THE CHEMISTRY OF ISOQUINOLINES

R. H. MANSKE

National Research Council of Canada, Ottawa, Canada

This review deals with (*a*) systematization of all reactions which lead to the synthesis of the isoquinoline nucleus, (*b*) the reactions of isoquinolines which are characteristic of the nucleus, and (*c*) reactions of substituted isoquinolines which are occasioned by the presence of the nucleus. The chemistry of the isoquinoline alkaloids is not specifically treated, except when it is included in one of the above categories.

As in the case of the quinolines, the syntheses of isoquinoline and its derivatives may be divided into a number of types, depending upon the point at which the hetero ring is closed. There are, therefore, five possible ways in which these compounds can be theoretically prepared, giving rise to five type syntheses: namely, ring closure between the nucleus and carbon atom 1 (Type I), between atoms 1 and 2 (Type II), between atoms 2 and 3 (Type III), between carbon atoms 3 and 4 (Type IV), and between carbon atom 4 and the nucleus (Type V). In each of the following formulas the dotted line indicates the point at which union is to be effected.

I   II   III   IV   V
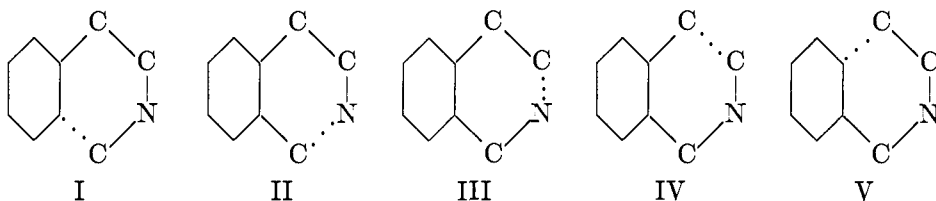
Mechanisms representative of all types are known, but in many cases the compounds obtained are keto derivatives of tetrahydroisoquinolines, some of which are convertible into isoquinolines or their tetrahydro derivatives only with difficulty. No attempt will be made in the following review to refer to all, or even most, of the many compounds which have been prepared (57). It is deemed sufficient to discuss the various synthetic procedures. It is hoped that the references cited will serve as a basis for a more thorough search of the literature on any particular phase of the subject.

Following the discussion of synthesis, there is a review of the reactions of isoquinolines. In this section those reactions which are common to organic compounds in general will not be treated.

It is difficult to review the chemistry of isoquinolines without reference to alkaloids, since much of the chemistry of the former has been built up in attempts to synthesize alkaloids or their degradation products. Then, too, many reactions of the isoquinolines have been encountered in researches concerned with alkaloids. Nevertheless, Henry (56) has adequately reviewed the subject of the isoquinoline alkaloids, both from the synthetic and the degradative points of view, so that references to alkaloid chemistry will be greatly restricted.

### I. SYNTHESES OF ISOQUINOLINE AND ITS DERIVATIVES

Type I: Syntheses from β-arylethylamines

The reactions described as of Type I (i.e., ring closure between the nucleus and what is to become the 1-carbon atom) necessitate as a primary starting material a β-arylethylamine or some substance which during the synthesis will give rise to such an amine or a derivative. Consequently, most of the researches dealing with the synthesis of β-arylethylamines have a direct bearing on the synthesis of isoquinolines. In this connection it is therefore pertinent to mention that Schales (92) has reviewed the literature on β-arylethylamines. Mention may also be made of the researches of Kindler and coworkers (64, 65) on new and improved syntheses of these bases and of their β-hydroxy derivatives. Important too is the work on the arylacetic and β-arylpropionic acids, the former of which are used as the source of the 1-benzyl substituent in the synthetic benzylisoquinolines (66).

