ISOQUINOLINES

PART TWO

This is the thirty-eighth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

ARNOLD WEISSBERGER, *Founding Editor*

ISOQUINOLINES.

PART TWO

Edited by

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Gary M. Coppola
Herbert F. Schuster

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To my brother Rick
—G.M.C.

To Didi, Oliver, and Rene
—F.G.K.

To my wife, Maro
my daughter, Kristiana
my son, Stefan
—H.F.S.

The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of chemistry. The diversity of synthetic methods utilized in this field, coupled with the immense physiological and industrial significance of heterocycles, combine to make the general heterocyclic arena of central importance to organic chemistry.

The Chemistry of Heterocyclic Compounds. published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has dealt with syntheses, reactions, properties, structure, physical chemistry and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance which impinge on almost all aspects of modern organic and medicinal chemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry*, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction creates as many problems as it solves, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry*, and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

EDWARD C. TAYLOR

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Preface

A large number of alkaloids and other natural products carry the isoquinoline skeleton. These natural products provide the basis for many intensive efforts towards the development of new and useful therapeutic agents. As indicated in the preface of *Isoquinolines: Part One* the purpose of the books on isoquinolines is dual: an introduction for the beginner interested in the general chemistry of isoquinolines and a source of detailed data for the frequent user.

Since the publication of Part One of the isoquinoline series in 1981, unfortunate factors delayed publication of the intended Parts Two, Three, and Four, which were originally targeted for the early 1980s. Because of the delay, the chapters in Part Two differ from the projected ones indicated in the contents of *Isoquinolines: Part One.*

We made a commitment in 1987 to see that the subsequent *Isoquinolines* volumes were published as soon as possible. This volume is the result of the work of authors who have been prompt in responding to our call to update their chapters.

The present volume gives details of the chemistry of the following isoquinoline derivatives: Halogenated and metallated isoquinolines and their hydrogenated derivatives; isoquinoline carboxylic acids and their hydrogenated derivatives; isoquinolines containing basic functions at the ring and their hydrogenated derivatives; and isoquinolines containing oxidized nitrogen functions and their hydrogenated derivatives. We wish to acknowledge our gratitude and appreciation for the efforts of the authors who contributed to this volume, thus making possible the expeditious publication of this book.

Many thanks are also given to the staff members of the library of Sandoz Research Institute for their much-needed help. Joyce Birch and Ellen Brennan have our appreciation and gratitude for their secretarial services. We also wish to acknowledge the silent support of our family members during the hours spent on editorial tasks.

F. G. KATHAWALA
GARY M. COPPOLA
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Sandoz Research Institute
East Hanover, New Jersey
May 1989

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ISOQUINOLINES

PART TWO

This is the thirty-eighth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

Chemistry of Heterocyclic Compounds, Volume 38
Edited by F. G. Kathawala, Gary M. Coppola, Herbert F. Schuster

CHAPTER 1

Halogenated and Metallated Isoquinolines and Their Hydrogenated Derivatives

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I. INTRODUCTION

This chapter reviews the preparation, properties, and reactions of halogenated isoquinolines and their hydrogenated derivatives. Also included are organometallic derivatives and complexes incorporating the isoquinoline nucleus.

Many of the possible mono and poly ring-halogenated isoquinolines have been reported and even those that have not yet been prepared may be synthesized by one or more of the general synthetic routes outlined here. Interest in these classes of compounds has centered around their potential utility as starting materials for biologically active preparations or as synthons for the synthesis of polycyclic natural products containing the isoquinoline nucleus.

Side-chain halogenated isoquinolines are versatile intermediates for the synthesis of potential biologically active molecules because of the relatively higher reactivity of side-chain halogens. However, they have not been included because they do not fall strictly under the defined scope of this chapter. Quarternary derivatives are not included; however, references to *N*-oxides have been made since they constitute important starting materials for certain halogenated isoquinolines.

Much of the early literature on halogenated isoquinolines sadly lacks experimental details; the tables of halogenated derivatives, are therefore, incomplete in certain respects.

Reports on organometallic derivatives of isoquinolines appearing in the literature mostly refer to complexes of ill-defined structure and properties. Nevertheless, they are presented in the tables along with the available details on their preparation and properties.

II. RING-HALOGENATED ISOQUINOLINES

A. Methods of Synthesis

(a) *General*

The success of the reaction and the nature of the isomers obtained in the various procedures for the synthesis of halogenated isoquinolines depend on the conditions used, the nature of substituents in the ring, and the nature of the halogens. Most of the work reported in the literature pertains to the synthesis of chloro- and bromoisoquinolines and their derivatives. Relatively few fluoro- and iodoisoquinolines have been prepared and their properties studied.

Benzene-ring-substituted haloisoquinolines are prepared essentially by direct halogenations or by the Sandmeyer reaction on the corresponding amino derivatives, while pyridine-ring-substituted haloisoquinolines have been prepared by any one of the halogenation procedures. Benzene-ring-substituted haloisoquinolines may also be prepared by starting with the appropriate halophenyl derivatives and building up the isoquinoline ring system by any of the well-known isoquinoline syntheses according to Bischler–Napieralski, Pictet–Spengler, Pictet–Gams, or Pomeranz–Fritsch reactions.[1] However, since the first three of these ring closures require activated benzene rings for cyclization to take place, such methods have not generally been preferred. In addition, since most of these synthetic methods yield hydrogenated isoquinoline derivatives, a final dehydrogenation step is also needed.

(b) *Halogenation of the Isoquinoline and its Salts*

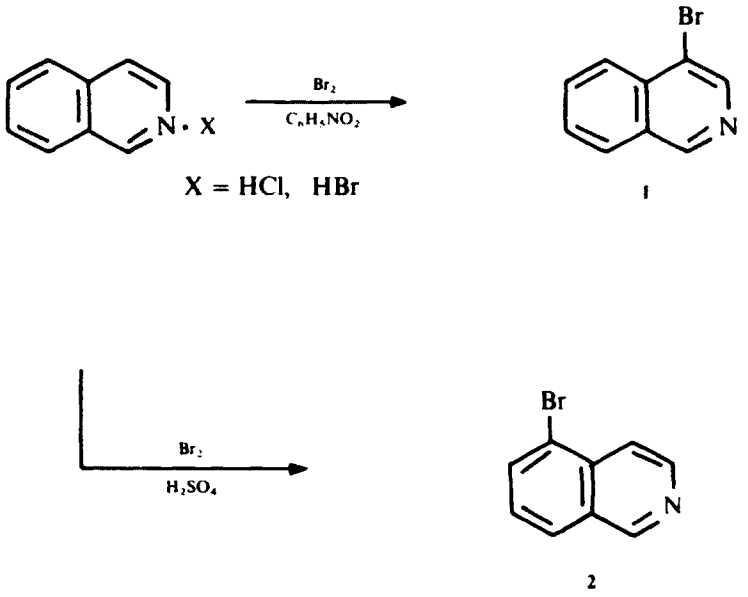
(i) Direct Halogenation

From π-electron density calculations, electrophilic substitution is predicted to take place at the 4 position of the isoquinoline nucleus.[2] However, direct halogenation of isoquinoline itself, in the absence of catalysts, does not proceed to any appreciable extent. Jansen and Wibaut[3] found that bromination at 300 °C in the gaseous phase produced no bromoisoquinoline; at 450 °C a small amount of 1-bromoisoquinoline was obtained along with some unidentified products. A recent French patent[4] describes the bromination of isoquinoline in nitrobenzene to yield the expected 4-bromoisoquinoline.

Edinger and Bossung[5] found that heating of isoquinoline dibromide or its hydrobromide or hydrochloride salt at 180–200 °C produced 4-bromoisoquinoline (**1**), besides higher brominated products.[6,7] It has been reported that a tribromoisoquinoline was obtained on warming an alcoholic solution of isoquinoline perbromide;[3] details are not available.

Bromination of the hydrobromide salt of isoquinoline at 180 °C gave a 73% yield of 4-bromoisoquinoline (**1**). More recently, Kress and Constantino[8] carried

out the reaction of isoquinoline hydrochloride in nitrobenzene with bromine at 180 °C and obtained an 81% yield of 4-bromoisoquinoline (Scheme 1).



Scheme 1

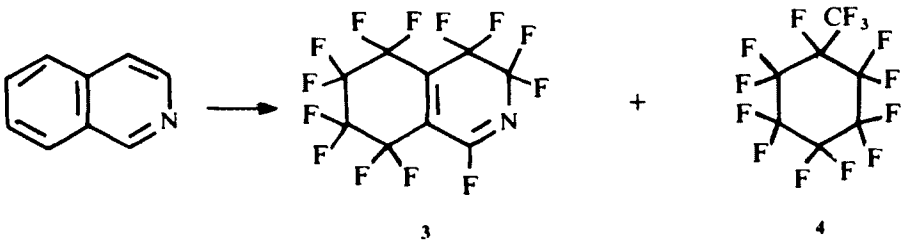
Direct bromination of isoquinoline has also been reported [9,10] in sulfur monochloride at reflux temperatures, again to yield 4-bromoisoquinolines. In all of these reactions, no attempt has been made to determine the extent of by-product formation consisting of isomeric bromo compounds or polybromo derivatives. At least in some of these cases, it does seem possible that 5-bromo derivatives are also formed.

Dewar and Maitlis[11] reported in 1957 that nitration in a strongly acid medium produced the 5-nitro derivative as the major product, indicating that the preferred electrophilic attack is at the 5 position under strongly acid conditions. Bromination in strong acid is reported to give 5-bromoisoquinoline (**2**).[10]

Iodination of isoquinoline in sulfuric acid is reported to yield both diiodo- and triiodoisoquinolines of undetermined orientation.[12] Iodination of 1,2,3,4-tetrahydroisoquinoline in sulfuric acid containing silver sulfate gave a mixture of 6-, 7-, and 8-iodo-1,2,3,4-tetrahydroisoquinolines.[13] However, iodination of isoquinoline with iodine in hydriodic acid yielded 4-iodoisoquinoline.[14]

Direct chlorination of isoquinoline in the vapor phase or through its hydrochloride salt to yield chloro derivatives has not been reported. Chlorination of isoquinoline with sulfur monochloride or sulfur dichloride is said to result in a trichloroisoquinoline as major product.[15,16] However, neither the orientation of the halogen atoms in this product nor the yield is reported.

When isoquinoline was passed over cesium tetrafluorocobaltate, a complex mixture of products was obtained, from which the perfluoroisoquinoline (3) and (4) were isolated[17] (Eq. 1).



3 4

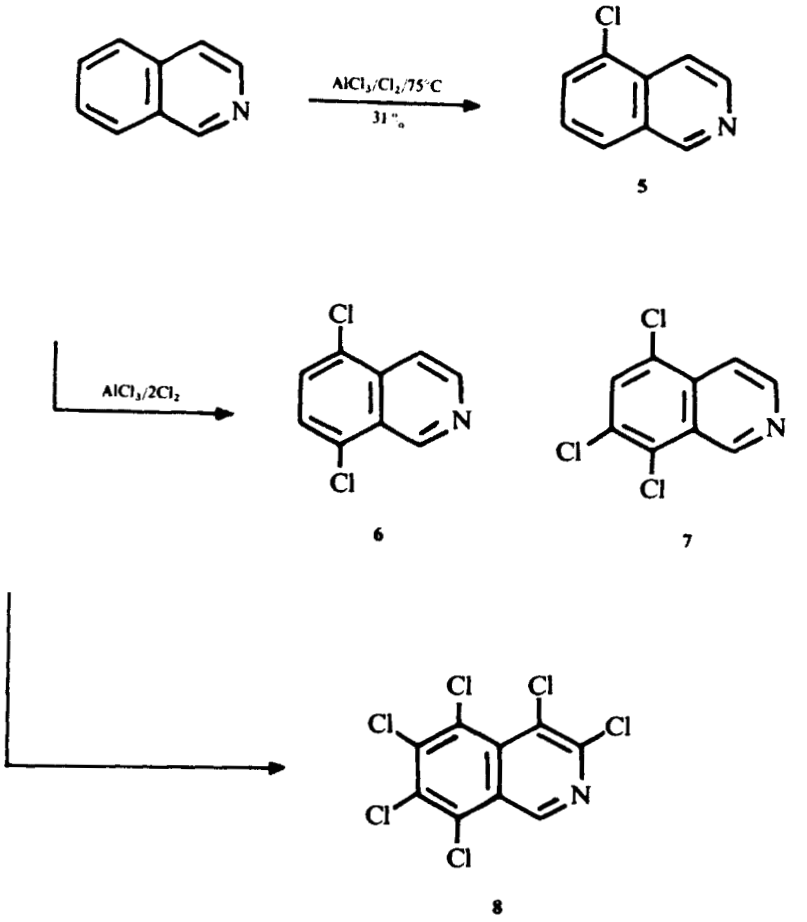
(1)

N-Methyl decahydroisoquinoline was fluorinated electrochemically to give, among other products, a mixture of *cis*- and *trans*-perfluoro derivatives.[18]

(ii) Swamping Catalyst Method

Chlorination and bromination of isoquinoline in the presence of aluminium chloride as a catalyst have been used extensively for the synthesis of chloro- and bromoisoquinolines. Halogenation of the aluminium chloride complexes of isoquinoline gave in good yields halogen derivatives substituted in the benzene ring.[19] The nature of the products and the sequence of the substitution reactions depend on the amount of halogen used, temperature, and time of reaction. Thus, chlorination at 75 °C yielded 31% of the 5-chloro isomer (**5**): with 2 eq. chlorine, 5,8-dichloro-(**6**) and further 5,7,8-trichloro derivatives (**7**) were obtained (Scheme 2). A modification of this method using a melt of isoquinoline and aluminium chloride at 105–110 °C has been employed to prepare 5,6,7,8-tetrachloroisoquinoline in low (2%) yield.[20] Similar reactions occurred with bromine; 5-bromo-, 5,8-dibromo-, 5,7,8-tribromo- and even 5,6,7,8-tetrabromoisoquinolines have been isolated. A patent[21] claimed the preparation of hexachloroisoquinoline (**8**) in 87% yield using this swamping catalyst method. Several interesting points emerge from this process. First, there is the possibility for preparing mono, di, and trihalo derivatives in a selective manner by a relay synthesis. To obtain, for example, a 5,6,8-trihalogeno derivative, it is advantageous to halogenate the 5,8-dihalo derivative, rather than direct halogenation with an excess of reagent. The orientation of the third-entering halogen in dihaloisoquinolines has led to the proposal of a canonical form, such as (**9**), as an important contributor in this reaction. The orientation of the products is consistent with the molecular orbital calculations of Dewar and Maitlis[11] for the protonated forms of isoquinoline.

Similarly, it was observed that 5,8-dibromoquinoline is converted to 5,7,8-tribromoquinoline in keeping with the canonical form (**10**) for the quinoline complex.



Scheme 2

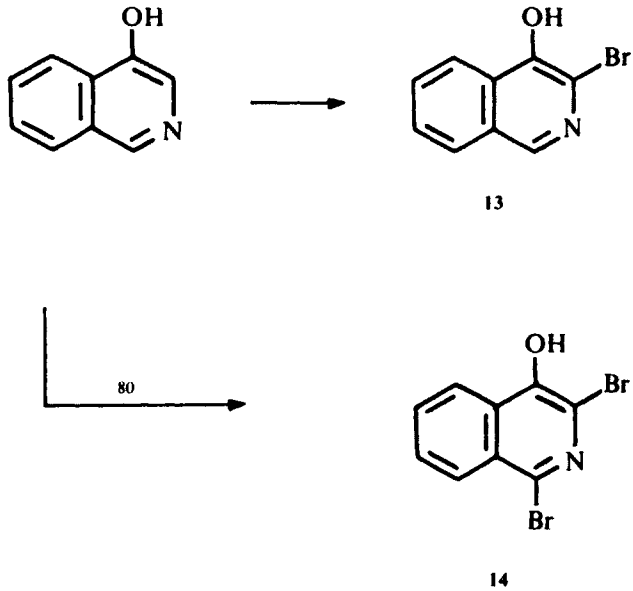
(iii) Halogenation of Activated Nucleus

Direct halogenation of isoquinolines carrying strong activating groups proceeds in moderate yields.[9,22] Thus, 7-acetamidoisoquinoline (**11**) upon chlorination gives the 7-acetamido-8-chloroisoquinoline (**12**) (Eq. 2). It is significant that such groups are capable of directing the entering substituent to the 8 position in perference to the normal 5 position.

(2)

11 **12**

4-Hydroxyisoquinoline, upon bromination in the presence of alkali at room temperature furnished[23] the 3-bromo compound (**13**) in 76% yield, whereas heating to 80 °C produced 1,3-dibromo-4-hydroxyisoquinoline (**14**) in 40% yield (Scheme 3).



Scheme 3

Bromination of alkoxy-substituted isoquinolines yielded the corresponding 8-bromo compounds.[24-27] Thus, 7-hydroxy-6-methoxyisoquinoline, on bromination with bromine in acetic acid containing sodium acetate, followed by methylation, gave **15** in 71% yield[26] (Eq. 3).

(3)

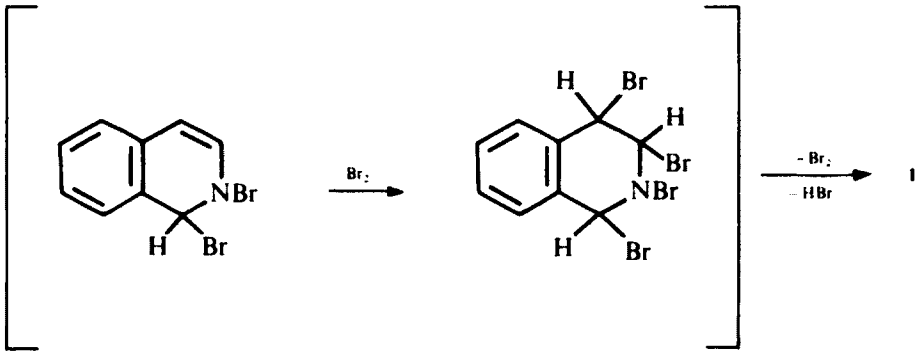
15

Bromination of the mercurated derivative of isoquinoline (**16**) led to 4-bromoisoquinoline (**1**) (Eq. 4).

(4)

16 1

Addition, followed by elimination, has been suggested as a plausible mechanism of this reaction[9,10,28] (Scheme 4).

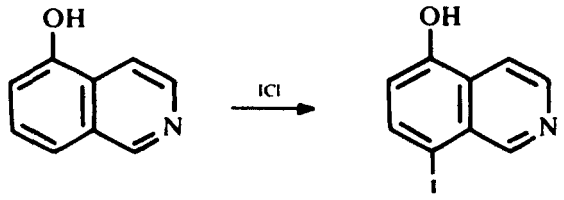


Scheme 4

With phosphorus pentabromide, isoquinoline-5-sulfonic acid yielded a mixture of mono- and dibromoisoquinolines of undetermined structure.[29]

Iodination gave even better results; at 20°C, iodine–potassium iodide converted 4-hydroxyisoquinoline to 4-hydroxy-3-iodoisoquinoline in 83% yield, while at 70°C, 1,3-diiodo-4-hydroxyisoquinoline was obtained.[23]

Iodination of 5-hydroxyisoquinoline takes place in the more activated benzene ring. Using iodine monochloride as reagent, 5-hydroxyisoquinoline was converted at 5°C to 5-hydroxy-8-iodoisoquinoline (**17**)[30] (Eq. 5).



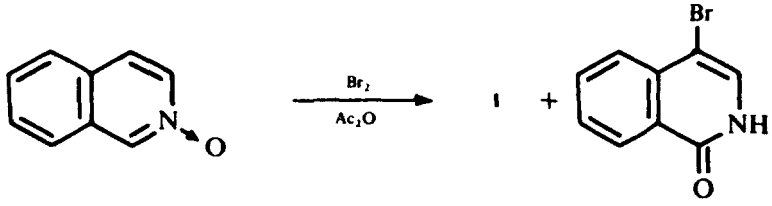
(5)

17

(c) *From N-Oxides*

(i) Halogenation of *N*-Oxides

Even though the electrophilicity in the isoquinoline nucleus is maximum at the 5 and 8 positions when halogenations are carried out in strongly acid medium, instances of a halogen atom entering the 4 position of the nucleus when a partial positive charge resides on the nitrogen atom are also known. Thus, isoquinoline *N*-oxide facilitates bromination and directs the entering bromine to the 4 position.[31] These reactions, however, produce the corresponding brominated isocarbostyrils as well, presumably by a rearrangement of the *N*-oxide under the reaction conditions. In certain cases, deoxygenation also results, for example, bromination of isoquinoline *N*-oxide in the presence of acetic anhydride gave a mixture of 4-bromoisocarbostyril and 4-bromoisoquinoline (**1**)[31] (Eq. 6).

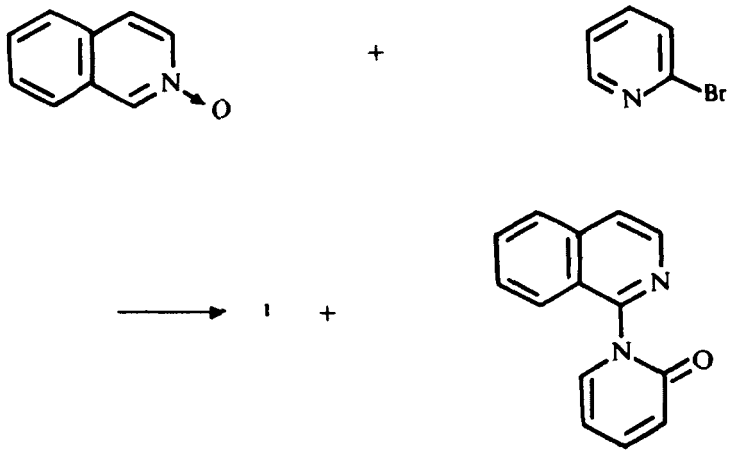


(6)

Isoquinoline *N*-oxide also reacts with cyanogen bromide in ethanol to give 4-bromoisocarbostyril in low yield (4.9%).[32]

It is interesting to note that heterocyclic halides do react with isoquinoline *N*-oxide to yield 4-haloisoquinolines. For example, 2-bromopyridine (Eq. 7), 1-bromoisoquinoline,[33] 1-chloroisoquinoline,[33] and 2-bromopyrimidine[34] react with isoquinoline *N*-oxides to yield 4-bromo- and 4-chloroisoquinolines as minor products.

The mechanism of these halogenation reactions has been discussed.[33] In a related reaction, *p*-toluenesulphonyl chloride reacts with isoquinoline *N*-oxide to yield 4-chloroisoquinoline in small amounts, besides 4-*p*-toluenesulfonamido isoquinoline and isocarbostyril.[33]

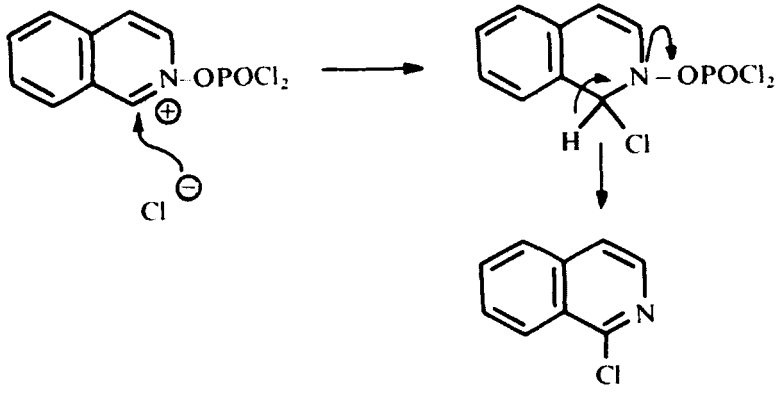


(7)

(ii) Rearrangements of *N*-Oxides

Rearrangements of isoquinoline *N*-oxides under Meisenheimer reaction conditions lead to 1-haloisoquinolines. The formation of the 1-chloro rather than the 3-chloro derivative is attributable to the greater electrophilicity of the 1 position. Of the chlorine-containing reagents, such as phosphorus oxychloride, phosphorus pentachloride, or sulfuryl chloride that form Meisenheimer complexes with isoquinoline *N*-oxide, phosphorus oxychloride is the most frequently used. Isoquinoline-*N*-oxide itself is converted to 1-chloroisoquinoline in 56% yield.[35] *p*-Toluenesulfonyl chloride also reacts in a similar fashion, but, as mentioned earlier, leads to a variety of other products. The mechanism of this reaction is illustrated in Scheme 5.

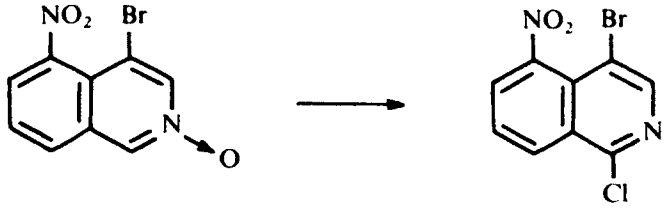
The reaction is also suited to the synthesis of 1-haloisoquinoline, especially 1-chloroisoquinolines[35] carrying other substituents in the nucleus. 7-Chloroiso-



Scheme 5

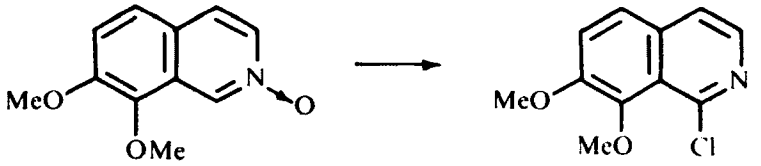
quinoline *N*-oxide yields 1,7-dichloroisoquinoline, while 6- or 7-methoxyisoquinoline *N*-oxides are converted to their respective 1-chloro derivatives in excellent yields (see also ref. 100). 4-Bromoisoquinoline can be transformed through its *N*-oxide into 1-chloro-4-bromoisoquinolines under the mild conditions of this reaction.[36]

Even the presence of a nitro group in the nucleus does not deter the facile rearrangement of isoquinoline *N*-oxide. Thus, 4-bromo-5-nitroisoquinoline *N*-oxide (**18**) yields the 1-chloro derivative (**19**)[37] (Eq. 8).



18 19 (8)

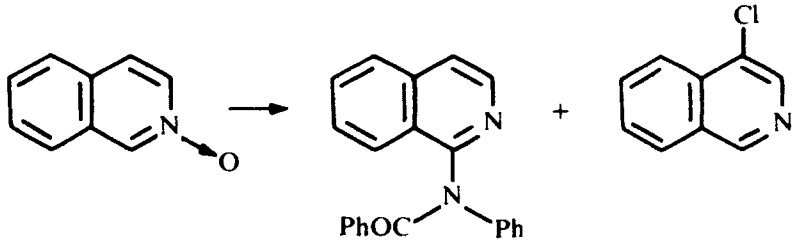
7,8-Dimethoxyisoquinoline *N*-oxide is readily converted into 1-chloro-7,8-dimethoxyisoquinoline (**20**)[38] (Eq. 9).



20 (9)

4-Azidoisoquinoline *N*-oxide on treatment with phosphorus oxychloride yields the azido-1-chloroisoquinoline in 62% yield.[39]

4-Chloroisoquinoline was obtained in 23% yield during direct acylamination of isoquinoline *N*-oxide using *N*-phenyl benzimidoyl chloride[40] (Eq. 10).



(10)

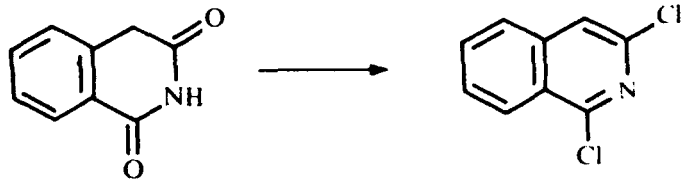
(*d*) *Conversion of Hydroxyisoquinolines*

A facile method for the preparation of 1-chloro- and 1,3-dichloroisoquinolines and the corresponding bromo analogs involves the treatment of the hydroxy derivatives with reagents like phosphorus oxychloride or bromide. Thus,

isocarbostyril[41] and homophthalimide[42] are readily converted to 1-chloroisoquinoline (**21**) and 1,3-dichloroisoquinoline (**22**), respectively, by reaction with phosphorus oxychloride (Eqs. 11 and 12).

(11)

21

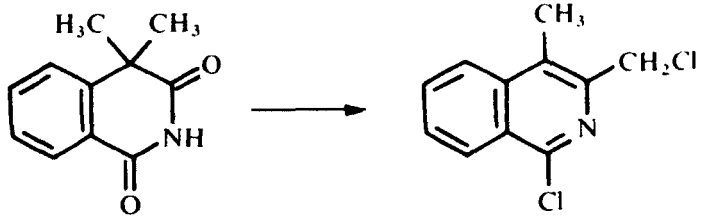


(12)

22

More recent work[43] has established that the reaction of anhydrous phosphorus oxychloride with homophthalimide results in the formation of 3-chloroisocarbostyril, which in turn can be converted to 1,3-dichloroisoquinoline. On the other hand, the presence of moisture or a trace of concentrated hydrochloric acid effects the direct conversion of homophthalimide to 1,3-dichloroisoquinoline. Thus, by selecting the reaction conditions, it is possible to prepare 3-chloroisocarbostyril or 1,3-dichloroisoquinoline.

The rearrangement of α,α-dialkyl homophthalimides with phosphorus oxychloride has been studied in detail[44-48] (Eqs. 13 and 14).



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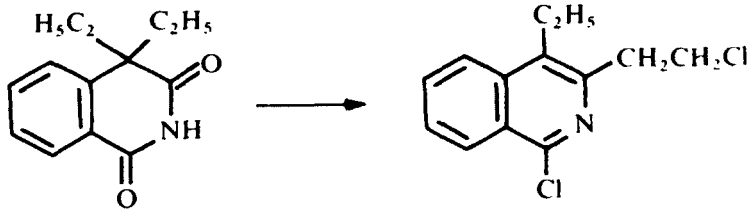
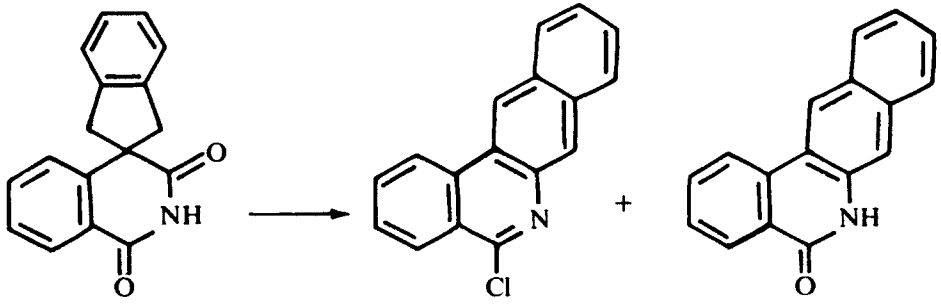


(14)

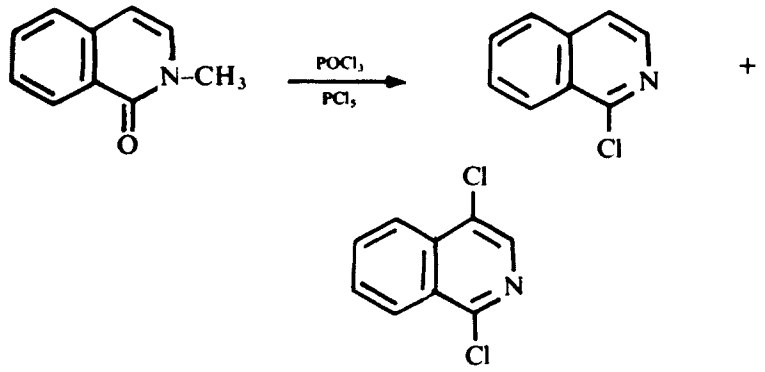
Starting with a 4-spirohomophthalimide (**23**), it was possible to effect a skeletal rearrangement to generate a benzophenanthridine system[49] (Eq. 15).



23

(15)

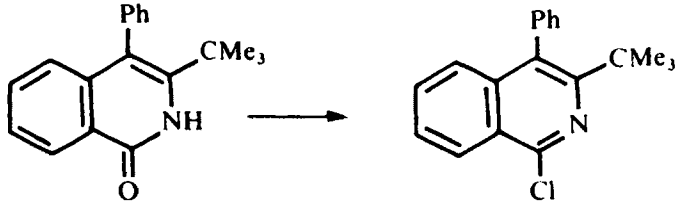
A series of substituted 1-chloroisoquinolines were prepared from isocarbostyrils using phosphorus oxychloride.[50] A mixture of phosphorus oxychloride and phosphorus pentachloride has been employed for the conversion of *N*-methyl isocarbostyril to 1-chloroisoquinoline. The driving force for the demethylation must be the formation of a fully aromatic system. Also obtained in this reaction is 1,4-dichloroisoquinoline (**24**) (Eq. 16). These experiments were carried out in connection with synthetic experiments related to indole alkaloids (see Section III. E, ref. 196).



24

(16)

In the preparation of 3-substituted 4-arylisoquinolines, which are useful as antidiabetics, the intermediate **26** was prepared from the corresponding carbostyril **25**[51] (Eq. 17).

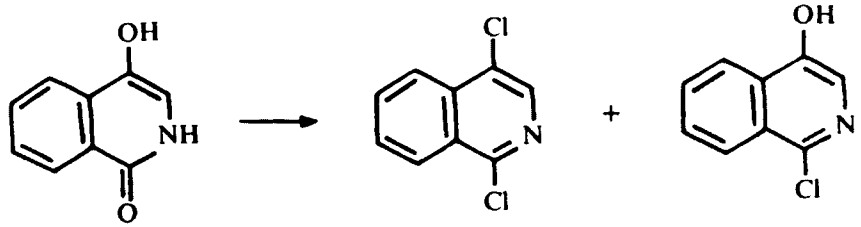


25 26 (17)

The conversion of 6-hydroxyisocarbostyril to 1,6-dichloroisoquinoline (**27**)[52] is an unexpected reaction, since phenolic hydroxyl groups normally do not undergo replacements with chlorine. The conditions for effecting this transformation, are, however, much more drastic than those used for isocarbostyril (Eq. 18).

27 (18)

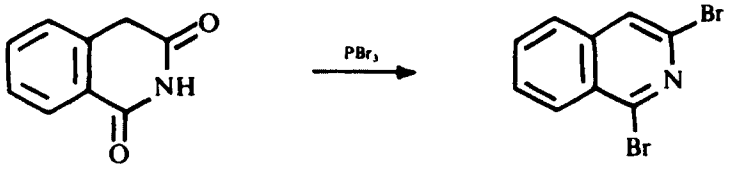
The reaction of 4-hydroxyisocarbostyril (**28**) with phosphorus oxychloride proceeds very sluggishly to yield a mixture of 1,4-dichloro (**24**) and 1-chloro-4-hydroxyisoquinoline (**29**)[41] (Eq. 19).



28 24 29 (19)

The need for the presence of a trace of moisture or free acid in phosphorus oxychloride[43,53] for the ready conversion of homophthalimides or isocarbostyrils to chloroisoquinolines is further emphasized in the case of the synthesis of 7-nitro-1,3-dichloroisoquinoline from 7-nitrohomophthalimide.[54] Failure to reproduce this reaction may be attributed to the use of the "anhydrous" reagent since the authors mention that in the case of the successful reaction an "aged" sample of reagent was employed.

Phosphorus tribromide converts homophthalimide to 1,3-dibromoisoquinoline (**30**)[54] (Eq. 20).



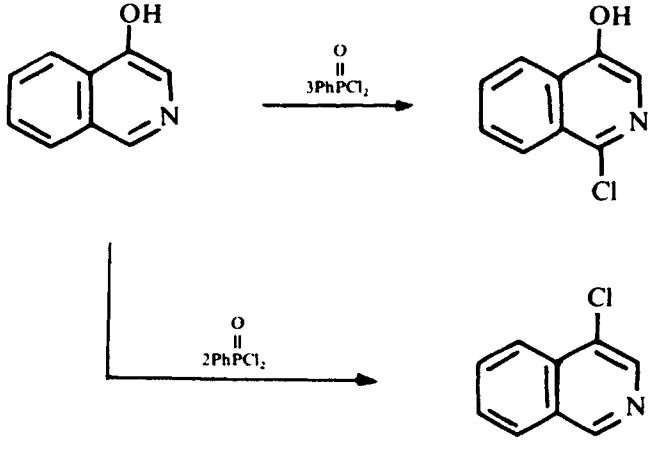
(20)

30

Under forced conditions, 3-hydroxy-5,6,7,8-tetrahydroisoquinoline undergoes concomitant dehydrogenation to yield 3-bromoisoquinoline[55-57] and a dibromoisoquinoline of undetermined orientation.[55] Both from the melting point and the logistics of this reaction, the compound seems to be the 1,3 isomer.

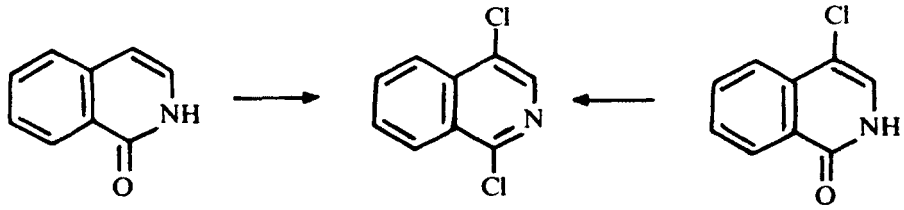
It has been suggested that phenylphosphonic dichloride is a better reagent for chlorodehyroxylation since its boiling point is higher. However, experience with this reagent does not justify this generalization. 4-Hydroxyisoquinoline gave a better yield of the 4-chloro compound with phosphorus oxychloride than with phenylphosphonic dichloride. The nature of the products obtained in the reaction with the latter reagent depended on the amount of reagent used. In the presence of 3 equivalents of reagent, selective chlorination of 4-hydroxyisoquinoline to 1-chloro-4-hydroxyisoquinoline resulted, whereas with 2 equivalents, the product is 4-chloroisoquinoline[58] (Scheme 6).

Isocarbostyril was directly converted to 1,4-dichloroisoquinoline in 50% yield on reaction with phosphorus pentachloride,[59] identical with the product ob-



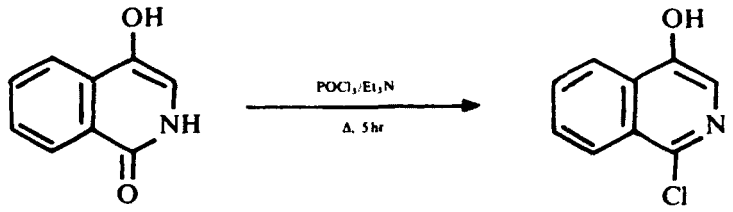
Scheme 6

tained from 4-chloroisocarbostyril (Scheme 7). The tendency of phosphorus pentachloride to also function as a chlorinating agent in addition to its role as a chlorodehydroxylating agent has largely precluded its use as a useful reagent for the synthesis of 1-chloroisoquinolines from isocarbostyrils.



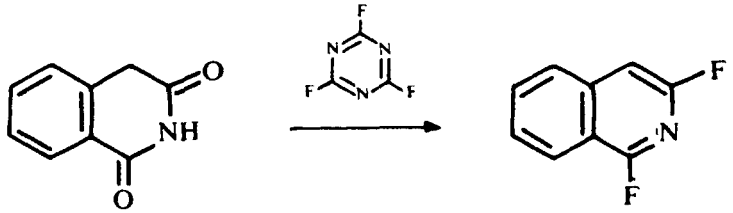
Scheme 7

A French patent[60] describes the conversion of 4-hydroxyisocarbostyril to 1-chloro-4-hydroxyisoquinoline with phosphorus oxychloride in the presence of triethylamine (Eq. 21). This compound was used as an intermediate for the synthesis of 1-(2-dialkylaminoethoxy)-4-alkoxyisoquinolines.



(21)

The conversion of homophthalimide to 1,3-difluoroisoquinoline (**31**) has been accomplished with the use of 2,4,6-trifluoro-1,3,5-triazine as the fluorodehydroxylating agent[61] (Eq. 22).



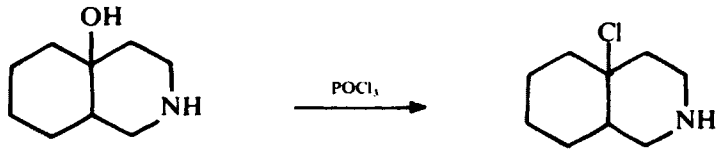
(22)

31

4-Hydroxy-1,2,3,4-tetrahydroisoquinoline (**32**) reacts with phosphorus oxychloride to provide the 4-chloro derivative (**33**)[36] (Eq. 23).

32 33 (23)

The synthesis of chloro decahydroisoquinoline (**35**) by the reaction of a hydroxy derivative (**34**) with phosphorus oxychloride has also been reported[62] (Eq. 24).



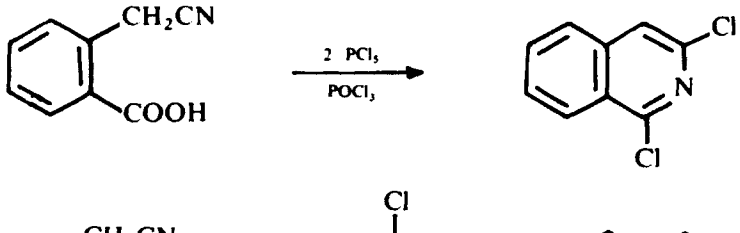
34 35 (24)

(*e*) *Building up of the Pyridine Ring of Isoquinolines*

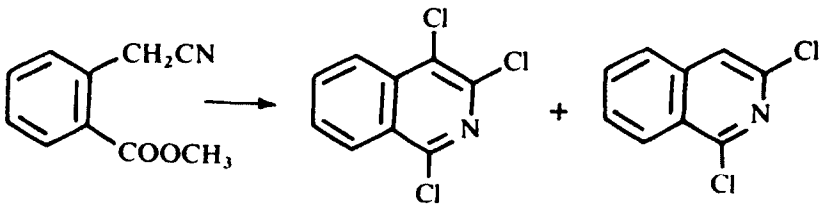
(i) Through Nitrilium Salts or Their Equivalents

The cyclization of dinitriles by anhydrous halogen acids, leading to 1-halo-3-aminoisoquinolines, was first reported by Johnson and Nasutavicus[63,64] in 1962. The reaction was successful (yields 52–95%) with hydrogen bromide and iodide, but not with hydrogen chloride. The resulting amino compounds have been converted to 3-hydroxy derivatives on reaction with nitrous acid.[63]

Similarly, *o*-cyanomethyl benzoic acid is converted into 1,3-dichloroisoquinoline in 94% yield[65] with 2 molar equivalents of phosphorus pentachloride in phosphorus oxychloride (Eq. 25). The methyl ester (**36**) also reacts with phosphorus pentachloride to give a mixture of 1,3-dichloro- and 1,3,4-trichloroisoquinolines[66] (Eq. 26) along with traces of 3-chloroisocarbostyril.

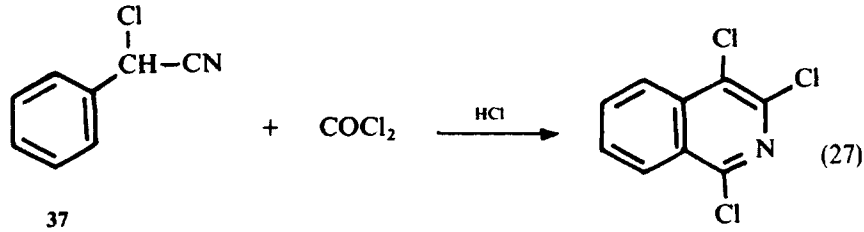


(25)

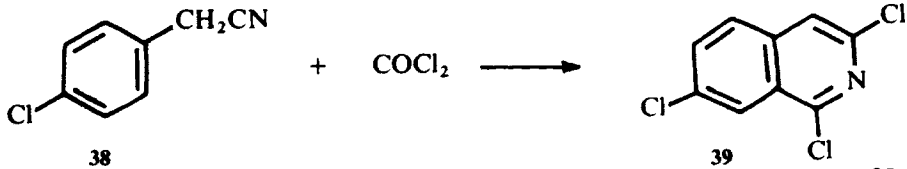


36 (26)

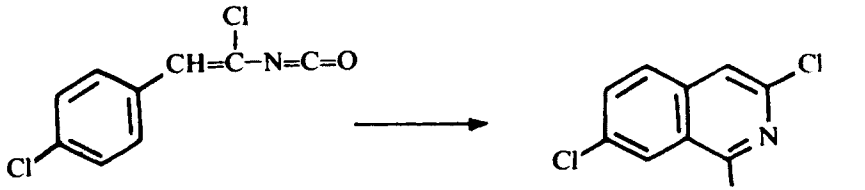
Yet another type of intramolecular cyclization leading to haloisoquinolines is the reaction of phosgene with nitriles. For example, α-chlorophenylacetonitrile (**37**) is converted into 1,3,4-trichloroisoquinoline, although in poor yield (Eq. 27), while *p*-chlorophenylacetonitrile (**38**) is converted to 1,3,7-trichloroisoquinoline (**39**)[67] (Eq. 28). More successful is the thermal cyclization of styrylisocyanate **40** to yield 3,7-dichloroisocarbostyril (**41**) which then is easily converted to 1,3,7-trichloroisoquinoline[67] (Eq. 29).



37 (27)



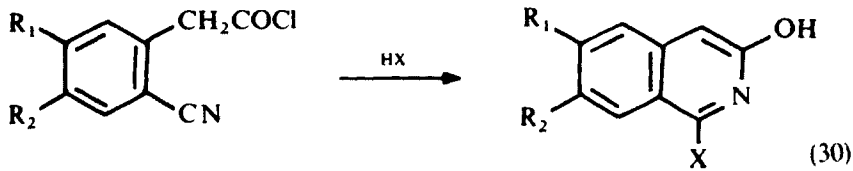
38 **39** (28)



40 **41** (29)

Strongly electron-withdrawing groups reduce the electrophilic intramolecular cyclization of the isocyanate at the *ortho* position.[67]

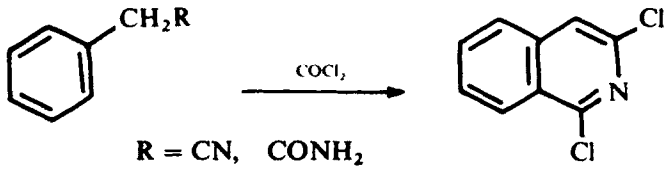
The case of an acid chloride intramolecularly cyclizing with a nitrile group is illustrated by the synthesis of a series of haloisoquinolines in the presence of anhydrous hydrogen halide[68] (Eq. 30).



(30)

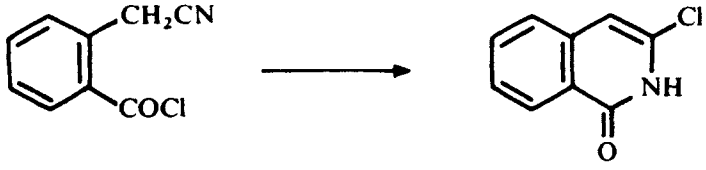
X = Cl, Br, I
R_1 = H, Cl, Br, OMe, Me
R_2 = H, OMe, Me

Even benzylcyanide and phenylacetamide react with phosgene to give 1,3-dichloroisoquinoline[67] (Eq. 31).



(31)

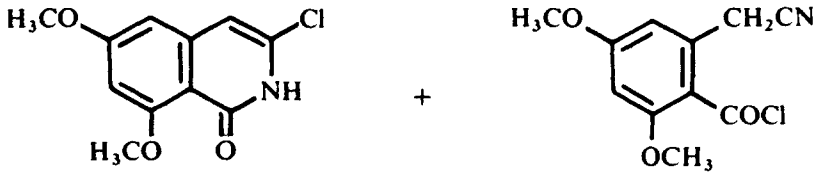
Saturating 2-cyanomethylbenzoyl chloride in dioxane with hydrogen chloride and heating for a few hours at 60–70 °C leads to 3-chloroisocarbostyril[69] (Eq. 32).



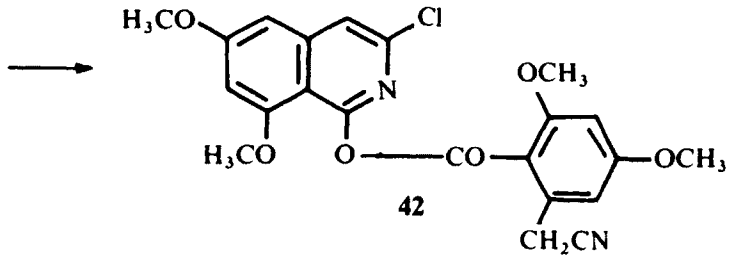
(32)

Extension of this reaction to the synthesis of other heterocyclic derivatives proved equally successful.[70–72]

The ease of these cyclizations depends on the acid concentration. At low concentrations, acylation of the initially formed isocarbostyril also occurs. One such example is the formation of **42**[69, 72] (Eq. 33).

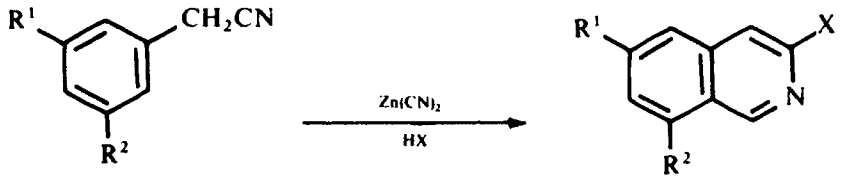


(33)



42

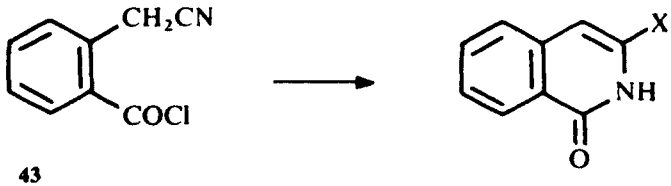
Synthesis of a series of methoxy and hydroxy haloisoquinolines has been achieved by the Gattermann reaction on phenylacetonitriles[73] (Eq. 34).



(34)

$R^1 = R^2 = OH$ X = Cl
$R^1 = R^2 = OH$ X = Br
$R^1 = OH$ $R^2 = OCH_3$ X = Br

3-Bromo- and 3-iodoisocarbostyrils can also be obtained in quantitative yield from the reaction of 2-cyanomethyl benzoyl chloride (**43**) with hydrogen bromide and hydrogen iodide, respectively[69] (Eq. 35).



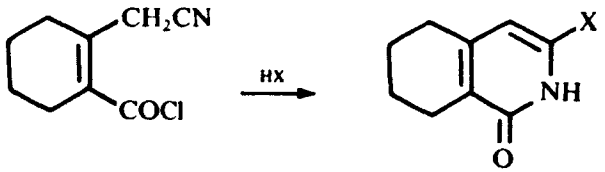
43

(35)

X = Br, I

These intramolecular cyclizations leading to halogenated isoquinolines give good yields, irrespective of the nature and position of substituents on the benzene ring, and hence offer a distinct advantage over the other isoquinoline syntheses.

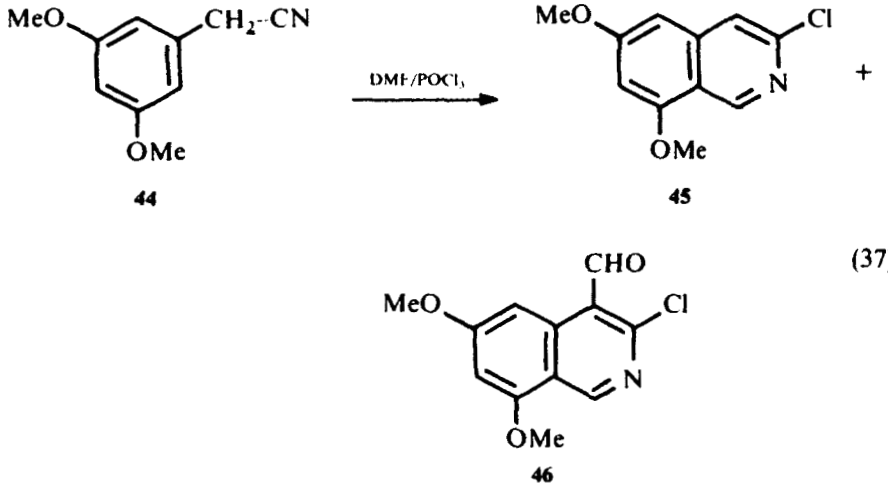
Nitrilium salts have also been used to prepare hydrogenated derivatives of halogenated isoquinolines. Thus, treatment of α-cyanomethylcycloalkene carboxylic acid chlorides with hydrogen halides result in moderate yields of hydrogenated isocarbostyril derivatives[71] (Eq. 36).



(36)

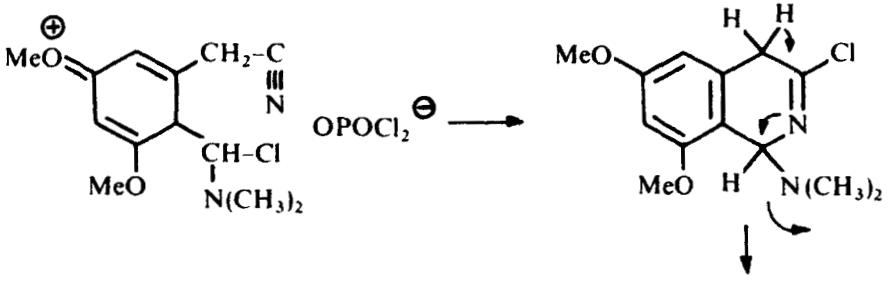
X = Cl, Br, I

The conversion of 3,5-dimethoxyphenylacetonitrile (**44**) to 3-chloro-6,8-dimethoxyisoquinoline also takes place under Vilsmeier conditions.[74, 75] During attempts to prepare formyl derivatives[76] of the acetonitriles, it was found that **44** gave, in up to 65% yield, compound **45** contaminated with small amounts of the 4-formyl derivative (**46**) (Eq. 37).



44 45 46 (37)

The mechanism of this reaction is believed to involve an initial intermediate attack of the Vilsmeier species, followed by cyclization and aromatization[76] (Scheme 8).



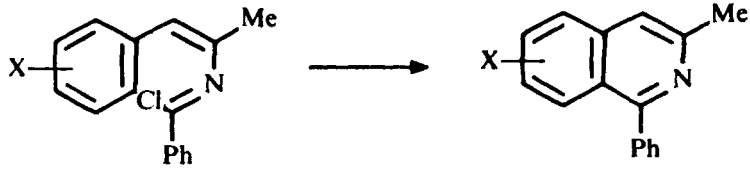
Scheme 8 45

Halogenated 1,3-dimethylisoquinolines (**48**) were obtained[77] by *in situ* cyclization using phosphorus pentoxide of the imidoyl chlorides **47** formed by Beckmann rearrangement of the oximes derived from 4-aryl-3-methyl-3-buten-2-ones (Eq. 38).

47 48 (38)

X = 6-Cl, 7-Cl

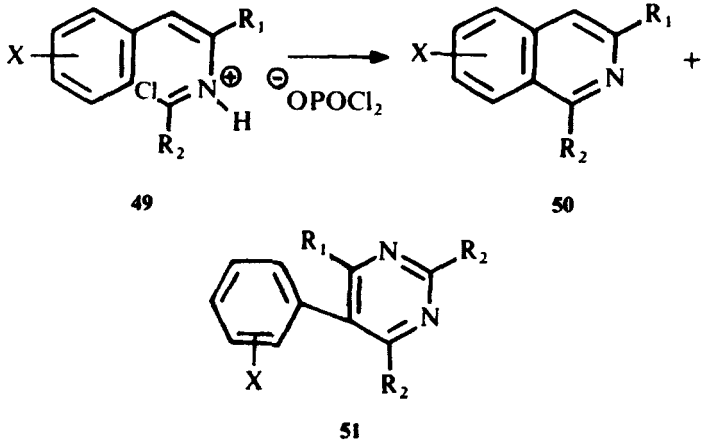
Halogenated 1-phenyl-3-methylisoquinolines were prepared similarly[78] (Eq. 39).



(39)

X = 5-Cl, 6-Cl, 7-Cl

The reaction of halogenated benzyl ketones with nitriles and phosphorus oxychloride gave compounds of type **49**, which reacted to yield haloisoquinolines **50** and aryl pyrimidines **51**[79] (Eq. 40).



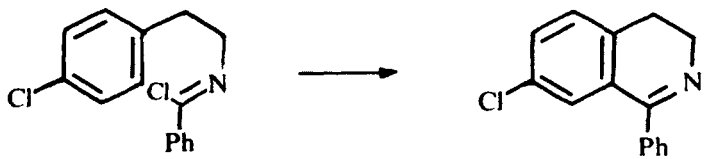
49 **50**

51

(40)

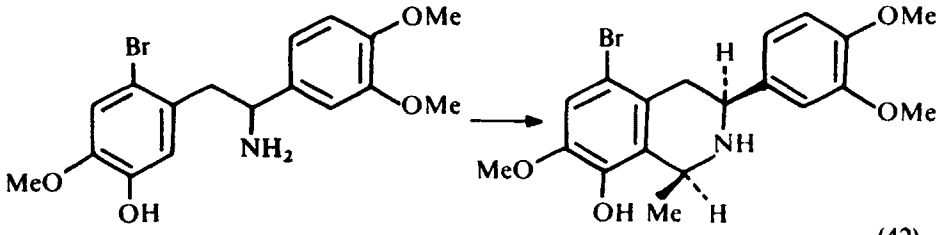
X = Cl, R_1 = Me, R_2 = H, Me, Ph, CH_2Ph

A Hungarian patent[80] describes the cyclization of substituted imidoyl chlorides using phosphorus oxychloride or thionyl chloride in the presence of various Lewis acids to give 3,4-dihydroisoquinolines (Eq. 41).



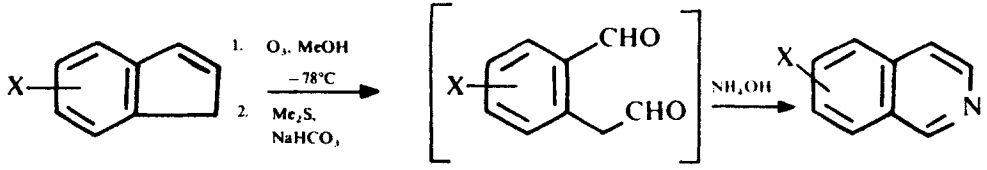
(41)

A stereoselective synthesis of the *cis*-1-methyl-3-aryl-1,2,3,4-tetrahydroisoquinoline (**53**) was carried out by cyclocondensation of **52** with acetaldehyde[81] (Eq. 42).



52 53 (42)

Starting from substituted indenes, 6- and 7-bromo and iodoisoquinolines can be prepared by a general procedure. Ozonolysis of the indenes, followed by reductive work-up and treatment with ammonium hydroxide, gave the isoquinolines in 58–70% yield. Isoquinoline formation seems to be independent of the electron-withdrawing nature of the substituents[82] (Scheme 9).

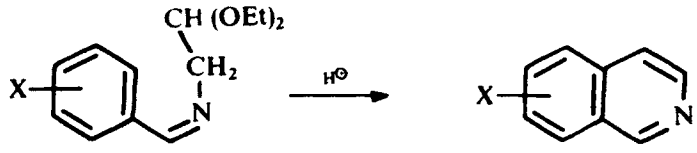


X = 6-Br, 6-I, 7-Br, 7-I

Scheme 9

(ii) Pomeranz–Fritsch Synthesis

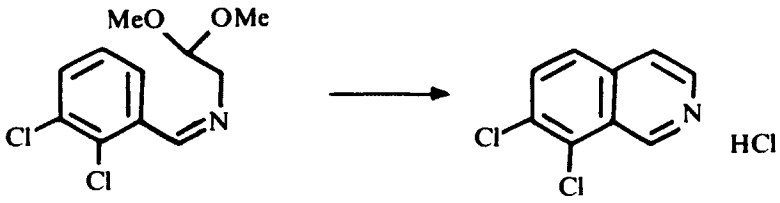
The Pomeranz–Fritsch synthesis provides a direct entry to halogenated isoquinolines not easily prepared by other methods. Moreover, unlike the Bischler–Napieralski or the Pictet–Spengler synthesis, it provides the fully aromatic isoquinolines rather than partially hydrogenated isoquinolines (Eq. 43). Both benz-chloro- and bromoisoquinolines have been prepared by this procedure, but the yields are far from satisfactory.[22, 83] Starting from *o*-, *m*-, or *p*-bromobenzalaminoacetals, 8-bromo, a mixture of 5- and 7-bromo, and 6-bromoisoquinolines were obtained in 29, 65, and 6% yields, respectively.[84]



X = 5, 6, 7, or 8 Cl or Br

1,2,3,4-Tetrahydroisoquinolines with chlorine substituted in the benzene ring have been found to inhibit the enzyme phenylethanolamine *N*-methyltransferase (PNMT). Hence, considerable efforts have been made to use the Pomeranz–Fritsch reaction for their synthesis and to develop milder conditions and modifications leading to better yields. In a series of mono-, di-, and trichloro-substituted isoquinolines[20], the yields of cyclization of the appropriate benzylideneamines using sulfuric acid varies from 6 to 54%. This variation has been explained by the concomitant formation of phenyloxazoles.[85]

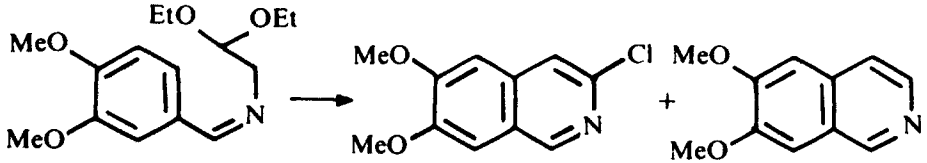
7,8-Dichloroisoquinoline was prepared as shown below and reduced in a subsequent step to the 1,2,3,4-tetrahydroisoquinoline[20, 86] (Eq. 44).



(44)

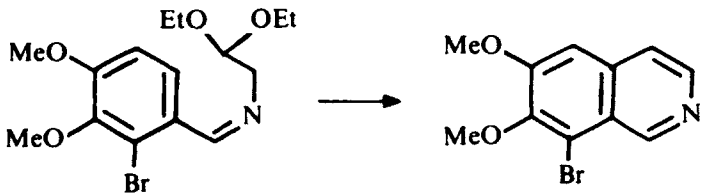
7,8-Dichloro-1,2,3,4-tetrahydroisoquinoline, labeled with ^{14}C in position 1 has been similarly prepared[87] starting from $2,3\text{-}Cl_2C_6H_3\,{}^{14}CHO$.

Other cyclizing agents that have been used include halosulfonic acid.[88] (Eq. 45).



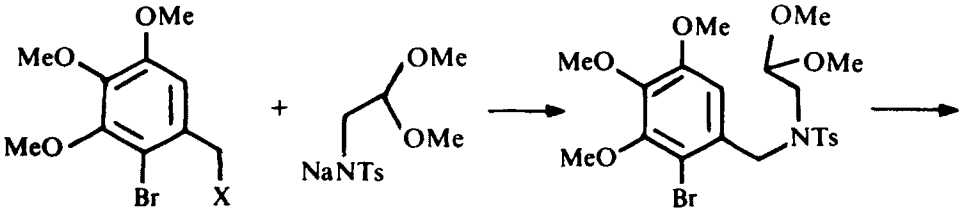
(45)

8-Bromo-6,7-dimethoxyisoquinoline was prepared via a modification of the Pomeranz–Fritsch procedure developed by Bewis *et al.*[89] using boron trifluoride–acetic acid in trifluoroacetic anhydride to bring about the cyclization[90] (Eq. 46).



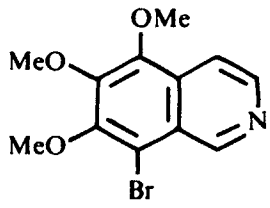
(46)

A two-step synthesis of isoquinolines has been devised. Treatment of benzylic halides and mesylates with the sodium anion of *N*-tosyl aminoacetaldehyde dimethylacetal (**54**) led to **55**, cyclization of which led to the isoquinoline **56**[91] (Scheme 10).



54 55

X = Br, OMs Ts = Tosyl

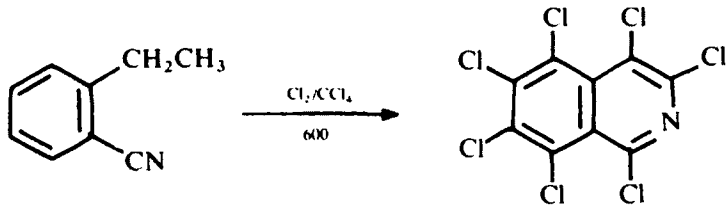


56

Scheme 10

(iii). One-Step Perchloroisoquinoline Synthesis

An intramolecular chlorination–cyclization reaction has been reported[92] to yield perchloroisoquinoline (57) in 25% yield (Eq. 47).



(47)

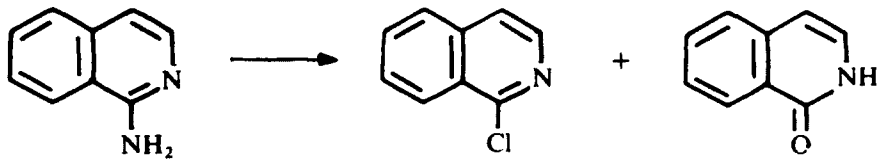
57

(*f*) *Sandmeyer and Schiemann Reactions*

(i) Sandmeyer Reaction

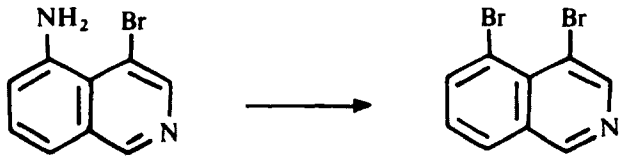
In many ways, the Sandmeyer and Schiemann reactions constitute the most general synthetic methods for the synthesis of haloisoquinolines. The limitation, of course, is the availability of the appropriately substituted aminoisoquinolines. Other complications of the Sandmeyer reaction, such as deaminations and formation of hydroxy compounds, are also potential drawbacks.

Tschitschibabin noted that 1-aminoisoquinoline is converted to a mixture of 1-chloroisoquinoline and isocarbostyril under Sandmeyer conditions.[93] (Eq. 48).



(48)

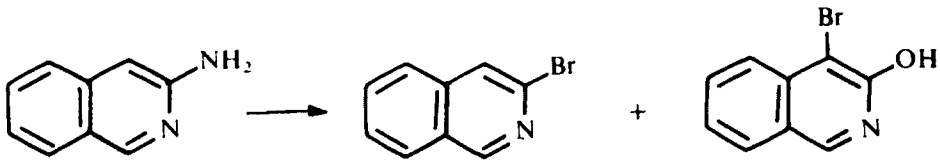
A monoamino-4-bromoisoquinoline of undetermined orientation was subjected to the Sandmeyer reaction and a dibromo derivative was obtained[94] (Eq. 49). Recent work indicates that the product is 4,5-dibromoisoquinoline (**58**); consequently, the starting material should be designated as a 5-amino-4-bromoisoquinoline.



(49)

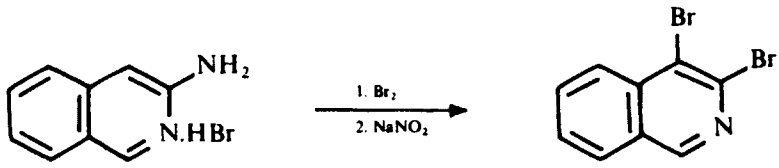
58

Similarly, the bromoisoquinoline obtained from an aminoisoquinoline appears to be the 5-bromo compound from its reported melting point.[54, 95] Also, from dipole moment studies Le Fevre and Le Fevre had concluded that the structure of the nitroisoquinoline from which this aminoisoquinoline was prepared is the 5-isomer.[96] 3-Aminoisoquinoline yields the 3-bromo derivative.[97] Later work has shown that this reaction produces, additionally, a 47% yield of 3-hydroxy-4-bromoisoquinoline (**59**)[98] (Eq. 50).



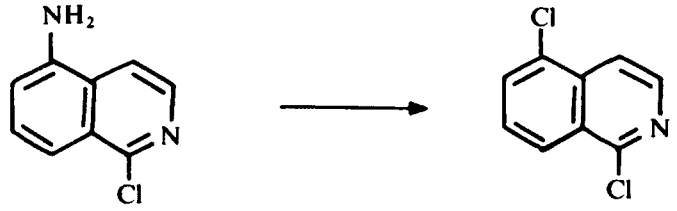
59 (50)

A Sandmeyer reaction on the perbromide of 3-aminoisoquinoline hydrobromide afforded 3,4-dibromoisoquinoline (**60**) in 80% yield[98] (Eq. 51).



60 (51)

4-Aminoisoquinoline has been converted to 4-chloroisoquinoline,[99] while 1-chloro-5-aminoisoquinoline (**61**) yields 1,5-dichloro compound (**62**) in 50% yield[100] (Eq. 52).



(52)

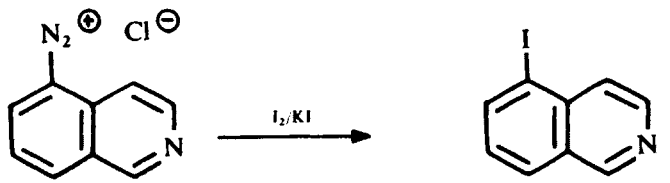
61 **62**

5- and 7-Aminoisoquinolines undergo Sandmeyer reactions to give the corresponding chloro compounds.[22] The Sandmeyer reaction has also been employed for the synthesis of other chloro- and bromoisoquinolines and their hydrogenated derivatives.[54, 101-107] A Sandmeyer reaction on 1-amino-isoquinoline *N*-oxide (**63**) is reported[108] to yield 1-chloroisoquinoline (Eq. 53).

(53)

63

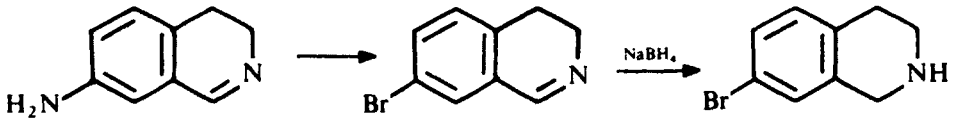
Iodoisoquinolines are prepared by diazotization of aminoisoquinolines and treatment of the diazo intermediates with iodine–potassium iodide (Eq. 54). Among the compounds prepared are 5-iodoisoquinoline[109] and 8-hydroxy-5-iodoisoquinoline.[30]



(54)

The Sandmeyer reaction has also been utilized for the synthesis of halodihydroisoquinolines. Thus, 7-amino-3,4-dihydroisoquinoline was converted in 67% yield to the 7-bromo compound[110, 111] which, on reduction with sodium borohydride, yielded 7-bromo-1,2,3,4-tetrahydroisoquinoline[111] (Scheme 11).

4-Amino-1,2,3,4-tetrahydroisoquinoline (**64**), upon diazotization, yielded the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**65**)[36] (Eq. 55).



Scheme 11

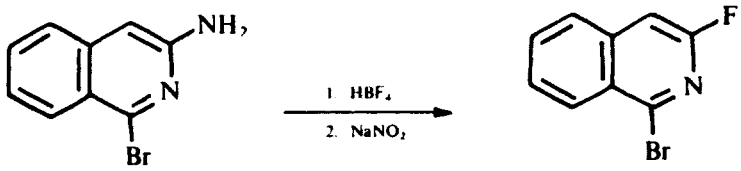
(55)

64 65

7-Amino-1,2,3,4-tetrahydro-2-methylisoquinoline under Sandmeyer conditions gave the corresponding 7-bromo compound in 87% yield.[112]

(ii) Schiemann Reaction

The Schiemann reaction,[113] which involves the reaction of diazonium chloride with fluoboric acid, has been successfully used for the synthesis of fluoroisoquinolines in moderate yields. Thus, 1-,3-,4-, and 5-fluoroisoquinolines have been prepared from the corresponding aminoisoquinolines in 13, 49, 36, and 67% yields, respectively.[114] In all cases, not unexpectedly, hydroxyisoquinolines are by-products of these reactions. 3-Amino-1-bromoisoquinoline produces 1-bromo-3-fluoroisoquinoline (**66**) under similar conditions.[115] (Eq. 56).



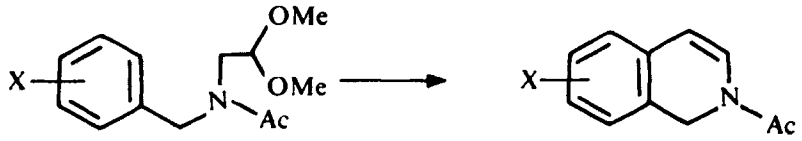
(56)

66

(g) *Friedel–Crafts-Type Ring Closure*

Friedel–Crafts-type ring closures have been reported for the syntheses of 1,2-dihydro-[116] and 1,2,3,4-tetrahydroisoquinolines.[117–121]

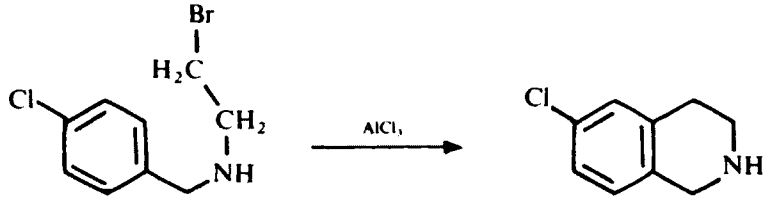
Cyclization of compounds **67** using a slurry of aluminium chloride in 1,2-dichloroethane afforded *N*-acetyl-1,2-dihydroisoquinolines **68** which could then be reduced to the corresponding 1,2,3,4-tetrahydroisoquinolines[116] (Eq. 57).



67 68 (57)

X = 6-Cl, 7-Cl, 8-Cl, 7-F, 6,7-diCl, 7,8-diCl

Friedel–Crafts ring closure also leads to 1,2,3,4-tetrahydroisoquinolines. By this method, 6-chloro-1,2,3,4-tetrahydroisoquinoline (**70**) was obtained in 60% yield from **69**[117] (Eq. 58).



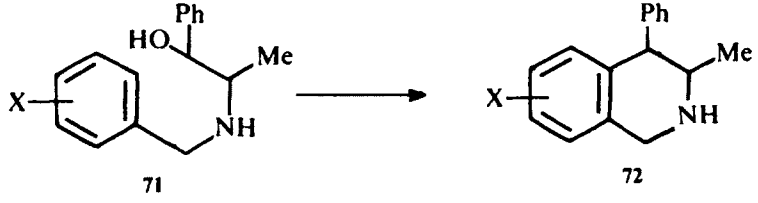
69 70 (58)

Several halogen-substituted 1,2,3,4-tetrahydroisoquinolines have been prepared using a melt of aluminium chloride and ammonium chloride to effect cyclization[118] (Eq. 59)

(59)

Z = OH, Cl X = 8-Cl, 8-Br, 6,7-diCl, 6,7,8-triCl

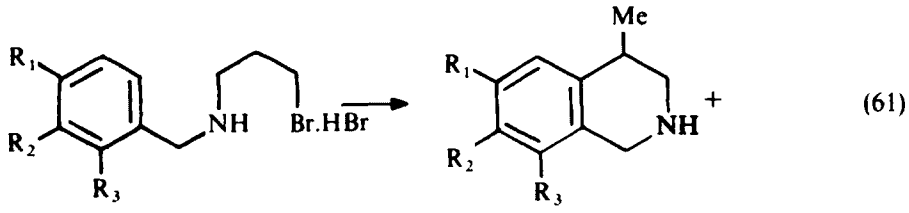
Ring closure of 2-benzylamino-1-arylethanols leads to 4-aryl-1,2,3,4-tetrahydroisoquinolines.[119–122] For example,[119] **71**, on cyclization with hydrobromic acid, yielded **72** (Eq. 60).



71 72 (60)

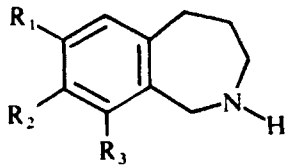
X = 6-Cl, 8-Cl

Chlorine-substituted 1,2,3,4-tetrahydroisoquinolines **74** were obtained as the major products of cyclization of the appropriate benzylaminopropyl bromides using a melt of aluminium chloride and ammonium chloride; the expected benzazepine **75** was also obtained as a minor product in one case[123] (Eq. 61).



(61)

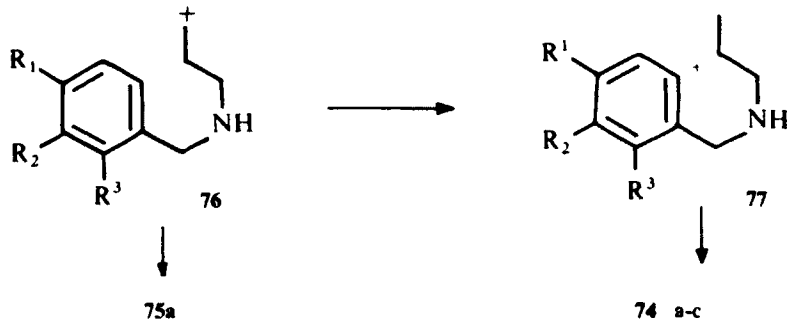
73 **74**



75

a $R_1 = Cl$ $R_2 = H$ $R_3 = H$
b $R_1 = H$ $R_2 = H$ $R_3 = Cl$
c $R_1 = H$ $R_2 = Cl$ $R_3 = Cl$

Such observations have precedence in Friedel–Crafts literature and are rationalized by an isomerization of the initially formed carbonium ion **76** to the more stable 2° carbonium ion **77**. Thus, in **73a–c**, attack by the carbonium ion on the deactivated ring is slow relative to isomerization to **77**, resulting in predominant formation of **74a–c** (Scheme 12).



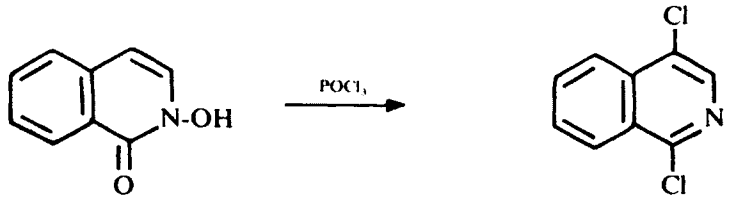
Scheme 12

(*h*) *Miscellaneous Methods*

(i) Rearrangements

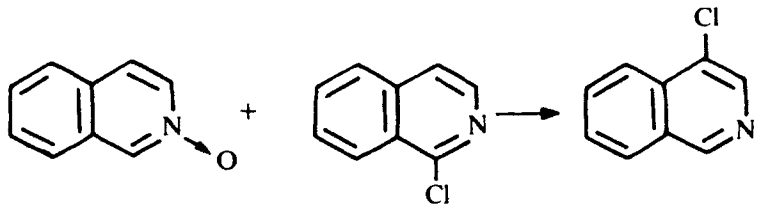
Rearrangements leading directly to haloisoquinolines have not been of much preparative value in isoquinoline chemistry. The cyclic hydroxamic acid *N*-hydroxyisocarbostyril (**78**) reacts with phosphorus oxychloride to yield 1,4-

dichloroisoquinoline[59] (Eq. 62). This reaction highlights the susceptibility of the 4 position to oxidative halogenation. Another example of halogenation, presumably resulting from a rearrangement of an *N*-oxide rather than a direct attack by halogen, is the conversion of isoquinoline *N*-oxide to 4-bromoisoquinoline with bromine in refluxing acetic anhydride[31] [see section A(*c*)(i)].



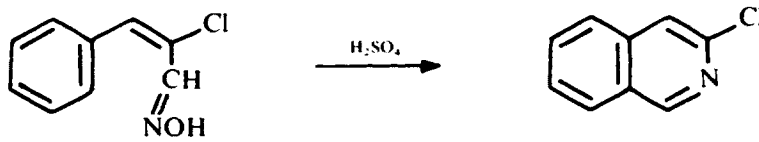
78 (62)

Bromo- and chloroheterocycles also halogenate isoquinoline *N*-oxide in the 4-position[33] (Eq. 63) [see Section A(*c*)(i)].



(63)

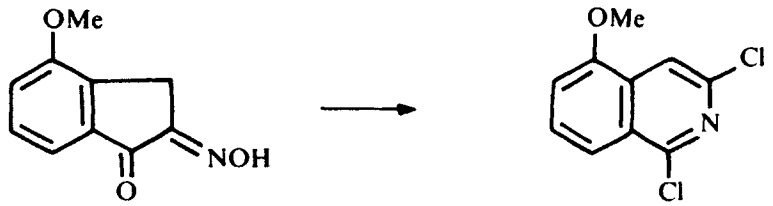
Two reactions have been reported wherein halogenated isoquinolines are formed by a Beckmann type of reaction. As early as 1895, Goldschmidt reported the formation of 3-chloroisoquinoline in low yield by the action of phosphorus pentoxide or sulfuric acid on α-chlorocinnamaldehyde oxime[124] (Eq. 64).



(64)

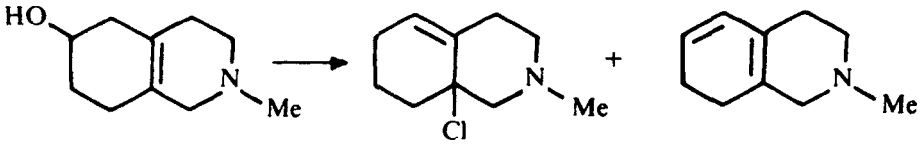
Ring enlargement with subsequent chlorodehydroxylation may be the route to the formation of substituted 1,3-dichloroisoquinolines from 2-oximino-1-indanones.[70]

The reaction proceeds equally well with the 5- and 6-methoxy isomers and the 5,6-dimethoxyindanedione monoximes to lead to the corresponding isoquinolines[70,72] (Eq. 65).

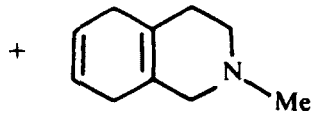


(65)

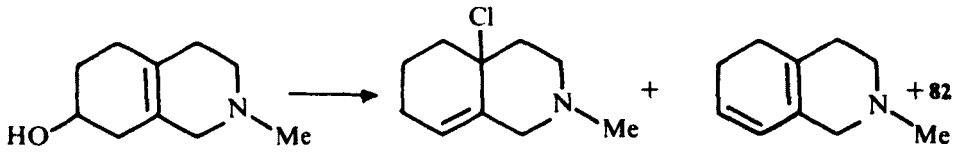
Treatment of the hydroxy-substituted isoquinoline **79** and **83** with phosphorus oxychloride in pyridine at 0 °C led to, among other products, the angular chlorinated hydrogenated isoquinolines **80** and **84**[125] (Eqs. 66 and 67).



79 **80** **81**



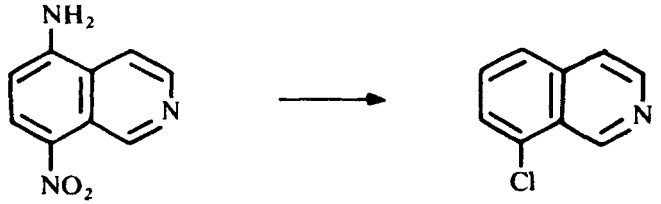
82 (66)



83 **84** **85** (67)

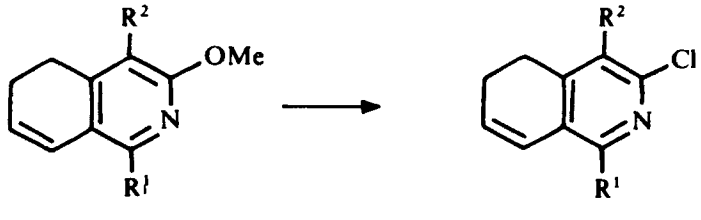
(ii) Replacement Reactions

During an attempt to prepare 8-nitroisoquinoline from 5-amino-8-nitroisoquinoline (**86**) by deamination, Keilin and Cass observed that the product (obtained in 70% yield) was actually 8-chloroisoquinoline[101] (Eq. 68). Such nucleophilic displacements of nitro groups by chlorine with the evolution of nitrous acid have been reported in literature,[126-128] although not in such high yields.



86 (68)

Under Vilsmeier–Haack conditions, 3-alkoxy-5,6-dihydroisoquinolines and 3-alkoxy-5,6,7,8-tetrahydroisoquinolines are converted to the corresponding 3-chlorocompounds[129] (Eqs. 69 and 70).

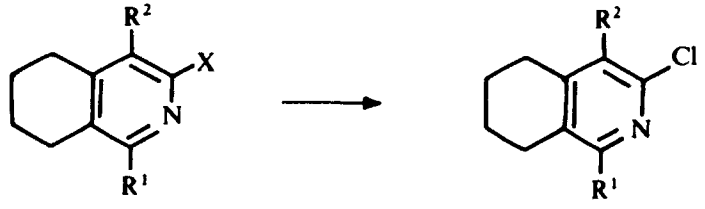


(69)

R^1 = Me, R^2 = CN

R^1 = Ph-CH_2, R^2 = CN

R^1 = Me, R^2 = H

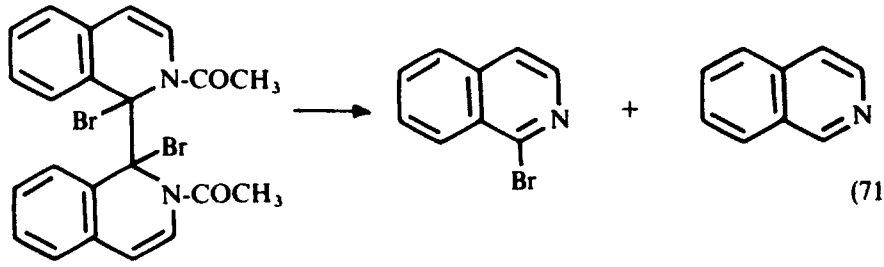


(70)

X = OMe, OH, OCH_2Ph
R^1 = Me, CH_2Ph, H
R^2 = CN, H

(iii) Cleavage Reactions

The base-catalyzed cleavage of bisisoquinoline (**87**) has been reported to lead to a 1-bromoisoquinoline[130] (Eq. 71).

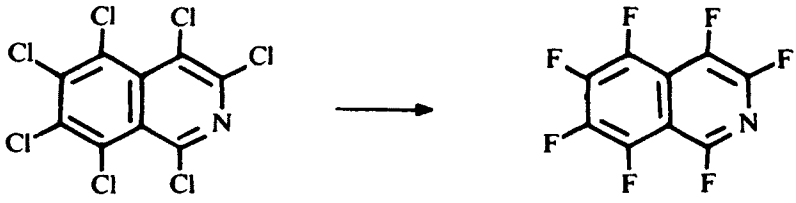


87

(71)

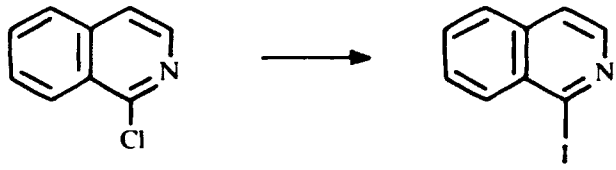
(iv) Interconversions

Replacement of one halogen by another has also been used for the synthesis of certain difficult to obtain isoquinoline derivatives. Thus, heptachloroisoquinoline heated at 420 °C with potassium fluoride is converted into heptafluoroisoquinoline[21] (Eq. 72).

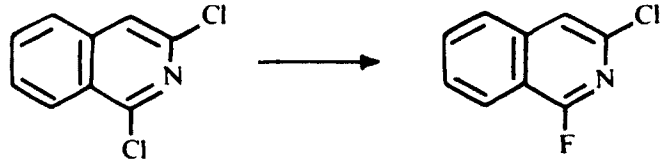


(72)

Among other reported reactions of this type are the replacements of chlorine by iodine[131] in 1-chloroisoquinoline (Eq. 73) and of chlorine by fluorine in 1,3-dichloroisoquinoline. In the latter instance, it was possible to selectively replace the 1-chlorine, keeping intact the 3-substituent[115] (Eq. 74)



(73)

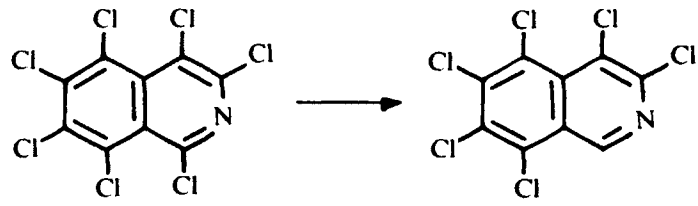


(74)

Chlorine- and bromine-substituted isoquinolines can be converted in good yields to the corresponding iodo compounds through intermediate trimethylstannyl derivatives (see Section vi. c).

(v) Selective Reduction

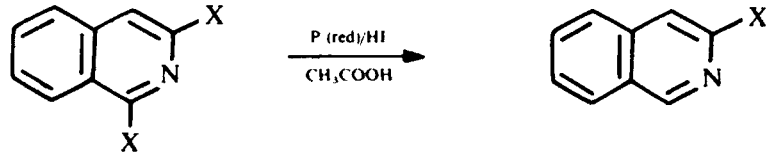
Electrolytic reduction of polyhaloisoquinolines is reported to yield compounds containing fewer halogens. Heptachloroisoquinoline was electrolytically reduced to hexachloro- (**88**) and even pentachloroisoquinoline[132] (Eq. 75).



(75)

88

Chemical or catalytic reduction of 1,3-dichloro or 1,3-dibromoisoquinoline leads to 3-chloro- or 3-bromoisoquinoline (Eq. 76); the greater susceptibility of the 1-halogen toward hydrogenolysis is utilized in this reaction.[54]

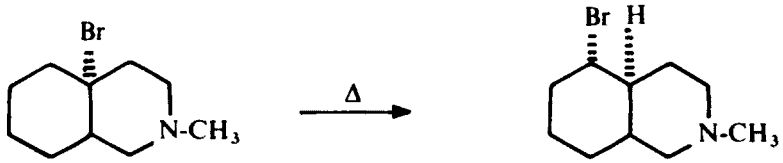


(76)

X = Cl 57%
X = Br 72%

(vi) Other Methods

The bromodecahydroisoquinoline (**89**) possessing an angular bromine underwent thermally induced isomerization to a ring-brominated decahydroisoquinoline (**90**)[133] (Eq. 77).

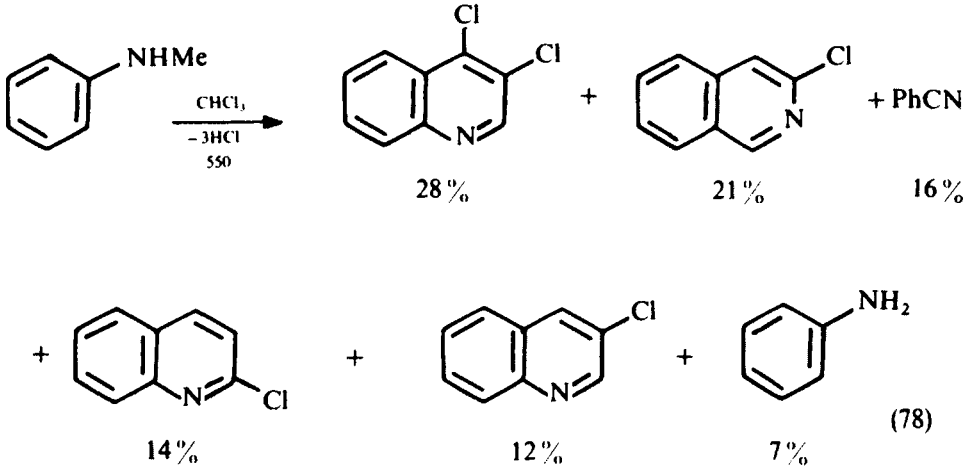


(77)

89 **90**

Similarly, 10-chloro-*N*-methyldecahydroisoquinoline also undergoes multiple isomerization to a mixture of 5,6 and 7-chloro derivatives.[62]

3-Chloroisoquinoline has been reported to be formed in 21% yield by a vapor-phase reaction of chloroform with *N*-methylaniline[134] (Eq. 78).

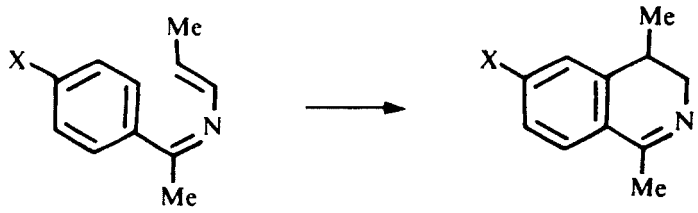


(78)

7,8-Dichloro-1,2,3,4-tetrahydroisoquinoline is aromatized by rat-liver microsomes to the corresponding isoquinoline.[135]

Attempts to overcome the disadvantages of the Bischler–Napieralsky, Pictet–Gams, and Pomeranz–Fritsch reactions which do not work well with

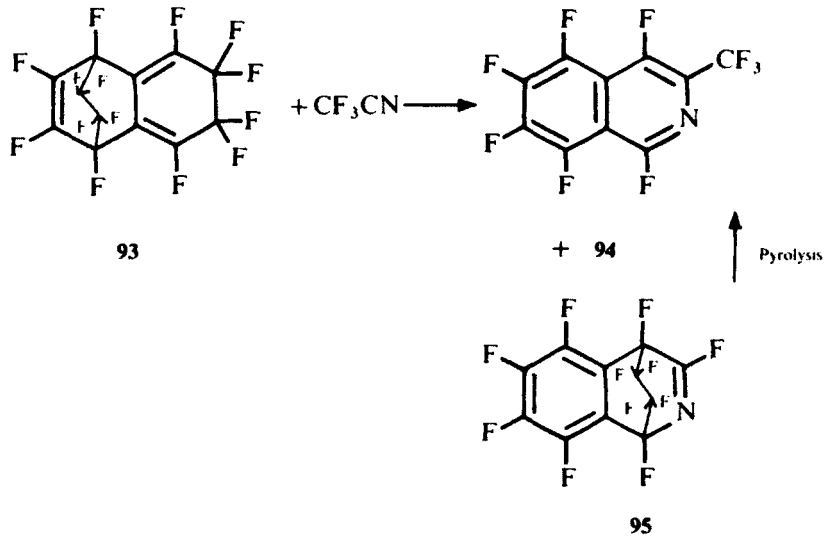
electron-withdrawing substituents continue to engage the attention of chemists. Thermal electrocyclization of 1-aryl-2-aza-1,3-pentadiene (**91**) led to the 3,4-dihydroisoquinolines (**92**) in about 60% yield[136] (Eq. 79).



(79)

91 X = Cl, F **92**

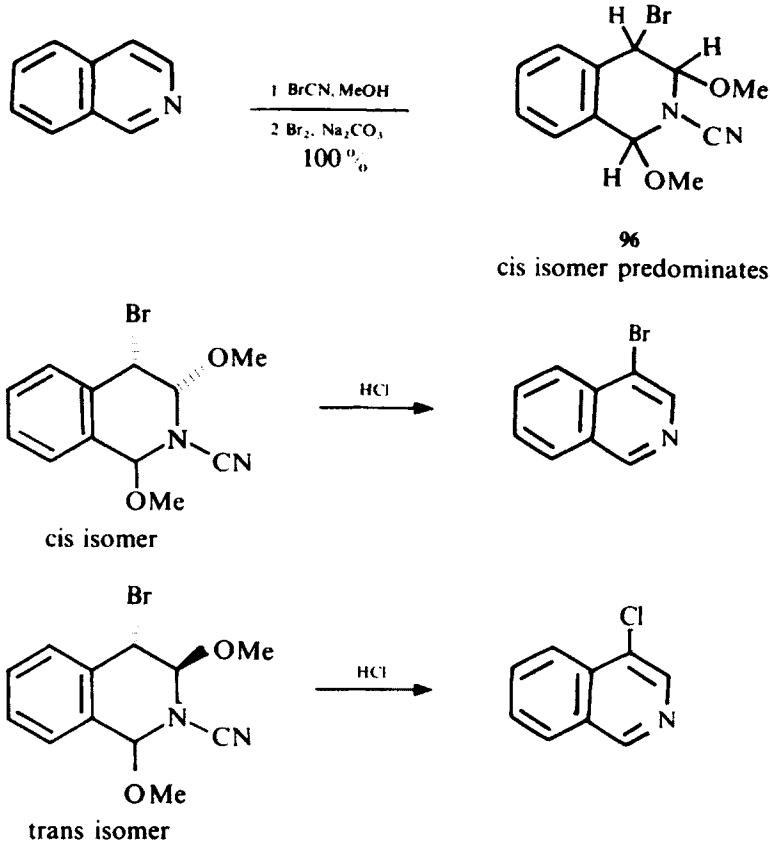
The Diels–Alder reaction of perfluorotricyclo [6,2,2,$0^{2,7}$] dodeca-2,6,9-triene (**93**) with trifluoroacetonitrile led to perfluoro-3-methylisoquinoline (**94**) and the perfluoro compound (**95**), which upon pyrolysis is converted to **94**.[137] (Scheme 13).



Scheme 13

4-Bromoisoquinoline has been obtained by the acidic hydrolysis of 1,3-dimethoxy-4-bromo-2-cyano-1,2,3,4-tetrahydroisoquinoline (**96**), where the hydrogen atoms in positions 3 and 4 are cis oriented. Similar hydrolysis of the trans isomer gave 4-chloroisoquinoline[138] (Scheme 14).

4-Bromoisoquinoline has also been obtained from 2-cyano-1-methoxy-1,2-dihydroisoquinoline (**97**).[139] The various reactions are summarized in Scheme 15.

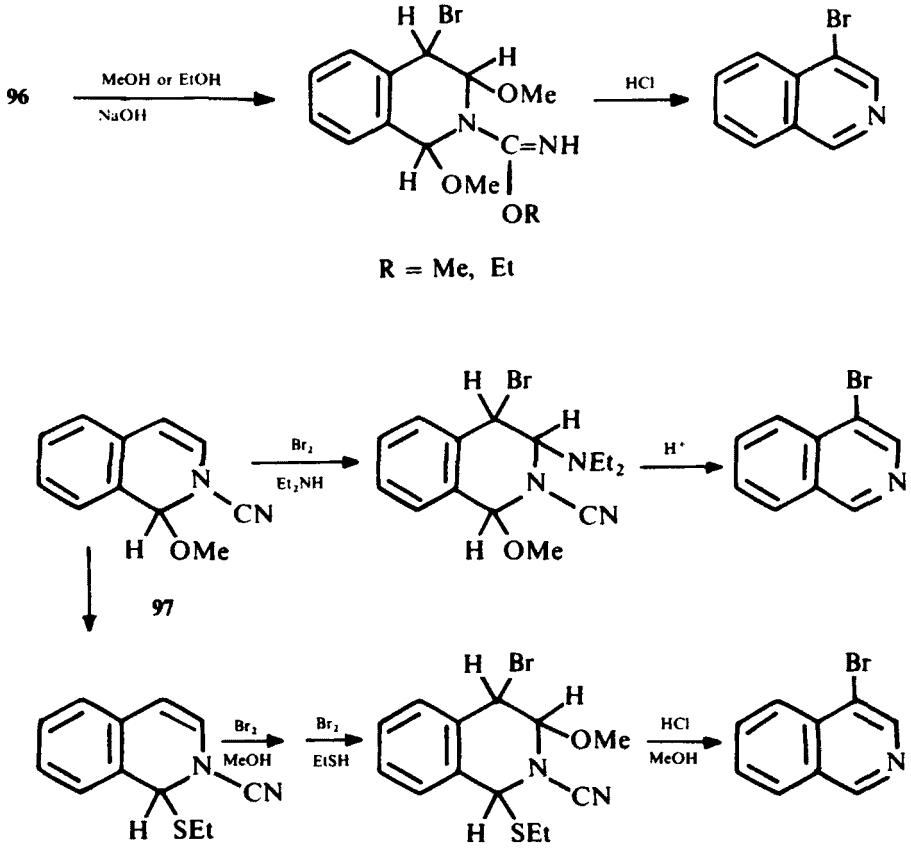


Scheme 14

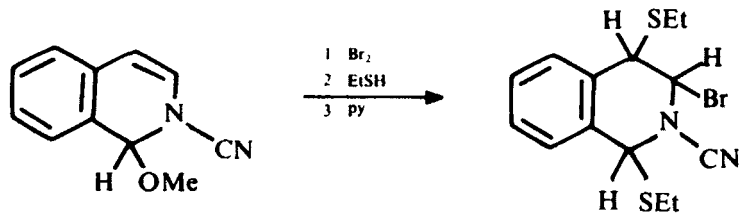
Treatment of 2-cyano-1-methoxy-1,2-dihydroisoquinoline with bromine followed by ethanethiol and then pyridine gave 3-bromo-2-cyano-1,2-diethylthio-1,2,3,4-tetrahydroisoquinoline (Scheme 16).

B. Bromoisoquinolines

The preparation of monobromoisoquinolines has been reviewed.[140] Among the monobromoisoquinolines, the two isomers that have attracted most attention are the 4-bromo- and the 5-bromoisoquinolines. The former is prepared most conveniently by bromination of isoquinoline hydrochloride or hydrobromide with bromine[6, 8] and the latter by bromination of isoquinoline in the presence of aluminium chloride as catalyst.[19] 1-Bromoisoquinoline has been prepared from isocarbostyril;[3] however, not many reports are available on this compound, presumably since the 1-chloro derivative is easily accessible and suitable for further reactions.



Scheme 15



Scheme 16

It would, however, seem reasonable that the 1-bromo isomer can also be easily made by a Meisenheimer rearrangement of isoquinoline *N*-oxide with phosphorus oxybromide. 6-Bromo- and 7-bromoisoquinolines are obtained in fair to good yields from the corresponding bromoindenes by way of intermediate formation of homophthaldehydes.[82] 7-Bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline was prepared in excellent yield by a Sandmeyer reaction of the

corresponding 7-amino compound.[112] 8-Bromo-1,2,3,4-tetrahydroisoquinoline was obtained in 59% yield by a Friedel–Crafts-type ring closure of 2-benzylaminoethanols.[118]

Among the dibromoisoquinolines, 1,3-dibromoisoquinoline is conveniently prepared from homophthalimide,[54] 5,8-dibromoisoquinoline from isoquinoline by bromination in the presence of aluminium chloride[19] and 4,5-dibromo by a Sandmeyer reaction on 5-amino-4-bromoisoquinoline.[94, 104]

5,7,8-Tribromoisoquinoline is prepared in 75% yield from 5,8-dibromoisoquinoline by bromination in the presence of aluminium chloride.[19]

C. Chloroisoquinolines

Several mono-,[20, 219] di-, tri-, and tetrachloroisoquinolines have been synthesized.

1-Chloroisoquinoline may be prepared by a number of methods; the preferred processes, however, are reaction of isocarbostyril[41, 50] or isoquinoline *N*-oxide[35] with phosphorus oxychloride; 3-chloroisoquinoline is prepared by the selective reduction of 1,3-dichloroisoquinoline.[42] Unlike the 4-bromo derivative, the 4-chloroisoquinoline has not been prepared by direct chlorination. The two methods reported are the conversions of 4-hydroxyisoquinoline with phenyl phosphonic chloride[58] and 4-amino isoquinoline under Sandmeyer conditions.[99]

5-Chloroisoquinoline is formed by chlorination by the swamping catalyst process;[19] the yield, however, is much lower than in the case of the 5-bromo derivative. All the benz-substituted chloroisoquinolines can be made most conveniently by the Sandmeyer reaction on the corresponding amino compounds or by Pomeranz–Fritsch reaction of the corresponding benzylidene aminoacetals.[20] 8-Chloro-1,2,3,4-tetrahydroisoquinoline has been obtained by Friedel–Crafts-type ring closure of the corresponding 2-benzylamino ethanols using a melt of aluminium chloride and ammonium chloride.[118]

1,3-Dichloroisoquinoline is obtained in high yield from homophthalimide on reaction with phosphorus oxychloride or phenylphosphonic chloride.[42, 58] While 1,4-dichloroisoquinoline has been reported to be obtained in 100% yield by the action of phosphorus pentachloride on isocarbostyril[59], other dichloroisoquinolines and trichloroisoquinolines are prepared by methods described in Sections II.A(*b*) (ii) and II.A(*d*) (ii)

D. Fluoroisoquinolines

The relatively few fluoroisoquinolines reported in the literature have been synthesized by the Schiemann reaction, starting with the appropriate amino compounds. 7-Fluoro-1,2,3,4-tetrahydroisoquinoline was obtained by Friedel–Crafts ring closure of the corresponding *N*-acetyl-benzyl aminoacetal,

followed by reduction of the 1,2-dihydroisoquinoline obtained and hydrolysis.[116] 1,3-Difluoroisoquinoline is prepared from homophthalimide,[61] while fully fluorinated isoquinoline is obtained from heptachloroisoquinoline.[21] Lithium aluminium hydride reduction selectively removes the 1-fluorine, yielding hexafluoroisoquinoline.

E. Iodoisoquinolines

Not many iodoisoquinolines are reported in the literature. The Sandmeyer reaction[84, 114] and the replacement of chlorine by iodine[131] are the methods of choice for the synthesis of iodoisoquinolines. 1-, 3-, and 4-iodoisoquinolines have been obtained in excellent yields from the corresponding trimethylstannyl compounds (see Section VI. D). Both 6- and 7-iodoisoquinolines can be obtained from the corresponding indenes.[82]

Intramolecular cyclization of *o*-cyanophenylacetic acids and derivatives yield iodoisoquinolines.[72] Iodination of the isoquinoline nucleus, activated by the hydroxy group using iodine monochloride or even iodine in potassium iodide, has also been successfully utilized for the synthesis of certain derivatives.

F. Isoquinolines Substituted by Different Halogens

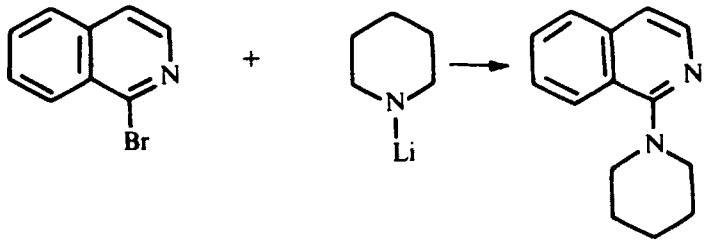
Mixed haloisoquinolines have been prepared by various methods. For example, 1-bromo-3-fluoroisoquinoline is obtained by a Schiemann reaction on 3-amino-1-bromoisoquinoline,[115] while 4-bromo-1-chloroisoquinoline is conveniently prepared by the Meisenheimer rearrangement of 4-bromoisoquinoline *N*-oxide.[36] In general, 1-chloroisoquinoline carrying other substituents, halogens or otherwise, are preferably synthesized from the *N*-oxides.

III. REACTIONS OF HALOGENATED ISOQUINOLINES

A. Nucleophilic Replacements

Among all the possible haloisoquinolines, the compounds carrying a 1-halogen are the most susceptible to nucleophilic displacements. Such reactivity is entirely analogous to the increased activity of the 2 and 4 halogens in halogenated pyridines and quinolines. Molecular orbital calculations using the isolated molecule, localization and delocalization approaches, and correlation with experimental activation and free energies in nucleophilic substitutions substantiate the increased activity of the 1-halogen atom[141] followed by the 3-isomer. In the case of fluoroisoquinolines, only the 1-isomer underwent halogen atom replacement when treated with sodium hydroxide.[115] The mechanism of

this nucleophilic substitution has been investigated in the case of the reaction of 1-bromoisoquinoline with lithium piperidide, quantitating the products of this reaction. Thus, in this reaction, 1-piperidinoisoquinoline was formed in 91.5% yield, isoquinoline in 1%, and 1-bromoisoquinoline was recovered in 3% yield (Eq. 80).



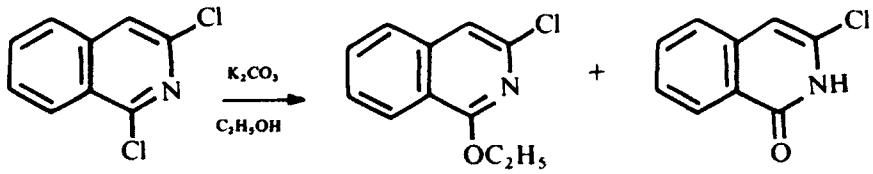
(80)

Other studies to evaluate the kinetics of the reaction of 1-chloroisoquinoline with sodium ethoxide,[143] dimethylamine,[144] and piperidine[145] are also reported.

The variation in the reactivity of halogen atoms caused by the fusion of a benzene ring to 2- or 4-chloropyridines in various possible ways with respect to bond fixation has also been studied.[146]

1-Haloisoquinolines are readily converted to isocarbostyrils either directly under hydrolytic conditions or stepwise through a 1-acetoxy derivative. They are also formed as by-products during nucleophilic displacement reactions on 1-haloisoquinolines.

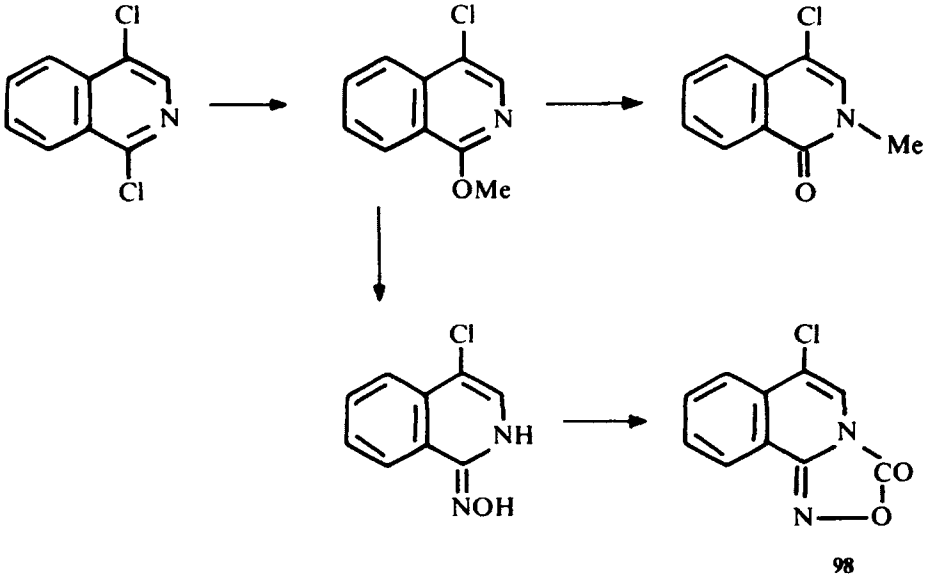
1,3-Dichloroisoquinoline reacts with sodium methoxide[42] to yield 1-methoxy-3-chloroisoquinoline, while with alcoholic potash, a mixture of 3-chloroisocarbostyril and 3-chloro-1-ethoxyisoquinoline is obtained[42] (Eq. 81).



(81)

Similarly, *p*-chloroaniline and *β*-diethylaminoethylamine react with 1,3-dichloroisoquinoline to yield 1-substituted products, keeping the 3-chlorine atom intact. Under more drastic conditions, 1,3-disubstituted derivatives are also obtained.[147]

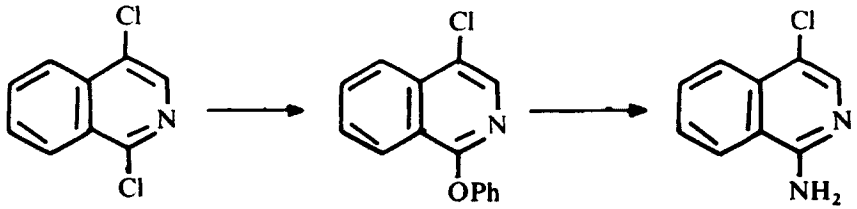
Treatment of 1,4-dichloroisoquinoline with sodium methoxide affords 4-chloro-1-methoxyisoquinoline.[148, 149] This, in turn, was converted to 4-chloro-2-methylisocarbostyril, which is useful in the control of rice blast.[148] The reaction of 4-chloro-1-methoxyisoquinoline with hydroxylamine, followed by treatment with phosgene in pyridine, led to **98**[149] (Scheme 17).



98

Scheme 17

When 1,4-dichloroisoquinoline is heated with phenol and potassium hydroxide, 4-chloro-1-phenoxyisoquinoline was obtained, which was further converted to 1-amino-4-chloroisoquinoline (Scheme 18). 1-Aminoisoquinoline was prepared by the same sequence starting from 1-chloroisoquinoline.[150]



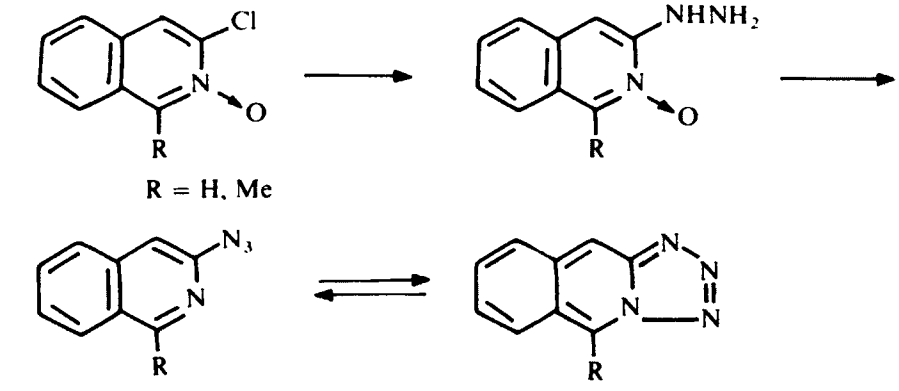
Scheme 18

Linearly fused tetrazole systems can be synthesized starting from 3-chloroisoquinoline *N*-oxides.[151, 152] (Scheme 19).

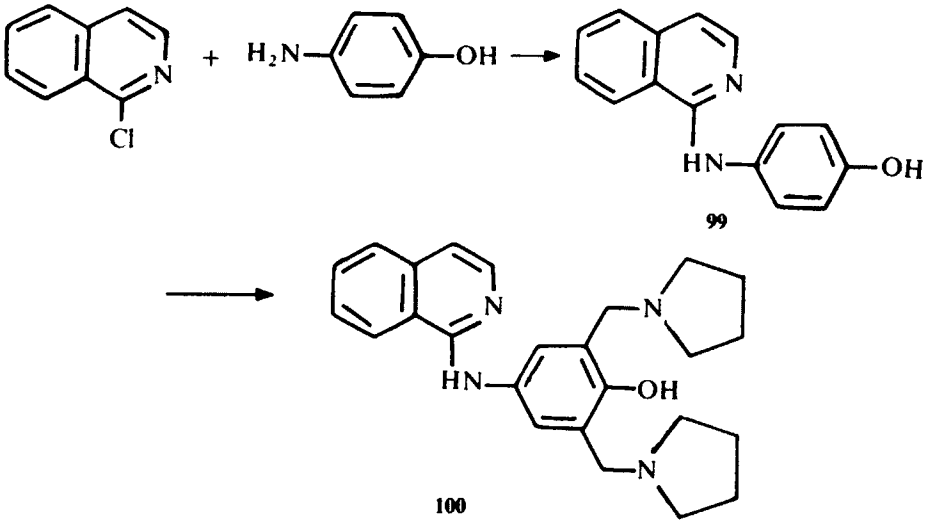
1-Bromoisoquinoline or 1-chloroisoquinoline reacts with amide in ammonia,[153] secondary amines,[145] and anilines[147] to yield 1-aminoisoquinolines.

To test the antiarrythmic and parasympatholytic properties of substituted phenols, 1-chloroisoquinoline was treated with *p*-aminophenol. Bisaminomethylation of 1-(4-hydroxyanilino)isoquinoline (**99**) then gave compound **100**[154] (Scheme 20).

A dibromoisoquinoline has been reported to have been converted to an aminobromoisoquinoline.[155]

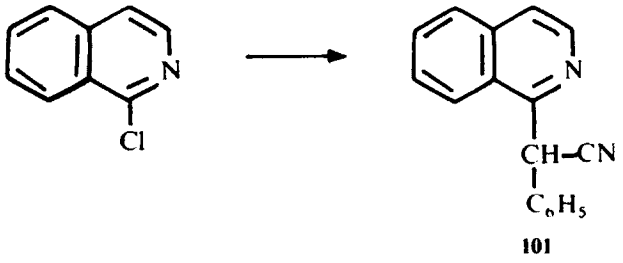


Scheme 19



Scheme 20

1-Chloroisoquinoline reacts with active methylene compounds under base catalysis. Thus, in the presence of sodium amide, 1-chloroisoquinoline even reacts with phenylacetonitrile[35, 156] to yield compound (**101**) (Eq. 82).

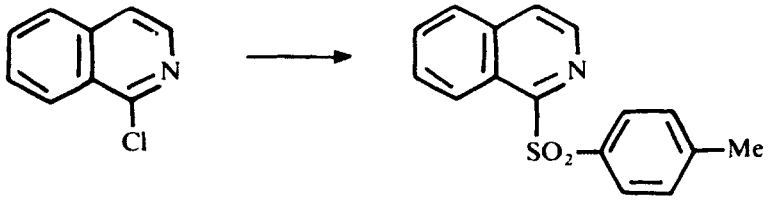


(82)

101

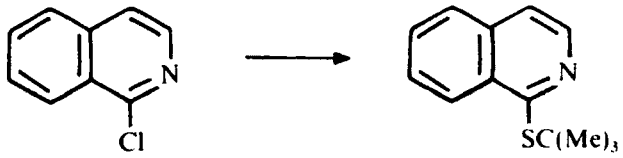
Nucleophilic aromatic substitution of 1-chloroisoquinoline by carbanions of 2-phenylalkanenitriles generated in a catalytic two-phase system has been reported.[157]

When 1-chloroisoquinoline is reacted with sodium *p*-toluenesulfinate, the corresponding sulfone is formed.[158] (Eq. 83).



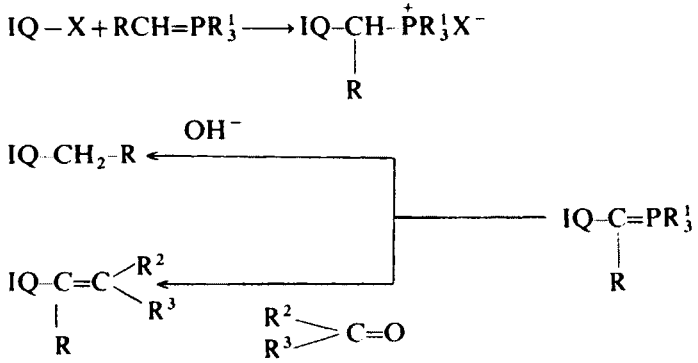
(83)

t-Butylthioethers can be obtained by reaction of 1-chloroisoquinoline with sodium *t*-butylthiolate suspension[159] (Eq. 84).



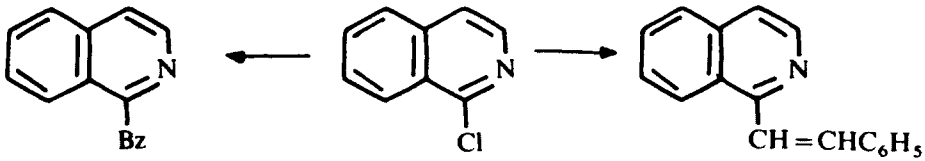
(84)

1-Chloroisoquinoline can be alkylated or alkenylated by reaction with a Wittig reagent (alkylidene phosphorane), and hydrolysis of the resulting ylide to yield the alkyl derivative or reaction with a carbonyl compound to yield the alkenyl derivative (Scheme 21).



Scheme 21

Thus, 1-chloroisoquinoline reacts with methylene triphenylphosphorane, followed by reaction with benzaldehyde, to yield 1-styrylisoquinoline and with benzylidene tri-*n*-butylphosphorane to yield 1-benzylisoquinoline[160] (Scheme 22).



Bz = benzyl

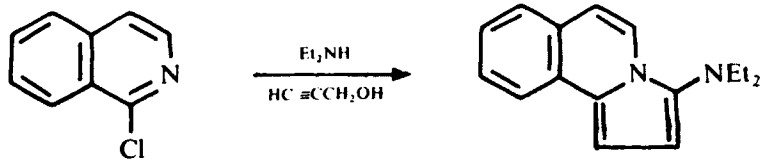
Scheme 22

In a similar fashion, papaverine is synthesized in one step by reaction of 1-chloro-6,7-dimethoxyisoquinoline with the Wittig reagent formed from veratryl chloride and tri-*n*-butylphosphine.[160]

Alkylation[39, 161] and arylation[161, 162] of haloisoquinolines can be effected efficiently by palladium[39] or nickel phosphine-catalyzed[161, 162] coupling with Grignard reagents. Thus, 4-methylisoquinoline was obtained from 4-bromoisoquinoline, while 1-methyl-, 1-ethyl- and 1-benzylisoquinolines were obtained by coupling with the corresponding Grignard reagents using [($NiCl_2$ (dppp)$_2$)] as catalyst.[161] This coupling reaction has also been used to synthesize the precursors for isoquinoline alkaloids, cryptostyline II (Scheme 23) and methopholine.[161]

It has been found that the order of reactivity of positional isomers of haloisoquinolines in the coupling reaction follows that reported by Dyall.[163] Thus, 1-and 5-haloisoquinolines reacted much faster than the 6-, 7-, and 8-isomers.[162]

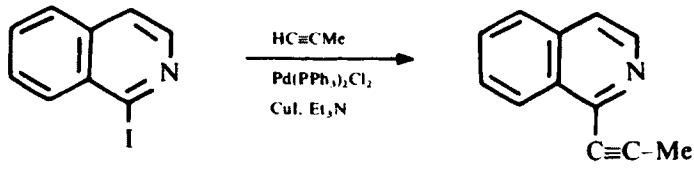
Treatment of 1-chloroisoquinoline with propargyl alcohol and diethylamine yields the pyrrolo [2, 1-a] isoquinoline derivative **102**[164] (Eq. 85).



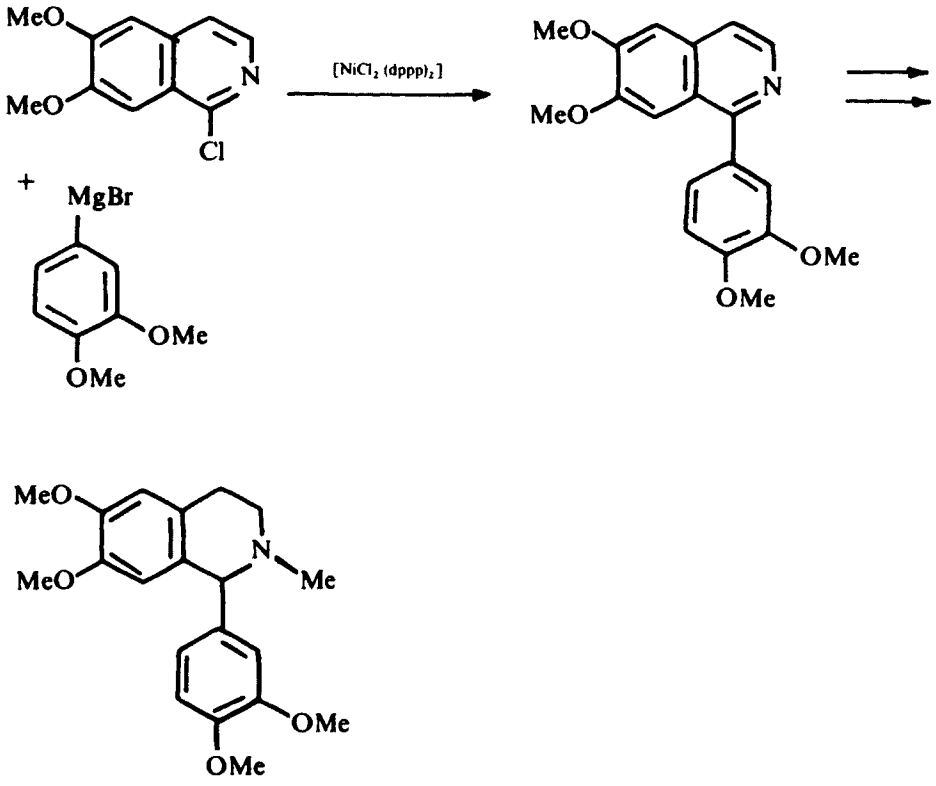
(85)

102

Monosubstituted acetylenes can be condensed efficiently with bromo- or iodoisoquinolines using a palladium–phosphine complex in the presence of copper iodide.[14, 165] Thus, 1-propynylisoquinoline was obtained[165] (Eq. 86).



(86)

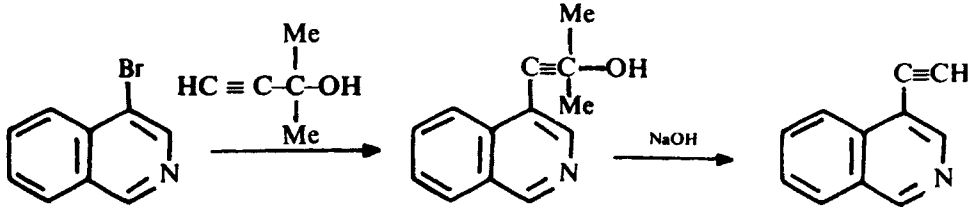


Cryptostyline II

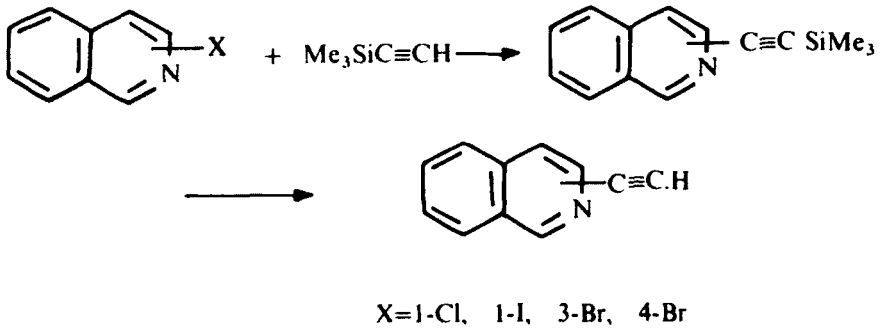
Scheme 23

This method has been extended to the preparation of ethynylisoquinolines by use of 2-methyl-but-3-yn-2-ol as the protected acetylene source[166] (Scheme 24).

Ethynylisoquinolines can also be prepared using trimethylsilylacetylene and subsequent removal of the trimethylsilyl groups using aqueous methanolic potassium hydroxide[167] (Scheme 25).



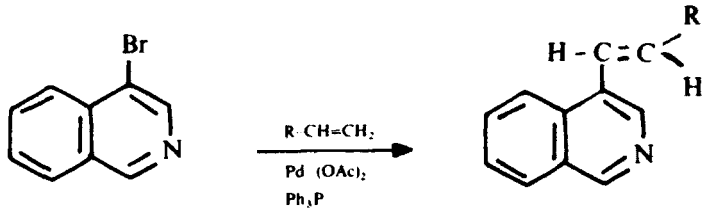
Scheme 24



X=1-Cl, 1-I, 3-Br, 4-Br

Scheme 25

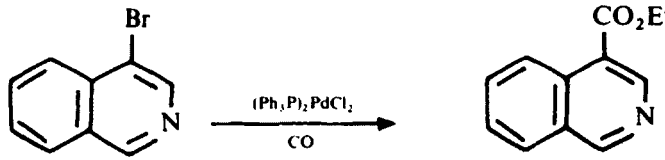
4-Bromoisoquinoline can be coupled with olefins in the presence of palladium acetate and triphenylphosphine[168] (Eq. 87).



(87)

R = COOEt, CN, Ph

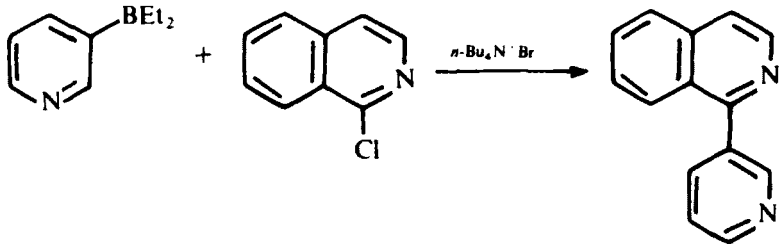
4-Bromoisoquinoline was carbonylated in ethanol containing palladium phosphine catalyst to produce 4-carbethoxyisoquinoline (**103**)[169] (Eq. 88).



(88)

103

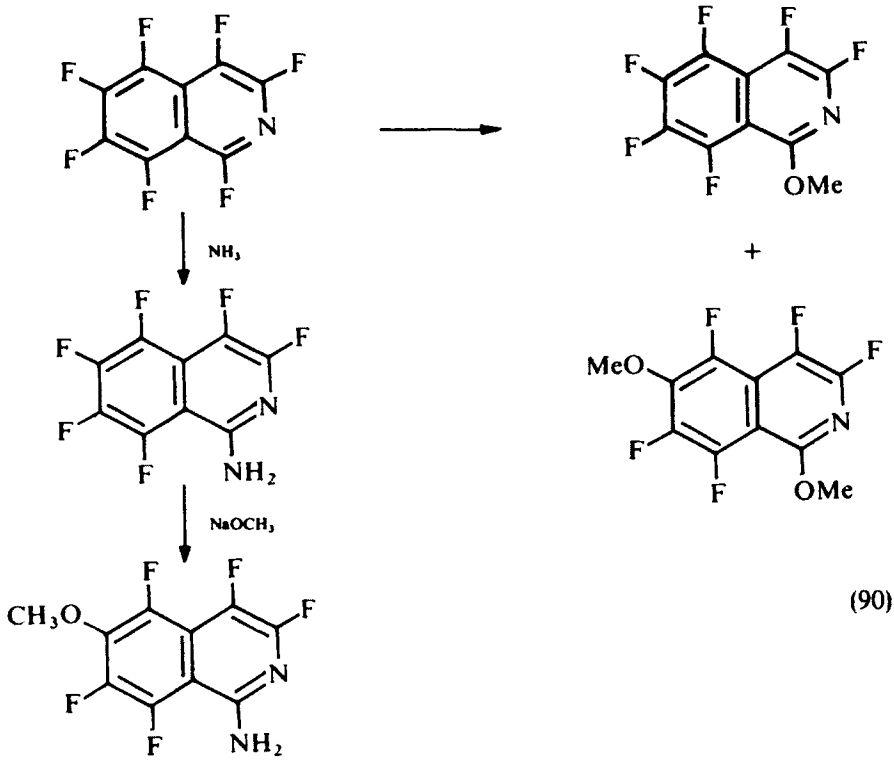
3-Isoquinolylpyridine is synthesised by palladium-catalyzed cross-coupling of diethyl-(3-pyridyl) borane with 1-chloroisoquinoline in the presence of base[170] (Eq. 89).



(89)

The α-L-arabinofuranosyl-4-bromoisoquinolinium salt has been prepared by treatment of the sugar bromide with 4-bromoisoquinoline in the presence of base tetrabutylammonium bromide, and the hydrolysis studied to obtain information on enzymic and nonenzymic glycoside hydrolysis.[171] Similar experiments with α-D-xylopyranosyl and α-D-glucopyranosyl salts of 4-bromoisoquinoline were interpreted in terms of a failure of the antiperiplanar lone-pair hypothesis in glycoside hydrolysis.[172]

The reaction of heptafluoroisoquinoline with sodium methoxide occurs both at the 1-fluoro and 6-fluoro positions to provide a mixture of 1-methoxy and 1,6-dimethoxy fluorinated isoquinolines. When using ammonia, only the 1-amino-hexafluoroisoquinoline is formed. Subsequent treatment with sodium methoxide then furnishes 1-amino-6-methoxypentafluoroisoquinoline[173] (Eq. 90).

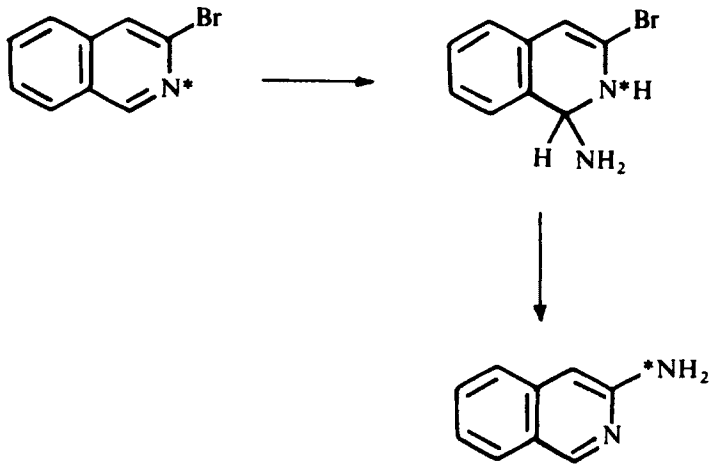


(90)

Similarly, the reaction of heptafluoroisoquinoline with hydrazine hydrate and lithium aluminium hydride occurs only at the 1-fluorine position.[173] Heptafluoroisoquinoline is more reactive toward nucleophiles than pentafluoropyridines.

3-Bromo and 3-chloroisoquinolines react with ammonia to yield 3-amino isoquinoline.[54,153] The reaction of 3-bromoisoquinoline and amide ion in liquid ammonia has been shown to proceed through a ring-opening route. Using the ^{15}N-labeled 3-bromoisoquinoline derivative, it was established that 55% of the

3-aminoisoquinoline forms by ring opening and that the amide ion adds to position 1 prior to rearrangement,[153] (Scheme 26).

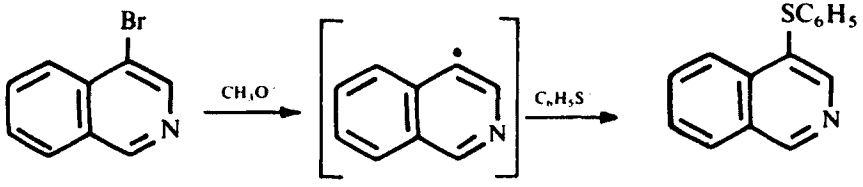


Scheme 26

The reaction of 4-haloisoquinolines with KNH_2 in liquid ammonia yields a mixture of products involving abnormal addition–elimination sequences. The mechanism of formation of various products is reported[174] (see Section III. B).

Bromoethoxyisoquinolines with the substituents in the pyridine ring generally undergo simple nucleophilic substitution of the bromine atom with potassium amide in liquid ammonia to give the corresponding amino compounds. However, 4-bromo-3-ethoxyisoquinoline yields a complex mixture of products.[175]

4-Bromoisoquinolines also may be forced to undergo nucleophilic displacement reactions. Thus, 4-bromoisoquinoline reacts with cuprous cyanide in *N*-methylpyrrolidone to yield 4-cyanoisoquinoline,[176] while reaction with ammonia in the presence of copper sulfate gives the 4-amino derivative.[177] 4-Bromoisoquinoline reacts with sodium thiophenolate in methanol at 147 °C to yield 4-thiophenylisoquinoline.[178] In the presence of methoxide ion, isoquinoline is also formed by a reductive dehalogenation. This reaction occurs through a radical chain route initiated by methoxide ion (Scheme 27). The absence of 4-methoxyisoquinoline in the product indicates the superiority of the benzene thiolate in trapping the isoquinolyl radical.

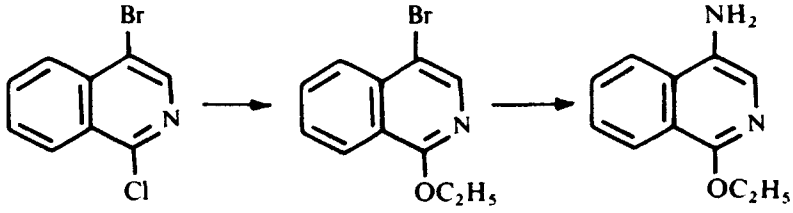


Scheme 27

The exclusive formation of 4-phenylthioisoquinoline in the absence of methoxide proceeds possibly by an ionic route.

The 4-isoquinolyl radical has been generated photochemically from 4-bromoisoquinoline, and its reactivity toward hydrogen abstraction and nucleophilic addition has been compared with the corresponding 3-pyridyl and 3-quinolyl radicals.[179]

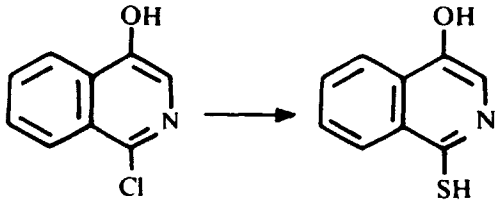
4-Bromo-1-chloro-isoquinoline has been reacted with sodium ethoxide to give 4-bromo-1-ethoxyisoquinoline (**104**), which in turn was converted to 4-amino-1-ethoxyisoquinoline (**105**)[36] (Eq. 91).



(91)

104 **105**

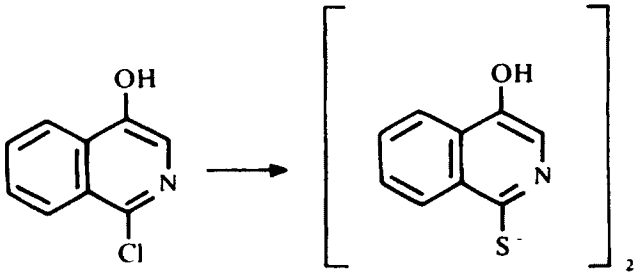
1-Chloro-4-hydroxyisoquinoline reacts with hydrogen sulfide in pyridine to yield 4-hydroxy-1-mercaptoisoquinoline (**106**) in 85% yield[180] (Eq. 92).



(92)

106

Thiourea, on the other hand, yields an isoquinolyl disulfide (**107**), presumably through the intermediacy of an isothiouronium salt which undergoes hydrolysis and oxidation[180] (Eq. 93).



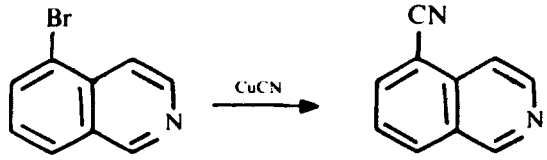
(93)

107

1,1'-Diselenobisisoquinoline was obtained by reaction of sodium hydroselenide with 1-chloroisoquinoline (see Section VI. A).

4-Chloroisoquinoline can be converted into 4-bromoisoquinoline by bromination of a mercury complex.[181] However, the same derivative can be obtained by bromination of mercury derivatives of isoquinoline itself. Interconversions of 1-haloisoquinolines also constitute other examples of replacement reactions. These have been dealt with in Section II. A(*h*)(iv).

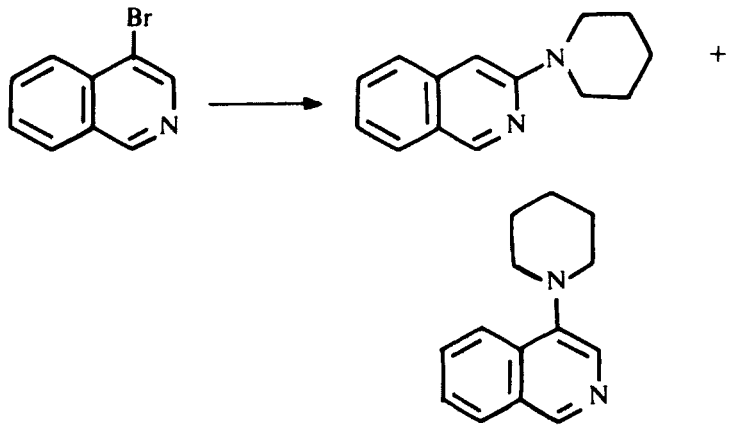
The bromine atom in 5-bromoisoquinoline undergoes replacement by cyanide ion by reaction with cuprous cyanide[84] (Eq. 94). Performing the reaction in dimethyl sulfoxide has been reported to give better yields.[182]



(94)

B. Di-Dehydroisoquinolines

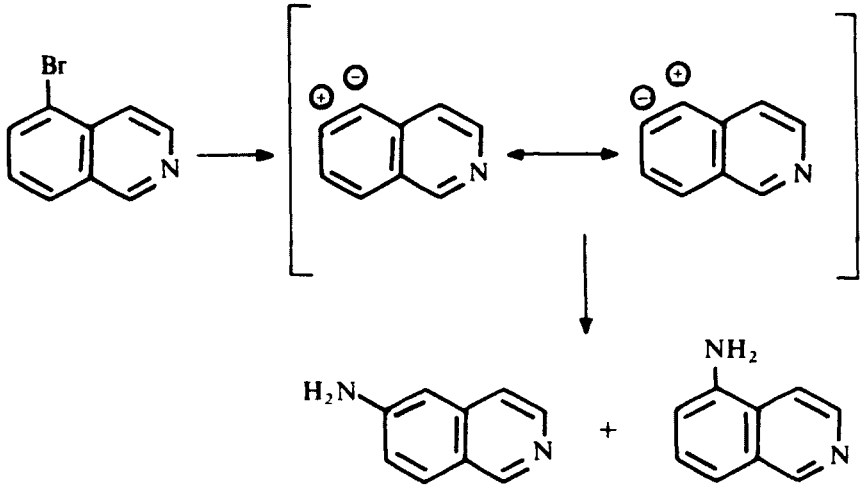
Unlike in the quinoline series, very little work has been reported on dehydroisoquinolines. 3,4-Di-dehydroisoquinoline is reported to be formed from 4-bromoisoquinoline with anhydrous piperidine to form the 3- and 4-piperidino isoquinolines in yields of 4 and 35%, respectively.[183,184] (Eq. 95).



(95)

A convenient preparation of 6-aminoisoquinoline in 47% yield consists of the reaction of 5-bromoisoquinoline with potassium amide in liquid ammonia.[185] As expected, 5-aminoisoquinoline was also isolated (21% yield) (Scheme 28).

The reaction of piperidine with 4-haloisoquinoline was reinvestigated by Sanders et al.[174] These authors obtained in addition to the expected 4-piperidinoisoquinoline, 1-piperidino- and 3-piperidinoisoquinolines. The forma-

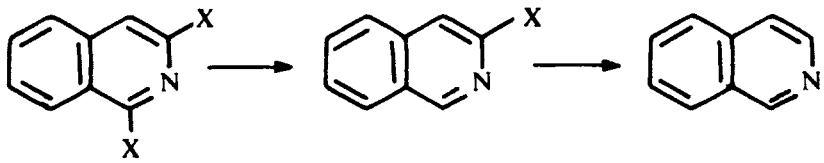


Scheme 28

tion of the 1-isomer is explained by an abnormal addition–elimination (AE_a) mechanism (Scheme 29), and the authors claim that the 3-piperidino isomer also probably results from an addition–elimination, rather than proceeding through a 3,4-didehydroisoquinoline, as suggested earlier.[183]

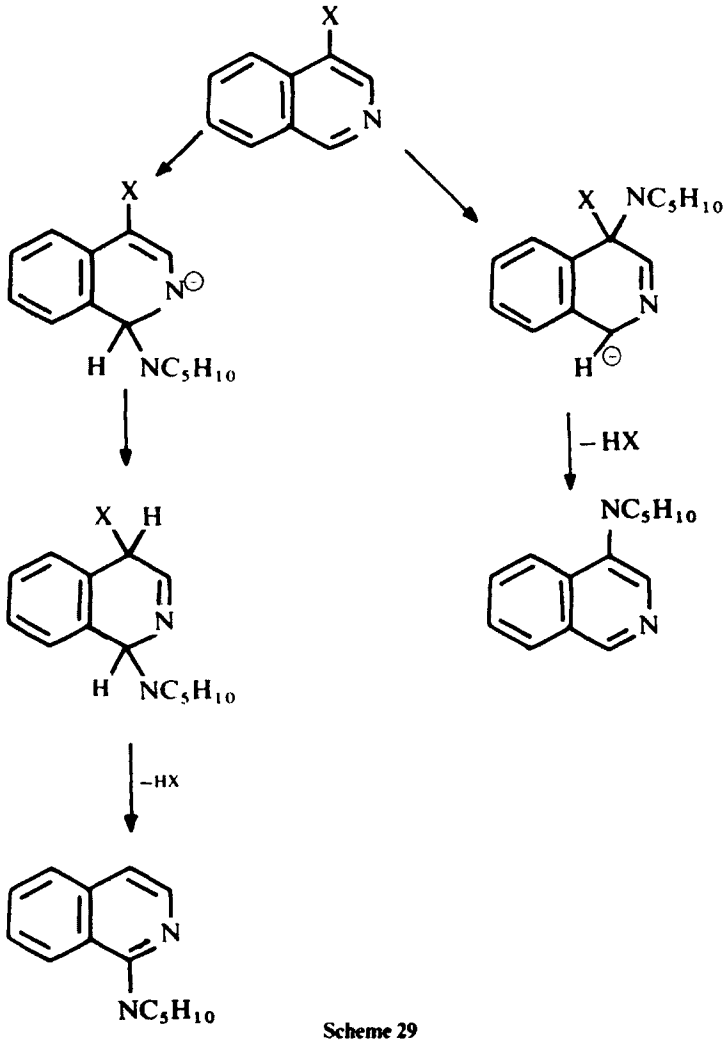
C. Reduction of Haloisoquinolines

Selective removal of halogen atoms from the isoquinoline nucleus has been effectively used as a method of synthesis of isoquinoline derivatives. 1,3-Dichloroisoquinolines under the action of red phosphorus and iodine[42] yield, in a stepwise manner, 3-chloroisoquinoline and isoquinoline (Eq. 96). Raney nickel in an alkaline medium also yields similar results both with 1,3-dichloro- as well as 1,3-dibromoisoquinoline.

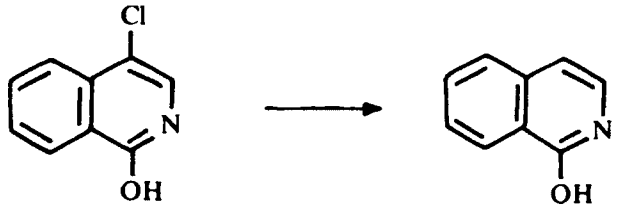


X = Br, Cl (96)

4-Chloroisocarbostyril is reduced catalytically in the presence of palladium–charcoal to isocarbostyril[59] (Eq. 97).



Scheme 29

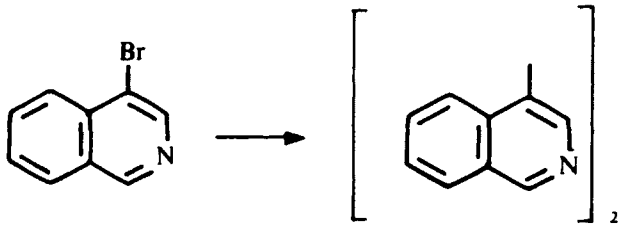


(97)

1-Bromo-4-(4-aminophenyl)isoquinoline is debrominated to the corresponding isoquinolines by stannous chloride–hydrochloric acid.[186]

A series of 3-hydroxyisoquinolines was prepared by the catalytic hydrogenation of 1-chloro-3-hydroxyisoquinolines.[68]

4-Bromoisoquinoline is converted during hydrogenation with palladium–calcium carbonate catalyst to bisisoquinoline (**108**)[187] (Eq. 98), while with sodium hydrazide in hydrazine, it undergoes reductive dehalogenation to isoquinoline.[188]



(98)

108

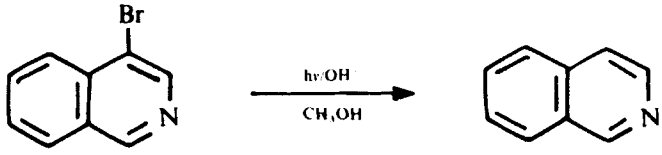
Sodium thiophenolate in the presence of sodium methoxide converts 4-bromoisoquinoline to a mixture of 4-phenylmercaptoisoquinoline and isoquinoline, while in the absence of the base, the former is the only product[178] (Eq. 99) (see also Scheme 27).

(99)

Electrolytic reduction of heptachloroisoquinoline yields hexachloro- and pentachloroisoquinolines[132] [see Section II. A(*h*) (v)].

1,3-Dichloro-5,6,7,8-tetrahydroisoquinoline is reductively dehalogenated by zinc and acetic acid to 5,6,7,8-tetrahydroisoquinoline[189] while 4-chloro-1,2,3,4-tetrahydroisoquinoline undergoes conversion to 1,2,3,4,-tetrahydroisoquinoline during catalytic hydrogenation.[36]

Photodebromination of 4-bromoisoquinoline has been recently reported[190] in the presence of alkali and methanol. The debromination involves electron donation to the excited bromoisoquinoline and abstraction of hydrogen radical from methanol (Eq. 100) (see also Section III.A).



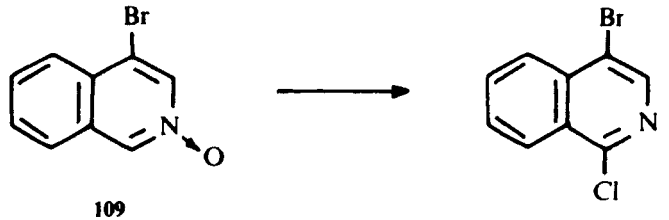
(100)

D. *N*-Oxidation

Halosubstituted isoquinolines undergo *N*-oxidation with the usual reagents, but peracetic acid is the preferred reagent. 1-Chloroisoquinoline, however, on

treatment with hydrogen peroxide and acetic acid was converted into 4-chloroisocarbostyril in 20–24% yield. [59]

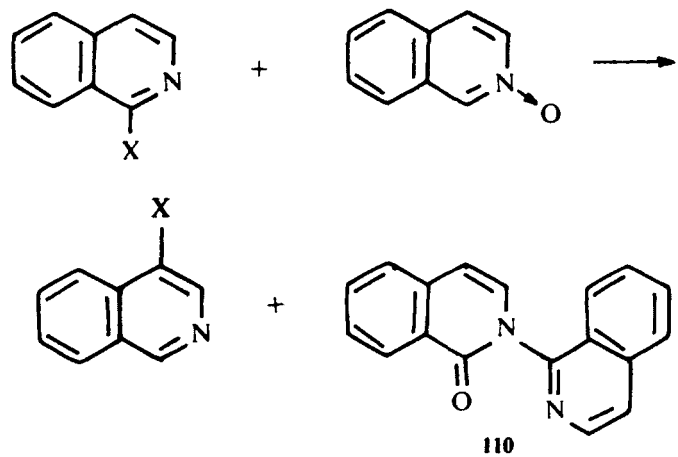
The versatility of the *N*-oxides for further activating the nucleus toward substitution reactions, their facile deoxygenations with phosphorus trichloride, and the diverse rearrangements that these derivatives undergo have made this class of compounds valuable intermediates for the synthesis of isoquinoline derivatives. For example, except for the 1-fluoroisomer, none of the fluoroisoquinolines have a replaceable halogen. In the corresponding *N*-oxides, however, replacements could be effected with nucleophilic reagents in all fluoroisoquinolines except in those cases where the fluorine atom is in the 5 and 7 position.[115] The *N*-oxide can also be used for the introduction of a halogen (especially chlorine or bromine) in the 1 position of the isoquinoline nucleus. 4-Bromoisoquinoline undergoes ready *N*-oxidation and the product (**109**) can easily be converted to 4-bromo-1-chloroisoquinoline by the action of phosphorus oxychloride[191] (Eq. 101) [see Section II. A (*c*) (ii)].



(101)

109

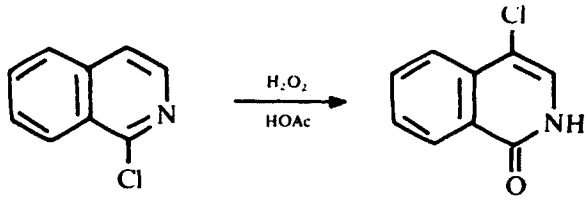
1-Bromo- and 1-chloroisoquinolines react with isoquinoline *N*-oxide to form 4-bromo- and 4-chloroisoquinolines[33] (Eq. 102) along with a substituted isocarbostyril derivative (**110**).



(102)

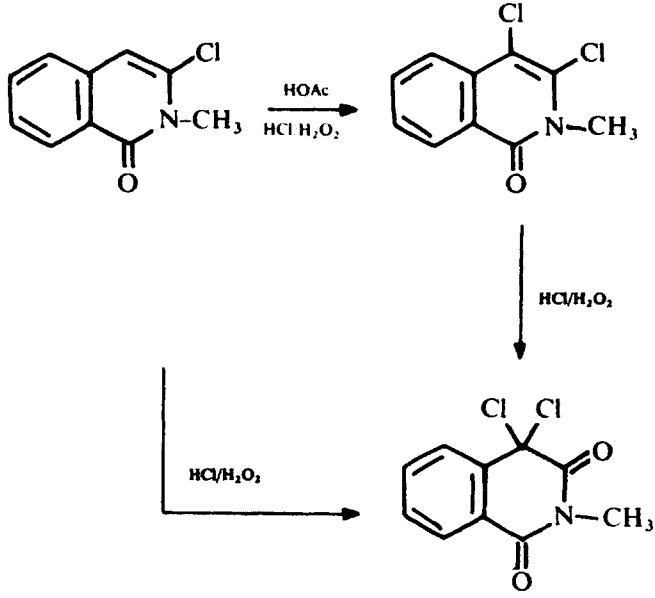
110

On oxidation with hydrogen peroxide and acetic acid, 1-chloroisoquinoline gives, in 87% yield, 4-chloroisocarbostyril[59] (Eq. 103) which is easily convertible into 1,4-dichloroisoquinoline. In a series of related rearrangements, it was found



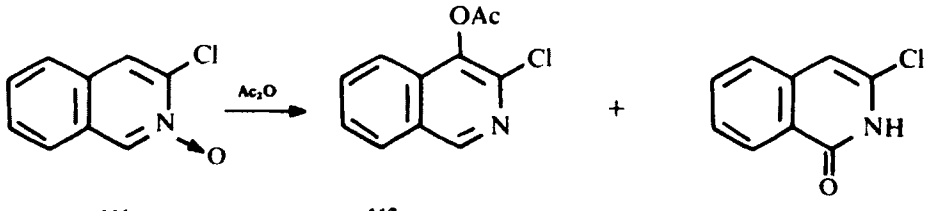
(103)

that 3-chloro-*N*-methylisocarbostyril was converted to α-dichlorohomophthalimide or 3,4-dichloro-*N*-methyl isocarbostyril by choosing the reaction conditions[43] (Scheme 30).



Scheme 30

3-Chloroisoquinoline *N*-oxide (**111**) on treatment with acetic anhydride is converted into a mixture of 4-acetoxy-3-chloroisoquinoline (**112**) and 3-chloroisocarbostyril[192] (Eq. 104).

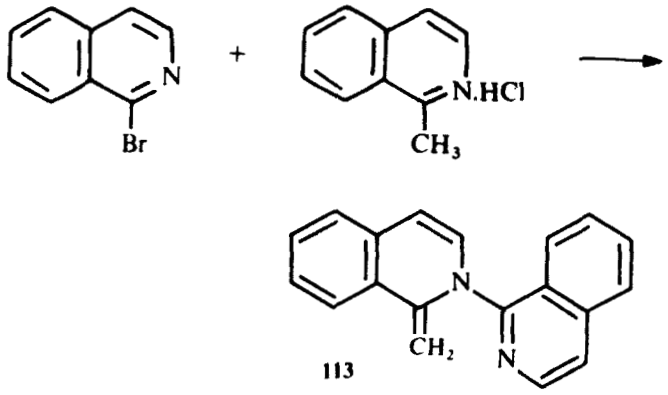


111 **112**

(104)

E. Other Reactions

Unlike the case of the reaction of 2-methylquinoline with 2-chloroquinoline,[193] which yields 2,2',2''-triquinolylmethane, 1-bromoisoquinoline *N*-alkylates 1-methyl isoquinoline hydrochloride to yield a 1-methylene isoquinoline derivative (**113**) in 44% yield[194] (Eq. 105).

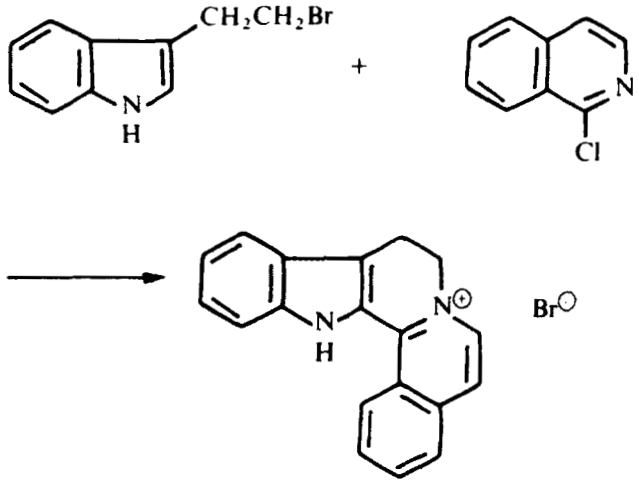


(105)

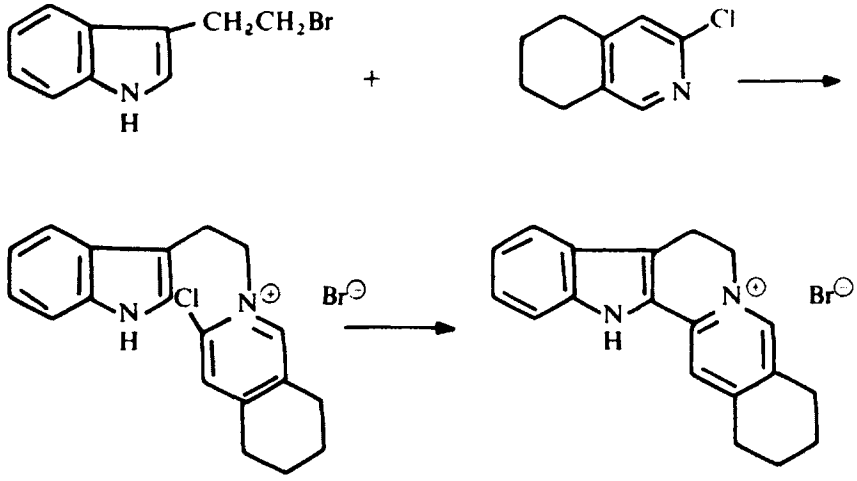
113

1-Chloroisoquinoline and 3-chloro-5,6,7,8-tetrahydroisoquinoline have been employed for the synthesis of polycyclic indole systems and alkaloids of the Sempervirine class (Schemes 31 and 32). Their reactions with 3-β-bromoethylindoles have been studied in detail.[195, 196]

1-(3-Benzyloxy-4-methoxybenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline (**114**) has been used for the preparation of the oxoaporphine alkaloid



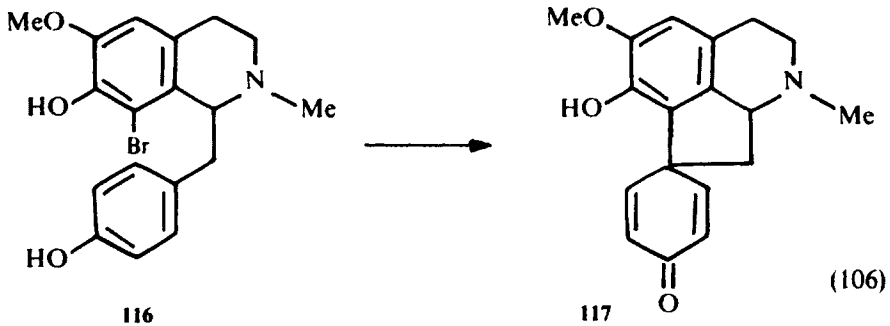
Scheme 31



Scheme 32

atheroline (**115**) in a series of steps, including oxidation followed by debenzylation and photolysis in the presence of sodium hydroxide[197, 198] (Scheme 33). The corresponding 10, 11-oxoaporphine was also obtained during photolysis.

Photolysis of the 8-bromo-1,2,3,4-tetrahydroisoquinoline **116** in alkaline solution led to (±)-glaziovine (**117**)[25, 199] (Eq. 106).



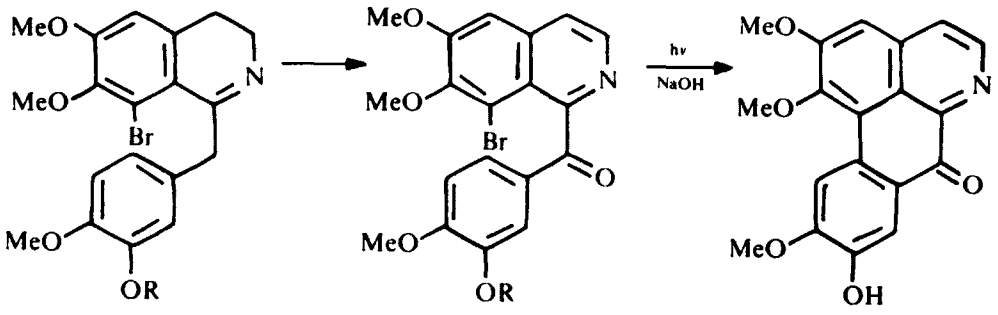
(106)

116 **117**

The protoberberine alkaloid caseadine has been synthesized, starting from 8-benzyloxy-1-chloro-7-methoxyisoquinoline and dimethoxyhomophthalic anhydride.[200] In a similar fashion, 1-chloroisoquinoline was treated with glutaconic anhydride and α-methylhomophthalic anhydride.[201]

Several syntheses of ellipticine and its derivatives, which are useful as antitumor agents, have been reported in a series of steps starting from substituted haloisoquinolines.[202–205]

A bromoisoquinoline has also been used for the synthesis of the azafluoranthene alkaloids rufescine and imelutine.[206]

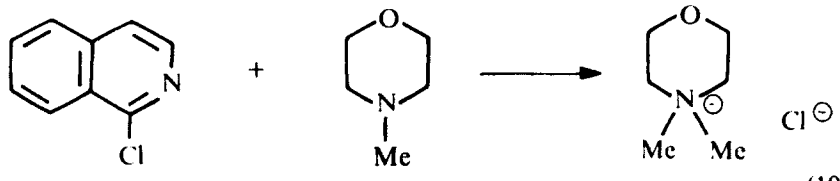


114 R = Bz, H 115

Scheme 33

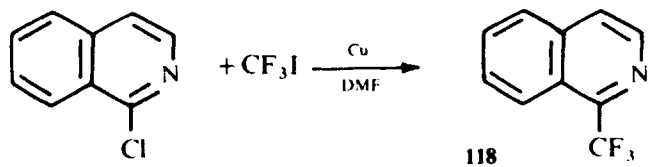
The bisbenzylisoquinoline alkaloids trilobine, isotrilobine, and obaberine have been synthesized starting from *O*-benzyl-8-bromo-*N*-norarmepavine.[207]

Reaction of 1-chloroisoquinoline with 4-methyl morpholine and trimethylamine yields, as the only isolable products, the quaternary methyl chloride of these bases[208] (Eq. 107). It is possible that the normal quaternary product with isoquinoline formed initially may be sufficiently reactive to generate methylchloride, which in turn quaternizes the 4-methylmorpholine or trimethylamine.



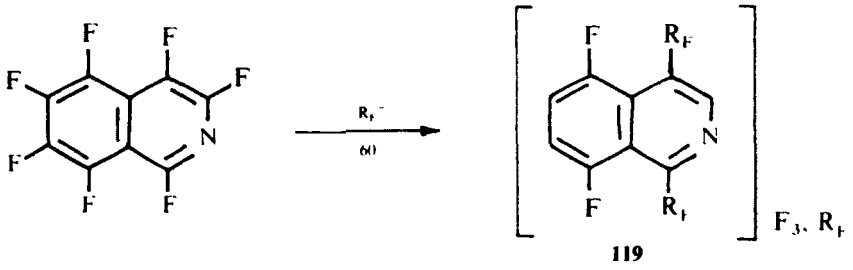
(107)

1-Trifluoromethylisoquinoline (**118**) has been prepared by the action of trifluoromethyl iodide on 1-chloroisoquinoline or 1-iodoisoquinoline in the presence of copper[209, 210] (Eq. 108).



118 (108)

The multiple thermally induced isomerization of bromo and chloro decahydroisoquinoline has already been reported [see Section II.A(*h*) (v)].



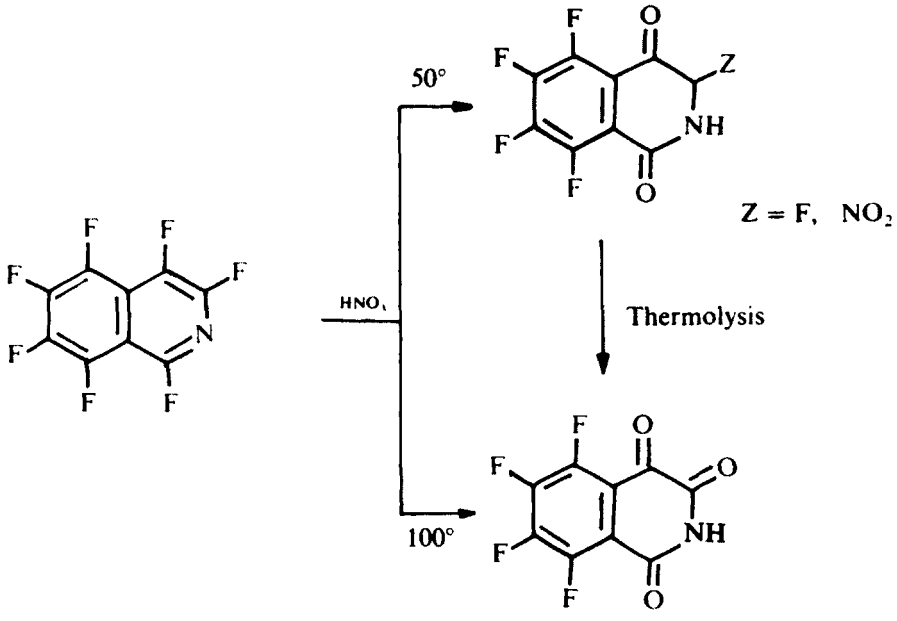
119

$$R_F = -CF\ \ (CF_3)\ \ CF_2 \cdot CF_3 \tag{109}$$

When perfluoroisoquinoline was perfluoroalkylated with octafluorobut-2-ene a complex mixture of products was obtained,[211] the major component being **119** (Eq. 109).

