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Advances in the Chemistry of α, α, α′, α′-Tetrasubstituted Piperidines

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The stages in the development of the chemistry of piperidines with a sterically hindered nitrogen atom and the practical importance of compounds of this class are examined. The methods of synthesis of 2,2,6,6-tetra-alkylpiperidines published in the literature, and their chemical properties and reactions are surveyed: processes occurring without the growth of a carbon skeleton, condensations with the formation of new C-C bonds, and reactions involving a change in the heterocyclic skeleton of the molecules. The characteristics of the stereochemistry and in particular of the conformations of 2,2,6,6-tetrasubstituted piperidines are analysed.
The bibliography includes 174 references.

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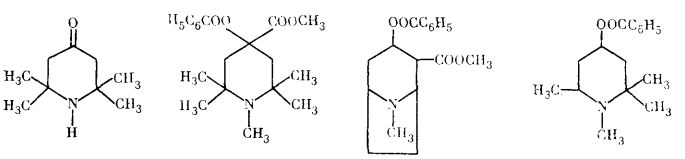
I. INTRODUCTION

The introduction of various kinds of substituents into the α- and α′-positions relative to the nitrogen atom in N-heterocyclic systems leads to a significant alteration of the chemical properties of the compounds. Effects of this kind were examined in our previous study[1] for N-heteroaromatic substances in relation to 2,6-disubstituted pyridines.

In contrast to heteroaromatic derivatives, where various electromeric effects (both effects transmittable via the bonds and "shield effects"), play an important role, steric effects associated with the shielding of the heterocyclic nitrogen atom are of primary importance for heteroparaffins of the type of α,α,α′,α′(2,2,6,6)-tetrasubstituted piperidine. Unfortunately the number of theoretical studies on this problem is inadequate and the reviews devoted to the synthesis and chemical reactions of 2,2,6,6-tetrasubstituted piperidines are altogether lacking. The thorough review articles and monographs on iminoxy-radicals of the type of 2,2,6,6-tetramethylpiperidin-1-yloxy-radical are the only exception.[2-17]

II. STAGES IN THE DEVELOPMENT OF THE CHEMISTRY OF α,α,α′,α′-TETRASUBSTITUTED PIPERIDINES

Studies on 2,2,6,6-tetrasubstituted piperidines having a hindered heterocyclic nitrogen atom were begun more than a hundred years ago when triacetoneamine was isolated from the products of the interaction of acetone with ammonia and its structure was established as 2,2,6,6-tetramethyl-4-piperidinone (I).[18,19] For a long time, the study of compounds of this series reduced to the synthesis of derivatives of compound (I) involving the carbonyl group and the nitrogen of the piperidine ring. Data on the local anaesthetic activity of α-eucaine (II), a derivative of 1,2,2,6,6-pentamethylpiperidine which is a cheaper, less toxic, and more heat resistant analogue of cocaine (III), were published in the only communication on the biological properties of substances of this type.[20] However, in view of the intense local irritant action of compound (II), it was soon eliminated from medical practice by β-eucaine (IV), which is free from this disadvantage:

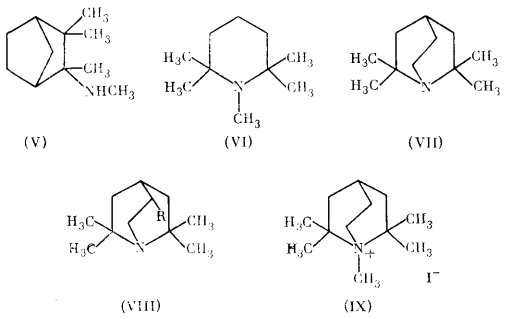


(I) (II) (III) (IV)

A new stage in the study of 2,2,6,6-tetrasubstituted piperidines was begun in the 1950's in connection with the search for ganglion-blocking agents. By that time it had been established that, in contrast to the ganglion-blocking quaternary ammonium compounds widely used in medical practice but poorly assimilated from the gastrointestinal tract and secondary amines with a hindered nitrogen atom of the type of camphonium (V), which exert a secondary central activity (depression of the central nervous system, tremor), 2,2,6,6-tetramethylpiperidines unsubstituted in the 1-position and 1-alkyl-2,2,6,6-tetramethylpiperidines, which exhibit an intense ganglion-blocking activity, are rapidly assimilated following peroral administration and are free from side effects on the central nervous system.[21] Among compounds of this group, the most active proved to be 1,2,2,6,6-pentamethylpiperidine (VI) which has been introduced into medical practice under the names pempidine, pyrilene, genoriol, perolysen, etc. and is still used as an effective ganglion-blocking agent.[22-24]

The study of numerous analogues of compound (VI) [25-35] showed that steric hindrance of the nitrogen atom is a more important factor for the ganglion-blocking activity of compounds of this type than a change in the structure of the heterocycle. An increase in the bulk of the substituent at the nitrogen atom lowers the activity. The introduction of a

double bond into the ring does not affect the activity but reduces the duration of action and increases the toxicity:[27-29]



(V) (VI) (VII)

(VIII) (IX)

Ganglion-blocking and sedative properties have also been shown by triacetoneamine (I),[36-38] which has been given the name tempidone in Bulgaria. Further studies designed to search for ganglion-blocking agents more active than pyrilene led to the development of new methods of synthesis of 2,2,6,6-tetramethylpyridines[28,39-41] and then to the synthesis of the quinuclidine analogue of compound (VI)—the medicinal drug temekhin (VII).[42] The latter exhibits an activity which is three times more selective than that of pyrilene (VI) in relation to muscarinic cholinoceptor autonomic ganglia, the cortical substance of suprarenal glands, and carotid body without influencing the nicotinic cholinoceptor system of skeletal muscles. Temekhin is characterised by a broad spectrum of its therapeutic activity, is manufactured by the chemical-pharmaceutical industry of the USSR, and is used in medicine as a ganglion-blocking and hypotensive agent.[43] The additional introduction of the 8-methyl-group into the temeckin molecule to give compound (VIII, R = CH_3) increased somewhat the toxicity of the preparation with retention of its activity. The increase in the length of the 8-alkyl chain or conversion into 8-substituted functional derivatives (VII) leads to a further increase of toxicity with the simultaneous reduction of the ganglion-blocking effect.[44-46] The activity of the preparation changes in another direction on quaternisation as the bridgehead nitrogen atom. 2,2,6,6-Tetramethylquinuclidine methiodide (IX), which has been called imequine,[47] is also manufactured by the chemical-pharmaceutical industry of the USSR and is used in medical practice for the creation of artificial hypotonia in surgical operations, in the treatment of the oedemas of the lungs and the brain and the chronic hypotonia associated with kidney failure, and for the prevention and arrest of hypertonic crises. In all cases imequine behaves as a drug which is stronger, more easily controlled, less toxic, and more convenient for practical use than a preparation having a different chemical structure (arfonad) used for such purposes outside the USSR.[43]

The organisation of the manufacture of initially pyrilene and then temekhin and imequine, whose synthesis is based on the use of triacetoneamine(I), created a realistic industrial raw material base for the preparation of various derivatives of 2,2,6,6-tetramethylpiperidine.

