Some Aspects of Reduced Quinoline Chemistry

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Received July 15, 1997
Revised April 30, 1998

Different synthetic paths that produce the reduced quinoline cycle are discussed: among them intramolecular cyclization, intra- and inter [4+2] cycloaddition reactions and other methods. Some chemical properties of tetrahydroquinolines are also analyzed.

J. Heterocyclic Chem., **35**, 761 (1998).

1. Introduction

By looking at the number of different cases in which quinoline and its hydrogenated derivatives play a key role, it is clear that they belong to a class of valuable compounds. They can be found as components in medicines, pesticides, chemical preservatives and as intermediates in synthetic processes.

Hydrogenated quinoline derivatives are of special interest as medicines, covering a wide spectrum of biological activity. The quinoline and tetrahydroquinoline rings are the basic unit of a series of natural alkaloids. Some compounds that show this structural feature are hypertensive and have been applied to treat encephalic nerve irregularities [1,2]. It was discovered that derivatives of 1,2,3,4-tetrahydroquinoline exhibit analgesic [3], anticancer [4,5], antiamebic [6], and contraceptive activities [7]. Some reports included their use as anticoaguiants [8], antiarrhythmics [9], immunosuppressant inhibitors [10] or as virucides [11].

Besides all the useful applications previously described, numerous studies were made during the last few years to evaluate the potential of several tetrahydroquinoline derivatives as pesticides. As a result, substances with herbicide, fungicide, insecticide or growth regulation capabilities were discovered [12-16].

2,2,4-Trimethyl-6-ethoxy(ethyl)-1,2-dihydroquinolines serve as antioxidants that stabilize lipidic veterinary drugs [17,18]. Other similar compounds are excellent polymerization inhibitors for olefins, oils and rubbers [19-21]. The (tetrahydro)quinoline fragment is also present in the structure of some dyes [22-24].

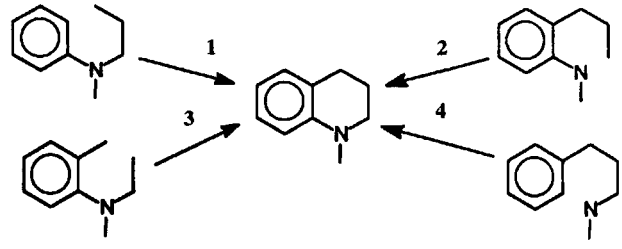
2. Synthesis of Partially Hydrogenated Quinoline Derivatives

The classic Skraup, Döebner-Miller, Combes, Friedlender and Pfitzeinger syntheses are the methods usually followed to construct the quinoline cycle. In some reactions, the substituted dihydroquinolines are intermediate products, generally not isolated. Given the practical importance of hydrogenated quinoline derivatives, which can be compared to that of quinoline bases, Jones reviewed some of the special synthetic methods to obtain di-, tetra-, octa- and decahydroquinolines [25,26].

Because of their large diversity, it is not an easy task to devise a detailed classification of the available synthetic methods related to these compounds. In this review, we intend to describe only the inter- and intramolecular cyclization reactions that produce hydrogenated quinolines and their oxo derivatives. The methods related to the reduction of the quinoline ring are not discussed here.

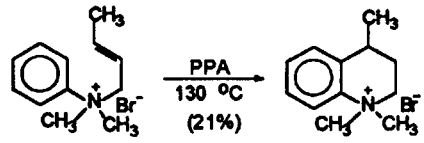
2.1 Intramolecular Cyclization

The most general method to obtain tetrahydroquinolines involves an intramolecular cyclization starting either from a substituted aniline derivative (routes **1**, **2** and **3**) or from a monosubstituted benzene (route **4**).



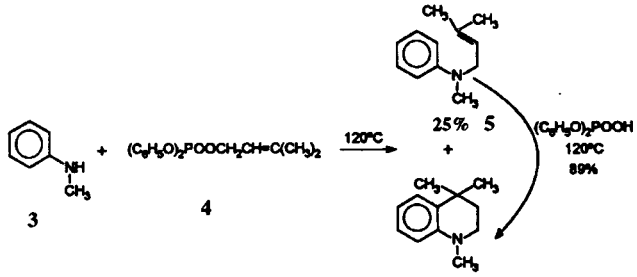
2.1.1 Route 1

The intramolecular alkylation of 2-butenyl dimethyl phenyl ammonium bromide **1** in the presence of polyphosphoric acid (PPA) produces 1,1,4-trimethyl-1,2,3,4-tetrahydroquinolinium bromide **2** [27].



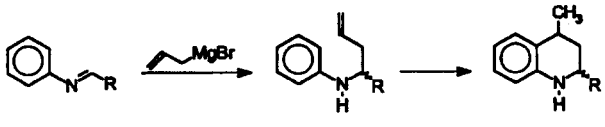
1 2

The alkylation of *N*-methylaniline **3** with 3-methyl 2-butenyl diphenyl phosphate **4** is carried out in autoclave at 120°, under these conditions, the reaction produces a mixture of the *N*-substituted aniline **5** (25%), and the tetrahydroquinoline **6** (62%) [28,29]. In the last step, **5** transforms into **6** in 89% yield when treated with $(C_6H_5O)_2POOH$ at 120°.



3 4

The imines **7** were the starting materials to obtain the 2,4-disubstituted 1,2,3,4-tetrahydroquinolines **9** *via* homallylamines **8** under acidic conditions (concentrated sulfuric acid) [30]. The reaction products are formed as a mixture of diastereomers.



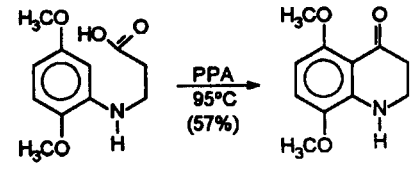
7 8 9

R = C_6H_5, α-Py, β-Py, γ-Py *cis/trans*

In chloric acid, the cyclization of *N*-[(3-hydroxy-4,4-dimethyl)pentyl]aniline generates a mixture of 4-methyl-4-*i*-propyl- and 4-*t*-butyl-1,2,3,4-tetrahydroquinoline [31]. The former tetrahydroquinoline is the main product as a consequence of a Wagner-Meerwein rearrangement occurring to the starting alcohol.

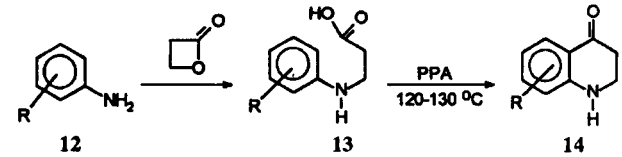
The 4-oxotetrahydroquinoline derivatives are obtained in good overall yields from β-(*N*-phenyl)aminopropionic acids and their acid chlorides [32-35]. The cyclization of these acids is made with phosphorus pentoxide while the acid halides require aluminum chloride, the conditions of the Friedel-Crafts reaction.

The cyclocondensation of β-(*N*-2,4-dimethoxyphenyl)-aminopropionic acid **10**, in presence of polyphosphoric acid at 95° produces the 5,8-dimethoxy-4-oxo-1,2,3,4-tetrahydroquinoline **11** (57% conversion) [36]. This compound is an important intermediate in the synthesis of 8-azajuglones. The synthesis of analog derivatives is described [37,38].



10 11

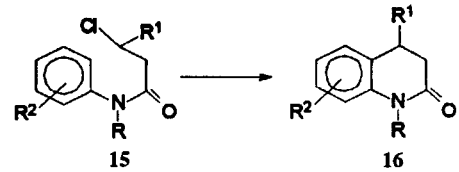
In turn, β-(*N*-aryl)aminopropionic acids **13** can be obtained from substituted anilines and oxooxetane. In these reactions, zinc chloride could be used as a cyclization agent [39].



12 13 14

R =	6-F	8-F	8-Br
% =	31	100	100

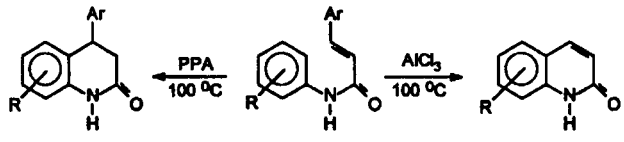
The Friedel-Crafts intramolecular cyclization of different anilides of β-halogen substituted propionic acids allows the synthesis of 3,4-dihydro-2-oxoquinolines. The reaction was performed for the first time in 1927 by Mayer [40]. Using this approach, the derivatives **16** were obtained from the anilides **15** in the presence of either aluminum chloride or the zinc chloride-sodium chloride system [41-45].



15 16

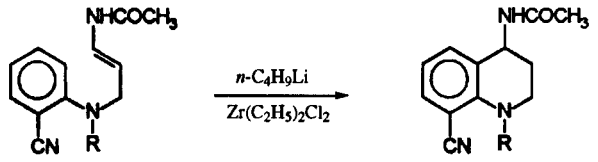
R = H, CH_3, C_6H_5, Ts; R^1 = H, CH_3; R^2 = H, 8-CH_3, 6(8)-Cl, 6(8)-OH

The cinnamanilides constitute another series of starting reagents that are very useful to synthesize 4-aryl-3,4-dihydro-2-oxoquinolines. Their cyclization is accomplished under conditions of acidic catalysis or by photolysis. For example, compounds **18** are obtained in hot polyphosphoric acid [46-52], but if aluminum chloride is used, the aryl substituent of anilides **18** is eliminated, producing the quinolin-2(1*H*)-ones **19**.



18 17 19

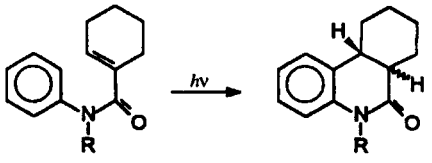
R = 4-CH_3, 4-OCH_3, 4-Cl



22 23

R = H, Ts

The photolytic cyclization of unsaturated anilides allows also the formation of 3,4-dihydro-2-oxoquinoline derivatives [53,54]. Ninomiya and coworkers [55] described the synthesis of compound **21** as a result of the uv irradiation of enamide **20**.



