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γ-Piperidinones in Organic Synthesis

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Methods for the synthesis of γ-piperidinones and their derivatives, including physiologically active compounds, are considered and the results of studies designed to establish the structures of certain tertiary γ-piperidinols are discussed. Research on the applications of γ-piperidinones in the syntheses of various heterocyclic compounds is surveyed.
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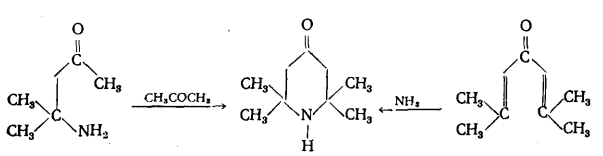
I. INTRODUCTION

Among piperidine derivatives, γ-piperidinones are of primary importance from synthetic, theoretical, and applied standpoints. The development of the synthetic chemistry of piperidine and of the conformational analysis of substituted piperidine bases as well as the synthesis of effective medicinal drugs and of new nitrogen-containing heterocyclic systems are all branches of the chemistry of heterocyclic compounds associated with γ-piperidinones.

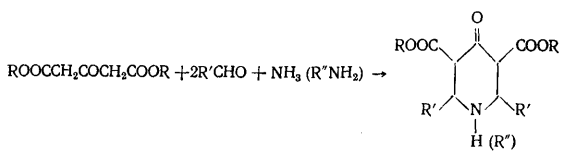
This paper deals with studies carried out mainly in the last twelve years, which characterise the development of certain branches of the chemistry of piperidine and of heterocyclic compounds related synthetically to γ-piperidinones. Studies designed to determine the steric structures of tertiary γ-piperidinols—the starting materials for the synthesis of effective analgesics—are also considered. In the solution of the problems of the configuration and conformation of compounds of this type contradictory con clusions have sometimes been reached. Numerous experimental data have now been obtained, which makes possible an objective and correct conclusion about the steric structures of γ-piperidinols.

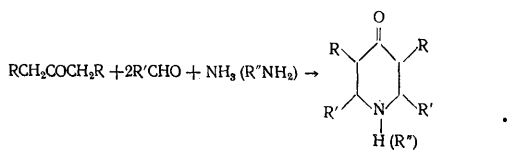
The methods of synthesis of γ-piperidinones are comparatively limited, and can be assigned to two groups as regards the type of reactions involved.

1. The condensation of carbonyl compounds with ammonia or primary amines: of acetone with ammonia (the synthesis of triacetoneamine), of diacetoneamine with ketones, of acetonedicarboxylate esters with aldehydes and ammonia or primary amines, of ketones of β-ketoacid esters with aldehydes and ammonia or primary amines, and of divinyl ketones with ammonia or primary amines. The methods of synthesis of γ-piperidinones from 2-cinnamoyloxirans and primary amines [1,2], from alkenyl β-diethylaminoethyl ketones and methyl amine [3,4], and from diacetone alcohol, ketones, and ammonia [5] are similar to the last method described above. The first γ-piperidinone—2,2,6,6-tetramethyl-4-piperidinone—has been synthesised by the above procedures:

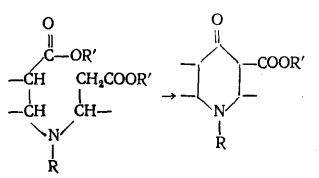


as well as many γ-piperidinones with different ring substituents:





2. Cyclisation of aminodicarboxylate esters by the Dieckmann method:

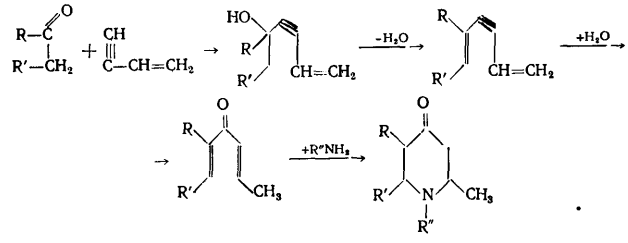


The bibliography of many studies concerning the development of methods of synthesis of γ-piperidinones has been published by Bel'skii et al. [6]

The alkylation and acylation of γ-piperidinones unsubstituted at the nitrogen atom as well as their cyanoethylation have been described. The synthesis of *N*-halogeno-γ-piperidinones has been reported. Treatment of triacetoneamine with perchloryl fluoride led to the isolation of 1-fluoro-2,2,6,6-tetramethyl-4-piperidinone [7]. When 2,5-dimethyl-4-piperidinone hydrochloride is treated with sodium hypochlorite, 1-chloro-2,5-dimethyl-4-piperidinone is formed and is then converted under alkaline conditions into 2,5-dimethyl-1,2-dehydro-4-piperidinone. The latter was isomerised to 2,5-dimethyl-5,6-dihydro-4-pyridone [8]. 1-Amino-2,6-diphenyl-4-piperidinone has been isolated on reducing the corresponding *N*-nitrosopiperidinone with lithium tetrahydroaluminate [9]. Bis-(2,2,6,6-tetramethyl-4-oxo-1-piperidyl) disulphide, which is formed on treating triacetoneamine with sulphur dichloride, dissociates at temperatures in the range 90–200°C with formation of stable radicals [10]. It has been established by spectroscopic methods that the tautomeric equilibrium involving 3,5-diethoxycarbonyl-4-piperidinones is to a large extent displaced towards the enolic form, which is stabilised as

the chelate[11]. The ketonic and enolic forms of 3,5-diethoxycarbonyl-1-ethyl-2,6-diphenyl-4-piperidinone have been isolated[12]. The ratio of the *cis*- and *trans*-isomers of 1-alkyl-2,5-dimethyl-4-piperidinones has been determined chromatographically as a function of different substituents at the nitrogen atom. Under alkaline conditions, the equilibrium is displaced towards the *cis*-form on passing from the methyl to the t-butyl group[13].

Nazarov and his coworkers have made a significant contribution to the development of the chemistry of γ-piperidinones. The consecutive reactions which they devised, namely the condensation of vinylacetylene with ketones and dehydration of the resulting vinylacetylenic alcohols to divinylacetylenic hydrocarbons followed by the hydration of the latter to divinyl ketones, constitute a simple and easy method of synthesis of these previously difficult to obtain compounds.



Before Nazarov's work, the only divinyl ketone derivatives used in the syntheses of γ-piperidinones were phoronone and dibenzylideneacetone. Nazarov's method made it feasible to synthesise γ-piperidinones with a wide variety of substituents in the piperidine ring, the mode of substitution depending on the structure of the ketones used in the condensation with vinylacetylene. 1,2,5-Trimethyl-4-piperidinone is synthesised by this method under industrial conditions[14].

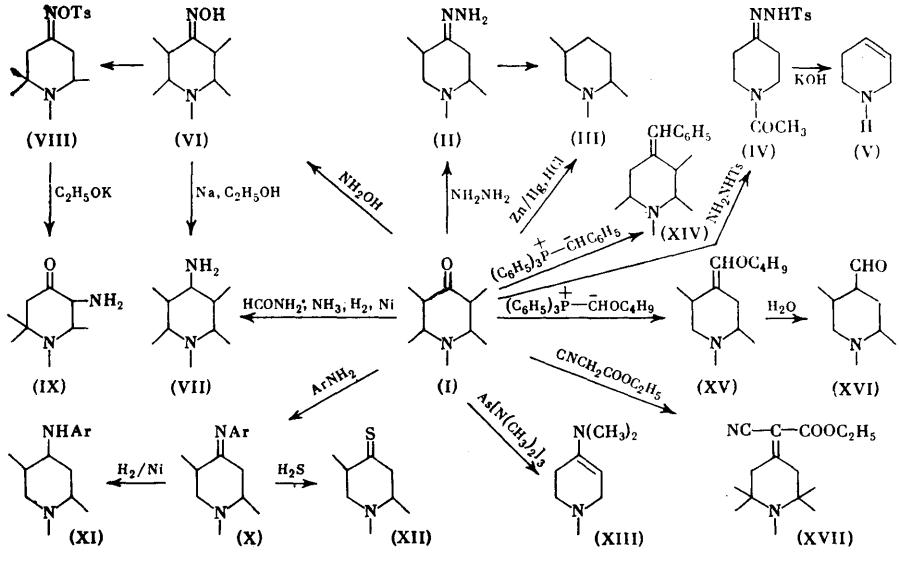
Tetrahydro-γ-pyrones, which are obtained, like γ-piperidinones, from divinyl ketones, are converted into γ-piperidinones by reaction with primary amines[15-17]. The conversion of 2,6-dimethyl-4-pyrone into 1,2,6-trimethyl-4-piperidinone via 1,2,6-trimethyl-4-pyridone and 1,2,6-trimethyl-4-piperidinol has been described[18].

A wide variety of reactions of γ-piperidinones involving the carbonyl group have been examined in a number of studies (Schemes 1 and 2). The reduction of γ-piperidinones (I) to piperidines (III) has been achieved via their hydrazones (II)[9,19-25] and also by the Clemmensen method[25]. Thermal decomposition of 1-acetyl-4-piperidinone toluene-*p*-sulphonylhydrazone in the presence of potassium hydroxide gave a quantitative yield of 1,2,5,6-tetrahydropyridine (V).[26] 1-Acetyl-3-ethoxycarbonyl-4-piperidinone was converted similarly into 1,2,5,6-tetrahydronicotinic acid[27]. The hydrazones of triacetoneamine substituted in the amino-group[28] as well as the hydrazones of this piperidinone with different substituents at the ring nitrogen atom (hydroxy-, nitroso-, etc.)[29] are used as polymer stabilisers. After the oxidation of 3,5-dimethyl-2,6-diphenyl-4-piperidinone semicarbazone with $[2NH_4NO_3 \cdot Ce(NO_3)_4]$, a similarly substituted piperidinone was isolated. Its configuration has been determined[30].

The replacement of carbonyl oxygen by an amino-group in γ-piperidinones has been achieved by reducing their oximes (VI),[21,31-33] by the reaction of the piperidinones with formamide[34], and by reductive amination[35,36]. A number of acyl derivatives of γ-aminopiperidinones (VII) obtained in this way have been described[37]. β-Amino-γ-piperidinones (IX) have been synthesised by treating the sulphonate esters of γ-piperidinone oximes (VIII) with potassium ethoxide[38]. A number of Schiff bases (X), obtained from γ-piperidinones and primary amines, have been described; some of them have been reduced to aryl-(4-piperidyl)amines (XI).[39-43] Treatment of *N*-(1,2,5-trimethyl-4-piperidylidene)aniline with hydrogen sulphide yielded 1,2,5-trimethyl-4-thiopiperidinone (XII).[44] The hydrochloride of 1-methyl-4-thiopiperidinone was isolated in the form of a polymer after treating 1-methyl-4-piperidinone with hydrogen sulphide in an alcoholic solution of hydrogen chloride[45].

The interaction of 1-methyl-4-piperidinone with tris-(dimethylamino)arsine led to the formation of an enamine derived from piperidine, namely 1-methyl-4-dimethylamino-1,2,5,6-tetrahydropyridine (XIII).[46] Its analogue, 1-benzyl-5-methyl-4-(1-pyrrolidinyl)-1,2,5,6-tetrahydropyridine, has been described[47]. 4-Benzylidene-2,6-dimethyl- and 4-benzylidene-3-methyl-2,6-diphenylpiperidines (XIV) have been synthesised by the interaction

Scheme 1



of the corresponding piperidinones with triphenylbenzylidenephosphine[48]. (1-Methyl-$\Delta^{4,\alpha}$-4-piperidyl)acetonitrile and ethyl (1-methyl-$\Delta^{4,\alpha}$-4-piperidyl)acetate have been synthesised by the Wittig reaction from 1-methyl-4-piperidinone[49]. An analogue of the ethyl ester with a benzoyl group attached to the nitrogen atom has been described[50]. Ethyl (1-benzoyl-3-ethyl-$\Delta^{4,\alpha}$-4-piperidyl)-acetate has been obtained by the same procedure[51]. Hydrolysis of 4-butoxymethylene-1,2,5-trimethylpiperidine (XV), which is obtained from 1,2,5-trimethyl-4-piperidinone and butoxymethylenetriphenylphosphine, results in the formation of 4-formyl-1,2,5-trimethylpiperidine (XVI)[52]. This aldehyde has also been obtained from the same piperidinone and chloromethyl ether[53].