4-Bromoisoquinoline on nitration, yields 4-bromo-5-nitroisoquinoline, which possesses fungicidal activity. Other derivatives with halogen and/or nitro substituents were also prepared.[212]

Oxidation of perfluoroisoquinoline with fuming nitric acid at 50°C gives 5,6,7,8-perfluoro-1,2,3,4-tetrahydro-3-nitro-1,4-dioxoisoquinoline which, on thermolysis, yields 5,6,7,8-tetrafluoro-1,3,4-trioxo-1,2,3,4-tetrahydroisoquinoline, which can also be obtained directly from perfluoroisoquinoline by nitration at 100°C [213] (Scheme 34).



Scheme 34

IV. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF HALOISOQUINOLINES

The monohaloisoquinolines are colorless liquids or low-melting solids originally isolated as their hydrohalides or picrates. They are, however, readily distillable liquids, and isomers can be separated by fractional distillation.

The ultraviolet (UV) spectra of all seven possible monochloroisoquinolines have been reported.[214] The effect of halogen substituents on the UV spectra of isoquinoline itself has also been determined.[215] The absorption spectra of 1-fluoro-, 3-fluoro-, and 4-fluoroisoquinolines have been published.[216]

The infrared (IR) spectra of a number of isoquinoline derivatives have been reported.[217, 218] However, these data are of only supportive value in the structural elucidation of haloisoquinolines.

The dipole moments of several monohaloisoquinolines have been measured.[94, 219] Based on dipole moments, some structural assignments have been made for other isoquinoline derivatives.[94]

The PK_a's of 4-bromo and a few other substituted isoquinolines are reported in connection with a study on the ionization constants of 3-substituted pyridines, quinolines, and isoquinolines.[220]

The NMR spectrum of isoquinoline itself has been studied in detail. Based on the values of chemical shifts and coupling constants, it has been possible to assign structures to the mono- and polyhaloisoquinolines obtained from various reactions. Of the many monobromoisoquinolines, the 4-bromo isomer has been studied in detail. Extensive spin-decoupling experiments have enabled the determination of the magnitude and relative sign of the long-range coupling constants in 4-bromoisoquinoline.[221] The use of europium shift reagent, Eu $(fod)_3$, was of considerable assistance in the unambiguous assignment of orientation in 3-bromo-, 3,4-dibromo-, and 4-bromo-3-hydroxyisoquinolines.[98] The chemical shifts of H-1, H-3, and H-4 have been determined and the substituent effects of several isoquinolines halogenated in the pyridine nucleus have been studied.[222]

The product of bromination of 4-bromoisoquinoline in the presence of a swamping catalyst, aluminium chloride, has been assigned the 4,5,8-tribromo structure based on an AB quartet at δ7.8, resulting from the two adjacent protons at C_6 and C_7 of the nucleus.[104]

The ^{13}C-NMR shifts have been assigned for chloro-, dichloro-, and chloromethylisoquinolines and some of their *N*-oxides,[223] and for fluoro methyl-1,2,3,4-tetrahydroisoquinolines.[224] Substituent chemical shifts (SCS) are noticed for substitution by both chlorine and fluorine atoms. Chlorine substituent effects have been noted in the alpha, ortho, meta, para and peri positions. The alpha SCS effects vary widely from 1.1 ppm upfield in 1-chloroisoquinoline to 0.7 ppm downfield in 4-chloroisoquinoline. These effects, in comparison with those in literature, allow the extent of steric and nitrogen lone-pair contribution to be defined in modifying SCS effects, and these have been shown to be roughly additive.[223]

Fluorine substitution in the phenyl ring manifests itself in two ways.[224] There is a striking effect on the ^{13}C chemical shift, the carbon bearing the fluorine atom being deshielded by >30 ppm, whereas the carbon ortho to fluorine shows a large upfield shift $\simeq$ 14 ppm, the carbon para to fluorine a shielding effect of $\simeq$ 5 ppm, and the carbon meta to fluorine experience a deshielding effect of 1–2 ppm.

In addition, because of fluorine substitution, there is a characteristic regular pattern in the aromatic region of the proton-decoupled spectrum.

$$^1J \simeq 245 \text{ Hz} > > ^2J \simeq 18\text{–}20 \text{ Hz} > ^3J \simeq 6\text{–}9 \text{ Hz} > ^4J \simeq 1.5\text{–}4 \text{ Hz}$$

The ^{19}F-NMR spectra of fluoroisoquinolines have been measured.[225,226] Both chemical shifts and coupling constants are of value in the assignment of structures. The large peri 1,8 and 4,5 couplings of the order of 60–65 Hz and 50 Hz are of considerable assistance in identifying the substitution patterns.[173] For example, the structures of products obtained from the reaction of sodium methoxide with heptafluoroisoquinoline have been unambiguously established by correlation of the chemical shifts and coupling constants in their ^{19}F NMR spectra.

While mass spectral fragmentation patterns of isoquinoline, alkyl and hydroxy isoquinoline, and isoquinoline *N*-oxide[227] and 1,2,3,4-tetrahydroisoquinolines[228] have been studied in some detail, there has been little systematic study of the mass spectra of haloisoquinolines.

V. USES

None of the haloisoquinolines or their simple derivatives has been known to be useful as pharmaceutical agents. Several chloro-1,2,3,4-tetrahydroisoquinolines are inhibitors of the enzyme phenylethanolamine *N*-methyltransferase. 7,8-Dichloro-1,2,3,4-tetrahydroisoquinoline displays a marked hypotensive activity[229,230] and is under clinical investigation.[20] 6,7-Dichloro-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline is useful as a β-adrenergic receptor blocking agent.[231] Perfluoro-2-methyl decahydroisoquinoline has been examined as a potential blood substitute.[232] Reports on the synthesis of many derivatives as potentially biologically active preparations are available. Thus, 1-β-dialkylaminoalkyl isoquinolines synthesized for antimalarial screening from 1-chloroisoquinoline[100] were devoid of such activity, as was the case of 1-anilino derivatives.[147]

A French patent claims the uses of 4-alkoxy-1-(2-di-alkylaminoethoxy)isoquinolines as local anesthetics,[60] while a group of substituted 1-chloroisoquinolines are also claimed to have local anesthetic, in addition to antispasmodic activity.[50]

The bronchodilatory activity of derivatives of 1-chloro-6,7-dimethoxyisoquinoline has been reported.[233] Products derived from 7-chloro-1-methylmercapto-3,4-dihydroisoquinoline have reportedly antitussive and antifibrillatory properties.[234]

In view of the reported amoebicidal properties of iodohydroxyquinolines, similar derivatives in the isoquinoline series have been prepared.[30] However, none of them exhibited any antiamoebic activity at the doses employed.

Several imidazolylisoquinolines have been prepared by treating the corresponding 1-chloroisoquinolines with imidazoles in the presence of base and their hypolipemic and hypoglycemic activities have been tested.[235]

In a search for CNS-active compounds, ethyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate was treated with different substituted 1-chloroisoquinolines to obtain the corresponding substitution products.[236]

As part of a program to synthesize nitro heterocycles with antimicrobial activity, 1-chloro-4-nitroisoquinoline was reacted with oxazolidin-2-one and thiazolidin-2-one in the presence of sodium hydride, or condensed with aminoacetaldehyde dimethylacetal, followed by cyclization, to get products which, however, showed no appreciable *in vivo* activity.[237]

Hydroxyalkylamino-substituted isoquinolines variously useful as sympatholytics, β-blockers, and antihypertensives have been prepared by the reaction of the appropriate alcohols with substituted 1-haloisoquinolines.[238-240]

Substituted 1,3-dichloroisoquinolines, when treated sequentially with thiomorpholine or its oxide and then with piperazine derivatives, lead to compounds that inhibit platelet aggregation.[241]

7-Chloro-8-nitroisoquinoline was converted to the 7-benzylthio derivative by treatment with benzylmercaptan and reduction. This was further transformed in a series of steps to thiadiazolotetrahydroisoquinoline, which showed antidepressant activity.[242] Replacement of the chlorine of substituted 3-chloroisoquinolines with piperidino or piperazino derivatives led to compounds with antidepressant activity.[243] Quinolizinone derivatives useful as antidepressants and anti-Parkinson agents have been prepared, starting from the corresponding 3,4-dihydroisoquinolines.[244]

Bistetrahydroisoquinoline derivatives, which are potent inhibitors of the enzyme phenylethanolamine-*N*-methyltransferase, have been obtained by acylation of 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline hydrochloride with the appropriate ω-haloacyl halides, followed by alkylation with a second molecule of 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline and reduction of the amide.[245]

Iminodisulfamides were obtained by treatment of halo-1,2,3,4-tetrahydroisoquinolines with $(ClSO_2)_2NH$ and tested for antiallergic activity.[246] 7-Chloro-3,4-dihydro-1-phenylisoquinoline was tested for antiallergic activity.[247]

Chlorine-substituted *s*-triazolo [3,4-a]isoquinolines, useful in the treatment of inflammatory disorders, were obtained by cyclization of hydrazinoisoquinolines with the appropriate acid or anhydride.[248]

Halogen-substituted isoquinolines were among several other-substituted isoquinolines that were converted to imidazolinylaminoisoquinolines which were useful as antihypertensives.[249]

1-Chloro-3-(2-pyridyl)isoquinolines have been prepared and found to exhibit antimycoplasmal activity in the presence of copper.[250]

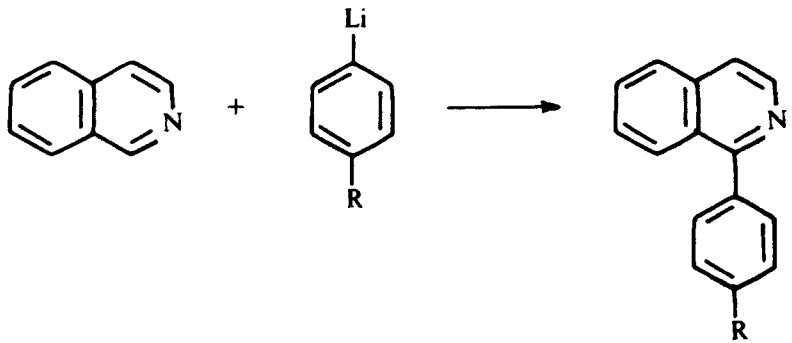
Among other 8-substituted 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines, the corresponding 8-halo compounds have been tested for renal vasodilator activity.[251]

3-Chloro-5-acetamidoisoquinoline has been found to have herbicidal activity,[252] while 4-bromo-5-nitroisoquinoline has fungicidal activity.[212,252] Other halogen-substituted isoquinolines have been prepared by a Sandmeyer or Schiemann reaction of the corresponding aminoisoquinolines and their activity tested.[252]

VI. ORGANOMETALLIC DERIVATIVES OF ISOQUINOLINES

A. Lithium Salts

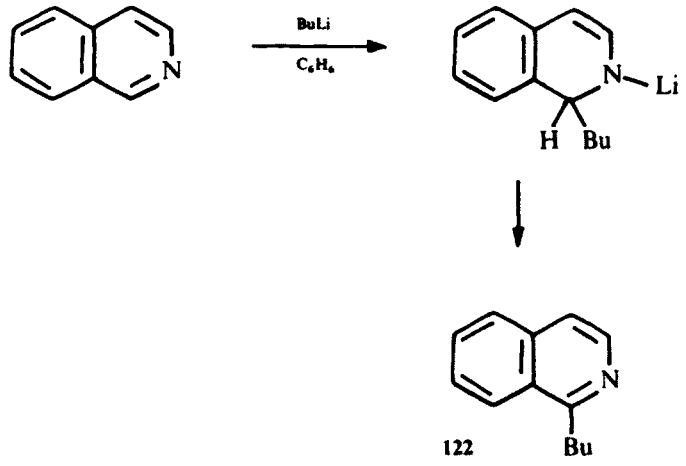
Phenyllithium is reported to react with isoquinoline to form 1-phenyl isoquinoline (**120**), which was characterizad as its picrate.[253] The phenyllithium adduct, which is presumably the intermediate, has not been isolated. A similar reaction of *p*-anisyllithium with isoquinoline yielded 1-*p*-anisylisoquinoline (**121**)[253] (Eq. 110).



120 R = H
121 R = OMe (110)

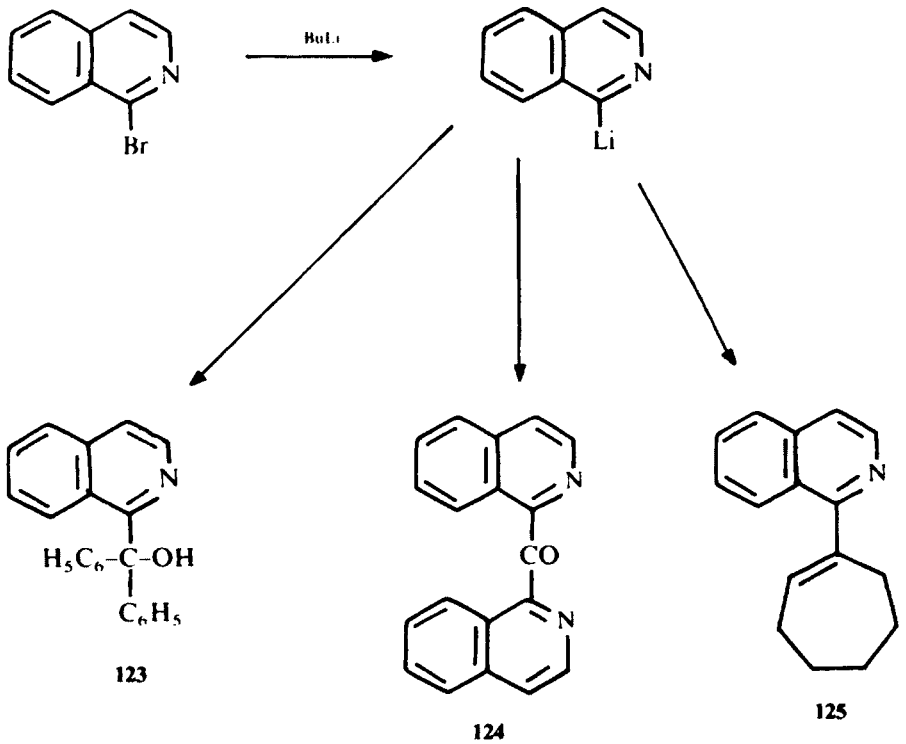
Reaction of isoquinoline with butyllithium in benzene solution yields an unstable adduct which undergoes decomposition (Scheme 35) to yield 1-butyl isoquinoline (**122**).[254] Phenyllithium, under the same conditions, did not yield a pure product.

The first report on the preparation of 1-isoquinolinyl lithium appeared in 1957.[255] The procedure involved a low-temperature halogen–metal interconversion of 1-bromoisoquinoline with *n*-butyllithium. Here again, the intermediate 1-isoquinolinyl lithium was not isolated, but was directly used for further reaction, for example, with benzophenone,[255] carbon dioxide,[255] and cycloheptanone[256] (Scheme 36) to give **123**, **124**, and **125**, respectively.



122

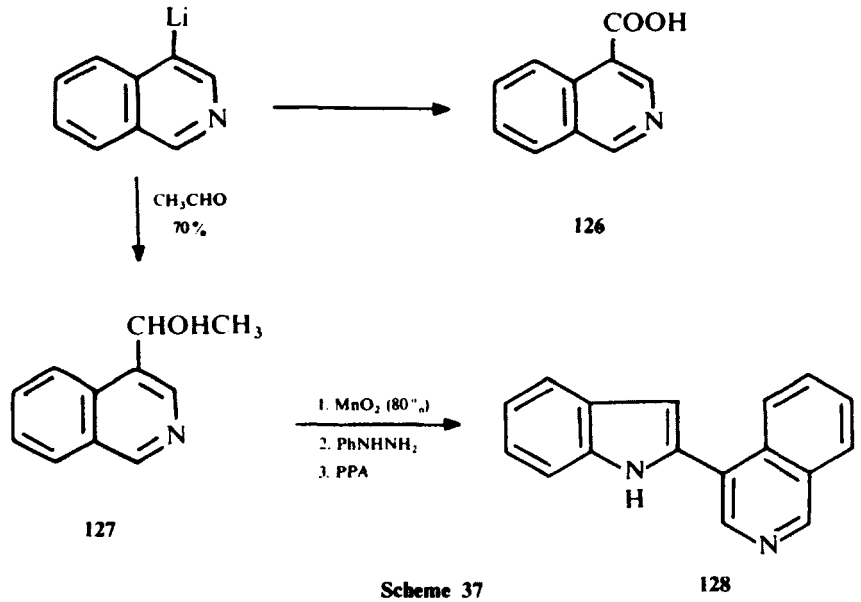
Scheme 35



123 124 125

Scheme 36

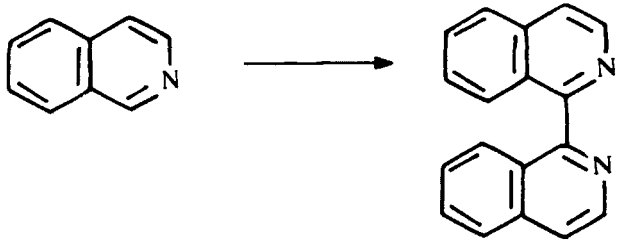
By a similar procedure, 4-bromoisoquinoline was converted through 4-isoquinolinyl lithium to 4-isoquinoline carboxylic acid (**126**) in 40% yield and to 4-α-hydroxyethylisoquinoline (**127**) by treatment with acetaldehyde[257] (Scheme 37). This was oxidized to the corresponding ketone, reacted with phenyl hydrazine, and the phenyl hydrazone cyclized with polyphosphoric acid to 4-indol-2-yl isoquinoline (94% yield).



Scheme 37

On carbonation, both the acid and ketone are possible products, the latter being formed by the attack of the organolithium compound on the initial carboxylic acid.

When isoquinoline is treated with lithium di-isopropylamide in HMPA, a dimer is obtained, presumably through an intermediate α-lithio derivative. However, attempts to trap this intermediate were unsuccessful.[258] (Eq. 111).



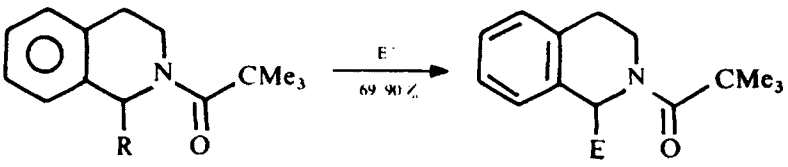
(111)

The functionalization of the pyridine ring of isoquinoline and quinoline by direct metallation has been studied.[259] Thus, reaction of isoquinoline with *n*-butyllithium and potassium *t*-butoxide resulted in metallation of the pyridine

ring. The extent of metallation was small when isoquinoline was treated with equimolar quantities of potassium *t*-butoxide and lithium diisopropylamide in tetrahydrofuran–hexane and HMPA, as shown by isolation of the deuterated isoquinoline. However, reaction with dimethylsulfide after generating the lithio derivative by treatment of isoquinoline with lithium diisopropylamide–potassium *t*-butoxide yielded 4-methylthioisoquinoline in 60% yield.

2-Pivaloylisoquinoline can be quantitatively converted to the 1-lithio derivative (*t*-butyllithium and tetramethylenediamine), which then reacts with a variety of electrophiles to give the corresponding 1-substituted compounds[260] (Eq. 112).

Dimerization of the lithiated derivative occurs with iodine to give **129**.

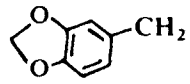


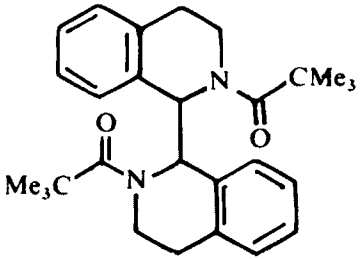
(112)

R = H
R = Li

E = Si $(CH_3)_3$, Sn $(C_4H_9)_3$, C_2H_5CHOH,

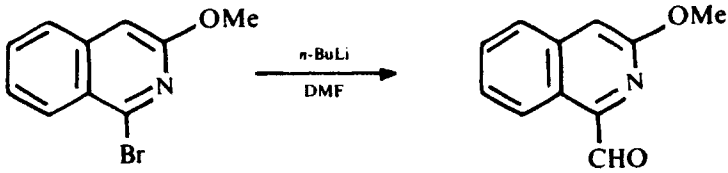
C_6H_5CHOH,  , $(C_6H_5)_2$ COH, CH_3,

$CH_3(CH_2)_7$, $(CH_3)_2CH$, 



129

3-Methoxy-1-isoquinoline carboxaldehyde was obtained by the treatment of 1-bromo-3-methoxyisoquinoline with *n*-butyllithium followed by dimethylformamide[261] (Eq. 113).



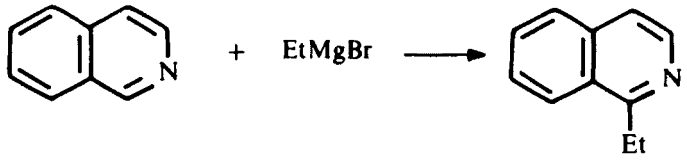
(113)

In a similar manner, 4-isoquinoline carboxaldehyde was prepared from 4-bromoisoquinoline and used for the preparation of thromboxane synthetase inhibitors by reaction with ethyl *p*-amino benzoate to give the corresponding Schiff base, followed by reduction of the imino group.[262]

In connection with the work on 3,4-didehydroisoquinoline (see Section III.B), 4-bromoisoquinoline is reported to be unreactive to lithium piperidide and piperidine. No 3- or 4-piperidylisoquinoline was isolated. The reason for this has been ascribed to the stability of the 4-bromo-1-lithioisoquinoline.

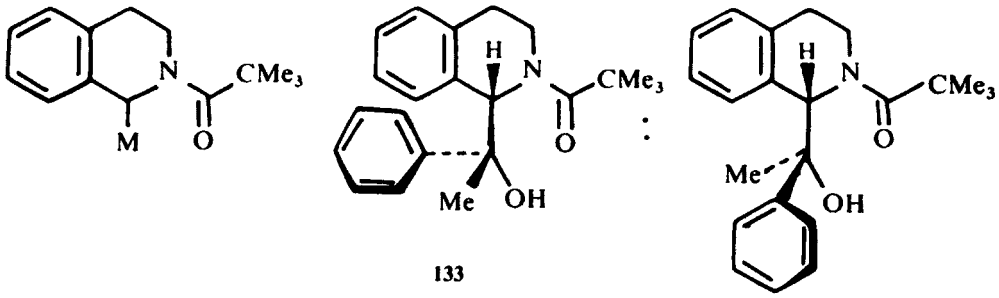
B. Grignard Reaction

Isoquinoline reacts with ethylmagnesium bromide to directly form 1-ethylisoquinoline in 66% yield[263] (Eq. 114). The reaction takes place only when the reactants are heated in an autoclave at 150–160°C. The structure of the product was not rigorously established by the authors, but in view of the greater reactivity of the 1-position, the assignment should be correct.



(114)

The 1-bromomagnesium derivative of *N*-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**130**) adds in a highly stereoselective manner to acetophenone. This has been shown by X-ray analysis of the major product 1-(α-hydroxy-α-methylbenzyl)-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**133**). The lithio derivative (**131**) reacts in a much less stereoselective fashion.[264]



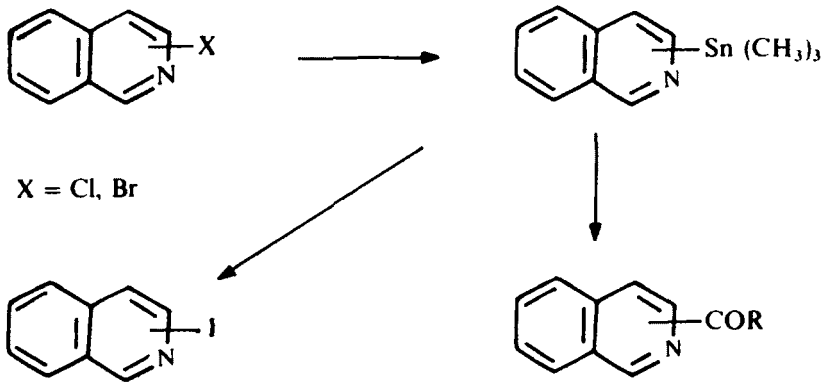
133

130 = M = H
131 = M = Li
132 = M = Mg

96 : 4

C. Tin Compounds

Trimethylstannyl derivatives of isoquinolines can be prepared from the corresponding haloisoquinolines by treatment with trimethylstannyl sodium. These stannyl derivatives readily react with iodine to give the corresponding iodo compounds[265] and with acyl chlorides to give the corresponding ketones in good yield.[266] 1-Trimethylstannylisoquinoline reacts directly with acylchlorides, whereas the 3-and 4-trimethylstannylisoquinolines require catalysis using palladium chloride or $PdCl_2(PPh_3)_2$ (Scheme 38).



Scheme 38

D. Other Organometallic Derivatives

Numerous reports describe the formation of metallic derivatives of isoquinolines. However, the majority of these do not strictly fall under the category of organometallic compounds; rather, they are to be classified as complexes. The structures of these complexes are not clearly elucidated and they are not of much synthetic value, as judged by available reports. They do not undergo selective preferential reactions useful in synthetic chemistry for which the more conventional organometallics are reputed. Exceptions are indicated; side-chain-metallated isoquinolines are not included.

(*a*) *Group IB Elements*

(i) Copper

Crystalline complexes of isoquinoline with copper salts have been described by many workers. Among these are complexes containing cupric formate,[267]

acetate,[268,269] benzoate,[270,271] oxalate,[272] chloride,[273,274] iodide,[275,276] cyanate,[277] isocyanate,[278,279] thiocyanate,[280] and azide.[281] Many copper complexes of organic aldehydes, ketones, phenols, and acids react with isoquinoline to form mixed-ligand complexes such as those with salicylaldehyde,[282] acetoacetanilide,[283] *o*-hydroxyacetophenone,[284] acetylacetone,[285] chloroacetylacetone,[286] thenoyltrifluoroacetone,[287] pivaloyltrifluoroacetone,[287] 2,4,6-trichlorophenol,[288] 2,4,6-tribromophenol,[289] ethylacetoacetate,[290] trichloroacetic acid,[291] phenylacetic acid,[292] alkoxy and aryloxy acetic acids,[293] alkylthioacetic acids,[294,295] dithiocarbamic acid,[285] *m*-methoxybenzoic acid,[296] and biphenyl-2,2′-dicarboxylic acid.[297] Even compounds containing copper oxides[298] are reported. The halogenation of CuI complexes containing isoquinoline as the nitrogen-donor ligand yield higher halogenated complexes.[299]

The stereochemistry of the mononuclear copper-formate and acetate complexes with isoquinoline at room temperature and in a frozen glass at 77°K has been studied by ESR.[300] A copper formate–isoquinoline complex has been used as a catalyst to obtain benzophenone azine from $Ph_2C{=}NH$ and oxygen.[301]

(ii) Silver

By treating a concentrated solution of silver nitrate or silver perchlorate with isoquinoline, complexes designated as $Ag(IQ)NO_3$ and $Ag(IQ)_2ClO_4$ are obtained. These compounds are sparingly soluble in organic solvents and have sharp melting points.[302]

Thiocyanato and cyanato complexes of silver containing isoquinoline as the donor ligand have been characterized.[303] Isothiocyanatochromates of bisisoquinoline–silver complexes are also reported.[304] A silver picolinate isoquinoline complex has also been obtained.[305]

(*b*) *Group IIA Elements*

(i) Calcium

According to a Patent,[306] purification of isoquinoline from an impure fraction may be accomplished through its calcium chloride adduct $[(IQ)_2CaCl_2]$ which readily decomposes in water.

(*c*) *Group IIB Elements*

(i) Zinc

Slow addition of diethyl or dimethyl zinc to an excess of isoquinoline in an inert atmosphere resulted in a 1:1 complex.[307,308]

Zinc dithiocarbamate reacts with isoquinoline to furnish $[(Me_2N{-}CS_2)_2 Zn(IQ)_n]$ ($n=1$ or 2) in high yields. These compounds are claimed to have fungicidal properties.[309]

Other complexes include those with zinc chloride,[310] mixed ligand complexes of zinc halide with thiourea and isoquinoline,[311] zinc cyanate,[312] zinc selenocyanate,[313] zinc thiocyanate,[314] and zinc nitrite.[315] Zinc acetylacetonate also reacts with isoquinoline in methanol to form mixed-ligand complexes.[316]

Other zinc complexes are those with salicylaldehyde,[282] *o*-hydroxyacetophenone,[284] acetoacetanilide,[283] tetraphenylporphyrin,[317] chloroacetylacetone,[318] thenoyltrifluoroacetone,[287] pivaloyltrifluoroacetone,[287] ethylacetoacetate,[290] trichloroacetic acid,[291] phenylacetic acid,[292] piperidyl dithiocarbamate,[319] and biphenyl-2,2′-dicarboxylic acid.[297]

The preparations and structures of zinc, cadmium, and mercury complexes of isoquinoline have been described.[320]

The zinc chloride–isoquinoline complex $[ZnCl_2(IQ)_2]$ catalyzes the rate of acylation of aniline with naphthoic anhydride.[321]

(ii) Cadmium

Complexes of cadmium thiocyanate,[322,323] iodide,[324] chloride, and bromide[325] with isoquinoline have been reported. Other complexes include those with acetoacetanilide,[283] *o*-hydroxyacetophenone,[284] 3-and 4-picoline *N*-oxide,[326] and piperidyl[327,328] and morpholyldithiocarbamate.[327] Manganese-doped cadmium–chloride complexes with isoquinoline containing 1% cadmium ions have been prepared.[329]

(iii) Mercury

Mercury–cyanate complexes with isoquinoline[330] and mixed-ligand complexes of mercuric chloride with thiosalicylic acid and isoquinoline[331] have been reported.

(*d*) *Group IIIA Elements*

(i) Aluminium

Triethylaluminium reacts with isoquinoline at 0°C to yield a 1:1 adduct.[332] Such complexes have been used for the determination of active hydrogen and in spectrophotometric methods.[333,334]

(*e*) *Group IIIB Elements*

(i) Lanthanide Series

(1) Cerium. When hydrogen chloride is passed through ceric chloride in aqueous solution, isoquinoline added, and hydrogen chloride again passed through the solution and the solution concentrated, a white solid of the complex $(IQH)_2$ $[CeCl_5]$ is obtained.[335]

(2) Holmium. The holmium complex $[(IQH)_2\ HoCl_5 \cdot 3H_2O]$ is obtained in the same way as the cerium complex.[336]

(3) Ytterbium. Ytterbium chloride reacts with oxalic acid and isoquinoline to give a white complex of the formula $[(IQH)\ Yb(C_2O_4)_2\ 3H_2O]$.[336]

(ii) Actinide Series

(1) Thorium. Isoquinoline complexes have been reported with thorium perchlorate,[337] nitrate,[338] and thiocyanate.[338]

(2) Uranium. Uranium chloride reacts with isoquinoline[339] in a 1:2 or 1:3 ratio to yield discrete complexes of the formula $[UCl_5(IQ)_n]$ where $n = 2$ or 3. Uranium chloride reacts with isoquinoline in the presence of thionyl chloride to give reddish-brown complexes.[340,341] When uranyl chloride saturated with hydrogen chloride is treated with isoquinoline and hydrogen chloride is again passed through, yellow $[(IQH)_2UO_2Cl_4]$ is obtained.[342] Other complexes of uranium with isoquinoline include those of uranyl phenyl acetate[343] and lactate.[344]

(*f*) *Group IVA Elements*

(i) Germanium

Germanium tetrahalides on reaction with isoquinoline as a 1% solution in hexane give the insoluble 1:2 adducts. The chloride, fluoride, and bromide complexes have been prepared.[345]

(ii) Tin

Alkyl and aryltin halides form adducts with isoquinoline to yield various derivatives.[346-353]

(iii) Lead

Lead chloride complexes of isoquinoline are obtained by treatment of the lead salt with isoquinoline or by treatment of hexachloroplumbic acid with isoquinoline hydrochloride in hydrochloric acid.[354]

(*g*) *Group IVB Elements*

(i) Titanium

Coordination compounds of titanium tetrahalides were obtained by the direct reaction of the dry reagents with isoquinoline in benzene.[355] During reactions in thionyl chloride, complexes, incorporating the solvent, such as $[(IQ)_2TiCl_4\ \frac{1}{2}SOCl_2]$ resulted.[356]

(ii) Zirconium

The structure of the addition compounds of zirconyl halides with isoquinoline were postulated to be $[(ZrOCl_2)(IQ)]$.[357] Zirconium perchlorate reacts with excess isoquinoline to give $[ZrO(ClO_4)_2\ 4IQ]$.[337]

(*h*) *Group VA Elements*

(i) Antimony

The preparation, characteristics, and crystallographic data on isoquinoline-antimony tribromide complex have been reported.[358] By adding a solution of antimony oxide in concentrated hydrochloric acid to a diazotized solution of 5-aminoisoquinoline, a sodium isoquinoline-5-stibonate was prepared.[359] An antimony complex of the formula $[IQH]\ [(X_4C_6H_2O_2)\ SbX'_2]$ has been prepared, where $X_4C_6H_2O_2$ = pyrocatechol derivative; X = H, halogen and X′ = Cl, Br.[360]

(*i*) *Group VB Elements*

(i) Vanadium

Vanadium oxychloride in chloroform yields a violet-red complex $[VOCl_3(IQ)]$[361], whereas in carbon tetrachloride, a dark-brown hygroscopic solid $[VOCl_3.3IQ]$ is obtained.[362] Vanadium oxydichloride forms $[VO(IQ)_2Cl_2]$.[363] Vanadium tetrachlorideisoquinoline adduct $[VCl_4\ IQ]$ is prepared in anhydrous carbon tetrachloride.[364] Vanadium dihalideisoquinoline adducts have also been reported from ethanol.[365]

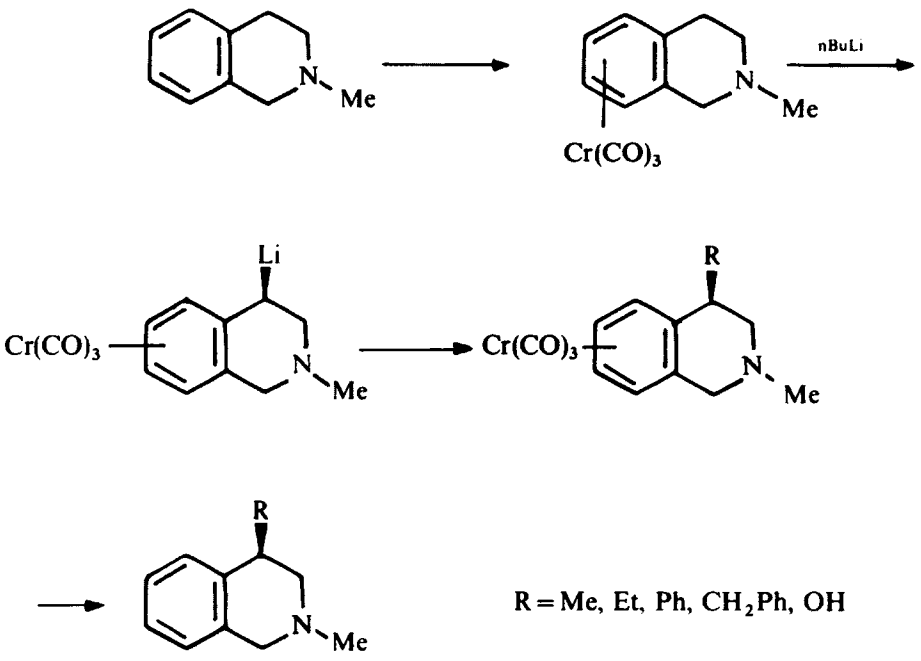
Vanadyl sulfate in methanol on treatment with isoquinoline forms $[VO(IQ)\ SO_4]$,[366] just as potassium hexathiocyanato vanadate with the base also yields a complex.[367] Vanadyl acetylacetonate forms a complex with isoquinoline.[368]

(*j*) *Group VIB Metals*

(i) Chromium

A mixed-ligand complex of chromium chloride with thiourea and isoquinoline has been reported.[369] Chromic oxide dissolved in glacial acetic acid, saturated with hydrogen chloride, treated with isoquinoline, and resaturated with the gas gives dark-red $[IQH)\ [CrOCl_4]$.[370] When this reaction mixture is refluxed and resaturated with hydrogen chloride, a purple powder of $[IQH]_2[CrCl_5(HO_2C\ Me)]$[371] is obtained. Using hydrogen bromide instead of hydrogen chloride as first described and keeping the resulting reaction mixture for several weeks at 0 °C gave $[IQH]\ [CrBr_4(HO_2CMe)_2]$.[371] Isoquinoline complexes have also been obtained with $K(CrO_3Cl)$[372] and nitrilotriacetic acid.[373]

Thermolysis of chromium hexacarbonyl with 1,2,3,4-tetrahydroisoquinoline or *N*-methyl-1,2,3,4-tetrahydroisoquinoline gives complexes of the formula [THIQ $Cr(CO)_3$] and [*N*-MeTHIQ $CrCO_3$]. The *N*-methyl-1,2,3,4-tetrahydroisoquinoline chromium carbonyl complex can be selectively deprotonated in the 4-exo position by butyllithium and then treated with electrophiles to give the corresponding 4-substituted products,[374,375] which can be subsequently decomplexed by exposure of the ether solutions to air (Scheme 39).



Scheme 39

(ii) Molybdenum

Molybdenum complexes with isoquinoline that have been reported are $[(IQ)_3H_3As(Mo_3O_{10})_4]$,[376] $[(IQ)_3H_3AsTh(Mo_3O_{10})_4]$[376] and $[MoOCl_3(IQ)_2]$.[377]

(*k*) *Group VIIB Elements*

(i) Manganese

Manganese(II) chloride, bromide, iodide, and thiocyanate react with isoquinoline in alcoholic medium to give complexes with σ-bonded nitrogen donors.[378] Mangenese(II) chloride and isoquinoline also yield a yellow complex

of the formula $[MnCl_2(IQ)_5]$.[310] Mixed-ligand complexes of bis(acetylacetonyl)manganese with isoquinoline have been described.[379] A manganesecyanato complex of isoquinoline has been formulated as $[Mn(IQ)_4(NCO)_2]$.[380] A similar selenocyanate complex has also been reported.[381]

Halogenation of dihalocomplexes of manganese(II) containing nitrogen donor ligands have been reported.[382] When $[n\text{-cepy}]_2\ [MnCl_4]$, where *n*-cepy = *n*-cetylpyridine, is treated with isoquinoline, a complex of the formula $[n\text{-cepy}]_2\ [MnCl_4(IQ)_4]$ is obtained. When heated to 100 °C, this complex yielded $[n\text{-cepy}]_2\ [MnCl_4(IQ)_2]$.[383] An isoquinoline complex of manganese with biphenyl-2,2′-dicarboxylic acid has been reported.[297]

(*l*) *Group VIII Elements*

(i) Iron

During his studies on the complexes of ferro- and ferricyanides with organic bases, Cumming has described the formation of various complexes of isoquinoline containing iron. Examples are $[(IQ)_2 2Na_4Fe(CN)_6 \cdot H_2O]$,[384] $[(IQ)_3H_4Fe(CN)_6]\cdot EtOH$,[385] $[(IQ)_3H_4Fe(CN)_6 3EtOH]$,[385] and $[(IQ)_3Fe(CN)_6 0.5\ EtOH]$.[386] All these complexes are colored crystalline compounds.

Other iron complexes include those of cyclohexylxanthate,[387] dimethyl glyoxime,[388] malonic acid, succinic acid, glutaric acid, adipic and diphenic acids,[389] and the cyano[390] and acetate derivatives.[391] The iron–tetraphenylporphyrin complex with isoquinoline has also been reported.[392] When $[Me_4N]\ [FeCl_4]$ is treated with isoquinoline, two complexes are formed, depending upon the amount of isoquinoline used.[393] An East German patent reports the synthesis of phenylisocyanate by the carbonylation of nitrobenzene in the presence of a palladium complex $[(Bu_4N)_2Pd_2Cl_6]$ and isoquinolinium tetrachloroferrate.[394]

(ii) Cobalt

A number of complexes of cobalt salts with isoquinoline are reported. Thus, cobalt thiocyanate with isoquinoline forms $[Co(SCN)_2(IQ)_2]$,[395] $[Co(SCN)_2\ 4\ IQ]$;[396] metal cyanamides form $Co(IQ)_4\ [N(CN)_2]_2$,[397] which decomposes when heated in carbon tetrachloride to give $Co(IQ)_2\ [N(CN)_2]_2$.[397]

Cobalt chloride[310,398] and sulfate[399] complexes with isoquinoline are prepared by the addition of the isoquinoline in a solvent to the reagents. In an attempt to synthesize vitamin B_{12} model compounds, several complexes of cobalt salts have been prepared.[400] Cobalt nitrite[401] and acetylacetonate[402] readily form complexes $Co(IQ)_4(ONO)_2$ and $Co(acac)_2\ (IQ)_2$. Cobalt biphenyl-2,2′-dicarboxylate,[297] trichloroacetate,[291,403] dichloroacetate,[403] phenylacetate,[292] benzoate,[271] substituted benzoates,[404] diphenate,[405] succinate,[406] glutarate,[406] adipate,[406] malonate,[406] and alkanoate complexes[407] with isoquinoline have been reported. Other complexes include those with ethylenedia-

mine,[408,409] 1,10-phenanthroline,[410] succinimide,[411] phthalimide,[411] ethyl acetoacetate,[290] dibenzoylmethane,[412,413] salicylaldehyde,[414] tetraphenylporphyrin,[415] acetoacetanilide,[283] *o*-hydroxyacetophenone,[284] and trialkylphosphate derivatives.[416,417] *cis*-$CoCl(en)_2$ (IQ) cations were resolved using Na Sb (III) (+) tartarate and the active cations isolated.[408,409] Dichloro and dibromo cobalt isoquinoline complexes $[Co(IQ)_2 X_2]$ upon halogenation yield mixed-halogen complexes.[418] In addition, mixed-ligand complexes like $[Co(tu)_2(SCN)_2 (IQ)_4]$,[419] where tu = thiourea, $[Co(ABT)(SCN)_2(IQ)_4]$,[420] where ABT = 2-aminobenzothiazole, and $[Co(acac)(mbt)(IQ)_2]$,[421] where acacH = acetylacetonate and Hmbt = 2 mercaptobenzothiazole have been obtained.

The autooxidation of *p*-xylene in the presence of cobalt and manganese–isoquinoline complexes has been studied in various solvents.[422]

(iii) Nickel

Nickel compounds also form ready complexes with isoquinolines. Among those that have been reported are: $[Ni(IQ)_2 (H_2O)_2]^{2+}$;[423] $[Ni(IQ)_2Br]$;[424] $[Ni(IQ)I_2]$;[424] $[Ni(IQ)_4 (NO_2) X Ni(IQ)_4 (ONO)_2]$;[425] $[NI(Ac_2CH)_2(IQ)_2]$;[426] $[Ni(bzac)_2(IQ)_2]$;[427] $[Ni(IQ)_2(NO_2)_2]$;[428] $[NiC_2O_4IQ]$;[429] [Ni(Cldpti) $(IQ)_2$];[430] $[NiCl_2(IQ)_4]$; $[Ni\ Cl_2(IQ)_2]$;[431,432] $[NiL_2(IQ)_2]$,[290] HL = ethylacetoacetate; $[Ni(IQ)_4I_6]$;[433] $Ni[O_2P(OR)_2]_2 \cdot 2IQ$;[434] $[NiL \cdot 4IQ]$, LH_2 = biphenyl-2,2′-dicarboxylic acid;[297] $[Ni(C_6H_5CO_2)_2\ (IQ)_2]$;[271] $[NiL_2 (IQ)_2]$,[291,403] LH = CCl_3CO_2H; $[Ni(RCO_2)_2(IQ)_2]$;[407] $[Ni\ L_2\ (IQ)_2]$[435] HL = diethyl malonate; $[Ni(PhCH_2CO_2)_2\ (IQ)_2]$;[292] $K[Ni(IQ)_2L(H_2O)\ (OH)]$,[436] H_2L = malonic, succinic, glutaric, and adipic acid; $[Ni\ L_2(IQ)_2]$,[283] HL = acetoacetonilide; $[Ni(Cl_2CHCO_2)_2(IQ)_4]$; $[Ni\ (Cl_2CHCO_2)_2(IQ)_2]$;[403] $[Me_4N]_2$ $[Ni(SCN)_4\ (IQ)_2]$;[437] $[Ni(C_9H_{10}O_2N_3)\ (IQ)_2]$;[438] $C_9H_{10}O_2N_3$ = anion of 3-(*p*-acetophenyl)-1-methyltriazene-*N*-oxide; $[NiL_2\ (IQ)_2]$, HL = *o*-hydroxyacetophenone;[284] and $K[Ni(L)_3\ (IQ)(H_2O)_2]$,[411] L = succinimide, phthalimide. Also prepared were coordination compounds of the formula [Ni(β-dikhydth-2H)IQ] where the nickel chelates were prepared by treatment of the Schiff bases derived from compounds with nickel acetate.[439]

(iv) Ruthenium

The two isomeric ruthenium carbonyl–isoquinoline complexes of the formula $[HRu_3(CO)_{10}\ (IQ)]$ were obtained by treatment of $[Ru_3(CO)_{10}(NCMe)_2]$ with isoquinoline.[440]

(v) Rhodium

Rhodium(III) complexes of the formula $[Rh(IQ)_4Cl_2]\gamma$ have been synthesized and characterized.[441] Various cationic complexes of rhodium have been prepared: $[Rh\ (CO)(IQ)\ L_2]ClO_4$,[442] L = (*p*-tolyl)$_3$P, Ph_3 As, Ph_3 P; $[(COD)Rh(IQ)_2]ClO_4$,[443] COD = 1,5-cyclooctadiene; $[(CO)_2$ $Rh(IQ)_2]ClO_4$;[443] $[CO(PPh_3)Rh(IQ)_2]ClO_4$;[443] $[(COD)Rh(IQ)PPh_3)]$

ClO_4;[443] $[(CO)_2Rh(PPh_3)(IQ)]ClO_4$;[443] [(NBD) $Rh(IQ)_2]BPh_4$,[444] NBD = norbornadiene; $[Rh(NBD)(IQ)_2]$ ClO_4,[445,446] and $[Rh(NBD)(IQ)(PPh_3)]$ ClO_4.[445,446] Some of these have been investigated as catalysts for the hydrogenation of cyclic and terminal olefins.[446]

(vi) Palladium

Palladium chloride quantitatively precipitates isoquinoline as an insoluble complex $[(IQ)_2PdCl_2]$.[447] The interaction of palladium carboxylate with isoquinoline gives complexes of the type $[Pd(OCOR)_2(IQ)_2]$ with unidentate carboxylate groups.[448] Complexes of noble metals with isoquinoline have been recommended as catalysts for preparing isocyanates.[449-451] *Trans*-$[Pd(IQ)_2Cl_2]$ has been used to catalyze the hydrogenation of nitrobenzene, nitrotoluene, chloronitrobenzene, and dinitrobenzenes to anilines.[452] The 2,2-dimethylallyl palladium chloride–isoquinoline complex has been prepared and temperature-dependent processes studied by ^1H NMR.[453]

(vii) Osmium

Triosmium dodecacarbonyl reacts with isoquinoline to give two isomers of the formula $[HOs_3(IQ)(CO)_{10}]$, where isoquinoline is metallated in the 1,2 or 2,3, positions. The structures have been assigned by ^1H NMR spectra.[454] Osmium tetroxide–isoquinoline complexes have been prepared[455,456] and serve as a source of OsO_4 while fixing and staining biological specimens for electron microscopy.[457] Other osmium complexes that have been prepared include those formed from osmium tetroxide with alkynes and dienes in the presence of isoquinoline[458] and substituted nitrido complexes of osmium with isoquinoline.[459]

(viii) Iridium

Mononuclear and dinuclear diolefinic cationic iridium complexes with neutral monodentate and bidentate sulfur ligands have been reported, for example, [Ir(COD) L (IQ)] ClO_4, where COD = 1,5-cyclooctadiene, L = tetrahydrothiophene, trimethylene sulphide, SMe_2, or SEt_2 and [(COD)(IQ) Ir(L – L) Ir(IQ)(COD)] $(ClO_4)_2$, where L – L = 1,4-dithiocyclohexane, (*t*-BuS)$_2$ $(CH_2)_2$ or $(MeS)_2$.[460]

(ix) Platinum

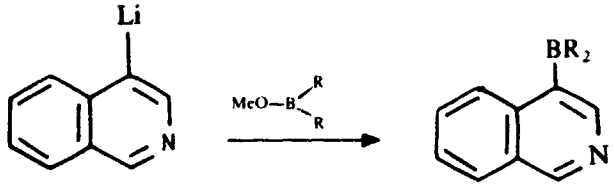
The photochemical isomerization of *cis*-$[Pt(IQ)_2Cl_2]$ to the trans complex has been reported.[461] Irradiation of *trans*-$[PtCl_2(C_2H_4)IQ]$ in chloroform led to isomerization to the corresponding cis complex.[462,463] Other platinum complexes prepared include $[PtH(IQ)(PBz_3)]_2BPh_4$,[464] where PBz = tribenzylphosphine, and [PtCl(L)(IQ)],[465] L = allyl or 2-methylallyl.

E. Nonmetallic Derivatives

(*a*) *Boron*

Sodium borohydride in neutral or alkaline solution at room temperature reacts with isoquinoline salts to form *N*-substituted borazans,[466] whereas esters of metaboric acid form adducts in high yield.[467] Other boron complexes include $[(IQ)BH_2Br]$,[468] $[(IQ)_2BH_2]^+PF_6^-$, and $IQ\text{-}BH_3$.[469]

Treatment of 4-bromoisoquinoline with *n*-butyllithium affords the 4-lithio derivative which, when treated with dialkyl methoxyboranes, provide, the corresponding derivatives **134** and **135**[470] (Eq. 115).



(115)

134 $BR_2 = BEt_2$
135 BR_2 = 9-BBN

(*b*) *Silicon*

Silicon tetrachloride, bromide, and iodide react with isoquinoline to form complexes of the formula $[SiX_4\ (IQ)_4]$[471] where X = Cl, Br, or I. The structure and reactions of the complex of silicon tetrafluoride have been the subject of a detailed study.[472] Hydrolysis gives silica among other products (Eq. 116)

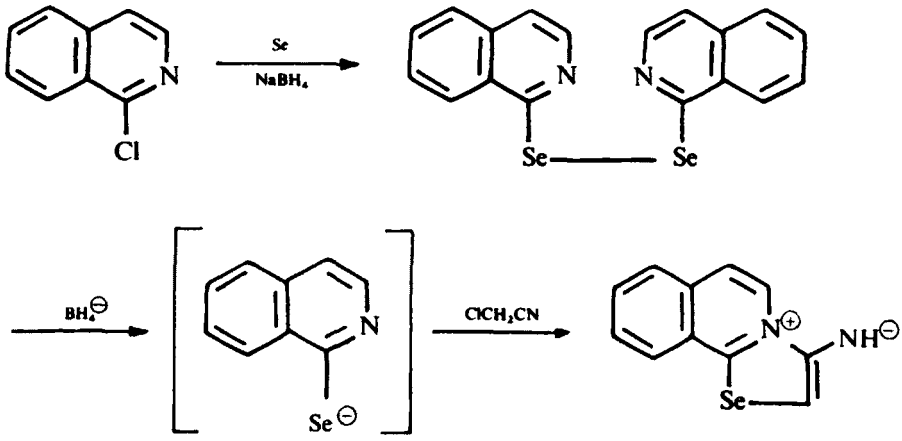
$$3SiF_4\ (IQ)_2 + H_2O \rightarrow 2(IQ)_2H_2SiF_6 + 2IQ + SiO_2 \qquad (116)$$

Silicon tetrathiocyanate, on reaction with isoquinoline, forms a complex $[Si(NCS)_4\ 2(IQ)]$ that turns yellowish in air and decomposes above 100 °C.[473]

The 1-lithio derivative of 2-pivaloyl-1,2,3,4-tetrahydroisoquinoline reacted with trimethylsilylchloride to produce the corresponding 1-trimethylsilyl derivative[260] (see Section VI. A).

(*c*) *Selenium*

A complex of isoquinoline with selenium dioxide melts at 67–68 °C and has been formulated as $[IQ \cdot 2SeO_2]$.[474] A selenium isoquinoline complex has been reported to have antineoplastic activity.[475]



Scheme 40

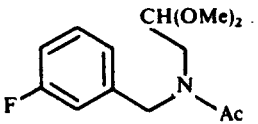
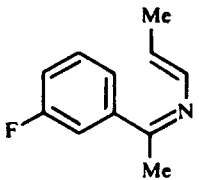
1,1'-Diselenobisisoquinoline was obtained by treatment of 1-chloroisoquinoline with sodium hydroselenide,[476] which was generated from selenium and sodium borohydride (Scheme 40).

VII. Tables of Halogenated Isoquinoline and Isoquinoline Organometallic Derivative

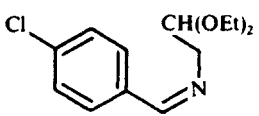
A. Fluoroisoquinolines

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1-F	1-Aminoisoquinoline	Schiemann reaction	13	b.p. 208	114
	1-Chloroisoquinoline	Gabriel's method	73	b.p. 235	115
3-F	3-Aminoisoquinoline	Schiemann reaction	49	b.p. 251	114
4-F	4-Aminoisoquinoline	Schiemann reaction	36	b.p. 236	114
5-F	5-Aminoisoquinoline	Schiemann reaction	67	43	114
6-F	6-Aminoisoquinoline	Schiemann reaction	54	52	115
7-F	7-Aminoisoquinoline	Schiemann reaction	15	27	115
8-F	8-Aminoisoquinoline	Schiemann reaction	89	30	115
1,3-diF	Homophthalimide	2,4,6-Trifluoro-1,3,5-triazine		57	61
3,4,5,6,7,8-hexaF	Heptafluoroisoquinoline	$LiAlH_4$	-	b.p. 68 (1 mm)	172
heptaF	Heptachloroisoquinoline	KF	83	44.5-45.0	21
3,4,5,7,8-pentaF-1,6-di-OCH_3	Heptafluoroisoquinoline	NaOMe	75	99-100	172
3,4,5,6,7,8-hexaF-1-OH	Heptafluoroisoquinoline	aq. NaOH	46	178-182	477
3,4,5,6,7,8-hexaF-1-OCH_3	Heptafluoroisoquinoline	NaOMe	47	86-87	172
	3,4,5,6,7,8-Hexafluoro--1-hydroxyisoquinoline	CH_2N_2	80	86-87	477

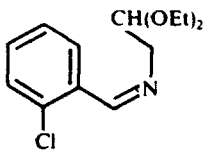
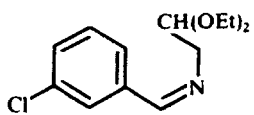
A. Fluoroisoquinolines (*Continued*)

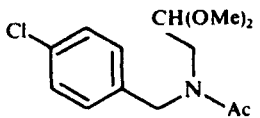
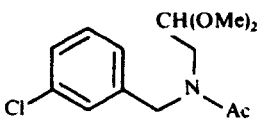
Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1,3,4,5,7,8-HexaF 6-OCH_3	1-Amino-3,4,5,7,8-pentafluoro-6-methoxyisoquinoline	HF, $NaNO_2$	40	32–33	172
7-F-1,2,3,4-tetrahydro		$AlCl_3$; H_2,Pt; HCl			116
7-F-1, 4-diMe-1,2,3,4-tetra-hydro		Pyrolysis; $NaBH_4$ reduction	65	220–222 (HCl)	136
PerF-3-CH_3	Perfluoro-bicyclo-[6,2,2,$0^{2,7}$] dodeca 2,6,9-triene	Diels–Alder reaction with CF_3CN	30–35	30	137
1,3,3,4,4,5,5,6,6,7,7,8,8-tridecaF-3,4,5,6,7,8-hexa-hydro	IQ	Caesium tetra fluorocobaltate 335–350°C		122.5–124.5	17

B. Monochloroisoquinolines

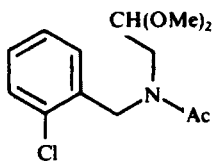
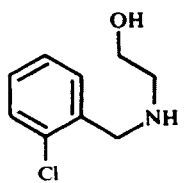
Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1-Cl	Isocarbostyril	$POCl_3$		37–38	41
	Isocarbostyril	$POCl_3$		b.p. 114–116 (9 mm)	50
	2-Methylisocarbostyril	$^{\text{a}}POCl_3/PCl_5$	40	b.p. 145 (15 mm)	196
	Isoquinoline-2-oxide	$POCl_3$	56	b.p. 135–140 (10 mm)	35
	1-Aminoisoquinoline-2-oxide	$NaNO_2$,HCl, Cu_2Cl_2	22	b.p. 130–135 (4 mm)	108
3-Cl	1,3-Dichloroisoquinoline	HI/red P or Sn/HCl		47–48	42
4-Cl	4-Hydroxyisoquinoline	$PhPOCl_2$	36	b.p.127–131 (9 mm)	58
	4-Aminoisoquinoline	HCl, $CuSO_4$, $NaNO_2$	43.6	28.5–29.5	99
	Isoquinoline-2-oxide	1-Chloroisoquinoline	10.5	195 (Picrate)	33
	Isoquinoline-2-oxide	Tosylchloride	3.3		33
5-Cl	Isoquinoline	$AlCl_3$, 1 eq. Cl_2	31	72–74	19
	5-Aminoisoquinoline	Sandmeyer reaction	60	73–74	22
6-Cl		Pomeranz - Fritsch reaction	14		83

B. Monochloroisoquinolines (*Continued*)

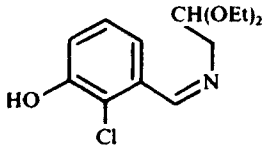
Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
7-Cl	7-Aminoisoquinoline	Sandmeyer reaction		44–45	22
	7-Aminoisoquinoline	Sandmeyer reaction	75	45	100
8-Cl	5-Amino-8-nitroisoquinoline	Sandmeyer reaction	70	55–56	101
	8-Nitroisoquinoline-2-oxide	PCl_3; reduction: Cu_2Cl_2, $NaNO_2$		55	102
		Pomeranz–Fritsch reaction	9	55–56	83, 101
4α-Cl-decahydro	4α-Hydroxydecahydroisoquinoline	$POCl_3$	21	141–142	62
6α-Cl-decahydro	$\Delta^{5,6}$ and $\Delta^{5,7}$ Octahydroisoquinoline	HCl	51	205–206.5	62
5 + 7-Cl (mixture)		Pomeranz–Fritsch reaction	25–38		22, 83
6-Cl-3, 4-dihydro	-	—	—	222 (HCl)	478
1-Cl-5,6,7,8-tetrahydro	1-Oxy-5,6,7,8-tetrahydroisoquinoline	$POCl_3$		135–136 (Picrate)	36

4–Cl–5,6,7,8-tetrahydro	4-Hydroxy-5,6,7,8-tetrahydroisoquinoline	$POCl_3$	77	201 (Picrate)	36
5–Cl,5,6,7,8-tetrahydro	—	—	—	—	479
6–Cl–1,2,3,4-tetrahydro	*N*-(2-bromoethyl)-*p*-chlorobenzylamine	$AlCl_3$	60	b.p. 100 (5 mm)	177
4–Cl	Isoquinoline-2-oxide	$PhC(Cl)=NPh$	23	b.p. 90 (0.5 mm)	40
5–Cl–1,2,3,4-tetrahydro	5-Chloroisoquinoline	Diborane reduction	31	171–172	20
6–Cl–1,2,3,4-tetrahydro	6-Chloroisoquinoline	Diborane reduction	40	229–231 (HCl)	20
		$AlCl_3$;H_2/Pt; HCl			116
7–Cl–1,2,3,4-tetrahydro	7-Chloroisoquinoline	H_2/PtO_2	33	213–214.5	20
		$AlCl_3$; H_2/Pt; HCl			116

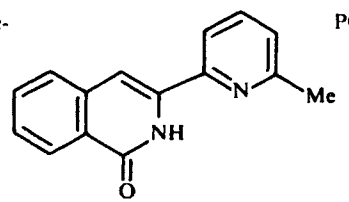
B. Monochloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
8-Cl-1,2,3,4-tetrahydro	8-Chloroisoquinoline	H_2/PtO_2	67	245–247	20
		$AlCl_3$; H_2/Pt; HCl	—		116
		$AlCl_3$ NH_4Cl	60		118

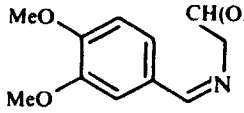
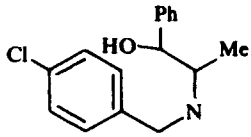
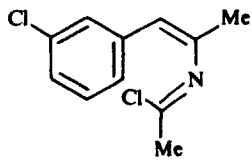
C. Substituted Monochloroisoquinolines

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1-Cl-3-OH	2-Cyanophenyl acetic acid	PCl_5, HCl	79	205–206	72
1-Cl-4-OH	4-Hydroxyiso-carbostyril	$PhPOCl_2$	33	194–195	58
	4-Hydroxyiso-carbostyril	$PhPOCl_2$	23	192–194	192
	4-Hydroxyiso-carbostyril	$POCl_3$, Et_3N		220–226(?)	60
1-Cl-5-OH	5-Hydroxyiso-carbostyril	$POCl_3$		225–230	480
3-Cl-1-OH	3-Chloro-1-fluoro-isoquinoline	Hydrolysis	10	218	115
	Homophthalimide	$POCl_3$	72	219–220	43
	o-Cyanomethylbenzoic acid	PCl_5	94	218	65
	o-Cyanomethylbenzoic acid	PCl_5	81	210–215	69
3-Cl-4-OH	3-Chloro-4-acetoxy-isoquinoline	Hydrolysis	77	168–169	192
4-Cl-1-OH	1-Chloroisoquinoline	H_2O_2/HCl	87	235–237	59
8-Cl-7-OH		H_2SO_4	64	230–231	22
1-Cl-4-OCH_3	1-Chloro-4-hydroxy-isoquinoline	CH_3I		76	60, 179
1-Cl-5-OCH_3	1-Hydroxy-5-methoxy-isoquinoline	$POCl_3$	70	137	100
1-Cl-6-OCH_3	6-Methoxyisoquinoline-2-oxide	$POCl_3$	70	77	100
1-Cl-7-OCH_3	7-Methoxyisoquinoline-2-oxide	$POCl_3$	75	176	100
3-Cl-1-OCH_3	1,3-Dichloroiso-quinoline	NaOMe			42
1-Cl-4-OC_2H_5	1-Chloro-4-hydroxy-isoquinoline	C_2H_5I		109	60
3-Cl-4-$OCOCH_3$	3-Chloroisoquinoline-2-oxide	Ac_2O	49	113–114	192
7-Cl-3, 4-di-hydro-1-SCH_3	7-Chloro-3,4-dihydro-isothiocarbostyril	CH_3I		185 (HI)	234
3-Cl-6,8-di-OH	3-Chloro-6,8-dimethoxy-isoquinoline	HI	82.5	242–243	73

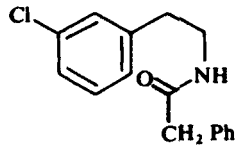
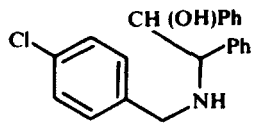
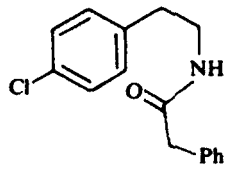
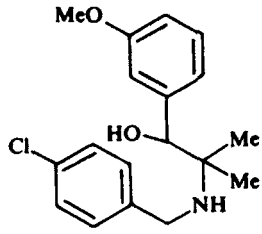
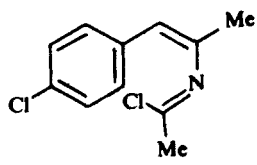
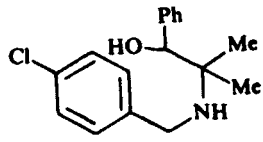
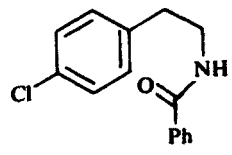
C. Substituted Monochloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1-Cl-3-OH-6-OMe	2-Cyano-5-methoxyphenylacetic acid	PCl_5; HCl	72	211	72
1-Cl-3-OH-7-OMe	2-Cyano-4-methoxyphenylacetic acid	PCl_5; HCl	70	230–232	72
3-Cl-1-OH-5-OMe	2-Cyanomethyl-3-methoxybenzoyl chloride	HCl	72	246–247	72
3-Cl-1-OH-6-OMe	2-Cyanomethyl-4-methoxybenzoyl chloride	HCl	100	228–229	72
3-Cl-1-OH-7-OMe	2-Cyanomethyl-5-methoxybenzoyl chloride	HCl	50	241	72
1-Cl-6,7-diOCH_3	6,7-Dimethoxyisocarbostyril	$POCl_3$		193–194 (Picrate)	38
3-Cl-1,6-diOCH_3	1,3-Dichloro-6-methoxyisoquinoline	NaOMe	21	126–128	70
3-Cl-1,7-diOCH_3	1,3-Dichloro-7 methoxyisoquinoline	NaOMe	59	88–89	70
3-Cl-6,8-diOCH_3	3,5-Dimethoxyphenyl acetonitrile	Gatterman reaction	54	160	73
	3,5-Dimethoxyphenyl acetonitrile	Vilsmeier reaction	62	159–160	74, 76
1-Cl-6, 7-di OMe-3-OH	2-Cyano-4,5-dimethoxyphenylacetic acid	PCl_5; HCl	69	226–227	72
3-Cl-6,7-diOMe-1-OH	2-Cyanomethyl-4,5-dimethoxy benzoylchloride	HCl	74	264–265	72
3-Cl-6, 8-di OMe-1-OH	2-Cyanomethyl-4,6-dimethoxy benzoyl-chloride	HCl	77	201–202	72
3-Cl-6,7,8-triOMe-1-OH	2-Cyanomethyl-4,5,6-trimethoxy benzoyl-chloride	HCl	40	211–212	72
1-Cl-7,8-diOCH_3	7,8-Dimethoxyisocarbostyril	$POCl_3$			38
4-N_3-1-Cl	4-Azido-isoquinoline-2-oxide	$POCl_3$	62	82–83	39
1-Cl-3-(6-Me-2-pyridyl)		$POCl_3$	69	142.5–143.5	250

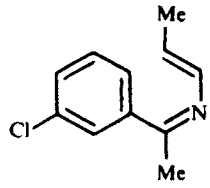
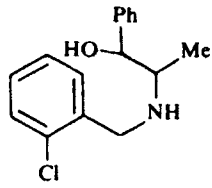
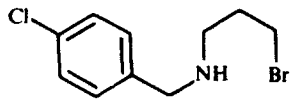
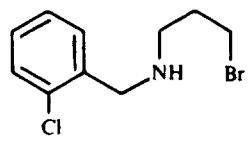
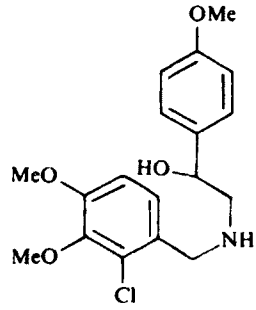
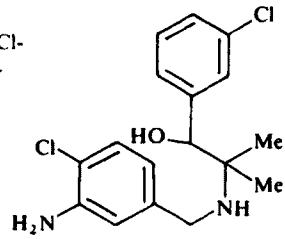
C. Substituted Monochloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
3-Cl-6,7-diOMe		$ClSO_3H$	53	134–135	88
1-Bz-3-Cl-4-CN-5,6,7,8-tetrahydro	1-Benzyl-4-cyano-3-methoxy-5,6,7,8,-tetrahydroisoquinoline	$POCl_3$/DMF	52	68	129
3-Cl-1-Me-5,6,7,8-tetrahydro	3-Methoxy-1-methyl-5,6,7,8-tetrahydroisoquinoline	$POCl_3$/DMF	56	57	129
3-Cl-4-CN-5,6,7,8-tetrahydro	4-Cyano-3-methoxy-5,6,7,8-tetrahydro isoquinoline	$POCl_3$/DMF	20	85–86	129
3-Cl-4-CN-1-Me-5,6,7,8-tetrahydro	4-Cyano-3-hydroxy-1-methyl-5,6,7,8-tetrahydroisoquinoline	$POCl_3$/DMF	38	105	129
	4-Cyano-3-methoxy-1-methyl-5,6,7,8-tetrahydroisoquinoline	$POCl_3$/DMF	70	105	129
	3-Benzyloxy-4-cyano-1-methyl-5,6,7,8-tetrahydroisoquinoline	$POCl_3$/DMF	70	105	129
3-Cl-4-CN-1-Me-5,6-dihydro	4-cyano-1-methyl-3-methoxy-5,6-dihydroisoquinoline	$POCl_3$/DMF	69	110	129
1-Bz-3-Cl 4-CN-5,6-dihydro	1-benzyl-4-cyano-3-methoxy-5,6-dihydro isoquinoline	$POCl_3$/DMF	40	72	129
3-Cl-1-Me 5,6-dihydro	3-Methoxy-1-methyl-5,6-dihydroisoquinoline	$POCl_3$/DMF	65	78–79	129
6-Cl-3-Me 4-Ph-1,2,3,4-tetrahydro		HBr	66	298–300	119
6-Cl-1,3-diMe		P_2O_5	48	55–56	77

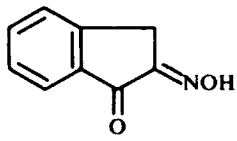
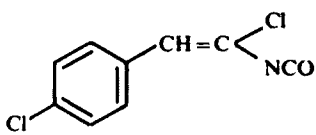
C. Substituted Monochloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1-Bz-6-Cl 3,4-dihydro			92	146–148 (Picrate)	481
6-Cl-3,4 diPh-1,2,3,4-tetrahydro		HBr	43	121–123	121
1-Bz-7-Cl 3,4-dihydro			41	176–177	481
6-Cl-3,3-diMe-4-(3-OMephenyl) 1,2,3,4-tetrahydro		CH_3SO_3H			482
7-Cl-1,3-diMe		P_2O_5	31	75–76	77
6-Cl-3,3-diMe 4-Ph-1,2,3,4-tetrahydro		H_2SO_4	—	276–277	481
7-Cl-1-Ph-3,4-dihydro			—	234–236	247

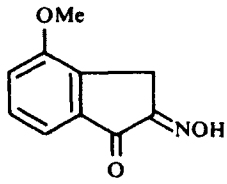
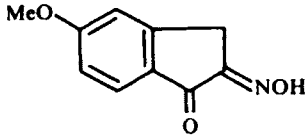
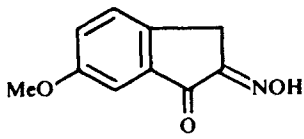
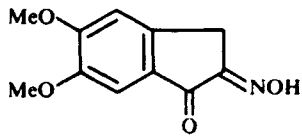
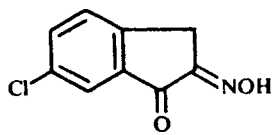
C. Substituted Monochloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
7-Cl-1,4-diMe-1,2,3,4-tetrahydro		Pyrolysis reduction	60	256–260 (HCl)	136
8-Cl-3-Me-4-Ph-1,2,3,4-tetrahydro		HBr	13	218–220	119
6-Cl-4-Me-1,2,3,4-tetrahydro		$AlCl_3$, NH_4Cl melt	64		123
8-Cl-4-Me-1,2,3,4-tetrahydro- and 5-Cl isomer		$AlCl_3$, NH_4Cl, melt	54 + 14		123
8-Cl-6,7-diOMe-4-(4-OMephenyl)-1,2,3,4-tetrahydro		CF_3COOH			122
7-NH_2-6-Cl-3,3-diMe-4-(3-Cl-phenyl)-1,2,3,4-tetrahydro		PPA	—	—	482

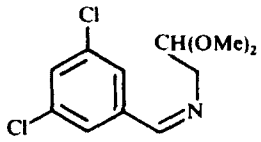
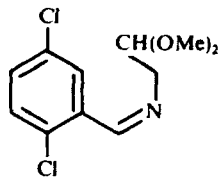
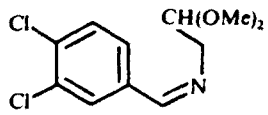
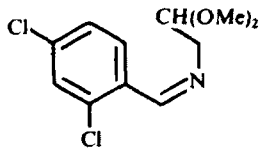
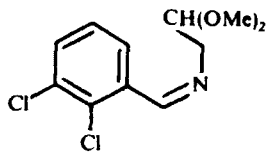
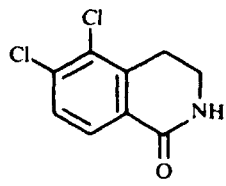
D. Polychloroisoquinolines

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1,3-diCl	Homophthalimide	$POCl_3$		122–123	42
	Homophthalimide	$PhPOCl_2$	87	120–121	58
	2-Cyanomethyl-benzoic acid	PCl_5, $POCl_3$	94	120	65
	2-Cyanomethyl benzoic acid methyl ester	PCl_5	Traces		66
		PCl_5	61	120	70
1,4-diCl	4-Hydroxyiso-carbostyril		Poor	88–89	41
	4-Cl-isocarbo-styril	$POCl_3$	50	92	59
	Isocarbostyril	PCl_5	100	92	59
	N-Methylisocarbo-styril	$POCl_3/PCl_5$	16	89–90	196
	2-Hydroxyisocarbo-styril	$POCl_3$	44	90.5–92	192
1,5-diCl	5-Amino-1-chloro-isoquinoline	Sandmeyer reaction	50	147	100
1,6-diCl	6-Hydroxy iso-carbostyril	$POCl_3$		95–96	52
1,7-diCl	7-Chloroisoquino-line	H_2O_2, $POCl_3$	90	138	100
	7-Hydroxyisocarbo-styril	$POCl_3$			52
5,8-diCl	Isoquinoline	$AlCl_3$ 2 eq. Cl_2	57	115–117	19
1,6-diCl-3-OH	2-Cyano-5-chloro-phenylacetic acid	PCl_5/HCl	80	219–221	72
3,7-diCl-1-OH	5-Chloro-1-cyano-methyl benzoyl chloride	HCl	68	253–254	72
3,7-diCl-1-OH		Heat		253–257	67

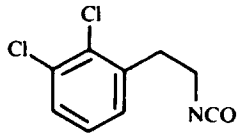
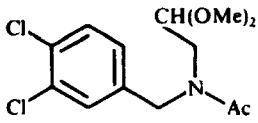
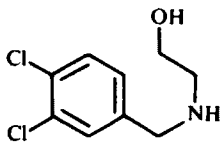
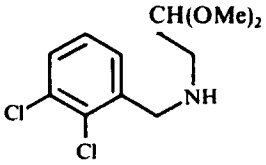
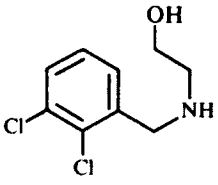
D. Polychloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1,3-diCl-5-OCH_3		PCl_5, HCl	54	166–167	70
1,3-diCl-6-OCH_3		PCl_5, HCl	57	91–93	70
1,3-diCl-7-OCH_3		PCl_5,HCl	62	169–170	70
1,3-diCl-6,7-diOCH_3		PCl_5, HCl	76	200–201	70
1,3,4-triCl	4-Chlorophenyl-acetonitrile	$COCl_2$	44	141–143	67
	2-Cyanomethyl benzoic acid-methyl ester	PCl_5	92	138	66
1,3,7-triCl		PCl_5	77	166–168	109
	4-Chlorophenyl-acetonitrile	$COCl_2$	17	168–170	67
	3,7-Dichloroiso-carbostyril	$COCl_2$	93		67
5,7,8-tri-Cl	5,8-Dichloro-isoquinoline	$AlCl_3$,Cl_2	87	177–178	19
triCl	Isoquinoline	S_2Cl_2	–	124	15, 16
pentaCl	Heptachloroiso-quinoline	Electrolytic-reduction	–		132

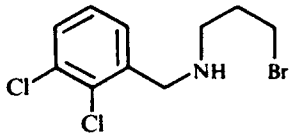
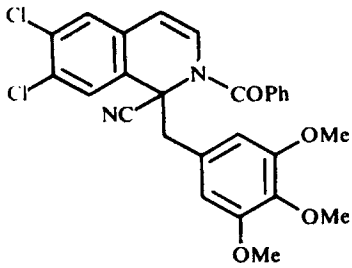
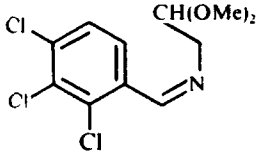
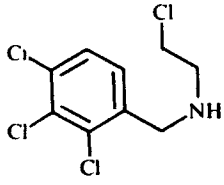
D. Polychloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
hexaCl	Heptachloroisoquinoline	Electrolytic reduction			132
	Isoquinoline	$AlCl_3$, Cl_2	87	174	21
heptaCl	Isoquinoline	Two-stage chlorination	68	126–128	21
	o-Ethylbenzonitrile	Cl_2/CCl_4, 600 °C	25		92
5,7-diCl		H_2SO_4	54	155–156	20
5,8-diCl		H_2SO_4	16	117–118	20
6,7-diCl		H_2SO_4	9	227(d)	20
6,8-diCl		H_2SO_4	<1	238(d)	20
7,8-diCl		H_2SO_4	56.6	225–226 (HCl)	86
			49	222–224 (HCl)	20
5,6-diCl-1,2,3,4-tetrahydro		BH_3		250–252 (HCl)	20

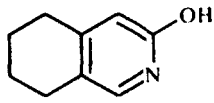
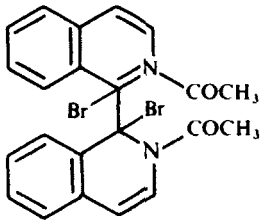
D. Polychloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (C)	Ref.
5,6-diCl-1-OH		$AlCl_3$	50	202–204	20
5,7-diCl-1,2,3,4-tetrahydro	5,7-Dichloro-isoquinoline	H_2/PtO_2	47	300(d) (HCl)	20
5,8-diCl-1,2,3,4-tetrahydro	5,8-Dichloro-isoquinoline	H_2/PtO_2	55	311(d) (HCl)	20
6,7-diCl-1,2,3,4-tetrahydro	6,7-Dichloro-isoquinoline	H_2/PtO_2	29	269–274 (HCl)	20
		$AlCl_3$; H_2/Pt; HCl		271–273 (HCl)	116
6,7-diCl-1,2,3,4-tetrahydro		$AlCl_3$/NH_4Cl	41		118
6,8-diCl-1,2,3,4-tetrahydro	6,8-Dichloro-isoquinoline	H_2/PtO_2	43	296(d) (HCl)	20
7,8-diCl-1,2,3,4-tetrahydro	7,8-Dichloro-isoquinoline	H_2/PtO_2	48	225–227 (HCl)	20
		$AlCl_3$; H_2/Pt; HCl	—	222.5–225 (HCl)	116
		NH_4Cl, $AlCl_3$ melt	80		118

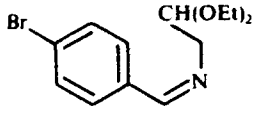
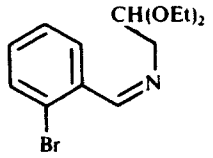
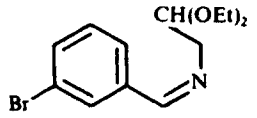
D. Polychloroisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
7,8-diCl-4-Me-1,2,3,4-tetrahydro		$AlCl_3$, NH_4Cl melt	72		123
6,7-diCl-1-(3,4,5-triOMe benzyl)		BTEAC NaOH	98	211–212	231
6,7,8-triCl		H_2SO_4	6	205–207 (CH_3SO_3H)	20
5,7,8-triCl-1,2,3,4-tetrahydro	5,7,8-Trichloro isoquinoline	Diborane	50	178–179 (Maleate)	20
6,7,8-triCl-1,2,3,4-tetrahydro	6,7,8-Trichloroisoquinoline	Diborane	52	193–194 (Maleate)	20
		$AlCl_3$/ NH_4Cl	51		118
5,6,7,8-tetraCl	Isoquinoline	$AlCl_3$ + Cl_2	2	210–212	20
5,6,7,8-tetraCl-1,2,3,4-tetrahydro	5,6,7,8-Tetrachloro-isoquinoline	Diborane	50	>300 (HCl)	20

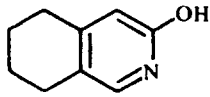
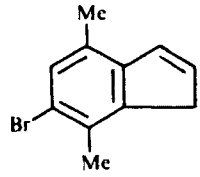
E. Bromoisoquinolines

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1-Br	Isocarbostyril	PBr_3		41–42	3
3-Br	3-Aminoisoquinoline	HBr, $NaNO_2$	45	63–64	97
	3-Aminoisoquinoline	HBr, $NaNO_2$	47	-	98
	1,3-Dibromoisoquinoline	Reduction	60	63–64	54
		$POBr_3$	47	61	55
4-Br	Isoquinoline-2-oxide	2-Bromopyridine	8		33
	Isoquinoline	$Br_2(PhNO_2)$	High		4
	Isoquinoline-2-oxide	2-Bromopyrimidine	7	—	34
	Isoquinoline	Br_2, HBr	53	38–39	177
	Isoquinoline	Br_2, HBr	76	39–40	483
	Isoquinoline	$Hg(OAc)_2$; Br_2	-	40; 179 (Nitrate)	28
	Isoquinoline	$Br_2(SO_2Cl_2$ or $S_2Cl_2)$	—	34–37	9
	Isoquinoline	2Br, 180		40	5
	Isoquinoline	$Hg(OAc)_2$, Br_2	—	—	181
	Isoquinoline	HBr; Br_2 (180°C) Hydrolysis	73.7	39–40	6
	Isoquinoline hydrochloride	Br_2, $(PhNO_2)$	81	41–42	8
	Isoquinoline-2-oxide	1-Bromoisoquinoline	8		9,33
		NaOH/EtOH reflux	40	41–41.5	130
5-Br	Isoquinoline	$AlCl_3$, Br_2	78	80–82	19
	Isoquinoline	$AlCl_3$, Br_2	44	82–84	484
	5-Aminoisoquinoline	HBr/$NaNO_2$; 0°C; CuBr/ HBr, 75°C	80.5	82–84	54, 95
			65	82	185

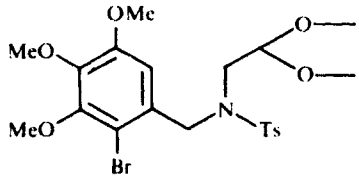
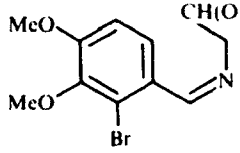
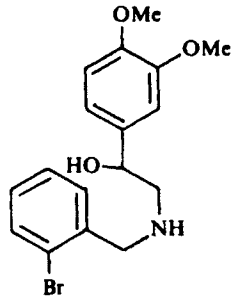
E. Bromoisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
6-Br		Pomeranz–Fritsch reaction	6		84
8-Br		Pomeranz–Fritsch reaction	29		84
5 and 7-Br (mixture)		Pomeranz–Fritsch reaction	65		84
7-Br-3,4-dihydro	7-Amino-3,4-dihydroisoquinoline	$HBr/NaNO_2$; 0 °C; CuBr/HBr, 75 °C	67	201–202 (HCl)	110, 111
7-Br-1,2,3,4-tetrahydro	7-Bromo-3,4-dihydroisoquinoline	$NaBH_4$	81	—	111
5-Br-decahydro	5-Hydroxy-decahydroisoquinoline	HBr	27	167 (HBr)	133
10-Br-decahydro	10-Hydroxydecahydroisoquinoline	HBr	47	110–114 (HBr)	133
1-Br-3-OH	3-Amino-1-bromoisoquinoline	HNO_2	Poor	179–181	63
	1-Cyanophenylacetic acid	HBr	83	179–182	72
3-Br-1-OH	*o*-Cyanomethylbenzoyl chloride	HBr	94	224–226	69, 72
3-Br-4-OH	4-Isoquinolinol	Br_2 (NaOH), 20 °C, 3 hr	76	145–146	23
4-Br-1-OH	Isoquinoline-2-oxide	Br_2/Ac_2O		248–250	31
	Isocarbostyril	HBr	3.6	248–249	59
4-Br-3-OH	3-Aminoisoquinoline	Sandmeyer reaction	22	209–211	98
4-Br-1-OC_2H_5	4-Bromo-1-chloroisoquinoline	NaOEt	77	63–64	36
3-Br-6,8 diOH	3,5-Dimethoxyphenyl acetonitrile	$Zn(CN)_2$ dry HBr		258–263	73
1-Br-3-OH 6-OMe	2-Cyano-5-methoxy phenyl acetic acid	HBr	73	191–193	72

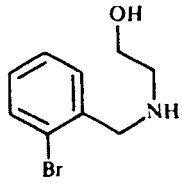
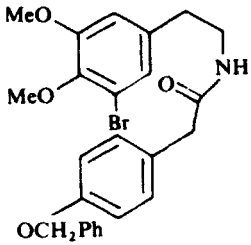
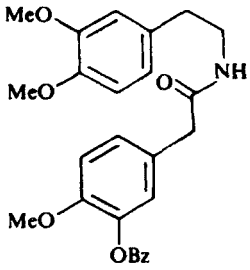
E. Bromoisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
3-Br-6-OH-8-OCH_3	3-Bromo-6,8-dimethoxy isoquinoline	HI, reflux 15 min	58	247–249	73
3-Br-6,8-diOCH_3	3,5-Dimethoxyphenyl acetonitrile	Gattermann reaction		159–160	73
1-Br-6,7-diOMe-3-OH	2-Cyano-4,5-dimethoxy phenylacetic acid	HBr	75	207–210	72
1,3-diBr	Homophthalimide	PBr_3		147	54
		$POBr_3$		144–145	55
3,4-diBr	3-Aminoisoquinoline	Sandmeyer reaction	80	92–93	98
5,8-diBr	Isoquinoline	$AlCl_3$, Br_2	61	114–115	19
4,5-diBr	4-Bromo-5-amino-isoquinoline	Sandmeyer reaction		138(?)	94
	4-Bromoisoquinoline	Bromination	72	112–113	104
	4-Bromo-5-amino-isoquinoline	Sandmeyer reaction		112–113	104
1,3-diBr-4-OH	4-Isoquinolinol	Br_2(NaOH) 80 °C, 3 h	40	161–163	23
1,6-diBr-3-OH	5-Bromo-2-cyano-phenyl acetic acid	HBr	89	197–199	72
4,5,8-triBr	4-Bromoisoquino-line	Br_2	86	165	104
5,7,8-triBr	5,8-Dibromoisoquino-line	$AlCl_3$, Br_2	75	200–201	19
6-Br	6-Bromoindene	O_3, MeOH, −78 °C; Me_2S, $NaHCO_3$; NH_4OH	70	42–43	82
6-Br-5,8-diMe		O_3; Me_2S, $NaHCO_3$, NH_4OH	95		203
7-Br	5-Bromoindene	O_3, MeOH, −78 °C; $NaHCO_3$ Me_2S	58	67–69	82
7-Br-2 Me-1,2,3,4-tetrahydro	7-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline	HBr/$NaNO_2$ (CuBr)	87	285–286 (HBr)	112

E. Bromoisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
8-Br-2-Me-5,6,7-triOMe 1,2,3,4-tetrahydro	5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline	CH_2O, $NaBH_4$; bromination		226–227 (HCl)	24
8-Br-5,6,7-triOMe		HCl; K.t. butoxide	83	64–67	91
					
8-Br-6,7-diOMe		$(CF_3CO)_2O$; $BF_3 \cdot HOAc$; NH_3	29	135–137	90
8-Br-6,7-diOMe	7-Hydroxy-6-methoxy isoquinoline	Br_2, HOAc NaOAc, methylation	71	220.5–223	26
8-Br-5-OEt-6-OMe-2-Me-1,2,3,4-tetrahydro	8-Amino-5-ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	Sandmeyer reaction	37	35	105
8-Br-4-(3',4'-diOMephenyl)-2-Me-1,2,3,4-tetrahydro		Methylation; $AlCl_3$	66	233–236	120
8-Br-5,6-diOMe-2-Me-1,2,3,4-tetrahydro	8-Amino-5,6-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	Sandmeyer	78	65	106
5-Bz-8-Br-2-Me-1,2,3,4-tetrahydro	5-Benzyloxy-2-methyl-1,2,3,4-tetrahydroisoquinoline	Bromination			27

E. Bromoisoquinolines (*Continued*)

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
8-Br-1,2,3,4-tetrahydro		$AlCl_3/NH_4Cl$	59	—	118
1-(4-OBzbenzyl)-8-Br-6,7-diOMe-3,4-dihydro		$POCl_3$, benzene	—	171–173	207
1-(3-OBz-3-OMebenzyl)-8-Br-6,7-diOMe-3,4-dihydro		Bischler-Napieralski		Yellowish syrup	198

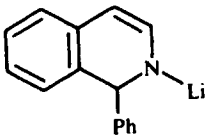
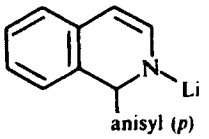
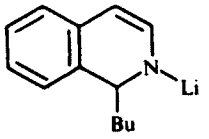
F. Iodoisoquinolines

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1-I	1-Chloroisoquinoline	NaI, HI		70–72	131
5-I	5-Aminoisoquinoline	$H_2SO_4/NaNO_2$	22	98	109
1-I-3-OH	2-Cyanophenylacetic acid	(1) PCl_5 (2) HI	81	154–157	72
3-I-1-OH	*o*-Cyanomethylbenzoyl chloride	$HI/NaHCO_3$	70	234–237	69, 72
3-I-4-OH	4-Hydroxyisoquinoline	I_2,KI	88	172–173	23
5-I-8-OH	5-Amino-8-hydroxy-isoquinoline	$NaNO_2$; I_2 KI; Ac_2O; Hydrolysis	92	185–188	30
8-I-5-OH	5-Hydroxyisoquino-line	ICl	31	213 (HCl)	30
1-I-3-OH-6-OMe	2-Cyano-5-methoxy-phenylacetic acid	PCl_5;HI	85	180–182	72
1-I-6,7-di-OMe-3-OH	2-Cyano-4,5-dimethoxy-phenylacetic acid	PCl_5;HI	61	220–222	72
Diiodo	Isoquinoline	I_2/H_2SO_4		151	12
1,3-diI-4-OH	4-Hydroxyisoquinoline	I_2, KI	50	137–139	23
5,7-diI-8-OH	5-Iodo-8-hydroxyiso-quinoline	ICl	70	208–210 (HCl)	30
6,8-diI-5-OH	6,8-Diiodo-5-acetoxyisoquinoline	NaOH	100	180–185	30
Triiodo	Isoquinoline	I_2/H_2SO_4	—		12
1-I	1-Trimethylstannyl isoquinoline	I_2	96	74–76	265
3-I	3-Trimethylstannyl-isoquinoline	I_2	94	59.5–60.5	265
4-I	Isoquinoline	I_2,HI, H_2O			14
	4-Trimethylstannyl-isoquinoline	I_2	95	93–94	265
6-I	6-Iodoindene	O_3, Me_2S $NaHCO_3$ NH_4OH	66	86–88(d)	82
7-I	5-Iodoindene	O_3, Me_2S, $NaHCO_3$; NH_4OH	58	124–(128(d)	82

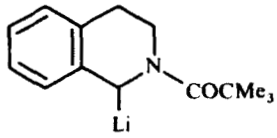
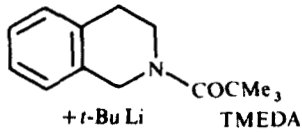
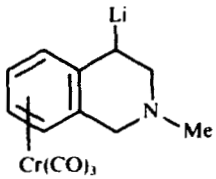
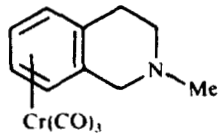
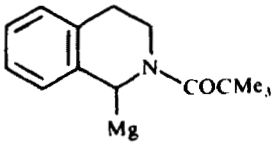
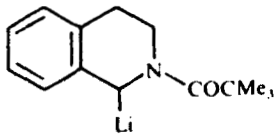
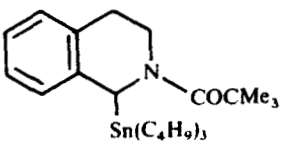
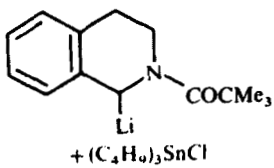
G. Isoquinolines Substituted with Different Halogens

Compound	Starting Material	Method	Yield (%)	m.p. (°C)	Ref.
1-Br-3-F	3-Amino-1-bromoisoquinoline	HBF_4, $NaNO_2$ steam dist.	28	60	115
4-Br-1-Cl	4-Bromoisoquinoline	H_2O_2/HOAc; $POCl_3$	73	98	36
3-Cl-1-F	1,3-Dichloroisoquinoline	Me_2SO_2, KF	23	67	115
5-Cl-8-F	5-Chloro-8-aminoisoquinoline	Schiemann reaction	21	93	115
1-Br-6-Cl-3-OH	2-Cyano-5-chlorophenylacetic acid	HBr	70	204–206	72
6-Br-1-Cl-3-OH	5-Bromo-2-cyanophenylacetic acid	PCl_5; HCl	70	226–227	72
6-Br-1-I-3-OH	6-Bromo-2-cyanophenylacetic acid	PCl_5; HCl	85	180–182	72
4-Cl-3,5,6,7,8-penta-F-1-OMe	4-Chloro-1,3,5,6,7,8-hexafluoroisoquinoline	NaOMe	—	72–73	173

H. Organometallic Derivatives of Isoquinolines

Compound	Method/Properties	m.p. (°C)	Ref.
	Lithium Complexes		
	IQ + Ph Li		253, 254
	IQ + *p*-anisyl Li		253
	IQ + Bu Li	—	254
1-IQLi	1-BrIQ + Bu Li		255
4-IQLi	4-BrIQ + *n*-BuLi		470, 257

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
			260
		—	374, 375
	Grignard Reagent		
IQ Mg Grignard	IQ + EtMgBr Autoclave		263
		—	264
	Magnesium bromide etherate pale yellow rhomb-shaped crystals		
	Tin Compounds		
1-TMSnIQ TMSn = trimethylstannyl	1-ClIQ + $NaSn(CH_3)_3$	b.p. 120–121 (4.5 mm)	265
3-TMSnIQ	3-BrIQ + $NaSn(CH_3)_3$	b.p. 118–120 (4.0 mm)	265
4-TMSnIQ	4-BrIQ + $NaSn(CH_3)_3$	b.p. 147–149 (3.0 mm)	265
		b.p. 210 (0.01 mm)	260

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
	Group IB		
Copper complexes			
$[(N_3)_2Cu(IQ)_2]$	Yellowish green; explodes at 197–200°C		280
$[Cu(IQ)_2Cl_2]$	Cu(II) salt + IQ	250	273
$[Cu(IQ)_2(NO_3)_2]$	Cu(II) salt + IQ	265	273
[Cu(IQ)I]	CuI (in aq. KI) + excess IQ	204	275
$[Cu_4O(IQ)_4Cl_6]$	$CuCl_2$ + NaOH + IQ	265	298
$[Cu_4O(IQ)_4Br_6]$	$CuBr_2$ + NaOH + IQ	217–219	298
$[Cu(OCN)_2(IQ)_2]$	KOCN + IQ + $Cu(NO_3)_2 \cdot 3H_2O$	—	276
$[Cu(HCOO)_2(IQ)_2 \cdot 2H_2O]$	$CuCO_3$–$Cu(OH)_2$ + 36% aq. boiling HCOOH → filtrate + IQ; blue crystals	—	267
$[CuC_2O_4 \cdot 2(IQ)]$	CuC_2O_4 + IQ	—	272
$[CuCl_4 \cdot (IQH)_2]$	$[Cu(IQ)_2] + Cl_2$; orange-yellow crystals	180	299
$[CuCl_2Br_2 \cdot (IQH)]$	$[Cu(IQ)_2Cl_2] + Br_2$; dark violet crystals	142	299
$[CuBr_4 \cdot (IQH)]$	$[Cu(IQ)_2] + Br_2$; dark violet crystals	130	299
$[Cu(NCO)_2(IQ)_2]$	$Cu(NO_3)_2$ + KNCO + IQ	—	278, 279
$[Cu(SCN)_2(IQ)_2]$	$Cu(SCN)_2$ + IQ	201	280
$[Cu(C_6H_5CO_2)_2(IQ)]$	IQ + anhydrous $Cu(C_6H_5CO_2)_2$; green solid	—	270, 271
$[Cu(C_6H_5CO_2)_2(IQ)_2]$	Excess IQ + anhydrous $Cu(C_6H_5CO_2)_2$; blue solid		270, 271
$[Cu(Sal)_2(IQ)_2]$ HSal = Salicylaldehyde	$Cu(Sal)_2$ + IQ; Blue or green needles	160	282
$[Cu_2(CH_3CO_2)_4(IQ)_2]$	$Cu(CH_3CO_2)_2$ + IQ; dark green microcrystals	158	268, 269

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
[CuL·2IQ] LH_2 = biphenyl-2,2'-dicarboxylic acid	CuL + IQ	—	297
[$CuL_2(IQ)_2$] HL = Ethyl acetoacetate	CuL_2 + IQ; green needles	215	290
[$Cu(OCH_3)$ (2,4,6-$OC_6H_2Cl_3$) (IQ)]	[$Cu(OCH_3)$ (2,4,6-$OC_6H_2Cl_3$)·CH_3OH] + IQ; dark green crystals	—	288
[$Cu_2Cl_4(IQ)_5$]	$CuCl_2$ + IQ; dark green silky needles	—	274
[$CuCl_2(IQ)_2$]	$CuCl_2$ + IQ; pale green solid	—	274
[$CuL_2(IQ)$] HL = 3-chloro-1,4-pentanedione	CuL_2 + IQ; green crystals	—	286
[$Cu(acac)_2(IQ)$] Hacac = acetylacetone		—	285
[$Cu(dtc)_2(IQ)$] Hdtc = dithiocarbamic acid		—	285
[$CuL_2(IQ)_2$] LH = CCl_3CO_2H	CuL_2 + IQ		291
[$Cu(ROCH_2CO_2)_2$ $(IQ)_2$] R = Ph, *o*-, *m*-, *p*-MeC_6H_4	$Cu(ROCH_2CO_2)_2·3H_2O$ + IQ	—	293
[Cu(OMe) ($OC_6H_2Br_3$-2,4,6)$_2$ IQ]	Cu(OMe)($OC_6H_2Br_3$-2,4,6)$_2$ MeOH + IQ	—	289
[$CuL_2(IQ)_2$] HL = $PhCH_2CO_2H$	$Cu(PhCH_2CO_2)_2$ + IQ; green crystals	—	292
[$CuL_2(IQ)$] HL = acetoacetantilide	$CuCl_2$ + acetoacetanilide + IQ; green crystals	254	283
[Cu(MB)$_2$ IQ]	—	—	296
[$Cu(MB)_2(IQ)_2$]· HMB = *m*-methoxybenzoic acid	—	—	296
[$Cu(L_2(IQ)_3$] L = isopropylthioacetate	$CuL_2·2H_2O$ + IQ; blue crystals	—	294, 295
[$CuL_2(IQ)$] HL = thenoyltrifluoroacetone, pivaloyltrifluoroacetone	CuL_2 + excess IQ; green crystals	—	287

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[Cu(RSCH_2CO_2)_2IQ]$ R = Me, Et, isoPr	$[Cu(RSCH_2CO_2)_2]$ hydrates + IQ		295
$[Cu(RSCH_2CO_2)_2(IQ)_2]$ R = isoPr			
$[Cu(RSCH_2CO_2)_2(IQ)_3]$ R = Me, Et, iso-Pr	$[Cu(RSCH_2CO_2)_2]$ hydrates + IQ		295
$[CuL_2(IQ)]$ HL = *o*-hydroxy acetophenone	$CuCl_2$ + dil NH_3 → Ppt. + IQ; green crystals	245	284
Silver complexes			
$[Ag(IQ)_2NO_3]$	IQ + conc. solution of the Ag salt	165	302
$[Ag(IQ)_2ClO_4]$	IQ + conc. solution of the Ag salt	215	302
[Ag(IQ) (NCO)]	IQ + conc. solution of the Ag salt	—	303
[Ag(IQ)SCN]	IQ + conc. solution of the Ag salt	—	303
$[Ag(IQ)_2\ Cr(NCS)_6]$	IQ + conc. solution of the Ag salt	—	304
$[Ag(IQ)_2\ Cr(NCS)_4\ A_2]$ A = aniline, *p*-toluidine	IQ + conc. solution of the Ag salt	—	304
$[AgL_2(IQ)_2]$ HL = picolinic acid	AgL_2 + IQ	102	305
	Group IIA		
Calcium complexes			
$[(IQ)_2CaCl_2]$	IQ-fraction + sat. aq. $CaCl_2$ → ppt. on cooling		306
	Group IIB		
Zinc complexes			
$[Et_2Zn(IQ)]$	IQ (excess) + Et_2Zn; viscous oil → light yellow needles from pentane	9–10	307
$[(Me_2NCS_2)_2Zn(IQ)_n]$ $n = 1, 2$	IQ + Zn-dithiocarbamate $n = 1$ $n = 2$	200–210 145–160	309
$[R_2Zn{\cdot}2(IQ)]$ R = Me, Et	R = Me R = Et	64 28	308
$[ZnL_2X_2(IQ)_2]$ L = Thioureas X = Cl, Br, I	ZnL_2X_2 + IQ		311

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[Zn(acac)_2 \cdot (IQ)]$	IQ + zinc acetylacetonate;	—	316
$[Zn(IQ)_2(NO_2)_2]$	$Zn(NO_2)_2$ + excess IQ	—	315
$[Zn(NCO)_2(IQ)_2]$	$Zn(NCO)_2$ + IQ	220	315
$[Zn(Sal)_2(IQ)_2]$ HSal = salicylaldehyde	$Zn(Sal)_2$ + IQ; white crystals	204	282
$[ZnL_2(IQ)_2]$ $HL = EtO_2CCH_2OMe$	ZnL_2 + IQ; white crystals	194	290
$[ZnCl_2(IQ)_2]$	$ZnCl_2$ + IQ; snow-white solid		310
[ZnL2IQ] LH_2 = biphenyl-2,2'-dicarboxylic acid	ZnL + IQ	—	297
$[Zn(NCSe)_2(IQ)_2]$	$Zn(NCSe)_2$ + IQ	128	313
[Zn(Pdtc)$_2$IQ)] (Pdtc = piperidyldithio carbamate)	Zn(Pdtc)$_2$ + IQ; white crystals	183	319
$[ZnL_2(IQ)_2]$ $LH = CCl_3CO_2H$	$Zn(CCl_3CO_2)_2$ + IQ; white crystals	—	291
$[Zn(PhCH_2CO_2)_2(IQ)_2]$	$Zn(PhCH_2CO_2)_2$ + IQ; white crystalline solid		292
[Zn(Clacac)$_2$(IQ)] HClacac = chloroacetylacetone	[Zn(Clacac)$_2$(H_2O)]	175	318
$[ZnL_2(IQ)]$ HL = acetoacetanilide	$ZnCl_2$ + acetoacetanilide + IQ	180	283
$[Me_4N]$ $[Zn(SCN)_4(IQ)_2]$	$[Me_4N]$ $[Zn(SCN)_4]$ + IQ; white crystalline solid	109	314
$[ZnL_2(IQ)]$ HL = thenoyltrifluoroacetone, pivaloyltrifluoroacetone	ZnL_2 + IQ; white crystals		287
$[ZnL_2(IQ)]$ LH = *o*-hydroxyacetophenone	$ZnCl_2$ + LH + dilute NH_3 → precipitate + IQ; white crystals	175	284
Cadmium complexes			
[Cd(Mdtc)$_2$IQ] Mdtc = morpholyldithio-carbamate	Cd(Mdtc)$_2$ + IQ; light rose-colored solid	> 280	327

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[Cd(Pdtc)_2(IQ)_3]$ Pdtc = piperidyldithio-carbamate	$Cd(Pdtc)_2$ + IQ; shining grey solid	130	327
$[Cd(SCN)_2(IQ)_4]$	$Cd(SCN)_2$ + excess IQ; white crystalline solid	110	322
$[CdI_2(3\text{-pic-NO})(IQ)_2]$	$[CdI_2(3pic\text{-}NO)]$ + IQ; pale yellow needles	180	326
$[CdI_2(4\text{-pic-NO})(IQ)_2]$	$[CdI_2(4\text{-pic-NO})]$ + IQ; pale yellow needles	165	326
$[(Et_4N)][CdI_3(IQ)_2]$	$(Et_4N)_2CdI_4$ + IQ; white needles	148	324
$[IQH]_2[CdX_2Cl_2]$	$[Cd(IQ)_2X_2]$ + slight excess IQ + Cl_2		325
X = Cl	White crystals	150	
X = Br	Pale brown crystalline solid	225(d)	
$[Cd(IQ)_2X_2]$			325
X = Cl			
X = Br			
$[CdL_2(IQ)_2]$ HL = acetoacetanilide	$CdCl_2$ + acetoacetanilide + IQ; white crystals	248	283
$[Me_4N]_2[Cd(SCN)_4(IQ)_2]$	$[Me_4N]_2[Cd(SCN)_4]$ + IQ		323
$[Cd(Pdtc)_2(IQ)]$ Pdtc–piperidyldithio-carbamate	$Cd(Pdtc)_2$ + IQ; brownish-white crystalline solid		328
$[CdL_2(IQ)]$ HL = *o*-hydroxyacetophenone	$CdCl_2$ + HI + dilute NH_3 → precipitate + IQ; white crystals	205	284
$[Cd(Mn)(IQ)Cl_2]$ (Manganese-doped Mn ions present at a nominal value of 1%)	$CdCl_2$ + $MnCl_2$ + IQ	—	329
Mercury complexes			
$[Hg(IQ)(CN)_2]$	Excess IQ + $Hg(CN)_2$	206	330
$[HgL_2Cl_2(IQ)_2]$ HL = thiosalicyclic acid	HgL_2Cl_2 + IQ; white amorphous solid	173	331

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
	Group IIIA Elements		
Aluminium complexes			
$[(Et_3Al)(IQ)]$ or $[(Et_2AlH)(IQ)]$	$IQ + Et_3Al$ (or Et_2AlH)	—	332
$[(Et_2AlH)(IQ)_2]$	IQ (excess) + Et_2AlH	—	334
	Group IIIB Elements		
Lanthanide series			
Cerium complexes			
$[(IQH)_2\,CeCl_5]$	$CeCl_3 + HCl_{(g)} + IQ$; white solid	—	335
Holmium complexes			
$[(IQH)_2HoCl_5 \cdot 3H_2O]$	$HoCl_3 \cdot 6H_2O + HCl_{(g)} + IQ$; Cream crystals	265–275	336
Ytterbium complexes			
$[(IQH)Yb(C_2O_4)_2 \cdot 3H_2O]$	$YbCl_3 \cdot 6H_2O$ + oxalic acid + IQ; white solid	234(d)	336
Actinide series			
Thorium complexes			
$[Th(ClO_4) \cdot 8IQ]$	$Th(ClO_4)$ + excess IQ	185–187	337
$[Th(NO_3)_4 \cdot 2IQ]$	$Th(NO_3)_4$ + IQ; white solid		338
$[Th(NCS)_4 \cdot 4IQ]$	$Th(NCS)_4$ + excess IQ; pinkish-white solid	—	338
Uranium complexes			
$[UCl_5(IQ)_n]$ $n = 2, 3$	$IQ + UCl_5$; in $SOCl_2$	Decomposes > r.t	339
$[(IQH)_2UOCl_5 \cdot IQ]$	$IQ + UCl_5 + SOCl_2$; reddish-brown solid	-	340
$[IQH]_2[UOCl_5]$	$IQ + UCl_5 + SOCl_2$; reddish-brown solid	—	341
$[(IQH)_2\,UO_2Cl_4]$	$HCl_{(g)}$ + uranyl chloride + $IQ + HCl_{(g)}$; yellow solid	219	342
$[UO_2(PhCH_2CO_2)_2(IQ)H_2O]$	Excess $IQ + UO_2(PhCH_2CO_2)_2$; bright yellow solid	240–242 (d)	343

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[UO_2L(IQ)H_2O]$ HL = lactic acid	Excess IQ + $UO_2(C_3H_5O_3)\cdot 2H_2O$; yellow compound	248 (d)	344
	Group IVA		
Germanium complexes			
$[GeX_4\cdot 2(IQ)]$ X = Cl, Br, F	GeX_4 + IQ		345
Tin complexes			
$[Ph_3SnCl(IQ)]$	Excess IQ + Ph_3SnCl	110	346
$_2SnCl(IQ)]$	Excess IQ + Ph_3SnCl	169	346
$[Pr_3SnCl(IQ)]$	Tri(*n*-propyl)tin chloride + IQ	141–142	347
$[Ph(nBu)SnCl_2(2IQ)]$	Phenyl(*n*-butyl)tin dichloride + IQ	114–115	348
$[PhSnCl_3\cdot 2(IQ)]$	Excess IQ + Ph_3SnCl	—	349
$[Pr_2SnCl_2(2IQ)]$	Di(*n*-propyl)tin-dichloride + IQ	158–159	350
$[(IQ)_2SnCl_4]$	White	225	356
$[R_xSn_{4-x}\cdot 2IQ]$	Organotin halide + IQ		351
R_xSn_{4-x} =			
$BuSnCl_3$		134	
$BuSnBr_3$		94–96	
$PhSnCl_3$		> 300	
Bu_2SnCl_2		106–108	
Bu_2SnBr_2		102–104	
Ph_2SnCl_2		182	
Ph_2SnBr_2		170	
Ph_2SnI_2		122	
$(p\text{-tolyl})_2SnCl_2$		172	
$(p\text{-tolyl})_2SnBr_2$		182	
$(o\text{-tolyl})_2SnCl_2$		164	
Ph_3SnCl		106–107	
$[(Et)(Ph)SnCl_2\cdot 2IQ]$	Allylphenyltin dichloride + IQ; white	114–116	352
$[(nPr)(Ph)SnCl_2\cdot 2IQ]$	White solid	118–119	352
$[(nBu)(Ph)SnCl_2\cdot 2IQ]$	White solid	114–115	352
$[R_1R_2SnCl_2\cdot 2IQ]$	IQ + dialkyltin dichloride		353
R_1 = Me, R_2 = Et		147–149	
R_1 = Et, R_2 = *n*-Pr		85–86	
R_1 = *n*-Pr, R_2 = *n*-Bu		107–108	

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
Lead complexes			
$[(IQH)_2PbCl_6]$	H_2PbCl_6 + excess IQ·HCl	—	354
$[PbCl_4 \cdot 2IQ]$	$PbCl_4$ + IQ	—	354
	Group IVB		
Titanium complexes			
$[(IQ)_2TiCl_4 \cdot \frac{1}{2}SOCl_2]$	$TiCl_4$ + IQ in $SOCl_2$; red	176–8	356
$[TiX_4(IQ)]$ X = F, Cl, Br	IQ + TiX_4;	—	355
Zirconium complexes			
$[(ZrOCl_2)(IQ)]$	Excess IQ + $ZrOCl_2$	Decomposes > 230	357
$[ZrO(ClO_4)_2 \cdot 4IQ]$	Zirconium perchlorate	165–167	337
	Group VA		
Antimony complexes			
$[H(IQ)SbBr_4)]$	IQ + $SbBr_3$ in conc. HBr		358
$[C_9H_7NaNO_3Sb]$	5-Aminoisoquinoline + Sb_2O_3	—	359
$[IQH(X_4C_6H_2O_2)SbX'_2]$ $X_4C_6H_2O_2$ = pyrocatechol derivative X = H, halo X′ = Cl, Br		—	360
	Group VB		
Vanadium complexes			
$[VOCl_3(IQ)]$	$VOCl_3$ + IQ; violet-red powder	—	361
$[VCl_4(IQ)_2]$	IQ + VCl_4; brown semisolid turning green	—	364
$[VO(IQ)SO_4]$	$VOSO_4$ + IQ	—	366
$[VO(IQ)_2Cl_2]$	$VOCl_2$ + IQ	—	363
$[VO(acac)_2(IQ)]$	$VO(acac)_2$ + IQ		368
$[VOCl_3 \cdot 3IQ]$	IQ + $VOCl_3$	—	362
	Dark-brown hygroscopic solid		

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[V(IQ)_4X_2]$	$VX_2 \cdot xEtOH + IQ$ $x = 4$ or 6		365
X = Cl	Royal blue	—	
X = Br	Royal blue	—	
X = I	Blue	—	

Group VI B

Chromium complexes

$[Cr(tu)_2(IQ)_2Cl_2]Cl$ tu = thiourea	$Cr(tu)_3Cl_3$; green solid	138	369
$[IQH]\,[CrOCl_4]$	$CrO_3 + CH_3CO_2H + HCl_{(g)} + IQ$; dark red crystals	—	370
$[IQH]_2\,[CrCl_5(HO_2CMe)]$	$CrO_3 + CH_3CO_2H + HCl_{(g)} + IQ$; reflux; purple powder	—	371
$[IQH]\,[CrBr_4(HO_2CMe)_2]$	$CrO_3 + CH_3CO_2H + HBr + IQ$; brown powder contaminated with small amounts of $[IQH]\,[Br_3]$		371
$K[CrO_3Cl(IQ)]$	$K(CrO_3Cl) + IQ$; yellow-brown solid	no definite m.p.	372
$[Cr(NTA)\,(IQ)_2]$ H_3NTA = nitrilotriacetic acid		—	373
$[THIQ{\cdot}Cr(CO)_3]$ THIQ = 1, 2, 3, 4-tetrahydroisoquinoline	$THIQ + Cr(CO)_6$ Yellow-orange plates	63–64 —	374, 375
[*N*-MeTHIQ·$Cr(CO)_3$] *N*-MeTHIQ = *N*-Methyl-1,2, 3,4-tetrahydroisoquinoline	*N*-MeTHIQ + $Cr(CO)_6$; bright yellow needle	100–101	374, 375

Molybdenum complexes

$[(IQ)_3H_3As(Mo_3O_{10})_4]$	Arsenate solution + Na molybdate + HCl + IQ·HCl		376
$[(IQ)_3H_3AsTh(Mo_3O_{10})_4]$	Similar to above		376
$[MoOCl_3(IQ)_2]$	$[MoOCl_3(CH_3CN)_2] + IQ$; brown solid	—	377

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
	Group VIIB Metals		
Manganese complexes			
$[Mn(IQ)_2X_2]$ $X = Cl, Br, I, SCN$	$MnX_2 + IQ$	—	378
$[Mn(IQ)X_2$	$Mn(IQ)_2X_2 \rightarrow$ heat 125°–30°C several hours	—	378
$[Mn(acac)_2(IQ)_2]$ acac = acetylacetone	$Mn(acac)_2 \cdot 2H_2O + IQ$; deep-yellow crystalline solid	110	379
$[Mn(IQ)_4(NCO)_2]$	$Mn(NO_3)_2 + KCNO + IQ$	225	379
$[Mn(IQ)_4(NCSe)_2]$	$IQ + Mn(NCSe)_2$	165	381
$[MnCl_2(IQ)_5]$	$IQ + MnCl_2$ yellow crystals		310
[MnL·4IQ] LH_2 = biphenyl-2,2′-dicarboxylic acid	MnL + IQ	—	297
$[n\text{-cepy}]_2[MnCl_4(IQ)_4]$ *n*-cepy = *N*-cetylpyridine	$[n\text{-cepy}]_2[MnCl_4 + IQ]$ + excess IQ	68	383
$[n\text{-cepy}_2\ MnCl_4\ (IQ)_2]$	$[n\text{-cepy}]_2\ [MnCl_4(IQ)_4] \xrightarrow[100°]{\Delta}$	—	383
	Group VIII		
Iron complexes			
$[(IQ)_3 \cdot 2Na_4Fe(CN)_6 \cdot H_2O]$	$IQ + Na_4Fe(CN)_6 + HCl$; orange crystals	—	384
$[(IQ)_3 \cdot H_3Fe\text{-}(CN)_6\ \frac{1}{2}\ EtOH]$	Yellow rhombohedral crystals	—	385, 386
$[(IQ)_3 \cdot H_4Fe(CN)_6 \cdot 3EtOH]$	Lemon needles	—	385
$[Na_3Fe(CN)_5 \cdot IQ]$	$[Na_3Fe(CN)_5NH_3] +$ excess IQ	—	390
$[Fe(Chxn)_2(IQ)_2]$ Chxn-cyclohexylxanthate	Excess IQ + $[Fe(Chxn)_2(EtOH)_2]$; yellow solid		387
$[Fe(DgH)_2(IQ)_2]$ DgH_2 = dimethylglyoxime	Dimethylglyoxime + $FeSO_4 \cdot 7H_2O + IQ$	—	388
$[Fe(IQ)_2(acid)(OH)\ H_2O]$ acid = malonate, succinate, glutarate adipate, or diphenate ion		—	388
$[Fe^{II}\ Fe^{III}_2O(OAc)_6\ 3.5IQ]$	Base + $Fe^{II}Fe^{III}_2\ O(OAc)_6\ (H_2O)_3$	—	391

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[Fe_3O(OAc)_6(IQ)_3Cl]$		—	391
$[FeCl_2(IQ)_4]$		—	391
$[Me_4N][FeCl_4(IQ)_2]$	$[Me_4N][FeCl_4]$ + IQ; dark-yellow solid	235	393
$[Me_4N][FeCl_4(IQ)]$	$[Me_4N][FeCl_4]$ + IQ; yellow solid	249	393
Cobalt complexes			
$[Co(SCN)_2(IQ)_2]$	IQ + $CoCl_2$ + excess NH_4SCN; crystallizes out		395
$[Co(SCN)_2 \cdot 4(IQ)]$	IQ(excess) + ammonium thiocyanatocobaltate; rose colored	175	396
(a) $Co(IQ)_4[N(CN)_2]_2$	$Co(NO_3)_2 \cdot 6H_2O$ + $KN(CN)_2$ + IQ; microcrystals	—	397
(b) $\{Co(IQ)_2[N(CN)_2]_2\}$	$\{Co(IQ)_4[N(CN)_2]\}$ in CCl_4; reflux	—	397
$[CoCl_2 \cdot 4(IQ)]$	IQ + $CoCl_2$	—	398
$[CoSO_4(IQ)_2]$	$CoSO_4$ + IQ (excess)	—	399
$[CoX(DH)_2(IQ)]$ X = CN, NO_2, SeCN, SCN, Br D = dianion of dimethyl glyoxime	Dimethylglyoxime + IQ + Co salt	—	400
$[Co(IQ)_4(ONO)_2]$	Sodium cobaltinitrite + IQ (excess); orange crystals		401
$[Co(IQ)_3(NO_2)_2]$	Recrystallizing $Co(IQ)_4(ONO)_2$ from acetone; dark brown crystals	—	401
$[Co(acac)_2 \cdot (IQ)_2]$	Coacetylacetonate + IQ in hot EtOH	200	402
$[CoCl(en)_2(IQ)]Cl_2 \cdot H_2O$ en = ethylenediamine	IQ + *trans*$[CoCl_2(en)_2]Cl$ red-pink precipitate	—	408
$[Co(phen)(IQ)_2Cl_2]$ phen = 1,10-phenanthroline	Excess IQ + $[Co(phen)Cl_2]$ → red precipitate + air	—	410
$[Co(phen)(IQ)_2Cl_2O \cdot 5IQ]$	$[Co(phen)(IQ)_2Cl_2]$ + alcohol; red compound	—	410
$[CoL_2(IQ)_2]$ LH = $(EtO)_2PO_2H$, $(MeO)_2PO_2H$	CoL_2 + excess IQ	—	417
$[CoL_2(IQ)_2]$ L = EtO_2CCH_2OMe	CoL_2 + IQ; pink crystals	148	290

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[CoCl_2(IQ)_2]$	$CoCl_2$ + IQ; dark blue		310
$[CoL.nIQ]$ $n = 2,4$ LH_2 = biphenyl-2,2'-di carboxylic acid	CoL + IQ	—	297
$[Co(C_6H_5CO_2)_2(IQ)_2]$	$Co(C_6H_5CO_2)_2$ + IQ	—	271
$[Co(tu)_2(SCN)_2(IQ)_4]$ tu = thiourea	$[Co(tu)_2(SCN)_2]$ + IQ; pink crystalline solid	181	419
$[CoL_2(IQ)_2]$ HL = dibenzoylmethane	IQ + $CoL_2(H_2O)_2$	205	412
$[CoX(bzbz)(IQ)(H_2O)_2]$ Bbzbz = dibenzoylmethane X = Cl X = Br	IQ + cobaltous salt + dibenzoyl-methane yellow orange-yellow	—	413
$[Co(Sal)_2(IQ)_2]$ HSal = salicylaldehyde	$Co(Sal)_2$ + IQ; pink crystals	170	414
$[(IQ)_2Co(TPP)]^+ Br^-$ $TPPH_2$ = meso-tetraphenyl-porphyrin	IQ + Br − Co(TPP)		415
$Co[O_2P(OBu)_2]_2 \cdot 2IQ$	$Co[O_2P\cdot(OBu_2)_2$ + IQ	—	416
$[CoL_2(IQ)_2]$ $LH = CCl_3CO_2H$	CoL_2 + IQ; pink crystalline solid	—	291
$[Co(O_2CR)_2(IQ)_2]$ R = H, Me, Et, Bu,Pr, Iso-Pr	Co(II) alkanoate + IQ; formate and acetate—pink, others—red		407
$[IQH][CoX_2Br(IQ)]$ X = Br X = Cl	$[Co(IQ)_2X_2] + Br_2$	203 188	418
$[IQH][CoX_2Cl(IQ)]$ X = Cl X = Br	$Cl_2 + [Co(IQ)_2X_2]$	190 185	418
$[CoL_2(IQ)_2]$ $HL = PhCH_2CO_2H$	$Co(PhCH_2CO_2)$ + IQ; pink crystalline solid	—	292
$[Co(IQ)_2L]$ H_2L = succinic, glutaric, or adipic acid	CoL + IQ; blue compounds	—	406
$[Co(IQ)_4L]$ H_2L = malonic acid	CoL + IQ; pink		406
$[CoL_2(IQ)_2]$ HL = acetoacetanilide	$CoCl_2$ + acetoacetanilide + IQ	> 250	283
$[Co(Cl_2CHCO_2)_2(IQ)_2]$	$Co(Cl_2CHCO_2)_2$ + IQ	—	403
$[Co(Cl_2CHCO_2)_2(IQ)_4]$	IQ + $Co(Cl_2CHCO_2)_2$; pink	—	403

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[Co(F_3C{\cdot}CO_2)_2(IQ)_2]$	$IQ + Co(F_3C{\cdot}CO_2)_2$		403
$[Co(ABT)_2(SCN)_2(IQ)_4]$ ABT = 2-aminobenzothiazole	$[Co(ABT)_2(SCN)_2] + IQ$	162	420
$[Co(RC_6H_4CO_2)_2(IQ)_2]$ R = *o*-Me, *o*, *m*-Cl, *o*-, *m*-NO_2, and *m*-MeO	$Co(RC_6H_4CO_2)_2 + IQ$; pink compounds	—	404
[Co(acac) (mbt) $(IQ)_2$] acacH = acetyl acetonate Hmbt = 2-mercapto benzothiazole	[Co(acac) (mbt)] + excess IQ Red crystals	135	421
$K[CoL_3(IQ)_3]$ L = succinimide or phthalimide	Co ion + K salt of imide + IQ		411
$[CoL_2(IQ)_2]$ LH = *o*-hydroxyacetophenone	$CoCl_2$ + LH + dilute NH_3 → precipitate + IQ	135	284
[Co(DA) $(IQ)_2$] DA = deprotonated diphenic acid	$Co(OH)_2$ + diphenic acid + IQ	223	405
	Nickel Complexes		
$[Ni(IQ)_2(H_2O)_2]$ phenoxyacetate	IQ + Ni phenoxyacetate; light blue	—	423
(a) $[Ni(IQ)_2Br_2]$	$NiX_2 + IQ(1:4)$; heat, and cool for 24 h (a) Light blue	—	424
(b) $[Ni(IQ)_2I_2]$	(b) Greenish yellow	—	424
$[Ni(IQ)_4(NO_2)_2{\cdot}xNi(IQ)_4(ONO)_2]$	IQ + Ninitrite		425
$[Ni(Ac_2CH)_2(IQ)_2]$	$IQ + Ni(Ac_2CH)_2$ + hot EtOH	—	426
$[Ni(bzac)_2(IQ)_2]$		—	427
$[Ni(IQ)_2(NO_2)_2]$		—	428
$[NiC_2O_4(IQ)_2]$	$NiC_2O_4 + IQ$ in $CHCl_3$	—	429
[Ni(Cldtpi) $(IQ)_2$] CldtpiH = di(*p*-chlorophenyl) dithiophosphinic acid	$IQ + Ni(Cldtpi)_2$	—	430
$[NiCl_2(IQ)_4]$	Hydrated $NiCl_2$ + IQ green solid	—	431
$[NiCl_2(IQ)_2]$	Reflux $[NiCl_2(IQ)_4]$ in Et_2O, $CHCl_3$ or benzene as solvent Yellow solid	—	431

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
$[NiL_2(IQ)_2]$ HL = EtO_2CCH_2OMe	NiL_2 + IQ Blue needles	178	290
$[Ni(IQ)_4I_6]$	KI_3 + IQ + $NiCl_2 \cdot 6H_2O$ Brown	110(d)	433
$Ni[O_2P(OR)_2]_2 \cdot 2IQ$ R = Me, Et	$Ni[O_2P(OR)_2]_2$ + IQ Green solids		434
[NiL·4IQ] LH_2 = biphenyl-2,2′-dicarboxylic acid	NiL + IQ	—	297
$[Ni(C_6H_5CO_2)_2(IQ)_2]$	$Ni(C_6H_5CO_2)_2$ + IQ	—	271
$[NiL_2(IQ)_2]$ LH = CCl_3CO_2H	NiL_2 + IQ Green crystalline solid	—	291
$[Ni(RCO_2)_2(IQ)_2]$	Ni(II) alkanoate + IQ Light blue solids	—	407
$[NiL_2(IQ)_2]$ HL = diethyl malonate	Ni(II) malonate + IQ	—	435
$[Ni(PhCH_2CO_2)_2(IQ)_2]$	$Ni(PhCH_2CO_2)_2$ + IQ Green crystalline solid		292
$K[Ni(IQ)_2L(H_2O)(OH)]$ H_2L = malonic, succinic, glutaric, or adipic acid	$NiCl_2$ + H_2L + KOH (3 moles) KCl filtered and filtrate + IQ Light blue crystalline solids	—	436
$[NiL_2(IQ)_2]$	$NiCl_2$ + acetoacetanilide + IQ Green crystals	> 250	283
$[Ni(Cl_2CHCO_2)_2(IQ)_4]$	$Ni(Cl_2CHCO_2)_2$ + IQ	—	403
$[Ni(Cl_2CHCO_2)_2(IQ)_2]$	Blue		
$[Ni(F_3CCO_2)_2(IQ)_2]$	IQ + $Ni(F_3CCO_2)_2$ Light blue	—	403
$[Me_4N]_2[Ni(SCN)_4(IQ)_2]$	IQ + $[Me_4N]_2[Ni(SCN)_4]$ Light violet crystals		437
$[Ni(C_9H_{10}O_2N_3)_2(IQ)_2]$ $C_9H_{10}O_2N_3$ = anion of 3-(*p*-acetophenyl)-1-methyltriazene-*N*-oxide	$[Ni(C_9H_{10}O_2N_3)_2]$ + IQ + $NiCl_2 \cdot 6H_2O$	224 (d)	438
[Ni(Acachydth-2H)(IQ)] Acac = acetylacetone hydth = hydrazine-*S*-methylcarbodithioate	Schiff base + IQ + $Ni(OAc)_2 \cdot 4H_2O$	—	439
[Ni(Bzachydth-2H)(IQ)] Bzac = benzoylacetone hydth = as above	As above		439
[Ni(Bzacethydth-2H)(IQ)] Bzacet = benzoyl	Benzoylacetaldehyde Na salt + hydth	—	439

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
acetaldehyde hydth = as above	+ $Ni(OAc)_2 4H_2O$ + IQ		
$[NiL_2(IQ)_2]$ HL = *o*-hydroxyaceto-phenone	$NiCl_2$ + HL + dil · NH_3 → Precipitate + IQ green crystals	205	284
$K[Ni(L)_3(IQ)(H_2O)_2]$ L = succinimide, phthalimide	Metal ion + K salt of imide + IQ	—	411
	Ruthenium Complex		
$[HRu_3(CO)_{10}(IQ)]$ 1,2 and 2,3-isomer	$[Ru_3(CO)_{10}(NCMe)_2]$ + IQ	—	440
	Rhodium Complexes		
trans-$[Rh(IQ)_4\text{-}Cl_2]Y$		—	441
$[Rh(CO)(IQ)L_2]ClO_4$	$[Rh(CO)_2L_3]ClO_4$ + IQ	—	442
L = (*p*-tolyl)$_3$P	Yellow/orange yellow	205–207	
L = Ph_3As	Yellow/orange yellow	213–215	
L = Ph_3P	Yellow/orange yellow	194–195	
$[(CO)Rh(IQ)(PPh_3)_2]^+$	PPh_3 + $[CO(PPh_3)Rh(IQ)_2]\cdot ClO_4$ or PPh_3 + $[(CO)_2Rh(PPh_3)(IQ)]ClO_4$	—	443
$[(COD)Rh(IQ)_2]ClO_4$ COD = 1,5-cyclo-octadiene	IQ + $[(COD)_2Rh]ClO_4$ or IQ + $[(COD)RhCl]_2$ + $NaClO_4$ Yellow solid	165 (d)	443
$[(CO)_2Rh(IQ)_2]ClO_4$	CO + $[(COD)Rh(IQ)_2]ClO_4$	137	443
$[CO(PPh_3]Rh(IQ)_2]ClO_4$	PPh_3 + $[(CO)_2Rh(IQ)_2]ClO_4$ Yellow crystals	135	
$[(COD)Rh(IQ)(PPh_3)]ClO_4$	PPh_3 + $[(COD)Rh(IQ)_2]ClO_4$	—	443
$[(CO)_2(PPh_3)(IQ)]ClO_4$	CO + $[(COD)Rh(IQ)(PPh_3)]ClO_4$	115	443
$[(NBD)Rh(IQ)_2]^+ BPh_4^-$ NBD = norbornadiene	$[(NBD)RhCl_2]$ + IQ + $NaBPh_4$	—	444
$[Rh(NBD)(IQ_2]ClO_4$ NBD = norbornadiene	IQ + $[Rh(NBD)_2]ClO_4$	150–160 (d)	445,446
$[Rh(NBD)(IQ)(PPh_3)]ClO_4$	PPh_3 + $[Rh(NBD)(IQ)_2]ClO_4$	150(d)	446, 445
	Palladium Complexes		
IQ $PdCl_2$ complex			447
$[Pd(OCOCH_3)_2(IQ)_2]$	Metal–carboxylate + IQ		448

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
[IQ(1,2-dimethylallyl)$PdCl_2$]	(1,2-dimethylallyl)$PdCl_2$ + IQ Pale yellow solid	96–99	453
[Pd(IQ)$_2Cl_2$]	Pd(black) + IQ · HCl + c · HNO_3		450,451
trans-[Pd(IQ)$_2Cl_2$]	IQ + $PdCl_2$ + HCl Yellow compound		452
	Osmium Complexes		
[HOs_3(IQ)$(CO)_{10}$]	$Os(CO)_{12}$ + IQ chromatography		454
2,3-isomer	Yellow crystals	188(d)	
1,2-isomer	Yellow crystals	164–166	
[IQ · OsO_4]	OsO_4 + IQ	90–92(d)	455
IQ[$OsO_2(O_2C_2Me_4)$]	[IQ · OsO_4)] + tetramethylethylene Dark-brown solid		455
[Os(IQ)$_2O_2(O_2C_2Me_4)$]	—		455
[$Os_2O_4(O_4RCCR)$ (IQ)$_4$]	OsO_4 · IQ + RC≡CR′	—	458
R = H; R′ = H	or		
R = Ph; R′ = Ph	OsO_4 + RC≡CR′		
R = Me; R′ = Ph	+ excess IQ		
[$Os_2O_4(O_4C_8H_{12})$(IQ)$_4$]	OsO_4 + IQ + cycloocta-1,5-diene Brown crystals	—	458
[$OsO_2(O_2C_8H_{12})$(IQ)$_2$]	As above	—	458
[*n*-Pr_4N] [$OsNCl_4$(IQ)]	[*n*-Pr_4N] [$OsNCl_4$] + IQ	—	459
	Iridium Complexes		
[Ir(COD)(L)(IQ)ClO_4]	IQ + [Ir(COD)L_2]ClO_4		460
COD = 1,5-cyclooctadiene			
L = tetrahydrothiophene		120–124	
L = trimethylenesulphide		122–126	
L = SMe_2		106–112	
L = SEt_2		90–95	
[(COD)(IQ)Ir{μ-(L − L)} Ir(IQ)(COD)] $(ClO_4)_2$	IQ + [(COD) Ir{μ-(L − L)}$_2$ Ir(COD)] $(ClO_4)_2$		460
COD = 1,5-cyclooctadiene			
L − L = (*t*-BuS)$_2(CH_2)_2$		115–110	
L − L = 1,4-dithiacyclohexane		128–132	
L − L = $(MeS)_2$			
	Platinum Complexes		
trans-[Pt(IQ)$_2Cl_2$]	Irradiation of cis isomer with 366 nm Hg rays		461

H. Organometallic Derivatives of Isoquinolines (*Continued*)

Compound	Method/Properties	m.p. (°C)	Ref.
trans-$[PtCl_2(C_2H_4)IQ]$	$IQ + K[PtCl_3(C_2H_4)]$		462
$[PtH(IQ)(PBz_3)_2]BPh_4$ PBz = tribenzyl-phosphine	$IQ + PtH(NO_3)(PBz_3)_2 + NaBPh_4$ White crystalline solid	157–159	464
$[PtCl(allyl)(IQ)]$	$IQ + [PtCl(C_3H_5)_4]$ Pale yellow prisms	135–139	465
$[PtCl(C_4H_7)(IQ)]$	IQ + di-μ-chloro-di(2-methylallyl)platinum(II)	132–135	465
cis$[PtCl_2(IQ)(\eta\text{-}C_2H_4)]$	*trans*-$[PtCl_2(C_2H_4)(IQ)] \xrightarrow[366\text{ nm}]{h\nu}$ Orange-yellow solid		463
	Nonmetallic Derivatives		
Boron complexes			
Isoquinolineborazone	$NaBH_4 + IQ$ (salt)	Decomposes at 50	466
$MeBO_2$-IQ adduct	IQ + ester of metaboric acid		467
$[(IQ)BH_2Br]$	$(CH_3)_2S \cdot BH_2Br + IQ$ White solid	122–125	468
$[(IQ)_2BH_2]^+ PF_6^-$	$IQ + (CH_3)_2S \cdot BH_2Br \rightarrow$ Ppt. $+ NH_4PF_6$ White solid	178–179	468
$IQ\text{-}BH_3$	$IQ + BH_3 \cdot THF$	62–63	469
$4BR_2IQ$	$4\text{-BrIQ} + BuLi + MeOBR_2$		
$BR_2 = BEt_2$		> 300	470
BR_2 = 9-bora-bicyclo[3.3.1]nonane		> 300	
Silicon complexes			
$[SiX_4 \cdot (IQ)_4]$ X = Cl, Br, I	$IQ + SiX_4$		471
$[(IQ)_2H_2SiF_6]$	$SiF_4 \cdot (IQ)_2 + H_2O$		472
$[Si(NCS)_4 \cdot 2(IQ)]$	$IQ + Si(NCS)_4$	Decomposes at 100	473
Selenium complexes			
$[(IQ) \cdot SeO_2]$	$SeO_2 + IQ$ at 100°C	67–68	474

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CHAPTER II

Isoquinoline Carboxylic Acids and Their Hydrogenated Derivatives

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This chapter discusses the preparation, properties, and reactions of ring and side-chain isoquinoline and hydrogenated isoquinoline carboxylic acids, cyanides, and acid derivatives such as acid halides, amides, esters, and lactones. Acids such as sulfonic are also included. The literature is reviewed through mid-1987.

The tables in each section contain listings of the various derivatives and the individual reference should be consulted for specific details on all of the chemistry studied. Only a few typical references for such common conversions as esterification and hydrolysis are included in the text.

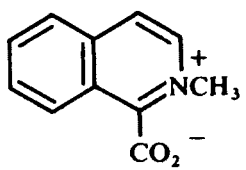
I. ISOQUINOLINES

This section includes all acid derivatives of the fully aromatic isoquinolines.

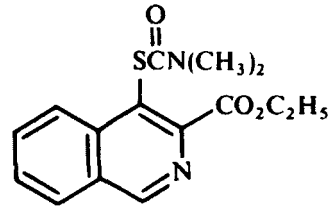
A. Isoquinolinecarboxylic Acids

Tables I. 1 (page 137), I. 2 (page 137), I. 3 (page 138) contain data on isoquinoloinecarboxylic acids with the carboxylic acid group attached directly to the ring, while Table I. 4 (page 138) contains those compounds in which the carboxylic acid group is in a side chain.

The hydrolysis of nitriles has been used to prepare various isoquinoline-1-[1,2], 4-[3-6], 5-[6,11], 6-[6,10] and 8-[6] carboxylic acids. A large number of isoquinoline-3-carboxylic acids have been prepared by ester hydrolysis,[12-18] while isoquinoline-1-carboxylic acids have been prepared both by ester and amide hydrolysis.[2,19] The thermally labile carboxylate **1** and the corresponding



1



2

TABLE I.1. Isoquinoline-1-Carboxylic Acids

Substituent	m.p. (°C)	Ref.
	161–162	2, 19, 21–23, 48–50
	HBr: 202–203	23, 49
($N^+-\bar{O}$xide)	129	2
(N^+-CH_3)	N/A	34
	146–149	20
5-NO_2[a]	166	1
5-OH[a]	219–220	1
	HCl: 192	1
5-NH_2	Picrate: 260	1
6,7-$(OCH_3)_2$	204–205	24
3-CH_3-6,7-$(OCH_3)_2$	203–204	51
	Picrate: 240	25

[a]IR in paper.

TABLE I.2. Isoquinoline-3-Carboxylic Acids

Substituent	m.p. (°C)	Ref.
	167–168	28, 30, 52, 53
(N^+-CH_3)	206–211	20, 34
(N^+-oxide)	211–211.5	52
X-Br	210	30
8-NO_2	230–240	29
3-OH	218–220	33a
4-OH[2]	194–197	35
4-SH	245–246	13
7-CH_3-6,8-$(OH)_2$	270	12
1-Cl-7,8-$(OCH_3)_2$	294	54
1-CH_3-6,7-$(OCH_3)_2$	217	14
1-OCH_3-7,8-$(OCH_3)_2$	185	16
1-OC_2H_5-7,8-$(OCH_3)_2$	153	16
1-OC_3H_7-7,80$(OCH_3)_2$	136	16
1-C_6H_5	221	36, 54c
1-OC_4H_9-7,8-$(OCH_3)_2$	127	16
1-C_6H_5-7-CH_3	227	36
1-Cl-4-CH_3	170–171	54a
1-OCH_3-4-CH_3	141–142	54b
1-C_6H_5-CO	158	54c
1-C_6H_5-5-OCH_3	213	36
1-C_6H_5-6,7-$(OCH_3)_2$	216 216.5	15
1-($C_6H_3[OCH_3]_2$-3,4)-6,7-$(OCH_3)_2$	212–213	18
1-($CH_2C_6H_3[OCH_3]_2$-3,4-6,7-$(OCH_3)_2$	175–176	18
	173	17
5,7-$(CH_3)_2$	230–232	54d
1-Cl-3-C_6H_5-	153	54a

[a]UV in paper.

TABLE I.3. Isoquinoline 4-, 5-, 6-, 7- and 8-Carboxylic Acid

Substituent	m.p. (°C)	Ref.
4-CO_2H	263–265	3, 5
	264–266	6
4-CO_2H-1-OH	295–296	55
4-CO_2H-1-NH_2	249–250	3
4-CO_2H-1-C_2H_5	222–223	4
5-CO_2H-3-Br[a]	251	31–33
5-CO_2H	280–282	6, 7, 10
	HCl: > 300	6
	272	56
	Picrate: 212–213	56
5-CO_2H-3-CHO	249–250	8
5-CO_2H-1-CHO	Thiosemicarbazone: 245–246	9
5-CO_2H-1-CH_3	297–300	9
5-CO_2H-3-$COCH_2CH_2CH_2OC_2H_5$	2,4-DNPH: 249	8
6-CO_2H	355–360	6
	352–356	10
7-CO_2H	287–290	10
	295–297	6
8-CO_2H	292–294	6

[a]UV in paper.

TABLE I.4. Isoquinolines with a Carboxylic Acid in a Side Chain

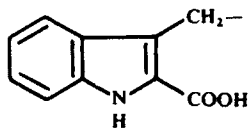
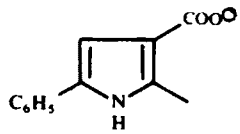
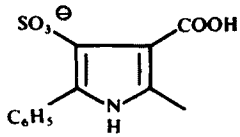
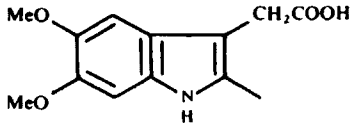
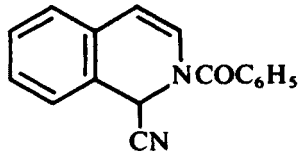
Substituent		m.p. (°C)	Ref.
1-CH_2CO_2H-3-Cl		90	57
1-$(CH_2)_3CO_2H$[a]		130–131	37
		126	58
1-$(CH_2)_3CO_2H$-4-CN		155–156	38
1-$(CH_2)_5CO_2H$[a,b]		107–108	39
1-($C_6H_4CO_2H$-2)-7-Cl		242–243	59,60
1-(C_6H_3Cl-3 or -5-CO_2H-2)		230	59,60
1-($C_6H_4CO_2H$-2)		285–287	59,60
		Picrate: 186	59,60
		158–160	61,62
		HCl: 195–196	61,62
1-($CH_2C_6H_2(OCH_3)_2$-4, 5-CO_2^--2)	(N^+H)	258	63
	(N^+H)	264–265	64

TABLE I.4. Isoquinolines with a Carboxylic Acid in a Side Chain (*Continued*)

Substituent		m.p. (°C)	Ref.
		(N⁺H) > 360	64
		262	65
2-$CH_2CH_2CO_2^-$		200–210	40
2-$CH_2CH(CO_2H)SO_3^-$[c]		302	66,75
2-$CH_2CH_2CO_2CO_2H$	Br^-[c]	211–212	40
	Cl^-	211–212	41
2-$COCH=CHCO_2^-$		102	43
2-$CH(CO_2)CH_2CO_2H$		118	43
2-$CH(CO_2H)CH_2CO_2^-$		149–150	42
4-CH_2CO_2H		HCl:241–243	67
	($N+CH_3ClO_4^-$)	191–192	46
4-CH_2CO_2H-6, 7-CH_2O_2		HCl:274	46,68
4-CH_2CO_2H-7, 8-CH_2O_2		HCl:209	46
4-CH_2CO_2H-3-$CH_3(N^+CH_3PF_6^-)$		208.5	47
4-CH_2CO_2H-7-CH_3O[a]		HCl:209–211	44
4-CH_2CO_2H-6, 7-$(OCH_3)_2$		HCl:228–230	68
4-CH_2CO_2H-7, 8-$(OCH_3)_2$[a,c]		HCl:194–195	45
4-C(=$CHC_6H_4NO_2$O2)CO_2H		246–247	67
4-C(=$CHC_6H_4NH_2$-2)CO_2H		279–281	67
4-C(=$CHC_6H_2NO_2$-2-CH_2O_2-4,5)-CO_2H-6,7-CH_2O_2[a,c]		HCl: > 340	68
4-C(=$CHC_6H_2NO_2$-2-CH_2O_2-4,5)CO_2H-6,7-$OCH_3)_2$		HCl: > 340	68
4-CH_2CO_2H-7-OCH_3-8-OC_2H_5		HCl:176.5–177	45a
4-$CH(CH_2C_6H_3CH_2O_2$-2,3)CO_2H-7,8-$(OCH_3)_2$[a,c]		HCl:183–185	45
4-C(=$CHC_6H_2NO_2$-2-$(OCH_3)_2$-4,5)CO_2H-6,7-$(OCH_3)_2$		N/A	68
6-$CH_2CH_2CO_2H$-3-OC_2H_5-7-CH_3[a]		188–190	69
7-$CH=CHCO_2H$		237–238	70
7-$CH(CH_3)CO_2H$-3-OCH_3		155.5–156.5	71
7-$CH=CHCO_2H$-1-C_6H_5		283–285	70

[a] IR in paper.
[b] UV in paper.
[c] NMR in paper.

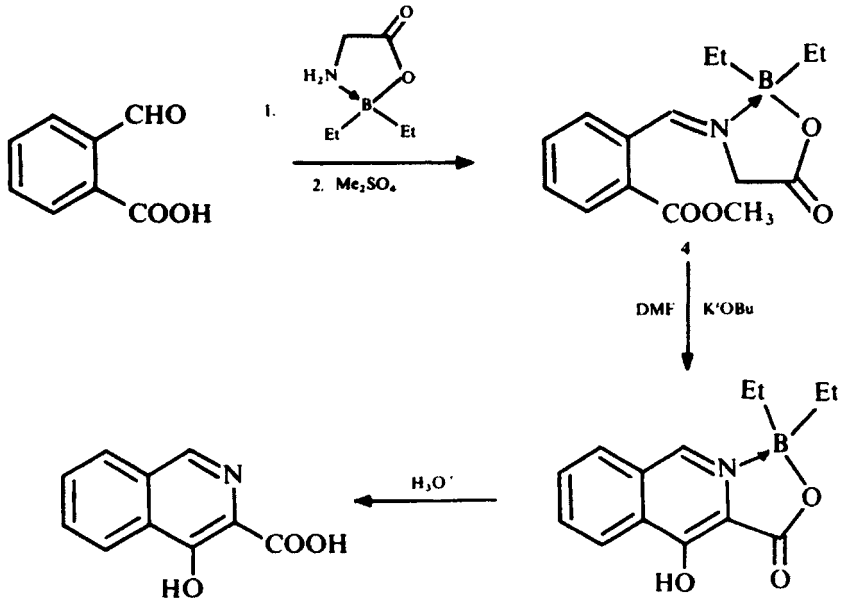
3-carboxylates have been obtained by ester hydrolysis of the corresponding methyl esters.[20] These readily undergo thermal decarboxylation.[34,35] In some cases, other functional groups also undergo hydrolysis. Thus acidic hydrolysis of **2** gives 4-mercaptoisoquinoline-3-carboxylic acid[13] and hydrolysis of methyl 6,8-dimethoxy-7-methylisoquinoline-3-carboxylate with hydriodic acid gives 6,8-dihydroxy-7-methylisoquinoline-carboxylic acid.[12] The hydrolysis of the Reissert compound **3** either with 50% sulfuric acid[21] or HBr in acetic acid[22,23] served as a route to isoquinoline-1-carboxylic acid.



3

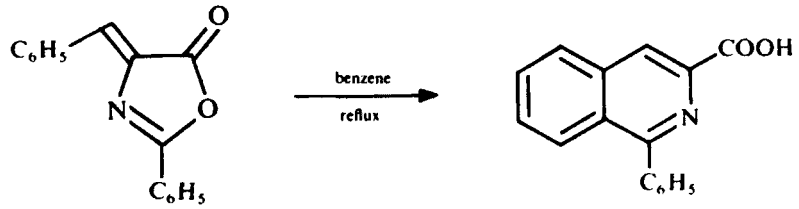
Oxidation of styryl groups with potassium permanganate[24] gives the corresponding isoquinoline-1-carboxylic acid. Use of manganese dioxide with 1- or 3-methyl isoquinolines give the manganese salts of the corresponding acids.[26] A vanadyl salt of isoquinoline-1-carboxylic acid has also been reported.[27] Oxidation of 3-methyl groups with selenium dioxide[28] or 3-formyl groups[29,30] gives isoquinoline-3-carboxylic acids. Isoquinoline-5-carboxylic acids have also been prepared by similar oxidation sequences.[31-33]

Treatment of **4** with potassium *t*-butoxide produced the boron complex of an isoquinoline-3-carboxylic acid **5** which on deboration gave 4-hydroxy-isoquinoline-3-carboxylic acid (**6**)[33a] (Eq. 1).



6 **5** (1)

Refluxing **7** in benzene results in an intramolecular alkyation to provide 1-phenylisoquinoline-3-carboxylic acid (**8**)[36] (Eq. 2).

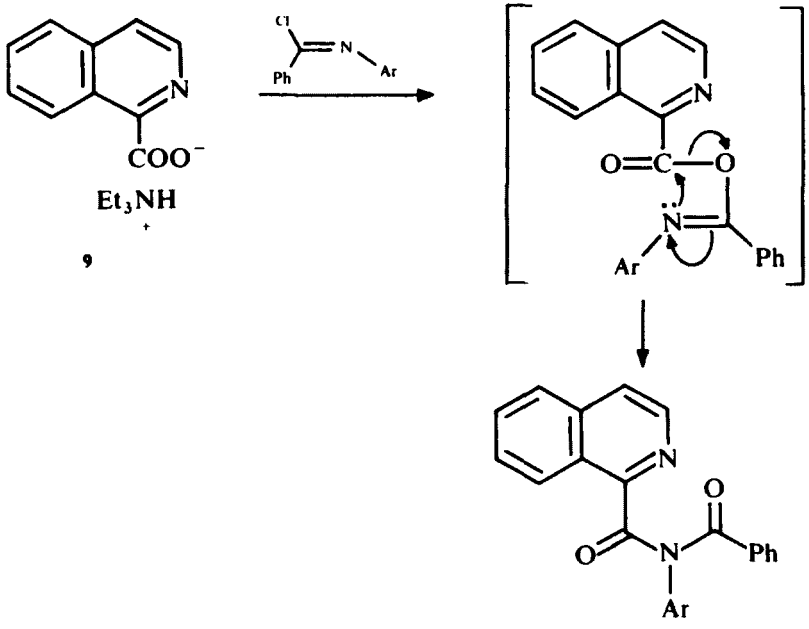


(2)

7 **8**

Isoquinoline-1-carboxylic acid has been converted to its *N*-oxide by treatment with peracetic acid.[2] This same *N*-oxide is also obtained by reacting isoquinoline-1-carboxamide *N*-oxide with nitrous acid.[2] Nitration of isoquinoline-1-carboxylic acid gives the 5-nitro derivative, which can be reduced to the 5-amino-derivative by catalytic hydrogenation.[1] Amination of isoquinoline-4-carboxylic acid with potassium amide gives the 1-amino derivative.[3]

The reaction of the triethylammonium salt of isoquinoline-1-carboxylic acid **9** with either *N*-phenyl- or *N*-(1-naphthyl) benzimidoyl chloride proceeds through an intramolecular O → N acyl migration to provide the unsymmetrical imides **10** or **11** in excellent yields[36a] (Eq. 3).



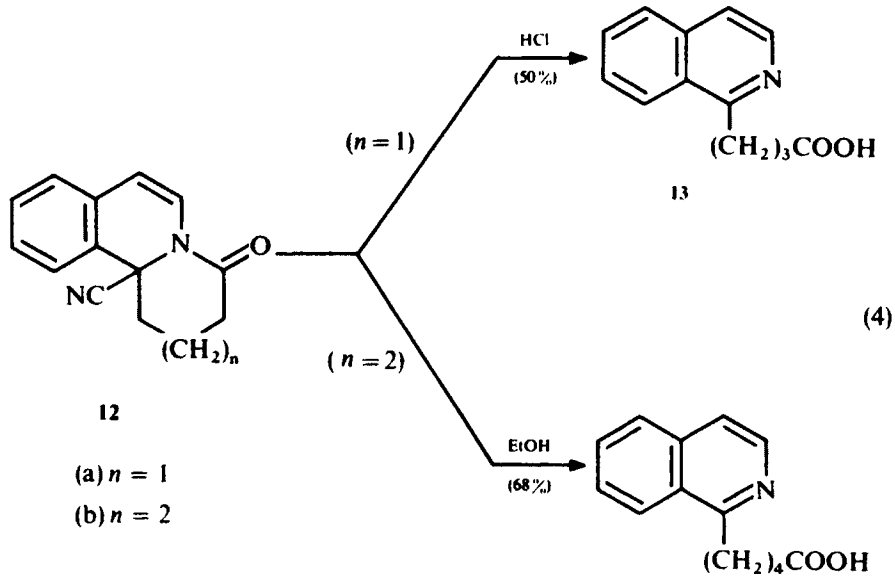
(3)

9

10 Ar = C_6H_5 (95%)

11 Ar = 1-naphthyl (80%)

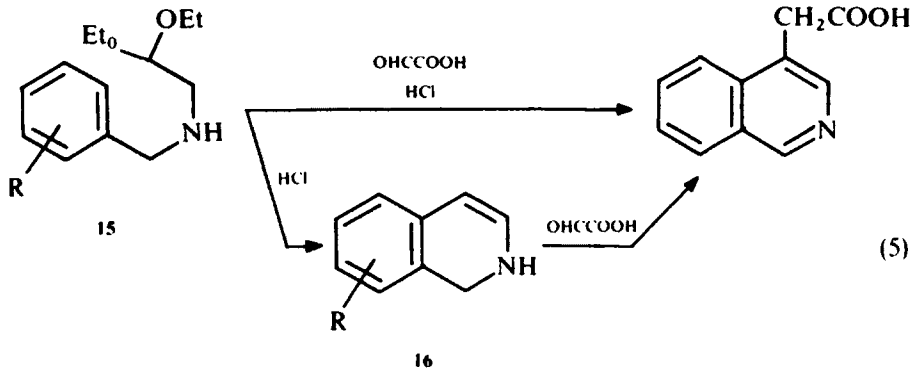
Hydrolysis of the Reissert compounds **12a** and **12b**[37] leads to acids **13** or **14**[37-39] (Eq. 4).



(4)

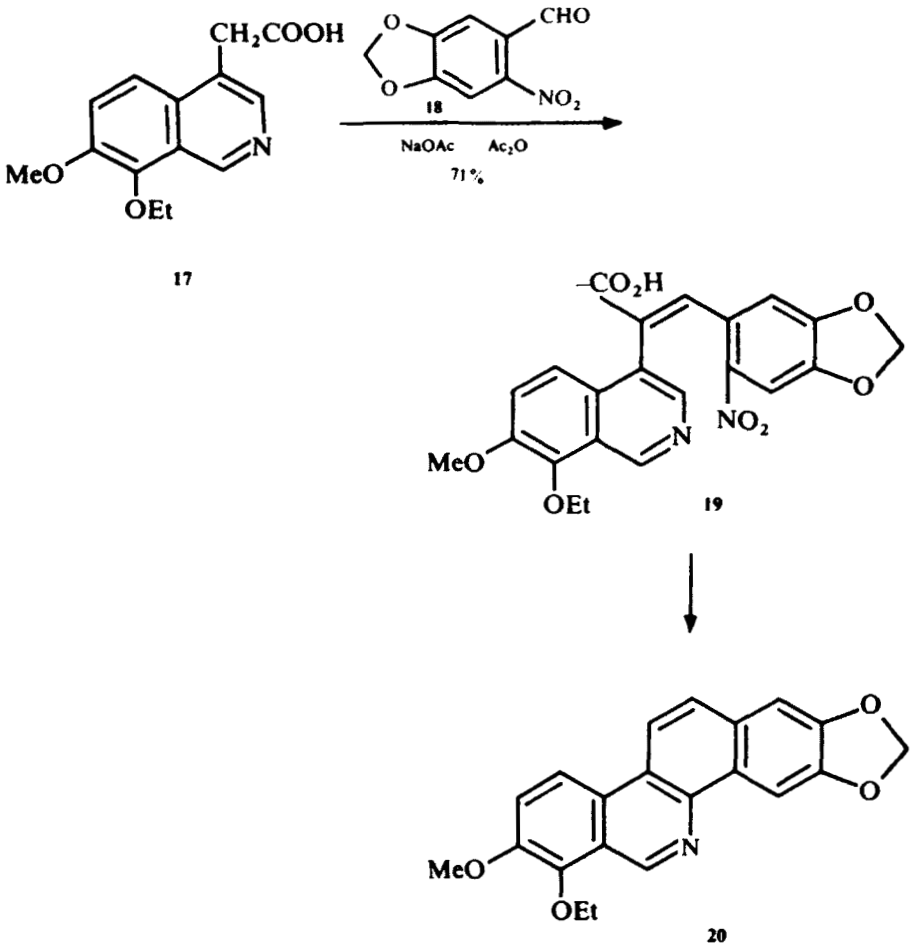
Reaction of isoquinoline with acrylic acid,[40] β-propiolactone,[41] and maleic acid[42] or anhydride[43] leads to isoquinolines with acid groups in a side chain on the 2 position.

Substituted-4-isoquinolinephenylacetic acid derivatives have been prepared through two different routes. One involves the acid-catalyzed cyclization using **15** with glyoxylic acid,[45-45a] while the other uses the reaction of 1,2-dihydroisoquinolines with either glyoxylic acid or ethyl iodoacetate[46-47a, 47b] (Eq. 5).



(5)

The condensation of 8-ethoxy-7-methoxy-4-isoquinoline acetic acid (**17**) with 6-nitropiperonal (**18**) yielded **19**, which upon reduction, diazotization, and decarboxylation provided the benzo[c]phenanthridine **20**[45a] (Eq. 6).



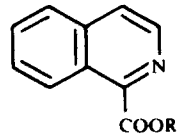
(6)

B. Isoquinolinecarboxylates

Tables I. 5 (p. 144), I. 6 (p. 144), I. 7 (p. 147), and I. 8 (p. 148) isoquinolinecarboxylates with the ester group attached directly to the ring, while Table I. 9 (page 149) contains those compounds in which the carboxylate group is in a side chain.

Esterification has been used as a route to a great variety of esters, both with the ester group on the ring and on the side chain.[1, 3, 6, 7, 11, 20–21, 23, 31–33, 44–45, 51, 54–55, 57, 72–73] Conversion of the acid chloride of 1-chloroisoquinoline-3-carboxylic acid to its ester also leads to the introduction of a 1-alkoxy group.[16] Ester interchange has also been used.[62] Acid-catalyzed hydrolysis of nitriles in alcoholic solvents has also been used as a route to esters.[67, 74] A variety of esters

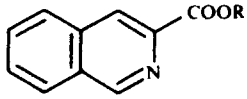
TABLE I.5. Isoquinoline-1-Carboxylates



R	Substituents	m.p. (°C)	Ref.
CH_3	—	b.p. 110/4	23
		Picrate: 147	23
		($N^+CH_3I^-$): 150–151	23
		($N^+CH_3BF_4^-$): 174–176	34
C_2H_5	—	b.p. 197–199/20	21
		b.p. 193–195/23	72
		49	72
		Picrate: 154–155	72
		($N^+CH_2COC_6H_5Br^-$) 160–162	110
C_2H_5[a]	5-OH	153–154	1
C_2H_5	5-NH_2	b.p. 190/0.5	1
CH_3	3-CH_3-6,7-$(OCH_3)_2$	151–153	51
		Picrate: 212	25
		Picrate: 216	51
C_2H_5[b]	6,7-$(OCH_3)_2$	styphnate: 180–181	86
C_2H_5	3-CH_3-6,7-$(OCH_3)_2$	86–87	51
		Picrate: 176–177	51
$CH(C_6H_5)COC_6H_5$	—	152.8–153	19

[a] IR in paper.
[b] UV in paper.

TABLE I.6. Isoquinoline-3-Carboxylates



R	Substituents	m.p. (°C)	Ref.
CH_3		(N^+-$CH_3BF_4^-$) 126–128	20
C_2H_5[a–c]	4-OH-7-Cl(N^+-$CH_2C_6H_5Cl$)	154–155	82, 83
CH_3	5-Cl-6,8-$(OH)_2$-7-CH_3	240	12
		O-acetyl: 184	12
C_2H_5		b.p 165–170/2	88
		b.p. 144–145/0.5	76, 77
		HBr: 203	54c
		Picrate: 153	77
		Picrate: 154-155	76
		Picrate: 157	88
		(N^+-CH_3I^-)[a–c] 162–163	80

TABLE I.6. Isoquinoline-3-Carboxylates (*Continued*)

R	Substituents	m.p. (°C)	Ref.
C_2H_5[a]	4-OH	78–80	35
		Picrate: 172	111
		($N^+CH_3ClO_4^-$) 157–158	111
CH_3	6,8-$(OH)_2$-7-CH_3	270	12
		O-benzoate: 238	12
CH_3[a–c]	6-NH_2-7-OCH_3	156–158	112
CH_3	1-Cl-7,8-$(OCH_3)_2$	166	54
C_2H_5	6-CH_3	104–105	88
		Picrate: 181–182	88
CH_3[a]	6,7-$(OCH_3)_2$	198–199	113
		209–210	91
C_2H_5	4-OH-7-OCH_3(N^+-$CH_2C_6H_5Cl$)	252–254	82
C_2H_5	1-C_6H_5-4-$OCOCH_3$	169–170	54c
CH_3[a–c]	1-CH_3-6-NH_2-7-OCH_3	N/A	112
CH_3	1-N_2H_3-7,8$(OCH_3)_2$	196–197	16
C_2H_5	1-Cl-7,8$(OCH_3)_2$	106	54
C_2H_5[a–c]	4-CH_2COCH_3(N–CH_3ClO_4)		
	(N^+–$CH_3ClO_4^-$)	155–157	80
CH_3	7-CH_3-6,8$(OCH_3)_2$	168	12
		Picrate: 238	12
	(N^+–CH_3I^-)	198	12
CH_3[a–c]	1-CH_3-6,7$(OCH_3)_2$	184–185	112
		224	14
CH_3	1,7,8-$(OCH_3)_2$	131	16, 54
C_2H_5	4-OH-6,7$(OCH_3)_2$ (N^+–CH_3Cl^-)	230–231	82
		221–223[a–c]	83
	(N^+–$CH_2C_6H_5Cl$)	192–194	82
		187–188[b, c]	83
C_2H_5	4-OH-7,8$(OCH_3)_2$ ($N^+CH_2C_6H_5Cl$)	141–143	83
C_3H_7	1-Cl-7,8$(OCH_3)_2$	102	54
C_2H_5	4-OC(=S)$N(CH_3)_2$	118–119	13
C_2H_5	4-SCO$N(CH_3)_2$	79–81	13
C_2H_5	1-CH_3-6,7-$(OCH_3)_2$	146	14
		185[b]	114
		164–165	85
CH_3	1-C_2H_5-6,7-$(OCH_3)_2$	258	14
CH_3	1-OC_2H_5-7,8-$(OCH_3)_2$	114	16
C_2H_5	1-N_2H_3-7,8-$(OCH_3)_2$	196–197	16
C_3H_7	1-N_2H_3-7,8$(OCH_3)_2$	169–172	16
C_2H_5[a–c]	4-$CH_2CO_2C_2H_5$ ($N^+CH_3ClO_4$)	141–143	80
C_4H_9	1-Cl-7,8$(OCH_3)_2$	77	54
C_2H_5	1-C_2H_5-6,7$(OCH_3)_2$	152	14
C_2H_5	1-OC_2H_5-7,8$(OCH_3)_2$	86	16
CH_3	1-OC_3H_7-7,8$(OCH_3)_2$	86	16
C_4H_9	1-N_2H_3-7,8$(OCH_3)_2$	169–170	16
CH_3	1-OC_4H_9-7,8$(OCH_3)_2$	85	16
C_2H_5	1-C_6H_5-4-OH	143–144	97
C_2H_5	4-$CH_2C_6H_5$ ($N^+CH_3ClO_4^-$)	177–179	80
C_3H_7	1-OC_3H_7-7,8$(OCH_3)_2$	69–70	16

TABLE I.6. Isoquinoline-3-Carboxylates (*Continued*)

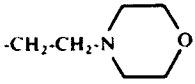
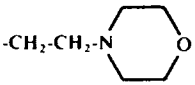
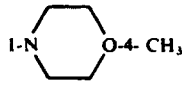
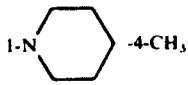
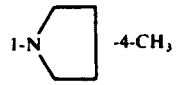
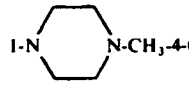
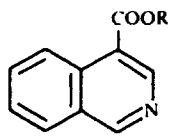
R	Substituents	m.p. (°C)	Ref.
CH_3	1-C_6H_5-6,7-$(OCH_3)_2$	172–173	15, 87
C_2H_5	1-$(SO_2C_6H_4CH_3$-4)-4-OH	87–90	115
C_2H_5[a–c]	4-$(CH_2C_6H_3O_2CH_2$-3, 4) (N^+–$CH_3ClO_4^-$)	248–250	80
C_2H_5	1-C_6H_5-6,7-$(OCH_3)_2$	170	84
		168–170	87
C_4H_9	1-OC_4H_9-7,8$(OCH_3)_2$	51–52	16
C_2H_5[a–c]	4-$(CH_2C_6H_3(OCH_3)_2$-3,4) ($N^+CH_3ClO_4^-$)	159–161	80
CH_3	1-$(CH_2C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	178	18
C_2H_5	1-$(C_6H_3(OCH_3)_2$-3, 4)-6,7$(OCH_3)_2$	210–213	18
CH_3	1-$(CH{=}CHC_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	175	14
C_2H_5	1-$(CH_2C_6H_3(OCH_3)_2$-3, 4)-6,7-$(OCH_3)_2$	141	17, 116
CH_3	1-$(CH_2C_6H_3OCH_3$-3-OC_2H_5-4)-6-OCH_3-7-OC_2H_5	187–189	81
$CH_2CH_2N(C_2H_5)_2$	1-C_6H_5-6, 7$(OCH_3)_2$	158.5–159	15
$CH_2C_6H_5$	1-C_6H_5-6, 7$(OCH_3)2$	126	87
		Picrate: 183–184	87
CH_3	1-$(CH_2C_6H_3(OC_2H_5)_2$-3,4)-6,7-$OC_2H_5)_2$	166	81
$CH_2CH_2N(C_2H_5)_2$	1-$(C_6H_3(OCH_3)_2$-3,4)-6,7$(OCH_3)_2$		
		HCl: 191–192	18
$CH_2CH_2N(C_2H_5)_2$	1-$(CH_2C_6H_3(OCH_3)_2$-3,4)-6,7$(OCH_3)_2$	HCl: 113–114	18
C_2H_5	5,7-$(CH_3)_2$	83–84	54d
C_2H_5	1-CH_3	104	96b
C_2H_5	1-$C_6H_5CH_2$	94	96b
CH_3	1-Cyclohexyl	135–136.5	96c
CH_3	1-Cyclopentyl	71.5–73	96c
C_2H_5	1-OC_2H_5-6,8-$(OBzl)_2$	128.5–130	96d
CH_3	1-Cl-4-CH_3	106–107	54a
	1-Cl-4-CH_3	HCl: 233–234	54a
$-CH_2-CH_2-NMe_2$	1-Cl-4-CH_3	HCl: 203–204	54a
$-CH_2-CH_2-NEt_2$	1-Cl-4-CH_3	HCl: 203	54a
$-(CH_2)_3NMe_2$	1-Cl-4-CH_3	HCl: 179–180	54a
$-(CH_2)_3N(C_4H_9)_2$	1-Cl-4-CH_3	HCl: 121–122	54a
$-CH(CH_3)CH_2N(C_4H_9)_2$	1-Cl-4-CH_3	HCl: 178–180	54a
CH_3	1-Cl-4-C_6H_5	HCl: 153	54a
	1-Cl-4-C_6H_5	HCl: 196–196.5	54a
$-CH_2-CH_2-NMe_2$	1-Cl-4-C_6H_5	HCl: 204–205	54a
$-CH_2-CH_2NEt_2$	1-Cl-4-C_6H_5	HCl: 185–186	54a
CH_3	1-$OCH_3$4-CH_3	215–216	54b

TABLE I.6. Isoquinoline-3-Carboxylates (*Continued*)

R	Substituents	m.p. (°C)	Ref.
CH_3		120.5–122	54b
CH_3		102–103	54b
CH_3		Picrate: 162–163	54b
CH_3		Picrate: 224.5–225	54b

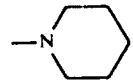
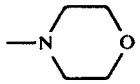
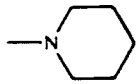
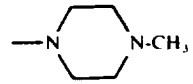
[a] UV in paper.
[b] IR in paper.
[c] NMR in paper.

