Wafaa.S. Hamama*, Osama.M. Abd El-Magid and Hanafi.H. Zoorob

Chemistry Department, Faculty of Science, Mansoura University, Egypt.
Corresponding author: e-mail: ws_hamama@hotmail.com; Fax: +20-50-2246254; Tel: +20-50-2242388
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This review summarises the structure, basicity, asymmetric organocatalysis, synthesis and reactions of quinuclidines. Quinuclidines are bicyclic saturated pyridin-containing compounds with rigid structures and a ring-juncture nitrogen atom. This review covers the period from 1984-2005.

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1. Introduction.

Many papers have been reported so far concerning the synthesis, catalysis or biological activity of quinuclidine (1-azabicyclo[2.2.2]octane) (**1**) [1], inasmuch as quinuclidine is part of the structure of a number of natural physiologically active compounds, such as cinchona and some indole alkaloids, and synthetic drugs [1-8]. These numerous papers have been occasionally summarized in some monographs [1] and reviews [2,4]. However, a sufficient number of reviews have not been currently provided. Thus, in this review, we summarize the literature on quinuclidine structure, basicity, asymmetric organocatalysis and synthesis encompassing years 1984-2005. In a previous review [9] we reported chemistry of bicyclic pyridines containing the ring-juncture nitrogen.

1

1.1. Structure and basicity:

Quinuclidine (**1**) is a saturated bicyclic system with a bridgehead nitrogen atom. It has, in contrast to tertiary aliphatic amines and N-substituted piperidines, a rigid structure. The atoms forming quinuclidine ring are incapable of changing their relative positions by rotation around bond axes. These bond axes are included in the bicyclic system with each ring in the boat form. In contrast to other 1-azabicycloalkanes, quinuclidine is notable for its high symmetry and for the insignificant bond strain. The nitrogen lone-pair electrons are sp^3-hybridized and are not subject to steric crowding [1].

The basicity of quinuclidine, which depends on the electron density at the nitrogen atom, is close to that of aliphatic amines and N-alkylpiperidines. In condensed benzo- and dibenzoquinuclidine systems, the basicity decreased due to the inductive effect of the benzene rings [1].

Similar to other tertiary aliphatic amines, quinuclidine easily forms salts with mineral and organic acids, and quaternary derivatives with alkyl halides, although it adds to 2,6-dichloro-9-thiabicyclo[3.3.1] nonane to give dicationic products [10a]. However, the rates of reaction of alkyl iodides with quinuclidine are higher than with tertiary aliphatic amines. The addition compound of trimethylborane with quinuclidine is more stable than the corresponding adducts of trialkylamines [1]. These results can be explained by the almost total absence of steric hindrance at the nitrogen lone-pair of the bicyclic compound.

Studies on the basicity of triethylamine [NEt_3] and quinuclidine [$N(CH_2CH_2)_3CH$] as Lewis base (LB) with trimethylboron as Lewis acid (LA) [10b] showed that the two bases should have similar electronic effects, but they should have different steric constraints. The nitrogen lone pair on quinuclidine should be more accessible to a Lewis acid than that of triethylamine. A measure of the strength of a Lewis acid-base interaction is the heat of reaction ΔH_{rxn}. The thermodynamic results are shown in Table 1. The more negative ΔH_{rxn}, the stronger the Lewis acid-base interaction.

Table 1

Heat of reaction (ΔH_{rxn}) as a parameter for strength of Lewis acid-base interaction.

LA	ΔH_f (LA)	LB	ΔH_f (LB)	ΔH_f (adduct)	ΔH_{rxn}
BMe_3	-24.60	NEt_3	-14.93	-38.09	1.44
BMe_3	-24.60	$N(CH_2CH_2)_3CH$	-8.18	-34.49	-1.71

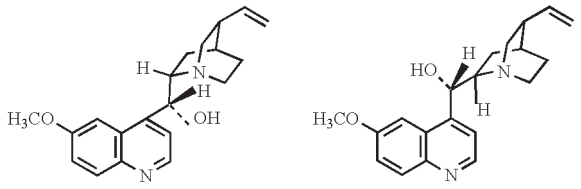
1.2. Asymmetric Organocatalysis.

Asymmetric organocatalysis, in which a chiral organic molecule catalyzes an enantioselective transformation, is a rapidly growing field. Accordingly, there has been a surge of interest in nucleophilic asymmetric catalysis as organic chemists have come to see the benefits and practicality offered by totally organic catalyst systems, especially their ease of handling and recovery [11]. In fact, some of the earliest discoveries in the field of asymmetric catalysis involved the use of organic nucleophiles. One pioneering study that was carried out by Pracejus reported the use of alkaloids to catalyze the alcoholysis of disubstituted ketenes to afford chiral alcohols in moderate enantioselectivity (ee) [12]. In the 1980s Wynberg developed an asymmetric β-lactone synthesis using ketenes, an activated aldehyde component, and a cinchona alkaloid catalyst [13].

diastereomeric pairs such as quinine (**2a**) and quinidine (**2b**) (Figure 1). Tamai and Romo have also used ketenes for the asymmetric synthesis of β-lactones [14,15]. Cinchona alkaloids have the status as general nucleophilic catalysts and ligands for many organic reactions [16].

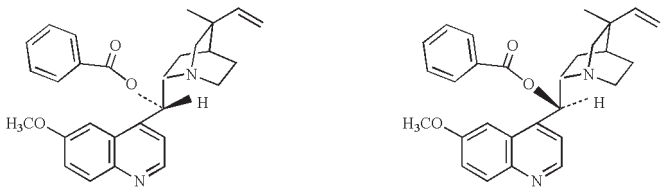
Taggi [17,18] found that a nucleophile such as benzoylquinine **3a** (Figure 2), an inexpensive [17] and versatile asymmetric catalyst, could be used in catalytic asymmetric synthesis of β-lactams *via* imine-lactonization process (Figure 3) in 65% yield, 99% ee and 99% dr (*cis*/*trans*) [18]. Additionally, he found that using benzoylquinidine (**3b**) (Figure 2) as a catalyst for the same synthesis, instead of **3a** inverted the stereochemistry of the product.

Cinchona alkaloids have a venerable history in the field of asymmetric synthesis owing to their firmly established ability to induce asymmetry and they are



2a-8S,9R-quinine **2b**-8R,9S-quinidine

Figure 1. Structures of quinine and quinidine.



3a **3b**

Figure 2. Structures of benzoylquinine and benzoylquinidine.

The cinchona alkaloids represent a class of natural product that possess several important features rendering them useful as asymmetric organocatalysts as in the case of widely used in asymmetric processes both in homogeneous and heterogeneous reactions such as the asymmetric-Michael addition Baylis-Hillman reaction),

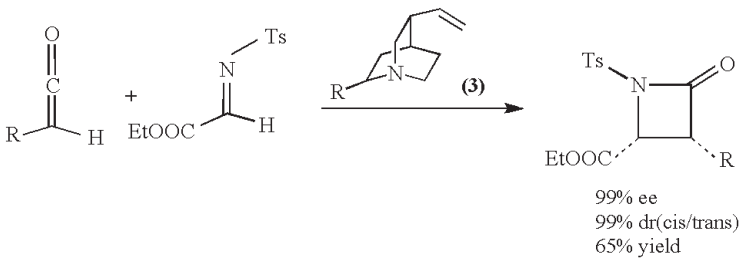


Figure 3. Synthesis of β,-lactams.

Sharpless dihydroxylation and hydrogenation reactions. The Baylis-Hillman reaction is an exquisite reaction as simple starting materials are converted into densely functionalized products. The reactivity of the catalysts based on their pK_a's and quinuclidine, which has the highest pK_a (Figure 4) was found to be the most active catalyst [19a].

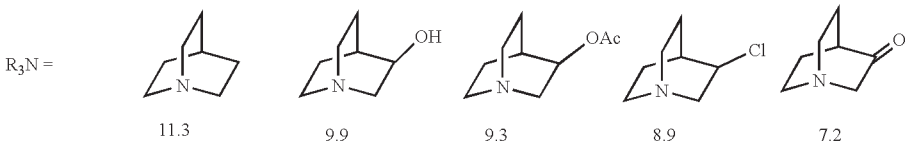
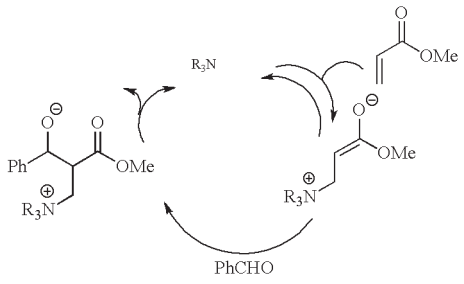


Figure 4. Quinuclidine based catalysts with their pK_a,s.

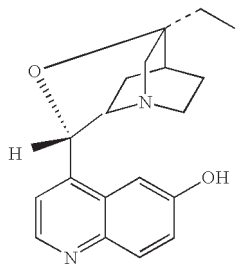
Scheme 1



Catalytic cycle of the Baylis-Hillman reaction.

Chiral quinuclidine derivatives were employed as catalysis in the Baylis-Hillman reaction [19b] and aza-Baylis-Hillman reaction. The ultimate example of asymmetric Baylis-Hillman [20] lies in an efficient, general catalyst that can be recovered and reused. Almost all of the chiral catalysts applied to the Baylis-Hillman [21,22] reaction have been plagued with low yields or low selectivities. Hatakeyama has developed the best cinchonidine ether (Figure 5) catalyst to date [23,24]. Amines **3** and **4** are derivatives of quinidine that give moderate yields and high selectivities.

The Baylis-Hillman reactions of various aryl aldehydes with methylvinylketone using different Lewis acid ($TiCl_4$, BCl_3, $ZrCl_4$) in the presence of Lewis bases **2** or **4** (chiral quinuclidine derivatives) shown in Figures **1** and **5**, afforded the chlorinated compounds, such as compound **5** as the major product in very high yields [19]. The Baylis-Hillman reaction is commonly used for the coupling of Michael acceptors with aldehydes and a quinidine-derived catalyst to give β-hydroxy-α-methylene esters, ketones/nitriles [24].



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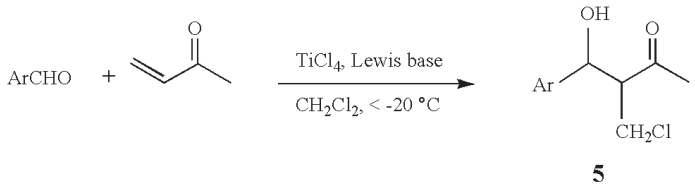
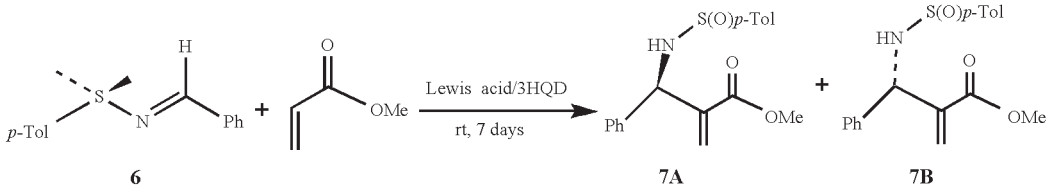


Figure 5. The chiral Lewis bases used for the Baylis-Hillman reaction.