20 21

cis/*trans*

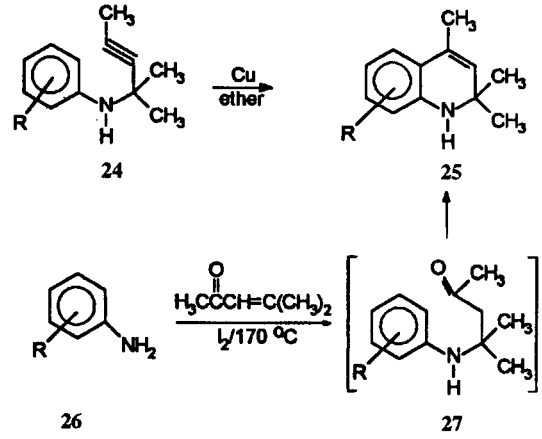
In this reaction, compound **21** appears as a mixture of stereoisomers were the cyclohexane and the tetrahydroquinoline rings are in the *cis*- or *trans*-configurations. The relative amount of the isomers depends on the nature of the solvent. In protic solvents like methanol, the *cis*-isomer is predominant whereas in aprotic solvents like benzene or diethyl ether, the *trans*-isomer is the major component.

In the Stork method, [56] ($Bu_3SnCl/NaBH_3CN/t$-BuOH), the *N*-alkyl(aralkyl)-*N*-iodo(bromo)phenylamides of buten-3-oic acids are used as starting materials to synthesize the *N*-substituted 1,2,3,4-tetrahydroquinolin- 2-ones [57]. Small amounts of *N*-substituted 2,3,4,5-tetrahydrobenzazepine are also obtained. The formation of these compounds occurs as a result of the radical 6-exo or 7-exo-cyclization.

When the *N*-(buten-3-yl)-*N*-methyl-*o*-chloroaniline reacts in the presence of a nickel catalyst with methylmagnesium bromide, a 91% yield of 1-methyl-4-methylene-1,2,3,4-tetrahydroquinoline is obtained. A further reduction transforms it in 1,4-dimethyl-1,2,3,4-tetrahydroquinoline [58].

The 4-acetylamino substituted tetrahydroquinolines **23** are synthesized by cyclization of *o*-(3-acetylamino-2-propenyl)aminobenzonitriles **22** with zirconocene dichloride and *n*-butyllithium [59].

It was also shown that 1,2-dihydroquinoline derivatives **25** can be prepared in diethyl ether from the *N*-(4-methyl-2-pentynyl-4)arylamines **24** and copper powder [60-62]. The classic method to obtain these derivatives [63-66] consisted in heating the mixture of aniline **26** and iodine up to 170°, followed by a slow addition of acetone or mesityl oxide.



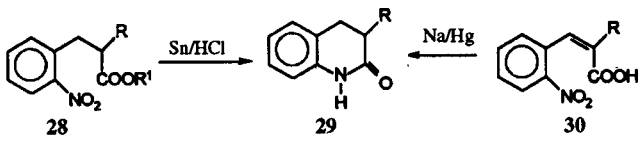
24 25

26 27

The first compounds obtained following this procedure were derivatives of quinolin-2(1*H*)- and 4(1*H*)-ones. The condensation products of the aniline **26** with the acetoacetic ester are the starting materials in the Conrad-Limpach and Knorr synthesis; depending on the temperature, the acetoacetic ester can react with the carbonyl or with the ethoxycarbonyl group. These methods allow the preparation of a large variety of quinolinones, versatile precursors in the synthesis of quinolines that show a potential physiological activity. Some new derivatives were also recently synthesized following this path [67-71].

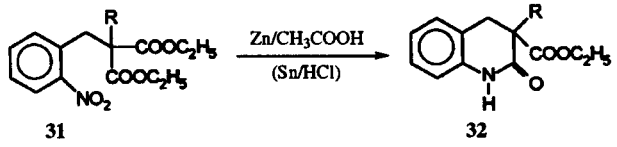
2.1.2 Route **2**

The 3,4-dihydroquinolin-2-ones **29** substituted on C(3) are prepared by the reductive cyclization of β-(*o*-nitrophenyl)propionic acid derivatives **28** or their esters with chlorhydric acid and tin [72-74]. The ketones **29** are also obtained by reduction of β-(*o*-nitrophenyl)acrylic acid derivatives **30** [75] or from 4-(*o*-nitrophenyl)-2-oxooxethanes with sodium amalgam [76]. The reduction with tin/hydrochloric acid can be replaced by a hydrogenation with palladium catalysts [77,78]. The reductive cyclization method was perhaps one of the first examples of the construction of the quinoline ring [79].



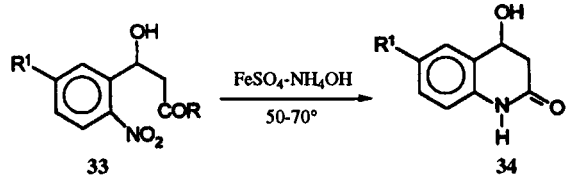
$R^1 = H, C_2H_5$

The reduction of the α-substituted malonic acid **31** with zinc in acetic acid produced the 3,3-disubstituted 2-oxotetrahydroquinolines **32** [80,81].



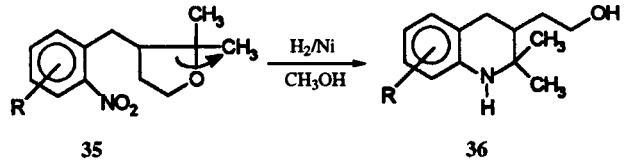
R = H, CH_3, C_6H_5

There are other examples of this type of cyclization. The 4-hydroxy-3,4-dihydro-2-oxoquinolines **34** are obtained from the β-(*o*-nitrophenyl)-β-hydroxypropionic acid derivatives **33** when treated with ferrous sulphate under mild cyclization conditions [82,83].



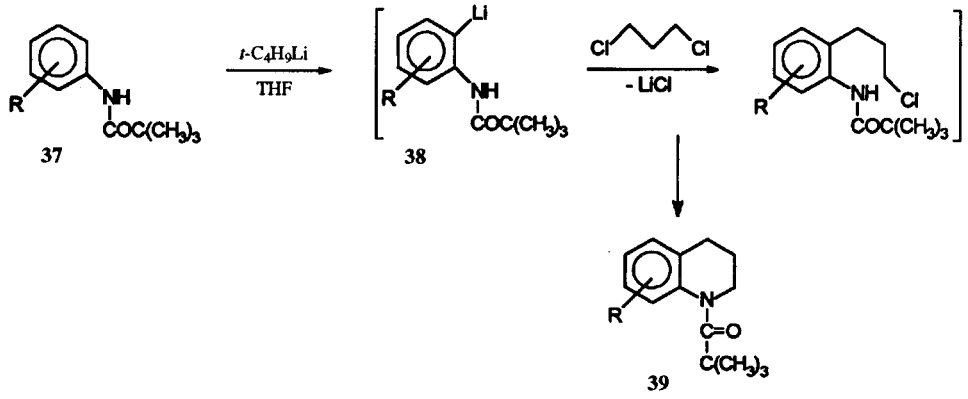
R = OH, NH_2; R^1 = H, Cl, OCH_3

The 6,7-dimethoxy- and 6,7-dioxymethylene-2,2-dimethyl-3-(β-oxyethyl)-1,2,3,4-tetrahydroquinolines **36** are prepared by the reductive cyclization on nickel Raney in methanol of 2,2-dimethyl-3-[2'-nitro-4'-5'-dimethoxy-(dioxymethylene)benzyl]tetrahydrofuranes **35**, which, in turn, are synthesized from 3-veratryl-4-piperonylbutyrolactones [84].



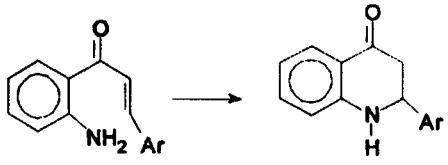
R = 6,7-$(OCH_3)_2$, 6,7-OCH_2O-

Route **2** allows also the synthesis of *N*-pivaloyl-1,2,3,4-tetrahydroquinolines **39** substituted on the benzene ring by treating the *o*-lithium-*N*-pivaloylanilines **38** with 1,3-dichloropropane [85].



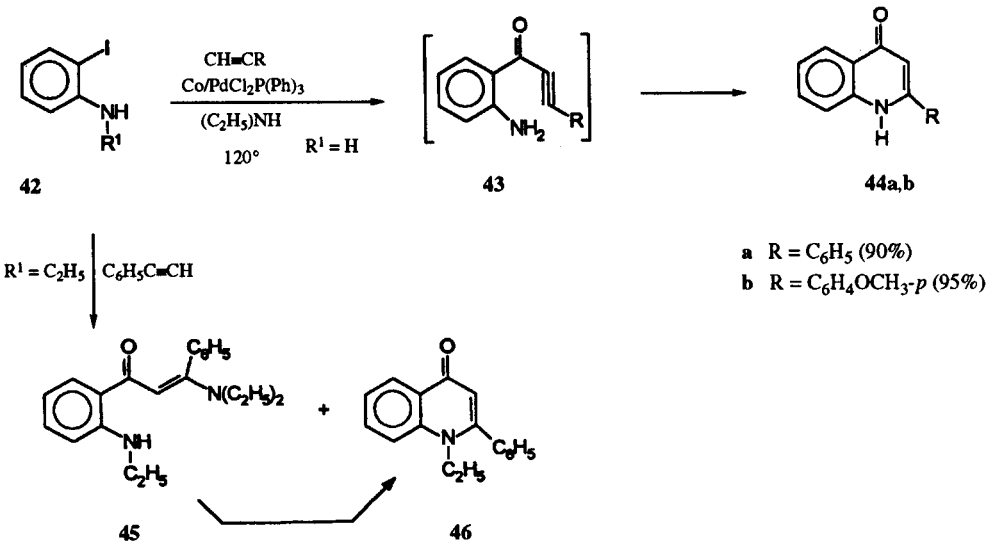
37 38 39

Although 2(4)-quinolone derivatives have been the subject of intensive studies [25,26] and there are different approaches to their syntheses, it is appropriate to mention here some effective methods to synthesize such derivatives by this way. For example, the treatment of *o*-substituted anilines **40** with 90% phosphoric acid or sodium ethoxide produces 2-arylquinolin-4-ones **41** in high yields [86,87].



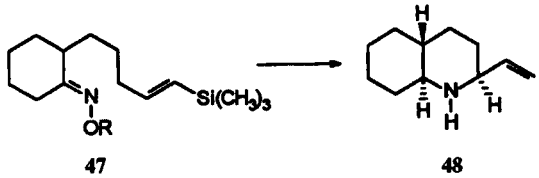
40 **41** Ar = C_6H_5, $C_6H_4CH_3$-*p*

The same starting materials give 3-arylquinolin-4-ones during the oxidative transformation in the presence of thallium nitrate [88]. The similar *o*-substituted anilines **43** are formed as addition intermediates during the interaction between *o*-iodoanilines **42** and terminal acetylenes in the presence of a palladium salt, diethylamine and CO at 120°. From these intermediates the corresponding 2-substituted quinolin-4-ones **44** are obtained in high yields [89]. In contrast, if the synthesis starts from *N*-ethyl-*o*-iodoaniline and phenylacetylene under the same conditions, two products, the *o*-substituted aniline **45** and the desired quinoline **46** are obtained in 52 and 20% yields, respectively. It is important to realize that the aniline **45** can be easily transformed into **46** by reaction with sodium hydride in tetrahydrofuran.