TABLE I.7. Isoquinoline-4-Carboxylate



R	Substituents		m.p. (°C)	Ref.
CH_3	1-Cl		60–62	117
CH_3			82	89
			81	6
C_2H_5			b.p: 132–137/1	21
			47–49	21
			47–48	3
			HCl: 160	3
C_2H_5	1-OH		226–227	55
CH_3	5-CO_2CH_3		136–138[a]	89
CH_3[a]	1-Cl-6,7-$(OCH_3)_2$		156–157	74
CH_3[a]	6.7-$(OCH_3)_2$		138	74
CH_3	$-NHCH_2CH_2OH$	BR^-	diHCl: 170	117
C_2H_5[a, b]	1-3-$(CH_3)_2$-5.8-$(OH)_2$		267	95, 96

TABLE I.7. Isoquinoline-4-Carboxylate (*Continued*)

R	Substituents		m.p. (°C)	Ref.
CH_3			79–80	117
CH_3			diHCl: 75–78	117
CH_3[a–c]	1,3-$(CH_3)_2$-5,8$(OCH_3)_2$		79–81	95, 96
CH_3	$-NHCH_2CH_2N(CH_3)_2$		diHCl: 240	117
CH_3			79–80	117
CH_3			diHCl: 194–196	117
t-C_4H_9[a–c]	1,3-$(CH_3)_2$-5,8$(OH)_2$		212	95, 96
CH_3	1-$(C_6H_4OCH_3$-4)	(N^+–Oxide)	180–180.5	118
C_2H_5[a–c]	1,3-$(CH_3)_2$-5,8$(OCOCH_3)_2$		118–119	95, 96
t-C_4H_9[a,b]	1,3-$(CH_3)_2$-5,8$(OCOCH_3)_2$		137–138	95, 96
C_2H_5	1-CH_3		75–6	118a
C_2H_5	1-C_2H_5		46–7	118a
C_2H_5	1-C_3H_7		b.p. 158–9/4	118a
C_2H_5	1-C_4H_9		b.p. 148–50/4	118a
C_2H_5	1-C_6H_5		181–182	118a

[a] IR in paper.
[b] UV in paper.
[c] NMR in paper.

TABLE I.8. Isoquinoline 5-,6-,7-, and 8-Carboxylates

Substituent	m.p. (°C)	Ref.
5-CO_2CH_3-3-Br	123 127	31, 33
5-CO_2CH_3	66[a,c] 64–66[a] 66 (various salts)	78 7 6 7, 11, 102, 119
6-CO_2CH_3	95	6
6-CO_2CH_3-7-OH[a–c]	120–121	92
6,7-$(CO_2C_2H_5)_2$-5,6-$(OH)_2$[a,b]	154–155	94
6-CO_2CH_3-7-$O_2CC_6H_5$[a,c]	196–197	92
6-CO_2CH_3-7-OH-1-$(CH_2C_6H_2(OCH_3)_3$-3,4,5)[a–c]	152–153	92

TABLE I.8. Isoquinoline 5-,6-,7-, and 8-Carboxylates (*Continued*)

Substituent	m.p. (°C)	Ref.
6-CO_2CH_3-5-OH-1-($CH_2C_6H_2(OCH_3)_3$-3,4,5)[a-c]	182–183	92
7-CO_2CH_3	100	6
	96–98	11
(N^+-C_2H_5 I^-)	217–218.6	11
7-CO_2CH_3-6-OH[a-c]	137–138	92
7-CO_2CH_3-6-$O_2CC_6H_5$[a,c]	116–117	92
8-CO_2CH_3	73	6

[a]IR in paper.
[b]UV in paper.
[c]NMR in paper.

TABLE I.9. Isoquinolines with an Ester in a Side Chain

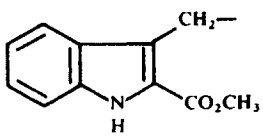
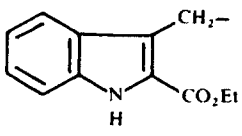
Substituent	m.p. (°C)	Ref.
1-$CH_2CO_2CH_3$-3-Cl	116–117	57
1-$COCH_2CO_2C_2H_5$	Picrate: 154–155	72
1-$CH_2COCO_2C_2H_5$	192–194	101
1-$C(CH_3)_2CO_2C_2H_5$-3-OH	98–99	93
1-$CH(CO_2C_2H_5)_2$-3-Cl	65–66	57
	b.p.: 150/1.8	57
	K salt: 278–280	57
1-$CH(CO_2C_2H_5)_2$[a]	Picrate: 190–192	39
1-$COCH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$[c]	116.5	100
1-$(CH_2)_4CO_2C_2H_5$[a]	oil	37
	Picrate: 109–110	37
1-$(CH(CH_3)CO_2C_4H_9$-sec-3-OH[a,b]	108–109	93
1-($C_6H_4CO_2CH_3$-4)	(N^+–Oxide) 225–226	118
1-$CH_2CH_2CH(CO_2C_2H_5)_2$	bp: 140/1.5	73
	Picrate: 188–190	73
	199–200	62
	Picrate: 234–235	62
1-($CH_2C_6H_2(OCH_3)_2$-4,5-CO_2CH_3-2) (N^+ –CH_3 I^-)	230–232	120
1-$CH{=}C(C_6H_5)CO_2C_2H_5$	134.5–135.5	103
	185–186	61

TABLE I.9. Isoquinolines with an Ester in a Side Chain (*Continued*)

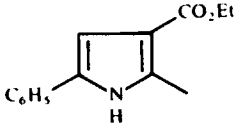
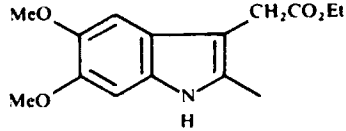
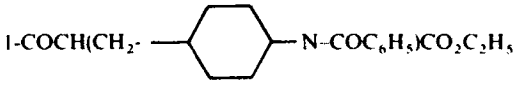
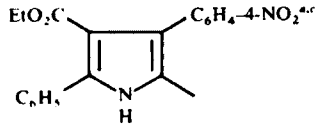
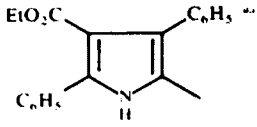
Substituent		m.p. (°C)	Ref.
		Picrate: 230–231	61
1-$CH_2CH(COC_6H_5)CO_2C_2H_5$		129–130	106
1-$C(CO_2CH_3)=C(COC_6H_5)CO_2CH_3$		176–178	108
		149–150	64
		94–96	65
1-$(CH(C_6H_4NO_2\text{-}4)CH(COC_6H_5)CO_2CH_3$		144–145	107
1-$CH(C_6H_5)CH(COC_6H_5)CO_2C_2H_5$		120–122	108
1-$CH(C_6H_4OCH_3\text{-}4)CH(COC_6H_5)CO_2CH_3$		132–133	107
		Picrate: 138	72
		224–225	109
		169–170	109
2-$C(=CHO^-)CO_2CH_3$[a–c]		193	104
2-$CH_2CH(SO_3^-)CO_2CH_3$		240	75
2-$CH_2CO_2C_2H_5$	Br^-[b]	185–186	98
2-$C(=CHO^-)CO_2C_2H_5$[a,c]		195–196	104
2-$CH_2CO_2C_2H_5$-1-CH_3	Br^-	200	121
2-$C(CO_2CH_3)=C(O^-)CO_2CH_3$[a–c]		180–181	104
2-$C(CO_2CH_3)=CHCO_2CH_3$	ClO_4^-	161–162	122
		Picrate: 173	122
2-$CH(CO_2C_2H_5)_2$	ClO_4^-	91–92	123
2-$C(CO_2C_2H_5)=C(O^-)CO_2C_2H_5$[a,c]		158–160	104
2-$CH_2CO_2C_2H_5$-1,3-$(CH_3)_2$ 6,7$(OCH_3)_2$	ClO_4^-[a]	206	124
2-$CH(C_6H_5)CO_2C_2H_5$	Br^-	104–105	123
2-$C(CO_2C_2H_5)=C(O^-)C_6H_5$[a–c]		195	104
2-$CH_2CO_2C_2H_5$-4-$NHCOC_6H_5$	Cl^-	N/A	125
		210[a]	126

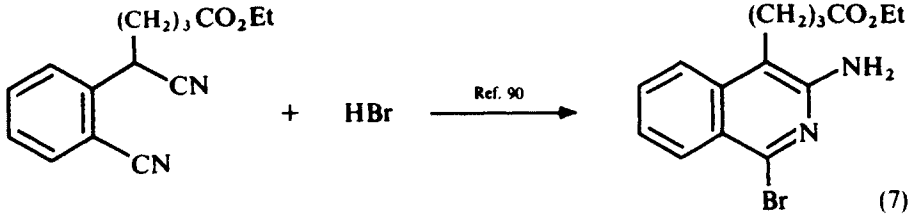
TABLE I.9. Isoquinolines with an Ester in a Side Chain (*Continued*)

Substituent		m.p. (°C)	Ref.
2-$CH_2CO_2C_2H_5$-4-$NHCO_2CH_2C_6H_5$	Br^-	111–112	105
3-$COCH_2CO_2C_2H_5$-6-CH_3O[a,c]		81–82	99
4-$CH_2CO_2C_2H_5$		62–64	67
4-$CH=CHCO_2C_2H_5$[a,c]	($N^+CH_3\ I^-$)	159–160	102
4-$CH_2CO_2C_2H_5$-7-CH_3O	($N^+CH_3\ I^-$)	117–119	44
4-$CH_2CO_2CH_3$-6,7-$(OCH_3)_2$[d]		HCl: 193–194	44
($N+CH_3\ I^-$)		169–171	44
4-$CH_2CO_2CH_3$-7,8-$(OCH_3)_2$		64–66	45
		HCl: 181–183	45
		Picrate: 182–184	45
3-$CH_2CO_2C_2H_5$		HBr: 205–207	54c
4-$CH=CHCO_2C_2H_5$		b.p. 180/2	102a
4-$(CH_2)_3CO_2C_2H_5$-1-Br-3-NH_2		222	90
		Picrate: 162	90
4-$CH_2CO_2C_2H_5$-7,8-$(OCH_3)_2$		80–81	45
4-$CH_2CO_2C_2H_5$-3-$CO_2C_2H_5$	($N^+CH_3\ ClO_4^-$)	141–143	80
4-$CH(C_6H_2O_2CH_2$-3,4-NO_2-6-)-CO_2CH_3[a,c]		150–151	45
4-$CH(CH_2C_6H_3O_2CH_2$-3,4)-CO_2CH_3-7,8-$(OCH_3)_2$[a,b]		142–143	45
		HCl: 130–132	45
	($N^+CH_3\ I^-$)	101–103	45
4-$CH(CH_2C_6H_5)CO_2C_2H_5$-7,8-$(OCH_3)_2$[a]		Picrate: 153–155	45
4-$COCO_2C_2H_5$-3-$(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	($N^+CH_3\ I^-$)[a,b]	199.5–201.5	79
4-$CH(CH_2C_6H_3(OCH_3)_2$-3,4)-CO_2CH_3-(7,8-$(OCH_3)_2$[a,c]		Picrate: 163.5–165	45
4-$CH(CH_2C_6H_3(OCH_3)_2$-3,4)-$CO_2C_2H_5$-7,8-$(OCH_3)_2$[a,c]		Picrate: 120–130	45
6-$CH_2CO_2C_2H_5$-3-OCH_3-7-CH_3[b,c]		57–58	69
6-$CH_2CO_2C_2H_5$-3-OC_2H_5-7-CH_3[c]		86–87	69
7-$CH_2CO_2CH_3$-3-OCH_3		49.5–51	71
7-$CH_2CO_2CH_3$-3-OCH_3		49.5–51	71a
7-$CH(CH_3)CO_2CH_3$-3-OCH_3		35–36	71a
1-$CH(CO_2Et)=C(NH_2)OEt$		138–140	71b
1-$CH(CO_2Et)=C(NH_2)_2$		193–194.5	71b

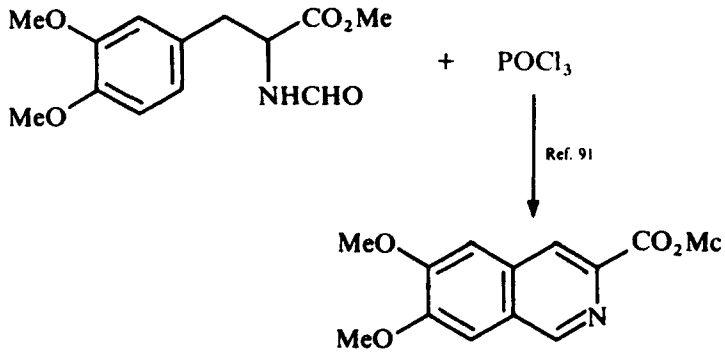
[a] IR in paper.
[b] UV in paper.
[c] NMR in paper.
[d] Mass spectroscopy in paper.

derived from dihydro- and tetrahydroisoquinolines have been dehydrogenated to the corresponding isoquinoline derivative.[15, 17–18, 71, 76–89] Treatment of 3,4-dihydroisoquinoline-3-carboxylic acid derivative with thionyl chloride in methanol gave the fully aromatic ester, while use of phosphorous pentachloride gave the dihydro ester.[15]

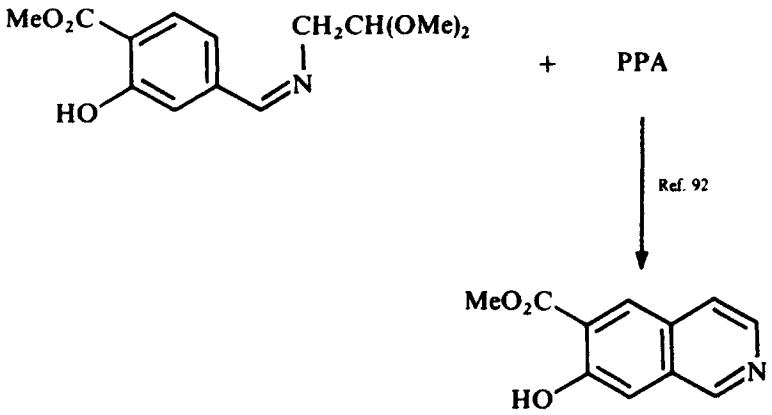
A variety of ring-closure methods have been used to prepare isoquinoline esters. Some of these are illustrated below:



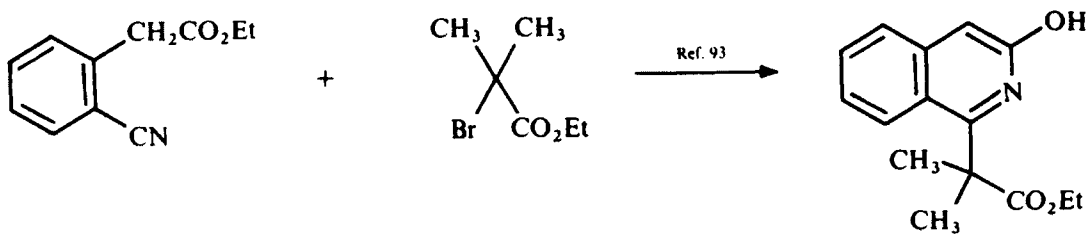
(7)



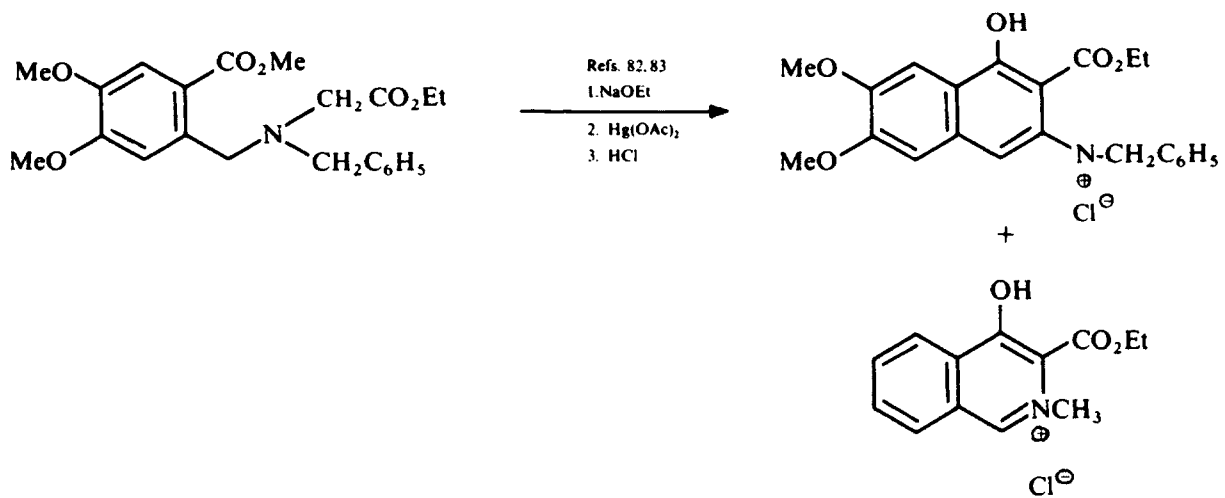
(8)



(9)


CH2CO2Et
CN
+
CH3
CH3
Br
CO2Et
Ref. 93
OH
N
CH3
CO2Et
CH3

(10)


MeO
CO2Me
CH2 CO2Et
N
MeO
CH2C6H5
Refs. 82, 83
1.NaOEt
2. Hg(OAc)2
3. HCl
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N-CH2C6H5
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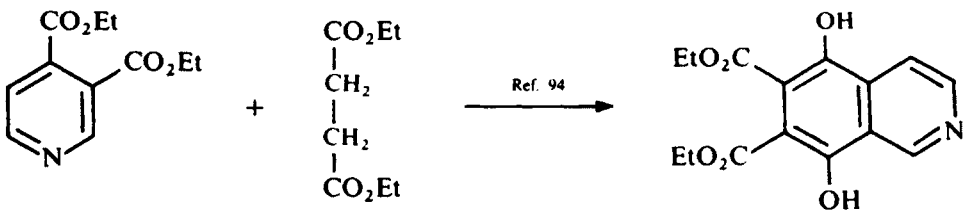
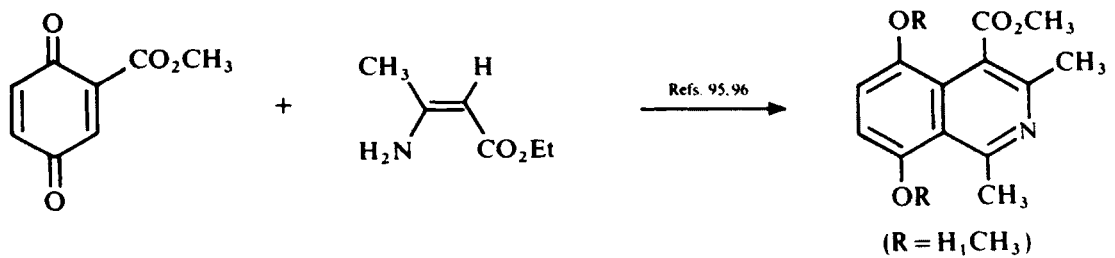
+
OH
CO2Et
NCH3
Cl⊖

(11)


CO2Et
CO2Et
N
+
CO2Et
CH2
CH2
CO2Et
Ref. 94
OH
EtO2C
EtO2C
N
OH

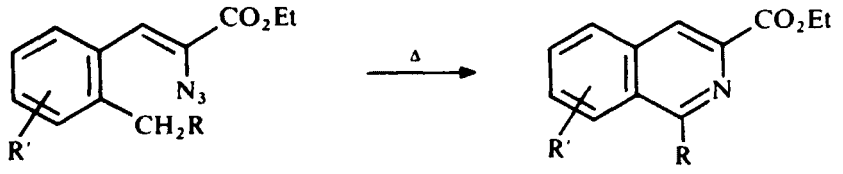
(12)


O
CO2CH3
O
+
CH3
H
H2N
CO2Et
Refs. 95,96
OR
CO2CH3
CH3
N
OR
CH3

(R = H, CH_3)

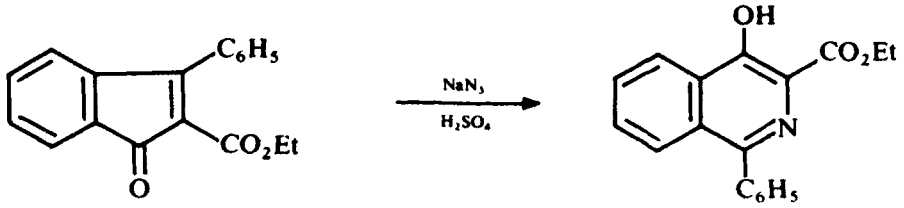
(13)

Mild thermal decomposition in boiling toluene or xylene of the azidocinnamates **21**, readily prepared from the corresponding aldehyde and ethyl azidoacetate, gives a series of 1-substituted isoquinoline-3-carboxylates **22**[54d, 96a-d] (Eq. 14).



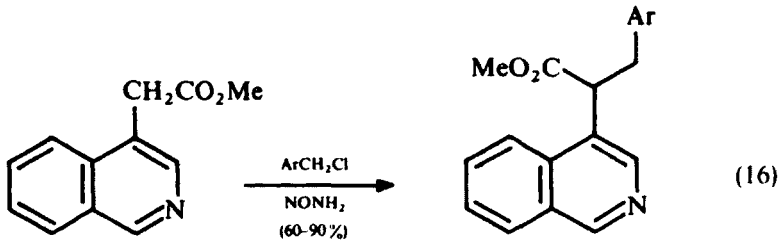
21 **22** (14)

Treatment of **23** with sodium azide and sulfuric acid leads to ring expansion to give ethyl 1-phenyl-4-hydroxyisoquinoline-3-carboxylate (**24**)[97] (Eq. 15).



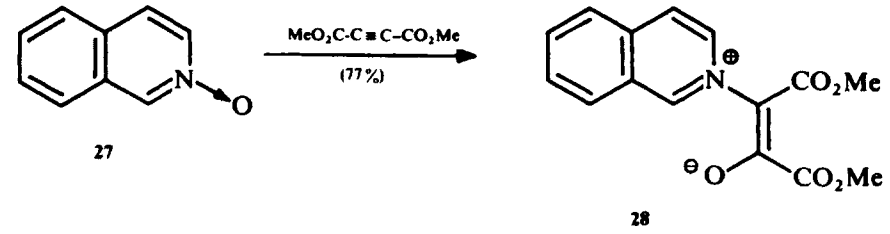
23 **24** (15)

Diethyl malonate has been used to displace substituents in the 1 position[39, 57] and to add to 1-vinylisoquinoline.[73] 1- and 3- isoquinolinecarboxylates have been condensed with acetates to give β-ketoesters.[72, 99, 100] Condensation of 1-methylisoquinoline with diethyl oxalate[101] and isoquinolinecarboxaldehydes with carboethoxymethylenetriphenylphosphorane[102] or ethyl phenylacetate[103] led to ester derivatives. Sodium-amide-catalyzed condensations of benzyl halides with **25** leads to **26**[45] (Eq. 16).



25 **26** (16)

The reaction of isoquinoline-*N*-oxide (**27**) with alkynes leads to the introduction of ester function into the 2 side chain. For example, the use of dimethyl acetylenedicarboxylate leads to **28** (Eq. 17).

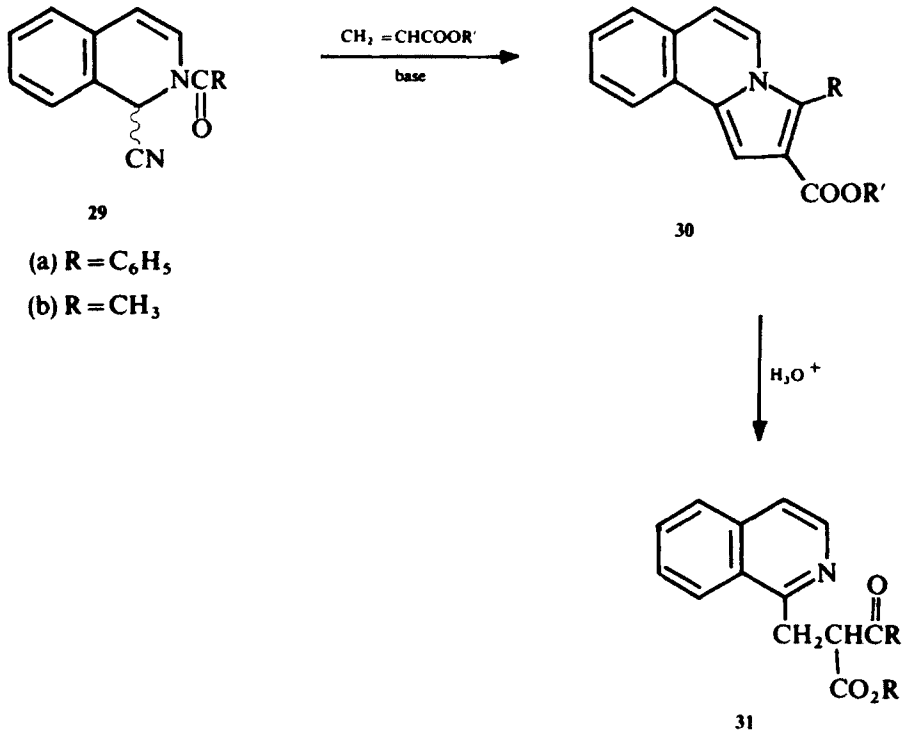


27 28

(17)

The mechanism for the formation of **28** via the expected 1,3-dipolar cycloaddition remains to be clarified. Other ester functions have been introduced into the 2 side chain by the use of appropriate substituted alkyl halides.[75,98,105]

The Michael reaction of Reissert compounds **29** with α,β-unsaturated compounds such as acrylates or cinnamates affords the 7,8-benzopyrrolidine **30**, which can be hydrolyzed to the keto ester **31**[106] (Eq. 18).



29 30

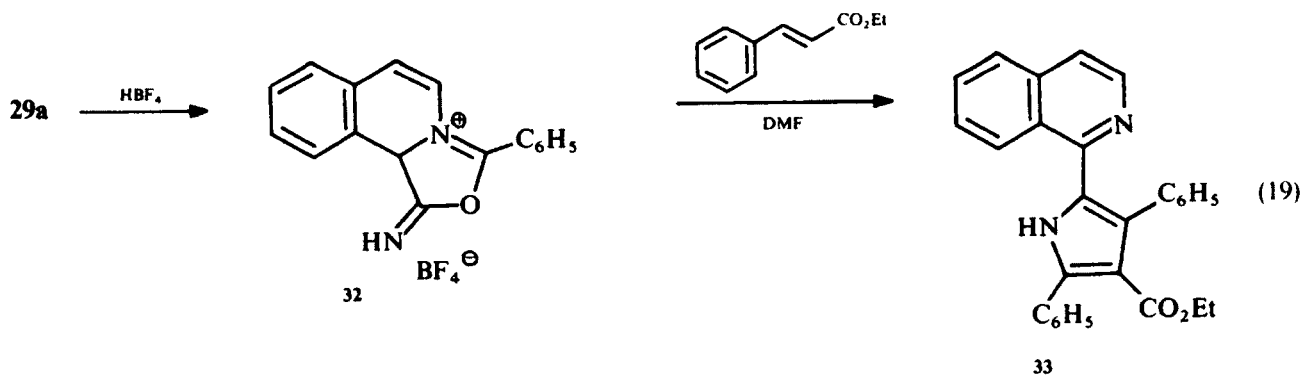
(a) $R = C_6H_5$

(b) $R = CH_3$

31

(18)

The regiospecific condensation of **32**, obtained by treating **29a** with fluoroboric acid, with ethyl cinnamate in DMF at room temperature provides in 64% yield ethyl 3,5-diphenyl-2-(1-isoquinolyl)pyrrole-4-carboxylate (**33**)[109] (Eq. 19).

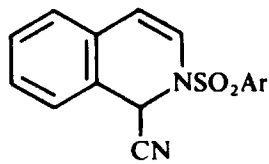


(19)

C. Cyanoisoquinolines

Displacement of halogens on the ring by reaction with cuprous cyanides[6,10,38,128,129] and halogens on the side chain by reaction with cyanide ion[67,69,130,131] has been used to prepare cyanoisoquinolines. Sulfonic acid groups have also been displaced by cyanide ion[7-8] and amine groups have been converted to cyano via the diazonium salt.[8-9] Various cyanodihydroisoquinolines have been dehydrogenated to cyanoisoquinolines.[4,132,133] Treatment of *N*-methyl-4-cyano-1,2-dihydroisoquinoline with perchloric acid or bromine gives the 4-cyanoisoquinolinium salts.[134] Cyanoisoquinolines have been obtained by phosphorus oxychloride dehydration of amides[38,135] and acetic anhydride dehydration of oximes.[136]

The reaction of isoquinoline-*N*-oxides with benzoyl chloride and cyanide ion[1,2,137,138a-c] or tosyl chloride and cyanide ion[139] gives rise to 1-cyanoisoquinolines. Trimethylsilycyanide has also been used.[139a] Treatment of 4-cyanoisoquinoline-*N*-oxide with potassium cyanide in dimethyl sulfoxide gives 1,4-dicyanoisoquinoline.[141,142] Treatment of Reissert compound **3** with phosphorus pentachloride,[21,142,143] thionyl chloride[144] or irradiation[145] affords 1-cyanoisoquinolines. The Reissert analog, **34** when treated with base[146-8] or sodium borohydride[149] also provides 1-cyanoisoquinolines. Isoquinoline-*N*-oxide and 2-cyanopropene gives a mixture that includes 1-cyanoisoquinoline.[150] The reaction of isoquinoline, potassium cyanide, and sulphuryl chloride gives 1-cyano-4-chloroisoquinoline;[143] use of base gives 1-cyanoisoquinoline, while an excess of potassium cyanide gives 3-cyanoisoquinoline-1-carboxamide. Irradiation of a number of isoquinolines and sodium cyanide has given cyanoisoquinolines.[143a]

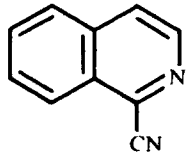


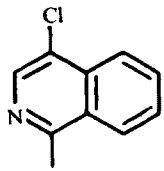
34

Cyanoisoquinoline-*N*-oxides have been prepared by peracetic acid oxidation of the cyanoisoquinolines[2,138a,141,151] and by treatment of isoquinoline-*N*-oxide with potassium cyanide and potassium ferricyanide.[152,153] The nitration of 1-cyanoisoquinoline-*N*-oxides has been studied.[138a,153a] Compound **35** and the corresponding amide are obtained from *o*-cyanobenzyl cyanide, formamide, and sodamide.[172a]

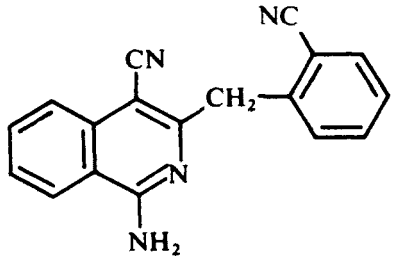
Reaction of 1-haloisoquinolines with benzylcyanides and amide ion gives **36**.[154-159]

TABLE I.10. 1-Cyanoisoquinolines

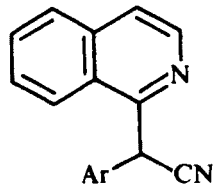


Substituent		m.p. (°C)	Ref.
(N^+-$CH_2C_6H_4OCH_3$-3 BF_4^-)		181–182	183
		90–90.5	2, 21, 39, 48, 139, 140, 142 146–150, 174, 175, 179–182
	(N^+-Oxide)	207	2, 152, 153, 179
4-Br		124–125	151
		122–123	148
	(N^+-Oxide)	204–205	151
		207–208	138a
4-Cl		122	143
5-HO		269–270[d]	1
3-CN		217–219	143
4-CN[d-f]		178.5	140, 141
3-CH_3		103–104	148
		N/A[b]	179
	(N^+-Oxide)	195–196	151
		N/A[b]	179
7-OCH_3		152–153	148
5-$NHCOCH_3$		260	138
4-C_2H_5[d-f]		54–55	137
6,7-$(OCH_3)_2$		198.4–199	144
4,5,6,7-$(OCH_3)_4$[d-f]		138–139	184
4-C_6H_5[d,f]		161–162	185
5-$OCOC_6H_5$[d]		152–153	1
3- or 4- 		245	146
4-$COC_6H_2(OCH_3)_3$-3,4,5		188–190	145
4-C_6H_5	(N^+-Oxide)	135–136	138b
5-NO_2	(N^+-Oxide)	227–228	138a, 153
6-NO_2	(N^+-Oxide)	224	138a, 153
8-NO_2		193	138a
6-NO_2		190–191	138

[a] MO calculation.
[b] Mass spectroscopy.
[c] Fluor. spectroscopy.
[d] IR in paper.
[e] UV in paper.
[f] NMR in paper.

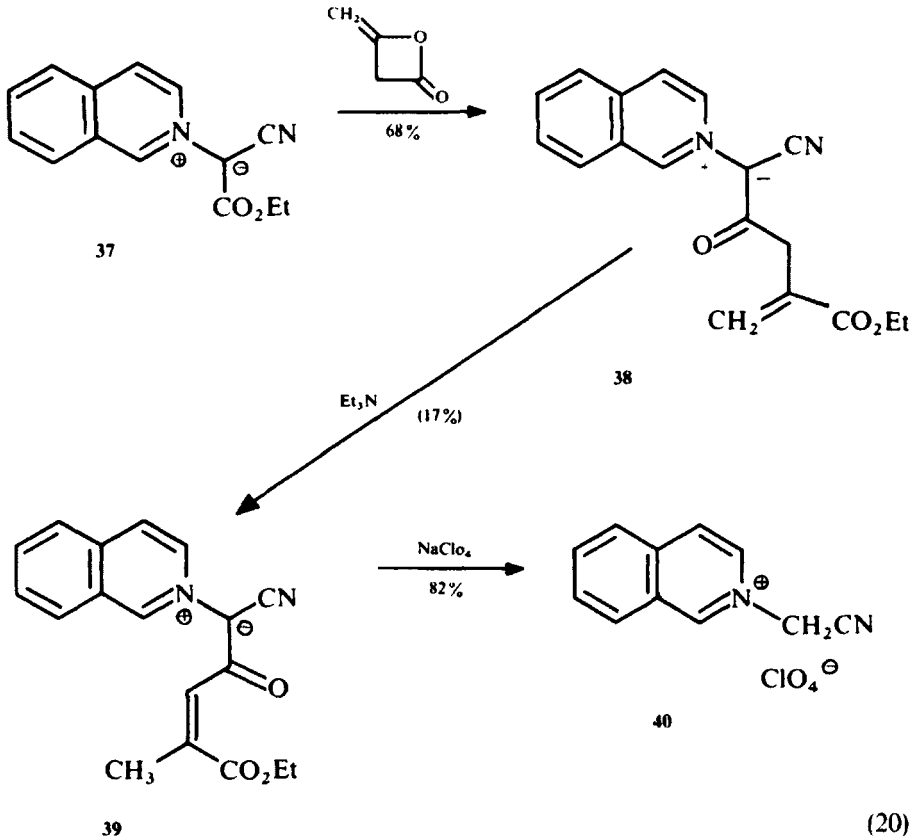


35



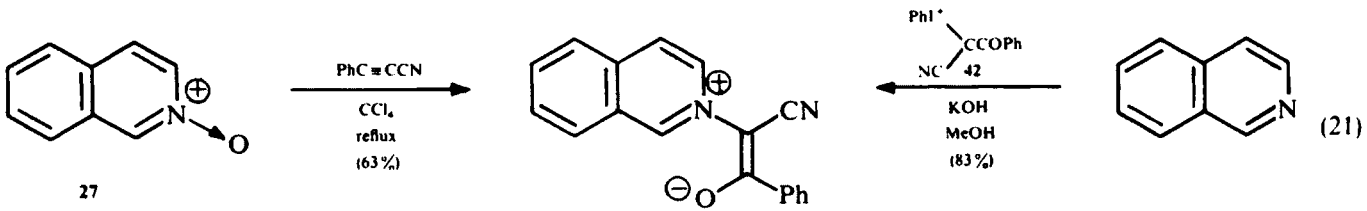
36

The reaction of isoquinoline with alkyl halides containing a cyano group has been used to introduce cyano groups into the 2 side chain.[160-166] The reaction of isoquinolinium cyanoethoxycarbonylmethylide **37** with diketene provides the adduct **38**, which can be thermally converted to isomer **39** or hydrolyzed to **40**[167] (Eq. 20).



(20)

The reaction of isoquinoline-*N*-oxide (**27**) with phenylcyanoacetylene provides the ylide **41** in 63% yield. Alternatively, **41** can be prepared in 83% yield by the reaction of isoquinoline with α-cyanophenacyliodinium ylid (**42**)[168] (Eq. 21).

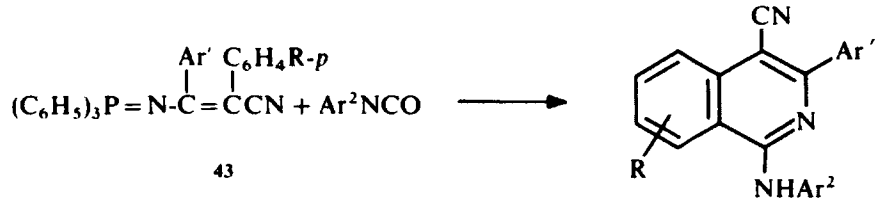


27 41

(21)

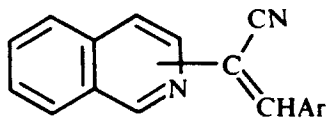
[61]

Phosphine *N*-(β-arylstyryl) imides (**43**) afford 3-aryl-1-arylamino-4-cyanoisoquinolines **44** in poor yields when treated with arylisocyanates[169] (Eq. 22).

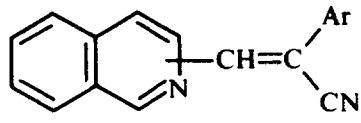


43 **44** (22)

While both 3- and 4-cyanomethylisoquinoline undergo condensations with aromatic aldehydes to give **45**,[67,130] benzylcyanides on the other hand condense with isoquinoline-1- and 3-carboxaldehydes to give **46**.[103,170]

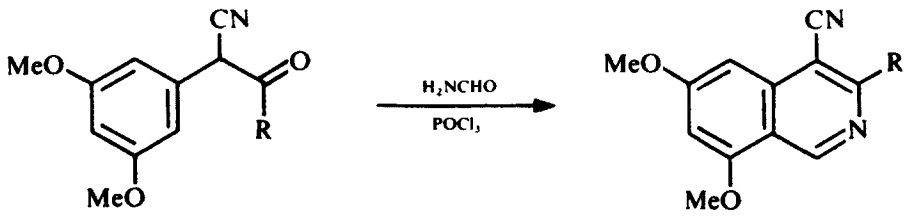


45



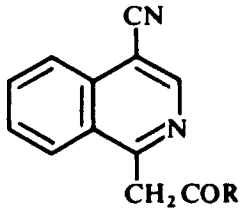
46

In an attempt to prepare analogs of agrimonolide, the following cyclization route has been used[171,172] (Eq. 23).

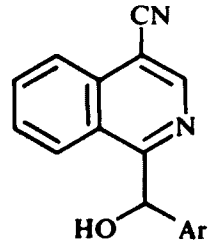


47 **48** (23)

The reaction of 4-cyanoisoquinoline with methyl ketones and sodium amide gives **49**[38] while aromatic aldehydes and cyanide ion give **50**.[173] Hueckel molecular orbital calculations have been carried out on 1-, 3-, and 4-cyanoisoquinolines to explain the reaction with Grignard reagents at the ring in the 4-cyanoisoquinolines and at the cyano group in the 1- and 3- cases.[174] Thus 1- and 3-cyanoisoquinolines with Grignard reagents gives the expected ketones.[146] While sodium borohydride does not react with 1- or 4-cyanoisoquinoline, 3-cyanoisoquinoline gives **51**.[157] It has been observed that 3-cyanoisoquinoline,

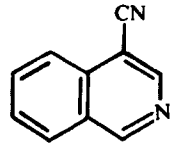


49



50

TABLE I.11. 4-Cyanoisoquinolines



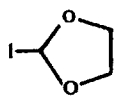
Substituent		m.p. (°C)	Spectroscopy	Ref.
—		104		6, 140
		101.5–103		17
		103–104	UV, IR	38
		HCl: 105		186
			MO Calculation	174
—	(N^+–Oxide)	221	IR, UV, NMR	141
	($N^+-CH_3\ Br^-$)	254	IR, UV	134
	($N^+CH_3ClO_4^-$)	160	IR, UV	134
	(N^+–$CH_2C_6H_5$-Br^-)	240		134
	(N^+–Oxide$^-$)	209		134a
1-OH		248–250	IR, UV	141
1-NH_2		254–255	IR, UV	38
1-CN		178.5	IR, UV, NMR	140, 141
1-CH_3		100–101	IR, UV	38
1-C_2H_5		87	IR	4
		85–86	UV, IR	133
		88	UV, NMR	137
1-CH_2SOCH_3		159–159.5		187
1-Cl-6,7-$(OCH_3)_2$		245	IR, NMR	74
6,8-$(OCH_3)_2$		201–202.5	IR, UV, NMR	171, 172
6,7-$(OCH_3)_2$		218–219	IR, NMR	74
	(N^+–$CH_2C_6H_3CH_2$-Br^-)	150		134a
1-CH_2COCH_3		202–204	IR, UV	38
1-NH_2-3-(O-$CNC_6H_4CH_2$)		223–224	IR, NMR, UV	172a
		139–141	NMR	188

TABLE I.11. 4-Cyanoisoquinolines (*Continued*)

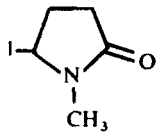
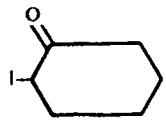
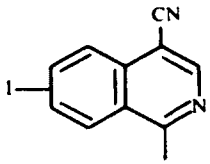
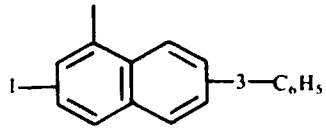
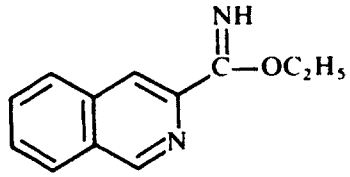
Substituent	m.p. (°C)	Spectroscopy	Ref.
1-$CH_2N(CH_3)CHO$	178–178.5	NMR	188
1-nC_3H_7	87–88		38
	87–90	UV	133
3-CH_3-6,7-$(OCH_3)_2$	218–219		189
3-CH_3-6,8-$(OCH_3)_2$	216–217	IR, UV, NMR	171, 172
1-$CH(OC)C_5H_4N$-4	199		173
1-$CH_2COC_2H_5$	169–170	IR, UV	38
1-$CH(CH_3)OCOCH_3$	114.5–115.5	NMR	188
1-$CH(SCH_3)OCOCH_3$	117–118		187
1-nC_4H_9	47–48.5	UV	133
1-$CH(CH_3)OC_2H_5$	62–63	NMR	188
3-C_2H_5-6,8-$(OCH_3)_2$	177	IR, UV, NMR	171, 172
1-OC_2H_5-6,7-$(OCH_3)_2$	192–193	IR, NMR	190
1-COC_4H_3O-2	194–196		173
	207–208	NMR	188
1-$CH_2CO(CH_2)_2CH_3$	167.5–168.5	IR, UV	38
1-$CH_2COCH(CH_3)_2$	206–207	IR, UV	38
1-$(CH_2)_3OC_2H_5$	53–54	UV	133
1-C_6H_5	141–142	UV	133
	198–200	IR, UV	38
1-$CH_2COCH_2CH(CH_3)_2$	149–150	IR, UV	38
1-$(CH_2)_5CO_2H$	155–156		38
1-$CH(OH)C_6H_4Cl$-2	169–170		173
1-$CH(OH)C_6H_4Cl$-4	189–190		173
1-$CH_2C_6H_5$	182–184		173
1-$CH_2COC_6H_5$	244–246	IR, UV	38
1-$COC_6H_4CH_3$-4	155–158		173
1-$COC_6H_4OCH_3$-4	187–189		173
1-$CH(OH)C_6H_4CH_3$-2	157–159		173
1-$CH(OH)C_6H_4CH_3$-3	127–129		173
1-$CH(OH)C_6H_4CH_3$-4	173–175		173
1-$CH(OH)C_6H_4OCH_3$-2	154–155		173
1-$CH(OH)C_6H_4OCH_3$-3	145–146		173
1-$CH(OH)C_6H_4OCH_3$-4	160–161		173
1-C_6H_5-6,8-$(OCH_3)_2$	193.5–194.5	IR, UV, NMR	171, 172
1-$CH(CH_3)COC_6H_5$	137–141	IR, UV	38
1-$CH(OH)C_6H_4NHCOCH_3$-4	244–245		173

TABLE I.11. 4-Cyanoisoquinolines (*Continued*)

Substituent	m.p. (°C)	Spectroscopy	Ref.
	310	IR, UV, NMR	38
1-$CH(C_2H_5)COC_6H_5$	130–131	IR, UV	38
3-$(CH_2CH_2C_6H_4OCH_3$-4)-6,7-$(OCH_3)_2$	150–151.5	IR, UV, NMR	171, 172
1-NHC_6H_5-3-C_6H_5-7-Cl	243–244	IR, UV	169
1-$(NHC_6H_4Cl$-4)-3-C_6H_5	289–290	IR, UV	169
1-NHC_6H_5-3-C_6H-$_5$	259-260	IR, UV	169
1-NHC_6H_5-3-$(C_6H_4CH_3$-4)	213–215	IR, UV	169
	207	IR, UV	169
3-OC_2H_5-8OH	225–7		169a
1-CH_3-3-OC_2H_5-OH	238–9		169a
3-OC_2H_5	77–9		169a
1-CH_3-3-OC_2H_5	125–127		169a
1,3-$(OC_2H_5)_2$	145–147		169a

when treated with sodium borohydride in pyridine is reduced to the tetrahydroisoquinoline with concomitant loss of the cyano group.[176]



51

The reaction of 1-cyanoisoquinoline with hydrazine[177] or hydroxylamine[177a] affords the expected nucleophilic addition products at the cyano function.

The photolysis of 1-cyano-3-substituted isoquinoline *n*-oxides **52** in acetone affords a series of benz[*d*]-1,3-oxazepines **53**[178,178a] (Eq. 24).

TABLE I.12. 2-, 3-, 5-, 6-, and 8-Cyanoisoquinoline

Substituent	m.p. (°C)	Ref.
2CN (BF_4^-)	102	191
3-CN	127.5–128	135, 136, 143a, 174, 175
5-CN	140–141	6, 7, 10, 128
	275–276	192
(N^+-CH_3I^-)	(other salts)	119, 186
6-CN	149–150	6, 10
8-CN	133	6
5- or 8-CN	135	56
1,3-$(CN)_2$	217–219	143
X, Y-$(CN)_2$	137	193
5-CN-1-CHO	185–187	9
Thiosemicarbazone:	247–248	9
5-CN-6-OCH_3	183–185	143a
8-CN-7-OCH_3	164–165	143a
8-CN-6,7-$(OCH_3)_2$	173	143a
5-CN-3-CHO	208–210	8
3-CN-1-CO_2H	200–203	143
3-CN-1-$CONH_2$	230–233	143
5-CN-1-CH_3	145–146	9
5-CN-3-CH_3	127–129	8
3-CN-1,4-$(OCOCH_3)_2$[b]	183–186	194
6-CN-7-(C_6H_4-NH_2-2)	218	195

[a] MO calculation in paper.
[b] IR, UV, and NMR in paper.

TABLE I.13. Isoquinoline Containing a Cyano Group in a Side Chain

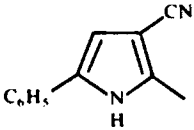
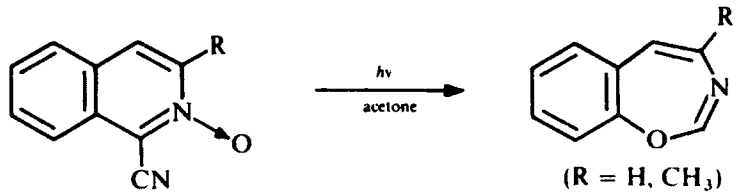
Substituent	m.p. (°C)	Spectroscopy	Ref.
1-CH_2CN	174	IR, UV	39
1-CH_2CN-3-CH_3	187–188		132
1-$(CH_2)_3CN$	b.p. 156/2.5		58
1-N(C_6H_5)CN	78		196
1-CH(C_6H_4Br-2)CN	152–155		159
1-CH(C_6H_5)CN	b.p. 170–180/0.005		154
	143–145		154, 157
	142–143		156
	142–143	IR, UV	39
1-CH($C_6H_4NH_2$-4)CN	100–105		158
2-C(CN)=C(C_6H_5)O^-	209–210	IR, NMR	168
1-CH=C(C_6H_5)CN	96.5–97		103
1-CH($C_6H_4OCH_3$-4)CN	b.p. 140–160/0.003		155
	142		155
	221.5–222	IR, NMR	64
	HCl:275–6		64

TABLE I.13. Isoquinoline Containing a Cyano Group in a Side Chain (*Continued*)

Substituent		m.p. (°C)	Spectroscopy	Ref.
2-CH_2CN	Br^-	196–197		164
		195		166
	(ClO_4^-)	177–178	NMR	163, 167
	(I^-)	161–162	NMR	160
2-CH_2CN-5-NO_2	(I^-)	169–170	NMR	160
1-C(CN)(OCOEt)(4-$NO_2C_6H_4$)		205–8		160a
1-C(CN)(OCOMe)(4-$NO_2C_6H_4$)		202–204		160a
1-C(CN)=C(CH_3)NH_2		177–178		160b
2-CH_2CH_2CN	(Cl^-)	220–222		161, 162
2-$CH(C_6H_5)CN$	(Br^-)	176		164
3-CH_2CN		49.5–450		130
3-CH_2CN-1-Cl-4-CH_3		154–156		131
3-C(=CHC_6H_5)CN		194		130
3-$CH(C_6H_5)CN$-1-C_2H_5		89–91	IR, UV, NMR	197
3-CH=C($C_6H_3(OCH_3)_2$-3,4)CN		147–148		170
	HCl	105–107		170
3-$CH(C_6H_5(OCH_3)_2$-3,4)-1-CH_3-6,7-$(CH_3O)_2$		121	IR, UV	197
	HCl	172		197
3-$CH(C_6H_5(OCH_3)_2$-3,4)-1-C_2H_5-6,7-$(CH_3O)_2$		135–137	IR, UV	197
	HCl	135–137		197
4-CH_2CN		109–110		67
4-C(=$CHC_6H_4NO_2$-2)CN		177–178		67
6-CH_2CH_2CN-3-OC_2H_5-7-CH_3		113–114	IR	69
3-(2CNC_6H_4)		104–105		197a
1-C(CN)=C(C_6H_5)NH_2		197–198		160b
3-CH_2CN-1-C_6H_5		158		54c
3-CH_2CN-1-COC_6H_5		107–108		54c
4-CH_2CN-1-C_6H_5		78–80		54c

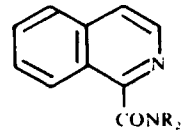


52 53 (R = H, CH_3) (24)

D. Isoquinoline Carboxamides

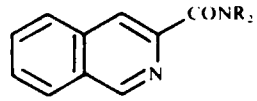
Tables I. 14 (page 168), I. 15 (page 168) and I. 16 (page 170) list isoquinolines with amide functions attached directly to the ring; Table I. 17 (page 171) includes amides in a side chain.

TABLE I.14. Isoquinoline-1-Carboxamides



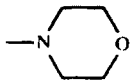
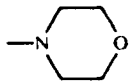
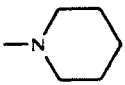
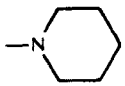
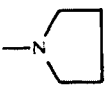
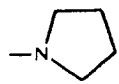
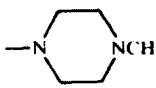
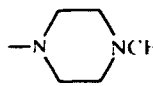
R_2	Substituent	m.p. (°C)	Ref.
H_2	4-Br	169–170	148
H_2		168–170	2, 49, 50, 148, 204, 205
	HBr:	275–276	49
	($N^+ - \bar{O}$xide)	283	2
H_2	3-CH_3	181–182	148
H_2	6,7-$(OCH_3)_2$	169–170	144
		168–169	203
H, C_6H_5		119–121	202
H, 1-$C_{10}H_7$		168–170	202
C_6H_5, COC_6H_5		206–208	36a
1-$C_{10}H_7$, COC_6H_5		216–218	36a

TABLE I.15. Isoquinoline-1-Carboxamides



R	Substituent	m.p., °C	Ref.
H_2	-	212–213	30, 52, 53, 135
H_2	1-C_6H_5-4-OH	271–273	97
H, $CH_2CH_2N(C_2H_5)_2$	1-Cl	77–78	201
		HCl:164–165	201
H, $CH_2CH_2N(C_2H_5)_2$	1-OCH_3	HCl:128–129	201
H, $C_6H_4CH_3$-2	6-CH_3O	124–125	99
H, $CH_2CH_2C_6H_4SO_2NH_2$-4	-	242–244	198, 199
H, $CH_2CH_2N(C_2H_5)_2$	1-OC_2H_5	HCl:163–164	201
H, $CH_2CH_2N(C_2H_5)_2$	1-OC_3H_7-*n*	HCl:177–178	201
H, $CH_2CH_2N(C_2H_5)_2$	1-OC_4H_9-*n*	HCl:180–181	201
H, $CH_2CH_2C_6H_4SO_2NH$-$CONHC_6H_{11}$-*n*	-	195–197	198, 199
H, $CH_2CH_2N(CH_3)_2$	1-OCH_3-4-CH_3	72–73	54b
H, $CH_2CH_2N(C_2H_5)_2$	1-OCH_3-4-CH_3	55–56	54b
H-$(CH_2)_3N(CH_2)_2$	1-OCH_3-4-CH_3	84–85	54b
H-$(CH_2)_3N(C_2H_5)_2$	1-OCH_3-4-CH_3	129–130	54b
H-$CH_2N(CH_5)_2$	1-Cl-4-CH_3	137	54b
H $CH_2CH_2N(C_2H_5)_2$	1-Cl-4-CH_3	98–99	54b

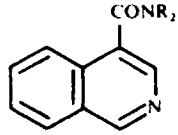
TABLE I.15. Isoquinoline-1-Carboxamides (*Continued*)

R_2	Substituent	m.p. (°C)	Ref.
$H\text{-}(CH_2)_3\text{-}N(CH_3)_2$	1-Cl-4-CH_3	156–157	54b
$H\text{-}(CH_2)_3\text{-}N(C_2H_5)_2$	1-Cl-4-CH_3	148–149	54b
NR_2 =			
	1-OCH_3-4-CH_3	136–137	54b
	1-Cl-4-CH_3	198–199	54b
	1-OCH_3-4-CH_3	90–92	54b
	1-Cl-4-CH_3	142–143	54b
	1-OCH_3-4-CH_3	100–101	54b
	1-Cl-4-CH_3	128	54b
	1-OCH_3-4-CH_3	108–109	54b
	1-Cl-4-CH_3	163–164	54b

Amides have most frequently been prepared from the nitrile [2,3,5,64,67,131,144,154–155,157,159] or from an amine and the carboxylic acid, ester, or acyl halide.[5,30,57,99,135,198–199,200–202] Base hydrolysis of the nitrile gives amide **54**, while hydrolysis with sulfuric acid gives **55**.[64]

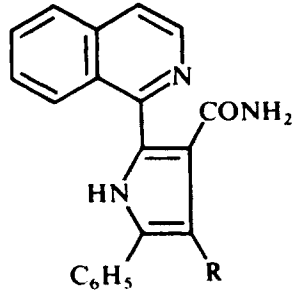
1-Carboxamides have been prepared by the action of acid[203] or hydrogen peroxide[204] on Reissert compounds **3**, or more conveniently by the action of concentrated base on **34**.[147–148,205] The *N*-oxide of isoquinoline-1-carboxamide can be prepared by the action of alkaline hydrogen peroxide on 1-cyanoisoquinoline-*n*-oxide or peracetic acid on isoquinoline-1-carboxamide.[2]

TABLE I.16. Isoquinoline-4-Carboxamides



R	Substituent	m.p. (°C)	Ref.
H_2		174.5–175.5	3
		168–172	5
	$(NCH_3Br^-)^{a,b}$	245	134
	(NCH_3I^-)	260	5
	$(N^+CH_3ClO_4^-)^{a,b}$	248	134
	$(N^+CH_3$ picrate)	226	134
	$(N^+CH_2CH_2C_6H_5Br^-)$	255	134
H_2	$1\text{-}CH_3{}^{a,b}$	183–185	38
H_2	$1\text{-}C_2H_5{}^{a,b}$	173–175	38
$(C_2H_5)_2$		b.p. 158–162/0.25	5
		HCl:138	5
		Picrate:195	5
		$(N^+CH_3I^-)$193	5
H, $CH_2C_6H_5{}^a$		168.5–169.5	200
H_2	$1\text{-}NH_2\text{-}3\text{-}CH_2C_6H_4\text{-}CN\text{-}O\text{-}$	233–235	172a
H_2	$6,7(OCH_3)_2$	254	134a
	$(N^+CH_2C_6H_3Cl_2\text{-}2,6)(Cl\text{-})$	210	134a

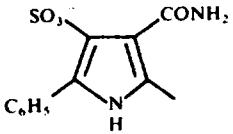
[a] IR in paper.
[b] UV in paper.



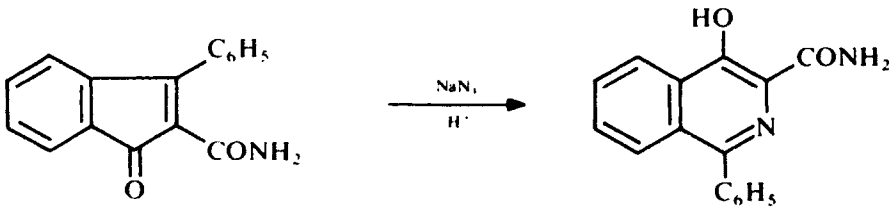
54 R = H
55 $R = SO_3^-$

Amides have been introduced in side chains in the 2 position by the reaction of isoquinolines with acrylamide[206-207] or with alkyl halides containing amide groups.[160,208] The equilibrium for pseudobase formation has been studied in these isoquinolinium salts.[160]

TABLE I.17. Isoquinolines Containing an Amide Group in the Side Chain

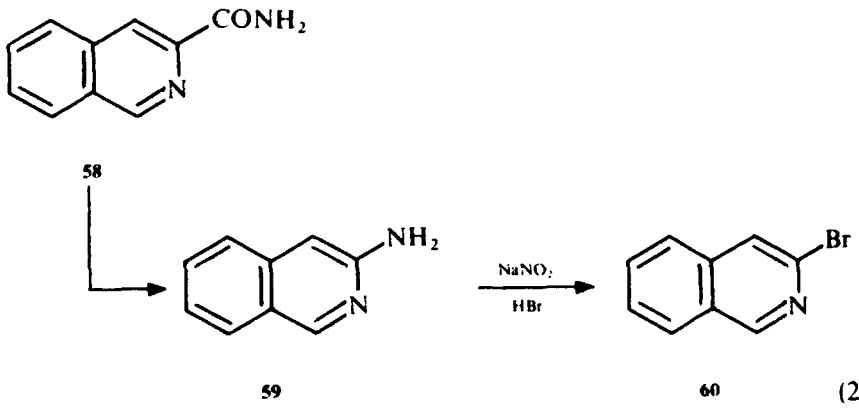
Substituent		m.p. (°C)	Ref.
1-CH_2CONH_2		204–205	210
		209–211	210a
1-$CH_2CONHCH_3$-3-Cl		191–192	57
1-$CH(C_6H_4Br$-2$)CONH_2$		173–173.5	159
	Picrate:	208	159
1-$CH(C_6H_5)CONH_2$		191–192	154, 157
	($N^+CH_3\ I^-$)	240–242	154
1-$CH{=}CHCONHC_6H_5$		163–166	212
	($N^+CH_3\ I^-$)	262–263	212
1-$CH_2CONHCH_2C_6H_5$-3-Cl		169–170	57
1-$CH(C_6H_4OCH_3$-4$)CONH_2$		205–206	155
	(N^+H)	303–305	64
2-CH_2CONH-5-NO_2[a]	I^-	233	160
2-CH_2CONH_2	Br^-	203	211
2-CH_2CONH_2[a]	I^-	194–196	160
2-$CH_2CH_2CONH_2$	Cl^-	210.5–212	206, 207
2-$CH(C_6H_5)CONHC_6H_5$	Cl^-	245	208
3-CH_2CONH_2-1-Cl-4-CH_3		219–220	131
4-CH_2CONH_2		219–220	67
3-CH_2CONH_2	1-COC_6H_5	185–187	54c
3-CH_2CONH_2	1-C_6H_5	201–204	54c
4-CH_2CONH_2	1-C_6H_5	190–192	54c
3-CH_2CONH_2	1-(4ClC_6H_4)	219–221	54c

Treatment of **56** with sodium azide and acid proceeds through ring expansion to give 1-phenyl-4-hydroxyisoquinoline-3-carboxamide (**57**)[97] (Eq. 25).



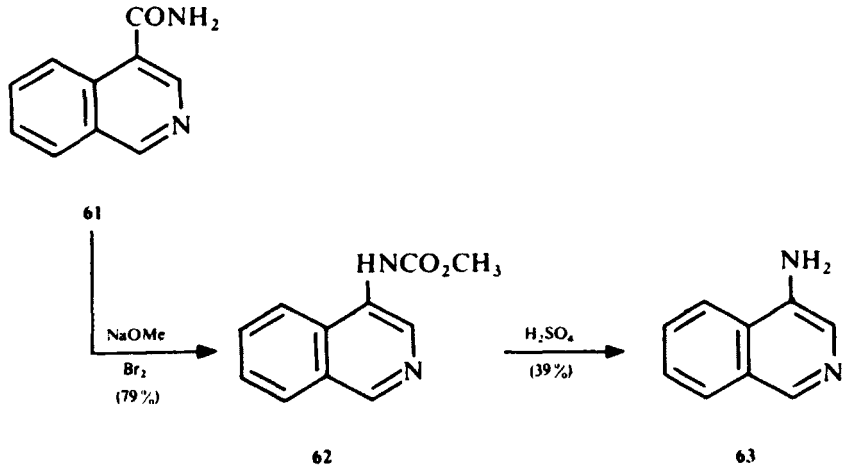
56 **57** (25)

3-Bromoisoquinoline (**60**), used to prepare 3,3′-bisisoisoquinoline by an Ullmann reaction, can be conveniently prepared from 3-aminoisoquinoline (**59**) derived from isoquinoline-3-carboxamide (**58**)[53] (Eq. 26).



(26)

The reaction of isoquinoline-4-carboxamide (**61**) with bromine and NaOMe proceeds through a Hofmann rearrangement to afford methylisoquinoline-4-carbamate (**62**), which was subsequently hydrolyzed to 4-amino isoquinoline (**63**) with 93% H_2SO_4.[209] (Eq. 27).



(27)

E. Miscellaneous Isoquinoline Carboxylic Acid Derivatives

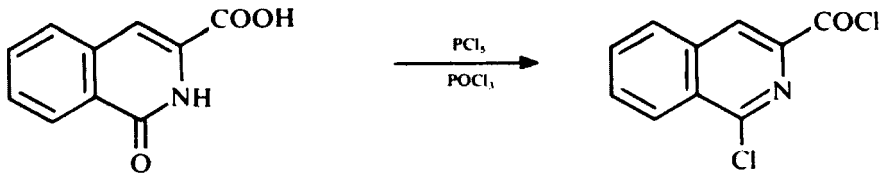
Derivatives such as acid chlorides, hydrazides, and azides are listed in Table I.18.

The action of phosphorus oxychloride–phosphorus pentachloride on **64** leads to **65**[54,201] (Eq. 28). A number of acid chlorides have been used as intermediates without characterization.

TABLE I.18. Miscellaneous Isoquinoline Carboxylic Acid Derivatives

Substituent	m.p. (°C)	Ref.
3-COCl-1-Cl	130–132	201
4-$CONHNH_2$-1-$NHNH_2$	236–238	117
3-COCl-1-Cl-7,8-$(OCH_3)_2$	168	54
3-C(=NH)OC_2H_5[a]	N/A	175
4-COO-5-1,3-$(CH_3)_2$-8-$(OCOCH_3)$[a–c]	189–191	95, 96
3-CON_3-1-C_6H_5-6,7-$(OCH_3)_2$	121–122	84
3-$CONHNH_2$-1-C_6H_5-6,7-$(OCH_3)_2$	215–216,	84
	217	87
3-COCl-1-Cl-4-CH_3	172–173	54a
3-COCl-1-Cl-4OCH_3	101–102	54b

[a]IR and NMR in paper.
[b]UV in paper.
[c]Lactone.



64 65 (28)

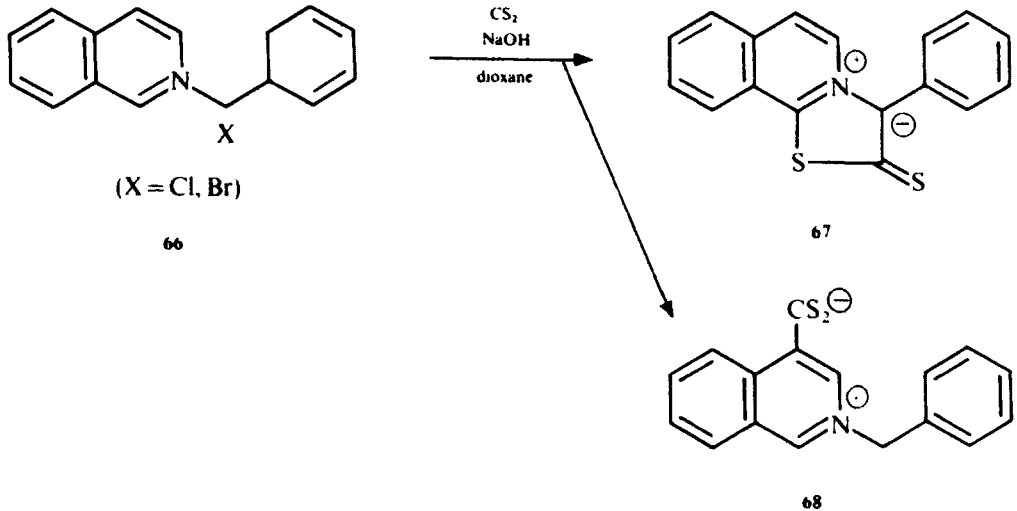
Hydrazides[84,117] and an azide[84] have been prepared in the usual manner from the ester.

F. Isoquinolinedithiocarboxylic Acids

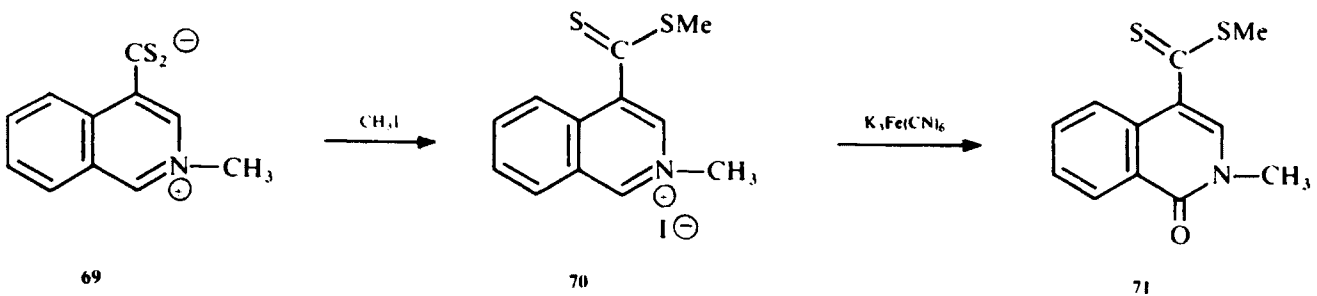
N-Benzylisoquinolium halides **66**, when combined with carbon disulfide in alkaline aqueous dioxane, give both the mesoionic 3-phenylthiazolo[2,3-a]isoquinolinium-2-thione betaine (**67**) and *N*-benzylisoquinolinium-4-dithiocarboxylate (**68**)[213,214] (Eq. 29).

The treatment of 2-methylisoquinolinium-4-dithiocarboxylate (**69**) with iodomethane in methanol affords the 2-methyl-4-(methylthio)thiocarbonylisoquinolinium iodide **70** in 93% yield. This is oxidized to methyl-2-methyl-1-oxo-1,2-dihydroisoquinoline-4-dithiocarboxylate (**71**) with potassium ferricyanide[215] (Eq. 30).

Reactions of 1-chloro-4-hydroxyisoquinoline with carbon disulfide and base led to the introduction of the dithiocarboxylate into the 3 position.[217]



(29)



(30)

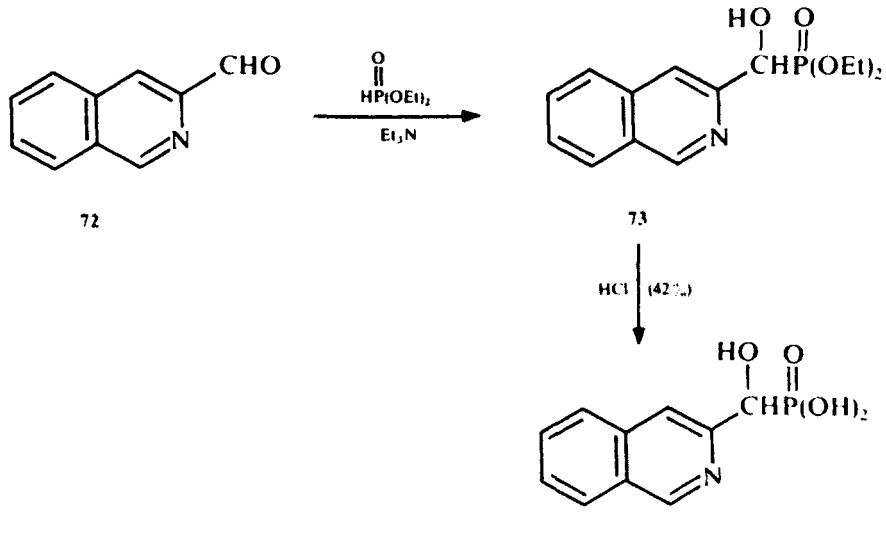
TABLE I.19. Isoquinoline dithiocarboxylic Acid Derivatives

Substituent		m.p. (°C)	Ref.
4-CS_2^-	(N^+CH_3)	280	215
4-CS_2CH_3[a,b]	($N^+CH_3I^-$)	187–188	215
4-CS_2^--3-CH_3[a]	(N^+CH_3)	280	216
3-CS_2CH_3-1-Cl-4-OH[a,b]		199	217
4-CS_2^-	($N^+CH_2C_6H_4Br$-3)	207–208	214
4-CS_2^-	($N^+CH_2C_6H_4Br$-4)	206–227	214
4-CS_2^-	($N^+CH_2C_6H_4Cl$-3)	210–213	214
4-CS_2^-	($N^+CH_2C_6H_4Cl$-4)	208–209	214
4-CS_2^-	($N^+CH_2C_6H_4F$-3)	204–205	213, 214
4-CS_2^-	($N^+CH_2C_6H_4$)	209–210	213, 214
4-CS_2^-	($N^+CH_2C_6H_4CH_3$-3)	198–199	214
4-CS_2^-	($N^+CH_2C_6H_4CH_3$-4)	198–201	213, 214
4-CS_2^-	($N^+CH_2C_6H_4OCH_3$-3)	215–218	214
4-CS_2^-	($N^+CH_2C_6H_4OCH_3$-4)	191–193	213, 214

[a]UV in paper.
[b]NMR in paper.

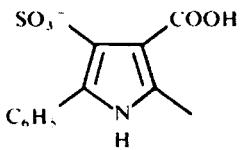
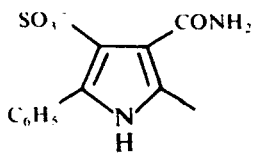
G. Isoquinoline Acids Containing Phosphorus, Sulfur, and Antimony

The reaction of isoquinoline-3-carboxaldehyde (**72**) with diethylphosphite and triethylamine leads to **73**, which can be hydrolyzed to **74**[218] (Eq. 31).



72 73 74 (31)

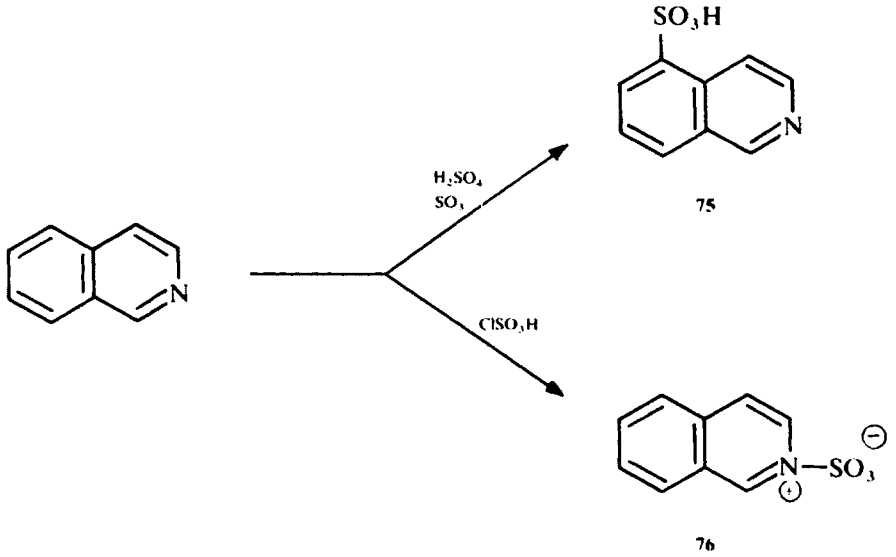
TABLE I.20 Isoquinoline Acid Derivatives of P, S, and Sb

Substituent		m.p. (°C)	Ref.
3-CH(OH)PO(OH)$_2$		238–239	218
3-CH(OH)PO(OC$_2$H$_5$)$_2$		HBr:139–139.5	218
5-SO$_3$H		N/A	1,7,223
X-SO$_3$H		N/A	224
2-SO$_3^-$	(N$^+$H)	250–254	219
3-SO$_3$H-4-OH		N/A	222
8-SO$_3$H-4-OH		N/A	221
5-SO$_3$H-1-CH$_3$		N/A	220
5-SO$_3$H-3-CH$_3$		420–430	8
5-SO$_3$H-1-CH=NNHCSNH$_2$		N/A	220
		314–316	9
2-CH$_2$CH(CO$_2$H)SO$_3^-$	(N$^+$H)[a]	302	66
		300	75
2-CH$_2$CH(CO$_2$CH$_3$)SO$_3^-$		240	75
5-SO$_3^-$-1-CH$_2$-N$^+$ 		>300	9
	(N$^+$H)	>360	64
	(N$^+$H)	303–305	64
		Na Salt:260	64
5-SbO$_3$HNa		>300	225

[a]NMR in paper.

Reaction of isoquinoline with fuming sulfuric acid leads to the formation of the 5-sulfonic acid **75**[1,7] Chlorosulfonic acid, however, leads to **76**[219] (Eq. 32).

Although both 1- and 3-methylisoquinolines undergo sulfonation in the 5 position,[8,220] 4-hydroxyisoquinoline gives the 8-sulfonic acid.[221] Oxidative sulfonation of 4-hydroxyisoquinoline takes place in the 3 position.[222]



(32)

H. Isoquinoline Ylides Containing Acidic Functions

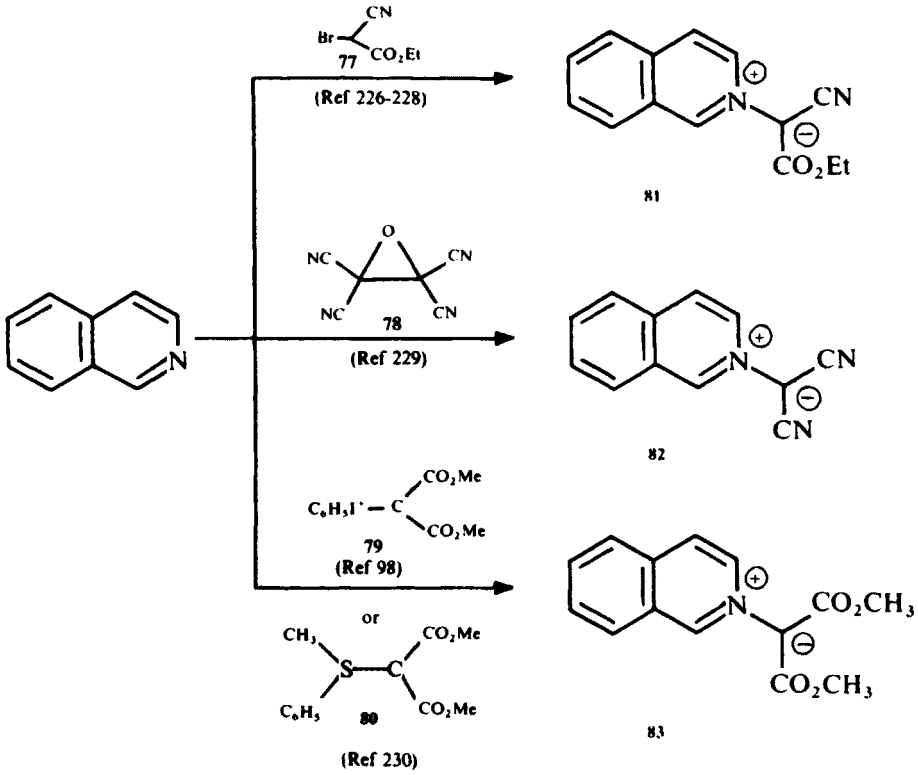
Heterocyclic *N*-ylides **81**–**83** can be prepared from isoquinoline reacting with compounds such as alkyl bromocyanoacetates (**77**),[226-228] tetracyanoethylene oxide (**78**),[229] bisethoxycarbonyl(phenyliodonio)methanide (**79**),[98] and **80**[230] (Scheme 1).

N-Phenacylisoquinolinium bromine (**84**) reacts with acrylonitrile in basic methanol to afford the heterocyclic *N*-ylide **85**, which is further cyclized with ammonium acetate in methanol to 3-(2-cyanoethyl)-2-phenyl-2,3-dihydroimidazo[2,1–9]isoquinoline (**86**) in 53% yield.[232] (Eq. 33).

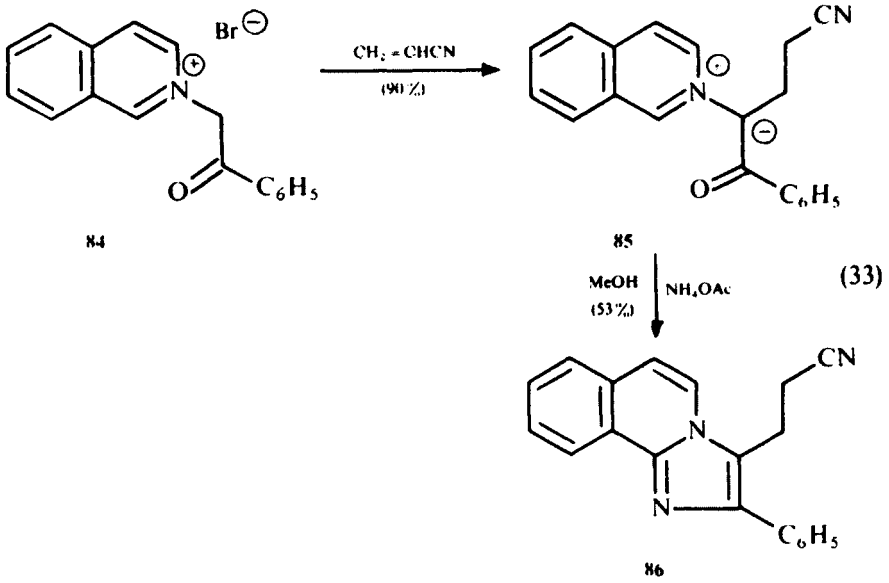
Isoquinolinium salts **87** also react with ketone thioacetals to give isoquinolinium allylides (**88**) in 30–50% yield[233] (Eq. 34).

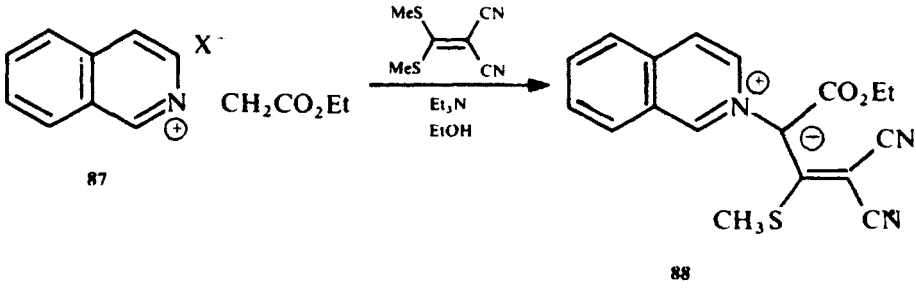
The reaction of isoquinoline with maleic anhydride in dry benzene yields **89**, which upon treatment with methanol yields **90**[43] (Eq. 35).

Interest has centered on the reaction of the heterocyclic *N*-ylides **81**–**83** with dicyanoacetylene,[234] dimethylacetylenedicarboxylate,[165] and other electrophilic reagents,[235,236] including UV irradiation.[237,238] Thermal decomposition of **83** to isoquinoline and carbenes has been investigated. These heterocyclic *N*-ylides have also been investigated as acid–base indicators,[240] as semiconductors,[241] and for the determination of benzoyl chloride, acetic anhydride, and phenyl isocyante.[242]


77
(Ref 226-228)
81
78
(Ref 229)
82
79
(Ref 98)
or
80
(Ref 230)
83

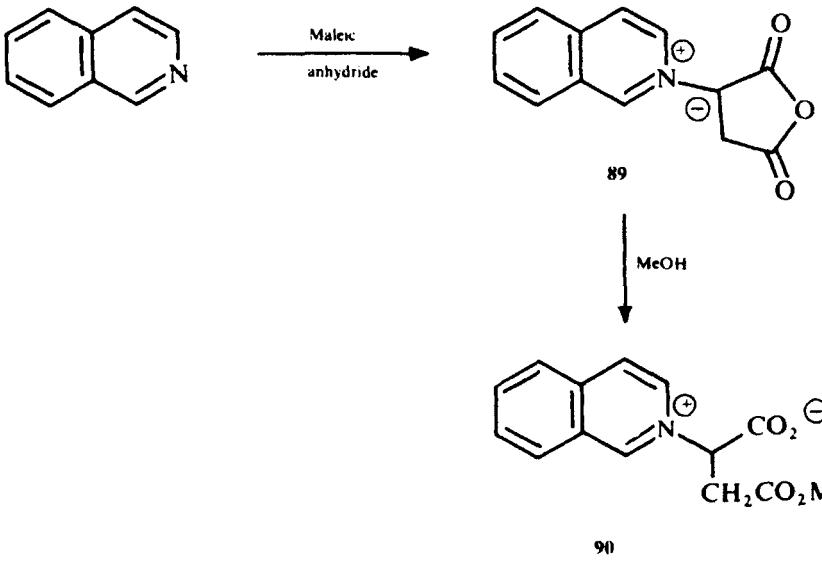
Scheme 1


84
CH₂=CHCN
(90%)
85
MeOH
(53%)
NH₄OAc
(33)
86



87 88

(34)



89 90

(35)

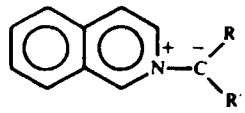
II. DIHYDROISOQUINOLINES

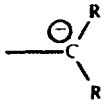
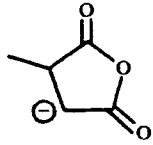
This section includes all dihydroisoquinolines containing acid functions.

A. 1,2,-Dihydroisoquinolines

Because of the large interest in Reissert compounds (*N*-acyl-1,2-dihydroisoquinaldonitriles), nitriles are treated in a separate section. For convenience

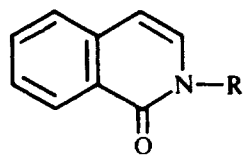
TABLE I.21. Isoquinoline Ylides



R	R'	m.p. (°C)	Ref.
CN	CN	253–254	228, 229
		N/A	238
CN	CO_2CH_3	159	226
		158–159[a,b]	237
		140	43
CN	$CO_2C_2H_5$	146–147	228
CO_2CH_3	CO_2CH_3	220–221[b]	98
		235–236[a,b]	227
CO_2CH_3	$C(SCH_3)=NCN$	228[a,b]	233
$CO_2C_2H_5$	$C(SCH_3)=NCN$	246[a,b]	233
$CO_2C_2H_5$	$CO_2C_2H_5$	195	123
		195[b]	98
		N/A	238
CO_2CH_3	$C(SCH_3)=C(CN)_2$	197[a,b]	233
CN	$COCH_2C(=CH_2)OCO_2CH_3$	122–124[a,c]	163, 167
$CO_2C_2H_5$	$C(SCH_3)=C(CN)_2$	146[a,b]	233
CN	$COCH=C(=CH_2)OCO_2C_2H_5$	155–156[a,c]	163, 167
CN	$COCH_2C(=CH_2)OCO_2C_2H_5$	102–103[a,b]	163, 167
CH_2CH_2CN	COC_6H_5	157	232
$CO_2C_2H_5$	$CONHC_6H_5$	N/A	240
$CO_2C_2H_5$	C_6H_5NHCS	N/A	240, 243
COC_6H_5	$C(SCH_3)=C(CN)_2$	250[a,b]	233

[a] IR in paper.
[b] UV in paper.
[c] NMR in paper.

and to reflect their true structure, compounds like **91** are treated in this section, although they have the same oxidation state as compounds in Section I.

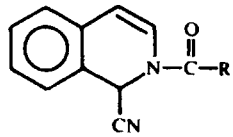


91

(*a*) *Nitriles*

The chemistry of *N*-acyl-1-1,2-dihydroisoquinaldonitriles has been the subject of comprehensive reviews.[244-245a] The application of these compounds to the synthesis of isoquinoline alkaloids has been reviewed,[246] as has their use in ring annulation reactions.[246a] Reissert compounds are covered in Tables II.1 (pages 181–188), II.2 (page 188) and II.3 (page 189) and their analogs in Table II.4 (page 190). Other nitriles derived from 1,2-dihydroisoquinolines are included in Tables II.5 (page 191), II.6 (page 192), and II.7 (page 193).

TABLE II.1. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines—Reissert Compounds



R	Substituent	m.p. (°C)	Spectroscopy	Ref.
CH_3	5-NO_2	186–187	IR, NMR	334
CH_3		119–120		247, 263, 352
		121–121.5	NMR	256
		N/A	MS	353
		N/A		249
CH_2CH_2Cl		130–131		302
CH_2CH_3		115–117		247; 352
CH_3	1-CH_3	95–96.5		281
CH_3	3-CH_3	99.5–100.5		281
		109–111		247
$CH_2CH_2CH_2Cl$		89–91		302, 354
$CH_2CH_2CH_3$		87–88		247, 352
C_3H_7-*i*		87–88		247
CH_3	1-C_2H_5	115–116		281
C_2H_5	3-CH_3	84.5–86		281
CH_3	5,7-$(OCH_3)_2$	175–194		256
C_4H_3O-2		112	IR, NMR	254
		110–111		247
C_4H_3S-2		153–154	IR, NMR	254
		150–151		302
$(CH_2)_3Cl$	3-CH_3	69–72	IR	37
$(CH_2)_4Cl$		104–106		302
C_4H_9-*n*		88–89		247
$CH(CH_3)_2$	3-CH_3	104.5–107.5		281
CH_3	1-$CH(CH_3)_2$	121.5–122		281
		N/A	NMR	332, 333
$(CH_2)_3Cl$	9-$C(SCH_3)$=S	136–138	NMR	37

TABLE II. 1. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines—Reissert Compounds (*Continued*)

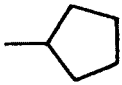
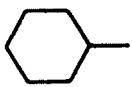
R	Substituent	m.p. (°C)	Spectroscopy	Ref.
		87–88		247
$(CH_2)_5Br$		95–96	IR	37
CH_3	1-$CH_2CH(CH_3)_2$	93–94		281
		N/A	NMR	332, 333
CH_3	3-CH_3-1-$CH(CH_3)_2$	114–114.5		281
		N/A	NMR	333
C_6H_4Cl-4	5-NO_2	199–200	IR, NMR	334
C_6H_5	4-Br	173		248
		N/A	NMR	331
C_6H_4Cl-4		155.2–155.8		269
		150–151		247
C_6H_4Cl-3		185–187		247
C_6H_4Cl-2		175.5–177.5		281
C_6H_5	4-Cl	163–165		143
C_6H_5	1-D	N/A	NMR	331
C_6H_4F-4		178–179		247
C_6H_5	5-F	179–180		271
$C_6H_4NO_2$-4		177–178		247
$C_6H_4NO_2$-3		183–184		247
C_6H_5	5-NO_2	148		248
C_6H_5	8-NO_2	181		248
C_6H_5		128–130		10, 19, 21, 22, 49, 64, 202, 213, 247, 248, 249, 254, 259, 293, 300, 301, 309, 310, 331, 355, 356–358
CH_3	2-[3-$NO_2C_6H_3N$]	227–228		311
$C_6H_4SO_3H$-3		175–176		148
C_4H_3S-2	6,7(OCH_3)$_2$	160–161	IR, NMR	254
C_4H_3S-2	6,7(OCH_3)$_2$	166–167	IR, NMR	254
		127–128		247
$CH(CH_3)_2$	1-$CH(CH_3)_2$	94–95		281
		N/A	NMR	333
$CH_2C_6H_5$		166–168		302
$C_6H_4CF_3$-4		159–160		247
C_6H_5	6,7-CH_2O_2	137–138	IR, NMR	280
		135–136		326d
		134–135		272–273
		168		359
CH_3	1-[2,4-(NO_2)$_2C_6H_3$]	193–195		311
C_6H_4Cl-2	3-CH_3	173–174.5		281
C_6H_4Cl-4	3-CH_3	122.5–124.5		281
$C_6H_4OCH_3$-4	4-Cl	152		146

TABLE II. 1. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines—Reissert Compounds (*Continued*)

R	Substituent	m.p. (°C)	Spectroscopy	Ref.
C_6H_5	3-CH_3-5-NO_2	159		248
C_6H_5	3-CH_3-8-NO_2	134		248
$C_6H_4CH_3$-4	5-NO_2	198–200	IR, NMR	334
$C_6H_4OCH_3$-4	5-NO_2	209–210	IR, NMR	334
C_6H_5	1-CH_3	120–121		265, 266
		118–120		10
		119–121		263
		N/A	MS	353
C_6H_5	3-CH_3	127–128		360
		139–140		281
		N/A	NMR	331
$C_6H_4CH_3$-4		127.5–128.5		281
		N/A	NMR	331
$C_6H_4CH_3$-2		168.5–169.5		281
$C_6H_4OCH_3$-4		175–176	NMR	256
		173–174		247, 259
		N/A		255
C_6H_5	7-CH_3O	144–146	NMR	279
$CH(CH_3)_2$	3-CH_3-1-$CH(CH_3)_2$	123.5–124.5		281
		N/A	NMR	333
C_6H_5	3-CH_3-5-CN	175		248
$CH=CHC_6H_5$		164–165		247
		160–162		263
C_6H_5	5-CO_2CH_3	121		248
C_6H_5	1-CS_2CH_3	174–176		265, 266
C_6H_4Cl-2	6,7-$(CH_3O)_2$	174–176		262
C_6H_5	1-C_2H_5	103		261
		108.5–110.5		281
$C_6H_4CH_3$-4	3-CH_3	128–129.5		281
		N/A	NMR	331
$C_6H_4CH_3$-2	3-CH_3	145–146		281
CH_3	1-$CH_2C_6H_5$	136–137.5		281
C_6H_5	6,7-$(OCH_3)_2$	156–157		361
		167–168	IR, UV, NMR	278
		159–162		325
		164	NMR	203, 254
		N/A	NMR	331
C_6H_5	7,8-$(OCH_3)_2$	158–159.5		309
		158		277
$C_6H_3(OCH_3)_2$-3,4		202.3–202.6		361
$C_6H_3(OCH_3)_2$-3,4		213–215	IR, UV	362
		N/A		249
$C_6H_3(OCH_3)_2$-2,3		132–133	IR, UV	362
C_6H_5	1-$CH_2CH=CH_2$	101–10.5	UV, NMR	329
$C_6H_3OCH_3$-4-Br-3	6,7-$(OCH_3)_2$	157–157.5		264

TABLE II. 1. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines—Reissert Compounds (*Continued*)

R	Substituent	m.p. (°C)	Spectroscopy	Ref.
C_6H_4Cl-2	1-$CH(CH_3)_2$	113–117		281
		N/A	NMR	333
C_6H_4Cl-4	1-$CH(CH_3)_2$	134.5–135.5		281
		N/A	NMR	333
C_6H_5	1-C_3H_7-*n*	120		261
		119–121		265, 266
C_6H_5	1-C_3H_7-*i*	128–130		265, 266
C_6H_5	1-$CH(CH_3)_2$	131–132.5		281
		N/A	NMR	332, 333
$C_6H_4OCH_3$-4	6,7-$(OCH_3)_2$	156.4–157.2		361
C_6H_5	5,6,7-$(OCH_3)_3$	165		276
		166–167		273
		167–168		326a
C_9H_{19}		53–55		247
$C_{10}H_7$-1		198–200		247
$C_{10}H_7$-2		165–167		247
$CH{=}CHC_6H_5$	6,7-$(OCH_3)_2$	164.8–165.4		361
C_6H_5	1-$CH_2CO_2C_2H_5$	129–131		265, 266
CH_3	1-[$CH(OCOCH_3)$ $C_6H_5NO_2-2$]	199–201	IR, NMR	363
C_6H_4Cl-2	3-CH_3-1-$CH(CH_3)_2$	180–180.5		281
		N/A	NMR	333
C_6H_5	1-C_4H_9-*n*	107		261
		106–107		266
C_6H_5	1-$CH_2CH(CH_3)_2$	84–85.5		281
		N/A	NMR	332, 333
$C_6H_4CH_3$-2	1-$CH(CH_3)_2$	121.5–123		281
		N/A	NMR	332, 333
C_6H_5	3-CH_3-1-$CH(CH_3)_2$	146–147		281
		N/A	NMR	333
$C_6H_4CH_3$-4	1-$CH(CH_3)_2$	145.5–146.5		281
		N/A	NMR	333
$C_6H_3(OCH_3)_2$-3,4	6,7-$(OCH_3)_2$	152–152.4		361
C_6H_5	4,5,6,7-$(OCH_3)_4$	136–137	NMR	184
$C_6H_3(OCH_3)_2$-2, 3	6,7-$(OCH_3)_2$	181		203
		163–165	UV	362
$C_6H_3(OCH_3)_2$-3,5	5,7-$(OCH_3)_2$	176–195		256
C_6H_5	2-[3-$NO_2C_5H_3N$]	230–231		311
$C_{10}H_7$-1	3-CH_3	198–199.5		281
C_6H_5	1-CH_2 	117–118	NMR	290
C_6H_5	1-CH_2 	125–127	NMR	290

TABLE II. 1. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines— Reissert Compounds (*Continued*)

R	Substituent	m.p. (°C)	Spectroscopy	Ref.
$C_6H_4CH_3$-2	1-$CH_2CH(CH_3)_2$	138–139.5		281
		N/A	NMR	332, 333
$C_6H_4CH_3$-2	3-CH_3-1-$CH(CH_3)_2$	183–184		281
		N/A	NMR	333
C_6H_5	6,7-$(OCH_3)_2$-1-$CH(CH_3)_2$	203–204		281
		N/A	NMR	332, 333
C_6H_5	1-$CH_2CH_2N^+Me_3$ I^-	224–225		73
C_6H_5	1-[2,4-$(NO_2)_2C_6H_3$]	163–164		311
C_6H_5	1-[4-$NO_2C_6H_4$]	N/A		261
C_6H_5	1-$CH(C_2H_3)CO_2C_2H_5$	160–161		281
C_6H_5	6,7-$(OCH_3)_2$-1-CH_2-	165–166	UV, IR, NMR	289
C_6H_5	-$CH_2CON(C_2H_5)_2$	137–138		302
C_6H_5	1-C_6H_5CO	183–184		263
C_6H_5	5-$OCOC_6H_5$	198		248
C_6H_5	1-[2-$IC_6H_4CH_2$]	150.5–151		300
		N/A	NMR	333
C_6H_5	4-$NHCOC_6H_5$	158		248
C_6H_5	1-[$CH_2C_6H_4$-NO_2-4]	203–204	NMR	310
C_6H_5	1-[2-$NO_2C_6H_4CH_2$]	143–144	UV, IR	299, 300
C_6H_5	1-$C_6H_5CH_2$	129		261
		123.5–125		281
		N/A	NMR	333
		Gum		266
		N/A		288
C_6H_5	5-$C_6H_5CH_2O$	N/A		283
C_6H_5	6,7-$(OCH_3)_2$-1-CH_2- 	169–171	NMR	290
C_6H_5	6,7-$(OCH_3)_2$-1-CH_2- 	154–155	NMR	290
$C_6H_4CH_3$-4	8-$C_6H_5CO_2$	207–207.5	IR, NMR	267
		N/A	NMR	331
$C_6H_4CH_3$-4	8-HO-1-C_6H_5CO	231–232	IR, NMR	267
C_6H_5	1-$CS_2CH_2C_6H_5$	139–141		266
C_6H_5	6-CH_3O-7-$C_6H_5CO_2$	N/A		319
C_6H_5	1-($CH_2C_6H_3NO_2$-2-OCH_3-3)	172.7–174.7		303, 304
		180–182	IR, UV, NMR	295
C_6H_5	1-[2-NO_2-4-$CH_3OC_6H_3CH_2$]	133–135		301
C_6H_5	1-[$CH_2C_6H_3$-NO_2-2-OCH_3-5]	100–138		294
C_6H_5	1-[2-$CH_3C_6H_4CH_2$]	145–147		266
		N/A	NMR	332

TABLE II. 1. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines Reissert Compounds (*Continued*)

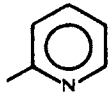
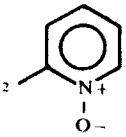
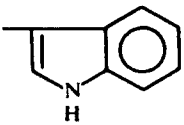
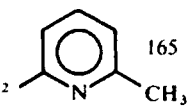
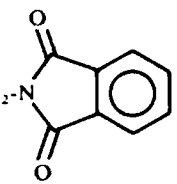
R	Substituent	m.p. (°C)	Spectroscopy	Ref.
$C_6H_4CH_3$-2	1-$CH_2C_6H_5$	150.5–152.5		281
		N/A	NMR	333
C_6H_5	7-OCH_3-8-$C_6H_5CH_2O$	135		267
		135		307
		132–133	NMR	364
		N/A		274
C_6H_5	6,7-$(OCH_3)_2$-1-CH_2- 	158		365
C_6H_5	6,7-$(OCH_3)_2$-1-CH_2- 	169–171		291
$C_{10}H_7$-1	1-$CH_2CH(CH_3)_2$	155–157		281
		N/A	NMR	333
$C_{10}H_7$-1	3-CH_3-1-$CH(CH_3)_2$	200–202		281
		N/A	NMR	333
C_6H_5	6-CO_2CH_3-7-$C_6H_5CO_2$	203	IR, UV, NMR	92
C_6H_5	6-CO_2CH_3-5-$C_6H_5CO_2$	194–195	IR, NMR	92
C_6H_5	1-CH_2- 	175–176		61
C_6H_5	1-[$CH_2C_6H_4$-$CH{=}CH_2$-4]	150.5–152.5	IR, UV, NMR	329
C_6H_5	1-[$CH_2C_6H_2$-NO_2-2-$(OCH_3)_2$-3,4]	208–209		293, 297, 298
C_6H_5	6,7-$(OCH_3)_2$-1-CH_2- 	165		292
C_6H_5	-CH_2-CH_2- 	204–205		302

TABLE II. 1. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines—Reissert Compounds (*Continued*)

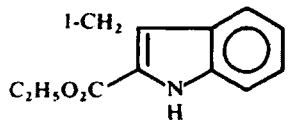
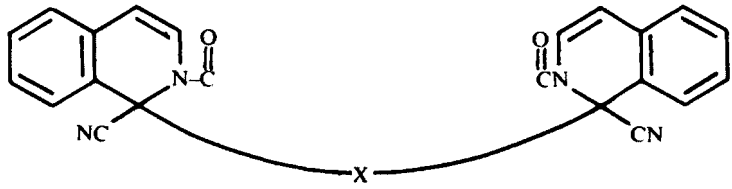
R	Substituent	m.p. (°C)	Spectroscopy	Ref.
C_6H_5	$-CH_2CH{=}CHC_6H_5$	78–80		302
$C_6H_4OCH_3$-4	7-OCH_3-8-[4-$CH_3OC_6H_4CO_2$]	86–88	IR, NMR	267
C_6H_5	7,8-$(OCH_3)_2$-1-[$CH_2C_6H_4OCH_3$-4]	196–198		309
C_6H_5	1-$CH_2C_6H_2(OCH_3)_3$-3,4,5	N/A		366
C_6H_5	1-[4-NO_2-2-*t*-$C_4H_9O_2CC_6H_3$]	166		261
C_6H_5		114–116		61
C_6H_5	6-CO_2CH_3-5-HO-1-[$CH_2C_6H_2$-$(OCH_3)_3$-3,4,5]	202–203	NMR, IR	92
C_6H_5	6-CO_2CH_3-7-HO-1-[$CH_2C_6H_2$-$(OCH_3)_3$-3,4,5]	205	UV, IR, NMR	92
C_6H_5	1-$(CH_2C_6H_4OCH_2C_6H_5$-4)	144–146		305
C_6H_5	7,8-$(C_6H_5CH_2O)_2$	N/A		284
C_6H_5	6,7-CH_2O_2-1-[3-$C_6H_5CH_2O$-4-$CH_3OC_6H_3CH_2$]	165–166	IR, NMR	280
C_6H_5	6,7-$(OCH_3)_2$-1-[5-$C_6H_5CH_2O$-4-CH_3O-2-NO_2-$C_6H_2CH_2$]	176–177	IR, UV, NMR	278
C_6H_5	5,6,7-$(OCH_3)_3$-1-[2-NO_2-3-$C_6H_5CH_2O$-4-CH_3O-$C_6H_2CH_2$]	181	NMR	276
C_6H_5	7,8-$(C_6H_5CH_2O)_2$-1-[$CH_2C_6H_2$-$(OCH_3)_3$-3,4,5]	N/A		284
C_6H_5	1-$CH_2C_6H_4$-  (polymer)	N/A	UV	329
$C_6H_4OCH_3$-4	7,8$(OCH_3)_2$	160–161		259a
$C_6H_4OCH_3$-4	5,6,7-$(OCH_3)_3$	153–154		259a
C_6H_5	6,7-Cl_2	194–196		366a
C_6H_5	2-(CH_2-C_6-$H_2(OCH_3)_3$-3,4,5)-6,7-Cl_2	193–195		366a
C_6H_5	1-(4-Picolyl)	137–138		366b
C_6H_5	1-(4-Picolyl)-6,7-$(OCH_3)_2$	192–193		366b
C_6H_5	1-Allyl	98–100		366b
C_6H_5	7-($4CH_3C_6H_7O$)	162–165		366c
C_6H_5	5-($4CH_3C_6H_4O$)	192–195		366c

TABLE II. 1. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines—Reissert Compounds (*Continued*)

R	Substituent	m.p. (°C)	Spectroscopy	Ref.
C_6H_5	1-(3-OCH_3-4-$CH_3C_6H_4$-$C_6H_3CH_2$-) 5-(4$CH_3C_6H_4O$)	72–75		366c
C_6H_5	6-OCH_3-7(4$CH_3C_6H_4O$)	94–97		366c
C_6H_5	1-(3,4-$(OCH_3)_2C_6H_3CH_2$-) 6-OCH_3-7(4$CH_3C_6H_4O$)	105–108		366c
C_6H_5	7-C_6H_5OCO	210–211		366c
C_6H_5	1-(4Br$C_6H_4CH_2$-) 7-C_6H_5OCO	180–181		366c
C_6H_5	5-Br	183–184		366c
C_6H_5	7-CH_3O-8-Br	161–162		366c
C_6H_5	1-(2-NO_2-3-$C_6H_5CH_2O$-4-$OCH_3C_6H_2CH_2$) 6,7-CH_2O_2	178–180		326d
C_6H_5	1-(2-NO_2-4-C_6H_5-$CH_2OC_6H_3CH_2$-) 5,6,7-$(OCH_3)_3$	156–157		326j
C_6H_5	6-CH_3O-7-$C_6H_5CH_2O$)	150–153		326l
C_6H_5	1-$C_6H_5CH_2$-6,7-OCH_3	153–155		259b
C_6H_5	1-(2$NO_2C_6H_4CH_2$)-6,7(OCH_3)$_2$	182–184		259b
C_6H_5	1-$C_6H_5CH_2$-5,6,7-$(OCH_3)_3$	138–139		259b
C_6H_5	1-(2$NO_2C_6H_4CH_2$)-5,6,7-$(OCH_3)_3$	127–128		259b
C_6H_5	1-C_6H_5-CH_2-6,7-CH_2O_2	146–148		259b
C_6H_5	1-(2$NO_2C_6H_4CH_2$)-6,7-CH_2O_2	177–178		259b

TABLE II.2 Bis-Reissert Compounds



R	Substituent	m.p. (°C)	Ref.
$(CH_2)_3$		130–132	302
$-CH_2-CH=CH-CH_2$		217–218	302

TABLE II.2. Bis-Reissert Compounds (*Continued*)

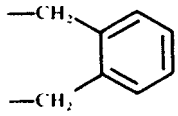
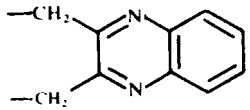
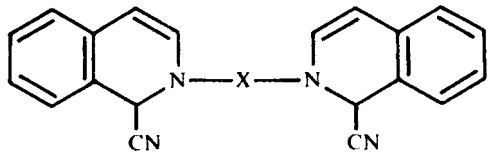
R_2	Substituent	m.p. (°C)	Ref.
		216–217	
		160–162	302
4-CH_2-C_6H_4-O-C_6H_4-CH_2-4		123–127	306
4-CH_2-C_6H_4-O-C_6H_4-CH_2-4	6-CH_3O	122–127	306
3-CH_2-($C_6H_3OCH_3$-6)-O-C_6H_4-CH_2-4		136–139	
3-CH_2-($C_6H_3OCH_3$-6)-O-C_6H_4-CH_2-4	6,7-OCH_2O	137–140	306
4-CH_2-C_6H_4-O-$C_6H_4CH_2$-4	6,7-$(OCH_3)_2$	130–133	306
3-CH_2-($C_6H_3OCH_3$-6)-O-C_6H_4-CH_2-4	6-CH_3O	129–133	306
2-CH_2-($C_6H_2(OCH_3)_2$-4,5)-O-($C_6H_3OCH_3$-6)-CH_2-3		134–136	306
2-CH_2-($C_6H_2(OCH_3)_2$-4,5)-O-($C_6H_3OCH_3$-6)-CH_2-3	6,7-OCH_2O	134–136	306
2-CH_2-($C_6H_2(OCH_3)_2$-4,5)-O-($C_6H_3OCH_3$-6)-CH_2-3	6-CH_3O	130–133	306
2-CH_2-($C_6H_2(OCH_3)_2$-4,5)-O-($C_6H_3OCH_3$-6)-CH_2-3	6,7-$(OCH_3)_2$	134–136	306
$(CH_2)_3$	6,7-$(OCH_3)_2$	84–100	366b
$(CH_2)_4$		200–201	366b
$(CH_2)_5$		185–187	366b

TABLE II.3 Bis-Reissert Compounds



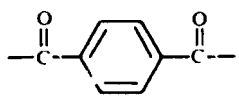
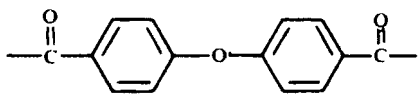
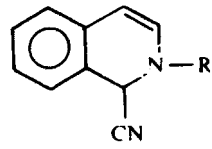
R	m.p. (°C)	Ref.
3-$SO_2C_6H_4$-3	184–185	148
$CO(CH_2)_4CO$	189–190	247, 352
	197–199	247
	140–163	366c

TABLE II. 4. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines—Reissert Analogs



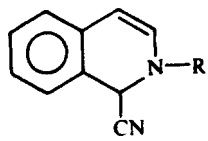
R	Substituent	m.p. (C)	Ref.
CO_2CH_3		83–85	337
$CO_2C_2H_5$		83–85[a]	338
		N/A	249
		N/A[b]	353
		84–86	337
		84–85[c]	336
$CO_2CH_2CCl_3$		104–106	337
$CO_2C_2H_5$	1-CH_3	72–73	337
		N/A[b]	353
$CO_2C_2H_5$	3-CH_3	46.5–49.5	281
$CO_2C_2H_5$	1-$CH(CH_3)_2$	66–67.5	281
		N/A[c]	333
$CO_2C_6H_5$		156–158	337
$CO_2C_2H_5^c$	3-CH_3-1-$CH(CH_3)_2$	N/A	333
$CO_2CH_2C_6H_5$		84–86	337
$CO_2C_6H_4OCH_3$-5		182–183	337
$CO_2CH_2C_6H_5$	3-CH_3	72.5–74.5	281
$CO_2CH_2C_6H_5$	3-CH_3-1-$CH(CH_3)_2$	N/A	333
$COSC_2H_5$		107–108	337
		N/A[b]	353
$CSOC_2H_5$		109–110[c]	336
$COSC_2H_5$	1-CH_3	79–81	337
	1-CH_3	N/A[b]	353
$CSOC_6H_5^c$		164	336
$CON(C_2H_5)_2$		100–102	339
$CON(C_6H_5)_2$		218–219	339
		N/A[b]	353
$-C(C_6H_5)=NC_6H_5$		HCl:277–278.5	48
		Picrate:225.5–226	48
$P(=S)(OCH_3)_2$		78–80	340
$P(=O)(OC_2H_5)_2$		60–61	340
$P(=S)(OC_2H_5)_2$		66–67	340
$P(=O)(OC_6H_5)_2$		111–113	340
$P(=O)(OC_6H_4CH_3$-4$)_2$		134–135	340
SO_2CH_3		130–132	148
$SO_2C_3H_7$-*n*		85–86	148
$SO_2C_6H_4Br$-4		119–122	148
$SO_2C_6H_5$	4-Br	149–150	148
$SO_2C_6H_4Cl$-4		93–96	148
$CON(CH_3)_2$		151–152	339a
$CON(C_6H_5)_2$	1-CH_3	161–163	339a
$SO_2C_6H_4F$-4		131–132	148

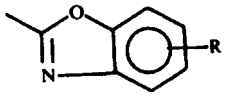
TABLE II.4. 1-Cyano-2-Acyl-1,2-Dihydroisoquinolines—Reissert Analogs (*Continued*)

R_2	Substituent	m.p. (°C)	Ref.
$SO_2C_6H_4NO_2$-4		143–146	148
$SO_2C_6H_5$		109–11[illegible]	147, 148
$SO_2C_6H_4$–CH_3-4[a]	4-Br	164	335
$SO_2C_6H_5$	3-CH_3	132–1[illegible]	148
$SO_2C_6H_5$	7-CH_3O	91–93	148
$SO_2C_6H_4CH_3$-4		101–103	148
		101[a]	335
$SO_2CH_2C_6H_5$		134–136	148
$SO_2C_6H_4OCH_3$-4		131–134	148

[a]UV, IR, and NMR in paper.
[b]MS in paper.
[c]NMR in paper.

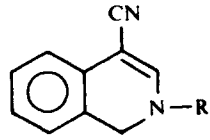
TABLE II. 5. Other 1-Cyano-1,2-Dihydroisoquinolines



R	Substituent	m.p. (°C)	Ref.
CH_3		92	342
C_2H_5		181.5–183	313
		53	342
CH_2OCH_3		63–64	344
$CH_2OC_2H_5$		51	344
NHC_6H_5		110	368
$CH_2C_6H_5$		83–84[a]	341
		81.5–83	313
		N/A	345
-$CH_2(C_6H_3(OCH_3)_2$-2,3)	6,7(OCH_3)$_2$	120–122	203
$CH_2(C_6H_3(OCH_3)_2$-3,4)	6,7(OCH_3)$_2$	117	343

[a]IR in paper.

TABLE II. 6. 4-Cyano-1,2-Dihydroisoquinoline



R	Substituent	m.p. (C)	Spectroscopy	Ref.
H		101.5–103.5	IR, UV, NMR	346
		Picrate:101.5–103.5		346
		N/A		369
CH_3		80	IR, UV, NMR	347
		N/A		346
H	1-CH_3	95–96		187
			UV	188a
H	1-CH_2OH	139–141	NMR	188
			UV	188a
Ms		130.5–131		370
H	1-CH_2CN	148–149	IR, NMR	187
$COCH_3$		156.5–157.5		369
H	1-C_2H_5	96	NMR, UV	137
		96	IR	4
		96	UV	133
		96–96.5		187
			UV	188a
CH_3	1-CH_3	80–81		187
H	1,1-$(CH_3)_2$	133–134		187
			uv	188a
H	1-$CHOHCH_3$	N/A	NMR	188
H	1-CH_3-1-CH_2OH	151–154	NMR	188
			UV	188a
H	1-CH_3SOCH_3	204–207		187
H		152 154	NMR	188
H	1-C_3H_7-*n*	75–76	UV	133
H	1-$C(CH_3)_2OH$	163–165	NMR	188
H	1-C_4H_9-*n*	64–65	UV	133
H	1,1-$(C_2H_5)_2$	113.5–114.5	UV	133
H	1-$(CH_2)_3OC_2H_5$	61–62	UV	133
H	1-C_6H_5	187–188.5	UV	133
		195–196		187
H	1,1-$(C_3H_7$-*n*$)_2$	128–129	UV	133
COC_6H_5		111–111.5		369
$CH_2C_6H_5$		120	IR, UV	134
H	1-$CH_2C_6H_5$	160–161	UV	133
Ts		142–143		370
H	1-CH_3-1-$CH_2C_6H_5$	118–120	NMR	187
H	1-$CH_2C_6H_5$-1-CH_2OH	176–178	NMR	188

TABLE II.6. 4-Cyano-1,2-Dihydroisoquinoline (*Continued*)

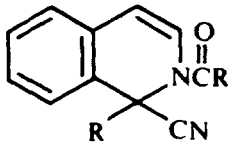
R_2	Substituent	m.p. (°C)	Spectroscopy	Ref.
Ts	1-CH_3	152–153		187
H	1,1-(C_4H_9-*n*)	b.p.:180–190 3	UV	133
COC_6H_5	1-CH_2SOCH_3	201–204		187
CH_3	1-CH_3-1-$CH_2C_6H_5$	113.5–114		187
Ts	1,1-$(CH_3)_2$	146–147		187
Ts	1-CH_2SOCH_3	186		187
H	1-CH_3-1-CH_2OTs	117.5–118.5		188a
CH_3	1=C_2H_5-1-CH_2-C_6H_5	174		187
Ts	1-C_6H_5	138–139		187
Ts	1=CH_3-1-$CH_2C_6H_5$	159–159.5		187
$CH_2C_6H_5$	1-$NHCOC_6H_5$	198		134a
$CH_2C_6H_5$	1-$NHCOC(CH_3)_3$	111		134a
$CH_2C_6H_5$	1-$NHCON(CH_3)_2$	176		134a
$CH_2C_6H_5$		105		134a

TABLE II. 7. Other Cyano-1,2-Dihydroisoquinolines

Substituent	m.p. (°C)	Ref.
2-CH-1-OH-4-Br	147	191
2-CH-1-OH	112–113	191
	118	348
2-CH-1-OCH_3	52	191
	N/A[a]	358
2-CH-1-O_2C-CH_3[a]	N/A	358
2-CH-1-OC_4H_9-*t*	97	191
2-CH-1-O-O-C_4H_9-*t*	90	191
2-CN-1,1=NC_6H_5	96	196
1-$CH(CN)_2$-2-CH=$CHCOCH_3$	111–113	350
1-$CH(CN)_2$-2CH=$CHCO_2CH_3$	132.5–137.5	351
1-CH(CN)CO_2CH_3-2-CH=$CHCOCH_3$	111–116	371
1-CH(CN)CO_2CH_3-2-CH=$CHCO_2CH_3$	110–112.5	351
1-CH(CN)CO_2CH_3-2-COC_6H_5	115	371
1-CH(CN)$CO_2C_2H_5$-2-COC_6H_5	111–112	372
2-CN-1-OCH_3		372a, b
2-CN-1-Br		372b
2-CN-1-OCH_3-5-NO_2		372b

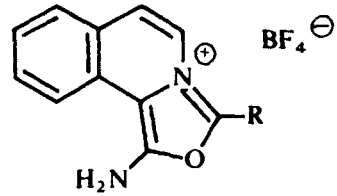
[a]NMR in paper.

Reissert compounds **92** are prepared from isoquinolines, potassium cyanide, and acid chlorides.[244, 245] on occasion, acid bromides and anhydrides have been used.[247] Generally, a methylene chloride–water solvent system is preferred[244, 245, 247, 248] but variations such as trimethylsilylcyanide–aluminum chloride[249] are sometimes used.



92 R = H

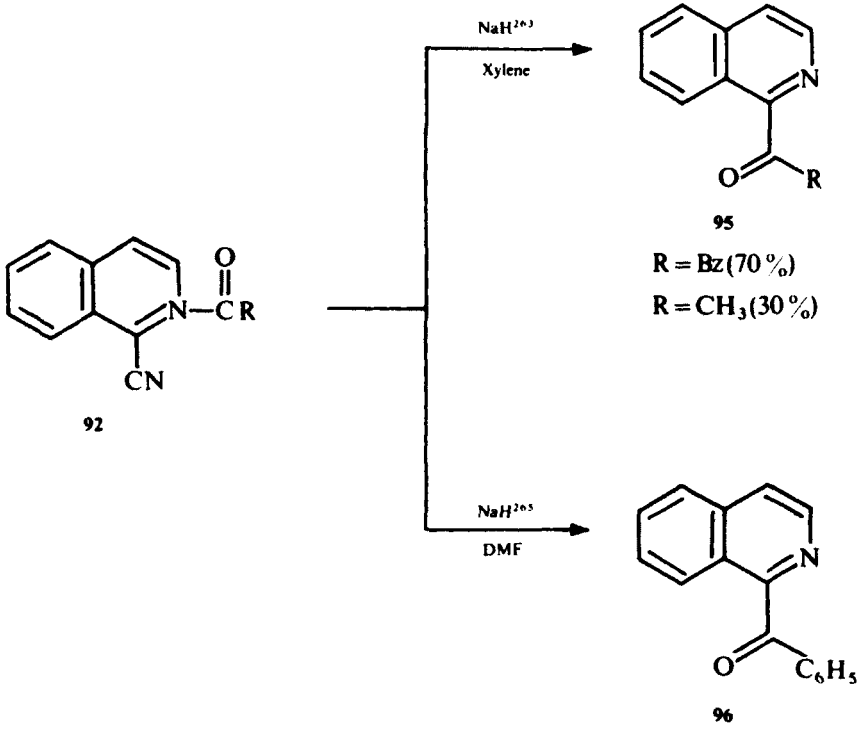
93 R = alkyl



94

Acid-catalyzed hydrolysis of Reissert compounds gives aldehydes derived from the acyl group.[244, 245, 247] Reissert salts[107, 108, 250–252] can be isolated and their structure has been studied[253–255] and shown to be **94**.[256] These have been reacted with benzhydrol,[257] 1,1-diphenylethylene,[257, 258] and vinylpyridine,[259] and so on.[109, 259a]

The 1-proton of **92** can be removed by a variety of bases,[244, 245, 259b] including sodium hydroxide or sodium hydroxide–TEBA,[260, 1] but preferably sodium hydride in dimethylformamide. The anion formed can undergo rearrangement to ketones **95** or **96**[146, 254, 262–266] (Scheme 2). It is of interest that in **97** that acyl



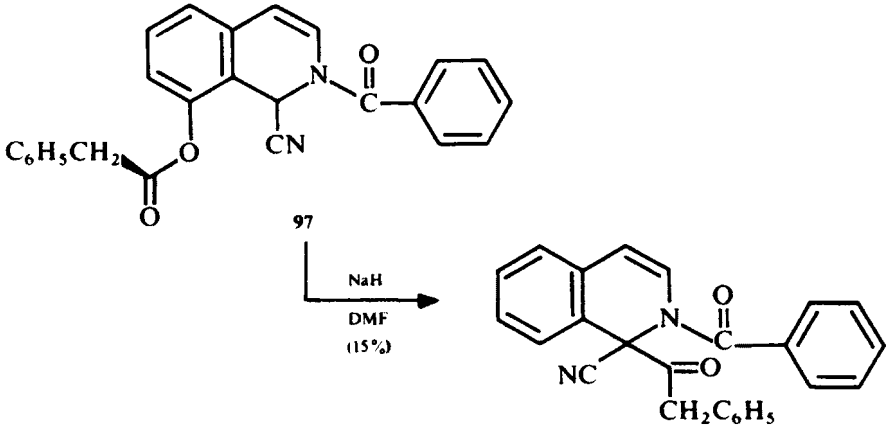
92

95

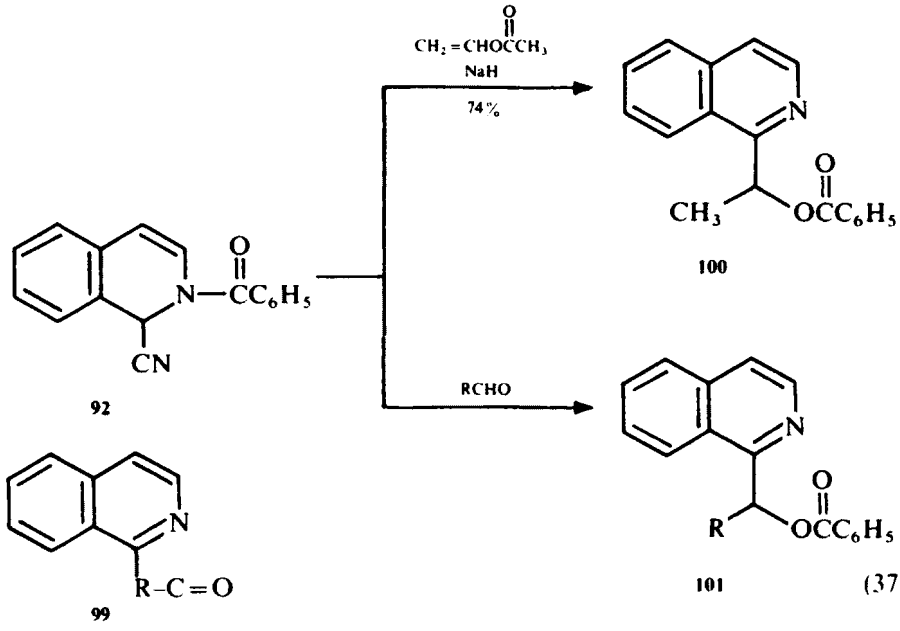
96

Scheme 2

group at C8 migrates to C-1 to provide **98**, although in poor yields[267] (Eq. 36). Rearrangement in the presence of Grignard reagents give the tertiary alcohol derived from reaction of the Grignard reagent with **99**.[268,269] In at least one case, phenyl lithium gives a similar product.[270] The anion of **92** can be alkylated to provide **93**,[61,92,184,261,262,265,266,271-310] arylated,[311,311a] can undergo the Michael condensation[106] as, for example, the reaction of **92** with vinyl acetate to afford **100**,[312] reacts with various aldehydes that rearrange to afford **101**,[254,260,262,302,313-320a] and reacts with reactive ketones,[260,302,321,322] lactones,[323] carbon disulfide,[37,266] and isocyanates[323a] (Eq. 37).

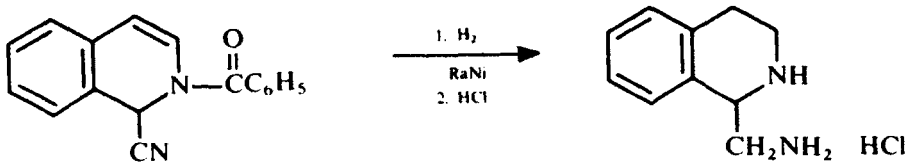


(36)



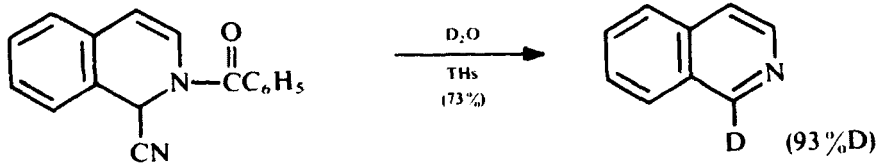
(37)

Base hydrolysis of **93** is an excellent route to 1-substituted isoquinolines. Catalytic hydrogenation of **92** provides a useful route for the preparation of 1-aminomethyltetrahydroisoquinoline **102**[324] (Eq. 38).



92 **102** (38)

A number of these reactions have been applied to the synthesis of a variety of alkaloids and alkaloid-related compounds[246] such as thalicarpine,[315-318] calycotomine,[325] armeparine,[326] O-methyldauricine,[264] and many others.[326a-e,326g-l] 1-Deuteroisoquinoline (**103**) has been obtained from **92**.[213]

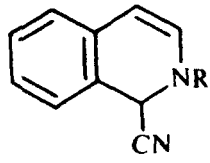


92 **103** (39)

These reactions have also been used to prepare a variety of polymeric isoquinolines.[327-330]

Oxidation of a Reissert compound gives the corresponding 1-cyano-isoquinoline.[330a] Oxidation with thallium(III) nitrate gave a tetrahydroisoquinoline derivative.[330b] Reaction with sulphuryl chloride and potassium cyanide resulted in addition to the 3,4position.[330c-e] Dichlorocarbene also adds to the 3,4position.[330f]

Various NMR studies related to the stereochemistry of **92** have been carried out.[331-334]



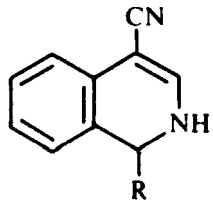
104

A number of analogs of Reissert compounds **104** R = SO_2R', CO_2R, $CONR_2'$, P(=Z) ('$OR)_2$, etc.] have been prepared from isoquinoline, cyanide ion and sulfonyl halides,[335] chloroformates,[336-338] carbamoyl chlorides,[339,339a] chlor-

ophosphates,[340] and *N*-phenylbenzimidyl chloride.[487] Alkylation of **104** ($R = CO_2R'$) proceeds as with **92**, although the reaction of the anion of **104** with aldehydes gives a tricyclic product.[337] The conversion of the cyano group of **104** ($R = CO_2R'$) to an amidoxime group takes place with hydroxylamine.[337]

The reaction of isoquinolinium salts with cyanide ion[203,341-343] or isoquinolines, alkyl halides, and cyanide ion[344,345] gives the pseudocyanides **104** (R = alkyl).

Grignard reagents react with 4-cyanoisoquinolines to give **105**.[4,133,187] 1-Substituted-4-cyanoisoquinolines react in a similar manner to give 1,1-disubstituted analogs.[133,187] The nitrogen in **105** can be alkylated or tosylated.[187] Reaction of 4-cyanoisoquinoline with phenyllithium, methyl sulfinyl carbanion, or the anion from acetonitrile also gives compounds of the type **105**[187].



105

Ultraviolet irradiation of 4-cyanoisoquinoline in the presence of propionic acid in benzene gives several products including **105** ($R = C_2H_5$),[137] while irradiation in the presence of alcohols gives **105** ($R = R'_2$ COH).[188]

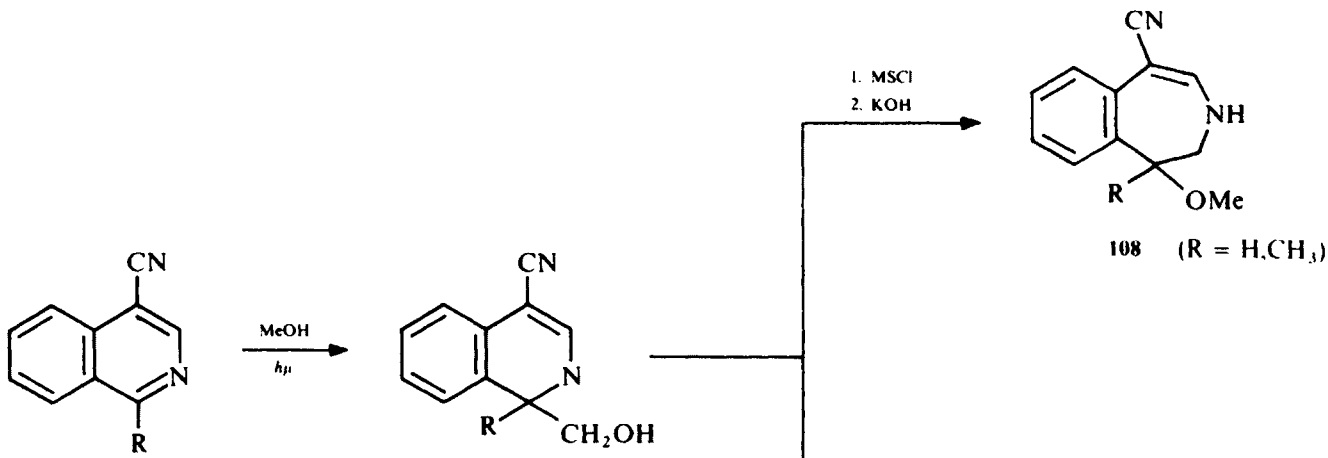
The mesylates of **107** undergo thermal ring expansion to 3H-4,5-dihydro-3-benzazepines **108** when warmed at 65°C in methanol with potassium hydroxide. Interestingly, the tosylate of **107** ($R = CH_3$) rearranges in refluxing pyridine to the dihydro-3-benzazepine **109** having an *exo*-methylene[188a] (Scheme 3).

Borohyride reduction of 4-cyanoisoquinolinium salts gives 4-cyano-*n*-substituted-1,2-dyhydroisoquinolines.[134,346,347]

Cyanogen bromide and isoquinoline[191,348] or 2-cyanoisoquinolinium fluoroborate and water[191] give 1-hydroxy-2-cyano-1,2-dihydroisoquinoline.

(2H)-dicyanomethylene isoquinoline **110**, when treated with aqueous sodium hydroxide and heated in an autoclave at 150°C for 5h, provides 1-methylisoquinoline **111** in 58% yield. The reaction of **110** with hydrazine affords 1-(3',5'-diaminopyrazolyl-4') isoquinoline **112** in 62% yield[349] (Eq. 40).

The reaction of isoquinoline with methylpropiolate and nitromethane provides mainly 1,2-dihydro-*N*-(*trans*-2-methoxycarbonylvinyl)-1-nitromethylisoquinoline **113a**.[351] Replacing nitromethane with methyl acetoacetate or cyanoacetate, acetyl acetone or malononitrile gives the corresponding derivatives **113b e**[350,351] (Eq. 41).

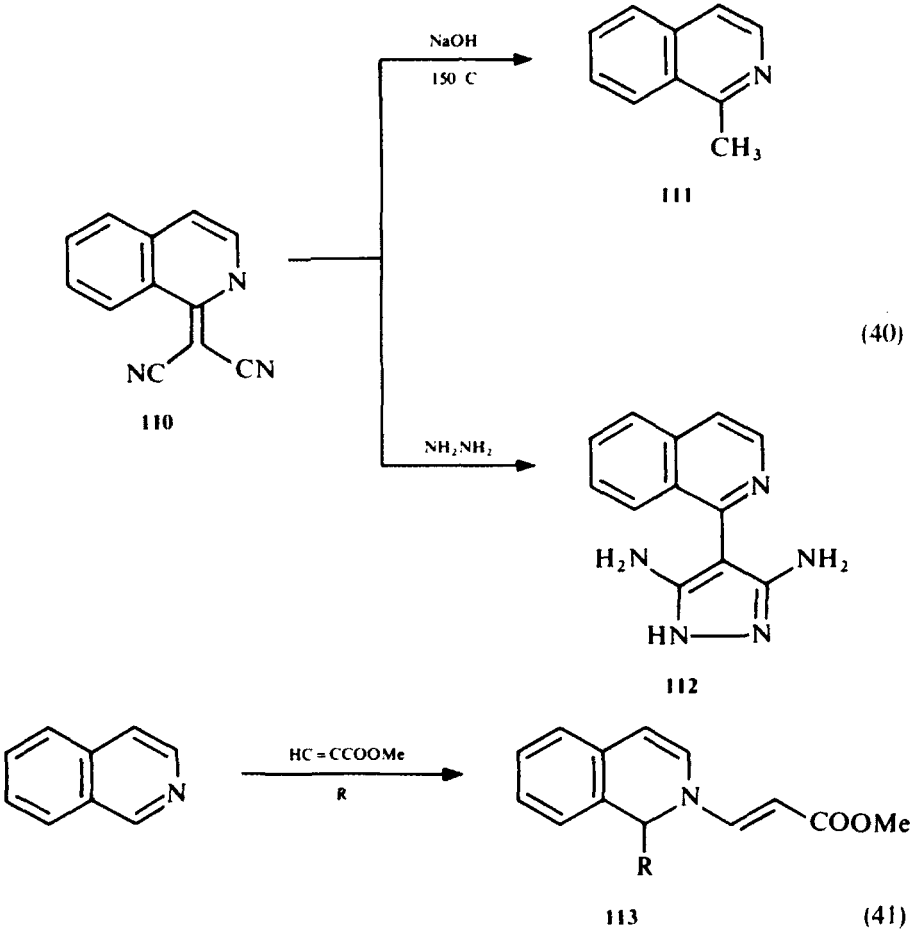


106

108 (R = H,CH_3)

109

Scheme 3



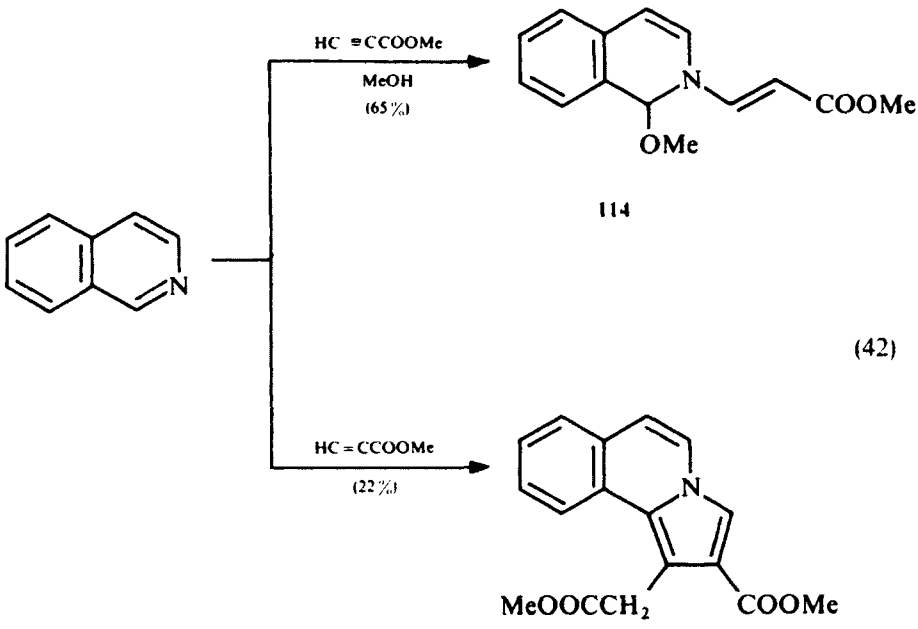
(40)

(41)

a.	CH_2NO_2	21
b.	Acetylacetone	51
c.	Methyl acetoacetone	29
d.	Methyl cyanoacetate	80
e.	Malononitrile	80

(*b*) *Other Acid Derivatives*

The reaction of isoquinoline with methyl propiolate gives, after recrystallization from methanol, **114**.[378] In the absence of methanol, isoquinoline and methyl propiolate react violently to produce the benzoindolizidine **115**[373] (Eq. 42).

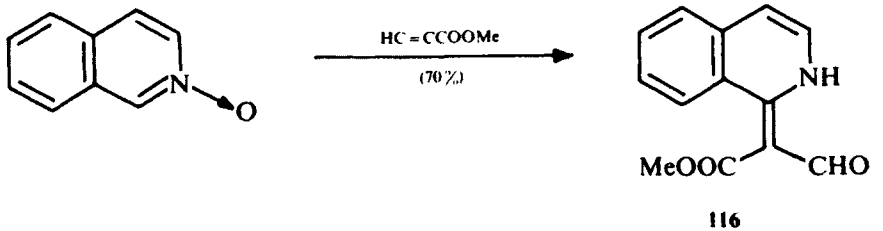


114

115

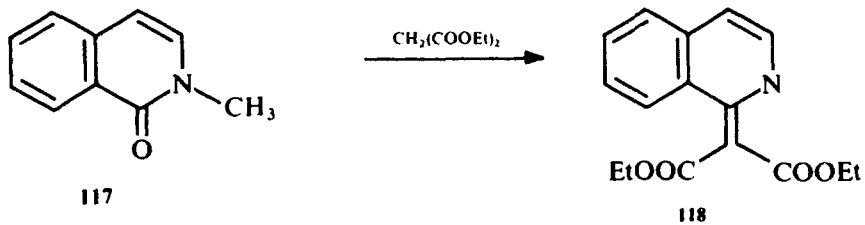
(42)

Use of isoquinoline *N*-oxide with methyl propiolate gives **116** (Eq. 43).[374] Similarly, the reaction of *N*-methyl-1,2-dihydroisoquinoline-2-one **117** with diethyl malonate affords **118**[375] (Eq. 44).



116

(43)

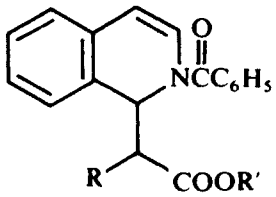


117

118

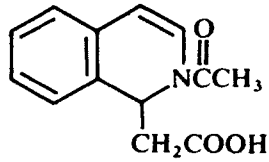
(44)

Reaction of isoquinoline, benzoyl chloride, and active methylene compounds gives **119**.[371,372] Use of acetic anhydride in place of the benzoyl chloride gives a similar product,[376] while isoquinoline and acetic anhydride alone gives **120**.[376]



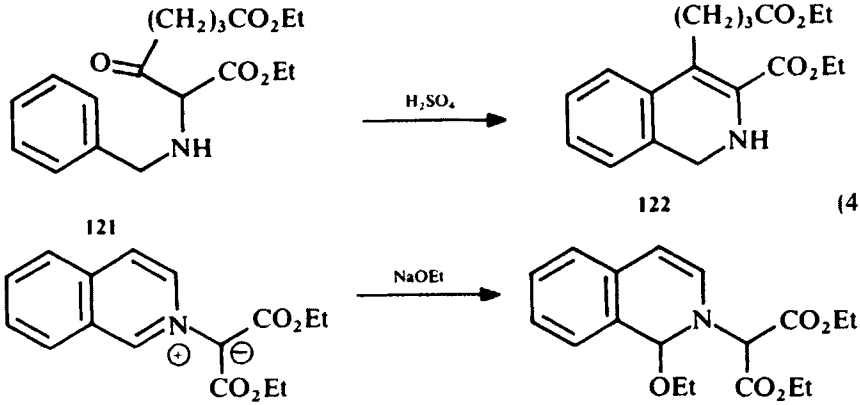
(R = CN , $COCH_3$)

119



120

A number of ring openings[43,377,378] and esterifications[376,378,379] have been used. Borohydride reduction of appropriately substituted isoquinolines has given the dihydroisoquinolines.[346,347] The reaction of **121** with sulfuric acid gives **122**[90] (Eq. 45). Reaction of the ylide **123** with sodium ethoxide gives the corresponding 1-ethoxy-1,2-dihydroisoquinolines **124**[239] (Eq. 46).



121 **122** (45)

123 **124** (46)

The above 1,2-dihydroisoquinolines are included in Table II.8 (page 203). Table II.9 (page 203), II.10 (page 205) and II.11 (page 208) include compounds of the type **91**.

A large number of isocoumarins containing various carboxylic acid functional groups have been reacted with ammonia or amines to give compounds of the type **91**.[80,117,380–391] A similar conversion of an isothiocoumarin-3-carboxylic acid has been reported.[392]

Spontaneous[79,134,347] or potassium-ferricyanide oxidation[134,215,393] of 1,2-dihydroisoquinolines leads to **91**. Catalytic hydrogenation of 4-cyano-1-hydroxyisoquinoline-*N*-oxide or reaction of benzoyl chloride and base with 4-cyanoisoquinoline-*N*-oxide leads to 4-cyanocarbostyril **91** (R = H).[140,141]

TABLE II. 8. Other Cyano-1,2-Dihydroisoquinoline Derivatives

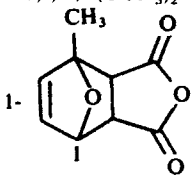
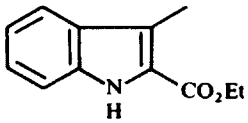
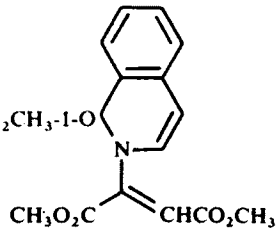
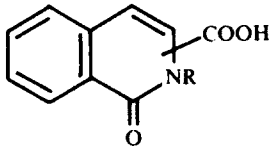
Substituents	m.p (°C)	Ref.
4-$CONH_2$[a,b]	196–197	346
4-$CONH_2$-2-CH_3[a–c]	180	347
	HCl: 227	347
	Picrate: 240	347
4-$CO_2C_2H_5$[a–c]	80–82	346
	Picrate: 140	346
1-$C(NH_2)$=NOH-2-$COCH_3$	194–196	416
	145	43
1,1=C(CHO)CO_2CH_3	N/A	374
1-CH_2CO_2H-2-$COCH_3$	165–166	376
	161–162	379
2-$CO_2C_2H_5$-1-$CONH_2$[a]	183–185	337
3-$CO_2C_3H_5$-2-CH_3	N/A	80
2-$CO_2C_3H_5$-1-$C(NH_2)$=NOH[a]	153–155	337
1-$CH_2CO_2CH_3$-2-$COCH_3$	b.p. 145–150/2	379
2-CH=$CHCO_2CH_3$-1-OCH_3[a]	101–102.5	373
2-$CH(CO_2CH_3)CH_2CO_2H$-1-OH	95–105	43
2-$CO_2C_2H_5$-1-$C(NH_2)$=$NOCO_2C_2H_5$[a]	133–134	337
1-$C(NH_2)$=NOH-2-COC_6H_5	182–183	416
1-CH(CN)CO_2CH_3-2-CH=$CHCOCH_3$	111–116	350
1-CH(CN)CO_2CH_3-2-CH=$CHCO_2CH_3$	110–112.5	351
4-$CONH_1$-(2,6$Cl_2C_6H_3CH_2$)	220	134a
1,1=$C(CO_2C_2H_5)_2$-2-CH_3	189–191	375
1-$C(CH_3)_2CO_2H$-2-$COCH(CH_3)_2$	136	378
1-CH(SH)CO_2H-2-COC_6H_5	141–142	377
1-$CH(COCH_3)CO_2CH_3$-2-CH=$CHCO_2CH_3$	95–97	351
1-$CH(CO_2C_2H_5)_2$-2-$COCH_3$[a,c]	b.p. 160–170/2	376
1-$C(CH_3)_2CO_2CH_3$-2-$COCH(CH_3)_2$	115–116	378
3-$CO_2C_2H_5$-4-$(CH_2)_3CO_2C_2H_5$	230	90
2-$CH(CO_2C_2H_5)_2$-1-OC_2H_5	145	239
1-$CH(C_6H_5)CO_2H$-2-$COCH_3$	186–187	376
1-CH_2(CN)CO_2CH_3-2-COC_6H_5	2 isomers 169–170 115	371
1-$CH(C_6H_5)CO_2CH_3$-2-$COCH_3$	144-145 2 isomers 112–113	376
1-CH(CN)$CO_2C_2H_5$-2-COC_6H_5	111–112	372
1-$CH_2CO_2C_2H_5$-1-CN-2-COC_6H_5	129–131	265, 266
1-$CH(COCH_3)CO_2C_2H_5$-2-COC_6H_5	120–122	372, 417
1-$CH(C_2H_5)CO_2C_2H_5$-1-CN-2-COC_6H_5	160–161	281
1-$CH(CO_2C_2H_5)_2$-2-COC_6H_5	86–87	372
	87	371
4-$COCO_2C_2H_5$-2-CH_3-3-($C_6H_5(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$[a–c]	146–148	79
1-  2-COC_6H_5	109–110	418

TABLE II. 8. Other Cyano-1,2-Dihydroisoquinoline Derivatives (*Continued*)

Substituents		m.p (C)	Ref.
	—1-CN-2-COC_6H_5	114–116	61
2-$C(CO_2CH_3)$=$CHCO_2CH_3$-1-O 		116 117	122
4-$CO_2C_2H_5$-1-CH_3		86–88	118a
4-$CO_2C_2H_5$-1-C_2H_5		85–86	118a
4-$CO_2C_2H_5$-1-C_3H_7		109–110	118a
4-$CO_2C_2H_5$-1-C_4H_9		Oil	118a

[a] UV in paper.
[b] IR in paper.
[c] NMR in paper.

TABLE II. 9. Carboxylic Acid Derivatives of 1,2-Dihydroisoquinoline-1-Ones



R	Substituent	m.p. (C)	Ref.
H	3-CO_2H	320	381, 419
		326–328	392
		> 300	399
		325–326	411
		318–320	407, 408
H	4-CO_2H	290	387
		N/A[b,c]	420
H	3-CO_2H-4-CH_3	335–336	54, 392, 421
CH_3	3-CO_2H	238	380
		238–240	392

TABLE II. 9. Carboxylic Acid Derivatives of 1,2-Dihydroisoquinoline-1-Ones (*Continued*)

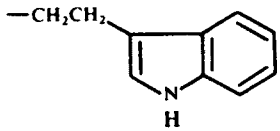
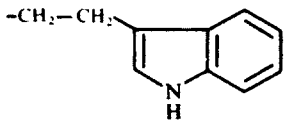
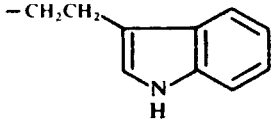
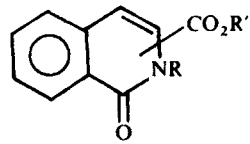
R	Substituent	m.p. (°C)	Ref.
CH_3[a,c]	4-CO_2H	262–263	396
		262	387
H	4-CO_2H-7-CH_3O	345	422
H	3-CO_2H-7-CH_3O-8-HO	315	385, 412
CH_3	3-CO_2H-5-CN	350–353	395
CH_3[a,b]	4-CO_2H-6,7-CH_2O_2	321–322	382
C_2H_5	3-CO_2H	202	380
		200–201	392
H	3-$CH(CH_3)CO_2H$	227–228	93
CH_3	3-CO_2H-4-CH_3	216–217	54b
CH_3[a,b]	4-CO_2H-7-CH_3O	263–264	382
H	3-CO_2H-6,7-$(OCH_3)_2$	313–314	385
H	3-CO_2H-5,8-$(OCH_3)_2$	274–275	385
H	3-CO_2H-7,8-$(OCH_3)_2$	257–258	392
		261	385, 402, 403
		N/A	389
CH_3	3-CO_2H-7-CH_3-O-8-OH	242–243	409
CH_3[a–c]	4-$CH{=}CHCO_2H$	260	102
H	3-$C(CH_3)_2CO_2H$	215	93
H	3-CO_2H-7-CH_3O-8-C_2H_5O	257–258	385
CH_3	3-CO_2H-7,8-$(CH_3O)_2$	198–199	392
		194–195	409
H	3-CO_2H-4,5,6-$(OCH_3)_2$	280	383
C_2H_5	3-CO_2H-7,8-$(OCH_3)_2$	128–130	392
H	4-CH_2CO_2H-5,6,7-$(OCH_3)_3$	242–244	388
$CH_2CH_2C(CH_3)(NH_2)CO_2H$		257	423
$CH_2CH_2CO_2C_2H_5$[a,b]	3-CO_2H	112–113	80
H	3-CO_2H-4-C_6H_5	325–327	97
C_6H_5	3-CO_2H	265	380
		272–273	392
C_6H_5	4-CO_2H	267	387
H	3-CO_2H-4-C_6H_5NH	250–256	407, 408
CH_3	4-CO_2H-5,6,7-$(OCH_3)_3$	220–222	382a
CH_3	4-CO_2H-6,7-$(OCH_3)_3$	311–312	382a
H	3-CH_2CO_2H-4-C_6H_5	242	386
	NH_4 salt:	217	386
$C_6H_5CH_2$	3-CO_2H	223–224	392
		207	384
$(CH_2)_3COCH_3$[a]	4-CO_2H-6,7-$(OCH_3)_2$	265–266	190
H[a,b]	4-CN-3-($CH_2C_6H_4CO_2H$-2)	243	410
$COCH(CH_3)_2$[a–c]	1-$C(CH_3)_2CO_2H$-3-CH_3	118–119	424
	3-CO_2H	206–207	390,425
		204–205	426

TABLE II. 9. Carboxylic Acid Derivatives of 1,2-Dihydroisoquinoline-1-Ones (*Continued*)

R	Substituent	m.p. (°C)	Ref.
	3-CO_2H-6,7-$(OCH_3)_2$	249.5–250	425,426
	3-CO_2H-7,8-$(OCH_3)_2$	249.5–250	390
CH_3	4-CO_2H-6,7-$(OCH_3)_2$ 3-[$C_6H_3(O_2CH_2)$-3,4]	256–258	426a

[a] IR in paper.
[b] NMR in paper.
[c] UV in paper.

TABLE II. 10. Carboxylate Derivatives of 1,2-Dihydroisoquinoline-1-Ones

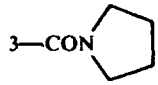
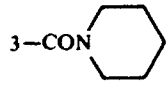
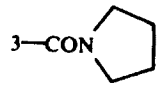
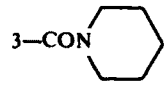
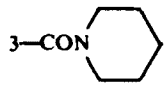
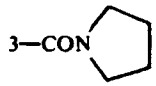
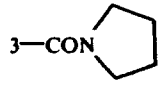
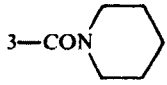


R	Substituent	m.p. (°C)	Ref.
H[a]	3-CO_2CH_3-4-OH-6 or 7-Cl	250	427
H	3-CO_2CH_3	160–161.5	428
		158–159	428a
		157–158	399
		161–162	411
H	4-CO_2CH_3	249–250	117
H[b]	5-CO_2CH_3	207–208	395
H	3-CO_2CH_3-4-OH	219–220	404
NH_2	4-CO_2CH_3	177	117
CH_3	3-CO_2CH_3	132–133	411
CH_3	4-CO_2CH_3	122–123	117
H	3-$CO_2C_2H_5$	147–148	411
H	4-$CO_2C_2H_5$	Na salt:227	387
H	3-$CO_2C_2H_5$-4-OH	194	429
		N.A.	430
H	4-CO_2CH_3-7-OCH_3	223–223.5	391
CH_3[a,c]	3-CO_2CH_3-4-OH	93–94	394
H	3-CO_2CH_3-5-OCH_3-8-OH	243–244	385
H	3-CO_2CH_3-7-OCH_3-8-OH	233	412
		233[a,b]	385

TABLE II. 10. Carboxylate Derivatives of 1,2-Dihydroisoquinoline-1-Ones (*Continued*)

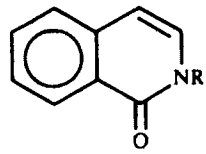
R	Substituent	m.p. (°C)	Ref.
H	3-CO_2CH_3-4-CH_3	214–216	54a
H	3-CO_2CH_3-4-C_6H_5	165–167	428a
H	3-$CO_2CH_3$4-$C_6H_5CH_3$-*p*	252–254	428a
CH_3[a,c]	3-CO_2CH_3-5-CN	132–133	395
H	3-CO_2CH_3-4-$OCOCH_3$	186–187	431
H[a]	3,5-$(CO_2CH_3)_2$-4-OH	194–196	405
H[a]	3,7-$(CO_2CH_3)_2$-4-OH	246–248	405
CH_3	4-$CO_2C_2H_5$	98	387,396
		100	347
CH_3[b,c]	3-CO_2CH_3-4-OCH_3	127–129	394
CH_3[b]	4-CO_2CH_3-7-OCH_3	147–148	382
H	3-CO_2CH_3-7,8-$(OCH_3)_2$	199	409
		198–199	385
		195	54, 402, 403
CH_3	3-CO_2CH_3-7-OCH_3-8-OH	148–149	409
H	3-$CO_2C_2H_5$-7-OCH_3-8-OH	207	385
H[a,b]	4-$CO_2C_2H_5$-3-CH_3-5,8-$(OH)_2$	256–258	95,96
R	4-C(SCH_3)=C(CN)CO_2R	N/A	432
CH_3[c]	4-CH=CHCO_2CH_3	75–76	102
H	3-$C(CH_3)_2CO_2CH_3$	163	93
H	3-$CH(CH_3)CO_2C_2H_5$	110	93
CH_3	4-$CO_2C_2H_5$-7-OCH_3	145–146	382
H	3-$CO_2C_2H_5$-7,8-$(OCH_3)_2$	179	54,402
		180	403
H[b]	4-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	280–281	190
CH_3	3-CO_2CH_3-7,8-$(OCH_3)_2$	160–161	385, 409, 412
CH_3	4-CO_2CH_3-6,7-$(OCH_3)_2$	192–193	382a
H	3-$CO_2C_2H_5$-6,8-$(OCH_2C_6H_5)_2$	163–164	96d
H	4-C(SCH_3)=C(CN)CO_2CH_3	N/A	433
CH_3	4-CH=CH$CO_2C_2H_5$	89–90	102
$CH_2CH_2CO_2C_2H_5$[a,b]	3-CO_2H	112–113	80
H	3-$C(CH_3)_2CO_2C_2H_5$	151	93
H	3-$CO_2C_3H_7$,7,8-$(OCH_3)_2$)	146	403
H	3-$CO_2C_4H_9$-7-OCH_3-8-OH	168	403
$CH_2CH_2CO_2C_2H_5$[a,b]	3-COOCO-4	151–153	80
CH_3[a,c]	5,7-$(CO_2C_2H_5)_2$-6-OH	159–161	434
H	3-$CH(CH_3)CO_2C_4H_9$-sec	Oil	93
H	3-$CO_2C_4H_9$-7,8-$(OCH_3)_2$	128	403
$CH_2CH_2CO_2C_2H_5$[b,c]	3-$CO_2C_2H_5$	Oil	80
N=CHC_6H_5	4-CO_2CH_3	132–134	117
H	3-$CO_2C_2H_5$-4-C_6H_5	148–151	97
C_6H_5	4-$CO_2C_2H_5$	118	387
$NHCONHC_6H_5$	4-CO_2CH_3	230	117
$(CH_2)_3COCH_3$[b,c]	4-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	120–121	190
H	3-$CH_2(C_6H_4CO_2CH_3$-2)-4-CN	195	410
CH_3[b]	3-CO_2CH_3-4-$OCH_2C_6H_5$	144–146	394
N=$CH(C_6H_3(OCH_3)_2$-3,4)			
	4-CO_2CH_3	187–189	117
$CH_2CH_2CO_2C_2H_5$	3,4-$(CO_2C_2H_5)$	Oil	80

TABLE II. 10. Carboxylate Derivatives of 1,2-Dihydroisoquinoline-1-Ones (*Continued*)

R	Substituent	m.p. (°C)	Ref.
$(CH_2)_3C(OCH_2)_2CH_3$[b,c]	4-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	107–108 199–200	190 79
H	3-CO_2CH_3-4-OH-6-NO_2	> 280	434a
H	3-CO_2CH_3-4-OH-7-NO_2	278–280	434a
CH_3	3-CO_2CH_3-4-OCH_3-6-NO_2	133–135	434a
CH_3	3-CO_2CH_3-4-OCH_3-7-NO_2	153–155	434a
H	3-CO_2CH_3-4-OH-8-NO_2	257–260	434a
H		213–214	428a
H		172–173	428a
H	 -4-CH_3	254–256	428a
H	 -4-CH_3	234–236	428a
H	 -4-C_6H_5	252–254	428a
H	 -4-C_6H_4-CH_3-*p*	269–271	428a
H	 -4-C_6H_4-OCH_3-*p*	258–261	428a
H	 -4-C_6H_4-OCH_3-*p*	263–266	428a

[a] UV in paper.
[b] IR in paper.
[c] NMR in paper.

TABLE II. 11. Other Derivatives of 1,2-Dihydroisoquinoline-1-Ones



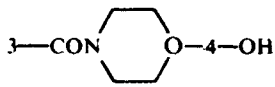
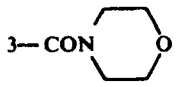
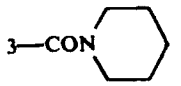
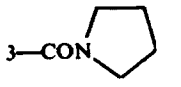
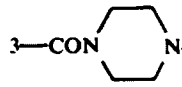
R	Substituent	m.p. (°C)	Spectroscopy	Ref.
H	4-CN	257–258		140, 141
		256–258	IR, UV	38
		258–259	IR, NMR	415
H	5-CN	275	IR, UV	395
OH	3-CN	232–234	UV, IR	406
H	3-CON_3	155		413
H	4-CON_3	150		413
H	3-$CONH_2$	276–277		400
		289		411
H	3-$CONHNH_2$	285		413
H	4-$CONHNH_2$	> 300		413
H	4-CN-6,7-CH_2O_2	> 340	NMR	415
CH_3	4-CN	198	IR, UV, NMR	347
		200–201		346
		197–199		393
NH_2	4-CN-3-SCH_3	165–167	IR, UV	435
H	3-$CONHCH_3$	227		400
CH_3	3-CO_2H-5-CN	350–353		395
H	4-CN-6,7-CH_2O_2-8-OCH_3	290–292		414
H	8-CO_2CH_3-3-CH_3-7-$OCOCH_3$	283		435a
CH_3	8-CO_2CH_3-3-CH_3-7-$OCOCH_3$	220		435a
C_2H_5	8-CO_2CH_3-3-CH_3-7-$OCOCH_3$	178		435a
C_3H_7	8-CO_2CH_3-3-CH_3-7-$OCOCH_3$	133		435a
$C_6H_5CH_2$	8-CO_2CH_3-3-CH_3-7-$OCOCH_3$	189		435a
		290–292	NMR	415
H	4-CN-3-C_2H_5	261–262		398
H	4-CN-6,7-$(OCH_3)_2$	293–294	IR	74
CH_3	4-CS_2CH_3	144	IR, UV, NMR	215
CH_3	3-CO_2CH_3-5-CN	132–133	IR, UV, NMR	395
$N{=}C(CH_3)_2$	4-CN-3-SH	221–223	IR, UV	435
H	4-CN-3-C_3H_7-*n*	221		397
CH_3	4-CN-3-C_2H_5	135–136		398
CH_3	4-CN-6,7-$(OCH_3)_2$	274–275	IR	190
CH_3	4-$CON(CH_3)_2$	160	IR, UV	134
H		324	IR, UV	217
H	4-$C(SCH_3){=}C(CO_2CH_3)CN$	N/A		433
R	4-$C(SCH_3){=}C(CO_2R')CN$	N/A		432

TABLE II. 11. Other Derivatives of 1,2-Dihydroisoquinoline-1-Ones (*Continued*)

R	Substituent	m.p. (°C)	Spectroscopy	Ref.
H	3-CONHC$_6$H$_5$	278		400
H	3-CONH$_2$-4-C$_6$H$_5$	224–226		97
CH$_2$C$_6$H$_5$	4-CN	132	IR, UV	134
CH$_3$	3-CONH(C$_6$H$_3$Cl$_2$-2,5)-4-OH	228–230		394
CH$_3$	3-CONH(C$_6$H$_4$Cl-4)-4-OH	239–241		394
CH$_3$	3-CONH(C$_6$H$_4$Cl-2(-4-OH	210–212		394
CH$_3$	3-CONH(C$_6$H$_4$Cl-3)-4-OH	228–230	IR, NMR	394
CH$_3$	4-CON(C$_2$H$_5$)$_2$	136	IR, UV	134
CH$_3$	3-CONH(C$_6$H$_3$Cl$_2$-2,4)-4-OH	233–234		394
CH$_2$CO$_2$H	H	245–247		433a
CH$_3$	3-CONH(C$_6$H$_4$NO$_2$-4)-4-OH	246		394
-(CH$_2$)$_3$COCH$_3$	4-CN-6,7-(OCH$_3$)$_3$	191–192	IR, NMR	190
(CH$_2$)$_3$COCH$_3$	4-CONH$_2$-6,7-(OCH$_3$)$_2$	257–258	IR	190
CH$_3$	3-CONHC$_6$H$_5$-4-OH	195–197		394
H	4-CN-3-(CH$_2$C$_6$H$_4$CO$_2$H-2)	240	UV	401
		243	IR, NMR	410
H	3-CON=CH(C$_6$H$_4$CO$_2$H-2)	251–253		400
CH$_3$	3-CONH(C$_6$H$_4$CF$_3$-3)-4-OH	196–199		394
H	4-CN-3-(C$_6$H$_4$OCH$_3$-2)-8-OCH$_3$	304–306	UV, IR, NMR	437
CH$_3$	3-CONH(C$_6$H$_4$CH$_3$-3)-4-OH	208–209		394
CH$_3$	3-CONH(C$_6$H$_4$CH$_3$-4)-4-OH	207–209		394
CH$_3$	3-CONH(C$_6$H$_4$OCH$_3$-2)-4-OH	177–180		394
H	4-CN-3-(CH$_2$C$_6$H$_4$CO$_2$CH$_3$-2)	195		410
H	3-CONH(CH$_2$)$_3$NH$_2$-4-(C$_6$H$_4$Cl-4)	188–190		438
-(CH$_2$)$_3$C(OCH$_3$)$_2$				
CH$_3$	4-CN-6,7-(OCH$_3$)$_2$	161–162	IR, NMR	190
H	3-CONH$_2$-4-CH$_3$	331–332		54a
CH$_3$	3-COCl-4-CH$_3$	97–98		54b
CH$_3$	3-CONH(CH$_2$)$_2$-N(CH$_3$)$_2$-4-CH$_3$	104–105		54b
CH$_3$	3-CONH(CH$_2$)$_2$-N(C$_2$H$_5$)$_2$-4-CH$_3$	86–87		54b
CH$_3$	3-CONH(CH$_2$)$_3$-N(CH$_3$)$_2$-4-CH$_3$	68–72		54b
CH$_3$		155–156		54b
CH$_3$		136–137		54b
CH$_3$		141–142		54b
CH$_3$		150–151		54b

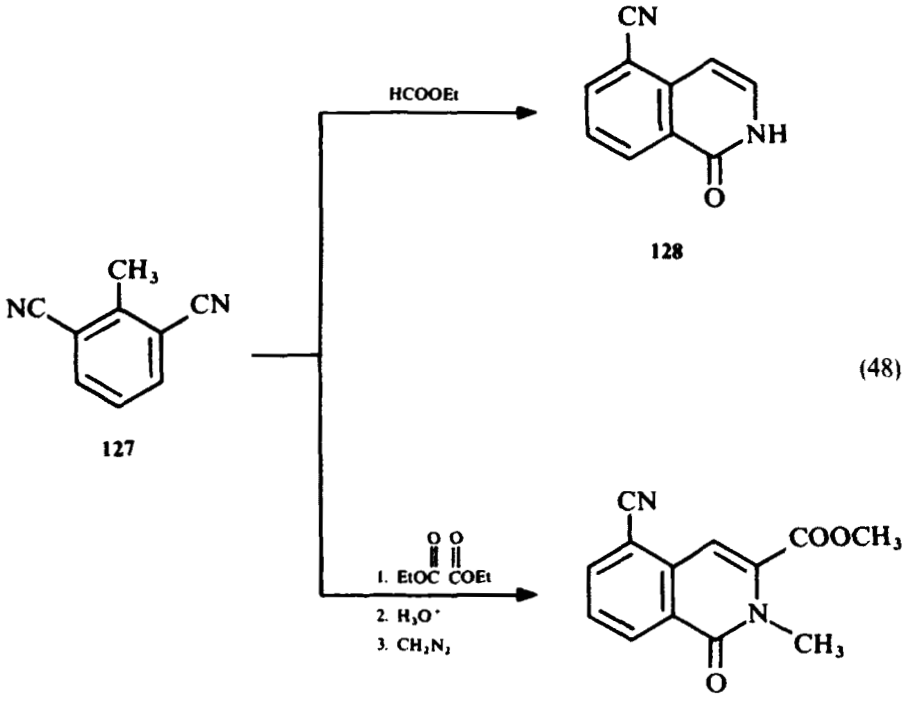
1-Chloro-[54] and 1-methoxy-[16] isoquinoline-3-carboxylic acids have been reacted with alcohols to give 3-carboxylate derivatives of **91**.