However, it was also recognized that the few cases describing the use of imines in the Baylis-Hillman reaction all employed the strongly electron withdrawing tosyl group on the nitrogen atom [25]. The reaction of *N*-(benzylidene)-*p*-toluenesulfinamide (**6**) with methyl acrylate in the presence of one of the most reactive amine catalyst, 3-hydroxy quinuclidine (3-HQD) afforded good yields and high diastereoselectivities. The results are summarized in Table 2 [26]. A sterically non-hindered tricyclic derivative of quinidine was

Table 2
Baylis-Hillman reactions of N-sulfinimine **6**.



Entry	Base	Lewis acid	Additive	Diastereomeric ratio, A:B (yield %)
1	3-HQD	-	-	12 : 88 (23)
2	3-HQD	$La(OTF)_3$	-	14 : 86 (54)
3	3-HQD	$La(OTF)_3$	$N(CH_2CH_2OH)_3$	23 : 77 (60)
4	3-HQD	$Al(Oi\text{-}Pr)_3$	-	14 : 86 (30)
5	3-HQD	$Zn(OTF)_2$	-	25 : 75 (65)
6	3-HQD	$Zr(Oi\text{-}Pr)_4$	-	17 : 83 (65)
7	3-HQD	$Sc(OTF)_3$	-	23 : 77 (78)
8	3-HQD	$Yb(OTF)_3$	-	20 : 80 (74)
9	3-HQD	$In(OTF)_3$	-	18 : 82 (89)
10	(S)-3-HQD	-	-	9 : 91 (21)
11	(R)-3-HQD	-	-	16 : 84 (34)

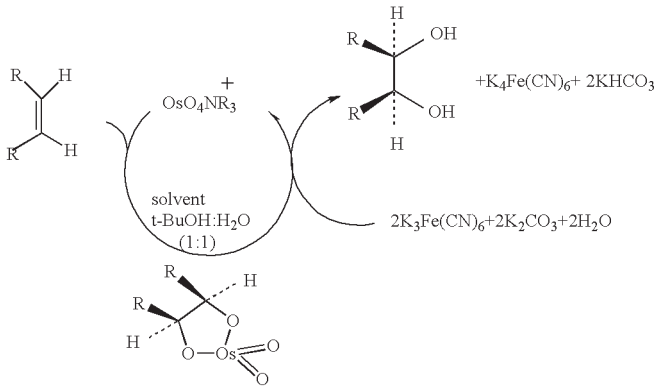


Figure 6. Catalytic cycle for Sharpless asymmetric dihydroxylation.

found to be the most efficient catalyst in transferring its chiral information [27].

Sharpless methods [28] for the asymmetric oxidation of alkenes, namely, asymmetric epoxidation (AE) and asymmetric dihydroxylation (AD) (Figure 6), were achieved by using a chiral ligand system for OsO_4. The most efficient ligands for promoting face-selective dihydroxylation of olefins were found to be bis-cinchona alkaloids such as the $(DHQD)_2PHAL$ system (Figure 7) [29,30].

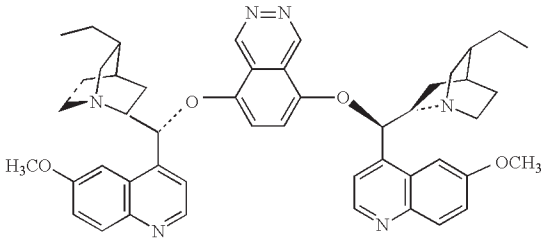


Figure 7. Structure of (DHQD)2PHAL.

Hydrogenations with a modified Pt-catalyst as well as the catalytic enantioselective alkylation under phase transfer catalysis have been achieved [31a]. Catalyst modification is applied widely in heterogenous catalytic hydrogenation. Selectivity and activity of a catalyst are influenced by the addition of organic modifiers either to the catalyst or to the reaction mixture. When the modifier is chiral, the reaction can be carried out enantioselectively [31b-d].

The two most important asymmetric catalyst types are platinum catalyst modified with cinchona alkaloids and related modifiers, successful for α-functionalized ketones

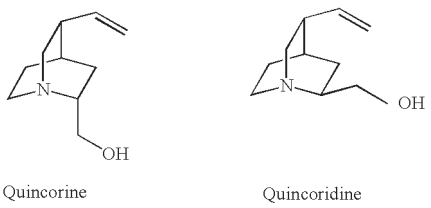


Figure 8. Quincorine (QCI) and quicoridine (QCD).

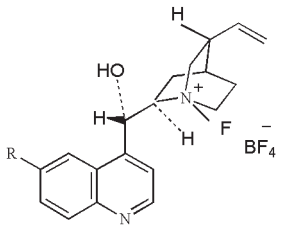
such as hydrogenation of ethyl pyruvate to ethyl acetate over cinchona-modified with ee's up to 98% and palladium catalysts modified with cinchona alkaloids which achieve ee's up to 94% for selected activated C=C bonds such as partial hydrogenation of a 4-methoxy-6-methyl-2-pyrone over cinchona-modified [32,33].

Quincorine (QCI) and quincoridine (QCD) (Figure 8) are also used to synthesize Pd and Pt complexes as chiral metal complexes. [34]. Cinchonine, quinine and quinidine were subjected to the fluorine-transfer procedure. All four N-fluorocinchonium salt (Figure 9) were evaluated in the fluorination reaction, with $F–Cd–BF_4$ giving the highest enantioselectivity with the fluorinated stereocenter having the (S)-configuration [35].

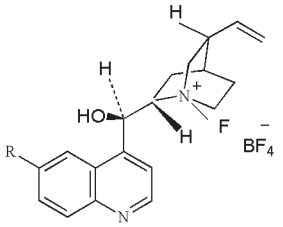
2. Synthesis of Quinuclidine and its Derivatives.

2.1. Methods of Constructing Quinuclidine Systems.

4-(Phenylacetyl)-*N*-benzylpiperidine (**8**) was cyclized by treatment with bromine in HOAc to give 19% of 2-phenyl-*N*- benzylquinuclidin-3-one (**9**), which was debenzylated to give 2-phenyl-3-quinuclidinone (**10**), then converted into 3-amino-2-aryl quinuclidines (**11**). These compounds are useful in the treatment of gastrointestinal disorders, inflammatory disorders, central nervous system disorders and pain [36a].

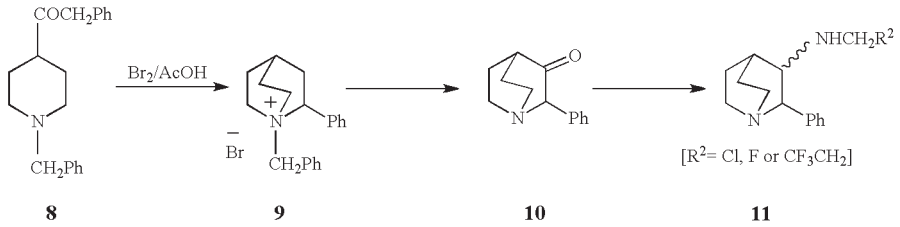


N-fluoroquinidiniumm tetrafluoroborate (R= OMe)
$F–Qd–BF_4$
N-fluorocinchoninium tetrafluoro borate (R= H)
$F–Cn–BF_4$



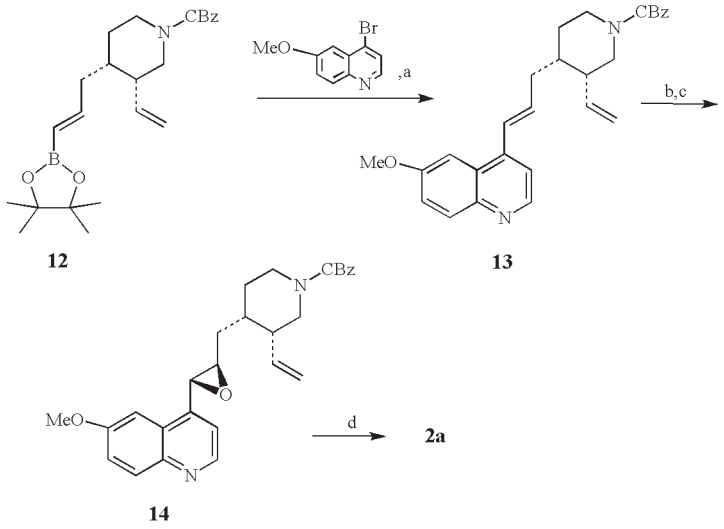
N-fluoroquininium tetrafluoroborate (R= OMe)
$F–Qn–BF_4$
N-fluorocinchonidinium tetrafluoroborate (R= H)
$F–Cd–BF_4$

Figure 9. Structures of N-fluorosalts for some cinchona alkaloids.

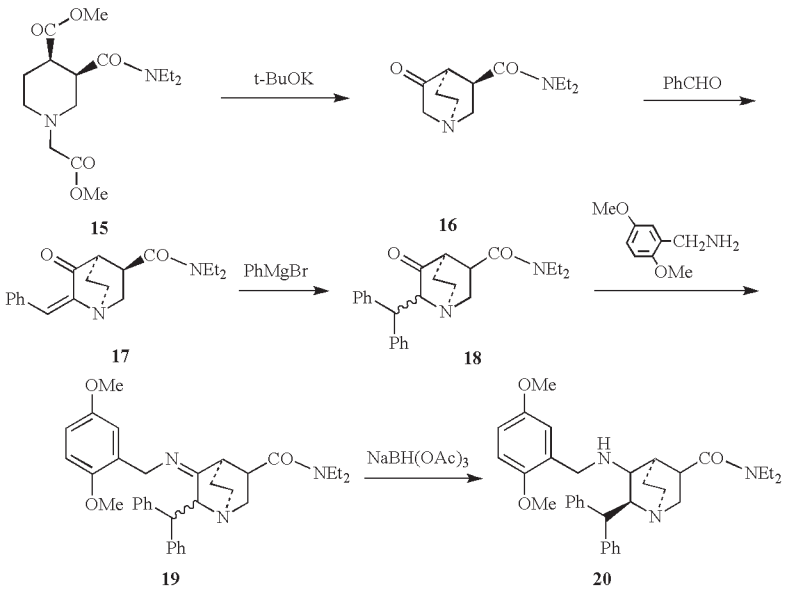


E-Vinyl pinacolatoboronic ester **12**, followed by cross coupling of boronate ester **12** with bromoquinoline gave *trans*-olefins **13**, followed by epoxidation afforded **14**. Removal of benzyl carbamate, followed by cyclization gave quinine (**2a**) [36b].

