STUDIES CONCERNING

PARTIALLY REDUCED NITROGEN HETEROCYCLES

A thesis submitted

by SIRI RAM CHHABRA

Supervisor: Dr.B.C.Uff

in partial fulfilment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

of

LOUGHBOROUGH UNIVERSITY OF TECHNOLOGY

Chemistry Department

April, 1971

To my wife

and

to my parents

ACKNOWLEDGEMENTS

I wish to express my deep and sincere gratitude to Dr. B.C.Uff for the excellent and considerate guidance and encouragement he provided throughout the project and for the knowledge he imparted to me.

I wish to express my thanks to the academic and technical staff of the chemistry department for their assistance during this work and to my typist for typing this thesis.

I acknowledge with gratitude financial assistance from Loughborough University of Technology.

I finally acknowledge the help and understanding of my parents and my wife, without which this work would not have been possible.

SUMMARY

Carbanion rearrangement studies on selected N-acyl-isoquinoline and -quinoline Reissert compounds have shown that alternative intramolecular rearrangements can compete successfully with the normal 1,2-acyl-migration. The observations have been rationalised mechanistically and their potential value in synthesis demonstrated. In particular the formation of a 1-benzoyl-8-hydroxyisoquinoline derivative has been effected from carbanion rearrangement of the corresponding 8-benzoyloxy Reissert compound. N-Crotonoylisoquinoline Reissert compound carbanion and analogous structures have been shown to undergo a complex reaction in which Michael type attack competes with the normal migration.

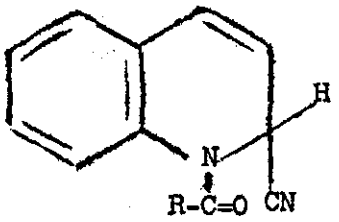
The synthesis of a new class of a compound, the cyclic N-acyl pseudo-base, has been examined and developed. Their formation as main products in the 5-nitroisoquinoline Reissert compound preparation has been shown to be general for a variety of acid chlorides and the reaction has been effected with other derivatives of isoquinoline, quinoline and with quinazoline. The chemistry of the system has been investigated and compared with that of the analogous Reissert system.

The proton magnetic resonance spectra of a large number of quinoline and isoquinoline Reissert compounds have been studied. The observation of long-range coupling of the hetero-ring protons in each system has permitted deductions regarding the stereochemistry of these structures. The apparently complex line structures given by the hetero-ring protons of certain of the quinoline Reissert compounds have been interpreted by use of AEX spectra calculations.

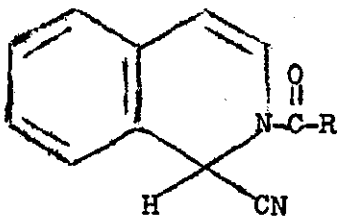
CONTENTS

INTRODUCTION

The studies of partially reduced nitrogen heterocycles described in this thesis relate principally to 1,2-dihydroisoquinoline and 1,2-dihydroquinoline systems of the Reissert type. N-Acyldihydroquinaldonitriles (1) and N-acyldihydroisoquinaldonitriles (2) are termed Reissert compounds after the discoverer, Arnold Reissert, who in 1905, following repeated failures to introduce the benzoyl group into the benzothiazole ring, carried out a systematic study of the benzoylation of cyclic tertiary amines.[1,2]



(1)



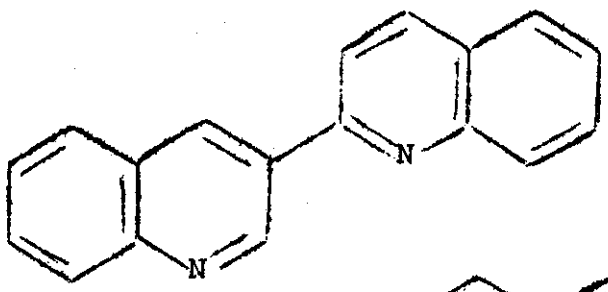
(2)

The reaction of benzoyl chloride with quinoline in aqueous potassium cyanide solution yielded the crystalline compound (1, R=Ph).[1] Other nitrogen heterocyclic compounds have since been shown to give Reissert compounds including isoquinoline,[2] phenanthridine,[3] and phthalazine.[4]

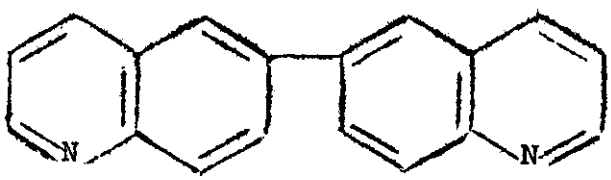
The preparation of Reissert compounds from a variety of acid chlorides has been reported.[5,6] The early preparations were carried out either in an aqueous medium[5] or a non-aqueous medium (e.g. anhydrous hydrogen cyanide in benzene as solvent).[7] A valuable development was the discovery by Popp and Blount in 1961 of the methylene-

chloride-water solvent system[8] for Reissert compound formation and this has since been used in a wide variety of cases.[6] The preparation of Reissert compounds in a one-phase system utilising aqueous dimethylformamide[9] or benzoyl cyanide[10] has also been examined but with limited success.

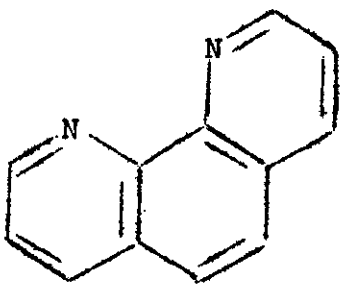
Although a wide variety of Reissert compounds have been prepared from quinoline and isoquinoline[6] relatively little study has been carried out concerning the Reissert reaction with diazaheterocyclic compounds. The literature[11,12] records the formation of a mono Reissert compound from 2,3'-biquinoline (3)[11] and a di-Reissert compound from 6,6'-biquinoline (4).[12] Further o-phenanthroline (5) does not give a Reissert compound[6,13] while m-phenanthroline gives a mono Reissert derivative (6).[6]



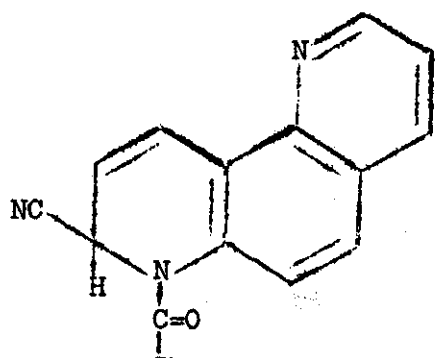
(3)



(4)

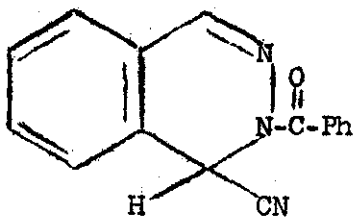


(5)

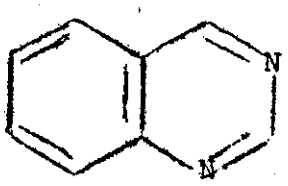


(6)

Recently Popp and Wefer[4] have obtained the mono Reissert compound (7) from phthalazine. In this thesis we report a study of the related diazaheterocyclic system quinazoline (8).



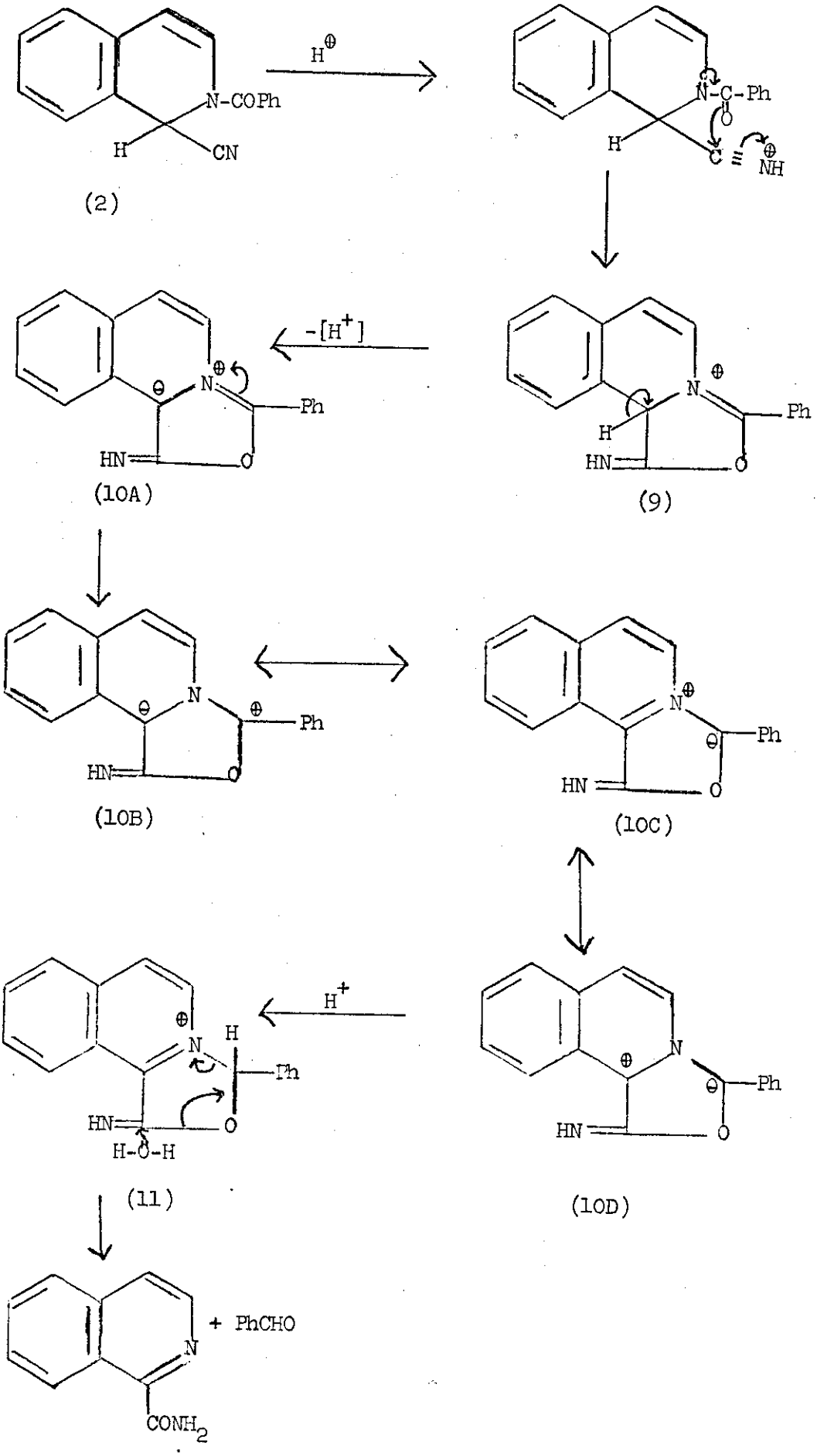
(7)



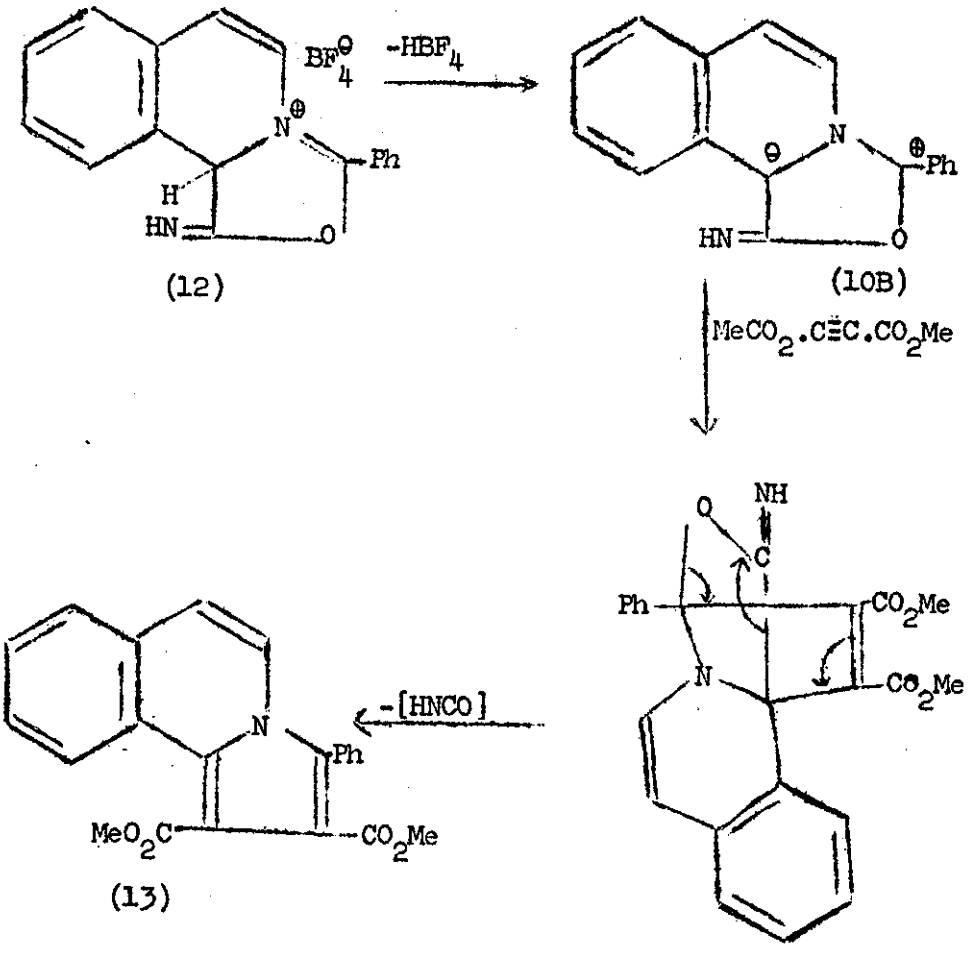
(8)

One of the interesting properties of Reissert compounds is the acid-catalysed hydrolysis. The products isolated include an aldehyde corresponding to the original acid chloride employed, a heterocyclic carboxylic acid and their derivatives. It was this reaction that attracted much attention in the early work on Reissert compounds, because the method represented a general route for the preparation of aldehydes from acid chlorides.[5,14] A reasonable mechanism has been proposed for the hydrolysis,[5,15] which involves the cyclic intermediates (9), (11) and probably mesoionic structures such as (10, A,B,C and D). (See p. 4).

Mechanism for the acid catalysed hydrolysis of a Reissert compound

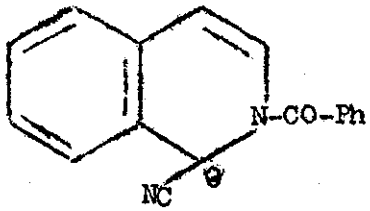


The intermediate (9) has been isolated as a salt[16] and the mesoionic intermediate (10) has been captured via a 1,3-dipolar cycloaddition.[17] In this reaction, the fluoroborate salt (12) of (9) was first obtained and reacted with dimethyl acetylene dicarboxylate to afford dimethyl 3-phenylpyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (13).



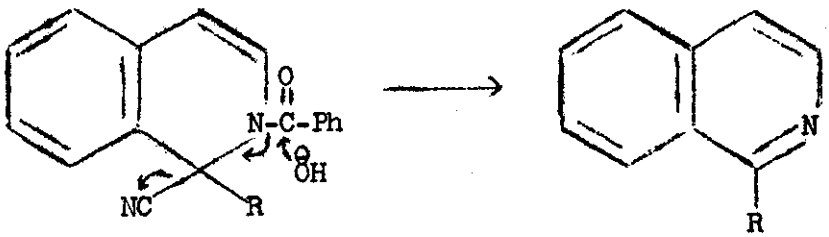
The reaction of Reissert compounds with base was first studied by Boekelheide and Weinstock,[18] who, using phenyllithium, generated the anion of the type (14) (from isoquinoline) by removal of the C-1 proton. Sodium[19,20] or sodium hydride[18] in hot xylene were also

used for carbanion generation.



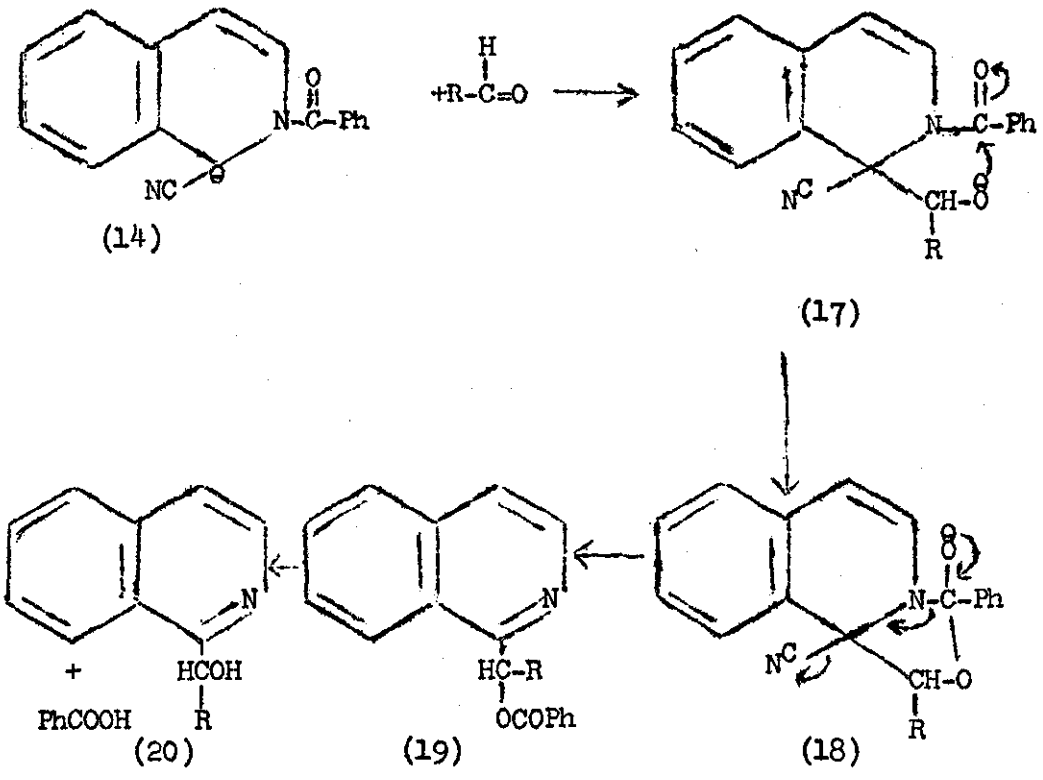
(14)

The authors[18] showed that the carbanion (14) could be alkylated with alkylhalides (RX) to give the substituted Reissert structure (15), which on basic hydrolysis gives the 1-substituted isoquinoline (16). 1-Benzyl-,1-methyl- and 1-butyl-isoquinoline were thus prepared from the isoquinoline Reissert compound.[18]

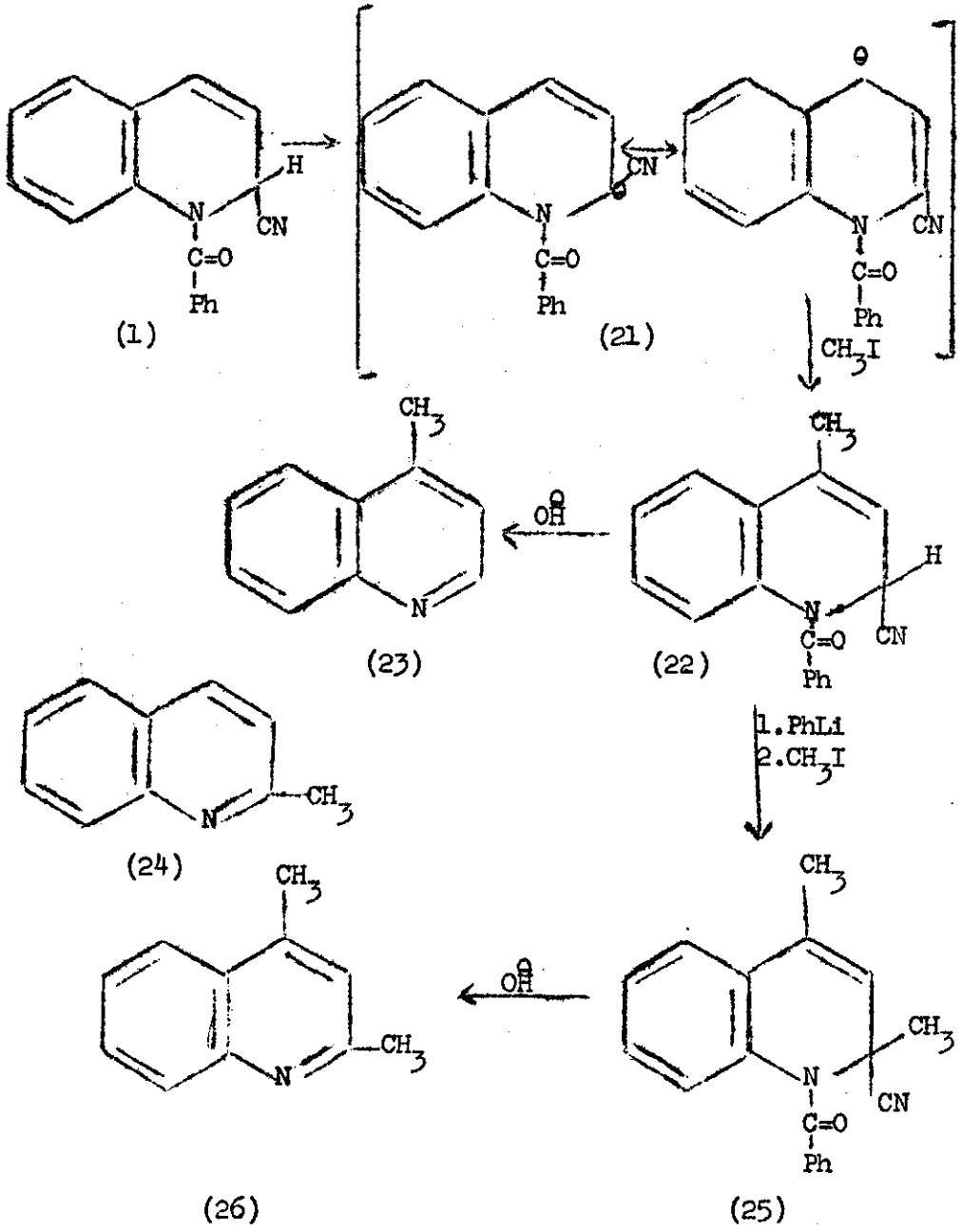


(15) (16)

A few years later McEwen and his co-workers[21,22] treated the Reissert anion with an aldehyde and obtained the carbinol benzoate (19), hydrolysis of which gave the corresponding carbinol (20). They showed the mechanism to involve initial nucleophilic attack by the anion of the Reissert compound (14) on the aldehyde to form (17), which then rearranges via the cyclic derivative (18) with elimination of lithium cyanide to afford (19).

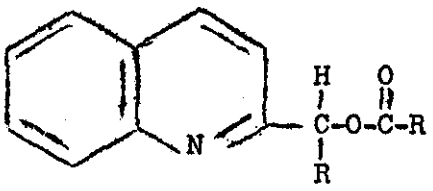


1-Benzoyl-1,2-dihydroquinaldonitrile (1,R=Ph) can similarly be converted to its conjugate base, (21), which with methyl iodide and subsequent hydrolytic cleavage gives lepidine (23) rather than quinaldine (24).[18] An analogous allylic type substitution in isoquinoline Reissert compound would not be possible without disturbing the aromaticity of the carbocyclic ring.



The intermediate alkylation product (22) is claimed to possess the 1,2-dihydro structure rather than the 1,4-dihydro structure.[23] Further reaction of (22) with phenyllithium and then methyl iodide gives (25), which leads to 2,4-dimethyl quinoline (26) on alkaline hydrolysis.[18] The overall yields of (23) and (26) are much smaller than the

yields of the various 1-alkyl isoquinolines (16).[18] However, the reaction of (21) with aldehydes takes place in the 2-position to give carbinol benzoate (27) by a mechanism similar to the one written for (19).[22]

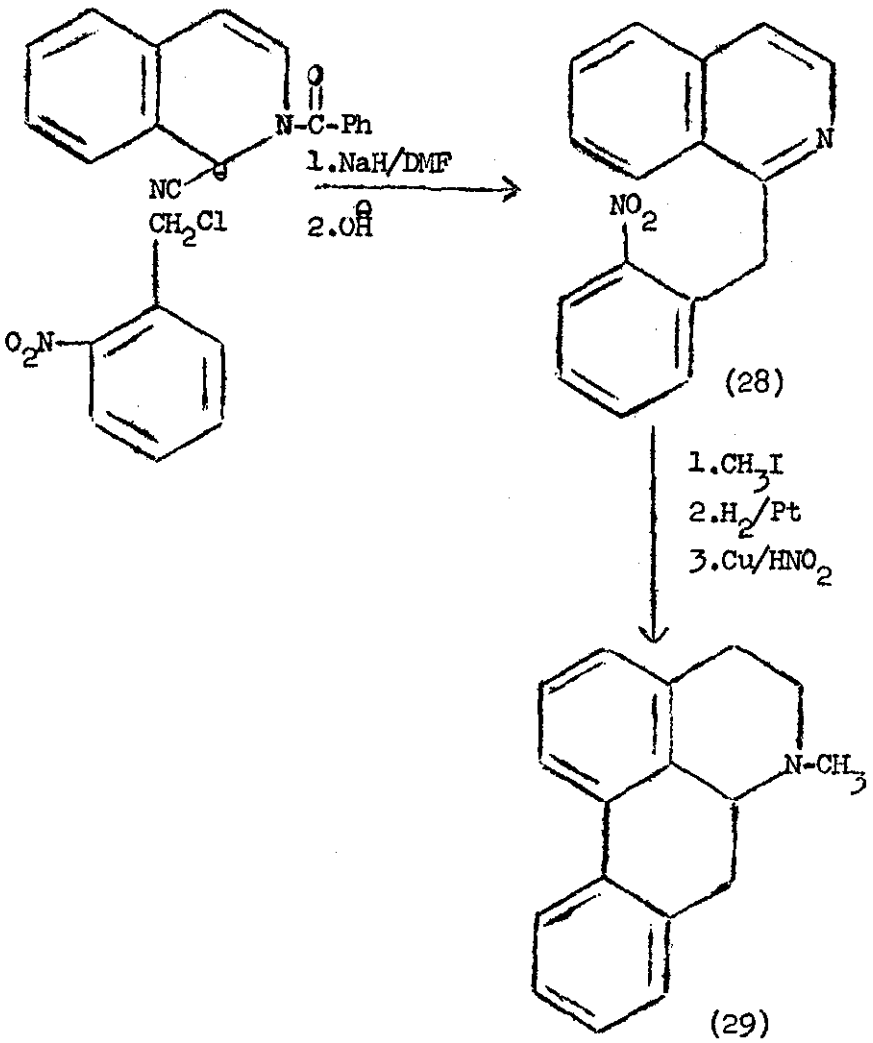


(27)

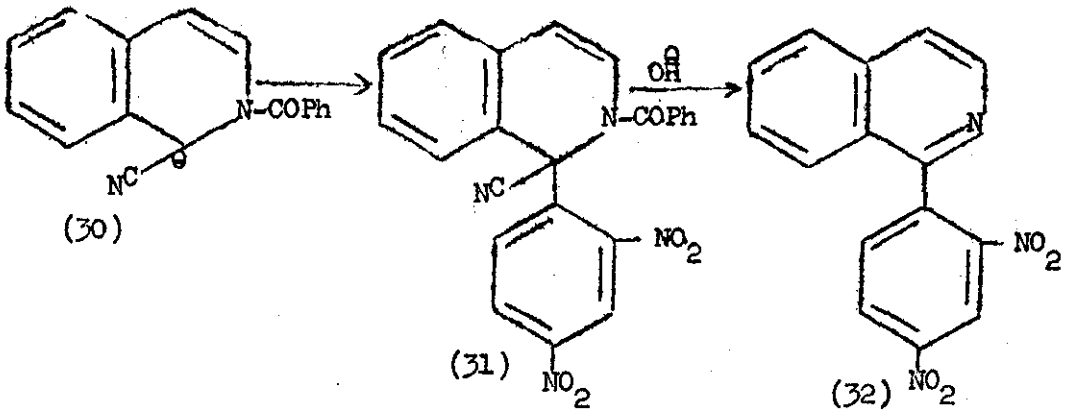
Carbanion generation thus far described involves the use of phenyllithium in ether-dioxan at low temperatures (-10 to -20°)[18,21,22] or the use of sodium or sodium hydride in refluxing xylene.[18,19,20] Recent work, however, in this laboratory[24] and America[25] has shown that the anion can be generated and caused to react at room temperature by use of sodium hydride in dimethylformamide. This reagent permits the reaction to be more easily carried out, gives consistently better yields, and is less demanding in steric requirements. Furthermore the production of the intermediate Reissert carbanion can readily be followed by observation of hydrogen gas evolution, which is not possible in the phenyllithium case.

The use of sodium hydride in dimethylformamide at room temperature[24,25] has greatly increased the utility of Reissert compounds particularly for the synthesis of 1-alkyl-2-benzoyl-1,2-dihydroisoquinaldonitriles (15)[26] and thus of 1- substituted isoquinoline derivatives.[27]

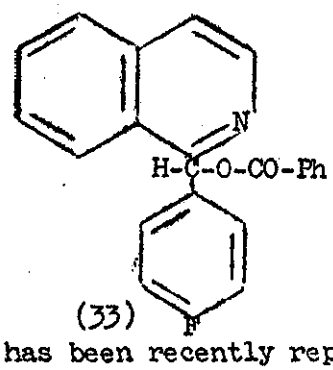
By use of this procedure, a synthesis of the aporphine system (29) has been achieved,[28] the key step of which involves the formation of 1-(o-nitrobenzyl)isoquinoline (28).

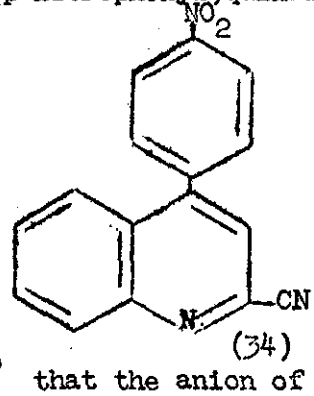


More recently the arylation of Reissert compounds has been reported.[29] Treatment of the anion (30), derived from isoquinoline Reissert compound and sodium hydride in dimethylformamide, with 2,4-dinitrofluorobenzene gave (31), and hence (32).

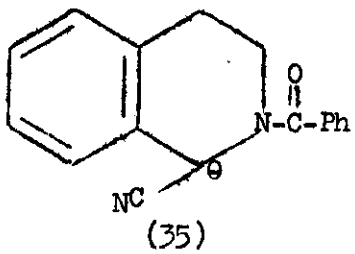


However, the reaction of (30) with p-fluorobenzaldehyde gives the ester (33).[29] Extension of this arylation to the quinoline series through reaction of (21) with p-nitrofluorobenzene gives 2-cyano-4-(p-nitrophenyl)quinoline (34).[29]



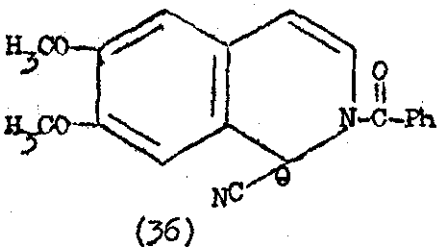


It has been recently reported[30] that the anion of dihydro Reissert compound (35) can also be alkylated readily. However, on hydrolysis loss of cyanide does not occur, the drive to aromatisation being absent.

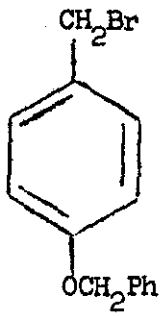


Reissert compounds have been employed in the synthesis of a number of alkaloids. By use of the anion of 6,7-dimethoxy-2-benzoyl-1,2-dihydroisoquinaldonitrile (36), papaverine (37)[21] has been synthesised by addition of 3,4-dimethoxybenzylchloride followed by hydrolysis. Similarly, armepavine (38) is

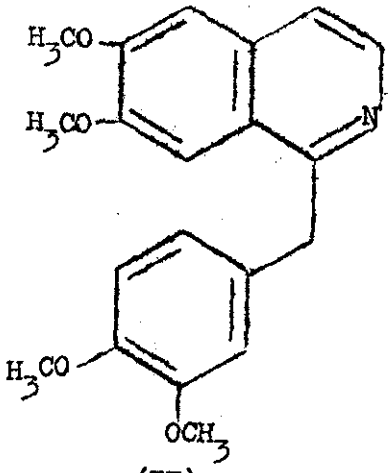
obtained by reaction of anion (36) with (39), followed by formation of the methiodide, reduction and debenzylation.[31]



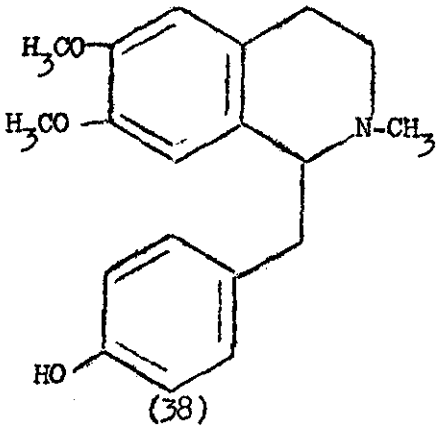
(36)



(39)

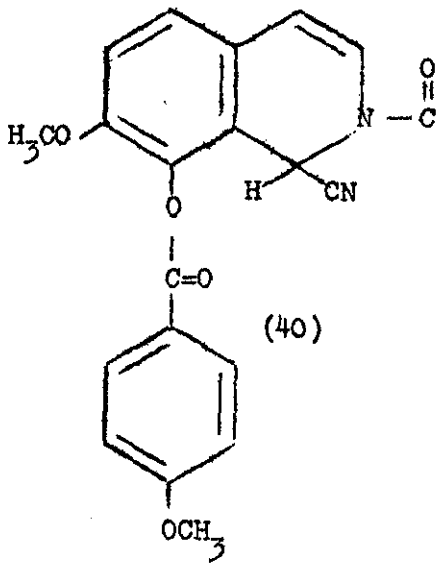


(37)

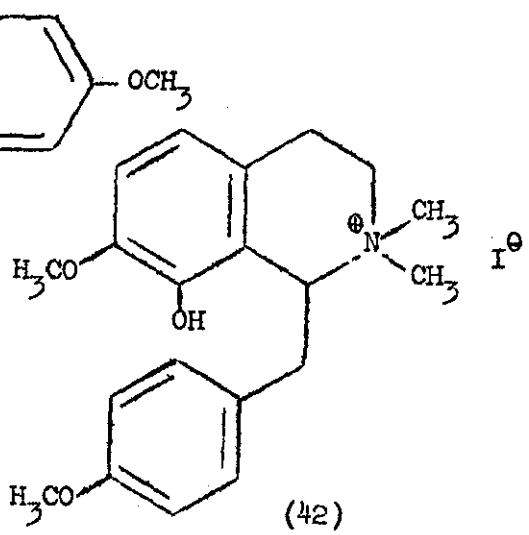


(38)

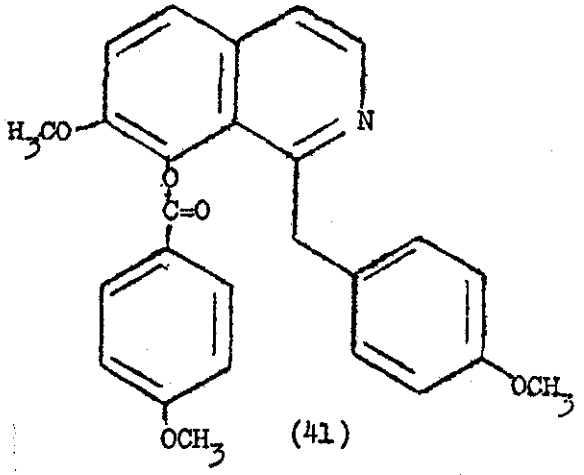
Further the alkaloid petaline (42) has been synthesised in this laboratory[32] through a sequence utilising the anion of (40) and anisyl chloride to give (41).



(40)

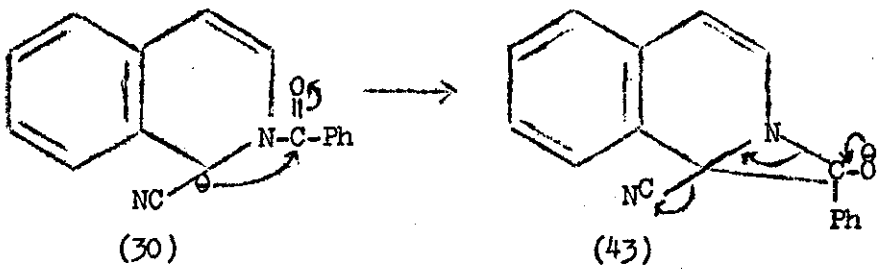


(42)

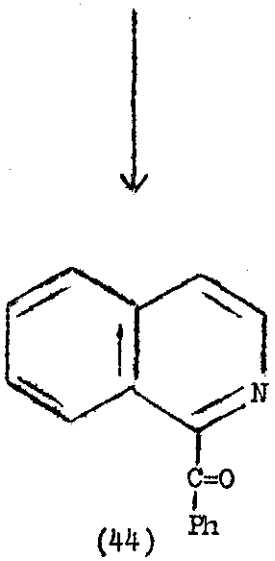


(41)

Another interesting property of the Reissert anion (21 or 30) is the tendency to undergo intramolecular rearrangement with elimination of the cyanide ion in the absence of competing electrophiles. For example (30) gives 1-benzoylisoquinoline (44), via the three-membered ring intermediate (43).[18]

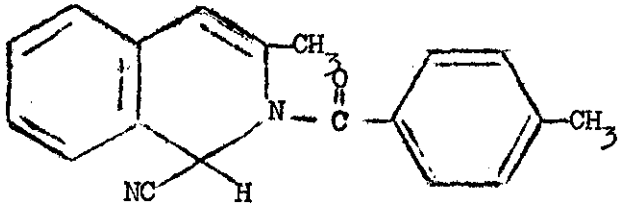


(30) (43)

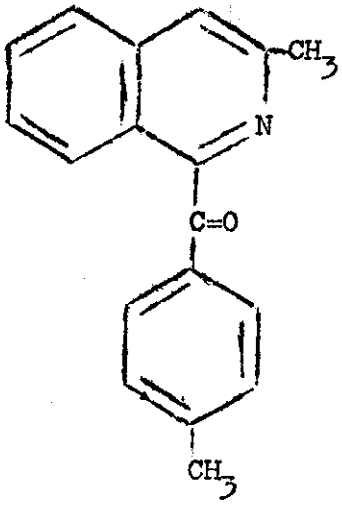


(44)

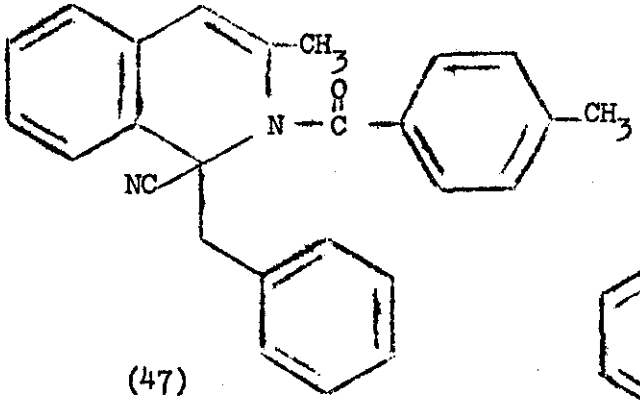
In the presence of electrophiles the 1,2-rearrangement is usually suppressed at lower temperatures (-20°) but a competitive reaction can result at 0° or above. For example if the anion of 3-methylisoquinoline Reissert compound (45) is generated with sodium hydride in dimethylformamide at 0° and reacted with benzyl chloride, the product is 1-p-toluoyl-3-methyl isoquinoline (46) and not the addition product (47).[32,33]



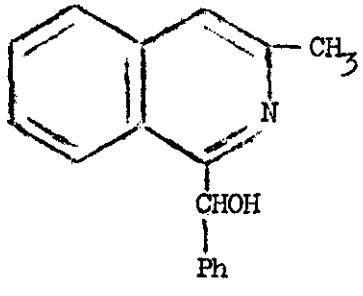
(45)



(46)



(47)



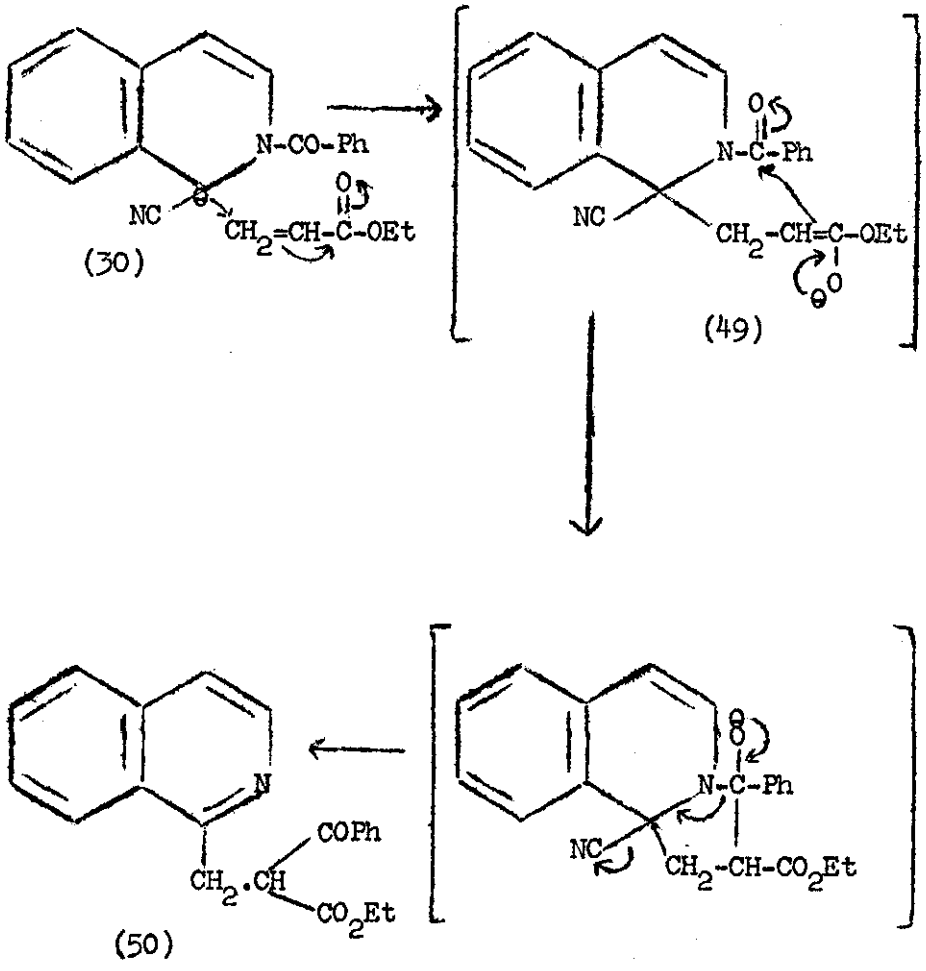
(48)

However, if benzaldehyde is the added electrophile, then addition becomes competitive with rearrangement. The rearrangement product (46) and addition product (48) are isolated in the approximate ratios of 2 to 1 respectively.[32,33]

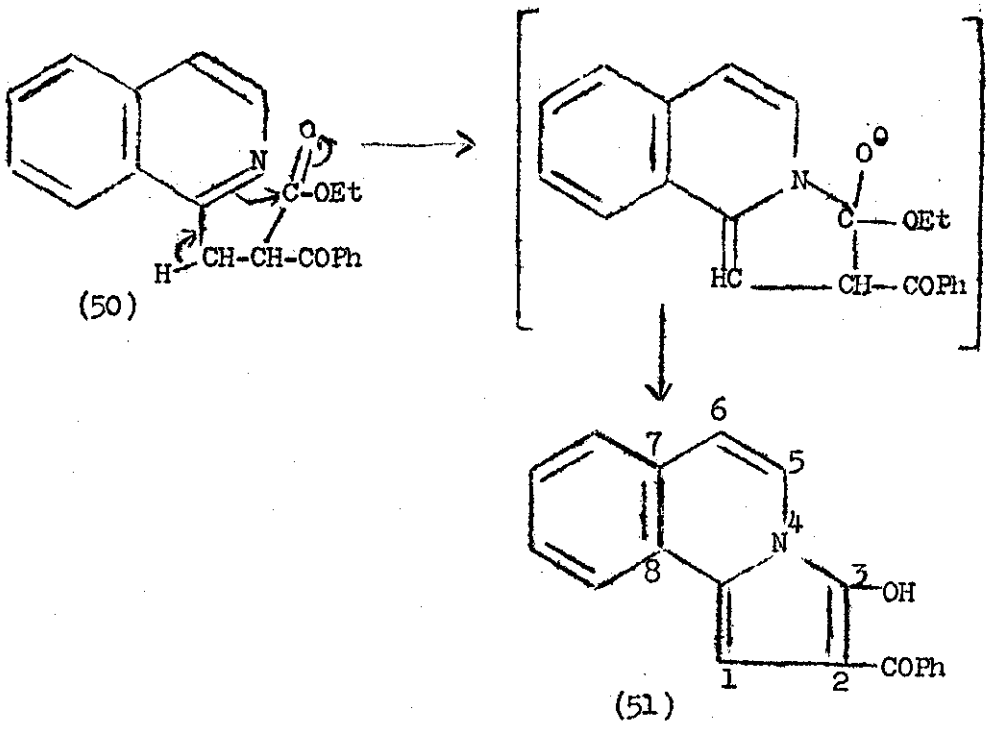
Competition of a different kind can arise if a bifunctional electrophile is added, for example when an

α,β-unsaturated carbonyl compound is used. Two sites are available for carbanion attack, either at the carbonyl group, or allylically, in Michael fashion, at the C=C double bond.

Condensation of (30) with ethyl acrylate results in Michael addition to give (49) as intermediate. The anion (49) then attacks the amide carbonyl intramolecularly to yield (50) with expulsion of cyanide ion.[34]

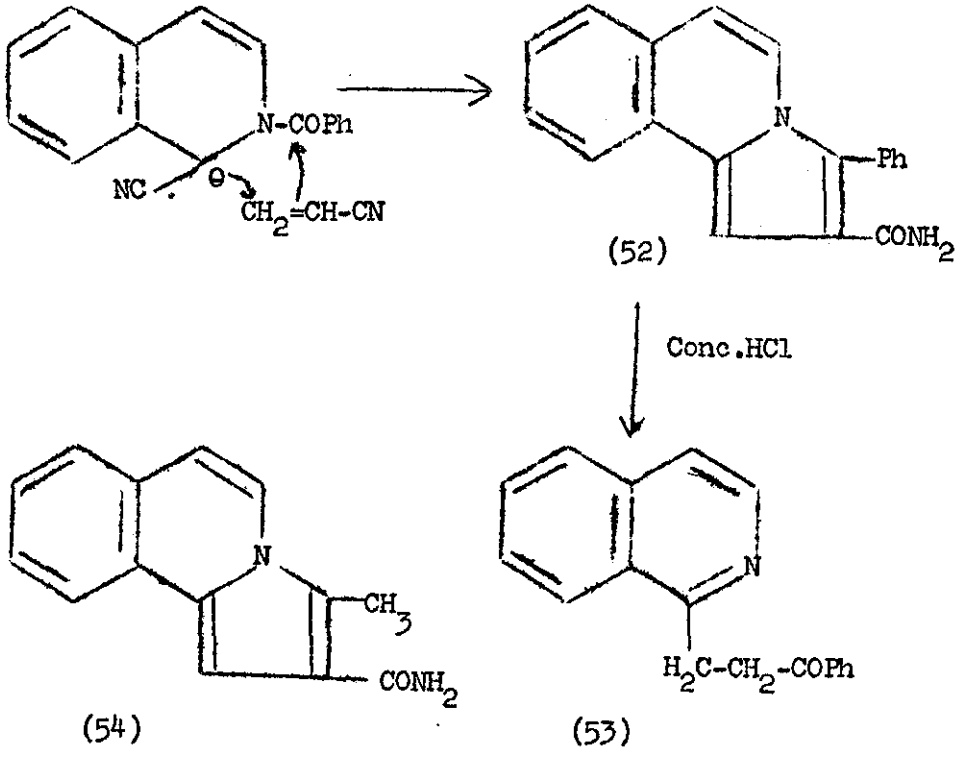


Sublimation of the ester (50) causes an internal cyclisation resulting in 2-benzoyl-3-hydroxy-7,8-benzoindolizine (51) with loss of ethanol.[34]



(50) (51)

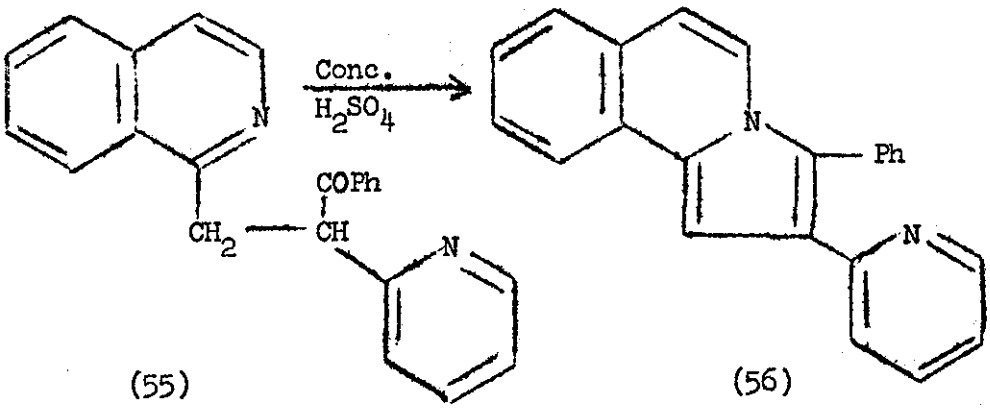
A benzoindolizine (benzopyrrocoline) structure (52) results directly if acrylonitrile replaces the ethyl acrylate in the condensation.[34]



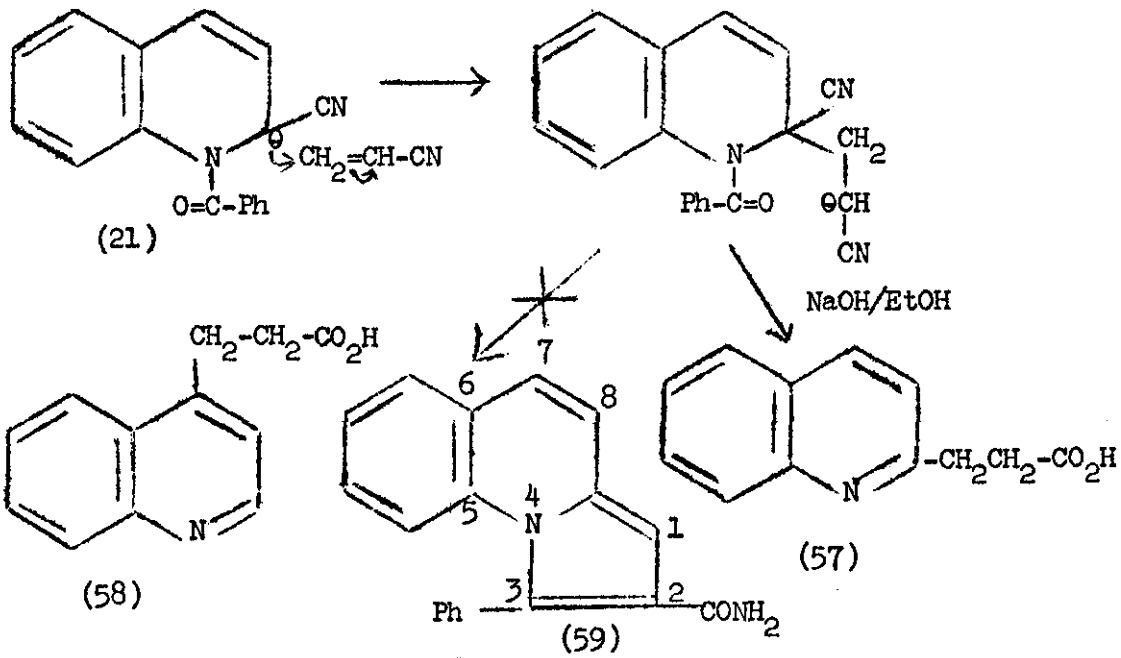
(54) (52) (53)

Action of concentrated hydrochloric acid on (52) causes opening of the five-membered ring to produce phenyl-β-(1-isoquinolyl)ethyl ketone (53).

Analogous reactions occur between acrylonitrile and N-acetyl-1,2-dihydroisoquinaldonitrile (giving 54), and between (30) and 2-vinylpyridine giving (55), which can be cyclised dehydratively to (56).[34]

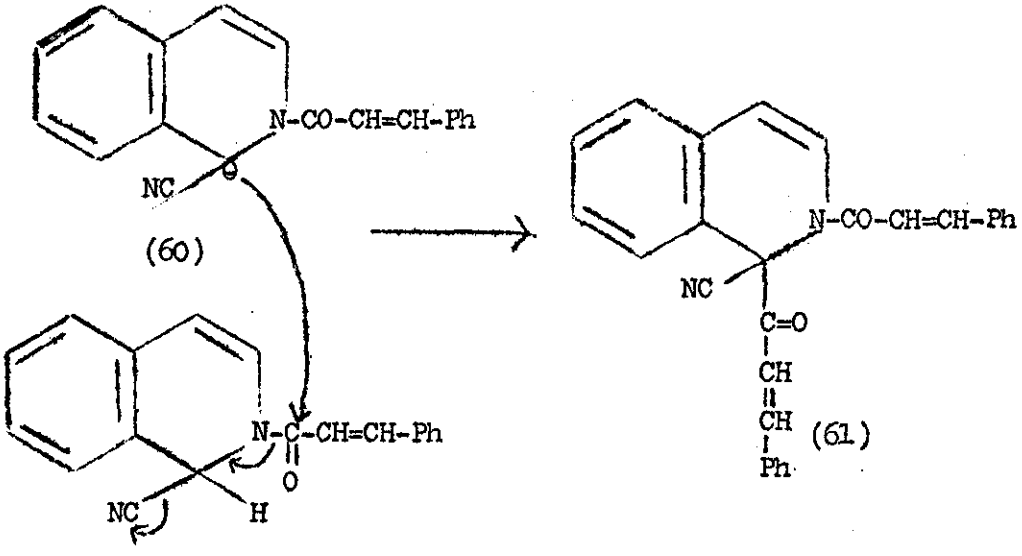


Reaction of the quinoline Reissert anion (21) with acrylonitrile is reported[34] to give a β-(quinolyl)-propionic acid (57). Whether the condensation afforded a 2-quinolyl or 4-quinolyl derivative (58) was not established.



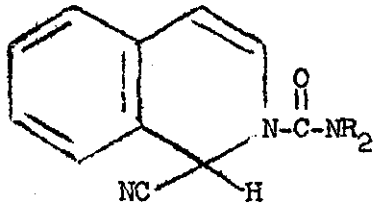
It would, however, seem possible to us that the product may be the 4-substituted quinoline (58) in view of the apparent absence of any 5,6-benzoindolizine (59).

Another interesting competitive reaction is the behaviour of the anion of N-cinnamoyl-1,2-dihydroisoquinaldonitrile (60).[18] The anion (60) attacks intermolecularly and in a non-Michael fashion to give the 1-substituted Reissert structure (61).[18]

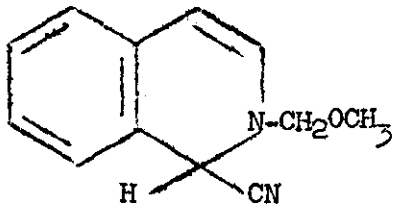


We here report examinations of some further competitive rearrangement reactions.

Reissert compound chemistry has, in recent years been extended to include a study of groups on the nitrogen atom other than simple acyl functions. For example reaction of isoquinoline, potassium cyanide and an N,N-disubstituted carbamoyl chloride gave (62,R=Ph or Et).[35] In contrast to the behaviour of the classical Reissert compound (2) the derivatives (62) were shown to be inert to both acid and base under the same conditions.