A new stimulus to the development of the chemistry of 2,2,6,6-tetrasubstituted piperidines was provided by studies and practical employment of iminoxy-radicals.[2-17] 2,2,6,6-Tetramethyl-4-oxopiperidine 1-oxide (X), which is an iminoxy-radical based on triacetoneamine whose stability is due to steric factors, was first obtained in a pure form in 1962.[48] This was followed by numerous studies of various methods of synthesis of 2,2,6,6-tetramethylpiperidin-1-yloxy-radicals and their reactions involving the participation of both the free-radical function and others in which the unpaired electron does not participate. Iminoxy-radicals of the 2,2,6,6-tetramethylpiperidine series are widely used in the solution of many theoretical and applied problems in experimental biophysics, the chemistry of high-molecular-weight compounds, analytical and forensic chemistry, biochemistry, and molecular biology (as spin labels and probes, paramagnetic inhibitors, and stabilisers), in instrument making (lasers and masers, current sources, magnetometers, and dosimeters), etc. The availability of fairly careful reviews and monographs on the chemistry and applications of paramagnetic 2,2,6,6-tetrasubstituted piperidin-1-yloxy-radicals[2-17] makes it possible to restrict the present review to the consideration of mainly only diamagnetic 2,2,6,6-tetrasubstituted piperidines, which are used in many instances as the starting materials for the synthesis of stable iminoxy-radicals.

At the present stage of development of the chemistry of 2,2,6,6-tetrasubstituted piperidines, a fairly vigorous development of all the trends established in this field as a result of historical factors has continued. The study of the theoretical and preparative problems of the chemistry of 2,2,6,6-tetrasubstituted piperidines has been concentrated in recent years on the elucidation of the characteristics of the conformation of sterically hindered piperidines, the determination of the contribution of axial and equatorial α-methyl groups to the stereochemistry of other substituents,[49-51] the ionisation potentials of the photochemical reactions of the test substances,[52-54] etc.

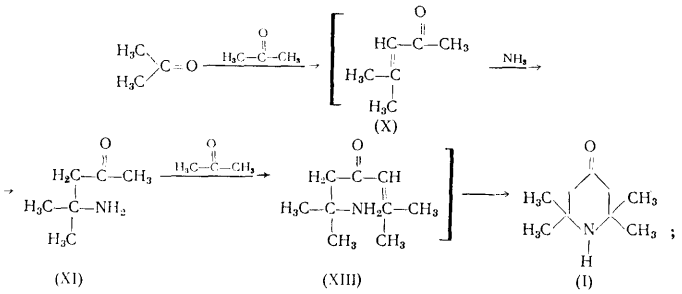
Together with the extensive studies on nitroxy-radicals, 2,2,6,6-tetramethylpiperidine-1-thiyl radicals,[55] 2,2,6,6-tetramethylpiperidine-1-nitrenes,[56] and 2,2,6,6-tetramethylpiperidin-1-yl radicals[57] have been obtained and have aroused interest.

Vigorous search for new biologically active 2,2,6,6-tetrasubstituted piperidines[53,54,58-66] is being continued and studies on the employment of compounds of this class for the formation of polymeric materials are developing.[67-72]

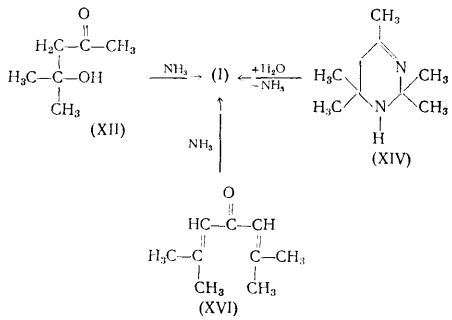
III. METHODS OF SYNTHESIS OF α,α,α′,α′-TETRASUBSTITUTED PIPERIDINE SYSTEMS

In considering the methods for the closure of 2,2,6,6-tetrasubstituted piperidine rings developed hitherto, one should note that attention has been concentrated on the synthesis of 2,2,6,6-tetramethyl-4-piperidinone (triacetoneamine). The vast majority of 2,2,6,6-tetrasubstituted piperidines known at present have been synthesised from triacetoneamine. According to the method[18] for the synthesis of compound (I) developed as early as 1874, ammonia was passed into acetone with heating.[19,73] Subsequently the process was carried out at room temperature and calcium chloride was added to the reaction mass to improve the absorption of ammonia and to bind the water formed during the reaction.[74-76] Different versions of this process have been developed: with the ammonia passed in several portions into a mixture of acetone and calcium chloride taking into account the amount of ammonia[40,77] and with subsequent maintenance of the reaction mass at 20 °C for 4 days[28,40,78] or with boiling it in the course of 6 h.[79] A special apparatus has been proposed for the reaction providing for the periodic separation of the calcium chloride solution[80,81] and it has been demonstrated that many protic and Lewis acids exert a catalytic influence on this process.[82-84] The application in this reaction of liquefied ammonia of the ammine complex of calcium chloride prepared beforehand has been described.[85] However, in all cases the reaction does not proceed unambiguously[78] and the yield of triacetoneamine relative to the acetone employed is about 30%.

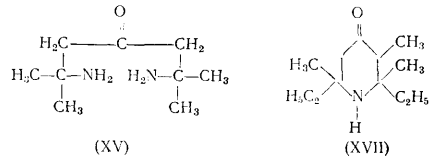
The interaction of acetone with ammonia apparently proceeds via the formation of mesityl oxide (X) and diacetoneamine (XI),[86] compound (XI) being the main reaction product at room temperature.[87] Diacetone alcohol (XII),[77] diacetonamine,[74,77,88] mesityl oxide,[77] acetonin (2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine) (XIV),[77,78,87,89] triacetonediamine (XV),[90] etc. have been detected as side products in the synthesis of triacetoneamine.



(X) (XI) (XIII) (I)



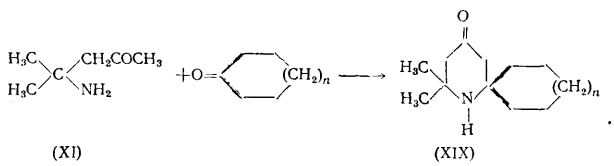
(XII) (XIV) (XVI)



(XV) (XVII)

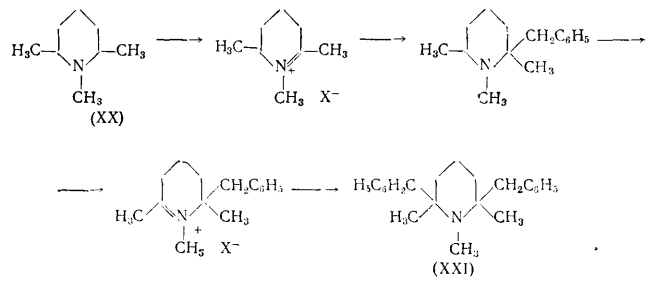
Triacetoneamine can also be obtained from phorone (XVI) and ammonia,[73,91,92] from acetonin (XIV) and water in the presence of calcium chloride,[78] and from diacetone alcohol (XII) by catalytic condensation with ammonia.[78] Despite the fact that the yields of triacetoneamine in the above reactions are somewhat higher (from 48 to 68%), the lower availability of the starting materials precludes preference being given to these procedures in the synthesis of compound (I) compared with the classical method involving the condensation of acetone with ammonia.