Substituted 3-aminoquinuclidine **20** was prepared *via* cyclization of piperidine-4-carboxylate **15** with *t*-BuOK followed by Aldol condensation of the quinuclidinone **16** with benzaldehyde. Grignard reaction of 2-benzylidene derivative **17** with PhMgBr afforded **18**. Its reaction with

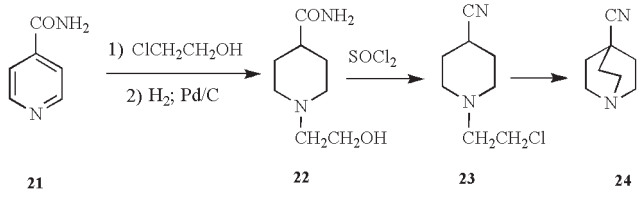


(a) $Pd(OAc)_2$; (b) $AD_{mix.B}$,$CH_3SO_2NH_2$, *t*-BuOH, H_2),O° C,(c) i-trimethyl orthoacetate,PPTS(cat.),CH_2Cl_2; ii- acetylbromide,CH_2Cl_2; iii-K_2CO_3,MeOH: (d) Et_2AlCl_2,thioanisole,O° C to rt, then microwave, 200 °C.



$2,5(OCH_3)_2C_6H_3CH_2NH_2$ followed by reduction of the crude imine **19** with $NaBH(OAc)_3$ afforded **20** as P antagonist substance [37].

4-Cyanoquinuclidine (**24**) was prepared from pyridine-4-carboxamide (**21**). Its alkylation with 2-chloroethanol, followed by hydrogenation gave *N*-(2-ethanol) piperidine-4-carboxamide (**22**), which on treatment with thionyl chloride was converted into *N*-(2-chloroethyl) piperidine-4-carbonitril (**23**). On cyclization of **23**, compound **24** was obtained [38].



The quinuclidine nucleus is the bridged bicyclic core of naturally occurring cinchona alkaloids [39]. The quinuclidine derivatives might be elaborated through the bridging annulation of β-enamino ester (*S*)-**27** *via* asymmetric Michael-type cyclization, prepared from β-keto ester (*E*)-**25b**. Cyclization of **25b** with $CsCO_3$ led in 44% yield an inseparable mixture of diastereomeric, racemic quinuclidinones (±)-**25c** and (±)-**26**. The diastereomeric ratio **26/25c** (1:1.5) was established. Cyclization of the chiral β-enamino ester (*S*)-**27**, prepared from β-keto ester **25b** and (*S*)-(-)-1-phenylethylamine furnished the quinuclidinone (3*R*,4*S*)-**26** in 68% yield (90% enantiomeric purity accompanied with 10% of its stereomer **25c**).

The syn relationship between the acetate side chain at C_3 and the keto group in **26** was proved through derivatization into the tricyclic lactam **28** [40]. Synthesis of cinchona alkaloids, exemplified by the traditional antimalarial drug (-)-quinine **5** [41], based on the stereocontrolled aldol condensation of the quinuclidinone and related molecules [42]. Furtheremore,

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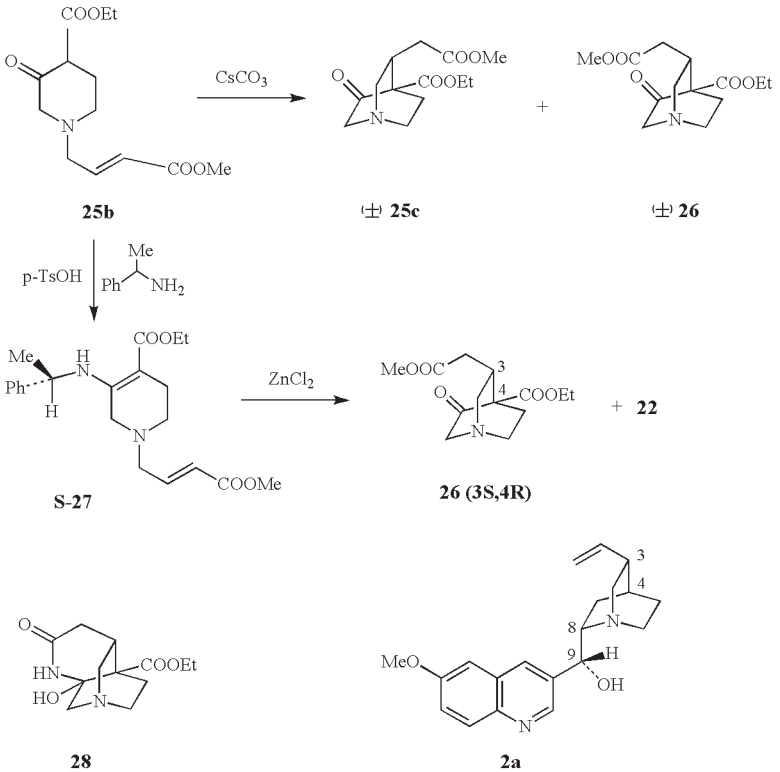
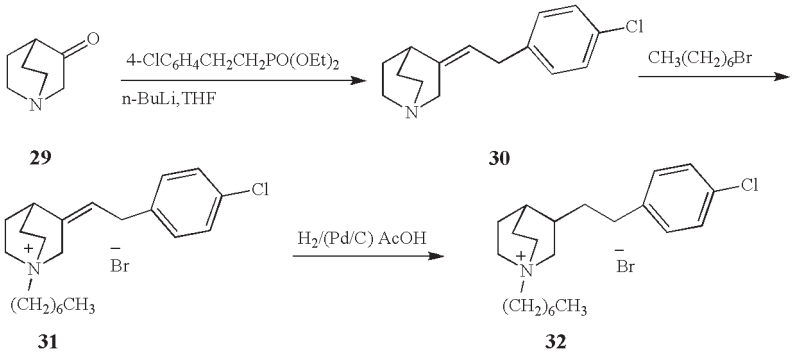
2.2. Methods of Introducing Constituents into the Quinuclidine Ring.

The Wadsworth-Emmons modification of the Witting reaction on quinuclidin-3-one (**29**) was carried out by

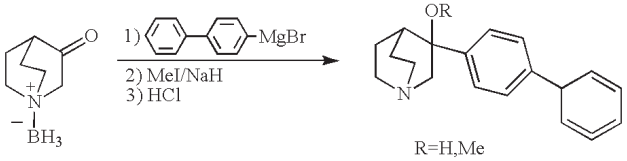


employing the anion derived from 2-(4-chlorophenyl)-ethylphosphonic acid diethyl ester as olefinating reagent, whereby the unstaturated quinuclidine derivative **30** was obtained. Its treatment with heptylbromide gave the quaternary ammonium salt **31**. Hydrogentation of **31** over Pd/C in acetic acid afforded the saturated ammonium salt **32**, which has cardiac electrophysiologiocal activity [43].



29 **30** **31** **32**

Reaction of the quinuclidin-3-one (N-B) borane complex (**33**) with the Grignard reagent from 4-(4-bromophenyl)benzene followed by methylation with MeI in the presence of NaH and subsequent deprotection of

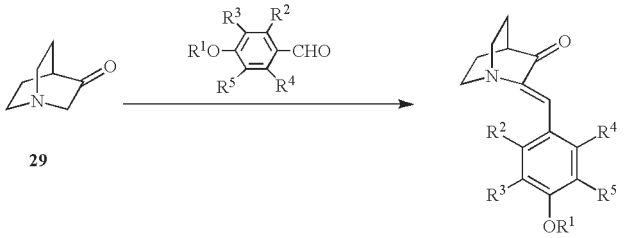


33 **34**

nitrogen atom with HCl gave the methyl ether **34** (squalene synthase inhibitor). In general, alkylation reactions of HO-substituted quinuclidines proceeded in poor yield, unless the quinuclidine ring nitrogen atom was protected as a borane complex [44].

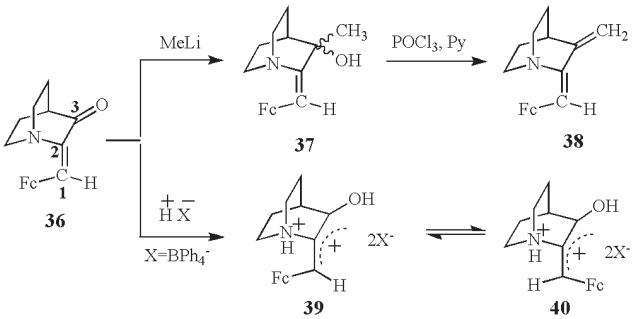
2-Benzylidine-3-quinuclidinone (**35**) was prepared *via* the base-catalysed condensation of quinuclidin-3-one (**29**) with benzaldehyde derivatives. However, when **35** was condensed with 4-(2-ethylhexyloxy)benzaldehyde gave the corresponding arylidine as a sunscreen agents [45].

The ferrocene (Fc) derivative, 2-ferrocenylmethylidenequinuclidone (**36**) [46,47] was prepared by condensation of 3-quinuclidene hydrochloride with ferrocenecarbaldehyde in the presece of base, was formed as



29 **35**

the *Z*-isomer **36**. Treatment of compound **36** with $HBPh_4$ yielded salts **39** and **40**.

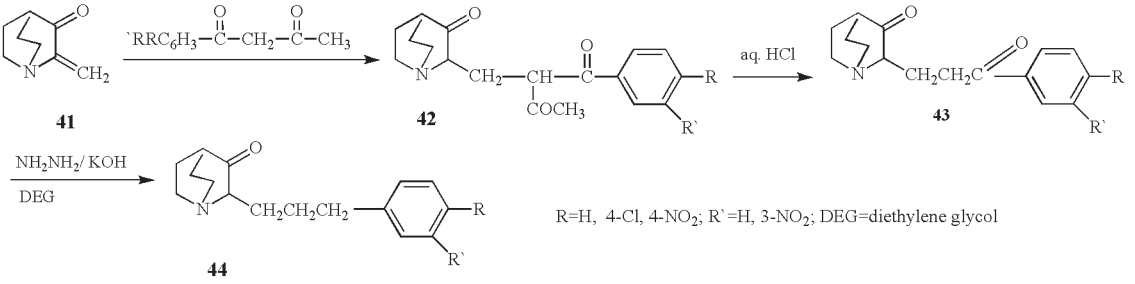


36 **37** **38** **39** **40**

Treatment of 2-methylene-3-quinuclidinone (**41**) with the appropriate benzoylacetone afforded compound **42**. Hydrolysis of **42** in aqueous hydrochloric acid readily proceeded to give diketones **43**. Wolff-Kishner reduction of **43** provided compound **44**, as antiarrhythmic agents [43].

(*R*)- and (*S*)-quinuclidine ester **50** as antimuscarinic bronchodilators [53].