The synthesis of Bischler and Napieralski (10) was achieved by heating the acetyl or the benzoyl derivative of β-phenylethylamine with phosphorus pentoxide or with zinc chloride at about 200°C. The products were 1-alkyl- or 1-aryl-
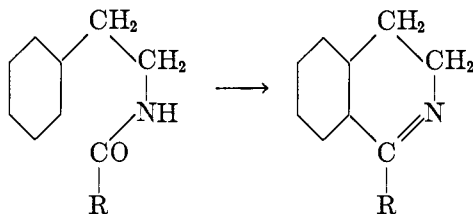
3,4-dihydroisoquinolines. The yields were only mediocre, but the later work of Pictet (81, 82) and of Decker (22, 23) and their coworkers effected material improvements so that the reaction became a practical one for the synthesis of isoquinoline alkaloids. The reaction is now generally carried out in boiling toluene or xylene in the presence of phosphorus pentoxide or phosphorus oxychloride, although aluminum chloride, ferric chloride, zinc chloride, and phosphorus pentachloride have been used. The benzylisoquinoline alkaloids,—laudanosine, laudanine, and papaverine; cotarnine and hydrastinine; salsoline, pectenine, and corypallin; and the anhalonium alkaloids,—have been synthesized by this reaction. When the β-aryl-β-hydroxyethylamines are used as the starting materials, an additional molecule of water is eliminated and isoquinolines are produced (79, 80).
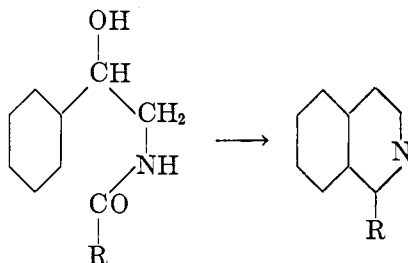
When R is phenyl, the double bond introduced as the result of ring closure can take only the position between carbon atom 1 and the nitrogen atom. When R is benzyl or a homologous radical, however, the double bond could be outside of the ring. This happens when the nitrogen is methylated. From phenylacetyl(β-phenylethyl)methylamine Hamilton and Robinson (53) obtained 1-benzal-N-methyltetrahydroisoquinoline.
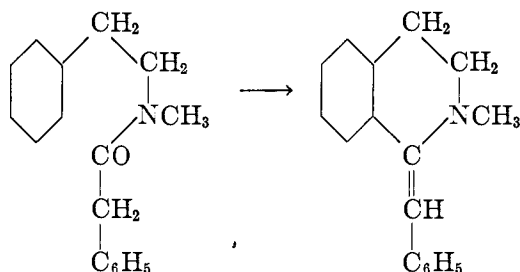
The record of complete failures does not include many examples. Formyl-(β-phenylethyl)amine yields only a small amount of dihydroisoquinoline (23), the main product being a complex aminomalonamide (20).

An important variation of the Bischler–Napieralski reaction was introduced by Pictet and Spengler (84), when they condensed aldehydes with β-arylethylamines and effected ring closure by means of hot hydrochloric acid. Phenylalanine yielded a small amount of an isoquinolinecarboxylic acid, but tyrosine
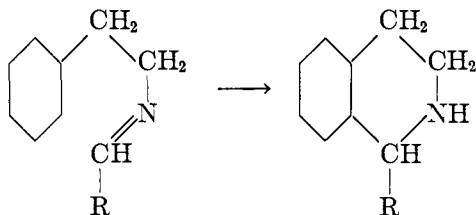
and tyramine gave better results. Decker and Becker (21) extended this work to the methylenedioxyarylamines and a number of aldehydes. The synthesis of harman from tryptophan (61, 77) is an example of a similar ring closure in which the carboxyl group is eliminated and the hydro-hetero ring is oxidized at the same time.

Of great biological interest is the condensation of β-arylethylamines with aldehydes and pyruvic acids under the so-called physiological conditions. Condensation is brought about at room temperature under controlled conditions of pH. Schöpf and Bayerle (94) condensed β-(3,4-dihydroxyphenyl)ethylamine hydrobromide with a slight excess of acetaldehyde. At 25°C. and pH 3 to 5 an 83 per cent yield of 1-methyl-6,7-dihydroxytetrahydroisoquinoline was obtained. Hahn and Schales (51, 52) succeeded in obtaining a 5 per cent yield of 3',4',6,7-bismethylenedioxytetrahydroprotopapaverine by condensing β-piperonylethylamine with homopiperonal under similar conditions. Such condensations under physiological conditions proceed easily only when the ring to which closure is effected is suitably substituted with free hydroxyl groups. It is argued that

such are the conditions which prevail in plants and that methylation and methyl-enation are subsequently achieved.