An analogous condensation of ethyl methyl ketone with ammonia has been used to synthesise 2,6-diethyl-2,3,6-trimethyl-4-piperidinone (XVII).[93] When diacetoneamine was allowed to react with cyclopentanone (XVIII, $n = 0$) and cyclohexanone (XVIII, $n = 1$), compounds (XIX, $n = 0$ and 1) were synthesised in yields of 20 and 54% respectively:[78]



(XI) (XIX)

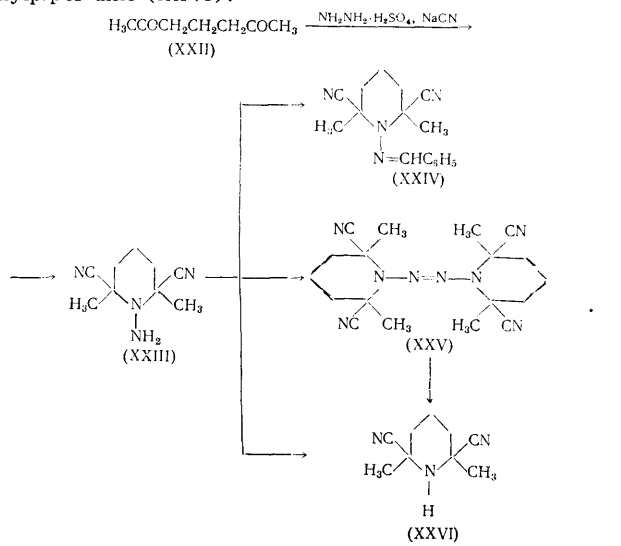
A novel method for the conversion of 1,2,6-trimethylpiperidine (XX) into 2,6-dibenzyl-1,2,6-trimethylpiperidine (XXI) consists in a twofold repetition of the reactions involving the oxidation of the piperidine derivative by mercury acetate to the corresponding Δ'-dehydro-derivatives in yields of the order of 66–67% and subsequent addition of benzylmagnesium bromide to the double bond in yields of 95–96% in accordance with the scheme[94]



(XX) (XXI)

Unfortunately analogous reactions using alkylmagnesium halides failed to yield satisfactory results.[94]

The reaction of heptane-2,6-dione (XXII) with hydrazine sulphate and sodium cyanide, which results in the formation of 1-amino-2,6-dicyano-2,6-dimethylpiperidine (XXIII), has been described. The latter reacts with benzaldehyde to form the benzylidene derivative (XXIV) and, on oxidation with potassium permanganate, it is converted into the tetrazine (XXV). The cleavage of the tetrazene with hydrobromic acid and treatment of the *N*-amino-compound (XXIII) with sodium nitrite in an acid medium led to 2,6-dicyano-2,6-dimethylpiperidine (XXVI):[95]



(XXII) (XXIV) (XXIII) (XXV) (XXVI)

IV. CHEMICAL REACTIONS OF α,α,α',α'-TETRASUBSTITUTED PIPERIDINES

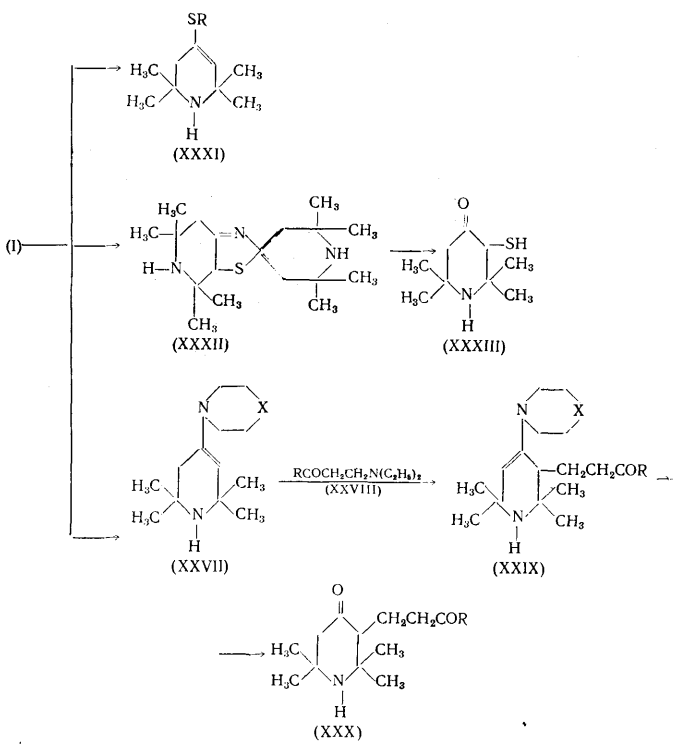
The comprehensive study of the reactivity of triacetoneamine has been important for the development of the chemistry of 2,2,6,6-tetrasubstituted piperidines.

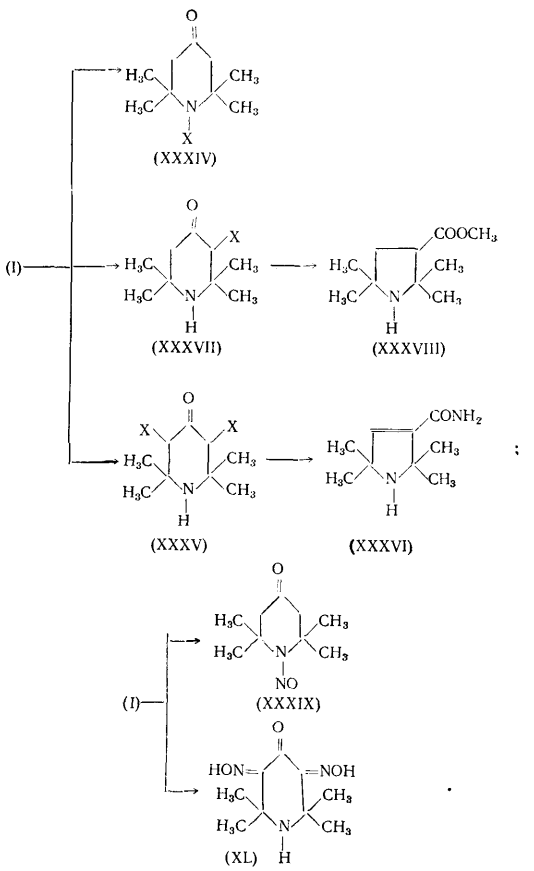
1. Reactions without the Growth of the Carbon Skeleton

Typical derivatives involving the carbonyl group of compound (I) were obtained already in the early stages of the investigation: the oxime,[96] the phenylhydrazone,[97] the

semicarbazone;[98] the hydrazone[39] and the methylhydrazone[67,99] were synthesised later.

