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STERIC CONFIGURATION OF PIPERIDINE DERIVATIVES

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The stereochemistry of various alicyclic compounds, particularly cyclohexane derivatives, has been much studied in the last 20–25 years, and the results obtained on the steric configuration of cyclohexane systems have served to a considerable extent as a basis for the "theory of conformational analysis".

The stereochemistry of monocyclic piperidine derivatives, in common with other heterocyclic compounds, has received comparatively little attention. The fundamental work of Fodor and his coworkers on the stereochemistry of heterocyclic compounds was mainly devoted to the spatial configuration of condensed piperidine systems (tropane alkaloids, morphine derivatives, etc.), and there have been comparatively few studies on the stereochemistry of monocyclic piperidine derivatives. The stereochemistry of piperidines is important not only for establishing the rules which determine the steric configuration of these systems, but also in their applications.

Many natural and synthetic nitrogen-containing heterocyclic compounds have a strong physiological action and are used as drugs; in particular, the powerful synthetic analgesics (morphine substitutes), the isomeric prodines, and the isomeric promedols, are piperidine derivatives. Many compounds of this series are powerful local anaesthetics.

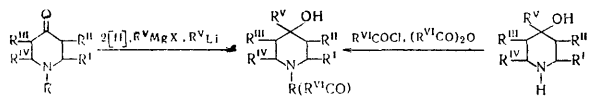
It has often been demonstrated that the effective physiological action of piperidine derivatives depends on their steric configuration: thus, for example, the isomeric prodines (1,3-dimethyl-4-phenyl-4-propionoxypiperidines) differ by a factor of about two in their analgesic activity, and a similar effect is found in the analgesic action of the isomeric promedols (1,2,5-trimethyl-4-phenyl-4-propionoxypiperidines). Similar variation occurs in the local anaesthetic action of compounds containing the piperidine ring: pseudotropine methiodide is more physiologically active than the corresponding *trans*-isomer[1], and the isomeric 1,2,5-trimethylpiperidin-4-olbenzoates have different anaesthetic activities[2].

The necessity for practical utilisation of certain piperidine derivatives as powerful analgesics and anaesthetics was one of the reasons which stimulated the study of the stereochemistry of this group of compounds.

The initial work was primarily preparative. We prepared the ring-substituted piperidines, isolated the stereoisomers predicted by theory, and studied their physiological activity. The most interesting pharmacologically were derivatives of the various piperidin-4-ols, and particular attention was paid to the synthesis of these alcohols and the development of methods for separating them into the individual stereoisomers.

The stereochemical study of piperidin-4-ols was also favoured by their comparative ease of preparation. Convenient methods were developed for preparing various piperid-4-one starting materials.

The piperidinols were prepared by reducing ring-substituted piperid-4-ones, by *N*-alkylating or *N*-acylating the *N*-unsubstituted piperidin-4-ols, or by means of organometallic compounds:



The three 2,5-dimethylpiperidin-4-ol stereoisomers (α, m.p. 97°–98°; β, m.p. 141°–142°; γ, m.p. 86°–87°) were obtained by reducing 2,5-dimethylpiperid-4-one[3,4]: the α-isomer with sodium in alcohol, the β-isomer by catalytic hydrogenation or with sodium ethoxide, and the γ-isomer by catalytic hydrogenation of 1-benzoyl(or acetyl)-2,5-dimethylpiperid-4-one followed by removal of the benzoyl or acetyl radical[2,5,6]. Various *N*-alkylated and *N*-acylated derivatives of secondary 2,5-dimethylpiperidin-4-ol isomers were prepared by alkylation or acylation.

α-1,2,5-trimethylpiperidin-4-ol (m.p. 72°–73°) was prepared by methylating α-2,5-dimethylpiperidin-4-ol and by reducing 1,2,5-trimethylpiperid-4-one. The other two 1,2,5-trimethylpiperidin-4-ol isomers (β, m.p. 77°–78° and γ, b_6 88°) were obtained by methylating the corresponding unsubstituted piperidinols or their derivatives[2,5].

Similar methods were used to prepare α-, β-, and γ-1-benzoyl-2,5-dimethylpiperidin-4-ol (m.p. 136°–137°, 134°–135°, and 159°–160° respectively)[2], α- and β-1-allyl-2,5-dimethylpiperidin-4-ol (b_2 98° and b_4 98°)[7,8], and α- and β-1-(3,3-dimethylallyl)-2,5-dimethylpiperidin-4-ol (m.p. 80°–81° and 68.5°–70°). α- and β-1-phenyl-2,5-dimethylpiperidinol (m.p. 75°–76° and 81°–82°) were prepared by reducing the corresponding piperidone by various methods[9].

To introduce an unsaturated substituent into position 4 of the piperidine ring, piperid-4-ones were condensed with acetylene, vinylacetylene, and phenylacetylene; the corresponding tertiary piperidin-4-ols are also formed in several stereoisomeric forms. α-, β-, and γ-1,2,5-trimethyl-4-ethynylpiperidin-4-ol (m.p. 73°–74°, 113°–114°, and 177°–178°) were obtained by condensing 1,2,5-trimethylpiperid-4-one with acetylene[10–12]; α- and β-1-allyl-2,5-dimethyl-4-ethynylpiperidin-4-ol (m.p. 92°–93° and 78°–79°) and γ- and β-1-(3,3-dimethylallyl)-2,5-dimethyl-4-ethynylpiperidin-4-ol (m.p. 90°–91° and 85°–86°)[13] were prepared analogously.