Kaufmann and Dürst (63) have modified the synthesis with formaldehyde by condensing the arylamine first with chloromethylmethyl ether. The N-methoxymethyl derivative may be isolated as an intermediate and the ring ultimately closed by treatment with phosphorus pentoxide or with hot dilute hydrochloric acid.

Type I: Other syntheses

There are a variety of reactions which yield β-arylethylamines as ultimate products. The intermediates are frequently obtainable as stable compounds and in some cases the disposition of reactive groups is such that ring closure to an isoquinoline is possible.

The Beckmann rearrangement of oximes leads to acyl or aroyl amines and, in the case of the oxime of cinnamaldehyde, the intermediate formylstyrylamine yields a small amount of isoquinoline (5, 44) when treated with phosphorus pentoxide. Zelinsky (102) had obtained an oily base from the oxime of styryl methyl ketone under similar conditions. This was shown by Goldschmidt (45) to be isoquinoline, not the expected 1-methylisoquinoline, which was only obtained at a later date by Burstin (14) from the same starting materials. Styryl phenyl ketone failed to yield an isoquinoline (46).

Much better yields of isoquinolines (in this case the 3,4-dihydro compounds) are obtainable from the oximes of saturated ketones. From the oxime of benzylacetone Pictet and Kay (82) obtained 1-methyl-3,4-dihydroisoquinoline in a yield of approximately 50 per cent. Sugasawa and Yoshikawa (98) condensed veratraldehyde with acetone, reduced the distryryl compound, and then prepared the oxime. The latter, on heating with phosphorus oxychloride in toluene, yielded a tetramethoxy-1-(β-phenylethyl)dihydroisoquinoline.

The Hofmann synthesis of amines produces as one of the intermediates an isocyanate (I), which might be expected to undergo ring closure with the forma-

I   II
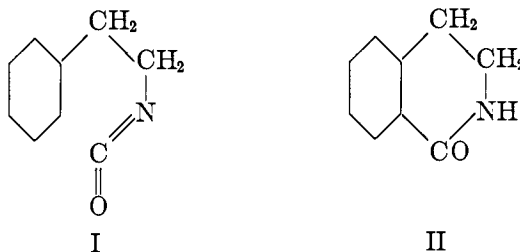
tion of dihydroisocarbostyril (II). Weerman and Jongkees (100) failed to achieve this synthesis with the unsubstituted compound. In the Curtius synthesis of amines it is easier to isolate the intermediate isocyanate, and Mohunta and Ray (75) have succeeded in effecting the ring closure of the isocyanate (III) to corydaldine (IV) by means of phosphorus oxychloride. The reaction is an adaptation of the more facile one in which the azide of β-3-indolylpropionic acid,

III IV
Corydaldine
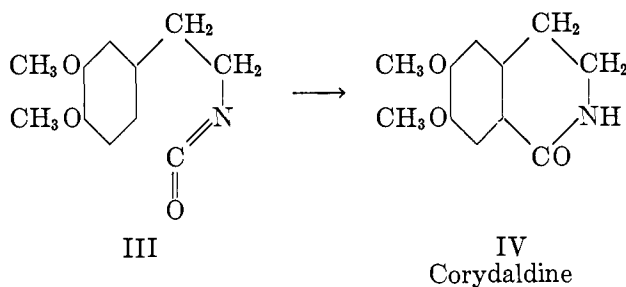
on boiling in benzene in a stream of hydrogen chloride, yielded 3-keto-3,4,5,6-tetrahydro-4-carboline (72). The earlier synthesis of corydaldine by Späth and Dobrowsky (95) was achieved by treating the reaction product of ethyl chloroformate and β-veratrylethylamine with phosphorus pentoxide in xylene. It is closely related to the above.

