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γ-PIPERIDONE IMINES AND ENAMINES IN ORGANIC SYNTHESIS (REVIEW)

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The methods of preparation, structure, and some chemical conversions of imines and enamines based on γ-piperidones were examined.

Azomethines and enamines are widely used in synthesis of different heterocycles [1-3]. Piperidone imines and enamines occupy a special position among these derivatives of carbonyl compounds. The interest in these piperidine bases is due to the broad spectrum of the biological activity of their derivatives, which are also convenient starting compounds in the construction of new heterocyclic systems.

Systematic research on the chemical transformations and biological activity of different γ-imino(amino)piperidines and enamines based on 4-piperidinones has been conducted for a number of years in the Department of Organic Chemistry of the Russian People's Friendship University. The results of these studies are generalized and the available published information on compounds of this type is reported in the present study.

SYNTHESIS AND STRUCTURE OF 4-PIPERIDINONE IMINES AND ENAMINES

The methods of synthesis of γ-piperidone imines and enamines are based on reactions of a nucleophilic addition of primary and secondary amines at the C=O group of γ-piperidones. This process is reversible, the reaction is conducted in protic solvents with azeotropic evaporation of water to shift the equilibrium toward formation of products, and different catalysts are used (*p*-TSA, glacial acetic acid, anhydrous zinc chloride, etc.).

There are more examples of synthesis of γ-iminopiperidines, since γ-iminopiperidines are the starting compounds in synthesis of several drugs [4, 5].

However, there were no published data on the isomerism and conformation of γ-iminopiperidines until recently. This is due to their comparative instability and the complexity of the isomeric composition.

The products of condensation of 1,2,5-trimethyl-4-piperidinone with aniline were investigated by NMR spectroscopy in [6]. Using the $^3J_{HH}$, $^1J_{CH}$, and $^1J_{CC}$ SSCC, it was found that N-(1,2,5-trimethyl-4-piperidylidene)aniline (I) is a mixture of three isomers which differ with respect to the position of the methyl groups at the $C_{(2)}$ and $C_{(5)}$ atoms of the piperidine ring and *Z,E*-isomerism at the C=N bond. Traces of the enamine form of this imine were also detected. Based on the data in [6], the following scheme of imine–enamine tautomerism was hypothesized for this γ-iminopiperidine. (See Scheme 1 at the top of the next page.)

This scheme can probably be considered common to γ-N-aryliminopiperidines in consideration of the structure of the starting ketone [7] and the factors that affect imine–enamine equilibrium.

The information on the structure of enamines obtained from γ-piperidones is limited. It was shown in [8] that there are two signals of olefin protons in the 3.77-4.25 ppm region in the PMR spectra of 1,2,5-trimethyl-4-morpholino(1-piperidino, pyrrolidinyl)piperidines II. These two signals could indicate that these enamines are a mixture of at least two isomers with

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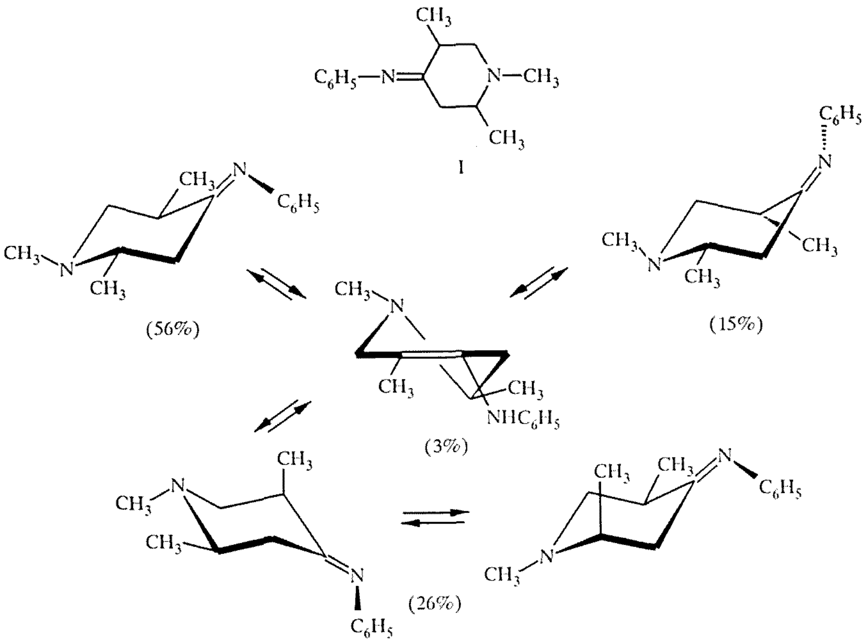
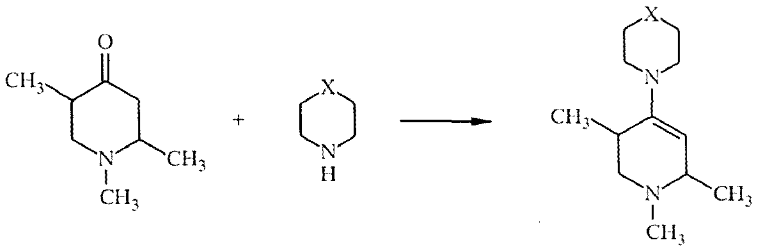
Scheme 1



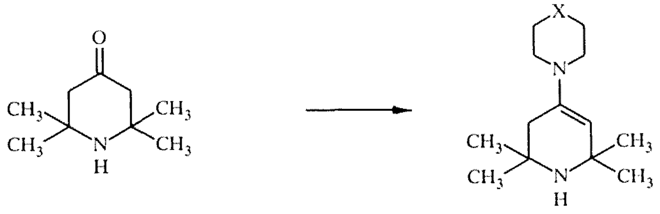
respect to the position of the methyl groups at $C_{(2)}$ and $C_{(5)}$ — *trans*-2*e*, 5*e*- and *cis*-2*e*, 5*a*-isomers (as in the case of 1,2,5-trimethyl-4-(*p*-hydroxyphenyl)-1,2,4,5-tetrahydropyridines [9]). These enamines were obtained with a yield greater than 50% when *p*-TSA was used as the catalyst.



