AN UP-TO-DATE ANALYSIS OF THE CHEMISTRY OF PIPERIDEINE-3* (REVIEW)

G. V. Grishina, S. O. Bachurin. S. E. Tkachenko, and N. S. Zefirov

The chemistry of piperideine-3 and its derivatives is generally linked with the synthesis of biologically active substances and medicinals. This review discusses the most interesting chemical reactions of piperideine-3 and its derivatives which have been discovered in the last 10-15 years.

The chemistry of piperideine-3 developed early and the first synthetic work in this area appeared at the end of the last century. Recent reviews have considered results from the 60s and 70s [1-8]. In the mid-80s when the possibilities of chemical transformation of the tetrahydropyridine nucleus appeared to be exhausted and interest in these compounds was fading, the high neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was discovered. As a result an enormous amount of medico-biological papers appeared. In consequence of the discovery that a substance used for many years by various researchers was highly neurotoxic, synthetic chemists addressed themselves to the problem of making derivatives of piperideine-3 with new types of biological activity.

But we shall first examine in some detail why the pharmacological and biochemical aspects of this class of compound have aroused such interest.

1. PHYSIOLOGICAL ACTIVITY

We note to begin with that many piperidine and more complex alkaloids contain the 3-piperideine nucleus [4].

Historically the first known were the alkaloids of the areca palm — arecoline Ia and arecaidine Ib, isolated in 1888-1891 by Johns. Guavicine Ic (norarecoidine) and guavacoline Id (norarecoline) were isolated later. Arecoline is similar in physiological activity to muscarine and acetylcholine. It lowers blood pressure, increases salivation, and causes myosis and contraction of smooth muscles. The tobacco alkaloids anatabine IIa and N-methylanatabine IIb (Späth, 1937), the secondary alkaloid lobeline (stereoisomers of lobinine and isolobinine III) are also derivatives of piperideine-3. The latter show strong nicotine like effects and stimulate respiration strongly.

The ergot alkaloids should also be noted - ergotamine, ergotoxin, ergometrine, etc., with the general formula IVa, and lysergic acid diethylamide IVb which is currently considered to be one of the most powerful synthetic hallucinogens. All of these alkaloids contain the 3-piperideine nucleus.

As this very brief cross section of alkaloids shows, the range of physiological of piperideine-3 derivatives is broad and varied. An analogous situation has been observed for medicinals. Chemical Abstracts citations for the R-N-4-arylpiperideine-3 structure alone show that more than 500 physiologically active substances containing the 3-piperideine fragment and possessing more than 30 types of biological activity have been patented recently. However a multitude of other compounds shows similar therapeutic effects (analgesic, neuroleptic, sedative, etc.). A new and unique type of physiological activity was observed in 1983 for 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) V. The clinical picture of Parkinsonism was observed when MPTP

*Dedicated to Professor A. R. Katritsky on his 65th birthday.

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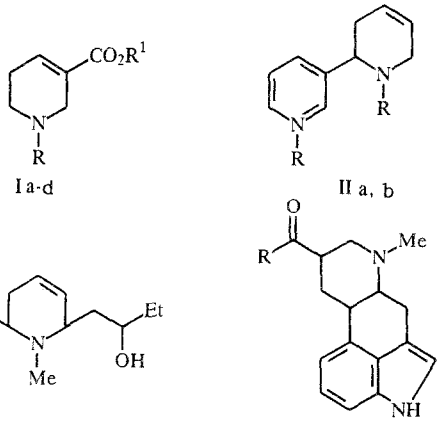
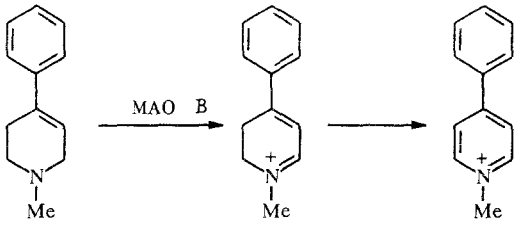


I a-d II a, b III IV a, b

I a R = R^1 = Me, b R = Me, R^1 = H, c R = R^1 = H, d R = H, R^1 = Me; II a R = H, b R = Me;
IV aR = NH-polypeptide, b R = NE_{12}

was given to mammals and man. Historically as a result of the study of unusual cases of Parkinsonism in young people who had taken the illegal narcotic derivative "synthetic heroin" (1-methyl-4-phenyl-4-propionyloxypiperidine hydrochloride -- an inverse analog of meperidine), it was established that MPTP causes specific degradation of the dopaminergic neurons of the *substantia nigra* of the brain and the development of a complex of behavioral symptoms corresponding completely to the picture observed in Parkinson's disease [5, 6].

A number of conclusions about the biochemical mechanism giving rise to the highly selective neurodegradative properties of MPTP have been drawn as a result of the many studies carried out recently [7, 8]. Because MPTP is not charged at physiological pH values it readily passes the blood-brain barrier and undergoes biotransformation: The two stage dehydrogenation catalyzed by monoaminooxidase B is of particular importance. The initially formed 2,3-dihydropyridinium compound VI (MPDP) is then oxidized to the 1-methyl-4-phenylpyridinium cation VII (MPP):



V VI VII

The pyridinium metabolite MPP VII is specifically transported into the reversible dopamine receptors of the dopamine neurons [9, 10] where it affects a number of intracellular targets. In particular it inhibits tyrosine-3-hydrocouplase [11] and oxidative phosphorylation in mitochondria [12] which causes destruction of the cells.

This sequence of reactions determines the high selectivity of MPTP relative to the dopamine neurons of the CNS permits a choice of neuroactive compounds among the large number of structurally similar compounds to be made.

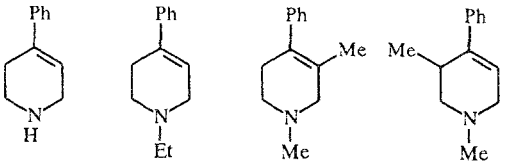
MPTP is being actively used at present in medico-biological studies to obtain a more satisfactory modelling of Parkinsonism in laboratory animals (monkeys, mice) in order to study the development of this neuropathology and to devise methods to prevent and to correct it pharmacologically [13]. The recent discovery of a series of 1,2,3,4-tetrahydroisoquinoline analogs of MPTP of natural (components of foods) and even endogenous origin has raised questions about their direct involvement in some types of idiopathic Parkinsonism [14]. On the other hand the wide distribution of structural analogs of MPTP as ecopoisons, pesticides, and medicinals provides the basis for an analysis of the ecotoxicological principles for the formation and development of similar illnesses [15, 16] and the establishment of structure-activity connections for a wide range of xenobiotics which are potential analogs of MPTP [17]. The MAO B catalyzed oxidation of MPP is highly structure specific and consequently a large body of research is connected with studies of the neurotoxicity of MPTP analogs. The following connections have been established:

1. Compounds with fully saturated of fully unsaturated pyridine rings are not substrates for MAO [18, 19].

2. A variety of MPTP analogs with different substituents in the phenyl ring (*p*-, *m*-OMe [20], *o*-Me [21]) undergo oxidation by MAO and are more or equally neurotoxic.

3. Neurotoxicity is almost completely lost when the 1-methyl substituent is replaced by ethyl (1-ethyl-4-phenyl-piperideine-3 (IX)) which permits the use of 1-ethyl derivatives for the synthesis of new medicinals without the formation of neurotoxic intermediates.

4. Homologs of MPTP with methyl groups in position 2, 3 or 5 in the heterocyclic ring (compounds X, XI) are not oxidized by MAO and consequently are not neurotoxic [22].



VIII IX X XI

Hence neurotoxicity is characteristic of a series of 1-methyl-4-arylpiperideine-3 derivatives while other 1-alkyl and 1-aryl derivatives are safe to handle.

Recently a number of ways have been found in which piperideine-3 derivatives are used for the synthesis of important biologically active materials with a variety of therapeutic effects. We shall therefore discuss below some methods of synthesis and the current state of piperideine-3 chemistry.

2. PREPARATIVE METHODS

Preparative methods for piperideine-3 derivatives may be divided into three types:

1) Dehydration of the corresponding alcohols — piperidol-4 derivatives.

