STUDIES IN ISOQUINOLINE CHEMISTRY

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A thesis

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To my wife

and

to my parents

ACKNOWLEDGEMENT

I wish to express my sincere thanks to Dr. B.C. Uff for his guidance and encouragement throughout this work.

I would like to thank my wife, Gillian, for typing this thesis and for much help with its preparation.

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SUMMARY

The use of Reissert compounds as intermediates for the synthesis of 1-benzylisoquinolines has been investigated. An improved method, utilising sodium hydride, for the generation of the carbanion of Reissert compounds and subsequent reaction with benzyl halides has been found and demonstrated to be a general procedure. This method has been successfully applied as the key stage in providing a new total synthesis of the alkaloid petaline.

The stereochemistry of the Reissert compound system has been elucidated by spectroscopic techniques.

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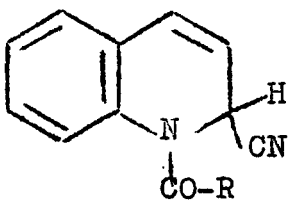
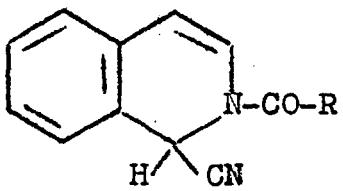
LIST OF FIGURES

INTRODUCTION

1-Acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) are known as Reissert compounds. These were discovered by Arnold



I



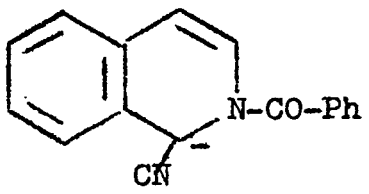
II

Reissert in 1905 when making a systematic study of the benzoylation of cyclic tertiary amines.[1,2] The reaction of benzoyl chloride with quinoline in aqueous potassium cyanide gave a crystalline compound (I).[1] This compound was found to undergo a remarkable acid-catalysed cleavage to benzaldehyde, quinaldic acid and in much smaller amounts, derivatives of the latter.

Other nitrogen heterocyclic compounds have since been shown to give Reissert compounds including isoquinoline,[2] phenanthrene,[3] and phthalazine,[4] and it has also been shown that hydrogen cyanide can replace potassium cyanide.[5] Interest in these compounds grew mainly because their preparation and subsequent acid-catalysed hydrolysis presented a general method for the preparation of aldehydes from acid chlorides.[6,7]

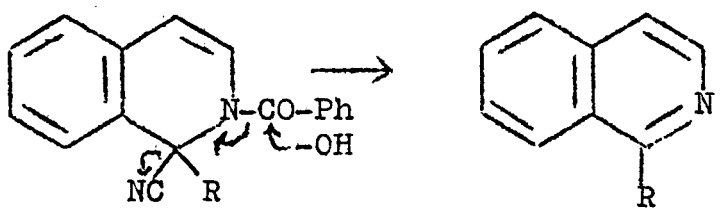
More recently the reaction of Reissert compounds with base has been studied. In 1952 Boekelheide and Weinstock[8] treated Reissert compounds with phenyl lithium

and so generated the anion of the type III (from isoquinoline) by the removal of the aldo-proton.



III

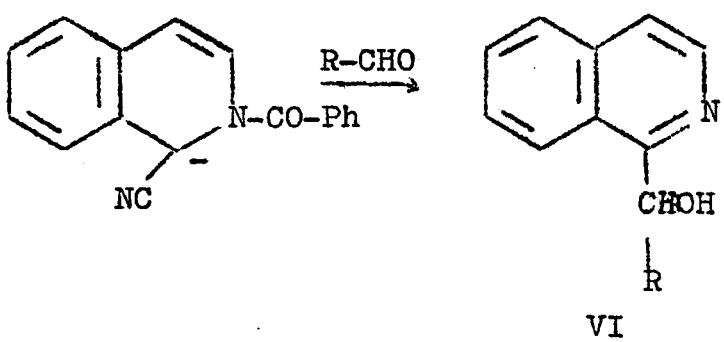
The authors[8] showed further that the carbanion (III) could be alkylated with alkyl halides (RX) to give first the substituted Reissert compound (IV), which on basic hydrolysis gives the 1-substituted isoquinoline(V). They obtained 1-benzyl, 1-methyl and



IV V

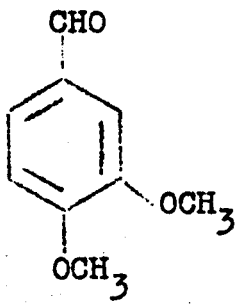
1-butyl isoquinoline in 78%, 58% and 41% yield respectively.

A few years later McEwen and his co-workers[9,10] showed that aldehydes react with the Reissert carbanion, in better yields than the corresponding halide (as might be expected from their greater nucleophilicity) giving the carbinol(VI)or its benzoate. For example

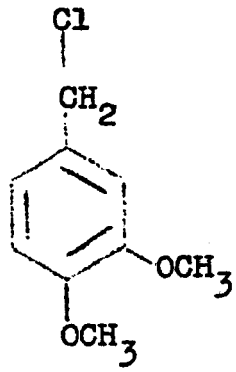


VI

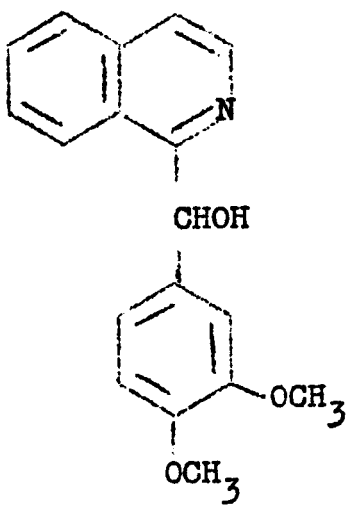
the anion (III) of N-benzoyl-1,2-dihydroisoquinaldonitrile (II, R=Ph) reacts with veratraldehyde (VII) to give the carbinol (VIII) in 78% yield, whilst with 3,4-dimethoxybenzyl chloride (IX) the substituted 1-benzylisoquinoline (X) is obtained in only 53% yield.[9]



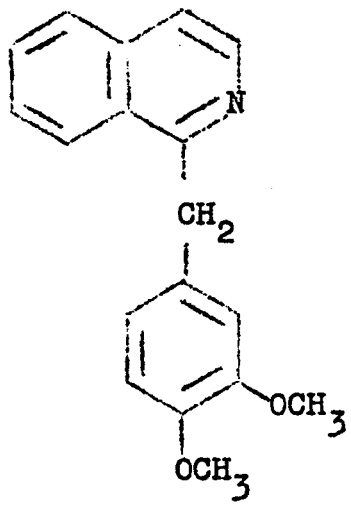
VII



IX

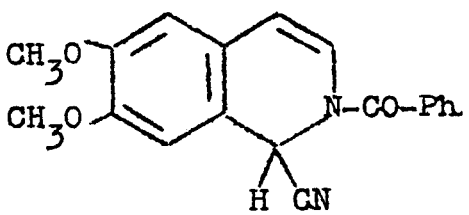


VIII

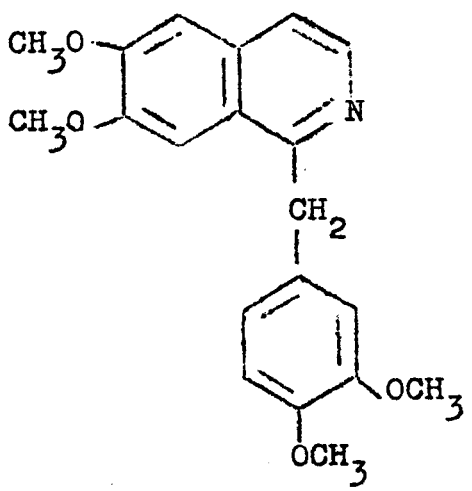


X

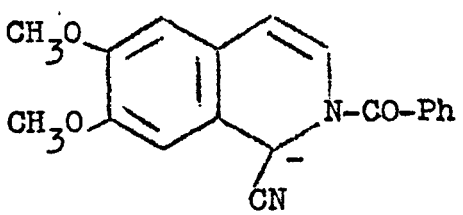
Reissert compounds have been used in the synthesis of a number of alkaloids. 6,7-Dimethoxyisoquinoline Reissert compound (XI) has been the precursor in most of these syntheses. These have included papaverine (XII)[9] (from addition of 3,4-dimethoxybenzyl chloride (IX) to the anion (XIII)) and armepavine (XIV), by reaction of



XI

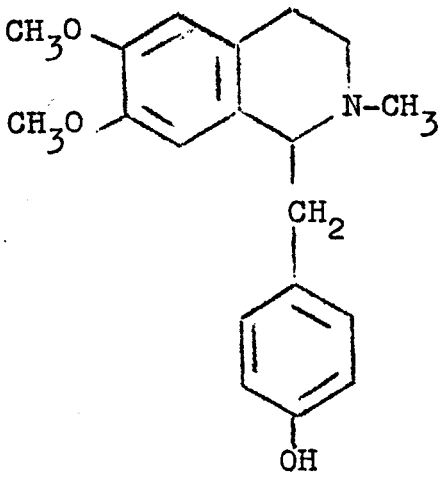


XII

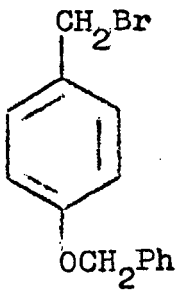


XIII

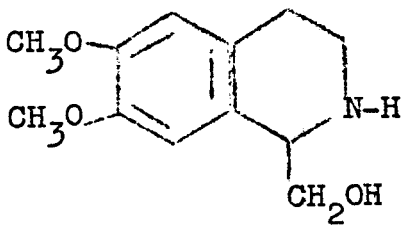
the anion (XIII) with XV, followed by preparation of the methiodide, reduction and debenzylation.[11] Further, calycotomine (XVI) is formed by reaction of the anion (XIII) with gaseous formaldehyde, followed by reduction;[12] and the bisbenzylisoquinoline alkaloid, O-methyldauricine



XIV

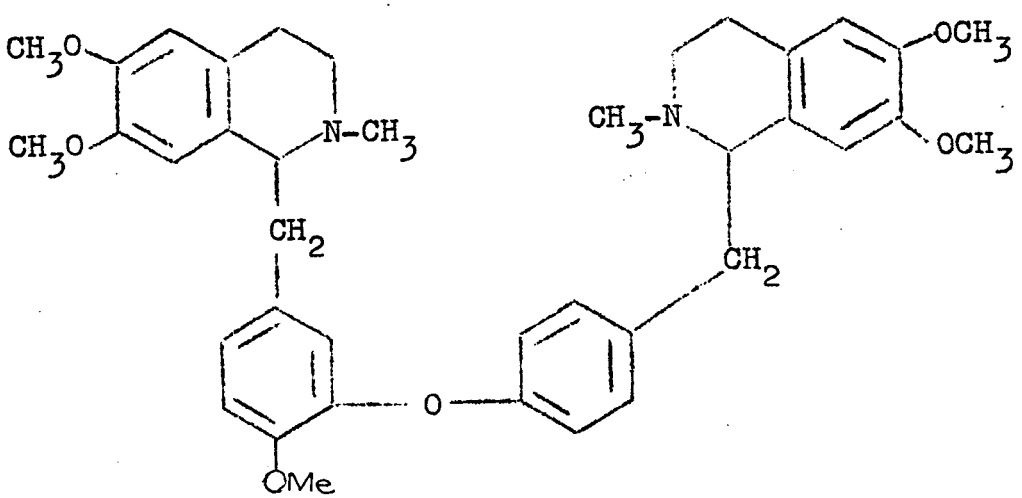


XV

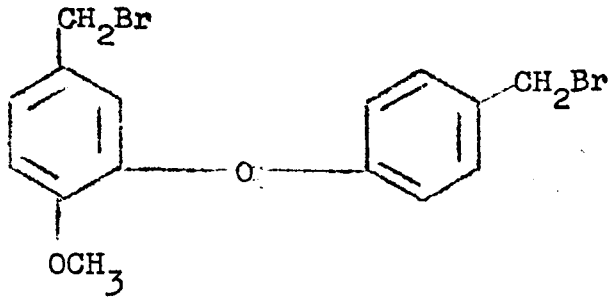


XVI

(XVII), by treatment of two moles of the Reissert compound anion (XIII) with the diphenyl ether (XVIII).[13]



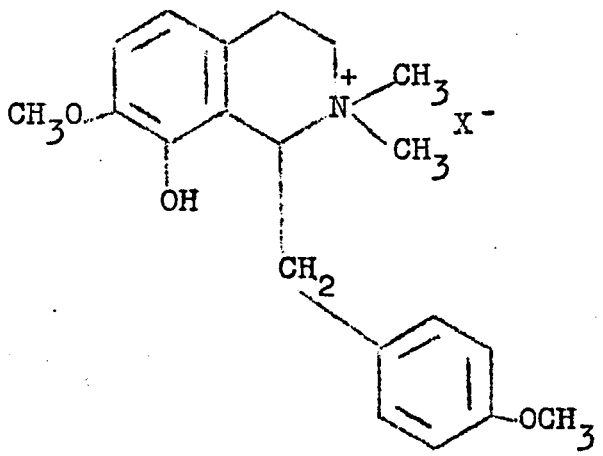
XVII



XVIII

We set out to further the investigation of the preparation of 1-benzylisoquinolines, using halide substitution, with the aim of achieving the synthesis of the quaternary alkaloid petaline (XIX). The disadvantage of using aldehydes, rather than halides in the substitution stage is that the carbinol produced (from the aldehyde) has been found difficult to reduce.[11,14]

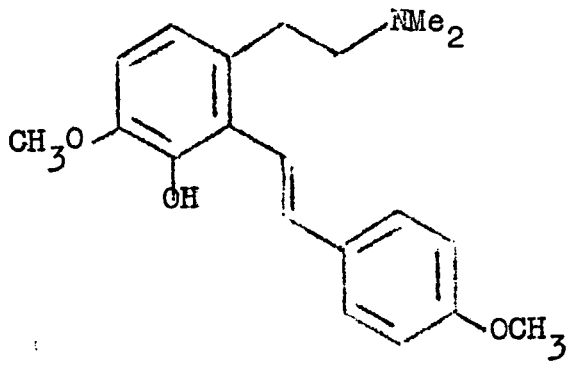
The alkaloid petaline (XIX) was isolated from the root tubers of Leontice Leontopetalum Linn. in the



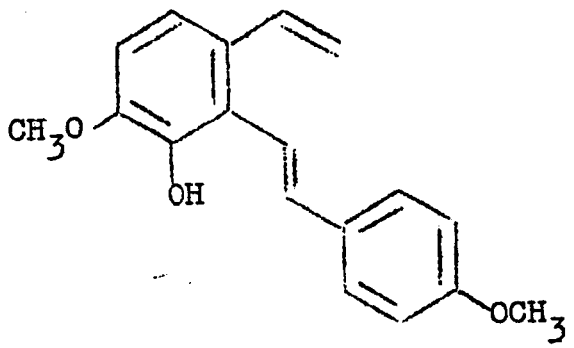
XIX

form of its reineckate by Mc Shefferty et al.[15] in 1956. The plant is found in countries bordering the Eastern Mediterranean.[16] The root "juice" is regarded in the Lebanon as a "kill or cure" for the treatment of epilepsy,[15] and has been used in the Lebanon and other countries for many local cures.[16] Petaline acts as a central nervous depressant in both mouse and rabbit and it also shows anti-acetylcholine activity on isolated skeletal frog muscle.[15]

The structure of the alkaloid, $C_{20}H_{26}O_3N^+X^-$, was elucidated[17] in late 1964 by Hofmann degradation to the methine base (XX), $C_{20}H_{25}O_3N$. The methohydroxide of this in turn undergoes Hofmann degradation to give trimethylamine and the styrene (XXI).

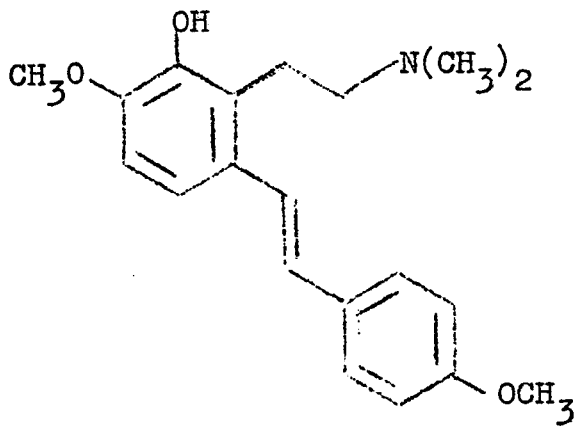


XX

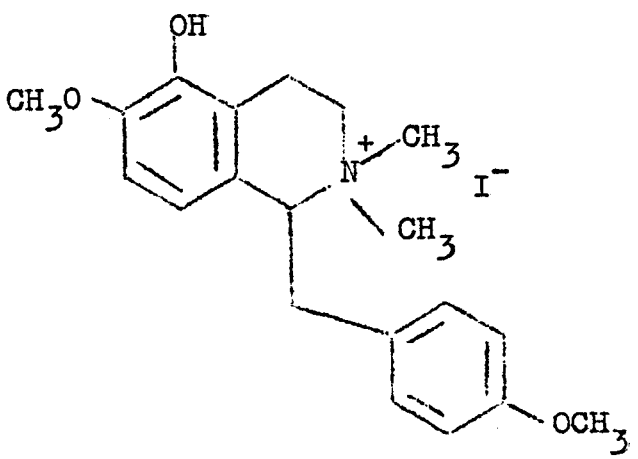


XXI

Oxidation of the O-methanesulphonyl derivative of petaline methine gave p-methoxybenzoic acid and 3-methanesulphonoxy-4-methoxy-phthalic acid. These findings and the spectral evidence gave two possible structures for petaline methine (XX and XXII). However, structure XXII was shown[17] to be incorrect by dissimilarity of petaline methine from a sample of synthetic XXII prepared from XXIII.

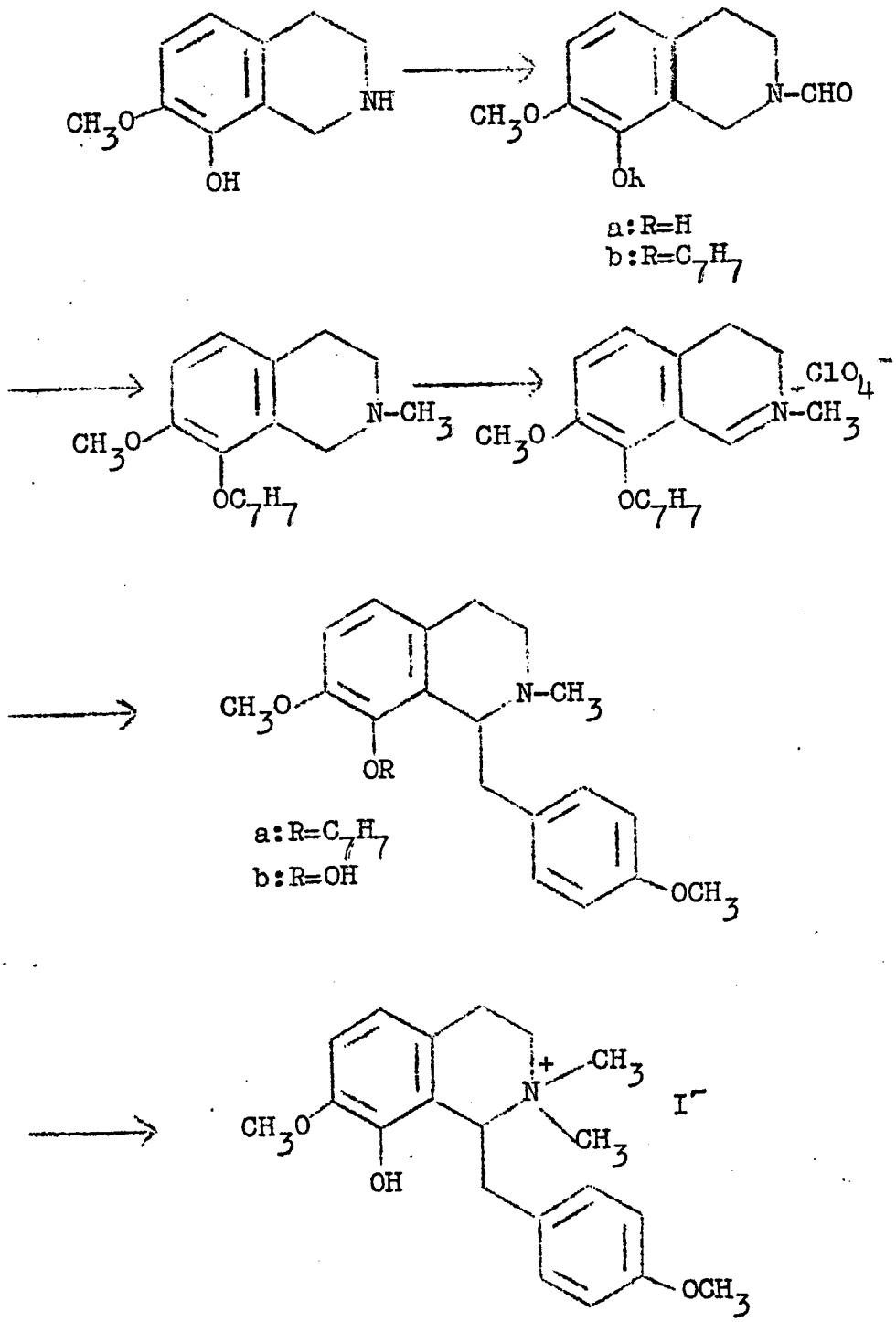


XXII

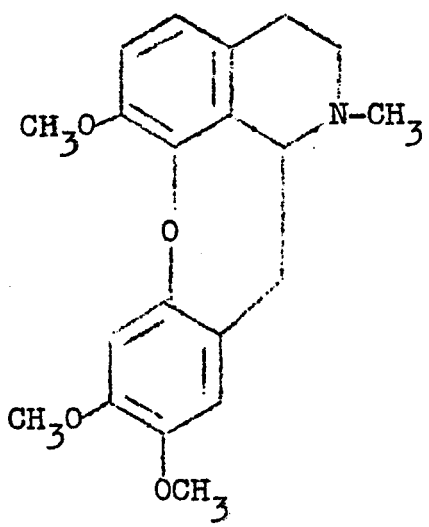


XXIII

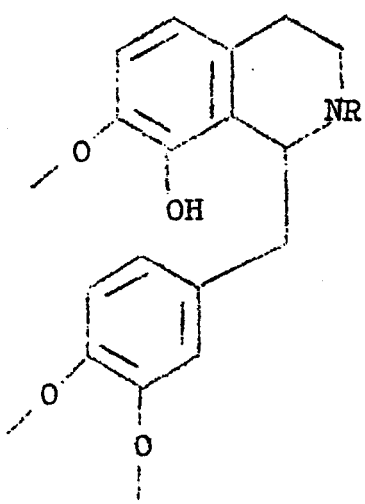
Whilst our work was in progress a total synthesis of racemic petaline was achieved by some American workers[18] but using a scheme quite different from our own, as outlined below:-



Before concluding this Introduction, in view of the current interest in biosynthesis, it would seem pertinent to comment on this topic with reference to petaline. Petaline is of particular interest since it is the only known simple benzylisoquinoline alkaloid with a 7,8-dioxygenation pattern. The only other alkaloids similarly substituted are the small group of tetracyclic cularine alkaloids[19-23], found in the genera Dicentra and Corydalis e.g. cularine (XXIV).

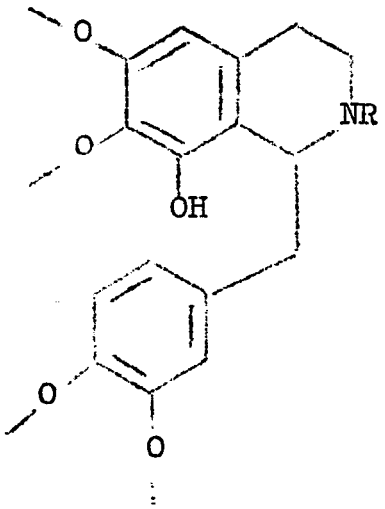


XXIV

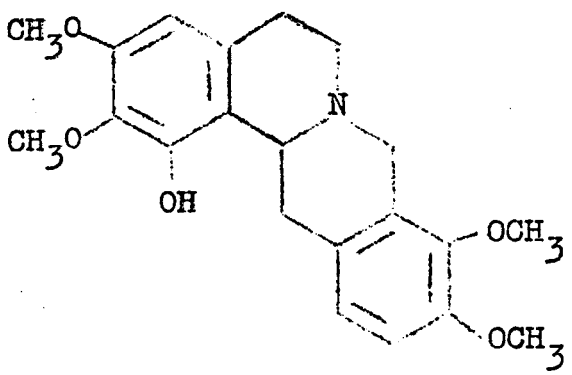


XXV

Two theories have been advanced for the biosynthesis of cularine. Manske[24] has suggested ring closure of an intermediate of type (XXV), whereas Bentley[25] favours a 6,7,8-trioxygenated isoquinoline (XXVI) as the precursor. This latter course requires subsequent removal of the unwanted C-6 substituent. It is of interest that the protoberberine alkaloid, capaurine (XXVII), which has the same oxygen substitution pattern as XXVI, occurs in the Corydalis species.[26]



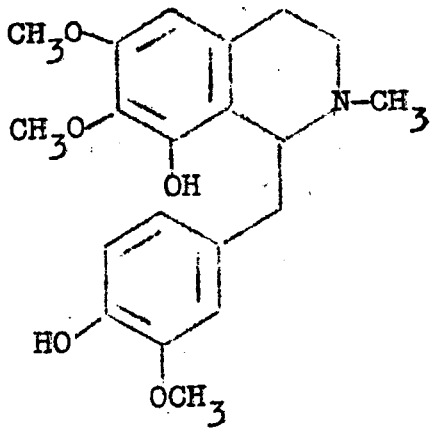
XXVI



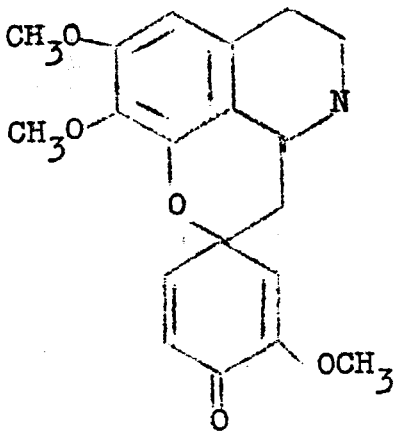
XXVII

Recently a biogenetic synthesis of the cularine system has been carried out.[27] The 6,7,8-trioxygenated 1-benzylisoquinoline (XXVIII) was oxidised by potassium ferricyanide in ammonium acetate at room temperature, to give the dienone (XXIX) which in strong acid undergoes a dieone-phenol rearrangement to give XXX.[27] The analogous case using a 7,8-dioxygenated system has not yet been attempted.

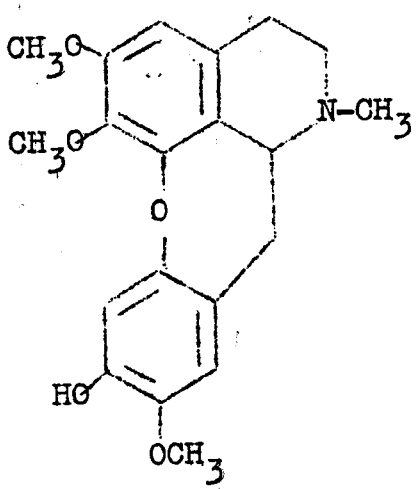
However, with the discovery of petaline it would seem to us that the simpler biogenetic scheme



XXVIII

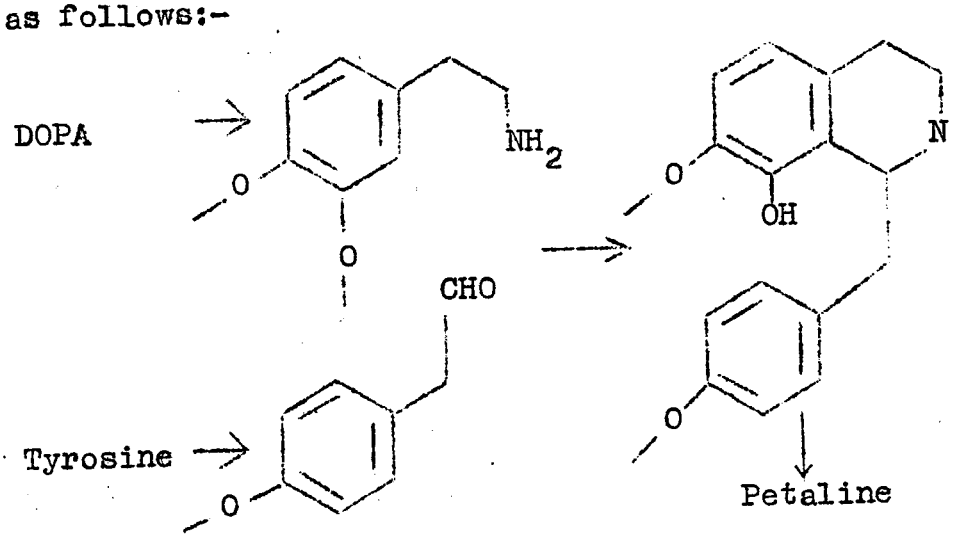


XXIX

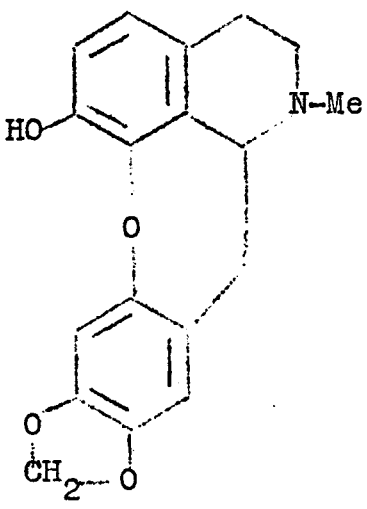


XXX

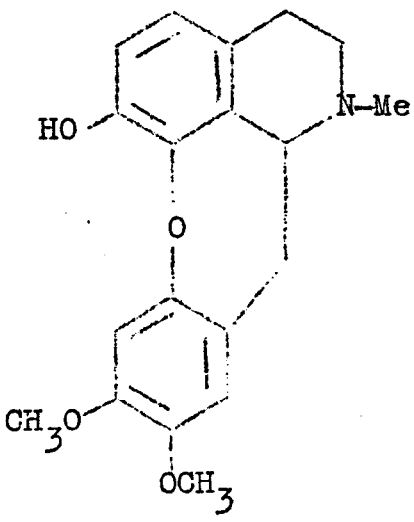
(via XXV) for cularine is quite acceptable and avoids the necessity for an extra oxygenation-deoxygenation process. Correspondingly petaline is likely to arise as follows:-



Methylation could occur before or after cyclisation and it is not possible to decide this without careful labelling experiments. The structures of cularicine (XXXI)[21] and cularidine (XXXII)[22,23] suggest methylation may follow the cyclisation stage in the biosynthesis of petaline.



