SYNTHESIS AND SPECTRAL STUDIES OF SOME QUINOLINE DERIVATIVES

by

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ABSTRACT OF THESIS

The present investigation was concerned with the synthesis and spectral studies of quinoline and quinolone derivatives.

The Combes synthesis of quinolines has been extended to the synthesis of several 2,4-dialkyl- substituted quinolines. The experimental procedures of the von Miller-Kinkelin and Beyer syntheses have been improved and the revised techniques applied to the synthesis of some new 3-alkyl- and 3,4-disubstituted- quinoline derivatives. The orientation effects in the Beyer synthesis with asymmetric ketones have been established.

A detailed study has been undertaken of the orientation effects in quinoline syntheses commencing from asymmetrically substituted aniline derivatives, reactions leading to quinolines substituted in the heterocyclic ring have especially been studied. Through the use of exhaustive analytical procedures, reliable properties and product ratios have been established. The nitration of 7-alkylquinolines has been re-investigated and clarified.

A study of long range ^{13}C - ^{1}H coupling constants at the methyl carbon in methylquinoline and methylquinolone derivatives has been undertaken. The coupling constants have been correlated with the appropriate ^{1}H - ^{1}H vicinal interactions and their diagnostic uses discussed. Certain long range ^{13}C - ^{1}H couplings at the ring carbons have also been investigated.

The chemical shift of the NH proton in a series of methyl substituted 2- and 4- quinolone derivatives has been determined and the results interpreted on the basis of steric inhibition to hydrogen bonding, which was confirmed by infra-red spectroscopy. The diagnostic value of the NH proton chemical shifts in the identification of quinolone alkaloids, for example, has been propounded.

The ^{13}C chemical shifts for a series of methyl substituted 2- and 4- quinolone derivatives have been determined. The use of ^{13}C n.m.r. spectroscopy to distinguish and differentiate between the two quinolone series has been discussed. A subsequent study of some 1-methyl-2-quinolone derivatives has shown that similar characteristic

peri-substituent effects to those previously noted in the naphthalene series also occur in the quinolones. These effects must be considered in the course of spectral assignments.

In the course of the present work, 54 new compounds have been synthesised and characterised.

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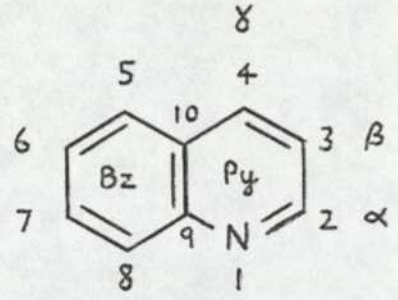
CHAPTER 1

LITERATURE SURVEY

1.1 INTRODUCTION

Quinoline was first isolated in an impure state by Runge[1] in 1834 from the distillation of coal tar. The substance obtained was a colourless liquid which was named leukol and this was undoubtedly contaminated with considerable amounts of isoquinoline and alkylquinolines. Later, Gerhardt[2] distilled quinine, cinchonine and strychnine with caustic potash and obtained a base which was named chinolein. Berzelius[3] subsequently confirmed that leukol and chinolein had the same structure.

The benzopyridine structure (I) for quinoline was first proposed by Körner[4] in 1871.



(I)

Koenigs[5] first synthesised quinoline in 1879 by passage of allylaniline over heated lead oxide.

The synthesis and chemistry of quinoline has been reviewed in detail.[6-9]

1.2 SYNTHESIS OF QUINOLINE DERIVATIVES

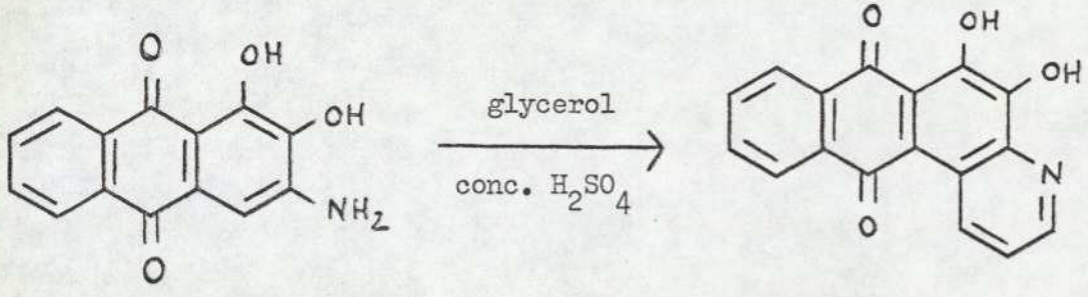
The synthetic routes to the quinoline nucleus have been reviewed elsewhere.[6-9] In the present review only those techniques of particular relevance to the present work will be considered.

1.2.1 SKRAUP SYNTHESIS

The Skraup synthesis is the most useful and versatile method for the preparation of quinoline derivatives and has been the subject of a comprehensive review.[10]

Koenigs[11] prepared quinoline by heating the condensation product of aniline and acrolein and thus anticipated the classical Skraup synthesis,[12] first reported in 1880.

The reaction was first performed[13] with a mixture of 3-nitro- and 3-aminoalizarin (II) to form alizarin blue (III); the discovery that the dye was a quinoline derivative led to the systematic investigation of the reaction by Skraup.[14-7]



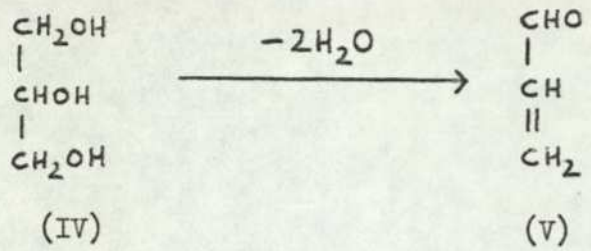
(II) (III)

The synthesis involved a series of reactions brought about by heating a primary aromatic amine, in which at least one position ortho to the amino group was unsubstituted, with glycerol, sulphuric acid and an oxidising agent. The product was a quinoline derivative which possessed only those substituents that were originally present in the aromatic amine. Quinolines substituted in the heterocyclic ring were obtained by a modified Skraup synthesis in which a substituted acrolein or a vinyl ketone was used in place of glycerol (see below).

The reaction occurs through four successive steps[8,10]:

1. Dehydration of glycerol (IV), to acrolein (V) under the influence of sulphuric acid.

2. Addition of aniline (VI) to the olefinic linkage of the acrolein to form an intermediate β-anilinopropionaldehyde (VII), and protonation to the carbonium ion (VIII).
3. Cyclisation to give the tetrahydroquinoline (IX), and dehydration to the 1,2-dihydroquinoline (X).
4. Oxidation of the dihydroquinoline to quinoline (I).



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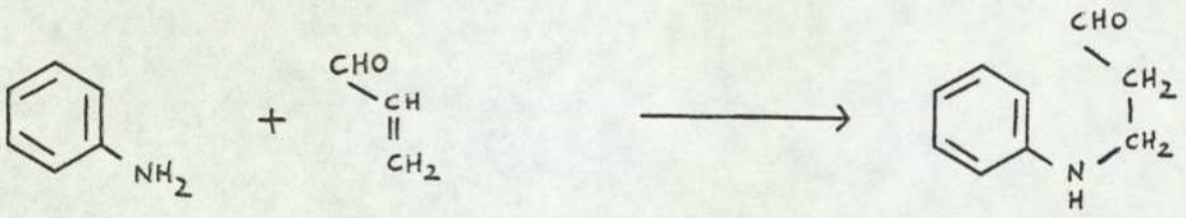

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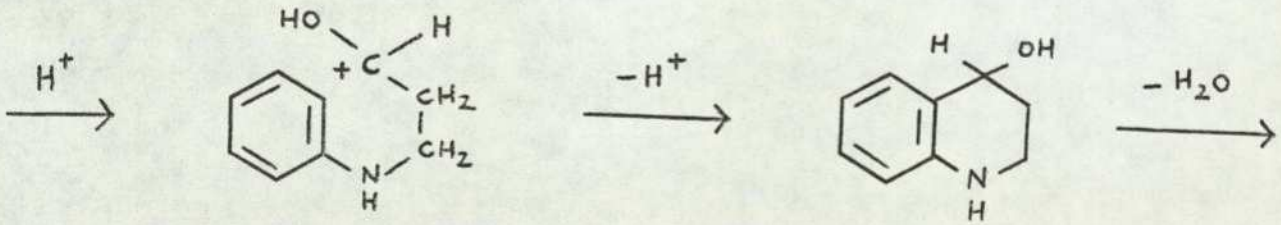

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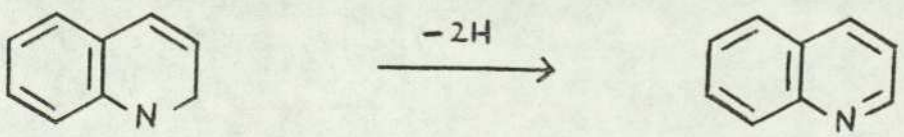
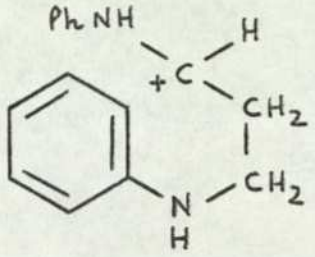


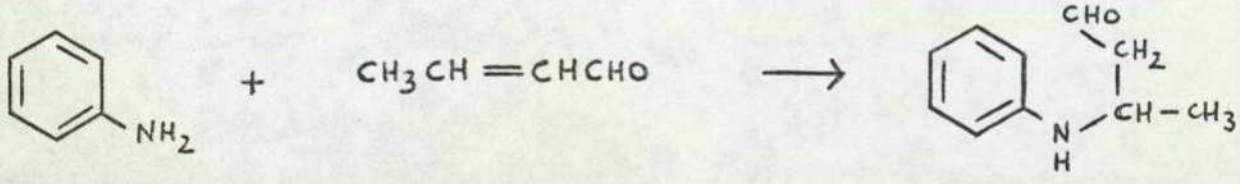
(X) (I)

It has also been suggested[18] that the cyclisation occurred through the anil (XI) with subsequent elimination of amine.



(XI)

The mechanism was supported by the formation of 2-methylquinoline (XIV) and not 4-methylquinoline (XVI) from aniline and crotonaldehyde (XII) via the intermediate β-arylaminoaldehyde (XIII). The production of 4-methylquinoline would have required the cyclisation of the Schiff base (XV) as originally (but incorrectly) suggested by Skraup.[16] The mechanism of the reaction has been further considered in detail.[9,19]



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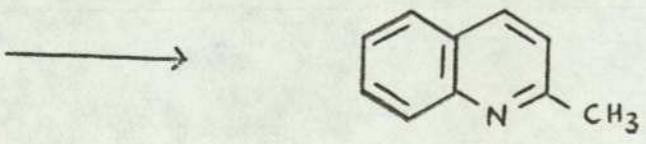

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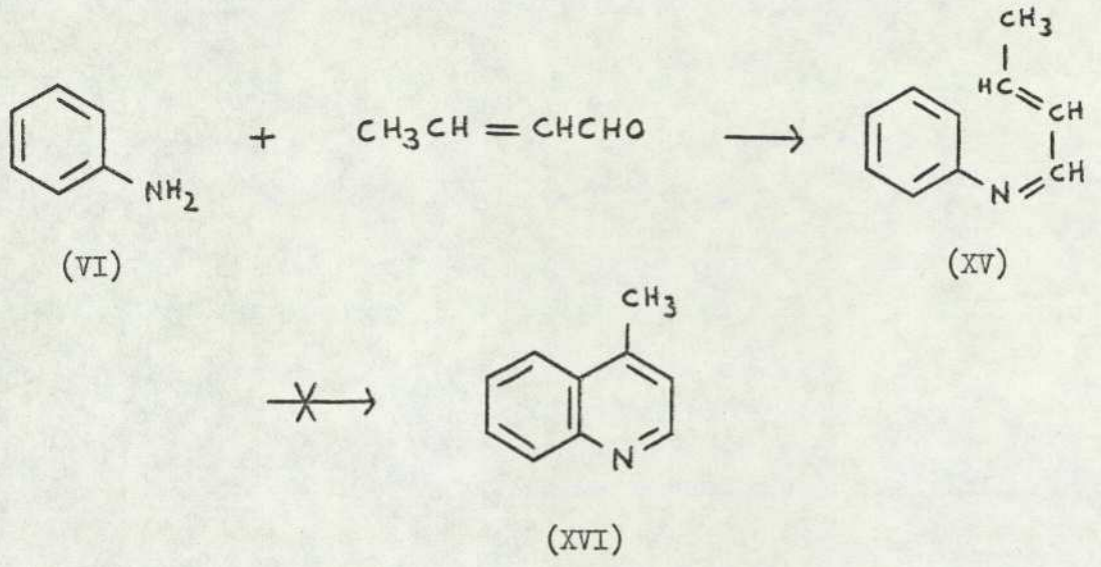


(VI) (XV)

(XVI)

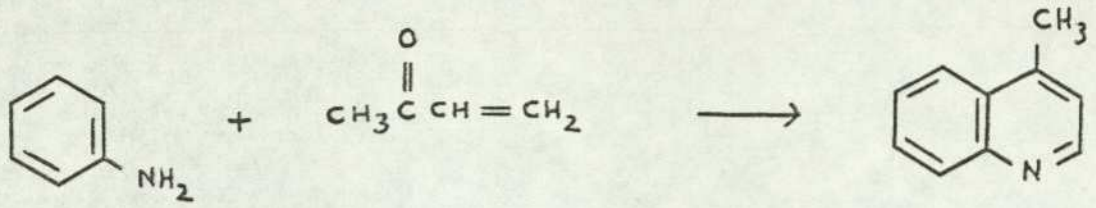
Attempts to obtain quinoline directly from aniline and acrolein have been unsuccessful[20] or have given poor yields,[21] which indicate that the acrolein be produced *in situ* if side reactions are not to preponderate.

The original Skraup synthesis has been extended to include the preparation of quinolines substituted in the pyridine ring through the use of α,β -unsaturated aldehydes and ketones. 2-Methylquinoline derivatives (XIV) are obtained in high yield by the addition of β -methylacrolein (crotonaldehyde, XII)[22] or 1,1,3-trimethoxybutane (3-methoxybutyraldehyde dimethyl acetal)[23] to a stirred mixture of sulphuric acid, an oxidant, and an aromatic amine at such a rate that a violent reaction is avoided. 2-Arylquinolines are similarly prepared through the use of β -phenylacrolein (cinnamaldehyde)[24] in place of crotonaldehyde.

The use of an α -substituted acrolein (e.g. methacrylaldehyde)[22,25] or a 2-substituted glycerol[26] as a condensing agent in the Skraup reaction produces a 3-substituted quinoline.

Campbell and co-workers[23,27,28] have synthesised a number of 4-methylquinoline derivatives (XVI) by condensation of methyl vinyl ketone (XVII) with aromatic amines under conditions somewhat milder than those normally employed. Since α,β -unsaturated ketones such as (XVII) polymerise to some extent under the conditions of the reaction, it was found expedient to employ compounds that yielded the required α,β -unsaturated ketones *in situ*; 4-chlorobutan-2-one,[29]

4-hydroxybutan-2-one[25] and 1,3,3-trimethoxybutane have all been used.



(VI) (XVII) (XVI)

In the case of simple methylquinolines such as (XIV) or (XVI) the required intermediates are commercially available, however, for more complex derivatives the appropriate reagents must first be synthesised, which may require multi-stage processes, some of which necessitate the use of vapour phase reactions at elevated temperatures.[30]

A disadvantage of the Skraup synthesis, undoubtedly characteristic of earlier reports, was that it involved a reaction of considerable violence. Subsequently several procedures have been proposed by which the reaction may be moderated. In the technique of Clark and Davis,[31] ferrous sulphate, which presumably functions as an oxygen carrier, was added to regulate the reaction. Further improvements have been achieved by the addition of acetic acid[32] or boric acid.[33] The mode of addition of the reactants has also been recognised[34] as an important factor in controlling the vigour of the reaction and influencing the yield of product. Slightly diluted sulphuric acid has also been claimed to eliminate violence, reduce the formation of tars, and thus permit large scale production.[35]

A variety of oxidising agents have been used in the Skraup reaction, in order to remove the two hydrogen atoms from the intermediate dihydroquinoline (X). The most useful oxidising agent is the nitro compound corresponding to the amine used in the synthesis, its reduction product thus becomes available for further reaction. Recently, however, Wahren[36] using nitrobenzene-^{15}N has shown that very little of the reduced nitro compound reacted to yield quinoline. Other oxidising agents used include m-nitrobenzenesulphonic acid or its salts,[22] arsenic pentoxide,[37]

ferric sulphate,[38] and iodine.[39] It has also been found that inorganic oxidising agents were particularly advantageous in reducing the quantity of tarry products formed during the reaction.[40]

A feature of particular interest in the Skraup reaction is the possibility of formation of two isomeric products by cyclisation of an asymmetrically substituted aniline derivative. This phenomenon is discussed in Section 1.3.

1.2.2 DOEBNER-VON MILLER SYNTHESIS

The Skraup synthesis (see Section 1.2.1) may be considered as a special example of the more general Doebner-von Miller procedure. This latter reaction has been reviewed briefly.[6-9,41]

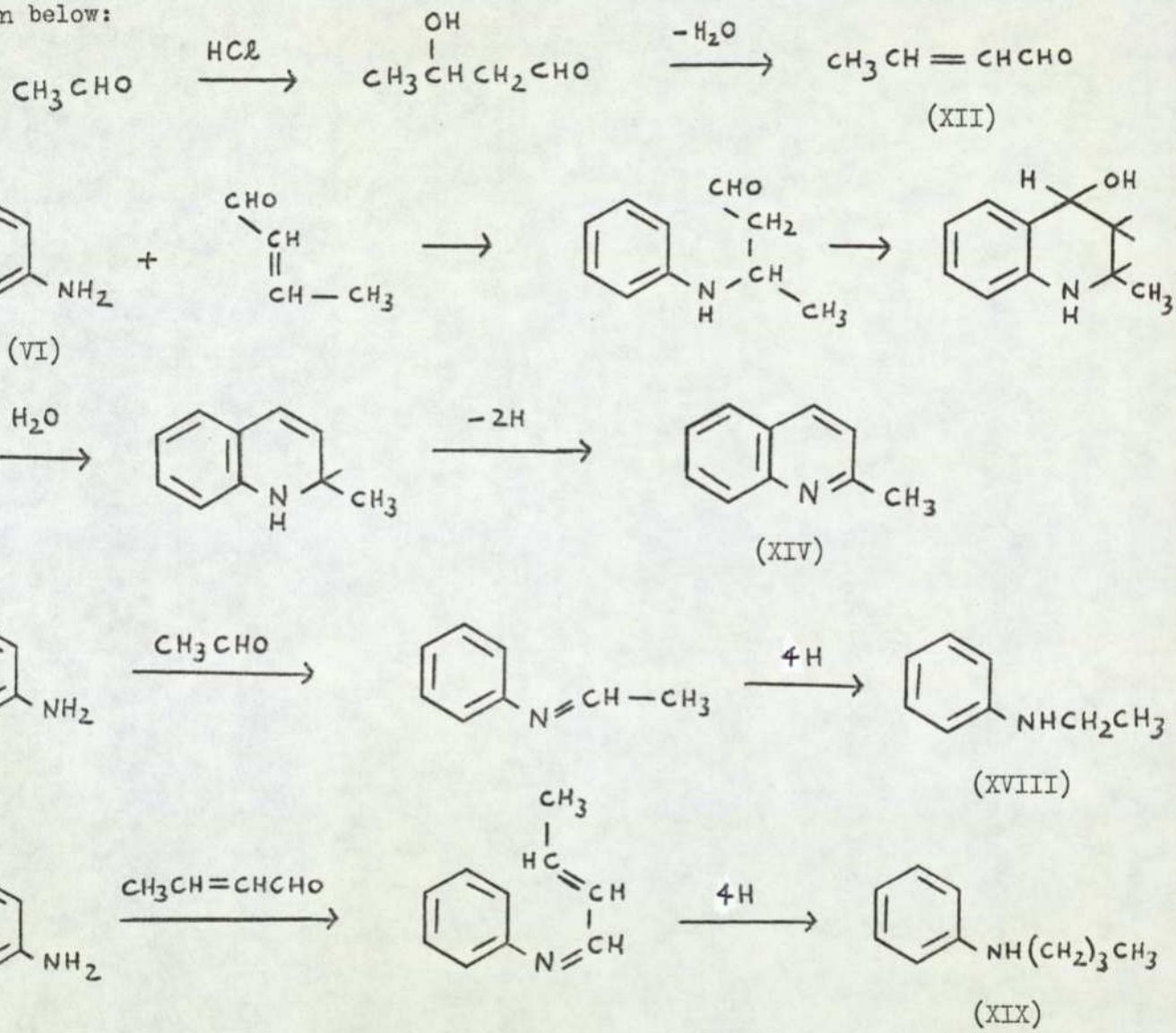
In 1881, Doebner and von Miller[42] substituted ethylene glycol for glycerol in the Skraup reaction and obtained a methyl homologue of quinoline which was called quinaldine. The same base was also obtained using paraldehyde as a reactant. The product was considered to arise through the production of crotonaldehyde and was subsequently formulated[43] as 2-methylquinoline.

The reaction conditions were later modified[44] such that aniline hydrochloride was treated with an aqueous solution of paraldehyde and the mixture allowed to stand in the cold. The reaction was then completed by warming on the water bath. Several other reactants, including ethylene glycol,[42] paraldehyde,[42] acetaldehyde,[44] lactic acid[45] and acetaldol,[46] have been used in the synthesis to yield quinaldine, all these reagents produce crotonaldehyde through the intermediate formation of acetaldehyde, but have been reported[7] to offer no advantage over the use of acetaldehyde itself.

The reaction has been extended to the synthesis of higher quinoline homologues, through the use of higher aliphatic aldehydes. Thus reaction of aniline with n-heptaldehyde yields 3-n-pentyl-2-n-hexylquinoline.[46]

A detailed study of the reaction has been undertaken by Mills, Harris and Lambourne.[47] The reaction conditions were modified such that acetaldehyde was employed in place of paraldehyde, the initiation period reduced to 30 minutes,

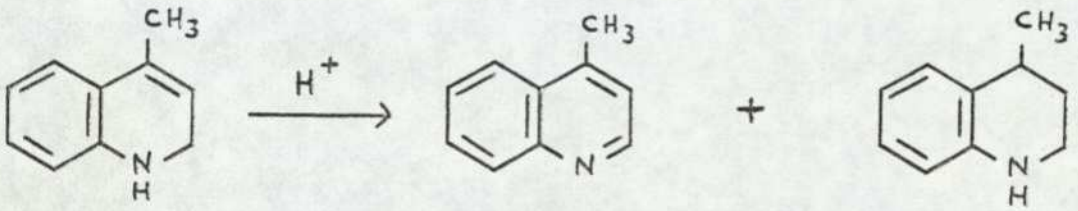
and the reaction completed by heating in the presence of zinc chloride. Omission of the salt was found to lead to diminished yields. Careful analysis of the by-products which accompanied the formation of quinaldine indicated that a considerable quantity of secondary bases were formed, which could be separated as nitroso-compounds by treatment with nitrous acid. The regenerated bases were identified as N-ethylaniline (XVIII), (already recognised as a by-product by Doebner and von Miller[48]) and N-(n-butyl)aniline (XIX). The formation of these by-products was accounted for[47] as shown below:



In general, the yields obtained in the Doebner and von Miller reaction, and the related Beyer synthesis[49] are very low. From a study of the conditions required to produce 4-methylquinoline derivatives in the Skraup synthesis Campbell and Schaffner[27] suggested that milder conditions be employed, and through the use of an ethanolic

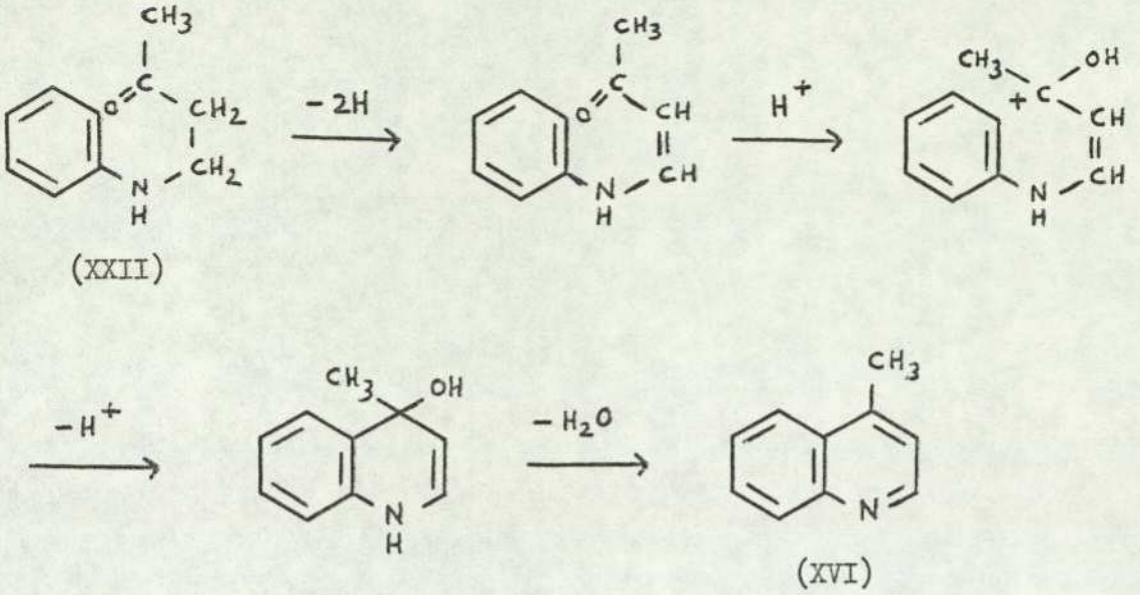
reaction medium with ferric chloride as oxidising agent and zinc chloride as condensing agent considerably increased yields of 4-methylquinoline derivatives were obtained. Subsequently Tertov and Ardashev[50] reported that dropwise addition of reactants also led to a further increase in the yield due to minimisation of side reactions. Very recently Leir[51] has proposed an alternative work-up procedure for isolation of the products from the Doebner-von Miller reaction. Addition of an equimolar amount of zinc chloride to the reaction mixture (before the traditional separation of primary and secondary bases) caused precipitation of a curdy solid, which after washing with propan-2-ol left a crystalline 2:1 complex of the quinaldine hydrochloride and zinc chloride. Treatment of the complex with concentrated ammonium hydroxide yielded the required quinaldine base in 42-55% yield.

Further studies of the mechanism of the reaction by Ogata et al.[52] have questioned the participation of the dihydroquinoline intermediate (XX). It was found that these compounds disproportionate exclusively in ethanolic hydrogen chloride to give 4-methylquinoline (XVI) and 1,2,3,4-tetrahydrolepidine (XXI).



(XX) (XVI) (XXI)

In a careful study[52] of the conversion of 4-anilinobutan-2-one (XXII) to 4-methylquinoline (XVI), no 1,2,3,4-tetrahydro-4-methylquinoline (XXI) could be detected and accordingly the reaction was re-formulated as shown below:

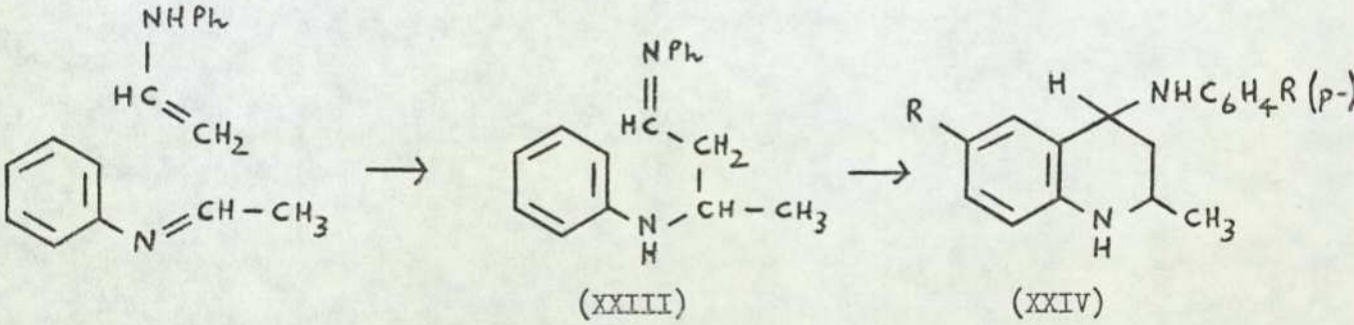


(XXII)

(XVI)

It was noted that under the conditions of the reaction, 4-anilinobutan-2-one (XXII) can be cleaved to give aniline and methyl vinyl ketone and the latter compound serves as the oxidising agent in the reaction.

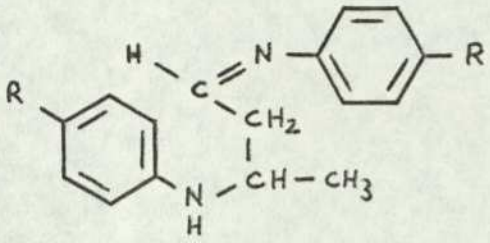
Other workers,[53] however, have concluded that crotonaldehyde (XII) is not necessarily an intermediate in the synthesis, and suggest that the key step in the reaction sequence is the condensation of N-ethylideneaniline (acetaldehyde "anil") to form the substituted aniline (XXIII) which may then undergo ring closure to yield quinaldine via 4-anilino-1,2,3,4-tetrahydroquinaldine. (XXIV, R = H)



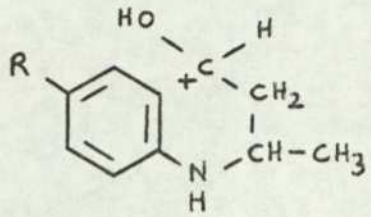
(XXIII) (XXIV)

The intermediate derivative (XXIV, R = CH_3) had originally[19] been assigned the double Schiff base structure (XXV, R = CH_3) as evidence for the ring closure through the protonated aldehyde (XXVI, R = CH_3). However, Dauphinee and Forrest,[54] on the basis of the n.m.r. spectrum of the intermediate concluded that the correct structure was (XXIV, R = CH_3), and that the ring closure must therefore occur via

a Schiff base and not through the free aldehyde.



(XXV)



(XXVI)

The Doebner-von Miller reaction is still widely used for the synthesis of quinoline derivatives substituted in the heterocyclic ring.

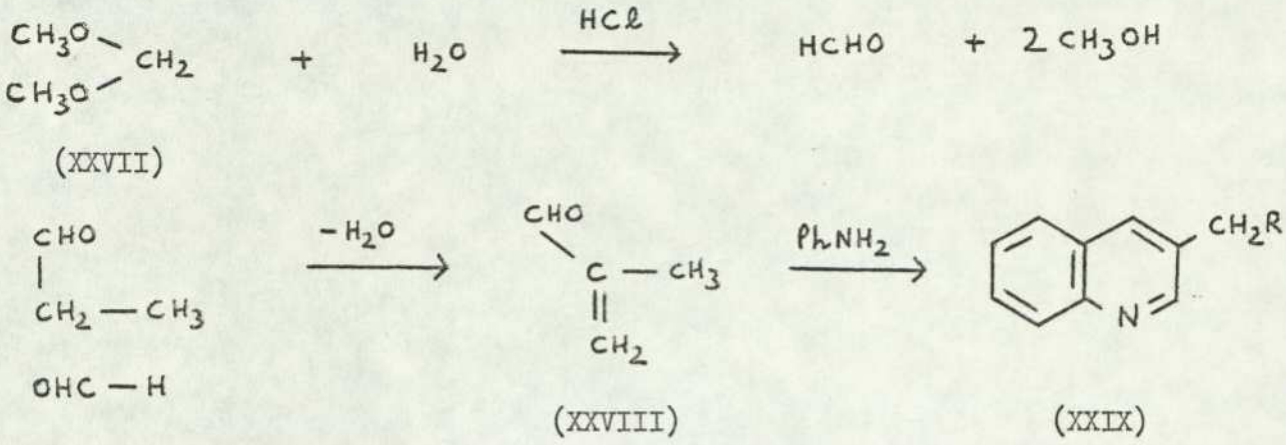
1.2.3 MODIFICATIONS TO THE DOEBNER-VON MILLER SYNTHESIS

The scope of the Doebner-von Miller synthesis has been extended by the introduction of two modifications to the original procedure. These are discussed in Sections 1.2.3a and 1.2.3b.

1.2.3a THE VON MILLER-KINKELIN SYNTHESIS

Use of a mixture of aldehydes in the Doebner-von Miller reaction would be expected to result in a complex mixture of products. However, if one aldehyde reactant lacked the necessary two α-hydrogen atoms required for condensation then certain of the possible modes of interaction could not occur and fewer products should result.

Using this approach von Miller and Kinkelin[55] extended the scope of the original reaction to the preparation of 3-methylquinoline through the use of propionaldehyde with formaldehyde as the second aldehyde. Reaction of methylal (formaldehyde dimethylacetal, XXVII) and propionaldehyde with aniline (VI) in the presence of hydrochloric acid produced a mixture of 3-methylquinoline and 2-ethyl-3-methylquinoline The reaction initially involved the generation of formaldehyde from its acetal (XXVI), followed by interaction with propionaldehyde to give 2-methylacrolein (XXVIII) which then reacted with aniline to give 3-methylquinoline (XXIX, R = H).



(XXVII)

(XXVIII)

(XXIX)

The 2-ethyl-3-methylquinoline by-product resulted from condensation of two moles of propionaldehyde *via* the normal Doebner-von Miller reaction. The products were separated by fractional crystallisation of the mixed picrate derivatives from ethanol, 3-methylquinoline picrate was the least soluble and separated first. An attempt to prepare quinoline itself by a similar reaction involving methylal and acetaldehyde was not successful.[55]

The von Miller-Kinkelin procedure offers a more convenient route to 3-methylquinoline compared to previous syntheses of this compound which required multi-stage sequences involving selective oxidation of alkyl groups and subsequent decarboxylation.[46]

About forty years later, Willimott and Simpson[56] reported a direct synthesis of 3-methylquinoline *via* a modified Friedländer reaction from *o*-nitrobenzaldehyde and propionaldehyde. Although this synthesis was a considerable improvement over the von Miller-Kinkelin procedure,[55] modification of the technique to enable methyl groups to be introduced into the carbocyclic ring would require the use of suitably substituted *o*-nitrotolualdehyde derivatives which are not readily available.

Accordingly, Poth and co-workers[57] in the course of their studies on the identification of coal tar bases, obtained an authentic sample of 3,8-dimethylquinoline by the von Miller-Kinkelin procedure. The pure base was obtained in 7% yield after regeneration from the pure picrate derivative after fractional crystallisation.

Utermohlen[22] later reported the preparation of 3-methylquinoline by a modified Skraup procedure with α-methylacrolein. Although the yield of product was good, the method posed severe limitations since α-methylacrolein is not readily available

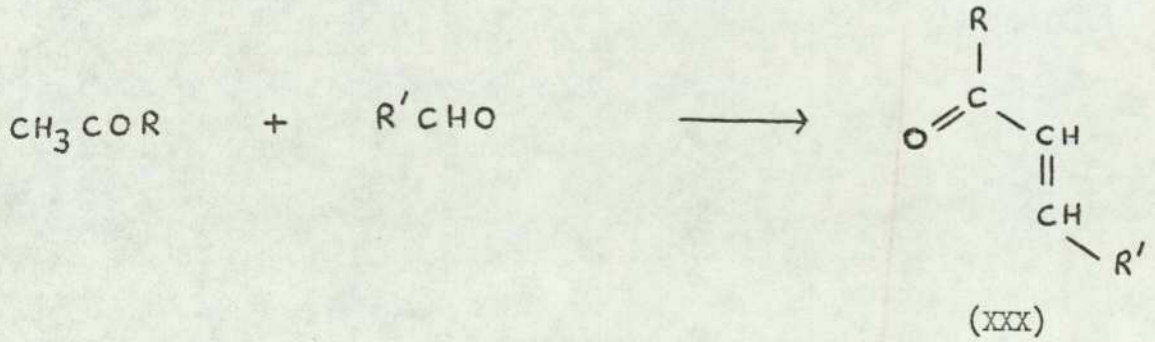
and is normally prepared with special equipment at elevated temperatures.[58]

Very recently Kaiser and Petty[59] have reported a convenient route to higher 3-alkylquinoline derivatives. Treatment of 3-methylquinoline with lithium diisopropylamide in tetrahydrofuran/hexamethylphosphoramide at -78° afforded 3-lithiomethylquinoline (XXIX, R = Li), which was reactive towards a variety of electrophiles. With alkyl halides, 3-alkylquinolines were obtained in good yield. Although this procedure presents a convenient route to 3-alkylquinolines, it is subject to certain restrictions. Initially the required 3-methylquinoline must be obtained by another route, and secondly certain 3-substituted quinolines which do not contain a methylene group affixed to the quinoline ring, cannot be obtained from 3-lithiomethylquinoline. Extension and improvements to the von Miller-Kinkelin procedure could provide useful routes to the latter compounds.

1.2.3b THE BEYER SYNTHESIS

Substitution of a methyl ketone for the second molecule of aldehyde in the Doebner-von Miller synthesis is known as the Beyer synthesis,[49] although it was first noted by Reed.[60]

The experimental procedure consisted of heating a suitably aged mixture of the aldehyde, methyl ketone and hydrogen chloride with an aromatic amine. The ageing process was carried out by saturation of the mixture of carbonyl compounds with dry hydrogen chloride and allowing the mixture to stand for 2 to 3 days, to allow production of the intermediate unsaturated ketone derivative (XXX) which then underwent a normal Doebner-von Miller synthesis.



(XXX)

In the original synthesis Beyer[49] obtained 2,4-dimethylquinoline from aniline, acetone and paraldehyde; 2-methyl-4-phenylquinoline was also obtained when

acetophenone was used in place of acetone. 4-Methylquinoline was obtained from aniline, methylal (formaldehyde dimethylacetal) and acetone; in all of the above reactions the yields obtained were very low.

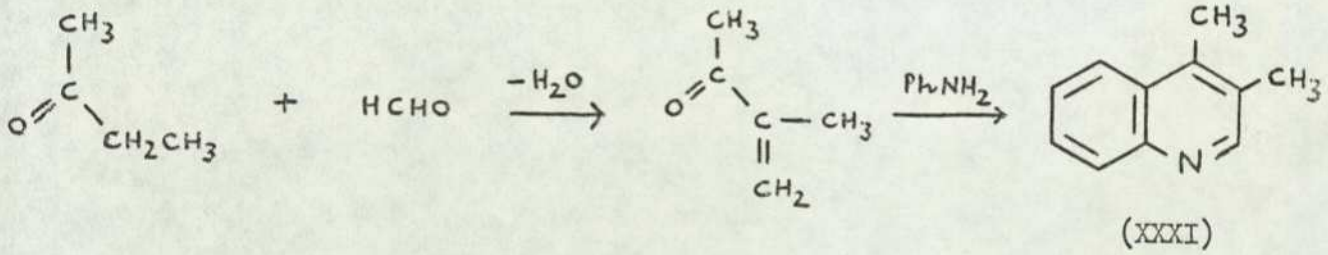
Pictet and Misner[61] later performed the Beyer reaction with a series of arylamines, methyl ketones and formaldehyde, the highest yield recorded was 4.3%.

Mikeska[62] slightly modified the procedure, by the use of 40% aqueous formaldehyde in place of methylal, and obtained 4-methylquinoline in 4.3% yield.

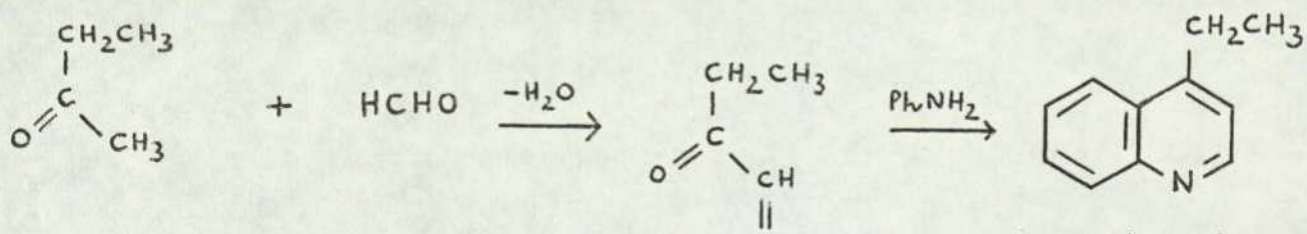
Tertov and Ardashev[50] performed a careful study of the conditions of the Beyer synthesis and concluded that improved yields of 4-methylquinoline derivatives could be obtained through use of an ethanolic reaction medium with low concentrations of the amine and paraformaldehyde in a vast excess of acetone in the presence of ferric chloride as oxidising agent and zinc chloride as condensing agent. The yield of 4-methylquinoline was raised to 15% (11.7% in the absence of zinc chloride). Syntheses of 4,6-dimethylquinoline and of 4,6,8-trimethylquinoline (37% yield) were also reported.

Subsequently Bach and Rast[63] reported a large scale synthesis of 4-methylquinoline which was performed in a methanolic reaction medium, and the product isolated *via* the potassium ferrocyanide addition compound. A 42% yield was reported.

Ardashev and Tertov[64] have also performed the Beyer synthesis with butanone and obtained 3,4-dimethylquinoline (XXXI) as the major product, formed through condensation of formaldehyde with the methylene protons of the ethyl group. The alternative product, 4-ethylquinoline (XXXII) was claimed to have been formed in very poor yield.



(XXXI)



(XXXII)

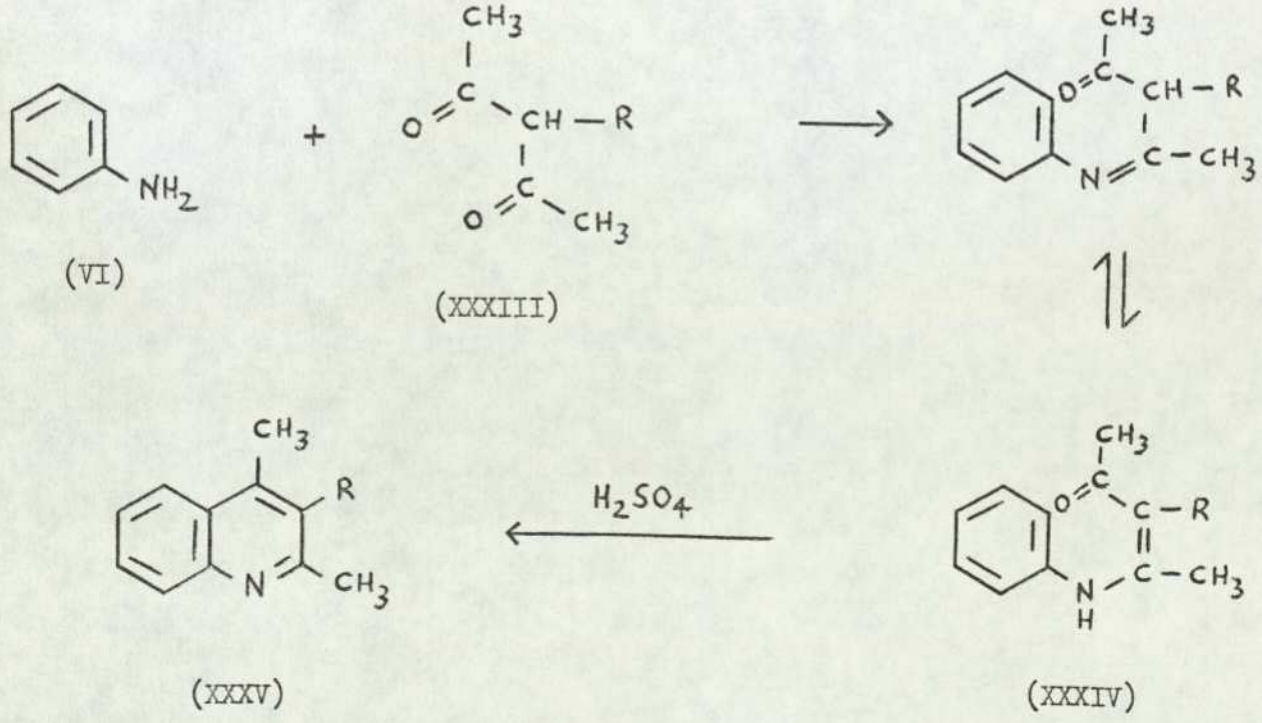
Hence, it would appear that the Beyer synthesis need not be restricted to reactions involving methyl ketones since the above reaction occurred to a greater extent at the ethyl group. However, a thorough survey of the literature has shown that syntheses commencing with higher alkyl- or aryl- ketones have not yet been attempted.

As an example, use of a symmetrical higher alkyl ketone such as pentan-3-one (diethyl ketone) would present a simple one stage route to 4-ethyl-3-methylquinoline for which reported preparations have necessitated multi-stage syntheses.[65,66]

In this respect it is perhaps useful to note that in the Pfitzinger reaction of isatin with asymmetric methyl ketones, condensation can occur through either the methyl or the methylene group leading to 2-substituted or 2,3-disubstituted quinoline-4-carboxylic acids respectively.[67]

1.2.4 THE COMBES SYNTHESIS

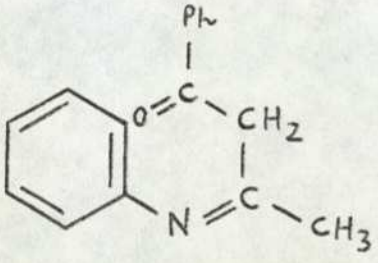
The Combes synthesis[68] involves condensation of a 1,3-diketone with a primary aromatic amine to give an anil which then undergoes cyclodehydration with concentrated sulphuric acid. Thus reaction of acetylacetone (XXXIII, R = H) and aniline (VI) gave 2,4-dimethylquinoline (XXXV, R = H) via the intermediate anil (XXIV, R = H).



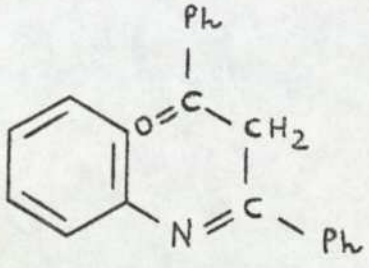
Combes[68] obtained 2,4-dimethylquinoline in high yield, and the general applicability of the reaction was demonstrated by the synthesis of 2,4,6-trimethylquinoline and of 2,3,4-trimethylquinoline (XXXV, R = CH_3).

Roberts and Turner[69] later made a detailed study of the reaction and found that there were a number of occasions when the synthesis was unsuccessful. It was concluded that when a strongly o-/p- directing group was present in a position meta to the nitrogen atom in the anil, ring closure proceeded readily, even when a similar group was present in an unfavourable position. However, when a strong o-/p-directing group was present in the position para to the nitrogen (i.e. in p-anisidine) then ring closure was prevented. With m-substituted anilines the tendency was for the predominant formation of the 7-substituted quinoline, rather than the 5-substituted product.

Beyer[70] established that the anils of benzoylacetone (XXXVI) and of dibenzoylmethane (XXXVII), prepared by direct combination at 150°, could also be cyclised in concentrated sulphuric acid to yield 2-methyl-4-phenylquinoline and 2,4-diphenylquinoline respectively the latter only with difficulty.



(XXXVI)

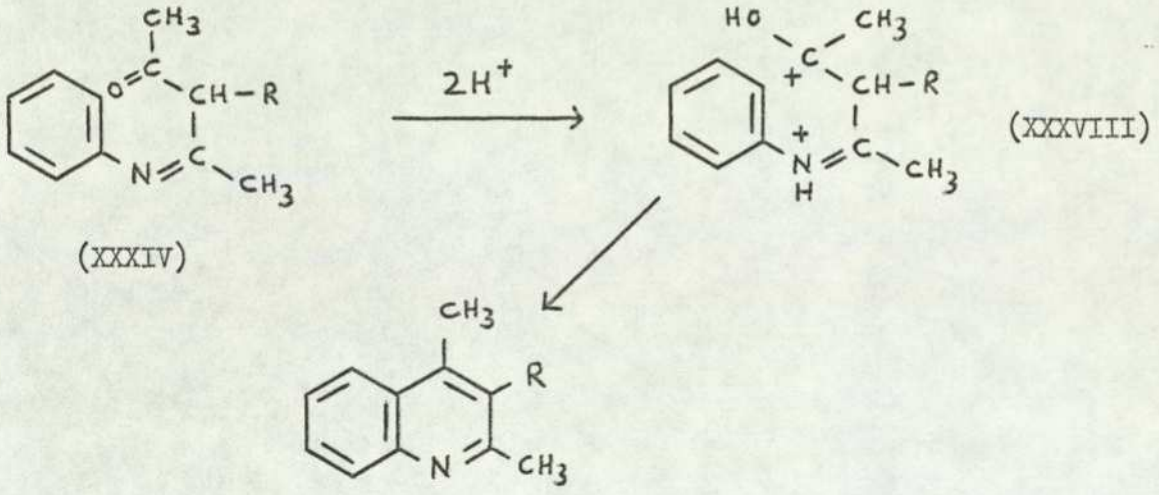


(XXXVII)

The Combes synthesis has also been applied to the synthesis of benzoquinolines commencing from naphthylamines[71,72] and to the synthesis of tetrahydroacridine and tetrahydrophenanthridine derivatives, e.g. commencing from the anil of 2-acetyl-5-methylcyclohexanone.[73]

A study of the mechanism of the Combes reaction has been carried out by Bonner and Barnard.[74] To account for the intermediate anil undergoing hydrolysis with dilute sulphuric acid, but ring closure with concentrated sulphuric acid it was suggested that the uncharged methyl β-phenyliminopropyl ketone (XXXIV, R = H)

was hydrolysed, but that cyclisation to the substituted quinoline occurred through a small percentage of the dication (XXXVIII, R = H).

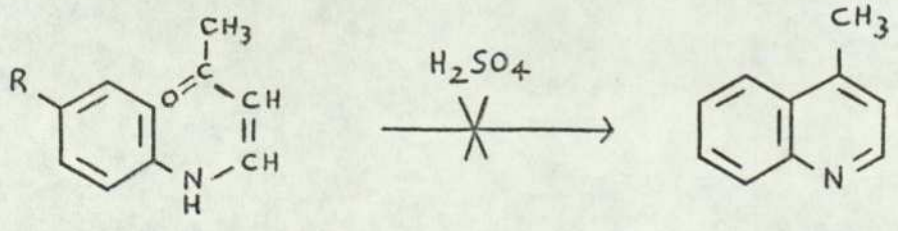


(XXXIV) (XXXVIII)

Subsequent studies of the mechanism have been reported by Born[75] and by Tamura and Yabe.[76,77] Born[75] supported the intervention of a protonated intermediate, and by conducting the cyclisation in sulphuric acid - $\underline{d}_2$, incorporation of deuterium into the 3-position of the quinoline was noted.

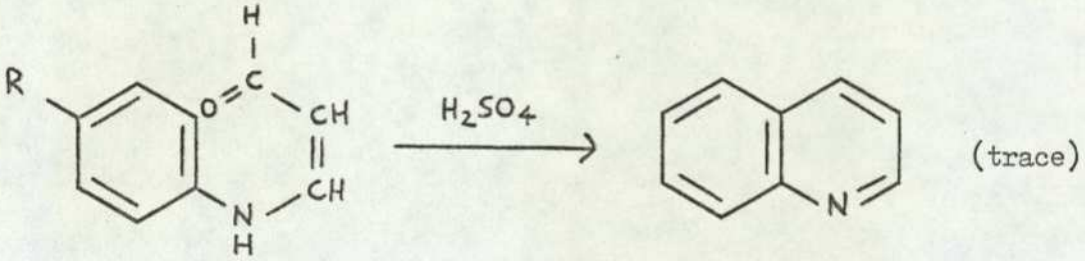
Tamura and Yabe[76] attempted cyclisation of the anil of p-chloroaniline (4-(p-chloroanilino)pent-3-ene-2-one) in more acidic media and at higher temperatures than had previously been employed by Combes[68] and by Roberts and Turner.[69] A satisfactory yield of 6-chloro-2,4-dimethylquinoline was obtained by conducting the reaction at 140°.

A previous attempt to prepare 4-methyl-quinoline (XVI) by cyclodehydration of 4-anilinobut-3-ene-2-one (XXXIX, R = H) by Thielpape[78] was unsuccessful.



(XXXIX) (XVI)

Tamura and Yabe[76] also failed to effect cyclisation of this compound, even after prolonged heating in oleum. Instead sulphanilic acid was precipitated from the reaction mixture which indicated that the anil (XXXIX, R = H) was sulphonated during the reaction, and the sulphonic acid group hindered the cyclodehydration. A synthesis commencing with 4-(p-chloroanilino)but-3-ene-2-one (XXXIX, R = Cl) was attempted, in which the halogen atom prevented the sulphonation of the aromatic ring at the para position, but this too was not successful. However, heating with sulphuric acid in dioxan did afford a small amount of 6-chloro-2-methylquinoline, presumably formed via hydrolysis products of the anil. Subsequently[77] cyclodehydration of 3-anilinopropenal (XL, R = H) in concentrated sulphuric acid was attempted but only a trace of quinoline (I) was obtained; again sulphonation of the starting material occurred.



(XL) (I)

The difference in reactivity of the various anils (XXXIV, XXXIX and XL) was attributed to steric repulsion between the methyl group beta to the carbonyl group and the ortho-hydrogen of the aromatic ring. From conformational studies it was concluded that (XXXIV) existed predominantly in the cis form which apparently favoured cyclodehydration rather than sulphonation. Since (XL) existed more in the trans-form, sulphonation should be favoured; accordingly cyclodehydrations of para-substituted 3-anilinopropenal derivatives (which would be less susceptible to sulphonation) were attempted. A good yield of 6-methylquinoline was obtained from (XL, R = CH_3), but no 6-chloroquinoline could be obtained from (XL, R = Cl). The addition of anhydrous aluminium chloride, however, was found to give improved yields and to effect certain cyclodehydrations which were not possible in the absence of this reagent, the results obtained are summarised in Table 1.2.1.

TABLE 1.2.1

Cyclodehydration of 3-anilinopropenal derivatives (XL).

(from reference 77)

R	Molar Ratio of $AlCl_3$	Yield of quinoline derivative (%)
H	3	64
CH_3	2	66
CH_3	3	78
Cl	3	40

The Combes reaction represents a useful synthesis of 2,4-dimethylquinoline derivatives. A thorough survey of the literature, however, has revealed that syntheses commencing with suitable β-diketones to give higher alkylated products have not been reported to date. Synthesis of such compounds by alternative traditional procedures[15,42,49] would either require complex intermediates or lead to mixtures of products. As an example 2,4-diethylquinoline could be produced *via* the Beyer synthesis[49] using propionaldehyde, butanone and aniline. However, 2-ethyl-3-methylquinoline and 2-ethyl-3,4-dimethylquinoline would also be produced simultaneously in the reaction.

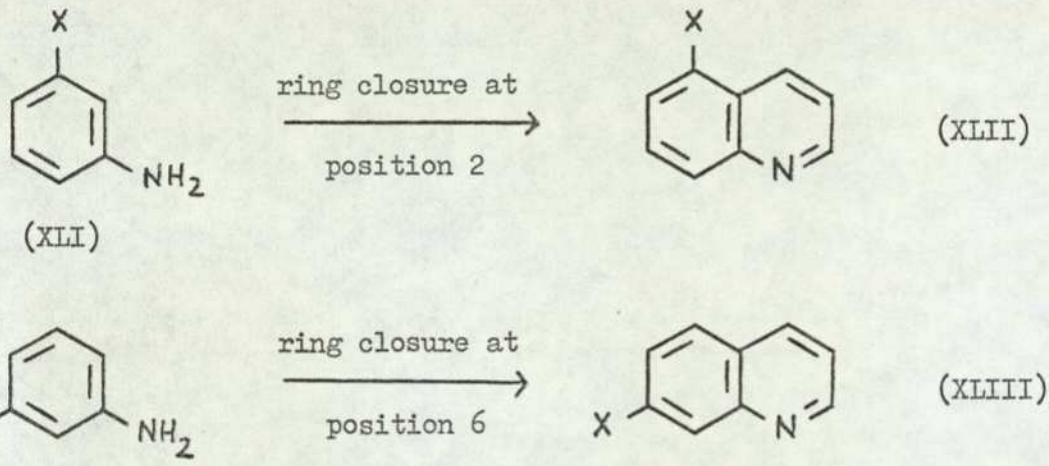
Certain higher 2,4-dialkylquinoline derivatives are known. These have mainly been obtained as by-products during alkylations of quinoline in which the major products were the 2- and 4- monoalkylated derivatives. The alkylation processes employed include the thermal rearrangement of *N*-ethylquinolinium iodide,[79] and selective homolytic alkylation by alkyl radicals,[80] and by photochemical methods.[81]

1.2.5 OTHER SYNTHESES OF QUINOLINE DERIVATIVES

There are numerous other syntheses of quinoline derivatives which have not been studied in the present work. These reactions have been reviewed in detail elsewhere.[6-9]

1.3 ORIENTATION EFFECTS IN THE SYNTHESIS OF QUINOLINE DERIVATIVES

A feature of particular interest in the Skraup reaction is the possibility of the formation of two isomeric products. An asymmetrically substituted aniline derivative with two vacant positions ortho to the amine group can product two different isomers since ring closure can occur at either vacant ortho position. Thus meta-substituted anilines (XLI, R = X) can give rise to 5-substituted quinolines (XLII, R = X) and 7-substituted quinolines (XLIII, R = X)



With ortho- and para- substituted anilines only one product is possible in each case. Ortho-Substituted anilines have one vacant ortho-position only and lead to 8-substituted quinolines. Although para-substituted anilines possess two vacant positions for cyclisation; due to their symmetry the same product, a 6-substituted quinoline, results in each case. The possible products that may be obtained from substituted anilines are shown in Table 1.3.1, from which it can be seen that only 3-substituted and 3,4-disubstituted anilines can yield more than one product in the Skraup reaction, and also in other syntheses of quinoline compounds involving ring closure in a similar manner.

A study of previous work including ring closures leading to quinoline derivatives with and without substituents in the heterocyclic ring is now presented. For the sake of brevity this discussion has been mainly confined to those reactions involving alkyl substituted aniline derivatives.

TABLE 1.3.1

Products from cyclisation of substituted aniline derivatives

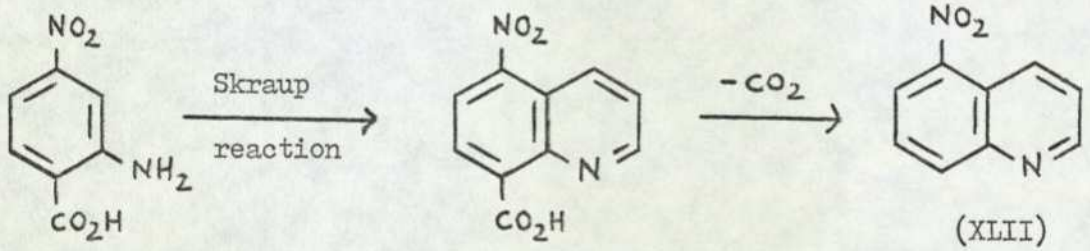
Aniline derivative	Quinoline products
monosubst.	
2- (o)	8-
3- (m)	5- & 7-
4- (p)	6-
disubst.	
2,3-	7,8-
2,4-	6,8-
2,5-	5,8-
3,4-	5,6- & 6,7-
3,5-	5,7-
2,6-	no product possible
trisubst.	
2,3,4-	6,7,8-
2,3,5-	5,7,8-
2,4,5-	5,6,8-
3,4,5-	5,6,7-
2,3,6- & 2,4,6-	no product possible
tetrasubst.	
2,3,4,5-	5,6,7,8-
2,3,4,6- & 2,3,5,6-	no product possible
pentasubst.	
2,3,4,5,6-	no product possible

1.3.1 REACTIONS GIVING QUINOLINES IN WHICH THE HETEROCYCLIC RING IS UNSUBSTITUTED

This section is confined to orientation effects in the Skraup reaction only.

Although the possibility of the production of two isomeric products in the reaction with m-toluidine was indicated by Skraup,[82] very few of the early attempts to evaluate the ratio of isomers produced were successful or reliable, the work being hindered by the difficulty of separation and identification of the isomers. The fact that often the 7-substituted quinoline only was reported may be attributed to the frequently greater solubilities and lower melting points of the 5-substituted quinolines and their salts, compared with those of the 7-isomers.

In the identification of the isomeric quinolines, chemical methods which involve an unambiguous synthesis of one of the isomers are extremely important. A general procedure is to cyclise an amine containing a readily removable blocking group in one ortho- position, in order to force the cyclisation to occur at the other free position; the blocking group is then removed. An example[83] is shown below:



(XLII)

Nitro groups have frequently been used as blocking groups. After cyclisation the group is removed by reduction followed by deamination via the diazonium salt.[83]

Skraup and Brunner[84] first reported the formation of two isomeric quinolines from m-toluidine in the reaction, the products were separated by fractional crystallisation, and pure 7-methylquinoline picrate (m.p. 237°) was reported. Although it was realised that one isomer had been produced in preference to the other, the ratio of isomers was not determined.

In contrast Druce[85] later suggested that 7-methylquinoline only was formed. In 1932, Jantzen[86] reported physical data for all the monomethylquinolines, but no preparative details were given. Pure 7-methylquinoline was stated to be a solid,

m.p. 39°, b.p. 257.6°. Later, in a study of the dipole moments of quinoline derivatives, Cumper, Redford and Vogel[87] carefully purified a commercial sample of 7-methylquinoline by five recrystallisations of the dichromate derivative from water. The purified base had m.p. 38° (picrate m.p. 243-4°).

Manske, Marion and Leger[25] have synthesised 5-methylquinoline by an unambiguous route. These workers also performed a Skraup reaction with m-toluidine, the product was considered to be a mixture of 5- and 7-methylquinolines with the latter predominant. 7-Methylquinoline picrate (m.p. 242°) was obtained, following several recrystallisations but physical properties for the pure base were not reported.

A detailed study of the products from a series of Skraup reactions using nine different meta-substituted anilines was undertaken in 1947 by Bradford, Elliott and Rowe.[83] The products were separated by fractional crystallisation of the isomeric quinolines or their salts and were identified by comparison with samples of the appropriate 5- and 7- substituted quinolines, previously prepared by unambiguous syntheses involving "blocking" techniques.