Bruckner and Krámli (13) described a synthesis of 1-alkyl-3-methyl-6,7-methylenedioxyisoquinolines. The N-acyl-β-hydroxyarylethylamines were obtained from isosafrole by a series of reactions involving nitroso compounds.

v. Braun and Wirz (11) prepared a series of β-arylethylglycines with or without a methyl group on the nitrogen. The acid chlorides of these (V) on treatment with aluminum chloride yielded not the expected homoisocarbostyrils but the tetrahydroisoquinolines (VI) together with carbon monoxide. When the

V VI
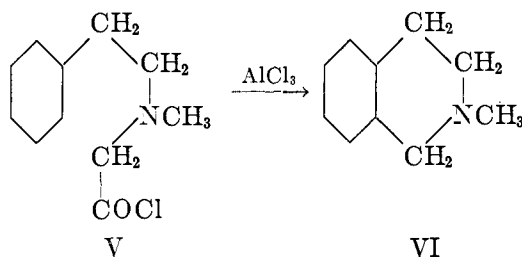
nitrogen was secondary, it was necessary to make the p-toluenesulfonyl derivative first.

Type II syntheses

The reactions classed as Type II which lead to the synthesis of isoquinoline derivatives are greatly limited in generality and in usefulness. The condensation of a β-arylethylamine containing a reactive ortho-substituent can yield a quinoline, but these compounds are in general accessible only with difficulty.

Bain, Perkin, and Robinson (2) utilized the hippuric acid condensation in converting o-carboxybenzaldehyde into 1-hydroxy-3-carboxyisoquinoline. The azlactone was hydrolyzed with 10 per cent caustic potash and the intermediate suffered ring closure during the course of the hydrolysis. Opianic acid gave the corresponding dimethoxy derivative. Dihydroisocarbostyril was prepared from N-benzoyl-β-(o-carboxyphenyl)ethylamine by Bamberger and Dieckmann (3). This particular reaction, however, can be of limited use only, because their ulti-

mate intermediate was prepared from N-benzoyltetrahydroisoquinoline by oxidation with permanganate.

More complex syntheses have been reported by Schneider and Schroeter (93) and by Gabriel (38).

Homophthalimide is 1,3-diketo-1,2,3,4-tetrahydroisoquinoline. It is obtainable from homophthalic acid by treatment with ammonia and when heated with zinc dust (70), or successively with phosphorus oxychloride and hydriodic acid (36), it yields isoquinoline. Homophthalimide is also obtainable from o-cyanobenzyl cyanide on hydrolysis with sulfuric acid (37) and both syntheses, but particularly the former, are of wide applicability.

Closely related to the above syntheses is one in which isocarbostyril is obtained directly. The amide of o-cyanocinnamic acid on treatment with sodium hypochlorite in methanol yields first the carbomethoxyl derivative of o-cyanostyrylamine. When the latter is heated with hydrochloric acid, ammonia, methanol, and carbon dioxide are eliminated and isocarbostyril is formed (39).

When the hydrochlorides of α,ω-diamino compounds in which the amino groups are separated by four or five carbon atoms are distilled, ammonia is eliminated and a pyrrolidine or a piperidine is formed. Helfer (55) distilled the dihydrochloride of β-(o-aminomethylphenyl)ethylamine and obtained tetrahydroisoquinoline in nearly 60 per cent yield. When homoxylylene dibromide is treated with aniline, it yields N-phenyltetrahydroisoquinoline. With dimethylamine a quaternary bromide is obtained (12).

