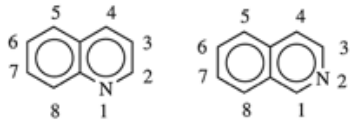
Kirk-Othmer Encyclopedia of Chemical Technology.

QUINOLINES AND ISOQUINOLINES

1. Introduction

Replacing one carbon atom of naphthalene with an azomethene linkage creates the isomeric heterocycles 1- and 2-azanaphthalene. Better known by their trivial names quinoline [91-22-5] **1** and isoquinoline [119-65-3] **2**, these compounds have been the subject of extensive investigation since their extraction from coal tar in the nineteenth century. The variety of studies cover fields as diverse as molecular orbital theory and corrosion prevention. There is also a vast patent literature. The best assurance of continuing interest is the frequency with which quinoline and isoquinoline structures occur in alkaloids and pharmaceuticals (1), eg, quinine [130-95-0] and morphine [57-27-2].



Alternative names for **1** and **2**, benzo[*b*]pyridine and benzo[*c*]pyridine, respectively, are now little used. These synonyms, like their modern counterparts, suggest an important generalization concerning the chemical behavior of these compounds and their many derivatives. Like naphthalene and pyridine, **1** and **2** are clearly aromatic, but less intensely than benzene. Resonance energy per π electron for benzene (0.065β), naphthalene (0.055β), and pyridine (0.058β) may be compared with quinoline (0.052β) and isoquinoline (0.051β) (2).

The close chemical relationship among these structural entities, as well as the uniqueness of **1** and **2**, have been evident from the time of the earliest structural studies. Permanganate oxidation of **1** (3) produces 2,3-pyridinedicarboxylic acid (quinolinic acid [89-00-9]) **3** (eq. 1), whereas similar treatment of **2** (4) yields a mixture of 3,4-pyridinedicarboxylic acid (cinchomeronic acid [490-11-9]) **4** and phthalic acid (eq. 2).

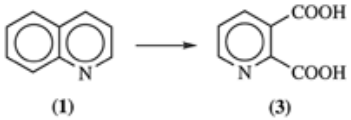


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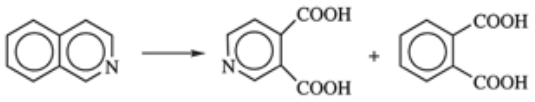
Table 1. Physical Properties of Quinoline and Isoquinoline[a]

	Value	
Property	Quinoline	Isoquinoline
mp, °C	−15.6	26.5
bp, °C	238	243
ΔH_{vap}, kJ/mol[b]	46.4	49.0
n_D^{20}	1.6268	1.6148
d^{20},g/cm^3	1.0929	1.0986
K_a	8.9×10^{-10}	2.5×10^{-9}
Viscosity at 30°C, mPa.s(=cP)	2.997	3.2528
T_c	509	530

[a]Refs. 4,5.
[b]To convert J to cal, divide by 4.186.



(2) (4) (2)

The continuing importance of these compounds has lead to a number of general and specific reviews. Five volumes of Weissberger's *The Chemistry of Heterocyclic Compounds* are essential reading for studies through 1977 and, in many instances, to 1990 (5). The second edition of a massive presentation of heterocyclic molecules covers the period through 1995 (6).

2. Physical Properties

Both **1** and **2** are weak bases, showing a pK_a of 4.94 and 5.40, respectively. Their facile formation of crystalline salts with either inorganic or organic acids and complexes with Lewis acids is in each case of considerable interest. Selected physical data for quinoline and isoquinoline are given in Table 1. References 5 and 7 substantially expand the range of data treated.

3. Chemical Properties

The presence of both a carbocyclic and a heterocyclic ring facilitates a broad range of chemical reactions for **1** and **2**. Quaternary alkylation on nitrogen takes place readily, but unlike pyridine, both quinoline and isoquinoline show addition by subsequent reaction with nucleophiles. Nucleophilic substitution is promoted by the heterocyclic nitrogen. Electrophilic substitution takes place much more easily than in pyridine, and the substituents are generally located in the carbocyclic ring.

4. Quinoline

4.1. Reactions

Quinoline exhibits the reactivity of benzene and pyridine rings, as well as its own unique reactions.

4.1.1. Nitration

As an aromatic system, **1** shows important synthetic and mechanistic nitro group chemistry. The experimental conditions employed usually determine the product structure. At 0°C mixed acid attacks the protonated quinoline to yield a 1:1 mixture of 5-nitroquinoline [607-34-1] and 8-nitroquinoline [607-35-2] (8). Under less acidic conditions, as with an acetic–nitric acid mixture or with dinitrogen tetroxide, 3-nitroquinoline [17576-53-3] is the primary product (9). In the absence of nitrous fumes the 3-nitro product is not formed. This result is rationalized as involving initial 1,2-addition of the reagent. If 1,2,3,4-tetrahydroquinoline [635-46-1] is the starting material, mixed acid attacks the aromatic ring and subsequent dehydrogenation produces 7-nitroquinoline [613-51-4] (10). Excellent yields of 3- or 7-nitroquinoline can be obtained selectively under mild conditions. Tetranitratotitanium(IV) at ambient temperature produces the 3-nitro isomer while tetranitratozirconium(IV) gives 90% of the 7-nitro product (11).

In many instances, beginning a synthesis with quinoline *N*-oxide [1613-37-2] facilitates the preparation of difficult compounds. Quinoline is converted to the *N*-oxide using hydrogen peroxide in acetic acid, and later reduced to the substituted quinoline. Warm mixed acid gives 4-nitroquinoline 1-oxide [56-57-5] in overall 65% yield (12). Depending on the reducing agent employed, either 4-nitroquinoline [3741-15-9] or 4-aminoquinoline [578-68-7] may be obtained.

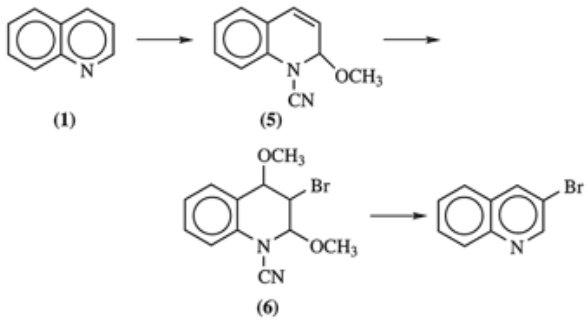
4.1.2. Sulfonation

The main sulfonation product of quinoline at 220°C is 8-quinolinesulfonic acid [85-48-3]; at 300°C. It rearranges to 6-quinolinesulfonic acid [65433-95-6] (13). Optimum conditions for sulfonation, 2 h at 140°C and a 1:4 quinoline/40% (wt) oleum ratio, produces 80% yield. The yield drops to 64% at 130°C with a 1:3 reactant ratio (14). Somewhat higher, but variable, yields of 8-quinolinesulfonic acid hydrochloride [85-48-3] have been reported with chlorosulfonic acid (15).

4.1.3. 1,2-Addition

Unlike pyridine, quinoline undergoes facile addition to the nitrogen-containing ring. Allylmagnesium chloride reacts with quinoline in deoxygenated tetrahydrofuran (THF) to produce 80% 2-allyl-1,2-dihydroquinoline [55570-23-5] (16). Depending on experimental conditions, either 2-propylquinoline [1613-32-7] or 2-propenylquinoline [57078-89-4] may be obtained. Similar results are observed with vinyl Grignard reagents (17) and with alkyllithium reagents (18). Phosphorylated 1,2-addition products have been obtained by acylating the ring nitrogen and treating the intermediate with trimethyl phosphite and sodium iodide (19).

Treatment of quinoline with cyanogen bromide, the von Braun reaction (20), in methanol with sodium bicarbonate produces a high yield of 1-cyano-2-methoxy-1,2-dihydroquinoline (**5**) [880-95-5] (21). Compound **5** is quantitatively converted to 3-bromoquinoline [5332-24-1], through the intermediate **6** [66438-70-8]. These conversions are accomplished by sequential treatment with bromine in methanol, sodium carbonate, or concentrated hydrochloric acid in methanol (eq. 3). Similar conditions provide high yields of 3-bromomethylquinolines.



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4.1.4. Amination

2-Aminoquinoline [580-22-3] is obtained from quinoline in 80% yield by treatment with barium amide in liquid ammonia (22). This product, as well as 3-aminoquinoline [580-17-6] and 4-aminoquinoline [578-68-7], may be obtained through nucleophilic substitution of the corresponding chloroquinolines with ammonia.

4.1.5. Halogenation

One review provides detailed discussion of direct and indirect methods for both mono- and polyhalogenation (23). As with nitration, halogenation under acidic conditions favors reaction in the benzenoid ring, whereas reaction at the 3-position takes place in the neutral molecule. Radical reactions in the pyridine ring can be important under more vigorous conditions.

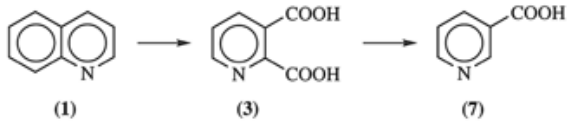
A quinoline-bromine adduct in hot carbon tetrachloride containing pyridine gives a 90% yield of 3-bromoquinoline (24); 3-chloroquinoline [612-59-9] is prepared by an analogous route, but in poorer yield. A quinoline-aluminum chloride complex heated with bromine gives a 78% yield of 5-bromoquinoline [165-18-3] (25). Equal quantities of 5- and 8-bromoquinoline [16567-18-3] are formed when quinoline is treated with 1 equiv of bromine in concentrated sulfuric acid containing silver sulfate (26).