The conclusions reached by Bradford, Elliott and Rowe[83] may be summarised as follows:

(i) Strongly ortho/para directing groups, e.g. methyl and hydroxyl groups, gave only the 7-substituted quinoline.

(ii) Relatively weaker ortho/para directing groups, e.g. chloro-, bromo-, and dimethylamino-, gave a mixture of 5- and 7-substituted quinolines in which the latter predominated.

(iii) meta-Directing groups, e.g. nitro-, carboxyl- and sulphonic acid groups, gave a mixture of 5- and 7- substituted quinolines in which the former predominated.

The samples of 7-methylquinoline obtained by Bradford et al.[83] (by unambiguous synthesis and also from the Skraup reaction) were reported to have b.p. 257°/754-6 mm., and to form a picrate, m.p. 242°, but the physical characteristics of the base (i.e. solid or liquid) were not reported. It would appear from these data that the purity of the product(s) was suspect. A simultaneous report by Pouterman and

Girardet[88] noted that both 5- and 7-methylquinoline were obtained in the reaction. Subsequently, Yoshikawa[89] also reported formation of both isomers.

Another study of the products of the Skraup reaction with meta-substituted anilines was carried out by Palmer[18] in 1962 using modern analytical techniques, including infra-red spectroscopy and gas-liquid chromatography, to analyse the products. It was shown that the product from m-toluidine consisted of 40% 5-methylquinoline and 60% 7-methylquinoline, and that the ratio varied only slightly with the concentration of sulphuric acid used. Pure 7-methylquinoline (as analysed by g.l.c.) was reported as a solid, m.p. 35-8°, picrate, m.p. 245°. It is noteworthy that the melting point of the picrate of pure 7-methylquinoline[18] was significantly higher than the values previously obtained by Skraup and Brunner,[84] Manske, Marion and Leger[25] and by Bradford, Elliott and Rowe[83] for the "pure" compound.

Palmer[18] concluded that, in general, 3- substituted anilines gave mixtures in which the 7- substituted quinolines predominated, however, exceptions could occur (e.g. with m-nitroaniline) where the substituent may deactivate the position para to it by an electromeric shift. Studies on the orientation effects in the Skraup synthesis for reactions commencing with 3,4-dimethylaniline have attracted far less interest. The reaction was first reported by Berend[90] in 1884, a yield of 50% was obtained but the isomers were not separated. Later Manske et al.[25] repeated the reaction and successfully isolated pure samples of both isomers, no ratio was recorded but the 6,7-isomer was considered to be present in the greater proportion. The identification of isomers was achieved by an unambiguous synthesis of 5,6-dimethylquinoline from 4,5-dimethyl-2-nitroaniline by a Skraup reaction, followed by removal of the nitro group by reduction and deamination.

Further unambiguous syntheses of 5,6- and 6,7-dimethylquinoline, from the respective dimethyl isatin derivatives, have been reported by King and Wright.[91] The properties of the products obtained were similar to those given by Manske et al.[25]

In the review of the Skraup synthesis, Manske[7] concluded that the general rule governing the orientation effects with 3,4-disubstituted anilines was that when one or both substitutuents were ortho-/para- directing the quinoline mixture obtained

from the aromatic amine consisted mainly of the 6,7-disubstituted quinoline with the 5,6-disubstituted quinoline present in lesser amount.

Palmer[18] extended the study of the orientation effects in the Skraup synthesis with meta-substituted anilines to include certain 3,4-disubstituted derivatives. With 3,4-dimethylaniline the composition of the product was 30% 5,6-dimethylquinoline and 70% 6,7-dimethylquinoline. From the limited number of 3,4-disubstituted anilines studied the generalisations of Manske[7] were confirmed and it was concluded that in the case of weakly ortho-/para- directing groups (such as halogen) there was a tendency towards 5,6-disubstitution as the electron releasing power of the 4- substituent increased.

1.3.2 REACTIONS GIVING QUINOLINES IN WHICH THE HETEROCYCLIC RING IS SUBSTITUTED

Unlike the detailed studies[18,83] of the orientation effects in the Skraup reaction with 3-substituted and 3,4-disubstituted anilines to produce 5- and 7-substituted and 5,6- and 6,7- disubstituted quinolines respectively, a comprehensive systematic investigation into similar effects to produce quinolines substituted additionally in the heterocyclic ring has not been undertaken.

However, although a number of isolated studies have been reported, it should be noted that much of the work dates from the very early period before reliable techniques for the separation and identification of the isomeric quinoline products became available. The work reported to date is collected in Table 1.3.2.

It is evident from Table 1.3.2 that few data concerning the precise isomer ratios for compounds substituted in the heterocyclic ring are available. Many workers have commented that one particular isomer was present in greater proportion[22,25] whilst in other cases the product was assigned as a single product, without consideration of the possible presence of the alternative isomer.[25,44,92,98,99] In other cases the presence of the second isomer was considered unlikely, however, no experimental evidence was presented to substantiate this assumption.[25,93,94]

Harz[95] realised that reaction of m-toluidine and propionaldehyde could lead to a mixture of products. However, since the picrate derivative gave a sharp

TABLE 1.3.2

ORIENTATION EFFECTS IN QUINOLINE SYNTHESIS

Isomeric quinolines synthesised	Composition of products (%)	Date	Ref.
2,5-/2,7- dimethyl	2,7 (a)	1884	44
	2,5 (S) 2,7 (G)	1942	25
3,5-/3,7- "	3,5 (10)* 3,7 (90)*	1942	25
	3,5 (S) 3,7 (G)	1943	22
4,5-/4,7- "	4,7 (a)	1913	92
	4,7 (b)	1942	25
2,3,5-/2,3,7- trimethyl	-	-	-
2,4,5-/2,4,7- "	2,4,7 (b)	1950	93
3,4,5-/3,4,7- "	3,4,7 (a)	1942	25
2,3,4,5-/2,3,4,7- tetramethyl	2,3,4,7 (b)	1946	94
2-ethyl-3,5-dimethyl-/ 2-ethyl-3,7-dimethyl-	? (d)	1885	95
2,5,6-/2,6,7- trimethyl	- (c)	1884	96,97
3,5,6-/3,6,7- "	-	-	-
4,5,6-/4,6,7- "	4,6,7 (a)	1965	98
2,3,5,6-/2,3,6,7- tetramethyl	-	-	-
2,4,5,6-/2,4,6,7- "	2,4,6,7 (a)	1958	99
3,4,5,6-/3,4,6,7- "	3,4,6,7 (b)	1968	100
2,3,4,5,6-/2,3,4,6,7- pentamethyl	2,3,4,6,7 (b)	1968	100
2-ethyl-3,5,6-trimethyl-/ 2-ethyl-3,6,7-trimethyl-	-	-	-

NOTES

(a) Product considered as isomer shown, no mention made of other isomer.

(b) Product considered to be substantially the isomer shown, possibility of formation of other isomer considered, but thought to be absent, or present in small amount only.

Cont....

TABLE 1.3.2 (Cont.)

(c) Possibility of isomeric products not considered.

(d) Possibility of isomeric products considered. Product thought to be a single compound, identity not established.

G Greater amount.

S Smaller amount.

* Tentative result.

melting point, the product was considered as a single substance of unknown identity.

Berend[96] and Merz[97] performed the Doebner-von Miller reaction with paraldehyde and 3,4-dimethylaniline to obtain a product which was referred to as "dimethylquinaldine". The possibility of isomeric products was not considered, however, the listing of their work in "Beilsteins Handbuch" refers to the product as 2,5,6- and/or 2,6,7- trimethylquinoline.[101a]

The isomer ratios reported by Manske et al.[25] in the synthesis of 3,5-/3,7- dimethylquinoline were considered very tentative.

In view of the lack of conclusive experimental data on the isomer ratios obtained in the above reactions, together with the doubts that exist concerning the possible presence of one or two products in certain reactions, a systematic study of these reactions would appear to be warranted.

1.3.3 SYNTHESIS AND NITRATION OF 7-ALKYLQUINOLINES

The discussion on sections 1.3.1 and 1.3.2 has been confined to quinoline syntheses commencing with 3-substituted and 3,4-disubstituted methyl anilines. In this section the orientation effects observed with asymmetric higher alkyl substituted aniline derivatives in quinoline syntheses will be considered.

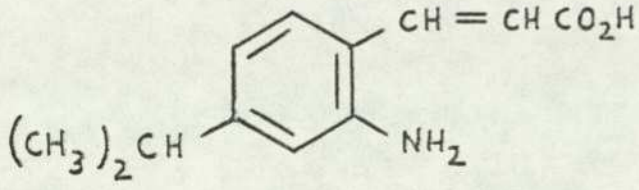
Unlike studies of the Skraup reaction and other quinoline syntheses commencing with m-toluidine, reactions commencing with m-(higher alkyl) substituted anilines have received much less attention.

Although m-toluidine is readily available, higher alkyl derivatives are generally not commercial products, and therefore require prior synthesis. The most attractive route would appear to be catalytic reduction of the appropriate m-nitrophenyl ketone. Using this technique Long and Schofield[102] obtained m-ethylaniline (39% yield) from m-nitroacetophenone with raney nickel as reducing agent.

The Skraup reaction with m-ethylaniline was first reported by Manske, Marion and Leger,[25] the product was considered as 7-ethylquinoline contaminated with a small amount of the 5-ethyl isomer. Long and Schofield[103] synthesised alkylquinolines by the Skraup reaction from m-ethyl-, m-(n-propyl)- and m-(n-butyl)- anilines and

(on the basis of the findings of Bradford et al.[83]) assumed that the products were chiefly or exclusively the corresponding 7-alkylquinolines.

The only other known 7-alkylquinoline is the 7-isopropyl derivative reported in 1886 by Widman.[104] However, this compound was obtained through a multi-stage unambiguous route commencing from p-isopropylpropionic acid and proceeding via the ring closure of 2-amino-4-isopropylcinnamic acid (XLIV).



(XLIV)

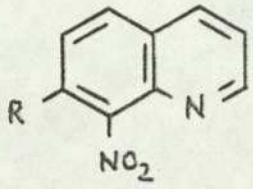
Buu-Hoi et al.[105] have reported the Combes reaction of acetylacetone and m-ethylaniline. The product obtained was considered to be 7-ethyl-2,4-dimethylquinoline, possibly contaminated with a small amount of the 5-ethyl isomer.

There have been a number of studies made of the nitration of 7-alkylquinolines.[103, 106, 107] In all cases the corresponding 8-nitroquinoline derivative (XLV) was identified as the main product but the nature of the minor products formed remains uncertain. Capps[107] starting from (impure) 7-methylquinoline showed that an unidentified minor product was neither 7-methyl-5-nitroquinoline (XLVI, R = CH_3) nor 7-methyl-6-nitroquinoline which implied that nitration had occurred in the pyridine nucleus. Long and Schofield[103] starting from (impure) 7-ethylquinoline assumed that the minor product of nitration was 7-ethyl-5-nitroquinoline (XLVI, R = C_2H_5) despite the earlier report[107] that nitration did not occur with 7-methylquinoline at the 5- position; nitration in the pyridine nucleus being considered to be extremely unlikely.[108]

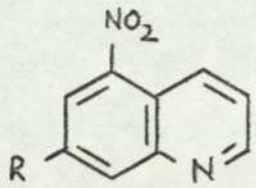
It now seems probable that the 7-alkylquinolines used in the above studies would have contained appreciable amounts of the 5-alkyl isomers, the nitration of which would have given rise to additional products.

In support of this proposal it is of interest to note that the minor product

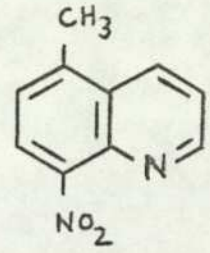
(m.p. 133-4°) isolated by Capps[107] from the nitration of (impure) 7-methylquinoline possessed very similar properties to synthetic 8-nitro-5-methylquinoline (XLVII), (lit.[25] m.p. 138°).



(XLV)



(XLVI)



(XLVII)

1.4 ^{1}H N.M.R. SPECTRAL STUDIES OF ALKYLQUINOLINE DERIVATIVES

1.4.1 GENERAL STUDIES - CHEMICAL SHIFTS AND COUPLING CONSTANTS

The proton nuclear magnetic resonance spectrum of quinoline was first reported in 1953 by Meyer, Saika and Gutowsky[109] during the early pioneering days of the technique. A 4172 gauss permanent magnet was employed and the ^{1}H nucleus detected at 17.78 MHz, with reference to water. Three signals were obtained with intensities of 1:1:5 respectively but no assignments were given.

Later developments in n.m.r. spectroscopy rapidly led to improved resolution and better separation by operation at higher magnetic fields. Pople, Schneider and Bernstein[110] studied liquid quinoline at 40 MHz, with reference to a water capilliary the spectrum obtained had well resolved signals. Assignments were performed by comparison with the literature spectrum[111] of pyridine. The lowest field quartet was assigned to H-2, whilst the other low field quartet was ascribed to H-8. This latter assignment was based on the spectrum of 8-methylquinoline in which this signal was absent. A high field quartet was distinguished and assigned to H-3. The heterocyclic ring protons were analysed as an ABX group, the quartet expected for H-4 was located in the central region of the spectrum which appeared as a complex multiplet. From the spectrum the following coupling constants were evaluated:

$$J_{23} = 5.0 \text{ Hz}, \quad J_{34} = 7.3 \text{ Hz}, \quad J_{78} \text{ ca. } 7 \text{ Hz}$$

The spectrum of 4,7-dimethylquinoline was also illustrated[110] and analysed by a first order treatment. Doublets for H-2 and H-3 appeared at low field and high field respectively with H-8 as a broad signal. The signals for H-5 and H-6 each appeared as doublets (J_{56} = 8.3 Hz); these assignments confirmed the tentative predictions previously given for quinoline.[110]

Schaefer and Schneider[112,113] later reported the n.m.r. spectra of quinoline and seven alkyl derivatives determined at 60 MHz in hexane, acetone and benzene solution. Solvent shifts were discussed and chemical shift data given. The improved resolution obtained at 60 MHz permitted determination of meta coupling constants, viz:

J_{24} = 1.6 - 1.8 Hz $\qquad$ J_{57} = 1.8 Hz

J_{68} = 2.1 Hz

Anet[114] measured the high resolution spectra of 8-methylquinoline, 5,7-dimethylquinoline and 5,7-dichloroquinoline. In the latter compound the H-4 signal appeared as a doublet of octets from which it was concluded that a long range cross-ring coupling (J = 0.8 Hz) was present. Comparison with the H-4 signals in the spectra of the other quinoline derivatives studied showed that the coupling involved H-8.

Seiffert[115] obtained a reasonable linear correlation between the out-of-plane C - H vibrations in the infra-red and the chemical shifts of the ring protons for fifteen (mostly polymethyl) quinoline derivatives.

Black and Heffernan[116] have fully analysed the spectra of quinoline and certain nitroquinoline derivatives, determined at 100 MHz. Quinoline was examined as the pure liquid and also in dilute solution in carbon tetrachloride and acetone, the nitroquinolines were examined in acetone solution. Chemical shifts and coupling constants were obtained for all the compounds and the experimental and calculated spectra were compared. The coupling constants were all assumed to be of the same sign, based on the earlier work of Paterson and Bigam,[117] which had demonstrated by double resonance techniques that J_{23}, J_{24} and J_{34} had the same sign. The spectral parameters reported for quinoline are shown in Table 1.4.1.

The proton assignments were later confirmed by Albert and Catterall[118] through the preparation of all the monodeuteroquinolines.

TABLE 1.4.1

N.M.R. Spectral data for quinoline

(from ref. 116)

Parameter	Pure liquid	5% solution in acetone	5% solution in CCl_4
H-2 (τ)	0.48	1.10	1.19
H-3	2.91	2.53	2.74
H-4	2.17	1.72	2.00
H-5	2.42	2.08	2.32
H-6	2.65	2.46	2.57
H-7	2.40	2.27	2.39
H-8	1.57	1.94	1.95
J_{23} (Hz)	4.3	4.3	4.3
J_{24}	1.8	1.8	1.8
J_{34}	8.3	8.3	8.3
J_{56}	8.2	8.1	8.2
J_{57}	1.6	1.5	1.5
J_{58}	0.3	0.5	0.6
J_{67}	6.8	6.8	6.9
J_{68}	1.1	1.1	1.2
J_{78}	8.3	8.4	8.6
J_{48}	0.9	0.8	0.7

Subsequent studies of the spectra of 2- and 4- methylquinoline have been performed by Mondelli and Merlini.[119] The samples were examined in carbon tetrachloride, chloroform-d, dimethyl sulphoxide and trifluoroacetic acid solution, in the latter solvent protonation occurred leading to downfield shifts for H-3 and H-4 and increased values of J_{23} and J_{34}.

Further studies of the n.m.r. spectra of quinoline derivatives in other acidic media have also been reported.[120]

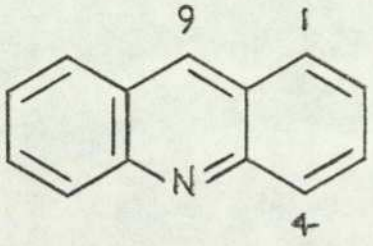
From the partial spectra of 3-, 6- and 7- methylquinoline, Ohtsuru et al.[121] concluded that the methyl substituent effect upon the chemical shift of the proton ortho to the site of substitution was transmitted to a greater extent through the aromatic C = C bond with the greater double bond character. With 3-methylquinoline, H-2 exhibited a 0.16 p.p.m. upfield shift, whilst H-4 was shifted by 0.28 p.p.m.

Further studies of the spectra of several alkylquinolines have been reported by Chakrabarty and Hanrahan.[122] Methyl substituent effects were confirmed and a reasonable correlation obtained between proton chemical shifts and the charge densities on the respective carbon atoms, with the exception of the 8- position. This latter discrepancy was considered to be caused by a deshielding effect of the nearby nitrogen loan pair. Later work by Taddei and co-workers[123] also indicated that position 8 was anomalous, furthermore it was found that the same effects also acted, in an attenuated form, on the proton chemical shifts of the methyl groups in monomethylquinoline derivatives.

The ortho coupling constant, J_{23}, has a particularly low value which has been considered[116] to be due to the close proximity of the nitrogen atom. Brignell et al.[124] have observed similar low values in quinoxaline derivatives (J_{23} = 1.7 - 1.9 Hz), and with pyridine (J_{23} = 5.5 Hz)[125] and pyrazine (J_{28} = 2.8 Hz),[126] all of which were influenced partially by bond fixation.

Jackman and Sternhell[127a] noted that the cross ring coupling between protons 4 and 8 which occurred in quinolines,[114] may also be observed in a number of other systems, such as $^5J_{37}$ coupling in indole. This type of coupling is facilitated between protons at the ends of a chain of configuration through a "zig-zag" path.

Long range spin-spin coupling between the peri protons H-4 and H-5 has not been reported for the quinoline system. The n.m.r. spectra of acridine (XLVIII) and its methyl derivatives have been studied and a number of long range couplings identified, and their signs determined by double resonance techniques. It was concluded[128] that



(XLVIII)

the sign of the inter-ring coupling constants alternated with the number of intervening bonds; $^{4}J_{1,9}$ was negative (-0.40 to -0.45 Hz) and $^{5}J_{4,9}$ (and by analogy $^{5}J_{4,8}$ in quinoline) was positive.

Solvent shift studies have been carried out by a number of workers.[112,113,116,129] It was suggested[116] that either n-hexane or carbon tetrachloride was a suitable reference solvent. In acetone and benzene solution and in the pure liquid, media effects occurred which followed certain trends of unknown cause. Further systemmatic studies of the shifts have been undertaken by Ronanye and Williams[130] and their diagnostic use for spectral interpretation discussed.

Further separation and simplification of signals in the n.m.r. spectra of quinoline derivatives may be achieved with the use of a lanthanide shift reagent (L.S.R.) through co-ordination with the nitrogen lone pair. An early example[131] illustrated the effect of tris(dipivalomethanato)europium upon 6-methylquinoline. In the normal spectrum, measured at 60 MHz, only three sets of signals could be distinguished; H-2, H-4/H-8 and H-3/H-5/H-7. Addition of the L.S.R. caused large shifts of the protons closest to the nitrogen atom (H-2 and H-8) and smaller shifts for the remaining protons. A readily interpretable spectrum with a separate signal for each proton was thereby obtained. Additional studies of the effects of L.S.R.'s have been reported by a number of authors.[132-134]

Further discussions of the n.m.r. spectra of quinoline and its alkyl derivatives have been presented by White and Williams[135] and by Batterham,[136a] both of these works list tabulated data, further spectra of quinoline derivatives are included in reference

spectra collections.[137]

The n.m.r. spectrum of quinoline oriented in the liquid crystalline phase Licristal phase 7A at 27° has been studied by Diehl and Zimmerman.[138]

1.4.2 BENZYLIC COUPLING IN METHYLQUINOLINE DERIVATIVES

Long range coupling in ^1H n.m.r. spectroscopy may be defined as coupling that extends over four or more bonds.[139] Benzylic coupling is a particular type of long range coupling and may be defined[140] as the interaction between protons bonded to sp^3-hybridised benzylic carbon atoms and ring protons in aromatic and heteroaromatic systems. Benzylic coupling effects have been discussed briefly within reviews dealing with general long range coupling.[127b,139-141]

Since long range coupling is weak, considerable advances in n.m.r. instrumentation were necessary before such interactions could be detected, accordingly certain signals which were initially described as "sharp" have subsequently been shown to possess additional splitting due to long range coupling.

The following generalisations concerning benzylic coupling constants have been established[140]:

(a) For methyl groups, and other freely rotating alkyl groups, $^4J_o^{CH_3,H}$ is either approximately equal to, or larger than $^6J_p^{CH_3,H}$ but always distinctly larger in absolute magnitude than $^5J_m^{CH_3,H}$. For benzene derivatives the magnitude of these couplings is ca. -(0.6 - 0.9), - (ca. 0.6) and $<$ + 0.4 Hz respectively.[142,143]

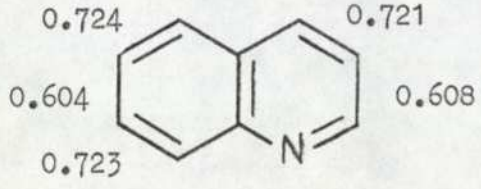
(b) For methyl groups, $J_o^{CH_3H}$ is directly,[144,145] but not necessarily linearly,[146] related to the π-bond order of the intervening double bond.

The first example of benzylic coupling in a methylquinoline derivative was observed by Pople, Schneider and Bernstein[110] in 1959. In the spectrum of 4,7-dimethylquinoline determined at 40 MHz, the signals of H-3, H-6 and H-8 were broadened, which was considered to result from unresolved quartets due to coupling with adjacent methyl groups.

Anet[114] noted that in the spectrum of 5,7-dimethylquinoline the signals of H-6

and H-8 were each broadened without observable structure, due to unresolved coupling with the methyl groups. Such additional coupling was not present in the spectrum of 5,7-dichloroquinoline.

In the course of their thorough study of benzylic coupling constants, Rottendorf and Sternhell[142] performed certain experiments to demonstrate the dependence of ortho-benzylic coupling upon bond order. The methyl group of 4-methylquinoline was split into a clear doublet ($J_{CH_3,H}$ = 0.95 ± 0.03 Hz) whilst the methyl group of 2-methylquinoline gave rise to a singlet (W_H = 0.76 Hz) at a resolution at which tetramethylsilane gave a singlet (W_H = 0.35 Hz) which indicated that $J_{CH_3,H-3}$ was less than ca. 0.4 Hz. With 2,6-dimethylquinoline, the 2-methyl group at 2.75 δ was a singlet (W_H = 0.98 Hz), whilst the 6-methyl group at 2.50 δ was an unresolved multiplet (W_H = 1.9 Hz). These results indicated that the magnitude of the ortho-benzylic coupling constant was related to bond order. Calculated bond orders for the quinoline ring system were presented in the following year by Coulson and Streitwieser:[147]



It is of interest to note the large differences between the 2,3- and 3,4-bond orders, and also the distinctive variations in the carbocyclic ring.

Further measurements of benzylic coupling constants in methylquinoline derivatives have been reported for 2- and 4-methylquinoline,[119,148] 2-chloro-4-methylquinoline,[149] and 8-methylquinoline,[150] in each case splitting at the methyl protons was observed. Long range couplings involving the methyl protons of 8-methylquinoline have been studied by Sterk and Wachmann.[151] The spectrum was determined at 100 MHz and the following coupling constants obtained through computer simulation techniques:

$$^{4}J_{o}^{CH_3,H} = -0.68 \text{ Hz}$$

$$^{5}J_{m}^{CH_3,H} = +0.29 \text{ Hz}$$

$$^{6}J_{CH_3,H\text{-}4} = -0.55 \text{ Hz}$$

However, it was also reported that ^{6}J coupling between methyl protons and out-of-ring protons did not occur; a personal communication[152] from Prof. Dr. Sterk has indicated that $^{6}J_{CH_3,H\text{-}4}$ should have read $^{6}J_{p}^{CH_3,H}$. That ^{6}J coupling to the para hydrogen did occur but that cross ring ^{6}J coupling was not observed was attributed to differing amounts of "through-space" interaction in the coupling mechanisms.

Chakrabarty and Hanrahan,[122] in the course of their studies of the spectra of alkylquinoline derivatives, noted that the H-3 resonance in 2,4-dimethylquinoline appeared as a poorly resolved doublet, and that there was also an indication of splitting in the methyl proton resonances. This effect was attributed to ortho-side chain coupling (J = 1 Hz) but the precise nuclei involved were not specified.

A comparison of benzylic coupling constants in methylquinoline derivatives with similar interactions in the few other heteroaromatic systems to receive attention is instructive.

In the pyridine series, in which no bond localisation is possible, coupling to both ortho-hydrogens occurred to almost the same extent, e.g. in 2-chloro-4-methyl-pyridine:[149]

$$J_{CH_3,H\text{-}3} = 0.8 \text{ Hz} \quad \text{and} \quad J_{CH_3,H\text{-}5} = 0.7 \text{ Hz}.$$

Bramwell and Randall[153] studied the isomeric picolines and through the use of double and triple resonance techniques, relative sign determinations were deduced. The results were in accordance with earlier values for toluene derivatives[143] and for 8-methylquinoline.[151] The following benzylic coupling constants were obtained for 3-methylpyridine:

$$J_{CH_3,H\text{-}4} = 0.7 \pm 0.05 \text{ Hz} \quad (\text{opposite sign to } J_{45})$$

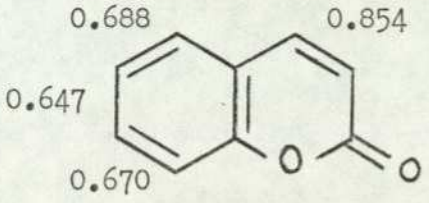
$$J_{CH_3,H\text{-}2} = J_{CH_3,H\text{-}6} = 0.65 \pm 0.05 \text{ Hz}$$

$$J_{CH_3,H\text{-}5} = 0.35 \pm 0.05 \text{ Hz} \quad (\text{same sign as } J_{45})$$

Similar results have also been reported by Bramwell and Wells[154] for methylpyrazine derivatives.

The only other system to have received detailed attention is the coumarin nucleus (XLIX), studied by Rowbotham and Schaefer,[155] their results are summarised in Table 1.4.2. Since the magnitude of $^4J_o^{CH_3,H}$ was known[144-6] to be dependent on the bond order of the intervening bonds the observed results were rationalised such that couplings involving the 5,6- or 7,8- bonds had a magnitude near 0.8 Hz, whilst those involving the 6,7- bond were lower and close to 0.6 Hz. The allylic coupling $^4J_o^{CH_3,H}$ in 3- and 4- methylcoumarin was, as expected, much larger than the benzylic couplings.

These conclusions were in accordance with the calculated π - bond orders for coumarin which appeared later[156] :



(XLIX)

TABLE 1.4.2

Benzylic (and allylic) coupling constants in methylcoumarin derivatives (from ref. 155)

Coupling (a)	methylcoumarin derivative				
	3-	4-	6-	7-	8-
$^4J_{34}$	-1.37	-1.28			
$^4J_{56}$			-0.81		
$^4J_{67}$			-0.60	-0.62	
$^4J_{78}$				-0.76	-0.81
$^5J_{57}$				+0.32	
$^5J_{68}$			+0.31		+0.35
$^6J_{58}$					-0.60

NOTES

(a) Benzylic coupling between methyl group and ring proton in position indicated.

In the light of subsequent results[142,147] and discussion[155] it is apparent that certain of the earlier reports concerning benzylic couplings in methylquinoline derivatives in which equal couplings across the 5,6-, 6,7- and 7,8- bonds were envisaged,[110,157] now require correction.

Rottendorf and Sternhell[142] in their initial paper on benzylic couplings commented that "more extensive and accurate data is needed to justify quantitative

conclusions." However, in the intervening years since this statement was made no such systematic study has been undertaken for methylquinoline derivatives.

1.5 ^{13}C N.M.R. SPECTRAL STUDIES OF QUINOLINE DERIVATIVES

The carbon isotope of interest to the nuclear magnetic resonance spectroscopist, ^{13}C, has a natural abundance of 1.1% and a spin quantum number I, of $\frac{1}{2}$. The most abundant isotope, ^{12}C, is non-magnetic and although this fact simplifies the proton spectra of organic molecules because of the consequent absence of spin-spin interactions, it has presented a sensitivity problem by restricting carbon magnetic resonance studies to the insensitive, less abundant ^{13}C.

The presence of the small abundance of natural ^{13}C may be observed in ^{1}H n.m.r. spectra through coupling to produce 'satellite' peaks from which values of $^{1}J_{C,H}$ couplings may be obtained.[127c] Indeed, much of the early data concerning these interactions was determined by this technique, and considerable attention was focussed upon these couplings and their relation to structure.

Although carbon magnetic resonance spectra were first observed by Lauterbur[158] in 1957, direct ^{13}C investigations were carried out in relatively few laboratories, because of the practical difficulties involved due to low sensitivity.

The technological advances through the 1960's have, to a large extent, now overcome the major problems associated with the direct detection of ^{13}C resonance signals, and spectra can now be determined in essentially routine fashion. The newer techniques which have facilitated the routine determination of spectra are:

(a) use of pulsed techniques

(b) use of "noise" decoupling

Originally spectra were determined[158] by rapid passage techniques using powerful radiofrequency fields, which produced inaccurate line positions and distorted, broadened peaks. Subsequently, with a highly stable field-frequency locking system multiple scan techniques were used in which the accumulated spectra were added in a Computer of Average Transients (C.A.T.)[159] In this technique the random noise

accumulated slower than the coherent signals and the consequent gain in signal-to-noise ratio was proportional to the square root of the number of scans taken. However, spectra still required lengthy accumulation times.

The major advance in ^{13}C n.m.r. techniques was the introduction of the pulsed "Fourier" technique.[160] The free induction decays after each pulse were digitised and accumulated and finally converted to an absorption spectrum by Fourier Transformation. Early fears that long ^{13}C relaxation times would mean slow pulsing rates seem in practice to have been unfounded. The signal-to-noise (S/N) gain with the pulsed technique was at least a factor of 10 in favourable cases, which gave a time gain over traditional continuous wave operation of about 100-fold.

The other significant contribution to ^{13}C n.m.r. techniques involved the use of double-resonance through which all proton coupled multiplets were collapsed simultaneously in the same experiment. This was accomplished by the use of "noise" or "broad-band" heteronuclear decoupling.[161] The technique offered three advantages, an improved S/N ratio (a 1:3:3:1 quartet should give a single line with a relative intensity of approximately 8); a simpler spectrum was produced (albeit with the loss of all ^{13}C - ^{1}H coupling information) and because of the positive Nuclear Overhauser Enhancement (N.O.E.) for ^{13}C nuclei directly bonded to protons, a further S/N gain of 2.988 could be achieved.[162]

Later advances, such as the use of "Gated" decoupling[163] and "quadrature" detection[164] have further increased the S/N ratio such that high resolution proton coupled ^{13}C spectra may now be obtained within a reasonable time.

Several monographs have appeared on the experimental techniques and assignment methods involved in ^{13}C n.m.r. spectroscopy.[164-9]

1.5.1 ^{13}C N.M.R. SPECTRAL STUDIES OF QUINOLINE DERIVATIVES - CHEMICAL SHIFTS

The ^{13}C n.m.r. spectra of pyridine and certain other simple monocyclic heterocycles were first measured by Lauterbur[170] in 1957 using the rapid passage technique. The α - and γ - carbons were each appreciably deshielded relative to benzene whilst the β - carbons were shielded. The shifts obtained were consistent with calculated values of π - electron densities, although exact correlations were

not possible.

The proton decoupled ^{13}C n.m.r. of pyridine was later determined by Pugmire and Grant,[171] the agreement with the results of Lauterbur[170] was remarkably good.

Pugmire et al.[172] were also the first group to study quinoline, reported in 1969. The spectrum was determined at 15 MHz with the neat liquid by the continuous wave technique with time averaging and proton decoupling, which gave nine peaks of unit height, hence differentiation of the bridgehead carbons was difficult. Assignments were performed by reference to the spectrum of pyridine,[171] since the α - carbons would each exhibit a large downfield shift these were assigned immediately. Other assignments were effected through the use of selective heteronuclear decoupling techniques. However, the H-5 and H-7 proton shifts were too close to allow a distinction to be made by this technique, and accordingly this ambiguity was resolved by elimination of the large proton splittings through the use of quinoline-5-d and quinoline-7-d. Additive relationships between certain structural features were noted which provided a reliable method for making assignments in cyclic systems. Inductive and resonance effects were concluded to be adequate to account for the carbon-13 chemical shift data.

Pregosin, Randall and White[173] later determined the proton decoupled ^{13}C n.m.r. spectra of quinoline and of quinoline-^{15}N by pulsed techniques.

Spectra were obtained for solutions in carbon tetrachloride, methanol and sulphuric acid. The results in carbon tetrachloride solution were in good agreement with the earlier work[172] upon the pure liquid. Carbon-nitrogen couplings, $J\ (^{13}C - {}^{15}N)$, were visible in the spectrum of quinoline-^{15}N as additional splittings which also facilitated assignments. The results obtained are shown in Table 1.5.1.

TABLE 1.5.1

Carbon-13 chemical shifts and J (^{13}C - ^{15}N) coupling constants in quinoline (50% w/v solution in CCl_4) (from reference 173)

Carbon	Chemical Shift (δ, p.p.m. from T.M.S.)	J (^{13}C - ^{15}N) (Hz)
C-2	150.89	1.4
C-3	121.67	2.7
C-4	136.12	3.5
C-5	128.46	ca. 0
C-6	126.95	0.9
C-7	129.86	3.9
C-8	130.50	9.3
C-9	149.28	0.6
C-10	128.89	2.1

The assignments in sulphuric acid solution were made by off-resonance techniques (identification of C-9 and C-10), ^{13}C - ^{15}N couplings (identification of C-2 and C-4) and the observed methyl substituent effects in 6- and 8- methylquinoline and their protonated species.

The changes in chemical shift on protonation of carbons C-2, C-3 and C-4 (-6.0, +1.1 and +13.3 p.p.m. respectively) were similar to those observed by Pugmire and Grant[171] for the pyridine - pyridinium change. Low field shifts were observed for C-5 to C-7 whilst C-8 exhibited a high field shift which was attributed to a nitrogen lone pair effect.

Breitmaier and Spohn[174] later studied the variation of the ^{13}C chemical shifts of quinoline as a function of pH in aqueous solutions, titration style curves were obtained from which pK_a values were determined using the Henderson-Hasselbach

equation. Carbons C-2, C-5 and C-9 exhibited upfield shifts, C-4, C-6 and C-7 exhibited downfield shifts whilst C-3, C-8 and C-10 showed little change, no explanation was given for the shifts which mainly occurred between pH 3 and pH 6. Van de Weijer et al.[175] subsequently extended this study to the diazanaphthalenes. In order to verify possible additivity rules the spectrum of quinoline was reconsidered, from which it was concluded that the assignments for C-5 and C-8 by Breitmaier and Spohn[174] should be reversed. Using this reversed assignment better correlations for the diazanaphthalenes were then obtained. The reversed assignments[175] for C-8 and C-5 indicate that these sites experience an upfield shift and little change respectively, in accordance with the earlier findings of Pregosin et al.[173]

Sadler[176] has reported a method for enhancement of quaternary signals in ^{13}C n.m.r. spectroscopy through the use of broad band decoupling at very low power levels. The technique removed long range couplings to quaternary carbons but did not effect the ^{1}J couplings at non-quaternary carbons, which resulted in increased intensity. The technique was demonstrated with several molecules, including quinoline.

Determinations of the ^{13}C n.m.r. spectra of methylquinoline derivatives are both scarce and brief. Kleinpeter and Borsdorf[177] studied 2-methylquinoline, whilst Garber et al.[178] studied 8-methylquinoline. In both cases the methylquinoline spectra were required only as model compounds for other studies and no detailed discussion was presented.

After the present work was completed, Johns and Willing[179] reported a detailed study of the ^{13}C chemical shifts of quinoline and of 2-, 3-, 4-, 6- and 8-methylquinoline. Spectra were determined by pulsed techniques at 20 MHz upon solutions in chloroform-d. Assignments were performed through use of off-resonance decoupled spectra, use of methyl substituent shift parameters derived from toluene[180] and from methylpyridines,[181] and also by utilisation of the lanthanide shift reagent, Eu $(fod)_3$. The assignments were confirmed by consideration of long range ^{13}C - ^{1}H coupling constants (see section 1.5.2).

Methyl substituent chemical shifts were derived and compared with effects in other series. The α - (+ 8.6 ± 0.9 p.p.m.), meta - (-0.3 ± 0.3 p.p.m.) and para - (-1.6 ± 0.3 p.p.m.) methyl substituent shifts were in close agreement with those

previously reported for the benzene[180] and pyridine[181] series. However, the ortho-substituent shifts were quite different. Substitution of a hydrogen by a methyl group in the quinoline molecule was found to induce shifts in opposite directions in the two ortho - carbon signals. No explanation of this effect, which was not shown in methylbenzene[180] and methylpyridine[181] derivatives, was given except that localisation of the double bonds in the quinoline ring system could be involved.

Henricks and Gross[182] have determined the ^{13}C chemical shifts of quinoline in the presence and absence of the relaxation reagent Cr $(acac)_3$ and noted that these cannot be assumed to be unaffected by the reagent. The effects were more noticeable in methanol solution than in chloroform, in the latter solvent shifts of up to 0.23 p.p.m. were observed. The results are shown in Table 1.5.2.

TABLE 1.5.2

Effect of Cr $(acac)_3$ upon ^{13}C chemical shifts in quinoline

(from ref. 182)

Carbon	^{13}C chemical shifts (p.p.m.) Without reagent (a)	With reagent (a)
C-2	150.41	150.48
C-3	121.08	121.23
C-4	136.07	136.30
C-5	127.78	127.91
C-6	126.55	126.64
C-7	129.48	129.51
C-8	129.48	129.51
C-9	148.28	148.25
C-10	128.30	128.29

NOTE (a) 0.125M solution of quinoline in $CDCl_3$, 0.1M Cr $(acac)_3$ added.

Studies of the effects of lanthanide shift reagents upon the ^{13}C n.m.r. of quinoline have also been reported.[134,183]

1.5.2 ^{13}C N.M.R. SPECTRAL STUDIES OF QUINOLINE DERIVATIVES - COUPLING CONSTANTS.

The earliest data on ^{13}C - ^{1}H coupling constants in quinoline derivatives were determined from 'satellite' peaks in ^{1}H n.m.r. spectra. Thus Tori and Nakagawa[184] obtained values of $^{1}J_{C,H}$ in a number of heteroaromatic molecules, the results obtained for quinoline derivatives are shown in Table 1.5.3.

TABLE 1.5.3

$^{1}J_{C,H}$ coupling constants in quinoline derivatives (from ref. 184)

Compound	$^{1}J_{C,H}$ (Hz)				
	2	3	4	8	CH_3
Quinoline	177.5	163.5			
2-Methylquinoline		160.8	156.8	160.0	126.8
3-Methylquinoline	174.8				127.3
4-Methylquinoline	175.0	162.0		160.0	127.4
6-Methylquinoline	176.6	164.0		160.0	126.8
7-Methylquinoline	175.8			159.8	126.5
8-Methylquinoline	176.8	162.4	162.0		127.0

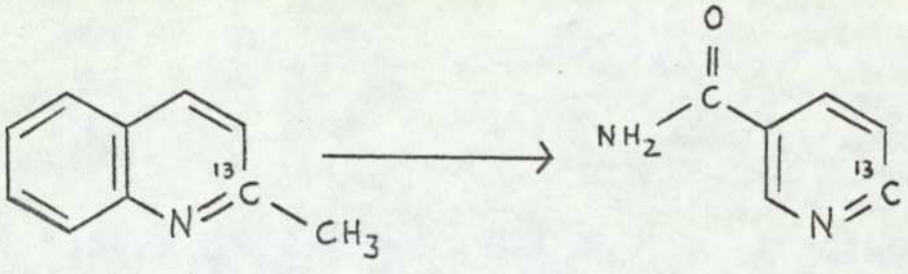
The results were consistent with the known dependence[185] of $J_{C,H}$ upon hybridisation. When an electronegative atom was bonded to the carbon, the percentage of s-character increased and an increased value of $^{1}J_{C,H}$ found for C-2 in quinoline. An attempt to correlate $J_{H,H}$ with the mean $J_{C,H}$ related to the two protons involved was presented, a graphical plot provided a relationship from which the value of one unknown coupling could be predicted from knowledge of the other.

Further values of $^{1}J_{C,H}$ at methyl carbons were later reported by Markgraf *et al.*[186] again determined from 'satellite' peaks.

Pregosin, Randall and White[173] have reported the ^{13}C n.m.r. spectrum of quinoline-^{15}N (see section 1.5.1). Although J (^{13}C - ^{15}N) couplings were determined, no data concerning J (^{13}C - ^{1}H) couplings was presented.

The first example of a long range ^{13}C - ^{1}H coupling in an alkylquinoline derivative was reported by Bryson *et al.*[187] in 1974.

The ^{1}H n.m.r. spectrum of 2-methylquinoline-2-^{13}C (L) was recorded as the pure liquid, in which the methyl group appeared as a doublet ($^{2}J_{C,H}$ = 6 Hz) and the H-3 proton as a doublet of doublets ($J_{3,4}$ = 8.5 Hz, $^{2}J_{C,H}$ = 3 Hz) the additional multiplicities being caused by coupling to the enriched ^{13}C nuclei. The use of non-radioactive labels as biological probes or tracer agents by virtue of their spectroscopic properties was illustrated by a sequence of reactions leading to nicotinamide-6-^{13}C (LI).



(L) (LI)

After the present work was completed a thorough study of the chemical shifts and ^{13}C - ^{1}H coupling constants of quinoline and five monomethylquinolines was reported by Johns and Willing.[179] The samples were examined as 50% solutions in chloroform-*d* and spectra were obtained by pulsed techniques with the aid of "gated" decoupling for the fully coupled spectra. The results obtained are shown in Table 1.5.4.

The magnitudes of the long range *ortho* ($^{2}J_{CCH}$) and *meta* ($^{3}J_{CCCH}$) coupling constants were similar to those previously observed in benzene[188] and pyridine[189] derivatives. The *meta* couplings (5.4 - 8.7 Hz) were larger than the *ortho* couplings, which were experimentally zero, except for those interactions associated with the nitrogen atom, i.e. $J_{2,3}$ and $J_{3,2}$ in which the couplings were 3.5 Hz and 8.0 Hz respectively. Vicinal (*peri*) $^{3}J_{CCCH}$ couplings between C-4 and H-5

TABLE 1.5.4

Long range ^{13}C - ^{1}H coupling

constants in quinoline and methylquinolines (Hz) (from ref. 179)

Compound	$J_{2,3}$	$J_{2,4}$	$J_{3,2}$	$J_{4,2}$	$J_{4,5}$
Quinoline	3.7	7.9	9.6	5.4	5.4
2-Methylquinoline	-	-	-	-	4.6
3-Methylquinoline	-	7.3	-	5.1	5.1
4-Methylquinoline	3.5	-	8.6	-	-
6-Methylquinoline	3.7	7.8	9.0	5.3	5.3
8-Methylquinoline	3.6	8.2	8.9	5.6	5.6

Compound	$J_{5,4}$	$J_{5,7}$	$J_{6,8}$	$J_{7,5}$	$J_{8,6}$
Quinoline	5.2	7.3	8.6	8.9	6.6
2-Methylquinoline	5.1	7.6	8.4	8.9	6.2
3-Methylquinoline	5.6	7.0	8.2	8.4	6.0
4-Methylquinoline	-	7.3	8.4	8.5	6.4
6-Methylquinoline	5.5	7.9	-	9.0	-
8-Methylquinoline	5.4	7.0	-	8.6	-

Compound	Couplings to/at methyl carbon								
2-Methylquinoline	$J_{Me,3}$	1.6	$J_{3,Me}$	3.5					
3-Methylquinoline	$J_{Me,2}$	2.4	$J_{Me,4}$	4.8	$J_{4,Me}$	5.1			
4-Methylquinoline	$J_{Me,3}$	5.0	$J_{3,Me}$	5.0					
6-Methylquinoline	$J_{Me,5}$	4.6	$J_{Me,7}$	4.6	$J_{5,Me}$	5.2	$J_{7,Me}$	5.1	
8-Methylquinoline	$J_{Me,7}$	4.6	$J_{7,Me}$	5.2					

and between C-5 and H-4 were also observed which were readily apparent in the fully coupled spectrum of quinoline. In contrast, no $^{4}J_{CCCCH}$ coupling between C-4 and H-8 or between H-8 and C-4 was observed and this cross-ring coupling was assumed to be less than 1 Hz. Long range couplings to, and occurring at, the methyl carbons were also observed (see Table 1.5.4) but these were not discussed. The long range couplings were used to confirm certain chemical shift assignments which were otherwise ambiguous (see also section 1.5.1).

Fomichev *et al.*[190] have also observed vicinal *peri* coupling, $^{3}J_{5,4}$ = 4.5 Hz, in 8-hydroxyquinoline.

Since there are very few studies of long range coupling constants in methylquinoline derivatives, particularly those interactions involving the methyl carbon, a brief survey of similar effects in closely related systems would seem appropriate.

Long range couplings in benzene were reported in 1967 by Weigert and Roberts.[191] Continuous wave techniques with spectrum accumulation were employed and the following couplings were identified:

$$J_{CCH} = +1.0 \text{ Hz}, \quad J_{CCCH} = +7.4 \text{ Hz} \quad \text{and} \quad J_{CCCCH} = -1.1 \text{ Hz}$$

Previously Karabatsos *et al.*,[192] on the assumption that the Fermi Contact term was the dominant contribution to the coupling, established that $^{13}C - {}^{1}H$ and $^{1}H - {}^{1}H$ coupling constants through similar networks were closely related. The following relationships were proposed:

$$J_{C-H} = J_{H-H} \times 0.30 \text{ (for } sp^3\text{-hybridised } {}^{13}C)$$

$$J_{C-H} = J_{H-H} \times 0.40 \text{ (for } sp^2\text{-hybridised } {}^{13}C)$$

$$J_{C-H} = J_{H-H} \times 0.61 \text{ (for sp-hybridised } {}^{13}C)$$

The relationships were verified by application to a number of simple *aliphatic* compounds. Application of the above relationships to benzene was undertaken by Weigert and Roberts.[191] The long range J_{CCH} and J_{CCCH} couplings were related to the appropriate H - H couplings with ethylene, butadiene and propene as model

compounds, the agreement obtained was excellent.

A brief review of the J_{C-H}/J_{H-H} ratio and its application to various systems has been presented by Marshall *et al.*[193]

A thorough study of the dependence of vicinal C,H spin-spin coupling upon stereochemical and structural effects has been made by Vögeli and von Philipsborn.[194] The effects of substituent electronegativity, π - bond order, bond angles, torsional angles and steric interactions were all considered. Although some of the factors were similar to those in vicinal H,H coupling additional effects could occur since the carbon involved in the coupling could belong to a variety of functional groups.

π - Bond order effects were observed in aromatic compounds. For *cis*-vicinal $^3J_{C,H}$ coupling across an aromatic double bond, a value of 4.7 Hz was observed for the methyl carbon (C-5') of 1,2,3,5-tetramethylbenzene. In 2-methylnaphthalene, two $^3J_{C,H}$ coupling constants were observed at the methyl carbon ($^3J_{C,H-1}$ = 5.1 Hz, $^3J_{C,H-3}$ = 4.1 Hz), the larger value was observed across the 1,2-double bond which (for naphthalene) was known to have the higher bond order. The sum of the two $^3J_{C,H}$ data for 1,2,3,5-tetramethylbenzene (9.4 Hz) and for 2-methylnaphthalene (9.2 Hz) were similar, hence π-electron delocalisation was clearly reflected in the vicinal C,H coupling constants.

The relation $J_{CH_3,H} \sim 0.6\ J_{H,H}$ was found to hold for both *cis* and *trans* coupling constants in a variety of structures, and therefore in olefinic and aromatic systems the same factors appeared responsible for both H,H and C,H interactions.

Long range couplings in a series of *para*-substituted toluene derivatives, including couplings involving the methyl carbons and hydrogens, have been studied recently by Shapiro.[195]

The methyl carbon appeared grossly as a quartet of triplets, through a large coupling to the three directly attached protons (J_{CH} = 125.4 - 127.1 Hz) and a three bond coupling to the 2- and 6- protons (J_{CCCH} = 4.0 - 4.3 Hz). A very weak coupling to the 3- and 5- protons was also detected at greater digital resolution (J_{CCCCH} = -0.4 to -0.7 Hz). Although the ^3J couplings were slightly smaller than in toluene they were then largely unaffected by the nature of the *para*-substituent.

Coupling of ring carbons with the methyl protons was also observed involving the α (^2J = -6.2 to -6.4 Hz) and ortho (^3J = 4.8 - 5.0 Hz) carbons. Both these couplings were slightly larger than their corresponding values for toluene, and independent of the nature of the para-substituent. The results were in agreement with certain theoretical calculations[196] which indicated that para- substitution should increase the magnitude of the ^3J coupling constants.

Detailed studies of long range ^{13}C - ^1H coupling constants in pyridine and certain other six-membered heterocyclic molecules were first reported by Weigert, Husar and Roberts.[197] The results obtained for pyridine were generally similar to the values for benzene[191] and are summarised in Table 1.5.5.

TABLE 1.5.5

Long range ^{13}C - ^1H coupling constants in pyridine (Hz)

(from ref. 197)

Carbon	J (^{13}C - ^1H) (Hz)				
	H-2	H-3	H-4	H-5	H-6
2	175.3	3.3	6.4	± 1.6	10.9
3	8.7	162.5	1.0	6.4	± 1.6
4	6.4	0.0	169.2	0.0	6.4

Because of the complexity of the pyridine spectrum certain methyl derivatives were also examined, however, since methyl proton decoupling was employed to remove certain couplings, splittings involving the methyl groups were not observed. As in the case of benzene,[191] the long range couplings obtained were related to proton - proton coupling in substituted ethylenes. Although the quantitative agreement with the theory of Karabatsos[192] was best for benzene, qualitative trends were correctly predicted throughout the heterocyclic series examined.

Further studies of long range couplings in pyridine derivatives have been reported by Hansen and Jacobsen,[189] and by Takeuchi and co-worker.[181,198] Most of the results obtained were for ring carbon - ring proton couplings, which were

consistent with earlier values.[197] A detailed discussion on the magnitude of the couplings and of their use in signal assignments has been presented by Takeuchi.[181]

Studies concerning the couplings at the substituent carbons (cyano or methyl) have received much less attention. The nitrile absorptions in 3-cyanopyridine and 4-cyanopyridine each appeared[198] as triplets (two ^{3}J couplings, each ca. 6 Hz) whilst that for 2-cyanopyridine was a triplet with weaker coupling (^{3}J, 1 Hz, 2 Hz).[198] The spectra obtained, however, were of poor S/N ratio and were not determined with particularly fine digital resolution and hence the results obtained, particularly for 2-cyanopyridine, need to be treated with reserve.

Takeuchi[181] later examined a series of methyl-, dimethyl- and trimethyl-substituted pyridine derivatives. The long range couplings determined which involved the methyl carbons or protons are summarised in Table 1.5.6.

The ^{2}J couplings between ring quaternary carbon and the adjacent methyl protons were each 6 Hz, it is interesting to recall that a similar coupling of 6 Hz had been reported by Bryson et al.[187] for C-2 in 2-methylquinoline-2-^{13}C.

The magnitude of the ^{3}J coupling appeared to be dependent upon the nature of the proton involved. The methyl carbon signal of 3-methylpyridine was a large quartet (^{1}J = 127 Hz) of doublets of doublets (^{3}J = 5 Hz and 3 Hz). The smaller of the two long range couplings was considered to be that involving the H-2 proton. The assignments were confirmed by reference to the spectrum of 3,4-dimethylpyridine in which both methyl groups exhibited the expected characteristic single fine splitting. The value of long range couplings at methyl groups as an assignment tool was demonstrated by reference to the spectrum of 2,3,6-trimethylpyridine.

The only other simple bicyclic heterocyclic system to have attracted detailed attention is the coumarin nucleus, studied by Cussans and Huckerby.[199] Complete assignments of chemical shifts and extensive assignments of ^{13}C - ^{1}H coupling constants for 3-, 4-, 6-, 7- and 8- methyl- and of 5,8- and 6,8- dimethylcoumarin were presented. In the case of ring carbon - ring proton interactions, large ^{3}J couplings to meta-protons were observed, whilst only isolated examples of ^{2}J or ^{4}J couplings, which were always of low magnitude could be detected. A three bond inter-ring

TABLE 1.5.6

Long range ^{13}C - ^{1}H couplings involving the methyl group (C, H) in methylpyridine derivatives. (from ref. 181)

Carbon	^{2}J (Hz)	^{3}J (Hz)
C-2	H-2' 6	H-3' 5
C-3	H-3' 6	H-2' 4
		H-4' 4
C-4	H-4' 6	H-3' 5
C-2'		H-3 2
C-3'		H-2 3
		H-4 5
C-4'		H-3 5

NOTE Carbons and protons numbered with (') are associated with the appropriate methyl group.

coupling between C-4 and H-5 was also observed ($J_{4,5}$ = 4.5 - 5.0 Hz), which was of similar magnitude to the corresponding peri coupling in quinolines.[179,190]

In most spectra the signals for the bridgehead carbons C-9 and C-10 were of low intensity, and exhibited complex splitting patterns which were not sufficiently intense for analysis. However, the signal for C-10 in 6,8-dimethylcoumarin appeared as a doublet (J = 8 Hz) which was tentatively assigned as $^{3}J_{10,3}$.

Introduction of a methyl substituent produced a new quaternary carbon which exhibited a quartet coupling constant ^{2}J (C - CH_3) of 5 - 6 Hz, whilst a quartet splitting ^{3}J (C - C - CH_3) of 5 - 6 Hz was produced at the carbons ortho to the site of substitution.

Long range couplings involving the methyl carbons were also observed and tabulated, but these were not discussed, these results are summarised in Table 1.5.7.

TABLE 1.5.7

Long range ^{13}C - ^{1}H coupling constants in methylcoumarin derivatives (from ref. 199)

^{3}J (C - H)	Hz
3' - 4	5
4' - 3	5.5
5' - 6	4.5
6' - 5	4
6' - 7	4
7' - 6	4.5
7' - 8	4.5
8' - 7	4.5 - 5.0

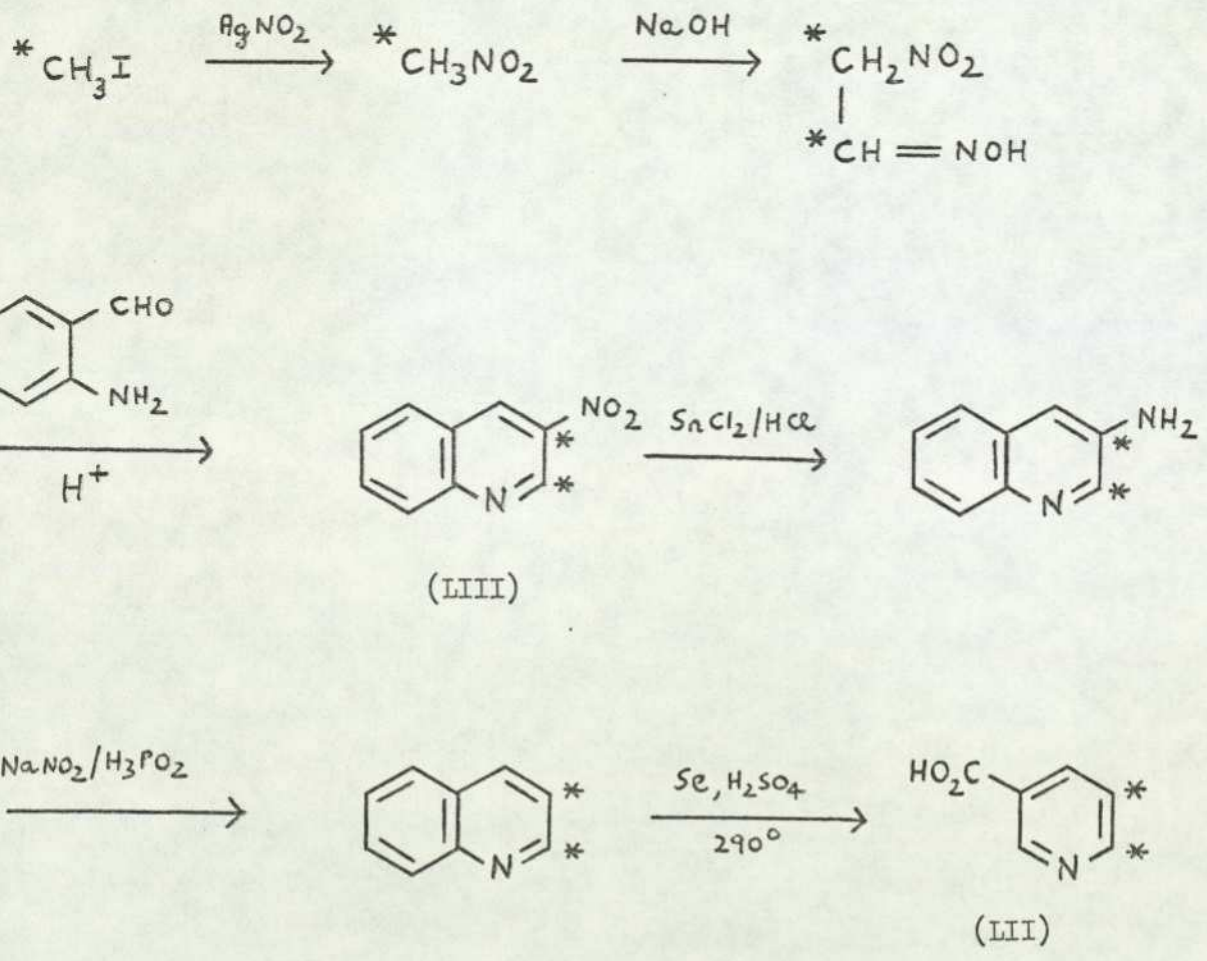
At the present time data concerning long range ^{13}C - ^{1}H coupling constants in alkylquinoline derivatives remains incomplete. Further parameters require to be measured before quantitative conclusions for diagnostic purposes can be proposed.

Spin - spin coupling between adjacent ^{13}C nuclei cannot normally be observed

since the natural abundance of such contiguous sites is only ca.0.01%. However, if ^{13}C - enriched samples are used then 'satellite' peaks appear in the proton decoupled ^{13}C n.m.r. spectrum, located centrally about singlet peaks arising from ^{13}C nuclei in natural abundance. Use of doubly labelled enriched samples results in sensitivity enhancement facilitating detailed examination of satellite peaks.

Doubly labelled samples have been employed to elucidate the course of biosynthetic pathways.

Leete[200] studied the incorporation of doubly labelled nicotinic acid (LII) into certain tobacco alkaloids and examined the results by ^{13}C n.m.r. spectroscopy. Doubly labelled nicotinic acid - 5,6 - $^{13}C_2$ (LII) was prepared from methyl iodide - ^{13}C via 3-nitroquinoline-2,3-$^{13}C_2$ (LIII), through the following sequence:



Satellites due to spin - spin coupling of the incorporated contiguous ^{13}C nuclei were observed at the enriched centres, in addition long range vicinal (three bond) and geminal (two bond) couplings were detected at other positions due to interaction with the enriched carbon nuclei. The results obtained are summarised in Table 1.5.8.

TABLE 1.5.8

^{13}C - ^{13}C Coupling constants in some doubly enriched (2,3 - $^{13}C_2$) quinoline derivatives (from ref. 200).

Quinoline derivative (2,3 - $^{13}C_2$)	$J_{C,C}$ (Hz)		
	$^1J_{2,3}$	$^1J_{3,4}$	Others
3-nitroquinoline	62.4	60	$^2J_{2,4}$ = 9; $^3J_{2,8}$ = 3; $^3J_{2,10}$ = 7.5; $^3J_{3,9}$ = 1(
3-aminoquinoline	56.3	58	-
quinoline	51.1	58	-

As far as the present author is aware, no studies of ^{13}C - ^{13}C couplings for methylquinoline derivatives have been reported.

1.6 ^{1}H N.M.R. SPECTRAL STUDIES OF QUINOLONES

1.6.1 TAUTOMERISM AND BONDING IN QUINOLONES

The tautomeric equilibria of heterocyclic compounds have received much attention and comprehensive reviews by Katritzky and his co-workers[201,202] and a review by Beak[203] have appeared. It is not proposed to discuss here the available evidence for the establishment of the tautomeric equilibrium, since this is outside the scope of the present work. It may be concluded[201-3] that in solution in a non-polar solvent at average concentration (e.g. 5 - 10% w/v), the hydrogen bonded lactam form of 2- or 4- pyridone or quinolone is strongly favoured.

There follows a report more pertinent to the present work in which the effects of substituents upon the degree of hydrogen bonding present is reviewed. In certain areas very little work upon the quinolone system has been reported, in these cases the closely related pyridone system will be considered instead.

U.V. Spectral Studies

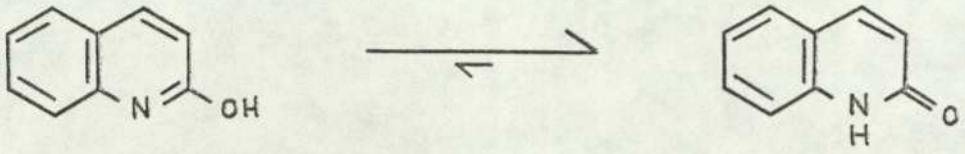
The earliest spectroscopic investigations of the quinolinol - quinolone system involved studies of their ultra-violet absorption spectra.