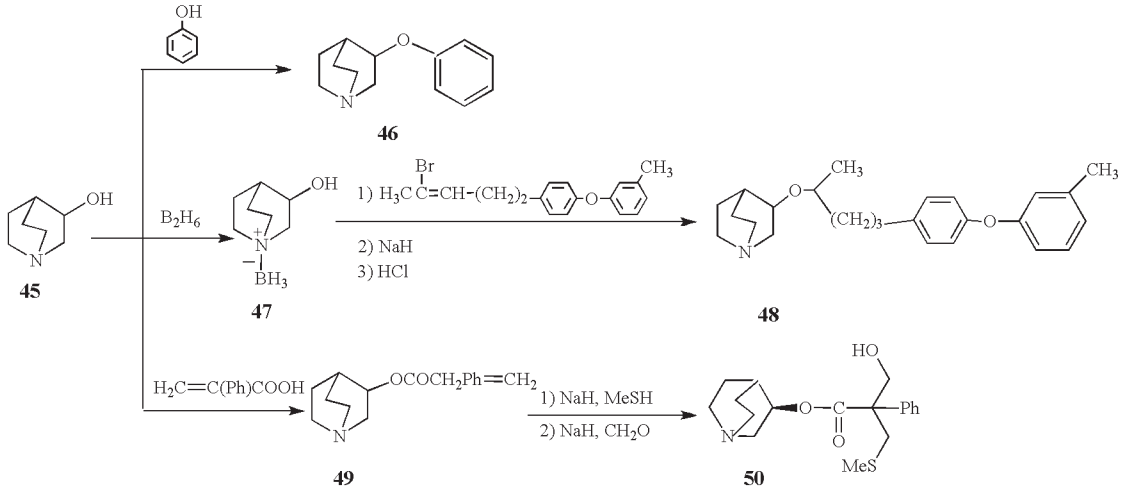
3-Quinuclidinol (**45**) was reacted with 2-hexyloxyphenyl isocyanate in PhMe to afford 70% of 2-hexyloxyphenylcarbamoyloxyquinuclidinium chloride



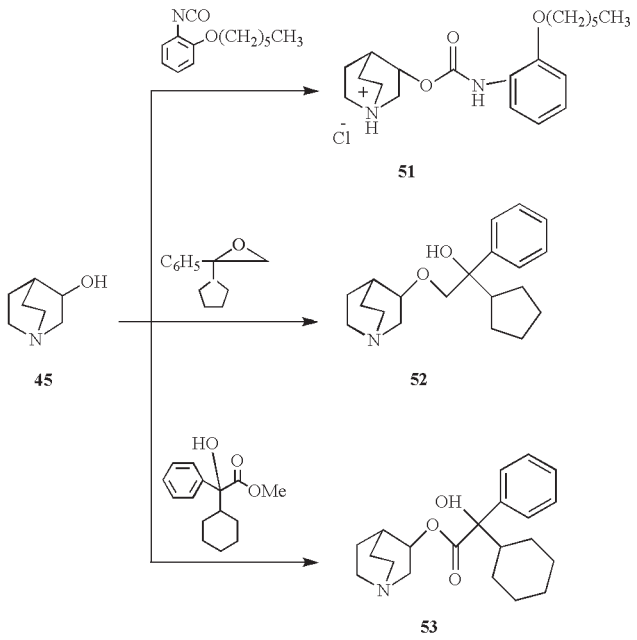
41 **42** **43** **44**

3-quinuclidinol (**45**) was condensed with PhOH to give compound **46** as psychanaleptic agent [49]. Another analogue to compound **46** evaluated as oxidosqualene cyclase as Antimicrobilal agent [50,51]. Compound **47**, which has high efficiency in liver membrane permeability and useful as squalene synthase inhibitors, was prepared by treatment of 3-quinuclidinol N-BH_3 complex (**47**) with NaH and then reacted with 5-[4-(3-methylphenoxy) phenyl]-2-pentenyl bromide to give **48** [52] after treatment with 10% aqueous HCl. Reaction of (*R*)-3-quinuclidinol (**45**) with phenylacrylic acid gave (*R*)-3-quinuclidinyl-2-phenylacrylate (**49**) which was treated with NaH and MeSH in $CHCl_3$ followed by NaH and paraformaldehyde in DMF to give (**51**) as tropical anesthetic [54]. In addition 3-(2-phenyl-2-cyclopentyl-2-hydroxyethoxy)quinuclidine (**52**) was prepared by catalytic trilation of 3-quinuclidinol (**45**) with 2-cyclopentyl-2-phenyloxirane [55]. Once more, 3-quinuclidinol (**45**) was reacted with methyl 2-cyclohexyl-2-hydroxy-2-phenylethanoate to give 3-(2-cyclohexyl-2-hydroxy-2-phenylacetate) quinuclidine (**53**) [56].

A potential muscarinic agent, 3-[(*N*-benzyl) acetamidoquinuclidin-2-ene (**56**) was prepared by acetylation of 3-benzylamine-3-cyanoquinuclidine (**55**), which was prepared from reaction of **54** with benzylamine [57].

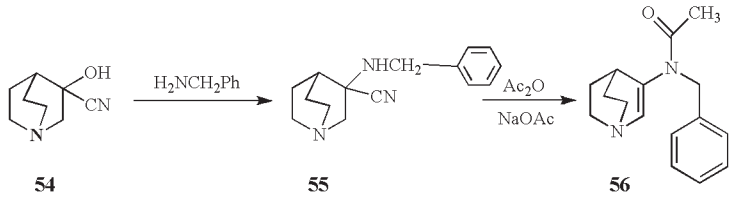


45 **46** **47** **48** **49** **50**



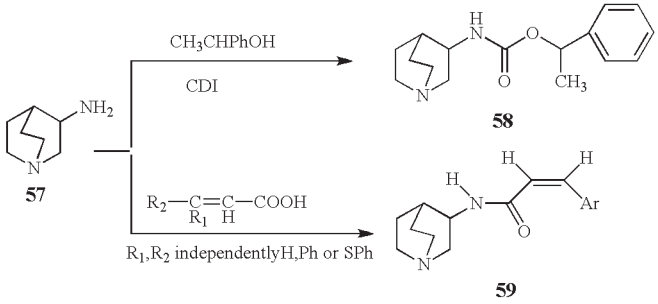
drochloride (**57**) [58]. Another example is the reaction of (*R*) 3-aminoquinuclidine (**57**) with *E*- 3-phenyl, or 3-(phenylthio) acrylic acid in the presence of 1-hydroxybenzotriazole hydrate, *O*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate and diisopropylethylamine in DMF to give (*R*),*E*-quinuclidine acrylamide derivative **59** which expected to have useful therapeutic activity [59,60].

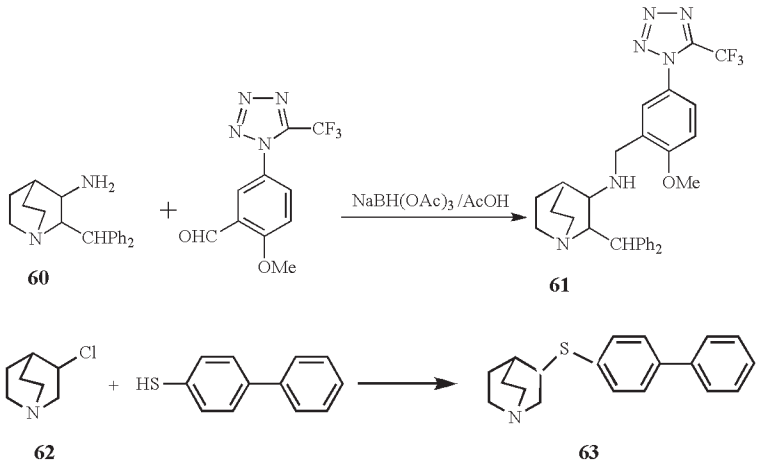
2-(Diphenymethyl)-3-aminoquinuclidine (**60**) was treated with 2-methoxy-5-[5-(trifluoromethyltetrazol-1-yl)]benzaldehyde in CH_2Cl_2 containing sodium triacetoxy borohydride and AcOH to give (**61**) [61], useful as P antagonist. Furthermore 3-chloroquinuclidine (**62**) was condensed with 4-PhC_6H_4SH to give biphenyl substituted quinuclidine **63** as squalene synthase inhibitors [62,63].



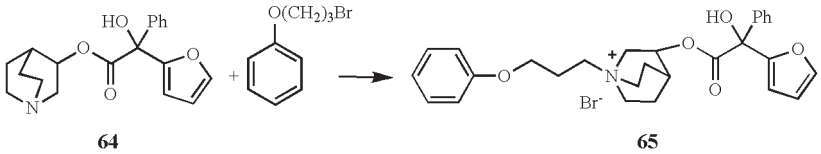
Moreover, the α-nicotinic acetylcholine receptor agonist quinuclidin-3-ylcarbamic acid derivative **58**, was prepared by treatment of 1-phenylethanol with carbonyldiimidazole (CDI) followed by addition of 3-aminoquinuclidine dihy-

Ultimately, the reaction of 3-phenoxypropyl bromide with (furan-2-yl)hydroxyphenyl- acetic acid quinuclidin-3-yl ester **64** produced 3-(2-furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(3-phenoxypropyl)quinuclidinium

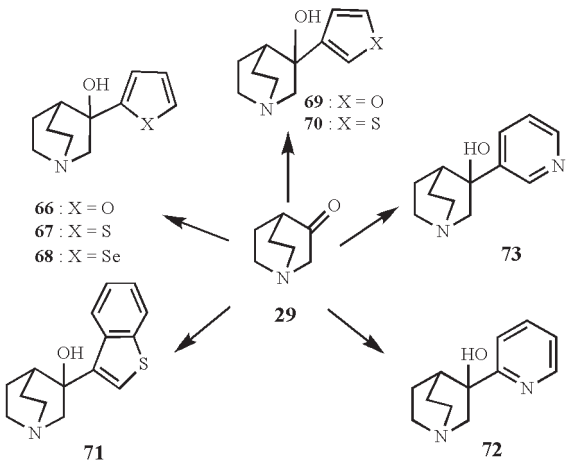




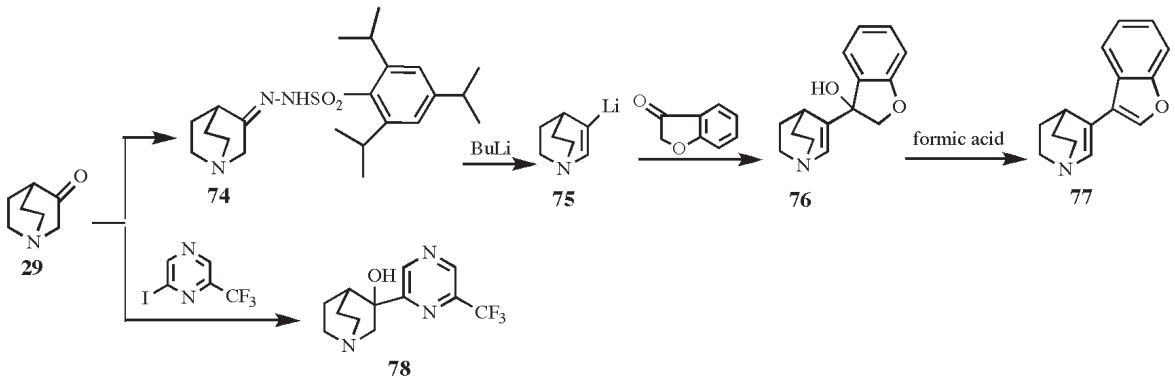
bromide(**65**) which is used as antimuscarinic agents [64,65].