XXXI



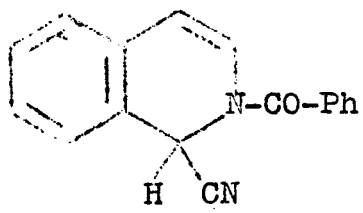
XXXII

In suggesting the biogenesis of petaline and cularine alkaloids are similar, it is relevant to mention that both petaline[28] and cularine[29] possess the same absolute configuration (R).

DISCUSSION

1. Preparation of Reissert Compounds.

Our initial studies comprised a brief examination of the preparation of Reissert compounds. The most convenient published procedure is that of Popp and Blount.[30] This involves stirring one mole of the isoquinoline (or quinoline), two moles of acyl chloride and three moles of potassium cyanide in a two phase system of methylene chloride and water. The generality of the method has been demonstrated by using various quinolines, isoquinolines and acid chlorides.[31-34] However, no investigation of the effect of varying the organic solvent in the two phase system has appeared in the literature (although various single phase systems have been assessed).[35] We thus examined other organic solvents in place of methylene chloride, for the preparation of N-benzoyl-1,2-dihydroisoquinaldonitrile (XXXIII).



XXXIII

The solvents employed are listed in table 1 and the yields of XXXIII indicated. In no case was any improvement shown over use of dichloromethane. The yield obtained in each case appeared to be approximately proportional to the solvent's dielectric constant and mutual

TABLE I

Preparation of isoquinoline Reissert compound (XXXIII) in various organic aqueous systems.

Organic Solvent	Yield of XXXIII %	Dielectric Constant[a]	A[b]	B[c]
Dichloromethane	66	9·08	0·14	2·00
1,2-Dichloroethane	48	10·36[d]	0·16	0·80
Chloroform	42	4·81	0·097	0·8
Benzene	26	2·28	0·06	0·08
Carbon tetrachloride	17	2·24	0·0084	0·08
Ether	9[e]			

a: Dielectric constants reported at 20^{o}.[36]

b: A = Solubility of water in the organic solvent as % $^{w}/_{w}$.[37]

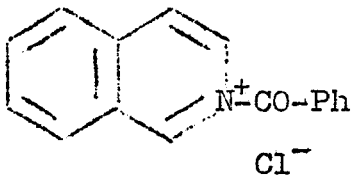
c: B = Solubility of the organic solvent in water as % $^{w}/_{w}$.[37]

d: At 25^{o}.[38]

e: Anomalous result due to precipitation - see text.

solubility in water (see table I). When using ether as the organic solvent we obtained an immediate precipitate of a white solid in good yield. The material proved highly hygroscopic and deteriorated rapidly in the atmosphere. It gave a positive Beilstein's test for

halogen and the n.m.r. spectrum suggested the salt (XXXIV). The compound was further stirred in water in



XXXIV

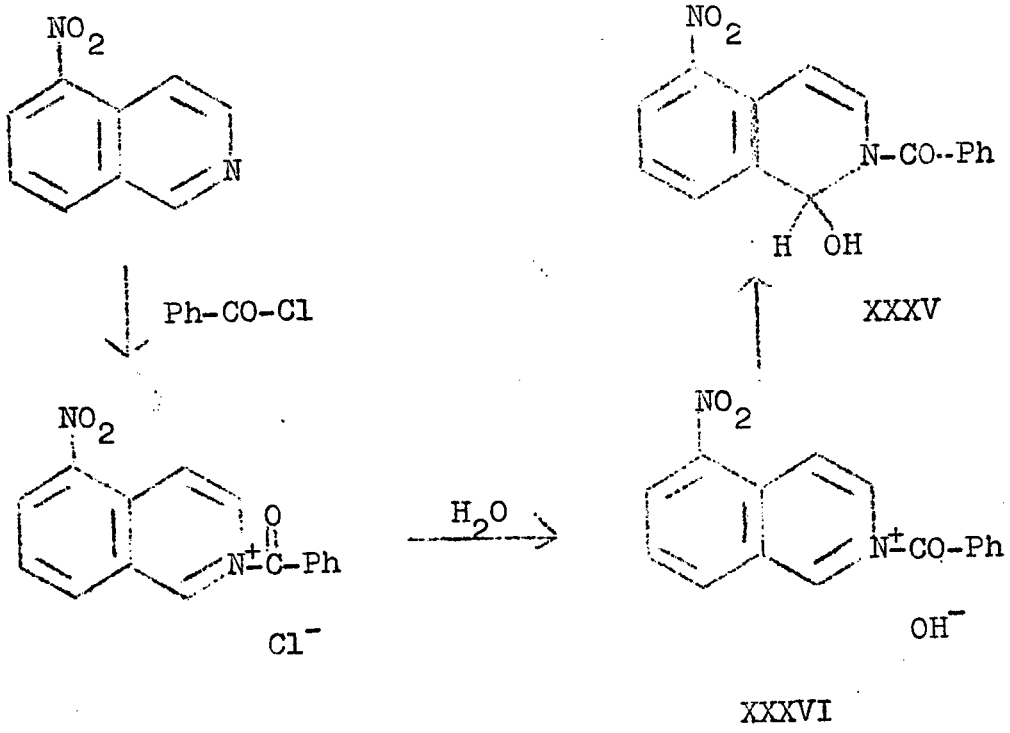
the presence of potassium cyanide for three hours. Extraction with benzene and subsequent work-up gave a small yield of isoquinoline Reissert compound. It would be expected that XXXIV would be an intermediate in the preparation of Reissert compounds,[7] but actual isolation of the quarternary chloride does not appear to have been reported previously.

A related phenomenon was interestingly observed when we attempted to prepare 5-nitroisoquinoline Reissert compound.

2. Reactions of 5-Nitroisoquinoline.

We attempted to prepare 5-nitroisoquinoline Reissert compound, again using the method of Popp and Blount.[30] A yellow solid precipitated in quantitative yield as the reaction proceeded, and was shown not to be the expected Reissert compound. Later we showed that the same yellow solid was precipitated when benzoyl chloride and the isoquinoline were stirred in methylene chloride and water only, i.e. in the absence of cyanide.

The precipitate analysed for $C_{16}H_{12}N_2O_4$ and gave the following spectral information: infra red: 1666cm.$^{-1}$ (amidic carbonyl), 1625 cm.$^{-1}$ (C=C), 3340 cm.$^{-1}$, broad (bonded OH), no C≡N absorption (in 2200-2300 cm.$^{-1}$ region); the n.m.r. consisted of a complex absorption from 1·8 to 3·4τ which included a clearly defined singlet at 2·36 τ. Assuming the singlet to be phenyl and so integrating for 5 protons the remainder of the spectrum represented 7 protons. This evidence could be accounted for by considering the precipitate to have structure (XXXV), i.e. a pseudo-base type of compound. This product (XXXV) could presumably have arisen thus:-



XXXVI

The structure designation was supported by the mass spectrum which showed a parent peak at 296 with the ratios $\frac{P+1}{P}$ and $\frac{P+2}{P}$ as calculated. The other main

peaks could be accounted for by a reasonable fragmentation pattern (see Figure 1).

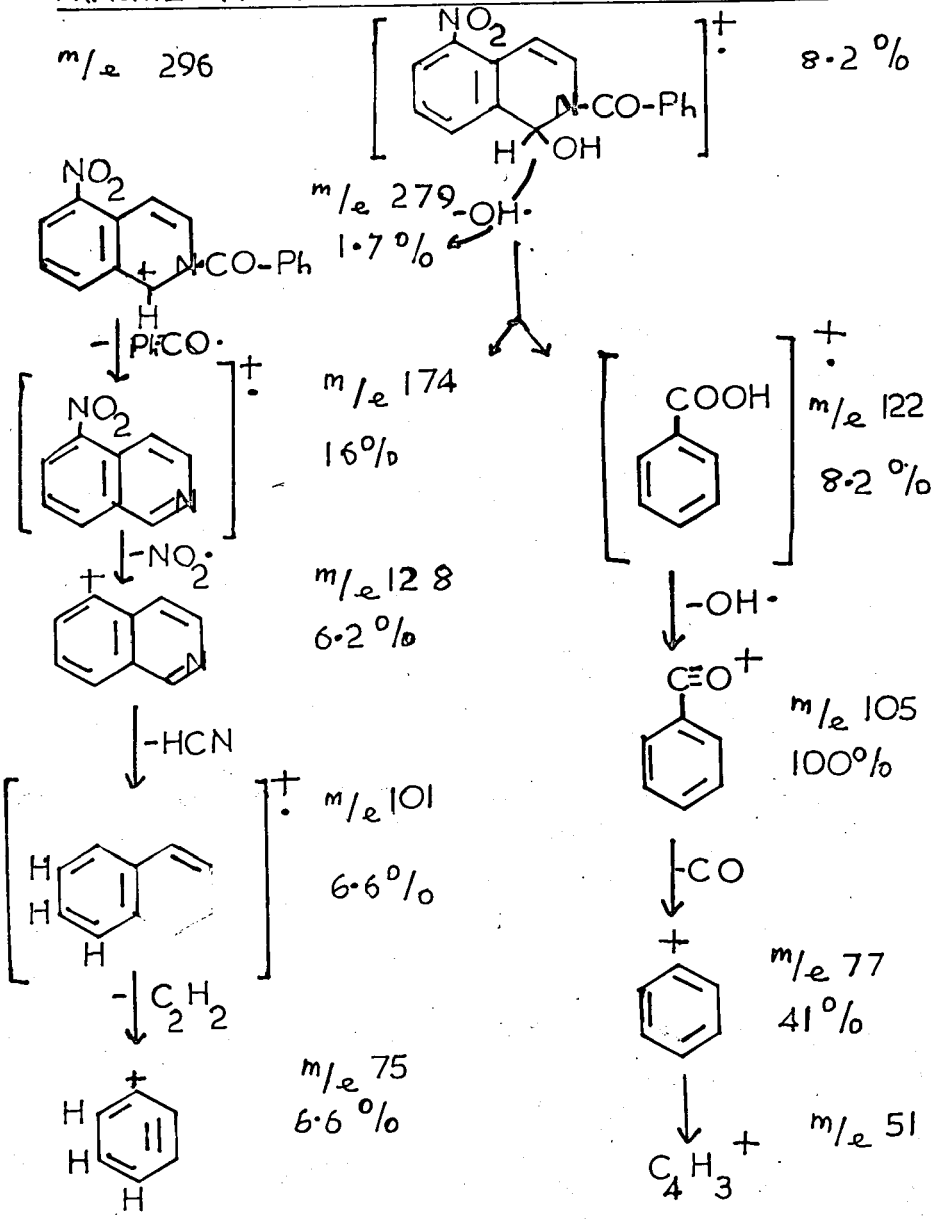
The pseudo-base was not very soluble in water or ether, suggesting that it was probably in the carbinolamine form (XXXV) rather than the ionic form (XXXVI). This was also indicated by the ultra-violet spectrum ($\lambda_{max.}$ at 213, 302, 352 mμ in methanol) which was markedly different from the spectrum of 5-nitroisoquinoline methiodide ($\lambda_{max.}$ at 222, 255, 328 mμ in methanol). Further, the ionic form (XXXVI) is unlikely on electronic grounds since the carbonyl grouping will tend to destabilise any adjacent positive charge.

It would appear that XXXV is the first N-acylisoquinoline pseudo-base to be observed. As formation of the pseudo-base occurs with 5-nitroisoquinoline but not in the preparation of other Reissert compounds, it suggests its formation is due to deactivation by the 5-nitro group. The nitro grouping will enhance the electrophilicity of the C-1 position, so facilitating conversion of (XXXVI) to (XXXV).

The effect of the 5-nitro group has also been noticed with N-methylisoquinolium salts. N-methylisoquinolium salts (XXXVII) on treatment with silver oxide give the strongly alkaline quaternary hydroxide (XXXVIII), which slowly transforms to the pseudo-base (XXXIX).[39] However, 5-nitroisoquinoline methiodide on treatment with silver oxide or ammonia leads directly

FIGURE I

FRAGMENTATION PATTERN OF THE PSEUDO-BASE (XXXV)



$\frac{P+1}{P}$ = 19·2 % (CALC.^{40} 18·4)

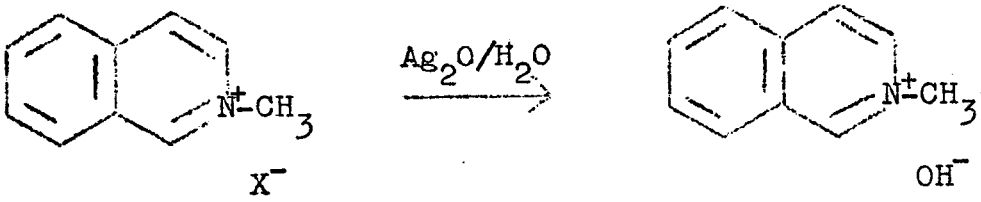
$\frac{P+2}{P}$ = 2·7 % (CALC.^{40} 2·7)

METASTABLE PEAKS AT 102·3 $\left(\frac{174^2}{296}\right)$

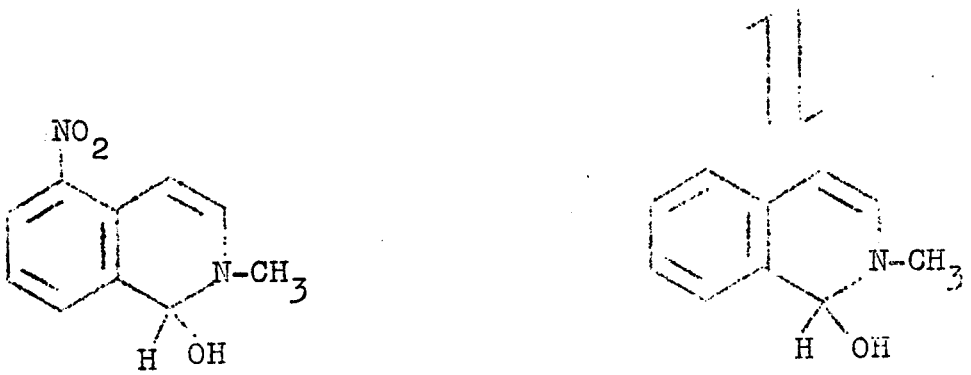
50·3 $\left(\frac{122^2}{296}\right)$

56·5 $\left(\frac{77^2}{105}\right)$

33·8 $\left(\frac{51^2}{77}\right)$



XXXVII XXXVIII



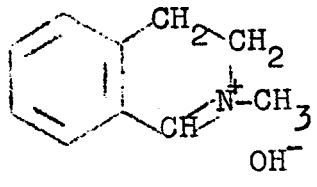
XL XXXIX

to the pseudo-base (XL).[39,41] In our N-acyl analogue it was not necessary to use basic conditions to obtain the pseudo-base.

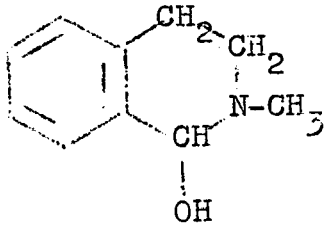
In 1905 Reissert claimed[42] to have formed the analogous N-acyl pseudo-base (XLI) from unsubstituted quinoline by treatment with benzoyl chloride and aqueous sodium hydroxide. However, it has subsequently been shown[43,44] that the compound was the amino-aldehyde (XLII). The equivalent reaction does not take place with isoquinoline.[43]

XLI XLII

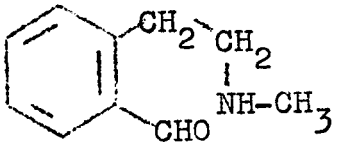
It has been suggested that pseudo-bases exist as a mobile tautomeric equilibrium of the quaternary hydroxide (e.g. XLIII), the carbinolamine (e.g. XLIV) and the amino-aldehyde (e.g. XLV),[45,46] but the existence of all three forms for any particular compound has not been demonstrated.[47] The simultaneous existence of both the carbinolamine and the amino-aldehyde has only been shown in one case.[48] We could find no evidence for, nor were we able to obtain, the amino-aldehyde form of XXXV.



XLIII



XLIV

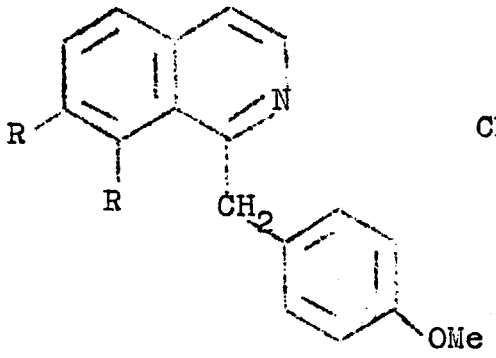


XLV

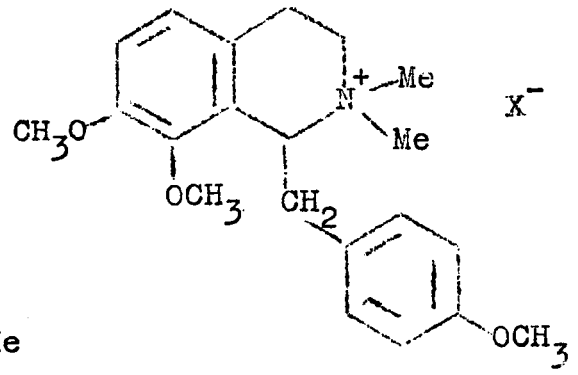
3. Synthesis of 1-Benzylisoquinolines-Phenyl Lithium Route.

(a) 1-Anisylisoquinoline

We required 1-anisyl-7,8-dimethoxyisoquinoline (XLVI, R = OCH_3) as an intermediate for the synthesis of O-methylpetaline (XLVII). As a preliminary invest-



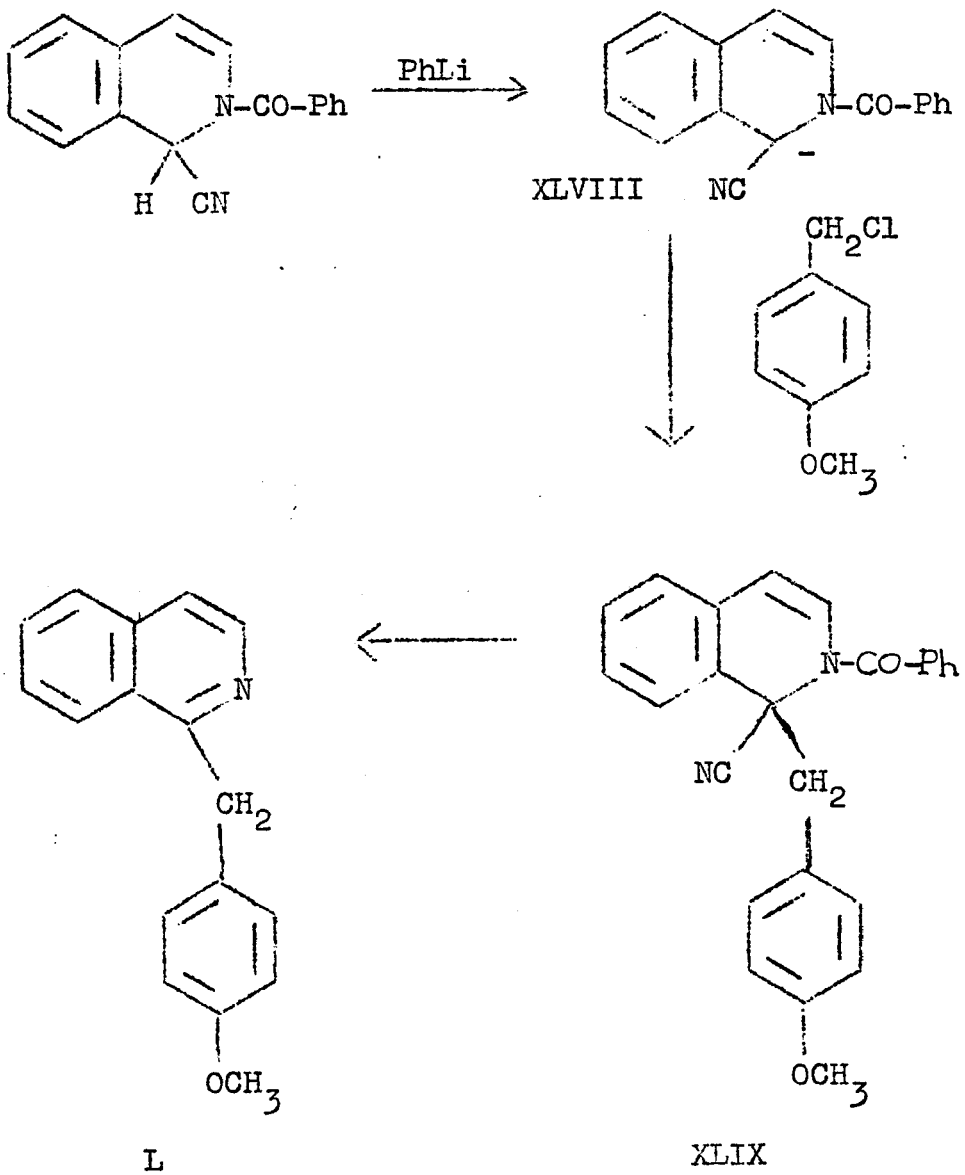
XLVI



XLVII

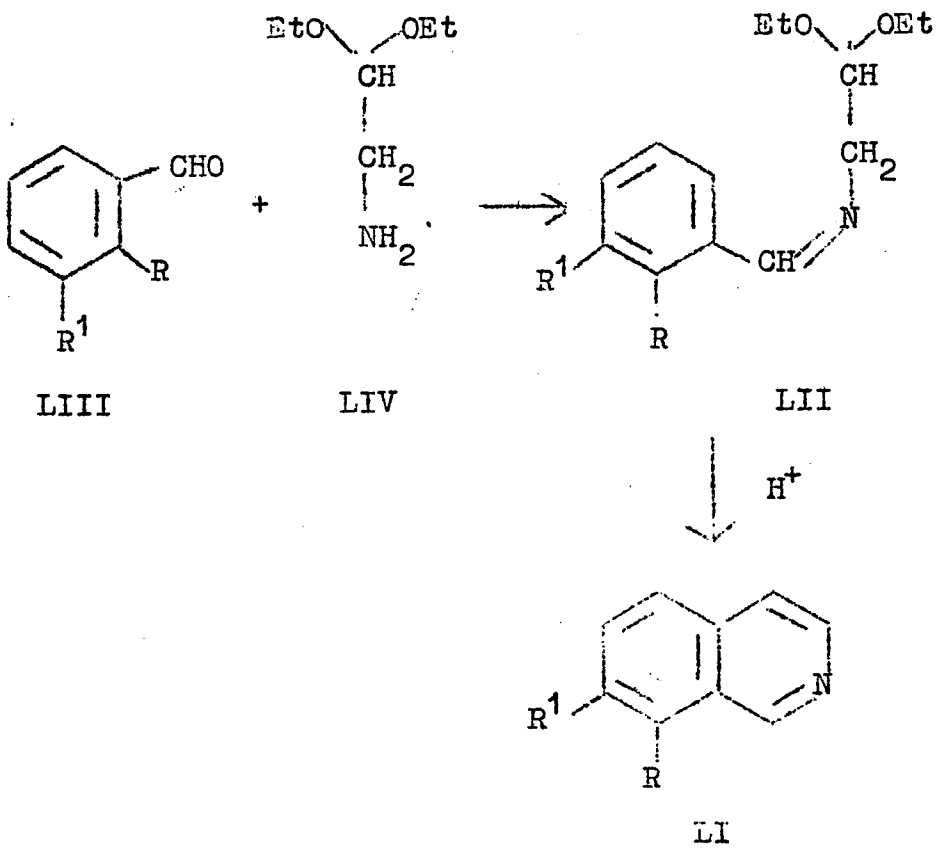
igation, formation of the simpler 1-anisylisoquinoline (XLVI, R = H) was investigated by treating the carbanion of isoquinoline Reissert compound (XLVIII) with anisyl chloride.[49]

The generation of the carbanion was achieved by Boekelheide and Weinstock's procedure[8] using phenyl lithium in tetrahydrofuran, at -5° to -10°. After the characteristic dark red colour of the anion appeared, anisyl chloride was added and the colour slowly faded. The substituted Reissert compound (XLIX) first formed was not isolated, but immediately hydrolysed by potassium hydroxide in aqueous ethanol to 1-anisylisoquinoline (L), in 66% overall yield. The reaction scheme is as follows:-



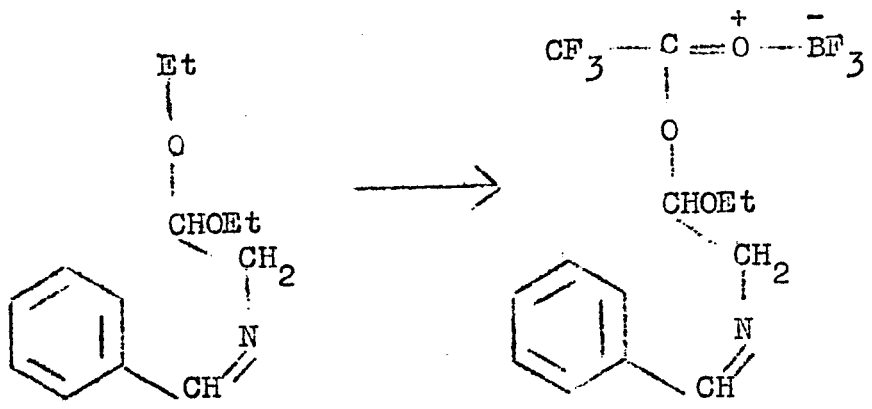
(b) Attempted Synthesis of 1-Anisyl-7,8-dimethoxy-isoquinoline.

The starting base 7,8-dimethoxyisoquinoline (LI, R = R^1 = OCH_3) can be prepared by the Pomeranz-Fritsch synthesis. This involves acid catalysed cyclisation of the Schiff base (LII) formed from condensation of the appropriate aromatic aldehyde (LIII) with aminoacetal (LIV). Acid cyclisation



LIII LIV LII LI

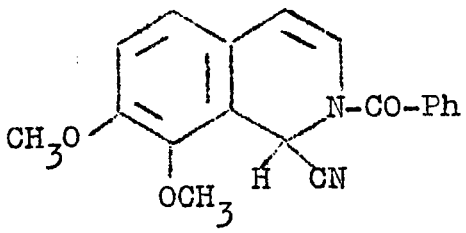
with sulphuric acid[50] and polyphosphoric acid[51] give low yields of 5% and 17% respectively of 7,8-dimethoxyisoquinoline (LV, $R=R^1=OCH_3$) from 2,3-dimethoxybenzylideneaminoacetal (LII, $R=R^1=OCH_3$). However, the cyclisation has been effected in good yield using trifluoroacetic anhydride in boron trifluoride-acetic acid complex.[52] These reagents fulfil two criteria for the effectiveness of the cyclisation: (a) the initial cleavage of the C-O bond in the acetal (LII) (a mixed ether) is greatly enhanced, and (b) an excellent leaving group is introduced into that position (combining the electron withdrawing effects of the functions, $-CF_3$, $=\overset{+}{O}-\overset{-}{B}F_3$ and $>C=O$, from the acetal C-O bond of LV).



LV

Using four moles of boron trifluoride-acetic acid complex and three moles of trifluoroacetic anhydride to one mole of the Schiff base, 7,8-dimethoxyisoquinoline was prepared in 39% yield of the pure redistilled compound.

7,8-Dimethoxyisoquinoline was converted to its Reissert compound (LVI) by the method of Popp and Blount[30] in 72% yield. The n.m.r. spectrum showed

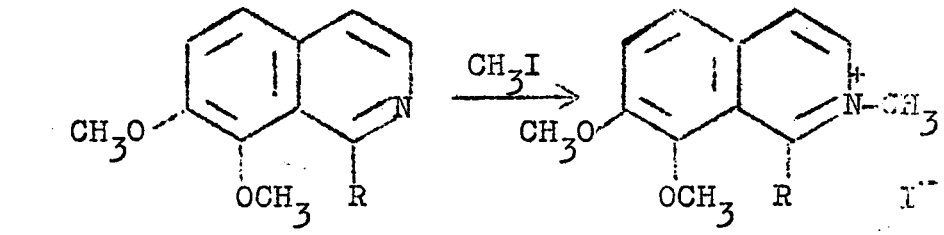


LVI

two methoxy peaks at 5·95τ and 6·1τ; the lower of these is probably the C_8 methoxy peak which is deshielded by the cyano[53] group irrespective of whether it is quasi-axial or quasi-equatorial.

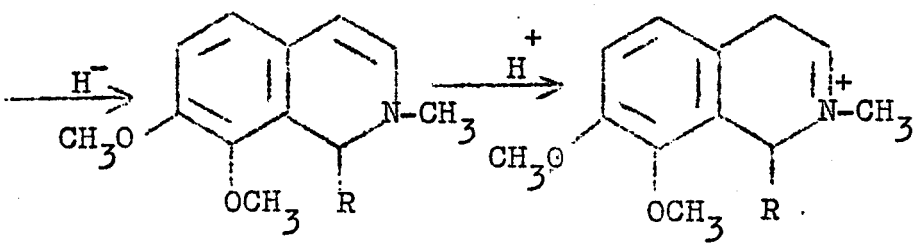
The anion of the Reissert compound was generated as

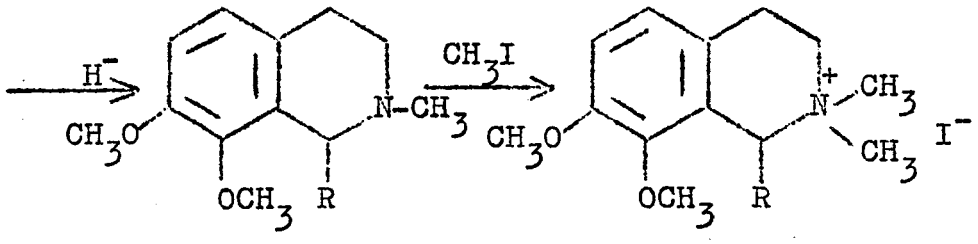
before and treated with anisyl chloride. Hydrolysis of the resultant product gave the isoquinoline (LVII) as



R=H or $-CH_2-C_6H_4-OCH_3$

LVII LVIII





LIX LX

an oil, which was converted to its methiodide (LVIII) and reduced by sodium borohydride in aqueous methanol[54] to the corresponding tetrahydroisoquinoline (LIX). The mechanism of reduction is presumably as shown (LVIII to LIX), similar to that proposed for the reduction

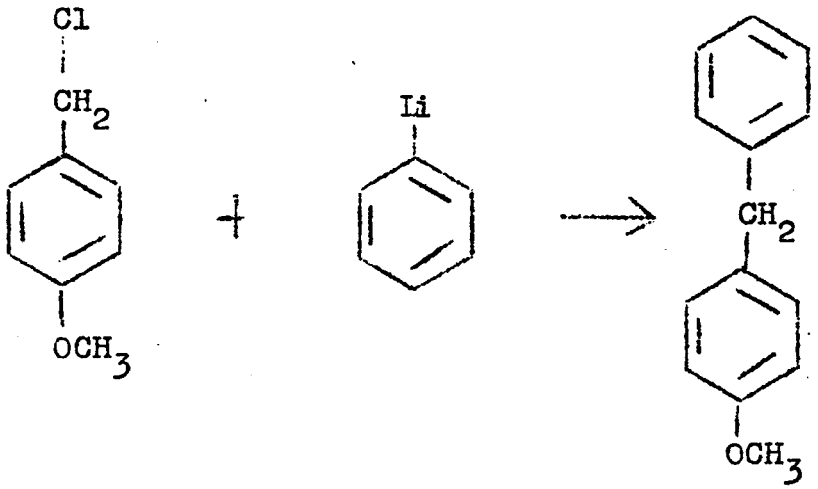
of pyridine.[55-57] The tetrahydroisoquinoline (LIX) was converted to its quaternary salt (LX) with methyl iodide.