The reaction of 2-methyl-4-hydroxyisocarbostryl **125** with aryl isocyanates in the presence of NaH-hexamethylphosphoramide provides 4-hydroxy-2-methyl isocarbostyril-3-carboxanilides **126** in poor to moderate yields[394] (Eq. 47).

125 **126**

(47)

The condensation of 2-methylisophthalonitrile **127** with ethyl formate in the presence of potassium *t*-butoxide yields *5*-cyanoisocarbostyril **128**. Similarly, condensation with ethyl oxalate followed by mild basic hydrolysis and diazomethane treatment provides 2-methyl-3-carbomethoxy-5-cyanoisocarbostyril **129**[395] (Eq. 48).



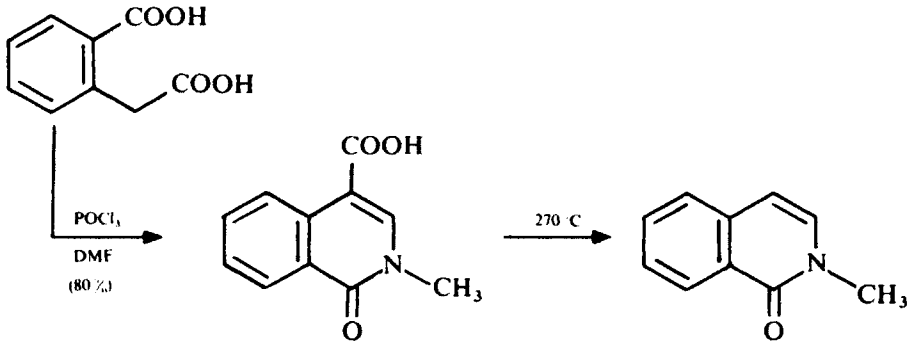
128

127

129

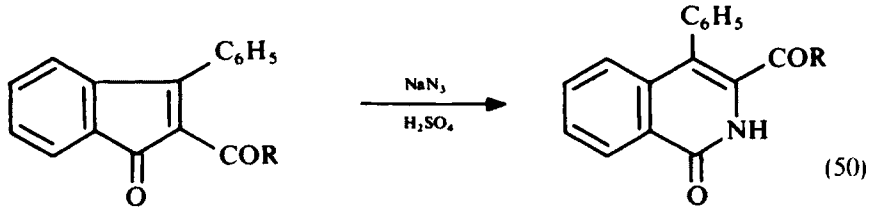
(48)

The reaction of homophthalic acid with the Vilsmeier reagent (DMF/$POCl_3$) at 100 °C provides an 80% yield of 2-methyl-4-carboxy-1(2H)isoquinoline **130**, which is quantitatively decarboxylated to give 2-methyl-1(2H)isoquinoline **131**[382,396] (Eq. 49). A variety of other cyclizations based on *o*-disubstituted benzenes have been used in this series.[93,397-401]



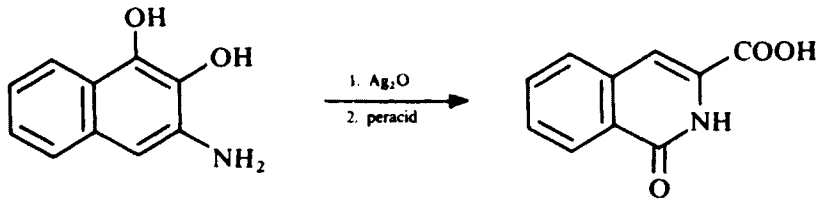
130 **131** (49)

The reaction of **132** with sulfuric acid and sodium amide gives **133**[97] (Eq. 50).



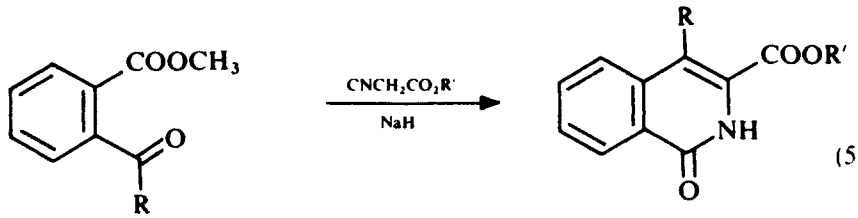
132 (R = NH_2,OEt) **133** (50)

Treatment of 2-phenyl-4-benzylidene-5-oxazolones[385,402,403] or phthalimidoacetates[404,405] with base gives rise to 3-carboxylic acid derivatives of **91**. Other cyclization[74] and rearrangement[406] reactions have been used, including treatment of **134** with silver oxide and then a peracid to give **135** (Eq. 51).[407,408]



134 **135** (51)

The reaction of isocyanides with methyl 2-formylbenzoate **136** in the presence of sodium hydride in DMF at 30–40 °C gives the isocarbostyril-3-carboxylates **137** in moderate yields[428a] (Eq. 52).



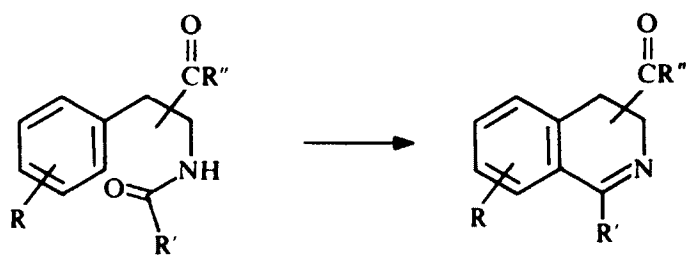
(52)

136 **137**

A variety of reactions, such as esterification,[80,102,382,385,396,399,403,409-411] ester hydrolysis,[93,97,190,385,387,391,395,409,412] and nitrile hydrolysis,[190,395] have been reported for the preparation of derivatives of **135**. Esters have been converted to amides[217] and hydrazides.[413] These latter compounds have been converted to azides and subjected to the Curtiss rearrangements.[413] The nitrogen in **91** (R = H) has been substituted by reaction with a variety of alkyl halides.[190,394] Heating of the 5,8- or 7,8-dimethoxy-3-carboxylic acid derivatives of **91** leads to the formation of the 5- or 7-methoxy-8-hydroxy-3-carbomethoxy derivative.[385,409,412] 4-Bromo derivatives of **91** have been reacted with cuprous cyanide to give 4-cyano derivatives.[393,414,415]

B. 3,4-Dihydroisoquinoline Derivatives

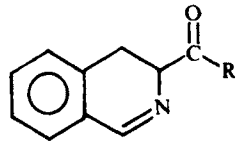
A large number of 3,4-dihydroisoquinolines containing acidic functional groups, particularly in the 1 and 3 positions and in the side chain, have been prepared by the Bischler–Napieralski reaction or some modification of it. Thus, amides of type **138** are cyclized to **139** with reagents such as phosphorus oxychloride, phosphorus pentoxide, polyphosphate ester, phosphorus pentachloride, or mixtures of the reagents.[15,17,18,84-86,92,132,439-489] (Eq. 53).



(53)

138 **139**

TABLE II.12. 3,4-Dihydroisoquinolines with Acidic Function on 3 Position



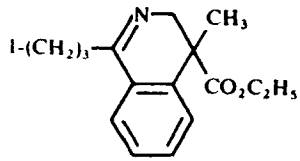
Substituent	m.p. (°C)	Ref.
3-CO_2H-1-CH_3-6,7-$(OH)_2$	N/A	514
3-CO_2R-1-R'-6,7$(OH)_2$	N/A	514, 515
3-CO_2H-1-CH_3-6,7-CH_2O_2	HCl: 230	473
3-CO_2H-1,3-$(CH_3)_2$	241–242	456
	HCl: 179–180	456
3-$CONH_2$-1,3-$(CH_3)_2$	137	504
	Picrate: 186–187	504
3-$CONHNH_2$-1,3-$(CH_3)_2$	164–165	508
3-CO_2H-1-C_2H_5-3-CH_3	171–172	458
3-CO_2CH_3-1,3-$(CH_3)_2$	Picrate: 182–183	455
3-CO_2H-1-CH_3-6,7-$(OCH_3)_2$	HCl: 205	473
3-$CO_2C_2H_5$-1-CH_3-6,7-CH_2O_2	96–97	473
	HCl: 194	473
	($N^+CH_3I^-$) 173	473
3-$CO_2C_2H_5$-1,3-$(CH_3)_2$	b.p.: 132–134/2-3	456
3-CO_2H-1-C_3H_7-*n*-3-CH_3	154–155	458
3-CO_2CH_3-1,3-$(CH_3)_2$-6,7-(OCH_3)-DL	101–103	450, 471
	HCl: 193–195	471
	($N^+CH_3I^-$) 215–217	471
	-L b.p.: 163–165/0.5	471
	HCl: 213–215	471
	-D 65–67	471
3-CO_2CH_3-1-SCH_3	HCl: 209–211	471
	141	508a
3-$CO_2C_2H_5$-1-CH_3-6,7-$(OCH_3)_2$	103	473
	Picrate: 189	85
	HCl: 155–160	473
3-$CO_2C_2H_5$-1-C_2H_5-3-CH_3	b.p.: 154–155/4–5	458
3-$CO_2C_2H_5$-1-C_3H_7-*n*-3-CH_3	b.p.: 160–165/4–5	458
3-CO_2CH_3-1-C_6H_5-6-OCH_3[a]	oil	479
3,3-$(CO_2C_2H_5)_2$-1-CH_3-6,7-CH_2O_2[b]	106	473
3-$CONHCH_2CH_2N(C_2H_5)_2$-6,7-CH_2O_2	Oxalate: 206–207	505
3-CO_2CH_3-1-C_6H_5-6,7-CH_2O_2	140.5	463
3-CO_2H-1-$CH_2C_6H_5$-3-CH_3	139–140	458
3-CO_2H-1-C_6H_5-6,7-$(OCH_3)_2$[a]	HCl: 205	479
3-CO_2H-1-C_6H_5-7-OH-6,8-$(OCH_3)_2$	196	474
	Picrate: 234–235	474
3-$CONHNHSO_2C_6H_5$-1,3-$(CH_3)_2$	202–203	508
3,3-$(CO_2C_2H_5)_2$-1-CH_3-6,7-$(OCH_3)_2$[b]	110	473
3-$CO_2(CH_2)_2N(C_2H_5)_2$-1,3$(CH_3)_2$[b]	b.p: 200–202/7–8	503
	Dipicrate: 112	503
3-CO_2CH_3-1-$(C_6H_3O_2CH_2$-3,4)-6,7-CH_2O_2	140–141	463

TABLE II.12. 3,4-Dihydroisoquinolines with Acidic Function on 3 Position (*Continued*)

Substituent	m.p. (°C)	Ref.
3-CO_2CH_3-1-C_6H_5-6,7-$(OCH_3)_2$	119.5–121	454
	122.5	463
3-$CO_2C_2H_5$-1-$ClCH_2$-3-CH_3[a]	120.5–121.5	15
	120[a]	479
	119–120[a]	443
	55–56 IR, NMR	508b
	HCl: 277–278	
3-$CO_2C_2H_5$-1-$(CH_2)_2CO_2C_2H_5$-6,7-$(OCH_3)_2$[b]		
($N^+CH_2C_6H_5$ I^-)	155–156	485, 516
($N^+CH_2C_6H_5$ Cl^-)	160–161	485, 516
3-$CO_2C_2H_5$-1-$CH_2C_6H_5$-3-CH_3	b.p.210–212/8–9	458
	94–95	458
3-CO_2CH_3-1-C_6H_5-3-CH_3-6,7-$(OCH_3)_2$-DL	105–107	471
	HCl: 172–173	471
3-$CO_2C_2H_5$-1-C_6H_5-6,7-$(OCH_3)_2$	Picrolonate: 193	84
3-CO_2CH_3-1-$CH_2CH_2C_6H_5$-6,7-CH_2O_2	111	463
3,3-$(CO_2C_2H_5)$-1-CH_3-6-$N(CH_2CH_2Cl)_2$	85–95	461
3-$CO_2C_2H_5$-3-CH_3-1-CH_2CH_2-N⟨cyclohexyl⟩	Picrate: 172	517
3-CO_2CH_3-6-OCH_3-1-CH_2-N⟨phthalimido⟩	202–204	476, 482, 483
3-CO_2CH_3-1-$CH_2C_6H_5$-3-CH_3-6,7-$(OCH_3)_2$-DL	HCl: 222–224	471
3-CO_2H-1-$CH_2CH_2(C_6H_4Cl$-4)-3-CH_3-6,7-$(OCH_3)_2$	N/A	450
3-CO_2H-1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	140	488
	147	17
	142–145	518
	147–148	81
3-CO_2CH_3-1-$CH{=}CH(C_6H_4Cl$-4)-3-CH_3-6,7-$(OCH_3)_2$	150–153	450, 471
	HCl: 224–228	471
(N^+CH_3 I^-)	177–180	471
3-$CO_2C_2H_5$-1-$CH_2CH_2C_6H_5$-6,7-$(OCH_3)_2$	N/A	470
3-CO_2CH_3-1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	125–126	488
	137–139	81
	125–128	18
3-$CO_2C_2H_5$-1-$(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	144–145	18
	HCl: 205–207	471
3-$CO_2C_2H_5$-1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	115	17
	HCl: 205–207	471
3-CO_2 laurate-1-CH_3-6,7-$(OH)_2$	N/A	514
3-CO_2CH_3-1-$CH{=}CH(C_6H_5(CH_3)_2$-3,4)-3-CH_3-6,7-$(OCH_3)_2$	130–135	471
3-CO_2CH_3-1-$CH_2(C_6H_3OC_2H_5$-4-OCH_3-3) -6-OCH_3-7-OC_2H_5	149–150	81

TABLE II.12. 3,4-Dihydroisoquinolines with Acidic Function on 3 Position (*Continued*)

Substituent	m.p. (°C)	Ref.
3-$CO_2(CH_2)_2N(C_2H_5)_2$-1-$CH_2C_6H_5$-3-CH_3[b]	b.p.: 215–216/2	503
3-CO_2CH_3-1-$CH_2(C_2H_5(OC_2H_5)_2$-3,4)-6,7-$(OC_2H_5)_2$	108–109	81
3-$CO_2C_2H_5$-3-CH_3	chloroplatinate: 241–242	517



[a] IR, NMR in paper.
[b] UV in paper.

TABLE II.13. 3,4-Dihydroisoqunolines with Acidic Function on Ring Positions other than 3

Substituent	m.p. (°C)	Ref.
4-CN-1,3-$(C_2H_5)_2$[a]	86–87	133
1-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	78–79	506
	79–80	86, 440, 494
	81.5–83	481
(N^+CH_3 I^-)	142	507
4-CN-1,3-$(C_3H_7$-*n*$)_2$[a]	86–87	133
4-$CO_2C_2H_5$-1-C_2H_5-6,7-$(OCH_3)_2$	b.p.: 150/0.01	486
	HCl: 228–230	486
1-$CONHC_6H_5$-6,7-$(OCH_3)_2$	Tartrate: 182	507
1-$CONHCH_2CH_2C_6H_5$	HCl: 191–193	448
	Picrate: 167–168	448
4-CN-1,3$(C_4H_9$-*n*$)_2$[a]	b.p.160–165/3	133
1-$CONHCH_2C_6H_5$-6,7-$(OCH_3)_2$[b]	159	507
	HCl: 222	507
1-CONH$(CH_2)_3$-N O-6, 7-$(OCH_3)_2$	137	507
	HCl: 175	507
(N^+CH_3 I^-)	243	507
1-$CONH(CH_2)_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$CH_2O_2$	145–157	506
	HCl: 167	506
7-CO_2CH_3-1-$CH_2(C_6H_2(OCH_3)_3$-3,4,5)-6-OH	HCl: 122–126	92
1-$CONH(CH_2)_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	146–147	506
	Picrate: 178	506

[a] UV in paper.
[b] IR in paper.
[c] NMR in paper.

TABLE II.14. 3,4-Dihydroisoquinolines with Acidic Function in Side Chain

Substituent	m.p. (°C)	Ref.
1-CH_2CONH_2	198–200	519
	HCl: 187–191	500
	HCl: 195–197	210
	HBr: 186–187	500
1-$CH_2CONHNH_2$	212	490
	HCl: 220	490
1-CH_2CN-6,7-CH_2O_2	187	449
1-$CH{=}CHCO_2H$	160–165	520
1-CH_2CN-3-CH_3	93–94	132
1-$CH_2CO_2CH_3$	b.p: 170/3	490
	HCl: 144	490
	Picrate: 153–154	490
($N^+CH_3I^-$)	178	490
2-$CH_2CH_2CONH_2$ Br^-	172	510
1-CH(CN)CH_3-6,7-(CH_2O_2)	Picrate: 178	449
2-$C(CO_2CH_3){=}CH\text{-}O^-$	144–145[a–c]	521
1-$C(CN){=}NOH$-6,7-$(OCH_3)_2$	210[a,c]	501
1-$(CH_2)_3CN$	bp: 154/0.8	58
1-CH_2CN-5,6-$(OCH_3)_2$	200–202[a,b]	475
1-CH_2CN-6,7-$(OCH_3)_2$	173	446, 501a, 501c
	HCl: 205–206	446
	Picrate: 225	446
1-$CH_2CO_2C_2H_5$	b.p: 138–140/0.13	491
	b.p.: 123–126/0.2	492
	b.p.: 156–158/1	490
	HCl: 107	
	Picrate: 134	490
1-$C(CONH_2){=}NOH$-6,7-$(OCH_3)_2$	238[a,b]	501
1-CH_2CONH_2-6,7-$(OCH_3)_2$	HCl: 203	500, 501c[a]
2-CH_2CONH_2-6,7-$(OCH_3)_2$ Cl^-	225	510
1-$CH_2CO_2C_2H_5$-6,7-CH_2O_2	146	445
	144–146	464
1-CH(CN)CH_3-6,7-$(OCH_3)_2$	Picrate: 186	449
2-$CH_2CH_2CONH_2$-6,7-$(OCH_3)_2$ Br^-	205	510
2-CH_2CONH_2-6,7,8-$(OCH_3)_3$ Cl^-	182	510
1-$(CH_2)_3CONHNH_2$-3-CH_3	Picrate: 173–174	447
1-$C(CN){=}NOH$-6,7-$(OC_2H_5)_2$	212	501
1-$(CH_2)_3$CN-6,7-$(OCH_3)_2$	HCl: 168–169	498
1-$(CH_2)_4CO_2CH_3$	b.p.: 179–180/1	522
1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	80–82	509
	86	445
	85.5–86.5	441
	84–85	442,495
	b.p.: 130/0.4	442
	HCl: 163–164	495
	Picrate: 161–163	442
	Picrate: 170–171	509
	HBr: 160	509

TABLE II.14. 3,4-Dihydroisoquinolines with Acidic Function in Side Chain (*Continued*)

R_2	Substituent	m.p. (°C)	Ref.
1-$CH_2CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		Oxalate: 111–112	444
		N/A	480
1-$(CH_2)_3CO_2H$-6,7-$(OCH_3)_2$		128–129[c]	493
		HCl: 258–261	493
		HCl 197–198	498
1-CH(OH)CH(OH)CO_2CH_3-6,7-$(OCH_3)_2$		HCl: 162–163[c]	451
2-$CH_2CH_2CONH_2$-6,7,8-$(OCH_3)_3$	Br^-	201	510
1-$C(CO_2C_2H_5)$=NOH-6,7-$(OCH_3)_2$		217	501
1-CH_2CONHN=CH$(C_4H_3O$-2$)_2$		275	490
1-$C(=CH_2)CO_2C_2H_5$-6,7-$(OCH_3)_2$		180–181	509
1-$(CH_2)_4CO_2C_2H_5$		b.p.: 184–185/1[a]	522
1-$(CH_2)_3CO_2C_2H_5$-3-CH_3		b.p.: 170–171/2–3[a, b]	447
1-$CH_2CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$		Oxalate: 112–113	444
	$(N^+CH_3I^-)$	149–151[c]	444
1-CH$(CH_3)CO_2C_2H_5$-6,7-$(OCH_3)_2$		HI: 155	495
	$(N^+CH_3I^-)$	155–156	495
1-$CH_2CH_2CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		HCl: 119–121	459
1-$CH_2CO_2C_2H_5$-6,7,8-$(OCH_3)_3$		120	445, 464
1-$(C_6H_4CO_2H$-2$)$-6,7-CH_2O_2		175	523
1-C(CN) $(CH_2CH_2CN)_2$		98–99.5	499
1-$CH_2CH(CF_3)CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		Oxalate: 128	469
		HCl: 192	459,469
1-$(CH_2)_6CO_2CH_3$		b.p.: 186–188/1	522
1-$C(C_2H_5)_2CO_2C_2H_5$		81–82[a]	468
1-$(CH_2)_3CO_2C_2H_5$-6,7-$(OCH_3)_2$		68–69[a]	465
		73–74	498
		HCl: 127–128	498
		HCl: 124–125	439
		Picrate: 172–173.5	439
	$(N^+CH_3I^-)$	171	498
1-$CH_2CH(CH_3)CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		b.p.: 215–218/0.075	452
		98.5–99.5	452
		Chloroplatinate: 161–162	452
		Oxalate: 136–138	469
		Oxalate: 139–140	459
1-CH(OH)CH(OH)CO_2CH_3-6,7-$(OC_2H_5)_2$		HCl: 174.5–175[a, c]	451
1-$CH(C_2H_5)CO_2C_2H_5$-6,7-$(OCH_3)_2$		HI: 130–132	496
1-CH_2CONHN=CHC_6H_5		205–210	490
1-CH_2CONHN=CH$(C_6H_4OH$-2$)$		188–190	490
2-$CH_2CONHC_6H_5$-1-CH_3	I^-	227–230	436,513
1-$CH(CO_2C_2H_5)CH_2CH_2CN$-6,7-$(OCH_3)_2$	$(N^+CH_3I^-)$	154–155	498

TABLE II.14. 3,4-Dihydroisoquinolines with Acidic Function in Side Chain (*Continued*)

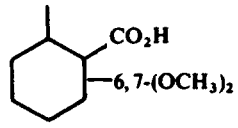
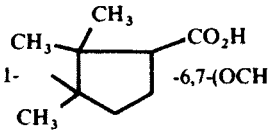
R_2	Substituent	m.p. (°C)	Ref.
1-CH(CH_2=CH-CH_2)$CO_2C_2H_5$-6,7-$(OCH_3)_2$		HBr: 137–138	496
1- 	($N^+CH_3I^-$)	201–202	487
1-$(CH_2)_6CO_2C_2H_5$		b.p.: 187–190/1[a]	522
1-$(CH_2)_3CO_2C_2H_5$-3-C_3H_7		b.p.: 94–95/0.1	462
1-$(CH_2)_4CO_2C_2H_5$-6,7-$(OCH_3)_2$		58–59[a]	467
		Picrate: 98–99	467
1-CH_2CH(C_3H_7)CH_2CO_2H-6,7-$(OCH_3)_2$		Picrate: 179–181	478
1-C(CN)=CHC_6H_5-6,7-CH_2O_2		180	449
		HCl: 204	449
1-$CH_2(C_6H_4$CN-4)-6,7-$(OCH_3)_2$		HCl: 209–211	460
		Picrate: 200–202	460
1-$CH_2CONHCH_2CH_2C_6H_5$		160–161	457
	($N^+CH_2C_6H_5Cl^-$)	160–161	485
	($N^+CH_2C_6H_5I^-$)	155–156	485
	($N^+CH_2C_6H_5I^-$)	155–156[b]	516
	($N^+CH_2C_6H_5Cl^-$)	160–161[b]	516
1-CH_2CH(C_3H_7)$CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		HCl: 177–178	478
		Oxalate: 125–127	459, 469
1-C(CN)=CH(C_6H_3)$_2CH_2$-3,4)-6,7-CH_2O_2		268–269	449
		HCl: 265	449
1-C(CN)=CH(C_6H_3-OH-3-OCH_3-4)-6,7-CH_2O_2		250	449
		HCl: 254	449
1-$CH(CO_2CH_3)$CH(C_6H_5)CH_3		b.p.: 232–234/2	524
		65	523
1-$(CH_2)_7$-CO_2CH_3-6,7-$(OCH_3)_2$		HCl: 129–131	525
1-$CH_2C(C_2H_5)_2CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		Oxalate: 107–108	469
1-$(CH_2)_4CO_2C_4H_9$-*n*-6,7-$(OCH_3)_2$		58–59[a]	467
1-CH_2CH(C_6H_5)$CH_2CO_2CH_3$-6,7-CH_2O_2		Oxalate: 159.5–160	459, 569
1-CH=CH($C_6H_4CO_2$H-4)-3-CH_3-6,7-$(OCH_3)_2$		HCl: 230–235	450
2-$CH_2(C_6H_4CO_2C_2H_5$-2)-6,7-$(OCH_3)_2$		Br: 165[a–c]	512
1-C$(CO_2C_2H_5)(CH_2CH_2CN)_2$-6,7-$(OCH_3)_2$		166–167	498
1-CH_2CH(C_6H_4Br-4)$CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		Oxalate: 126.5–128	459
1-CH_2CH(C_6H_4Cl-2)$CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		Oxalate: 136–137	459
1-CH_2CH(C_6H_4Cl-3)$CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		Oxalate: 103.5–106	459
1-CH_2CH(C_6H_4Cl-4)$CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		Oxalate: 135–137	459, 469
1-CH_2CH(C_6H_4F-4)$CH_2CO_2CH_3$-6,7-$(OCH_3)_2$		Oxalate: 141.5–142.5	459

TABLE II.14. 3,4-Dihydroisoquinolines with Acidic Function in Side Chain (*Continued*)

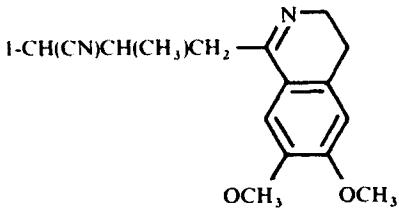
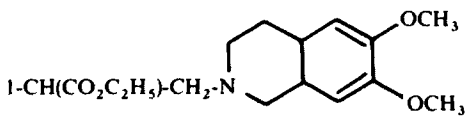
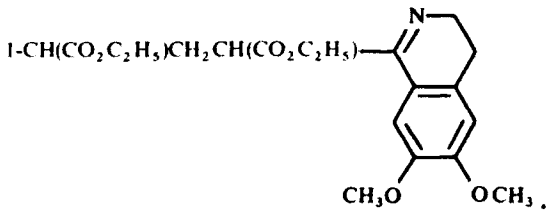
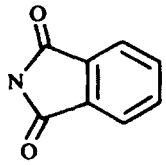
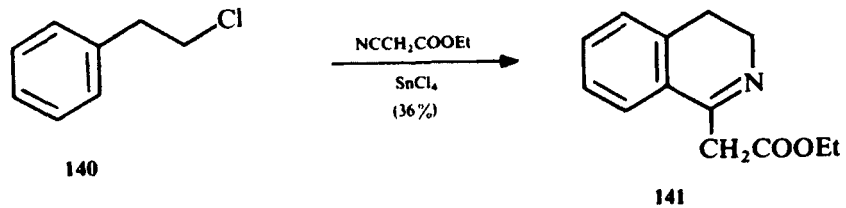
R_2	Substituent	m.p. (°C)	Ref.
1-CH($CH_2C_6H_5$)$CO_2C_2H_5$-6,7-(OCH_3)$_2$		103–104	496
		HCl: 166	496, 497
1-CH_2-CH(C_6H_5)$CH_2CO_2CH_3$-6,7-(OCH_3)$_2$		Oxalate: 120–122.5	469
		Oxalate: 125.5–126.5	459
1-CH_2(C_6H_2(OCH_3)$_2$-3,4-CO_2H-6)-6,7-(OCH_3)$_2$		140	489
1-CH_2(C_6H_2OH-3-OCH_3-4-$CO_2C_2H_5$-1)-6,7-(OCH_3)$_2$		HCl: 193.5	484
1-CH_2(C_6H_2(OCH_3)$_2$-3,4-CO_2CH_3-6)-6,7-(OCH_3)$_2$		125–126	489
1-CH_2CH($C_6H_3O_2CH_2$-3,4)-$CH_2CO_2CH_3$-6,7-(OCH_3)$_2$		Oxalate: 167–169	459, 469
1-CH_2CH($C_6H_4CH_3$-4)-$CH_2CO_2CH_3$-6,7-(OCH_3)$_2$		Oxalate: 123	469
1-CH_2CH($C_6H_4CH_3$-4)-$CH_2CO_2CH_3$-6,7-(OCH_3)$_2$		Oxalate: 137–139.5	459
1-CH_2CH($CH_2C_6H_5$)$CH_2CO_2CH_3$-6,7-(OCH_3)$_2$		Oxalate: 137–139	459, 469
1-CH_2CH($C_6H_4OCH_3$-4)-$CH_2CO_2CH_3$-6,7-(OCH_3)$_2$		Oxalate: 132–134	459, 469
4-$CH_2CH_2CO_2C_2H_5$-1-CH_2CH_2(C_6H_4Cl-4)-6,7-(OCH_3)$_2$		HCl: 174–175	477
4-$CH_2CH_2CO_2C_2H_5$-1-$CH_2CH_2C_6H_5$-6,7-(OCH_3)$_2$		HCl: 155–156	477
2-CH(C_6H_5)$CONHC_6H_5$-6,7-(OCH_3)$_2$		Cl^- 172[a,b]	526
		173–175[a,b]	466
		diHBr: 174–175	509
		6,7-(OCH_3)$_2$ 183–185	509
1-CH_2[$C_6H_3OCH_3$-4-($OC_6H_5OCH_3$-2-CH_2CH_2CN-4)-3]-6-OCH_3-7-O($C_6H_3OCH_3$-2-$CH_2CO_2CH_3$-5)		Picrate: 118–120	527

TABLE II.14. 3,4-Dihydroisoquinolines with Acidic Function in Side Chain (*Continued*)

R	Substituent	m.p. (°C)	Ref.
1-CH_2[$C_6H_3OCH_3$-4-($OC_6H_3OCH_3$-2-CH_2-CH_2-			
 -4)-3]-6-OCH_3-7-$O(C_6H_3OCH_3$-2-$CH_2CO_2CH_3$-5)			
		Pictrate: 178–179	527
	(N^+CH_3 I^-)	110–114	527
1-$CH(CH_3)CO_2CH_3$		130–135/1	490a
1-$CH(C_2H_5)CO_2CH_3$		135–140/1	490a
1-$CH(C_3H_7)CO_2CH_3$		144-145/1	490a
1-$CH(C_4H_9)CO_2CH_3$		162/1	490a
1-$CH(CH_3)CO_2C_2H_5$		152–155/1	490a
1-$CH(C_2H_5)CO_2C_2H_5$		144–146/1	490a
1-$CH(C_3H_7)CO_2C_2H_5$		160/1	490a
1-$CH(C_4H_9)CO_2C_2H_5$		170/1	490a
1-$CH(CH_3)CONHNH_2$		124–126	490a
		HCl: 99–100	490a
1-$CH(C_2H_5)CONHNH_2$		125–130	490a
		HCl: 100–105	490a
1-$CH(C_3H_7)CONHNH_2$		115–120	490a
		HCl: 100	490a
1-$CH(C_4H_9)CONHNH_2$		114–115	490a
		HCl: 125–130	490a

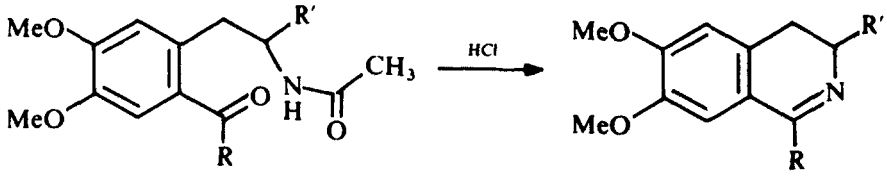
[a] IR in paper.
[b] UV in paper.
[c] NMR in paper.

Other cyclization reactions have also been used, such as the stannic-chloride-catalyzed reaction of β-chloroethylbenzene **140** and ethyl cyanoacetate to give **141**[490–492] (Eq. 54) and the reaction of compounds of the type **142** with hydrochloric acid to give **143**[450,493] (Eq. 55).



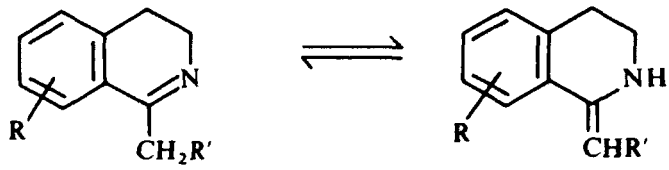
140 **141** (54)

These compounds are listed in Tables II.12 through II.14.



142 143 (55)

It has been reported that compounds believed to be **144**[442] are actually the tautomeric **145**.[494]

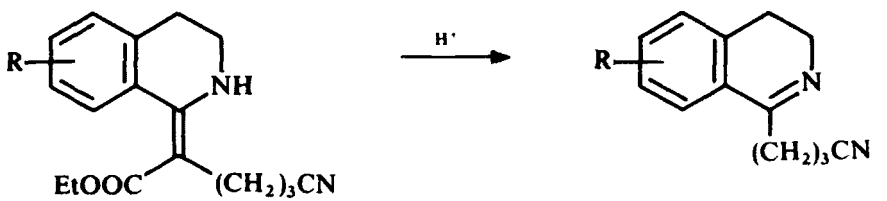


144 **145**

a. R′ = CO_2Et
b. R′ = $CONH_2$
c. R′ = CN

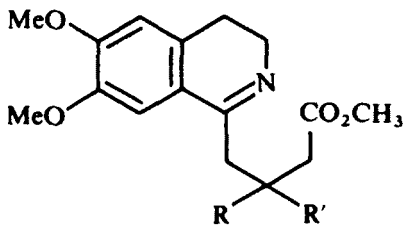
Alkylation of **145a**[495-97] or the reaction of **145c** with acrylonitrile[498, 99] provides derivatives **146**. The reaction of **145b** with acid yields **147**.[500] The reaction of **145b** or **145c** with nitrous acid gives **148**[501] (Scheme 4).

Interestingly, the reaction of **149** with acid occurs with hydrolysis and decarboxylation to afford **150**[498] (Eq. 56).

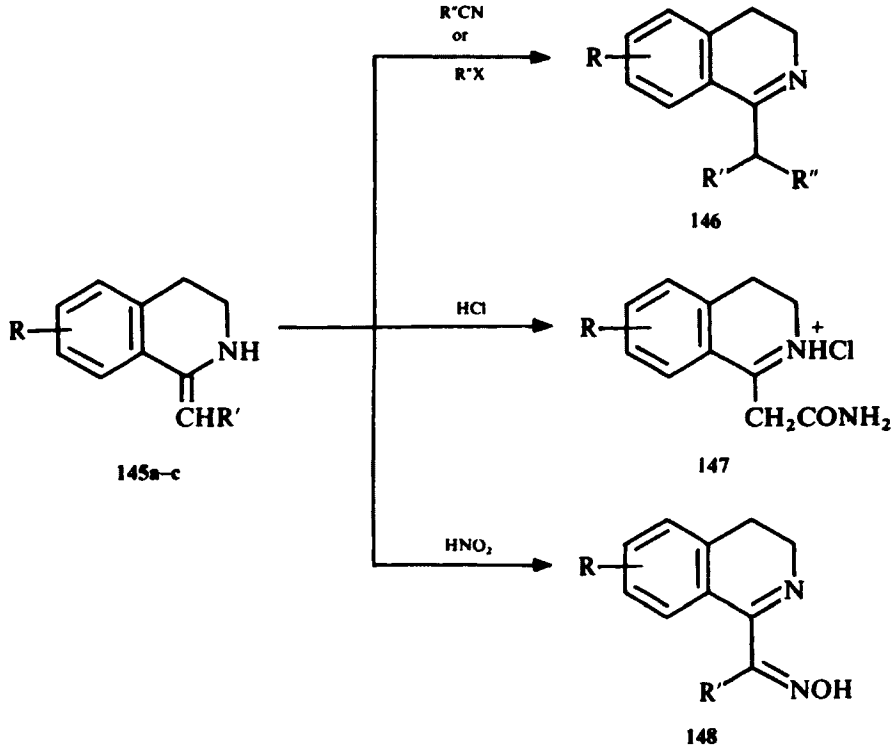


149 **150** (56)

Compounds of the type **151** undergo cyclization to tricyclic compounds.[459, 469]



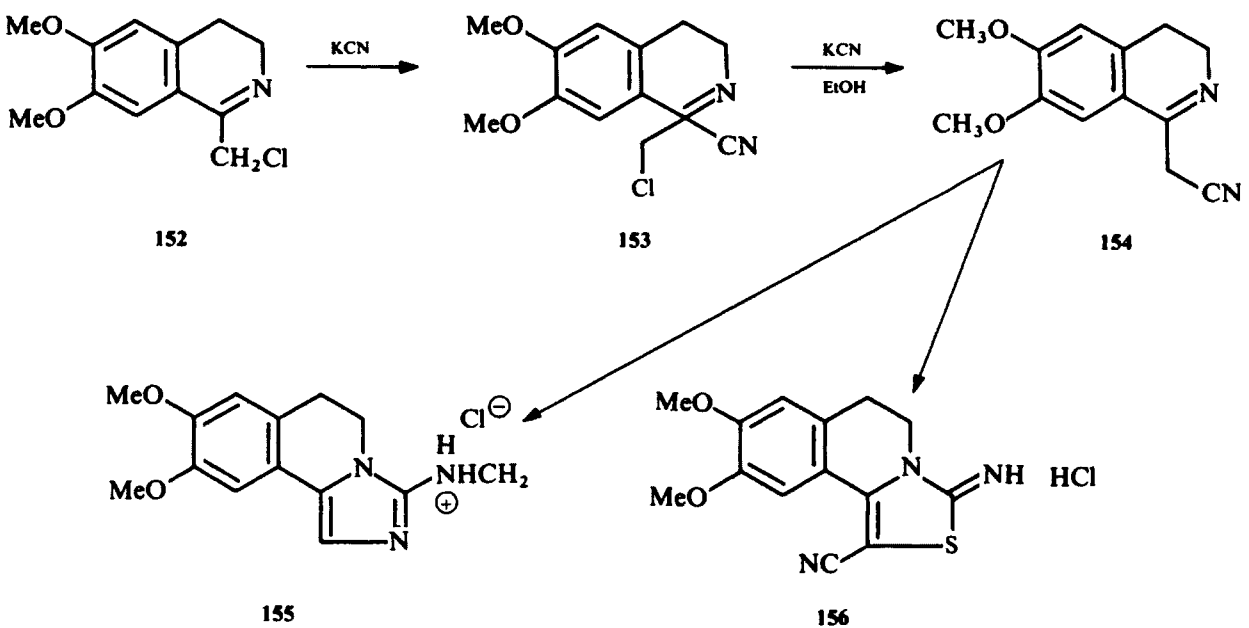
151



Scheme 4

1-Chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride **152** when treated with potassium cyanide affords **153**, which in the presence of potassium cyanide in reflexing ethanol yields 1-cyanomethyl-6,7-dimethoxy-3,4-dihydroisoquinoline **154**. This key intermediate has been transformed to either 3-benzyl-8,9-dimethoxy-5,6-dihyroamidazo [5,1-a] isoquinoline hydrochloride **155**[501a] or 1-cyano-3-imino-8,9-dimethoxy-3,4,5,6-tetrahydrothiazolo [4,3-a] isoquinoline hydrochloride **156**, which are interesting as drugs against heart disease. By using ^{14}C-labeled potassium cyanide, suitably labeled forms of these drugs have been prepared for pharmacological investigations[501a, b] (Scheme 5).

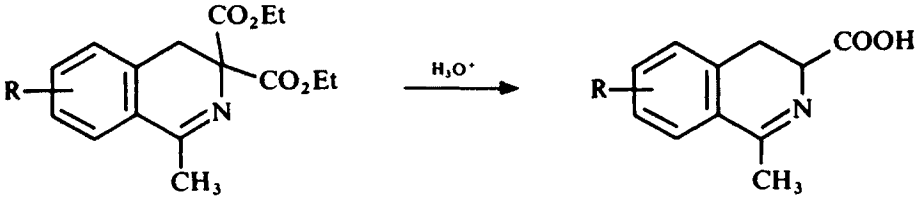
Various typical transformations such as ester hydrolysis,[17, 81, 455, 456, 458, 488, 489] esterification,[473, 498, 502, 503] conversion of esters to amides,[504–507] conversion of esters and hydrazides,[477, 490, 508] replacement of halogens by nitriles,[446, 449] and hydrolysis of nitriles[498, 509] have been reported. Treatment of 1,3-dimethyl-3,4-dihydroisoquinoline-3-carboxamide with alkaline bromine leads to the formation of 1,3-dimethyl-3,4-dihydroisoquinoline. Hydrolysis of **157** results in decarboxylation to **158**[473] (Eq. 57). Other examples of decarboxylation have been reported.[496, 498] Side chains containing acid functions have been introduced into the 2 position by alkylation.[436, 510–513]



152 153 154

155 156

Scheme 5



157 158 (57)

C. Miscellaneous Dihydroisoquinoline Derivatives

A number of dihydroisoquinolines other than 1,2- and 3,4-dihydro have been prepared and these are included in Table II.15.

TABLE II. 15. Miscellaneous Dihydroisoquinolines

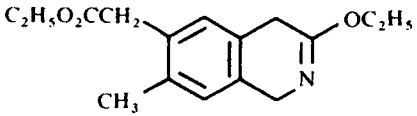
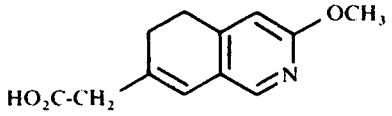
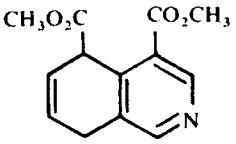
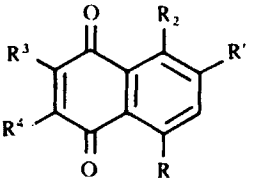
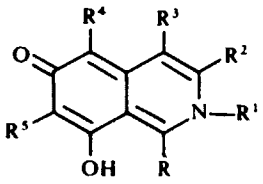
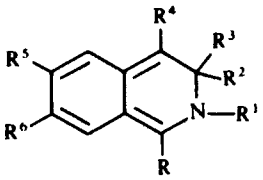
R	R^1	R^2	R^3	R^4	M.p., C	Spect.	Ref.
					95-96		69
					151-152		71
							
					89.5-90.5	IR, NMR	89
CH_3	CH_3	$CO_2C_2H_5$	H	H	103-103.5	UV, IR	95, 96
H	H	H	$CO_2C_2H_5$	$CO_2C_2H_5$	144-145	UV, IR	94
CN	H	H	H	OCH_3	242-243		514a

TABLE II.15. Miscellaneous Dihydroisoquinolines (*Continued*)

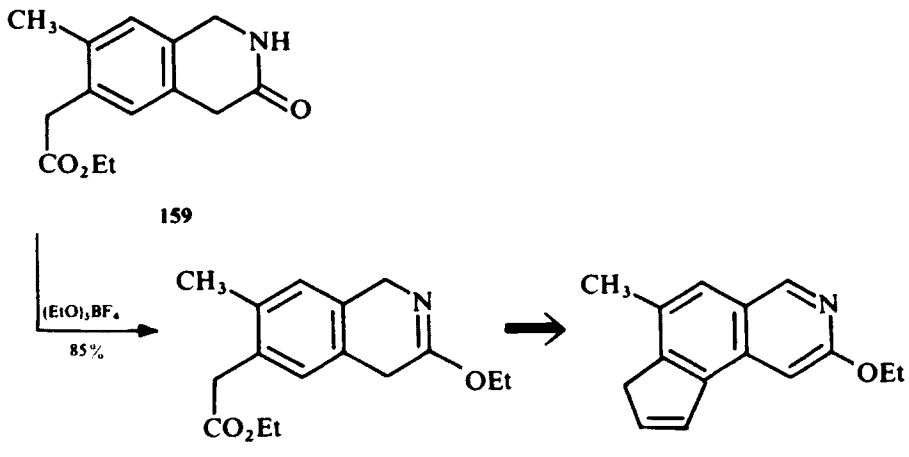
R	R^1	R^2	R^3	R^4	M.p., °C	Spect.	Ref.
							
CH_3	H	CH_3	H	$CONH_2$	H	280–283	UV 529
CH_3	CH_3	CH_3	H	$CONH_2$	H	278–280	UV 529
H	H	$-CH(CH_3)CH_2CH_3$	CH_3	H	CO_2H	238–240	528
							
H	H	H	H	H	$CH_2CO_2C_2H_5$	CH_3	238–240[a] 69
$N(CH_3)_2$	C_6H_5	= O	CN	H	H		240–242 530
$N(CH_3)_2$	C_6H_5	= S	CN	H	H		246–248 530
CN	CH_3	= NTosyl	H	H	H		220 531
$N(CH_3)_2$	C_6H_5	$= NC_6H_5$	CN	H	H		234–236 530

[a] UV, NMR in paper.

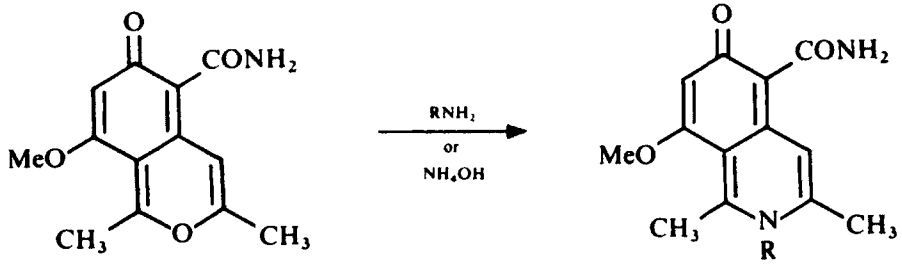
6-Carboethoxymethyl-7-methyl-1,2,3,4-tetrahydroisoquinoline-3-one **159** is converted in 85% yield to the corresponding ethyl ether **160** with triethyloxonium fluoroborate. Oxidation with DDQ, reduction with $LiAlH_4$, cyclization with fluorosulfonic acid, reduction of the ketone with $NaBH_4$, and dehydration affords 3-ethoxy-8-methyl-7(5)H-cyclopenta[f]isoquinoline **161**, a derivative designed to bind specifically to native DNA[69] (Eq. 58).

Oxidation of 5,8-dihydroxyisoquinoline containing carboethoxy groups with lead tetraacetate[94] or ferric chloride[95,96] leads to 5,8-dioxo-5,8-dihydro products. Dehydration of an 8-hydroxy-5,6,7,8-tetrahydro compound[71] or action of *p*-toluenesulfonyl chloride–pyridine on a 5,6,7,8-tetrahydroisoquinoline-1-oxide[89] leads to 5,6- and 7,8-dihydroisoquinolines, respectively.

Treatment of the pyronoquinonoid system **162** with a primary amine or concentrated ammonium hydroxide at RT easily displaces the oxygen to afford **163**[529,529a] (Eq. 59).

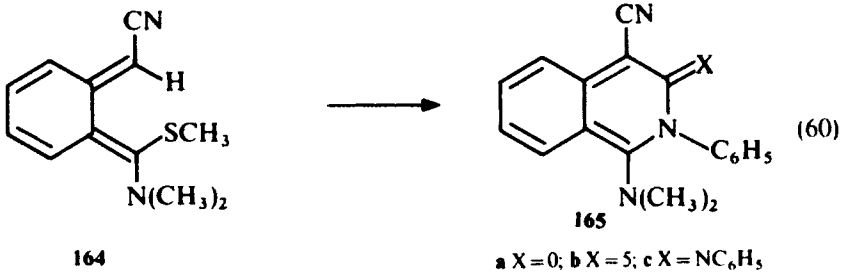


(58)



(59)

The stable *O*-quinodimethane 5-cyanomethylene-6-[(dimethylamino)(methylthio)methylene]-1,3-cyclohexadiene **164** undergoes cycloaddition reactions with phenylisocyanate, phenylisothiocyanate, or diphenyl carbodiimide to afford in good yields the 2,3-dihydroisoquinolines **165a–c**, respectively[530] (Eq. 60).



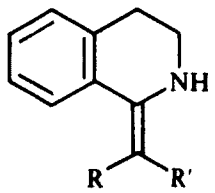
(60)

1,2-Dihydroisoquinolines[531] and 3-oxo-1,2,3,4-tetrahydroisoquinolines[69] have also been converted to 2,3-dihydroisoquinolines.

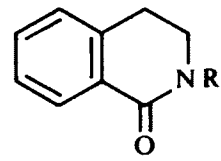
III. TETRAHYDROISOQUINOLINES

A. 1,2,3,4-Tetrahydroisoquinoline Derivatives

1,2,3,4-Tetrahydroisoquinolines containing various acid functional groups are included in Tables III.1–III.10. Compounds such as **166** (where R and/or R′ are acidic functional groups) are included in this section rather than with the dihydroisoquinolines, as are carbonyl compounds such as **167**. The various "one" derivatives are included in Tables III.11–III.14.

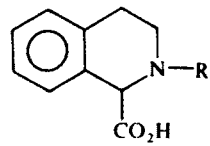


166



167

TABLE III.1. 1,2,3,4-Tetrahydroisoquinoline-1-Carboxylic Acids



R	Substituents		m.p. (°C)	Ref.
NO			N/A	650
H			161	142
			299	594
			162	368
			299	651
H	4,6-$(OH)_2$		238	542, 543
CH_3	4,6-$(OH)_2$-5-I		205–210	544
CH_3	4,6-$(OH)_2$-7-I		260	544
H	1-CH_3-6-OH		N/A	555
CH_3	4,6-$(OH)_2$		230–235	542–544
		cis	225	543, 544
		trans	224–225	543, 544
H	1-CH_3-4,6-$(OH)_2$		N/A	555
H	1-CH_3-6,7-$(OH)_2$		230–235	547
			240	652
			238–241	602
			N/A	534

TABLE III.1. 1,2,3,4-Tetrahydroisoquinoline-1-Carboxylic Acids (*Continued*)

R	Substituents	m.p. (°C)	Ref.
H	1-CH_3-6,7,8-$(OH)_3$	250	546
		HCl: 227–228	546
R		N/A	653
H	3-CO_2H-1-CH_3-6,7-$(OH)_2$	N/A	570
C_2H_5	4,6-$(OH)_2$	212	542, 543
H	6,7-$(OCH_3)_2$	252–257	549
		N/A	618, 619
H	1-CH_3-6-OH-7-OCH_3	205	551, 552
		254	546
		N/A	534
		HCl: 252	546
H	1-CH_3-6-OH-7-OCH_3(1-^{14}C)	252	564
H	1-C_2H_5-6,7-$(OH)_2$	243–244	602
		243	565
H	1-C_2H_5-6,7,8-$(OH)_3$	264	565
CH_3	3-CO_2H-1-CH_3-6,7-$(OH)_2$	N/A	570
H	1-CH_3-3,3=$CHCH_3$-4,6,7-$(OH)_3$	285	574
H	1-C_3H_7-6,7-$(OH)_2$	226	569
H	1-C_3H_7-5,6-$(OH)_2$	242	569
H[a]	6,7,8-$(OCH_3)_3$	238-240	587
H	1-$(CH_2)_3CH_3$-6,7-$(OH)_2$	241	565
$COCH_3$	6,7-$(OCH_3)_2$	207.5–210	549
		209–210	86
H	3-CO_2H-1-CH_3-6,7-$(OCH_3)_2$	N/A	570
H	1-$(CH_2)_3CH_3$-6-OH	255	565
H	1-$(CH_2)_3CH_3$-5,6-$(OH)_2$	255	565
CH_3[a]	6,7,8-$(OCH_3)_3$	245-246	587
H[a]	1,3-$(CH_3)_2$-3-$CO_2C_2H_5$-6,7-$(OH)_2$	218-220	568
H[a]	1,3-$(CH_3)_2$-3-$CO_2C_2H_5$-7,8-$(OH)_2$	248-250	568
H	1-$(CH_2)_5CH_3$-6-OH	249	565
H	1-$(CH_2)_5CH_3$-6,7-$(OH)_2$	239	565
H	1-$(CH_2)_5CH_3$-6,7,8-$(OH)_3$	240	565
COC_6H_5		120	594
$CH_2C_6H_5$		174-175	253
H	1-$CH_2C_6H_5$-6-OH	N/A	555
H	1-$CH_2C_6H_5$-5,6-$(OH)_2$	244–245	569
H	1-$CH_2C_6H_5$-6,7-$(OH)_2$	HCl: 240	547
		HCl: 243–246	534
H	1-$CH_2(C_6H_4OH$-4)-6-OH	N/A	555
H	1-$CH_2(C_6H_4OH$-2)-6,7-$(OH)_2$	HCl: 220	547
H	1-$CH_2(C_6H_4OH$-3)-6,7-$(OH)_2$	HCl: 255	547
H	1-$CH_2(C_6H_4OH$-4)-6,7-$(OH)_2$	HCl: 260	547, 547a
		N/A	652
H	1-$CH_2C_6H_5$-6,7,8-$(OH)_3$	239-240	546
		HCl: 245	546
H	1-$CH_2(C_6H_4OH$-4)-6,7,8-$(OH)_3$	258–260	546
		HCl: 268–270	546
H[a–d]	1-$CH_2(C_6H_3(OH)_2$-3,4)-6,7-$(OH)_2$		
		HCl: 287–295	572, 547a

TABLE III.1. 1,2,3,4-Tetrahydroisoquinoline-1-Carboxylic Acids (*Continued*)

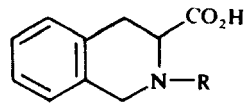
R	Substituents	m.p. (C)	Ref.
H	1-$(CH_2)_6CH_3$-6-OH	250	565
H	1-$(CH_2)_5CH_3$-5,6-$(OH)_2$	230	565
H	1-$(CH_2)_6CH_3$-5,6-$(OH)_2$	245	565
H	1-$(CH_2)_6CH_3$-6,7-$(OH)_2$	225	565
$CO_2CH_2C_6H_5$		N/A	651
H	1-C_6H_5-6,7-$(OCH_3)_2$	270–275	597, 598
H[a]	1-$CH_2C_6H_5$-6-OCH_3-7-OH	HCl:245–248	534
H	1-$CH_2(C_6H_4OH$-3)-6-OH-7-OCH_3	HCl:220	546
H[a]	1-$CH_2(C_6H_4OH$-4)-6-OH-7-OCH_3	270	534
H	1-$(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OH)_2$	190–200	550
H	1-$CH_2(C_6H_3OCH_3$-3-OH-4)-6,7-$(OH)_2$	230	547
		HCl:255–256	547, 547a
		N/A	652
H	1-$CH_2(C_6H_3OCH_3$-3-OH-4)-6,7,8-$(OH)_3$	HCl: 217–222	546
H	1-$CH_2(C_6H_3OCH_3$-4-OH-3)-6,7,8-$(OH)_3$	259–260	546
		HCl:252–253	546
H	1-$(CH_2)_7CH_3$-5,6-$(OH)_2$	241	565
H	1-$(CH_2)_7CH_3$-6,7-$(OH)_2$	226	565
H	1-$CH_2(C_6H_3O_2CH_2$-3,4)-6-OH-7-OCH_3	>250	556
$CH_2(C_6H_3(OCH_3)_2$-3,4)		164–165	362
$CH_2(C_6H_3(OCH_3)_2$-2,3)[b]		Perchlorate:190	362
H	1-$CH_2C_6H_5$-6,7-$(OCH_3)_2$	HCl:199–200	547
		HCl:180–185[a,b]	654
H[a]	1-$CH_2(C_6H_4OCH_3$-4)-6-OH-7-OCH_3	HCl:258–261	534
H[a]	1-$CH_2(C_6H_4OH$-4)-6,7-$(OCH_3)_2$	HCl:244–247	534
H	1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OH)_2$	229–230	569
H	1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-5,6-$(OH)_3$	234–236	569
H	1-$CH_2(C_6H_3$-OH-4-OCH_3-3)-6-OH-7-OCH_3	253	546
		HCl:252	546
H	1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7,8-$(OH)_3$	228-238	546
		HCl:260	546
H[b]	1-$CH_2(C_6H_3O_2CH_2$-2,3)-6,7-$(OCH3)_2$	275	603
H	6-OH-7-OCH_3	HCl:209–212	637a
H	1-$C_6H_5CH_2$-6-OH-7-OCH_3	HCl:245–249	637a
H	1-CH_3-6,7-$(OCH_3)_2$	298–300	637a
H	1-C_6H_5–CH_2-6,7$(OCH_3)_2$	281–286	637a
		HCl:238–240	637a
H	1-$[C_6H_2(OCH_3)_3$-3,4,5]-6-HO-7-OCH_3	HCl:252–254	637a
H	1-C_6H_5-6,7-$(OC_2H_5)_2$	255	578, 655
H[a]	1-$CH_2(C_6H_4OCH_3$-4)-6,7-$(OCH_3)_2$	HCl:278–281	534
H	1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6-OH-7-OCH_3	99–100	551, 552
H[a,b]	1-$(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	116–118	550
H	1-$CH_2(C_6H_2(OCH_3)_3$-3,4,5)-6,7,8-$(OH)_3$	241	546
		HCl:223–224	546
CH_3[a,b]	1-$CH_2(C_6H_3O_2CH_2$-2,3)-6,7-$(OCH_3)_2$	200–205	603

TABLE III.1. 1,2,3,4-Tetrahydroisoquinoline-1-Carboxylic Acids (*Continued*)

R	Substituents	m.p. (°C)	Ref.
$COCH_3$[a]	1-$CH_2(C_6H_4OCH_3$-4)-6-OH-7-OCH_3	143–145	534
$CH_2(C_6H_3(OCH_3)_2$-2,3)	6,7-$(OCH_3)_2$	183–185	362
$COCH_3$[a]	1-$CH_2(C_6H_4OCH_3$-4)-6,7-$(OCH_3)_2$	124–126	534
$CO_2C_2H_5$	1-$CH_2(C_6H_3O_2CH_2$-3,4)-6-$OCO_2C_2H_5$-7-OCH_3	253–256	556
COC_6H_5[a–c]	1-$CH_2(C_6H_3O_2CH_2$-2,3)-6,7-$(OCH_3)_2$	216–218	603
COC_6H_5	1-C_6H_5-6,7-$(OC_2H_5)_2$	247	540, 578

[a] NMR in paper.
[b] IR in paper.
[c] UV in paper.
[d] Mass spectroscopy in paper.

TABLE III.2. 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylic Acids



R	Substituents	mp. (°C)	Spectroscopy	Ref.
H		DL 331		428
		D 328.5		428
		L 327.5		428
		DL 313–316		656
		D 280		656
		L 274		656
		311		566
		311–312		567
		306–311 (no preheat)		583
		324–325 (preheat)		583
		HCl:305		567, 649a
		HCl:308–309		532, 532a
		Picrate:204		76
		N/A		636
H	7-OH	336–338		566
		195		571
		Picrate: 290		571
H	6,7-$(OH)_2$	277		569
H	6,7-$(OH)_2$(−)	286–288	MS, UV, IR, MNR	533
H	6,7-$(OH)_2$ (3S)	293–294	NMR	535

TABLE III.2. 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylic Acids (*Continued*)

R	Substituents		mp. (°C)	Spectroscopy	Ref.
CH_3			HCl:204–206		636
H	3-CH_3		>300		532a
H	1-CH_3-6-OH		269–272		584
H	6-OCH_3		302		88
			263–264		657
CH_3	6,7-$(OH)_2$	(3S)	253–255	NMR	535
H	7-OH-6-OCH_3	(3S)	268–269	NMR	535
H	6-OH-7-OCH_3	(3S)	290	NMR	535
H	1-CH_3-6,7-$(OH)_2$		206–208	IR, UV	112
H	1-CH_3-6,7-$(OH)_2$	(−)	N/A	UV, NMR	541
H	1-CH_3-6,7-$(OH)_2$	(1R, 3R)	285–287	NMR	537
H	1-CH_3-6,7-$(OH)_2$	(1S, 3S)	280–281	NMR	535
		(1R, 3S)	212	NMR	535
H	3-CH_3-6,7-$(OH)_2$		279–280	NMR	568
H	1-CH_2OH-6,7-$(OH)_2$		281–282		538, 539
$COCH_3$			173.2–175.8		532
			171–172		636
H	1-CO_2H-1-CH_3-6,7-$(OH)_2$		N/A		570
H	1,1-$(CH_3)_2$-6-OH		HCl:258	IR, UV, NMR	553
			N/A		561
CH_3	1-CH_3-6,7-$(OH)_2$	(1S, 3S)			
			HCl:225–227	NMR	535
	(1S, 3S)		HCl:227–228	NMR	535
CH_3	3-CH_3-6,7-$(OH)_2$		N/A		579
			268–270		579a
H	1-CH_3-7-OH-6-OCH_3	(1S, 3S)	295	NMR	535
	(1R, 3S)		260–261	NMR	535
H	1-CH_3-6-OH-7-OCH_3	(1S, 3S)	254–255	NMR	535
	(1R, 3S)		235–236	NMR	535
H	1,1-$(CH_3)_2$-6,7-$(OH)_2$		N/A		570
H	1,3-$(CH_3)_2$-6,7-$(OH)_2$		285–287	NMR	568
H	6,7-$(OCH_3)_2$		260	IR	479
			HCl:263–264	UV	113, 649a
H	1,3-$(CH_3)_2$-1-CO_2H-6,7-$(OH)_2$		N/A		570
H	1-CH_3-6,7-$(OCH_3)_2$	(1S, 3S)			
			HCl:214–215	NMR	537
	(1R, 3R)		HCl:222–223	NMR	537
H	1-CO_2H-1-CH_3-6,7-$(OCH_3)_2$		N/A		570
H	1-C_6H_5-OH-*cis*		254–256	IR, NMR	479
	-*trans*		240	IR, NMR	479
	-*trans*		sulfate:260		479
COC_6H_5		DL	160–163		428
		D	146–150		428
		L	152–153		428
			158–160		636
		DL	170–172		656
		D	156–158		656
		L	164		656

TABLE III.2. 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylic Acids (*Continued*)

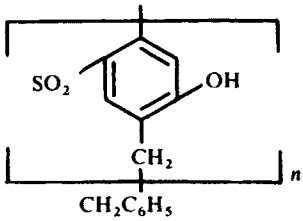
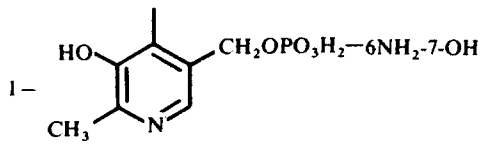
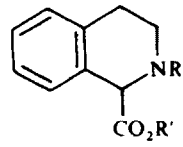
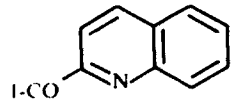
R	Substituents	mp. (°C)	Spectroscopy	Ref.
		N/A		658
$CH_2C_6H_5$		187–188		609, 610
H	1-C_6H_5-6-OCH_3-*trans*	HCl:249–250	IR	479
H	1-C_6H_5-3-CH_3-6,7-$(OH)_2$	258–259	NMR	568
H	1-$CH_2C_6H_5$-6,7-$(OH)_2$	221–223	NMR	568
$SO_2C_6H_4$ CH_3-4		152		659
H		N/A		660
H	1-$CH_2C_6H_5$-3-CH_3-6,7-$(OH)_2$	264–266	NMR	568
$CH_2(C_6H_4O$ CH_3-3)	6-OCH_3	223–225		657
$CH_2C_6H_3(OCH_3)_2$-3,4		180–185		613
$CH_2C_6H_5$	4-OH-6,7-$(OCH_3)_2$	HCl:215–216		605
$CH_2CH_2(C_6H_3(OCH_3)_2$-3,4)		157		600
H	3-CH_3-6,7$(OCH_3)_2$	HCl:231–233		649a
$CH_2CH_2C_6H_5(OCH_3)$-3,4		157		649a
$CH_2CH_2C_6H_3(OCH_3)_2$-3,4	6,7-$(OCH_3)_2$	179–182		649a
$CH_2CH_2C_6H_3(OCH_3)_2$-3,4	3CH_3-6,7$(OCH_3)_2$	189–192		649a
$CH_2CH_2C_6H_2(OCH_3)_3$-3,4,5	6,7-$(OCH_3)_2$	110–112		649a
$CH_2CH_2C_6H_2(OCH_3)_3$-3,4,5	7,8$(OCH_3)_2$	162–164		649a
$CH_2CH_2C_6H_3(OCH_3)_2$-3,4	1-CH_3-6,7$(OCH_3)_2$	157–158		649b
		(1535)157–158		649b
H	4-CH_3-6,7-$(OCH_3)_2$	259–263		649b
$CH_2CH_2C_6H_3(OCH_3)_2$-3,4	4-CH_3-6,7-$(OCH_3)_2$	160–162		649b

TABLE III.3. 1,2,3,4-Tetrahydroisoquinoline-1-Carboxylates



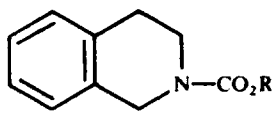
R	R^1	Substituent	m.p. (°C)	Ref.
H	CH_3		b.p.: 140/2	661
H	CH_3	4,6-$(OH)_2$	180	542,543
R	CH_3		N/A	653
CH_3	CH_3		Picrate: 160–161	23
H	C_2H_5	5-OH	202–203	1
CH_3	CH_3	4,6-$(OH)_2$	159–160	543,544
			161–163	542
H	C_2H_5	4,6-$(OH)_2$	194–195	542,543
H	C_2H_5	6-OCH_3	b.p.: 98–103/0.004	662
			Picrate: 167.5–168	622
CH_3	C_2H_5	4,6-$(OH)_2$	168	542
			170	543
C_2H_5	CH_3	4,6-$(OH)_2$	139–140	542,543
H	C_3H_7-*n*	4,6-$(OH)_2$	165–166	542,543
$COCH_3$[a]	C_2H_5	5-OH	148–149	1
H	CH_3	1-CH_3-6,7-$(OCH_3)_2$	b.p.: 110–120/0.001	602
H	C_2H_5	6,7-$(OCH_3)_2$	188–189	507
			73–74	663
			oxalate: 188–189	86
			N/A	481
CH_3	C_3H_7-*i*	4,6-$(OH)_2$	165	542
			168–170	543
CH_3	C_3H_7-*n*	4,6-$(OH)_2$	140	542
			157	543
H	C_4H_9-*i*	4,6-$(OH)_2$	148–149	542
$COCH_3$[a]	C_2H_5	1-CN	134–136	664
H	CH_3	1-C_2H_5-6,7-$(OCH_3)_2$	b.p.: 100–110/0.001	602
CH_3	C_2H_5	6,7-$(OCH_3)_2$	b.p.: 153/3	507
			Picrate: 171	507
CH_3	C_4H_9-*n*	4,6-$(OH)_2$	128	542
			143–145	543
CH_3	C_4H_9-*i*	4,6-$(OH)_2$	166–168	542,543
$COCH_2Cl$	C_2H_5	6,7-$(OCH_3)_2$	80.6–84.2	623–628
CH_3	C_5H_{11}-*n*	4,6-$(OH)_2$	130	542,543
CH_3	C_5H_{11}-*i*	4,6-$(OH)_2$	153–155	542,543
COC_6H_5	CH_3		105–108	594
H[a,b]	CH_3	1-$CH_2(C_6H_3O_2CH_2$-2,3)-6,7-$(OCH_3)_2$	Oil	603
H	C_2H_5	1-$CH_2(C_6H_3O_2CH_3$-3,4)-6-OH-7-OCH_3	Syrup	556
CH_3[a–c]	CH_3	1-$CH_2(C_6H_3O_2CH_2$-2,3)-6,7-$(OCH_3)_2$	112–114	603

TABLE III.3. 1,2,3,4-Tetrahydroisoquinoline-1-Carboxylates (*Continued*)

R	R^1	Substituent	m.p. (°C)	Ref.
CH_3[a,b]	CH_3	1-($C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	104–105	550
$CSNHC_6H_5$	CH_3		133–135	661
H	CH_3	1-$CH_2C_6H_5$-6,7-$(OCH_3)_2$	118	547
$CH_2(C_6H_4CH_2CO_2C_2H_5$-2)[a,c]	C_2H_5	6,7-$(OCH_3)_2$	92.5–93.5	481
COC_6H_5	CH_3		184–187	594
COC_6H_5[a–c]	CH_3	1-$CH_2(C_6H_3O_2CH_2$-2,3)-6,7-$(OCH_3)_2$	215–216	603
COC_6H_5	C_2H_5	1-C_6H_5-6,7-$(OC_2H_5)_2$	172	578

[a] IR in paper.
[b] NMR in paper.
[c] UV in paper.

TABLE III.4. 1,2,3,4-Tetrahydroisoquinoline-2-Carboxylates



R	Substituents	m.p. (°C)	Spectroscopy	Ref.
C_2H_5	7-OCH_3-8-OH	Syrup	IR, NMR	665
C_2H_5	1-CN-6,7-O_2CH_2	103–105	IR, NMR	338
$(CH_2)_2N(CH_3)_2$		b.p.: 186–189/5		666
	($N^+CH_3I^-$)	167–168		666
C_2H_5	7-OCH_3-8-$OCO_2C_2H_5$	b.p.: 205–210/0.8	IR, NMR	665
C_2H_5	1-$CH_2NHCO_2C_2H_5$	95–97		205
		103		356
C_2H_5	1-CH_3-6,7,8-$(OCH_3)_3$	b.p.: 160/0.05	IR	667
$CH_2C_6H_5$	1-CO_2H	N/A		651
CH_3	1-(2-pyridyl)-6,7-$(OCH_3)_2$	110–112		668
CH_3	1-(2-piperidyl)-6,7-$(OCH_3)_2$	246–247		668
C_2H_5	1,1 =CHC_6H_4I-2	92–93	IR, UV, MS, NMR	669
C_2H_5	1,1 =CHC_6H_5	87–88		646
		97–98		646
C_2H_5	3-CH_3-4-C_6H_5	b.p.: 158–159/0.4		670
C_2H_5	7-OCH_3-8-$OCH_2C_6H_5$	b.p.: 180/0.9	IR, NMR	665

TABLE III.4. 1,2,3,4-Tetrahydroisoquinoline-2-Carboxylates (*Continued*)

R	Substituents	m.p. (°C)	Spectroscopy	Ref.
C_2H_5	1-($C_6H_4NH_2$-)-6,7-(OCH_3)$_2$	N/A		671
C_2H_5	1,1=CH($C_6H_2OCH_2$-3,4-Br-2)-6,7-O_2CH_2	186.5–187	UV, NMR	645
C_2H_5	3-$CH_2SeC_6H_5$		NMR	671a
C_2H_5	1,1=CH(C_6H_4Cl-2)-6,7-(OCH_3)$_2$	169–170	644	
C_2H_5	1,1=CH(C_6H_4I-2)-6,7-(OCH_3)$_2$	135–136	IR, UV, NMR	669
C_2H_5	1,1=CHC_6H_5-6,7-(OCH_3)$_2$	122–124	IR, UV, NMR	642
		133–134		644
C_2H_5	1-CH_2($C_6H_4OCH_3$-4)-6,7-O_2CH_2	113–114		672
C_2H_5	1-CH_2(C_6H_2OH-4-OCH_3-3-Br-1)-6-OH-7-OCH_3	N/A		673
C_2H_5	1-CH_2($C_6H_2OCH_3$-4-OH-5-Br-2)-6-OH-7-OCH_3	138–139	IR	674
C_2H_5	1-$CH_2C_6H_5$-1-OH-6,7-(OCH_3)$_2$	Oil	NMR, IR, MS, UV	642
C_2H_5	1-CH_2(C_6H_4OH-4)-6,7-(OCH_3)$_2$	170–171		672
C_2H_5	1-CH_2($C_6H_3OCH_3$-4-OH-3)-6-OH-7-OCH_3	148–150	IR	675
C_2H_5	1-CH_2($C_6H_3OCH_3$-4-OH-3)-6-OCH_3-7-OH	Glass	NMR	676
C_2H_5	1-CH_2(C_6H_3OH-4-OCH_3-3)-6-OH-7-OCH_3	153–154		673
C_2H_5	1,1=CH(C_6H_2(OCH_3)$_2$-3,4-Br-2)-6,7-O_2CH_2	210–211		645
C_2H_5	1,1=CH(C_6H_2(OCH_3)$_2$-3,4-Cl-2)-6,7-O_2CH_2	208–209.5	NMR	645
CH_3	1,1=CH(C_6H_3(OCH_3)$_2$-2,5)-6,7-(OCH_3)$_2$	144–145	UV, IR, NMR	642
CH_3	1-CH_2($C_6H_3OCH_3$-4-OCO_2CH_3-3)-6-OCH_3	105		677
C_2H_5	1-CH(OAc)[C_6H_2-2-CH_2OH-3,4(OCH_3)$_2$]6,7-O_2CH_2	229–230		677a
C_2H_5	1-CH(OAc) [C_6H_2-2CHO-3,4(OCH_3)$_2$] 6,7-O_2CH_2	154–155		677a
C_2H_5	1-CH_2(C_6H_2Br-1-(OCH_3)$_2$-3,4)-7-OH-6-OCH_3	123–126	IR, UV, NMR	643
C_2H_5	1-CH_2($C_6H_2OCH_3$-4-OH-5-Br-2)-6-OH-7,8-(OCH_3)$_2$	136–137	IR, NMR	674
C_2H_5	1-CH_2($C_6H_3OCH_3$-4-OH-3)-6-OH-7,8-(OCH_3)$_2$	157–158	IR, NMR	654
C_6H_5	1-$CH_2C_6H_4$I-2	151–152	IR, MS, NMR	669
C_2H_5	1,1=CH(C_6H_2(OCH_3)$_2$-3,4-Br-2)-6,7-(OCH_3)$_2$	218.5–219.5		644
C_2H_5	3-CH_3-4-C_6H_5-6-$C(CH_3)_3$	93–95		670

TABLE III.4. 1,2,3,4-Tetrahydroisoquinoline-2-Carboxylates (*Continued*)

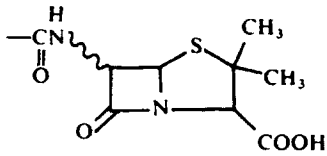
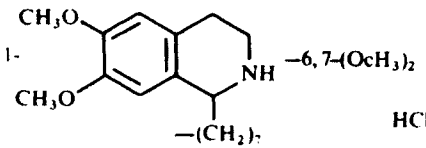
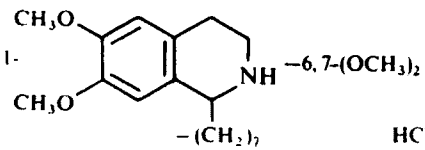
R	Substituents	m.p. (°C)	Spectroscopy	Ref.
C_2H_5	1,1=CHC_6H_5-6,7-$(OC_2H_5)_2$	151–152		578
C_2H_5	1-$(C_6H_4CO_2C_2H_5$-2)-6,7-$(OCH_3)_2$	N A		671
C_2H_5	1,1=$CH(C_6H_3(OCH_3)_2$-3,4) -6,7-$(OCH_3)_2$	144–146		646
		154–155		644
C_2H_5	1-$CH_2(C_6H_2(OCH_3)_2$-4,5-Br-2) -6-OH-5,7-$(OCH_3)_2$	180–181	IR	674
C_6H_5	1-$CH_2(C_6H_4$I-2)-6,7-$(OCH_3)_2$	160–161	IR, MS, NMR	669
C_2H_5	1-$CH_2(C_6H_3O_2CH_2$-3,4)-1-CO_2H-6 -$O_2COC_2H_5$-7-OCH_3	253–256		556
$CH_2C_6H_5$	1-$CH_2(C_6H_3$-OCH_3-4-OH-3)-6-OCH_3 -7-OH	86–88	NMR	676
$CH_2C_6H_5$		N A		651
C_2H_5	1,1-$C(C_6H_5)_2$-6,7-$(OCH_3)_2$	136–137.5		647
C_2H_5	1-$CH_2(C_6H_2OCH_3$-4-$OCH_2C_6H_5$-3 -Br-2)-5-Br-7-OCH_3-8-OH	149–151	IR, NMR	640,641
C_2H_5	1-$CH_2(C_6H_4OCH_2C_6H_5$-4)-6,7-$(OCH_3)_2$	97–99		672
C_2H_5	1-$CH_2(C_6H_2$Br-1-$(OCH_3)_2$-3,4)-6-OCH_3- 7-$OCH_2C_6H_5$	113–114	IR, NMR	643
C_2H_5	1-$CH_2(C_6H_2NO_2$-6-$(OCH_3)_2$-3,4)-6- OCH_3-7-$OCH_2C_6H_5$	125–127	IR	675
C_2H_5	1-$CH_2(C_6H_2OH$-6-$(OCH_3)_2$-3,4)-6- OCH_3-7-$OCH_2C_6H_5$	148–150		675
C_2H_5	1-$CH_2(C_6H_2NH_2$-6-$(OCH_3)_2$-3,4)-6- OCH_3-7-$OCH_2C_6H_5$	115–117		675
C_2H_5	1-$CH_2(C_6H_2(OCH_3)_2$-4,5-Br-2)-5,7- $(OCH_3)_2$-6-$OCH_2C_6H_5$	Syrup	IR, NMR	674
C_2H_5	1-$CH_2(C_6H_2OCH_3$-4-$OCH_2C_6H_5$-3-Br- 2)-5-Br-7-OCH_3-8-$OCO_2C_2H_5$	119–120	IR, UV, NMR	640, 641
C_2H_5		HCl: N A		525
CH_2CHOH CH_2OH		HCl: N A		678

TABLE III.4. 1,2,3,4-Tetrahydroisoquinoline-2-Carboxylates (*Continued*)

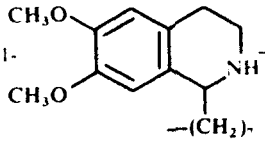
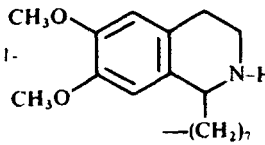
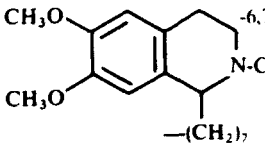
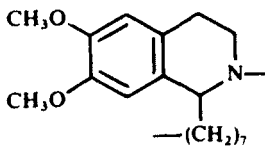
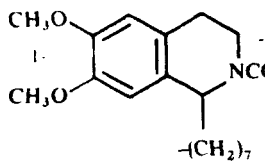
R	Substituents	m.p. (°C)	Spectroscopy	Ref.
C_2H_5	1-$CH_2(C_6H_4OCH_2C_6H_5$-4)-6-OCH_3-7-$OCH_2C_6H_5$	105–107		672
$C(CH_3)_3$		N/A		525
C_2H_5	1-$CH_2(C_6H_2(OCH_3)$-4-Br-2-$OCH_2C_6H_5$-5)-7-OCH_3-6-$OCH_2C_6H_5$	139–140		674
C_2H_5	1-$CH_2(C_6H_3OCH_2C_6H_5$-3-OCH_3-4)-6-OCH_3-7-$OCH_2C_6H_5$	134–135		672
C_2H_5	1-$CH_2(C_6H_3$-OCH_3-4-$OCH_2C_6H_5$-3)-6-$OCH_2C_6H_5$-7-OCH_3	138–140 N/A	IR	675 679
C_2H_5	1-$CH_2(C_6H_2OCH_3$-4-Br-2-$OCH_2C_6H_5$-5)-7,8-$(OCH_3)_2$-6-$OCH_2C_6H_5$	127–128	IR,NMR	674
$C_6H_4NO_2$-4		HCl: N/A		678
$C(CH_3)_3$		N/A		525
$C(CH_3)_3$		N/A		678
$C(CH_3)_3$		N/A		525

TABLE III.4. 1,2,3,4-Tetrahydroisoquinoline-2-Carboxylates (*Continued*)

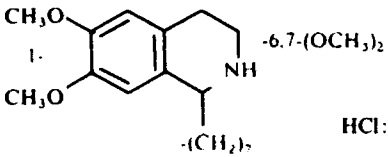
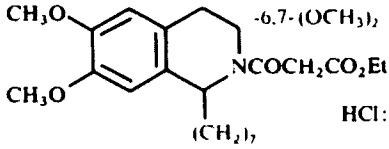
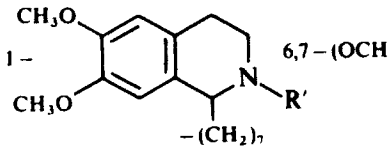
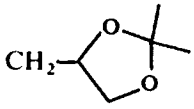
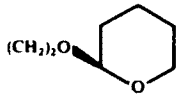
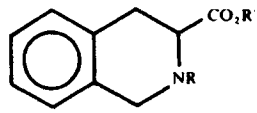
R	Substituents	m.p. (°C)	Spectroscopy	Ref.
C_6H_4-CO_2CH_3-2		HCl: N/A		678
$C(CH_3)_3$		HCl: N/A		678
$C(CH_3)_3$				
	R'			
	$COCH_2CO_2C_2H_5$	N/A		525
	$COCH_2NH(CH_2)_2CH_3$	HCl: N/A		678
		N/A		525
	$CO[C_6H_3(NO_2)_2$-3,5)]	N/A		525
	COC_6H_{11}	N/A		525
	$CO(CH_2)_5CH_3$	HCl: N/A		525
		N/A		525
	$COC_6H_4OCF_3$-4	N/A		525
	$COCH_2OC_6H_5$	N/A		525
	$COC_6H_4CO_2CH_3$-2	N/A		525
	CO-Adamantyl	N/A		525

TABLE III.5. 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylates



R	R'	Substituents		m.p. (°C)	Spectroscopy	Ref.
H	CH_3			b.p.: 110/0.03	IR, NMR	479
				HCl: 278		479
H	CH_3	7-OH		230		571
H	R	6,7-subst.,		N/A		558
H	R	1,1-subst.-6,7-$(OH)_2$		N/A		514,515
H	C_2H_5	6-F	(±)	HCl: 220–222		557
H	C_2H_5			b.p.: 115–121/0.2		601
				b.p.: 134/0.8		680
				b.p.: 124–125/0.6		532
				b.p.: 130–135/0.08		573
				b.p.: 165/2		567
				b.p.: 144–145/15		77
				b.p.: 97–98/0.1		77
				b.p.: 120/1		599
			(−)	b.p.: 140–142/2		557
			(+)	b.p.: 140–142/2		557
			(±)	b.p.: 138–140/2		557
				HCl: 178–180		680
				HCl: 203–205		573, 601
				HCl: 308–309		532
			(−)	HCl: 204–205		557
			(+)	HCl: 206–207		557
			(±)	HCl: 186–188		577
				Picrate: 198–199		601
				Picrate: 202–204		532
				Picrate: 198–200		573
				Picrate: 195–196		567
				Picrate: 204		77
				Picrate: 204		599
				Picrolonate: 225		567
				Picrolonate: 212–213		599
H	CH_3	6-OCH_3		Picrate: 185		88
H	CH_3	1-CH_3-6,7-$(OH)_2$		HCl: 226–228	IR,UV	112
H	CH_3	3-CH_3-6,7-$(OH)_2$		HCl: 246–248	NMR	568
CH_2CH_2CN	R	6,7-subst.		N/A		681
H	C_2H_5	6,7-O_2CH_2		b.p.: 183–185/1.5		682
H	C_2H_5	6,7-O_2CH_2	(±)	b.p.: 183–185/1.5		577
				HCl: 223–225		682
			(−)	HCl: 223–225		577
H	C_2H_5	3-CH_3		b.p.: 152–155/10		517
				Picrate: 179		517
H	$CH(CH_3)_2$			b.p.: 125/0.1		600, 649a

TABLE III.5. 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylates (*Continued*)

R	R^1	Substituents		m.p. (°C)	Spectroscopy	Ref.
CH_3	C_2H_5			b.p.: 140–142/6.5		622
				b.p.: 135–136/2	NMR,IR	557
		$(N^+CH_3I^-)$		186–188		622
				Picrate: 128–130		557
H	C_2H_5	6-OCH_3		b.p.: 160/2		88
				Picrate: 187–188		88
H	CH_3	1,3-$(CH_3)_2$-6,7-$(OH)_2$		191–193	NMR	568
H	CH_3	1,1-$(CH_3)_2$-6,7-$(OH)_2$		N/A		570
H	C_2H_5	1-CH_3-6,7-$(OH)_2$	(1S,3S)	161–162	NMR	537
			(1S,3S)	HCl: 229–230	IR,NMR	535
			(1R,3R)	HCl: 230–231		537
			(1R,3S)	HCl: 217–218		537
H	CH_3	6,7-$(OCH_3)_2$		210–214	IR,NMR	479
				HCl: 256	IR,NMR	479
				HCl: 244–245	UV	113
H	CH_3	6,8-$(OCH_3)_2$-7-CH_3		Picrate: 208		12
H	C_2H_5	6,7-$(OCH_3)_2$	(±)	b.p.: 184–187/1		557
			(±)	HCl: 214–215		557
				HCl: 215		683
$COCH_3$	C_2H_5	3-CN		143–145		583
CH_3	C_2H_5	1-CH_3-6,7-O_2CH_2		b.p.: 200–204/6		473
$COCH_3$	C_2H_5	1-CH_3-6,7-$(OH)_2$	(1R,3R)	185–186	IR,NMR	537
			(1R,3S)	162–163	IR,NMR	537
H	C_2H_5	1,3-$(CH_3)_2$-1-CO_2H-6,7-$(OH)_2$		218–220	NMR	568
H	C_2H_5	1,3-$(CH_3)_2$-1-CO_2H-7,8-$(OH)_2$		248–250	NMR	568
H	C_2H_5	1-CH_3-6,7-$(OCH_3)_2$		68–70	UV	85
$(CH_2)_3CN$	C_2H_5			b.p.: 170/1		599
H	CH_3	1-C_6H_5-6-OH-*cis*		185–186	IR,NMR	479
H	CH_3	1-C_6H_5-6-OH-*trans*		74	IR,NMR	479
$(CH_2)_4CN$	C_2H_5			b.p.: 175–180/0.1		614
$(CH_2)_3CN$	C_2H_5	6-OCH_3		b.p.: 210/2		88
$(CH_2)_2CO_2C_2H_5$	C_2H_5			b.p.: 160–161/4		614
				Picrate: 115–116		614
$COCH_3$	C_2H_5	1-CH_3-6,7-$(OCH_3)_2$	(1S,3S)	86–87	IR,NMR	537
			(1R,3R)	91–92	IR	537
			(1R,3S)	101–102	IR,NMR	537
$SO_2(C_6H_3NO_2$-2-Cl-4)	C_2H_5		(±)	101–103		557
$SO_2C_6H_4NO_2$-2	C_2H_5		(±)	94–96	IR	557
H	C_2H_5	1-C_6H_5-6-OH-*trans*		68	IR,NMR	479
$SO_2(C_6H_3$-NH_2-2-Cl-4)	C_2H_5		(±)	134–136		557
$SO_2C_6H_4NH_2$-2	C_2H_5		(±)	153–155	IR	557
CH_2CH $=CHCO_2C_2H_5$	C_2H_5			b.p.: 197–200/1.5		532
				b.p.: 181–184/0.7		532

TABLE III.5. 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylates (*Continued*)

R	R^1	Substituents	m.p. (°C)	Spectroscopy	Ref.
H	C_2H_5	1,1=$CHCO_2C_2H_5$-6,7-$(OCH_3)_2$	131–131.5	IR,NMR	684
$CH_2CH_2CO_2C_2H_5$	C_2H_5	6,7-O_2CH_2	Oil	IR,NMR	80
$(CH_2)_3CO_2C_2H_5$	C_2H_5		b.p.: 180–190/2-3		601
			b.p.: 170/1		599
H	C_2H_5	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 183–186/0.003		684
			77–78	IR	684
$CO(C_6H_3NO_2$-2-Cl-3)	C_2H_5		(−) 109–110		557
			(+) Liquid		557
$CO(C_6H_3NO_2$-2-F-4)	C_2H_5		(−) 85–87		557
			(+) 90–91		557
$CO(C_6H_3(NO_2)_2$-2,3)	C_2H_5		(−) 128–130		557
			(+) 128–130		557
$CO(C_6H_4NO_2$-2)	C_2H_5		(−) 98–99		557
			(+) 98–99		557
COC_6H_5	C_2H_5		79		77
$CH_2(C_6H_2NO_2$-2-Cl-5)	C_2H_5		(−) 66–68		557
			N/A		690, 691
$COC_6H_4NH_2$-2	C_2H_5		N/A		685
$CH_2(C_6H_4NO_2$-2)	C_2H_5		(+) 91–92		557
			(−) 88–89	IR	557
			N/A		686
$CH_2C_6H_5$	C_2H_5		b.p.: 175–177/1.3		634
H	C_2H_5	1-C_6H_5-6-OCH_3-*trans*	HCl: 217–218	IR	479
CH_3	C_2H_5	1-C_6H_5-OH-*trans*	Oil	IR,NMR	479
H	CH_3	1-C_6H_5-6,7-$(OCH_3)_2$-*trans*	118	IR,NMR	479
			HCl: 215		479
$CH_2(C_6H_4NH_2$-2)	C_2H_5		(+) 85–86		557
			(−) 84–85	IR	557
			N/A		686, 687
$(CH_2)_4CO_2C_2H_5$	C_2H_5		b.p.: 169–170/0.1		614
COC_6H_5	C_2H_5	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	110–111.5	IR	684
CH_3	C_2H_5	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 185–195/0.05		688
$CO(C_6H_3NO_2$-2-Cl-3)	C_2H_5	6,7-O_2CH_2	(−) 181–182		557
$CO(C_6H_3NO_2$-2-F-4)	C_2H_5	6,7-O_2CH_2	(−) 112–114		557
$CO(C_6H_4NO_2$-2)	C_2H_5	6,7-O_2CH_2	(−) 141–142		557

TABLE III.5. 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylates (*Continued*)

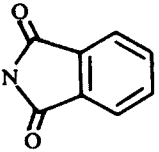
R	R^1	Substituents		m.p. (°C)	Spectroscopy	Ref.
$CO(C_6H_2NO_2$-2-O_2CH_2-3,4)	C_2H_5		(−)	140–142		557
			(+)	Liquid		557
$CO(C_6H_3NO_2$-2-OCH_3-5)	C_2H_5		(±)	130–131		557
$CH_2(C_6H_2NO_2$-2-O_2CH_2-4,5)	C_2H_5		(−)	87–89		557
$CH_2C_6H_4NH_2$-2	C_2H_5	6,7-O_2CH_2	(±)	111–113	IR	557
$CH_2C_6H_5$	C_2H_5	6-OCH_3		N/A		99
H	CH_3	1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6-7-$(OH)_2$	(1S,3S)	173–174	IR,NMR	576
			HCl:	144–147		576
			(1R,3S)	110–112	IR,NMR	576
			HCl:	185–188		576
			cis	173–174	IR,NMR	577
			trans	110–112	IR,NMR	577
$(CH_2)_5CO_2C_2H_5$	C_2H_5			b.p.: 174–176/0.3		614
$CH_2CH_2CH_2CO_2$-C_2H_5	C_2H_5	6,7-$(OCH_3)_2$		b.p.: 220–230/0.05		683
H	CH_3	6-OCH_3-1-CH_2-N 		138–140		476, 482, 483
$COCH_3$	CH_3	1-C_6H_5-6-O_2CCH_3-*cis*		169	IR,NMR	479
$COCH_3$	CH_3	1-C_6H_5-O_2CCH_3-*trans*		163	IR,NMR	479
$CO(C_6H_3NO_2$-2-Cl-3)	C_2H_5	6,7-$(OCH_3)_2$	(±)	163–166		557
$CO(C_6H_4NO_2$-2)	C_2H_5	6,7-$(OCH_3)_2$	(±)	141–144		557
$CO(C_6H_2NO_2$-2-$(OCH_3)_2$-3,4	C_2H_5		(−)	145–147		557
			(+)	150–152		557
$COCH_3$	CH_3	1-C_6H_5-6,7-$(OCH_3)_2$-*trans*		300	IR,NMR	479
$CH_2(C_6H_2NO_2$-$(OCH_3)_2$-3,4)	C_2H_5		(±)	131–133	IR	557
$CH_2(C_6H_3(OCH_3)_2$-3,4)	C_2H_5	6,7$(OCH_3)_2$		b.p.: 185–190/0.1		613
H	C_2H_5	3-CH_3-		81–84		649a
H	$CH(CH_3)_2$	6,7$(OCH_3)_2$		57–60		649a
H	$CH(CH_3)_2$	7,8$(OCH_3)_2$		b.p.: 130/0.03		649a
$CH_2CH_2C_6H_3$-$(OCH_3)_2$3,4	$CH(CH_3)_2$			b.p.: 180/0.06		649a
$CH_2CH_2C_6H_3$-$(OCH_3)_2$3,4	C_2H_5	6,7$(OCH_3)_2$		100–102		649a
$CH_2CH_2C_6H_3$-$(OCH_3)_2$3,4	$CH(CH_3)_2$	3-CH_3-6,7$(OCH_3)_2$		b.p.: 190/0.09		649a

TABLE III.5. 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylates (*Continued*)

R	R^1	Substituents	m.p. (°C)	Spectroscopy	Ref.
$CH_2CH_2C_6H_2(OCH_3)_3$-3,4,5	C_2H_5	6,7-$(OCH_3)_2$	92–94		649a
$CH_2CH_2C_6H_2(OCH_3)_3$-3,4,5	$CH(CH_3)_2$	7,8-$(OCH_3)_2$	b.p.: 150–185/0.05		649a
$CH_2CH_2C_6H_3(OCH_3)_2$-3,4	C_2H_5	1-CH_3-6,7-$(OCH_3)_2$	b.p.: 150–120/0.01		649b
H	C_2H_5	1-CH_3-6,7-$(OH)_2$	(1S3S)HCl: 220–221		649b
-CHO	C_2H_5	1-CH_3-6,7-$(OH)_2$	(1S3S)170–172		649b
$-CH_3$	C_2H_5	1-CH_3-6,7-$(OCH_3)_2$	(1S3S)HCl: 213		649b
H	C_2H_5	4-CH_3-6,7-$(OCH_3)_2$	67–78		649b
$CH_2CH_2C_6H_3(OCH_3)_2$-3,4	C_2H_5	4-CH_3-6,7-$(OCH_3)_2$	120–180/0.03		649b
$CH_2C_6H_5$	C_2H_5	4-OH-6,7-$(OCH_3)_2$	HCl: 198		82, 605
$CH_2C_6H_4NH_2$-2	C_2H_5	6,7-$(OCH_3)_2$	(±) 123–124	IR	557
COC_6H_5	C_2H_5	1-CH_3-6,7-$(OCH_3)_2$	(1S,3S) Oil	IR	537
H	CH_3	1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	(1S,3S) 126–128	IR,NMR	576
			(1R,3S) 95–96	IR,NMR	576
			1,3-*cis* 123–125		649
			cis 126–128		577
H	C_2H_5	1-$CH_2CH(C_6H_5)_2$-6,7-$(OCH_3)_2$	N/A		470
$CH_2CH_2C_6H_3(OCH_3)_2$-3,4	$CH(CH_3)_2$		b.p.: 180/0.6		600
CH_3	CH_3	1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	(1S,3S) 70–71	IR,NMR	576
			(1R,3S) 113–114	IR,NMR	576
$(CH_2)_3CO_2C_2H_5$	C_2H_5	6-OCH_3	b.p.: 200/2		88
$CH_2C_6H_5$	C_2H_5	1-$CH_2CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	α-isomer HCl: 172–173		485, 516
			β isomer 104.5–105.5		485, 516
			HCl: 147–148		485, 516
			Picrate: 122–123.5		485, 516

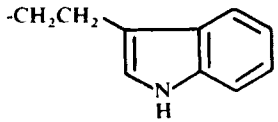
TABLE III.6. 1,2,3,4-Tetrahydroisoquinoline-4,5-,6-, and 7-Carboxylic Acid and Carboxylates

R	Substituent	m.p. (°C)	Spectroscopy	Ref.
CH_3	4-CO_2H	N/A		581
H	4-CO_2H-1,1-$(CH_3)_2$-6-OH	HCl: 295	IR, NMR	554
H	5-CO_2H-4,6,7-$(OH)_3$	HBr: 189–190		575
CH_3	5-CO_2H-7-NO_2	HCl: 239–242		192
H	5-CO_2H-1-CH_3-6,7-$(OCH_3)_2$	255–256		596
$COCH_3$	5-CO_2H-1-CH_3-6,7-$(OCH_3)_2$	178–179		596
H	7-CO_2H-1,1-$(CH_3)_2$-6-OH	N/A		562
H	4-$CO_2C_2H_5$	Picrate: 175–176		593
CH_3	4-CO_2CH_3	Picrate: 120		580, 581

TABLE III.6. 1,2,3,4-Tetrahydroisoquinoline-4,5-,6-, and 7-Carboxylic Acid and Carboxylates (*Continued*)

R	Substituent	m.p. (°C)	Spectroscopy	Ref.
H	4-$CO_2C_2H_5$-1,1-$(CH_3)_2$-6-OH HCl:	236	IR, NMR	554
CH_3	4-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	N/A		689
$CH_2CH_2CO_2C_2H_5$	4-$CO_2C_2H_5$	130.5–131.5		688
CH_3	4-$CO_2C_2H_5$-1-C_2H_5-6,7-$(OCH_3)_2$ HCl:	260		347
H	4-CO_2CH_3-3-C_6H_5-6,7-O_2CH_2			
	-trans	75.5–76.5	IR, NMR	548
	-cis HCl:	215–216	IR, NMR	548
CH_3	4-CO_2CH_3-3-C_6H_5-6,7-O_2CH_2-*trans*	127.5–129	IR	560
	-cis	135.5–1136.5		560
H	4-CO_2CH_3-3-C_6H_5-6,7-$(OCH_3)_2$-			
	trans	125–126	IR, NMR	548
	-cis	111.5–112.5	IR, NMR	548
H	4-CO_2CH_3-3-($C_6H_3O_2CH_2$-3,4)-6,7-$(OCH_3)_2$-*trans*	171–171.5	IR, NMR	548
	-cis	116–117	IR, NMR	635
CH_3	4-CO_2H-3-($C_6H_3O_2CH_2$-3,4)-6,7-$(OCH_3)_2$-*trans*	208–209	IR, NMR	635a
	-cis	229–230	IR, NMR	635a
CH_3	4-CO_2CH_3-3-C_6H_5-6,7-$(OCH_3)_2$-			
	trans	120–121	IR	560
	-cis	135–136		560
C_3H_7-*n*	4-CO_2CH_3-3-C_6H_5-6,7-O_2CH_2-*trans*	198–199	IR, NMR	635
	cis HCl:	148.5–150	IR, NMR	635
CH_3	4-CO_2CH_3-3-($C_6H_3O_2CH_2$-3,4)-6,7-$(OCH_3)_2$-*trans*	158–159	IR, NMR	548, 560
C_2H_5	4-CO_2CH_3-3-C_6H_5-6,7-$(OCH_3)_2$-			
	trans	107–107.5	IR, NMR	635
	-cis HCl:	116–117	IR, NMR	635
H	4-CO_2CH_3-3-($C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$-*trans*	185–186	IR, NMR	548
H	*cis*	130–131	IR, NMR	635
C_3H_7-*n*	4-CO_2CH_3-3-C_6H_5-6,7-$(OCH_3)_2$-			
	trans	106–107	IR, NMR	635
	-cis	116–117	IR, NMR	635
CH_3	4-CO_2CH_3-3-($C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$-*trans*	184–185	IR, NMR	559, 560
C_3H_7-*n*	4-CO_3CH_3-3-($C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$-*trans*	134–135	IR, NMR	635
	-cis	Oil	IR, NMR	635
$CH_2C_6H_5$	4-CO_2CH_3-3-C_6H_5-6,7-O_2CH_2			
	-trans	172–173	IR, NMR	635
	-cis	185–186	IR, NMR	635
$CH_2C_6H_5$	4-CO_2CH_3-3-C_6H_5-6,7-$(OCH_3)_2$			
	-trans	131.5–132.5	IR, NMR	635
	-cis	133–134	IR, NMR	635

TABLE III.6. 1,2,3,4-Tetrahydroisoquinoline-4,5-,6-, and 7-Carboxylic Acid and Carboxylates (*Continued*)

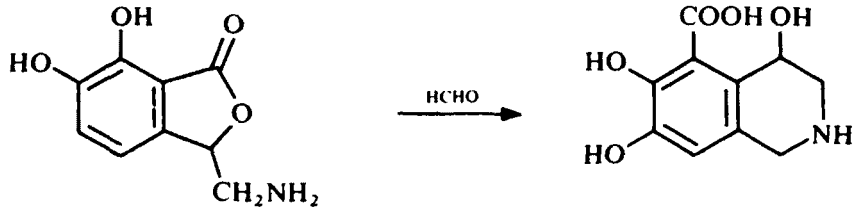
R	Substituents	m.p. (°C)	Spectroscopy	Ref.
CH_3	5-CO_2CH_3-7-NO_2	129–130		192
		HCl: 195–198		192
CH_3	5-CO_2CH_3	b.p.: 110/0.1	IR, NMR	78
		Picrate: 166–167		78
CH_3	5-CO_2CH_3-7-OH	180181		192
H	5-CO_2CH_3-4-OCH_3-6,7-$(OH)_2$	HCl: 181		575
CH_3	5-CO_2CH_3-7-NH_2	144–146		192
		HI: 219		192
C_2H_5	5-CO_2CH_3	187–188		11
CH_3	5-CO_2CH_3-7-$NHCOCH_3$	93–95		192
H	5-$CO_2C_2H_5$-4-OC_2H_5-6,7-$(OH)_2$	HCl: 171 172		575
-CH_2CH_2 				
	5-CO_2CH_3	130–131		119
		HBr: 204–206		119
		Picrate: 186–194		119
CH_3	5-CO_2CH_3-7-$NHCO(C_6H_2(OCH_3)_3$-3,4,5)	170–171		192
H	6-CO_2CH_3-1-$CH_2(C_6H_2(OCH_3)_3$-3,4,5)-7-OH	Oil	IR, NMR	92
		HCl: 186–188	UV	92
H	6-CO_2CH_3-1-$CH_2(C_6H_2(OCH_3)_3$-3,4,5)-5-OH	Oil	IR, NMR	92
		HCl: 213–215	UV	92
C_2H_5	7-CO_2CH_3	215.2–216.1		11
H	7-CO-C_2H_5-1,1-$(CH_3)_2$-6-OH	N/A		562
H	7-CO_2CH_3-1-$CH_2(C_6H_2(OCH_3)_3$-3,4,5)-6-OH	HCl: 135–138	IR, UV, NMR	92
CH_3	5-$CONHNH_2$-7-NO_2	185		192

(*a*) 1,2,3,4-*Tetrahydroisoquinolinecarboxylic Acids and Esters*

Since most synthetic procedures can be applied to all acidic derivatives of 1,2,3,4-tetrahydroisoquinolines and not just to carboxylic acids and esters, those methods will be discussed in this section and not repeated in Section III.A (*a*).

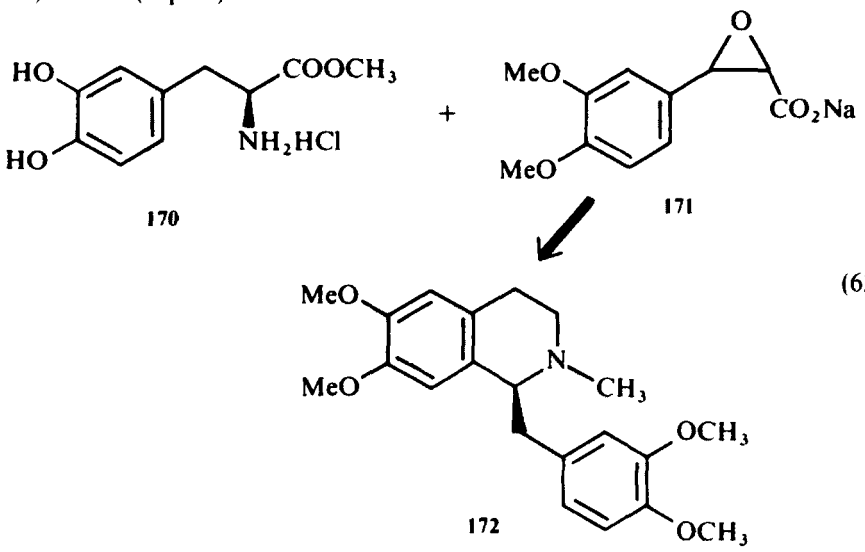
Perhaps the most frequently used synthetic procedure involves some variation of the Pictet–Spengler reaction, which is the condensation of a phenethylamine derivative with a carbonyl compound generally under mild acid catalysis.[80, 112, 113, 428, 479, 517, 532–574] Thus, phenylalanine derivatives provide the 3-

carboxylic acids or esters while pyruvates afford the 1-carboxylic acids or esters. 2-C^{14}-pyruvate has been used to introduce C^{14}.[564] A number of variations on this basic reaction have been reported. The reaction of **168** with formaldehyde gives 4,6,7-trihydroxy-1,2,3,4-tetrahydroisoquinoline-5-carboxylic acid (**169**)[575] (Eq. 61).



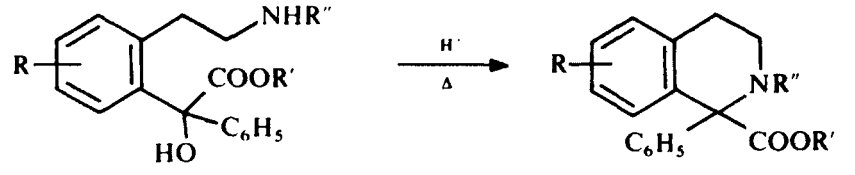
168 **169** (61)

The asymmetric Pictet–Spengler reaction of L-3-(3,4-dihydroxyphenyl)alanine methyl ester hydrochloride (**170**) with sodium (3,4-dimethoxyphenyl)glycidate (**171**) proceeds by a 1,3 transfer of asymmetry to afford, after appropriate chemical transformations, the benzylisoquinoline alkaloid (*S*)-laudanosine (**172**)[576, 577] (Eq. 62).



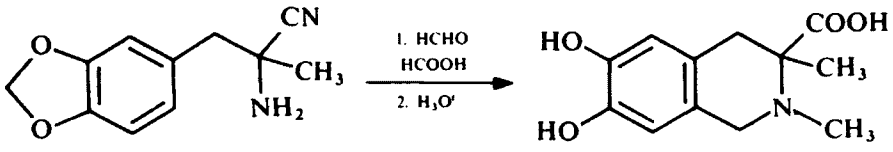
170 **171** **172** (62)

Treatment of **173** with acid leads to **174**[578] (Eq. 63).



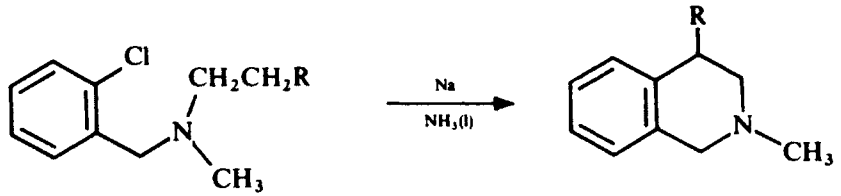
173 **174** (63)

Reaction of **175** with formaldehyde–formic acid followed by hydrolysis gave **176**[579] (Eq. 64).



175 **176** (64)

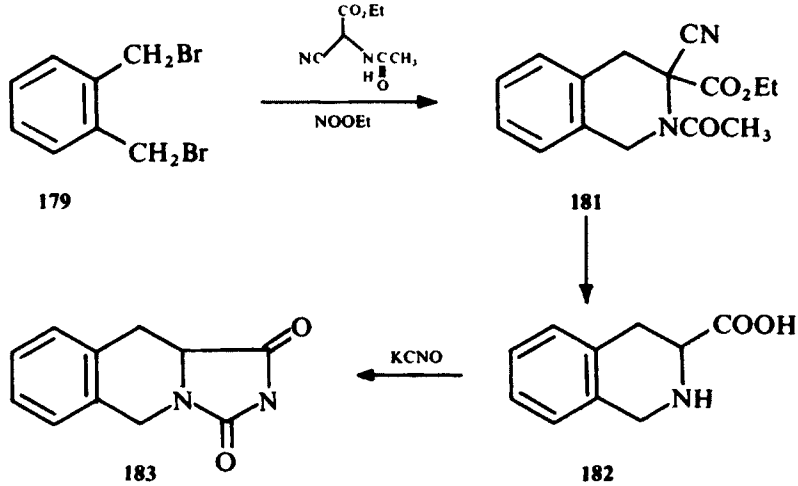
Reaction of **177** with sodium amide in liquid ammonia leads to **178**[580, 581] (Eq. 65). The cyclization of 2-(β-chloroethyl)-benzyl chlorides with amines has also been used to prepare tetrahydroisoquinolines.[582]



177

(R = $COOCH_3$,CN) **178** (65)

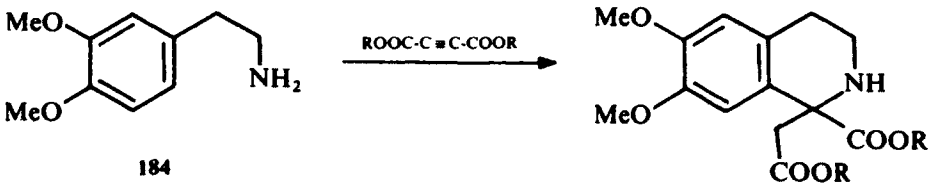
The base-catalyzed condensation of *o*-xylene bromide (**179**) with **180** provides in 43% yield ethyl 2-acetyl-3-cyano-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**181**), which can be hydrolyzed and decarboxylated to the amino acid **182**.[583] The reaction of **182** with potassium cyanate affords **183**[693a] (Eq. 66).



179 **181** (66)

183 **182**

The Michael adduct obtained from homoveratrylamine (**184**) reacting with an acetylenedicarboxylic ester cyclizes under mild conditions to give **185**[583a] (Eq. 67).



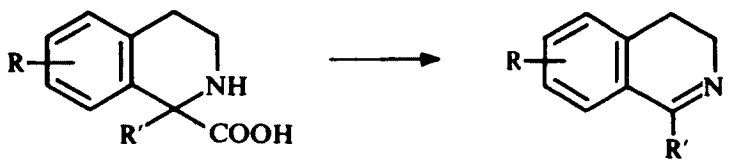
184 185 (67)

A number of compounds in this series have been isolated from natural sources.[533, 541, 584]

Reduction of dihydroisoquinolines containing acidic groups with borohydride, catalytic hydrogenation, and zinc and acid[86, 92, 134, 156, 347, 376, 436, 441, 442, 444, 445, 449, 451, 464, 468, 470, 473, 478–481, 485, 490, 491, 493, 495, 497, 506, 507, 513, 516, 527, 585–592] and reduction of isoquinolinium salts containing acidic groups with borohydride or catalytic hydrogenation[1, 5, 11, 23, 63, 105, 119, 126, 192, 347, 477, 593–595] has led to 1,2,3,4-tetrahydroisoquinolines containing acid derivatives. Oxidation of side chains[549, 596] and ring-cleavage reactions[597, 598] have also been used.

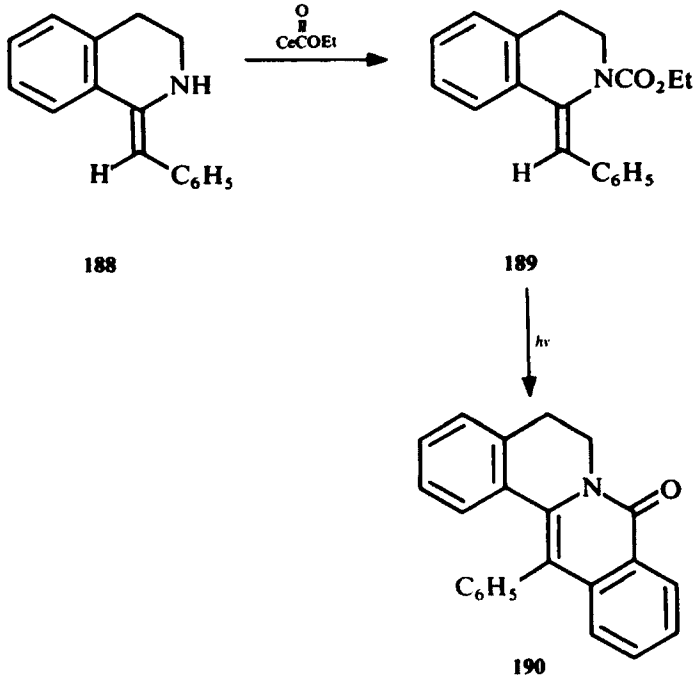
A variety of transformations typical of esters and acids have been reported. Thus both esterification[65, 192, 445, 479, 498, 532, 543, 544, 556, 557, 568, 571, 578, 594, 599–603] and ester hydrolysis[86, 126, 445, 502, 507, 537, 544, 547, 554, 562, 588, 590, 600, 603–613] have been reported. In addition, nitriles have been used to prepare both esters[491, 499, 573, 593, 599, 614] and acids.[192, 498, 534, 580, 581, 603, 615–617] Amides have been converted to acids,[253, 362, 615, 618, 619] acids to amides,[620, 621] and esters to amides[491, 563, 577, 621–633] and hydrazides.[192, 544] Lithium aluminium hydride reduction of esters and acids give primary alcohols.[497, 498, 593, 634, 635] Esterification of 4,6,7-trihydroxy-1,2,3,4-isoquinoline-5-carboxylic acid leads to the 4-alkoxy esters.[575]

Decarboxylations have also been reported. The decarboxylation of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids takes place more readily with NH than with *N*-methyl.[636] Oxidative decarboxylation of a series of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids, including the 7-hydroxy derivatives takes place easily, except in the case of the 7-methoxy derivative.[637, 637a] Treatment of **186** with hydriodic acid leads with decarboxylation to a 3,4-dihydroisoquinoline **187**[638, 639] (Eq. 68). The half-wave potential of a series of 1-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids has been studied.[534]



186 187 (68)

The reaction of chloroformates, particularly ethyl chloroformate[556, 640-643] with tetrahydroisoquinolines leads to *N*-carboalkoxy derivatives. The reaction of 1-benzylidene-2-carbethoxy-1,2,3,4-tetrahydroisoquinoline (**188**) with ethyl chloroformate leads to **189**,[578, 642, 644-646] which undergoes an oxidative irradiation to afford the oxyprotoberberine **190**[647] (Eq. 69).



188 **189** **190** (69)

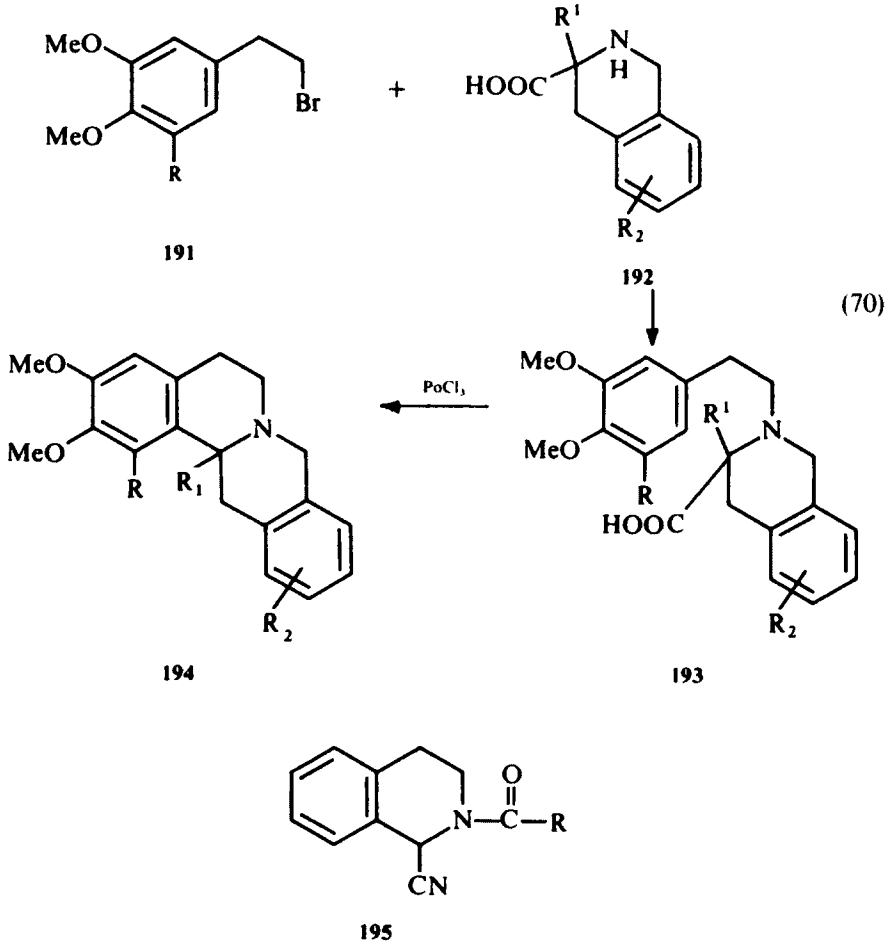
Compounds **194**, prepared from **193**, have been used to prepare berbines, a class of naturally occurring and synthetic isoquinoline alkaloids[649a, b] (Eq. 70).

The thin-layer chromatographic behavior of diastereomeric methyl 6,7-dialkoxy-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylates have been studied.[648] The stereochemistry involved in the synthesis of these compounds[548, 559-560] and an NMR study of the conformation of the compounds[635] has appeared. Isomerization reactions of certain methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylates have been studied in connection with alkaloid syntheses.[649]

(*b*) *Other* 1,2,3,4-*Tetrahydroisoquinoline Derivatives*

(i) Cyano, Amide, and Hydrazide Groups on the Ring

3,4-Dihydroisoquinolines behave in a similar manner to isoquinolines and react with acid chlorides and cyanide ion to give **195**[37, 249, 253, 256, 313, 534, 603, 655, 664, 693] Benzoyl cyanide also leads to the same



product.[597, 598] These compounds have been alkylated in the 1 position in the same manner as Reissert compounds.[342, 534, 603, 637a, 664, 692] Reaction of **3** with aqueous hypochlorous acid leads to **196**,[693] which when treated with Et_3N rearranges to the isochromene **197** (Eq. 71).

The fluoroborate salts of **195** have been investigated.[255] Reissert analogs of the type **195** ($R=OC_2H_5$) have been reacted with benzaldehyde to give **198**.[693a]

The reaction of 3,4-dihydroisoquinolinium salts with cyanide ions leads to the cyanides **199**.[203, 342, 343, 446, 453, 510, 618, 619, 628, 694–712] This reaction is reversible[694, 699–701, 707, 712] and the equilibrium has been studied.[713] While the reduction of **200b**[342] or **200c**[342a] with lithium aluminum hydride gives the 1-aminomethyl products **202b,c**, reduction of **200a** gives 1,1′-bis-(1,2,3,4-tetrahydroisoquinolyl) (**201**) (Eq. 72).

The conversion of **203** to 6.7-dimethoxy-1-cyano-2(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**204**) by reaction with hydrogen cyanide can be considered

TABLE III.7. 1,2,3,4-Tetrahydroisoquinoline Carbonitriles

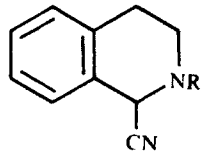
R	Substituents		m.p. (°C)	Ref.
	1-Cyano			
				
H[a]			160–162	664
			158–161	342a
CH_3			76–78	725
			77–78	705
$COCH_3$[a]			114–116	664
CO_2CH_3[a]			110–112	664
C_2H_5			51–52	342
CH_3	1-CH_3	($N^+CH_3I^-$)	159	342
CH_2OCH_3			82	342
CH_2CH_2OH			83.5	707
H	6,7-$(OCH_3)_2$		N/A	618, 619
CH_3	5-Br-6,7-O_2CH_2-8-OCH_3		152–153	725
$COCH_3$[a]	1-CH_3		142–143	664
$CO_2C_2H_5$[a]			99–100	664
CH_3	6,7-O_2CH_2-8-OCH_3		95–96	725
$CH_2CH_2CONH_2$			112	510
H	1-CH_2Cl-6,7-$(OCH_3)_2$		125	446
CH_3	6,7-$(OCH_3)_2$		127–128	619, 704, 725
$C_6H_5CH_2$	6,7-$(OCH_3)_2$		107–108	342a
$COCCl_3$	6,7-$(OCH_3)_2$		N/A	249
$CO_2C_2H_5$[a,b]	6,7-CH_2O_2		103–105	338
CH_2CONH_2	6,7-O_2CH_2-8-OCH_3		152.5	510
$COCH_3$[a]	1-C_2H_5		78–80	664
-$(CH_2)_2COCH_3$			95–97	712
$COCH_3$[a]	1-CH_2OCH_3		82–83	664
$COCH_3$	6,7-$(OCH_3)_2$		200	256
CH_2CONH_2	6,7-$(OCH_3)_2$		188	510
CH_3	1-CH_3-6,7-$(OCH_3)_2$		N/A	726
CH_2CH_2OH[a]	6,7-$(OCH_3)_2$		N/A	706
$COCH_3$[a]	1-$CO_2C_2H_5$		134–136	664
$CH_2CH_2CONH_2$	6,7-O_2CH_2-8-OCH_3		167	510
$CH_2CH_2CONH_2$	6,7-$(OCH_3)_2$		152	510
C_3H_7	6,7-$(OCH_3)_2$		70–72	725
			N/A	619
$(CH_2)_2CH_2OH$[a]	6,7-$(OCH_3)_2$		53–54	706
-$(CH_6H_3(NO_2)_2$-2,4-	5-Br		141	727
-$C_6H_3(NO_2)_2$-2,4	8-Br		183	727
-$C_6H_3(NO_2)$-2,4	5-Cl		143–144	727
-$C_6H_3(NO_2)_2$-2,4	8-Cl		176–177	727
$C_6H_3(NO_2)_2$-2,4	5-I		143	727
$C_6H_2Br_3$-2,4,6			130	694
$C_6H_3Cl_2$-2,4			144	694

TABLE III.7. 1,2,3,4-Tetrahydroisoquinoline Carbonitriles (*Continued*)

R	Substituents	m.p. (°C)	Ref.
$C_6H_3Cl_2$-2,5		175	694
C_6H_4Br-4		157–158	694
C_6H_4Cl-4		153–154	694
C_6H_4F-4		136	694
$C_6H_4NO_2$-2		151–152	694
$C_6H_4NO_2$-3		170–171	694
$C_6H_4NO_2$-4		151–152	694, 695
		142–143	695
C_6H_5		96–96.5	694
$-(CH_2)_2COCH_3$	6,7-O_2CH_2-8-OCH_3	210–212	712
$CO(CH_2)_3Cl$	6,7-$(OCH_3)_2$	158–159	37
CH_3	3-CH_2-CH=CH_2-6,7-$(OCH_3)_2$	73–75	700
		75	699
$-(CH_2)_2COCH_3$	6,7-$(OCH_3)_2$	116–117	712
COC_6H_5	3-OH-4-Cl	176–178	693
COC_6H_5		104–105	253
		123–124	256
		N/A	255
$CO_2C_6H_5$[a]		133–134	644
$SO_2C_6H_4$-CH_3-4	3,4-Br_2	118–118.5[a,b,c]	335
$-C_6H_3(NO_2)_2$-2,4	5-OCH_3	159	727
$-C_6H_3(NO_2)_2$-2,4	6-OCH_3	139	727
$-C_6H_3(NO_2)_2$-2,4	8-OCH_3	163	727
$SO_2C_6H_4$-CH_3-4	3-OH-4-Br	184[a–c]	335
$C_6H_4CH_3$-2		137	694
$-(CH_2)_2COCH_2CH_3$	6,7-$(OCH_3)_2$	104–106	712
COC_6H_5	1-CH_3-6-OCH_3-7-$OCH_2C_6H_5$	179–181	637a
COC_6H_5	1-$C_6H_5CH_2$-6-OCH_3-7-$OCH_2C_6H_5$	178–180	637a
$-C_6H_4Cl$-2	6,7-O_2CH_2-8-OCH_3	163–165	695
$-C_6H_4NO_2$-2	6,7-O_2CH_2-8-OCH_3	153–154	695
$-C_6H_4NO_2$-4	6,7-O_2CH_2-8-OCH_3	200–202	695
COC_6H_5	1-CH_3	162–163	342
CH_3	1-$CH_2(C_6H_4NO_2$-2)	98–100	41
CH_3	3-$CH_2(C_6H_4NO_2$-2)	102–103	41
$-C_6H_4NO_2$-2	6,7-$(OCH_3)_2$	151	695
$-C_6H_4NO_2$-4	6,7-$(OCH_3)_2$	179–180	695
CH_3	3-$CH_2C_6H_5$	87–88	701
$-CH_2CH(C_2H_5)COCH_3$	6,7-$(OCH_3)_2$	127–128	712
$-(CH_2)_2COCH(CH_3)_2$	6,7-$(OCH_3)_2$	82–83	712
$COCH_3$[a]	1-COC_6H_5	208–210	664
COC_6H_5	1-$COCH_3$	204–206	342
$COCH_3$[a]	1-$CH_2C_6H_5$	180–181	664
COC_6H_5	1-C_2H_5	137–139	342
COC_6H_5	1-CH_2SCH_3	90–91	342
COC_6H_5	1-CH_2OCH_3	110–112	342
COC_6H_5	6,7-$(OCH_3)_2$	212–213	313
		215–216[a]	603
$SO_2C_6H_4$-CH_3-4	3-OC_2H_5-4-Br	169[a–c]	335
CH_3	3-$CH_2C_6H_5$-7-OCH_3	109–110	701

TABLE III.7. 1,2,3,4-Tetrahydroisoquinoline Carbonitriles (*Continued*)

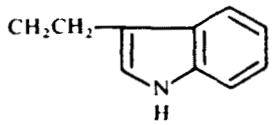
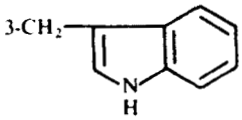
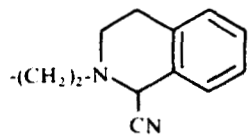
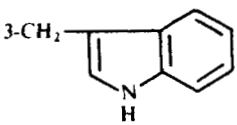
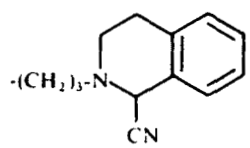
R	Substituents	m.p. (°C)	Ref.
COC_6H_5	1-CH_2CH_2CN	136	342
$CH_2(C_6H_3O_2CH_2$-3,4)	1-CH_2NO_2-6,7-O_2CH_2	151	728
		108–110 128–129	453 729
CH_3	3-$CH_2(C_6H_4Br$-4)-6,7-$(OCH_3)_2$	136–137	41
$SO_2C_6H_4$-CH_3-4	3-$OCH(CH_3)_2$-4-Br	166[a] [c]	335
CH_3	3-$CH_2C_6H_5$-6,7-$(OCH_3)_2$	140–141	698
CH_3	 6-OCH_3	153–154	708, 730[c]
CH_3	1-$CH_2C_6H_5$-3,3-$(CH_3)_2$-6-OCH_3	98	696
CH_3	3-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6-OCH_3	148.5–149.5	730
$CH_2(C_6H_3(OCH_3)_2$-2,3)	6,7-$(OCH_3)_2$	125	203
$CH_2(C_6H_3(OCH_3)_2$-3,4)	6,7-$(OCH_3)_2$	98	343
		200	342
COC_6H_5	3-$CH_2CH{=}CH_2$-6,7-$(OCH_3)_2$	N/A	692
CH_3	 6,7-$(OCH_3)_2$	149–150	708, 730[c]
COC_6H_5	1-$CON(C_2H_5)_2$	209	342
CH_3	3-$CH_2CH{=}CHC_6H_5$-6,7-$(OCH_3)_2$	99–100	699
CH_3	1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	145–147	702
CH_3	3-CH_2-$(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	129 115–117	698 697, 702
		172	342
$CH_2CH(CH_2C_6H_5)COCH_3$	6,7-$(OCH_3)_2$	107–109	712

TABLE III.7. 1,2,3,4-Tetrahydroisoquinoline Carbonitriles (*Continued*)

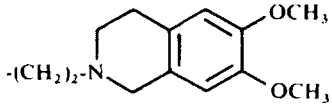
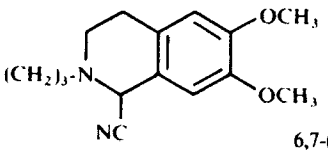
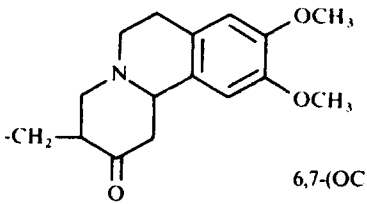
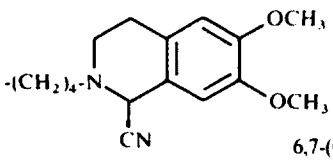
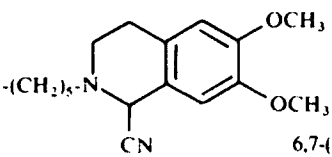
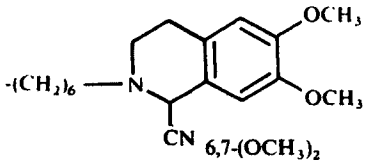
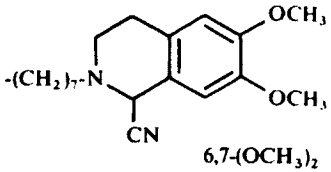
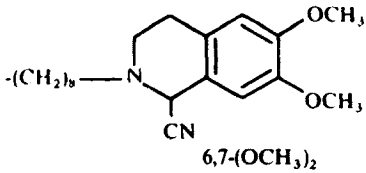
R	Substituents	m.p. (°C)	Ref.
COC_6H_5	1-COC_6H_5	218	342
COC_6H_5	1-$CSNHC_6H_5$	153–155	342
COC_6H_5	1-$CONHC_6H_5$	186	342
CH_3	3-CH_2-($C_6H_3(OC_2H_5)_2$-3,4)-6,7-$(OCH_3)_2$	141–142	697
CH_3	3-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OC_2H_5)_2$	93–94	697
COC_6H_5	1-C_6H_5-6,7-$(OCH_3)_2$	190	597, 598
COC_6H_5	6-OCH_3-7-$OCH_2C_6H_5$	178–180	534
COC_6H_5[a,b]	1-$CH_2C_6H_5$-C,7-$(OCH_3)_2$	185–186	603
	6,7-$(OCH_3)_2$	212–213	709
CH_3	3-CH_2-($C_6H_3(OC_2H_5)_2$-3,4)-6,7-$(OC_2H_5)_2$	106–108	697
COC_6H_5[a–c]	1-$CH_2(C_6H_3O_2CH_2$-3,4)-6,7-$(OCH_3)_2$	191–192	603
COC_6H_5[a–c]	1-$CH_2(C_6H_3O_2CH_2$-2,3)-6,7-$(OCH_3)_2$	187–188	603
COC_6H_5	1-C_6H_5-6,7-$(OC_2H_5)_2$	128–129	655
CH_3	3,4-$(CH_2C_6H_5)_2$-6,7-$(OCH_3)_2$	116–117	601
	6,7-$(OCH_3)_2$	153–154	709
	6,7-$(OCH_3)_2$	186	710, 711
	6,7-$(OCH_3)_2$	170	709
	6,7-$(OCH_3)_2$	145–146	709

TABLE III.7. 1,2,3,4-Tetrahydroisoquinoline Carbonitriles (*Continued*)

R	Substituents	m.p. (°C)	Ref.
	6,7-$(OCH_3)_2$	135–136	709
COC_6H_5[d]	1-$CH_2(C_6H_3(OCH_3)_{32}$-3,4)-3-CH_2-CH=CH-6,7-$(OCH_3)_2$	169–170	692
	6,7-$(OCH_3)_2$	138	709
	6,7-$(OCH_3)_2$	138	709
COC_6H_5	1-$CH_2(C_6H_4OCH_2C_6H_5$-4)-6,7-$(OCH_3)_2$	153–153	534

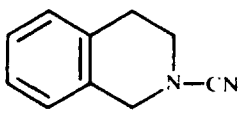
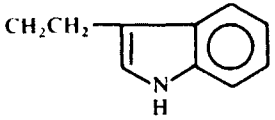
Substituents	m.p. (°C)	Ref.
2-Cyano 		
	b.p.: 125–130/0.05	719
	44	718
	52–53	348
	42.5–43.5	717
	43–44	723
	38–40	720
	N/A	714
	N/A[b]	731
Complex with $Ni(CO)_4$	117–124	718
5-OH	140–142	717
3-CF_3	61–62	715, 716, 732
5-CH_3	55–57	717
7-CH_3	75–75.5	717
1-CH_3-6-OH	95–97	717

TABLE III.7. 1,2,3,4-Tetrahydroisoquinoline Carbonitriles (*Continued*)

Substituents	m.p. (°C)	Ref.
1-C_2F_5	56–57	715, 716, 732
5-$NHCOCH_3$	192–193	717
1,3-$(OCH_3)_2$-4-Br	136	191
1,5-$(CH_3)_2$	67–68	717
1,8-$(CH_3)_2$	72.5–74	717
3,5-$(CH_3)_2$	77–78	717
6,7-$(OCH_3)_2$	124–126	719
1-CH_3-6-OH-7-OCH_3	96–98	719
1-C_3F_7	67–68	715, 716, 732
1-$(CH_2)_3$Br	N/A	617
1-CH_3-6,7-$(OCH_3)_2$	72–74	719
3-CH_3-6,7-$(OCH_3)_2$	97–101	717
1-$(CH_2)_3$CN	220–230/0.07	617
1-$(CH_2)_3CO_2H$	N/A	617
1-CH(OH)Ar	N/A	314
3-$(C_6H_2O_2$-4,5-$CH{=}CH_2)$-7,8-$(OCH_3)_2$	165–167	721, 722
3-$(C_6H_2O_2CH_2$-4,5-CH_2CH_2Br-2)-7,8-$(OCH_3)_2$	174–175	721, 722
6,7-$(OCH_2C_6H_5)_2$	101–103	717
1-CH_3-6,7-$(OCH_2C_6H_5)_2$	76–77	717
3-$(C_6H_2O_2CH_2$-4,5-$CH_2CH_2N(C_2H_5)_2$-7,8-$(OCH_3)_2$	127–128	721, 722
	HCl: 202–204	721, 722
	($NC_2^+H_5I^-$) 246–248	721, 722

R	Substituent	m.p. (°C)	Ref.
	3-,4- and 5-Cyano		
CH_3[a]	3-CN	71–72	622
$COCH_3$	3-CN-3-$CO_2C_2H_5$	143–145	583
$CH_2C_6H_5$	3-CN-1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$ (1S, 3S)	Oi	575
$CH_2C_6H_5$[a,b]	4-CN-3-$(C_6H_3O_2CH_2$-3,4)-6,7-$(OCH_3)_2$	156–157	724
$CH_2C_6H_5$	4-CN-3-$(C_6H_3(OCH_3)_2$-3,4)-6,7-O_2CH_2	N/A	733
$CH_2C_6H_5$[a,b]	4-CN-3-$(C_6H_4OCH_3$-4)-6,7-$(OCH_3)_2$	158.5–160	724
$CH_2C_6H_5$	4-CN-3-$(C_6H_3(OCH_3)_2$-3,4)-6-OCH_3	N/A	733
CH_3	5-CN	52	192
		b.p.: 75/0.1	192
CH_3[b]	5-CN-7-NO_2	111–112	192
	5-CN	185–187	119
		HBr: 222–225	119
		Picrate: 184–187	119
CH_3	3-CN-5-Br-8-NO_2	145–149	733a

[a] IR in paper.
[b] NMR in paper.
[c] UV in paper.
[d] Mass spectroscopy in paper.

TABLE III.8. 1,2,3,4-Tetrahydroisoquinoline with Amides and Hydrazides on Ring

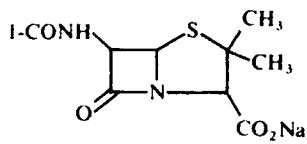
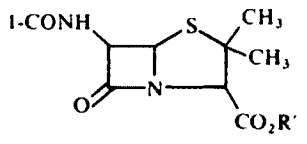
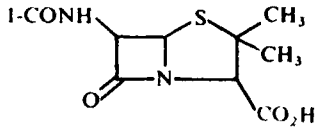
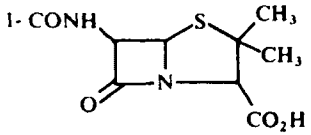
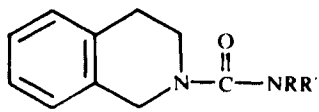
R	R^1	Substituents	m.p. (°C)	Ref.
		1-Position		
H		1-$CONH_2$	178–180[a,b]	176
			168–169	368
			180–183	205
			182–183	253
			HBr: 285–286	205
H		1-$CONHNH_2$-4,6-$(OH)_2$	212–215	544
CH_3		1-$CONHNH_2$-4,6-$(OH)_2$	222–224	544
H		1-$CONH_2$-6,7-$(OCH_3)_2$	N/A	618, 619
C_2H_5		1-$CONHNH_2$-4,6-$(OH)_2$	219–220	544
CH_3		1-$CONHN{=}C(CH_3)_2$-4,6-$(OH)_2$	204–206	544
H		1-$CONHC_6H_5$	138.5–139.4	202
CH_3		1-$CONHN{=}C(CH_3)C_2H_5$-4,6-$(OH)_2$	192–194	544
$CH_2C_6H_5$		1-$CONH_2$	150–151	253
			HCl: 251	253
H		1-$CONH(C_6H_4Cl$-4)-6,7-$(OCH_3)_2$	121.4–125.8	623–628
CH_3		1-$CONHN{=}CHC_6H_4OH$-4,6-$(OH)_2$	215	544
C_2H_5		1-$CONHC_6H_5$	101–102	202
			HCl: 244–246	202
H		1-$CONHC_6H_5$-6,7-$(OCH_3)_2$	162–165	623–628
			HCl: 237–245	623–628
H			180	651
$CH_2(C_6H_3(OCH_3)_2$-3,4)		1-$CONH_2$	179	362
			Perchlorate: 209–210	362
$CH_2(C_6H_3(OCH_3)_2$-3,4)		1-$CONH_2$	Perchlorate: 204–205	362
H		1-$CONHCH_2C_6H_5$-6,7-$(OCH_3)_2$	160–161	623–628
CH_3		1-$CONHC_6H_5$-6,7-$(OCH_3)_2$	175–177	623–628
COC_6H_5		1-CN-1-CH_2CH_2CN	136	342
$COCH_2Cl$		1-$CONHC_6H_5$-6,7-$(OCH_3)_2$	182–183	623–628
H		1-$CONH_2$-1-C_6H_5-6,7-$(OC_2H_5)_2$	156	655
			HCl: 163–165	655
R			N/A	734
CH_3		1-$CH(CN)(C_6H_2NO_2$-2-$(OCH_3)_2$-3,4)-6-OCH_3	125–127	735
H		1-$CONHC_6H_5$-1-CH_2-6,7-$(OC_2H_5)_2$	133	545
$CH_2(C_6H_3(OCH_3)_2$-2,3)		1-$CONH_2$-6,7-$(OCH_3)_2$	192	203
$CH_2(C_6H_3(OCH_3)_2$-3,4)		1-$CONH_2$-6,7-$(OCH_3)_2$	189–192	362
COC_6H_5		1-$CON(C_2H_5)_2$-1-CN	209	342

TABLE III.8. 1,2,3,4-Tetrahydroisoquinoline with Amides and Hydrazides on Ring (*Continued*)

R	R^1	Substituents	m.p. (°C)	Ref.
H		1-$CONHCH_2CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	142	506
COC_6H_5		1-$CONHC_6H_5$	186	342
H		1-$CONH_2$-1-$(C_6H_3(OC_2H_5)_2$-3,4)-6,7-$(OC_2H_5)_2$	117	655
			HCl: 186–188	655
$CH_2C_6H_5$				
			DL 120–200	651
$CO_2CH_2C_6H_5$				
			DL N/A	651

2-Position



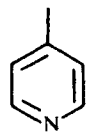
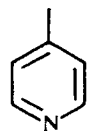
H	C_6H_4Cl-3	1,1=CH_2	80–85	736
H[b,c]	C_6H_5	1,1=CH_2	105–107	736
H	H	3,3-$(CH_3)_2$-1- 	180–180.5	737
H	H	1-CH_2Ar	N/A	314
R	R^1	4-OH-4-Ar	N/A	738
H	C_2H_5	3,3-$(CH_3)_2$-1- 	181–182	737
H	H	3-$(C_6H_2O_2CH_2$-4,5-CH=CH_2-2)-7,8-$(OCH_3)_2$	192–194	721, 722

TABLE III.8. 1,2,3,4-Tetrahydroisoquinoline with Amides and Hydrazides on Ring (*Continued*)

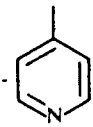
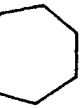
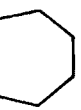
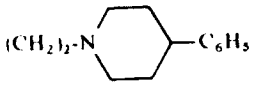
R	R^1	Substituents	m.p. (°C)	Ref.
H	C_6H_5	3,3-$(CH_3)_2$-1- 	165–166	737
H	CH_2CH_2-N 	1-C_6H_5-6,7-$(OCH_3)_2$	130–131	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-C_6H_5	101–103	739
H	$CH_2CH_2N(C_2H_5)_2$	1-C_6H_5-6,7-$(OCH_3)_2$	97–98	739
H	$(CH_2)_2$-N 	1-(C_6H_4F-4)-6,7-$(OCH_3)_2$	95–96	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-C_6H_5-6,7-O_2CH_2	121–122	739
H	CH_2CH_2-N 	1-C_6H_5-6,7-$(OCH_3)_2$	101–102	739
H	H	3-($C_6H_2O_2CH_2$-4,5- $CH_2CH_2N(C_2H_5)_2$-2-)-7,8-$(OCH_3)_2$	149.5–151	721, 722
H	$(CH_2)_3N(C_2H_5)_2$	1-C_6H_5-6,7-$(OCH_3)_2$	92–93	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-C_6H_5-6-OH-7-OCH_3	91–92	739
H	$(CH_2)_2$-N 	1-(C_6H_4Br-2)-6,7-$(OCH_3)_2$	146–149	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-($C_6H_3Cl_2$-2,6)-6,7-$(OCH_3)_2$	106–107	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-C_6H_5-6,7-$O_2C_2H_5$	112–113	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-(C_6H_4Br-2)-6,7-$(OCH_3)_2$	143–145	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-(C_6H_4Cl-2)-6,7-$(OCH_3)_2$	78–81	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-(C_6H_4Cl-4)-6,7-$(OCH_3)_2$	128–129	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-(C_6H_4F-4)-6,7-$(OCH_3)_2$	136-137	739
H	$CH_2CH_2N(C_3H_7\text{-}i)_2$	1-C_6H_5-6,7-$(OCH_3)_2$	109–110	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-(C_6H_4Br-2)-6,7-$(OCH_3)_2$	139–140	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-(C_6H_4Cl-2)-6,7-$(OCH_3)_2$	126–129	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-(C_6H_4Cl-4)-6,7-$(OCH_3)_2$	142–143	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-(C_6H_4F-4)-6,7-$(OCH_3)_2$	149–150	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-C_6H_5-6,7-$(OCH_3)_2$	136–138	739
H	$(CH_2)_2$-N 	1-($C_6H_4CH_3$-2)-6,7-$(OCH_3)_2$	165–167	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-$CH_2C_6H_5$-6,7-$(OCH_3)_2$	87–89	739

TABLE III.8. 1,2,3,4-Tetrahydroisoquinoline with Amides and Hydrazides on Ring (*Continued*)

R	R'	Substituents	m.p. (°C)	Ref.
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-$(C_6H_4CH_2$-2)-6,7-$(OCH_3)_2$	230–233	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-$(C_6H_4CH_3$-2)-6,7-$(OCH_3)_2$	145–146	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-$CH_2C_6H_5$-6,7-$(OCH_3)_2$	Oil	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-$(C_6H_4OC_2H_5$-2)-6,7-$(OCH_3)_2$	127–128	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-$(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	114–115	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-$(C_6H_4OC_2H_5$-2)-6,7-$(OCH_3)_2$	136–137	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-$(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	112–113	739
H		1-C_6H_5-6,7-$(OCH_3)_2$	166–167	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-C_6H_5-7-OCH_3-6-$OCH_2C_6H_5$	150–152	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-C_6H_5-7-$OCH_2C_6H_5$-6-OCH_3	142–144	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-C_6H_5-7-OCH_3-8-$OCH_2C_6H_5$	109–110	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-C_6H_5-7-$OCH_2C_6H_5$-6-OCH_3	109–111	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-C_6H_5-6-$OCH_2C_6H_5$-7-OCH_3	109–110	739
H	$(CH_2)_2N(C_3H_7\text{-}i)_2$	1-C_6H_5-6,7-$(OCH_2C_6H_5)_2$	132–133	739
H	$(CH_2)_2N(CH_3)(C_6H_{11})$	1-C_6H_5-6,7-$(OCH_2C_6H_5)_2$	123–124	739

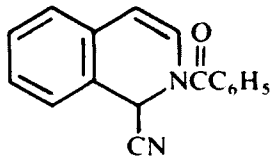
3-Position

CH_3	3-$CONH_2$	158–159[a]	622
		162–163	609, 610
H	3-$CONHNH_2$-1-CH_3-6,7-$(OCH_3)_2$	167–168	85
H	3-$CONH(CH_2)_2N(CH_3)_2$	bp: 192–195/0.1	629, 630
H	3-$CONHCH_2CH_2NRR'$	N/A	740
H	3-$CONH(CH_2)_2NHCH(CH_3)_2$	b.p.: 198–200/0.5	629, 630
H	3-$CONH(CH_2)_2N(C_2H_5)_2$	bp: 205–210/0.1	629, 630
$CH_2C_6H_5$	3-$CONH_2$	145–146	609, 610
H	3-$CONH(C_6H_4CH_3$-2)	N/A	741
$CH_2C_6H_5$	3-$CONH_2$-6,7-$(OCH_3)_2$	149–150	609, 610
$CH_2C_6H_5$	3-$CONHCH(CH_3)_2$	105–106	609, 610
H	3-$CONH_2$-1-$CH_2(C_6H_3(OCH_3)_2$-3,4-)-6,7-$(OCH_3)_2$		
	(1S, 3S)	196–198[a,b]	576
	(1R, 3S)	206–208[a,b]	649
	cis	196–198	577
CH_3	3-$CONH_2$-1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$		
	(1S, 3S)	149–151[a,b]	576
	cis	149–151	577
$CH_2C_6H_5$	3-$CONHC_6H_5$	125–126	609, 610
$CH_2C_6H_5$	3-$CONH_2$-1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$		
	(1S, 3S)	N/A[a,b]	576
		Picrate: 109–110	576
	cis	Picrate: 109–111	577
	(1R, 3S)	140[a]	649

TABLE III.8. 1,2,3,4-Tetrahydroisoquinoline with Amides and Hydrazides on Ring (*Continued*)

R	R^1	Substituents	m.p. (°C)	Ref.
		4-Position		
CH_3		4-CN	41.5–42.5	580, 581
			HCl: 224–226	580, 581
CH_3		4-$CONH_2$	152	134, 347
			153	580, 581
			180	5
			HCl: 200	580, 581
			HCl: 227	5
CH_3		4-$CON(CH_3)_2$	Picrolonate: 197	580, 581
CH_3		4-$CON(C_2H_5)_2$	b.p.: 125–135/0.01	581
			bp: 165–173/0.05	5
			oxalate: 190–192	581

[a]IR in paper.
[b]NMR in paper.
[c]UV in paper.



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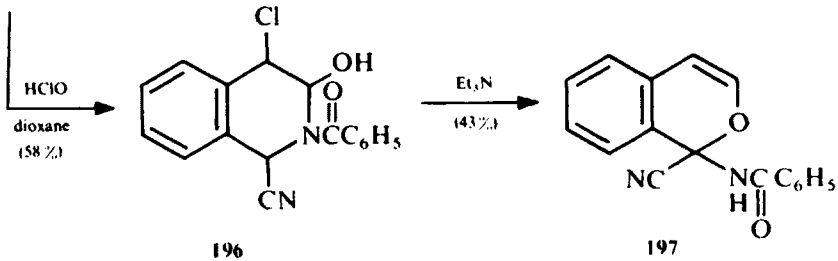
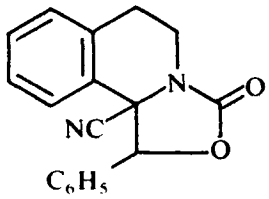
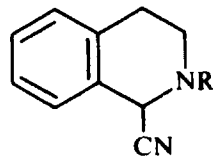


196 197

(71)



198



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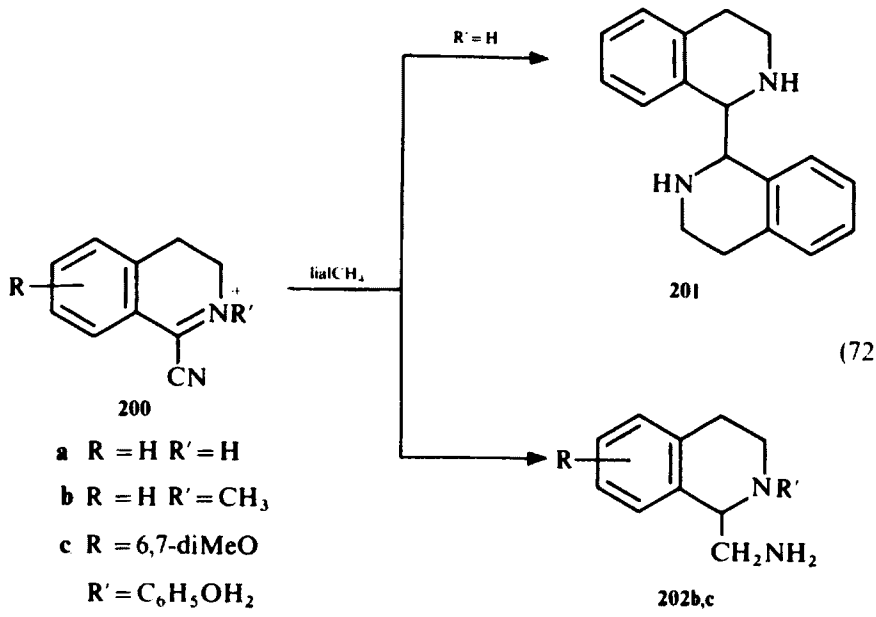
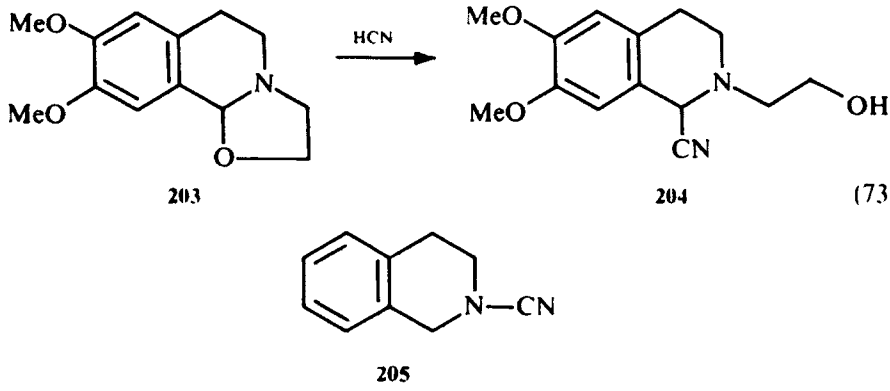


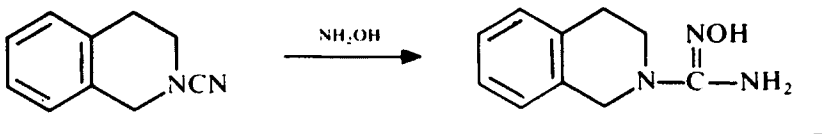
(72)

analogous to pseudobase formation[706] (Eq. 73). The reaction of 2-unsubstituted-1,2,3,4-tetrahydroisoquinolines with cyanogen bromide leads to the 2-cyano derivative **205**.[617, 714–22] Somewhat surprisingly, a 2-methyl-1,2,3,4-tetrahydroisoquinoline has also been reported to give the same product.[723]



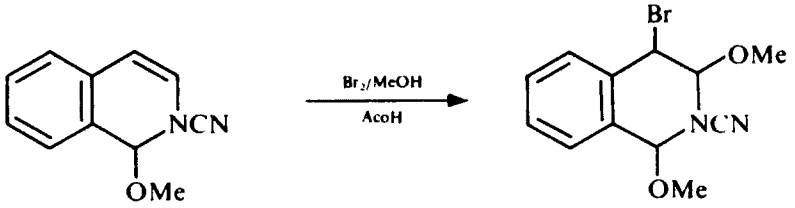
(73)

Reaction of compounds of the type **205** with hydroxylamine leads to the carboxamidoximes **206**[714–717] (Eq. 74), which are covered in another chapter.



(74)

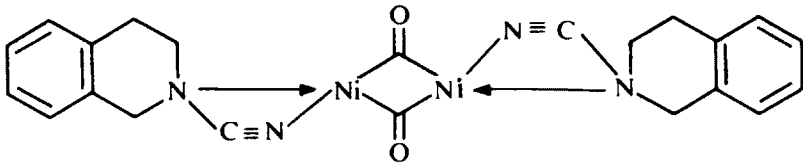
Reaction of 1-methoxy-2-cyano-1,2-dihydroisoquinoline (**207**) with bromine and methanol in acetic acid leads to the 1,3-dimethoxy-4-bromo derivative **208**[191] (Eq. 75).



(75)

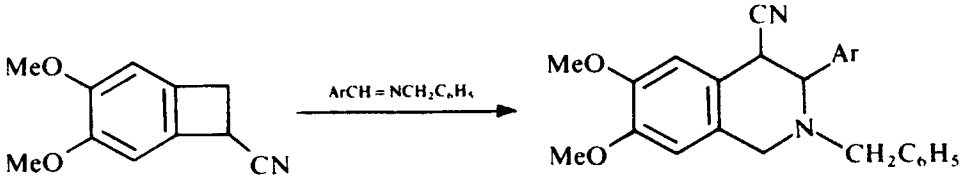
207 **208**

Reaction of **205** with nickel tetracarbonyl leads to the complex **209**.[718]



209

The 2-cyano group can be reduced to an *N*-methyl group with borohydride while the 4-bromo group in a 2-cyano compound can be easily displaced.[718a] The reaction of the benzocyclobutane with $ArCH{=}NCH_2C_6H_5$ leads to **211** and other products[724] (Eq. 76).

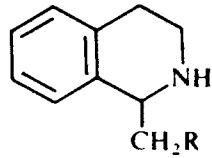


210 **211** (76)

In addition to interconversions discussed in the previous section, one might note conversion of nitriles to amides,[203,362,580,581,615,618,619,655,721] the hydrolysis of nitriles,[597,598,655] and the conversion of esters to hydrazides.[595] *N*-Substituted-3-cyano-1,2,3,4-tetrahydroisoquinolines can be decyanated with sodium in liquid ammonia.[721a]

(ii) Acidic Groups on Side Chains Attached to Carbon

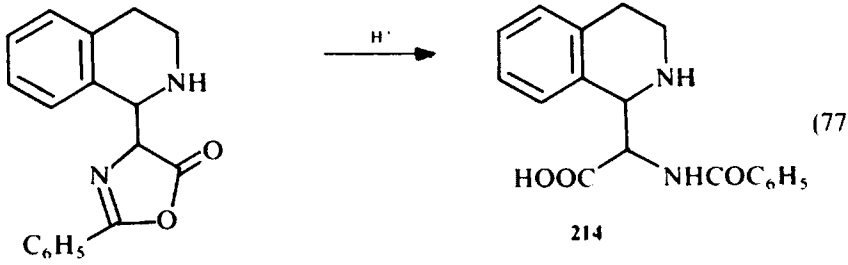
The reaction of 3,4-dihydroisoquinolines with potassium ethyl malonate or cyanoacetic acid gives side-chain derivatives of type **212**.[586,604,742–744] The reaction of β-arylethyl amines with diethyl ethoxymethylene–malononitrile gives



212

(R = CN, CO_2Et)

rise to compounds **212** (R=$CO_2C_2H_5$).[745-747] Treatment of **213** with acid leads to **214**[748] (Eq. 77).