The condensation of 1,2,5-trimethylpiperid-4-one with vinylacetylene produces two isomers of 1,2,5-trimethyl-4-vinyl ethynylpiperidin-4-ol, which on hydrogenation gave α- and β-1,2,5-trimethyl-4-butylpiperidin-4-ol (m.p. 91°–92° and 111°–112°)[10]; a third isomer (m.p. 69°–69.5°) was obtained from butyllithium and 1,2,5-trimethylpiperid-4-one.[6] Two isomers of 1,2,5-trimethyl-4-phenylethynylpiperidin-4-ol (m.p. 103°–104° and 139°–140°) were isolated from the reaction products of the corresponding piperidone with phenylacetylene[14].

The stereochemistry of tertiary piperidin-4-ols with aryl radicals in position 4 of the piperidine ring is of particular interest. Stereoisomeric piperidinols of this type were first described by Ziering and Lee[15], who reacted 1,3-dimethylpiperid-4-one with phenyllithium to obtain 1,3-dimethyl-4-phenylpiperidin-4-ol stereoisomers, which were then used to prepare the isomeric prodines. Similarly 1,2,5-trimethylpiperid-4-one gave three of the four theoretical isomers of 1,2,5-trimethyl-4-phenylpiperidin-4-ol (α, m.p. 106°–107°; β, m.p. 101°–102°; and γ, m.p. 107°–108°), which are starting materials for the synthesis of the promedol isomers[10,16].

Many tertiary piperidin-4-ols have now been obtained in several isomeric forms: 1,2,5-trimethyl-4-*p*-tolylpiperidin-4-ol (m.p. 113°–115° and 136°–137°); 1,2,5-trimethyl-4-cyclohexylpiperidin-4-ol (m.p. 92°–93.5° and 125°–126.5°); and 1,2,5,6-tetramethyl-4-phenylpiperidin-4-ol (m.p. 99°–99.5° and 126°–127°)[14]. A series of *N*-substituted 2,5-dimethyl-4-phenylpiperidin-4-ol isomers have been prepared: ethyl (m.p. 91° and 100°–101.5°), propyl (m.p. 53.5°–55° and 93°–94°), isopropyl (m.p. 63°–65°, 67°–69°, and 106°–107°), butyl (m.p. 71°–72° and 96°–96.5°), isobutyl (m.p. 27°–29° and 72°–73°), allyl (m.p. 93°–94° and 71°–72°), isopentyl (m.p. 83°–84° and 109°–110°)[17], 3,3-dimethylallyl (m.p. 109.5°–110.5°, 105.5°–106.5°, and 115.5°–116.5°), crotyl (m.p. 97°–98° and 102°–103°), 3-chlorocrotyl (m.p. 132°–133°, 134°–135°, and 110°–111°), and other similar compounds[18].

Only the physical constants of most of these piperidinols are known; their steric configuration has not been determined.

When stereoisomeric piperidinols were isolated, they were given arbitrary designations by Greek letters (α, β, γ), sometimes in order of melting point, the lowest melting isomer being called the α-isomer. When a piperidinol isomer is alkylated or acylated, the designation of the product remains that of the starting compound. The same designation is sometimes given to stereoisomeric piperidinols having various substituents in the piperidine ring on the basis of the comparative physiological activity of their derivatives.

Unfortunately, the accepted designations do not reflect the structure of the isomers. These designations are doubly subjective, and are often a convenience only for the initial workers. Sometimes they cause confusion. As will be shown below, β-prodine and α-promedol have identical steric configurations of the 3- and 4-substituents in the piperidine ring, and they have almost identical physiological activities; they ought therefore to have the same designation. To prevent confusion in naming the isomers, it is convenient (if the structure is known) to use the accepted nomenclature for indicating the position of a substituent; for example, β-prodine should be named, 1,3-dimethyl-4*ax*-phenyl-4-propionoxypiperidine, and α-promedol should be 1,2*eq*, 5*eq*-trimethyl-4*ax*-phenyl-4*eq*-propionoxypiperidine.

The fairly extensive experimental data on the preparation of isomers of a number of piperidine derivatives have served as a basis for studying their steric configuration.

The piperidine ring is not equivalent to cyclohexane, but the principles of conformational analysis as applied to the study of the steric configuration of cyclohexane derivatives can also be used for piperidines. The two ring systems, of course, differ, but the differences do not substantially affect the factors which determine the mutual influence of substituents in each of the rings. In passing from the cyclohexane to the piperidine system, one must consider the influence of the nucleophilic nitrogen atom in the piperidine ring on the steric configuration of the molecule, including the interaction between electrophilic ring substituents and the unshared electron pair of the piperidine ring nitrogen, and the steric position of substituents on the nitrogen.