Elemental analysis of the two methiodides (LVIII and LX) and the picrate of LVII showed that the addition of the anisyl group had not taken place, the products being 7,8-dimethoxyisoquinoline derivatives (LVII to LX R=H). This was verified by the n.m.r. spectrum of the tetrahydroisoquinoline (LIX) which showed no C-1 methine proton and only integrated for two aromatic and four methylene protons. The two methoxy peaks occured at the same chemical shift (6·1τ), in the absence of any effective anisotropic effects of the C-1 substituents.

The attempted synthesis of 1-anisyl-7,8-dimethoxyisoquinoline (LVII, R = anisyl) was repeated, under slighty modified conditions but again addition did not take place. The carbanion was generated at a slightly lower temperature, -10° to -15°.

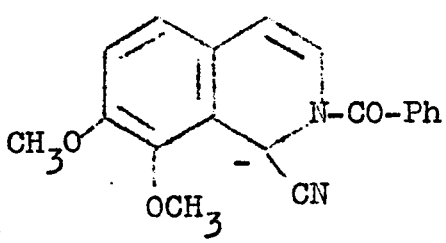
The question arises as to why the addition did not take place. The anion was formed to some extent as shown by the red colouration that appeared after addition of the phenyl lithium solution. It is probable that the anion was formed only in a small amount, as the red colour was not as intense as in subsequent reactions: however, the brown colour of the phenyl lithium solution tends to mask the colour, so making observation difficult. If the anion were

only formed to a small extent excess phenyl lithium could undergo side reactions, for example by attacking the anisyl chloride (to give LXI).

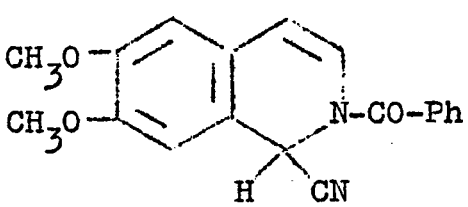


LXI

The formation of the Reissert carbanion (LXII) may be inhibited by steric hindrance of the methoxy group in the 8-position, making attack on the methine proton, by the relatively bulky phenyl anion, difficult.

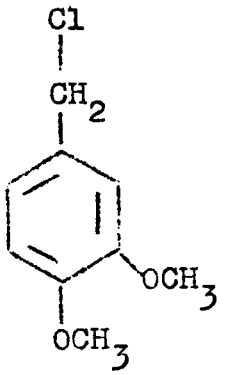


LXII

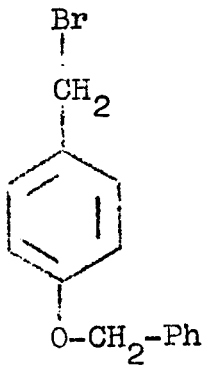


LXIII

Our result can also be compared with those of Popp et al.[9,11] using the analogous starting material N-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (LXIII). On addition of 3,4-dimethoxybenzyl chloride[9] (LXIV) to the anion of LXIII (generated by phenyl lithium) they obtained only 22% yield of the



LXIV



LXV

1-substituted isoquinoline and a similar yield of the corresponding adduct using p-benzyloxybenzyl bromide (LXV).[11]

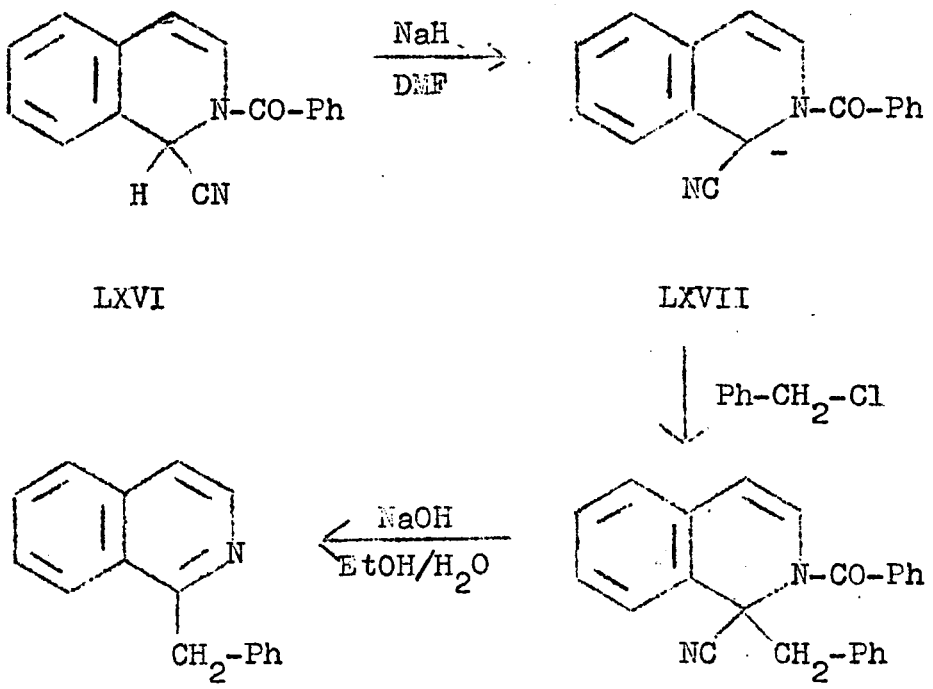
Since our starting isoquinoline (LVII, R=H) is clearly more hindered, a lower yield would be expected.

4. Synthesis of 1-Benzylisoquinolines-Sodium Hydride Route.

We thus looked for an improved method of generating the anion of a Reissert compound. It is only during recent years that the value of dipolar aprotic solvents in organic chemistry has been realised.[58] Sodium hydride in dimethylformamide[59] and in dimethylsulphoxide ("dimsyl sodium")[60,61] have been used to generate carbanions. Dimethylsulphoxide has the disadvantage that its melting point is 18·5°, making use at low temperatures difficult. Zaugg et al.[59] have used sodium hydride in dimethylformamide to generate the carbanion of active methylene compounds, which could be alkylated with the appropiate alkyl

halide.

These observations led us to investigate use of sodium hydride in dimethylformamide for generating the Reissert carbanion. Treatment of isoquinoline Reissert compound (LXVI) with sodium hydride in dimethylformamide at 0° (under nitrogen) resulted in immediate generation of the characteristic deep red colour of the carbanion (LXVII), with liberation of hydrogen gas. Addition of



LXVI LXVII

LXIX LXVIII

benzyl chloride caused the colour to fade. The mixture was worked-up after two hours, the excess sodium hydride being destroyed by ethanol, giving a mixture of the substituted Reissert compound (LXVIII) and 1-benzylisoquinoline (LXIX). The Reissert compound (LXVIII), which was not isolated, was then hydrolysed to LXIX with caustic soda in aqueous ethanol.

The overall yield of 1-benzylisoquinoline (LXIX) was 84% which showed an improvement over the phenyl lithium route (78%). The use of sodium hydride in dimethylformamide clearly provided a simpler route for generation and reaction of the Reissert carbanion and so we investigated its application for a number of substituted isoquinolines and benzyl halides. The general procedure adopted followed that as described above for the 1-benzylisoquinoline case. The results obtained are summarised in Table II.

As can be seen from the table, the use of sodium hydride in dimethylformamide gave improved yields in every case, particularly in the preparation of 1-anisyl-7,8-dimethoxyisoquinoline. This was obtained in 65% yield by the sodium hydride route, but failed completely when phenyl lithium was used.

The advantages of sodium hydride in dimethylformamide compared to phenyl lithium for generating the anion may be summarised:

(i) Improved yields of the resultant 1-benzylisoquinolines are given.

(ii) The method is less demanding in steric requirements, as shown by the formation of 1-anisyl-7,8-dimethoxyisoquinoline in good yield, which did not occur using phenyl lithium. It is likely that the small hydride ion can remove the hindered C-1 methine proton with greater ease, than the bulky phenyl ion, to form the Reissert anion.

TABLE II

Synthesis of 1-Benzylisoquinolines

Alkyl Halide	Product	Generation of Anion	Yield %
(a) Using isoquinoline Reissert compound.			
benzyl chloride	1-benzylisoquinoline	NaH/DMF	84
benzyl bromide	"	PhLi	78[a]
anisyl chloride (p-methoxybenzyl chloride)	1-anisylisoquinoline	NaH/DMF	72
"	"	PhLi	66
p-tolyl bromide	1-(p-methylbenzyl)-isoquinoline	NaH/DMF	78
p-nitrobenzyl bromide	1-(p-nitrobenzyl)-isoquinoline	NaH/DMF	65
3,4-dimethoxy-benzyl chloride	1-(3,4-dimethoxy-benzyl)- isoquinoline	NaH/DMF	82
"	"	PhLi	53[b]
3,4-dimethyl-benzyl chloride	1-(3,4-dimethyl-benzyl)- isoquinoline	NaH/DMF	86
piperonyl(3,4-methylenedioxy-benzyl) chloride	1-piperonyl-isoquinoline	NaH/DMF	75
(b) Using 7,8-dimethoxyisoquinoline Reissert compound.			
anisyl chloride	1-anisyl-7,8-dimethoxyisoquinoline	NaH/DMF	65
"	"	PhLi	0

a. ref. 8

b. ref. 9

(iii) The reaction takes place at a more convenient working temperature, 0° compared to -10° to -20°.

(iv) The reaction is easier to carry out, not involving the initial preparation and filtration of phenyl lithium.

(v) The reaction is easier to follow. The colour changes are distinct with no masking. In the phenyl lithium case, the brown colour of phenyl lithium tends to mask the colour of the anion, to some extent.

(vi) The production of the intermediate Reissert carbanion can be readily followed by observation of the hydrogen gas evolution, which is not the case when phenyl lithium is used.

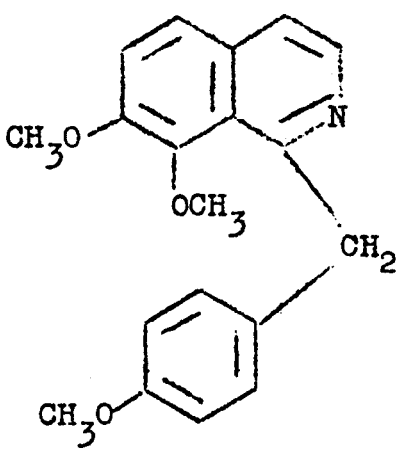
(vii) The amount of sodium hydride used was known accurately, since it can be weighed (as a 50% paste in oil) whereas it is necessary to titrate phenyl lithium solutions in order to assess their strength at all accurately.[62,63]

Our results[64] were published simultaneously with the analogous results of Popp and Wefer.[65] Although they generated the Reissert carbanion using sodium hydride in dimethylformamide, they have not applied the method to the synthesis of 1-benzylisoquinolines.

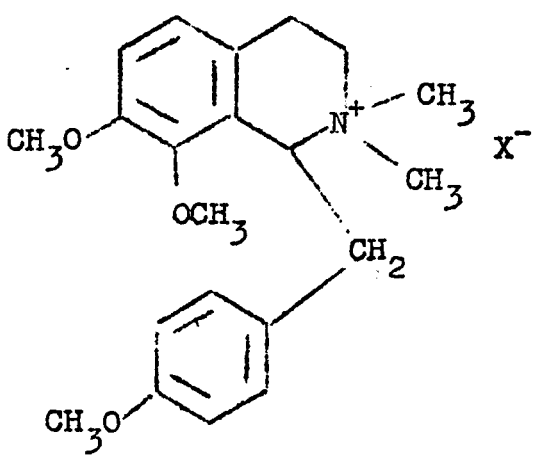
Application of our new method to the cases of 3-methyl and 4-bromoisoquinoline gave unusual and interesting results and these are discussed separately later in the thesis.

5. The Synthesis of O-Methylpetaline.

Having successfully prepared 1-anisyl-7,8-dimethoxyisoquinoline (LXX) by the above procedure we required to modify the structure so as to obtain O-methylpetaline (LXXI). The first stage was formation of the methiodide (LXXII). This was surprisingly difficult. Portions of 1-anisyl-7,8-dimethoxy-isoquinoline were warmed with methyl iodide in ether and although the typical cloudiness of the methiodide appeared, it was not possible to isolate it in any appreciable amount as a crystalline material. Using the method of Kametani and Fukumoto[54] (refluxing with methyl iodide, methyl alcohol and ether) was no more successful. Only a little of the crystalline meth-iodide was prepared after chromatography.

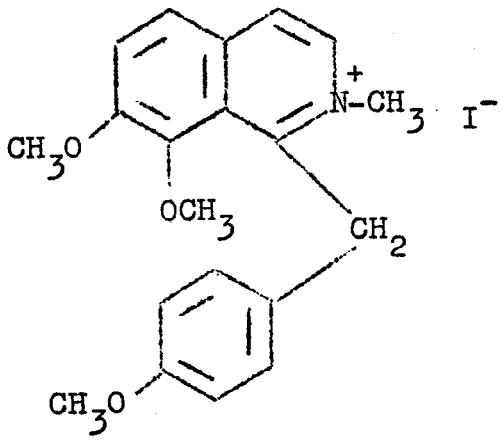


LXX

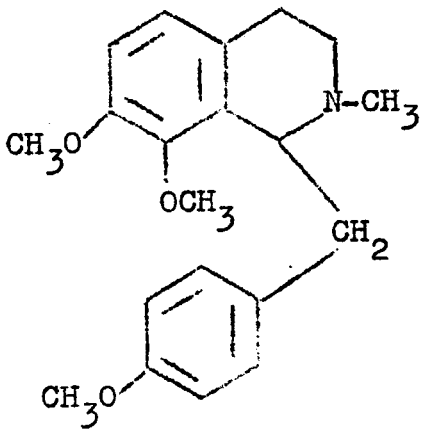


LXXI

Both the crystalline and non-crystalline methiodides were reduced separately, with sodium boro-hydride.[54] The tetrahydroisoquinoline (LXXIII) was



LXXII

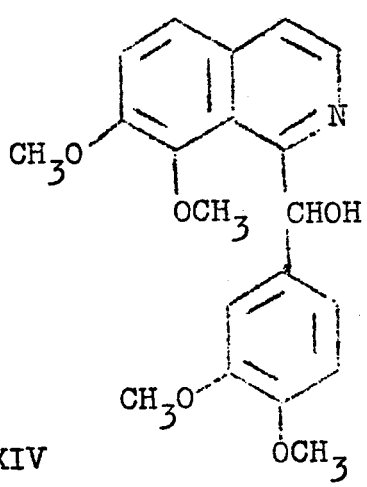


LXXIII

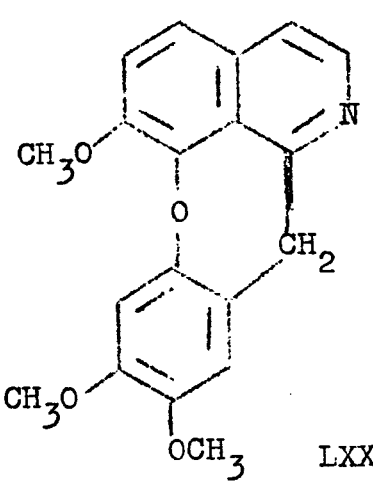
obtained as an oil which could not be induced to crystallise. This was converted to its methiodide. Again the methiodide was oily but repeated purification by column chromatography was successful in giving a small amount of crystalline O-methylpetaline iodide (LXXI, X=I).

Difficulties in crystallising sterically crowded methiodides of this type (viz. LXXI, X=I and LXXII) have been reported for analogous cases.

Bevis reported that he could not prepare the methiodide, acetate or oxalate of isopapaverinol (LXXIV).[14] He attributes this to the methoxy group in



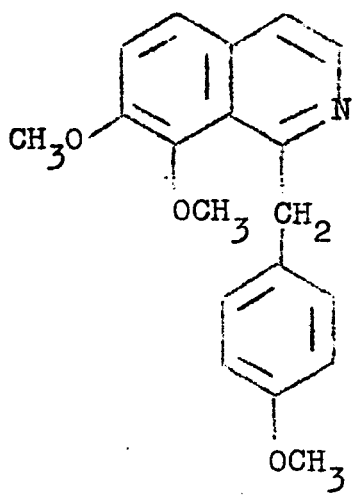
LXXIV



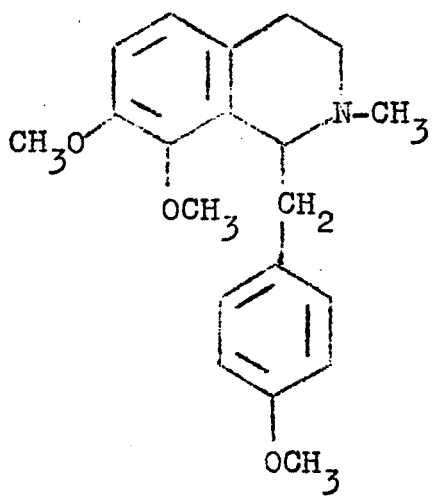
LXXV

the 8-position causing the benzyl group with its attached hydroxyl group, to crowd the nitrogen atom, thus making the formation of salts almost impossible.[14] Further, Kametani and Fukumoto found that unless the cularine precursor (LXXV) was crystalline it would not form a crystalline methiodide.[54] When the base (LXXV) was isolated as an oil it would only form oily methiodides, whose further processing was unrewarding.[54]

Models show that in both LXXVI and especially

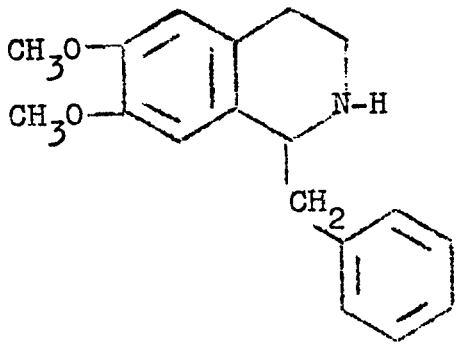


LXXVI

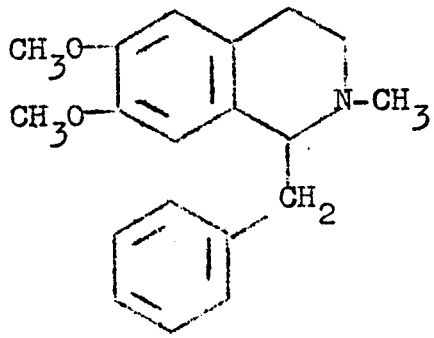


LXXVII

LXXVII the nitrogen is sterically encumbered, thereby causing quaternary salt formation to be unfavourable. Work on the 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines has shown[66,67] that the preferred conformation is that with the benzyl group lying near the nitrogen, as in LXXVIII, but when the nitrogen atom bears a methyl group the steric hindrance introduced causes the benzyl group to prefer to lie under the aromatic ring as in LXXIX.



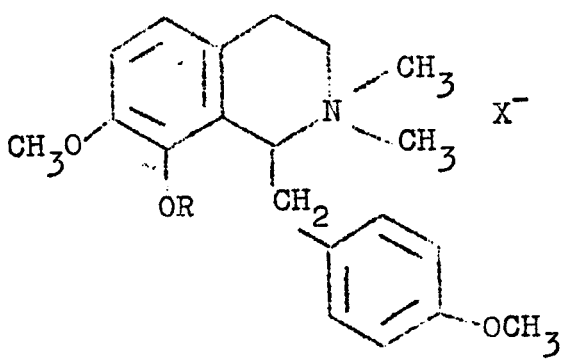
LXXVIII



LXXIX

With the 8-substituent present in our examples the benzyl group is not able to lie under the aromatic ring but will further crowd the nitrogen.

Proof of the structure of our synthetic O-methylpetaline iodide was achieved by comparison with a sample derived from natural petaline and also by degradation to a known petaline derivative. Authentic petaline reineckate[68] (LXXX, R = H, X = $[Cr(NH_3)_2(SCN)_4^-]$) was methylated with methyl iodide in the presence of sodium hydroxide to give O-methylpetaline reineckate (LXXX, R = CH_3, X = $[Cr(NH_3)_2(SCN)_4^-]$),

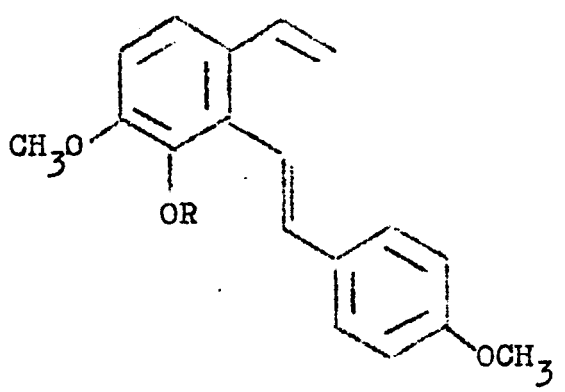


LXXX

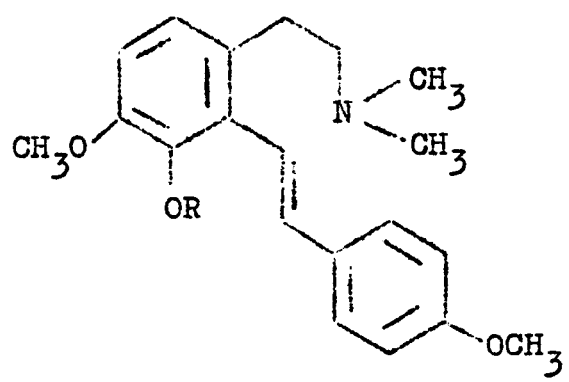
which was titrated with silver sulphate and then

barium iodide solutions to give the iodide (LXXX, R = CH_3, X = I). Comparison of the infra-red spectra of natural and synthetic O-methylpetaline iodides (LXXX, R = CH_3, X = I) showed the two to be identical. Identity in Rf value for t.l.c. of the two compounds on silica gel was demonstrated.

Further evidence was provided by conversion of our synthetic O-methylpetaline iodide (LXXX, R = H, X = I) to the known styrene (LXXXI, R = CH_3), formed from natural petaline.[69] McCorkindale et al. prepared (LXXXI, R = CH_3), by methylation of the corresponding phenol (LXXXI, R = H) which was the final Hofmann product obtained from petaline itself.[17,69]



LXXXI



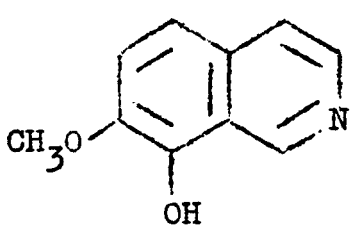
LXXXII

Our synthetic O-methylpetaline iodide (LXXX, R = H, X = I) was converted to its quaternary hydroxide by passage down an anion exchange resin column. Hofmann degradation was achieved on refluxing the hydroxide with methanolic sodium methoxide to give the methine (LXXXII, R = CH_3). The methiodide of LXXXII (R = CH_3) was prepared and converted to the corresponding metho-hydroxide, which underwent Hofmann degradation to give the styrene (LXXXI, R = CH_3) and trimethylamine characterised as its picrate (mixed m.p. with an authentic sample of trimethylamine picrate showed no depression).[70]

Our styrene (LXXXI, R = CH_3) had a similar infrared spectrum (KBr disc) and melting-point to that of an authentic sample prepared by McCorkindale et al.[69] from petaline, but unfortunately none of the authentic compound was available for comparison.

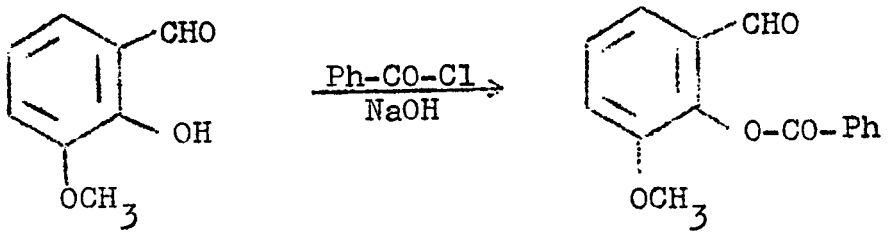
6. <u>The Total Synthesis of Petaline.</u>

The first stage of the total synthesis was to prepare the intermediate isoquinoline, 8-hydroxy-7-methoxyisoquinoline (LXXXIII). This was first

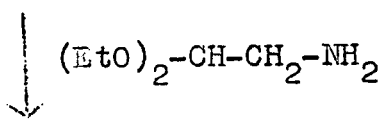


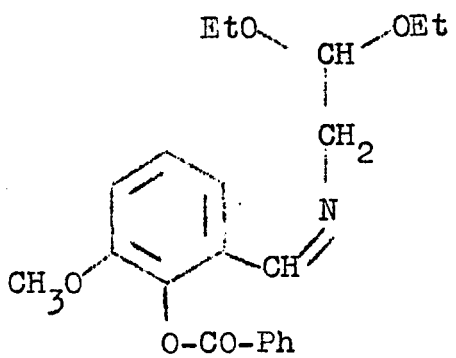
LXXXIII

attempted by the Pomeranz-Fritsch synthesis using the same method as for 7,8-dimethoxyisoquinoline (p.23). The phenolic hydroxyl group of the starting aldehyde, o-vanillin (LXXXIV) was protected by benzoylation (to LXXXV) in anticipation of giving a cleaner cyclisation reaction. However, repeated attempts to



LXXXIV LXXXV



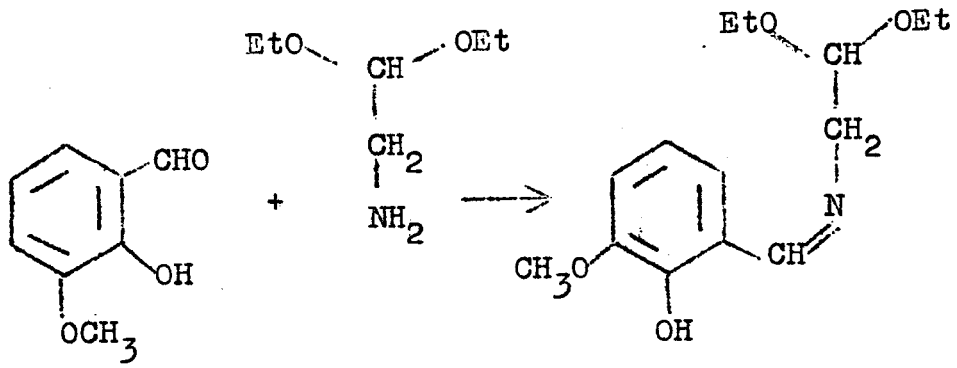


LXXXVI

cyclise the Schiff base (LXXXVI) gave only tars which could not be purified.

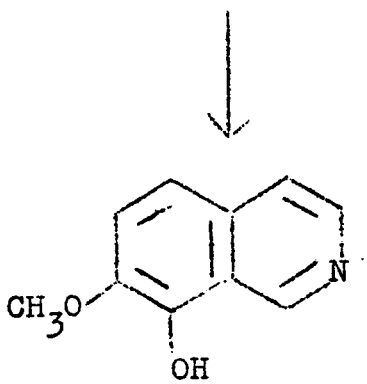
The procedure was therefore repeated in the absence of the benzoyl protecting group. o-Vanillin (LXXXVII) was condensed with aminoacetal to give the Schiff base (LXXXVIII), which on cyclisation with trifluoroacetic anhydride and boron trifluoride-acetic acid complex gave 8-hydroxy-7-methoxy-

isoquinoline (LXXXIX) in low yield after sublimation of the crude product. The cyclisation was also



LXXXVII

LXXXVIII

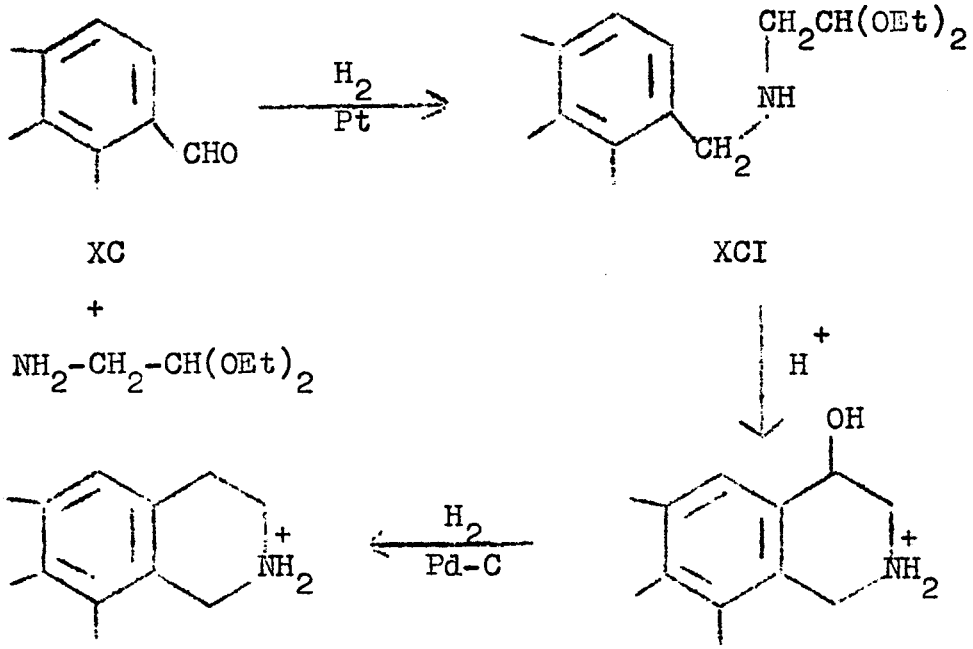


LXXXIX

attempted using polyphosphoric acid but purification of the resultant tary product was unprofitable. This was not altogether unexpected as polyphosphoric acid gives a lower yield of 7,8-dimethoxyisoquinoline than does the trifluoroacetic anhydride/boron trifluoride route (see p.23).