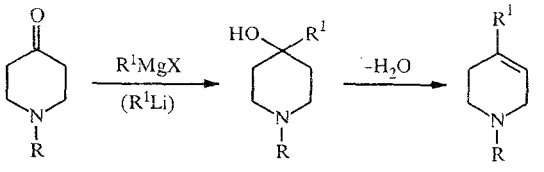
2) Incomplete reduction of pyridine derivatives.

3) Various types of cyclization and condensation reaction.

The first two methods have been known for a long time and have been described in various reviews [1, 2] and only their general characteristics will be mentioned. Attention will be directed mainly to various nontrivial condensation reactions which have been reported recently.

2.1. Dehydration of Piperidol-4 Derivatives

This method, which was first used in 1947 [23] is one of the most studied both in practice and in theory. It consists of the reaction of a piperidone-4 (XII) with an organometallic compound with subsequent dehydration of the tertiary alcohol formed to a piperideine-3 (XIV).



XII XIII XIV

Various organomagnesium and organolithium compounds are used to prepare the alcohols, but the latter give the higher yields. For example, the yields of alcohol in the reactions of 1-methylpiperidone-4 with phenyllithium and phenylmagnesium bromide were 76 and 35% respectively [24].

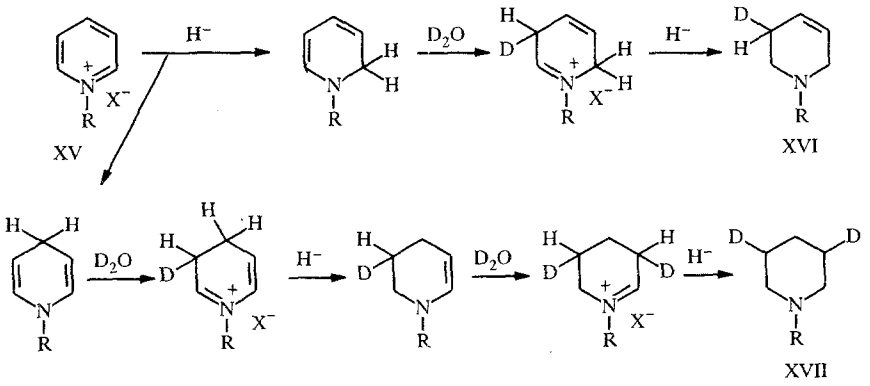
A variety of acidic reagents were used for the dehydration [25-28].

A detailed bibliography of papers concerned with the interaction of piperidones with organometallic compounds and the dehydration of the piperidol-4 derivatives produced is given in a review [29].

2.2 Incomplete Reduction of Pyridine Derivatives

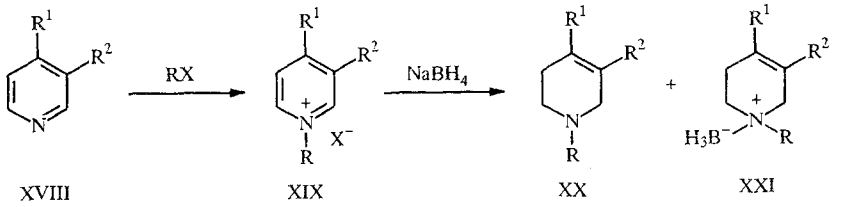
Studies in this area were carried out at the beginning of the 20th century. A considerable number of examples of reductions of the pyridine nucleus have been reported [2, 30] but only a few have preparative value.

Catalytic reduction, electroreduction and reduction with sodium in alcohol usually gave a mixture of various isomeric piperideines and piperidine derivatives [1, 2, 30]. The reduction of pyridine salts with metal hydrides in formic acid has the greatest value as a preparative method. As shown previously [31] the reaction may occur in two directions for the reduction of unsubstituted pyridine (sodium tetrahydroborate in water):



If 1,2-addition occurred initially reduction stopped at the stage of the tetrahydro derivative XVI. On the other hand, if 1,4-addition occurred as the first step complete reduction to the piperidine derivative XVII occurred. The direction of the reaction is determined by the substrate structure: The bulkier the substituent at nitrogen, the more readily the reaction occurs by the second route.

1,2-Addition occurs almost exclusively for 4-substituted pyridines. This method has been used successfully since the beginning of the 70s in the synthesis of a number of piperideine-3 derivatives [32-37] in relatively high yield by the reduction of pyridine salts XIX with sodium tetrahydroborate:



XVIII-XXI R = Me, $PhCH_2$; R^1, R^2 = Alk, Ar

The amine-borane complex XXI was formed as a by-product of reduction with sodium tetrahydroborate in water. A higher yield of the piperideine-3 with almost complete absence of complex XXI was obtained when the reduction was carried out in methanol [38].

A better method for the reduction of 4-substituted pyridines with electron withdrawing substituents (CN, COOR, $CONH_2$, CH=N−OH, etc.) is treatment of their salts with sodium cyanotrihydroborate in water or alcohol [39]. Yields reached 94%.

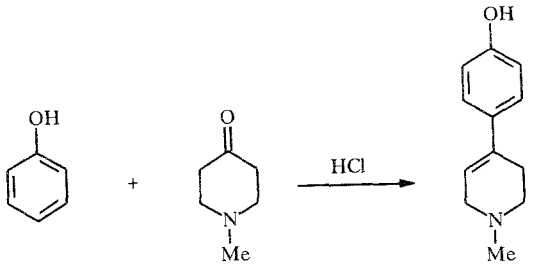
2.3 Condensation and Cyclization Reactions

Two types of reaction can be separated:

1) Reaction of compounds, one of which has a preformed 3-piperideine ring.

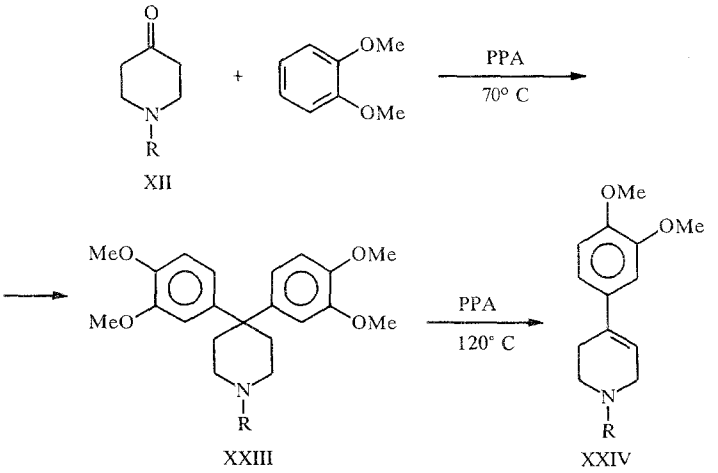
2) Reaction of noncyclic compounds with formation of the 3-piperideine nucleus.

Condensations of derivatives of piperidone-4 with various phenols belong to the first group. For example, reaction of 1-methylpiperidone-4 with phenol in the presence of an acid catalyst proceeded with electrophilic substitution on the phenol to give the piperideine-3 XXII [40].



XXII

Further investigation showed [41] that when different 1-alkylpiperidones-4 were heated with polyphenol ethers in the presence of polyphosphoric acid (PPA) 1-alkyl-4,4-diarylpiperidines (XXIII) were formed which could be converted further into 1-alkyl-4-arylpiperideines (XXIV):

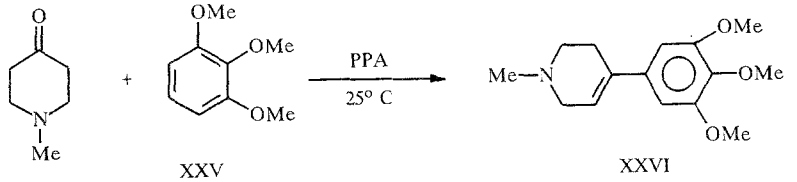


XII

XXIII

XXIV

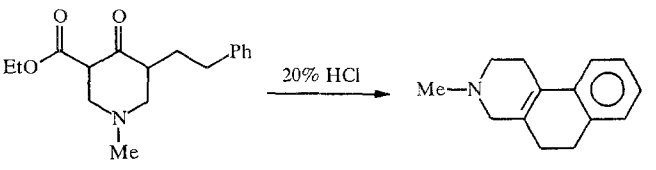
The methyl ether of pyrogallol (XXV) reacted instantaneously at room temperature to give the piperideine-3 (XXVI):



XXV

XXVI

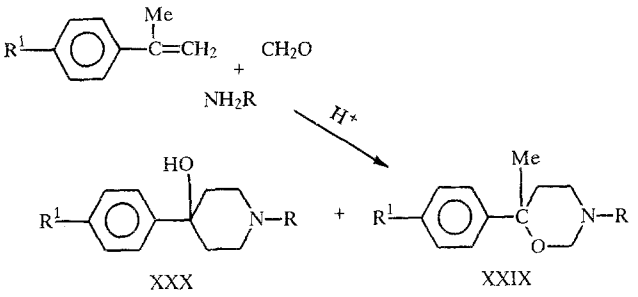
1-Methyl-5-(3-phenylethyl)-3-ethoxycarbonylpiperidone-4 (XXVII) underwent intramolecular condensation in acid medium to give a cyclic piperideine system (XXVIII) [42].