The Heck reaction [90] is another versatile method to prepare several quinolone-2 derivatives. The synthesis of such compounds has been reported as a result of heating *o*-iodoanilines and functionalized olefines in the presence of palladium acetate or palladium on activated charcoal [91-93]. In some of these reactions, the derivatives of tetrahydroquinoline are formed at the same time as the quinoline bases [90,94].

The diisobutylaluminum hydride promoted transformation of substituted cyclohexanone oxime **47** into 2-vinyldecahydroquinoline **48**, can also be considered as a construction of the hydrogenated quinoline system *via* route **2** [95].

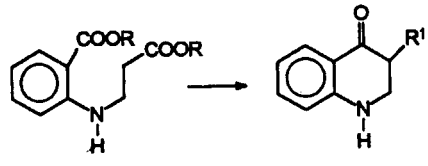


47 **48**

2.1.3 Route **3**

There are few examples in the literature that refer to the construction of the tetrahydroquinoline cycle *via* this route. The methods described in the following paragraphs are the best known.

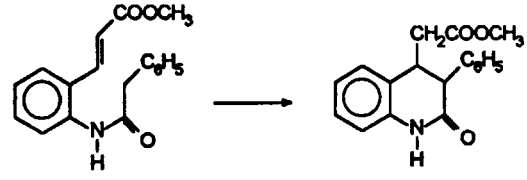
The 3-ethoxycarbonyl-4-oxotetrahydroquinoline **50a** can be obtained by heating the ethyl ester of the β-(*o*-ethoxycarbonylphenyl)aminopropionic acid **49a**, as a result of the Dieckman condensation [96]. A similar compound, 4-oxotetrahydroquinoline **50b** were also obtained by heating the acid **49b** with potassium acetate in acetic anhydride [97,98].



49a,b
a: R = C_2H_5
b: R = H

50a,b
a: R^1 = $COOC_2H_2$
b: R^1 = H

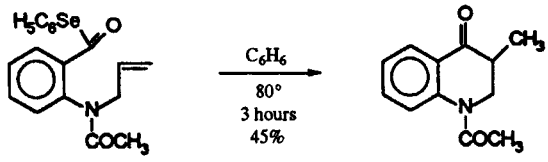
By a condensation reaction, of the Michael addition type, of compound **51**, the 3-phenyl-4-methoxycarbonylmethyl-2-oxotetrahydroquinoline **52** was synthesized with a 71% efficiency [99].



51 **52**

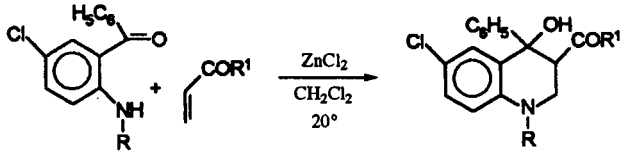
The Camps reaction [100], was applied to the synthesis of quinolin-2- and 4-ones [101,102]. Furthermore, the cyclization of *o*-carbonylic derivatives of the *N*-acylanilines was made in alkaline media by a condensation of the Claisen-Schmidt type.

The cyclization of compound **53** by radicals (Bu_3SnH, 2,2'-azobisisobutylonitrile) produced the 1-acetyl-3-methyl-4-oxotetrahydroquinoline **54** in 45% yield [103].



53 54

The condensation of the substituted 2-aminobenzophenones **55** with methylvinylketone or acroleine, in the presence of zinc chloride in dichloromethane at room temperature, produces the functionalized tetrahydroquinolines **56** [104].



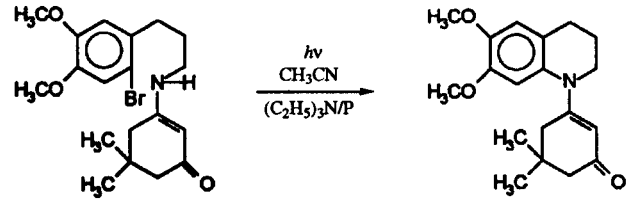
55 56

R = H, $R^1 = CH_3$	(50%)
$R = R^1 = CH_3$	(74%)
R = CH_3, R^1 = H	(41%)

2.1.4 Route **4**

This synthetic path refers to the cyclization of the aminopropylbenzenes either by photolysis or in the presence of a reduction or oxidation catalyst. The *N*H- and *N*-methyl(acetyl)-6-hydroxy-1,2,3,4-tetrahydro-7-methylquinolines are prepared by the oxidative cyclization of *N*-[3-(2',5'-dihydroxy-4'-methylphenyl)]propylamine and their respective *N*-methyl and *N*-acetyl derivatives [105]. The cyclization of *N*-chloro-*N*-methyl-(γ-phenyl)propylamine is promoted by ferrous sulphate. Under these conditions, *N*-methyl-1,2,3,4-tetrahydroquinoline is produced [106].

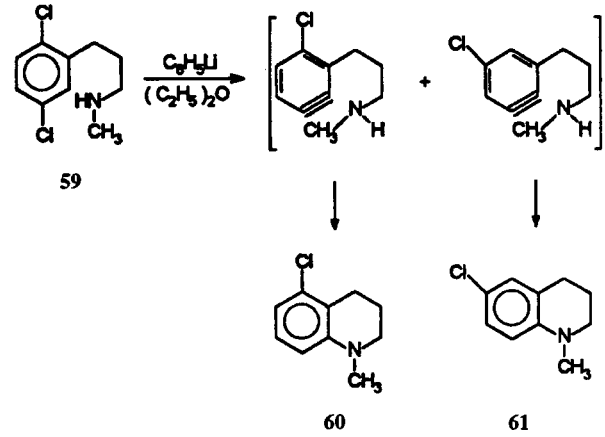
The photolysis of *N*-(3-oxo-5,5-dimethylcyclohexen-1-yl-1)-*N*-(γ-(2-bromo-4,5-dimethoxyphenyl)propyl)amine **57** gives a 33% of substituted 1,2,3,4-tetrahydroquinoline **58** [107].



57 58

Some 2-quinolone derivatives prepared by this route showed antimicrobial and antibacterial activities [108-113].

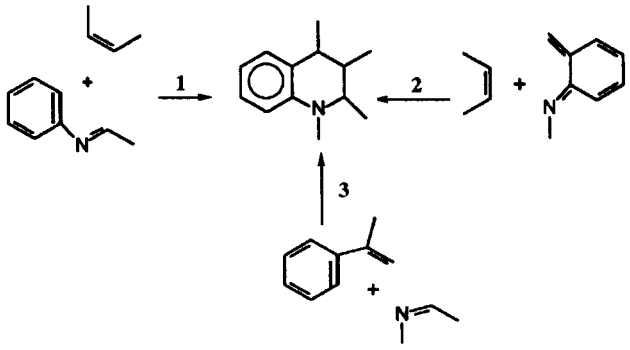
An interesting application of this type of cyclizations has been described by Huisgen and coworkers [114]. *N*-Methyl-*N*-γ-(2,5-dichlorophenyl)propylamine **59** reacted with phenyllitium in ether to produce a mixture of 5- and 6-chloro-1-methyl-1,2,3,4-tetrahydroquinolines **60,61** in a 3:1 ratio. The formation of these products involved benzine intermediates, as described in the following reaction scheme:



59 60 61

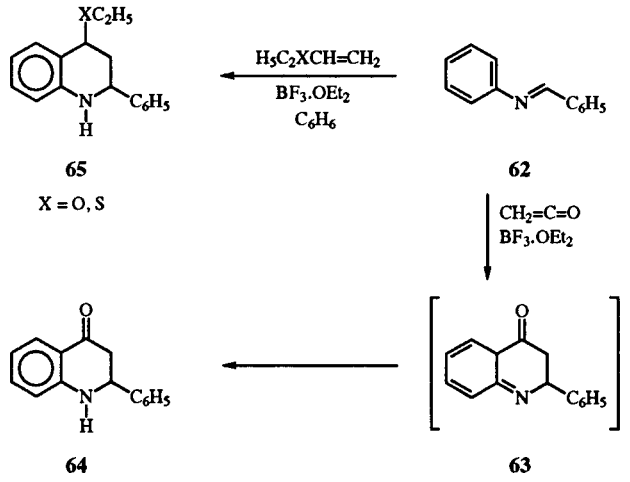
2.2 Intermolecular [4+2] Cycloaddition

The Diels-Alder reaction represents the most important route to the corresponding carbo- and heterocycles. Under this heading numerous syntheses of six membered heterocycles containing nitrogen can be found in the primary literature. Despite this fact, the methods to prepare tetra(deca)hydroquinolines using the above mentioned synthetic path have not been reviewed so far. These [4+2] cycloaddition reactions can be made following different paths, which depend on the nature of the reagents (routes **1-3**). Schiff bases are the more frequent starting materials because they participate as dienes (routes **1** and **2**) as well as dienophiles (route **3**).



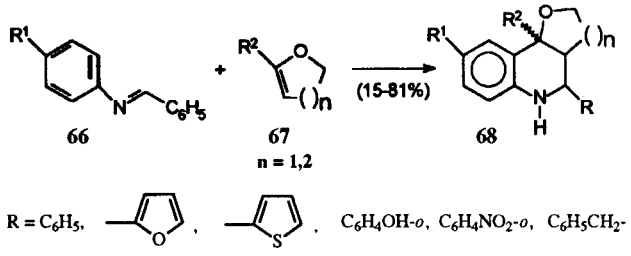
2.2.1 Route **1**

Povarov and coworkers [115-117] did the pioneer work using simple *N*-arylimines as dienes in cycloaddition reactions. They succeeded in reacting the *N*-arylimines as π-electron components (2-azadienes), where the C=C bond was part of the aromatic system. The activation of these azadienes was made with boron trifluoride etherate which coordinated to the nitrogen atom, and increased the electrophilic properties of the diene. The reaction of benzylideneaniline **62** with ketenes initially generates the adduct **63** which in turn, isomerizes to 2-phenyl-4-oxo-1,2,3,4-tetrahydroquinoline **64**. In a similar way, the 4-ethylmercapto(ethoxy)-2-phenyl-1,2,3,4-tetrahydroquinolines **65** are obtained when the imine **62** reacts with ethylvinyl sulfide or ethylvinyl oxide.