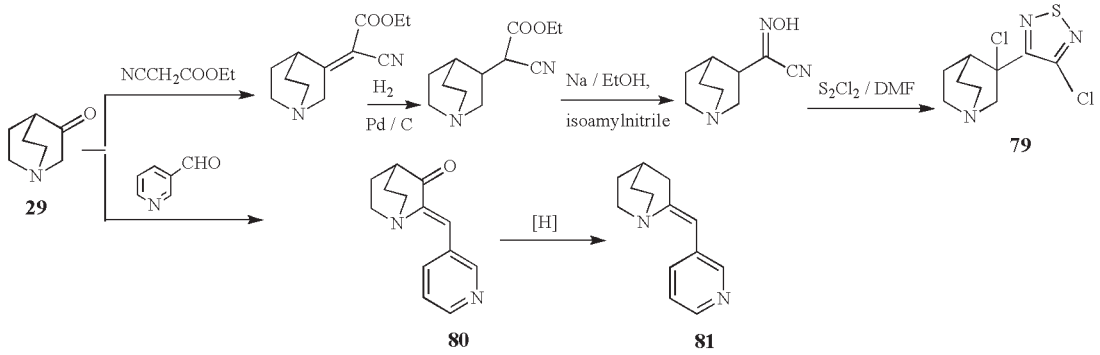
3-Heterocyclic-3-hydroxyquinuclidines **66-73** were synthesized by addition of **29** to the appropriate aryllithium compound in THF or ether. Dehydration of **66-71** and **73** to the corresponding quinuclidin-2-ene analogues was readily accomplished by heating a solution of the hydroxy compound in concentrated formic acid [66,67].



Since generation of 3-benzofuranyllithium and subsequent reactions with different electrophiles have most frequently resulted in low yield of the expected addition products due to the competitive ring opening of 3-benzofuranyllithium. Thus, the preparation of 3-(3-benzofuranyl)quinuclidin-2-ene (**77**) was made by treatment of the quinuclidin-3-[(2,4,6-triisopropylphenyl) sulphonyl] hydrazone (**74**) with *n*-BuLi whereby 3-lithioquinuclidin-2-ene (**75**) was generated. Its reaction with the commercially available 2,3-dihydrobenzofuran-3-one gave **76**. Dehydration of **76** to **77** was accomplished by heating a solution of **77** in formic acid [67]. Treatment of 2-iodo-6-(trifluoromethyl)pyrazine with quinuclidin-3-one (**29**) gave **78** [68].

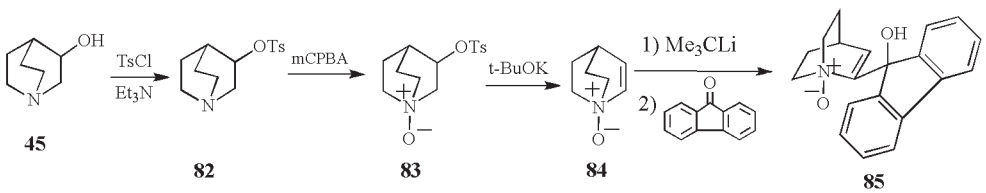


Reaction of **29** with $NCCH_2COOEt$ followed by hydrogenation of the intermediate cyanoester over Pd/C, then treatment of ethyl cyanoacetate derivative with Na/EtOH and isoamylnitrile and cyclization of the product with sulfur monochloride (S_2Cl_2)/DMF afforded the thiadiazolyl derivative **79** which is useful for treatment of Alzheimer's disease. However, 2-(3'-methylenepyridyl)-3-quinuclidinone (**80**), prepared from condensation of quinuclidin-3-one (**29**) with pyridine-3-carboxaldehyde, was reduced to give 2-(3-methylpyridyl)quinuclidine (**81**) which used as inhibitor of nicotinic cholinergic receptors [70].



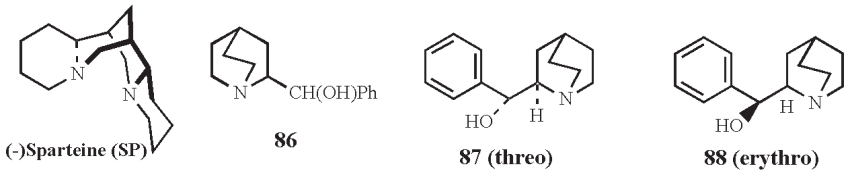
The use of quinuclidine N-oxide (**84**) as a potential replacement for hexamethylphosphoric triamide (HMPA) in a number of synthetically important reactions was very promising [71]. In order to increase the scope of this reagent system, Neil [72] investigated that the incorporation of additional metal binding sites -- to the nitrogen would increase the metal binding capability of these reagents and also he predicted that selective deprotonation of enamine N-oxide **84** at the unsaturated α-carbon should be possible, allowing for the functionalisation of this position.

Treatment of 3-quinuclidinol (**45**) with tosyl chloride in the presence of Et_3N gave 3-quinuclidinol tosylate (**82**) in 90% yield. Treatment of **82** with m-chloroperbenzoic acid (mCPBA) gave the quinuclidinol tosylate N-oxide (**83**) in 76% yield that undergoes elimination reaction with Me_3COK to give the enamine N-oxide **84** in 80% yield. This species has been shown to undergo clean lithiation at the vinylic position and the resulting carbanion can be trapped out with a range of electrophiles. Furthermore, treatment of **84** with Me_3CLi in THF followed by addition of 9-fluorenone gives the quinuclidine **85** in 85% yield [72].



Quinuclidine compounds have proved to be effective catalytic chiral control elements in a wide range of reactions [73-76]. Lygo have used Sharpless epoxidation to induce asymmetry and stereo divergent cyclization of the resulting diols to form quinuclidine alcohol **86** [77].

while no deprotonation is observed when **84** is treated with a preformed complex of RLi and (-)-sparteine. These results indicated that only a sequential association of **84** with RLi and (-)-sparteine leads to the complex undergoing enantioselective deprotonation [76].

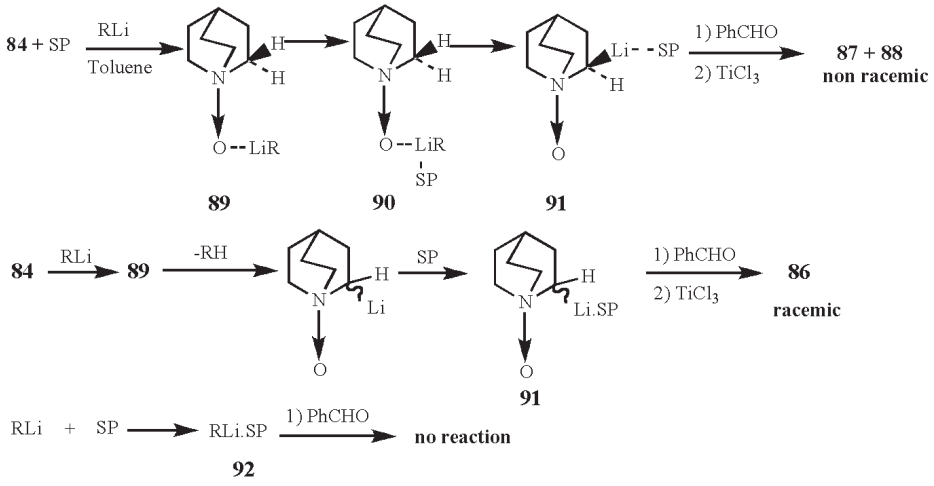


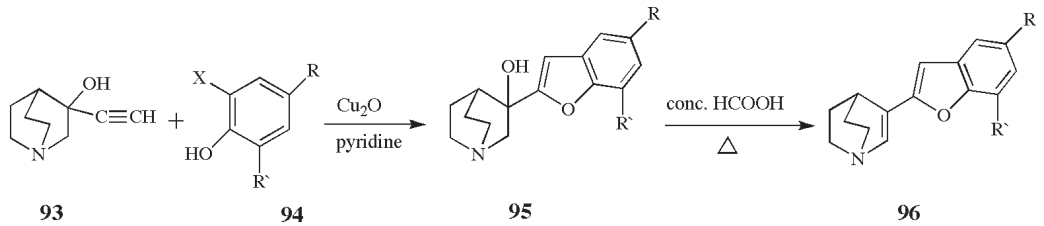
Kessar [78] describe the results concerning enantioselective synthesis of **86** using (-)-sparteine (SP) as an added chiral ligand in Barton elaboration of quinuclidine N-oxide (**84**) [79]. Sparteine mediated enantioinduction at carbanionic centres is a well estabilised strategy of asymmetric synthesis by work of Beak and Hoppe [80-82].

Addition of RLi to a mixture of quinuclidine N-oxide (**84**) and (-)-sparteine followed by quenching with benzaldehyde give threo (**87**, 34% ee) and erythro (**88**, 40% ee) adducts with moderate enantioselectivity. Reaction of RLi with (**84**) followed by treatment with (-)-sparteine prior to electrophile addition afforded racemic products

3-(2-Benzofuranyl)-3-quinuclidinols (**95**) (novel muscarinic antagonists) were synthesized by using the Stephens-Castro cyclization [83]. Thus, when 3-ethynyl-3-quinuclidinol (**93**) and the appropriate *ortho*-halogenated phenol (**94**) heated with Cu_2O in pyridine, the quinuclidinol derivative **95** was obtained. Dehydration of **95** to the corresponding quinuclidin-2-ene derivatives **96** was accomplished by heating in concentrated formic acid [84].

Preparation of quinuclidinyloxy-substituted oxadiazoles and related compounds as muscarinic and nicotinic cholinergic agent was carried out by lithiation of 3-quinuclidinol



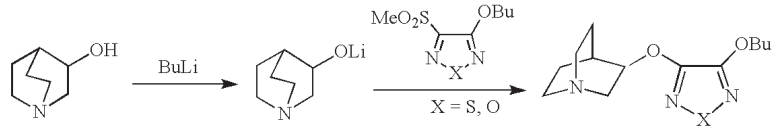


93 **94** **95** **96**

R = CHO, Br, H, F, NO_2; R` = OMe, H, Br, I, CHO

(45) with BuLi. Its etherification by 3-butoxy-4-(methanesulfonyl)-1,2,5-thia(oxa)diazole derivative in THF afforded 3-butyloxy-4-(1-quinuclidin-3-oxy)-1,2,5-thia(oxa)diazoles (97) [85-87].