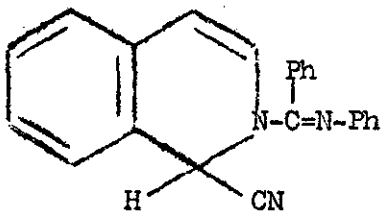


(62,R=Ph,Et)



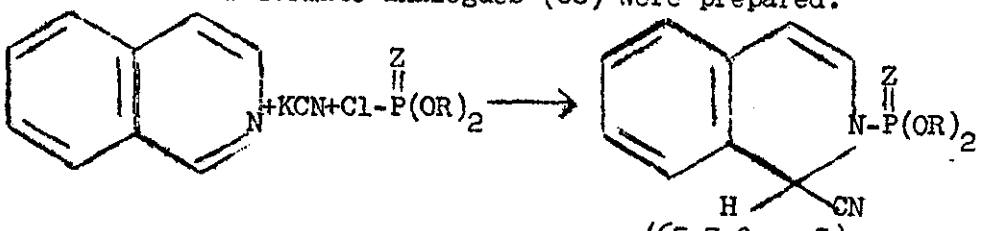
(63)

The N-alkyl analogue (63) is obtained by replacing the acyl chloride with chloromethyl methyl ether in the Reissert reaction.[36] Furthermore, derivative (64) resulted from use of hydrogen cyanide (rather than potassium cyanide) and N-phenylbenzimidyl chloride.[37]

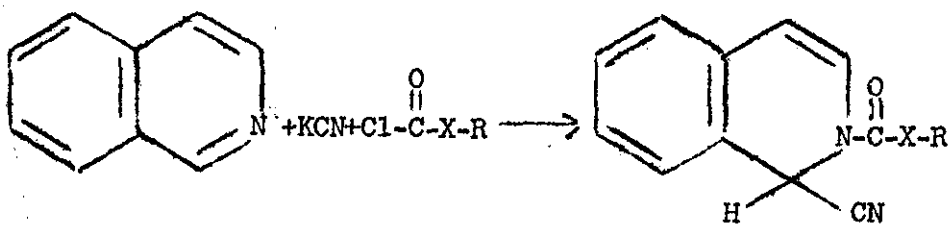


(64)

The phosphor us-containing Reissert compound analogues (65) were obtained by use of chlorophosphates or chlorothiophosphates.[38] Similarly, the chloroformate and chlorothioformate analogues (66) were prepared.[39]

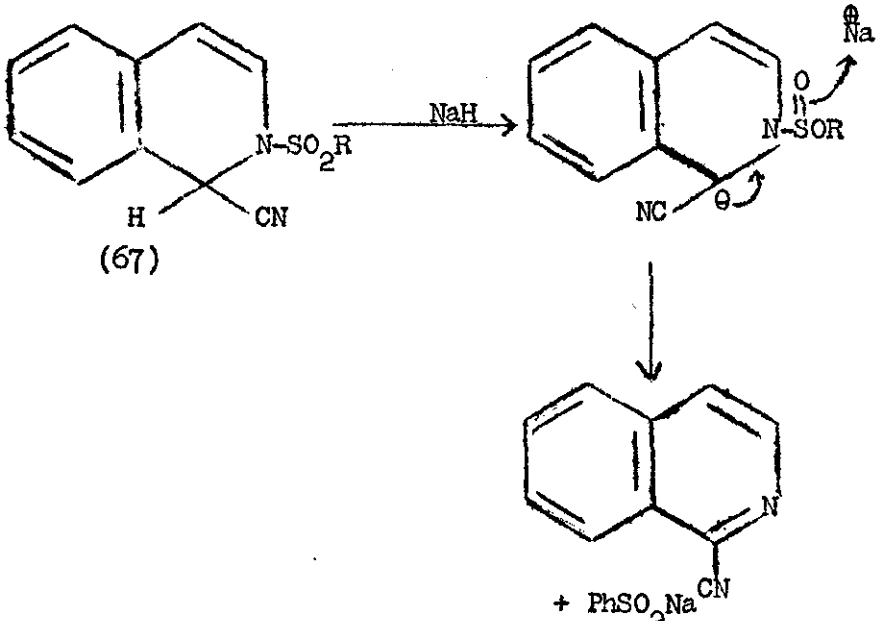


(65,Z=O or S)



(66,X=O or S)

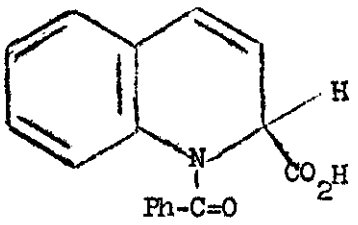
Compounds (65) and (66) undergo the alkylation reaction in the presence of sodium hydride and alkyl halide but in the presence of sodium hydride alone, they give isoquinaldonitrile and not the 1,2-rearrangement product. Similarly the aryl sulphonyl or alkyl sulphonyl analogues (67) give isoquinaldonitrile on treatment with a base such as sodium hydride, phenyllithium or 5% sodium hydroxide, even if in the presence of an alkyl halide or benzaldehyde, the alkylation or condensation not taking place, sodium benzenesulphinate being liberated.[40]



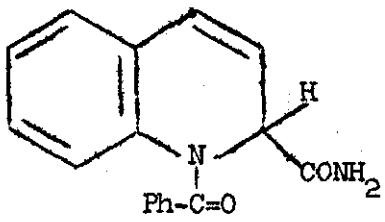
The reaction of isoquinoline with potassium cyanide and sulphuryl chloride has been investigated in this laboratory and has been shown[41] to give, depending upon the reaction conditions, 4-chloro-1-cyano-,1,3-dicyano-,1-amino carbonyl-3-cyano-,3-cyano- and 1-cyano-isoquinoline. These reactions are considered to proceed via intermediacy of a sulphonyl derivative of type (67) where R=Cl or CN. The route

provides for the direct introduction of chloro- and cyano-substituents into the hetero ring of isoquinoline.[41]

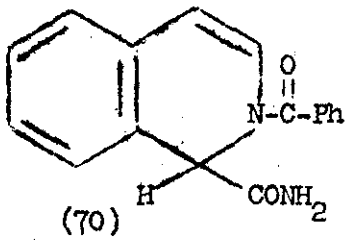
Studies have been furthered to obtain Reissert analogues with groups other than cyano. These include (68),[42] (69),[15] (70),[43] and (71).[44]



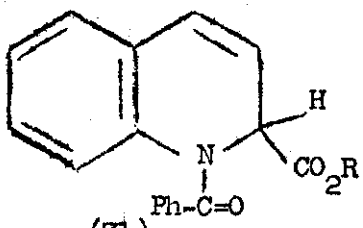
(68)



(69)



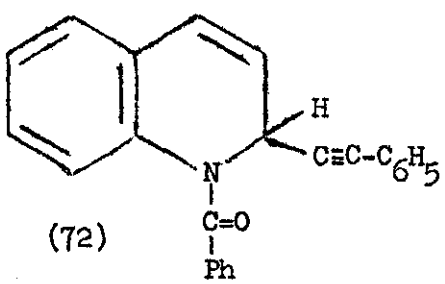
(70)



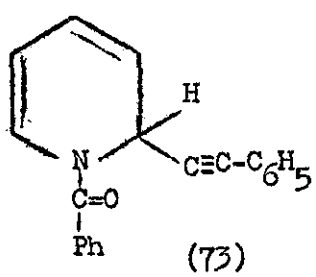
(71)

The amides (69) and (70) were prepared by action of hydrogen peroxide on the appropriate Reissert compounds.[15,43] The acid (68) was obtained from (69) by selective hydrolysis on an ion exchange resin[42] and the esters (71) were prepared from (68).[44]

The structures (72) and (73), where the cyano group is replaced by the phenylacetylide function result from benzoyl chloride, silver phenyl acetylide and the appropriate heterocycle.[45]



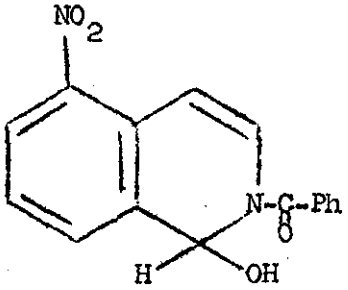
(72)



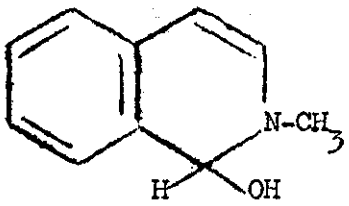
(73)

Compound (73) is of interest since a stable Reissert compound in the pyridine series has yet to be reported.

In 1968, J.R.Kershaw, in this laboratory, in an attempt to prepare the Reissert compound of 5-nitro-isoquinoline, obtained a novel Reissert analogue containing the cyano function replaced by hydroxyl, i.e. the N-acyl pseudo-base structure (74).[33,46] Structurally (74) is analogous to the well known N-alkyl pseudo-bases (75).



(74)



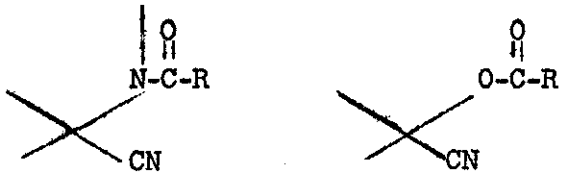
(75)

We have taken up this study and examined the formation and properties of this new type of system (74).

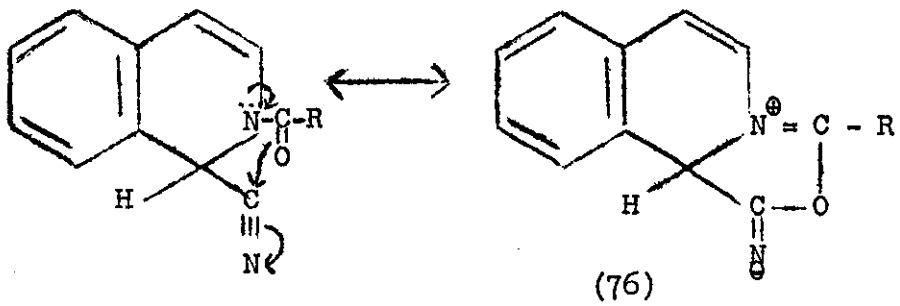
A number of reports have appeared on the spectroscopic properties of Reissert compounds. Their ultraviolet absorption spectra[47,48] have been compared with a number of other systems[47] and shown to support the assigned structure.[5]

The most striking feature of the infrared spectra of Reissert compounds is the weakness of the nitrile (in the region 2200-2300 $cm.^{-1}$). In ketone cyanohydrins, the nitrile band is also weak and disappears completely when the cyanohydrin is acylated.[5] Since Reissert compounds are nitrogen analogues of these acyl derivatives, as shown

in the partial structures given below, it might be expected that the cyanide peak is very weak for the same reason.



McEwen and Cobb[5] have suggested that the possible reason for the weakness of the nitrile absorption could be a contribution of the type (76).



(76)

Very recently, an account of the mass spectra of Reissert compounds has appeared.[49] It has been shown that a common feature in their fragmentation is the initial loss of the N-substituent and of either of the substituents attached to the adjacent sp^3 carbon atom.

We have examined in detail the proton magnetic resonance spectra of some isoquinoline and quinoline Reissert compounds, and deduced some information regarding the stereochemistry of these systems.

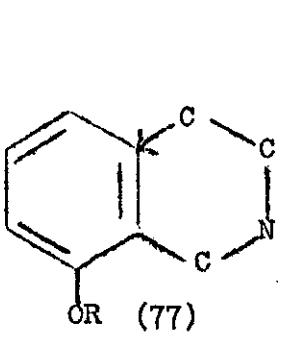
DISCUSSION

1. Rearrangement Studies of Reissert Compounds

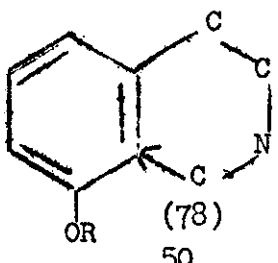
(a) Attempted improvements of the Pomeranz-Fritsch isoquinoline synthesis

As prelude to the preparation of substituted isoquinolines required for rearrangement studies we first briefly investigated the synthesis of the isoquinoline system itself, with a view to providing some improvement on existing methods, in particular on the Pomeranz-Fritsch synthesis.

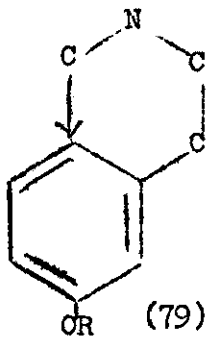
We required, among others, 8-substituted isoquinolines for our subsequent studies and the Pomeranz-Fritsch[50] route (see 77) is the only method which can provide, unequivocally, 8-substituted derivatives since the Bischler-Napieralski[51] route and Pictet-Spengler[52] route can go via (78) or (79) (the 6-substituted product normally predominating).



(77)

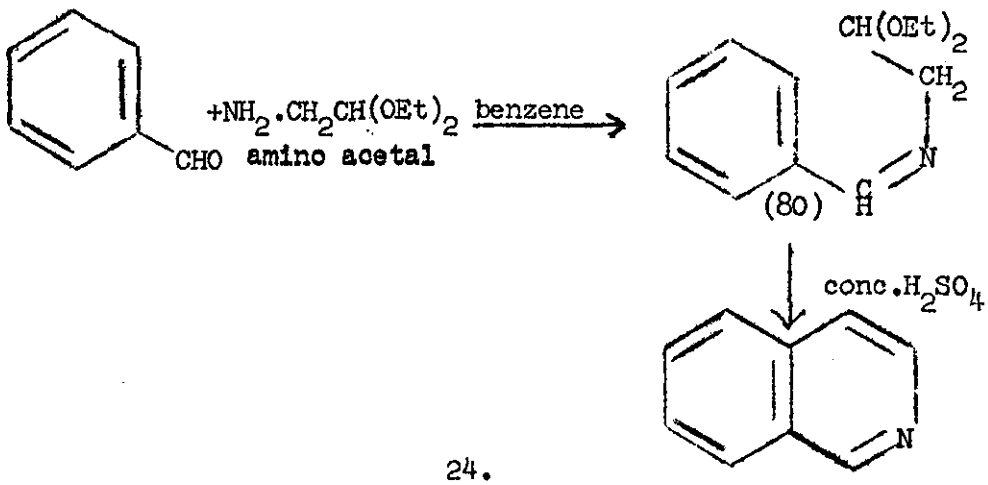


(78)



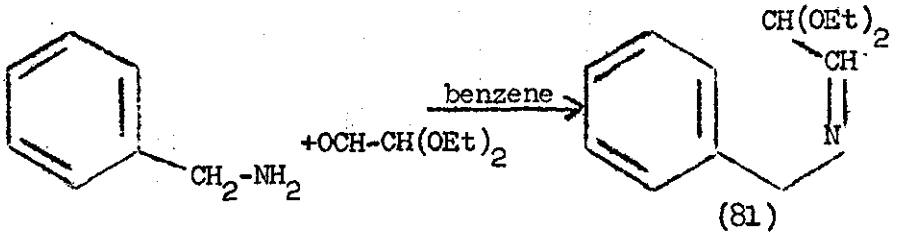
(79)

The classical Pomeranz-Fritsch[50] synthesis involves the steps as shown:

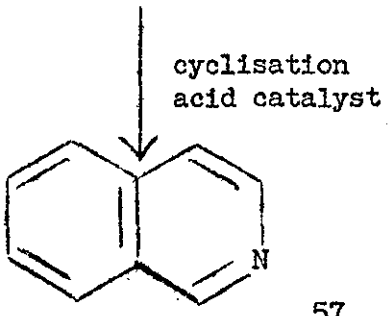


In the past, yields for the cyclisation step have tended to be disappointingly low,[50] i.e. often 20% or less. More recently other cyclisation reagents have been used, e.g. polyphosphoric acid,[53] orthophosphoric acid,[54] polyphosphoric acid/phosphorous oxychloride,[21] and trifluoroacetic anhydride/boron trifluoride.[55]

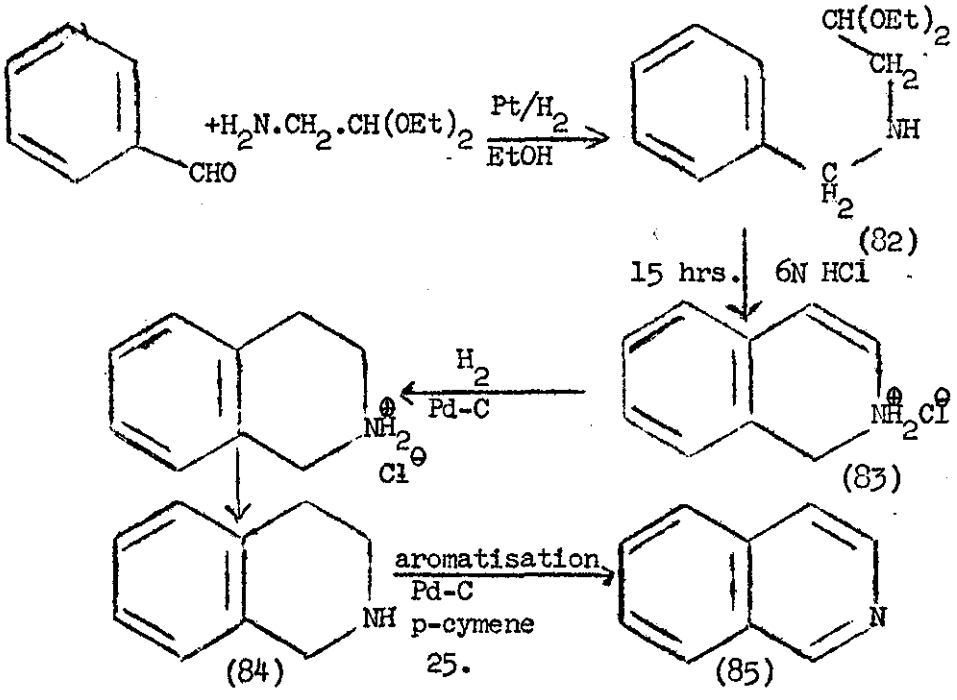
The first stage has also been varied, by Schlittler and Müller,[56] who used glyoxal hemiacetal to obtain Schiff base (81) isomeric (and possibly tautomeric) with (80).



(81)



A recent variation has been reported by Bobbitt et al.[57] according to the following scheme via the reduced Schiff base(82).

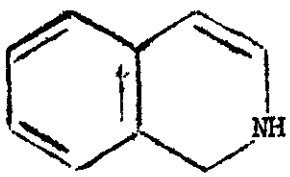


The method is reported to give good yields (80%) of the tetrahydro-base (84) but the aromatisation step is less satisfactory.

We have made two attempts to improve the Pomeranz-Fritsch reaction (i) by direct dehydrogenation of the dihydro free base of (83) in Bobbitt's route, using chloranil and (ii) by attempting to cyclise the Schiff base (80) and some analogous compounds, using refluxing diphenyl ether, by analogy with the Conrad-Limpach[58,59] quinoline synthesis.

(i) Chloranil dehydrogenation route

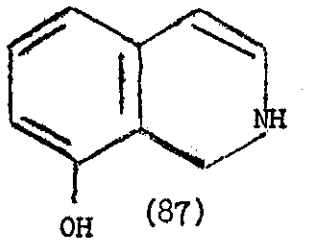
Bobbitt et al.[57] suggested the 1,2-dihydroisoquinoline system (86), (from 83) was not sufficiently stable to isolate and aromatise to (85), but Braude, Hannah and Linstead[60] have prepared simple N-alkyl-1,2-dihydroisoquinolines in 93% yield by the reduction of the corresponding isoquinoline alkiodides with lithium aluminium hydride.



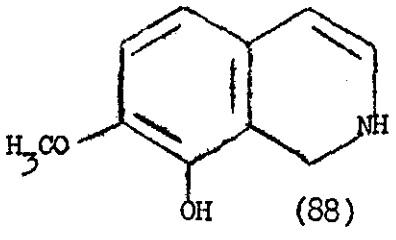
(86)

Further, Jackman and Packham[61] have reported the preparation of the parent base, 1,2-dihydroisoquinoline (from isoquinoline) and its successful dehydrogenation with chloranil in 55% yield.[61] In quoting some unpublished work, Jackman also claims[62] that the corresponding dihydroderivatives of pyridine, quinoline, acridine and phenanthridine can all be dehydrogenated by quinones, and in most cases the reactions are rapid. We,

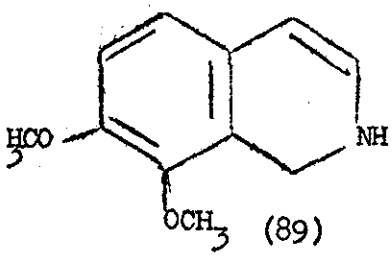
therefore, used the appropriate aldehydes to give rise to dihydroisoquinolines (87), (88), (89) and (90) when applied to Bobbitt's scheme basifying and extracting the product after acid treatment of the reduced Schiff base corresponding to (82).



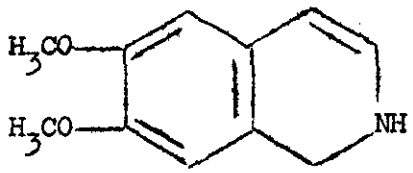
(87)



(88)



(89)

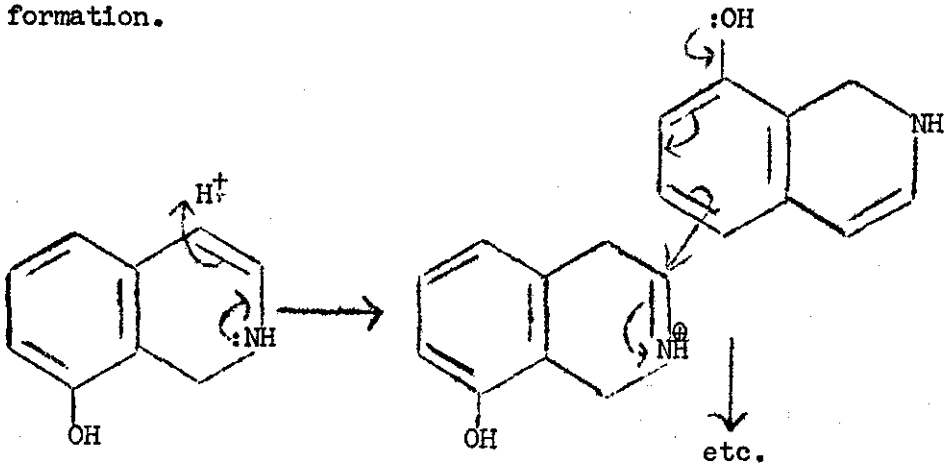


(90)

However, immediate chloranil treatment of the free bases either in dioxan at room temperature (with 88, 89 and 90), or in refluxing xylene (with 87) gave only intractable material which could not be purified.

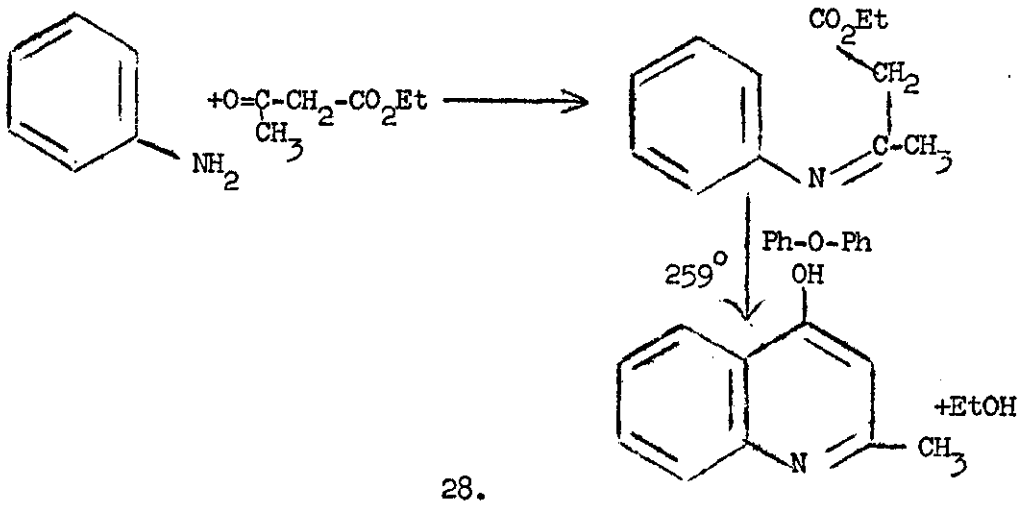
The failure of these reactions was surprising since it was anticipated that the electron donating substituents present would increase the sensitivity of the compounds towards the chloranil, as compared with 1,2-dihydroisoquinoline itself, which is known to undergo dehydrogenation by this route.[61] The results, therefore, suggest that the dihydroisoquinolines themselves, as formed in this procedure, were not adequately pure. Thus, further studies with higher potential quinones, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, were not pursued. It is possible that some polymerisation of the

dihydroisoquinolines[63] had occurred during the long acid treatment required in Bobbitt's procedure for their formation.

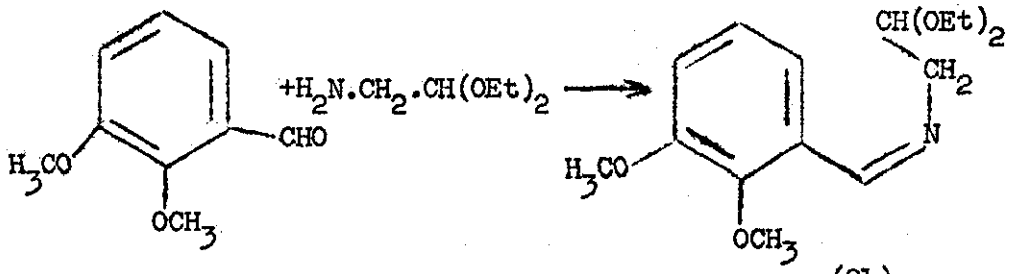


(ii) Use of diphenyl ether as cyclising agent

As already discussed on p.25 the Pomeranz-Fritsch method of preparation of isoquinolines employs an acid catalyst for the cyclisation step. Though the combination of aromatic aldehyde and aminoacetal affords the intermediate Schiff base usually in almost quantitative yield, the yield of the isoquinoline after cyclisation has been generally poor.[50] It was thus felt of interest to examine the cyclisation of the intermediate Schiff base using a high boiling inert solvent, by analogy with the Conrad-Limpach[58,59] synthesis of quinolines shown (which can give yields of over 80%):



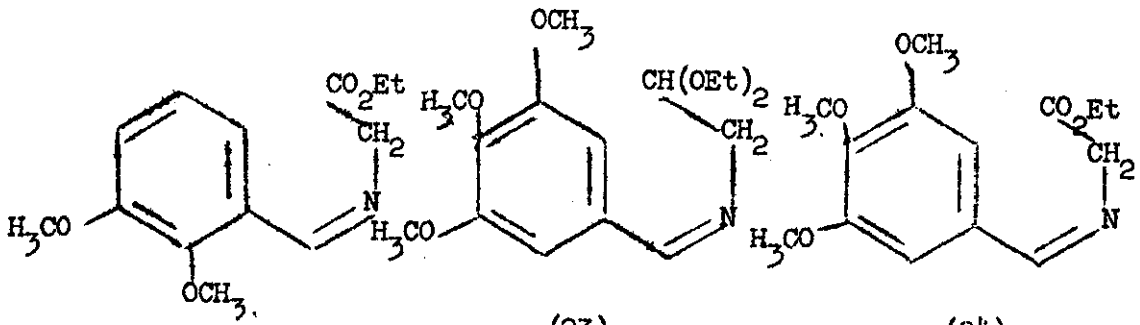
We thus attempted to apply the thermal cyclisation method to isoquinolines using diphenyl ether.



(91)

The Schiff base (91) was added rapidly to refluxing diphenyl ether (259°) and the heating continued for a further period of twenty minutes until no more alcohol distilled over. Work-up of the cooled solution yielded some unchanged Schiff base and tars.

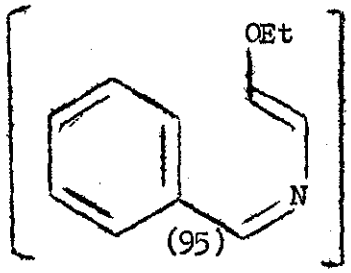
We further attempted the cyclisation on the Schiff bases (92), (93) and (94) prepared from the appropriate aromatic aldehyde and the amine.



(92) (93) (94)

Use of esters (92) and (94) allowed even closer analogy with the Conrad-Limpach method (than using an acetal). In (93) and (94), the presence of three methoxy groups in the benzene nucleus was designed to provide maximum activation of the benzenoid ring, but in every case only starting materials and tars were isolated.

It is surprising that corresponding compounds for the synthesis of quinolines give satisfactory yields under the same conditions. The presence of tars could be due to loss of one mole of ethanol from the Schiff base to give a diene of type (95) which could then polymerise.



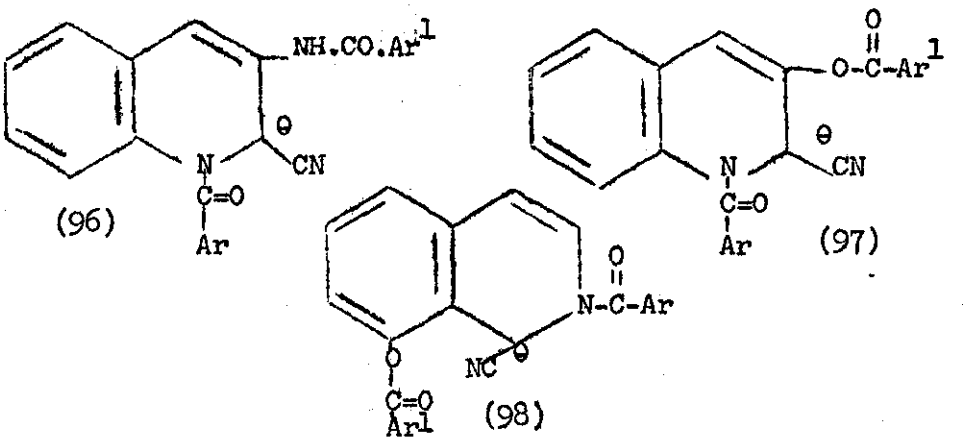
(95)

(b) Rearrangement Studies of Reissert Compounds

Our aims in studying the rearrangement reactions of the Reissert anion were two-fold. Firstly, we wished to investigate whether an alternative intramolecular acyl-rearrangement could compete successfully with the normal 1,2-acyl-rearrangement within the molecule, with a view to this providing new synthetic routes to substituted quinolines and isoquinolines of interest both intrinsically and potentially in alkaloid synthesis. Secondly, we wished to develop further the investigations involving Michael reactions carried out by previous workers,[18,34] as discussed in the Introduction (p. 15), to examine the interesting situation in which an intramolecular Michael reaction can compete with a 1,2-acyl-rearrangement, as contrasted with the intermolecular Michael reactions reported previously.[18,34]

(i) Competitive intramolecular acyl-rearrangements

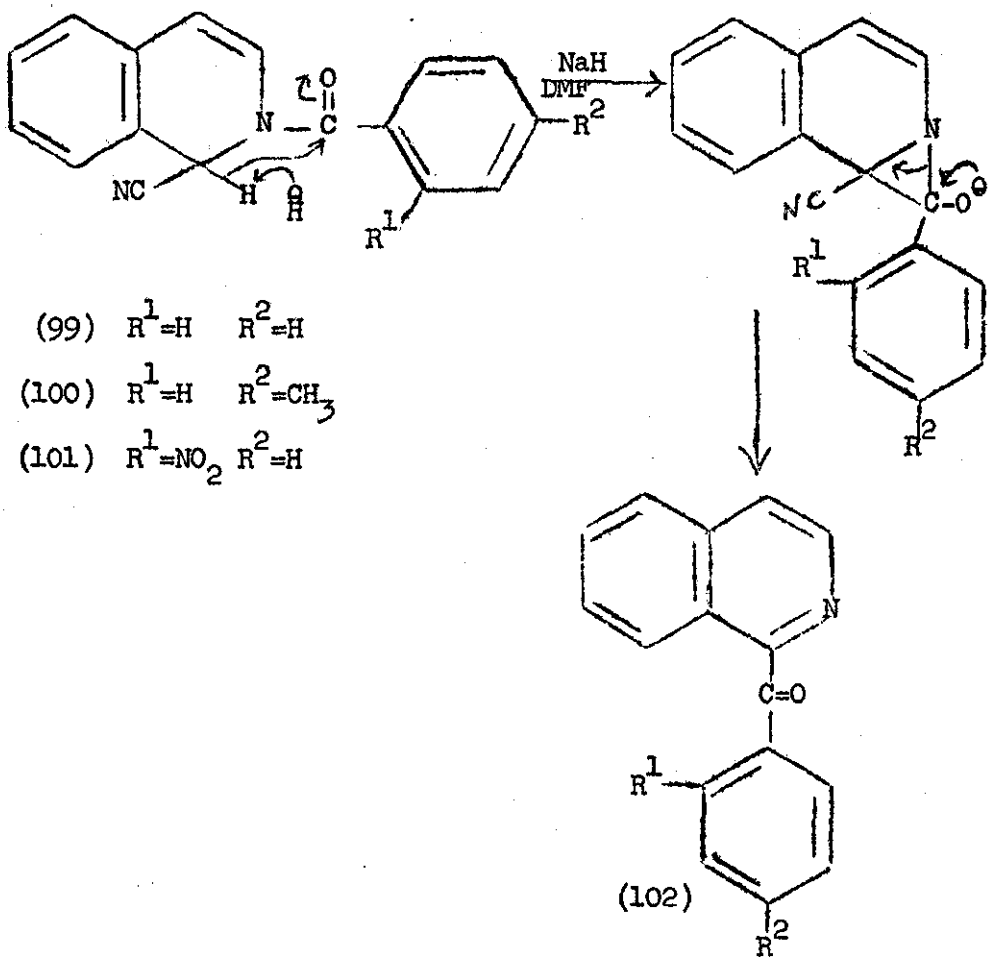
We examined three systems, (96), (97) and (98).



In the first system (96) the two acyl groups are both amidic in character, the possible rearrangements proceeding via either a three-membered or a four-membered ring intermediate. In cases (97) and (98) the amidic acyl is competing with the more electrophilic ester acyl function, which would rearrange via a four-membered (97) or five-membered (98) ring intermediate.

Study of Conditions

To confirm the best experimental conditions, rearrangements of the simple Reissert compounds (99), (100) and (101) were effected. Compounds (99), (100) and (101) were prepared by the method of Popp and Blount.[8] This involves stirring one mole of isoquinoline, two moles of acid chloride and three moles of potassium cyanide in a two phase system of methylene chloride and water. Treatment of the dimethylformamide solution of these Reissert compounds with sodium hydride caused the immediate appearance of a red colour (the carbanion) accompanied by evolution of hydrogen. After treatment with ice the corresponding aroylisoquinolines (102) were isolated and characterised. The lowest yield was from the p-toluoyl case (100), 50%, and highest for the o-nitro case (101), 67% with the unsubstituted compound (99) giving 56% ketone.



(99) R^1=H R^2=H

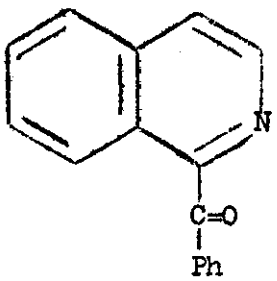
(100) R^1=H R^2=CH_3

(101) R^1=NO_2 R^2=H

This trend was supported by work published concurrently by Popp and Wefer[26] on the 1,2-acyl-rearrangement of a large number of quinoline and isoquinoline Reissert compounds. They obtained increased yields of the quinolyl and isoquinolyl ketones when the amidic phenyl ring carried electron withdrawing groups (such as Cl, Br and F), whereas the presence of electron releasing substituents (such as OCH_3) resulted in a decreased yield of rearranged products. These observations are easily derivable from the suggested intramolecular mechanism, the presence of electron withdrawing groups on the amidic phenyl ring making the carbon of the C=O group more positive in character and thus more susceptible to attack by the adjacent carbanion. With the electron releasing groups the reverse is true.

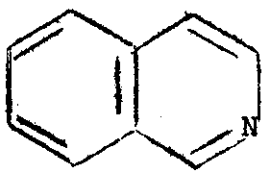
The mechanism has unequivocally been shown to be intramolecular rather than intermolecular by using mixed Reissert compounds starting materials and ^{14}C labelling.[64]

In the work-up procedure we have observed that the aroylisoquinolines (102) are not adequately extracted from organic solvents using dilute (2N-4N) hydrochloric acid. Stronger acid (i.e. $\geqslant$ 50% hydrochloric acid) is required. We confirmed this surprising observation by determining the pKa of 1-benzoylisoquinoline (103) and related substances. Determinations were carried out by the spectroscopic method.[65] The results confirm the weak basicity of (103)



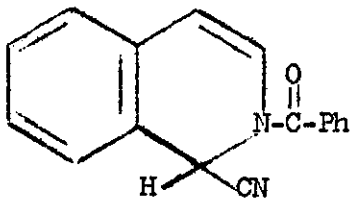
pK_a=2.22

(103)



pK_a=5.4

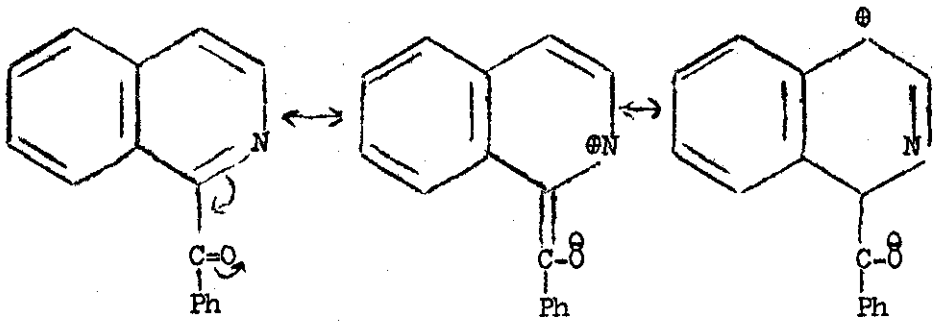
(104)



pK_a= ca. -6.3

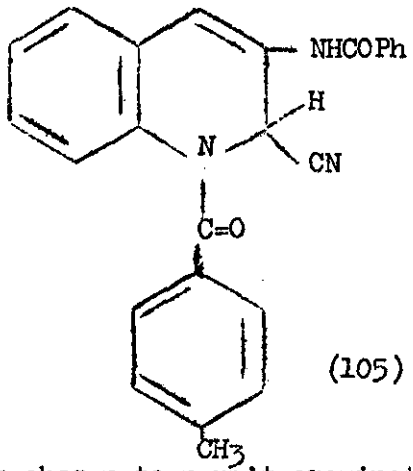
(99)

Thus it would seem that the nitrogen lone pair in (103) is in some way involved in conjugation. This could be due to resonance structures such as (103A) or (103B) which would make the nitrogen lone pair less available due to the positive charge on the ring. It is thought that such an effect has not been reported before. Isoquinoline (104) itself has a pKa of 5.4.[65] The Reissert compound (99) behaves as a typical amide with protonation probably occurring at the carbonyl oxygen (cf. N,N-dimethylbenzamide with pKa-1.62 and acetophenone, pKa-6.15).[66]



(103) (103A) (103B)

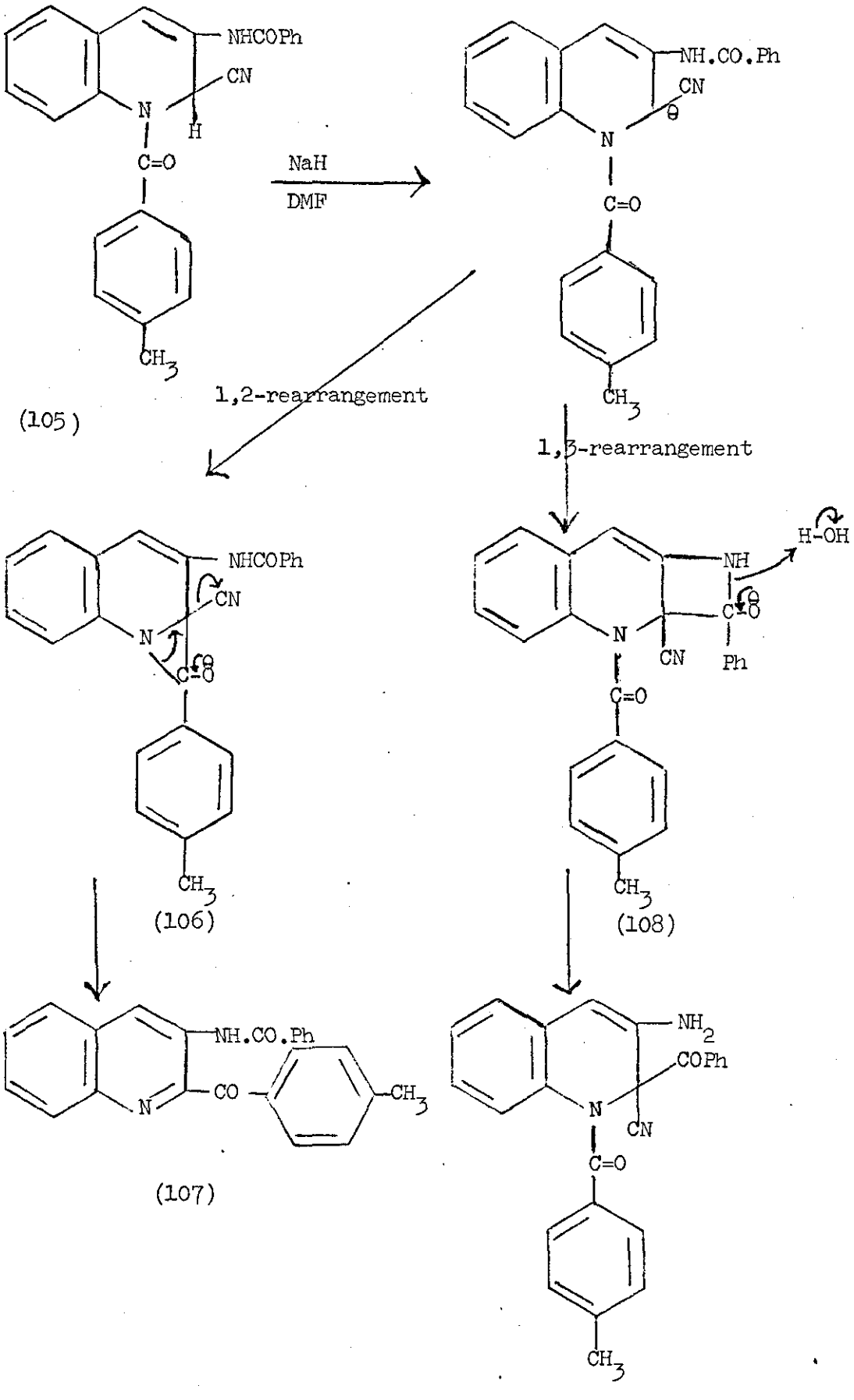
Rearrangement studies on 3-benzoylamino-1-p-toluoyl-1,2-dihydroquinaldonitrile (105)



(105)

Compound (105) was chosen to permit examination of whether a second aroyl group could compete successfully (to give 109) with the normal 1,2-rearrangement (to give 107). Attack at the C-3 amide carbonyl will give a less sterically strained intermediate (108) than the alternative course via (106). Offsetting this, however, we have the favourable drive to aromatisation of the 1,2-rearrangement, not present in the 1,3 alternative (see Scheme I, p. 35).

Scheme I Possible routes for rearrangement of carbanion of (105)



To assist following the reaction by n.m.r., we "tagged" one of the rearranging acyl groups by using the N-p-toluoyl Reissert compound (105). Such tagging does, of course, make the 1,2-rearrangement slightly less favourable, due to the inductive electron release of the p-methyl group.

The compound (105) was prepared in 76% yield by the Reissert reaction of 3-benzoylaminoquinoline with p-toluoyl chloride. Generation of the carbanion of (105) with sodium hydride and dimethylformamide proved difficult, the red colour appearing after two hours on heating up to 90°. The colour did not fade appreciably even after several hours. The usual work-up procedure gave negligible material soluble in dilute acid and chromatography of the neutral fraction gave two products, one yellow crystalline material, m.p. 163° in 26% yield, and a second which was shown to be the starting material (105) (50% recovery).

The n.m.r. spectrum of the yellow crystalline product showed an absorption at 0.31 τ (1H, broad singlet) which disappeared on shaking with deuterium oxide, 1.70-2.80 τ (14H, multiplet) and 7.57 τ (3H, singlet).

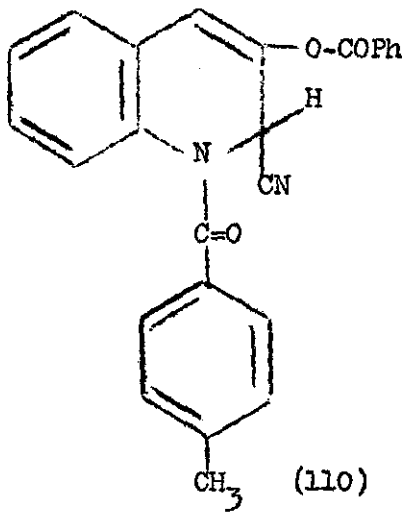
This data suggested the compound to be (107). The amide NH chemical shift is slightly lower (ca. 0.5 τ) than in the starting material (NH in (105) absorbs at 0.97 τ), presumably due to deshielding by the 2-carbonyl group in (107) and adjacent aromatic ring. The structure was further confirmed by the infrared spectrum (absorption at 1675 $cm.^{-1}$ (NHCO), 1650 $cm.^{-1}$ (-C=O at C-2, H-bonded to NH), 3320 $cm.^{-1}$ (NH)),

and by elemental analysis.

Again it is pertinent to note that this compound was not extracted with dilute acid and would appear to be a very weak base. The behaviour is analogous to that we observed with 1-benzoylisoquinoline (p. 33).

The isolation of the 1,2-rearrangement product indicates the drive to aromatisation to be the dominating factor. Nevertheless, the recovery of 50% of starting material suggests relatively poor generation of carbanion (the red colour being developed only under elevated conditions). This is likely to be due to the steric crowding faced by the hydride ion in reaching the C-2 methine proton.

Rearrangement studies on 3-benzoyloxy-1-p-toluoyl-1,2-dihydroquinaldonitrile (110).



(110)

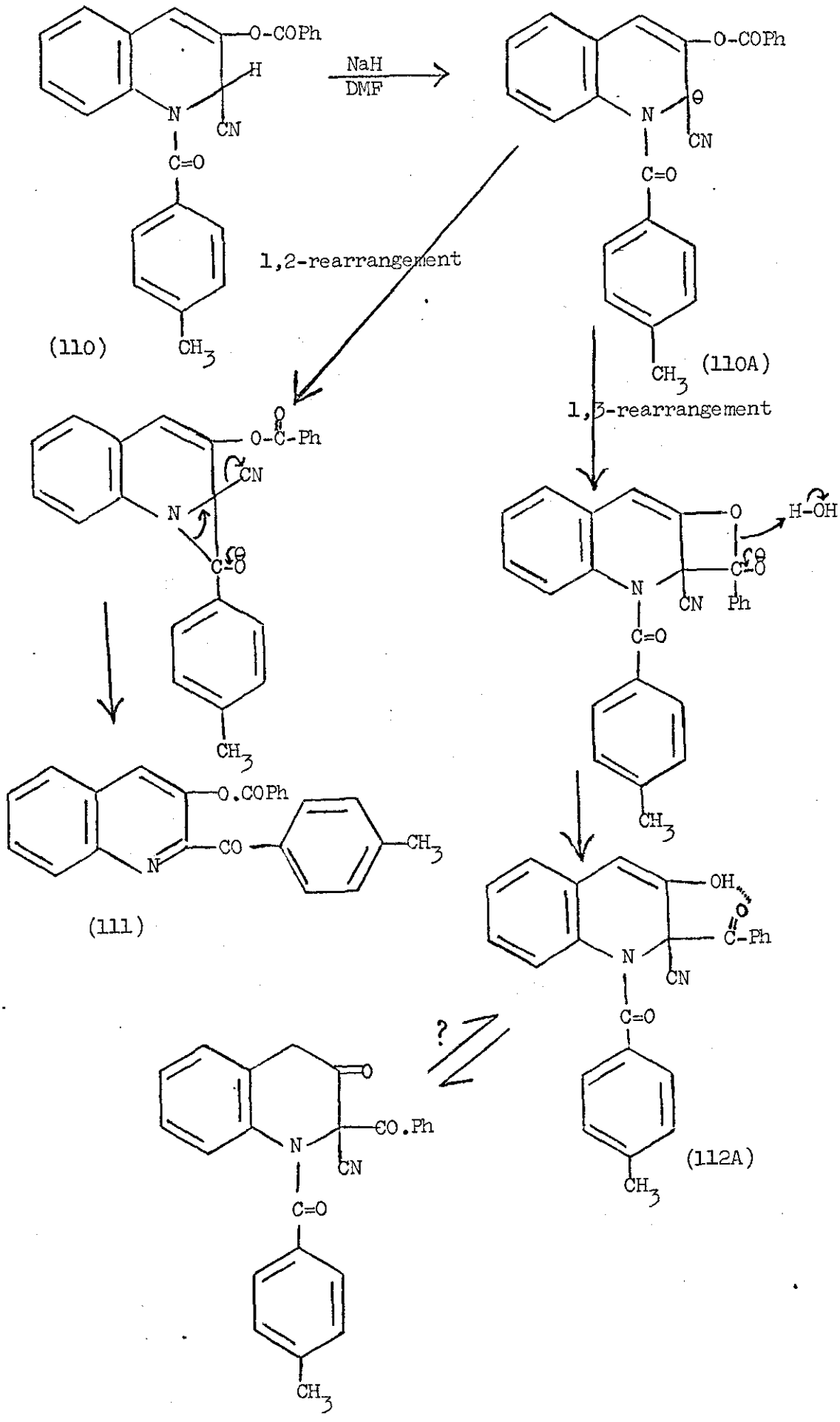
Compound (110) provides a better opportunity for competition to result on generation of the Reissert carbanion (110A) since now the more electrophilic ester is present at position 3. The result of this latter course would be to give (112A

or 112B) rather than (111) (see Scheme II, p. 39).

Compound (110) was prepared in 58% yield from 3-benzoyloxyquinoline by Reissert reaction with p-toluoyl chloride. Treatment of (110) with sodium hydride in dimethylformamide resulted in the immediate appearance of a red colour which did not fade appreciably even after stirring for several hours. The work-up procedure prior to acid or base extraction gave a mixture, the n.m.r. of which included two methyl groups at 7.64 τ and 7.67 τ respectively integrating almost in the same ratio. The multiplet at ca. 1.08 τ due to the ortho hydrogens in the C3-benzoyloxy group was also present (aromatic protons ortho to an ester group generally resonating at lower field than when ortho to an amide group).[67] However the singlet at 3.63 τ, attributable to the methine C2-H in the n.m.r. spectrum of (110) was absent, so indicating absence of starting material. The two methyl groups present are therefore likely to be due to the products (111) and (112).

Sodium hydroxide extract of this crude product yielded, on acidification, a yellow amorphous powder, m.p. 185-215°, which unfortunately could not be crystallised. The n.m.r. spectrum, however, gave support to the compound being the 1,3-rearrangement product (112) in its (hydrogen bonded) enolic form (112A). Resonances occurred at 1.70-2.90 τ, complex multiplet, 15H, (aromatic, enol OH and C4-H) and at 7.60 τ, singlet, 3H, methyl. The infrared spectrum showed $\nu_{max.}$ 3140 cm.$^{-1}$ broad band, bonded OH, 2240 cm.$^{-1}$, weak,

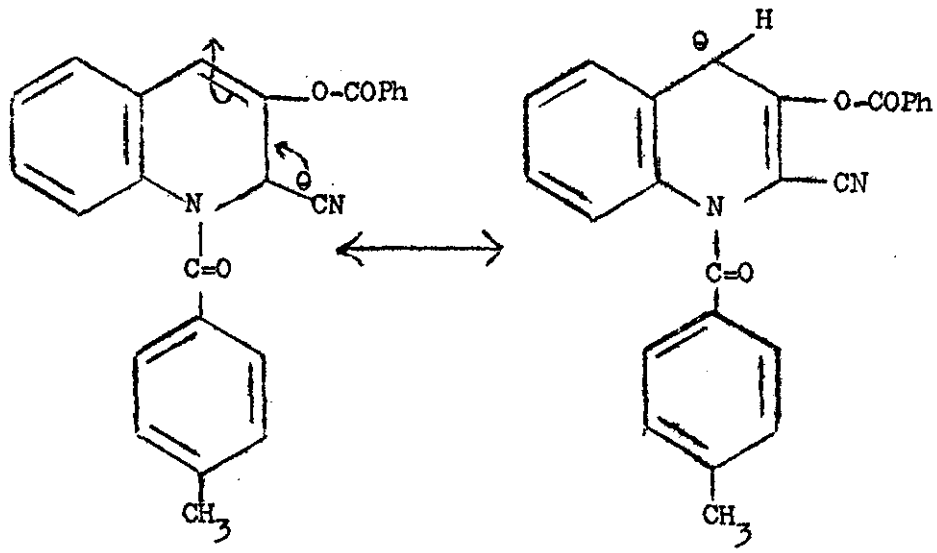
Scheme II Possible routes for rearrangement of carbanion of (110)



C≡N, 1705 cm.$^{-1}$, amidic carbonyl (out of plane) and 1685 cm.$^{-1}$, diaryl ketone (H-bonded). The higher absorption (1705 cm.$^{-1}$) of the amidic carbonyl could be due to the bulky benzoyl group at C-2 causing reduction of the p-π overlap in the N-C=O grouping.

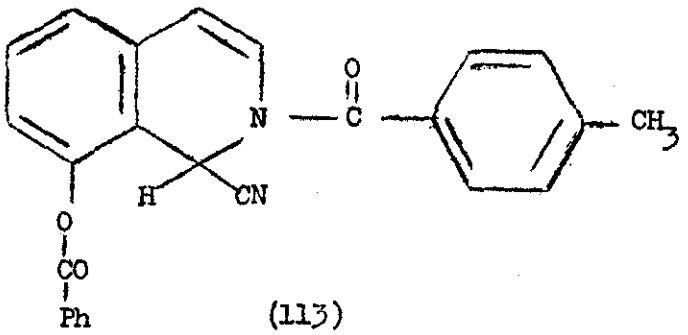
Although the n.m.r. spectrum of the crude product suggested the structure (111) to be present in almost equal proportion, attempts to isolate (111) in pure form, from the non-base soluble material, were unfortunately not successful.

Thus the reaction was disappointing in that pure products could not be obtained, but the spectroscopic evidence obtained suggests that the ester carbonyl of the starting material (110) is competing to an appreciable extent with the normal 1,2-amide rearrangement. The failure to obtain pure products may be due to the presence of small amounts of by-products possibly resulting from intermolecular reactions of the allylic anion (110B), in resonance with (110A).



(110A) (110B)

Rearrangement studies on 8-benzoyloxy-2-p-toluoyl-1,2-dihydroisoquinaldonitrile (113)

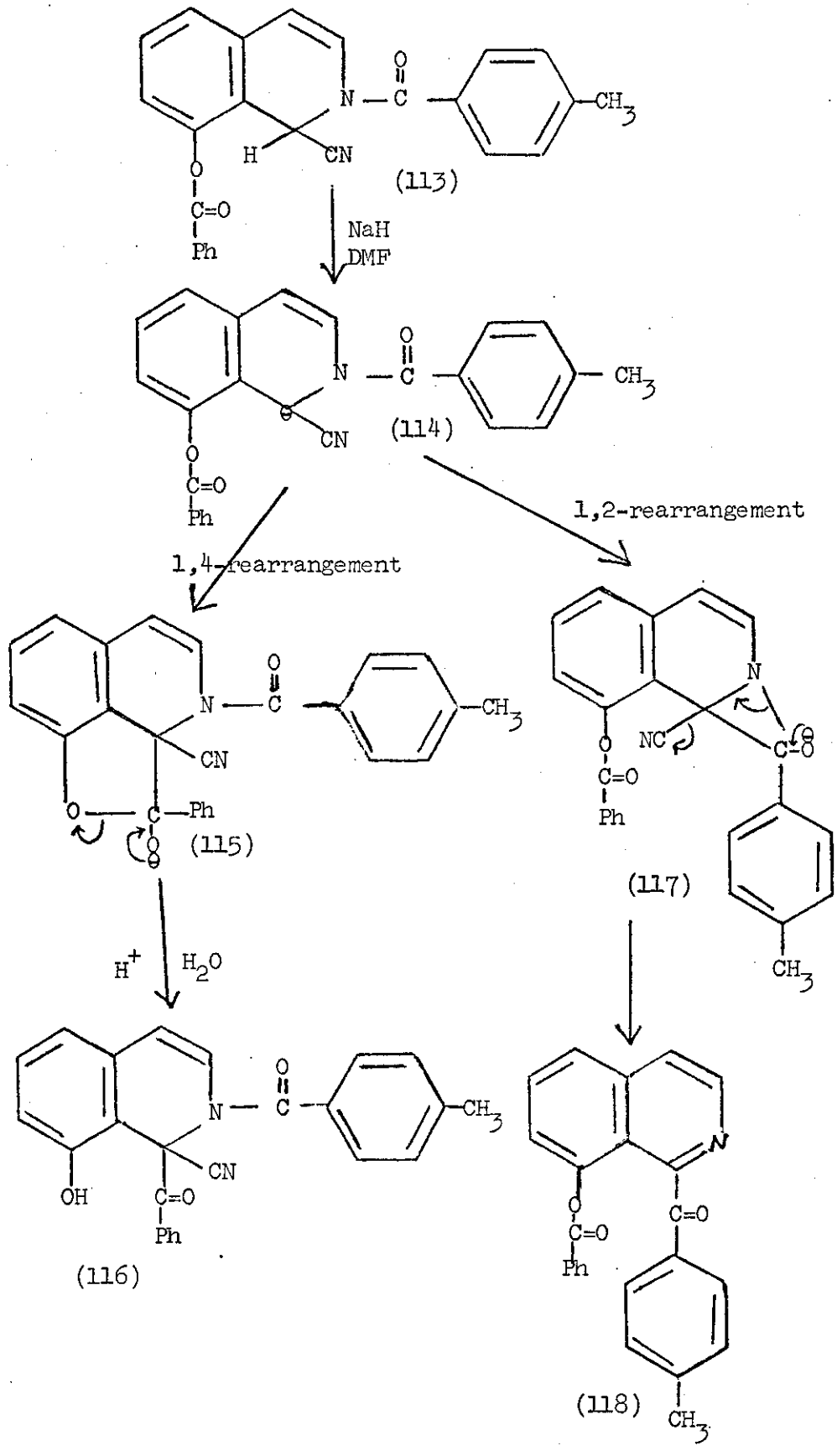


(113)

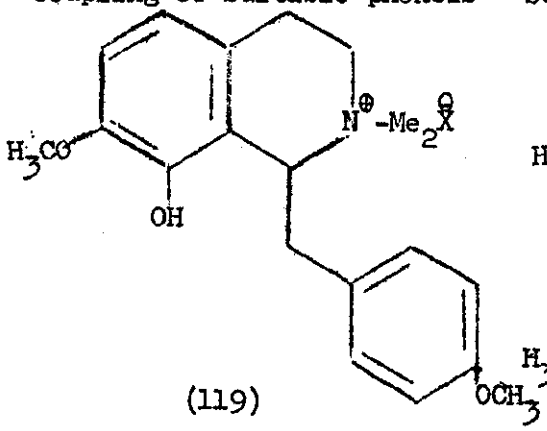
Having obtained some evidence that C-3 ester group in the quinoline Reissert compound (110) could compete with the 1,2-amide rearrangement, it was of interest finally to examine the rearrangement behaviour of (113). It was also attractive in view of its possible application to the synthesis of certain 1-benzylisoquinoline alkaloids. The C-1 carbanion (114) generated from (113) can attack the C-8 ester carbonyl resulting in a little strained 1,4-rearrangement *via* the 5-membered ring intermediate (115) to give the phenol (116). Alternatively, the less electrophilic amide carbonyl can be attacked giving 1,2-rearrangement. This would involve the more favourable entropy factor and the added driving force of aromatisation, to give (118) via (117) (see Scheme III, p. 42).

Apart from its mechanistic interest the value of the reaction synthetically is that if the route *via* (115) is followed then the procedure could be used as key stage in the synthesis of 8-oxygenated benzylisoquinolines, for example, the alkaloid petaline (119) containing the

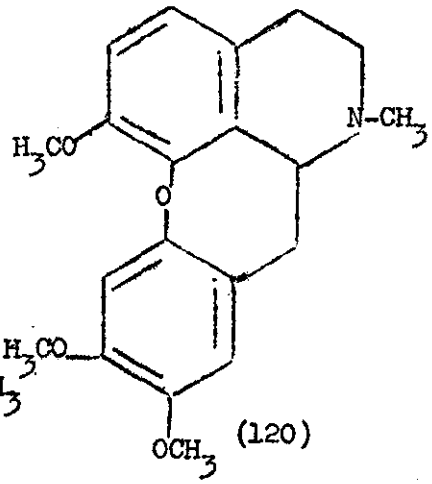
Scheme III Possible routes for rearrangement of carbanion of (113)



7-methoxy-8-hydroxy groupings.[68] Furthermore the tetracyclic cularine alkaloids (e.g. 120) could be elaborated by oxidative coupling of suitable phenols[69] so produced.

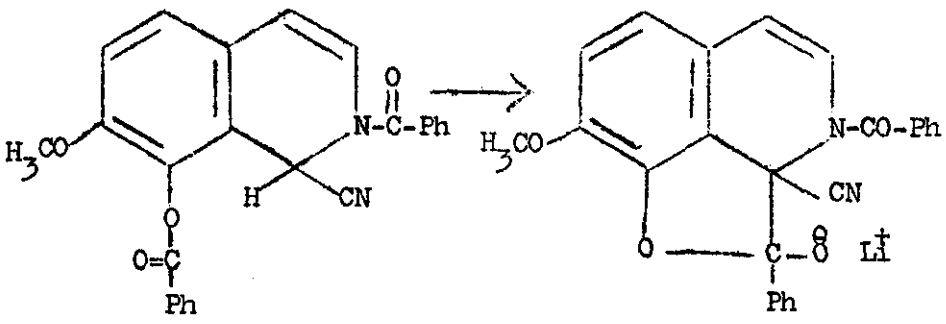


(119)



(120)

A rearrangement analogous to that with (113) has been attempted previously[70] on compound (121) as a model for the synthesis of cularine (120). The reaction, however, was not successful, although evidence was obtained for the formation of intermediate (122) which precipitated from the (less-polar) tetrahydrofuran solution.[70]

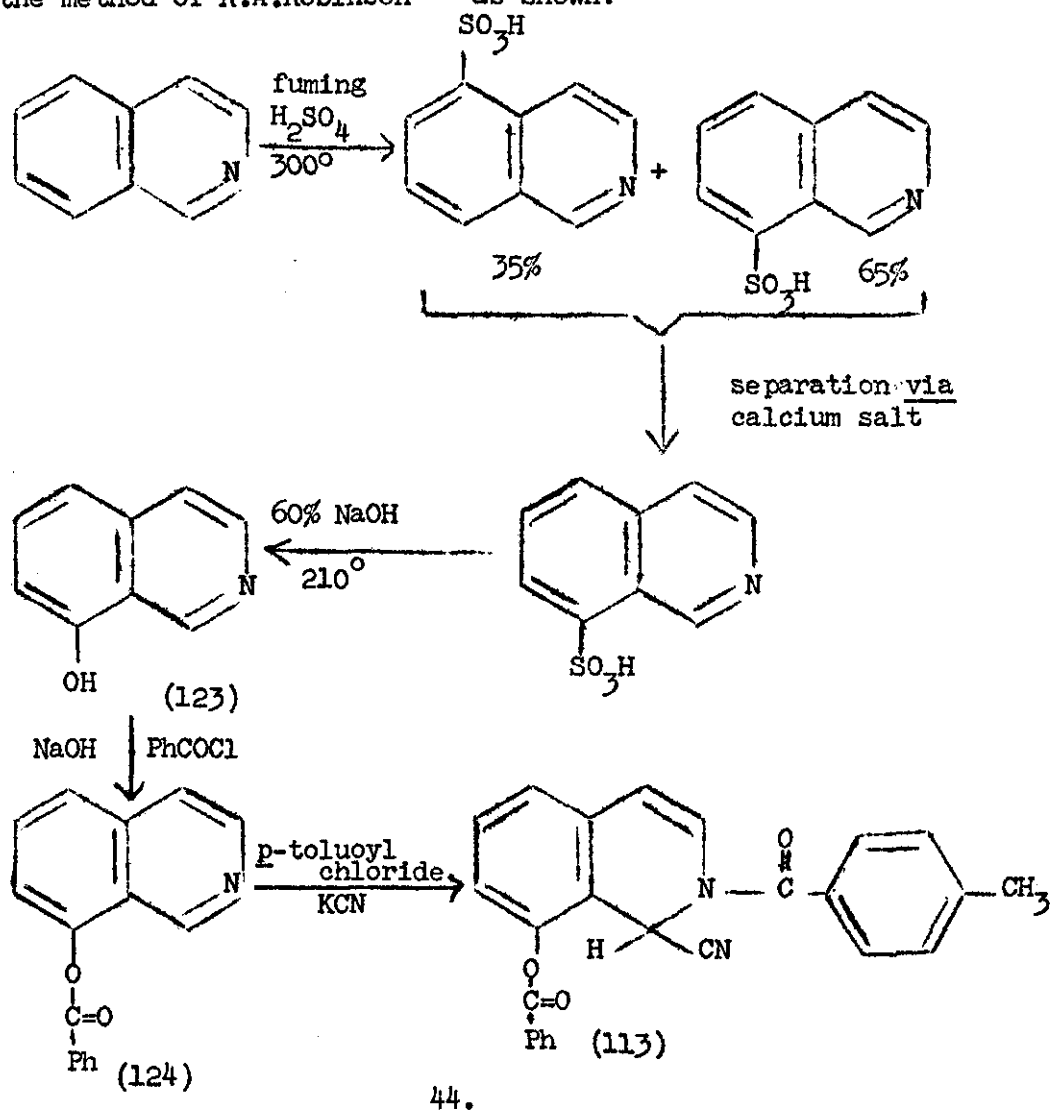


(121) (122)

The base used[70] was phenyllithium, in tetrahydrofuran at -20°, and since that time the much improved reagent system, sodium

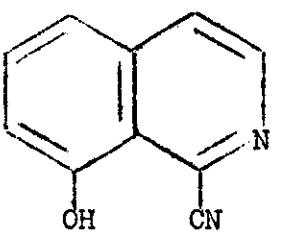
hydride in dimethylformamide, has been developed in our laboratory[24] and America.[25] We considered it likely that the dipolar solvent dimethylformamide would maintain any ionic intermediates in solution.