Quinolinium chloride in nitrobenzene reacts with excess bromine to give an 81% yield of 3-bromoquinoline (27). It seems likely that the 1,2-dibromo complex is actually being brominated.

Direct iodination or fluorination leads to ill-defined products and fragmentation, respectively. Sandmeyer chemistry and nucleophilic substitution of chloroquinolines have proved useful alternative routes.

4.1.6. Oxidation

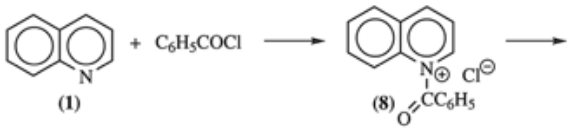
The synthesis of quinolinic acid and its subsequent decarboxylation to nicotinic acid [59-67-6] (**7** in eq. 4) has been accomplished directly in 79% yield using a nitric–sulfuric acid mixture > 220°C (28). A wide variety of oxidants have been used in the preparation of quinoline *N*-oxide. This substrate has proved to be useful in the preparation of 2-chloroquinoline [612-62-4] and 4-chloroquinoline [611-35-8] using sulfuryl chloride (29). The oxidized nitrogen is readily reduced with dimethyl sulfoxide (DMSO) (30).



(1) (3) (7) (4)

4.1.7. Quaternary Salts

The ring nitrogen of quinoline reacts with a wide variety of alkylating and acylating agents to produce useful intermediates like *N*-benzoylquinolinium chloride [81045-42-3] **8**. The quinoline 1,2-adducts, eg, *N*-benzoyl-2-cyano-1,2-dihydroquinoline [13721-17-0] **9**, or Reissert compounds (31), formed with potassium cyanide can produce 2-carboxyquinoline [93-10-7] **10** or 2-cyanoquinoline [1436-43-7] **11** (eqs. 5 and 6).



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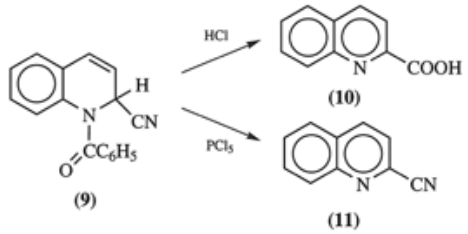
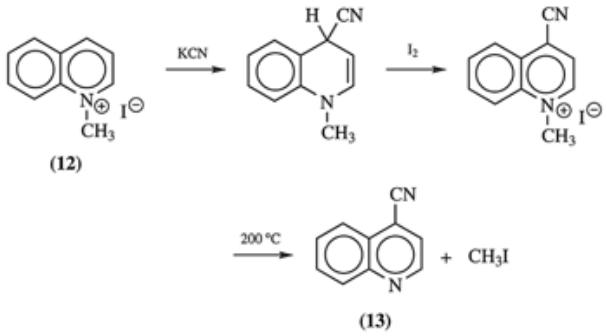


(6)

Excellent yields of the former product are also obtained with quinoline *N*-oxide. Improved yields of Reissert compounds are found under phase-transfer conditions (32). The regiochemistry of the method changes dramatically with *N*-alkylquinolinium salts, eg, *N*-methylquinolinium iodide [3947-76-0] **12**, which forms 4-cyanoquinoline [2973-27-5] **13** (eq. 7) (33), through the intermediary in this example of *N*-methyl-4-cyano-1,4-dihydroquinoline [828-69-3] and *N*-methyl-4-cyanoquinolinium iodide [64275-22-5] (eq. 7).



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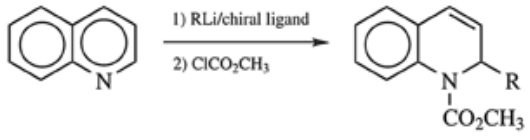
4.1.8. Alkylation and Arylation

The direct introduction of carbon–carbon bonds in quinoline rings takes place in low yield and with little selectivity. One interesting report involves carboxylic acids with ammonium persulfate and silver nitrate (34). More recently a variety of metals have been shown to be effective catalysts. Excellent yields of substituted dihydroquinolines have been obtained with active methylene compounds in the presence of lithium chloride (35). Quinolines activated by acyl chlorides react with ethynyltrimethylsilane in the presence of iridium complexes to produce good yields of 2-substituted 1,2-dihydroquinolines (36). A rather similar report using indium and phenyl chloroformate gives excellent results with allyl bromides (37). High regioselectivity along with promising enantioselectivity for 2-alkyl-1,2-dihydroquinoline has been obtained using alkyl lithium in the presence of (−)sparteine (eq. 8) (38).



(8)

4.1.9. Reduction

Quinoline may be reduced rather selectively, depending on the reaction conditions. Raney nickel at 70–100°C and 6–7 MPa (60–70 atm) results in a 70% yield of 1,2,3,4-tetrahydroquinoline [635-46-1] (39). Temperatures of

210–270°C produce only a slightly lower yield of decahydroquinoline [2051-28-7]. Catalytic reduction with platinum oxide in strongly acidic solution at ambient temperature and moderate pressure also gives a 70% yield of 5,6,7,8-tetrahydroquinoline [10500-57-9] (40). Further reduction of this material with sodium–ethanol produces 90% of *trans*-decahydroquinoline [767-92-0] (41). Reductions of the quinoline heterocyclic ring accompanied by alkylation have been reported (42). Yields vary widely, sodium borohydride-acetic acid gives 17% of 1,2,3,4-tetrahydro-1-(1,1,1-trifluoroethyl) quinoline [57928-03-7] and 79% of 1,2,3,4-tetrahydro-1-isopropylquinoline [21863-25-2]. This latter compound is obtained in the presence of acetone; the use of cyanoborohydride reduces the pyridine ring without alkylation.

4.2. Manufacture from Coal Tar

Commercially, quinoline is isolated from coal tar distillates (43). Tar acids are removed by caustic extraction, and the oil is distilled to produce the methylnaphthalene fraction (230–280°C). Washing with dilute sulfuric acid produces sulfate salts, from which the tar bases are liberated by treatment with caustic followed by distillation. Commercial quinoline is at least 90% pure with a distillation range of 2°C from 235 to 238°C, and a specific gravity of 1.095 at 15.5°C. Chromatographic composition of this product is typically 92% quinoline and 5% isoquinoline by weight. Studies of the composition of crude tar bases in the distillation range 230–265°C show the presence of at least trace amounts of all monomethylquinolines, 2,8-dimethylquinoline [1463-17-8], and some homologues of isoquinoline (44).

Many forms of chromatography have been used to separate mixtures of quinoline and isoquinoline homologues. For example, alumina saturated with cobalt chloride, reversed-phase liquid chromatography, and capillary gas chromatography (gc) with deactivated glass columns have all been employed (45,46).

A 90% yield of isoquinoline (>95% pure) was reported by treating a crude fraction with hydrochloric acid followed by addition of an alcholic solution of cupric chloride in a mole ratio of 1:2 $CuCl_2$/isoquinoline (47). A slightly lower yield of 2-methylquinoline [91-63-4] (97.5% pure) was obtained from bituminous coal using 30% aqueous urea to form a clathrate (48).

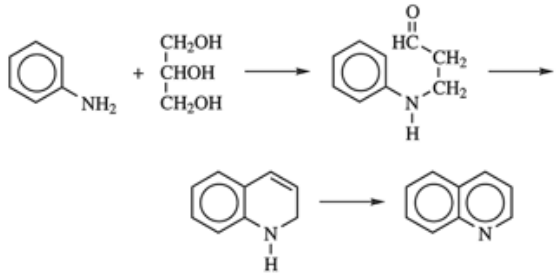
4.2.1. Syntheses of Quinolines

The large number of alkaloids and medicinal compounds that contain the quinoline ring has created a long and active search for synthetic routes. Several classical routes were developed in the nineteenth century and, with many modifications are still used.

4.2.2. Skraup Synthesis

This general method, used for many quinolines, consists of heating a primary aniline with glycerol, concentrated sulfuric acid, and an oxidizing agent (49). Often the nitrobenzene corresponding to the aniline employed is used as the oxidant, and iron(II) sulfate is added to moderate the usually violent exothermic process. It is probable that the glycerol is dehydrated to acrolein that undergoes conjugate addition to the aniline (eq. 9). The formation of quinoline has been reported in the 80–90% range. The use of compounds related to the acroleins, such as crotonaldehyde and methyl vinyl ketone, allow substitutents to be placed in the heterocyclic ring. With ortho- and para-substituted anilines, a single product is usually found; meta derivatives produce mixtures. The nature of the substituent in the starting material is important. The presence of electron-withdrawing groups favors the production of 5-substituted quinolines, whereas with electron-donating groups the 7-substituted product

dominates.



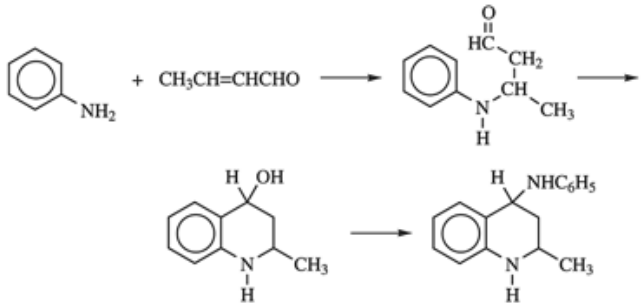
(9)

A review of the use of indium metal in organic synthesis (50) summarizes work on a mild alternative to the Skraup method. By carrying out the reaction on silica gel in the presence of indium chloride it was possible to convert a variety of substituted anilines and alkyl vinyl ketones into quinolines in excellent yield.