On interaction with morpholine and piperidine, triacetoneamine is converted in 75–80% yields into the corresponding enamines (XXVII), which give rise to 3-substituted triacetoneamines (XXX) in yields of ~80% on condensation with Mannich bases (XXVIII) and subsequent acid cleavage of compounds (XXIX).[100]





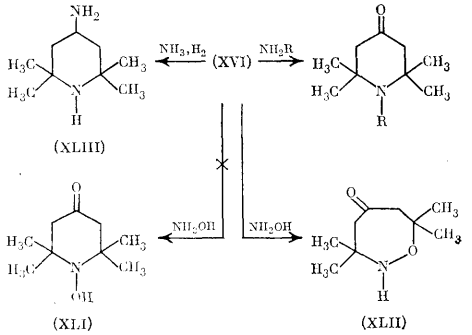
Compound (I) reacts with ethanethiol and thiophenol in an alcoholic hydrochloric acid solution and is converted into *S*-substituted 4-mercapto-2,2,6,6-tetramethyltetrahydropyridines (XXXI),[101] while the interaction with sulphur and ammonia gives rise to 5,5,7,7-tetramethyl-1,2,5,6,7,7a-hexahydrothiazolo[5,4-*c*]pyridine-2,4-spiro-4-(2′,2′,6′,6′-tetramethylpiperidine) (XXXII), which readily hydrolyses to 3-mercapto-2,2,6,6-tetramethyl-4-piperidinone (XXXIII).[80]

Compound (I) reacts with halogens in polar media to form the *N*-halogeno-derivative (XXXIV)[101–103] or, under more severe conditions, 3,5-dihalogeno-derivatives (XXXV), where X = Cl or Br.[91,102] On treatment with ammonia, the latter undergo ring contraction with formation of 2,2,5,5-tetramethyl-2,5-dihydropyrrole-3-carboxamide (XXXVI).[91] In non-polar media, the halogenation of compound (I) makes it possible to obtain the 3-monohalogeno-derivatives (XXXVII, X = Cl or Br), which react with sodium methoxide to give the methyl ester of 2,2,5,5-tetramethylpyrrolidine-3-carboxylic acid (XXXVIII) as a result of ring contraction.[104] In acetonitrile or aqueous methanol, compound (I) reacts with $FClO_3$ to form the *N*-fluoro-derivative (XXXIV, X = F) and the reaction is of first order with respect to each reactant.[105] Depending on the reaction conditions, the nitrosation of compound (I) can proceed with formation of the *N*-nitroso-derivative (XXXIX)[106] or the derivatives (XL) substituted in the 3,5-positions.

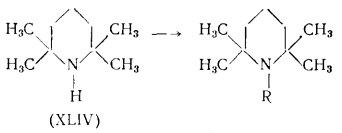
The *N*-halogenation[107] and *N*-nitrosation processes[56,57,108] have been used also in the case of other 2,2,6,6-tetrasubstituted piperidines. 1-Chloro-2,2,6,6-tetramethylpiperidine has found an application as a chlorinating agent.[107]

1,2,2,6,6-Pentamethyl-4-piperidinone has been obtained by methylating triacetoneamine with methyl iodide. However, a more convenient and more general method for the introduction of the *N*-methyl group into 2,2,6,6-tetramethylpiperidine derivatives proved to involve their treatment with a mixture of formaldehyde and formic acid.[39,40,109,110] In order to obtain compounds with more bulky substituents at the nitrogen atom, derivatives of 2,2,6,6-tetramethylpiperidine are treated with the corresponding halogen-containing compounds or epoxyethane derivatives.[27,41,64,111–116]

Another version of the synthesis of *N*-alkyl- and *N*-arylalkyl-2,2,6,6-tetramethylpiperidines involves the interaction of the corresponding primary amines with phorone.[73] It is noteworthy that the analogous reaction of phorone with hydroxylamine does not lead to 1-hydroxytriacetoneamine (XLI), as described previously,[90] but to hexahydro-3,3,7,7-tetramethyl-1,2-oxazepin-5-one (XLII).[117] 4-Amino-2,2,6,6-tetramethylpiperidine (XLIII) has been obtained by the reductive ammination of phorone with ammonia and hydrogen at 110–150 °C and 100–180 atm in the presence of various catalysts:[118]

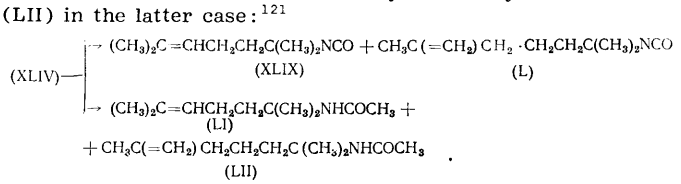


On reaction with butyl-lithium and subsequent treatment with alkyl halides, 2,2,6,6-tetramethyl-1-propynylpiperidine (XLV), synthesised by alkylating 2,2,6,6-tetramethylpiperidine (XLIV), was converted into the αβ-ynamino-derivative (XLVI) which gives rise to the corresponding amides (XLVII) on hydration:[119]

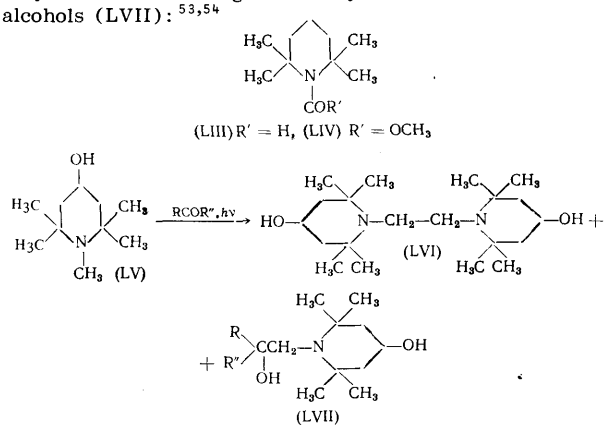


(XLV) R = C≡CCH$_3$,
(XLVI) R = C≡CCH$_2$R′,
(XLVII) R = COCH$_2$R′,
(XLVIII) R = COC$_6$H$_5$.

