4-[4,5-(methylendioxy)-2-nitrophenyl]butan-2-one **140m**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 4,5-(methylenedioxy)-2-nitrobenzaldehyde (3.0 g, 15 mmol), methyl vinyl ketone (1.1 g, 13 mmol) and DABCO (0.09 , 0.8 mmol). Work-up and flash chromatography [on silica; elution with hexane-EtOAc (2:3)] gave, as yellow crystals, *4-hydroxy-3-methylene-4-[4,5-(methylenedioxy)-2-nitrophenyl]butan-2-one* **140m** (1.4 g, 33 %), m.p. 100 - 103 °C (Found M^+: 265.05794. $C_{12}H_{11}NO_6$ requires *M*, 265.05864); ν_{max} (nujol)/ cm^{-1} 3463 (OH) and 1662 (C=O); δ_H (400MHz; $CDCl_3$) 2.37 (3H, s, CH_3), 3.44 (1H, d, OH), 5.75 and 6.12 (2H, 2xs, $C=CH_2$), 6.19 (2H, s, OCH_2O), 6.25 (1H, d, C*H*OH), 7.27 (1H, s, Ar-H) and 7.52 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 26.0 (CH_3), 67.6 (CHOH), 103.7 ($C=CH_2$), 105.7 (OCH_2O), 107.8 ($C=CH_2$), 126.1 (C-2'), 134.1 (C-3'), 141.9 (C-1'), 147.3 (C-4'), 149.1 (C-6'), 152.3 (C-5') and 200.0 (C=O); *m/z* 265 (M^+, 10 %) and 188 (100).

1-Hydroxy-1-(3-methoxy-2-nitrophenyl)-2-methylenepentan-3-one **140o** ✓

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 3-methoxy-2-nitrobenzaldehyde (2.0 g,11 mmol), ethyl vinyl ketone (1.39 g, 16 mmol) and DABCO (0.062 g, 0.55 mmol). Work-up and flash chromatography [on silica; elution with hexane-EtOAc-$CHCl_3$ (1:1:3)] gave, as a brownish oil, *1-hydroxy-1-(3-methoxy-2-nitrophenyl)-2-methylenepentan-3-one* **140o** (2.63 g, 89.7 %) (Found M^+-NO_2: 219.10138. $C_{13}H_{15}NO_5$ requires *M*-NO_2, 219.10212); ν_{max} /cm^{-1} (nujol) 3410 (OH) and 1668

(C=O); δ_H (400 MHz; $CDCl_3$) 1.06 (3H, q, CH_3CH_2, 2.71 (2H, t, CH_3CH_2), 3.49 (1H, d, OH), 3.87 (3H, s, OCH_3), 5.65 (1H, d, CHOH), 5.89 and 6.20 (2H, 2xs, $C=CH_2$), 6.98 (1H, d, Ar-H), 7.14 (1H, d, Ar-H), 7.43 (1H, t, Ar-H); δ_C (100 MHz; $CDCl_3$) 7.9 (CH_3CH_2), 31.0 (CH_3CH_2), 56.4 (CHOH), 69.4 (OCH_3), 112.0 ($C=CH_2$) and 119.4 ($C=CH_2$), 127.4 (C-5'), 131.1 (C-6'), 135.5 (C-4'), 140.1 (C-3'), 146.9 (C-1'), 150.8 (C-2') and 202.6 (C=O); *m/z* 219 (M^+-NO_2, 78%) and 57 (100).

Attempted preparation of 1-(2,6-dinitrophenyl)-1-hydroxy-2-methylenepentan-3-one **140p**

A solution of ethyl vinyl ketone (0.32 g, 38 mmol), 2,6-dinitrobenzaldehyde (0.5 g, 3 mmol) and DABCO (0.029 g, 0.26 g) in methanol (10 ml) was stirred at room temperature for 20 days. The crude product was purified by flash chromatography [on silica; elution with EtOAc-hexane-$CHCl_3$ (3:1:1)] to afford only a trace quantity of what was indicated by ^1H NMR analysis to be the desired product.

1-(2-Chloro-6-nitrophenyl)-1-hydroxy-2-methylenepentan-3-one **140n**

The procedure described for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was followed, using 2-chloro-6-nitrobenzaldehyde (0.5 g, 3 mmol), ethyl vinyl ketone (0.35 g, 4.1 mmol) and DABCO (0.03 g, 0.3 mmol). Work-up and flash chromatography [on silica; elution with hexane-EtOAc-$CDCl_3$ (1:2:1)] gave, as pale brown crystals, *1-(2-chloro-6-nitrophenyl)-1-hydroxy-2-methylenepentan-3-one* **140n** (0.27 g, 25 %), m.p. 77 - 79 °C (Found M^+- NO_2: 223.05111. $C_{12}H_{12}NO_4Cl$ requires *M*-NO_2, 223.05258); ν_{max} (nujol)/cm^{-1} 3389