The amide phenyl was again "tagged" with a methyl group to assist n.m.r. interpretation and to discourage carbanion attack at the amide carbonyl. The compound (113) was prepared in 50% yield by the Reissert reaction of 8-benzoyloxyisoquinoline (124) with p-toluoyl chloride. 8-Benzoyloxyisoquinoline was prepared by benzoylating 8-hydroxyisoquinoline (123) under the usual Schotten-Baumann conditions. 8-Hydroxyisoquinoline (123), in turn was prepared from isoquinoline by the method of R.A.Robinson[71] as shown:-



When the dimethylformamide solution of (113) was treated with sodium hydride at room temperature, the red carbanion colouration appeared only after 40 minutes. Presumably the steric crowding around the C-1 methine proton made approach of the hydride ion difficult. The red colour became intense within a further period of ten minutes. After six hours under nitrogen the colour had faded slightly and the mixture was worked-up. Two fractions, one acid soluble and the other non-basic were obtained.

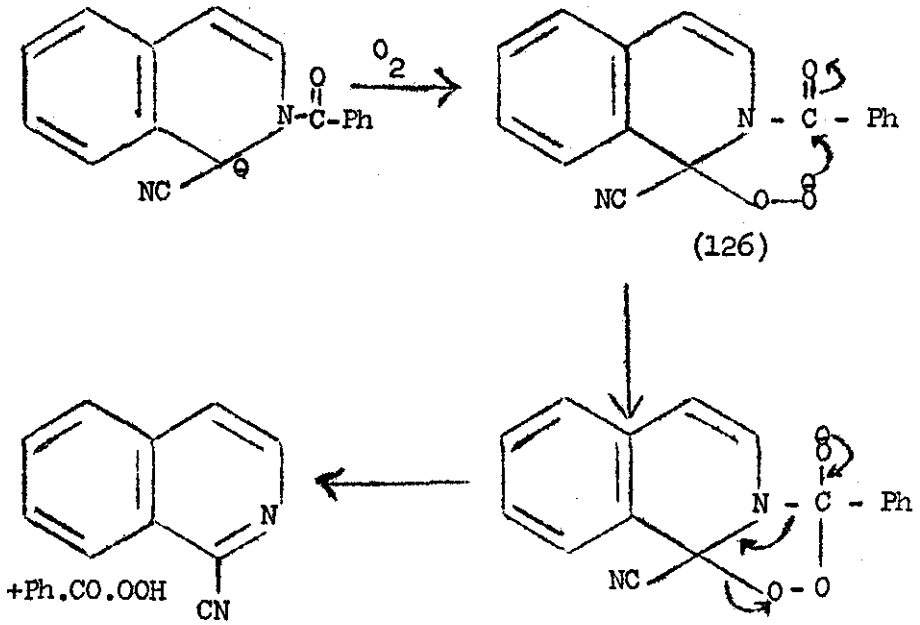
The acid soluble product (isolated in 3% yield) was recrystallised from methanol, m.p. 218°. From its mass spectrum (molecular ion peak at 170) the product appeared possibly to be 8-hydroxyisoquinaldonitrile (125) and gave the following supporting evidence. The n.m.r. spectrum in deuterated acetic acid (CD_3COOD) showed absorption at 1.30 τ (doublet, 1H, C3-H, $J_{3,4}$= 6Hz), 1.97 τ (doublet, 1H, C4-H, $J_{4,3}$= 6Hz) and 2.05-3.00 τ (multiplet, 3H, aromatic). The infrared spectrum showed peaks at 3400 $cm.^{-1}$ (OH) and 2160 $cm.^{-1}$ (C≡N).



(125)

The formation of small quantities of isoquinaldonitriles during Reissert carbanion reactions is not without precedent having been reported for example by Rose and McEwen[72] and by Popp

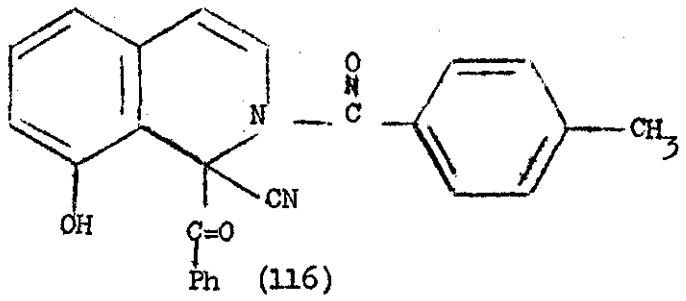
et al.[73] None of the authors gives any explanation for the formation of nitrile. However, it has recently been shown in this laboratory[74] that when such rearrangements are carried out in an atmosphere of oxygen, the isoquinaldonitrile is the chief product. The following mechanism involving the peroxy anion (126) is thought to occur.[74]



Thus the formation of the 3% of (125) is likely to be due to a small amount of oxygen present. The peroxy anion intermediate formed (corresponding to (126)) will attack one of the aroyl groups, the other being presumably hydrolysed in the basic conditions at the commencement of the work-up.

The non-basic fraction was shown by thin layer chromatography (t.l.c.) to contain four compounds, one of which corresponded to starting material. Of the remaining spots two were very weak and not further investigated. Preparative layer chromatography permitted separation and purification of the fourth compound which was shown to be phenolic (positive ferric chloride test). The n.m.r. showed absorption

at 0.37 τ (1H, broad band) which disappeared on deuteration, 2.20-3.70 τ (13H, multiplet, aromatic protons), 4.03 τ (1H, doublet, J=8Hz) and 7.60 τ (3H, singlet). This data is in good accord with the 1,4-rearrangement structure (116). The band at 0.37 τ is attributable to OH, the doublet to the C4-H (compares with starting material) and the singlet at 7.60 τ to the CH_3 group. The C3-H is obscured in the aromatic envelope.



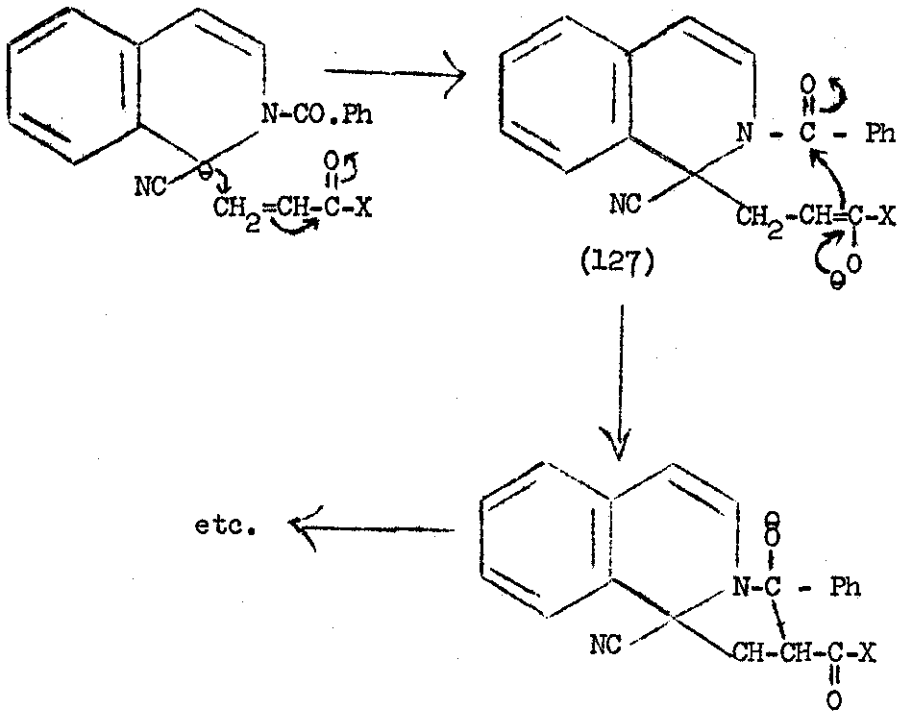
(116)

The infrared spectrum showed peaks at 1630 $cm.^{-1}$ (C3-C4 double bond), 1665 $cm.^{-1}$ (N-C=O), 1695 $cm.^{-1}$ (CO.Ph at C-1), 2220 $cm.^{-1}$, very weak (C≡N) and broad band at 3200 $cm.^{-1}$ (bonded OH). The structure designation was further confirmed by elemental analysis.

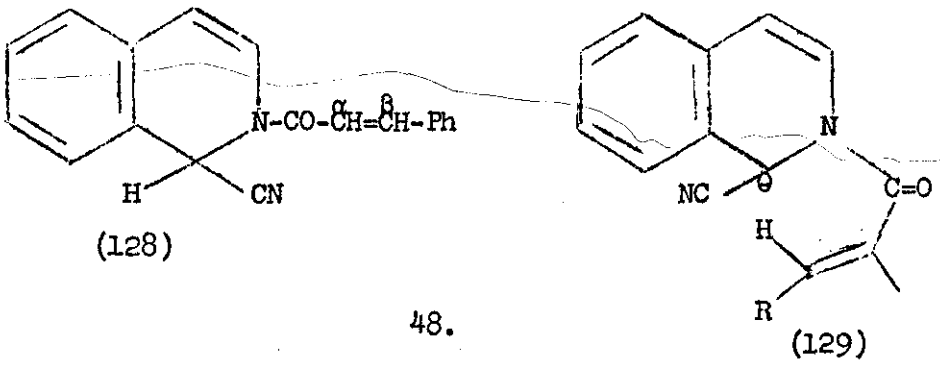
Thus the preferred route for the reaction was the 1,4-rearrangement involving 8-ester group, the alternative 1,2-rearrangement not being observed to any detectable extent. The product (116) was given in relatively low yield (15%) and this would be a limitation to use of the method in alkaloid synthesis. It would seem in part to be due to incomplete carbanion generation, as evidenced by the presence of starting material at the end of the reaction. Clearly the C-1 position is heavily sterically crowded.

(ii) Competitive acyl-rearrangements versus Michael reactions

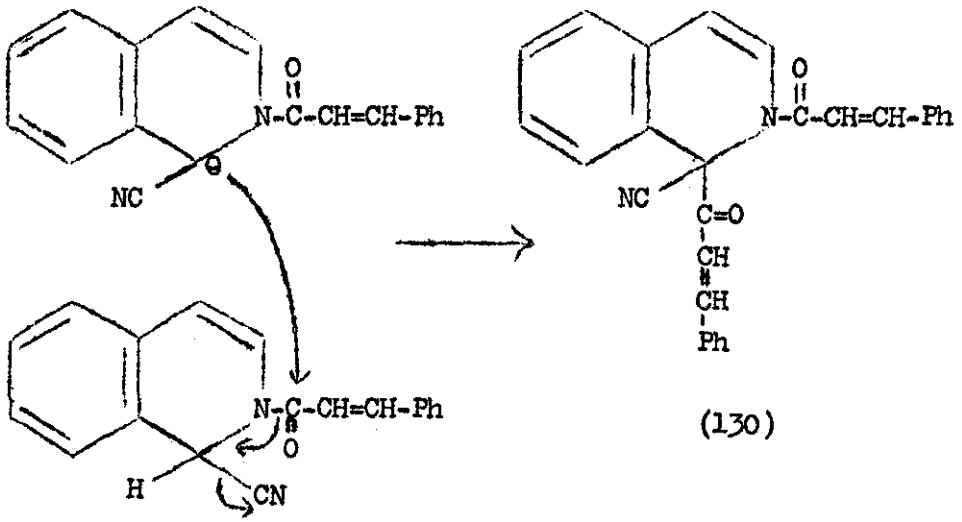
As outlined in the Introduction (p. 15) a number of Reissert carbanion reactions have been carried out with α,β-unsaturated carbonyl compounds and analogous structures, resulting in Michael attack followed by intramolecular attack by the intermediate (e.g. 127) on the N-aroyl carbonyl of the Reissert compound, the final product depending on the nature of the α,β-unsaturated starting material.[18,34]



Only one example has been reported of a Reissert carbanion reaction in which a competing intramolecular Michael reaction is possible. This was with the cinnamoyl isoquinoline Reissert compound (128).[18]



Here the carbanion has the choice of attacking the carbonyl direct, or alternatively, Michael-wise at the β -carbon. Models suggest the β-carbon can approach slightly closer to C-1 (2.2 Å) than can the carbonyl carbon (2.3Å) (see 129). However, neither rearrangement occurred[18] but instead an intermolecular reaction ensued in non-Michael fashion giving (130).

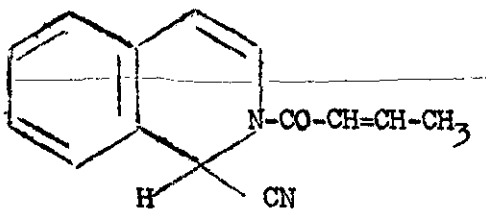


(130)

Thus a number of alternative paths are available for reactions of this kind.

Rearrangement studies on N-crotonoyl-1,2-dihydroisoquinaldonitrile (131)

In view of the above discussion we considered it would be of interest to examine the more reactive starting material (131) i.e. the crotonoyl analogue of the cinnamoyl case (128).



(131)

The Reissert compound (131) was prepared according to the standard procedure,[8] using crotonoyl chloride and potassium cyanide. When the dimethylformamide solution of (131) was treated with sodium hydride at room temperature, the carbanion colour appeared immediately. After stirring the mixture for four hours under nitrogen and usual work-up procedure followed by chromatography, a colourless crystalline material, m.p. 233-234°, was isolated as the major product. Elemental analysis gave the empirical formula as $C_{27}H_{23}N_3O_2$ and this was supported as the molecular formula by an accurate mass measurement (measured mass, 421.1780, calculated mass for $C_{27}H_{23}N_3O_2$, 421.1790). This corresponds to double the molecular formula of the starting material less the elements of HCN.

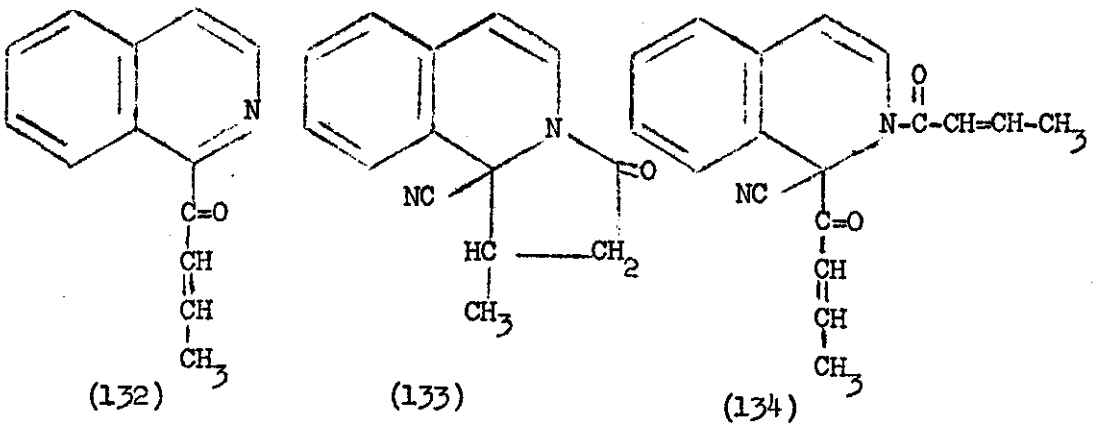
The infrared spectrum showed absorption at 1628 $cm.^{-1}$, 1650 $cm.^{-1}$, 1695 $cm.^{-1}$ and a broad band at 3180 $cm.^{-1}$ The n.m.r. spectrum, run at 220 MHz, was well resolved and consisted of bands as shown in Table I, accounting for the 23 protons,

Table I N.m.r. spectrum details for product from reaction of the anion of (131)

Chemical shift τ	Integration	Multiplicity	Notes
-0.65	1H	broad singlet	disappeared on adding D_2O
1.40	1H	doublet	J=5.6 Hz
1.50	1H	multiplet	
2.10-2.45	4H	multiplet	
2.60-2.90	4H	multiplet	
3.04	1H	doublet	J=7.0 Hz
3.83	1H	doublet	J=7.0 Hz
4.75	1H	quartet	J=7.0 Hz
7.50-8.15	3H	multiplet	
8.35	3H	doublet	J=7.0 Hz
9.72	3H	doublet	J=7.0 Hz

The ultraviolet spectrum showed λ_{max}^{MeOH} 220 nm. (ε 53371), 263 (29560), 312 (6021) and 324 (6842).

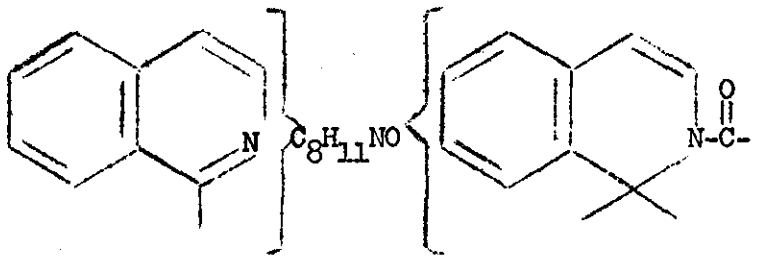
It was obvious from the molecular formula that the product was neither the simple 1,2-rearrangement product (132) nor an internal Michael product such as (133). Furthermore it was not compound (134) - the analogous structure to that of the product from the cinnamoyl case (130).



(132) (133) (134)

The fact that the molecular formula corresponded to a combination of two molecules of starting material ($C_{14}H_{12}N_2O_2$) with loss of the elements of HCN suggested that on linking together possibly one dihydroisoquinoline Reissert structure has been left intact, and the other undergone a 1,2-type rearrangement liberating CN and leaving a fully aromatic isoquinoline moiety. This possibility is borne out by the n.m.r. spectrum. The doublet at 1.40 τ with J=5.6 Hz has a chemical shift and coupling constant comparable to that of the C-3 proton in the n.m.r. spectrum of isoquinoline itself (i.e. at τ 1.48, J=5.8-6Hz).[75] Furthermore no singlet is present at ca. 0.74 τ which suggests there is not

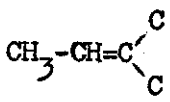
a vacant C-1 position on the isoquinoline moiety. The two doublets at 3.04 τ and 3.83 τ respectively, with J=7Hz, are typical for C-3 and C-4 protons in Reissert type structures (e.g. see Table IV p.110). Also the ultraviolet spectrum of isoquinoline,[76] ($\lambda_{max.}$ 218 nm (ε.,79000), 266 (3900), 305 (2000), 318 (3000)) and that of starting material (131) ($\lambda_{max.}$ 228 nm (ε , 10525), 295 (11003) and 310 (20332)) additively bear comparison with that of the product. On recording the ultraviolet spectrum in methanol containing a drop of hydrochloric acid, $\lambda_{max.}$ 220 nm shifts to 230 nm (as for isoquinoline).[77] From these observations, a possible partial structure for the product can be written as



(135)

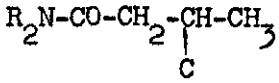
Considering again the n.m.r. spectrum, there would appear to be two methyl groups at 8.35 τ and 9.72 τ each split into doublets with J=7.0 Hz. This suggests both CH_3 groups are next to a CH grouping. The possibility of a grouping of the type CH_3-CH=CH-, which is present in the starting material, is unlikely because of the absence of allylic coupling in the methyl signal (allylic coupling in starting material = 1.5 Hz). The quartet at 4.75 τ with J=7.0 Hz integrates for one proton and could be due to an olefinic proton (=CH) next to a methyl and spin-decoupling indeed showed it to be coupling with the

methyl signal at 8.35 τ. This suggested the grouping (136) to be present, the chemical shift of the methyl group being typical for a methyl adjacent to an olefin.[18]



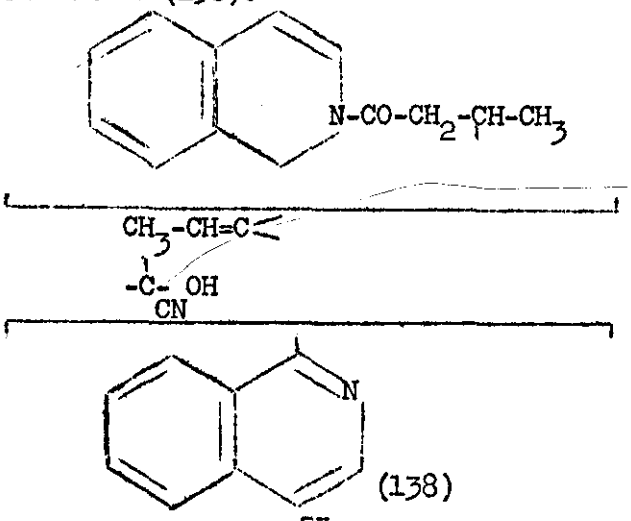
(136)

The multiplet between 7.50-8.15 τ integrates for three protons and could be due to an AEX system arising from a grouping such as CH_2-CH-. Furthermore the typical chemical shift of a CH_2 flanked by a -$CONR_2$ and alkyl residue is 7.77 τ.[78] Also on irradiating the methyl signal at 9.72 τ, the multiplet between 7.50-8.15 τ became simpler. This, therefore, suggests the grouping (137) to be present.



(137)

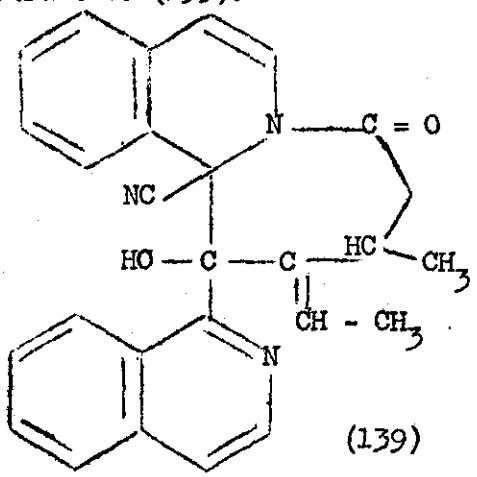
Summarising thus far, the groupings allocated leave the elements of -C-OH and CN remaining. The low field signal at -0.65 τ which disappears on deuteration is, therefore, likely to correspond to the OH group supported by the infrared absorption at 3180 $cm.^{-1}$, a bonded OH. The structure can now be written as (138).



(138)

The nitrile absorption is not observable in the infrared, but this is the usual case with Reissert compounds.[5]

To account for all these observations, we suggest the product has the structure (139).

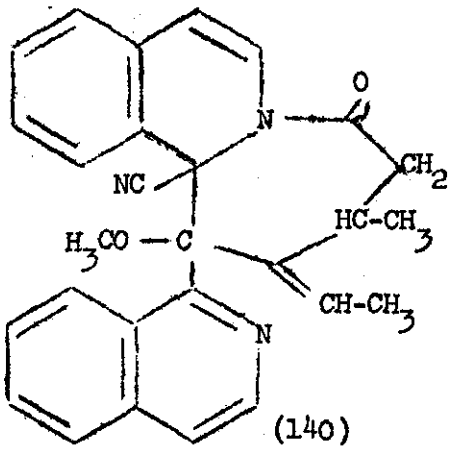


(139)

The coupling of the C3-H with C4-H in the Reissert moiety was further confirmed by spin-decoupling.

The product (139) when treated with sodium hydride in dimethylformamide followed by methyl iodide gave a new compound m.p. 221°, which crystallised from ethyl acetate. The mass spectrum showed the molecular ion to be at 435, i.e. an increase in molecular weight of 14. The n.m.r. spectrum included a sharp singlet at 6.91τ, a value allocable to an aliphatic methoxyl.[78] There was no signal present at -0.65τ and the spectrum remained unchanged on shaking with deuterium oxide. The remainder of the spectrum corresponded with that of the starting material (139). No absorption for an -OH group was present in the infrared spectrum. The ultraviolet spectrum was also similar to that of the starting material except that it was unchanged on addition of alkali, whereas the starting material showed a bathochromic shift (of the 263 nm band) under these conditions.

This information is accounted for by structure (140) in which the hydroxyl of (139) has been methylated.



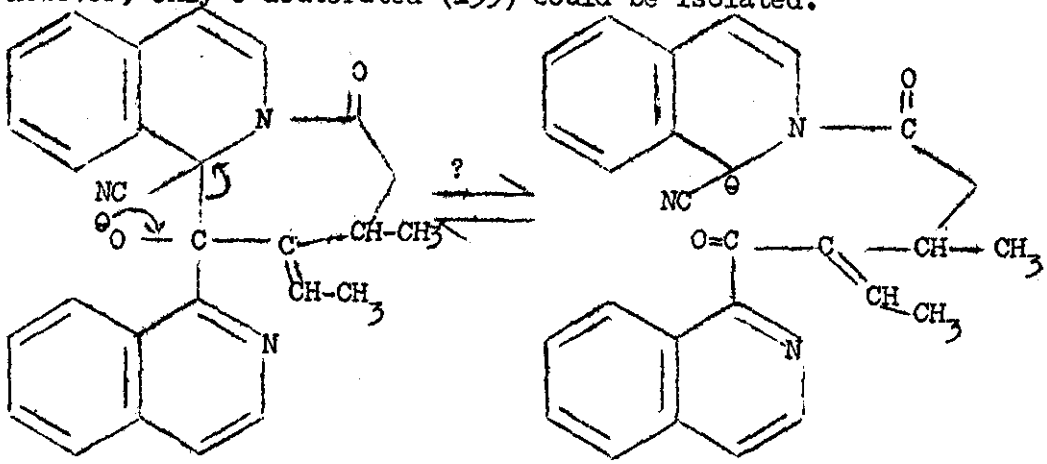
(140)

The exceptionally high chemical shift (9.72 τ) for the CH_3 in the CH_3-CH-CH_2-CO- moiety can be explained by reference to models. From models it appears that a relatively unstrained conformation for the molecule is one in which the methyl group is under the isoquinoline ring, thus causing shielding by the aromatic ring. Furthermore, in this preferred conformation, the amide carbonyl is twisted out of plane and thus possesses more true carbonyl character. This accounts for the carbonyl absorption (1695 $cm.^{-1}$) in the infrared spectrum of (139). The absorption at 1650 $cm.^{-1}$ can be attributed to the C=N in the isoquinoline ring.

Further attempts to investigate the structure (139) met with only limited success. Hydrogenation over platinum in ethanol resulted in slow uptake of approximately two mole equivalents of hydrogen but the product appeared to be a mixture and could not be characterised. Treatment of (139) with sodium borohydride gave no reaction, whereas lithium aluminium hydride in dry tetrahydrofuran gave a mixture which could not be resolved.

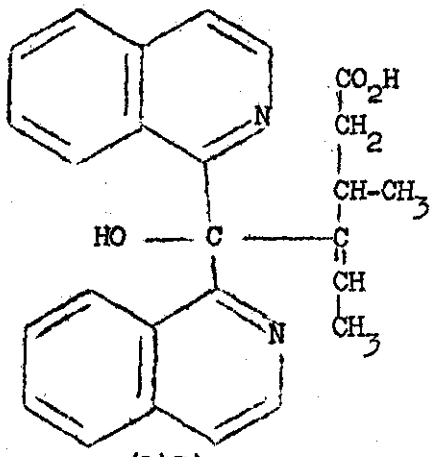
We considered it possible that in base the carbinol anion

(141) could be in equilibrium with the ring opened carbanion (142). We attempted to capture (142) by rapid addition of deuterium oxide to a solution of (139) in dimethylformamide. However, only O-deuterated (139) could be isolated.

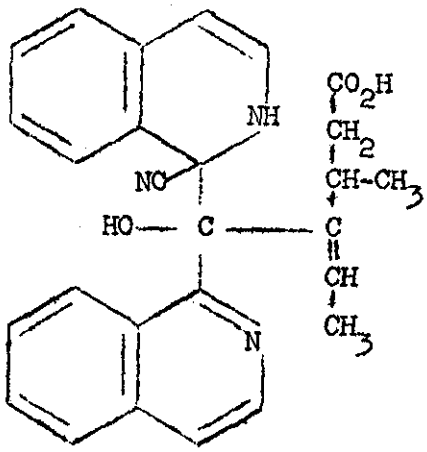


(141) (142)

Lastly we endeavoured to cleave the amide C-N bond of (139). Use of strong acid conditions left only starting material, as also did use of sodium hydroxide in aqueous ethanol. However, on refluxing with strong potassium hydroxide solution in ethanol for several hours a yellow amorphous powder was given on work-up. The compound again could not be obtained analytically pure but the infrared spectrum of the powder showed absorption at 1730 $cm.^{-1}$ and 3220 $cm.^{-1}$ (broad) (saturated aliphatic acid) and broad absorption at 3410 $cm.^{-1}$ (NH and/or OH). The n.m.r. spectrum of the powder could not be obtained because of its insolubility in the available solvents. The product could, therefore, be either (143) or (144). Attempts to esterify the acid were unsuccessful.



(143)



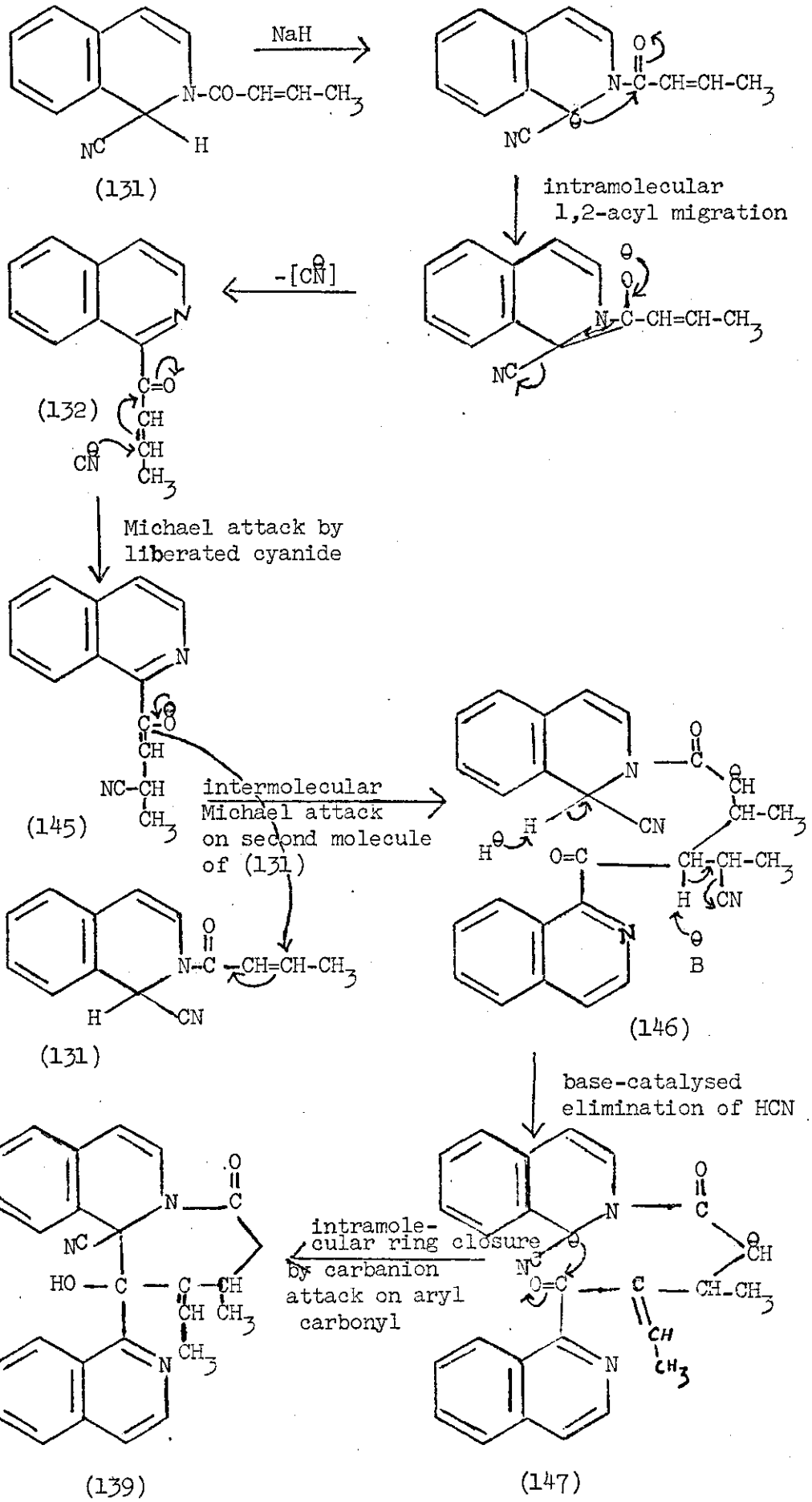
(144)

It remains to discuss a likely mechanism for the formation of (139). We outline a possible route below. (Scheme IV, p. 58).

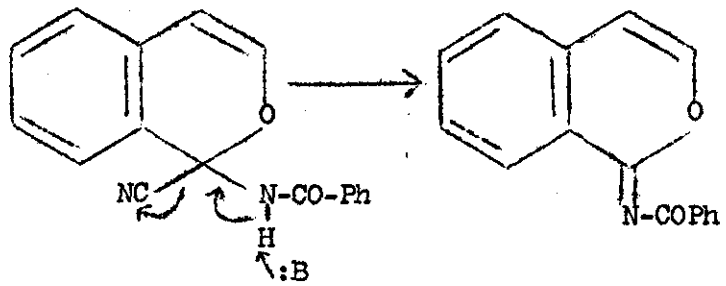
The suggested first step is the normal 1,2-rearrangement of Reissert compound (131) to give α,β-unsaturated ketone (132) which is then attacked by the liberated cyanide ion Michael-wise to give (145). This intermediate (145) can then attack intermolecularly the second molecule of (131) again Michael-wise, to give intermediate (146). Under the basic conditions, HCN is eliminated to give the conjugated enone (147). Finally the C-1 anion in (147) can attack the aryl carbonyl to give (139) with ring closure.

These steps, therefore, are all of the types met previously (i.e. Michael or direct addition to carbonyl) with the exception of the cyanide elimination step. An analogy to this has, however, been obtained in this laboratory[79] in that elimination of the elements of HCN occurs under basic conditions on treatment of the

Scheme IV A possible mechanism for the formation of (139)



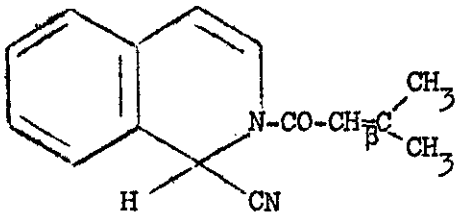
isochromene (148) with base (triethylamine or sodium hydroxide) at room temperature to give the iminoisochromene (149)



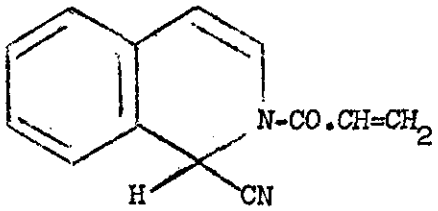
(148) (149)

Rearrangement studies on N-acryloyl-1,2-dihydroisoquinaldonitrile (151) and derivatives (150) and (152)

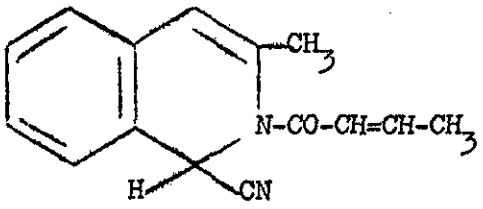
We briefly investigated the carbanion rearrangement of the analogous systems (150), (151) and (152), but the investigations did not, in the event, prove very fruitful.



(150)



(151)



(152)

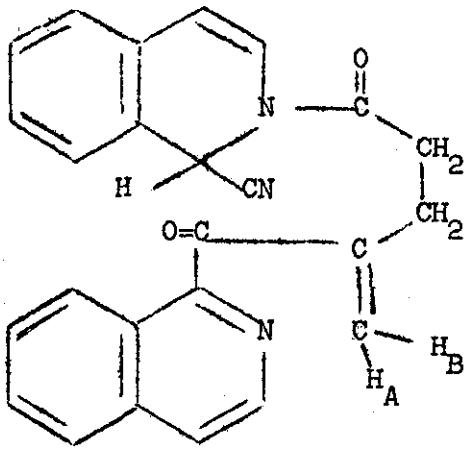
All the three compounds (150), (151) and (152) were prepared by the standard procedure using the appropriate isoquinoline

and acid chloride, in yields of 98%, 12% and 70% respectively.

Rearrangement studies on the β,β-dimethylacryloyl compound (150) repeatedly gave an inseparable mixture. The only product which could be isolated from the acid extract was 1-cyano-isoquinoline.

Compound (151), N-acryloyl-1,2-dihydroisoquinaldonitrile, on treatment with sodium hydride in dimethylformamide gave two products, one of which was 1-cyanoisoquinoline (yield, 1%) which presumably arose from access of some oxygen. The other product, 5%, analysed for $C_{25}H_{19}N_3O_2$ i.e. twice the molecular formula of the starting material less HCN. Its ultraviolet and infrared spectrum were comparable with those of (139) but the n.m.r. spectrum differed. The bands allocable to the isoquinoline and Reissert type structural units were still present. However, no low field absorption was present and no exchange occurred on deuterium oxide addition. Absorption in the 7.30-8.60 τ region now integrated for four protons and was a complex multiplet (possibly ABCD type). The only other absorptions above the 13 protons in the aromatic region were two doublets centred at 5.42 τ and 5.92 τ respectively each with a coupling constant of 15 Hz.

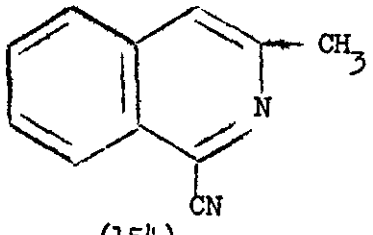
Thus the reaction course is not entirely analogous with the crotonyl case (139) and we are not able to put forward with any confidence a structure for this compound. Our working hypothesis for the product was (153), the open chain analogue of (139).



(153)

The structure (153) is in accord with most of the spectroscopic information and is supported by the infrared with two absorptions in the carbonyl region, 1694 cm.$^{-1}$ (aryl carbonyl) and 1660 cm.$^{-1}$ (N-C=O). However, the feature that remains unsatisfactory is the very large coupling constant (15.0 Hz) for the doublets at 5.42τ and 5.92τ. These would have to be attributed to the methylene protons (H_A and H_B in (153)), but J for such olefinic geminal protons would not be expected to have such a high value.[80]

We lastly reacted (152), the 3-methyl-crotonoyl-analogue of (151), with sodium hydride in dimethylformamide at room temperature and obtained two products. One analysed for 3-methylisoquinaldonitrile (154) (yield 2%) and the other (though not obtained pure) had an n.m.r. spectrum revealing features similar to that obtained for (139).



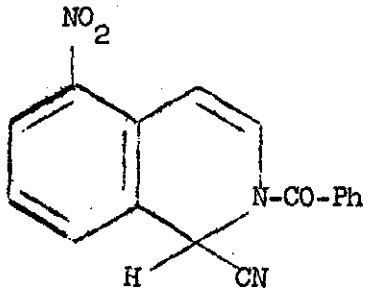
(154)

Absorption at 3.04 τ (for C3-H) in the Reissert moiety (of 139) was absent and C4-H appeared at 4.0 τ as quartet with allylic coupling constant $J_{C4\text{-}H,\ C3\text{-}Me}$ = 1.5 Hz. The doublet at 1.40 τ (attributable to C3-H in isoquinoline moiety of (139)) was also absent. The mass spectrum of the impure product showed a molecular ion peak at 449, demonstrating once again the combination of two moles of the starting material (152) minus the atoms of HCN. Unfortunately the compound could not be obtained in a pure state for further analysis, despite repeated chromatography.

2. N-Acyl Pseudo-Base Studies

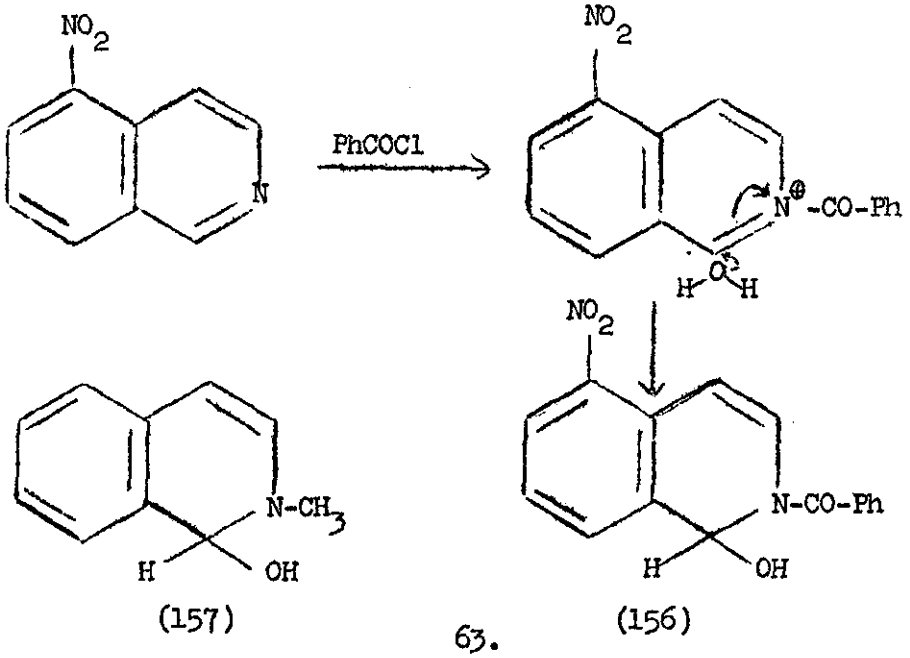
(a) Reissert reaction with 5-Nitroisoquinoline

Popp and Blount[81] have reported the preparation of 5-nitroisoquinoline Reissert compound (155) using the normal procedure with potassium cyanide and benzoyl chloride, in 10% yield. However, when Kershaw[82] attempted to prepare this compound in these laboratories by the same method, he obtained a yellow precipitate in almost quantitative yield, during the course of the reaction.



(155)

He showed this not to be the expected Reissert compound but the analogous structure (156) in which cyanide is replaced by hydroxyl. The compound is formally comparable with the well-known N-alkyl pseudo-bases (e.g. 157) and it represents the first reported example of a cyclic N-acyl pseudo-base.

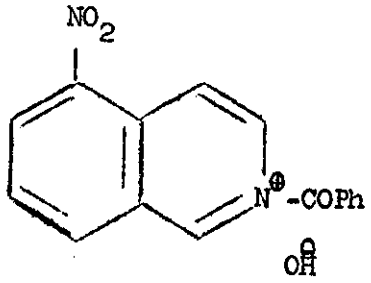


(157) (156)

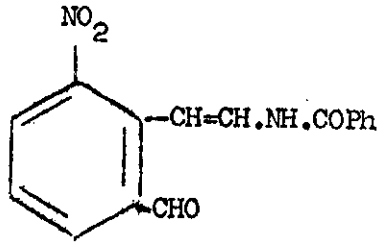
The allocation of structure (156) was confirmed by infrared, n.m.r. and mass spectrometry by Kershaw.[82] He did not carry his studies on this topic any further and we have subsequently taken up this investigation.

Kershaw[82] had been unable to isolate any of the authentic 5-nitroisoquinoline Reissert compound (155) in contrast to the American group[81] who claimed (155) to be the only product from the reaction. We thus repeated the reaction under the same conditions as Kershaw[82] and examined carefully the filtrate after removal of the precipitated pseudo-base. A small residue was obtained on work-up which was chromatographed on alumina to give the authentic Reissert compound (155), m.p. 149[81] in 1% yield, which crystallised from ethanol and provided the calculated elemental analysis.

Kershaw's designation of the structure as the carbinolamide (156) rather than the ionic form (158) or open-chain aldehyde (159) rested principally on the infrared spectrum which showed bands at 3385 cm.$^{-1}$ (broad, OH), 1663 cm.$^{-1}$ (amide carbonyl) and no C-H stretch bands attributable to aldehyde in the 2700-2900 cm.$^{-1}$ region.



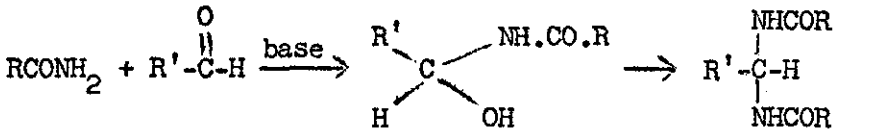
(158)



(159)

Having obtained the authentic Reissert compound (155) we were now able to compare its ultraviolet spectrum with that of (156). These showed close similarity (Figure 1) thus providing further support for the carbinolamide structure (156) designation, and we have published these findings.[46]

As indicated above, system (156) appears to be the first example of a stable cyclic N-acyl pseudo-base, although open chain analogues are known.[83] Acylated amino-alcohols (160) can be formed from amides and aldehydes in the presence of base or acid.[83]



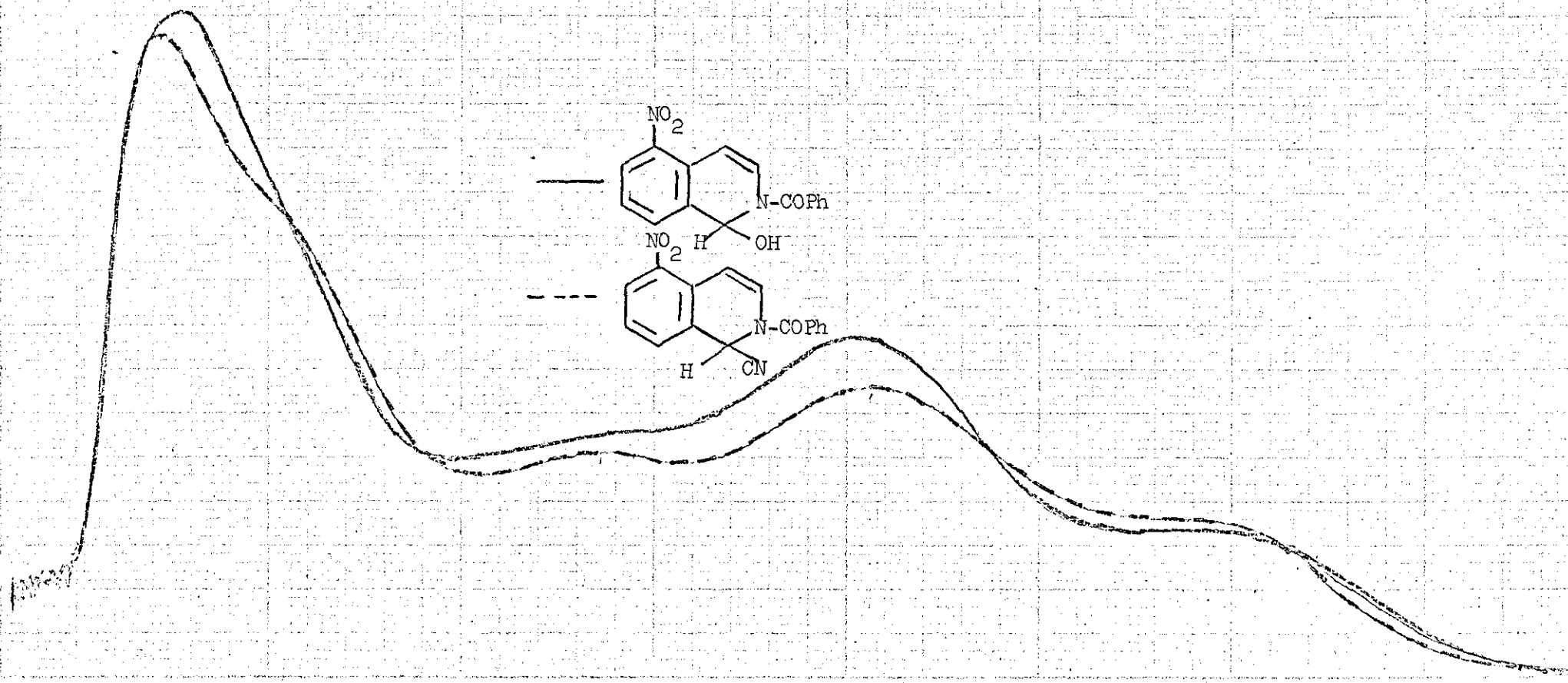
(160) (161)

The reaction, however, usually does not stop at the carbinolamide stage (160), but progresses further to the alkylidene - or arylidene - bisamide (161).[83]

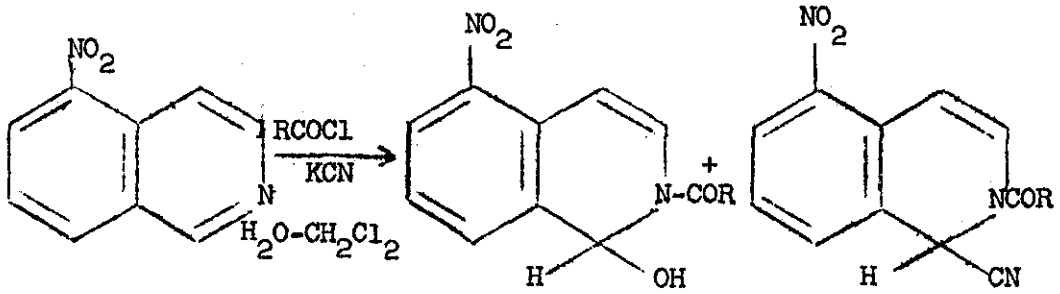
It was thus clearly of interest to establish (i) the generality, or otherwise, of the behaviour of 5-nitroisoquinoline towards other acid chlorides under normal Reissert reaction conditions (ii) the chemistry of the N-acyl pesudo-bases formed and (iii) the possible formation of N-acyl pseudo-bases from other isoquinolines and from related heterocyclic systems.

We firstly, therefore, examined the Reissert reaction of 5-nitroisoquinoline with acid chlorides other than benzoyl chloride. It was found that in each case the reaction proceeded in the same manner as for the benzoyl chloride case, the major product precipitating from solution and proving to have the

Figure I Ultraviolet spectra of N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline and N-benzoyl-5-nitro-1,2-dihydroisoquinaldonitrile



N-acyl pseudo-base structure. The corresponding Reissert compounds were isolated only with difficulty in small yields from the mother liquors of the reactions after removal of pseudo-base. The yields of pseudo-base and Reissert compound obtained from 5-nitroisoquinoline are summarised in Table II below.



(162) (163)

Table II. Products from treatment of 5-nitroisoquinoline with various acid chlorides and potassium cyanide.

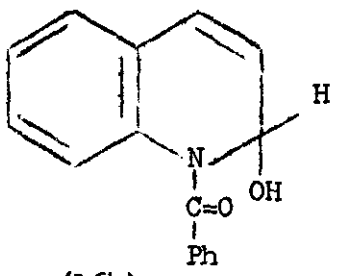
Acid chloride RCOCl	N-Acyl pseudo-base (162) yield %	Reissert compound (163) yield %
Benzoyl	90	1
Toluoyl	67	4
p-Chlorobenzoyl	60	0.6
Anisoyl	70	5
Acetyl	74	2

Normal reaction time was three hours but if the mixture was stirred for a longer time (up to 20 hours) the Reissert compounds could be obtained in slightly better yield (5-10%).

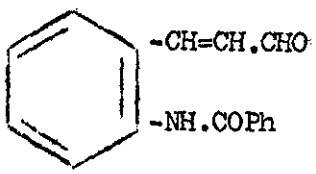
All the N-acyl pseudo-bases obtained were pale yellow in colour (tail end absorption in ultraviolet, Fig. I) and insoluble in water, ether, benzene and chloroform. Practically all could be crystallised from 95% ethanol. Their structures (162) were in accord with their infrared (broad band ca. 3400 $cm.^{-1}$, OH and no C-H stretch bands attributable to aldehyde in the 2700-2900 $cm.^{-1}$ region), n.m.r. (absence of an aldehyde proton signal) spectra and elemental analyses.

It thus appears that the reaction of 5-nitroisoquinoline with acid chlorides and potassium cyanide to give N-acyl pseudo-bases as the major product is a general reaction.

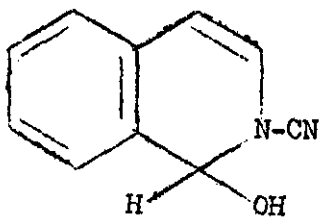
In 1905 Reissert[1] claimed to have formed the analogous N-acyl pseudo-base (164) from unsubstituted quinoline by treatment with benzoyl chloride and aqueous sodium hydroxide. However, it was subsequently shown[2,84,85] that the compound was the aminoaldehyde (165). The equivalent reaction does not take place with isoquinoline.[2]



(164)

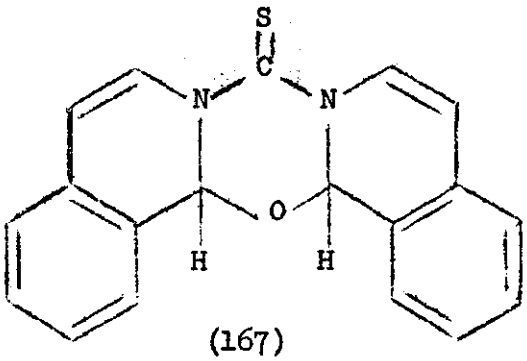


(165)

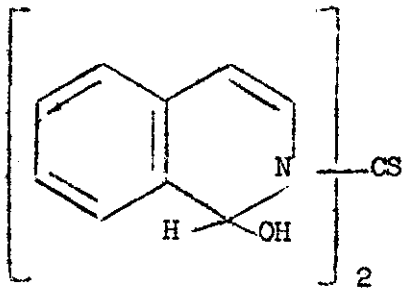


(166)

Although stable N-cyano pseudo-bases (e.g. 166) have been reported (resulting from reaction of isoquinoline with aqueous cyanogen bromide), a nearer analogy to our findings is provided in a concurrent observation of Hull[87] that treatment of isoquinoline with thiophosgene in alkali gives products including (167). This is assumed to be formed by dehydration of (168) (which was not isolated).

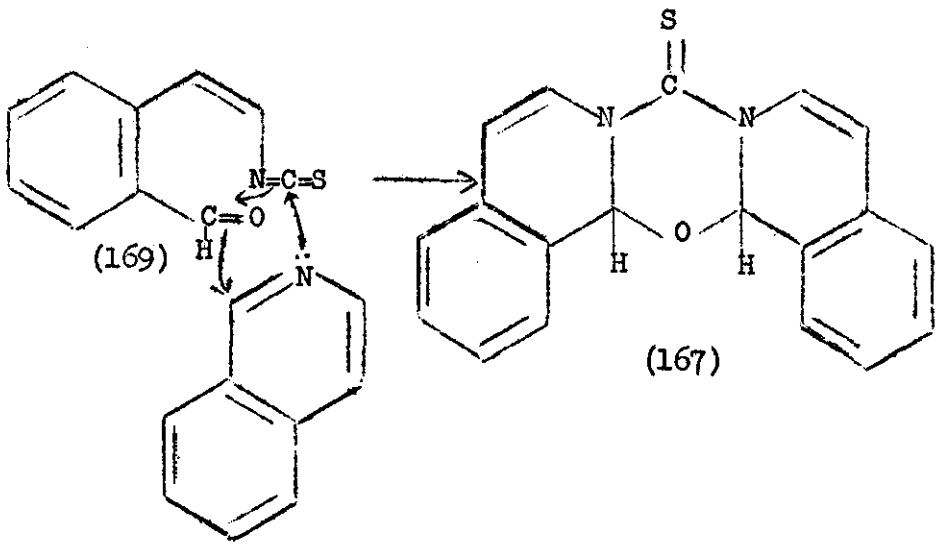


(167)



(168)

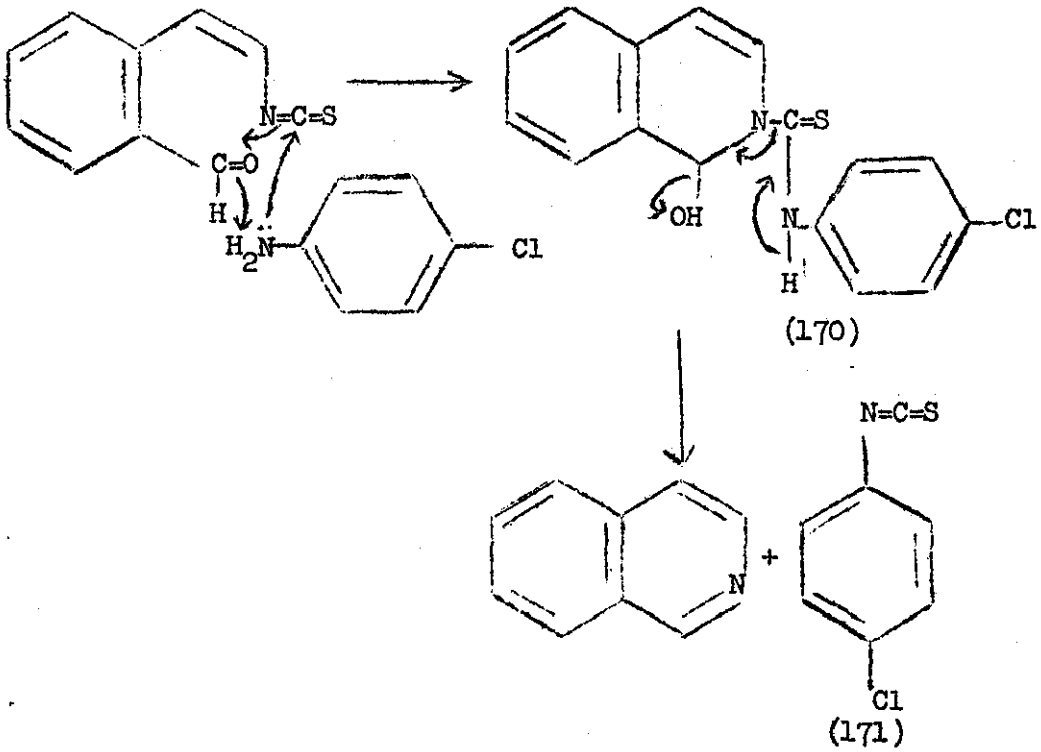
However, in a private communication to us, subsequently, Hull[88] has proposed an alternative mechanism using the open chain form of the pseudo-base (169), which he isolated when using sodium hydroxide (in the absence of potassium cyanide).[87]



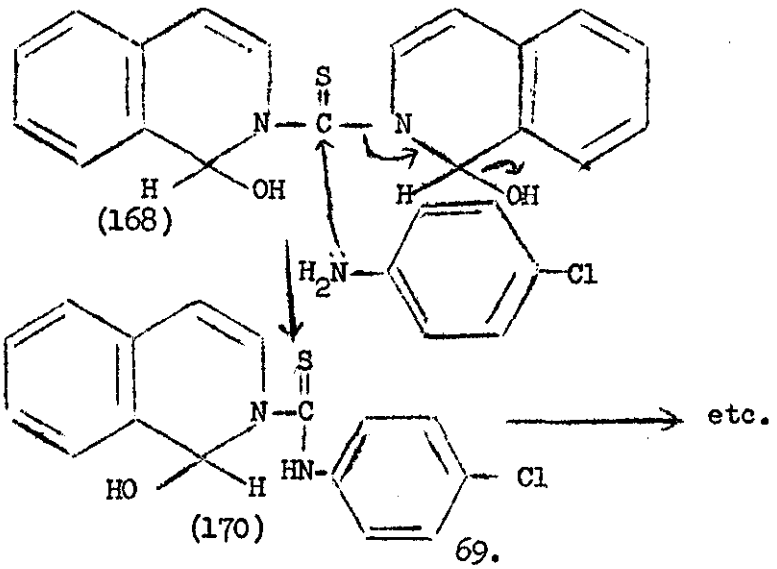
(169)

(167)

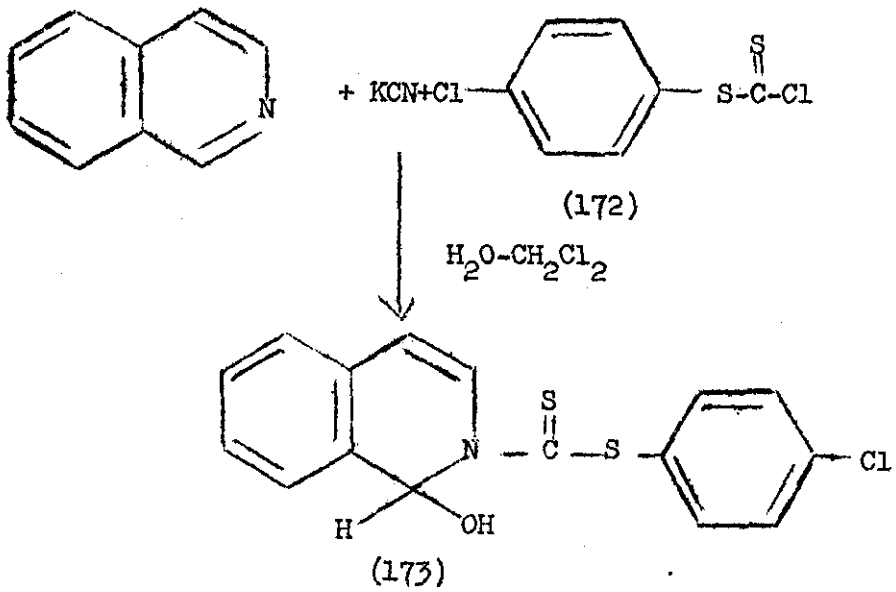
The evidence claimed to support the involvement of structure (169) was obtained by conducting the reaction in the presence of p-chloroaniline when p-chlorophenylisothiocyanate (171) could be isolated.[88]



However, it would appear to us that the result could be explained by intervention of the p-chloroaniline in the initially proposed sequence prior to (and in place of) the dehydration step.