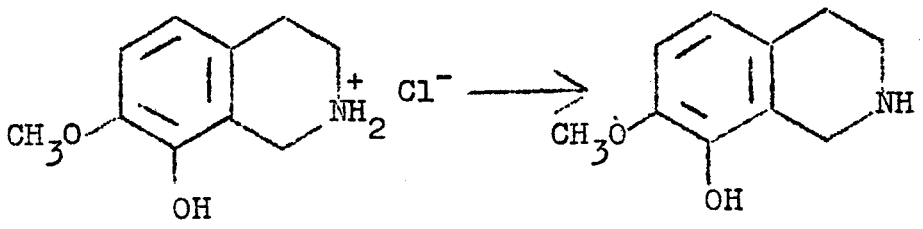
In view of the limited success of Pomeranz-Fritsch reactions we examined an alternative approach to 8-hydroxy-7-methoxyisoquinoline, stemming from the work of Bobbitt et al. on the synthesis of 1,2,3,4-

tetrahydroisoquinolines.[71] Their scheme[71,72] is basically a reductive Pomeranz-Fritsch synthesis. The aldehyde (XC) is combined with a molar amount of aminoacetal and reduced in situ to give the dihydro Schiff base (XCI). On standing overnight in 6N



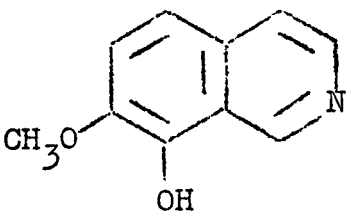
hydrochloric acid this cyclises to XCII which is hydrogenated to give the 1,2,3,4-tetrahydroisoquinoline hydrochloride (XCIII).

We prepared 8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (XCIV) in good yield (87%) using this method. However, aromatisation of XCV to 8-hydroxy-7-methoxyisoquinoline (XCVI) proved difficult. The difficulty is probably due to the instability of the intermediate tetrahydroisoquinoline (XCV).[71] Dehydrogenation of 8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline by heating under reflux with



XCIV

XCV

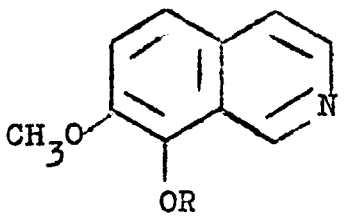


XCVI

palladium-on-charcoal in p-cymene,[71] under nitrogen gave varied success. Yields of XCVI from XCIV, after purification by sublimation varied between 2% and 49%. Use of cyclohexanol in place of p-cymene gave no improvement in yield. Dehydrogenation with iodine[73,74] and with chloranil[75,76] failed to yield any of the required isoquinoline.

Having obtained sufficient 8-hydroxy-7-methoxyisoquinoline we examined protection of the 8-hydroxy group using a methoxymethyl substituent. This is relatively small and is stable to basic conditions, which are obtained in the subsequent stages of this synthesis and is easily removed by acid. Using the method of Edwards and Wilson[77] we did not obtain any of the required product (XCVII, R = CH_3-O-CH_2) only

starting material. Attempts to prepare methoxymethyl ethers of analogous heterocyclic compounds, 4-hydroxy and 8-hydroxyquinoline, using the method of Edwards et al.[77,78] were unsuccessful or gave poor yields.



XCVII

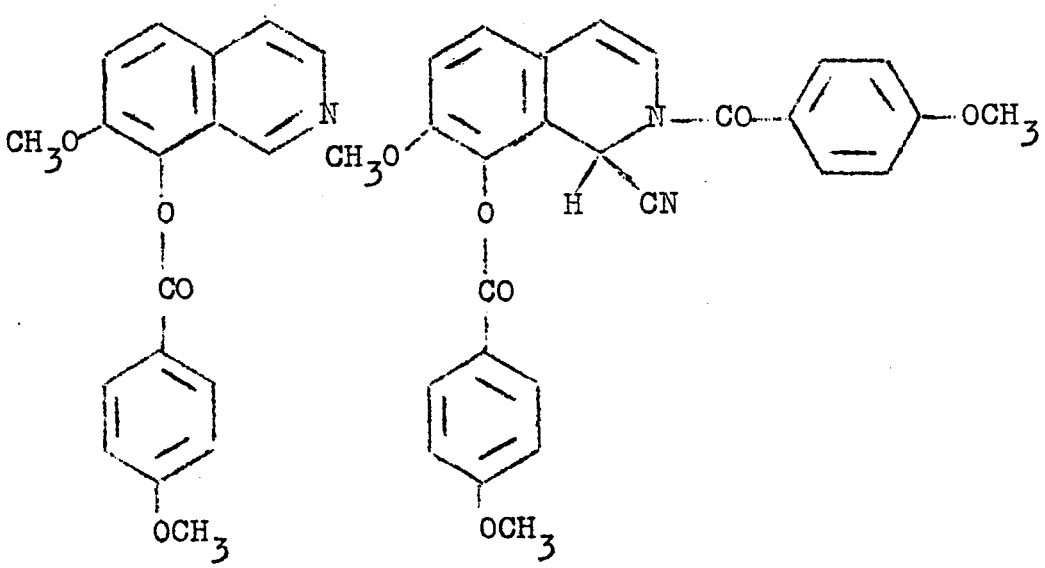
We therefore protected the hydroxyl group by benzylation, which again yields a base-stable system but unfortunately is more demanding sterically. 8-Benzyloxy-7-methoxyisoquinoline (XCVII, R = CH_2Ph) was obtained as a red crystalline solid. It is interesting to note that on addition of benzyl chloride and chlorodimethyl ether to the potassium salt of 8-hydroxy-7-methoxyisoquinoline and chlorodimethyl ether to the sodium or potassium salts of 8-hydroxyquinoline an immediate deep red colouration appeared. The red colour may indicate the presence of a charge transfer complex. Charge transfer complexes are known between aromatic compounds and halides,[79] the halide being the acceptor and the aromatic compound the donor, e.g. the 3:1 complex between quinoline and iodoform.[80,81] In the hydroxy isoquinolines the phenol group, especially if in its ionic form, should increase the electron availability of the donor.

We could not however prepare a Reissert compound[30]

of 8-benzyloxy-7-methoxyisoquinoline, starting material being obtained unchanged on every attempt. This lack of reactivity might be due to a charge transfer complex.

Having obtained little success in the use of protecting groups we proceeded to effect Reissert compound formation directly on 8-hydroxy-7-methoxyisoquinoline. 4-Methoxybenzoyl chloride (anisoyl chloride) was used instead of benzoyl chloride so that if a 1,2 or 1,8-rearrangement of the anisoyl group took place in the later carbanion reaction instead of (or in conjunction with) substitution, the required methoxy group would be in the 4' position.

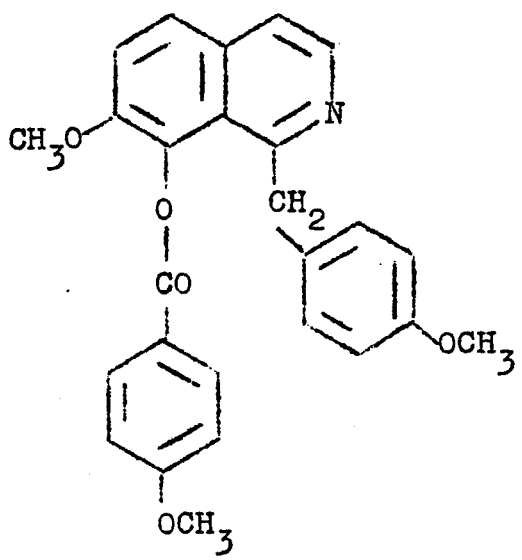
Treatment of 8-hydroxy-7-methoxyisoquinoline (XCVII, R = H) under the conditions of Popp and Blount[30] gave 8-anisoyloxy-7-methoxyisoquinoline (XCVIII) as the major product and this was further reacted to give the Reissert compound (XCIX) in an overall yield of 22%.



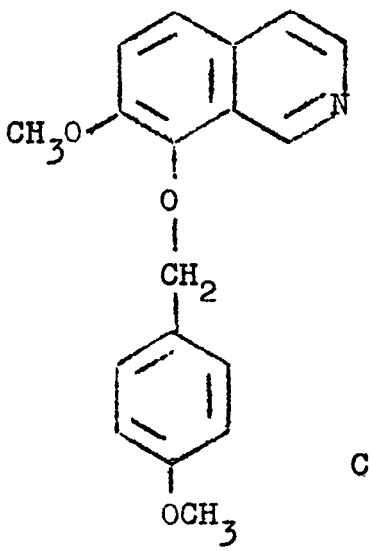
XCVIII

XCIX

The anion of XCIX was generated with sodium hydride in dimethylformamide and reacted with anisyl chloride. The product from acid extraction was separated by column chromatography and gave the required product C in 45% yield together with a small amount of CI. Compound CI presumably results from



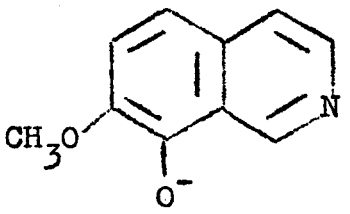
C



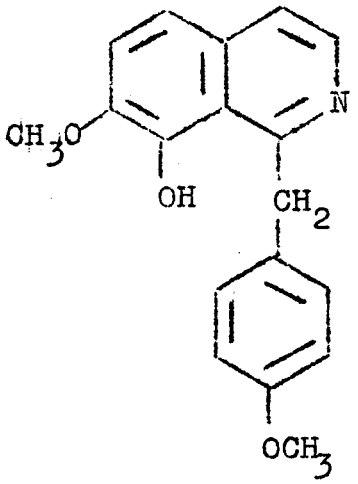
CI

hydrolysis of XCIX in the work-up (with sodium ethoxide, formed by destroying sodium hydride with ethanol). This would give the anion (CII) which must have reacted with some excess anisyl chloride present to give CI.

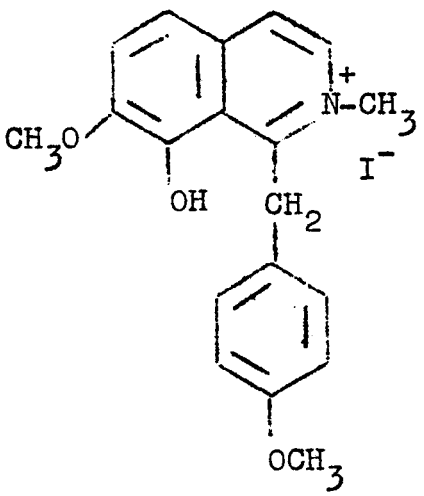
Hydrolysis of C with sodium hydroxide in aqueous ethanol gave the petaline precursor 1-anisyl-8-hydroxy-7-methoxyisoquinoline (CIII). Compound CIII was converted to its methiodide[54] (CIV) and then reduced by sodium borohydride[54] to give the tetrahydroisoquinoline (CV). This was obtained as an oil which could not be induced to crystallise but was converted[54]



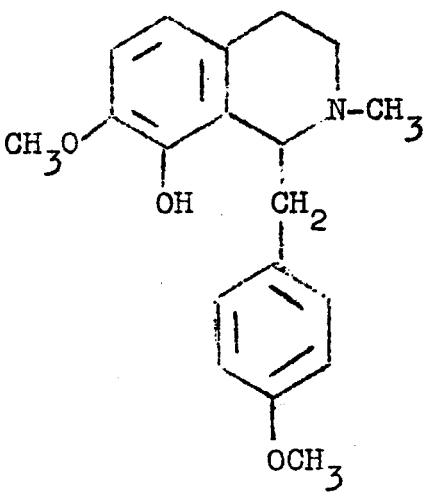
CII



CIII

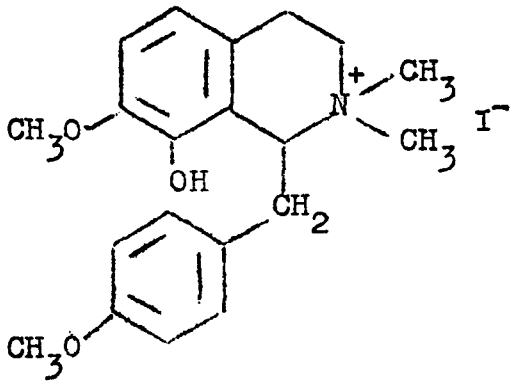


CIV

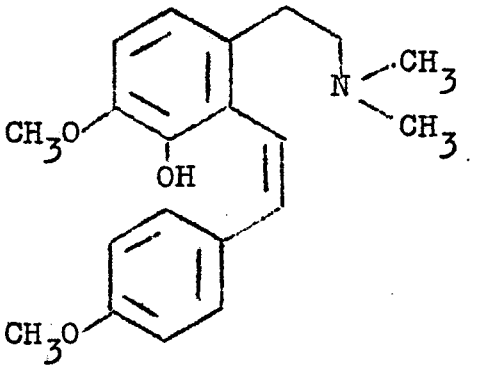


CV

directly to its methiodide (CVI). This was also obtained as an oil. However, repeated column chromatography and recrystallisation from acetone was successful in giving a small amount of racemic petaline iodide (m.p. 133-7°, Grethe et al.[18] reported the m.p. as 134-8°). The infra-red spectra of natural and synthetic petaline iodide were identical. Natural petaline iodide was prepared from the reineckate[68] by titration with silver sulphate and then barium



CVI



CVII

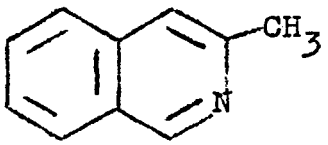
iodide solutions. Identity in Rf value for t.l.c. of the natural and synthetic samples on silica gel was demonstrated.

Further proof for the structural assignment CVI to our product was provided by Hofmann degradation to petaline methine[17] (CVII) on an anion exchange resin column. The product (CVII) was shown to be identical by melting point and mixed melting point with an authentic sample,[17] kindly provided by Dr. N.J. McCorkindale of Glasgow University. The compounds also had identical t.l.c. Rf values (on silica gel) and gave identical colours with ferric chloride solution (as described[17] for the authentic material).

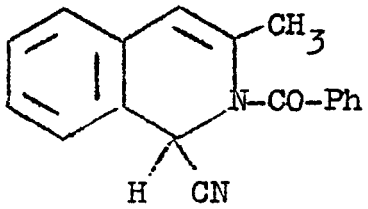
7. Reactions of 3-Methylisoquinoline.

Whilst studying the general application of our sodium hydride/dimethylformamide method for the preparation of 1-benzylisoquinolines (p. 28) two interesting exceptions were observed. The first was for the case of 3-methylisoquinoline.

3-Methylisoquinoline (CVIII) was converted to



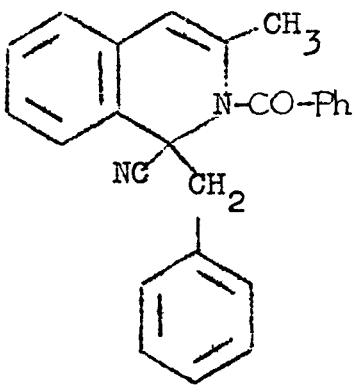
CVIII



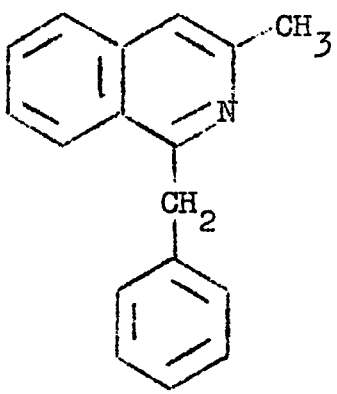
CIX

its Reissert compound (CIX) by the method of Popp and Blount.[30]

On treatment of the anion of CIX with benzyl chloride we expected to obtain initially the substituted Reissert compound (CX) which on basic hydrolysis would give 1-benzyl-3-methylisoquinoline (CXI).



CX

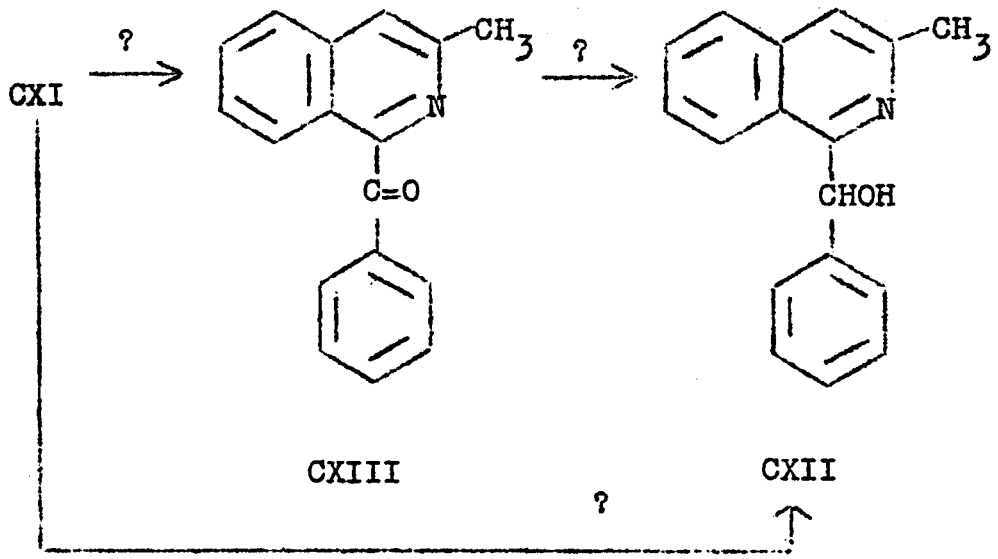


CXI

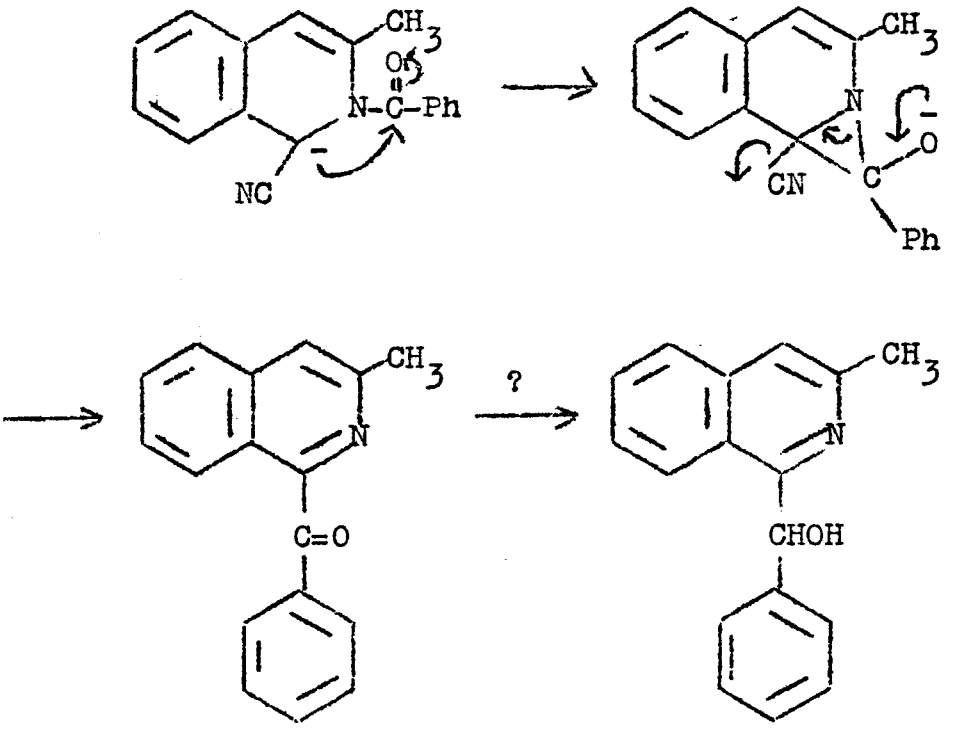
We obtained the resultant isoquinoline on basic hydrolysis of the initial product. This analysed for $C_{17}H_{15}NO$ (whereas CXI requires $C_{17}H_{15}N$) and showed absorption attributable to OH in the infra-red spectrum. The n.m.r. spectrum revealed a singlet, integrating for two protons at 3·70 τ, which on deuterium exchange gave a singlet at 3·62 τ, integrating for one proton,

which was much sharper than the original signal, suggesting the grouping $\geq$CHOH was present. These results led us to the conclusion that the product obtained was the carbinol (CXII).

This product could have arisen by one of two routes. Firstly, oxidation of the methylene group of the expected product (CXI) could have occurred, to give CXII directly or via the ketone CXIII. Ready oxidation of the CH_2 group of benzylisoquinolines has been observed.[82,83] Such a reaction, however, usually generates the ketone (CXIII). For example purification of 3,4-dihydropapaverine on an alumina column is sufficient to give some 3,4-dihydropapaveraldine.[84]



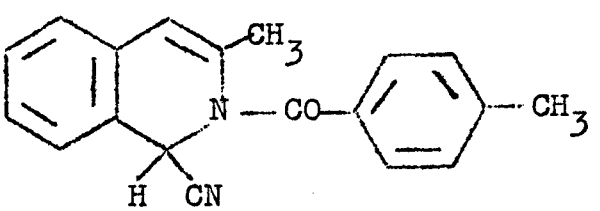
Alternatively, the oxygen function could have been introduced as the result of a 1,2-rearrangement of the type shown:-



CXIII CXII

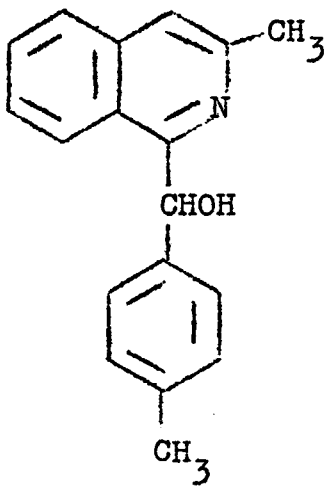
This would again go through the benzoyl adduct (CXIII) which would then require reduction. 1,2-Rearrangements of Reissert compounds have been demonstrated[8] when carbanion formation is not followed by addition of alkyl halide.

To establish whether the reaction involved substitution or rearrangement the experiment was repeated, but using the Reissert compound (CXIV), prepared from p-toluoyl chloride. Addition of benzyl

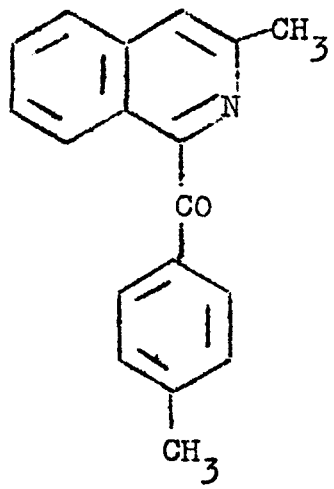


CXIV

chloride, work-up and hydrolysis as before gave CXV. This showed that the carbinols (CXII and CXV) were



CXV



CXVI

formed by rearrangement followed by reduction and that no substitution, by benzyl chloride, had taken place.

Examination of the product obtained prior to the alkaline hydrolysis stage revealed presence of the ketone (CXIII) and the toluoyl analogue (CXVI) from the two sequences respectively. The identity of CXIII was confirmed by reduction with sodium borohydride to the corresponding alcohol CXII. Further dichromate oxidation of the carbinol (CXII) obtained in the original reaction sequences refurnished the ketone (CXIII).

As additional confirmation the two Reissert compounds were rearranged in the absence of benzyl chloride. The ketone (CXIII) was obtained from CIX on acid extraction of the product (no basic hydrolysis).

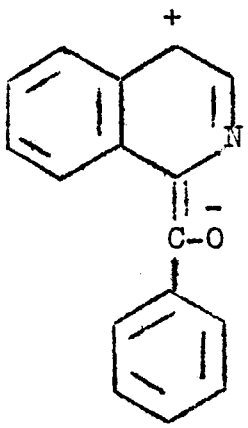
However, the toluoyl Reissert compound (CXIV) gave a mixture of the ketone (CXVI) and the carbinol (CXV) on acid extraction of the reaction mixture, prior to basic hydrolysis. After basic hydrolysis of the residue the product was entirely the carbinol (CXV).

We thus investigated why the ketones had been reduced to the corresponding alcohols. Possibly sodium hydride was acting as a reducing agent. Normally sodium hydride or other bases, will remove the α-hydrogen from the ketone causing condensation reactions of the aldol type. In our examples the ketones (CXIII and CXVI) have no α-hydrogens. Thus the ketone (CXIII) was stirred with sodium hydride and dimethylformamide and worked-up but examination of the product showed that no reduction had taken place. Therefore though sodium hydride is a ready source of hydride ions, it does not appear to act as a reducing agent.

We then considered whether the reduction occurred during the hydrolysis with sodium hydroxide in aqueous ethanol. We found that when an alcoholic solution of the ketone (CXIII) was refluxed with an aqueous sodium hydroxide solution, 85% reduction occurred to the alcohol (CXII). This was surprising and therefore we examined the reduction process in detail. Our results are discussed in the next section.

It was noticed during this work that the ketones (CXIII and CXVI) were not readily extracted with dilute acid. It therefore appeared that 1-benzoyl-

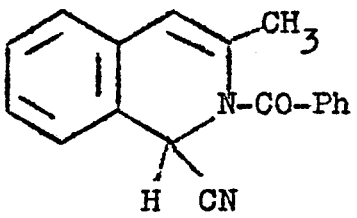
isoquinolines are weak bases and thus not readily extracted into acid compared with 1-benzylisoquinolines or the substituted isoquinoline carbinols (e.g. CXII). This is borne out by pKa measurements undertaken in this Department[85] which have shown that 1-benzoyl-isoquinoline to have a pKa of only 2·22[85], whereas the pKa of isoquinoline is 5·40.[86] This could be due to resonance structures of the type CXVII which make



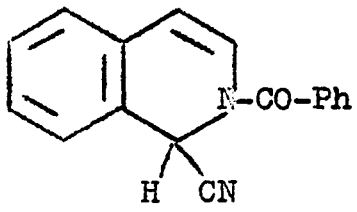
CXVII

the nitrogen lone pair less available due to the positive charge on the ring.

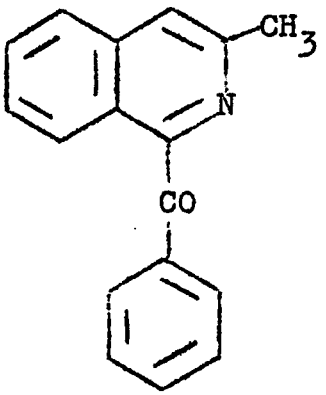
We have shown that under optimum conditions the rearrangement of 3-methylisoquinoline Reissert compound (CXVIII) to give 1-benzoyl-3-methylisoquinoline (CXIX) occurs in 90% yield; whereas with isoquinoline Reissert compound (CXX) only 60% of 1-benzoylisoquinoline (CXXI) was obtained under the same conditions. This indicates clearly that the methyl group in the 3 position enhances the rearrangement and is borne out in that in the 3-methylisoquinoline Reissert compound/halide reaction rearrangement occurs exclusively; whereas



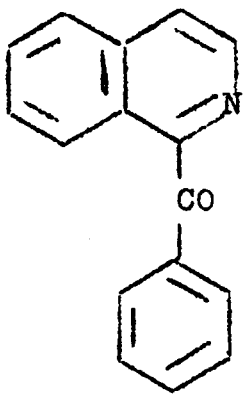
CXVIII



CXX



CXIX



CXXI

for the unsubstituted isoquinoline Reissert compound/ halide reaction substitution occurs exclusively.*

Aldehydes are more electrophilic than halides and react with Reissert carbanions more readily.[9,11] We thus wondered whether rearrangement or addition would take place when using an aldehyde, p-tolualdehyde, as the electrophile with the carbanion of N-benzoyl-1,2-dihydro-3-methylisoquinaldonitrile (CXVIII). The n.m.r. of the products revealed that both rearrangement and addition had taken place in the approximate ratios of 2 to 1 respectively. Thus the increased reactivity of an aldehyde compared to a halide was demonstrated.

It is interesting to note that using sodium hydride to generate the anion, the aldehyde addition

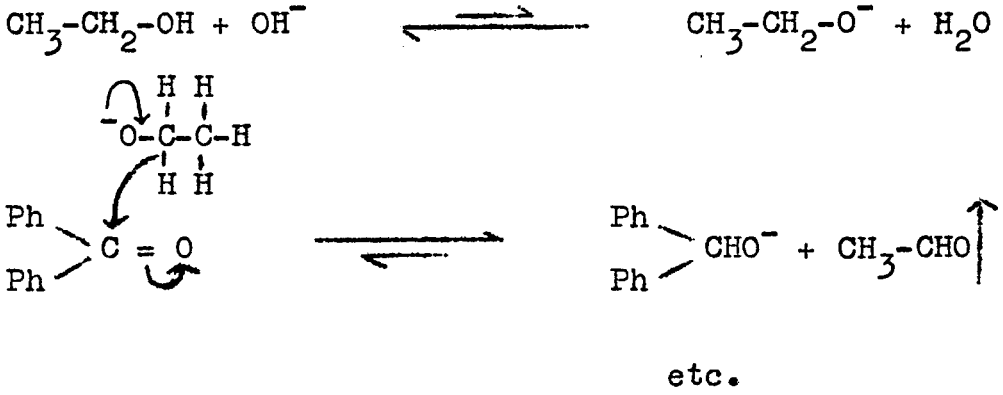
* The stereochemistry is discussed on p. 76

product was isolated as the carbinol and not its benzoate as obtained using phenyl lithium to generate the anion.[9,10,11,87] The benzoate was probably hydrolysed by sodium ethoxide, from addition of ethyl alcohol to sodium hydride, in the work-up.

8. Reduction Studies.

Having demonstrated that the reduction of 1-benzoyl-3-methylisoquinoline occurred during reflux with sodium hydroxide in aqueous ethanol it was necessary to establish why reduction had taken place and if the reaction were general. We therefore treated a number of diaryl ketones by refluxing them in ethanol with an aqueous solution of sodium hydroxide (see Table III). In general the yields of reduced products were in the region of 80% or better.

It seemed apparent that the only source of hydride was from the ethanol, acting as ethoxide, analogous to (aluminium) isopropoxide in the Meerwein-Ponndorf-Verley reaction.[88] The mechanism of the reduction is therefore presumably:-



etc.

TABLE III

Reduction of Diaryl Ketones with

Sodium Hydroxide/Ethanol/Water

Ketone	Product	Time of Reflux (Hours)	Yield %
1-Benzoyl-3-methylisoquinoline	Phenyl-1-(3-methyl-isoquinoline) carbinol	7	85
1-Benzoyl-isoquinoline	Phenyl-1-isoquinoline carbinol	7	85
Benzophenone	Benzhydrol	3½	86
Fluorenone	Fluorenol	5	79
Benzoin	Mesohydrobenzoin	3½	79
Xanthone		4	0
1-Benzoylnapthalene	Phenyl-1-napthyl carbinol	4	78
Benzoquinone		4	0
Anthraquinone		4	0
Chalkone	Phenyl styryl carbinol	4 8	84 89

The fact that sufficient sodium ethoxide is formed in the presence of water for the reduction to occur so readily is surprising.