(OH) and 1664 (C=O); δ_H (400MHz; $CDCl_3$) 1.07 (3H, t, CH_3CH_2), 2.73 (2H, m, CH_3CH_2), 3.54 (1H, d, OH), 5.89 and 6.29 (2H, 2xs, $C=CH_2$), 6.22 (1H, d, CHOH), 7.36 (1H, t, Ar-H), 7.49 (1H, d, Ar-H) and 7.60 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 8.0 (CH_3CH_2), 31.1 (CH_3CH_2), 68.8 (CHOH), 122.7 ($C=CH_2$), 126.7 ($C=CH_2$), 129.2 (C-3'), 131.9 (C-2'), 133.1 (C-4'), 135.5 (C-1'), 145.7 (C-5'), 151.4 (C-6') and 202.4 (C=O); *m/z* 223 (M^+-NO_2, 3 %) and 57 (100).

3.2.2. Optimisation studies

Following examination of various parameters the following conditions were found to be optimal.

3.2.2.1. General procedure

A solution of the 2-nitrobenzaldehyde derivative (1 eq.), the activated alkene (1.5 eq.) and DABCO (0.05 eq.) in chloroform (2 ml) was stirred at room temperature for 6 days to give the crude product which was purified by flash chromatography to afford the Baylis-Hillman product. Application of this procedure typically gave the expected products in significantly improved yields (60-95%; see **Table 2**, p. 48).

3.2.2 Reductive Cyclisation

3.2.2.1. Catalytic Hydrogenation

3.2.2.1.1. General Procedure

A mixture of the Baylis-Hillman product (4.18 mmol) and 10 % palladium-on-carbon catalyst (0.15g) in ethanol (50ml) was stirred under hydrogen at atmospheric pressure for 90 min. The catalyst was filtered off and the solvent was evaporated from the filtrate *in vacuo*. The residue was dissolved in CH_2Cl_2, and the solution was dried with anhydrous $MgSO_4$ and the solvent evaporated *in vacuo* to give the crude product, which was purified by flash chromatography.

3-Methyl-2-quinolone **149a**, *3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline* **150a** *and 4-hydroxy-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline* **145a**

Following the general procedure, methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140a** was hydrogenated in the presence of palladium-on-carbon catalyst. The crude product was purified by flash chromatography [on silica; elution with hexane-EtOAc (3:2)] to give three fractions.

Fraction 1: 3-Methyl-2-quinolone **149a** (0.10g, 15 %), as a brownish oil, (Found M^+: 159.18701. Calc. for $C_{10}H_9ON$: *M*, 159.18711); ν_{max} /cm^{-1} (nujol) 1649 (C=O); δ_H (400 MHz; $CDCl_3$) 2.27 (3H, s, CH_3), 7.18 (1H, d, Ar-H), 7.23 (1H, t, Ar-H), 7.42 (1H, m, Ar-H), 7.50 (1H, d, Ar-H), 7.62 (1H, s, 4-H) and 10.26 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 16.8 (CH_3), 115.6, 120.3, 122.4, 126.8, 129.3 and 130.0 (Ar-C), 137.5 (C-5), 163.0 (Ar-C) and 164.5 (C=O).

Fraction 2: 3-Methyl-2-oxo-1,2,3,4-tetrahydroquinoline **150a,** as a brown oil, (0.31g, 41 %) (Found

MH^+: 162.091892. Calc for $C_{10}H_{12}NO$: *MH*$^+$, 162.091889); ν_{max} /cm^{-1} (nujol) 1664 (C=O); δ_H (400 MHz; $CDCl_3$) 1.27 (3H, d, CH_3), 2.69 (1H, m, CH_3CH), 2.97 (2H, dd, CH_2), 6.71 (1H, d, Ar-H), 6.97 (1H, t, Ar-H), 7.16 (1H, d, Ar-H), 7.55 (1H, br s, NH) and 7.59 (1H, t, Ar-H); δ_C (100 MHz; $CDCl_3$) 15.3 (CH_3), 33.5 (CH_2), 35.0 (CH_3CH), 114.9 (C-5), 122.9 (C-6), 123.7 (C-4a), 127.5 (C-7), 128.1 (C-8), 137.1 (C-8a) and 174.1 (C=O); *m/z* 162 (*MH*$^+$,100 %).