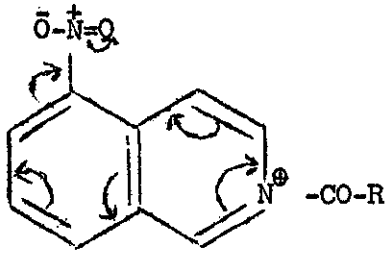
Our preference for the involvement of the pseudo-base (168) rather than the open-chain aldehyde form (169) finds some support in the results of Popp and Klinowski,[89] published subsequent to our studies. They report that the Reissert reaction of isoquinoline with (p-chlorophenylthio)thiocarbonyl chloride (172) gives the cyclic form of the N-thioacyl pseudo-base (173) and none of the corresponding open chaim form, and no Reissert compound analogue.



(173)

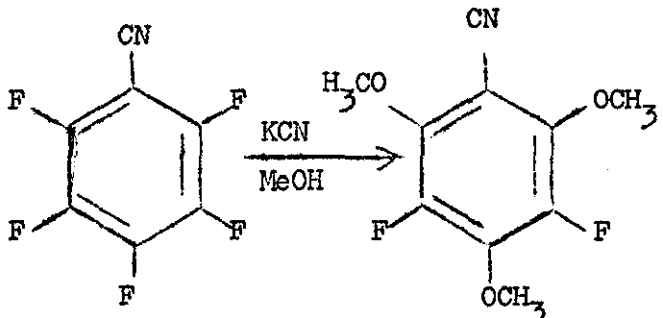
The possibility of (173) existing as an open-chain aldehyde tautomer was excluded by the infrared spectrum and by the lack of an aldehyde proton signal in the n.m.r.[89]

Possible reasons for the remarkable change in behaviour in the Reissert reaction using 5-nitroisoquinoline or thiocarbonyl chlorides are of interest. Possibly the increased positive character of C-1 resulting from the electron withdrawing 5-nitro group promotes solvation at the C-1 position in the quaternary intermediate (174), thus resulting in a reaction with solvent.



(174)

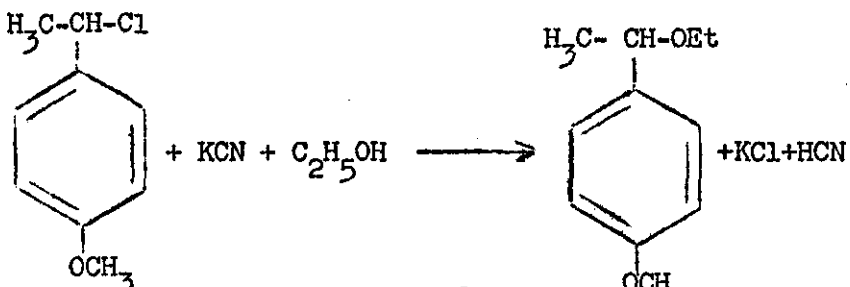
There are examples in the literature of cyanide in an alcohol resulting in solvent attack (giving, however, a substitution product rather than an addition product). For example pentachloropyridine on treatment with sodium cyanide in methanol gives a methoxylated chloropyridine;[90] furthermore, pentafluorobenzonitrile (175) when treated with excess of potassium cyanide in methanol gives (176) in 24% yield.[91]



(175) (176)

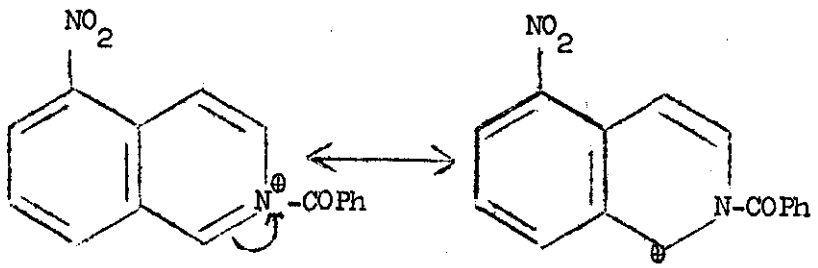
Cyanide in methanol in these examples results in methoxyl substitution despite the fact that methanol is a much weaker nucleophile than cyanide.

An aliphatic analogy is provided by the reaction of p-(α-chloroethyl)anisole (177) with alcoholic potassium cyanide giving a nearly quantitative yield of the ethyl ether (178) and none of the expected nitrile.[92]



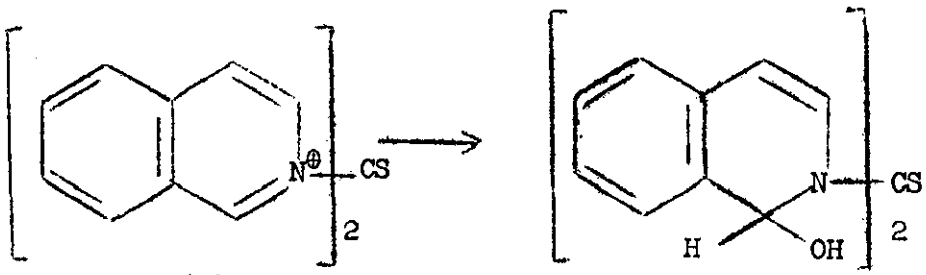
(177) (178)

If a carbonium ion is involved as intermediate in this latter reaction then formation of the ether could result from solvation of the ion. In our Reissert reaction it can be argued that C-1 atom in (174) is at least an incipient carbonium ion (as 179) and so might behave likewise.



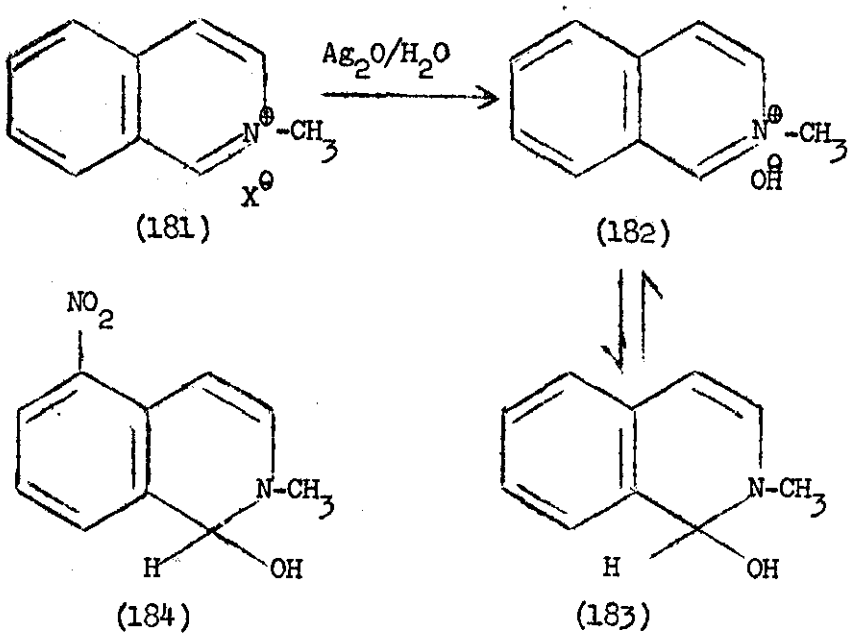
(174) (179)

Alternatively, the principle of soft and hard acids and bases[93] may be invoked in that the effect of the 5-nitro group is to enhance the hardness of the C-1 centre so favouring attack by the hard base, H_2O (or $O\overset{\ominus}{H}$), rather than the soft base, $C\overset{\ominus}{N}$. Hull[87] employs this explanation for the thiocarbonyl case (p.68). His quaternary compound (180), obtained from isoquinoline and thiophosgene, has a relatively soft centre at the thiocarbonyl group to that at C-1. Consequently attack by hard $O\overset{\ominus}{H}$ (rather than soft $C\overset{\ominus}{N}$) takes place at C-1 giving rise to (168).



(180) (168)

The effect of the 5-nitro group has also been noticed with N-methylisoquinolinium salts. N-Methylisoquinolinium salts (181) on treatment with silver oxide give the strongly alkaline quaternary hydroxide (182), which slowly transforms to the pseudo-base (183).[94] However, 5-nitroisoquinoline methiodide on treatment with silver oxide or ammonia leads directly to the pseudo-base (184).[94,95]



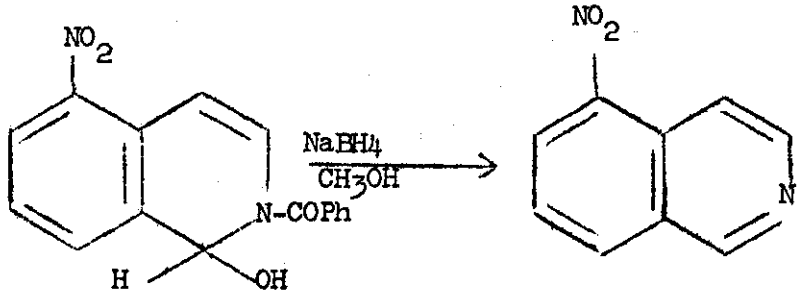
(181) (182) (184) (183)

(b) Chemistry of the N-Acyl Pseudo-Base System

To investigate further the chemistry of N-acyl pseudo-bases, the behaviour of the parent (N-benzoyl) pseudo-base (156) was examined. The pseudo-base structure shows three centres of interest for study (i) possible opening of the hetero-ring at the C1-N bond, (ii) reactions of C1-OH group and (iii) reactions of C3-C4 double bond.

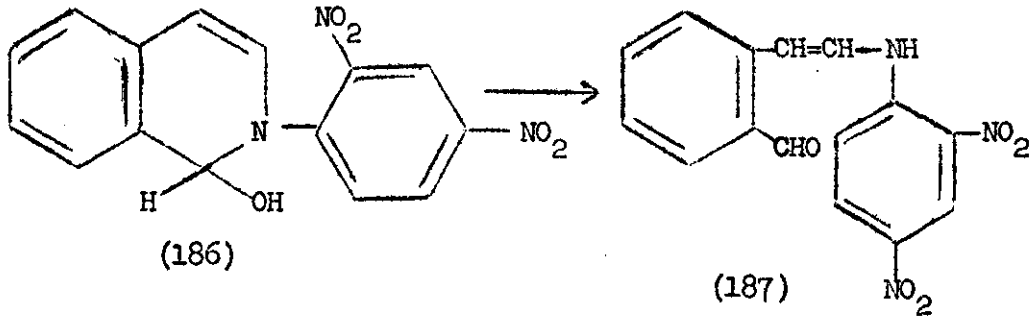
(i) Potential ring-opening reactions

We attempted to cleave reductively the Cl-N bond of the carbinolamide grouping in (156) using sodium borohydride in methanol but obtained instead only 5-nitroisoquinoline (185).



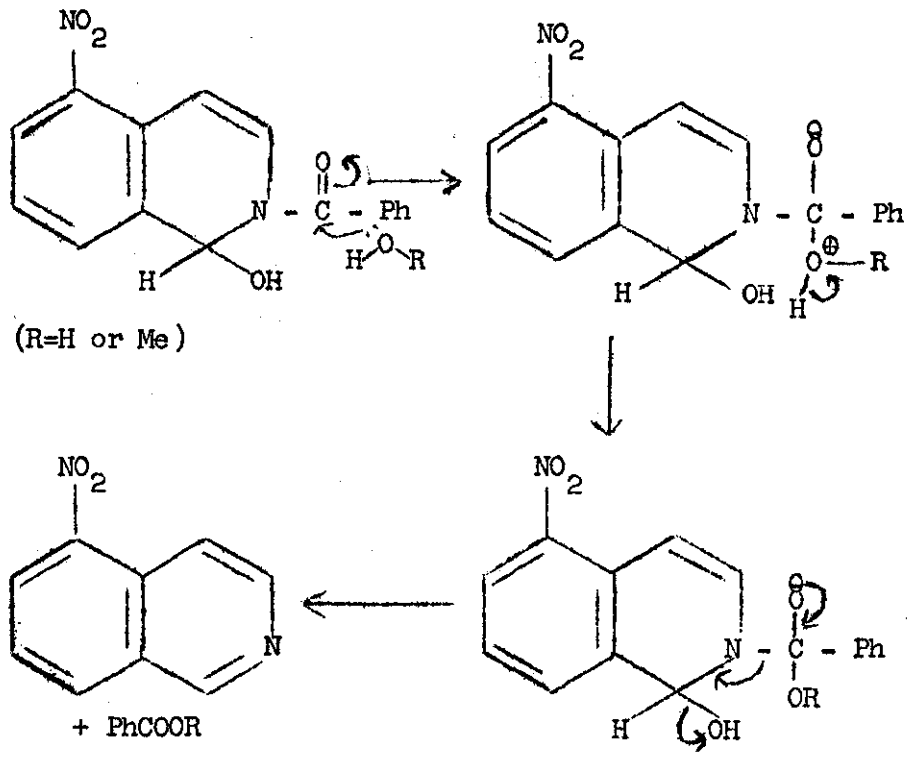
(156) (185)

The N-aryl pseudo-base (186) is reported to be converted to its aminoaldehyde tautomer (187) by heating in aqueous dioxan for two hours.[96] Application of the same conditions to our system (156) resulted, however, in no reaction. Continued reflux for a further period of twelve hours caused break down to 5-nitroisoquinoline and benzoic acid (confirmed by mixed melting points).



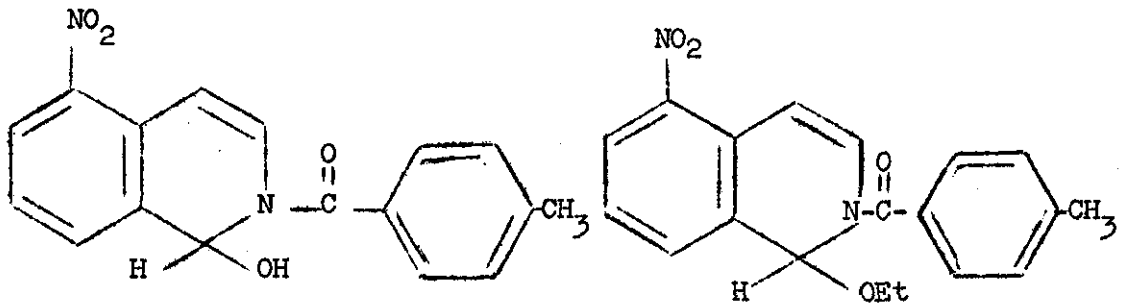
(186) (187)

Thus N-acyl pseudo-base formation would appear to be easily reversed under hydrolytic conditions, this reaction proceeding in preference to hetero-ring opening.



(ii) Reactions of the C1-OH group

Whilst crystallising the p-toluoyl pseudo-base (188) from ethanol, we obtained a new compound, with a relatively low melting point (119° as compared with 184° for the pseudo-base itself), which was soluble in chloroform.

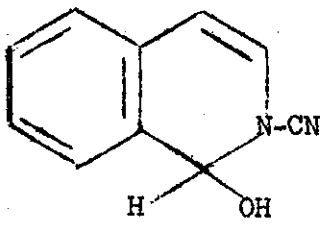


(188) (189)

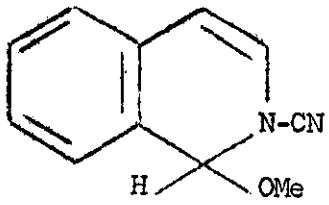
The infrared spectrum showed a strong peak at 1065 cm.$^{-1}$ attributable to an ether grouping which was absent in the infrared spectrum of the uncrystallised material. The n.m.r. spectrum included signals at 6.28 τ (quartet, 2H, J=8 Hz),

8.84 τ (triplet, 3H, J=8Hz) appropriate for an O-ethyl group. Thus spectroscopic evidence suggested the compound was the O-ethyl derivative (189) of (188) and this was supported by elemental analysis. To obtain (188) in pure form, the crystallisation was effected with acetone.

Johnson[86] has reported isolation of similar derivatives e.g. (190) from the N-cyano pseudo-base (166) by using (a) methanol/acetic acid, (b) methanol/triethylamine and (c) by converting (166) to its fluoroborate salt by condensing with boron trifluoride (ethyl ether complex in tetrahydrofuran and then reacting the fluoroborate with methanol/triethylamine).

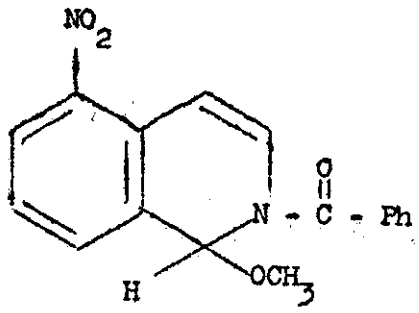


(166)



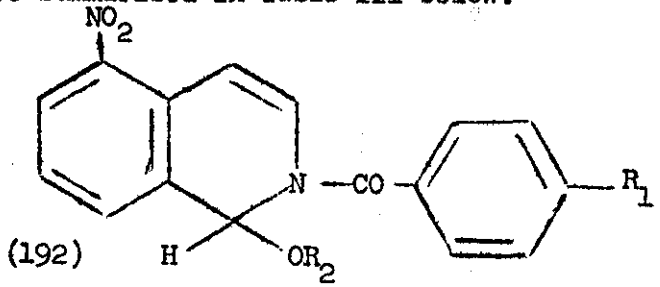
(190)

When we applied his conditions to our N-acyl system, in every case complete hydrolytic breakdown took place to yield 5-nitroisoquinoline and methyl benzoate. It seemed surprising that our pseudo-base was not stable even under so mild acidic or basic conditions. Even reflux of the parent pseudo-base (156) in methanol for half an hour gave 5-nitroisoquinoline and methyl benzoate. Stirring the reaction at room temperature gave only starting material. However, warming the pseudo-base (156) in methanol at 40-45° overnight gave quantitative conversion to the O-methyl derivative (191). The n.m.r. spectrum of (191) included a singlet at 6.62 τ (3H, OMe).



(191)

We repeated the reaction with other N-acyl pseudo-bases and in every case, the O-methyl derivative was obtained in good yield and could be satisfactorily crystallised. Similar experiments with ethanol yielded O-ethyl derivatives. These results are summarised in Table III below.



(192)

Table III. Formation of N-acyl-1-alkoxy-5-nitro-1,2-dihydro-isoquinolines (192)

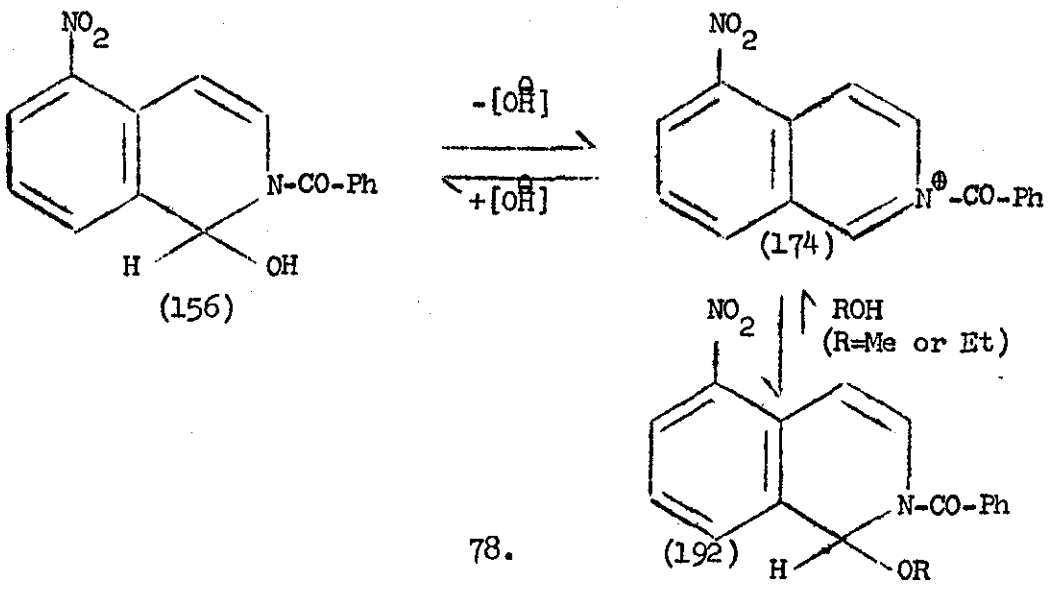
R_1	R_2	Yield %	m.p.
H	Me	96	115-115.5°
	Et	68	108-109°
CH_3	Me	96	128-128.5°
	Et	99	118-119°
Cl	Me	29	173-174°
	Et	30	150-151°
OCH_3	Me	98	186-187°
	Et	83	137-138°

The infrared spectrum of all these derivatives showed a strong peak attributable to the ether group at ca. 1060cm.$^{-1}$ and no absorption in the region 3300-3500 cm.$^{-1}$ Further the

amidic carbonyl absorption appeared at ca. 1680 cm.$^{-1}$, slightly higher than for the corresponding pseudo-bases (ca. 1660 cm.$^{-1}$). This higher frequency for the carbonyl group could be due to a steric effect of the relatively bulky C-1 alkoxy group reducing the coplanarity and hence p-π overlap of the amide system.

The ether derivatives were further characterised by elemental analysis and by their n.m.r. spectra. The spectra showed the C-1 methine proton at ca. 3.40 τ as a singlet, finely split (J= 1.3 Hz) by long range coupling with the C-3 proton. The C-3 proton, therefore, appeared as a quartet ($J_{3,4}$=8.0 Hz), centered at ca. 3.0 τ. The C-4 proton doublet in Reissert compounds normally appeared at ca. 3.9 τ but in the 5-nitroisoquinoline derivatives is deshielded by the nitro group, resonating at ca. 3.15 τ. The significance of the long range C-1 - C-3 coupling with regard to stereochemistry is discussed subsequently (p. 114) in relation to similar observations we have made with Reissert compounds.[97]

Exchange of methoxyl or ethoxyl for hydroxyl under the conditions discussed is probably the result of an equilibrium effect involving the N-acyl isoquinolinium ion (174) as an intermediate.

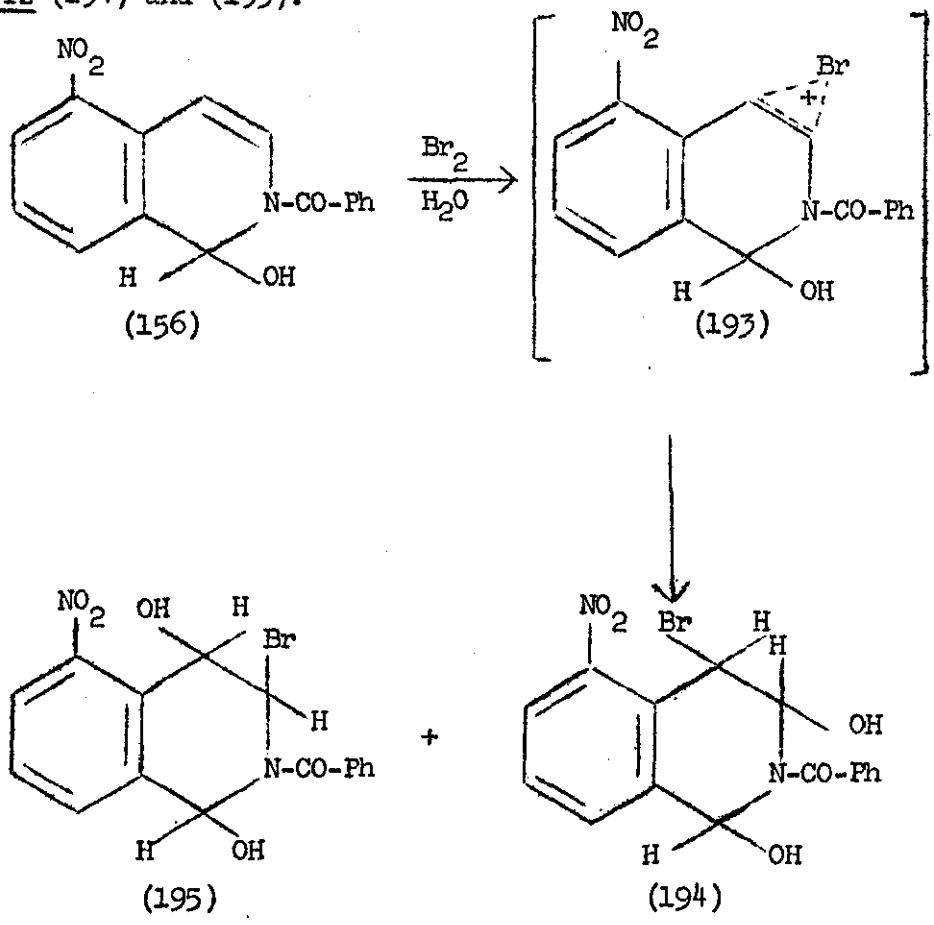


Alcohols and water are classified as hard bases but one would anticipate water to be the harder.[93] In our case, therefore, it would appear that in the conversion of the pseudo-base (156) to the ether (192) the equilibrium is being forced the "wrong" way by the large excess of alcohol present. The process can, however, be readily reversed by stirring the ether with aqueous dioxan at room temperature.

(iii) Reactions of the C3-C4 double bond

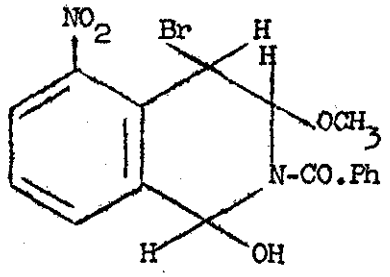
Bromohydrin Formation

It was anticipated that addition of the elements of HOBr to the N-benzoyl pseudo-base (156) would proceed through the brominium ion intermediate (193) to give two possible products, viz (194) and (195).

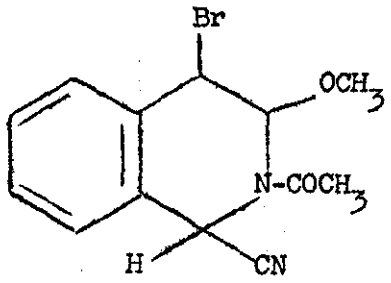


Addition of one equivalent of bromine in aqueous tetrahydrofuran to the pseudo-base (156) resulted in immediate discharge of the bromine colour. Work up and chromatography gave an oil which crystallised from methanol as colourless needles. The infrared spectrum of the compound showed a strong broad absorption at 3340 cm.$^{-1}$ (OH) and 1630 cm.$^{-1}$ The n.m.r. spectrum included a broad singlet at 4.50τ which integrated for two protons and which disappeared on shaking the sample with deuterium oxide, suggesting thereby the presence of two -OH groups in the molecule. The mass spectrum of the compound had molecular ion peaks at 392 and 394 in the ratio 1:1 revealing the presence of one bromine atom. The ultraviolet spectrum showed $\lambda_{max.}$ at 225nm , analogous to that observed for N-methyl-1,2,3,4-tetrahydroisoquinoline.[98] This evidence was therefore in accord with a single bromohydrin having been formed. We considered the structure of the product to be (194) rather than (195) on account of the low amide carbonyl absorption (1630 cm.$^{-1}$) which could result from hydrogen bonding of the C3-OH, and also on account of mechanistic considerations discussed below.

On repeating the bromination but in methanol containing a trace of acetic acid, the O-methylbromohydrin (196) was formed and the amide carbonyl absorption returned to its normal position, 1663 cm.$^{-1}$ This result also indicated that the hydrogen bonding in the former case was not due to the C1-OH. Amide absorption was also at 1663 cm.$^{-1}$ in the analogous product (197) which we prepared from addition of bromine in methanol to N-acetyl-1,2-dihydroisoquinaldonitrile.

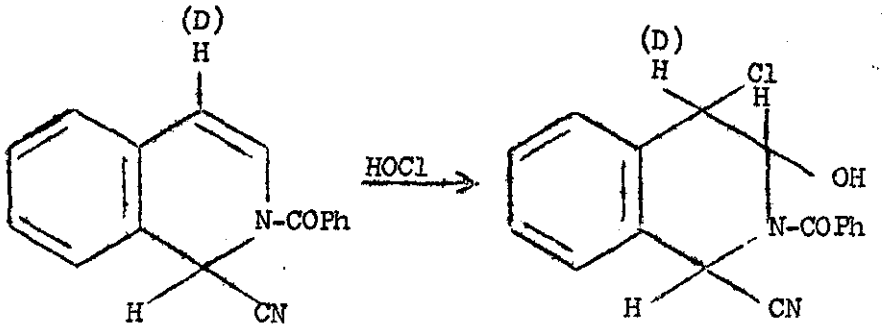


(196)



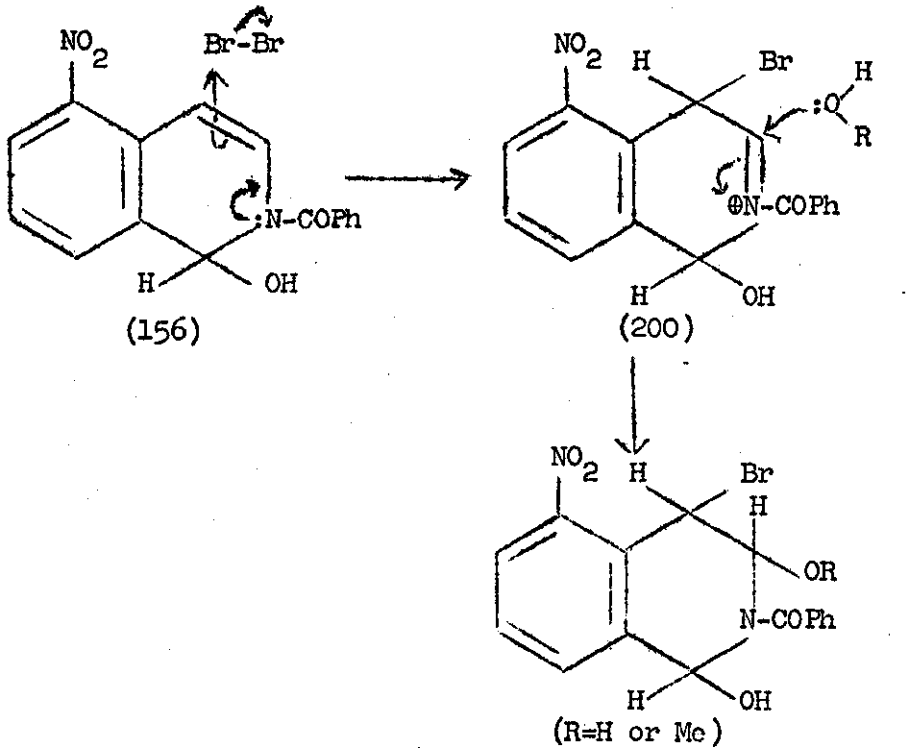
(197)

The structure assignment (194) is further supported by other work carried out in this laboratory[99] to determine the orientation of addition of the elements of hypochlorous acid to Reissert compound (198). In this case it has been unequivocally shown by deuterium labelling at C-4 that the chlorine atom becomes attached at that position giving (199).[99]

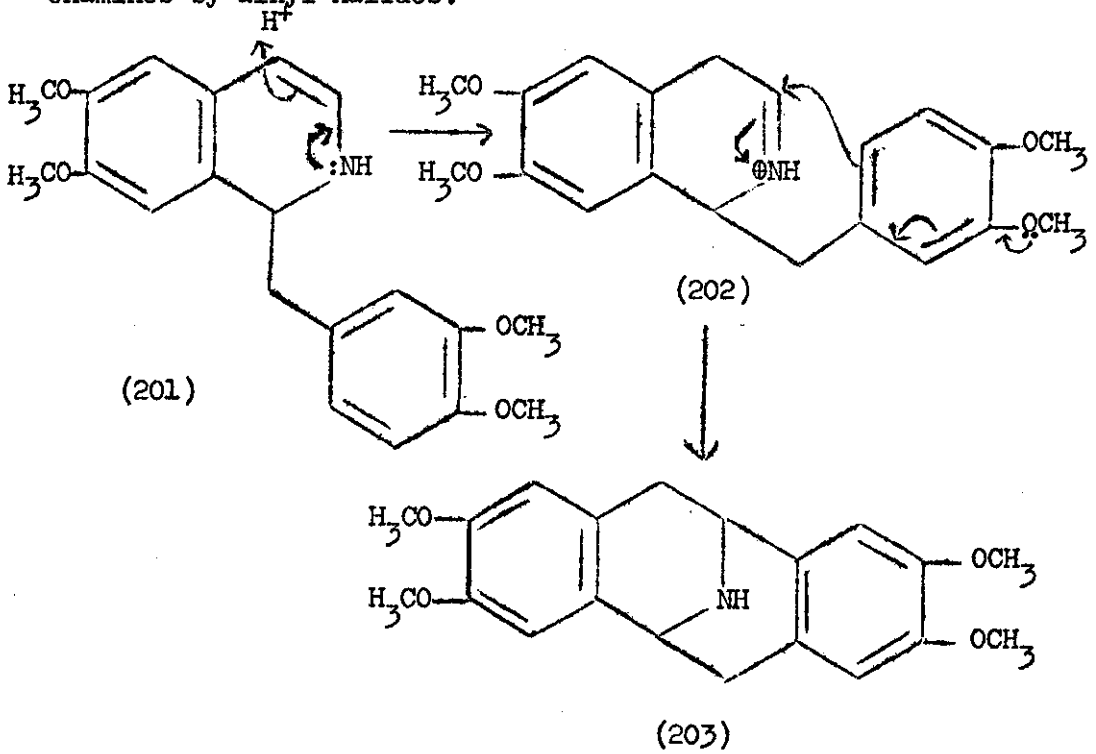


(198) (199)

The absence of the isomer (195) suggests, for the mechanism, not normal addition with the C3-C4 double bond acting as an isolated alkene, but rather electrophilic halogenation at C-4 utilising the enamine character of (156) to give intermediate (200) which is then intercepted by nucleophilic attack at C-3 by water or methanol.

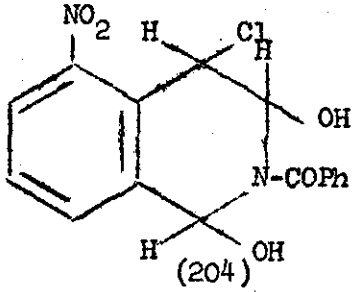


Participation of the enamine character of a 1,2-dihydroisoquinoline in a reaction has been illustrated elsewhere,[100,101,102] for example, in the synthesis of pavine (203),[101] as shown in (201) ⟶ (202) ⟶ (203), which involves initial electrophilic attack that is closely related to the known alkylation of enamines by alkyl halides.[103]



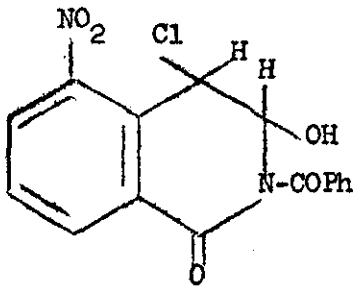
Reaction with hypochlorous acid

By analogy with the bromohydrin formation discussed above and the formation of chlorohydrin (199) from Reissert compounds[99] we expected that the reaction of our pseudo-base (156) with hypochlorous acid would yield the chlorohydrin (204).

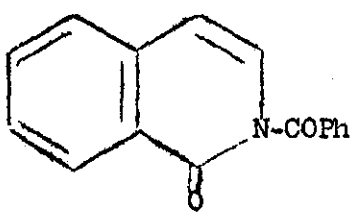


(204)

However, on reaction under similar conditions, two products were obtained neither of which was the expected compound (204). The major product (36% yield) crystallised from methanol and analysed for $C_{16}H_{11}N_2O_5Cl$. This was confirmed by mass spectrometry which showed molecular ion peaks at 346 and 348 in the intensity ratio 3:1. The infrared spectrum included values for $\nu_{max.}$ at 1665, 1682, 1710 and 3440 $cm.^{-1}$ The n.m.r. spectrum consisted of a multiplet of 8 protons (1.4τ - 2.6 τ) and three other protons at 3.90 τ (doublet, J=3.0 Hz), 3.9 τ (broad singlet, disappeared on deuteration) and 4.07 τ (doublet, J=3.0 Hz) respectively. In accord with these facts, we propose the structure (205) for the product.

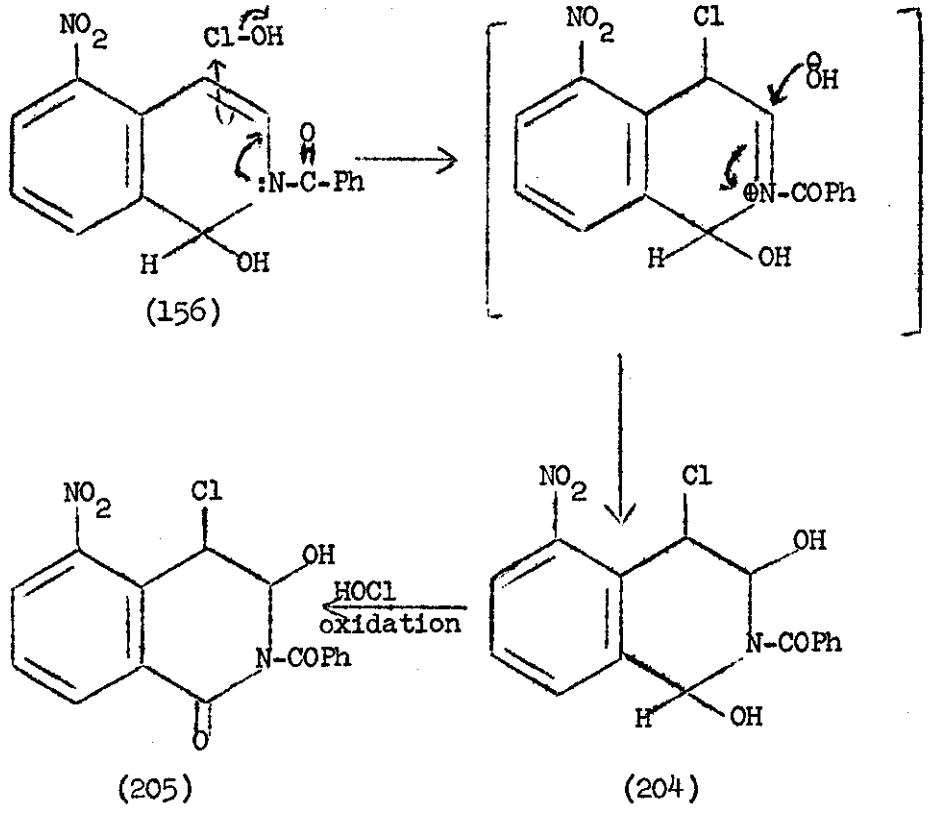


(205)

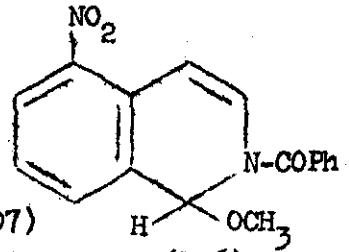


(206)

The absorption at 1710 cm.$^{-1}$ in the infrared spectrum could be due to the C-1 ketone, and at 3440 cm.$^{-1}$ to the C3-OH. The origin of the three carbonyl absorptions for (205) is not understood but may be due to a combination effect of the imide carbonyl stretching frequencies. However, the reported[104] infrared spectrum of (206), with $\nu_{max.}$ 1660 (shoulder), 1680 and 1715 cm.$^{-1}$ supports our allocation. The two doublets at 3.90 τ and 4.07 τ with J=3Hz in the n.m.r. spectrum are attributable to C3-H and C4-H respectively (or vice versa). A likely mechanism for the reaction is indicated, one step being the oxidation by the hypochlorous acid.[105]

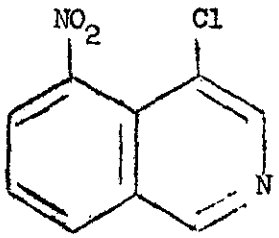


We also obtained compound (205) when (207) was employed as starting material. Presumably, under the conditions of the reaction (207) is in equilibrium with (156) (see p. 78)



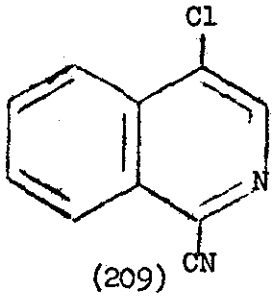
(207)

The minor product from (156), isolated in 2% yield analysed for $C_9H_5N_2O_2Cl$ (supported by mass spectrum) i.e. a monochloromononitroisoquinoline and crystallised from ethanol. We suggest the compound is 4-chloro-5-nitroisoquinoline (208) in view of the following information. The n.m.r. spectrum showed an absorption at 0.53 τ, singlet, 1H, allocable to the C1-H, since this is normally at low field[75] (0.7 τ in isoquinoline,[75] deshielded further in our case by the 5-nitro group). Further resonances occurred at 1.26 τ, singlet, 1H, C3-H, two split doublets at 1.46 τ and 1.65 τ with J=7.7Hz and 1.5Hz, C-6 and C.8 protons ortho and meta coupled; and an unsymmetrical triplet at 2.10 τ with J=7.7Hz, C7-H.

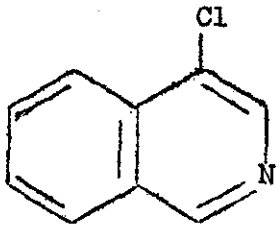


(208)

It seems likely that the chlorine is attached to C-4 rather than C-3 because the chemical shift of the band attributable to the C3-H at 1.26 τ is comparable to those shown by the known 4-chloroisoquinolines (209) and (210). The reported value for the C3-H in (209) is 1.3 τ[106] and in (210) 1.5 τ[107] which is close to our value considering the electron withdrawing effect of the C5-nitro group.



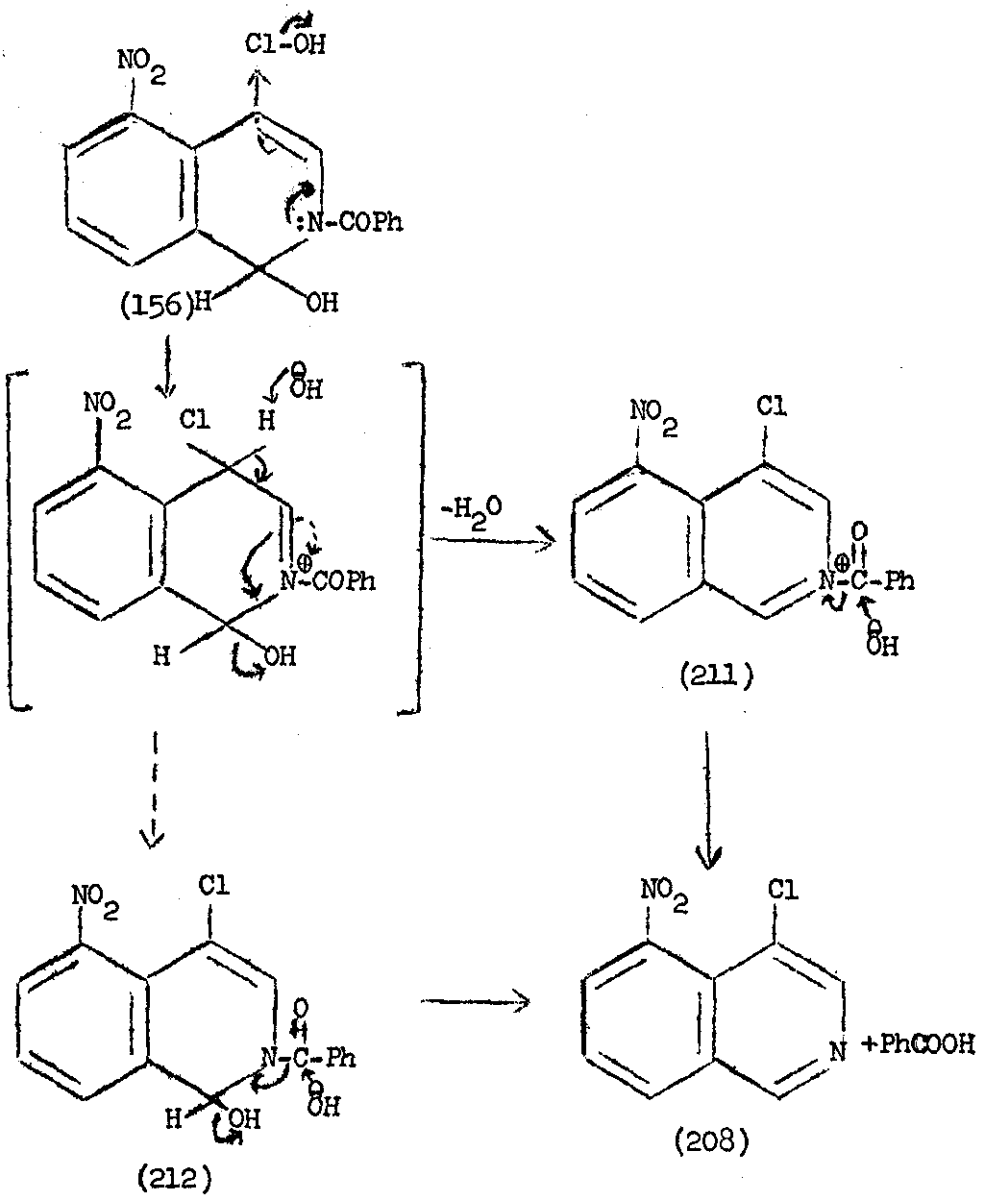
(209)



(210)

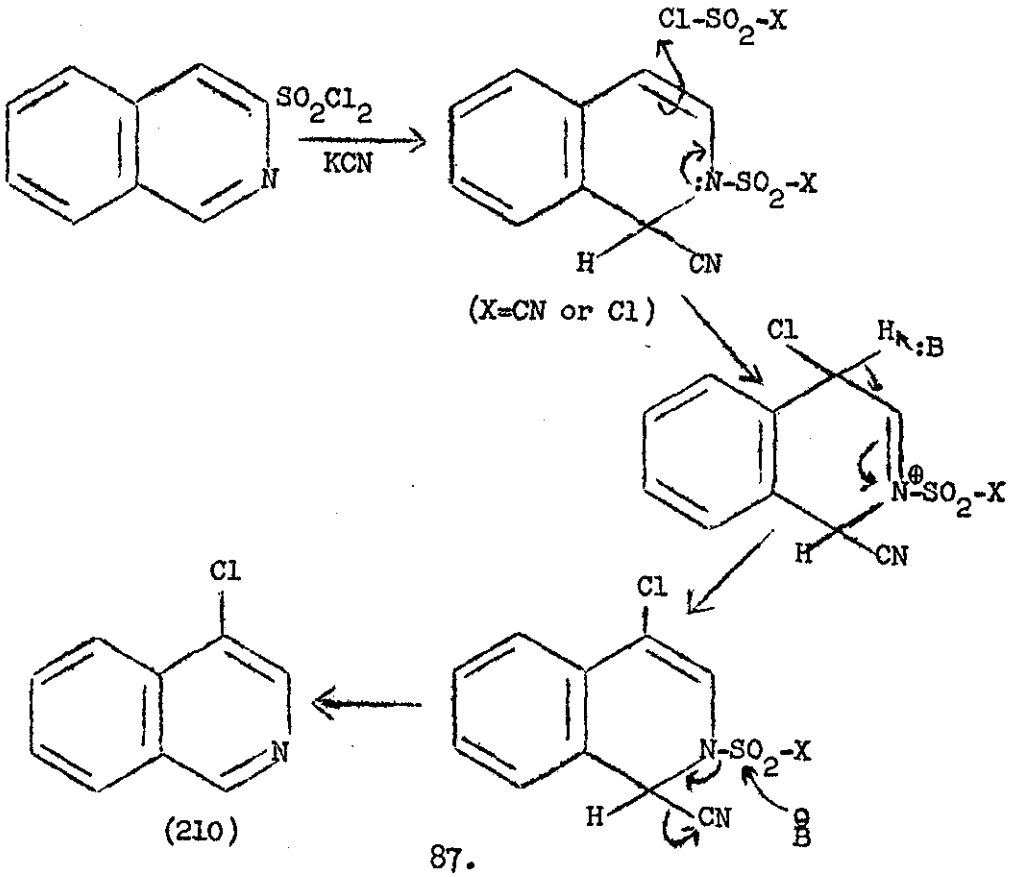
Furthermore the signal assigned to the C3-H is sharp. Had it been due to C4-H, it is likely it would have been broader due to homoallylic coupling with C8-H (as observed in isoquinoline[75]).

A possible mechanism for the formation of (208) is shown.



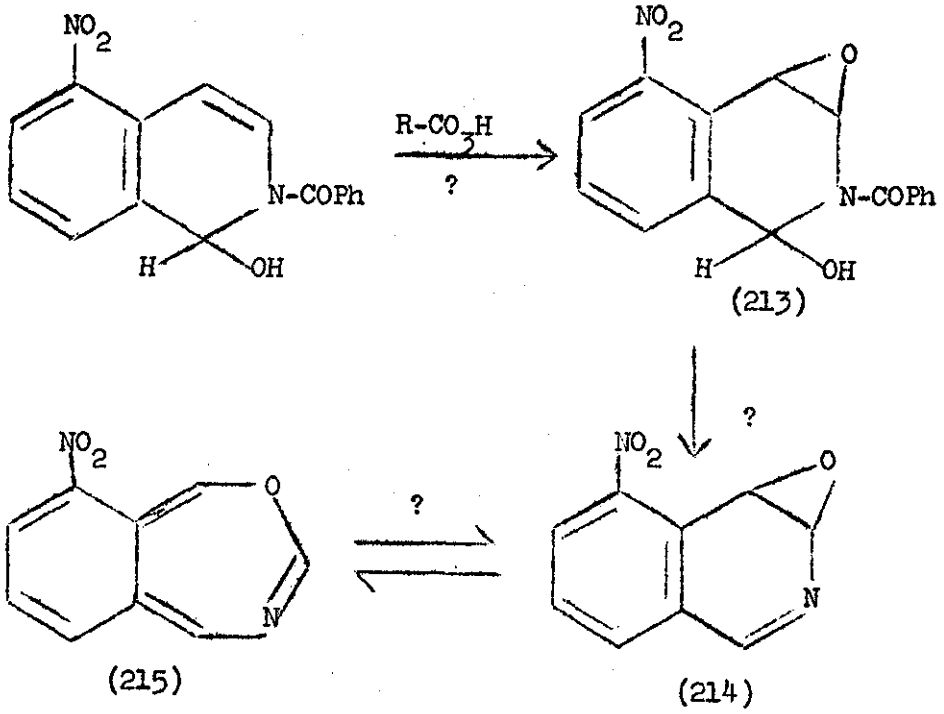
Electrophilic halogenation at C-4 again utilises the enamine character of (156). Instead of hydroxyl attack then taking place at C-3, attack proceeds at the C-4 proton perhaps giving 1,4-elimination of water and (211) and hence (208). Alternatively a two stage elimination could give (208) via (212). The 1,4-elimination would be assisted by the driving force of aromatisation. It would appear that the attack of $OH^{\ominus}$ at C-3 to give (204) is clearly preferred to C4-H attack since (208) is obtained only in 2% yield.

4-Chloroisoquinoline (210) itself has been obtained in this laboratory[108] from a reaction which affords interesting mechanistic comparison with the above. The product arises from treatment of isoquinoline with sulphuryl chloride and potassium cyanide, and the chloroisoquinoline is again found only as a minor constituent (0.3%)[108] (the major product being 1-aminocarbonyl-3-cyanoisoquinoline).[108]



Reaction with monoperphthalic acid

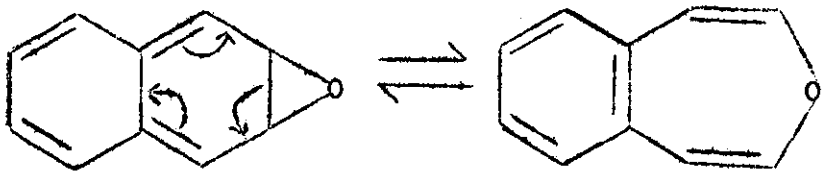
Olefins can be converted to epoxides with organic peracids,[109] and we thus proceeded to investigate such a reaction with our N-acyl pseudo-base (156) to see if the C3-C4 double bond could behave likewise to afford the epoxide (213). The attraction of this reaction was the possibility that the epoxide (213) if formed might then be converted to the novel isoquinoline 3,4-epoxide (214).



It is likely that conversion of (213) to (214) could be accomplished with some readiness because we have already demonstrated (p. 74) that the N-acyl pseudo-base system tends to break down under even mild acid or base conditions.

The preparation of an epoxide such as (214) has not yet been reported in the literature although studies on the aromatic carbocyclic analogues have been advanced.[110-113] For example,

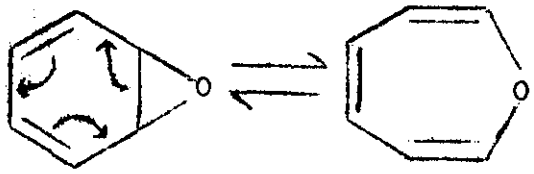
benz[d]oxepin (217), the valence tautomer of naphthalene 2,3-epoxide (216) was obtained by a modified Wittig reaction from phthalaldehyde and the bisphosphonium salt (218);[110] also p.m.r. studies indicate a fast and reversible valence tautomerisation between benzene oxide (219) and oxepin (220).[112]



(216) (217)

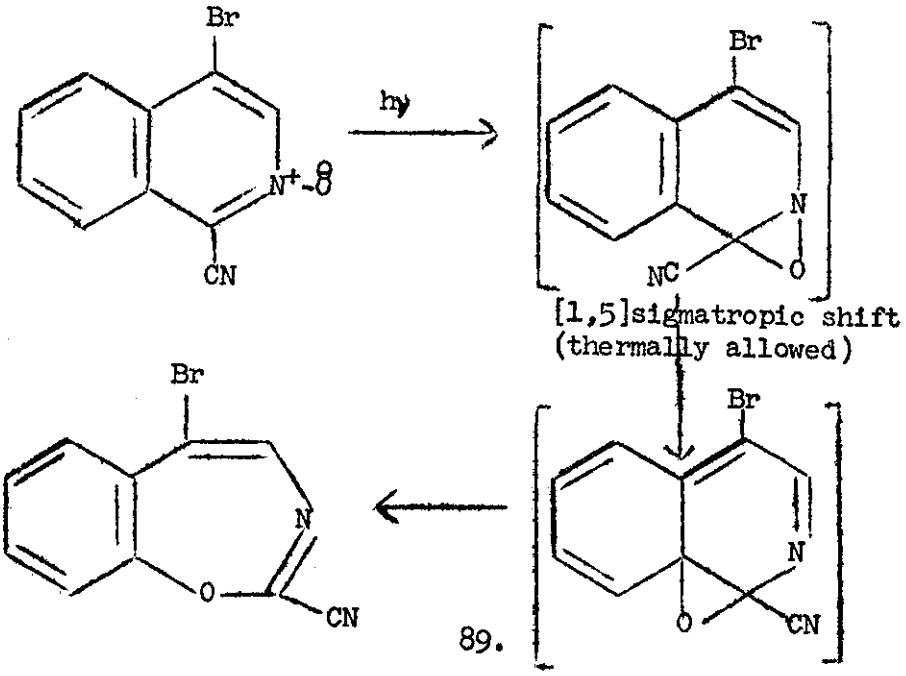
$O(CH_2.\overset{+}{P}.Ph_3)_2$

(218)



(219) (220)

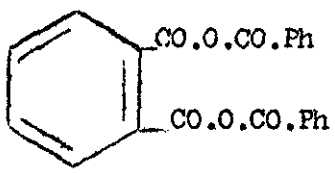
Furthermore, isoquinoline-[114] and quinoline-N-oxides[115] on ultraviolet irradiation give rise to benzoxazepines which are postulated as forming via the intermediacy of fused oxiran or azoxiran systems, for example as shown.[114]



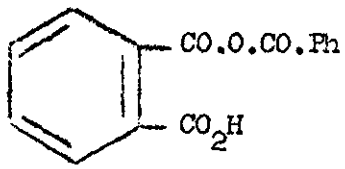
However, with our N-acyl pseudo-base we have unfortunately not succeeded in isolating any epoxide (214) or valence isomer (215), the reaction interestingly taking an alternative course.

We selected monoperphthalic acid for the study since it has the advantage of reasonable stability[116] and the reactions can be conducted in chloroform, ether or dioxan, the insoluble phthalic acid formed readily being separated.

The pseudo-base (156) was dissolved in dioxan and monoperphthalic acid solution in ether added in slight excess. The reaction mixture was kept at room temperature and its progress followed by t.l.c. After five days, the solution was filtered to remove precipitated phthalic acid and the filtrate worked up to give, after chromatography, two products. The minor product, m.p. 110° (yield 2%) appeared to be the mixed di-anhydride (221) from its spectral data: the infrared spectrum showed $\nu_{max.}$ 1790 and 1765 cm.$^{-1}$ and mass spectrum a molecular ion peak at 374.