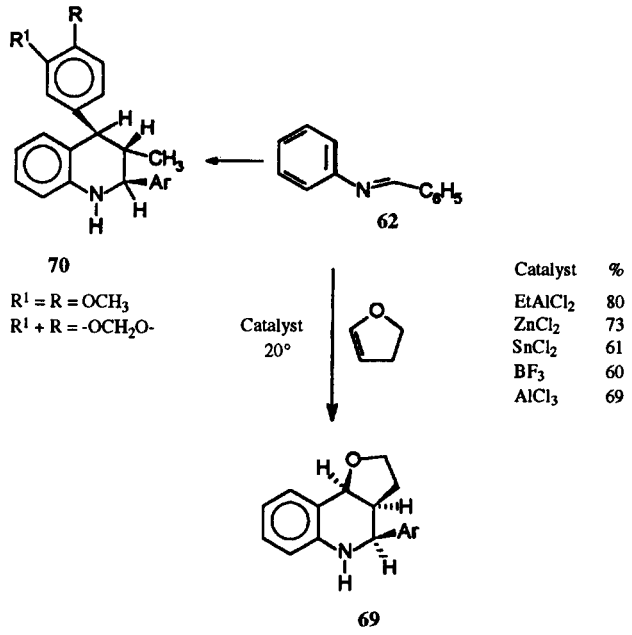
Later research on this reaction allowed increasing the number of dienophiles able to add to Schiff bases through a cycloaddition [4+2] mechanism. Among them, 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran and their homologues turned out to be very active dienophiles [118,119].

The pyrano(furo)tetrahydroquinolines **68** were isolated as a single stereoisomer, but the spatial arrangement of the substituents was not established. At the end of the sixties and the beginning of the seventies, a series of studies were made to establish the stereochemistry of these reactions. In particular, the interaction of different anils with 2,3-dihydro-5-methylfuran was studied [120-123].

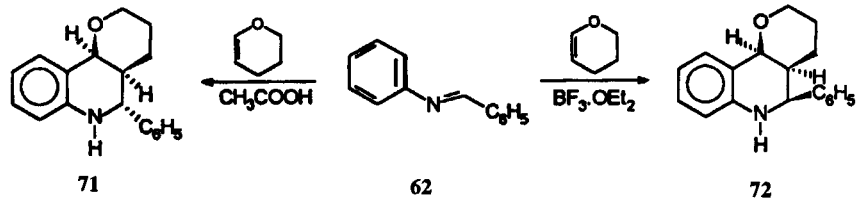


It was established that in the cycloaddition of dihydrosilvan to the *N*-arylimines, a *cis*-addition takes place giving equal amounts of two stereoisomers which differentiate each other by the configuration of carbon C(2) on the tetrahydroquinoline ring. The authors could synthesize a considerable number of tetrahydroquinolines condensed with the furan ring; the reactions were all carried at room temperature, using benzene as solvent. The influence of the solvent polarity on the stereoisomers formation was not taken into account.

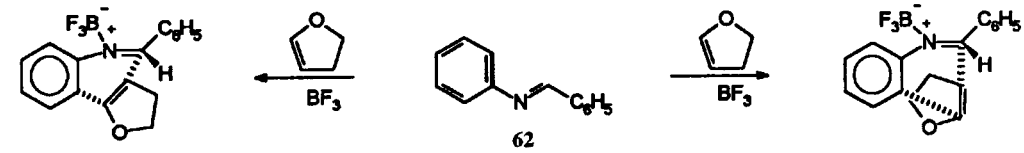
Years later, Kametani and coworkers [124,125] studied the Lewis acid catalyzed addition of dihydrofurans and dihydropyrans to Schiff bases. They demonstrated that toluene and the presence of different Lewis acids made the cycloaddition of 2,3-dihydrofuran and the imine **62** occur in a stereospecific way forming the endo adduct **69** [126,127]. With styrene derivatives identical results were obtained but the yields of the corresponding tetrahydroquinolines **70** were low (16-29%) [128].



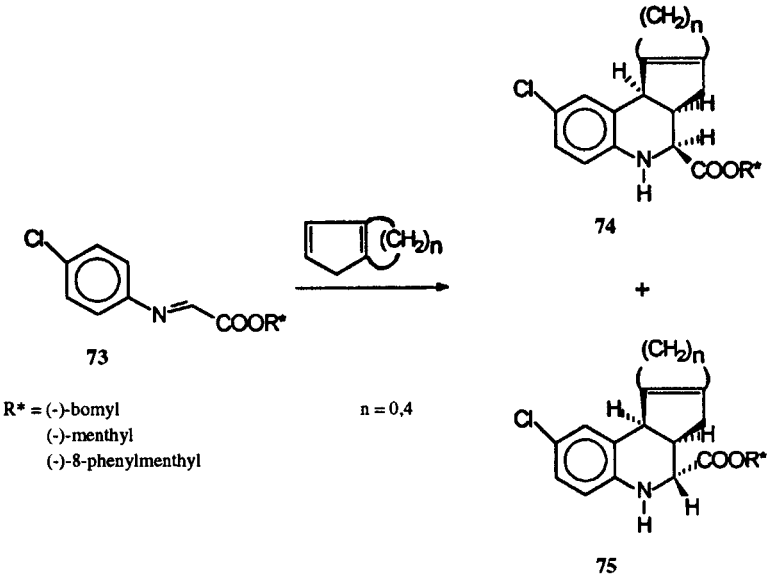
Some stereochemical peculiarities of this reaction were found by Gilchrist [129], who proved that the cyclization of the imine **62** with 3,4-dihydro-2*H*-pyran, catalyzed with boron trifluoride etherate, favored the endo adduct **72**. On the other hand, the exo adduct **71** was formed in acetic acid. The endo adduct **72** was also obtained when the cyclization was carried in the presence of ferric chloride [130]. Initially [131], the structure of 1,2-diphenylazetidino[2,3-*b*]pyran was erroneously given to **72** studying this type of cycloaddition in the presence of montmorillonite.



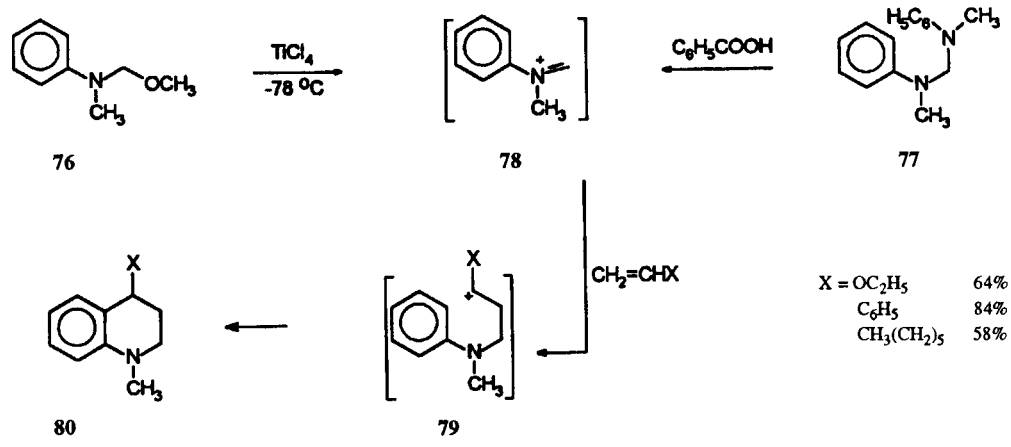
The theoretical foundations of the Lewis acid catalyzed cycloaddition reaction of *N*-arylimines with 2,3-dihydrofuran were presented by Lucchini and coworkers [132], who proposed that the exo adduct could form when the approximation path of the reagents followed the Si-Si direction. But if the Si-Re direction is the chosen one, the cycloaddition product is the endo adduct. The reaction could take place either through a concerted mechanism or through a series of sequential steps in a zwitter-ionic mechanism. The same authors established that an increase in the solvent polarity favored the exo adduct in the product mixture, and therefore, they proposed that the formation of the endo adduct (Si-Re approach direction) corresponded to a concerted mechanism for a [4+2] cycloaddition. The zwitter-ionic mechanism is more probable to participate in the formation of the exo adduct (Si-Si approach direction).



To obtain tetrahydroquinolines non substituted in C(2) but annulated in the positions 3 and 4 with tetrahydropyran or tetrahydrofuran rings, the *S*-triazine is used as starting material [125]. The presence of Lewis acids (boron trifluoride etherate, titanium tetrachloride), in the cycloaddition of chiral imines **73** with cyclopentadiene and indene produces a mixture of optically active diasteroisomers, the polycyclic systems of tetrahydroquinoline **74**, **75**. Under these conditions the endo addition prevails [133]. Hydrogenated derivatives of phenanthridine are obtained from benzylideneanilines and 1-cyclohexenylethylic ether [134].



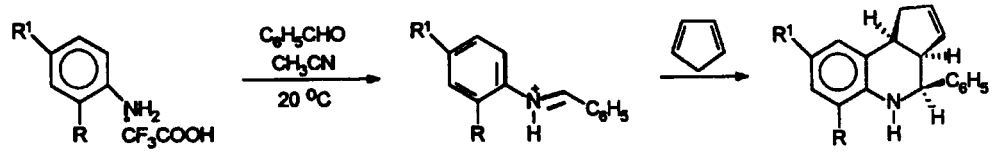
The chemical behavior of Schiff bases with vinyl ethylic ether in presence of $Ni(CO)_4$ or $Co_2(CO)_8$, was evaluated by Hagihara and collaborators [135,136]. It was shown that $Ni(CO)_4$ favored tetrahydroquinolines, while $Co_2(CO)_8$ produces a mixture of tetrahydroquinolines and quinolines. *N*-Methyl-aryliminium ions **78** generated *in situ* by addition of Brönsted or Lewis acids from *N*-methyl-*N*-alkylanilines **76**, **77**, could be used as very versatile starting materials to build tetrahydroquinoline rings; these ions reacted with electron rich alkenes to form the C(4)-substituted 1-methyl-1,2,3,4-tetrahydroquinolines **80** [137-139].