Fraction 3: *4-Hydroxy-3-methyl-2-oxo–1,2,3,4-tetrahydroquinoline* **145a** (0.12g, 18 %), as a brown oil, (Found MH^+: 178.086922. $C_{10}H_{12}NO_2$ requires *MH*$^+$, 178.086804); ν_{max} /cm^{-1} (nujol) 3423 (OH) and 1648 (C = O); δ_H (400 MHz; $CDCl_3$) 1.67 (3H, d, CH_3), 2.79 (1H, m, CH_3CH), 4.58 (1H, s, CHOH), 4.74 (1H, d, OH), 6.97 (1H, d, Ar-H), 7.17 (1H, d, Ar-H), 7.19 (1H, t, Ar-H), 7.28 (1H, t, Ar-H) and 10.47 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 10.4 (CH_3), 41.4 (CH_3CH), 70.8 (CHOH), 115.4, 123.5, 128.0,129.7, 133.3 and 133.9 (Ar-C) and 167.5 (C=O); *m/z* 178 (*MH*$^+$, 38 %) and 154 (100).

2,3-Dimethylquinoline **147c** *and 2,3-dimethylquinoline* N*-oxide* **148c**

Following the general procedure, 4-hydroxy-3-methylene-4-(2-nitrophenyl)butanone **140c** was hydrogenated in the presence of palladium-on-carbon catalyst. The crude product was purified by flash chromatography [on silica gel; elution with hexane-EtOAc (1:3)] to give two fractions.

Fraction 1: 2,3-Dimethylquinoline **147c** (0.14g, 20 %), as brownish crystals, m.p. 39-43 °C (Found: M^+ 157.08929. Calc. for $C_{11}H_{11}N$: *M*, 157.08915); ν_{max} /cm^{-1} (nujol) 1662 (N=C); δ_H (400MHz;

$CDCl_3$) 2.44 (3H, s, CH_3), 2.68 (3H, s, CH_3), 7.45 (1H, m, Ar-H), 7.59(1H, m, Ar-H), 7.70 (1H, d, Ar-H), 7.82 (1H, s, Ar-H) and 7.99 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 19.6 (CH_3), 23.5 (CH_3), 125.3 (C-4a), 125.5 (C-8a), 126.0 (C-6), 127.4 (C-7), 130.0 (C-5), 134.9 (C-2), 135.1 (C-3), 146.1 (C-4) and 158.9 (C-8); *m/z* 157 (M^+, 100%).

Fraction 2: 2,3-Dimethylquinoline *N*-oxide **148c** (0.4g, 52 %), as yellowish crystals, m.p. 111-114 °C (Found M^+: 173.08338. Calc. for $C_{11}H_{11}NO$: *M*, 173.08406); ν_{max} / cm^{-1} (nujol) 1655 (N=C) and 1317 (N-O); δ_H (400 MHz; $CDCl_3$) 2.47 (3H, s, CH_3), 2.70 (3H, s,CH_3), 7.50 (1H, s, Ar-H), 7.56 (1H, t, Ar-H), 7.65 (1H, t, Ar-H), 7.69 (1H, d, Ar-H) and 8.72 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.8 (CH_3), 20.3 (CH_3), 119.6 (C-6), 125.3 (C-2), 125.5 (C-3), 127.3 (C-4a), 127.9 (C-7), 129.2 (C-8a), 130.9 (C-5), 139.9 (C-4) and 146.5 (C-8); *m/z* 173 (M^+, 82 %) and 156 (100).

2,3-Dimethyl-(6,7-methylenedioxy)quinoline **147m**

Following the general procedure, 4-hydroxy-2-methylene-4-[4,5-(methylenedioxy)-2-nitrophenyl]butan-3-one **140m** was hydrogenated in the presence of palladium-on-carbon catalyst. The crude product was purified by flash chromatography [on silica gel; elution with hexane-EtOAc (1:3)] to give, as yellowish crystals, 2,3-dimethyl-(6,7-methylenedioxy)quinoline **147m** (0.22 g, 26 %), m.p. 120-124 °C (Found M^+: 201.07910. Calc. for $C_{12}H_{11}NO_2$: *M*, 201.07923); ν_{max} /cm^{-1} (nujol) 1238 (C=N); δ_H (400 MHz; $CDCl_3$) 2.37 (3H, s, CH_3), 2.59 (3H, s, CH_3), 6.04 (2H, s, OCH_2O), 6.94 (1H, s, Ar-H), 7.28 (1H, s, Ar-H) and 7.64 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 19.3 (CH_3), 23.1 (CH_3), 101.4 (OCH_2O), 102.0 (C-6), 105.0 (C-7), 123.9 (C-2), 126.5 (C-3), 134.7 (C-8), 144.2 (C-

4a), 147.0 (C-5), 149.8 (C-8a) and 156.3 (C-4); *m/z* 201 (M^+, 35 %) and 145 (100).

2-Ethyl-3-methylquinoline **147h** *and 2-ethyl-3-methylquinoline* N-*oxide* **148h**

Following the general procedure, 1-hydroxy-2-methylene-5-(2-nitrophenyl)pentan-3-one **140h** was hydrogenated in the presence of palladium-on-carbon catalyst. The crude product was purified by flash chromatography [on silica gel; elution with hexane-EtOAc (1:2)] to give two fractions.