(2,2,6,6-Tetramethyl-4-piperidylidene)cyanoacetate ester (XVII), formed on condensation of the cyanoacetate ester with triacetoneamine, is used as an intermediate in the synthesis of the medicinal drug "Temekhin"[42,54]. An analogous compound has been described[55]. The condensation of 1,2,6-trimethyl-4-piperidinone with malonodinitrile gave 4-dicyanomethylene-1,2,6-trimethylpiperidine[56].

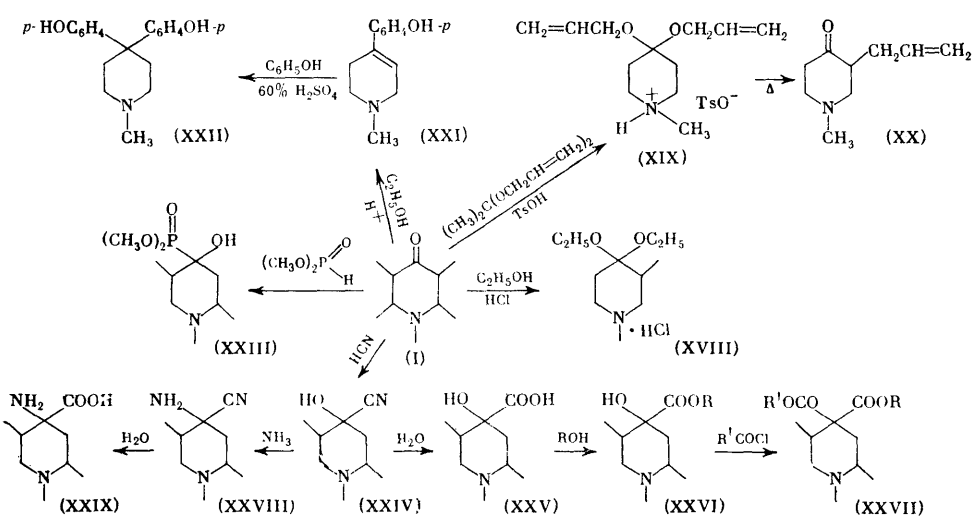
Scheme 2 presents reactions involving addition to the carbonyl group of γ-piperidinones. Triacetonamine ketals have been obtained by treating triacetoneamine with a mixture of the alcohol and benzene in the presence of toluene-*p*-sulphonic acid[57]. On crystallising γ-piperidinone hydrochlorides from an ethanol–ether mixture, their diethyl ketals (XVIII) are readily formed[58,59]. The quaternary salt (XIX) of toluene-*p*-sulphonic acid and 4,4-diallyloxy-1-methylpiperidine, obtained from piperidinone and acetone diallyl ketal in the presence of toluene-*p*-sulphonic acid, was converted into 3-allyl-1-methyl-4-piperidinone (XX) by heat treatment[60]. The condensation of 1-methyl-4-piperidinone with phenols under acid conditions has been investigated. Condensation with phenol led to the isolation of 4-(*p*-hydroxyphenyl)-1-methyl-1,2,5,6-tetrahydropyridine (XXI), which is converted into 4,4-di-(*p*-hydroxyphenyl)-1-methylpiperidine (XXII) on further interaction with phenol[61].

The condensation of 2,5-dimethyl- and 1,2,5-trimethyl-4-piperidinones with dimethyl phosphite has been achieved which led to the formation of 2,5-dimethyl and 1,2,5-trimethyl-4-(OO-dimethylphosphono)-4-piperidinols (XXIII)[62,63]. Diallyl phosphite and dipropargyl phosphite were used in analogous syntheses[64]. The usual procedures have been used to synthesise from γ-piperidinones the cyanohydrins (XXIV) and from the latter the hydroxy-acids (XXV) and their esters involving the carboxy-group [compounds (XXVI)] and the hydroxy-group [compounds (XXVII)].[65-71] Pinacones of the piperidine series—4-aryl(diaryl)-4-hydroxypiperidylmethanols[72]—have been obtained from γ-alkoxycarbonyl-γ-hydroxypiperidines and their pinacoline rearrangement to γ-acyl-γ-arylpiperidines has been carried out[73]. The conversion of γ-piperidinone cyanohydrins into γ-dialkylamino-γ-cyanopiperidines has been described and the latter have been converted into γ-dialkylaminopiperidines and γ-alkyl (aryl)piperidines[74,75]. γ-Amino-γ-carboxypiperidines (XXIX) have been obtained both from γ-amino-γ-cyanopiperidines (XXVIII)[76] and from γ-carboxy-γ-hydroxypiperidines (XXV).[77]

The second group of reactions of γ-piperidinones consists of their condensation reactions (Scheme 3). When γ-piperidinones (I) are condensed with benzaldehyde, both 3-benzylidene-[compounds (XXX)] and 3,5-dibenzylidene-derivatives [compounds (XXXI)] are formed[78-82]. Similar condensations with various aromatic aldehydes, including heterocyclic aldehydes, have been described[83-85]. 1-Acetyl-3-methoxycarbonyl-2,5-dimethyl-4-piperidinone (XXXII) has been obtained by the condensation of the corresponding piperidinone with dimethyl carbonate in the presence of sodium ethoxide[86]. The condensation of 1,2,5-trimethyl-4-piperidinone with formaldehyde, resulting in the 3-hydroxymethyl derivative (XXXIII) of this piperidinone, has been achieved[87]. 3-Dialkylaminomethyl-4-piperidinones (XXXIV) have been obtained by the Mannich condensation of γ-piperidinones[88-90]. Ethyl β-(3-ethoxycarbonyl-1-methyl-4-oxo-3-piperidyl)propionate (XXXV) has been obtained from 3-ethoxycarbonyl-1-methyl-4-piperidinone and ethyl acrylate in the presence of sodium hydride[58,91].

The cyanoethylation of γ-piperidinones with alkyl substituents in the β-position, which leads to the formation of β-alkyl-β-cyanoethyl-γ-piperidinones (XXXVI), has been described[92-95]. Further cyanoethylation of such piperidinones yielded $\beta\beta'$-di-(2-cyanoethyl)- and $\beta\beta\beta'$-tri-(2-cyanoethyl)-γ-piperidinones[96]. The condensation of 1,2,5-trimethyl-4-piperidinone (as well as its *N*-unsubstituted analogue) with bis-(β-methylvinyl) ketone leads to

Scheme 2



the formation of 1,2,5-trimethyl-5-(5-methyl-3-oxohex-4-en-1-yl)-4-piperidinone (XXXVII).[97] When 2,5-dimethyl-4-piperidinone was condensed with α-vinylpyridine in the presence of sodium, 2,5-dimethyl-5-[β-(2-pyridyl)-ethyl]-4-piperidinone (XXXVIII) was obtained[98].

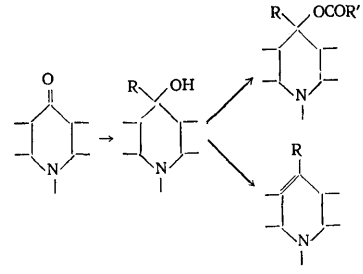
Treatment of 1-alkoxy-3-methoxycarbonyl-4-piperidinones with methyl iodide in the presence of sodium ethoxide yields 1-alkoxy-3-methoxycarbonyl-3-methyl-4-piperidinones[99]. The synthesis of 3-allyl-1-benzyl-4-piperidinone by alkylating 1-benzyl-4-piperidinone with allyl bromide after its preliminary treatment with sodium t-butoxide has been described[100]. Similar alkylation of γ-piperidinones has been described in another communication[55]. Treatment of 3-ethoxycarbonyl-1-methyl-4-piperidinone with benzyldimethylphenylammonium chloride and with allyldimethylphenylammonium bromide followed by hydrolysis and decarboxylation of the alkylation products yielded 3-benzyl(allyl)-1-methyl-4-piperidinones[101]. 1-Benzoyl-3-ethoxycarbonyl-3-propargyl-4-piperidinone (XXXIX) has been obtained from 1-benzoyl-3-ethoxycarbonyl-4-piperidinone and propargyl bromide[47].

Iminoxy-radicals (free radicals), which are chemically based on triacetoneamine and its derivatives substituted in the γ-position, occupy an independent place in the chemistry of γ-piperidinones[102-104].

II. SYNTHESES OF PHYSIOLOGICALLY ACTIVE PIPERIDINE DERIVATIVES FROM γ-PIPERIDINONES

The first physiologically active piperidine derivatives described, including medicinal drugs, consisted of esters of secondary γ-piperidinols. More than 80 reports have been published in which the reduction of γ-piperidinones to γ-piperidinols by various methods and their esterification are described. Some of the esters exhibit physiological activity, but have not found applications for different reasons. α-Eucaine (4-benzoyloxy-4-methoxycarbonyl-1,2,2,6,6-pentamethylpiperidine) and β-eucaine (4-benzoyloxy-2,2,6-trimethylpiperidine), which are powerful anaesthetics but exhibit an undesirable secondary activity, as well as a mydriatic preparation eucatropine (euphthalmine) (the ester of 1,2,2,6-tetramethyl-4-piperidinol and mandelic acid) are nowadays only of historical interest.

The esters of tertiary γ-piperidinols proved to be piperidine derivatives, obtainable from γ-piperidinones, which are important from the practical point of view. Various methods have been used to synthesis γ-hydroxy-derivatives with a tertiary hydroxy-group from γ-piperidinones; one of these involves the preparation of γ-piperidinols with the aid of organomagnesium and organolithium compounds[12,18,19,23,58,60,99-101,105-176]. Certain tertiary γ-piperidinols have been obtained from γ-piperidinones by the Reformatskii reaction[177,178]. The condensation of γ-piperidinones with ketones in the presence of ion-exchange resins, which results in the formation of tertiary γ-piperidinols containing β-hydroxyalkyl groups in the 4-position, has been described[179]:

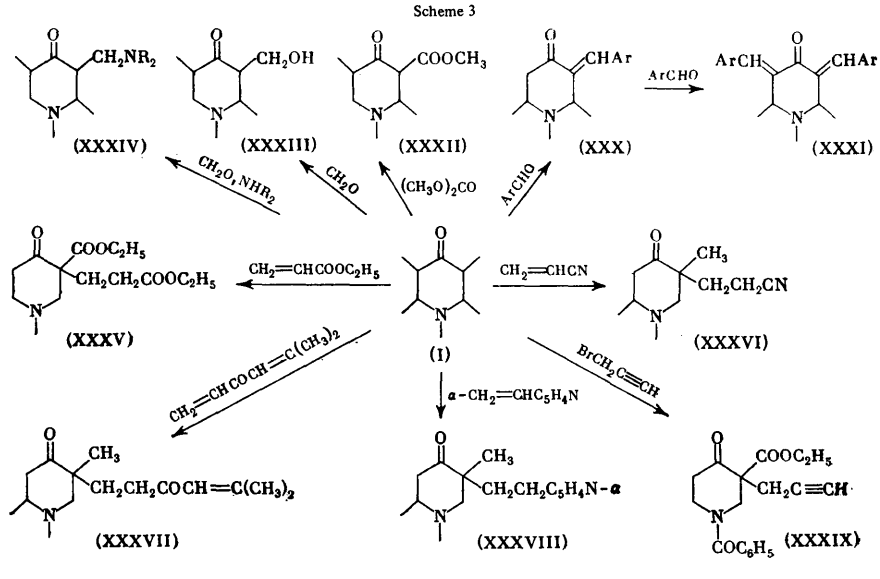


Many of the γ-piperidinols synthesised have been isolated in the form of individual isomers. Apart from the esterification of tertiary γ-piperidinols in order to obtain pharmacologically active compounds[18,19,99-101,105-109,112,114,116,117,120-122,124-126,128,129,131-133,135-137,139,142,146,148,150,155,158,167,170-175,180-197], their dehydration has also been studied, mainly in connection with the determination of the configurations of γ-piperidinols and the synthesis of piperidines which were used in the syntheses of pyridine bases[107,110,113,115,117,127,144-147,151,156,157,162,168,176,178,198-205].

The syntheses of tertiary γ-piperidinols and their esters have been carried out on a large scale. Effective analgesics have been found amongst them.