76 78 77

80 79

It is believed [139] that the reaction of the iminium cation **78** with olefins involves an electrophilic addition to the C=C bond of the alkene to generate the carbocation **79**, which in turn, fuses itself to form the tetrahydroquinoline ring **80** through an intramolecular electrophilic alkylation. The iminium cations formed *in situ* from *N*-(α(-methoxy-(β,β-difluor[(β,β,β-trifluor]ethyl)diphenylamines behave the same way. The cycloaddition of these cations to alkenes or alkanes produce the corresponding 1-phenylsubstituted tetrahydro- and dihydroquinolines [140]. It was also demonstrated that, in the presence of trifluoroacetic acid, the iminium cations can be easily obtained from substituted anilines and benzaldehyde [141]. These ions **82** react with cyclopentadiene and produce the tetrahydroquinolines **83** in high yields, annulated in the endo direction with the cyclopentene fragment on positions C(3) and C(4). Under similar conditions, the tetrahydroquinoline ring is also obtained from the benzylideneaniline trifluoroacetates.

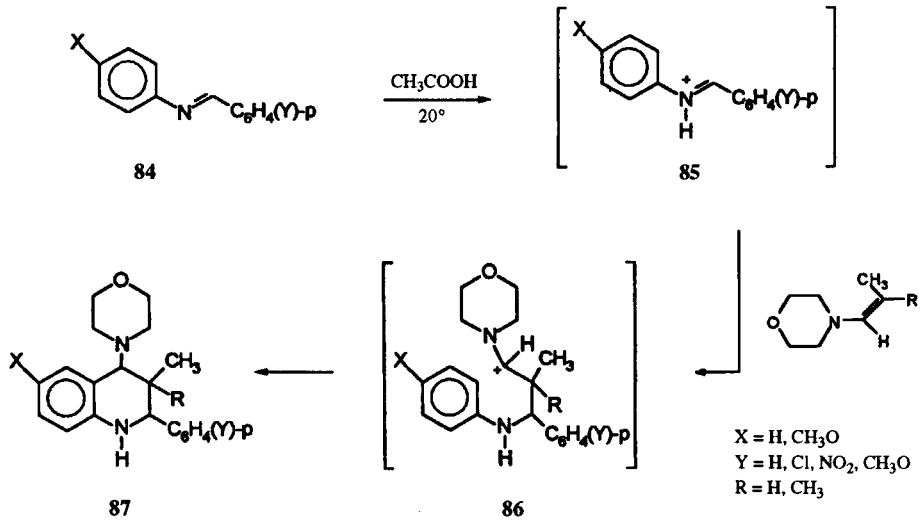


81 82 83

R = H, R¹ = COOH 85%
R = COOH, R¹ = H 82%

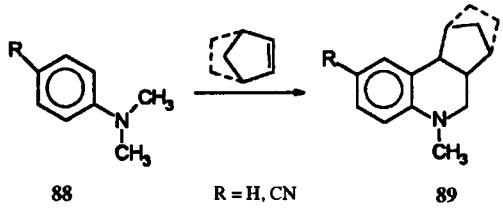
R = Cl, R¹ = H 90%
R = R¹ = H 71%

In an acid medium the enamines that possess α hydrogens, react by a 1,4-cycloaddition path with different benzylideneanilines **84** to produce tetrahydroquinoline derivatives **87**.

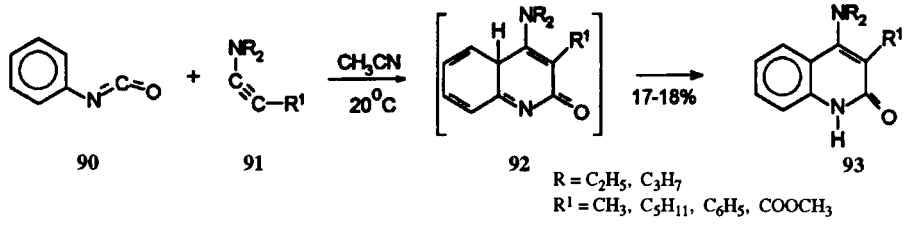


The mechanism for this reaction, proposed by Nomura and coworkers [142], involves the electrophilic addition of the iminium cation **85** to the C=C bond of the enamine and the intramolecular electrophilic alkylation of the carbocation **86**.

In the previous examples, the iminium salts intervene like heterodienes in a reaction known as a cycloaddition [4+ + 2]. This explanation supports also the similar formation of 1-methyl-6-cyanotetrahydroquinoline **89** when the *N,N*-dimethylaniline **88** (and its *p*-cyano derivative) and the 2-norbornene (or cyclopentene) are irradiated in methylene chloride in the presence of $FeSbF_6$, although the mechanism involves the participation of free radicals [143,144].

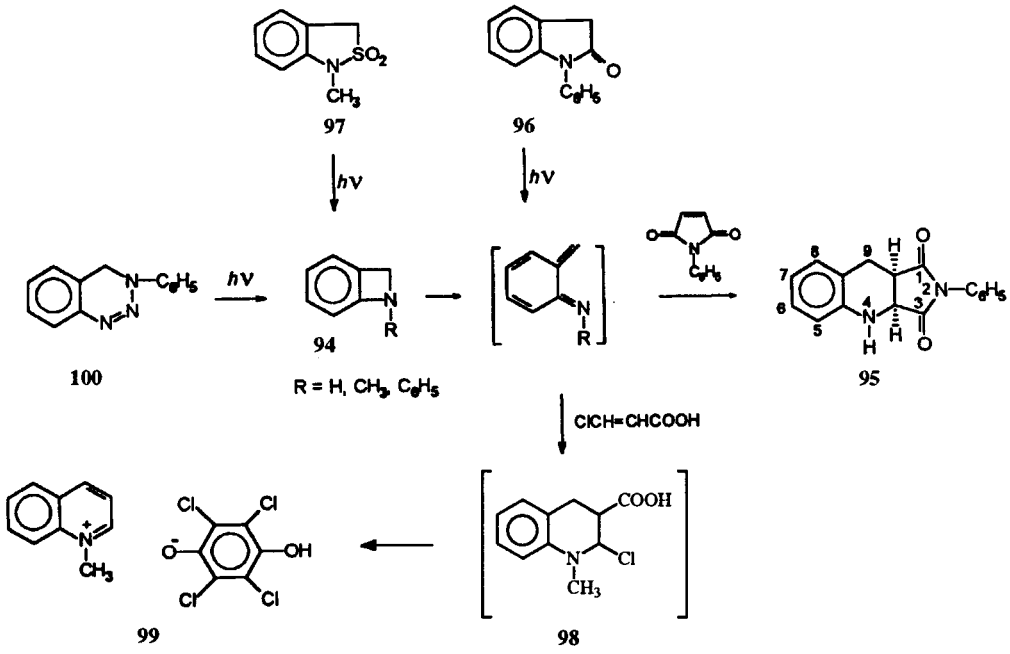


The synthesis of 4-aminoquinolin-2(1*H*)-ones from ynamines and phenyl isocyanate constitute a singular example of [4+2] cycloaddition, where the dienophiles are acetylenic compounds [145,146].



2.2.2 Route **2**

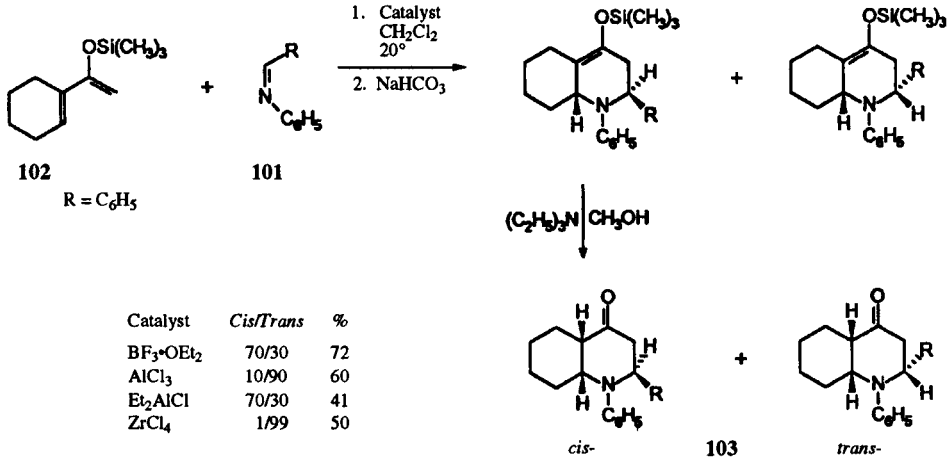
The use of the *o*-quinonemethide imines in building the tetrahydroquinoline ring has been studied in very few cases [147]. The *o*-quinonemethide imines could be generated by thermal or photolytic processes. For example, if benzoazetidine **94** (R = C_6H_5) is heated to 220° in the presence of *N*-phenylmaleinimide, the [b] condensed quinoline **95** is obtained [148]. The same compound is



formed when an ethereal mixture of *N*-phenylindan-2-one (**96**) and *N*-phenylmaleinimide is irradiated with uv light [149]. The benzoazetidine **94** (R = CH_3) may be generated by irradiation of benzothiozoline **97**; in this process, the ultraviolet light induces the opening of the pentagonal heterocycle and the elimination of sulphur dioxide. Also, by a [4+2]-cycloaddition scheme, the photolysis of **94** occurs in the presence of *trans*-β-chloroacrylic acid to form the tetrahydroquinoline **98**, which decomposes to the salt **99** when treated with $NaHCO_3$ [150].

2.2.3 Route **3**

Presently, one of the best synthetic paths to prepare the decahydroquinolin-4-ones is the reaction of benzylideneanilines with cyclic analogs of Danishefsky dienes. So, the *N*-phenylimines **101**, in presence of Lewis acids, react with trimethylsilyl-1-acetylcyclohexene **102** in ether to produce the decahydroquinolin-4-one derivatives **103** with good yields [151,152]. To obtain the *cis*-isomer **103** with a high degree of selectivity *t*-butyldimethylsilyl triflate is used as a catalyst [153].



102 R = C_6H_5 **101**

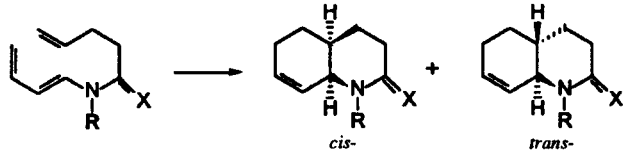
Catalyst	*Cis/Trans*	%
BF_3•OEt_2	70/30	72
$AlCl_3$	10/90	60
Et_2AlCl	70/30	41
$ZrCl_4$	1/99	50

103

There are other methods [26] to synthesize the per- and octahydroquinolines using cyclohexanone as the starting material.