2-Quinolone was first studied by Hartley and Dobbie[204] as early as 1899, however, the spectra obtained were of low precision. Comparison of the spectrum of 2-hydroxyquinoline with those of the O- and N- methylated derivatives led to the conclusion that the parent compound existed in the oxo form. Although the spectral curves obtained were later shown to be inaccurate the original conclusions were upheld.

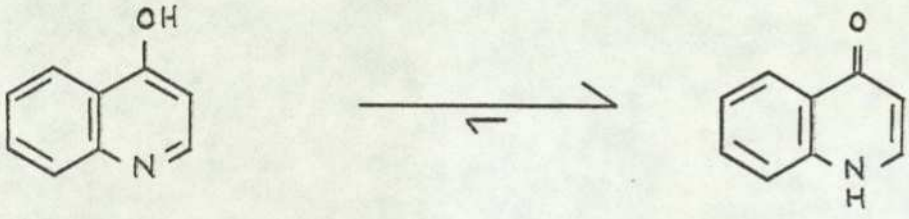
In 1942, Specker and Gawrosch proved conclusively that in methanolic solution 2- and 4- pyridone existed predominantly as the amido form by a spectral comparison with their O- and N- methyl derivatives. Furthermore, addition of alkali led to spectral changes which were ascribed to a change towards the enol form. The spectrum of 3-hydroxypyridine, however, was not greatly affected by either alkali or acid.[205]

Ewing and Steck[206] observed that the spectra of 3-, 6-, 7- and 8- quinolinols each exhibited bathochromic shifts in both acidic and basic solutions as expected of phenolic quinolines. However, 2-hydroxyquinoline (LIV), and 4-hydroxyquinoline (LV)

showed almost identical spectra in neutral, acidic and basic solution; the absence of a bathochromic shift in basic solution suggested the absence of a phenolic hydroxyl group and hence these compounds were considered to exist predominantly in the 2-quinolone (LVI) and 4-quinolone (LVII) forms. It was also concluded[206] that 4-quinolone was more phenolic in nature than 2-quinolone.



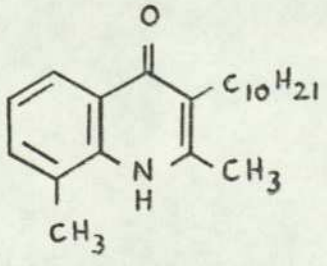
2-hydroxyquinoline (LIV) 2-(1H)-quinolone (LVI)



4-hydroxyquinoline (LV) 4-(1H)-quinolone (LVII)

In a later study[207] of a series of substituted 4-quinolone derivatives, certain 8-substituted compounds exhibited slight (unexplained) spectral differences from other isomeric compounds. Further details of the ultra-violet spectra of substituted 2-quinolones have been reported by Ricketts and Wicke,[208] however, no detailed correlations were presented.

A study of the variation of tautomeric equilibria, in 4-pyridone and 4-quinolone, with solvent polarity has recently been reported by Frank and Katritzky.[209] Since the parent compounds were sparingly soluble, 2,6-di-tertbutyl-4-pyridone and 3-decyl-2,8-dimethyl-4-quinolone (LVIII) were studied.



(LVIII)

The decyl-4-quinolone exhibited a clear sequence of decrease in extinction with solvent polarity but no significant change occurred for the parent 4-quinolone. In cyclohexane solution comparable amounts of both tautomeric forms were considered to be present.

Beak[203] determined the U.V. spectrum of 2-pyridone at very high dilution (10^{-7}M) in cyclohexane solution, 2-hydroxypyridine was detectable and an equilibrium constant of 1.6 (pyridone/hydroxypyridine) obtained. For this work a special spectrometer which accepted extra long path length cells (3 metres) was employed. Beak[203] also remarked that interpretation of solution tautomeric equilibria, measured at concentrations of greater than 0.001M, in terms of the relative stabilities of the isolated monomers was at risk unless the possible dominating effects of solvation and association had been examined.

Beak and co-workers[210] then considered the early work of Frank and Katritzky[209] and suggested that the interpretation of equilibria determined on associated material in terms of the relative energies of the monomers would be erroneous and that the proposed correlation of equilibrium constants with solvent polarity was open to question. Vapour-pressure osmometric studies[210] of 4-pyridone solutions suggested that the molecule was very strongly associated, however, direct determination of the degree of association in cyclohexane was precluded by limited solubility.

It was considered[210] that the complication of association could be removed by operation at very low concentrations, however, such an approach could render the chromophore of interest beyond the limit of detection. An alternative approach was the study of compounds such as (LVIII) which were originally chosen[209] for their improved solubility. The decyl-4-quinolone (LVIII) would be expected to be less associated than the parent heterocycle (see also later discussion) and had been shown (by vapour-phase osmometry)[210] as essentially monomeric in chloroform at the concentrations previously used[209] to measure the U.V. spectra. The correlations for the equilibrium constant of substituted systems, such as (LVIII), were therefore accorded more significance than those of the parent system.

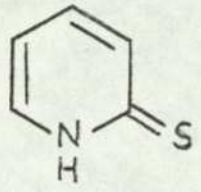
Gas-phase ultra-violet spectra have suggested that monomeric 2- and 4-

hydroxypyridines are the dominant species present.[211]

Crystallographic Studies

An X-ray crystallographic study of 2-pyridone has been reported by Penfold.[212] The bond lengths between heavy atoms were obtained from which the structure of the potentially tautomeric compound was deduced as the pyridone form. In the crystal strong hydrogen bonds linked individual molecules into endless helices.

Penfold[213] later determined the crystal structure of 2-pyridthione (LIX). The



(LIX)

arrangement of molecules in the unit cell was the same as 2-pyridone but there was, however, a fundamental difference in space such that the pyridthione molecules were linked only in pairs. This was considered to be due to weaker hydrogen bonding between nitrogen and sulphur because of the lower electronegativity of the latter compared with oxygen.

Kalman and co-workers[214] recently reported a crystal structure determination of 2-quinolone. The weakened aromatic character of the lactam ring was shown by its distorted planarity which formed a dihedral angle of 1.3° with the fairly planar benzene ring. The molecules, similarly to 2-hydroxyquinoxaline were linked together by infinite chains of hydrogen bonds (N....O = 2.80, H.....O = 1.89 Å, $\angle$ NH.....O = 167.4°) along the screw axes parallel to the shortest crystallographic axis.

From the above work it may be concluded that in the crystal, 2-pyridone and 2-quinolone are hydrogen bonded to form infinite chains.

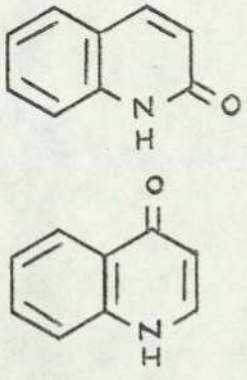
Infra-Red Spectral Studies

Infra-red spectral studies of 2- and 4- pyridone have attracted much interest but less work has been performed in the quinolone series.

In 1956, Gibson et al.[216] studied the infra-red spectra of several pyridone and

quinolone derivatives; although certain spectral data had been reported earlier, (for example upon 1-methyl-3-hydroxy-4-pyridone)[217]. The spectra of 2-pyridone, 6-methyl-2-pyridone, 3-hydroxypyridine, 2-quinolone and 4-methyl-2-quinolone were examined as potassium chloride discs, as nujol mulls and in solution in chloroform and/or carbon tetrachloride. The presence of strong $\nu_{C=O}$ absorption bands was indicative of the oxo form in all of the compounds studied, except 3-hydroxypyridine which instead exhibited an ν_{O-H} absorption. It was also noted that "the possibility that intermolecular bonding in the pyridones gave rise to the doublet around 1650 and 1670 cm^{-1} could be disregarded since dissolution in chloroform and carbon tetrachloride and dilution caused no shift or change in the intensity of these bands."

Mason[218] has studied the infra-red spectra of several N-heteroaromatic hydroxy compounds and concluded that 2- and 4- quinolones were NH --- O hydrogen bonded with distances of 2.6 - 3.0 Å between the centres. The ν_{N-H} and $\nu_{C=O}$ absorptions occurred at slightly different frequencies as indicated below:



quasi-o-quinonoid amide

ν_{N-H} 3360 - 3420 cm^{-1}

$\nu_{C=O}$ 1654 - 1687 cm^{-1}

quasi-p-quinonoid amide

ν_{N-H} 3415 - 3445 cm^{-1}

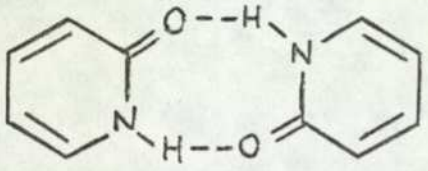
$\nu_{C=O}$ 1630 - 1645 cm^{-1}

A study of the infra-red spectra of a series of 1-methyl-2-quinolone derivatives in carbon disulphide solution has been reported by Cook *et al.*[219] Differentiation between isomeric compounds using the "fingerprint" region of the spectrum was discussed.

McCorkindale[220] carried out a thorough study of the carbonyl absorptions of 2- and 4- quinolone derivatives to secure a spectral technique to differentiate between the isomeric series. Although it was known[218] that 2-quinolones generally absorbed at 1660 - 1650 cm^{-1}, a study of a large variety of model compounds indicated that

increasing numbers of both 2- and 4- quinolone derivatives absorbed in the intermediate frequency region, viz 1647 - 1631 cm^{-1}. From a thorough study of sixty-five 2- and 4- quinolone derivatives, the 2-quinolone band was found empirically to have a characteristic shape and a high intensity, which allowed 2-quinolones to be distinguished from 4-quinolones which absorbed in the same frequency region. The technique was applied to confirm the 2-quinolone structure of certain alkaloids.

The infra-red spectra of a number of pyridone derivatives have been recorded by Katritzky and Jones,[221] tentative assignments of the bands, including a detailed assessment of the ring stretching modes, were proposed. Both pyridone series were found to be strongly hydrogen bonded, as shown by the position and broad nature of the ν_{N-H} peaks. Molecular weight determinations[222] indicated that 2-pyridone was dimeric in solution in non-polar solvents, and presumably existed as (LX).



(LX)

Bellamy and Rogasch[223] reported a similar simultaneous study of the infra-red spectrum of 2-pyridone in the solid state as a nujol mull and in carbon tetrachloride solution. In the ν_{N-H} region, the spectrum of the solid was typical of a cis-lactone and showed the main peak at 3100 cm^{-1}. The solution spectrum was different and suggested that stronger hydrogen bonds were present in the latter medium. The bonded ν_{N-H} was assigned as 2825 cm^{-1} whilst free ν_{N-H} absorbed at 3413 cm^{-1}. The subsidiary peaks were tentatively assigned in terms of overtone and combination bands. Upon deuteration the ν_{N-D} band appeared as a doublet at 2205 and 2170 cm^{-1} with some subsidiary peaks. The NH : ND ratio was low (1.29) which arose from a weaker 'hydrogen' bond in the deuterated compound in solution. The spectrum of 2-pyridthione was also examined. This compound gave spectra which were essentially the same in the solid state and in carbon tetrachloride solution from which it was assumed that the dimeric structure in the solid,[213] also persists

in solution.

A Japanese worker, Shindo,[224] also studied the infra-red spectra of a series of substituted pyridone and quinolone derivatives concurrently with the studies in England.[221,223]

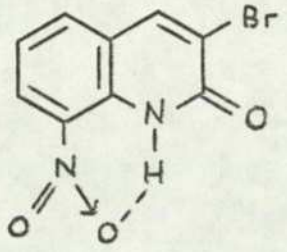
The ν_{N-H} region of the spectrum in particular was investigated with sodium chloride and lithium fluoride prisms, the latter offering higher resolution resulting in complex spectra with numerous closely spaced bands. The broad absorption from 3200 cm^{-1} to 2400 cm^{-1} was attributed to N - H stretching modes, since all the peaks disappeared on deuteration. For 2-quinolone, ν_{N-H} was at 2985 cm^{-1} and ν_{N-D} at 2283 cm^{-1}.

In dilute carbon tetrachloride solution (0.025M) a sharp band near 3400 cm^{-1} appeared which increased in intensity on further dilution, suggestive of intramolecular hydrogen bonding. Since the precise positions and relative intensities of the associated peaks did not vary, only one species of associated molecules, similar to the dimer (LX) proposed by Katritzky and Jones,[221] was considered to be present. (This dimer was suggested by reference to the crystal structure of 2-pyridone,[212] which was mistakenly considered by Shindo[224] to consist of simple dimeric units). 2-Pyridone and 2-quinolone molecules were considered to be almost completely associated, involving extremely strong hydrogen bonding, at a concentration above 0.025M in carbon tetrachloride; even at 0.0005M the associated state was still dominant.

Substituted 2-pyridone derivatives generally exhibited similar spectra to the parent compound; however, 8-substituted 2-quinolones showed entirely different behaviour in the N - H stretching region from the other isomeric derivatives and from the parent compound. In the solid state 8-methoxy- and 8-bromo- derivatives (three examples) showed a strong peak in the 3120 - 3160 cm^{-1} region and in the 2305 - 2315 cm^{-1} region on deuteration, due to normal hydrogen bonded NH (ND) absorptions. (N - H/N - D ratio = 1.34 - 1.36, characteristic of monomeric N - H, compare reference 223). These spectra did not exhibit any fine structure when examined with the lithium fluoride prism. However, in solution a strong, sharp band due to free N - H absorption in the region of 3360 - 3420 cm^{-1} was observed, even

at a concentration of 0.025M in carbon tetrachloride, indicative of intermolecular hydrogen bonding of weakened strength, comparable to that observed in carboxylic acid derivatives. This effect was considered by Shindo[224] to be due to "the steric inhibition of a bulky substituent at 8- position from the sufficient proximity of N - H group to the carbonyl group of another molecule to form a stable dimer".

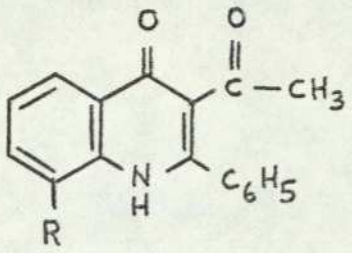
8-Nitro-2-quinolone derivatives (2 examples) exhibited only a sharp band in the 3280 - 3330 cm^{-1} region both in the solid and in chloroform solution. On deuteration a sharp band in the 2435 - 2490 cm^{-1} region appeared. These results were consistent with the formation of intramolecular hydrogen bonding as shown in (LXI), which prevented formation of intermolecular bonding.



(LXI)

Similar instances of inhibition of hydrogen bonding in 2,6-disubstituted phenols have previously been reported by Coggeshall[225] from a comparison of their ν_{O-H} absorptions.

Staskun[226] has measured the infra-red spectra of a series of 3-acetyl-2-aryl-4-quinolone derivatives, as expected the ν_{N-H} region was very broad. However, the spectra of certain 8-substituted derivatives (e.g. LXIIa) were different and instead a sharp absorption in the 3300 - 3400 cm^{-1} region was observed (free ν_{N-H}). It was suggested that in 3-acetyl-2,8-diphenyl-4-quinolone (LXIIb) the 2, 3, and 8 substituents acted together to form a combination which sterically prevented or hindered association via hydrogen bonding. No reference to the earlier work of Shindo,[224] however, was given.

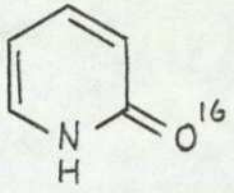


a, R = CH_3

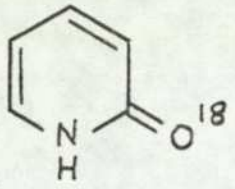
b, R = C_6H_5

(LXII)

Keller et al.[227] have studied the infra-red spectra of 2-pyridone (LXIIIa) and also of 2-pyridone-^{18}O (LXIIIb) with particular reference to the carbonyl stretching absorption, in order to verify certain spectral assignments.



(LXIIIa)



(LXIIIb)

At high concentration in chloroform solution an additional absorption at 1685 cm^{-1} and 1667 cm^{-1} for the unlabelled and labelled compounds respectively was observed. The relative intensity of this band and the other two bands attributed to C = O stretchings, 1674.5 and 1657.5 cm^{-1} were all concentration dependent.

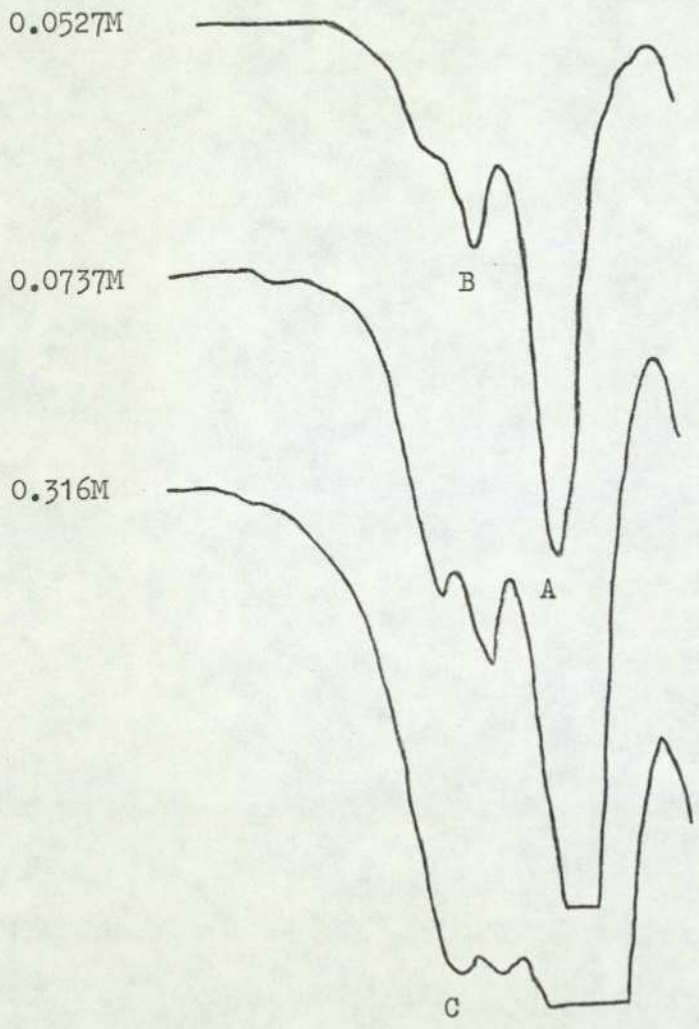
The bands were assigned as 1674.5 cm^{-1} - monomeric species; 1657.5 cm^{-1} - dimeric species; 1685 cm^{-1} - dimeric or possibly polymeric species. At low concentrations the monomer and cyclic dimer were favoured, but at higher concentration the polymeric species appeared to be favoured. This was the first instance where polymeric species had been postulated for 2-pyridone in solution, however, evidence had been reported[212] from X-ray studies for a polymer in the solid state. Moreover, the solid state spectrum[216] exhibited an absorption near 1680 cm^{-1} which could be attributed to polymeric absorption as that reported[227] in chloroform solution.

Further studies of the infra-red spectrum of 2-pyridone-^{18}O were performed simultaneously by Coburn and Dudek.[228] Their studies were performed in carbon tetrachloride solution at much lower concentrations than used by Keller et al.[227] At concentrations below 0.001M the 1673 cm^{-1} peak was the most prominent, whilst at

FIGURE 1.6.1

Concentration dependence in the infra-red spectrum of 2-pyridone-^{16}O in chloroform solution (cm^{-1})

(From ref. 227)



A - 1657.5 cm^{-1}

B - 1674.5 cm^{-1}

C - 1685.0 cm^{-1}

0.003M the shoulder at 1673 cm^{-1} and the 1656 cm^{-1} peak were of equal intensity. A weak shoulder at 1682 cm^{-1} was also observed in more concentrated solutions. Exact assignments of these peaks were not given, although their frequencies and solution dependence were similar to the earlier report,[227] the results were consistent with the formation of a very strong dimer in solution which dissociated only at very low concentrations.

Coburn and Dudek[229] also studied the spectrum of 4-pyridone-^{18}O. It was concluded that 4-pyridone was much more highly associated through hydrogen bonding than 2-pyridone. Vapour-phase osmometric measurements of dilute (0.005 - 0.01M) solutions of 4-pyridone in chloroform indicated that the measured molecular weight corresponded to a trimer.

Concurrent studies of the spectra of 2-pyridone also led Kulevsky and Reineke[230] to suggest that solutions in carbon tetrachloride above 0.0025M concentration may contain linear dimers or higher polymers or both.

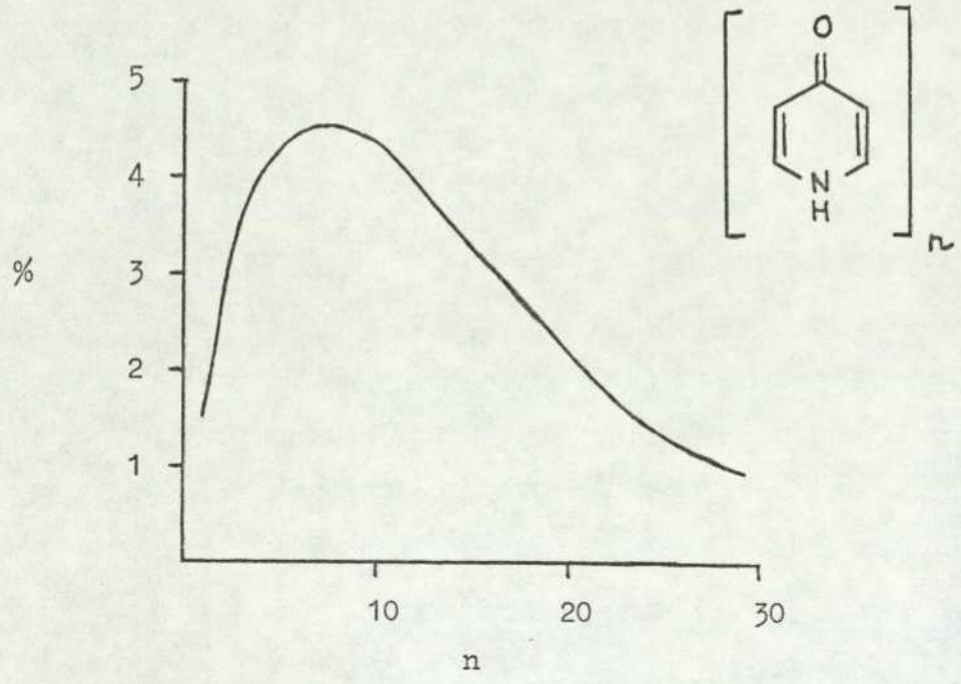
A very recent report[210] concerning the association of 4-pyridone considered that the compound was extensively self-associated in chloroform solution as determined by vapour-phase osmometry. The association was analysed as a statistical distribution of oligomers (see Figure 1.6.2) from studies of molecular weight as a function of dilution. For the above model, less than 30% of the material would be monomeric. It was noted[210] that in order to perform ultra-violet studies upon non-associated species (see earlier discussion, page 60) a compound such as 2,6-di-tertbutyl-4-pyridone originally chosen for its favourable solubility, should instead be used. Such 2,6-disubstitution could be expected to offer substantial hindrance to hydrogen bonding. Another compound suggested for study was 3-decyl-2,8-dimethyl-4-quinolone, (similarly selected previously[209] on solubility grounds). It was again considered that the substituents present in this compound might offer substantial hindrance to association by hydrogen bonding.[231] In this respect it is of interest to recall that earlier Staskun[226] had remarked that the 2, 3, and 8 substituents in the 4-quinolone together formed a combination which sterically prevented or hindered such association.

A thermodynamic study by infra-red spectroscopy of the association of 2-quinolone and 2-quinolone-acid dimers has been reported by Petersen.[232] Spectra were determined

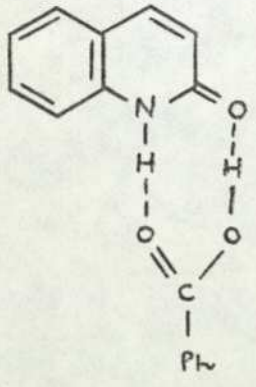
FIGURE 1.6.2

Composition of oligomers to n = 29 for 0.025M 4-pyridone in chloroform

(from reference 210)



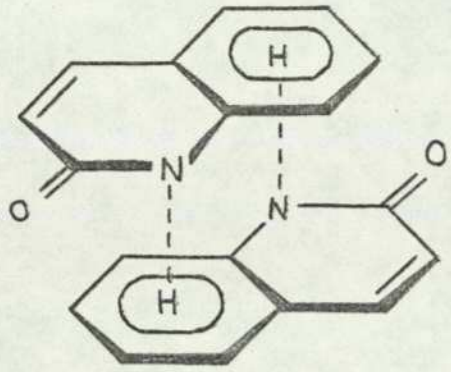
in carbon tetrachloride solution (0.00197 - 0.000197M) over the temperature range 8 - 65°. 2-Quinolone showed absorption bands at 1680 cm^{-1} (free $\nu_{C=O}$); 1664 cm^{-1} (bonded $\nu_{C=O}$) and 3400 cm^{-1} (free ν_{N-H}). The 2-quinolone-benzoic acid mixed dimer (LXIV) absorbed at 1648 cm^{-1} (quinolone $\nu_{C=O}$) and 1674 cm^{-1} (acid $\nu_{C=O}$).



(LXIV)

From a consideration of thermodynamic properties the major associated species were regarded as cyclic dimers and not linear or larger complexes. Comparison of the intensities of the free carbonyl and free N - H bands showed an excess of the former, particularly at low temperatures, furthermore a free carbonyl absorption still persisted after the free N - H band had almost vanished. The formation of

a small amount of cyclic dimer via a π-hydrogen bond (LXV) was proposed as an explanation for the excess carbonyl, since the additional existence of this dimer would cause the free N - H to decrease at a faster rate than the free C = O in accordance with the spectral results.



(LXV)

Similar associations have been reported[233] in phenolic systems in which the hydrogen of the phenolic OH formed a π-hydrogen bond with aromatics. An analogous association had also been proposed[234] for the dimerisation of pyrrole through association of the N - H proton of one molecule with the π-electron ring of the second.

Nuclear Magnetic Resonance Spectral Studies

This section is devoted only to those n.m.r. studies which have been directly concerned with the study of tautomeric equilibria and/or the extent of hydrogen bonding in pyridone and quinolone derivatives. A discussion of the remaining chemical shifts and coupling constants for these systems is presented in Sections 1.6.2 and 1.6.3 respectively.

Hampson and Mathias[235] reported the ^{14}N chemical shifts of 8-hydroxyquinoline, 2-quinolone and 4-methyl-2-quinolone with reference to the nitrate nitrogen of 4.5M ammonium nitrate in 3M aqueous hydrochloric acid solution as 95, 238 and 238 p.p.m. respectively. The shifts were consistent with the lactam structure of the quinolone (see also Section 1.7.2).

Coburn and Dudek[228] measured the ^{1}H n.m.r. spectrum of 2-pyridone-^{15}N in a series of solvents. The NH proton absorbed at -3.60 τ in carbon tetrachloride, chloroform-d, and methylene chloride and at -1.47, -2.72 and -3.17 τ respectively in dimethylsulphoxide, pyridine and acetone-d_6. Such a low field signal was

characteristic of very strong hydrogen bonding. In all cases a singlet was observed at room temperature indicative of rapid chemical exchange, when the chloroform-d solution was cooled to -56°, a 90 Hz ^{15}N - ^{1}H coupling constant was obtained which suggested that the relative amount of the lactim form was below 2%.

Similar studies were later reported[229] with 4-pyridone-^{15}N. The NH proton appeared as a singlet at -3.92 τ in chloroform-d. The absence of coupling to the nitrogen-15 nucleus, even in dimethylsulphoxide, was taken as an indication of rapid chemical exchange. Poor solubility prevented low temperature studies in chloroform solution.

Cox and Bothner-By[236] examined the ^{1}H n.m.r. spectra of 2-pyridone and the corresponding protonated species in a series of solvents. The NH proton appeared at -2.05 τ (presumably in chloroform solution) which suggested the presence of hydrogen bonded dimers. An increase in the magnitude of the J_{34} and J_{56} coupling constants was also observed for the 2-pyridone series compared with the corresponding pyridine derivatives as a consequence of the increased double bond character between these positions required by the lactam tautomer. (See also section 1.6.3).

N.m.r. studies of other 2-pyridone derivatives have been reported by Bell et al.[149] In all cases the NH protons absorbed at very low field (-3.17 - 3.43 τ) in chloroform-d solution.

Diaz and Joseph-Nathan[120] determined the spectra of quinoline, 8-hydroxyquinoline and 2-methyl-4-quinolone, in acetic acid and trifluoroacetic acid solution. The H-3 signal of the last named compound showed a significant upfield shift (ca. 1 p.p.m.) in both solvents which was attributed to the smaller degree of aromatic character consistent with the 4-quinolone structure.

Other Studies

From a study of resonance energies (by pK_a methods) the differences in aromaticity between lactim and lactam forms was found to be significantly less for the 2-quinolone series than for the pyridones.[237]

1.6.2 N.M.R. SPECTRAL STUDIES - CHEMICAL SHIFTS

Although much data is available on the nuclear magnetic resonance spectra of quinoline derivatives, reports of spectral studies on the quinolone systems are scarce. However, some detailed studies of the related 2- and 4- pyridone systems have been performed and collections of spectral data have been compiled and discussed.[135,136]

An introductory discussion concerning the spectra of 2- and 4- pyridone derivatives will first be presented, representative chemical shifts are shown in Table 1.6.1.

The formation of an exocyclic double bond at positions 2- and 4- of the pyridine ring and the resulting substitution on N-1 causes disruption of the aromatic system. This loss of aromaticity is evident from the n.m.r. spectra, such that pyridone derivatives exhibit spectra which more closely resemble extended polyene systems than those of true pyridines. This is particularly evident from the chemical shift of H-3 which exhibits a characteristic upfield shielding effect.

Elvidge and Jackman[240] defined an aromatic compound as one which could sustain a ring current. Their calculations, which included a number of inherent uncertainties, suggested that 2-pyridone had about 35% of the aromatic character of benzene, which corresponded to a stabilisation of 12-15 K cal./mole.

As discussed previously (see Section 1.6.1) the low field shift of the NH was indicative of hydrogen bonding.

N.m.r. spectral data for quinolone derivatives are very scarce and a collection of the available chemical shifts is given in Table 1.6.2. The information for the 4-quinolone system is particularly sparse. The apparent lack of data is probably a reflection of the limited solubility of quinolone derivatives in the more usual n.m.r. solvents, hence many authors have employed trifluoroacetic acid as solvent, and accordingly chemical shift data for the NH proton was lost. Apart from the information assembled by Buchardt and Kemler[243] for the identification of some 2-quinolone derivatives obtained from photochemical syntheses, no substantial spectral study has been performed. Most of the references are to isolated reports in which spectra were determined only for identification or comparative purposes. Consideration of the available data shows that the NH signal appeared at very low field (-3.42 to

TABLE 1.6.1

N.m.r. Chemical Shifts for 2- and 4- Pyridone

Compound	Chemical Shift (τ) NH	H-2	H-3	H-4	H-5	H-6	Ref.
2-pyridone ($DMSO-d_6$)	-1.17	-	3.65	2.59	3.85	2.65	238
4-pyridone ($DMSO-d_6$)	-1.10	2.22	3.73	-	3.73	2.22	238
pyridine (CCl_4)	-	1.48	2.84	2.46	2.84	1.48	239

TABLE 1.6.2

N.M.R. Chemical Shifts of 2- and 4- Quinolone Derivatives (excluding 1-substituted compounds)

Substituted Quinolone	Solvent	Chemical Shift (τ) H-3	H-2 or H-4	H-5	H-6	H-7	H-8	NH	CH_3	Ref.
2-quinolones										
nil	$CDCl_3$	3.35 (b)	2.27 (b)	← 2.36 - 2.71 →				-2.6	-	241
nil	DMSO-d_6			2.23	2.71	2.39	2.53			242
nil	TFA	2.55	1.23	← 2.0 (a) →				-		243
nil	DMSO-d_6	3.43	2.09					-1.78		244a
3-Me	TFA	-	1.50	← 2.1 (a) →				-	7.45	243
3-Et	TFA	-	1.48	← 2.1 (a) →				-	8.53 (CH_2 7.00)	243
3-Br	TFA	-	1.45	← 2.4 (a) →				-	-	243
4-Me	TFA	2.67	-	← 2.0 (a) →				-	7.03	243
4-Me	DMSO-d_6	3.36	-	← 2.40 (a) →				-1.82	7.46	245
4-Me	DMSO-d_6	3.50	-	← 2.13 - 2.78 →				-2.3	7.51	137a
4-Me	DMSO-d_6	3.58	-	2.25 (c)	← 2.6 (a) →				7.57	246
4-Me	$CDCl_3$								7.47	149
4-Cl	TFA	2.72	-	← 2.3 (a) →				-		243
4-Br	TFA	2.53	-	← 2.1 (a) →				-		243
4-CH_2CH_2Ph	DMSO-d_6							-2.20		245

Cont....

TABLE 1.6.2 (Cont.)

Substituted Quinolone	Solvent	Chemical Shift (τ) H-3	H-2 or H-4	H-5	H-6	H-7	H-8	NH	CH_3	Ref.
4-C_5H_{11}	DMSO-d_6							-2.14		245
4-CH_2CHMe_2	DMSO-d_6							-3.42		245
5-Me	TFA	2.65	1.13	←	2.2 (a)		→	-	7.22	243
6-Me	TFA	2.60	1.33	←	2.2 (a)		→	-	7.37	243
6-Cl	TFA	2.73	1.58	←	2.2 (a)		→	-		243
6-Br	TFA	2.80	1.63	←	2.2 (a)		→	-		243
6-OCH_3	TFA	3.17	1.52	←	2.6 (a)		→	-	6.02	243
7-Me	TFA	2.75	1.43	←	2.3 (a)		→	-	7.37	243
7-Cl	TFA	2.83	1.57	←	2.3 (a)		→	-		243
8-Me	$CDCl_3$	3.36 (b)	2.24 (b)	←	2.50 - 3.04		→	0.0	7.46	241
8-Me	TFA	2.63	1.37	←	2.2 (a)		→	-	7.22	243
8-Cl	$CDCl_3$	3.34 (b)	2.34 (b)	←	2.36 - 2.97		→	0.8		241
8-OCH_3	TFA	2.70	1.45	←	2.5 (a)		→	-	5.87	243
5,8-Me_2	$CDCl_3$	3.47 (b)	2.17 (b)		2.91/3.21 (d)				7.54	241
6,8-Me_2	$CDCl_3$	3.45 (b)	2.40 (b)	2.92	-	2.92	-	-0.2	7.51 7.65	241
4-CH_3-6-OCH_3	TFA	2.87	-	←	2.4 (a)		→	-	7.15 OCH_3 5.97	243

Cont....

TABLE 1.6.2 (Cont.)

Substituted Quinolone	Solvent	Chemical Shift (τ) H-3	H-2 or H-4	H-5	H-6	H-7	H-8	NH	CH_3	Ref.
4-quinolones										
nil	DMSO-d_6			2.00	2.79	2.45	2.52			242
nil	D_2O/DCl	3.01	1.45	←	1.97 - 2.64		→	-		137b
2-Me	DMSO-d_6/$CDCl_3$	3.91	-	1.76	← 2.21 - 2.87		→	-1.75	7.55	137c
2-Me	TFA	2.76	-	1.91	1.91	2.11	1.43	-		120
2-Me	AcOH	3.31	-	2.24	2.24	2.50	1.80	-		120
2,3-Cyclopenteno	DMSO-d_6			1.80 (c)	←	2.6 (a)	→	-1.97	$(CH_2)_2$ 7.12 CH_2 7.90	246

NOTES

(a) Centre of aromatic multiplet.

(b) H-3 and H-4 assigned in reverse.

(c) Signal assigned to either H-5 or H-8

(d) Assignments to H-5/H-7 not given.

-1.75 τ) in chloroform-d or dimethylsulphoxide-d_6 solution, with the exception of certain 8-substituted derivatives reported by Johnston et al.[241] which absorbed in the -0.2 to 0.8 τ region. No explanation has been offered for these upfield shifts.

The signal for H-3 in the lactam ring of both 2- and 4-quinolone occurred at high field, as experienced[238,239] with the respective pyridone compounds. From the limited data available H-3 appears to be generally further upfield in 4-quinolones than in 2-quinolones. Buchardt et al.[243] reported the spectra of a number of 2-quinolone derivatives obtained in trifluoroacetic acid solution, but no discussion was offered. Both H-3 and H-4 exhibit downfield shifts, since protonation occurs in this medium. Similar results for the 4-quinolone series have been described by Diaz and Joseph-Nathan.[120]

An interesting effect, evident in the reported[243] spectrum of 5-methyl-2-quinolone is a characteristic peri-deshielding effect of H-4. A similar effect may also be observed in the reported spectrum[241] of 5,8-dimethyl-2-quinolone in chloroform-d solution.

In the 4-quinolones, from the limited data available, H-5 appears to be similarly deshielded by the peri-carbonyl group which could present a possible method for differentiation between the two quinolone series, (see also page 63).

4-Quinolone derivatives have generally received very little attention, presumably due to their extremely limited solubilities. Introduction of suitable substituents, particularly long aliphatic chains, has been found to improve solubility as demonstrated by Frank and Katritzky[209] in their U.V. spectral studies with 3-decyl-2,8-dimethyl-4-quinolone in chloroform solution. Replacement of the NH group by N - CH_3 would also be expected to result in greatly improved solubility.

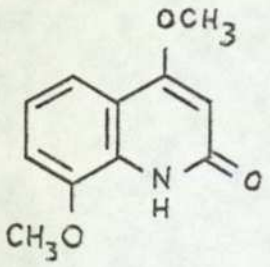
Quinolone alkaloids

Certain quinolone derivatives occur naturally. Over 130 quinolone alkaloids of established structure have been isolated from rutaceous plants and the natural products containing the 2- and 4-quinolone nucleus have recently been reviewed.[247]

Very few alkaloids containing the basic 2- or 4- quinolone nucleus (i.e. with preservation of the NH group) are known. Such compounds also contain additional methoxy groups on the quinolone ring, and all include a 4-methoxy substituent.

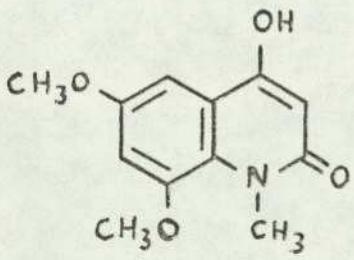
Establishment of their structures has previously presented some difficulties.

Edulitine was first isolated by Sondheimer and co-workers[248] in 1956, it was shown to have molecular formula $C_{11}H_{11}O_3N$ and to contain two methoxy groups, and a hydroxydimethoxyquinoline structure was proposed. On the basis of spectral data (I.R., U.V., M.S. and N.M.R.), Toube, Murphy and Cross[249] deduced that the compound was 4,8-dimethoxycarbostyril (LXVI). The NH proton gave a broad signal at 1.1 τ in chloroform-d solution, (see also Section 1.6.3). The structure of the alkaloid was later confirmed by unambiguous synthesis.[250,251] The n.m.r. spectrum of the synthetic and natural materials were identical.[250]

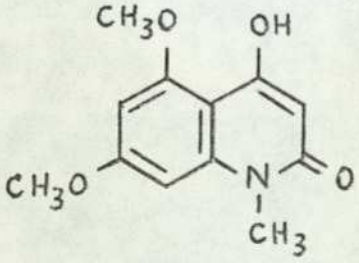


(LXVI)

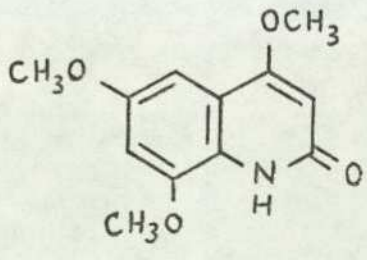
Crow and Hodgkin[252] isolated an alkaloid from halfordia kendack which was named halfordamine. From the spectral data (I.R., U.V., M.S. and N.M.R.) the structure of the compound was proposed as either (LXVIIa or LXVIIb), each of which contained a 1,3-dimethoxybenzene nucleus, however, a definitive conclusion could not be drawn other than that (LXVIIa) was preferred.



(LXVIIa)



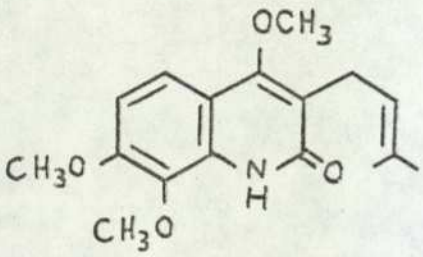
(LXVIIb)



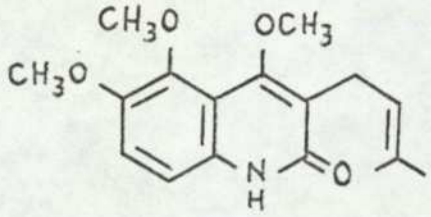
(LXVIII)

Further consideration of the spectral data later led to the suggestion[253,254] that halfordamine was probably 4,6,8-trimethoxy-2-quinolone (LXVIII). That the compound was not the 4,5,7-trimethoxy derivative was confirmed by an independent synthesis commencing from 2,4-dimethoxyaniline. The n.m.r. spectrum[252] of the natural product (solvent not stated) exhibited an exchangeable hydrogen at 0.32 τ However, the n.m.r. spectrum of the synthetic sample[255] was taken in trifluoroacetic acid and hence did not exhibit an NH peak, (see also Table 1.6.3).

After an investigation of the roots of dictamnus albus L, Storer and Young[256] isolated an alkaloid which was named preskimmianine. Consideration of spectral data led to the conclusion that the alkaloid had either structure (LXIXa) or (LXIXb).

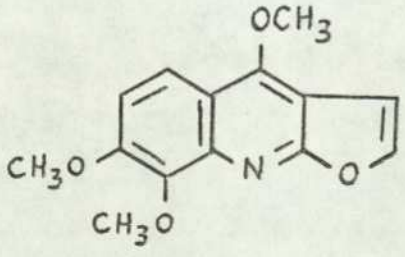


(LXIXa)



(LXIXb)

Since structure (LXIXa) possessed a similar methoxyl substitution pattern to the furanoquinoline alkaloid skimmianine (LXX), it was considered that this was the more likely structure which was then verified by synthesis.



(LXX)

The n.m.r. spectra (in chloroform-d) of the natural and synthetic[257] materials were identical, each with an exchangeable N - H proton at 0.85 τ , (see also Table 1.6.3).

TABLE 1.6.3

N.M.R. Spectra of Some 2-Quinolone Alkaloids

Compound	Chemical Shift (τ) NH	H-3	H-5	H-6	H-7	OCH_3	Ref
edulitine (a)	1.1	4.04	←	2.43 - 3.13	→	6.05 6.06	250
halfordamine (b)	0.32	4.05		3.15/3.37 (c)		6.05 6.08 6.16	252
preskimmianine (a)	0.85	-		2.52/3.15 (c)		6.03 6.03 6.06	257

NOTES (a) In $CDCl_3$.

(b) Solvent not specified.

(c) Precise assignments not specified - see discussion.

Wratten et al.[258] have examined a marine pseudomonad which demonstrated antibiotic activity and obtained two novel antibacterial compounds which were identified as 2-n-pentyl-4-quinolone and 2-n-heptyl-4-quinolone, however, no n.m.r. data was given.

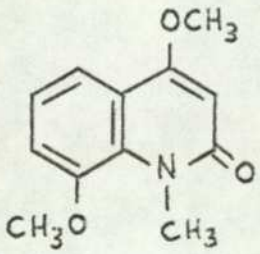
2- and 4- quinolone alkalcids which possess a N - CH_3 function in place of the N - H group, are more numerous,[247] and certain examples have been collected in Figure 1.6.3. The n.m.r. spectra of these alkaloids have been briefly reviewed,[264] and a compilation of representative chemical shifts is included in Table 1.6.4.

The present author is unaware of any systematic study of the methyl chemical shifts of 1-methyl-2-quinolone derivatives. Details of the few reported chemical shifts of simple derivatives are included in Table 1.6.4.

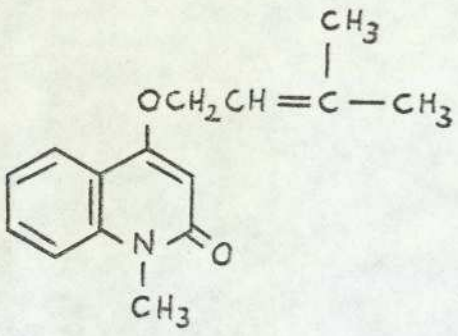
The N - CH_3 protons absorb in a narrow region (6.1 - 6.46 τ) and appear to

FIGURE 1.6.3

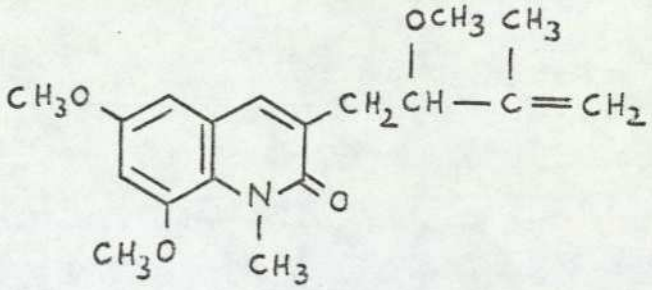
Examples of 1-methyl-2-quinolone alkaloids



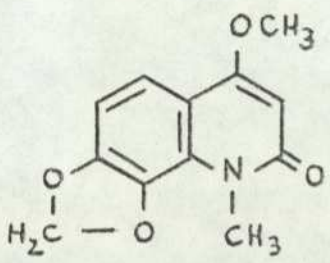
Folimine[259]



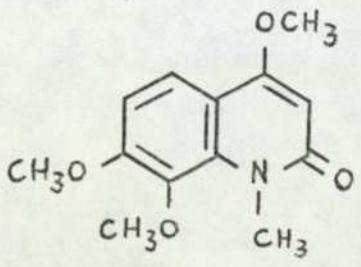
Ravenine[260]



Ptelefoline methyl ether[261]



Casimiroine[262]



4,7,8-trimethoxy-1-methyl-2-quinolone[263]

be comparatively unaffected by variation of solvent. Differentiation between N - CH_3 and O - CH_3 signals (the latter occur at 6.06 and 6.20 τ) has presented some difficulties, (see Table 1.6.5). The lactam ring proton occurs in a similar upfield position to that in the 2-(1H)-quinolone series.

Spectra of simple 1-methyl-4-quinolone derivatives are very limited. A consideration[247] of the n.m.r. spectra of a series of 1-methyl-4-quinolone alkaloids has suggested that these compounds may be differentiated from the 2-quinolone series by consideration of the H-5 signal which was characteristically deshielded by the adjacent carbonyl group.

TABLE 1.6.4

N.M.R. Spectra of some 1-methyl-2- (and 4-) quinolone derivatives including certain alkaloids (a)

Substituted Quinolone	Solvent	Chemical Shift (τ) H-2 or H-4	H-3	H-5	H-6	H-7	H-8	N-CH_3	Other	Ref.
2-quinolones										
nil	$CDCl_3$	-	-					6.32		265
nil	TFA	-	-					5.66		265
nil	DMSO-d_6	2.05	3.33	←	2.1 - 2.9		→	6.35		266
nil	$CDCl_3$	2.36	3.32					6.30		267
nil	AcOH	2.18	3.19					6.30		268
nil	D_2SO_4/AcOH	1.32	2.48					5.78		267
3-Me	$CDCl_3$	(b)	-	←	2.4 - 3.1 (b)		→	6.25	CH_3 7.72	268
4-Me	DMSO-d_6	-	3.42	2.73 (c)	← ~ 2.6		→	6.33	CH_3 7.57	246
4-Me	$CDCl_3$	-	3.55	←	2.8 - 3.1		→	6.46	CH_3 7.67	269
4-MeO	$CDCl_3$	-	3.95	1.97	← 2.23 - 2.85		→	6.35	OCH_3 6.06	270
folimine	$CDCl_3$ (?)	-	4.06	2.55	3.03	3.03	-	6.20	OCH_3 6.20	259
ravenine	$CDCl_3$ (?)	-	3.93	←	1.9 - 2.82		→	6.35	OCH_2 5.36	260
ptelefoline methyl ether	- (d)		-		3.1/3.3 (e)			6.1 (e)	OCH_3 6.07 (e)	261
Casimiroine	$CDCl_3$	-	4.08	2.43	3.20	-	-	6.17 (e)	OCH_3 6.08 (e) OCH_2O 3.93	271
4-quinolones										
2-MeO	$CDCl_3$	-	4.20	1.62	← 2.30 - 2.85		→	6.41	OCH_3 6.11	270

TABLE 1.6.4 (Cont.)

NOTES

(a) Side chain protons other than CH_3, OCH_3 etc. have not been included for certain alkaloids.

(b) H-4 included in aromatic multiplet.

(c) Assigned to H-5 or H-8.

(d) Solvent not specified.

(e) Not specifically assigned.

1.6.3 N.M.R. SPECTRAL STUDIES - COUPLING CONSTANTS

As previously mentioned in Section 1.6.2 above, although much data is available on the n.m.r. spectra of quinoline derivatives, reports of spectral studies on the quinolone series are scarce. However, some detailed studies of the related 2- and 4- pyridone systems have been performed and collections of spectral data have been compiled and discussed.[135,136b]

A short introduction concerning 2- and 4- pyridone derivatives will first be presented, representative coupling constants are shown in Table 1.6.5.

The formation of an exocyclic double bond at the 2- or 4- position of the pyridine ring, and the resulting substitution on N-1 causes disruption of the aromatic ring. This loss of aromaticity is evident from the n.m.r. spectrum, such that variations of the magnitudes of coupling constants compared with pyridine result.

Such effects were first discussed for 2-pyridones by Cox and Bothner-By.[236] For normal 2-substituted pyridines J_{34} was 7.98 - 8.38 Hz which increased to ca. 9.2 Hz in the 2-pyridones. Similarly, J_{56} was 4.83 - 5.24 Hz in the normal 2-substituted pyridines, and 6.51 - 6.76 Hz in the 2-pyridones. The increase in magnitude for J_{34} and J_{56} in the 2-pyridones compared to their values in other 2-substituted pyridines was the expected trend since the 2-pyridones have more double bond character between these positions than the normal aromatic pyridines.

Vögeli and von Phillipsborn[238] later confirmed the earlier observations,[236] and further commented that J_{45} decreased in the 2-pyridones. In addition in the 4-pyridone series, which did not form part of the earlier study,[236] a similar increase of J_{23} was observed. These increases were all compatible with the expected π-bond order alternation in the pyridone series.

An earlier study of 2- and 4- pyridone derivatives had been performed by Bell et al.[149] Although similar ring coupling constants were obtained their significance was not discussed since the work was mainly concerned with long range couplings at the methyl groups. Such coupling only occurred between methyl protons and one ortho- and the para- ring protons. The selective ortho-coupling occurred across bonds with increased π-character as illustrated by 4-methyl-2-pyridone

TABLE 1.6.5

Coupling Constants for 2- and 4- pyridone (Hz)

Coupling Constant	2-pyridone[238] ($DMSO-d_6$)	4-pyridone[238] ($DMSO-d_6$)	pyridine[239] (CCl_4)
J_{23}	-	7.15	4.86
J_{34}	9.3	-	7.66
J_{45}	6.6	-	7.66
J_{56}	6.55	7.15	4.86
J_{25}	-	0.25	0.98
J_{26}	-	1.5	-0.13
J_{35}	1.2	2.7	1.36
J_{36}	0.75	0.25	0.98
J_{46}	2.2	-	1.85

($J_{CH_3.H-3}$ = 0.8 Hz) and 5-methyl-2-pyridone ($J_{CH_3.H-6}$ = 1.0 Hz).

Very few studies of coupling constants for 2- and 4- quinolone derivatives have been undertaken. The available data has been assembled in Table 1.6.6 and represents a collection of isolated reports mainly determined for structural identification with no discussion of the significance of the parameters. Data for coupling constants determined for certain 2-quinolone alkaloids have also been included in Table 1.6.6.

Inspection of the data in Table 1.6.6 indicates that the ortho couplings in the lactam ring (J_{23} and J_{34}) are increased compared with their respective values in quinoline. These coupling constants for the quinolone derivatives are similar to the increased values observed[236,238] with 2- and 4- pyridone, see Table 1.6.5.

Long range allylic coupling between the 4-methyl protons and H-3 has also been observed in 4-methyl-2-quinolone, across a bond with increased π-electron character, similar effects have been noted in the pyridone series.[149]

Further correlations and discussion on coupling constants in the carbocyclic ring are hampered through lack of sufficient data.

TABLE 1.6.6

Coupling constants reported for 2- and 4- quinolone derivatives

Compound	Solvent	Coupling Constants (Hz) J_{23}	J_{34}	J_{56}	J_{57}	J_{67}	$J_{CH_3 \cdot H\text{-}4}$	Ref.
2-quinolone	$CDCl_3$		9.0					241
"	TFA		9					243
1-Me-2-quinolone	DMSO-d_6		9.7					266
4-Me-2- "	$CDCl_3$						1.3	149
4-Me-2- "	DMSO-d_6						1.1	246
4-Me-2- "	DMSO-d_6						ca. 1	137a
1,4-Me_2-2-quinolone	DMSO-d_6						1.1	246
4-MeO-1-Me- "	$CDCl_3$			7.5	2			270
5-Me- "	TFA		9					243
6-Me- "	TFA		9					243
7-Me- "	TFA		9					243
8-Me- "	TFA		9					243
8-Me- "	$CDCl_3$		9.6					241
5,8-Me_2 "	$CDCl_3$		9.0			6.3		241
6,8-Me_2 "	$CDCl_3$		9.3					241
preskimmianine	$CDCl_3$			9 (a)				257
halfordamine	TFA				2 (a)			255

Cont.....

TABLE 1.6.6 (Cont...)

Compound	Solvent	Coupling Constants (Hz) J_{23}	J_{34}	J_{56}	J_{57}	J_{67}	$J_{CH_3 \cdot H-4}$	Ref.
halfordamine	- (b)				3 (a)			252
ptelefoline Me ether	- (b)				2.5 (a)			257
4-quinolone	D_2O/DCl	~7						137b
2-MeO-1-Me-4-quinolone	$CDCl_3$			7.5	2			270

NOTES

Many other 2-quinolone derivatives also show J_{34} = 9 Hz in TFA (see ref. 243).

(a) Not assigned in original, (two coupling constants possible).

(b) Not specified.

1.7 ^{13}C AND NITROGEN N.M.R. SPECTRAL STUDIES OF QUINOLONES

1.7.1 ^{13}C N.M.R. SPECTRAL STUDIES

Carbon-13 N.M.R. spectra of pyridone derivatives have attracted some interest, [238,272a,273-6] however, as far as the present author is aware, no reports of similar studies of quinolone derivatives had been reported at the outset of the present work.

The ^{13}C n.m.r. spectrum of 2-pyridone (LXIII) was first reported in 1972 by Johnson and Jankowski[272a] as part of their spectral compilation. The spectrum was determined by pulsed techniques in chloroform-d solution. The carbonyl carbon appeared at 165.3 δ , but the remaining signals were only tentatively assigned. Signals at 106.7 and 120.1 δ were ascribed to C-5/C-3 (or vice versa) whilst the peaks at 134.8 and 141.6 δ were ascribed to C-4/C-6 (or vice versa).

A simultaneous report by Miyajima et al.[273] included reversed assignments for the C-3 (107.5 δ) and C-5 (121.6 δ) signals for 2-pyridone in dimethylsulphoxide-d_6 solution. Attempts to correlate the observed shifts with other pyridine derivatives led to anomalous results due to assignment discrepancies.

A later study by Turner and Cheeseman[274] included the ^{13}C n.m.r. spectra of 2- and 4-pyridone determined in carbon disulphide solution. The earlier assignments for 2-pyridone were tabulated and the revised assignments for C-3/C-5 suggested by Miyajima et al.[273] were supported. The original tentative assignments for C-4 and C-6 suggested by Johnson and Jankowski[272a] were reversed and given as 135.6 δ (C-6) and 141.3 δ (C-4). These reversed assignments were supported by determination of $^{1}J_{CH}$ coupling constants, that for $J_{6,6}$ (179 Hz) was greater than that for $J_{4,4}$ (159 Hz) in common with results for pyridine derivatives.[239] A thorough study of the ^{13}C n.m.r. spectra of the isomeric 1H-pyridones, 1-methyl pyridones and methoxypyridines has been reported by Vögeli and von Philipsborn.[238] Further revisions to the assignments for 2-pyridone were suggested such that the original assignments for C-3/C-5 suggested by Johnson and Jankowski,[272a] and the reversed assignment for C-2/C-6 as suggested by Turner and Cheeseman[274] were favoured. In each case the assignments were confirmed by determination of $^{1}J_{CH}$ coupling constants.

Takeuchi and Dennis[275] later reported the proton coupled spectra of 2- and

4- pyridone and determined a number of long range coupling constants (^{13}C - ^{1}H). From the multiplicities of the signals obtained the corrected assignments given by Vögeli and von Philipsborn[238] were confirmed.

A summary of the literature values for the chemical shifts of 2- and 4- pyridone is given in Table 1.7.1, which includes revised assignments of earlier values based on the later work.

TABLE 1.7.1

^{13}C n.m.r. chemical shifts for 2- and 4- pyridone (a)

Compound	Solvent	C-2	C-3	C-4	C-5	C-6	Ref.
2-pyridone	DMSO-d_6	162.3	119.8	140.8	104.8	135.2	238
"	"	163.3	120.7	141.8	105.8	136.2	275
"	$CDCl_3$	165.3	120.1	141.6 (6)	106.7	134.8 (4)	272a
"	DMSO-d_6	165.0	121.6 (5)	143.3 (6)	107.5 (3)	137.1 (4)	273
"	CS_2	163.1	120.0 (5)	141.3	105.4 (3)	135.6	274
"	Me_2CO	165.0	121.0	142.3	106.7	136.2	276
4-pyridone	DMSO-d_6	139.8	115.9	175.7	115.9	139.8	238
"	"	140.6	117.0	177.1	117.0	140.6	275
"	CS_2	140.0	116.1	176.4	116.1	140.0	274
"	Me_2CO	141.6	116.7	176.4	116.7	141.6	276

NOTE (a) numbers in parentheses denote carbon atom to which the peak was incorrectly assigned in the original work.

Vögeli and von Philipsborn[238] and Stefaniak[276] have noted the variations between the ^{13}C n.m.r. spectra of 2- and 4- pyridone and that of 3-hydroxypyridine and have commented upon the value of ^{13}C n.m.r. spectroscopy as a quantitative tool for the assessment of tautomerism and aromaticity.

The ^{13}C n.m.r. spectra of 2- and 4- pyridthione in chloroform solution have been determined by Still *et al.*[277] The chemical shifts and $^{1}J_{CH}$ coupling constants were

generally similar to their oxygenated counterparts except that the range of the aromatic chemical shifts was smaller. The chemical shifts of the thiocarbonyl group were further deshielded compared to the appropriate pyridone derivatives, viz: 2-pyridthione - 176.4 δ ; 4-pyridthione - 189.8 δ , however, the difference (ca. 14 δ) between the two series was similar.

Several workers have measured $^1J_{CH}$ coupling constants as an aid to spectral assignments, particularly to distinguish between C-4 and C-6 in 2-pyridone.[238,274,275] The results obtained are summarised in Table 1.7.2.

Table 1.7.2

^1J (^{13}C - ^1H) coupling constants in pyridone derivatives.

Compound	^1J (^{13}C - ^1H) (Hz)					
	J_{22}	J_{33}	J_{44}	J_{55}	J_{66}	Ref.
2-pyridone	-	165	159	170	180	238
"	-	165	158	170	179	275
"	-	165 (a)	159	174 (a)	179	274
4-pyridone	180	160	-	160	180	238
"	179	164	-	164	179	275
"	178	164	-	164	178	274

NOTE (a) J_{33}/J_{55} assigned in reverse in original work

Takeuchi and Dennis[275] have also measured long range coupling constants for 2- and 4- pyridones. From the more complex nature of the high field signal at 105.8 δ , this resonance was ascribed to C-5. Since the signal at 120.7 δ only exhibited one long range coupling it was readily ascribed to C-3 to confirm the assignments of Vögeli and von Philipsborn.[238] The results obtained are shown in Table 1.7.3.

As in the pyridine series,[181] three bond long range couplings were generally larger than the two bond interactions. The variation of long range couplings in

TABLE 1.7.3

Long range ^{13}C - ^{1}H coupling constants in 2- and 4- pyridone (from ref. 275)

Signal	Multiplicity and splitting pattern (Hz)					
	2-pyridone			4-pyridone		
C-2	oct.	$^{3}J_{2,6}$	10	dd	$^{3}J_{2,6}$	10
		$^{3}J_{2,4}$	7		$^{2}J_{2,3}$	3
		$^{2}J_{2,3}$	2			
C-3	d	$^{3}J_{3,5}$	6	t	$^{3}J_{3,5}$	4
					$^{2}J_{3,2}$	4
C-4	dd	$^{3}J_{4,6}$	8	t	$^{3}J_{4,2}$	8
		$^{2}J_{4,3}$	2		$^{3}J_{4,6}$	8
C-5	oct.	$^{3}J_{5,3}$	8	t	$^{3}J_{5,3}$	4
		$^{2}J_{5,6}$	3*		$^{3}J_{5,6}$	4
		$^{2}J_{5,4}$	2*			
C-6	dd	$^{3}J_{6,4}$	8	dd	$^{3}J_{6,2}$	10
		$^{2}J_{6,5}$	5		$^{3}J_{6,5}$	3

* - assignments may be reversed.

the pyridine and pyridone rings were compared and discussed.[275]

As far as the present author is aware no reports of ^{13}C n.m.r. spectral studies of quinolone derivatives had been reported when the present work was initiated. Reports of the ^{13}C n.m.r. spectra of some condensed quinolone alkaloids including meloscine (LXXI)[278,279] and melochinone (LXXII)[280] have appeared.

1.7.2 NITROGEN N.M.R. SPECTRAL STUDIES

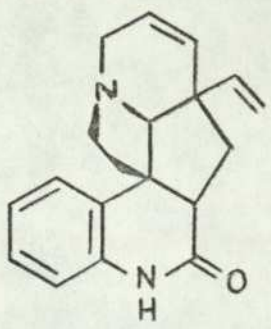
Hampson and Mathias[235] have reported ^{14}N chemical shifts for quinoline, 2-quinolone and 4-methyl-2-quinolone which clearly support the quinolone structure, (see Section 1.6.1).