II

X = O, CH_2

Strong resinification occurs in synthesis of enamines from N-unsubstituted piperidines in the presence of this catalyst, and benzoic acid is used instead for this reason. For example, when 2,2,6,6-tetramethyl-4-piperidinone is boiled with morpholine or piperidine in toluene in the presence of benzoic acid, the corresponding enamines III are obtained with a yield of 76-80% [10].



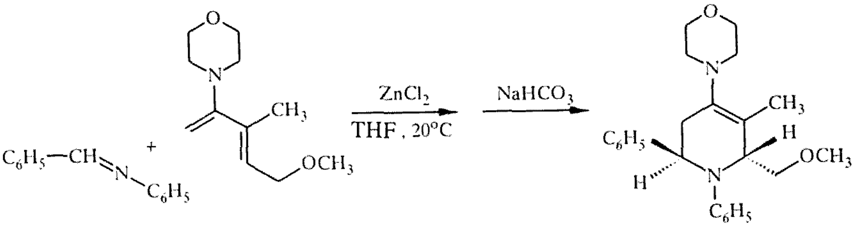
III

X = O, CH_2

It is generally not possible to isolate the enamine obtained from N-phenyl-4-piperidinone and pyrrolidine in pure form since it decomposes during distillation [11]. However, its formation is confirmed by the data in the PMR spectra — the existence of a triplet signal at 4.15 ppm which corresponds to the vinyl proton in the enamine.

It was possible to conduct an x-ray structural analysis of one enamine of the piperidine series. Crystalline enamine V, isolated as one stereoisomer, was obtained with a yield of 52% in the reaction of 3-methyl-5-methoxy-2-morpholino-1,3-

pentadiene (IV) with N-benzylidenaniline in the presence of $ZnCl_2$. The substituents at $C_{(2)}$ and $C_{(6)}$ atoms have the *trans*-position [12, 13].

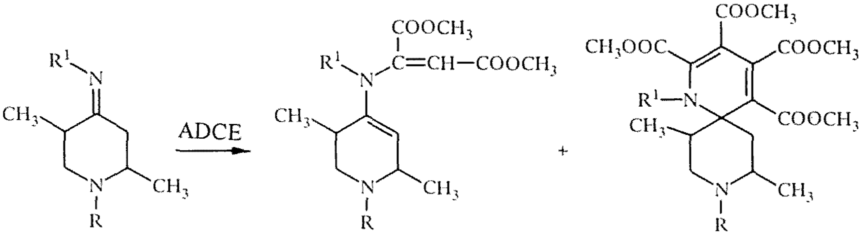


V

This is a new method of synthesis of N-aryl-substituted enamines of the piperidine series.

REACTION OF γ-PIPERIDONE IMINES AND ENAMINES WITH ELECTROPHILIC REAGENTS

The reaction of 1,4-dipolar cycloaddition discovered by Huisgen [14] has been used to obtain the aza analogs of alkaloids of the histrionicotoxin group containing a 1-azaspiro[5,5]undecane system. Condensation of acetylenedicarboxylic acid dimethyl ester (ADCE) with different γ-iminopiperidines was conducted for this purpose [15-18]. Both 1:1 (compound VI) and 1:2 (spiro compound VII) adducts were obtained.



VI VII

$R = CH_3$, $R^1 = C_6H_5$; $R = CH_3$, $R^1 = C_6H_4CH_3$-*p*; $R = CH_3$, $R^1 = C_6H_4OCH_3$-*o*; $R = CH_3$, $R^1 = C_6H_4OCH_3$-*p*; $R = CH_2C_6H_5$, $R^1 = C_6H_5$

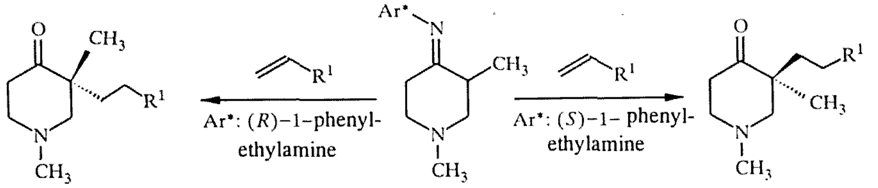
In conducting the reaction with equimolecular quantities of the reactants, compounds VI significantly predominate, and their yield increases with an increase in the polarity of the solvent, while the yield of spirans VII is 4-20%. With a 1:2 ratio of the reactants in absolute ether, 1:2-adducts predominate, and their yield attains 30-50%.

According to the TLC data, enamines VI are formed as two geometric isomers. The chromatographically separated isomers are *cis-trans*-configuration isomers of the dimethoxycarbonylvinyl group in N-(1-R-2,5-dimethyl-3-piperidinen-4-yl)-N-(1,2-dimethoxycarbonyletheno)arylamines (VI). The configuration of the 2- and 5-CH_3 groups in the piperidine ring has not been established.