2.3 Intramolecular Diels-Alder Reaction

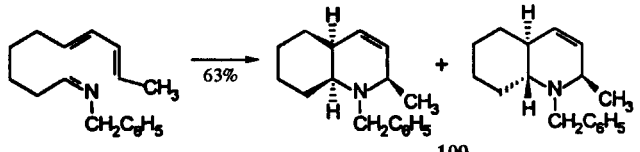
The intramolecular Diels-Alder reaction of appropriate substrates is a very effective method to synthesize hydrogenated derivatives of quinoline, which are the precursors of some quinoline alkaloids. It was verified that trienes **104** and **105** in a 5% toluene solution, were transformed into the corresponding octahydroquinoline derivatives **106** and **107**, when heated in an autoclave at 190° [154]. Oppolzer and Fröstl proposed that the conformational effects on the transition state were responsible for the large influence that the amide group has on the diastereoselectivity of the cyclization (100% for the *cis* isomer).



104 R = $COOCH_3$, X = 2H
105 R = C_3H_7, X = O

106 84%: 100-0
107 62%: 41-59

By contrast, through the cyclization of azatriene **108**, the formation of the *trans*-octahydroquinoline isomer **109** prevails although the configuration of this isomer is also closely related to the conformation of the reaction transition state. Furthermore, it was demonstrated that the use of the iminium ions increases significantly the yields of the products in these reactions [155].



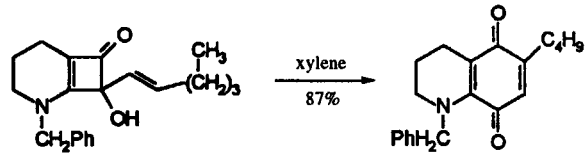
108

109
cis/trans
29:71

2.4 Other Methods

This section is devoted to the description of the methods that involve rearrangements and condensations and are useful to produce saturated quinolines. For example, the condensation of ethoxymethylenemalononitrile with the dimethylic ester of the 3-oxoheptanodioic acid produces the 8-cyano-5-hydroxy-6-methoxycarbonyl-1,2,3,4-tetrahydroquinolin-2-one in 89% yield [156].

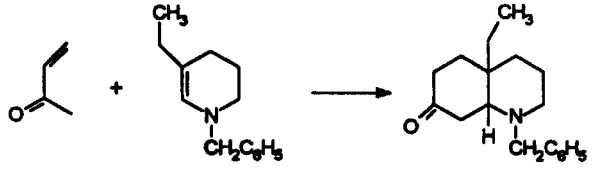
The norbornenylquinolin-2(1*H*)-one is obtained with a 14% efficiency upon heating to 80° the *N*-acetyl-2-bromoaniline with norbornandiene, in the presence of CO, $Pd(PPh_3)_4$ and potassium acetate in anisole; the thermal decomposition of the norbornenylquinolin-2(1*H*)-one at 170-180° produces the quinolin-2-(1*H*)-one [157]. In the same way, thermolysis of piperido[2,3-*a*]cyclobutene **110** promotes the formation of tetrahydro-8-azajuglones **111** [158].



110 **111**

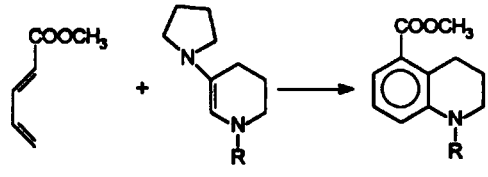
Derivatives of indanone and 2-methylindole have also been used as starting materials in the synthesis of several quinolines. The synthesis of 1,3-dimethyl-1,2-dihydroquinoline can be prepared at 100°, by methylation of 2-methylindole in the presence of an excess of methyl iodide [159]. The corresponding 2- and 4-oxotetrahydroquinolines are also obtained, in low yields, from 2-indanone and azetidin-2-one derivatives [159-161].

The condensation of 1-benzyl-3-ethyl-1,4,5,6-tetrahydropyridine **113** with methylvinylketone **111** yields 7-oxoperhydroquinoline **113** [162].



112 **113** **114**

1-Substituted 1,4,5,6-tetrahydro-3-(pirrolidinyl-1)pyridines **116** react with the methyl ester of 2,4-pentadienecarboxylic acid **115** by a similar process of [4+2] cycloaddition to produce 1-substituted 5-carbomethoxy-1,2,3,4-tetrahydroquinolines **117** [163].



115 **116** **117**

The intramolecular cyclization methods of derivatives of aniline and benzene, to obtain tetrahydroquinolines and dihydroquinolines, were mainly developed at the beginning of the century. Today, these methods are slowly losing their popularity to intermolecular cyclization methods; among the latter, the cycloaddition [4+2] that uses the imines (Schiff bases) as starting materials seems to be the most important one.

3. Some Chemical Properties of Hydrogenated Quinolines

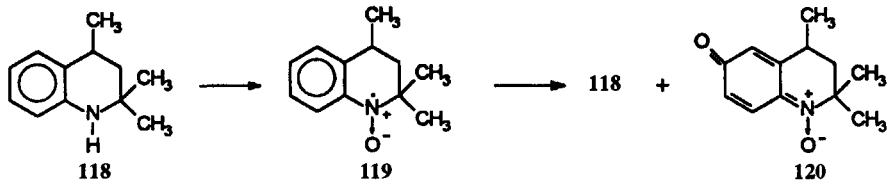
1,2,3,4-Tetrahydroquinoline behaves chemically as a secondary aromatic amine. Some chemical transformations of this heterocyclic system are presented in the following sections.

3.1 Oxidation

Chromic acid as well as iodine easily oxidizes the tetrahydroquinoline to quinoline. 4-Hydroxy-1,2,3,4-tetrahydroquinoline transforms into the corresponding oxo-derivative under the conditions of the Oppenauer oxidation, but in a very low yield. Nevertheless, 1-benzoyl-1,2,3,4-tetrahydroquinolin-4-one is formed in a 70% yield when 1-benzoyl-4-hydroxy-1,2,3,4-tetrahydroquinoline is oxidized by chromic anhydride [164].

Oxidation of 1,2,3,4-tetrahydroquinolines to 1-hydroxy-1,2,3,4-tetrahydroquinolin-2-ones by hydrogen peroxide occurs in the presence of different catalysts ($Na_2WO_4 \cdot 2H_2O$, H_2WO_4, SeO_2, $Mo(CO)_6$, $Na_2MoO_4 \cdot 2H_2O$). These oxidation products are particularly interesting because they are biologically active [165,166].

The oxidation of C(2) and C(4) substituted tetrahydroquinolines produces the corresponding imine-oxide radicals [167]. Hydrogen peroxide stabilized by the ions of the wolframic, molybdenic or vanadic acids acts as a weak and selective oxidation agent. Paramagnetic *N*-oxide **119** was prepared by heating to reflux a benzene solution of 2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline **118** and *t*-butyl hydroperoxide in the presence of cobalt stearate. The radical can be separated by column chromatography on aluminum oxide as an intensely red colored viscous oil [168,169]. The formation of the imine-oxide radicals may be accompanied by dimerization [170]. The *N*-oxides of type **119** decompose easily to the initial tetrahydroquinoline and the nitrone **120** [171].

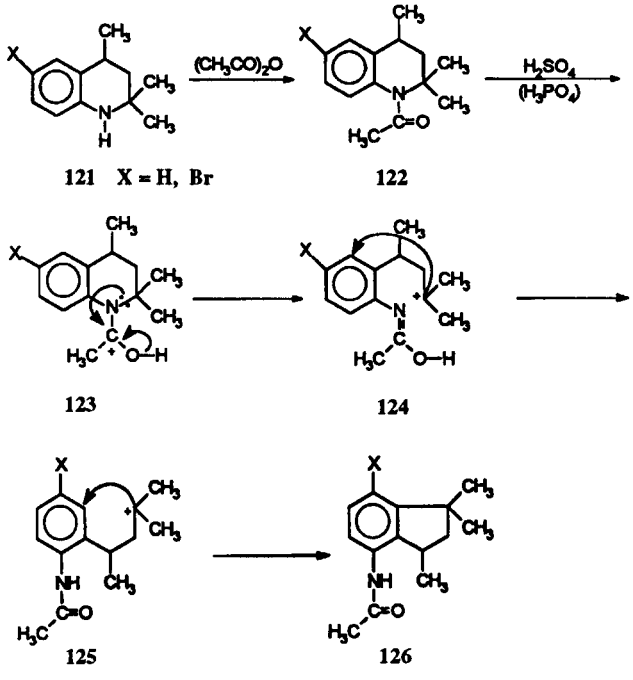


4-Acetoxy-1-acetyl-1,2,3,4-tetrahydroquinoline and 1-acetyl-1,2-dihydroquinoline are obtained by autoxidation of 1,2,3,4-tetrahydroquinoline in the presence of catalytic amounts of transition metal acetates and ammonium bromide in acetic anhydride [172]. In the reaction, the following systems proved to be very good catalysts: Co^{+2}, NH_4Br, Co^{+2}-Mn^{+2}-NH_4B and Co^{+2}-Ce^{+3}-NH_4Br.

3.2. *N*-Acylation, *N*-Alkylation and *N*-Amination of Tetrahydroquinolines and Their Rearrangements

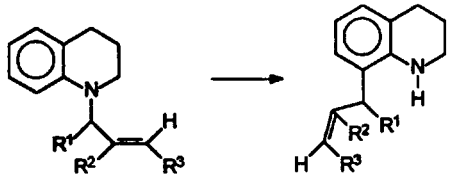
Perhaps the most interesting chemical properties of the tetrahydroquinolines are related to the different transformations that their *N*-substituted derivatives undergo. For instance, when *N*-benzoyltetrahydroquinoline, obtained under the conditions of the Brown reaction, from 1,2,3,4-tetrahydroquinoline and benzoyl chloride is heated with phosphorus pentachloride, a decrease in the size of the piperidine ring of the tetrahydroquinoline is observed. As a result, the structural isomer 2,3-dihydro-2-methylindoline is formed [173]. Exhaustive Hofmann and Ende methylation of the tetrahydroquinoline also induces the opening of the heterocyclic ring [174].

The *N*-acetyltetrahydroquinolines **122** isomerize to 4-aminoindanes **126** when treated with strong mineral acids, according to the following reaction scheme that has been proposed by Cliffe and coworkers [175].



The key steps of this transformation are the protonation of the acetyl carbonyl group, the rupture of the N-C(2) bonds and the intramolecular electrophilic alkylation reaction of the intermediate carbocation.

N-Alkenyl derivatives **127** were studied under the conditions of the Claisen transposition (Claisen amino-transposition) [176-178]. Lewis or Brönsted acids transform these compounds into their 8-alkenyltetrahydroquinoline isomers **128**, which offer great possibilities in the synthesis of lilolidine alkaloids, because the alkenyl fragment is located in an ortho position in relation to the NH group.