Similar studies have also been reported[276,281] in the pyridone series. The ^{14}N chemical shifts for pyridine and 3-hydroxypyridine have been determined as 63 and 85 p.p.m. whilst for 2- and 4- pyridone the shifts were 209 and 201 p.p.m. respectively.[281]

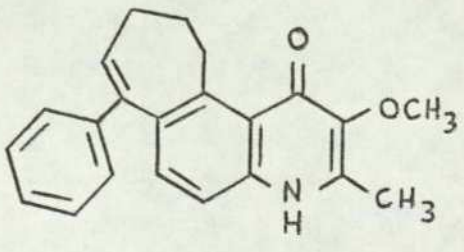
3-Hydroxypyridine also gave a significantly broader peak than the pyridone derivatives.[276]

Details of the studies[228,229] of ^{15}N - ^{1}H coupling constants for 2- and 4-pyridone have been previously discussed in Section 1.6.1. No studies of N - ^{1}H coupling constants have yet been reported for the quinolone series, however, a one-bond ^{15}N - ^{1}H interaction for the quinolinium ion in fluorosulphonic acid solution of 96 Hz has been determined.[282]

The present author is unaware of any studies of the ^{15}N n.m.r. spectra of pyridone or quinolone derivatives. This is undoubtedly due to the poor solubility of these compounds and the prohibitive costs of ^{15}N - enriched materials.



(LXXI)



(LXXII)

CHAPTER 2

OBJECT OF RESEARCH

This work originated with the requirement for certain alkylquinoline derivatives as authentic reference materials for gas-liquid chromatography. Reference to the literature revealed a wide divergence of physical properties for certain compounds and for their simple functional derivatives, whilst the synthetic pathways to other compounds required multi-stage sequences.

Since it has been noted by several workers that reliable physical properties were an essential requisite for the identification of quinoline derivatives obtained through degradation of natural products, the present work was initiated with the aim of securing such constants.

Furthermore, the claim that a number of well known syntheses were of general applicability was applied experimentally with the aim of providing more direct routes to difficultly accessible quinoline derivatives. The confused nature of the literature regarding orientation effects in the synthesis of quinoline derivatives, particularly in the presence of substituents in the heterocyclic ring, has also been thoroughly re-investigated to provide reliable quantitative results.

A survey of the n.m.r. spectral literature has shown that detailed, standardised information for quinoline and quinolone derivatives was scarce. ^{1}H n.m.r. spectral parameters for a series of methyl substituted 2- and 4- quinolone derivatives were therefore determined to provide reliable information for possible diagnostic purposes.

No ^{13}C n.m.r. spectral data was available for the quinolones whilst that reported for quinoline dealt with chemical shifts and short range couplings only. ^{13}C n.m.r. spectral parameters for a series of alkylquinoline and alkylquinolone derivatives were therefore determined to provide more information for these systems.

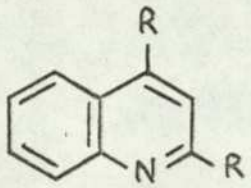
CHAPTER 3

SYNTHESIS OF QUINOLINE DERIVATIVES

3.1 COMBES SYNTHESIS

3.1.1 INTRODUCTION

The Combes synthesis[68] involves condensation of a β-diketone, $RCOCH_2COR$ (LXXIII) with an aniline derivative to give a 2,4-di-R-substituted quinoline derivative (LXXIV). To date only β-diketones in which R = CH_3 or C_6H_5 have been employed. In the present work a series of β-diketones, containing higher alkyl groups, have been prepared and employed in this synthesis.



(LXXIV)

3.1.2 EXPERIMENTAL

3.1.2.1 Synthesis of ethyl n-valerate

Concentrated sulphuric acid (13 ml.) was added dropwise to a stirred mixture of ethanol (29g., 0.63 mole) and n-valeric acid (61.2g., 0.6 mole). The mixture was boiled under reflux for 30 minutes, cooled and neutralised with sodium carbonate solution. The crude ester was washed with calcium chloride solution (25%, 3 x 30 ml.) to remove any remaining ethanol and then separated and dried over anhydrous magnesium sulphate. Ethyl n-valerate (72g., 92%) was obtained as a colourless liquid, b.p. 145-7°/759 mm., n_D^{20} 1.4012. (lit.[283] b.p. 144.6°/736.5 mm., n_D^{20} 1.412)

By a similar procedure, the following esters were also prepared :

Ethyl isobutyrate (48g., 65%) was obtained as a colourless liquid, b.p. 110-2°/760 mm., n_D^{20} 1.3901, lit.[283] b.p. 110°.

Ethyl pivalate (42g., 51%) was obtained as a colourless liquid, b.p. 118-9°/760 mm., n_D^{20} 1.3912, lit.[283] b.p. 118.5°, n_D^{20} 1.3912.

Ethyl propionate (b.p. 98°/760 mm.) and ethyl n-butyrate (b.p. 120°/760 mm.) were commercial samples and were redistilled before use.

3.1.2.2 Synthesis of heptan-3,5-dione (LXXIII, R = C_2H_5)[284]

(i) Sodium metal (10g., 0.48 mole) was cut into small pieces and stored under xylene. A portion of the metal (1.0g.) was cautiously added to well agitated liquid ammonia (300 ml.), to produce a blue colouration. In order to catalyse the conversion of the sodium to sodamide, a crystal of ferric nitrate was added, which caused the blue colouration to disappear. The remainder of the sodium metal was then added in small portions and when the addition was complete, the mixture was stirred for a further 15 minutes. Excess ammonia was then slowly evaporated off on the water bath and sufficient anhydrous ether added to maintain the volume at 300 ml. When all the ammonia had been removed, the suspension of sodamide in ether was boiled under reflux for 5 minutes and allowed to cool.

(ii) Sodamide (30g., 0.6 mole)[a] was suspended in dry ether (300 ml.) and a solution of methyl ethyl ketone (21.6 g., 0.3 mole) dissolved in dry ether (50 ml.) added slowly over a period of 5-10 minutes. The mixture was continually stirred throughout. A solution of ethyl propionate (61.3g., 0.6 mole) was then added and the mixture boiled under gentle reflux for 2 hours on the water bath. During this period the mixture changed in colour from yellow to cream. The reaction mixture was then poured into water (300 ml.), neutralised with dilute hydrochloric acid, and the product extracted with ether. The ether was removed and the residue dissolved in methanol. A hot filtered solution of copper acetate (40g.) in distilled water (350 ml.) was then added when the blue copper salt immediately precipitated. The precipitate was filtered off, washed with petroleum ether (40° - 60°, 100 ml.) and drained. Recrystallisation of a sample from methanol gave the purified copper salt as blue needles, m.p. $207\text{-}8^\circ$ (lit.[284] m.p. $209\text{-}10^\circ$). The bulk of the unrecrystallised salt was shaken with dilute sulphuric acid (500 ml.) and ether (200 ml.) until the ether layer was pale yellow. The ether layer was separated, and dried over anhydrous magnesium sulphate. Removal of the solvent left

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Note (a) - as prepared in Section 3.1.2.2 (i)

heptane-3,5-dione (16.5g., 43%) as a pale yellow liquid, b.p. 80°/30 mm. (lit.[284] b.p. 78-80°/30 mm.). By a similar procedure, further β-diketones (LXXIII) were synthesised. The results are shown in Table 3.1.1. Acetylacetone was commercially available and was re-distilled before use. (b.p. 139/760 mm.)

3.1.2.3 Synthesis of 2,4-diethylquinoline (LXXIV, R = C_2H_5)[287]

(i) A mixture of freshly redistilled aniline (9.12 ml., 0.1 mole) and heptan-3,5-dione (14.1g., 0.11 mole) was boiled under gentle reflux for 1½ hours and then cooled. Distilled water (50 ml.) was then added and the product extracted with benzene and dried over anhydrous magnesium sulphate. Removal of the solvent left crude heptan-3,5-dione monoanil (16.4g., 81%) as a yellow oil which was used in the next stage without further purification.

(ii) Concentrated sulphuric acid (90 ml.) was cooled to below 5°C and the crude anil prepared above (16.4g.) was added in 1 ml. portions over a period of 15 minutes. The solution was then heated on the water bath for an additional 30 minutes. After cooling, the reaction mixture was made alkaline with solid sodium hydroxide and the product was extracted with ether and dried over anhydrous magnesium sulphate. Removal of the solvent left 2,4-diethylquinoline (8.7g., 47%)[b] as a pale yellow liquid, b.p. 286-7°/760 mm. (lit.[79] b.p. 282.8 - 284.8°). By a similar procedure, further 2,4-dialkylquinolines (LXXIV) were synthesised. In certain cases, analysis of the initial product by gas-liquid chromatography indicated the presence of unreacted amine. This was accordingly removed by a diazotisation technique[47] as described in Section 3.2.2.1.

The results obtained are shown in Tables 3.1.2, 3.1.3 and 3.1.4.

Note (b) - yield based on aniline originally used.

TABLE 3.1.1

Synthesis of β-dicarbonyl compounds (LXXIII)

R	Yield (%)	b.p. (lit.)	Copper salt	
			m.p.	lit.[284]
C_2H_5	43	80°/30 mm.(a)	207-8°	209-10°
n-C_3H_7	70	98-100°/20 mm.(b)	158°	156-7°
iso-C_3H_7	45	70-5°/6 mm.(c)	117-9°	113-4° (d)
n-C_4H_9	83	100-5°/10 mm. (e)	142°	-
tert-C_4H_9	15	90-5°/18 mm. (f)	196°	197-8°

Notes (a) lit.[284] b.p. 78-80°/30 mm.

(b) lit.[284] b.p. 101-2°/20 mm.

(c) lit.[285] b.p. 75-7°/7 mm.

(d) lit.[285] m.p. 113-4°

(e) lit.[286] b.p. 110-23°/14 mm.

(f) lit.[284] b.p. 96-7°/20 mm.

TABLE 3.1.2

Synthesis of 2,4-disubstituted quinolines (LXXIV)[a]

R	Yield (%)[b]	b.p. (lit.)	picrate m.p. (lit.)
CH_3	92	266°/758 mm. (c)	195-6° (d)
C_2H_5 (e)	47	286-7°/760 mm. (f)	177-8° (g)
n-C_3H_7	38	309°/760 mm. (h)	120-1°
iso-C_3H_7	11	299°/760 mm. (h)	156-7° (j)
n-C_4H_9	42	335°/760 mm. (h)	135-6°
tert-C_4H_9	0 (k)	-	-

Notes

(a) See Table 3.1.3 for analytical data.

(b) Based on aniline originally used.

(c) lit.[288] b.p. 264-6°/758 mm.

(d) lit.[25] m.p. 196°.

(e) Also prepared the chloroplatinate derivative, m.p. 224° (decomp.), lit.[79] m.p. 217°. Found: Pt: 24.8, Calc. for $C_{26}H_{32}Cl_6N_2Pt$: Pt, 25.0%.

(f) lit.[79] b.p. 282.8 - 284.8°.

(g) lit.[81] m.p. 174-5°.

(h) Determined by micro Siwoloboff technique.

(j) lit.[81] m.p. 156-8°.

(k) The crude intermediate anil was obtained in 30% yield.

TABLE 3.1.3

Elemental analysis of 2,4-disubstituted quinolines (LXXIV)

R	Molecular Formula	Calc.			Found		
		C	H	N	C	H	N
C_2H_5 (a)	$C_{13}H_{15}N$	84.3	8.2	7.6	84.1	8.3	7.8
C_2H_5 picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.4	4.5	13.6
n-C_3H_7	$C_{15}H_{19}N$	84.4	9.0	6.6	84.3	8.9	6.6
n-C_3H_7 picrate	$C_{21}H_{22}N_4O_7$	57.0	5.0	12.7	56.9	4.9	12.5
iso-C_3H_7	$C_{15}H_{19}N$	84.4	9.0	6.6	84.2	8.8	6.7
n-C_4H_9	$C_{17}H_{23}N$	84.6	9.6	5.8	84.3	9.5	5.9
n-C_4H_9 picrate	$C_{23}H_{27}N_4O_7$	58.6	5.8	11.9	58.7	5.9	12.0

Note (a) Also calcd. for $C_{13}H_{15}N$: M: 185.3,

Found: M (non-aqueous titration) : 186.1

TABLE 3.1.4

N.M.R. Spectra of 2,4-disubstituted quinolines (LXXIV)[a]

R	Chemical Shift (τ)			
	H-3(b)	H-5/H-8(b)	H-6/H-7(b)	Alkyl groups
CH_3	3.15	2.03 - 2.35	2.42 - 2.80	7.45 (s, CH_3 (2) 7.55 (s, CH_3 (4)
C_2H_5	3.04	1.96 - 2.25	2.41 - 2.77	7.08 (q, J 7.5 Hz, CH_2 (2) 7.12 (q, J 7.5 Hz, CH_2 (4) 8.64 (t, J 7.5 Hz, CH_3 (2) 8.71 (t, J 7.5 Hz, CH_3 (4)
n-C_3H_7	3.06	2.02 - 2.26	2.42 - 2.79	7.08 (t, J 7.5 Hz, CH_2 (2) 7.15 (t, J 7.5 Hz, CH_2 (4) 8.14, 8.25 (2 sextets, central CH_2) 9.01 (t, J 7.5 Hz, CH_3)
iso-C_3H_7	2.94	2.00 - 2.22	2.38 - 2.50	6.37 (sept., J 7 Hz, CH (2 6.83 (sept., J 7 Hz, CH (4 8.65 (2 d, J 7 Hz, CH_3)
n-C_4H_9	3.07	2.05 - 2.29	2.46 - 2.84	7.07 (t, J 7 Hz, CH_2 (2) 7.14 (t, J 7 Hz, CH_2 (4) 8.14 - 8.77 (m, middle CH_2CH_2) (c) 9.04 (t, J 7 Hz, CH_3)

Notes (a) N.M.R. : 100 MHz, CCl_4 solution.

(b) H-3 was a broadened singlet and H-5/H-8 and H-6/H-7 were each complex multiplets.

(c) Actually two overlapped sextets and quintets.

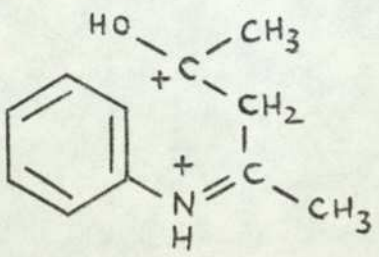
3.1.3 DISCUSSION

As reviewed in the literature survey (see Section 1.2.4), both the modified forms of the Skraup[10] and Doebner-von Miller[42] reactions could be utilised to effect the synthesis of 2,4-dialkylquinoline derivatives. However, these syntheses would either require difficultly accessible starting materials or could result in mixed products. It would therefore appear from the present work that the use of higher alkyl substituted β-diketones in the Combes synthesis[68] offers the most convenient route to 2,4-dialkylquinoline derivatives.

The yield of straight chain 2,4-dialkylquinolines was halved on changing from methyl to ethyl, but further increases in the size of the alkyl substituents caused only slight further reductions in the yields. However, the two branched chain homologues were obtained in much poorer yield, and the 2,4-di-tertbutyl derivative was isolated in only a trace quantity (as possibly detected by g.l.c.).

The cause of the diminished yields, particularly in the case of the di-tertbutyl compound could be due to steric effects in the intermediate anil which may result in a reduction of the proportion of the cis-form which undergoes cyclodehydration more readily.[77]

Moreover, Bonner and Barnard[74] have suggested that cyclisation occurred through a small percentage of the dication (XXXVIII). The increased inductive effect (+I)



(XXXVIII)

of the larger alkyl groups would be expected to enhance the formation of this diprotonated species and hence could lead to diminished yields in the case of the higher alkylquinolines and also with the branched products.

The properties of the 2,4-disubstituted derivatives and of their picrate derivatives synthesised during the course of the present work compared well with the values reported by previous workers.

From the properties of the sample synthesised in the present work, it would appear that the "diethylquinoline" isolated by Reher[79] from the thermal rearrangement of N-ethylquinolinium iodide, was 2,4-diethylquinoline. This is to be expected since 2-ethyl- and 4-ethylquinoline were also identified and the formation of a 2,4-disubstituted derivative would be in accordance with the products obtained from the analogous thermal rearrangement of N-ethylpyridinium iodide.[289]

In 1908, van Hove[290] heated quinoline hydrochloride with isopropanol at 160° for several days. From the reaction mixture, a product was isolated which analysed as a dipropylquinoline (b.p. 300-20°, picrate, m.p. 160-1°). From a consideration of the results of later studies upon the photochemical[81] and homolytic[291] alkylation reactions of quinoline, the most probable disubstituted product formed would have been the 2,4-derivative. From the properties of the synthetic sample obtained in the present work it would appear that the "diisopropylquinoline" obtained by van Hove[290] was 2,4-diisopropylquinoline.

The identities of the 2,4-dialkylquinolines prepared in the present work were confirmed by n.m.r. spectroscopy. That a 2,4-disubstituted derivative had been obtained was readily deduced from the presence of an aromatic upfield singlet (slightly broadened by benzylic coupling) assigned to the isolated H-3 proton.

The n.m.r. spectra obtained in the present work compared favourably with those recorded by earlier workers.[81,292] However, one discrepancy did occur with 2,4-diisopropylquinoline. In the reported spectrum[81] determined at 60 MHz the signal for the H-3 proton occurred at 6.74 δ (3.26 τ), however, in the present work this proton absorbed at 2.94 τ at 100 MHz. The same solvent (carbon tetrachloride) was used for both measurements, the remainder of the two spectra were almost identical. In order to elucidate this anomaly the literature spectra of several substituted pyridine derivatives have been examined, and the results are collected in Table 3.1.5.

TABLE 3.1.5

Chemical shift of H-3 proton in a series of pyridine derivatives (a)

Substituted pyridine	Chemical shift (τ) of H-3 (lit.)	Relative change (p.p.m. (b)
2,6-Me_2	3.03 (244b)	-0.07
2,6-(t-Bu)$_2$	2.96 (244c)	
2,4-Me_2	3.00(137d) (c)	-0.15
2,4-(t-Bu)$_2$	2.85 (244d)	
2,4,6-Me_3	3.41 (244e)	-0.50
2,4,6-(t-Bu)$_3$	2.91 (244f)	

Notes (a) N.M.R. - 60 MHz, CCl_4

(b) (t-Bu deriv.) - (Me deriv.), negative sign denotes downfield shift.

(c) In $CDCl_3$.

It is apparent that substitution of a methyl (i.e. a straight chain) by a tert-butyl group (i.e. a branched chain) at positions 2- and/or 4- and/or 6- of the pyridine nucleus, results in a downfield shift of the H-3 proton. The cause of this shift is uncertain, since the increased positive inductive effect of a tert-butyl group, compared with that of a methyl group, would be expected to increase the electron density at position 3 and result in an upfield shift. The observed downfield shift could possibly result from the bulky nature of tert-butyl groups which may distort the planarity of the pyridine ring, or possibly may occur through hyperconjugative effects.

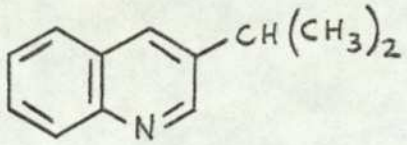
The downfield shift of 0.21 p.p.m. for the H-3 signal of 2,4-diisopropylquinoline, compared with the dimethyl derivative, is therefore considered to be more reliable than the upfield shift of 0.09 p.p.m. obtained by previous workers.[81]

3.2 VON MILLER - KINKELIN SYNTHESIS

3.2.1 INTRODUCTION

The von Miller - Kinkelin modification[55] of the Doebner - von Miller synthesis[42,44] of quinoline derivatives involves the use of two different aldehydes, one of which does not contain an α-hydrogen atom. Through the "crossed" reaction a 3-methylquinoline derivative may be obtained.

In the present work the reaction conditions have been improved and the synthesis extended to produce 3-isopropylquinoline (LXXV).



(LXXV)

3.2.2 EXPERIMENTAL

3.2.2.1 Synthesis of 3-methylquinoline (XXIX, R = H)[293]

(using the original technique of von Miller and Kinkelin)[55]

Freshly distilled aniline (50g., 0.54 mole) was placed in a three necked flask, fitted with a reflux condenser. Concentrated hydrochloric acid (120 ml.) was slowly added to produce a paste of aniline hydrochloride which was then allowed to cool. A mixture of dimethoxymethane (formaldehyde dimethyl acetal, methylal) (50g.) and propionaldehyde (50g.), which had been previously saturated with dry hydrogen chloride gas, was then slowly added to the aniline hydrochloride paste. During the addition the paste dissolved and the reaction commenced. After the subsidence of the initial reaction the mixture was then boiled under reflux for 6 hours, cooled, made strongly alkaline with sodium hydroxide solution and steam distilled (ca. 10 hours).

The steam distillate was acidified with dilute hydrochloric acid and the acidic and neutral impurities were removed by ether extraction. The aqueous solution was then made alkaline with sodium hydroxide solution, cooled and extracted with ether. Removal of the solvent left the crude product. In order to remove any unreacted aniline and secondary amine by-products, a diazotisation technique[47] was employed.

The crude product was dissolved in dilute hydrochloric acid, cooled to 5° in an ice-salt bath and diazotised by the addition of a concentrated solution of sodium nitrite. The diazotisation was tested for completeness with starch-iodide paper. The mixture was allowed to warm up to room temperature to allow most of the evolved gases to escape and the nitrosamines were then removed by extraction with ether, and the ether extract discarded. Dilute sulphuric acid (100 ml.) was added to the aqueous layer which was warmed on the water bath for 1 hour to remove any residual amounts of nitrogen and to convert the original diazotised primary amine to the corresponding phenol. The solution was then made strongly alkaline with concentrated sodium hydroxide and was steam distilled. The steam distillate was acidified with dilute hydrochloric acid and the acidic and neutral impurities were removed by extraction with ether. The aqueous solution was then made alkaline, extracted with ether and dried over anhydrous magnesium sulphate. Evaporation of the solvent left the final product, a mixture of 3-methylquinoline (XXIX, R = H) and 2-ethyl-3-methylquinoline, as a pale yellow oil (5.5 g.) which was analysed by gas-liquid chromatography using 10% silicone SE52 and 20% diglycerol columns (see Section 4.2.3.2). The results obtained are shown in Tables 3.2.1 and 3.2.3.
By a similar procedure, further 3-methylquinoline derivatives were synthesised and isolated as their picrate derivatives after fractional crystallisation (see sections 3.2.2.2 and 3.2.2.3 below). The results are shown in Tables 3.2.1 and 3.2.3.

3.2.2.2 Separation of 3-methylquinoline

(i) Picric acid (1g.) in boiling ethanol (10 ml.) was added to a solution of the final reaction product obtained in section 3.2.2.1 above (1g.) in boiling ethanol (10 ml.) to form the mixed picrate which was collected and washed with ethanol. The mixed picrate was obtained as small yellow needles, m.p. 163-4°. Decomposition of the picrate with sodium hydroxide solution (see section 3.2.2.3) and analysis by gas-liquid chromatography (see section 4.2.3.2) showed the presence of both 3-methylquinoline and 2-ethyl-3-methylquinoline.
(ii) The crude picrate was then fractionally crystallised from a large volume of ethanol to yield pure (g.l.c. after decomposition) 3-methylquinoline picrate, m.p. 188 - 9°. (lit.[25] m.p. 190°).

3.2.2.3 Regeneration of pure 3-methylquinoline from the picrate derivative

Pure 3-methylquinoline picrate (see section 3.2.2.2) was suspended in sodium hydroxide solution and the solution heated slowly. Near the boiling point the picrate derivative dissolved and decomposed to form a brown coloured solution with the quinoline visible as globules on the surface. The mixture was then steam distilled. The steam distillate was dissolved in dilute hydrochloric acid and acidic or neutral impurities were removed by extraction with ether. The solution was then made alkaline, the product extracted with ether and dried over anhydrous magnesium sulphate. Removal of the solvent left pure 3-methylquinoline as a pale yellow oil, b.p. 258-9°/760 mm., n_D^{20} 1.6140 (lit.[86] b.p. 259.6°/760 mm., n_D^{20} 1.6171). N.M.R. (100 MHz, CCl_4) : 1.38 τ (1H, d, J_{24} = 2.0 Hz, H-2), 1.97 τ (1H, d, J_{78} = 8.0 Hz, H-8), 2.32 τ (1H, bs, H-4), 2.38 - 2.73 τ (3H, m, H-5, H-6, H-7), 7.62 τ (3H, s, CH_3).

3.2.2.4 Separation of 2-ethyl-3-methylquinoline

The final reaction product obtained in section 3.2.2.1 above was allowed to stand, and after about one month, 2-ethyl-3-methylquinoline, which was formed as the by-product, crystallised out. The crystals were separated by filtration under vacuum and recrystallised from hexane. 2-Ethyl-3-methylquinoline was obtained as colourless prisms, m.p. 55-6°. (lit.[46] m.p. 57°). N.M.R. (100 MHz, CCl_4) : 2.09 τ (1H, d, J_{78} = 8 Hz, H-8), 2.39 τ (1H, bs, H-4), 2.43 - 2.80 τ (3H, m, H-5, H-6, H-7), 7.12 τ (2H, q, J = 7.5 Hz, $\underline{CH_2}CH_3$), 7.62 τ (3H, s, CH_3), 8.64 τ (3H, t, J = 7.5 Hz, $CH_2\underline{CH_3}$).

The picrate crystallised from ethanol as fine yellow needles, m.p. 194-5° (lit.[46] m.p. 195°).

TABLE 3.2.1

Preparation of 3-methylquinolines by the original von Miller-Kinkelin procedure.[57]

Aniline Reactant	Quinoline Products	Yield	Approx. Composition (%) (a)
aniline	3-methyl-	5.5g. (b)	42
	2-ethyl-3-methyl-		58
o-toluidine	3,8-dimethyl-	3.3g.	89
	2-ethyl-3,8-dimethyl-		11
p-toluidine	3,6-dimethyl-	2.5g.	53
	2-ethyl-3,6-dimethyl		47
m-toluidine	3,5-dimethyl-	2.2g.	12
	3,7-dimethyl-		34
	2-ethyl-3,5-dimethyl-		14
	2-ethyl-3,7-dimethyl-		40
2,3-dimethyl-	3,7,8-trimethyl-	0.75g. (c)	50
	2-ethyl-3,7,8-trimethyl-		50
2,4-dimethyl-	3,6,8-trimethyl-	0.8g.	89
	2-ethyl-3,6,8-trimethyl-		11
2,5-dimethyl-	3,5,8-trimethyl-	1.1g.	65
	2-ethyl-3,5,8-trimethyl-		35
3,4-dimethyl-	3,5,6-trimethyl-	2.8g.	9
	3,6,7-trimethyl-		18
	2-ethyl-3,5,6-trimethyl-		73 (d)
	2-ethyl-3,6,7-trimethyl-		

Notes (a) from uncorrected g.l.c. peak areas.

(b) 6.4% yield, based on mean molecular weight of the mixture of quinoline products obtained.

(c) 0.7% yield, based on mean molecular weight of the mixture of quinoline products obtained.

(d) did not separate.

3.2.2.5 Synthesis of 3-methylquinoline (XXIX, R = H)[294]
(using an ethanolic reaction medium and dropwise addition of reactants).

A mixture of ethanol (60 ml.) and concentrated hydrochloric acid (30 ml.) was placed in a 3-necked flask, fitted with two separating funnels and a reflux condenser, and ferric chloride hexahydrate (50g.) and crushed fused zinc chloride (5g.) added. When the salts had dissolved the solution was boiled gently under reflux. A solution of freshly redistilled propionaldehyde (30 ml.) and ethanol (30 ml.) was placed in one separating funnel, and the other was charged with a solution of freshly redistilled aniline (30 ml., 0.33 mole) in ethanol (30 ml.). A solution of paraformaldehyde (10g.) in ethanol (55 ml.) and concentrated hydrochloric acid (5 ml.) was also prepared and kept at about 60° to maintain the solution. At two minute intervals approx. 1 ml. of each solution in each of the two separating funnels was added to the reactants in the flask, followed by 1 ml. of the paraformaldehyde solution which was added down the condenser. The three reagent solutions were added over a total period of two hours; when the additions were completed the reaction mixture was finally boiled under reflux for a further one hour. The solvent and other residual volatiles were then removed by distillation to a maximum temperature of 120°. At this stage no tar was apparent.

The residual mixture was then made alkaline and steam distilled to obtain the crude product.

The crude product was isolated, purified *via* diazotisation and finally obtained as described in section 3.2.2.1 above.

The final product, a mixture of 3-methylquinoline (XXIX, R = H) and 2-ethyl-3-methylquinoline was obtained as a pale yellow oil which was analysed by gas-liquid chromatography using 10% silicone SE52 and 20% diglycerol columns. (See section 4.2.3.2). The results obtained are shown in Tables 3.2.2 and 3.2.3.

By a similar procedure, further 3-methylquinoline derivatives were synthesised, and isolated as their picrate derivatives after fractional crystallisation (see sections 3.2.2.2 and 3.2.2.3). The results obtained are shown in Tables 3.2.2 and 3.2.3.

3.2.2.6 Synthesis of 3-isopropylquinoline (LXXV)[294]

The procedure for the synthesis of 3-methylquinoline derivatives was employed (see above, section 3.2.2.5) except that freshly redistilled isovaleraldehyde (44.4 ml.) was used in place of propionaldehyde. The final product, a mixture of 3-isopropylquinoline (LXXV) and 2-isobutyl-3-isopropylquinoline was obtained as a pale yellow oil (6.8g.), which was analysed by gas-liquid chromatography using a 10% silicone SE-30 column, operated isothermally at 180° with a carrier gas flow rate of 60 ml./min. The relative retention times of the components were 3.3 and 6.6 respectively with reference to quinoline = 1.0. The mixed picrate derivative was prepared and pure 3-isopropylquinoline picrate obtained by fractional crystallisation (see above, section 3.2.2.2). Pure 3-isopropylquinoline picrate crystallised from ethanol as yellow needles, m.p. 206-7° (lit.[295] m.p. - (not given)). Found: C, 54.2; H, 3.8, N, 13.8%. Calculated for $C_{18}H_{16}N_4O_7$: C, 54.0 ; H, 4.0 ; N, 14.0%). Decomposition of the pure picrate derivative (see above, section 3.2.2.3) afforded pure 3-isopropylquinoline as a yellow oil. N.M.R. (100 MHz, $CDCl_3$) : 1.26τ(1H, d, J_{24} = 2.1 Hz, H-2); 2.01τ(1H, d, J_{78} = 8.2 Hz, H-8); 2.16τ(1H, bs, H-4); 2.27 - 2.66τ(3H, m, H-5, H-6, H-7); 6.89τ(1H, sept., J = 7 Hz, C<u>H</u>); 8.73τ(6H, d, J = 7 Hz, CH_3).

$^{13}C - \{^1H\}$ N.M.R. (15 MHz, $CDCl_3$, multiplicities in off-resonance spectrum given): 151.2δ(d, C-2); 146.9δ(s, C-9); 141.1δ(s, C-3); 131.8δ(d, C-4); 129.1δ(d); 128.5δ(d); 128.3δ(s, C-10); 127.4δ(d); 126.5δ(d); 31.9δ (d, CH); 23.6δ(q, CH_3)

TABLE 3.2.2

Preparation of 3-methylquinolines by a modified von Miller-Kinkelin procedure

Aniline Reactant	Quinoline Products	Yield	Approx. Composition (%)
aniline	3-methyl-	10.9g. (b)	47
	2-ethyl-3-methyl-		53
m-toluidine	3,5-dimethyl-	9.9g.	14
	3,7-dimethyl-		33
	2-ethyl-3,5-dimethyl-		12
	2-ethyl-3,7-dimethyl-		41
2,3-dimethyl-	3,7,8-trimethyl-	13.5g. (c)	63
	2-ethyl-3,7,8-trimethyl-		37
2,4-dimethyl-	3,6,8-trimethyl-	7.2g.	90
	2-ethyl-3,6,8-trimethyl-		10
2,5-dimethyl-	3,5,8-trimethyl-	10.2g.	79
	2-ethyl-3,5,8-trimethyl-		21

Notes (a) from uncorrected g.l.c. peak areas.

(b) 20.9% yield, based on mean molecular weight of the mixture of quinoline products obtained.

(c) 22.5% yield, based on mean molecular weight of the mixture of quinoline products obtained.

TABLE 3.2.3

Properties and spectroscopic data for synthesised 3-methylquinoline derivatives

Quinoline Products	Picrate m.p. (lit.)	Relative Retention Times (a) Diglycerol (140°)	Silicone SE52 (175°)
3-methyl-	188-9° (190°)[25]	1.23	1.52
2-ethyl-3-methyl-		0.69	2.56
3,5-dimethyl-	- (220°)[25]	1.75	2.39 (c)
3,7-dimethyl-	239-40° (244°)[25]	1.53	2.18
2-ethyl-3,5-dimethyl-		0.95	3.97 (c)
2-ethyl-3,7-dimethyl-		0.85	3.74
3,6-dimethyl-	250° (253°)[25]	1.55	2.23
2-ethyl-3,6-dimethyl-		0.88	3.88
3,8-dimethyl-	207-8° (210°)[25]	0.55	1.59
2-ethyl-3,8-dimethyl-		0.24	2.69
3,5,8-trimethyl- (b)	210-1° (b)	0.79	-
2-ethyl-3,5,8-trimethyl-		0.39	-
3,6,8-trimethyl- (b)	222-3° (b)	0.72	-
2-ethyl-3,6,8-trimethyl-		0.36	-
3,7,8-trimethyl- (b)	204-5° (b)	0.80	-
2-ethyl-3,7,8-trimethyl-		0.43	-
3,5,6-trimethyl-		3.01	-
3,6,7-trimethyl- (b)	245-6° (b)	2.75	-
2-ethyl-3,5,6-trimethyl-		1.65 (d)	-
2-ethyl-3,6,7-trimethyl-			-

Notes (a) relative to quinoline = 1.00.

(b) see Table 3.2.4 for analytical and spectroscopic data.

(c) peak not completely separated.

(d) did not separate.

TABLE 3.2.4

Properties of trimethylquinolines and of their picrate derivatives

Trimethylquinoline Derivative	m.p.	Molecular Formula		C (%)	H (%)	N (%)
3,5,8-	61-2° (a)	$C_{12}H_{13}N$	Found	83.9	7.6	8.0
			Calc.	84.2	7.7	8.2
3,5,8- picrate	210-1° (b)	$C_{18}H_{16}N_4O_7$	Found	54.2	4.0	13.9
			Calc.	54.0	4.0	14.0
3,6,8-	31-2° (a)(c)	$C_{12}H_{13}N$	Found	84.3	7.8	8.0
			Calc.	84.2	7.7	8.2
3,6,8- picrate	222-3° (b)	$C_{18}H_{16}N_4O_7$	Found	53.9	4.1	13.8
			Calc.	54.0	4.0	14.0
3,7,8-	66-7° (a)	$C_{12}H_{13}N$	Found	84.5	7.8	8.3
			Calc.	84.2	7.7	8.2
3,7,8- picrate	204-5° (b)	$C_{18}H_{16}N_4O_7$	Found	54.1	4.0	14.0
			Calc.	54.0	4.0	14.0
3,6,7-	111-2° (a)	$C_{12}H_{13}N$	Found	84.5	7.9	8.3
			Calc.	84.2	7.7	8.2
3,6,7- picrate	245-6° (b)	$C_{18}H_{16}N_4O_7$	Found	53.8	4.1	13.9
			Calc.	54.0	4.0	14.0

Notes (a) colourless prisms, from hexane.

(b) yellow needles, from ethanol

(c) John and Case[296] report b.p. 105-6°/0.5 mm., but no m.p.

Cont.....

TABLE 3.2.4 (Cont.)

N.M.R. spectral data (100 MHz, CCl_4)

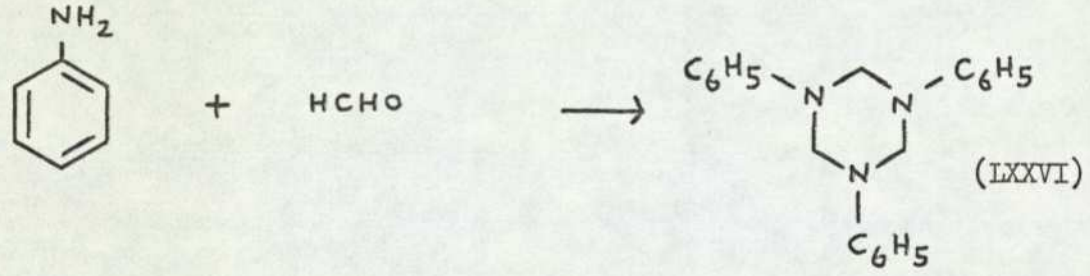
Trimethyl-quinoline derivative	Chemical shift (τ) H-2	H-4	H-5	H-6	H-7	H-8	Methyl groups and Coupling Constants
3,5,8-	1.39	2.04	-	2.78	2.93	-	7.32, 7.46, 7.53 J_{24} = 2.2 Hz J_{67} = 7.1 Hz
3,6,8-	1.46	2.41	2.83	-	2.83	-	7.32, 7.55, 7.58 J_{24} = 2.2 Hz
3,7,8-	1.42	2.38	2.70	2.86	-	-	7.33, 7.58, 7.58 J_{24} = 2.2 Hz J_{56} = 8.3 Hz
3,6,7-	1.49	2.38	2.68	-	-	2.39	7.55, 7.55, 7.61 J_{24} = 2.2 Hz

3.2.3 DISCUSSION

As reviewed in the literature survey (see section 1.2.3a), syntheses of 3-alkylquinoline derivatives usually require difficultly accessible materials and condensing agents. The present procedure, an improvement to the von Miller-Kinkelin technique,[55] offers the advantage that only readily available reagents are required. Although the yields obtained are still modest, since the required reactants are generally cheap, syntheses may be conducted economically on a large scale.

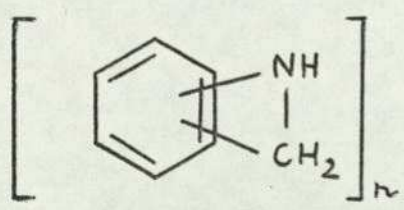
The classical Doebner-von Miller[42,44] and Beyer[49] syntheses resulted in very poor yields, owing to a preponderance of side reactions.

Tollens[297] reported that aniline reacted with formaldehyde to form 1,3,5-triphenyl-hexahydro-1,3,5-triazine (LXXVI); some methylenedianiline $(C_6H_5NH)_2CH_2$ and polymeric methyleneanilines have also been detected.[298]

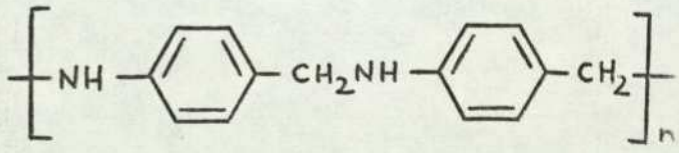


(LXXVI)

Furthermore, when the triazine (LXXVI) was heated in an acidic medium, polymeric anhydro 4-aminobenzylalcohol, $(C_7H_7N)_n$ (LXXVIIa) was formed,[299] the constitution of which was later formulated as (LXXVIIb) by Frey.[300]



(LXXVIIa)



(LXXVIIb)

The triazine (LXXVI) has also been reported to yield methylenedianiline when heated with aniline.[301]

If the above reactions were allowed to predominate, then the yield and quality of the quinoline product would correspondingly diminish. Accordingly,

dropwise addition of all reactants was employed in the present work.

This mode of addition of the reactants would also be expected to reduce the proportion of the 2-alkyl substituted by-product by lessening the probability of the "normal" self condensation reaction of two molecules of the heavier aldehyde reactant. Hence the formation of the 3-alkylquinoline through the "crossed" condensation with formaldehyde should become more favoured. Such an enhancement has been obtained in the preparation of 3-methylquinoline, however, it was only slight (42% (Table 3.2.1) compared with 47% (Table 3.2.2), but for the other reactions the proportions of the 3-substituted quinoline was much greater (see Table 3.2.2).

Since it has been found beneficial to employ milder conditions[27,50] in the related Beyer synthesis, through the use of an alcoholic reaction medium with ferric chloride as oxidising agent and zinc chloride as condensing agent, similar conditions were used in the present work.

This modified procedure resulted in increased yields and was also found to be suitable for the synthesis of some new trimethylquinoline derivatives in satisfactory yield. Previous attempts to produce these compounds by the original technique were not very successful due to particularly poor yields being obtained. (Compare Tables 3.2.1 and 3.2.2).

Kaiser and Petty[59] have recently reported a new convenient route to 3-alkylquinoline derivatives through lithiation and alkylation of 3-methylquinoline. However, this technique is subject to two restrictions, initially the quinoline must be obtained through another technique. Secondly compounds such as 3-isopropylquinoline (LXXV), which do not contain a methylene group affixed to the quinoline ring, cannot be obtained from 3-lithiomethylquinoline (XXIX, R = Li).

The present synthesis provides a convenient means of securing this compound through the use of isovaleraldehyde as the second aldehyde reactant and is to be preferred to the earlier preparation of 3-isopropylquinoline reported by Spady,[295] which required a multi-stage sequence involving selective oxidation of alkyl groups with subsequent decarboxylation.

The composition of the initial mixed reaction products was assessed by

gas-liquid chromatography using both polar and non-polar stationary phases. With the non-polar silicone SE52 phase, elution resulted in order of boiling points. With the polar phase, diglycerol, advantage was taken of the "ortho effect" as observed by Fitzgerald[302] through which compounds with an alkyl substituent adjacent to nitrogen were eluted faster compared with other related compounds of similar boiling point. Accordingly, the desired 3-alkylquinolines were eluted first from the non-polar column, but last from the polar column.

Pure samples of the desired 3-alkylquinolines were readily separated from the 2,3-dialkyl-substituted by-products by fractional crystallisation of the mixed picrate derivatives from ethanol. In all cases the 3-alkylquinoline picrates separated first as the least soluble fractions. Decomposition of the pure picrate derivatives with sodium hydroxide solution gave the pure quinoline derivatives. A sample of 2-ethyl-3-methylquinoline was also isolated by filtration (see section 3.2.2.4) and used as a standard to confirm the identities of the gas-liquid chromatographic peaks.

The identities of the pure 3-alkylquinoline products were also confirmed by n.m.r. spectroscopy. All compounds exhibited a low field peak for H-2 at ca. 1.5 τ which appeared as a fine doublet (J_{24} = 2.1 Hz) and confirmed that the 3-position was occupied. This technique was also used to assess the composition of the initial products since the n.m.r. spectrum exhibited certain signals characteristic of each product, viz: 3-methylquinoline (H-2: fine doublet) and 2-ethyl-3-methylquinoline (CH_2: quartet). A comparison of the respective integrals provided an assessment of the product composition; the results obtained were very similar to the gas-liquid chromatographic analyses.

The identity of 3-isopropylquinoline was also supported by ^{13}C n.m.r. spectroscopy. The proton decoupled spectrum exhibited a quaternary peak at 141.1 δ, assigned to C-3. In this case a substituent chemical shift of 20.2 p.p.m. was observed compared with 20.1 p.p.m. reported for the α-effect in cumene (isopropylbenzene)[303].

3.3 BEYER SYNTHESIS

3.3.1 INTRODUCTION

The Beyer Synthesis[49] involves condensation between and aldehyde and a methyl ketone and subsequent reaction with an aniline derivative to give a 4-substituted quinoline.

Although the reaction has been considered[6,304] to be limited to methyl ketones, in the reported reaction with butanone[64] the predominant condensation involved the methylene protons of the ethyl group.

In the present work the use of further ketones, both alkyl and aryl has been studied.

3.3.2 EXPERIMENTAL

3.3.2.1 Synthesis of 4-ethyl-3-methylquinoline[305]

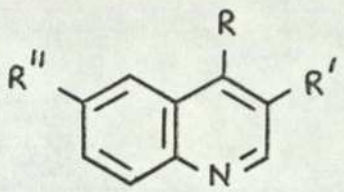
A mixture of ethanol (60 ml.), pentan-3-one (30 ml., 0.28 mole), ferric chloride hexahydrate (50 g.), anhydrous zinc chloride (5 g.) and concentrated hydrochloric acid (30 ml.) was placed in a three necked flask fitted with a reflux condenser and two separating funnels. In one of the funnels was placed a mixture of aniline (30 ml., 0.32 mole), pentan-3-one (30 ml., 0.28 mole) and ethanol (10 ml.) and in the other a solution of paraformaldehyde (9.2g.) dissolved in a mixture of ethanol (65 ml.) and concentrated hydrochloric acid (5 ml.). The contents of the flask were heated to gentle reflux, and then at 2 minute intervals ca. 1 ml. of each of the solutions in the funnels was added; the total period of the addition was about 2 hours. When the addition was complete the reaction mixture was boiled under reflux for a further one hour. The solvent and other residual volatiles were then removed by distillation to a maximum temperature of 100°. The residual mixture was then made alkaline and steam distilled to obtain the crude product.

The crude product was then isolated, purified via diazotisation and finally obtained as described in section 3.2.2.1 above. 4-Ethyl-3-methylquinoline was obtained as a pale yellow oil. (2.6g., 5%).

N.M.R. (100 MHz, CCl_4); 1.54 τ (1H, s, H-2); 2.00 - 2.26 τ (2H, m, H-5 & H-8); 2.47 - 2.77 τ (2H, m, H-6 & H-7); 7.11 τ (2H, q, J = 7.5 Hz, $C\underline{H}_2CH_3$); 7.70 τ (3H, s, CH_3); 8.85 τ (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$).

The picrate crystallised from ethanol as slender, yellow needles, m.p. 199-200° (lit.[65] m.p. 196-7°). Found : C, 54.2; H, 3.9; N, 13.9%. Calculated for $C_{18}H_{16}N_4O_7$: C, 54.0; H, 4.0; N, 14.0%. By a similar procedure, further 3,4-dialkylquinolines (LXXVIII) were synthesised. The results obtained are shown in Tables 3.3.1 and 3.3.2.

Additionally, through the use of arylketones, $ArCOCH_2R'$, certain 4-substituted quinolines (LXXVIII, R = C_6H_5, R' as in arylketone above) were also synthesised. The results obtained are shown in Tables 3.3.1 and 3.3.2.



(LXXVIII)

TABLE 3.3.1

Preparation of quinoline derivatives (LXXVIII) by the Beyer synthesis

Compound No.	R	R'	R''	Yield(%)	m.p. (lit.)	m.p. picrate (lit.)
	CH_3	H	H	15	-	220° (220°)[25]
1	CH_3	CH_3	H	12 (a)	72° (b) (73-4°)[64]	220° (221°)[25]
	C_2H_5	H	H	- (a)	-	- (200°)[29]
2	C_2H_5	CH_3	H	5	- (b)	199-200° (196-7°)[65]
3	C_2H_5	CH_3	CH_3	25	68-9° (b)	205-6° (b)
4	n-C_3H_7	C_2H_5	H	1.5	- (b)	173-4° (172-3°)[66]
5	C_6H_5	H	H	2	59° (b,c) (61-2°)[306,307]	229° (229-229.5°)[308]
6	C_6H_5	CH_3	H	2	98-9° (b) (84-7°)[309]	229-30° (b)

Notes (a) Product consisted largely of 3,4-dimethylquinoline, no 4-ethylquinoline could be detected.

(b) See Table 3.3.2 for analytical and spectroscopic data.

(c) Product did not crystallise for several months.[307]

TABLE 3.3.2

Properties of quinoline derivatives

Analytical Data		Elemental Analysis					
Compound No. (a)	Molecular Formula	Calc.			Found		
		C	H	N	C	H	N
3	$C_{13}H_{15}N$	84.3	8.2	7.6	84.4	8.1	7.7
3 picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.2	4.6	13.3
4 picrate	$C_{22}H_{16}N_4O_7$	58.9	7.6	12.5	59.1	3.3	12.5

Spectroscopic Data (N.M.R. - 100 MHz, CCl_4, τ p.p.m.)

Compound No. (a)

1 - 1.54 (1H, s, H-2); 2.04 - 2.26 (2H, m, H-5 & H-8); 2.45 - 2.76 (2H, m, H-6 & H-7); 7.54 (3H, s, CH_3); 7.66 (3H, s, CH_3).

2 - see section 3.3.2.1

3 - 1.55 (1H, s, H-2); 2.16 (1H, d, J_{78} = 8.4 Hz, H-8); 2.40 (1H, bs, H-5); 2.69 (1H, d of d, J_{78} = 8.4 Hz, J_{57} = 1.8 Hz, H-7); 7.03 (2H, q, J = 7.5 Hz, $C\underline{H}_2CH_3$); 7.49 (3H, s, CH_3); 7.61 (3H, s, CH_3); 8.77 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$).

4 - 1.30 (1H, s, H-2); 1.90 - 2.06 (2H, m, H-5 & H-8); 2.31 - 2.60 (2H, m, H-6 & H-7); 6.96 (2H, t, J = 7.5 Hz, $C\underline{H}_2CH_2CH_3$); 7.17 (2H, q, J = 7.5 Hz, $C\underline{H}_2CH_3$); 8.34 (2H, sextet, J = 7.5 Hz, $CH_2C\underline{H}_2CH_3$); 8.71 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 8.91 (3H, t, J = 7.5 Hz, $CH_2CH_2C\underline{H}_3$).

Mass Spectrum: m/e 199.1359 (M^+, calcd. for $C_{14}H_{17}N$: 199.1361.)

5 - 1.06 (1H, d, J_{24} = 4.2 Hz, H-2); 1.68 - 2.57 (9H, m, H-5 to H-8 & Ph), 2.69 (1H, d, J_{24} = 4.2 Hz, H-3). (Determined at 60 MHz).

6 - 1.28 (1H, s, H-2); 1.98 (1H, d of dd, J_{78} = 8.2 Hz, H-8; 2.20 - 2.84 (8H, m, H-5 to H-7 & Ph); 7.77 (3H, s, CH_3).

Notes (a) Compound Nos. as used in Table 3.3.1.

3.3.3 PRODUCT RATIOS IN THE BEYER SYNTHESIS

3.3.3.1 Introduction

When the Beyer synthesis is conducted with an asymmetric ketone, in which both groups contain α-hydrogen atoms, two reaction pathways are possible. In the reaction of aniline and butanone, 3,4-dimethylquinoline (XXXI) was the major product. However, although it was claimed[64] that the alternative product 4-ethylquinoline (XXXII) was formed, no confirmatory experimental evidence was given.

In the present work, in connection with studies upon the orientation effects in quinoline syntheses (see Chapter 4), a careful examination was undertaken in order to establish whether any of the 4-ethyl substituted derivative was formed.

3.3.3.2 Experimental

3.3.3.2.1 Synthesis of 3,4,6,7-tetramethylquinoline

(i) The procedure described previously (see section 3.3.2.1) was employed using butanone (2 x 0.28 mole) and 3,4-dimethylaniline (39.0g., 0.32 mole). The product, almost pure 3,4,6,7-tetramethylquinoline (3.6g., 6.0%) was obtained as a tan solid, m.p. 118-22°. The picrate crystallised from ethanol as microscopic yellow needles, m.p. 249-50°.

(ii) Careful fractional crystallisation of the initial picrate derivative (1.0g.) from a large volume of ethanol (1000 ml.) afforded pure (g.l.c. after decomposition) 3,4,6.7-tetramethylquinoline picrate as slender long yellow needles, m.p. 251-2°. Found: C, 55.2; H, 4.3; N, 13.7%. Calculated for $C_{19}H_{18}N_4O_7$; C, 55.1; H, 4.4; N, 13.5%.

Decomposition of the pure picrate with sodium hydroxide (see section 3.2.2.3) afforded pure (g.l.c.) 3,4,6,7-tetramethylquinoline as colourless prisms (from hexane), m.p. 124-5°. (lit.[100] m.p. 124-5°) Found: C, 84.3; H, 8.0; N, 7.3%. Calculated for $C_{13}H_{15}N$: C, 84.3; H, 8.2; N, 7.6%. N.M.R. (100 MHz, CCl_4): 1.63 τ (1H, s, H-2); 2.36 τ (1H, bs, H-8); 2.50 τ (1H, bs, H-5); 7.56, 7.62, 7.62, 7.67 τ (12H, s, 2s, s, CH_3).

(iii) Fractional crystallisation of the initial picrate from ethanol was continued to yield several further fractions, each of which was analysed (g.l.c. after decomposition)

and found to contain 3,4,6,7-tetramethylquinoline only. When no further precipitation occurred the final solution was evaporated to dryness to obtain the residue as a yellow crystalline solid (0.05g., 5% of initial starting picrate).

The residual picrate was decomposed with sodium hydroxide (see section 3.2.2.3) and the liberated quinolines analysed by n.m.r. spectroscopy which indicated the presence of 4-ethyl-6,7-dimethylquinoline.

N.M.R. (100 MHz, CCl_4): 1.50 τ (1H, d, J_{23} = 4.3 Hz, H-2); 1.62 τ*; 2.28 τ (1H, bs, H-8); 2.36 τ*; 2.45 τ (1H, bs, H-5); 2.50 τ*; 3.04 τ (1H, d, J_{23} = 4.4 Hz, H-3); 7.03 τ (2H, q, J = 7.5 Hz, $C\underline{H}_2CH_3$); 7.56, 7.62, 7.62, 7.67 τ (6H, 2s, CH_3 and 12H, 4s, CH_3*); 8.66 τ (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$).

* - peaks for 3,4,6,7-tetramethylquinoline (see also section 3.3.3.2.1 (ii)).

Frequency sweep spin decoupling of the doublet at 1.50 τ caused the doublet at 3.04 τ to collapse to a singlet.

From a comparison of the respective areas of the H-5 and H-8 peaks the proportion of 4-ethyl-6,7-dimethylquinoline present was estimated to be 33%. The ratio of 3,4,6,7-tetramethylquinoline : 4-ethyl-6,7-dimethylquinoline was therefore 98.33 : 1.66 or 1 : 0.017. The preparative yield of 4-ethyl-6,7-dimethylquinoline in the Beyer synthesis was 0.1%.

3.3.4 DISCUSSION

As reviewed in the literature survey, in many standard texts (e.g. ref. 304) the Beyer synthesis has been considered as limited to methyl ketones only. The present study has shown that the synthesis may be effected with a variety of non-methyl ketones, such as pentan-3-one, heptan-4-one and propiophenone. However, in all cases the yields obtained were very low, despite the more favoured conditions[27,50] introduced for the modified von Miller-Kinkelin reaction (see section 3.2) being employed. The low yields are consistent with the known poor reactivity of aldehydes with alkanones in the aldol condensation,[310a] particularly in the case of heptan-4-one and higher homologues.

Nevertheless, the "one-pot" nature of the Beyer synthesis does offer a more convenient synthesis of certain substituted quinoline derivatives compared with the alternative procedures. For example, the preparation of 4-ethyl-3-methylquinoline

may be accomplished *via* a one-step Beyer synthesis from pentan-3-one (5% yield), which is considered more convenient than the alternative multi-stage procedure reported by Wohnlich[65] as shown in Scheme 3.3.1.

When the reaction was performed with butanone the major product isolated was 3,4-dimethylquinoline (see Table 3.3.1) consistent with the earlier work of Tertov and Ardashev.[64] These workers claimed that 4-ethylquinoline was also produced in the reaction but no experimental evidence to support this claim was offered other than that repeated crystallisation of the product would remove the 4-ethylquinoline impurity.

Production of the 3,4-disubstituted product is consistent with the known behaviour of ketones of the type (LXXIX, R = alkyl, aryl or H; R' = alkyl or aryl) with aldehydes

$$\overset{1}{CH_3}\overset{2}{CO}\overset{3}{CHRR'}$$

(LXXIX)

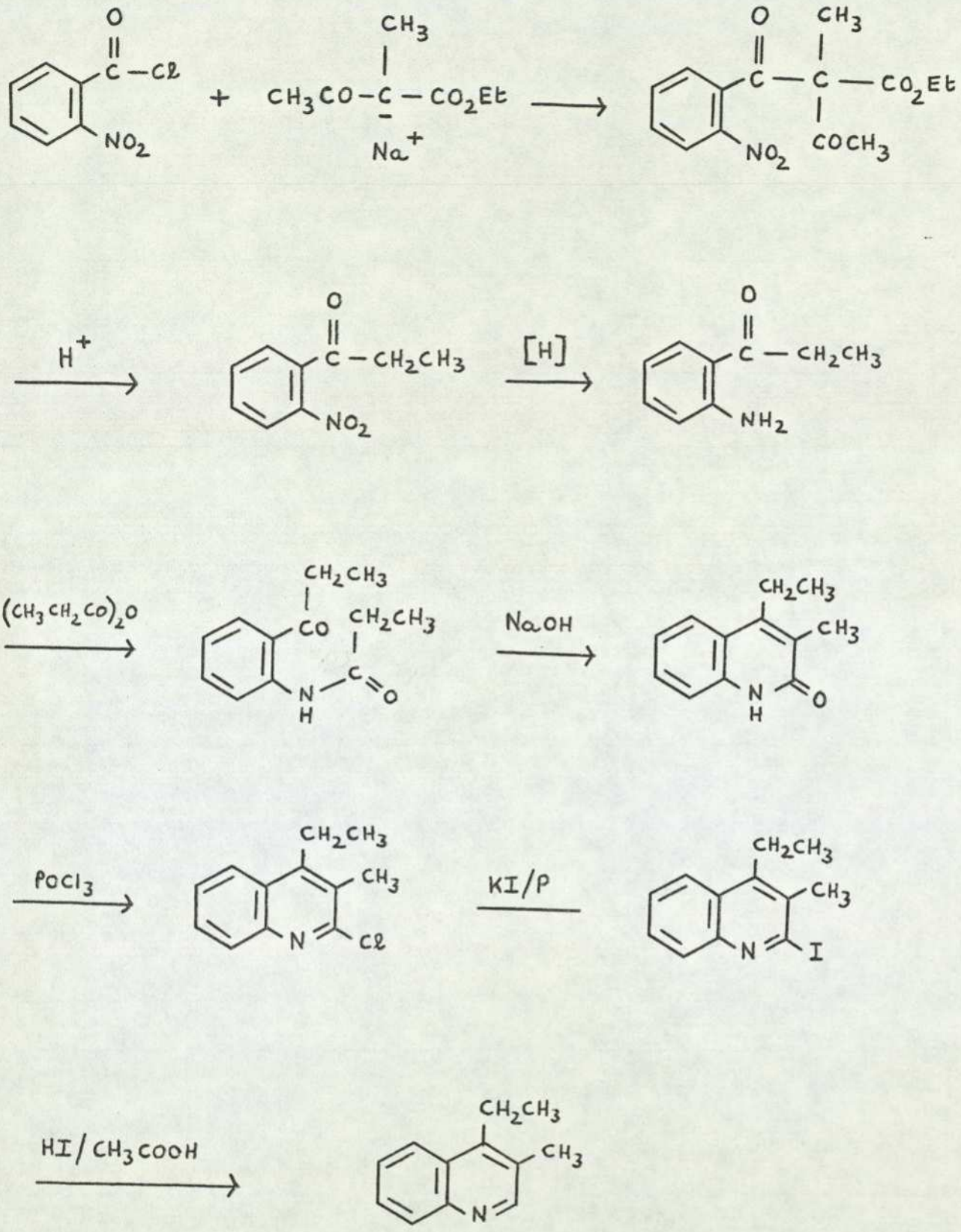
in the aldol condensation. In acid medium all methyl *n*-alkyl ketones have been reported to participate in 3-condensation.[310b]

In order to assess whether any 1-condensation occurred in the Beyer synthesis, leading to the 4-substituted quinoline, a synthesis using butanone and 3,4-dimethylanilin was thoroughly examined. The reason for the choice of amine was twofold:

(a) the reaction was also required as an example of the "orientation effects in quinoline syntheses" studies (see Chapter 4),

(b) the expected 6,7-disubstituted quinoline products should produce simple singlet first order n.m.r. spectra which could be used quantitatively with the minimum possible chance of signal overlap.

The main product obtained was 3,4,6,7-tetramethylquinoline (6% yield). That this compound (and all of the other 3,4-disubstituted products) was substituted in this manner was readily deduced from n.m.r. spectroscopy since all these compounds exhibited a low field peak for H-2 at *ca.* 1.2 - 1.5 τ which appeared as a sharp singlet. The lack of any significant coupling to this proton confirmed that both positions 3- and 4- were occupied.



Scheme 3.3.1

Synthesis of 4-ethyl-3-methylquinoline
(1913, Wohnlich[65])

No 4-ethyl-6,7-dimethylquinoline could be detected in the initial product, hence a careful quantitative fractional crystallisation of the picrate derivative was performed. Several fractions of pure 3,4,6,7-tetramethylquinoline picrate (m.p. 251-2°) were separated over a period of a few weeks whilst the solution volume was progressively reduced. When, eventually, no more of the tetramethylquinoline separated the remaining liquor (which was of low bulk) was carefully evaporated to dryness. Decomposition of the residual picrate and analysis of the liberated bases by n.m.r. indicated the presence of 4-ethyl-6,7-dimethylquinoline. The familiar A_3B_2 pattern for the ethyl group was readily apparent and in the low field area of the aromatic region (ca. 1.5τ) two signals were present, a singlet and a doublet (J = 4.3 Hz). The former signal was caused by residual 3,4,6,7-tetramethylquinoline whilst the latter was due to the 4-ethyl derivative. This was confirmed by the presence of an additional doublet (J = 4.4 Hz) at 3.04 τ, assigned to H-3, which collapsed to a singlet upon spin decoupling the appropriate H-2 doublet. From a comparison of the areas of the respective H-5 and H-8 signals the composition of the mixture was assessed.

The ratio of products in this particular example of the Beyer synthesis was found to be 98.33 : 1.66 in favour of the 3,4-disubstituted derivative.

The Beyer synthesis may therefore be employed with (i) alkyl methyl ketones, (ii) aralkyl ketones and (iii) symmetrical alkyl ketones to produce a variety of 3,4-disubstituted quinoline derivatives. The small proportion of 4-alkylquinoline formed in reaction type (i) may readily be removed through simple recrystallisation of the picrate derivative.