213 214

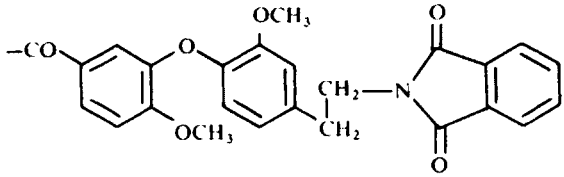
(77)

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon

R	Substituent	m.p. (°C)	Ref.
	Carboxylic Acids		
NO	1-CH_2CO_2H	167–169	611
		170	765
H	1-CH_2CO_2H	239–241	766
		219–220	764
		HCl: 183–184	590, 611
$COCH_3$	1-CH_2CO_2H	165–166	376, 765a
		161–163	590, 765b
H	1-CH_2CO_2H-6,7-$(OCH_3)_2$	HCl: 218–218.5	91
		HCl: 204	767
		HCl: 232	768
		N/A	620
CN	1-$(CH_2)_3CO_2H$	N/A	617
CHO	1-CH_2CO_2H-6,7-$(OCH_3)_2$	155–156	769
		153–155[a,b]	770
CH_3	1-CH_2CO_2H-6,7-$(OCH_3)_2$	HCl: 217–218	768
		HCl: 200–203	769
		MeI: 183–185	769a
SO_2CH_3	1-CH_2CO_2H-6,7-$(OCH_3)_2$ (±)	120	502
H	1-$CH_2COCH_2CO_2H$-6,7-$(OCH_3)_2$	101–103	742–744, 771, 772
		107–110	604

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

R	Substituent		m.p. (°C)	Ref.
$COCH_3$	1-CH_2CO_2H-6,7-$(OCH_3)_2$	(±)	154–155	502
		(−)	99–102	502
			N/A	773
H	1-$(CH_2)_3CO_2H$-6,7-$(OCH_3)_2$		212	498
			HCl: 218–219[c]	493
H	1-$C(CH_3)_2CO_2H$-6,7-$(OCH_3)_2$		b.p.: 179–181/0.5	774
			74.5–76	774
			Picrate: 141–142	774
H	1-$CH(C_2H_5)CO_2H$-6,7-$(OCH_3)_2$		b.p.: 170–175/0.04	774
			HCl: 134.5–135	774
			Picrate: 113–114.5	774
CH_3	1-$(CH_2)_2CO_2H$-6,7-$(OCH_3)_2$		HCl: 250	480
H	1-$(CH_2)_4CO_2H$-6,7-$(OCH_3)_2$		Syrup	467
H	1-$C(C_2H_5)_2CO_2H$-6,7-$(OCH_3)_2$		b.p.: 160–163/0.02	774
			65–67	774
			HCl: 159	774
			Picrate: 163–165	774
CH_3	1-$(C_6H_4COH_2$-2)-6,7-$(OCH_3)_2$		Picrate: 152–153	487
$SO_2C_6H_5$	1-CH_2CO_2H-6,7-$(OCH_3)_2$		171–172[b]	770
H	1-$CH_2N(COC_6H_{11})CH_2CO_2H$		N/A	775
$CO_2CH_2C_6H_5$	1-CH_2CO_2H-6,7-$(OCH_3)_2$		N/A	620
CH_3	1-$CH_2(C_6H_2(OCH_3)_2$-3,4-CO_2H-6)-6,7-$(OCH_3)_2$		141–143[a–b]	776
$COCH_3$	1-$CH(NHCOC_6H_5)CO_2H$-1-C_6H_5-6,7-$(OC_2H_5)_2$		193–195	748
CH_3	7-$O(C_6H_3$-OCH_3-2-$CH_2CO_2CH_3$-5)-6-OCH_3-1-			



			Picrate: 103–105	527
CH_3	8-$CH=CHCO_2H$-5-OCH_3		260–265	777
			N/A[a]	778
CH_3	8-$CH_2CH_2CO_2H$-5-OCH_3		212	777
			N/A[a]	778

Esters

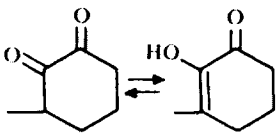
H	1-$CH_2CO_2CH_3$		b.p.: 153–155/2	490
			Picrate: 182	490
H	1-$CH_2CO_2C_2H_5$		b.p.: 112–114/0.05	491
H	1-$CH_2CO_2C_2H_5$		b.p.: 145–150/3–4	490
			b.p.: 120/0.4	751
			b.p.: 120/0.5[a]	749

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

R	Substituent	m.p. (°C)	Ref.
		b.p.: 123–129/1	765a
		b.p.: 111–114/0.5[a,c]	589
		b.p.: 128–134/0.2	590
		Picrate: 132	490
CH_3	1-$CH_2CO_2CH_3$	HCl: 142.5–144	779
H	1-$CH(CH_2OH)CO_2CH_3$	N/A	374
H	1-$CH_2CO_2CH_3$-6-OCH_3	176–178.5	621
CH_3	1,3-$(CH_2CO_2CH_3)_2$	NA	779a
CH_3	1-$CH_2CO_2C_2H_5$-3-$CH_2CO_2CH_3$	NA	779a
$COCH_3$	1-$CH_2CO_2CH_3$	91–93	379
H	1-$CH_2CO_2C_2H_5$-6,7-O_2CH_2	b.p.: 145/0.03	464
		58	445,464
		Oxalate: 157	445
CH_3	1-$CH_2CO_2C_2H_5$	b.p.: 98–106/0.3[a,c]	589,769a
H	1-$CH_2CO_2C_2H_5$-5-OCH_3	Oil[a]	751
H	1-$CH_2CO_2C_2H_5$-6-OCH_3	b.p.: 130–132/0.02	464
		b.p.: 132/0.02	445
		Oxalate: 148–150	464
		Oxalate: 150	445
H	1-$CH_2CO_2C_2H_5$-7-OCH_3	N/A	621
CH_3	1-$CH_2CO_2C_2H_5$-6,7-O_2CH_2	HCl: 134–136[a]	589
	($N^+CH_2C_6H_5$ Br^-)	180–182[a,c]	589
H	1-$CH_2CO_2C_2H_5$-5,6-$(OCH_3)_2$	71–72[a]	751
H	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	77.5–78	91
		72–76	604
		78	445
		77–78	441,442
		78–79[a–c]	764
		(+) 85.5–86.5	757
		(−) 86–87	757
		Oxalate: 155	764
		Oxalate: 164	445
		Oxalate: 136–164	745–747
		Oxalate: 170.5–172	757
		Oxalate: 169.5–171	757
		Sulfate: 171	445
H	1-$CH(OH)CH(OH)CO_2CH_3$-6,7-$(OCH_3)_2$		
		HCl: 243–245[a,c]	451
CH_2CH_2CN	1-$CH_2CO_2C_2H_5$	b.p.: 170–175/0.4	763
		86[a]	780
CHO	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	107.5–108[a,b]	770
H	1-$CH(CH_2CH(CH_3)_2)CO_2CH_3$	69	445
		Oxalate: 176	445
H	1-$CH(C_2H_5)CO_2CH_3$-6,7-$(OCH_3)_2$	82–83	445
H	1-$CH(CH_3)CO_2C_2H_5$-6,7-$(OCH_3)_2$	54–55	495
		HI: 166	495
		HCl: 183[a,c]	586
		HCl: 170[a,c]	586

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

R	Substituent	m.p. (°C)	Ref.
CH_3	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	HCl: 179–183	745–747
		HBr: 178	781
	($N^+CH_3I^-$)	167–168	781
		172	769a
	($N^+CH_2C_6H_5$ Br^-)	190–192	589
		N/A	756
H	1-$CH_2CO_2C_2H_5$-6,7,8-$(OCH_3)_3$	b.p.: 168/0.01	445, 464
SO_2CH_3	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$ (+)	114–115	502
CH_3	1-$CH(CO_2C_2H_5)OCOCH_3$-6,7-O_2CH_2	Oil[a,c]	782
CH_3	1-$CH_2CO_2C_2H_5$-1-CH_3-6,7-$(OCH_3)_2$	MeI: 158–159	769a
CH_2CN	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	78[a]	783
H	1-$CH_2COCH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	HCl: 173–174	604
$COCH_3$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$ (±)	94–95	502
		(+) 113–114	502
H	1-$C(C_2H_5)_2CO_2C_2H_5$	HCl: 187–188	468
H	1-$(CH_2)_3CO_2C_2H_5$-6,7-$(OCH_3)_2$	HCl: 175–176	498
CH_3	1-$CH_2CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 170/0.25	591
		HCl: 194–196	591
		HCl: 187–190[c]	444
CH_3	1-$CH(CH_3)CO_2C_2H_5$-6,7-$(OCH_3)_2$	HI: 164–165	495
CH_2CH_2OH	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	N/A	784
H	1-$CH(OH)CH(OH)CO_2CH_3$-6,7-$(OC_2H_5)_2$	HCl: 170–171	451



	1-$CH_2CO_2CH_3$	111–112[a,b]	785,786
	1-$CH_2CO_2C_2H_5$	N/A[a]	749
H	1-$CH_2CO_2C_2H_5$-1-CH_3-6,7-$(OC_2H_5)_2$		
		HCl: 140	545
		Picrate: 209	545
$CH_2CH_2CO_2CH_3$	1-$CH_2CO_2C_2H_5$-6,7-O_2CH_2	b.p.: 180–183/0.01	445
CH_3	1-$CH(CO_2C_2H_5)OCO_2C_2H_5$-6,7-$O_2CH_2$	153–154.5[a,c]	787
		HCl: 173–176	787
$CH_2CH_2CO_2C_2H_5$	1-$CH_2CO_2C_2H_5$	b.p.: 167–170/0.5	763
H	1-$CH_2CO_2C_2H_5$-3-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 183–186/0.0003	684
		77–78[a]	684

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

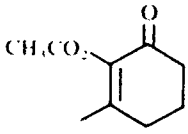
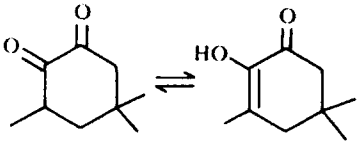
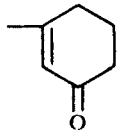
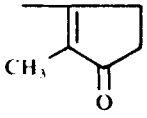
R	Substituent	m.p. (°C)	Ref.
$C(=O)NH_2$	1-$C(C_2H_5)_2CO_2C_2H_5$	153–154[a,c]	468
H	1-$(CH_2)_4CO_2C_2H_5$-6,7-$(OCH_3)_2$		
		Picrate: 115–116[a]	467
CH_3	1-$(CH_2)_3CO_2C_2H_5$-6,7-$(OCH_3)_2$	HI: 119–121	498
$CH_2CH_2CO_2C_2H_5$	1-$CH_2CO_2C_2H_5$-6,7-O_2CH_2	b.p.: 180–183/0.01	464,762
$CH_2CH_2CO_2C_2H_5$	1-$CH_2CO_2C_2H_5$-6-OCH_3	b.p.: 170–175/0.03	464
		b.p.: 170–175/0.02	762
		b.p.: 175/0.03	445
CH_3	1-$CH_2CO_2C_2H_5$-3-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 185–195/0.05	688
$CH_2CH_2CO_2CH_3$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	121–122	445
$C(=S)NHCH_3$	1-$C(C_2H_5)_2CO_2C_2H_5$	165–166	468
H	1-$C(C_2H_5)_2CO_2CH_2CH_2Cl$-6,7-$(OCH_3)_2$	72	774
		Picrate: 188–189	774
H	1-$CH_2CH(C_3H_7)CH_2CO_2CH_3$-6,7-$(OCH_3)_2$	HCl: 138–159	478
	1-$CH_2CO_2CH_3$	HCl: 93–96[a,b]	785,786
	1-$CH_2CO_2CH_3$	110–111[a,b]	785,786
	1-$CH_2CO_2C_2H_5$-6-OCH_3	Oil[a,b]	788
	1-$CH_2CO_2C_2H_5$-6-OCH_3	181–182[a–c]	788
		Picrate: 161–162	788
$CH_2CO_2C_2H_5$	1-$CH_2CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 210/0.01	592
		Picrate: 123–124	592
$CH_2CH_2CO_2C_2H_5$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 197–201/0.02	464,762
		b.p.: 180/0.01	445
		37–39	445,464
		Picrate: 117–118	789

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

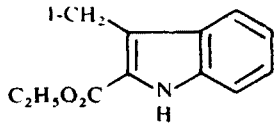
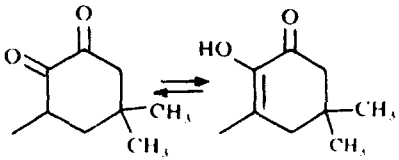
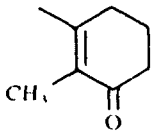
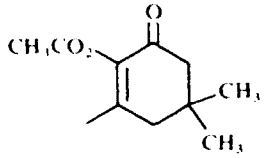
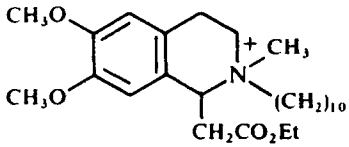
R	Substituent	m.p. (°C)	Ref.
H	1-$CH_2CH(OH)CH(CH_3)(CH_2)_4CO_2C_2H_5$	82–83[a,c]	708
H		199–200	61
		Picrate: 206–207	61
CH_3	1-$CH_2CH(CO_2C_2H_5)(C_6H_4Cl$-4)	179–185	591
$SO_2C_6H_5$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	90.5–91.5[a]	770
	1-$CH_2CO_2C_2H_5$	110–111[a,b]	786
	1-$CH_2CO_2C_2H_5$-6-OCH_3	154[a,c]	788
$CH_2C(C_2H_5)(CO_2H)_2$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	69–70	445
$CH_2CO_2C_2H_5$	1-$CH_2CH(CH_3)CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 215–225/0.05	592
		Picrate: 114	592
$CH_2CH_2CO_2C_2H_5$	1-$CH(CH_3)CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 198–205/0.1	790
		N/A	586
$CH_2CH_2CO_2C_2H_5$	1-$CH(C_2H_5)CO_2CH_3$-6,7-$(OCH_3)_2$	b.p.: 190/0.001	445
$CH_2CH(CH_3)CO_2C_2H_5$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	83–84	789
$CH_2CH_2CO_2C_2H_5$	1-$CH_2CO_2C_2H_5$-6,7,8-$(OCH_3)_3$	b.p.: 180/0.01	464,762
CH_3	1-$CH(C_6H_5)CO_2C_2H_5$-3-CH_3-6,7-O_2CH_2	111–112	791
$CSNH(C_6H_4F$-3)	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	169–179	764
H	1-$CH(CH_2C_6H_5)CO_2C_2H_5$-6,7-$(OCH_3)_2$	62–63	497
	1-$CH_2CO_2CH_3$	123–124[a,b]	785,786
$CH_2C(CH_3)(CO_2CH_3)_2$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	89–91	792

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

R	Substituent	m.p. (°C)	Ref.
$CH_2CH_2CO_2C_2H_5$	1-$CH(C_2H_5)CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 198–210/0.1	790
$CH_2CH(C_2H_5)CO_2C_2H_5$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 185–190/0.06	445
		76–77	441,442
		78–79	585
H	1-$CH_2CH(OH)CH(CH_3)(CH_2)_4CO_2C_2H_5$-6,7-$(OCH_3)_2$	82–83[a,c]	793
CH_3	1-$CH_2(C_6H_2(OCH_3)_2$-4,5-CO_2CH_3-2)-6,7-$(OCH_3)_2$	127–128	63
		130–132	120
CH_3	1-$CH_2(C_6H_2(OCH_3)_2$-CO_2CH_3-6)-6,7-$(OCH_3)_2$	130–131[a–c]	776
$CH_2C(C_2H_5)(CO_2CH_3)_2$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	116–118	445
		118–120	445
$CH_2CH_2CO_2C_2H_5$	1-$CH(C_3H_7)CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 221–226/0.1	790
H	1-$C(C_2H_5)_2CO_2CH_2CH_2N(C_2H_5)_2$-6,7-$(OCH_3)_2$	Dipicrate: 131–132.5	774
$C(=S)NHC_6H_4Br$-4	1-$C(C_2H_5)_2CO_2C_2H_5$	156–157	468
$C(=S)NHC_6H_4Cl$-4	1-$C(C_2H_5)_2CO_2C_2H_5$	162–163[a]	468
$C(=O)NHC_6H_4Cl$-4	1-$C(C_2H_5)_2CO_2C_2H_5$	99–100	468
$C(=O)NHC_6H_5$	1-$C(C_2H_5)_2CO_2C_2H_5$	142–143	468
$CSNH(C_6H_4N(CH_3)_2$-4)	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	140–142	764
$CH_2CH_2CO_2C_2H_5$	1-$CH(C_4H_9$-*n*$)CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 221–226/0.1	790
$CH_2CH_2CO_2C_2H_5$	1-$CH(C_4H_9$-*i*$)CO_2C_2H_5$-6,7-$(OCH_3)_2$	b.p.: 224–228/0.1	790
COC_6H_5	1-$CH_2CO_2C_2H_5$-3-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	110–111.5[a]	684
$CH_2C(C_4H_9)(CO_2CH_3)_2$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	80–81	445
$CH_2C(CH_2CH(CH_3)_2)(CO_2CH_3)_2$	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	93–94	445
CH_3	1-[$CH_2C_6H_2$-4,5-$(OCH_3)_2$-CO_2CH_3]-6,7-OCH_3	120	790a
$CH_2C_6H_5$	1-$CH_2CH_2CO_2C_2H_5$-3-$CO_2C_2H_5$-6,7-$(OCH_3)_2$		
	α-isomer	HCl: 172–173	485,516
	β-isomer	104.5–105.5	485,516
		HCl: 147–148	485,516
		Picrate: 122–123.5	485,516
H	3-$CH_2CO_2C_2H_5$	b.p.: 131–134/0.15	491
$(CH_2)_2CO_2C_2H_5$	3-$CH_2CO_2C_2H_5$	b.p.: 178/0.06	573
H	4-$CH_2CO_2CH_3$	HCl: 170–173	593
CH_3	4-$CH_2CO_2CH_3$	b.p.: 98/0.05	595
CH_3	4-$CH_2CO_2CH_3$-1-CH_3	b.p.: 94–96/0.05	595
$CH_2C_6H_5$	4-$CH_2CO_2CH_3$	b.p.: 155–160/0.002	593
CH_3	4-$COCO_2C_2H_5$-3-$(C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$	146–148[a,b]	79
$CH_2CH_2C_6H_4Cl$-4	4-$CH_2CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	HCl: 169–171	477
$CH_2CH_2C_6H_5$	4-$CH_2CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	HCl: 145–147	477

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

R	Substituent	m.p. (°C)	Ref.
	Acidic Functional Groups		
H	1-C(=NOH)CO_2H	145–146[a–c]	611
H	1-CH_2CONH_2	171.5–172	563
		HCl: 231–233	589
NO	1-CH_2CN-6,7-O_2CH_2	138	449
H	1-CH_2CN-6,7-O_2CH_2	93	449
		HCl: 254	449
		Picrate: 190	449
CH_3	1-[$CH_2C_6H_2$-4,5-$(OCH_3)_2$-2-CHOHCN]-6,7-$(OCH_3)_2$	130	790a
CH_3	1-$CH(C_6H_5)CO_2C_2H_5$	105–107	769a
		MeI: 144–145	769a
CH_3	1-$CH(C_6H_5)CO_2C_2H_5$-6,7-$(OCH_3)_2$	107–108	769a
		MeI: 116–119	769a
CH_3	1-$CH(CO_2CH_3)_2$-6,7-$(OCH_3)_2$	68–70	769a
CH_3	1-$CH(CO_2CH_3)_2$	57–58	769a
	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	MeI: 80–110	769a



H	1-$CH_2CONHCH_3$	109–109.5	491
H	1-CH_2CONH_2-7-OCH_3	215–217	621
H	1-C(CN)=NOH-6,7-$(OCH_3)_2$	192[a,b]	501
H	1-CH_2CN-5,6-$(OCH_3)_2$	N/A	475
H	1-CH_2CN-6,7-$(OCH_3)_2$	120[a]	586
H	1-CH_2CONH_2-6,7-$(OCH_3)_2$	166–169.5	631,632
CN	1-$(CH_2)_3CN$	b.p.: 220–230/0.07	617
SO_2CH_3	1-$CH_2CONHNH_2$-6,7-$(OCH_3)_2$	71–72	502
H	1-$(CH_2)_3CN$-6,7-$(OCH_3)_2$	HCl: 187–188	498
H	1-$CH_2CONHCH_2CH_2OH$-6,7-$(OCH_3)_2$	114–115	563
$CH_2CO_2C_2H_5$	1-CH_2CH_2CN	b.p.: 210/1	795
		Picrate: 137–137.5	795
H	1-$CH_2CONHCH_2CH=CH_2$-6,7-$(OCH_3)_2$	92–94	563
H	1-$CH_2CONHCH(CH_3)_2$-6,7-$(OCH_3)_2$	N/A	620
H	1-$CH_2CONH(CH_2)_3OH$-6,7-$(OCH_3)_2$	115–119	563,631,632
H	1-$CH_2CONHC_4H_9$-*n*-6,7-$(OCH_3)_2$	87–88	563,631,632
H	1-$CH_2CONHC_4H_9$-*i*-6,7-$(OCH_3)_2$	105–108	563,631,632
H	1-$CH_2CONHCH_2C_6H_5$	110–111	621

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

R	Substituent	m.p. (°C)	Ref.
$CH_2CH_2CO_2C_2H_5$	1-CH_2CN-6,7-$(OCH_3)_2$	76[a]	586
H	1-$CH_2CONHC_5H_{11}$-*i*-6,7-$(OCH_3)_2$	74–76	563
H	1-$CH_2CONHCH_2CH_2C_6H_5$	106–107	621
		N/A	621
$COCH_3$	1-CH_2CN	127	765b
$COCH_3$	1-$CH(CN)_2$	156	765b
H	1-$CH_2CONHC_6H_5$-6,7-$(OCH_3)_2$	120	661
H	1-$CH_2CONHAr$-6,7-$(OCH_3)_2$	N/A	620
H	1-$CH_2CONHC_6H_{11}$-6,7-$(OCH_3)_2$	N/A	620
H	1-$CH_2CONHCH_2CH_2N(C_2H_5)_2$-6,7-$(OCH_3)_2$		
		88–92	563
COC_6H_5	1-CH_2CH_2CN-1-CN	136	342
$COCH_2Cl$	1-$CH_2CONHCH_2C_6H_5$	121–122	621
H	1-$CH_2CONHCOC_6H_5$-6,7-$(OCH_3)_2$	173.5–175.5	631,632
$CO_2CH_2C_6H_5$	1-CH_2CONHR	N/A	620
H	1-$CH_2CONHCH_2CH_2CH_2C_6H_5$-6-$OCH_3$	54–58	621
H	1-$CH_2CONHCH_2C_6H_5$-6,7-$(OCH_3)_2$	129–132	563,621
		129.5–132.5	631,632
		194.5–199	632
CH_3	1-$CH(CN)(C_6H_3O_2CH_2$-3,4)-6,7-$(OCH_3)_2$	171	796
$COCH_2Cl$	1-$CH_2CONHCH_2CH_2C_6H_5$	107–108	621
H	1-$CH_2CONHCH_2CH_2C_6H_5$-6,7-$(OCH_3)_2$	114–116	563,631, 632
	R	144–145	621
	L	143–144	621
$COCH_2Cl$	1-$CH_2CONHCH_2CH_2C_6H_5$-7-OCH_3	N/A	621
$COCH_2Cl$	1-$CH_2CONHCH_2C_6H_5$-6,7-$(OCH_3)_2$	153–154	621
$COCH_2Cl$	1-$CH_2CONHCH_2CH_2C_6H_5$-6,7-$(OCH_3)_2$	72–74	621
	R	129–130	621
	S	126–127	621
CH_3	1-CH_2CH_2-$C(CN)(CH(CH_3)_2)(C_6H_3(OCH_3)_2$-3,4)	N/A	797
CH_3	3-CH_2CN	b.p.: 110–114/0.35[a]	758
		90–91	758
CH_3	4-$CH_2CONHNH_2$	129	595
CH_3	4-$CH_2CONHNH_2$-1-CH_3	127[a,b]	595
$CH_2C_6H_5$	4-CH_2CN	b.p.: 185–190/0.002	593

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

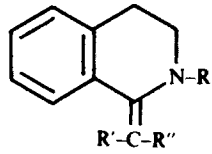
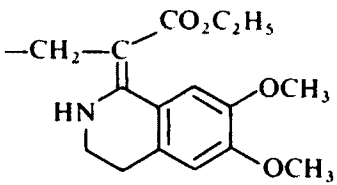
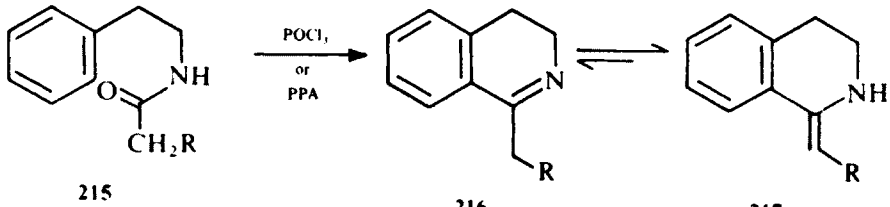
R	R′	R″	Substituent	m.p. (°C)	Ref.
		Unsaturated Side Chain			
					
H	H	CN		98.5–99[a,b]	499
H	H	$CONH_2$		106.5–107.5	500
				N/A	798
H	CO_2H	NHOH		145–146[a–b]	611
MS	H	CN		103–104[a,c]	799
H	H	$CONH_2$	7-OCH_3	142–143	621
D	D	$CO_2C_2H_5$		b.p.: 116/0.005[a]	750
H	CO_2CH_3	CHO		N/A	800
H	H	CH_2CH_2CN		b.p.: 175/1[a]	754
				HCl: 125–127	754
				Picrate: 128–129	754
H	H	CN	6,7-$(OCH_3)_2$	170–171	499
H	H	$CO_2C_2H_5$		b.p.: 117–120/0.001	750
H	H	CO_2CH_3	3-$CH_2CO_2CH_3$	b.p.: 140/0.08	499
				29–31.5[a,c]	750
				Picrate: 144–145	751
				N/A	749
				N/A	779a
H	CH_3	CO_2CH_3		58–59	521
H	H	$CONH_2$	6,7-$(OCH_3)_2$	163–164	500
H	CN	CH_2CH_2CN		137–138	499
H	CH_3	CH_2CH_2CN		b.p.: 162–165/3–4[a]	754
				Picrate: 110–112	754
H	H	$CH_2CH_2CO_2CH_3$		b.p.: 163/18	753
				Picrate: 116	753
H	H	$CO_2C_2H_5$	5-OCH_3	75–76	750
				65–68[a,c]	751
H	H	$CO_2C_2H_5$	6-OCH_3	70–72	749
				N/A	662
MS	H	$CO_2C_2H_5$		77.5–78.3[a,c]	799
H	CO_2CH_3	$COCO_2CH_3$		N/A	800
H	H	$CH_2CH(CH_3)CO_2CH_3$		b.p.: 170/1	753
				85–86	750
H	H	$CO_2C_2H_5$	5,6-$(OCH_3)_2$	83–84[a,c]	751
				81–82[a,c]	494
H	H	$CO_2C_2H_5$	6,7-$(OCH_3)_2$	86–87	499
				Picrate: 172–173	494
				466	800a
H	CN	$CO_2C_2H_5$		Hbr: 194–5	800a

TABLE III.9. 1,2,3,4-Tetrahydroisoquinolines with Acidic Function in Side Chain or Carbon (*Continued*)

R	R′	R″	Substituent	m.p. (°C)	Ref.
H	H	CN		97–98	800a,b
H	CH_2CH_2CN	CH_2CH_2CN		b.p.: 225–230/1	753
				83	753
				Picrate: 133	753
				HCl: 146	753
H	$CO_2C_2H_5$	CH_2CH_2CN		b.p.: 205–208/5	753
				Picrate: 117	753
H	H	$CONHC_6H_4Cl$-3		150–155[c]	736
H	H	$CONHC_6H_5$		103[b,c]	736
H	$CO_2C_2H_5$	$CH_2CH_2COCH_3$		b.p.: 194/4	753
				Picrate: 138–140	753
H	$CO_2C_2H_5$	$CH_2CH_2CO_2CH_3$		205–212	753
H	CN	CH $=C(C_2H_5)CO_2C_2H_5$		159–160[b]	755
H	$CO_2C_2H_5$	CH_2CH_2CN	6,7-$(OCH_3)_2$	96–99	498
H	$CO_2C_2H_5$	$CH_2CH(CH_3)$-CO_2CH_3		b.p.: 203–205/2	753
H	H	$CO_2C_2H_5$	3-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	131–131.5[a,c]	684
H	$CH_2CH_2CO_2CH_3$	$CH_2CH_2CO_2CH_3$		b.p.: 207–215/1	753
H	C_6H_5	CH_2CH_2CN		99–100[a]	754
H	H	$CONHC_6H_5$	6,7-$(OCH_3)_2$	143–144	661
CH_3	$CO_2C_2H_5$	CH_2CH_2CN	6,7-$(OCH_3)_2$	144–145	498
H	$CO_2C_2H_5$	$CONHC_6H_5$		128–130	661
H	$CONHC_6H_4Cl$-3	$CONHC_6H_4Cl$-3		170[c]	736
H	$CONHC_6H_5$	$CONHC_6H_4Cl$-3		150–151	736
H	$CONHC_6H_5$	$CONHC_6H_5$		165–167[b,c]	736
H	$CONHC_6H_4CH_3$-3	$CONHC_6H_4CH_3$-3		165–168	736
H	$CO_2C_2H_5$			180.5–182[b]	755

[a] IR in paper.
[b] UV in paper.
[c] NMR in paper.

Cyclization of **215a–c** with phosphorus pentoxide or polyphosphoric acid[499,500,749–751] affords **216**[442,752] (Eq. 78). Based on IR and NMR spectral studies, compounds **216** have the preferred structures **217**.[494,499,750]



215

a R = CN

b R = $CONH_2$

c R = CO_2Et

216 **217** (78)

Catalytic reduction of **217** takes place readily.[621,661,662,749,751] to give **212**. A variety of reagents such as acrylonitrile and acrylates add to **217**[498,499,753,754] to afford **218** while formaldehyde gives **219**[755] (Eq. 79).

Catalytic hydrogenation of **220** provides **221**[521] (Eq. 80).

The reaction of phenylisocyanate with 1-methyl-3,4-dihydroisoquinoline (**222**) gives a variety of products, depending upon reaction conditions.[661,736] Reaction at 110°C gives **217e** (R = $CONHC_6H_5$), while at room temperature the reaction takes place at nitrogen to give **223**. Continuing the reaction at room temperature for a more extended time gives **224**[736] (Eq. 81).

The absolute configuration[756] and resolution[502,756,757] of a number of compounds of type **212** has been studied.

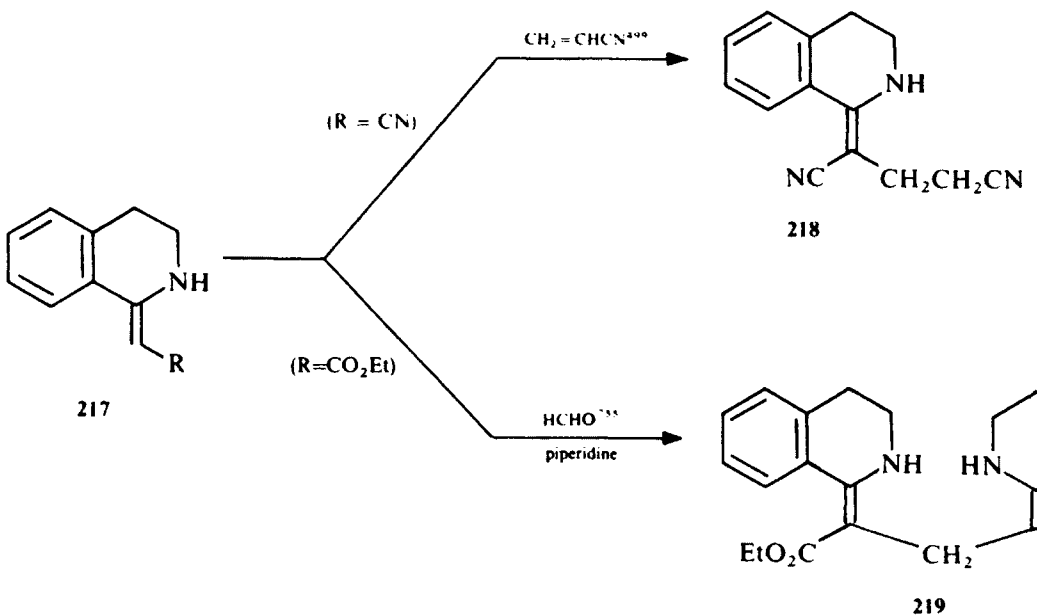
Haloalkyl side chains have been reacted with cyanide ion to give cyanoalkyl side chains.[593, 617, 758]

A variety of cyclization reactions have been carried out on side-chain acid derivatives leading to tri- and tetracyclic products. The reaction of **225** with base or thermally[606, 608, 759–761] gives rise to diazepine derivatives **226** (Eq. 82).

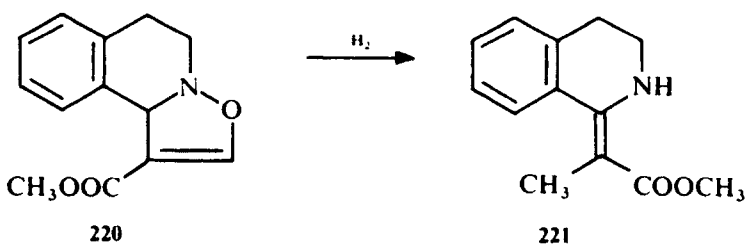
Photocyclization of **227** has been used to prepare various aporphines **228**[669, 673, 675] (Eq. 83). A number of Dieckmann-type condensations have been carried out between 1 and 2 and between 2 and 3 side chains to give the expected products.[464, 592, 601, 683, 762–763] other cyclizations involving an acidic group in a side chain on the 1 position have also been studied.[498, 563, 590–591, 617, 764]

(iii) Acidic Groups on Side Chains Attached to Nitrogen

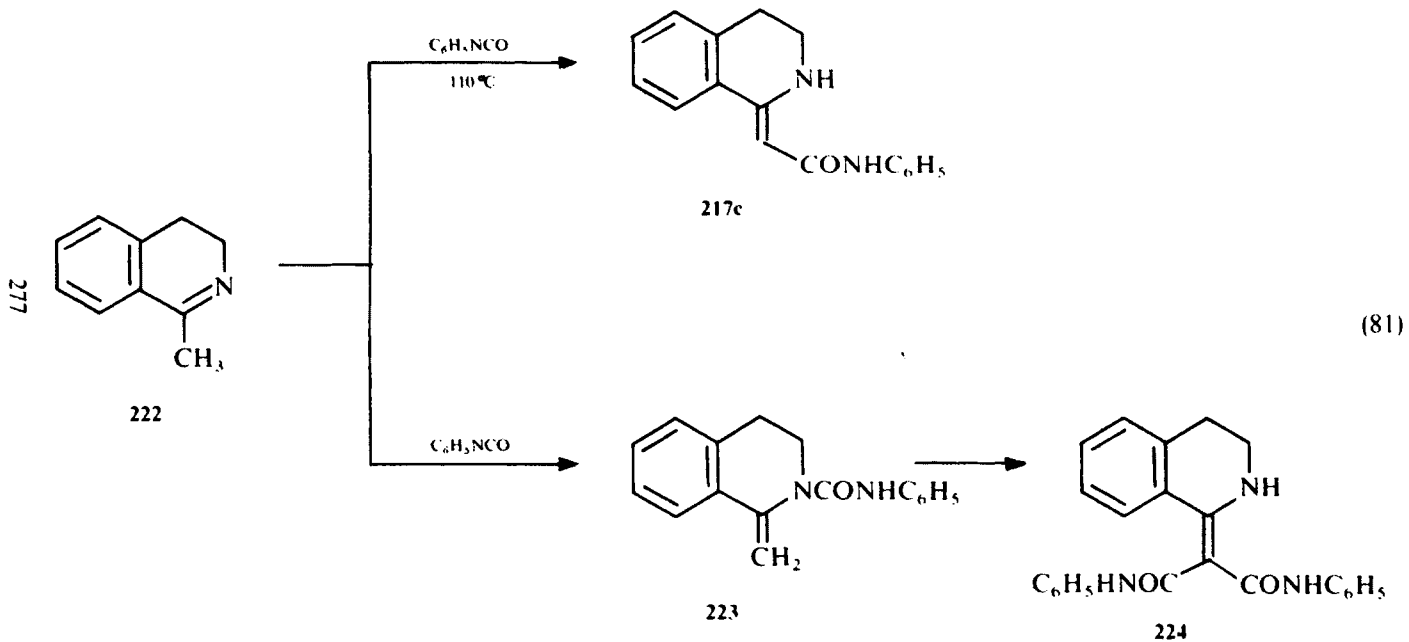
Acidic functional groups in side chains are introduced onto nitrogen by reaction with reagents such as acrylonitrile,[464, 573, 616] acrylates,[586, 688, 762, 689, 790, 801–802] ethoxymethylene malonates,[803] and various alkyl halites containing acidic functional groups.[88, 464, 510, 536, 606, 612, 633, 683, 804–808] Reaction of 1,2,3,4-tetrahydroisoquinoline with formaldehyde and sodium cyanide gives the 2-cyanomethyl derivative.[615]


CH2=CHCN
(R = CN)
NH
NC
CH2CH2CN
218
NH
R
217
(R=CO2Et)
HCHO
piperidine
NH
HN
EtO2C
CH2
CO2Et
219

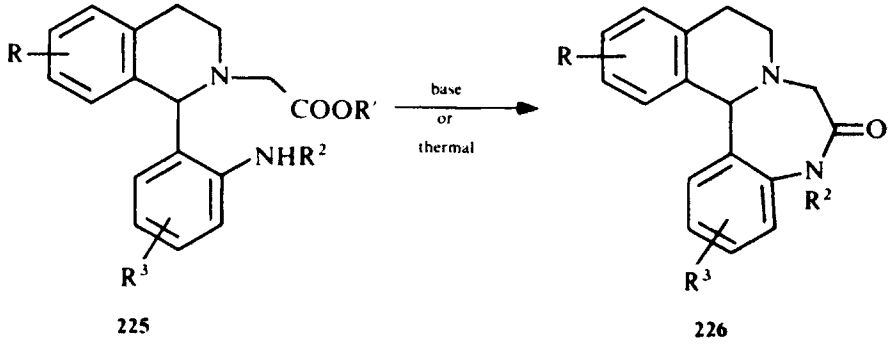
(79)


H2
N
O
CH3OOC
220
NH
CH3
COOCH3
221

(80)

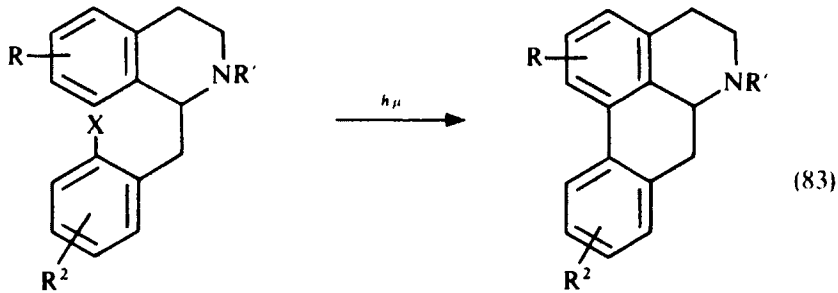

277
222
C_6H_5NCO
110℃
217c
C_6H_5NCO
223
$NCONHC_6H_5$
CH_2
224
C_6H_5HNOC
$CONHC_6H_5$
NH

(81)



225 226

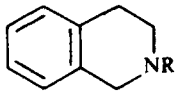
(82)



227 228

(83)

TABLE III.10. 1,2,3,4-Tetrahydroisoquinolinium Salts with Acidic Function on Side Chain in 2 Position



R	Substituent	m.p. (°C)	Ref.
$-CH_2CN$		b.p.: 170–190/24	807, 808
		N/A	809
CH_2CO_2H	4-NH_2	HCl: 163–165[a]	126
$COCH_2CN$		105–106	810
CH_2CH_2CN		b.p.: 150–151/0.02	811
		b.p.: 160–162/2.5	616
		b.p.: 195–205/10	809
$CH_2CH(SO_3^-)CO_2H$		265[b]	812
$CH_2CH_2CO_2H$		169–170	616
	(N^+–$\bar{O}$xide)	148–149[b]	811
$CH_2CH_2CONH_2$		83	813
$CH{=}C(CN)_2$		122–123	803

TABLE III.10. 1,2,3,4-Tetrahydroisoquinolinium Salts with Acidic Function on Side Chain in 2 Position (*Continued*)

R	Substituent	m.p. (°C)	Ref.
$CH_2CH_2CONH_2$	1-CN	112	510
$CH_2CH{=}CHCO_2H$		189–191	612, 814
$C(=CHOH)CO_2CH_3$		203–205[a]	104
$(CH_2)_2CN$	3-CH_2OH	b.p.: 150/0.05	573
$CH_2CH{=}CHCONH_2$		204–206	612
		164–166	814
		HCl: 204–206	814
CH_2CONH_2	6,7-O_2CH_2-8-OCH_3	170	510
$CH_2CH(SO_3^-)CO_2CH_3$		265[b]	812
$CH_2CH_2CO_2CH_3$		HCl: 157–158	815
$CH(CH_3)CO_2CH_3$		b.p.: 160/1	633
		b.p.: 164/1	805
$CH_2CO_2C_2H_5$		b.p.: 91–94/0.01	816
		b.p.: 180–182/.5	817
		Picrate: 147–148.5	816
$CON(CH_3)CONHCH_3$		34	818
		b.p.: 218–220/0.7	818
$CH(CH_2OH)CO_2CH_3$		b.p.: 145–150/0.003[a]	521
$CH_2CON(CH_3)_2$		b.p.: 132–134/0.09	819
$(CH_2)_2CONHCH_3$		b.p.: 162–170/0.1	819
$CH_2CO_2C_2H_5$	4-NH_2	N/A	125
		diHCl: 167–171	105
$CH_2CH_2CH(NH_2)CO_2H$		223–224	820
$CH_2C(CH_3)(NH_2)CO_2H$		264–265	821
CH_2CONH_2	6,7-$(OCH_3)_2$	157.5	510
CH_2CONH_2	1-CN-6,7-O_2CH_2-8-OCH_3	152.5	510
$CH_2CH{=}CHCO_2CH_3$		b.p.: 117–118/0.08	612, 814
		HCl: 194–196	612, 814
CH_2CONH_2	1-CN-6,7-$(OCH_3)_2$	188	510
$CH_2CH{=}CHCONHCH_3$		111–112	612, 814
$CH_2CH_2CONH_2$	6,7-O_2CH_2-8-OCH_3	135	510
$CH_2CH_2CO_2C_2H_5$		188–189/15	802
	(N^+OHCl^-)	122–123[b]	811
$CH_2CH(CH_3)CO_2CH_3$		b.p.: 95/0.05	801
$(CH_2)_2CONHC_2H_5$		b.p.: 156–164/0.1	819
$(CH_2)_2CON(CH_3)_2$		b.p.: 152–155/0.1	819
$CH_2CH_2CONH_2$	6,7-$(OCH_3)_2$	Picrate: 184	510
$CH{=}C(CN)CO_2C_2H_5$		108–110	803
$CH_2CH_2CONH_2$	1-CN-6,7-O_2CH_2-8-OCH_3	167	510
$CH_2CH_2CONH_2$	1-CN-6,7-$(OCH_3)_2$	152	510
$CH_2CH{=}CHCON(CH_3)_2$		HCl: 211–212.5	612, 814

TABLE III.10. 1,2,3,4-Tetrahydroisoquinolinium Salts with Acidic Function on Side Chain in 2 Position (*Continued*)

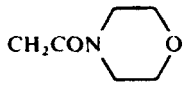
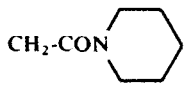
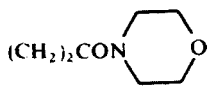
R	Substituent	m.p. (°C)	Ref.
$CH_2CH{=}CHCONHC_2H_5$		128–129	612, 814
		HCl: 197.5–198.5	612, 814
$CH_2CO_2C_2H_5$	1-CH_2CH_2Cl	b.p.: 182–185/0.1	795
		Picrate: 125	795
$CH_2CH{=}CHCONHCH_2CH_2OH$		HCl: 167–169	612
		b.p.: 165–170/0.1	806
$CH(CH_3)CH_2CO_2C_2H_5$		b.p.: 114/0.25	822
$CH_2CO_2C_2H_5$	1-CH_2CH_2OH	Picrate: 149–149.5	795
$CH_2CH_2CO_2CH_3$	6,7-$(OCH_3)_2$	b.p.: 110–111/21	815
		HCl: 177–178	815
$CH_2CON(C_2H_5)_2$		b.p.: 130–138/0.09	819
$(CH_2)_2CONHCH(CH_3)_2$		b.p.: 150–165/0.09	819
$(CH_2)_2CONHC_3H_7$		b.p.: 160–170/0.08	819
$CH_2CH{=}CHCO_2CH(CH_3)_2$		HCl: 193–194	612, 814
		b.p.: 147–150/0.09	806
		b.p.: 172–194/0.1 Oxalate: 145	896 806
$CH_2CH{=}CHCONHC_3H_7$-*i*		162–163	612, 814
		HCl: 201–203	612, 814
$CH_2CH{=}CHCONHC_3H_7$-*n*		120	612, 814
		HCl: 175–178	612, 814
$CH_2CO_2C_2H_5$	1-CH_3-6,7-$(OCH_3)_2$	b.p.: 180/0.5	509
		HBr: 186–188	509
$CH_2CH_2CO_2CH_3$	6-OC_2H_5-7-OCH_3	HCl: 192–193	815
CH_2CH_2CN	3-CO_2R-6,7-subst.	N/A	681
CH_2CN	1-($C_6H_3NH_2$-2-Cl-5)	125–127	823
CH_2CN	1-($C_6H_3NH_2$-2-NO_2-5)	222–225	823
CH_2CO_2	1-($C_6H_3NH_2$-2-Cl-5)	163–165	760, 761, 824
CH_2CO_2	1-($C_6H_3NH_2$-2-NO_2-5)	210	760
		203–204	825
CH_2CO_2H	1-($C_6H_4NH_2$-2)	95–130	760
CH_2CO_2H	1-($C_6H_4NH_2$-2)	N/A	606
$CH{=}C(CO_2C_2H_5)_2$		210/1.1	803
$(CH_2)_4CN$	3-$CO_2C_2H_5$	b.p.: 175–180/0.1	614

TABLE III.10. 1,2,3,4-Tetrahydroisoquinolinium Salts with Acidic Function on Side Chain in 2 Position (*Continued*)

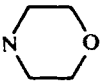
R	Substituent	m.p. (°C)	Ref.
$CH_2CH=CHCON$ 		HCl: 207–210	612
$(CH_2)_3CN$	3-$CO_2C_2H_5$-6-OCH_3	b.p.: 210/2	88
$(CH_2)_2CO_2C_2H_5$	3-$CO_2C_2H_5$	b.p.: 160–161/4	614
		Picrate: 115–116	614
$-CH_2CH_2CO_2C_2H_5$	4-$CO_2C_2H_5$	130.5–131.5	485
$CH_2CH=CHCONHC_4H_9$-*sec*		129.5–130	612, 814
		HCl: 189–192	612, 814
$CH_2CH=CHCON(C_2H_5)_2$		HCl: 178–181	612, 814
$(CH_2)_2CON$ 		b.p.: 170–178/0.08	806
		Picrate: 108	806
$-C_6H_4(CH(CH_3)CO_2H$-4)		N/A	588
CH_2CO_2H	1-($C_6H_3NHCH_3$-2-Cl-5)	115–122	760
		N/A	892
CH_2CO_2H	1-($C_6H_3NHCH_3$-2-NO_2-5)	155	760
$CH_2CONHC_6H_5$	1-CH_3	HCl: 184–187	436, 513
$-CH(CH_3)CONHC_6H_5$		101	633
CH_2CO_2H	1-($C_6H_4NHCH_3$-2)	125	760
$CH_2CH=CHCO_2C_2H_5$	3-$CO_2C_2H_5$	b.p.: 197–200/1.5	532
		b.p.: 181–184/0.7	532
$CH_2CH_2CO_2C_2H_5$	3-$CO_2C_2H_5$-6,7-O_2CH_2	Oil[a, b]	80
$(CH_2)_2CON(C_2H_5)_2$		b.p.: 154–163/0.12	819
$(CH_2)_3CO_2C_2H_5$	3-$CO_2C_2H_5$	b.p.: 180–190/203	601
$(CH_2)_2CO_2C_2H_5$	3-$CH_2CO_2C_2H_5$	b.p.: 178/0.06	573
$(CH_2)_3CO_2C_2H_5$	1-CH_3-6,7-$(OCH_3)_2$	HBr: 164–165	509
$CH_2CH=CHCONHC_6H_5$		169–172	612
		HCl: 195–198	612
CH_2CH_2CN	3-CH_3-4-C_6H_5	132–133	670
$-CH_2CH_2CO_2H$	1-($C_6H_4OCH_3$-3)-7-Cl	HCl: 204–206	826
$-CH_2CH_2CO_2H$	1-($C_6H_4CH_3$-3)	HCl: 202	826
$CH_2CO_2C_2H_5$	1-($C_6H_3NH_2$-2-Cl-5)	N/A	760
CH_2CO_2H	1-($C_6H_3NHCH_3$-2-Cl-5)-4-CH_3	260–266	606, 760
$-CH_2CH_2CO_2H$	1-($C_6H_4OCH_3$-3)	HCl: 204–206	826
$C_6H_4CO_2H$-4	3-CH_3-6,7-$(OCH_3)_2$	220–223	582
$CH_2CO_2C_2H_5$	1-($C_6H_3NH_2$-2-NO_2-5)	150	760
$CH_2CH_2CONH_2$	3-CH_3-4-C_6H_5	102–103	670
$CH_2CO_2C_2H_5$	1-($C_6H_4NH_2$-2)	100–103	761

TABLE III.10. 1,2,3,4-Tetrahydroisoquinolinium Salts with Acidic Function on Side Chain in 2 Position (*Continued*)

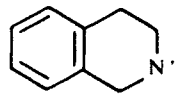
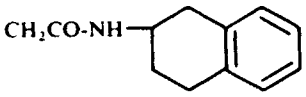
R	Substituent		m.p. (°C)	Ref.
CH_2CO_2H	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$		181–183	608
$CH_2CONHNH_2$	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$		174–176	827
$CH_2CH{=}CHCONHC_6H_{11}$			183–185	612
			HCl: 181–183	612
$(CH_2)_4CO_2C_2H_5$	3-$CO_2C_2H_5$		b.p.: 169–170/0.1	614
$(CH_2)_3CO_2C_2H_5$	3-$CO_2C_2H_5$-6-OCH_3		b.p.: 200/2	88
$CH_2CH{=}CHCON(C_3H_7\text{-}n)_2$			HCl: 128.5–130	612, 814
CH_2CONH_2	1- 	Cl^-	N/A	510
$CH_2CO_2C_2H_5$	4-$NHCOC_6H_5$		99[a]	126
$-CH_2CH_2CO_2H$	1-($C_6H_3(CH_3)_2$-3,5)		HCl: 203	826
$-C_6H_4(CH(CH_3)CO_2C_2H_5$-4)			N/A	588
CH_2CO_2H	1-($C_6H_3NHCH_3$-2-Cl-5)-4,4-(CH_3)$_2$		212–216	760
$CH_2CO_2CH_3$	1-($C_6H_3NHCH_3$-2-Cl-5)-4-CH_3		111–113	606, 760
			99–102	760
$CH_2CO_2C_2H_5$	1-($C_6H_3NHCH_3$-2-Cl-5)	(+)	113–114	760
		(−)	112–113	760
			83–84	760
			155	825
			N/A	824
$-CH_2CH_2CO_2H$	1-($C_6H_3(OCH_3)_2$-2,3)		HCl: 118–120	826
$CH_2CH_2CO_2H$	1-($C_6H_3(OCH_3)_2$-3,5)		HCl: 202–204	826
$CH_2CO_2C_2H_5$	1-($C_6H_3NHCH_3$-2-NO_2-5)		119–120	760
$CH_2CO_2C_2H_5$	1-($C_6H_4NHCH_3$-2)		98–100	760
$CH_2CO_2C_2H_5$	1-(2-pyridyl)-6,7-(OCH_3)$_2$		155–157	668
$(CH_2)_5CO_2C_2H_5$	3-$CO_2C_2H_5$		b.p.: 174–176/0.3	614
$(CH_2)_3$	3-$CO_2C_2H_5$-6,7-(OCH_3)$_2$		b.p.: 220–230/0.05	683
$(CH_2)_5CO_2(CH_2)_2N^+(CH_3)_3I^-$	($N^+CH_3I^-$)		135–137	828
$(CH_2)_4CO_2(CH_2)_3N^+(CH_3)_3I^-$	($N^+CH_3I^-$)		124–130	828
$CO\text{-}C_6H_4CO_2CH_3$-2	1,1=CH_2-6,7-(OCH_3)$_2$		136–138[a]	829
$CH_2CO_2C_2H_5$	1-($C_6H_3NHCH_3$-2-CF_3-5)		80–82	759, 761
			81–83	760
CH_2CN	1-($C_6H_4NO_2$-3)-6,7-(OC_2H_5)$_2$		124	615
			b.p.: 190–220/0.1	806
			85	806

TABLE III.10. 1,2,3,4-Tetrahydroisoquinolinium Salts with Acidic Function on Side Chain in 2 Position (*Continued*)

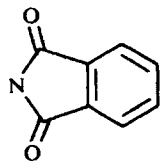
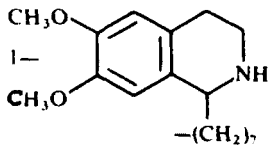
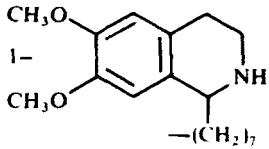
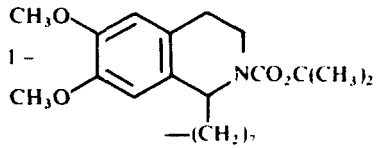
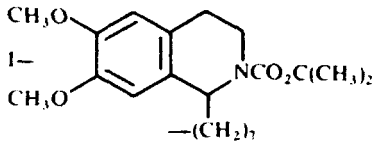
R	Substituent	m.p. (°C)	Ref.
$CH_2CO_2CH_3$	1-($C_6H_3NHCH_3$-2-Cl-5)-4,4-(CH_3)$_2$	111–113	760
$C_6H_4CO_2C_2H_5$-4	3-CH_3-6,7-(OCH_3)$_2$	139–141	582
$-CH_2CH_2CO_2H$	1-($C_6H_2(OCH_3)_3$-3,4,5)	HCl: 232–233	826
$-CH_2CONHCH(CH_3)-CH_2C_6H_5$	3-CH_3	b.p.: 197–203/0.5	536
$CH_2CO_2C_2H_5$	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	99–102	827
$CH_2CO_2C_2H_5$	1-(2-piperidyl)-6,7-(OCH_3)$_2$	diHBr: 218–220	668
$CH_2CO_2C_{10}H_{10}$(1-menthyl)			
	($N^+CH_3I^-$)	130–131	830
	($N^+C_4H_9I^-$)	155–156	830
		140–141	820
	($N^+C_3H_7$-*i*-I^-)	146–148	830
		161–163	830
	(N^+CH_2–CH=CH_2I^-)	138–140	830
	($N^+C_5H_{11}I^-$)	156–158	830
	($N^+C_7H_{17}I^-$)	169–170	830
CH_2CH=$CHCON(C_4H_9$-*n*$)_2$		95–98	814
		HCl: 95–98	612
CH_2CN	1-($C_6H_4OCH_3$-2)-6,7-(OC_2H_5)$_2$	131	615
$CH_2(C_6H_4CH_2CO_2C_2H_5$-2)	1-$CO_2C_2H_5$	92.5–93.5[a,c]	481
$CH_2CH_2CO_2(C_6H_2(C(CH_3)_2)_2$-3,4-OH-4)		N/A	831
$C_6H_4CO_2H$-4	3-CH_3-7-OCH_3-6-$O_2CC_6H_5$	212–215	582
$CH(C_6H_5)CONHC_6H_5$	6,7-(OCH_3)$_2$	194[a]	526
CH_2CN	1-($C_6H_3(OC_2H_5)_2$-3,4)-6,7-(OC_2H_5)$_2$	137	615
CH_2CO_2H	1-($C_6H_3(OC_2H_5)_2$-3,4)-6,7-(OC_2H_5)$_2$	116–117	615
CH_2CONH_2	1-($C_6H_3(OC_2H_5)_2$-3,4)-6,7-(OC_2H_5)$_2$	184–185	615
CH_2CONHN=$CHC_6H_4NO_2$-2	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	163–166	827
CH_2CONHN=$CHC_6H_4NO_2$-4	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	205–207	827
CH_2CONHN=CHC_6H_5	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	225–227	827
CH_2CONHN=CHC_6H_4OH-2	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	223–225	827
$CH_2CH_2C(CO_2C_2H_5)_2$- 		100–102	820
CH_2CONHN=$CHC_6H_4CH_3$-2	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	212–214	827
CH_2CONHN=$CHC_6H_4CH_3$-3	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	210–213	827

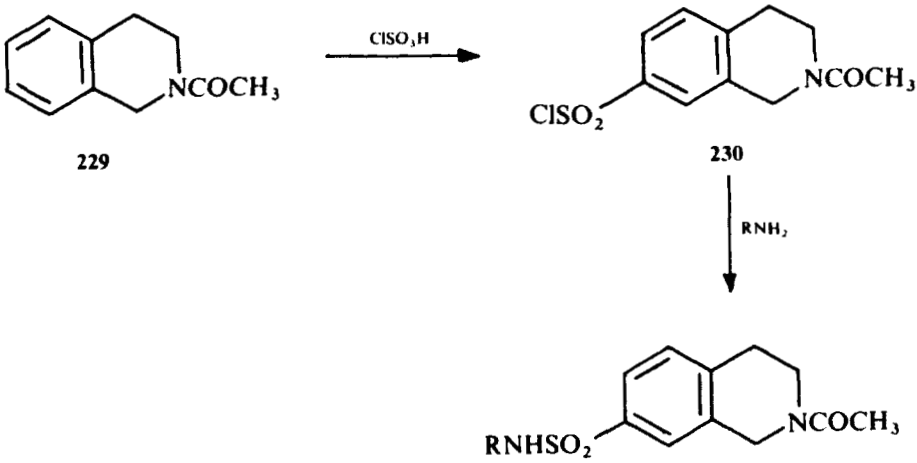
TABLE III.10. 1,2,3,4-Tetrahydroisoquinolinium Salts with Acidic Function on Side Chain in 2 Position (*Continued*)

R	Substituent	m.p. (°C)	Ref.
$CH_2CONHN=CHC_6H_4OCH_3$-2	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	191–194	827
$CH_2CONHN=CHC_6H_4OCH_3$-3	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	200–201	827
$CH_2CONHN=CHC_6H_3OH$-4-OCH_3-3	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	164–168	827
$CH_3CONHN=CHC_6H_4CH_3$-4	1-($C_6H_4NH_2$-2)-6,7-(OCH_3)$_2$	220–224	827
$CH_2CONHN=CHCH=CHC_6H_5$	1-($C_6H_4NH_2$)-6,7-(OCH_3)$_2$	196–198	827
$(CH_2)_4CONH(CH_2)_2$-($C_6H_3(OCH_3)_2$-3,4)	1-C_3H_7-6,7-(OCH_3)$_2$	HCl: 198–199	804
$(CH_2)_2CH(CH_3)(CH_2)_3CONH$-$(CH_2)_2(C_6H_3(OCH_3)_2$-3,4)	1-CH_3-6,7-(OCH_3)$_2$	Picrate: 116.5–117	832
$(CH_2)_2CO_2Na$			
	6,7-(OCH_3)$_2$	N/A	678
$COCH_2CO_2C_2H_5$			
	6,7-(OCH_3)$_2$	HCl: N/A	525
$COCH_2CO_2C_2H_5$			
	6,7-(OCH_3)$_2$	N/A	525
$COC_6H_4CO_2CH_3$-2			
	6,7-(OCH_3)$_2$	N/A	525

[a] IR in paper.
[b] NMR in paper.
[c] UV in paper.

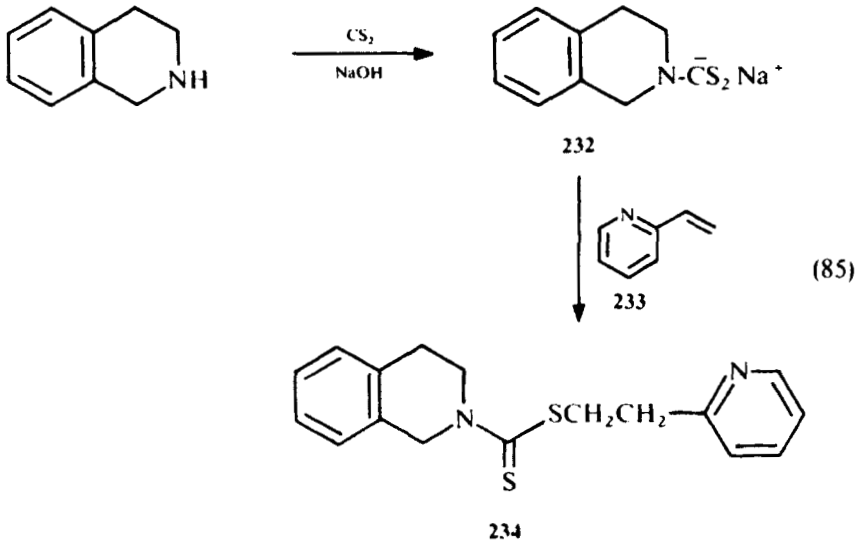
(iv) Sulfur-Containing Acid Derivatives

Reaction of chlorosulfonic acid with 2-acetyl-1,2,3,4-tetrahydroisoquinoline (**229**) gives **230**, which has been converted to **231**[833] (Eq. 84).



229 **230** **231** (84)

Tetrahydroisoquinoline reacts with carbon disulfide and sodium hydroxide to give **232**,[834] which affords **234** when treated with 2-vinylpyridine (**233**)[836] (Eq. 85).

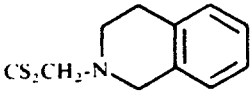
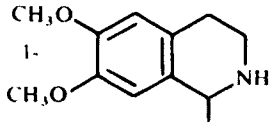
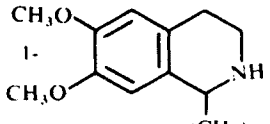


232 **233** (85)

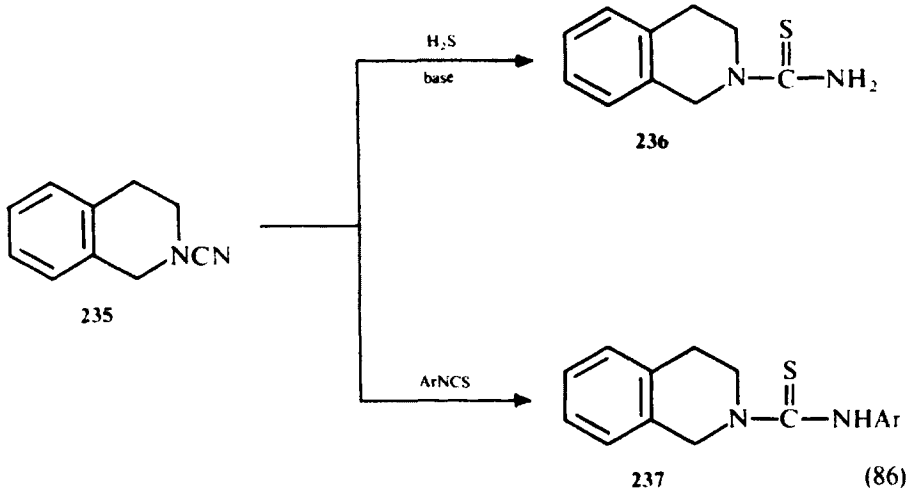
234

The reaction of 2-cyano-1,2,3,4-tetrahydroisoquinoline (**235**) with hydrogen sulfide and base gives **236**,[719] while the reaction with aryl isothiocyanates provides **237**[764] (Eq. 86).

TABLE III.11. Sulfur-Containing Acidic Functional Groups

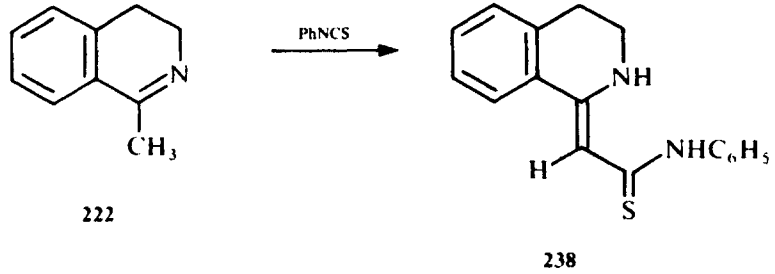
R	Substituent	m.p. (°C)	Ref.
SO_2NH_2		157–159	838
CS_2	Tetrahydroisoquinoline salt	172–174	54, 837, 839–40
		178	836
CS_2Na		199–200	834
CS_2Zn		251–252	834
$CSNH_2$		165–167	719
		160–161	841
$COCH_3$	7-CO_2Cl	N/A	842
$COCH_3$	7-CO_2NH	N/A	842
$CH_2CH(CO_2H)SO_3^-$		265[a]	812
$CSNH_2$	6,7-$(OCH_3)_2$	171–172	719
$CSNH_2$	1-CH_3-6-OH-7-OCH_3	172–174	719
$CH_2CH(CO_2CH_3)SO_3^-$		265[a]	812
$CSNH_2$	1-CH_3-6,7-$(OCH_3)_2$	138–140	719
$C_6H_4SO_3H$-4		236–237	843
$C_6H_4SO_2NH_2$-4		182–184	843
SO_2NH_2	1-$CH_2C_6H_5$	135–137	838
$CS_2CH_2CH_2$– 		76	836
$CSNHC_6H_5$	1-CO_2CH_3	133–135	661
$COCH_2CH_2C_6H_5$	7-SO_2NH_2	N/A	842
H	1,1=CHCSNHC$_6$H$_5$-6,7-$(OCH_3)_2$	815	661
		98–99	844
$CSNH(C_6H_4F$-3)	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	169–170	764
$CSNH(C_6H_4$-N$(CH_3)_2$-4)	1-$CH_2CO_2C_2H_5$-6,7-$(OCH_3)_2$	140–142	764
$COCH_2CH_2C_6H_5$	7-$SO_2NHCONHC_6H_{11}$	N/A	842
$COCH(CH_3)C_6H_5$	7-$SO_2NHCONHC_6H_{11}$	N/A	845, 846
SO_3Na			
	$-(CH_2)_7$ 6,7-$(OCH_3)_2$	N/A	678
$(CH_2)_2SO_3H$			
	$-(CH_2)_7$ 6,7-$(OCH_3)_2$ HCl	N/A	678

[a]NMR in paper.



(86)

The reaction of 1-methyl-3,4-dihydroisoquinoline (**222**) with phenyl isothiocyanate gives **238**[661] (Eq. 87).



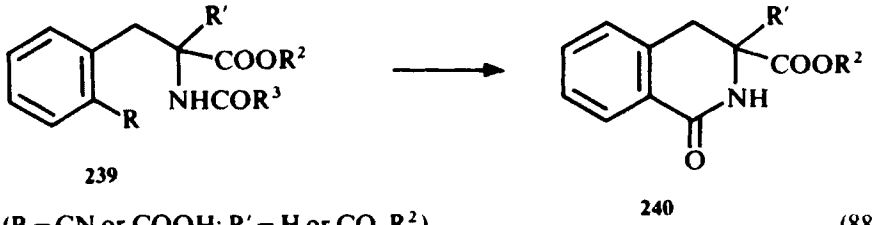
(87)

(c) 1,2,3,4-*Tetrahydroisoquinoline-one Derivatives*

(i) 1-Ones

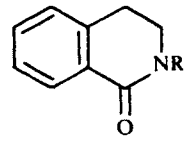
This section covers compounds of the general type **167**, which contain acidic functional groups.

A variety of methods have been used to synthesize compounds in this series. Introduction of a carboxylic acid into the 3-position has involved cyclizations starting from **239** to give **240**[428, 656] (Eq. 88).



(R = CN or COOH; R' = H or CO_2R^2) (88)

TABLE III.12. 1,2,3,4-Tetrahydroisoquinoline-1-One Derivatives



R	Substituent		m.p. (°C)	Spectroscopy	Ref.
		Esters			
H	3-CO_2CH_3	DL	115–116.5		428
		DL	114–115		656
		D	88–89.5		428
		D	90–91		367
		D	87–89		656
		L	88–89.5		428
		L	76		656
			159–160		422
H	5-CO_2CH_3		126–127	IR	395
CH_3	3-CO_2CH_3		56–57	IR	758
		D	Oil		860
			N/A	NMR	857
H	3-CO_2CH_3-3-CH_3	RS	181–183	IR, NMR	847
		S+	104.5–105.5		847
		R−	104.5–105.5		847
H	3-$CO_2C_2H_5$		N/A	NMR	857
H	4-$CO_2C_2H_5$		106	IR	848, 849
H	4-$CO_2C_2H_5$-6-OH		Oil		849
H	4-$CO_2C_2H_5$-3-CO_2H		297–298		422
H	3-$CO_2CH(CH_3)_2$-7-OCH_3-8-OH		123–124		649a
H	3-$CO_2CH(CH_3)_2$-7,8-$(OCH_3)_2$		116–117		649a
CH_3	3-$CH_2CO_2CH_3$		b.p.:163–165/0.3	IR, NMR	855
H	4-$CO_2C_2H_5$-6-CH_3O		160	IR	848, 849
H	3-($CO_2C_6H_4NO_2$-4)	D	195–198		856
H	4-CO_2CH_3-3-C_6H_5-*trans*		156–157	IR, NMR	852
H	4-CO_2CH_3-3-($C_6H_3O_2CH_2$-3,4)-*trans*		199–200	IR, NMR	852
CH_3	4-CO_2CH_3-3-C_6H_5-*trans*		107–108	IR, NMR	852
CH_3	4-CO_2CH_3-3-C_6H_5-6,7-O_2CH_2-*trans*		151–152	IR	559, 852
C_2H_5	4-CO_2CH_3-3-C_6H_5-*trans*		103–104	IR, NMR	852
CH_3	3-($C_6H_4OCH_3$-2)-4-CO_2CH_3-*trans*		144–145	IR, NMR	851
		-*cis*	150–151	IR, NMR	851
CH_3	4-CO_2CH_3-3-($C_6H_3O_2CH_2$-3,4)-6,7-(CH_2O_2)-*trans*		181–182	IR, NMR	852
C_3H_7-*n*	4-CO_2CH_3-3-C_6H_5-*trans*		164–165	IR, NMR	852
C_3H_7-*i*	4-CO_2CH_3-3-C_6H_5-*trans*		118–119	IR, NMR	852
CH_3	4-CO_2CH_3-3-($C_6H_3(OCH_3)_2$-3,4)-*trans*		111–112	IR, NMR	852
CH_3	4-CO_2CH_3-3-C_6H_5-6,7-$(OCH_3)_2$-*trans*		155–156	IR, NMR	559, 852
CH_3	4-CO_2CH_3-3-($C_6H_3O_2CH_2$-3,4)-6,7-$(OCH_3)_2$-*trans*		194–195	IR	559

TABLE III.12. 1,2,3,4-Tetrahydroisoquinoline-1-One Derivatives (*Continued*)

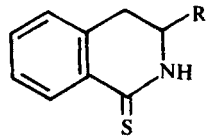
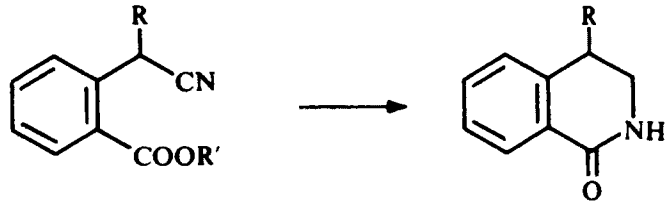
R	Substituent		m.p. (°C)	Spectroscopy	Ref.
$CH(C_6H_5)CO_2C_2H_5$	6,7-$(OCH_3)_2$		88		598
CH_3	4-CO_2CH_3-3-($C_6H_3(OCH_3)_2$-3,4)-6,7-$(OCH_3)_2$-*trans*		62–63	IR	559
C_6H_5	4-CO_2CH_3-3-C_6H_5-*trans*		162–163	IR, NMR	852
CO_2CH_3			155–157		508a
$CH_2CO_2CH_3$			101–103		779a
$CO_2CH(CH_3)_2$	7,8-$(OCH_3)_2$		88–90		649a
	Acid Derivatives (Other than Esters)				
H	3-CO_2H	DL	238.5–240.5		428
		DL	235–237		656
		D	232.5–234		428
		D	241–242		367
		D	234–236.5		656
		L	236–238		428, 656
			320.5–321.5		422
CH_2CO_2H			187		510
		Picrate:	174		510
H	3-CO_2H-3-CH_3	R	197–198		847
CH_3	3-CH_2CN		b.p.:170/0.4		758
			82–83	IR	758
H	3-CO_2H-4-$CO_2C_2H_5$		297–298		422
$(CH_2)_2CO_2H$	6,7-$(OCH_3)_2$		174–175		861
H	4-CO_2H-3-C_6H_5-*trans*		189–190	IR, NMR	852
H	4-CO_2H-3-($C_6H_3O_2CH_2$-3,4)-*trans*		247–248	IR	852
CH_3	3-C_6H_5-4-CO_2H-*trans*		207	IR, NMR	851
			205–206	IR, NMR	852
CH_3	3-C_6H_5-4-CO_2H-*cis*		201–202	IR, NMR	851
CH_3	4-CO_2H-3-C_6H_5-6,7-(CH_2O_2)-*trans*		225–227	IR	852
C_2H_5	4-CO_2H-3-C_6H_5-*trans*		205–206	IR	852
CH_3	3-($C_6H_4OCH_3$-2)-4-CO_2H-*trans*		231–232	IR, NMR	851
	-*cis*		228–229	IR, NMR	851
C_3H_7-*n*	4-CO_2H-3-C_6H_5-*trans*		167–168	IR	852
C_3H_7-*i*	4-CO_2H-3-C_6H_5-*trans*		184–185	IR	852
CH_3	4-CO_2H-3-C_6H_5-6,7-$(OCH_3)_2$-*trans*		225–226	IR	852
CH_3	4-CO_2H-3-($C_6H_3(OCH_3)_2$-3,4)-*trans*		193–194	IR	852
$CH(C_6H_5)CO_2H$	6,7-$(OCH_3)_2$		206		598
			N/A		526

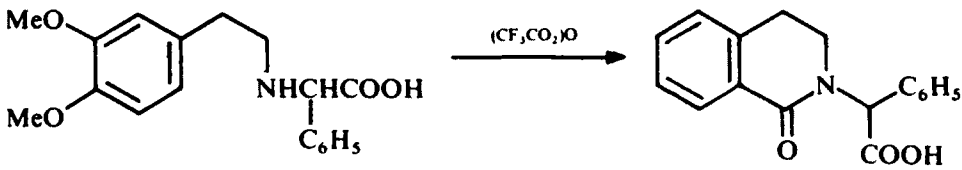
TABLE III.12. 1,2,3,4-Tetrahydroisoquinoline-1-One Derivatives (*Continued*)

R	Substituent	m.p. (°C)	Spectroscopy	Ref.
CH_3	4-CO_2H-3-($C_6H_3O_2CH_2$-3,4) -6,7-(OCH_3)$_2$-*trans*	228–229	IR	852
		204–205	IR	559
CH_3	4-CO_2H-3-(C_6H_3(OCH_3)$_2$-3,4) -6,7-(OCH_3)$_2$-*trans*	118–119	IR	559
C_6H_5	4-CO_2H-3-C_6H_5-*trans*	203–204	IR, NMR	852
N=CHC_6H_5	3-C_6H_5-4-CO_2H-*trans*	206	IR, NMR	851
	-*cis*	206	IR, NMR	851
CH_3	3,3-(C_6H_5)$_2$-4-CO_2H	253–255	IR, NMR	851
$CH(C_6H_5)$ CO_2H	6,7-(OC_6H_5)$_2$	234		598
H	3-CO_2H-7-OCH_3-8-OH	250–251		649a

Compounds of the type **240** have also been prepared from methyl phenylalaninates by reaction with phosgene followed by aluminum chloride.[367, 847] Cyclization of compounds of the type **241** leads to **242**[848–850] (Eq. 89). Treatment of **243** with trifluoroacetic anhydride yields **244**[598] (Eq. 90).

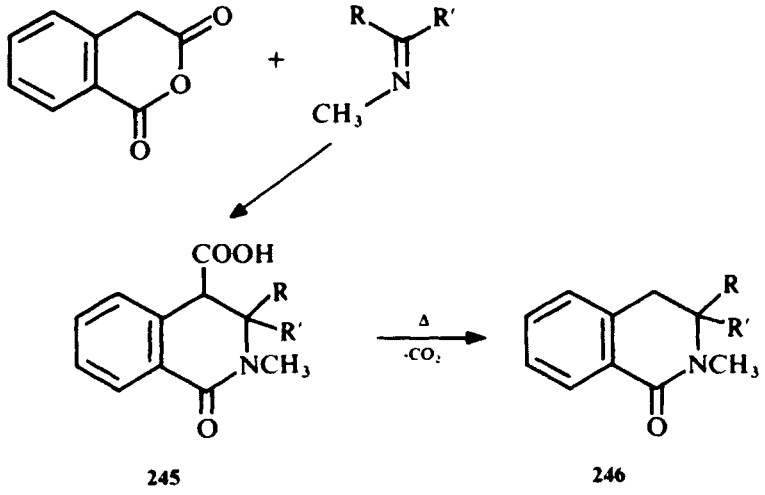


241 (R = CO_2Et or CH_2CN) **242** (89)



243 **244** (90)

The condensation of a variety of aldimines and ketimines with homophthalic anhydride gives rise to **245**.[851, 852] In one case trans products were obtained,[852] but in another cis and trans isomers were isolated from this reaction and the effect of reaction conditions on isomer ratios were studied.[851] Heating **245** (R = H; R' = C_6H_5) results in a decarboxylation to afford **246**[851] (Equation 91).

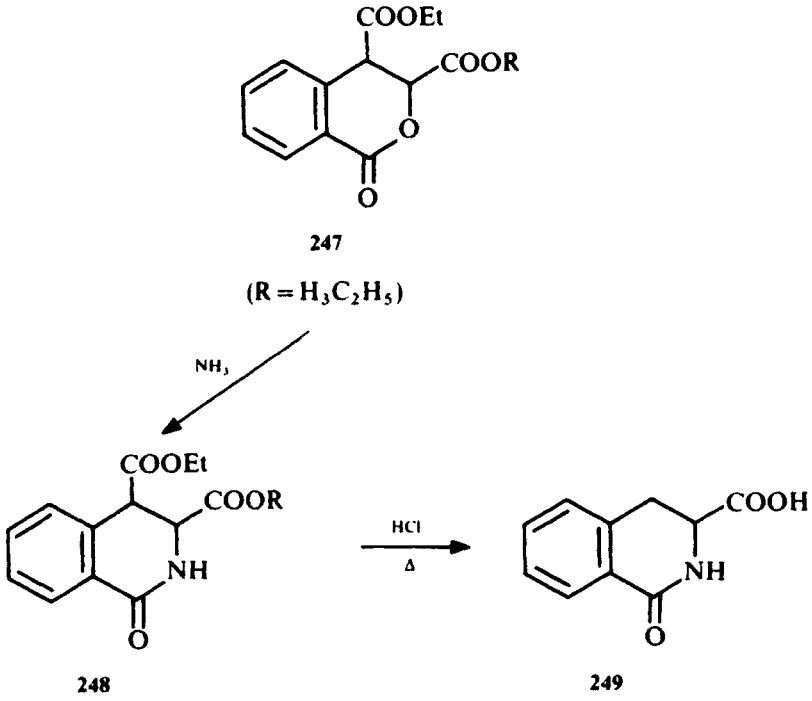


(91)

245 246

Potassium permanganate oxidates of some 4-carbomethoxy-1,2,3,4-tetrahydroisoquinolines gave the methyl esters of **245**.[852]

The isocoumarin **247** reacts with ammonia to give **248**. Heating of **248** with hydrochloric acid affords the 3-carboxylic acid **249**[422] (Eq. 92).



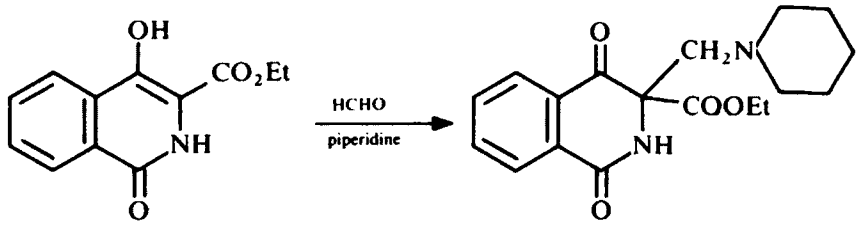
247

$(R = H_3C_2H_5)$

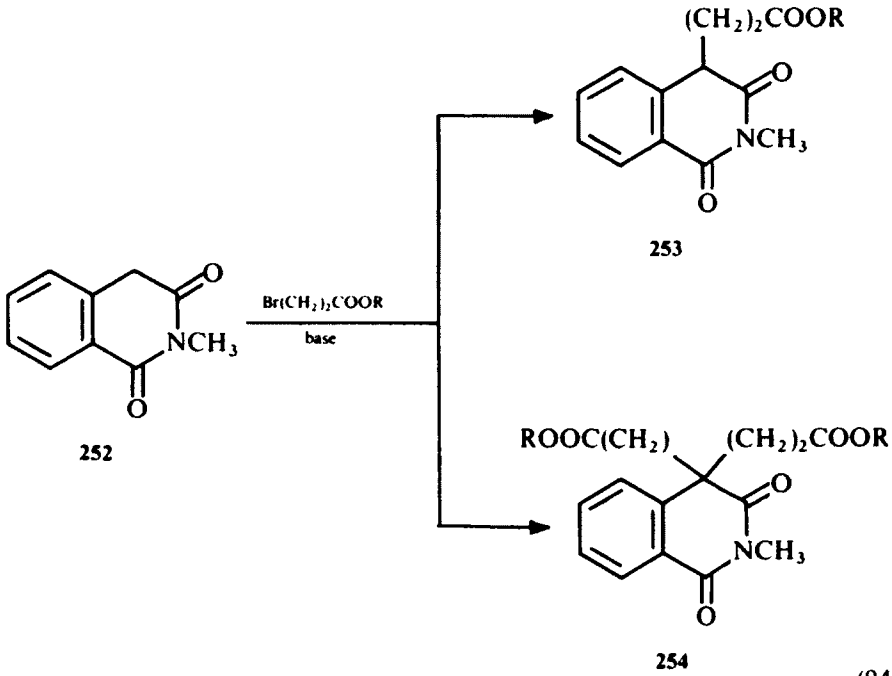
248 249 (92)

Oxidation of series of 4-carbomethoxy-1,2,3,4-tetrahydroisoquinolines with potassium permanganate leads to compounds in this series,[559] as does reduction of a 3,4 double bond by catalytic hydrogenation.[395]

The Mannich condensation of **250** with formaldehyde and piperidine leads to **251**[853] (Eq. 93). Base-catalyzed alkylation of **252** with a series of ω-bromoesters affords the 4- and 4,4-disubstituted compounds **253** and **254**, respectively[854] (Eq. 94).



250 **251** (93)



253 **252** **254** (94)

Compound **253** can be alkylated with methyliodide to give the 4-methyl analog.[854] Similar reactions have been used to convert ring NH to *N*-methyl.[758]

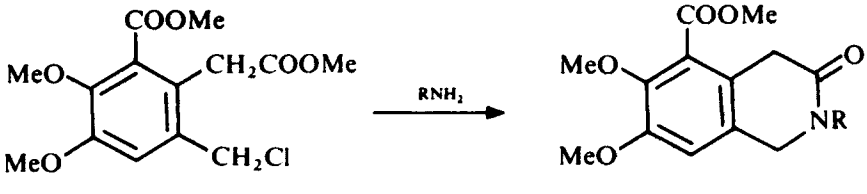
Various esterification[367, 422, 598, 656, 847, 851, 852] and ester-hydrolysis[559, 854] reactions have been carried out in this series. 3-Chloromethyl groups have been

reacted with cyanide ion to introduce cyano groups[758] and cyano groups have been hydrolyzed to esters.[855]

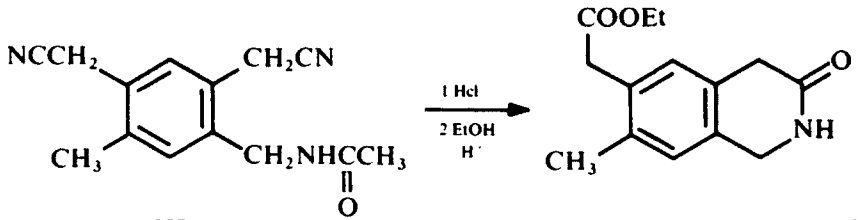
A substantial amount of work has been done in studies of α-chymotrypsin with esters of compounds of the type **240**. α-Chymotrypsin hydrolysis of the DL esters of **240**, for example, yields the D acid and L ester.[428, 847, 856] The kinetics of this hydrolysis have been studied,[428] as have the effects of conformation.[857, 858] The compounds **240** are considered as cyclic analogs of *N*-acetyl-L-phenylalanine and the usefulness and limitations of such cyclized substrates has been discussed.[367, 847, 856, 859]

(ii) 3-Ones

A number of compounds **256** with esters in the aromatic ring have been prepared by the condensation of **255** with primary amines[862, 863] (Eq. 95). Reaction of **257** with hydrochloric acid followed by esterification provides **258**[69] (Eq. 96).

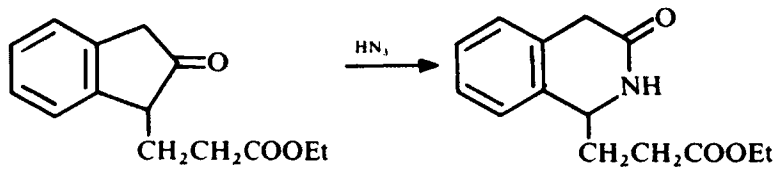


255 **256** (95)



257 **258** (96)

Ring expansion of ethyl β-2-oxoindenylpropionate (**259**) by reaction with hydrazoic acid affords **260**[864] (Eq. 97).

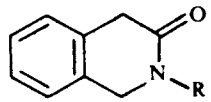


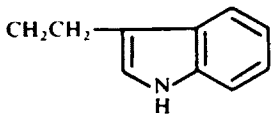
(97)

259 **260**

Reaction of compounds of the type **256** with ethyl chloroacetate and ethoxide introduces a 2-ethoxy-carbonylmethyl group which has been hydrolyzed to an acid and converted to an amide.[865]

TABLE III.13. 1,2,3,4-Tetrahydroisoquinoline-3-one Derivatives



R	Substituent	m.p. (°C)	Ref.
H	6-$CH_2CO_2C_2H_5$-7-CH_3	164–166[a]	69
H	1-$CH_2CH_2CO_2C_2H_5$	N/A	864
C_3H_7-*n*	5-CO_2CH_3-6,7-$(OCH_3)_2$	86–87	862
CH_2CO_2H	4,4-$(C_6H_5)_2$	229–230	865
	5-CO_2CH_3-6,7-$(OCH_3)_2$	170–171	863
$CH_2CH_2C_6H_3(OCH_3)_2$	5-CO_2CH_3-6,7-$(OCH_3)_2$	140	862
$CH_2CO_2C_2H_5$	4,4-$(C_6H_5)_2$	147–148	865
$CH_2CONHCH_2CH_2N(CH_3)_2$	4,4-$(C_6H_5)_2$	188–189	865
$CH_2CONHC_6H_5$	4,4-$(C_6H_5)_2$	206–207	865
$CH_2CO_2CH_2CH_2N(C_2H_5)_2$	4,4-$(C_6H_5)_2$	210	865
$NHCOCH_3$	1-CO_2CH_3	178–180	865a
$NHCOC_6H_5$	1-CO_2CH_3	173–175	865a
$NHCOC_6H_2$-3,4,5$(OCH_3)_3$	1-CO_2CH_3	247–248	865a
$NHCOCH_2C_6H_4$-4-F	1-CO_2CH_3	157–159	865a
NH_2	1-CO_2CH_3	183–185	865a
$NHCOCH_3$	1-$CONH_2$	248–250	865a
$NHCOC_6H_5$	1-$CONH_2$	281–282	865a

[a]IR and NMR in paper.

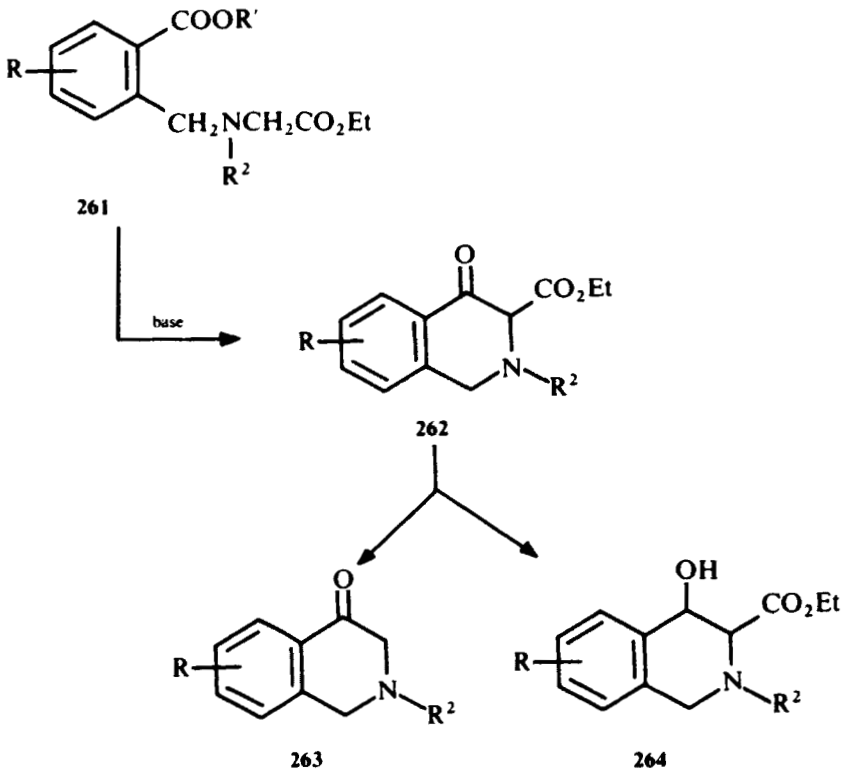
(iii) 4-Ones

A number of compounds **262** have been prepared by base-catalyzed cyclization **261**.[82, 83, 111, 866] Hydrolysis of the ester group in **262** leads to decarboxylation[111, 866] to afford **263**. Reaction of **262** with cupric acetate leads to the 4-hydroxyisoquinoline derivative **264**[111](Eq. 98).

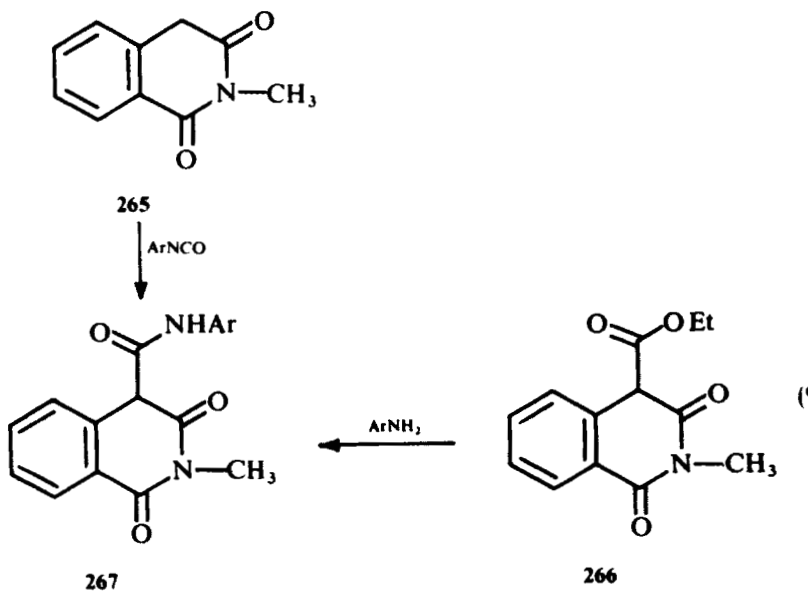
(iv) 1,3-Diones

Treatment of 2-methylisoquinoline-1,3-(2H, 4H)-dione (**265**) with aryl isocyanates provides the 4-carboxyanilide **267**,[867–869] which may also be prepared from the aminolysis of **266**[867, 869] (Eq. 99).

Some of these compounds have antiinflammatory action.[867, 870] A study of the keto–enol tautomerization of **267** has shown that the enol tautomer makes little or no contribution.[869]

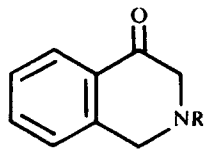

COOR'
R
CH2NCH2CO2Et
R2
261
base
O
CO2Et
R
N
R2
262
O
R
N
R2
263
OH
CO2Et
R
N
R2
264

(98)


O
N—CH3
O
265
ArNCO
O
NHAr
O
N—CH3
O
267
ArNH2
O
OEt
O
N—CH3
O
266

(99)

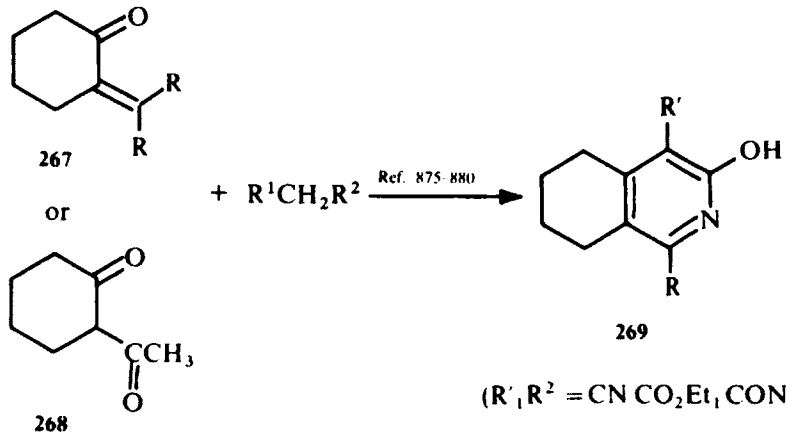
TABLE III.14. 1,2,3,4-Tetrahydroisoquinoline-4-One Derivatives



R	Substituent	m.p. (°C)	Spectroscopy	Ref.
CH_3	3-$CO_2C_2H_5$	b.p: 130/0.65		111
		Picrate: 128–129		111
		HCl: 137		111
		HBr: 172		111
		chloroplatinate: 176–177		111
CH_3	3-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	HCl: 131		82
		HCl: 105–152	IR, UV, NMR	83
C_6H_5	3-$CO_2C_2H_5$	132–134		866
$CH_2C_6H_5$	3-$CO_2C_2H_5$-7-Cl	91–93		82, 83
		HBr: 154–157		82
		HBr: 146–151	IR, UV, NMR	83
$CH_2C_6H_5$	3-$CO_2C_2H_5$	HBr: 144		866
$CH_2C_6H_5$	3-$CO_2C_2H_5$-7-OCH_3	103–107	IR, UV	83
		101–107		82
		HCl: 170–174		82, 83
$CH_2C_6H_5$	3-$CO_2C_2H_5$-6,7-$(OCH_3)_2$	HCl: 166–167		82
		HCl: 153–156	IR, UV, NMR	83
$CH_2C_6H_5$	3-$CO_2C_2H_5$-7,8-$(OCH_3)_2$	HCl: 134–135	IR, UV, NMR	83

B. 5,6,7,8-Tetrahydroisoquinoline Derivatives

The major entry into derivatives of the 5,6,7,8-tetrahydroisoquinolines has involved base-catalyzed ring-closure reactions of which the following are typical:



(100)

TABLE III.15. 1,2,3,4-Tetrahydroisoquinoline-Dione Derivatives

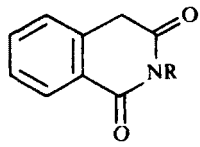
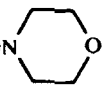
R	Substituent	m.p. (°C)	Ref.
	1,3-Dione 		
H	4-$CONHCH_3$	254–255	867
CH_3	4-$CONH_2$	214–215	867
H	4-$CO_2C_2H_5$	238–240	867
H	4-$CH_2CO_2CH_3$	185.5–187[a,b]	850
CH_3	4-CH_2CO_2H	164	854
H	4-$CONHC_2H_5$	252–253	867
CH_3	4-$CONHCH_3$	250–251	867
		160–162	867
H	4-$CONHC_2H_5$-7-Cl	237–238	867
$CH_2CH=CH_2$	4-$CONH_2$	205–206	867
CH_3	4-$CH_2CH_2CO_2H$	122–123[a,c]	872
		127	854
CH_3	4-$CO_2C_2H_5$	113–115	867, 868
CH_3	4-$CONHC_2H_5$	230–231	867
CH_3	4-$CONHC_2H_5$-7-Cl	218–219	867
CH_3	4,4-$(CH_2CO_2H)_2$	212	854
CH_3	4-$CONHCH_2$-$CH=CH_2$	206–207	867
CH_3	4-$CONHC_3H_7$	209–210	867
H	4-$CONHC_2H_5$-6,7-$(OCH_3)_2$	255–257	867
CH_3	4-CON 	182–184	867
CH_2-$CH=CH_2$	4-$CONHC_3H_5$	189–191	867
C_3H_7-*i*	4-$CONHC_2H_5$	173–174	867
CH_3	4-CON 	160–161	867
CH_3	4-$CONHCH_2CO_2C_2H_5$	180–182	867
CH_3	4-$CH_2CH_2CO_2C_2H_5$	Oil	854
CH_3	4-$CONHC_4H_9$	176–177	867
CH_3	4-$CONHC_2H_5$-6,7-$(OCH_3)_2$	250–251	867
H	4-$CONH(C_6H_4Cl$-4)-7-Cl	240–241	867
H	4-$CONH(C_6H_3Cl_2$-2,5)	242–243	867
H	4-$CONH(C_6H_3Cl_2$-3,4)	239–241	867

TABLE III.15. 1,2,3,4-Tetrahydroisoquinoline-Dione Derivatives (*Continued*)

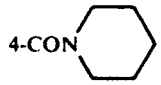
R	Substituent	m.p. (°C)	Ref.
H	4-CONH(C_6H_4Br-4)	246–248	867
H	4-CONH(C_6H_4Cl-2)	223–224	867
H	4-CONH(C_6H_4Cl-3)	232–234	867
H	4-CONH(C_6H_4Cl-4)	243–245	867
H	4-CONHC_6H_5-6-Cl	224–226	867
C_6H_4Cl-3	4-CONH$_2$	227–229	867
H	4-CONH(C_6H_4F-4)	242–244	867
H	4-CONHC_6H_5	249–250	867
C_6H_5	4-CONH$_2$	192–194	867
CH_3	4,4-($CH_2CH_2CO_2H$)$_2$	200	854
H	4-CONHC_6H_{11}	223–225	867
CH_3	4-CON 	164–165	867
CH_3	4-$CH_2CH_2CO_2C_2H_5$-4-CH_3	77	854
CHRCONR^{1}R^2	4,4-(CH_3)$_2$	N/A	607
H	4-CONH($C_6H_4CF_3$-4)	250–251	867
CH_3	4-CONH($C_6H_3Cl_2$-2,4)	222–225	867
		204–205	867
CH_3	4-CONH($C_6H_3Cl_2$-3,4)	219–220	867
CH_3	4-CONH($C_6H_3Cl_2$-2,3)	217–219	867
CH_3	4-CONH($C_6H_3Cl_2$-3,5)	228–229	867
CH_3	4-CONH(C_6H_4Br-4)	227–228	867
		228–229	869
CH_3	4-CONH(C_6H_4Cl-2)	212–213	868
		211–213	867
CH_3	4-CONH(C_6H_4Cl-3)	203–205	867
		206–208	869
CH_3	4-CONH(C_6H_4Cl-4)	213–214	867, 869
CH_3	4-CONH(C_6H_4F-3)	217	869
CH_3	4-CONH(C_6H_4F-4)	222–224	867, 869
H	4-CONH(C_6H_4Cl-4)-7-OCH_3	280–282	867
		221–222	867
H	4-CONH($C_6H_4CH_3$-2)	242–243	867
H	4-CONH($C_6H_4CH_3$-3)	232–233	867
H	4-CONH($C_6H_4CH_3$-4)	236–237	867
CH_3	4-CONHC_6H_5	246–247	867
		243–244	868, 869
$CH_2C_6H_5$	4-CONH$_2$	222–223	867
CH_3	4-CONHC_6H_5-7-Cl	238–239	867
H	4-CONHC_6H_5-7-OCH_3	271–273	867

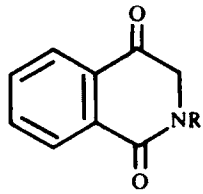
TABLE III.15. 1,2,3,4-Tetrahydroisoquinoline-Dione Derivatives (*Continued*)

R	Substituent	m.p. (°C)	Ref.
H	4-CONH($C_6H_4OCH_3$-2)	210–211	867
H	4-CONH($C_6H_4OCH_3$-4)	237–238	867
CH_3	4-CONH($C_6H_4SO_2NH_2$-4)	231–232	869
CH_2CONH_2	4,4-($CH_2CH=CH_2$)$_2$	N/A	871
CH_3	4-CONHC_6H_{11}	221–223	867
CH_3	4-CONH(C_6H_3Cl-2-CF_3-5)	205–206	867
CH_3	4-CONH($C_6H_4CF_3$-3)	188–189	869
		188–190	867
CH_3	4-CONH($C_6H_4CF_3$-4)	210–211	867, 869
CH_3	4-CONH($C_6H_4NO_2$-2)	235–236	868
CH_3	4-CONHCH$_2$($C_6H_3Cl_2$-3,4)	224–225	867
CH_3	4-CONH($C_6H_3Cl_2$-2,4)-7-OCH_3	210–211	867
CH_3	4-CON(CH_3)(C_6H_4Cl-4)	156–158	867
CH_3	4-CONH(C_6H_3Cl-2-CH_3-4)	202.5–204	867
CH_3	4-CONH(C_6H_3Cl-3-CH_3-4)	213–214	867
CH_3	4-CONH(C_6H_3Cl-3-CH_3-2)	240–240.5	867
CH_3	4-CONH($C_6H_3CH_3$-2-Cl-4)	237–238	867
C_6H_4Cl-3	4-CONHC_2H_5	211–212	867
CH_3	4-CONH($C_6H_3OCH_3$-2-Cl-5)	208.5–209.5	867
CH_3	4-CONH(C_6H_4Cl-4)-7-OCH_3	222	867
CH_3	4-CONH(C_6H_4Cl-2)-7-OCH_3	216.5–217	867
H	4-CONH(C_6H_4Cl-4)-6,7-(OCH_3)$_2$	260–261	867
H	4-CONH(C_6H_3(CH_3)$_2$-3,4)	245–246	867
CH_3	4-CONHCH$_2C_6H_5$	171–173	867
CH_3	4-CONH($C_6H_4CH_3$-2)	224–225	867
		221–223	868
CH_3	4-CON(CH_3)C_6H_5	160–162	869
CH_3	4-CONH($C_6H_4CH_3$-3)	224–225	867, 869
CH_3	4-CONH($C_6H_4CH_3$-4)	232–234	867, 869
H	4-CONH($C_6H_4OC_2H_5$-2)	203–205	867
H	4-CONH($C_6H_4OC_2H_5$-4)	232–233	867
CH_3	4-CONHC_6H_5-7-OCH_3	223–225	867
CH_3	4-CONH($C_6H_4OCH_3$-2)	197–198	867, 868
CH_3	4-CONH($C_6H_4OCH_3$-3)	206–207	869
CH_3	4-CONH($C_6H_4OCH_3$-4)	222–224	867, 869
H	4-CONH(C_6H_3(OCH_3)$_2$-2,4)	223–225	867
H	4-CONH(C_6H_3(OCH_3)$_2$-2,5)	197–198	867
H	4-CONHC_6H_5-6,7-(OCH_3)$_2$	251–252	867
CH_3	4,4-($CH_2CO_2C_2H_5$)$_2$	118	854
CH_3	4,4-(CH_2)$_3CO_2H$)$_2$	144	854
CH_3	4-CONH($C_6H_4COCH_3$-3)	117–178	867, 869

TABLE III.15. 1,2,3,4-Tetrahydroisoquinoline-Dione Derivatives (*Continued*)

R	Substituent	m.p. (°C)	Ref.
C_6H_4Cl-3	4-$CONHC_3H_7$	195–197	867
CH_3	4-$CONH(C_6H_4Cl$-2)-6,7-$(OCH_3)_2$	247–249	867
CH_3	4-$CONH(C_6H_4Cl$-4)-6,7-$(OCH_3)_2$	227–228	867
CH_3	4-$CONH(C_6H_3(CH_3)_2$-3,5)	253–254	867
CH_3	4-$CONH(C_6H_3(CH_3)_2$-3,4)	214–216	867
CH_3	4-$CONH(C_6H_3(CH_3)_2$-2,4)	227–228	867
CH_3	4-$CONH(C_6H_3(CH_3)_2$-2,5)	243.5–244	867
CH_3	4-$CONH(C_6H_3(CH_3)_2$-2,6)	250	867
CH_3	4-$CONHCH_2CH_2C_6H_5$	201–202	867
CH_3	4-$CONH(C_6H_3OCH_3$-2-CH_3-5)	212.5–214	867
CH_3	4-$CONH(C_6H_3OCH_3$-4-CH_3-2)	213.5–214	867
CH_3	4-$CONHCH_2(C_6H_4OCH_3$-4)	172–176	867
CH_3	4-$CONH(C_6H_4OC_2H_5$-2)	220–221	867
CH_3	4-$CONH(C_6H_4OC_2H_5$-4)	212–214	867
		210–211	869
CH_3	4-$CONHC_6H_5$-6,7-$(OCH_3)_2$	237–238	867
CH_3	4-$CONH(C_6H_4OCH_3$-4)-7-OCH_3	222–224	867
CH_3	4-$CONH(C_6H_4OCH_3$-2)-7-OCH_3	192–194	867
CH_3	4-$CONH(C_6H_3(OCH_3)_2$-2,4)	203–204	867
CH_3	4-$CONH(C_6H_3(OCH_3)_2$-2,5)	183–184	867
CH_3	4-$CONH(C_6H_3(OCH_3)_2$-3,5)	209–210	867
C_6H_4Cl-3	4-$CONHCH_2CO_2C_2H_5$	174–175	867
CH_3	4-$CONH(C_6H_4CO_2C_2H_5$-2)	128–130	867
CH_3	4-$CONH(C_6H_4CO_2C_2H_5$-4)	229–230	867, 869
CH_3	4-$CONH(C_6H_4CH_3$-2)-6,7-$(OCH_3)_2$	242–243	867
CH_3	4,4-$(CH_2CH_2CO_2C_2H_5)_2$	89–90[a,c]	872
		89	854
$CH_3C(CH_3)(CO_2C_2H_5)_2$	4,4-$(CH_3)_2$	101–102	873
C_6H_4Cl-3	4-$CONH(C_6H_3Cl_2$-2,5)	222–223	867
	$CH_2C(C_6H_5)(CN)COCH_3$4,4-$(CH_3)_2$	104–105	873
C_6H_4Cl-3	4-$CONHC_6H_{11}$	237–238	867
CH_3	4,4-$((CH_3CH_2)_3CO_2C_2H_5)_2$	65	854
C_6H_4Cl-3	4-$CONHCH_2C_6H_5$	201–203	867

1,4-Diones

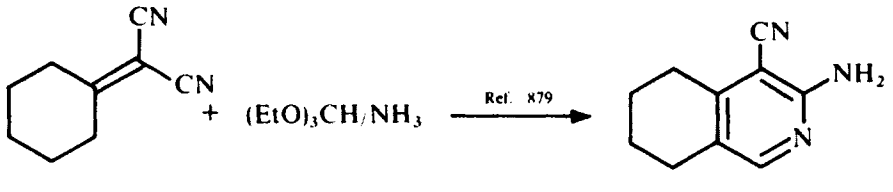


H	3,3 = C(SCH$_3$)CN	208[a–c]	217

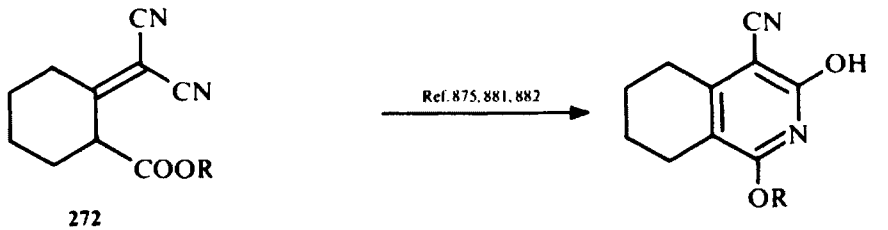
TABLE III.15. 1,2,3,4-Tetrahydroisoquinoline-Dione Derivatives (*Continued*)

R	Substituent	m.p. (°C)	Ref.
H	3,6-$(CO_2C_2H_5)_2$	184–185	874
H	3-$CO_2C_2H_5$-3-CH_2-N⟨⟩	118	854
		Picrate: 161–162	853

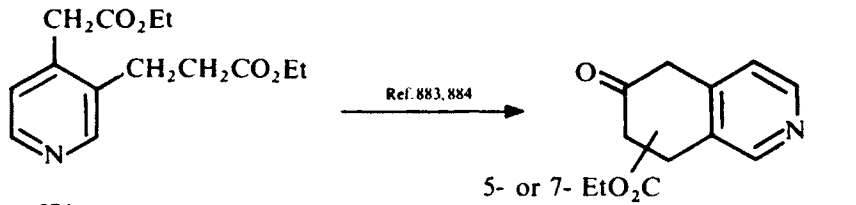
[a] IR in paper.
[b] UV in paper.
[c] NMR in paper.



270 271 (101)

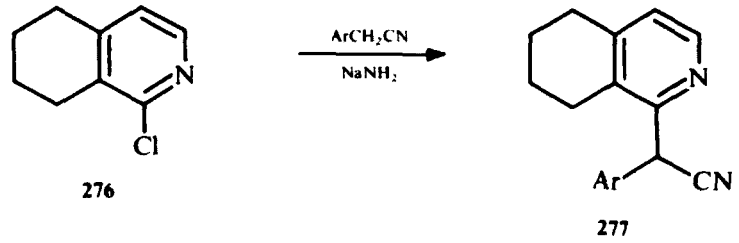


272 273 (102)



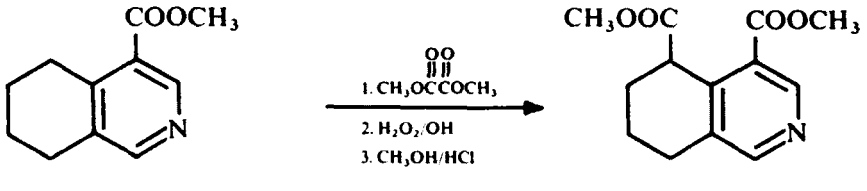
274 275 (103)

1-Chloro-5,6,7,8-tetrahydroisoquinoline (**276**) has been converted to **277** by reaction with benzyl cyanides and sodium amide[855-890] (Eq. 104). This nitrile has been hydrolyzed to the amide, as have other nitriles in the tetrahydro series.[135,891] The reaction of methyl 5,6,7,8-tetrahydroisoquinoline-4-

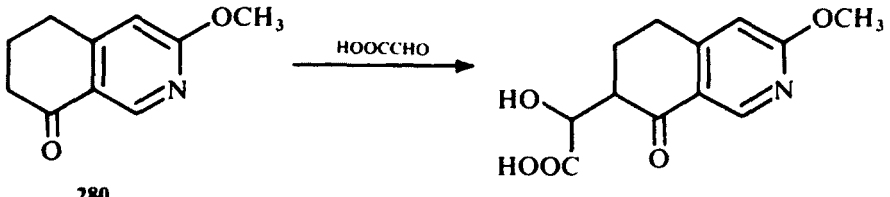


276 277 (104)

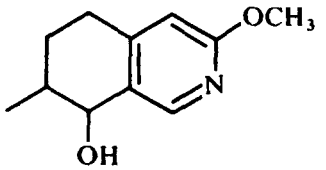
carboxylate (**278**) with methyl oxalate, followed by hydrogen peroxide oxidation and esterification, yields **279**[89] (Eq. 105), while reaction of 3-methoxy-5,6,7,8-tetrahydroisoquinoline-8-one (**280**) with glyoxylic acid gives **281**,[71] which undergoes dehydration, reduction, esterification, and reduction to afford **282**[71] (Eq. 106).



278 279 (105)

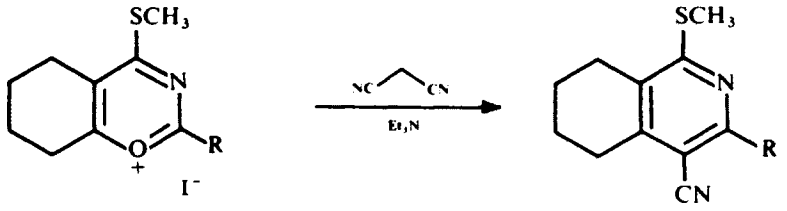


280 281



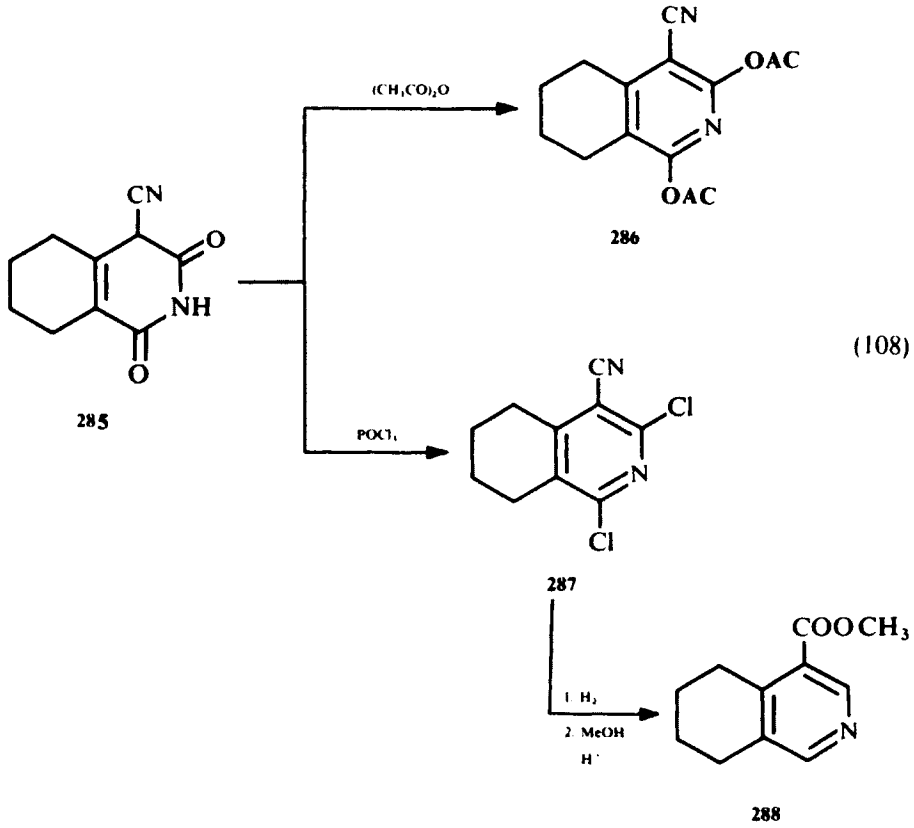
282 (106)

The reaction of the salt **283** with malononitrile and triethylamine affords 1-methylthio-4-cyano-3-substituted-5,6,7,8-tetrahydroisoquinolines **284**[892] (Eq. 107).

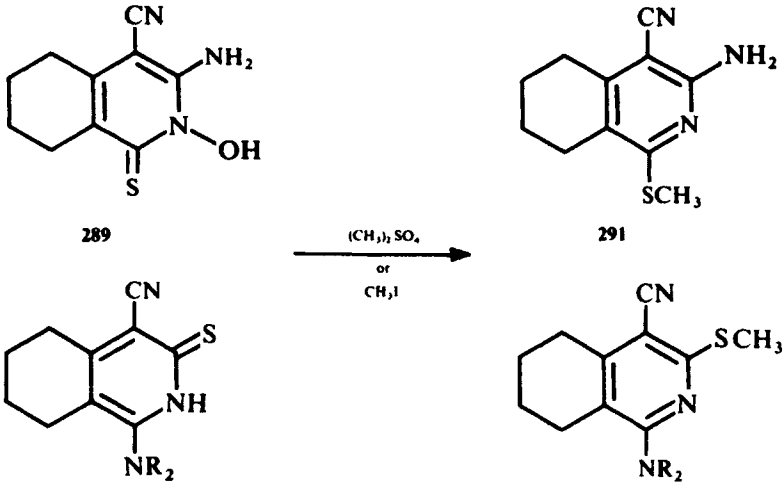


283 284 (107)

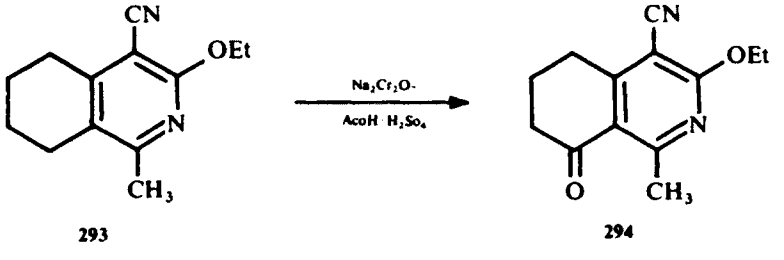
Treatment of **285** with acetic anhydride[893] or phosphorus oxychloride[894] gives the 1,3-diacetate **286** or 1,3-dichloro **287** derivatives, respectively. The chlorines can be removed by hydrogenolysis to give the 4-cyano compound, which can be further hydrolyzed to methyl ester **288**[894] (Eqn. 108). Treatment of thiones such as **289** or **290** with methylsulfate or methyliodide affords 4-cyano-1- or -3-thiomethyl-5,6,7,8-tetrahydroisoquinolines **291** or **292**[895,896] (Eq. 109). Decarboxylation of **295** affords 4-cyano-3-ethoxy-5,6,7,8-tetrahydroisoquinoline (**296**)[878] (Eq. 110). Reaction of **297** with vinyl magnesium bromide and then condensation with 2-methylcyclopentane-1,3-dione provides the azasteroid precursor **298**[897] (Eq. 111). Reaction of **299** with guanidine carbonate



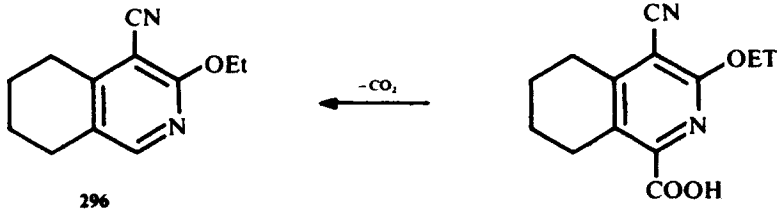
(108)

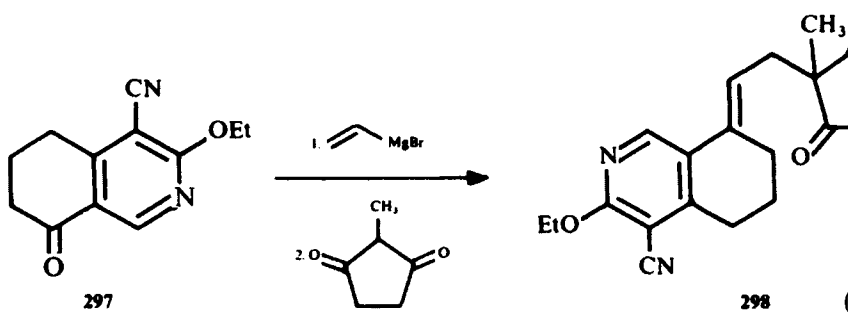

CN
NH2
N
OH
S
289
(CH3)2SO4
or
CH3I
291
SCH3
290
NR2
292

(109)


CN
OEt
N
CH3
293
Na2Cr2O7
AcoH H2SO4
294
O
+

(110)


CN
OEt
N
296
-CO2
OET
COOH
295


CN
OEt
N
O
297
1.
MgBr
CH3
2.
O
CH3
O
N
EtO
CN
298

(111)

TABLE III.16. 5,6,7,8-Tetrahydroisoquinolines with Acid-Type Functional Groups

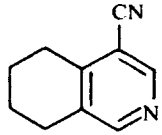
Substituent	m.p. (°C)	Ref.
4—cyano Derivatives		
		
1,3-Cl_2	74–75	894
3-Cl	132–134	879
H	38–40	894
3-OH	256–258	879
1,3-$(OH)_2$	N/A	882
	280–283	881
	278–287	875
3-NH_2	194–196	879
1-CH_3-3-Cl	98–99	879
	100–100.5[a,b]	876
1-CH_3-3-OH	> 360	879
	357–359[a–c]	876
	> 320[a,c]	875
1-OCH_3-3-OH	172–174[a,c]	875
1-SCH_3-3-NH_2 [N^+ Oxide$^-$]	209–212	895
[$N^+C_6H_5{}^{11}CH_3SO_4^-$]	172–173	896
1-OH-3-OC_2H_5	178–179	896a
1-C_2H_5-3-Cl	77–79	879
3-OC_2H_5	82–83	878
1-C_2H_5-3-OH	325–328	879
1-OC_2H_5-3-OH	196–198	881
	196–197[a,c]	875
	N/A	882
1-OH-3-OC_2H_5	179–180[a–c]	878
1-CO_2H-3-OC_2H_5	139–140[f]	878
1-CH_3-3-OC_2H_5-8,8 = O	91–92[a,c]	878
	N/A	897
1-CH_3-3-OC_2H_5	114–115[a–c]	878
1,3-$(OCOCH_3)_2$	78–80	893
1-$COCH_3$-3-OC_2H_5	Oil[a–c]	878
1-CO_2CH_3-3-OC_2H_5	90–91[a–c]	878
1-$OCOCH_3$-3-OC_2H_5	101–102[a–c]	878
1-OC_2H_5-3-$OCOCH_3$	92–93[a–c]	878
1,3-$(OC_2H_5)_2$	N/A	882
1-CH_3-3-OC_2H_5-8-OH-8-CH=CH_2	N/A	897

TABLE III.16. 5,6,7,8-Tetrahydroisoquinolines with Acid-Type Functional Groups (*Continued*)

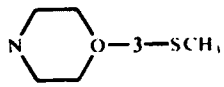
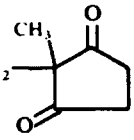
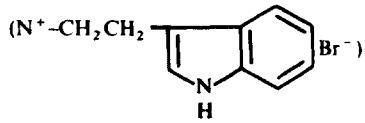
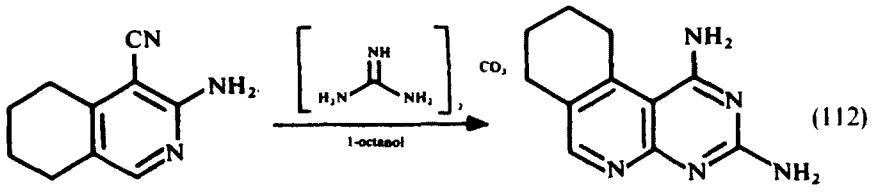
Substituent	m.p. (°C)	Ref.
1- 	174–175	895
1-(C_6H_4Cl-4)-3-Cl	108–109	879
1-C_6H_5-3-Cl	172–174	879
1-(C_6H_4Cl-4)-3-OH	325–328	879
1,3-$(OH)_2$	280–285	897a
1-C_6H_5-3-OH	335–338	879
1-$NHNH_2$-3-NHC_6H_5	230–232[a,c]	896
1-$CH_2C_6H_5$-3-Cl	73–74	879
1-$CH_2C_6H_5$-3-OH	253–255	879
1-$NHCH_3$-3-NHC_6H_5	186–187[a,c]	896
1-SCH_3-3-($NHCOC_6H_4$Cl-4)	220	892
1-SCH_3-3-$NHCOC_6H_5$	226–227	892
1-SCH_3-3-($NHCOC_6H_4CH_3$-4)	243	892
1-CH_3-3-OC_2H_5-8,8=CH-CH_2 	N/A	897
Acid Type Groups Other than 4-Cyano		
1-CO_2H-3-OC_2H_5-4-CN	139–140[c]	878
1-CO_2CH_3-3-OC_2H_5-4-CN	90–91[a,c]	878
1-(*o*-$C_6H_4CO_2H$-4)	N/A	898
1-$CH(C_6H_5)CN$	100	890
	b.p.: 160–170/0.003	886, 887
	140–142	886, 887
1-$CH(C_6H_5)CONH_2$	149–151	890
($N^+CH_3I^-$)	208–210	890
	142–143	886, 887
1-$CH(C_6H_4OCH_3$-4)CN	Picrate: 218	885, 888, 889
1-$CH(C_6H_4OCH_3$-4)$CONH_2$	136–137	885, 888, 889
1-$CH(C_6H_3(OCH_3)_2$-3,4)CN	Oil	885
1-$CH(C_6H_3(OCH_3)_2$-3,4)$CONH_2$	228	885
2-CH_2CN Cl^-	N/A	899
2-$CH_2CO_2CH_3$ Br^-	133–135	899
3-SO_3H	350	891
3-CN	65–66	891

TABLE III.16. 5,6,7,8-Tetrahydroisoquinolines with Acid-Type Functional Groups (*Continued*)

Substituent		m.p. (°C)	Ref.
3-CO_2H		207.5–208	891
		209–210	900
		206	901
3-$CONH_2$		195–196	135
3-$CO_2C_2H_5$		b.p.: 115/2	900
		Picrate: 150–151	900
4-$CONH_2$-3-OH		294	891
4-CO_2H-1-CH_3-3-OH		259–260[a]	876
4-CO_2CH_3		b.p.: 116–118/0.3	894
4-$CO_2C_2H_5$-3-OH		164–166	877
4,5-$(CO_2CH_3)_2$		115–116[a,b]	89
	(N^+ Oxide)	119–120[a,b]	89
4-$CO_2C_4H_9$-*t*		b.p.: 128–130/0.7	894
4-CO_2CH_3-3-CH_3		205–206	901a
		190–191	894
4-$CO_2C_2H_5$-3,8-$(CH_3)_2$-5-C_3H_7-*i*		Picrate: 113–114[b]	880
5- or 7-$CO_2C_2H_5$-6,6 = 0		192	883, 884
		Pictrate: 179	883, 884
		HCl: 160	883, 884
7,7=$CHCO_2H$-3-OCH_3-8,8 = 0		221–222	71
7-CH_2CO_2H-3-OCH_3-8,8 = 0		174–176	71
7-CH(OH)CO_2H-3-OCH_3-8,8 = 0		165–166	71
7,7=$CHCO_2CH_3$-3-OCH_3-8,8 = 0		111–112	71
7-$CH_2CO_2CH_3$-3-OCH_3-8,8 = 0		107–108.5	71
7,7=$CHCO_2CH_3$-3-OCH_3-8-OH		N/A	71
7-$CH_2CO_2CH_3$-3-OCH_3-8-OH		92–96	71
3-CH_3O-7=$CHCO_2H$8 = 0		221–222	71a
3-CH_3O7=$CHCO_2CH_3$8 = 0		111–112	71a
3-CH_3O7=$CHCO_2CH_3$8-OH		141–142	71a
4-CN-1-CH_3-3 = 0		357	884a
4-CN-1-CH_3-3 = $C(CN)_2$		310	884a

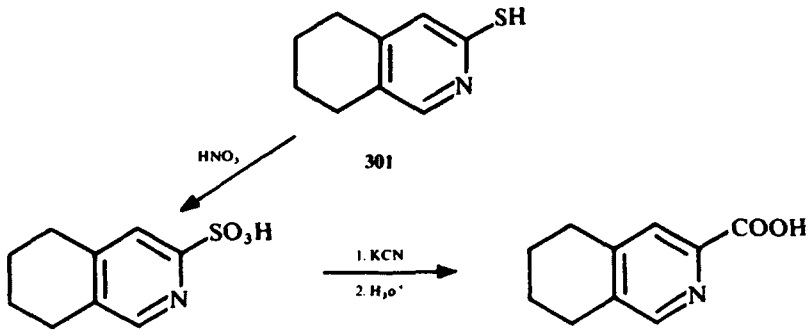
[a] IR in paper.
[b] NMR in paper.
[c] UV in paper.

yields 1.3-diamino-7,8,9,10-tetrahydropyrimido[4,5-6]isoquinoline (**300**)[879] (Eq. 112).



299 **300** (112)

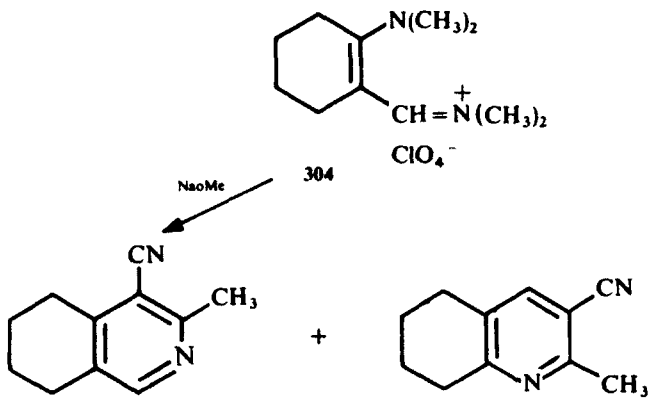
3-Mercapto-5,6,7,8-tetrahydroisoquinoline (**301**) has been oxidized with nitric acid to the corresponding sulfonic acid **302**,[891] which upon treatment with potassium cyanide gives the 3-cyano compound, which can be hydrolyzed to the 3-carboxylic acid **303**[891] (Eq. 113). The 3-acid has also been obtained through a sequence involving reaction of the 3-chloro compound with cuprous cyanide–potassium cyanide.[900]



301

302 **303** (113)

The reaction of **304** with sodium methoxide gives **305** and **306**[901a] (Eq. 114).



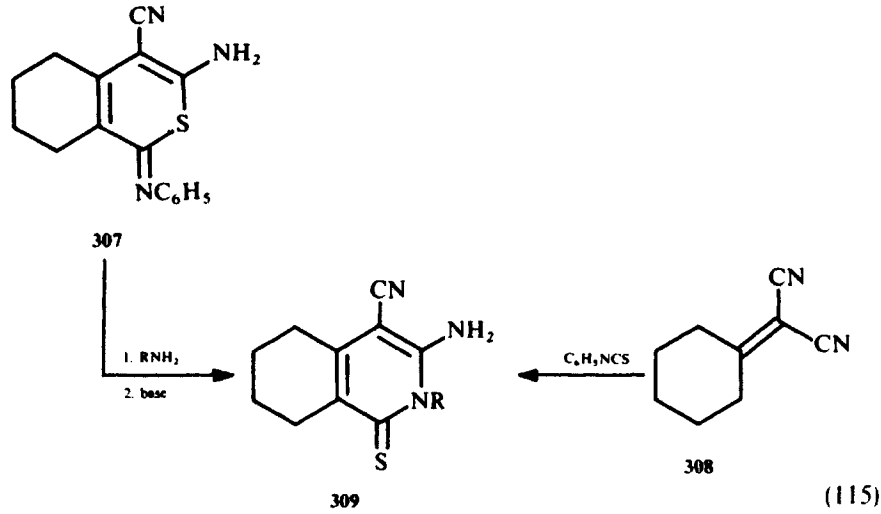
304 (114)

305 **306**

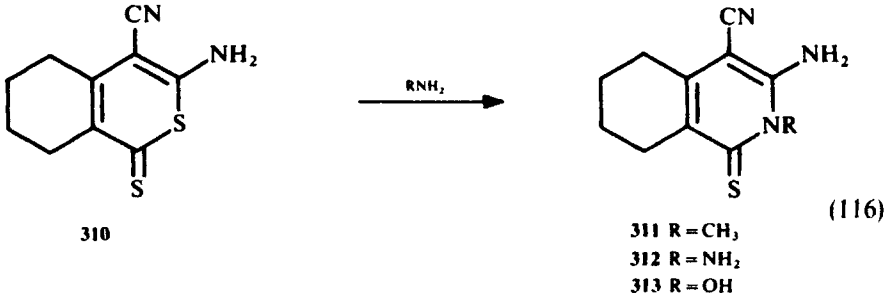
IV. HEXAHYDROISOQUINOLINES

A. 1,2,5,6,7,8-Hexahydroisoquinolines

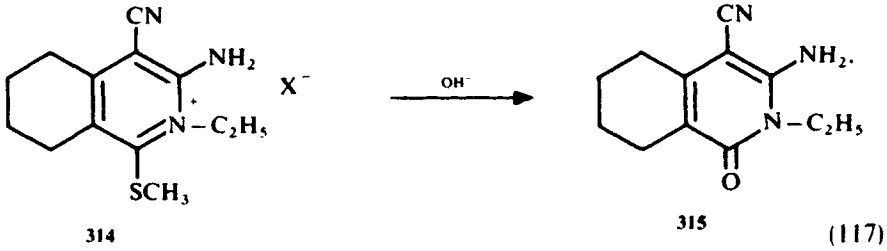
Reaction of **307** with base gave **309** ($R = C_6H_5$)[895] which was also obtained by reaction of **308** with phenyl isothiocyanate[896] (Eq. 115). A group of compounds **311**–**313** were obtained by reacting **310** with methylamine, hydrazine, and hydroxylamine,[895] respectively (Eq. 116). The oxo analog **315** was obtained by the action of base **314**[896] (Eq. 117).



(115)

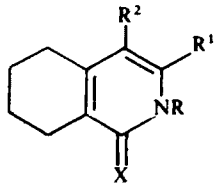


(116)



(117)

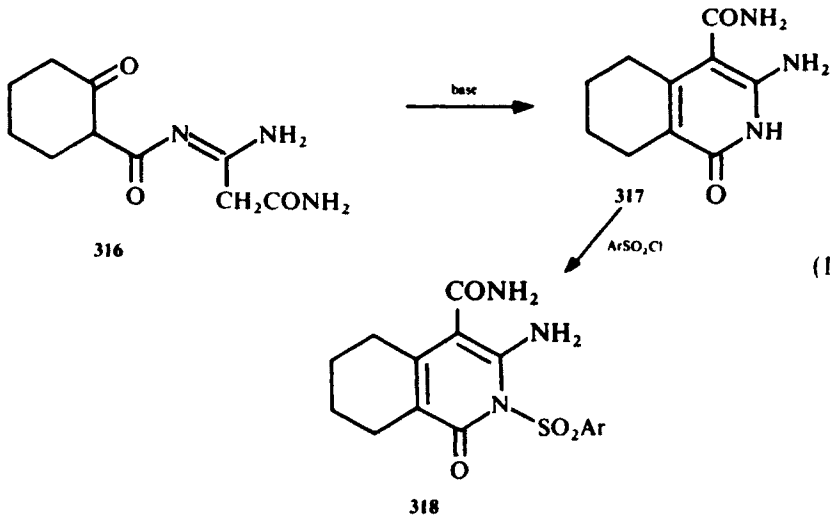
TABLE IV.1. 1,2,5,6,7,8-Hexahydroisoquinolines



X	R	R^1	R^2	m.p.(°C)	Ref.
S	OH	NH_2	CN	132–134	895
S	NH_2	NH_2	CN	245–247[a]	895
O	H	NH_2	$CONH_2$	200	902
S	CH_3	NH_2	CN	243–245[a]	895
O	H	$CO_2C_2H_5$	OH	222	429
O	C_2H_5	NH_2	CN	278[a,b]	896
S	C_6H_5	NH_2	CN	266–268	895
				269–270[a]	896
O	H	$NHSO_2C_6H_4NHCOCH_3$-4	$CONH_2$	400	902
O	H	OC_2H_5	CN	129–130	896a
O	H	OCH_3	CN	162–163	896a

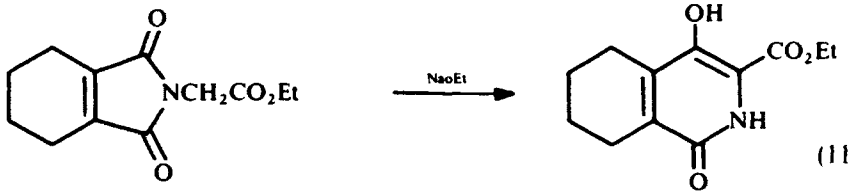
[a]UV in paper.
[b]IR in paper.

The oxo analog **317** was obtained from **316**. Further reaction of the amine group with arylsulfonyl chlorides provides **318**[902] (Eq. 118).



(118)

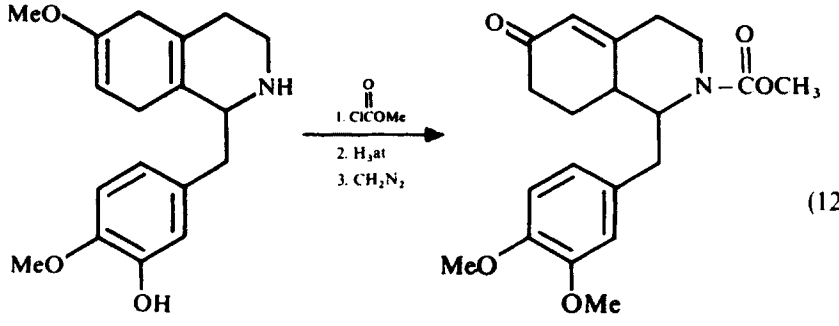
Compound **320** has been obtained through the action of sodium ethoxide on **319**[429] (Eq. 119).



319 320 (119)

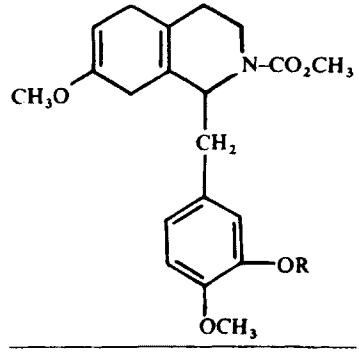
B. 1,2,3,4,5,8,-Hexahydroisoquinolines

The reaction of **321** with methyl chloroformate, followed by hydrolysis[903] and reaction with diazomethane[904] affords **322** (Eq. 120).



321 322 (120)

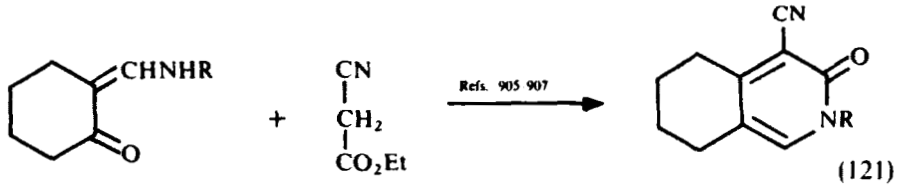
TABLE IV.2. 1,2,3,4,5,8-Hexahydroisoquinolines



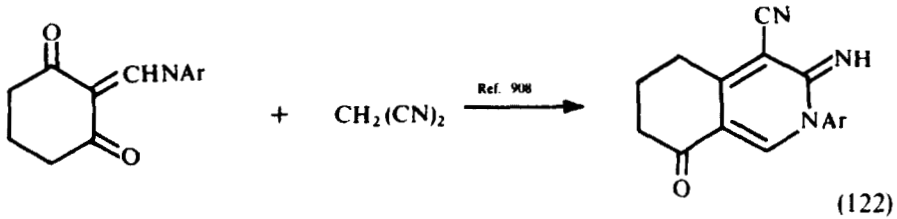
R	m.p.(°C)	Ref.
H	144	903
CH_3	115–116	904
CO_2CH_3	134–136	903

C. 2,3,5,6,7,8-Hexahydroisoquinolines

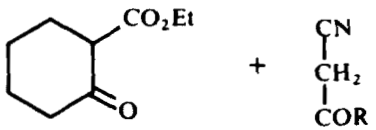
These compounds, listed in Table IV.3, have been prepared primarily by paths involving cyclization reactions such as



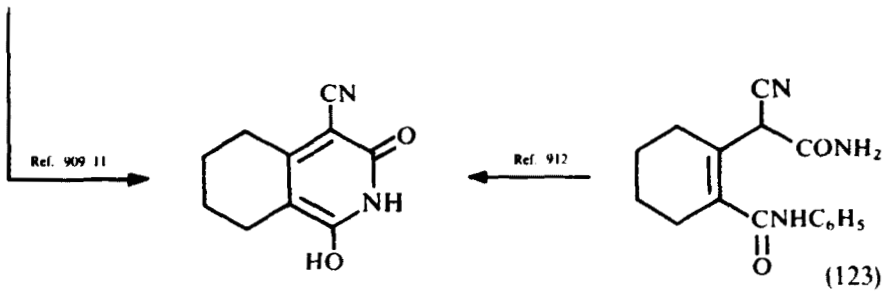
(121)



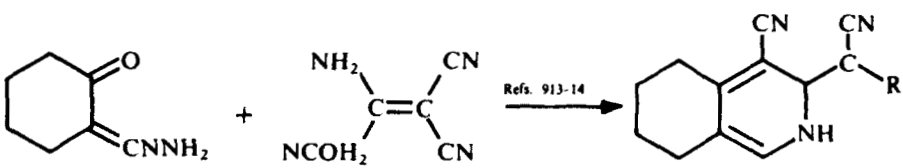
(122)



(R = NH_2 or OC_2H_5)



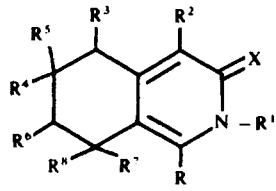
(123)



(R = CN or $CONH_2$)

(124)

TABLE IV.3. 2,3,5,6,7,8-Hexahydroisoquinolines



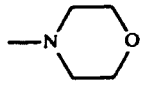
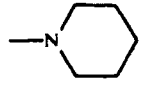
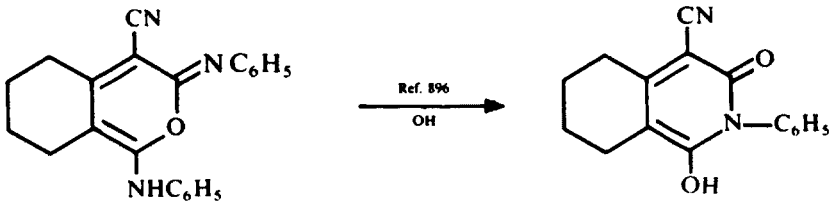
X	R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	m.p.(°C)	Ref.
O	H	H	CN	H	H	H	H	H	H	223	905
O	HO	H	CN	H	H	H	H	H	H	278–280[a]	912
										N/A	911
										278	910
O	H	H	CO_2H	H	H	H	H	H	H	224	905
O	HO	H	$CONH_2$	H	H	H	H	H	H	184–185[a]	912
										183–184	909
O	NH_4OH		CN	H	H	H	H	H	H	320–321	912
O	H	CH_3	CN	H	H	H	H	=O		N/A	906
O	H	H	CN	CH_3	H	H	H	H	H	118	905
										188[a]	32
O	H	H	CN	H	CH_3	H	H	H	H	228	905
O	H	H	CN	H	H	H	CH_3	H	H	233	905
O	H	H	CO_2H	CH_3	H	H	H	H	H	284	905
O	H	H	CO_2H	H	CH_3	H	H	H	H	235	905
O	H	H	CO_2H	H	H	H	CH_3	H	H	216	905
O	H	H	$CONH_2$	CH_3	H	H	H	H	H	269–270	32
$=CH(CN)_2$	H	H	CN	H	H	H	H	H	H	253	913
O	H	H	CN	H	H	H	H	=O		>290	913[a]
$=C(CN)CONH_2$											
	H	H	CN	H	H	H	H	H	H	310	914
O	H	CH_3	CN	H	CH_3	CH_3	H	=O		213–215	907
S											
		H	CN	H	H	H	H	H	H	216–218	895
S											
		H	CN	H	H	H	H	H	H	216–218	895
O	H	C_6H_5	CN	H	H	H	H	=O		N/A	906
										233–235	907
O	OH	C_6H_5	CN	H	H	H	H	H	H	253[a,b]	896
O	$CH_2C_6H_5$										
		H	CN	H	H	H	H	H	H	245–248	915

TABLE IV.3. *(Continued)*

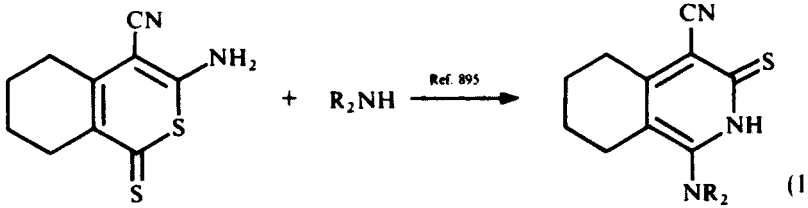
X	R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	m.p. (°C)	Ref.
O	OCH_3	C_6H_5		CN	H	H	H	H	H	137[a,b]	896
=NH	H	$C_6H_3Cl_2$-3,5		CN	H	CH_3	CH_3	H	=O	270[c]	908
=O	H	C_6H_5		CN	H	CH_3	CH_3	H	=O	241–244	907
=NH	H	$C_6H_4NO_2$-4		CN	H	CH_3	CH_3	H	=O	280[a]	908
=NH	H	C_6H_5		CN	H	CH_3	CH_3	H	=O	230[a,c]	908
=NH	H	C_6H_5		CO_2H	H	CH_3	CH_3	H	=O	330[a,c]	908
=NH	H	$C_6H_4CH_3$-4		CN	H	CH_3	CH_3	H	=O	210[a]	908
=O	H	C_6H_5		CN	H	C_6H_5	H	H	=O	242–244	907

[a] IR in paper.
[b] UV in paper.
[c] NMR in paper.

Transformation of the heterocyclic systems **323** and **325** have led to the 4-cyano-2,3,5,6,7,8-hexahydroisoquinolines **324** and **326**, respectively (Eqs. 125 and 126).



323 **324** (125)



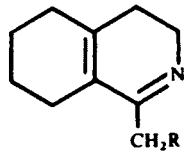
325 **326** (126)

The cyano group in a number of these compounds has been hydrolyzed to a carboxylic acid[905, 908] or an amide[32, 912]. Decarboxylation has also been observed[32, 905].

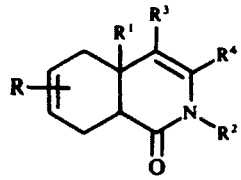
D. Miscellaneous Hexahydroisoquinolines

A number of 3,4,5,6,7,8- and 1,2,5,8,9,10-hexahydroisoquinolines are shown in Table IV.4. The reaction of **327** with sodium ethoxide gives ring expansion to

TABLE IV.4. Miscellaneous Hexahydroisoquinolines

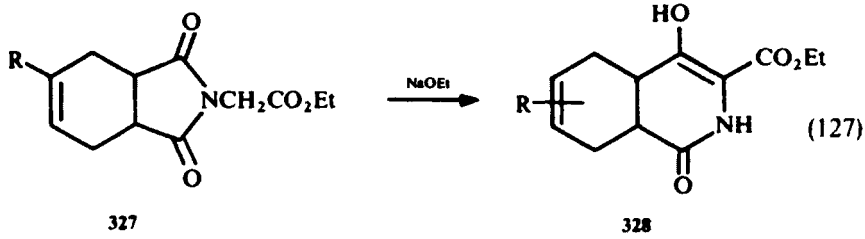


R	m.p.(°C)	Ref.
CN	Perchlorate:134–134.5	500
$CNOH_2$	Hydrochloride:153.5–155	500
$CH_2CO_2C_2H_5$	b.p.:125–130/0.01	916



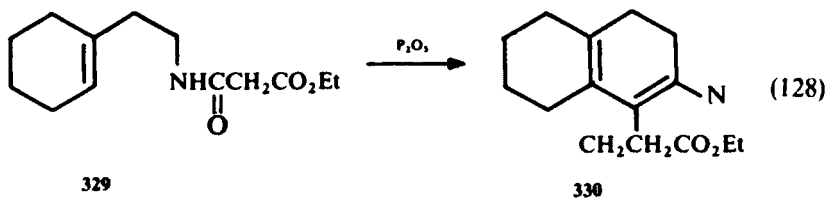
R^4	R^3	R	R^1	R^2	m.p.(°C)	Ref.
$CO_2C_2H_5$	OH	6- or 7-Cl	H	H	193–195	429
$CO_2C_2H_5$	OH	H	H	H	148–150	429
$CO_2C_2H_5$	OH	6- or 7-CH_3	H	H	168–169	429
H	H	6,7(CH_3)$_2$	*cis*-CN	CH_3	79–81	916a, b
H	H	6,7(CH_3)$_2$	*cis*-CO_2CH_3	CH_3	b.p. 151/3	916a,b
H	H	6,7(CH_3)$_2$	*trans*-CO_2CH_3	CH_3	107–108	916a,b
H	H	6,7(CH_3)$_2$	*trans*-CN	CH_3	154–156	916a,b

328[429] (Eq. 127). Phosphorus pentoxide-catalyzed cyclization of **329** provides **330**[916] (Eq. 128).



(127)

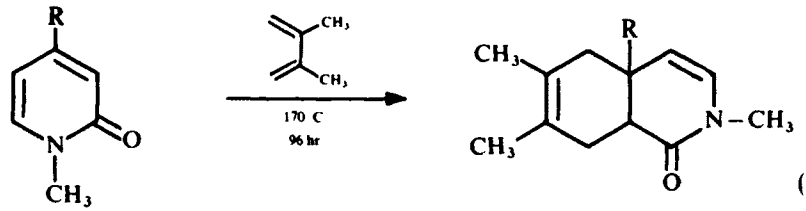
327 **328**



(128)

329 **330**

The condensation of 4-cyano- or 4-methoxycarbonyl-1-methyl-2(1H)pyridone **331a** or **331b** with 2,3-dimethyl-1,3-butadiene affords **332**[916a,b] (Eq. 129).



(129)

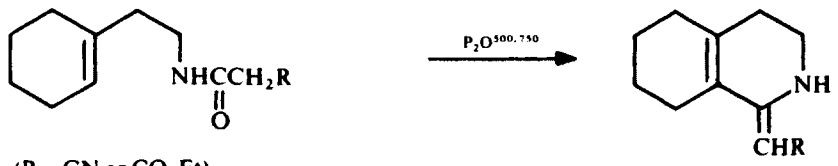
331 **332**

a R = CN
b R = CO_2Et

V. OCTAHYDROISOQUINOLINES

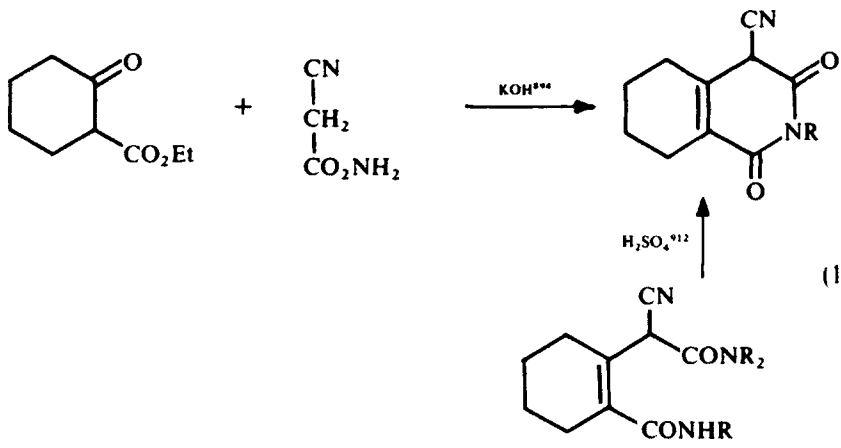
A. 1,2,3,4,5,6,7,8-Octahydroisoquinolines

A number of cyclization reactions have been used to prepare compounds in this series, for example,

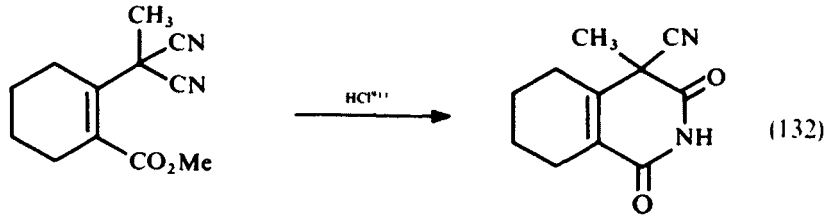


(R = CN or CO_2Et)

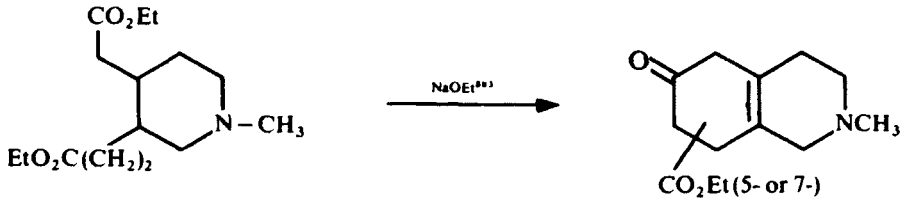
(130)



(131)

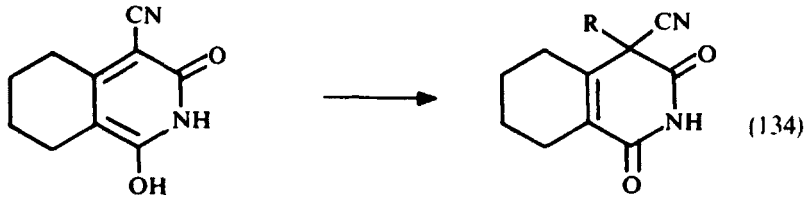


(132)



(133)

The hexahydroisoquinoline **333** has been alkylated to give **334**[911] which can then be alkylated on the ring nitrogen (Eq. 134).

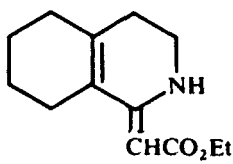


(134)

333 **334**

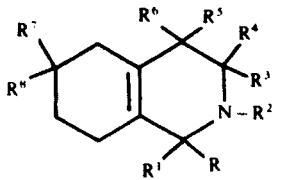
Other compounds in this series have been prepared by catalytic hydrogenation of 3,4,5,6,7,8-hexahydroisoquinolines[916] and by the action of sodium borohydride on 5,6,7,8-tetrahydroisoquinolium salts[899]. Methyl chloroformate has been used to introduce an *N*-carbomethoxy group.[917]

Cyano groups have been hydrolyzed to amides[500, 912] and esters to carboxylic acids[445] in this series. Carboxylic acids have been reduced to alcohols.[916] Spectral and deuterium labeling studies of **335** indicate that the carbonyl group is hydrogen bonded to the NH.[750]



335

TABLE V.1. 1,2,3,4,5,6,7,8-Octahydroisoquinoline



R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	m.p. (°C)	Ref.
=O		H	=O		CN	H	H	H	280–282	894
									205–206[a]	912
=O		H	=O		CN	CH_3	H	H	158–159[a,b]	911
=CHCN		H	H	H	H	H	H	H	120–121.5	500
H	H	CH_2CN	H	H	H	H	H	H	Oxalate-144–145	899
=CHCONH$_2$		H	H	H	H	H	H	H	146–147	500
H	CH_2CO_2H	H	H	H	H	H	H	H	229	445
									hydrochloride: 218–219	445
H	H	CH_2CONH_2	H	H	H	H	H	H	149–150	899
									hydrochloride: 134–136	899
H	H	$CO_2C_2H_5$	H	H	H	H	H	H	96/0.1	918, 919
									102–105/0.15	918, 919
H	H	$CH_2CO_2CH_3$	H	H	H	H	H	H	87–88/0.01	899
									Oxalate:147–150	899
=O		H	=O		CN	$CH_2CH=CH_2$	H	H	109–112[a,b]	911
=O		C_2H_5	=O		CN	CH_3	H	H	65–66[a,b]	911
=CHCO$_2$C$_2$H$_5$		H	H	H	H	H	H	H	55–56[a–c]	750
									120–125/0.02	750
									picrate:96–97	750
=CDCO$_2$C$_2$H$_5$		D	H	H	H	H	H	H	48–50[a]	750

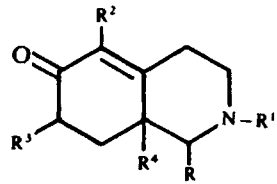
H	$CH_2CO_2C_2H$	H	H	H	H	H	H	H	90–100/0.01	445
H	H	CH_3	H	H	H (5 or 7 $CO_2C_2H_5$)	H	=O		Oil	883
H	$(CH_2)_2CO_2C_2H_5$	H	H	H	H	H	H	H	Oil	916
=O		C_2H_5	=O		CN	$CH_2CH{=}CH_2$	H	H	Oil[a,b]	911
=O		C_6H_5	=O		CN	H	H	H	266–268[a]	912
=O		C_6H_5	=O		$CONH_2$	H	H	H	206–208[a]	912
H	H	$CO_2C_2H_5$	C_6H_5	H	H	H	H	H	147–150/0.07	918, 919, 919a
H	$CH_2(C_6H_2Br\text{-}2\text{-}OCH_3\text{-}4\text{-}OH\text{-}5)$	CO_2CH_3	H	H	H	H	OH	H	179–181.5	917
H	$CH_2(C_6H_3OH\text{-}3\text{-}OCH_3\text{-}4)$	CO_2CH_3	H	H	H	H	OH	H	Foam[a]	917
H	$CH(CONH_2)(C_6H_4\text{-}OCH_3\text{-}4)$	CH_3	H	H	H	H	H	H	picrate:126–128	888, 889
H	$CH_2C_6H_3(OCH_3)_2$	CO_2CH_3	H	H	H	H	=O		106–108	904

[a]IR in paper.
[b]NMR in paper.
[c]UV in paper.

B. 1,2,3,4,6,7,8,9-Octahydroisoquinolines

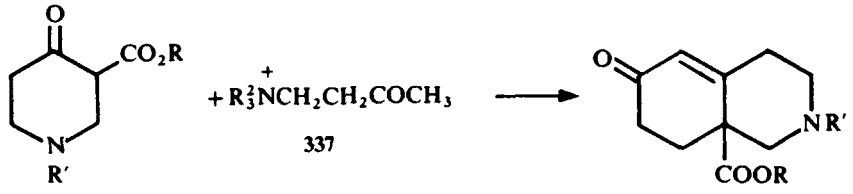
Octahydroisoquinolines of the type **338** have been synthesized either by dehydration of a 10-hydroxydecahydroisoquinoline[920–923] or by reaction of *N*-substituted-3-carboalkoxy-4-piperidones **336** with **337**[924–927] (Eq. 135).

TABLE V.2. 1,2,3,4,5,6,7,8,9-Octahydroisoquinoline



R	R^1	R^2	R^3	R^4	m.p. (°C)	Ref.
H	CH_3	CO_2CH_3	H	H	Oil[a,b]	929
H	CH_3	H	H	CO_2CH_3	Oil	925
H	CH_3	H	H	$CO_2C_2H_5$	135–145/760	927
					135–135/5	926
					130–135/0.1	930
					92–94	927
					90–92	926
					88–90	930
				Hydrochloride:	187–188	927
				Picrate:	181–183	926
				Picrate:	185–186	927
H	CH_3	CH_3	H	$CO_2C_2H_5$	140–150/4	926
				Picrolonate:	185–186	926
H	CH_3	H	CH_3	$CO_2C_2H_5$	140–150/4	926
				Picrolonate:	169–175	926
H	C_2H_5	H	H	$CO_2C_2H_5$	153–155/0.8	924
				Picrate:	170–171[c]	924
$CH_2C_6H_5$	$COCH_3$	H	H	CO_2H	165[a,c]	923
$CH_2(C_6H_2Br$-2-OCH_3-4-OH-5)	CO_2CH_3	H	H	H	148–151[a,b]	917
$C_6H_5CH_2$	$COCH_3$	H	H	CO_2CH_3	149–150	922
					150–152	923
					152–154	920, 921
$C_6H_4OCH_3$-4	$COCH_3$	H	H	CO_2CH_3	135–137	920
H	CH_3	–O–C_6H_3CN-5-OCH_3-1				
			H	$CO_2C_2H_5$	171–172	928
$C_6H_3(OCH_3)_2$-3,4	$COCH_3$	H	H	CO_2CH_3	173.5–174.5	920

[a] IR in paper.
[b] NMR in paper.
[c] UV in paper.



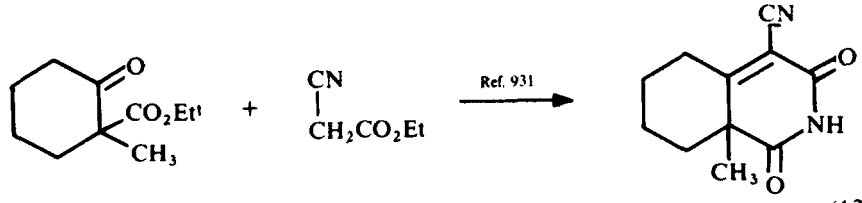
336 338 (135)

Similar reactions involving vinyl keytones have also been used.[928-930]

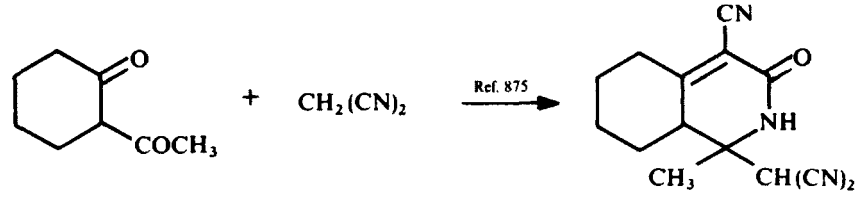
Hydrolysis of carboxylates and esterification of carried out in this series.[923] In the case of a 5-aryloxy compound, irradiation yields a tetracyclic product.[928]

C. 1,2,3,5,6,7,8,9-Octahydroisoquinolines

Reaction of cyclohexanone derivatives with active methylene compounds has been used as a synthetic route to octahydroisoquinolines:



(136)



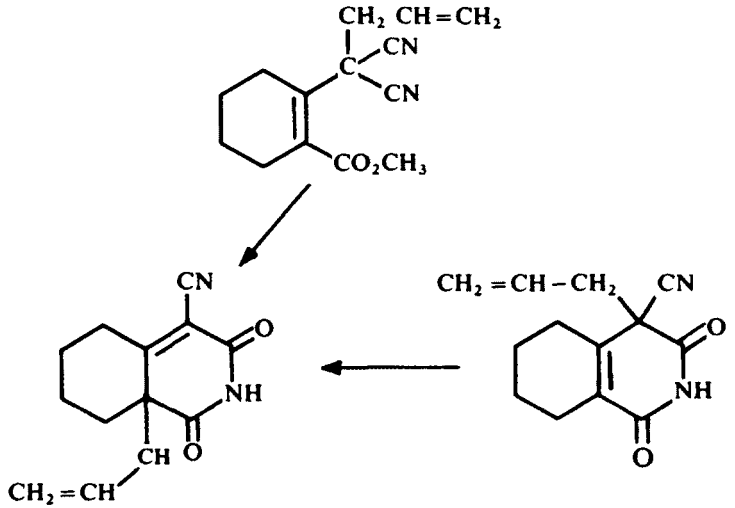
(137)

Allylic rearrangements[911] may also accompany the cyclization reaction (Eq. 138)

Dehydration of the appropriately substituted 10-hydroxydecahydroisoquinolines also leads to this series.[893]

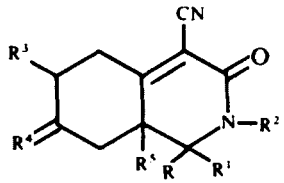
D. Miscellaneous Octahydroisoquinolines

A number of octahydroisoquinolines not included in Tables V.1–V.3 are discussed here and included in Table V.4.



(138)

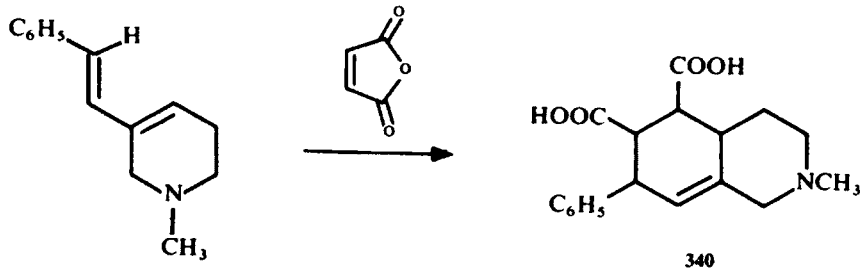
TABLE V.3. 1,2,3,5,6,7,8,9-Octahydroisoquinoline



R	R^1	R^2	R^3	R^4	R^5	m.p. (°C)	Ref.
=O		H	H	H_2	Br	154–155[a]	932
=O		H	H	H_2	CH_3	232–233	893
						230–231	931
=O		H	H	H_2	C_2H_5	244–246	893
=O		H	H	H_2	$CH_2CH=CH_2$	190–191[a,b]	911
=O		CH_3	H	H_2	C_2H_5	125–127	893
CH_3	$CH(CN)_2$	H	H	H	H_2	>320[b]	875
=O		CH_3	$CO_2C_2H_5$	O	H	235–237	893
=O		C_2H_5	H	H_2	$CH_2CH=CH_2$	92–94[b,c]	911

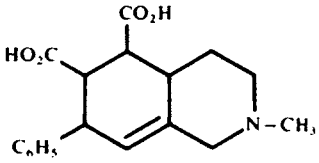
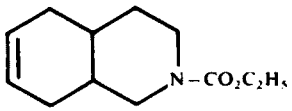
[a]Mass spectroscopy and X ray in paper.
[b]IR in paper.
[c]NMR in paper.
[d]UV in paper.

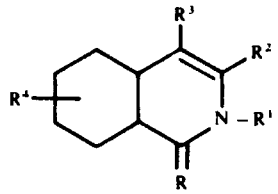
The reaction of **339** with maleic anhydride affords 2-methyl-7-phenyl-1,2,3,4,5,6,7,10-octahydroisoquinoline-5,6-dicarboxylic acid **340**[933] (Eq. 139).



339 **340** (139)

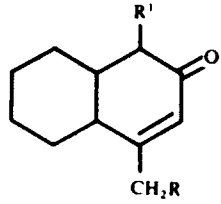
TABLE V.4. Miscellaneous Octahydroisoquinolines

	m.p. (°C)	Ref.
	N/A	933
	b.p.: 120/12	937

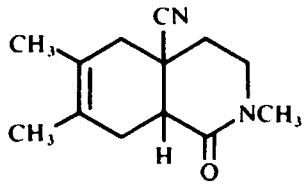


R	R^1	R^2	R^3	R^4	m.p. (°C)	Ref.
O	H	$CO_2C_2H_5$	HO	H	155–157	429
O	H	$CO_2C_2H_5$	HO	6- or 7-CH_3	154–155	429
H_2	CH_2CH_2	H	$CO_2C_4H_9$-t	H	133–134	894

TABLE V.4. Miscellaneous Octahydroisoquinolines (*Continued*)

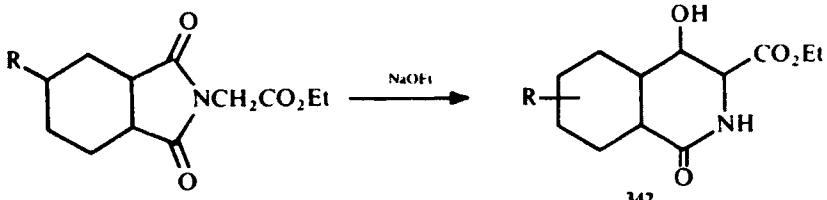


R	R^1	m.p. (°C)	Ref.
H	CN	358–360	938
C_6H_5	CN	245–248	935, 936
C_6H_5	CO_2H	206–207	934
C_6H_5	$CONH_2$	257–258	934



	m.p. (°C)	Ref.
cis	53–55	916a
trans	110–111	916a

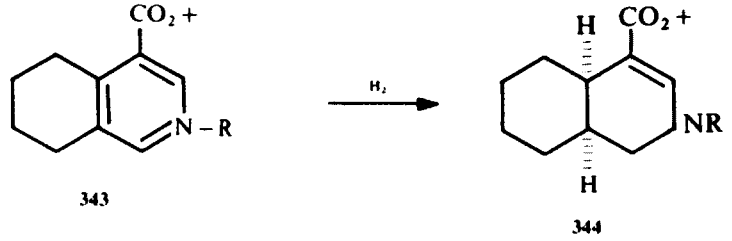
Treatment of **341** with sodium ethoxide gives rise to **342**[429] (Eq. 140).



(140)

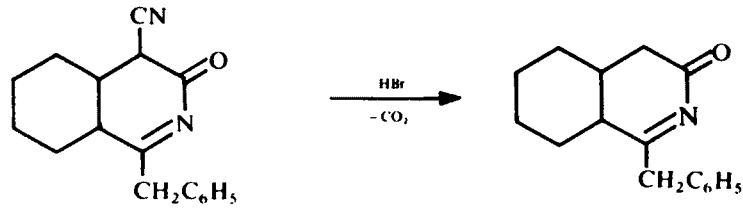
The *cis*-1,2,5,6,7,8,9,10-octahydroisoquinoline **344** has been obtained by the catalytic hydrogenation of the corresponding 5,6,7,8-tetrahydro compound **343**[894] (Eq. 141).

Base-catalyzed condensations and ring closure have also been used to obtain the 3,4,5,6,7,8,9,10-octahydroisoquinolines. Hydrolysis of an amide in this series



343 344 (141)

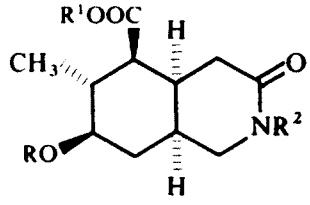
leads to a carboxylic acid which can be decarboxylated at 210°C.[934] Treatment of cyano compound **345** with HBr results in hydrolysis and decarboxylation to afford **346**[935, 936] (Eq. 142).



345 346 (142)

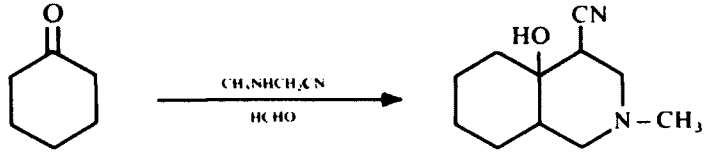
VI. DECAHYDROISOQUINOLINES

The decahydroisoquinolines with acid-type functional groups are included in Tables VI.1–VI.6. Table VI.1 lists compounds without a ring carbonyl, while the other tables include various decahydroisoquinoline-ones. Of particular note are Tables VI.3–VI.5, which include a variety of 3-ones, such as **347**, which have been used in the synthesis of analogs of reserpine.



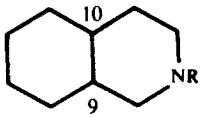
347

A number of isoquinolinium salts,[11] 1,2,3,4-tetrahydroisoquinolines,[1, 939] 5,6,7,8-tetrahydroisoquinolines,[885] and other partially reduced isoquinolines[940, 941] have been reduced to decahydroisoquinolines. Various cyclohexene[942, 943] and tetrahydropyridine[849] derivatives have been used in condensation reactions. For example, the condensation of cyclohexanone with formaldehyde and $CH_3NHCH_2CH_2CN$ affords **348**[944] (Eq. 143).



348 (143)

TABLE VI.1. Decahydroisoquinoline Derivatives Without Ring Carbonyl



R	Substituent		m.p. (°C)	Ref.
H	3-CO_2H	cis	256–257	939
			HCl: 235–236	939
H	4-CO_2H-3-OH		221	135
CH_3	1-CO-O-10 (lactone)		120–130/0.007	347
			122	943
			Picrate: 234	943
CH_3	9-CO-O-6 (lactone)		146–148/4	940, 941
			Picrate: 206–208	940, 941
			HCl: 278–280	940, 941
CH_2CN			164–170/25	947, 948
CH_3	4-CN-10-OH		167–168	948a
			N/A	944
H	5-CO_2CH_3-6-OH	trans, cis	159–160[a]	929
			139–144[a]	945, 946
		trans,trans	153–155[a]	929
$COCH_3$	1-CO_2H-5,5=O		172–173[a]	1
CN	5-CO_2CH_3-6-OH	trans,cis	125.5–127	929
		trans,trans	152–153.5	929
CH_2CN	3-CH_3		146–162/20	947, 948
H	3-$CO_2C_2H_5$		166–168	939
H	4-$CO_2C_2H_5$-3-OH		168	135
CH_3	5-CO_2CH_3-6-OH		N/A	929
$CO_2C_2H_5$	6-O–C(=O)-4 (lactone)		190–200/1	849
			40–41[a]	849
CH_2CH_2CN	3-CH_3		122–134/0.4	947, 948
CH_3	9-$CO_2C_2H_5$		98–102/4	941, 976
			HCl: 182–183	976
C_2H_5	5-CO_2CH_3		168–169	11

TABLE VI.1. Decahydroisoquinoline Derivatives Without Ring Carbonyl (*Continued*)

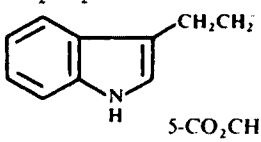
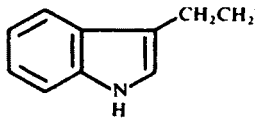
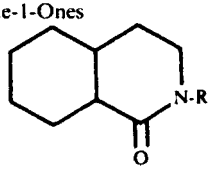
R	Substituent		m.p. (°C)	Ref.
C_2H_5	7-CO_2CH_3		205.4–206	11
CH_3	1-$CO_2C_2H_5$-10-OH		110–140/0.006	943
CH_3	4-$CO_2C_2H_5$-10-OH		142–143/4	948a
			59–60	948a
			HCl: 198–199	948a
			Picrate: 173–174	948a
CH_3	9-$CO_2C_2H_5$-6-OH		152–153/4	940, 941
CN	5-CO_2CH_3-6-$OCOCH_3$	trans,cis	105–106[b]	929
		trans,trans	118–120[b]	929
$COCH_3$	1-$CO_2C_2H_5$-5,5=O		175/0.1[a]	1
$COCH_3$	1-$CO_2C_2H_5$-5-OH		200/0.4	1
H	1-CO–O-10 (lactone) 1-$CH_2C_6H_5$		135/0.04	942
			96	942
			Picrate: 218–220	942
CH_3	4-CN-10-$OCOC_6H_5$		164–166	948a
CH_3	1-CO–O-10 (lactone) 1-$CH_2C_6H_5$		86	942
			Picrate: 220–222	942
$(CH_2)_3CO_2$-C_2H_5	3-$CO_2C_2H_5$		168–172/0.75	939
$COCH_3$	9-CO–O-6 (lactone) 1-$CH_2C_6H_5$-10-OH		214–216	922
$COCH_3$	9-CO_2H-10-OH-1-$CH_2C_6H_5$		255	923
$COCH_3$	9-CO_2H-6,10-$(OH)_2$-1-$CH_2C_6H_5$	axial	249–252	922
CH_3	1-CH($C_6H_4OCH_3$-4)-$CONH_2$		Picrate: 126–128	885
$COCH_3$	9-CO–O–CH_2–O-10-1-$CH_2C_6H_5$		240–242	922
$COCH_3$	1-$CO_2C_2H_5$-5,5=NNH($C_6H_3(NO_2)_2$-2,4)		90–92	1
CH_3	9-$CO_2C_2H_5$-6-O-CO($C_6H_4NO_2$)-4		109	940, 941
$COCH_3$	9-CO_2CH_3-10-OH-1-$CH_2C_6H_5$		173[a]	923
$COCH_3$	9-CO_2CH_3-6,10-$(OH)_2$-1-$CH_2C_6H_5$	axial	196–198[a]	922
CH_3	1-CH($C_6H_3(OCH_3)_2$-3,4)-$CONH_2$		Picrate: 192	885
$COCH_3$	9-CO_2H-10-OH-1-CH_2-C_6H_5-6,6-SCH_2CH_2S		260–262/0.01	923
	5-CO_2CH_3-6-OH	trans	114–116	945
			117–118[a,c]	946
		Perchlorate:	205–208	945, 946
		17α	143–144	929
		17β	78–84	929
$COCH_3$	9-CO_2CH_3-1-$CH_2C_6H_5$-10-OH-6,6-$O(CH_2)_2O$		163–166	920

TABLE VI.1. Decahydroisoquinoline Derivatives Without Ring Carbonyl (*Continued*)

R	Substituent		m.p. (°C)	Ref.
	5-CO_2CH_3-6-$OCOCH_3$	trans	88–91[a,b]	946
		17α	167–169[b]	929
		17β	153–154[b]	929
$COCH_3$	9-CO_2H-10-OH-1-$CH_2C_6H_5$-6,6=$NNH(C_6H_3(NO_2)_2$-2,4)		232–234	923
$COCH_3$	9-CO_2CH_3-1-$CH_2C_6H_5$-10-OH-6,6 =$NNH(C_6H_3(NO_2)_2$-2,4)		244–246	920
$CO_2C_6H_5$	5-CO_2CH_3-6-OCH_3-7-$OCOC_6H_2$-3,4,5$(OCH_3)_3$		97	946a

[a]IR in paper.
[b]NMR in paper.
[c]UV in paper.