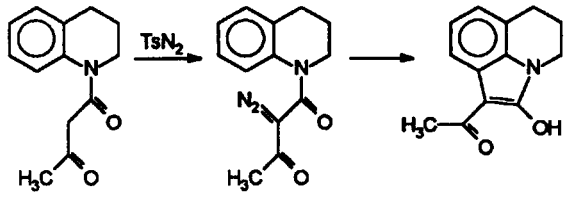


a $R^1 = R^3 = CH_3$, $R^2 = H$;
b $R^1 = R^2 = R^3 = H$;
c $R^1 + R^3 = (CH_2)_2$, $R^2 = H$;
d $R^1 + R^3 = (CH_2)_3$, $R^2 = H$

The most effective catalysts in this reaction are zinc chloride and *p*-toluenesulfonic acid. Nevertheless, it has also been reported that the transposition of the *N*-allyltetrahydroquinoline **127b** occurs only when the reaction is catalyzed by boron trifluoride etherate.

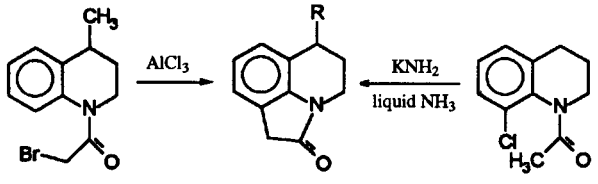
N-Substituted tetrahydroquinolines are widely used in the synthesis of tricyclic systems where the tetrahydroquinoline fragment appears annulated in positions 1,2 and 1,8a, with pyrrole, pyrrolidine, pyrrolinone or piperidine cycles. Compounds containing these tricyclic systems display a large array of biologic activities [179-184]. Among them, the 1,2,6-tetrahydropyrrolo[3,2,1-*ij*]quinolines are particularly important because their structure is the basic unit of the lilolidine alkaloids [185].

Acylation of 1,2,3,4-tetrahydroquinoline with β-ketobutanoyl chloride produces *N*-(1,3-dioxobutyl)tetrahydroquinoline **129** which converts into 1-(2-diazo-1,3-dioxo butyl)-1,2,3,4-tetrahydroquinoline **130** when treated with tosyl azide or sodium hydride. Further reflux over sodium acetate produces the compound **130** to fuse and affords 1-acetyl-2-hydroxy-3,4,5,6-tetrahydropyrrolo[3,2,1-*ij*]-quinoline **131** [186].



129 130 131

2-Oxo-1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines **133** are prepared by an intramolecular alkylation of *N*-bromoacetyl- and *N*-chloroacetyltetrahydroquinolines. The reaction is promoted by anhydrous aluminum chloride. Bioactivity studies showed that compounds **133** possess high antidepression activity [187]. These heteropolycycles are also produced in the reaction of 1-acetyl-8-chlorotetrahydroquinoline **134** with potassium amide in liquid ammonia [188].



132 133 134

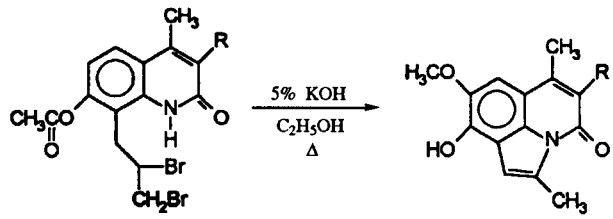
R = H, CH_3

The synthesis of 1,2,5,6-tetrahydropyrroloquinolin-2-one **136** can also be realized from tetrahydroquinolines **135** by reaction with the methyl ester of the trifluoropiruvic acid [189,190].

135 136

R = H, $C(CF_3)_2OH$

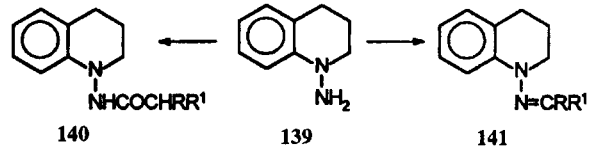
In turn, the pyrrolo[3,2,1-*ij*]quinolin-4-ones **138** are obtained by cyclization of 8-(2',3'-dibromopropyl)-7-methoxycarbonylquinolin-2(1*H*)-ones **137** in a basic medium [191].



137 138

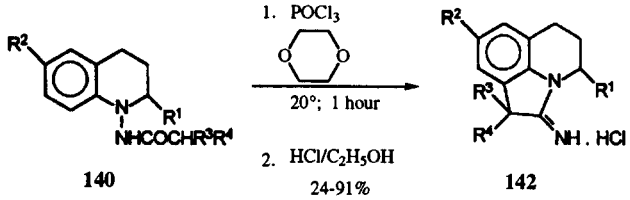
R = H, CH_3

N-Aminotetrahydroquinoline derivatives are very useful intermediates in organic synthesis. The reaction of 1,2,3,4-tetrahydroquinoline with nitrous acid occurs smoothly to produce the *N*-nitroso derivative, which can be reduced to 1-amino-1,2,3,4-tetrahydroquinoline **139** [192]. In a further reaction, the latter can either undergo acylation to generate the 1-acylaminotetrahydroquinoline **140** or condense with carbonylic compounds to obtain the 1-*N*-alkylideneaminotetrahydroquinolines **141** [193].



140 139 141

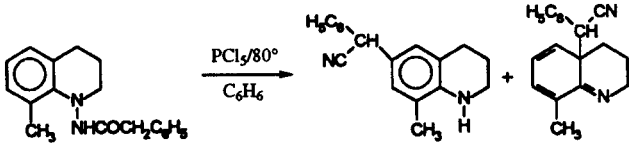
The action of electrophilic agents over compounds **140** can induce their transposition to the 2-iminopyrrolidino-[3,2,1-*ij*]quinolines **142** [193,194]. It is a general reaction, known as the Kost reaction [195]. The rearrangement occurs only when the C(8) position of the tetrahydroquinoline ring is free.



140 142

R^1 = H, CH_3; R^2 = H, CH_3, Cl, CH_3O; $R^3 + R^4$ = -$(CH_2)_5$-, C_6H_5, H, CH_3

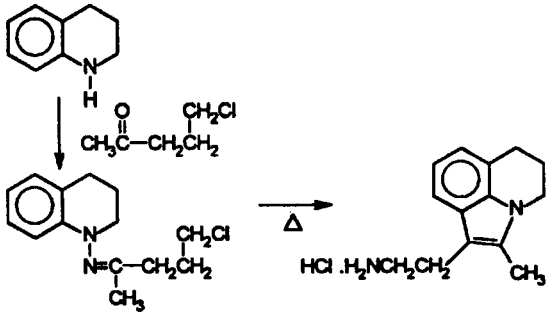
When 8-methyl-*N*-phenylacetylamino-1,2,3,4-tetrahydroquinoline **143** is heated to reflux with phosphorus pentachloride in benzene, the principal product of transposition is 6-cyanobenzyl-8-methyl-1,2,3,4-tetrahydroquinoline **144**. Small quantities of 4a-cyanobenzyl-8-methyl-2,3,4,4a-tetrahydroquinoline **145** and bis-phenylacetonitrile were also formed [196,197].



143 **144** 54% **145** 10%

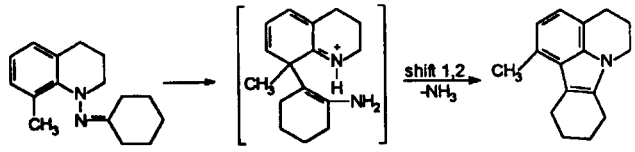
Under the same conditions, the major component obtained from the 6,8-dimethyl-1-phenylacetylamino-1,2,3,4-tetrahydroquinoline was 4a-cyanobenzyl-6,8-dimethyl-2,3,4,4a-tetrahydroquinoline, the dimethyl analog of compound **145** [196].

From the hydrazones of 1-amino-1,2,3,4-tetrahydroquinoline tricyclic systems have also been synthesized. For example, 1-(β-aminoethyl)-5,6-dihydro-2-methylpyrrolo[3,2,1-*ij*]quinoline **147** is prepared by heating under reflux 1,2,3,4-tetrahydroquinoline with the methyl-γ-chloropropylketone in methanol. This reaction involves the generation of hydrazone **146**, which, under these particular conditions transposes to the heterocycle **147** [194].



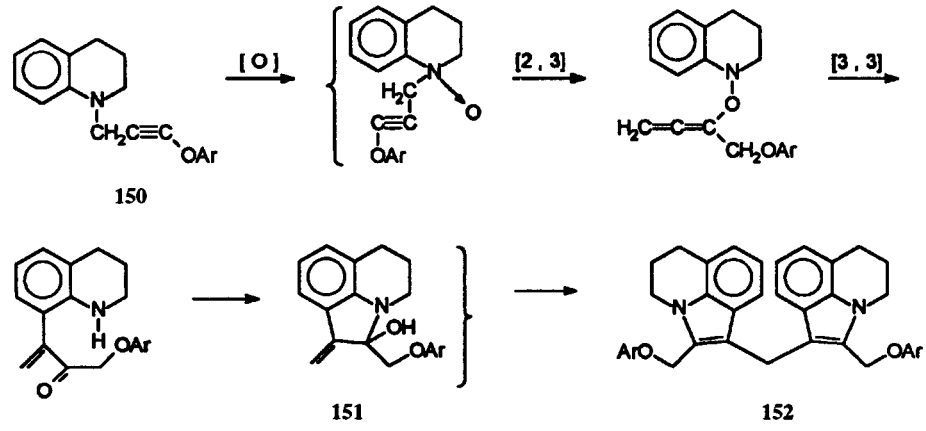
146 **147**

Hydrochloric, sulfuric, and glacial acetic acids transform hydrazone **148** into 1'-methyl-4',5',6',7',9,10,11-octahydropyrido[3,2,1-*jk*]carbazol **149** [196]. In the reaction, the methyl group of the starting tetrahydroquinoline undergoes a 1,2 shift from C(8) to C(7).



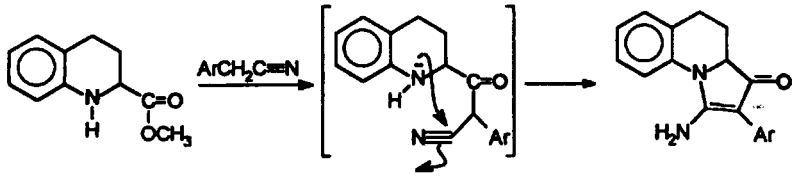
148 **149**

The oxidative cyclization of *N*-substituted tetrahydroquinolines **150** with *m*-chloroperoxybenzoic acid leads to the formation of bis(pyrrolo[3,2,1-*ij*]quinolinyl)methane derivatives **152**; the intermediates **151** have not been isolated under the reaction conditions [198].