CHAPTER 4

ORIENTATION EFFECTS IN THE SYNTHESIS OF QUINOLINE DERIVATIVES

4.1 INTRODUCTION

Quinoline syntheses which involve ring closure of an asymmetric aniline derivative can result in the formation of two isomeric quinoline products.[10]

Previous studies of these orientation effects have been limited to those syntheses in which the heterocyclic ring was unsubstituted. In the present work a detailed study has been made of the composition of the isomeric products formed from reactions with m-toluidine and with 3,4-dimethylaniline in a variety of syntheses to afford isomeric products substituted at different positions in the quinoline ring. The syntheses and reactants employed are summarised in Table 4.1.

4.2 ORIENTATION EFFECTS IN THE SYNTHESIS OF QUINOLINE DERIVATIVES

4.2.1 GENERAL NOTES

(i) The synthetic procedures given below (section 4.2.2) have been classified by the substituents present in the heterocyclic ring. In all cases the amine reactants used were:

(a) m-toluidine (freshly redistilled, b.p. 203-4°/760 mm.)

(b) 3,4-dimethylaniline (freshly redistilled, b.p. 226-7°/760 mm., m.p. 50-1°).

(ii) The reaction mixtures were separated, analysed and the final products identified by the general procedures described in section 4.2.3.

(iii) The results are collected in section 4.2.4.

4.2.2 SYNTHETIC PROCEDURES

4.2.2.1 Heterocyclic ring unsubstituted

(The Skraup synthesis, preparation of 5-/7- methylquinoline and of 5,6-/6,7-dimethylquinoline).

TABLE 4.1

Synthesis of quinoline derivatives

Heterocyclic ring substituents	Synthesis and reactants used	Previous workers' references(a)	
		m-toluidine	3,4-dimethyl-aniline
NIL	Skraup (glycerol)	18,25,83	18,25,90
2-methyl-	Doebner-von Miller (acetaldehyde)	25,44	96,97
3-methyl-	modified Doebner-von Miller (dimethoxymethane/paraformaldehyde)	22,25	-
4-methyl-	(i) Skraup (methyl vinyl ketone) (ii) Knorr (ethylacetoacetate)	25,92	98
2-ethyl-3-methyl-	Doebner-von Miller (propionaldehyde)	95	-
2,4-dimethyl-	Combes (pentan-2,4-dione)	93	99
3,4-dimethyl-	Beyer (butanone, paraformaldehyde)	25	100
2,3,4-trimethyl-	Combes (3-methylpentan-2,4-dione)	94	100

Notes (a) References are given to reactions commencing with m-toluidine or with 3,4-dimethylaniline to produce the same products as obtained in the present work. The preparative method used is not necessarily the same as used in the present work.

The general procedure of Clarke and Davies[31] was employed using the amine (0.2 mole) ferrous sulphate (8g.), glycerol (68.7 ml., 0.94 mole), arsenic pentoxide (45.9g., 0.2 mole) and concentrated sulphuric acid (40 ml.)

4.2.2.2 2-Substituted derivatives

(The Doebner-von Miller Synthesis, preparation of 2,5-/2,7-dimethylquinoline and of 2,5,6-/2,6,7-trimethylquinoline).

The general procedure of Mills, Harris and Lambourne[47] was employed using the amine (0.2 mole), concentrated hydrochloric acid (68 ml.), freshly distilled acetaldehyde (22.0g., 0.5 mole), and zinc chloride (5g.).

4.2.2.3 3-Substituted derivatives

(The modified Doebner-von Miller Synthesis, preparation of 3,5-/3,7-dimethylquinoline and of 3,5,6-/3,6,7-trimethylquinoline).

The synthesis of these compounds has been described previously; 3,5-/3,7-dimethylquinoline (see section 3.2.2.1 and 3.2.2.5) and 3,5,6-/3,6,7-trimethylquinoline (see section 3.2.2.1).

4.2.2.4 4-Substituted derivatives

(a) (The Skraup synthesis, preparation of 4,7-dimethylquinoline and 4,6,7-trimethylquinoline).

The general procedure of Campbell and Schaffner[27] was employed using the amine hydrochloride (0.0625 mole), ferric chloride hexahydrate (27g., 0.1 mole), anhydrous zinc chloride (1 g.), ethanol (45 ml.) and methyl vinyl ketone (95%, 4.2 ml., 0.05 mole).

(b) (The Knorr synthesis, preparation of 4,7-dimethyl- and 4,6,7-trimethylquinoline).

(i) The synthesis of the appropriate 4-methyl-2-quinolone derivatives has been described elsewhere (see sections 6.3.1 and 6.3.2).

(ii) The appropriate 2-chloro-4-methylquinoline derivatives were synthesised by the general procedure of Michailov[311] using the quinolone (0.05 mole) and phosphorus oxychloride (9.3 g., 0.06 mole). 2-chloro-4,7-dimethylquinoline (90% yield) crystallised from ethanol as colourless needles, m.p. 49 - 50°.

(Found : C, 68.9; H, 5.3; N, 7.4; Cl, 18.7%. Calculated for $C_{11}H_{10}NCl$: C, 68.9; H, 5.3; N, 7.3; Cl, 18.5%.)

N.M.R. (100 MHz, $CDCl_3$) : 2.32τ(1H, d, J_{56} = 8.2 Hz, H-5); 2.36τ (1H, bs, H-8); 2.76τ(1H, d of d, J_{56} = 8.2 Hz, J_{68} = 2.0 Hz, H-6); 2.99τ(1H, s, H-3); 7.43τ(3H, s, CH_3 (4)); 7.49τ(3H, s, CH_3 (7)).

2-Chloro-4,6,7-trimethylquinoline (75% yield) crystallised from ethanol as colourless needles, m.p. 137-8° (Found: C, 70.2; H, 6.1; N, 6.9; Cl, 17.0%. Calculated for $C_{12}H_{12}NCl$: C, 70.0; H, 5.9; N, 6.8; Cl, 17.2%).

N.M.R. (100 MHz, $CDCl_3$) : 2.38τ(1H, s, H-8); 2.49τ(1H, s, H-5); 3.01τ(1H, s, H-3); 7.44τ(3H, s, CH_3(4)), 7.58τ(6H, s, CH_3 (6 & 7)).

(iii) The 4-methylquinoline derivatives were synthesised from the appropriate 2-chloro-4-methylquinoline derivatives by the general procedure of Michailov[311] using the chloroquinoline (0.03 mole), concentrated hydrochloric acid (30 ml.) and tin dust (15g.).

4.2.2.5 2,3-Disubstituted derivatives

(The Doebner-von Miller synthesis, preparation of 2-ethyl-3,5-/3,7-dimethylquinoline and of 2-ethyl-3,5,6-/3,6,7-trimethylquinoline).

The general procedure of Mills, Harris and Lambourne[47] was employed using the amine (0.2 mole), concentrated hydrochloric acid (68 ml.), freshly distilled propionaldehyde (29.0g., 0.5 mole) and zinc chloride (5g.).

4.2.2.6 2,4-Disubstituted derivatives

(The Combes synthesis, preparation of 2,4,7-trimethylquinoline and of 2,4,6,7-tetramethylquinoline).

The general procedure described previously (see section 3.1.2.3) was employed using the amine (0.1 mole) and pentan-2,4-dione (11.0g., 0.11 mole).

4.2.2.7 3,4-Disubstituted derivatives

(The Beyer synthesis, preparation of 3,4,7-trimethylquinoline and of 3,4,6,7-tetramethylquinoline).

The general procedure described previously (see section 3.3.2.1) was employed using the amine (0.32 mole), butanone (0.56 mole), ferric chloride hexahydrate (50g.), anhydrous zinc chloride (5g.) and paraformaldehyde (9.2 g.). The synthesis of 3,4,6,7-tetramethylquinoline has been previously described in detail (see section 3.3.3.2.1).

4.2.2.8 2,3,4-Trisubstituted derivatives

(The Combes synthesis, preparation of 2,3,4,7-tetramethylquinoline and of 2,3,4,6,7-pentamethylquinoline).

The general procedure described previously (see section 3.1.2.3) was employed using the amine (0.1 mole) and especially purified (see section 4.2.2.8.1) 3-methylpentan-2,4-dione (12.5g., 0.11 mole).

4.2.2.8.1 Synthesis of 3-methylpentan-2,4-dione (methylacetylacetone).

Initial experiments using a commercial sample of 3-methylpentan-2,4-dione gave impure products due to the presence of pentan-2,4-dione in the sample (as detected by gas-liquid chromatography). Accordingly, a sample of 3-methylpentan-2,4-dione was synthesised and especially purified.

(i) Synthesis of acetylacetone sodio derivative

The method of Shepherd[312] was employed. Acetylacetone sodio derivative (70% yield) was obtained as colourless plates, m.p. 205° (lit.[313] m.p. 217-9°).

(ii) Synthesis of 3-methylpentan-2,4-dione

The method of Shepherd[312] was employed. The crude product obtained (28% yield) was analysed by gas-liquid chromatography and found to contain pentan-2,4-dione (ca. 5-10%) as an impurity. Accordingly the product was carefully purified via the copper salt.

The crude 3-methylpentan-2,4-dione (32g., 0.28 mole) was dissolved in an equal volume of methanol and a hot filtered solution of copper acetate (90.8g., 0.5 mole) in water (800 ml.) was added. A greyish-green precipitate was formed

which was filtered off, washed with a little petroleum ether (60-80°) and dried at 90°. The complex was then recrystallised several times from methanol to eventually afford the copper salt as greyish-green plates, m.p. 197-204° (decompn.), lit.[314] m.p. 200-30° (decompn.).

The purified copper salt was shaken with dilute sulphuric acid (600 ml.) and ether (200 ml.) and the layers separated. The aqueous layer was re-extracted with ether (2 x 200 ml.) and the ether extracts combined and dried over anhydrous magnesium sulphate. Removal of the solvent left 3-methylpentan-2,4-dione (21% recovery) as a pale yellow liquid, b.p. 169-71°/759 mm. (lit.[315] b.p. 170-2°/760 mm.). The product was analysed by gas-liquid chromatography and found to be free from pentan-2,4-dione.

N.M.R. (100 MHz, CCl_4): -6.25τ (0.35H, s, O<u>H</u>, enol); 6.48τ (0.65H, q, J = 7 Hz, C<u>H</u>, keto); 7.93τ (6H, s, terminal C<u>H</u>$_3$, enol and keto); 8.21τ (1.05H, s, central C<u>H</u>$_3$, enol); 8.80τ (1.95H, d, J = 7 Hz, central C<u>H</u>$_3$, keto).

4.2.2.9 <u>Synthesis of 2,4,5,6,8-pentamethylquinoline</u>

The general procedure described previously (see section 4.2.2.6) was used. The product (15.5g., 80%) was obtained as colourless prisms (from hexane), m.p. 72-3° (lit.[94] m.p. 75°).

N.M.R. (100 MHz, CCl_4): 2.86τ (1H, s, H-7); 3.17τ (1H, s, H-3); 7.26, 7.40, 7.43, 7.46, 7.67τ (15H, 5s, CH_3).

The picrate crystallised from ethanol as yellow needles, m.p. 183-4° (lit.[94] m.p. 171-2°).

4.2.3 SEPARATION, ANALYSIS AND IDENTIFICATION OF REACTION PRODUCTS

4.2.3.1 General Procedure

(i) A sample of the initial reaction product was analysed by gas-liquid chromatography (see section 4.2.3.2) and by nuclear magnetic resonance spectroscopy (see section 4.2.3.3). Special care was exercised to obtain a uniform sample for the analyses, in the case of solid samples an aliquot of the homogeneous melt was used.

(ii) From another sample of the initial reaction product (obtained as in (i) above) a picrate derivative was prepared. Picric acid (2g.) in boiling ethanol (20 ml.) was added to a solution of the initial reaction product (2g.) in boiling ethanol (20 ml.) The picrate, was collected and washed with a little ethanol, and a melting point determined, the derivative was usually obtained as small or microscopic yellow needles.

A small sample of the picrate was decomposed with sodium hydroxide solution (see section 3.2.2.3) and the liberated bases analysed by gas-liquid chromatography (see section 4.2.3.2) which usually indicated that the quinoline content in the initial reaction mixture and in the picrate were similar and that no separation had been effected. In the case of the 2-substituted quinolines, which were particularly soluble in ethanol, a partial separation was indicated. The melting points of the initial picrate derivatives are shown in Table 4.2.

(iii) The initial picrate derivative (1.0g.) was dissolved in boiling ethanol (200 ml. - 2000 ml.) and the hot solution filtered through a fine filter paper into an especially cleaned beaker. (The exact volume of ethanol required was dependent upon the solubility of the picrate derivative and was determined by experience). The solution was cooled and allowed to stand at room temperature for 1 to 3 days during which time any precipitated picrate derivative which had formed was collected. The remaining solution was then reduced in volume by 10% and again allowed to stand. This technique was repeated until the required separation had been achieved. The total time taken varied from 1 day to 6 weeks, but was normally 3-4 days.

Small samples of the precipitated picrate derivatives obtained were decomposed with sodium hydroxide solution (see Section 3.2.2.3) and the liberated bases were

analysed by gas-liquid chromatography (see section 4.2.3.2) in order to ascertain which fractions contained the appropriate pure 7-methyl- or 6,7-dimethyl derivative. The pure picrate, which was usually obtained as long slender yellow needles, was submitted to elemental analysis and a melting point determined. The results obtained are shown in Table 4.2.

(iv) The pure picrate derivative was decomposed with sodium hydroxide solution (see section 3.2.2.3) and the pure quinoline base isolated by steam distillation and finally purified by distillation (at 760 mm.) or by recrystallisation (from hexane). The final purified product was analysed by gas-liquid chromatography (see Section 4.2.3.2) and by Nuclear Magnetic Resonance Spectroscopy (see Section 4.2.3.3). The results are shown in Tables 4.3 and 4.5.

4.2.3.2 Gas-Liquid Chromatography

The following gas-liquid chromatographic conditions were employed for the analysis of the quinoline derivatives:

Instrument:	Perkin Elmer model 800
Detector:	Flame ionisation
Column:	4' x $\frac{1}{4}$" loaded with 20% diglycerol on celite (60-80 mesh).
Column Temperature:	140°
Injector Temperature:	300°
Carrier Gas:	Nitrogen, flow rate 80 ml./min.
Solvent used:	Ether

The results of the gas-liquid chromatographic analyses are shown in Tables 4.6 and 4.7.

For the estimation of isomer ratios, a direct comparison of the areas of the respective peaks was used. Response factors from known quantities of authentic samples with respect to an internal standard were determined for the 5-methylquinoline/7-methylquinoline mixture and found to be close to unity. Since this made very little difference to the isomer ratio such a procedure was not applied to the other analyses.

4.2.3.3 Nuclear Magnetic Resonance Spectroscopy

N.m.r. spectra were determined on a Varian Associates HA-100D spectrometer operating at 100 MHz. Samples were dissolved in carbon tetrachloride, and tetramethylsilance was used as the internal standard.

Spectra were normally determined with a 1000 Hz (10τ) sweep width, expansions of the methyl groups were performed with a 100 Hz (1τ) sweep width, to facilitate accurate measurement of peak areas.

For the determination of isomer ratios, direct comparison of the areas of the respective methyl peaks was used.

The results of the n.m.r. analyses are shown in Tables 4.5 and 4.6.

4.2.4 RESULTS

The results obtained are summarised in Tables 4.2 - 4.7.

TABLE 4.2

Properties of quinoline picrate derivatives

Substituted quinoline (no.)	Initial picrate m.p.	Lit. m.p.	Final picrate m.p. (a)	Lit. m.p.
7-Me	235° (b)	235° (25)	245-6° (d)	242° (25), 245° (18)
6,7-Me_2	260-2° (c)	-	278-9° (d)	278° (25)
2,7-Me_2	180-2° (b)	-	194-5° (d)	196° (25)
2,6,7-Me_3 (1)	202-5° (c)	-	221-2° (d)	-
3,7-Me_2	197-202° (b,e)	-	239-40° (d)	244° (25), 240.5° (22)
3,6,7-Me_3 (2)	198-202° (c,e)	-	245-6° (d)	-
4,7-Me_2 (f)	233-4°	230° (83)	235-6° (d)	230° (92)
4,6,7-Me_3 (f) (3)	264-5°	-	266-7° (d)	-
2-ethyl-3,7-Me_2 (4)	211-3° (b)	219-20° (95)	222-3° (d)	219-20° (95)
2-ethyl-3,6,7-Me_3 (5)	220-1° (c)	-	228-9° (d)	-
2,4,7-Me_3 (10)	233-4°	234-6° (93)	235-6° (d)	234-6° (93)
2,4,6,7-Me_3 (6)	238-9°	-	239-40° (d)	-
3,4,7-Me_3 (11)	227-8°	229° (25)	228-9° (d)	229° (25)
3,4,6,7-Me_4 (7)	249-50°	-	251-2° (d)	-
2,3,4,7-Me_4 (8)	215-6°	-	217-8° (d)	-
2,3,4,6,7-Me_5 (9)	225-6°	-	227-8° (d)	-

Notes (a) - see Table 4.4 for analytical data.

(b) - also contains 5-isomer (g.l.c. after decompn.)

(c) - also contains 5,6-isomer (g.l.c. after decompn.)

(d) - pure (g.l.c. after decompn.)

(e) - also contains 2-ethyl substituted by-products (see section 3.2.2.1)

(f) - similar results obtained for products from the Knorr and Skraup reactions.

TABLE 4.3

Properties of quinoline derivatives

Substituted quinoline (no.)	Yield (%) (a)	Initial m.p.	Lit. m.p.	Final m.p. (b,c)	Lit. m.p.
7-Me	71	b.p. 255-60°/760 mm. n_D^{20} 1.6147	b.p. 257.6°/760 mm. (86) $n_D^{20.8}$ 1.6149 (316)	m.p. 37 - 8°	39° (86)
6,7-Me_2	68	50-5°	-	57-8°	58° (25)
2,7-Me_2	19	b.p. 264-6°/760 mm.	b.p. 265°/745 mm. (317)	59-60°	61° (25)
2,6,7-Me_3 (1)	16	60-70°	69-70° (96)	73-4°	-
3,7-Me_2	- (d)	-	b.p. 270-1.5° (22)	78-9°	80° (25)
3,6,7-Me_3 (2)	- (d)	80-95°	-	111-2°	-
4,7-Me_2	44 (e)	b.p. 280-5°/760 mm.	b.p. 283° (318)	b.p. 284°/757 mm.	b.p. 283° (318)
4,6,7-Me_3 (3)	37 (e)	90-5°	-	95-6°	-
4,7-Me_2	52 (f)	b.p. 280-5°/760 mm.	-	b.p. 283-4°/760 mm.	-
4,6,7-Me_3	44 (f)	92-5°	-	95-6°	-
2-ethyl-3,7-Me_2 (4)	6	25-32°	40-1° (95)	40-1°	40-1° (95)
2-ethyl-3,6,7-Me_3 (5)	20	95-103°	-	113-4°	-
2,4,7-Me_3 (10)	85	b.p. 283-5°/760 mm.	-	b.p. 283-5°/760 mm. n_D^{22} 1.5990	b.p.103-4°/ 1.5 mm. n_D^{20} 1.5997 (93)

Cont....

TABLE 4.3 (Cont.)

Substituted quinoline (no.)	Yield (%) (a)	Initial m.p.	Lit. m.p.	Final m.p. (b,c)	Lit. m.p.
2,4,6,7-Me_4 (6)	90	76-9° (b.p. 308-10°/772 mm.)	-	79-80°	79-80° (99)
3,4,7-Me_3 (11)	9	73-6°	-	76-7°	78° (25)
3,4,6,7-Me_4 (7)	6	118-22°	-	124-5°	124-5° (100)
2,3,4,7-Me_4 (8)	17	114-6°	79° (94)	119-20°	-
2,3,4,6,7-Me_5 (9)	22	144-6°	-	145-6°	144-5° (100)

Notes (a) - Initial yield of (mixed) quinolines.

(b) - Purified product, from decomposed picrate derivative after fractional crystallisation.

(c) - See Table 4.4 for analytical data.

(d) - See section 3.2.

(e) - *via* Knorr synthesis. (% yield from 2-chloro-4-methylquinoline derivative given).

(f) - *via* Skraup synthesis.

TABLE 4.4

Elemental Analyses of Quinoline products

Compound Number (a)	Molecular Formula	Calc.			Found		
		C	H	N	C	H	N
1	$C_{12}H_{13}N$	84.2	7.7	8.2	84.5	7.8	8.3
1 picrate	$C_{18}H_{16}N_4O_7$	54.0	4.0	14.0	53.9	4.1	13.8
2	$C_{12}H_{13}N$	84.2	7.7	8.2	84.6	7.9	8.3
2 picrate	$C_{18}H_{16}N_4O_7$	54.0	4.0	14.0	53.9	4.1	13.9
3	$C_{12}H_{13}N$	84.2	7.7	8.2	84.4	7.7	7.9
3 picrate	$C_{18}H_{16}N_4O_7$	54.0	4.0	14.0	53.8	4.2	14.0
4	$C_{13}H_{15}N$	84.3	8.2	7.6	84.4	7.9	7.7
4 picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.3	4.3	13.6
5	$C_{14}H_{17}N$	84.4	8.6	7.0	84.3	8.4	6.9
5 picrate	$C_{20}H_{20}N_4O_7$	56.1	4.7	13.1	56.3	4.7	13.1
6 picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.0	4.4	13.6
7 picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.2	4.3	13.7
8	$C_{13}H_{15}N$	84.3	8.2	7.6	84.2	8.2	7.5
8 picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.3	4.2	13.7
9 picrate	$C_{20}H_{20}N_4O_7$	56.1	4.7	13.1	55.9	4.6	12.8

(a) - Compound Nos. as shown in Tables 4.2 and 4.3.

Notes - Satisfactory elemental analyses (C, H, N) were also obtained for the following known compounds: 6, 7, 9, 10, 10 picrate, 11, 11 picrate.

TABLE 4.5

N.M.R. Spectra of quinoline derivatives (100 MHz), CCl_4, τ p.p.m.)

R^2	R^3	R^4	Chemical Shift (a) H-2	H-3	H-4	H-5	H-6	H-7	H-8	Methylene groups & coupling constants
7-methyl derivatives										
CH_3	H	H	(7.37)	2.96	2.20	2.50	2.85	(7.49)	2.31	J_{34} = 8.3 Hz J_{56} = 8.3 Hz J_{68} = 1.7 Hz
H	CH_3	H	1.44	(7.55)	2.33	2.53	2.82	(7.48)	2.27	J_{24} = 2.1 Hz J_{56} = 8.4 Hz J_{68} = 1.7 Hz
H	H	CH_3	1.45	3.06	(7.48)	2.34	2.82	(7.53)	2.22	J_{23} = 4.2 Hz, J_{56} = 8.4 Hz J_{68} = 1.8 Hz
C_2H_5	CH_3	H	(8.66)	(7.63)	2.41	2.58	2.88	(7.51)	2.30	CH_2 = 7.14 τ $J_{CH_2.CH_3}$ = 7.5 Hz J_{56} = 8.3 Hz, J_{68} = 1.7 Hz
CH_3	H	CH_3	(7.47)	3.19	(7.54)	2.41	2.89	(7.54)	2.34	J_{56} = 8.4 Hz, J_{68} = 1.8 Hz
H	CH_3	CH_3	1.57	(7.66)	(7.51)	2.32	2.84	(7.55)	2.31	J_{56} = 8.5 Hz, J_{68} = 1.7 Hz
CH_3	CH_3	CH_3	(7.44)	(7.74)	(7.56)	2.36	2.88	(7.52)	2.38	J_{56} = 8.6 Hz, J_{68} = 1.8 Hz
6,7-dimethyl derivatives										
H	H	H	1.36	2.87	2.17	2.62	(7.57,7.60) (b)		2.26	J_{23} = 4.2 Hz, J_{34} = 8.3 Hz J_{24} = 1.9 Hz
CH_3	H	H	(7.40)	3.00	2.30	2.70	(7.62,7.67) (b)		2.33	J_{34} = 8.2 Hz

Cont.....

TABLE 4.5 (Cont.)

R^2	R^3	R^4	H-2	H-3	H-4	H-5	H-6	H-7	H-8	Methylene groups & coupling constants
H	CH_3	H	1.49	(7.61)	2.38	2.68	(7.55,7.56)(b)		2.29	J_{24} = 2.2 Hz
H	H	CH_3	1.52	3.07	(7.46)	2.50	(7.62)	(7.62)	2.29	J_{23} = 4.3 Hz
C_2H_5	CH_3	H	(8.66)	(7.63)	2.48	2.73	(7.60,7.63)(b)		2.33	CH_2 : 7.15 τ
										$J_{CH_2.CH_3}$ = 7.5 Hz
CH_3	H	CH_3	(7.45)	3.16	(7.49)	2.54	(7.61)	(7.61)	2.37	-
H	CH_3	CH_3	1.63	(7.67)	(7.56)	2.50	(7.62)	(7.62)	2.36	-
CH_3	CH_3	CH_3	(7.46)	(7.75)	(7.57)	2.56	(7.63)	(7.63)	2.45	-
H	H	C_2H_5	1.50	3.04	(8.66)	2.45	(7.62)	(7.62)	2.28	CH_2 : 7.03 τ
										$J_{CH_2.CH_3}$ = 7.5 Hz
										J_{23} = 4.4 Hz
5-methyl derivatives (c)										
CH_3	H	H	(7.36)	2.92	2.02	(7.45)	2.52-2.68 (m)		~ 2.2	J_{34} = 8.6 Hz
C_2H_5	CH_3	H	(8.67)	(7.72)	~2.3	(7.53)	(e)		2.20	CH_2 : 7.14 τ
										$J_{CH_2.CH_3}$ = 7.5 Hz

Cont.....

TABLE 4.5 (Cont.)

R^2	R^3	R^4	H-2	H-3	H-4	H-5	H-6	H-7	H-8	Methylene groups & coupling constants
5,6-dimethyl derivatives (d)										
CH_3	H	H	(7.40)	2.98	2.04	(7.60)	(e)	2.73	2.35	J_{34} = 8.5 Hz J_{78} = 8.5 Hz
C_2H_5	CH_3	H	(8.66)	(e)	2.17	(7.54)	(e)	2.73	2.33	CH_2 : 7.14 τ $J_{CH_2.CH_3}$ = 7.5 Hz J_{78} = 8.2 Hz

Notes (a) - Values in parentheses are for the appropriate substituted methyl group.

(b) - Exact assignments uncertain.

(c) - In admixture with 7-methyl isomer.

(d) - In admixture with 6,7-dimethyl isomer.

(e) - Peak obscured.

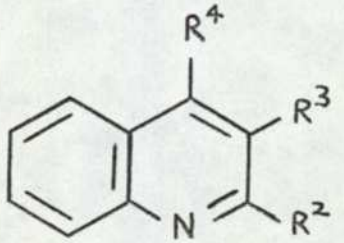


TABLE 4.6

Isomer Ratios of 5-/7- methyl- and 5,6-/6,7- dimethyl-quinoline derivatives

Heterocyclic Ring Substituents	Composition of mixture (%) (a)		Composition of mixture (%) (a)	
	5-Me	7-Me	$5,6\text{-Me}_2$	$6,7\text{-Me}_2$
Nil	30	70	25	75
2-Me	30	70	29	71
3-Me	27	73	28	72
4-Me (via Knorr)	0	100	1	99 (b)
4-Me (via Skraup)	0	100	1	99 (b)
2-ethyl-3-Me	27	73	21	79 (c)
$2,4\text{-Me}_2$	0	100	0	100
$3,4\text{-Me}_2$	0	100	0	100
$2,3,4\text{-Me}_3$	0	100	0	100
4-Et				excess (d)

Notes (a) - by n.m.r. and g.l.c.

(b) - by g.l.c. only

(c) - by n.m.r. only

(d) - by n.m.r. only - see Section 3.3.3.2

TABLE 4.7

Gas-liquid chromatographic data for alkylquinoline derivatives (20% diglycerol column at 140°)

Substituted quinoline	Relative Retention Time (a)	Ratio 5-/7- or 5,6-/6,7-
5-methyl-	1.43	1.17
7-methyl-	1.22	
2,5-dimethyl-	1.22	1.17
2,7-dimethyl-	1.04	
3,5-dimethyl-	1.75	1.14
3,7-dimethyl-	1.53	
4,5-dimethyl-	2.91	1.29
4,7-dimethyl-	2.25	
5,6-dimethyl-	2.54	1.11
6,7-dimethyl-	2.28	
2,5,6-trimethyl-	2.06	1.11
2,6,7-trimethyl-	1.85	
3,5,6-trimethyl-	3.01	1.09
3,6,7-trimethyl-	2.75	
4,5,6-trimethyl-	5.35 (b)	1.32
4,6,7-trimethyl-	4.05 (b)	
2,4,7-trimethyl-	1.78	
3,4,7-trimethyl-	- (c)	
2,4,6,7-tetramethyl-	3.19	
3,4,6,7-tetramethyl-	- (c)	
2,3,4,7-tetramethyl-	- (c)	
2,3,4,6,7-pentamethyl-	- (c)	

Cont.....

TABLE 4.7 (Cont.)

Substituted quinoline	Relative Retention Time (a)	Ratio 5-/7- or 5,6-/6,7-
2-ethyl-3,5-dimethyl-	0.95	1.11
2-ethyl-3,7-dimethyl-	0.85	
2-ethyl-3,5,6-trimethyl-	1.65 (d)	1.00
2-ethyl-3,6,7-trimethyl-	1.65 (d)	

Notes (a) Relative to quinoline = 1.00.

(b) Very broad peak.

(c) Retention times too long. Single peak only obtained with 10% silicone SE52 column operated isothermally at 225°.

(d) Could not be separated, even upon reducing temperature to 115°.

4.2.5 DISCUSSION

Previous detailed studies of the orientation effects in quinoline syntheses have been limited to derivatives unsubstituted in the heterocyclic ring.[18,83] Although a few isolated reports of the composition of the products obtained from reactions with m- and 3,4-disubstituted anilines to give heterocyclic ring substituted quinolines have appeared (see Table 4.1) no systematic detailed study has been performed. Such a programme has been carried out in the present work under controlled experimental conditions, since it is not unusual for the recorded properties of a compound to vary by more than reasonable experimental error when determined by different investigators.

To facilitate comparison of results additional methyl substituents were generally introduced, except that for preparative convenience propionaldehyde was used as a reactant in the Doebner-von Miller synthesis to produce the 2-ethyl-3-methyl-substituted quinoline.[46,95] Alternative preparations of the 2,3-dimethylquinoline derivatives were less readily performed.

One experimental difficulty was encountered in the present work. Commercial samples of 3-methylpentan-2,4-dione were generally found to be contaminated with pentan-2,4-dione. A Combes syntheses[68] with such samples resulted in products in which a signal for the H-3 proton was still evident in the n.m.r. spectrum.

To overcome this problem a sample of 3-methylpentan-2,4-dione was prepared and especially purified *via* the copper salt. The quinoline products obtained using the purified material exhibited no H-3 signal. It was found that the melting point of the synthesised sample of 2,3,4,7-tetramethylquinoline was considerably different from the literature value.[94] It is considered that the earlier sample (similarly obtained through the Combes synthesis) must have been impure. Such discrepancies were not experienced during the preparation of 2,3,4,6,7-pentamethylquinoline since the earlier synthesis[100] of this compound involved a Skraup reaction with 3-methylpent-3-ene-2-one.

The major problem encountered in the earlier studies was the estimation of the composition of the mixed quinoline products obtained. Although the possibility of

the two isomeric products was originally noted in 1884 by Skraup,[82] very few of the early attempts to evaluate the ratio of isomers produced were successful or reliable, the work being hampered by the difficulty of separation and identification of the isomers. The fact that often the 7-substituted quinoline only was reported may be attributed to the frequently greater solubilities and lower melting points of the 5-substituted quinolines and their salts, compared with those of the corresponding 7-isomer.

It was not until 1962 that the composition of the products in the classical Skraup reaction with m-toluidine were eventually reliably clarified by Palmer[18] using modern analytical techniques, including gas-liquid chromatography. In addition, the properties of 7-methylquinoline (m.p. 37-8°, picrate m.p. 245-6°, see Tables 4.2 and 4.3) have frequently been quoted in error in the past, emphasising the many occasions when samples were obtained and considered as pure, but which were no doubt contaminated with 5-methylquinoline.

In the present work it was therefore considered essential that the analytical procedures used be unequivocal, and hence three independent techniques were employed, viz:

(a) gas-liquid chromatography

(b) ^{1}H nuclear magnetic resonance spectroscopy

(c) fractional crystallisation of the picrate derivative.

The respective merits and deficiencies of these procedures will now be considered.

(a) Gas-Liquid Chromatography

Palmer[18] has previously shown that mixtures of 5-/7- methylquinoline and of 5,6-/6,7- dimethylquinoline may readily be analysed by gas-liquid chromatography. A column of poly (propene adipate) was employed. Fitzgerald[302] has concluded that the most useful column for the separation of quinoline mixtures was diglycerol, however, the volatility limits of this material meant that good separations could only be effected at the cost of time and gradual loss of phase. Furthermore, the highly polar diglycerol gave symmetrical peaks whereas non-polar phases were found

to show a strong tendency to "tail". Rezl[319] has also reported satisfactory separations of methylquinolines on a diglycerol column.

Diglycerol was therefore chosen as the stationary phase for the present work to afford the best separation of components with the most symmetrical peaks to facilitate accurate quantitative analysis.

In all cases the 7-substituted isomer was eluted before the 5-substituted isomer.

That the identities of the peaks were in this order was confirmed by reference to earlier reports[302,319] and also by peak enhancement techniques using the separated pure components. With the diglycerol column 2-substituted compounds exhibited shortened retention times due to the "ortho effect" as noted by Fitzgerald.[302]

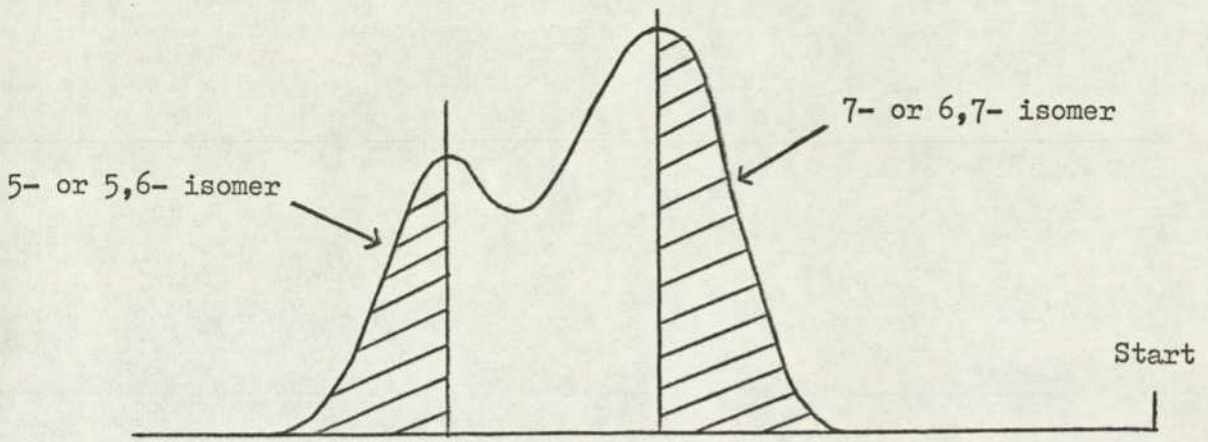
However, even with the diglycerol column complete separation of 5- and 7-methylquinoline could not be achieved (see Table 4.7). Trial runs using a lower carrier gas flow and/or lower column temperature were performed; although slightly better separations were obtained the increased tailing and broadening of the peaks made these alternatives unrealistic.

The normal technique of estimation of peak areas (multiplication of peak height by peak width at mid-height) could not be applied in the present work since the close proximity of the two peaks rendered the latter reading unavailable. Accordingly, the ratio of peak areas was obtained by comparison of the area of the right hand side of the 7- (or 6,7-) isomer with the left hand side of the 5- (or 5,6-) isomer (see Figure 4.1).

This method has merit in that the curves involved represent a pure compound just starting to be eluted (7- or 6,7- isomer) or just completing elution (5- or 5,6- isomer). In order to obtain maximum symmetry of the peaks, overloading of the column was avoided and peaks were attenuated to sufficient height such that "tailing" did not exaggerate the peak width at mid-height.

Although diglycerol afforded the best separation of the quinoline products the possibility still existed that such a separation may not be feasible for certain pairs of isomeric quinolines. For this reason analysis of the reaction

FIGURE 4.1



products was not restricted solely to gas-liquid chromatography, the alternative techniques of n.m.r. spectroscopy and fractional crystallisation of the picrate derivative being employed. In the event this pessimism was fully justified since it did not prove possible to separate 2-ethyl-3,5,6-trimethylquinoline and 2-ethyl-3,6,7-trimethylquinoline by g.l.c. (see Table 4.7). However, the alternative analytical techniques did indicate the presence of both products and a satisfactory estimation of the isomer ratio was obtained.

(b) ^{1}H Nuclear Magnetic Resonance Spectroscopy

This technique proved to be most valuable for the analysis of the isomeric products. The presence of one or two compounds was usually immediately evident.

With mixtures of the 5- and 7- methyl isomers, two separate methyl signals could usually be observed in the 7-8 τ region as sharp singlets. A satisfactory estimate of the composition of the product was then obtained by comparison of the areas of these peaks (peak height x width at mid-height) from suitably expanded spectra.

The identity of the products was assessed from the carbocyclic aromatic region (1.5 - 3.0 τ) of the spectrum, viz:

(i) The 5-substituted isomer will produce a complex second order 3-spin multiplet whilst the pure 7-substituted isomer will give rise to a first order spectrum approximating to an AMX system.

(ii) For reactions commencing with 3,4-dimethyl-aniline the n.m.r. spectra of the quinoline products are very simple. The carbocyclic ring protons of a 5,6-disubstituted derivative occur as two doublets (H-7 and H-8, mutually coupled), alternatively for a 6,7-disubstituted derivative two broadened singlets (H-5 and H-8, mutually weakly coupled) would be expected.

In certain cases the methyl groups of these isomers overlapped, (since they are more numerous and $CH_3(6)$ and $CH_3(7)$ are chemically and magnetically very similar), in these cases the isomer ratios were obtained by comparison of appropriate aromatic signals.

Further comments concerning the nuclear magnetic resonance spectra are given at the end of the discussion.

(c) Fractional Crystallisation of the Picrate Derivatives

This is an old established process[320] which nevertheless is capable of excellent results. In the present work fractional crystallisation of the mixed picrate derivatives from ethanol presented a convenient, reliable technique for the isolation of pure samples of the 7- or 6,7- substituted isomers which were present in larger amounts and always crystallised first from ethanol. The crystallisations were performed only in order to secure an authentic sample of one product for identification purposes, and no attempt was made to obtain pure samples of the respective 5- or 5,6-substituted isomers.

By comparison of the melting points of the initial and final samples of the picrates, the presence of one or two isomeric quinoline products could be deduced as shown by the examples considered below (see also Table 4.2):

(i) 2,4,6,7-tetramethylquinoline picrate

(Initial m.p. 238-9°: Final m.p. 239-40°)

The increase in melting point is slight and represents recrystallisation only. Hence only one isomer was originally present. (Result confirmed by g.l.c. and n.m.r.)

(ii) 6,7-dimethylquinoline picrate

(Initial m.p. 260-2°; Final m.p. 278-9°).

The increase in melting point is quite significant, therefore fractional

crystallisation and separation have occurred. The original product must have been a mixture of the 5,6- and 6,7-isomers. (Result confirmed by g.l.c. and n.m.r.) Similar increases in melting point (in the range 8-18°) were obtained for all the other 5-/7- methyl and 5,6-/6,7- dimethyl quinoline couples studied.

(iii) 3,6,7-trimethylquinoline picrate

(Initial m.p. 198-202°; Final m.p. 245-6°).

The increase in melting point is considerable. Since the original product consisted of four components (see also section 3.2.2) it was not possible to deduce the proportion or even the existence of isomeric products. Hence the necessity for the use of g.l.c. and n.m.r. techniques.

Consideration of the melting points of the picrate derivatives therefore presents a method by which the existence of one or two isomeric products may readily be established, without the need of other analytical equipment. Since the technique of fractional crystallisation is well established[320] it is perhaps surprising that more reliable results were not obtained by some of the earlier workers.

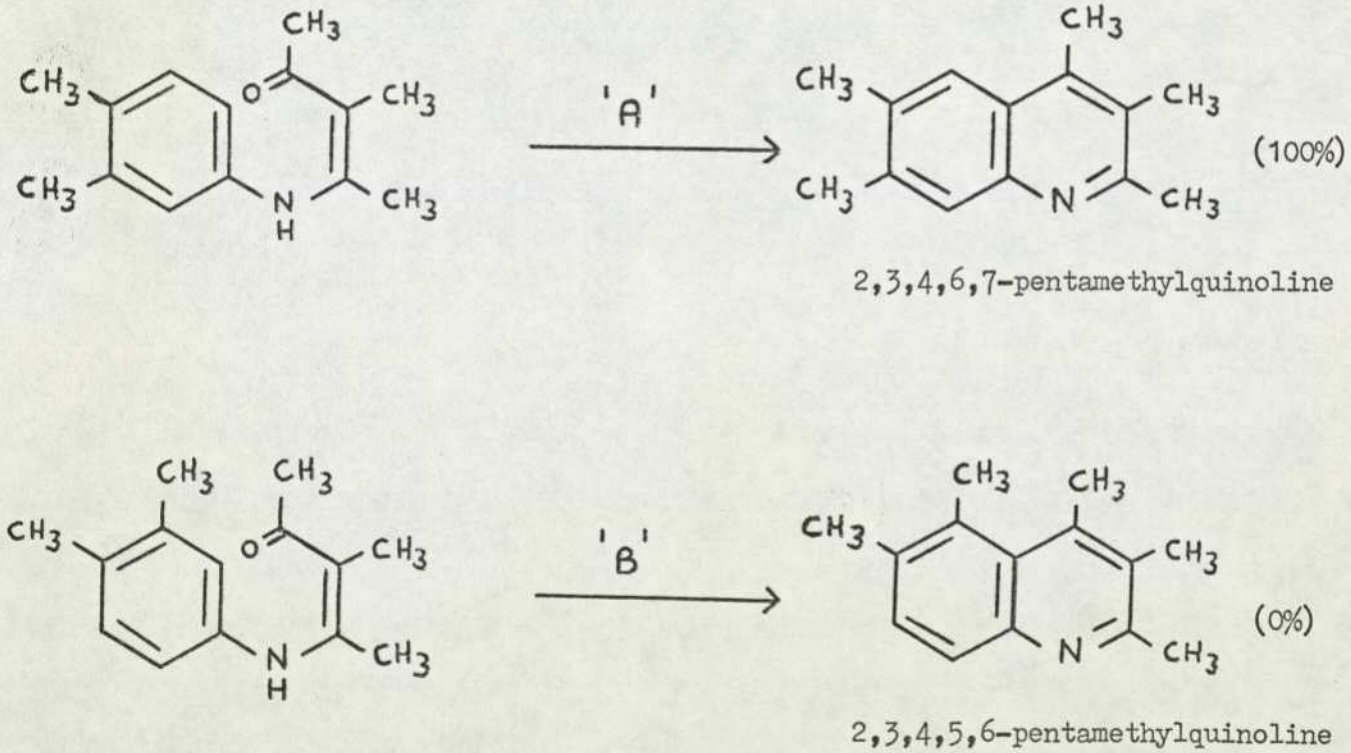
The results of the orientation effect studies are collected in Table 4.6. It is apparent that the ratios are largely unaffected by the introduction of substituents at the 2- and/or 3- positions only, but that introduction of a 4-methyl group causes the proportion of 5- or 5,6- substituted isomer to be reduced to almost zero. (A very small quantity of a product suspected to be 4,5,6-trimethylquinoline was detected by gas-liquid chromatography). In the presence of 2,4- and 3,4-dimethyl- and of 2,3,4-trimethyl- substituents, none of the 5- or 5,6- substituted isomers could be detected. This last result was also substantiated from the results of the orientation effects studies (1-condensation versus 3-condensation of methyl ketones) in the Beyer synthesis with 3,4-dimethylaniline. (See also section 3.3.2.2). The product obtained consisted mainly of 3,4,6,7-tetramethylquinoline (98.3%), after careful fractional crystallisation of the picrate derivative a residue remained which contained some 4-ethyl-6,7-dimethylquinoline. Since the minute proportion

(1.7%) of the latter product could readily be detected but the presence of any 3,4,5,6-tetramethylquinoline was still not apparent, then the extent of the alternative mode of cyclisation in this synthesis must be exceptionally low, and most likely zero.

The lack of formation of the 5- or 5,6- isomer may be attributed to steric hindrance by the 4-methyl substituent. Clearly ring closure by process 'A' is much less subject to steric hindrance than by process 'B' as illustrated in Scheme 4.1 in the case of 2,3,4,6,7-pentamethylquinoline.

SCHEME 4.1

Steric hindrance in quinoline synthesis.



It should be emphasised that where a choice of cyclisation routes is possible, then the least hindered pathway occurred exclusively. However, in those cyclisation reactions leading to products in which both 4- and 5- methyl groups were present, but where there was no alternative cyclisation process possible, then ring closure by the hindered pathway does still occur with little significant decrease in yield as shown in Table 4.8.

TABLE 4.8

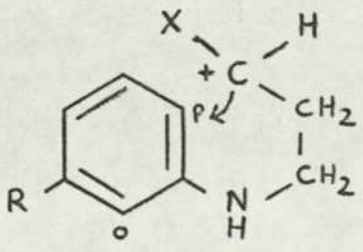
Synthesis of Polymethylquinolines

Product synthesised	Yield (%)	Section
2,4,5,6-tetramethylquinoline (a)	0	4.2.2.6
2,4,6,7-tetramethylquinoline (a)	90	4.2.2.6
2,4,5,6,8-pentamethylquinoline (b)	80	4.2.2.9

Notes (a) Combes reaction with 3,4-dimethylaniline.

(b) Combes reaction with 2,4,5-trimethylaniline. (3,4,6-trimethylaniline).

The Skraup reaction has been considered[18,321] to be compatible with attack by a fully charged carbonium ion (e.g. LXXX) on the position of maximum electron density. This was supported by the reaction with m-nitroaniline in which 5-nitroquinoline predominated due to para-deactivation by the nitro group.[18]



X = NHAr or OH

(LXXX)

With m-methyl and 3,4-dimethyl substituted aniline derivatives the enhanced proportion of the 7- or 6,7- isomer may be accounted for by several factors. Statistically, either isomer is equally probable; electronically the weak inductive effect of the methyl substituent(s) would not be expected to favour either route. It is therefore possible that the 7-isomer predominates mainly through steric effects since para-cyclisation is the least hindered pathway.

That the ortho-cyclisation pathway is completely ineffective in the presence of an additional methyl group leading to a 4-substituted quinoline clearly demonstrates the extreme sensitivity of the Skraup reaction to steric effects. It may therefore be concluded that unhindered para-cyclisation is always preferred, when possible, except when a para-electron withdrawing group (such as nitro[18] or carboxyl[83]) is present which can exert such a strong electronic effect as to outweigh the steric hindrance.

The present study has been limited to steric effects by methyl groups upon quinoline syntheses commencing with asymmetric methyl substituted aniline derivatives. In order to obtain more substantiative conclusions further studies employing alternative substituents need to be performed.

Since Skraup reactions with m-methyl- and 3,4-dimethylaniline derivatives have been shown to give mixed quinoline products it would seem likely that similar mixtures could result from syntheses commencing with higher alkyl substituted anilines. However, if the products so obtained were considered as single entities and further reactions performed, multiple products of uncertain constitution could result. Such a sequence of reactions is discussed and unravelled in section 4.3.

Further notes on n.m.r. spectra

In the present study ^{1}H n.m.r. spectroscopy was used to identify the products obtained. Since the range of compounds studied was quite extensive some characteristic effects in the spectra have been established which do not appear to have been recorded previously in the quinoline series. These effects, which concern the peri-positions 4 and 5, will now be briefly considered.

In the quinoline derivatives studied, in carbon tetrachloride solution the

signal for H-4 generally appeared at 2.2 - 2.4τ; introduction of a 5-methyl substituent resulted in a downfield shift to ca. 2.0τ. Similarly the H-5 proton, which generally absorbed at 2.5 - 2.7τ, moved downfield to 2.3 - 2.5 τ when a 4-methyl substituent was introduced. The above shifts are examples of peri-deshielding effects which appear to be quite characteristic. Similar effects have been noted for other substituents in polycyclic systems.[127d]

The recognition of these peri-effects is important in the assignment of certain signals, particularly that corresponding to H-4, which may occur upfield or downfield from H-8 in methylquinoline derivatives. Two examples are provided by 2-ethyl-3,6,7-trimethylquinoline (H-4 : 2.48 τ , H-8 : 2.33 τ - each broadened singlets) and 2,5,6-trimethylquinoline (H-4 : 2.04 τ , H-8 : 2.35 τ - each doublets, peri-deshielding effect present).

4.3 SYNTHESIS AND NITRATION OF 7-ALKYLQUINOLINES

4.3.1 INTRODUCTION

Since the Skraup reaction with m-toluidine has been shown to produce a mixture of 5- and 7- methylquinoline (see sections 4.1 and 4.2) the reaction with m-ethylaniline has been re-investigated.

The unidentified products previously obtained in the nitration of 7-alkylquinolines have been examined and identified.

4.3.2 EXPERIMENTAL

4.3.2.1 Skraup reaction with m-ethylaniline[322]

(Synthesis of 7-ethylquinoline).

The general procedure of Clarke and Davies[31] was employed using freshly distilled m-ethylaniline (17.5g., 0.14 mole), ferrous sulphate (5.0g.), glycerol (43.4 ml., 0.59 mole), arsenic pentoxide (20.3g., 0.09 mole) and concentrated sulphuric acid (40 ml.). The steam distillate obtained after diazotisation was extracted with ether and dried over anhydrous magnesium sulphate. Removal of the solvent left crude 7-ethylquinoline (4g., 30%) as a yellow oil which was analysed by gas-liquid chromatography (see section 4.2.3.2) and by nuclear magnetic resonance spectroscopy (see section 4.2.3.3) and found to be a mixture of 7-ethyl- and 5-ethylquinoline (75 : 25).

N.M.R. (100 MHz, CCl_4, peaks characteristic of 5-ethylquinoline only, for n.m.r. of pure 7-ethylquinoline see section 4.3.2.2(c)): 8.74 τ (3H, t, J = 7.5 Hz, CH_3); 7.06 τ (2H, q, J = 7.5 Hz, CH_2); 1.86 τ (1H, d of dd, J_{34} = 8.7 Hz, J_{24} = 1.8 Hz, J_{48} = 0.8 Hz, H-4)*.

4.3.2.2 Purification of 7-ethylquinoline[322]

(a) The mixed picrate derivative was prepared as described previously (see section 4.2.3.1 (ii)) and was obtained as small yellow needles, m.p. 232-3°. (lit.[103] m.p. 231-3°). Decomposition with dilute sodium hydroxide and analysis of the liberated bases by gas-liquid chromatography indicated that the composition had not been

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* See also section 4.3.3

affected.

(b) Fractional crystallisation of the mixed picrate from ethanol as described previously (see section 4.2.3.1 (iii)), afforded pure (g.l.c. after decomposition) 7-ethylquinoline picrate as long yellow needles, m.p. 240-1°. (Found: C, 52.7; H, 3.4; N, 14.7 %. Calculated for $C_{17}H_{14}N_4O_7$: C, 52.9; H, 3.7; N, 14.5 %)

(c) Decomposition of the pure picrate derivative with dilute sodium hydroxide solution as described previously (see section 3.2.2.3) afforded, after steam distillation, pure 7-ethylquinoline as colourless prisms (from hexane), m.p. 32-3°. (lit.[103] n 1.6012) (Found: C, 84.1; H, 7.2; N, 9.0 %. Calculated for $C_{11}H_{11}N$: C, 84.0; H, 7.1; N, 8.9%).

N.M.R. (100 MHz, CCl_4) : 8.65 τ (3H, t, J = 7.5 Hz, CH_3); 7.28 τ (2H, q, J = 7.5 Hz, CH_2); 2.79 τ (1H, d of d, J_{23} = 4.2 Hz, J_{34} = 8.2 Hz, H-3); 2.72 τ (1H, d of d, J_{56} = 8.2 Hz, J_{68} = 1.5 Hz, H-6); 2.39 τ (1H, d, J_{56} = 8.2 Hz, H-5); 2.17 τ (1H, br, H-8); 2.02 τ (1H, d of d, J_{34} = 8.3 Hz, J_{24} = 1.7 Hz, H-4); 1.24 τ (1H, d of d, J_{23} = 4.1 Hz, J_{24} = 1.7 Hz, H-2).

MS m/e (relative intensity): 157.0895 (M^+, $C_{11}H_{11}N$, 75), 158 (9), 156 (43), 155 (5.5), 154 (9.5), 143 (12), 142 (100), 141 (11), 129 (12), 128 (6), 116 (6), 115 (12), 89 (5.5), 77 (6).

4.3.2.3 Combes reaction with m-ethylaniline[322]

(Synthesis of 7-ethyl-2,4-dimethylquinoline)

The general procedure described previously was employed (see section 3.1.2.3) using freshly distilled m-ethylaniline (6g., 0.05 mole) and pentan-2,4-dione (5g., 0.05 mole). The initial product was analysed by gas-liquid chromatography and found to be heavily contaminated with unreacted m-ethylaniline, which was removed by a diazotisation technique, (see section 3.2.2.1).

7-Ethyl-2,4-dimethylquinoline (3.5g., 38%) was obtained as a yellow oil, b.p. 302-4°/771 mm., n_D^{20} 1.5890 (lit.[105] b.p. 298°/751 mm., $n_D^{22.5}$ 1.5951).

N.M.R. (100 MHz, CCl_4): 8.72 τ (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); 7.60 τ , 7.46 τ (6H, 2s, CH_3); 7.26 τ (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$); 3.27 τ (1H, s, H-3); 2.90 τ (1H, d of d, J_{56} = 8.2 Hz, J_{68} = 1.8 Hz, H-6); 2.66 τ (1H, d, J_{56} = 8.2 Hz, H-5); 2.33 τ (1H, bs, H-8).

The picrate crystallised from ethanol as yellow needles, m.p. 197-8° (lit.[105] m.p. 210°). (Found: C, 55.3; H, 4.4; N, 13.5%. Calculated for $C_{19}H_{18}N_4O_7$ C, 55.1; H, 4.4; N, 13.5%). **Decomposition of the picrate with dilute sodium** hydroxide solution (see section 3.2.2.3) and analysis of the liberated base by n.m.r. spectroscopy and gas-liquid chromatography showed none of the 5-ethyl isomer, nor any unreacted m-ethylaniline, to be present.

4.3.2.4 Nitration of 7-alkylquinoline[322]

The nitration procedure of Long and Schofield[103] was used. A stirred solution of the impure 7-alkylquinoline (from the Skraup reaction) (3g.) in concentrated sulphuric acid (7.5 ml.) was treated with a solution of fuming nitric acid (1.5 ml.) in concentrated sulphuric acid (5 ml.) the temperature being kept below 5°. The solution was allowed to stand for 30 minutes and then poured on to ice and the precipitated major nitration product (8-nitro derivative) was collected and recrystallised from ethanol and charcoal. The acidic mother liquor was then treated with successive portions of aqueous ammonia and the precipitated minor nitration products were collected and recrystallised from ethanol and charcoal. One fraction only was obtained from 7-ethylquinoline, whilst several fractions were obtained from 7-methylquinoline (see Table 4.9). The properties of the nitration products are shown below:

1. 7-Ethyl-8-nitroquinoline (2.35g., 61%) was obtained as cream needles, m.p. 137-8° (lit.[103] m.p. 136°). (Found: C, 65.2; H, 4.8; N, 14.1%. Calculated for $C_{11}H_{10}N_2O_2$ C, 65.3; H, 5.0; N, 13.9%).

N.M.R. (100 MHz, Me_2CO-d_6): 8.62 τ (3H, t, J = 7.5 Hz, CH_3); 7.18 τ (2H, q, J = 7.5 Hz, CH_2); 2.47 τ (1H, d of d, J_{34} = 8.4 Hz, J_{23} = 4.2 Hz, H-3); 2.35 τ (1H, d, J_{56} = 8.2 Hz, H-6); 1.91 τ (1H, d, J_{56} = 8.2 Hz, H-5); 1.58 τ (1H, d of d, J_{34} = 8.4 Hz, J_{24} = 1.7 Hz, H-4); 1.08 τ (1H, d of d, J_{23} = 4.1 Hz, J_{24} = 1.7 Hz, H-2).

MS m/e (relative intensity): 202.0745 (M^+, $C_{11}H_{10}N_2O_2$, 82), 185 (100), 172 (19), 157 (35), 156 (19), 155 (37), 154 (67), 144 (18), 143 (48), 142 (29), 141 (20), 130 (41), 129 (89), 128 (48), 127 (22), 117 (27), 116 (57), 101 (17), 77 (25), 75 (20), 63 (15), 51 (17).

2. 5-Ethyl-8-nitroquinoline (15 mg., 0.4 %) was obtained as cream plates, m.p. 52-3°. (lit.[103] m.p. 47-9°)*. (Found: C, 65.5; H, 5.1; N, 13.7%. Calculated for $C_{11}H_{10}N_2O_2$ C, 65.3; H, 5.0; N, 13.9%).

N.M.R. (100 MHz, Me_2CO-d_6): 8.62 τ (3H, t, J = 7.5 Hz, CH_3); 6.17 τ (2H, q, J = 7.5 Hz, CH_2); 2.49 τ (1H, broadened d, J_{67} = 7.9 Hz, H-6); 2.30 τ (1H, d of d, J_{34} = 8.7 Hz, J_{23} = 4.2 Hz, H-3); 1.95 τ (1H, d, J_{67} = 7.9 Hz, H-7); 1.32 τ (1H, d of d, J_{34} = 8.1 Hz, J_{24} = 1.7 Hz, H-4); 1.02 τ (1H, d of d, J_{23} = 4.1 Hz, J_{24} = 1.7 Hz, H-2).

MS m/e (relative intensity): 202.0744 (M^+, $C_{11}H_{10}N_2O_2$, 100), 203 (14), 172 (41), 157 (31), 156 (22), 154 (18), 144 (56), 143 (16), 141 (13), 140 (16), 129 (25), 128 (17), 127 (14), 117 (14), 116 (12), 115 (11), 77 (11), 51 (11), 39 (11).

3. 7-Methyl-8-nitroquinoline, (for yield, see Table 4.9) was obtained as pale yellow needles, m.p. 185-6° (lit.[107] m.p. 186-7°).

N.M.R. (100 MHz, CF_3COOH): 6.95 τ (3H, s, CH_3); 1.92 τ (1H, d, J_{56} = 8.5 Hz, H-6); 1.73 τ (1H, d of d, J_{34} = 7.8 Hz, J_{23} = 6.1 Hz, H-3); 1.48 τ (1H, d, J_{56} = 8.5 Hz, H-5); 0.67 τ (1H, d of d, J_{34} = 7.8 Hz, H-4); 0.67 τ (1H, d of d, J_{23} = 6.1 Hz, H-2).

MS m/e (relative intensity): 188.0583 (M^+, $C_{10}H_8N_2O_2$, 100), 171 (46), 158 (24), 143 (20), 142 (52), 141 (37), 130 (29), 129 (15), 116 (25), 115 (29), 77 (14), 63 (13).

4. 5-Methyl-8-nitroquinoline, (for yield, see Table 4.9) was obtained as pale yellow needles, m.p. 138° (lit.[25] m.p. 138°).

N.M.R. (100 MHz, CF_3COOH): 6.92 τ (3H, s, CH_3); 1.96 τ (1H, broadened d, J_{67} = 8.0 Hz, H-6); 1.65 τ (1H, d of d, J_{34} = 8.8 Hz, J_{23} = 5.6 Hz, H-3); 0.89 τ (1H, d, J_{67} = 8.0 Hz, H-7); 0.58 τ (1H, d of d, J_{23} = 5.6 Hz, J_{24} = 1.5 Hz, H-2); 0.46 τ (1H, d of d, J_{34} = 8.8 Hz, J_{24} = 1.5 Hz, H-4).

MS m/e (relative intensity): 188.0589 (M^+, $C_{10}H_8N_2O_2$, 54), 158 (35), 142 (23), 141 (14), 140 (20), 130 (100), 116 (20), 115 (46), 103 (15), 89 (16), 77 (19), 63 (20), 51 (16), 39 (21).

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* - for product provisionally identified as 7-ethyl-5-nitroquinoline.

5. 5-Methyl-6-nitroquinoline, (for yield, see Table 4.9) was obtained as tan needles, m.p. 166-7° (lit.[323] m.p. 165°).

N.M.R. (100 MHz, CF_3COOH): 6.97 τ (3H, s, CH_3); 1.69 τ (1H, slightly broadened d, J_{78} = 9.2 Hz, H-8); 1.75 τ (1H, d of d, J_{34} = 8.5 Hz, J_{23} = 5.5 Hz, H-3); 1.54 τ (1H, d, J_{78} = 9.2 Hz, H-7); 0.75 τ (1H, d of d, J_{23} = 5.5 Hz, J_{24} = 1.4 Hz, H-2); 0.50 τ (1H, d of d, J_{34} = 8.5 Hz, J_{24} = 1.4 Hz, H-4).

MS m/e (relative intensity): 188.0583 (M^+, $C_{10}H_8N_2O_2$, 27), 172 (17), 171 (100), 158 (21), 157 (9), 144 (15), 143 (45), 142 (31), 141 (37), 130 (18), 116 (50), 115 (32), 114 (16), 89 (16), 77 (13), 63 (14), 39 (11).

TABLE 4.9

Products from the nitration of impure 7-methylquinoline (a)

Fraction No.	Precipitated at pH	Weight (g.)	Composition (%) (b,c)
1	(d)	2.730	7-Me-8-NO_2Q (100)
2	2.5	0.610	5-Me-8-NO_2Q (87)
			5-Me-6-NO_2Q (13)
3	3.5	0.194	5-Me-8-NO_2Q (46)
			5-Me-6-NO_2Q (54)
4	11.0	0.229	5-Me-8-NO_2Q (57)
			5-Me-6-NO_2Q (43)
5	14.0	- (e)	-

Notes (a) Composition of reactant: 7-methylquinoline (70.1%), 5-methylquinoline (29.9%).

(b) Determined from respective areas of CH_3 peaks in n.m.r. spectrum.

(c) % yields, based on respective methylquinolines, 7-methyl-8-nitroquinoline (99%), 5-methyl-8-nitroquinoline (64%), 5-methyl-6-nitroquinoline (24%).