The *N*-benzoyl derivative (XLVIII) has been obtained by the reaction of compound (XLIV) with benzoyl chloride in benzene in 55% yield.[120,121] However, the reaction with phosgene and acetyl chloride resulted in the opening of the piperidine ring with formation of 1,1,5-trimethylhex-4-enyl isocyanate (XLIX) and 1,1,5-trimethylhex-5-enyl isocyanate (L) in the former case and *N*-(1,1,5-trimethylhex-4-enyl)-acetamine (LI) and *N*-(1,1,5-trimethylhex-5-enyl)acetamide (LII) in the latter case:[121]



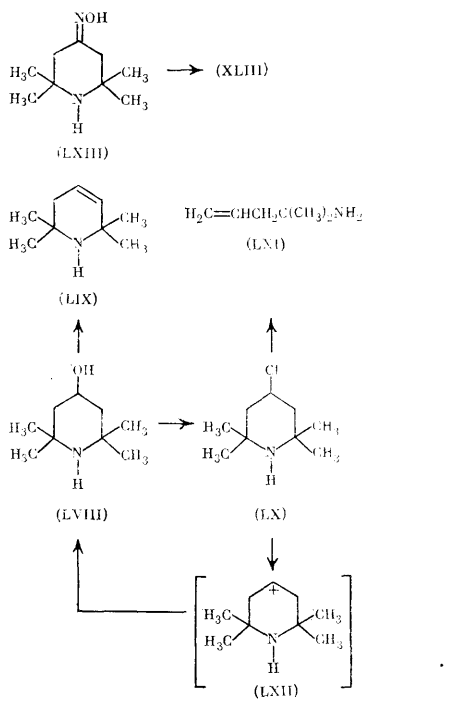
1-Methoxycarbonyl-2,2,6,6-tetramethylpiperidine (LIV) has been obtained by the electrochemical oxidation of 1-formyl-2,2,6,6-tetramethylpiperidine (LIII) in methanol at a platinum anode,[122] while in the photochemical oxidation of 1,2,2,6,6,-pentamethyl-4-piperidinol (LV) by ketones the process involves the *N*-methyl group with formation of the dimeric product (LVI) and 2,2,6,6-tetramethyl-4-piperidinols alkylated at the nitrogen atom by the residues of the tertiary alcohols (LVII):[53,54]



(LIII) R′ = H, (LIV) R′ = OCH$_3$

The oxo-group is usually eliminated from the 4-position of triacetoneamine and other 2,2,6,6-tetramethyl-4-piperidinones by the Wolff–Kishner reduction with hydrazine hydrate and potassium hydroxide in triethylene glycol,[76,120] ethylene glycol,[40] or glycerol[28] in 50–70% yields. In the reactions with sodium tetrahydroborate,[93] lithium tetrahdyroaluminate,[109] sodium in alcohol, sodium amalgam,[93] and hydrogen in the presence of a nickel catalyst[109] or in the electrochemical reduction,[123] the products are, as was to be expected, the corresponding 2,2,6,6-tetramethyl-4-piperidinols. Under these conditions, the alcohol (LVIII), with the equatorial disposition of the hydroxy-group and the chair configuration of the heterocycle, was obtained from triacetoneamine.[124] On treatment with thionyl chloride, the above alcohol is readily converted into the dehydropiperidine derivative (LIX), but, on reaction with hydrochloric acid, compound (LVIII) gives rise to 4-chloro-2,2,6,6-tetramethylpiperidine (LX).[125] On alkaline hydrolysis, the chloride (LX) undergoes synchronous fragmentation with formation of 2-amino-2-methylpent-4-ene (LXI) and is simultaneously converted at a lower rate into 2,2,6,6-tetramethyl-4-piperidinol via the carbonium ion (LXII)[126] (see the Scheme below).

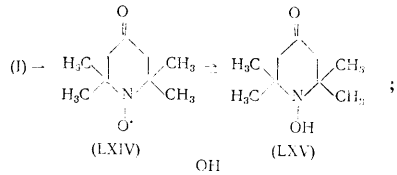
Scheme



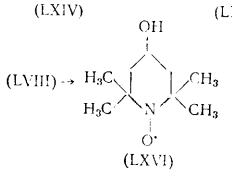
In order to investigate the spasmolytic and antiviral activities, the esters of the alcohol (LVIII) were obtained[127,128] and were used to synthesise the guanidine derivatives.[39] The reduction of the oxime of triacetoneamine (LXIII), both catalytic and with lithium tetrahydroaluminate, yielded 4-amino-2,2,6,6-tetramethylpiperidine.[39]

Cautious oxidation of triacetoneamine with hydrogen peroxide in the presence of catalysts (tungsten, molybdenum, or vanadium salts) leads to the stable iminoxy-radical (LXIV),[48] which forms an oxime, a semicarbazone, and a 2,4-dinitrophenylhydrazone,[48] undergoes the Wolff–Kishner reduction[129] and the Beckmann rearrangement,[130,131] enters into a modified Wittig reaction,[132] and gives rise to a spirohydantoin derivative[133] without involving the centre where the unpaired electron is localised. At the same time the catalytic

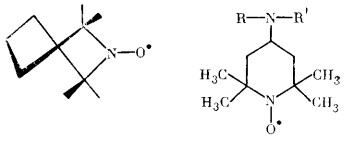
reduction of compound (LXIV) in the presence of palladium leads to a diamagnetic substance—1-hydroxytriacetoneamine (LXV).[48] Fermi's salt (potassium nitrosodisulphonate) is used to convert the *N*-hydroxy-compounds (LXV) into the iminoxy-radical (LXIV):[134]



(LXIV) (LXV)

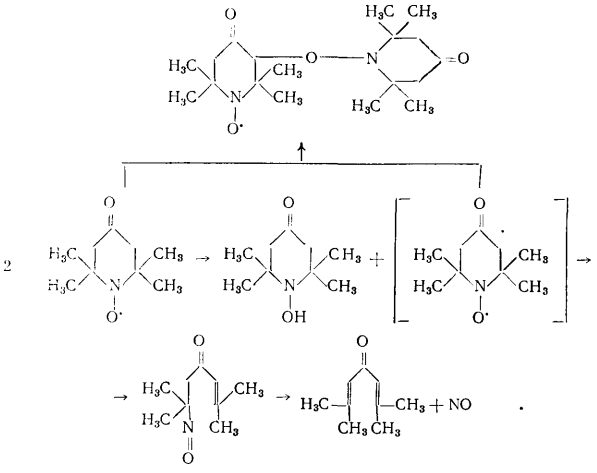


(LXVI)



(LXVII) (LXVIII)

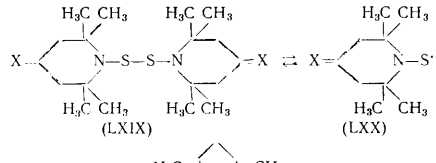
The corresponding 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yloxy-radical (LXVI) has been obtained by oxidising compound (LVIII) with hydrogen peroxide.[135] The use of peracids for the same purpose involves simultaneously the 4-hydroxy-group, converting it into the oxo-group.[136] The 2,2,6,6-tetramethyl-4-oxo-piperidin-1-yloxy-radical (LXIV) has the symmetrical twist-conformation (LXVII) in the solid state,[137] while in the gas phase[138] and in solution[139] the nitrogen atom is at the apex of the pyramid. The relative instability of compound (LXIV) is associated with the activation of the hydrogen atoms in the 3- and 5-positions adjoining the carbonyl group, which leads to a slow disproportionation of the radical in accordance with the scheme[140]