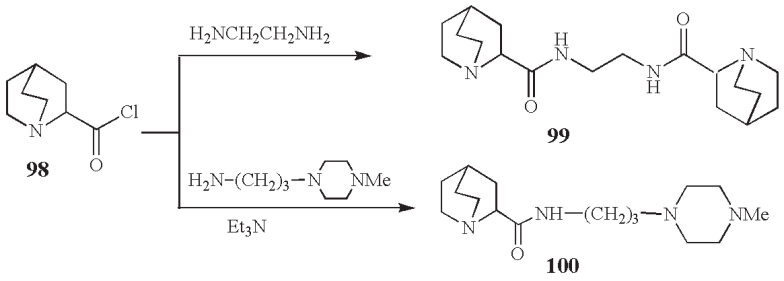
Total synthesis of the 5-HT_3 [91,92] receptor antagonist palonosetron (**107**) used as anti-emetic in cancer chemotherapy is prepared by condensation of 1,8-naphthalic anhydride with 3-aminoquinuclidine (**57**) to give



45 **97**

Ethylenediamine reacts with 2-quinuclidinylcarbonyl chloride (**98**) to give the corresponding dimer **99** [88]. Furthermore, compound **98** was reacted with 3-(4-methylpiperazin-1-yl) propylamine in C_6H_6 in the presence of Et_3N to yield **100** [89]. Analogous compounds were prepared using 4-phenyl piperazine, 4-aminomorphiline and furfurylamine instead of 3-(4-methylpiperazin-1-yl)propylamine.

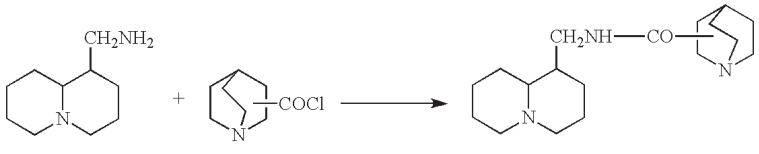
the imide **103** which was isolated as the trifuluoroacetic acid (TFA) salt. The imide **103** was subjected to catalytically hydrogenation to reduce one of the aromatic rings producing **104**. Selective reduction of the carbonyl group of the imide **104** at C-3 to a hydroxyl group is made by using sodium borohydride to give **105**. The selectivity of the borohydride reduction for the C-3 carbonyl group closer to the alicyclic ring over the C-1 car-



98 **99** **100**

Synthesis of 1-substituted derivatives of quinolizidine **101** by N-acylation of 1-(aminomethyl)quinolizidine with 2-and 3-quinuclidincarbonylchloride hydrochlorides gave the amides **102** [90].

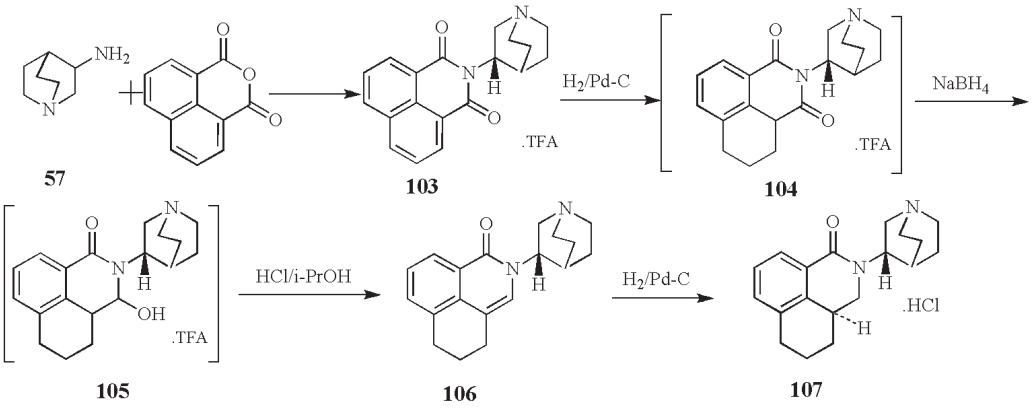
bonyl next to the aromatic nucleous was rationalized by steric hindrance of approach of the hydride. Compound **105** was dehydrated to **106**, which was converted to palonosetron (**107**) by catalytic hydrogenation of the



101 **102**

free base of **106**.The serotonin 5-HT_3 receptor subtype is unique among the receptors for this neurotransmitter because it has been demonstrated to be a ligand-gated ion channel capable of mediating rapid intercellular communication [93].

The general route for the synthesis of compounds in the above scheme is exemplified by the preparation of the pyrido[4,3-*b*]indolones **112**. Treatment of N-quinuclidinyl-3-amide derivative **118** with 2-equivalent of BuLi produced the dilithio derivative which was then

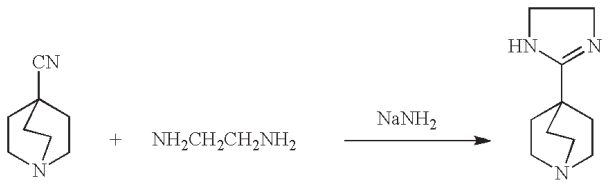


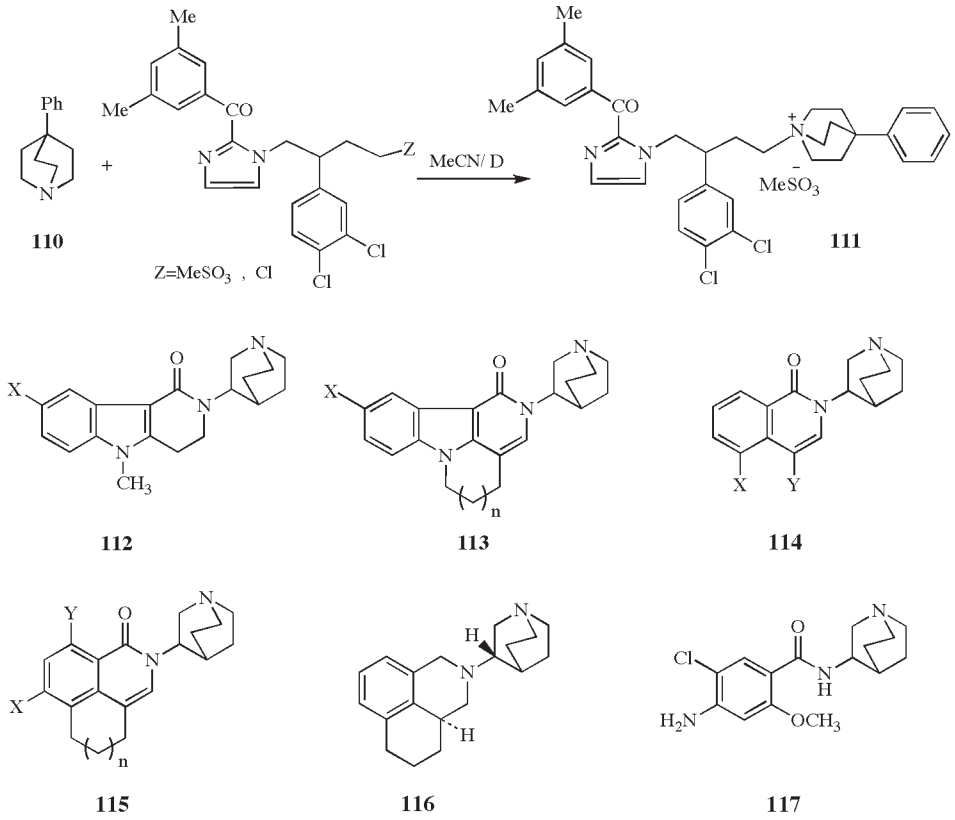
4-Heterocyclic quinuclidine **109** was prepared by condensation of 4-cyanoquinuclidine (**108**) with ethylenediamine and *tert*-butyl alcohol in the presence of $NaNH_2$ in THF to give 4-(2-imidazolin-2-yl) quinuclidine (**109**) [94].

Reaction of 4-phenylquinuclidine (**110**) with 1-methylsulfonyloxy-3-(3,4-dichlorophenyl)-4-[2-(3,5-dimethylbenzoyl)imdazol-1-yl]butane in MeCN under reflux gave **111** as tachykinin antagonists [95]. Several series of N-(quinuclidin-3-yl)aryl and heteroary-fused pyridones **112-116** [96] and benzamide **117** [97] were synthesized [98].

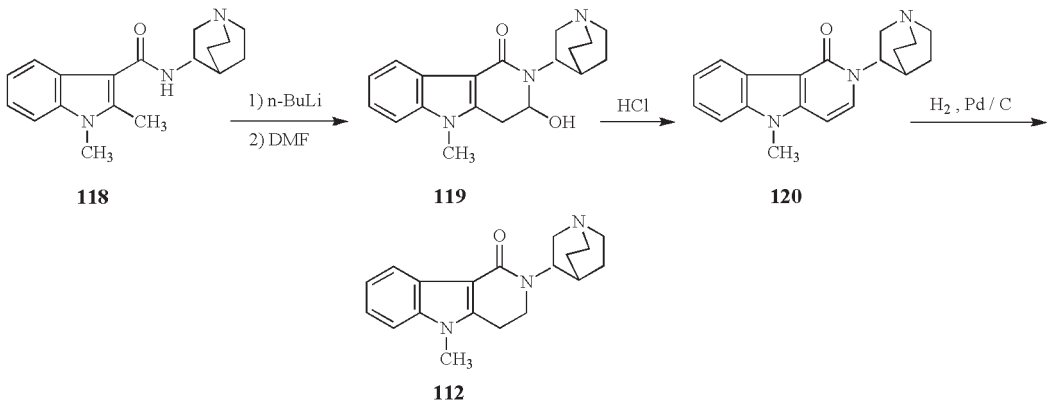
quenched with DMF to provide the amidol **119**. Without isolation, this intermediate was dehydrated by treatment with aqueous HCl to yield **120**. Catalytic hydrogenation of **120** afforded 2-(quinuclidin-3-yl)-2,3,4,5-tertrahydro-5-methyl-1*H*-pyrido[4,3-*b*]indol-1-one hydrochloride (**112**) as 5-HT_3 receptor antagonist [98].