Moderate yields of 2-(methylthio)quinolines have been prepared by the cyclocondensation of aromatic amines with 3-bis(methylthio)acrolein. The condition are much milder than the original approach and the thiol group can be removed or converted to other functional groups (51).

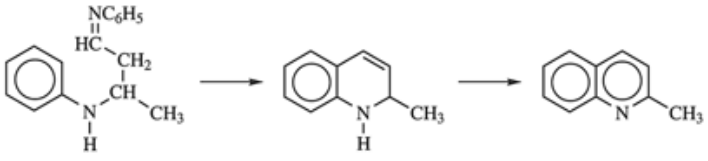
4.2.3. Döbner-von Miller Synthesis

A much less violent synthetic pathway, the Döbner-von Miller, uses hydrochloric acid or zinc chloride as the catalyst (52). As in the modified *Skraup*, α,β-unsaturated aldehydes and ketones make the dehydration of glycerol unnecessary, and allow a wider variety of substitution patterns. No added oxidant is required. With excess aniline the reaction proceeds as follows (eq. 10):



(10)

or as shown in equation 11:



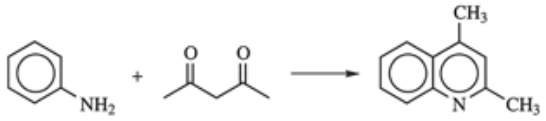
(11)

The mechanism of both syntheses has been studied in detail, and is well summarized (53,54). Interesting questions remain; eg, in neither of these sequences is it certain whether the carbonyl compound or its Schiff base is undergoing Michael addition.

A number of improvements have been made in these syntheses. For example, the use of ethanolic ferric chloride and zinc chloride produces a good yield of 2-isopropylquinoline [17507-24-3] from isovaleraldehyde (55). The purification of 2-methylquinoline is facilitated through precipitation. A crude quinaldine hydrochloride and zinc chloride complex is prepared, and then treated with aqueous base (56).

4.2.4. Combes Synthesis

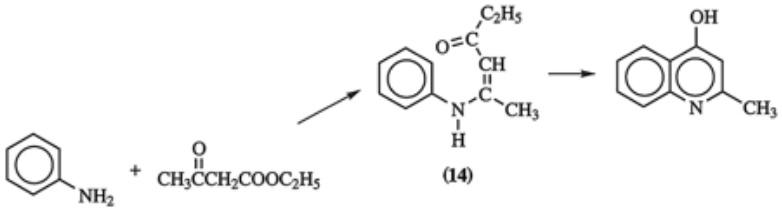
When aniline reacts with a 1,3-diketone under acidic conditions, a 2,4-disubstituted quinoline results, eg, 2,4-dimethylquinoline [1198-37-4] from 2,4-pentadione (eq. 12) (57). A similar result has been been reported using a mixture of an aldehyde and a ketone (58).



(12)

4.2.5. Conrad-Limpach-Knorr Synthesis

When a β-keto ester is the carbonyl component of these pathways, two products are possible, and the regiochemistry can be optimized. Aniline reacts with ethyl acetoacetate below 100°C to form 3-anilinocrotonate (**14**), which is converted to 4-hydroxy-2-methylquinoline [607-67-0] by placing it in a preheated environment at 250°C. If the initial reaction takes place at 160°C, acetoacetanilide (**15**) forms and can be cyclized with concentrated sulfuric acid to 2-hydroxy-4-methyl-quinoline [607-66-9] (59). This example of kinetic versus thermodynamic control has been employed in the synthesis of many quinoline derivatives (eqs. 13 and 14). They are useful as intermediates for the synthesis of chemotherapeutic agents.



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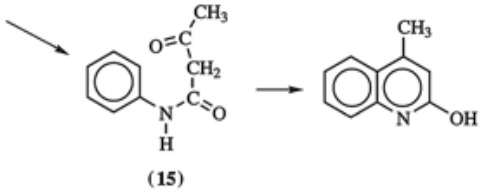
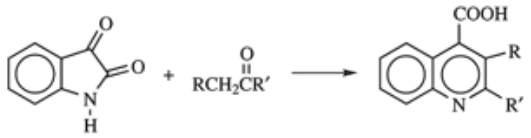


(14)

4.2.6. Pfitzinger Reaction

Quinoline-4-carboxylic acids are easily prepared by the condensation of isatin [91-56-5] (**16**) with carbonyl compounds (60). The products (eq. 15) may be decarboxylated to the corresponding quinolines. The reaction of isatin with cyclic ketones has been reported, eg, the addition of cyclohexanone (eq. 16) gives the tricyclic intermediate (**17**) [38186-54-8], which upon oxidation, produces quinoline-2,3,4-tricarboxylic acid [16880-83-4]

(61).



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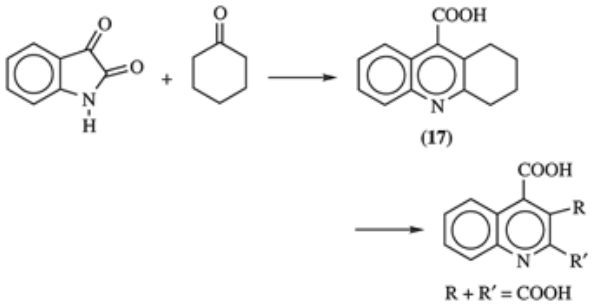
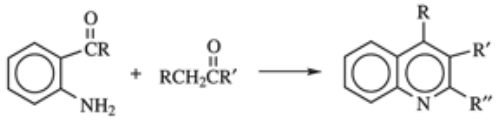


(16)

4.2.7. Frieländer Synthesis

The methods cited thus far all suffer from the mixtures that usually result with meta-substituted anilines. The use of an ortho-disubstituted benzene for the subsequent construction of the quinoline avoids the problem.

In the Frieländer synthesis (62) a starting material like 2-aminobenzaldehyde reacts with an α-methyleneketone in the presence of base (eq. 17). The difficulty of preparing the required anilines is a limitation in this approach, but 2-nitrocarbonyl compounds and the subsequent reduction of the nitro group present a useful modification (63).



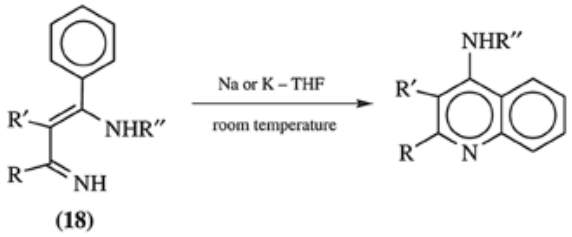
(17)

A detailed study of the mechanism of this reaction suggests possible future modifications (64). Two central points involve the balance between thermodynamic and kinetic control and product variation under acidic and basic conditions. Another major contribution to quinoline synthesis is the report of the use of ionic liquids and iron chloride hexahydrate as a catalyst. Quite satisfactory yields were obtained under environmentally friendly conditions (65).

4.2.8. New Synthetic Approaches

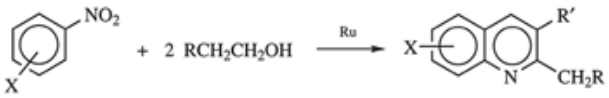
There have been a number of efforts to prepare quinolines by routes quite different from the traditional methods. In one, the cyclization of 3-amino-3-phenyl-2-alkenimines (**18**) using alkali metals leads to modest yields of various 4-arylaminoquinolines (eq. 18) (66). Because this structure is found in many natural products

and few syntheses exist, the method should be studied further.



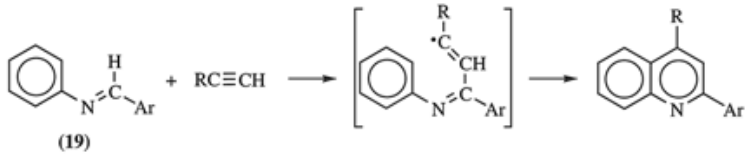
(18)

Studies of the synthesis of quinolines using transition-metal catalysts and non-acidic conditions (67) have determined that ruthenium(III) chloride is the most effective of a wide range of catalysts. The reaction between nitrobenzene and 1-propanol or 1-butanol gives 65 and 70% yields of 2-ethyl-3-methylquinoline [27356-52-1] and 3-ethyl-2-propylquinoline [3290-24-2], respectively, (eq. 19).



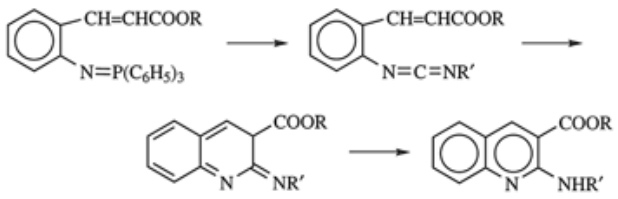
(19)

The reaction of *N*-benzylideneaniline [538-51-2] (**19**) with alkynes leads to quinolines substituted in the hetrocyclic ring (eq. 19) (68). Except for benzylidenes bearing nitro substituents, the reaction occurs in good yield and under mild conditions.



(20)

The presence of an intermediate radical merits further study, especially in the light of an excellent review of such chemistry showing that few quinolines have been examined (69). The availability of pathways to generate biradicals and their importance in biochemical situations led to a study of their use in quinoline synthesis (70). Modest yields of only two examples are presented, but this pathway does present an alternative to be examined. An intramolecular Diels-Alder cyclization produces excellent yields of 2-aminoquinoline-3-carboxylate esters (71). Equally fine yields of the required carbodiimides were reported, making this an attractive route to an unusual substitution type (eq. 21).