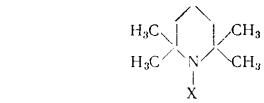
The iminoxy-radical (LXIV) can be used for the effective binding of the benzoyl and benzyl radicals. Acylation of the iminoxy-radical (LXVI) at the hydroxy-groups proceeds without involving the radical centre.[8,135,141–145] Substituted 4-amino-2,2,6,6-tetramethylpiperidin-1-yloxy-radicals (LXVIII) have been obtained by the reductive amination of compound (LXIV) by primary and secondary amines in the presence of sodium cyanohydroborate at pH 5–9.[146–150]

The study of the mechanism of the oxidation of compound (XVIII) by cumenyl hydroperoxide showed that the rate-determining stage is the formation of the N-radical-cation, which reacts with the excess hydroperoxide and is converted into an intermediate quaternary *N*-hydroxyammonium salt, which dissociates to the iminoxy-radical.[151] Many other methods of synthesis of various stable nitroxy-radicals by the oxidation of 2,2,6,6-tetrasubstituted piperidines and via a wide variety of reactions of 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yloxy-, 2,2,6,6-tetramethyl-4-oxopiperidin-1-yloxy, and 4-aminopiperidin-1-yloxy-radicals without involving the *N*-oxy-group have been published in the literature. These methods have been described in detail in reviews.[2–7] Problems concerning the relation between the electronic structure of the iminoxy-radicals and their acute toxicity have been considered.[152]

Further investigations showed that compounds (I) and (XLIV) react with sulphur dichloride in dimethylformamide and are converted into the disulphides (LXIX), which dissociate on heating to 2,2,6,6-tetramethylpiperidine-1-thiyl radicals (LXX), which readily dimerise on cooling.[55] In less polar solvents (hexane, ether) the process leads towards the formation of polysulphides containing from three to five sulphur atoms.[55]

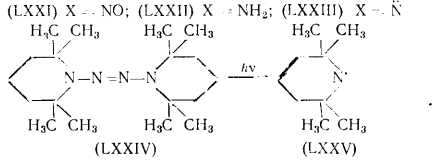


(LXIX) (LXX)



(LXXI)—(LXXIII)

(LXXI) X = NO; (LXXII) X = NH_2; (LXXIII) X = N



(LXXIV) (LXXV)

The reduction of 2,2,6,6-tetramethyl-1-nitrosopiperidine (LXXI) with lithium tetrahydroaluminate yielded 1-amino-2,2,6,6-tetramethylpiperidine (LXXII),[153] whose treatment with t-butyl hypochlorite in ether at −78 °C in the presence of triethylamine led to the formation of *N*-(2,2,6,6-tetramethylpiperidine)nitrene (LXXIII).[56] Other nitrenes of this type have been described in the literature.[154–156] The ultraviolet spectrum of compound (LXXIII), recorded at −78 °C, is characterised by an appreciable absorption due to the $n\pi^*$ transition, while the intense absorption at 1595 cm^{-1} in the infrared spectrum indicates a considerable amount of double bond character in the N–N group in the ground state. At 0 °C the nitrene (LXXIII) readily decomposes and the rate of decomposition in solutions is inversely proportional to the solvent polarity. There is a simultaneous bimolecular reaction leading to the formation of 1,1-tetrazene (LXXIV).[56] The photolysis of compound (LXXIV) generates the 2,2,6,6-tetramethylpiperidinyl radical (LXXV), which is much less stable than iminoxy-radicals. It readily splits off hydrogen from solvents and is readily oxidised by oxygen to the nitroxide {the labelled [^{17}O] nitroxide has been synthesised using $^{17}O_2$}.[57] The 2,2,6,6-tetramethyl-4-oxopiperidinyl radical, whose stability is low, has been obtained by the photolysis of *N*-bromotriacetoneamine (XXXIV, X = Br).[157]

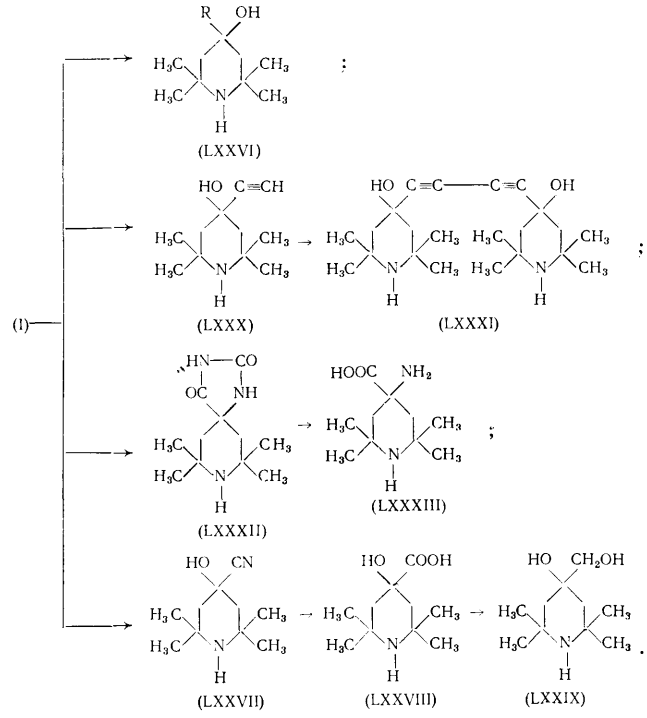
2. Reactions Involving the Formation of New C–C Bonds at the Piperidine Ring

Together with the reactions described above, which take place mainly without the growth of the carbon skeleton at the piperidine ring, processes involving the formation of new C–C bonds due to various condensations involving the heterocyclic skeleton of the molecule occupy an important place in the chemistry of 2,2,6,6-tetrasubstituted piperidines.