150 151 152

C(2)-Substituted 1,2,3,4,-tetrahydroquinolines are used in the synthesis of pyrrolo[1,2-*a*]tetrahydroquinolines, compounds that proved their utility against amoeba infections [199]. Tetrahydroquinoline derivatives **155** annulated in positions 1,2 of the pyrrole ring are obtained in the presence of sodium *t*-butylate from 2-methoxycarbonyl-1,2,3,4-tetrahydroquinoline **153** and phenylacetonitriles [200]. The reaction involves two steps: (1) the acylation of the methylenic group of the nitriles by the initial ester and (2) the nucleophilic cyclization of the intermediate **154**, induced by the attack of the electron pair of the tetrahydroquinoline nitrogen atom on the CN triple bond.

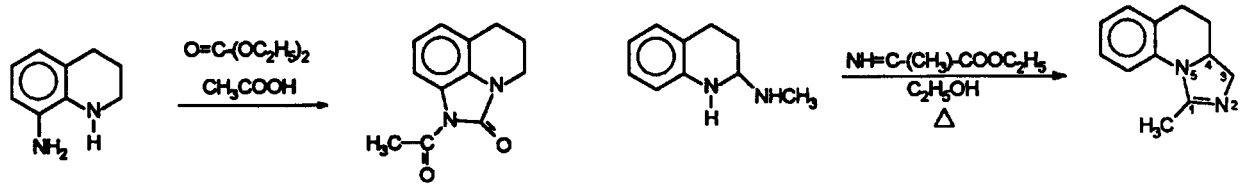


153 154 155

Ar = C_6H_5, *o*-ClC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4

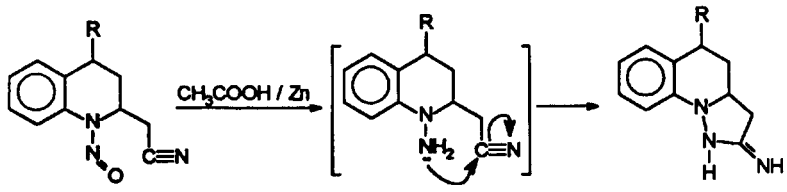
The polycyclic imidazo- and pyrazoloquinoline systems could also be obtained from the C(2) or C(8) subsituted tetrahydroquinolines. The synthesis of 1,2,4,5-tetrahydro-2-oxo-imidazo[3,2,1-*ij*]quinolines **157** is achieved by condensation of 8-amino-1,2,3,4-tetrahydroquinolines **156** with diethyl carbonate in acetic acid. The reaction products show a moderate fungicide activity [201].

Condensation of 2-methylamino-1,2,3,4-tetrahydroquinoline **158** with α-iminoethyl propionate in absolute ethanol produces the imidazo[1,5-*a*]quinoline **159** [202].



156 157 158 159

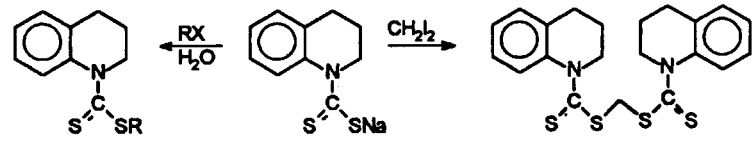
Zinc in acetic acid promotes the reductive cyclization of 2-cyanomethyl-*N*-nitrosotetrahydroquinolines **160**, forming the 5-iminopyrazolono[2,3-*a*]quinolines **162** [203,204].



160 **161** **162**

Ferrocene and 1,2,3,4-tetrahydroquinoline form the tetrahydroquinolinoferrocenic complex under reflux in the presence of aluminum chloride and powder aluminum. The methylation of the complex with methyl iodide in tetrahydrofuran and potassium *t*-butylate produces 1,4,4-trimethyltetrahydroquinolinoferrocene [205].

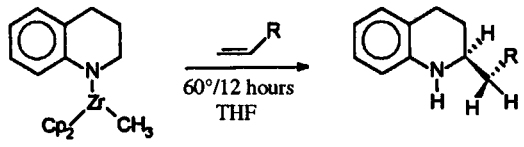
1,2,3,4-Tetrahydroquinoline treated with carbon disulfide in the presence of sodium hydroxide, produces the tetrahydroquinoline *N*-dithiocarbamate **163**. A further alkylation with RX or CH_2I_2 in water generates the corresponding esters of the tetrahydroquinolinedithiocarbamic acid **164**, in the first case, or methylene-bis[1,2,3,4-tetrahydroquinolin-1-yl)dithiocarbamate] **165** in the second case [206].



164 **163** **165**

R = C_2H_5, $CH_2C_6H_5$, $CH_2COC_6H_5$

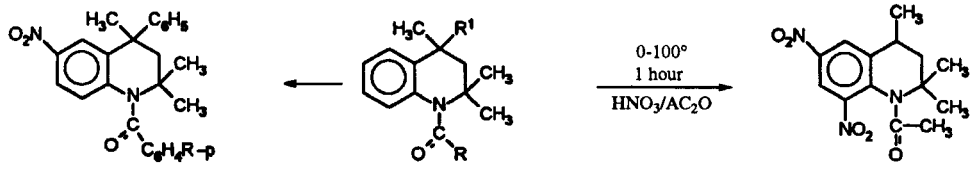
The acylation of the 1,2,3,4-tetrahydroquinoline with the dichlorides of the pyridine-2,6-dicarbonic acids produces the 2,6-di-(tetrahydroquinoline-*N*-carbonyl)pyridine [207]. If the nitrogen atom in the tetrahydroquinoline is bonded to electron acceptor groups, the α hydrogen atoms of the tetrahydroquinoline ring acquire a certain acidic character and, therefore, can be substituted in alcaline conditions by an alkyl group. This is one of the methods to prepare 2-alkyl-substituted tetrahydroquinolines [208]. Another method has been recently proposed by Coles, Whitby and Blagg [209] using zirconium organic compounds. The 1,2,3,4-tetrahydroquinoline was initially treated with *n*-butyllitium and zirconocene to obtain the *N*-zirconium substituted tetrahydroquinoline **166**, which converted to 2-alkyl-1,2,3,4-tetrahydroquinoline **167**, when heated in the presence of olefines.



166 167

3.3 Electrophilic Substitution Reactions

The nitration is perhaps the reaction of this type most studied and it is carried out with a previous protection of the amine group [16]. So, in the nitration of *N*-aroyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinolines **168** with nitric acid in acetic anhydride at 0-5° the 6-nitroderivate **169** is obtained with a 90% yield as a unique isomer. When the reaction system is heated for a longer time a second nitro group can be introduced to form 1-acetyl-6,8-dinitro-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline **170**.



169 **168** **170**

R = H, alquil, Cl, Br

R = CH_3, Ar, R^1 = H, C_6H_5

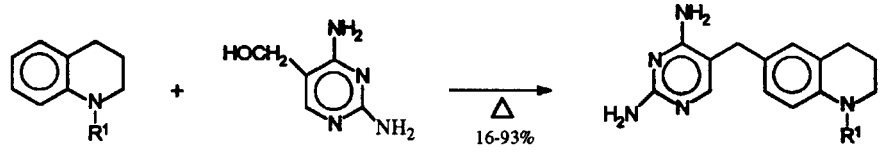
The nitration of tetrahydroquinolines with a nitrating mixture, and with no protection of the NH group produces, depending on the reaction temperature, 8-nitro or 7,8-dinitro derivatives. The 6-nitro and the 6,8-dinitrotetrahydroquinolines act as very strong acaricides [16].

The bromination and hydroxylation of tetrahydroquinolines **171** in the presence of superacids at low temperatures (-40°) yield the corresponding 5(7)-bromo- and 5(7)-hydroxytetrahydroquinolines [210]. The heteromethylation of the same tetrahydroquinolines using 2,4-diamino-5-hydroxymethylpyrimidine **172** in a mixture of acetic and chlorhydric acids produces the 6-(2,4-diaminopyrimidylmethyl-5)-1,2,3,4-tetrahydroquinolines **173** [211,212].

4. Conclusions

From what has been reviewed above, it is clear that organic chemists are very interested in hydrogenated quinoline derivatives. The chemistry of tetrahydrogenated quinolines is very similar to that of quinolines, but it is only from the former that different tricyclic structures can be obtained. These compounds are particularly important given their potential biological activity.

The methods described herein to obtain partially hydrogenated quinolines, mainly tetrahydroquinolines, are rational and effective and are often the only ones available to synthesize functionalized di- and tetrahydroquinolines.



171 **172** **173**

R^1 = H, CH_3, C_2H_5, $CH_2CH_2OCH_3$

Furthermore, these methods also allow the construction of di- and tetrahydroquinoline spiro derivatives. The study of the latter is the main concern in our laboratory and the cumulative information about these compounds will be published elsewhere.

5. Addendum

During the preparation of this manuscript some novel work in this field of quinoline chemistry appeared in the literature. *N*-Propargylanilines were cyclized to 2,2-disubstituted 1,2-dihydroquinolines by refluxing them in toluene containing copper(I) chloride [213]. An efficient and highly enantioselective synthesis of (*S*)-(-)-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline, a key intermediate in the synthesis of (*S*)-(-)-nadifloxacin, was carried out by using a cross-coupling reaction [214]. The 1,2,3,4-tetrahydroquinoline-8-sulfonic acid and its chlorides, which can be used as intermediates for antithrombotics, were prepared in seven steps from *o*-nitroiodoaniline [215]. 4-Ethoxy-1,2,3,4-tetrahydroquinoline is formed by one-pot reaction, mediated with uv light, from nitroarene, ethanol and TiO_2 [216]. The electrophile-initiated cyclization of some 2-allylanilines and their amides in the presence of iodine yielded the 3-iodo-1,2,3,4-tetrahydroquinolines [217]. Intermolecular polar [$4\pi^+ + 2\pi$] cycloaddition of cationic 2-azadienes from thiomethylamines or α-arylaminosulfones and α-arylaminonitriles with formation of tetrahydroquinoline derivatives was reported [218-220]. Finally, lanthanide and ytterbium(III) triflates were used as catalysts in imino Diels-Alder reactions for constructing quinoline derivatives [221,222].

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