Primary amines react with isocoumarins to give in most cases quantitative yields of the corresponding isoquinoline derivatives. Gabriel (32, 33, 34, 35) prepared the compound I (R = H; R' = C₆H₅). This on treatment with
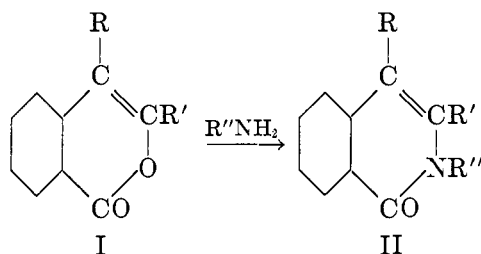
ammonia yields 3-phenylisocarbostyril (II) (R = R″ = H; R' = C₆H₅). The reaction has been extended by Heilmann (54) and by Bethmann (9). The isocoumarins are difficultly accessible compounds and a variety of syntheses have been elaborated. The reaction of benzoyl chloride with o-cyanobenzyl cyanide, whereby 3-phenyl-4-cyanoisocoumarin may be obtained (42), is not as suitable for analogous alkyl compounds because the yields are low (43). Ingenious, but applicable only to the synthesis of isocoumarin, is the oxidation of β-naphthoquinone with sodium hypochlorite. The isocoumarin and the intermediate carboxylic acid on treatment with ammonia yield isocarbostyril and isocarbostyril-3-carboxylic acid, respectively (4).

The esters of isocoumaric acid (III) may be prepared by the Claisen con-

III
Isocoumaric acid

IV
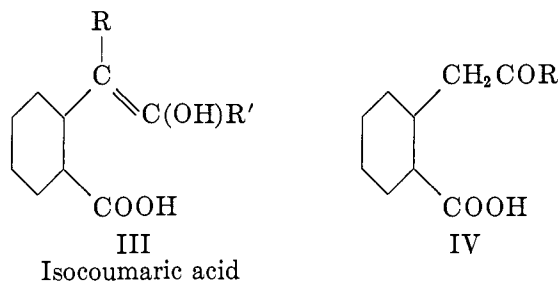
densation of the esters of homophthalic acid with aliphatic and aromatic esters. Treatment of these with ammonia yields isocarbostyrils (24). The o-phenacyl- and o-acetonyl-benzoic acids (IV) (R = C_6H_5 or CH_3) are the ketonic tautomers of isocoumaric acids, and as such condense with primary amines to yield iso-carbostyrils (33, 48). The reaction has been extended to a number of hydroxy- and ethoxy-isocoumarins by Fritsch (30). The action of hydrazines on iso-coumarins yields compounds which are either the N-aminoisocarbostyrils or seven-membered ring compounds containing two nitrogen atoms in the ring. On reduction with zinc and hydrochloric acid, they lose ammonia or arylamines and thus behave like substituted hydrazines. The products are isocarbostyrils in which the nitrogen atom is secondary (48, 71, 101).

Type III syntheses

In the reactions of Type III, ring closure is brought about by a union between the nitrogen atom and what is to become carbon atom 3 in the ring. No un-ambiguous examples of such a synthesis are known. It is probable that many of the reactions described as of Type II properly belong here. The exact mechanism, however, is obscure and for the present purpose of no consequence.

Type IV syntheses

Ring closure between carbon atoms 3 and 4 to yield isoquinolines is restricted to a few examples, all of which involve the condensation of a nuclear carboxyl with an active hydrogen.

The first and typical example is one discovered by Gabriel and Colman (40, 41), in which ethyl phthalimidoacetate was treated with sodium ethylate. A modified Dieckmann reaction takes place, in which the phthalimido ring is first opened and then re-formed at the methylene carbon. The ultimate product is 3-carbethoxy-4-hydroxyisocarbostyril. The synthesis is limited to phthalimido derivatives containing a group which will undergo the Claisen condensation. Phthalimido derivatives of simple ketones (68), but not benzylphthalimide, yield isocarbostyrils. When the phthalyl derivatives of amino acids, other than that of glycine, are used, the carboxyl group is eliminated and the products are 3-alkyl(or aryl)-4-hydroxyisocarbostyrils (40, 99). In a few cases this reaction has been applied to compounds substituted in the phthalyl moiety (29, 69).