(d) As diluted.

(e) No further precipitate after 10 days.

4.3.3 DISCUSSION

Re-investigation of the Skraup synthesis with m-ethylaniline and subsequent analysis of the reaction product by gas-liquid chromatography and n.m.r. spectroscopy has shown that a mixture of 7-ethylquinoline (75%) and 5-ethylquinoline (25%) was formed. Pure 7-ethylquinoline has been isolated as a low melting solid from the pure picrate derivative obtained after fractional crystallisation from ethanol. That previous workers[25,103] similarly obtained a mixed quinoline product is evident from a comparison of the recorded properties of their products with those obtained in the present work, as shown in Table 4.10.

TABLE 4.10

Properties of 7-ethylquinoline

Sample	Properties	
	Long and Schofield[103]	Present work
Mixture of 5- and 7-ethylquinoline	n 1.6012 (a)	oil
Pure 7-ethylquinoline	-	m.p. 32-3°
Mixture of 5- and 7-quinoline picrate	m.p. 231-3° (a) m.p. 229° (a,b)	m.p. 232-3°
Pure 7-ethylquinoline picrate	-	m.p. 240-1°

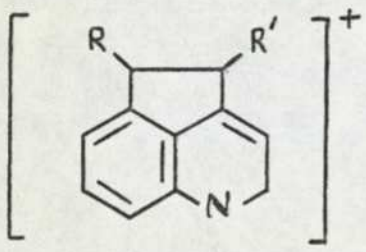
Notes (a) data for product assumed to be pure 7-ethylquinoline.

(b) Reference 25.

The present author would like to correct an assignment error in the published n.m.r. spectrum of 5-ethylquinoline.[322] The signal at 1.86τ should be ascribed to H-4, and the coupling constants should be re-designated as J_{34} = 8.7 Hz, J_{24} = 1.8 Hz, J_{48} = 0.8 Hz. (See also section 4.3.2.1). This revised assignment

is consistent with a peri-deshielding effect at the H-4 proton as subsequently observed with other 5-methyl- and 5,6-dimethyl- substituted quinoline derivatives (see also section 4.2.5, and Table 4.5).

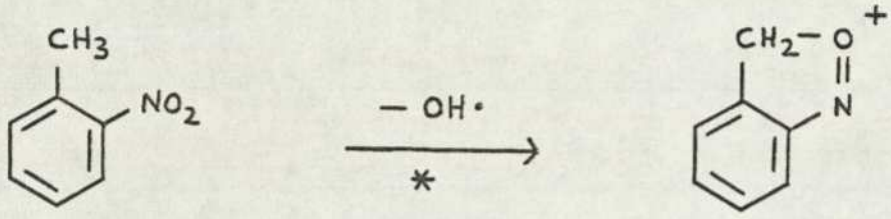
The mass spectrum of 7-ethylquinoline has previously been reported by Djerassi and co-workers[324] using an (impure) sample provided by Schofield[103]. The mass spectrum determined in the present work was similar to that obtained previously[324] except that greater intensities were exhibited by the M^+ and $(M - H)^+$ ions. Draper and McLean[325] have noted that expulsion of an alkyl group occurred most readily from 5-alkylquinolines, consistent with the increased intensity of the base peak (m/e 142) observed in the reported spectrum of 7-ethylquinoline. Since Djerrasi and co-workers[324] have also determined the mass spectra of 7-(n-propyl)-quinoline and 7-(n-butyl)quinoline upon samples of similar origin, it is therefore to be expected that these are in some doubt, since the presence of the 5-isomer as impurity could lead to the formation of certain cyclic ions of the type (LXXXI).



Likewise the n.m.r. solvent shift data reported by Schaefer[113] for 7-ethyl-quinoline must also be treated with caution.

The Combes synthesis with m-ethylaniline and pentan-2,4-dione previously performed by Buu-Hoï et al.[105] has also been repeated. In this reaction only 7-ethyl-2,4-dimethylquinoline was detected upon ring closure as shown by gas-liquid chromatographic, n.m.r. spectroscopic and fraction crystallisation studies, consistent with the results obtained with m-toluidine (see section 4.2). The variation in the melting point of the picrate derivative obtained in the present work (197-8°) compared with that reported previously (210°)[105] is attributed to the contamination of the earlier sample with unreacted m-ethylaniline, which was especially removed in the present work by a diazotisation technique.

The nitration of 5-/7-methyl- and of 5-/7-ethyl- quinoline mixtures has been repeated using identical experimental conditions[103] and the products identified by n.m.r. spectroscopy and by mass spectrometry. Products with a nitro group ortho to an alkyl group may be identified from their mass spectra by the facile loss of OH· from the parent ion as reported for o-nitrotoluene.[326]



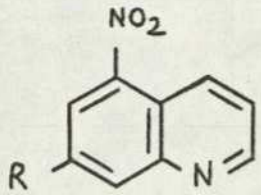
The other isomeric alkyl nitrocompounds would be expected to suffer stepwise ejection of NO· and CO in common with m- and p- nitrotoluenes.[326]

In the nuclear magnetic resonance spectra, long range benzylic coupling effects were useful to distinguish between alkyl groups which were coupled with ring protons across the 5,6- and 7,8- bonds and those which exhibited almost negligible coupling across the 6,7- bond.[142]

Nitration of the 7-alkylquinoline mixtures gave the 8-nitro derivative as the major product, consistent with the previous work.[103,106,107] The identity of this product was confirmed by the ejection of OH· from the parent ion in the mass spectrum and by the lack of significant benzylic coupling of the 7-alkyl protons with an aromatic proton in the n.m.r. spectrum.

The minor product from the nitration of (impure) 7-ethylquinoline has been identified as 5-ethyl-8-nitroquinoline, formed from the 5-ethylquinoline present. The melting point of the product (m.p. 52-3°) obtained in the present work was very similar to that of the impurity (m.p. 47-9°) reported by Long and Schofield.[103] The mass spectrum did not exhibit an $(M-17)^+$ ion, instead stepwise ejection of NO· and CO occurred. In the n.m.r. spectrum the high field doublet at 2.49 τ for H-6 was broadened by benzylic coupling, and sharpened upon spin decoupling of the methylene protons. There was no evidence of any fine doublets (J = 2-3 Hz) which would be expected from 7-ethyl-5-nitroquinoline (XLVI, R = C_2H_5) the minor product

suggested by Long and Schofield,[103] as a result of meta coupling between H-6 and H-8.



(XLVI)

Nitration of (impure) 7-methylquinoline was performed under similar conditions. After removal of the major nitration product successive additions of aqueous ammonium hydroxide afforded a series of fractions (see Table 4.9) consisting of a mixture of the minor products, 5-methyl-8-nitroquinoline (identified as described for the respective ethyl analogue and also by comparison with an authentic sample) and 5-methyl-6-nitroquinoline. The base peak in the mass spectrum of the latter product was the $(M-17)^+$ ion and in the n.m.r. spectrum the high field doublet at 2.69 τ for H-8 was slightly broadened by long range cross-ring coupling to H-4 (J_{48} = 0.8 Hz)[114] but was not affected by spin decoupling of the methyl protons.

Nitration of 7-alkylquinolines therefore resulted in the exclusive formation of the 8-isomer, which is the only position in the carbocyclic ring fully conjugated (ortho) with the methyl group, after consideration of the lesser degree of π-character of the 6,7-bond.

Nitration of 5-methylquinoline occurred at both positions 8 (73%) and 6 (27%), since both positions were fully conjugated (para- and ortho respectively) with the methyl group. The ratio of products was consistent with nitration at a single ortho and a para position.

Nitration of 5-ethylquinoline occurred mainly at the 8-position, however, since a quantitative recovery of products was not attempted in this reaction, the possible formation of some 5-ethyl-6-nitroquinoline cannot be excluded.

Furthermore, the product regarded by Long and Schofield[103] as 7-(n-butyl)-5-nitroquinoline (m.p. 73-4°) should now be considered as 5-(n-butyl)-8-nitroquinoline, and the physical properties of 7-(n-propyl)quinoline and 7-(n-butyl)quinoline and of their picrate derivatives should be viewed with caution, as it is most probable that the isolated products contained appreciable quantities of the 5-isomers.[101b]

CHAPTER 5

STUDIES OF LONG RANGE ^{13}C - ^{1}H COUPLING CONSTANTS IN METHYLQUINOLINES

5.1 INTRODUCTION

Long range coupling between protons and carbon nuclei separated by three bonds is well known.[221a] Recently, the determination of long range (^{3}J) ^{13}C - ^{1}H coupling constants in methylpyridine derivatives has been reported.[181] In the present work similar coupling constants have been studied for methylquinoline derivatives, in order that the results may be compared and correlated.

5.2 SYNTHESIS OF COMPOUNDS

2-Methylquinoline (b.p. 246-7°/760 mm.), 4-methylquinoline (b.p. 262-3°/760 mm.), 6-methylquinoline (b.p. 257-8°/760 mm.), 8-methylquinoline (b.p. 246-7°/760 mm.) and 6-methoxyquinoline (b.p. 280-2°/760 mm.) were commercially available and were redistilled before use.

3-Methylisoquinoline (m.p. 67-8°) was commercially available and was redistilled before use.

2-Chloro-4-methylquinoline (m.p. 57-8°) was commercially available and was recrystallised from ethanol before use.

The following compounds have been synthesised elsewhere, reference is given to the appropriate section:

2,4-dimethylquinoline (3.1.2.3)

3,4-dimethylquinoline (3.3.2.1)

2,4,7-trimethylquinoline (4.2.2.6)

5.2.1 3-METHYLQUINOLINE

This compound, prepared by the method of Willimott and Simpson,[56] was obtained as a pale yellow oil, b.p. 258-9°/760 mm., n_D^{20} 1.6140 (lit.[86] b.p. 259.5°/760 mm., n_D^{20} 1.6171).

N.M.R. spectrum - see section 3.2.2.3.

The picrate crystallised from ethanol as yellow needles, m.p. 188-9° (lit.[25] m.p. 190°)

5.2.2 2,3-DIMETHYLQUINOLINE

This compound, prepared by the method of Plant and Rosser,[327] was obtained as colourless prisms (from hexane), m.p. 68-9° (lit.[25] m.p. 70°). N.M.R. spectrum - see Table 5.1.

The picrate crystallised from ethanol as stout yellow needles, m.p. 233-4° (lit.[25] m.p. 235°).

5.2.3 2,3,4-TRIMETHYLQUINOLINE

This compound, was prepared by the procedure described previously (see section 4.2.2.8) using aniline (4.7g., 0.05 mole) and especially purified 3-methylpentan-2,4-dione (see section 4.2.2.8.1)(6.3g., 0.055 mole). 2,3,4-Trimethylquinoline (3.25g., 38%) was obtained as colourless prisms (from hexane), m.p. 94-5° (lit.[328] m.p. 92°) N.M.R. spectrum - see Table 5.1.

The picrate crystallised from ethanol as long yellow needles, m.p. 225-6° (lit.[328] m.p. 216°).

5.2.4 2,4,6,8-TETRAMETHYLQUINOLINE

This compound was prepared by the procedure described previously (see section 4.2.2). The product crystallised from hexane as colourless prisms, m.p. 86-7° (lit.[329] m.p. 86°).

N.M.R. spectrum - see Table 5.1.

The picrate crystallised from ethanol as yellow needles, m.p. 208-9°. (Found: C, 55.2; H, 4.3; N, 13.5%. Calculated for $C_{19}H_{18}N_4O_7$: C, 55.1; H, 4.4; N, 13.5%).

5.2.5 CARBOCYCLIC RING SUBSTITUTED QUINOLINES

The remaining quinoline derivatives were synthesised by the general procedure of Clarke and Davies[31] as described previously (see section 4.2.2.1). The results obtained as shown in Table 5.2.

N.M.R. spectra - see Table 5.1.

TABLE 5.1

N.M.R. SPECTRA OF QUINOLINE DERIVATIVES

(100 MHz, CCl_4, τ p.p.m.) (a)

Substituted quinoline	H-2	H-3	H-4	H-5	H-6	H-7	H-8	Coupling Constants
2,3-dimethyl-	(7.45)	(7.69)	2.43	← 2.45 to 2.83 →			2.14	J_{78} = 8.2 Hz
								J_{68} = 1.7 Hz
2,3,4-trimethyl-	(7.44)	(7.75)	(7.56)	(b)	← 2.48 to 2.80 →		(b)	
2,4,6,8-tetramethyl-	(7.44)	3.14	(7.52)	2.67	(7.60)	2.81	(7.33)	
6-chloro-8-methyl-	1.21	2.71	2.10	2.48	-	2.57	(7.26)	J_{23} = 4.2 Hz
								J_{34} = 8.5 Hz
								J_{24} = 1.8 Hz
								J_{57} = 2.2 Hz

Notes (a) Values in parentheses are for the appropriate substituted methyl group.

(b) H-5/H-8 appeared as a multiplet at 2.12 - 2.32 τ .

TABLE 5.2

Synthesis of quinoline derivatives

Substituents	b.p. (lit.)	Picrate m.p. (lit.)
6-chloro-8-methyl-	m.p. 65-6° (65.5°)[330]	225-6° (223-4°)[331]
5,8-dimethyl-	267-8°/760 mm., (265°/736 mm.)[332]	185-6° (186°)[25]
6,8-dimethyl-	266°/756 mm. (268-9°)[333]	230-1° (230°)[25]
7,8-dimethyl-	267°/759 mm., n_D^{20} 1.6160	198-9° (198°)[25] (a)

Note (a) Styphnate, yellow prisms, m.p. 178°. (lit.[25] m.p. 179°).

5.3 CARBON-13 N.M.R. SPECTROSCOPY

Two instruments were used in the present work. Both utilised pulsed techniques with Fourier Transformation. In all cases samples were examined at natural abundance in chloroform-d solution, the solvent provided the internal deuterium lock signal. Chemical shifts are given in δ (p.p.m. relative to T.M.S.).

The instruments employed and the operating conditions used were:

(1) Bruker HX-90E spectrometer, operating at 22.63 MHz, spectra determined by Physical Chemical Measurements Unit, Harwell.

Pulse width 7 μ sec; repetition time 1-7 seconds.

Proton decoupled spectra

Spectral width 6000 Hz with 8192 data points (*); number of pulses accumulated 100-1000.

Proton coupled spectra

Spectral width 600 Hz with 8192 data points (*); number of pulses accumulated: 4000 - 9000. (22,000 for 3-methylquinoline).

(2) Jeol JNM-FX-60 spectrometer, operating at 15.00 MHz. Spectra determined following installation of spectrometer at The City University, from January, 1977.

Pulse width 8 μsec (45°); repetition time 4 seconds.

Proton decoupled spectra

Spectral width 4000 Hz with 4096 data points (*); number of pulses accumulated: 1000 - 5000.

Proton coupled spectra

"Gated" decoupling was used.[163]

Spectral width 500 Hz with 4096 data points (*); number of pulses accumulated: 4000 - 10,000.

Note (*) - Before Fourier Transformation.

5.4 ASSIGNMENT TECHNIQUES AND RESULTS

Chemical shifts obtained are shown in Tables 5.3 and 5.4. Assignments were made by comparison with reported data for quinoline[172,173] and also from additivity relationships from methyl substituent parameters derived from toluene.[180] Initially, it was not found possible, however, to assign unequivocally the carbon resonances for C-5 to C-8 for compounds which had methyl substituents in the heterocyclic ring only.

After the present work had been completed,[334] Johns and Willing[179] reported a detailed analysis of the ^{13}C n.m.r. spectra of quinoline and selected methylquinolines. Using their assignments,[179] Substituent Chemical Shifts (S.C.S.) have been calculated for the carbocyclic ring carbon shifts upon introduction of methyl substituents into the heterocyclic ring. Assignments for C-5 to C-8 in heterocyclic ring substituted dimethyl- and trimethyl- substituted quinolines could then be made. The results obtained are shown in Table 5.5. Short range couplings (^1J) at the methyl carbons are reported in Table 5.4.

Long range couplings (^3J) at the ring carbons (when determined) are reported in Table 5.3.

Long range couplings (^3J) at the methyl carbons are reported in Table 5.6.

Other long range couplings are discussed and reported in Section 5.5.

TABLE 5.3

^{13}C Chemical Shifts for methylquinolines (ring carbons) (a,b)

Compound (c)	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
2-MeQ (e)(f)	158.7	121.7	135.8	(125.5, 127.4, 128.6, 129.2) (d)				147.8	126.3
3-MeQ (e)(g)	152.2	130.2	134.4	(126.3, 127.1, 128.2, 129.1) (d)				146.5	128.0
4-MeQ (e)(h)	149.7	121.6	144.0	(123.6, 126.0, 128.9, 129.7) (d)				147.7	128.0
2,3-Me_2Q (e)	158.6	129.7	134.9	(125.4, 126.6, 128.1, 128.2) (d)				146.4	127.3
2,4-Me_2Q (e)	158.2	122.3	143.7	(123.4, 125.2, 128.8, 129.0) (d)				147.5	126.3
3,4-Me_2Q (e)	152.2	129.3	140.7	(123.2, 126.0, 127.7, 129.8) (d)				146.7	128.2
2,3,4-Me_3Q (e)	158.0	128.9	140.1	(123.4, 125.2, 127.6, 129.0) (d)				145.7	126.9
2-Cl-4-MeQ (e)(m)	150.3	122.2	147.5	(123.7, 126.5, 128.9, 130.0) (d)				147.6	126.7
8-MeQ (e)(j)	149.0	120.6	136.0	125.8	126.1	129.5	136.9	147.3	128.1
5,8-Me_2Q	148.3	120.0	131.9	131.8	126.4	128.9	134.8	147.5	127.3
6,8-Me_2Q	148.2	120.6	135.3	124.6	135.7	131.8	136.5	146.0	128.3
7,8-Me_2Q	149.9	119.6	135.8	124.7	129.3	134.1	136.9	147.3	126.5
6-Cl-8-MeQ	149.2	121.6	135.1	124.2	131.4	129.9	139.3	145.5	128.6
6 MeO Q	147.8	121.2	134.5	105.1	157.7	122.1	130.8	144.5	129.3
3-MeisoQ (k)	152.2(1)	151.8	118.6	(126.0, 126.4, 127.6, 130.3) (d)				127.1	118.6

Cont....

TABLE 5.3 (Cont.)

Notes (a) In δ (p.p.m.) from T.M.S.

(b) For chemical shifts of methyl carbons, see Table 5.4.

(c) Q - quinoline, isoQ - isoquinoline, Me - methyl, Cl - chloro, MeO - methoxy.

(d) Assignments for carbocyclic ring carbons are uncertain. See also Table 5.5 (for quinoline derivatives only).

(e) See also Table 5.5.

(f) Lit.[177] 161.6 (C-2), 124.8 (C-3), 138.7 (C-4), 150.7 (C-9), 130.5 (C-10).
(Determined in CS_2, lit. data converted using δ_{CS_2} = 193.7 p.p.m.
lit.[179] 158.2 (C-2), 121.7 (C-3), 135.6 (C-4), 147.9 (C-9), 126.4 (C-10).

(g) lit.[179] 152.2 (C-2), 130.1 (C-3), 134.3 (C-4), 146.6 (C-9), 128.1 (C-10).

(h) lit.[179] 149.8 (C-2), 121.6 (C-3), 143.9 (C-4), 147.8 (C-9), 128.0 (C-10).

(j) lit.[179] 120.6 (C-3), 125.8 (C-5), 126.1 (C-6), 128.2 (C-10), 129.4 (C-7), 135.8 (C-4), 137.1 (C-8), 147.5 (C-9), 149.0 (C-2).
lit.[178] 120.1, 125.1, 125.5, 127.5, 128.8, 135.3, 136.4, 146.6, 148.3.

(k) lit.[272b] 118.2 (C-4), 125.7, 126.0, 126.7 (C-9), 127.3, 130.0, 136.4 (C-10), 151.5 (C-3), 151.8 (C-1).

(l) Absorption for C-1.

Cont.....

TABLE 5.3 (Cont.)

(m) Aromatic $^{1}J_{CH}$ and $^{3}J_{CCCH}$ coupling constants determined were:

$^{1}J_{3,3}$ = 169 Hz, $^{3}J_{3,Me}$ = 5.6 Hz

$^{1}J_{5,5}$ = 160 Hz, $^{3}J_{5,7}$ = 7.0 Hz

$^{1}J_{6,6}$ = 162 Hz, $^{3}J_{6,8}$ = 8.2 Hz

$^{1}J_{7,7}$ = 161 Hz, $^{3}J_{7,5}$ = 8.7 Hz

$^{1}J_{8,8}$ = 164 Hz, $^{3}J_{8,6}$ = 7.0 Hz

TABLE 5.4

^{13}C chemical shifts and one bond coupling constants for methylquinolines (methyl carbons) (a, b, c).

Compound (d)	C-2'	C-3'	C-4'	C-5'	C-6'	C-7'	C-8' (f)
2-MeQ	25.2 (127)						
3-MeQ		18.5 (127)					
4-MeQ			18.2 (127)				
2,3-Me_2Q	23.4 (127)	19.3 (127)					
2,4-Me_2Q	25.0 (127)		18.1 (127)				
3,4-Me_2Q		17.1 (127)	13.7 (127)				
2,3,4-Me_3Q	24.7 (127)	15.5 (127)	14.0 (127)				
2-Cl-4-MeQ			18.4 (128)				
6-MeQ					21.3 (127)		
8-MeQ							18.1 (127)
5,8-Me_2Q				18.1 (127)			18.1 (127)
6,8-Me_2Q					21.4 (127)		18.0 (127)
7,8-Me_2Q						20.5 (127)	13.3 (127)
6-Cl-8-MeQ							17.7 (128)
6MeOQ					55.2 (144)(e)		
3-MeisoQ		24.2 (127)					

Cont....

TABLE 5.4 (Cont.)

Notes (a) Chemical shifts are in δ (p.p.m. from T.M.S.), values in parentheses are ^{1}J in Hz.

(b) Carbons numbered with (') are associated with the methyl group.

(c) For chemical shifts of ring carbons, see Table 5.3.

(d) Q = quinoline, isoQ = isoquinoline, Me = methyl, Cl = chloro, MeO = methoxy.

(e) ^{1}J = 143 Hz from satellite peaks in ^{1}H n.m.r. spectrum.

(f) literature values : 2-MeQ - 25.1 (127)[179]

3-MeQ - 18.4 (127)[179]

4-MeQ - 18.2 (127)[179]

6-MeQ - 21.2 (127)[179]

8-MeQ - 18.1 (127)[179]

3-MeisoQ - 24.1 (-)[272b]

TABLE 5.5

Revised assignments for carbocyclic ring carbons in methylquinoline derivatives, after work of Johns and Willing.[179]

Compound (e)	Substituent Chemical Shifts (p.p.m.) C-5	C-6	C-7	C-8	Revised Assignments (δ, p.p.m.)(d) C-5	C-6	C-7	C-8
Q (a)	127.6	126.4	129.2	129.4	-	-	-	-
2-MeQ (b)	(-0.2)	(-0.9)	(0.0)	(-0.8)	127.4	125.5	129.2	128.6
3-MeQ (b)	(-0.5)	(-0.1)	(-1.0)	(-0.3)	127.1	126.3	128.2	129.1
4-MeQ (b)	(-4.0)	(-0.4)	(-0.3)	(+0.3)	123.6	126.0	128.9	129.7
$2,3\text{-Me}_2\text{Q}$ (c)	(-0.7)	(-1.0)	(-1.0)	(-1.1)	126.6	125.4	128.1*	128.2*
$2,4\text{-Me}_2\text{Q}$ (c)	(-4.2)	(-1.3)	(-0.3)	(-0.5)	123.4	125.2	128.8*	129.0*
$3,4\text{-Me}_2\text{Q}$ (c)	(-4.5)	(-0.5)	(-1.3)	(0.0)	123.2	126.0	127.7	129.8
$2,3,4\text{-Me}_3\text{Q}$ (c)	(-4.7)	(-1.4)	(-1.3)	(-0.8)	123.4	125.2	127.6	129.0
2-Cl-4-MeQ	-	-	-	-	123.7	126.5	130.0**	128.9**

Notes (a) - Data ex. reference 179.

(b) - Calculated S.C.S. using data in Table 5.3, assignments made after work of Johns and Willing.[179]

(c) - Calculated S.C.S. using data for 2-MeQ, 3-MeQ and 4-MeQ.

(d) - lit.[179] 2-MeQ : 127.3 (C-5), 125.4 (C-6), 129.1 (C-7), 128.7 (C-8).
3-MeQ : 127.1 (C-5), 126.3 (C-6), 128.2 (C-7), 129.2 (C-8).
4-MeQ : 123.6 (C-5), 126.1 (C-6), 128.8 (C-7), 129.8 (C-8).

(e) Q = quinoline, Me = methyl, Cl = chloro.

* - assignments may be reversed.

** - assignments based on long range ^{13}C - ^{1}H coupling constants, could be reversed.

TABLE 5.6

Long range $^{13}C - {}^{1}H$ coupling constants for methylquinolines (a)

	^{3}J	Hz	^{3}R (b,c)	^{4}J	Hz	^{4}R (b,c)
C-2'	^{3}J (C-2' - H-3)	2	0.5 (e)	^{4}J (C-2' - H-4)	1	0.6
C-3'	^{3}J (C-3' - H-2)	3	0.7 (e)			
	^{3}J (C-3' - H-4)	5	0.6			
C-4'	^{3}J (C-4' - H-3)	5	0.6	^{4}J (C-4' - H-2)	1	0.6
C-5'	^{3}J (C-5' - H-6)	5	0.6			
C-6'	^{3}J (C-6' - H-5)	5	0.6			
	^{3}J (C-6' - H-7)	4	0.6			
C-7'	^{3}J (C-7' - H-6)	4	0.6			
C-8'	^{3}J (C-8' - H-7)	5	0.6			
C-3' (d)	^{3}J (C-3' - H-4)	3	0.5			

Notes (a) Carbons numbered with (') are associated with the methyl group.

(b) For definition of ^{3}R and ^{4}R see discussion, section 5.6.

(c) Values used for ^{3}J (H - H) as reported by Black and Heffernan for quinoline (ref. 116) and for isoquinoline (ref. 335).

(d) Isoquinoline.

(e) A mean value of ^{3}J = 2.5 Hz gives ^{3}R = 0.6

5.5 ADDITIONAL LATER STUDIES

Comparison of the results obtained in the present work with those of Johns and Willing[179] revealed a discrepancy in the assignments of C-5 and C-7 in 6-methylquinoline, as shown in Table 5.7.

The present worker did not study 6-methylquinoline originally, the assignments for this compound were obtained through a comparison of calculated substituent chemical shift (S.C.S.) data for 8-methylquinoline and 6,8-dimethylquinoline, as shown in Table 5.7.

That the assignments for 6,8-dimethylquinoline were correct has been confirmed by the use of S.C.S. and additivity effects to predict the chemical shifts of 2,4,6,8-tetramethylquinoline. Reversal of the assignments of C-5 and C-7 was inconsistent with the experimental spectrum obtained, see Table 5.8.

Johns and Willing[179] assigned the resonances for C-5 and C-7 from a consideration of the relative complexities of the signals in the ^{13}C proton coupled spectrum, see Scheme 5.1.

This assignment discrepancy has been resolved through selective low power heteronuclear decoupling experiments. The decoupler was positioned very accurately ($\pm$ 1 Hz) and checked by a ^{1}H homonuclear irradiation. Continuous wave heteronuclear decoupling was then performed with a very low power level (ca. 8% of that required for normal 'noise' decoupling). This experiment was performed simultaneously by the present author and also by Johns and Willing[336] in Australia. The results obtained by the present worker are shown in Figure 5.1.

Since this experiment selectively removed the long range ^{3}J couplings to the methyl protons but did not affect the ring carbon - ring proton interactions, the signals for C-5 and C-7 were simplified. It is apparent that the upfield signal, assigned by the present author to C-5, appeared as a doublet of triplets ($^{1}J_{5,5}$ and $^{3}J_{5,4} \sim {}^{3}J_{5,7}$) whilst the low field signal was a doublet of doublets ($^{1}J_{7,7}$ and $^{3}J_{7,5}$) as expected for C-7 (see Scheme 5.1). Similar results were obtained by Johns and Willing[336] and their assignments have now been revised.[337]

TABLE 5.7

Substituent Chemical Shifts for C-5 and C-7

in some quinoline derivatives

Compound (a)	Chemical Shift (δ, p.p.m.)		Substituent Chemical Shift (p.p.m.)	
	C-5	C-7	C-5	C-7
Q (b)	127.6	129.2	0	0
8-MeQ	125.8	129.5	-1.8	+0.3
6,8-Me_2Q	124.6	131.8	-3.0	+2.6
6-MeQ (Calc.)	126.4	131.5	-1.2	+2.3
6-MeQ (Expt.) (b)	131.4	126.5		
6-MeQ (Expt.) (c)	126.4	131.5		

Notes (a) Q = quinoline, Me = methyl.

(b) Data ex. reference 179.

(c) Present work. Remainder of $^{13}C-\{^{1}H\}$ spectrum given below:

149.3 (C-2), 146.7 (C-9), 136.2 (C-6), 135.1 (C-4),

128.9 (C-8), 128.1 (C-10), 120.8 (C-3).

lit.[179] 149.3 (C-2), 147.0 (C-9), 135.9 (C-6), 135.0 (C-4),

129.1 (C-8), 128.2 (C-10), 120.8 (C-3).

TABLE 5.8

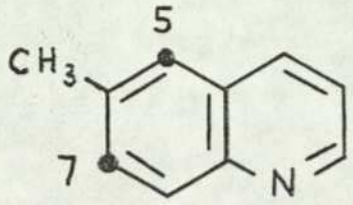
Experimental and calculated ^{13}C chemical shifts for 2,4,6,8-tetramethylquinoline

Ring Carbon	Substituent Chemical Shifts (p.p.m.)(a)		Chemical Shifts of 2,4,6,8-Me_4Q (δ, p.p.m.)	
	2,4-Me_2Q	6,8-Me_2Q	Calculated	Observed
C-2	+8.3	-2.0	156.5	156.6
C-3	+1.7	-0.2	122.4	122.7
C-4	+8.3	-0.3	143.7	143.5
C-5	-4.1	-3.0	120.5	120.7
C-6	-1.1	+9.4	134.7	134.6
C-7	-0.2	+2.4	131.4	131.6
C-8	-0.2	+7.2	136.4	136.8
C-9	-0.5	-2.3	145.5	145.7
C-10	-1.7	+0.1	126.6	126.6

Notes (a) Compared to quinoline as reported in reference 179.

SCHEME 5.1

Long range ^{13}C - ^{1}H couplings predicted for C-5 and C-7 in 6-methylquinoline (from reference 179).



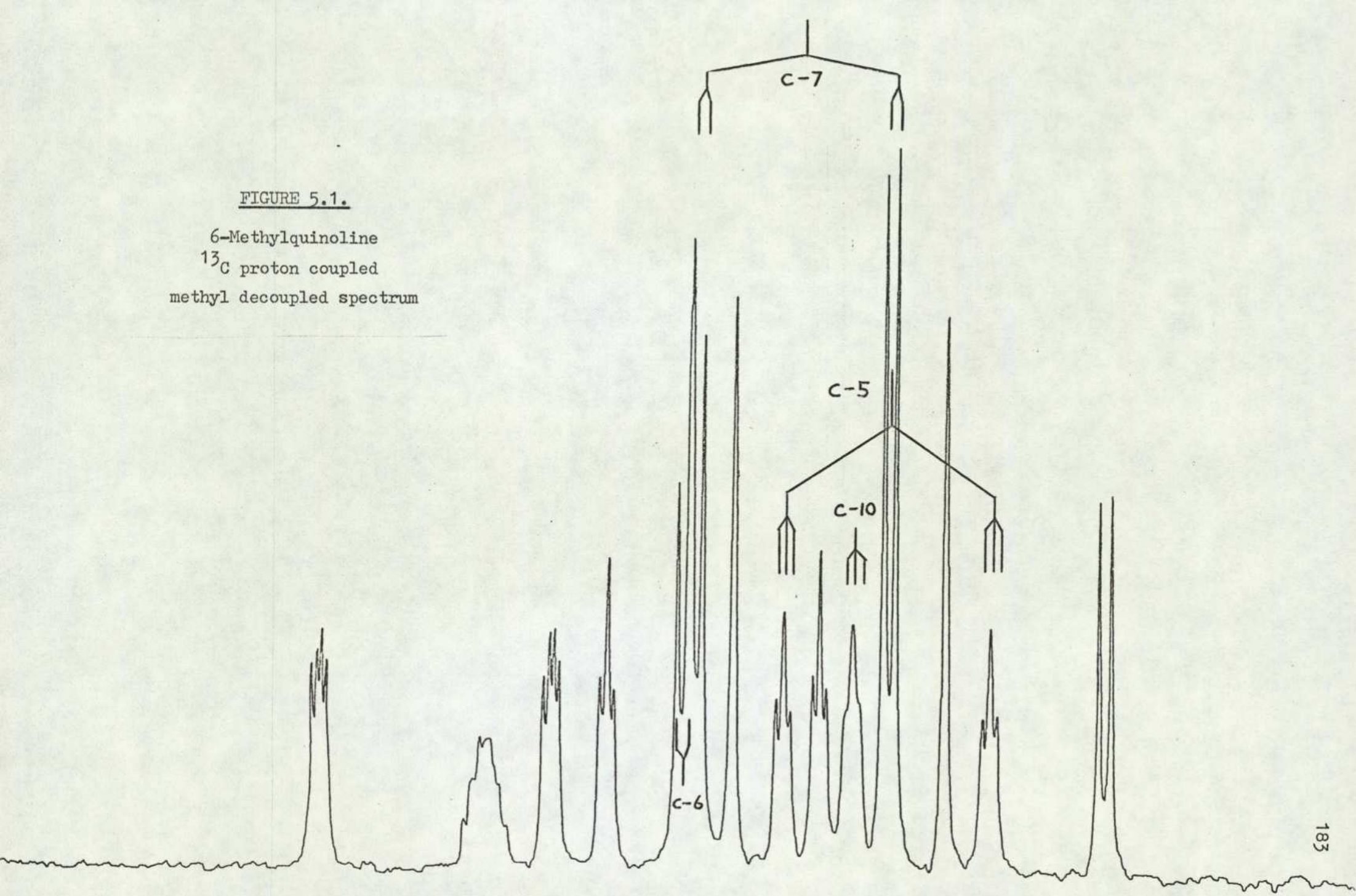
Couplings present at C-5 (a)		Couplings present at C-7 (a) (b)	
$^{1}J_{5,5}$	(d)	$^{1}J_{7,7}$	(d)
$^{3}J_{5,4}$	(d)	$^{3}J_{7,5}$	(d)
$^{3}J_{5,7}$	(d)	$^{3}J_{7,6'}$	(q)
$^{3}J_{5,6'}$	(d)		

Notes (a) Resulting multiplicities shown in parentheses.

(b) The upfield signal was the least complex in the experimental spectrum[336] and was accordingly assigned to C-7.

FIGURE 5.1.

6-Methylquinoline
^{13}C proton coupled
methyl decoupled spectrum

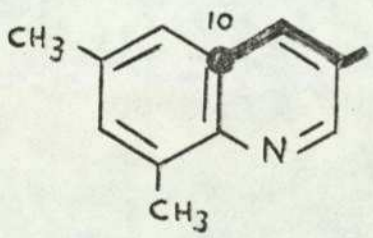


Closer observation of the proton coupled, methyl proton decoupled spectrum of 6-methylquinoline (see Figure 5.1) revealed that the signal for C-10 appeared as a poorly resolved triplet and that the C-6 signal was a well resolved doublet. ($^3J_{6,8}$ - partially obscured by part of the C-7 signal). In their original work, Johns and Willing[179] commented that the bridgehead carbons gave signals of such low intensity that no attempt was made to measure the couplings at these signals. Since the above signals for the C-6 and C-10 carbons were better resolved it would appear that couplings to quaternary carbons may be obtained provided that the number of such couplings was reduced, preferably to a single interaction.

Accordingly, some preliminary studies of couplings at the bridgehead quaternary carbons have been performed with suitably substituted polymethylquinoline derivatives. The results obtained are shown in Scheme 5.2 and in Figures 5.2 and 5.3.

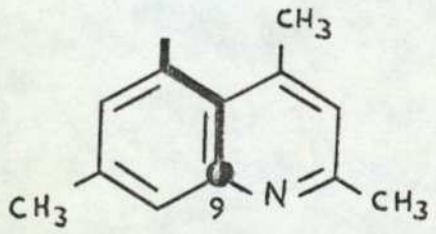
SCHEME 5.2

Long range ^{13}C - ^{1}H coupling constants involving the bridgehead carbons in methylquinolines.



6,8-dimethylquinoline

$^3J_{10,3}$ = 7.1 Hz



2,4,7-trimethylquinoline (a)

$^3J_{9,5}$ = 6.4 Hz

Notes (a) - 2,4,7-trimethylquinoline, $^{13}C - \{^1H\}$ spectrum:

158.7 (C-2), 148.3 (C-9), 144.1 (C-4),
139.3 (C-7), 128.5 (C-8), 127.7 (C-6),
124.7 (C-10), 123.4 (C-5), 122.1 (C-3).

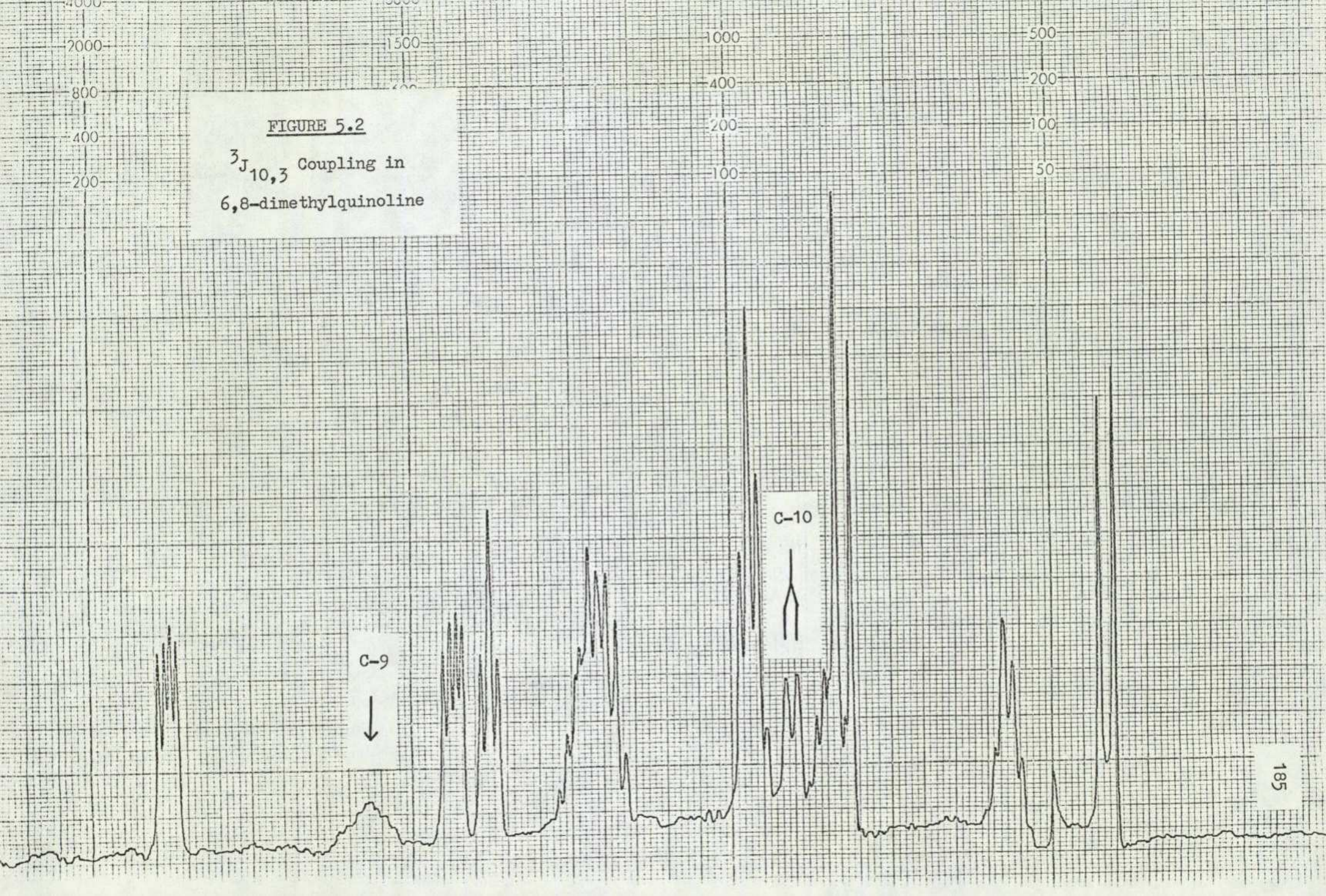


FIGURE 5.2

$^{3}J_{10,3}$ Coupling in 6,8-dimethylquinoline

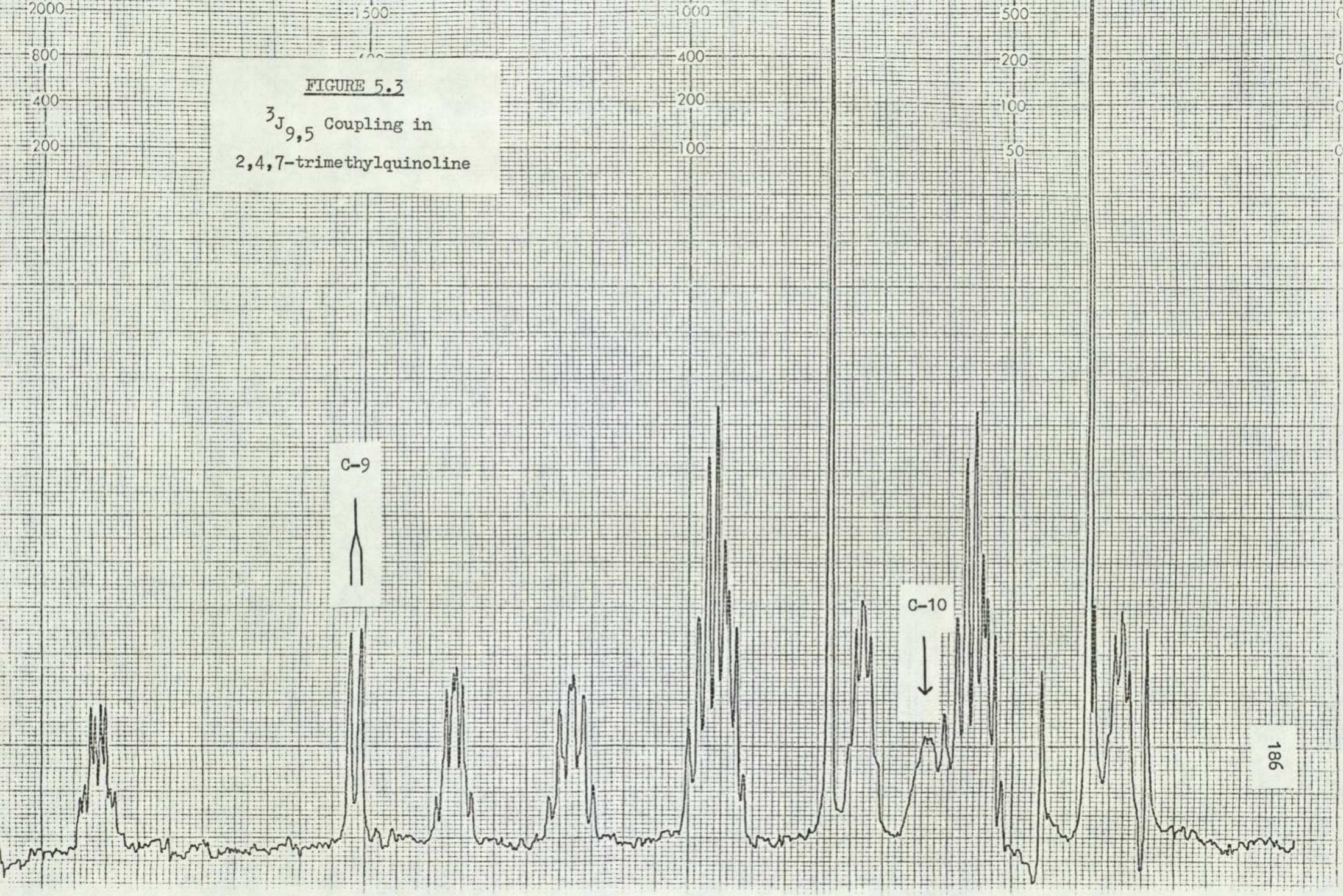


FIGURE 5.3

$^{3}J_{9,5}$ Coupling in

2,4,7-trimethylquinoline

5.6 DISCUSSION

Comments concerning the assignments of signals, together with discrepancies with other workers[179] have been given above.

Since the present work was completed[334] further studies of the ^{13}C n.m.r. spectra of methylquinoline derivatives have appeared.

Smith and co-workers[338] reported chemical shifts for all seven monomethylquinolines, nine dimethylquinolines and various methylisoquinolines. The results obtained were generally in accordance with the earlier studies.[179,334] The earlier assignments[179] of C-5 and C-7 in 6-methylquinoline (see also section 5.5) were reversed in accordance with the present work. In addition, the assignments for C-7 and C-8 in 7,8-dimethylquinoline as determined in the present work[334] were also reversed. Substituent chemical shift parameters were calculated and compared with the results of the present work, and reasonable agreement between observed and calculated S.C.S. effects found.

Takai and co-workers[339] measured the ^{13}C chemical shifts of a series of 6-substituted quinoline derivatives (including methyl- and methoxy- substituted), the assignments were in accordance with the present work.[334] A correlation between substituent shifts observed in the naphthalene, quinoline and quinoxaline series was attempted.

Examination of the long range ^{13}C - ^{1}H couplings at ring carbons[179] has enabled certain preliminary results to be obtained concerning such interactions at the bridgehead carbons. Consideration of ^{3}J couplings only, indicated that C-9 could couple to H-2, H-4, H-5 and H-7 and C-10 to H-3, H-6 and H-8. Through the use of suitably substituted polymethylquinolines certain of these positions were blocked which allowed measurement of the remaining splitting. This procedure has been satisfactorily applied to the determination of $^{3}J_{10,3}$ in 6,8-dimethylquinoline and $^{3}J_{9,5}$ in 2,4,7-trimethylquinoline, which support the initial hypothesis that ^{3}J couplings only were involved. Further work, however, is needed to substantiate this postulation and to measure the remaining coupling constants. Cussans and Huckerby[199] have reported a broadened doublet (J = 8 Hz) for C-10 in 6,8-dimethylcoumarin, tentatively assigned to $^{3}J_{10,8}$ in agreement with the present work.

Interestingly, the C-10 signals in both 6-methylcoumarin and 8-methylcoumarin were found to be complex.

The remainder of the present discussion is concerned with long range $^{13}C - {}^{1}H$ couplings which were observed at the methyl carbons. Under conditions of proton coupling each methyl carbon appeared as a quartet (^{1}J = 127 Hz). The ^{1}J values obtained were in good agreement with earlier values obtained from satellite peaks in the ^{1}H n.m.r. spectrum.[184] Each of the quartet peaks was then further split through coupling with the ring proton(s). This coupling was mainly confined to ortho protons (i.e. ^{3}J) although weaker coupling to meta protons (i.e. ^{4}J) was observed in certain cases. Takeuchi[181] did not observe any such ^{4}J couplings in the methylpyridine series.

Representative examples for the heterocyclic ring carbons were provided by the spectra for the C-3' (^{3}J) and C-2' (^{4}J) signals for 2,3-dimethylquinoline (see Figures 5.4 (a) and 5.4 (b)) which each exhibited coupling to H-4, and for the C-3' (^{3}J) and C-4' (^{4}J) signals for 3,4-dimethylquinoline (see Figures 5.4 (c) and 5.4 (d)) which each exhibited coupling to H-2. The methyl carbons of 2,4-dimethylquinoline each showed coupling (^{3}J) to H-3 (see Figures 5.5 (a) and 5.5 (b)) whilst C-3' in 3-methylquinoline exhibited coupling to each of H-2 and H-4 (see Figure 5.5 (c)). That these fine splittings were due to coupling of methyl carbons with ring protons was confirmed by examination of the methyl carbon spectrum of 2,3,4-trimethylquinoline which showed no fine splitting to be present.

The value of ^{3}J across the 2,3-bond was approximately the same whether the coupling involved C-2' - H-3 (2 Hz) or C-3' - H-2 (3 Hz); similar results applied to the 3,4-bond where stronger coupling occurred, viz. C-3' - H-4 (5 Hz) and C-4' - H-3 (5 Hz). (See Table 5.6). The above variation in the magnitude of coupling across different bonds was similar to that experienced for $^{1}H - {}^{1}H$ benzylic coupling. Thus, the methyl protons in 4-methylquinoline coupled with H-3 much more strongly than the methyl protons of 2-methylquinoline which exhibited little coupling.[142]

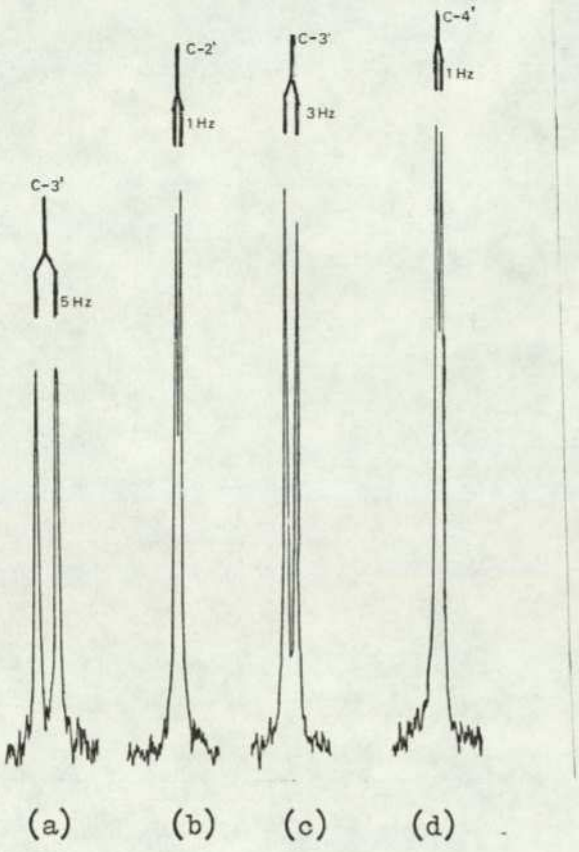


FIGURE 5.4 Fine splittings observed for methyl carbons of methylquinolines

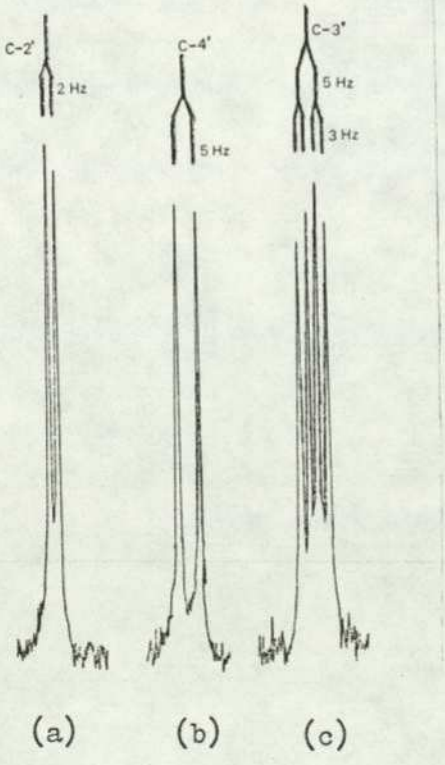
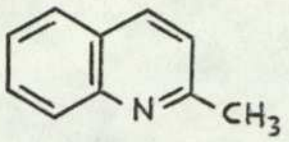
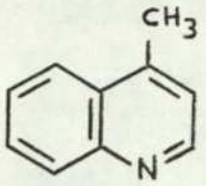


FIGURE 5.5 Fine splittings observed for methyl carbons of methylquinolines.



^4J (CH_3, H-3) ~ 0

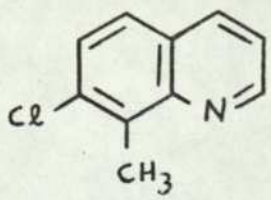


^4J (CH_3, H-3) = 0.95 Hz

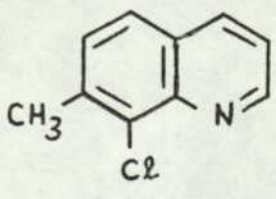
At first sight, a correlation between benzylic coupling and the long range ^3J (^{13}C - ^1H) couplings reported in the present work appeared possible.

As previously noted by Takeuchi,[181] the use of this additional coupling for diagnostic purposes, in the same manner that benzylic coupling has been employed, should prove valuable.

In the carbocyclic ring of methylquinoline derivatives, similar ^3J (^{13}C - ^1H) couplings occurred, however, no ^4J couplings were discernible in the derivatives studied. It was noted that coupling across the 5,6-bond (C-5' - H-6 = 5 Hz, C-6' - H-5 = 5 Hz) and 7,8-bond (C-8' - H-7 = 5 Hz) was greater than that across the 6,7-bond (C-6' - H-7 = 4 Hz, C-7' - H-6 = 4 Hz). The similarity between the greater value of the ^3J methyl carbon - ring proton and the occurrence of ^1H - ^1H benzylic coupling across certain bonds was again apparent. The diagnostic value of this difference in coupling, although smaller, could nevertheless still prove valuable. However, the unequivocal assignment of a particular methyl carbon signal, in which fine splitting would be expected to be either present or absent, may readily be established. Such an example is provided by the assignments of C-7' and C-8' in 7,8-dimethylquinoline. Likewise the isomeric 7-chloro-8-methylquinoline (LXXXII) and 8-chloro-7-methylquinoline (LXXXIII) could readily be differentiated since additional long range coupling (^3J) at the methyl carbons would only occur with the latter compound.



(LXXXII)



(LXXXIII)

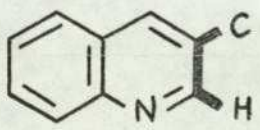
Since this type of long range ^{13}C - ^{1}H coupling can be detected across the 2,3- and 6,7- bonds in quinoline derivatives it is particularly useful for diagnostic purposes in cases where the additional effects of ^{1}H - ^{1}H benzylic coupling are inconclusive, as in the case of the chloromethylquinoline derivatives (LXXXII) and (LXXXIII).

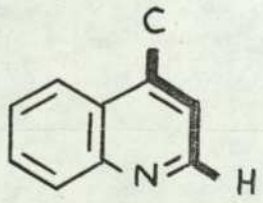
However, it was significant that little or no benzylic coupling occurred across the 2,3- or 6,7- bonds in methylquinoline derivatives, whereas ^{3}J (^{13}C - ^{1}H) coupling did occur, but to a reduced extent. Accordingly, the magnitude of the methyl carbon - ring proton long range coupling did not appear directly dependent upon the extent of excess π-bond order as envisaged for benzylic coupling.[139,146]

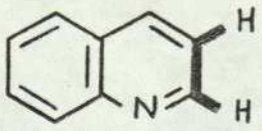
Since these long range ^{13}C - ^{1}H coupling constants did not appear to be linked to benzylic coupling a correlation with the appropriate vicinal ortho proton - proton coupling constants would therefore seem conceivable. Such a relationship between ^{13}C - ^{1}H and ^{1}H - ^{1}H coupling constants has been suggested[192] for similar environments. Using selected model compounds Weigert and Roberts[191] have related the long range coupling constants J (CCCH) and J (CCCCH) in benzene to the appropriate proton - proton couplings.

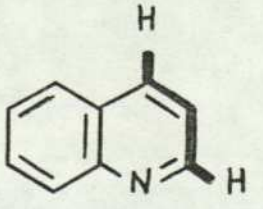
To test the validity of a correlation for the long range coupling constants reported in the present work with the appropriate proton - proton coupling constants the following relationships are proposed:

$$^{3}R = \frac{^{3}J\ (C\text{-}H)}{^{3}J\ (H\text{-}H)} \qquad ^{4}R = \frac{^{4}J\ (C\text{-}H)}{^{4}J\ (H\text{-}H)}$$









The results obtained are shown in Table 5.6, the values used for ^{3}J (H-H) and ^{4}J (H-H) have been reported by Black and Hefferman[116] and were obtained for quinoline in carbon tetrachloride solution. The above relationships are satisfied for both rings of the quinoline system, and also for the 3,4-bond of the isoquinoline ring. (See also Table 5.6).

In order to test the relationship further, long range ^{3}J (^{13}C - ^{1}H) coupling constants in some methylquinolone derivatives have also been determined. The results have been discussed in Section 7.4, the relationship was again satisfied.

The proposed relationships may also be successfully applied to the methyl carbon - ring proton couplings in the methylpyridine series as obtained by Takeuchi,[181] the correlation is presented in Table 5.9.

TABLE 5.9

Correlation of long range ^{13}C - ^{1}H coupling constants with ^{1}H - ^{1}H coupling constants for methylpyridines.

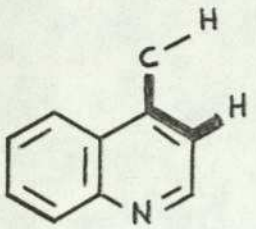
	^{3}J (Hz)(a)		^{3}R (b)
C-2'	^{3}J (C-2' - H-3)	2	0.4
C-3'	^{3}J (C-3' - H-2)	3	0.6
C-3'	^{3}J (C-3' - H-4)	5	0.7
C-4'	^{3}J (C-4' - H-3)	5	0.7

Notes (a) Results from reference 181.

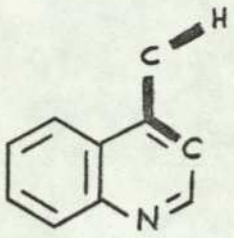
(b) For definition of ^{3}R, see Discussion, section 5.6.
Values used for ^{3}J (H - H) as reported by Castellano *et al.*[239] for pyridine in carbon tetrachloride solution.

A ring carbon - methyl proton coupling constant has also been measured.[334] The sample used was 2-chloro-4-methylquinoline; the C-3 signal was a doublet of quartets (^{1}J = 169 Hz), the fine splitting being due to coupling to the methyl protons. (^{3}J = 6 Hz) Johns and Willing[179] later reported J = 5 Hz for ^{3}J (C-3 - H-4') in

4-methylquinoline. It is interesting to note that the magnitude of this coupling and that of ^{3}J (C-4' - H-3), which each occur through the 3,4-bond, are very similar.



$^{3}J = 5$ Hz



$^{3}J = 6$ Hz

The proton coupled spectrum of 6-methoxyquinoline has also been examined. The methoxyl carbon was a quartet ($^{1}J = 144$ Hz) with no fine splitting, ^{4}J (COCCH), evident.

Long range couplings across four bonds have also been observed in the heterocyclic ring of methylquinoline derivatives, such ^{4}J couplings were not observed in the methylpyridine series.[181] Correlation with the appropriate H - H coupling was again satisfactory, as shown in Table 5.6.

In methylquinoline derivatives, two bond ring carbon - ring proton interactions have only been detected[179] when the position adjacent to the nitrogen atom was involved. Similar considerations could, presumably, apply to the ^{4}J couplings, which often resemble ^{2}J interactions.

Furthermore, since the heterocyclic ring <u>meta</u>-vicinal coupling constant ($J_{2,4}$) is greater[116] than those in the carbocyclic ring ($J_{5,7}$ and $J_{6,8}$) then the respective ^{4}J (^{13}C - ^{1}H) couplings would be expected to be diminished and more difficult to resolve, in accordance with the present work.

CHAPTER 6

^{1}H N.M.R. SPECTRAL STUDIES OF 2(1H)- AND 4(1H)-QUINOLONE DERIVATIVES

6.1 INTRODUCTION

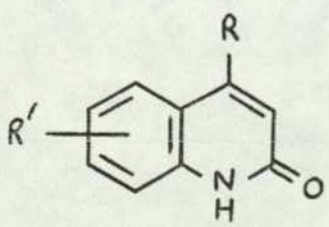
The present ^{1}H n.m.r. spectral studies were concerned with the variation of the chemical shift of the NH proton with the substitution pattern of the quinolone derivative. Furthermore, since reports of the ^{1}H n.m.r. spectra of 2- and 4-quinolone derivatives appeared to be scarce, (see section 1.6.2) a systematic study of the spectral parameters for these compounds has been undertaken.

Previous workers[120,243,340] have either employed trifluoroacetic acid as solvent, or did not report data for the NH signal,[242,246] in addition some previous assignments[120,241] require correction. Long range allylic coupling constants in the lactam rings have also been determined.

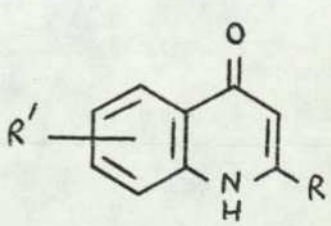
6.2 SYNTHESIS OF COMPOUNDS

(i) 2-Quinolone (m.p. 199-200°), 4-methyl-2-quinolone (m.p. 222-3°), 4-quinolone (m.p. 200-2°) and 2-methyl-4-quinolone (m.p. 235-6°) were available commercially and were recrystallised from water before use.

(ii) The remaining alkyl substituted 4-methyl-2-quinolone derivatives (LXXXIV, R = CH_3 R' = various) were prepared *via* the Knorr synthesis[318] as described in sections 6.3.1 and 6.3.2.



(LXXXIV)



(LXXXV)

(iii) 8-Methoxy-4-methyl-2-quinolone was synthesised by the general procedure described in sections 6.3.1 and 6.3.2 except that the cyclisation of o-methoxyacetoacetanilide (see Table 6.1) was effected with polyphosphoric acid.[341]

The properties of the product are shown in Tables 6.2 and 6.3.

(iv) The 2-quinolone derivatives bearing no 4-methyl substituents (LXXXIV, R = H) were synthesised through the appropriate methyl substituted quinoline N-oxide, followed by treatment with aqueous alkaline benzoyl chloride.[342] The properties of the products obtained are shown in Tables 6.4 and 6.5.

(v) When the reaction described in section 6.2 (iv) was performed with 8-methyl- and 5,8-dimethyl- quinoline N-oxides the required 2-quinolone derivatives were not obtained; instead a small yield of the corresponding 3-hydroxyquinoline derivative was isolated, the identity of which was confirmed by n.m.r. spectroscopy, see Table 6.6.