In *N*-substituted piperidines the substituent may be equatorial or axial. Koczka and Bernáth[19] studied the steric position of the piperidine *N*-methyl group of codeine. Treatment of codeine with benzyl iodide gave an *N*-benzylcodeine iodide of m.p. 178°, and treatment of *N*-benzylnorcodeine with methyl iodide gave a product of m.p. 217°; it was suggested that the compounds differ only in the disposition of the substituents on the piperidine ring nitrogen.

Fodor had earlier studied the stereochemistry of the nitrogen in heterocyclic compounds by the formation of quaternary ammonium compounds from pseudotropine and *N*-ethoxycarbonylmethylnorpseudotropine[20]. Treatment of the former with ethyl iodoacetate and the latter with methyl iodide gave quaternary ammonium compounds differing in the disposition of the substituents on the nitrogen.

On the basis of these studies, it has been suggested that the nitrogen atom is an asymmetric centre, and in consequence that the lone pair of electrons on the nitrogen in tertiary *N*-derivatives occupies a definite tetrahedral position.

A study of the optical anisotropy of piperidine has shown that the molecule has the chair form with the >N–H bond in the axial position[21]; for *N*-substituted monocyclic piperidine derivatives, the nitrogen substituents are most probably (from the point of view of the steric interaction of the ring and nitrogen substituents) in the equatorial position.

The equatorial position of the *N*-methyl group in morphine and α-prodine has been demonstrated by X-ray structure analysis of their crystalline salts. Aroney and Le Fèvre[22] used data on the Kerr effect, refractive indices, dielectric constants, and densities of benzene solutions of 1-phenylpiperidine and 1-*p*-nitrophenylpiperidine to calculate the polarisation, dipole moments, and molecular Kerr constants; comparison of the experimental results with those calculated for the various possible conformations showed that these compounds have the chair-structure with the *N*-phenyl groups in the equatorial position. However, the *N*-substituent of the piperidine ring may, as shown by Closs[23], change its conformation under certain conditions, *i.e.* axial–equatorial isomerism may occur. This was demonstrated by study of the nuclear magnetic resonance spectra of certain tropine and pseudotropine derivatives.

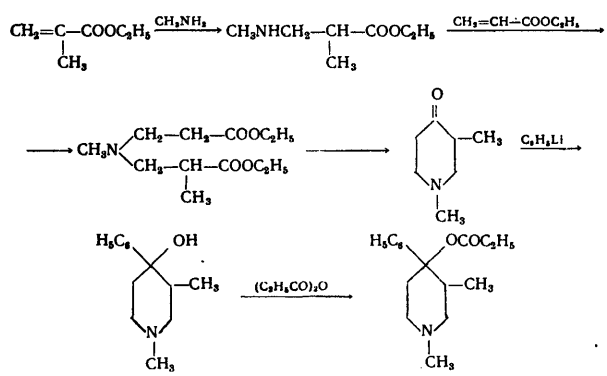
Comparison of the nuclear magnetic resonance spectra of pseudotropine ethiodide, in which the *N*-methyl group is axial, with those of ethyl norpseudotropine methiodide, in which the methyl group is equatorial, showed that the peak at higher field corresponds to the isomer with the equatorial methyl group. Pseudotropine methiodide showed two peaks of equal intensity.

These spectra have been compared with the nuclear magnetic resonance spectra of pseudotropine hydrochloride obtained at various acidities. The spectrum of this compound in aqueous solution at pH 1 has two doublets, which merge into a single peak at pH 6. This has been explained as due to rapid exchange of a proton with the solvent, which is connected with the rapid interconversion of the isomers differing in the position of the *N*-methyl group (axial or equatorial).

In studying the stereochemistry of substituted piperidines, in some cases the possibility of easy inversion of the piperidine ring itself must be taken into account; this causes difficulties in studying the conformation of some piperidines. Naturally, with polycyclic compounds, where the piperidine ring is fixed in a definite steric configuration, the stereochemical problems can be more definitely answered. The tendency of *N*- and *C*-substituted piperidines towards inversion of the piperidine ring and the probability of existence of either conformational isomer are to a large extent determined by the nature and position of the substituents in the piperidine ring [*C*-substituents? (Ed. of Translation)].

The stereochemistry of piperidin-4-ols and their derivatives has recently been studied in particular detail, especially the above-mentioned 1,3-dimethyl-4-phenylpiperidin-4-ol and 1,2,5-trimethyl-4-phenylpiperidin-4-ol isomers and their propionates, *i.e.* the isomeric prodines and isomeric promedols.