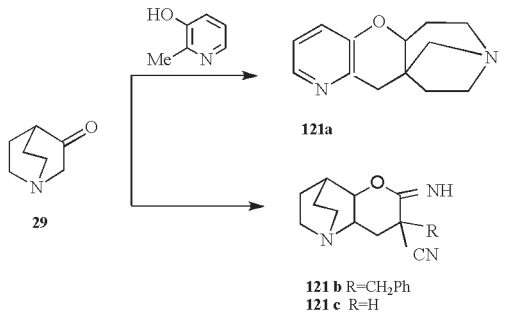
Condensation of quinuclidine-3-one (**29**) with 2-methyl-3-hydroxypyridine and the product obtained was cyclized with rearrangement to give **121a** [99a] as α,β-nicotinic receptor ligands. Also1-azabicyclo-[2.2.2]octane-3-one (**29**) as hydrocloride salt react with ylidene nitrile through photo-thermal reaction condi-





tions to give 4-benzyl-5-imino-3-phenyl-6-oxa-1-aza-tricyclo[6.2.2.$0^{2,7}$] dodec-2(7)-ene-4-carbonitrile (**121b**) *via* intermolecular double Micheal reaction, whereas, 5- imino-3-phenyl-6-oxa-1-aza-tricyclo-[6.2.2.$0^{2,7}$] dodec-2(7)-ene-4-carbonitrile (**121c**) was achieved *via* thermal condition only [99b].

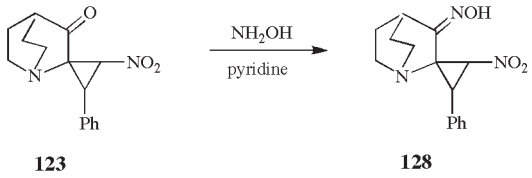




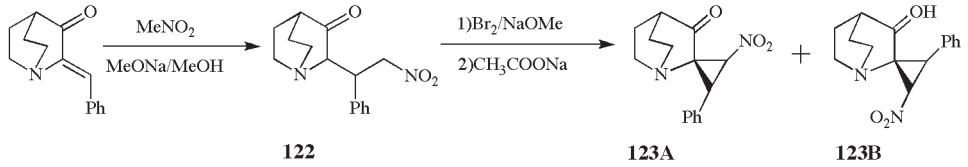
3'-Keto-1-nitro-2-phenylspiro(cyclopropane-3,2'-quinuclidine) (**123**) was synthesized according to the method of Smith and Engelhardt [100]. Micheal addition of nitromethane anion to 2-benzylidine-3-quinuclidinone gave 2-(2-nitro-1-phenylethyl)-3-quinuclidinone (**122**) as an equimolar mixture of diastereomers. Bromination of **122** followed by dehydrobromination in the presence of base produced **123** [101] as the only stereoisomers in a moderate yield. Alternatively, direct oxidation of **122** using potassium hexacyanoferrate produced an equimolar mixture of the isomers **123A** and **123B**. Compound **123** was a key intermediate to synthesize fused heterocyclic ring with quinuclidine moiety.

the fused pyrrolidone derivative **126**. The Lewis acid, iron trichloride, smoothly converts **123** into **127** in a moderate yield [101].

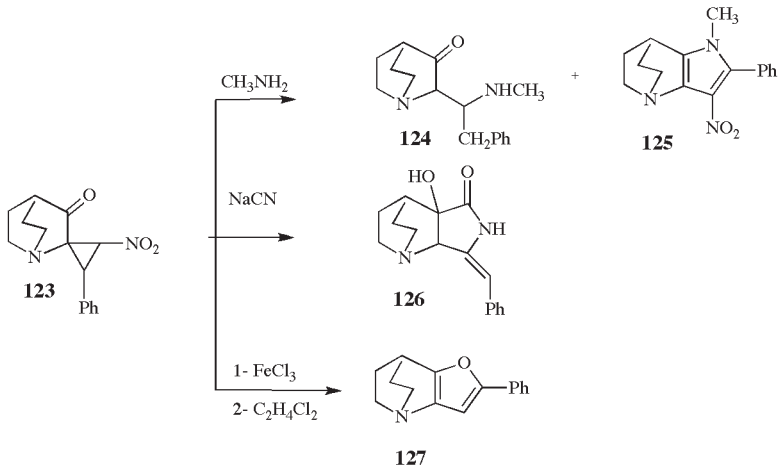
Condensation of **123** with hydroxylamine hydrochloride in pyridine gave **128** [101]. However, new quinuclidine derivative with 3-spiro annelated oxathioline **131**, furanone **133** and pyrrolionone **135** heterocycles with antimuscarinic properties have been synthesized from 3-mesyloxy (**130**), 3-acetoxy (**132**) and 3-acetamidoquinuclidine-3-carbonitrile (**134**), respectively by treatment with base [57].

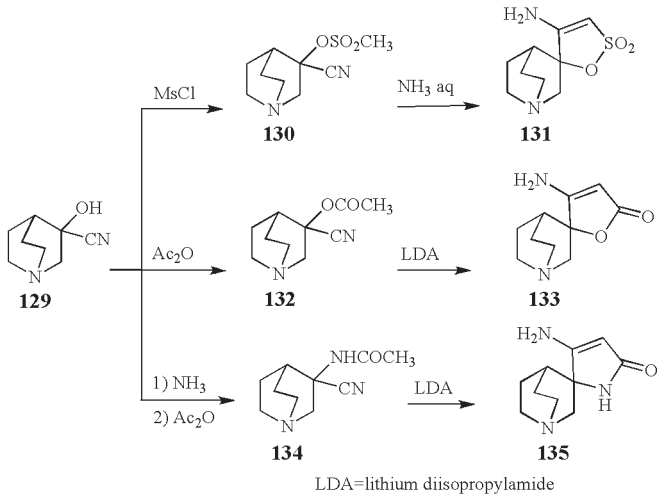


The precursor *tert*-butyl-2-(3-hydroxyquinuclidin-3-yl) acetate, was prepared by addition of Me_3COAc then



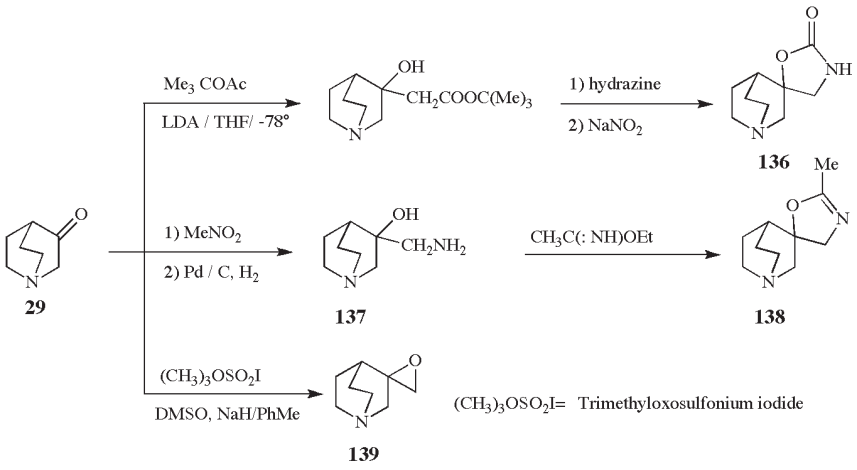
Reaction of **123** with methylamine gave methylamino derivative **124** together with the pyrrole derivative **125**. However reaction of **123** with sodium cyanide produced quinuclidin-3-one (**29**) to lithium diisopropylamide (LDA) in THF at -78 ºC. This was converted to the hydrazide, which in aqueous HCl was treated with





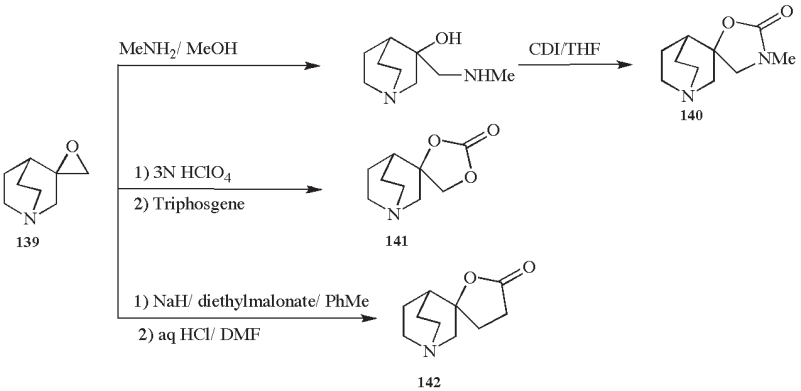
aqueous $NaNO_2$ at 0 ºC to give 3-spiro[quinuclidine-3,5'-oxazolidine]-2'-one hydrochloride (**136**) [102].

ethyl acetamidate hydrochloride to give 3-spirooxazoline quinuclidine derivative (**138**) as cholinergic agents [103].



Condensation of quinuclidin-3-one (**29**) with $MeNO_2$ followed by hydrogenation over Pd/C gave 3-aminomethylquinuclidin-3-ol (**137**). The latter was stirred with

Quinuclidin-3-one (**29**) when treated with trimethyloxosulfonium iodide, DMSO, and NaH in PhMe afforded 3-methylenequinuclidine oxide (**139**) in 86.2% yield [104].

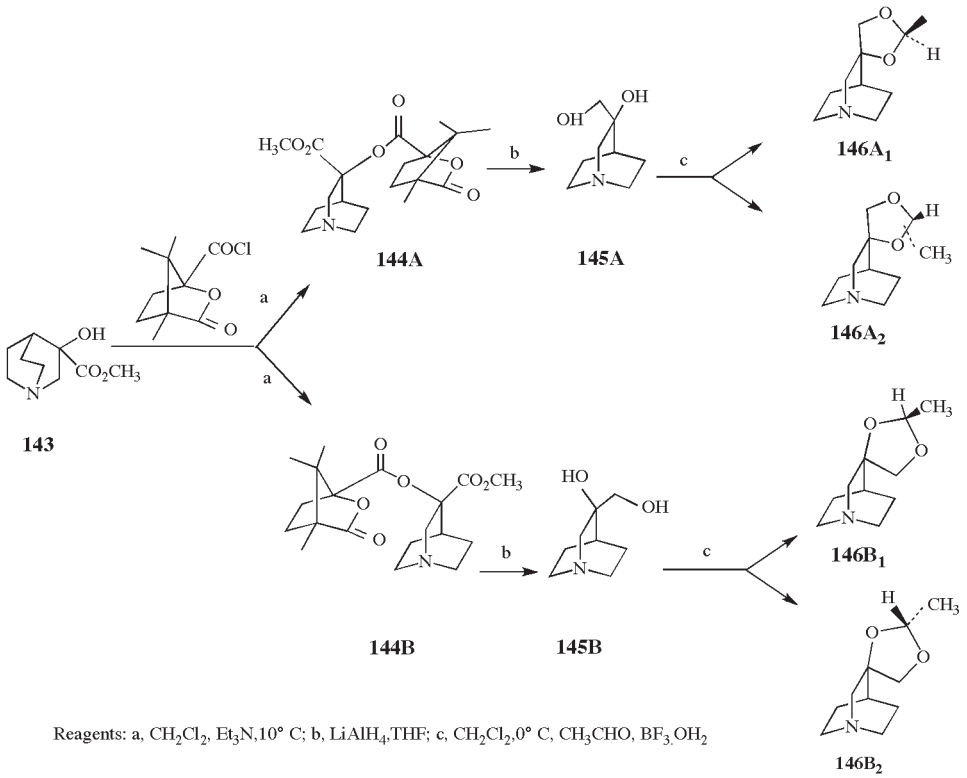


A number of quinuclidine derivatives were synthesised due to their muscarinic agonist activity, [106-108] for example, the synthetic route to the separated isomers of **146** *via* the diastereomeric camphanate ester **144** derived from (-)-camphanic acid chloride was achieved. Thus, the camphanate esters **144** were separately reduced with $LiAlH_4$ to give two enantiomeric diols **145**, which were converted directly to the spiro dioxalane. In each case, the concomitant introduction of a second chiral center generated two new diastereomeric compounds. The two dioxolanes (**146A$_1$**, and **146A$_2$**) derived from **144A** and, of course, (**146B$_1$**, and **146B$_2$**) derived from **144B** were also readily distinguished by the appearance of the **AB** pattern resulting from the methylene protons in the dioxolane ring [106].

of the hydroxy ester **147** with hydrazine followed by Curtius rearrangement [105]. Moreover, spirooxazolidinone **149** and spiroimidazolidinone **150** derivatives may be synthesized through the amino intermediate **148** as presented in the following scheme [105].