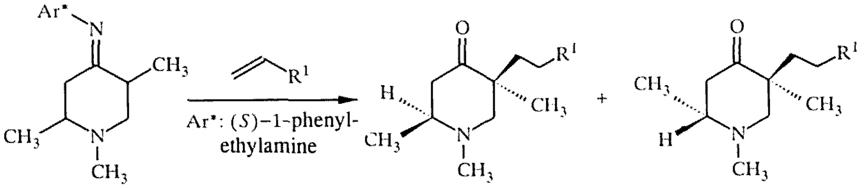
Alkylation of chiral imines obtained from racemic 3- and 2,5-substituted 4-piperidinones with electron-deficient alkenes is a common method of asymmetric synthesis of 3,3-di- and 2,5,5-tri-substituted 4-piperidinones of high optical purity [19-22]. (See scheme at the top of the next page.)

Enamines with a tetra-substituted $C_{(3)}-C_{(4)}$ double bond are the reactive form in which these chiral imines react with electron-deficient alkenes.

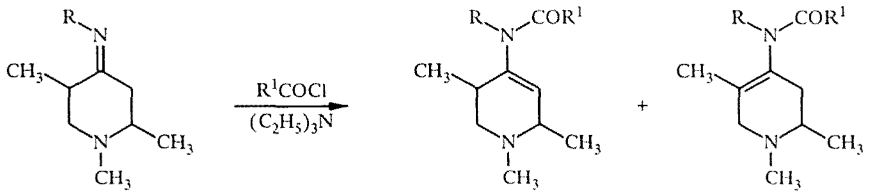
Reactions of acylation of imines have been used in the synthesis of some natural compounds, alkaloids of the protoberberine and β-lactam antibiotic type in particular. The piperidine ring is a structural fragment of some natural and synthetic biologically active compounds; for this reason, amides with a γ-piperidone substituent synthesized from 4-N-substituted iminopiperidines can be used in synthesizing such substances. However, examples of acylation of γ-iminopiperidines are limited to only two studies [23, 24]. Acylation of N-(1,2,5-trimethyl-4-piperidylidene)-β-vinylhydroxyethylamine was investigated in [23]. The substances obtained — isomeric Δ^3- and Δ^4-amidopiperideines — were investigated as mixtures. The formation of a mixture of Δ^3- and Δ^4-isomers was also observed in acylation of N-(1,2,5-trimethyl-4-piperidylidene)arylamines [24, 25]. Isomers of the Δ^3 series — compounds VIII — were separated by chromatography of the reaction mixtures of products of the reaction of these imines with acetyl(propionyl, benzoyl) chlorides [25]. Isomers of the Δ^4 series (compounds IX) could not be isolated in pure form.



R^1 = CN, $COOCH_3$, $COCH_3$



R^1 = CN, $COOCH_3$



VIII IX

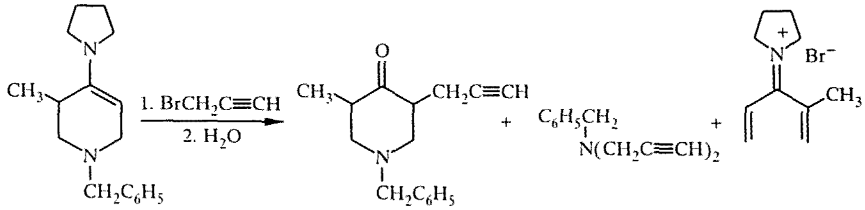
R = $-CH_2CH_2OCH=CH_2$: R^1 = CH_3, C_2H_5, C_3H_7 (VIII+ IX); R = C_6H_5 : R^1 = CH_3 (VIII.1), C_2H_5 (VIII.2), C_6H_5 (VIII.3); R = $C_6H_5CH_2$: R^1 = CH_3 (VIII.4), C_2H_5 (VIII.5), C_6H_5 (VIII.6)

A mixture of isomeric urethanes with a different position of the double bond in the piperideine ring is also formed in the reaction of these iminopiperidines with ethyl chlorocarbonates. Ethyl-N-[1,2,5-trimethyl-Δ^3 (Δ^4)piperidein-4-yl]-N-phenyl(benzyl) carbamates could not be separated chromatographically [26].

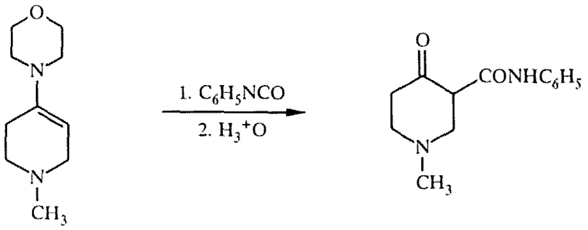
The NMR spectroscopic study of the conformational characteristics of the separated enamidopiperidines VIII is difficult due to amide rotation of the N-aryl-N-acylamino fragment around the $C_{(4)}-N$ bond, which broadens all signals. For compound VIII.3 whose spectrum was recorded in DMSO-D_6 at 100°C, it was possible to assign all signals and to determine the vicinal J_{HH}. Based on these constants, the compound was assigned a half-chair conformation with *trans*-2*e*', 5*a*' position of the methyl groups. Similar data were also obtained for compound VIII.6.

The products of acylation and alkylation of γ-piperidone enamines are of interest as the starting substances in syntheses of condensed polynuclear N-containing heterocycles. In some cases, such heterocycles are formed in one stage without separation of intermediate products.