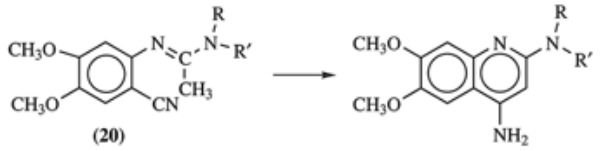
(21)

Two additional examples of quinoline syntheses involving a Diels-Alder reaction provide very high selectivity under mild conditions. In the presence trifluoromethanesulfonic acid aldimines react with silyl enol

ethers to give excellent yields of cycloaddition intermediates that may be oxidized without purification to the corresponding quinoline (72).

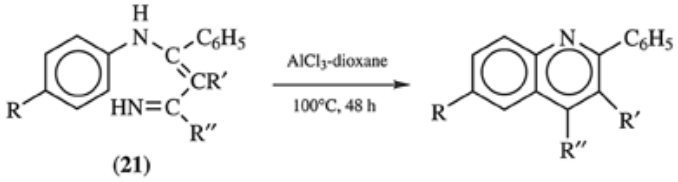
In a similar reaction, an aluminum chloride–triethyamine complex induces aldimines to react with isoeugenol producing tetrahydroquinolines (73). The regio- and stereochemistry are discussed.

Good yields of 2,4-diaminoquinolines are obtained through either Lewis acid- or base-induced cyclization of 2-amidinobenzonitriles (**20**) (74). The method avoids both the harsh conditions and lack of regiospecificity characteristic of earlier preparations (eq. 22).



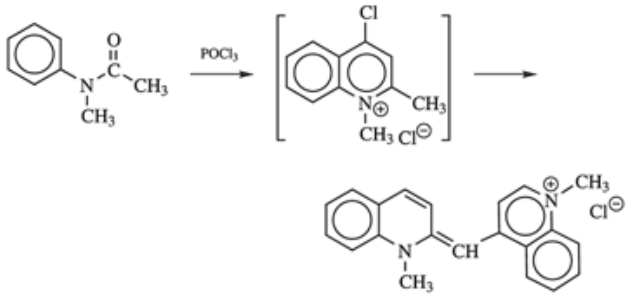
(**20**) (22)

The Lewis Acid-catalyzed cyclization of 3-amino-2-alkenimines (**21**) leads to a wide variety of alkyl- and aryl- substituted quinolines (75). The high regiospecificity and the excellent yields obtained make this process promising (eq. 23).



(**21**) (23)

The importance of quinolinium salts to dye chemistry accounts for the long, productive history of their synthesis. The reaction of *N*-methylformanilide with ketones, aldehydes, ketone enamines, or enol acetates in phosphoryl chloride leads to high yields of *N*-methylquinolinium salts (eq. 24) (76).



(24)

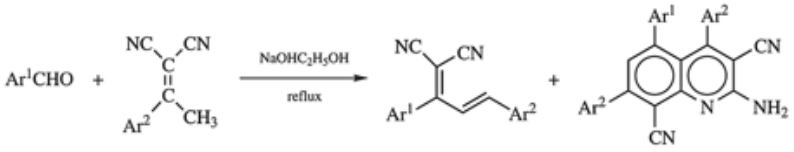
A report of a ring-closure reaction leading to quinolines opens interesting possible approaches to the synthesis of highly substituted compounds (77). The condensation of acylaldehydes with arylethylidenemalononitriles can produce quinolines in addition to the normal dienes. While the yields were modest in the two cases examined, the method is attractive for its mild conditions and extensive range of substituted products possible

Table 2. Commercially Available Quinolines and Isoquinolines

	Price (2005),$		
Compound	Lancaster[a]	Aldrich[b]	ACROS[c]
quinoline	191.30/2.5 kg	101.00/500 g	92.60/500 g
2-methylquinoline	37.70/100 g	218.50/500 g	118.30/250 mL
3-methylquinoline	40.30/5 g	57.50/5 g	59.80/5 g
4-methylquinoline	142.50/50 g	186.00/100 g	176.90/100 g
2-chloroquinoline	195.80/25 g	235.50/25 g	95.60/5 g
2-hydroxyquinoline	69.00/5 g	96.10/5 g	273.80/25 g
4-hydroxyquinoline	166.20/10 g	180.00/10 g	171.60/10 g
2-quinoline-carboxylic acid	78.00/10 g	90.60/10 g	86.70/10 g
isoquinoline	136.00/500 g	171.00/500 g	162.80/500 g
1-isoquinoline-carboxylic acid	49.80/5 g	196.00/25 g	42.90/5 g

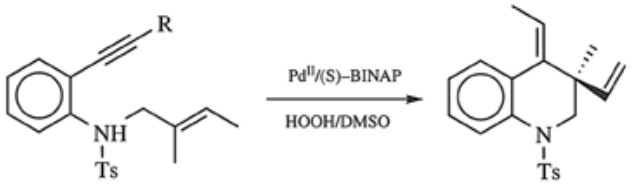
[a]Ref. 79.
[b]Ref. 80.
[c]Ref. 81.

(eq. 25).



(25)

The synthesis of reduced quinolines through the cyclization of a 1,7-enyne system (**22**) is reported to give excellent enantioselectivity (eq. 26) (78), where BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.



(26)

4.3. Economic Aspects

There is little evidence of large scale demand for either quinoline or isoquinoline. The U.S. Tariff Commission reports no longer show separate production or sales data for any quinoline derivative. A number of these compounds are available as fine chemicals; representative examples are found in Table 2. The principal supplier of quinoline and quinoline still residue is Koppers Chemical.

4.4. Toxicology

Quinoline is a poison when it enters the body by any of the normal routes, ie, ingestion, or subcutaneous or intraperitoneal injection. Even contact with the skin produces a moderate toxic reaction, and can result in severe irritation. There is evidence that quinoline is mutagenic, and long exposure can produce lung problems. Quinoline vapors cause irritation of the nose, throat, and bronchial tubes; they also cause headaches, nosebleed, and difficult breathing. Higher exposure may cause a possibly fatal buildup of fluids in the lungs. Toxicity data are typically LD_{50} (rat) 330 mg/kg, and dermal LD_{50} (rat) 540 mg/kg.

Quinoline derivatives are also dangerous; eg, 8-quinolinol [148-24-3] is especially toxic intraperitoneally; LD_{50} (mouse) 48 mg/kg. This compound is known to cause neoplasma of various parts of the body when ingested, implanted, or administered intravenously (82–85).

4.5. Uses

4.5.1. Antioxidants

The 1,2-dihydroquinolines have been used in a variety of ways as antioxidants. For example, 1,2-dihydro-2,2,4-trimethylquinoline [147-47-7] along with its 6-decyl [81045-48-9] and 6-ethoxy [91-53-2] derivatives have been used as antiozonants and stabilizers (86). A polymer of the parent compound [26780-96-1] is used in resins, copolymers, lubricant oils, and synthetic fibers (87). These same compounds react with aldehydes and the products are useful as food antioxidants (88). A cross-linked polyethylene prepared with peroxides and other monomers in the presence of 1,2-dihydro-2,2,4-trimethyl-6-ethoxyquinoline produces polymers with a chemically bonded antioxidant (89).

4.5.2. Corrosion Inhibitors

Steel-reinforcing wire and rods embedded in concrete containing quinoline or quinoline chromate are less susceptible to corrosion (90). Treating the surface of metals with 8-hydroxyquinoline [148-24-3] makes them resistant to tarnishing and corrosion (91). Ethylene glycol-type antifreeze may contain quinoline, 2-chloro- [612-62-4], 4-amino- [578-68-7], 8-nitro- [607-35-2], or 8-hydroxyquinoline to prevent corrosion (92).

4.5.3. Agricultural Chemicals

A herbicide possessing activity comparable to 2,4-D is found in compounds like quinolyl esters of *N*-substituted dithiocarbamic acids (93). These products result when the salt formed from carbon disulfide and primary or secondary aliphatic amines reacts with 2-vinylquinoline [772-03-2]. When applied properly 7-chloroquinoline [612-61-3] appears to be an environmentally safe weed control with its ability to prevent seed germination (94). The corresponding *N*-oxide [22614-94-4] has been used to destroy broad-leaved weeds. A wide variety of compounds containing the quinoline system are herbicides (95). Derivatives and salts of 8-quinolinecarboxylic acid [86-59-9] as well as quinolyl carbamates are each useful insecticides; the latter do not appear to affect desirable insects or fish when used moderately (96). The copper salt of 8-hydroxyquinoline is an effective fungicide. Very low concentrations of 1-naphthols and hydroxyquinolines repel termites (97). The yield and quality of cotton crops has been improved by coating the seed with quinoline *N*-oxide before sowing (98).

4.5.4. Polymers

Quinoline and its derivatves may be added to or incorporated in polymers to induce ion-exchange properties. For example, phenol–formaldehyde polymers have been treated with quinoline, quinaldine [91-63-4], or lepidine [491-35-0] (99). Resins with variable basic exchange capacities have been prepared by treating Amberlites with 2-methylquinoline (quinaldine) (100). Platinum-group metals form complexes with chelating polymers derived from various 8-mercaptoquinoline [491-33-8] derivatives (101). Hydroxy-substituted

quinolines have been incorporated in phenol–formaldehyde resins (102). Stannic chloride catalyzes the condensation of bis(chloromethyl)benzene with quinoline (103).