Fraction 1: 2-Ethyl-3-methylquinoline N-oxide **148h** (0.31g, 39 %), as brown crystals, m.p. 66-69 °C (Found M^+: 187.09970. $C_{12}H_{13}NO$ requires *M*, 187.09812); ν_{max} /cm^{-1} (nujol) 1280 (N-O) and 1611 (N=C); δ_H (400 MHz; $CDCl_3$) 1.30 (3H, t, CH_3CH_2), 2.49 (3H, s, CH_3), 3.18 (2H, q, CH_2), 7.53 (1H, s, Ar-H), 7.55 (1H, t, Ar-H), 7.65 (1H, t, Ar-H), 7.90 (1H, d, Ar-H) and 8.92 (1H, d, Ar-H); δc (100 MHz; $CDCl_3$) 9.6 (CH_3CH_2), 19.5 (CH_3), 21.7 (CH_2), 119.8 (C-4), 125.4 (C-5), 127.1 (C-6), 127.7 (C-7), 128.3 (C-3), 129.2 (C-8), 130.5 (C-4a), 141.1 (C-8a) and 151.2 (C-2); *m/z* 187 (M^+, 28 %) and 170 (100).

Fraction 2: 2-Ethyl-3-methylquinoline **147h** (0.25g, 34 %), as a brownish oil, (Found M^+: 171.1048. Calc. for $C_{12}H_{13}N$: M, 171.1052); ν_{max} /cm^{-1} (nujol) 1603 (N=C); δ_H (400 MHz; $CDCl_3$) 1.36 (3H, t, CH_3CH_2), 2.48 (3H, s, CH_3), 3.00 (2H, q, CH_2), 7.44 (1H, t, Ar-H), 7.57 (1H, t, Ar-H), 7.67 (1H, d, Ar-H), 7.78 (1H, s, Ar-H) and 8.00 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 12.8 (CH_3CH_2), 19.1 (CH_3), 29.5 (CH_2), 125.6 (C-6), 126.6 (C-7), 127.3 (C-2), 128.3 (C-5), 128.5 (C-4), 129.4 (C-3), 135.7 (C-8), 147.8 (C-4a) and 163.3 (C-8a); *m/z* 171 (M^+, 64 %) and 170 (100).

3-(Phenoxysulfonyl)quinoline N-*oxide* **148f**

Following the general procedure, phenyl 3-hydroxy-3-(2-nitrophenyl)propene-2-sulfonate **140f** (1.4g, 4.2 mmol) was hydrogenated in the presence of palladium-on-carbon catalyst. The crude product was purified by flash chromatography [on silica gel; elution with hexane-EtOAc (3:1)] to give, as an oil, *3-(phenoxysulfonyl)quinoline N-oxide* **148f** (0.04 g, 4 %) (Found M^+: 301.0686. $C_{15}H_{11}NO_3S$ requires *M*, 301.0771); ν_{max} /cm^{-1} (nujol) 1264 (N=C); δ_H (400MHz; $CDCl_3$) 7.08 (1H, d, Ar-H), 7.32 (2H, s, Ar-H), 7.78 (2H, t, Ar-H), 7.94 (2H, t, Ar-H), 8.13 (1H, s, Ar-H), 8.26 (1H, s, 4-H), 8.77 (1H, t, Ar-H) and 8.86 (1H, s, 2-H); δ_C (100 MHz, $CDCl_3$) 120.2 (C-2), 122.1 (C-6), 125.9 (C-3), 127.8 (C-5), 128.3 (C-4a), 129.9 (Ar-C), 130.1 (Ar-C), 130.3 (C-8a), 130.6 (Ar-C), 132.5 (C-8), 133.6 (Ar-H), 143.8 (C-4) and 149.2 (C-7); *m/z* 301 (M^+,1 %) and 71(100).

1-(2-Aminophenyl)-2-phenylsulfonylpropanol **161e**

Following the general procedure, 1-(2-nitrophenyl)-2-(phenylsulfonyl)-2-propenol **140e** was hydrogenated in the presence of palladium-on-carbon catalyst. The crude product was purified by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] to give, as yellow crystals, *1-(2-aminophenyl)-2-(phenylsulfonyl)propanol* **161e** (0.39 g, 43 %), m.p. 63-66 °C (Found MH^+: 292.10812. $C_{15}H_{17}NSO_3$ requires MH^+, 292.10840); ν_{max} /cm^{-1} (nujol) 3366 (OH) and 3162 (NH_2); δ_H (400 MHz; $CDCl_3$) 0.81 / 1.24‡ (3H, d, CH_3), 3.41/ 4.09 (1H, m, SO_2CH), 5.02 (1H, d,CHOH),

‡ Chemical shift data cited in this format, here and elsewhere, refer to signals corresponding to the diastereomeric components.