In support of this mechanism we found that using tetrahydrofuran instead of ethanol, no reduction occurred in contrast to the use of sodium ethoxide.

Further, the formation of acetaldehyde was confirmed by passing a stream of nitrogen over the refluxing mixture, the acetaldehyde being carried out and isolated as its 2:4-dinitrophenyl hydrazone.

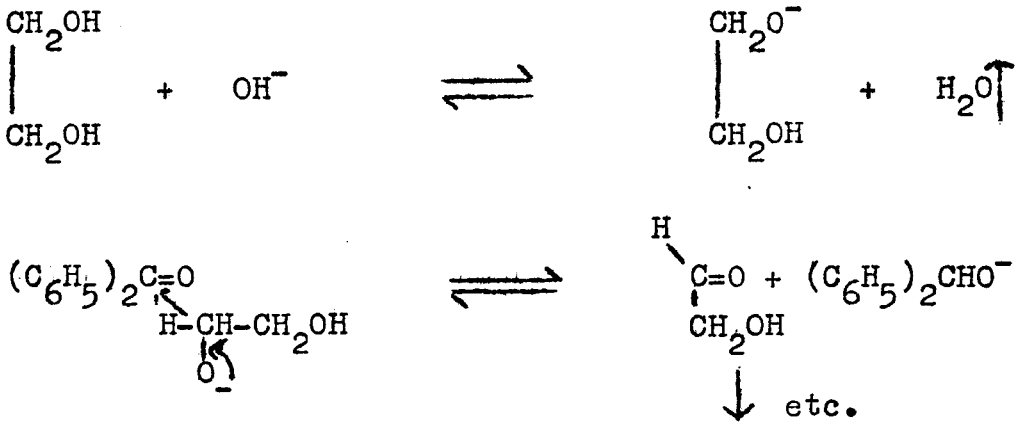
The reduction is therefore similar to the Meerwein-Ponndorf-Verley reduction.[88] The yields that we obtained were in general about 10% lower than those obtained using the milder aluminium isopropoxide procedure[88], but in one case, chalkone, we obtained a higher yield, 89% compared to 76%.[89]

The literature reveals little use of sodium ethoxide or sodium hydroxide/ethanol/water as reducing agents on account of their tendancy to cause condensation side reactions.[90] The milder aluminium alkoxides were preferred.[88] Sodium ethoxide in dry ethanol was used to reduce bridging ketones,[91] whereas potassium hydroxide in methanol caused dissociation of these compounds.[91] Other sodium alkoxides have been used with varying success e.g. sodium isopropoxide,[90,92] and sodium benzylate.[93]

In 1908 Montague reduced benzophenone by heating at 100° with potassium hydroxide in ethanol for two days[94], and carried out a systematic study of the effects of various substituents on the ease of reduction of benzophenones.[94-99]

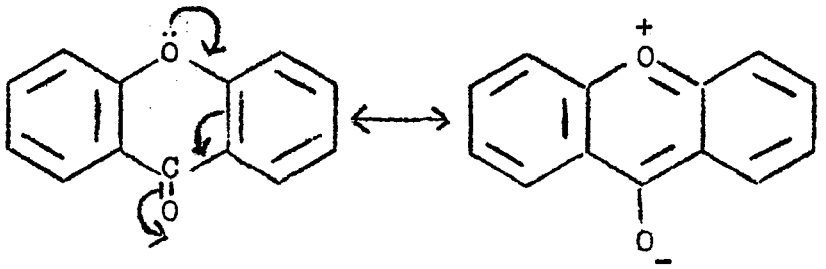
Recently Kleinfelter effected some reductions with potassium hydroxide in ethylene glycol solution. He obtained a 92% reduction of benzophenone after 24

hours reflux.[100]



Sodium and potassium hydroxides, ethanol and water have been used in high pressure and temperature reductions of ketones. Hargreaves and Owen reduced some aliphatic ketones, at 240°, in a rocking autoclave in yields of 20 to 50% with potassium and sodium hydroxides in aqueous ethanol.[101] Rubin has used potassium hydroxide in ethanol (alone) at 200° under pressure to reduce aliphatic ketones.[102] Zagoumenny, in 1877, reduced benzophenone by heating it in a sealed tube with sodium hydroxide, water and ethanol at 160° but does not state the yield obtained.[103]

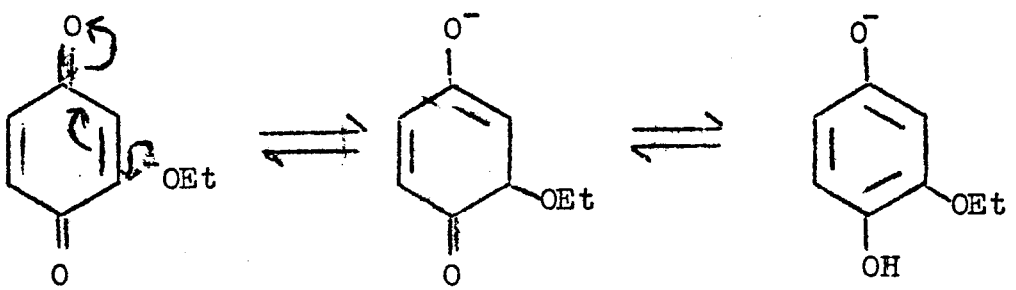
It will be noted from table III that the reduction process failed in the cases of xanthone, benzoquinone and anthraquinone, though these compounds are reduced under Meerwein-Ponndorf-Verley conditions.[88] A possible reason why xanthone is not reduced under our conditions could be that resonance hybrids of the type shown can contribute to its structure. Such hybrids may be favoured under polar conditions and will reduce



the electrophilic character of the carbonyl carbon, making hydride attack harder. Similar considerations may apply to benzophenone and anthraquinone, but to a lesser extent as there is no ring atom with unshared electrons.

Anthraquinone is more difficult to reduce than benzoquinone (E_o = 0·154 and 0·715 volts respectively,[104] in ethanol) and therefore if reduction fails in the latter it would be expected to in the former.

A further possibility with benzoquinone is that ethoxide attacks the quinone (an $\alpha\beta$-unsaturated ketone) to give CXXII. When the solvent is distilled off at

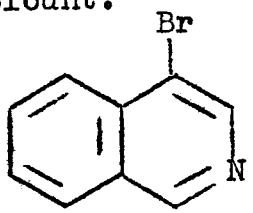


CXXII

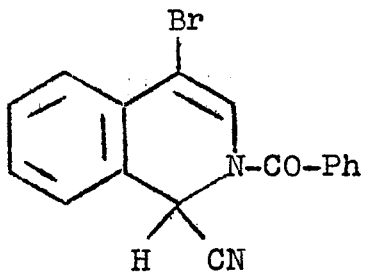
the end of the reaction, the equilibrium is forced to the left to give starting material. It is worth noting that 2:5-diethoxybenzoquinone is produced on treatment of p-benzoquinone with ethyl alcohol and fused zinc chloride.[105]

9. Reactions of 4-Bromoisoquinoline.

4-Bromoisoquinoline (CXXIII) was converted to its Reissert compound (CXXIV) by the method of Popp and Blount.[30]

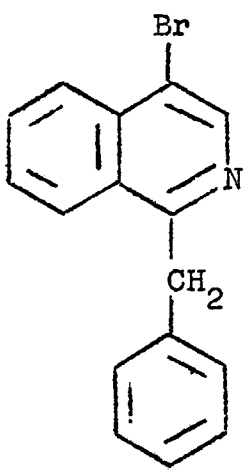


CXXIII

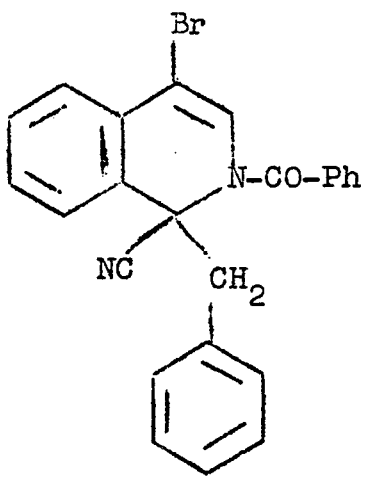


CXXIV

Generation of the Reissert carbanion with sodium hydride in dimethylformamide followed by reaction with benzyl chloride gave the expected product 1-benzyl-4-bromoisoquinoline (CXXV) directly, and from base hydrolysis of its Reissert compound (CXXVI) as the major product of the reaction. Thin



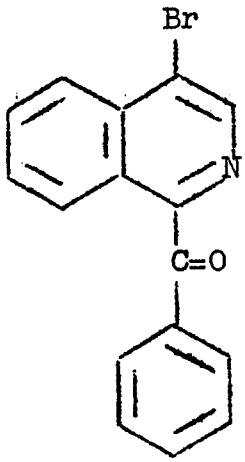
CXXV



CXXVI

layer chromatography showed the presence of another compound which was produced in one run as the only product in excellent yield.

Repeating the reaction with no halide present we obtained the expected rearrangement product, 1-benzoyl-4-bromoisoquinoline (CXXVII). Again thin layer chromatography revealed the presence of a small amount of the same by-product.



CXXVII

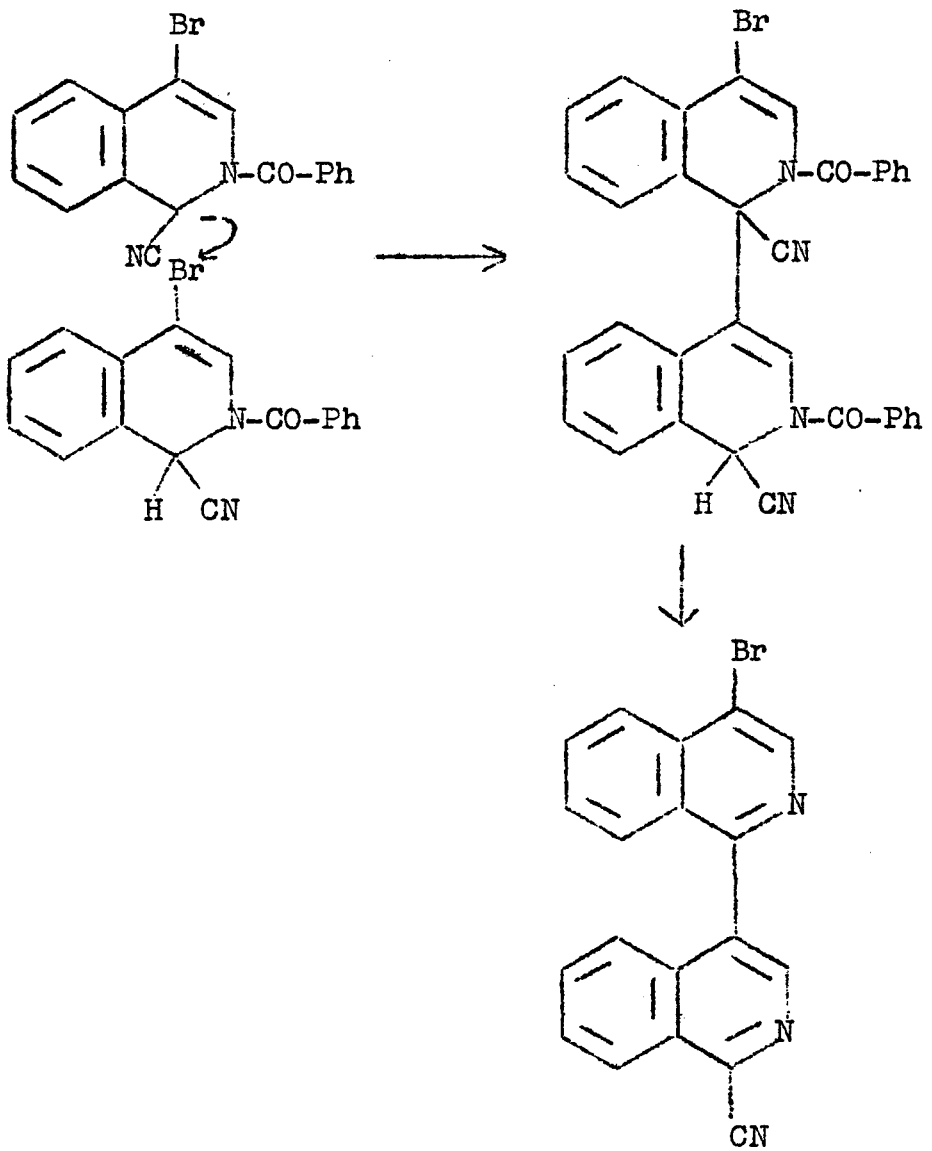
Elemental analysis of the unknown compound gave an empirical formula of $C_{19}H_{10}N_3Br$. The infra-red spectrum showed a nitrile peak (2240 cm^{-1}) and a peak at 1620 cm^{-1} (C = C). The n.m.r. spectrum showed no C-1 proton in the usual region (~0·5τ) and has no peak above 2·5τ.

The mass spectrum showed a parent peak of 361 or 359 (Br^{81} or Br^{79}) and the $\frac{P+1}{P}$ and $\frac{P+2}{P}$ ratios were as expected for $C_{19}H_{10}N_3Br$. The most striking feature of the spectrum is a very intense P-1 peak, which is not shown in the mass spectra of either 4-bromo-isoquinoline or its Reissert compound.

The ultra-violet spectrum had $\lambda_{max.}$ at 218 mμ (ε116,000), 283 (ε9,500) 294 (ε10,000) and 334 mμ

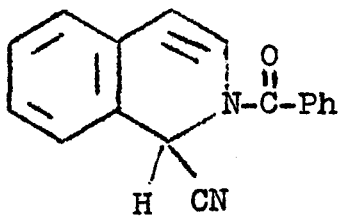
(ε16,000) compared with 4-bromoisoquinoline ($\lambda_{max.}$ 219 (ε74,000), 277 (7,200), 289 (6,200), 311 (4,400), 324 (5,400) mμ) and 4-bromoisoquinoline Reissert compound (208 (16,500), 231 (18,000), 310 (10,300) mμ).

The intense P-1 peak rules out our original thought of structure CXXVIII.



CXXVIII

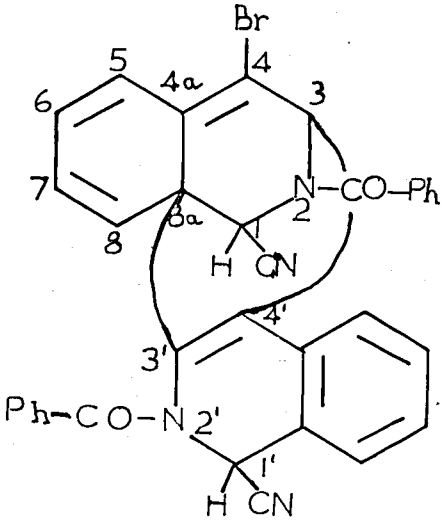
An alternative process which may have occurred is elimination of hydrogen bromide from the 3,4-position of the Reissert compound (CXXIV) under the strongly basic conditions, to give the cycloalkyne (CXXIX). Elimination of hydrogen halide, including



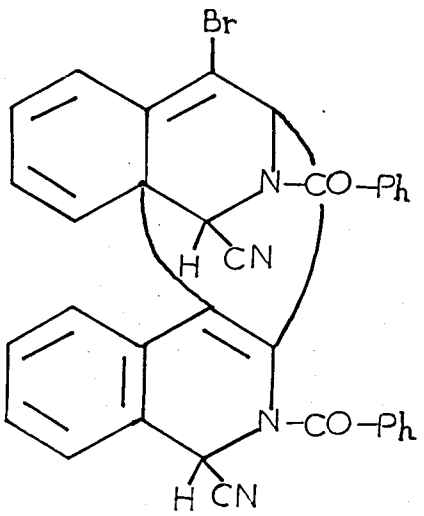
CXXIX

hydrogen bromide, to give a cycloalkyne,[106] benzyne[106] or heteraryne[107] under such conditions is not uncommon. The cycloalkyne (CXXIX) could then attack the styrene system of the Reissert compound (CXXIV) in a Diels-Alder manner to give a 1,4-adduct (either CXXX or CXXXI). Analogous 1,4-adducts are known, resulting from addition of benzyne to styrene[108] and also to substituted styrenes.[109,110] Adduct CXXX is sterically preferable as this has the two isoquinoline ring systems <u>trans</u> to each other, rather than <u>cis</u> as in CXXXI.

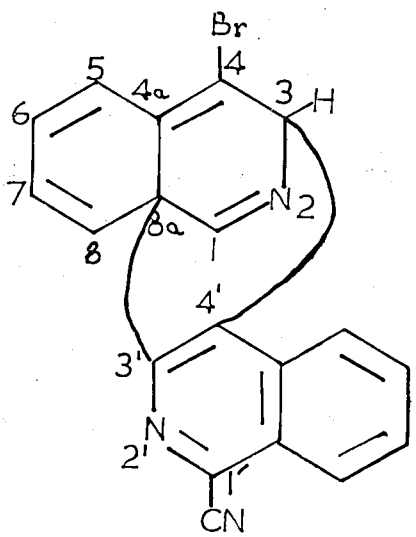
We suggest hydrolysis of CXXX then gives CXXXII, which presents good agreement with the analytical and spectral evidence obtained for our unknown product. The C-1 proton of CXXXII (see numbering on diagram) would not now be as strongly deshielded as in a normal isoquinoline and may well occur within the aromatic multiplet, rather than in the 0·0-0·7τ region. The



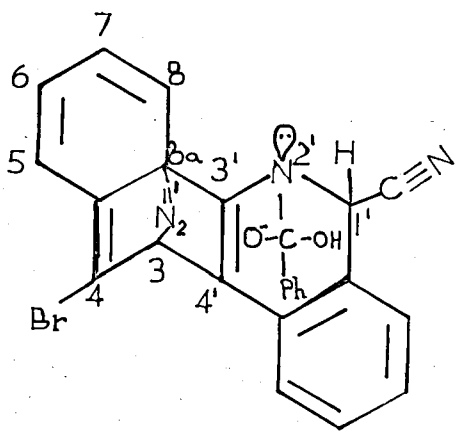
CXXX



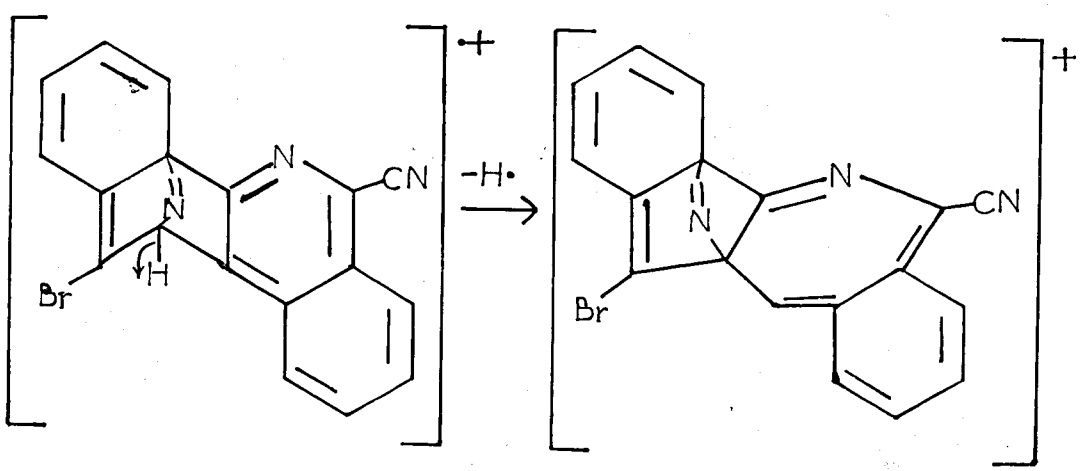
CXXXI



CXXXII



CXXXV



CXXXIII CXXXIV

strong P-1 peak in the mass spectrum can be accounted for by the likely loss of the tertiary C-3 hydrogen which in both allyic, and α to an aromatic ring. This loss of hydrogen will probably be assisted by a concerted rearrangement of the heteroring as shown (CXXXIII $\longrightarrow$ CXXXIV), giving an azatropylium system analogous to the well established toluene $\xrightarrow{-H\cdot}$ tropylium behaviour in the mass spectrometer.[111] The ultra-violet spectrum of our product is typical of an isoquinoline, but with some added structure in the 300-340 mμ region. This may well be accounted for by the presence, in CXXXII, of the cyano chromophore and the conjugated bromo-triene system.

It will be noted from structure CXXXII that it is suggested that the 1'-cyanide group is not eliminated during hydrolysis of the di-Reissert compound adduct (CXXX). This requires the hydrolysis to proceed with loss of hydrogen instead of cyanide from the 1'position. The preferred sterochemistry during the elimination can be expected to involve a trans-coplanar arrangement of the relevant atoms at the 1'- and 2'-positions. A study of models of CXXXV shows the sterically least hindered conformation contains the nitrile group equatorial rather than axial, so minimising non-bonded interactions which would otherwise occur between an axial cyanide and the bridged-ring system. C-1 elimination of hydrogen in Reissert compounds during base hydrolysis has been

reported with certain 2-arylsulphonyl-1,2-dihydroisoquinaldonitriles to give 1-cyanoisoquinoline.[112]

10. Spectra of Reissert Compounds.

(a) Nuclear Magnetic Resonance.

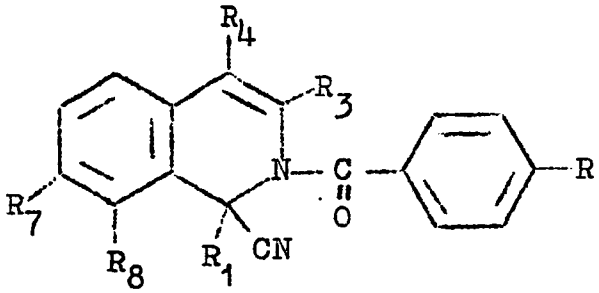
We have examined the n.m.r. spectra of a number of isoquinoline Reissert compounds and observed that the signal attributable to the C-1 proton occurs as a finely split singlet. Correspondingly the expected doublet for the C-3 proton is also finely split by the same J value. We thus considered that long-range coupling was occurring between the C-1 and C-3 protons, and this deduction was confirmed by the evidence outlined below. Further, it enabled us to study the preferred stereochemistry of the Reissert compound system. (Our observations have been supported by others of Chhabra and Uff and we have jointly reported the results.[113])

The n.m.r. information we obtained for a variety of Reissert compounds is summarised in table IV.

In each case the coupling between the C-1 and C-3 protons was slightly less than 1 c.p.s. Supporting evidence that the coupling observed was between C-1 and C-3 protons was provided by deuteration studies. On exchange of the C-1 proton for deuterium in CXXXVIa effected by addition of deuterium oxide to the Reissert compound carbanion (generated by sodium hydride in dimethylformamide), followed by neutralisation with

TABLE IV

N.m.r. Spectral Data*



CXXXVI

CXXXVI	R_1	R_3	R_4	R_7	R_8	R	C-1 Proton τ	C-3 Proton τ	$J_{1,3}$ c.p.s.
a	H	H	H	H	H	H	3·42 D	3·36 Q	0·8
b	D	H	H	H	H	H	-	3·36 D	-
c	H	H	Br	H	H	H	3·44 D	3·00 D	0·9
c**	H	H	Br	H	H	H	3·44 S	Sat.	-
d	H	H	H	OMe	OMe	H	3·06 D	3·39 Q	0·9
e	H	Me	H	H	H	H	3·50 S	-	-
f	H	Me	H	H	H	Me	3·50 S	-	-
g	H	H	H	OMe	OCOPhOMe	OMe	3·40 D	3·34 Q	0·8

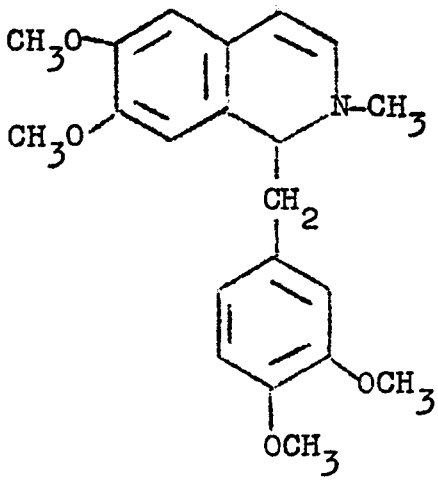
S=Singlet: D=Doublet: Q=Quartet: Sat.=Saturated
*Recorded with $CDCl_3$ as solvent at 60 Mc./sec., except for d at 40 Mc./sec.
**C-1 Proton spin-decoupled by saturation at 3·00τ.

carbon dioxide,[114] the deuterated compound (CXXXVIb) showed only a doublet for the C-3 proton in place of

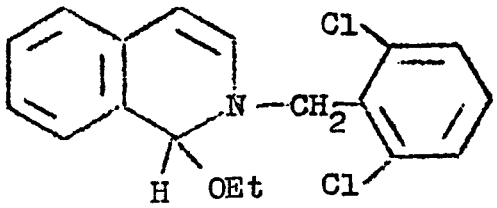
the quartet in CXXXVIa. A spin-decoupling experiment provided further evidence of long-range coupling in that the C-1 proton doublet of CXXXVIc collapsed to a singlet on saturation of the C-3 proton signal. Furthermore, in CXXXVIe and CXXXVIIf where the 3-position was substituted with methyl, the C-1 hydrogen absorption was unsplit. In these cases (CXXXVIe and f) allylic coupling was observed, of approximately 1·5 c.p.s., between the C-3 methyl and the C-4 proton.

Long-range coupling between protons separated by four or more bonds has recently been observed for a number of compounds[115] and it appears that a near planar zig-zag arrangement of the atoms concerned is required.[116,117]

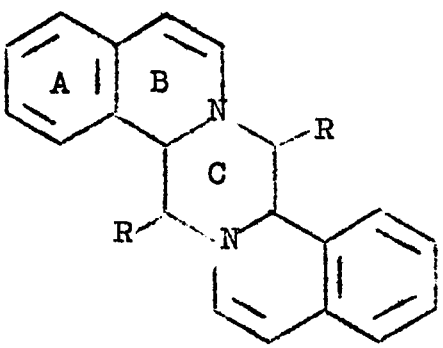
The value of the coupling constant suggests that the five atoms involved are adopting a conformation near planar, but not completely so. (For a planar arrangement the coupling constant usually falls within the range 1 to 3 c.p.s.[117] For an unstrained system Barfield has calculated a maximum value 1·2 c.p.s.[118]) The presence of coupling in Reissert compounds 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 CXXXVII). 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[119] (CXXXVIII) and it would also



CXXXVIII



CXXXIX

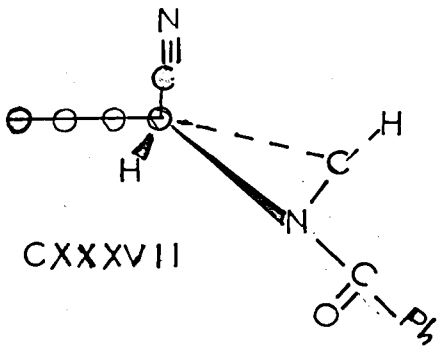


CXL

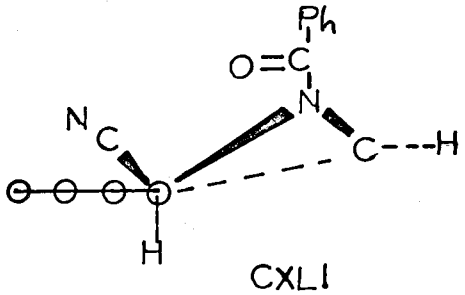
where R can be -CO-Ar
or
-CO-Me

appear to be the case for CXXXIX[120] and CXL[121] each of which shows similar long-range coupling.

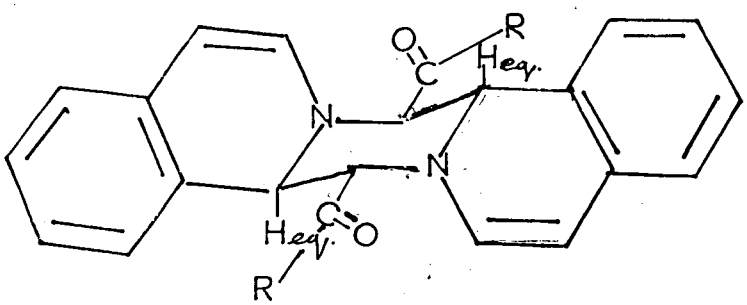
Models show in each case that non-bonded interactions are minimised by the C-1 substituent occupying the quasi-axial position. If the C-1 hydrogen were quasi-axial in Reissert compounds (CXLI) then steric interaction would result between the quasi-equatorial cyanide and the amidic phenyl ring. In 1,2-dihydro-



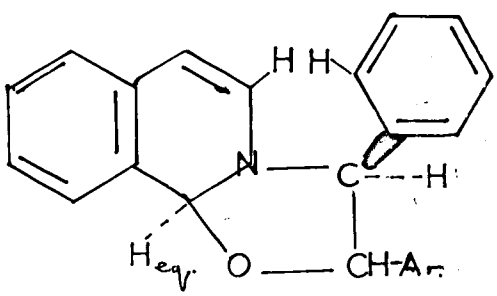
CXXXVII



CXLI



CXLII

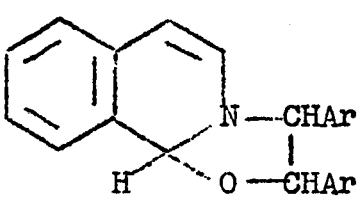


CXLIV

papaverine (CXXXVIII) a quasi-equatorial 1-benzyl group would present serious steric encumberance with the C-8 proton and also the N-methyl group. The quasi-axial C-1 ethoxy group in CXXXIX minimises non-bonded interactions between the ortho-chlorines and the oxygen of the ethoxy group.

The n.m.r. spectrum reported by Ahlbrecht et al.[121] for CXL shows that the compound is sterically symmetrical. Although the authors[121] do not discuss the stereochemistry of CXL we have examined models of the system and conclude there are only three symmetrical forms of CXL with ring C in the chair form. (The boat form is unlikely as it would introduce more elipsed interactions.) Models further suggest that the least hindered of these conformations has the C-1 proton quasi-equatorial (see CXLII).

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 in CXLIII since here its signal is reported to be unsplit.[120] A quasi-equatorial C-1 hydrogen in CXLI



CXLIII

would cause a phenyl ring <u>trans</u> related to it (and α to N) to meet steric crowding with the isoquinoline

C-3 hydrogen (CXLIV). Such an interaction is removed with a quasi-axial C-1 hydrogen.