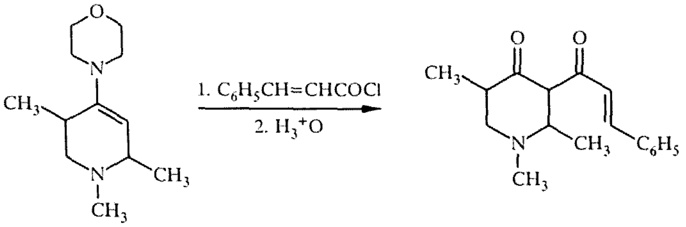
Alkylation of γ-piperidone enamines is hindered by the possibility of irreversible alkylation of the piperidine nitrogen atom. In alkylation of 1-benzyl-5-methyl-4-(pyrrolidinyl-1)piperideine-3, benzyldipropargyl bromide and N-(2-methyl-1,4-dipentalidene-3)pyrrolidinium bromide are formed in significant quantities together with the product of C-alkylation [11].



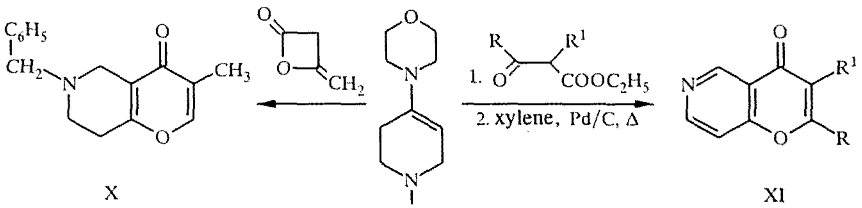
γ-Piperidone enamines are converted into analides of the corresponding piperidic acids by isocyanates. 1-Methyl-4-oxopiperidine-3-carboxylic acid anilide is obtained by this method [27].



Acylation of γ-piperidone enamines also takes place ambiguously. In [8], the heterocyclic diketone 1,2,5-trimethyl-3-cinnamoyl-4-piperidone was separated chromatographically with a low yield (9%) in the reaction of 1,2,5-trimethyl-4-morpholinopiperideine with cinnamic acid chloride.



Condensation of 1-benzyl-4-morpholino-3-piperideine with diketone takes place with the formation of azachromone X with a yield of 65% [28]. This enamine is condensed similarly with β-keto acid esters. Azachromones XI are obtained as a result of debenzylation and aromatization of the initially formed adduct [29].

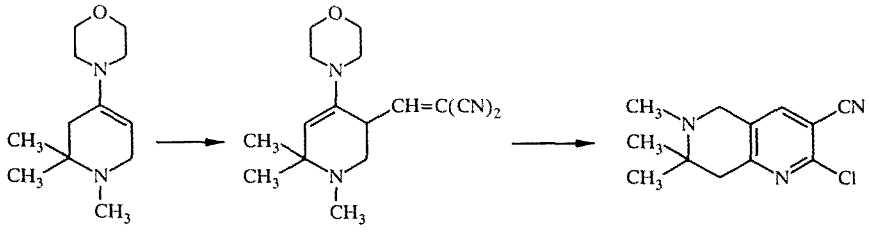


X

XI

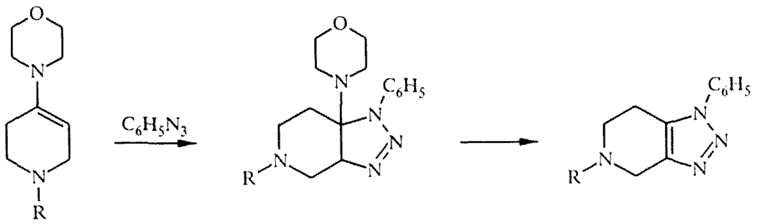
$R = R^1 = CH_3$, 70%
$R = C_6H_5$, $R^1 = H$, 52%

The intermediate product of the reaction of 1,2,2-trimethyl-4-morpholinopiperideine with ethoxymethylenemalononitrile — 1,2,2-trimethyl-5-(2,2-dicyanovinyl)-4-morpholino-3-piperideine (XII) — was isolated in [30]. It was used in synthesis of 2-chloro-6,7,7-trimethyl-3-cyano-5,6,7,8-tetrahydro[1,6]naphthyridine.



XII

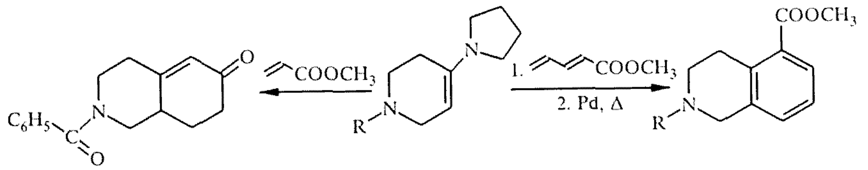
The reaction of 1-methyl(benzyl)-4-morpholino-3-piperideine with phenyl azide takes place like the reaction of [2+3]-cycloaddition with formation of bicycle XIII [1].



$R = CH_3, CH_2C_6H_5$

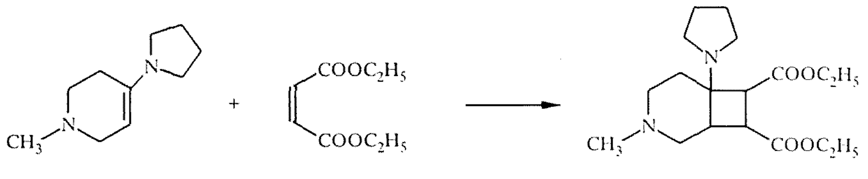
XIII

γ-Piperidone enamines are convenient synthons in construction of a tetrahydroisoquinoline ring. For example, 6-oxo-2-benzoyl-1,2,3,4,6,7-hexahydro-5H-isoquinoline has been synthesized from 1-benzoyl-4-pyrrolidino-3-piperideine and methyl vinyl ketone with a yield of 32% [31, 32]. 1,2,3,4-Tetrahydro-5-carbomethoxyisoquinolines are obtained in condensation of similar enamines with penta-1,3-dienecarboxylic acid methyl ester [33]. These derivatives are used in synthesis of the alkaloids yohimbine and quinine.