4.41 (2H, br s, NH_2), 4.55 (1H, br s, OH), 6.62 (1H, m, Ar-H), 6.75 (1H, t, Ar-H), 6.85 (1H, d, Ar-H), 7.07 (1H, m, Ar-H), 7.21 (1H, t, Ar-H), 7.60 (1H, m, Ar-H), 7.70 (1H, m, Ar-H), 7.82 (1H, t, Ar-H) and 7.94 (1H, d, Ar-H); δc(100 MHz; CDCl3) 6.73 / 12.93 (CH_3); 62.3 / 62.6 ($CHCH_3$), 66.3 / 75.2 (CHOH), 116.3 / 117.1, 117.9 / 118.4, 122.6 / 124.0, 126.3 / 128.4, 128.8 / 129.1 (Ar-C), 129.3 / 129.7 and 133.9 / 137.0 (Ar-C), 142.2 (Ar-C), 144.3 (Ar-C) and 145.6 (C-NH_2); *m/z* 292 (MH^+, 34 %) and 122 (100).

3-(2-aminophenyl)-3-hydroxy-2-methylpropanenitrile **161d**

Following the general procedure, 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanenitrile **140d** (0.66g, 4.2 mmol) was hydrogenated in the presence of palladium-on-carbon catalyst. The crude product was purified by flash chromatography [on silica; elution with benzene-EtOAc (2:1)] to give, as a brown oil, *3-(2-aminophenyl)-3-hydroxy-2-methylpropanenitrile* **161d** (0.43 g, 50 %) (Found MH^+: 177.102697. $C_{10}H_{13}N_2O_2$ requires MH^+, 177.102788); ν_{max}(nujol) /cm^{-1} 3371 (OH) and 2244 (CN); δ_H (400 MHz; $CDCl_3$) 1.08 / 1.35 (3H, d, CH_3), 3.24 / 3.39 (1H, m, CHCN), 3.93 (1H, br s, OH), 4.57 / 4.72 (1H, d, C*H*OH), 6.64 (1H, d, Ar-H), 6.70 (1H, m, Ar-H), 6.76 (1H, d, Ar-H), 7.11 (1H, m, Ar-H) and 7.12 (2H, br s, NH_2); δ_C (100 MHz; $CDCl_3$) 14.2 /15.3 (CH_3), 30.26 /30.9 (CH_3*C*H), 75.0 (CHOH), 117.7 /117.5 (C-4'), 118.3 /118.3 (C-5'), 121.2 /122.0 (C-1'), 122.7 /124.0 (C-2'), 128.5 /129.3 (C-6'), 129.6/129.8 (C-3') and 144.5 /145.0 (CN); *m/z* 177 (MH^+, 68 %) and 122 (100).

6-Chloro-3-methyl-2-quinolone **149l**, *6-chloro-4-hydroxy-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline* **145l** *and 6-chloro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline* **150l**

Following the general procedure, methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate **140l** was hydrogenated in the presence of the palladium-on-carbon catalyst. The crude product was purified by flash chromatography [on silica; elution with hexane-EtOAc (1:2)] to give three fractions.

Fraction 1: 6-Chloro-3-methyl-2-quinolone **149l** (0.08g, 11 %), as brownish crystals, m.p. 200-204 °C (Found M^+: 193.02885. $C_{10}H_8NOCl$ requires *M*, 193.02895); ν_{max} /cm^{-1} (nujol) 1655 (C=O) and 721 (C-Cl); δ_H (400 MHz; $CDCl_3$) 2.26 (3H, s, CH_3), 7.21 (1H, m, Ar-H), 7.40 (1H, d, Ar-H), 7.49 (1H, d, Ar-H), 7.61 (1H, s, Ar-H) and 9.96 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 16.8 (CH_3), 115.7 (C-5), 117.1 (C-3), 120.3 (C-7), 122.5 (C-8), 127.3 (C-6), 129.4 (C-4), 137.4 (C-4a), 137.6 (C-8a) and 174.8 (C-2); *m/z* 193 (*M*$^+$, 10 %) and 159 (100).

Fraction 2: 6-Chloro-4-hydroxy-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline **145l** (0.07g, 9 %), as brown crystals, m.p. 105-109 °C (Found M^+: 211.03657. $C_{10}H_{10}NO_2Cl$ requires *M*, 211.03952); ν_{max} (nujol) / cm^{-1} 1662 (C=O) and 721 (C-Cl); δ_H (400 MHz; $CDCl_3$) 2.28 / 2.36 (3H, s, CH_3), 2.74 (1H, m, CH_3CH), 2.97 / 3.01 (1H, d, CHOH), 7.20 (1H, t, Ar-H), 7.28 (1H, t, Ar-H), 7.46 (1H, t, Ar-H), 7.58 (1H, d, Ar-H), 8.34 (1H, br s, OH) and 11.67 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 16.7 (CH_3), 34.8 (CHOH), 112.9 (C-6), 115.9 (C-7), 122.5 (C-5), 126.8 (C-8), 129.7 (C-3), 134.4 (C-4a), 137.7 (C-8a) and 175.0 (C=O); *m/z* 211 (*M*$^+$, 18 %) and 159 (100).