Methylquinolines react with chloromethylphenyl groups of cross-linked polymers to form anion-exchange resins (104).

4.5.5. Metallurgy

The extraction and separation of metals and plating baths have involved quinoline and certain derivatives. Aldehydes react with 2- or 4-methylquinoline, and the product improves ductility, brightness, and leveling of nickel deposits in baths containing nickel, chloride, and sulfate (105). Soft-zinc electroplating baths have included 8-hydroxyquinaldine [826-81-3] (106). Copper-plating baths containing quinoline or benzoquinoline have shown promise in the manufacture of printed-circuit boards, and electroforming or rotogravure applications. Desirable qualities include smooth, ductile, and uniformly lustrous deposits as well as high throwing power in aqueous acidic baths (107). A bright tin electroplating bath for steel sheets employs 8-hydroxyquinoline as a brightener (108).

The extraction of metal ions depends on the chelating ability of 8-hydroxyquinoline. Modifications of the structure can improve its properties, eg, higher solubility in organic solvents (109). The extraction of nickel, cobalt, copper, and zinc from acid sulfates has been accomplished using 8-hydroxyquinoline in an immiscible solvent (110). In the presence of oximes, halo-substituted 8-hydroxyquinolines have been used to recover copper and zinc from aqueous solutions (111). Dilute solutions of heavy metals, such as mercury, cadmium, copper, lead, and zinc can be purified using quinoline-8-carboxylic acid adsorbed on various substrates (112).

Polymers containing 8-hydroxyquinoline appear to be selective adsorbents for tungsten in alkaline brines (113). In the presence of tartrate and citrate, quinaldic acid [93-10-7] allows the separation of zinc from gallium and indium (114). Either of these compounds can selectively separate lead and zinc from oxide ores as complexes (115). It is also possible to separate by extraction micro quantities of rhenium(VII), using quinoline in basic solution (116). The presence of large excesses of tungsten(VI), copper(II), vanadium(V), chromium(VI), and molybdenum does not interfere with this process. Cobalt, copper, and nickel have been separated by extraction with 8-sulfamidoquinolines (117).

4.5.6. Catalysts

A small amount of quinoline promotes the formation of rigid foams from diols and unsaturated dicarboxylic acids (118). Acrolein and methacrolein 1,4-addition polymerization is catalyzed by lithium complexes of quinoline (119). Organic bases, including quinoline, promote the dehydrogenation of unbranched alkanes to unbranches alkenes using platinum on sodium mordenite (120). The peracetic acid epoxidation of a wide range of alkenes is catalyzed by 8-hydroxyquinoline (121). Hydroformylation catalysts have been improved using 2-quinolone [59-31-4] (122).

4.5.7. Analytical Reagents

The chelating property of quinolines, eg, 8-hydroxy derivatives, make them useful in metal gravimetric applications; however, few are any longer of practical importance. Amino- and sulfur-substituted quinolines have also been employed in metal analysis (123,124).

4.5.8. Medicine

A wide variety of alkaloids contain the quinoline ring system; this fact accounts, in large measure, for the extensive synthetic research reported (125). In addition to the naturally occurring compounds, a large number of synthetic quinolines have been prepared and studied for use in medicine. Table 3 presents selected examples.

Table 3. Quinoline-Derived Drugs Marketed in the United States[a]

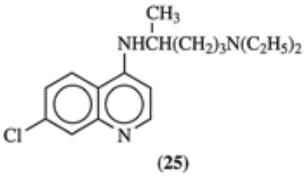
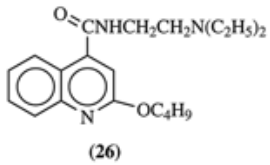
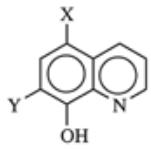
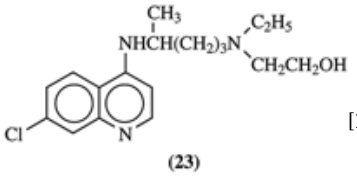
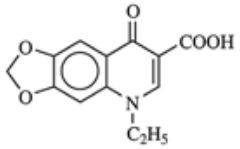
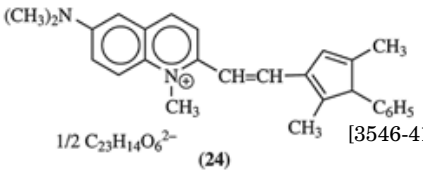
Structure	CAS Number	Application	Brand name (manufacturer)
 (25) 7-chloro-4-[(4-diethylamino-1-methylbutyl) amino] quinoline	[54-05-7]	antirheumatic	Aralen (Winthrop)
 (26) 2-butoxyquinoline-4-carboxylic acid, β-diethylaminoethylamide	[61-12-1]	local anesthetic	Nupercaine (Ciba)
 (27) 5-chloro-7-iodo-8-hydroxyquinoline X = Cl Y = I	[130-26-7]	wound antiseptic	Vioform (Ciba)
5,7-diiodo-8-hydroxyquinoline X = Y = I	[83-73-8]	intestinal antiseptic	Yodoxin (Glenwood)
5,7-dichloro-8-hydroxyquinoline X = Y = Cl	[8067-69-4]	intestinal antiseptic	Quinolor (Squibb)

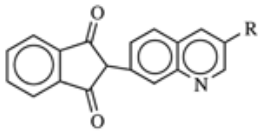
Table 3. ***Continued***

Structure	CAS Number	Application	Brand name (manufacturer)
 (23) 4-(4-[ethyl-(2-hydroxyethyl)amino]-1-methylbutylamino)-7-chloroquinoline	[118-42-3]	antirheumatic, antimalarial	Plaquenil (Winthrop)
 (28) 1-ethyl-6,7-methylenedioxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	[14698-29-4]	antibacterial	Utibid (Warner)
 (24) 2-[2-(2,5-dimethyl-1-phenyl-3-pyrrolyl)vinyl]-6-dimethylamino-1-methylquinolinium pamoate	[3546-41-6]	anthelmintic	Povan (Parke-Davis)

[a]Refs. 126,127,128.

4.5.9. Quinoline Dyes

The reaction of 2-methylquinoline with phthalic anhydride produces a 2:1 mixture of 2-(2-quinolinyl)-1,3-indandione [83-08-9] (**29**, R = H) and 2-(6-methyl-2-quinolinyl)-1,3-indandione [6493-58-9] (**29**, R = CH_3).



(29)

This mixture is known as Quinoline Yellow A [8003-22-3] (CI 47000) and is most widely used with polyester fibers (129). Upon sulfonation, the water-soluble Quinoline Yellow S or Acid Yellow 3 [8004-92-0] (CI 47005) is obtained. This dye is used with wool and its aluminum salt as a pigment. Foron Yellow SE-3GL (CI Disperse Yellow 64) is the 3-hydroxy-4-bromo derivative. Several other quinoline dyes are commercially available and find applications as biological stains and analytical reagents (130).

4.6. Derivatives

Small amounts of alkyl quinolines are present in the tars resulting from the carbonization and liquefaction of coal (131). Good yields of 4-methylquinoline, 4,6-dimethylquinoline [826-77-7], and 4,8-dimethylquinoline [13362-80-6] are obtained from 4-(diethylamino)-2-butanone and the appropriate aniline. This approach is a promising addition to the traditional syntheses discussed earlier (132). Vinylacetylene reacts with mercuric chloride and either aniline or *p*-toluidine to yield 4-methyl- and 4,6-dimethylquinoline, respectively (133).

The greater reactivity of 2- and 4-alkylquinolines allows them to condense with benzaldehyde to produce 2-β-styrylquinoline [4945-26-0] and 4-β-styrylquinoline [13362-63-5]. This chemistry is also useful with the pyridine carboxaldehydes to form adequate yields of the corresponding 2-[2-(2-pyridinyl)vinyl]quinoline [13206-41-2], 2-[2-(2-pyridinyl)vinyl]quinoline [1586-51-2], or 2-[2-(4-pyridinyl)vinyl]quinoline [18633-00-6] (134).

The methyl group attached to quinoline undergoes reactions analogous to those of other arenas. The chlorination of 2-methylquinoline in the presence of acetic acid or phosphorus pentoxide produces 88% of pure 2-(trichloromethyl)quinoline [4032-53-5] (135). Methyl groups in the heterocyclic ring are oxidized to carboxylic acids when their palladium chloride complex is treated with hydrogen peroxide (136).

4.6.1. Hydroquinolines

Pyrans formed by reaction of α,β-unsaturated aldehydes with 1-ethoxycyclohexene and treated with hydroxylamine are converted in good yield to 5,6,7,8-tetrahydroquinolines (137). These compounds can be dehydrogenated to the corresponding quinolines. The parent reduced product has been prepared by heating *O*-allylcyclohexanone oxime (138).

1,2,3,4-Tetrahydroquinoline [635-46-1] shows the properties of a monoalkylaniline, and its chemistry has been reviewed (139). It forms an *N*-nitroso derivative, which rearranges readily to 6-nitro-1,2,3,4-tetrahydroquinoline [14026-45-0]. Mild oxidation with potassium permanganate in acetone forms 3,3′,4,4′-tetrahydro-1,1′-(2*H*,2′*H*)biquinoline [34555-59-4] that can be converted to 1′,2′,3,3′,4,4′-hexahydro-6,6(2*H*′,2′*H*)biquinoline [53899-16-4] by a benzidine-type rearrangement. Indole is formed by the thermolysis of 1,2,3,4-tetrahydroquinoline in a moist atmosphere at above 650°C (140).