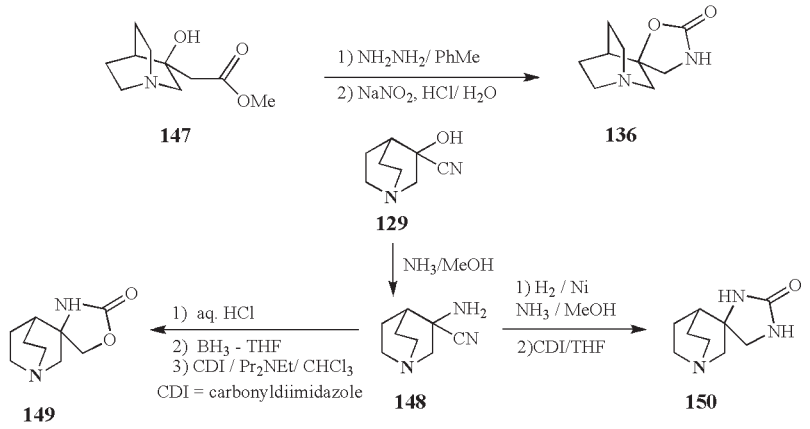
3. Reactions of Quinuclidine Derivatives.

(*R*)-Quinuclidin-3-ol (**45**), is useful as an intermediate for drug synthesis, pesticides and other physiologically active substances. It is manufactured by stereoselictive reduction of quinuclidin-3-one (**29**) in aqueous medium in the presence of Alcaligenes, Corynebacterium, Arthrobactor, Filobasidium, Rhodotorula, Aureobasidium or Yarrowia [109].



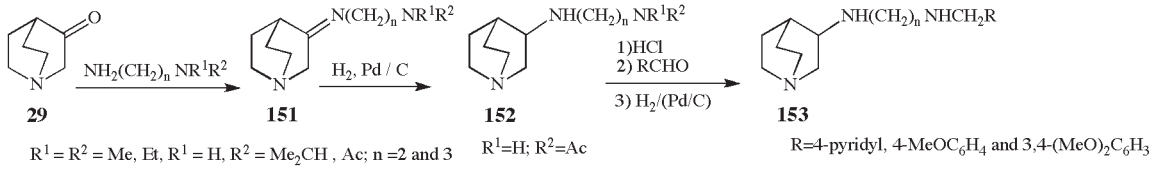
The spirooxazolidinone **136** has a potent full agonist at the rate α_7 nicotinic receptor was achieved by the reaction

Various Schiff bases (**151**) were prepared from quinuclidin-3-one (**29**) and the appropriate amine, $NH_2(CH_2)_n$



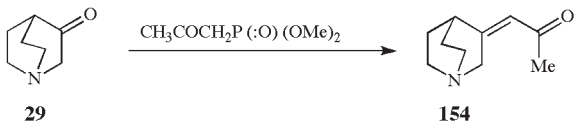
NR^1R^2. The Schiff bases were hydrogenated on Pd/C to yield the corresponding amines (**152**). Deacetylation of **152** (R^1= H, R^2= Ac) with HCl and reaction with different aldehydes followed by hydrogenation afforded the corresponding **153** derivatives [110].

thesis will provide access to a new class of dopamine transporter inhibitors that may be useful in the development of medications for the treatment of cocaine abuse. For example, 2-butyl-3-phenylquinuclidine (**159**) was prepared as presented in the following scheme starting from 2-methylene-3-quinuclidinone (**41**) [112]. Reaction of **41**



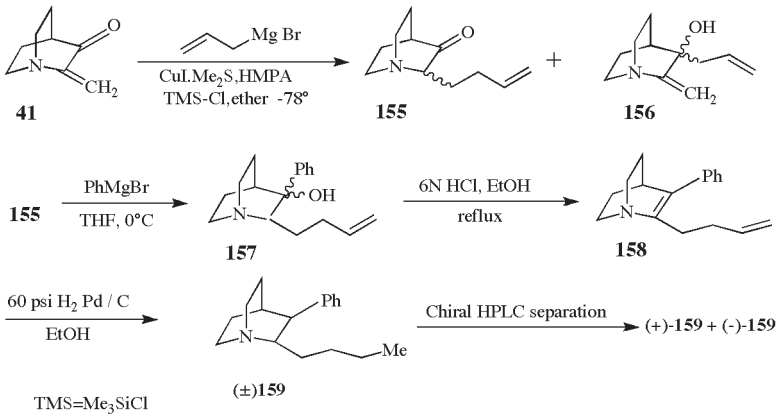
Wittig-type reaction of quinuclidin-3-one (**29**) with $CH_3COCH_2P(:O)(OMe)_2$ in aqueous NaOH gave *E*-isomer **154** which was isolated as oxalate as in 21% yield. Its *Z*-isomer showed nicotinic cholinegic activity [111].

with allylmagnesium bromide in the presence of CuI, Me_2S and Me_3SiCl at -78 ºC furnished the conjugate addition product **155** in 47% yield along with the 1,2-addition product **156** in 12% yield. Addition of phenylmagnesium bromide to **155** was carried out in THF at 0 ºC to give **157**,



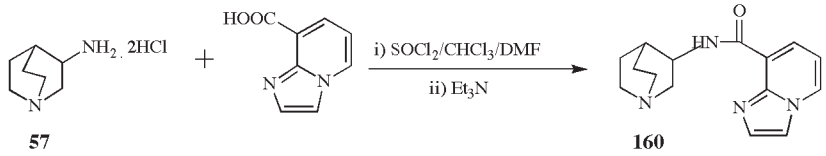
The synthesis of 2-alkyl-3-aryl substituted quinuclidines has been accomplished in a four step sequence. This synwhich were treated with (1:1) mixture of EtOH an 6N HCl under reflux condition to give the dehydrated compound

158. Reduction of the double bonds was carried out using standard hydrogenation condition (60 psiH_2, pd/C,EtOH) to provide enantiomers **159** which were separated by using chiral HPLC.



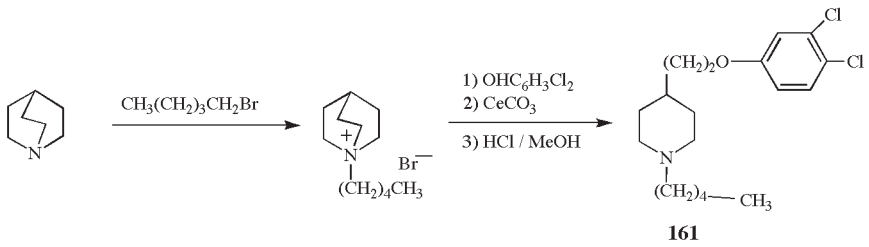
Amidation of (*R*)-3-aminoquinuclidine dihydrochloride with different aromatic or heterocyclic acid derivatives has been implemented [113-116]. As an example, compound **160** was obtained by treatment of imidazo[1,2-*a*]pyridine-8-carboxylic acid.2HCl in $CHCl_3$/DMF with $SOCl_2$ followed by addition of 3-aminoquinuclidine.2HCl (**57**) and Et_3N. Compound **160** is useful as 5-HT_3 antagonist [113].

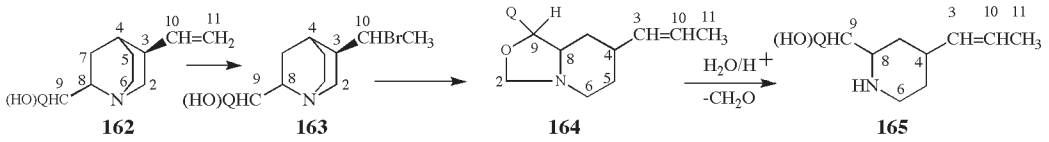
Hydrobromination of cinchona alkaloid vinyl groups **162** afforded 10-bromo-10,11-dihydro diastereomers **163** with an additional stereogenic center at C-10. These derivatives are convenient substrates for new transformation of the parent alkaloids [118-120]. Then



rearrangement of 10-halo derivatives **163** to **164**, which results in the formal loss of the C-2 carbon atoms in the form of formaldehyde, gave nicinquines [121]. Treatment of a mixture of 4-cyanoquinuclidine (**108**) in

Quinuclidine was quaternized with 1-bromopentane and





162 **163** **164** **165**

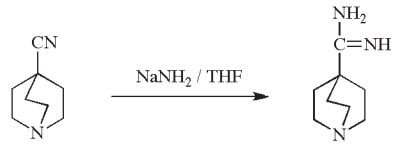
a: 8R, 9S-cinchonine
b: 8S, 9R-quinine

a: 8R, 9S-10-bromo-10,11-dihydrocinchonine
b: 8S, 9R,10R-10,11-dihydroquinine
c: 8S, 9R,10S-10-bromo-10,11-dihydroquinine

a: 4S, 8R, 9S
b: 4S, 8S, 9R

a: 4S, 8R, 9S
b: 4S, 8S, 9R

162, 163, 164, 165; Q=quinolyl



108 **166**

BuOH with $NaNH_2$ suspended in THF gave 74% yield of 4-carbamoylquinuclidine (**166**) [122].

4. Conclusions.

The present review has outlined the structure, basicity, its uses as asymmetric organocatalysis, and the progress of synthetic routes and some reactions of quinuclidines, which is a nitrogen bicyclic bridged-ring structure, in the last two decades. The vast majority of these important compounds still require further exploration and application, especially as nucleophilic asymmetric catalysts and as sunscreen, antiarrhythmic, antidiarrheal and antimuscarinic agents. Also, it revealed that their alkaloids derivatives (cinchona alkaloids), and in particular cinchonidine are versatile chiral modifiers of Pt and Pd in heterogeneous asymmetric hydrogenation and as chiral Lewis bases used for the Baylis-Hillman reaction.

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