Fraction 3: 6-Chloro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline **1501** (0.17g, 24 %), as yellowish crystals, m.p. 95-98 °C (Found M^+: 195.03684. $C_{10}H_{10}NOCl$ requires *M*, 195.03563); ν_{max} (nujol) /cm^{-1} 1662 (C=O); δ_H (400 MHz; $CDCl_3$) 1.28 (3H, d, CH_3), 2.69 (1H, m, CH_3CH), 2.99 (2H, dd, CH_2), 6.71 (1H, d, Ar-H), 6.97 (1H, t, Ar-H), 7.14 (1H, d, Ar-H) and 7.50 (1H, br s, NH); δc (100 MHz; $CDCl_3$) 15.3 (CH_3), 33.4 (C-4), 35.1 (C-3), 115.2 (C-4a), 122.9 (C-7), 123.4 (C-8a), 127.4 (C-5), 127.9 (C-8), 137.1 (C-6) and 175.0 (C-2); *m/z* 195 (M^+, 4 %) and 161 (100).

3.2.2.2. Reduction with Tin Chloride[56]

3.2.2.2.1. General Procedure

To a solution of the substrate in absolute EtOH (10 ml) was added $SnCl_2.2H_2O$ (5 eq.). The mixture was stirred at 70 °C under nitrogen for 5 hours and then, after cooling, poured on to ice. The resulting mixture was made slightly basic (pH 7 - 8) by the addition of saturated aq. $NaHCO_3$, and then extracted repeatedly with EtOAc. The combined organic phases were thoroughly washed with saturated brine and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to afford the crude product.

Methyl 1,2-dihydroquinoline-3-carboxylate **162a**

The general procedure was followed, using methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)-propanoate **140a** (1.19 g, 5 mmol) and $SnCl_2.2H_2O$ (5.64 g, 25 mmol) in MeOH (10 ml).† The crude product was purified by flash chromatography [on silica; elution with hexane-EtOAc (1:3)] to afford , as an off-white powder, *methyl 1,2-dihydroquinoline-3-carboxylate* **162a** (0.47 g, 50 %), m.p. 175-177 °C (Found M: 189.07852. $C_{11}H_{11}NO_2$ requires *M*, 189.07898); ν_{max} (nujol) /cm^{-1} 1642 (C=O); δ_H (400 MHz; $CDCl_3$) 3.55 (3H, s, CH_3), 4.56 (2H, s, CH_2), 7.21 (1H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.47 (1H, m, Ar-H), 7.55 (1H, d, Ar-H), 7.87 (1H, s, Ar-H) and 12.27 (1H, br s, NH); δ_C (100MHz; $CDCl_3$) 59.0 (CH_3), 69.3 (C-2), 115.8 (C-5), 120.0 (C-3), 122.6 (C-6), 127.6 (C-7), 129.9 (C-8), 130.0 (C-4a), 136.3 (C-3), 137.6 (C-8a) and 163.2 (C=O); *m/z* 189 (M^+, 18 %) and 159 (100).

Ethyl 1,2- dihydroquinoline-3-carboxylate **162b**

Method 1:

The general procedure was followed, using ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **140b** (1.26 g, 5 mmol) and $SnCl_2.2H_2O$ (5.64 g, 25 mmol). The crude product was purified by flash chromatography [on silica; elution with hexane-EtOAc (1:3)] to

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† Use of ethanol as solvent resulted in transesterification to afford the ethyl ester **162b** (see method 2 below).

afford, as whitish powder, *ethyl 1,2- dihyhroquinoline-3-carboxylate* **162b** (0.15 g, 15 %), m.p. 170-172°C (Found M^+: 203.09556. $C_{12}H_{13}NO_2$ requires *M*, 203.09463); ν_{max} (nujol)/cm^{-1} 1662 (C=O); δ_H (400 MHz; $CDCl_3$) 1.26 (3H, t, CH_3), 3.69 (2H, q, CH_2CH_3), 4.56 (2H, s, CH_2), 7.22(1H, t, Ar-H), 7.44 (1H, t, Ar-H), 7.59 (1H, d, Ar-H), 7.95 (1H, s, Ar-H) and 9.95 (1H, br s, NH); δ_C (100MHz; $CDCl_3$) 15.3 (CH_3), 66.7 (OCH_2), 67.2 (C-2), 115.3 (C-5), 120.1 (C-3), 122.7 (C-6), 127.8 (C-7), 129.9 (C-8), 130.7 (C-4a), 136.0(C-4), 137.3 (C-8a) and 162.5 (C=O); *m/z* 204 (M^+, 1 %) and 159 (100).