4.6.2. Hydroxyquinolines (Quinolinols)

A number of methods have been employed for their preparation. A modified Chichibabin reaction of quinoline in fused KOH–NaOH at 240°C produces 70% of 2-hydroxyquinoline [59-31-4] (141). Alternative names based on the facile keto–enol tautomerism of two of these compounds are 2(1*H*)- and 4(1*H*)-quinolinone; none of the other quinolinols show this property. The treatment of 3-hydroxyquinoline [580-18-7] with aqueous sodium hydroxide at 300°C gives 88% 2-hydroxyquinoline (142). 7-Chloro-4-hydroxyquinoline [86-99-7] can be prepared in 93% yield by ring closure, hydrolysis, and decarboxylation using various acid catalysts (143).

Both 5-hydroxyquinoline [578-67-6] and 8-hydroxyquinoline [148-24-3] have been prepared in good yields by the acid hydrolysis of the appropriate aminoquinoline at temperatures of 180–235°C (144). The latter compound has been prepared in several different ways, including sulfonation-fusion of quinoline. Hydrolysis of 8-chloroquinoline [611-33-6] gives a 93% yield, whereas 80% is obtained in a modified Skraup synthesis with *o*-aminophenol (145,146).

Dihydroxyquinolines are found in nature and may be prepared synthetically. Heating 3,1-benzoxazin-4-ones with strong base or sequential treatment of *N*-acetoacetylanthranilate with base, then acid, produce 2,4-dihydroxyquinoline [70254-43-2] (147,148). An enzymatic preparation of 4,5-dihydroxyquinoline has been reported (149).

Direct halogenation of 8-hydroxyquinoline has been used as a route to 5,7-dihalo derivatives. Compounds of this type reported include 5,7-dichloro-8-hydroxyquinoline [733-76-2] (150), 5,7-dibromo-8-hydroxyquinoline [521-74-4] (151), 5-chloro-8-hydroxyquinoline [130-16-5], and 5-chloro-7-iodo-8-hydroxyquinoline [130-26-7] (152).

4.6.3. Haloquinolines

2-Chloroquinoline [612-62-4] and 4-chloroquinoline [611-35-8] are prepared from the corresponding hydroxyquinoline by reaction with phosphorus oxychloride and phosphorus pentachloride. Reactions of substituted anilines with acrylic acid in the presence of hydroquinone gives the 3-anilinopropionic acid that is treated with iodine and phosphorus oxychloride to give the corresponding 4-chloroquinoline (153). Chloroanilines have been used and several dichloroquinolines obtained, eg, 4,6-dichloroquinoline [4203-18-3], 4,7-dichloroquinoline [86-98-6], and 4,8-dichloroquinoline [21617-12-9] (154).

4.6.4. Aminoquinolines

The reduction of nitroquinolines and the displacement of halo derivatives represent the most common methods for the preparation of aminoquinolines. A 72% yield of 8-aminoquinoline [578-66-5] has been obtained by treating 8-hydroxyquinoline with ammonium sulfite (155). An interesting rearrangement has been reported in which quinazoline 3-oxide reacts with active methylene compounds to make various 3-substituted 2-aminoquinolines (156).

4.6.5. Aldehydes, Ketones, and Acids

As with many aromatic compounds, the oxidation of methyl groups is an attractive synthetic route to both aldehydes and carboxylic acids in the quinolines. The hydrolysis of dibromomethyl groups has also been used for aldehydes and the hydrolysis of nitriles for carboxylic acids. Detailed reviews of the synthesis of these compounds have appeared (5).

4.6.6. Biquinolines

The standard synthetic methods, with bifunctional molecules, eg, aromatic diamines, or using the Ulmann synthesis leads generally to the 2,2′-bisquinoline structure. Heating *N*,*O*-di(4-quinolyl)hydroxylamine causes rearrangement to 3,3′-(4-amino-4′-hydroxyl)biquinoline [64372-81-2] (157).

4.6.7. Benzoquinolines

Because certain alkaloids are characterized by these more elaborate fused-ring systems, their synthesis has been reviewed in detail (158). Heating 4-methoxy-1-naphthylamine with epichlorohydrin produces a modest yield of 3-hydroxy-6-methoxy-1,2,3,4-tetrahydrobenzo[*h*]quinoline [38149-41-9], which can be aromatized, also in small yield, to 6-methoxybenzo[*h*]quinoline [38419-43-1] (159).

4.6.8. Mercaptoquinolines (Quinolinethiols)

Mercaptoquinolines are usually prepared using the diazotization of amines, the reduction of sulfides or sulfonyl chlorides, or displacement of active halogen (160,161,162).

5. Isoquinoline

The early structural evidence, physical properties, and aromaticity of isoquinoline have been discussed at the beginning of this article. Two additional trivial names are encountered occasionally: 2-benzazine and leucoline. The widespread occurrence of this structure in such important alkaloids as those found in cactus, opium and curare has created a long-standing interest in its synthesis and properties (1,5).

5.1. Reactions

In general, isoquinoline undergoes electrophilic substitution reactions at the 5-position and nucleophilic reactions at the 1-position. Nitration with mixed acids produces a 9:1 mixture of 5-nitroisoquinoline [607-32-9] and 8-nitroisoquinoline [7473-12-3]. The ratio changes slightly with temperature (163,164). Sulfonation of isoquinoline gives a mixture with isoquinoline-5-sulfonic acid [27655-40-9] as the principal product.

Amination of isoquinoline with sodamide in neutral solvents gives 1-aminoisoquinoline [1532-84-9]. This product is converted to 1-hydroxyisoquinoline [491-30-5] by diazotization and hydrolysis. Either this compound or 3-methylisoquinoline [1125-80-0] can be obtained in excellent yields by the same modified Chichibabin reaction described for 2-hydroxyquinoline (141).

Direct bromination of isoquinoline hydrochloride in a solvent like nitrobenzene gives an 81% yield of 4-bromoisoquinoline [1532-97-4]. By contrast, bromination of an isoquinoline-aluminum chloride complex with bromine vapor gives a 78% yield of 5-bromoisoquinoline [34784-04-8].

Continued bromination leads to 5,8-dibromoisoquinoline [81045-39-8] and 5,7,8-tribromoisoquinoline [81045-40-1].

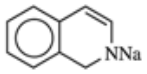
The oxidation of isoquinoline has also been examined using ruthenium tetroxide. In this instance, the surprising observation that phthalic acid is the only significant product (58%) was made; this fact is both important and difficult to explain (165). Isoquinoline is also oxidized to its *N*-oxide by peracids. Isoquinoline *N*-oxide [1532-72-5] has also been obtained from 2-(2,4-dinitrophenyl)isoquinolinium chloride [33107-14-1] by refluxing with hydroxylamine hydrochloride in concentrated hydrochloric acid (166).

The *N*-oxides of isoquinolines have proved to be excellent intermediates for the preparation of many compounds. Trialkylboranes give 1-alkyl derivatives (167). With cyanogen bromide in ethanol ethyl *N*-(1- and 4-isoquinolyl)carbamates are formed (168). A complicated, but potentially important reaction is the formation of 1-acetonylisoquinoline and 1-cyanoisoquinoline [1198-30-7] when isoquinoline *N*-oxide reacts with methacrylonitrile in the presence of hydroquinone (169). Isoquinoline *N*-oxide undergoes direct acylamination with *N*-benzoylanilino-isoquinoline salts to form 1-*N*-benzoylanilinoisoquinoline [53112-20-4] in 55% yield (170). A similar reaction of *N*-sulfinyl-*p*-toluenesulfonamide leads to 1-(tosylamino)isoquinoline [25770-51-8], which is readily hydrolyzed to 1-aminoisoquinoline (171).

Isoquinoline can be reduced quantitatively over platinum in acidic media to a mixture of *cis*-decahydroisoquinoline [2744-08-3] and *trans*-decahydroisoquinoline [2744-09-4] (41).

Hydrogenation with platinum oxide in strong acid, but under mild conditions, selectively reduces the benzene ring and leads to a 90% yield of 5,6,7,8-tetrahydroisoquinoline [36556-06-6] (39,40). Sodium hydride, in dipolar aprotic solvents like hexamethylphosphoric triamide, reduces isoquinoline in quantitative yield to the sodium adduct **30** [81045-34-3] (172). The adduct reacts with acid chlorides or anhydrides to give *N*-acyl derivatives which are converted to 4-substituted 1,2-dihydroisoquinolines. Sodium borohydride and carboxylic acids combine to provide a one-step reduction–alkylation (42). Sodium cyanoborohydride reduces isoquinoline

under similar conditions without *N*-alkylation to give 1,2,3,4-tetrahydroisoquinoline [91-21-4]. Reaction of this compound with cyanamide gives an 87% yield of 2-amidino-1,2,3,4-tetrahydroisoquinoline [1131-64-2] (173).



(30)

Isoquinoline also forms Reissert compounds when treated with benzoyl chloride and alkyl cyanide (31), especially under phase-transfer conditions (32). The *N*-phenylsulfonyl Reissert has been converted to 1-cyanoisoquinoline with sodium borohydride under mild conditions (174). When the *N*-benzoyl-1-alkyl derivative is used, reductive fission occurs and the 1-alkylisoquinoline is obtained.