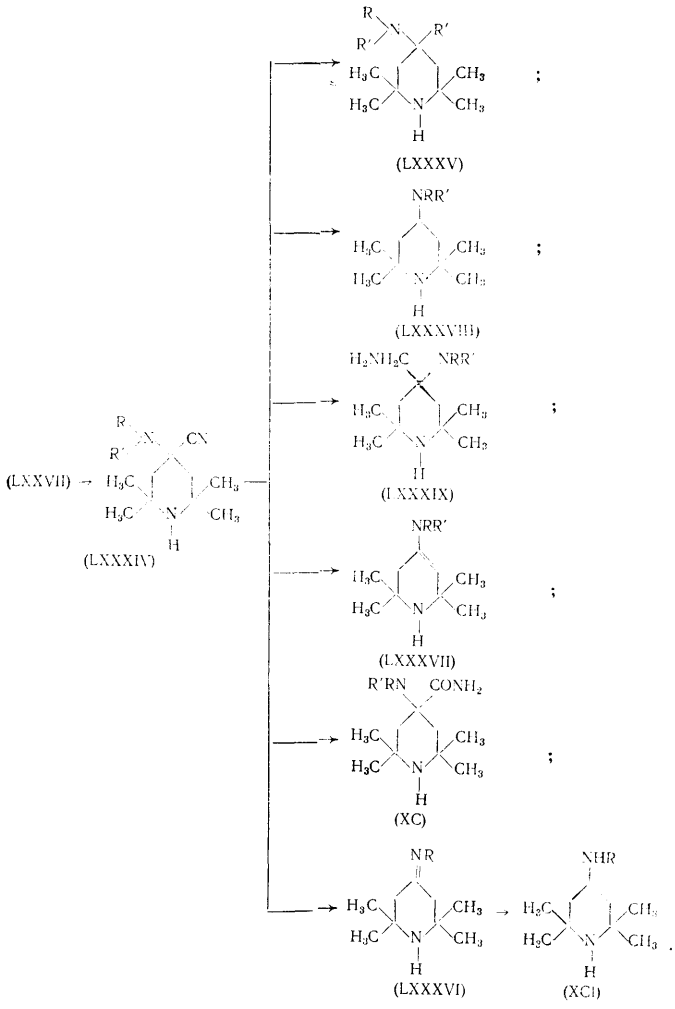
Using the appropriate Grignard reagents, 4-ethyl-(4-phenyl)-4-hydroxy-2,2,6,6-tetramethylpiperidines (LXXVI, R = C_2H_5 or C_6H_5) have been synthesised from triacetoneamine,[158] while the reaction with acetone cyanohydrin yielded 4-cyano-4-hydroxy-2,2,6,6-tetramethylpiperidine (LXXVII),[109] which was hydrolysed to 4-hydroxy-2,2,6,6-tetramethylpiperidine-4-carboxylic acid (LXXVIII)[109] and reduced to the diol (LXXIX).

Compound (I) has been converted by acetylene synthesis into 4-ethynyl-4-hydroxy-2,2,6,6-tetramethylpiperidine (LXXX), whose oxidation by oxygen in the presence of copper ammine gives rise to 1,4-bis(4-hydroxy-2,2,6,6-tetramethylpiperidin-4-yl)butadiene (LXXXI).[39] The triple bonds were reduced catalytically in the formation of compound (LXXXI).[39]

Compound (I) has been converted by reaction with sodium cyanide and ammonium carbonate into the piperidinohydantoin derivative (LXXXII),[115] which was then hydrolysed to the aminoacid (LXXXIII):



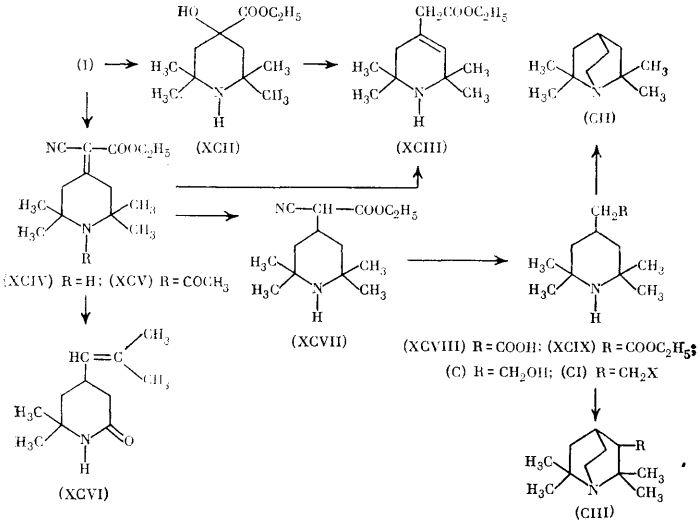
The reaction of the cyanohydrin (LXXVII) with ammonia or various aliphatic and aliphatic-aromatic amines in methanol readily gives rise to 4-amino-4-cyano-2,2,6,6-tetramethylpiperidines (LXXXIV) even at 0–20 °C.[110,111] Aromatic amines do not enter into this reaction.[110] The interaction of the aminonitriles (LXXXIV) with Grignard reagents leads to 4-alkyl-4-amino-2,2,6,6-tetramethylpiperidines (LXXXV),[111] while heating of compounds (LXXXIV) above 50 °C causes the splitting of hydrogen cyanide and the formation of the imino-derivatives (LXXXVI) or (in the case of tertiary amines) the enamines (LXXXVII).[110] On treatment with lithium tetrahydroaluminate, the aminonitriles (LXXXIV) readily lose their cyano-group and are converted into the *N'*-substituted 4-amino-2,2,6,6-tetramethylpiperidines (LXXXVIII) and only in the case where R = H and R' = H or $CH_2C_6H_5$ in compound (LXXXIV) are the triamines (LXXXIX) produced.[110] The hydrolysis of the nitrile group to the amide group in the aminonitriles (LXXXIV) is achieved with 90% sulphuric acid at 100 °C. Triacetoneamine is then formed together with the aminoamides (XC).[112] The imino-derivatives (LXXXVI) have been reduced catalytically to the corresponding amines (XCI).[159]



The condensation of triacetoneamine with ethyl bromoacetate under the conditions of the Reformatskii reaction results in the formation of 4-ethoxycarbonylmethyl-4-hydroxy-2,2,6,6-tetramethylpiperidine (XCII),[160] which can be dehydrated to the unsaturated ester (XCIII) by reaction with thionyl chloride or phosphoryl chloride. The corresponding methyl ester and the free acid have also been obtained from the product of the reaction of compound (I) with cyanoacetic ester.[160] The Knoevenagel condensation of compound (I) with cyanoacetic ester takes place readily in the presence of ammonium acetate in boiling benzene in the course of 1 h. More prolonged boiling in benzene or the use of higher-boiling solvents (toluene, xylene) lead to

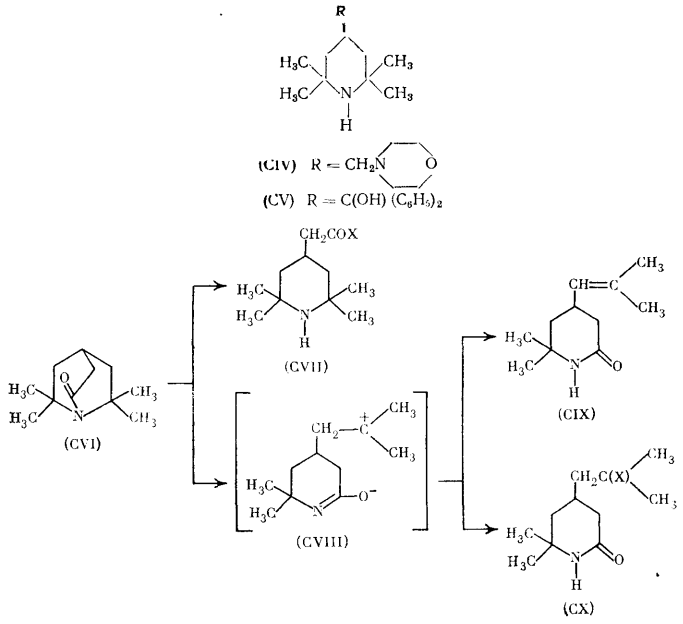
the *N*-acetylation of compound (XCIV) and the rearrangement of the resulting compound (XCV) to the unsaturated piperidinone (XCVI).[160] The hydrolysis of the nitriloester (XCIV) and subsequent partial decarboxylation are accompanied by the migration of the double bond to an endocyclic position and the ester (XCIII) is obtained after subsequent esterification.[161] Catalytic reduction of the exocyclic double bond in compound (XCIV) with the aid of palladium proceeds much more readily than the reduction of the endocyclic double bond in compound (XCIII). In order to synthesise the saturated acid (XCVIII), compound (XCIV) is therefore hydrogenated in a neutral medium in the presence of a palladium catalyst (in the presence of nickel or in hydrogenation using palladium and platinum in an acid medium, the nitrile group is involved) and the resulting compound (XCVII) is hydrolysed and partly decarboxylated. The high yield in the intermediate stages make it possible to carry out the process without isolating compounds (XCIV), (XCVII), and (XCVIII) and to obtain compound (XCIV) after esterification in an overall yield of 50% relative to triacetoneamine.[161]