Closely related but distinctly novel is the modification described by Fischer and Krollpfeiffer (28). **2,3,4**-Trisubstituted pyrroles condense with phthalic anhydride in the presence of acetic anhydride to give rise to compounds of formula I. It is probable that an *o*-carboxybenzoylpyrrole is formed as an intermediate.

I

Tetraalkylpyrroles give the same product, one alkyl group being eliminated.

Type V syntheses

There is no isoquinoline synthesis as elegant and useful as the Skraup quinoline synthesis. Nevertheless some reactions classed as Type V (i.e., ring closure between carbon atom 4 and the nucleus) bear a close resemblance to some of the modifications of the Skraup synthesis. Staub (97), as the result of a comprehensive study, has defined the structural conditions necessary for the formation of isoquinoline derivatives. Ring closure can occur only in compounds of formula I or II, the conjugated double bonds being actually or potentially

present. The terminal carbon carries an OH or OR group which is eliminated during the condensation. Benzalaminoacetal, on treatment with phosphorus oxychloride or sulfuric acid, gives isoquinoline in a yield of about 50 per cent (30, 85, 86). Here, the elimination of one OC_2H_5 group produces the required second double bond. In the synthesis from benzylaminoacetaldehyde (27) ring closure is effected by oleum, which oxidizes the benzyl to a benzal derivative, the enol of the resulting compound having formula II. Rügheimer and Schön (91), in their synthesis of 6,7-dimethoxyisoquinoline by a similar method, used arsenic pentoxide as the oxidizing agent. In Perkin and Robinson's (76) synthesis of the 7,8-dimethoxy derivative, ring closure was effected by 70 per cent sulfuric acid. The necessary acetal, with one actual double bond, was obtained by condensing aminoacetal with 2,3-dimethoxybenzaldehyde. The enolic form of benzoylaminoacetal has one actual and one potential double bond

and yields isocarbostyril on treatment with sulfuric acid (30). When there is a
m-hydroxyl or m-alkoxyl group in the benzene nucleus, ring closure yields the
7- rather than the 5-substituted isoquinolines (31).

Benzoylaminoacetic acid, when treated with an excess of phosphorus penta-
chloride, yields 1,4-dichloroisoquinoline, presumably by way of 4-hydroxy-
isocarbostyril (90). An analogous reaction using 3,4-dimethoxybenzalglycine
failed to yield an isoquinoline (76).

Basu (6) and Basu and Banerjee (7) have adapted the Guareschi synthesis
(50) of pyridines and its modification by Knoevenagel and Fries (67) to the
synthesis of bz-hexahydroisoquinolines. In the first example, ethyl cyclo-
hexanonecarboxylate was condensed with cyanoacetamide to yield compound
III. In the second example, oxymethylenecyclohexanone was treated with
ammonia and the resulting aminomethylene compound was condensed with
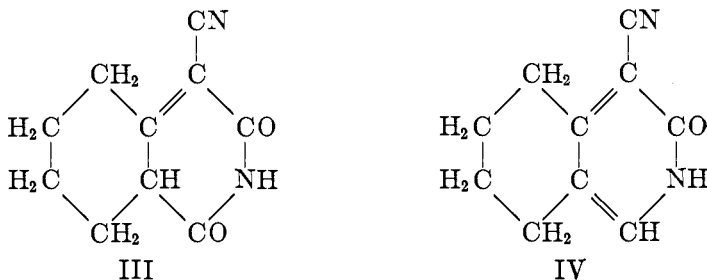
ethyl acetoacetate in the presence of sodium. The resulting substance (IV)
on hydrolysis yielded the corresponding acid, which was easily decarboxylated
and converted into isoquinoline by distillation with zinc dust.

Miscellaneous syntheses

Only two syntheses of isoquinoline are considered here and both depend upon
pyrolysis. Graebe and Pictet (49) obtained a small yield of a base, by distilling
N-methylisoindolinone with zinc dust, which was later identified as iso-
quinoline (78).

When benzalethylamine is passed through a hot tube, some isoquinoline can
be isolated from the mixture of products (83).