Method 2:

When methyl 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **150a** was reacted with $SnCl_2.2H_2O$ using ethanol as solvent, the transesterified product, ethyl 1,2-dihydroquinoline-3-carboxylate **162b** (0.12g, 13 %) was obtained.

3-Acetyl-1-hydroxy-1,2-dihydroquinoline **163c**

The general procedure was followed, using 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **140c** (0.44 g, 2 mmol) and $SnCl_2.2H_2O$ (2.25 g, 10 mmol) in MeOH (4 ml). The crude product was purified by flash chromatography [on silica gel; elution with hexane-EtOAc (2:3)] to afford, as a yellow powder, *3-acetyl-1-hydroxy-1,2-dihydroquinoline* **163c** (0.07 g, 21 %), m.p. 77-80 °C (Found MH^+: 191.086798. $C_{11}H_{11}O_2N$ requires MH^+, 191.086804); ν_{max} (nujol) /cm^{-1} 1622 (C=O); δ_H (400MHz; $CDCl_3$) 2.45 (3H, s, CH_3), 5.01 (2H, s, CH_2), 6.81 (1H, d, Ar-H), 7.13 (1H, t, Ar-H), 7.29 (1H, m, Ar-H), 7.33 (1H, s, OH), 7.38 (1H, s, OH), 7.43 (1H, d, Ar-H) and 7.48 (1H, s, 4-H); δ_C

(100MHz; $CDCl_3$) 25.8 (CH_3), 77.2 (C-2), 116.5 (C-5), 124.3 (C-6), 125.6 (C-3), 130.0 (C-7), 134.4 (C-8), 138.3 (C-4), 142.5 (C-4a), 150.3 (C-8a) and 198.5 (C=O); *m/z* 190 (M^+, 87 %) and 189 (100).

1-Hydroxy-3-propanoyl-1,2-dihydroquinoline **163h**

The general procedure was followed, using *1-hydroxy-2-methylene-1-(2-nitrophenyl)pentan-3-one* **140h** (0.47 g, 2 mmol) and $SnCl_2.2H_2O$ (2.26 g,10 mmol) in MeOH (4 ml) . The crude product was purified by flash chromatography [on silica; elution with hexane-EtOAc-$CHCl_3$ (1:2:1)] to afford, as yellow crystals, *1-hydroxy-3-propanoyl-1,2-dihydroquinoline* **163h** (0.04 g, 10 %), m.p. 85-89 °C (Found MH^+: 204.102416. $C_{12}H_{13}NO_2$ requires MH^+, 204.102454); ν_{max} (nujol)/cm^{-1} 1628 (C=O); δ_H (400MHz; $CDCl_3$) 1.16 (3H, t, CH_3), 2.84 (2H, q, CH_3CH_2), 4.98 (2H, s, CH_2), 6.81 (1H, d, Ar-H), 7.11 (1H, t, Ar-H), 7.27 7(1H, t, Ar-H), 7.34 (1H, s, OH), 7.42 (1H, d, Ar-H) and 7.49 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 8.5 (CH_3), 30.6 (CH_3CH_2), 77.1 (C-2), 116.5 (C-5), 124.3 (C-6), 125.3 (C-3), 129.8 (C-7), 134.3 (C-8), 136.8 (C-4), 142.0 (C-4a), 150.2 (C-8a) and 201.1 (C=O); *m/z* 204 (MH^+, 83 %) and 203 (100).

1-Hydroxy-8-methoxy-3-propanoyl-1,2-dihydroquinoline **162o**

The general procedure was followed, using 1-hydroxy-2-methylene-1-(3-methoxy-2-nitrophenyl)pentan-3-one **140o** (1.33g, 5.01 mmol) and SnCl.(5.64g, 24.9 mmol). The crude product was purified by flash chromatography [on silica; elution with hexane-EtOAc (1:2)] to afford, as yellow crystals, *1-hydroxy-8-methoxy-3-propanoyl-1,2-dihydroquinoline* **162o** (0.70 g, 64 %), m.p. 55 58 °C (Found MH^+: 218.118132. $C_{13}H_{15}NO_2$ requires MH^+, 218.118104); ν_{max} (nujol)/ cm^{-1} 3160

(NH) and 1691 (C=O); δ_H (400 MHz; $CDCl_3$) 1.34 (3H, t, CH_3), 3.03 (2H, q, CH_3CH_2), 4.02 (3H, s, OCH_3), 4.90 (2H, s, CH_2), 6.70 (1H, d, Ar-H), 7.32 (1H, t, Ar-H), 7.35 (1H, S, OH), 7.38 (1H, d, Ar-H) and 7.99 (1H, s, 4-H); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 28.8 (CH_3CH_2), 55.1 (OCH_3), 62.0 (CH_2), 107.6 (C-5), 118.9 (C-6), 125.9 (C-7), 128.10 (C-4a), 132.7 (C-8a), 134.0 (C-4), 138.9 (C-3), 154.8(C-8) and 160.9 (C=O); *m/z* 218 (MH^+,100%).