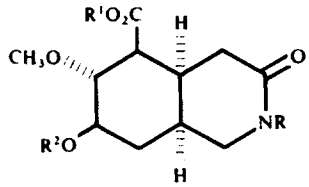
TABLE VI.2 Decahydroisoquinoline-1-Ones



R	Substituent	m.p. (°C)	Ref.
H	4-CN-3,3=O-7,7=O-10-OH	220	893
H	4-CO_2H (2 isomers)	225	949
		188–189	949
H	4-CN-3,3=O-9-CH_3-10-OH	282–285	893
CH_3	4-CN-3,3=O-10-OH	190–192	893
H	4-CO_2CH_3 (4 isomers)	220–221	949
		141–142	949
		160–161	949
		205–206	949
H	4-CN-3,3=O-9-C_2H_5-10-OH	232–234	893
H	4-$CO_2C_2H_5$ (4 isomers)	182[a]	849, 949
		158[a]	849, 949
		136[a]	849, 949
		82[a]	849, 949
H	4-CN-6-$CO_2C_2H_5$-3,3=O-7,7=O-10-OH	214–216	893
CH_3	7-$CO_2C_4H_9$-*t*-6,6=O-10-C_6H_5-*trans*	155–158[b,c]	950
CH_3	7-$CO_2C_4H_9$-*t*-6,6=O-10-($C_6H_4OCH_3$-3)-*trans*	159–161[a–c]	951
	cis	Oil	951

[a]IR in paper.
[b]NMR in paper.
[c]UV in paper.

TABLE VI.3. Decahydroisoquinoline-3-Ones: *Cis*-Junction-6-Methoxy with 7-Oxygen Function and 5-Acid Function



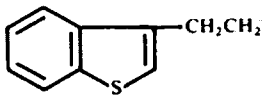
R[c]	R[1]	R[2]	m.p. (°C)	Ref.
$C_6H_5CH_2CH_2$	H	CH_3	178–181	977
			184	978
4-Br-IndEt	H	H	248–250	979
6-Br-IndEt	H	H	166–170	979
4-Cl-IndEt	H	H	140–145	979
5-Cl-IndEt	H	H	180–190	980, 981
6-Cl-IndEt	H	H	160–165	980
			130–133	979
IndEt	H	H	(±)243–247	964
			(+)139–141	964
			(−)139–140	964
			155	982
$3\text{-}CH_3OC_6H_4CH_2CH_2$	H	CH_3	148–149[a]	983
$4\text{-}CH_3OC_6H_4CH_2CH_2$	H	CH_3	168	977, 978
$3,4\text{-}(OCH_3)_2C_6H_3CH_2CH_2$	H	H	209–210	977
$3,4\text{-}CH_2O_2C_6H_4CG_2CH_2$	H	CH_3	180–181	984, 985
$4,7\text{-}Cl_2$-IndEt	H	CH_3	127	961, 980
$6,7\text{-}Cl_2$-IndEt	H	CH_3	230	980
			240	957, 961
$5,6\text{-}CH_2O_2$-IndEt	H	H	(+)154–155	979
			(−)151–153	979
	H	CH_3	199–201	986
			199–201[a]	987
5-Cl-IndEt	H	CH_3	185	988
5-F-IndEt	H	CH_3	190–193	989
			193[b]	970
			193	990
$5\text{-}CH_3O\text{-}7\text{-}Cl$-IndEt	H	H	211–212	991
$C_6H_5CH_2CH_2$	$COCH_3$	CH_3	124	972, 977
IndEt	H	CH_3	192.5–193.5	992
			223	990, 993

TABLE VI.3. Decahydroisoquinoline-3-Ones: *Cis*-Junction-6-Methoxy with 7-Oxygen Function and 5-Acid Function (*Continued*)

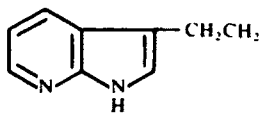
R^c	R^1	R^2	m.p. (°C)	Ref.
4-CH_3-IndEt	H	H	155–160	955
6-CH_3-IndEt	H	H	153–155	955, 994
4-CH_3O-IndEt	H	H	235–237	979
5-CH_3O-IndEt	H	H	136–153	994
			280	995
			162	980
			153	996
			162	961
6-CH_3O-IndEt	H	H	150	962, 997, 998
			140–150	960
7-CH_3O-IndEt	H	H	145–147	979
6-CH_3S-IndEt	H	H	153–155	955
3,4-$(OCH_3)_2C_6H_3CH_2CH_2$	H	CH_3	112	977, 978
5-Cl-Ind-$CH(C_2H_5)CH_2$	H	H	185	999
6-CH_3O-7-Cl-IndEt	H	CH_3	244	961, 980
	$COCH_3$	CH_3	N/A	1000
3-$CH_3OC_6H_4CH_2CH_2$	$COCH_3$	CH_3	101–103[a]	983
5-CH_3-IndEt	H	CH_3	202–203	989–990, 1001
6-CH_3-IndEt	H	CH_3	218	980, 1002
7-CH_3-IndEt	H	CH_3	180	961, 980
IndEt	H	CH_3, 8-CH_3	148–151	1003
			161–162	1020
5-CH_3O-IndEt	H	CH_3	190.5–191.5	990, 1004, 100
			190	961, 980
6-CH_3O-IndEt	H	CH_3	233	1006
			(±)175, 198–200	992
			(+)188–189	992
			188	1007
			193	990
			191–193	752
7-CH_3O-IndEt	H	CH_3	125	961, 980
6-C_2H_5O-IndEt	H	H	152–154	979
6-CH_3O-Ind$(CH_2)_3$	H	H	238	1008
6-CH_3O-Ind-CH_2-$CH(CH_3)$	H	H	N/A	1009
5-CH_3S-IndEt	H	CH_3	190–191	989, 1001
			183–186	990
7-CH_3S-IndEt	H	CH_3	174–175	1010

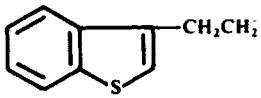
TABLE VI.3. Decahydroisoquinoline-3-Ones: *Cis*-Junction-6-Methoxy with 7-Oxygen Function and 5-Acid Function (*Continued*)

R^c	R^1	R^2	m.p. (°C)	Ref.
6-C_2H_5S-IndEt	H	H	160–164	955
5,6-$(OCH_3)_2$-IndEt	H	H	128–130	979
4-$CH_3OC_6H_4CH_2CH_2$	$COCH_3$	CH_3	147	972, 977
			N/A	1011
3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2$	H	CH_3	149–151	971, 1012
4,7-Cl_2 IndEt	$COCH_3$	CH_3	210	961, 980, 1013
			242	1014
6,7-Cl_2-IndEt	$COCH_3$	CH_3	180	957, 961, 980
4-Cl-IndEt	$COCH_3$	CH_3	130	980
4-Cl-IndEt	$COCH_3$	CH_3	198	988
			218	1015
7-Cl-IndEt	$COCH_3$	CH_3	130	961
5-F-IndEt	$COCH_3$	CH_3	200–202	989
			200–202[a]	970
			202	1016
IndEt	$COCH_3$	CH_3	180.5	992
			215–217	752, 993
6-CH_3O-Ind-CH_2-$CH(CH_3)$	H	CH_3	N/A	1009
6-CH_3O-Ind-$C(CH_3)_2CH_2$	H	H	N/A	1017
5-C_2H_5O IndEt	H	CH_3	199.5–201	989, 990, 1001
6-*n*-C_3H_7O-IndEt	H	H	160–162	979
6-*i*-C_3H_7O-IndEt	H	H	158–161	979
3,4-$(OCH_3)_2C_6H_3CH_2CH_2$	$COCH_3$	CH_3	152–153	977
			152	972
6-CH_3-7-Cl-IndEt	$COCH_3$	CH_3	125–130	961, 980
5-Cl-6-CH_3O IndEt	$COCH_3$	CH_3	232	961, 980
6-Cl-7-CH_3O-IndEt	$COCH_3$	CH_3	188	957, 961, 980, 1018
5-CH_3O-7-Cl-IndEt	$COCH_3$	CH_3	204–205	991
5-CH_3-IndEt	$COCH_3$	CH_3	184–185	989, 1001
			N/A	1019
7-CH_3-IndEt	$COCH_3$	CH_3	226	961, 980
IndEt	$COCH_3$	CH_3, 8-CH_3	208–210	1003, 1020
5-CH_3S-IndEt	$COCH_3$	CH_3	148–150	989, 1001
5-CH_3O-IndEt	$COCH_3$	CH_3	141–142	961, 980
			181–182	1004, 1005
6-CH_3O-IndEt	$COCH_3$	CH_3	239–240	1021
			238–240	752
			184	963, 1022
			178–183	960
			239–240	959

TABLE VI.3. Decahydroisoquinoline-3-Ones: *Cis*-Junction-6-Methoxy with 7-Oxygen Function and 5-Acid Function (*Continued*)

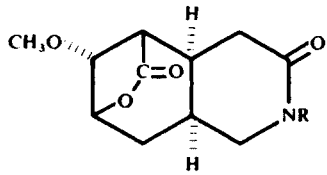
R^e	R^1	R^2	m.p. (°C)	Ref.
			184	1007
			200	1006
			162–184	997, 998
7-CH_3O-IndEt	$COCH_3$	CH_3	180	961, 980
3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2$	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	N/A	971, 1012
6-*i*-PrO-IndEt	H	CH_3	110	1023
6-C_4H_9O	H	H	136	979
4,5-Benzo-IndEt	H	CH_3	237	1024
5,7-$(CH_3)_2$-IndEt	$COCH_3$	CH_3	200	1025
Ind-$C(CH_3)_2CH_2$	$COCH_3$	CH_3	N/A	1026
6-CH_3O-Ind$(CH_2)_3$	$COCH_3$	CH_3	175	1008
6-CH_3O-IndCH$(CH_3)CH_2$	$COCH_3$	CH_3	208	1027, 1028
			N/A	966
5,7-$(OCH_3)_2$-IndEt	$COCH_3$	CH_3	212	968
6-$(CH_3)_2N$-IndEt	$COCH_3$	CH_3	N/A	1029
5-BuO-IndEt	H	CH_3	158	1023
6-BuO-IndEt	H	CH_3	212	1023
7-BuO-IndEt	H	CH_3	175–180	1023
3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2$	$COCH_3$	CH_3	137.5–138.5	954, 971
7-C_3H_7-IndEt	$COCH_3$	CH_3	200	1030
Ind-CH$(C_3H_7$-*n*$)CH_2$	$COCH_3$	CH_3	N/A	1031
Ind-CH$(C_3H_7$-*i*$)CH_2$	$COCH_3$	CH_3	N/A	1032
			146, 204	969
6-CH_3O-Ind-$C(CH_3)_2CH_2$	$COCH_3$	CH_3	N/A	1017
6-*i*-PrO-IndEt	$COCH_3$	CH_3	190–200	1023
4,5,6-$(OCH_3)_3$-IndEt	$COCH_3$	CH_3	230	956, 961, 965, 980
4,5-Benzo-IndEt	$COCH_3$	CH_3	262	1024
5-$C_6H_5CH_2O$-IndEt	H	H	125–128	979
6-$C_6H_5CH_2O$-IndEt	H	H	159–165	979
6-BuO-IndEt	$COCH_3$	CH_3	159	1023
7-BuO-IndEt	$COCH_3$	CH_3	150	1023
IndEt	$CO(C_6H_4NO_2$-4)	CH_3	143–145	958
6-$C_6H_5CH_2O$-IndEt	H	CH_3	224	1023
Ind	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	130	962
$C_6H_5CH_2CH_2$	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	154–156	977, 1033
6-$C_6H_5CH_2O$-IndEt	$COCH_3$	CH_3	175	1023
3-$CH_3OC_6H_4CH_2CH_2$	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	128–129[a]	983
3,4-$CH_2O_2C_6H_4CH_2CH_2$	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	157–158.5	985
			157–158.5b	984

TABLE VI.3. Decahydroisoquinoline-3-Ones: *Cis*-Junction-6-Methoxy with 7-Oxygen Function and 5-Acid Function (*Continued*)

R[a]	R[1]	R[2]	m.p. (°C)	Ref.
4-$CH_3OC_6H_4CH_2CH_2$	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	95–100	977
			100	1033
	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	177–179	986
			177–179[b]	987
5-Cl-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	249	961
5-F-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	208	989, 1016
			208[b]	970
IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	219–220	958, 993
			130	992
3,4-$(OCH_3)_2C_6H_3CH_2CH_2$	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	103–105	977
			105	1033
5-CH_3-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	215–217	989, 1001
7-CH_3-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	186	961
IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3, 8-CH_3	223–224	1003, 1020
5-CH_3S-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	149–151	989, 1001
7-CH_3S-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	153–155	1010
5-CH_3O-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	240	961, 980
6-CH_3O-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3		
		(±)	178	992
		(−)	126–129	992
			126–129	962, 1007
6-CH_3O-IndEt	$COCH{=}CH(C_6H_2(OCH_3)_3$-3,4,5)	CH_3		
		(+)	123–125	992
5-C_2H_5O-IndEt	$CO(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	113–114	989, 1001
IndEt	$COCH{=}CHC_6H_2(OCH_3)_3$-3,4,5)	CH_3	164–166	958
6-CH_3O IndEt	$COCH{=}CH(C_6H_2(OCH_3)_3$-3,4,5)	CH_3	120	962
			217–218	958
5-CH_3O Ind $CH(C_2H_5)CH_2$	$COCH_3$	CH_3	145	967

[a]IR in paper.

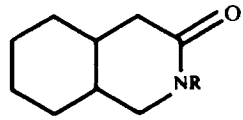
TABLE VI.4. Decahydroisoquinoline-3-Ones: *Cis*-Junction-5,7-Lactones-6-Methoxy



R[c]		m.p. (°C)	Ref.
4-Br-IndEt		225–226	1034
6-Br-IndEt		168–171	1034
4-Cl-IndEt		209–210	1034
6-Cl-IndEt		145–147	1034
IndEt		177–178	964
		178	982
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$		Amorphous	977, 1035
5,6-CH_2O_2-IndEt		219–220	1034
5-CH_3O-7-Cl-IndEt		196–198	991
4-Cl-7-CH_3O-IndEt		190	956, 957, 1036
6-CH_3-IndEt		169–171	994
Ind $CH_2CH(CH_3)$	D	193–194	1034
	L	126–128	1034
IndEt -8-CH_3		248–250	1003
4-CH_3O-IndEt		175–177	1034
5-CH_3O-IndEt		198–200	995
		178–180	994, 996, 1034
6-CH_3O-IndEt		175	963, 997, 998
		170–171	740
		169–171	1034
		185.5[a]	752
7-CH_3S-IndEt		203–205	1010
5-Cl-Ind-$CH(C_2H_5)CH_2$		198	999
6-CH_3-Ind-$CH_2CH(CH_3)$	L	227–229	1034
6-CH_3O-Ind-$CH(CH_3)CH_2$		N/A	966
6-CH_3O-Ind-$CH_2CH(CH_3)$		230	1009
6-C_3H_7O-IndEt		N/A	1034
6-CH_3O-Ind-$C(CH_3)_2CH_2$		N/A	1017
4,5,6-$(OCH_3)_3$-IndEt		185	965
6-C_4H_9O-IndEt		117	1034
5-$C_6H_5CH_2O$-IndEt		198–200	1034
6-$C_6H_5CH_2O$-IndEt		203	1034

[a] IR in paper.

TABLE VI.5. Other 3-One Derivatives



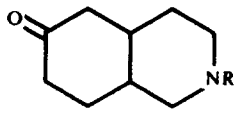
R[c]	Substituent	m.p. (°C)	Ref.
H	4-CN-1,1=O-7,7=O-10-OH	220	893
H	4-CO_2H-*trans*	113–115	231
H	4-CN-1,1=O-9-CH_3-10-OH	282–285	893
CH_3	4-CN-1,1=O-10-OH	190–192	893
H	4-CN-1,1=O-9-C_2H_5-10-OH	232–234	893
H	4-$CO_2C_2H_5$	160–185/0.4	231
	-*trans*	114–115	231
	-*cis*	136–140/0.022	231
H	4-CN-6-$CO_2C_2H_5$-1,1=O-7,7=O-10-OH	214–216	893
H	4-CO_2H-6-$C(CH_3)_3$-*trans*	133–135	952
		133–135[a]	953
	-*cis*	178	952
H	9-CO_2H-6-$C(CH_3)_3$-*cis*	>300	952, 953
H	4-$CO_2C_2H_5$-6-$C(CH_3)_3$-*trans*	92–93	952
		92.5–93.5[a, b]	953
H	-*cis*	138–140	952
		138–140[a, b]	953
H	9-$CO_2C_2H_5$-6-$C(CH_3)_3$-*cis*	99–100.5[a]	952, 953
IndEt	5-CO_2CH_3-7-OH-*trans,trans*	215	1037, 1038
IndEt	-*trans,cis*	216–217	1037, 1038
IndEt	-*cis,trans*	92–94	1037, 1038
IndEt	-*cis*	93–95[a]	1039
$CH_2CH_2(C_6H_4OCH_3$-4)	5-CO_2CH_3-6-CH_3-7-OH-*cis*	219–220	1040, 1041
6-CH_3O-IndEt	5-CO-O-7-(lactone)-6-CH_3-*cis*	186–188[a]	1042
6-CH_3O IndEt	-*trans*	201.5–203	1042
6-CH_3O-IndEt	5-CO-O-7-(lactone)-6-OCH_3-*trans*	184.5–185.5	1043
6-CH_3O-IndEt	5-CO_2H-6-CH_3-*cis*	222–224[a]	1042
$CH_2CH_2(C_6H_4OCH_3$-4)	5-CO_2CH_3-6-C_2H_5-7-OH-*cis*	216–216.5	1040, 1044
6-CH_3O-IndEt	5-CO_2CH_3-6-CN-7-OH-*cis*	233	1045
IndEt	5-CO_2CH_3-7-$OCOCH_3$-*cis*	185–186[a]	1039
6-CH_3O-IndEt	5-CO_2CH_3-6-CH_3-*cis*	190–192	1042
6-CH_3O-IndEt	5-CO_2CH_3-6-CH_3-7-OH-*trans,trans*	171–172	1042
	-*trans,cis*	211–212	1042
IndEt	5-CO-O-7-(lactone)-*trans*	113–114	1037, 1038
		222–223	1037, 1038
6-CH_3O-IndEt	5-CO_2H-6-OC_3H_7-*i*-7-OH-*cis*	139	979
$CH_2CH_2(C_6H_4OCH_3$-4)	5-CO_2CH_3-6-C_2H_5-7-$OCOCH_3$-*cis*	248–250	1040

TABLE VI.5. Other 3-One Derivatives (*Continued*)

R	Substituents	m.p. (°C)	Ref.
6-CH_3O-IndEt	5-CO_2CH_3-6-CN-7-$OCOCH_3$-*cis*	200	1045
6-CH_3O-IndEt	5-CO_2CH_3 6-CH_3-7-$OCOCH_3$-*cis*	165–167	1042
$CH_2CH_2(C_6H_4OCH_3$-4)	5-CO_2CH_3-6-CH_3-7-$OCO(C_6H_2(OCH_3)_3$-3,4,5) *cis*	219–222	1040, 1041
IndEt	5-CO_2CH_3-7-$OCO(C_6H_2(OCH_3)_3$-3,4,5)-*cis*	174–175[a]	1039
$CH_2CH_2(C_6H_4OCH_3$-4)	5-CO_2CH_3-6-C_2H_5-7-$OCO(C_6H_2(OCH_3)_3$-3,4,5)-*cis*	230–232	1040, 1044

[a]IR in paper.
[b]NMR in paper.

TABLE VI.6. Decahydroisoquinoline-6-Ones



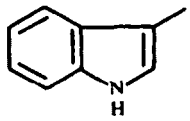
R	Substituent	m.p. (°C)	Ref.
CH_3	5-CO_2CH_3-*trans*	73–74[a]	929
CH_3	9-CO_2CH_3-10-OH	143–150/0.9	973
		Picrate: 185–186.5	973
CH_3	9-$CO_2C_2H_5$	151–153/8	941
		Picrolonate: 184–186	941
$COCH_3$	9-CO_2H-1-$CH_2C_6H_5$-10-OH	(±) 215–217[a]	923
		(+) 132–133, 208–214	922
		(−) 140, 204–210	922
	(+) Strychnine salt: 248–251		922
	(−) Strychnine salt: 162–166		922
$COCH_3$	9-CO_2CH_3 1-$CH_2C_6H_5$ 10-OH	(±) 224	920, 921
		(±) 222–224	923
		(+) 166–168	922
		(−) 166–168	922
$COCH_3$	9-CO_2H-1-$CH_2(C_6H_4OCH_3$-4)-10-OH	179–181[a]	923
CH_3	7-$CO_2C_4H_9$-*t*-1,1=O-10-C_6H_5-*trans*	155–158[b,d]	950
$COCH_3$	9-CO_2CH_3-1-$CH_2C_6H_5$-5-CH_3-10-OH	175–176	920
$COCH_3$	9-CO_2CH_3 1-$CH_2(C_6H_4OCH_3$ 4)-10-OH	156–158	920, 923
$COCH_3$	9-CO_2H-1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-10-OH	206–209[a]	923

TABLE VI.6. Decahydroisoquinoline-6-Ones (*Continued*)

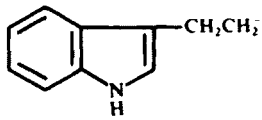
R	Substituents	m.p. (°C)	Ref.
CH_3	7-$CO_2C_4H_9$-*t*-1,1=O-10-($C_6H_4OCH_3$-3)-*trans*	159–161[a,b,d]	951
	-*cis*	Oil	951
$COCH_3$	9-CO_2CH_3-1-$CH_2(C_6H_3(OCH_3)_2$-3,4)-10-OH	165–166	920, 923

[a] IR in paper.
[b] NMR in paper.
[c] UV in paper.
[d] Mass-spectroscopy in paper.

[e] Ind =



IndEt =



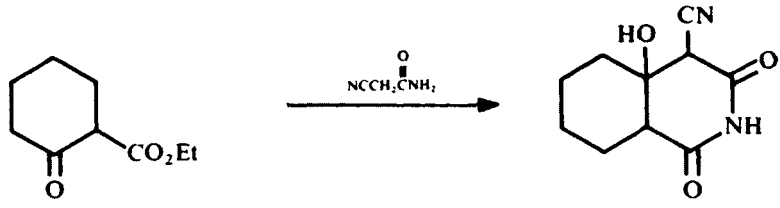
Reduction of yohimbine oxindole iminoether also gives rise to compounds in this series, which can be reconverted into yohimbine derivatives.[945-946a]

Acid-type functional groups have been introduced into the 2 position by the usual alkylation reactions.[929, 939, 947, 948] Ester hydrolysis[1, 135] esterification,[923, 939] and lactone formation[943] have also been observed.

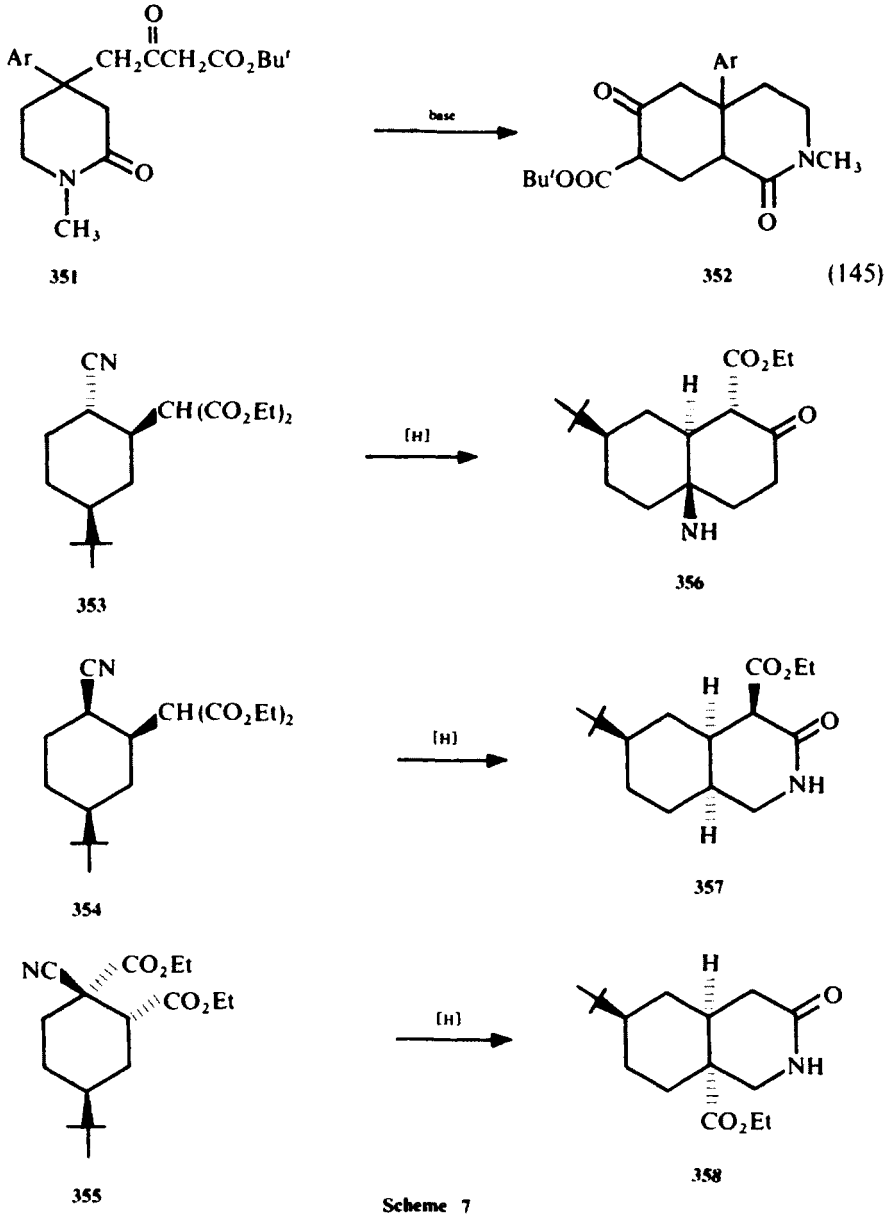
1-One derivatives have generally been prepared by condensation reactions. The condensation of ethyl cyclohexanone-2-carboxylate (**349**) with cyanoacetamide,[893] or the treatment of **351** with base[950, 951] affords the diones **350** or **352** (Eqs. 144 and 145).

An NMR study of the stereochemistry[952, 953] of the cyclization[231] of diethyl 2-cyanocyclohexylmalonate to 4-ethoxycarbonyldecahydroisoquinoline-3-one has been studied. Thus, the reduction of **353**, **354**, and **355** gives **356**, **357**, and **358**, respectively.[952, 953] (Scheme 7).

While all three esters can be hydrolyzed to the corresponding acids, only the acids derived from **356** and **357** undergo decarboxylation.



349 **350** (144)



351 352 (145)

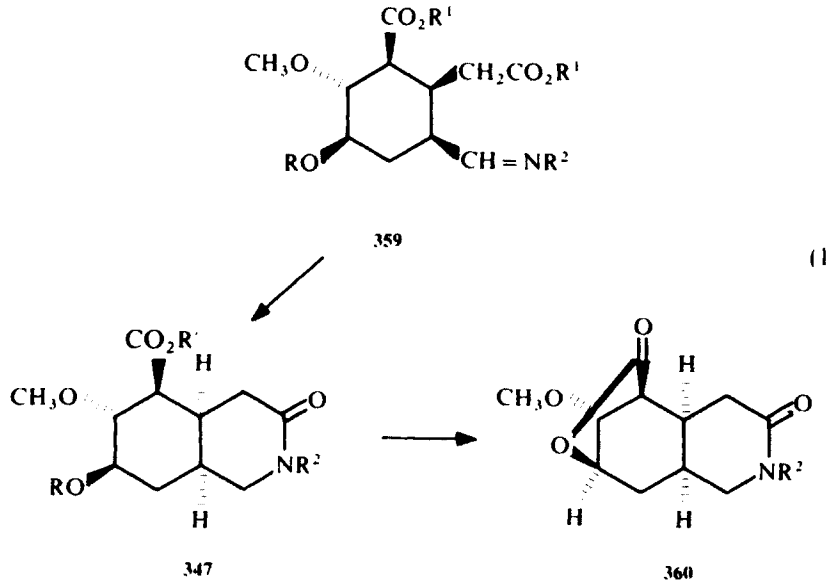
353 356

354 357

355 358

Scheme 7

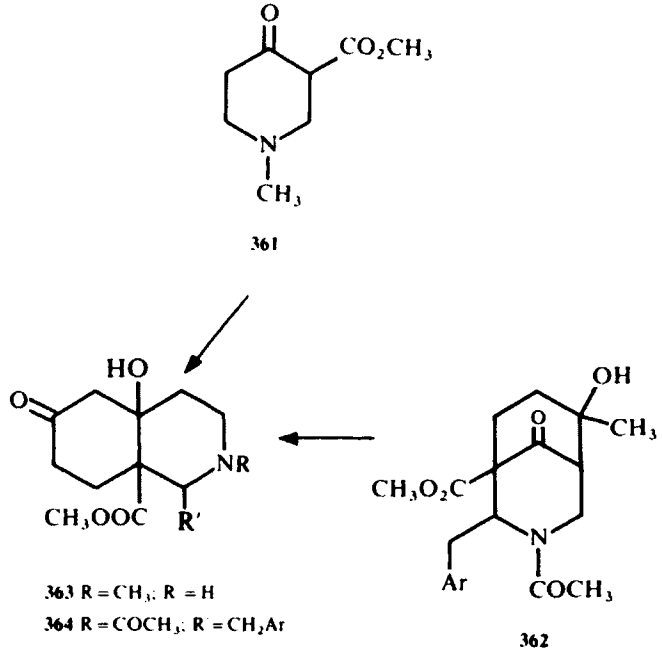
A large number of compounds of the type **347** have been prepared in connection with studies of reserpine analogs. Table VI.3 should be consulted for reference to specific cases. In general, a compound of the type **359** is reduced and cyclized to **347**.[954-959] Ester hydrolysis,[960, 961] esterification,[962] and lactone formation to **350**[956, 957, 963-966] have been extensively used in this series (Eq. 146).



(146)

The sequence is generally completed by cyclization of **347** or **360** to reserpine analogs.[967-972]

The condensation of methyl vinyl ketone with **361**[973] or treatment of **362** with alkoxide[920, 923] gives rise to either **363** or **364**, respectively (Eq. 147).



Esterification and ester hydrolysis take place with **364**.[922, 923] Sulfuric acid causes dehydration of **364**,[922, 923] while treatment of **363** with hydrochloric acid[973] or **364** with phosphoric acid[923] results in dehydration and decarboxylation. The 6-oxo group in **347** greatly increases hydrolysis of the ester, as well as the acidity of the corresponding acid as compared to the corresponding compound lacking the 6-oxo group, which is more stable to treatment with base. The kinetics[974, 975] and stereochemistry[922] of this facile-base hydrolysis have been studied.

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CHAPTER III

Isoquinolines Containing Basic Functions at the Ring and Their Hydrogenated Derivatives

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I. INTRODUCTION

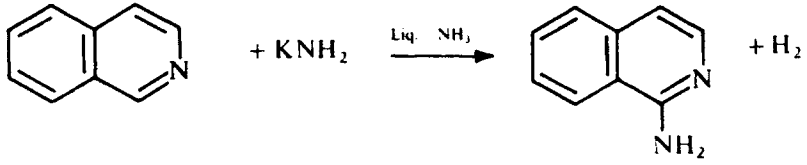
In view of the wide distribution of naturally occurring, basically substituted isoquinolines, the importance of these compounds, many of which are pharmacologically active, as intermediates in the field of natural product and medicinal chemistry is obvious. This chapter reviews the literature associated with all types of isoquinolines bearing basic substituents directly at the ring position. Sufficiently significant unusual reactions or properties are discussed.

II. PREPARATION OF ISOQUINOLINES HAVING A BASIC GROUPING AT POSITION 1

The introduction of basic groupings at position 1 of the isoquinoline nucleus may be effected either by ring-closure reactions, in which the basic grouping is already present in the noncyclized precursor; by replacement of existing substituents at the 1 position, most commonly halogen, but methyl sulfinyl and methyl sulfonyl have been reported; or by direct nucleophilic substitution. Ring-closure reactions most commonly are reported for the preparation of partially hydrogenated isoquinolines having basic substituents with the alternate methods (substitution or replacement of existing substituents) being primarily used in the formation of basically substituted unsaturated isoquinolines.

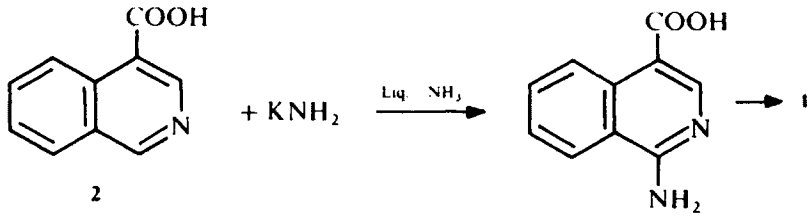
A. 1-Aminoisoquinolines

1-Aminoisoquinoline **1** has been prepared by Bergstrom[1] utilizing a Chichibabin reaction of potassium amide on isoquinoline under low-temperature conditions in liquid ammonia (Eq. 1).



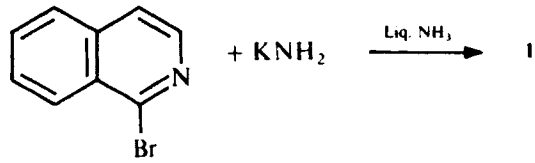
1 (1)

Alternate aminating reagents may be used, including barium amide, sodium amide, and fused eutectic mixtures of sodium and potassium amide.[2] Although yields are not improved (approximately 60–70%), the use of alternate solvents and higher temperatures, such as that of boiling xylene, are allowed if eutectic mixtures are employed. The use of *N,N,N',N'*-tetramethylethylenediamine and sodium amide in xylene for the synthesis of 1-aminoisoquinoline **1** has been reported to produce good yields by Giorgi-Renault.[3] Addition of potassium nitrate to the reaction medium produces no increase in product yield, but results in the production of less hydrogen.[1] Application of this methodology for the synthesis of 3-methyl-1-aminoisoquinoline has demonstrated that improved yields may be obtained when potassium nitrate is included in the reactants, but only very low yields are obtained using potassium amide in the absence of potassium nitrate.[4] Amination of isoquinoline 4-carboxylic acid **2**, using potassium amide in liquid ammonia to yield the corresponding 1-amino derivative, has been reported by Bergstrom and Rodda.[5] Subsequent decarboxylation of **3** by heating yields **1** (Eq. 2).



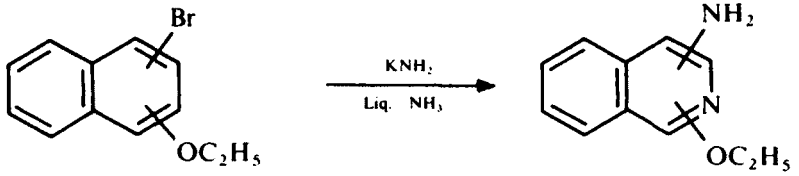
2 3 (2)

The amination of 1-bromoisoquinoline by potassium amide in liquid ammonia proceeds in high yield to **1** by an addition–elimination mechanism[6] (Eq. 3).



(3)

Several 1- and 3-aminoethoxyisoquinolines **4** may be prepared by displacement of bromide by the amide ion[7] (Eq. 4).

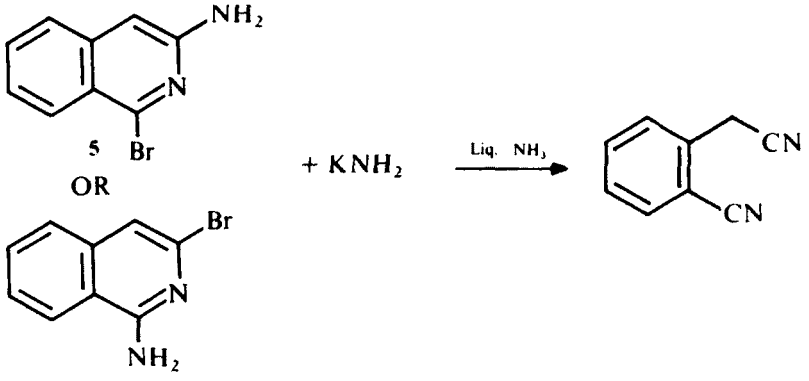


4

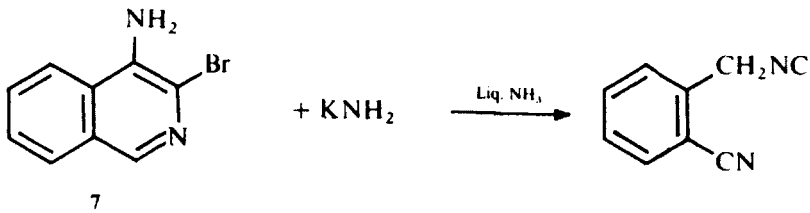
1-Br, 4-OC_2H_5
4-Br, 1-OC_2H_5
3-Br, 1-OC_2H_5
1-Br, 3-OC_2H_5
3-Br, 4-OC_2H_5 (4)

4-Bromo-3-ethoxyisoquinoline does not yield the corresponding aminoisoquinoline, but produces a complex mixture of products.[7]

Treatment of 3-amino-1-bromoisoquinoline **5** (and other analogs **6** and **7**) with potassium amide in liquid ammonia for extended periods of time (24 h) produces high yields of ring-fission product[8] (Eqs. 5 and 6).

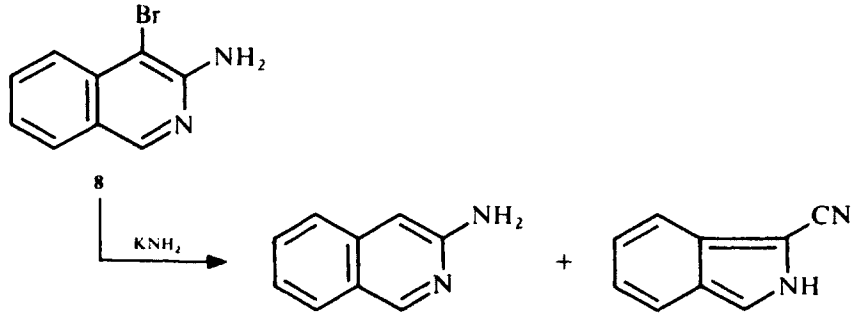


(5)



(6)

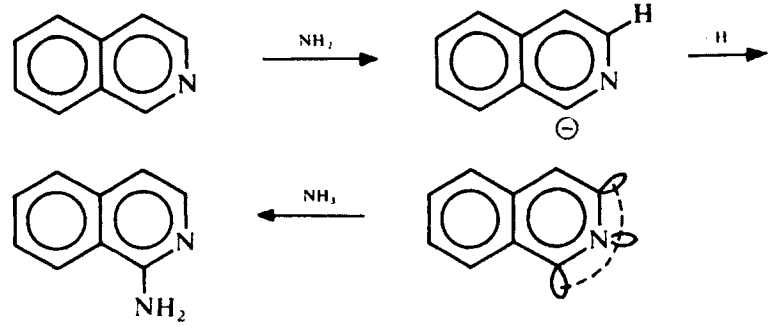
3-Amino-4-bromoisoquinoline **8** (a positional isomer of **5**) unexpectedly undergoes a novel ring transformation when similarly treated; 3-cyanoisoindole and 3-aminoisoquinoline are isolated. The proposed mechanism involves a Wolff-type rearrangement (Eq. 7).



(7)

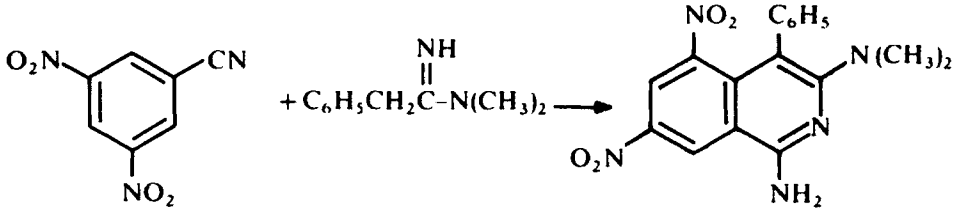
This unprecedented ring transformation does not occur with 1-amino-4-bromoisoquinoline under similar conditions over a 6-h period.[8]

The exclusive formation of 1-aminoisoquinoline in the Chichibabin reaction is not unexpected from examination of the charge densities of the isoquinoline nucleus. The formation of a 1,3-aryne intermediate resulting from hydride-ion elimination from the 3 position has been proposed[9] (Eq. 8).



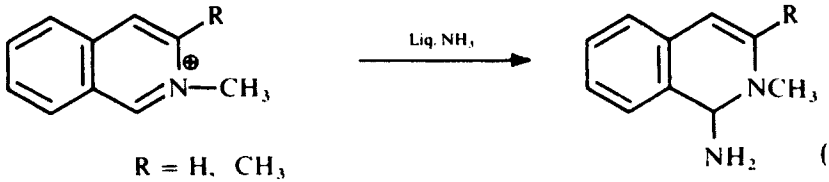
(8)

More recent work by Zoltewicz and co-workers [10] provides spectral (NMR) evidence for the formation of Meisenheimer-type complexes, (anionic σ complexes) which have been long postulated, but largely uncharacterized, during the reaction of amide ions with hetarenes in liquid ammonia. During a study of Meisenheimer complexes, Strauss and Bard[11] observed the formation of the 1-aminoisoquinoline **10** in good yield from the 3,5-dinitrobenzonitrile **9** (Eq. 9).



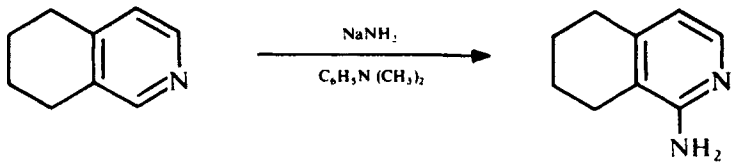
9 10 (9)

Quaternized isoquinolines, on treatment with liquid ammonia in the absence of amide ion, have been shown to give 1-amino-1,2-dihydroisoquinolines **11**[12] (Eq. 10). Remarkably, this covalent amination occurs in minutes below 0 °C and no starting material is detectable in the reaction mixture by NMR spectroscopy.



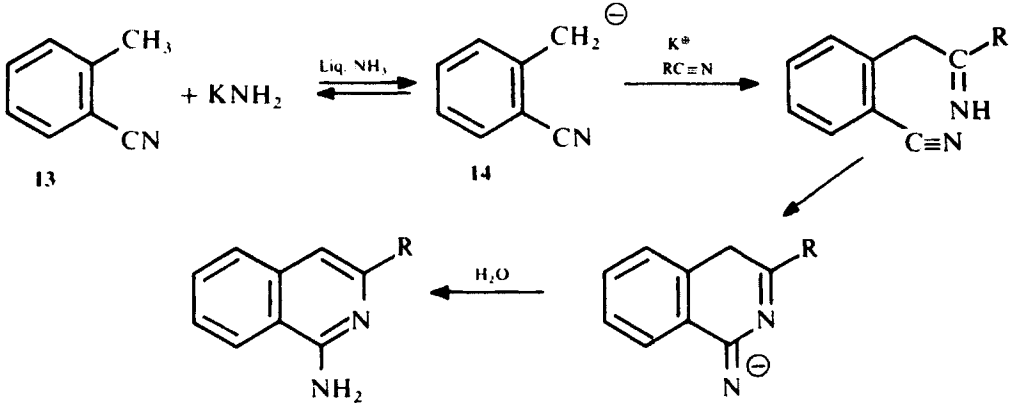
R = H, CH_3 **11** (10)

Adaptation of the Chichibabin reaction for the synthesis of 1-amino-5,6,7,8-tetrahydroisoquinoline **12** has been reported using dimethylaniline as the solvent and sodium amide as the aminating reagent.[13] Excellent yields (85%) of the product are obtained (Eq. 11).



12 (11)

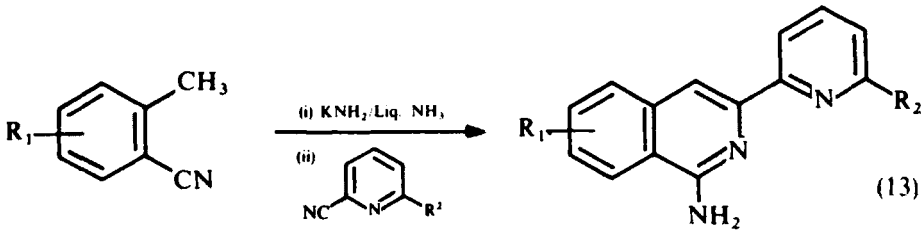
Benzonitriles have been employed in a novel synthesis of 3-substituted 1-aminoisoquinolines using a ring-closure procedure.[14] 2-Methylbenzonitrile **13** was converted to its carbanion by treatment with potassium amide in liquid ammonia. Reaction of the carbanion with varying aryl or alkyl nitriles yields the corresponding imine, which undergoes intramolecular cyclization; hydrolysis of the cyclized product gives the target compounds **15** in poor to moderate yields, depending on the 3 substituent (Eq. 12).



13 **14** **15** (12)

For this reaction to be successful, addition of the base to the nitrile group of **13** should not occur, although the base must be strong enough to form the carbanion **14**.

A large series of antimycoplasmal 1-amino-3-(2-pyridyl) isoquinolines **16** have been synthesized by Pijper and co-workers[15] utilizing basic reaction conditions and a variety of starting materials (Eq. 13).



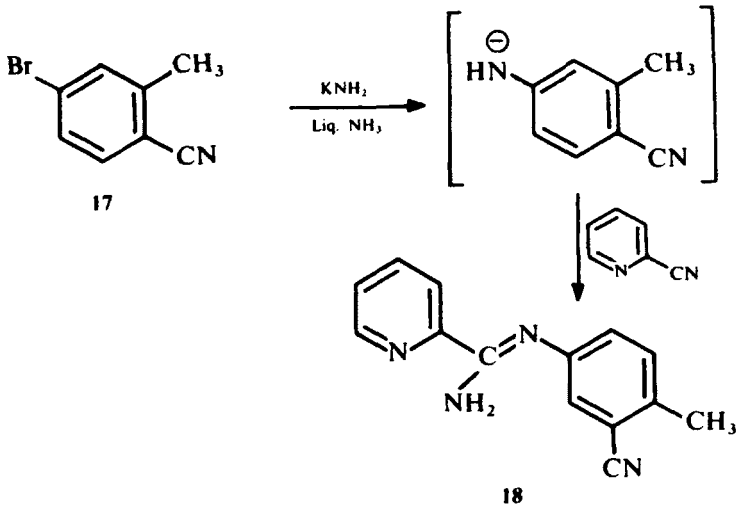
(13)

16

$R_1 = 5\text{-}CH_3$; $6\text{-}CH_3$; $8\text{-}CH_3$; $7\text{-}C_2H_5$; $8\text{-}C_2H_5$; $6,7\text{-}(OCH_3)_2$; 5-Cl; 6-Cl; 7-Cl; 8-Cl; 6-Br; 7-I

$R_2 = CH_3$; C_2H_5

The 4-bromo compound **17** yields an unexpected product **18**, as explained by Eq. 14.[15]



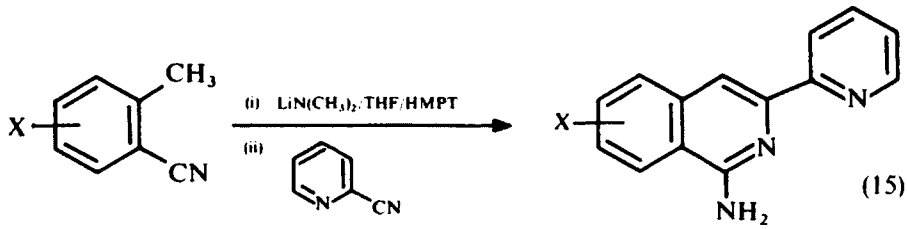
17

(14)

18

Changing reaction conditions to those of Eq. 13 causes the desired reaction for the 4-bromo compound **17** to take place[15] (Eq. 15).

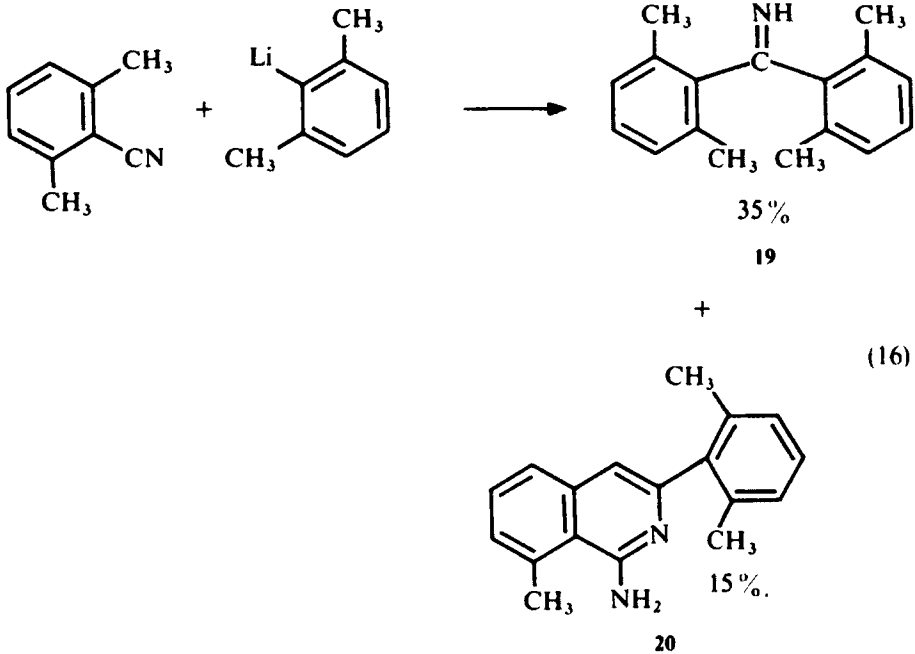
The preparation of a 3-aryl-1-aminoisoquinoline has been reported by Van der Goot[16] during some studies of the reaction of 2,6-dimethylphenyllithium on 2,6-dimethylbenzonitrile (Eq. 16). In addition to the desired product (**19**), a small



X = 4-Br; 5-I

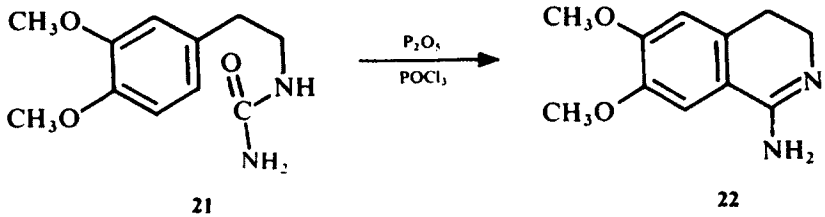
(15)

amount (15%) of the 1-aminoisoquinoline **20** is formed. Replacement of the base (phenyllithium) by lithium diisopropylamide gives the preferential production of a 1-aminoisoquinoline (80% yield).



(16)

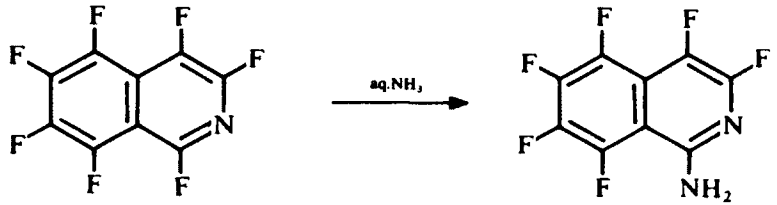
The Bischler–Napieralski ring closure of *N*-(3,4-dimethoxyphenylethyl) urea **21** to 6,7-dimethoxy-1-amino-3,4-dihydroisoquinoline **22** has been reported in good yields (70%)[17] (Eq. 17).



21 **22**

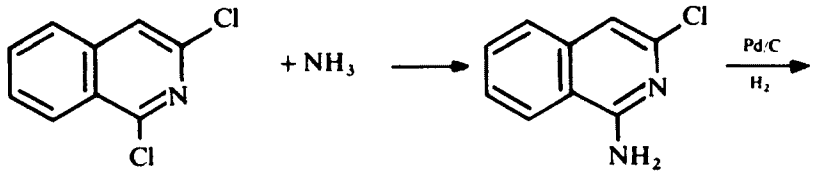
(17)

The lability of the halogen atoms substituted at the 1 position of isoquinoline has been extensively used as a means of introducing various basic groupings into that position. For example, perfluoroisoquinoline **23** can be readily transformed into its 1-amino derivative **24** by treatment with aqueous ammonia[18] (Eq. 18).



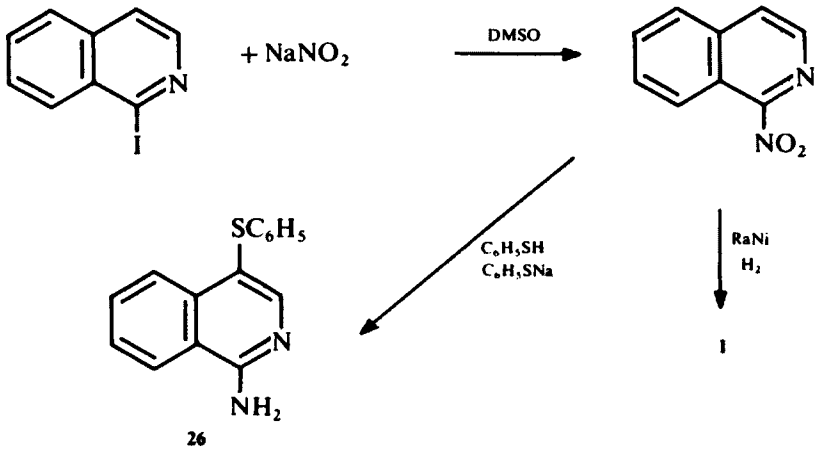
23 **24** (18)

Monoamination of 1,3-dichloroisoquinoline occurs preferentially at the reactive 1 position on treatment with ammonia.[19] Dehalogenation of the resulting 1-amino-3-chloroisoquinoline **25** over palladium catalyst yields **1** (Eq. 19).



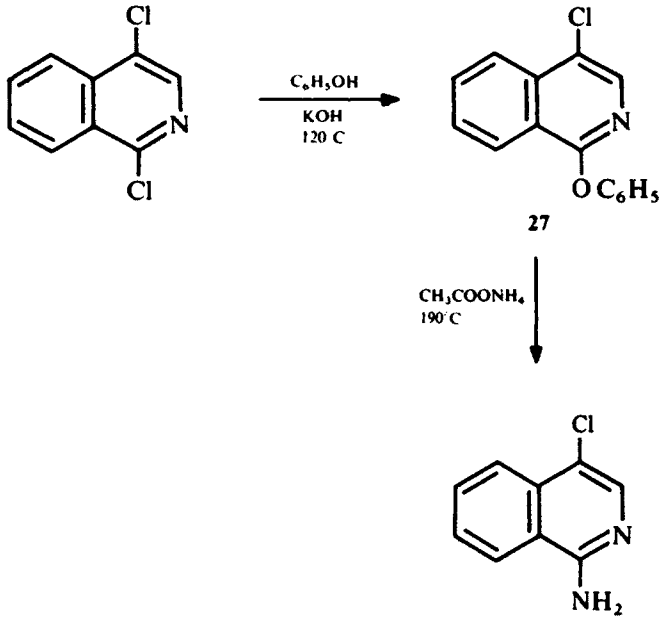
25 (19)

As an alternative for the synthesis of **1** using this approach, 1-nitroisoquinoline may be prepared from 1-iodoisoquinoline by treatment with sodium nitrate.[20] Reduction of the nitro grouping over Raney nickel or by sodium phenyl sulfide in benzenethiol, produces the amine. Concurrent substitution at the 4 position (**26**) occurs in the latter reduction (Eq. 20).



26 (20)

Selective amination into the 1 position of 1,4-dichloroisoquinoline may be accomplished through the 1-phenoxy-4-chloro derivative **27**[21] (Eq. 21).



(21)

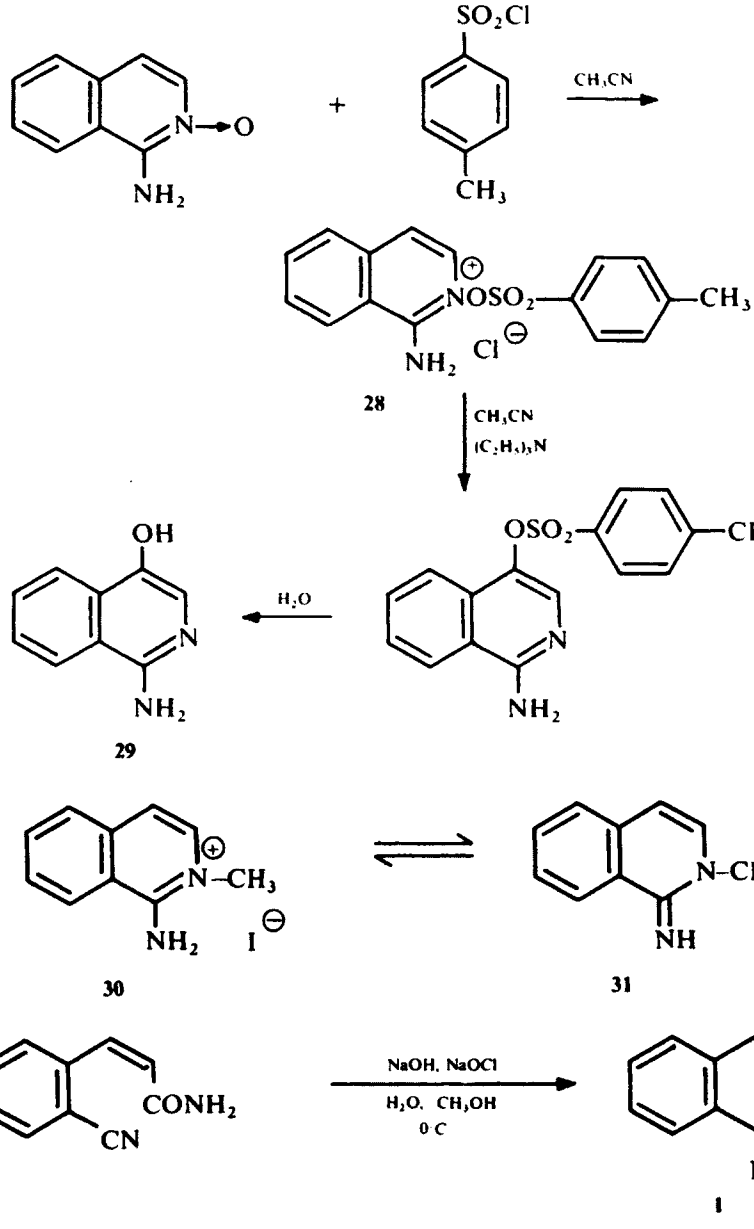
Hydroxylation of the *N*-oxide of **1**[22] at the 4 position has been achieved by treatment with arenesulfonyl chlorides.[23] Migration of the *O*-tosyl grouping from the intermediate salt **28** occurs in acetonitrile containing triethylamine, which on hydrolysis yields the 1-amino-4-hydroxyisoquinoline **29** (Eq. 22). Significant differences appear to exist on similar treatment of the analogous 2-aminoisoquinoline *N*-oxide, migration of the *O*-tosyl grouping taking place to distant positions (e.g., position 6) in the nonheterocyclic ring.

The tautomerism of 1-aminoisoquinolines has been the center of several studies concerning the aromaticity of isoquinolinoid forms **30** as opposed to the isoquinolonoid form **31**.

It appears that there is much less difference between these tautomers than between the pyridine and pyridone analogs.[24] Assignment of an imine structure to these isoquinolines substituted at the α-position has been confirmed by physical and spectral studies. Ultraviolet spectral characteristics,[25] as well as ionization constants,[26] confirm that protonation first occurs at the heterocyclic nitrogen and that indeed an imine structure prevails (**31**).

A mild synthesis for 1-aminoisoquinoline **1** has recently been described by Brettle and Mosedale.[27] Hypochlorite treatment of the carboxamide (Eq. 24) under basic conditions facilitates ring closure to yield 1-aminoisoquinoline.

Bischoff[28] has found that condensation of malonodinitrile with cyclohexanone-2-carboxamide under Knoevenagel condensation conditions yields 1-amino-4-cyano-2,3,5,6,7,8-hexahydroisoquinolin-3-one **32**. The reaction occurs



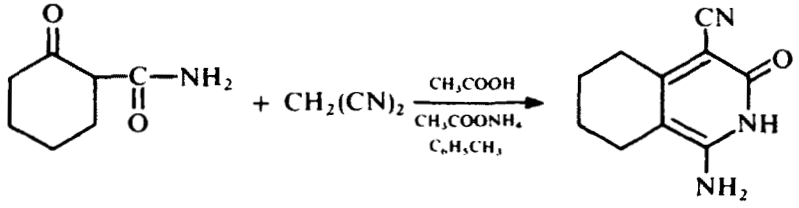
(22)

(23)

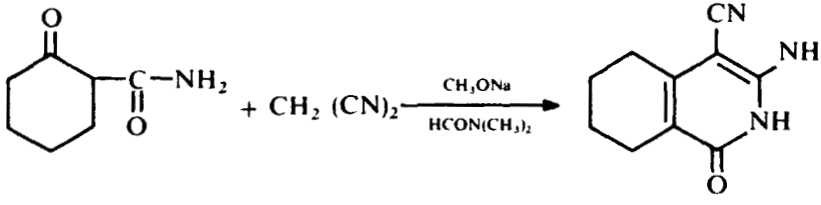
(24)

through a nitrile–carboxamide rearrangement (Eq. 25). A similar reaction under basic conditions yields 3-amino-4-cyano-1,2,5,6,7,8-hexahydroisoquinolin-1-one **33** (Eq. 26).

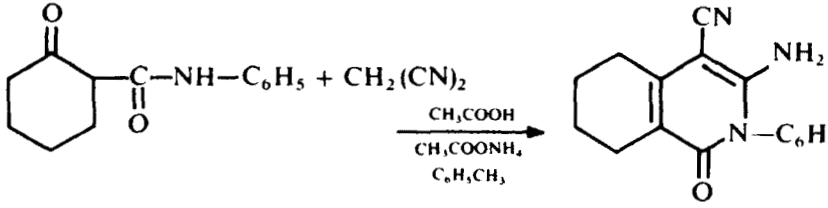
Under the Knoevenagel conditions of Eq. 25, *N*-phenylcyclohexanone-2-carboxamide yields 3-amino-4-cyano-2-phenyl-5,6,7,8-tetrahydroisoquinolin-1-one **34**[28] (Eq. 27).



32 (25)



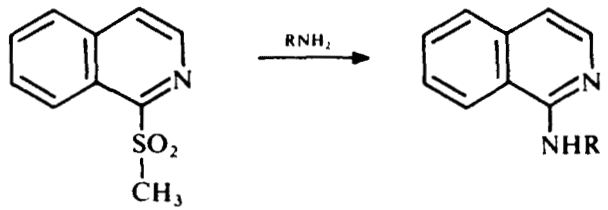
33 (26)



34 (27)

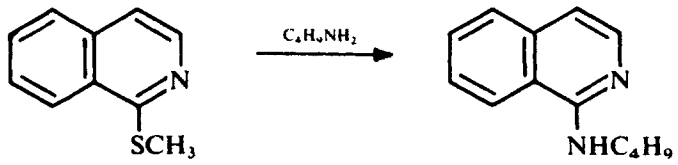
B. 1-Alkylaminoisoquinolines

In addition to standard reactions for the alkylation of aromatic amines, substituted 1-aminoisoquinolines have been prepared by several alternate procedures. Barlin and Brown[29] reported that 1-methylsulfonylisoquinoline **35** is quite reactive toward nucleophiles and that high yields of 1-methylamino and 1-propylaminoisoquinolines can be obtained by treatment of the sulfonyl compound with the appropriate amine (Eq. 28).



35 R = alkyl grouping (28)

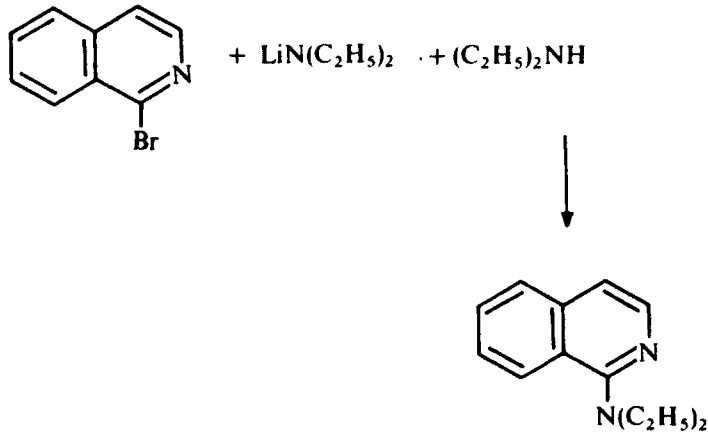
Additional studies have demonstrated that 1-methylsulfinylisoquinoline **36** also gives excellent yields of 1-butylaminoisoquinoline **37**[30] (Eq. 29).



(29)

36 **37**

The formation of 1-diethylaminoisoquinoline **38** from 1-bromoisoquinoline has been reported by Kauffmann et al.[31] Diethyllithium amide and diethylamine replaces the bromine atom by an addition-elimination type mechanism to give good yields of the product (Eq. 30).



(30)

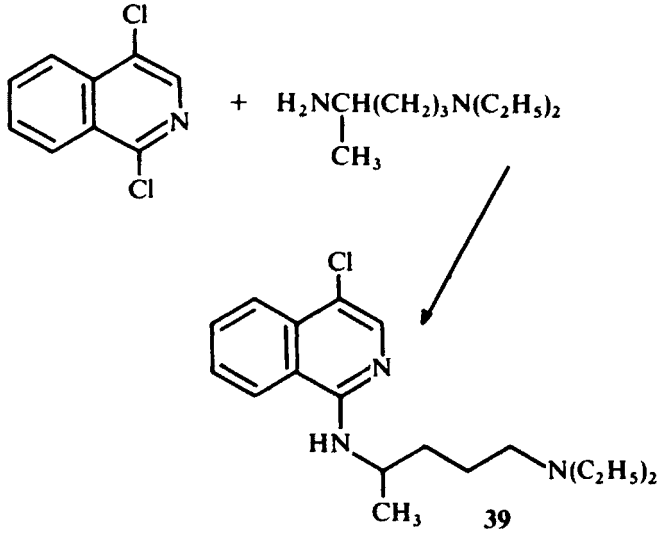
38

Alkylation of 1-aminoisoquinoline to give dialkylated products in high yields has been achieved by treatment with alkyl halides in the presence of sodium amide in liquid ammonia.[32, 33]

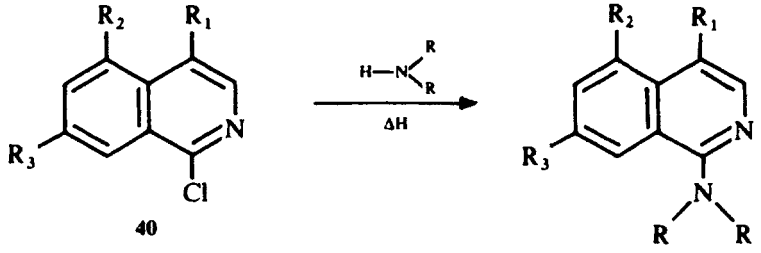
The lability of the halogen at position 1 of isoquinoline has been utilized in the synthesis of several 1-aminoalkylaminoisoquinolines,[34] as well as several halogenated 1-methylbutylaminoisoquinolines[35] (e.g., **39**). A typical preparation is shown in Eq. 31 for those compounds that possess antimalarial properties.

Antiinflammatory 1-alkylamino and 1-alkylpiperazinylisoquinolines **41** may be synthesized from the 1-chloroisoquinolines **40**, as shown in Eq. 32.[36]

Dealkylation of 1-dialkylaminoisoquinolines under varying strengths of hydrobromic acid to give either monoalkylamino or totally dealkylated products has been described.[37] Some alkylamino 3,4-dihydroisoquinolines **43** were prepared during extensive studies by Roushdi et al.[38, 39] on mercuric chloride and Bischler–Napieralski type cyclodesulphurizations of thioureas **42**, as shown in Eq. 33.

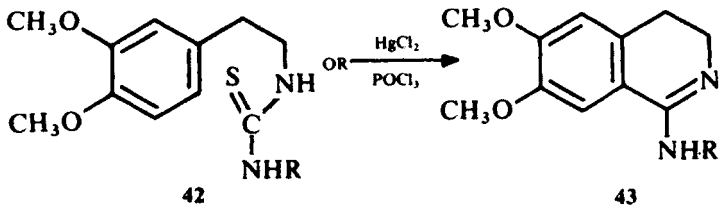


(31)



(32)

R_1 = H; C_6H_5; 4-$OCH_3C_6H_4$; 4-Cl-C_6H_4; *o*-tolyl
R_2 = H; CH_3
R_3 = H; OCH_3; Cl

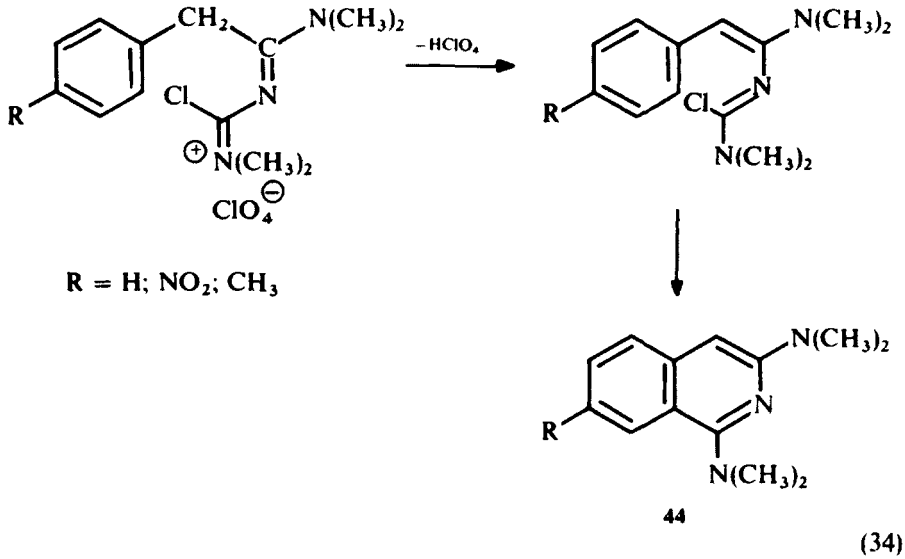


(33)

R = alkyl, aryl grouping

While in general aromatic moieties are used for R (Eq. 33), *n*-butyl, isopropyl, and benzyl functions give good yields of the corresponding dihydroisoquinoline of the type **43**.

The preparation of 1-alkylaminoisoquinolines through ring-closure methods is shown by the synthesis of variously 7-substituted 1,3-bis(dimethyl) aminoisoquinolines **44**. The terminating steps in the process are shown in Eq. 34.[40]

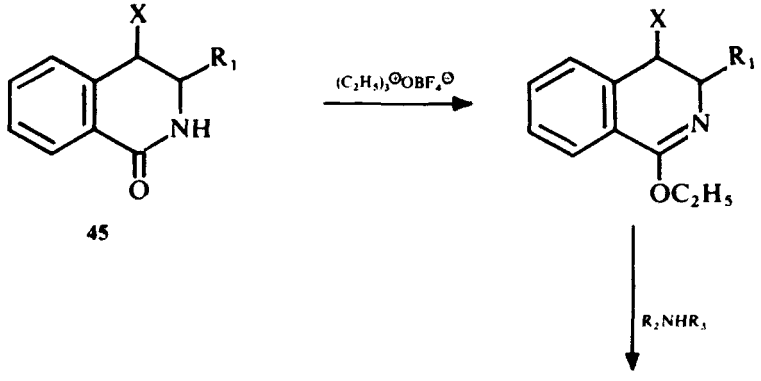


R = H; NO_2; CH_3

44

(34)

1-Alkylaminoisoquinolines **46** may also be prepared from the corresponding 1-isoquinolones **45**[41] (Eq. 35).



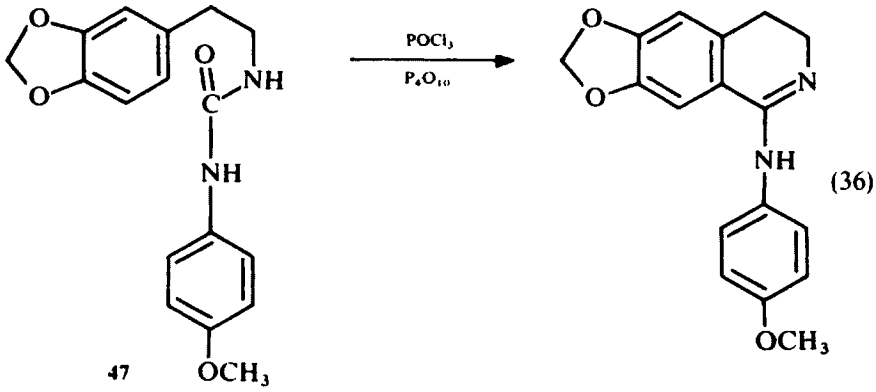
45

(35)

X = H; OH
R_1 = H; CH_3
R_2 & $R_3 \neq C_6H_5$

46

However, *N*-arylamines did not react in the second step and the *N*-arylisoquinoline could only be obtained by cyclization of the appropriate urea **47**[41] (Eq. 36).



47 (36)

C. 1-Arylaminoisoquinolines

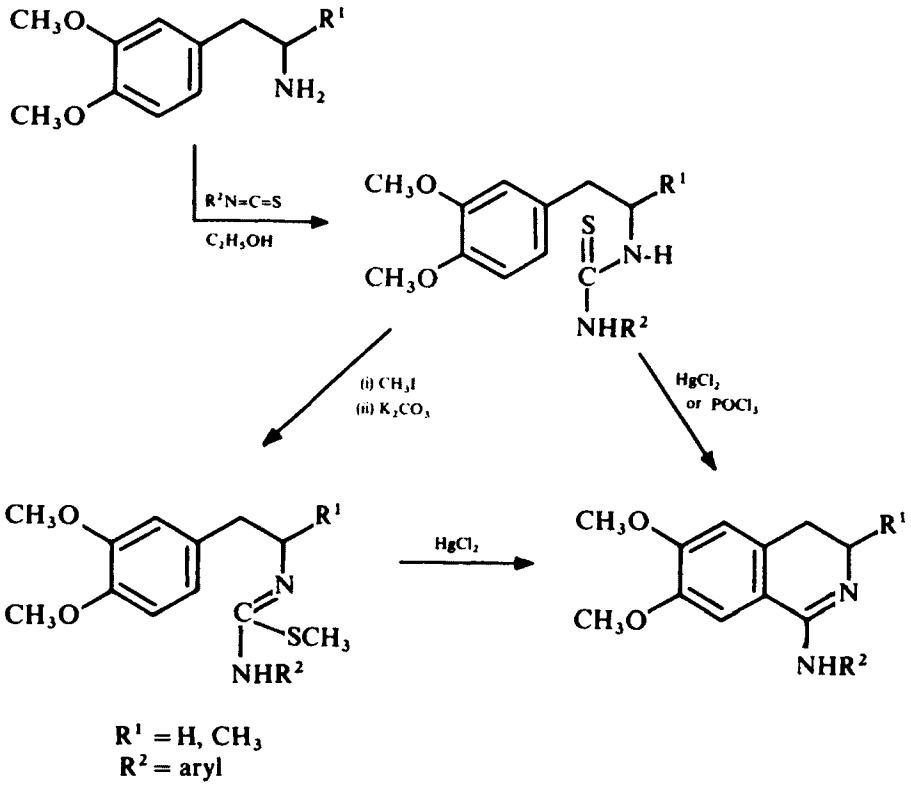
Isoquinolines of this type have been prepared by ring-closure reactions most notably of the Bischler–Napieralski type. Several reports of the synthesis of arylamino- and substituted arylaminoisoquinolines are available.[38, 39, 42-44] The cyclodesulfurization of thioamides and thioureas (previously noted) with mercuric chloride[38, 39] gives excellent yields (75–80%) of several arylamino-3-methyl-3,4-dihydroisoquinolines. Optimal conditions necessitate the use of 5 moles of the mercuric compound in refluxing chloroform.[39] Poor yields (23–75%) are obtained using phosphorus oxychloride. The absence of the 3-methyl group in the noncyclized precursor allows good yields of the cyclic product, using phosphorus oxychloride as the cyclizing agent, although polyphosphoric acid is not too effective. The general preparations are shown in Scheme 1.

As already noted, Bischler–Napieralski ring closures have most commonly been reported for the synthesis of compounds in this group. Appropriately substituted phenylethyl ureas **48** (prepared from the action of phenylethylisocyanates with various anilines), on ring closure with phosphorus oxychloride, yield the corresponding 1-substituted anilino-3,4,-dihydroisoquinolines **49**.[45] These substituted isoquinolines are amidines and thus exhibit the expected tautomerism **49**⇌**50**, as shown in Eq. 37.

Metal reductions (e.g., Al/Hg) of **51** yield the corresponding tetrahydroisoquinoline derivative **52**[45] (Eq. 38).

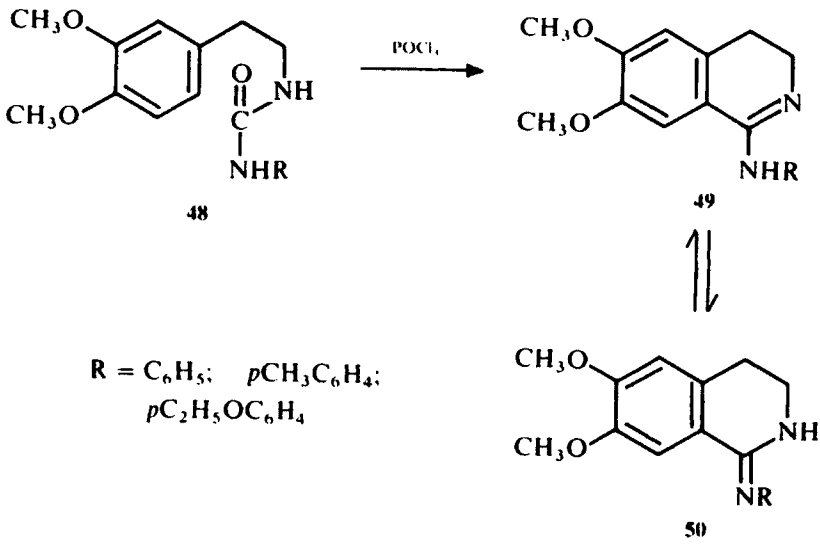
In the course of investigations toward some synthetic antimalarial agents, the reaction of substituted anilines with 1,3-dichloro- and 1-chloroisoquinoline has been studied.[46, 47] As anticipated, replacement of the labile 1-halogen readily occurs, yielding the desired 1-anilinoisoquinoline **53** (Eq. 39).

The isolation of 1-anilinoisoquinolines in good yields from the base-catalyzed ring opening of pyridino-2:1(a)-isoquinolines **54** has also been reported[48] (Eq. 40).



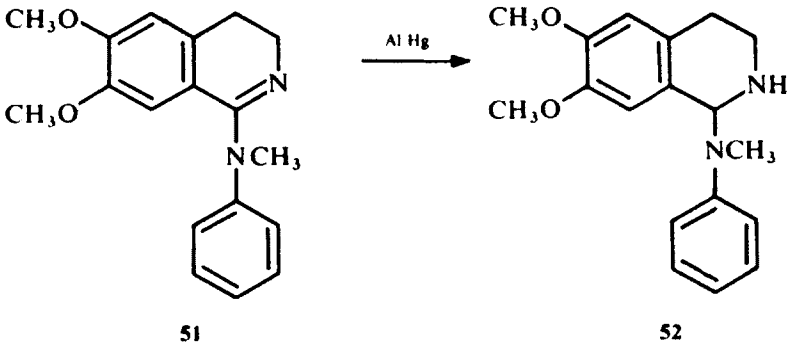
$R^1 = H, CH_3$
$R^2 =$ aryl

Scheme 1



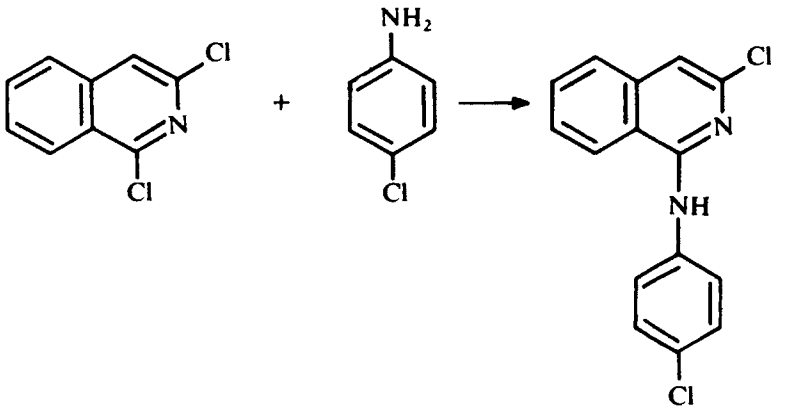
(37)

R = C_6H_5; $pCH_3C_6H_4$; $pC_2H_5OC_6H_4$



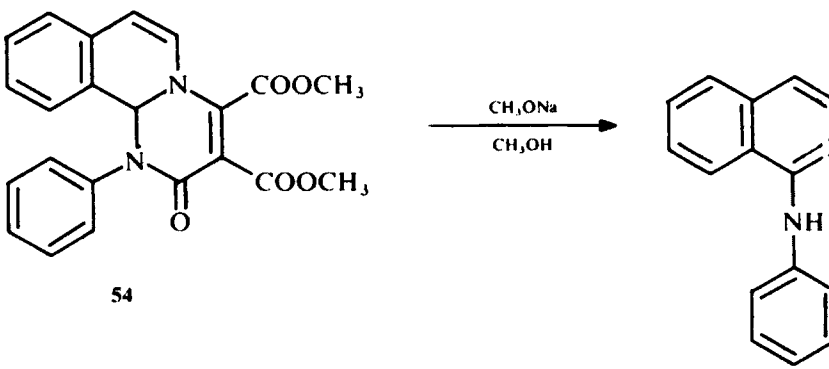
(38)

51 52



(39)

53

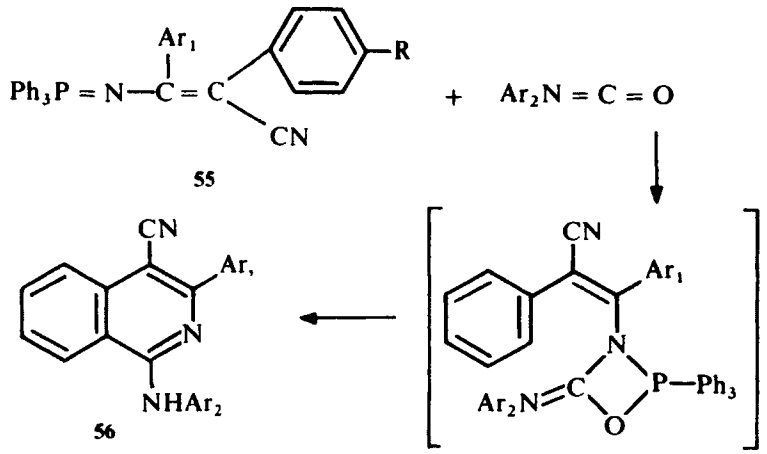


54

(40)

Several arsonoanilinoisoquinolines have been synthesized during some studies on potential trypanocidal and spirocheticidal isoquinolines.[49] 1-Chloroisoquinolines, on heating with the appropriate anilinoarsonic acid, give varying yields of the desired product, depending on the arsonic acid used.[49] The

cyclization of *N*-substituted phosphine imides **55** on treatment with aryl isocyanates yields variously substituted 1-arylaminoisoquinolines **56**[44] (Eq. 41).

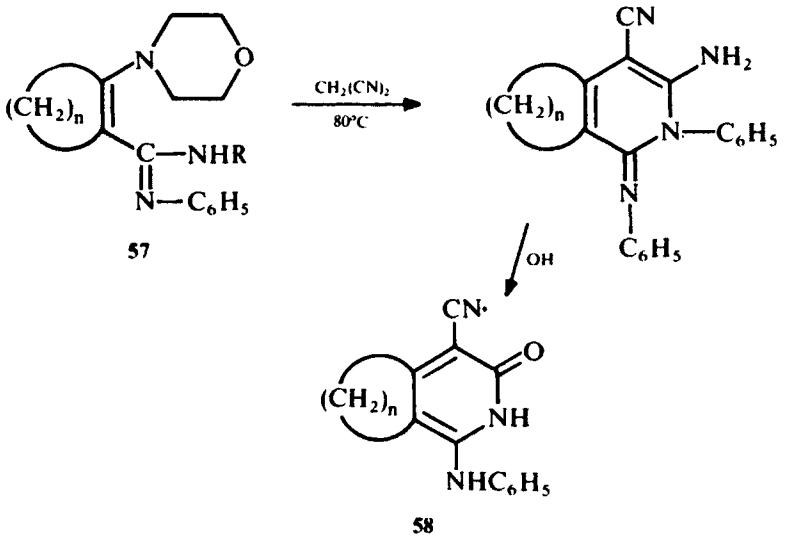


55 **56**

Ar_1, Ar_2 = aryl
Ph = C_6H_5
R = H, Cl

(41)

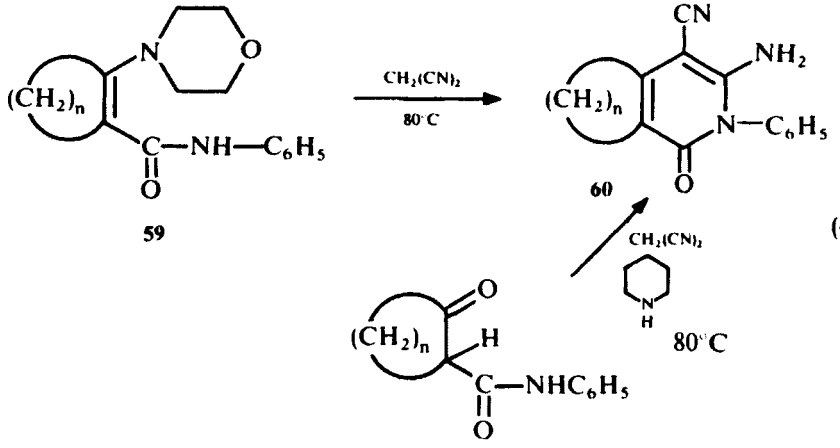
Derivatives of cyclohexanone and cycloheptanone 2-carboxylic acids **57** (and **59**) may be transformed using malonitrile into 1- (and 3)-aminoisoquinolines **58** (and **60**)[50] (Eqs. 42 and 43).



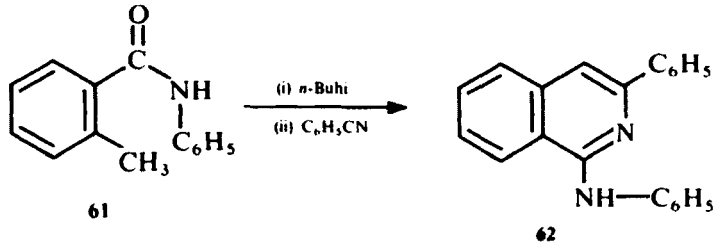
57 **58**

(42)

2-Methyl-*N*-phenylbenzamide **61** has been converted to *N*, 3-diphenyl-1-aminoisoquinoline **62** by a ring-closure reaction using *n*-butyllithium followed by addition of benzonitrile[51] (Eq. 44).



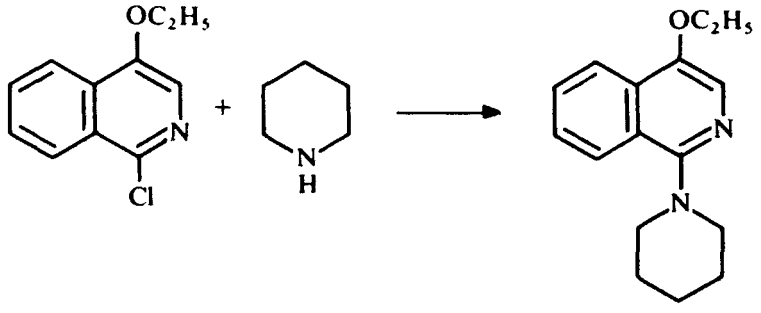
(43)



(44)

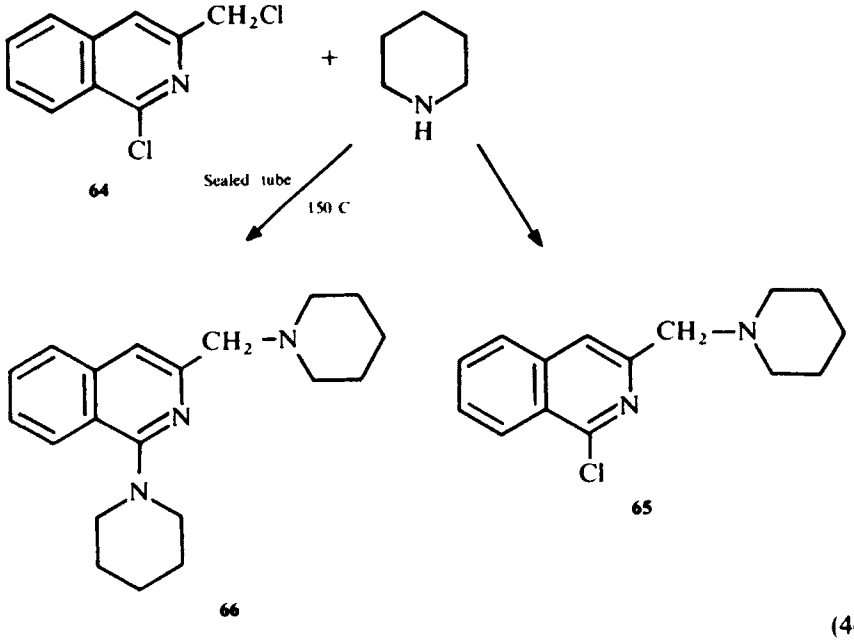
D. 1-Piperidylisoquinolines

The preparation of isoquinolines having heterocyclic substitutions with the heteroatom directly at the isoquinoline ring has been approached by several alternate methods. The most obvious route is by way of the replacement of the labile chlorine atom of 1-chloroisoquinolines; various secondary bases including piperidine, pyrollidine, morpholine, and piperazine have been used[52-54] (e.g., Eq. 45). Good yields of the products (e.g., **63**) are obtained in both polar and nonpolar solvents.



(45)

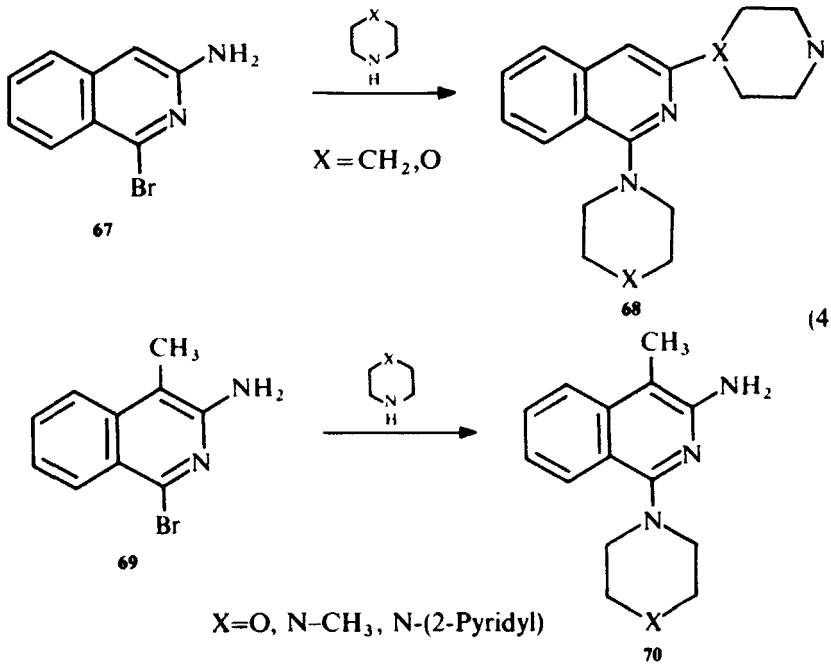
Displacement of the 1-chloro grouping of 1-chloro-3-chloromethylisoquinoline **64** by several heterocyclic secondary amines, as well as by some aliphatic amines, has been accomplished.[54] Under mild conditions, amination of the chloromethyl grouping occurs (**65**), but under more severe conditions (sealed tube, 150 °C), disubstitution at both the side chain and the ring takes place (**66**). Yields of the disubstituted compounds are in the range 35–80% (Eq. 46).



(46)

Nitration of **64** occurs at the 5 position; similar mild treatment of the nitrated product with various heterocyclic secondary amines (as in Eq. 46) may yield the monosubstituted or the disubstituted product, depending on the secondary base used.[53, 54] 1-(and 3-)Aminoisoquinolines **68** and **70** may be synthesized by heating 1-bromo-3-aminoisoquinoline **67** or 1-bromo-3-amino-4-methylisoquinoline **69** with various *N*-heterocycles (Eq. 47).[55]

A similar route to that outlined in Eq. 30 may be used for the preparation of 1-piperidylisoquinoline;[31] piperidine and its *N*-lithium derivative displace the halogen of 1-bromoisoquinoline to give the product in good yield. Displacement of the halogen of 1-chloro-4-carboxylic acid esters of isoquinoline occurs in a manner similar to that shown in Eq. 46.[56] Lithiated pyridines **71** have been used in the synthesis of 1-piperidinyl and 1-pyrollidinyl-5,8-epoxydihydroisoquinolines by Berry and co-workers.[57] Reduction of the 5,8-epoxide **72**, followed by aromatization and dehalogenation of the chlorine atoms substituted at the 3 and 4 positions of the isoquinoline ring yields, in the case of the use of the piperidyl derivative, 1-piperidinoisoquinoline **74** and, under alternate reducing conditions, its 4-chloro analog **73**. The general procedure is shown in Eq. 48.



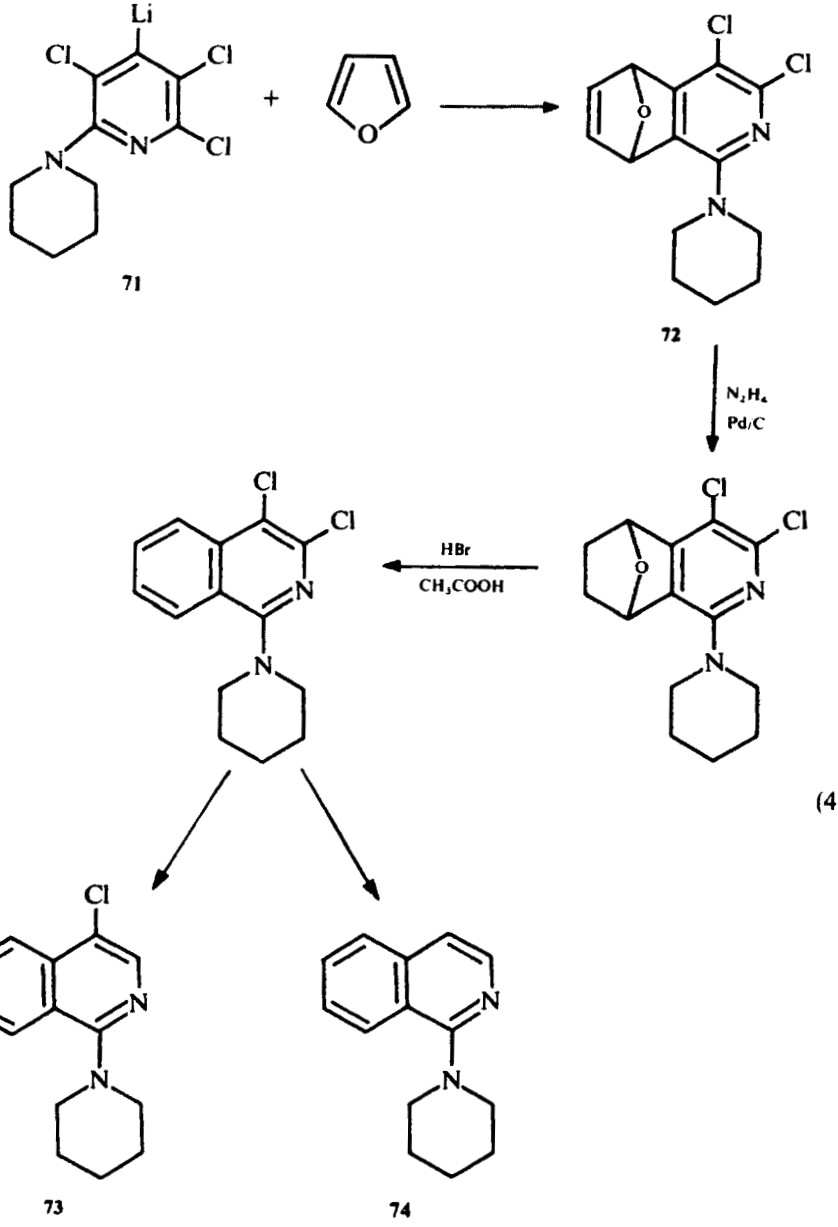
(47)

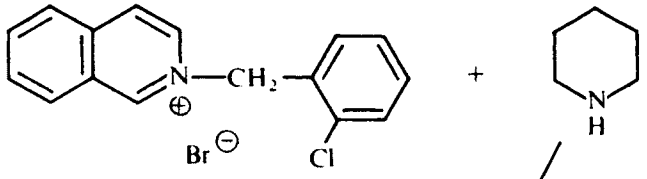
Piperidine adducts of 2-substituted isoquinolines **75** yield 1-piperidino-1,2-dihydroisoquinolines **76**.[58] Various aralkyl substitutions at the 2 position have been employed (Eq. 49).

Monofluorinated isoquinoline *N*-oxides (e.g., **77**) have been used for the preparation of piperidyl (and hydrazino) isoquinolines (**78**) by Bellas and Suschitzsky (Eq. 50).[59] Treatment of the fluoro compound with the nucleophile gives the substituted product in good yield. The studies of these workers indicate that the nucleophilic reactivity of isoquinoline *N*-oxides, based on fluorine mobility, is $1 \gg 3 > 4 > 6 > 8$.

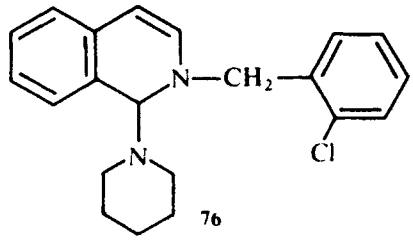
E. 1-Hydroxyaminoisoquinolines

The synthesis and rearrangements of 1-aryl-1-hydroxyamino-1,2,3,4-tetrahydroisoquinolines **80** have been the subject of several comprehensive studies by Gardent et al.[60-63] 1-Aryl-3,4-dihydroisoquinolines **79** prepared by Bischler–Napieralski ring closures, on treatment with hydroxylamine hydrochloride, yield **80** by addition across the 1,2 double bond.[61, 62] Several variations have been made in the nature of aryl grouping. Isoquinolones **81** are produced from the phosphorous-pentoxide-catalyzed Beckmann rearrangement when the isoquinoline nitrogen is unsubstituted, and ring cleavage products **84** when the heteroatom is ethylated (**82, 83**) (Scheme 2).[61, 62]


Li
Cl
Cl
Cl
N
N
71
+
O
Cl
Cl
O
N
N
72
N_2H_4
Pd/C
Cl
Cl
O
N
N
HBr
CH_3COOH
Cl
Cl
N
N
(48)
Cl
N
N
73
N
N
74

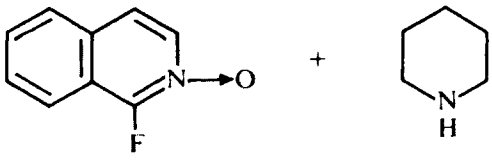


75

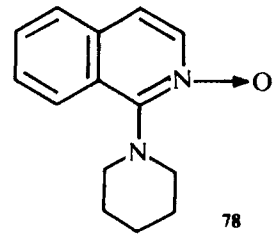


76

(49)



77



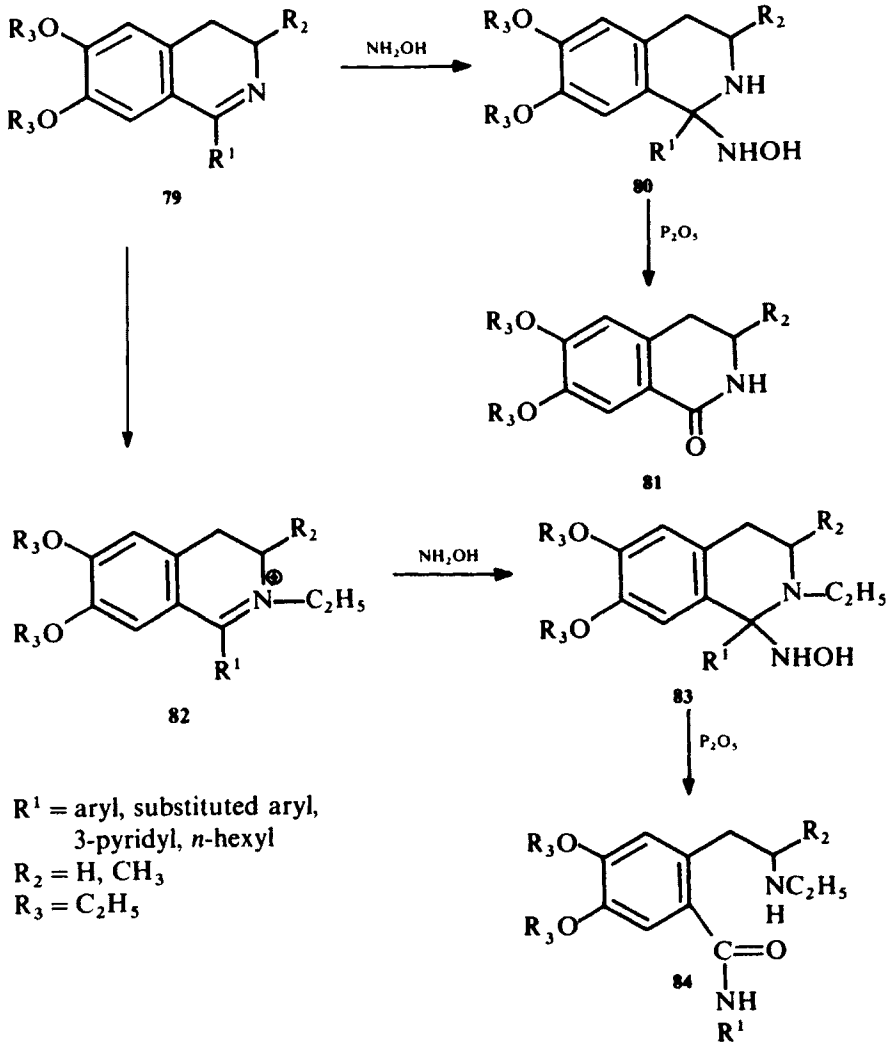
78

(50)

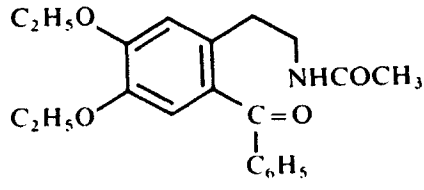
Additional investigations[63] have shown that upon treatment with acetic anhydride, **79** produces a complex mixture. Fractionation of this mixture yields a major product, **85**, which on reaction with hydroxylamine hydrochloride recyclizes to produce a compound of general formula **80**.

F. 1-Hydrazinoisoquinolines

Three general approaches for the synthesis of 1-hydrazinoisoquinolines are available. The most commonly used method takes advantage of the lability of halogens at the 1-position of isoquinoline.

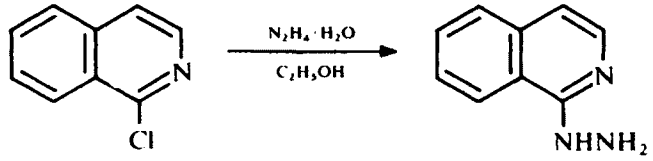

NH₂OH
P₂O₅
NH₂OH
P₂O₅
79
80
81
82
83
84
R¹ = aryl, substituted aryl, 3-pyridyl, n-hexyl
R₂ = H, CH₃
R₃ = C₂H₅

Scheme 2



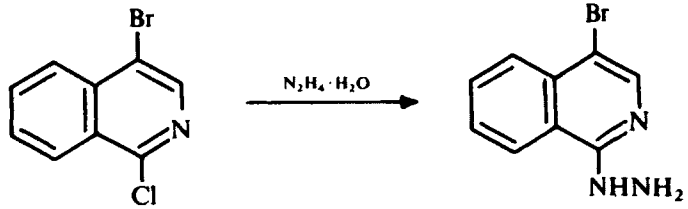
85

1-Chloroisoquinolines, on treatment with hydrazine hydrate in ethanol, gives good yields of the hydrazine compound **86**[52, 64] (e.g., Eq. 51).



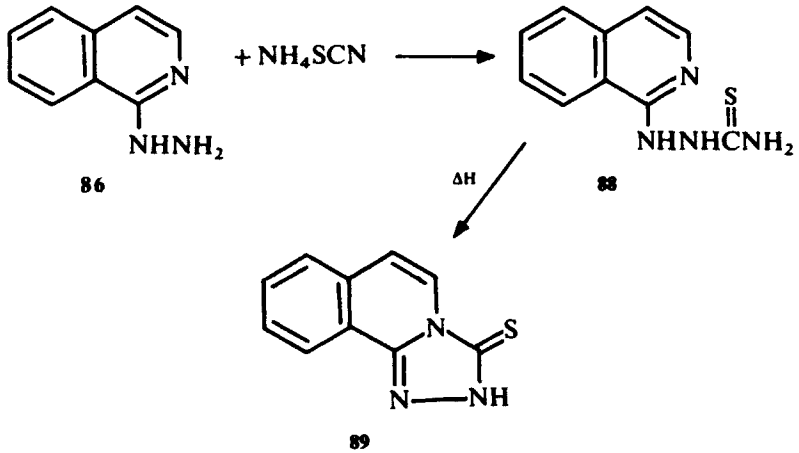
86 (51)

Excellent yields of variously substituted 1-hydrazinoisoquinolines (e.g., **87**) may be obtained[65] using the same approach as in Eq. 51. Various substituents (methoxyl and methyl) at several positions have been studied, including 1,4-dichloro- and 1-chloro-4-bromo analogs (see Eq. 52), with high yields (50–95%) in all cases.



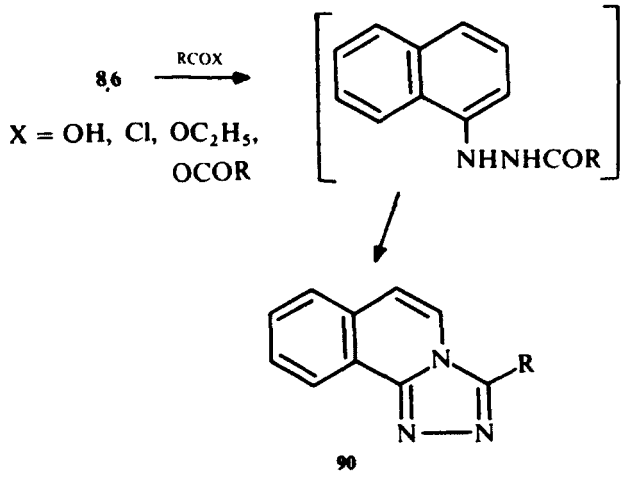
87 (52)

Subsequent substitution of the hydrazino grouping with ammonium thiocyanide (or ethylchloroformate) yields the thiosemicarbazide **88** (or urethane), which on thermal treatment produces the triazoloisoquinoline **89** (Eq. 53). Mechanisms for the ring formation have been proposed.[65]



86 **88** **89** (53)

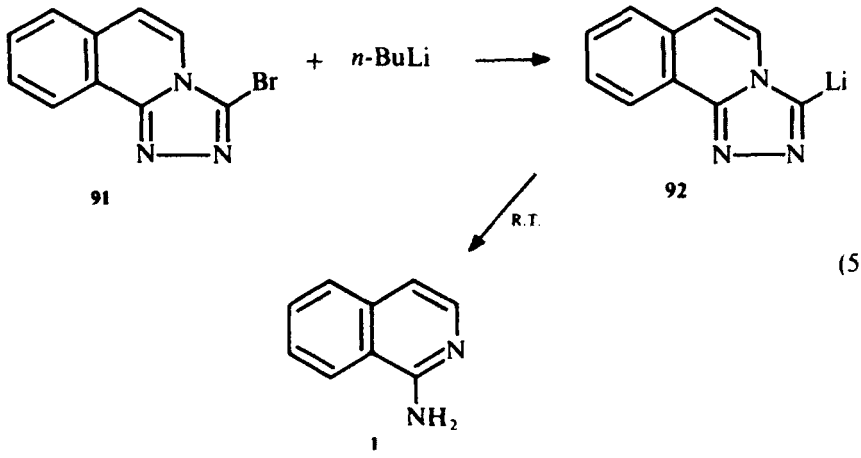
Alternate preparations of triazoloisoquinolines **90** from **86** have been reported by the treatment of **86** with carboxylic acid derivatives[69] (Eq. 54).



90

(54)

The 3-bromo analog of these *s*-triazoloisoquinolines **91** on treatment with *n*-butyllithium yields the lithiated derivative **92**. This compound is stable at low temperatures (−70 °C), but decomposes to yield 1-aminoisoquinoline **1** at room temperature[66] (Eq. 55).



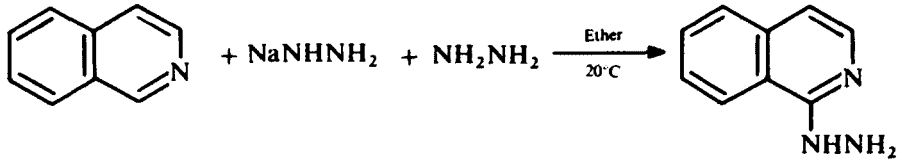
91 92 1

(55)

Heptafluoroisoquinoline, on treatment with hydrazine hydrate, similarly yields 1-hydrazinohexafluoroisoquinoline, from which the hydrazone may be readily obtained.[18] The direct introduction of the hydrazine grouping into isoquinoline has been achieved using controlled mixtures of sodium hydrazide and hydrazine[67, 68] (Eq. 56).

Modifications of this methodology are available for the introduction of alkylated (CH_3) hydrazide moieties.[70]

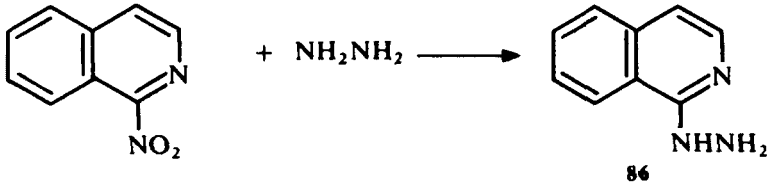
As an alternate route, the treatment of 1-nitroisoquinoline with hydrazine hydrate gives good yields of **86**[20] (Eq. 57).



Ratio 1:5:3

86

(56)

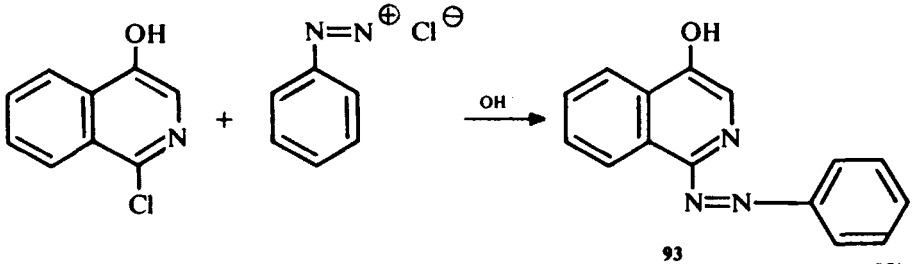


86

(57)

1-Hydrazinoisoquinolines have been shown to possess properties that lower blood pressure.[71]

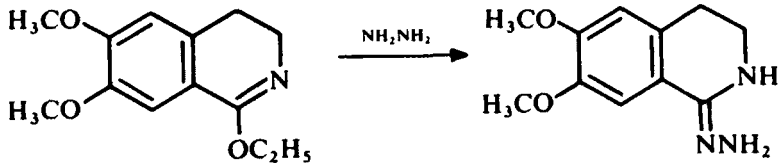
Isoquinolines substituted at the 1 position with diazonium groupings **93** may be prepared by displacement of the halogen at position 1 by diazonium salts[72] (Eq. 58).



93

(58)

1-Hydrazonoisoquinoline **95** may be prepared from lactim ether **94**[73] by direct reaction with hydrazine (Eq. 59).



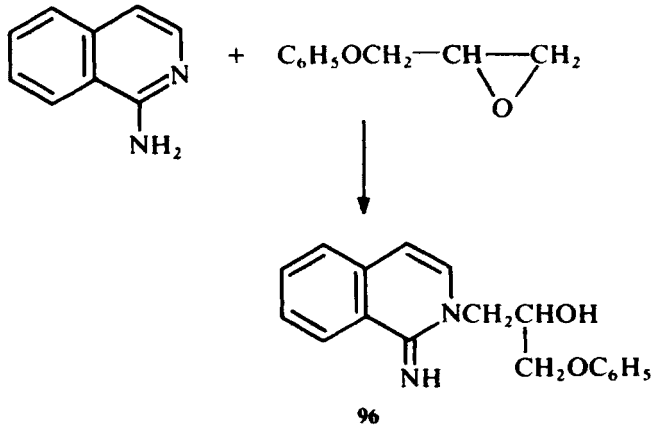
94 **95**

(59)

G. 1-Iminoisoquinolines

As noted in Section I. A, studies on the tautomerism of 1-aminoisoquinoline **1** show that an imine structure prevails and, thus, it is not surprising that **1** has

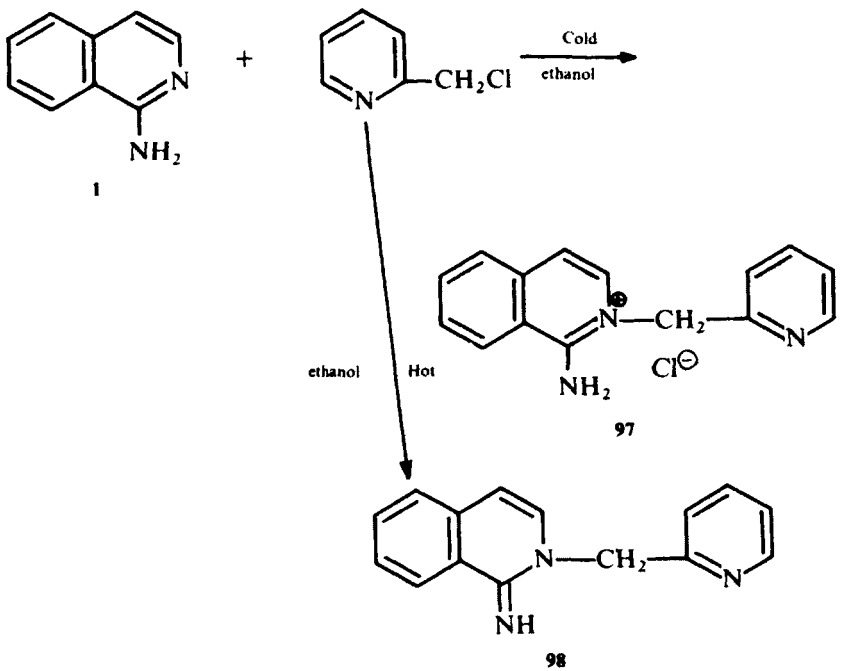
been used in the synthesis of various 1-iminoisoquinolines. *N*-(2-Hydroxy-3-phenoxypropyl)-1-imino-1,2-dihydroisoquinoline **96** may be isolated from the treatment of **1** with phenoxypropylene oxide in methanol[74] (Eq. 60). Base hydrolysis of **96** readily yields the corresponding 1-isoquinolone.



(60)

96

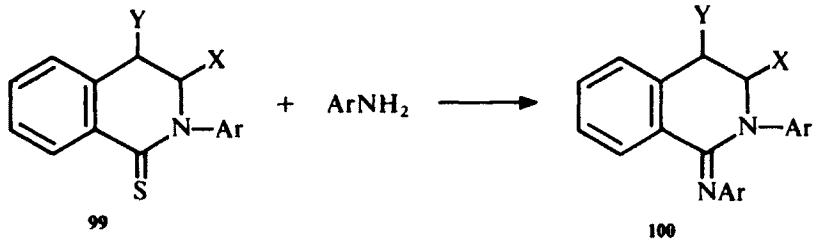
The formation of 1-imino-2-(2-pyridylmethyl)-1,2-dihydroisoquinoline **98** occurs on reaction of **1** with 2-chloromethylpyridine in boiling ethanol, whereas quaternization of the heterocyclic nitrogen of **1** takes place in cold ethanol, resulting in **97**[75] (Eq. 61).



(61)

1 **97** **98**

Several 1-phenyliminoisoquinolines (e.g., **100**) have been prepared by a facile procedure described by Legrand and Lozac'h[76] (Eq. 62). 1-Isoquinolinethiones **99**, on treatment with primary aromatic amines in the absence of strong acids, yield products such as **100**. Hydrolysis readily affords the corresponding 1-isoquinolone.

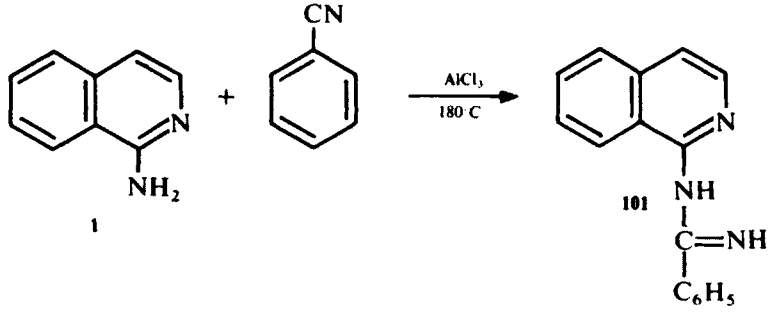


99 **100**

$X = C_6H_5$; $pCH_3C_6H_4$; $pCH_3OC_6H_4$
$Y = H$; C_6H_5
$Ar = C_6H_5$; $o,pCH_3C_6H_4$; o,p-$CH_3OC_6H_4$; $pClC_6H_4$ (62)

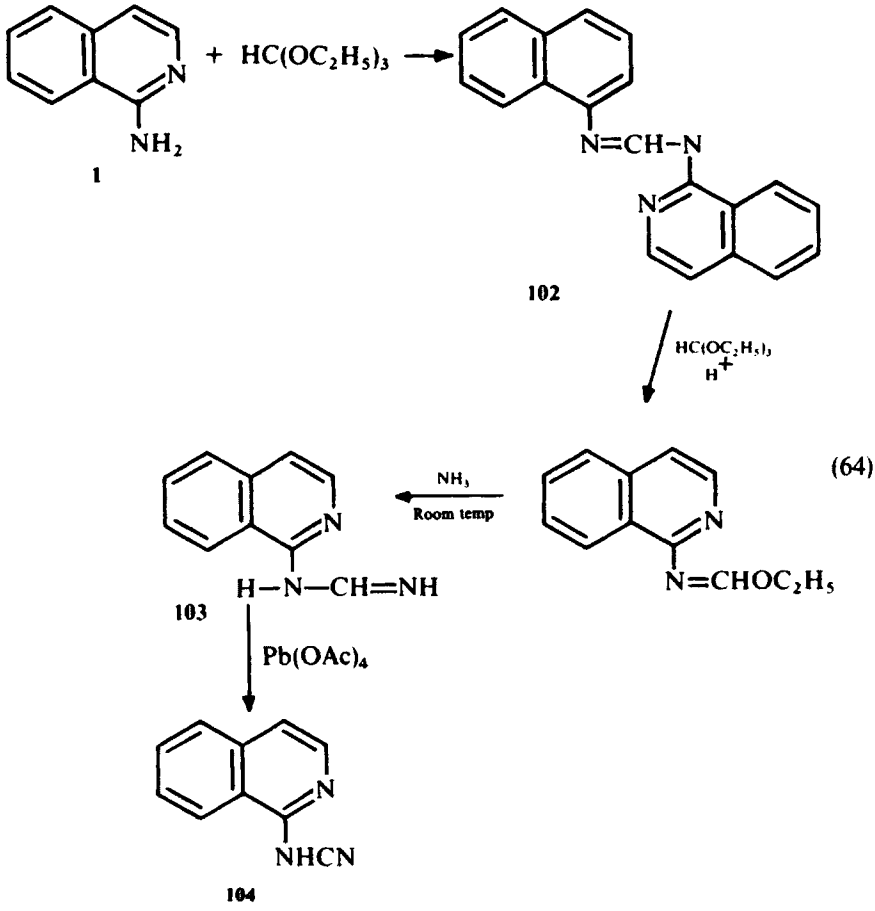
H. 1-Amidinoisoquinolines

The preparation of 1-isoquinolylbenzamidines **101** may be effected by the treatment of 1-aminoisoquinoline **1** with benzonitrile in the presence of a Lewis acid[77] (Eq. 63).



1 **101** (63)

The preparation of the analogous formamidine **103** necessitates the use of orthoformic ester, followed by hydrolysis and amination of the initially formed diisoquinolinyl formamidine **102** (Eq. 64).



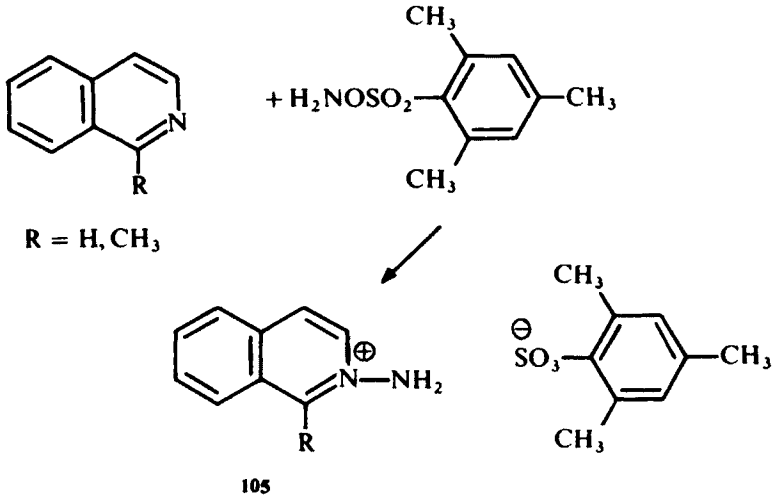
(64)

III. PREPARATION OF ISOQUINOLINES HAVING A BASIC GROUPING AT POSITION 2

A. 2-Aminoisoquinolines

2-Aminoisoquinolines may be considered to be hydrazines in which one of the nitrogens has been incorporated into the isoquinoline ring structure. Thus, derivatives (particularly acyl derivatives) have been the subject of several studies in the formation of polycylic tetrazines and several rearrangement reactions.

Isoquinoline (or its 1-methyl analog) has been converted to its 2-amino derivative **105** by treatment with *O*-mesitylenesulfonyl hydroxylamine[78] or hydroxylamine *O*-sulfonic acid.[79, 80] The product **105** may be isolated as its mesitylene sulfonate salt[78] (Eq. 65) or converted to a suitable halide salt by treatment with the hydrohalide.[79, 81]



(65)

Several ring-substituted isoquinolines may be used as substrates to prepare the corresponding *N*-aminoisoquinolinium salts (e.g., R = 3-Me; R = 6-Me; R = 8-Me; R = 7-OMe)[82, 83] (e.g., 2-$COOC_2H_5$)[84, 85] (Eq. 65).

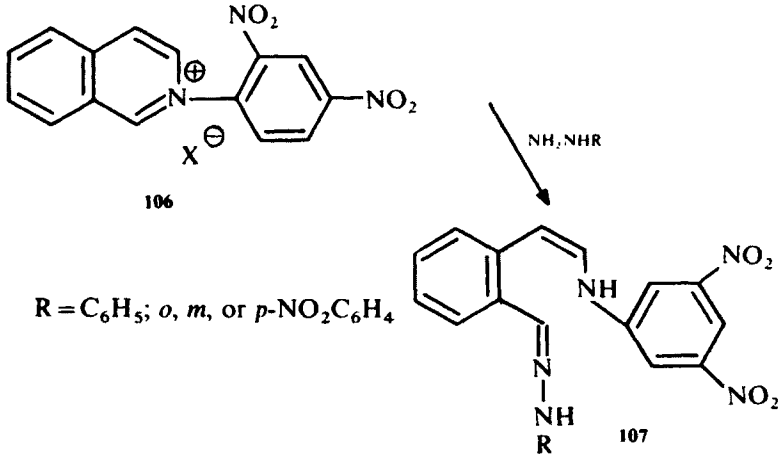
Interestingly, acyl ylides of 2-aminoisoquinoline undergo a photochemical 1,2-migration leading to the formation of 1-acylaminoisoquinolines.[78, 81, 86] This contrasts with comparable studies utilizing pyridinium betaines in which ring expansion occurs to yield diazepines. The 1,2-migration in the isoquinoline series is proposed to occur by way of a diaziridine intermediate.[78]

While less relevant to the discussion of compounds in this group of isoquinolines, the "reverse migration" has been observed during the synthesis of a large number of 2-arylaminoisoquinolines, the migration occurring by way of a ring-opening followed by recyclization. 2,4-Dinitrophenylisoquinolinium salts **106**, on treatment with variously substituted arylhydrazines, undergo cleavage of the 1,2 bond of the isoquinoline ring to give an arylhydrazine **107**. Subsequent recyclization yields the 2-arylaminoisoquinolium salt **109**, from which *N*-substituted iminoisoquinolium betaines **108** are obtained[86, 135] (Eq. 66).

The synthesis of 2-amino-1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-4-ethyl-3-methylisoquinolinium salts **110**, using a wide variety of ring-closing media, has been reported by Korosi[87] (Eq. 67).

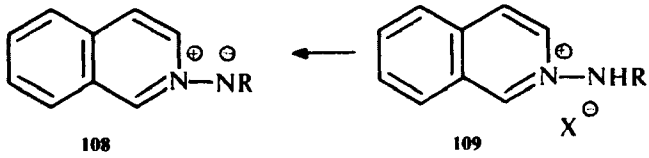
Dimerization of 2-aminoisoquinolinium betaine **111** in the presence of potassium carbonate and in dimethylformamide occurs, yielding the tetrazine derivative **112**[88] (Eq. 68).

Dimers similar to **112** have been reported from the treatment of 2-aminoisoquinolinium chloride with phenyl isocyanate or phenyl isothiocyanate.[89] 1,3-Dimethyl-6,7-dimethoxyisoquinoline perchlorate **113**, on treatment with hydrazine hydrate or phenylhydrazine, produces the 2-amino derivative **114** in high yield[90] (Eq. 69).

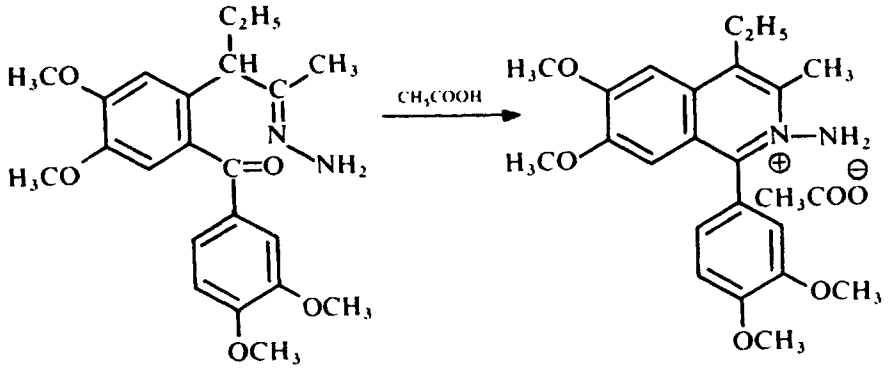


106 107

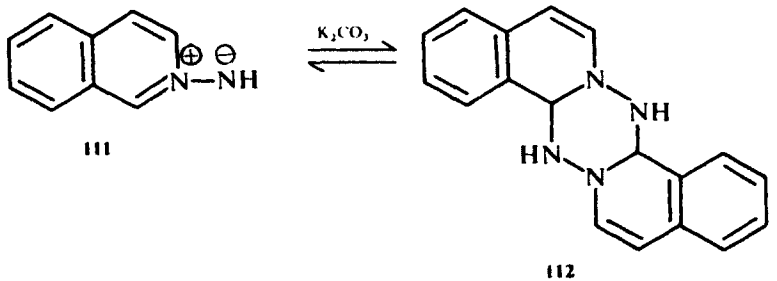
$R = C_6H_5$; *o*, *m*, or *p*-$NO_2C_6H_4$ (66)



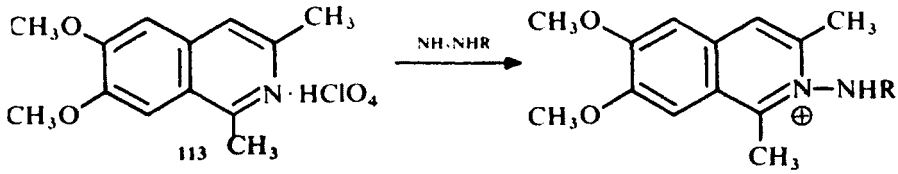
108 109



110 (67)



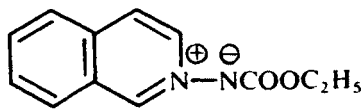
111 112 (68)



113 R = H, C_6H_5 114 (69)

N-Acylimino- and *N*-sulfonyl-aminoisoquinolinium chlorides and their dipolar bases have been synthesized by

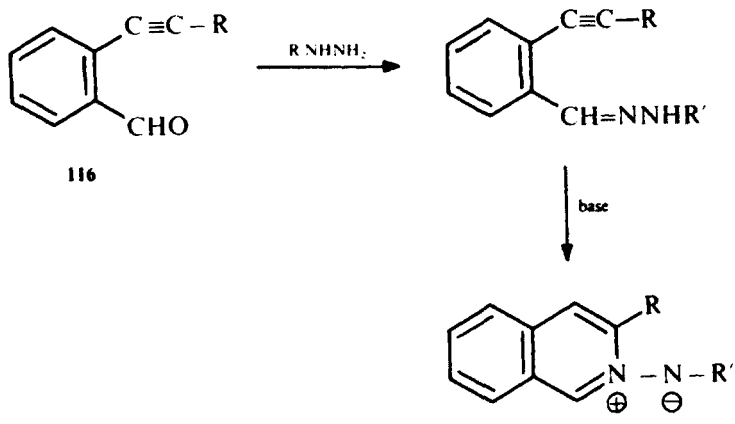
(1) ring closure of compounds of the type **107** where R is an acyl or sulfonyl grouping,[89]
(2) acylation of 2-aminoisoquinolinium chloride,[89]
(3) transacylations of *N*-(2-isoquinolinyl)-ethoxy carbonylamidate **115**[89]



115

(4) treatment of isoquinolinium salts with acylhydrazines.[91]

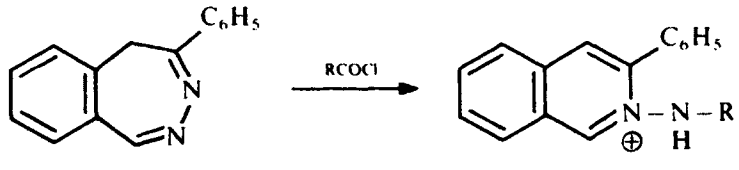
2-Iminoisoquinolines **117** have been reported as a result of the unanticipated base-induced cyclization of 2-ethynylbenzaldehyde **116** during an attempted synthesis of benzodiazepines[92] (Eq. 70).



116 117 (70)

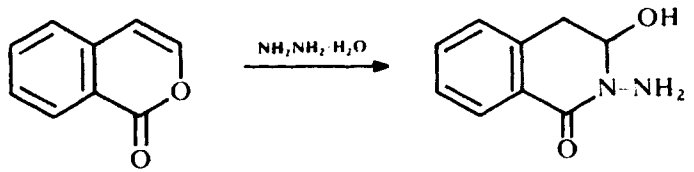
The acyl halide treatment of the benzodiazepine **118** results in the unexpected production of isoquinoline imine salts in good yield[93] (Eq. 71).

Treatment of isocoumarins with hydrazines may be used to form 2-aminoisoquinolones.[94] The reaction of isocoumarin **119** with hydrazine produces high yields of 2-amino-1(2H)-isoquinolone **120**[95] (Eq. 72).

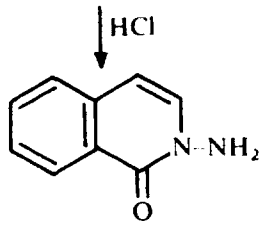


118

$R = CH_3CO$ (71)



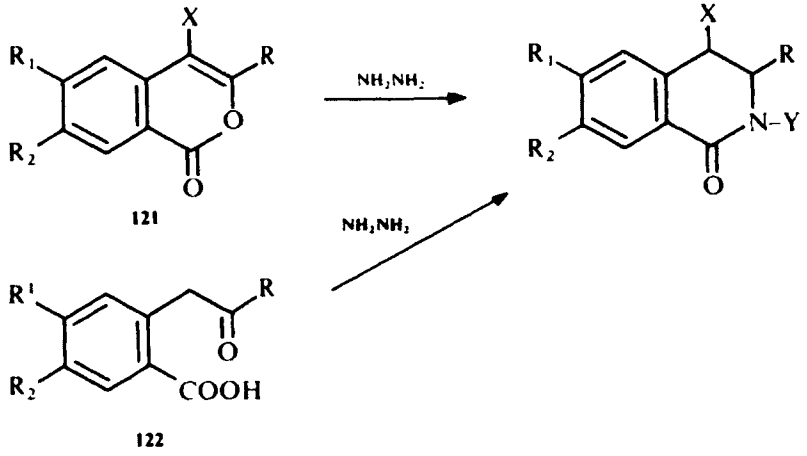
119



(72)

120

This reaction has been developed for the synthesis of a large variety of substituted analogs of **120** from substituted isocoumarins **121** or 2-carboxybenzylalkyl ketones **122**[95] (Eq. 73).



122

(73)

$R = CH_3$; C_2H_5; C_3H_7

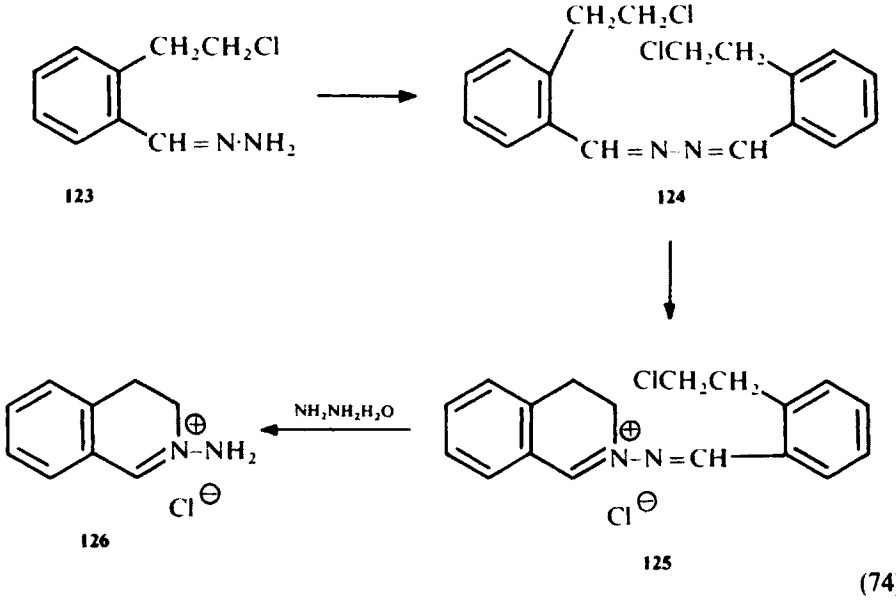
$R_1R_2 = H$; CH_3; C_2H_5; C_3H ; OCH_3

$X = H$; COOH

$Y = NH_2$; $NHCOCH_3$; $N = CHC_6H_5$

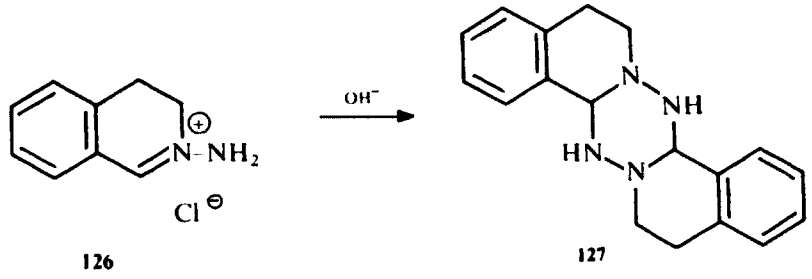
B. 2-Amino-3,4-Dihydroisoquinolines

Ring-closure reactions may be employed for the synthesis of the title compounds of this group. 2(2-Chloroethyl)-benzaldines **123** yield a dimer **124**, which in methanol cyclizes to produce a 2-benzylideneamino-3,4-dihydroisoquinolinium salt **126**.[96] Reduction with hydrazine hydrate readily produces the 2-amino-3,4-dihydroisoquinolinium salt **125**.[96]



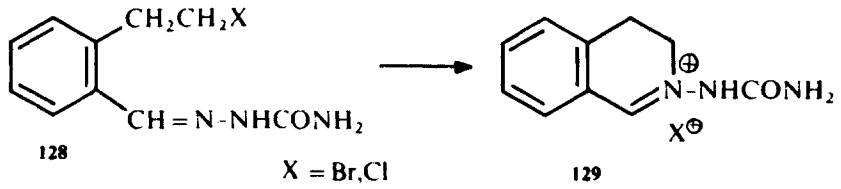
(74)

Dimerization of **126** under basic conditions has been used for the synthesis of the tetrazine derivative **127**[96] (Eq. 75).



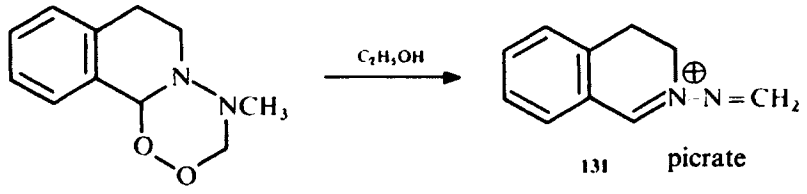
(75)

The careful heating of the carboxamidine **128**, in a reaction analogous to Eq. 74, results in cyclization, yielding the 3,4-dihydroisoquinolinium derivative **129**[96] (Eq. 76).



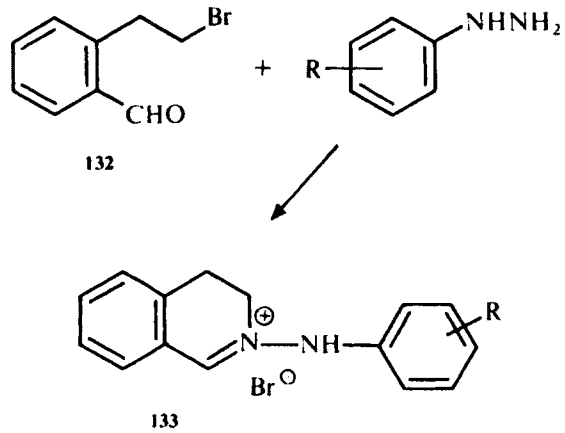
(76)

In a related study, dioxadiazines of the type **130** rapidly decompose in high yield to produce **131** at a rate dependent on solvent and the addition of acids or bases, indicative of a polar fragmentation[97] (Eq. 77).



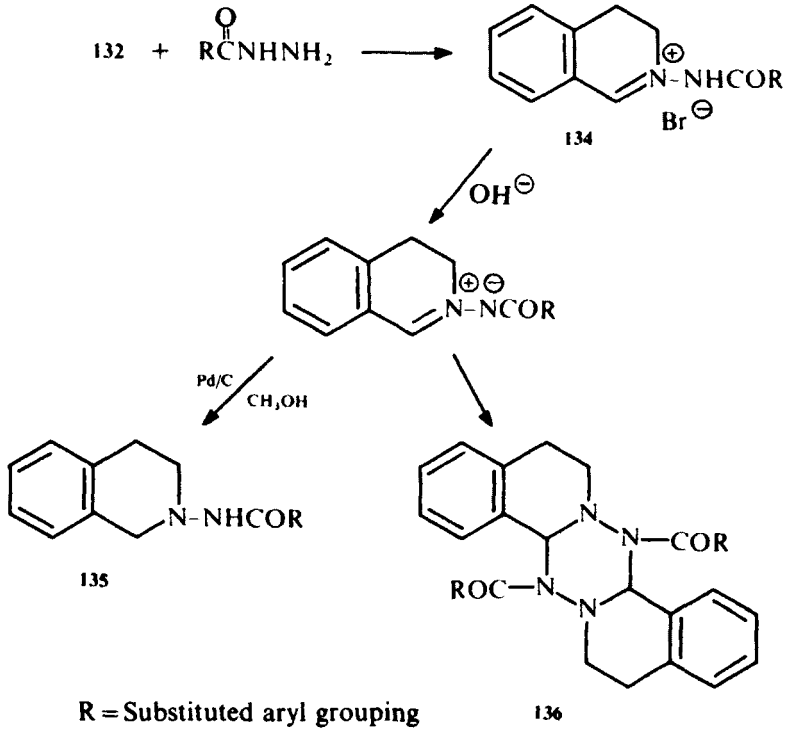
(77)

2-Arylamino-3,4-dihydroisoquinolines **133** have been synthesized by the reatment of the benzaldehyde derivative **132** with phenyl hydrazines[97] (Eq. 78).



(78)

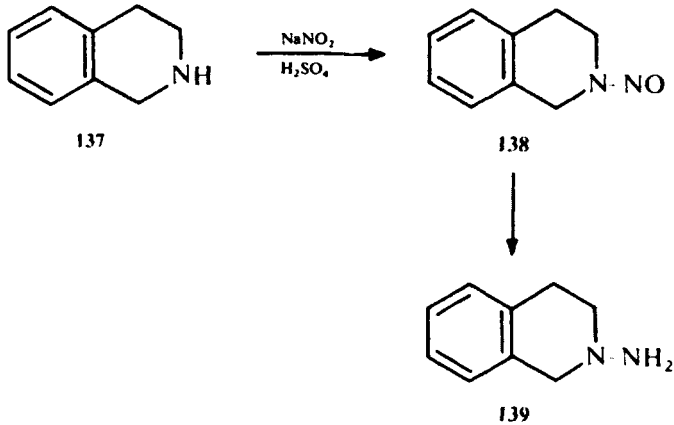
Compounds of type **132**, on treatment with alkenes, alkynes, and nitriles yield pentacyclic tetrazines;[98, 99] similar treatment of **133** with carbonyl compounds yields oxadiazolidines.[100] Benzoylhydrazine treatment of **132** provides an efficient synthesis of *N*-acylimino-3,4-dihydroisoquinolinium betaines **134**, which are converted to tetrazines **136** analogous to Eq. 75, as well as to the 1,2,3,4-tetrahydroisoquinoline analog **127**[99] (Eq. 79).



(79)

C. 2-Amino-1,2,3,4-Tetrahydroisoquinolines

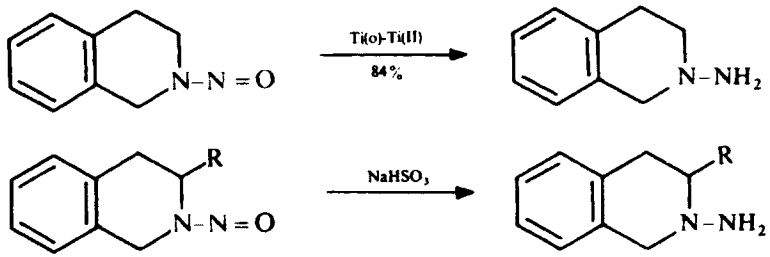
Diazotization of 1,2,3,4-tetrahydroisoquinoline **137** yields the *N*-nitroso derivative **138**, which on reduction with lithium aluminum hydride gives excellent yields (75%) of the corresponding 2-amino-1,2,3,4-tetrahydroisoquinolines **139**[101] (Eq. 80). Alternate reductions, including hydrazine hydrate,[102] zinc



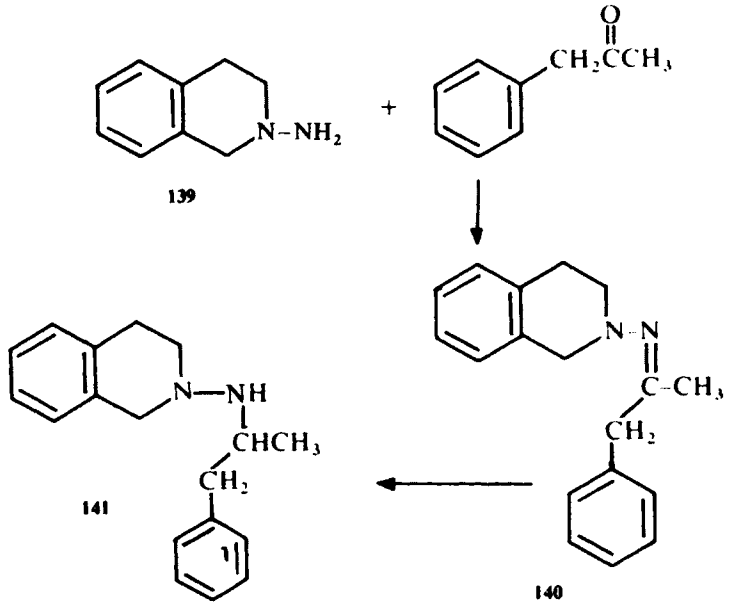
(80)

amalgam,[103] or zinc and acetic acid[104] have been conducted with several substituted derivatives of **137**.

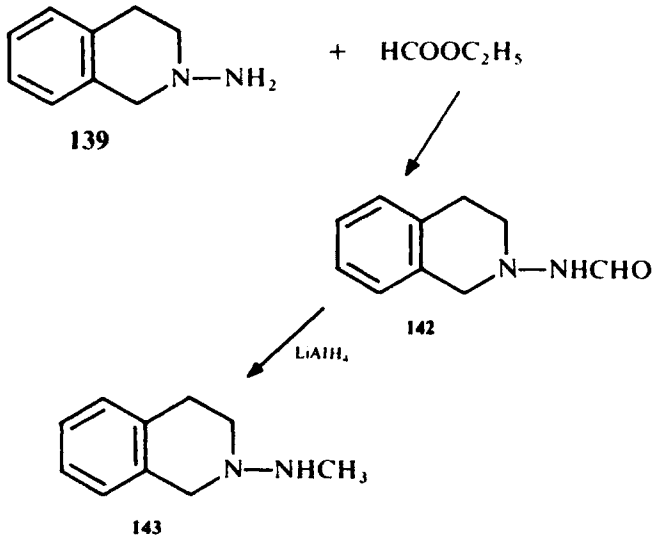
Reports have appeared indicating that low-valent titanium reagents[105] (Eq. 81) and sodium bisulfite[106] (Eq. 82) may be used as alternate reducing agents. The uniqueness of the titanium reagent in its selectivity for the *N*-nitroso function enables many other reducible groups to be included in the molecule and be unaffected.



Condensation of 2-amino-1,2,3,4-tetrahydroisoquinoline **139** with various aldehydes or ketones to yield the Schiffs base **140** has been used as a route for the synthesis of 2-alkylamino analogs **141**[103, 107, 108] (e.g., Eq. 83).

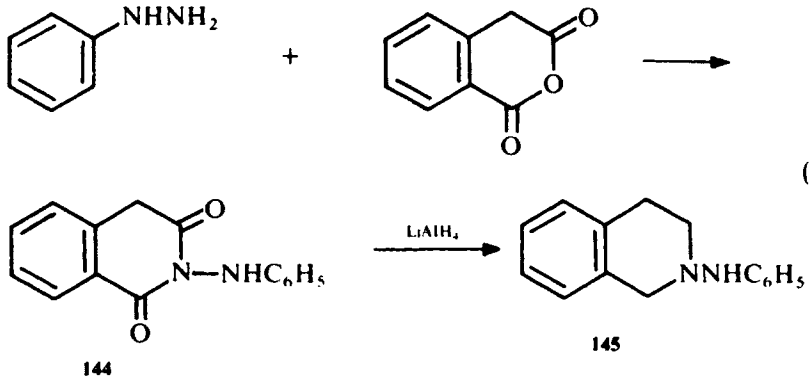


Intermediates of the type **140** have been studied for both antihypertensive[107] and anticancer[108] activity. Formic ester treatment of **139** followed by lithium aluminum hydride reduction of the *N*-formyl intermediate **142** gives 2-methylamino-1,2,3,4-tetrahydroisoquinoline **143**[107] (Eq. 84).



(84)

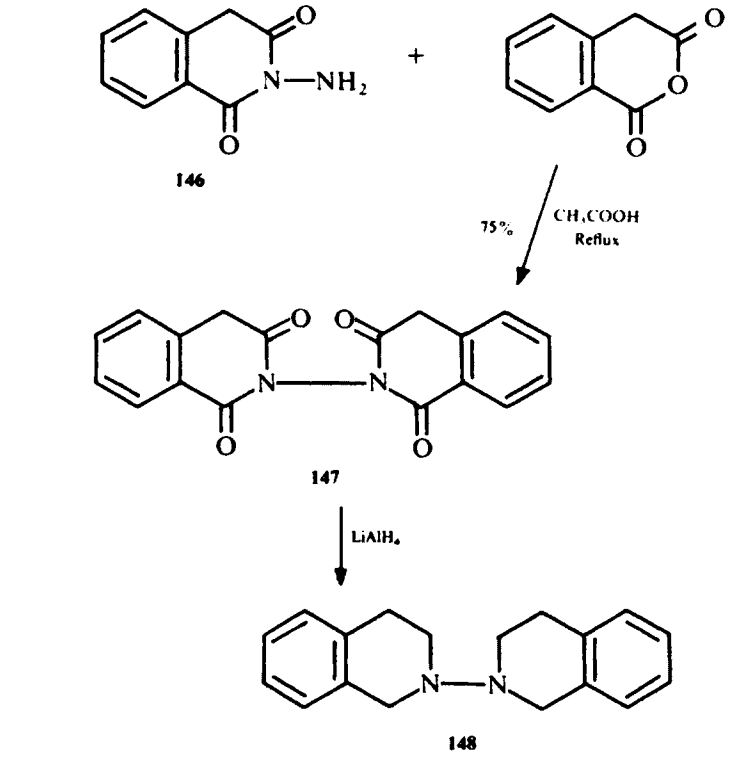
Isoquinolones may be used in the synthesis of 2-arylamino-1,2,3,4-tetrahydroisoquinolines. In an attempted preparation of diazepines by the action of phenylhydrazine on homophthalic anhydride, the isoquinolinedione **144** was isolated. Lithium aluminum hydride reduction of **144** afforded the 1,2,3,4-tetrahydroisoquinoline **145**[109] (Eq. 85).



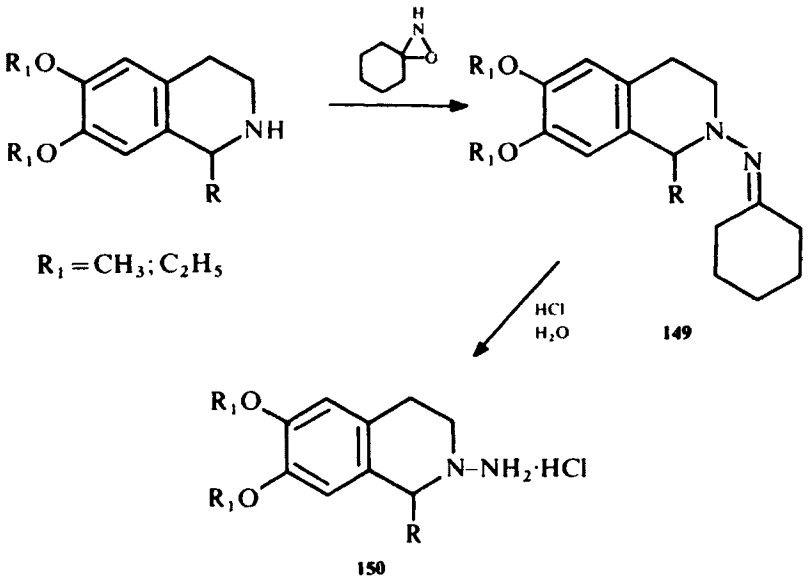
(85)

In an analogous reaction, homophthalic anhydride treatment of the isoquinolinedione **146** results in the formation of an isoquinolinedione dimer **147**, which on reduction yields the 1,2,3,4-tetrahydroisoquinoline dimer **148**[109] (Eq. 86).

N-Amination of variously substituted 1,2,3,4-tetrahydroisoquinolines occurs on treatment with 3,3-pentamethylene oxaziridine. The resulting hydrazones **149** may be converted to the corresponding 2-aminoisoquinolines **150** by hydrolysis[110] (Eq. 87).

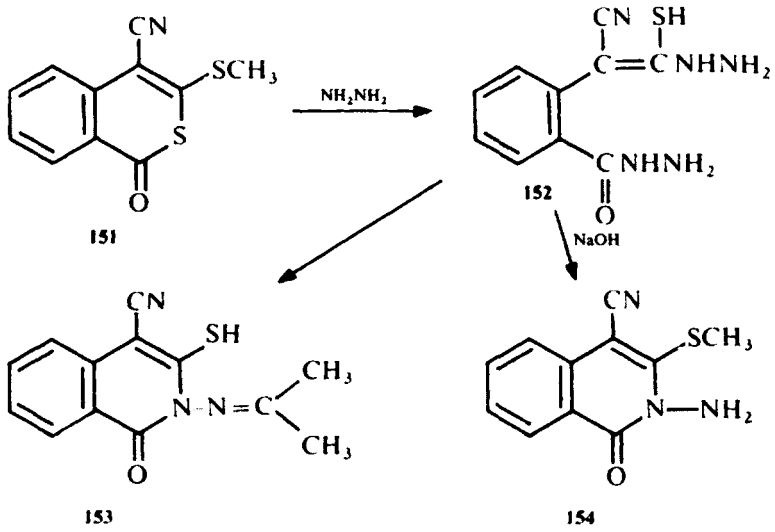

146
75%
CH3COOH
Reflux
147
LiAlH4
148

(86)


R1O
R1O
NH
R
R1 = CH3; C2H5
HCl
H2O
149
N-NH2·HCl
150

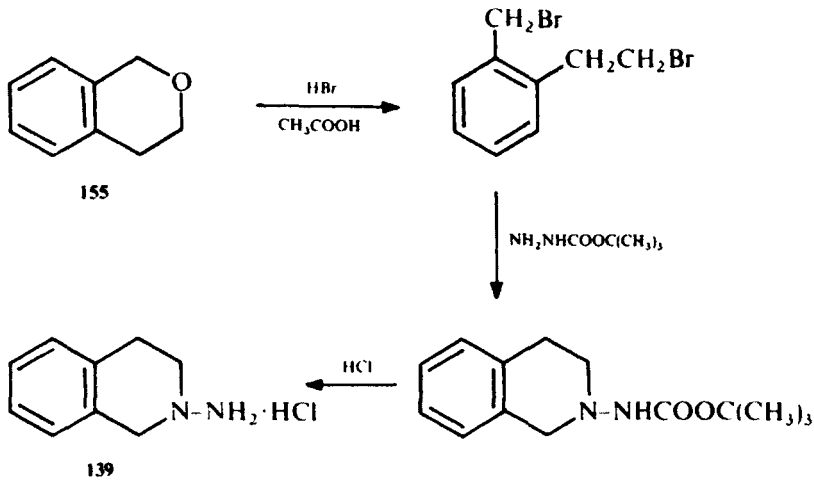
(87)

Some studies of 3-methylthio-4-cyanothioisocoumarins **151** yielding 2-amino-1-isoquinolones have been reported[111] (Eq. 88). Treatment of **151** with hydrazine results in ring cleavage to form **152**, which may be recyclized with base to the 2-aminoisoquinolone **154** or with acetone to give the 2-iminoisoquinolone **153**[111] (Eq. 88).



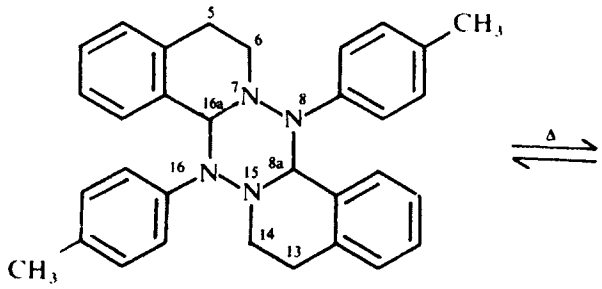
(88)

A novel synthesis of 2-amino-1,2,3,4-tetrahydroisoquinoline hydrochloride from isochroman has been reported. The acid-catalyzed ring opening of the chroman **155**, followed by treatment of the carboxylate ester of hydrazine, yields an intermediate which readily hydrolyzes to 2-amino-1,2,3,4-tetrahydroisoquinoline **139**[112] (Eq. 89).

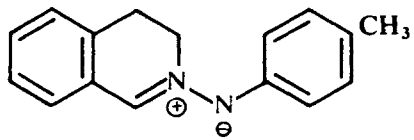


(89)

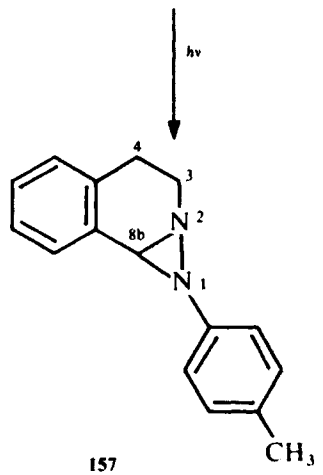
A unique isoquinoline derivative having a basic nitrogen bonded to both the 1 and 2 positions of 1,2,3,4-tetrahydroisoquinoline [8bH-3,4-dihydro-1-(4-methylphenyl)-diazirino-[3,1-a]isoquinoline] **157** has been synthesized in high yield from the irradiation of 5,6,8a,13,14,16a-hexahydro-8,16-di-(4-methylphenyl)*s*-tetrazino [6,1-a:3,4-a] diisoquinoline **156**[113] (Eq. 90).



156

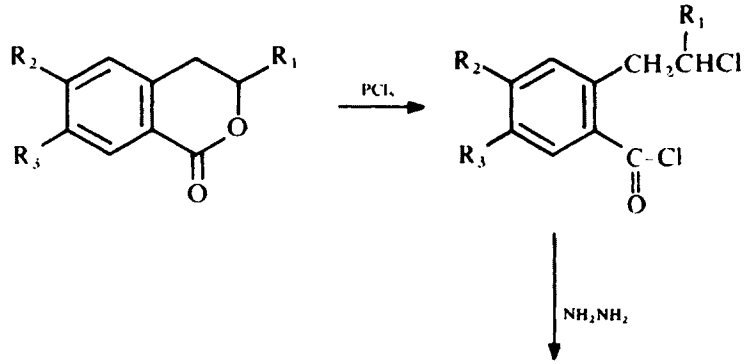


(90)



157

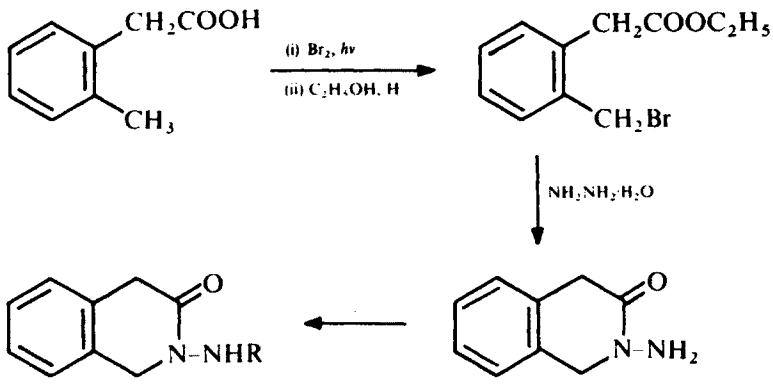
The synthesis of several 2-amino-1,2,3,4-tetrahydroisoquinolones has been achieved involving hydrazine or phenylhydrazine as a ring-closing reagent. Some 1- (**158**) and 3-(**159, 160**) isoquinolones and 1,3-diisoquinolones (**161**) are shown an examples (Eqs. 91–94[114-117]).



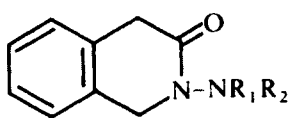
(91)

$R_1 = H; CH_3$
$R_2 = H; OCH_3$
$R_3 = H; CH_3; OCH_3; Cl; NO_2; NH_2; OH$

158

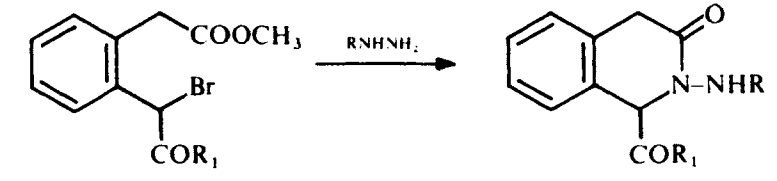


(92)



159

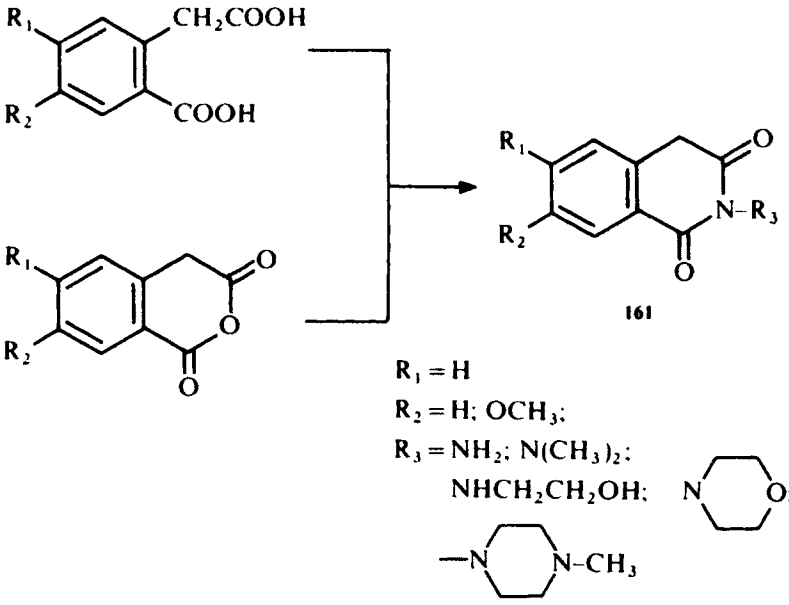
$R = H; CH_3; COCH_3; COC_6H_5; COC_6H_3Cl_2; SO_2C_6H_5; CONH_2; CONHC_6H_5; =CHC_6H_5; =CHC_6H_3Cl_2$
$R_1 = CH_3$
$R_2 = CH_3; SO_2C_6H_5$



160 (93)

$R = H; C_6H5$

$R_1 = OCH_3; NH_2$



161 (94)

$R_1 = H$

$R_2 = H; OCH_3;$

$R_3 = NH_2; N(CH_3)_2;$

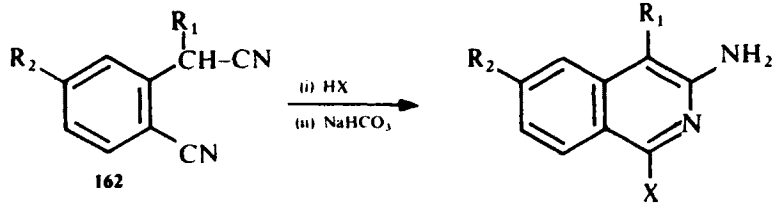
$NHCH_2CH_2OH;$

IV. PREPARATION OF ISOQUINOLINES HAVING A BASIC GROUPING AT POSITION 3

A. 3-Aminoisoquinolines

Treatment of dinitriles of the type **162** under anhydrous conditions with hydrogen bromide or hydrogen iodide results in a high-yielding cyclization to produce 3-aminoisoquinolines **163**[118] (Eq. 95). The use of HCl in this procedure does not give the ring-closed product. Adaptation of this excellent synthesis to the preparation of a wide variety of 3-aminoisoquinolines has been reported[118-121] (Eq. 95).