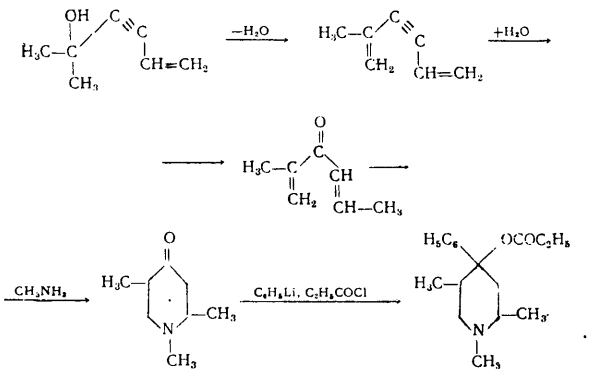
The 1,3-dimethyl-4-phenylpiperidin-4-ol isomers and the corresponding α- and β-prodines have been prepared by Ziering and Lee as follows[15]:



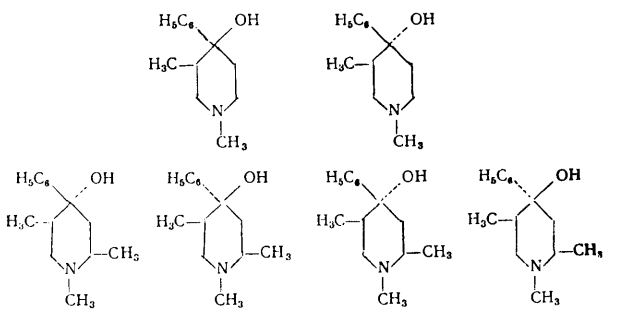
The isomeric prodines are widely used abroad as anaesthetics. Their stereochemistry has been studied by Ziering and Beckett and coworkers (these studies are considered below); they give opposite steric configurations to the α- and β-prodines.

The preparation of the isomeric promedols, which are the main analgesics used in the Soviet Union, was the result of

several years work by Nazarov and coworkers [3,10,16,24-27]. At present the industrial preparation is as follows:



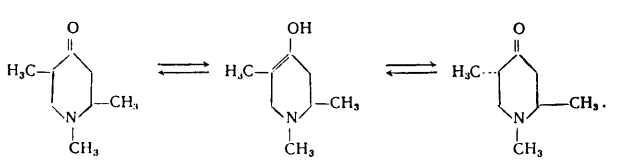
The structures of α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and some of their analogues and derivatives are considered below; these structures are directly related to the configurations of promedol and α-promedol. The 1, 3-dimethyl-4-phenylpiperidin-4-ol molecule has two, and the 1, 2, 5-trimethyl-4-phenylpiperidin-4-ol molecule has three asymmetric carbon atoms; consequently the former can exist in two and the latter in four geometrically isomeric forms:



Establishing the configurations of these analgesics would enable the analgesic action of these substances to be correlated with their steric structure, and might also solve certain problems of the mechanism of the biological action of the analgesics.

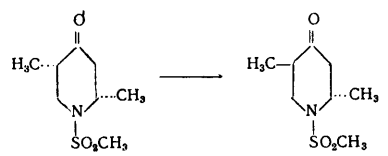
cis- and *trans*-1, 2, 5-Trimethylpiperid-4-one

Two geometrical isomers of 1, 2, 5-trimethylpiperid-4-one are theoretically possible, differing in the steric disposition of the 2- and 5-methyl groups:



They are easily interconverted, and it is therefore difficult to identify the isomers as their derivatives. The existence of *cis*- and *trans*-forms of 1, 2, 5-trimethylpiperid-4-one is definitely shown by the reaction of the piperidone with organometallic compounds, which yields the piperidinols corresponding to both isomeric piperidones [16].

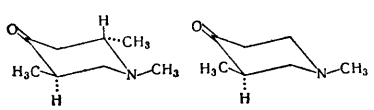
Individual stereoisomers of the 1-acyl-2, 5-dimethylpiperid-4-one series have been isolated and studied [4]. Because of the considerably reduced basic properties of the piperidine ring, interconversion of the 1-acyl-2, 5-dimethylpiperid-4-one isomers takes place unidirectionally and at higher temperatures. For example, 1-mesyl-2, 5-dimethylpiperid-4-one is obtained as two isomers, melting at 76°–78° and 98°–100°. The lower-melting isomer is less stable, and on heating is converted into the more stable isomer of m.p. 98°–100°:



cis-isomer m.p. 76°–78° *trans*-isomer m.p. 98°–100°

The more stable *N*-substituted 2, 5-dimethylpiperid-4-one isomers must correspond with the piperidones with *trans*-equatorial methyl groups, in accordance with the structure of 1, 4-substituted cyclohexanes [28]; it is known that "di- and poly-substituted cyclohexane derivatives usually take up that conformation in which a majority of the substituents are equatorial" [29].

For 2, 2, 6-trimethylpiperid-4-one, the more stable structure is that with the maximum number of equatorial substituents [30]; consequently, the quantitatively predominant isomer of 1, 2, 5-trimethylpiperid-4-one must be the *trans*-isomer with equatorial methyl groups. The 3-methyl group of 1, 3-dimethylpiperid-4-one, the starting material for the preparation of the prodine isomers, is also in the equatorial position:



α-Prodine and Promedol; β-Prodine and α-Promedol

Of the stereoisomers α- and β-1, 3-dimethyl-4-phenylpiperidin-4-ol and γ- and α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and their propionate hydrochlorides, the following are analogues in a chemical and pharmacological sense: (a) α-1, 3-dimethyl-4-phenylpiperidin-4-ol and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and the corresponding propionate hydrochlorides α-prodine and promedol; (b) β-1, 3-dimethyl-4-phenylpiperidin-4-ol and α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and the corresponding propionate hydrochlorides β-prodine and α-promedol.