(221)

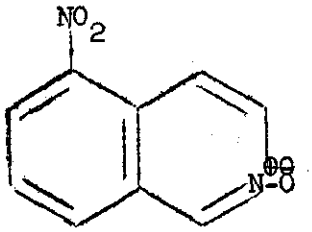


(222)

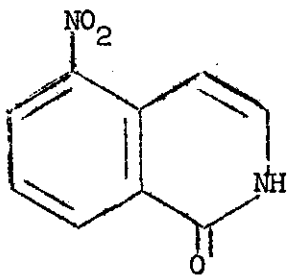
We attempted to confirm this designation, but on repeating a synthesis reported in the literature[117] to give (221) we obtained a compound m.p. 132° (lit.[117] 132°) which appeared to us to be the monoanhydride (222). It would thus appear the literature report[117] is in error.

The major product (yield, 31%) melted at 250°. Accurate

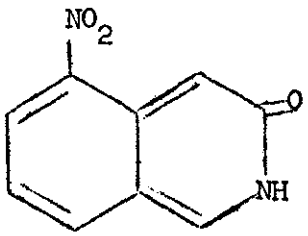
mass measurement gave the composition $C_9H_6N_2O_3$ to the product. The molecular formula suggested the product might be the epoxide (214) or another structural isomer such as 5-nitroisoquinoline N-oxide (223) or a hydroxy-5-nitroisoquinoline. The infrared spectrum included a peak at 1690 $cm.^{-1}$ indicating the presence of carbonyl in the molecule. The n.m.r. spectrum included a broad singlet at -1.8 τ which disappeared on deuteration, thus revealing the presence of OH or NH in the compound.



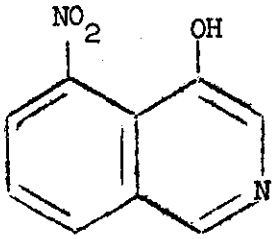
(223)



(224)



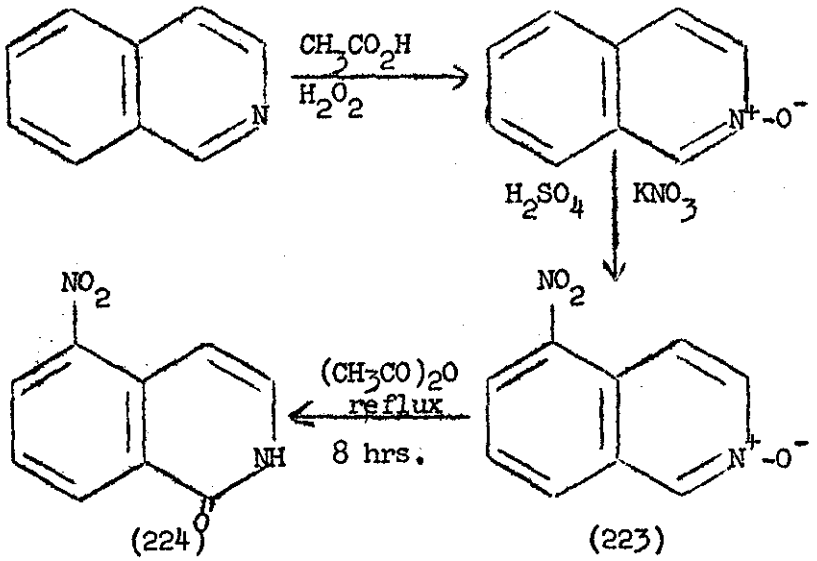
(225)



(226)

These facts appeared to rule out the epoxide (214) and benzoxazepine (215) and also the N-oxide (223). The isoquinolone form of a hydroxyisoquinoline remained, however, a possibility, the likely structures being (224) or (225) (structure 226 necessarily being in the hydroxy form). Fortunately, 5-nitroisocarbostyril (224) has been reported in the literature[118] with a melting point close to that observed for our product. We thus

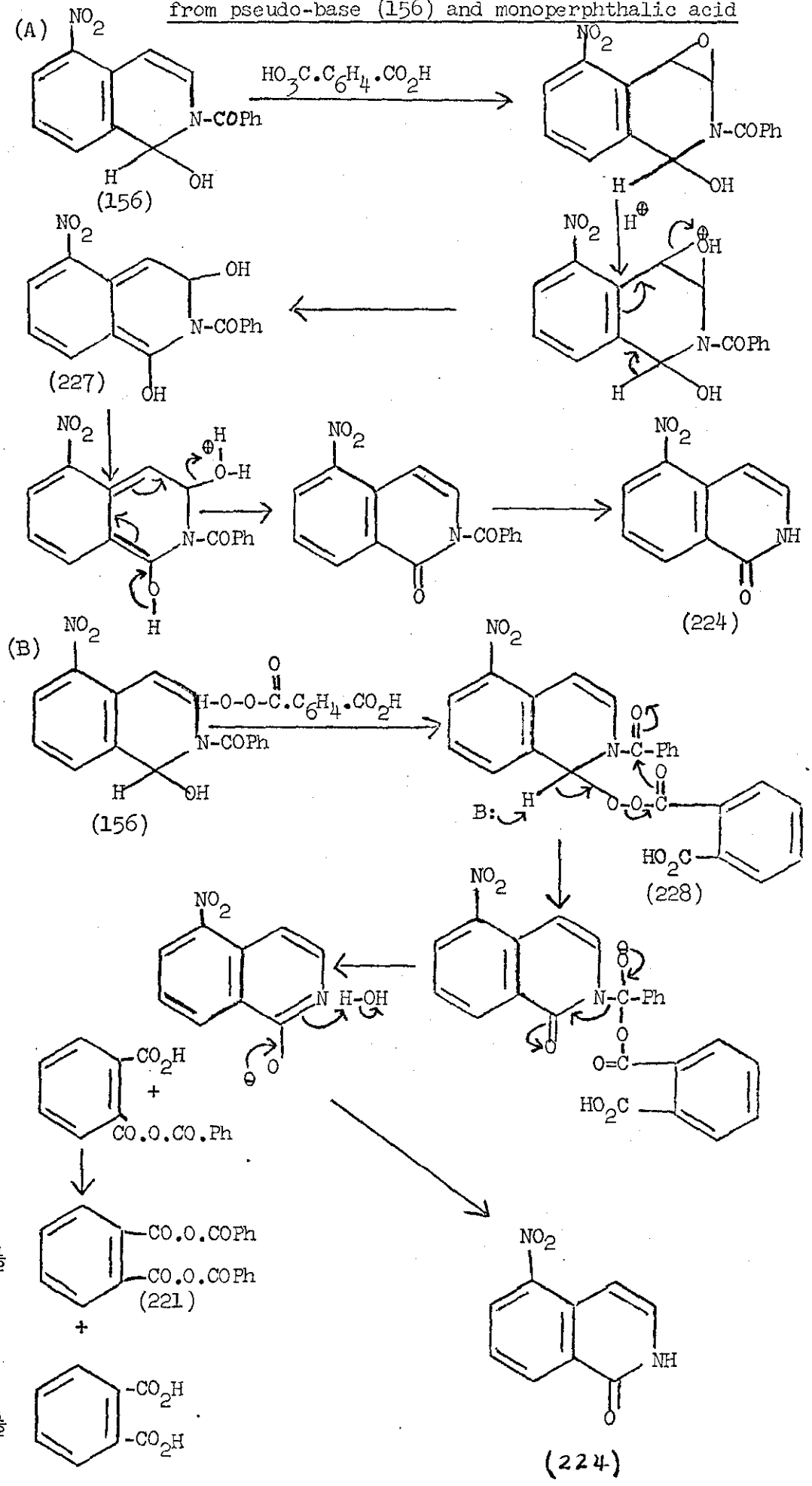
prepared 5-nitrisocarbostyril as shown,[118] by rearrangement of 5-nitroisoquinoline N-oxide.



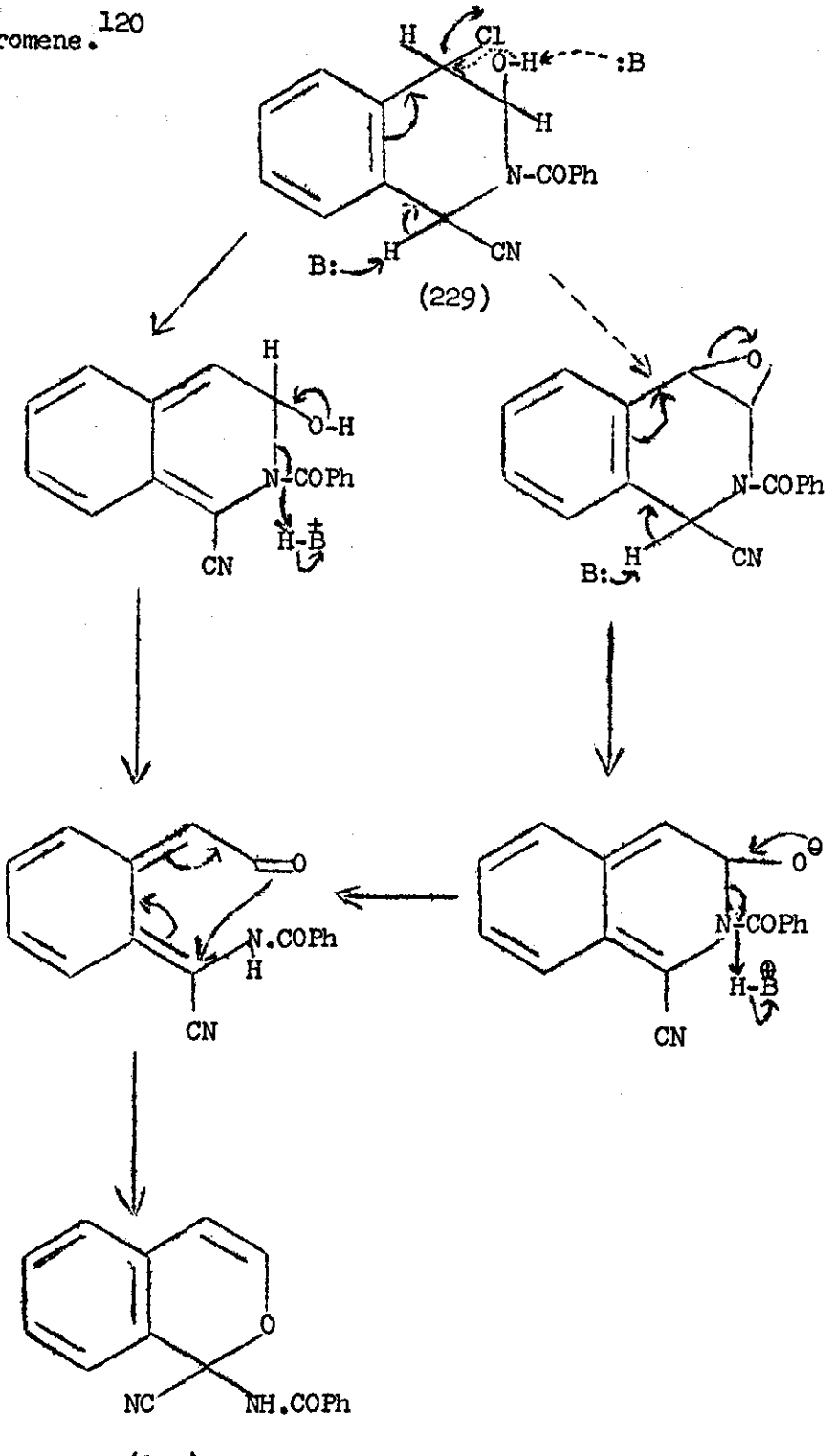
The compound (223) was synthesised by nitration of isoquinoline N-oxide using the method of Ochiai and Ikehara.[119] Comparison of infrared, ultraviolet and n.m.r. spectra demonstrated the product (224) to be identical with our compound and the mixed melting point was undepressed.

The course of the reaction can be rationalised by two possible mechanisms, (A) and (B) as shown (Scheme V p. 93).

Scheme V Possible mechanisms for the formation of 5-nitroisocarbostyril from pseudo-base (156) and monoperphthalic acid



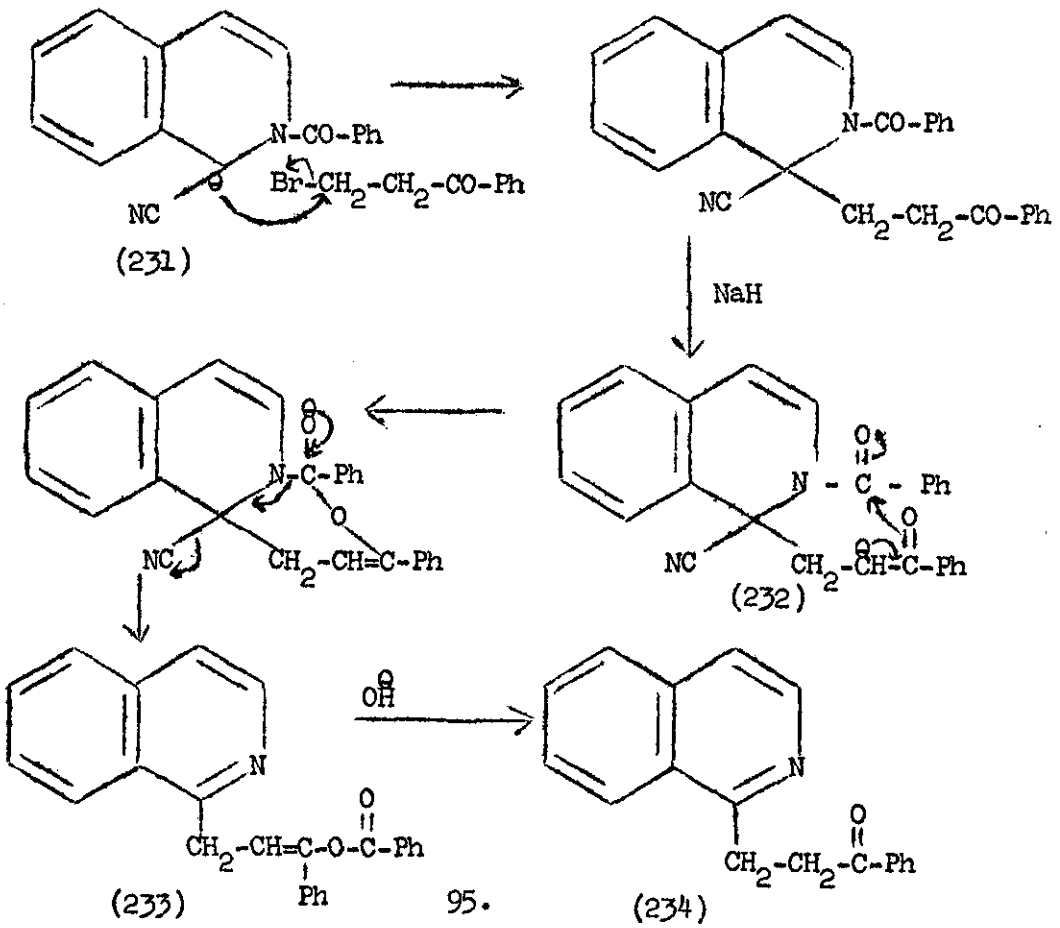
The 1,4-elimination in mechanism (A) to give an o-quinonoid intermediate (227) has an analogy, although under basic conditions, in the base catalysed dehydrochlorination of (229), resulting in the rearranged compound (230), an iso-chromene.[120]



(230)

In mechanism (B), assuming slow esterification occurs to give the perester (228), it is possible that this could break down as shown since carbonyl forming eliminations of peresters are known to proceed readily, e.g. with only weak base catalysis, e.g. pyridine.[121] It is possible, in view of our earlier discussion (p. 74), that a little of the N-acyl pseudo-base breaks down to provide 5-nitroisoquinoline as catalyst for this purpose.

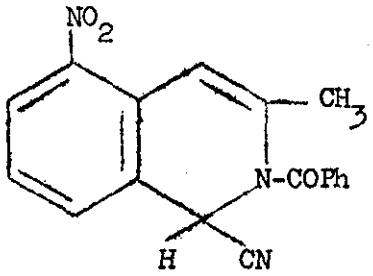
The intramolecular nucleophilic attack of the perester carbonyl oxygen on the N-acyl carbonyl carbon via a seven membered transition state (228) is to some extent mechanistically analogous to the behaviour of (232), an intermediate during the reaction of Reissert anion (231), with β-bromopropiophenone, to give the enol ester (233) and hence (234).[122] Mechanism (B) also could account for the formation of the dianhydride (221).



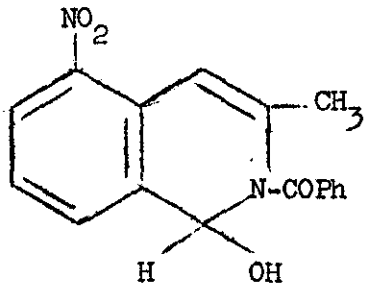
(c) Investigation of the Synthesis of other N-Acyl Pseudo-Base Systems

(i) Reissert reaction with 3-methyl-5-nitroisoquinoline

We further set out to investigate the synthesis of some other potential N-acyl pseudo-base systems. Popp and Blount[81] have reported the preparation of 3-methyl-5-nitroisoquinoline Reissert compound (235) in 83% yield but in view of our results with 5-nitroisoquinoline we considered the reaction was worth repeating.



(235)



(236)

After work up and chromatography we obtained Reissert compound (235) in 57% yield and, pleasingly, some other material which analysed for the new pseudo-base (236), in 9% yield. The structure of (236) was established by infrared ($\nu_{max.}$ 3430 cm.$^{-1}$ (OH), 1650 cm.$^{-1}$(N-C=O); n.m.r. (1.8 - 2.9 τ, multiplet, 8H, aromatic; 3.11 τ, quartet, C4-H, $J_{C4-H,C3-Me}$= 1.5Hz; 3.43 τ, doublet, C1-H, $J_{C1-H,C1-OH}$=6Hz; 5.3 τ, doublet, C1-OH, $J_{C1-OH,C1-H}$=6Hz, 8.1 τ, 3H, doublet, $J_{C3-Me,C4-H}$= 1.5Hz); mass spectrum (molecular ion peak at 310) and finally by elemental analysis.

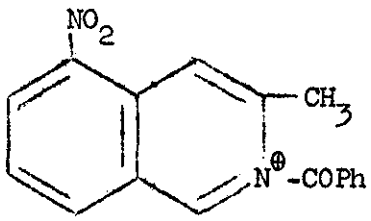
The lower frequency of the amidic carbonyl (1650 cm.$^{-1}$) in the infrared spectrum is possibly due to the steric effect of C3-Me group, causing the C=O group to lie predominantly on the opposite side i.e. in close proximity to the C1-OH and

thus permit hydrogen-bonding.

The N-acyl pseudo-base (236) also resulted from use of aqueous potassium hydroxide (40% yield) or even water alone (37% yield) in the Reissert reaction, i.e. with the exclusion of cyanide. However, it should be noted that in all the three reactions mentioned above, 50-60% of the starting material was recovered and the yields are based on the amount of isoquinoline recovered.

It was interesting to note that the pseudo-base (236) is unstable specially in the presence of air and slowly decomposes to the starting material. The decomposition is catalysed if a small amount of the starting material (the isoquinoline) is present.

The lower yield of the pseudo-base (236) in the Reissert reaction could be due to the inductive effect of 3-methyl group militating against the electron withdrawing character of 5-nitro group so that the effective hardness of C-1 centre in the quaternary intermediate (237) is reduced, thereby reducing the attack of hard base H_2O (or $\overset{\ominus}{O}H$).

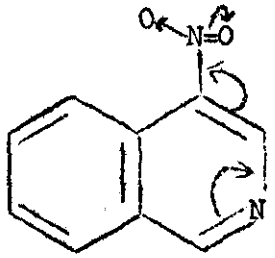


(237)

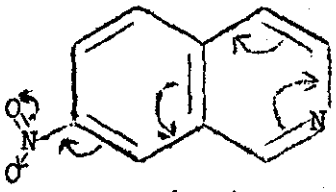
(ii) Reissert reaction with 4-nitro- and 7-nitro-isoquinoline and isoquinoline-5-sulphonic acid

By analogy with 5-nitroisoquinoline one would expect 4-nitroisoquinoline (238), 7-nitroisoquinoline (239) and isoquinoline-5-sulphonic acid (240) to yield pseudo-bases because in these derivatives the electron withdrawing groups are

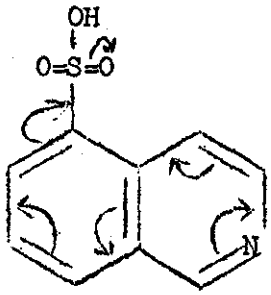
in the suitable positions to increase the positive character of C-1 atom as shown.



(238)

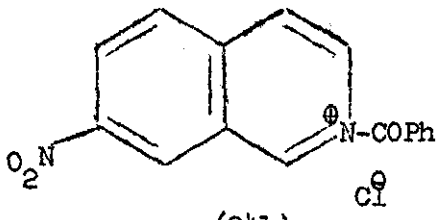


(239)



(240)

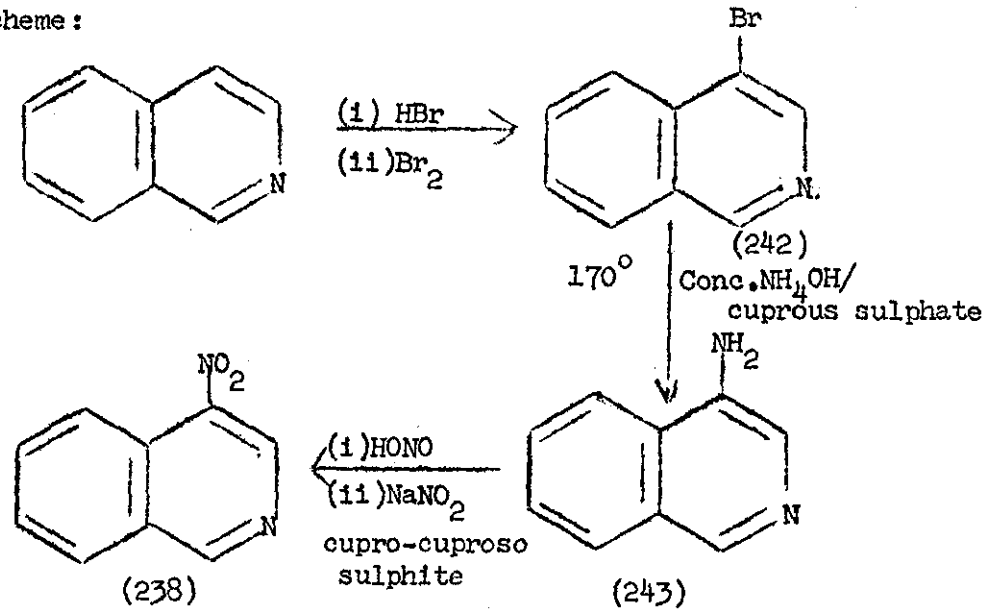
However, when subjected to the Reissert reaction none of these compounds afforded any pseudo-base or Reissert compound. In all the experiments, the starting materials were recovered except in the case of 7-nitroisoquinoline which also gave a small amount of what appeared to be the quaternary salt (241).



(241)

Treatment of (241) with potassium hydroxide resulted in the liberation of starting material.

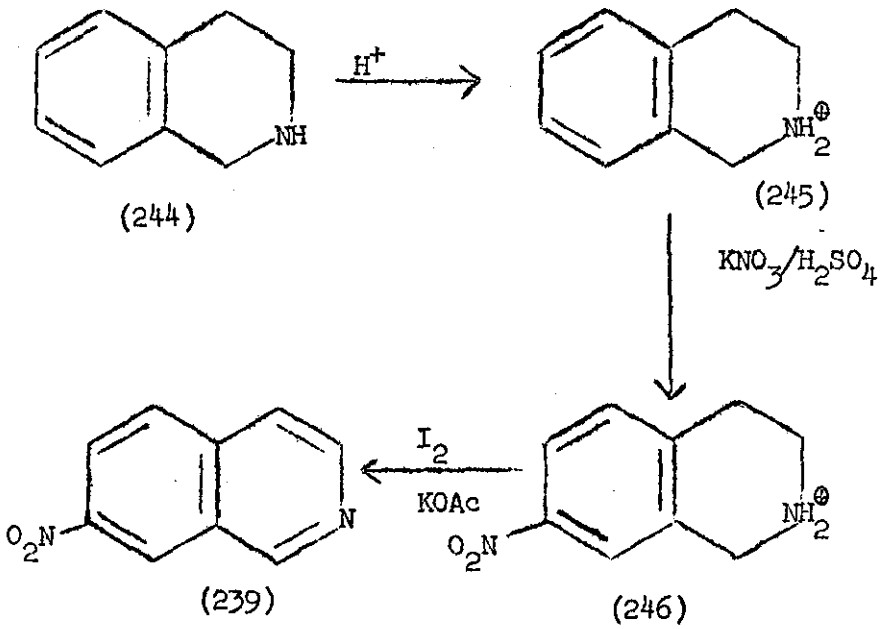
4-Nitroisoquinoline was prepared according to the following scheme:



4-Bromoisoquinoline (242) was prepared according to the method of Bergstrom and Rodda,[123] by heating isoquinoline hydrobromide with bromine 170-180°. The bromination at C-4 constitutes one of the rare examples in the isoquinoline series of direct substitution in the hetero-ring (as the usual positions for electrophilic substitutions are 5 and 8).

Nucleophilic substitution by amide ion on (242) led to 4-amino-isoquinoline (243). This was performed by heating (242) with concentrated ammonium hydroxide and hydrated cuprous sulphate in a shaking autoclave.[124] When (243) was subjected to the Sandmeyer conditions, it gave 4-nitroisoquinoline[125] in the presence of cupro-cuproso sulphite, $Cu^{I}_{2}Cu^{II}_{2}(SO_3)_3$.

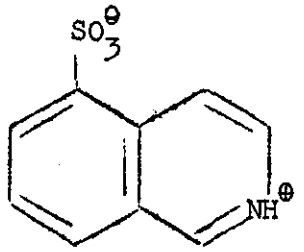
7-Nitroisoquinoline was prepared by the following sequence:



Nitration of the 1,2,3,4-tetrahydroisoquinoline (244) gave the 7-nitro derivative (246)[126] presumably through substitution in the cation (245), which is more highly activated in the 5- and 7-positions owing to the unfavourable inductive effect

of the $-\overset{+}{N}H_2-$ group. Compound (246) was dehydrogenated in 25% yield using iodine and potassium acetate, by the method of Potter and Taylor,[127] to give (239).

The failure of 4-nitroisoquinoline to give pseudo-base or Reissert compound may be, in part, due to its weak basicity (pK_a = 1.35)[125] so that the initial step, the formation of the quaternary salt, does not take place. In the case of the 5-sulphonic acid it appears that the isoquinoline is alread· present in the salt form such as (247) and does not react further. Attempts to make the ester were unsuccessful.

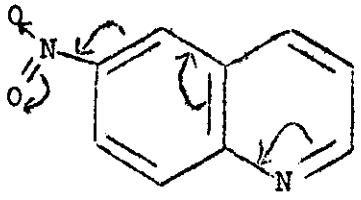


(247)

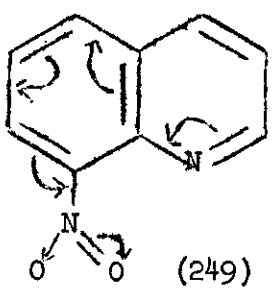
7-Nitroisoquinoline does yield the quaternary salt (241) but why it does not proceed further is not understood. Possibly by careful variation of the conditions one might achieve reaction.

(iii) Reissert reaction with 6-Nitro- and 8-Nitroquinoline

We considered that the presence of a nitro group at position 6 or 8 in quinoline (248 and 249) might increase the hardness of C2-position and thus the Reissert reaction with these compounds yield pseudo-bases.



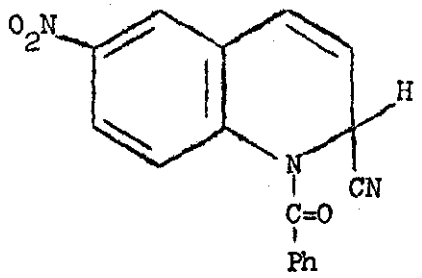
(248)



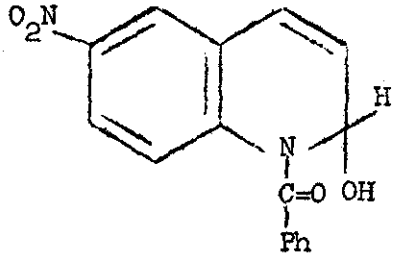
(249)

With 6-nitroquinoline

The Reissert reaction with 6-nitroquinoline has been reported[128] to give the normal Reissert compound (250) in 29% yield. We repeated the experiment under similar conditions, stirring for eight hours and obtained only the Reissert compound (250), in practically the same yield.



(250)

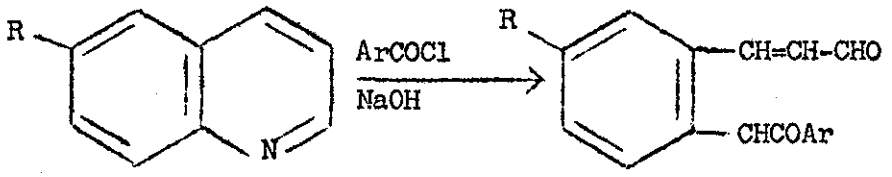


(251)

We then repeated the reaction using potassium hydroxide in place of cyanide and obtained a product (32% yield) which was slow moving on t.l.c. and was shown subsequently to be the required pseudo-base, 1-benzoyl-2-hydroxy-5-nitro-1,2-dihydroquinoline (251). About 90% unchanged quinoline was recovered. The structure of (251) was in accord with the spectral data. The infrared spectrum showed absorption at 3320 $cm.^{-1}$ (OH) and 1643 $cm.^{-1}$ (N-C=O). The n.m.r. spectrum included a broad singlet at 3.5 τ which disappeared on deuteration. The mass spectrum (molecular ion peak at 296) and elemental analysis confirmed the molecular formula. The compound (251) therefore represents the first example of a cyclic N-acyl pseudo-base in the quinoline series.

As mentioned earlier (p. 67) Reissert himself claimed[1] to

have formed the N-acyl pseudo-base of unsubstituted quinoline but this was subsequently shown[2,84,85] to be the open chain form (253, R=H) and some other examples have been demonstrated by Elliott[84] (252 ⟶ 253) with 6-substituted quinolines, as shown :-



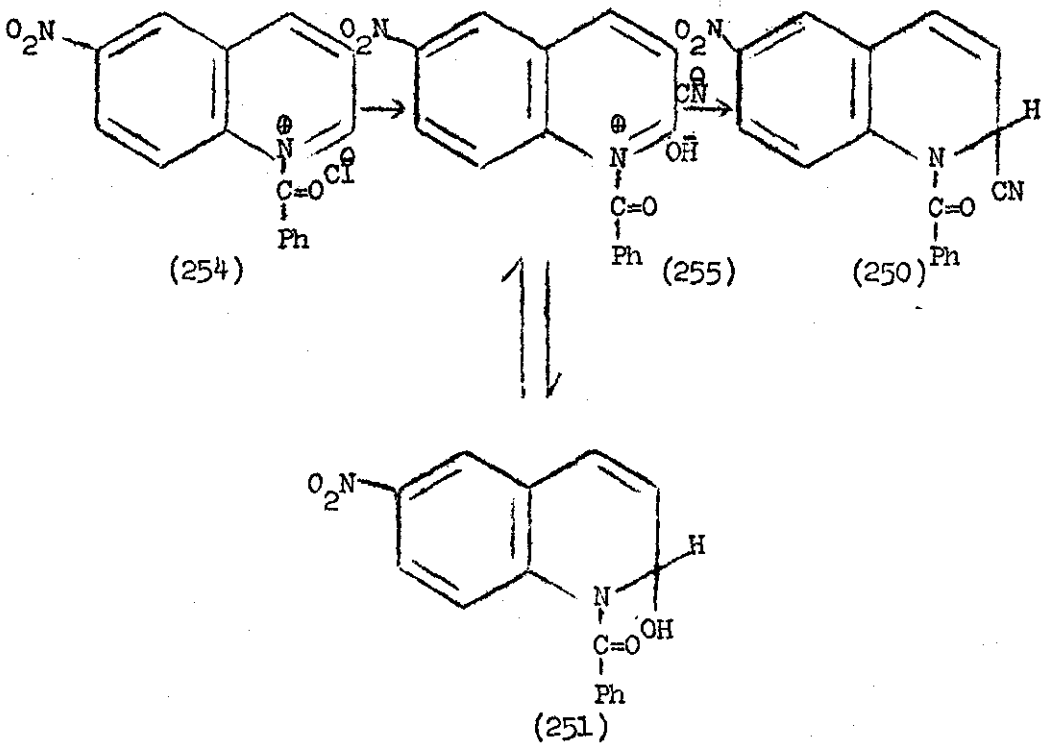
(252, R=H,-CH_3,-Cl -OCH_3,-Br) (253)

Elliott, however, failed to isolate any product when using 6-nitroquinoline.[84] That our product was the cyclic structure (251) and not the open chain aldehyde tautomer (253, R=NO_2,Ar=Ph) was evidenced by the infrared spectrum and by the lack of an aldehyde proton signal in the n.m.r.

After having obtained the authentic pseudo-base (251) in the absence of cyanide we again repeated the original Reissert reaction (cyanide present) and followed its progress by t.l.c. After the shorter time of three hours a spot corresponding in Rf value to the pseudo-base had clearly built up, and work up at that stage gave the pseudo-base (43% yield), identical to (251) by infra-red spectrum and mixed melting point. The yield is based on recovered starting material (90%).

From this experiment we conclude that the pseudo-base (251) is in equilibrium in solution with the intermediate (255) and on stirring for a longer time is slowly transformed to the Reissert compound (250) via the ionic form (255). Thus, in this case, the Reissert compound (250) is the thermodynamically controlled

product (but this need not necessarily be the case in the other pseudo-base reactions).

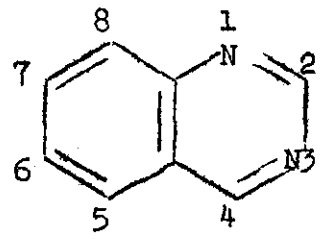


In view of the large amounts of starting material recovered, it appears that the C=O of the N-acyl group in (254) is a slightly harder centre than the C-2 so that the hard base H_2O ($O\overset{\ominus}{H}$) preferentially attacks the C=O group to reform quinoline and sodium benzoate.

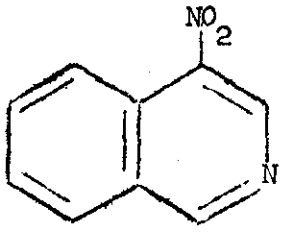
With 8-nitroquinoline

The attempted Reissert reaction with 8-nitroquinoline (249) gave back the starting material in almost quantitative yield. In this case the steric hindrance of the nitro group in 8-position might explain the failure of the reaction, since there are examples in the literature of the normal Reissert reaction being unsuccessful in 8-substituted cases.[9,128]

(d) Reissert reaction with Quinazoline

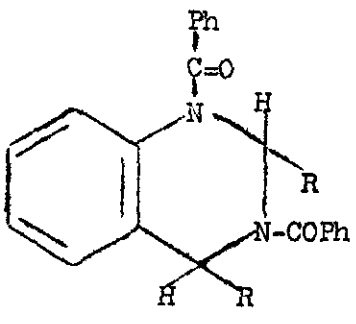


(256)

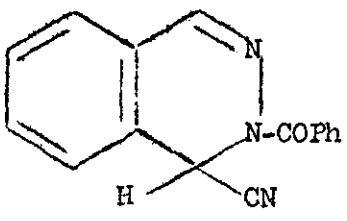


(238)

We investigated the use of quinazoline (256) as a potential N-acyl pseudo-base precursor because it is considered [129] that the N-1 in (256) has electron withdrawing properties comparable to those of the nitro group in 4-nitroisoquinoline (238). As discussed on p. 100, 4-nitroisoquinoline, due to its low pKa value, failed to react in the Reissert reaction, but quinazoline with pKa = 3.51[130] was thought more promising. The system was further of interest since, as already mentioned in the Introduction (p. 2), relatively little study has been carried out concerning the Reissert reaction with diazaheterocyclic systems.[6] It was thus of interest to see if quinazoline could yield the di-Reissert structure (257). A related heterocyclic system, phthalazine, has been reported[4] to give mono-Reissert compound (258) even when excess of benzoyl chloride and potassium cyanide are employed.[4]

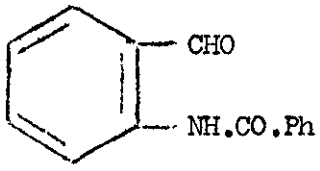


(257,R=CN or OH)



(258)

We attempted the Reissert reaction of quinazoline by the standard procedure[8] with benzoyl chloride (4 moles) and potassium cyanide (6 moles). After work-up and chromatography, we obtained as major product a low melting solid (m.p. 73°) in 31% yield. Elemental analysis and accurate mass measurement gave the composition as $C_{14}H_{11}NO_2$ which indicated the product was neither the normal mono- or di-Reissert compound nor the mono- or di-N-acyl pseudo-base. The n.m.r. showed a split singlet (J=0.8Hz) at 0.04 τ, that this was probably an aldehyde proton was indicated by its persistence on deuterium exchange. Further, a broad singlet at -2.1 τ could be attributed to an NH group as it disappeared with difficulty on shaking with deuterium oxide. The infrared spectrum gave a strong peak at 1675 cm.$^{-1}$ (with shoulders at 1660 cm.$^{-1}$ and 1695 cm.$^{-1}$) presumably due to the carbonyl absorption of the aldehyde (supported by the characteristic aldehyde C-H stretch bands at 2760 cm.$^{-1}$ and 2850 cm.$^{-1}$) and of an amide (supported by the NH absorption at 3300 cm.$^{-1}$). A possible structure which would fit the analytical and spectroscopic data is o-formylbenzanilide (259).

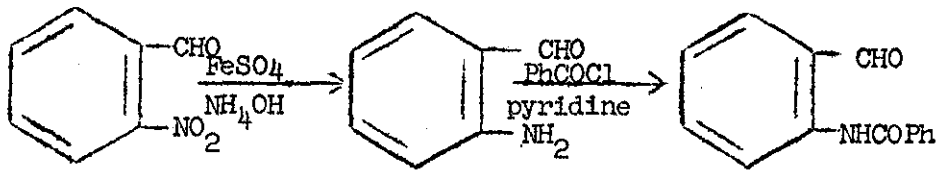


(259)

The splitting in the proton signal of the CHO, by interaction with a ring proton has also been observed[131] in other o-substituted benzaldehydes. The size of the splitting varies

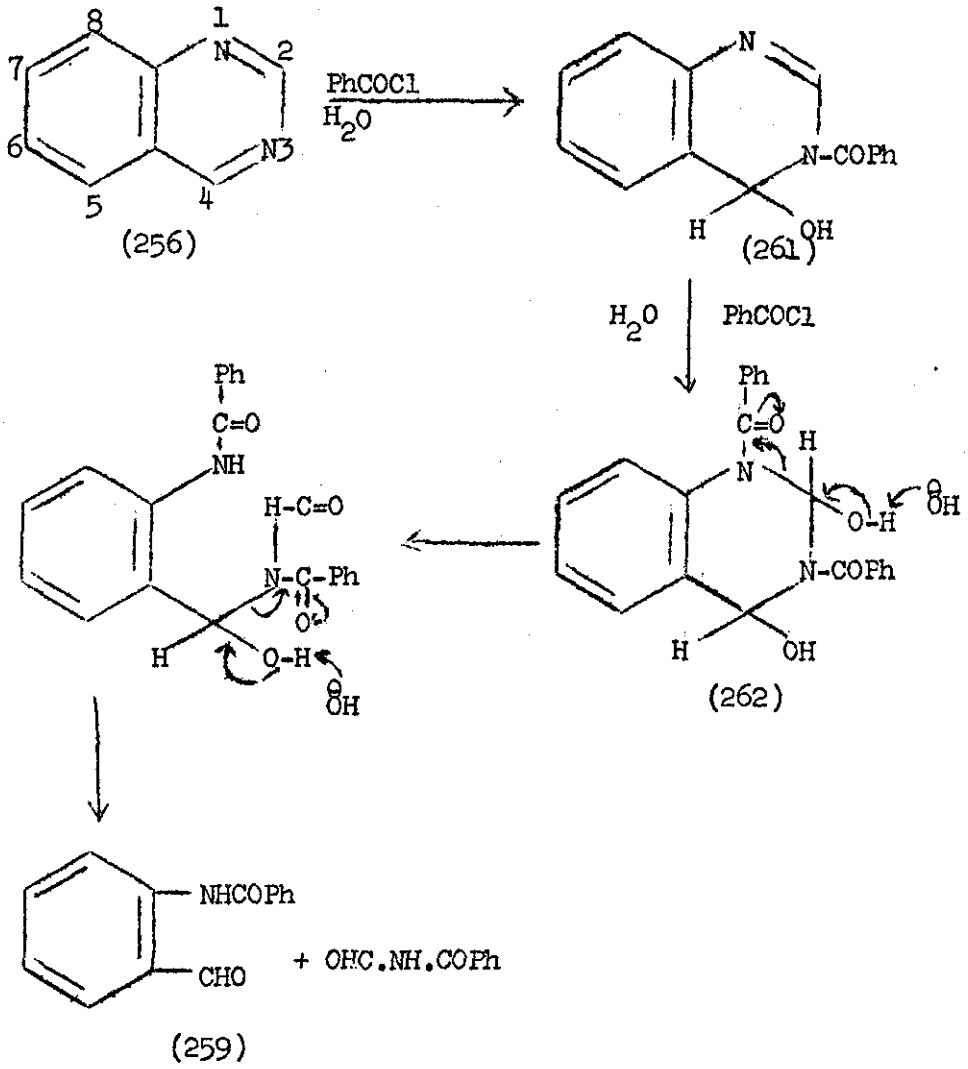
from 0.31 Hz to 0.80Hz depending on the nature of the o-substituent.[131]

The compound (259) is known[132] and the reported melting point, 73°, coincides with that shown by our product. However, we sought to confirm the designation by preparing some authentic o-formylbenzanilide. o-Nitrobenzaldehyde was reduced with ferrous sulphate and ammonia according to the method of Smith and Opie[133] to give (260) which on benzoylation in pyridine afforded o-formylbenzanilide (259), identical with our product (spectral comparison and mixed melting point).



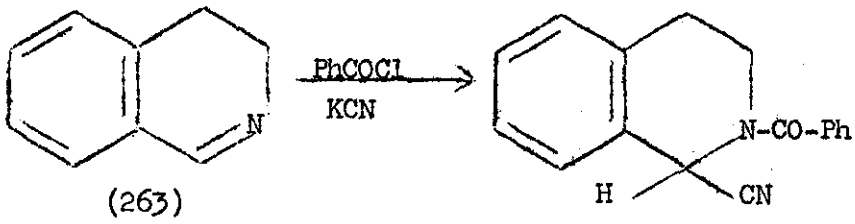
(260) (259)

The mechanism for the above reaction must involve the opening of the quinazoline ring. We suggest the following steps (p.107):



The N-3 (isoquinoline type, pKa=5.42) is considered[134] slightly more basic than N-1 (quinoline type, pKa=4.90) and thus would be quaternised first, and this could be followed by the attack of $\overset{\ominus}{O}H$ or H-O-H) at C-4 to give the mono N-acyl pseudo-base (261). We postulate the attack of $\overset{\ominus}{O}H$ (or H_2O)rather than $\overset{\ominus}{C}N$ due to the inductive electron withdrawing character of N at 1-position. Another molecule of benzoyl chloride now adds to the Schiff base N-1 to give the quaternary salt (not shown) which is again attacked, at C-2, by $\overset{\ominus}{O}H$ (or H_2O) due to electron withdrawal by $-\overset{\oplus}{N}=$ at 1-position and by the N at

the 3-position. Such addition across the double bond in a dihydro structure (such as 261) is not unreasonable since 3,4-dihydroisoquinoline (263) has been shown[135] to yield the dihydro Reissert compound (264).



(263) (264)

The carbinolamide structures in the tetrahydroquinazoline intermediate (262) can now undergo the ring opening to give (259), the 1,2 bond possibly breaking first by analogy with the ring opening in the case of quinoline (p. 67)[2,84,85], followed by the 3,4-bond, the N-3 now carrying two (electron withdrawing) carbonyls to promote cleavage.

The mechanism outlined above does not involve the $CN^{\ominus}$ nucleophile. If this hypothesis is correct then the use of potassium hydroxide or even water alone in the Reissert reaction should yield the same product viz (259). Indeed when the reaction was repeated in the absence of cyanide (i) with potassium hydroxide and (ii) with water only, in both cases the o-formylbenzanilide was formed in 73% and 83% yield respectively.

Attempts to isolate any of the intermediates by using lesser amounts of reagents were unsuccessful, starting material being recovered along with the same product (259).

3. Stereochemistry and N.m.r. Spectra of Reissert Systems

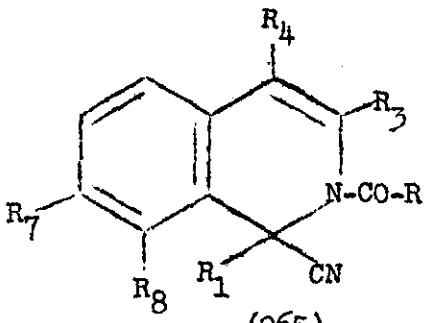
N.m.r. spectroscopy has been increasingly used over recent years to solve problems of stereochemistry of organic compounds.[136] The n.m.r. spectra of Reissert compounds has not been discussed in any detail in the literature. We have, therefore, examined the n.m.r. spectra of a large number of known and new isoquinoline and quinoline Reissert compounds and used this information to comment on the stereochemistry of these systems.

(a) Isoquinoline Reissert Compounds

As indicated in Table IV (p.110) we have observed that the signal attributable to the C-1 proton occurs as a finely split singlet in all cases so far examined by us. Correspondingly the expected doublet for the C-3 proton is also finely split by the same J value. We thus considered that long-range coupling was occurring between the C-1 and C-3 protons. The observation of this long-range coupling phenomenon was made jointly with J.R.Kershaw[137] in this laboratory and for the sake of completeness compounds examined by him (i.e. compounds 265k⟶265p) are included in the Table IV. We have jointly published some of these observations in a preliminary communication.[97] Dr.Kershaw did not subsequently examine the spectra of any further isoquinoline Reissert compounds or quinoline Reissert compounds. The long-range C1-C3 coupling was confirmed by spin decoupling and by replacement of the C-1 proton by deuterium in (265a), i.e. (265k) when the n.m.r. spectrum showed only a doublet for the C-3 proton in place of a quartet.[137] The n.m.r. spectrum

Table IV

N.m.r. spectra* details of some isoquinoline Reissert compounds (265)



(265)

265	R	R_1	R_3	R_4	R_7	R_8	C-1 proton τ	C-3 proton τ	C-4 proton τ	$J_{1,3}$ Hz	$J_{3,4}$ Hz
a	$-C_6H_5$	H	H	H	H	H	3.42D	3.36Q	3.94D	0.80	8.0
b	p-CH_3-C_6H_4	H	H	H	H	H	3.46D	3.33Q	3.96D	0.80	8.0
c	o-NO_2-C_6H_4	H	H	H	H	H	3.19D	3.76Q	4.02D	0.85	8.0
d	p-CH_3-C_6H_4	H	H	H	H	OCOPh	3.33D	3.27Q	3.95D	0.80	8.0
e	-CH=CH-Ph	H	H	H	H	H	3.31D	3.04Q	3.83D	0.90	8.0
f	$-CH_3$	H	H	H	H	H	3.35D	3.28Q	3.96D	0.80	8.0
g	$-CH=CH_2$	H	H	H	H	H	3.40D	3.16Q	3.46D	0.85	8.0
h	$-CH=CH-CH_3$	H	H	H	H	H	3.38D	3.12Q	3.88D	0.85	8.0
i	$-CH=CH-CH_3$	H	CH_3	H	H	H	3.38S	-	3.69Q	-	1.5‡
j	$-CH=C(CH_3)_2$	H	H	H	H	H	3.43D	3.21Q	4.03D	0.80	8.0
k**	$-C_6H_5$	D	H	H	H	H	-	3.36D	3.95D	-	8.0
l	$-C_6H_5$	H	H	Br	H	H	3.44D	3.00D	-	0.90	-
m	$-C_6H_5$	H	H	H	OCH_3	OCH_3	3.06D	3.39Q	4.00D	0.90	8.0
n	$-C_6H_5$	H	CH_3	H	H	H	3.50S	-	3.77Q	-	1.5‡
o	p-CH_3-C_6H_4	H	CH_3	H	H	H	3.50S	-	3.67Q	-	1.5‡
p	p-CH_3O-C_6H_4	H	H	H	OCH_3	p-CH_3O-C_6H_4-CO-O-	3.40D	3.34Q	3.94D	0.80	8.0

S = Singlet: D = Doublet: Q = Quartet

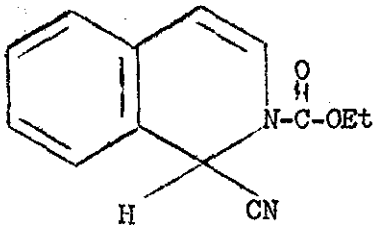
* Recorded with $CDCl_3$ as solvent at 60 MHz, except for n at 40 MHz

** 265k - 265p spectra reported by J.R.Kershaw.[97, 137]

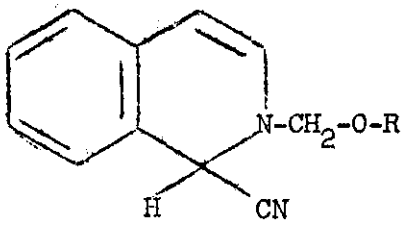
‡ Values for $J_{C4\text{-}H,C3\text{-}Me}$

of N-benzoyl-1,2-dihydroisoquinaldonitrile (265a) is reproduced in Figure II.

Subsequent to publication of our results, long- range coupling between the C-1 and C-3 protons has been reported for some other Reissert analogues *viz.* the N-ethoxycarbonyl derivative (266)[87] and N-alkyl Reissert compound (267)[36]

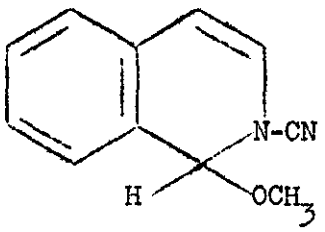


(266)

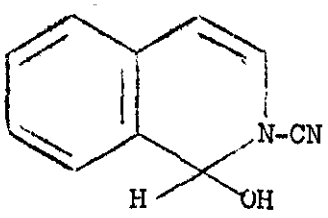


(267)

Bramley and Johnson[85] surprisingly report zero coupling between the C-1 and C-3 protons in 1-methoxy-N-cyano-1,2-dihydroisoquinoline (268). To re-examine their result, therefore, we synthesised (268)[85] *via* the hydroxy-analogue (269)[85] whose n.m.r. they do not discuss. In each case, we found long-range coupling of $J_{1,3}$= 1.0 Hz, clearly in evidence.



(268)



(269)

Long-range coupling between protons separated by four or more sigma bonds has been reported for a number of compounds [138,139] and it appears that a near planar zig-zag arrangement of the atoms concerned is required.[140,141] The value of the

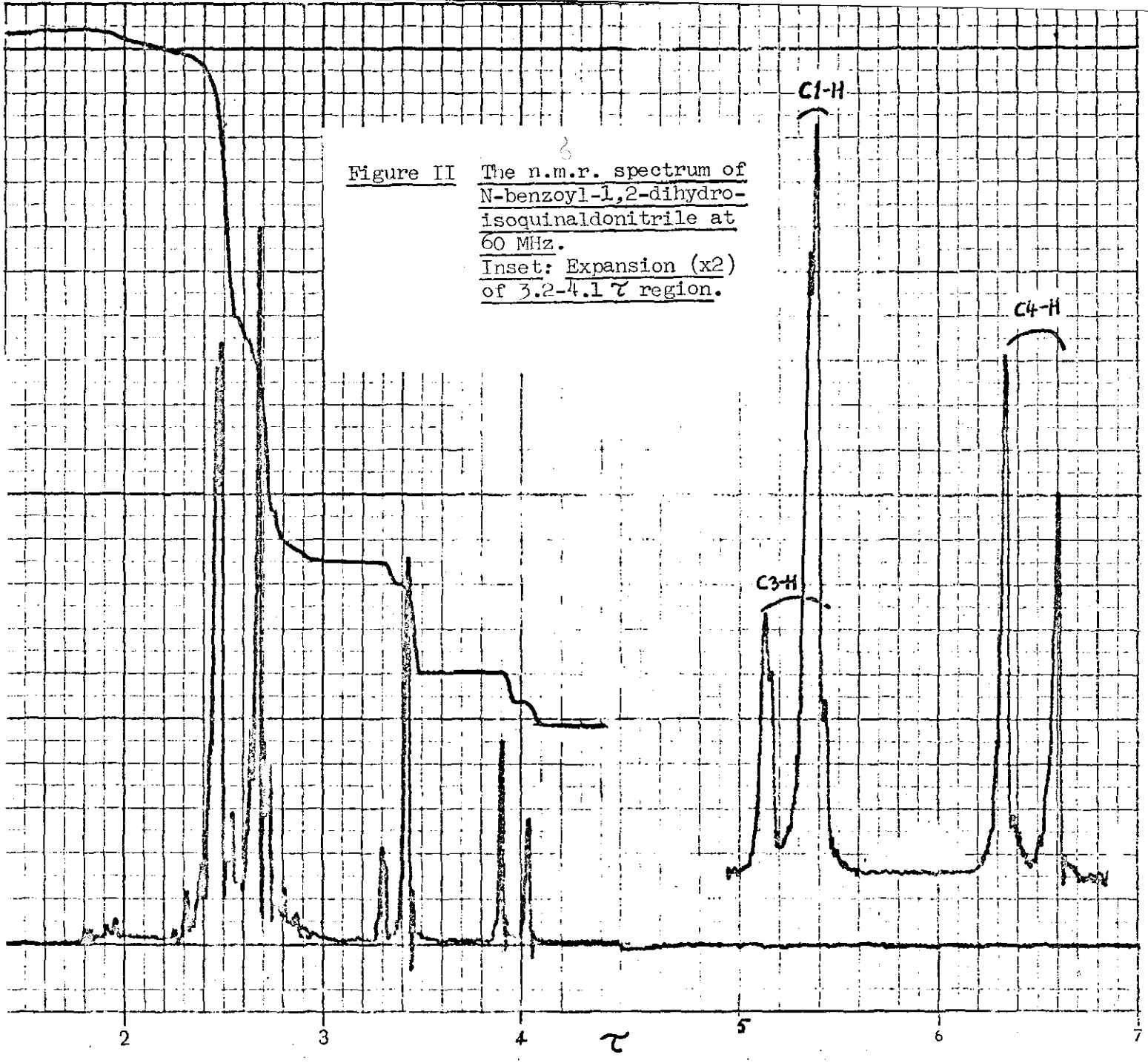
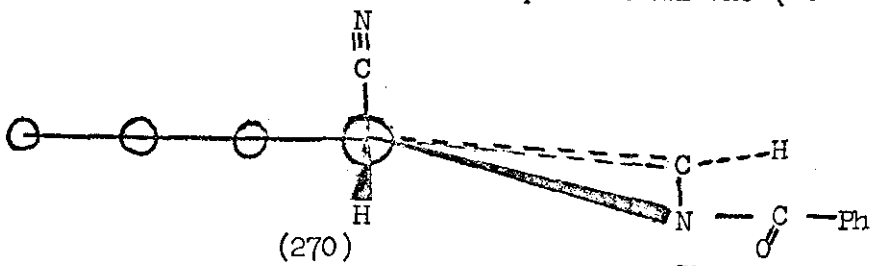
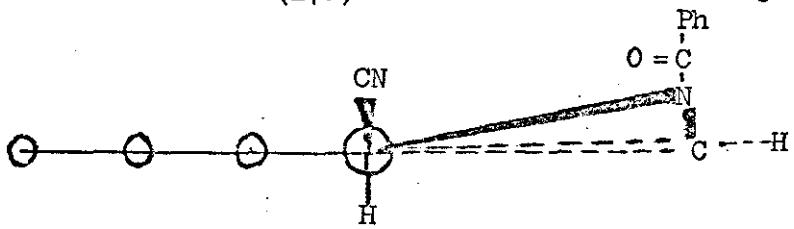


Figure II The n.m.r. spectrum of N-benzoyl-1,2-dihydro-isoquinaldonitrile at 60 MHz.
Inset: Expansion (x2) of 3.2-4.1 τ region.

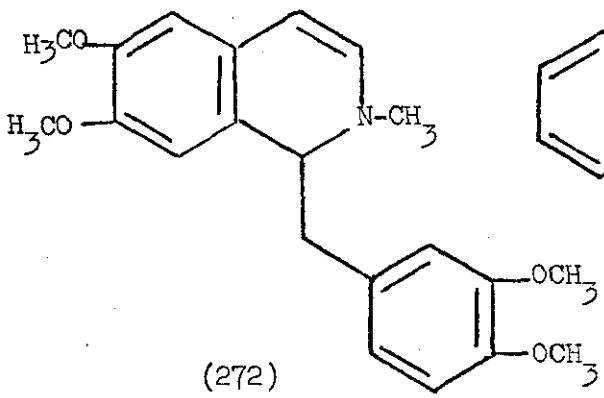
coupling constant in Reissert compounds suggests that the five atoms involved are adopting a conformation near planar, but not completely so. For a planar arrangement the coupling constant usually falls within the range 1-3 Hz.[141] For an unstrained system Barfield has calculated a maximum value of 1.2 Hz.[142] The presence of coupling in Reissert compounds, therefore indicates that the hydrogen atom at C-1 prefers to adopt a quasi-equatorial conformation and the nitrile substituent a quasi-axial one (as in 270)



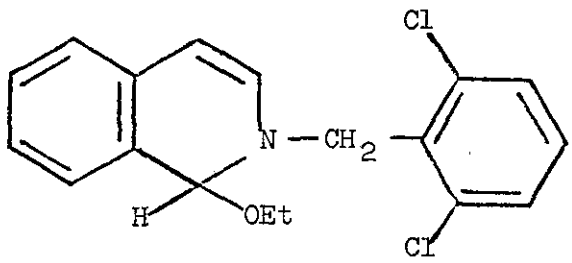
(270)



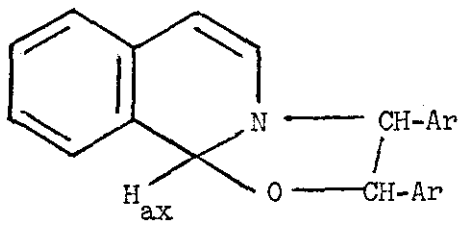
(271)



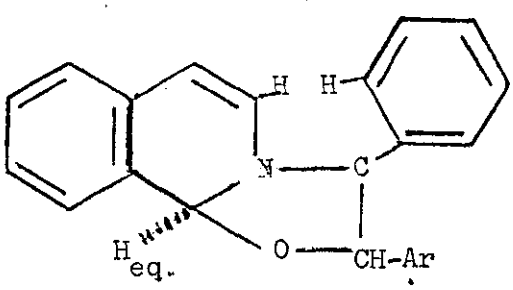
(272)



(273)



(274)



(275)

This conformation with a quasi-equatorial C-1 hydrogen is similar to that suggested recently for another 1,2-dihydroisoquinoline, viz. 1,2-dihydro-N-methylpapaverine (272)[143] and it would also appear to be the case for (273) which shows similar long-range coupling (1.25 Hz).[144] Models show in each case that non-bonded interactions are minimised by the C-1 substituent occupying the quasi-axial position. If the C-1 hydrogen were quasi-axial in Reissert compound (271) then steric interactions would result between the quasi-equatorial cyanide and the amidic phenyl ring. In the 1,2-dihydropapaverine (272) a quasi-equatorial 1-benzyl group would present steric encumbrance with the C-8 proton and also the N-methyl group. Likewise the quasi-axial C-1 ethoxy group in (273) minimises non-bonded interactions between the ortho chlorines and the oxygen of the ethoxy group.

It is interesting to note, however, that the C-1 hydrogen must be adopting the quasi-axial position when the carbon atom -1 is part of the five membered ring, since here its signal is reported to be unsplit.[144] Although we could construct models of both stereoisomers (274) and (275) it was evident that the quasi-equatorial C-1 hydrogen in (275) would cause the aromatic ring trans related to it (on the carbon α to N) to meet steric crowding with the isoquinoline C-3 hydrogen. Such an interaction is avoided with the C-1 hydrogen quasi-axial (274). No details of the stereochemistry of (275) have been published.