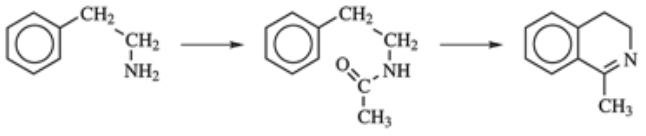
Isoquinoline reacts with aliphatic carboxylic acids photolytically or with a silver catalyst to give excellent yields of alkylation products by decarboxylation (175). This method has been used to prepare 2-benzoylisoquinolines bearing a variety of aromatic substituents in the 1-position (176).

5.2. Synthesis of Isoquinoline and Isoquinoline Derivatives

5.2.1. Bischler-Napieralski Reaction

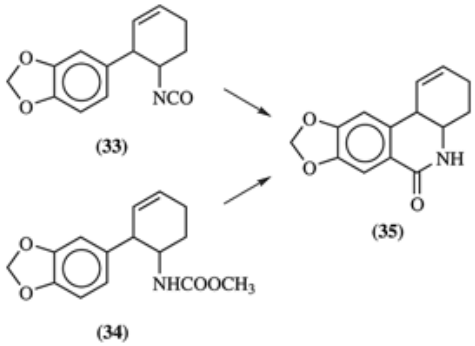
This synthetic method involves the cyclodehydration of *N*-acyl derivatives of β-phenethylamines (**31**) to 3,4-dihydroisoquinolines, such as 1-methyl-3,4-dihydroisoquinoline [2412-58-0] (**32**, eq. 27) (177).

Lewis acids, such as phosphorus pentoxide, polyphosphoric acid, or zinc chloride, are employed using a dry inert solvent. The 3,4-dihydroisoquinoline can either be dehydrogenated to an isoquinoline or reduced to a tetrahydroisoquinoline.



(31) (32) (27)

Several modified forms of this synthesis are available. For example, treatment of either isocyanate (**33**) or urethane (**34**) derivatives with phosphoryl chloride followed by stannic chloride has been reported to give the substituted isoquinoline [80388-01-8] (**35**) (eq. 28) (178).

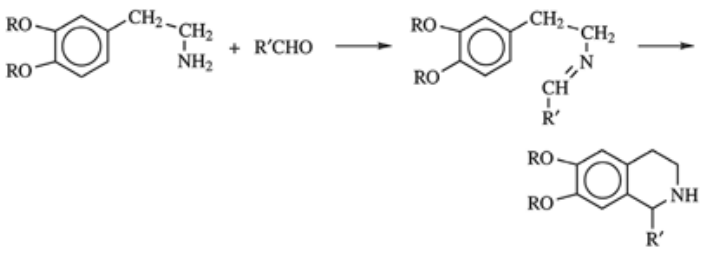


(33) (34) (35) (28)

The Pictet-Gams method involving the cyclization of β-hydroxy- or β-methoxy-β-phenethylamides, and produces the isoquinoline derivative rather than the reduced form. A further extension of the method is based on a methoxyethylamine.

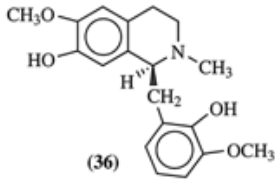
5.2.2. Pictet-Spengler Synthesis

An acidic catalyst results in the condensation of β-phenethylamines with carbonyl compounds to give 1,2,3,4-tetrahydroisoquinolines (eq. 29) (179).



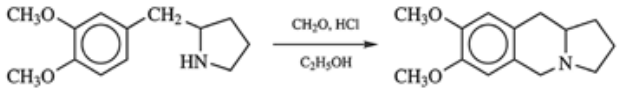
(29)

An enzyme-catalyzed application has been used to prepare the enantiomers of hydroxy-substituted tetrahydroisoquinolines (180). The synthesis of (*S*)-reticuline [485-19-8] (**36**) has been reported using similar methodology (181). The substitution of formic acid and paraformaldehyde in this method leads to lower reaction temperatures, freedom from hydrolysis of protective groups and improved yields (182).



(36)

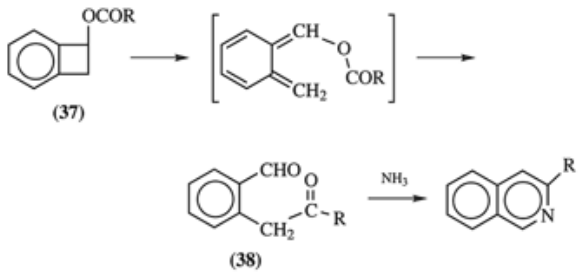
Another limitation in the original method lies in the preparation of 3-alkyl derivatives. This shortcoming has been addressed by two quite different approaches. An investigation of β-arylalkylamines showed that they undergo smooth Pictet-Spengler ring closure (eq. 30) (183).



(30)

Similarly successful studies have been conducted on the flash vacuum pyrolysis of acyloxybenzocyclobutenes (**37**) to 2-formylbenzyl ketones (**38**) (eq. 31). The latter react with ammonium acetate to form a variety of

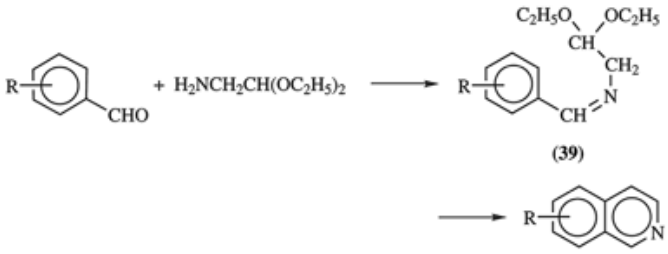
3-alkylisoquinolines in acceptable to excellent yields (184).



(31)

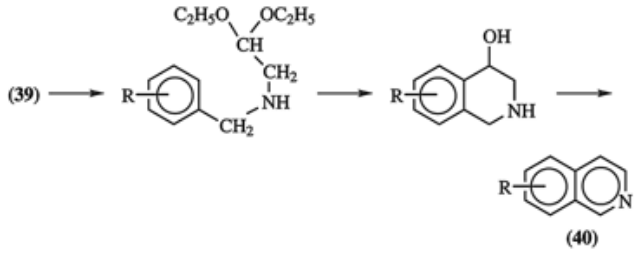
5.2.3. Pomeranz-Fritsch Synthesis

Isoquinolines are available from the cyclization of benzalaminoacetals under acidic conditions (185). The cyclization is preceded by the formation of a Schiff base (**39**) (eq. 32). Although the yields are modest, polyphosphoric acid produces product in all cases, and is especially useful for 8-substituted isoquinolines (186).



(32)

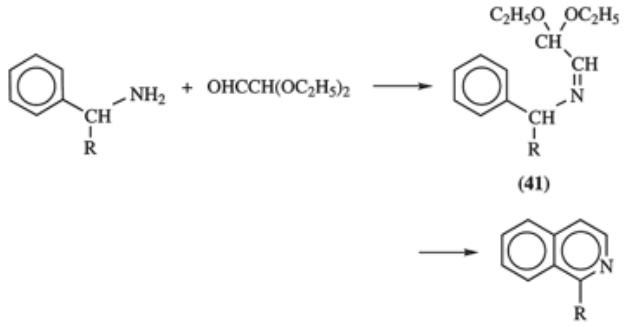
An important modification improves the yields by first reducing the Schiff base to an amine, which is then cyclized to a 4-hydroxy intermediate (eq. 33) (187). This compound is converted to the 1,2,3,4-tetrahydroisoquinoline (**40**). The entire process takes place under mild conditions and in good yield.



(33)

A variation involves the reaction of benzylamine with glyoxal hemiacetal (eq. 34) (188). Cyclization of the intermediate **41** with sulfuric acid produces the same isoquinoline as that obtained from the Schiff base derived from an aromatic aldehyde and aminoacetal. This method has proved especially useful for the synthesis

of 1-substituted isoquinolines.



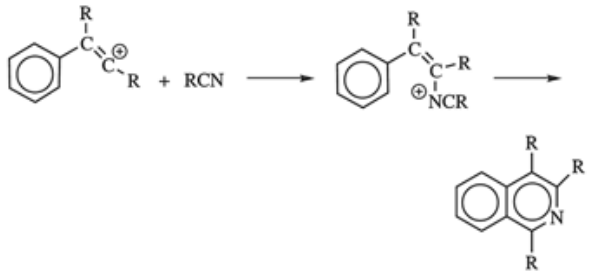
(41)

(34)

5.2.4. Miscellaneous Synthetic Reactions

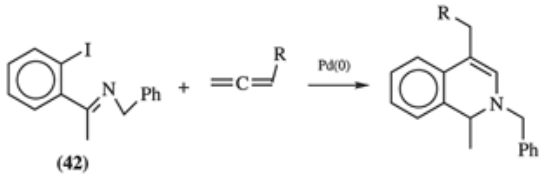
A number of *o*-disubstituted benzenes have been used to prepare isoquinolines. For example, the Radziszewski method and subsequent dehydration converts *o*-cyanomethylbenzoic acid to homophthalimide [88-97-1] in 90% yield (189). Reaction of the same acid with sodium cyanide at 215°C produces 3-(*o*-carboxylbenzoyl)-4-cyano-1(2*H*)-isoquinoline [81045-38-7] (190). Homophthalimide reacts with acetic anhydride to produce 4-acetylisochroman-1,3-dione, which is converted to 3-methyl-1-(2*H*)-isoquinoline [59816-89-6] or 2,3-dimethyl-1-(2*H*)-isoquinolone [7114-78-5] in good yield (191). These products are also obtained from the cyclization of *trans*-β-styrylisocyanates formed by thermal Curtius reactions of *trans*-cinnamoyl azides (192).