Accordingly, samples of the required 8-methyl-2-quinolones were obtained *via* the method of Johnston, Luker and Williams.[241]

Samples of 8-methyl-, 5,8-dimethyl- and 6,8-dimethyl-2-quinolone were kindly supplied by Dr. K.M. Johnston, Southend College of Technology and Dr. R.G. Shotter, Polytechnic of Central London. The samples were recrystallised before use (see Table 6.4), spectral data is shown in Table 6.5.

(vi) A sample of 6,7-dimethoxy-2-quinolone[343] was kindly supplied by Dr. G.R. Pettit, Cancer Research Institute, Arizona State University. Spectral data is shown in Table 6.5.

(vii) The 2-methyl-4-quinolone derivatives (LXXXV, R = CH_3, R' = various) were prepared *via* the Conrad-Limpach synthesis,[350] as described in section 6.3.3.

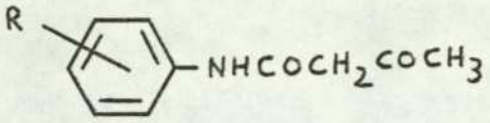
6.3 SYNTHETIC PROCEDURES

6.3.1 SYNTHESIS OF ACETOACETO-o-TOLUIDIDE (LXXXVI, R = o-CH_3)

A mixture of ethylacetoacetate (30g., 0.23 mole) and freshly distilled o-toluidine (24g., 0.22 mole) was heated rapidly and kept at the boiling point for 1 - 1.5 minutes under an air condenser, and then allowed to cool. The cooled mixture set to a mass of crystals which was collected and recrystallised from ethyl acetate. Acetoaceto-o-toluidide (26.1g., 62%) was obtained as colourless needles, m.p. 107-8°. (lit.[92]

m.p. 107-8°).

By a similar procedure, further acetoacetanilide derivatives (LXXXVI) were synthesised. The results are shown in Table 6.1.



(LXXXVI)

6.3.2 SYNTHESIS OF 4,8-DIMETHYL-2-QUINOLONE (LXXXIV, R = CH_3, R' = 8-CH_3)

Acetoaceto-o-toluidide (25g., 0.13 mole) was added portionwise to concentrated sulphuric acid (25 ml.) and the mixture heated on the water bath for 15 minutes. The reaction mixture was poured into water (250 ml.) and the precipitated solid filtered off and recrystallised from an ethanol-water solvent pair. 4,8-Dimethyl-2-quinolone (18.6g., 83%) was obtained as colourless fine needles, m.p. 217-8°. (lit.[344] m.p. 217-8°). By a similar procedure, further 4-methyl-2-quinolone derivatives (LXXXIV, R = CH_3) were synthesised, the results obtained are shown in Tables 6.2 and 6.3.

6.3.3 SYNTHESIS OF 2-METHYL-4-QUINOLONE DERIVATIVES (LXXXV, R = CH_3)

(i) A solution of the appropriate aniline derivative (0.1 mole), ethyl acetoacetate (13g., 0.1 mole) and glacial acetic acid (1.0 ml.) in benzene (100 ml.) was placed in a Dean and Stark apparatus equipped with a reflux condenser. The mixture was boiled under gentle reflux until the theoretical quantity of water (1.8 ml.) had been collected, (ca. 2-3 hours). The solvent was removed and the crude aminocrotonate distilled in vacuo (10 mm. pressure).

(ii) Diphenyl ether (25 ml.) was boiled under reflux and the crude aminocrotonate prepared above was added dropwise over 15 minutes. The solution was heated at the boiling point for a further 30 minutes and then cooled. Petroleum ether (b.p.

60-80°, 100 ml.) was added, with continuous agitation, and the mixture allowed to stand until the quinolone derivative separated. The product was collected, washed with a little petroleum ether and dried. Recrystallisation from water afforded the pure 2-methyl-4-quinolone derivatives as colourless needles. The products obtained are described in Tables 6.7 and 6.8.

TABLE 6.1

Synthesis of acetoacetanilide derivatives (LXXXVI)

R	Yield (%)	m.p. (lit.)	Molec. Formula	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
o-Me	62	107-8° (107-8°)[92]	$C_{11}H_{13}NO_2$		———			———	
m-Me	41	55-6° (57-8°)[92]	$C_{11}H_{13}NO_2$		———			———	
p-Me	42	94-5° (94-5°)[92]	$C_{11}H_{13}NO_2$		———			———	
2,3-Me_2	41	77-8°	$C_{12}H_{15}NO_2$	70.2	7.4	6.8	70.1	7.4	6.9
2,4-Me_2	75	87-8° (88-9°)[344]	$C_{12}H_{15}NO_2$		———			———	
2,5-Me_2	40	96-7° (98-9°)[344]	$C_{12}H_{15}NO_2$		———			———	
3,4-Me_2	(a)	(a)	$C_{12}H_{15}NO_2$		———			———	
3,5-Me_2	44	154-6° (b)[345]	$C_{12}H_{15}NO_2$	70.2	7.4	6.8	70.5	7.4	7.0
o-Et	43	84-5°	$C_{12}H_{15}NO_2$	70.2	7.4	6.8	70.3	7.5	7.0
p-Et	43	80-2° (82.5-83.5)[346]	$C_{12}H_{15}NO_2$		———			———	
o-MeO	62	88-9° (87°)[347]	$C_{11}H_{13}NO_3$		———			———	
p-MeO	85	118-9° (118-9°)[348]	$C_{11}H_{13}NO_3$		———			———	

Notes (a) - Product could not be crystallised. Crude product used directly in next stage.

(b) - 3,5-Dimethylacetoacetanilide has been reported in the literature, but no physical constants were given.[345]

TABLE 6.2

Synthesis of 4-methyl-2-quinolone derivatives (LXXXIV, R = CH_3)

R'	Yield (%)	m.p. (lit.)	Molecular Formula	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
6-Me	87	256-7° (249-50°)[344]	$C_{11}H_{11}NO$		———			———	
7-Me	62	220-1° (220°)[92]	$C_{11}H_{11}NO$		———			———	
8-Me	83	217-8° (217-8°)[344]	$C_{11}H_{11}NO$		———			———	
5,7-Me_2	71	281-3°	$C_{12}H_{13}NO$	77.0	7.0	7.5	76.9	7.1	7.4
5,8-Me_2	72	234-5° (234-5°)[344]	"		———			———	
6,7-Me_2	50	264-5°	"	77.0	7.0	7.5	77.1	7.0	7.3
6,8-Me_2	67	260-1° (252-3°)[344]	"		———			———	
7,8-Me_2	87	219-20°	"	77.0	7.0	7.5	77.2	7.0	7.4
6-Et	43	190-1°	$C_{12}H_{13}NO$	77.0	7.0	7.5	77.1	7.0	7.4
8-Et	54	173-4°	"	77.0	7.0	7.5	77.0	7.1	7.5
6-MeO	55	274-5° (273-5°)[348]	$C_{11}H_{11}NO_2$		———			———	
8-MeO	65	190-1° (189.5-190.5°)[341]	"		———			———	

TABLE 6.3

N.M.R. Spectra of 4-methyl-2-quinolone derivatives (LXXXIV, R = CH_3)(a,b)

(100 MHz, $CDCl_3$, τ p.p.m.)

R'	H-3	H-4	H-5	H-6	H-7	H-8	Other signals, unassigned peaks and coupling constants
6-Me	3.45	(7.53)	2.56	(7.58)	← 2.68 - 2.69 →		-
7-Me	3.47	(7.54)	2.47	2.98	(7.56)	2.75	J_{56} = 8.1 Hz, J_{68} = 1.6 Hz
8-Me	3.47	(7.53)	← 2.41 - 2.96 →			(7.48)	-
5,7-Me_2	3.55	(7.33)	(7.29)	3.20	(7.64)	2.95	
5,8-Me_2	3.54	(7.34)	(7.28)	3.12	2.83	(7.59)	J_{67} = 7.5 Hz
6,7-Me_2	3.48	(7.54)	2.62	-	-	2.78	(7.65, 7.68)
6,8-Me_2	3.50	(7.55)	2.69	(7.62)	2.83	(7.55)	-
7,8-Me_2	3.54	(7.57)	2.59	2.98	-	-	J_{56} = 8.3 Hz (7.60,7.61)
6-Et	3.45	(7.53)	2.57	(8.75)	2.79	2.60	CH_2 - 7.29 τ $J_{CH_2.CH_3}$ = 7.5 Hz J_{78} = 8.3 Hz.
8-Et	3.48	(7.53)	← 2.43 - 2.86 →			(8.69)	CH_2 - 7.11 τ $J_{CH_2.CH_3}$ = 7.5 Hz
6-MeO(c)	3.63	(7.60)	(d)	(6.11)	(d)	(d)	
8-MeO	3.47	(7.53)	← 2.68 - 3.08 →			(6.03)	

Notes (a) - Values in parentheses are for the appropriate substituted methyl group.

(b) - For chemical shift of NH see Table 6.10.

(c) - In DMSO-d_6

(d) - H-5, H-7, H-8 : 2.70 - 2.94 τ , 3H, m

TABLE 6.4

Properties of 2-quinolone derivatives (LXXXIV, R = H)

R'	m.p.	m.p. (lit.)	
5-Me	179-200° (a)	227-8°	(243)
6-Me	237-8°	236-8°	(243)
7-Me	179-200° (a)	198-9°	(243)
8-Me	221-2° (b)	221-2°	(243)
$5,8\text{-Me}_2$	206-7° (b)	199.5 - 200.5°	(243)
$6,8\text{-Me}_2$	202-3° (b)	201-2°	(241)
$6,7\text{-(MeO)}_2$	231-2° (c)	231°	(343)

Notes (a) Mixture of 5- and 7- isomers.

(b) Recrystallised samples ex. K.M. Johnston and R.G. Shotter.

(c) Sample ex. G.R. Pettit.

TABLE 6.5

N.M.R. Spectra of 2-quinolone derivatives (LXXXIV, R = H)(a,b)

(100 MHz, $CDCl_3$, τ p.p.m.)

R'	H-3	H-4	H-5	H-6	H-7	H-8	Other signals and Coupling Constants
6-Me	3.29	2.23	2.66	(7.60)	2.66	2.77	J_{34} = 9.5 Hz
6-Me(c)	3.56	2.20	2.59	(7.67)	2.66	2.80	J_{34} = 9.5 Hz, J_{78} = 8.5 Hz, J_{57} = 1.8 Hz
7-Me	3.35	2.26	2.59	3.00	(7.57)	2.74	J_{34} = 9.5 Hz, J_{56} = 8.0 Hz, J_{68} = 1.6 Hz
8-Me	3.35	2.27	← 2.56 - 2.98 →			(7.49)	J_{34} = 9.5 Hz
5,8-Me_2	3.35	2.06	(7.50)	3.10	2.81	(7.50)	J_{34} = 9.7 Hz, J_{67} = 7.5 Hz
6,8-Me_2	3.38	2.34	2.85	(7.65)	2.85	(7.49)	J_{34} = 9.4 Hz
6,7-$(MeO)_2$	3.41	2.31	3.08(e)	(6.03, 6.10)(d)		3.10 (e)	J_{34} = 9.3 Hz

Notes (a) - Values in parenthesis are for the appropriate substituted methyl group.

(b) - For chemical shift of NH see Table 6.10.

(c) - In DMSO-d_6

(d) - Exact assignments uncertain.

(e) - Assignments could be reversed.

TABLE 6.6

Properties of 3-hydroxyquinoline derivatives

Substituted 3-hydroxyquinoline	m.p. (lit.)	N.M.R. (a)
8-Me	219-22° (b)	-0.25 (1H, br, OH), 1.39 (1H, d, J_{24} 2.8 Hz, H-2), 2.25 - 2.79 (3H, m, H-5, H-6, H-7), 2.52 (1H, d, J_{24} 2.8 Hz, H-4), 7.33 (3H, s, CH_3).
5,8-Me_2	211-3° (c)	-0.19 (1H, br, OH), 1.41 (1H, d, J_{24} 2.8 Hz, H-2), 2.46 (1H, d, J_{24} 2.8 Hz, H-4), 2.79 (2H, s, H-6, H-7), 7.37, 7.48 (6H, 2s, CH_3).

Notes (a) N.M.R. - 100 MHz, DMSO-d_6, τ p.p.m.

(b) Lit.[349] m.p. 211°.

(c) Found: C, 76.1; H, 6.3; N, 8.0% Calc. for $C_{11}H_{11}NO$ C, 76.3; H, 6.4; N, 8.1%.

TABLE 6.7

Properties of 2-methyl-4-quinolone derivatives (LXXXV, R = CH_3)

R'	m.p.	m.p. (lit.)	Molecular Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
5-Me	274-6°	274° (351)	$C_{11}H_{11}NO$		———				
6-Me	279-80°	278-9° (351)	"		———				
7-Me	260-75° (a)	255-70° (352)	"		———				
8-Me	269-70°	263-4° (351)	"		———				
5,6-Me_2	271-3° (b)	-	$C_{12}H_{13}NO$	77.0	7.0	7.5	76.9	7.0	7.3
5,7-Me_2	285-7° (c)	288° (352)(d)	$C_{12}H_{15}NO_2$	70.2	7.4	6.8	70.1	7.4	6.7
5,8-Me_2	246-7°	248° (351)	$C_{12}H_{13}NO$		———				
6,7-Me_2	271-3° (b)	-	"	77.0	7.0	7.5	76.9	7.0	7.3
6,8-Me_2	273-4°	273° (351)	"		———				
7,8-Me_2	292-4°	-	"	77.0	7.0	7.5	76.8	6.8	7.4
5,6,8-Me_3	285-6°	285° (350)	$C_{13}H_{15}NO$		———				
6-Et	224-5°	-	$C_{12}H_{13}NO$	77.0	7.0	7.5	77.2	7.1	7.4
8-Et	203-5°	-	"	77.0	7.0	7.5	77.1	7.0	7.5

Notes (a) - In admixture with the 2,5-dimethyl isomer.

(b) - Mixture of 2,5,6- and 2,6,7- trimethyl isomers.

(c) - Monohydrate.

(d) - Lit. value for compound analysed as anhydrous.

TABLE 6.8

N.M.R. Spectra of 4-quinolone derivatives (LXXXV, R = CH_3)(a,b)

(100 MHz, DMSO-d_6, p.p.m.)

R'	H-2	H-3	H-5	H-6	H-7	H-8	Other signals and Coupling constants
5-Me	(7.71)	4.17	(7.19)	3.06	← 2.51 - 2.72 →		J_{67} = 7.1 Hz
6-Me	(7.67)	4.10	2.17	(7.62)	(2.59, 2.60)[c]		
7-Me	(7.61)	4.13	2.07	2.83	(7.68)	2.77	J_{56} = 8.2 Hz
8-Me	(7.64)	4.12	2.14	2.91	2.62	(7.53)	
5,6-Me_2	- (d)	4.22	(7.22)	- (d)	2.80	2.66	J_{78} = 8.1 Hz
5,7-Me_2	(7.76)	4.27	(7.27)	3.27	(7.69)	2.96	
5,8-Me_2	(7.66)	4.18	(7.26)	3.17	2.76	(7.57)	J_{67} = 7.2 Hz
6,7-Me_2	- (d)	4.18	2.22	- (d)	- (d)	2.76	
6,8-Me_2	(7.66)	4.12	2.31	(7.62)	2.75	(7.52)	
7,8-Me_2	(e)	4.12	2.16	2.90	(e)	(e)	J_{56} = 8.3 Hz
5,6,8-Me_3	(7.77)	4.21	(7.28)	(7.68)	2.81	(7.59)	
6-Et	(7.67)	4.12	2.13	8.80	2.57	2.57	CH_2 - 7.32 τ $J_{CH_2.CH_3}$ = 7 Hz
6-Et (f)	(7.53)	3.80	1.84	(8.78)	2.59	2.30	CH_2 - 7.28 τ $J_{CH_2.CH_3}$ = 7.5 Hz
							J_{78} = 8.5 Hz J_{57} = 2.0 Hz
8-Et	(7.59)	4.05	2.04	2.79	2.54	(8.76)	CH_2 - 7.05 τ $J_{CH_2.CH_3}$ = 7 Hz

Cont.....

TABLE 6.8 (Cont.)

Notes (a) Values in parentheses are for the appropriate substituted methyl group.

(b) For chemical shift of NH, see Table 6.11.

(c) Exact assignments uncertain.

(d) Assignment of methyl groups uncertain, for respective isomers.

(e) Methyl groups at 7.60, 7.60, 7.63 τ.

(f) In $CDCl_3$.

6.4 ^{1}H N.M.R. SPECTRAL STUDIES

6.4.1 INTRODUCTION

The present study was concerned with the variation of the chemical shift of the NH protons, for a series of 2- and 4- quinolone derivatives.

Details of the spectra of the aromatic and lactam ring regions of these compounds are shown in Tables 6.3, 6.5 and 6.8.

Details of long-range allylic couplings in methylquinolone derivatives, and of ortho-vicinal coupling constants in the lactam ring are shown in Table 6.9.

6.4.2 TECHNIQUES OF N.M.R. SPECTROSCOPY

Solutions of approx. 5% w/v concentration were used.

The 2-quinolone derivatives were examined in $CDCl_3$ solution, however, the 4-quinolone derivatives were generally not sufficiently soluble to be examined in this solvent. Accordingly, the 4-quinolone derivatives were examined in dimethylsulphoxide-d_6 solution. In order to afford a comparison of the results for 2- and 4- quinolone derivatives certain quinolones were also examined in both solvents when possible.

In order to assess whether there was any significant variation of the ortho-vicinal coupling constant of the 4-quinolone derivatives, when measured in dimethylsulphoxide-d_6 solution, a spectrum of 4-quinolone in saturated $CDCl_3$ solution was also determined by pulsed techniques. The operating conditions for this experiment were as follows:

Instrument : Jeol JNM-FX-60 spectrometer, operating at 59.75 MHz, dual $^{13}C/^{1}H$ probe used.

Solution : Saturated solution in $CDCl_3$ (ca. 0.1% w/v).

Pulse width : 34 μsec.(90°).

Pulse repetition rate : 4 sec.

Spectral width : 1000 Hz.

No. of data points : 4096 (before transformation). No. of pulses accumulated : 1160

In the case of the 4-methyl-2-quinolone derivatives the allylic coupling at the methyl group was normally discernible under standard operating conditions, and very substantial splitting was obtained when a narrow sweep width (100 Hz) was employed.

In the case of the 2-methyl-4-quinolone derivatives the smaller allylic coupling at the methyl group was only detected when the spectrum was expanded. Furthermore, since dimethylsulphoxide was required as the solvent, the viscous nature of the solutions obtained normally prevented high resolution from being achieved. An acceptable result was eventually obtained for 2-methyl-4-quinolone after rigourous purification of the compound by repeated recrystallisation. In other cases overlap of the sample and solvent signals did not permit measurement of the required coupling constant.

For both series of compounds the allylic coupling constants were measured at the methyl group, since this was considered to be the most accurate value, through the threefold increase in sensitivity over the ring protons. In all cases the correct assignment of the appropriate methyl group was confirmed through a spin decoupling experiment by irradiation at H-3.

6.4.3 RESULTS

The chemical shift of the NH protons for a series of substituted 2- and 4-quinolone derivatives are shown in Tables 6.10 and 6.11.

The effects of variation of concentration has been studied for two representative examples from the 2-quinolone series and the results obtained are shown in Table 6.12.

The effects of variation of solvent has also been studied (see also section 6.4.2) the results obtained are shown in Tables 6.13 and 6.14.

TABLE 6.9

Allylic coupling in 2- and 4- quinolone derivatives

2-quinolones (LXXXIV) (a)			4-quinolones (LXXXV) (b)		
R	R'	$^4J_{CH_3.H-3}$ (Hz)	R	R'	$^4J_{CH_3.H-3}$ (Hz)
H	H	(c)	H	H	(d)
H	6-Me	(c)	H	H	(e)
H	8-Me	(c)	CH_3	H	0.55
CH_3	H	1.15	CH_3	6-Me	0.6 (f)
CH_3	6-Me	1.1	CH_3	8-Me	0.6 (f)
CH_3	7-Me	1.15			
CH_3	8-Me	1.15			
CH_3	6,7-Me_2	1.1			
CH_3	7,8-Me_2	1.15			
CH_3	6-Et	1.20			
CH_3	8-Et	1.20			

Notes (a) N.M.R. - 100 MHz, 5% w/v $CDCl_3$ solution.

(b) N.M.R. - 100 MHz, 5% w/v DMSO-d_6 solution.

(c) ortho-vicinal coupling constant, J_{34} = 9.5 Hz.

(d) ortho-vicinal coupling constant, J_{23} = 7.4 Hz

(e) ortho-vicinal coupling constant, J_{23} = 7.3 Hz, in saturated (ca. 0.1 % w/v) $CDCl_3$ solution, determined by pulsed technique, (see section 6.4.2).

(f) Approx. value only due to poor resolution.

TABLE 6.10

Chemical shift of NH protons for a series of 2-quinolone derivatives

(100 MHz, $CDCl_3$, τ p.p.m.) (a)

Substituted 2-quinolone	NH (τ)	Substituted 2-quinolone	NH (τ)
4-H	-2.81	8-Me	-0.02
4-Me	-2.60	4,8-Me_2	-0.05
5-Me	ca -2.5	5,8-Me_2	-0.24
6-Me	-2.24	6,8-Me_2	-0.47
7-Me	-2.82	4,5,8-Me_3	0.99
4,6-Me_2	-2.38	4,6,8-Me_3	0.48
4,7-Me_2	-2.53	4,7,8-Me_3	0.29
4,5,7-Me_3	-1.85 (b)	4-Me-8-Et	0.11
4,6,7-Me_3	-2.34	4-Me-8-MeO	0.83
4-Me-6-Et	-2.74		
4-Me-6-MeO	- (c)		
6,7-$(MeO)_2$	-3.11		

Notes (a) - Peak normally appeared as a broad signal.

(b) - Sample sparingly soluble, ca 1% w/v solution, see also Table 6.12.

(c) - Sample not sufficiently soluble, see also Table 6.13.

TABLE 6.11

Chemical shift of NH protons for a series of 4-quinolone derivatives

(100 MHz, DMSO-d_6, τ p.p.m.)(a)

Substituted 4-quinolone	NH (τ)	Substituted 4-quinolone	NH (τ)
2-H	-1.70	$2,8\text{-Me}_2$	-0.36
2-Me	-1.65	$2,6,8\text{-Me}_3$	-0.32
$2,6\text{-Me}_2$	-1.54	$2,7,8\text{-Me}_3$	-0.24
$2,7\text{-Me}_2$	-1.47 (b)	2-Me-8-Et	-0.41
$2,6,7\text{-Me}_3$	-1.36 (b)		
2-Me-6-Et	-1.50	$2,5,8\text{-Me}_3$	0.08
$2,5\text{-Me}_2$	-1.36 (c)	$2,5,6,8\text{-Me}_4$	0.16
$2,5,6\text{-Me}_3$	-1.21 (b)		
$2,5,7\text{-Me}_3$	-1.14		

Notes (a) Peak normally appeared as broad signal.

(b) Determined on mixed sample of isomers.

(c) Also, chemical shift of NH at -1.34 τ for sample of 2,5-dimethyl isomer, in admixture with 2,7-isomer.

TABLE 6.12

Concentration effect studies for some 2-quinolone derivatives

Substituted 2-quinolone	Concentration (% w/v in $CDCl_3$)	Chemical shift of NH (τ)
4,6-Me_2	5	-2.38
	2.5	-2.30
	1	-2.18
	0.5	-1.82
4,8-Me_2	5	-0.05
	2.5	0.21
	1	0.68
	0.5	0.99

TABLE 6.13

Chemical shifts of NH protons of 2-quinolone derivatives in $CDCl_3$ and DMSO-d_6 solution.

Substituted 2-quinolone	NH Chemical Shift (τ p.p.m.)	
	In $CDCl_3$	In DMSO-d_6
4-H	-2.81	-1.67
4-Me	-2.60	-1.54
6-Me	-2.24	-1.63
4,6-Me_2	-2.38	-1.44
4-Me-6-Et	-2.74	-1.47
4-Me-6-MeO	-	-1.41
6,7-$(MeO)_2$	-3.11	-1.53
8-Me	-0.02	-0.85
4,8-Me_2	-0.05	-0.62
6,8-Me_2	-0.47	-0.79
4-Me-8-Et	0.11	-0.73
4-Me-8-MeO	0.83	-0.45

TABLE 6.14

Chemical shifts of NH protons of 4-quinolone derivatives in $CDCl_3$ and DMSO-d_6 solution

Substituted 4-quinolone	NH Chemical Shift (τ) In $CDCl_3$	In DMSO-d_6
2-H	-	-1.70
2-Me	-	-1.65
2,6-Me_2	-	-1.54
2-Me-6-Et	-3.11	-1.50
2,8-Me_2	-	-0.36
2-Me-8-Et	0.60	-0.41

6.5 DISCUSSION

In the course of studies on the synthesis of certain alkylquinolines (see section 4.2.2.4b) the use of the Knorr synthesis[318] involved the preparation of a series of 4-methyl-2-quinolone derivatives (LXXXIV, R = CH_3, R' = various) and subsequent removal of oxygen.

Examination of the intermediate 2-quinolone derivatives by n.m.r. spectroscopy (see Section 6.4) led to the observation that a methyl substituent at position 8 caused an upfield chemical shift for the NH proton of about 2-3 p.p.m. in $CDCl_3$ compared with alkylquinolones with no such substituent at position 8. (see Table 6.10) Subsequently a series of 2-methyl-4-quinolone derivatives (LXXXV, R = CH_3, R' = various) was prepared by the Conrad-Limpach procedure[350] and these showed a similar upfield shift of about 1-2 p.p.m. in dimethyl sulphoxide-d_6 solution (see Table 6.11).

That the above shifts were not caused by concentration effects was demonstrated for two representative samples from the 2-quinolone series, the results are reported in Table 6.12. Although further dilution did cause an upfield shift, this was considerably less than that caused by the introduction of the 8-methyl substituent. This concentration effect also accounted for the smaller chemical shift obtained for 4,5,7-trimethyl-2-quinolone (see Table 6.10), since this compound was particularly insoluble. The extent of the concentration effect was much larger for the 8-methyl derivative than for the 6-methyl derivative.

2- and 4-Quinolone derivatives are known[201] to be extensively hydrogen bonded in solution. Furthermore, Shindo[224] reported that certain polysubstituted 8-bromo- and 8-methoxy-2-quinolones exhibited different N-H absorptions in their infra-red spectra which was considered to result from a reduction in hydrogen bonding.

The upfield n.m.r. chemical shifts observed in the present work for compounds with an 8-methyl substituent may therefore be considered also to result from an inhibition of hydrogen bonding. That the compounds were intermolecularly hydrogen bonded may be deduced from the dilution effect studies which caused a further reduction of bonding and an additional upfield chemical shift (see Table 6.12). Moreover, since the additional shift was larger for 4,8-dimethyl-2-quinolone (Δ = 1.04 τ) than for 4,6-dimethyl-2-quinolone (Δ = 0.56 τ) over the same

concentration range the bonding present in the former compound appeared to be weaker than that in the latter.

Introduction of a methyl substituent at various positions of the quinolone ring was found to induce upfield chemical shifts for the NH proton (p.p.m.), both individually or in combination in the quinolone derivatives studied (LXXXIV, R = CH_3) and (LXXXV, R = CH_3) as shown in Table 6.15.

TABLE 6.15

Upfield chemical shifts induced by substitution of methyl groups in various positions of the quinolone ring (p.p.m.).

Ring position	2	4	5	6	7	8
2-quinolone	-	0.2	0.7	0.2	0.1	2.5
4-quinolone	0.05	-	0.4	0.1	0.2	1.4

The data in Table 6.15 (obtained from Tables 6.10 and 6.11), although not precise, show the particular significance of the 8-substituent compared with all other positions, and also that a methyl substituent at position 5 did have a slightly greater effect than when at positions 6 or 7.

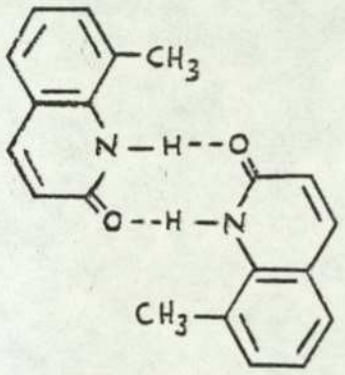
However, since all the 8-methyl substituted quinolone derivatives previously studied also possessed an additional methyl group (a 4-methyl group in the 2-quinolone series, and a 2-methyl group for the 4-quinolones) the possibility could not be excluded that the inhibiting effect of the 8-methyl substituent was only significant in the presence of the additional methyl group. In this respect the proposal of Staskun[226] that the 2-, 3- and 8- substituents acted together to form a combination which sterically hindered hydrogen bonding in 3-acetyl-2,8-diphenyl-4-quinolone should be recalled.

A study of a series of substituted 2-quinolone derivatives, bearing no 4-methyl substituent, was therefore undertaken and the results included in Table 6.10. The upfield shift of the NH proton in 8-methyl-2-quinolone was almost identical to that

observed for the 4,8-dimethyl derivative. The inhibition of hydrogen bonding was therefore caused almost exclusively by the 8-methyl substituent, and the additional 4-methyl group exerted very little effect (see Table 6.15).

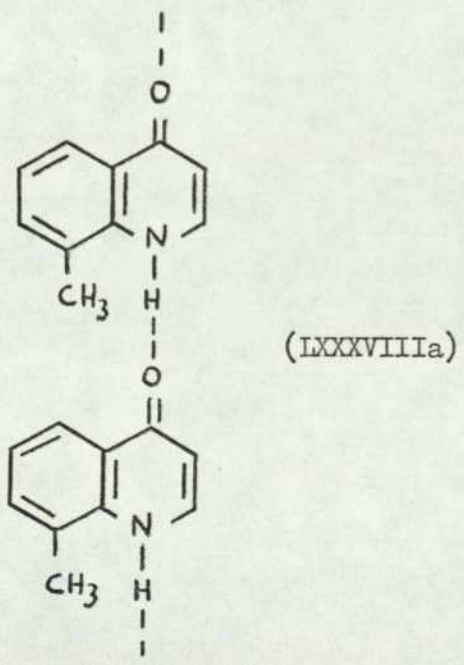
From the above studies it was clear that compounds with an 8-methyl substituent, either alone or in combination, were less bonded in solution.

However, if 2-quinolone derivatives exist in solution as a similar dimeric species (LXXXVII) to that proposed[221] for 2-pyridone, it would be difficult to envisage how such a steric effect could be significant, furthermore 4-quinolone derivatives could not form a dimer of this type at all.

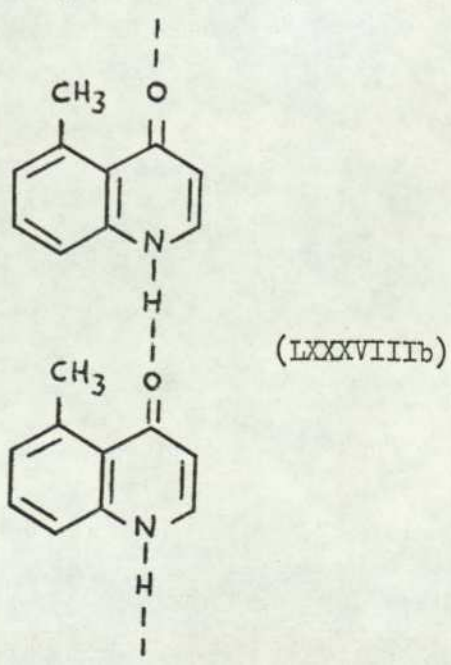


(LXXXVII)

If, however, only one hydrogen bond was involved in linking adjacent molecules, similar to the helical structure determined by Penfold[212] for the structure of 2-pyridone in the crystalline state, then an 8-substituent would be expected to exert such a steric effect. Consideration of the corresponding structures (LXXXVIIIa and LXXXVIIIb) for 4-quinolone indicated that both 5- and 8- substituents would be expected to have similar space requirements, and hence similar inhibition effects, which was not consistent with the experimental results obtained (see Table 6.11).

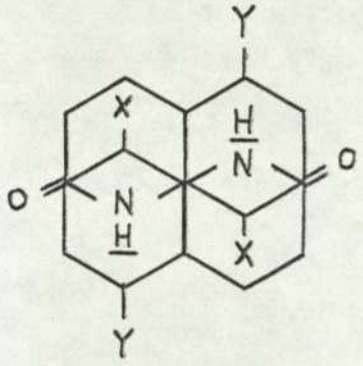


(LXXXVIIIa)

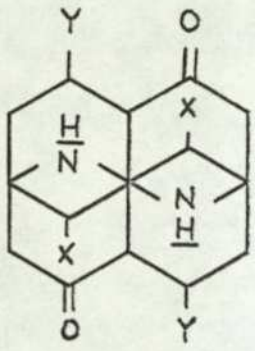


(LXXXVIIIb)

The experimental observations, however, were completely consistent with the proposal of Petersen[232] that the structure of quinolones in solution involved cyclic dimers formed by π-hydrogen bonds in addition to those with carbonyl-hydrogen bonds. Peterson's structure (LXV) may be represented in diagrammatic form by (LXXXIX) which shows the particular significance of the 8-substituent. The corresponding 4-quinolone form is represented by (XC).



(LXXXIX)



(XC)

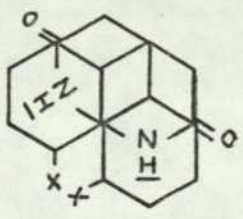
H - H bonded by π-bond.

X = 8-substituent

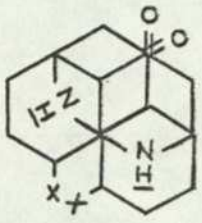
Y = 5-substituent

The lack of effect by a 5-substituent in the two structures (LXXXIX) and (XC) should be particularly noticed.

Other arrangements, which also involve two π-hydrogen bonds such as (XCI) and (XCII) are possible which would again be sensitive to a substituent at position 8.

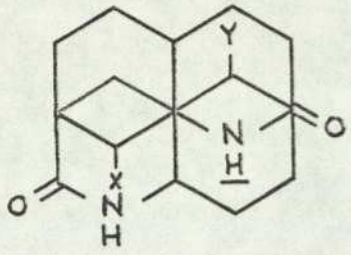


(XCI)

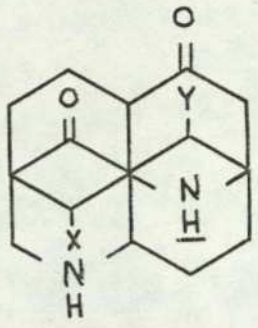


(XCII)

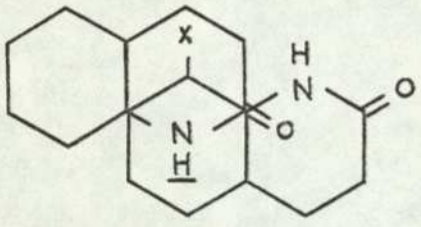
In addition, a series of less favourable structures involving only one π -hydrogen bond (XCIII) may be postulated, viz. (XCIIIa), (XCIIIc), and (XCIIIe) for the 2-quinolones and (XCIIIb), (XCIIId) and (XCIIIf) for the 4-quinolones. Of these (XCIIIc) and (XCIIId) would be subject to steric interference by an 8-substituent, (XCIIIe) and (XCIIIf) by a 5-substituent and (XCIIIa) and (XCIIIb) by both 5- and 8- substituents. In all cases the effects at other positions would be less significant. The intermediate inhibition effect of the 5-substituent (see Table 6.15) is consistent with the existence of varying amounts of some or all of the above less favoured structures.



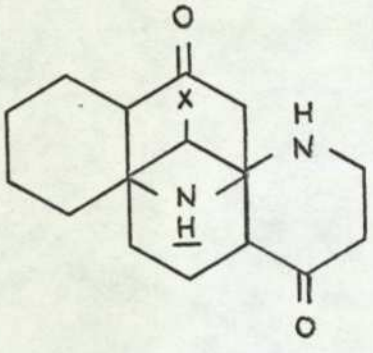
(XCIIIa)



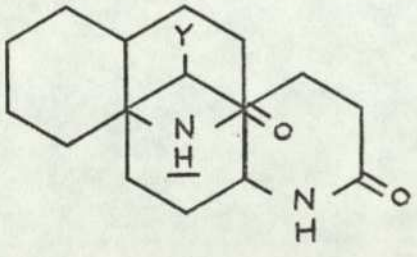
(XCIIIb)



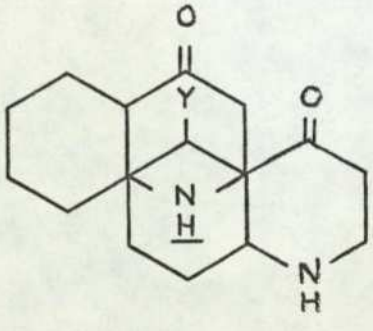
(XCIIIc)



(XCIIId)



(XCIIIe)



(XCIIIf)

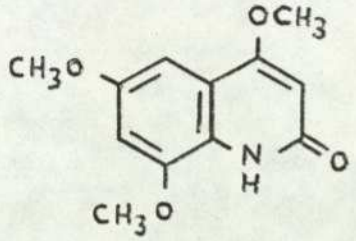
X = 8-substituent

Y = 5-substituent

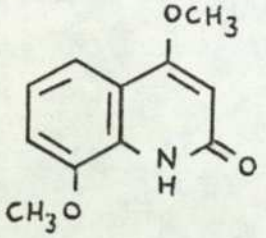
A comparison of NH chemical shifts in chloroform-d and dimethyl sulphoxide-d_6 solution has also been performed, and the results shown in Tables 6.13 and 6.14. The results for certain ethyl- and methoxyl- substituted derivatives have also been included (see also later discussion). The values in DMSO-d_6 solution afforded a comparison of the results for 2- and 4-quinolone derivatives which indicated that an upfield shift of the NH proton produced by an 8-substituent occurred in both solvents, but to a lesser extent in the more polar dimethylsulphoxide compared with chloroform. The range of chemical shifts observed was slightly greater for the 4-quinolone series in each solvent.

This characteristic upfield chemical shift of the NH protons provides valuable evidence for the presence of an 8-substituent in the quinolone ring and is more definitive than the concurrent changes in the N - H stretching region of the infra-red spectrum.[224]

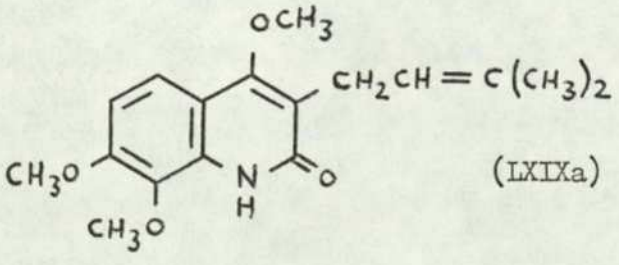
For example, the presence of the 8-methoxyl substituent in the quinolone alkaloids halfordamine (LXVIII),[252-4] edulitine (LXVI),[248-51] and preskimmianine (LXIXa)[257] may be readily deduced from the reported chemical shifts of the NH protons, 0.32 τ for halfordamine,[252] 1.1 τ for edulitine,[249] and 0.85 τ for preskimmianine.[257]



(LXVIII)



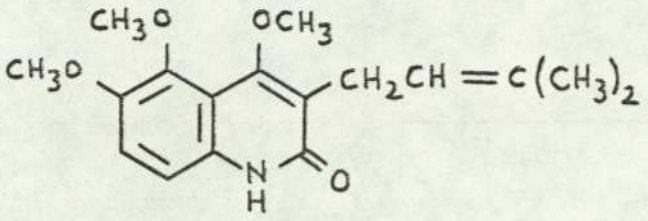
(LXVI)



(LXIXa)

The structure of (LXVI) remained unknown for several years[248] whilst that of (LXVIII) was initially open to doubt.[252] In the case of preskimmianine the structure was initially deduced from spectral data as either (LXIXa) or the isomeric

structure (LXIXb)[257].



(LXIXb)

The structure was eventually confirmed as (LXIXa) by consideration of other constituents of the same root and by subsequent unambiguous synthesis.[257] Clearly, consideration of the chemical shift of the NH proton of preskimmianine would immediately have rendered the alternative structure (LXIXb) unlikely.

Since the NH protons in these alkaloids all absorbed at a considerably higher field than the methyl substituted 2-quinolones studied in the present work, in order to confirm the proposed diagnostic validity some model compounds containing methoxyl substituents were later studied and the results shown in Tables 6.10 and 6.13. The shifts obtained were particularly characteristic, furthermore the chemical shift of the NH proton of 8-methoxy-4-methyl-2-quinolone occurred upfield from the corresponding dimethyl derivative, at a value similar to the shifts reported[249,252,257] for the 2-quinolone alkaloids.

Some measurements with ethyl-substituted compounds have also been performed, and the results reported in Tables 6.10 and 6.11.

The presence of the larger ethyl group did not significantly vary the observed chemical shift for the NH proton compared with that for the corresponding methyl derivative. Since the ethyl-substituted 2-methyl-4-quinolone derivatives were more soluble in chloroform, measurement of their spectra was possible which allowed additional comparisons of the NH proton shifts of 2- and 4- quinolone derivatives in this solvent to be performed (see also Tables 6.13 and 6.14).

In conclusion, the inhibition of π-hydrogen bonding is suggested as a dominant factor which contributes to the upfield chemical shift of the NH protons in 2- and 4- quinolone derivatives. This effect has been demonstrated to be characteristic and of a sufficient magnitude to be used as a diagnostic test in the identification

of unknown compounds, such as quinolone alkaloids.

It has recently been suggested by Beak[210] that studies of tautomeric equilibria in the pyridone and quinolone series were best performed upon the monomeric species (see also section 1.6.1). The complication of association could be removed by operation at very low concentration which may render detection difficult. The alternative approach was to study a compound such as 3-decyl-2,8-dimethyl-4-quinolone (LVIII), originally chosen[209] for its favourable solubility, which would be expected to be less associated than the parent heterocycle.[231]

The present work has shown that the quinolone (LVIII) would be less bonded in solution and that other similar compounds which contained an 8-substituent only could also be employed in such a study. Furthermore, the ethyl substituted compounds studied in the present work exhibited favourable solubility characteristics.

6.6 INFRA-RED SPECTRAL STUDIES

6.6.1 INTRODUCTION

The present study of the ^{1}H n.m.r. spectra of 2- and 4- quinolone derivatives was concerned with the variation of chemical shift of the NH protons, which was dependent upon the nature and strength of the hydrogen bonding present (see section 6.5).

This phenomenon has also been verified from infra-red spectral studies of the N - H bonds which exhibit characteristic stretching vibrations in the 3000 - 3600 cm^{-1} region, the shape and position of which are dependent upon the degree of hydrogen bonding.[353]

6.6.2 TECHNIQUES OF INFRA-RED SPECTROSCOPY

Samples were studied as weak solutions (usually 2% w/v concentration) in ethanol-free chloroform.

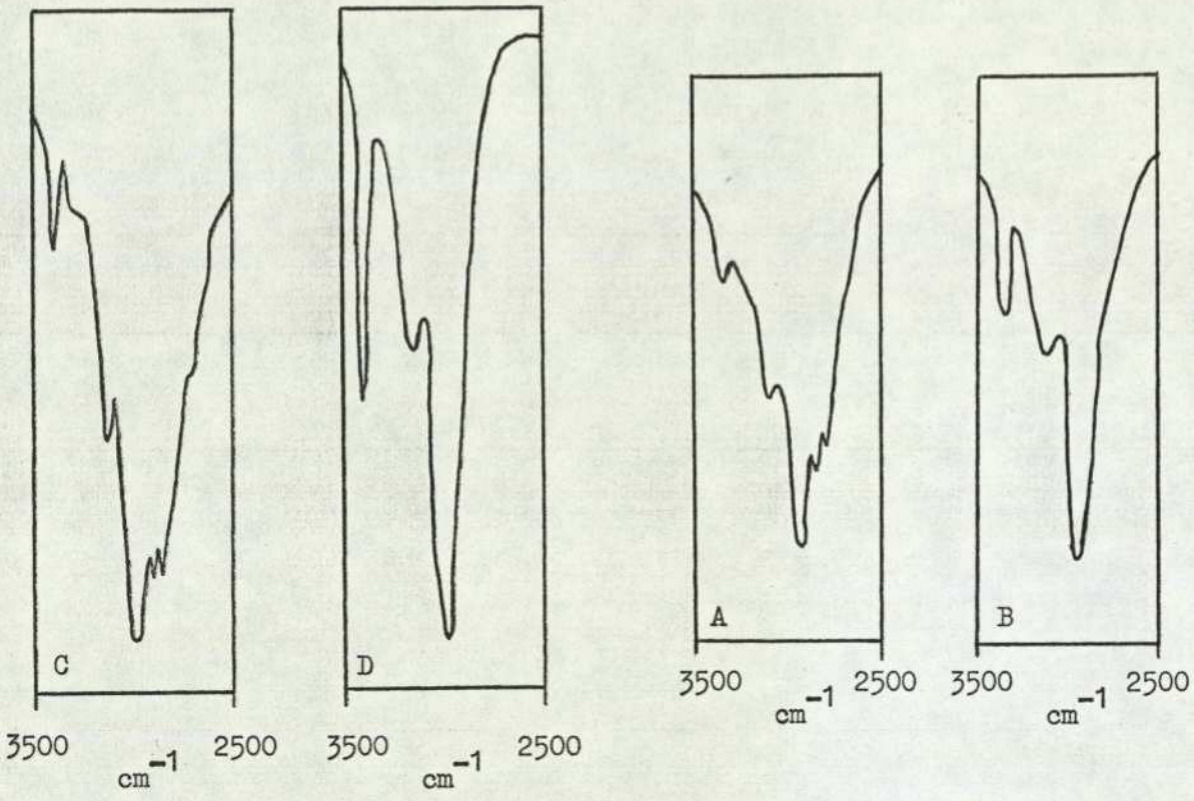
Since commercial chloroform contained ca. 1% ethanol as a preservative, the latter was removed by passage through a column containing activated alumina immediately prior to use.[354] The sample solution was contained in a fixed pathlength cell (0.1 mm.) and the reference solvent contained in a variable pathlength cell, which was adjusted to produce matched path lengths. With this procedure a straight line absorption could be obtained for the region of interest. This check procedure was repeated at frequent intervals between the spectral measurements.

Spectra were obtained over the range 3500 - 2500 cm^{-1} using a Perkin Elmer 'Infracord' spectrophotometer.

Due to limited solubility in chloroform, the infra-red spectra of the 4-quinolone derivatives could not readily be obtained, hence the present study was restricted to the more soluble 6-ethyl- and 8-ethyl-2-methyl-4-quinolone derivatives.

6.6.3 RESULTS

The spectra obtained for 6-methyl-, 8-methyl-, 4,6-dimethyl-, and 4,8-dimethyl-2-quinolone are shown in Figure 6.1. All the other 2-quinolone derivatives exhibited similar spectra as exemplified by the 8-substituted and 8-unsubstituted derivatives shown in Figure 6.1. The results obtained for the two 4-quinolone derivatives



A - 6-methyl-2-quinolone (1:5 % w/v, saturated solution).

B - 8-methyl-2-quinolone

C - 4,6-dimethyl-2-quinolone

D - 4,8-dimethyl-2-quinolone

FIGURE 6.1

Infra-red spectra of selected 2-quinolone derivatives.

(2% w/v solution in ethanol-free chloroform, 0.1 mm. path length).

studied were also consistent with these general considerations.

6.6.4 DISCUSSION

The spectra of the 2- and 4- quinolone derivatives examined in the present work exhibited characteristic features. All the derivatives bearing a substituent (methyl, ethyl or methoxy) at the 8-position gave rise to a sharp ν_{N-H} (free) absorption at 3380 - 3440 cm^{-1} whilst the corresponding compounds which were unsubstituted at the 8-position absorbed considerably less strongly in this region.

In addition, the absorption in the 2600 - 3200 cm^{-1} region (ν_{N-H} (bonded)) was generally more broadened and complex for the 8-unsubstituted compounds compared with the 8-substituted derivatives. The spectra were consistent with the reduced degree of hydrogen bonding of the 8-substituted derivatives in accordance with the conclusions from the ^{1}H n.m.r. spectral studies (see section 6.5).

The results were also in accordance with the earlier studies reported by Shindo,[224] which showed that in 7,8-dimethoxy-, 3-ethyl-4,7,8-trimethoxy- and 3,5,7,8-tetrabromo-2-quinolones there was a steric inhibition to the formation of a stable dimer and a consequent reduction of hydrogen bonding.

On the basis of an infra-red spectral study of 3-acetyl-2,8-diphenyl-4-quinolone, Staskun[226] proposed that the 2-, 3- and 8- substituents acted <u>together</u> to form a combination which sterically hindered hydrogen bonding.

The present work has shown that the inhibition of hydrogen bonding noted by the earlier workers[224,226] is caused almost exclusively by the 8-substituent only, and that other substituents exert very little additional effect.

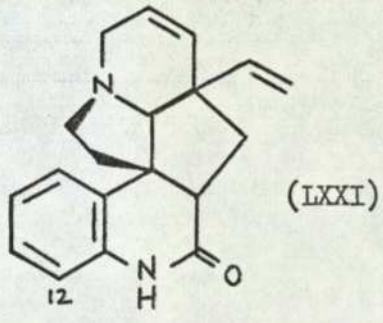
CHAPTER 7

^{13}C N.M.R. SPECTRAL STUDIES OF 2(1H)- and 4(1H)-QUINOLONE DERIVATIVES

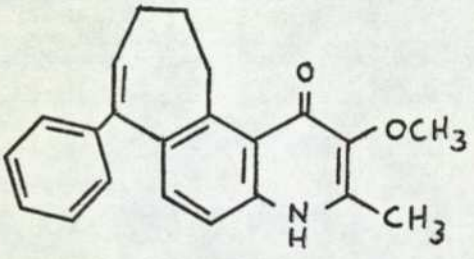
7.1 INTRODUCTION

Recently ^{13}C magnetic resonance studies of pyridone derivatives have attracted some interest.[238,272a,273-6] However, as far as the present author is aware no studies have yet been reported for the quinolone series although a report of the ^{13}C n.m.r. spectra of some condensed quinolone alkaloids, including meloscine (LXXI)[278,279] and melochinone (LXXII)[280] have appeared.

In the present study the ^{13}C n.m.r. spectra of a series of 2- and 4- quinolone derivatives are presented.



(LXXI)



(LXXII)

7.2 CARBON-13 N.M.R. SPECTROSCOPY

Samples were examined at natural abundance. Due to their limited solubility in chloroform, this solvent was not suitable for the majority of the ^{13}C n.m.r. studies, it was therefore found necessary to employ a solvent mixture which comprised 9:1 dimethylsulphoxide-$\underline{d}_6$: chloroform-$\underline{d}$ for the measurements. This solvent mixture was suitable for both the 2- and 4-quinolone series. For $^{13}C - \{^1H\}$ spectra about 2000 pulses were required for the most soluble compounds and about 15,000 pulses (overnight accumulation) for the majority of samples. However, the least soluble derivative (4,6,8-trimethyl-2-quinolone) required about 60,000 pulses. Low solubility prevented the use of off-resonance decoupled spectra, except in a few favourable cases.

Details of the instruments employed and of the operational parameters used have been described in section 6.3. The following additional technique was also employed using the Jeol JNM-FX-60 spectrometer :

Selective proton decoupled spectrum

Pulse width 5 μ sec. (30°), repetition rate 5 seconds.

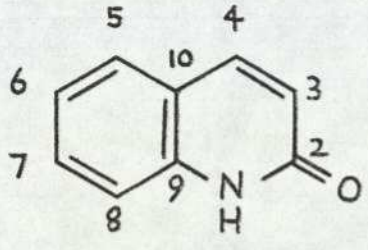
Spectral width 4000 Hz with 4096 data points (*).

Number of pulses accumulated: 10,000 - 15,000.

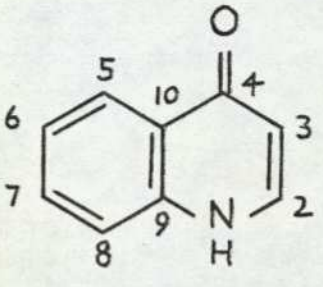
Decoupling : low power ^{1}H continuous wave decoupling was used (ca. 40% of the power required for a normal off-resonance spectrum).
The position of irradiation was checked by a ^{1}H homonuclear decoupling experiment.

7.3 RESULTS

The results obtained for the ^{13}C -$\{^{1}H\}$ spectra are shown in Tables 7.1 to 7.4, the following numbering schemes have been used:



2(1H)-quinolone (LVI)



4(1H)-quinolone (LVII)

Substituent Chemical Shift (S.C.S.) parameters have also been determined to test their additivity. The results obtained are shown in Table 7.5. A comparison of the calculated and experimental shifts for 4,6-dimethyl- and 4,8-dimethyl-2-quinolones is also presented.

Certain long range coupling constants have also been determined (see also section 5.6), which are reported in Table 7.6.

In order to facilitate discussion and comparison, the ^{13}C chemical shifts for 2- and 4-quinolone and for certain related compounds are also shown in Figure 7.1.

TABLE 7.1

^{13}C n.m.r. spectra of 2-quinolone derivatives (ring carbons)

Substituted 2-quinolone	Chemical Shift (δ , p.p.m. from T.M.S.) (a)								
	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
nil	162.0	121.7*	140.1	127.8	121.9*	130.2	115.2	139.0	119.1
nil (b)	164.8	121.5	141.0	127.7	122.6	130.6	116.3	138.7	120.0
4-Me	161.6	120.9	147.7	124.5	121.5	130.1	115.4	138.7	119.6
6-Me	161.9	121.7	139.9	127.3	130.6	131.4	115.0	136.8	119.1
8-Me	162.4	121.5	140.7	125.9	121.5	131.5	123.4	137.3	119.2
8-Me (b)	163.3	121.4	141.3	126.0	122.2	131.8	123.2	136.8	119.7
$4,6\text{-Me}_2$	161.5	120.8	147.4	124.1	130.4	131.3	115.4	136.6	119.5
$4,7\text{-Me}_2$	161.9	119.8	147.7	124.4	123.0	140.2	115.2	138.8	117.6
$4,8\text{-Me}_2$	161.8	120.6	148.1	122.5	121.2	131.4	123.5	137.0	119.7
$4,5,7\text{-Me}_3$	161.0	121.6	149.4	135.9	127.2	140.5	114.4	139.0	116.9
$4,6,7\text{-Me}_3$	161.6	119.7	147.3	124.5	129.8	139.3	115.8	136.9	117.7
$4,6,8\text{-Me}_3$	161.7	120.6	147.9	122.1	130.1	132.7	123.4	135.0	117.6
6-Et-4-Me (b)	164.5	120.4	149.0	122.8	138.4	130.7	116.8	136.7	120.4

Notes (a) In 9:1 DMSO-d_6 : $CDCl_3$

(b) Determined in $CDCl_3$ solution.

* - assignments may be reversed.

TABLE 7.2

^{13}C n.m.r. spectra of 2-quinolone derivatives

(methyl carbons)

Substituted 2-quinolone	Chemical shift (δ, p.p.m. from T.M.S.) (a)		
4-Me	18.4 (4)		
6-Me	20.3 (6)		
8-Me	17.2 (8)		
8-Me (b)	16.8 (8)		
4,6-Me_2	18.5 (4)	20.6 (6)	
4,7-Me_2	18.4 (4)	21.2 (7)	
4,8-Me_2	17.3 (8)	18.7 (4)	
4,5,7-Me_3	20.7 (c)	24.2 (c)	24.9 (c)
4,6,7-Me_3	18.4 (4)	19.0 (6)*	19.6 (7)*
4,6,8-Me_3	17.2 (8)	18.8 (4)	20.4 (6)
6-Et-4-Me (b)	19.1 (4)	15.8 (6)	28.7 (CH_2)

Notes (a) Assignments of methyl groups shown in parentheses.

(b) In $CDCl_3$, all other samples determined in 9:1 DMSO-d_6 : $CDCl_3$ solution.

(c) Assignments, uncertain at this stage, see also Section 7.4.

* - assignments may be reversed.

TABLE 7.3

^{13}C n.m.r. spectra of 4-quinolone derivatives (ring carbons)

Substituted 4-quinolone	Chemical shift (δ , p.p.m. from T.M.S.) (a)								
	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
nil	139.5	108.8	177.2	125.0	123.1	131.5	118.4	140.1	125.9
2-Me	149.5	108.4	176.8	124.8	122.6	131.3	117.7	140.2	124.6
$2,5\text{-Me}_2$	147.7	110.2	179.6	139.1	125.0	130.3	115.8	141.8	122.8
$2,6\text{-Me}_2$	149.1	108.1	176.7	124.1	131.8	132.6	117.6	138.2	124.5
$2,8\text{-Me}_2$	149.9	108.7	177.0	122.3*	122.8*	132.3	125.8	138.8	124.8
$2,5,8\text{-Me}_3$	148.1	110.7	180.0	136.8	124.8	131.4	123.2	140.3	123.2
$2,6,8\text{-Me}_3$	149.4	108.5	177.0	122.1	133.6	131.3	125.6	136.9	124.8
$2,7,8\text{-Me}_3$	149.7	108.3	177.1	122.0	124.9	139.3	123.2	138.9	123.2

Notes (a) In 9:1 DMSO-d_6 : $CDCl_3$

* - assignments may be reversed.

TABLE 7.4

^{13}C n.m.r. spectra of 4-quinolone derivatives

(methyl carbons)

Substituted 4-quinolone	Chemical shift (δ, p.p.m. from T.M.S.) (a)		
2-Me	19.5 (2)		
2,5-Me_2	18.9 (2)	23.1 (5)	
2,6-Me_2	19.4 (2)	20.7 (6)	
2,8-Me_2	17.5 (8)	19.8 (2)	
2,5,8-Me_3	17.7 (8)	19.4 (2)	23.3 (5)
2,6,8-Me_3	17.4 (8)	19.7 (2)	20.5 (6)
2,7,8-Me_3 (b)	13.1 (8)	19.8 (2)	20.4 (7)

Notes (a) Assignments of methyl groups shown in parentheses.
All samples measured in 9:1 DMSO-d_6 : $CDCl_3$

(b) Assignments made from consideration of methyl carbon shifts of 7,8-dimethylquinoline (see Table 5.4).

TABLE 7.5

Substituent Chemical Shift (S.C.S.) parameters for some methyl 2-quinolone derivatives (p.p.m.)

Ring Carbon	Quinolone derivatives						
	4-Me	6-Me	8-Me	$4,6\text{-Me}_2$		$4,8\text{-Me}_2$	
				Calc.	Obs.	Calc.	Obs.
C-2	-0.4	-0.1	+0.4	-0.5	-0.5	0.0	-0.2
C-3 (a)	-0.8	0.0	-0.2	-0.8	-0.9	-1.0	-1.1
C-4	+7.6	-0.2	+0.6	+7.4	+7.3	+8.2	+8.0
C-5	-3.3	-0.5	-1.9	-3.8	-3.6	-5.2	-5.3
C-6 (a)	-0.4	+8.7	-0.4	+8.3	+8.5	-0.8	-0.7
C-7	-0.1	+1.2	+1.3	+1.1	+1.1	+1.2	+1.2
C-8	+0.2	-0.2	+8.2	0.0	+0.2	+8.4	+8.3
C-9	-0.3	-2.2	-1.7	-2.5	-2.4	-2.0	-2.0
C-10	+0.5	0.0	+0.1	+0.5	+0.4	+0.6	+0.6

Notes (a) Chemical shifts used were: C-3 121.7 δ

C-6 121.9 δ

TABLE 7.6

Long range ^{13}C - ^{1}H coupling constants in some methylquinolone derivatives (a)

Compound	^{1}J	^{3}J	$^{3}R_{(b,c)}$
4-Me-2-quinolone	128 Hz (C-4')	6 Hz (C-4' - H-3)	0.6
6-Et-4-Me-2-quinolone (d)	128 Hz (C-4')	6 Hz (C-4' - H-3)	0.6
2-Me-4-quinolone	129 Hz (C-2')	4.5 Hz (C-2' - H-3)	0.6

Notes (a) Carbons numbered with (') are associated with the methyl group. For solvents used, see Tables 7.1 and 7.3.

(b) For definition of ^{3}R, see Section 5.6.

(c) Values used for ^{3}J (H - H) were taken from Section 6.4, Table 6.9.

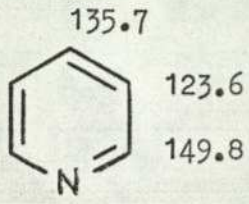
2-quinolone : J_{34} 9.5 Hz

4-quinolone : J_{23} 7.4 Hz

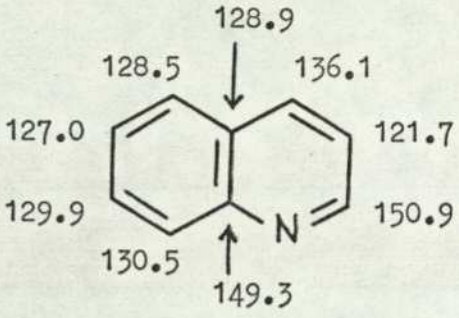
(d) Improved solubility obtained with 6-ethyl-4-methyl- derivative.

FIGURE 7.1

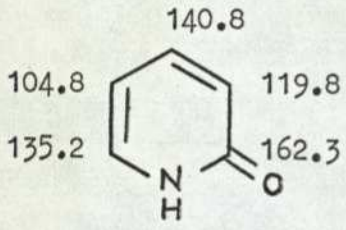
^{13}C Chemical shifts for pyridine and quinoline derivatives (δ , p.p.m. from T.M.S.)



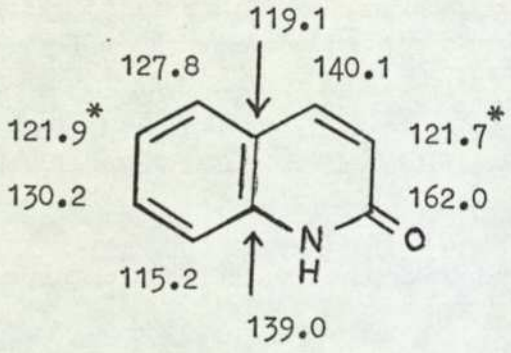
pyridine[272c]



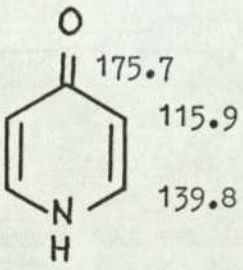
quinoline[173]



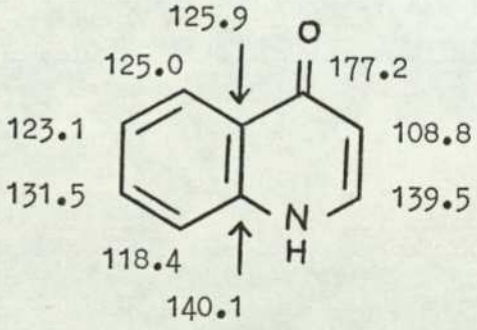
2-pyridone[238]



2-quinolone (a)



4-pyridone[238]



4-quinolone (a)

NOTES (a) present work.