The reaction of phenyllithium with 1,3-dimethylpiperid-4-one and 1,2,5-trimethylpiperid-4-one gives α-1,3-dimethyl-4-phenylpiperidin-4-ol and γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol in about the same predominating quantity (75–80%) as compared with the other isomers of these piperidinols[31,32]. α-Prodine and promedol are very similar in their analgesic action. It has been shown in Mashkovskii's laboratory that promedol is about 2–3 times as effective an analgesic as morphine (tests on rats); α-prodine is also about twice as active as morphine[33].

β-1,3-Dimethyl-4-phenylpiperidin-4-ol and α-1,2,5-trimethyl-4-phenylpiperidin-4-ol are also formed from phenyllithium and the corresponding piperidones in about the same yields, but considerably lower (20–25%) than the piperidinols corresponding to α-prodine and promedol. β-Prodine and α-promedol also have similar analgesic activity: they are about 4–6 times as active as morphine.

These facts are a sufficient basis for the simultaneous consideration of the structures of (a) α-prodine and promedol, and (b) β-prodine and α-promedol.

Comparison of the Steric Configuration of the Prodine and Promedol Isomers with that of the Piperidine Portion of the Morphine Molecule

Morphine occupies a special place in the history of organic chemistry and especially the chemistry of medicinals. The alkaloid was first obtained pure from opium in 1805 by Sertürner[34], but its structure was not determined until 120 years later[35]. Recently morphine has been synthesised[36,37], and this was the decisive proof of Robinson's proposed structure for morphine.

The guiding light in the search for synthetic analgesics has always been the chemistry of morphine and related alkaloids. The morphine molecule has served as the model for hundreds of different compounds, reproducing individual sections of its molecule. Compounds whose molecules reproduce the piperidine portion of the morphine molecule have in fact proved to be fairly effective analgesics.

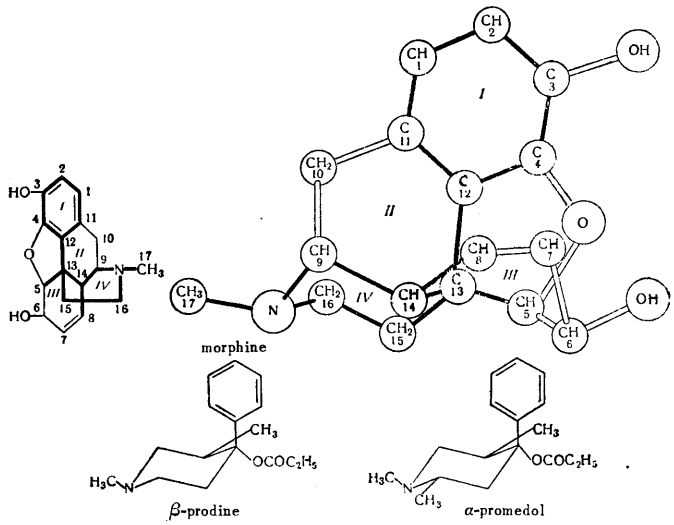
The molecules of the prodines and promedols and the known analgesic Lydol (1-methyl-4-phenyl-4-ethoxycarbonylpiperidine)[38,39] also have structural elements in common with the piperidine portion of the morphine molecule: they all contain an aryl radical and an oxygen-containing group in the 4-position of the piperidine ring.

The steric configuration of the morphine molecule has now been established by various chemical and physicochemical methods, and has been confirmed by X-ray structure analysis of morphine hydriodide dihydrate[40].

The molecule is T-shaped, with the atoms lying in two almost perpendicular planes, one containing the benzene ring *I*, the oxygen-containing ring, and the cyclohexane ring *II*, and the other containing the cyclohexene ring *III* and the piperidine ring *IV*; the last ring has an almost true chair form. The *N*-methyl group is *cis* relative to the C_9-C_{10} bond.

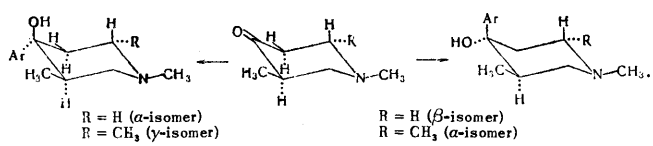
Just as the structure of the morphine molecule has been the foundation for preparative studies on synthetic analgesics, its stereochemistry has to a certain extent been the starting point in the study of the configuration of synthetic analgesics.

Considering the comparatively high analgesic action of morphine, the more active of the isomeric piperidine derivatives which are analgesics would be expected to be the isomer having the spatial configuration which is the same as that of the piperidine portion of the morphine molecule. This is one of the principles underlying the suggestions already made[33] regarding the steric configuration of α- and β-prodine.



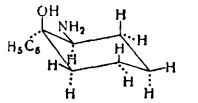
From this point of view β-prodine and α-promedol (the most active analgesics of the compounds under consideration) should have the structure in which the piperidine ring is in the chair form, the 4-phenyl radical is *cis* with respect to the 3-methyl group (or 5-methyl group in the case of α-promedol), and the propionoxy-group is equatorial and the 4-phenyl radical axial.