The ethers of tertiary γ-piperidinols have been inadequately investigated, partly due to certain difficulties in their synthesis. A method has been developed for the conversion of the esters of such alcohols into ethers by heating them with an excess of hydrogen chloride in an

Scheme 3



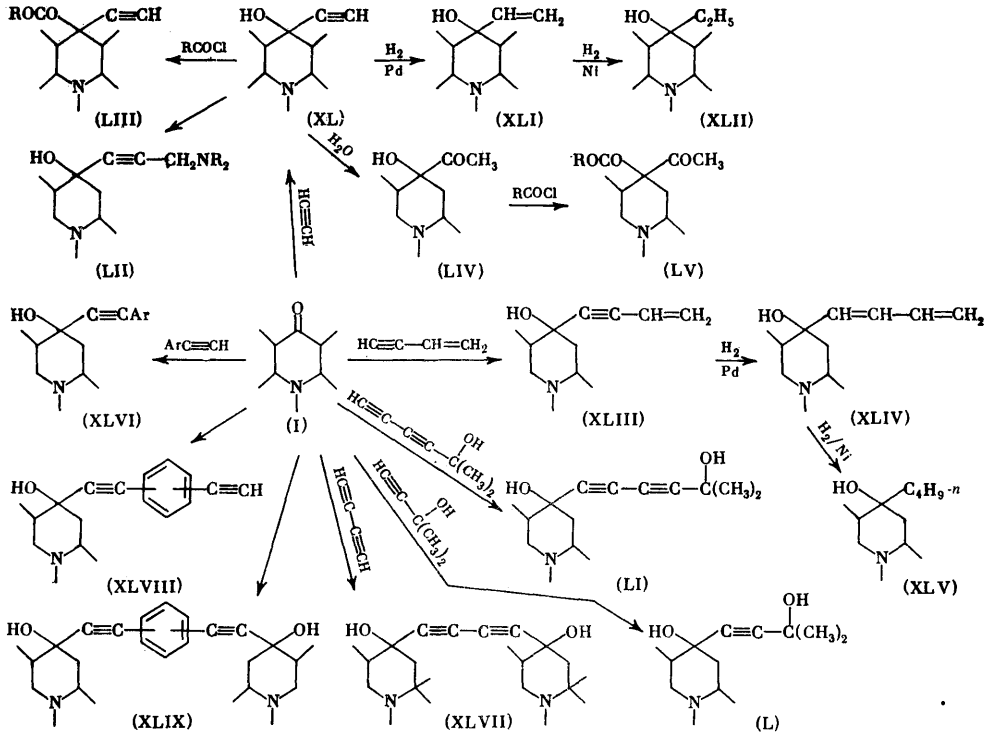
alcoholic solution. Thus 1-benzyl-4-ethoxy-4-α-furyl-3-methylpiperidine, which exhibits a considerable analgesic activity, has been obtained from 1-benzyl-4-α-furyl-3-methyl-4-propionyloxypiperidine[141,206,207]. The cyanoethylation of tertiary γ-piperidinols in the presence of potassium hydroxide leads to the formation of γ-(2-cyanoethoxy)piperidines[208]. The condensation of γ-piperidinones with acetylenic compounds has been carried out by familiar methods (Scheme 4). Many 4-ethynyl-4-piperidinols (XL) have obtained from γ-piperidinones (I), with various substituents in the ring and at the nitrogen atom, by condensation with acetylene; in many instances isomeric piperidinols were isolated and their steric structures established. Partial [to γ-vinylpiperidinols (XLI)] and complete to [γ-ethylpiperidinols (XLII)] hydrogenation of the ethynyl group has been achieved[69,112,180,184,209-233]. 4-Vinylethynylpiperidinols (XLIII) have been synthesised by condensing γ-piperidinones with vinylacetylene or vinylethynylmagnesium bromide. Partial [to piperidinols (XLIV)] and complete [to piperidinols (XLV)] hydrogenation of the vinylethynyl group has been achieved[112,114,234]. Analogous condensations of γ-piperidinones have been carried out with phenylacetylene[117,146,225,235,236] and naphthylacetylenes[237] [the synthesis of the piperidinols (XLVI)]. 4-Butadiynyl-4-piperidinols have been synthesised by the Chodkiewicz–Cadiot method from 4-ethynyl-4-piperidinols and bromo-derivatives of monosubstituted acetylenes[238]. The condensation of 2,2,5-trimethyl-4-piperidinone with diacetylene yielded a diacetylenic glycol—di-(4-hydroxy-2,2,5-trimethyl-4-piperidyl)-diacetylene (XLVII). An analogous glycol was obtained by the oxidative dimerisation of individual isomers from 4-ethynyl-1,2,5-trimethyl-4-piperidinol and was then hydrogenated[232,239,240]. Similar glycols have also been described[218].

Diethynylbenzenes with the ethynyl groups and other substituents in different positions in the benzene ring have been condensed with 1,2,5-trimethyl-4-piperidinone and condensation products involving both one [compounds (XLVIII)][238,241] and two [compounds (XLIX)][241,242] ethynyl groups have been obtained. The condensation of 1,2,5-trimethyl-4-piperidinone with ethynyldimethylmethanol [the synthesis of the glycol (L)][243] and of 2,5-dimethyl-4-piperidinone with diethynyldimethylmethanol [the synthesis of the glycol (LI)][219] have been achieved.

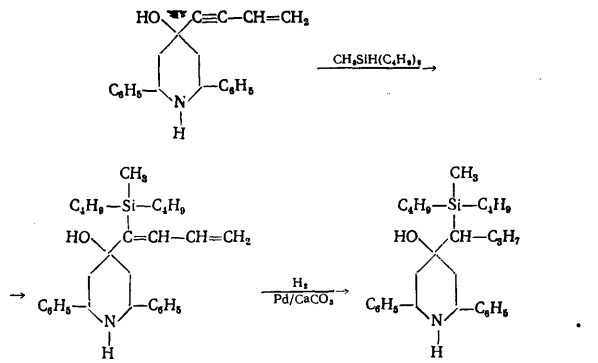
A large number of dialkylaminomethylethynyl derivatives (LII) of acetylenic piperidinols (XL) with terminal acetylenic hydrogen have been synthesised from the latter by the Mannich method[193,217,224,231,244-249]. The condensation of acetylenic piperidinols with ketones[250] and the cyanoethylation of the resulting glycols have been investigated[251]. The esters (LIII) of the acetylenic alcohols (XL) have been obtained and the triple bond has been hydrated [the synthesis of 4-acetyl-4-piperidinols (LIV) and their esters (LV)] and a number of other reactions involving the ethynyl group have been carried out[69,71,146,213,216,221,223,231,238,252-263]. The aminomethylation[264] and cyanoethylation[265-267] of acetylenic γ-piperidinols at the hydroxy-group as well as the preparation of their carbamates have been described. 4-Vinyl-4-piperidinols, obtained by the partial hydrogenation of 4-ethynyl-4-piperidinols by oxidation with hydrogen peroxide, have been converted into 4-epoxy-4-hydroxy-derivatives of piperidine.

Only limited studies have been made of the synthesis of silicon-containing piperidine derivatives, including tertiary γ-piperidinols. When 2,6-diphenyl-4-vinyl-ethynyl-4-piperidinol was treated with dibutylmethylsilane in the presence of a Spier catalyst, 4-(1-dibutylmethylsilylbuta-1,3-dienyl)-2,6-diphenyl-4-piperidinol was

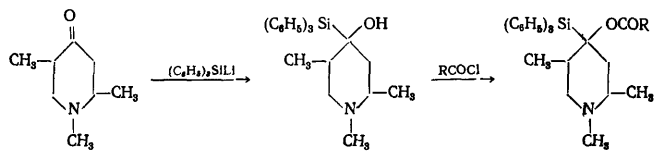
Scheme 4



isolated and then converted by hydrogenation into 4-(1-dibutylmethylsilyl-1-butyl)-2,6-diphenyl-4-piperidinol. An analogous reaction has been carried out with 1,2,5-trimethyl-4-vinylethynyl-4-piperidinol[268]:



Another example is provided by the synthesis of the isomeric 1,2,5-trimethyl-4-triphenylsilyl-4-piperidinols and their esters from 1,2,5-trimethyl-4-piperidinone and triphenylsilyl-lithium[269]:

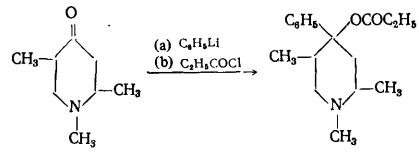


Pharmacological study of secondary and tertiary γ-piperidinols has shown that they are as a rule physiologically inactive. The analgesic activity of the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols has been erroneously reported[270]. However, tertiary γ-piperidinols include the neuroplegic preparation 4-*p*-chlorophenyl-1-(3-benzoyl-1-fluoropropionyl)-4-piperidinol. According to preliminary data[269], 1,2,5-trimethyl-4-triphenylsilyl-4-piperidinol exhibits a bactericidal activity.

The most active analgesics proved to be the esters of propionic acid and tertiary γ-piperidinols with a phenyl substituent in the 4-position. Two of these preparations have been introduced into medical practice, namely prodine (α-prodine, Nisentil, anedol) and promedol, and have found extensive applications and have significantly limited the use of morphine as an analgesic.

Prodine (the hydrochloride of 1,3-dimethyl-4-phenyl-4-propionyloxypiperidine) was obtained as follows. The cyclisation of (β-methoxycarbonylethyl)-(β-methoxycarbonylpropyl)methylamine results in the formation of 5-methoxycarbonyl-1,3-dimethyl-4-piperidinone, from which 1,3-dimethyl-4-piperidinone is formed after hydrolysis and decarboxylation[271]. The reaction of this piperidinone with phenyl-lithium yielded a mixture of isomeric 1,3-dimethyl-4-phenyl-4-piperidinols and then the propionate esters of both isomers (α-prodine and β-prodine)[109]. The high analgesic activity of prodine has been reported[105]. The synthesis of compounds analogous to prodine has been described in reports of independent investigations[108,110].

1,2,5-Trimethyl-4-piperidinone is used in the synthesis of promedol (the hydrochloride of 1,2,5-trimethyl-4-phenyl-4-propionyloxypiperidine)[116,272]. In the technique employed promedol is obtained without isolating 1,2,5-trimethyl-4-phenyl-4-piperidinol by treating with propionyl chloride the lithium alkoxide derived from this alcohol:



The following method is more rational: synthesis of 1,2,5-trimethyl-4-phenyl-4-piperidinol, isolation (crystallisation and chromatographic separation) of the γ-isomer from the mixture of isomers, and esterification of the γ-isomer (yield more than 90%) with propionic anhydride in the presence of pyridine.

III. THE STERIC STRUCTURES OF CERTAIN TERTIARY γ-PIPERIDINOLS

Numerous studies have been devoted to the stereochemistry of secondary and tertiary γ-piperidinols. Studies of this kind are being vigorously continued also at the present time. In this review our aim is to examine research in this field associated with the chemistry of γ-piperidinols. This was done to some extent in a previous review[273], but the latter has already become obsolete.

We shall consider only studies associated with the investigation of the configurations and conformations of isomeric 1,3-dimethyl-4-phenyl-4-piperidinols and 1,2,5-trimethyl-4-phenyl-4-piperidinols. The choice of these compounds is dictated by several factors. In the first place, the γ-piperidinols are used as the starting materials in the syntheses of effective analgesic medicinal preparations—the isomeric prodines and the isomeric promedols. Among the numerous derivatives of γ-piperidinones, only these compounds have found extensive applications in medicinal practice. The conformational analysis of piperidine derivatives was initiated in studies undertaken to investigate the stereochemistry of the above piperidinols using in the first place chemical and then spectroscopic methods. Many workers who studied the structures of the isomeric prodines and promedols frequently reached contradictory conclusions. Whereas in the case of the isomeric 1,3-dimethyl-4-phenyl-4-piperidinols these contradictions were fairly rapidly eliminated, in the case of the 1,2,5-trimethyl analogues they accumulated in the course of time, which not only interfered with the solution of this specific problem but to some extent inhibited the development of the conformational analysis of piperidine systems. Unfortunately the authors who categorically adhered to an erroneous treatment of the mixture of isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols[270,274] later changed their views without reporting any reasons for the earlier incorrect conclusions[261,275].