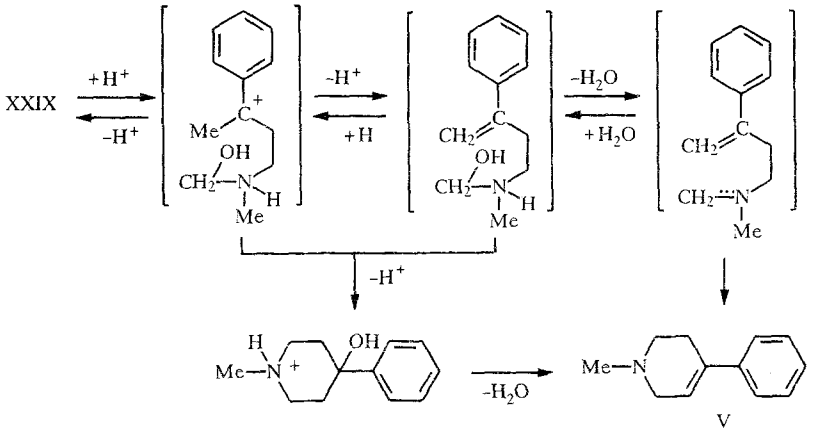
XXVII

XXVIII

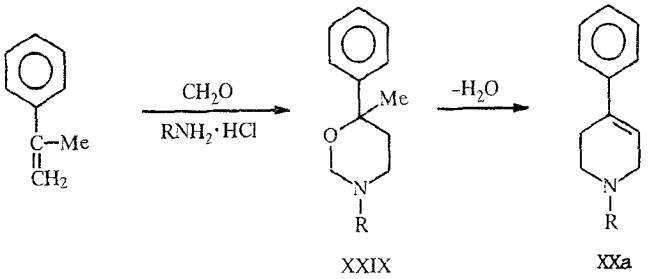
Formation of a 3-piperideine ring by cyclization was first observed in studies of the aminomethylation of olefins [43, 44]. The 1,3-oxazine XXIX was formed by the interaction of α-methylstyrene with formaldehyde and methylamine (or its hydrochloride). Its isomer, 1-alkyl-4-phenylpiperidole-4, XXX, was also isolated. Dehydration of the latter gave piperideine-3 derivatives.



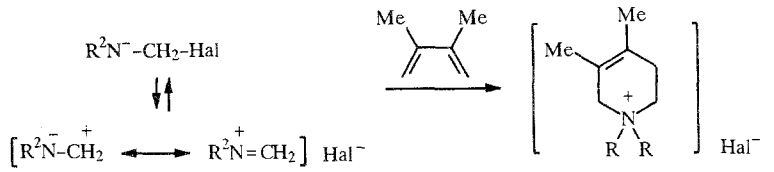
The formation of the piperidols XXX alongside the 1,3-oxazines suggested that the 1,3-oxazines rearranged to the piperidols under the influence of acid by the following proposed route [45, 46]:



It was later established that 1-alkyl-4-phenylpiperideine-3 XXX were obtained directly from α-methylstyrene, formaldehyde and an ammonium or alkylammonium salt in acid media without isolation of the 1,3-oxazine intermediates [44, 45].



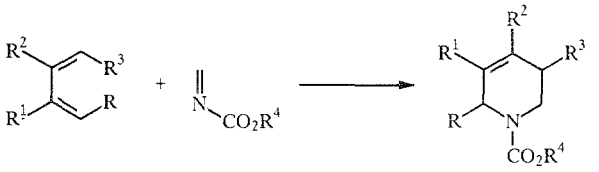
Another method for the formation of piperideine-3 quaternary salts is a Diels-Alder type reaction of α-halogenamines with 2,3-dimethylbutadienes [47, 48]. In particular the reaction methylenediethylammonium chloride with the butadiene gave the piperideine-3 salts XXXI:



XXXI

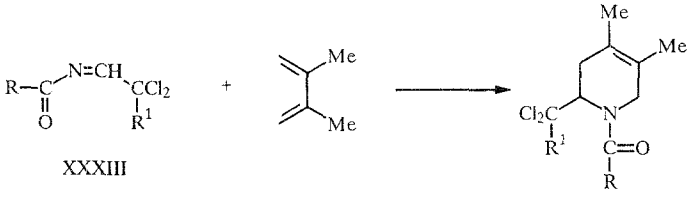
R = Et; Hal = Cl, Br

This method was used later by a different group to prepare both substituted and unsubstituted 1,2,3,6-tetrahydropyridines, e.g., the polysubstituted 1-acylpiperideine-3 XXXII [48].



R = Alk XXXII

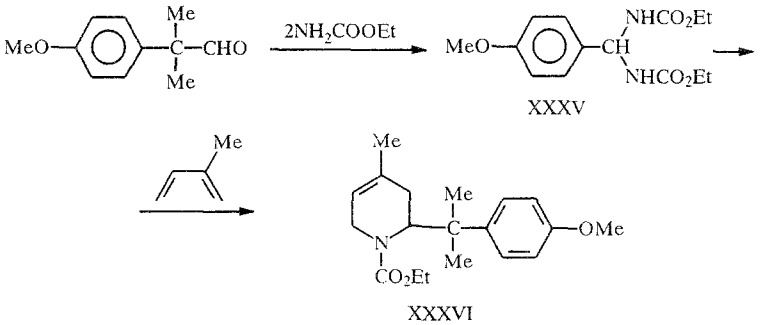
The method of preparing 2-(1,1-dichloroalkyl) piperideines-3 XXXIV by the reaction of the N-acylimines XXXIII with 2,3-dimethylbutadiene has been patented [49].



XXXIII XXXIV

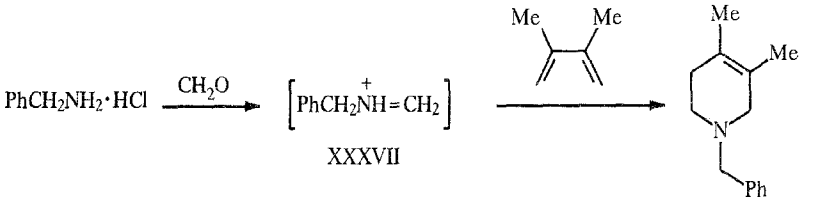
R = R^1 = Alk, Ar

The reaction isoprene with aminal (XXXV) occurs analogously [50]:

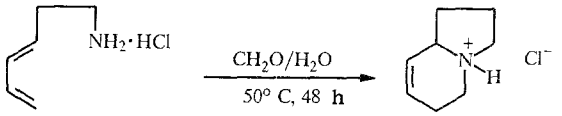


XXXV XXXVI

As a rule the dienophiles in the examples given above contain an electron withdrawing substituent on nitrogen. However an analogous Diels-Alder reaction was reported in 1985 [51] in which various dienes reacted under mild conditions in aqueous media with an unactivated dienophile, the iminium ion XXXVII formed *in situ* under Mannich reaction conditions:



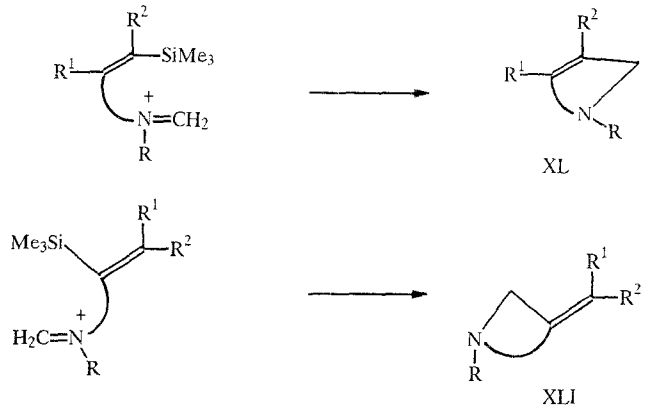
The hydrogenated indolizine XXXVIII was formed in high yield by intramolecular cycloaddition from (*E*)-4,6-heptadienylamine (XXXIX) under the influence of 37% formalin:



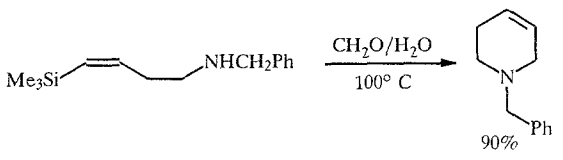
XXXIX XXXVIII 95%

Clearly this reaction is of fundamental, as well as practical, interest since it provides another possible mechanism fore the formation of natural alkaloids containing the piperideine-3 nucleus.