The n.m.r. spectra of Reissert compounds show only one (doublet) peak for the C-1 proton. Therefore, the C-1 hydrogen

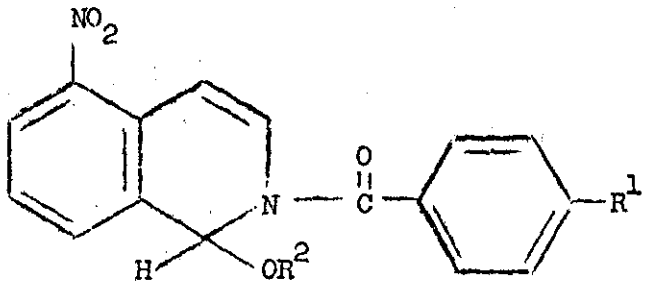
is either completely in the quasi-equatorial conformation or, more likely, the hetero-ring is flipping rapidly between the two conformations (270 and 271) and the n.m.r. spectrometer is seeing an average position of the C-1 hydrogen. We have investigated this point by use of variable temperature n.m.r. We observed the C-1 proton signal moved about 0.2 p.p.m. downfield on cooling from $+100^{\circ}$ to -70° (in acetone). The accompanying small change in coupling constant ($J_{1,3}$) could not be observed accurately due to the insufficient sensitivity of the instrument.

An equatorial C-1 proton is more deshielded by the aromatic ring than is an axial one.[145,146] Also one would expect the anisotropy effect of the σ -bond system surrounding C-1 to cause deshielding of an equatorial proton (relative to an axial one).[147] Thus the movement of the C-1 proton to a lower value as the temperature decreases suggests that the proton is spending more time in the preferred, quasi-equatorial conformation. Cooling was not sufficient to "freeze out" the equatorial isomer entirely (when the chemical shift would have reached a constant value).

Related to the Reissert compounds we have examined the n.m.r.spectra of the N-acyl pseudo-base alkoxy derivatives (276) (discussed earlier p. 77) and again found C1-C3 long-range coupling. The results are summarised in Table V p.115 . The size of the coupling constant (1.3 Hz) suggests the system (276) would have the preferred conformation with the C1-H quasi-equatorial and the alkoxy group quasi-axial. Here the five atoms involved would be expected to adopt a conformation rather more planar[80] than in the case of Reissert compounds (265) where J_{C1-C3}= 0.9 Hz.

Table V

N.m.r. Spectra* details of N-acyl-1-alkoxy-5-nitro-1,2-dihydroisoquinolines (276)



(276)

R^1	R^2	τ			$J_{1,3}$ Hz	$J_{3,4}$ Hz
		C_1-H D	C_3-H Q	C_4-H D		
H	Me	3.41	2.96	3.17	1.3	8.0
H	Et	3.31	2.94	3.14	1.3	8.0
CH_3	Me	3.42	2.93	3.19	1.3	8.0
CH_3	Et	3.33	2.96	3.17	1.3	8.0
Cl	Me	3.43	2.96	3.15	1.3	8.0
Cl	Et	3.37	3.01	3.16	1.3	8.0
OCH_3	Me	3.44	2.91	3.18	1.3	8.0
OCH_3	Et	3.35	2.90	3.14	1.3	8.0

D = Doublet Q = Quartet

* Spectra recorded with $CDCl_3$ as solvent at 60 MHz

(b) Quinoline Reissert Compounds

We have prepared a number of quinoline Reissert compounds (277) and examined their n.m.r. spectra with a view again to obtaining some information regarding the stereochemistry of the system involved. The information obtained is summarised in Table VI, p.117.

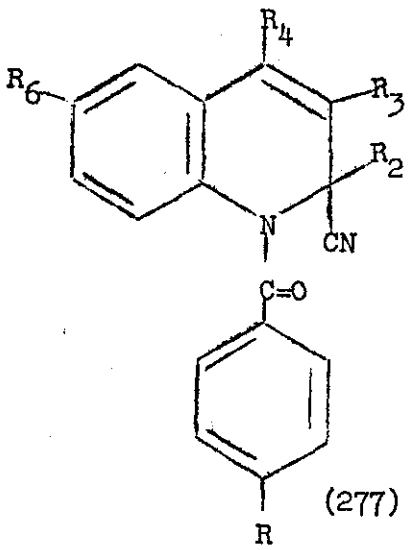
The analysis of the 60 MHz n.m.r. spectra of the compounds other than (277 a, l, n and p) was relatively straightforward i.e. in the cases where either C-3 or C-4 is substituted. When position 3 was substituted as in (277 c, e, f and g), the C-2 proton appeared as a singlet. Supporting evidence that this singlet was due to the C-2 proton was provided by deuterium studies. Replacement of the C-2 proton (3.72 τ) for deuterium in (277c) to give (277d) was effected by addition of deuterium oxide to the Reissert compound carbanion (generated by use of sodium hydride in dimethylformamide),[24] followed by neutralisation with carbon dioxide.[97,148] The deuterated compound (277d) showed no absorption at 3.72 τ .

When position 4 was substituted as in (277j), C-2 and C-3 both appeared as doublets with $J_{2,3}$= 7.3 Hz. In (277h), when C-4=CH_3, the C-3 proton appeared as a split doublet with $J_{3,2}$= 6.4Hz and $J_{3,Me}$ (allylic coupling)= 1.7 Hz, both J values being normal as expected.[149] Once again the replacement of the C-2 proton with deuterium in (277h) and (277j), to give (2771) and (277k) respectively, simplified the spectrum with the C-3 proton in (277k) appearing as a singlet and as an allylically split singlet (J=1.7Hz) in (2771).

In all the cases listed in Table VI, the C-4 proton is masked within the aromatic multiplet and could not be located.

Table VI

N.m.r. spectra* details of some quinoline Reissert compounds (277)



(277)

277	R_2	R_3	R_4	R_6	R	C-2 proton τ	C-3 proton τ	$J_{2,3}$ Hz	$J_{3,4}$ Hz	$J_{2,4}$ Hz
a	H	H	H	H	H	3.82**	3.92**	6.27**	9.31**	-1.01**
b	D	H	H	H	H	-	3.87D	-	9.00	-
c	H	Br	H	H	H	3.76D	-	-	-	0.4
d	D	Br	H	H	H	-	-	-	-	-
e	H	NHCOPh	H	H	H	2.31 b.s	-	-	-	Ca.0
f	H	O.COPh	H	H	H	3.60 b.s	-	-	-	Ca.0
g	H	O.COPh	H	H	CH_3	3.63 b.s	-	-	-	Ca.0
h	H	H	CH_3	H	H	3.86D	4.10Q	6.40	1.7‡	-
i	D	H	CH_3	H	H	-	4.10D	-	1.7‡	-
j	H	H	O.COPh	H	H	3.53D	3.84D	7.3	-	-
k	D	H	O.COPh	H	H	-	3.84S	-	-	-
l	H	H	H	CH_3	H	3.84**	3.95**	6.25**	9.21**	-0.71**
m	D	H	H	CH_3	H	-	3.87D	-	9.00	-
n	H	H	H	H	CH_3	3.85**	3.94**	6.00**	7.13**	+0.47**
p	H	H	H	NO_2	H	3.87**	3.73**	6.54**	9.42**	-0.52**

S = singlet, D = Doublet, Q = Quartet, b.s. = broad singlet

* Spectra were recorded in $CDCl_3$ at 60 MHz, except for a,c,l,n and p at 100 MHz.

** Valuesdarived from ABX spectra interpretation - see p.118ff.

‡ Values for $J_{C\ 3\text{-}H,C4\text{-}Me}$

Analysis of the n.m.r. spectra of quinoline Reissert compounds (277a), (277 l), (277n) and (277p), unsubstituted at positions 2, 3 and 4.

When none of the C2-H, C3-H or C4-H positions in N-aroyl quinoline Reissert compounds (277) was substituted, the n.m.r. spectra were complex and the interpretation using first order principles difficult. In each of the four cases (277 a, l, n and p), the type of spectrum obtained is shown in Figure III, the example illustrated being that for N-benzoyl-1,2-dihydroquinaldonitrile (277a). The part of the spectrum between 3.7 and 4.0 τ integrated for two protons, considered to be C-2 and C-3. First order approach to the analysis of the spectrum would require the C-3 proton to appear as a quartet (coupling with the C-2 and C-4 protons) and the C-2 proton as a doublet (coupling with the C-3 proton) or possibly as a split doublet (by further allylic coupling with the C-4 proton). Close examination of the 60 MHz spectrum revealed the presence of four unsymmetrical lines with a very intense singlet imposed over the quartet. Deuteration of the C-2 proton in (277 a and l) simplified the spectra and the deuterated compounds (277b) and (277m) showed only a doublet (in the 3.7 to 4.0 τ region) with a coupling constant of 9.0 Hz (presumably $J_{3,4}$) centred at 3.87 τ. The value of this coupling constant is typical for cis olefins.[149] Regarding the undeuterated spectra (277 a, l, n and p), because the difference in the chemical shifts of C-2 and C-3 protons is less than their coupling constants (see Table VI p. 117) so it could be assumed that the C-2, C-3 and C-4 protons form

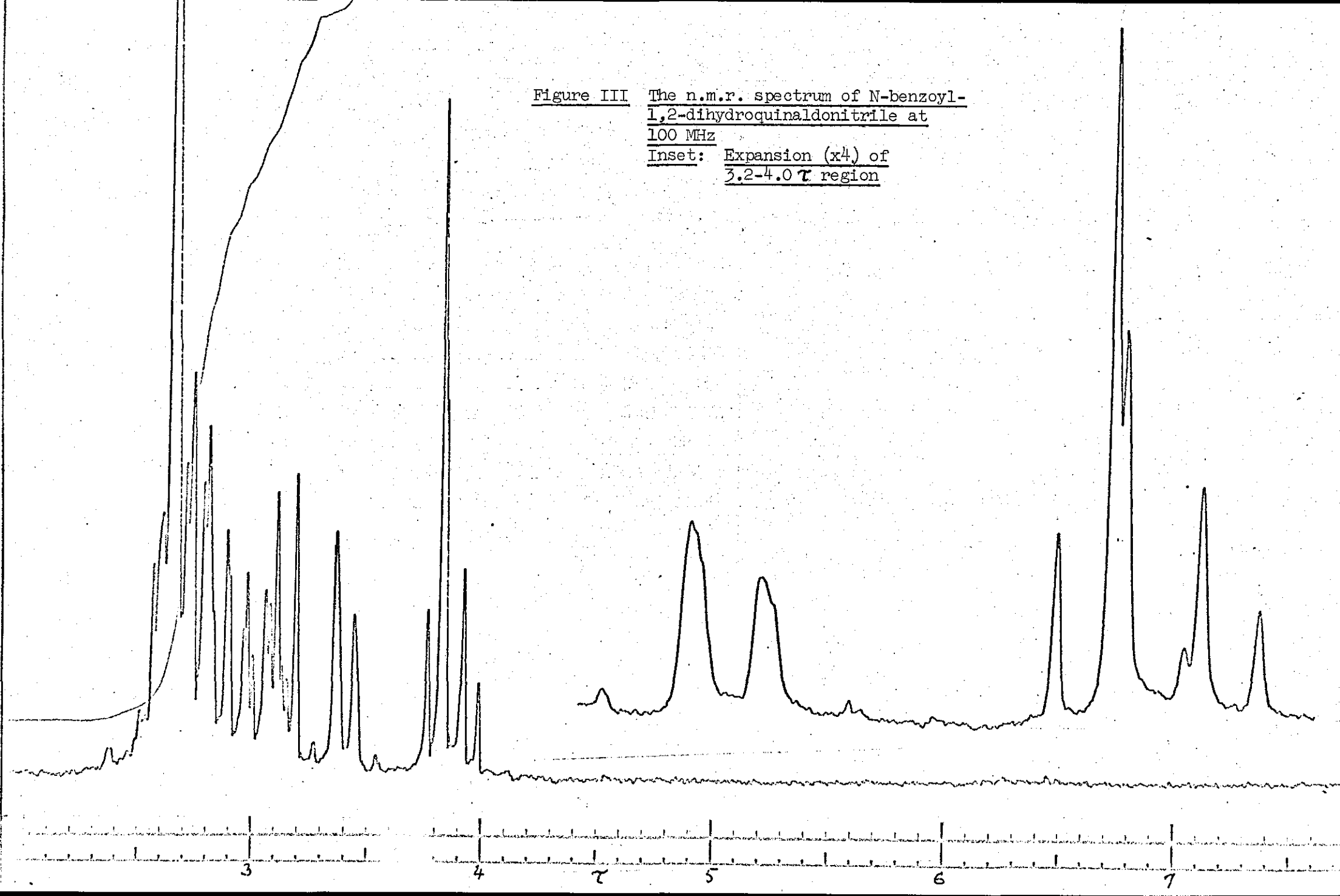
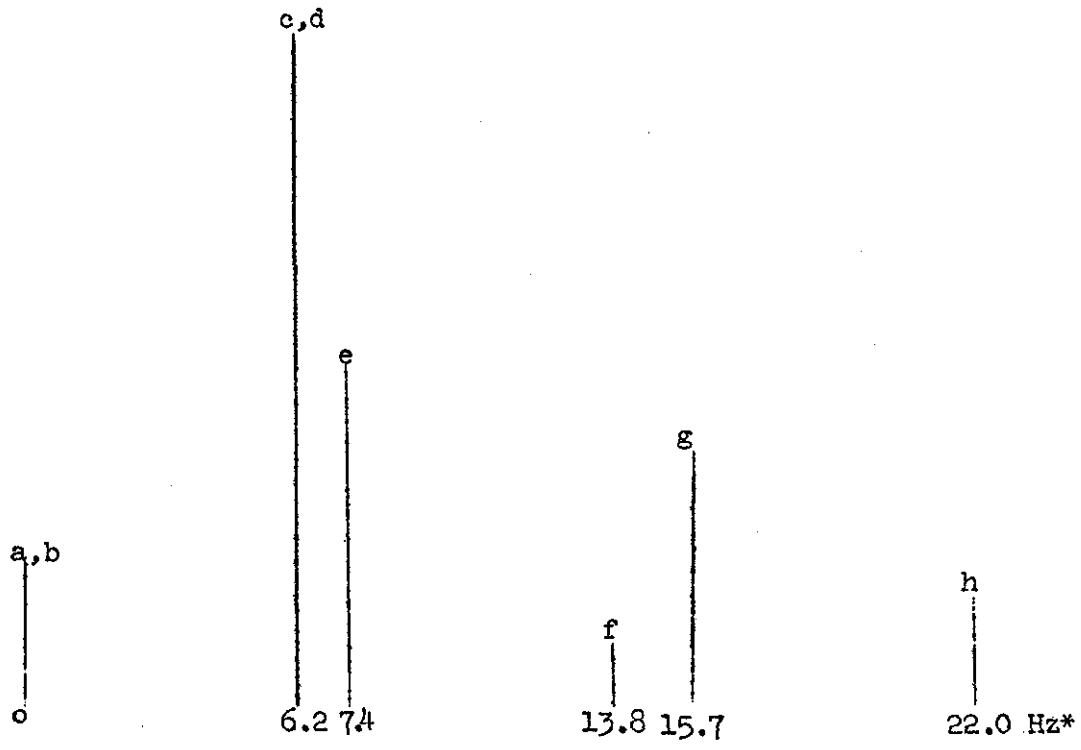


Figure III The n.m.r. spectrum of N-benzoyl-1,2-dihydroquinaldonitrile at 100 MHz
Inset: Expansion (x4) of 3.2-4.0 τ region

an ABX system with the C-3 and C-2 protons constituting the AB part and the C-4 proton (which is chemically well shifted from C-2 and C-3 protons) forming the X part.

In order to analyse the ABX system, we obtained the spectra for the four compounds on a 100 MHz instrument. Even on this instrument, the AB region (due to C-3 and C-2 protons) in each case consisted of six lines (see the spectrum of 277a Figure III p. 118) though theoretical considerations would require 8 lines for the AB region. It was thought likely the other two lines are overlapping and for case (277a) we show in the schematic representation below the allocation of the eight lines.



* Hz values measured relative to a,b signal.

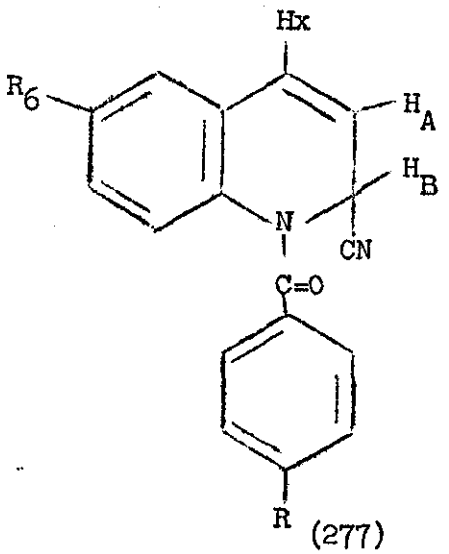
In order to get the required intensity (weak - strong - strong - weak), AB- and AB+ quartets can be assigned as

a	c	e	f		b	d	g	h
1	3	5	7		2	4	6	8

Using the method of Pople, Schneider and Bernstein,[150] we have calculated the ABX spectra for the four cases (277 a, l, n and p) (see Experimental Section p. 180 for details). The results obtained are summarised in Table VII below:

Table VII

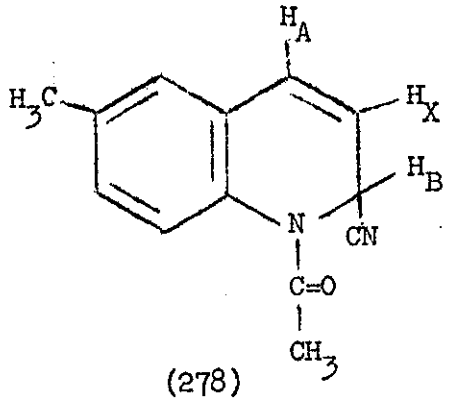
N.m.r. parameters calculated from ABX spectra of (277 a,l,n and p)



(277)

277	R	R_6	Calculated Hz J_{AB}	J_{AX}	J_{BX}	ν_A τ	ν_B τ
a	H	H	6.27	9.31	-1.01	3.92	3.82
l	H	CH_3	6.25	9.21	-0.71	3.95	3.84
n	CH_3	H	6.00	7.13	+0.47	3.94	3.85
p	H	NO_2	6.54	9.42	-0.52	3.73	3.87

In each of these spectra, the analysis of the X-region (due to the C-4 proton) could not be achieved as it was masked under the aromatic region. To overcome this we synthesised compound (278) which could be expected to have a simpler aromatic region. The spectrum of this compound was recorded on 100 MHz instrument and the ABX part of the spectrum is shown in Figure IV



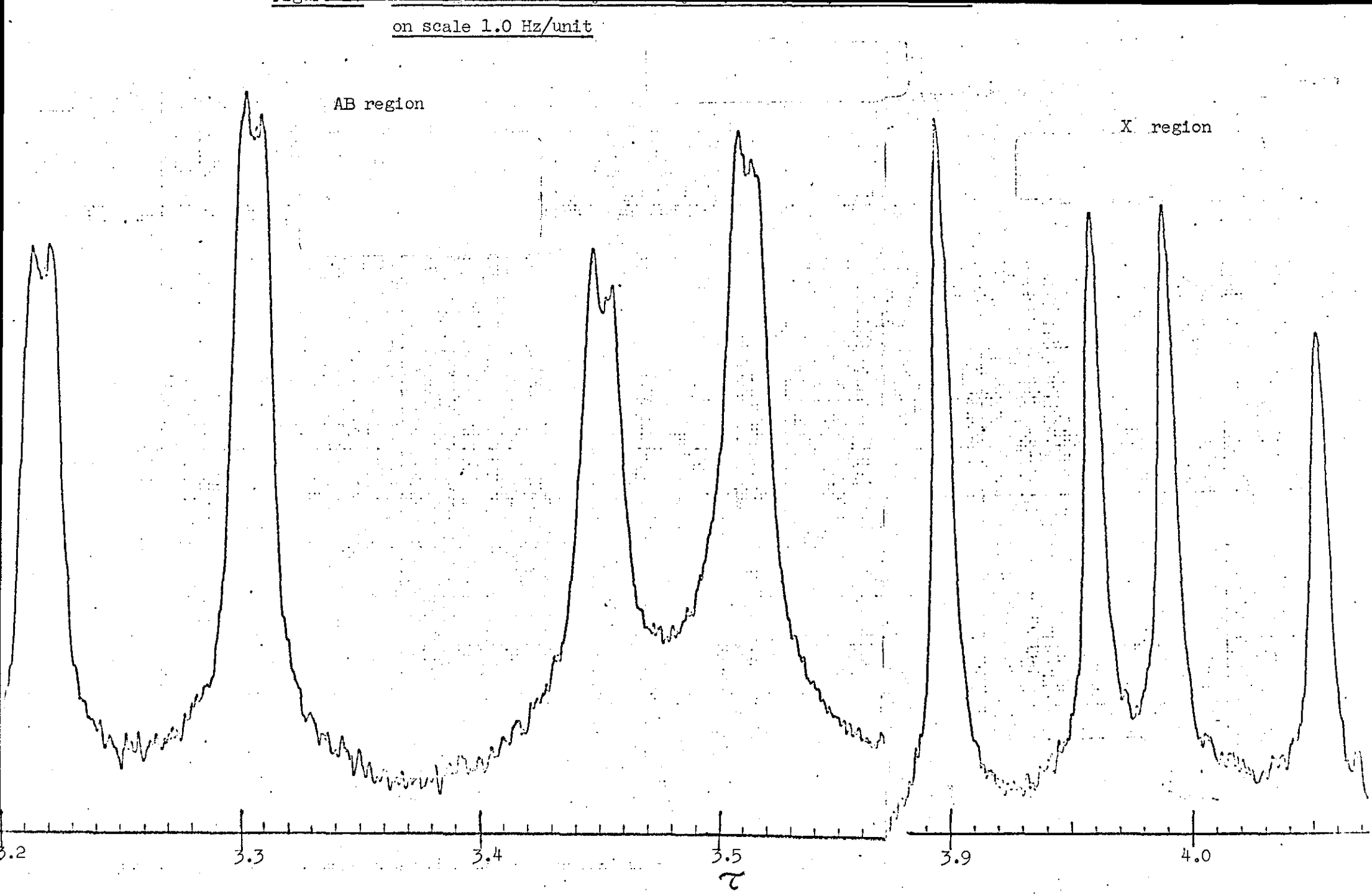
(278)

Comparison with Figure III (p.118) shows that this ABX system is markedly different from that obtained for compounds (277 a, l, n and p). The four lines of the X-region (one proton) are now at high field and the eight lines of the AB region (two protons) are at low field. Such an ABX system (more correctly an AMX system) can be solved by a first order approach (see Experimental Section p. 190). The values of the coupling constants and chemical shifts obtained are as follows : J_{AX}= 9.3 Hz, J_{BX}= 6.3 Hz, J_{AB}= 0.7 Hz, ν_A = 3.32 τ, ν_B = 3.54 τ and ν_X = 3.99 τ. Comparison of these values with those in Table VII p.120reveals that in this case the X-region is due to C3-H and the C-4 proton resonates at 3.32 τ.

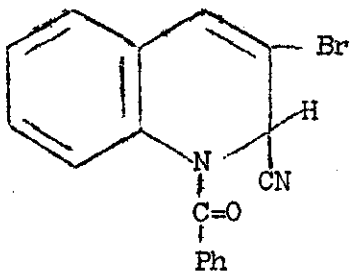
The Stereochemistry

As already mentioned on p.116, we studied all the spectra

on scale 1.0 Hz/unit



in detail in order to get some information regarding the stereochemistry of the system. In particular, we were interested to note the possible allylic coupling between C-2 and C-4 protons. The results obtained above show that the values of the allylic coupling constants vary between -1.01 to +0.47 Hz. Further evidence for this observable splitting between C-2 and C-4 protons was gained by recording the spectrum of compound (279) in which C-3 is substituted. As mentioned on p.116 , the spectrum of this compound on a 60 MHz instrument showed C2-H as singlet at 3.72 τ although the width at the half-peak height was slightly more than that for the TMS peak.

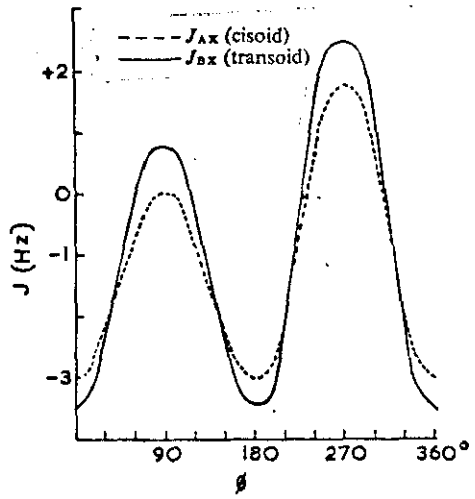


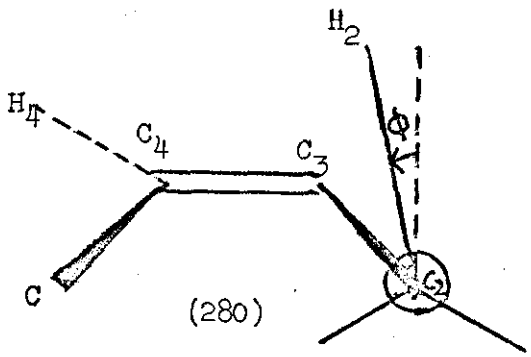
(279)

However, on recording the spectrum on 100 MHz instrument, the C2-H appeared as a doublet with splitting equal to 0.4Hz. The value is slightly less than the values obtained for the compounds (277) and (278) but it is not surprising because it is known[151] that the electronegative substituents (Br, Cl, OH for example) cause slight variations in the allylic coupling constants though it is difficult to decide whether the variation is due to changes in the electron densities or is a secondary effect due to slight changes in bond angles accompanying partial rehybridisation. From study of aliphatic,[152] olefinic,[153] and heterocyclic[154] compounds one would expect that purely electronic factors should be important.

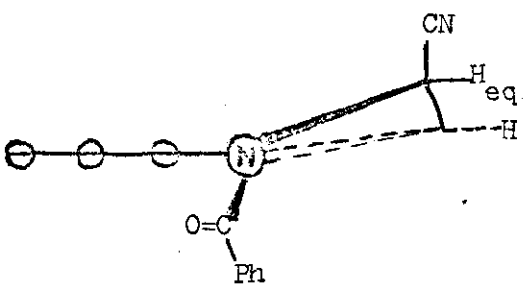
Now this size of the allylic coupling constant in quinoline Reissert compounds gives useful information regarding the stereochemistry of the hetero-ring. In general, it is known that allylic coupling constants[155] may be either positive or negative in sign.[156] The effect is mainly transmitted through the π-electron system[155] and the values of allylic couplings fall in the range -3 to +2 Hz.[80] From the experimental data[80, 138, 157, 158] and theoretical considerations,[142] a correlation (Figure V) between the allylic coupling constants and the angle ϕ has been established.[80,157] The angle ϕ is defined as in (280).

Figure V Variation of allylic coupling constants with stereochemistry.

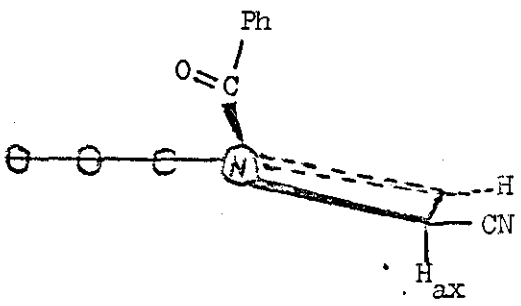




(280)



(281).

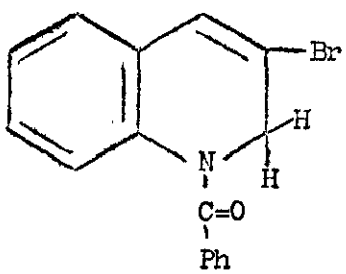


(282)

The values calculated above for $J_{2,4}$ range between -1.01 and +0.47 Hz, and correspond to values of ϕ of between 217-232° according to the Figure V. If the ring was "frozen" in the conformation with the C-2 proton quasi-equatorial as shown in (281) the value of ϕ would be 242°, which would move to 182° on flipping to the quasi-axial position (282). Thus the value of ϕ observed is an average weighted toward the C2-H occupying a quasi-equatorial environment.

The values recorded for the (vicinal) $J_{2,3}$ coupling (Table VII) show less variation than do the $J_{2,4}$ values but are of the correct order to correspond with the C-2 proton being in an average position weighted toward the quasi-equatorial environment. Accurate angle correlation curves for $\overset{H}{\underset{|}{=}}C-C-H$ related protons are not available[80] but approximate to the Karplus relationship for vicinal protons on fully saturated carbons.[80]

In an attempt to observe an axial C-2 proton, to see whether a larger allylic coupling occurred, we prepared N-benzoyl-3-bromo-1,2-dihydroquinoline (283) from 3-bromoquinoline by lithium aluminium hydride reduction[159] and benzoylation.



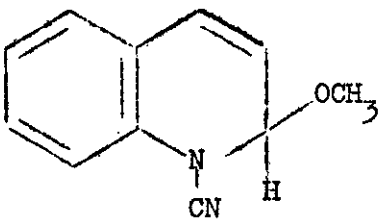
(283)

The n.m.r. spectrum of (283) showed a split signal centred at 5.25 τ with splitting equal to 1.3 Hz. This signal integrated

for two protons and must be due to methylene protons. Further that this signal was not in fact two singlets (due to different chemical shifts of two protons on C-2) was shown by saturating the C-4 signal, when C-2 methylene proton signal collapsed to a sharp singlet of increased intensity.

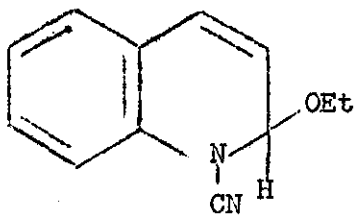
Although numerically larger, the observed J value is of little consequence, however, showing the hetero-ring is flipping rapidly at room temperature and the n.m.r. spectrometer cannot distinguish the two protons on C-2. On cooling the sample to -50° the spectrum showed no appreciable change. Further lowering of the temperature could not be achieved due to limitations of solvent.

The conformation with a quasi-equatorial C-2 hydrogen in quinoline Reissert compounds would also appear to be the case for some other 1,2-dihydroquinolines viz (284), (285), (286) and (287), the reported[85] $J_{2,4}$ values falling within the same range as those observed by us.



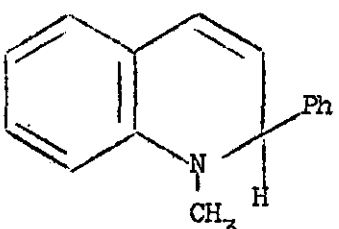
(284)

$J_{2,4}$= -0.5 Hz



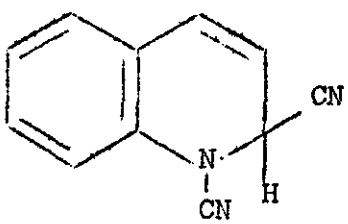
(285)

$J_{2,4}$= -0.6 Hz



(286)

$J_{2,4}$= + 0.5 Hz



(287)

$J_{2,4}$= -0.5 $\pm$ 0.5 Hz

Further, models of quinoline Reissert compound show that the non-bonded interactions are minimised by the C-2 cyanide occupying the quasi-axial position. If the C-2 cyanide were equatorial in these Reissert compounds then steric interaction would result between it and amidic phenyl ring.

It thus appears that quinoline Reissert compounds have a ste reochemistry comparable to that of isoquinoline Reissert compounds.

EXPERIMENTAL

Unless otherwise stated the following conditions apply.

Infrared spectra were determined using potassium bromide discs for solids, or using thin films in the case of liquids, on Perkin-Elmer 237 or 257 grating spectrophotometers. Ultraviolet spectra were determined in methanolic or ethanolic solutions on a Unicam S.P. 800 spectrophotometer.

N.m.r. spectra were determined at 60 MHz for solutions in deuterochloroform (unless otherwise stated), using tetramethylsilane as internal standard with a Perkin-Elmer R10 instrument. N.m.r. spectra at 100 MHz and 220 MHz were carried out by the Physico-Chemical Measurements Unit, Harwell. Mass spectra were obtained on an A.E.I. MS12 spectrometer. Accurate mass measurements were carried out on an A.E.I. MS902 spectrometer at the Physico-Chemical Measurements Unit, Aldermaston.

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. The majority of elemental analyses were carried out by Beller, Microanalytisches Laboratorium, Göttingen. The remainder were analysed in the department (Mr.K.R.Scott) or by Mr.T.J.Spencer, Nottingham University.

Column chromatography was carried out on neutral alumina, Brockmann activity 3, unless otherwise stated. Preparative thin layer chromatography (p.l.c.) was performed on plates, 1m. x 20 cm., or 20 cm. x 20 cm. (0.5 mm. layers), spread with silica gel PF 254. Thin layer chromatography (t.l.c.) was carried out with aluminium oxide GF 254 or silica gel GF 254 (0.25 mm. layers).

Diethyl ether and petroleum ethers were dried with sodium wire. Benzene and dimethylformamide were dried by distillation

and collection of the middle fraction.

Acid chlorides employed were prepared by heating the corresponding acid (1 mol.) with thionyl chloride (1.1 mol.) until evolution of hydrogen chloride and sulphur dioxide ceased. The product was then vacuum distilled.

The following abbreviations are used in the text :-

s = singlet

d = doublet

t = triplet

q = quartet

m = multiplet

b = broad

w = weak

sh= shoulder

I would like to thank Mrs. S. Ralkar (n.m.r. spectra), Mr.K.R.Scott (microanalyses) and Mr.J.L.Kumar (mass spectra) for their technical assistance.

1. Rearrangement Studies of Reissert Compounds

(a) Attempted improvements of the Pomeranz-Fritsch isoquinoline synthesis

(i) Chloranil dehydrogenation route

Attempted preparation of 8-hydroxyisoquinoline: dehydrogenation using chloranil in xylene at reflux temperature

A mixture of salicylaldehyde (3.05 g., 0.025 mol.) and aminoacetal (3.33 g., 0.025 mol.) in ethanol (66 ml.) was added to platinum oxide (0.25 g.) in ethanol (17 ml.) which had been pre-reduced. The mixture was shaken at room temperature and pressure until uptake of hydrogen ceased (ca. 6 hours). The catalyst was filtered off and the solvent evaporated under vacuum. The residue was taken up in hydrochloric acid (6N, 125 ml.), washed with ether (40 ml.) and allowed to stand overnight. The solution was basified with ammonium hydroxide to pH 8, and extracted with chloroform, dried (K_2CO_3) and the solvent evaporated to give free base as colourless crystalline solid (3 g.), m.p. 170°, assumed to be 8-hydroxy-1,2-dihydroisoquinoline.

The product (1.5 g., 0.01 mol.) from the above reaction was immediately heated under reflux with chloranil (2.5 g., 0.01 mol.) and xylene (30 ml.) for five hours, cooled and 60/80 pet.ether (30 ml.) added to precipitate the tetrachlorohydroquinone. No precipitation occurred but instead an intractable mass was obtained which could not be processed further.

Attempted preparation of 8-hydroxy-7-methoxyisoquinoline: dehydrogenation using chloranil in dioxan at room temperature

Using o-vanillin (6.0g., 0.04 mol.) and aminoacetal (5.3g., 0.04 mol.), 8-hydroxy-7-methoxy-1,2-dihydroisoquinoline

was prepared in the same manner as described in the previous experiment. The crude product was converted to its hydrochloride by dissolving in ether and passing dry hydrogen chloride gas over the surface. The hydrochloride (0.7 g.) was filtered and dried. Basification of this hydrochloride gave the dihydro-base (0.5g., 7%).

An orange solution of chloranil (1 g., 4 m.mol.) in dioxan (30 ml.) was added rapidly to a solution of 8-hydroxy-7-methoxy-1,2-dihydroisoquinoline (0.7 g., 4m.mol.)in dioxan (5 ml.) at room temperature. A deep wine red colour was immediately produced and after twenty minutes the solvent was evaporated at reduced pressure. The residue, a brown tar, was dissolved in benzene and extracted with hydrochloric acid (2N). Basification of the acid solution and subsequent work-up afforded a very small amount of basic material which could not be satisfactorily characterised.

Attempted preparation of 7,8-dimethoxyisoquinoline, and of 6,7-dimethoxyisoquinoline

Use of the above procedures with 2,3-dimethoxybenzaldehyde and with 3,4-dimethoxybenzaldehyde gave only intractable material which could not be processed further.

(ii) Use of diphenyl ether as cyclising agent

Attempted cyclisation of 2,3-dimethoxybenzalaminoacetal

2,3-Dimethoxybenzaldehyde (8.3 g., 0.05 mol.) and aminoacetal (6.65 g., 0.05 mol.) were heated under reflux in dry benzene (200 ml.) for half an hour, and for a further two hours with the addition of Dean-Stark trap. Removal of solvent

left the Schiff base, 2,3-dimethoxybenzalaminoacetal (14.0g., 98%). The infrared spectrum showed no absorption at 1690 $cm.^{-1}$ (aromatic aldehyde). N.m.r, τ 1.46 (s,1H,Ar-CH=N), 2.8-3.3 (m,3H, aromatic protons), 5.32 (t,1H,-O-CH-O-), 6.18 (s,6H, 2X-OCH_3), 6.0-6.7 (m,6H,3X-CH_2), 8.85 (t, 6H,2X-CH_3).

In a 250 cc three-necked flask equipped with a dropping funnel, a sealed mechanical stirrer and an air reflux condenser (6") was placed diphenyl ether (100 ml.). The diphenyl ether was stirred and heated at reflux temperature, while 2,3-dimethoxybenzalaminoacetal (14.0 g.) was added rapidly through the dropping funnel. Stirring and refluxing were continued for ten minutes after the addition was complete. At the top of the air condenser a distillation head was attached to a water-cooled condenser to permit collection of ethanol formed in the condensation reaction. When no further ethanol distilled over (ten minutes), the reaction mixture was allowed to cool to room temperature and 60/80 petroleum ether (ca. 200 ml.) added. The mixture was extracted with 2N hydrochloric acid. The acid extract was basified (pH=9) with ammonium hydroxide solution, extracted with chloroform, dried (K_2CO_3) and evaporation of the solvent afforded a brown syrupy liquid (2.2 g.). Vacuum distillation of this gave a product (0.164 g.) at 100-130°/0.35 mm (lit.[160] 107-109°/0.15 mm., 120-3°/0.01 mm).

The product did not yield any picrate or methiodide. The infrared and n.m.r. spectra were similar to those obtained for 2,3-dimethoxybenzalaminoacetal.

Attempted cyclisation of ethyl(2,3-dimethoxybenzalamino)acetate

To glycine ethyl ester hydrochloride (8.0 g.) was added 0.88 ammonia dropwise until alkaline. Dry benzene (200 ml.) was added and the precipitated ammonium chloride filtered off. The solution was dried (Na_2SO_4) and evaporation of the solvent gave glycine ethyl ester (4.0 g., 67%). $\nu_{max.}$ 1735 $cm.^{-1}$ (ester carbonyl), 3380 $cm.^{-1}$ (NH).

To glycine ethyl ester (4.0 g., 0.04 mol.) was added 2,3-dimethoxybenzaldehyde (6.6 g., 0.04 mol.) and the corresponding Schiff base (9.0 g., 90%) was obtained in the same manner as described in the previous experiment (p.130). $\nu_{max.}$ 1735 $cm.^{-1}$ (ester C=O) and no absorption at 3380 $cm.^{-1}$ (NH).

Cyclisation was attempted in the same manner as described in the previous experiment (p.131) except that the Schiff base was added to refluxing diphenyl ether at such a rate which did not allow the temperature to fall below 250°. After work-up, the product obtained had infrared spectrum identical to that of Schiff base.

Attempted cyclisation of 3,4,5-trimethoxybenzalaminoacetal and of ethyl (3,4,5-trimethoxybenzalamino)acetate

The above procedure (p.130ff) were again employed, starting with 3,4,5-trimethoxybenzaldehyde (2.0 g., 0.01 mol.) and the appropriate amine but cyclisation yielded only starting materials and tars.

1. (b) Rearrangement Studies of Reissert Compounds

(i) Competitive intramolecular acyl rearrangements

Preparation of Reissert Compounds

General Procedure

The acid chloride (32 m.mol.) was added over two hours to a stirred mixture of the quinoline or isoquinoline (16 m.mol.) in methylene chloride (20 ml.) and potassium cyanide (48 m.mol.) in water (8 ml.). After additional stirring for two hours (in the case of isoquinolines) or 6 to 8 hours (in the case of quinolines), the layers were separated and the water layer washed with methylene chloride (10 ml.). The combined methylene chloride extracts were washed with water, 2N hydrochloric acid, water, 2N sodium hydroxide and water. The dried (sodium sulphate) methylene chloride solution was slowly evaporated to give the Reissert compound.

N-Benzoyl-1,2-dihydroisoquinaldonitrile

Use of isoquinoline (2.0 g., 16 m.mol.) and benzoyl chloride (3.6 ml., 32 m.mol.) in the general procedure gave N-benzoyl-1,2-dihydroisoquinaldonitrile (2.25 g., 56%). Recrystallisation from ethyl acetate gave colourless rhombs, m.p. 128° (reported[8], 124-5°). $\nu_{max.}$ 2250 cm.$^{-1}$ (w) (CN), 1665 cm.$^{-1}$(CO); τ 2.0-3.0 (m, 9H, aromatic protons), 3.36 (q, 1H, C3-H, $J_{3,1}$ = 0.8 Hz., $J_{3,4}$ = 8.0 Hz). 3.42 (d, 1H, C1-H, $J_{1,3}$ = 0.8 Hz), 3.94 (d, 1H, C4-H, $J_{4,3}$ = 8.0 Hz.).

Rearrangement of N-benzoyl-1,2-dihydroisoquinaldonitrile

A suspension of sodium hydride (50% in oil, washed with dry petrol, 0.12 g., 5 m.mol.) was added slowly to the stirred solution of N-benzoyl-1,2-dihydroisoquinaldonitrile (1.3 g., 5 m.mol.) in dry dimethylformamide (30 ml.) at 0° under nitrogen.

A red colour appeared immediately with the evolution of hydrogen. Stirring was continued for thirty minutes at 0°, and two hours at room temperature, during which time the colour faded to pale pink. The reaction mixture was then poured on to ice (500 g.) and the product 1-benzoylisoquinoline isolated. Recrystallisation from hexane gave colourless needles, m.p. 74-75° (lit.[18] 76-77°) (0.65 g., 56%).

Preparation and rearrangement of N-(p-toluoyl)-1,2-dihydroisoquinaldonitrile

Use of isoquinoline (2.0 g., 16 m.mol.) and p-toluoyl chloride (4.7 g., 32 m.mol.) in the general procedure (p.133) gave N-(p-toluoyl)-1,2-dihydroisoquinaldonitrile (3.1g., 74%), which was recrystallised from a mixture of ether and petroleum ether (60/80), as buff coloured stout needles, m.p. 132-133° (Found: C, 78.52; H, 5.11; N, 10.27. $C_{18}H_{14}N_2O$ requires C, 78.81; H, 5.14; N, 10.21%); $\nu_{max.}$ 2220 cm.$^{-1}$ (w) (CN), 1670 cm.$^{-1}$ (CO); τ 2.3 - 2.9 (m, 8H, aromatic proton), 3.33 (q, 1H, C3-H, $J_{3,4}$ = 8.0 Hz, $J_{3,1}$ = 0.8 Hz), 3,46 (d, 1H, C1-H, $J_{1,3}$ = 0.8 Hz), 3.96 (d, 1H, C4-H, $J_{4,3}$ = 8.0 Hz), 7.60 (s, 3H, $-CH_3$).

When N-(p-toluoyl)-1,2-dihydroisoquinaldonitrile (1.4 g., 5 m.mol.) was treated with sodium hydride (0.12 g., 5 m.mol.) in the same manner as described on p. 133, 1-(p-toluoyl)isoquinoline (0.62 g., 50%) was obtained, which was recrystallised from diethyl ether as colourless needles, m.p. 84.5-85° (Found: C, 82.62; H, 5.11; N, 5.83. $C_{17}H_{13}NO$ requires C, 82.57; H, 5.30; N,5.66%); $\nu_{max.}$ 1672 cm.$^{-1}$ (CO);

τ 1.44 (d, 1H, C3-H, $J_{3,4}$ = 5.6 Hz), 1.6-3.0 (m, 9H, aromatic), 7.70 (s, 3H, $-CH_3$).

The picrate of 1-(p-toluoyl)isoquinoline was prepared in absolute ethanol. Recrystallisation from the same solvent gave bright yellow needles, m.p. 172-172.5° (Found: C, 57.99; H, 3.32; N, 11.85. $C_{23}H_{16}N_4O_8$ requires C, 57.98; H, 3.39; N, 11.76%).

Preparation and rearrangement of N-(o-nitro)benzoyl-1,2-dihydroisoquinaldonitrile

To o-nitrobenzoic acid (20 g.) taken in dry benzene (70 ml.) was added thionyl chloride (8.5 ml.) and refluxed at 100° for one hour (when the evolution of hydrogen chloride and sulphur dioxide ceased). After cooling, the benzene was evaporated at room temperature. The acid chloride obtained was used without distillation.(due to possible explosion hazard.[161])

Use of isoquinoline (4.0 g., 32 m.mol.), o-nitrobenzoyl chloride (11.5 g., 64 m.mol.) and potassium cyanide (6.2 g., 96 m.mol.) in the general procedure (p. 133) gave N-(o-nitro)-benzoyl-1,2-dihydroisoquinaldonitrile (0.2 g., 2%), which crystallised from ethyl acetate as pale yellow needles, m.p. 154-155° (Found: C, 66.67; H, 3.55; N, 13.89. $C_{17}H_{11}N_3O_3$ requires C, 66.88; H, 3.63; N, 13.77%); $\nu_{max.}$ 1660 $cm.^{-1}$ (CO), 1630 $cm.^{-1}$ (C3=C4); τ 1.5-3.0 (m, 8H, aromatic), 3.19 (d, 1H, C1-H, $J_{1,3}$ = 0.85 Hz), 3.76 (q, 1H, C3-H, $J_{3,4}$ = 8.0 Hz, $J_{3,1}$ = 0.85 Hz), 4.02 (d, 1H, C4-H, $J_{4,3}$ = 8.0 Hz).

Treatment of N-(o-nitro)benzoyl-1,2-dihydroisoquinaldonitrile

(0.15 g., 0.5 m.mol.) with sodium hydride (0.012 g., 0.5 m.mol.) in dimethylformamide (10 ml.) in the same manner as described on p. 133 gave 1-(o-nitro)benzoylisoquinoline(0.091 g., 67%). Recrystallisation from ethyl acetate gave buff needles, m.p. 206-208° (Found: N, 10.16. $C_{16}H_{10}N_2O_3$ requires N, 10.07%). The n.m.r. spectrum included τ 1.25 (d, 1H, C3-H, $J_{3,4}$ = 8.0 Hz).

Determination of pK_a values * (spectroscopic method)[65]

1-Benzoylisoquinoline

A stock solution of the compound was prepared in acetone. Aliquots (5 ml.) of this solution were pipetted into 50 ml. graduated flasks and acetone removed at the pump.

Solutions were prepared by dissolving the compound in (a) dilute sodium hydroxide solution (b) 10% sulphuric acid solution (c) solutions of intermediate acid strengths.

The spectra of solutions (a) and (b) were measured on a Unicam SP 600 spectrophotometer and the wavelength of maximum absorption of the protonated species noted. This was considered the "analytical" wavelength. The spectra were measured accurately at this wavelength, in a thermostatted cell using a Hilger Watt "Unispek" spectrophotometer.

The strengths of the sulphuric acid solutions were measured by titrations with standard sodium hydroxide solution and the pH of the solutions calculated from the activity coefficient data of Harned and Owen.[162]

*The author thanks Dr.P.Tickle for technical guidance.

The pK_a of 1-benzoylisoquinoline was then calculated (Table VIII) from the equation :-

$$pH = pK_a - \log \frac{\varepsilon - \varepsilon_B}{\varepsilon_{BH^+} - \varepsilon}$$

$$= pK_a - \log \frac{A - A_B}{A_{BH^+} - A}$$ since we have constant concentration (c) and cell path length (l), and $A = \varepsilon cl$

where ε_B = molar absorptivity of the unprotonated form at the analytical wavelength.

ε_{BH^+} = Molar absorptivity of the protonated form at the analytical wavelength.

ε = Molar absorptivity of the solution containing both protonated and unprotonated species at the analytical wavelength.

A_B, A_{BH^+}, A = corresponding absorbances (read from machine)

Table VIII: pK_a Determination of 1-Benzoylisoquinoline

analytical wavelength = 232 nm.

$A_B = 0.314$, $A_{BH^+} = 0.667$

Solution	pH	A	pK_a
A	1.444	0.622	2.279
B	1.665	0.588	2.205
C	1.879	0.549	2.178

Mean pK_a value of 1-benzoylisoquinoline = 2.22

Measurement of pK_a of N-benzoyl-1,2-dihydroisoquinaldonitrile

The above procedure was again followed. The spectra of the Reissert compound was measured in 30% and in concentrated

sulphuric acid (98%) on a Unicam SP 800 spectrophotometer and wavelength of maximum absorption of the protonated species again noted as the analytical wavelength . The molar absorptivity of the compound in various solutions of aqueous sulphuric acid were measured at this wavelength in a thermostatted cell using a Hilger Watt "Unispek" spectrophotometer.

The acidity functions (H_o) of the sulphuric acid solutions were calculated from the data of Paul and Long[163] and the pK_a of the compound calculated from the equation

$$H_o = pK_a - \log \frac{\varepsilon - \varepsilon_B}{\varepsilon_{BH^+} - \varepsilon}$$

$$= pK_a - \log \frac{A - A_B}{A_{BH^+} - A} \quad \text{as before}$$

Table IX: pK_a Determination of N-benzoyl-1,2-dihydroisoquinaldonitrile

Analytical wavelength = 400 nm.

$A_B = 0.370$, $A_{BH^+} = 0.03$

Solution strength (H_2SO_4 in water)	H_o	A	pK_a
71.54% w/w	-5.85	0.271	-6.23
73.25% w/w	-5.93	0.285	-6.40

Mean pK_a value = -6.3

This value is only approximate as the acid solutions of the Reissert compound were fading rapidly.

Rearrangement studies on 3-benzoylamino-1-p-toluoyl-1,2-dihydroquinaldonitrile

3-Benzoylaminoquinoline

The method used was similar to that reported by Hamer[164] for the preparation of 3-cinnamoylaminoquinoline.

3-Aminoquinoline (4.3 g., 0.03 mol.) was dissolved in chloroform and while kept cool was treated with benzoyl chloride (7.0 ml., 0.03 mol.) also in chloroform solution; heat was evolved and a red solution resulted. The calculated quantity of 1N.NaOH (1.2 g. in 30 ml. of water) was added and the mixture shaken until almost colourless. The benzoyl derivative was filtered off and recrystallisation from 95% ethanol gave 3-benzoylaminoquinoline as colourless needles, m.p. 199-199.5° (4.6 g., 62%) (Found:C, 77.47; H, 5.06; N, 11.52. $C_{16}H_{12}N_2O$ requires C, 77.40; H, 4.87; N, 11.28%), $\nu_{max.}$ 3300 cm.$^{-1}$ (NH), 1675 cm.$^{-1}$ (CO); τ (DMSO-d_6) 0.67 (d, 1H, C2 or C4-H, $J_{2,4}$ = 2.5Hz), 1.02 (d, 1H, C4 or C2-H), $J_{4,2}$ = 2.5 Hz), 1.6-2.6 (m, 10H, aromatic and NH).

3-Benzoylamino-1-p-toluoyl-1,2-dihydroquinaldonitrile

Use of 3-benzoylaminoquinoline (2.0g., 8 m.mol.) and p-toluoyl chloride (2.5 g., 16 m.mol.) in the general procedure (p. 133) gave 3-benzoylamino-1-p-toluoyl-1,2-dihydroquinaldonitrile (2.4 g., 76%), which crystallised from 95% ethanol as colourless plates, m.p. 170-171° (Found: C, 76.54; H, 4.94; N, 10.55; $C_{25}H_{19}N_3O_2$ requires C, 76.32; H, 4.87; N, 10.68%); $\nu_{max.}$ 3320-3380 cm.$^{-1}$ (NH), 1688 cm.$^{-1}$ (NHCO),1670 cm.$^{-1}$ (N-C=O); τ 0.97 (b.s., 1H, exchangeable, NH), 2.31 (s, 1H, C2-H), 7.70 (s, 3H, CH_3).

Rearrangement reaction on 3-benzoylamino-1-p-toluoyl-1,2-dihydroquinaldonitrile

A suspension of sodium hydride (50% in oil, washed with dry petrol, 0.061 g., 2.5 m.mol.) in dimethylformamide was added slowly to the stirred solution of 3-benzoylamino-1-p-toluoyl-1,2-dihydroquinaldonitrile (1.0 g., 2.5 m.mol.) in dimethylformamide (20 ml.) at 0° under nitrogen. No colour change took place, and the temperature was raised steadily to 90° when after two hours a red colour appeared. Stirring was continued overnight, although no appreciable fading of the red colour resulted. The contents were poured on to ice, the precipitated product was filtered and washed several times with water. The product was dissolved in chloroform and extracted several times with 60% HCl. The acid extracts and the chloroform solution were worked-up separately.

The acid extracts. The acid extract was basified with ammonium hydroxide and extracted with chloroform, dried (K_2CO_3) and evaporation of the solvent gave a brown oil (ca. 10 mg.) which was not further analysed.

The chloroform solution was dried (Na_2SO_4) and evaporated to obtain a solid product (0.8 g.). The chromatography on neutral alumina in 90% benzene and 10% ethyl acetate gave two fractions.

The first fraction was 3-benzoylamino-2-p-toluoylquinoline (0.242 g., 26%, or 52% based on recovered starting material). Recrystallisation from ethyl acetate gave pale yellow stout needles, m.p. 162.5-163° (Found: C, 78.98; H, 5.24; N,7.99.

$C_{24}H_{18}N_2O_2$ requires C, 78.67; H, 4.95; N, 7.65%); $\nu_{max.}$ 3320 cm.$^{-1}$ (NH), 1650 cm.$^{-1}$ (diaryl ketone), 1675 cm.$^{-1}$ (NHCO); τ 0.31 (b.s., 1H, exchangeable, NH), 1.7-2.8 (m, 14H, aromatic protons), 7.57 (s, 3H, CH_3).

The second fraction was shown to be the starting material (0.5 g., 50% recovery) by identical n.m.r. and infrared spectra.

Rearrangement studies on 3-benzoyloxy-1-p-toluoyl-1,2-dihydroquinaldonitrile

3-Hydroxyquinoline

3-Aminoquinoline (4.3 g., 0.03 mol.) was converted to diazonium chloride by the method of Abramovitch[165] which was then hydrolysed by the method of Albert and Phillips[166] to give 3-hydroxyquinoline (3.2 g., 75%), m.p. 198-199° (lit.[166] m.p. 198°).

3-Benzoyloxyquinoline

Using the method of Cavallito and Haskell,[167] 3-hydroxyquinoline (2.9g., 0.03 mol.) was converted into 3-benzoyloxyquinoline (3.2 g., 62%), m.p. 66-67° (reported[167] 67°). $\nu_{max.}$ 1740 cm.$^{-1}$ (ester C=O); τ 1.08 (d, 1H, C2-H, $J_{2,4}$=2.4 Hz. (cf. reference 168)), 1.4-2.8 (m, 10H, aromatic).

3-Benzoyloxy-1-p-toluoyl-1,2-dihydroquinaldonitrile

Use of 3-benzoyloxyquinoline (3.0 g., 12 m.mol.) and p-toluoyl chloride (3.72 g., 24 m.mol.) in the general procedure (p. 133) gave a brown syrup. Trituration with ethanol for several hours solidified the compound. Recrystallisation from 95% ethanol gave 3-benzoyloxy-1-p-toluoyl-1,2-dihydroquinaldonitrile as colourless needles, m.p. 111-112° (2.1g., 58%) (Found: C, 76.42; H, 4.79; N, 7.39.

$C_{25}H_{18}N_2O_3$ requires C, 76.13; H, 4.60; N, 7.10%); $\nu_{max.}$ 1740 cm.$^{-1}$ (ester C=O), 1660 cm.$^{-1}$ (N-C=O); τ ca. 1.8 (m, 2H, orthohydrogens of benzoyloxy group),[67] 2.2-3.5 (m, 15H, aromatic and C4-H), 3.63 (s, 1H, C2-H), 7.65 (s, 3H, CH_3).

Rearrangement reaction on 3-benzoyloxy-1-p-toluoyl-1,2-dihydroquinaldonitrile

A suspension of sodium hydride (0.061 g., 2.5 m.mol.) in dimethylformamide was added slowly to the stirred solution of 3-benzoyloxy-1-p-toluoyl-1,2-dihydroquinaldonitrile (1.0 g., 2.5 m.mol.) in dimethylformamide (20 ml.) at 0° under nitrogen. A red colour appeared after five minutes. Stirring was continued overnight and the contents were poured on to ice. The reddish yellow solution was neutralised with dilute HCl (pH =7) and the precipitated product filtered, washed with water and dried. This product appeared to be a mixture of 3-benzoyloxy-2-p-toluoylquinoline and 2-benzoyl-3-hydroxy-1-p-toluoylquinaldonitrile, showing the following in the n.m.r; τ ca. 1.9 (2H, orthohydrogens of the C3-benzoyloxy group), 2.0-3.4 (m, 27H, aromatic protons), 7.64 (s, 3H, methyl), 7.67 (s, 3H, methyl).

The product was dissolved in chloroform and extracted with 2N sodium hydroxide solution. The sodium hydroxide extract was acidified and extracted with chloroform, dried (Na_2SO_4) and evaporation of the solvent gave a yellow amorphous powder, m.p. 185-215°, which could not be crystallised. This product, considered to be 2-benzoyl-3-hydroxy-1-p-toluoylquinaldonitrile showed absorptions in the n.m.r. at

τ 1.7-2.9 (m, 15H, aromatic, enol OH and C4-H), 7.60 (s,3H,methyl) and by infrared with $\nu_{max.}$ 3140 cm.$^{-1}$ (bonded OH), 2240 cm.$^{-1}$ (w) (CN), 1705 cm.$^{-1}$ (amidic carbonyl out of plane), 1685 cm.$^{-1}$ (diaryl ketone). The non-base soluble material proved intractable and could not be purified.

Rearrangement studies on 8-benzoyloxy-2-p-toluoyl-1,2-dihydroisoquinaldonitrile.

Isoquinoline (64.5 g., 0.5 mol.) was converted into its sulphate by treating with 98% sulphuric acid (50 g.). Recrystallisation from 95% ethanol gave colourless needles m.p. 198° (lit.[71] 206°) (106 g., 93%). Isoquinoline sulphate (78 g., 0.34 mol.) was converted to 8-hydroxyisoquinoline hydrochloride (4.9 g., 8%) by the method of Robinson.[71] The base obtained from this salt was recrystallised from ethanol to give 8-hydroxyisoquinoline as buff needles, m.p. 215° (lit.[71] 213°) (Found : C, 74.30; H, 4.94; N, 9.73. C_9H_7NO requires C, 74.47; H, 4.86; N, 9.65%), $\nu_{max.}$ 3440 cm.$^{-1}$ (OH); τ(CD_3COOD) 0.28 (s, 1H, C1-H), 1.50 (d, 1H, C3-H, $J_{3,4}$=6.0 Hz), 1.85 (d, 1H, C4-H, $J_{4,3}$= 6.0 Hz.), 2.06 (t, 1H, C6-H, J=8.0 Hz.), 2.46 (q, 1H, C5 or C7-H, $J_{5,7}$ = 2.5 Hz, $J_{5,6}$ = $J_{6,7}$ = 8.0 Hz.), 2.70 (q, 1H, C7 or C5-H).

8-Benzoyloxyisoquinoline.

8-Hydroxyisoquinoline (2.0 g., 14 m.mol.) was converted into 8-benzoyloxyisoquinoline using the usual Schotten-Baumann conditions.[169] The semi-solid obtained was chromatographed on neutral alumina in ether and methanol. Recrystallisation from ether/40-60 pet.ether gave pale pink needles, m.p.76-77° (2.0 g., 59%) (Found: C, 76.92; H, 4.45; N, 5.62.