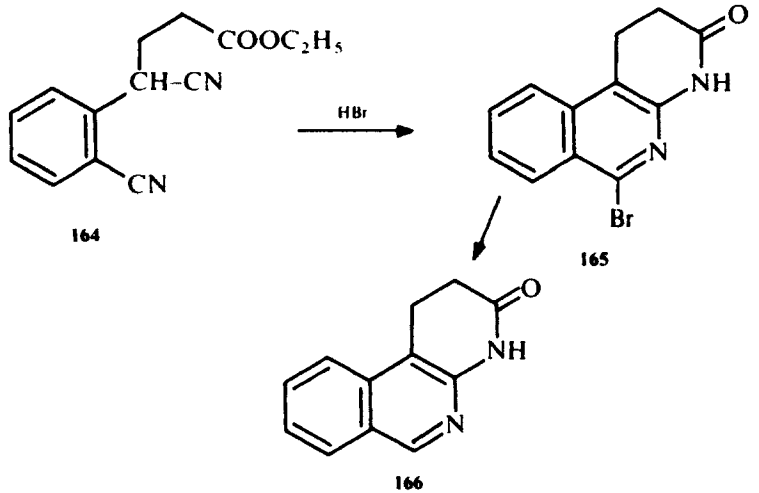
If R_1 in Eq. 95 is a propionic ester moiety **164**, a 1,8-naphthyridine derivative **165** is obtained, from which the bromine can be readily removed by hydrogenation to **166**[118] (Eq. 96).



162 163

$R_1 = H; CH_3; C_2H_5;$
$CH_2C_6H_5; CH_2CH_2C_6H_5;$
$C_6H_44NH_2; C_6H_42NH_2; C_6H_4NHC_2H_5$
$R_2 = H; OCH_3$
$X = Br; I$

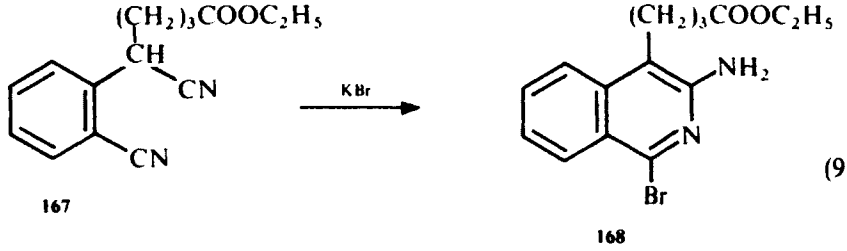
(95)



164 165 166

(96)

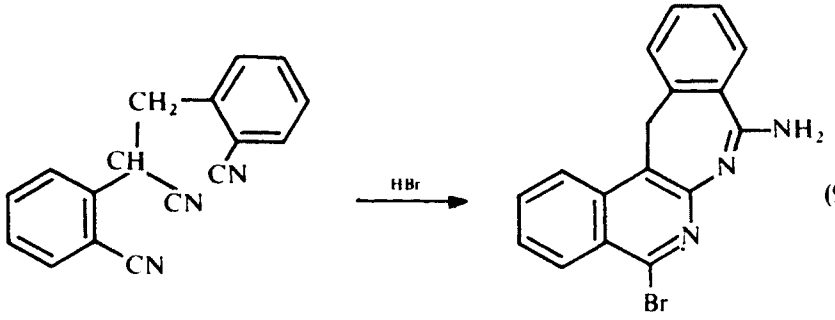
In view of this, it is surprising that the successful closure (**168**) of butyrate esters at position R_1 (**167**) has been reported[121] (Eq. 97).



167 168

(97)

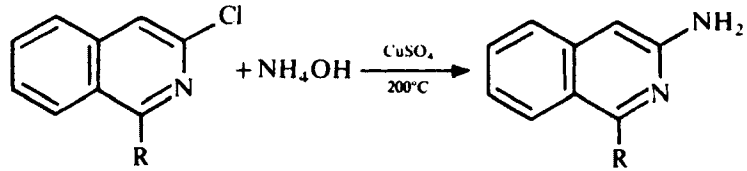
This synthesis has been adapted for the preparation of the benzoisoquinoline azepine derivative **169**[118] (Eq. 98).



(98)

169

The amination of 3-chloroisoquinolines (Eq. 99) over copper catalysts may be used as an approach for the synthesis of 3-aminoisoquinolines.[122] This procedure has also been adopted for the preparation of ^{15}N analogs.[123]



(99)

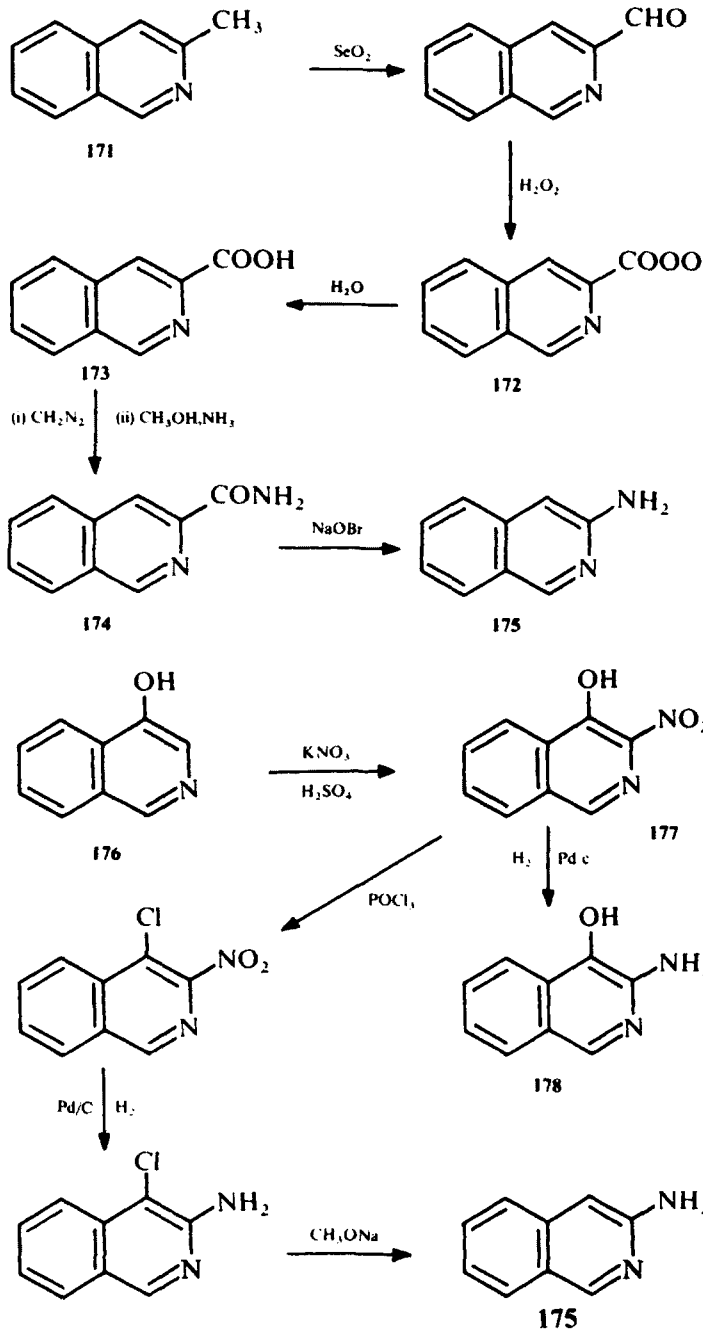
170 R = H, CH_3

1-Methyl-3-aminoisoquinoline is unexpectedly obtained when R grouping in **170** is $-CH_2CONHR$.[122] The amination of 3-chloroisoquinoline (**170**, R=H), using potassium amide in liquid ammonia, gives satisfactory yields of **93** (R = H). The amination occurs by addition of the nucleophile and ring-opening and ring-closure mechanisms (ANRORC).[6]

Prior to the development of Johnson's procedure,[118] several indirect routes to the 3-aminoisoquinolines were used. 3-Methylisoquinoline **171**, for example, may be oxidized in two stages to the peracid **172**, from which isoquinoline-3-carboxylic acid **173** is obtained. Formation of the amide **174** is followed by Hofmann degradation to produce the desired 3-aminoisoquinoline **175**[124, 125] in fair overall yield (Eq. 100).

Nitration of 4-hydroxyisoquinoline **176** occurs very readily at the 3 position of the isoquinoline ring (**177**), probably due to the + tautomeric effect of the hydroxyl group. Reduction of the 3-nitro grouping readily produces the amine **177** (Eq. 101), which itself is not stable, but can be isolated in a stable form as the salt or the triacetyl derivative.[126] Chlorination ($POCl_3$) of **177** readily occurs at the 4 position, which on subsequent reduction and boiling with sodium methoxide removes the 4-hydroxyl grouping, yielding 3-aminoisoquinoline **175**[126] (Eq. 101).

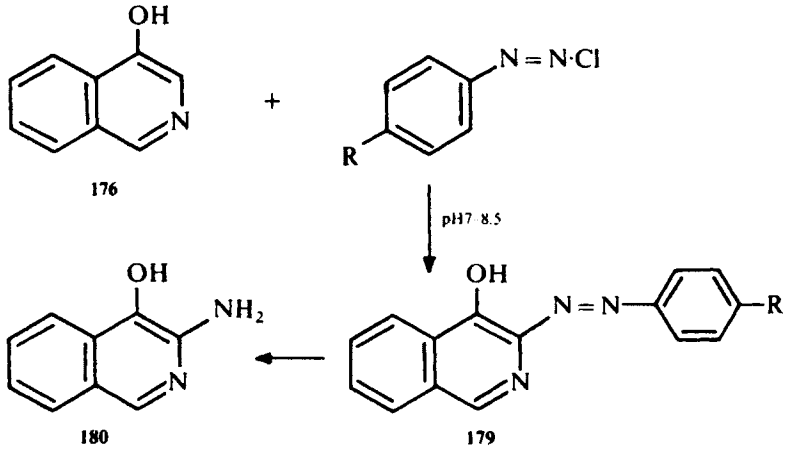
4-Hydroxyisoquinoline **176** has been employed in an alternate synthesis of 3-amino-isoquinolines by coupling with several *p*-substituted phenyl diazonium salts to yield the corresponding 3-diazonium isoquinoline **179**[127] (Eq. 102).



(100)

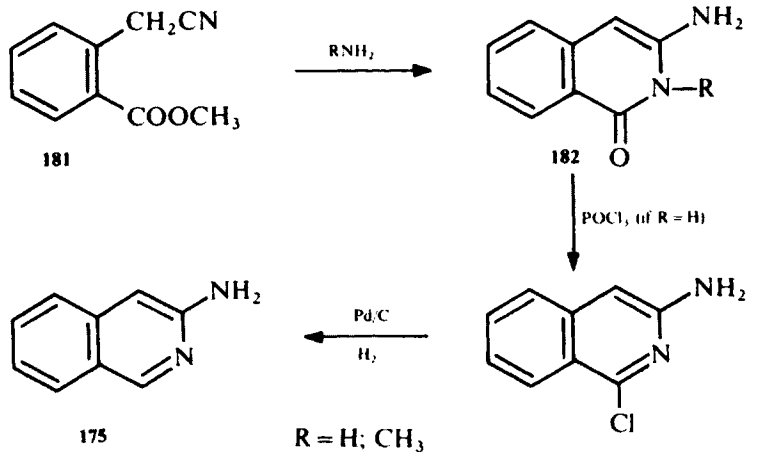
(101)

Stannous-chloride reduction readily affords the 3-aminoisoquinoline **180**. A two-molar quantity of the diazonium salt (Eq. 102) results in substitution at both the 1 and 3 positions of the 4-hydroxyisoquinoline.



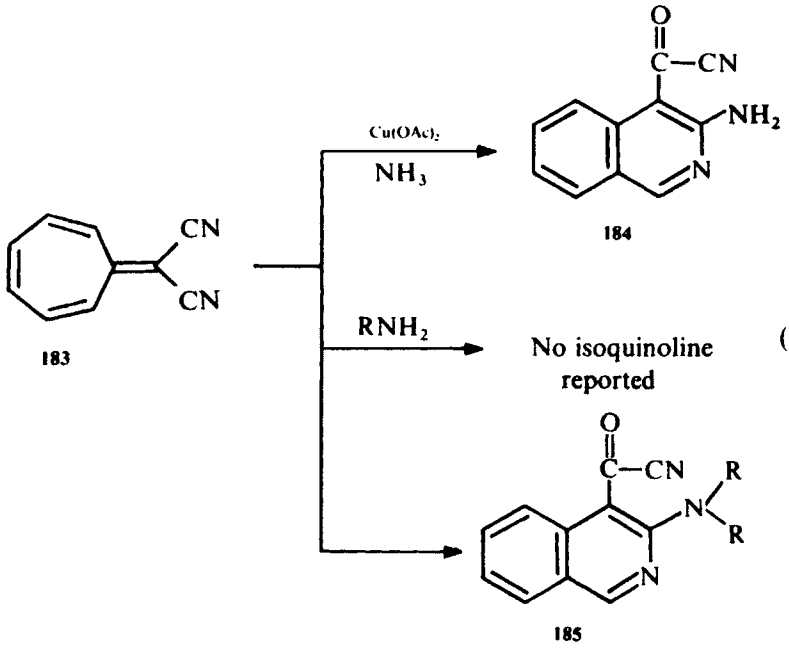
(102)

The ring closure of methyl *o*-cyanomethylbenzoates **181** on treatment with primary amines yields 3-aminoisoquinolin-1-ones **182**.[19] Subsequent chlorination with phosphorus oxychloride and dehalogenation over palladium on charcoal provides **175** (Eq. 103).

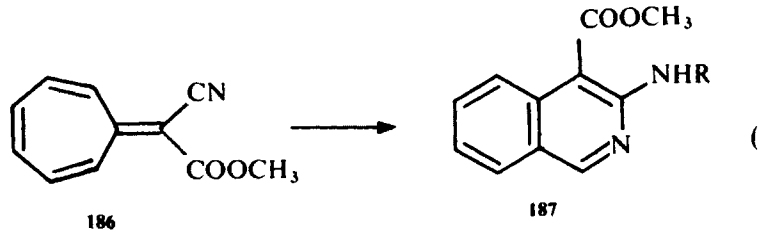


(103)

Oxidative aminations of substituted heptafulvenes to yield 3-aminoisoquinolines have been reported by Kikuchi.[128] The reaction of 8,8-dicyanoheptafulvene **183** with ammonia in the presence of copper(II) acetate, and with dimethylamine and various *N*-heterocyclic secondary amines with copper(II) acetate, yields the corresponding 3-aminoisoquinoline-4-carbonitriles **184** and **185** (Eq. 104). However, similar reactions with primary amines yield substituted cycloheptapyrroles.

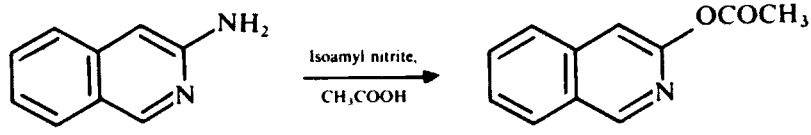


Substituted 3-aminoisoquinolines **187** may be obtained in 20–50% yield from primary amines under similar conditions, using 8-cyano-8-methoxycarbonyl-heptafulvene **186** (Eq. 105).



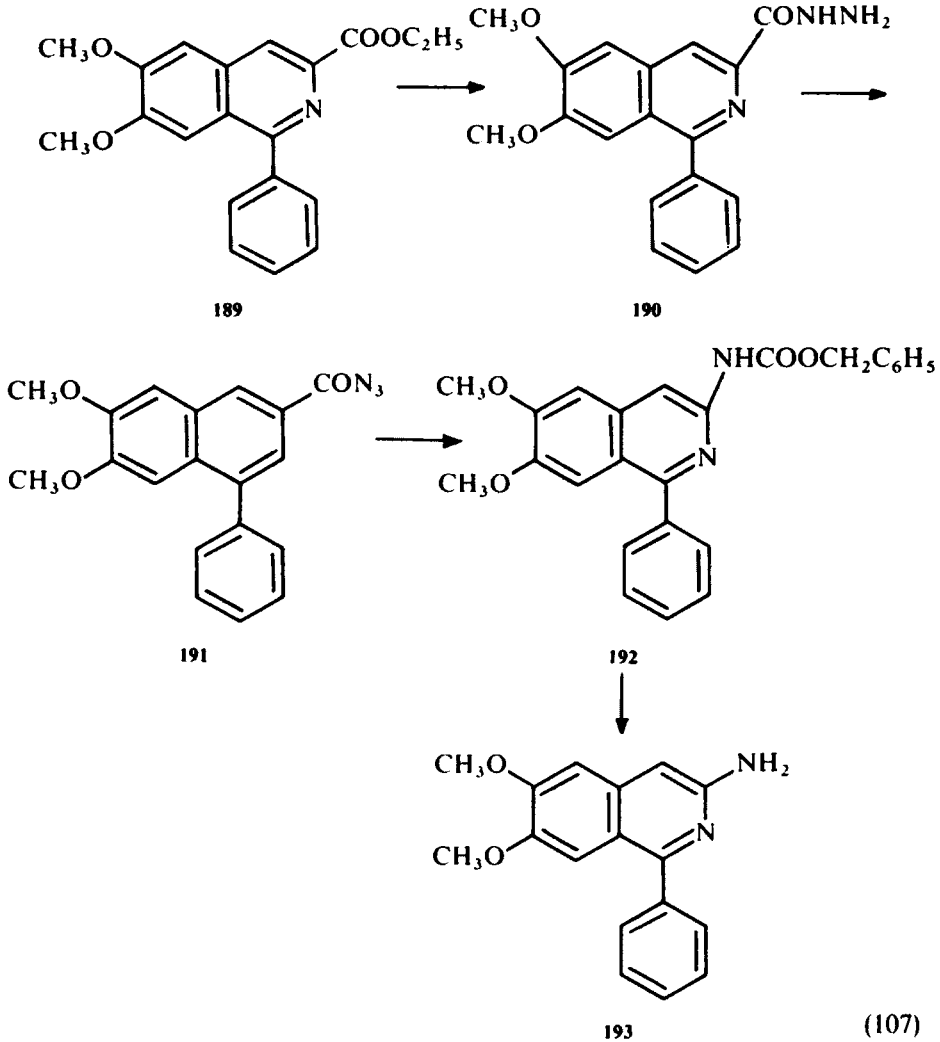
The 3-aminoisoquinoline cation (pK_a 5.05) has been shown by UV studies to essentially correlate with the neutral species of 3-isoquinolone.[129] Bromination and thiocyanation of 3-aminoisoquinoline occurs readily at the 4 position.[118,130] Diazotization of the 3-amino grouping of **175** occurs as expected, from which the 3-haloisoquinoline can be obtained in moderate yields by the usual procedures.[131–133] Isolation of 3-acetoxyisoquinoline **188** in good yield occurs by treatment of **175** with isoamylnitrite in acetic acid, a rare example of the transformation of an aryldiazonium acetate (or its tautomer) to the corresponding phenol acetate[133] (Eq. 106).

The substituted 3-aminoisoquinoline **193** may be prepared from the corresponding 3-isoquinoline ethyl carboxylate **189** by formation of the hydrazide **190** and azide **191**, which is converted by Curtius degradation to the benzylurethane



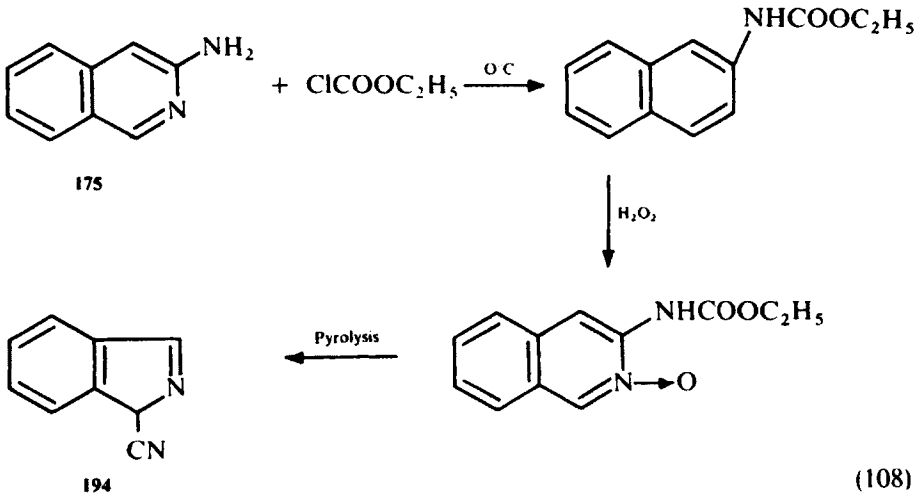
175 188 (106)

192. The amine **193** may be obtained from **192** by acid hydrolysis or catalytic hydrogenation over palladium on charcoal[134] (Eq. 107).



189 190 191 192 193 (107)

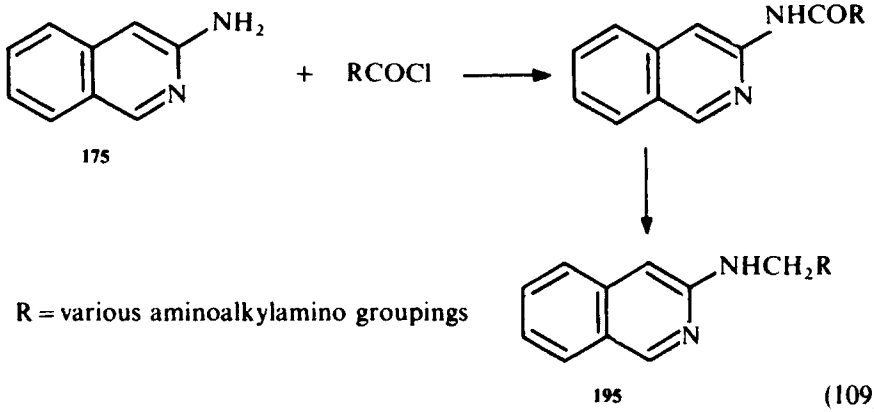
The ethoxycarbonylation of **175**, by way of ethylchloroformate treatment, has been studied by Brown and Smith[136] during some investigations on heteroaryl nitrenes; ring contraction to form 1-cyanoisoindoles **194** occurs on pyrolysis (Eq. 108).



(108)

B. 3-Alkylaminoisoquinolines

A series of variously substituted 3-alkylaminoisoquinolines **195** as potential antimalarials have been prepared by the treatment of 3-aminoisoquinoline with the appropriate acyl halide, followed by reduction (lithium aluminum hydride, diborane)[119] (Eq. 109). In most instances, additional heteroatoms were incorporated in the alkyl side chain.

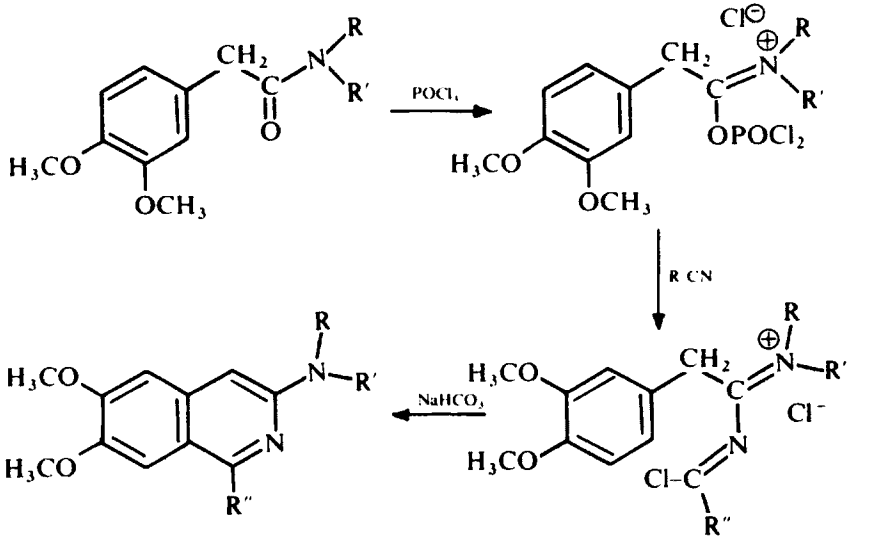


R = various aminoalkylamino groupings

(109)

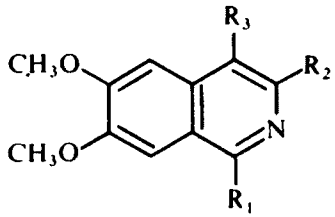
The reactions outlined in Eq. 110 facilitate the synthesis of several variations in substitution of the 3-amino function.[137] Table IV. 1 summarizes some examples that have been prepared.

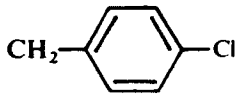
3-Morpholino- (**196**, **197**) and 3-piperidinoisoquinolines (**198**) may also be prepared from the parent isoquinoline under the oxidative conditions shown in Eq. 111.[138]

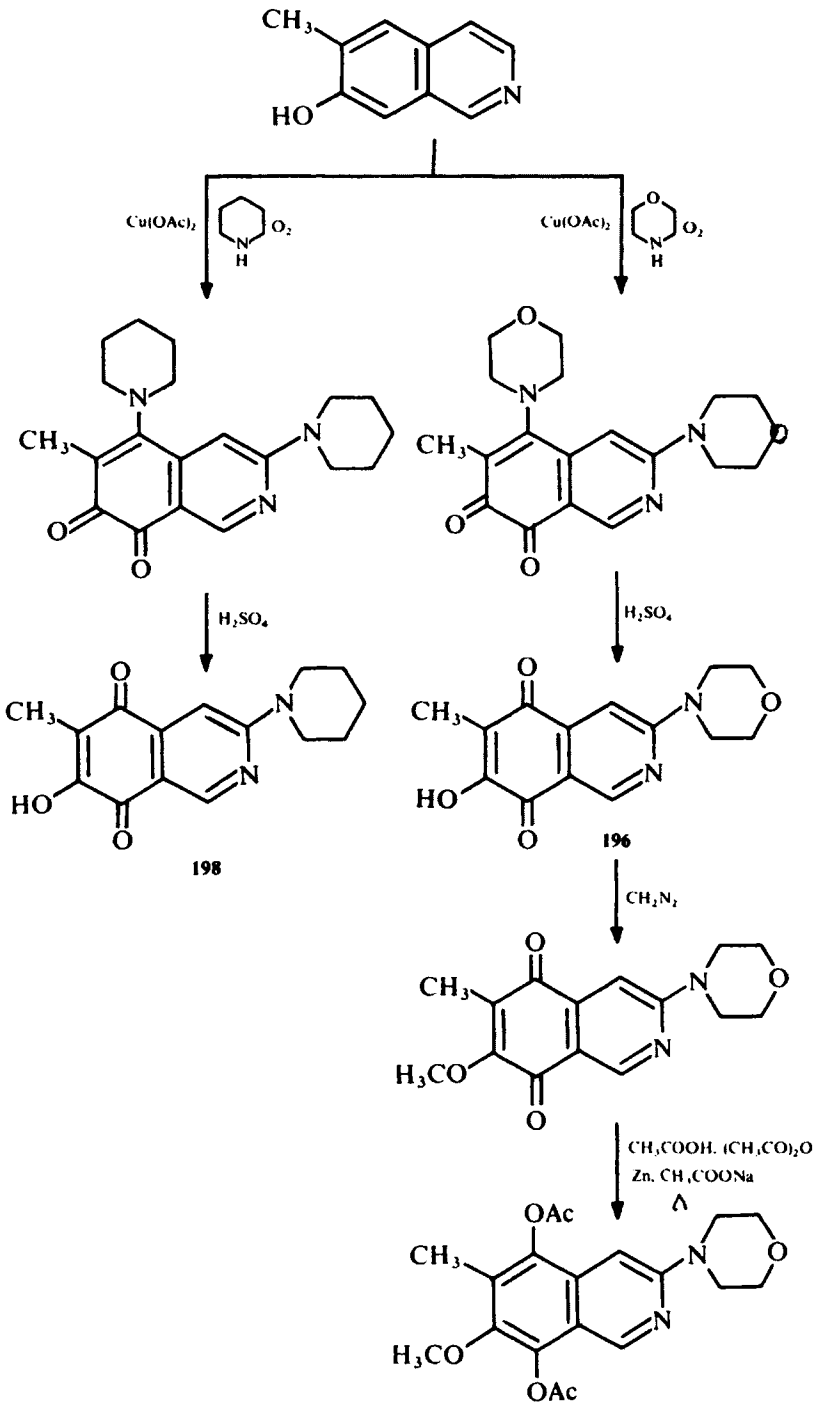


(110)

TABLE IV.1 8-3-Alkylaminoisoquinolines Prepared According to Eq. 110[137]

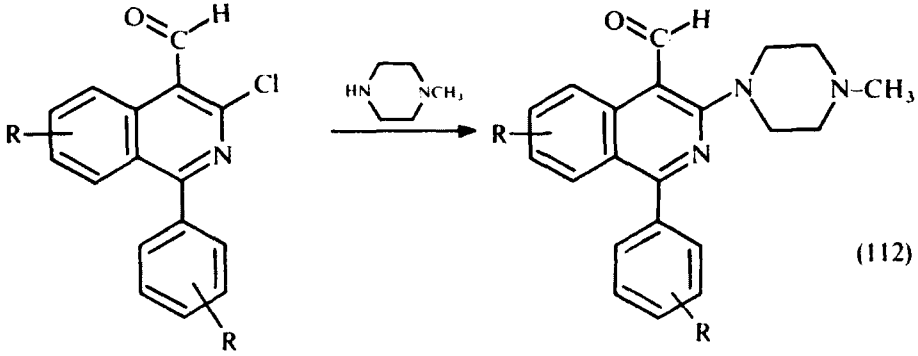


R_1	R_2	R_3
CH_3	$R(CH_3)CH_2CH_2OH$	H
CH_3	$N(CH_3)C_6H_5$	H
$(CH_2)_4Cl$	Morpholino	H
CH_3	Morpholino	H
	Morpholino	H
CH_2CH_3	Morpholino	C_6H_5
$N(CH_3)_2$	Pyrollidyl	H
CH_2CH_2Cl	Morpholino	H
$CH_2C_6H_5$	Morpholino	H
CH_3	$N(CH_3)_2$	H
CH_2CH_2Cl	$N(CH_3)_2$	H


CH3
HO
N
Cu(OAc)2
O2
H
Cu(OAc)2
O2
H
CH3
O
O
N
O
H2SO4
H2SO4
HO
198
196
CH2N2
H3CO
CH3COOH, (CH3CO)2O
Zn, CH3COONa
Δ
OAc
OAc
197

(111)

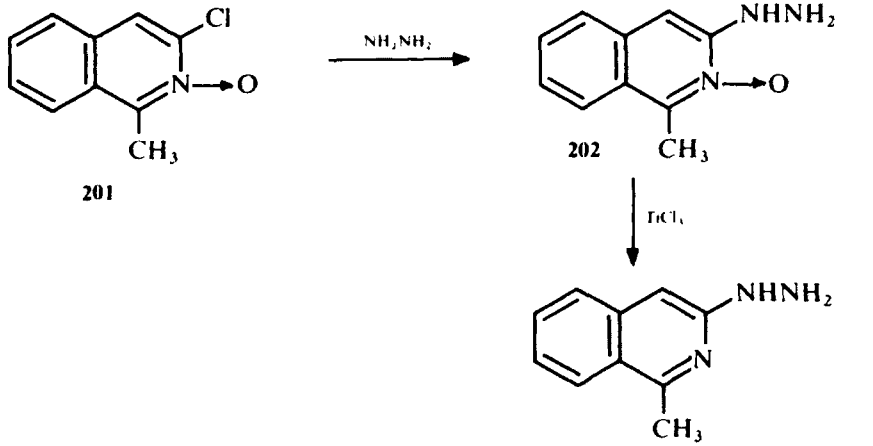
3-Piperazinoisoquinolines **200** may be prepared directly from the corresponding 3-chloroisoquinolines **199**[139] (Eq. 112).



199 **200** (112)

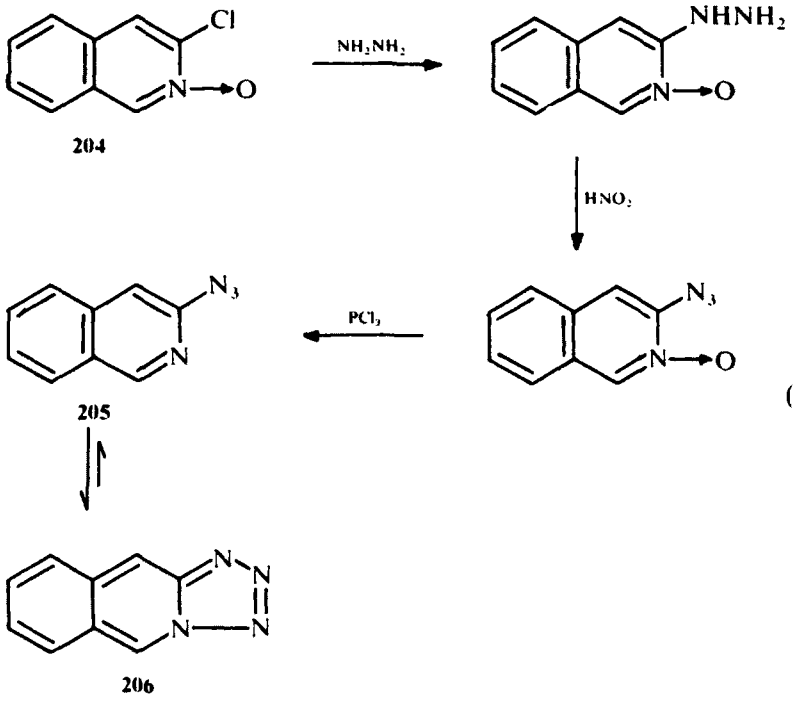
C. 3-Hydrazinoisoquinolines

The synthesis of the 3-hydrazinoisoquinoline **203** may be accomplished by the reaction of hydrazine with the corresponding 3-chloroisoquinoline *N*-oxide **201**[140] via the intermediary hydrazino *N*-oxide **202** (Eq. 113).



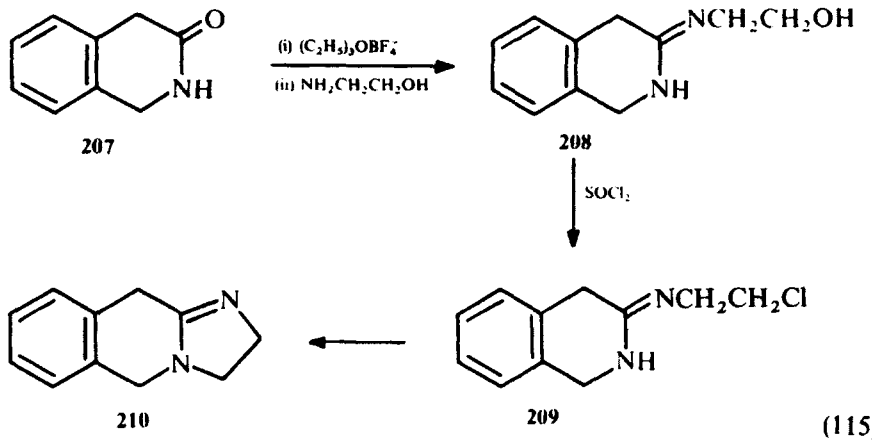
201 **202** **203** (113)

During a study of the preparation of 3-azidoisoquinoline **205** from 3-chloroisoquinoline *N*-oxide **204** (via its 3-hydrazino derivative), it was shown that the azido form **205** is dominant in solution, whereas the cyclic tetrazolo form **206** is dominant in the crystalline state. Nitrous acid treatment of 3-hydrazinoisoquinoline yields the corresponding azide[140] (Eq. 114).



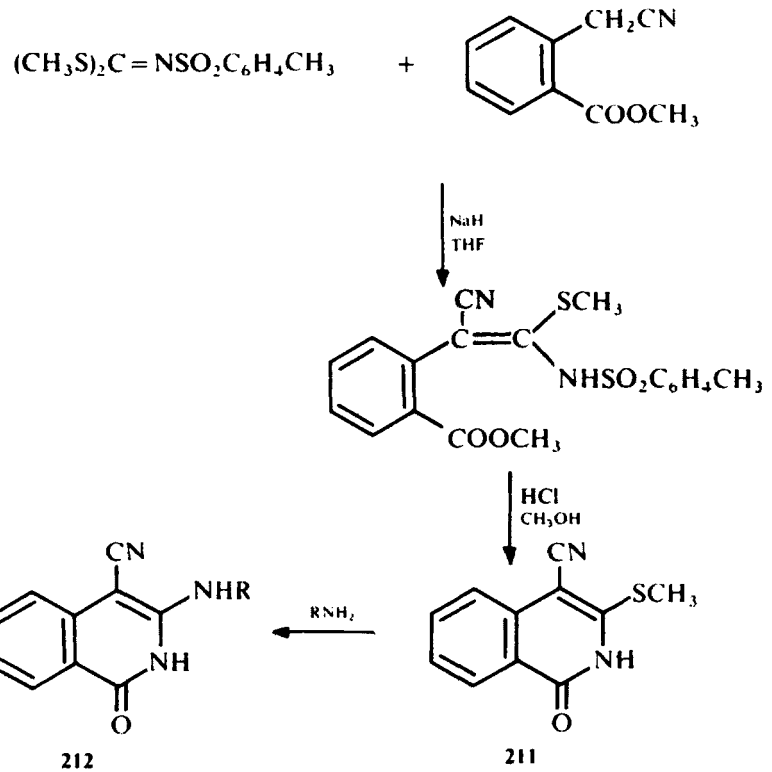
D. 3-Aminodihydroisoquinolines

1,4-Dihydroisoquinoline-3-one has been used for the synthesis of a 3-imino-isoquinoline **208** (Eq. 115) during the course of some studies on potential antihypertensive agents.[141] Treatment of the iosquinolin-3-one with triethyloxonium tetrafluoroborate, followed by ethanolamine, yields the 3-imino com-



pound **208**. Conversion to the chloro analog **209** by reaction with thionyl chloride gives a product which may be cyclized to an imidazoisoquinoline derivative **210**.

Tominaga[142] has described the synthesis of some substituted 3-amino-1,2-dihydroisoquinolinones **212** by replacement of the 3-thiomethyl grouping of the corresponding isoquinolone **211** (Eq. 116).



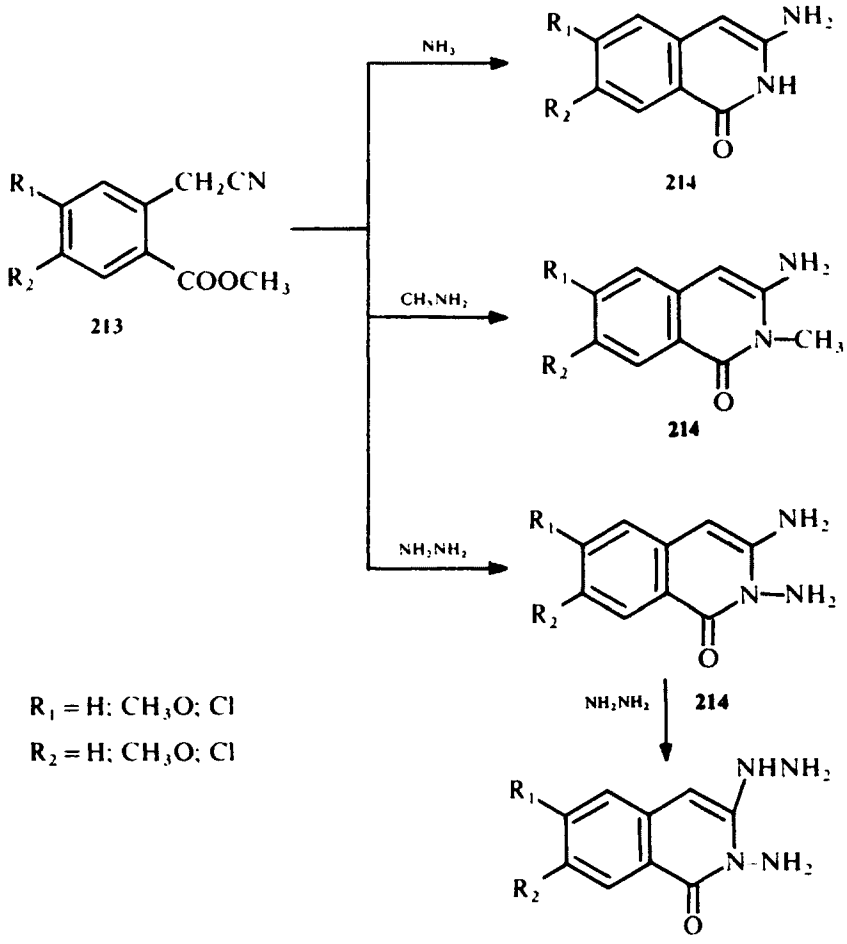
212 **211**

$R = CH_2CH_2OH;\ CH_2C_6H_5$ (116)

Methyl (2-cyanomethyl) benzoates[212] may be reacted with aqueous ammonia, hydrazine, methylamine, or other substituted primary or secondary amines to yield the corresponding 3-amino **214** (or 3-hydrazino **215**) 1-isoquinolones[143] (Eq. 117).

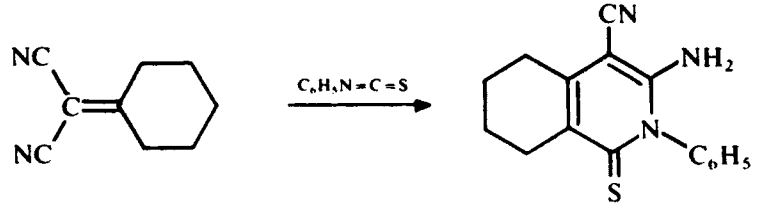
E. 3-Amino-5,6,7,8-Tetrahydroisoquinolines

A series of reactions of a 6-amino-thiopyranthione **216** with several bases has been reported by Gewald et al.[144] The corresponding 3-aminoisoquinoline derivatives (**217**–**223**) are obtained as products (Scheme 3). The treatment of



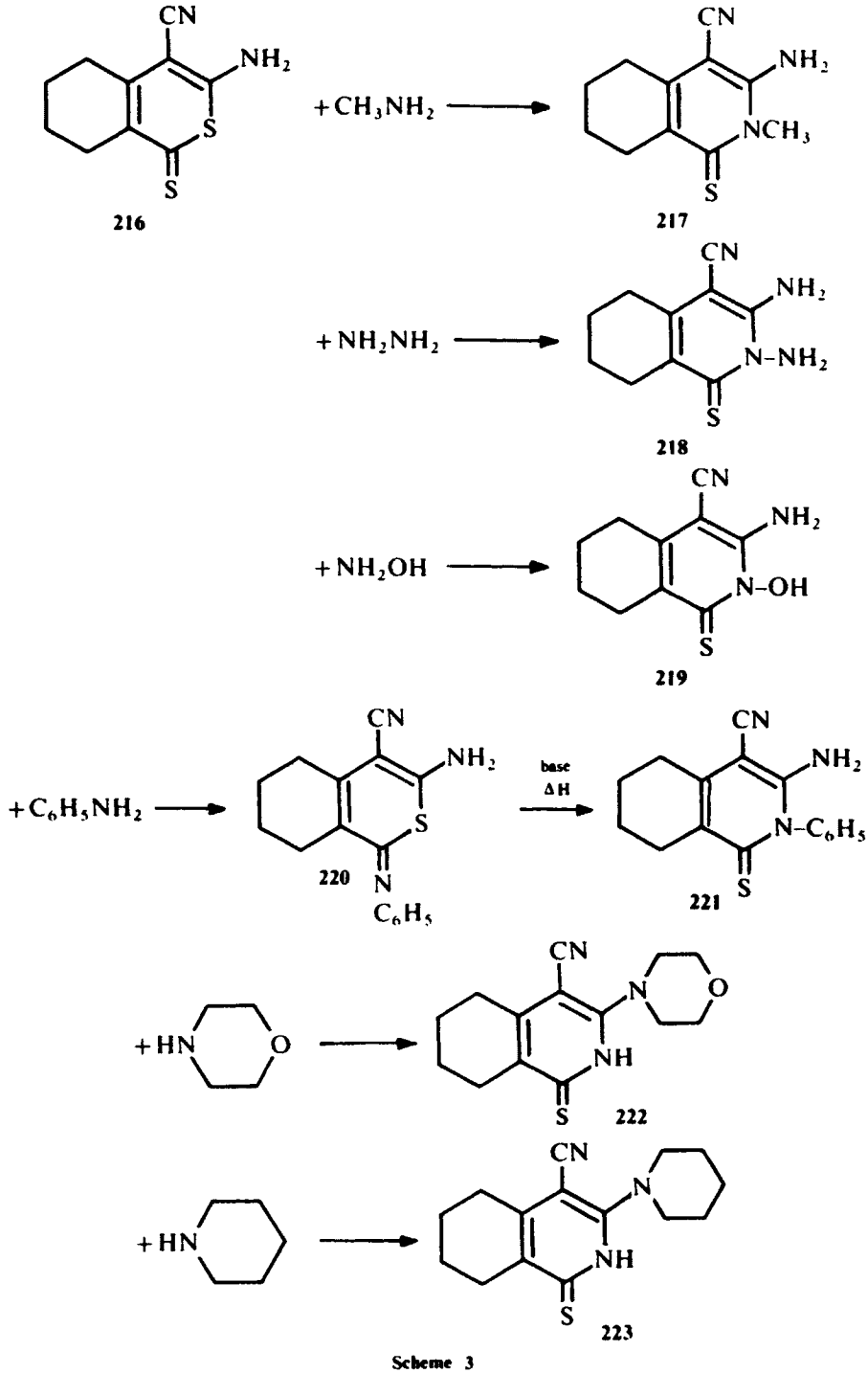
(117)

variously substituted alkylidenemalononitriles **224** with phenyl isothiocyanate yields a 3-aminoisoquinolin-1-thione **225** (Eq. 118).[145]



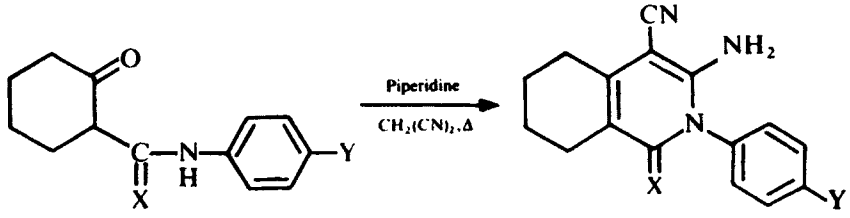
(118)

Several modifications of the 1-thione grouping have been made, in addition to a similar study with the oxygen analog of **225** (prepared by employing phenylisocyanate in Eq. 118 in place of the isothiocyanate[145]).


CN
NH2
S
S
216
+CH3NH2
NCH3
217
+NH2NH2
N-NH2
218
+NH2OH
N-OH
219
+C6H5NH2
220
C6H5
base
ΔH
N-C6H5
221
+HN
O
NH
222
223

Scheme 3

A route for the synthesis of 1-oxo-(or thio)-2-phenyl-3-amino-4-cyano-1,2,5,6,7,8-hexahydroisoquinolines **226** has been reported by Bogdanowicz–Szured.[146] The reaction is believed to involve enamine formation, reaction of the enamine with malononitrile, elimination of the amine, and cyclization. The reaction may be carried out in one step (Eq. 119).

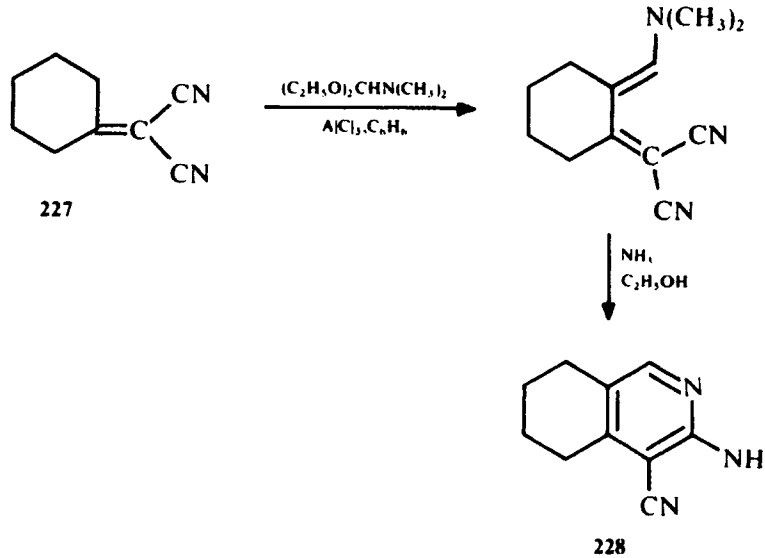


226

X = O; S

Y = H; CH_3; Cl; Br (119)

3-Amino-4-cyano-5,6,7,8-tetrahydroisoquinoline **228** may be synthesized from dinitrile **227** according to procedures outlined by Granik et al.[147] (Eq. 120).

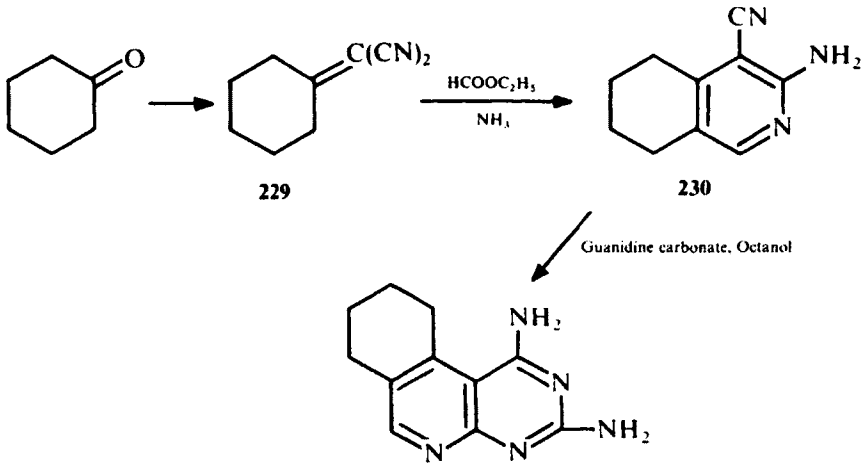


227

228

(120)

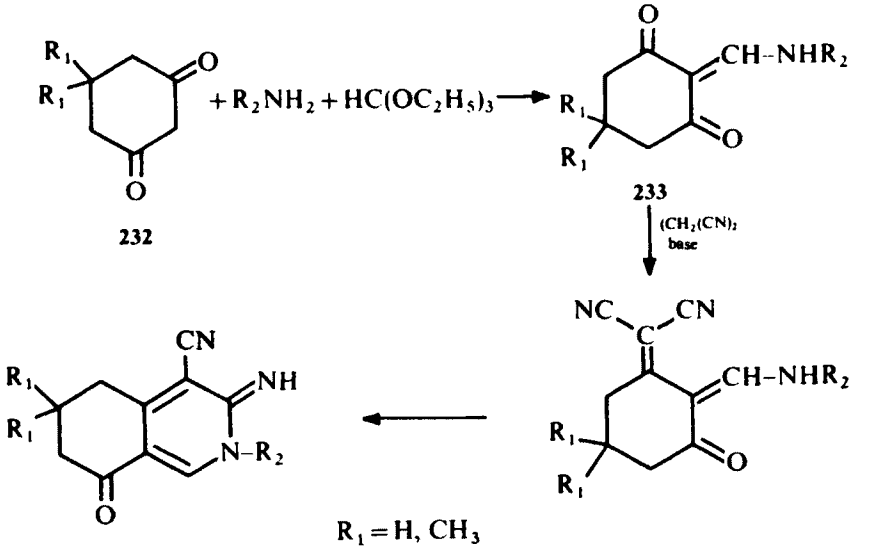
A novel approach to the preparation of isoquinolines substituted at the 3 position with basic groupings is reported in recent studies of the synthesis of 3-imino- and 3-aminoisoquinolines, saturated in the nonheterocyclic ring, from various cyclohexanones. Cyclohexylidene malononitrile **229** (produced by treating cyclohexanone with malononitrile), cyclizes on exposure to ethyl formate and ammonia, yielding the 3-amino-5,6,7,8-tetrahydroisoquinoline derivative **230**[148] (Eq. 121).



(121)

Direct annelation of **230** with guanidine carbonate in octanol produces the pyrimidine derivative **231**, a potential folate antagonist.[148]

An alternate procedure for the preparation of substituted 3-iminohexahydroisoquinolines **234** utilizes the reaction of 1,3-cyclohexanediones **232** with aromatic amines and triethyl formate. The intermediary enaminoketone **233** is treated with malononitrile and either piperidine or potassium hydroxide; cyclization then occurs to produce the 3-imino-2,3,5,6,7,8-hexahydroisoquinoline **234**[149] (Eq. 122).



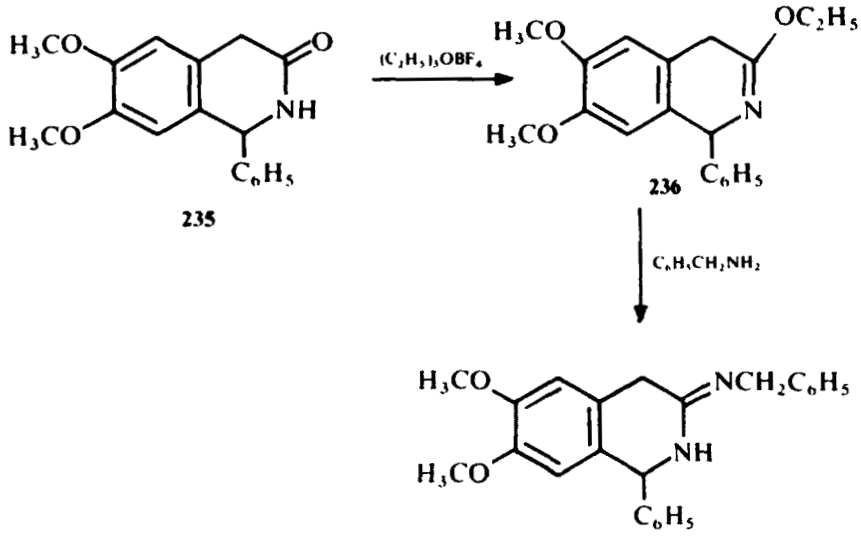
$R_1 = H, CH_3$

$R_2 = C_6H_5$; $pNO_2C_6H_4$;

$pCH_3C_6H_4$; $3,5Cl_2C_6H_3$

(122)

The 3-iminoisoquinoline derivative **237** may be prepared from the isoquinolone **235** via the lactim ether **236**. Treatment of the lactim ether with a primary amine enables substitution of the corresponding imine at the 3 position [73] (Eq. 123).

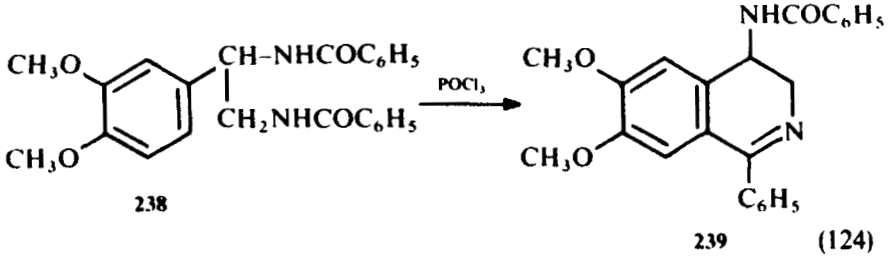


(123)

V. PREPARATION OF ISOQUINOLINES HAVING A BASIC GROUPING AT POSITION 4

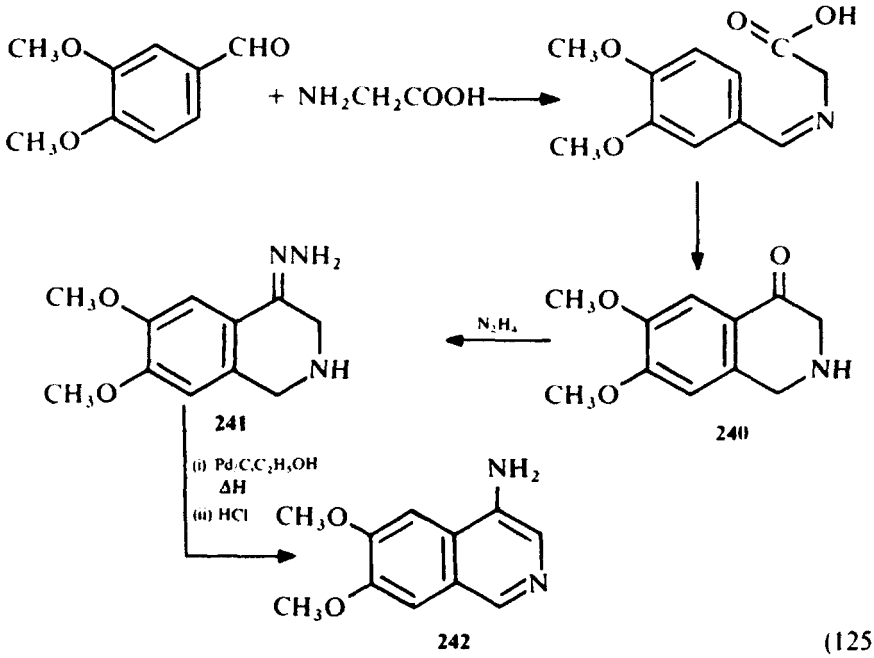
A. 4-Aminoisoquinolines

Ring-closure reactions of the Bischler–Napieralski type may be used to prepare the difficult to access isoquinoline derivatives of this group. Substituted benzoyl urethanes **238**, on treatment with phosphorus oxychloride, ring close to produce 3,4,-dihydroisoquinolines substituted at the 4 position with an amino function (**239**)[150] (Eqn. 124).



(124)

The use of phosphorus pentoxide does not proceed as smoothly as does the phosphorus-oxychloride-catalyzed closure.[150] As an alternate procedure, the preparation of 4-isoquinolones **240**, followed by treatement with hydrazine hydrate, aromatization, and hydrolysis of the intermediary hydrazone **241**, results in good yields of the 4-aminoisoquinoline **242**[151] (Eq. 125).



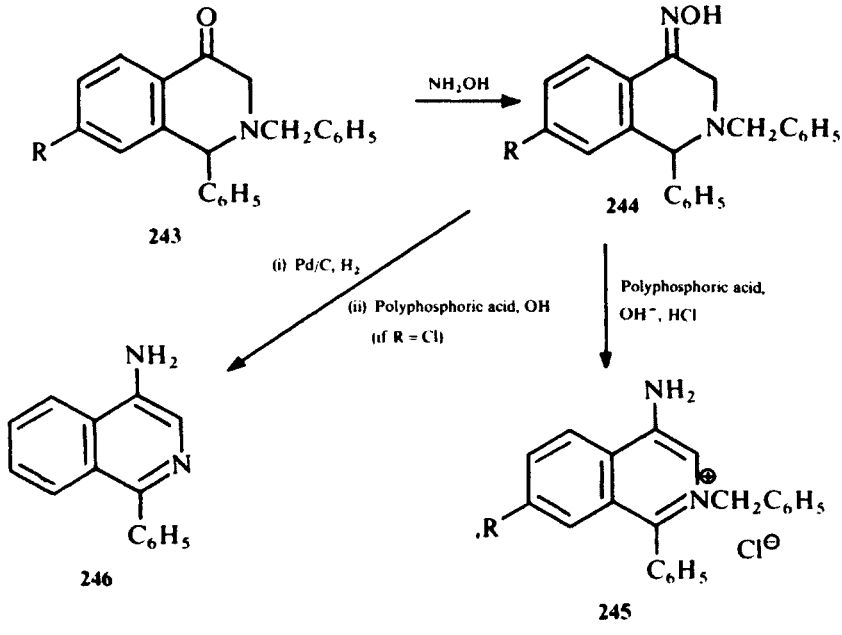
(125)

The polyphosphoric acid ring closure of the condensation product of glycine and 3,4-dimethoxybenzaldehyde provides an example of one approach for the synthesis of 4-isoquinolone **240**.[151] The use of 4-isoquinolones to prepare 4-aminoisoquinolines has also been reported by Fryer et al.[152] during studies on ring-expansion products (benzodiazepines) of isoquinolones. The oxime **244** of the 4-isoquinolone **243**, on treatment with polyphosphoric acid, gives the Schroeter rearranged product, as 4-aminoisoquinoline derivative **245** (Eq. 126). An alternate route yields **246** from **244**.

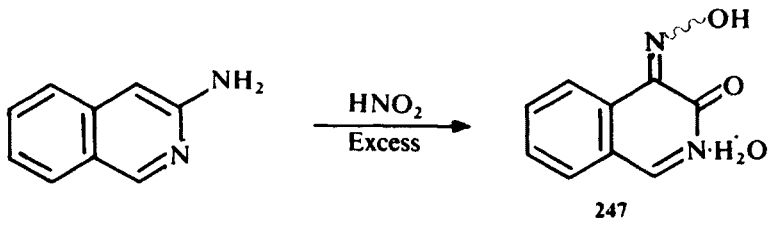
The treatment of 3-aminoisoquinoline with a threefold excess of nitrous acid yields 3,4-isoquinolinedione-4-oxime hydrate **247**[153] (Eq. 127). The potential of this oxime for conversion to the amine is apparent.

The most widely reported method for the synthesis of 4-aminoisoquinolines involves the treatment at high temperatures of 4-haloisoquinolines (**248**) (usually bromo) with ammonium hydroxide in the presence of cupric sulfate[1,5,154-158] (Eq. 128).

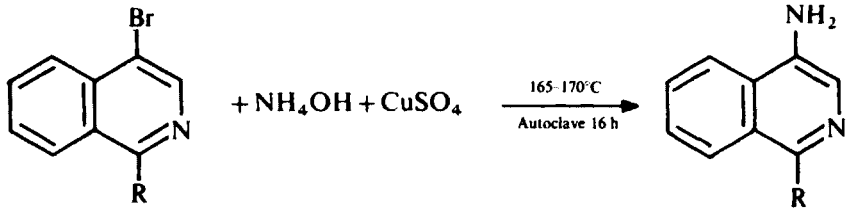
A small amount of the bisisoquinoline derivative **249** has been isolated in the case of the 1-ethoxy derivative.[155]



R = Cl; OCH_3 (126)

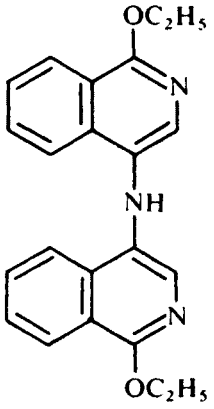


(127)

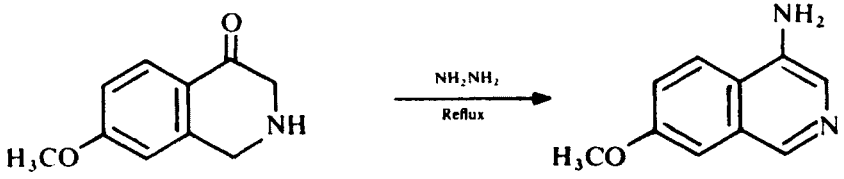


R = H; OC_2H_5 (128)

Hydrazine may be used to aromatize the 4-isoquinolone **250** and simultaneously introduce an amino grouping at the 4 position, producing fair yields of 4-amino-7-methoxyisoquinoline **251**[159] (Eq. 129).



249

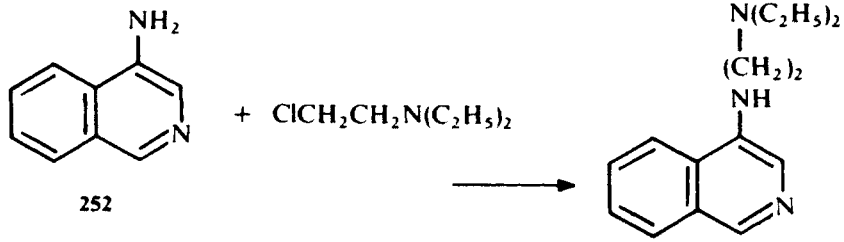


250 251

(129)

B. 4-Alkylaminoisoquinolines

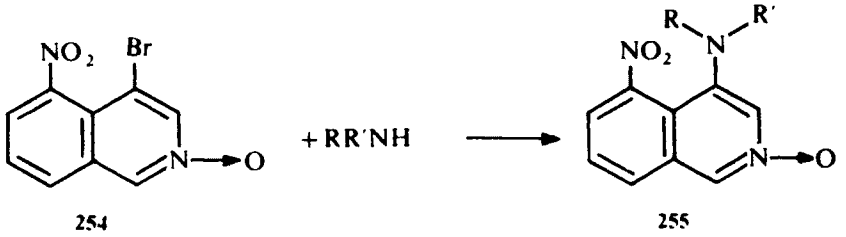
Substitution of the 4-amino grouping of **252** to form secondary amines proceeds normally on contact with alkyl halides; for example, high yields of 4[[2-(diethylamino)ethyl]amino]-isoquinoline **253** have been obtained [160] (Eq. 130).



252 253

(130)

Various heterocyclic and aliphatic amines react exothermically with 5-nitro-4-bromoisoquinoline *N*-oxide (**254**) in ethanol to give poor to moderate yields, depending on the base used, of the corresponding 4-aminoisoquinoline **255**[53] (Eq. 131). Under more drastic conditions (absence of solvent and heating under reflux), 5-nitro-1,4,-diaminoisoquinolines result.[53]



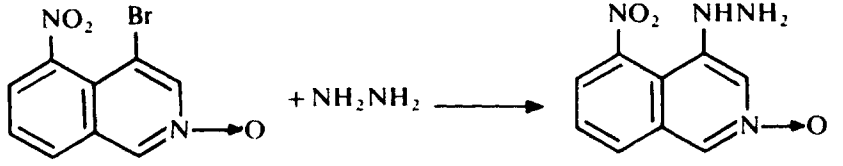
254 255

(131)

Several heterocyclic secondary amines may be used in Eqs. 131 and 132, including piperidine, pyrrolidine, morpholine, and *N*-methylpiperazine.[53]

C. 4-Hydrazinoisoquinolines

Under the mild conditions noted for the general preparation of 4-alkylamino-isoquinolines, the reaction of hydrazine with 5-nitro-4-bromoisoquinoline *N*-oxide **254** produces the 4-hydrazine analog **256** in fair yields (62%)[53] (Eq. 132).



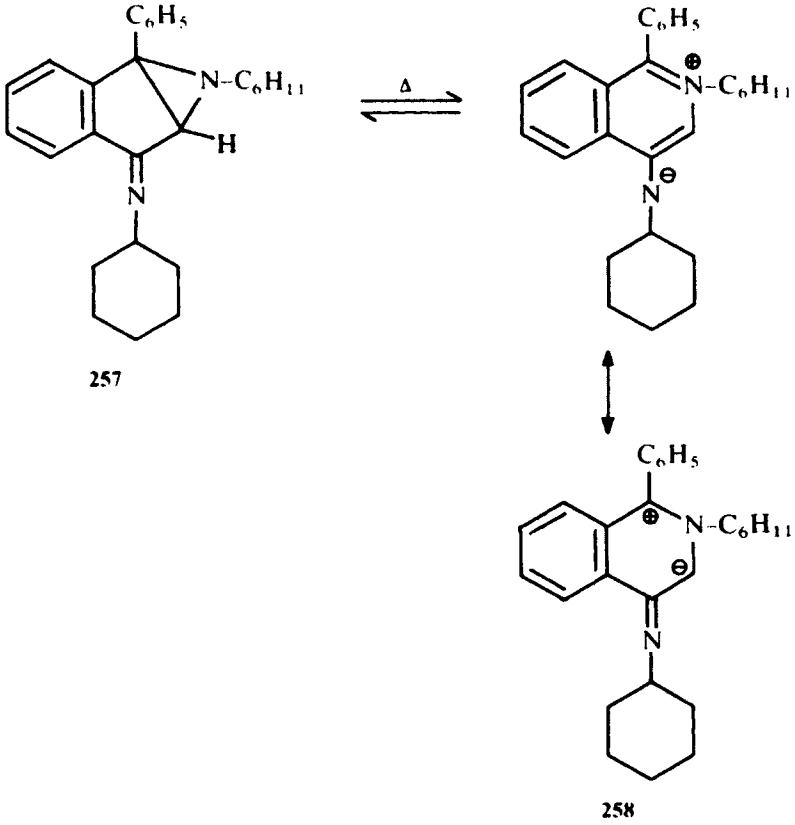
256 (132)

Diazotization of **252**, followed by stannous-chloride reduction of the diazonium salt, provides a straightforward synthesis of 4-hydrazinoisoquinoline.[161]

D. 4-Iminoisoquinolines

4-Iminoisoquinolines have been studied during some thermally disallowed valence tautomerizations of 1-cyclohexyl-6(cyclohexylimino)-1a-phenylindano [1, 2-b] aziridine (**257**) to yield the isoquinolinium 4-imine **258**[162] (Eq. 133). Solutions of the aziridine (**257**) in xylene or toluene at 135°C produce an intense purple color, due to the imine **258**, which fades upon exposure to sunlight or in the presence of oxygen, peroxides, halogens, acids, or bases.

Although thermally forbidden, the valence tautomerization is aided by relief of the ring strain of the aziridine **257** and a gain in resonance energy by the imine **258**.



(133)

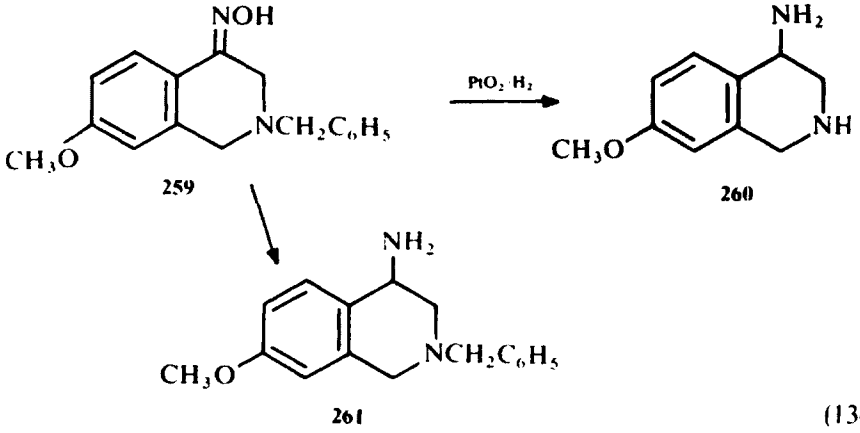
E. 4-Amino-1,2,3,4-Tetrahydroisoquinolines

The reduction of hydroxyimines (oximes) (e.g., **259**) over platinium oxide readily provides an approach for the synthesis of the corresponding amino derivatives, for example, **260**.[152] An alternate reduction of oxime **259** with lithium aluminum hydride allows the retention of the *N*-benzyl grouping, yielding 4-amino-2-benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinoline **261**[152] (Eq. 134).

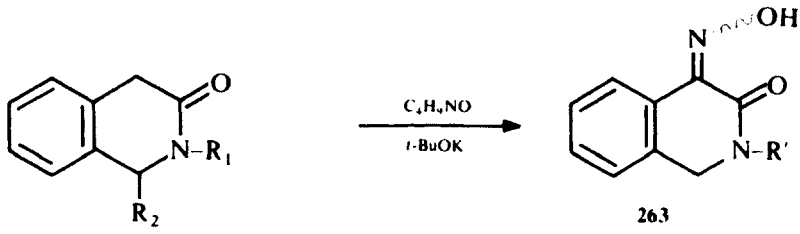
4-Hydroxyimino-1,4-dihydro-3(2H)-isoquinolinones **263** may be prepared by a one-step reaction of the corresponding 3-isoquinolone **262** with butyl nitrite in the presence of base[163,164] (Eq. 135).

Catalytic hydrogenations over platinium oxide, of various 4-aminoisoquinoline derivatives, have been used as a general procedure for the synthesis of the corresponding tetrahydro derivatives (Eq. 136).

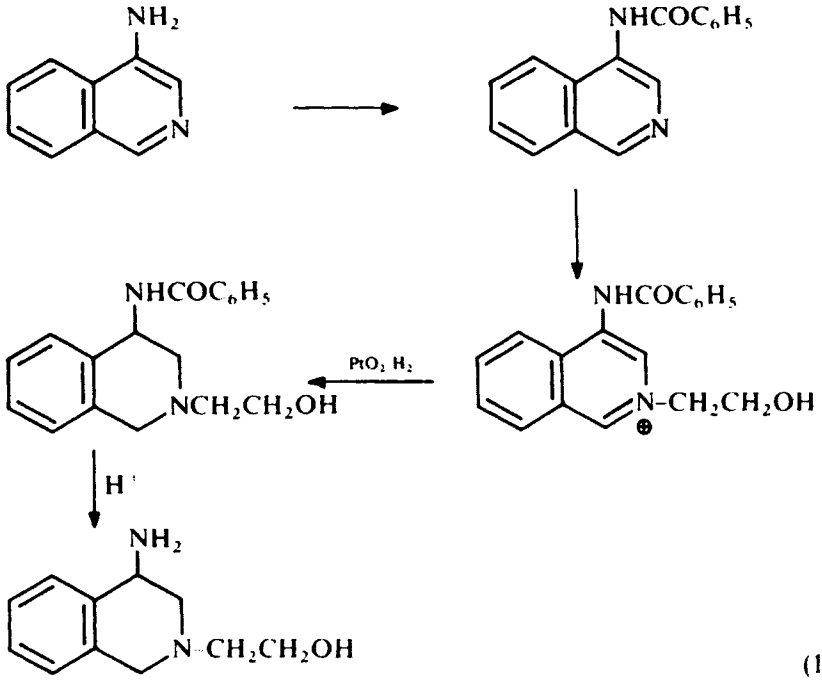
A one-stage reductive formylation of isoquinoline to 4-methylamino-1,2,3,4-tetrahydroisoquinoline (**264**) has been reported by Baxter and co-workers[165]


NOH
NCH2C6H5
CH3O
259
PtO2, H2
NH2
NH
CH3O
260
NH2
NCH2C6H5
CH3O
261

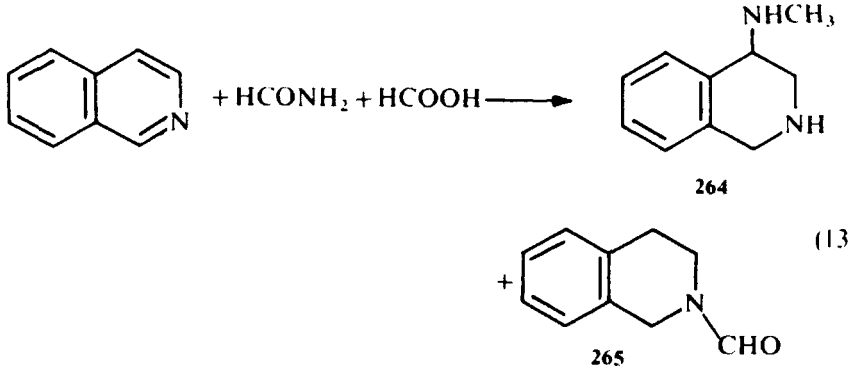
(134)


O
N–R1
R2
262
C4H9NO
t-BuOK
N
OH
O
N–R'
263

(135)


NH2
N
NHCOC6H5
N
NHCOC6H5
N–CH2CH2OH
PtO2, H2
NHCOC6H5
NCH2CH2OH
H+
NH2
N–CH2CH2OH

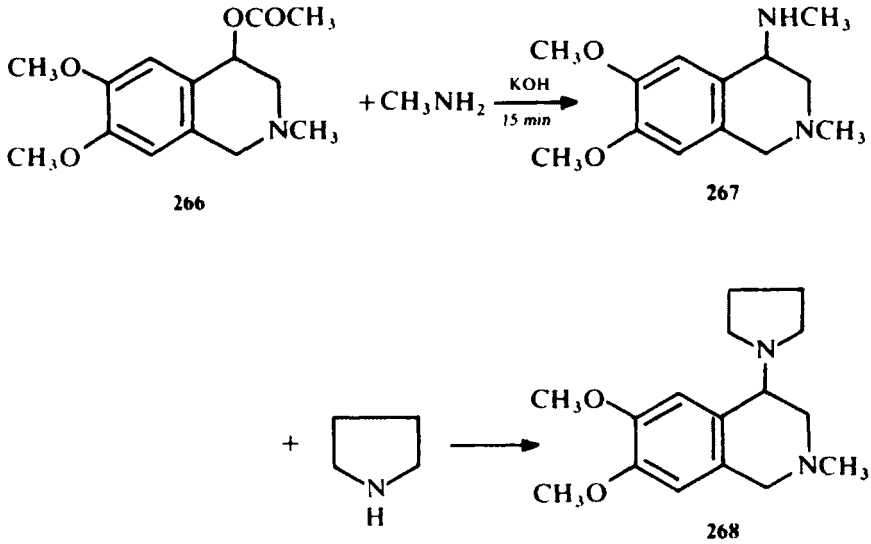
(136)



(137)

(Eq. 137). The anticipated *N*-formyl-1,2,3,4-tetrahydroisoquinoline **265** is isolated in addition to the desired **264**.

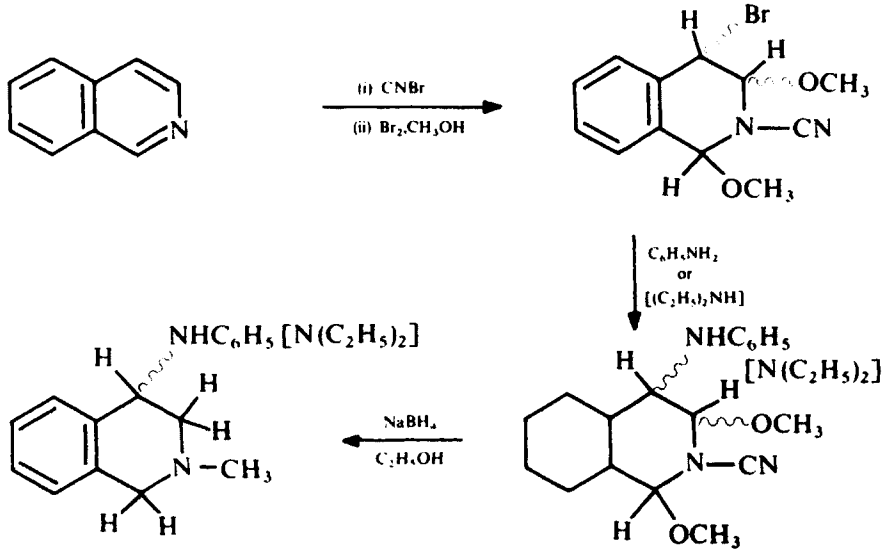
The attack of nucleophiles on 4-acetoxy-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (**266**) results in the rapid displacement of the 4-acetoxy grouping.[166] The synthesis of 4-methylamino- **267** and 4-pyrrolidinyl-1,2,3,4-tetrahydroisoquinolines **268** can be effected by this procedure[167] (Eq. 138).



(138)

A facile method for producing 4-anilino- (or diethylamino)-2-methyl-1,2,3,4-tetrahydroisoquinolines **269** in high yield from isoquinoline has been described by Sugiura and Hamada[168] (Eq. 139).

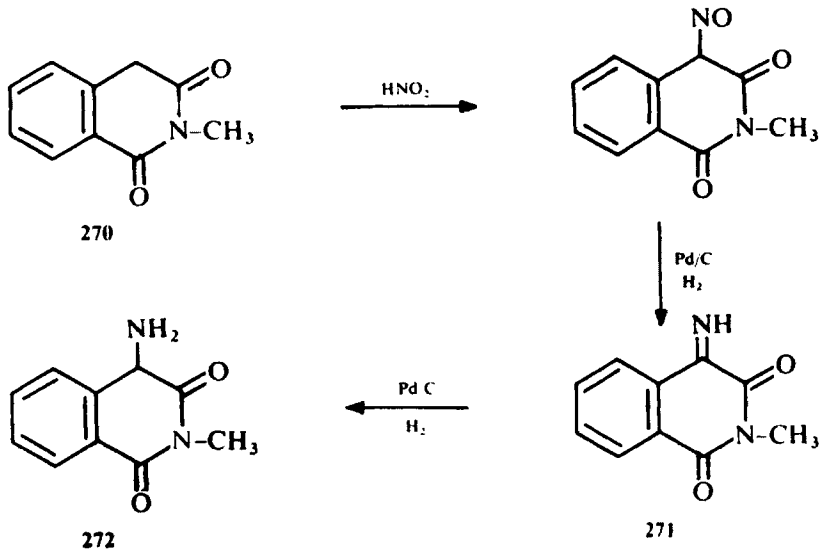
Nitrosation of the isoquinoline dione **270**, followed by careful catalytic reduction, yields 4-imino-2-methylisoquinoline-1,3(2H,4H)-dione **271**. This



269

(139)

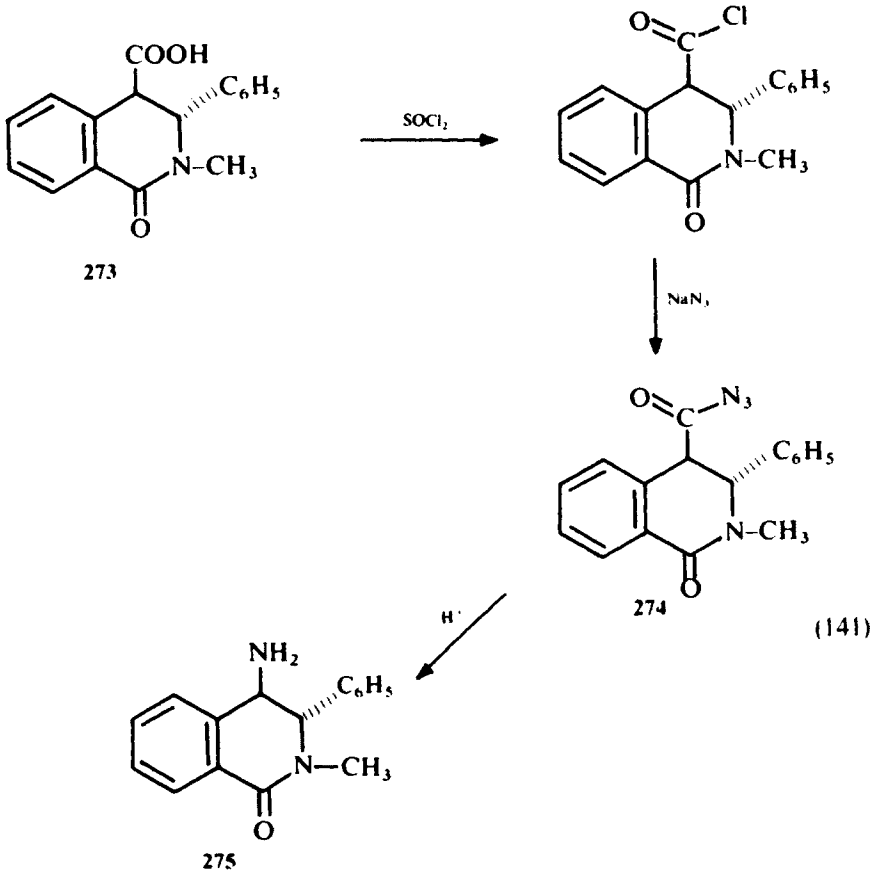
imino derivative provides ready access to the 4-amino compound **272** by hydrogenation[169] (Eq. 140).



270 271 272

(140)

The 3,4-dihydroisoquinolone-4-carboxylic acid **273** may be converted to the corresponding 4-aminoisoquinolone **275** through a Curtius rearrangement of the intermediate azide **274**, as shown in Eq. 141.[170]

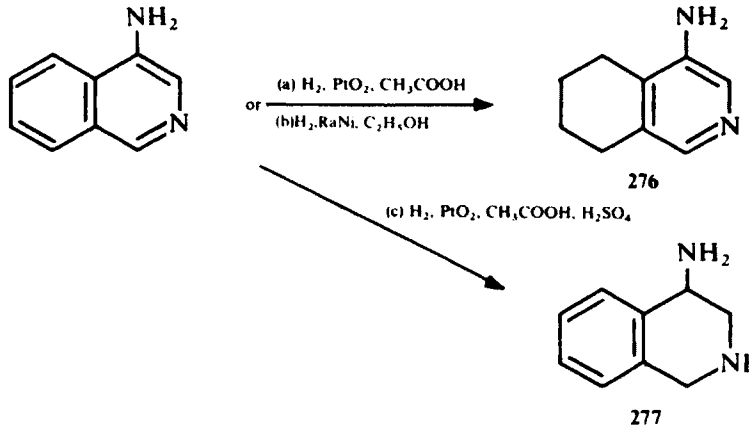


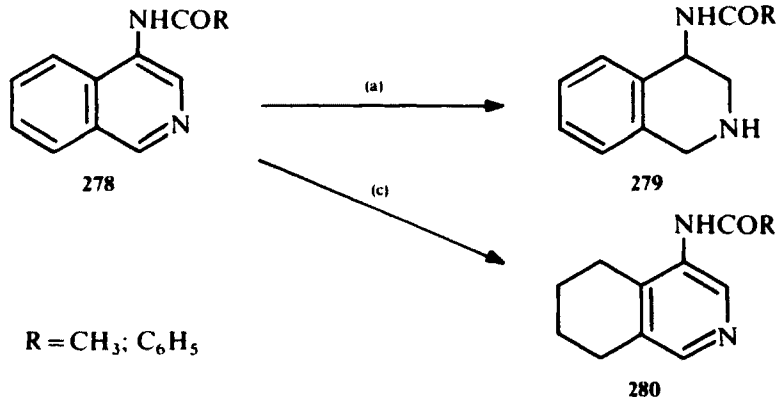
(141)

F. 4-Amino-5,6,7,8-Tetrahydroisoquinolines

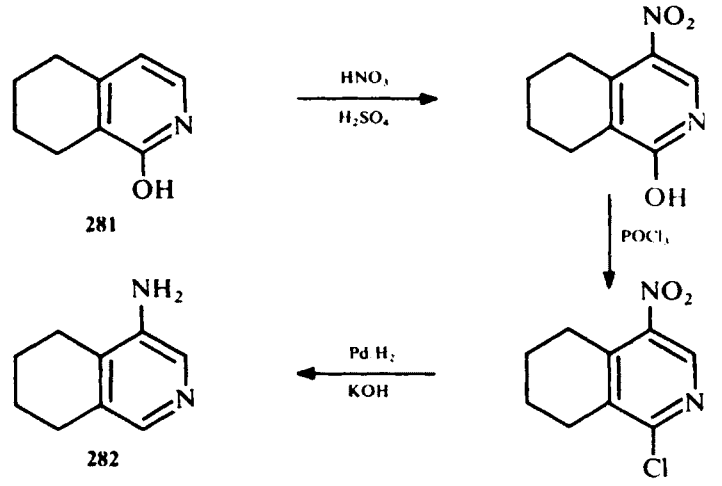
The catalytic hydrogenation of 4-aminoisoquinoline (**252**) over either platinum oxide in acetic acid or Raney nickel in ethanol yields 4-amino-5,6,7,8-tetrahydroisoquinoline **276**[171,172] or **277** (Eq. 142). The hydrogenation of 4-benzamido or 4-acetamidoisoquinoline **278** under similar conditions yields the normally expected 1,2,3,4-tetrahydroisoquinolines **279** (Eq. 142). However, the reduction of the amidoisoquinolines **278** over platinum oxide in acetic acid containing a small amount of 50% sulfuric acid produces the corresponding 5,6,7,8-tetrahydroisoquinoline **280**[172] (Eq. 142).

The hydrogenation of 1-ethoxy-4-aminoisoquinoline over platinum oxide in acetic acid yields, as expected, the corresponding 5,6,7,8-tetrahydroisoquinoline analog.[171] Nitration of 5,6,7,8-tetrahydroisocarbostyril **281** to the 4-nitro derivative provides an additional route of synthesis of the 4-amino compound **282**[171] (Eq. 143).


NH2
N
(a) H2, PtO2, CH3COOH
or
(b)H2,RaNi, C2H5OH
276
(c) H2, PtO2, CH3COOH, H2SO4
277


NHCOR
N
278
(a)
(c)
279
280
R = CH3; C6H5

(142)

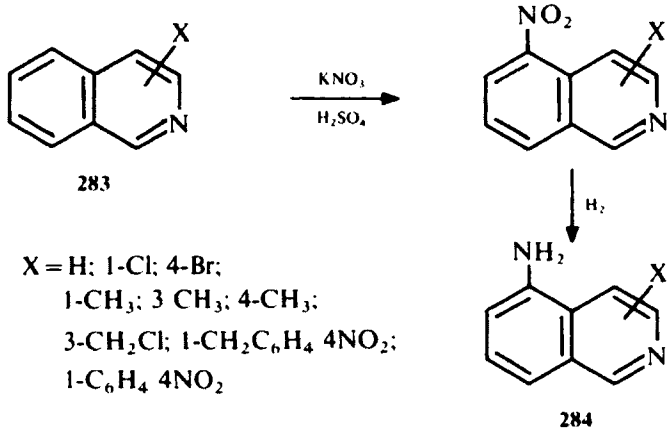

HNO3
H2SO4
NO2
OH
281
POCl3
Pd H2
KOH
NH2
Cl
282

(143)

VI. PREPARATION OF ISOQUINOLINES HAVING A BASIC GROUPING AT POSITION 5

A. 5-Aminoisoquinolines

The nitration of isoquinoline, preferentially at the 5-position, has been used almost exclusively for the synthesis of 5-aminoisoquinolines. Incorporation of various substituents into the heterocyclic ring of **283** does not affect the ability to introduce the nitro grouping at the 5 position. Several reductive procedures are available for conversion of the nitro group to an amine (**284**), including hydrogenations over Raney nickel,[34,49,154,173] platinum oxide,[174,175] palladium on charcoal,[176] stannous chloride and hydrochloric acid,[4,177,178,179] hydrazine hydrate and Raney nickel,[180] iron and hydrochloric acid,[181] and titanium(III) chloride,[182] as well as electrolytic reductions.[183,184] A summary of the reactions studied is shown in Eq. 144.



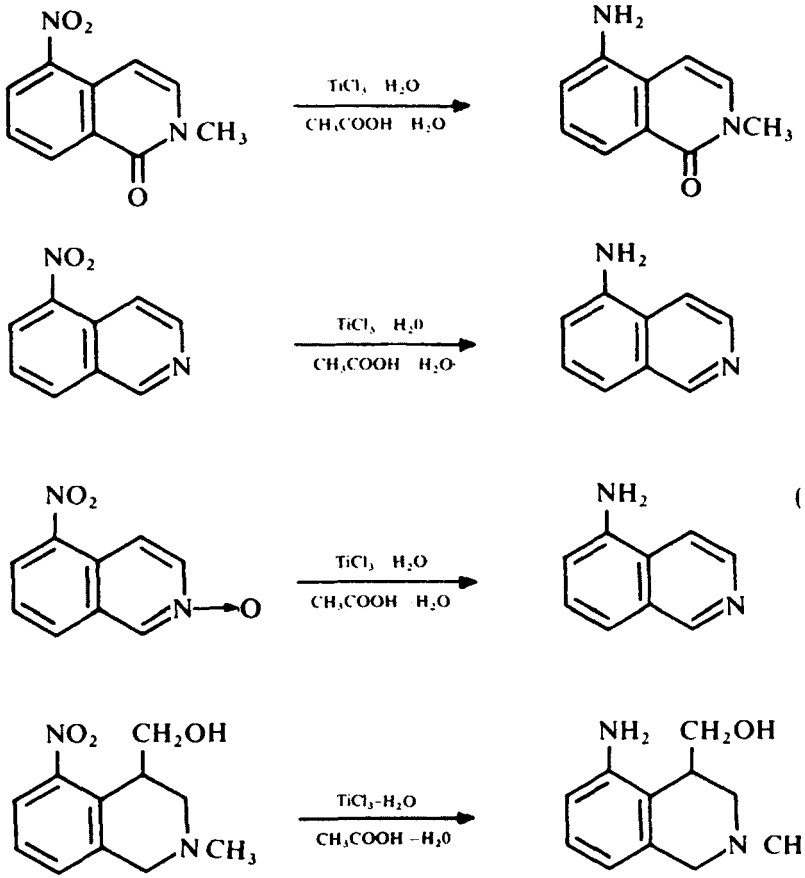
X = H; 1-Cl; 4-Br;
1-CH_3; 3 CH_3; 4-CH_3;
3-CH_2Cl; 1-$CH_2C_6H_4$ 4NO_2;
1-C_6H_4 4NO_2

(144)

To optimize yields in the reduction step it is desirable to purify the nitro compound.[178] In some investigator's experiences, the stannous chloride reduction is a more consistent procedure for optimal yields of the amine.[178,179] The use of titanium(III) chloride in aqueous acetic acid conditions at room temperature is reported to be an improved method; several 5-nitroisoquinolines have been prepared in support of this[182] (Eq. 145).

As an alternative, isoquinoline-*N*-oxide **287** may be nitrated with the production of both the 5- (**288**) and 8-nitro (**289**) analogs.[185] Selective reductions of the nitro group may be used to yield either mixtures of the 5-aminoisoquinoline **290** and its tetrahydro derivative **291** (palladium on charcoal in an acidic medium) or mixtures of 5-aminoisoquinoline **290** and its *N*-oxide **292** (palladium on charcoal in a neutral medium) (Eq. 146).

Treatment of the *N*-oxide **288** with tosyl chloride in the presence of base introduces the tosyloxy grouping at the 4 position. Hydrogenation over Raney



(145)

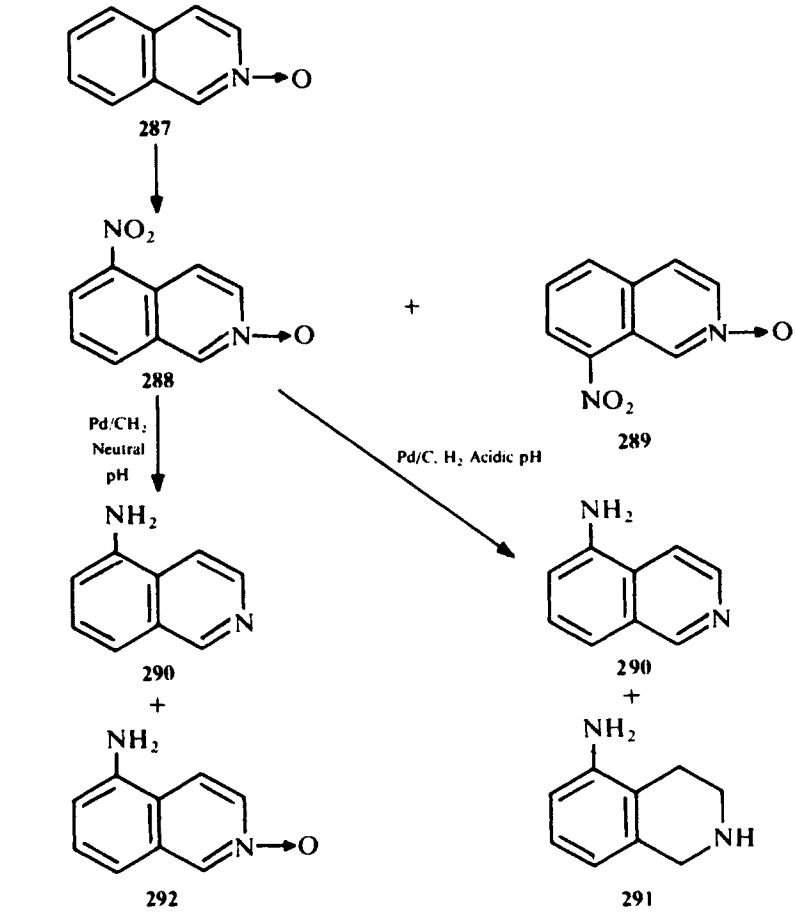
nickel yields the corresponding 5-amino-4-tosyloxyisoquinoline **294**[186] (Eq. 147). 5-Nitro-1-isoquinolone **293** is produced as an additional product from the tosylation step.[186]

Studies carried out by Taurins[187] during an attempt to introduce the thiocyanate grouping into 5-aminoisoquinoline reveal that thiocyanation occurs solely at the 8 position and not at the anticipated 6 position. The implication of this finding, in connection with the synthesis of various thiazoloisoquinolines, is considered in more detail in Section IX.A, Eq. 183.

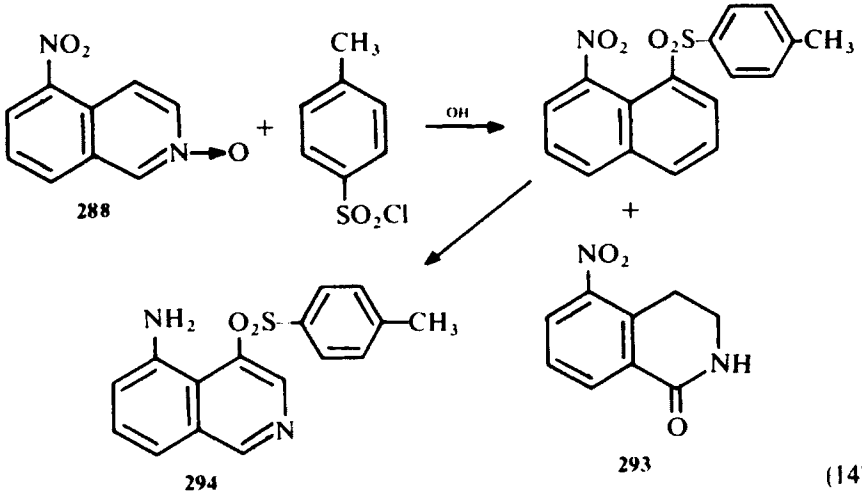
Methodology for the annelation of aromatic rings in the synthesis of 5-aminoisoquinolines **296** has been reported (Eq. 148).[188] The last step includes a furan intermediate **295**, which undergoes a Diels–Alder type reaction.

B. 5-Alkylaminoisoquinolines

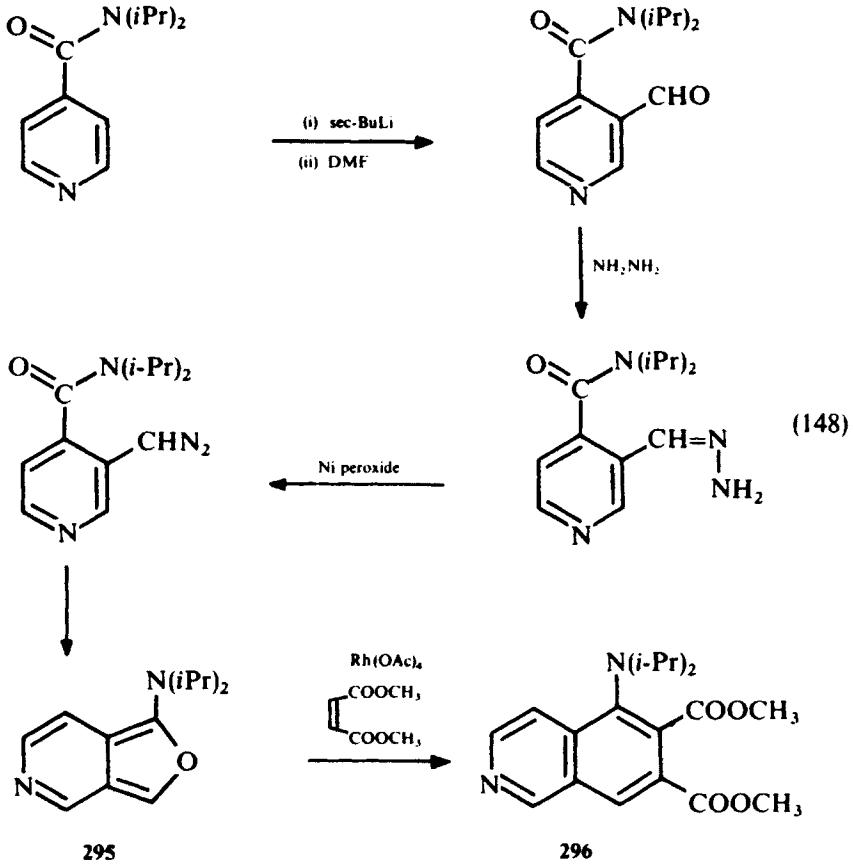
Since neither the alkylation of 5-aminoisoquinoline nor the treatment of 5-halogen-substituted isoquinolines with amines proceeds smoothly, alternate


287
NO2
288
+
NO2
289
Pd/CH3
Neutral
pH
Pd/C, H2 Acidic pH
NH2
290
+
NH2
292
NH2
290
+
NH2
NH
291

(146)

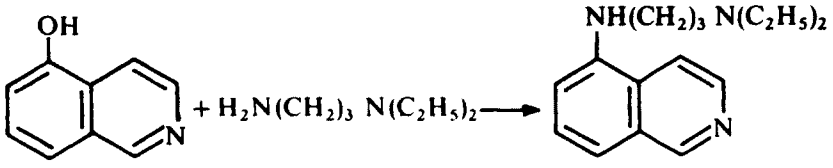

NO2
288
+
CH3
SO2Cl
OH
NO2 O2S CH3
+
NO2
NH
O
293
NH2 O2S CH3
294

(147)



(148)

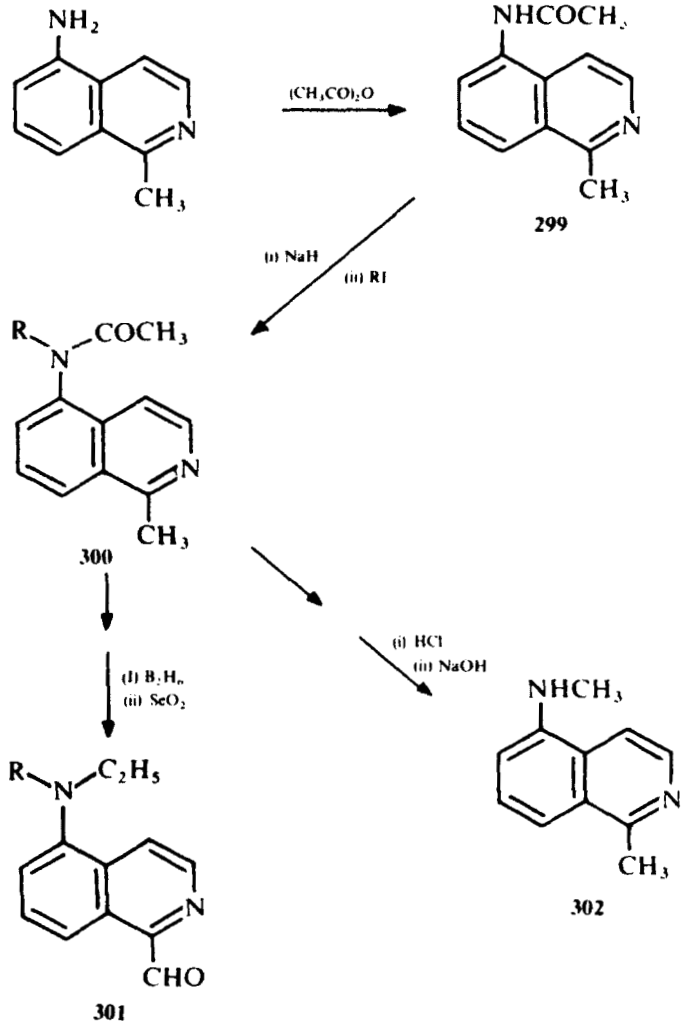
methods for the synthesis of these derivatives must be used.[189] Alkylation of the 5-amino grouping by the standard procedures results in the preferential quaternization of the heterocyclic nitrogen.[189] Bucherer treatment of 5-hydroxyisoquinoline **297** enables the introduction of alkylamino groups at the 5 position **298**[189] (e.g., Eq. 149).



(149)

As an alternate procedure, the indirect alkylation of 5-aminoisoquinoline has been accomplished.[190] 5-Acetamido-1-methylisoquinoline (**299**), on treatment with sodium hydride followed by an alkyl iodide, yields the alkylated amide **300**. Borohydride reduction produces the tertiary amine **301**. Acid–base mani-

pulation of **300** yields the secondary amine **302**. A summary of these procedures is shown in Eq. 150.

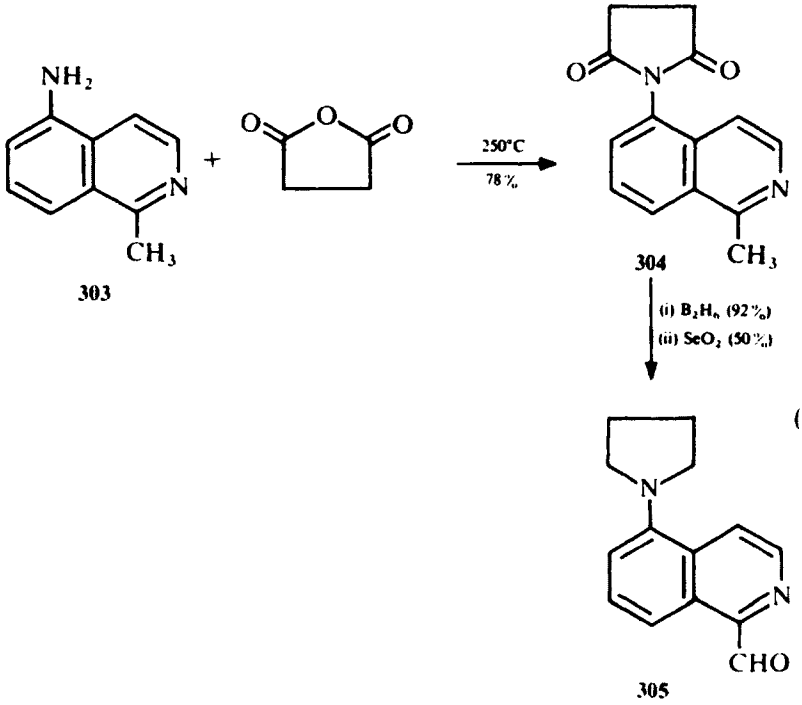


(150)

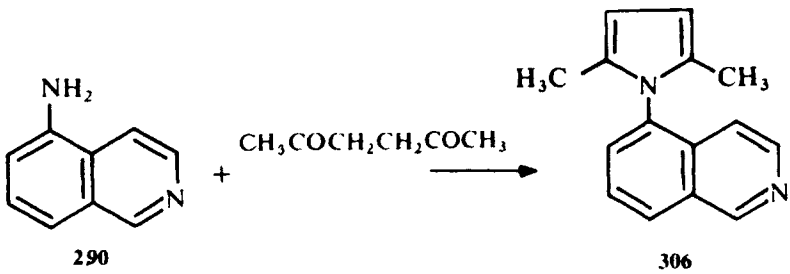
During the course of the work cited in Eq. 150, the synthesis of 5-pyrrolidylisoquinolines from 5-amino-1-methylisoquinoline (**303**) was reported.[190] Contact of **303** with succinic anhydride yields the imide **304**, which on reduction with diborane produces the pyrrolidinyl derivative **305** (Eq. 151).

A similar procedure may be used for the preparation of the 2,5,-dimethylpyrrolidinyl analog **306**[156] (Eq. 152), acetonylacetone replacing the succinic anhydride of Eq. 151.

During the course of the synthesis of a novel fluorescent labeling agent, 5-dimethylamino-2-oxidoisoquinolin-1-yldiazomethane **307**, an alternative alkyl-

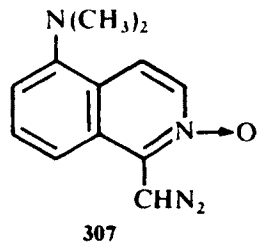


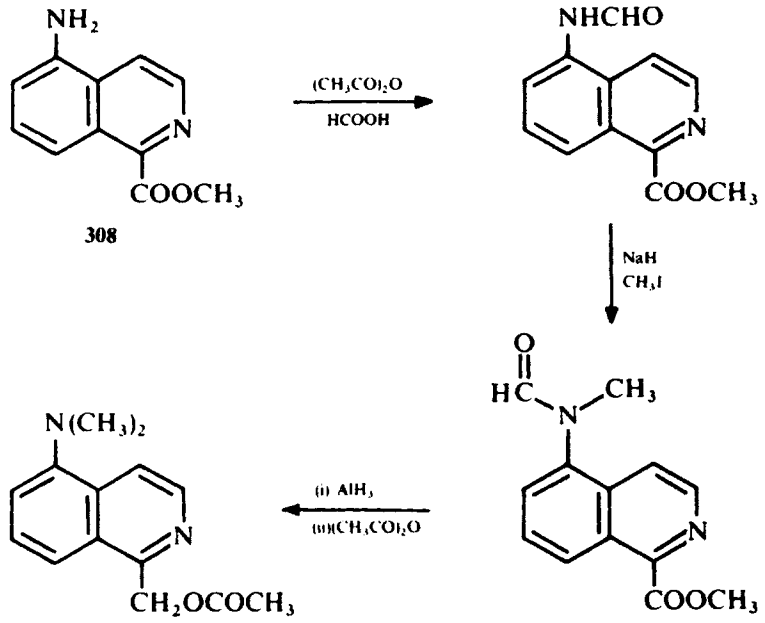
(151)



(152)

ation of the 5-aminoisoquinoline **308** has been achieved using the methods shown in Eq. 153.[191]





(153)

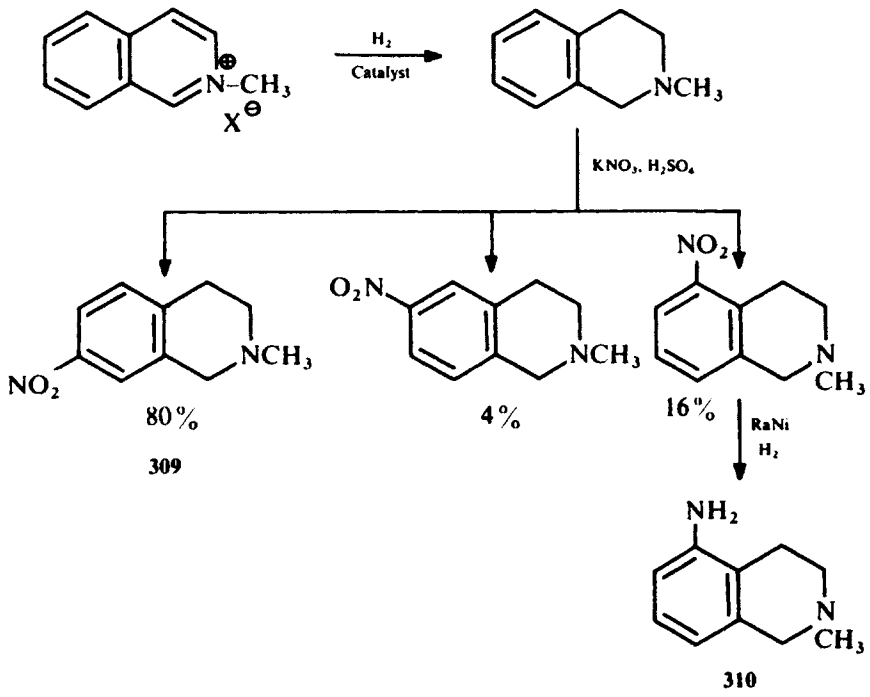
C. 5-Amino-1,2,3,4-Tetrahydroisoquinolines

While it is a relatively simple procedure to prepare these derivatives by catalytic hydrogenation of either the 5-nitro or 5-aminoisoquinolines,[192-194] the nitration of 1,2,3,4-tetrahydroisoquinoline (as an initial step in their synthesis) has been reported.[195] Although this approach is of primary benefit in the synthesis of 7-aminotetrahydroisoquinolines **309**, a significant amount of substitution occurs at the 5 position during the nitration step. This provides an alternate route for the synthesis of 5-amino-1,2,3,4-tetrahydroisoquinolines **310** (Eq. 154).

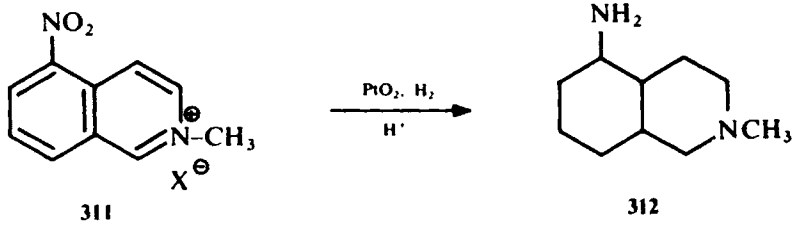
D. 5-Aminodecahydroisoquinolines

The low-pressure hydrogenation of 5-nitroisoquinolinium salts **311** over platinum oxide in acidic media gives good yields of the fully reduced amine **312**[174] (Eq. 155). Separation of two of the four possible diastereoisomeric amines has been achieved by fractional recrystallization of the acetamides, followed by hydrolysis of the purified amides. Conversion of the amines to the known alcohols by deamination with nitrous acid, coupled with spectral data, confirmed evidence for the stereochemical assignments.

Alternate high-pressure hydrogenations of the 5-nitroisoquinolinium salt **311** over Raney nickel at elevated temperatures also yields the fully reduced product



(154)

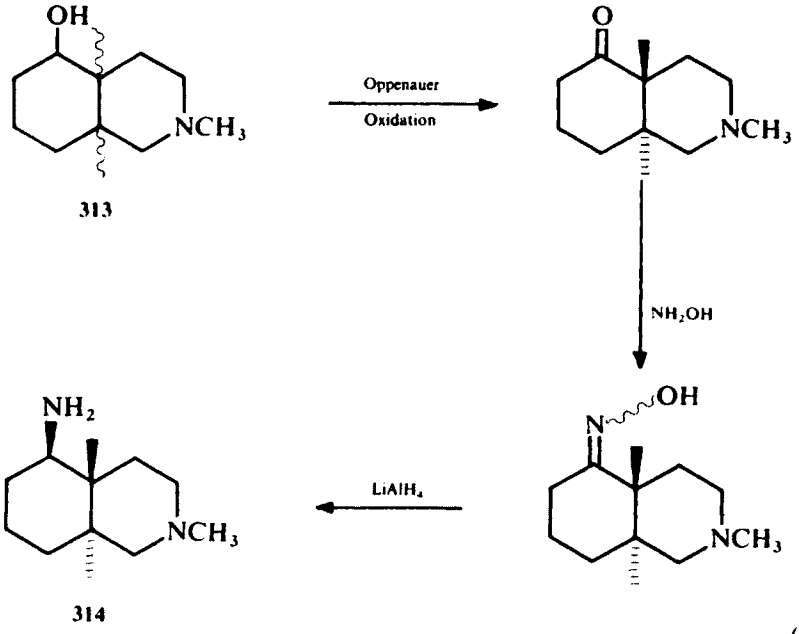


(155)

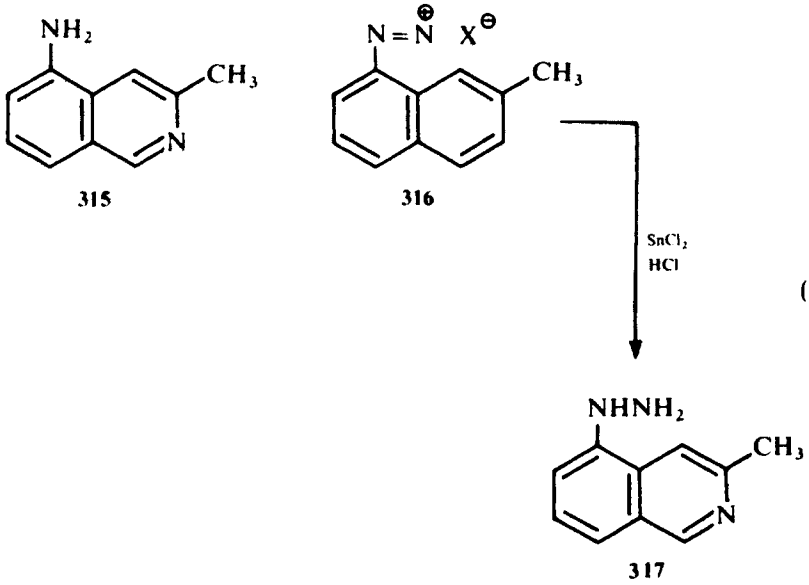
312.[196] The stereoselective synthesis of 5-amino-2-methyl-*trans*-decahydroisoquinoline **314** may be accomplished from the isomeric 5-hydroxy compounds **313**, as shown in Eq. 156.

E. 5-Hydrazinoisoquinolines

Diazotization of the amino group of 5-aminoisoquinolines (e.g., **315**), followed by reduction of the diazonium salt **316** with stannous chloride and hydrochloric acid, produces yields of the hydrazine derivative **317**[198] (Eq. 157).

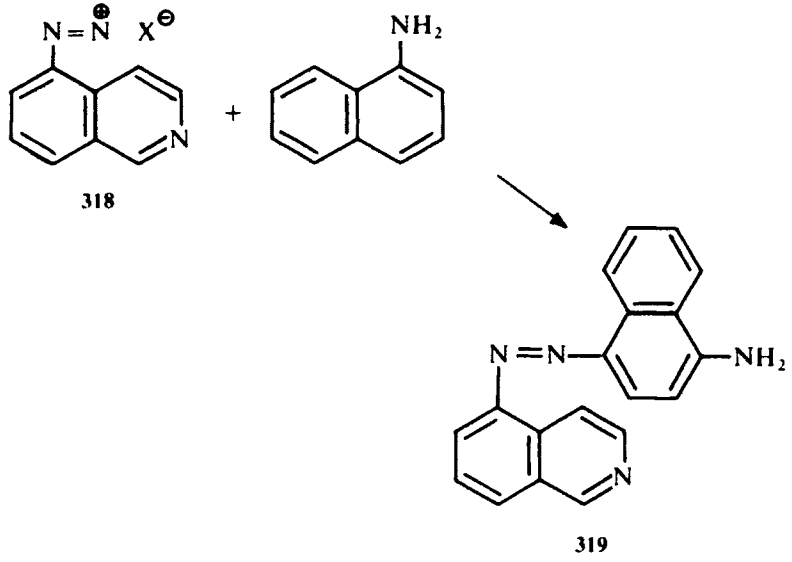


(156)



(157)

The electrophilic substitution of 1-naphthylamine by the diazonium salt of 5-aminoisoquinoline (**318**) has been reported for the synthesis of some antischistosomicidal azoisoquinolines **319**[181] (Eq. 158).

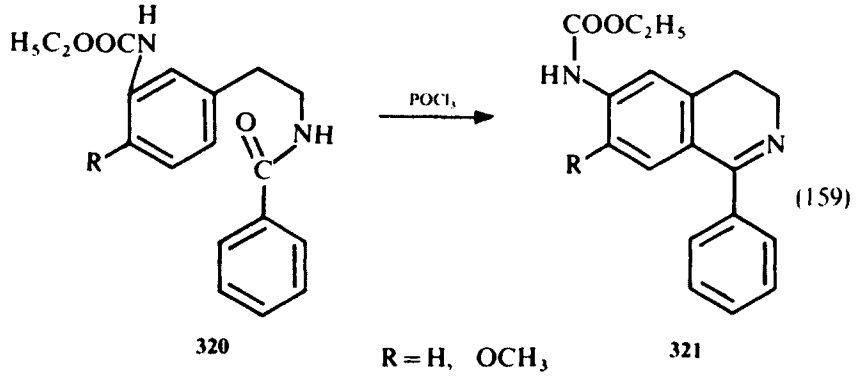


318 319

(158)

VII. PREPARATION OF ISOQUINOLINES HAVING A BASIC GROUPING AT POSITION 6

The synthesis of derivatives of this group by Bischler–Napieralski ring-closure reactions is the most commonly reported procedure. Several studies by Ishiwata and his co-workers[200,201] have been reported, incorporating the phosphorus oxychloride closure of 3-phenylethylamides bearing *m*-acylamido groupings **320**. Ring closure occurs para to the acylamido grouping, thus yielding derivatives of 6-amino-3,4,-dihydroisoquinoline **321**[200] (Eq. 159).

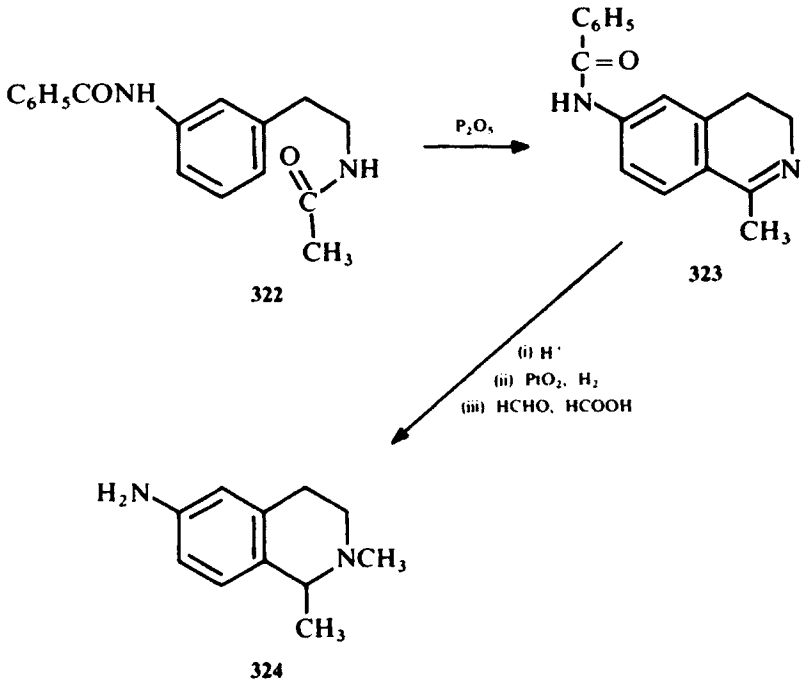


320 R = H, OCH_3 321

(159)

The ability to ring-close compounds not bearing activating methoxyl groupings provides a significant improvement over the previously used procedures involving the nitration of isoquinolines and subsequent reduction to the amine. The combination of the inherent low-yield nitration and the formation of alternate positions of substitution by the nitro grouping results in extremely low-yield reaction. The ethoxycarbamido grouping appears to be an excellent nitrogen-containing substituent for accelerating the Bischler–Napieralski closure, presumably as a result of its increasing electron density at the position of closure. Originally, it was thought that the closure was extremely position-specific,[200] however, more detailed studies have revealed that the ratio of ortho to para closure is 1:3.5, thereby yielding 8-amino-3,4-dihydroisoquinolines in preference to the 6-positional analog.[202] Subsequent reduction of the 1,2-double bond of the dihydroisoquinoline **321** with sodium borohydride readily produces the corresponding tetrahydroisoquinoline, which on hydrolysis affords the free 6-amino grouping. Reactions of this type are utilized in the synthesis of cularine alkaloids (6,7-dioxygenated benzylisoquinolines).[199,203] In this work, the purpose of these reactions is to allow the ring closure of normally difficult to close systems. The presence of the 6-amino substituent (in the form of the acylamido grouping) facilitates ring closure and allows manipulation to the desired oxygen functions.

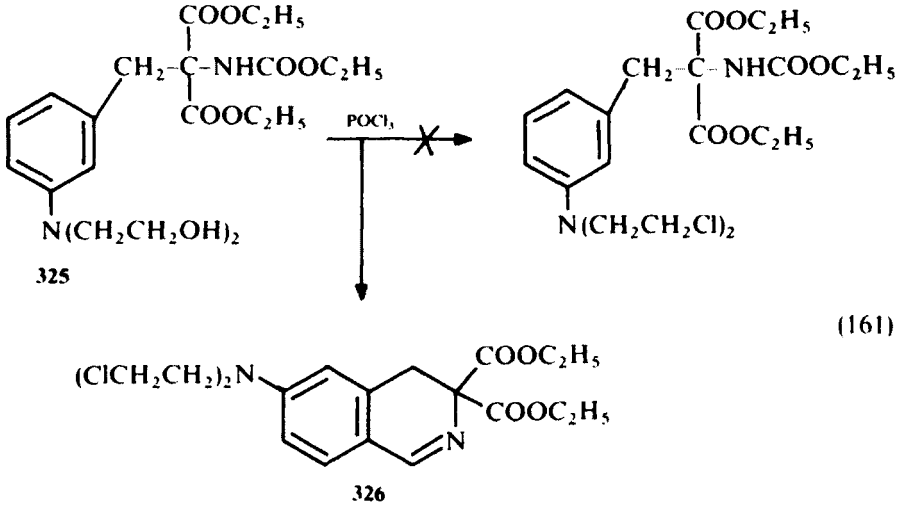
Alternate Bischler–Napieralski ring closures utilize *p*-benzamido α-phenylethylamides **322** as substrate and phosphorous pentoxide as the Lewis acid[205] (Eq. 160).



322 323 324

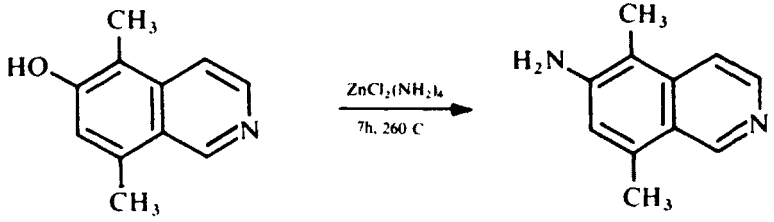
(160)

Hydrolysis of the amide (**323**), followd by formylation and hydrogenation of the double bond, yields the 6-amino-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline **324**. Attempts to chlorinate some *N'N'*-dihydroxyalkylated anilines (**325**) with phosphorus oxychloride leads to a Bischler-Napieralski closed product **326**[207] (Eq. 161).



(161)

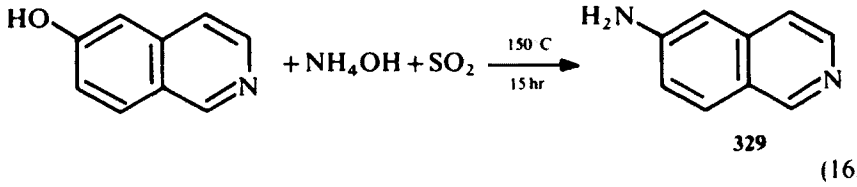
Displacement of the hydroxyl group of 6-hydroxyisoquinoline **327** has been utilized as a synthesis for the 6-aminoisoquinoline **328** in good yields (68%)[206] (Eq. 162).



(162)

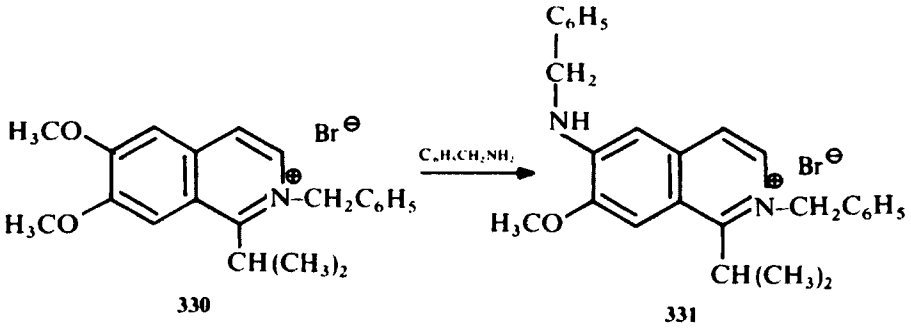
The Bucherer reaction has also been utilized in the synthesis of 6-aminoisoquinoline **329** as an intermediate for pyridocarbazole synthesis[207] (Eq. 163).

The 6-methoxy group of certain isoquinolinium salts (**330**, **332**) may be replaced by nucleophilic substitution to yield 6-methylamino or 6-benzylaminoisoquinolines **331** and **333**. However, when 1-isopropyl-6,7-dimethoxy-2-benzylisoquinolinium bromide **330** is reacted with methylamine, displacement of the 6-methoxy group occurs as expected; in addition, replacement of the 2-benzyl group by methyl occurs (**334**)[208] (Eq. 164).

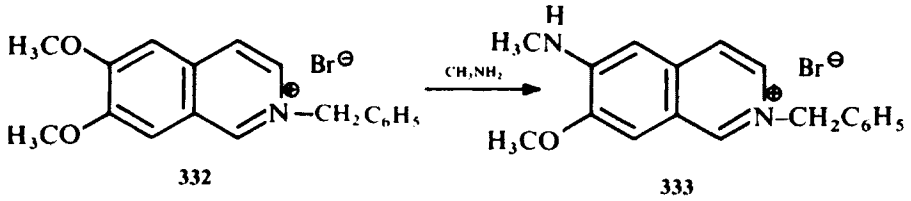


329

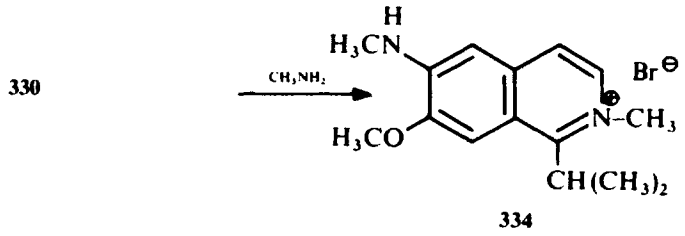
(163)



330 331



332 333

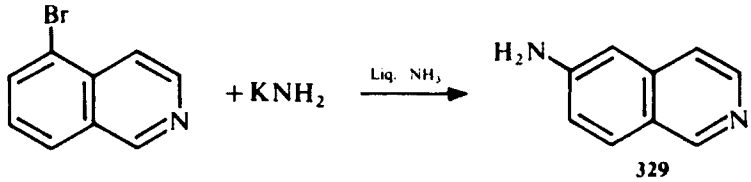


334

(164)

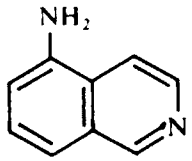
Amination of 5-bromoisoquinoline may be accomplished with potassium amide in liquid ammonia.[209] The preferential production of 6-aminoisoquinoline (47%) **329** over the 5-amino compound (21%) **335** occurs (Eq. 165).

An efficient synthesis for 6-nitro-3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines (and thus the amino analogs) has been reported by Trepanier and Sunder.[210] These previously difficult to prepare compounds do not possess activating groups (i.e., OCH_3), and thus are poor products for synthesis by Bischler–Napieralski, Pictet–Spengler, or Pomeranz–Fritsch ring closures. *N*-



329

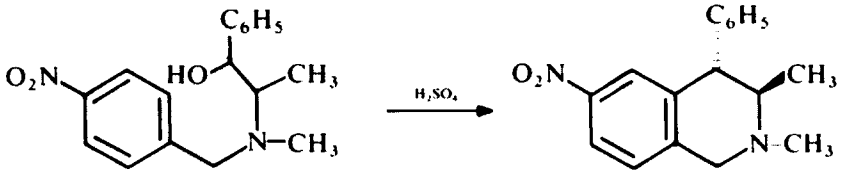
+



335

(165)

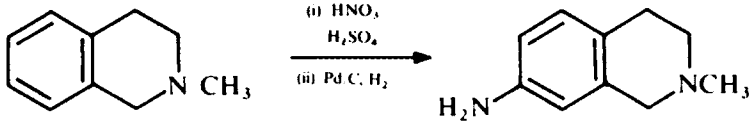
Benzylephedrine **336** may be cyclodehydrated by sulfuric acid for 1 h to give the 6-nitro-1,2,3,4-tetrahydroisoquinoline derivatives **337** (Eq. 166).



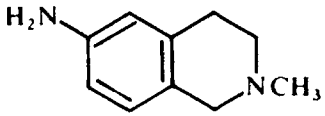
336 337

(166)

The nature and position of the substituent on the aromatic ring does not appear to influence the success of the ring closure in this reaction. However, *N*-substituted benzoylephedrines do not cyclodehydrate. As an alternative procedure, the nitration of 1,2,3,4-tetrahydroisoquinolines has been reported to yield the 6-nitro analog as the minor product, from which the amine may be obtained by reduction[211] (Eq. 167). Additional studies on the nitration of 1,2,3,4-tetrahydroisoquinolines are shown in Eq. 154.



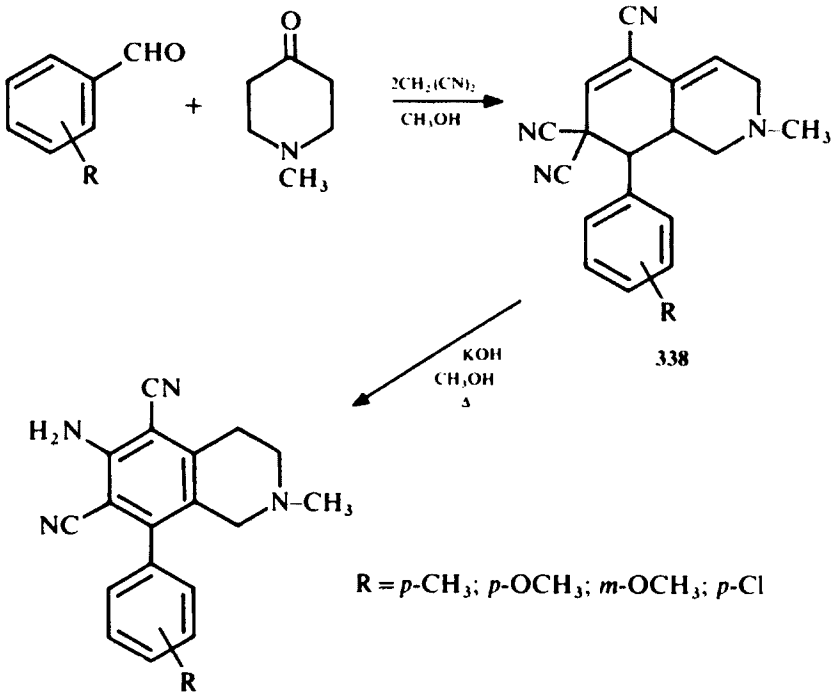
+



(167)

ratio 6 : 1

The reaction of 1-methyl-4-piperidone with a substituted benzaldehyde under reaction conditions outlined by Andresen and Pedersen[212] yields an isoquinoline ring system bearing a 6-amino group. The initial product **338** may be converted to a 1,2,3,4-tetrahydroisoquinoline **339** by treatment with base (Eq. 168).



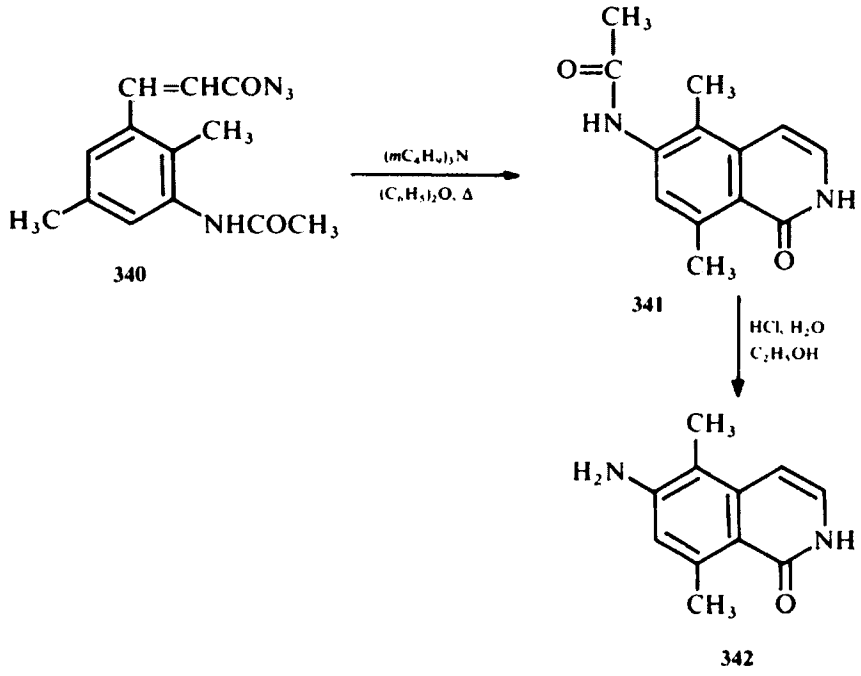
(168)

The base-catalyzed cyclization of the cinnamic acid azide **340** results in the 6-acetamido isoquinoline **341**. Hydrolysis of the intermediary acetamide yields 6-amino-5,8-dimethylisoquinolin-1 (2H)-one **342**[213,214] (Eq. 169).

Cyclization of appropriately substituted tertiary alcohols (e.g., **343**) with concentrated sulfuric acid has been used in the synthesis of 6- (or 7- or 8-)-amino-1,2,3,4-tetrahydroisoquinolines **344**[215] (Eq. 170).

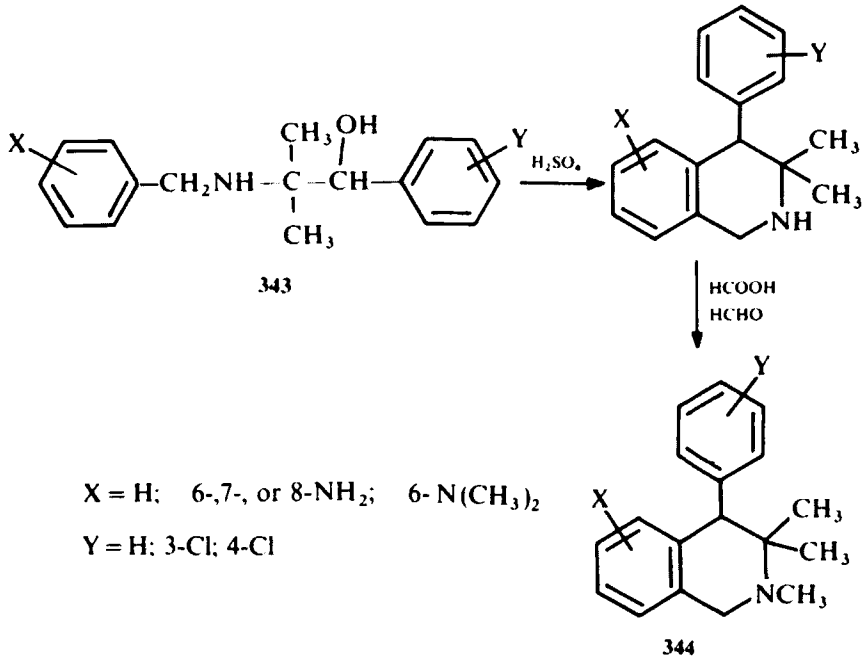
The synthesis and elucidation of the stereochemistry of some diastereoisomers of 6-amino-2-methyldecahydroisoquinoline **347** has been described.[216] The synthesis of 6-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline **346** was achieved by nitration of 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline **345** (Eq. 171) followed by reduction and dehalogenation.

Spectral and chemical evidence (deamination with nitrous acid to the known hydroxy compounds) confirmed the major isomers isolated to be 6β-amino-2-methyl-*cis*-(4aα,8aα) and 6α-amino-2-methyl-*trans*-(4aβ,8aα)-decahydroisoquinoline. A small amount of the 6β-amino-2-methyl-*cis*-(4aβ,8aβ)-



340 341 342

(169)

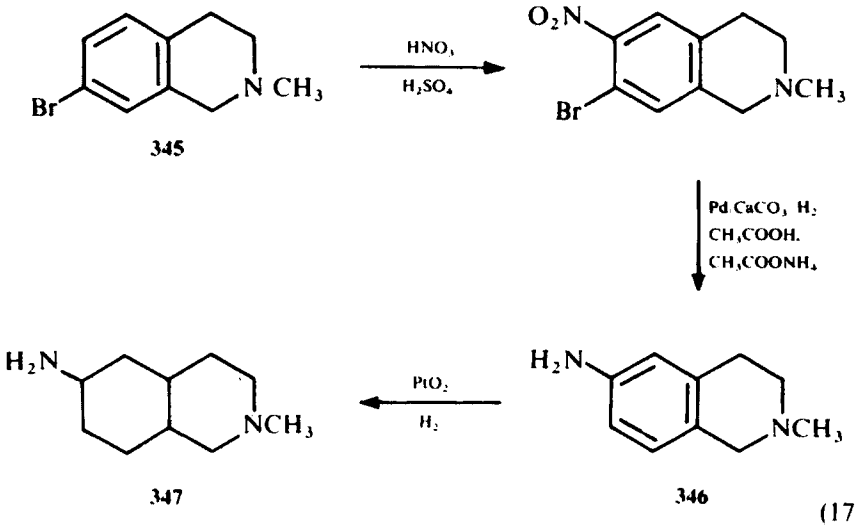


343 344

X = H; 6-,7-, or 8-NH_2; 6-$N(CH_3)_2$

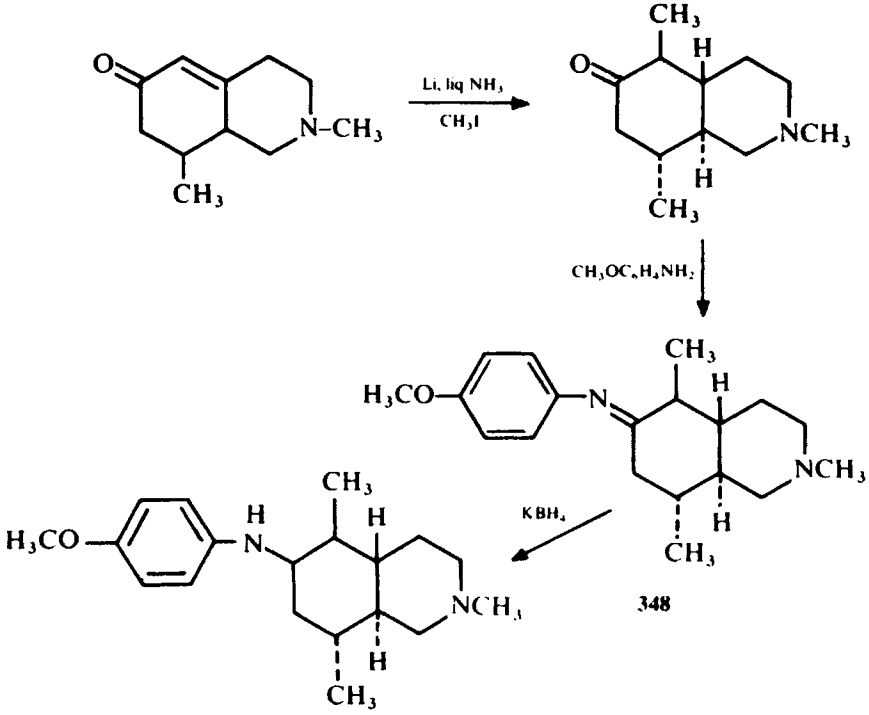
Y = H; 3-Cl; 4-Cl

(170)



(171)

decahydroisoquinoline was isolated. Introduction of a substituted 6-amino grouping into the decahydroisoquinoline nucleus has been achieved from the corresponding 6-isoquinolone **348** using *p*-methoxyaniline followed by a borohydride reduction[217] (Eq. 172).



(172)

VIII. PREPARATION OF ISOQUINOLINES HAVING A BASIC GROUPING AT POSITION 7

In general, three procedures are available for the preparation of derivatives of this group of isoquinolines:

(1) Nitration of existing substituted reduced isoquinolines, followed by reduction of the nitro grouping.
(2) Condensation of nitroaralkyl halides with appropriate amines, again followed by reduction of the nitro group.
(3) Replacement of existing substituents at the 7 position by contact with organic bases.

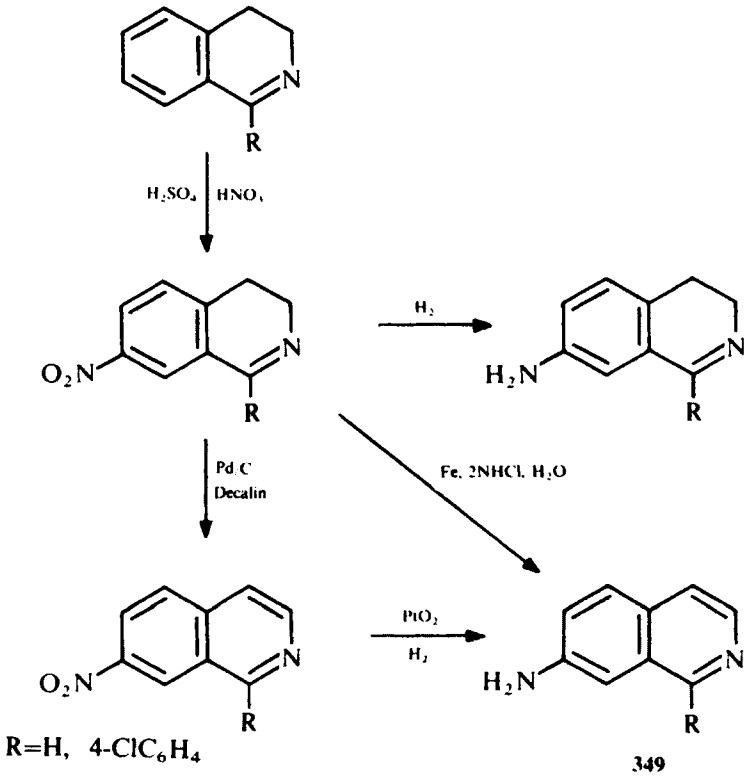
A. Nitration of Partially Reduced Isoquinolines

Direct nitration has been carried out most frequently with 3,4-dihydro[219] and 1,2,3,4-tetrahydroisoquinolines[212,217,220] as the substrates. The nitrated products are generally obtained in low yields, owing to the generally poor yields of nitration and substitution occurring at alternate positions on the benzenoid ring of the reduced isoquinoline (Eq. 154). While these studies utilized low-yield nitration procedures, experiences in the authors' laboratories have shown that the use of trifloromethane sulfonic acid–nitric acid mixtures[221] is far superior. No differences in the position of substitution ($7 \gg 5 \gg 6$) are obtained and overall yields of the nitrated products are significantly improved (70%, compared with approximately 30% for the classical nitrations).

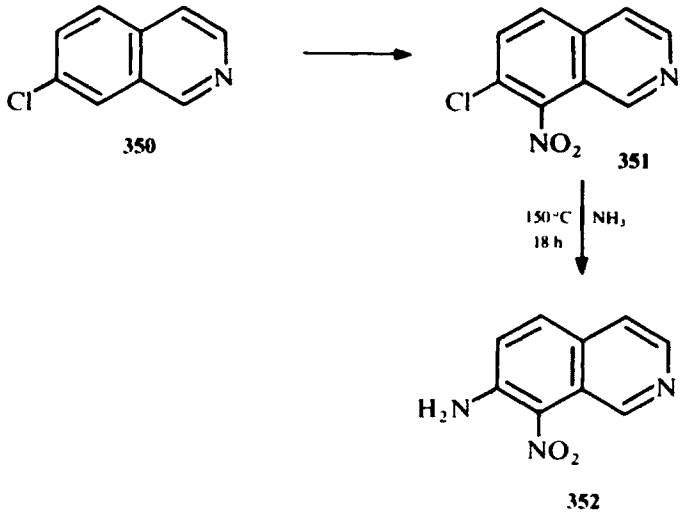
Several catalytic methods for reduction of the nitro grouping are available, including palladium on charcoal,[212] platinum oxide,[217,219] and iron and HCl.[220] In some instances, the preparation of the fully unsaturated 7-aminoisoquinoline was accomplished using the last catalyst. In general, the synthesis of the unsaturated compound from the partially reduced isoquinolines is achieved by aromatization of the heterocyclic ring of the nitrated product with palladium on charcoal in decalin.[219] Subsequent reduction of the nitro grouping over palladium catalyst, as previously noted, yields the desired compound **349**.[219] In summary, the pathways to 7-aminoisoquinolines by these approaches are shown in Eq. 173.

The nitration of 7-chloroisoquinoline **350** to yield the 8-nitro derivative **351** has been utilized in the preparation of 7-amino-8-nitroisoquinoline **352**[199] (Eq. 174).

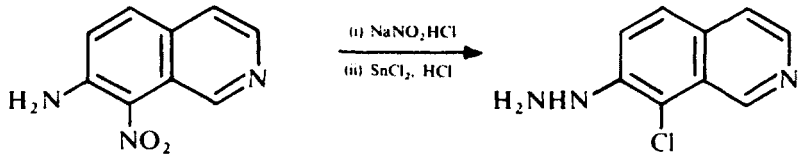
Formation of the diazonium salt of the 7-amino grouping of **352** labilizes the 8-nitro grouping such that treatment with hypophosphorous acid in the presence of HCl produces 8-chloroisoquinoline.[199,222] In a similar manner, 7-amino-8-nitroisoquinoline **352** may be used to prepare 7-hydrazino-8-chloroisoquinoline **353**[199] (Eq. 175).


R
H_2SO_4 | HNO_3
O_2N
R
H_2
H_2N
R
Pd/C
Decalin
Fe, 2NHCl, H_2O
O_2N
R
PtO_2
H_2
H_2N
R
R=H, 4-ClC_6H_4
349

(173)


Cl
350
Cl
NO_2
351
150°C | NH_3
18 h
H_2N
NO_2
352

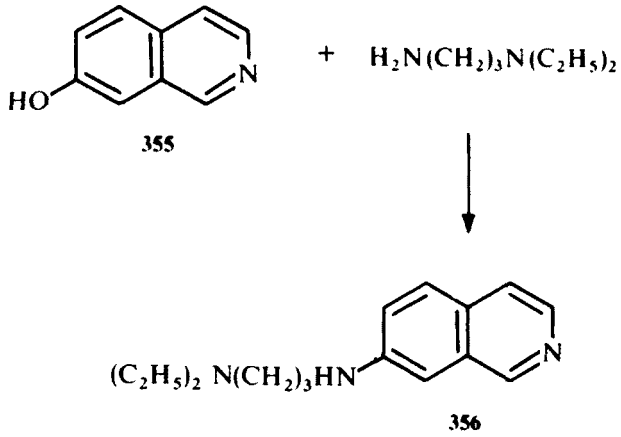
(174)



353 354

(175)

Attempts to prepare 7-amino-8-chloroisoquinoline **358** by the Bucherer reaction of 7-hydroxy-8-chloroisoquinoline have not been successful; however, 7-aminoisoquinoline is obtained.[199] 7-Hydroxyisoquinoline **355** also successfully yields 7-dialkylaminoalkylaminoisoquinoline **356** according to Bucherer procedures using dialkylaminoalkylamines[233] (Eq. 176).



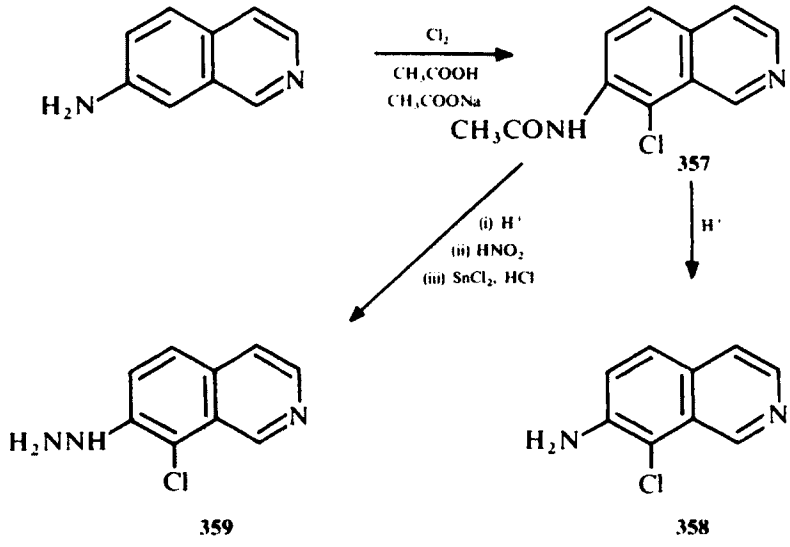
355 356

(176)

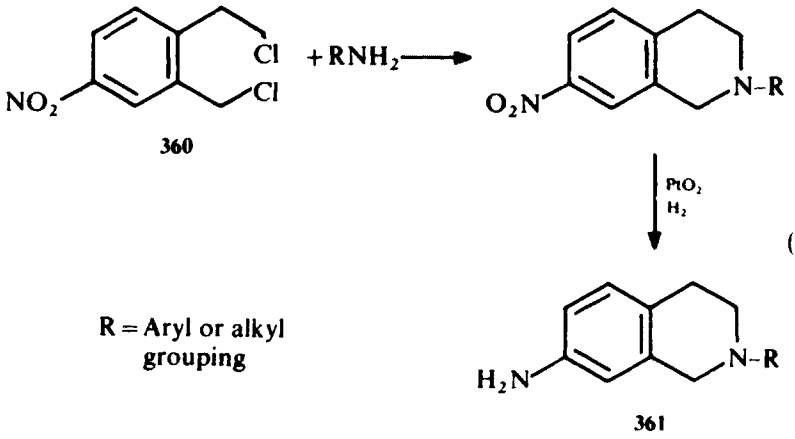
Treatment of 7-aminoisoquinoline with chlorine in sodium acetate–acetic acid produces 7-acetamido-8-chloroisoquinoline **357**, from which **358** may be obtained by hydrolysis. Diazotization of the 7-amino group of **358**, followed by reduction with stannous chloride, provides an alternate synthesis for the hydrazine **359**[199] (Eq. 177).

B. Condensation of Amines with Nitroaralkyl Halides

The preparation of 7-amino-2-substituted 1,2,3,4-tetrahydroisoquinolines **361** has been accomplished by the condensation of a variety of aryl[224] or alkylamines[224,225] with nitroaralkyl halides **360** (Eq. 178). Reduction of the nitro grouping over platinum catalyst provides the desired amino compounds (**361**).



(177)

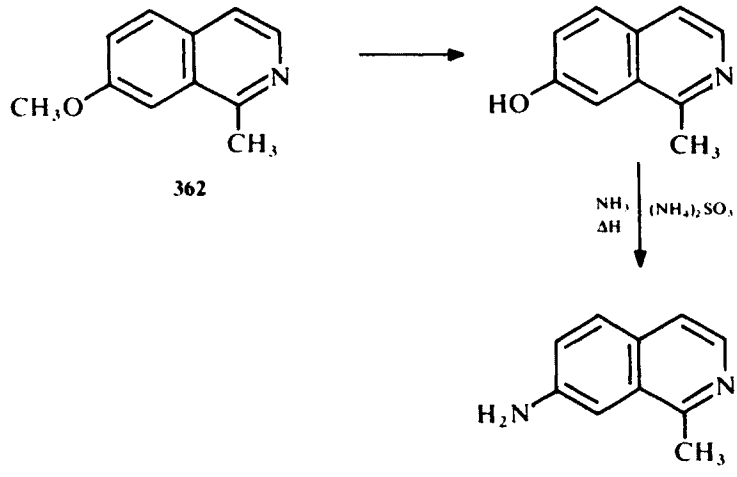


(178)

C. Replacement of Existing Groupings at the 7 position

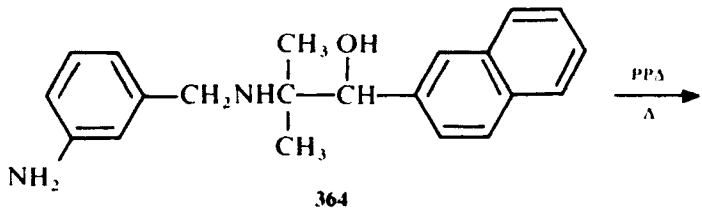
While it is feasible to approach the synthesis of 7-aminoisoquinoline as described in Section VIII.A and B, alternate procedures are also available.[226] Demethylation of 7-methoxyisoquinolines **362**, followed by amination using Bucherer reaction conditions, gives high yields of the 7-amino compound **363** (Eq. 179).

The polyphosphoric acid cyclization of tertiary alcohols **364** has been reported as a method for the preparation of 7-amino-1,2,3,4-tetrahydroisoquinolines **365**[227] (Eq. 180).

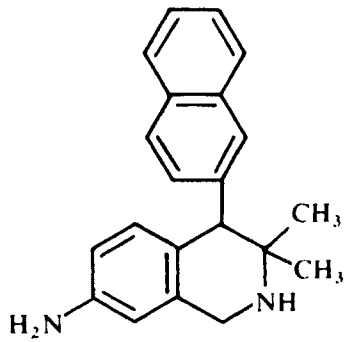


362 363

(179)



364



365

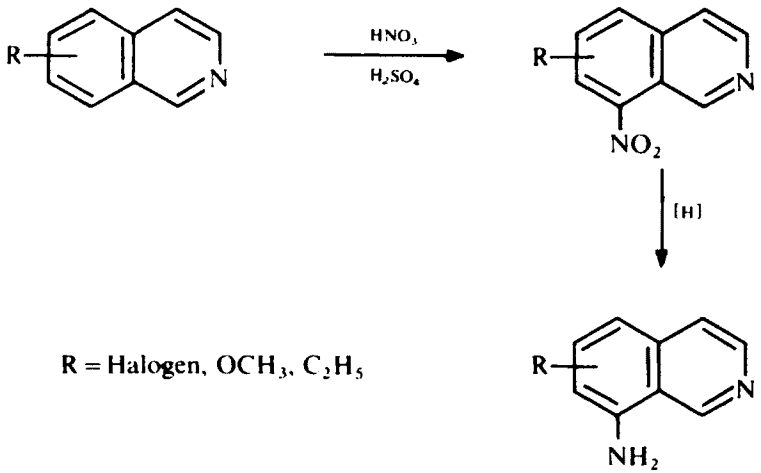
(180)

IX. PREPARATION OF ISOQUINOLINES HAVING A BASIC GROUPING AT POSITION 8

A. 8-Aminoisoquinolines

The synthesis of these derivatives is commonly reported in the literature, primarily because of the ease with which it is possible to introduce nitrogen-

containing substituents (in the form of nitro groupings) directly at the 8 position of isoquinoline by electrophilic substitution. The use of methoxyl, chloro, and other halogen substituents to direct the course of nitration into the 8 position has been extensively described. 7-Methoxy,[227] 5-acetamido,[187] 5-chloro[198,225] and 5-bromo isoquinolines,[228] and 5,6,-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[232] all give good yields of the 8-nitro analog. Reduction with palladium on charcoal and hydrazine hydrate[229,230] or stannic chloride,[229] or by hydrogenation over palladium on charcoal,[187,228] calcium carbonate,[225] or Raney nickel[231] gives excellent yields of the amine **366** (Eq. 181). In the case of the halogenated compounds, the halogen may be retained in the reduction step by an appropriate choice of reducing conditions (palladium on charcoal[229] or Raney nickel[231]).



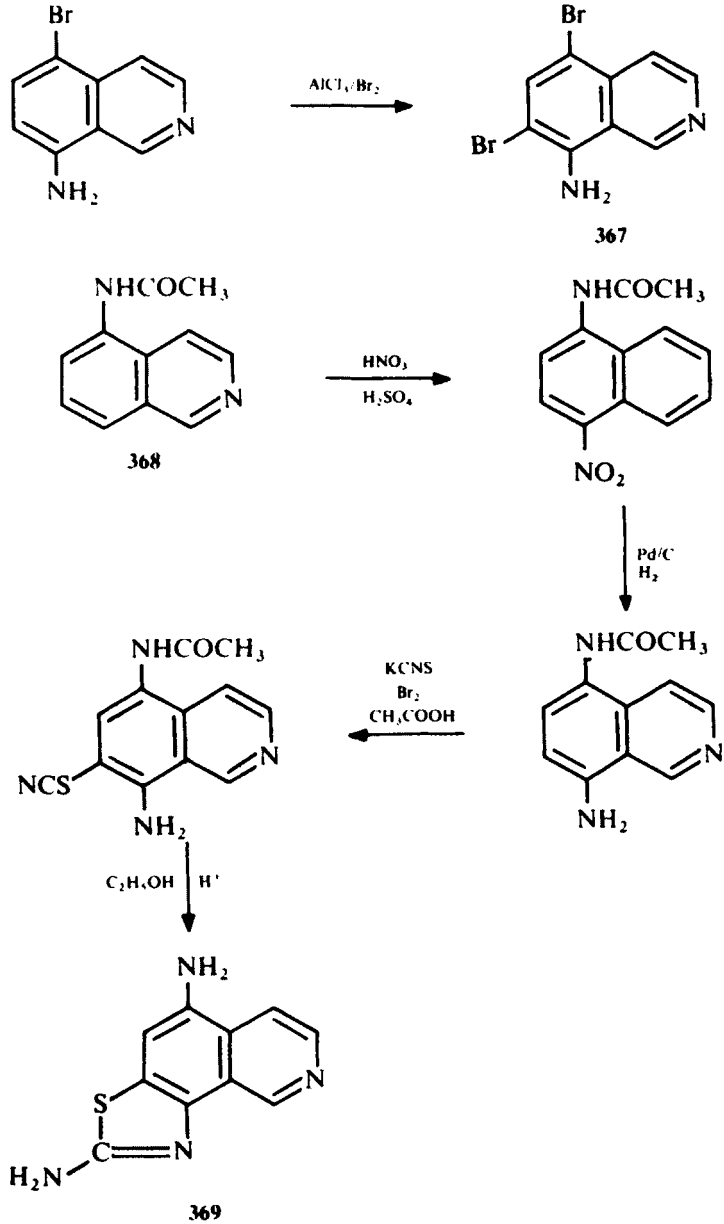
(181)

366

The nitration of unsubstituted isoquinoline at 0°C produces the expected 5 and 8 positional isomers in the ratio of 90:10. When the temperature is raised to 100°C, the amount of the 8-nitro compound in the ratio increases to 85:15. The nitration of isoquinoline *N*-oxide yields the 8-nitro compound as a secondary product (as previously noted, Eq. 146[185]). Catalytic hydrogenation over palladium on charcoal provides excellent yields of 8-aminoisoquinoline.[185]

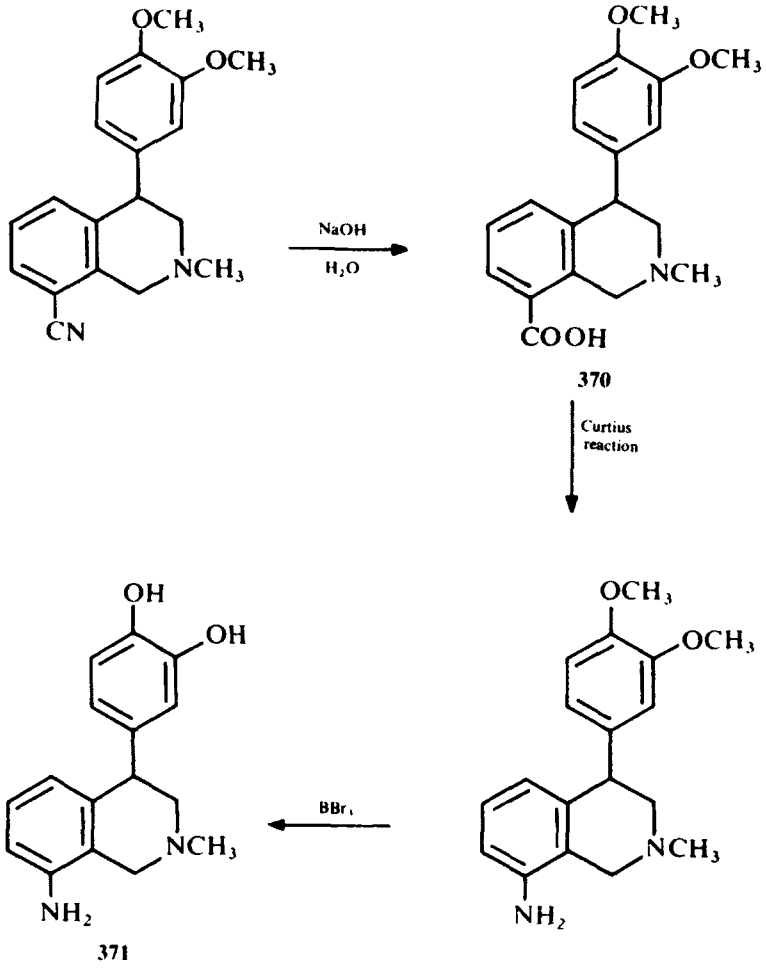
The halogenation of 8-aminoisoquinolines using the "swamping catalyst" technique[228] enables the introduction of the halogen at the 7 position **367**, providing a grouping for further manipulation (Eq. 182). The formation of an aluminum-chloride complex with the heteroatom deactivates the ring such that substitution occurs only in the benzenoid ring.

8-Aminoisoquinolines may be utilized as precursors for the synthesis of thiazolo-[4,5-h]-isoquinolines **369**.[187] The nitration of the 5-acetamidoisoquinoline **368** at the 8 position provides the basis for the construction of the 4,5-thiazoline ring system at the h bond of isoquinoline (Eq. 183).