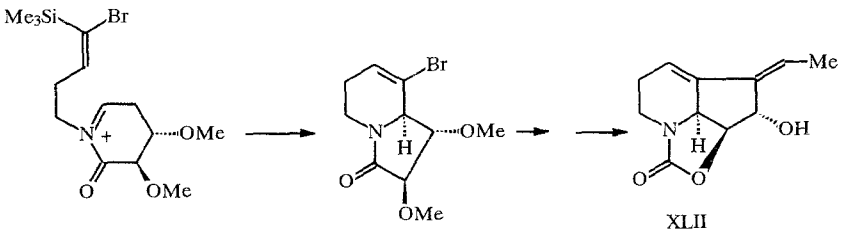
A new method for the synthesis of 1,2,3,6 -tetrahydropyridines using vinylsilyliminium salts has been developed recently. Depending on the structure of the initial vinylsilylamine, piperideines-3 XL or XLI, which contain *an endo-* or an *exo*-double respectively, are formed in the Mannich reaction:



The reaction occurs in excellent yield (>90%) in a variety of solvents: acetonitrile, acetic acid, water.



A similar reaction was used successfully to obtain the 3-piperideine unit in alkaloids, e.g., it was the key step in the synthesis of the antibiotic (+)-streptazoline XLII [53]



This concisely characterizes the traditional and recently discovered methods for preparing piperideine-3 derivatives. The remainder of the review will be concerned with the use of these compounds in synthetic schemes.

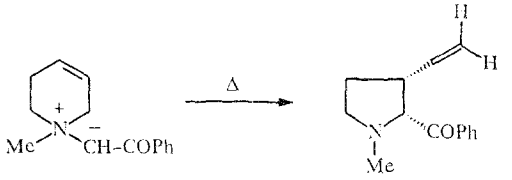
3. USE OF PIPERIDEINE-3 DERIVATIVES IN ORGANIC SYNTHESIS

The chemical properties of piperideine-3 derivatives which derive from the presence of an isolated double bond in the ring and the secondary or tertiary amine group have been well described in previous reviews [2, 29] and we shall not be concerned with them here.

The most interesting aspects of piperideine-3 chemistry are reactions in which the double bond and the nitrogen atom participate simultaneously. e.g., 1,2-ylid rearrangements of the Meisenheimer and Stevens type, the Grove cyclization, and the recently developed strategy for the synthesis of alkaloids using the metallated Δ^3-piperideine structure. These and other reactions of piperideine-3 derivatives are examined below.

3.1 Ylid Rearrangements

A [3+2]-ylid rearrangement to give only the *cis*-isomer of the pyrroline XLIV was observed on pyrolysis of the ylid XLIII [54]:

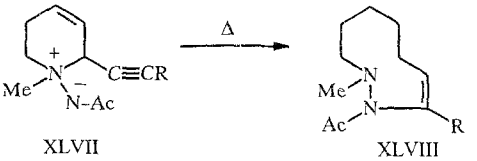


XLIII XLIV

Under the same conditions the 1,2-sigmatropic rearrangement of the five-membered ylid Δ^3-pyrroline XLV gave the piperideine-3 XLVI.

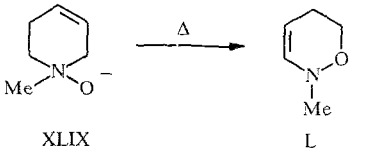
XLV XLVI

The 2-ethynyl substituted ylid XLVII with an *endo* double bond gave the cyclic acylhydrazine XLVIII [55].



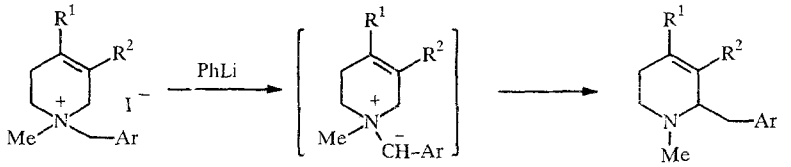
XLVII XLVIII

Recently Meisenheimer rearrangements of piperideine-3 N-oxides have been reported, e.g., thermolysis of 1-alkylpiperideine-3 N-oxides XLIX gave tetrahydro-1,2-oxazines L predominantly [56]:



XLIX L

The Stevens rearrangement of a series of piperideine-3 derivatives is one step in the synthesis of a number of medicinals, e.g., the series of piperideine-3 derivatives LI:



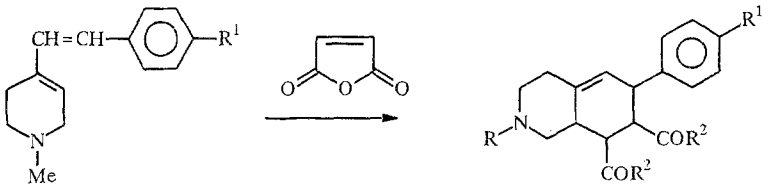
LI

R^1, R^2 = Alk, Ar

It is known that by-products are formed in the Stevens rearrangement [57], but the series of piperideine-3 derivatives LI was formed in sufficiently high yield by this route [31, 58-60].

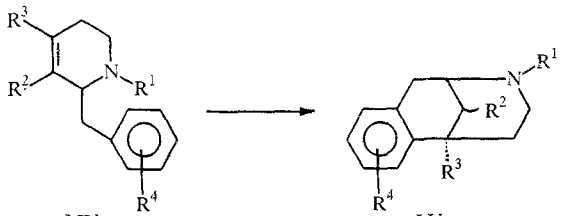
3.2. Cyclization Reactions

A large number of drugs of the isoquinoline series LIII with a broad spectrum of physiological activity [61-63] were synthesized by the Diels-Alder reaction of 1-alkyl-4-(2-aryl)vinyl-1,2,3,6-tetrahydropyridines LII with various dienophiles:



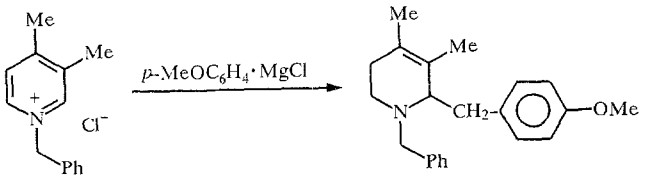
LII LIII

In order to create an "ideal" analgesic with minimum side effects and no physical dependency, syntheses of various parts of the morphine molecule were studied, in particular 4-phenylpiperidines, morphinanes, and 6,7- and 7,8-benzomorphanes. Grove cyclization of 2-arylmethylpiperideines-3 uncovered a new and general route to the synthesis of various benzomorphans LV, among which were compounds with strong analgesic activity:



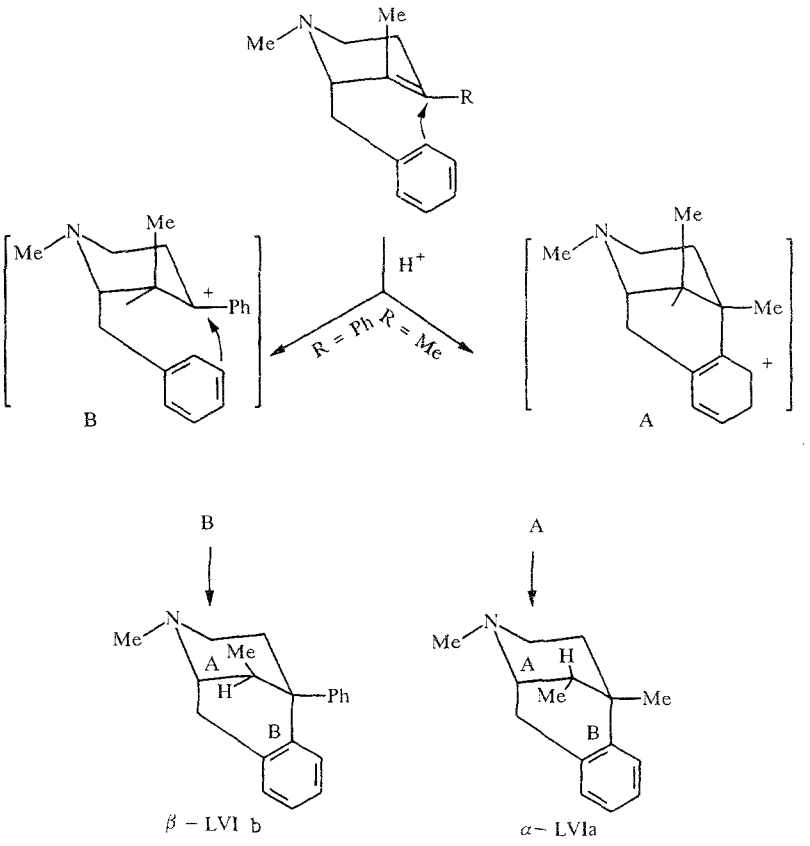
LIV LV

The basis for the Grove intramolecular cyclization is electrophilic substitution of the aromatic ring by a carbocationic center which arises from protonation of the $C_{(3)}$-$C_{(4)}$ double bond of the piperideine-3 derivatives LIV [32, 59]. Hydrobromic acid, phosphoric acid or polyphosphoric acid were used as the condensing medium. A large number of benzomorphans LV or practical importance were obtained by this route [32, 59, 60, 64-68], in particular the known analgesic pentazocine (LV, R^1 = R^2 = Me, R = $-CH_2-CH=CMe_2$) [69]. The starting piperideines LIV are obtained either by the Stevens rearrangement, as shown above, or by treatment of a pyridinium salt with a Grignard reagent [64], for example:



LIV

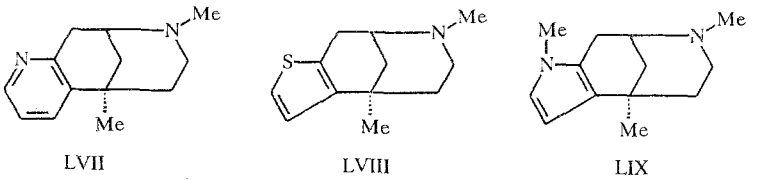
Investigation of the stereochemistry of the Grove cyclizations of various piperideine-3 derivatives showed that acid cyclization of 3,4-dialkylpiperideines gave predominantly either the *cis* isomers (relative to ring B) or the α-benzomorphans LVIa. The *trans*-isomers or β-benzomorphans LVIb were formed practically exclusively on cyclization of 3-alkyl-4-phenylpiperideines [68].



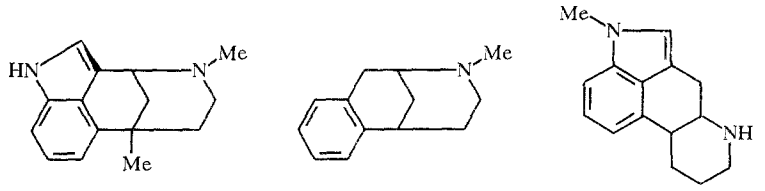
The exclusive formation of the β-benzomorphans LVIb from 3-alkyl-4-phenylpiperideines-3 is explained by the existence of the stable *trans*-benzylcarbenium ion B, stabilized by the 4-phenyl group, cyclization of which leads to the β-isomer LVIb only [68].

The discovery of a method for the synthesis of α- and β benzomorphans opened up interesting possibilities for the synthesis of new analgesics. It should be noted that β-benzomorphans have much greater analgesic activity than the α-isomers, although the stereochemistry of the latter is analogous to that of the morphine molecule.

The Grove cyclization was extended to aromatic heterocycles as a result of which pyridomorphans LVII, thienomorphans LVIII, and pyrrolomorphans LIX were obtained, all of which have high analgesic activity [70-72].

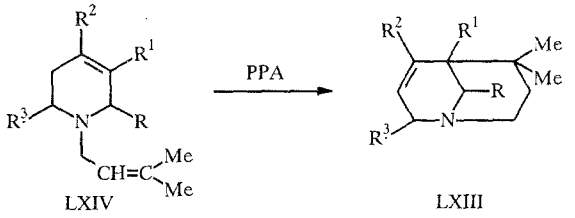


This same concept was the basis for the synthesis of a new class of biologically active compounds, the indolomorphans LX [73], the structures of which contain both a morphine-like fragment (6,7-benzomorphan LXI) and a fragment of the sporine alkaloids (ergomine, LXII):



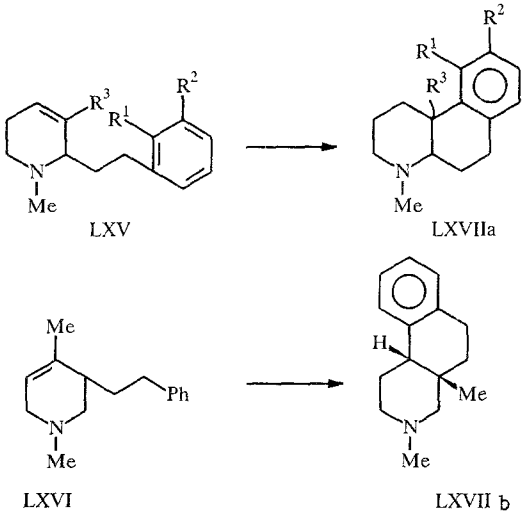
LX LXI LXII

The synthesis of the azabicyclononenes LXIII by the acid cyclization of 1-allylpiperideine-3 derivatives LXIV is also a natural extension of the Grove cyclization [74-76]:



LXIV LXIII

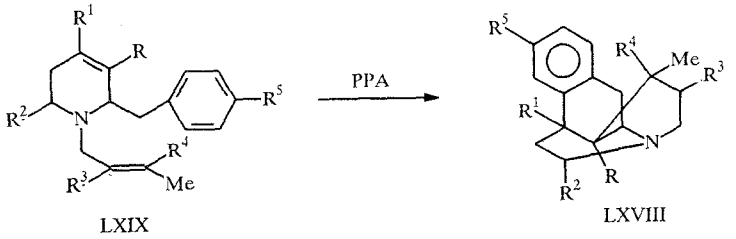
Under the same conditions 2-phenethyl- (LXV) and 3 -phenethylpiperideines LXVI cyclize readily to give the tricyclic piperidines LXVII a,b:



LXV LXVIIa

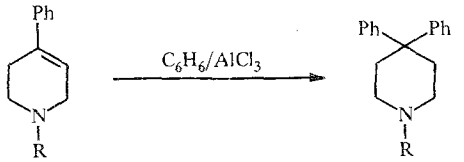
LXVI LXVII b

A logical extension of the syntheses cited above is the preparation of various benzazocines LXVIII 1-allyl-2-arylmethyl derivatives of piperideine-3 LXIX, which combine powerful analgesic activity with low toxicity [77].



LXIX LXVIII

A few reactions are known based on the electrophilic substitution of aromatic compounds by carbenium ions generated from piperideine-3. One of the simplest is the Fridel-Crafts synthesis of the 4,4-diphenylpiperidines LXX which are used to treat Parkinsonism [78].



LXX

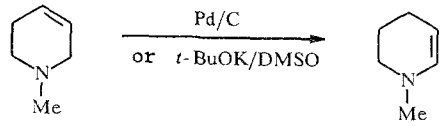
From the results cited it is considered that the Grove cyclization is one of the most promising methods for piperideine-3 use.

3.3. Metallation of Piperideine-3 Derivatives

Another recent rapidly developing field is the metallation of derivatives of piperideine-3 for the synthesis of new biologically active materials.