* assignments may be reversed.

7.4 DISCUSSION

The proton decoupled ^{13}C n.m.r. spectrum of 2-quinolone determined in $CDCl_3$ solution consisted of nine peaks. Three peaks were of considerably reduced intensity and were ascribed to "quaternary" carbons, i.e. carbon nuclei which were not directly bonded to hydrogen. As the pulse repetition rate used to obtain the spectrum was comparatively fast (4 seconds) and since quaternary carbons have much longer relaxation times, T_1, compared with methyl, methylene or methine carbons, they appear much weaker and may be readily assigned.[169] The low intensity peaks were therefore ascribed to C-2, C-9 and C-10. The most downfield signal was assigned to C-2, the carbonyl group, since the chemical shift of this signal, 164.8 δ, was similar to that reported for the carbonyl group of 2-pyridone.[238]

The remaining quaternary signals at 138.7 δ and 120.0 δ were tentatively assigned to C-9 and C-10 respectively by comparison with the appropriate signals observed for quinoline.[173] These tentative assignments were later confirmed by an additional technique (see also later discussion).

The remaining assignments were then made by comparison with the respective shieldings reported for pyridine,[272c] pyridone[238] and quinoline[173] where appropriate and also by selective methyl substitution with the use of Substituent Chemical Shifts. (S.C.S.)

From a comparison with the reported chemical shift parameters (see Figure 7.1) the most downfield non-quaternary carbon of 2-quinolone was expected to be C-4. This tentative assignment was confirmed by the use of methyl S.C.S. effects by the following procedure.

The six equivalent carbons of benzene occur at 128.7 δ; introduction of a methyl group to produce toluene resulted in characteristic shifts of the aromatic carbon signals. C-1 (quaternary signal) was deshielded appreciably by +9.1 p.p.m., and C-4 shielded by -3.1 p.p.m., the perturbations at C-2 and C-3 were small, +0.6 and -0.2 p.p.m. respectively.[180] The use of the more significant methyl S.C.S. effects at the C-1 (α) and C-4 (<u>para</u>) positions were used to assign the ring carbons in the present work. For example, the lowest field aromatic carbon at 140.1 δ (in $CDCl_3$/ DMSO-<u>d</u>$_6$ has previously been tentatively assigned as C-4. In the spectrum of

4-methyl-2-quinolone such a signal was not present, instead a new quaternary signal appeared at 147.7 δ , a shift of +7.6 p.p.m. None of the other low field signals exhibited such a deshielding effect, and hence C-4 in 2-quinolone could be definitively assigned as the peak at 140.1 δ . In 4,7-dimethyl-2-quinolone a new quaternary signal was introduced at 140.2 δ whilst the peak at 130.1 δ in 4-methyl-2-quinolone was absent. Accordingly the signal at 130.2 δ in the original 2-quinolone spectrum could be assigned to C-7. In this manner all of the ring carbons in 2- and 4-quinolone were assigned, except that for C-3, for which no suitable substituted compounds were available. Since a non-quaternary peak close to 121 δ was present in all of the derivatives studied which did not exhibit any significant downfield shift, this was assigned to C-3 by default. As the signal for H-3 was well separated from the aromatic protons in the ^{1}H n.m.r. spectrum of 2-quinolone (see Section 6.2, Table 6.3) the preliminary assignment of C-3 was confirmed through a selective proton decoupling experiment at H-3 (see section 7.2).

Some comments on the ^{13}C n.m.r. spectra of quinolone derivatives will now be presented.

2-Quinolones

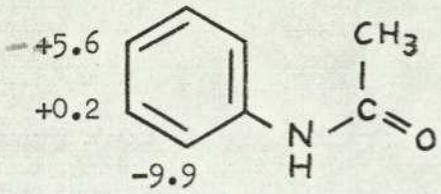
The signal for the carbonyl group appeared at 162.0 δ and showed little variation with changes of substitution. It has been found previously (see section 6.5) that the ^{1}H chemical shift of the NH proton in substituted 2-quinolone derivatives was effected by substitution at the 8-position due to inhibition of hydrogen bonding. It was proposed that the dominant factor which appeared to contribute to the observed chemical shift of the NH proton was the degree of π -hydrogen bonding present. Since this type of bonding would not be expected to effect the ^{13}C chemical shift of the carbonyl group to any significant extent, the near constant nature of this parameter would appear to lend support to the earlier proposal. The chemical shift of the carbonyl group was very similar to that observed for 2-pyridone.[238]

The signals for C-3 and C-4 were also similar to their respective lactam ring carbons in 2-pyridone.[294]

The C-5 signal appeared at 127.8 δ in 2-quinolone and at 124.5 δ in the 4-methyl derivative, which indicated that a pronounced peri-shielding effect had occurred.

Consideration of the spectra of 6-methyl- and 8-methyl-2-quinolone confirmed that a peri-shielding effect by the 4-methyl substituent did occur, and almost identical shifts for C-5 in 4-methyl-, 4,6-dimethyl- and 4,8-dimethyl-2-quinolone (-3.3, -3.2 and -3.4 p.p.m. compared to the respective unsubstituted quinolone derivative) were observed which further confirmed the peri-shielding effect of the 4-methyl group which was γ to C-5. Recently Cussans and Huckerby[199] have noted a similar peri-shielding effect of -3.5 p.p.m. at C-5 in the spectrum of 4-methylcoumarin. The C-5 signal in 2-quinolone was also further shielded when an additional para-substituent was present in accordance with similar effects found in methylbenzene derivatives.[180]

The signals for C-6 and C-7 appeared at 121.9 (121.7) and 130.2 δ respectively, that for C-6 was more shielded than its counterpart (127.0 δ) in quinoline.[173] An upfield shift was, however, not unexpected since such an effect did occur in the aromatic model compound acetanilide (XCIV), for the para-carbon.[166d]



(XCIV)

Substituent Chemical Shifts (p.p.m.) shown.

The signal for C-8 appeared at 115.2 δ a 15.3 p.p.m. upfield shift from its corresponding shielding in quinoline.[173] Substitution of a methyl group at position 8 caused the characteristic deshielding and quaternising effect which confirmed the assignment. Similar upfield shifts to that observed for C-8 in 2-quinolone have also been reported for the condensed quinolone alkaloids, such as C-12 in meloscine (LXXI)[278,279] and also for the ortho-carbons in the aromatic model compound, acetanilide (XCIV).[166d] This characteristic high field signal should prove valuable in the identification of 8-substituted 2-quinolone derivatives by ^{13}C n.m.r. spectroscopy.

The C-9 signal occurred at 139.0 δ , an upfield shift of 10.3 p.p.m. compared with its shielding in quinoline.[173] However, the chemical shift of C-9 was similar to that of C-6 in 2-pyridone[238] where the environment was more comparable.

The remaining bridgehead carbon, C-10, appeared at 119.1 δ , an upfield shift of 9.8 p.p.m. compared to quinoline.[173] Likewise this signal could be compared with C-5 in 2-pyridone,[238] since both were para to the carbonyl group. Each position experienced a pronounced shielding effect, but the quinolone carbon was shielded to a lesser extent, possibly since it was a quaternary site.

The respective assignments of the bridgehead carbons were confirmed by assessment of shielding effects, particularly those caused by para-methyl groups.[180] Thus C-9 experienced such an upfield shift when a 6-methyl group was present whilst C-10 experienced a similar effect in the presence of a 7-methyl group.[355]

Substituent Chemical Shift (S.C.S.) parameters for the ring carbons of 4-, 6- and 8-methyl-2-quinolone have also been determined and the results shown in Table 7.5. A comparison of the calculated and experimental shifts for 4,6-dimethyl- and 4,8-dimethyl-2-quinolones has also been presented, no value showed a discrepancy of greater than 0.2 p.p.m. which confirmed their additivity.

The methyl carbons all absorbed in the 17-25 δ region. In the case of 4,5,7-trimethyl-2-quinolone the chemical shifts appeared anomalous and the precise assignments were uncertain (see Table 7.2).

A subsequent study of the spectra of a series of 1-methyl-2-quinolone derivatives has also been undertaken.(see also Chapter 8)[356,357] In the ^{13}C n.m.r. spectrum of 1,8-dimethyl-2-quinolone,[357] the off-ring carbons exhibited a characteristic downfield shift of 7.1 p.p.m., parallel effects were observed for other peri-dimethyl substituted derivatives. Other workers[358,359] have also noted similar deshielding effects with 1,8-dimethylnaphthalene.

Consideration of this additional peri-methyl substituent effect permitted assignment of the methyl resonances for 4,5,7-trimethyl-2-quinolone. The observed shifts were rationalised since the 4- and 5- methyl groups should each experience a peri-substituent effect and the signals were accordingly assigned as:

20.7 δ (7-CH_3) ; 24.2 δ (4-CH_3 or 5-CH_3) ;

24.9 δ (5-CH_3 or 4-CH_3)

4-Quinolones

The carbonyl carbon (C-4) appeared at 177.2 δ , similar to the reported

shielding of the carbonyl carbon of 4-pyridone.[238] As with 2-quinolone, the chemical shift showed little variation upon the introduction of an 8-methyl substituent. The carbonyl carbon did exhibit a characteristic downfield shift upon introduction of a 5-methyl group.

The signal for C-2 appeared at a similar shift to that observed with 4-pyridone,[238] an upfield shift occurred upon introduction of a 5-methyl substituent.

The C-3 signal occurred far upfield (108.8 δ), the assignment was confirmed by a specific proton decoupling experiment at H-3. The C-3 signal of 4-pyridone[238] likewise appeared at high field (115.9 δ) but not to the same extent. A downfield shift was experienced in the presence of a 5-methyl substituent.

The C-5 signal occurred at 125.0 δ , introduction of a methyl group at this position induced an unusually large deshielding effect (+14.1 p.p.m.) compared with the effect (+9.1 p.p.m.) observed for toluene.[180] This large effect was, however, consistent with the introduction of a peri-methyl substituent (see later discussion).

The signals for C-6, C-7 and C-8 appeared only slightly different fields compared with their respective shifts in the 2-quinolone series, the identification of 8-substituted 4-quinolones may again be readily achieved by ^{13}C n.m.r. spectroscopy.

The C-9 signal occurred at 140.1 δ , an upfield shift of 9.2 p.p.m. with respect to its position in quinoline.[173] The chemical shift was comparable with that of C-2 in 4-pyridone,[238] since both carbons are meta to a lactam carbonyl group and exhibit similar shielding. A characteristic deshielding effect occurred upon introduction of a 5-methyl substituent.

The other bridgehead carbon, C-10, appeared at 125.9 δ , and exhibited a comparatively small shift of 3.0 p.p.m. compared to its shielding in quinoline.[173] Introduction of a carbonyl group into the pyridine nucleus to produce 4-pyridone resulted in shielding of both C-3 carbons by 7.7 p.p.m., a total shielding effect of 15.4 p.p.m. In 4-quinolone, C-3 was shielded by 12.9 p.p.m. and C-10 by 3.0 p.p.m. a total shielding effect of 15.9 p.p.m. Although the total effect was similar the distribution of the effect was different, this may be due to the quaternary nature of C-10, or there may be some other mechanism operative, such as a peri-substitution effect. In this respect it should be noted that the C-3 carbons in 2-pyridone[238]

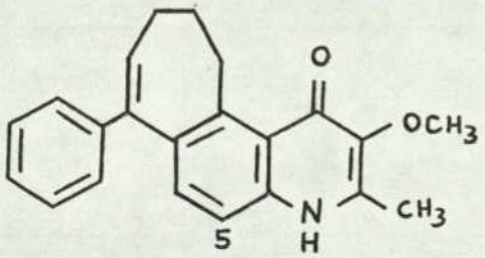
and 2-quinolone, although similarly ortho to a carbonyl group, were shielded to a limited extent only.

The characteristic shifts described above which occurred upon the introduction of the 5-methyl group may be rationalised through the additional involvement of a peri-methyl substituent effect.[357] In the 4-quinolone system such an effect would involve CH_3 (5) and the carbonyl group and result in characteristic variations in the ring carbon chemical shifts at C-3, C-4, C-5, C-6 and C-10.

Although the ^{13}C n.m.r. spectra of 2- and 4-quinolone derivatives exhibited some similarities, differentiation between the two series of compounds could readily be accomplished since the chemical shifts of the carbonyl carbons and of the C-3 carbons were well separated (see Figure 7.1). In both series of compounds the high field signals for C-8 should prove of value in the identification of 8-substituted derivatives.

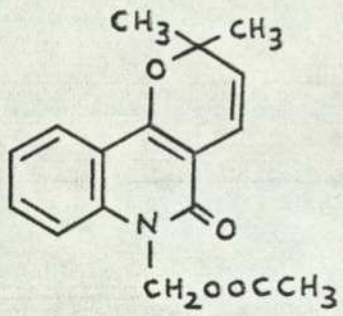
Recently Kapadia et al.[280] have commented upon the need of a general spectral technique for the identification of the pyridone (or quinolone) system as well as the distinction between its 2- and 4- isomers. Clearly ^{13}C n.m.r. spectroscopy could well fulfil this need. These workers[280] encountered problems in the identification of the quinolone ring system in the quinolone alkaloid melochinone (LXXII), isolated from melochia tomentosa L, the structure of which was eventually resolved by X-ray crystallographic studies.

The ^{13}C n.m.r. spectrum of this alkaloid exhibited a low intensity quaternary peak at 175.8 δ, characteristic of the carbonyl group of 4-quinolone. Furthermore, an absorption at 115.5 δ, which appeared as a doublet in the off-resonance spectrum, was also present. This peak was characteristic of C-8 in 4-quinolones and may be assigned to C-5 of melochinone.

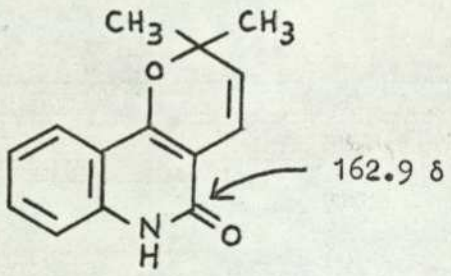


(LXXII)

Stermitz and Sharifi[360] have employed the chemical shift parameters obtained in the present work for the assignment of the chemical shifts of the pyranoquinoline alkaloids zanothophylline (XCV) and flindersine (XCVI).

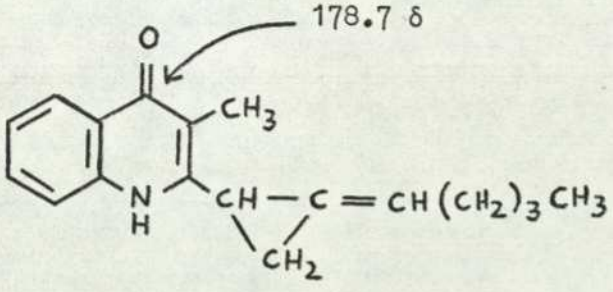


(XCV)



(XCVI)

Evans, Napier and Fletton[361] have also used the chemical shift parameters obtained in the present work in the course of their structural analysis of a new quinoline compound G1499-2 isolated from the fermentation broth of Cytophaga johnsonii, which was identified as 3-methyl-2-(2-pentylidenecyclopropyl)-4-quinolone (XCVII).



(XCVII)

Studies of the determination of long range (^3J) ^{13}C - ^1H coupling constants in the methylquinoline series have been discussed in Chapter 5. It was proposed that these long range coupling constants could be correlated with the appropriate proton-proton coupling constants through the following relationship:

$$^3R = \frac{^3J\ (C - H)}{^3J\ (H - H)}$$

In order to test this relationship further, similar long range ^{13}C - ^{1}H coupling constants in the methylquinolone series have also been determined, and the results shown in Table 7.6. Due to bond fixation in the quinolone derivatives, the appropriate proton-proton coupling constants have values different from their quinoline counterparts. The relationship was again found to be satisfied.

CHAPTER 8

^{1}H and ^{13}C N.M.R. SPECTRAL STUDIES OF 1-METHYL-2-QUINOLONE DERIVATIVES

8.1 INTRODUCTION

This subsequent study was a continuation of the work described in Chapters 6 and 7.

Since there are a number of alkaloids which do not contain an NH proton but which instead possess a 1-methyl group (see section 1.6.2, Figure 1.6.4) it was considered that a study of the ^{1}H and ^{13}C chemical shifts of the N-CH_3 groups could provide useful diagnostic information. In addition, the greater solubility of these compounds would facilitate the measurements.

8.2 SUMMARY OF RESULTS AND DISCUSSION

The ^{1}H chemical shifts of the N-CH_3 protons were all in the 6.24 - 6.46 τ region. Although compounds with an 8-methyl substituent did exhibit a slight downfield shift this was too small to be of diagnostic value. Full details of the results have been reported in reference 356.

The ^{13}C chemical shifts of the 1-methyl-2-quinolone derivatives were generally similar to those of the appropriate 2(1H)-quinolones which confirmed the earlier assignments.

The N - CH_3 and 8 - CH_3 carbons (differentiated by means of the ^{13}C proton coupled spectrum) each exhibited a characteristic peri-deshielding effect. The N - CH_3 carbons normally occurred at 29.1 - 29.4 δ , but in the presence of a 8-methyl group, the absorption was shifted downfield to 36.4 - 36.5 δ . (38.7 δ in the case of 1,7,8-trimethyl-2-quinolone). The C - CH_3 (8) carbon also experienced characteristic deshielding effects.

Similar deshielding effects by peri-methyl groups have also been noted by other workers[358,359] from studies upon 1,8-dimethylnaphthalene and a comparison of such effects in the naphthalene and quinolone series has been performed.

Consideration of the above peri-methyl substituent effects has enabled certain inconsistencies which were encountered in the ^{13}C n.m.r. spectra of 2- and 4- quinolones

to be resolved. The methyl resonances of 4,5,7-trimethyl-2-quinolone were rationalised and assigned, and peri-substituent effects between CH_3-5 and the carbonyl group envisaged to account for certain characteristic shifts experienced in the 4-quinolone series (see section 7.4).

Full details of the results and an extended discussion have been reported in reference 357.

REFERENCES

1. F. F. Runge, Ann. Physik. Chem., 1834, (2), 31, 65.
2. C. Gerhardt, Annalen, 1842, 42, 310; Ann. Chim. Phys., 1843, (3), 7, 251.
3. J. J. Berzelius, Jahresber. Fortsch. Chem. Mineral. Jakob Berzelius, 1844, 23, 357.
4. A. Calm, K. V. Buchka and G. Körner, "Die Chemie des Pyridines und seiner Derivatives," Friedrich Viewig und Sohn, Braunschweig, 1889-91, p. 23.
5. W. Koenigs, Ber., 1879, 12, 453.
6. R. C. Elderfield, "Heterocyclic Compounds," Wiley, New York, 1952, Vol. 4, pp. 1-343.
7. R. H. F. Manske, Chem. Rev., 1942, 30, 113.
8. N. Campbell in "Rodds Chemistry of Carbon Compounds," Elsevier, Amsterdam, 2nd. edn., 1976, S. Coffey, ed., Vol. IV, part F, pp. 231-356.
9. G. Jones in "The Chemistry of Heterocyclic Compounds," Vol. 32, "Quinolines, part 1," A. Weissberger and E. C. Taylor, eds., Wiley, London, 1977, pp. 1-318.
10. R. H. F. Manske and M. Kulka, Org. Reactions, 1953, 7, 59.
11. W. Koenigs, Ber., 1880, 13, 911.
12. Z. H. Skraup, Monatsh., 1880, 1, 316.
13. M. Prud'homme, Bull. Soc. chim. France, 1877, 28, 62.
14. Z. H. Skraup, Sber. Akad. Wiss. Wien, 1881, 83, 434.
15. Z. H. Skraup, Ber., 1881, 14, 1002.
16. Z. H. Skraup, Ber., 1882, 15, 893.
17. Z. H. Skraup, Monatsh., 1882, 3, 531.
18. M. H. Palmer, J. Chem. Soc., 1962, 3645.
19. G. M. Badger, H. R. Crocker, B. C. Ennis, T. A. Gayler, W. E. Matthews, W. G. C. Raper, E. L. Samuel and T. M. Spotswood, Austral. J. Chem., 1963, 16, 814.
20. T. Heou-Feo, Bull. Soc. chim. France, 1935, 2, 90.
21. H. L. Yale and J. Bernstein, J. Amer. Chem. Soc., 1948, 70, 254.

22. W. P. Utermohlen Jnr., J. Org. Chem., 1943, 5, 544.

23. K. N. Campbell, G. H. Helbing and J. F. Kerwin, J. Amer. Chem. Soc., 1946, 68, 1840.

24. E. Murmann, Monatsh., 1904, 25, 621.

25. R. H. F. Manske, L. Marion and F. Leger, Canad. J. Res., 1942, 20B, 133.

26. G. Darzens and M. Meyer, Compt. rend., 1934, 198, 1428.

27. K. N. Campbell and I. J. Schaffner, J. Amer. Chem. Soc., 1945, 67, 86.

28. K. N. Campbell, A. H. Sommers, J. F. Kerwin and B. K. Campbell, J. Amer. Chem. Soc., 1946, 68, 1851.

29. J. Kenner and F. S. Statham, Ber., 1936, 69B, 16.

30. Röhm and Hass A.-G., Ger. pat., 634,501 (1936).

31. H. T. Clarke and A. W. Davies, Org. Synth., Coll. Vol. I, 1948, 478.

32. B. E. Cohn and R. G. Gustavson, J. Amer. Chem. Soc., 1928, 50, 2709.

33. E. W. Cohn, J. Amer. Chem. Soc., 1930, 32, 3685.

34. R. H. F. Manske, A. E. Ledingham and W. R. Ashford, Canad. J. Res., 1949, 27F, 359.

35. I. G. Farbenindustrie A.-G., Brit. pat., 394,416 (1934).

36. M. Wahren, Tetrahedron, 1964, 20, 2773.

37. C. A. Knueppel, Ber., 1896, 29, 703.

38. E. de B. Barnett, Chem. News, 1920, 121, 205.

39. J. T. Hewitt and T. F. West, U.S. pat., 2,358,162 (1944).

40. L. G. Wolfe, Project Report, The City University, June 1968.

41. C. Masulli, Chimica (Milan), 1951, 6, 50.

42. O. Doebner and W. von Miller, Ber., 1881, 14, 2812.

43. O. Doebner and W. von Miller, Ber., 1882, 15, 3075.

44. O. Doebner and W. von Miller, Ber., 1883, 16, 2464.

45. O. Wallach and M. Wüsten, Ber., 1883, 16, 2007.

46. O. Doebner and W. von Miller, Ber., 1884, 17, 1712.

47. W. H. Mills, J. E. G. Harris and H. Lambourne, J. Chem. Soc., 1921, 111, 1294.

48. O. Doebner and W. von Miller, Ber., 1884, 17, 1698.

49. C. Beyer, J. prakt. Chem., 1886, (2), 33, 393.

50. B. A. Tertov and B. I. Ardashev, Zhur. Obshch. Khim., 1957, 27, 3026 ; Engl. transl., J. Gen. Chem. U.S.S.R., 1957, 27, 3056.

51. C. M. Leir, J. Org. Chem., 1977, 42, 911.

52. Y. Ogata, A. Kawasaki and S. Suyama, J. Chem. Soc. (B), 1969, 805.

53. T. P. Forrest, G. A. Dauphinee and W. F. Miles, Canad. J. Chem., 1969, 47, 2121

54. G. A. Dauphinee and T. P. Forrest, Chem. Commun., 1969, 327.

55. W. von Miller and F. Kinkelin, Ber., 1887, 20, 1916.

56. S. G. Willimott and I. A. Simpson, J. Chem. Soc., 1926, 2807.

57. E. J. Poth, W. A. Schulze, W. A. King, W. C. Thompson, W. M. Slagle, W. W. Floyd and J. R. Bailey, J. Amer. Chem. Soc., 1930, 52, 1239.

58. M. Gallagher and R. L. Hasche, U.S. pat., 2,245,582 (1941) ; 2,246,037 (1941).

59. E. M. Kaiser and J. D. Petty, J. Org. Chem., 1976, 41, 716.

60. J. H. Reed, J. prakt. Chem., 1885, 32, 630.

61. A. Pictet and R. R. Misner, Ber., 1912, 45, 1800.

62. L. A. Mikeska, J. Amer. Chem. Soc., 1920, 42, 2396.

63. G. Bach and K. H. Rast, J. prakt. Chem., 1962, 17, 63.

64. B. I. Ardashev and B. A. Tertov, Zhur. Obshch. Khim., 1956, 26, 218 ; J. Gen. Chem. U.S.S.R., 1956, 26, 233.

65. E. Wohnlich, Arch. Pharm., 1913, 251, 526.

66. D. J. Cook and W. E. Schelwalt, Proc. Indiana Acad. Sci., 1964, 74, 183.

67. M. H. Palmer and P. S. McIntyre, J. Chem. Soc. (B), 1969, 539.

68. A. Combes, Bull. Soc. chim. France, 1888, 49, 89 ; Compt. rend., 1888, 106, 142.

69. E. Roberts and E. E. Turner, J. Chem. Soc., 1927, 1832.

70. C. Beyer, Ber., 1887, 20, 1767.

71. A. Combes, Compt. rend., 1888, 106, 1536.

72. R. Huisgen, Annalen, 1949, 564, 16.

73. W. Borsche, Annalen, 1910, 377, 70.

74. T. G. Bonner and M. Barnard, J. Chem. Soc., 1958, 4176.

75. J. L. Born, J. Org. Chem., 1972, 37, 3952.

76. S. Tamura and E. Yabe, Chem. Pharm. Bull. (Tokyo), 1973, 21, 2105.

77. S. Tamura and E. Yabe, Chem. Pharm. Bull. (Tokyo), 1974, 22, 2982.

78. E. Thielpape, Ber., 1912, 55, 127.

79. L. Reher, Ber., 1887, 20, 2734. (Literature values quoted are those given for "diethylquinoline")

80. F. Minisci, R. Bernadini, F. Bertini, R. Galli and M. Perchinummo, Tetrahedron, 1971, 27, 3575.

81. R. Noyori, M. Kato, M. Kawanisi and H. Nozaki, Tetrahedron, 1969, 25, 1126.

82. Z. H. Skraup, Monatsh., 1884, 5, 531.

83. L. Bradford, T. J. Elliott and F. M. Rowe, J. Chem. Soc., 1947, 437.

84. Z. H. Skraup and P. Brunner, Monatsh., 1886, 7, 139.

85. J. G. F. Druce, Chem. News, 1918, 117, 346.

86. E. Jantzen, Dechema Monograph., 1932, No. 48, 35.

87. C. W. N. Cumper, D. G. Redford and A. I. Vogel, J. Chem. Soc., 1962, 1176.

88. E. Pouterman and A. Girardet, Experimentia, 1947, 3, 28.

89. T. Yoshikawa, Yakugaku Zasshi, 1961, 81, 1601.

90. L. Berend, Ber., 1884, 17, 1489.

91. H. King and J. Wright, Proc. Roy. Soc. London, 1948, 135B, 271.

92. A. J. Ewins and H. King, J. Chem. Soc., 1913, 103, 104.

93. R. Adams and J. Campbell, J. Amer. Chem. Soc., 1950, 72, 1021.

94. N. P. Buu-Hoi and D. Guettier, Rec. Trav. chim., 1946, 65, 502.

95. K. Harz, Ber., 1885, 18, 3384.

96. L. Berend, Ber., 1884, 17, 653.

97. W. Merz, Ber., 1884, 17, 1158.

98. M. Gandino, Belg. pat., 667,052 (1965).

99. T. G. Bonner and M. Barnard, J. Chem. Soc., 1948, 4181.

100. F. H. Case and H. H. Wisneski, J. Heterocycl. Chem., 1968, 5, 789.

101. "Beilsteins Handbuch der Organischen Chemie," (a) Vol. 20, Springer-Verlag, Berlin, 1935, p. 415 ; (b) Vol. 20, III and IV Supplement, part 5, Springer-Verlag, Berlin, 1978, pp. 3519-3580.

102. R. Long and K. Schofield, J. Chem. Soc., 1953, 2066.

103. R. Long and K. Schofield, J. Chem. Soc., 1953, 2350.

104. O. Widman, Ber., 1886, 19, 255.

105. N. P. Buu-Hoi, P. Jacquignon and E. Allegrini, J. Chem. Soc., 1961, 4836.

106. A. Tomisek, B. Graham, A. Griffith, C. S. Pease and B. E. Christensen, J. Amer. Chem. Soc., 1946, 68, 1587.

107. J. D. Capps, J. Amer. Chem. Soc., 1947, 69, 179.

108. K. Schofield, Quart. Rev., 1950, 4, 382.

109. L. H. Meyer, A. Saika and H. S. Gutowsky, J. Amer. Chem. Soc., 1953, 75, 4567.

110. J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, pp. 268-9.

111. H. J. Bernstein and W. G. Schneider, J. Chem. Phys., 1956, 24, 469.

112. T. Schaefer and W. G. Schneider, J. Chem. Phys., 1960, 32, 1218.

113. T. Schaefer, Canad. J. Chem., 1961, 39, 1864.

114. F. A. L. Anet, J. Chem. Phys., 1960, 32, 1274.

115. W. Seiffert, Angew. Chem. Int. Edn. Engl., 1962, 1, 215.

116. P. J. Black and M. L. Heffernan, Austral. J. Chem., 1964, 17, 558.

117. W. G. Paterson and G. Bigam, Canad. J. Chem., 1963, 41, 1841.

118. A. Albert and G. Catterall, J. Chem. Soc. (C), 1967, 1533.

119. R. Mondelli and L. Merlini, Tetrahedron, 1966, 22, 3253.

120. E. Diaz and P. Joseph-Nathan, Spectrochim. Acta, 1969, 25A, 1547.

121. M. Ohtsuru, K. Tori and H. Watanabe, Chem. Pharm. Bull. (Tokyo), 1967, 15, 1015

122. M. R. Chakrabarty and E. S. Hanrahan, J. Mol. Spectrosc., 1969, 30, 348.

123. G. Barbieri, R. Benassi, P. Lazzeretti, L. Schenetti and F. Taddei, Org. Magn. Reson., 1975, 7, 451.

124. P. J. Brignell, A. R. Katritzky, R. E. Reavill, G. W. H. Cheeseman and A. A. Sarsfield, J. Chem. Soc. (B), 1967, 1241.

125. W. G. Schneider, H. J. Bernstein and J. A. Pople, Canad. J. Chem., 1957, 35, 1487.

126. K. Tori and M. Ogata, Chem. Pharm. Bull. (Tokyo), 1964, 12, 272.

127. L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, Oxford, 1969 ; (a) pp. 333-4, (b) pp. 330-1, (c) p. 140, (d) pp. 204-7.

128. O. Sciacovelli and W. von Philipsborn, Org. Magn. Reson., 1971, 3, 339.

129. L. W. Reeves and K. O. Strømme, Canad. J. Chem., 1961, 39, 2318.

130. J. Ronayne and D. H. Williams, J. Chem. Soc. (B), 1967, 805.

131. Anon, Perkin Elmer N.M.R. Quarterly, 1971, No. 1, 2.

132. C. Beaute, Z. W. Wolkowski and V. T. Nguyen, Tetrahedron Lett., 1971, 817.

133. W. L. F. Armarego, T. J. Batterham and J. R. Kershaw, Org. Magn. Reson., 1971, 3, 575.

134. M. Hirayama and Y. Hanyu, Bull. Chem. Soc. Japan, 1973, 46, 2687.

135. R. F. M. White and H. Williams, Phys. Methods Heterocycl. Chem., 1971, 4, 121.

136. T. J. Batterham, "N.M.R. Spectra of Simple Heterocycles," Wiley, New York, 1973 ; (a) pp. 303-13, (b) pp. 48-9.

137. "The Aldrich Library of N.M.R. Spectra," Aldrich Chem. Co., Milwaukee, 1974, C. J. Pouchert and J. R. Campbell, eds., Vol. 9 ; (a) spectrum no. 101D, (b) spectrum no. 102A, (c) spectrum no. 103A, (d) spectrum no. 8D.

138. P. Diehl and H. Zimmermann, Org. Magn. Reson., 1976, 8, 155.

139. S. Sternhell, Rev. Pure Appl. Chem., 1964, 14, 15.

140. S. Sternhell, Quart. Rev., 1966, 23, 236.

141. Anon, Perkin Elmer N.M.R. Quarterly, 1974, No. 13.

142. H. Rottendorf and S. Sternhell, Austral. J. Chem., 1964, 17, 1315.

143. G. Kotowycz and T. Schaefer, Canad. J. Chem., 1966, 44, 2743.

144. H. M. McConnell, J. Chem. Phys., 1959, 30, 26.

145. J. V. Acrivos, Mol. Phys., 1962, 5, 1.

146. D. J. Blears, S. S. Danyluk and T. Schaefer, Canad. J. Chem., 1968, 46, 654.

147. C. A. Coulson and A. Streitwieser, "Dictionary of π-Electron Calculations," Pergamon, Oxford, 1965, p. 297.

148. R. Mondelli and L. Merlini in "Nuclear Magnetic Resonance in Chemistry," Proceedings of Symposium held at Cagliari, Sardinia, Italy, September 1964, B. Pesce, ed., Academic Press, New York, 1965, p. 243.

149. C. L. Bell, R. S. Egan and L. Bauer, J. Heterocycl. Chem., 1965, 2, 420.

150. M. Nonoyama, J. Organomet. Chem., 1974, 74, 115.

151. H. Sterk and A. Wachmann, Z. Naturforsch., 1976, 31A, 71.

152. H. Sterk, University of Graz, Austria, personal communication.

153. M. R. Bramwell and E. W. Randall, Spectrochim. Acta, 1970, 26A, 1877.

154. A. F. Bramwell and R. D. Wells, Tetrahedron, 1972, 28, 4155.

155. J. B. Rowbotham and T. Schaefer, Canad. J. Chem., 1973, 51, 953.

156. J. Gayoss, H. Bouanani and A. Boucekkine, Bull. Soc. chim. France, 1974, 538.

157. A. Rosowsky and E. J. Modest, J. Org. Chem., 1965, 30, 1832.

158. P. C. Lauterbur, J. Chem. Phys., 1957, 26, 217.

159. M. P. Klein and G. W. Barton, Rev. Sci. Instr., 1963, 34, 754.

160. R. R. Ernst and W. A. Anderson, Rev. Sci. Instr., 1966, 37, 93.

161. R. R. Ernst, J. Chem. Phys., 1966, 45, 3845.

162. K. F. Kuhlmann and D. M. Grant, J. Amer. Chem. Soc., 1968, 70, 7355.

163. R. Freeman, J. Chem. Phys., 1970, 53, 457.

164. K. Müllen and P. S. Pregosin, "Fourier Transform N.M.R. Techniques, A Practical Approach," Academic Press, London, 1976, pp. 140-1.

165. G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley, New York, 1972.

166. J. B. Stothers, "Carbon-13 N.M.R. Spectroscopy," Academic Press, New York, 1972 ; (a) pp. 485-93, (b) p. 348, (c) p. 94, (d) p. 197.

167. T. C. Farrar and E. D. Becker, "Pulse and Fourier Transform N.M.R.," Academic Press, London, 1971.

168. E. Breitmaier and W. Voelter, "^{13}C N.M.R. Spectroscopy, Methods and Applications," Verlag-Chemie, Weinheim, 1974.

169. P. S. Pregosin and E. W. Randall, Det. Org. Struct. Phys. Methods, 1971 4, 263.

170. P. C. Lauterbur, J. Chem. Phys., 1965, 43, 360.

171. R. J. Pugmire and D. M. Grant, J. Amer. Chem. Soc., 1968, 90, 697.

172. R. J. Pugmire, D. M. Grant, M. J. Robins and R. K. Robins, J. Amer. Chem. Soc. 1969, 91, 6381.

173. P. S. Pregosin, E. W. Randall and A. I. White, J. Chem. Soc. Perkin Trans. II, 1972, 1.

174. E. Breitmaier and K. H. Spohn, Tetrahedron, 1973, 29, 1145.

175. P. van de Weijer, H. Thijsse and D. van de Meer, Org. Magn. Reson., 1976, 8, 187.

176. I. H. Sadler, J. Chem. Soc. Chem. Commun., 1973, 809.

177. E. Kleinpeter and R. Borsdorf, J. prakt. Chem., 1973, 315, 765.

178. A. R. Garber, P. E. Garrou, G. E. Hartwell, M. J. Smas, J. R. Wilkinson and L. J. Todd, J. Organomet. Chem., 1975, 86, 219.

179. S. R. Johns and R. I. Willing, Austral. J. Chem., 1976, 29, 1617.

180. W. R. Woolfenden and D. M. Grant, J. Amer. Chem. Soc., 1966, 88, 1496.

181. Y. Takeuchi, Org. Magn. Reson., 1975, 7, 181.

182. P. M. Henrichs and S. Gross, J. Magn. Reson., 1975, 17, 399.

183. A. A. Chalmers and K. G. R. Pachler, Tetrahedron Lett., 1972, 4033.

184. K. Tori and T. Nakagawa, J. Phys. Chem., 1964, 68, 3163.

185. J. N. Shoolery, J. Chem. Phys., 1959, 31, 1427.

186. J. H. Markgraf, R. J. Katt, W. L. Scott and R. N. Shefrin, J. Org. Chem., 1969, 34, 4131.

187. T. A. Bryson, J. C. Wisowaty, R. B. Dunlap, R. R. Fisher and P. D. Ellis, J. Org. Chem., 1974, 39, 1158.

188. A. R. Tarpley and J. H. Goldstein, J. Phys. Chem., 1972, 76, 515.

189. M. Hansen and H. J. Jakobsen, J. Magn. Reson., 1973, 10, 74.

190. A. A. Fomichev, Yu. S. Ryabokobylko, A. V. Kessenikh, A. Ataev, B. V. Parusnikov, I. A. Krasavin and V. M. Dziomko, Khim. Geterotsikl. Soedin., 1977, 1235.

191. F. J. Weigert and J. D. Roberts, J. Amer. Chem. Soc., 1967, 89, 2967.

192. G. J. Karabatsos, J. D. Graham and F. M. Vane, J. Amer. Chem. Soc., 1962, 84, 37.

193. J. L. Marshall, D. E. Miller, S. A. Conn, R. Seiwell and A. M. Ihrig, Acc. Chem. Res., 1974, 7, 333.

194. U. Vögeli and W. von Philipsborn, Org. Magn. Reson., 1975, 7, 617.

195. M. J. Shapiro, J. Org. Chem., 1978, 43, 212.

196. R. Wasylishen and T. Schaefer, Canad. J. Chem., 1973, 51, 961.

197. F. J. Weigert, J. Husar and J. D. Roberts, J. Org. Chem., 1973, 38, 1313.

198. Y. Takeuchi and N. Dennis, J. Amer. Chem. Soc., 1974, 96, 3657.

199. N. J. Cussans and T. N. Huckerby, Tetrahedron, 1975, 31, 2591.

200. E. Leete, Bioorg. Chem., 1977, 6, 273.

201. A. R. Katritzky and J. M. Lagowski, Adv. Heterocycl. Chem., 1963, 1, 339.

202. J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, "The Tautomerism of Heterocycles," Adv. Heterocycl. Chem., Suppl. No. 1, 1976, pp. 1-213.

203. P. Beak, Acc. Chem. Res., 1977, 10, 186.

204. W. N. Hartley and J. J. Dobbie, J. Chem. Soc., 1899, 75, 640.

205. H. Specker and H. Gawrosch, Ber., 1942, 75, 1338.

206. G. W. Ewing and E. A. Steck, J. Amer. Chem. Soc., 1946, 68, 2181.

207. E. A. Steck, G. W. Ewing and F. C. Nachod, J. Amer. Chem. Soc., 1949, 71, 238.

208. J. A. Ricketts and B. Wicke, Proc. Indiana Acad. Sci., 1965, 75, 96.

209. J. Frank and A. R. Katritzky, J. Chem. Soc. Perkin Trans. II, 1976, 1428.

210. P. Beak, J. B. Covington and J. M. Zeigler, J. Org. Chem., 1978, 43, 177.

211. P. Beak, F. S. Fry, J. Lee and F. Steele, J. Amer. Chem. Soc., 1976, 58, 171.

212. B. R. Penfold, Acta Cryst., 1953, 6, 591.

213. B. R. Penfold, Acta Cryst., 1953, 6, 707.

214. B. Ribár, I. Janić, A. Kálmán and G. Argay, Cryst. Struct. Commun., 1977, 6, 677.

215. A. Stepien, M. J. Grabowski, M. Cygler and E. Wajsman, Acta Cryst., 1976, B32, 2048.

216. J. A. Gibson, W. Kynaston and A. S. Lindsey, J. Chem. Soc., 1955, 4341.

217. R. Adams, V. V. Jones and J. L. Johnson, J. Amer. Chem. Soc., 1947, 69, 1810.

218. S. F. Mason, J. Chem. Soc., 1957, 4874.

219. D. J. Cook, R. S. Yunghans, T. R. Moore and B. E. Hoogenboom, J. Org. Chem., 1957, 22, 211.

220. N. J. McCorkindale, Tetrahedron, 1961, 14, 223.

221. A. R. Katritzky and R. A. Jones, J. Chem. Soc., 1960, 2947.

222. A. R. Katritzky, unpublished results. (cited in references 221 and 223).

223. L. J. Bellamy and P. E. Rogasch, Proc. Roy. Soc. London, 1960, 257A, 98.

224. H. Shindo, Chem. Pharm. Bull. (Tokyo), 1959, 7, 407.

225. N. D. Coggeshall, J. Amer. Chem. Soc., 1947, 69, 1620.

226. B. Staskun, J. Chem. Soc. (C), 1966, 2311.

227. G. H. Keller, L. Bauer and C. L. Bell, Canad. J. Chem., 1968, 46, 2475.

228. R. A. Coburn and G. O. Dudek, J. Phys. Chem., 1968, 72, 1177.

229. R. A. Coburn and G. O. Dudek, J. Phys. Chem., 1968, 72, 3681.

230. N. Kulevsky and W. Reineke, J. Phys. Chem., 1968, 72, 3339.

231. A. R. Katritzky, private discussion with Prof. P. Beak (cited in reference 210).

232. J. C. Petersen, J. Phys. Chem., 1971, 75, 1129.

233. E. Osawa, T. Kato and Z. Yoshida, J. Org. Chem., 1967, 32, 2803.

234. M. Gomel and H. Lumbroso, Bull. Soc. chim. France, 1962, 2200.

235. P. Hampson and A. Mathias, Chem. Commun., 1967, 371.

236. R. H. Cox and A. A. Bothner-By, J. Phys. Chem., 1969, 73, 2465.

237. M. J. Cook, A. R. Katritzky, P. Linda and R. D. Tack, J. Chem. Soc. Perkin Trans. II, 1973, 1080.

238. U. Vögeli and W. von Philipsborn, Org. Magn. Reson., 1973, 5, 551.

239. S. Castellano, C. Sun and R. Kostelnik, J. Chem. Phys., 1967, 46, 327.

240. J. A. Elvidge and L. M. Jackman, J. Chem. Soc., 1961, 859.

241. K. M. Johnston, R. M. Luker and G. H. Williams, J. Chem. Soc. Perkin Trans. I, 1972, 1648.

242. H. Sterk and H. Holzer, Org. Magn. Reson., 1974, 6, 133.

243. O. Buchardt, P.L. Kumler and C. Lohse, Acta Chem. Scand., 1969, 23, 159.

244. "Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, 1966 et seq., ^{1}H n.m.r. spectra ; (a) number 6891M, (b) number 11793M, (c) number 9708M, (d) number 10509M, (e) number 8015M, (f) number 9709M.

245. J. F. Wolfe, G. B. Trimitsis and D. R. Morris, J. Org. Chem., 1969, 34, 3263.

246. D. J. Gale and J. F. K. Wilshire, Austral. J. Chem., 1974, 27, 1295.

247. M. Sainsbury in "Rodds Chemistry of Carbon Compounds," Elsevier, Amsterdam, 2nd edn., 1978, S. Coffey, ed., Vol. IV, part G, pp. 171-255.

248. J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, J. Chem. Soc., 1956, 4170.

249. T. P. Toube, J. W. Murphy and A. D. Cross, Tetrahedron, 1967, 23, 2061.

250. T. Kappe and E. Ziegler, Tetrahedron Lett., 1968, 1947.

251. N. S. Narasimhan and R. H. Alurkar, Chem. and Ind., 1968, 515.

252. W. D. Crow and J. H. Hodgkin, Austral. J. Chem., 1968, 21, 3075.

253. P. Venturella, A. Bellino and F. Piozzi, Chem. and Ind., 1972, 887.

254. R. Storer and D. W. Young, Tetrahedron Letters, 1972, 1555.

255. R. Storer and D. W. Young, Tetrahedron, 1973, 29, 1215.

256. R. Storer and D. W. Young, Tetrahedron Letters, 1972, 2199.

257. R. Storer and D. W. Young, Tetrahedron, 1973, 29, 1217.

258. S. J. Wratten, M. S. Wolfe, R. J. Andersen and D. J. Faulkner, Antimicrob. Agents Chemother., 1977, 11, 411.

259. D. M. Razzakova, I. A. Bessanova and S. Yu. Yunosov, Khim. Prir. Soedin., 1972, 8, 133.

260. B. D. Paul and P. K. Bose, J. Indian Chem. Soc., 1968, 45, 552.

261. J. Reisch, K. Szendrei, I. Novak, E. Minkler, J. Korosi and K. Csedo, Tetrahedron Lett., 1972, 449.

262. A. Meisels and F. Sondheimer, J. Amer. Chem. Soc., 1957, 79, 6328.

263. R. Storer, D. W. Young, D. R. Taylor and J. M. Warner, Tetrahedron, 1973, 29, 1721.

264. T. A. Crabb, Ann. Rep. N.M.R. Spectrosc., 1975, 6A, 249.

265. J. C. N. Ma and E. W. Warnhoff, Canad. J. Chem., 1965, 43, 1849.

266. M. Mottier, Helv. Chim. Acta, 1975, 58, 337.

267. C. H. Wang, Chem. Pharm. Bull. (Tokyo), 1973, 21, 2760.

268. Y. Sato, H. Kojima and H. Shirai, Tetrahedron, 1974, 30, 2695.

269. J. Metzger, H. Larivé, R. Dehnilauler, R. Baralle and C. Gaurat, Bull. Soc. chim. France, 1969, 1266.

270. H. Ishi, H. Ohida and J. Haginiwa, Yakugaku Zasshi, 1972, 92, 118.

271. "High Resolution N.M.R. Spectra Catalogue," N. S. Bhacca et al., eds., Varian Associates, Palo Alto, 1962, spectrum no. 291.

272. L. F. Johnson and W. C. Jankowski, "Carbon-13 N.M.R. Spectra," Wiley, New York, 1972 ; (a) spectrum no. 107, (b) spectrum no. 369, (c) spectrum no. 106.

273. G. Miyajima, Y. Sasaki and M. Suzuki, Chem. Pharm. Bull. (Tokyo), 1972, 20, 429.

274. C. J. Turner and G. W. H. Cheeseman, Org. Magn. Reson., 1974, 6, 663.

275. Y. Takeuchi and N. Dennis, Org. Magn. Reson., 1975, 7, 244.

276. L. Stefaniak, Tetrahedron, 1976, 32, 1065.

277. I. W. J. Still, N. Plavac, D. M. McKinnon and M. S. Chauhan, Canad. J. Chem., 1976, 54, 280.

278. M. Daudon, M. H. Mehri, M. M. Plat, E. W. Hagaman, F. M. Schell and E. Wenkert, J. Org. Chem., 1975, 40, 2838.

279. M. Daudon, M. H. Mehri, M. M. Plat, E. W. Hagaman, and E. Wenkert, J. Org. Chem., 1976, 41, 3275.

280. G. J. Kapadia, B. D. Paul, J. V. Silverton, H. M. Fales and E. A. Sokoloski, J. Amer. Chem. Soc., 1975, 97, 6814.

281. M. Witanowski, L. Stefaniak, H. Januszewski and G. A. Webb, Tetrahedron, 1971, 27, 3129.

282. T. Axenrod, M. J. Wieder, G. Berti and P. L. Barili, J. Amer. Chem. Soc., 1970, 92, 6066.

283. "Dictionary of Organic Compounds," I. Heilbron et al., eds., Eyre and Spottiswoode, London, 4th edn., 1965.

284. J. T. Adams and C. R. Hauser, J. Amer. Chem. Soc., 1944, 66, 1220.

285. G. T. Morgan and C. J. A. Taylor, J. Chem. Soc., 1925, 127, 803.

286. O. Diels and H. Schrum, Annalen, 1937, 530, 83.

287. P. A. Claret and A. G. Osborne, Org. Prep. Proced., 1970, 2, 305.

288. A. Ferratini, Gazzetta, 1893, 23, 105.

289. P. A. Claret and G. H. Williams, J. Chem. Soc. (C), 1969, 146.

290. T. van Hove, Bull. Classe Sci., Acad. roy. Belg., 1908, 540.

291. K. C. Bass and P. Nababsing, J. Chem. Soc. (C), 1970, 2169.

292. E. J. Zobian, W. S. Kelley and H. C. Dunathan, J. Org. Chem., 1964, 29, 584.

293. P. A. Claret and A. G. Osborne, Chem. and Ind., 1970, 401.

294. P. A. Claret and A. G. Osborne, J. Chem. Tech. Biotechnol., 1979, 29, 175.

295. I. V. Spady, Ber., 1885, 18, 3373.

296. K. C. John and F. H. Case, J. Chem. Eng. Data, 1968, 13, 568.

297. B. Tollens, Ber., 1884, 17, 653.

298. L. Pratesi, Gazzetta, 1885, 14, 351.

299. Kalle and Co., Ger. pat., 95, 184 (1897).

300. K. Frey, Helv. Chim. Acta, 1935, 18, 491.

301. Meister Lucius & Brüning Farbwerke, Ger. pat., 53, 937 (1889).

302. J. S. Fitzgerald, Austral. J. Appl. Sci., 1961, 12, 51.

303. D. Lauer, E. L. Motell, D. D. Traficante and G. E. Maciel, J. Amer. Chem. Soc., 1972, 94, 5335.

304. J. E. Gowan and T. S. Wheeler, "Name Index of Organic Reactions," Longmans, London, 1961, p. 72.

305. P. A. Claret and A. G. Osborne, Org. Prep. Proced. Internat., 1974, 6, 149.

306. W. Koenigs and J. Nef, Ber., 1886, 19, 2427.

307. G. M. Badger, J. W. Cook, and T. Walker, J. Chem. Soc., 1948, 2011.

308. J. Glinka, Roczniki Chem., 1965, 39, 885.

309. A. Marsili, Ann. Chim. (Rome), 1962, 52, 3.

310. A. T. Nielsen and W. J. Houlihan, Org. Reactions ; (a) 1968, 16, 28, (b) 1968, 16, 31.

311. G. I. Michailov, Zhur. Obshch. Khim., 1936, 6, 511.

312. T. M. Shepherd, Chem. and Ind., 1970, 567.

313. L. F. Hatch and G. Sutherland, J. Org. Chem., 1948, 13, 251.

314. D. P. Graddon and R. A. Schulz, Austral. J. Chem., 1965, 18, 1731.

315. A. W. Johnson, E. Markham and R. Price, Org. Synth., 1962, 42, 75.

316. J. W. Brühl, Z. phys. Chem., 1896, 21, 385.

317. A. M. Spivey and F. H. S. Curd, J. Chem. Soc., 1949, 2656.

318. L. Knorr, Annalen, 1888, 245, 357.

319. V. Rezl, Chem. prumysl., 1962, 12, 246.

320. See for example, L. Gatterman, "The Practical Methods of Organic Chemistry," Engl. edn. transl. by W. B. Shober, MacMillan, New York, 1896, pp. 11-4.

321. W. Klyne and P. B. de la Mare, Progr. Stereochem., 1958, 2, 65.

322. P. A. Claret and A. G. Osborne, Tetrahedron, 1977, 33, 1765.

323. R. Huisgen, Annalen, 1948, 559, 101.

324. S. D. Sample, D. A. Lightner, O. Buchardt and C. Djerrasi, J. Org. Chem., 1967, 32, 997.

325. P. M. Draper and D. B. MacLean, Canad. J. Chem., 1970, 48, 738.

326. J. H. Beynon, R. A. Saunders and A. E. Williams, "Mass Spectra of Organic Molecules," Elsevier, Amsterdam, 1968, pp. 325-30.

327. S. G. P. Plant and R. J. Rosser, J. Chem. Soc., 1929, 1861.

328. J. von Braun, W. Gmelin and A. Petzold, Ber., 1924, 57B, 382.

329. L. A. Mikeska and E. Q. Adams, J. Amer. Chem. Soc., 1920, 42, 2394.

330. T. Mazonski, T. Mielecki and E. Sucharda, Roczniki Chem., 1936, 16, 519.

331. T. A. Irving, J. L. Greene Jnr., J. G. Petersen and J. D. Capps, J. Amer. Chem. Soc., 1950, 72, 4069.

332. E. Lellmann and H. Alt, Annalen, 1887, 237, 307.

333. L. Berend, Ber., 1884, 17, 2716.

334. P. A. Claret and A. G. Osborne, Org. Magn. Reson., 1976, 8, 147.

335. P. J. Black and M. L. Heffernan, Austral. J. Chem., 1966, 19, 1287.

336. S. R. Johns and R. I. Willing, C.S.I.R.O., Melbourne, Australia, personal communication.

337. S. R. Johns, R. I. Willing, P. A. Claret and A. G. Osborne, Austral. J. Chem., 1979, 32, 761.

338. J.-A. Su, E. Siew, E. V. Brown and S. L. Smith, Org. Magn. Reson., 1977, 10, 122.

339. H. Takai, A. Odani and Y. Sasaki, Chem. Pharm. Bull. (Tokyo), 1978, 26, 1672.

340. W. Werner, Tetrahedron, 1969, 25, 255.

341. S. Nakano, Yakugaku Zasshi, 1960, 80, 1510.

342. F. Montanari and L. Pentimalli, Gazzetta, 1953, 83, 273.

343. G. R. Petit, B. Stevenson and G. Gever, Org. Prep. Proced. Internat., 1971, 3, 393.

344. C. E. Kaslow and B. E. Sommer, J. Amer. Chem. Soc., 1946, 68, 644.

345. A. Kettrup, Fresenius Z. Anal. Chem., 1969, 246, 108.

346. H. J. Harris and K. Weller, J. Inorg. Nuclear Chem., 1971, 33, 547.

347. O. G. Backeberg, J. Chem. Soc., 1933, 6031.

348. K. N. Campbell, R. S. Tipson, R. C. Elderfield, B. K. Campbell, M. A. Clapp, W. J. Gensler, D. Morrison and W. J. Moran, J. Org. Chem., 1946, 11, 803.

349. T. Nakashima and I. Susuki, Chem. Pharm. Bull. (Tokyo), 1969, 17, 2293.

350. M. Conrad and L. Limpach, Ber., 1888, 21, 523.

351. B. P. Bangdiwala and C. M. Desai, J. Indian Chem. Soc., 1953, 30, 655.

352. O. G. Backeberg and C. A. Freidmann, J. Chem. Soc., 1938, 972.

353. L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen, London, 1960, p. 253.

354. A. D. Cross and R. A. Jones, "An Introduction to Practical Infra-Red Spectroscopy," Butterworths, London, 3rd. edn., 1969, p. 33.

355. P. A. Claret and A. G. Osborne, Spectrosc. Letters, 1975, 8, 385.

356. P. A. Claret and A. G. Osborne, Spectrosc. Letters, 1978, 11, 345.

357. P. A. Claret and A. G. Osborne, Spectrosc. Letters, 1978, 11, 351.

358. N. K. Wilson and J. B. Stothers, J. Magn. Reson., 1974, 15, 31.

359. D. Doddrell and P. R. Wells, J. Chem. Soc. Perkin Trans. II, 1973, 1333.

360. F. R. Stermitz and I. A. Sharifi, Phytochemistry, 1977, 16, 2003.

361. J. R. Evans, E. J. Napier and R. A. Fletton, J. Antibiotics, 1978, 31, 952.

APPENDIX

LIST OF PUBLICATIONS

The following publications, directly concerned with the present work, have been published by the author:

1. A Convenient Synthesis of 3-Methylquinolines from Dimethoxymethane, by P.A. Claret and A.G. Osborne, Chem. and Ind., 1970, 401.
2. 2,4-Diethylquinoline - An Extension of the Combes Synthesis, by P.A. Claret and A.G. Osborne, Org. Prep. Proced., 1970, 2, 305-8.
3. 3,4-Dialkylquinolines by an Extension of the Beyer Synthesis, by P.A. Claret and A.G. Osborne, Org. Prep. Proced. Int., 1974, 6, 149-53.
4. N.M.R. Spectral Studies of some Quinolone Derivatives. Effect of Substitution on the Degree of Hydrogen Bonding, by P.A. Claret and A.G. Osborne, Spectrosc. Letters, 1974, 7, 503-10.
5. N.M.R. Spectral Studies of Quinoline Derivatives, Long Range ^{13}C - ^{1}H Coupling Constants in Methylquinoline Derivatives, by P.A. Claret and A.G. Osborne, Org. Magn. Reson., 1976, 8, 147-50.
6. N.M.R. Spectral Studies of some Quinolone Derivatives. Part II. Further Studies of the Effect of Substitution on the Degree of Hydrogen Bonding, by P.A. Claret and A.G. Osborne, Spectrosc. Letters, 1976, 9, 157-66.
7. N.M.R. Spectral Studies of some Quinolone Derivatives. Part III. Carbon-13 Magnetic Resonance Spectral Studies of 2- and 4-Quinolone Derivatives, by P.A. Claret and A.G. Osborne, Spectrosc. Letters, 1976, 9, 167-75.
8. N.M.R. Spectral Studies of some Quinolone Derivatives. Part IV. The Unique Effect of the 8-Substituent upon the Degree of Hydrogen Bonding and a Study of some Model Compounds for the Identification of Alkaloids, by P.A. Claret and A.G. Osborne, Spectrosc. Letters, 1977, 10, 25-33.
9. N.M.R. Spectral Studies of some Quinolone Derivatives. Part V. Further Studies of the Carbon-13 Magnetic Resonance Spectra of 2- and 4- Quinolone Derivatives, by P.A. Claret and A.G. Osborne, Spectrosc. Letters, 1977, 10, 35-42.

10. Synthesis and Nitration of 7-Alkylquinolines, by P.A. Claret and A.G. Osborne, Tetrahedron, 1977, 33, 1765-7.

11. N.M.R. Spectral Studies of some Quinolone Derivatives. Part VI. N-Methyl-2-Quinolone Derivatives, by P.A. Claret and A.G. Osborne, Spectrosc. Letters, 1978, 11, 345-50. COPY ATTACHED.

12. N.M.R. Spectral Studies of some Quinolone Derivatives. Part VII. Carbon-13 Magnetic Resonance Spectral Studies of N-Methyl-2-Quinolone Derivatives and an Examination of peri-substituent Effects, by P.A. Claret and A.G. Osborne, Spectrosc. Letters, 1978, 11, 351-60. COPY ATTACHED.

13. Improvements to the von Miller-Kinkelin Reaction. Synthesis of 3-Methylquinolines and of 3-Isopropylquinoline, by P.A. Claret and A.G. Osborne, J. Chem. Tech. Biotech., 1979, 29, 175-9.

14. Single-frequency Proton Decoupling in ^{13}C N.M.R. Spectra. ^{13}C Chemical Shifts and Methyl Substituent Chemical Shifts in Methylquinolines, by S.R. Johns, R.I. Willing, P.A. Claret and A.G. Osborne, Austral. J. Chem., 1979, 32, 761-8. COPY ATTACHED.

The following publications, in the related fields of quinoline chemistry and nuclear magnetic resonance spectroscopy, have also been published by the author:

15. Simple Technique for the Identification of (Quinoline) Isomers by Gas-Liquid Chromatography Coupled with Infra-Red Spectroscopy, by A.G. Osborne, Lab. Practice, 1971, 20, 579-80.

16. 2,4,5,8-Tetramethylquinoline. A Clarification, by P.A. Claret and A.G. Osborne, Org. Prep. Proced. Int., 1972, 4, 225-6.

17. Spin-spin Coupling of peri-Protons in Quinolines, by P.A. Claret and A.G. Osborne, Spectrosc. Letters, 1973, 6, 103-4.

18. Carbon-13 Magnetic Resonance Spectral Studies of Quinoline Derivatives. Assignments of Bridgehead Carbons, by P.A. Claret and A.G. Osborne, Spectrosc, Letters, 1975, 8, 385-90.

19. Mass Spectral Studies of Biheteroaryls. Part I. Bipyridyls and Biquinolyls, by A.G. Osborne, Spectrosc. Letters, 1977, 10, 777-82.

20. Use of Long Range ^{13}C - ^{1}H Coupling Constants for Structural Assignments of Juglone Derivatives, by G. Castillo, G.J. Ellames, A.G. Osborne, and P.G. Sammes, J. Chem. Res. (S), 1978, 45; J. Chem. Res. (M), 1978, 836-51.

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N.M.R. Spectral Studies of some Quinolone Derivatives. Part VI. N-Methyl-2-Quinolone Derivatives, by P.A. Claret and A.G. Osborne, *Spectrosc. Letters*, 1978, *11*, 345-50.

N.M.R. Spectral Studies of some Quinolone Derivatives. Part VII. Carbon-13 Magnetic Resonance Spectral Studies of N-Methyl-2-Quinolone Derivatives and an Examination of peri-substituent Effects, by P.A. Claret and A.G. Osborne, *Spectrosc. Letters*, 1978, *11*, 351-60.

Single-frequency Proton Decoupling in ^{13}C N.M.R. Spectra. ^{13}Chemical Shifts and Methyl Substituent Chemical Shifts in Methylquinolines, by S.R. Johns, R.I. Willing, P.A. Claret and A.G. Osborne, *Austral. J. Chem.*, 1979, *32*, 761-68.