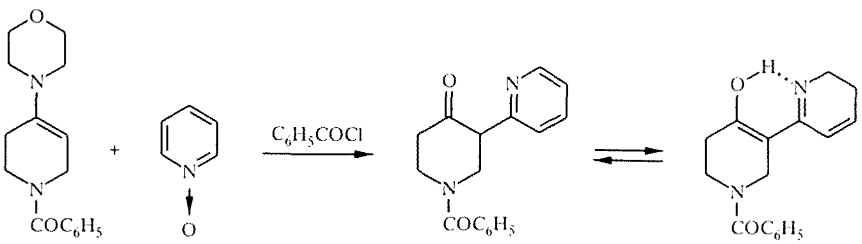


$R = CH_3, CH_2C_6H_5, COC_6H_5$

In the reaction of 1-methyl-4-(pyrrolidinyl-1)piperideine-3 with diethyl maleate, 3-methyl-6-pyrrolidinyl-3-azabicyclo[4.2.0]octane-7,8-dicarboxylic acid diethyl ester is formed with a quantitative yield [34].



The reaction of heteroarylation of γ-piperidone enamines is also a function of the character of the substituent at the piperidine nitrogen atom. No defined substances could be separated from the reaction of N-methyl- and N-benzyl-4-piperidone enamines with pyridine N-oxide in the presence of an acylating agent. When electron-acceptor substituents (acetyl, benzoyl, carbethoxy) are present at the nitrogen atom, γ-piperidone enamines enter into the heteroarylation reaction [35-37]. For example, in the reaction of 1-benzoyl-4-morpholino-3-piperideine with pyridine N-oxide in the presence of benzoyl chloride with subsequent hydrolysis, 1-benzoyl-3-(2-pyridyl)-4-piperidone (XIV) was separated and exists in the enol form [35].



XIV

γ-Piperidone enamines react with quinoline and isoquinoline N-oxides similar to pyridine N-oxides [36].

REACTION WITH NUCLEOPHILIC REAGENTS

γ-Iminopiperidines have been most widely used in synthesis of secondary γ-aminopiperidines — key substrates for fabrication of several drugs.

Reduction of γ-iminopiperidines is the basic method of obtaining such aminopiperidines. Another convenient method of obtaining 4-R-substituted 4-N-aminopiperidines is the reaction of γ-iminopiperidines with organometallic compounds.

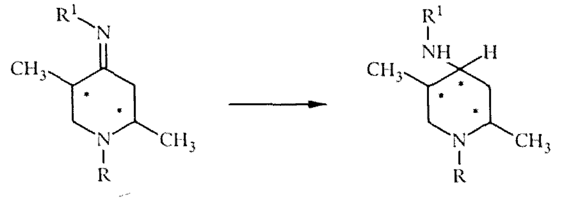
1. Hydride Reduction of 1-Substituted 2,5-Dimethyl-4-N-aryl(hetaryl, alkyl)aminopiperidines

Like the C=O bond, the azomethine bond in γ-iminopiperidines is easily reduced by metal hydride complexes, as well as catalytically. Sodium borohydride has become the most common reducing agent for the C=N bond in such imines. Examples of reduction of 1-R-4-N-iminopiperidines unsubstituted in the piperidine ring and chemical transformations of the amines formed are given in the review in [4].

When there are substituents in the piperidine ring of γ-iminopiperidines, hydride reduction causes the formation of a mixture of stereoisomers, which significantly complicates their use in subsequent transformations and especially in the study of the physiological activity of their derivatives.

The study of reduction of 1-substituted 2,5-dimethyl-4-N-aryl(hetaryl, alkyl)iminopiperidines was initiated for synthesis of compounds of the 4-anilidopiperidine series — analogs of the existing analgesics fentanyl and sufentanil [5].

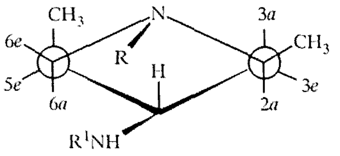
Mixtures of secondary γ-aminopiperidines XVI are formed in reduction of imines XV with sodium borohydride in ethanol or methanol [15, 16, 38-42]. The formation of four geometric isomers (Scheme 2) is theoretically possible with the appearance of a third asymmetric $C_{(4)}$ carbon atom.



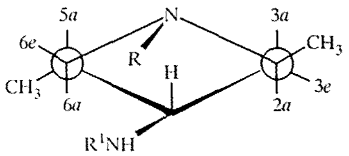
XV XVI

R = CH_3, $CH_2C_6H_5$, $CH_2CH_2C_6H_5$, $CH_2CH(OH)C_6H_5$; R^1 = aryl, hetaryl, alkyl

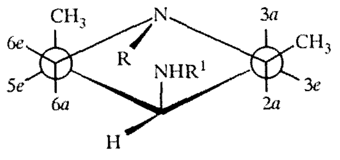
Scheme 2



A: $R^1 = C_6H_5$, $R = CH_3$ (30%); R^1 = 2-C_5H_4N, $R = CH_3$ (15%)



Б: $R^1 = C_6H_5$, $R = CH_3$ (23%); R^1 = 2-C_5H_4N, $R = CH_3$ (12%)