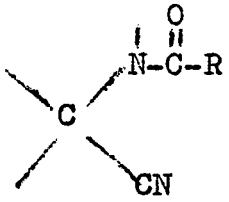
The n.m.r. spectrum of Reissert compounds shows only one (doublet) peak for the C-1 hydrogen. Therefore, the C-1 hydrogen is either completely in the quasi-equatorial conformation or, more likely, the hetero-ring is flipping rapidly between the two conformations (CXXXVII and CXLI) and the n.m.r. spectrometer is seeing an average position of the C-1 hydrogen. We have investigated this point by variable temperature n.m.r. studies. As the temperature was lowered the C-1 proton signal moved about 0·2 p.p.m. downfield on cooling from $+100^{\circ}$ to -70° (in acetone).

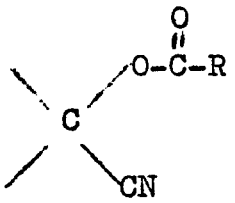
An equatorial C-1 proton is more deshielded by the aromatic ring than is an axial one.[122,123] Also one would expect the anisotropy effect of the σ-bond system surrounding C-1 to cause deshielding of an equatorial proton (relative to an axial one).[124] Thus the movement of the C-1 proton to a lower τ value as the temperature decreases shows 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).

(b) Infrared Spectra.

The most striking feature about the infrared spectra of Reissert compounds is the weakness of the nitrile peak (in the region 2200-2300 $cm.^{-1}$). It is

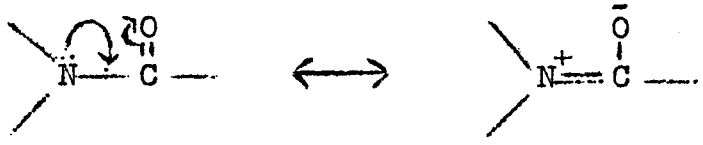
normally only just visible when recorded on a grating instrument. The intensity of the nitrile absorption is dependant on the structure of the rest of the molecule.[125] In ketone cyanohydrins the nitrile band is weak and disappears completely when the cyanohydrin is acylated.[7]





Since Reissert compounds are nitrogen analogues of these acyl derivatives it might be expected that the nitrile absorption is very weak for the same reason.

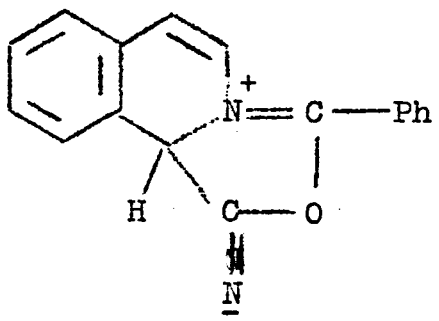
The carbonyl group appears at 1666 $cm.^{-1}$ in Reissert compounds, which is quite normal for amides and sp^2 hybridisation can be assumed for the nitrogen. If sp^3 hybridisation were the case absorption would be at a higher frequency,[126] due to lack of overlap of the amidic nitrogen non-bonded electrons with the carbonyl π-system. Such overlap with sp^2 hybridisation, gives the amide C-N bond some double bond character and the carbonyl some single bond character. Thus the



carbonyl bond lengthens and its frequency falls.

McEwen and Cobb[7] suggested that a possible reason for the weakness of the nitrile absorption was

a contribution of the type (CXLV). Assuming sp^2

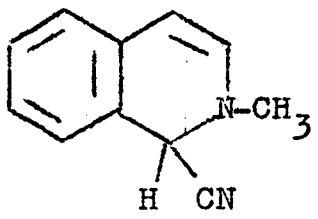


CXLV

hybridisation of the amide nitrogen, and with C-1 proton quasi-equatorial, as shown by the n.m.r. studies (p. 66), the nearest the carbonyl oxygen can approach the nitrile carbon in 3·4 Å,* too great a distance to permit significant partial bond formation. Thus the suggestion of McEwen and Cobb must be considered unsatisfactory. If the C-1 proton were quasi-axial the carbonyl oxygen to nitrile carbon distance is only 2·4 Å.* If the nitrogen were sp^3 hybridised there are four possible conformations, one of which has the C-1 proton quasi-equatorial and the carbonyl oxygen 2·4 Å* from the carbon of the nitrile.

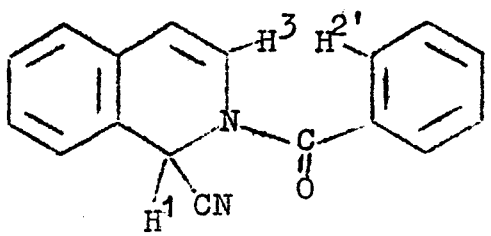
We prepared CXLVI to compare the intensity of its nitrile absorption with that of Reissert compounds. Though in CXLVI the nitrile is weak, it is not as weak as in Reissert compounds, showing that the carbonyl group has an important inductive effect on the strength of the nitrile absorption.

*Estimated with Dreiding models.

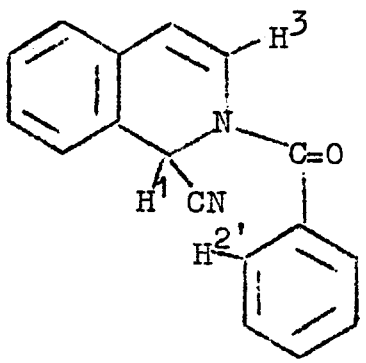


CXLVI

For resonance in amides the nitrogen must be sp^2 hybridised. The phenyl group and the C_3-C_4 double bond will also be approximately in the same plane to permit overlap of the whole π-system. This gives the two preferred rotational isomers (CXLVII and CXLVIII).



CXLVII



CXLVIII

Models show that slightly less steric encumberance will be experienced by CXLVII than CXLVIII, since in CXLVIII H-2' will approach both the nitrile and H-1, while in CXLVII H-2' only approaches H-3. However, when a methyl is in the 3 position isomer CXLVIII will be preferred, which will expose the carbon of the carbonyl to the carbanion at C-1, thus explaining why rearrangement occurs rather than substitution of a halide.

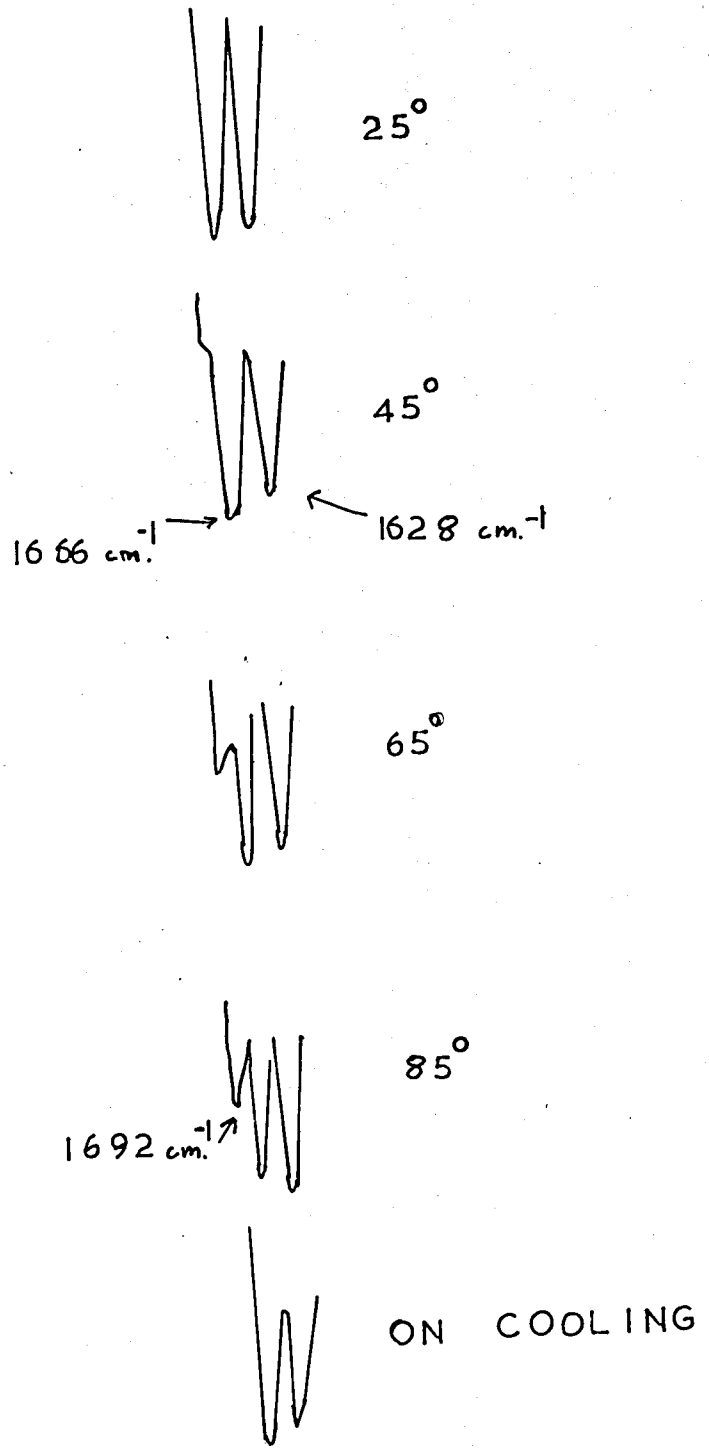
We have further investigated the structure of Reissert compounds by variable temperature studies. When the temperature is increased a new peak appears at 1692 $cm.^{-1}$ with a corresponding decrease in the size of the peak at 1666 $cm.^{-1}$. On cooling the higher peak disappears and the 1666 $cm.^{-1}$ peak returns to its original size (see Figure II).

If the reason for the weakness of the nitrile absorption was due to a structure of type CXLV, then on heating there should be an increase in the nitrile absorption as less of the cyclic structure (CXLV) will be present. There was no noticeable change in the nitrile region.

The higher peak, at 1692 $cm.^{-1}$, presumably results from rotation of the N-C bond, when the nitrogen lone pair and carbonyl group are no longer in the same plane. Thus the carbonyl will be similar to that in acetophenone the absorption of which appears at about 1690 $cm.^{-1}$ (1689 $cm.^{-1}$,[127] 1691 $cm.^{-1}$,[128]

FIGURE II

CHANGE WITH TEMP. OF IR. SPECTRUM



1692 cm.$^{-1}$,[129]).

The enthalpy difference between two forms of a compound, using variable temperature infrared spectrometry is given by the equation[130]:-

$$\Delta H = \frac{T_1 T_2}{T_1 - T_2} \; R \ln \frac{A_1^{\,1} A_2^{\,2}}{A_2^{\,1} A_1^{\,2}}$$

where T_1 and T_2 are the temperatures and

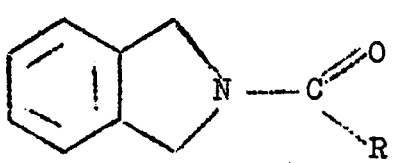
$A_1^{\,1}$ = area of peak 1 at T_1

$A_1^{\,2}$ = " " " 1 " T_2

$A_2^{\,1}$ = " " " 2 " T_1

$A_2^{\,2}$ = " " " 2 " T_2

A value of $\Delta H = 21 \pm 4$ kcal./mole was obtained. This figure is a measure of the energy barrier to rotation of the C-N amide bond or the resonance energy of the amidic system. Our figure is in good agreement with theoretical values[131,132] and values obtained for other amidic systems by n.m.r. spectroscopic studies,[133-138] for example with those of Gerig[133] for the similar N-acyldihydroisoindoles (CXLIX).



CXLIX

R	ΔH, Kcal./mole	ΔG, Kcal./mole
CH_3	20	20
OCH_3	19	17
Ph	19	17

The slightly higher value in our case could be attributable to resonance overlap with the styrene system of the Reissert compound.

EXPERIMENTAL

Unless otherwise stated the following conditions apply.

Infrared spectra were determined as nujol mulls or thin films (in the case of liquids) on Perkin-Elmer 237 or 257 spectrometers. Ultraviolet spectra were determined in methanol on a Unicam S.P. 800 machine. N.m.r. spectra were determined in deuterochloroform with tetramethylsilane as internal standard at 60 Mc./sec. on a Perkin-Elmer R10 instrument. Mass spectra were obtained on the A.E.I. M.S.9. machine at Manchester University, and we are most grateful to Dr. G.F. Smith for providing this facility.

Melting points are uncorrected.

Benzene, diethyl ether and petroleum ether were dried with sodium wire. Chloroform was dried with calcium carbonate. Tetrahydrofuran was dried by heating under reflux over sodium, distillation on to potassium and distillation from potassium when required for use. Dimethylformamide was dried by distillation and collection of the middle fraction.

Column chromatography was carried out on neutral alumina, Brockmann activity 1. Thin layer chromatography was carried out on 20 cm. plates, 0·25 mm. thick, spread with Kieselgel G.F. 254.

The following abbreviations are used in the text:-

s = singlet

d = doublet

t = triplet

q = quartet

m = multiplet

v = very

w = weak

b = broad

st = strong

sh = shoulder

dec = decomposed

I would like to thank Mr. S.R. Chabbra, Mr. F.M. Jiggins (n.m.r. spectra), Mr. K.R. Scott and Mr. R. White (microanalysis) for their technical assistance.

1. Preparation of Reissert Compounds.

N-Benzoyl-1,2-dihydroisoquinaldonitrile.

Potassium cyanide (16 g.) in water (40 ml.) was added to isoquinoline (10 g.) in dichloromethane (100 ml.). Benzoyl chloride (18 ml.) was added dropwise over 2 hours to the vigorously stirred two-phase system. After stirring for an additional 30 minutes the layers were separated.

The organic layer was washed with water, 2N-hydrochloric acid, water, 2N-sodium hydroxide, water and dried (Na_2SO_4). Concentration of the solvent gave the Reissert compound (13·8 g., 69%). Recrystallisation from ethyl acetate gave N-benzoyl-1,2-dihydroisoquinaldonitrile (13·1 g., 66%) as colourless rhombs, m.p. 123-125° (reported,[30] m.p. 124-125°). τ 2·46 (s, 5H, phenyl group), 2·65 (m, 4H, aromatic protons), 3·36 (q, 1H, C-3 proton), $J_{3,4}$ = 8 c.p.s., 3·42 (d, 1H, C-1 proton), $J_{1,3}$ = 0·8 c.p.s., 3·94 (d, 1H, C-4 proton); $\nu_{max.}$ 1666 (CO), 1630 (C=C), 2250 $cm.^{-1}$ (CN); $\lambda_{max.}$ 213, 228, 294, 309 sh.

Variation of solvent.

The experiment was repeated but using other organic solvents in place of methylene chloride. Solvents examined were 1,2-dichloroethane, chloroform, benzene, carbon tetrachloride and ether. The results of these experiments are summarised in table I (p. 15).

Using ether.

On repeating the above experiment using ether

(100 ml.) as solvent a white precipitate was formed immediately on stirring benzoyl chloride (18 ml.) with isoquinoline (10 g.). This was filtered off to give what was considered to be N-benzoylisoquinolinium chloride (15 g., 75%) as colourless highly hygroscopic rhombs m.p. 140-142°; n.m.r. in D_2O, τ 0·70 (s, 1H, C-1 proton), 1·23 to 2·3 (m, 11H, aromatic protons); positive Beilstein's test for halogen.

N-Benzoylisoquinolinium chloride (12 g.) and potassium cyanide (12 g.) in water (80 ml.) were stirred for 3 hours at room temperature. The aqueous solution was extracted with benzene and worked-up as in the previous experiment to give N-benzoyl-1,2-dihydroisoquinaldonitrile as colourless rhombs, m.p. 120-122° (reported,[30] m.p. 124-125°). i.r. identical with that of the previous sample.

2. Reactions of 5-Nitroisoquinoline.

Attempted preparation of 5-nitroisoquinoline Reissert compound.

Potassium cyanide (11·2 g.) in water (40 ml.) was added to 5-nitroisoquinoline (10 g.) in dichloromethane (100 ml.). Benzoyl chloride (13·2 ml.) was added dropwise to the vigorously stirred two-phase system. A quantitative precipitation of yellow solid took place as the reaction proceeded. This was filtered off and recrystallised from ethyl acetate-ethanol as yellow needles, m.p. 187-188°(Found: C, 65·0; H, 4·1;

N, 9·5. $C_{16}H_{12}N_2O_4$ requires C, 64·9; H, 4·1; N, 9·5%). n.m.r. in $DMSOd_6$, τ 1·8 to 3·4 (m, 7H, aromatic protons), 2·36 (s, 5H, phenyl group); $\nu_{max.}$ 1666 (CO), 1625 (C=C), 3340 $cm.^{-1}$ b. (bonded OH); $\lambda_{max.}$ 212, 304 and 356 mμ (ε 27,000, 15,800 and 6,800). This evidence indicated the product obtained to be not the expected Reissert compound but N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline.

Reaction of 5-nitroisoquinoline with benzoyl chloride and water.

Benzoyl chloride (4 ml.) in dichloromethane (15 ml.) was added dropwise to a vigorously stirred two-phase system of 5-nitroisoquinoline (3 g.) in methylene chloride (40 ml.) and water (20 ml.) for 30 minutes. Work-up as in the previous reaction gave N-benzoyl-1-hydroxy-5-nitro-1,2-dihydroisoquinoline as yellow needles, m.p. 185-188°, which was identical (mixed m.p. and i.r. spectrum) with a sample prepared in the previous experiment.

3. Synthesis of 1-Benzylisoquinolines-Phenyl Lithium Route.

(a) 1-Anisylisoquinoline.

Anisyl chloride.

Anisyl alcohol (20 g.) on treatment with thionyl chloride in dry benzene gave[49] anisyl chloride (18·5 g., 82%) as a colourless liquid, b.p. 56°/1·2 x 10^{-2}mm. (lit.,[49] b.p. 59-60°/10^{-2}mm.). n.m.r. in CCl_4, τ 2·95

(q, 4H, aromatic protons), 5·52 (s, 2H, CH_2), 6·32 (s, 3H, OCH_3); $\nu_{max.}$ 1615, 1520 (C=C, aromatic), 1255 (C-O-C), 830 (C-H 1,4 disub.), 760 $cm.^{-1}$ (C-Cl).

1-Anisylisoquinoline.

To a solution of N-benzoyl-1,2-dihydroisoquinaldonitrile (4·75 g., 0·018 mole) in dry tetrahydrofuran (50 ml.) maintained and stirred at -5° to -10° under dry, oxygen-free nitrogen, was added a solution of phenyl lithium, prepared[63] from bromobenzene (10 ml.) and lithium (1 g.), in dry tetrahydrofuran (50 ml.). A dark red colour appeared. Anisyl chloride (4 g., 0·025 mole) in dry tetrahydrofuran (10 ml.) was slowly added and the mixture stirred for 1 hour at -5° to -10° and then overnight at room temperature, after which time the colour had changed to yellow-brown. The solvent was removed by evaporation to give 1-anisyl-N-benzoyl-1,2-dihydroisoquinaldonitrile as an oil. This was dissolved in ethanol (250 ml.) and refluxed for 2 hours with a solution of potassium hydroxide (100 g.) in water (200 ml.). After removal of alcohol the residue was partitioned between benzene and water. The benzene extract was washed with water, extracted with acid, basified, extracted with chloroform and dried (K_2CO_3). On evaporation 1-anisylisoquinoline was obtained as an oil (4·54 g., 66%). Purification by column chromatography and recrystallisation from 60-80° petrol gave 1-anisylisoquinoline as yellow needles m.p. 68·5 to 69·5° (Found:C, 82·8; H, 6·1; N,

5·8. $C_{17}H_{15}NO$ requires C, 81·9; H, 6·1; N, 5·6%). The picrate was prepared by precipitation from the hydrochloride in water and recrystallised as bright yellow needles from ethanol, m.p. 167-168° (Found: C, 57·4; H, 3·6. $C_{23}H_{18}N_4O_8$ requires C, 57·7; H, 3·8%).

(b) Attempted Synthesis of 1-Anisyl-7,8-dimethoxyisoquinoline.

7,8-Dimethoxyisoquinoline.

Trifluoro-acetic acid (100 ml., 149 g.) was allowed to stand with phosphorus pentoxide (100 g.) for 24 hours. The mixture was distilled and the distillate redistilled from a second quantity of phosphorus pentoxide (50 g.) through a Vigreaux column to give trifluoro-acetic anhydride, b.p. 39-41° as a colourless liquid.

A mixture of 2,3-dimethoxy-benzaldehyde (10 g., 0·0604 mole) and aminoacetal (8·1 g. 0·061 mole) in benzene (150 ml.) was refluxed under a Dean-Stark trap for 3 hours. Removal of solvent and excess aminoacetal left the Schiff base, 2,3-dimethoxy-benzylideneaminoacetal, as a pale yellow oil.

The Schiff base was stirred at 0° under anhydrous conditions. Trifluoro-acetic anhydride (38 g., 3 moles) was added slowly, followed by boron trifluoride-acetic acid complex (40% BF_3, 41 g., 4 moles), a bright cherry-red colour developing. The mixture was allowed to stand at room temperature for two days, the colour changing to a deep brown.

The whole mixture was added to ice-water, with stirring, and allowed to stand for 1½ hours to break up the boron trifluoride-acetic acid complex and hydrolyse excess trifluoro-acetic anhydride. The mixture was treated with ammonia solution (25%), to pH 6, the yellow colour becoming orange. Some brown tar that formed was decanted off, and further basification with ammonia, to pH 9, gave a cream suspension. This was extracted with chloroform, dried (Na_2SO_4) and evaporated to give a brown oil.

The brown tar was warmed with hydrochloric acid (2N) and filtered. The acid solution was extracted twice with benzene and ether, and than basified with ammonia solution, to pH 9. This was extracted with chloroform, dried, and evaporated to give more brown oil.

The brown oil, crude 7,8-dimethoxyisoquinoline (6·0 g., 58%), was distilled to give pure 7,8-dimethoxyisoquinoline (4·1 g., 39%) as a pale yellow oil (b.p. 86-90°/10^{-2}mm.). τ0·30 (s, 1H, C-1 proton), 1·45 (d, 1H, C-3 proton), 2·45 (m, 3H, C-4,5 and 6 protons), 5·95 (s, 3H, C-8 OCH_3), 6·05 (s, 3H, C-7 OCH_3).

<u>N-Benzoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile.</u>

7,8-Dimethoxyisoquinoline (2·4 g.) gave N-benzoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile (3·2 g., 72%) as cream rhombs, m.p. 154-156° (reported[52] m.p. 155-157°), by the dichloromethane/

water method (p. 81). τ at 40 Mc./sec. 2·4 (s, 5H, phenyl group), 3·0 (m, 2H, C-5 and 6 protons), 3·06 (d, 1H, C-1 proton), $J_{1,3}$ = 0·9 c.p.s., 3·39 (q, 1H, C-3 proton), $J_{3,4}$ = 8 c.p.s., 4·0 (d, 1H, C-4 proton), 5·95 (s, 3H, C-8 OCH_3), 6·05 (s, 3H, C-7 OCH_3); $\nu_{max.}$ 1660 (CO), 2240 $cm.^{-1}$ vw (CN).

Attempted preparation of 1-anisyl-7,8-dimethoxyisoquinoline.

N-Benzoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile (2·5 g.) was treated with phenyl lithium followed by anisyl chloride and worked-up as described for the preparation of 1-anisylisoquinoline (p. 84). The final product proved to be 7,8-dimethoxyisoquinoline (1·1 g., 81%) as an oil. Its picrate crystallised as bright yellow needles from ethanol, m.p. 181-182° dec (Found: C, 48·7; H, 4·0. Calc. for $C_{17}H_{14}N_4O_9$: C, 48·8; H, 3·4%). The product was further characterised as its methiodide by warming with methyl iodide in dry ether. Recrystallisation from ethyl alcohol gave pure 7,8-dimethoxyisoquinoline methiodide as yellow needles, m.p. 174-176° (Found: N, 4·1. Calc. for $C_{12}H_{14}NO_2I$: N, 4·2%).

7,8-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.

7,8-Dimethoxyisoquinoline methiodide (0·25 g.) was reduced in methanol with sodium borohydride[54] to give 7,8-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (0·15 g., 94%) as a pale yellow glass. τ at 40 Mc./sec. 2·1 (s, 2H, C-5 and 6 protons), 6·1

(s, 6H, two OCH_3 groups), 6·3 (bs, 2 H, C-1 protons), 7·18, 7·24 (2 x t, 4H, C-3 and C-4 protons), 7.45 (s, 3H, N-Me).

The product was further characterised as its methiodide, which crystallised as fine white needles from ethanol, m.p. 163-164° (Found: C, 45·4; H, 5·5; N, 4·0. $C_{13}H_{20}NO_2I$ requires C, 44·7; H, 5·8; N, 4·0%).

Repeated attempted preparation of 1-anisyl-7,8-dimethoxyisoquinoline.

The reaction was repeated as described on p. 87 but at the lower temperature of -10° to -15°. The product again proved to be 7,8-dimethoxyisoquinoline. Its picrate crystallised as bright yellow needles from ethanol, m.p. 180-182°, which was identical (mixed m.p.) with a sample prepared previously (p. 87). Its methiodide crystallised as yellow needles, m.p. 174-176°, also identical (mixed m.p.) with a sample prepared previously (p. 87).

4. Synthesis of 1-Benzylisoquinolines-Sodium Hydride Route.

General method.

A suspension of sodium hydride (50% in oil, washed with dry 60-80° petrol, 0·6 g., 0·012 mole) in dry dimethylformamide (25 ml.) was stirred at 0° under nitrogen. The N-benzoyl-1,2-dihydroisoquinaldonitrile (0·0115 mole) in dimethylformamide (15 ml.) was added, a deep red colour developing with the evolution of

hydrogen gas. After about 10 minutes, the benzyl halide (0·012 mole) was added over half an hour. The mixture was then stirred for a further half an hour at 0° and for 2 hours at room temperature, after which the colour was pale pink.

Ethanol was added to destroy excess sodium hydride and most of the solvent was distilled off, at reduced pressure. Benzene and water were added and the layers separated. The benzene layer was washed with water, extracted with acid, basified, extracted with chloroform and dried (K_2CO_3). Evaporation gave the 1-benzylisoquinoline.

The benzene solution was evaporated to give the substituted Reissert compound as an oil, to which ethanol (150 ml.) and a solution of sodium hydroxide (50 g.) in water (50 ml.) was added. The mixture was refluxed for $2\frac{1}{2}$ hours after which the ethanol was distilled off and the product extracted with benzene. The benzene extract was worked-up as above to give more of the 1-benzylisoquinoline. Column chromatography was used to purify the 1-benzylisoquinolines.

The n.m.r. data for the 1-benzylisoquinolines is given in table V.

1-Benzylisoquinoline.

Use of benzyl chloride in the general procedure (p. 88) gave 1-benzylisoquinoline as a pale yellow oil. Its hydrochloride crystallised from ethanol/ether as colourless needles m.p. 172-173° (lit.,[140] m.p. 175°).

The picrate crystallised from ethanol as yellow needles m.p. 180-182° (lit.,[140] 182°). The methiodide crystallised from ethanol/ether as golden yellow plates, m.p. 247-249° (lit.,[140] m.p. 247-248°) (Found: C, 56·7; H, 4·7; N, 3·6. Calc. for $C_{17}H_{16}NI$: C, 56·5; H, 4·5; N, 3·9%).

1-Anisylisoquinoline.

Use of anisyl chloride in the general procedure (p. 88) gave 1-anisylisoquinoline (72%), which crystallised from 60-80°petroleum ether as cream needles, m.p. 68·5-69·5° (Found: C, 82·8; H, 6·1; N, 5·8. Calc. for $C_{17}H_{15}NO$: C, 81·9; H, 6·1; N, 5·6%). Its picrate crystallised from ethanol as yellow needles, m.p. 166-168°, identical (mixed m.p.) with a sample prepared previously (p. 84).

1-(-p-Tolyl)isoquinoline.

Use of p-tolyl bromide in the general procedure (p. 88) gave 1-(p-tolyl)isoquinoline (78%) as an oil. Its picrate crystallised from ethanol as yellow needles, m.p. 178-179° (Found: C, 59·8; H, 3·9; N, 12·1. $C_{23}H_{18}O_7N_4$ requires C, 59·7; H, 3·9; N, 12·1%). The methiodide crystallised from ethanol as yellow plates, m.p. 249-251° (Found: C, 57·8; H, 4·8; N, 3·8. $C_{18}H_{18}NI$ requires C, 57·7; H, 4·8; N, 3·7%).

1-(p-Nitrobenzyl)isoquinoline.

Use of p-nitrobenzyl bromide in the general method (p. 88) gave 1-(p-nitrobenzyl)isoquinoline (65%) which crystallised from ether as cream needles m.p.

108-109° (Found: C, 72·6; H, 4·7; N, 10·5. $C_{16}H_{12}N_2O_2$ requires C, 72·7; H, 4·6; N, 10·6%). The picrate crystallised from ethanol as fine needles m.p. 212-215° (Found: N, 14·1; $C_{22}H_{15}N_5O_9$ requires N, 14·2%). The methiodide crystallised from ethanol as yellow prisms, m.p. 195-197° (Found: C, 50·1; H, 5·6. $C_{17}H_{15}N_2O_2I$. C_2H_5OH requires C, 50·4; H, 4·7%).

3,4-Dimethoxybenzyl chloride.

3,4-Dimethoxybenzyl alcohol (10 g.) on treatment with thionyl chloride in dry benzene[49] gave 3,4-dimethoxybenzyl chloride (5·1 g., 4·7%) as a colourless liquid, b.p. 90-93°/0·1mm. (lit.,[139] b.p. 128-129°/11mm., 133-137°/13mm). n.m.r. in CCl_4, τ 3·1 to 3·4 (m, 3H, aromatic protons), 5·53 (s, 2H, CH_2), 6·27 (s, 6H, two OCH_3 groups); $\nu_{max.}$ 1605, 1595 (C=C), 690 cm.$^{-1}$ (C-Cl).

1-(3,4-Dimethoxybenzyl)isoquinoline.

Use of 3,4-dimethoxybenzyl chloride in the general procedure (p. 88) gave 1-(3,4-dimethoxybenzyl)-isoquinoline (82%), which crystallised from ether as colourless plates m.p. 92-93° (Found: C, 77·5; H, 6·2; N, 5 0. Calc. for $C_{18}H_{17}NO_2$: C, 77·4; H, 6·1; N, 5·0%). $\nu_{max.}$ 1615, 1605 cm.$^{-1}$ (C=C). The picrate crystallised from ethanol as yellow needles, m.p. 165-166° (reported[9] m.p. 165-165·5°) (Found: C, 56·8; H, 4·1; N, 10·9. Calc. for $C_{24}H_{20}N_4O_9$: C, 56·7; H, 4·0; N, 11·0%). The methiodide crystallised from ethanol as yellow plates m.p. 175-177° (Found: N, 3·2. Calc.

for $C_{19}H_{20}NO_2I$: N, 3·2%).

1-(3,4-Dimethylbenzyl)isoquinoline.