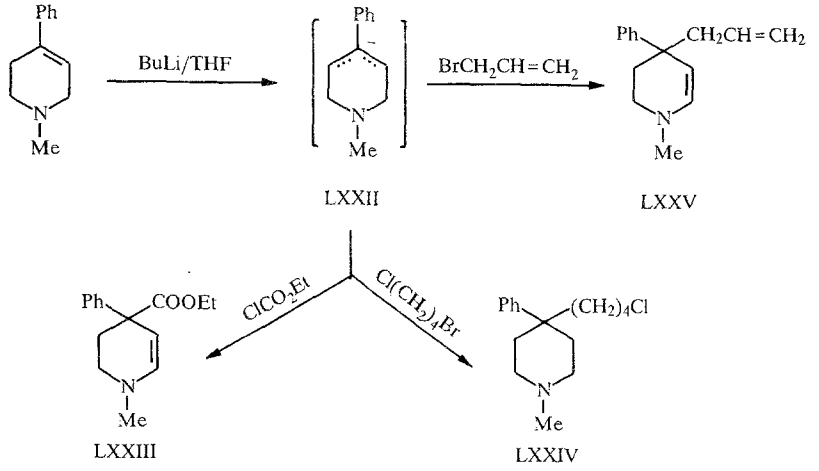
The relative stability of 6—membered cyclic allylamines - piperideines-3 - and the isomeric enamines - piperideines-2 - has provoked discussion for a long time. Experimental confirmation of the greater stability of the cyclic enamine form - piperideines-2 - obtained only relatively recently has resolved the controversy.

The piperideine-3 itself isomerized to piperideine-2 catalytically [79, 80] or in the presence of strong base [81]:

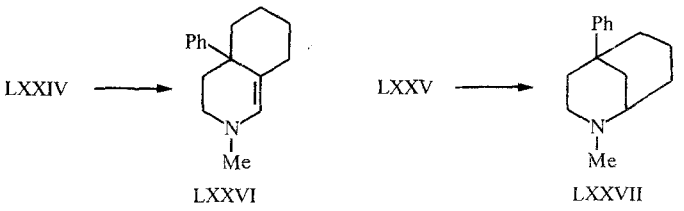


Results from the study of the isomerization of piperideine-3 derivatives found wide use in the synthesis of a variety of alkaloids very rapidly.

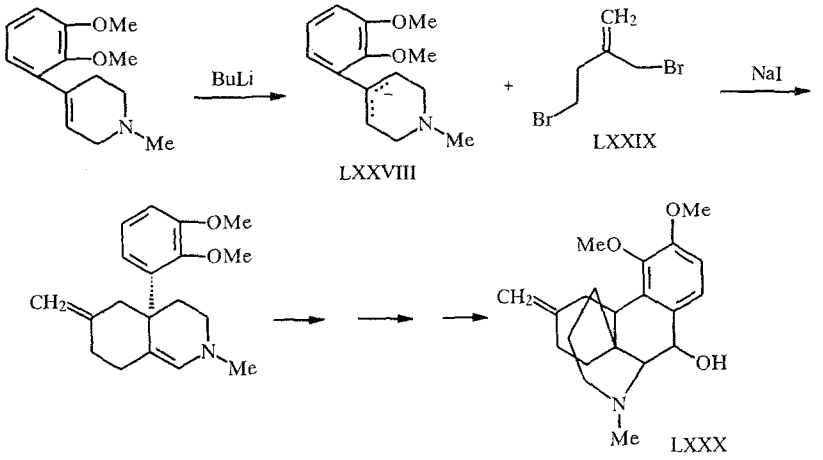
One of the first reports was an American patent [82] in which the enamine LXXIII, required in one step in the synthesis of the analgesic meperidine, was obtained by successive metallation and acylation of 1-methyl-4-phenylpiperideine-3 (LXXI):



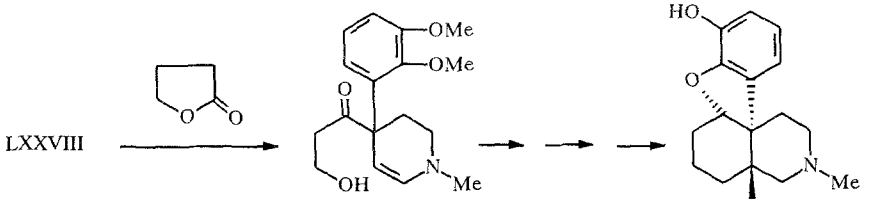
Evans has shown the synthetic potential of the γ-anion LXXII in a number of papers. Alkylation of anion LXXII with 1,4-chlorobromobutane or allyl bromide gave the cyclic enamines LXXIV and LXXV which contain quaternary $C_{(4)}$ centers and are precursors for the synthesis of different sections of the morphine molecule - octahydroisoquinoline LXXVI and morphane LXXVII [83].



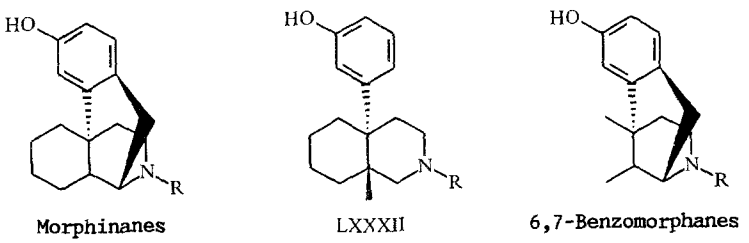
The synthetic strategy of preparing and using metallated enamines developed by Evans and his co-workers has proved very valuable in the synthesis of various alkaloids, among them (±)-morphine and its fragments. Alkylation of the γ-anion LXXVIII with the dibromide LXXIX is the key step in the total synthesis of the precursor of (±)-morphine LXXX [84].



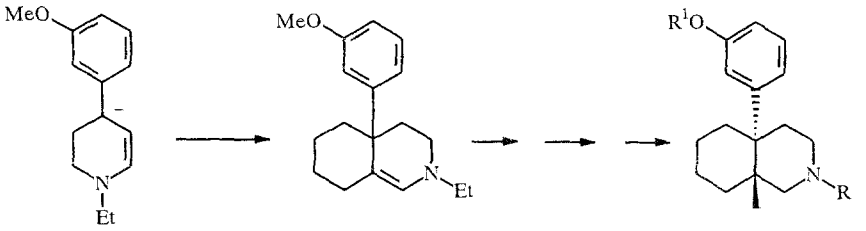
Another part of the morphine molecule - decahydroisoquinoline LXXXI - was synthesized by acylation of the anion LXXVIII with γ-butyrolactone [85]:



Much attention has been paid in the study of structure–activity correlations to N-substituted *trans*-4*a*-aryldecahydroisoquinolines LXXXII among which are effective analgesics with strong affinities for the μ- and κ-receptors of the brain. The receptor selectivity, the high analgesic activity, and the close structural connection between the isomers of LXXXII and the morphinanes and the 6,7-benzomorphanes has stimulated the search for simple routes to obtain these compounds [86, 87].

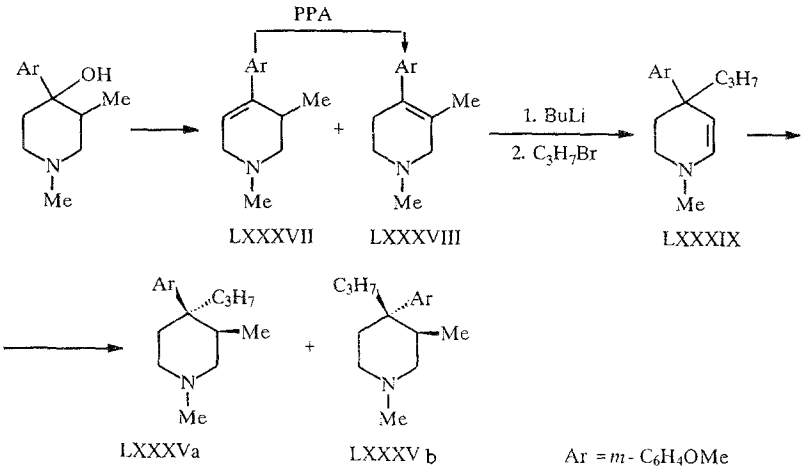


The γ-anion LXXXIII, generated from 1-ethylpiperideine-3, gave the 1-ethyl analog LXXXIV by the synthetic scheme shown above for the octahydroisoquinoline LXXVI. Subsequent reduction, N-desalkylation and N-alkylation gave a series of N-substituted *trans*-4*a*-aryl derivatives LXXXII.