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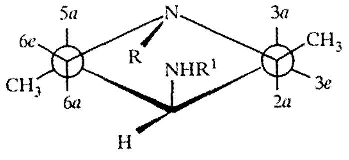
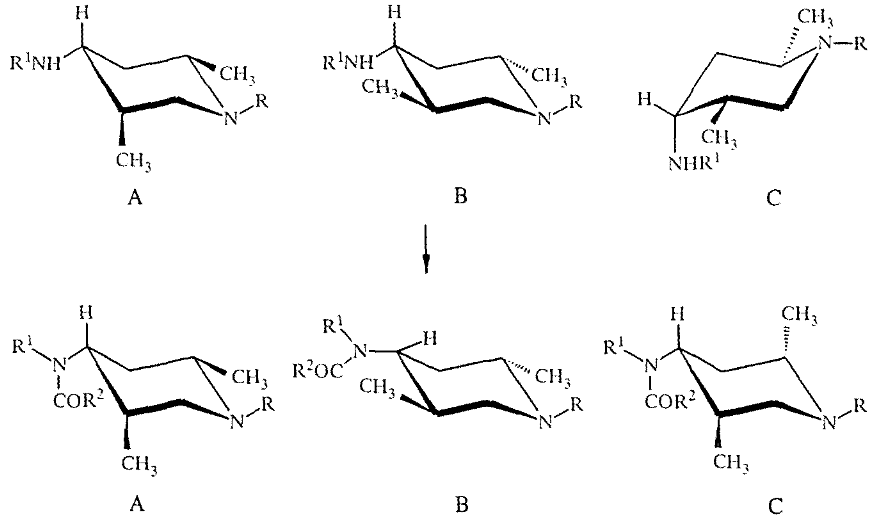


B: $R^1 = C_6H_5$, $R = CH_3$ (20%); R^1 = 2-C_5H_4N, $R = CH_3$ (8%)

Individual isomers of 1,2,5-trimethyl-4-N-phenylaminopiperidine were first described in [4], in which the structure of two chromatographically separated stereoisomers was established: with *cis*-2*e*,5*a* and *trans*-2*e*,5*e* position of the methyl groups and an equatorially oriented phenylamine group. It was shown in [43] that a third isomer with the structure of 1-methyl-2*e*, 5*e*-dimethyl-4*a*-phenylaminopiperidine is formed together with these two isomers. Similar results were obtained in chromatographic separation of 1,2,5-trimethyl-4-N-(2-pyridyl)aminopiperidine.

Separation of three stereoisomeric aminopiperidines during acylation is indirect confirmation of the formation of three stereoisomers in the series of 1-substituted 2,5-dimethyl-4-N-aminopyridines [43-46] (Scheme 3). High-frequency NMR spectroscopy [43, 44], XSA [45], and mass spectrometry [47] were used to establish the configuration and conformation of these isomers.

Scheme 3



XVII $R^1 = R^2 = C_6H_5$, $R = CH_3$; XVIII $R^1 = C_6H_5$, $R^2 = C_2H_5$, $R = CH_2CH_2C_6H_5$

It should be noted that in acylation of the individual stereoisomers of 1,2,5-trimethyl-4-N-phenylaminopiperidine, the piperidine ring in the isomer of amide XVIIC is converted with respect to the starting stereoisomer, amine XVIC, that is, the methyl groups have a less advantageous diaxial conformation. The cause of this is the bulky amide substituent at the $C_{(4)}$ atom which attempts to occupy the equatorial position, resulting in interconversion of the ring. The important dependence of the vicinal SSCC on the solvent in isomer XVIIC nevertheless indicates that the equilibrium 2*a*, 4*e*, 5*a* ⇄ 2*e*, 4*a*, 5*e* exists for manifest predominance of the 2*a*, 4*e*, 5*a* conformation, and it is shifted to the diequatorial form in going from C_6D_6 to the polar solvent $CDCl_3$ [44].

The formation of 1*e*-(2-phenylethyl)-2*a*,5*a*-dimethyl-4*a*-(N-propionylanilido)piperidine (XVIIIC), the most active stereoisomer of the analgesic "Fenaridin" [48, 49], can be explained similarly.

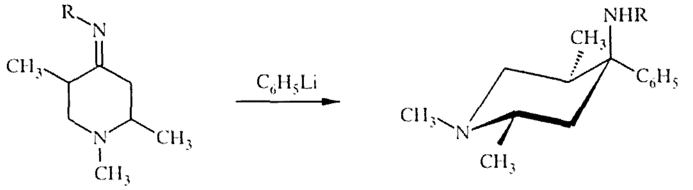
The separation of three stereoisomers as a result of reduction of 1-substituted 2,5-dimethyl-4-N-iminopiperidines thus indicates equally probable axial and equatorial attacks of the hydride hydrogen of the C=N bond of *trans*-2*e*,5*e*-isomers of imines XV and axial attack at the C=N bond of *cis*-2*e*,5*a*-isomers of these imines. Equatorial attack does not occur in this case for steric reasons.

2. Reaction with Organometallic Compounds

The reaction of 1-substituted 2,5-dimethyl-4-N-aryliminopiperidines with organometallic compounds is usually investigated to search for physiologically active compounds in the series of 4-aminopiperidine derivatives formed on one hand, and on the other, to use such compounds as synthons for obtaining different heterocycles, including ones with a spiro structure.

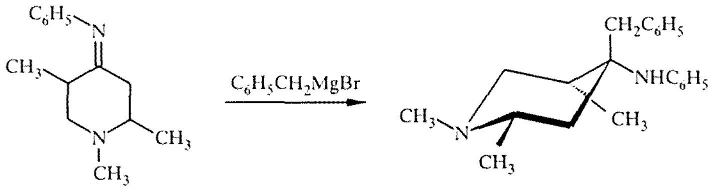
Formation of four geometric isomers should be expected in the reaction of these imines with Grignard reagents. Actually, all four isomers are not formed.