II. REACTIONS OF ISOQUINOLINE AND ITS DERIVATIVES

The reactions of isoquinoline and its derivatives may be divided into those
which are not dependent upon the reactivity of substituents and those which are.
Reactions which are common to organic compounds in general and are not de-
pendent upon the presence of the isoquinoline part of the molecule will not
come under consideration in this review.

A. Reactions not involving substituents

The reduction of isoquinolines to the tetrahydro bases can be brought about
by tin and hydrochloric acid (58) or catalytically in the presence of platinum

oxide (88). When isoquinoline is oxidized in alkaline solution with permanganate, there is formed a mixture of pyridine-3,4-dicarboxylic acid, phthalic acid, and oxalic acid as well as ammonia and a mixture of unidentified compounds (58). When the oxidation is carried out in neutral solution with permanganate, the chief product is phthalimide (47). Oxidation with perbenzoic acid yields isoquinoline N-oxide (73).

When isoquinoline is treated with bromine, there is formed an addition product which when heated to 180–200°C. yields a py-bromoisoquinoline. The latter on oxidation with permanganate yields a bromopyridinedicarboxylic acid of uncertain constitution (26).

The nitration of isoquinoline in fuming sulfuric acid yields a nitro derivative which on oxidation with nitric acid or with permanganate yields 3-nitrophthalic acid (17). It is, therefore, a 5- or an 8-nitroisoquinoline or a mixture of these (1). Similarly, sulfonation yields a mixture of the α- and β-isoquinolinesulfonic acids which are separable by means of their barium salts. The α-form predominates when the reaction is carried out at 115°C., and the β-form at 250–260°C. (18, 19). When the barium salt of the α-sulfonic acid is heated in a current of hydrogen with potassium ferrocyanide, a small yield of a bz-cyanoisoquinoline is obtained. The cyano group of this compound is saponifiable only with difficulty (62).

When isoquinoline is treated with sodium amide in neutral solvents, it yields 1-aminoisoquinoline. The latter does not yield a diazo compound, but on treatment with nitrous acid is converted to isocarbostyril (15). The introduction of an alkyl group into the 1-position by means of the Grignard reaction was described by Bergstrom and McAllister (8). There is first formed an addition compound which suffers a rearrangement when heated to 150–160°C.

The reaction of benzoyl chloride with isoquinoline yields only an unstable addition compound from which isoquinoline can be easily regenerated. In the presence of added potassium cyanide, there is formed 1-cyano-N-benzoyl-1,2-dihydroisoquinoline. This on hydrolysis with hydrochloric acid yields isoquinoline-1-carboxylic acid and benzaldehyde (89). The reaction is strictly analogous to the preparation of quinaldinic acid and benzaldehyde from quinoline and the same reagents.

B. Reactions involving substituents

Under this heading will be discussed the limited number of reactions directly involving substituents of the isoquinoline molecule and the rather special reactions of the 3,4-dihydroisoquinolines. The latter are obtained directly in the Bischler–Napieralski synthesis and are in general the most readily accessible of the entire group. They may be dehydrogenated to isoquinolines by heating with palladium at about 180°C. (96).
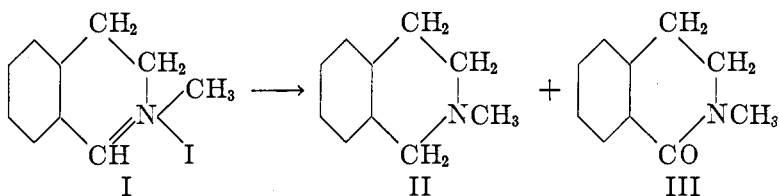
The hydroxyisoquinolines with the hydroxyl group in the pyridine nucleus are soluble in alkali but in general not soluble in dilute acids. The hydroxyl is replaceable by chlorine by means of phosphorus oxychloride (42). When there are two hydroxyls, either one or both of them may be replaced by chlorine (40).