The preparation of a mixture of isomeric 1,3-dimethyl-4-phenyl-4-piperidinols and the hydrochlorides of their propionates—the α-isomer (m.p. 212–214 °C; 220–221 °C according to other data[125]) and the β-isomer (m.p. 190 to 192 °C; 195–196 °C according to other data[125])—was first reported by Ziering and Lee[109], who also presented the experimental results for the isolation of the enantiomers of β-prodine with the aid of D-tartaric and L-malic acids. The diastereoisomers of 1,3-dimethyl-4-phenyl-4-piperidinol were designated as α-form (m.p. 100–101 °C) and the β-form (m.p. 116–118 °C) (the hydrochlorides of the corresponding propionates were indicated above). The

following configuration, later shown to be erroneous, was initially attributed to them (on the basis of infrared spectroscopic data alone[276]): *cis*-disposition of the methyl group at $C_{(3)}$ and of the phenyl group at $C_{(4)}$ for the α-form and *trans*-disposition of the same substituents for the β-form[109,124]. Erroneous configurations were also assigned to structural analogues of the above α- and β-forms of piperidinols containing substituents other than the methyl group at $C_{(3)}$. The fact that these conclusions concerning structure, for example, for the α- and β-isomers of 3-allyl-1-methyl-4-phenyl-4-piperidinols[124], were unsound was demonstrated by Bell and Portoghese[60].

The problem of the configurations and conformations of the α- and β-isomers of 1,3-dimethyl-4-phenyl-4-piperidinols was solved initially by chemical and then by spectroscopic methods. The steric structures of the α- and β-isomers of 1,3-dimethyl-4-phenyl-4-piperidinols and their analogues (the α- and β-series), with other substituents at the nitrogen and $C_{(3)}$ atoms, were studied in a number of investigations. It was established that the proportion of piperidinols of the α-series is much greater than that of the compounds of the β-series owing to more favourable steric conditions for the formation of the former with the *trans*-disposition of the substituent at $C_{(4)}$ relative to that at $C_{(3)}$. The esters of the β-isomers of piperidinols hydrolyse at a higher rate than those of the α-isomers[277] and the β-isomers are more readily esterified than the α-isomers (axial hydroxy-group). The interaction of β-isomers of piperidinols with thionyl chloride involves the exchange of the hydroxy-group for chlorine, while the reaction of the α-isomers involves mainly dehydrochlorination. On the basis of these data, it was concluded initially that the α-isomer of the piperidinol corresponding to prodine has the structure of 1,3*e*-dimethyl-4*e*-phenyl-4-piperidinol[136,278,279]. It was established that the α- and β-isomers of piperidinols have infrared spectra with characteristic features[125].

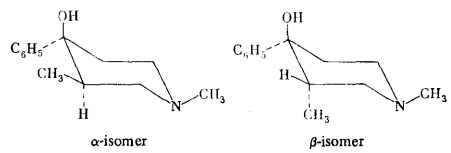
X-Ray diffraction analysis of α-prodine (the hydrochloride of the propionate of the α-isomer of 1,3-dimethyl-4-phenyl-4-piperidinol) showed that its molecule has the "chair" conformation with the phenyl group in the equatorial position, while the methyl group at $C_{(3)}$ is in the *trans*-position relative to the phenyl group at $C_{(4)}$.[280,281] X-Ray diffraction study of the hydrobromide and hydrochloride of β-prodine led to the conclusion that its molecule also has "chair" conformation, and that the methyl group at $C_{(3)}$ and the equatorial phenyl group are in the *cis*-positions[282-284]. An analogous conclusion about the configurations and conformations of the α-isomer of 1,3-dimethyl-4-phenyl-4-piperidinol (the CH_3 and equatorial C_6H_5 groups in the *trans*-position) and the β-isomer (the CH_3 and equatorial C_6H_5 groups in the *cis*-position) was reached on the basis of a study of their ^1H NMR spectra[150,285-288] as well as the spectra of their esters[289].

The results obtained in a study of the products of the dehydration of the isomeric α- and β-1,3-dimethyl-4-phenyl-4-piperidinols under the conditions of acid catalysis (*trans*-elimination, E2 mechanism) were also used to demonstrate the configurations of these piperidinols. Dehydration of the β-isomer under comparable conditions leads to the formation of 1,5-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine, while dehydration of the α-isomer results in the formation of approximately equal amounts of 1,3-dimethyl-4-phenyl, and 1,5-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridines[151]. The same results were obtained in a study of the dehydration of the 4-*o*-tolyl analogues of the α- and β-isomers of this piperidinol[162].

The synthesis of the enantiomers of the α-isomer of 1,3-dimethyl-4-phenyl-4-piperidinol from the enantiomers of 3-allyl-1-methyl-4-phenyl-4-piperidinol has been achieved. Treatment of the optical isomers of this piperidinol with osmium tetroxide and then with sodium periodate yielded the enantiomers of the 3-formylmethyl derivative, which was isolated in the form of hemiacetals. Decarbonylation of the latter yielded the enantiomers of the α-isomer of 1,3-dimethyl-4-phenyl-4-piperidinol $\{[\alpha]_D = +5.6$ and $[\alpha]_D = -5.8\}$.[290] The synthesis of α- and β-prodines (hydrochlorides) labelled with tritium in the phenyl group and the isolation of their optical isomers have been described. The following characteristics of the optical isomers were obtained:

(+)-[^{3}H] C_6H_5-α — m.p. 190—191°, $[\alpha]_D = +35.3°$;
(−)-[^{3}H] C_6H_5-α — m.p. 194—195°, $[\alpha]_D = -37.5°$;
(+)-[^{3}H] C_6H_5-β — m.p. 185—186°, $[\alpha]_D = +66.8°$;
(−)-[^{3}H] C_6H_5-β — m.p. 190—191°, $[\alpha]_D = -71°$.

The separation of the isomeric piperidinols into their enantiomers, which were subsequently propionylated, was achieved with the aid of tartaric and dibenzoyltartaric acids. It was established that the (+)-enantiomers are more active analgesics than the (−)-enantiomers[172,291]. Thus (+)-α-prodine is 25 times more active than (−)-α-prodine; the analogous β-prodines have activities differing by a factor of 13.[292] Thus one may assume that the problem of the configurations and conformations of the α- and β-isomers of 1,3-dimethyl-4-phenyl-4-piperidinols has been solved[293].



The problem of elucidating the steric structures of the three isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols, which are formed when 1,2,5-trimethyl-4-piperidinone reacts with phenyl-lithium, is more complex: the α-isomer (m.p. 106—107°C) from which α-promedol is derived (its analgesic activity is higher than that of morphine approximately by a factor of 4—6), the β-isomer (m.p. 102—103°C) from which isopromedol is derived (more active than promedol by a factor of 2—3), and the γ-isomer (m.p. 107—108°C) from which promedol is derived (more active than morphine by a factor of 2—3).[116] The racemic promedol was resolved into enantiomers; it was established that the (+)-enantiomer is approximately 9 times more active than the (−)-enantiomer[175]. The formation of only these three isomeric piperidinols has now been established by careful and repeated studies of the products of the reaction of 1,2,5-trimethyl-4-piperidinone with phenyl-lithium.

The existence of two isomers (*trans*- and *cis*- with respect to the methyl groups at $C_{(2)}$ and $C_{(5)}$ in 1,2,5-trimethyl-4-piperidinone) gave rise to no doubts, because interaction of this piperidinone with phenyl-lithium leads to the formation of three isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols. Experimental study of the isomerism of this piperidinone, which confirmed its existence in the *trans*- and *cis*-forms with the former, containing equatorial methyl groups, greatly predominating, was carried out with the aid of its ^1H NMR spectrum and the exchange of α-protons for deuterium[294]. The isolation of the *trans*-isomer of 1,2,5-trimethyl-4-piperidinone has been described[130].

In one of the first studies [127] associated with the solution of the problem of the configurations and conformations of the α- and γ-isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinone chemical methods were used. The α- and γ-isomers of 2,5-dimethyl-, 1,2,5-trimethyl-, and 1-acetyl-2,5-dimethyl-4-phenyl-4-piperidinols were synthesised and related to one another by the usual transformations. The γ-isomers greatly predominated in the synthesis of the first two piperidinols. Since the N⇌O acyl migration takes place in the γ-isomer of 1-acetyl-2,5-dimethyl-4-phenyl-4-piperidinol, it was concluded that the hydroxy-group in this isomer is in the axial position. In the α-isomer the N→O acyl migration takes place under more severe conditions with inversion of the configuration at $C_{(4)}$, since the same acetoxy-derivative is formed as from the γ-isomer. These transformations indicate the identical *trans*-equatorial dispositions of the methyl groups at $C_{(2)}$ and $C_{(5)}$ (the most favourable conformation for both the initial piperidinone and the piperidinols) in the α- and γ-isomers and of the equatorial disposition of the hydroxy-group in the α-isomer.

The same conclusion was reached in a study of the chromatographic mobilities of the γ- and α-isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinol [295]. An analogous relation has been established for the γ- and α-isomers of 1,2,5-trimethyl-4-*m*.-tolyl-4-piperidinol [157]. A quantitative study has been made [296] of the esterification of the α- and γ-isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinol and it has been shown that the α-isomer, with the equatorial hydroxy-group, is esterified much faster than the γ-isomer. The same behaviour has been established in a study of the hydrolysis of the esters of both these isomeric piperidinols.

The infrared spectra of the γ- and β-isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinol have the same characteristics as the spectra of the analogous 3-alkyl-4-aryl-4-piperidinols with the *trans*-disposition of the alkyl and aryl groups [200].

The configuration of the α-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidinol has been indirectly confirmed [273, 289, 297]. Since β-prodine and α-promedol have almost the same analgesic activities in the series of the isomeric prodines and promedols, it has been suggested that they have the same *cis*-configurations of the CH_3 group in the β-position and the C_6H_5 group in the γ-position, which proved to be true.

Erroneous conclusions about the configurations and conformations of the isomeric α-, β-, and γ-1,2,5-trimethyl-4-phenyl-4-piperidinols were reached [270]. Unfortunately, in order to determine the steric structures of these isomers, the authors confined themselves to the results of qualitative esterification and dehydration experiments, which could not serve as a basis for the solution of conformational problems. The structure of 1,2*e*,5*e*-trimethyl-4*e*-phenyl-4-piperidinol was attributed to the α-isomer (m.p.106–107°C), which is actually 1,2*e*,5*e*-trimethyl-4*a*-phenyl-4-piperidinol, the structure of 1,2*a*,5*e*-trimethyl-4*a*-phenyl-4-piperidinol was attributed to the β-isomer (m.p. 102–103°C), which is actually 1,2*a*,5*e*-trimethyl-4*e*-phenyl-4-piperidinol, and the structure of 1,2*e*,5*e*-trimethyl-4*a*-phenyl-4-piperidinol was attributed to the γ-isomer (m.p. 107–108°C), which is actually 1,2*e*,5*e*-trimethyl-4*e*-phenyl-4-piperidinol. Shvetsov and Kucherov [270] also failed to take into account the published experimental data [127] concerning the determination of the structures of the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols. In estimating the rates of esterification of γ-piperidinols isomeric at $C_{(4)}$ conclusions inconsistent with the fundamental principles of conformational analysis were reached [196,298]. Solely on the basis of "qualitative" observations, it was concluded erroneously that "the axially oriented hydroxy-group is more readily esterified ... than the equatorial hydroxyl" [196]. This conclusion conflicts with the above quantitative data for the esterification of the α- and γ-isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinol [296].

Erroneous conclusions about the structures of the promedol and α-promedol piperidinols were reached in a study [274] related to a series of previous investigations [72,212, 253]. Since the compounds to which the authors [274] related the steric structures of the α- and γ-isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinol are the isomeric 4-ethynyl-1,2,5-trimethyl-4-piperidinols and 4-cyano-4-hydroxy-1,2,5-trimethylpiperidines, we need point out the erroneous conclusions concerning these compounds only, leaving aside other compounds described (the authors' [274] ideas about the steric structures of these compounds have now changed). The structure with the *cis*-disposition of the methyl group at $C_{(3)}$ and of the ethynyl group at $C_{(4)}$ was attributed arbitrarily [274] to the γ-isomer (m.p. 177 to 178°C) of 4-ethynyl-1,2,5-trimethyl-4-piperidinol. On the basis of chromatographic data alone, this conclusion was amended [299] and the structure with the *trans*-disposition of the same substituents was attributed to the above compound. Thus the conclusions concerning the steric structures of many derivatives of γ-piperidinols, including the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols [72,212, 253,274], were erroneous.

Shvetsov et al. [274] converted the γ-isomer of 4-cyano-1,2,5-trimethyl-4-piperidinol (m.p. 141–143°C) into the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidinol. However, since the erroneous configuration with the *cis*-disposition of the methyl group at $C_{(3)}$ and of the cyano-group at $C_{(4)}$ was attributed to the above cyanohydrin (later amended [275]), an erroneous conclusion was also reached about the structures of the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols.