As a function of the structure of the organometallic reagent, its addition takes place with the formation of one (stereospecific) or several (nonsterospecific) isomers. The stereochemistry of addition of organometallic compounds to γ-iminopiperidines had not been investigated prior to our studies. It was possible to hypothesize that predominant equatorial attach of RMgX at the C=N bond will result in predominant formation of *cis*-isomers of amines with axial position of N-arylamine fragments, as in the case of imines of the 2-R-substituted cyclohexanone series. This takes place in the reaction of 1,2,5-trimethyl-4-N-phenyl(benzyl)iminopiperidines with phenyllithium [50, 51]. The structure of the isolated isomers was established by nuclear Overhauser enhancement difference spectroscopy. They have the structure of 1-methyl-2*e*,5*e*-dimethyl-4*e*-phenyl-4*a*-N-phenyl(benzyl)aminopiperidines.



R = C_6H_5, $C_6H_5CH_2$

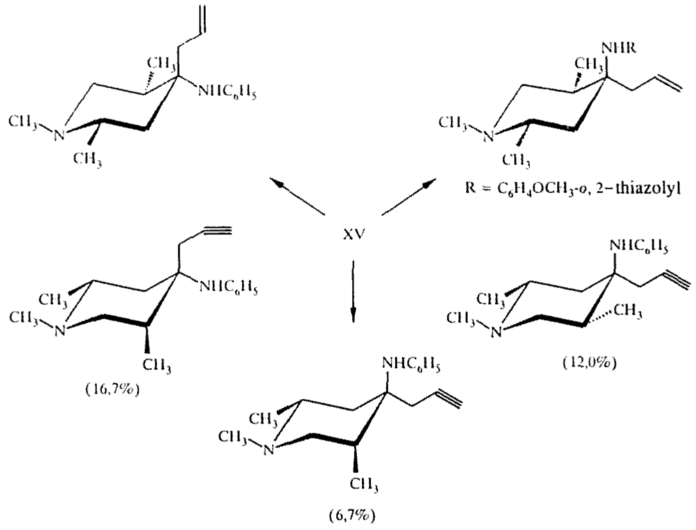
The reaction of imine I with benzylmagnesium bromide also takes place stereospecifically with the formation of one isomer. Only one isomer of 1,2,5-trimethyl-4-benzyl-4-piperidinol was also obtained in [52] from 1,2,5-trimethyl-4-piperidinone and benzylmagnesium bromide. It is important that 1-methyl-2*e*,5*a*-dimethyl-4*a*-benzyl-4*e*-N-phenylaminopiperidine is obtained from imine I and benzylmagnesium bromide, i.e., axial incorporation of the benzyl radical takes place in this case [51].



The reactions of imine I with phenyllithium and benzylmagnesium bromide probably take place by different mechanisms, respectively through a four-term transitional state and with the participation of a resonance-stabilized benzyl anion, which causes the stereospecificity of these reactions.

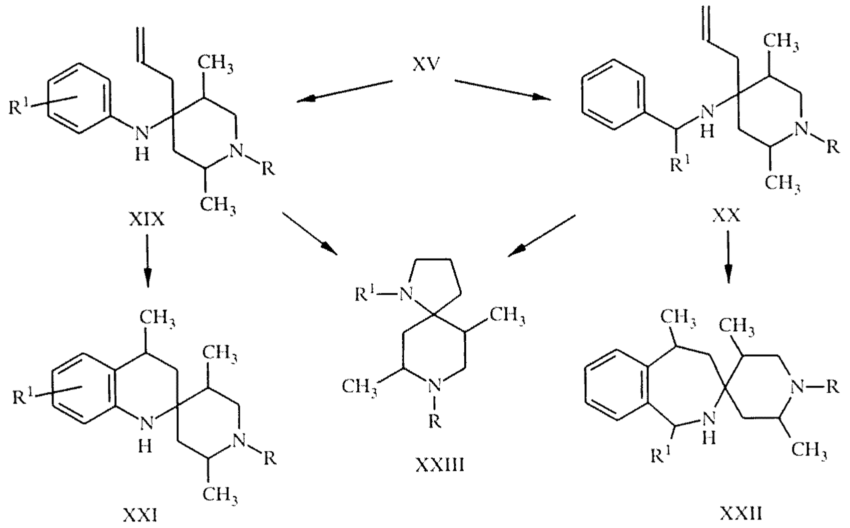
In contrast, the reaction of γ-iminopiperidines with allyl (propargyl)magnesium bromides takes place nonstereospecifically and results in the formation of a mixture of stereoisomers by axial and equatorial attacks [51, 53, 54]. Due to the close chromatographic mobility of 4-allyl-4-N-arylaminopiperidines, all of the stereoisomers cannot be separated in pure form. However, individual stereoisomers with axial and equatorial orientation of the arylamine fragment are separated in the case of the allyl derivative.

Three spectrally characterized individual isomers were separated in the case of 1,2,5-trimethyl-4-propargyl-4-N-phenylaminopiperidine [51].



The corresponding combination of two or more groups capable of reacting with subsequent transformation into a heterocycle in one molecule allows synthesis of alkaloid-like compounds.