The Ritter reaction with unsaturated carbenium ions under either silver-assisted solvolysis or photolytic conditions leads to excellent yields of isoquinolines (eq. 35) (193). The ease of preparation of the required vinyl bromides makes an attractive route to highly substituted isoquinolines.



(35)

Using palladium metal as a catalyst it is possible to form isoquinolines from imines of iodinated benzaldehydes (**42**) and allenes (eq. 36) (194).



(42)

(36)

A somewhat similar intramolecular cyclization reaction involving *o*-cyano- or *o*-isocyano-β,β-difluorostyrenes can form isoquinolines or quinolines, respectively (195). This method also helps to solve the difficulty cited earlier concerning the preparation of fluoro derivatives.

Isoquinoline itself reacts smoothly with acetylenedicarboxylates in the presence of isocynates to provide an attractive entry to bridgehead nitrogen heterocycles (196).

5.2.5. Alkyl Isoquinolines

Coal tar contains small amounts of 1-methylisoquinoline [1721-93-3], 3-methylisoquinoline [1125-80-0], and 1,3-dimethylisoquinoline [1721-94-4]. The 1- and 3-methyl groups are more reactive than others in the isoquinoline nucleus and are readily oxidized with selenium dioxide to form the corresponding isoquinoline aldehydes (197). These compounds can also be obtained by the hydrolysis of the dihalomethyl group. The 1- and 3-methylisoquinolines condense with benzaldehyde in the presence of zinc chloride or acetic anhydride to produce 1- and 3-styrylisoquinolines. Radicals formed by decarboxylation of carboxylic acids react to produce 1-alkylisoquinolines.

The hydroisoquinolines are more susceptible to ring cleavage than the isoquinolines. Ring cleavage occurs with nitrogen elimination when 3,4-dihydroisoquinolines are heated with alkali and dimethyl sulfate. The resulting *o*-acetylstyrenes form in moderate to excellent yield (199). If there is no 1-substituent, the product is an aldehyde. Ring opening without loss of nitrogen occurs if the 3,4-dihydroisoquinoline [3230-65-7] is heated with formaldehyde, formic acid, and diethylamine or sodium formate to form the *o*-substituted *N,N*-dimethylphenethylamine (200).

5.2.6. Hydroxyisoquinolines

In addition to the ring-closure reactions previously cited, a variety of reduction methods are available for the synthesis of these important ring systems. Lithium aluminum hydride or sodium in liquid ammonia convert isoquinoline to 1,2-dihydroisoquinoline (198). Further reduction of this intermediate or reduction of isoquinoline with tin and hydrochloric acid, sodium and alcohol, or catalytically using platinum produces 1,2,3,4-tetrahydroisoquinoline [91-21-4]. Other reduction reactions have already been described.

Hydroxy groups in the 5-, 6-, 7-, and 8-position show phenolic reactions; eg, the Bücherer reaction leads to the corresponding aminoisoquinolines. Other typical reactions include: the Mannich condensation, azo-coupling reactions, and nitrosation. Both *O*-methyl and *N*-methyl derivatives are obtained from the methylation of 1-hydroxyisoquinoline [491-30-5] indicating both tautomeric forms are present. Distillation of various hydroxy compounds, eg, 1- and 4-hydroxyisoquinoline [3336-49-0], with zinc dust removes the oxygen. Treatment of 1-isoquinolinol with phosphorus tribromide yields 1-bromoisoquinoline [1532-71-4] (201).

5.2.7. Haloisoquinolines

The Sandmeyer reaction is commonly used to prepare chloroisoquinolines from the amino compound. The corresponding hydroxy compounds are also used by treatment with chlorides of phosphorus. The addition of bromine to a slurry of isoquinoline hydrochloride in nitrobenzene gives a 70–80% yield of 4-bromoisoquinoline [1532-97-4]. Heating 1-chloroisoquinoline [19493-44-8] with sodium iodide and hydriodic acid gives 1-iodoisoquinoline [19658-77-6] (202).

The halogen substituents of isoquinoline undergo typical reactions of similar heterocycles. Heating 1-iodoisoquinoline with sodium nitrite at 100°C gives 1-nitroisoquinoline [19658-76-5] (202). Both 1- and 3-bromoisoquinoline react with potassium amide in liquid ammonia to give excellent yields of the corresponding amines (203). The reaction of 5-bromoisoquinoline [34784-04-8] with potassium amide in liquid ammonia at −33°C gives 47% 6-aminoisoquinoline [23687-26-5] and 21% 5-aminoisoquinoline [1125-60-6] (204). This latter amine can be converted to 5-bromoisoquinoline by the Sandmeyer reaction.

5.3. Toxicology

Isoquinoline is a poison when ingested or injected intraperitoneally. Even in cases of skin contact it is moderately toxic. As in the case of quinoline, its vapors are irritating to the eyes, nose, and throat. Exposure causes

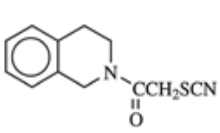
headaches, dizziness, and nausea. Rapid adsorption through the skin makes it a dangerous chemical. Its toxicity is oral LD_{50} (rat), 360 mg/kg, and dermal LD_{50} (rabbit), 590 mg/kg (82,83,84,85).

5.4. Uses

Isoquinoline and isoquinoline derivatives are useful as corrosion inhibitors, antioxidants, pesticides, and catalysts. They are used in plating baths and miscellaneous applications, such as in photography, polymers, and azo dyes. Numerous derivatives have been prepared and evaluated as pharmaceuticals. Isoquinoline is a main component in quinoline still residue bases, which are sold as corrosion inhibitors and acid inhibitors for pickling iron and steel.

4-Aminoisoquinoline is a component of an ethylene glycol-based corrosion inhibiting antifreeze agent (205). Various compounds related to *s*-triazolo[5,1*a*]isoquinoline [34784-04-8] are antioxidants, corrosion inhibitors, and acid acceptors (206). Other effective corrosion inhibitors for steel are 1,2-dihydroisoquinoline-1-phosphonate [39233-31-3] and its *N*-methyl analog [39233-30-2] (207). Compounds related to the catacols, eg, 6,7-dihydroxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid [62356-02-9] have found use as antioxidants for fats and oils (208,209).

A number of isoquinoline derivatives have fungicidal properties, eg, 1,2,3,4-tetrahydroisoquinolines bearing acyl nitrogen substituents like **43** [41910-26-3] (210). Substituted isoquinolines, eg, **44**, have proven to be effective in controlling undesired vegetation, insects, acarina, and fungi (211).



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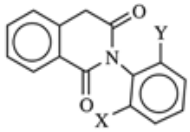


(44)

Isoquinolines are used in catalytic (112), photographic (213), and dye applications (214). A great many alkaloids and synthetic medicinal compounds are isoquinoline derivatives. The principal drugs containing this structure and marketed in the United States are listed in Table 4.

Table 4. Isoquinoline-Derived Drugs Marketed in the United States[a]

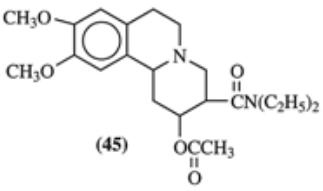
Structure	CAS Number	Application	Brand name (manufacturer)
 (45) 2-acetoxy-9,10-dimethoxy-1,3,4,6,7,11-*b*-hexahydro-2*H*-benzo[*a*]quinolizin-3-carboxylic acid diethylamide	[63-12-7]	antiemetic, tranquilizer	Quantrol (Roerig)

Table 4. ***Continued***

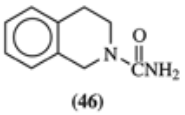
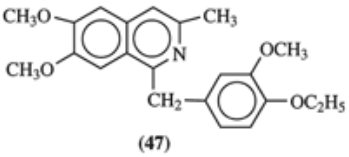
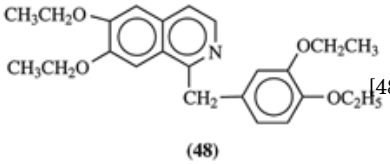
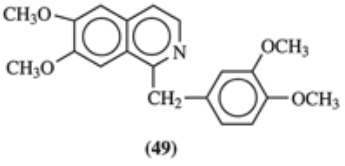
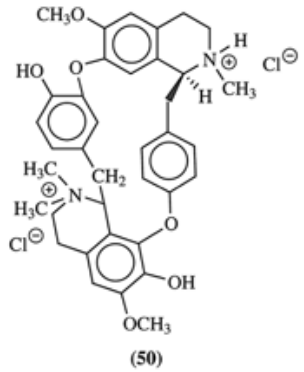
Structure	CAS Number	Application	Brand name (manufacturer)
 (46) 1,2,3,4-tetrahydroisoquinoline-2-carboxamidine	[1131-64-2]	muscle relaxant	Declinax (Hoffmann-LaRoche)
 (47) 1-(4-ethoxy-3-methoxybenzyl)-6,7-dimethoxy-3-methylisoquinoline	[147-27-3]	spasmolytic	Paveril (Lilly)
 (48) 1-(3,4-diethoxybenzyl)-6,7-diethoxyisoquinoline	[486-47-5]	spasmolytic	Ethoquin (Ascher)
 (49) papaverine	[58-74-2]	spasmolytic, vasodilator	Papaverine HCl (Lilly)

Table 4. ***Continued***

Structure	CAS Number	Application	Brand name (manufacturer)
 (50) *d*-tubocurarine chloride	[57-94-3]	muscle relaxant	Tubocurarine (Abbott, Lilly)

[a]Refs. 125,126,127.

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