Subsequent studies confirmed the conclusions about the steric structures of the promedol alcohols arrived at by Prostakov and coworkers [127,273]. X-Ray diffraction of the α- and γ-isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinol confirmed the *trans*-equatorial disposition of their methyl groups at $C_{(2)}$ and $C_{(5)}$ as well as the axial disposition of the phenyl group in the α-isomer and its equatorial disposition in the γ-isomer [300].

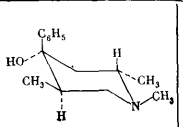
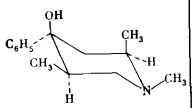
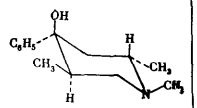
These conclusions [127,273] about the configurations and conformations of the α- and γ-isomers and also about the configuration of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidinol were fully confirmed in a study [301] based on infrared and ^1H NMR spectroscopic data. The inverted form, proposed previously by Prostakov and Mikheeva [273], was established for the conformation of the β-isomer. The occurrence of the chair–boat equilibrium, with the chair conformation predominating, was also demonstrated in solutions of the α- and β-isomers.

The ratio of the conformers of the isomeric promedols in solution was estimated from the difference between the free energies of the conformations with axial and equatorial phenyl groups. It follows from this estimate that conformers with the axial phenyl group constitute 97% of the α-isomer (alphapromedol, $\Delta F = -2.1$ kcal mole^{-1}), 62% of the β-isomer (isopromedol, $\Delta F = -0.3$ kcal mole^{-1}), while the corresponding conformer of the γ-isomer (promedol, $\Delta F = +7$ kcal mole^{-1}) does not exist [302].

By analysing ^{13}C NMR spectra, taking into account earlier studies, the following conclusions have been

reached [303] about the structures of the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidinols and their esters. The tentative conformations in deuterochloro-form are: α-isomer—1,2*e*,5*e*-trimethyl-4*a*-phenyl-4-piperidinol (the substance has the same conformation in the solid state); β-isomer—1,2*a*,5*e*-trimethyl-4*e*-phenyl-4-piperidinol; γ-isomer—1,2*e*,5*e*-trimethyl-4*e*-phenyl-4-piperidinol:(the substance has the same conformation in the solid state). The Table presents data for the true conformations of the isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinol.

The configurations and conformations of the isomers of 1,2,5-trimethyl-4-phenyl-4-piperidinols.

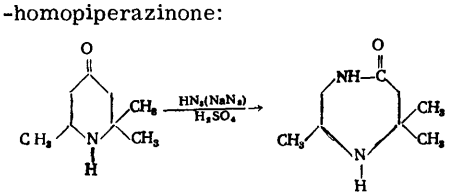
Isomer	M.p., °C (Ref.116)	Structure of isomers	Studies in which their structure has been proved	Studies in which erroneous conclusions about the structures were reached
α	106—107		127,273,295,296, 297*,300*,301, 303*,304	270, 274
β	102—103		200***,301,303**	143, 270
γ	107—108		127,273,295,296, 300,301,303—306	270, 274

*Designated by the authors as the β-isomer [205,303].
**Designated by the authors as the α-isomer [205,303].
***Configuration.

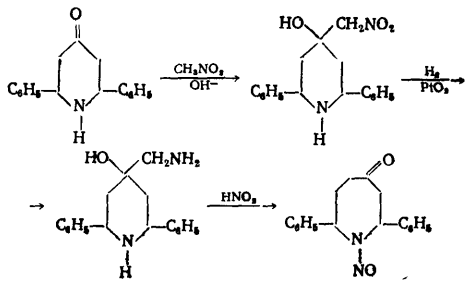
Thus, one may assume that the problems concerning the structures of γ-piperidinols, constituting the basis of effective analgesics, which has been discussed for many years, sometimes from opposed standpoints, have now been solved and that the conformational analysis of piperidine systems is now a fairly established part of the chemistry of nitrogen-containing heterocycles.

IV. γ-PIPERIDINONES IN SYNTHESES OF HETEROCYCLIC COMPOUNDS

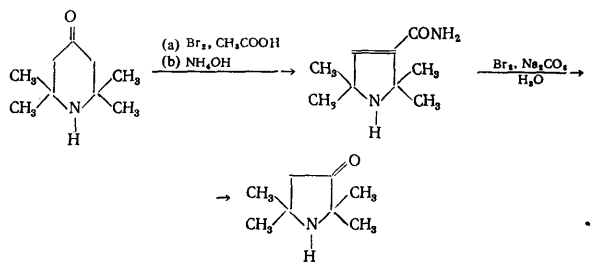
γ-Piperidinones are widely used in the syntheses of various heterocyclic compounds. Several examples of reactions of γ-piperidinones involving ring expansion have been described. 2,2,6-Trimethyl-4-piperidinone has been converted by the Schmidt reaction into 2,7,7-trimethyl-5-homopiperazinone:



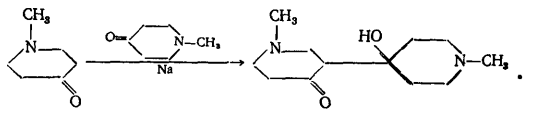
Analogous transformations have been achieved also for other γ-piperidinones [307-309]. The condensation of 2,6-diphenyl-4-piperidinone with nitromethane yielded 4-nitromethyl-2,6-diphenyl-4-piperidinol, which was reduced to 4-aminomethyl-2,6-diphenyl-4-piperidinol. Treatment of the latter with nitrous acid leads to the formation of 1-nitroso-2,7-diphenyl-1-aza-4-cycloheptanone[9]:



1-Benzyl-1-aza-3-cycloheptanone has been obtained from 1-benzyl-4-piperidinone by treating the latter with *N*-nitrosomethylurethane in the presence of barium oxide [310]. The synthesis of 2,2,5,5-tetramethyl-3-pyrrolidinone from triacetoneamine is an example of transformations of γ-piperidinones involving ring contraction. The amide of 2,2,5,5-tetramethyl-Δ^3-pyrrolinecarboxylic acid was obtained by treating with ammonia 3,3-dibromo-2,2,6,6-tetramethyl-4-piperidinone (formed on bromination of triacetoneamine) and was converted into a substituted 3-pyrrolidinone [311]:

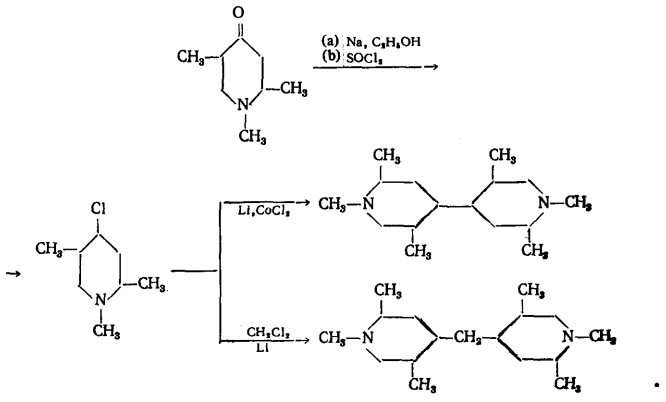


Several methods of synthesising di- and tri-piperidines from γ-piperidinones have been described. Intermolecular condensation of 1-methyl-4-piperidinone yielded a ketol—1-methyl-4-(1-methyl-4-oxo-3-piperidyl)-4-piperidinol [312]:

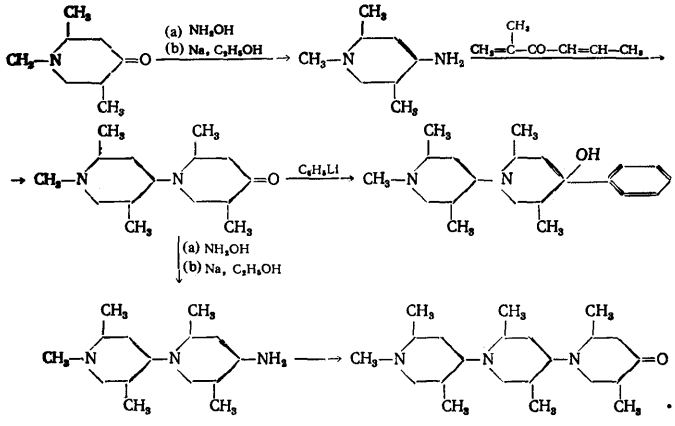


Bis(1,2,5-trimethyl-4-piperidyl) was obtained by treating 4-chloro-1,2,5-trimethylpiperidine with lithium or sodium in the presence of $CoCl_2$. Bis-(1,2,5-trimethyl-4-piperidyl)methane is formed from the same

halogeno-derivative and methylene chloride in the presence of lithium [313]:

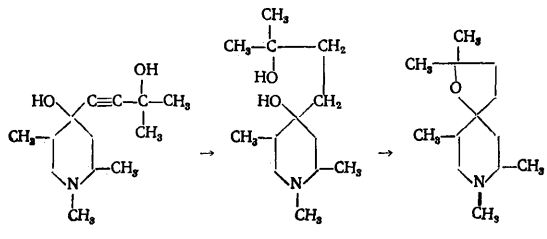


Condensation of 4-amino-1,2,5-trimethylpiperidine (obtained from the oxime of 1,2,5-trimethyl-4-piperidinone) with isopropenyl propenyl ketone yielded 2,5-dimethyl-1-(1,2,5-trimethyl-4-piperidyl)-4-piperidinone. Analogous transformations of this bicyclic system—the conversion of the oxo-group into an oxime group and then an amino-group and condensation of the resulting amine with isopropenyl propenyl ketone—led to the synthesis of terpiperidyl—2,5-dimethyl-4-(2,5-dimethyl-4-oxo-1-piperidyl)-1-(1,2,5-trimethyl-4-piperidyl)piperidine [153]:



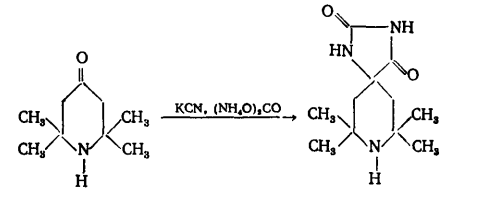
Synthesis of Spiro-compounds

The hydrogenation of 4-(3-hydroxy-3-methylbut-1-ynyl)-1,2,5-trimethyl-4-piperidinol (obtained by condensing 2,5-dimethyl-4-piperidinone with ethynyldimethylmethanol and subsequent *N*-methylation) results in the formation of a γ-glycol, the treatment of which with 10% sulphuric acid leads to its conversion into 2,2,7,8,10-pentamethyl-1-oxa-8-azaspiro[4,5]decane [243]:

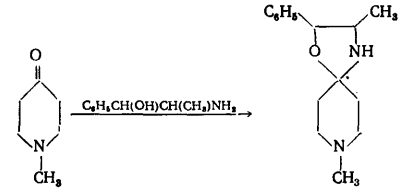


An analogous spiro-compound—2,2,7,10-tetramethyl-3-oxo-1-oxa-8-azaspiro[4,5]decane—is formed under the conditions of the hydration of the triple bond of 4-(3-hydroxy-3-methylbut-1-ynyl)-2,5-dimethyl-4-piperidinol [314]. Similar spiro-compounds have been described in other communications [315,316].