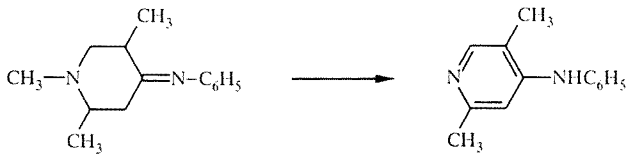
The products of addition of allylmagnesium bromide to γ-iminopiperidines — substituted homoallylamines XIX, XX — were used in syntheses of new heterocyclic spiro compounds: 1,2,3,4-tetrahydrospiro[quinoline-2,4'-piperidines] (XXI), 1,2,4,5-tetrahydro-3H-spiro[2-benzazepine-3,4'-piperidines] (XXII), and spiro[pyrrolidine-2,4'-piperidines] (XXIII). In acid cyclization of 4-allyl-4-N-arylamino-substituted piperidines, spirans XXI [53, 55] are obtained with a yield of 30-77%, while spiro compounds XXII (yield of 20-52%) are obtained from 4-allyl-4-N-benzyl(1-phenylethyl)aminopiperidines [56, 57].



Another direction of cyclization of γ-allyl-γ-arylaminopiperidines XIX, XX is due to the reaction of aminomercuration and closing of the allyl radical at the nitrogen atom with formation of spirans XXIII (yield of 17-23%) [58].

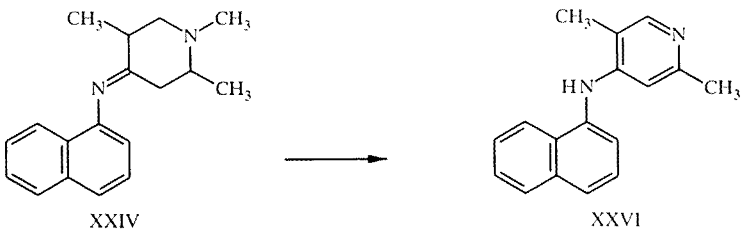
CATALYTIC CONVERSIONS OF 1,2,5-TRIMETHYL-N-(4-PIPERIDYLIDENE)ARYLAMINES

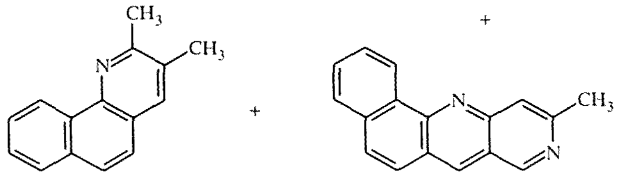
Catalytic conversions of these derivatives have been inadequately studied, but it has been shown that 1,2,5-trimethyl-4-phenyliminopiperidine is converted into 2,5-dimethyl-4-phenylaminopyridine on K-12 catalyst at 410-415°C [59, 60], which can be considered as a method for synthesis of difficult-to-obtain arylaminopyridines and their derivatives.



It has been proposed that N-(1,2,5-trimethyl-4-piperidylidene)-α-(XXIV) and β- (XXV) naphthylamines be used to obtain compounds containing a naphthyridine ring [61, 62].

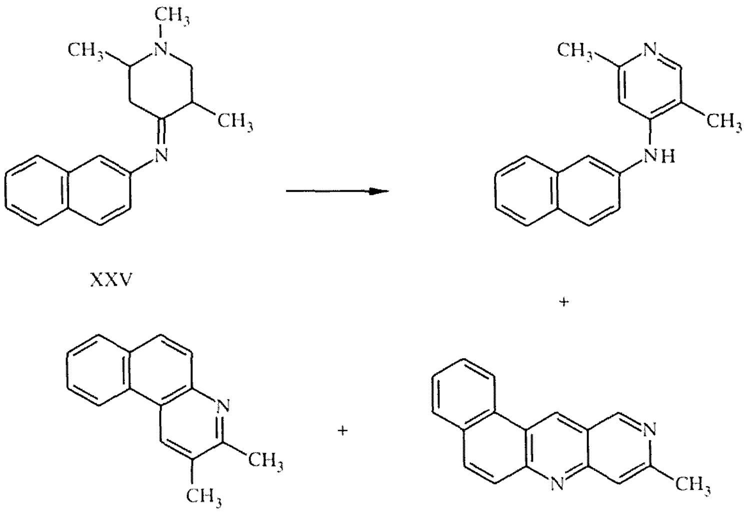
N-(2,5-Dimethyl-4-piperidyl)-α-naphthylamine (XXVI), 9-methylnaphtho[1,2-*b*]-[1,6]naphthyridine (XXVII), and 2,3-dimethyl-4-azaphenanthrene (XXVIII) were obtained from imine XXIV on K-16 catalyst at 380-420°C.





XXVIII XXVII

In similar conditions, N-(2,5-dimethyl-4-piperidyl)-β-naphthylamine (XXIX), 9-methylnaphtho[2,1-*b*][1,6]naphthyl-pyridine (XXX), and 2,3-dimethyl-1-azaphenanthrene (XXXI) were obtained from imine XXV.



XXV

XXXI XXX

These compounds are formed as a result of associated and successive reactions of dehydrogenation and N-demethylation of the piperidine ring, hydrogenation of the C=N bond, and dehydrocyclization of the starting imines.

Substances having analgesic activity comparable to the activity of promedol, antidepressants, and psychostimulants, substances having elevated antisecretory activity, calcium channel blockers, and others have been found among the γ-imino-amino)piperidines and their derivatives synthesized in our laboratory.

The information in the present review generalizes the results of the first stage of investigation of imines and enamines — derivatives of piperidine. If we consider that accessible methods of synthesis of γ-piperidones with a different type of substituents and position in the ring have now been developed, the development of the chemistry of these heterocyclic compounds has great prospects even in this first stage, especially in the search for effective physiologically active substances, and this has already been confirmed in practice.

The use of imines and enamines with piperidine (piperideine) fragments as synthons for obtaining nitrogen-containing heterocycles with a complex structure, in many cases similar to alkaloids, is also promising.

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