Use of 3,4-dimethylbenzyl chloride in the general method (p.88) gave 1-(3,4-dimethylbenzyl)-isoquinoline (86%) as an oil. $\nu_{max.}$ 1620 cm.$^{-1}$ (C=C). The hydrochloride crystallised from ethanol as colourless needles, m.p. 215°(dec) (Found: N, 4·4. $C_{18}H_{18}NCl$ requires N, 4·4%). The picrate crystallised from ethanol as yellow needles, m.p. 169-170° (Found: C, 60·5; H, 4·1; N, 10·7. $C_{24}H_{20}N_4O_7$ requires C, 60·5; H, 4·2; N, 11·8%). The methiodide crystallised from ethanol as golden yellow needles, m.p. 188-190° (Found: C, 56·4; H, 4·8; N, 3·7. $C_{19}H_{20}NI$ requires C, 56·3; H, 5·1; N, 3·6%).

Piperonyl chloride (3,4-methylenedioxybenzyl chloride).

Piperonyl alcohol (20 g.) on treatment with thionyl chloride in dry benzene[49] gave piperonyl chloride (16·0 g., 71%) as a colourless liquid, b.p. 71-76°/0·5 mm. (lit.,[139] b.p. 89-91°/1 mm.). n.m.r. in CCl_4, τ 3·18 to 3·40 (m, 3H, aromatic protons), 4·13 (s, 2H, methylenedioxy group), 5·60 (s, 2H, benzyl CH_2); $\nu_{max.}$ 685 cm.$^{-1}$ (C-Cl).

1-Piperonylisoquinoline.

Use of piperonyl chloride in the general method (p.88) gave 1-piperonylisoquinoline (75%), which crystallised from ether as colourless needles, m.p. 80-81° (Found: C, 77·7; H, 5·2; N, 5·3. $C_{17}H_{13}NO_2$ requires C, 77·5; H, 5·0; N, 5·3%). The picrate crystallised from ethanol

TABLE V

1-Benzylisoquinolines: N.m.r. Spectral Data

1-Substituent	C-3 Proton (τ)	Aromatic Protons (τ)	CH_2 (τ)	Other Protons (τ)
Benzyl	1·43,d	1·9 (q, 1H, C-4 proton), 2·45 (m, 9H)	5·35,s	
Anisyl	1·44,d	1·88 (q, 1H, C-4 proton), 2·3 to 3·5 (m, 8H)	5·39,s	6·42 (s, 3H, OCH_3)
p-Tolyl	1·51,d	1·76 to 3·05 (m, 9H)	5·40,s	7·79 (s, 3H, CH_3)
p-Nitro	1·46,d	1·75 to 2·65 (m, 9H)	5·23,s	
3,4-Dimethoxy	1·52,d	1·7 to 2·7 (m, 5H), 3·1 to 3·27 (m, 3H, benzyl group)	5·41,s	6·25 (s, 6H, two OCH_3 groups)
3,4-Dimethyl	1·54,d	1·8 to 3·1 (m, 8H)	5·47,s	8·00 (s, 6H, two CH_3 groups)
Piperonyl	1·53,d	1·9 (q, 1H, C-4 proton), 2·2 to 2·7 (m, 4H) 3·25 (m, 3H, benzyl group)	5·47,s	4·24 (s, 2H, OCH_2O)

as yellow needles, m.p. 179° (dec) (Found: C, 56·2; H, 3·4; N, 11·2. $C_{23}H_{16}N_4O_9$ requires C, 56·1; H, 3·3; N, 11·4%).

Preparation of 1-anisyl-7,8-dimethoxyisoquinoline.

N-Benzoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile (2·0 g.) was treated with sodium hydride and anisyl chloride by the method as described on p. 88. After evaporation of the solvents and separation between benzene and water, the benzene layer was extracted with acid and then evaporated to a small volume. Cream rosettes crystallised out on standing, recrystallisation from benzene gave 1-anisyl-2-benzoyl-7,8-dimethoxy-1,2-dihydroisoquinaldonitrile (0·74 g., 27%) as cream rosettes, m.p. 196-198° (Found: C, 73·5; H, 5·5; N, 6·5. $C_{27}H_{24}N_2O_4$ requires C, 73·6; H, 5·5; N, 6·4%). τ 5·82 (s, 3H, C-8 OCH_3), 6·17 (s, 3H, C-7 OCH_3), 6·33 (s, 3H, anisyl OCH_3); $\nu_{max.}$ 1668 (CO), 2250 cm.$^{-1}$ w (CN).

The acid extract was worked-up and the substituted Reissert compound was hydrolysed as described (p. 88) to give 1-anisyl-7,8-dimethoxyisoquinoline as a pale yellow oil which could not be obtained as a solid on column chromatography. τ 1·68 (d, 1H, C-3 proton), 2·43 to 3·34 (m, 7H, aromatic protons), 5·17 (s, 2H, CH_2), 6·12 (s, 3H, OCH_3), 6·25 (s, 3H, OCH_3), 6·33 (s, 3H, anisyl OCH_3). The picrate crystallised as small yellow needles from ethanol, m.p. 194° (Found: C, 55·7; H, 4·0; N, 10·3. $C_{25}H_{22}N_4O_{10}$ requires C, 55·8;

H, 4·1; N, 10·4%).

5. The Synthesis of O-Methylpetaline.

1-Anisyl-7,8-dimethoxyisoquinoline methiodide.

1-Anisyl-7,8-dimethoxyisoquinoline (1·0 g.) gave by warming with methyl iodide in dry ether (and also by refluxing with methyl iodide in methanol[54]) the methiodide as an oil (1·4 g.). Purification by column chromatography gave the crystalline methiodide (3 5 mg.) as yellow prisms from ethanol/ether, m.p. 139-140° (dec).

1-Anisyl-7,8-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.

1-Anisyl-7,8-dimethoxyisoquinoline methiodide (35 mg.) was reduced in methanol with sodium borohydride[54] to give 1-anisyl-7,8-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline as a colourless oil (approx. 20 mg.) which could not be induced to crystallise.

O-Methylpetaline iodide.

1-Anisyl-7,8-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (approx. 20 mg.) was converted to its methiodide, O-methylpetaline iodide (approx. 10 mg.) which after purification by column chromatography crystallised as cream needles from ethanol/ether, m.p. 73-76° (Found: C, 53·6; H, 5·9. $C_{21}H_{28}O_3NI$ requires C, 53·7; H, 6·0%). I.r. ($CHCl_3$ and CCl_4) identical with sample prepared from natural petaline

(see following experiment). Rf (1:1 $CHCl_3$/EtOH) 0·725.

Crude O-methylpetaline iodide was obtained as an oil which could not be induced to crystallise by carrying out the previous experiments with non-crystalline 1-anisyl-7,8-dimethoxyisoquinoline methiodide.

Preparation of O-methylpetaline iodide from natural petaline reineckate.

Petaline reineckate[68] (approx. 15 mg.) was refluxed in methanol (10 ml.) with methyl iodide (5 ml.) and sodium hydroxide (1 drop) for 3 hours. The solution was neutralised with dilute hydrochloric acid, evaporated under reduced pressure. Water was added and the aqueous layer extracted with chloroform, dried (K_2CO_3) and evaporated to give O-methylpetaline reineckate. This was then dissolved in acetone and titrated with silver sulphate solution until no further precipitate of silver reineckate was formed. Sulphate ions were displaced by quantitative precipitation with barium iodide solution, the solution filtered, the precipitate washed with acetone, and the combined filtrate and washings evaporated to give O-methylpetaline iodide (approx. 8 mg.) as cream needles from ethanol/ether, m.p. 75-77°. I.r. ($CHCl_3$ and CCl_4) identical with synthetic O-methylpetaline (see preceeding experiment). Rf (1:1 $CHCl_3$/EtOH) 0·725, on silica-gel thin layer plates.

Hofmann exhaustive methylation and degradation of O-methylpetaline.

The crude synthetic O-methylpetaline iodide (50 mg.) in methanol was eluted through a Permutit "De-Acidite" FF anionic exchange column (water regain 0·6-1·0, OH form). The brown eluate was evaporated to dryness, dissolved in methanol (20 ml.) and refluxed with sodium methoxide (1 g.) for 3 hours under nitrogen. Water (10 ml.) was added to the reaction mixture which was then neutralised with acetic acid and extracted several times with chloroform, dried (K_2CO_3) and evaporated. The residue was then refluxed with methyl iodide (3 ml.) in dry acetone (10 ml.) for 2 hours and then evaporated to give the methiodide. This was treated as before by elution through the anionic exchange column and then refluxed with sodium methoxide in methanol under nitrogen. The nitrogen stream was passed through a saturated ethanolic picric acid solution, from which trimethylamine picrate precipitated, m.p. 210-212° (reported[70] m.p. 216°), undepressed on admixture with an authentic sample.

The main reaction mixture was worked-up to give the nitrogen-free product, 2,3,4'-trimethoxy-6-vinylstilbene (approx. 6 mg.) from benzene/petroleum ether (40-60°), as cream needles, m.p. 166-169° (reported,[69] m.p. 168-170°). The i.r. (KBr disc) was similar to that of an authentic sample the 2,3,4'-trimethoxy-6-vinylstilbene.[68]

6. The Total Synthesis of Petaline.

2-Benzoyloxy-3-methoxy-benzaldehyde.

o-Vanillin (10 g.) and sodium hydroxide (2·7 g.) were dissolved in water (50 ml.), shaken with benzoyl chloride (9·3 g.) in ether (40 ml.) for $2\frac{1}{2}$ hours. The layers were separated. The ether layer was dried (Na_2SO_4) and evaporated to give a brownish solid. This was recrystallised from ether to give 2-benzoyl-3-methoxybenzaldehyde (9·2 g., 55%) as colourless needles, m.p. 86-88° (reported,[142] m.p. 90°) (Found: C, 70·7; H, 4·9. Calc. for $C_{15}H_{12}O_4$: C, 70·3; H, 4·7%). $\nu_{max.}$ 2776 (aldehyde C-H), 1735 (ester CO), 1700 $cm.^{-1}$ (aldehyde CO).

Attempted synthesis of 8-benzoyloxy-7-methoxyisoquinoline.

2-Benzoyl-3-methoxybenzaldehyde (8·5 g.) was refluxed with aminoacetal (4·5 g.) in benzene (50 ml.) under a Dean-Stark trap for 3 hours. Removal of the solvent gave the Schiff base, 2-benzoyl-3-methoxybenzylideneaminoacetal as a pale yellow oil. This was treated with trifluoroacetic anhydride in boron trifluoride-acetic acid complex as described in the preparation of 7,8-dimethoxyisoquinoline (p. 85), but on work-up only tars were obtained which proved intractable.

8-Hydroxy-7-methoxyisoquinoline.

o-Vanillin (30 g.) was refluxed with aminoacetal (26·5 g.) in benzene (100 ml.) under a Dean-Stark trap for 3 hours. Removal of the solvent gave the

Schiff base, 2-hydroxy-3-methoxy-benzylideneaminoacetal as a pale yellow oil. This was treated with trifluoroacetic anhydride in boron trifluoride-acetic acid complex as described in the preparation of 7,8-dimethoxyisoquinoline (p. 85). Work-up gave a resinous product (7 g.) which on sublimation gave 8-hydroxy-7-methoxyisoquinoline (0·8 g., 2%). Recrystallisation from ethanol gave pure 8-hydroxy-7-methoxyisoquinoline (0·52 g.) as straw needles, m.p. 180-182° (reported,[52] 182-183°). n.m.r. in CD_3COOD, τ 0·29 (s, 1H, C-1 proton), 1·53 to 2·4 (m, 4H, aromatic protons), 5·95 (s, 3H, C-7 OCH_3).

Attempted preparation of 8-hydroxy-7-methoxyisoquinoline using polyphosphoric acid.

A mixture of o-vanillin (25 g.) and aminoacetal (22·1 g.) in benzene (150 ml.) was refluxed under a Dean-Stark trap for 4 hours. Removal of the solvent gave the Schiff base, 2-hydroxy-3-methoxy-benzylideneaminoacetal as a pale yellow oil. This was added to polyphosphoric acid (800 g.) at 50° and the swirled mixture stood overnight (under a drying tube), then added to ice-water. The work-up (as described for 7,8-dimethoxyisoquinoline p. 85) gave a tar, which on column chromatography gave various solid fractions, but the n.m.r. of these showed that none was the required isoquinoline.

8-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride.

A mixture of o-vanillin (5·0 g., 0·03 mole) and aminoacetal (4·0 g., 0·03 mole) in ethanol (80 ml.) was added to platinum oxide (0·3 g.) in ethanol (20 ml.) which had been pre-reduced. The mixture was reduced at room temperature and pressure until hydrogenation ceased (about 9 hours). The catalyst was filtered off and the solvent evaporated. The residue was taken up in hydrochloric acid (6N, 150 ml.) washed with ether (50 ml.) and allowed to stand overnight. Palladium-on-carbon catalyst (5% Pd., 3 g.) was added and the solution reduced at room temperature and pressure until hydrogenation ceased (about 18 hours). The catalyst was filtered off and the solvent removed by evaporation to give 8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (6·2 g., 87%) as a pale yellow solid, m.p. 253-258°. Recrystallisation from ethanol gave cream needles, m.p. 277-280° (reported,[71] 282-283°) (3·8 g., 62%). 8-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline picrate crystallised as yellow needles from ethanol, m.p. 204-206° (lit., 204-206°) (Found: N, 13·4. Calc. for $C_{16}H_{16}N_4O_9$: N, 13·7%).

<u>8-Hydroxy-7-methoxyisoquinoline by dehydrogenation.</u>

<u>(a) Dehydrogenation with palladium-on-charcoal in p-cymene.</u>

8-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1·3 g.) was dissloved in water, neutralised, extracted with chloroform, dried (Na_2SO_4) and evaporated to give the free base. This was immed-

iately dissolved in p-cymene (200 ml.) and refluxed with palladium-on-carbon catalyst (10% Pd., 0·75 g.) for 2 hours. The solvent was evaporated and the crude material sublimed and recrystallised from ethanol to give 8-hydroxy-7-methoxyisoquinoline (0·52 g., 49%) as straw coloured needles, m.p. 181-183° (reported,[52] 183-184°) (Found: C, 68·2; H, 5·5; N, 7·8. Calc. for $C_{10}H_9NO_2$: C, 68·6; H, 5·5; N, 8·0%). n.m.r. in CD_3COOD, τ0·34 (s, 1H, C-1 proton), 2·50 (m, 4H, aromatic protons), 5·95 (s, C-7 OCH_3). The picrate crystallised from ethanol as yellow needles, m.p. 218-220°.

(b) Dehydrogenation with iodine.

8-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2·0 g.) was converted to 8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (1·1 g.). This was refluxed with iodine (4·5 g.) and sodium acetate (3 g.) in ethanol (70 ml.) for 3 hours.[74] Work-up gave a brown solid which could not be purified.

(c) Dehydrogenation with chloranil.

8-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1·0 g.) was converted to the free base. This was refluxed with chloranil (4 g.) in dioxan (100 ml.) for 3 hours.[75] Work-up gave a product which proved unrewarding on further processing.

Attempted preparation of 8-methoxymethoxy-7-methoxyisoquinoline.

Monochloromethyl methyl ether (1 ml.) in dry acetone (5 ml.) was added during 15 minutes to a

stirred refluxing solution of 8-hydroxy-7-methoxy-isoquinoline (520 mg.) in dry acetone (20 ml.) containing anhydrous potassium carbonate (2 g.). During the addition the solution became deep red. The mixture was allowed to cool and filtered, the solid being washed with acetone. Evaporation gave an oil which was washed in benzene repeatedly with 2N-sodium hydroxide, then with water, dried ($MgSO_4$) and evaporated to give an oil (184 mg.). The n.m.r. of this oil showed that it was not the required 8-substituted-isoquinoline.

The sodium hydroxide wash was neutralised, extracted with chloroform, dried ($MgSO_4$) and evaporated to give 8-hydroxy-7-methoxyisoquinoline (90 mg.).

8-Benzyloxy-7-methoxyisoquinoline.

8-Hydroxy-7-methoxyisoquinoline (1 g.) was dissolved in a solution of potassium hydroxide (0·4 g.) in water (1 ml.) and diluted with ethanol (25 ml.). The mixture was refluxed, under nitrogen, with benzyl chloride (1 ml.) for 5 hours. The colour became red immediately on addition of benzyl chloride. The deep red solution was evaporated, dissolved in chloroform, washed with dilute sodium hydroxide (x3) and with water (x3) and the solvent evaporated to give a red solid (0·9 g.). Purification by column chromatography gave 7-methoxy-8-benzyloxyisoquinoline (0·7 g.) from benzene as red needles, m.p. 185-188°. τ 0·63 (s, 1H, C-1 proton), 2·56 to 3·00 (m, 8H) 3·57 (d, 1H,

aromatic protons), 4·72 (s, 2H, CH_2), 6·13 (s, 3H, OCH_3). The picrate crystallised from ethanol as yellow needles, m.p. 189-191° (Found: C, 55·3; H, 3·9. Calc. for $C_{23}H_{18}N_4O_9$: C, 55·8; H, 3·7%).

Attempted preparation of N-benzoyl-8-benzyloxy-7-methoxy-1,2-dihydroisoquinaldonitrile.

8-Benzyloxy-7-methoxyisoquinoline (0·5 g.) was treated with potassium cyanide and benzoyl chloride in methylene chloride/water by the method previously described (p. 81). After work-up the i.r. of the product was identical with that of the starting material.

Anisoyl chloride.

Anisic acid (20 g.) on treatment with thionyl chloride in dry benzene[49] gave anisoyl chloride as a colourless glass, b.p. 96-98°/2 mm., m.p. 23° (lit.,[70] b.p. 160-164°/35 mm., 145°/14 mm., m.p. 22°). τ 2·00 (d, 2H, C-2 and C-6 protons), 3·10 (d, 2H, C-3 and C-5 protons), 6·14 (s, 3H, OCH_3); $\nu_{max.}$ 1772, 1740 (acid chloride CO), 1602 (C=C, aromatic).

N-Anisoyl-8-anisoyloxy-7-methoxy-1,2-dihydroisoquinaldonitrile.

8-Hydroxy-7-methoxyisoquinoline (0·7 g.) was treated with potassium cyanide (1·0 g.) and anisoyl chloride (1·5 ml.) in methylene chloride/water by the method previously described (p.81). Work-up gave an oily product (0·6 g.) which on addition of ethyl acetate precipitated a cream solid. Recrystallisation from ethanol/ether gave 8-anisoyloxy-7-methoxyisoquinoline

(0·2 g.) as cream needles, m.p. 204-206° (Found: C, 69·9; H, 5·1; N, 5·1. $C_{18}H_{15}NO_4$ requires C, 69·9; H, 4·9; N, 4·5%). n.m.r. $CD_3COOD/CDCl_3$, τ 0·25 (s, 1H, C-1 proton), 1·35 (d, 1H, C-3 proton), 1·60 to 3·0 (m, 7H, aromatic protons), 5·93 (s, 3H, C-7 OCH_3), 6·05 (s, 3H, anisoyl OCH_3); $\nu_{max.}$ 1730 cm.$^{-1}$ (CO aryl ester).

8-Anisoyloxy-7-methoxyisoquinoline (0·15 g.) was treated with potassium cyanide (0·2 g.) and anisoyl chloride (0·25 ml.) in methylene chloride/water by the previously described method (p. 81). Work-up of this reaction and of the mother liquors of the previous reaction gave N-anisoyl-8-anisoyloxy-7-methoxy-1,2-dihydroisoquinaldonitrile (0·50 g., 23%) from ethyl acetate as the mono-ethyl acetate (cream needles), m.p. 86-88° (Found: C, 66·1; H, 5·8; N, 5·4; $C_{27}H_{22}O_6N_2 \cdot C_4H_8O_2$ requires C, 66·6; H, 5·4; N, 5·0%). τ 1·63 to 3·13 (m, 10H, aromatic protons), 3·34 (q, 1H, C-3 proton), $J_{3,4}$ = 8·0 c.p.s., 3·40 (d, 1H, C-1 proton), $J_{1,3}$ = 0·8 c.p.s., 3·94 (d, 1H, C-4 proton), 5·87 (q, 2H, CH_2 of ethyl acetate), 6·06 (s, 3H, C-7 OCH_3), 6·16 (s, 6H, two OCH_3), 7·97 (s, 3H, CH_3 of acetate), 8·75 (t, 3H, CH_3 of ethyl); $\nu_{max.}$ 1745 (CO, saturated ester), 1730 (CO, aryl ester), 1665 cm.$^{-1}$ (CO, amide).

1-Anisyl-8-anisoyloxy-7-methoxyisoquinoline.

N-Anisoyl-8-anisoyloxy-7-methoxy-1,2-dihydroisoquinaldonitrile (0·44 g.) was treated with sodium hydride (0·15 g.) and anisyl chloride (0·2 g.) in

dimethylformamide (30 ml.) by the method as described on p. 88. After work-up acid extraction of the reaction mixture and separation by column chromatography gave 1-anisyl-8-anisoyloxy-7-methoxyisoquinoline (0·15 g., 45%) as cream needles from benzene, m.p. 134-138°; τ 2·18 to 3·40 (m, 12H, aromatic protons), 5·54 (s, 2H, CH_2), 6·25 (s, 6H, anisyl and anisoyl OCH_3), 6·28 (s, 3H, C-7 OCH_3). And also 8-anisyloxy-7-methoxyisoquinoline (approx. 30 mg.) from benzene as red needles, m.p. 165-170°; τ 0·27 (s, 1H, C-1 proton), 1·63 to 3·40 (m, 8H, aromatic protons), 4·64 (s, 2H, CH_2), 6·20 (s, 6H, two OCH_3).

1-Anisyl-8-hydroxy-7-methoxyisoquinoline.

1-Anisyl-8-anisoyloxy-7-methoxyisoquinoline (0·15 g.) in ethanol (35 ml.) was refluxed for 2 hours with sodium hydroxide (10 g.) in water (20 ml.). Removal of the ethanol, neutralisation and extraction with chloroform gave 1-anisyl-8-hydroxy-7-methoxyisoquinoline (90 mg., 88%) from ethanol as cream needles, m.p. 195-197° (Found: C, 72·8; H, 6·4; N, 5·0. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7%). n.m.r. in $CD_3COOD/CDCl_3$, τ 1·80 to 3·14 (m, 8H, aromatic protons), 5·34 (s, 2H, CH_2), 6·10 (s, 3H, C-7 OCH_3), 6·17 (s, 3H, anisyl OCH_3).

Petaline iodide.

1-Anisyl-8-hydroxy-7-methoxyisoquinoline (70 mg.) was converted to its methiodide (0·11 g.) by refluxing with methyl iodide in methanol. Reduction of the methiodide (0·11 g.) in methanol with sodium borohydride[54]

gave 1-anisyl-8-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (50 mg.) as a colourless oil which could not be induced to crystallise. The tetrahydroisoquinoline was converted with methyl iodide in methanol[54] to its methiodide, racemic petaline iodide, obtained as an oil. Purification by column chromatography gave the methiodide as a pale yellow solid (15 mg.) (Found: N, 2·7. $C_{20}H_{26}O_3NI$ requires N, 3·1%). Recrystallisation from acetone gave the hemiacetonate, m.p. 133-137° (lit.,[18] 134-138°). I.r. (nujol mull) was identical with a sample prepared from natural petaline (see following experiment). Rf (EtOH) 0·64 on silica gel thin layer plate.

Petaline iodide from natural petaline reineckate.

Petaline reineckate[68] (15 mg.) in acetone was titrated with silver sulphate solution and then with barium iodide solution to give natural petaline iodide (10 mg.), m.p. 140-143°. I.r. (nujol mull) identical with the racemic petaline iodide prepared in the previous experiment. Rf (EtOH) 0·64 on silica gel thin layer plate.

Hofmann degradation of racemic petaline iodide.

The racemic petaline iodide (10 mg.) in methanol was eluted through a Permutit "De-Acidite" FF anionic exchange column (water regain 0·6-1·0, OH form) to give the methine, N,N-dimethyl-[3-hydroxy-4-methoxy-2-(p-methoxy styryl)-phenyl]-ethylamine, m.p. 119-121° (lit.,[15] 119-120°) (Found: N, 4·2. $C_{20}H_{25}NO_3$ requires

N, 4·3%). The Rf values of our sample and the authentic sample were identical (0·28 in 1:1 $CHCl_3$/EtOH on t.l.c.). A deep purple colouration was obtained with ferric chloride in methanol.

7. Reactions of 3-Methylisoquinoline.

N-Benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile.

3-Methylisoquinoline (10 g.) gave on treatment with potassium cyanide and benzoyl chloride in dichloromethane/water (as described on p. 81) N-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile (14·9 g., 78%) from ethyl acetate as cream rhombs, m.p. 134-135° (Found: C, 78·8; H, 5·6; N, 10·2. $C_{18}H_{14}N_2O$ requires C, 78·8; H, 5·2; N, 10·2%). τ 2·66 (m, 9H, aromatic protons), 3·50 (s, 1H, C-1 proton), 3·77 (d, 1H, C-4 proton), $J_{3Me,4H}$ = 1·5 c.p.s., 8·23 (d, 3H, CH_3); $\nu_{max.}$ 1667 (CO), 2240 cm.$^{-1}$ vw (CN).

Reaction of N-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile with benzyl chloride.

N-Benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile (5·0 g.) was treated with sodium hydride (0·88 g.) and benzyl chloride (2·32 g.) by the method as described on p. 88. Acid extraction after work-up gave 1-benzoyl-3-methylisoquinoline (1·3 g., 29%) from ether as colourless rhombs, m.p. 99-99·5° (Found: C, 82·5; H, 5·3; N, 5·6. $C_{17}H_{13}NO$ requires C, 82·6; H, 5·3; N, 5·6%). τ 1·84 to 2·75 (m, 10H, aromatic protons), 7·30 (s, 3H, CH_3); $\nu_{max.}$ 1682 cm.$^{-1}$ (CO).

TABLE VI

Summary of Reactions of 3-Methyl-

Isoquinoline Reissert Compounds

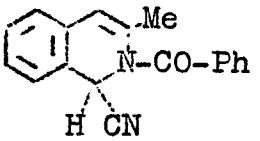
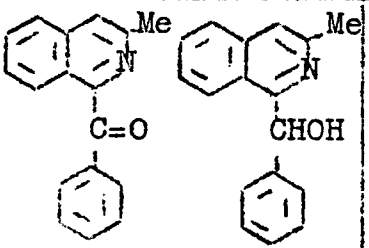
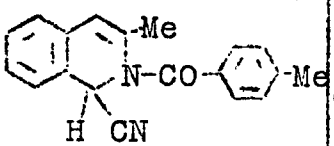
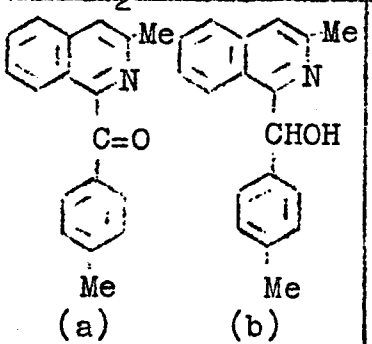
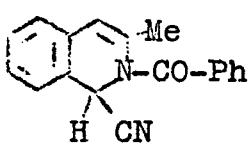
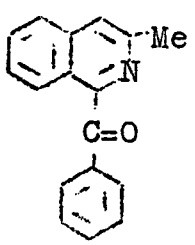
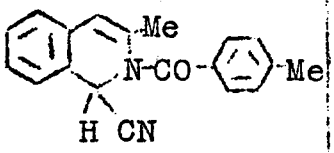
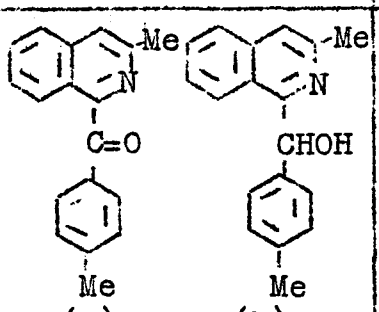
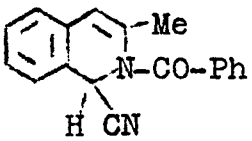
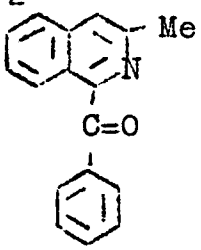
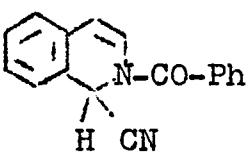
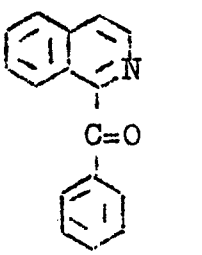
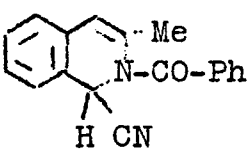
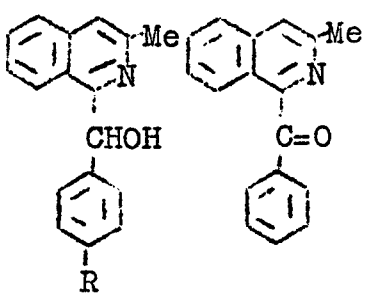
Reissert Compound	Halide etc.	Products	Yield %
	benzyl chloride	 (a) (b) (a) on acid extraction (b) on acid extraction after reflux with EtOH/ $NaOH/H_2O$	(a) 29 (b) 51 (no substitution product)
	benzyl chloride	 (a) (b) (a) on acid extraction (b) on acid extraction after reflux with EtOH/ $NaOH/H_2O$	(a) 12·5 (b) 52 (no substitution product)
	none	 on acid extraction	78

TABLE VI-Continued

Reissert Compound	Halide etc.	Products	Yield %
	none	 (a) (b) (a+b) on acid extraction (b) on acid extraction after reflux with EtOH/$NaOH/H_2O$	(a+b) 17 (b) 49
	none		90
	none		60
	p-tolu-aldehyde	 (a) (b) rearrangement R=H addition R=Me	(a) R=H 51 R=Me 25 (b) 2

After hydrolysis in ethanol (100 ml.) with sodium hydroxide (50 g.) in water (50 ml.) followed by acid extraction, the work-up gave phenyl-1-(3-methyl-isoquinolyl) carbinol (2·3 g., 51%). Recrystallisation from ether gave the carbinol as colourless stars, m.p. 104-104·5° (Found: C, 81·6; H, 6·7; N, 5·2. $C_{17}H_{15}NO$ requires C, 81·9; H, 6·1; N, 5·6%). τ 2·04 to 2·86 (m, 10 H, aromatic protons), 3·70 (s, 2H, CHOH group, addition of CD_3COOD/D_2O contracts to 3·62, s, 1H, CH), 7·27 (s, 3H, CH_3); $\nu_{max.}$ 3190 $cm.^{-1}$ (OH). The picrate crystallised from ethanol as yellow needles, m.p. 180-181° (Found: C, 57·7; H, 4·0; N, 11·7. $C_{23}H_{18}N_4O_8$ requires C, 57·7; H, 3·8; N, 11·7%).

p-Toluoyl chloride.

p-Toluic acid (30 g.) on treatment with thionyl chloride (45 ml.)[142] gave p-toluoyl chloride (26·2 g., 78%) as a colourless liquid, b.p. 218-220° (lit.,[70] 214-216°).