The chloro compounds react with sodium methylate, yielding the corresponding methyl ethers, and heating with hydrogen iodide and phosphorus yields isoquinolines (2). The hydroxy compounds when heated with zinc dust in an atmosphere of hydrogen yield isoquinolines (42). When 1,4-dihydroxy-3-methylisoquinoline is heated with hydrogen iodide and phosphorus to 180°C., there is formed 3-methylisocarbostyril. At 240°C. the second hydroxyl is reduced and 3-methylisoquinoline is obtained (40).

Mills and Smith (74), in the course of their studies of the reactivity of methyl groups in heterocyclic bases, condensed 1-methylisoquinoline with benzaldehyde and obtained 1-styrylisoquinoline. Attempts to obtain 3-styrylisoquinoline from 3-methylisoquinoline failed. There seems to be no record of attempts to condense these methylisoquinolines with the other reagents which have been successfully condensed with quinaldine and with lepidine (i.e., chloral, phthalic anhydride, etc.).

Isoquinoline and its derivatives react with alkyl halides, yielding alkylisoquinolinium halides (16, 59). These halides are for the most part soluble in water and yield on treatment with excess fixed alkali insoluble oily precipitates of uncertain structure. Oxidation with potassium ferricyanide in alkaline solution yields N-alkylisocarbostyrils.

Of special interest are the reactions of 3,4-dihydroisoquinoline with a number of reagents. The corresponding methiodide (I) on treatment with alkali undergoes a reduction–oxidation dismutation which is strictly analogous to the Canniz-


zaro reaction. The products are N-methyltetrahydroisoquinoline (II) and the corresponding 1-keto derivative (III) (87). The reaction is of importance in the chemistry of the phthalide-isoquinoline alkaloids. The latter on mild oxidation yield compounds analogous to compound I with alkoxyl groups in the benzene nucleus. The corresponding bases are obtained by adding an excess of a strong alkali to an aqueous solution of the salt. Two of the formulas which have been proposed for the free bases IV and V have received wide recognition.
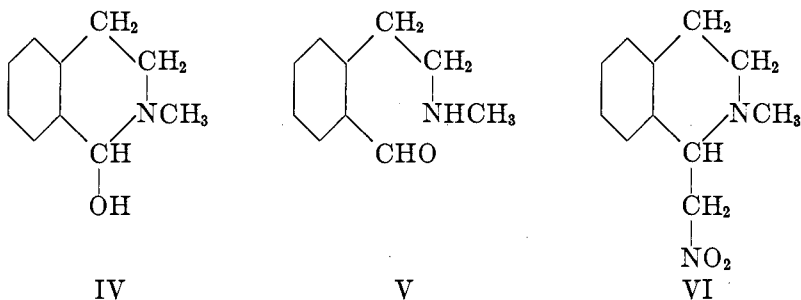
The former (IV) accounts for the ease with which these compounds condense with a variety of reagents. With nitromethane the product has formula VI (60), and the reaction product with meconine or with a substituted meconine and cotarnine are stereoisomers of narcotine (60). Formula V accounts adequately for the Cannizzaro reaction noted above.

Of special importance in alkaloid syntheses is the reduction of methiodides of dihydroisoquinolines. This is readily accomplished by a variety of reducing agents, of which zinc and acetic or hydrochloric acid is one of the most convenient. The products are N-methyltetrahydroisoquinolines and it is in this form that most of the isoquinoline alkaloids occur in nature.

Corydaldine (i.e., 6,7-dimethoxytetrahydroisocarbostyril; VII) is obtainable by oxidizing corydaline (25). It yields a crystalline N-nitroso derivative which on treatment with alkali is converted into the lactone (VIII).
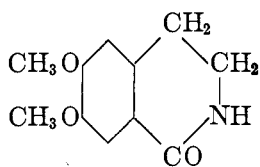
VII
Corydaldine
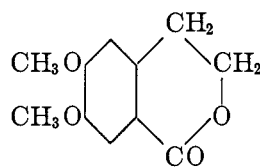
VIII

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