Influence of Steric Factors on the Reaction of 1,3-Dimethylpiperid-4-one and 1,2,5-Trimethylpiperid-4-one with Aromatic Organometallic Compounds



In the reaction of 1,3-dimethylpiperid-4-one and 1,2,5-trimethylpiperid-4-one with phenyllithium the aryl radical could enter in either the equatorial or axial position, but from the point of view of steric factors it is more probable that the phenyl radical, and other substituents of large size, would enter from the sterically less hindered side, *i.e.* from the peripheral side of the ring. With an axial phenyl radical, there is 1,3-interaction between the phenyl group and the axial hydrogen at C_2 and C_6, and this structure is therefore less favoured than the conformation in which the radical at C_4 is equatorial. This point of view is in full accord with suggestions made about the conformation of cyclohexane derivatives with a large substituent in the ring: the presence of a large substituent prevents the occurrence of any considerable quantities of the conformation having this substituent in the axial position[41].

From a study of the conformation of the isomeric 2-amino-1-phenylcyclohexanols, it was concluded that "in the presence of a large substituent the predominant conformation is that in which this substituent (*e.g.* the phenyl group) is equatorial and the hydroxy-group axial".



It can be considered a rule that "the more stable chair form sterically, is that in which substituents of high steric requirement occupy equatorial positions and those of low steric requirement occupy axial positions"[28].

Assuming that steric factors determine the relative proportions of α- and β-1,3-dimethyl-4-arylpiperidin-4-ol formed when 1,3-dimethylpiperid-4-one reacts with aromatic organometallic compounds, Beckett and coworkers[42] studied the reaction of this piperidone with various lithium aryls whose structure was expected to hinder or prevent the possibility of the aryl group entering in the axial position. Phenyllithium and *m*- and *p*-tolyllithium were found to give a mixture of piperidinols containing a considerably predominant quantity of one of the isomers. With *o*-tolyllithium, *o*-methoxyphenyllithium, and 2,6-dimethylphenyllithium, the products consisted almost exclusively of only one of the isomeric piperidinols, which, like those formed predominantly in the other reactions, belongs to the α-series. The configurational identity of these piperidinols of the α-series, and similarly of all piperidinols of the β-series, has been proved spectroscopically.

From the above theoretical considerations and experimental results, α-1,3-dimethyl-4-phenylpiperidin-4-ol and γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol have an equatorial phenyl radical and an axial hydroxy-group; β-1,3-dimethyl-4-phenyl piperidin-4-ol and α-1,2,5-trimethyl-4-phenylpiperidin-4-ol have the opposite configuration at C_4.

Becket *et al.*[43] have made a systematic study of the stereochemical directivity of the reaction of 1-(2-phenylethyl)-, 1-(2-phenylethyl)-3-methyl-, 1-(2-phenylethyl)-3-ethyl-, and 1-(2-phenylethyl)-3-n-propylpiperid-4-one with phenyllithium, *o*-, *m*-, and *p*-tolyllithium, *o*-anisyllithium, and 2,6-dimethylphenyllithium; in each case the predominant isomer was the piperidinol with the aryl group in the *trans*-position to the 3-alkyl group. A small amount of the *cis*-isomer was isolated only in the case of 1-(2-phenylethyl)-3-methyl-4-phenylpiperidin-4-ol, by saponification of the corresponding propionic acid ester obtained by fractional crystallisation of the mixed piperidinol propionates. The equatorial position of the propionoxy-group in the ester of the piperidinol of *cis*-structure is shown by its considerably greater ease of saponification in comparison with the ester of the piperidinol of *trans*-structure.

All the piperidinols with the 4-aryl group *trans* to the 3-alkyl group have peaks in the infra-red spectrum at 990–1010 and 1350–1385 cm^{-1}. The corresponding *cis*-piperidinols have a peak at 1040–1050 cm^{-1}.

Similar conclusions on the steric configuration of the isomeric piperidinols were made by Beckett and coworkers[44] in their study of the reaction of phenyllithium with 1-(2-phenylethyl)-2-methyl-, 1-(2-phenylethyl)-2,6-dimethyl- and *cis*-2,6-dimethylpiperid-4-one.

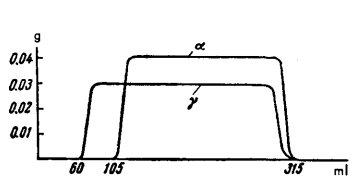
Two stereoisomers of 1-(2-phenylethyl)-2-methyl-4-phenylpiperidin-4-ol were obtained, formed in the ratio 2:1. From a consideration of the stereochemical factors influencing the reaction between the piperidone and the phenyllithium, the study of the infra-red spectra of the piperidinol isomers and their chemical properties, the 1-(2-phenylethyl)-2-methyl-4-phenylpiperidin-4-ol formed in greater quantity was assigned the configuration in which the 2-methyl and 4-phenyl groups are equatorial and the 4-hydroxy-group is axial. The other isomer has the reverse configuration of the hydroxy-group and phenyl radical at C_4.