$C_{16}H_{11}NO_2$ requires C, 77.09; H, 4.45; N, 5.62%); $\nu_{max.}$ 1740 cm.$^{-1}$ (ester C=O); τ 0.47 (s, 1H, C-1H), 1.36 (d, 1H, C3-H, $J_{3,4}$= 6.0 Hz), ca. 1.64 (m, 2H, ortho hydrogens of C8-benzoyloxy group), 2.1-2.6 (m, 7H, other aromatic protons).

8-Benzoyloxy-2-p-toluoyl-1,2-dihydroisoquinaldonitrile

Use of 8-benzoyloxyisoquinoline (1.65 g., 6.5 m.mol.), p-toluoyl chloride (2.04 g., 13 m.mol.) and potassium cyanide (1.3 g., 19.5 m.mol.) in the general procedure (p. 133) gave 8-benzoyloxy-2-p-toluoyl-1,2-dihydroisoquinaldonitrile (1.3 g., 50%). Recrystallisation from ethyl acetate gave colourless needles, m.p. 207-207.5° (Found: C, 75.97; H, 4.59; N, 6.94. $C_{25}H_{18}N_2O_3$ requires C, 76.13; H, 4.60; N, 7.10%); $\nu_{max.}$ 2260 cm.$^{-1}$ (w) (CN), 1735 cm.$^{-1}$ (ester C=O), 1660 cm.$^{-1}$ (N-C=O); τ ca. 1.72 (m, 2H, benzoyloxy ortho hydrogens), 2.2-3.1 (m,10H, aromatic protons), 3.27 (q, 1H, C3-H, $J_{3,4}$= 8Hz, $J_{1,3}$ = 0.8 Hz), 3.33 (d, 1H, C1-H, $J_{1,3}$ = 0.8 Hz), 3.95 (d, 1H, C4-H, $J_{4,3}$ = 8.0 Hz.), 7.62 (s, 3H, CH_3).

Rearrangement reaction on 8-benzoyloxy-2-p-toluoyl-1,2-dihydroisoquinaldonitrile.

A suspension of sodium hydride (0.03 g., 1.15 m.mol.) in dimethylformamide was added slowly to the stirred solution of 8-benzoyloxy-2-p-toluoyl-1,2-dihydroisoquinaldonitrile (0.45 g., 1.15 m.mol.) in dimethylformamide (20 ml.). After 40 minutes, a red colour started appearing with the evolution of hydrogen. Stirring was continued for 30 minutes at 0° and for the next 6 hours at room temperature, during which time the colour faded slightly. The reaction mixture was then

poured on to ice to give a yellow solution which was neutralised with dilute hydrochloric acid. The solution was extracted with chloroform several times, dried (Na_2SO_4) and evaporation of the solvents (chloroform and dimethylformamide) left a yellow oil. The yellow oil was taken in chloroform and extracted several times with ca. 50% hydrochloric acid. The chloroform layer and the acid extract were worked-up separately.

The acid extract was basified with ammonium hydroxide and extracted with chloroform using a liquid-liquid continuous extractor. The chloroform extract was dried (K_2CO_3) and evaporated to give a light brown crystalline material (14 mg., 3%), m.p. 214-218°. Recrystallisation from methanol gave a compound considered to be 1-cyano-8-hydroxyisoquinoline, m.p. 216-218°. $\nu_{max.}$ 3400 cm.$^{-1}$ (OH), 2160 cm.$^{-1}$ (CN); τ(CD_3COOD) 1.30 (d, 1H, C3-H, $J_{3,4}$= 6 Hz.), 1.97 (d, 1H, C4-H, $J_{4,3}$ = 6 Hz.), 2.05-3.0 (m, 3H, other atomatic protons); m/e 170.

The chloroform layer was dried (Na_2SO_4) and evaporated to give a yellow syrup (0.2 g.) which could not be induced to crystallisation. Purification by preparative layer chromatography in 95% benzene and 5% ethyl acetate gave four products. One had the R_f (=0.744) corresponding to that of the starting compound. Two were minor fractions (R_f,0.457 and 0.628) and were not investigated further. The fourth was a light yellow amorphous solid (68 mg., 15%). Recrystallisation from methanol gave 1-benzoyl-8-hydroxy-2-p-toluoyl-1,2-dihydroisoquinaldonitrile as pale brown rhombs, m.p. 231-232° (Found N, 6.70. $C_{25}H_{18}N_2O_3$ requires N, 7.10); $\nu_{max.}$ 3200 cm.$^{-1}$ (bonded OH), 2220 cm.$^{-1}$(CN), 1695 cm.$^{-1}$ (diaryl ketone),

1665 cm.$^{-1}$ (N-C=O), 1630 cm.$^{-1}$ (C3=C4); τ (DMSO-d_6)0.55 (b.s., 1H, exchangeable, OH), 2.2-3.8 (m, 13H, aromatic and C3-H), 4.02 (d, 1H, C4-H), $J_{4,3}$ = 8.0 Hz), 7.60 (s, 3H, CH_3).

(ii) Competitive acyl-rearrangements versus Michael reactions

Rearrangement studies on N-crotonoyl-1,2-dihydroisoquinaldonitrile

N-Crotonoyl-1,2-dihydroisoquinaldonitrile

Use of isoquinoline (4.0 g., 32 m.mol.) and crotonoyl chloride (6.5 g., 64 m.mol.) in the general procedure (p. 133) gave N-crotonoyl-1,2-dihydroisoquinaldonitrile (3.80 g., 55%). Recrystallisation from 95% ethanol gave colourless stout needles, m.p. 141-141.5° (Found: C, 75.08; H, 5.49; N, 12.32. $C_{14}H_{12}N_2O$ requires C, 74.99; H, 5.38; N, 12.49%); $\nu_{max.}$ 2220 cm.$^{-1}$ (w) (CN), 1675 cm.$^{-1}$ (N-C=O), 1645 and 1630 cm.$^{-1}$ (C=C double bonds); τ 2.4-3.0 (m, 5H, aromatic protons and β-proton in N-CO-$\overset{\alpha}{C}H=\overset{\beta}{C}H-CH_3$), 3.12 (q, 1H, C3-H, $J_{3,4}$ = 8.0 Hz., $J_{1,3}$=0.85Hz.), 3.38 (d, 1H, C1-H, $J_{1,3}$= 0.85 Hz.), 3.72 (α proton in crotonoyl moiety : multiplet collapsed to doublet (J=14.0 Hz.) on saturating the methyl resonance at 8.05), 3.88 (d, 1H, C4-H, $J_{4,3}$= 8.0 Hz.), 8.05 (split doublet, 3H, methyl, $J_{CH_3,\beta\text{-}H}$=7.0 Hz., $J_{CH_3,\alpha\text{-}H}$=1.5 Hz.), $\lambda_{max.}$ 228 nm. (ϵ , 10525), 295 (11005), 310 (20332); m/e 224.

Rearrangement reaction on N-crotonoyl-1,2-dihydro-isoquinaldonitrile

A suspension of sodium hydride (0.24 g., 0.01 mol.) in dimethylformamide was added slowly to the stirred solution of N-crotonoyl-1,2-dihydroisoquinaldonitrile (2.24 g., 0.01 mole.) in dimethylformamide (30 ml.) at 0° under nitrogen. The

usual work-up procedure gave a solid product, which was chromatographed on alumina in 90% benzene and 10% ethyl acetate to yield colourless syrup (0.67g., 32%) as the major rearrangement product. Recrystallisation from ethyl acetate gave colourless shining plates, m.p. 233-234° (Found: C,76.63; H, 5.63; N, 9.97. $C_{27}H_{23}N_3O_2$ requires C, 76.94; H, 5.50; N, 9.97%); accurate mass measurement gave measured mass, 421.1780. Calculated mass for $C_{27}H_{23}N_3O_2$, 421.1790. $\nu_{max.}$ 3180 cm.$^{-1}$ (bonded OH), 1695 cm.$^{-1}$ (N-C=O out of plane), 1650 cm.$^{-1}$ (C=N-), 1628 cm.$^{-1}$ (double bond). τ : see Table I, p. 50 ; $\lambda_{max.}$ 220 nm. (ϵ 53371), 263 (29560), 312 (6021), 324 (6842); m/e 421.

Treatment of rearrangement product with NaH/CH_3I.

A suspension of sodium hydride (6 mg., 0.25 m.mol.) in dimethylformamide (5 ml.) was added to the stirred solution of the rearrangement product (0.1 g., 0.25 m.mol.) in dimethylformamide (20 ml.). No red colour appeared. The mixture was heated up to 90° for one hour and methyl iodide (1 ml.) added; stirring continued for a further period of 30 minutes and then the reaction mixture was poured on to ice. The precipitated product was filtered, washed with water and dried. Preparative layer chromatography on silica in 80% benzene and 20% ethyl acetate gave the O-methyl derivative of the rearrangement product (89.3 mg., 89%). Recrystallisation from ethyl acetate gave colourless rhombs, m.p. 220-221° (Found: C, 77.34; H, 5.84; N, 9.67. $C_{28}H_{25}N_3O_2$ requires C, 77.22; H, 5.79; N, 9.65%); $\nu_{max.}$ 1690 cm.$^{-1}$ (N-C=O, out of plane), 1620 cm.$^{-1}$

(double bond); τ 1.49 (d, 1H, C3-H in isoquinoline moiety), 1.8-3.3 (m, 10H, aromatic including C3-H (Reissert moiety) at 2.93 as doublet), 3.77 (d, 1H, C4-H of Reissert moiety, $J_{4,3}$ = 7.0 Hz.), 4.63 (q, 1H, =CH), 6.91 (s, 3H, OCH_3), 7.4-7.9 (m,3H, $CH-CH_2$), 8.13 (d, 3H, CH_3), 9.46 (d, 3H, CH_3, J=7.0 Hz); $\lambda_{max.}$ 218 nm., 265.5, 308, 321.5; m/e 435.

Hydrogenation of the rearrangement product

Rearrangement product (0.1 g., 0.25 m.mol.) was dissolved in ethanol and platinum oxide (0.01 g.) was added. The product was reduced at room temperature and pressure until uptake of hydrogen ceased. The catalyst was filtered off and the solvent evaporated under vacuum. Preparative layer chromatography on alumina in 80% benzene and 20% ethyl acetate gave the hydrogenated rearrangement product, corresponding to the uptake of two mol. of hydrogen, as the major product (52 mg., 52%). The product was recrystallised from ethanol, m.p. 295-297° (Found: C, 77.47; H, 6.88; N, 9.96. $C_{27}H_{27}N_3O_2$ requires C, 76.21; H, 6.40; N, 9.88%); $\nu_{max.}$ 1660, 1405, 1300 and 750 $cm.^{-1}$; τ 2.8-3.0 (m, 8H, aromatic protons), 5.6-8.0 (m, 13H), 8.85 (d, 3H, CH_3), 10.05 (d, 3H, CH_3); $\lambda_{max.}$ 210, 240, 280 nm.

Treatment of the rearrangement product with NaH/D_2O

A suspension of sodium hydride (6 mg., 0.25 m.mol.) in dimethylformamide (5 ml.). was added to the stirred solution of the rearrangement product (0.1 g., 0.25 m.mol.) in dimethylformamide (20 ml.). The mixture was heated up to 90° and excess of D_2O added. The solvent was evaporated

under high vacuum to dryness. The residue was recrystallised from ethyl acetate to give a crystalline product. The n.m.r. spectrum showed absence of low field signal (-0.65 τ) but was otherwise unchanged. The infrared spectrum was identical with that of the starting material.

Attempted cleavage of the amide C-N bond in the rearrangement product by use of strong base

The rearrangement product (0.5 g., 1.25 m.mol.) was dissolved in ethanol (40 ml.) and to it was added potassium hydroxide (5 g.) dissolved in water (5 ml.). The mixture was refluxed for 25 hours, cooled and solvent evaporated. The residue was dissolved in excess of water and neutralised. A yellow product precipitated out and was filtered. Recrystallisation from methanol gave a yellow amorphous powder, m.p. 200° (decomposition). $\nu_{max.}$ 3410 cm.$^{-1}$ (NH and/or OH), 3220 and 1730 cm.$^{-1}$ (saturated aliphatic acid). Attempts to esterify this acid using methanol saturated with hydrogen chloride gas were unsuccessful.

Rearrangement studies on N-(β,β-dimethyl)acryloyl-1,2-dihydroisoquinaldonitrile:

N-(β,β-Dimethyl)acryloyl-1,2-dihydroisoquinaldonitrile

Use of isoquinoline (8.0 g., 0.064 mol.) and β,β-dimethylacryloyl chloride (14.64 g., 0.128 mol.) in the general procedure (p.133) gave N-(β,β-dimethyl)acryloyl-1,2-dihydroisoquinaldonitrile (14.5 g., 98%). Recrystallisation from ethyl acetate gave colourless needles, m.p. 110-110.5°

(Found: C, 75.48; H, 5.93; N, 11.83. $C_{15}H_{14}N_2O$ requires C, 75.60; H, 5.92; N, 11.76%), $\nu_{max.}$ 2225 cm.$^{-1}$ (w) (CN), 1665 cm.$^{-1}$ (N-C=O), 1620 cm.$^{-1}$ (C3=C4); τ 2.5-3.05 (m, 4H, aromatic protons), 3.21 (q, 1H, C3-H, $J_{3,4}$= 8.0 Hz., $J_{3,1}$ = 0.8 Hz), 3.43 (d, 1H, C1-H, $J_{1,3}$ = 0.8 Hz.), 4.03 (d, 1H, C4-H, $J_{4,3}$= 8.0 Hz.), 4.10 (m, 1H, α-proton), 7.96 (d, 3H, CH_3, $J_{CH_3,\alpha\text{-H}}$=1.5 Hz.), 8.13 (d, 3H, CH_3); m/e 238.

Rearrangement reaction on N-(β,β-dimethyl)acryloyl-1,2-dihydroisoquinaldonitrile

N-(β,β-Dimethyl)acryloyl-1,2-dihydroisoquinaldonitrile (4.0 g., 17 m.mol.) was treated with sodium hydride (0.4 g., 17 m.mol.) in the same manner as described on p.146. The crude product was dissolved in chloroform and extracted with 60% hydrochloric acid. The acid extract and organic layers were worked-up separately.

The acid extract was neutralised with ammonium hydroxide solution and extracted with chloroform; dried (K_2CO_3) and evaporation of the solvent yielded brown gum. Chromatography on alumina in 80% benzene and 20% ethyl acetate gave 1-cyanoisoquinoline (25 mg., 3%). Recrystallisation from 40/60 pet. ether gave colourless needles, m.p. 75-76° (lit.[170] 78°). $\nu_{max.}$ 2233 cm.$^{-1}$ (CN), 1627 cm.$^{-1}$ (C=C); τ 1.33 (d, 1H, C-3 proton, $J_{3,4}$= 6.0 Hz), 1.63 (m, 1H, C8-H), 1.8-2.3 (m, 4H, other aromatic protons); m/e 154.

The chloroform layer was dried (Na_2SO_4) and the solvent evaporated to give dark brown material which was mixture of several compounds (t.l.c.) and could not be resolved.

Rearrangement studies on N-acryloyl-1,2-dihydroisoquinaldonitrile

N-Acryloyl-1,2-dihydroisoquinaldonitrile

Use of isoquinoline (8 g., 0.064 mol.) and acryloyl chloride (11.2 g., 0.128 mol.) in the general procedure (p. 133) gave N-acryloyl-1,2-dihydroisoquinaldonitrile (1.5 g., 12%). Recrystallisation from ethyl acetate gave pale yellow diamonds, m.p. 151-152° (Found: C, 74.50; H, 4.99; N, 13.37. $C_{13}H_{10}N_2O$ requires C, 74.27; H, 4.79; N, 13.33%); $\nu_{max.}$ 2245 cm.$^{-1}$ (CN), 1665 cm.$^{-1}$ (N-C=O), 1628 cm.$^{-1}$ (C=C); τ 2.4-3.0 (m, 4H, aromatic protons), 3.16 (q, 1H, C3-H, $J_{3,4}$= 8.0 Hz., $J_{1,3}$= 0.85 Hz.), 3.38 (m, 1H, α-H), 3.40 (d, 1H, C1-H, $J_{1,3}$= 0.85 Hz.), 3.46 (d, 1H, C4-H, $J_{4,3}$= 8.0 Hz.), 3.6-4.2 (m, 2H, β-2H); m/e 210.

Rearrangement reaction on N-acryloyl-1,2-dihydroisoquinaldonitrile

N-Acryloyl-1,2-dihydroisoquinaldonitrile (1.05 g., 5m.mol.) was treated with sodium hydride (0.12 g., 5 m.mol.) in dimethylformamide (20 ml.) in the same manner as described in the previous experiment. The acid extract and chloroform layer were worked-up separately.

The acid extract was basified with ammonium hydroxide and extracted with chloroform. Dried (K_2CO_3) and evaporation of the solvent gave brown solid. Chromatography on alumina in 90% benzene + 10% ethyl acetate gave 1-cyanoisoquinoline (11 mg.1%). Recrystallisation from 40/60 pet.ether gave colourless needles, m.p. 77° (lit.[170] 78°).

The chloroform layer was dried (Na_2SO_4) and the solvent evaporated to afford dark brown gum. Chromatography on alumina gave the rearrangement product (56 mg., 5%).

Recrystallisation from 95% ethanol gave colourless needles, m.p. 226-227° (Found: C, 76.41; H, 4.83; N, 10.66. $C_{25}H_{19}N_3O_2$ requires C, 76.32; H, 4.87; N, 10.68%); accurate mass measurement gave measured mass, 393.1467; Calculated mass for $C_{25}H_{19}N_3O_2$, 393.1478; $\nu_{max.}$ 2275 cm.$^{-1}$ (w) (CN), 1694 cm.$^{-1}$ (aryl alkyl ketone), 1660 cm.$^{-1}$ (N-C=O), 1621 cm.$^{-1}$ (C=C); τ 1.52 (d,1H, C3-H isoquinoline type, J=5.75 Hz.), 1.56 (m,1H, C8-H isoquinoline type), 2.1-2.6 (m,4H, aromatic protons), 2.7-3.0 (m,5H, aromatic protons), 3.04 (d,1H, C3-H in Reissert compounds, $J_{3,4}$= 7.0 Hz.), 3.90 (d,1H, C4-H Reissert type, $J_{4,3}$= 7.0 Hz.), 5.42 (d, 1H, J=15.0 Hz.), 5.92 (d, 1H, J=15.0 Hz.), 7.3-8.6 (m, 4H, CH_2-CH_2 ABCD type); $\lambda_{max.}$ 217.5 nm (ϵ 36294), 262.5 (30245), 312(5523), 322.5 (6312); m/e 393.

Rearrangement studies on N-crotonoyl-3-methyl-1,2-dihydroisoquinaldonitrile

N-Crotonoyl-3-methyl-1,2-dihydroisoquinaldonitrile

Use of 3-methylisoquinoline (10 g., 0.07 mol.) and crotonoyl chloride (14.6 g., 0.14 mol.) in the general procedure (p. 133) gave N-crotonoyl-3-methyl-1,2-dihydroisoquinaldonitrile (11.6 g., 70%). Recrystallisation from ethyl acetate gave pale yellow rhombs, m.p. 117-118° (Found: C, 75.68; H, 5.80; N, 11.70. $C_{15}H_{14}N_2O$ requires C, 75.60; H, 5.92; N, 11.76%); $\nu_{max.}$ 2240 cm.$^{-1}$ (w) (CN), 1665 cm.$^{-1}$ (N-C=O), 1630 cm.$^{-1}$ (C=C); τ 2.6-3.35 (m, 5H, aromatic and β-H), 3.38 (s, 1H, C1-H), 3.69 (q, 1H, C4-H , $J_{C4\text{-}H,\ C3\text{-}Me}$= 1.5 Hz.), 3.96 (dq, 1H, α-H, $J_{\alpha,\beta}$=14.0 Hz., $J_{\alpha\text{-}H,\beta\text{-}CH_3}$ = 1.5 Hz.), 7.73 (d, 3H, C3-Me, $J_{C3\text{-}Me,C4\text{-}H}$= 1.5 Hz.), 8.13 (split doublet, 3H,β-CH_3, $J_{CH_3,\beta\text{-}H}$= 7.0 Hz., $J_{CH_3,\alpha\text{-}H}$= 1.5Hz.), m/e 238.

Rearrangement reaction on N-crotonoyl-3-methyl-1,2-dihydroisoquinaldonitrile

N-Crotonoyl-3-methyl-1,2-dihydroisoquinaldonitrile (2.0 g., 8.4 m.mol.) was treated with sodium hydride (0.2 g., 8.4 m.mol.) in dimethylformamide (30 ml.) in a manner similar to that described in the previous experiment. The acid extract and chloroform layer were worked-up separately.

Acid extract:- Usual work-up procedure and chromatography gave 1-cyano-3-methylisoquinoline (30 mg., 2%). Recrystallisation from 40/60 pet. ether gave colourless needles, m.p. 103-104° (lit.[171] 105-106°); $\nu_{max.}$ 2233 cm.$^{-1}$ (CN); τ 1.8 (m, 1H, C8-H), 2.25 (s, 1H, C4-H), 2.05-2.45 (m, 3H, other aromatic protons), 7.30 (s, 3H, CH_3); m/e 168.

The chloroform layer was dried (Na_2SO_4) and evaporation of solvent gave a dark brown syrup. Chromatography on alumina in benzene and ethyl acetate gave a yellow oil which could not be crystallised. N.m.r. spectrum included τ 1.55 (m, 1H), 4.0 (q, 1H, C4-H in a Reissert moiety, $J_{C3\text{-}CH_3,C4\text{-}H}$ = 1.5 Hz.), 4.76 (q, 1H, J= 7.0 Hz.), 7.16 (s, 3H, C3-Me in an isoquinoline moiety), 7.55 (d, 3H, C3-Me in a Reissert moiety, $J_{C3\text{-}Me,C4\text{-}H}$ = 1.5 Hz.), 8.40 (d, 3H, CH_3, J=7.0 Hz.), 9.53 (d, 3H, CH_3); m/e 449.

2. N-Acyl Pseudo-Base Studies

(a) Reissert reaction with 5-nitroisoquinoline

Preparation of 5-nitroisoquinoline

Isoquinoline (41.0 g., 0.32 mol.) was converted to 5-nitroisoquinoline by the method of Dewar and Maitlis[172] utilising fuming nitric acid and concentrated sulphuric acid. Recrystallisation from aqueous ethanol gave 5-nitroisoquinoline as pale yellow fine needles, m.p. 108-109° (reported[172] 110.5-111.5°) (40.0g., 73%); τ 0.61 (s,1H, C1-H), 1.2-2.5 (m, 5H, aromatic protons).

Reaction of 5-nitroisoquinoline with acid chlorides and potassium cyanide

General procedure

The acid chloride (0.032 mol.) was added over a period of two hours to a stirred mixture of 5-nitroisoquinoline (0.016 mol.) in methylene chloride (20 ml.) and potassium cyanide (0.048 mol.) in water (8 ml.). Immediately a yellow precipitate appeared which increased with the continued addition of acid chloride. The stirring was continued for an additional two hours and the yellow precipitate of N-acyl pseudo-base, N-acyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline was filtered at the pump, washed with water, dried and recrystallised from an appropriate solvent. From the filtrate, the organic layer was washed with water, 2N hydrochloric acid, water, 2N sodium hydroxide and finally with water again. The solution was dried (Na_2SO_4) and evaporation of the solvent gave residue which was chromatographed on alumina in

benzene and ethyl acetate (80:20) to give the Reissert compound, N-acyl-5-nitro-1,2-dihydroisoquinaldonitrile. The yields obtained are recorded in Table II (p. 66).

Use of benzoyl chloride in the above procedure gave N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline which was recrystallised from ethanol and ethyl acetate to give yellow needles, m.p. 189-190° (lit.[82] 187-188°); τ (DMSO-d_6) 1.6-2.9 (m, 10H), 3.0-3.4 (m, 2H); $\nu_{max.}$ 3385 cm.$^{-1}$ (b) (bonded OH), 1663 cm.$^{-1}$ (N-C=O), 1625 cm.$^{-1}$ (C=C). Also formed was N-benzoyl-5-nitro-1,2-dihydroisoquinaldonitrile which was recrystallised from ethanol to give yellow plates, m.p. 148-149° (lit.[81] 148°) (Found: C, 67.10; H, 3.79; N, 13.96. $C_{17}H_{11}N_3O_3$ requires C, 66.88; H, 3.63; N, 13.77%); $\nu_{max.}$ 1665 cm.$^{-1}$ (N-C=O), 1620 cm.$^{-1}$ (C=C); τ 1.6-2.7 (m,8H, aromatic protons), 3.06 (s,2H), 3.25 (s,1H); $\lambda_{max.}$ 211 nm. (ε 18950), 268 (6805), 303 (8750), 352 (4454).

Use of p-toluoyl chloride in the general procedure (p. 154) gave 1-hydroxy-5-nitro-N-p-toluoyl-1,2-dihydroisoquinoline which was recrystallised from acetone to give yellow needles, m.p. 183-184° (Found: C, 65.86; H, 4.57; N, 9.13. $C_{17}H_{14}N_2O_4$ requires C, 65.80; H, 4.55; N, 9.03%); $\nu_{max.}$ 3395 cm.$^{-1}$ (b) (OH), 1668 cm.$^{-1}$ (N-C=O), 1624 cm.$^{-1}$ (C=C); τ (DMSO-d_6) 1.8-3.6 (m, 11H, aromatic and C-1, C-3, C-4, OH protons), 7.71 (s, 3H, CH_3); m/e 310. Also formed was 5-nitro-N-p-toluoyl-1,2-dihydroisoquinaldonitrile which was recrystallised from 95% ethanol to give fine yellow needles, m.p.198-200° (Found: C, 67.64; H, 4.12; N, 13.31. $C_{18}H_{13}N_3O_3$ requires

C, 67.70; H, 4.11; N, 13.16%); $\nu_{max.}$ 1688 cm.$^{-1}$ (N-C=O), 1623 cm.$^{-1}$ (C=C); τ 1.8-3.4 (m, 10H, aromatic, C-1, C-3 and C-4 protons), 7.60 (s, 3H, CH_3); m/e 319.

Use of p-chlorobenzoyl chloride in the general procedure (p. 154) gave N-p-chlorobenzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline which on recrystallisation from 95% ethanol gave yellow needles, m.p. 179-180° (Found: C, 58.07; H, 3.60; N, 8.46. $C_{16}H_{11}N_2O_4Cl$ requires C, 58.11; H, 3.35; N, 8.47%); $\nu_{max.}$ 3415 cm.$^{-1}$ (b) (OH), 1665 cm.$^{-1}$ (N-C=O), 1625 cm.$^{-1}$ (C=C); τ (DMSO-d_6) 1.85-3.60 (m, 11H, aromatic and other protons). Also formed was N-p-chlorobenzoyl-5-nitro-1,2-dihydroisoquinaldonitrile which on recrystallisation from ethyl acetate gave deep yellow plates, m.p. 199-200° (Found: C, 59.98; H, 3.16; N, 12.39. $C_{17}H_{10}N_3O_3Cl$ requires C, 60.09; H, 2.97; N, 12.37%); $\nu_{max.}$ 2245 cm.$^{-1}$ (w) (CN), 1673 cm.$^{-1}$ (N-C=O), 1620 cm.$^{-1}$ (C=C), 1520 cm.$^{-1}$ (NO_2); τ 1.7-2.8 (m, 7H, aromatic protons), 3.12 (s, 2H), 3.36 (s,1H).

Use of anisoyl chloride in the general procedure (p. 154) gave N-anisoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline which on recrystallisation from 95% ethanol gave yellow needles, m.p. 167-169° (Found: C, 62.93; H, 4.29; N, 8.58. $C_{17}H_{14}N_2O_5$ requires C, 62.57; H, 4.32; N, 8.59%); $\nu_{max.}$ 3400 cm.$^{-1}$ (b) (OH), 1665 cm.$^{-1}$ (N-C=O), 1618 cm.$^{-1}$ (C=C); τ (DMSO-d_6) 1.7-3.6 (m, 11H, aromatic, C-1, C-3, C-4 and OH protons). Also formed was N-anisoyl-5-nitro-1,2-dihydroisoquinaldonitrile which on recrystallisation from ethyl acetate gave deep yellow plates, m.p. 209-210° (Found: C, 64.32;

H, 3.82; N, 12.63. $C_{18}H_{13}N_3O_4$ requires C, 64.47; H, 3.91; N, 12.53%); $\nu_{max.}$ 2245 cm.$^{-1}$ (w) (CN), 1663 cm.$^{-1}$ (N-C=O), 1630 cm.$^{-1}$ (C=C); τ 1.7-3.0 (m 7H, aromatic protons), 3.10 (b.s., 2H), 3.40 (s,1H), 6.10 (s, 3H, OCH_3).

Use of acetyl chloride in the general procedure (p. 154) gave N-acetyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline which on recrystallisation from 95% ethanol gave yellow plates, m.p. 174-176° (Found: C, 56.71; H, 4.31; N, 12.05. $C_{11}H_{10}N_2O_4$ requires C, 56.41; H, 4.30; N, 11.96%); $\nu_{max.}$ 3370 cm.$^{-1}$ (b) (OH), 1673 cm.$^{-1}$ (N-C=O), 1620 cm.$^{-1}$ (C=C); τ (DMSO-d_6) 1.8-2.8 (m, 4H, aromatic and OH protons), 2.15-2.5 (m, 3H, C-1, C-3 and C-4 protons), 7.61 (s, 3H, CH_3). Also formed was N-acetyl-5-nitro-1,2-dihydroisoquinaldonitrile which on recrystallisation from ethyl acetate gave yellow needles, m.p. 186-187° (Found: C, 59.32; H, 3.88; N, 1740. $C_{12}H_9N_3O_3$ requires C, 59.26; H, 3.73; N, 17.28%); $\nu_{max.}$ 2250 cm.$^{-1}$ (w) (CN), 1653 cm.$^{-1}$ (N-C=O), 1620 cm.$^{-1}$ (C=C); τ 1.8-3.3 (m, 6H, aromatic, C-1, C-3 and C-4 protons), 7.69 (s, 3H, CH_3).

2.(b) Chemistry of the N-Acyl Pseudo-Base System

(i) Potential ring-opening reactions

Attempted reductive cleavage of the Cl-N bond using sodium borohydride in methanol

To a suspension of N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline (1.0 g.) in methanol (50 ml.) was added sodium borohydride (1 g.) slowly with stirring. The solution became clear after stirring for a further period of 24 hours.

Solvent was evaporated and the residue was partitioned between chloroform and water. Chloroform layer was washed with sodium hydroxide and water, dried (Na_2SO_4) and evaporation of the solvent gave light brown material. Recrystallisation from 40/60 pet.ether gave needles, m.p. 107-109° (lit.[172] m.p. of which showed no depression on admixture with 5-nitro-isoquinoline prepared previously (p.154).

(ii) Reactions of the Cl-OH group

Preparation of N-acyl-1-alkoxy-5-nitro-1,2-dihydro-isoquinolines

General procedure

Preparation of O-methyl derivatives

The N-acyl pseudo-base (0.5 g.) was taken in methanol (50 ml.) and stirred at 45-50° for several hours (Table X p.160). After cooling, the solvent was evaporated to obtain a yellow solid. Chromatography on neutral alumina in benzene gave the N-acyl-1-methoxy-5-nitro-1,2-dihydroisoquinoline which was recrystallised from methanol.

Preparation of O-ethyl derivatives

The N-acyl pseudo-base (0.5 g.) was taken in absolute ethanol (40 ml.) and refluxed for 1-4 hours (Table X p.160), the reaction being followed by t.l.c. After cooling, the solvent was evaporated and the residue chromatographed on alumina in benzene and ethyl acetate.

The N-acyl-1-ethoxy-5-nitro-1,2-dihydroisoquinoline obtained was recrystallised from 95% ethanol.

The results are summarised in Tables III (p.77),

X (p. 160) and XI (p. 161).

Conversion of N-benzoyl-1-methoxy-5-nitro-1,2-dihydro-isoquinoline into N-benzoyl pseudo-base

N-Benzoyl-1-methoxy-5-nitro-1,2-dihydroisoquinoline (0.5 g.) was taken in aqueous dioxan (40 ml., ca. 25%) and stirred at room temperature. A yellow precipitate started appearing and was complete after 20 minutes (by t.l.c., no starting material present). The precipitated solid was filtered and dried. The solid had an identical infrared spectrum with that of authentic N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline prepared previously (p. 155).

(iii) Reactions of the C3-C4 double bond

Bromohydrin formation

To a solution of N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline (1.0 g., 3 m.mol.) in aqueous tetrahydrofuran (100 ml., 66%) was added bromine (0.5 g., 3 m.mol.). The bromine colour disappeared immediately. The solution was poured into water (300 ml.) and extracted with ether; dried (Na_2SO_4) and evaporation of the solvent gave brown viscous oil (1.4 g.). Chromatography on silica in 95% ethyl acetate and 5% methanol gave N-benzoyl-4-bromo-1,3-dihydroxy-5-nitro-1,2,3,4-tetrahydro-isoquinoline as an oil (1.2 g., 92%). Recrystallisation from methanol gave colourless stout needles, m.p. 153-154° (Found: C, 49.04; H, 3.47; N, 7.22. $C_{16}H_{13}N_2O_5Br$ requires C, 48.87; H, 3.33; N, 7.13%); $\nu_{max.}$ 3340 $cm.^{-1}$ b (OH), 1630 (N-C=O); τ 1.8-2.8 (m, 8H, aromatic protons),

TABLE X: Preparation of N-acyl-1-alkoxy-5-nitro-1,2-dihydroisoquinolines

N-Acyl-1-alkoxy substituents	Temperature	Reaction Time (hours)	Crystals	Molecular Formula	Found % C	H	N	Calculated % C	H	N
N-benzoyl-1-methoxy-	45-50°	12	whispy yellow needles	$C_{17}H_{14}N_2O_4$	65.63	4.66	8.94	65.80	4.55	9.03
N-benzoyl-1-ethoxy-	Reflux	3	yellow needles	$C_{18}H_{16}N_2O_4$	66.64	5.03	8.62	66.66	4.97	8.64
N-p-toluoyl-1-methoxy-	45-50°	22	yellow needles	$C_{18}H_{16}N_2O_4$	66.56	5.07	8.74	66.66	4.97	8.64
N-p-toluoyl-1-ethoxy-	*	*	yellow plates	$C_{19}H_{18}N_2O_4$	67.39	5.48	8.38	67.44	5.36	8.28
N-p-chlorobenzoyl-1-methoxy-	45-50°	20	long yellow needles	$C_{17}H_{13}N_2O_4Cl$	59.44	3.86	7.96	59.21	3.80	8.13
N-p-chlorobenzoyl-1-ethoxy-	Reflux	4	fine yellow needles	$C_{18}H_{15}N_2O_4Cl$	60.44	4.29	7.74	60.26	4.21	7.81
N-p-anisoyl-1-methoxy-	45-50°	20	yellow needles	$C_{18}H_{16}N_2O_5$	63.53	4.60	8.21	63.52	4.74	8.23
N-p-anisoyl-1-ethoxy	Reflux	1	pale yellow needles	$C_{19}H_{18}N_2O_5$	64.54	4.95	7.80	64.40	5.12	7.91

*Product obtained directly on attempted recrystallisation of 1-hydroxy-5-nitro-N-p-toluoyl-1,2-dihydroisoquinoline from ethanol.

TABLE XI: N.m.r. and infrared spectra details of N-acyl-1-alkoxy-5-nitro-1,2-dihydroisoquinolines

N-Acyl-1-alkoxy-substituents	τ				$J_{1,3}$ Hz	$J_{3,4}$ Hz	Other protons τ	Infrared spectra cm^{-1}
	Aromatic protons	C-1 proton (d)	C-3 proton (q)	C-4 protons (d)				
N-benzoyl-1-methoxy-	1.7-2.8 (m,8H)	3.41	2.96	3.17	1.3	8.0	6.62 (s,3H,OCH_3)	1680 (N-C=O) 1620 (C=C) 1057 (ether)
N-benzoyl-1-ethoxy-	1.8-2.8 (m,8H)	3.31	2.94	3.14	1.3	8.0	6.29 (q,2H,CH_2) 8.84 (t,3H,CH_3)	1681 (N-C=O) 1623 (C=C) 1065 (ether)
N-p-toluoyl-1-methoxy-	1.8-2.8 (m, 7H)	3.42	2.93	3.19	1.3	8.0	6.53 (s,3H,OCH_3) 7.62 (s,3H,CH_3)	1682 (N-C=O) 1623 (C=C) 1060 (ether)
N-p-toluoyl-1-ethoxy-	1.8-2.8 (m,7H)	3.33	2.96	3.17	1.3	8.0	6.28 (q,2H,CH_2) 7.60 (s,3H,ar.CH_3) 8.83 (t,3H,CH_3)	1674 (N-C=O) 1620 (C=C) 1065 (ether)
N-p-chlorobenzoyl-1-methoxy	1.7-2.8 (m,7H)	3.43	2.96	3.15	1.3	8.0	6.61 (s,3H,OCH_3)	1680 (N-C=O) 1623 (C=C) 1050 (ether)
N-p-chlorobenzoyl-1-ethoxy	1.7-2.8 (m,7H)	3.37	3.01	3.16	1.3	8.0	6.32 (q,2H,CH_2) 8.83 (t,3H,CH_3)	1683 (N-C=O) 1624 (C=C) 1055 (ether)
N-p-anisoyl-1-methoxy-	1.7-2.8 (m,7H)	3.44	2.91	3.18	1.3	8.0	6.15 (s,3H,ar.OCH_3) 6.62 (s,3H,Cl-OCH_3)	1678 (N-C=O) 1624 (C=C) 1060 (ether)
N-p-anisoyl-1-ethoxy-	1.7-2.8 (m,7H)	3.35	2.90	3.14	1.3	8.0	6.15 (s,3H,OCH_3) 6.28 (q,2H,CH_2) 8.83 (t,3H,CH_3)	1675 (N-C=O) 1620 (C=C) 1055 (ether)

3.55 (b.s., 1H, C1-H), 4.23 (d, 2H, C3 and C4 protons), 4.50 (b.s., 2H, exchangeable, 2 OH); $\lambda_{max.}$ 225 nm., m/e 392:394 (1:1).

O-Methylbromohydrin formation

N-Benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline (0.5 g., 1.5 m.mol.) was taken in methanol (40 ml.) containing acetic acid (1 ml.). The mixture was heated for fifteen minutes and cooled. Bromine (0.25 g., 1.5 m.mol.) was added. The bromine colour disappeared immediately. The solution was poured in water and extracted with ether, dried (Na_2SO_4) and evaporation of the solvent gave N-benzoyl-4-bromo-1-hydroxy-3-methoxy-5-nitro-1,2,3,4-tetrahydroisoquinoline (0.4 g., 59%). Recrystallisation from methanol gave colourless long fine needles, m.p. 148-150° (Found: C, 50.45; H, 3.95; N, 7.31. $C_{17}H_{15}N_2O_5Br$ requires C, 50.14; H, 3.71; N, 6.88%); $\nu_{max.}$ 3460 cm.$^{-1}$ b (OH), 1663 cm.$^{-1}$ (N-C=O), 1050 cm.$^{-1}$ (ether); τ 1.6-2.6 (m, 10H), 3.85 (d, 1H), 4.61 (b.s., 1H, exchangeable, C1-OH), 6.52 (s, 3H, OCH_3); m/e 406;408 (1:1).

Preparation of N-acetyl-4-bromo-3-methoxy-1,2,3,4-tetrahydro-isoquinaldonitrile

N-Acetyl-1,2-dihydroisoquinaldonitrile (1.0 g., 5 m.mol.) on treatment with bromine (0.8 g., 5 m.mol.) in methanol (80 ml.) by the same method as described for the last experiment gave thick brown syrup (1.2 g; 80%). Recrystallisation from methanol gave N-acetyl-4-bromo-3-methoxy-1,2,3,4-tetrahydro-isoquinaldonitrile as colourless rhombs, m.p. 155-156° (Found: C, 50.56; H, 4.29; N, 9.14. $C_{13}H_{13}N_2O_2Br$ requires C, 50.50;

H, 4.24; N, 9.06%); $\nu_{max.}$ 2240 cm.$^{-1}$ w (CN), 1663 cm.$^{-1}$ (N-C=O), 1055 cm.$^{-1}$ (ether); τ (DMSO-d_6) 2.2-2.7 (m, 4H, aromatic protons), 3.95 (s,1H, C1-H), 4.20 (d, 1H, C3-H), $J_{3,4}$= 3.0 Hz), 4.30 (d,1H,C4-H , $J_{4,3}$= 3.0 Hz), 6.71 (s,3H, OCH_3), 7.66 (s, 3H, CH_3); m/e 308 and 310 (1:1).

Reaction of N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline with hypochlorous acid

Hypochlorous acid was prepared from the addition of a solution of sodium hypochlorite (12% w/v available chlorine) (50 ml.) to 2N nitric acid (50 ml.). The strength was determined as 0.57% hypochlorous acid by titration with sodium thiosulphate, using potassium iodide-starch solution as indicator.

A stirred solution of N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline (1.0 g., 3.0 m.mol.) in dioxan (50 ml.) was treated with the freshly prepared hypochlorous acid solution (30 ml., 3.2 m.mol.) dropwise at room temperature until a slight excess was present (tested by potassium iodide/starch paper). The solution was stirred for a further period of one hour and the solvent evaporated. The residue was washed with water and recrystallisation from methanol gave N-benzoyl-4-chloro-3-hydroxy-5-nitro-1,2,3,4-tetrahydroisoquinolone (0.4 g., 36%) as colourless rhombs, m.p. 226-227° (Found: C, 55.34; H, 3.51; N, 8.23. $C_{16}H_{11}N_2O_5Cl$ requires C, 55.42; H, 3.19; N, 8.08%); $\nu_{max.}$ 3440 cm.$^{-1}$ (OH), 1710, 1682, 1665 cm.$^{-1}$ (CO-N-CO); τ (DMSO-d_6) 1.4-2.6 (m, 8H, aromatic protons), 3.90 (d, 1H, C3 or C4-H, $J_{3,4}$= 3.0 Hz), 3.9 (b.s., 1H, exchangeable, C3-OH), 4.07 (d, 1H, C4 or C3-H); m/e 346 and 348 (3:1).

The mother liquor was concentrated and chromatographed on alumina in benzene and ethyl acetate to afford 4-chloro-5-nitroisoquinoline (15 mg., 2%). Recrystallisation from 95% ethanol gave pale yellow needles, m.p. 180-182° (Found: C, 52.04; H, 2.52; N, 13.27. $C_9H_5N_2O_2Cl$ requires C, 51.81; H, 2.41; N, 13.43%); $\nu_{max.}$ 1625 cm.$^{-1}$ (C=N), 1575 cm.$^{-1}$ (NO_2); τ 0.53 (s,1H,C1-H), 1.26 (s, 1H, C3-H), 1.46 (split doublet, 1H, C6-H, $J_{6,7}$ = 7.7 Hz, $J_{6,8}$ = 2.5 Hz), 1.65 (split doublet, 1H, C8-H, $J_{8,7}$ = 7.7 Hz, $J_{8,6}$ = 2.5 Hz), 2.10 (unsymmetrical triplet, C7-H, $J_{7,6} = J_{7,8}$ = 7.7 Hz); m/e 208 and 210 (3:1).

Reaction of N-benzoyl-1-methoxy-5-nitro-1,2-dihydroisoquinoline with hypochlorous acid

N-Benzoyl-1-methoxy-5-nitro-1,2-dihydroisoquinoline (0.2 g.) was treated with freshly prepared hypochlorous acid (6 ml.) by the same method as described in the previous experiment and work-up procedure followed. Recrystallisation from methanol gave colourless rhombs, m.p. 226-227°. The compound, N-benzoyl-4-chloro-3-hydroxy-5-nitro-1,2,3,4-tetrahydroisoquinolone (95 mg., 42%), had the identical infrared and n.m.r. spectrum as that prepared on p. 163 , mixed m.p. undepressed.

The mother liquor was concentrated and chromatographed on silica plates in 80% benzene and 20% ethyl acetate to afford 5-nitroisoquinoline (65 mg., 58%). Recrystallisation from aqueous ethanol gave yellow needles, m.p. 109-110° (lit.,[172] 110°).

Reaction of N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline with monoperphthalic acid

An ether solution of monoperphthalic acid was prepared by the method of Royals and Harrell[173] utilising phthalic anhydride and alkaline hydrogen peroxide and its strength determined as ca. 0.5 molar by titrating with sodium thiosulphate.

N-Benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline (0.5 g., 1.5 m.mol.) was dissolved in dry dioxan (40 ml.) and to it was added monoperphthalic acid solution in ether (10 ml., 2.25 m.mol.). The reaction mixture was kept at room temperature and its progress followed by t.l.c. After five days, the solution was filtered to remove precipitated phthalic acid and 2N sodium hydroxide solution was added to the filtrate to destroy excess of monoperphthalic acid. The solvent was evaporated under vacuum and the residue was partitioned between water and chloroform. The chloroform layer was washed with water, dried (Na_2SO_4) and evaporation of the solvent gave light brown solid. Chromatography on a silica column in chloroform gave two compounds. The first compound, considered to be dibenzoic phthalic anhydride (20 mg., 2%), crystallised from benzene and 60/80 pet. ether as colourless needles, m.p. 110° (lit.[117] 131-132°). The infrared spectrum showed $\nu_{max.}$ 1790 cm.$^{-1}$, 1765 cm.$^{-1}$ (open chain anhydride); τ 1.9 (m, 6H, ortho hydrogens to $\overset{O}{\overset{\|}{C}}$-O grouping), 2.1-2.8 (m, 8H, other aromatic protons); m/e 374. The second compound was 5-nitroisocarbostyril (0.1 g., 31%) which crystallised from ethyl acetate as yellow needles, m.p. 250-251° (softening at 220°) (lit.[118] 251-252°

with softening at 227°). Accurate mass measurement gave measured mass, 190.0375; calculated mass for $C_9H_6N_2O_3$, 190.0378. $\nu_{max.}$ 3180 cm.$^{-1}$ (NH), 1690 cm.$^{-1}$ (C=O), 1637 cm.$^{-1}$ (C=C), 1530 cm.$^{-1}$ (NO_2); τ (DMSO-d_6)-1.8 (b.s., 1H, exchangeable, NH), 1.2-1.7 (m, 2H, C-6 and C-8 H), 2.34 (t, 1H, C7-H, $J_{6,7} = J_{7,8} = 8.0$ Hz), 2.53 (d, 1H, C3-H, $J_{3,4} = 7.0$ Hz), 3.01 (d, 1H, C4-H, $J_{4,3} = 7.0$ Hz); $\lambda_{max.}$ 221 nm. (ε 13694), 256 (8645), 310 (5135), 322 (4536), 370 (4108); m/e 190.

Attempted preparation of dibenzoic phthalic anhydride

The method reported by Zeavin and Fisher [117] was followed. A mixture of sodium phthalate (10.5 g., 0.05mol.) and benzoyl chloride (14.05 g., 0.1 mol.) was heated at 120° for 12 hours. After cooling, the mixture was shaken with warm benzene and filtered hot. Addition of 60/80 pet. ether gave long white needles (9.50 g., 70%), m.p. 132° (lit.[117] 132°). The compound was considered to be the monoanhydride and showed $\nu_{max.}$ 3200-2600 cm.$^{-1}$ (-COOH), 1860 cm.$^{-1}$, 1780 cm.$^{-1}$ (open chain anhydride), 1725 cm.$^{-1}$ (acid C=O); m/e 270.

Preparation of 5-nitroisocarbostyril

Isoquinoline 2-oxide[104] (2.5 g., 17 m.mol.) was converted into 5-nitroisoquinoline 2-oxide (2.0 g., 62%) by the method of Ochiai and Ikehara.[119] Recrystallisation from acetone gave yellow needles, m.p. 221-222° (lit.[119] 220°); $\nu_{max.}$ 1530 cm.$^{-1}$ (NO_2); τ(DMSO-d_6) 0.86 (s, 1H, C1-H), 1.3-2.4 (m, 5H, other aromatic protons).

5-Nitroisocarbostyril was prepared by the method of Wenkert, Johnston and Dave.[118] A solution of 5-nitroisoquinoline-N-oxide (0.43 g.) in acetic anhydride (5 ml.) was heated on the steam bath for 8 hours and then evaporated under reduced pressure. A mixture of the crystalline residue and 10% sodium carbonate was heated on the steam bath for 30 minutes and then filtered. Crystallisation of the product from methanol gave 5-nitroisocarbostyril (0.3 g., 70%) as buff needles, m.p. 249-251° (lit.[118] 251-252°); infrared, n.m.r. and ultraviolet spectra were identical with that obtained for the sample described on p. 165 and mixed m.p. undepressed.

2. (c) Investigation of the Synthesis of other N-Acyl Pseudo-Base Systems

(1) Reissert reaction with 3-methyl-5-nitroisoquinoline

Using the method of Elderfield et al.[174], 3-methylisoquinoline (9.0 g.) was converted into 3-methyl-5-nitroisoquinoline (7.0 g., 60%). Recrystallisation from aqueous ethanol gave yellow needles, m.p. 106-108° (lit.[174] 105-108.5°); τ 0.78 (s, 1H, C1-H), 1.53 (split doublet, 1H, C6-H, $J_{6,7}$ = 8.0 Hz., $J_{6,8}$ = 2.5 Hz), 1.80 (s, 1H, C4-H), 1.80 (split doublet, 1H, C8-H, $J_{8,7}$ = 8.0 Hz.), 2.44 (t, 1H, C7-H, $J_{7,6} = J_{7,8}$ = 8.0 Hz.).

Benzoyl chloride (2.5 ml., 2.2 m.mol.) was added over two hours to a stirred mixture of 3-methyl-5-nitroisoquinoline (2.0 g., 1.1 m.mol.) in methylene chloride (20 ml.) and potassium cyanide (2.0 g., 3.3 m.mol.) in water

(5 ml.). After an additional two hours of stirring, the layers were separated. The methylene chloride solution was washed with water, 2N hydrochloric acid, water, 2N sodium hydroxide and water, dried and evaporation of the solvent gave a deep yellow oil. Chromatography on alumina in benzene and ethyl acetate (80:20) gave N-benzoyl-3-methyl-5-nitro-1,2-dihydroisoquinaldonitrile (0.8 g., 57% based on recovered starting material) which on recrystallisation from 95% ethanol gave yellow needles, m.p. 159-160° (lit.[81] 159°). Also obtained was N-benzoyl-1-hydroxy-3-methyl-5-nitro-1,2-dihydroisoquinoline (0.12 g., 9% based on recovered starting material) which on recrystallisation from aqueous acetone gave yellow needles, m.p. 151-152° (Found: C, 65.94; H, 4.56; N, 9.01. $C_{17}H_{14}N_2O_4$ requires C, 65.80; H, 4.55; N, 9.03%); $\nu_{max.}$ 3430 cm.$^{-1}$ (OH), 1650 cm.$^{-1}$ (N-C=O); τ (DMSO-d_6) 1.8-2.9 (m, 8H, aromatic protons), 3.11 (q, 1H, C4-H, $J_{C4-H,\ C3-Me}$ = 1.5 Hz.), 3.43 (d, 1H, C1-H, $J_{C1-H,\ C1-OH}$ = 6.0 Hz.), 5.30 (d, 1H, C1-OH, exchangeable, $J_{C1-OH,\ C1-H}$ = 6.0 Hz.), 8.10 (d, 3H, C3-Me, $J_{C3-Me,\ C4-H}$ = 1.5 Hz.); m/e 310.

The unreacted 3-methyl-5-nitroisoquinoline was recovered from the acidic washings (1.2 g., 60%).

The above procedure was repeated twice (a) using potassium hydroxide (2.0 g.) when the pseudo-base, N-benzoyl-1-hydroxy-3-methyl-5-nitro-1,2-dihydroisoquinoline (0.45 g., 40% based on recovered starting material(1.0 g., 50%))was obtained (b) using water alone when the pesudo-base (0.72 g., 37% based on recovered starting material (1.1 g., 55%)).was obtained.

(ii) Reissert reaction with 4-nitro- and 7-nitroisoquinoline and isoquinoline-5-sulphonic acid

Reissert reaction with 4-nitroisoquinoline

(a) Preparation of 4-bromoisoquinoline

The compound was prepared according to the method of Bergstrom and Rodda.[123] The hydrobromide salt of isoquinoline (64.5 g., 0.5 mol.) was heated with bromine (27.5 ml.) at 170-180°. The pure 4-bromoisoquinoline (42.0 g., 40%) was collected by vacuum distillation (b.p. 108°/0.8 mm.) and crystallised from pet.ether (40/60), m.p. 39° (lit.[123] 38-39°).

(b) Preparation of 4-aminoisoquinoline

The compound was prepared[124] by heating 4-bromoisoquinoline (20.0 g.), concentrated ammonia (density, 0.88) (64 ml.) and hydrated copper sulphate (1.2 g.) at 165-170° in a shaking autoclave for 16 hours. The product was isolated and crystallised from benzene (6.3 g., 45%), m.p. 106° (lit.[124] 107°).

(c) Preparation of 4-nitroisoquinoline

4-Aminoisoquinoline (3.0 g.) was converted to 4-nitroisoquinoline (0.4 g., 11%) according to the method of Bryson[125] using sodium nitrite and cupro-cuproso sulphite.[175] Recrystallisation from aqueous ethanol gave yellow needles, m.p. 63-64° (lit.[125] 64.5°).

Reissert reaction with 4-nitroisoquinoline

Use of 4-nitroisoquinoline (0.32 g., 1.8 m.mol.), benzoyl chloride (0.5 ml., 3.6 m.mol.) and potassium cyanide (0.38g.,

5.4 m.mol.) in the procedure described on p. 167 gave only starting material (0.3 g., 94% recovery).

Reissert reaction with 7-nitroisoquinoline

7-Nitroisoquinoline was prepared according to the method reported in the literature.[127] 1,2,3,4-Tetrahydroisoquinoline (10.5 g.) was converted into the sulphate and nitrated using potassium nitrate (10.0 g.) in sulphuric acid (density 1.84, 50 ml.) according to the method of McCoubrey and Mathieson.[126] The free base, 7-nitro-1,2,3,4-tetrahydroisoquinoline was unstable and was converted into the hydrochloride (4.4 g., 25%). Dehydrogenation using iodine (11.2 g.) and freshly fused potassium acetate (9.3 g.) by the method of Potter and Taylor[127] gave 7-nitroisoquinoline (0.8 g., 25%). Recrystallisation from light petroleum (b.p. 100-120°) gave buff coloured needles, m.p. 174-176° (lit.[127] 176-177°); τ 0.53 (s, 1H, C1-H), 1.07 (d, 1H, C8-H, $J_{8,6}$ = 2.5 Hz.), 1.26 (d, 1H, C3-H, $J_{3,4}$ = 6.0 Hz.), 1.55 (split doublet, 1H, C6-H, $J_{6,5}$ = 9.0 Hz.), 2.02 (d, 1H, C5-H, $J_{5,6}$ = 9.0 Hz.), 2.23 (d, 1H, C4-H, $J_{4,3}$ = 6.0 Hz.); m/e 174.

Using 7-nitroisoquinoline (0.2 g., 1.12 m.mol.), benzoyl chloride (0.26 ml., 2.24 m.mol.) and potassium cyanide (0.22 g., 3.36 m.mol.) in the procedure described on p.167 gave a brown compound (0.1 g.) which was considered to be N-benzoyl-7-nitroisoquinolinium chloride. A small amount of this compound was dissolved in hot distilled water and silver nitrate solution added: a white precipitate soluble in ammonium hydroxide resulted. A Beilstein test for halogen was positive.

Unreacted 7-nitroisoquinoline was recovered from the acidic washings (0.1 g. 50%).

N-Benzoyl-7-nitroisoquinolinium chloride obtained above was taken in dichloromethane (10 ml.) and a solution of potassium hydroxide (0.5 g.) in water (1.5 ml.) added. The two phase system was stirred for three hours. After the usual work-up procedure, a tan coloured product was obtained. This was 7-nitroisoquinoline, m.p. 173-176° (lit.[127] 176-177°).

Reissert reaction with isoquinoline 5-sulphonic acid

The procedure described on p.167 was followed but no reaction took place. Isoquinoline 5-sulphonic acid was recovered in quantitative yield.

(iii) Reissert reaction with 6-Nitro- and 8-Nitroquinoline

Reissert reaction with 6-Nitroquinoline

Use of 6-nitroquinoline (2.0 g., 11.2 m.mol.), benzoyl chloride (2.6 ml., 22.4 m.mol.) and potassium cyanide (2.2 g., 33.6 m.mol.) in the general procedure (p. 133) i.e. stirring for eight hours gave N-benzoyl-6-nitro-1,2-dihydroquinaldonitrile (0.78 g., 23%). Recrystallisation from ethyl acetate gave pale yellow needles, m.p. 204-206° (reported[128] 201-202°); $\nu_{max.}$ 2245 cm.$^{-1}$ (w) (CN), 1664 cm.$^{-1}$ (N-C=O), 1614 cm.$^{-1}$ (C=C), 1516 cm.$^{-1}$ (NO_2); τ 1.88 (d, 1H, C5-H, $J_{5,7}$ = 2.5 Hz.), 2.20 (q, 1H, C7-H, $J_{7,5}$ = 2.5 Hz., $J_{7,8}$ = 8.75 Hz.), 2.61 (s, 5H, phenyl group), 3.07 (d, 1H, C8-H, $J_{8,7}$ = 8.75 Hz.), 3.27 (d, 1H, C4-H, $J_{4,3}$ = 9.0 Hz.), 3.65 - 3.91 (m, 2H, C2 and C3-H).

The above reaction was repeated using potassium hydroxide (2.2 g.). The usual work-up procedure and chromatography on alumina gave N-benzoyl-2-hydroxy-6-nitro-1,2-dihydroquinoline (0.11 g., 32% based on recovered starting material (1.8 g., 90%)). Recrystallisation from ethyl acetate gave colourless rhombs, m.p. 189-190° (Found: C, 65.04; H, 4.23; N, 9.62. $C_{16}H_{12}N_2O_4$ requires C, 64.86; H, 4.08; N, 9.46%); $\nu_{max.}$ 3320 cm.$^{-1}$ (OH), 1643 cm.$^{-1}$ (N-C=O); τ (DMSO-d_6) 1.64 (d, 1H, C5-H, $J_{5,7}$ = 2.5 Hz.), 2.04 (split doublet, 1H, C7-H, $J_{5,7}$ = 2.5 Hz., $J_{7,8}$ = 8.8 Hz.), 2.47 (s, 5H, phenyl group), 2.72 (d, 1H, C8-H, $J_{8,7}$ = 8.8 Hz.), 2.93 (d, 1H, C4-H, $J_{4,3}$ = 9.0 Hz.), 3.50 (b.s., 1H, C2-OH, exchangeable), 3.53 (q, 1H, C3-H, $J_{3,4}$ = 9.0 Hz., $J_{3,2}$ = 5.1 Hz.), 4.03 (q, 1H, C2-H, $J_{2,3}$ = 5.1 Hz., $J_{H,OH}$ = 1.7 Hz.); m/e 296.

The Reissert reaction using potassium cyanide was again repeated and the progress of the reaction followed by t.l.c. After three hours, the reaction was worked-up in the usual manner. Chromatography on alumina in benzene and ethyl acetate gave N-benzoyl-2-hydroxy-6-nitro-1,2-dihydroquinoline (0.15 g., 43% based on recovered starting material (1.8 g., 90%)). Recrystallisation from ethyl acetate gave colourless rhombs, m.p. 189-190°. The compound had identical infrared spectrum with that obtained above and the mixed m.p. was undepressed.

Reissert reaction with 8-nitroquinoline

The general procedure (p. 133) was followed but no reaction took place and the starting material was recovered in almost quantitative yield.

2. (d) Reissert reaction with Quinazoline

Benzoyl chloride (1.8 ml., 8 m.mol.) was added over two hours to a stirred mixture of quinazoline (0.52 g., 4 m.mol.) in methylene chlorine (10 ml.) and potassium cyanide (1.6 g., 12 m.mol.) in water (4 ml.). After stirring for an additional period of two hours, the reaction was worked-up and an oily product obtained. Chromatography on alumina in benzene gave low melting solid (0.25 g., 31%), o-formyl-benzanilide. Recrystallisation from 40/60 pet. ether gave colourless needles, m.p. 73° (lit.[132] 73°) (Found: C, 74.69; H, 4.98; N, 6.14. $C_{14}H_{11}NO_2$ requires C, 74.65; H, 4.92; N, 6.22%); $\nu_{max.}$ 3300 cm.$^{-1}$ (NH), 2850 and 2760 cm.$^{-1}$ (aldehyde C-H stretch), 1675 cm.$^{-1}$ (sh. 1660 and 1695 cm.$^{-1}$)(CHO and NHCO); τ -2.10 (b.s., 1H, exchangeable, NH), 0.04 (d, 1H, CHO, J=0.8 Hz.), 1.04 (split doublet, 1H, ortho ring proton to CHO group), 1.6-3.0 (m, 8H, other aromatic protons); m/e 225; accurate mass measurement gave measured mass, 225.0785; calculated mass for $C_{14}H_{11}NO_2$, 225.0790.