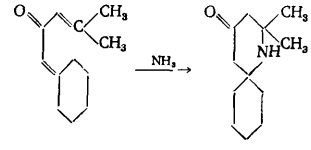
7,7,9,9-Tetramethyl-1,3,8-triazaspiro[4,5]decane-2,4-dione has been obtained from triacetoneamine, potassium cyanide, and ammonium carbonate. Analogous spiro-compounds have been synthesised from triacetoneamine substituted at the nitrogen atom [317] and also from 1,2,5-trimethyl-4-piperidinone cyanohydrin [318]. The syntheses of spirohydantoins, obtained from 1-alkyl-4-piperidinones, have been described [319,320]:



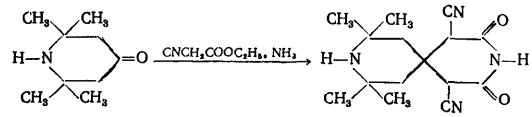
The condensation of 1-methyl-4-piperidinone with norephedrine leads to the formation of 3,8-dimethyl-2-phenyl-1-oxa-4,8-diazaspiro[4,5]decane [321]



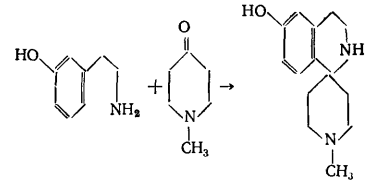
Analogous compounds substituted in the oxazolidine ring nitrogen have been described [322]. The reaction of the product of the condensation of mesityl oxide and cyclohexanone with ammonia (the method of synthesis of γ-piperidinones from divinyl ketones) yielded 2,2-dimethyl-4-oxo-1-azaspiro[5,5]undecane [323]:



The condensation of triacetoneamine with cyanoacetic ester and ammonia, resulting in the formation of 1,5-dicyano-8,8,10,10-tetramethyl-3,9-diazaspiro[5,5]-undecane-2,4-dione, has been achieved [324]:

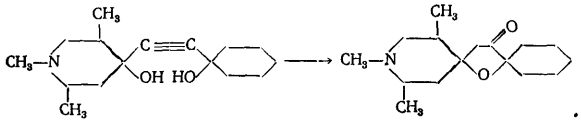


1'-Methyl-6-hydroxyspiro[1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine] is formed when 3-(β-aminoethyl)-phenol is condensed with 1-methyl-4-piperidinone [325]:

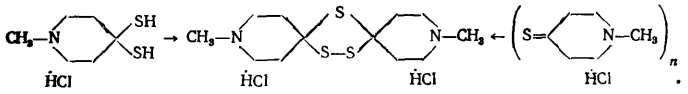


An analogous compound has been obtained from 2-amino-1-(3-hydroxyphenyl)ethanol [322].

The hydration of the triple bond of 4-[1-hydroxy-(1-cyclohexyl)ethynyl]-1,2,5-trimethyl-4-piperidinol involves the cyclodehydration of the resulting ketoglycol and leads to the formation of 1,3,4-trimethyl-14-oxo-7-oxa-3-azaspiro[5,1,5,2]pentadecane [252]:

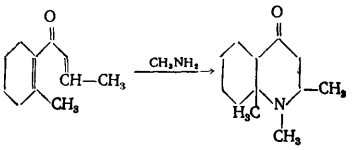


The crystallisation of the hydrochloride of 4,4-dimercapto-1-methylpiperidine and of the polymer of the hydrochloride of 1-methylthio-4-piperidinone (both substances have been obtained from 1-methyl-4-piperidinone) led to the isolation of the hydrochloride of dispiro-1,2,4-tritolane [45]:

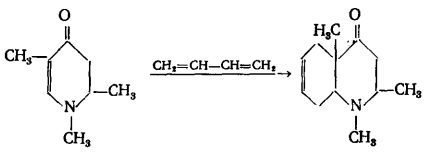


The Synthesis of Condensed Heterocyclic Compounds

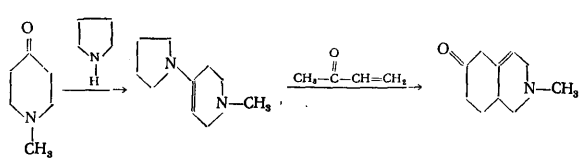
The method of synthesis of γ-piperidinones from divinyl ketones has been used to synthesise 1,2,8a-trimethyldecahydro-4-quinolinone, formed in the condensation of 2-methyl-Δ^1-cyclohexenyl propenyl ketone with methylamine [326]:



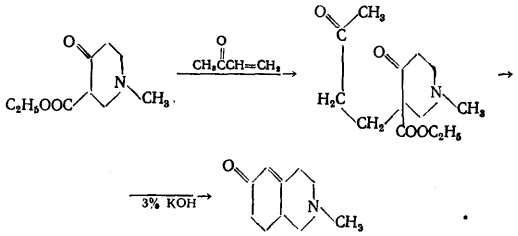
1,2,4a-trimethyl-1,2,3,4,4a,5,8,8a-octahydro-4-quinolinone is formed by the Diels–Alder reaction from 1,2,5-trimethyl-4-oxo-1,2,3,4-tetrahydropyridine (obtained from 1,2,5-trimethyl-4-piperidinone) and butadiene [327]:



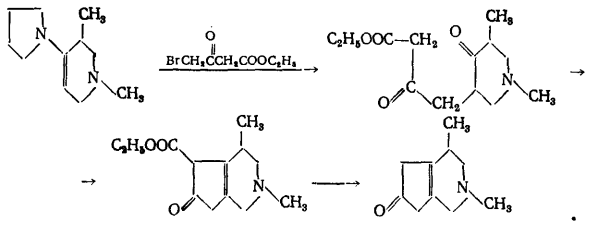
The condensation of 1-methyl-4-piperidinone with pyrrolidine results in the formation of 1-methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine, the reaction of which with methyl vinyl ketone gives 2-methyl-1,2,3,5,6,-7,8,8a-octahydro-6-isoquinolinone [328]:



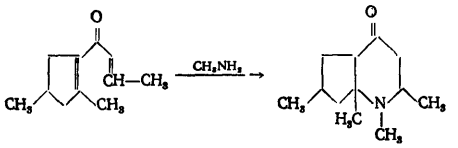
The condensation of 3-ethoxycarbonyl-1-methyl-4-piperidinone with methyl vinyl ketone has been used to synthesise 2-methyl-1,2,3,4,6,7,8,8a-octahydro-6-isoquinolinone [329]:



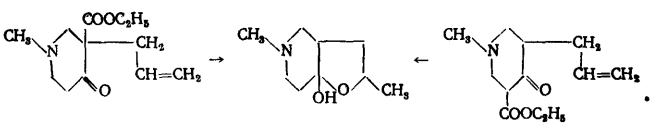
5-(γ-Ethoxycarbonyl-β-oxopropyl)-1,3-dimethyl-4-piperidinone, obtained from 1,5-dimethyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine by cyclisation under the influence of potassium t-butoxide and subsequent decarboxylation of the condensation product, was converted into 2,4-dimethyl-2,3,4,5,6,7-hexahydro-1H-2-(6-pyrindinone) [47]:



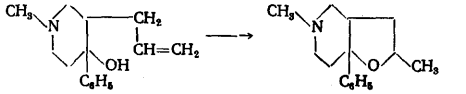
2,4-Dimethyl-Δ^1-cyclopentyl propenyl ketone (a divinyl ketone) reacts with methylamine and is converted into 1,2,6,7a-tetramethylperhydro-(4-pyrindinone) [326]:



7a-Hydroxy-2,5-dimethylperhydrofuro[3,2-c]pyridine is formed on heating 3-allyl-3-ethoxycarbonyl-1-methyl-4-piperidinone as well as 3-allyl-5-ethoxycarbonyl-1-methyl-4-piperidinone with 20% hydrochloric acid. It is suggested that the removal of the ethoxycarbonyl group is accompanied by the simultaneous hydration of the double bond in the allyl group, which is followed by the formation of a hemiacetal [100,101]:

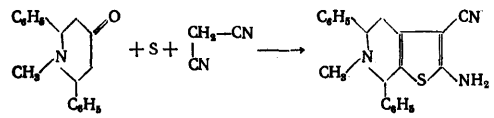


2,5-Dimethyl-6a-phenylperhydrofuro[3,2-c]pyridine was obtained under analogous conditions from 3-allyl-1-methyl-4-phenyl-4-piperidinol [100]:



The condensation of 1-methyl-2,6-diphenyl-4-piperidinone with malonodinitrile in the presence of sulphur has been achieved and 2-amino-3-cyano-6-methyl-5,7-diphenyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine was obtained and

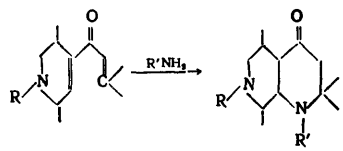
was used in the synthesis of the condensed system of pyridothienopyrimidine [330]:



The analogous condensation of 1-(β-hydroxyethyl)-4-piperidinone with ethyl cyanoacetate and sulphur yielded 2-amino-3-ethoxycarbonyl-6-(β-hydroxyethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine [331].

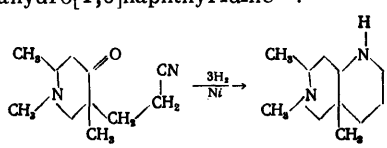
Synthesis of Fully or Partly Hydrogenated Naphthyridines

1,2,3,6-Tetrahydro-4-pyridyl vinyl ketones, substituted in the nitrogen-containing ring and in the β-position of the vinyl group, which are obtained from γ-piperidinones via 4-ethynyl-4-piperidinols [332] or 4-vinylethynyl-4-piperidinols [333], are converted into substituted perhydro-1,7-naphthyridines on reacting with primary amines:

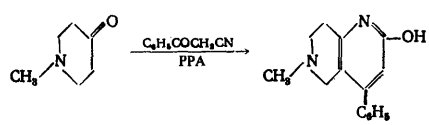


The same divinyl ketones have been used in the syntheses of piperidine–thiopyran (reaction with hydrogen sulphide) and piperidine–pyran (reaction with water) condensed systems [334,335].

Catalytic hydrogenation of 5-(β-cyanoethyl)-1,2,5-trimethyl-4-piperidinone led to the isolation of 4*a*,6,7-trimethyldecahydro[1,6]naphthyridine [92]:

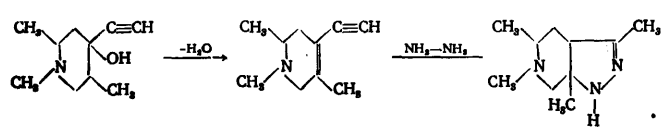


The condensation of 1-methyl-4-piperidinone with benzoylacetonitrile in the presence of polyphosphoric acid (PPA) led to the formation of 2-hydroxy-6-methyl-4-phenyl-5,6,7,8-tetrahydro[1,6]naphthyridine [336]:

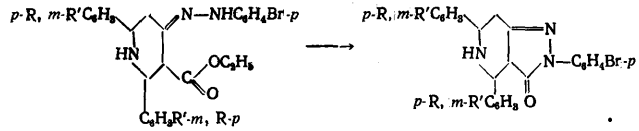


The Synthesis of the Condensed System Comprising Piperidine and Pyrazole

When the product of the dehydration of 4-ethynyl-1,2,5-trimethyl-4-piperidinol reacts with hydrazine hydrate, 2*a*,4,5,7-tetramethyl-2*a*,3,4,5,6,6*a*-hexahydropyrazolino[5,4-*c*]pyridine is formed [337]:

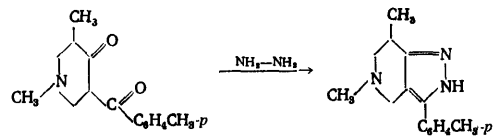


The intramolecular condensation of the *p*-bromophenylhydrazone of 3-ethoxycarbonyl-2,6-di-(*m*-methoxy-*p*-hydroxyphenyl)-4-piperidinone results in the formation of the corresponding 2,4,6-triaryl-3-oxo-3,3*a*,4,5,6,7-hexahydropyrazolo[4,3-*c*]pyridine [338]:

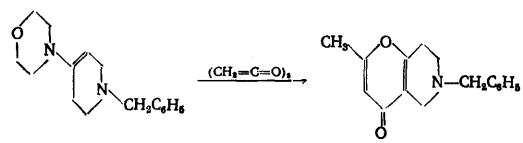


The syntheses of analogous condensed systems have also been described [339,340].