The reduction of the ester (XCIX) with lithium tetrahydroaluminate, the subsequent substitution of the hydroxy-group by halogen, and cyclisation lead to 2,2,6,6-tetramethylquinuclidine (CII):[42,161]



Treatment of compound (XCVII) with alkyl halides in the presence of alkali metal alkoxides makes it possible to obtain derivatives *C*-alkylated in the side chain which have been converted into 3-alkyl-2,2,6,6-tetramethylquinuclidines (CIII) in accordance with schemes analogous to that described above.[44]

The conversion of the acid (XCVIII) into morpholide and the reduction of the latter with lithium tetrahydroaluminate led to the formation of 2,2,6,6-tetramethyl-4-(*N*-morpholinomethyl)piperidine (CIV) [46] and the reaction of the ester (XCIX) with phenyl-lithium afforded (2,2,6,6-tetramethylpiperidin-4-yl)diphenylmethanol (CV).[46]



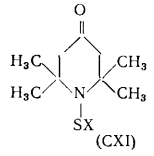
The conversion of the acid (XCVIII) into the chloride and treatment of the latter with triethylamine made it possible to synthesise 6,6,7,7-tetramethyl-2-quinuclidinone (CVI) [162,163]— a compound which is formally a bicyclic amide. However, its rigidly fixed structure with its unbound electron pair of the bridgehead nitrogen atom directed in space along the symmetry axis of the molecule rules out the possibility of the overlap of the above pair of *p* electrons with the π electrons of the C=O bond. As a result, compound (CVI) lacks the mesomeric effects characteristic of amides, the nitrogen atom exerts a purely inductive influence on the neighbouring carbonyl group, and compound (CVI) lacks amide properties but is a highly reactive acylating agent.[164,165] Its bridgehead nitrogen atom retains its highly nucleophilic properties in quaternisation and protonation reactions (pK_a = 6.37 ± 0.05 in water) and its carbonyl group has ketone and not amide properties [in the infrared spectra ν(CO) = 1755 cm^{-1} for the base, 1811 cm^{-1} for the hydrochloride, and 1820 cm^{-1} for the methiodide; it is reduced by lithium tetrahydroaluminate to CHOH and not to the CH_2 group, etc.]. Compound (CVI) reacts with various protic nucleophiles (water, alcohols, amines, etc.), the reaction involving the dissociation of the CO–N bond and the formation of 2,2,6,6-tetramethylpiperidine-4-acetic acid or its derivatives (esters, amides, etc.) (CVII). The reaction with nucleophiles in aprotic media (phenyllithium in ether, phosphorus pentachloride in benzene, excess of acetone cyanohydrin, lithium tetrahydroaluminate) entails the dissociation of the N–$C(CH_3)_2$ bond and the carbonium ion (CVIII) formed initially is stabilised either via deprotonation with formation of 4-(2-methyl-1-propenyl)-2-piperidinone (CIX) or via the addition of nucleophilic residues and the formation of substances of type (CX).

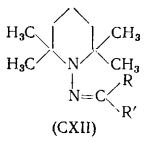
V. CHARACTERISTIC FEATURES OF THE CONFORMATIONS OF SHIELDED PIPERIDINE DERIVATIVES

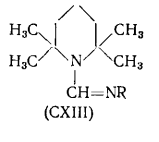
Data concerning the conformation of the 2,2,6,6-tetramethylpiperidin-1-yloxy-radical, a stable iminoxy-radical, have already been presented above. In recent years increasing attention has been devoted to the investigation of the characteristic features of the conformations of diamagnetic

sterically hindered 2,2,6,6-tetra-substituted piperidines. The preferential chair conformation of triacetoneamine and 1,2,2,6,6-pentamethyl-4-piperidinone has been established by ^{1}H NMR and the dipole moment and electro-optical Kerr effect methods, in the latter case with an equatorial orientation of the N–CH_3 group.[166–168] For the corresponding 2,2,6,6-tetramethyl-4-phenyl-4-piperidinol and 1,2,2,6,6,-pentamethyl-4-phenyl-4-piperidinol, there is an equilibrium between the chair and boat conformations with a 10% content of the latter, stabilised by an intramolecular hydrogen bond.[167,169] In the series of 1-*S*-substituted triacetoneamines (CXI, X = CCl_3, C_6H_5, t-C_4H_9, or CH_3), the activation energy for rotation about the N–S bond is significantly lower than in the corresponding 2,2,6,6-unsubstituted 4-piperidinones.[170]

The application of ^{1}H and ^{13}C NMR and X-ray diffraction showed that the conformational changes in compounds of the type of derivatives of 2,2,6,6-tetramethyl-1-piperidinyliminomethylene (CXII) [49,171–174] and 2,2,6,6-tetramethyl-1-piperidinylmethyleneimine (CXIII) [173] are hindered and that their preferred conformation is one where the planes of the N=C bond and of the piperidine ring are at right angles. On passing to 2,6-dimethylpiperidine derivatives, the planes of the N=C bond and the piperidine ring are coplanar for axial methyl groups and at right angles for equatorial methyl groups. *N*-Nitroso-2,2,6,6-tetramethylpiperidine has a coplanar arrangement of the planes of the piperidine ring and the N=O group.[49–51]


(CXI)


(CXII)


(CXIII)

Photoelectron spectroscopic studies have shown that the introduction of four methyl groups in the 2,2,6,6-positions in the piperidine ring lowers the ionisation potential of the free electron pair of the nitrogen by 0.66 eV,[52] and the contribution of each axial methyl group is ~0.26 eV and that of the equatorial methyl group is ~0.1 eV.

Thus the introduction of 2,2,6,6-substituents into the piperidine ring lowers the conformational mobility of the latter, facilitates its opening accompanied by various rearrangements, increases the stability of nitroxy-, nitrothiyl, and other free radicals, increases significantly the ganglion-blocking activity of the compounds, and almost completely abolishes their analgesic activity.

The above effects are associated mainly with the steric influence of the four α,α,α′,α′-substituents and create a basis for the practical application of substances of this class.

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