LXXXIII LXXXIV LXXXII R^1 = Me

An interesting report on the metallation of enamines is a new route to the synthesis of the analgetic (±)-picenadol LXXXVa [88, 89], the enantiomer of which is agonistic and antagonistic to the morphine like effect [90].



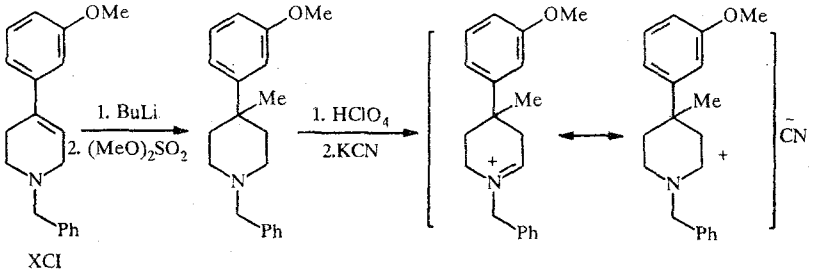
LXXXVII LXXXVIII LXXXIX

LXXXVa LXXXV b Ar = *m*-C_6H_4OMe

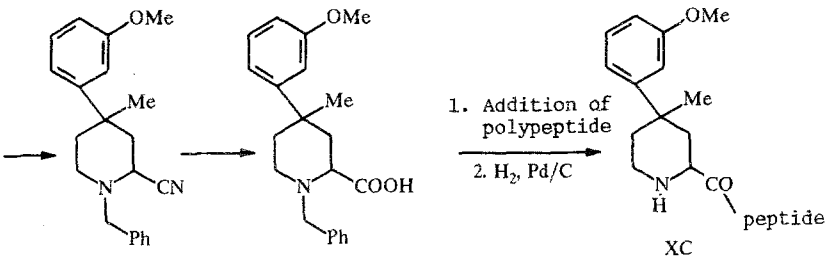
Synthesis of the predecessor of picenadol, the enamine LXXXIX, by the scheme described above includes the formation of a mixture of isomeric piperideines-3, LXXXVII and LXXXVIII, thermal isomerization of which in the presence of PPA led to the single 3,4-disubstituted piperideine LXXXVIII, metallation and alkylation of which then gave the enamine LXXXIX.

Another stereochemical difficulty occurred on reduction of the enamine LXXXIX to (±)-picenadol LXXXV: depending on the conditions (the medium, reducing agent, catalyst) and the chemical purity of the enamine LXXXIX various ratios of the *cis*- and *trans*-isomers LXXXVa and LXXXVb were formed. The best *cis/trans* ratio, 75:25, was obtained in the presence of Pd/C or $Pd/CaCO_3$ in triethylamine.

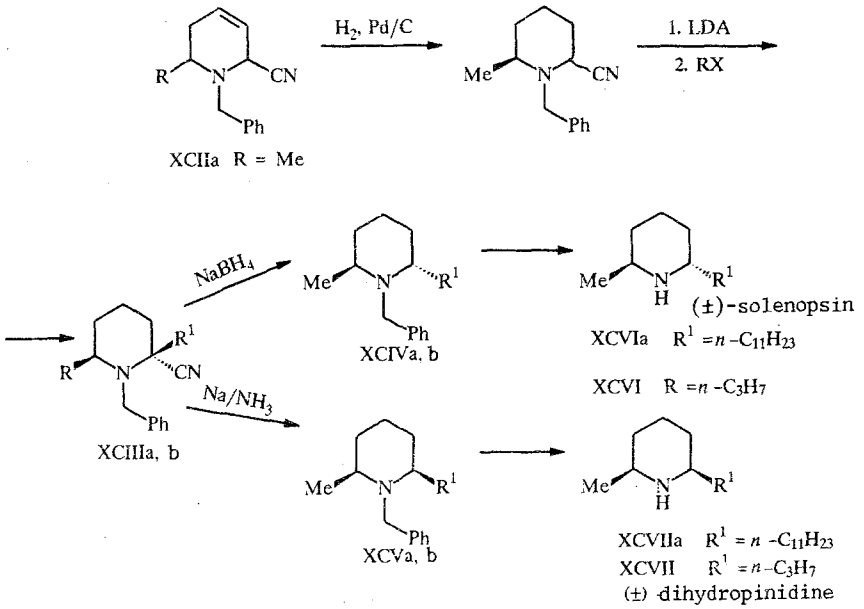
It also appeared useful to synthesize the enkephalin analog XC by metallation of 1-benzyl-4-(3-methoxyphenyl)piperideine-3 (XCI) as follows [91]:



XCI

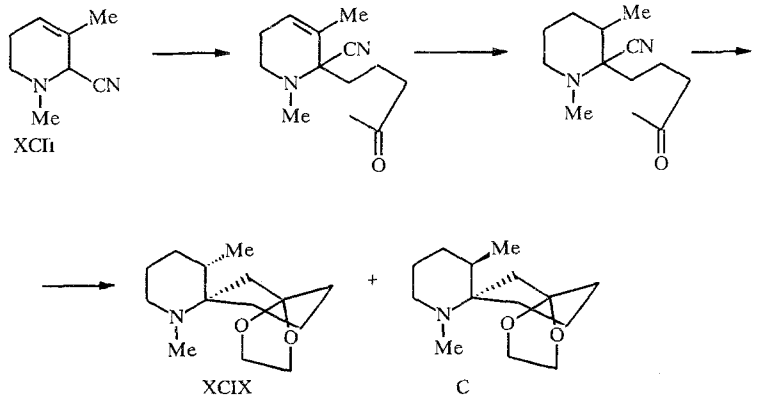


An interesting synthetic development was obtained by using 2-cyano-piperideine-3. Husson [92, 93] developed a general route for the stereoselective synthesis of a series of *cis*- and *trans*-2,6-dialkylpiperidine alkaloids, in particular (±)-solenopsin (XCVIa), (±)-dihydropinidine (XCIVb), and others. The key step in this strategy is the effective reductive decyanation of the common α-aminonitrile synthon XCII.