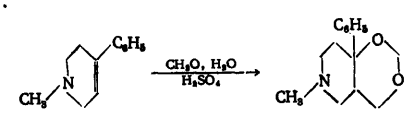
5,7-Dimethyl-3-*p*-tolyl-4,5,6,7-tetrahydropyrazolo-[4,3-*c*]pyridine has been obtained by the reaction of 1,3-dimethyl-5-*p*-methylbenzoyl-4-piperidinone with hydrazine [341]:



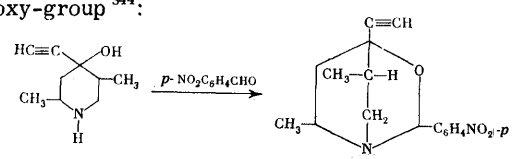
The analogous tetrahydropyrazolopyridine has been synthesised by condensing 1-acetyl-3-ethoxycarbonyl-4-piperidinone with phenylhydrazine [307]. 1-Benzoyl-4-morpholino-1,2,3,6-tetrahydropyridine (an enamine obtained from 1-benzyl-4-piperidinone) condensed with diketen to form 6-benzyl-2-methyl-5,6,7,8-tetrahydro-6-azochromone [342]:



6-Methyl-8*a*-phenyl-4*a*,5,6,7,8,8*a*-hexahydropyrido-[4,5α]-1,3-dioxan has been synthesised by the Prins reaction from the product of the dehydration of 1-methyl-4-phenyl-4-piperidinol (obtained from 1-methyl-4-piperidinone) [343]:

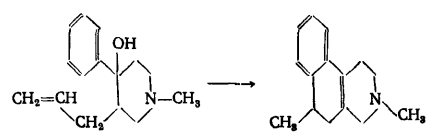


6-Ethynyl-4,7-dimethyl-2-*p*-nitrophenyl-1-oxa-3-azabicyclo[2,2,2]octane has been obtained from the γ-isomer of 4-ethynyl-2,5-dimethyl-4-piperidinol (with an axial hydroxy-group [344]:

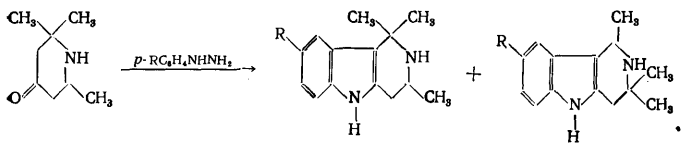


Synthesis of Tricyclic Heterocycles

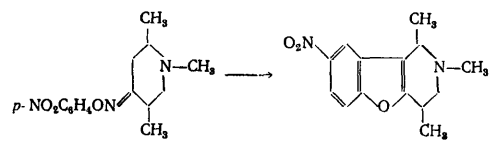
3-Allyl-1-methyl-4-phenyl-4-piperidinol, obtained from the corresponding γ-piperidinone, is converted on heating with 20% hydrochloric acid into 2,9-dimethyl-1,2,3,4,9,10-hexahydro-2-azaphenanthrene [100]:



The Fischer cyclisation of the arylhydrazones of certain γ-piperidinones has been investigated. In particular, the formation of 2,4,4-trimethyl-1,2,3,4-tetrahydro-γ-carboline and its isomer as regards the positions of the substituents in the nitrogen-containing six-membered ring has been demonstrated using the arylhydrazone of 2,2,6-trimethyl-4-piperidinone as an example. Analogous syntheses have also been described [345]:

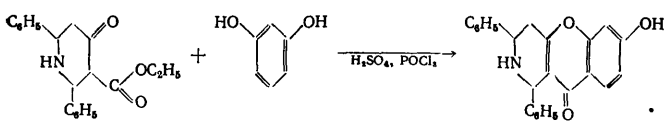


The cyclisation of the *p*-nitrophenylether of the oxime of 1,2,5-trimethyl-4-piperidinone to give 1,2,4-trimethyl-8-nitro-1,2,3,4-tetrahydrobenzofuro[3,2-*c*] pyridine has been achieved [346]:



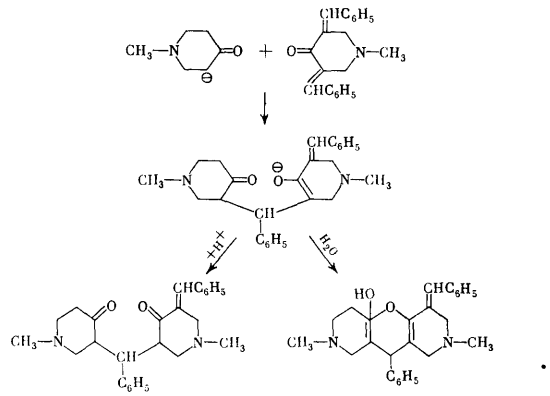
The condensation of *o*(*p*)-nitrophenyl ethers of the oximes of 1,3-dialkyl-4-piperidinones in ethanol in the presence of hydrogen chloride yielded 2,4-dialkyl-4*a*-ethoxy-1,2,3,4,4*a*,9*b*-hexahydro-6(8)-nitrobenzofuro[3,2-*c*]pyridine [347].

The condensed system comprising a partly hydrogenated pyridine and benzopyran has been obtained by the reaction of 3-ethoxycarbonyl-2,6-diphenyl-4-piperidinone with resorcinol [348]:

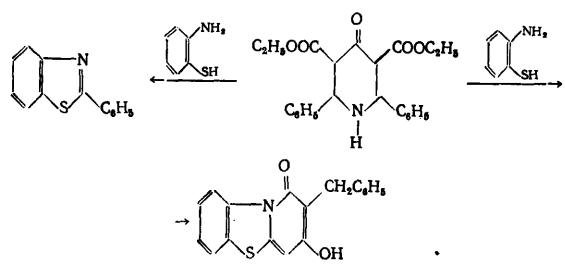


5-Oxo-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]-pyridines, substituted similarly in the dehydropiperidine and benzene rings, have been described in patents [349,350].

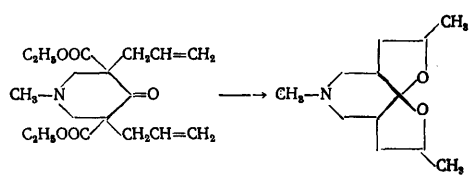
A complex mixture of substances is formed when γ-piperidinones interact with aromatic aldehydes in the presence of bases. When 1-methyl-4-piperidinone condenses with benzaldehyde, 3-benzylidene-5-[α-(1-methyl-4-oxo-3-piperidyl)benzyl]-1-methyl-4-piperidinone and 4-benzylidene-10*a*-hydroxy-2,7-dimethyl-9-phenyl-10-oxa-2,7-diaza-9*H*-1,2,3,4,5,6,7,8,8*a*,10*a*-decahydroanthracene are formed in addition to 3,5-dibenzylidene-1-methyl-4-piperidinone [80]. It has been suggested that there is initial Michael addition of the piperidinone anion to 3,5-dibenzylidene-1-methyl-4-piperidinone, whereupon the resulting enolate anion is converted in two steps into the above heterocyclic compounds [351,352]:



The reaction of *o*-aminothiophenol with 3,5-diethoxycarbonyl-2,6-diphenyl-4-piperidinone in boiling xylene led to the isolation of 2-phenylbenzothiazole and 2-benzyl-3-hydroxy-1-oxo-1*H*-benzo[*d*]pyrido[2,1-*b*]thiazole [353]. Their formation involves the cleavage of the piperidine ring, the mechanism of which has not so far been elucidated:

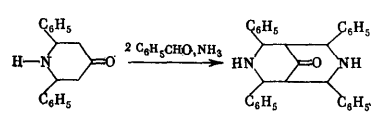


Hydrolysis of the diethyl ester of 3,5-diallyl-1-methyl-4-oxopiperidine-3,5-dicarboxylic acid followed by its decarboxylation is accompanied by the hydration of the allyl groups and the formation of the acetal derivative of 1,5′,5″-trimethylbis(tetrahydrofurano)-3′,2′:3,4;2″,3″:4,5-piperidine [354]:



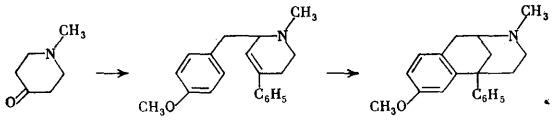
Synthesis of Bispidines

9-Oxo-2,4,6,8-tetraphenylbispidine is formed from 2,6-diphenyl-4-piperidinone, benzaldehyde, and ammonia [355]. Bispidines have also been synthesised by the condensation of γ-piperidinones with formaldehyde and methylamine [356,357]:



2-*p*-Methoxybenzyl-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was obtained by a series of successive transformations (phenyl-lithium synthesis, dehydration, formation of a salt with *p*-methoxybenzyl chloride, and its

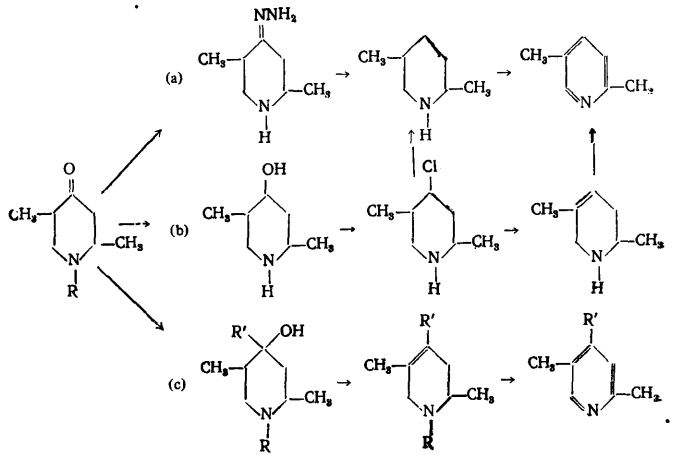
intramolecular Stevens rearrangement) from 1-methyl-4-piperidinone and was then converted by the Graebe method into a substituted benzomorphan [358]:



An analogous synthesis has been achieved starting from 1,3-dimethyl-4-piperidinone [359]. After treating 2-benzyl-1-methyl-4-piperidinone with 48% hydrobromic acid, 5-hydroxy-2-methyl-6,7-benzomorphan was isolated [360].

The ease of formation of γ-piperidinones substituted in a wide variety of ways makes it possible to employ them for the synthesis of pyridine bases. It has been shown for 2,6-diphenyl-4-piperidinol that, when it is treated with sulphur *in vacuo* up to 200°C, 2,6-diphenylpyridine is formed in approximately 90% yield [19]. It has been reported that tertiary γ-piperidinols are converted into pyridine bases on heating to 220–240°C with 20 wt.% of a palladium catalyst [134]. Pyriding has been obtained in a yield exceeding 90% on dehydrogenating piperidine (5% Pd, 300–400°C) [361]. A method has been developed for the dehydrogenation of piperidine bases to pyridine bases with the aid of a pyridine N-oxide [362].

In order to obtain pyridine bases from γ-piperidones, the following procedures are used: (a) reduction of γ-piperidinones by the Wolff–Kishner method to substituted piperidines with subsequent dehydrogenation in the presence of industrial K-12 and K-16 type catalysts [363]; (b) reduction of γ-piperidinones to γ-piperidinols, the replacement of the hydroxy-group in the latter by a halogen and then of the halogen by hydrogen, and dehydrogenation (or dehydrochlorination), dehydrogenation being the last stage; the yield in the dehydrogenation stage is more than 90%; [23,24,363]: (c) the conversion of γ-piperidinones into secondary and also tertiary piperidinols and their dehydration followed by the dehydrogenation and *N*-dealkylation of the resulting tetrahydropyridines [144–146, 202,203,364–368]

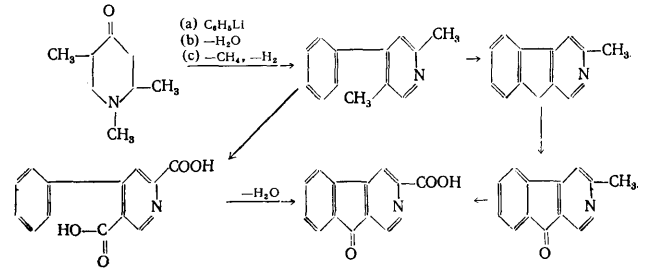


More than 150 individual pyridine bases with different structures have been obtained by means of these synthetic procedures from 1,2,5-trimethyl-4-piperidinone alone [34, 144–146,156–158,202,237,269,363–366,369–389].

γ-Piperidinones have become important starting materials in the syntheses of individual and substituted pyridine bases having specified structures. The study of the hydrogenation of 4-aryl- and 4-alkylaryl-pyridines obtained in this way established that, in the presence of catalysts such as rhenium heptasulphide, platinum sulphide, and palladium sulphide, only the pyridine ring undergoes selective hydrogenation, 4-aryl- and 4-alkyl-aryl-piperidines being formed in yields up to 99, 93, and 40% respectively. If the hydrogenation is carried out in alcohol, *N*-alkylation takes place simultaneously [390–393].