Three isomers of 1-(2-phenylethyl)-2,6-dimethyl-4-phenylpiperidin-4-ol were isolated, in the ratio 9:2:1. The predominant isomer has equatorial 6-methyl and 4-phenyl groups and axial 2-methyl and 4-hydroxy-groups; the next most frequent piperidinol differs from the first in having an equatorial 2-methyl group, and the third isomer has equatorial 2- and 6-methyl and 4-hydroxy-groups, and the 4-phenyl radical in the axial position.

Thus in all the examples considered, the predominant piperidinol isomer has, as a rule, the 4-phenyl radical in the equatorial position.

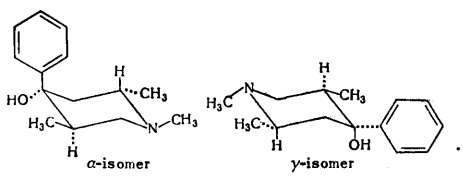
Chromatographic Study of Isomeric Piperidinols

Isomers with polar functional groups behave differently when chromatographed. It has often been demonstrated, particularly with steroids, that alcohols with an equatorial hydroxy-group are more strongly adsorbed, and therefore less easily eluted from a chromatographic column, than alcohols with an axial hydroxy-group[45]. The behaviour of α- and γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol on chromatography has been studied in connection with the stereochemistry of promedol and α-promedol[31,46]; alumina adsorbs the α-isomer considerably more strongly than the γ-isomer. Under comparable conditions (1.5 g of piperidinol, column 50 × 1.5 cm, 69 g of alumina, with chloroform as solvent) the eluate volume is 60 ml for the γ-isomer and 105 ml for the α-isomer. The solubilities of the α- and γ-forms in chloroform are respectively 64 g and 70 g in 100 ml of chloroform at 20°. From these results, it is considered that the hydroxy-group is axial in the γ-isomer and equatorial in the α-isomer.



Elution of the 1,2,5-trimethyl-4-phenylpiperidin-4-ol stereoisomers from a chromatographic column.

In considering the results of the chromatographic analysis of γ- and α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol the possibility of inversion of the piperidine ring must be borne in mind. This isomerisation clearly does not take place during chromatography. The inverted chair form of the γ-isomer would be extremely unstable, because all the substituents except the hydroxy-group would be axial. More probable would be the formation of the inverted isomer of the α-piperidinol with the equatorial phenyl group. If it be assumed that under the influence of the alumina the piperidine ring of the α-piperidinol undergoes inversion during the chromatography, the inverted form would have an equatorial hydroxy-group, as in the case of the γ-isomer; if this took place, the experimentally observed difference in the behaviour of these alcohols on chromatography would clearly not be found.



In the chromatography of α- and γ-1, 2, 5-trimethyl-4--phenylpiperidin-4-ol, the interaction between the polar groups of the amino-alcohols and the adsorbent must be taken into account. One of the causes of this interaction is the formation of hydrogen bonds between the adsorbent and the piperidinol molecules[47]

Steric factors affect the interaction between the adsorbent and the hydroxy- and amino-groups of the piperidinol isomers to different extents. In the case of the γ-isomer the equatorial position of the large phenyl radical and the position of the methyl group on the nitrogen hinder the interaction between the polar groups and the alumina; in the α-isomer the hydroxy-group and the piperidine nitrogen are not screened in this way. α- and γ-2, 5-Dimethyl-4--phenylpiperidin-4-ol, which on methylation are converted to α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol respectively, behave in the same way on chromatography; the α-isomer is more strongly adsorbed by the alumina and is less easily eluted than the γ-isomer.

There are indications that the smallest deviation from the rules of behaviour of isomeric alcohols on chromatography would be expected in partition chromatography[45,48], and Savord found that steroid alcohols with an axial hydroxy--group travel faster on the paper than their equatorial epimers. From this point of view the results obtained by Ziering *et al.*[49] by paper chromatography of the α- and β-1, 3-dimethyl-4-phenylpiperidin-4-ol isomers are of interest. Using t-pentyl alcohol–di-n-butyl ether–water (80:7:13) as solvent, they obtained the following values Rf at the indicated pH values:

	pH 6.3	pH 4.9	pH 3.6	pH 2.2
α-isomer	0.65	0.58	0.46	0.27
β-isomer	0.64	0.48	0.37	0.19

Thus the α-isomer of 1, 3-dimethyl-4-phenylpiperidin-4-ol (the structure analogue of γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol) travels faster on paper, and these piperidinols therefore have an axial hydroxy-group.

Esterification of the Isomeric Piperidinols and Saponification of Their Esters

Alcohols with an equatorial hydroxy-group are more easily esterified than alcohols with an axial hydroxy-group, and correspondingly esters with an equatorial acyloxy--group are more easily hydrolysed than those with an axial acyloxy-group. Since β-prodine is more easily hydrolysed than α-prodine, Beckett and coworkers[50] consider the propionoxy-group to be equatorial in the former and axial in the latter. Study of the esterification of α- and γ-1, 2, 5--trimethyl-4-phenylpiperidin-4-ol with propionyl chloride in benzene at 80° led to similar conclusions:

Duration of reaction, min	Yield of 1,2,5-trimethyl-4-phenyl--4-propionoxypineridine, %	
	α-isomer	γ-isomer
15	78	19.4
30	—	19.4
45	84	21.2
60	87.4	22.9