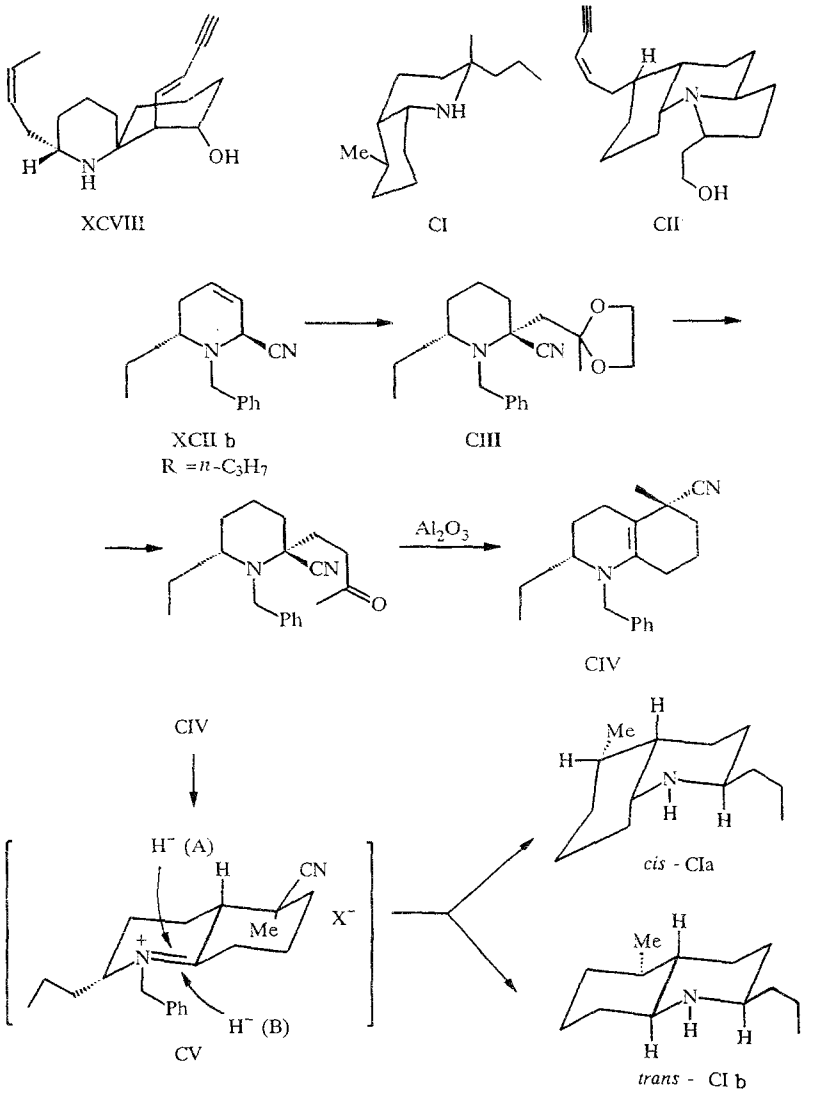


As shown in the scheme, 2-alkyl-2-cyanopiperidine (XCIIIa and b) can be stereospecifically (Na/NH_3, THF, −78°C) transformed into the *cis*-isomers XCVa,b or with moderate stereospecificity ($NaBH_4/CH_3OH$) into the *trans*-isomers, from which the alkaloids solenopsin (XCVIa) and dihydropinidine (XCVIIb) were obtained by N-debenzylation [94].

A neat spiroannelation of the ambident 2-cyanopiperideines gave the diastereoisomers XCIX and C which are fragments of the alkaloid histrionicotoxin (XCVIII) [95].

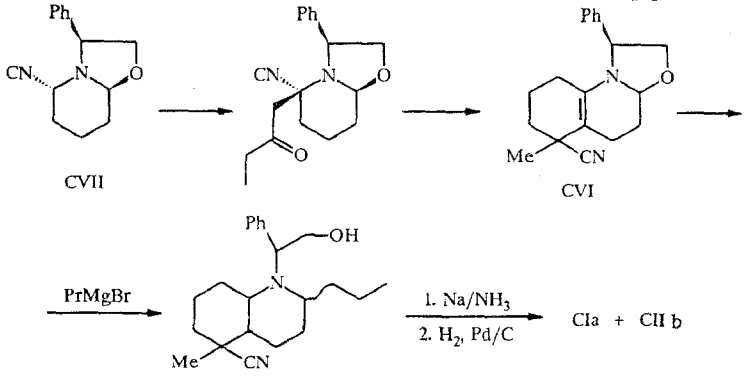


In the asymmetric synthesis of the *cis*-decahydroquinoline alkaloids pumiliotoxin C (PTX-C) (CI) and hefirotoxin (CII) both of which were isolated from the cutaneous secretions of the Panamanian frog *Dendrobates*, the enamine C was used as a common synthon. Stereospecific cyclization of the intermediate CIII made from 2-cyanopiperideine-3 XCIIb on activated alumina gave the enamine CIV only.

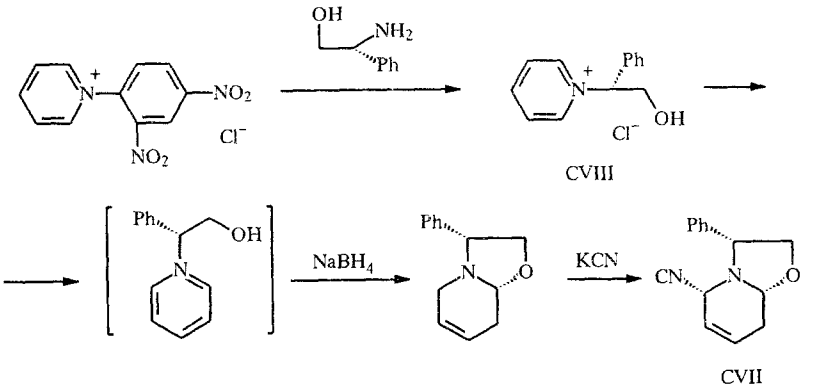


Subsequent reduction of enamine CIV with $NaBH_4$, decyanation and N-debenzylation led to a 95:5 of *cis*- (CIa) and *trans*- (CIb) isomers of the decahydroquinoline. The principal *cis*-isomer CIa is PTX-C, the predominant formation of which is explained by the sterically favorable attack of the hydride ion at the double bond of the intermediate CV from above the molecule (path A).

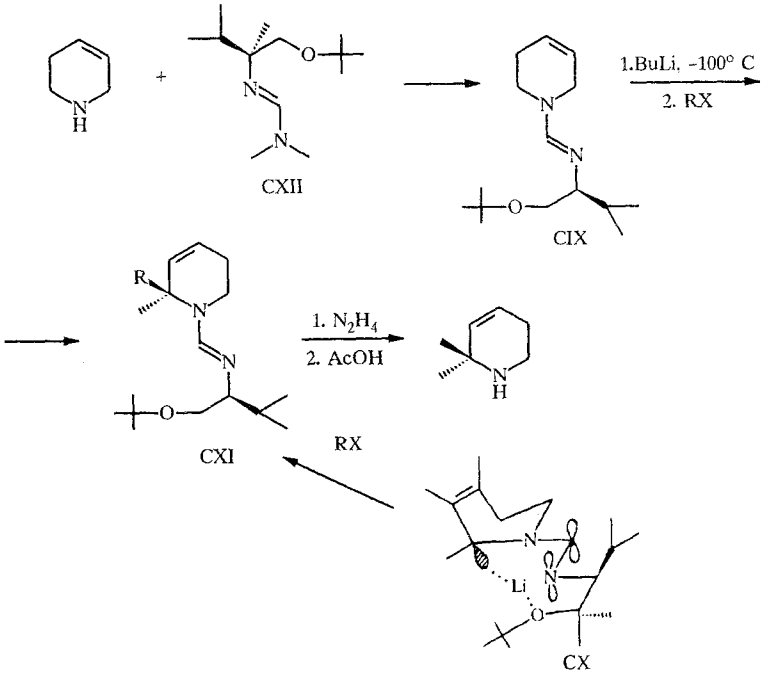
Another route to the asymmetric synthesis of *trans*-CIb and PTX-C (CIa) includes as the key step the formation of the enamine CVI, which is formed in a series of reactions from chiral 2-cyano-6-oxazolopiperidine CVII [96]:



A 7:3 mixture of (−)-PTX-C (CIa) and (+)-*trans*-CIb is formed with the stereoisomers having opposite configuration at $C_{(2)}$. The lower stereoselectivity in this asymmetric synthesis arises because the intermediate in the addition of the Grignard reagent to the enamine CVI, which is formed by opening of the oxazolidine ring, is practically planar. The starting oxazolidine was obtained by consecutive interaction of (*R*)- or (*S*)-phenylglycinol on Zincke's salt, reduction of the pyridinium salt CVIII with $NaBH_4$ and treatment with KCN [97]:



In a series of brilliant papers Meyers [98-100] proposed a general strategy for the effective asymmetric alkylation of piperideines via metallation of the N-*tert*-butylformamidine CIX in which $C_{(2)}$-deprotonation occurs readily because of "allyl" activation. The subsequent high stereocontrol of alkylation results because the methylated formamidine CXI exists in conformation CX, stabilized by the orthogonality of the α-aminocarbanion orbital and the N−C−N fragment.



Subsequent quenching of the lithium intermediate CX with an alkyl halide occurs exclusively as an enantioselective "equatorial" alkylation to give the (*2S*)-piperidine CXI with high optical purity. The highest enantioselectivity (99%) was achieved on alkylating the formamidine CIX which was prepared from (*1S, 2S*)-1-phenyl-2-amino-1,3-bistrimethylsiloxypropane (CXII) [101, 102].

Meyer's strategy for the highly effective enantioselective α-alkylation of piperidines was the basis for the synthesis of the analgetic metazocine in 96% enantiomeric purity [99] and was used successfully in the synthesis of precursors of the alkaloids terbine, codeine, (+)-reticuline [103], (−)-indoloquinolizine [104] and (−)-yohimbine [105].

This analysis of the current development of piperideine-3 chemistry demonstrates the promising and yet to be exhausted potential of this class of compound.

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