The Bucherer reaction of 8-hydroxyisoquinoline has been successfully used for the synthesis of both 8-aminoisoquinoline and its 8-aminopropyldiethylamino derivative.[222]

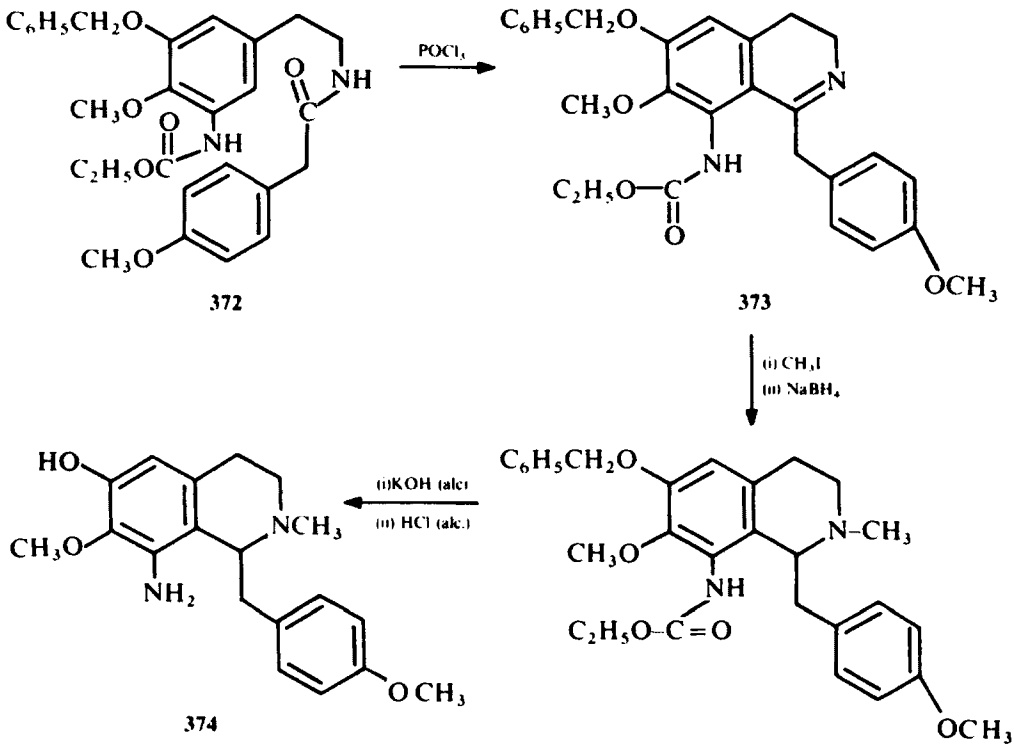
The synthesis of the 8-amino-1,2,3,4-tetrahydroisoquinoline **371** may be accomplished from the 8-substituted isoquinoline carboxylic acid **370** using a Curtius reaction (Eq. 184).[232,233]



(184)

The synthesis of 8-aminoisoquinoline may also be accomplished by ring-closure reactions using either sulfuric acid[234] or Bischler–Napieralski conditions.[235-238] The incorporation of *m*-acylamido groupings in various phenylethylamides (as described for the preparation of the 6-substituted compounds) is well documented.[235-238] The addition of a *m*-benzyloxy grouping (**372**) to these *m*-acylamidophenylethylamides allows only one position of closure and gives a single product—a 1,6,7-trisubstituted 8-acylamido-3,4-dihydroisoquinoline **373** (Eq. 185). Subsequent reduction and hydrolysis yields the corresponding 8-amino-1,2,3,4-tetrahydroisoquinoline **374**, a general structure important in the elucidation of the homolinearisine alkaloids.[236-238]

Appropriately substituted *o*-toluidine derivatives **375** and **377** may be ring-closed using sulfuric acid to yield 8-amino-1,2,3,4-tetrahydroisoquinolines **376** and **378**[239] (Eq. 186).



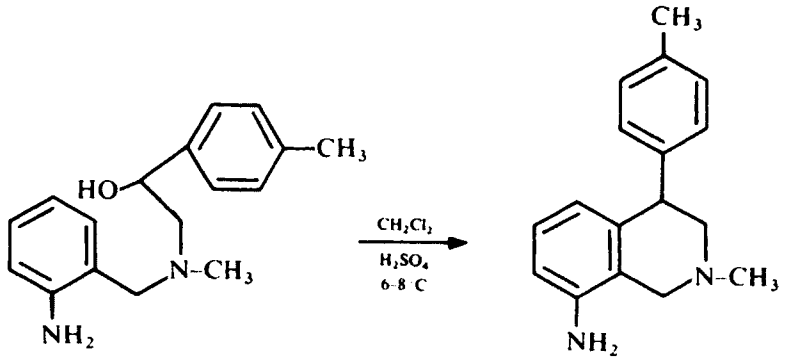
(185)

An unusual synthesis of 5-hydroxy-8-aminoisoquinoline **380** has been reported by Fieser,[183] involving the electrophilic substitution of 5-hydroxisoquinoline with benzene diazonium chloride in the presence of base with subsequent reduction of the intermediate 8-diazonium isoquinoline compound **379** (Eq. 187).

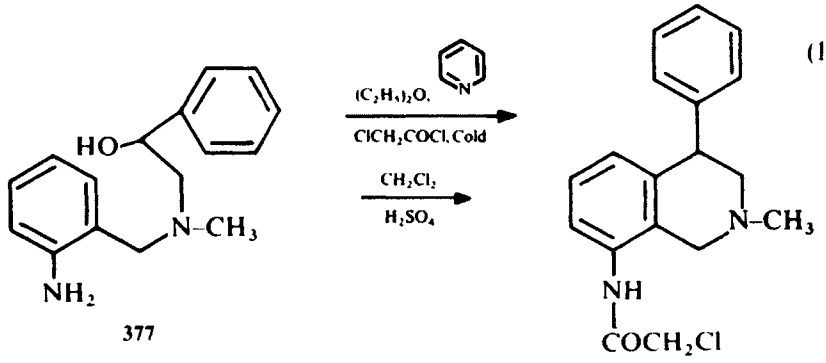
In a study related to Fieser's,[183] pursuant to the investigation of some arsonoarylaminoisoquinolines, a series of 8-azobenzenearsonic acids have been prepared.[49] Coupling of various 5-aminoisoquinolines with several diazotized anilinoarsonic acids results in the introduction of the azobenzene arsonic acid grouping at the 8 position, comparable to structure **379** (Eq. 187).

The copper acetate oxidation of 6-hydroxyisoquinoline, in the presence of piperidine or morpholine, produces the 8-piperidino- (or morpholino-) isoquinoline-5,6,dione **381**[240] (Eq. 188).

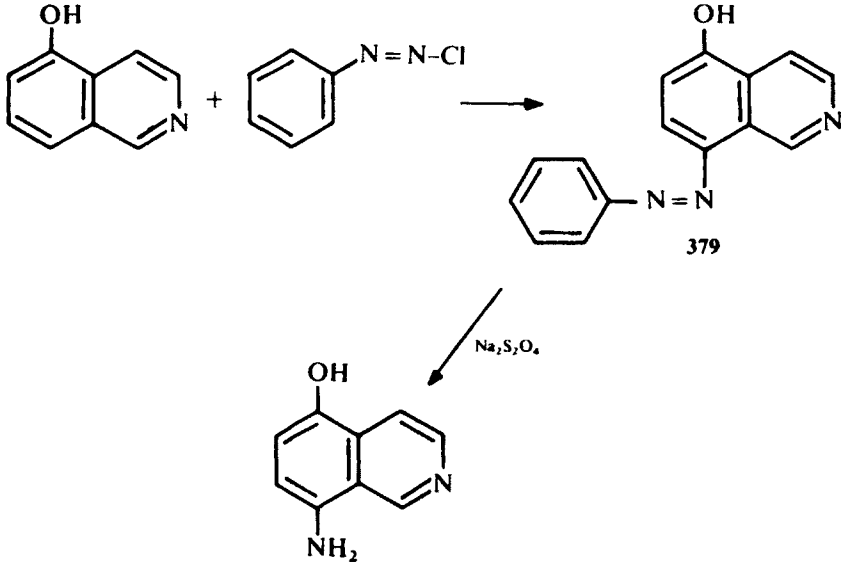
The swamping-catalyst technique[228] for the synthesis of 5-bromo-8-nitroisoquinoline was employed to produce three diastereoisomeric 8-amino-2-methyldecahydroisoquinolines.[241] Depending on the reducing conditions, subsequent quaternization, followed by selective concurrent catalytic hydrogenation and dehalogenation, enabled the isolation of 8-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline **382** or three of the possible four diastereoisomeric 8-amino-2-methyldecahydroisoquinolines **383** (Eq. 189).



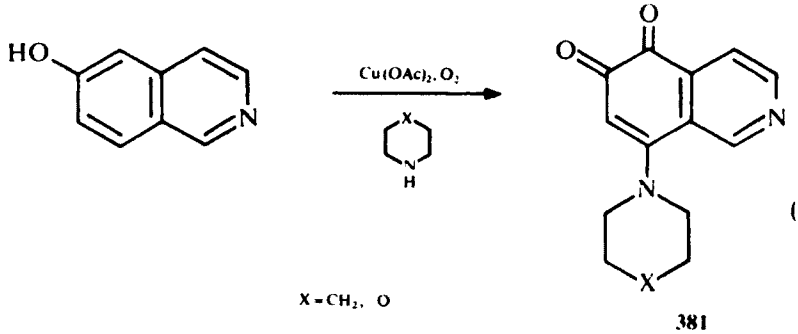
375 376



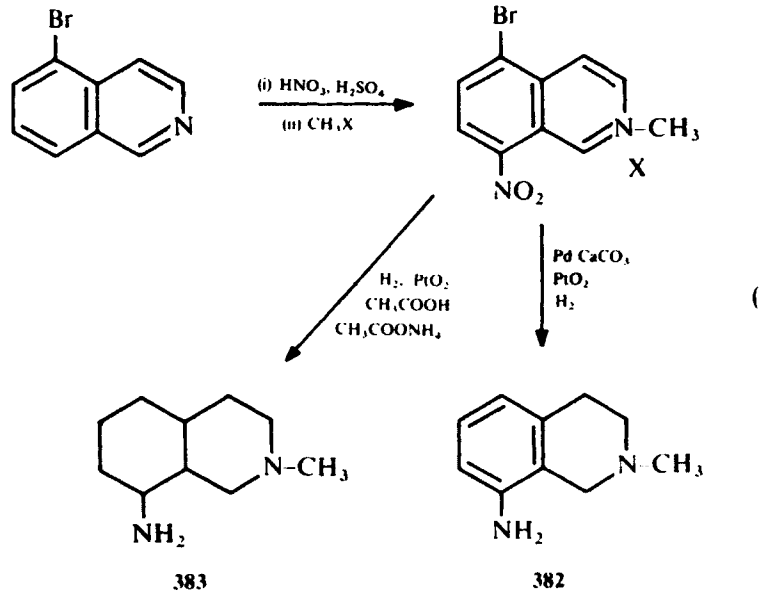
377 378 (186)



379 380 (187)



(188)

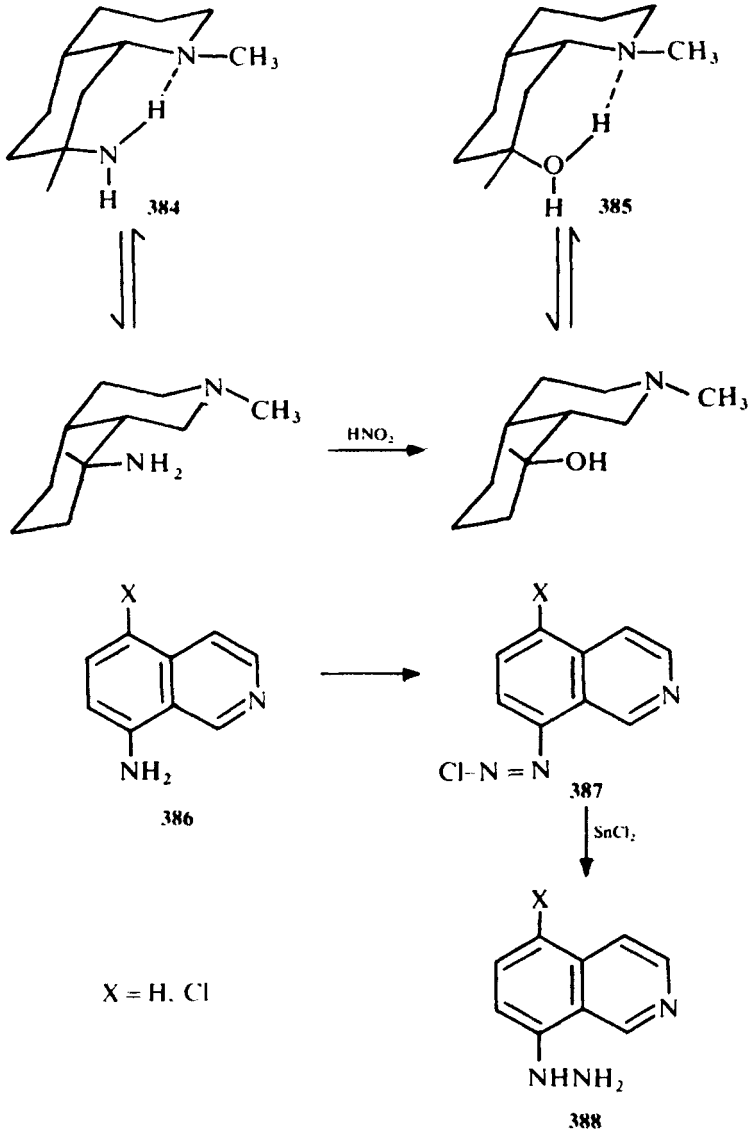


(189)

One of the cis ring-junction isomers demonstrated intra molecular hydrogen bonding, the axial amino group forming a bond with the heteroatom. Proof of the stereochemistry of the three isomers was obtained from both spectral data and deamination with nitrous acid to the known alcohols. Unexpectedly, the axial amine **384** gives high yields of the axial alcohol **385**, which is not in conflict with the established high-yield conversions of equatorial amines due to the conformational equilibrium of the axial amine (Eq. 190).

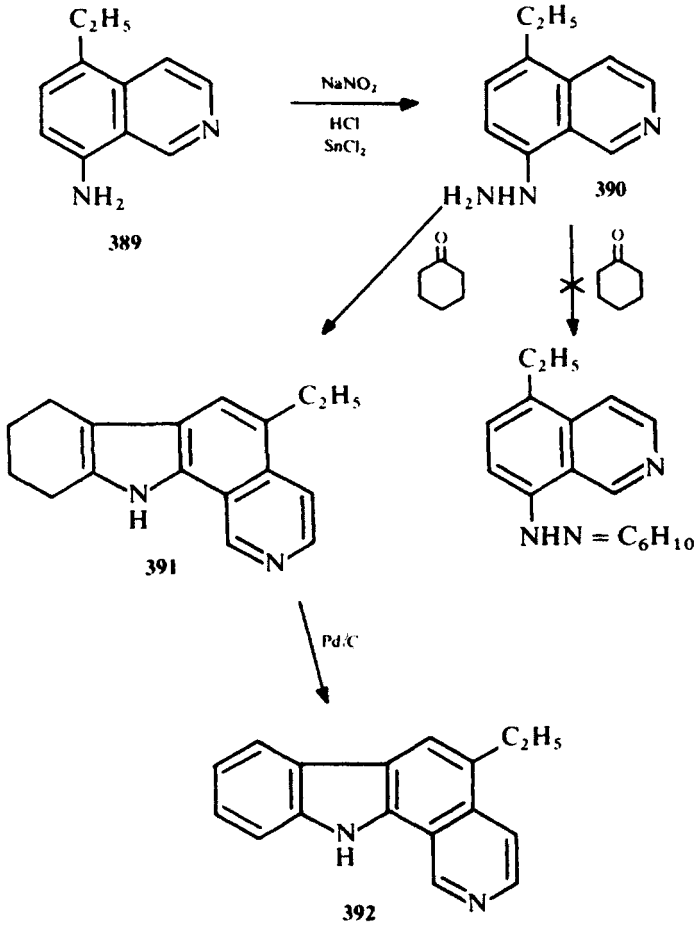
B. 8-Hydrazinoisoquinolines

8-Aminoisoquinolines **386** have been employed in the synthesis of the hydrazine analogs **388** by way of the formation of the diazonium salt **387**, followed by reduction using stannous chloride in HCl[198,242] (Eq. 191). Yields on



the order of 80% are obtained.[198] These hydrazines may be utilized as intermediates for the preparation of 1-*H*-pyrrolo-[3,4-h]-isoquinolines.[242]

Treatment of the 8-aminoisoquinoline **389** with sodium nitrite in hydrochloric acid also yields the 8-hydrazinoisoquinoline derivative **390**[243] (Eq. 192). Attempts to prepare its *N*-cyclohexyl hydrazide derivative by reaction of **390** with cyclohexanone does not proceed smoothly; Fisher indolization occurs to yield the pyridocarbazole derivative **391**. Dehydrogenation of **391** over palladium on charcoal readily affords the aromatized analog **392** (Eq. 192).



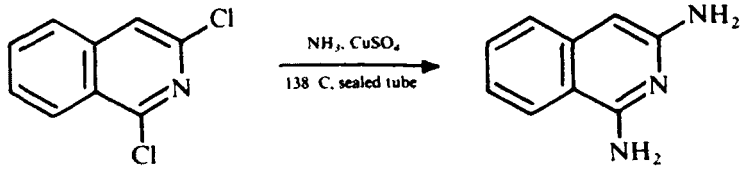
(192)

X. PREPARATION OF ISOQUINOLINES HAVING BASIC GROUPINGS AT TWO POSITIONS

A. 1,3-Diaminoisoquinolines

Two procedures are available for the synthesis of these disubstituted isoquinolines. 1,3-Dichloroisoquinoline **393**, on treatment with ammonia and copper sulfate in a sealed vessel at elevated temperature, gives good yields (60%) of the desired 1,3-diaminoisoquinoline **394**[244] (Eq. 193). The omission of the copper salt from the reaction results in amination at the 1 position only.[244]

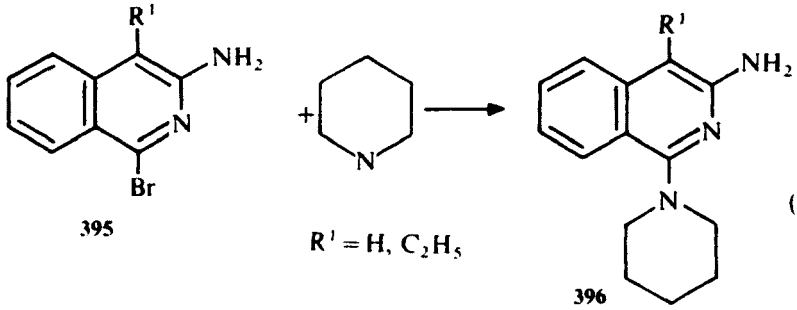
The amination of unsubstituted isoquinoline using sodamide in dimethylaniline yields only small quantities of 1,3-diaminoisoquinoline (9%).[244]



(193)

393 394

1-Halo-3-aminoisoquinolines, the typical products of the Johnson and Nasutavicus[118] synthesis of 3-aminoisoquinolines, have been used for the preparation of 1,3-diamino compounds, making use of the previously noted lability of halogens substituted at the 1 position of isoquinoline.[245] 1-Piperidino and (1-*N*-1,2,3,4-tetrahydroisoquinolinyl)-3-aminoisoquinolines **396** are produced by the reaction of the corresponding secondary amines with the haloaminoisoquinoline **395** in moderate yields[245] (Eq. 194).



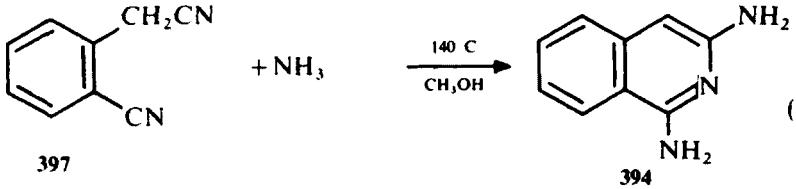
(194)

395

$R^1 = H, C_2H_5$

396

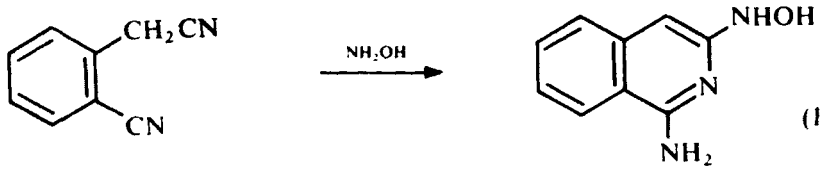
The alternative procedure to the methods already described involves treatment of *o*-cyanobenzyl cyanides **397** with ammonia at high temperature,[246] resulting in yields on the order of 70% (Eq. 195).



(195)

397 394

Nitrosation has been shown to occur at the 4 position of 1,3-diaminoisoquinolines.[246] The addition of hydroxylamine to *o*-cyanobenzylcyanide **397** has been shown to give high yields of 1-amino-3-hydroxyaminoisoquinoline **398**[247] (Eq. 196).

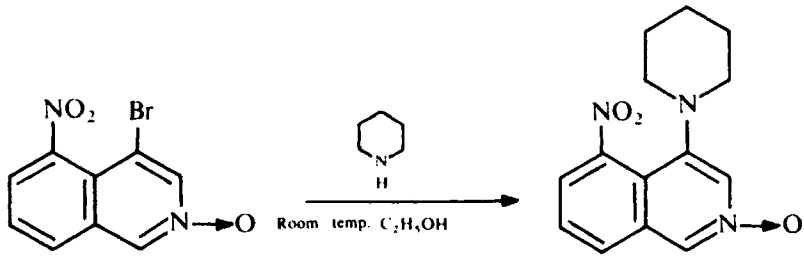


(196)

397 398

B. 1,4-Diaminoisoquinolines

As noted with the 4-aminoisoquinolines, the 1,4-diaminoisoquinolines are similarly difficult to prepare; however, isoquinoline *N*-oxides can provide a basis for a route of synthesis. 5-Nitro-4-bromoisoquinoline *N*-oxide (**399**), on treatment with secondary bases (e.g., piperidine, piperazine, morpholine, or diethylamine) in ethanol, readily affords the 4-amino-substituted analog **400** in yields dependent on the amine[53] (Eq. 197). Reduction of the *N*-oxide followed by chlorination of the resulting 4-amino-substituted isoquinoline with phosphorus oxychloride at the 1 position gives a product **401** from which the 1,4-diamine **402** may be obtained by a second exposure to secondary amine. As an alternative, if the same basic groupings at both the 1 and 4 positions are desired, **399** may be treated with the secondary amine under reflux in the absence of solvent[53] (Eq. 197).



399 **400**

(197)

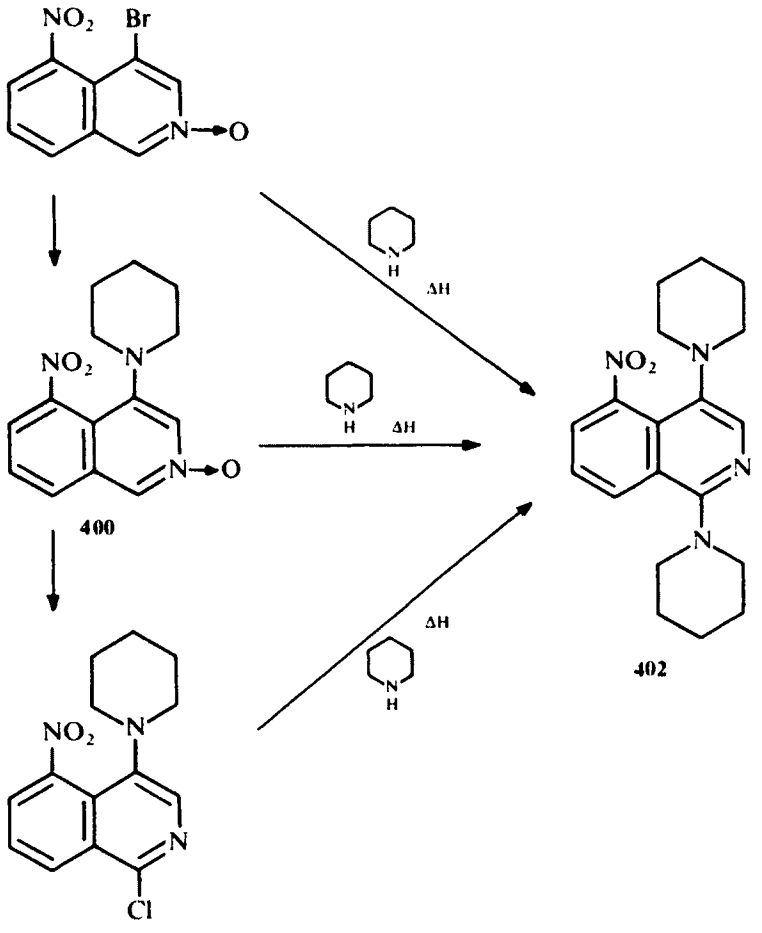
As a logical extension of these findings, the refluxing of 4-bromoisoquinoline *N*-oxide with secondary amines in the absence of solvent to yield the 1,4-diaminoisoquinoline is possible.[53] A summary of the routes available to the 1,4-dipiperidinoisoquinolines is shown in Eq. 198.

C. 2,3-Diaminoisoquinolines

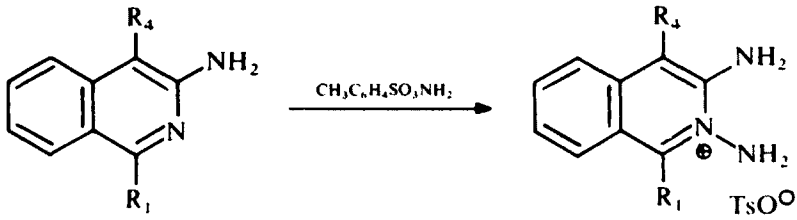
2,3-Diaminoisoquinolines **403** may be prepared from the corresponding 3-aminoisoquinolines by treatment with *p*-toluenesulfonamide[248] (Eq. 200).

D. 5,8-Diaminoisoquinolines

The nitration of isoquinoline provides a route for the inclusion of basic groupings at both the 5 and 8 positions. Reduction of 5-nitroisoquinoline to the amine, followed by treatment with diazotized sulfanilic acid, results in the introduction of the diazosulfanilic acid grouping at the 8 position (**404**).[178]



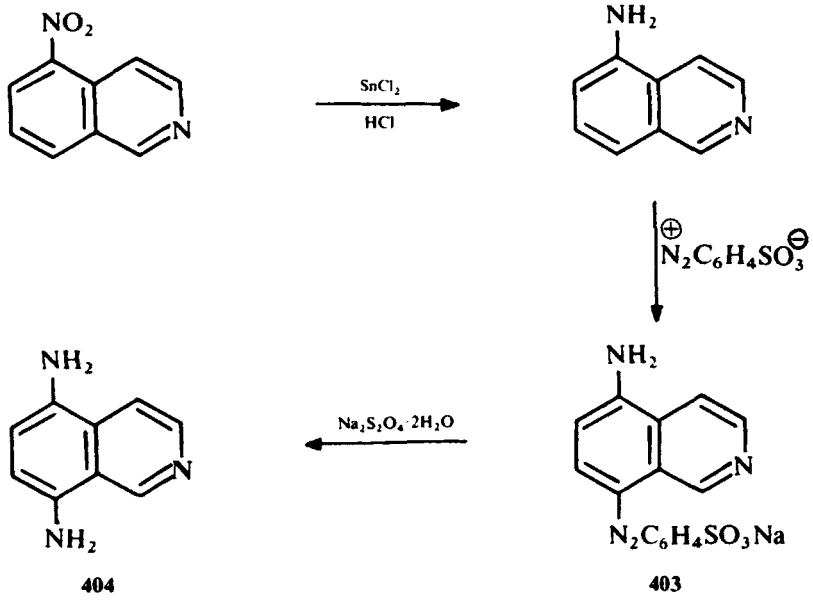
(198)



403

(200)

Sodium hydrosulfite reduction of the diazo grouping of **403** to the amine affords the 5,8-diamine **404**[178] (Eq. 201). These compounds provide an excellent route to isoquinoline-5,8-diones.



(201)

3-Methylisoquinoline and 7-methoxyisoquinoline have been aminated a similar manner.[184] In the case of 7-methoxyisoquinoline, the initial nitration occurs at the 8-position, with the diazosulfanilic acid grouping attacking the 5 position of the subsequently prepared 7-methoxy-8-aminoisoquinoline.[184]

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CHAPTER IV

Isoquinolines Containing Oxidized Nitrogen Functions and Their Hydrogenated Derivatives

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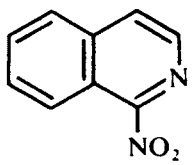
I. INTRODUCTION

The literature survey for this chapter covered all papers abstracted in Volumes 1–105 of *Chemical Abstracts*. The nitroisoquinolines represent the largest class of isoquinoline derivatives containing oxidized nitrogen functionalities. These derivatives are discussed in Section II, which includes a consideration of nitro derivatives of all oxidation states of the isoquinoline ring system. The few examples known of nitrosoisoquinolines are discussed in Section III. Sections IV–VIII treat the chemistry of the various diaza- and triaza-functionalized isoquinoline derivatives.

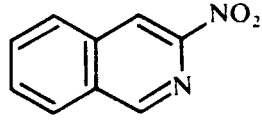
II. NITROISOQUINOLINES

Approximately 50% of all known nitroisoquinolines are derivatives of 5-nitroisoquinoline, while approximately 25% bear 7-nitro substituents. The high proportion of isoquinoline derivatives with the nitro group at one of these two sites is a direct reflection of the predominant C-5 nitration of aromatic isoquinolines [Section II.A (b)] and C-7 nitration of both 3,4-dihydroisoquinolines [Section II.A (d)] and 1,2,3,4-tetrahydroisoquinolines [Section II.A (e)]. There are few known dinitroisoquinoline derivatives, and apparently no examples of isoquinolines bearing three or more nitro groups as substituents on ring atoms.

The parent 1-nitroisoquinoline (**1**) appears to be the only example known of an isoquinoline bearing a 1-nitro substituent. This compound has been prepared by treating[1] 1-iodoisoquinoline with sodium nitrite in dimethyl sulfate (?) at 100°C, and also by the oxidation of the unstable 1-nitrosoisoquinoline with ozone.[2]



1



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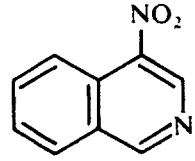
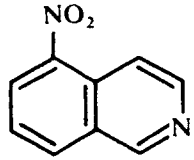


3

The parent 3-nitroisoquinoline (**2**) appears to be unknown, although a number of more highly substituted 3-nitroisoquinoline derivatives have been reported.[3–6]

4-Nitroisoquinoline (**3**) is available in low yield from the nitration of isoquinoline in acetic anhydride,[7] or via two different multistep routes. The C-4 nitro group has been introduced by nitrite attack after diazotization of 4-aminoisoquinoline,[8] or by nitration of 1-aminoisoquinoline followed by the removal of the amino group in several steps.[9]

5-Nitroisoquinoline (**4**) is the major product from the mixed-acid (HNO_3—H_2SO_4) nitration of isoquinoline[10–17] [Section II.A (a)]. It is also available from the deoxygenation of 5-nitroisoquinoline-*N*-oxide,[10] and the decarboxylation of 5-nitroisoquinoline-1-carboxylic acid.[18] This latter route has also been used[19] for the preparation of 1-deuterio-5-nitroisoquinoline from the deuterated carboxylic acid.



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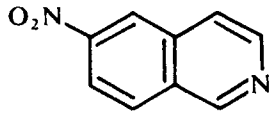
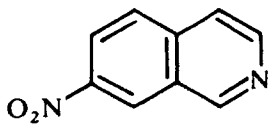


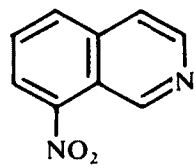
5

6-Nitroisoquinoline (**5**) is available[20] in good yields in a one-pot synthesis from the ozonolysis of 6-nitroindene to the nitro-substituted homophthalaldehyde, which is subsequently ring-closed to 6-nitroisoquinoline with ammonia. This compound has also been made by the mercuric acetate oxidation of its 1,2,3,4-tetrahydro derivative,[21,22] and also from deoxygenation of its *N*-oxide.[22,23] However, these latter routes are of no synthetic interest, since these precursors are only available in trace amounts from nitration reactions.

7-Nitroisoquinoline (**6**) is available from the aromatization of either its 3,4-dihydro derivative[24] or its 1,2,3,4-tetrahydro derivative.[21,25] These latter species are each obtained in good yields in the nitration of the corresponding partially reduced isoquinolines. 7-Nitroisoquinoline is also available[20] from 5-nitroindene in a manner analogous to that described above for its 6-nitro isomer.



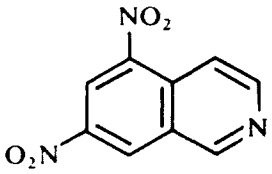
6



7

8-Nitroisoquinoline (**7**) is the minor product (10–15%) in the nitration of isoquinoline in mixed-acid media[10,14] [Section II.A(a)]. It has also been made via deoxygenation of its *N*-oxide,[10,26] and via decarboxylation of its 3-carboxylic acid derivative.[27]

There seem to be only three known dinitroisoquinolines lacking further substituents, and even in one of these, the orientation of the two nitro groups has not been definitely established. In 1893, Claus and Hoffmann[11] reported a dinitroisoquinoline (m.p. 238.5°C) from the "high-temperature" nitration (KNO_3—H_2SO_4) of isoquinoline. Gensler[28] suggested that this product is 5,7-dinitroisoquinoline (**8**), apparently assuming that it was formed via the nitration of 5-nitroisoquinoline, and that the introduction of the second nitro group was



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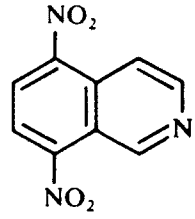

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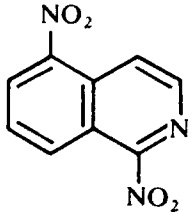
controlled by the meta-directing effect of the 5-nitro group. However, in the patent literature,[29,30] Serban reports the nitration of 5-nitroisoquinoline in KNO_3–H_2SO_4 at 180°C to give a product (m.p. 241–242°C) in 10% yield which "nuclear magnetic resonance spectra confirmed" to be 5,8-dinitroisoquinoline (**9**), although the spectral data do not seem to have been reported. This is almost certainly the same product reported by Claus and Hoffmann, given the similar nitration conditions and melting points of the products. A definitive structural proof seems to be required, and should probably include an investigation of the products of nitration of both 7- and 8-nitroisoquinolines.

1,5-Dinitroisoquinoline (**10**) (m.p. 195–200°C) was also reported by Serban[29,30] as the product from the nitration of 1-nitroisoquinoline, although a structural proof was not given. 4,6-Dinitroisoquinoline (**11**) (m.p. 182–183°C), which appears to be the only dinitroisoquinoline for which an unambiguous structural proof is available, was obtained[31] in good yield from the mixed-acid nitration of bis-1,1′-(2-acetyl-1,2-dihydroisoquinoline) [Section II.A(c)].



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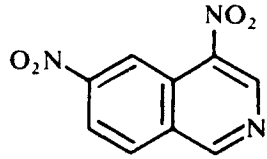

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Several dinitro derivatives of 1,2,3,4-tetrahydroisoquinoline[32,33] [Section II.A(e)], dinitro 1(2H)-isoquinolinones[34–36] [Sections II.A(f) and II.C], and a dinitro 1,3-isoquinolinediamine[37] (Section II.C) are also known. A dinitro derivative of undetermined structure was also reported[38] from the nitration of isoquinoline-*N*-oxide with concentrated nitric acid in the presence of P_2O_5.

A. Nitration of Isoquinolines

Nitration of the appropriately substituted isoquinoline ring system is by far the commonest route used for the introduction of a nitro group as a substituent on a ring-carbon atom.

(*a*) *Isoquinoline and Isoquinolinium Cations*

The nitration of isoquinoline in a mixture of nitric and sulfuric acids (or the equivalent KNO_3 in H_2SO_4) gives a mixture of 5- and 8-nitroisoquinolines. The ratio of these isomeric products is relatively temperature-insensitive,[10] with the 9:1 ratio in favor of C-5 nitration at 0°C changing only to 85% of the 5-nitro isomer and 15% of the 8-nitro isomer at 100°C. Under these mixed-acid nitration conditions, nitration gives a product distribution typical of other electrophilic substitution reactions upon isoquinoline.[39] Competition experiments indicated[10] that mixed-acid nitration of isoquinoline occurs 25 times faster than the nitration of quinoline, although kinetic data under similar conditions suggest only a 14-fold difference in the reactivities of these two heterocycles during nitration.[40] The standardized rate constants developed by Katritzky and co-workers[41] suggest an even smaller difference in the rates of nitration, with the isoquinolinium cation reacting four- to six-fold faster than the quinolinium cation. These standardized rate constants also indicate that the isoquinolinium cation is nitrated more than 10^7-fold more slowly than is naphthalene under the same conditions.

The kinetics of the nitration of isoquinoline have been investigated by Moodie and co-workers[40,42,43] in 67.7–83.7% sulfuric acid at 25 and 80°C, and activation parameters have been determined in 81.3% sulfuric acid. Over this acidity range, the rates of nitration of isoquinoline and the *N*-methyl isoquinolinium cation are very similar, and plots of log k_{obs} v. $(H_R + \log a_{H_2O})$ are linear and parallel for these two substrates. This is a clear indication that under these acidic conditions nitration occurs on the isoquinolinium cation rather than the neutral isoquinoline molecule. The observed acidity dependence is also consistent with nitronium cation (NO_2^+) being the active nitrating species. Partial rate factors relative to benzene for the nitration of the isoquinolinium cation at C-5 and C-8 are 9×10^{-6} and 1×10^{-6}, respectively, in these acidic solutions (assuming a 9:1 isomer distribution in the product[10]).

Nitration of isoquinoline-*N*-oxide also gives approximately 90% nitration at C-5 and 10% nitration at C-8 in HNO_3—H_2SO_4 mixtures.[10] The acidity dependence of the rate of nitration of this *N*-oxide also parallels the data for isoquinoline and both the *N*-methyl and *N*-methoxyisoquinolinium cations.[42] Thus, the *N*-oxide also reacts in its protonated form (the *N*-hydroxyisoquinolinium cation) in these highly acidic nitration media. The relative reactivities of these four isoquinolinium cations (**12**) toward nitration are summarized in Table II.1.

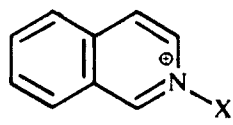

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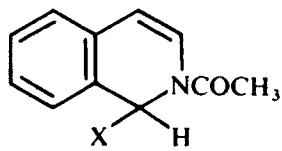
TABLE II.1. Relative Rates of Nitration of Isoquinolinium Cations (12)

X	Rel. Rate[a]	$-d(\log k_{obs})/d(H_R + \log a_{H_2O})$[a]	$\log k_2^0(M^{-1}s^{-1})$[b]
H	1.0	1.01	−5.16
CH_3	1.0	1.01	−4.93
OH	0.47	0.96	−5.58
OCH_3	0.13	0.98	−6.13

[a]In 76.3% H_2SO_4 at 25 °C; data from references 40, 42, 43.
[b]Standardized rate constants at $H_0 = -6.6$ and 25 °C from reference 41.

Nitration conditions other than the mixed-acid media discussed above have occasionally been used, with nitro isomer distributions other than the usual C-5 (major) and C-8 (minor) nitration products being found. Yields in these alternative nitrations are usually quite low. 4-Nitroisoquinoline has been isolated in 14% yield from the nitration of isoquinoline with nitric acid in acetic anhydride.[7] This reaction presumably proceeds via nitration of a 1,2-dihydroisoquinoline intermediate such as **13** (X = ONO_2 or $OCOCH_3$) [cf. nitration of bis-1,1'-(2-acetyl-1,2-dihydroisoquinoline) in Section II.A(c)]. Electrophilic attack at C-4 of such 1,2-dihydroisoquinoline enamines is known to be quite facile.[44–46] Such a mechanism is analogous to that proposed for the bromination of isoquinoline to give 4-bromoisoquinoline in the absence of Lewis acid catalysts.[47]



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Nitration of isoquinoline-*N*-oxide with fuming nitro acid is reported[22] to give very low yields of a mixture of the 5-, 6-, and 8-nitro *N*-oxides, with the unusual C-6 nitration product predominating (maximum yield ≈ 7%) under certain conditions.

(*b*) *Substituted Isoquinolines**

Numerous substituted isoquinolines have been nitrated in mixed nitric–sulfuric acids, with the conditions of Le Fevre and Le Fevre[12] being most commonly used. Reaction products isolated in the cases investigated to date are

*Isoquinolinones are discussed separately in Section II.A (f).

collected in Table II.2. In most cases these nitrations were performed as part of a synthetic procedure, and the major product was isolated and purified without any attempt being made to isolate any minor nitration products which may have been present. Careful studies[27,48,49] of the nitration of 3-methylisoquinoline have revealed that 3-methyl-5-nitroisoquinoline predominates over its 8-nitro isomer in the ratio 5:1.

From a perusal of Table II.2 it is clear that most substituents do not alter the preference of the isoquinoline system for nitration at C-5 and C-8. The only clear exceptions in the table to this generalization are the 1-amino and 4-hydroxy isoquinolines which apparently nitrate at C-4 and C-3, respectively,[9,3] although the nitration of 1-aminoisoquinoline is said to give a sulfur-containing product of uncertain structure.[9] Thus, the activating effect of these two substituents upon the pyridine ring apparently outweighs the normal deactivation of such rings by the ring-nitrogen atom.

TABLE II.2. Nitration of Isoquinolines in HNO_3—H_2SO_4

Substituent(s)	Products(s)[a]	Ref.
H	5-NO_2,8-NO_2	10–17
1-CH_3	5-NO_2	50, 51
1-$(CH_2)_4CH_3$	5-NO_2	29, 30
1-C_6H_5	1-(3-$NO_2C_6H_4$)-5-NO_2	52
1-$CH_2C_6H_5$	1-(4-$NO_2C_6H_4CH_2$)-5-NO_2	53, 54
1-(4-$NO_2C_6H_4CH_2$)	5-NO_2	52, 55
1-CO_2H	5-NO_2	18
1-Cl	5-NO_2	56–58
1-NH_2	4-NO_2[b]	9
1-NO_2	1,5-$(NO_2)_2$	29, 30
2-oxide	5-NO_2,8-NO_2	10, 26, 38, 59
3-CH_3	5-NO_2,8-NO_2	15, 27, 29, 30, 48
3-Cl	5-NO_2	29, 30, 60
4-$CH_2C_6H_5$	4-(4-$NO_2C_6H_4CH_2$), 4-(4-$NO_2C_6H_4CH_2$)-5(or 8)-NO_2	61, 62
4-Br	5-NO_2,8(?)-NO_2	29, 30, 63, 64
4-OH	3-NO_2	3
4-OTs	3-NO_2-4-OH	3
5-CH_2CH_3	8-NO_2	65
5-Br	8-NO_2	66–68
5-Cl	8-NO_2	69
5-$NHCOCH_3$	8-NO_2	70
5-NO_2	5,8-$(NO_2)_2$(?)[c]	29, 30
7-Cl	8-NO_2	69
7-OH	8-NO_2	71
7-OCH_3	8-NO_2	72
1-CN-2-oxide	5-NO_2,6-NO_2,8-NO_2	22, 23
1-Br-3-$NHCOCH_3$	5(?)-NO_2	73
1-Cl-3-CH_2CH_3	5-NO_2	58
1,3-Cl_2	5-NO_2	74, 75

TABLE II.2. Nitration Isoquinolines in HNO_3—H_2SO_4 (*Continued*)

Substituent(s)	Products(s)[a]	Ref.
1,4-$(CH_3)_2$	5-NO_2	76
1-OCH_2CH_3-4-CO_2H	5-NO_2	79
1-CH_3-5-CH_2CH_3	8-NO_2	65
1-CH_3-5-Cl	8-NO_2	77
3-CH_3-4-OAlkyl	5(?)-NO_2	78
1-Cl-3-CH_2Cl-4-CH_3	5-NO_2	80
1-(3,4-$(OCH_3)_2C_6H_3CH_2$) -6,7-$(OCH_3)_2$[d]	1-(4,5-$(OCH_3)_2$-2-$NO_2C_6H_2CH_2$)	81–83
5,8-$(CH_3)_2$-6-OH	**14**	84
5,8-$(CH_3)_2$-6-OCH_3	**14**	84
1-(2-$BrC_6H_4CH_2$) -3-OH-6,7-$(OCH_3)_2$	4-NO_2	121
1,1'-Biisoquinoline	5-NO_2,5,5'-$(NO_2)_2$	31

[a] Site of nitration is shown; all other substituents are the same as in the starting material unless indicated otherwise.

[b] Nitration at room temperature with KNO_3—H_2SO_4 gave an unidentified sulfur-containing compound (m.p. 250°C). The presence of the 4-nitro substituent in this product was established by deamination.

[c] See text [Section II.A(a)].

[d] Nitration of papaverine with concentrated HNO_3.

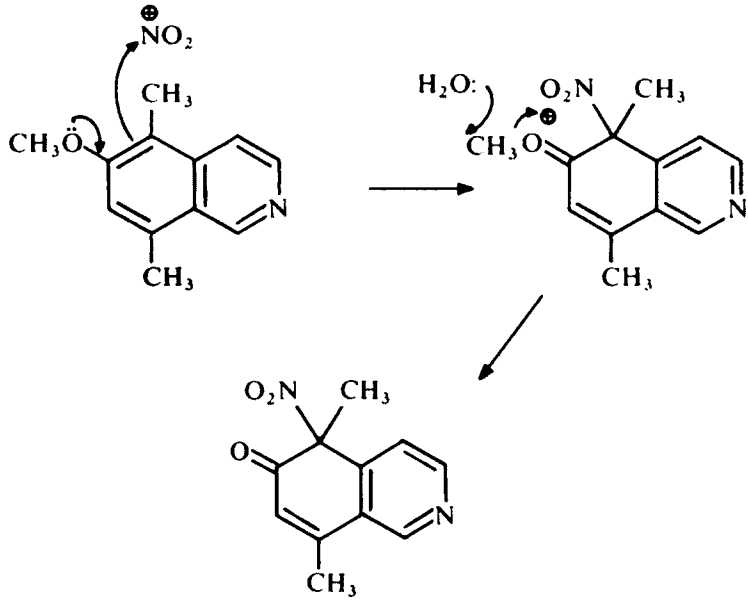
The presence of another aromatic ring in the molecule, from a pendant phenyl or benzyl substituent, usually leads to initial nitration in this substituent ring, followed by nitration upon the isoquinoline ring system.

When nitration at C-5 is blocked by a prior substituent at this site, complete nitration usually occurs at the secondary C-8 site. The presence of an ortho/para directing group at C-7 also appears to lead to predominant C-8 nitration, irrespective of whether this substituent is activating (OH, OCH_3) or deactivating (Cl). With the exception of the 1-NH_2 and 4-OH cases mentioned above, the presence of a variety of substituents upon the pyridine ring does not alter the preference for predominant C-5 nitration. The 4-tosyloxy derivative is presumably (although not necessarily) detosylated before nitration, since it gives the same product as is obtained in the nitration of 4-hydroxyisoquinoline.

Mixed-acid nitration of 1-cyanoisoquinoline-*N*-oxide gives low yields of the 5-nitro and 6-nitro derivatives, with the latter isomer predominating under some conditions.[22,23] However, nitration of this species with fuming nitric acid gives a mixture of mainly the 6- ($\approx$50% yield) and 8-nitro ($\approx$10% yield) derivatives, although some deoxygenation also occurs. The related result for isoquinoline-*N*-oxide itself was commented upon in Section II.A(a).

The mixed-acid nitration of 5,8-dimethyl-6-methoxyisoquinoline is unusual[84] and interesting because both of the usual C-5 and C-8 nitration sites are blocked. The product (**14**) clearly results from the combination of the usual directing effect

of the ring-nitrogen atom with the directing effects of the 6-OCH_3 and 8-CH_3 substituents. Attack at C-7 is precluded by the necessity for complete disruption of aromatic character in the σ-complex intermediate for which Kekulé resonance contributions are not possible when the positive charge is located on oxygen. A simple mechanism for this nitration requires demethylation following formation of the C-5 σ-complex intermediate. The same product (**14**) has also been obtained from the nitration of 5,8-dimethyl-6-hydroxyisoquinoline with nitric acid in acetic anhydride.[84] These reactions are quite analogous to the nitrations of 1-methyl-2-naphthol and 1,4-dimethyl-2-naphthol to give 1-methyl-1-nitro-2-oxonaphthalene derivatives.



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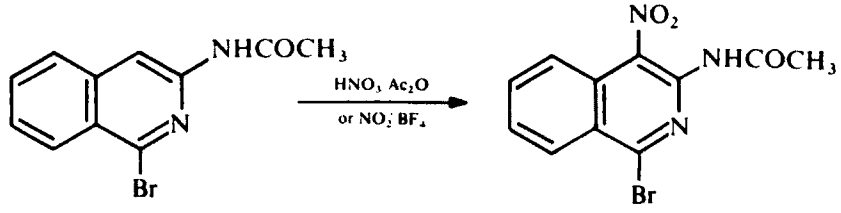
Nitration of 3-acetamido-1-bromoisoquinoline with nitric acid in acetic anhydride at room temperature occurs at C-4 in 50% yield,[73] and this same product is also obtained upon nitration with nitronium tetrafluoroborate in a mixture of tetramethylene sulfone and nitromethane.[73] The usual nitric–sulfuric acid nitration of **15** occurs in the homocyclic ring[73] and presumably gives the 5-nitro isomer of **16**, although the structure of this product was not definitely established. The reaction via the nitronium salt must involve the neutral molecule of **15** in which the activating effect of the acetamido group is apparently sufficiently great to offset the deactivating effects of the bromine and ring-nitrogen atoms, and allow electrophilic attack in the heterocyclic ring. Even though the same electrophile is involved in the mixed-acid nitration, the isoquinoline is present essentially completely as the isoquinolinium cation under these conditions, and the additional deactivation of the heterocyclic ring as a

result of the positive charge results in electrophilic attack in the less-deactivated homocyclic ring.



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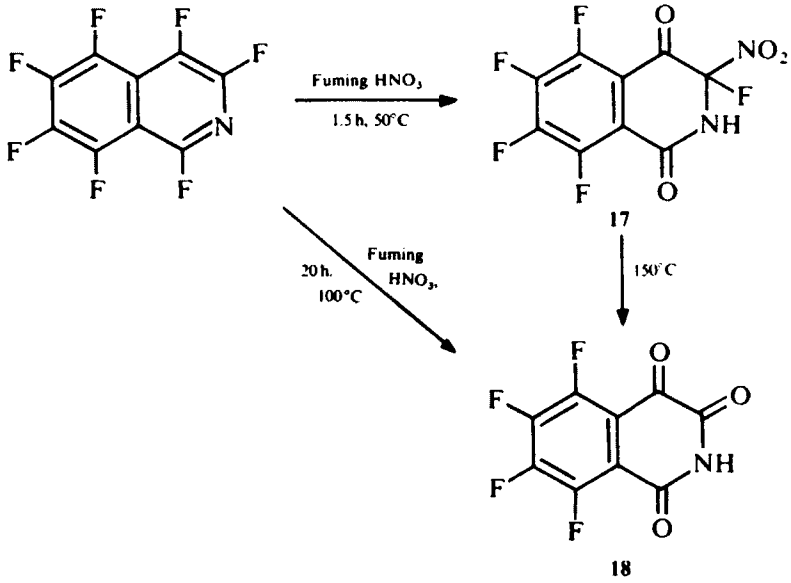
Nitration of perfluoroisoquinoline in fuming nitric acid at 50°C gives **17** in 78% yield.[6] This 3-nitroisoquinoline derivative undergoes a thermal decomposition to **18** at 150°C. This same 1,3,4-isoquinoline-trione is also obtained upon extended nitration of perfluoroisoquinoline at 100°C.



(*c*) *1,2-Dihydroisoquinolines*

1,2-Dihydroisoquinolines are enamines and, consistent with this functionality, they are observed[44] to undergo electrophilic attack at C-4, which is the β-carbon atom of the enamine moiety. In principle, nitration at C-4 of these species should therefore be possible, although in acidic solutions such nitration must compete with protonation at this β-carbon atom. There are relatively few examples of the nitration of 1,2-dihydroisoquinolines. This is probably attributable in large part

to the relative instability of these partially reduced isoquinoline derivatives.[44] However, it should be noted that the few successful 1,2-dihydroisoquinoline nitrations discussed below each occur on an *N*-acylated derivative, in which C-4 protonation is relatively unfavorable.

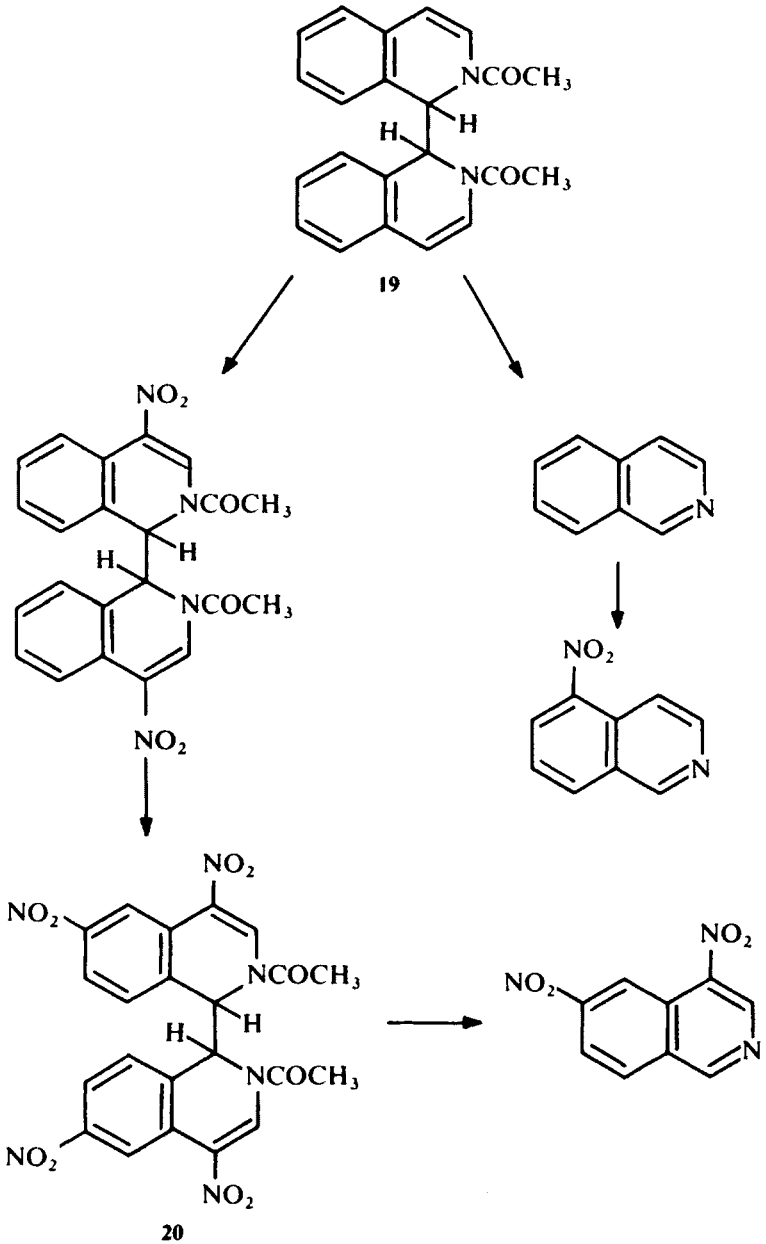
The C-4 nitration of isoquinoline in acetic anhydride was discussed above [Section II.A (a)] in terms of electrophilic attack upon the 1,2-dihydroisoquinoline derivative **13**. In a similar reaction, the nitration of several 1-benzyl-2-benzoyl-1,2-dihydroisoquinolines in nitric and acetic acids at 90°C gives good yields of the corresponding 4-nitro derivatives.[85]

The nitration of bis-1,1′-(2-acetyl-1,2-dihydroisoquinoline) (**19**) in HNO_3–H_2SO_4 gives[31] a mixture of 5-nitroisoquinoline (37%) and 4,6-dinitroisoquinoline (63%). The reaction conditions are known to lead to cleavage of the C(1)–C(1′) bond and deacetylation. The 5-nitroisoquinoline presumably arises from the nitration of isoquinoline produced by the oxidation and deacetylation of **19**. The dinitration reaction can best be understood as an initial facile electrophilic attack at C-4 of the enamine moiety of each dihydroisoquinoline ring in **19**. Further nitration of the 4-nitro-1,2-dihydroisoquinoline derivative at C-6 is consistent with the expected directing effects upon the homocyclic ring in this species. Subsequent oxidation and deacetylation of the 1,1′-bis-(2-acetyl-1,2-dihydro-4,6-dinitroisoquinoline) (**20**) would then lead to 4,6-dinitroisoquinoline. This sequence of events is indicated because no 4-nitroisoquinoline was observed among the reaction products (although it should be noted that not all the starting material is accounted for) and, if formed, such a doubly deactivated heteroaromatic system would be unlikely to be nitrated under the reaction conditions. The observed products also suggest that the 4-nitro substituent hinders the oxidation of the bis-(dihydroisoquinoline) system relative to the parent compound.

The good yield of 4,6-dinitroisoquinoline obtained in this reaction suggests that the nitration of *N*-acyl 1,2-dihydroisoquinolines bearing suitable protecting groups at C-4 may be a useful route to substituted 6-nitroisoquinolines, which may not otherwise be readily accessible.

In principle, all 1,2-dihydronitroisoquinolines are accessible via reduction of the corresponding nitroisoquinolinium cations[86] (hydride ion addition), although the only significant work of this type seems to be devoted to 1,2-dihydro-5-nitroisoquinolines. Thus, 5-nitroisoquinoline[87] and the 2-methyl-5-nitroisoquinolinium cation[88] have each been reduced by sodium borohydride in aqueous methanol to 1,2-dihydro-5-nitroisoquinoline and its *N*-methyl derivative, respectively. 5-Nitroisoquinolinium cations have also been reduced to their 1,2-dihydro derivatives using 1,4-dihydronicotinamides.[89,90]

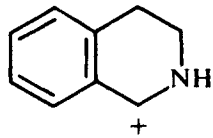
Various C-1-substituted 1,2-dihydronitroisoquinolines are also available from nucleophilic additions to nitroisoquinolinium cations. The acetone enolate ion has been demonstrated to readily add to 5-nitroisoquinolinium cations.[91–93] 5-Nitroisoquinoline and 8-nitroisoquinoline give only poor yields of the Reissert compounds under the usual reaction conditions, although 3-methyl-5-nitroisoquinoline does give a reasonable yield of the Reissert C-1 cyanide



adduct.[94, 95] It has been shown that these poor yields are attributable to the preference for hydroxide ion addition to C-1 of the *N*-acyl isoquinolinium cations in these reactions.[95] Good yields of the 5-nitroisoquinoline Reissert compounds are accessible when the reaction is performed in a two-phase system in the presence of a phase-transfer catalyst.[122]

(*d*) *3,4-Dihydroisoquinolines*

Mixed-acid nitration of 3,4-dihydroisoquinolines results in substitution at C-7 (unless this site is blocked by another substituent) and/or on a pendant phenyl ring of a substituent. All cases reported to date are collected in Table II.3. Predominant C-7 nitration is consistent with the expected directing effects from the alkyl unit and the carbocation in electrophilic attack on the resonance contributor **21** of the 3,4-dihydroisoquinolinium cation, which is the major species in solution under acidic nitrating conditions. The directing effect of the carbocationic center in **22** is also seen in the meta nitration of the substituent phenyl ring in 1-phenyl-3,4-dihydroisoquinoline.[52] These theoretical considerations also suggest that C-5 is the most likely alternative nitration site if C-7 is blocked. The only example[96] of such a reaction is the nitration of 3,4-dihydro-6-methoxy-7-isoquinolinol, which undergoes nitration at C-8, although this example is complicated by the conflicting directing and steric effects of the hydroxy and methoxy substituents.



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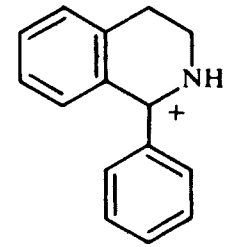

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TABLE II.3. Nitration of 3,4-Dihydroisoquinolines in HNO_3 H_2SO_4

Substituent(s)	Product(s)[a]	Ref.
H	7-NO_2	24
1-CH_3	7-NO_2	98
1-C_6H_5	7-NO_2	99
	1-(3-$NO_2C_6H_4$)-7-NO_2[b]	52
1-(4-ClC_6H_4)	7-NO_2	97
	1-(4-Cl-3-$NO_2C_6H_3$)-7-NO_2	97
1-(3-$NO_2C_6H_4$)	7-NO_2	52
1-(4-$NO_2C_6H_4$)	7-NO_2	53, 55
1-(4-Cl-3-$NO_2C_6H_3$)	7-NO_2	97
1-(3,4-$(CH_3O)_2C_6H_3$)	1-(4,5-$(CH_3O)_2$-2-$NO_2C_6H_2$)	100
6-OCH_3-7-OH	8-NO_2[c]	96
3,4-$(CH_3)_2$-1-(4-$NO_2C_6H_4$)	7-NO_2	52

[a]Site of nitration is shown; all other substituents are the same as in the starting material unless otherwise indicated.
[b]Nitration with concentrated HNO_3.
[c]Nitration with 40% HNO_3 with a catalytic amount of $NaNO_2$.

Dehydrogenation of 3,4-dihydro-7-nitroisoquinolines over palladium black is a useful route[24, 52, 97] to fully aromatic 7-nitroisoquinolines.

(e) *1,2,3,4-Tetrahydroisoquinolines*

The mixed-acid nitration of a 1,2,3,4-tetrahydroisoquinoline gives the 7-nitro derivative as the major product when C-7 is initially unsubstituted (Table II.4). However, minor amounts of the 5- and 6-nitro derivatives are also obtained in these reactions. The products from the nitration of 2-methyl-1,2,3,4-tetrahydroisoquinoline have been carefully investigated by three groups of workers. Durand-Henchoz and Moreau[101] and Mathison and Tidwell[32] each report the formation of the *N*-methyl 7-, 5-, and 6-nitro products in the ratio 20:4:1. Ochiai and Nakagome[21] originally reported the 6-nitro derivative as the predominant minor product, but this assignment was subsequently challenged.[101] Confusion arises in the assignment of the position of the nitro group via reduction to the amine and then diazotization to the phenol, because the 5-hydroxy and 6-hydroxy derivatives of 2-methyl-1,2,3,4-tetrahydroisoquinoline have the same melting point. It seems likely that the French workers' structural assignments are correct, and this then further suggests that the minor product reported by Ochiai and Nakagome[21] as the 6-nitro derivative in the nitration of 1,2,3,4-tetrahydroisoquinoline is probably also the 5-nitro isomer. The assign-

TABLE II.4. Nitration of 1,2,3,4-Tetrahydroisoquinolines

Substituent(s)	Product(s)[a]	Ref.
H	7-NO_2, 6(?)-NO_2[b]	21, 24 33
2-CH_3	7-NO_2, 5-NO_2, 6-NO_2	21, 32, 101
2-$(CH_2)_3CH_3$	7-NO_2	24
2-$CH_2C_6H_5$	7-NO_2	24
2-$COCH_3$	7-NO_2, 7-NO_2-1-oxo	21
7-NO_2	5,7-$(NO_2)_2$	33
2-CH_3-5-CN	7-NO_2	103
2-CH_3-7-Br	6-NO_2, 8-NO_2, 6,8-$(NO_2)_2$	32
1-(3,4-$(CH_3O)_2C_6H_3CH_2$)-6,7-(OCH_2O)[c]	1-(4,5-$(CH_3O)_2$-2-$NO_2C_6H_2CH_2$)	100, 104
1-(4-$(C_6H_5CH_2O)C_6H_4CH_2$)-2-CH_3-6-OCH_3-7-OH[d]	8-NO_2	105
1-(3,4-$(OCH_2O)C_6H_3CH_2$)-2-CH_3-6-OCH_3-7-OCH_2CH_3[c]	1-(4,5-(OCH_2O)-2-$NO_2C_6H_2CH_2$)	106
2,3-$(CH_3)_2$-6,7-$(OCH_3)_2$	8-NO_2	107

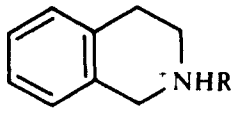
[a] Site of nitration is shown; all other substituents are the same as in the starting material unless otherwise indicated.

[b] See text.

[c] Nitration with nitric acid in acetic acid.

[d] Nitration with sodium nitrite in concentrated HNO_3.

ment of the 7- and 5-nitro derivatives as the main nitration products of the cation **23** is consistent with the ammoniomethyl substituent on the aromatic ring being meta-directing and the 2-ammonioethyl substituent being ortho-para-directing; in the nitration of the ammonium cations **24**, $n = 1$ leads to 88% meta nitration, whereas only 19% meta nitration is observed[102] for $n = 2$.



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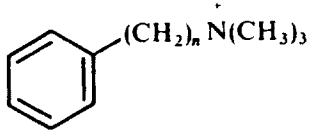
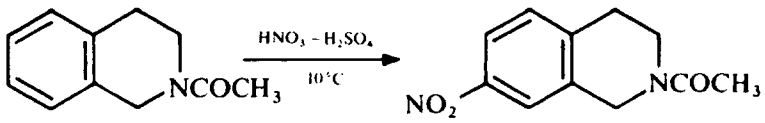


24

Nitration of 2-acetyl-1,2,3,4-tetrahydroisoquinoline is unusual. In addition to the expected C-7 nitration product, some oxidation of the C-1 methylene group of this nitration product is also observed.[21] Yields of 24 and 10% were reported for **25** and **26**, respectively. Oxidation at C-1 may occur either before or after nitration. A number of examples are known in which C-7 nitration occurs in a 1-isoquinolinone having C-4 blocked [Section II.A(f)].



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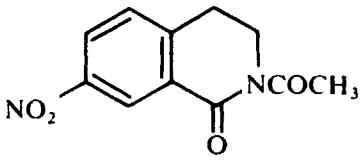

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The products obtained from the nitration of 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline are very sensitive to the reaction conditions.[32] When a 1:1 mole ratio of KNO_3 and the isoquinoline derivative is used in concentrated H_2SO_4 at 0–5°C, a mixture of the 6- (86%) and 8-nitro (14%) derivatives is obtained. The use of larger amounts of KNO_3 at room temperature leads to a reasonable yield of the 6,8-dinitro product. 5,7-Dinitro-1,2,3,4-tetrahydroisoquinoline has also been reported among the nitration products from 1,2,3,4-tetrahydroisoquinoline under mild conditions.[33]

2-Acetyl-6-nitro-7-isoquinolinol has been reported[33] among the reaction products in the diazotization of 2-acetyl-7-amino-1,2,3,4-tetrahydro-

isoquinoline. This is presumably formed via the nitration of the 7-hydroxy derivative.

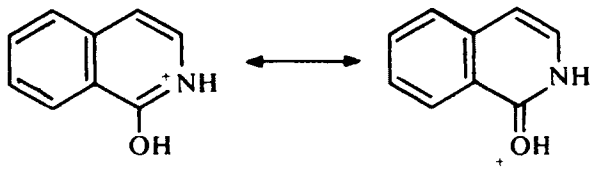
2-Methyl-5-nitro-1,2,3,4-tetrahydroisoquinolines have been prepared[88,108] by the reduction of the isoquinolinium cations with excess sodium borohydride in methanolic solution. This method should also be a general route to other 1,2,3,4-tetrahydronitroisoquinolines.

The dehydrogenation of 7-nitro-1,2,3,4-tetrahydroisoquinolines to the aromatic 7-nitroisoquinolines is possible using either iodine and potassium acetate[25] or mercuric acetate,[21] and should also be applicable to the aromatization of other 1,2,3,4-tetrahydroisoquinolines.

(*f*) *1(2H)-Isoquinolinones*

Nitration of 1(2H)-isoquinolinone (isocarbostyril) with potassium nitrate in sulfuric acid at room temperature was reported to yield approximately equal amounts of the 5- and 7-nitro derivatives plus another minor nitration product (m.p. 234–236°C) of undetermined structure.[109] This latter product was later suggested[110] to be 4-nitro-1(2H)-isoquinolinone. Nitration of 2-methyl-1(2H)-isoquinolinone under these conditions also gave approximately equal amounts of the 5- and 7-nitro derivatives, as well as minor amounts of the 4-nitro and 4,7-dinitro derivatives.[36] Nitration occurs at C-7 in low yield when 4-bromo-2-methyl-1(2H)-isoquinolinone is treated with KNO_3 in concentrated H_2SO_4 at room temperature.[36]

In these strongly acidic conditions, the isoquinolinone would exist predominantly as its conjugate acid (**27**) ($pK_a = -1.2$),[112] and so one might predict predominant C-5 nitration as occurs with the cations of other substituted isoquinolines [Section II.A.(b)]. The presence of appreciable amounts of the 7-nitro derivative is unknown in the nitration of other isoquinolinium cations and, in particular, 1-ethoxyisoquinoline is reported to give only the 5-nitro derivative under similar conditions.[9]



27

Nitration at C-4 is expected in the neutral 1(2H)-isoquinolinone molecule by analogy with[113] other electrophilic substitutions at C-4 in this species. Accordingly, 4-nitro-1(2H)-isoquinolinone is the sole product isolated (in 65% yield) upon treatment of 1(2H)-isoquinolinone with acetyl nitrate.[111] Nitration at C-4 is also observed in good yield when either 1(2H)-isoquinolinone or its 2,3-

dimethyl derivative is treated with concentrated nitric acid near room temperature.[36] 2-Methyl-5-nitro-1(2H)-isoquinolinone is also converted to its 4,5-dinitro derivative under these conditions.[36] Nitration of 3-phenyl-1(2H)-isoquinolinone in acetic acid is reported[114] to occur at C-4, and only the C-4 nitrated product has been isolated from the nitration of 2-methyl-1(2H)-isoquinolinone with either nitric acid in acetic anhydride or nitrous acid in acetic acid.[110]

It seems clear that all of these C-4 nitration reactions in nitric-acid solutions are occurring via the small concentrations of the neutral 1(2H)-isoquinolinone species that is present in these acidic media. The relative rates of hydrogen exchange on 1(2H)-isoquinolinone in acidic solutions are found[109] to be C-4 $\gg$ C-5 $\approx$ C-7 $\gg$ C-3,6,8 so that predominant C-4 nitration is consistent with this observation. All of these data suggest that the conjugate acid **27** is drastically deactivated toward electrophilic attack relative to its neutral conjugate base. Only in concentrated sulfuric acid solutions, where there is no significant amount of neutral species present, does the nitration occur via the cation **27**, resulting in approximately equal amounts of C-5 and C-7 nitration,[36, 109] which is also consistent with the observed equal rates of proton exchange at these two sites.[109]

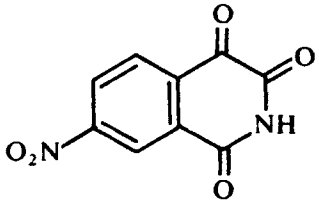
Nitration of 5,6,7,8-tetrahydro-1(2H)-isoquinolinone with HNO_3—H_2SO_4 gives the expected 4-nitro derivative.[9] Treatment of 3,4-dihydro-1(2H)-isoquinolinone with 1 equivalent of nitric acid in sulfuric acid at 0°C gives the 7-nitro derivative in 95% yield.[115] However, in concentrated HNO_3, this substrate gives a 1:1 mixture of the 7-nitro and 2,7-dinitro derivatives.[115] This latter product is a rare example of an *N*-nitro isoquinoline derivative.

Nitration of 6,7-dimethoxy-2-methyl-1(2H)-isoquinolinone is claimed[116] to give the 5- (or 8-) nitro derivative; however, the evidence against C-4 nitration seems to be based simply upon the observation that the 3,4-dihydro derivative gives the same nitration product. Thus dehydrogenation of the C(3)—C(4) bond occurs in the nitration medium, but it is not clear whether this oxidation precedes or follows nitration. If the oxidation were to precede nitration, the C-4 nitration product cannot be ruled out on the basis of the available evidence. On the other hand, a 5- (or 8-) nitro product would be consistent with the dimethoxy benzene ring being more highly activated toward electrophilic attack than the *N*-methylpyridinone ring. A similar nitration of the 6,7-methylenedioxy derivative has also been reported[116, 117].

Oxidation accompanying nitration has also been found[118, 119] for the reaction of homophthalimide [1,3(2H,4H)-isoquinolinedione] with nitric acid in acetic acid. Both the 7-nitro oxidation product (**28**) and the nonnitrated oxidation product (**29**) were isolated. This suggests that nitration precedes oxidation in this case, and C-7 oxidation of **30** is consistent with the observed site of nitration of 3,4-dihydroisoquinolinium cations [Section II.A(d)].

Consistent with this interpretation, nitration of **31** in which the C-4 oxidation site is blocked also leads to the C-7 nitration product.[80]

N-Alkyl 1(2H)-isoquinolinones are available from the corresponding *N*-alkyl isoquinolinium cations via oxidation of their C-1 hydroxide ion adducts (pseudobases) in aqueous base. Ferricyanide ion (Decker oxidation) has been



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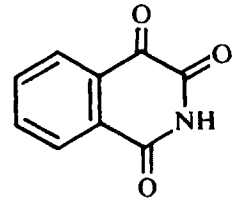

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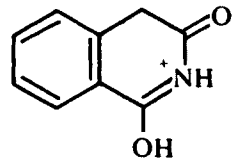

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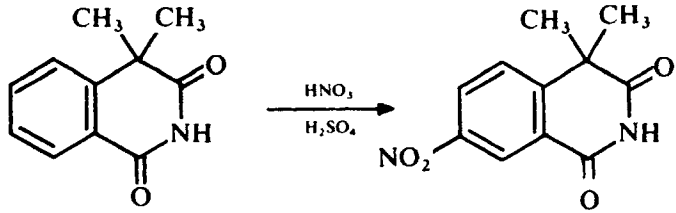

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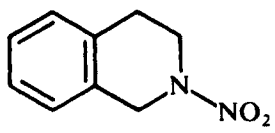
shown to cleanly oxidize 5-nitroisoquinolinium cations in this way[19, 123, 124], as does the *N*-methyl isoquinolinium cation.[125] These reactions should be equally applicable to other nitroisoquinolinium cation oxidations. The oxidation of any *N*-alkyl 1,2-dihydronitroisoquinoline which is unsubstituted at C-1 should also give the corresponding 1(2H)-isoquinolinone.

(*g*) *N-Nitration*

1,2,3,4-Tetrahydro-2-nitroisoquinoline (**32**) has been prepared by heating 1,2,3,4-tetrahydroisoquinolinium nitrate with zinc chloride in acetic anhydride.[120] 3,4,-Dihydro-2,7-dinitro-1(2H)-isoquinolinone (**33**) is one of the products from the nitration of 3,4-dihydro-1(2H)-isoquinolinone in fuming nitric acid.[115]



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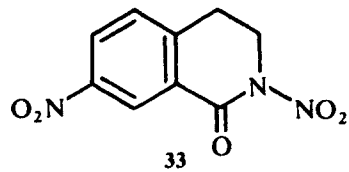


33

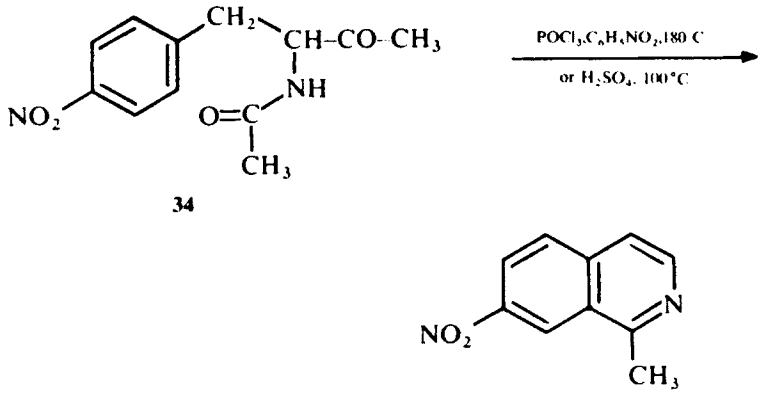
B. Nitroisoquinolines via Nucleophilic Substitution

1-Nitroisoquinoline has been made[1] by treating 1-iodoisoquinoline with sodium nitrite at 100°C.

4-Nitroisoquinoline has been synthesized[8] by diazotizing 4-aminoisoquinoline and then displacing the diazonium substituent with excess nitrite ion.

C. Nitroisoquinolines from Ring-Closure Reactions

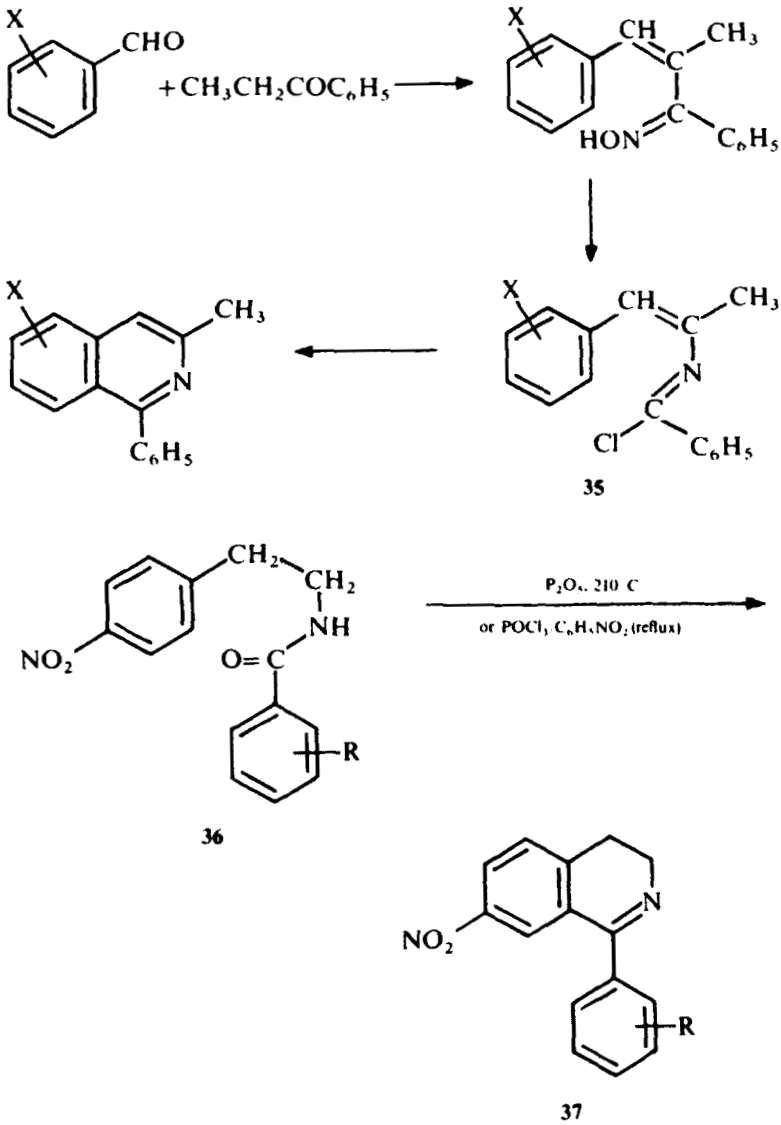
The classical synthetic routes to isoquinolines (Bischler–Napieralski, Pictet–Spengler, Pictet–Gams, and Pomeranz–Fritsch) involve ring-closure of the pyridine ring via electrophilic attack of a suitably activated side chain on the homocyclic ring.[126] The presence of a nitro group as a substituent on the homocyclic ring is expected to drastically hinder such ring-closures by virtue of the strong deactivating effect of this substituent on electrophilic aromatic substitution reactions. The most successful nitroisoquinoline synthesis via such an electrophilic ring-closure seems to be the synthesis of 1-methyl-7-nitroisoquinoline by Ghosh and Dutta[127] using a modified Bischler–Napieralski synthesis. Thus, the precursor **34** was closed in 72% yield using $POCl_3$ in nitrobenzene at 180°C, or in 40% yield using concentrated sulfuric acid at 100°C.



34

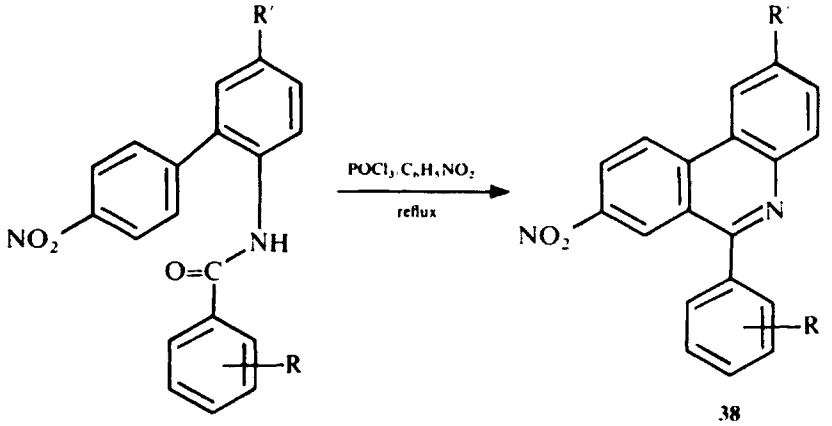
A related reaction is the ring-closure of an *N*-(β-methylstyryl)-benzimidoyl chloride (**35**) with P_2O_5 to the corresponding 3-methyl-1-phenylisoquinoline.[128] The 5- and 7-nitro derivatives have been prepared via this route in reasonable yields from 2- and 4-nitrobenzaldehydes, respectively.

The only successful 3,4-dihydronitroisoquinoline syntheses via the Bischler–Napieralski procedure appear to be those recorded by McCoubrey and Mathieson.[52,55] Thus, treatment of the *N*-(4-nitrophenethyl)amides **36** with either P_2O_5 at 210°C or $POCl_3$ in refluxing nitrobenzene (180°C) gave poor yields of the 3,4-dihydro-7-nitroisoquinolines **37** (R = 4-NO_2, 13% yield;



R = 3-NO_2, 2% yield; R = H, 2% yield). The identity of the latter product has subsequently been challenged.[99]

The poor yields in these reactions are in sharp contrast to the generally excellent yields obtained in the synthesis of the nitrophenanthridines (**38**) by ring-closure of their precursors with $POCl_3$ in refluxing nitrobenzene.[129, 130] This phenanthridine synthesis may alternatively be considered as a special case of the Pictet–Gams synthesis for which there appear to be no examples of the successful preparation of nitroisoquinolines.



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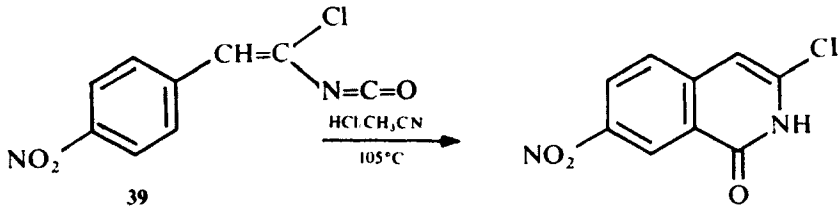
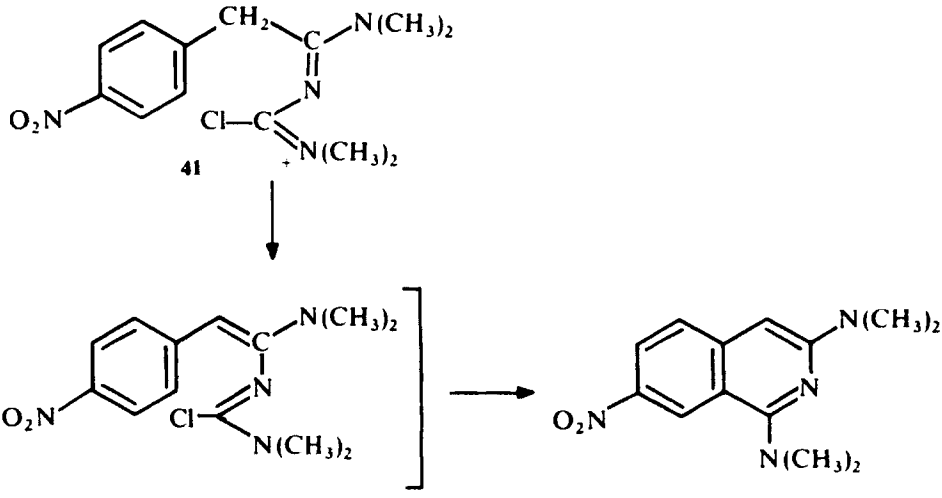
Ohoka and co-workers[131] obtained trace amounts of **40** from the ring-closure of **39** using hydrogen chloride in acetonitrile at 105°C for 140 h.

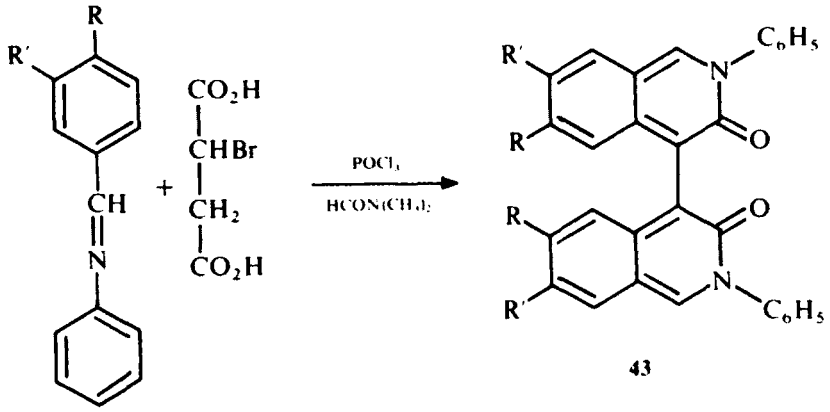


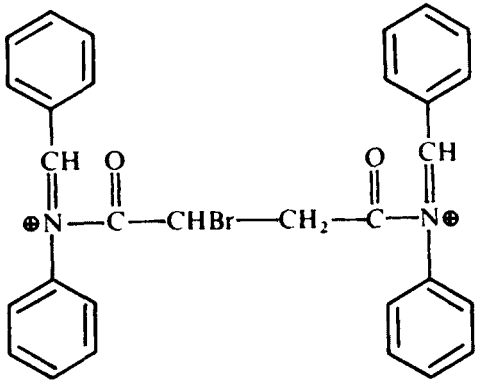
39 40

Boyd and co-workers[151] obtained high yields of 1,3-bis(dimethylamino)-7-nitroisoquinoline from the cyclization of the azapropenylium cation **41** in aqueous sodium carbonate solution.



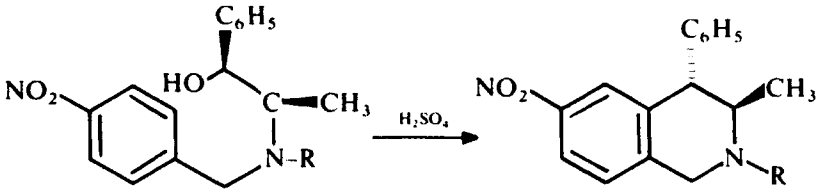
The 4,4'-bisisoquinoline derivatives **43**: R = H, R' = NO_2 and **43**: R = NO_2, R' = H have been obtained[132] in low yields (10 and 3%, respectively) by treatment of the appropriate nitrobenzylideneaniline (**42**) with bromosuccinic acid and $POCl_3$ in dimethyl formamide. In the case of the unsubstituted benzylideneaniline, the dication, **44**, was established as an intermediate in this reaction; however, the mechanism of the subsequent ring-closure steps was not investigated.





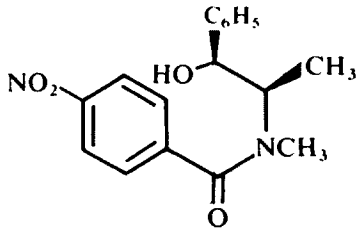
44

The 6-nitro-1,2,3,4-tetrahydroisoquinoline derivative, **46**: R = CH_3, has been obtained[133] in 79% yield by the ring-closure of *erythro-N*-(4-nitrobenzyl)ephedrine (**45**: R = CH_3) in concentrated sulfuric acid at room temperature. This reaction owes its facility to the ready formation of a benzylic carbocation which acts as the electrophile in a subsequent attack upon the nitrophenyl ring.



45 46

The corresponding 4-nitrobenzoyl derivative **47** does not give the 3,4-dihydro-6-nitro-1(2H)-isoquinolinone under these conditions, although the corresponding reaction does occur in the absence of the nitro group. Ring-closure of **45**: R = H in polyphosphoric acid gives only a 9% yield of **46**: R = H, while attempted ring-closure in concentrated hydrobromic acid gave only degradation products.[134]



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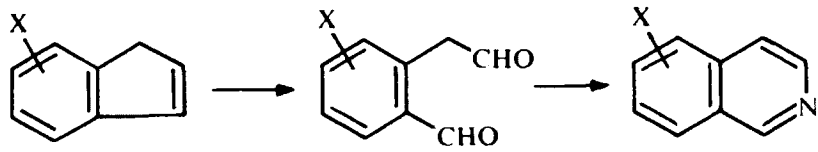
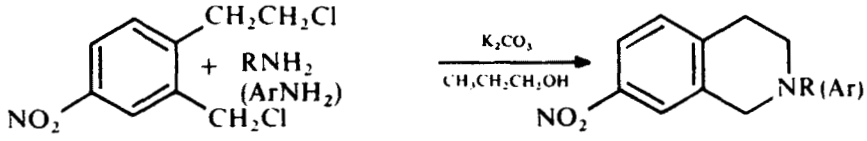
A number of successful nitroisoquinoline syntheses involve ring-closure to form the pyridine ring on a nitrobenzene derivative that bears suitably activated carbon substituents. These substituents ultimately become C-1 and C-4 of the isoquinoline ring system. Miller and Frincke[20] developed a general isoquinoline synthesis of this type starting from an appropriately substituted indene. In a one-pot synthesis, the indene (**48**) is ozonolyzed to the homophthalaldehyde (**49**), which is then treated with ammonia to give the isoquinoline upon ring-closure. They showed that this route is applicable to the preparation of 6-nitroisoquinoline (from 6-nitroindene) and also 7-nitroisoquinoline (from 5-nitroindene) in >60% yields.



48 49

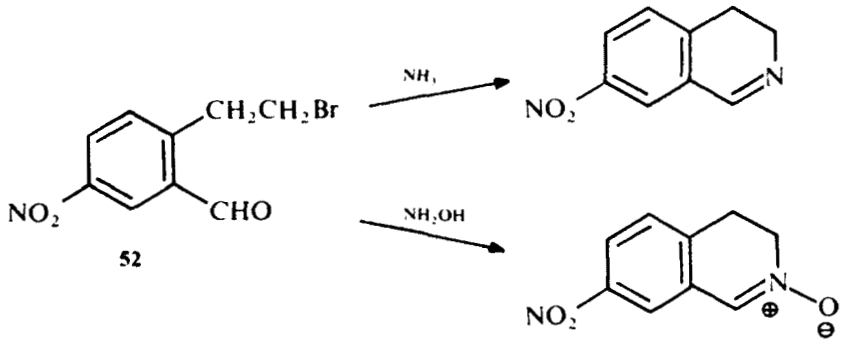
Beeby and Mann[135, 136] synthesized a variety of *N*-substituted 7-nitro-1,2,3,4-tetrahydroisoquinolines in good yields by refluxing 2-(2-chloroethyl)-5-nitrobenzyl chloride (**50**) with the appropriate amine or aniline in propanol in the



50 51

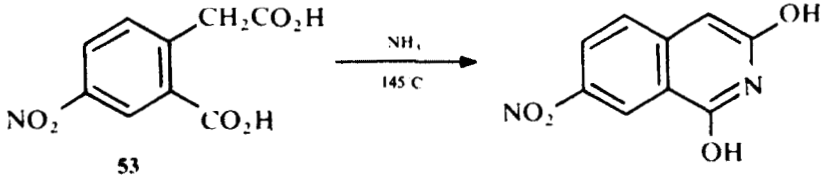
presence of potassium carbonate. McCoubrey and Mathieson[24] also used a similar reaction for the preparation of **51** : R = $CH_2C_6H_5$, while Lusinchi and co-workers[137] have prepared **51** : R = CH_3 in this way.

Schmitz[138] treated 2-(2-bromoethyl)-5-nitrobenzaldehyde (**52**) with ammonia to give 7-nitro-3,4-dihydroisoquinoline in 43% yield, while use of hydroxylamine in this reaction gave the corresponding *N*-oxide in 75% yield.[139]



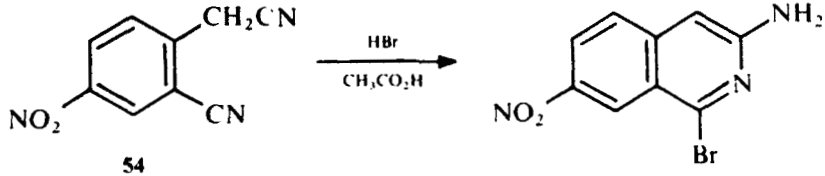
52

Treatment of 4-nitrohomophthalic acid (**53**) with ammonia in 1,2-dichlorobenzene at 145°C gives quantitative yields of 7-nitro-1,3-isoquinolinediol.[66, 140]



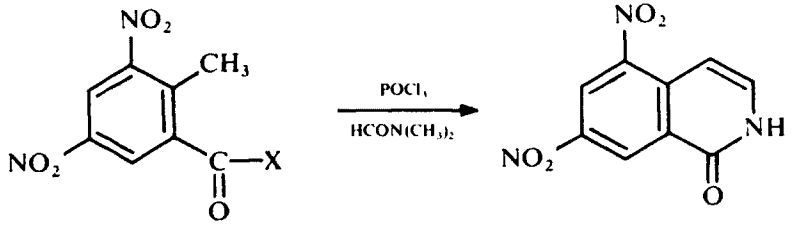
53

The reaction of 2-cyano-4-nitrobenzyl cyanide (**54**) with 30% HBr in acetic acid gives good yields of 3-amino-1-bromo-7-nitroisoquinoline.[73, 141]



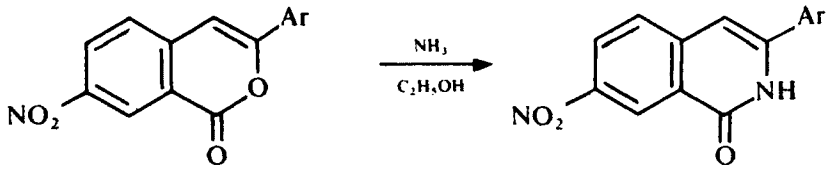
54

Zbarskii and co-workers[35] reported the reaction of **55** (X = Cl or OH) with $POCl_3$ and dimethylformamide to give 5,7-dinitro-1(2H)-isoquinolinone.



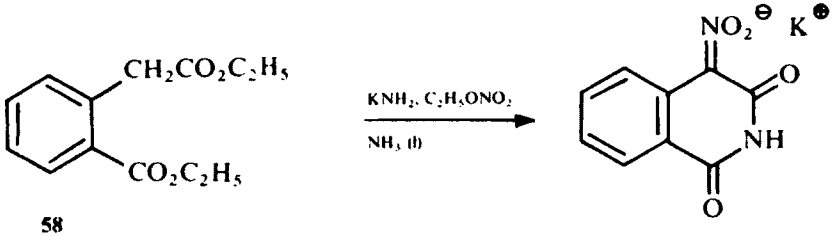
55

Related to these ring-closure reactions is the synthesis of the 7-nitro-1(2H)-isoquinolinones **57** by treatment of the corresponding 7-nitroisocoumarins (**56**) with ammonia in refluxing aqueous ethanol.[142] Yields of 60% are reported for six phenolic substituents at C-3 in **56**. This reaction presumably involves opening of the lactone ring to give the amide, followed by ring-closure to the isoquinolinone. In a similar reaction, 2-methyl-5-nitro-1(2H)-isoquinolinone has been prepared[143] from the reaction between 5-nitroisocoumarin and methylamine.



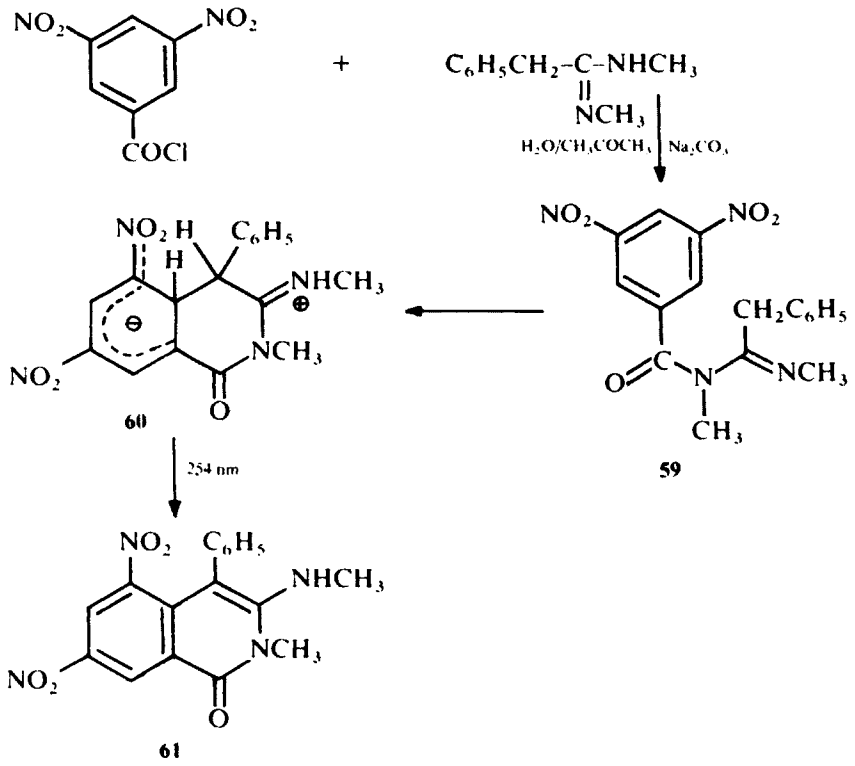
56 57

An unusual combined nitration and ring-closure has been reported by Feuer and Monter.[144] Treatment of diethyl homophthalate (**58**) with ethyl nitrate and potassium amide in liquid ammonia gave the potassium salt of 4-nitro-1,3(2H,4H)-isoquinolinedione in 19% yield. The nitration step in this reaction presumably occurs via nucleophilic attack of the carbanion on the nitrogen atom of ethyl nitrate. Ring-closure by successive intermolecular and intramolecular ester aminolyses may either precede or follow the nitration step.



58

Kaito and Kasuya[34] reported an unusual synthesis of the 5,7-dinitro-1(2H)-isoquinolinone derivative **61**. Condensation of 3,5-dinitrobenzoyl chloride with *N*,*N*′-dimethylbenzylamidine in basic solution gives the zwitterionic species **60** via the intermediate amide **59**. Photolysis of **60** at 254 nm, or merely exposure to sunlight, converts **60** to **61**.

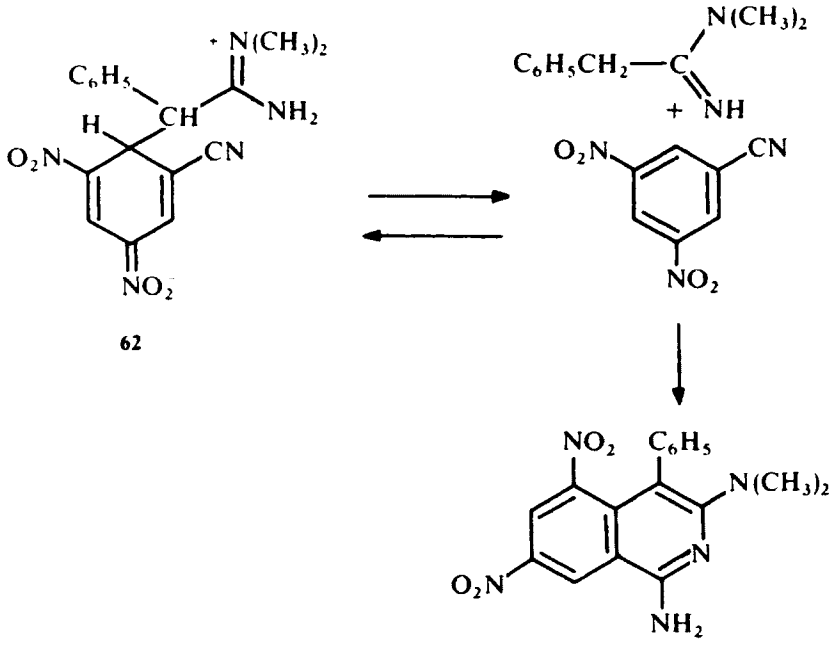


In a reaction that is apparently closely related to the previous example, Strauss and Bard[37] observed the facile reaction between 3,5-dinitrobenzonitrile and α-phenyl-*N*,*N*-dimethylacetamidine in dimethylsulfoxide at 50–60°C to give 1-amino-3-dimethylamino-5,7-dinitro-4-phenylisoquinoline (**63**). No intermediates were observed when this reaction is followed by ^{1}H NMR spectroscopy, although an apparently nonproductive σ-complex (**62**) is formed immediately upon mixing the reagents. This complex is suggested[37] to rearrange to **63** via dissociation to starting materials.

D. Nitroisoquinolines via Rearrangements

There are a number of examples of the synthesis of nitroisoquinolines via the rearrangement of the nitro derivatives of other bicyclic ring systems. The indene to isoquinoline[20] and the isocoumarin to isoquinolinone[142, 143] rearrangements mentioned above (Section II.C) are formally examples of this class of reaction.

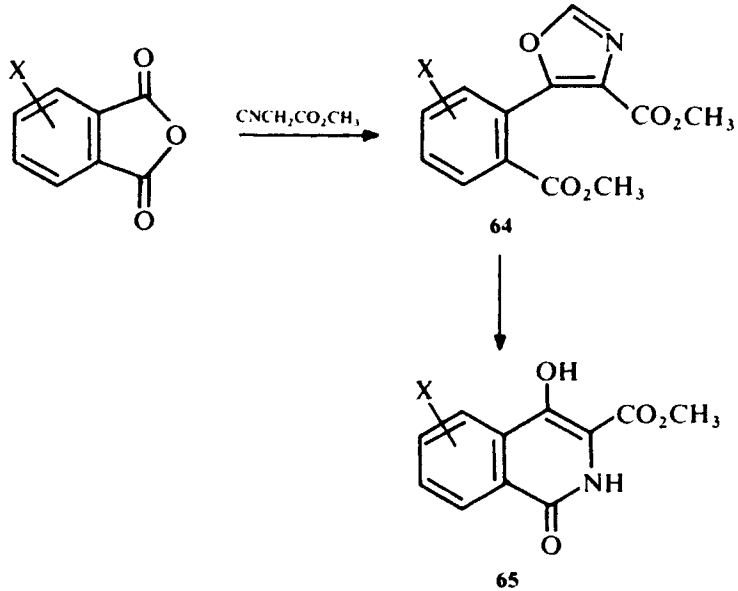
Nunami and co-workers[145, 146] have developed a general synthesis of 1,2-dihydro-4-hydroxy-1-oxo-3-isoquinolinecarboxylate esters (**65**) from appropriate ring-substituted phthalic anhydrides. The anhydride is converted to the oxazole derivative **64**, using methyl isocyanoacetate in a base-catalyzed process.



62

63

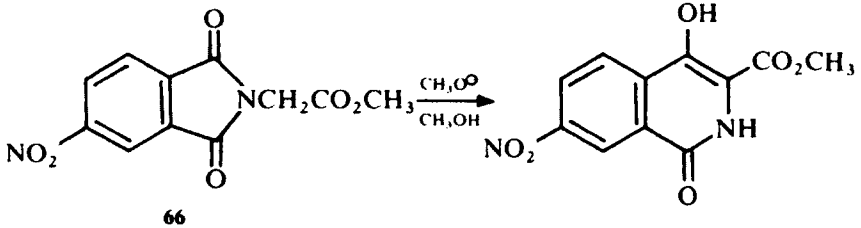
This oxazole can then be converted to the substituted 1(2H)-isoquinolinone with methanolic 2*N* HCl. 3-Nitrophthalic anhydride gives both the 5- and 8-nitro isoquinoline derivatives after separation of the isomeric nitrophenyl oxazoles, while 4-nitrophthalic anhydride gives the 6- and 7-nitro isoquinoline derivatives.



64

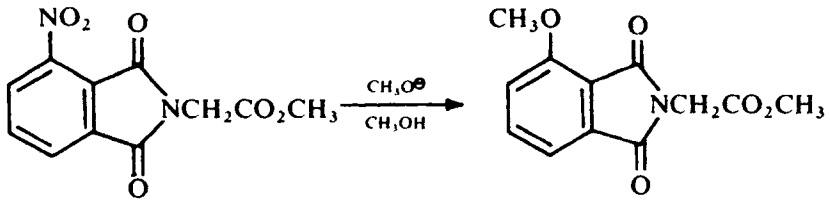
65

An example of the Gabriel–Colman rearrangement has been reported by Caswell and Kao[147] for the synthesis of 7-nitro-1(2H)-isoquinolinone (in 15% yield) by the reaction of methyl 4-nitrophthalimido-acetate (**66**) in basic methanolic solution.



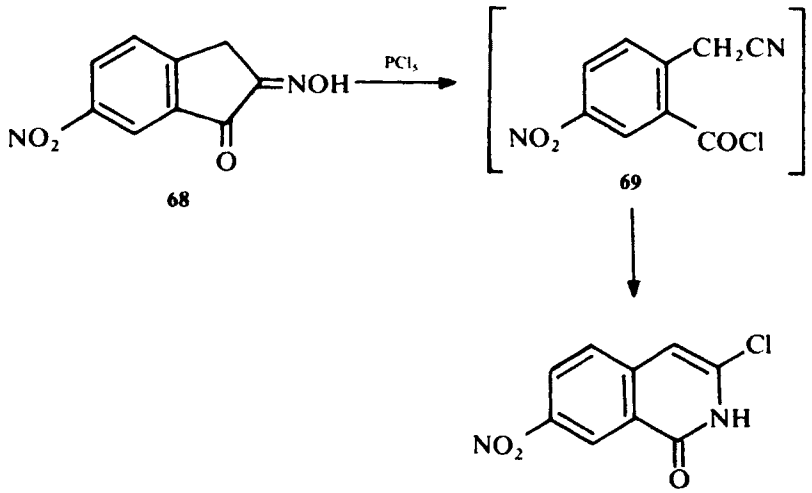
66

It should be noted that under the same conditions, the 3-nitro isomer of **66** gives the substitution product **67**, rather than undergoing rearrangement to the corresponding nitroisoquinolinone.



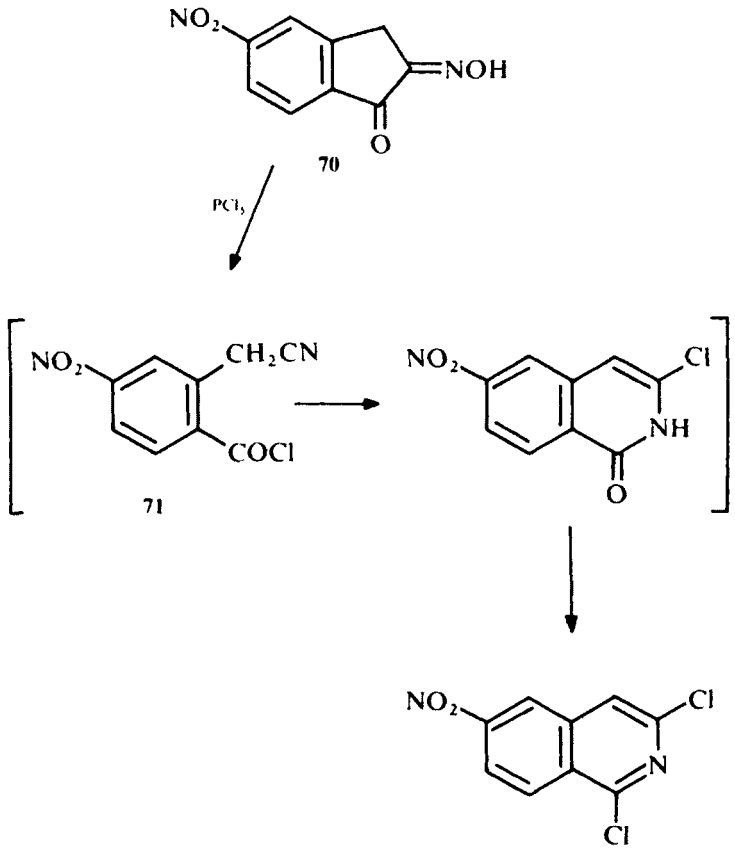
67

Simchen and Kramer[148] report the conversion of the 2-oxime (**68**) of 6-nitro-1,2-indandione to 3-chloro-7-nitro-1(2H)-isoquinolinone in quantitative yield upon treatment with PCl_5.

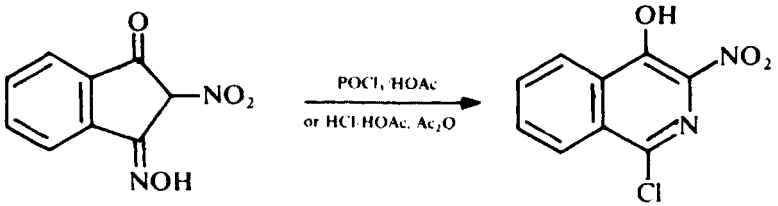


68 **69**

Under similar conditions, the isomeric 5-nitro 2-oxime (**70**) is converted to 1,3-dichloro-6-nitroisoquinoline in 64% yield.[149] The ring-opened intermediates **69** and **71** are proposed in these reactions.

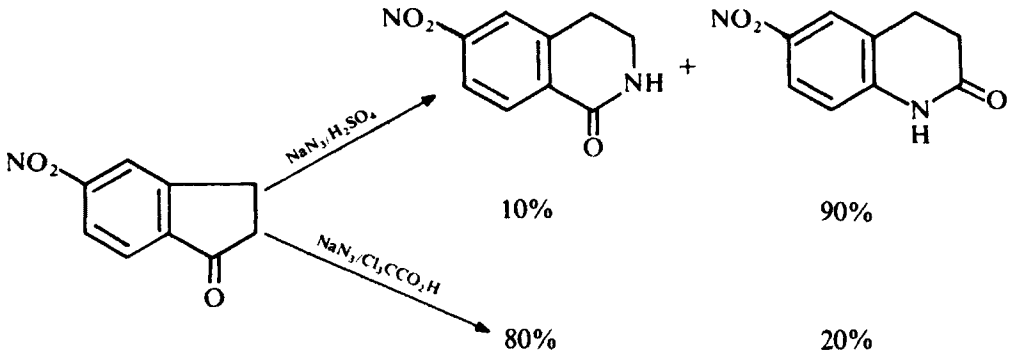


The Beckman rearrangement of 2-nitro-1,3-indandione oxime (**72**) to 1-chloro-3-nitro-4-isoquinolinol has been reported by Vanags and Vitols,[4] using either $POCl_3$ in acetic acid (85% yield) or HCl in an acetic acid–acetic anhydride mixture (67% yield). This represents one of the few available routes for the introduction of a 3-nitro substituent onto the isoquinoline ring system.



72

Tomita and co-workers[150] have studied the Schmidt reaction of the 5- and 6-nitro-1-indanones (**73** and **74**). For both isomers, the use of sulfuric acid as the reaction medium results in predominant aryl migration to give the quinolinones as the major products and only small amounts (10–20%) of the isoquinolinones via alkyl group migration. However, in trichloroacetic acid, alkyl migration predominates and the 6- and 7-nitro-3,4-dihydro-1(2H)-isoquinolinones constitute 80% of the rearrangement products.



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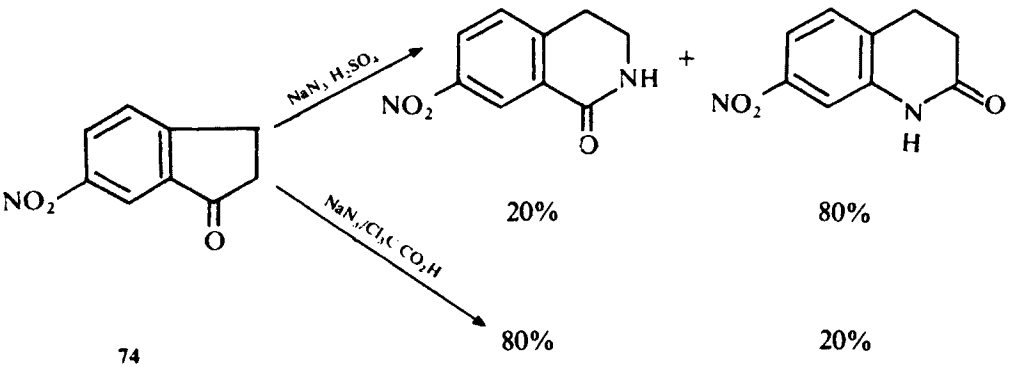
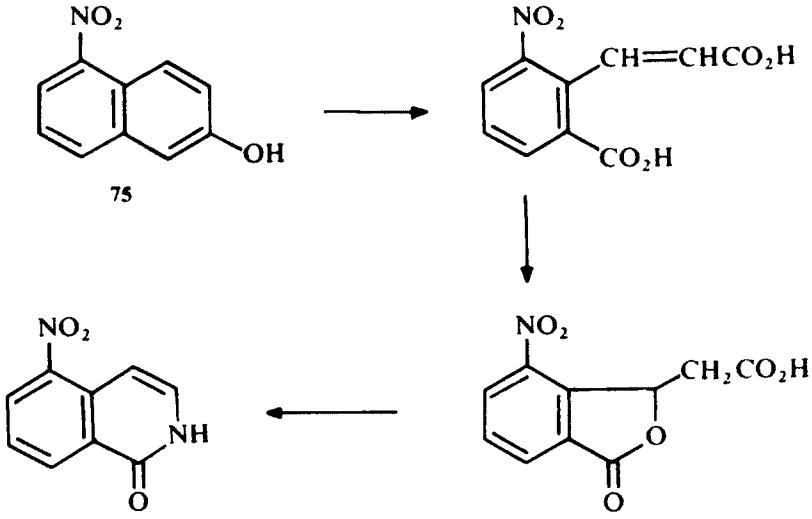


74

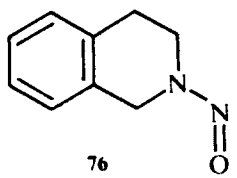
Petrova and Sazonova[156] report a five-step synthesis of 5-nitro-1(2H)-isoquinolinone from 5-nitro-2-naphthol. This route involves oxidative cleavage of the naphthol to 2-carboxy-5-nitrocinnamic acid, which is then closed to a lactone via an intramolecular Michael addition. Elaboration of this lactone to an amide, followed by treatment with hypochlorite, gave the observed product. This route should also be applicable to other nitro-1(2H)-isoquinolinone derivatives, provided a source of the appropriate *o*-carboxycinnamic acids can be found.



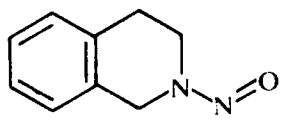
III. NITROSOISOQUINOLINES

A. *N*-Nitroso Derivatives

1,2,3,4-Tetrahydroisoquinolines, like acyclic secondary amines, are converted to their *N*-nitroso derivatives upon treatment with nitrous acid (i.e., $NaNO_2$ in mineral acid). Nitrosation of the parent 1,2,3,4-tetrahydroisoquinoline in this way,[152-154] or with amyl nitrite,[155] gives the 2-nitroso derivative, which exists in organic solvents as an equilibrium mixture of geometric isomers [**76** (syn) and **77** (anti)]. ^{1}H NMR spectral analyses of this equilibrium mixture indicate that in both benzene[152] and deuterochloroform[153,155] the syn isomer (**76**) predominates (70%) over the anti isomer (**77**) (30%).



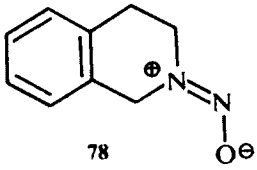
76



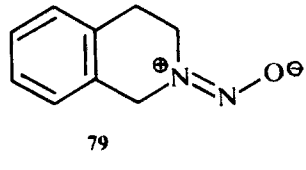
77

This observation of both stereoisomers in an equilibrium mixture by ^{1}H NMR spectroscopy clearly indicates that restricted rotation exists about the N—N bond, and this presumably arises from a major contribution from the resonance contributors **78** and **79** to the electronic structures of these *N*-nitroso species.

Similar stereoisomerism has also been reported[155] for 1-methyl-2-nitroso-1,2,3,4-tetrahydroisoquinoline, and although such isomerism does not appear to have been reported for other substituted *N*-nitroso 1,2,3,4-tetrahydroisoquinol-



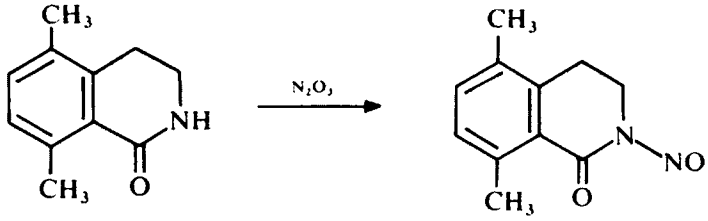
78



79

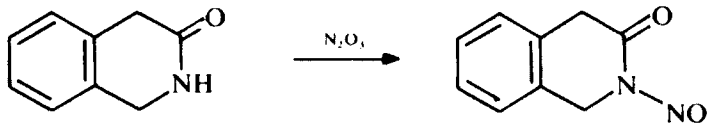
ines, it clearly must be considered in assigning structures to all such derivatives. In particular, the possibility that solid 2-nitroso-1,2,3,4-tetrahydroisoquinolines may exist as mixtures of stereoisomers makes the use of melting points quite unreliable for the characterization of such *N*-nitroso derivatives. Characterization of these species in this way was often attempted[157–166] before the availability of modern spectroscopic techniques.

Nitrosation with N_2O_3 has also occasionally been used for the formation of *N*-nitroso isoquinoline derivatives. Good yields (88%) of **81** may be obtained[167] from the treatment of **80** with N_2O_3 in an acetic acid–acetic anhydride–pyridine mixture, although such 3,4-dihydro-1(2H)-isoquinolinones have also been nitrosated with nitrous acid.[168]



80 81

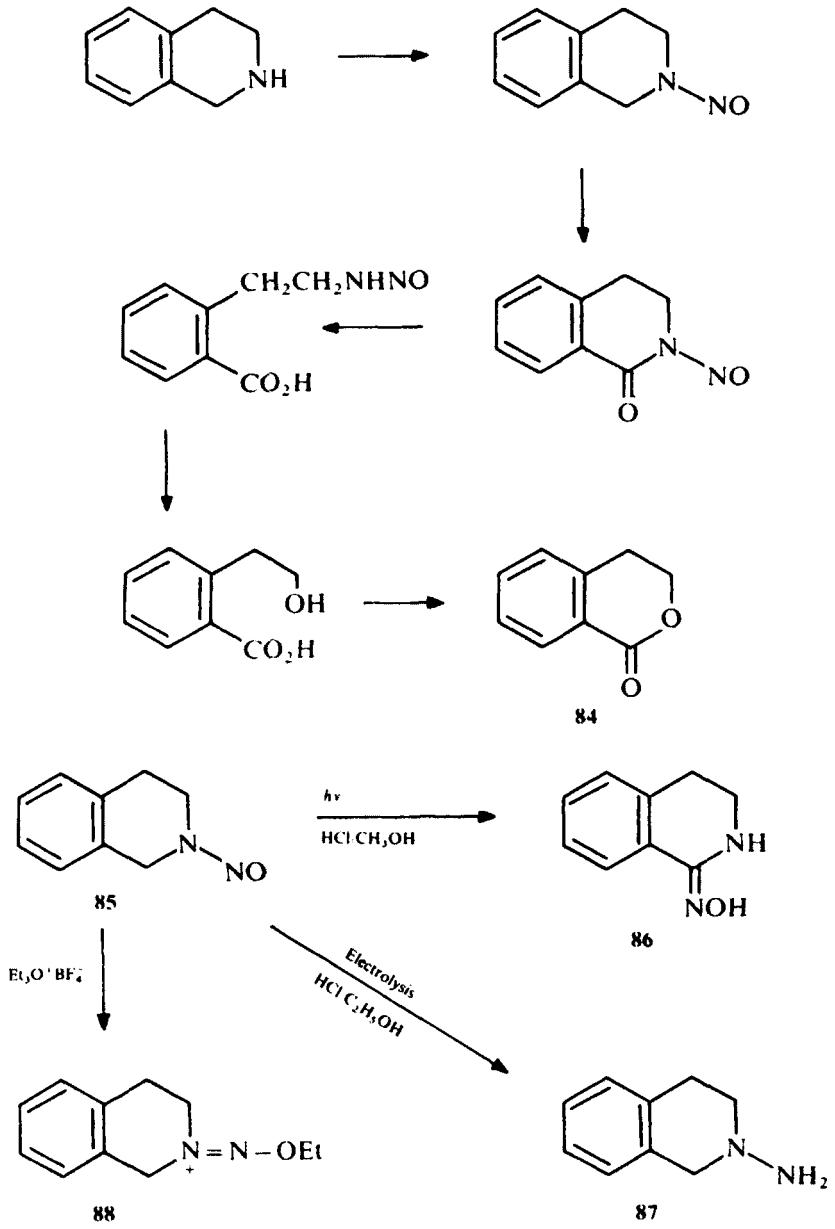
Treatment of **82** with N_2O_3 in acetic acid–acetic anhydride at 0°C gave **83** in 75% yield.[169] Nitrosation of a 1,4-dihydro-3(2H)-isoquinolinone has also been reported by White and co-workers,[170] but the reaction conditions were not specified.



82 83

The reaction of 1,2,3,4-tetrahydroisoquinoline with N_2O_3 in acetic acid at 80°C produces phthalic acid and the lactone **84**, which has been suggested[171] to arise via the route indicated. The 2-benzoyl and 2-isoamyl derivatives of 1,2,3,4-tetrahydroisoquinoline also suffer ring-cleavage reactions under these same reaction conditions.[171]

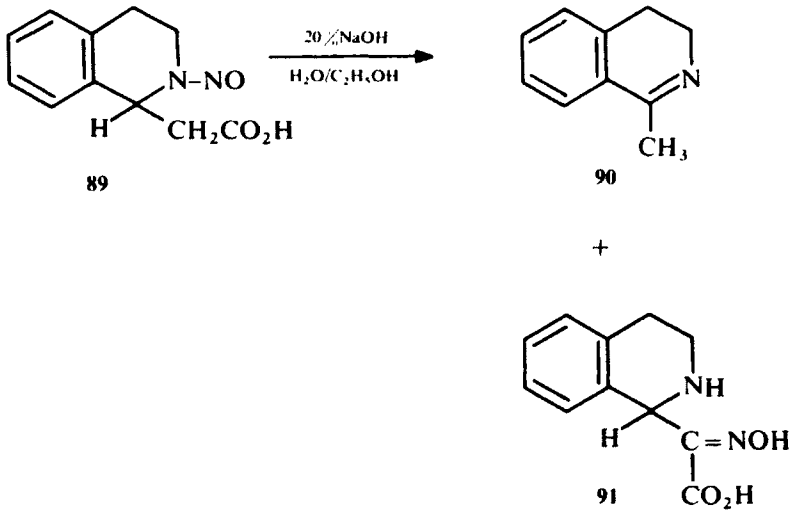
Several reactions which are potentially synthetically useful have been briefly reported for *N*-nitroso 1,2,3,4-tetrahydroisoquinolines. Photolysis of **85** in acidic methanol gives[172] the 1-oxime **86**, while electrolysis[173] in acidic ethanol gave the



N-amino derivative **87**. The *O*-ethylation[153] of **85** with triethyloxonium tetrafluoroborate gave **88**. The ESR spectrum of the radical anion of 2-nitroso-1,2,3,4-tetrahydroisoquinoline has been briefly reported.[174]

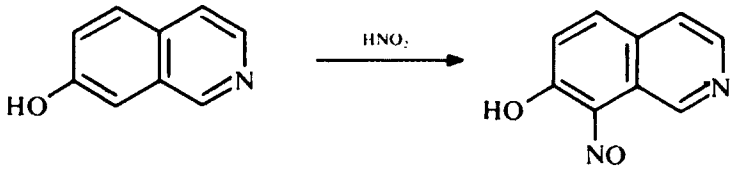
When 2-nitroso-1,2,3,4-tetrahydroisoquinoline is refluxed in 20% NaOH in aqueous ethanol, it is converted[155] to 3,4-dihydroisoquinoline. The 1-methyl

derivative behaves similarly; however, under the same conditions, 2-nitroso-1,2,3,4-tetrahydro-1-isoquinolineacetic acid, **89**, gives[155] a 20% yield of the elimination–decarboxylation product (**90**) and 70% yield of the oxime rearrangement product (**91**).



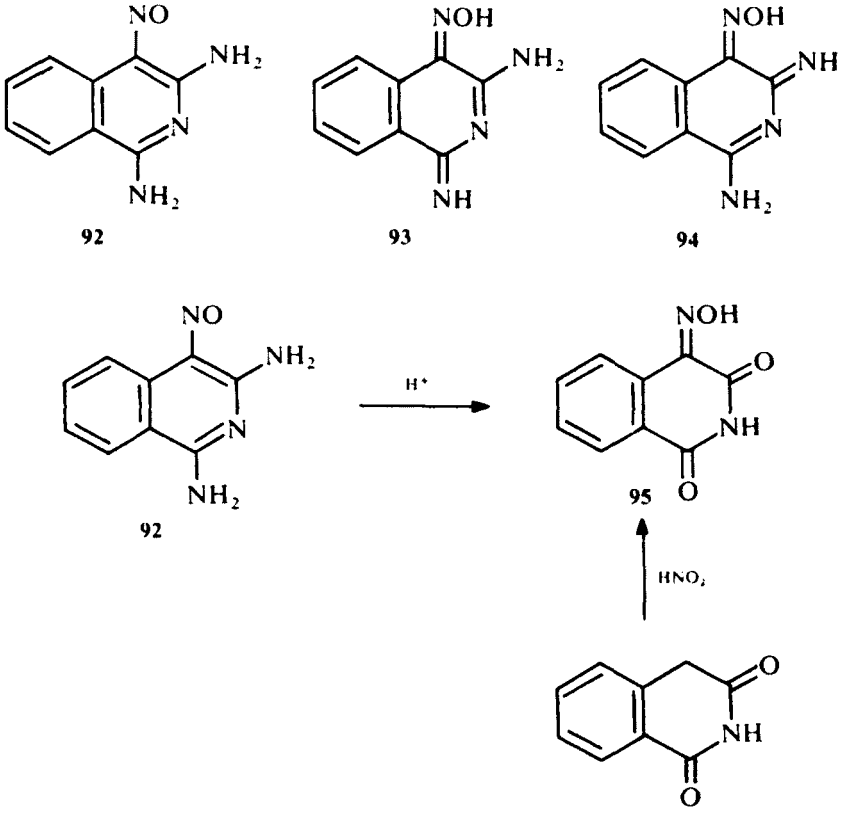
B. *C*-Nitroso Derivatives

There are few examples of *C*-nitroso isoquinoline derivatives in the chemical literature. 1-Nitrosoisoquinoline is the only unsubstituted derivative that has been reported,[2] and it was found to be too unstable to allow its isolation. Treatment of 7-isoquinolinol with nitrous acid is reported[175] to yield its 8-nitroso derivative in 92% yield.



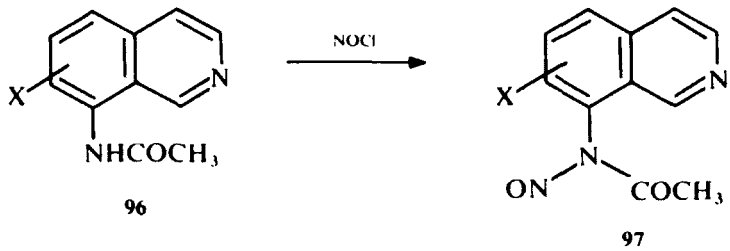
1,3-Diaminoisoquinoline undergoes[176] nitrosation at C-4. The product of this reaction is potentially a tautomeric mixture of **92**, **93**, and **94**. The nitroso tautomer **92** is favored on the basis of spectral properties over either of the two hydroxyimino tautomers.

Prolonged acid treatment of **92** converts[176] it into **95**, which is identical with the product of nitrosation of homophthalimide.[176, 177] Spectral properties suggest that the oxime **95** is the major tautomer in this case, rather than any of the possible 4-nitroso tautomers.



C. *N*-Nitrosoamido Derivatives

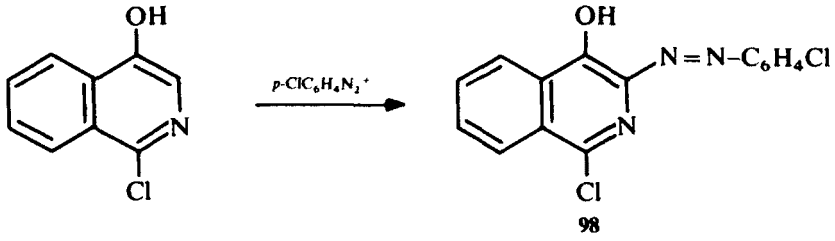
The 8-acetamidoisoquinolines (**96**: X = H, 5-Cl, 7-OCH_3) have been converted to the corresponding *N*-nitrosoacetamido derivatives **97** by treatment with nitrosyl chloride.[178]



IV. AZOISOQUINOLINES

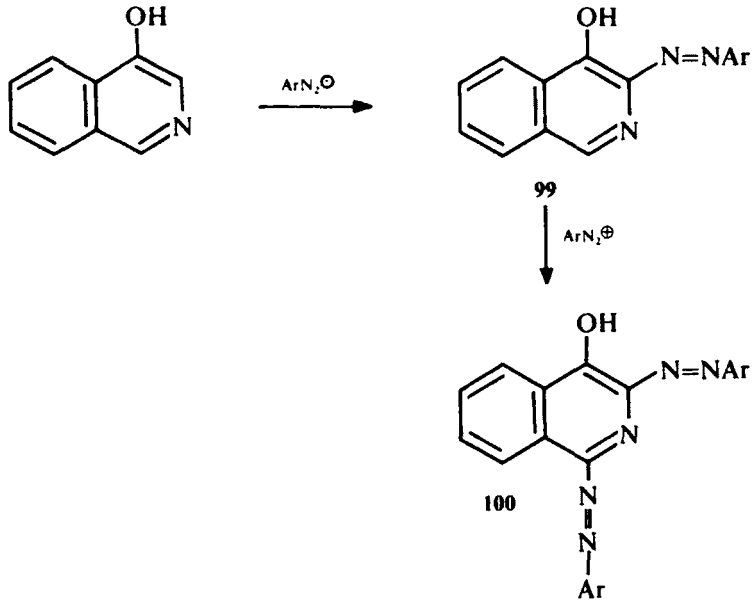
A. By Coupling Isoquinolines with Diazonium Cations

Isoquinolines activated to electrophilic attack by the presence of a hydroxyl substituent in either the homocyclic or heterocyclic ring have been coupled with aryl diazonium ions. The azo substituent is introduced either ortho or para to the hydroxyl substituent of the isoquinoline. Thus, 1-chloro-4-isoquinolinol has been coupled[179] with the 4-chlorophenyl diazonium ion to give the 3-(4-chlorophenylazo) derivative (**98**).

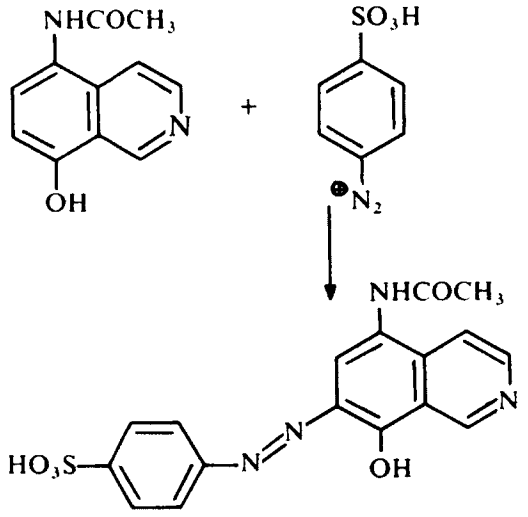


98

4-Isoquinolinol has been coupled with a variety of para-substituted phenyl diazonium ions (H, NO_2, Br, SO_3H, OCH_3, CH_3) to give both the 3-arylazo (**99**) and 1,3-bis(arylazo) (**100**) coupling products in good yields.[180]

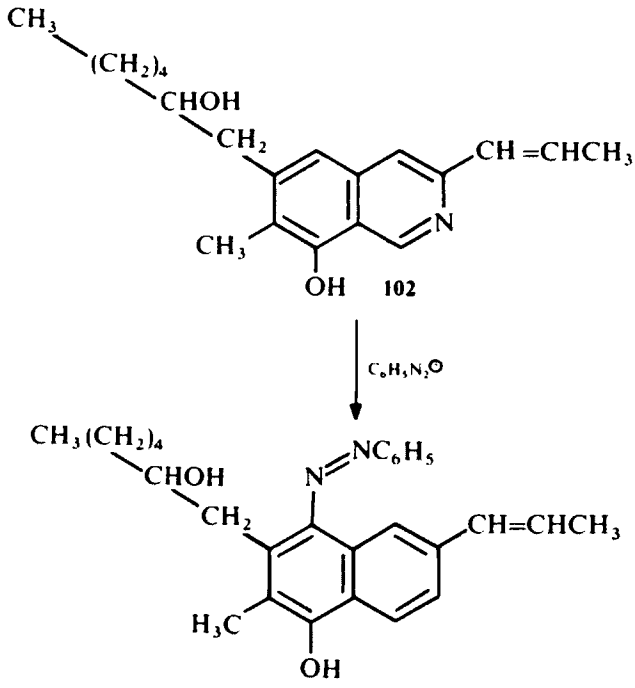


5-Acetamido-8-isoquinolinol has been coupled[181] with the diazonium ion from 4-aminobenzenesulfonic acid to give the 7-azo derivative **101**.



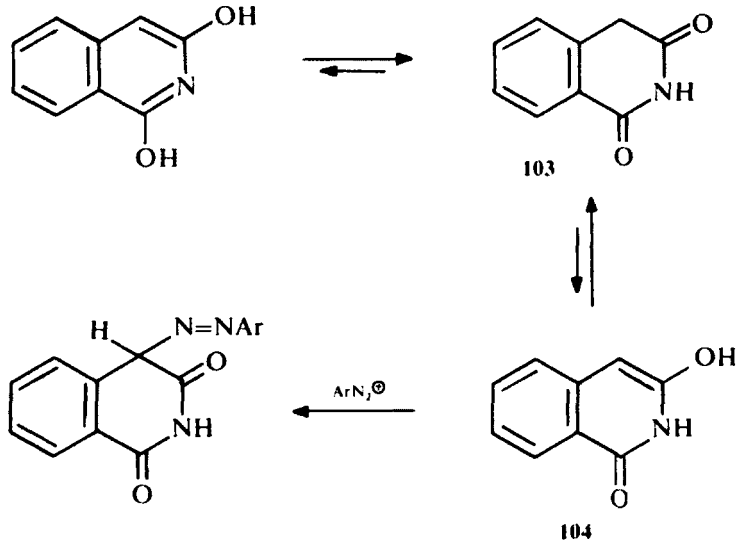
101

The 8-isoquinolinol derivative **102** couples at the vacant C-5 position with the phenyl diazonium cation.[182]

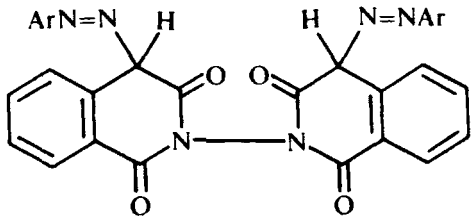


5-Isoquinolinol has been coupled with the 4-sulfonamidophenyl diazonium ion to give the 6- (or 8-) azo derivative.[183]

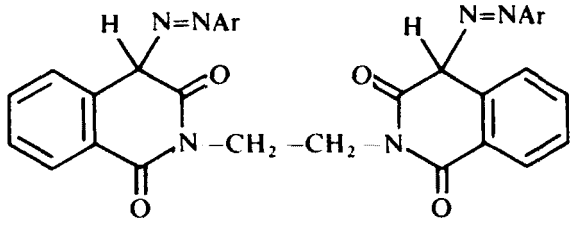
The largest group of azoisoquinoline derivatives has been made[183–197] by coupling aromatic diazonium ions with homophthalimide [1,3(2H,4H)-isoquinolinedione, **103**], which is the predominant tautomeric form of 1,3-isoquinolinediol. Diazo coupling with **103** or any of its *N*-substituted derivatives invariably occurs at C-4, presumably via reaction of the diazonium cation with the enol tautomer (**104**).



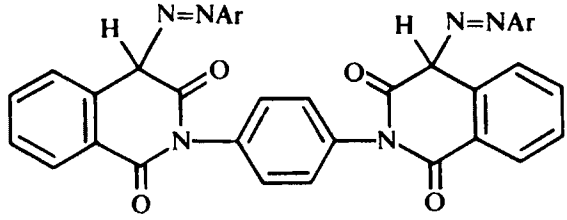
A number of bis(4-azohomophthalimides) of the general formula of **105–107** have been similarly prepared.[198]



105

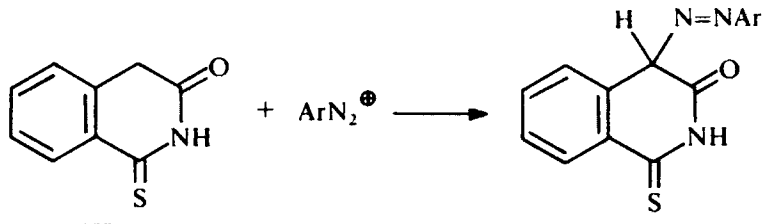


106

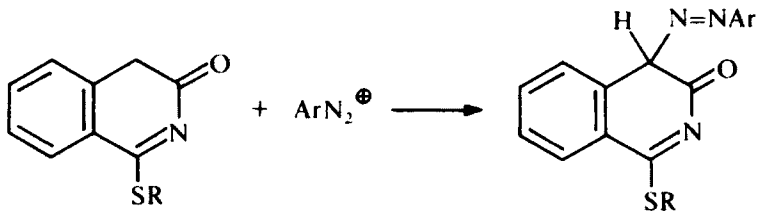


107

The azo coupling of 1-thiohomophthalimides (**108**) with a series of para-substituted phenyl diazonium ions has been reported,[199] and the corresponding methylthio (**110**: R = CH_3) and benzylthio (**110**: R = $CH_2C_6H_5$) derivatives have also been coupled[200] to give **111**.

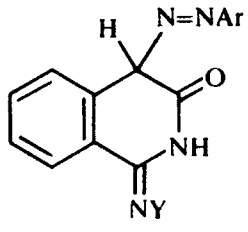


108 109



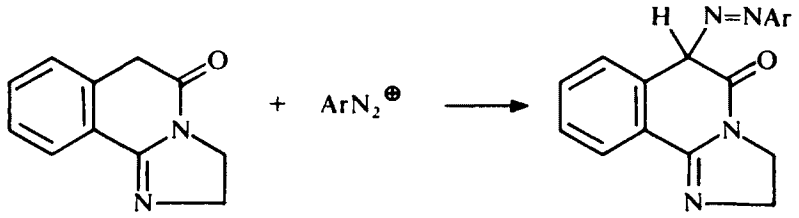
110 111

Both **109** and **111** react[199, 200] with phenylhydrazine to give the phenylhydrazones **112**: Y = NHC_6H_5, while **111** has also been treated with hydroxylamine to give the oxime **112**: Y = OH, and with aniline to give **112**: Y = C_6H_5.



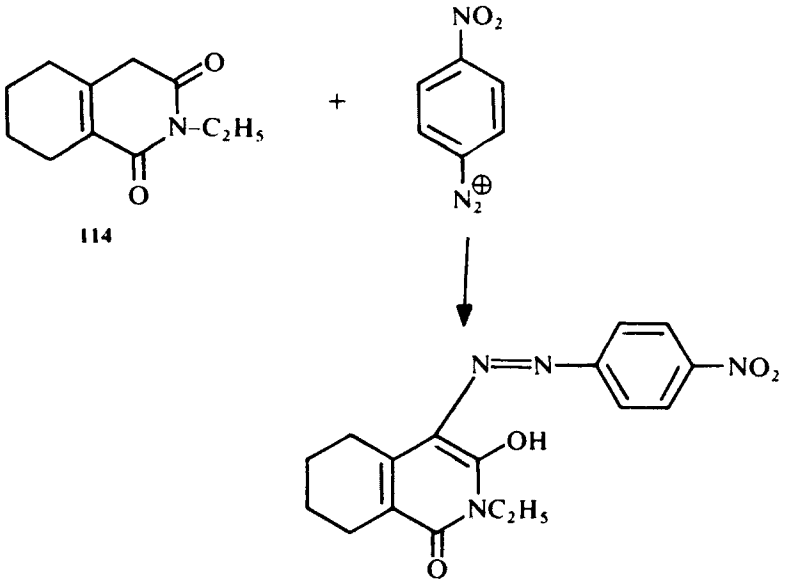
112

The coupling of **113** with a series of substituted phenyl diazonium ions has been reported.[201]



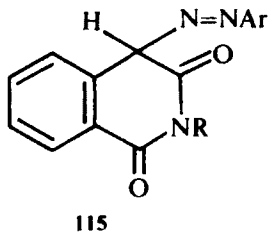
113

N-Ethyl tetrahydrophthalimide (**114**) has been coupled with the 4-nitrophenyl diazonium cation.[202]

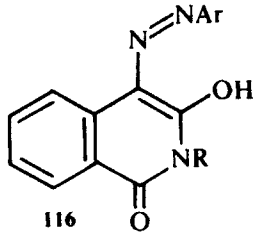


114

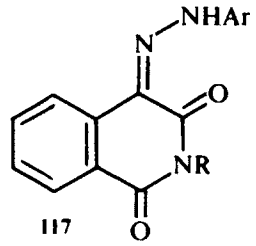
All the 4-azohomophthalimide derivatives mentioned above can potentially exist in a number of tautomeric forms. Various hydroxy tautomers (e.g., **116**) and also the hydrazone tautomer **117**, are possible in addition to the 4-azo-



115



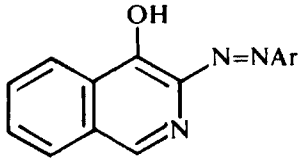
116



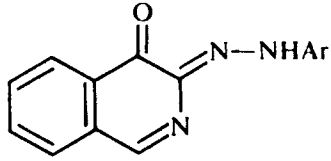
117

1,3(2H,4H)-isoquinolinedione tautomer **115**, which is usually indicated as the structure of the product from the reactions mentioned above.

There does not appear to have been a spectroscopic investigation designed to establish the major component of the tautomeric mixture for any of the 4-azohomophthalimide derivatives mentioned in this section. The designation of these compounds as the **115** species may be incorrect, since α-azoketones in other systems have been shown[203-205] spectroscopically to exist predominantly in the hydrazone tautomeric forms. In particular, IR and electronic spectral data have been interpreted[205] to indicate that 3-phenylazo-4-isoquinolinols (**118**) exist predominantly in the quinone-hydrazone tautomeric form **119**. This interpretation is also claimed to be supported by theoretical calculations.[206]

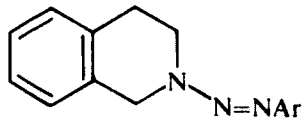


118



119

1,2,3,4-Tetrahydroisoquinoline couples[207, 208] with diazonium cations at the ring-nitrogen atom to give *N*-azoisoquinoline derivatives of the type **120**.

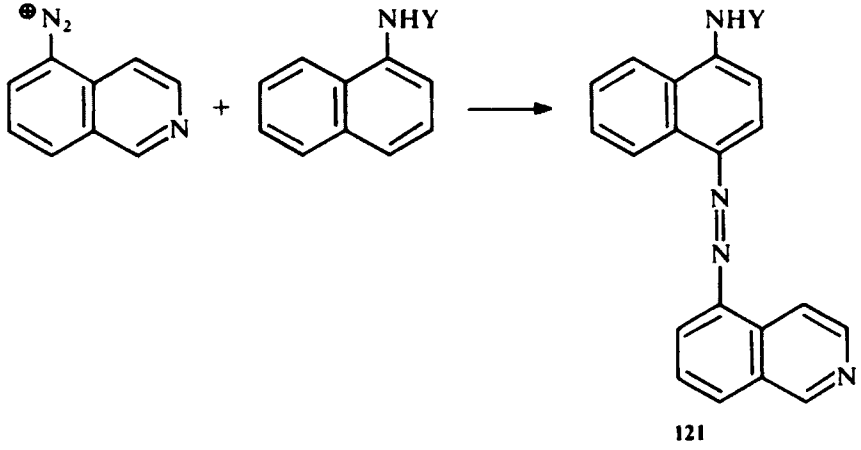


120

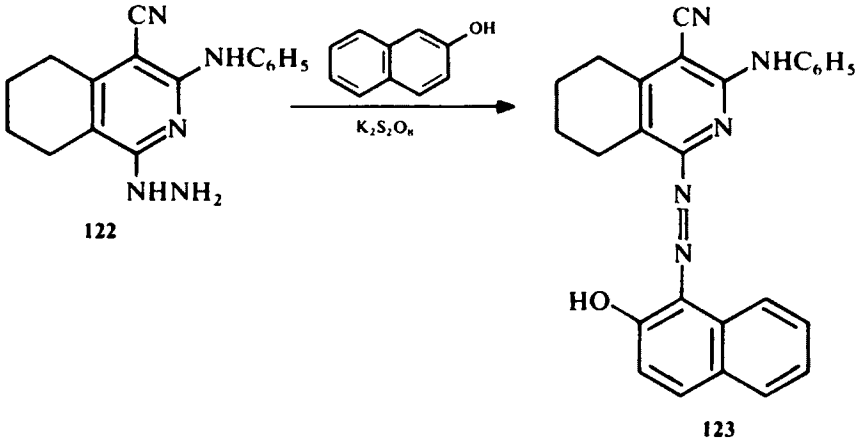
B. From Isoquinolinediazonium Cations

In addition to forming azoisoquinolines by coupling activated isoquinolines with aryl diazonium cations, as discussed in the previous section, this same class of compounds can also be made by coupling isoquinoline diazonium cations with suitably activated aromatic molecules. There are several examples of this route in the literature. Thus, 5-aminoisoquinoline has been diazotized and then coupled[209, 210] with 1-naphthylamine and several of its *N*-substituted derivatives to give the 5-naphthylazoisoquinolines **121**: Y = H, $(CH_2)_2N(CH_3)_2$, $(CH_2)_3N(CH_3)_2$. Similarly, the 4-, 5-, and 7-aminoisoquinolines have been coupled via their diazonium cations to the para position of *N*,*N*-dimethylaniline.[211]

Treatment of the 1-hydrazinoisoquinoline derivative **122** with potassium persulfate in acid solution in the presence of 2-naphthol gave[212] the azo derivative **123**, which is presumably formed via persulfate oxidation of the hydrazino group to the diazonium cation, which then couples with the naphthol.



121

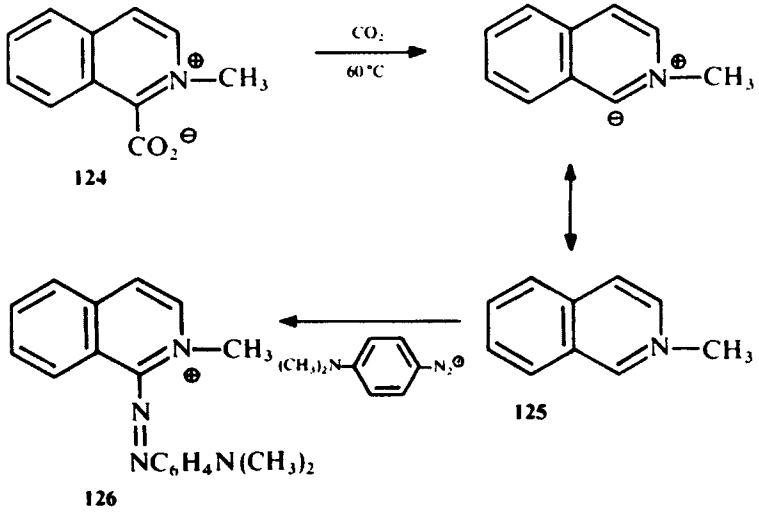


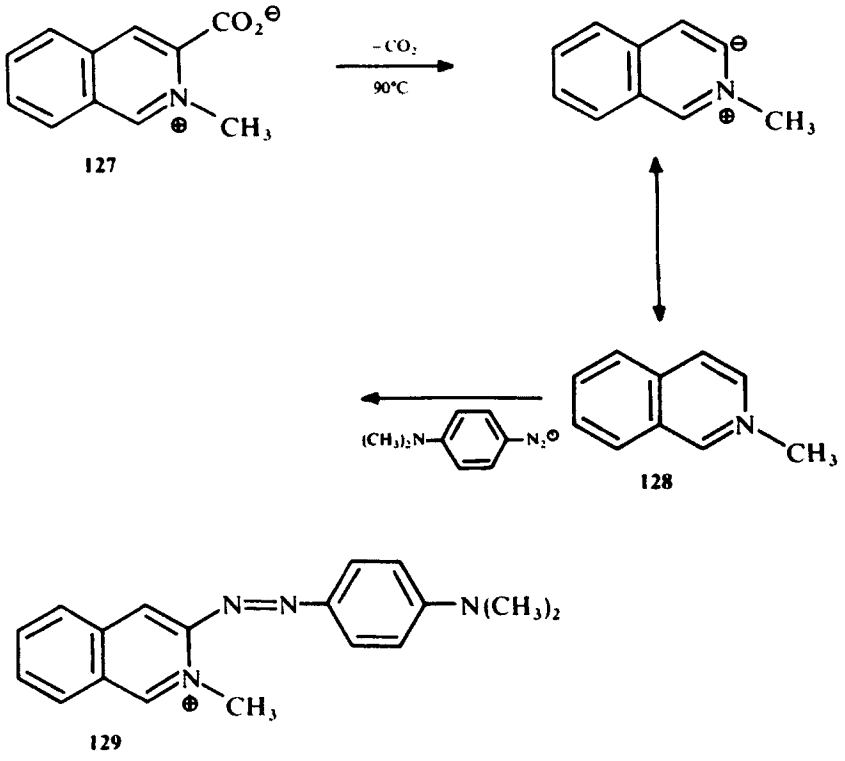
122 123

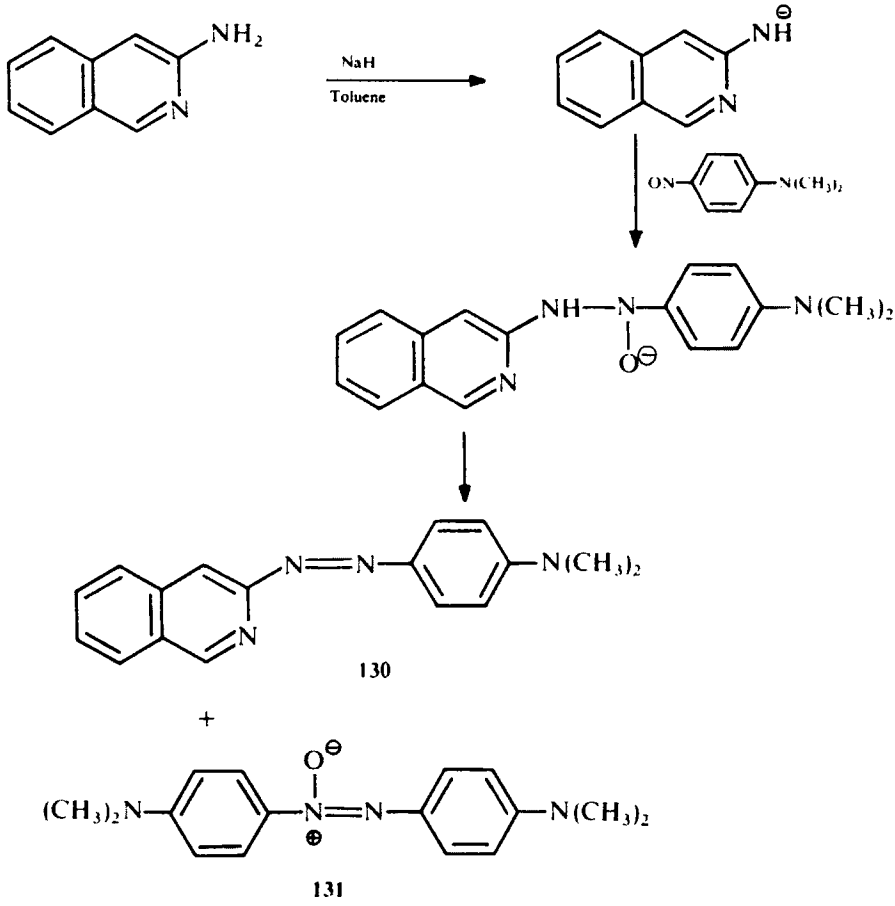
C. Other Azoisoquinoline Syntheses

The zwitterions **124** and **127** decarboxylate upon heating to give the ylide-carbenes **125** and **128**, respectively. In the presence of diazonium ions, azo-coupling products are formed. Thus, heating **124** in *N*-methylpyrrolidone at 60°C in the presence of the 4-dimethylaminophenyl diazonium cation gave **126** in 89% yield,[213, 214] while **127** was converted into **129** at 90°C in similar yield.[214]

3-(4-Dimethylaminophenylazo)isoquinoline **130** has been made[214] by generating the amide conjugate base of 3-aminoisoquinoline using sodium hydride in toluene, and then treating this anion with *N*,*N*-dimethyl-4-nitrosoaniline. A significant amount of 4,4'-azoxybis(*N*,*N*-dimethylaniline) **131** is also produced in this reaction.

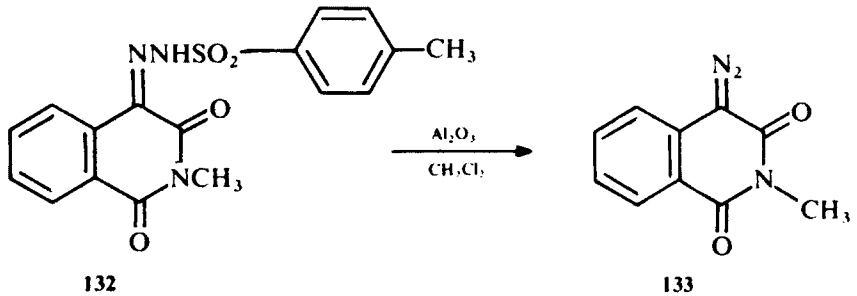

CO2
60°C
CO2⊖
124
125
126
(CH3)2N
N2⊕
NC6H4N(CH3)2


CO2⊖
-CO2
90°C
127
128
(CH3)2N
N2⊕
N(CH3)2
129

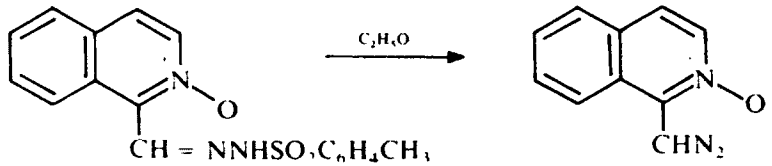


V. DIAZOISOQUINOLINES

The derivative **133** appears to be the only known isoquinoline bearing a ring-diazo substituent. This compound was prepared[215] in 90% yield by treatment of the tosylhydrazone **132** with aluminum oxide in dichloromethane.



The *N*-oxide (**134**) of 1-isoquinolinyldiazomethane has been made by an analogous route.[216]

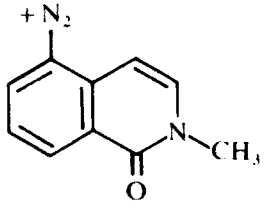


134

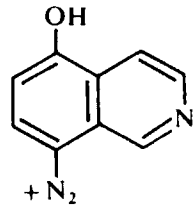
VI. ISOQUINOLINE DIAZONIUM CATIONS

The replacement of the amino group of aminoisoquinolines by other substituents via diazotization and then nucleophilic displacement of molecular nitrogen from the diazonium cation has been routinely used for synthetic purposes in the isoquinoline series. The intermediate isoquinoline diazonium cations are usually generated in solution and then subsequently reacted without first being isolated. Other chapters in these volumes should be consulted for such synthetic applications of isoquinoline diazonium cations (also references 217 and 218). Examples of the coupling of these diazonium ions with suitably activated aromatic amines or phenols to produce arylazoisoquinolines are given in Section IV.B.

The tetrafluoroborate salts of the 1- and 5-isoquinoline diazonium cations have been isolated;[219] however, the corresponding 3- and 4-isoquinoline diazonium salts decompose at room temperature to the 3- and 4-fluoroisoquinolines, respectively.[219] 3-Chloro-5-isoquinolinediazonium tetrafluoroborate has been isolated and converted to 3-chloro-5-fluoroisoquinoline upon heating.[29, 30] The tetrafluoroborate salt of the diazonium cation **135**, and the metaphosphate salt of **136** have also been reported.[220 221]



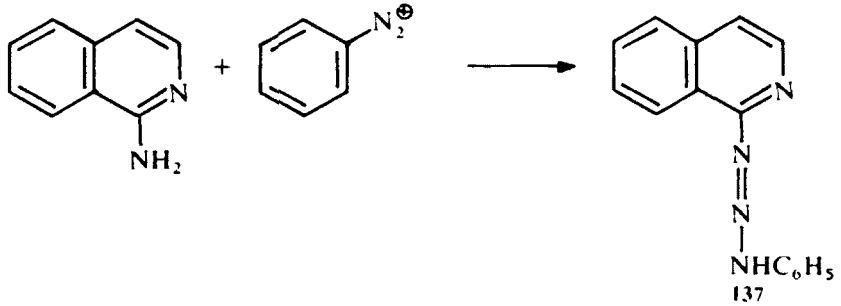
135



136

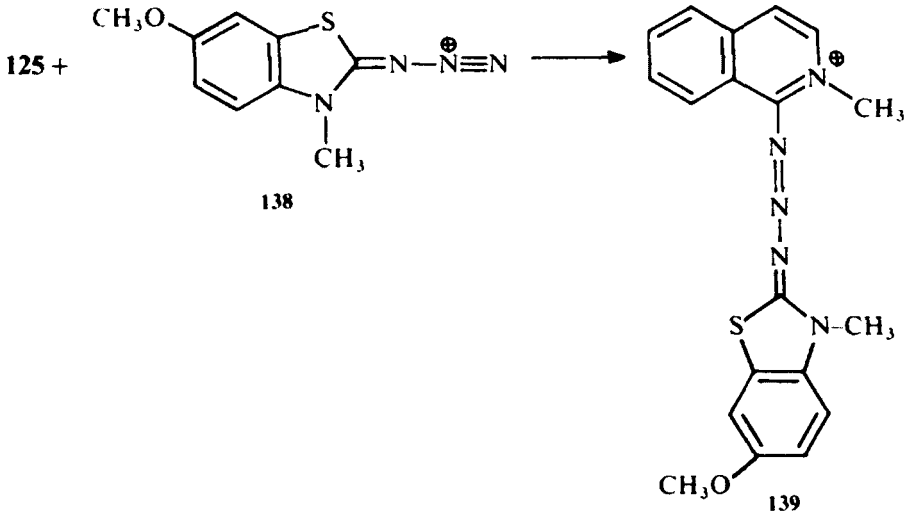
VII. TRIAZENOISOQUINOLINES

1-Aminoisoquinoline couples[222] with the phenyl diazonium cation to give **137**.



137

The ylide (carbene) **125**, formed by the decarboxylation of the zwitterionic **124** couples with electrophiles, for example, with the azidobenzothiazolium ion **138**, to give[213, 214] the triazenoisoquinolinium cation **139**.



138

139

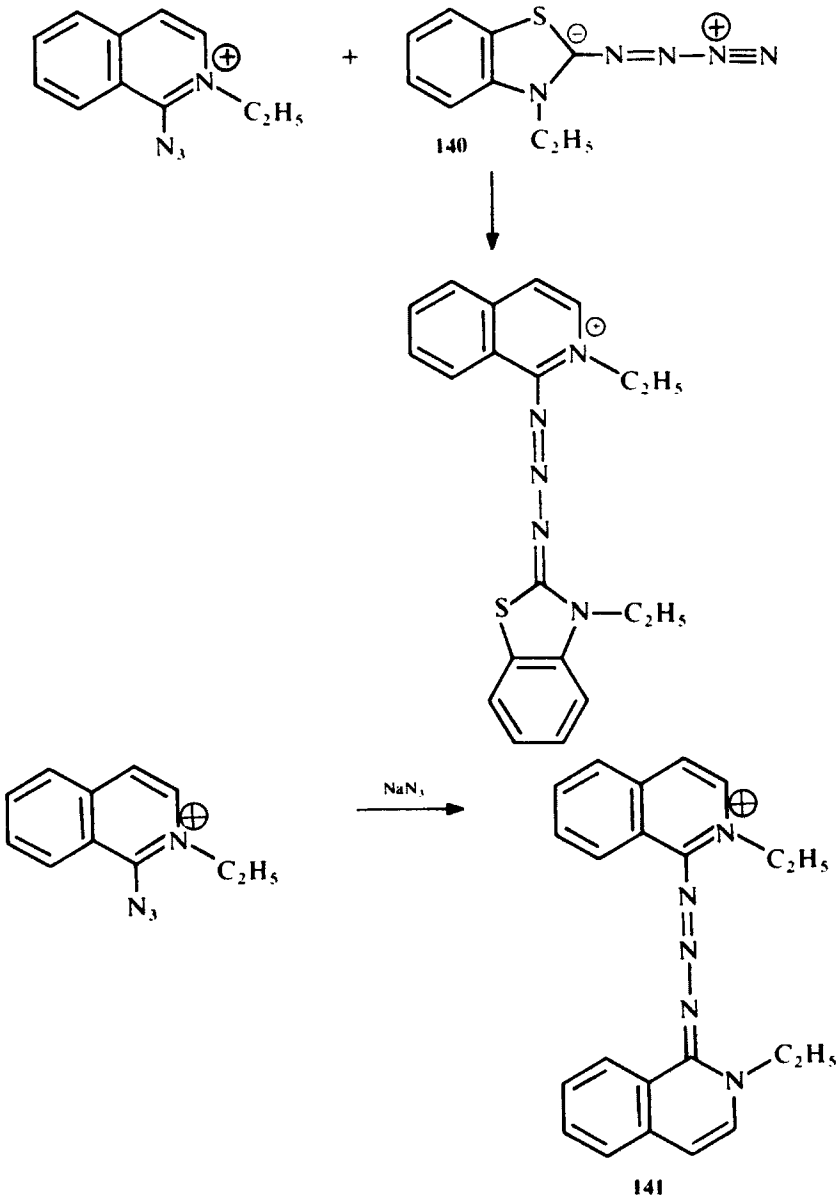
An *N*,*N*′-diethyl analog of **139** has also been reported[223] from the reaction of the 1-azido-2-ethylisoquinolinium cation with the diazoazobenzothiazoline **140**.

Treatment of the 1-azido-2-ethylisoquinolinium cation with sodium azide produces[224] the bisisoquinoline triazene cation **141**.

VIII. AZIDOISOQUINOLINES

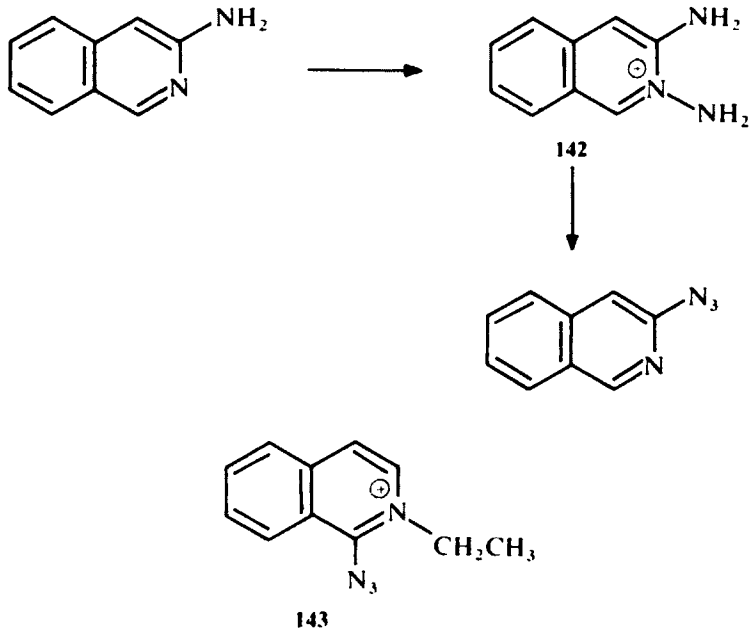
There are two general routes available for the synthesis of azidoisoquinolines.

1. The corresponding aminoisoquinoline is diazotized with nitrous acid to the diazonium cation, which is subsequently decomposed in the presence of sodium azide. This route has been successfully applied to give high yields of 4-azidoisoquinoline[225–227] and its 4-methyl and 4-phenyl derivatives,[227] 5-azidoisoquinoline[226] and 8-azido-5-chloroisoquinoline.[226]



2. Diazotization of an hydrazinoisoquinoline also leads to the corresponding azidoisoquinoline. This route has been used for the preparation of 3-azidoisoquinoline and several of its substituted derivatives.[228, 229]

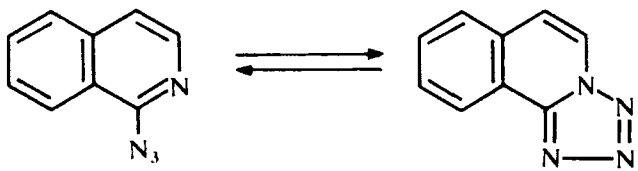
3-Azidoisoquinolines have also been prepared[229] by the diazotization of 2,3-diaminoisoquinolinium cations (**142**), which are available from the treatment of 3-aminoisoquinoline with *O*-tosyl hydroxylamine.



143

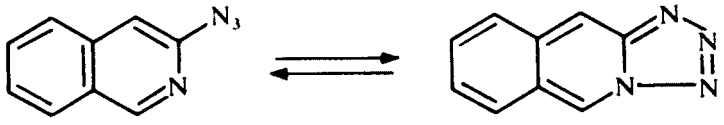
The 1-azido-2-ethylisoquinolinium cation **143** has been made by refluxing[230] the corresponding 1-chloro cation with sodium azide in methanol.

The chemistry of the 1-azido and 3-azido isoquinolines, and their derivatives, is complicated by their ring-chain tautomerism with their tetrazoloisoquinoline isomers. For 1-azidoisoquinoline (**144**), this equilibrium heavily favors tetrazolo[1,5-a]isoquinoline (**145**), even in the solid state at room temperature.[231] The 1-azido species has been characterized spectrally at $-196°C$ by sublimation of **145** at temperatures above 150°C, and collection of the gaseous **144** in a cold trap. The isomerization of **144** back to **145** is complete at temperatures above $-10°C$.



144 145

The equilibration of 3-azidoisoquinoline **146**, and its tetrazolo[1,5-b]isoquinoline isomer **147** is solvent-dependent, and equilibrium ratios of these two isomers, and several of their C-1 and C-2 substituted derivatives have been evaluated[228, 229] by ^{1}H NMR spectroscopy. The equilibrium tetrazole:azide ratio is 1.5 in dimethyl sulfoxide, but only 0.15 in deuterochloroform. *C*-Methyl substituents enhance the stability of the tetrazole form, whereas *C*-bromo



146 147

substitution favors the azido isomer. In trifluoroacetic acid solution, the protonated tetrazole is the predominant species.

A wide variety of 6-azido-decahydroisoquinoline derivatives have been reported in the patent literature.[232-234]

IX. REFERENCES

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