Attempted reduction of methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-methylenepropanoate **140k** *with stannous chloride*

To a solution of methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-methylenepropanoate **140k** (0.94g,) in absolute EtOH was added $SnCl_2.2H_2O$ (3.8g, 16.8mmol). The mixture was to stirred at 70 ^{0}C under nitrogen for 5 hours and the solution was allowed to cool and then poured on to ice. The resulting mixture was made slightly basic by adding aqueous sodium carbonate. Extraction afforded none of the expected product.

3.2.3. Interconversion of quinoline and quinoline-*N*-oxide derivatives

3.2.3.1. Oxidation of 2,3-dimethylquinoline **147c** with MCPBA[57]

To a stirred solution of 2,3-dimethylquinoline **147c** (0.1 g, 0.6 mmol) in $CHCl_3$ (0.6 ml) was added MCPBA (0.11g, 0.64 mmol), portionwise, during 3 min. at room temperature. The mixture was stirred for 24 hours, and then any excess MCPBA destroyed (as indicated by wet starch-iodide paper)

by the addition of solid $Na_2S_2O_5$. Dissolved *m*-chlorobenzoic acid was precipitated from the solution as the potassium salt by the addition of solid K_2CO_3 with stirring. The solids were removed by filtration, and the solvent was removed from the filtrate *in vacuo* to give a yellow solid. ^1H NMR analysis revealed the presence of some unreacted starting material, and further MCPBA (0.1 g) was added and the mixture stirred for another 24 hours. After work-up, 2,3-dimethylquinoline *N*-oxide **148c** was obtained as a yellow powder (0.09 g, 78 %).

3.2.3.2. Deoxygenation of 2,3-dimethylquinoline N-oxide **148c**

2,3-Dimethylquinoline *N*-oxide **148c** (0.08 g,0.46 mmol) and DMF (8 ml) were stirred together at room temperature. PBr_3 (0.2 ml, 0.7 mmol) was added and stirring continued for 1 hour. The mixture was poured into saturated aqueous $NaHCO_3$, and the resulting mixture extracted with EtOAc (3x 20 ml). The extracts were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried (anhyd. $MgSO_4$) and filtered. The solvent was removed *in vacuo* to give 2,3-dimethylquinoline **147c**(0.06g, 77 %).

3.2.3.3. Selective *in situ* oxygenation and deoxygenation reactions

A: *Formation of the mixture of 2,3-dimethylquinoline* **147c** *and its N-oxide* **148c**

A mixture of 3-hydroxy-2-methylene-3-(2-nitrophenyl)butan-2-one **140c** (0.5g, 2.26 mmol) and 10% palladium-on-carbon catalyst(40 mg) dissolved in methanol (40 ml) was subjected to hydrogenation

(see general method, p 81) for 3 hours. The catalyst was filtered off and the solvent evaporated from the filtrate *in vacuo*. The residue was dissolved in CH_2Cl_2, dried (anhydrous $MgSO_4$), and the solvent evaporated *in vacuo* to afford, as a brown oil, a mixture of 2,3-dimethylquinoline **147c** and 2,3-dimethylquinoline *N*-oxide **148c** (0.409g).

B: Formation of 2,3-dimethylquinoline N-*oxide* **148c** *from the mixture*

To a stirred solution of the foregoing mixture (0.135g) of 2,3-dimethylquinoline **147c** and 2,3-dimethylquinoline *N*-oxide **148c** in $CHCl_3$ (0.5 ml) was added MCPBA (0.107 g), portionwise, over 15 minutes at room temperature. The mixture was stirred for 24 hours, before any excess MCPBA (wet starch-iodide paper) was destroyed by the addition of solid $Na_2S_2O_5$. Dissolved *m*-chlorobenzoic acid was precipitated from solution as the potassium salt by the addition of solid K_2CO_3 with stirring. The solids were removed by filtration and the filtrate dried ($MgSO_4$); the solvent was removed *in vacuo* to give, as yellow crystals, 2,3-dimethylquinoline *N*-oxide **148c** (0.116g, 85 %)

C: Formation of 2,3-dimethylquinoline **147** *from the mixture*

A mixture (0.125g) of 2,3-dimethylquinoline **147c** and 2,3-dimethylquinoline *N*-oxide **148c** in DMF (3 ml) was stirred at room temperature. PBr_3 (0.2 ml, 0.7 mmol) was added and stirring continued for 1 hour. The mixture was poured into saturated aqueous $NaHCO_3$, and the resulting mixture extracted with EtOAc (3x20 ml). The extracts were combined, washed with saturated aqueous $NaHCO_3$, and brine, dried (anhyd. $MgSO_4$) and filtered. The solvent was removed from the filtrate

in vacuo to give, as yellow crystals, 2,3-dimethylquinoline **147c** (0.107g, 86%).

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