The above reaction was repeated (i) using potassium hydroxide when o-formylbenzanilide was obtained in 73% yield (ii) using water alone when o-formylbenzanilide was obtained in 83% yield.

Preparation of o-formylbenzanilide

Using the method of Smith and Opie,[133] o-nitrobenzaldehyde (3.0 g.) was converted into o-aminobenzaldehyde, which was, without purification, dissolved in pyridine (20 ml.) and benzoyl chloride (2.5 ml.) added. The mixture was stirred for 45 minutes and then poured into 2N hydrochloric acid (100 ml.).

The acid solution was extracted with chloroform and the chloroform extracts washed with saturated sodium carbonate solution, dried (Na_2SO_4) and evaporation of the solvent gave a dark brown syrup. Chromatography on alumina in benzene gave o-formylbenzanilide (0.8 g., 18%). Recrystallisation from 40/60 pet.ether gave colourless needles, m.p. 73-74° (lit.[132] 73°). The compound had identical R_f value (0.66) and infrared spectrum with that obtained above and the mixed melting point was undepressed.

3. Stereochemistry and N.m.r. Spectra of Reissert Systems

(a) Isoquinoline Reissert Compounds

Of the Reissert compounds examined (Table IV, p.110) the following have not yet been described elsewhere.

N-Cinnamoyl-1,2-dihydroisoquinaldonitrile

Use of isoquinoline (4.0 g., 0.032 mol.), cinnamoyl chloride (11.2 g., 0.064 mol.) and potassium cyanide (6.2 g., 0.096 mol.) in the general procedure (p. 133) gave N-cinnamoyl-1,2-dihydroisoquinaldonitrile (6.4 g., 73%). Recrystallisation from ethyl acetate gave colourless rhombs, m.p. 164-165° (lit.[18] 160-162°); $\nu_{max.}$ 2220 cm.$^{-1}$ (w) (CN), 1660 cm.$^{-1}$ (N-C=O), 1620 cm.$^{-1}$ (C=C); τ 2.12 (d, 1H, α-proton in -CO-$\overset{\alpha}{C}$H=$\overset{\beta}{C}$H-Ph, $J_{\alpha,\beta}$= 14.0 Hz), 2.3-2.9 (m, 9H, aromatic protons), 3.04 (q, 1H, C3-H, $J_{3,4}$= 8.0 Hz, $J_{1,3}$=0.9 Hz), 3.18 (d, 1H, β-H, $J_{\beta,\alpha}$= 14.0 Hz), 3.31 (d, 1H, C1-H, $J_{1,3}$= 0.9 Hz), 3.83 (d, 1H, C4-H, $J_{4,3}$= 8.0 Hz).

N-Acetyl-1,2-dihydroisoquinaldonitrile

Use of isoquinoline (4.0 g., 0.032 mol.), acetyl chloride (4.9 g., 0.064 mol.) and potassium cyanide (6.0 g., 0.096 mol.) in the general procedure (p. 133) gave N-acetyl-1,2-dihydroisoquinaldonitrile (3.5 g., 58%). Recrystallisation from 95% ethanol gave colourless stout needles, m.p. 118° (lit.[176] 119-120°); $\nu_{max.}$ 2230 cm.$^{-1}$ (w) (CN), 1680 cm.$^{-1}$ (N-C=O), 1630 cm.$^{-1}$ (C=C); τ 2.4-3.0 (m, 4H, aromatic protons), 3.28 (q, 1H, C3-H, $J_{3,4}$= 8.0 Hz, $J_{3,1}$= 0.8 Hz), 3.35 (d, 1H, C1-H, $J_{1,3}$= 0.8 Hz), 3.96 (d, 1H, C4-H, $J_{4,3}$= 8.0 Hz), 7.80 (s, 3H, CH_3).

N-Cyano-1-hydroxy-1,2-dihydroisoquinoline

The title compound was prepared in 40% yield according to the method of Johnson[86] from isoquinoline and cyanogen bromide. Recrystallisation from acetone gave colourless needles, m.p. 112-113° (decomposition) (lit.[86] 112-113° (decomposition)); $\nu_{max.}$ 3300 cm.$^{-1}$ (OH), 2220 cm.$^{-1}$ (CN), 1650 cm.$^{-1}$ (C=C); τ (DMSO-d_6) 2.3-3.0 (m, 5H, aromatic and OH protons), 3.33 (q, 1H, C3-H, $J_{3,4}$= 8.0 Hz, $J_{3,1}$= 1.0 Hz), 3.77 (d, 1H, C1-H, $J_{1,3}$= 1.0 Hz), 3.92 (d, 1H, C4-H, $J_{4,3}$= 8.0 Hz).

N-Cyano-1-methoxy-1,2-dihydroisoquinoline

N-Cyano-1-hydroxy-1,2-dihydroisoquinoline (0.86 g.) was heated under reflux with methanol (6 ml.) in the presence of glacial acetic acid (0.05 ml.) for 15 minutes. The work-up procedure reported by Johnson[86] was followed and N-cyano-1-methoxy-1,2-dihydroisoquinoline (0.6 g., 64%) obtained was recrystallised from 40/60 pet. ether as colourless needles, m.p. 56° (lit.[86] 52°); $\nu_{max.}$ 2230 cm.$^{-1}$ (CN), 1640 cm.$^{-1}$ (C=C), 1060 cm.$^{-1}$ (ether); τ 2.4-3.0 (m, 4H, aromatic protons), 3.57 (q, 1H, C3-H, $J_{3,4}$= 8.0 Hz, $J_{3,1}$= 1.0 Hz), 4.00 (d, 1H, C4-H, $J_{4,3}$= 8.0 Hz), 4.04 (d, 1H, C1-H, $J_{1,3}$= 1.0 Hz), 6.66 (s, 3H, OCH_3).

Variable temperature n.m.r. of N-benzoyl-1,2-dihydroisoquinaldonitrile

The variation with temperature of the C-1 proton signal of N-benzoyl-1,2-dihydroisoquinaldonitrile is shown in Table XII, p.177.

Table XII

Variable temperature n.m.r. of N-benzoyl-1,2-dihydro-isoquinaldonitrile

Temperature	Chemical shift of the C-1 proton doublet with respect to the centre of the C-3 proton quartet*, in p.p.m. (at 60 MHz).	
	in $CDCl_3$	in acetone
100°	+ 0.08	+ 0.07
80°	+ 0.07	+ 0.05
60°	+ 0.06	+ 0.02
40°	-	0.00
35°	+ 0.05	-
20°	+ 0.04	- 0.02
0°	+ 0.01	- 0.05
-20°	- 0.03	-
-40°	- 0.05	-0.09
-70°	-	-0.13

* C-3 signal constant with respect to TMS.

Positive sign indicates movement to higher field.

The accompanying small change in coupling constant ($J_{1,3}$) could not be observed accurately due to the insufficient sensitivity of the instrument.

3. (b) Quinoline Reissert Compounds

By use of the general procedure (p.133) the following compounds which have not been described elsewhere in this thesis, were prepared.

N-Benzoyl-1,2-dihydroquinaldonitrile (85%), as colourless fine needles from 95% ethanol, m.p. 154-155° (lit.[176] 154-155°); $\nu_{max.}$ 2215 cm.$^{-1}$ (w) (CN), 1665 cm.$^{-1}$ (N-C=O), 1605 cm.$^{-1}$ (C=C); τ 2.4-3.5 (m, 10H, aromatic and C-4 protons), 3.6-4.1 (m, 2H, C-2 and C-3 protons, see Table VI p. 117).

N-Benzoyl-3-bromo-1,2-dihydroquinaldonitrile (5%),as colourless fine needles from 95% ethanol, m.p. 123-124° (lit.[128] 125°); $\nu_{max.}$ 1668 cm.$^{-1}$ (N-C=O), 1610 cm.$^{-1}$ (C=C); τ 2.2-3.6 (m,10H, aromatic and C-4 protons), 3.76 (d, 1H, C2-H, $J_{2,4}$= 0.4 Hz).

N-Benzoyl-3-benzoyloxy-1,2-dihydroquinaldonitrile (54%), from 3-hydroxyquinoline (p. 141), as buff coloured needles from 95% ethanol, m.p. 181-182° (lit.[128] 179-180°) (Found: C, 75.59; H, 4.41; N,7.52. $C_{24}H_{16}N_2O_3$ requires C, 75.78; H, 4.24; N,7.37%); $\nu_{max.}$ 1745 cm.$^{-1}$ (ester C=O), 1665 cm.$^{-1}$ (N-C=O), 1600 cm.$^{-1}$ (C=C); τ 1.6-1.9 (m, 2H, benzoyloxy ortho hydrogens), 2.1-3.45 (m, 13H, aromatic and C-4 protons), 3.60 (b.s., 1H, C2-H).

N-Benzoyl-4-methyl-1,2-dihydroquinaldonitrile (70%), as colourless fine needles from 95% ethanol, m.p. 167-168° (lit.[128] 173-175°) (Found: C, 78.65; H, 5.42; N, 10.11. $C_{18}H_{14}N_2O$ requires C, 78.81; H, 5.14; N, 10.21%); $\nu_{max.}$ 2215 cm.$^{-1}$ (w) (CN), 1660 cm.$^{-1}$ (N-C=O), 1605 cm.$^{-1}$ (C=C); τ 2.0-3.5 (m, 9H, aromatic protons), 3.86 (d, 1H, C2-H,

$J_{2,3}$= 6.4 Hz), 4.10 (q, 1H, C3-H, $J_{2,3}$= 6.4 Hz, $J_{C3-H,C4-Me}$= 1.7 Hz), 7.78 (d, 3H, CH_3, $J_{C4-Me, C3-H}$= 1.7 Hz).

N-Benzoyl-4-benzoyloxy-1,2-dihydroquinaldonitrile (98%), from 4-hydroxyquinoline as colourless needles from glacial acetic acid, m.p. 155-157° (lit.[128] 157-158°); $\nu_{max.}$ 2220 cm.$^{-1}$ (w) (CN), 1745 cm.$^{-1}$ (ester C=O), 1668 cm.$^{-1}$ (N-C=O), 1600 cm.$^{-1}$ (C=C), τ 1.6-1.9 (m, 2H, benzoyloxy ortho protons), 2.1-3.45 (m, 12H, aromatic protons), 3.53 (d, 1H, C2-H, $J_{2,3}$= 7.3 Hz), 3.83 (d, 1H, C3-H, $J_{3,2}$= 7.3 Hz).

N-Benzoyl-6-methyl-1,2-dihydroquinaldonitrile (96%), as buff coloured needles from 95% ethanol, m.p. 142-144° (lit.[128] 144°); $\nu_{max.}$ 2240 cm.$^{-1}$ (w) (CN), 1665 cm.$^{-1}$ (N-C=O), 1610 cm.$^{-1}$ (C=C), τ 2.4-3.7 (m, 9H, aromatic and C-4 protons), 3.7-4.2 (m, 2H, C-2 and C-3 protons, see Table VI p. 117), 7.78 (s, 3H, CH_3).

N-p-Toluoyl-1,2-dihydroquinaldonitrile (74%), as colourless stout needles from 95% ethanol, m.p. 152° (lit.[64] 149.5-150.2°) (Found: C, 79.05; H, 5.40; N, 10.42. $C_{18}H_{14}N_2O$ requires C, 78.81; H, 5.14; N, 10.21%); $\nu_{max.}$ 2240 cm.$^{-1}$ (w) (CN), 1650 cm.$^{-1}$ (N-C=O), 1615 cm.$^{-1}$ (C=C); τ 2.4-3.5 (m, 9H, aromatic and C-4 protons), 3.6-4.1 (m, 2H, C-2 and C-3 protons, see Table VI p. 117), 7.64 (s, 3H, CH_3).

N-Acetyl-6-methyl-1,2-dihydroquinaldonitrile (27%), as colourless rhombs from ether/ 40-60 pet.ether, m.p. 80-81° (Found: C, 73.76; H, 5.80; N, 13.28. $C_{13}H_{12}N_2O$ requires C, 73.56; H, 5.70; N, 13.20%); $\nu_{max.}$ 2240 cm.$^{-1}$ (w) (CN), 1660 cm.$^{-1}$ (N-C=O), 1620 cm.$^{-1}$ (C=C); τ (see analysis p.190) 2.8-3.0 (m, 3H, aromatic protons), 3.32 (q, 1H,

C4-H, $J_{4,3}$= 9.3 Hz, $J_{4,2}$= 0.7 Hz), 3.54 (q, 1H, C2-H, $J_{2,3}$= 6.3 Hz, $J_{2,4}$= 0.7 Hz), 3.99 (q, 1H, C3-H, $J_{3,2}$= 6.3 Hz, $J_{3,4}$= 9.3 Hz), 7.64 (s, 3H, $COCH_3$), 7.78 (s, 3H, C6-CH_3); m/e 212.

Preparation of 2-deutero Reissert compounds

General procedure

The quinoline Reissert compound (0.3 g.) dissolved in dimethylformamide (5 ml.) was added to a stirred suspension of sodium hydride (0.2 g.) in dimethylformamide (10 ml.) at -5 to 0° under nitrogen. After one minute, deuterium oxide (2 ml.) was added and after a further stirring of two minutes, the mixture was neutralised with carbon dioxide.[148] The solution was poured into ice and the precipitated solid filtered. The solid was dissolved in chloroform and the solution washed with water, 2N hydrochloric acid and water, dried (Na_2SO_4) and evaporation of the solvent gave the 2-deuteroquinaldonitrile.

All the 2-deutero quinoline Reissert compounds listed in Table VI (p. 117) were prepared by this procedure and their n.m.r. spectra measured. A summary of the relevant τ values appears in Table VI (p. 117).

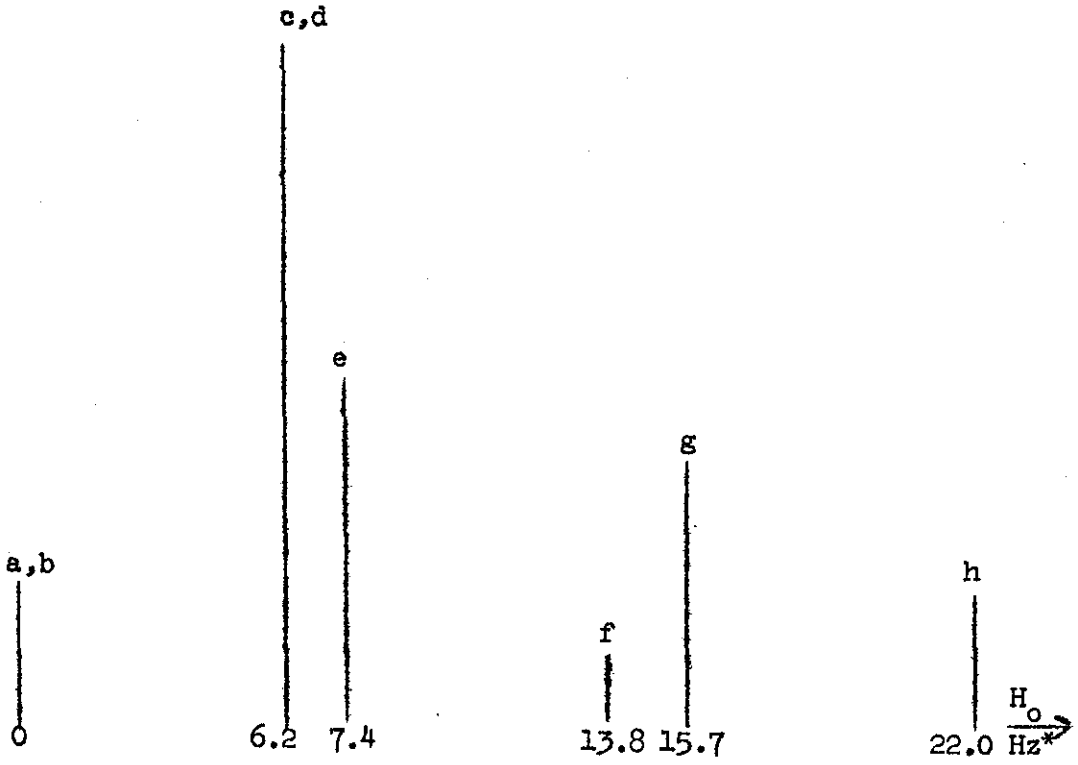
Analysis* of the n.m.r. spectra of quinoline Reissert compounds, unsubstituted at positions 2, 3 and 4

The analysis is based upon that given by Pople, Schneider and Bernstein.[150]

(i) N-Benzoyl-1,2-dihydroquinaldonitrile

Shown below is a schematic representation of the C-2, C-3 proton region (AB region) of the 100 MHz n.m.r. spectrum of N-benzoyl-1,2-dihydroquinaldonitrile. The arbitrary zero is at 3.78τ with respect to TMS.

* The author is grateful to Dr.B.Scanlon for helpful discussions.



*Hz values measured relative to a,b signal, from low to high field.

In order to get the required intensity (weak-strong-strong-weak), AB- and AB+ quartets can be assigned as

a	c	e	f	b	d	g	h
1	3	5	7	2	4	6	8

J_{AB} = separation $_{1-3}$ = sep. $_{2-4}$ = sep. $_{5-7}$ = sep. $_{6-8}$

= 6.2 = 6.2 = 6.4 = 6.3 Hz

= 6.27 Hz.

The separations between the centres of the doublets forming the AB- and AB+ quartets are designated by D+ and D- and are conveniently measured as half the spacing between lines 1 and 5 (or 3 and 7) for one and between lines 2 and 6 (or 4 and 8) for the other: the higher value always assigned by D+.

$2D_+$ = separation $_{2-6}$ = sep. $_{4-8}$

= 15.7 = 15.8 Hz

= 15.75 Hz $\quad\quad\quad\quad$ $\therefore D_+ = 7.87$ Hz

$2D_-$ = sep. $_{1-5}$ = sep. $_{3-7}$

= 7.4 = 7.6 Hz

= 7.5 Hz $\quad\quad\quad\quad$ $\therefore D_- = 3.75$ Hz

ν_{AB} is the mean of all eight lines in the AB region, or alternatively the mean of the mid points of the two AB quartets

$\nu_{AB} = \frac{1}{2}$ (mid pt. of 3 and 5 + mid pt. of 4 and 6)

$= \frac{1}{2}$ (6.8 + 10.95) = 8.87 Hz

$\frac{1}{2}$ $(J_{AX} + J_{BX})$ = separation between the mid points of the two quartets

= 10.95 - 6.80 = 4.15 Hz

$\therefore J_{AX} + J_{BX} = 8.30$ Hz

$D_+ \sin 2\phi_+ = \frac{1}{2} J_{AB}$

$7.87 \sin 2\phi_+ = \frac{1}{2}$ (6.27)

$\therefore \sin 2\phi_+ = \frac{6.27}{2 \times 7.87} = 0.3984$

$\therefore 2\phi_+ = 23^\circ 29'$ or $156^\circ 31'$

$D_- \sin 2\phi_- = \frac{1}{2} (J_{AB})$

$3.75 \sin 2\phi_- = \frac{1}{2}$ (6.27)

$\sin 2\phi_- = \frac{6.27}{2 \times 3.75} = 0.836$

$2\phi_- = 56^\circ 43'$ or $123^\circ 17'$

It is generally possible to assess which combination of angles is correct from the X-part of the spectrum. In this case, the X-part is masked under the aromatic region which complicates the analysis. However, using all the four possible combination of angles, we have calculated J_{AX} and

J_{BX} for every combination as shown below:

$2\phi_+$	$2\phi_-$	cos $2\phi_+$	cos $2\phi_-$	
$23^\circ\ 29'$	$56^\circ\ 43'$	0.9172	0.5488	——(1)
$23^\circ\ 29'$	$123^\circ\ 17'$	0.9172	-0.5488	——(2)
$156^\circ\ 31'$	$56^\circ\ 43'$	-0.9172	0.5488	——(3)
$156^\circ\ 31'$	$123^\circ\ 17'$	-0.9172	-0.5488	——(4)

Using (1) set of angles

$$D_+ \cos 2\phi_+ = \tfrac{1}{2}(\nu_A - \nu_B) + \tfrac{1}{4}(J_{AX} - J_{BX})$$

$$7.87 \times 0.9172 = \tfrac{1}{2}(\nu_A - \nu_B) + \tfrac{1}{4}(J_{AX} - J_{BX}) \text{——(5)}$$

$$D_- \cos 2\phi_- = \tfrac{1}{2}(\nu_A - \nu_B) - \tfrac{1}{4}(J_{AX} - J_{BX})$$

$$3.75 \times 0.5488 = \tfrac{1}{2}(\nu_A - \nu_B) - \tfrac{1}{4}(J_{AX} - J_{BX}) \text{——(6)}$$

substracting (6) from (5)

$$7.87 \times 0.9172 - 3.75 \times 0.5488 = \tfrac{1}{2}(J_{AX} - J_{BX})$$

$$5.161 = \tfrac{1}{2}(J_{AX} - J_{BX})$$

$$\therefore J_{AX} - J_{BX} = 10.32 \text{ Hz}$$

now $J_{AX} + J_{BX} = 8.30$ Hz——— (7)

$$\therefore J_{AX} = 9.31 \text{ Hz}$$
$$J_{BX} = -1.01 \text{ Hz} \quad \text{——— (A)}$$

Using (2) set of angles,

$$J_{AX} - J_{BX} = 18.554 \text{ Hz}$$

Using (7), $J_{AX} = 13.42$ Hz

$J_{BX} = -5.12$ Hz ——————— (B)

Using (3) set of angles, $J_{AX} - J_{BX} = -18.554$ Hz

Using (7) $J_{AX} = -5.12$ Hz

$J_{BX} = +13.42$ Hz ——(C)

Using (4) set of angles, $J_{AX} - J_{BX} = -10.322$ Hz

Using (7) $J_{AX} = -1.01$)
$J_{BX} = +9.31$) ——— (D)

Now when C-2 proton was replaced by deuterium in the compound, the spectrum simplified, C-3 appearing as doublet with $J_{3,4}$ i.e. $J_{AX} = 9.0$ Hz. This observed value suggests that only the (A) combination of values is possible. Adding (5) and (6), $\nu_A - \nu_B = 9.28$ Hz

Now by definition $\nu_A = \nu_{AB} + \frac{1}{2}(\nu_A - \nu_B)$

$= 8.87 + 4.64$

$= 13.51$ Hz from the arbitrary zero

$\nu_B = \nu_{AB} - \frac{1}{2}(\nu_A - \nu_B)$

$= 8.87 - 4.64$

$= 4.23$ Hz from the arbitrary zero

Now the arbitrary zero is 3.78τ with respect to TMS

∴ Chemical shift of proton A $= 3.78 + \frac{13.51}{100} = 3.92\tau$

Chemical shift of proton B $= 3.78 + \frac{4.23}{100} = 3.82\tau$

Hence all the required parameters are

$J_{AB} = 6.27$ Hz	$2J_{AB} = 12.54$ Hz	$D_+ = 7.87$ Hz
$J_{AX} = 9.31$ Hz	$J_{AX} + J_{BX} = 8.30$ Hz	$D_- = 3.75$ Hz
$J_{BX} = -1.01$ Hz	$\nu_{AB} = 8.87$ Hz	$\sin 2\phi_+ = 0.3984$
		$\sin 2\phi_- = 0.836$

As a check, these figures were used to calculate the transition energies (frequencies) and relative intensities of the lines in the AB region as shown below:

Line 1

$$\text{Frequency} = \nu_{AB} + \tfrac{1}{4}(-2\,J_{AB} - J_{AX} - J_{BX}) - D_{-}$$

$$= 8.87 + \tfrac{1}{4}(-12.54 - 8.30) - 3.75$$

$$= -0.09 \text{ Hz} \equiv 3.78\tau$$

$$\text{Intensity} = 1 - \sin 2\phi_{-}$$

$$= 1 - 0.836 = 0.164$$

Line 2

$$\text{Frequency} = \nu_{AB} + \tfrac{1}{4}(-2\,J_{AB} + J_{AX} + J_{BX}) - D_{+}$$

$$= 8.87 + \tfrac{1}{4}(-12.54 + 8.30) - 7.87$$

$$= -0.06 \text{ Hz} \equiv 3.78\tau$$

$$\text{Intensity} = 1 - \sin 2\phi_{+}$$

$$= 1 - 0.3984 = 0.6016$$

Line 3

$$\text{Frequency} = \nu_{AB} + \tfrac{1}{4}(+2\,J_{AB} - J_{AX} - J_{BX}) - D_{-}$$

$$= 8.87 + \tfrac{1}{4}(12.54 - 8.30) - 3.75$$

$$= 6.18 \text{ Hz} = 3.84\tau$$

$$\text{Intensity} = 1 + \sin 2\phi_{-}$$

$$= 1 + 0.836 = 1.836$$

Line 4

$$\text{Frequency} = \nu_{AB} + \tfrac{1}{4}(+2\,J_{AB} + J_{AX} + J_{BX}) - D_{+}$$

$$= 8.87 + \tfrac{1}{4}(12.54 + 8.30) - 7.87$$

$$= 6.21 \text{ Hz} \equiv 3.84\tau$$

$$\text{Intensity} = 1 + \sin 2\phi_{+}$$

$$= 1 + 0.3984 = 1.3984$$

Line 5

$$\text{Frequency} = \nu_{AB} + \tfrac{1}{4}(-2J_{AB} - J_{AX} - J_{BX}) + D_-$$

$$= 8.87 + \tfrac{1}{4}(-12.54 - 8.30) + 3.75$$

$$= 7.41 \text{ Hz} \equiv 3.85\tau$$

$$\text{Intensity} = 1 + \sin 2\phi_-$$

$$= 1 + 0.836 = 1.836$$

Line 6

$$\text{Frequency} = \nu_{AB} + \tfrac{1}{4}(-2J_{AB} + J_{AX} + J_{BX}) + D_+$$

$$= 8.87 + \tfrac{1}{4}(-12.54 + 8.3) + 7.87$$

$$= 15.68 \equiv 3.94\tau$$

$$\text{Intensity} = 1 + \sin 2\phi_+$$

$$= 1 + 0.3984 = 1.3984$$

Line 7

$$\text{Frequency} = \nu_{AB} + \tfrac{1}{4}(2J_{AB} - J_{AX} - J_{BX}) + D_-$$

$$= 8.87 + \tfrac{1}{4}(12.54 - 8.30) + 3.75$$

$$= 13.68 \text{ Hz} \equiv 3.93\tau$$

$$\text{Intensity} = 1 - \sin 2\phi_-$$

$$= 1 - 0.836 = 0.164$$

Line 8

$$\text{Frequency} = \nu_{AB} + \tfrac{1}{4}(2J_{AB} + J_{AX} + J_{BX}) + D_+$$

$$= 8.87 + \tfrac{1}{4}(12.54 + 8.30) + 7.87$$

$$= 21.95 \text{ Hz} \equiv 4.00\tau$$

$$\text{Intensity} = 1 - \sin 2\phi_+$$

$$= 1 - 0.3984 = 0.6016$$

The calculated line spectrum (using the above values) and the observed spectrum are shown in Figure VI.

CALCULATED

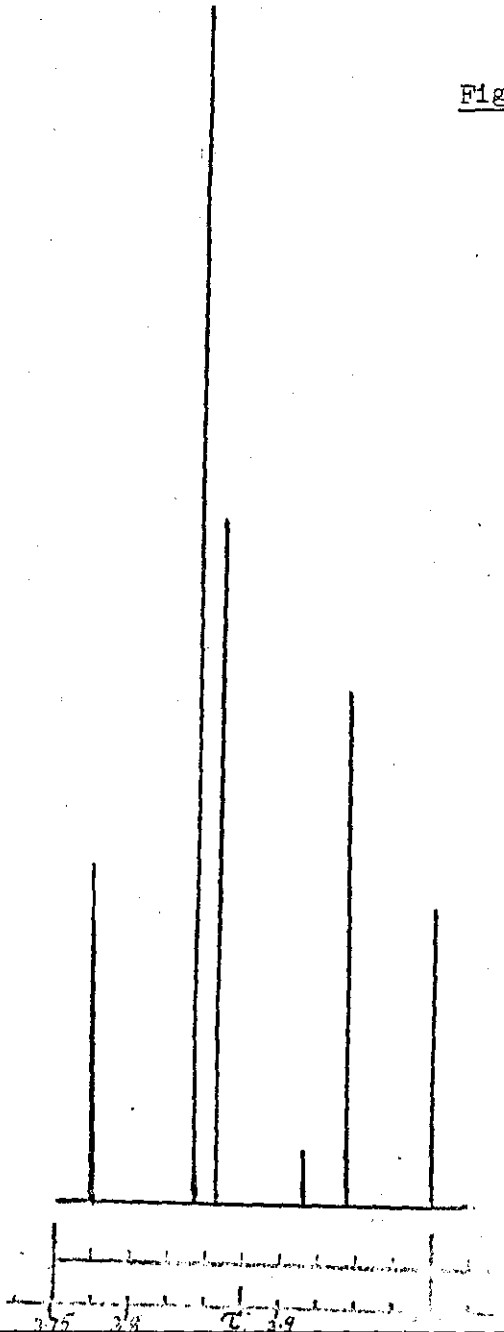
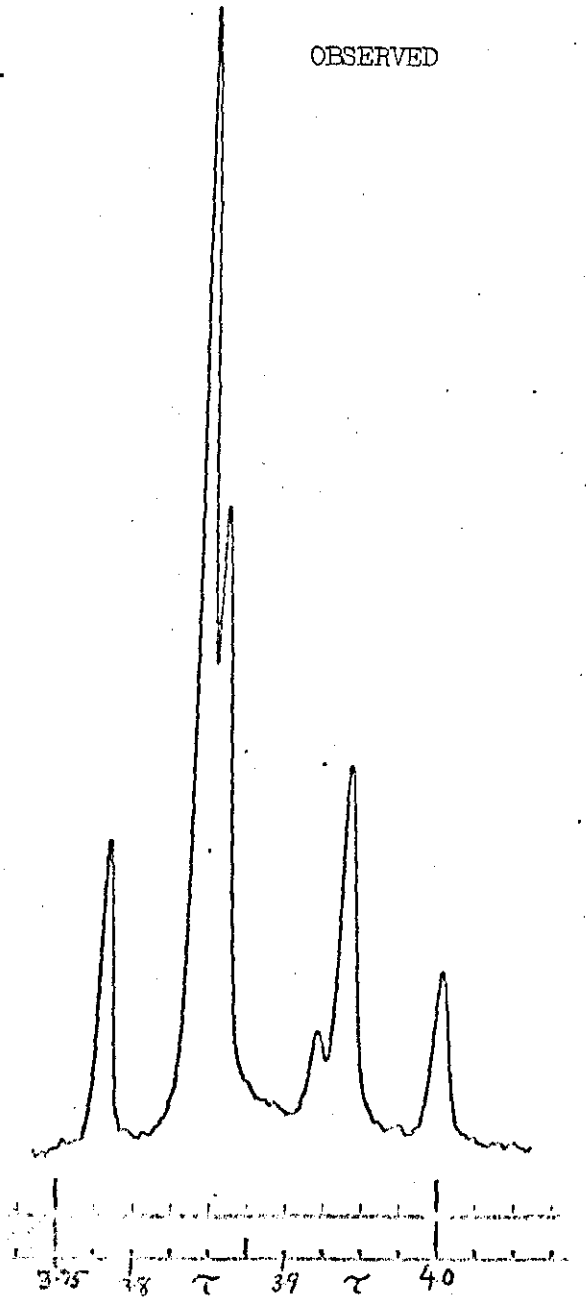


Figure VI Calculated and Observed line spectrum of AB region of N-benzoyl-1,2-dihydroquinaldonitrile, 3.75-4.00 τ region on scale 2.5 Hz/unit

OBSERVED



The calculated relative peak intensities and the observed relative peak intensities are tabulated below for comparison.

Table XIII

Line No.	Calculated relative* peak intensities (mm.)	Observed relative peak intensities (mm).
1+2	27.1	40.0
3+4	117.2	148.0
5	65.7	83.0
6	50.0	50.0
7	5.7	15.5
8	21.4	23.7

*Measured and calculated relative to line 6.

Observed and calculated intensities are in only fair agreement which suggests that the spectrum is not a true ABX spectrum but has some ABC character. Secondly, the simple additive rule as used for lines 1 and 2, and, 3 and 4 is not strictly appropriate as the lines are separated by a finite width though very small (0.03 Hz).

N-Benzoyl-6-methyl-1,2-dihydroquinaldonitrile

Line assignment from the 100 MHz spectrum, were made as shown below, reading from low to high field. The arbitrary zero is at 3.80 τ

Relative position:	0	6.2	8.6	14.9	17.1	23.4 Hz
Assignment:	1,2	3,4	5	7	6	8

By the same procedure as given in the previous example, the following parameters were obtained :

J_{AB} = 6.25 Hz ν_{AB} = 9.52 Hz Sin $2\phi_+$ = 0.3747

J_{AX} = 9.21 Hz D_+ = 8.57 Hz Sin $2\phi_-$ = 0.7235

J_{BX} = -0.71 Hz D_- = 4.32 Hz ν_A = 3.95 τ

ν_B = 3.84 τ

Line frequencies and relative intensities obtained are tabulated below:

Line No.	Frequency (τ)	Relative intensity
1	3.80	0.2765
2	3.80	0.6253
3	3.86	1.7235
4	3.86	1.3747
5	3.88	1.7235
6	3.97	1.3747
7	3.95	0.2765
8	4.03	0.6253

N-p-Toluoyl-1,2-dihydroquinaldonitrile

Line assignments, from the 100 MHz spectrum, were made as shown below, reading from low to high field. The arbitrary zero is at 3.82 τ .

Relative position:	0	5.7	6.0	12.2	13.6	19.9 Hz
Assignment:	1,2	3,4	5	7	6	8

After calculations, the following parameters were obtained:

J_{AB}= 6.0 Hz ν_{AB}=7.75 Hz Sin $2\phi_+$ = 0.4300

J_{AX} = 7.13 Hz D_+ = 7.0 Hz Sin$2\phi_-$ = 0.9645

J_{BX}= 0.47 Hz D_-= 3.1 Hz ν_A = 3.94 τ

ν_B = 3.85 τ

Line frequencies and relative intensities obtained were as follows:

Line No.	Frequency (τ)	Relative intensity
1	3.82	0.0355
2	3.82	0.57
3	3.88	1.9645
4	3.88	1.43
5	3.88	1.9645
6	3.96	1.43
7	3.94	0.0355
8	4.02	0.57

N-Benzoyl-6-nitro-1,2-dihydroquinaldonitrile

Line assignments, from the 100 MHz spectrum, made are shown below, reading from high to low field. The arbitrary zero is at 3.91τ

Relative position:	26.50	20.00	17.60	11.10	6.58	0 Hz
Assignment:	8	6	7	5	4,3	2,1

The usual calculations gave the following parameters:

J_{AB} = 6.54 Hz $\quad \nu_{AB}$ = 11.06 Hz $\quad$ Sin $2\phi_+$ = 0.3276

J_{AX} = 9.42 Hz $\quad D_+$ = 9.98 Hz $\quad$ Sin $2\phi_-$ = 0.5913

J_{BX} = -0.52 Hz $\quad D_-$ = 5.53 Hz $\quad \nu_A = 3.73\,\tau$

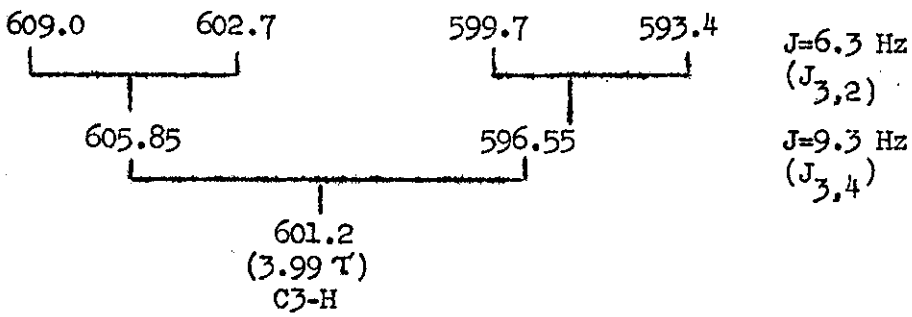
$\nu_B = 3.87\,\tau$

Using the above values, line frequencies and relative intensities were calculated and are summarised below:

Line No.	Frequency (τ)	Relative Intensity
1	3.91	0.4087
2	3.91	0.6724
3	3.84	1.5913
4	3.84	1.3276
5	3.80	1.5913
6	3.69	1.3276
7	3.73	0.4087
8	3.64	0.6724

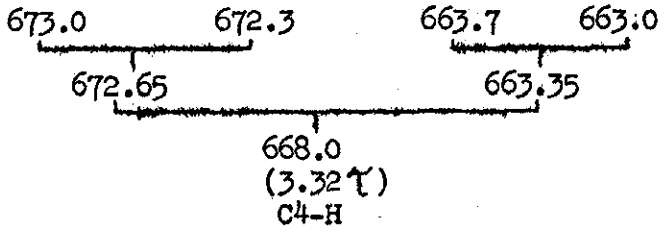
Analysis of N.m.r. spectrum of N-acetyl-6-methyl-1,2-dihydroquinaldonitrile

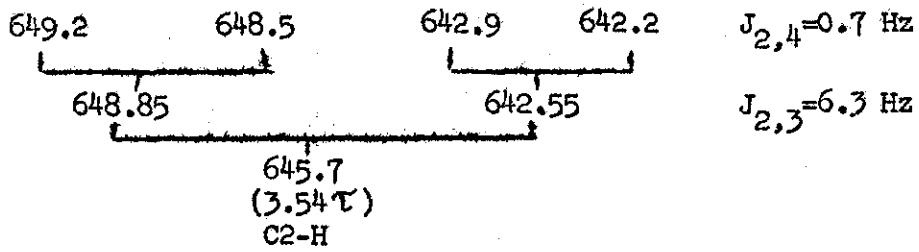
The ABX (more correctly the AMX) part of the spectrum is shown in Figure IV (after p.121). The high field quartet integrates for one proton and represents the X-region. Two coupling constants can be derived from this quartet. Thus if we note the position of the individual peaks in Hz from TMS, we have



By comparison with the previous results (p.180 ff), the figures of 6.3 Hz and 9.3 Hz can only be $J_{3,2}$ and $J_{3,4}$ respectively. Thus this quartet represents C3-H, its chemical shift being 601.2 Hz from TMS or 3.99 τ . These figures of coupling constants are also seen in the two low field quartets (AB region) which

also show a splitting of 0.7 Hz ($J_{2,4}$) thus:





To summarise, therefore, the required parameters are as follows:

ν_{C2-H} = 3.54 τ $J_{2,3}$ = 6.3 Hz

ν_{C3-H} = 3.99 τ $J_{2,4}$ = 0.7 Hz

ν_{C4-H} = 3.32 τ $J_{3,4}$ = 9.3 Hz

The Stereochemistry

Preparation of N-benzoyl-3-bromo-1,2-dihydroquinoline

A solution of 3-bromoquinoline (3.0 g., 15 m.mol.) in dry ether (30 ml.) was added dropwise in ca. 20 minutes to a refluxing solution of lithium aluminium hydride (1.1 g.) in dry ether (90 ml.). The mixture was refluxed for five hours and then chilled to 0°. The complex was decomposed by addition of a slight excess of water. The sludge was filtered off and washed with ether (40 ml.). Evaporation of the filtrates under reduced pressure yielded 3-bromo-1,2-dihydroquinoline (2.8 g., 93%).

The product was dried completely and dissolved in dry pyridine (25 ml.) and benzoyl chloride (2.5 ml.) added,

and the mixture heated at 100° for 30 minutes. After cooling, water (100 ml.) was added and the solution extracted with chloroform. The chloroform extract was washed with sodium bicarbonate solution and then with water, dried (Na_2SO_4) and evaporation of the solvent gave a brown syrup (4.35 g.). Chromatography on neutral alumina in benzene gave N-benzoyl-3-bromo-1,2-dihydroquinoline (3.0 g., 45% overall). Recrystallisation from ether/40-60 pet. ether gave colourless shining rhombs, m.p. 123-124° (Found: C, 61.28; H, 4.00; N, 4.65. $C_{16}H_{12}NOBr$ requires C, 61.16; H, 3.85; N, 4.46%); $\nu_{max.}$ 1650 cm.$^{-1}$ (N-C=O); τ 2.2-3.6 (m, 10H, aromatic protons including C4-H at 1.05); 5.25 (d, 2H, C2-2H, $J_{2,4}$= 1.3 Hz). On saturating the signal at 5.25 τ, the signal at 1.05 τ became sharp and, therefore must be due to the C4-H.

REFERENCES

1. A.Reissert, Ber., 1905, 38, 1603.
2. A.Reissert, Ber., 1905, 38, 3415.
3. G.Wittig, M.A.Jesaitis and M.Glos, Annalen, 1952, 577, 1.
4. F.D.Popp and J.M.Wefer, Chem.Comm., 1967, 59; F.D.Popp, J.M.Wefer and C.W.Klinowski, J.Heterocyclic Chem., 1968, 5, 879.
5. W.E.McEwen and R.L.Cobb, Chem.Rev., 1955, 55, 511.
6. F.D.Popp, Adv.Heterocyclic Chem., 1968, 9, 1.
7. J.M.Groscheintz and H.O.L.Fischer, J.Amer.Chem.Soc., 1941, 63, 2021.
8. F.D.Popp and W.Blount, Chem.and Ind.,1961, 550.
9. I.W.Elliott, J.Amer.Chem.Soc., 1955, 77, 4408.
10. S.L.Tan, Ph.D. Thesis, Loughborough University of Technology, 1970, p.72.
11. K.V.Ihnatowicz and S.Niementowski, Ber., 1919, 52, 186.
12. K.Ueda, J.Pharm.Soc.Japan, 1937, 57, 825; Chem.Abs., 1938, 32, 1265.
13. E.J.Corey, A.L.Borror, and T.Foglia, J.Org.Chem., 1965, 30, 288.
14. E.Mossetting, Org.Reactions, 1954, 8, 218.
15. R.L.Cobb and W.E.McEwen, J.Amer.Chem.Soc., 1955, 77, 5042.
16. J.W.Davis, J.Org.Chem., 1960, 25, 376.
17. W.E.McEwen, I.C.Mineo, T.H.Shen and G.T.Han, Tetrahedron Letters, 1968, 5157.
18. V.Boekelheide and J.Weinstock, J.Amer.Chem.Soc., 1952, 74, 660.

19. V.Boekelheide and C.Ainsworth, J.Amer.Chem.Soc., 1950, 72, 2134.

20. V.Boekelheide and C.Liu, J.Amer.Chem.Soc.,1952, 74, 4920.

21. F.D.Popp and W.E.McEwen, J.Amer.Chem.Soc., 1957, 79, 3773.

22. L.R.Walters, N.T.Iyer and W.E.McEwen, J.Amer.Chem.Soc., 1958, 80, 1177.

23. As for ref. 5, p. 528 and ref. 6, p.12.

24. J.R.Kershaw and B.C.Uff, Chem.Comm., 1966, 331.

25. F.D.Popp and J.M.Wefer, Chem.Comm., 1966, 207.

26. F.D.Popp and J.M.Wefer, J.Heterocyclic Chem., 1967, 4, 183.

27. B.C.Uff and J.R.Kershaw, J.Chem.Soc.(C), 1969, 666.

28. J.L.Neumeyer, B.R.Neustadt and J.W Weintraub, Tetrahedron Letters, 1967, 3107.

29. R.Piccirilli and F.D.Popp, Canad.J.Chem., 1969, 47, 3261.

30. M.Shamma and C.D.Jones, J.Org.Chem., 1970, 35, 3119.

31. H.W.Gibson, F.D.Popp and A.C.Noble, J.Heterocyclic Chem., 1966, 3, 99.

32. J.R.Kershaw, Ph.D.Thesis, Loughborough University of Technology, 1968, p.47.

33. B.C.Uff, J.R.Kershaw and S.R.Chhabra, Chem.Soc. Autumn Meeting, Keele, 1968, Abstract F9.

34. V.Boekelheide and J.C.Godfrey, J.Amer.Chem.Soc., 1953, 75, 3679.

35. F.D.Popp, J.M.Wefer and A.Catala, J.Heterocyclic Chem., 1965, 2, 317.

36. H.Bohme and R.Schweitzer, Chem.Ber.,1969, 102, 3606.

37. P.Davis and W.E.McEwen, J.Org.Chem.,1961, 26, 815.

38. C.M.Spatz and F.D.Popp, J.Heterocyclic Chem., 1968, 5, 497; R.W.Young and E.Gelblum, U.S.Patent, 3,249,614 (1966).

39. F.D.Popp, L.E.Katz, C.W.Klinowski and J.M.Wefer, J.Org.Chem.,1968, 33, 4447.

40. J.M.Wefer, A.Catala and F.D.Popp, J.Org.Chem., 1965, 30, 3075

41. G.W.Kirby, S.L.Tan and B.C.Uff, Chem.Comm.,1969, 1075.

42. R.F.Collins, Chem. and Ind., 1957, 736.

43. L.R.Walters, J.Chem.and Eng.Data, 1964, 9, 248.

44. L.R.Walters, J.Chem.and Eng.Data, 1965, 10, 79.

45. T.Agawa and S.I.Miller, J.Amer.Chem.Soc., 1961, 83, 449.

46. B.C.Uff, J.R.Kershaw and S.R.Chhabra, Tetrahedron Letters, 1969, 1687.

47. R.F.Collins and T.Henshall, J.Amer.Chem.Soc., 1958, 80, 159.

48. I.W.Elliott and R.B.McGriff, J.Org.Chem., 1957, 22, 514.

49. F.D.Popp, K.T.Potts and R.Armbruster, Org.Mass Spectrometry, 1970, 3, 3075.

50. W.J.Gensler, Org.Reactions, 1951, 6, 191.

51. W.M.Whaley and T.R.Govindachari, Org.Reactions, 1951, 6, 74.

52. W.M.Whaley and T.R.Govindachari, Org.Reactions, 1951, 6, 151.

53. C.Djerassi, F.X.Markley and R.Ehrlich, J.Org.Chem., 1956, 21, 975; M.J.Bevis, E.J.Forbes and B.C.Uff, Tetrahedron, 1969, 25,1585.

54. L.K.Dalton, S.Demerac, B.C. Elmes, J.W.Loder, J.M.Swan and T.Teitei, Austral.J.Chem., 1967, 20, 2715.

55. M.J.Bevis, E.J.Forbes, N.N.Naik and B.C.Uff, Tetrahedron, 1971, 27, in press

56. E.Schlittler and J.Müller, Helv.Chim.Acta, 1948, 31, 914.

57. J.M.Bobbitt, J.M.Kiely, K.L.Khanna and R.Edermann, J.Org.Chem., 1965, 30, 2247.

58. M.Conrad and L.Limpach, Ber., 1887, 20, 944.

59. G.A.Reynolds and C.R.Hauser, Org.Synth., 1955, Coll.Vol. III, p. 593.

60. E.A.Braude, J.Hannah and R.Linstead, J.Chem.Soc., 1960, 3247.

61. L.M.Jackman and D.I. Packham, Chem. and Ind., 1955, 360.

62. L.M.Jackman, Adv.Org.Chem., 1960,2, 329.

63. S.F.Dyke and M.Sainsbury, Tetrahedron, 1965, 21, 1907.

64. A.P.Wolf, W.E.McEwen and R.H.Glazier, J.Amer.Chem.Soc., 1956, 78, 861.

65. A.Albert and E.P.Serjeant, "Ionisation Constants of Acids and Bases", Methuen and Co.Ltd., London, 1962, pp. 69-92.

66. D.D.Perrin, "Dissociation Constants of Organic Bases in Aqueous Solutions", Butterworths, London, 1965, pp. 417, 420.

67. "N.M.R. Spectra Catalogue", Varian Associates, Pablo Alto, California, 1963, Vol.1, Spectrum 192.

68. N.J.McCorkindale, D.S.Magrill, M.Martin-Smith, S.J.Smith and J.B.Stenlake, Tetrahedron Letters, 1964, 3841; G.Grethe, M.Uskokovic and A.Brossi, ibid., 1966, 1599; idem, J.Org.Chem., 1968, 33, 2500; G.Grethe, H.L.Lee, M.R.Uskokovic and A.Brossi, Helv.Chim.Acta, 1970, 53, 874.

69. T.Kametain, T.Kikuchi and K.Fukumoto, Chem.Comm., 1967, 546.

70. B.C.Uff, Ph.D.Thesis, University of Birmingham, 1962, p.83.

71. R.A.Robinson, J.Amer.Chem.Soc., 1947, 69, 1944.

72. N.C.Rose and W.E.McEwen, J.Org.Chem., 1958, 23, 337.

73. F.D.Popp, Private communication, 1969.

74. As for ref. 10, p.74.

75. P.J.Black and M.L.Heffernan, Austral.J.Chem., 1966, 19, 1287.

76. A.I.Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon Press, Oxford, 1964. p. 185.

77. G.W.Ewing and E.A.Steck, J.Amer.Chem.Soc., 1946, 68, 2181.

78. R.M.Silverstein and G.C.Bassler, "Spectrometric Identification of Organic Compounds", Wiley, New York, 2nd Ed. 1967, pp. 142 and 137.

79. As for ref. 10, p.54.

80. S.Sternhell, Quart.Rev., 1969, 23, 236.

81. F.D.Popp and W.Blount, J.Org.Chem., 1962, 27, 297.

82. As for ref. 32, p.16.

83. H.E.Zaugg and W.B.Martin, Org.Reactions, 1965, 14, 91.

84. I.W.Elliott, J.Org.Chem., 1964, 29, 305.

85. R.Bramley and M.D.Johnson, J.Chem.Soc., 1965, 1372.

86. M.D.Johnson, J.Chem.Soc., 1962, 283; 1964, 200.

87. R.Hull, J.Chem.Soc.(C), 1968, 1777.

88. R.Hull, Private communication, 1970.

89. F.D.Popp and C.W.Klinowski, J.Chem.Soc.(C), 1969, 741.

90. R.C.B.McBeth and B.C.Uff, Chemistry Department Project summaries, Loughborough University of Technology, 1966-67, 8, 164.

91. E.Felstead, H.C.Fielding and B.J.Wakefield, J.Chem.Soc.(C), 1966, 708.

92. D.T.Mowry, Chem.Rev., 1948, 42, 196; R.Quelet, Bull.Soc.chim.(France), 1940, 7, 205.

93. R.G.Pearson, J.Chem.Ed.,1968, 45, 581; Survey Prog.Chem., 1969, 5, 22; R.G.Pearson and J.Songstad, J.Amer.Chem.Soc., 1967, 89, 1827.

94. W.J.Gensler, "Heterocyclic Compounds", ed. R.C. Elderfield, Wiley, New York, 1952, 4, 469.

95. A.Claus and K.Hoffmann, J.prakt.Chem., 1893, 47, 252.

96. D.Beke and Cs. Szantay, Annalen, 1961, 640, 127.

97. S.R.Chhabra, J.R.Kershaw and B.C.Uff, Tetrahedron Letters, 1967, 3199.

98. L.Lang, "Absorption Spectra in the Ultraviolet and Visible Region", Publishing House of the Hungarian Academy of Sciences, Budapest, 1962, Vol.III, diagram 382, p. 81-82.

99. G.W.Kirby, S.L.Tan and B.C.Uff, Chem.Comm., 1970, 1138; as for ref. 10, p.43.

100. D.W.Brown, S.F.Dyke and M.Sainsbury, Tetrahedron, 1969, 25, 101; S.F.Dyke, M.Sainsbury, D.W.Brown and M.N.Parlfreyman, ibid., 1969,25, 5365; P.Bichant, G.Thuillier and P.Rumpf, Compt.Rend., 1969, 268C, 993.

101. A.R.Battersby and R.Binks, J.Chem.Soc., 1955, 2888.

102. S.F.Dyke and M.Sainsbury, Tetrahedron, 1967, 23, 3161; F.Bruckhausen, Arch.Pharm., 1922, 261, 28; R. Grewe, N. Kruger and E.Vandernidin, Chem.Ber., 1964, 97, 120.

103. G.Stork, A.Brizzolara, H.Landesman, J.Szmuszkovicz and R.Terrell, J.Amer.Chem.Soc.,1963, 85, 207.

104. M.M. Robison and B.C.Robison, J.Org.Chem., 1956, 21, 1337; as for ref. 10, p.118.

105. F.A.Cotton and G.Wilkinson, "Advanced Inorganic Chemistry", Interscience, New York, 1966, p.569.

106. As for ref. 10, p.14.

107. As for ref. 10, p.102.

108. As for ref. 10, p.24.

109. D.Swern, Chem.Rev., 1949, 45, 1; Org.Reactions, 1953, 7, 378; J.B.Lee and B.C.Uff, Quart.Rev., 1967, 21, 429.

110. K.Dimroth and G.Pohl, Angew.Chem., 1961, 73, 436.

111. E.E.Schweizer and R.Schepers, Tetrahedron Letters, 1963, 979.

112. E.Vogel, W.A.Boll and H.Gunther, Tetrahedron Letters, 1965, 609.

113. H.Gunther, Angew.Chem.Internat.Edn.,1965, 4, 975.

114. O.Simonsen, C.Lohse and O.Buchardt, Acta. Chem. Scand., 1970, 24, 268.

115. M.Ishikawa, C.Kaneko, I.Yokoe and S.Yamada, Tetrahedron, 1969, 25, 295. Also see O.Buchardt, A.M.Duffield and C.Djerassi, Acta Chem.Scand., 1969, 23, 126.

116. A.Baeyer and V.Villiger, Ber., 1901, 34, 762; P.N.Chakravorty and R.H.Levin, J.Amer.Chem.Soc., 1942, 64, 2317.

117. Z.M.Zeavin and A.M.Fisher, J.Amer.Chem.Soc., 1932, 54, 3738.

118. D.E.Wenkert, B.R.Johnston and K.G.Dave, J.Org.Chem., 1964, 29, 2534.

119. E.Ochiae and M.Ikehara, J.Pharm.Soc.Japan, 1953, 73, 666.

120. G.W.Kirby, S.L.Tan and B.C.Uff, Chem.Comm., 1970, 1138; and private communication, 1970.

121. A.G.Davies, "Organic Peroxides", Butterworths, London, 1961, p.183.

122. J.M.Wefer and F.D.Popp, J.Org.Chem., 1967, 32, 1999.

123. F.W.Bergstrom and J.H.Rodda, J.Amer.Chem.Soc., 1940, 62, 3030.

124. J.J.Craig and W.E.Cass, J.Amer.Chem.Soc., 1942, 64, 783.

125. A.Bryson, J.Amer.Chem.Soc., 1960, 82, 4871.

126. A.McCoubrey and D.W.Mathieson, J.Chem.Soc., 1951, 2851.

127. M.D.Potter and E.P.Taylor, J.Chem.Soc., 1953, 1320.

128. F.D.Popp, W.Blount and P.Melvin, J.Org.Chem., 1961, 26, 4930.

129. W.L.F.Armarego, J.Chem.Soc., 1962, 4094.

130. As for ref. 66, p.277.

131. D.G. deKowalewski and V.J.Kowalewski, Anales.Asoc.quim.argentina, 1960, 48, 157.

132. I.Heilbron, A.H.Cook, H.M.Bunbury and D.H.Hey, "Dictionary of Organic Compounds", Eyre and Spottiswoode, London, 3rd Edn., 1953, Vol.1, p.68.

133. L.I.Smith and J.W.Opie, Org.Synth., 1955, Coll.Vol.III, p.56.

134. W.L.F.Armarego, "Quinazolines", Interscience, London, 1967, p.27; J.W.Bunting and W.G.Meathrel, Canad.J.Chem., 1970, 48, 3449.

135. I.W.Elliott and J.O.Leflore, J.Org.Chem., 1963, 28, 3181.

136. E.L.Eliel, Chem.and Ind., 1959, 568; R.U.Lemieux, R.K.Kullnig, H.J.Bernstein and W.G.Schneider, J.Amer.Chem.Soc., 1958, 80, 6098; K.L.Williamson and W.S.Johnson, ibid., 1961, 83, 4623.

137. As for ref. 32, p.66.

138. S.Sternhell, Rev.Pure Appl.Chem. (Australia), 1964, 14, 15.

139. M.Barfield and B.Chakrabarti, Chem.Rev., 1969, 69, 757.

140. A.Rassat, C.W.Jefford, J.N.Lehn and B.Waegell, Tetrahedron Letters, 1964, 233.

141. E.W.Garbish, Chem.and Ind., 1964, 1715.

142. M.Barfield, J.Chem.Phys., 1964, 41, 3825.

143. D.H.R.Barton, R.H.Hesse and G.W.Kirby, J.Chem.Soc., 1965, 6379.

144. H.Ahlbrecht and F.Krohnke, Tetrahedron Letters, 1967, 967.

145. C.E.Johnson and F.A.Bovey, J.Chem.Phys., 1958, 29, 1012.

146. J.A.Elvidge, "Nuclear Magnetic Resonance for Organic Chemists", ed. D.W.Mathieson, Academic Press, London, 1967, p.36.

147. E.L.Eliel, N.L.Allinger, S.J.Angyal and G.A.Morrison, "Conformational Analysis", Interscience, New York, 1965, p.152.

148. D.J.Bennet, G.W.Kirby and V.A.Moss, Chem.Comm., 1967, 218.

149. As for ref. 78, p.145.

150. J.A.Pople, W.G.Schneider and H.J.Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, 1959, pp. 132-138.

151. E.B.Whipple, J.H.Goldstein and G.R.McClure, J.Amer.Chem.Soc., 1960, 82, 3811.

152. H.J.Bernstein and N.J.Sheppard, J.Chem.Phys., 1962, 37, 3012.

153. T.Schaefer, Canad.J.Chem., 1962, 40, 1.

154. J.I.Musher and R.G.Gordon, J.Chem.Phys., 1962, 36, 3097.

155. M.Karplus, J.Chem.Phys., 1960, 33, 1842.

156. A.A.Bothner-By, C.Naar Colin and H.Gunther, J.Amer.Chem.Soc., 1962, 84, 2748; P.Laszlo and P.V.R.Schleyer, J.Amer.Chem.Soc., 1964, 86, 1171.

157. G.P.Newsoroff and S.Sternhell, Tetrahedron Letters, 1968, 6117.

158. L.M.Jackman and S.Sternhell, "Applications of N.m.r. Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, p.316.

159. E.A.Braude, J.Hannah and R.P.Linstead, J.Chem.Soc., 1960, 3249.

160. As for ref. 70, p.150.

161. A.I.Vogel, "Practical Organic Chemistry", Longmans, London, 3rd Edn., 1959, p.792.

162. H.Harned and B.Owen, "The Physical Chemistry of Electrolytic Solutions", Reinhold Publishing Corporation, New York, 1964, p. 746.

163. M.A.Paul and F.A.Long, Chem.Rev., 1957, 57, 1.

164. F.M.Hamer, J.Chem.Soc., 1921, 1432.

165. R.A.Abramovitch, J.Chem.Soc., 1954, 3839.

166. A.Albert and J.N.Phillips, J.Chem.Soc., 1956, 1294.

167. C.J.Cavallito and T.H.Haskell, J.Amer.Chem.Soc., 1944, 66, 1166.

168. P.J.Black and M.L.Heffernan, Austral.J.Chem., 1966, 19, 1287.

169. As for ref. 161, p. 582.

170. As for ref. 132, p. 628.

171. As for ref. 10, p.30.

172. M.J.S.Dewar and P.M.Maitlis, J.Chem.Soc., 1957, 2521.

173. E.E.Royals and L.L.Harrell, J.Amer.Chem.Soc., 1955, 77, 3405.

174. R.C.Elderfield, J.M.Lagowski, O.L.McCurdy and S.L.Wythe, J.Org.Chem., 1958, 23, 435.

175. H.H.Hodgson, A.P.Mahadevan and E.R.Ward, Org.Synth., 1955, Coll. Vol. III, p.341.

176. F.D.Popp and A.Soto, J.Chem.Soc., 1963, 1760.