N-p-Toluoyl-3-methyl-1,2-dihydroisoquinaldonitrile.

3-Methylisoquinoline (5 g.) gave on treatment with potassium cyanide (6 g.) and p-toluoyl chloride (9 ml.) in dichloromethane/water (as described on p. 81) N-p-toluoyl-3-methyl-1,2-dihydroisoquinaldonitrile (5·9 g., 59%) from ethyl acetate as colourless needles, m.p. 126-126·5° (Found: C, 78·9; H, 6·3; N, 9·5. $C_{19}H_{16}N_2O$ requires C, 79·1; H, 5·6; N, 9·7%). τ 2·67 (q, 4H, toluoyl group), 2·72 (m, 4H, aromatic protons), 3·50 (s, 1H, C-1 proton), 3·67 (d, 1H, C-4 proton),

$J_{3Me,4H}$ = 1·5 c.p.s., 7·61 (s, 3H, CH_3 of toluoyl group), 8·19 (d, 3H, C-3 CH_3); $\nu_{max.}$ 1667 (CO), 2240 cm.$^{-1}$ vw (CN).

Reaction of N-p-toluoyl-3-methyl-1,2-dihydroisoquinaldonitrile with benzyl chloride.

N-p-toluoyl-3-methyl-1,2-dihydroisoquinaldonitrile (3 g.) was treated with sodium hydride (0·53 g.) and benzyl chloride (1·4 g.) by the method as described on p. 88.

Acid extraction after work-up gave an oil (0·5 g.). The n.m.r. spectrum showed that the oil was a mixture of 3-methylisoquinoline (30%) and 3-methyl-1-(p-toluoyl)isoquinoline (70%). $\nu_{max.}$ 1680 cm.$^{-1}$ (CO).

From the hydrolysed fraction was obtained p-tolyl-1-(3-methylisoquinolyl) carbinol (1·3 g., 53%). Recrystallisation from ether gave colourless needles, m.p. 102-103° (Found: C, 81·7; H, 6·4; N, 5·3. $C_{18}H_{17}NO$ requires C, 82·1; H, 6·5; N, 5·3%). τ 2·03 to 3·03 (m, 9H, aromatic protons), 3·71 (s, 1H, CH of CHOH group), 3·92 (bs, 1H, OH, disappears on addition of CD_3COOD/D_2O), 7·26 (s, 3H, C-3 CH_3), 7·76 (s, 3H, tolyl CH_3); $\nu_{max.}$ 3320 cm.$^{-1}$ (OH).

Rearrangement of N-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile.

N-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile (5·0 g.) was treated with sodium hydride (0·88 g.) by the method as described on p. 88. Acid extraction after work-up gave 1-benzoyl-3-methylisoquinoline (4·5 g.,

97·5%). Purification by column chromatography and recrystallisation from ether gave 1-benzoyl-3-methylisoquinoline (3·5 g., 78%), m.p. 99-99·5°; identical (mixed m.p., n.m.r. and i.r. spectra) with a sample previously prepared (p. 107).

Rearrangement of N-p-toluoyl-3-methyl-1,2-dihydroisoquinaldonitrile.

N-p-toluoyl-3-methyl-1,2-dihydroisoquinaldonitrile (1·8 g.) was treated with sodium hydride (0·31 g.) by the method as described on p. 88.

Acid extraction after work-up gave a mixture of an oil (0·3 g.); $\nu_{max.}$ 3320 cm.$^{-1}$ (OH), 1680 cm.$^{-1}$ (CO).

From the base hydrolysed fraction was obtained p-tolyl-1-(3-methylisoquinolyl) carbinol (0·85 g., 49%). Recrystallisation from ether gave colourless needles, m.p. 101-102°; identical (mixed m.p., n.m.r. and i.r. spectra) with a sample previously prepared (p. 111).

Reduction of 1-benzoyl-3-methylisoquinoline with sodium borohydride.

1-Benzoyl-3-methylisoquinoline (0·5 g.) was reduced in methanol (30 ml.) with sodium borohydride (0·08 g.).[54] Recrystallisation from ether gave phenyl-1-(3-methylisoquinolyl) carbinol (0·41 g., 81%) as colourless stars, m.p. 102-104°; identical (mixed m.p. and i.r. spectrum) with a sample prepared previously (p. 107).

Oxidation of phenyl-1-(3-methylisoquinolyl) carbinol.

Phenyl-1-(3-methylisoquinolyl) carbinol (200 mg.)

was oxidised in glacial acetic acid (15 ml.) with sodium dichromate (0·24 g.).[87] Recrystallisation from ether gave 1-benzoyl-3-methylisoquinoline (108 mg.,55%) as colourless rhombs, m.p. 94-96°; identical (mixed m.p. and i.r. spectrum) with a sample prepared previously (p. 107).

Attempted reduction of 1-benzoyl-3-methylisoquinoline with sodium hydride.

1-Benzoyl-3-methylisoquinoline (300 mg.) in dimethylformamide (10 ml.) was added to a stirred suspension of sodium hydride (60 mg.) in dimethylformamide (20 ml.), under nitrogen at room temperature. After 4 hours, ethanol was added to destroy the sodium hydride, evaporated and the residue partitioned between benzene and water. The benzene layer was washed with water, extracted with acid, the extract basified, extracted with chloroform and dried (K_2CO_3) to give 1-benzoyl-3-methylisoquinoline; identical (i.r. spectrum) with starting material.

Reduction of 1-benzoyl-3-methylisoquinoline in ethanol with aqueous sodium hydroxide.

1-Benzoyl-3-methylisoquinoline (350 mg.) in ethanol (200 ml.) was refluxed with sodium hydroxide (50 g.) in water (50 ml.) for 7 hours. Ethanol was removed and the product extracted with benzene, dried (K_2CO_3) and evaporated to phenyl-1-(3-methylisoquinolyl) carbinol. Recrystallisation from ether gave colourless stars (300 mg., 85%), m.p. 103-104°; identical (mixed

m.p. and i.r. spectrum) with a sample prepared previously (p. 107).

Rearrangement of N-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile.

N-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile (1 g.) was treated with sodium hydride (0·08 g.) by the method as described on p. 88. Excess sodium hydride was destroyed with ethanol and evaporation gave a solid. (Not separated between benzene and water and then acid extracted-see p. 111.) Recrystallisation from ether gave 1-benzoyl-3-methylisoquinoline (0·8 g., 90%) as colourless rhombs, m.p. 98-99°; identical (mixed m.p., n.m.r. and i.r. spectra) with a sample previously prepared (p. 107).

Rearrangement of N-benzoyl-1,2-dihydroisoquinaldonitrile.

N-Benzoyl-1,2-dihydroisoquinaldonitrile (3 g.) was treated with sodium hydride (0·6 g.) by the method as described on p. 88. Excess sodium hydride was destroyed with ethanol and evaporation gave an oil. Column chromatography and recrystallisation from ether gave 1-benzoylisoquinoline (1·6 g., 60%) as cream needles, m.p. 74-76° (lit.,[8] m.p. 76-77°). τ 1·40 (q, 1H, C-3 proton) 1·70 to 2·73 (m, 10H, aromatic protons); $\nu_{max.}$ 1680 cm.$^{-1}$ (CO).

Reaction of N-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile with p-tolualdehyde.

N-Benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile (1 g.) was treated with sodium hydride (0·18 g.) and

p-tolualdehyde (1·0 g.) by the same method as described on p. 88 (when a benzyl halide replaced the aldehyde).

Acid extraction gave an oil (0·2 g.); τ 2·07 to 3·06 (m, 20 squares, aromatic protons), 3·74 (s, 4 squares, CHOH, CD_3COOD/D_2O goes to 3·64, s, 2 squares, CH), 7·32 (s, $6\frac{1}{2}$ squares, C-3 CH_3), 7·81 (s, $5\frac{3}{4}$ squares, tolyl CH_3). This showed the oil to be a mixture of p-tolyl-1-(3-methylisoquinolyl) carbinol (90%) and 1-benzoyl-3-methylisoquinoline (10%).

From the base hydrolysed fraction was obtained an oil (0·65 g.); τ 2·06 to 2·90 (m, 10H, aromatic protons), 3·71 (s, 2H, CHOH, addition of CD_3COOD/D_2O goes to 3·68, s, 1H, CH), 7·30 (s, 3H, C-3 CH_3 group), 7·37 (s, tolyl CH_3-integral indicates 12%). This showed the oil to be a mixture of phenyl-1-(3-methylisoquinolyl) carbinol (88%) and p-tolyl-1-(3-methylisoquinolyl) carbinol (12%).

1-Benzoyl-3-methylisoquinoline (2%), phenyl-1-(3-methylisoquinolyl) carbinol (51%) and p-tolyl-1-(3-methylisoquinolyl) carbinol (25%) was thus obtained from the two fractions.

8. Reduction Studies.

Reduction of diaryl ketones with sodium hydroxide/ethanol/water. General method.

The diaryl ketone (1 g.) in ethyl alcohol (200 ml.) was refluxed with sodium hydroxide (50 g.) in water (50 ml.). The ethanol was removed and the

product partitioned between water and chloroform. The chloroform extract was dried (K_2CO_3) and evaporated to give the carbinol. This was purified by column chromatography and recrystallisation. The results are shown in table VII.

Reduction of benzophenone with sodium ethoxide.

Benzophenone (1 g.) in ethanol (100 ml.) was refluxed with sodium ethoxide (prepared from sodium (4 g.) in anhydrous ethanol (50 ml.)) for 3½ hours. After removal of the solvent, water was added. The aqueous solution was extracted with chloroform, dried (K_2CO_3) and evaporated. Column chromatography and recrystallisation from petroleum ether (40-60°) gave benzhydrol (0·95 g., 94%) as colourless silky needles, m.p. 68-69° (lit.,[70] 69°). $\nu_{max.}$ 3340 cm.$^{-1}$ (OH).

Attempted reduction of benzophenone with tetrahydrofuran as solvent.

Benzophenone (1·g.) in tetrahydrofuran (200 ml.) was refluxed with sodium hydroxide (50 g.) in water (50 ml.) for 3½ hours. Work-up, as in reduction with sodium hydroxide/ethanol/water (p. 115), gave benzophenone; identical (mixed m.p. and i.r. spectrum) with starting material.

Attempted reduction of xanthone with sodium ethoxide.

Xanthone (1 g.) was treated as was benzophenone (see above). The product was identical (i.r. spectrum and m.p.) with starting material.

TABLE VII

Reduction of Diaryl Ketones with Sodium Hydroxide/Ethanol/Water

Ketone	Product	Time of Reflux (Hours)	Yield %	m.p. of Product	$\nu_{max.}$ (OH) $cm.^{-1}$
1-Benzoylisoquinoline	Phenyl-1-isoquinolyl carbinol[a]	7	85	106-108° b,c	3350
Benzophenone	Benzhydrol[d]	3½	86	66-67° e,f	3300
Fluorenone[g]	Fluorenol	5	79	152-153° b,h	3450
Benzoin[g]	Mesohydrobenzoin[i]	3½	79	133-134° j,k	3350
Xanthone		4	0		
1-Benzoylnapthalene	Phenyl-1-napthyl carbinol	4	78	84-86° b,l	3450
Chalkone	Phenyl styryl carbinol[m]	4 8	84 89	56-58° b,n	3350
p-Benzoquinone		4	0		
Anthraquinone		4	0		

Key to Table VII.

a: τ 1·46 (d,1H, C-3 proton), 1·93 to 2·84 (10H, aromatic protons), 3·63 (s, 2H, CHOH, addition of $CD_3COOD/CDCl_3$ contracts to 3·60, s, 1H, CH).

b: Recrystallised from ether.

c: Lit., m.p. 106°,[143] 108-109·5°.[10]

d: 3:5 Dinitrobenzoate m.p. 139-140°, lit.,[70] m.p.142°.

e: Recrystallised from 40-60° petroleum ether.

f: Lit.,[70] m.p. 69°.

g: Nitrogen passed over refluxing mixture and into 2,4-dinitrophenylhydrazine reagent, acetaldehyde 2,4-dinitrophenylhydrazone crystallised from ethanol, m.p. 144-146° (lit.,[70] 147°); identical (mixed m.p.) with an authentic sample.

h: Lit.,[70] m.p. 153°.

i: Dibenzoate m.p. 240-242°, lit.,[70] m.p. 247°.

j: Recrystallised from benzene.

k: Lit.,[70] m.p. 139°.

l: Lit.,[139] m.p. 85-86°.

m: $\simeq$ 2·3 to 3·4 (m, 12H, aromatic and CH=CH protons), 5·65 (s, 1H, CH), 5·92 (bs, 1H, OH; addition of CD_3COOD/D_2O disappears).

n: Lit.,[139] m.p. 58-59°.

9. Reactions of 4-Bromoisoquinoline.

N-Benzoyl-4-bromo-1,2-dihydroisoquinaldonitrile.

4-Bromoisoquinoline (10·0 g.) gave on treatment with potassium cyanide (9·4 g.) and benzoyl chloride (10·8 ml.) in dichloromethane/water (as described on p. 81) N-benzoyl-4-bromo-1,2-dihydroisoquinaldonitrile (4·4 g., 27%) from ethyl acetate as cream rhombs, m.p. 172-173° (lit.,[32] m.p. 173°) (Found: C, 60·4; H, 3·2; N, 8·2. Calc. for $C_{17}H_{11}N_2OBr$: C, 60·2; H, 3·3; N,

8·3%). τ 2·20 to 2·85 (m, 9H, aromatic protons), 3·00 (d, 1H, C-3 proton), $J_{1,3}$ = 0·9 c.p.s., 3·44 (d, 1H, C-1 proton); $\nu_{max.}$ 1665 (CO), 1625, 1605 cm.$^{-1}$ (C=C); $\lambda_{max.}$ 208, 231, 310 mμ (ε16,500, 18,000 and 10,300); the mass spectrum is shown in figure III.

Reaction of N-benzoyl-4-bromo-1,2-dihydroisoquinaldonitrile with benzyl chloride.

Experiment a

N-Benzoyl-4-bromo-1,2-dihydroisoquinaldonitrile (1·5 g.) was treated with sodium hydride (0·22 g.) and benzyl chloride (0·57 g.) by the method as described on p. 88. After addition of ethanol and removal of the solvents, the reaction mixture was partitioned between benzene and water. The benzene solution was washed with water and evaporated to give a solid. This was recrystallised from ethyl acetate as fine cream needles, m.p. 245-246° (Found: C, 63·4; H, 3·0; N, 11·7; Br, 22·2. $C_{19}H_{10}N_3Br$ requires C, 63·4; H, 2·8; N, 11·7; Br, 22·2%). τ, 1·05 to 2·50 (m, 10H); $\nu_{max.}$ 2240 (CN), 1620 cm.$^{-1}$ (C=C); $\lambda_{max.}$ 218, 283, 294 and 334 mμ (ε 116,000, 9,500, 10,000 and 16,000); the mass spectrum is shown in figure IV; Rf ($CHCl_3$) 0·28 on t.l.c.

Experiment b

N-Benzoyl-4-bromo-1,2-dihydroisoquinaldonitrile (2·5 g.) was treated with sodium hydride (1 g.) and benzyl chloride (1 ml.) as described in the previous experiment (a). Acid extraction after work-up gave an oil. T.l.c. in chloroform gave two spots, the minor

FIGURE III

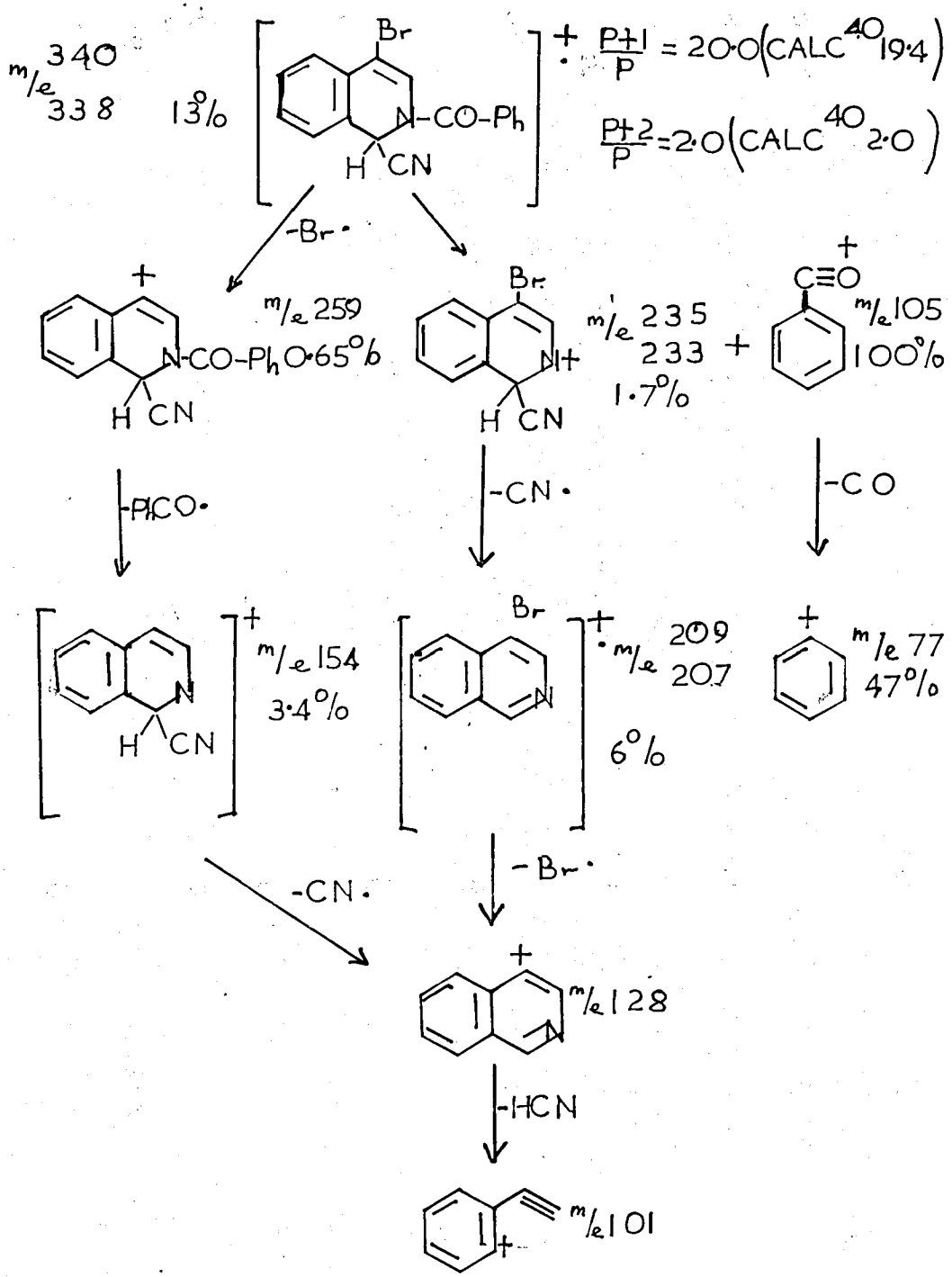
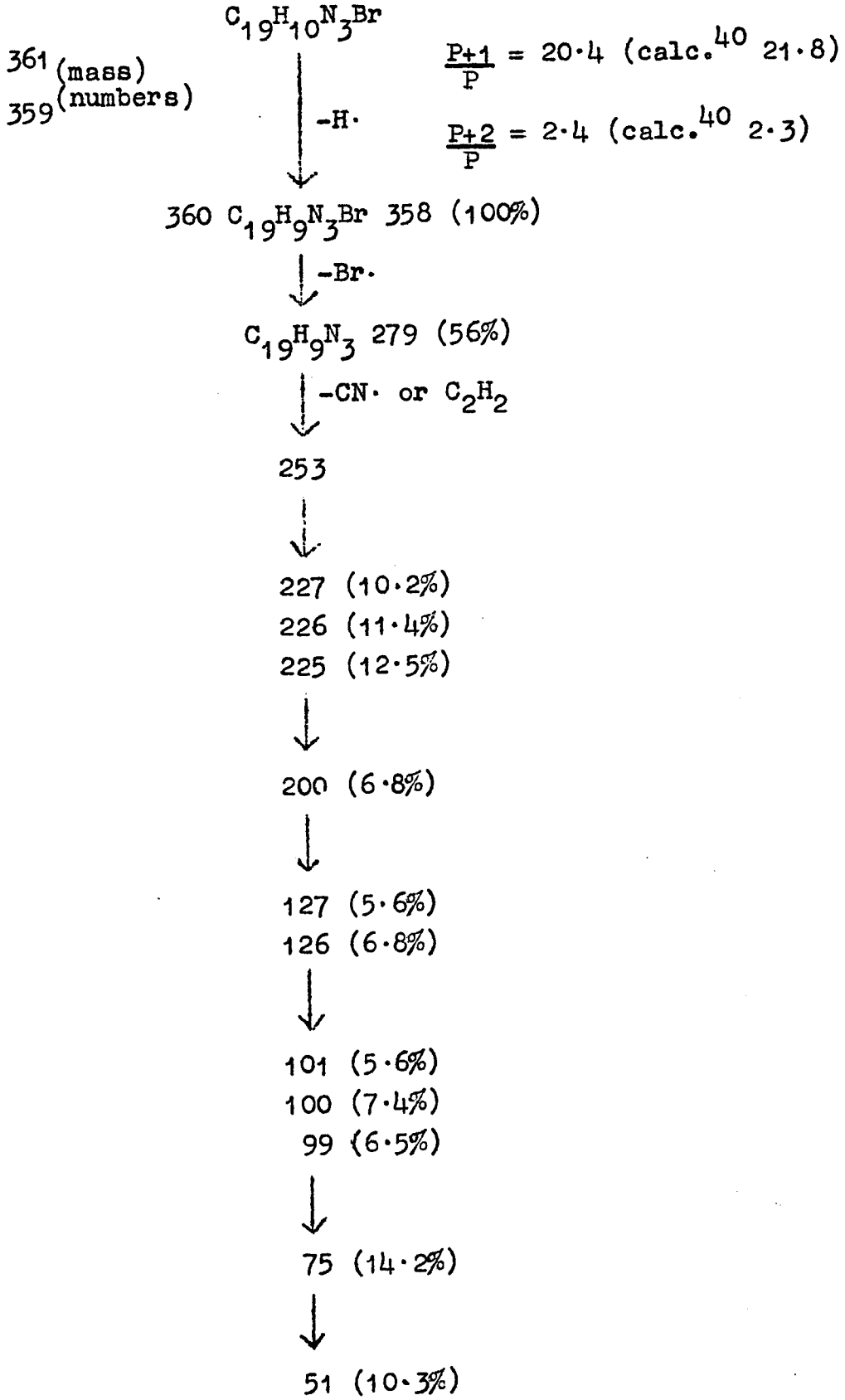

m/e 340
m/e 338
13%
Br
N-CO-Ph
H CN
P+1/P = 20·0 (CALC 40 19·4)
P+2/P = 2·0 (CALC 40 2·0)
-Br·
m/e 259
N-CO-Ph 0·65%
H CN
m/e 235
233
1·7%
Br
C≡O
m/e 105
100%
-PhCO·
-CN·
-CO
m/e 154
3·4%
m/e 209
207
6%
m/e 77
47%
-CN·
-Br·
m/e 128
-HCN
m/e 101

FIGURE IV


$C_{19}H_{10}N_3Br$
361 (mass)
359 (numbers)
$\frac{P+1}{P}$ = 20·4 (calc.^{40} 21·8)
$\frac{P+2}{P}$ = 2·4 (calc.^{40} 2·3)
-H·
360 $C_{19}H_9N_3Br$ 358 (100%)
-Br·
$C_{19}H_9N_3$ 279 (56%)
-CN· or C_2H_2
253
227 (10·2%)
226 (11·4%)
225 (12·5%)
200 (6·8%)
127 (5·6%)
126 (6·8%)
101 (5·6%)
100 (7·4%)
99 (6·5%)
75 (14·2%)
51 (10·3%)

one having Rf 0·28, coincident with that for the compound, m.p. 245-246°, obtained in experiment (a).

Column chromatography gave 1-benzyl-4-bromoisoquinoline (0·9 g., 41%) as an oil; τ 1·41 (s, 1H, C-3 proton), 1·9 to 3·1 (m, 9H, aromatic protons), 5·38 (s, 2H, CH_2). The picrate crystallised as yellow needles from ethanol, m.p. 253-255° (Found: N, 10·1. $C_{22}H_{15}N_4O_7Br$ requires N, 10·6%).

The acid insoluble fraction on work-up gave an oil. T.l.c. of this showed it was mainly N-benzoyl-4-bromoisoquinaldonitrile.

Rearrangement of N-benzoyl-4-bromo-1,2-dihydroisoquinaldonitrile.

N-Benzoyl-4-bromo-1,2-dihydroisoquinaldonitrile (3 g.) was treated with sodium hydride (0·5 g.) in dimethylformamide (55 ml.), (in the absence of benzyl halide), by the method as described on p. 88. After work-up and separation between benzene and water, the benzene layer was dried (K_2CO_3) and evaporated to give the crude product (1·7 g.). Column chromatography gave 1-benzoyl-4-bromoisoquinoline (0·9 g., 33%) as colourless plates from ether, m.p. 136-137°; τ 1·11 (s, 1H, C-3 proton), 1·5 to 2·75 (m, 9H, aromatic protons); $\nu_{max.}$ 1680 cm.$^{-1}$ (CO). The picrate crystallised from ethanol as yellow rhombs, m.p. 166-167° (Found: C, 48·9; H, 2·6; N, 10·5. $C_{22}H_{13}N_4O_8Br$ requires C, 48·8; H, 2·4; N, 10·4%).

A second fraction (0·4 g.) was obtained from

column chromatography. T.l.c. in chloroform indicated it to be a mixture of N-benzoyl-4-bromoisoquinaldonitrile (Rf = 0·585) and the compound, m.p. 245-246° (Rf = 0·28) obtained in experiment (a) (p. 119).

10. Spectra of Reissert Compounds.

(a) Nuclear Magnetic Resonance.

General.

Data on the Reissert compounds are included with the experimental details as prepared. A summary of relevant τ values appears in table IV on p. 67.

N-Benzoyl-1-deutero-1,2-dihydroisoquinaldonitrile.

N-Benzoyl-1,2-dihydroisoquinaldonitrile (0·3 g.) in dimethylformamide (5 ml.) was added to sodium hydride (0·2 g.) in dimethylformamide (10 ml.) at 0°. After 1 minute deuterium oxide (2 ml.) was then added and after a further two minutes the mixture was neutralised with carbon dioxide.[114] Removal of the solvent gave a residue which was dissolved in benzene, washed with water and then acid, dried (K_2CO_3) and evaporated to give a solid. This was recrystallised from ethyl acetate to give the N-benzoyl-1-deutero-1,2-dihydroisoquinaldonitrile (0·2 g.), m.p. 119-121°; τ 2·1 to 2·7 (m, 9H, aromatic protons), 3·36 (d, 1H, C-3 proton), $J_{3,4}$ = 8 c.p.s., 3·95 (d, 1H, C-4 proton). There was no absorption corresponding to the C-1 proton (at 3·42 τ) showing that 100% incorporation of deuterium had occurred.

Variable temperature n.m.r.

The variation with temperature of the C-1 proton signal of isoquinoline Reissert compound is shown in table VIII.

TABLE VIII

Variable Temperature N.m.r.

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 Mc./sec.).	
	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 tetramethylsilane.

(b) Infrared Spectra.

General.

Data on the Reissert compounds are included with experimental details, as prepared.

N-Methyl-1,2-dihydroisoquinaldonitrile.

Potassium cyanide (12 g.) in water (50 ml.) was added to isoquinoline methiodide (10g.) in water (80 ml.). The mixture was vigorously stirred for half an hour, a white solid precipitating out. This was filtered off and recrystallised from ethyl acetate to give N-methyl-1,2-dihydroisoquinaldonitrile (3·9 g., 58%) as colourless plates, m.p. 93-94° (Found: C, 77·4; H, 6·2; N, 16·2. $C_{11}H_{10}N_2$ requires C, 77·6; H, 5·9; N, 16·5%). τ 2·7 to 3·1 (m, 4H, aromatic protons), 3·96 (q, 1H, C-3 proton), $J_{3,4}$ = 8 c.p.s., $J_{1,3}$ = 0·8 c.p.s., 4·36 (d, 1H, C-4 proton), 4·82 (d, 1H, C-4 proton), 7·13 (s, 3H, CH_3). $\nu_{max.}$ 2230 w (CN), 1630 $cm.^{-1}$ (C=C).

Variable temperature infrared spectra with N-benzoyl-1,2-dihydroisoquinaldonitrile.

These studies were carried out on the Unicam S.P. 100 spectrometer, using the R.I.I.C. variable temperature unit with a silver chloride cell. The temperature was measured with a thermocouple and potentiometer (which was previously calibrated).

A diagram of the relevant changes in the spectrum is shown in Figure II, after p. 76.

ΔH measurements can be calculated by[130]:-

$$\Delta H = \frac{T_1 T_2}{T_1 - T_2} R \ln \frac{A_1^1 A_2^2}{A_2^1 A_1^2}$$

where T_1 and T_2 are the temperatures and

A_1^1 = area of peak 1 at T_1

A_1^2 = " " " 1 " T_2

A_2^1 = " " " 2 " T_1

A_2^2 = " " " 2 " T_2

(a) Using nujol as solvent.

$T_1 = 85^\circ$ $\quad$ $T_2 = 65^\circ$

$A_1^1 = 33$ $\quad$ $A_2^1 = 108$

$A_1^2 = 7$ $\quad$ $A_2^2 = 112$

$\Delta H = 22{\cdot}4$ Kcal./mole

(b) Using tetrachloroethylene as solvent.

$T_1 = 77^\circ$ $\quad$ $T_2 = 55^\circ$

$A_1^1 = 152$ $\quad$ $A_2^1 = 1100$

$A_1^2 = 42$ $\quad$ $A_2^2 = 3380$

$\Delta H = 24{\cdot}2$ Kcal./mole

(c) Using carbon tetrachloride as solvent.

$T_1 = 77^\circ$ $\quad$ $T_2 = 55^\circ$

$A_1^1 = 72$ $\quad$ $A_2^1 = 440$

$A_1^2 = 53$ $\quad$ $A_2^2 = 1820$

$$\Delta H = 18 \text{ Kcal./mole}$$

Accuracy was estimated at $\pm$ 4 Kcal./mole.

Average value $\Delta H = 21 \pm 4$ Kcal./mole.

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