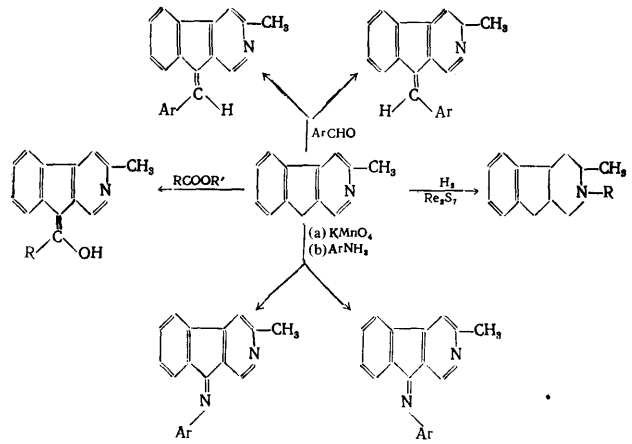
A characteristic feature of the structure of many pyridine bases obtained from 1,2,5-trimethyl-4-piperidinone is that the β-position contains a methyl group and the γ-position an aryl or alkylaryl group. These features have been used to synthesise condensed polycyclic nitrogen-containing heterocyclic compounds from such pyridine bases by dehydrocyclisation at 500–560°C in the presence of K-12 and K-16 catalysts.

2-Azafluorenes are formed from 4-aryl-3-methyl-pyridines, while 2,4-diaryl-3-methylpyridine gives rise to 2-aza and 4-aza-fluorenes [394]. An example of such syntheses is proved by the preparation of 3-methyl-2-azafluorenone and 9-oxo-2-azafluorene-3-carboxylic acid [373,395]. 9-Oxo-2-azafluorene-4-carboxylic acid was obtained similarly [203]:

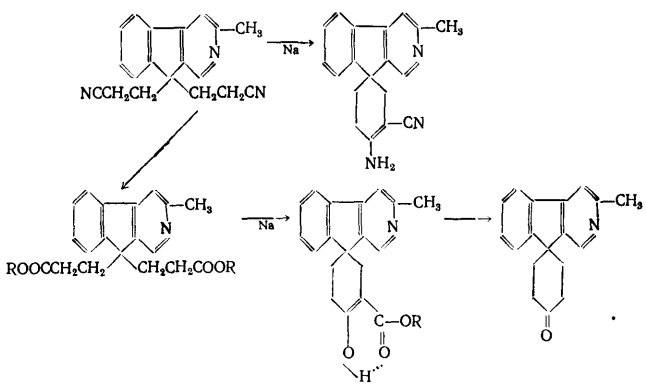


4-Aryl-2,5-dimethylpyridines with different alkyl substituents in the benzene ring have also been used to synthesise 2-azafluorenes [168,374]. The dehydrocyclisation of 3-methyl-2,4,6-triphenylpyridine (obtained from 1,3-dimethyl-2,6-diphenyl-4-piperidinone) leads to the formation of 1,3-diphenyl-2-azafluorene and 1,3-diphenyl-4-azafluorene. The former has also been obtained in the dehydrocyclisation of 2,6-diphenyl-4-*o*-tolylpyridine [176]. 3-Methyl-2-azafluorenone has been used in the syntheses of many 9-aryl(alkylaryl)-3-methyl-2-azafluorenols and their esters [396]. The geometrical isomers of 9-arylidene derivatives of 2-azafluorene and 3-methyl-2-azafluorene have been obtained in a study of their condensation with aromatic aldehydes, and it has been established that they are readily interconverted [397]. *N*-(3-Methyl-2-aza-9-fluorenylidene)arylamines, formed on condensation of 3-methyl-2-azafluorenone with aromatic amines, exist in the form of an equilibrium mixture of the *cis*- and *trans*-isomers (^{1}H NMR data) [398]. The enolic form is the stable structure of 9-acyl(aroyl) derivatives of 2-azafluorenes, its stabilisation being due to the interaction of the acid enolic hydrogen with the nitrogen of the pyridine ring [399,400]. When 3-methyl-2-azafluorene was reduced with sodium in alcohol, two isomers of 2-methyl-5*H*-indano[2,1-*c*]-piperidine were isolated [401] and their structures were subsequently examined [402,403]. It has been shown in a number of instances that the hydrogenation of substituted 2-azafluorenes in the presence of rhenium heptasulphide is selective, only the pyridine ring being hydrogenated with simultaneous reduction of the oxo- and hydroxy-groups in the 9-position and alkylation at the nitrogen atom when the hydrogenation is carried out in alcohol.

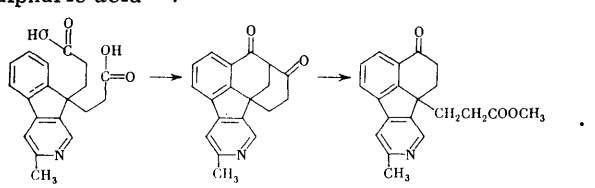
Two isomers of the indanopiperidine were also obtained in this instance[404,405].



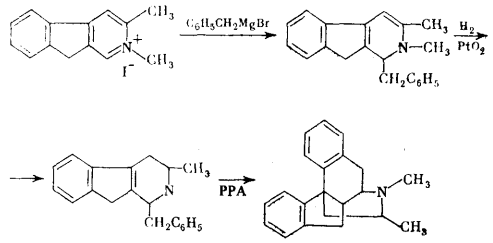
A new heterocyclic system—4′-amino-3′-cyano-3-methylspiro[2-azafluorene-9,1′-cyclohex-3′-ene]—has been obtained by the Dieckmann condensation from 9,9-di-(β-cyanoethyl)-3-methyl-2-azafluorene (synthesised by the Michael reaction from 3-methyl-2-azafluorene), while the condensation of 9,9-di-(β-ethoxycarbonylethyl)-3-methyl-2-azafluorene gave 3′-alkoxycarbonyl-4′-hydroxy-3-methylspiro[2-azafluorene-9,1′-cyclohex-3′-ene], which was subsequently converted into a spiroketone [406]. Analogous spirostructures have been obtained by the reaction of 3-methyl-2-azafluorene with αβ-unsaturated acid esters in the presence of sodium:



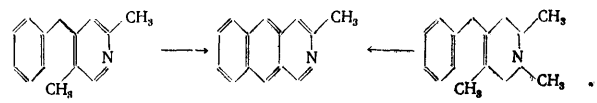
A new heterocyclic system—9-methyl-4,13-dioxo-8-aza-4,5,6,6a-tetrahydro-5,6a-propanofluoranthene—has been obtained by the cyclodehydration of 9,9-di-(β-carboxyethyl)-3-methyl-2-azafluorene under the influence of polyphosphoric acid. 6a-(2-Methoxycarbonylethyl)-9-methyl-4-oxo-8-aza-4,5,6,6a-tetrahydrofluoranthene is formed from this compound on treatment with methanol and sulphuric acid[407]:



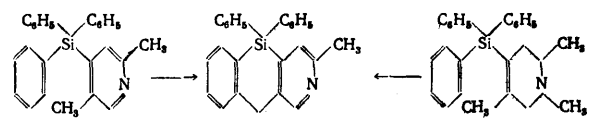
An analogue of morphinan—2,3-dimethyl-6,7-benzo-5,9-(1′,2′-indano)-2-azabicyclo[3,3,1]non-6-ene—has been obtained from the methiodide of 3-methyl-2-azafluorene by a series of consecutive transformations[408]:



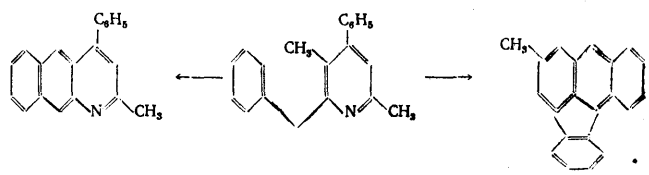
4-(2,5-Dimethyl)pyridines have been used to synthesise many benzo[g]isoquinolines, which have been little investigated. The same method (catalytic dehydrocyclisation) was used[383,385,396,409]:



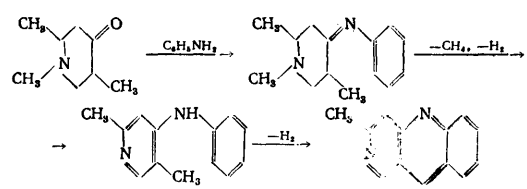
2,5-Dimethyl-4-triphenylsilylpyridine (it was synthesised from 1,3,6-trimethyl-4-triphenylsilyl-1,2,3,6-tetrahydropyridine) also undergoes dehydrocyclisation with formation of 2-methyl-9,9-diphenyl-9,10-dihydro-9-sila-3-aza-anthracene[410]:



The benzo[g]quinoline structure is formed on dehydrocyclisation of 2,5-dimethyl-4-phenyl-6-benzylpyridine, the products being 2-methyl-3-azabenzo[f]fluoranthene together with 2-methyl-4-phenylbenzo[g]quinoline[387]:

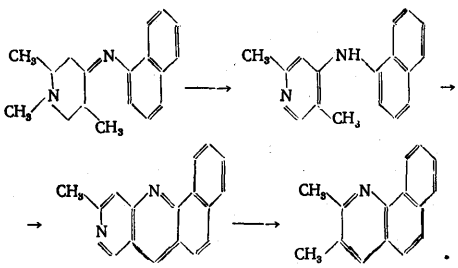


Yet another application of γ-piperidinones in the syntheses of heterocyclic compounds has been developed—the preparation from the latter of Schiff bases[41] and their catalytic transformations. It has been established[369] that *N*-(1,2,5-trimethyl-4-piperidylidene)aniline (obtained from 1,2,5-trimethyl-4-piperidinone and aniline) is converted in the presence of the K-12 catalyst at 470°C into (2,5-dimethyl-4-pyridyl)phenylamine, from which 7-methyl-2,3-benzo-1,6-naphthyridine is formed in the presence of the same catalyst[395]. The Schiff base obtained from 4-amino-1,2,5-trimethylpiperidine and benzaldehyde is converted into αβ′-lutidine at 400°C:[377]



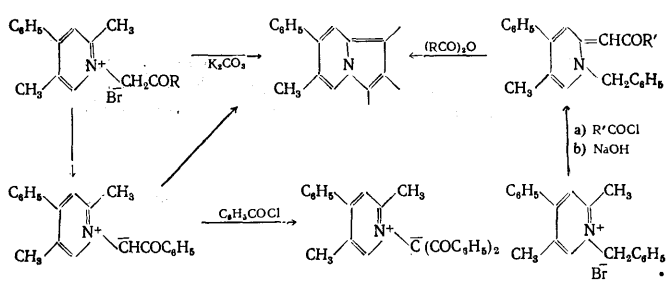
The reactions under analogous conditions of the Schiff bases obtained from 1,2,5-trimethyl-4-piperidinone and naphthylamines take place in a more complex manner.

N-(2,5-Dimethyl-4-pyridyl)-α-naphthylamine, 9-methylnaphtho[1,2-*b*][1,6]naphthyridine, and 2,3-dimethyl-4-azaphenanthrene have been obtained from *N*-(1,2,5-trimethyl-4-piperidylidene)-α-naphthylamine. The last Schiff base is apparently formed as a result of the degradation of naphthonaphthyridine[411]:

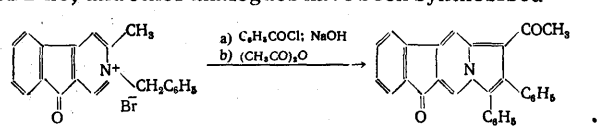


The following compounds were isolated after the analogous reactions of *N*-(1,2,5-trimethyl-4-piperidylidene)-β-naphthylamine: *N*-(2,5-dimethyl-4-pyridyl)-β-naphthylamine, 9-methylnaphtho[2,1-*b*][1,6]naphthyridine, and 2,3-dimethyl-1-azaphenanthrene[412].

The availability of substituted pyridine bases obtained from γ-piperidinones made it possible to expand the research into indolizine systems. Indolizines have been obtained directly from the quaternary *N*-β-oxoalkylpyridinium salts, from 1-benzyl-5-methyl-4-phenyl-3-phenacylidene-1,2-dihydropyridine, and from pyridine ylides. The stable dibenzoylmethylides were isolated in the study of the last group of compounds[368,413-415]:



A condensed system comprising indene and indolizine, namely 1-acetyl-5-oxo-2,3-diphenyl-5*H*-indeno[2,1-*f*]-indolizine, and other analogues have been synthesised[413,414]:



It follows from the present review that γ-piperidinones play an appreciable role in the development of the chemistry of piperidine and certain other heterocyclic compounds. The synthetic possibilities of γ-piperidinones in this respect have apparently been by no means exhausted.

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