The esterification of the isomers of 1-(2-phenylethyl)--2-methyl-4-phenylpiperidin-4-ol has also been studied[51]. The *trans*-isomer (referring to the relative positions of the methyl and phenyl radicals) of this piperidinol (m.p. 98°) reacts with ketene to form the ester, but the *cis*-isomer (m.p. 79°) is not esterified under these conditions, indicating that the hydroxy-group is equatorial in the former and axial in the latter. *Trans*-1-(2-phenylethyl)-2-methyl-4--phenylpiperidin-4-ol has a peak in the infra-red spectrum at 1030 cm^{-1}, like β-1, 3-dimethyl-4-phenylpiperidin-4-ol, and this confirms that the steric configurations of these piperidinols are identical.

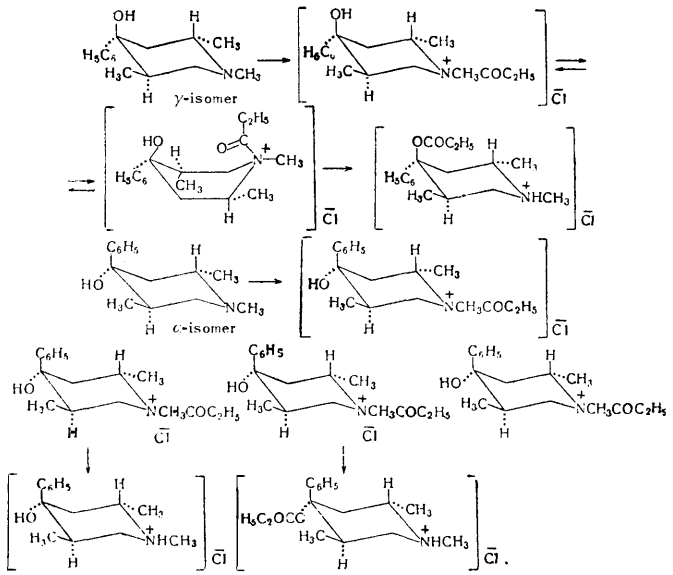
Analogous spectrographic data have been given to prove that *cis*-1-(2-phenylethyl)-2-methyl-4-phenylpiperidin-4--ol and α-1, 3-dimethyl-4-phenylpiperidin-4-ol have the same conformation.

Under comparable conditions α-1, 2, 5-trimethyl-4--phenyl-4-propionoxypiperidine is much more readily saponified than the γ-isomer: the former (α-promedol) is 73% hydrolysed by heating with 5% alcoholic KOH for 15 min at 80°, while the latter (promedol) is not hydrolysed under these conditions. The esterification of α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and the hydrolysis of their esters clearly indicate that the hydroxy-group is equatorial in the α-isomer and axial in the γ-isomer.

Esterification of these piperidinols does not cause inversion of the configuration at C_4. Hydrolysis of promedol and α-promedol gives the initial piperidinols in quantitative yield.

With α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol, esterification takes a different course: the γ-isomer produces the corresponding propionate hydrochloride, but the α-isomer, in addition to the propionate hydrochloride, produces a considerable amount (sometimes up to 50%) of the piperidinol hydrochloride. This difference is due to the steric configuration of the isomeric piperidinols. Piperidine bases form salts with organic acid chlorides, and this is evidently the first step in the esterification of the α- and γ-piperidinols. The subsequent migration of the acyl radical towards the hydroxyl oxygen takes place intramolecularly with the γ-isomer and intermolecularly with the α-isomer. Because of this, esterification of γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol gives the ester

hydrochloride, while the α-isomer gives the ester hydrochloride and also the piperidinol hydrochloride:



Esterification of α- and γ-1, 2, 5-trimethyl-4-phenyl piperidin-4-ol thus furnishes additional proof of their configuration.

Reaction of α- and β-1, 3-Dimethyl-4-phenylpiperidin-4-ol with Thionyl Chloride

Beckett *et al.*[42] showed that α-1, 3-dimethyl-4-phenylpiperidin-4-ol and 1-methyl-4-phenylpiperidin-4-ol are easily dehydrated by thionyl chloride. This reaction and the ease of elimination indicate that the hydroxy-group of the initial piperidinols is axial, since it is then that conditions for *trans*-elimination are stereochemically realisable.

With thionyl chloride, β-1, 3-dimethyl-4-phenylpiperidin-4-ol gives the corresponding 4-chloro-derivative in high yield; this reaction is only possible if the hydroxy-group of the initial piperidinol is equatorial, the reaction passing through the intermediate formation of a compound of the piperidinol with the thionyl chloride, the intermediate then decomposing to form the chloro-compound; it is known that this does not cause inversion of configuration[52-56].

Dehydration of α- and γ-1, 2, 5-Trimethyl-4-phenylpiperidin-4-ol

Observations on the dehydration of α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol[57] without study of the kinetics or the reaction mechanism can hardly give reliable data for deciding the configuration of these compounds. It is well known that many dehydration and dehydrohalogenation reactions produce an unsaturated compound which does not correspond in configuration to the initial compound, since the elimination often takes place with a change of configuration at one of the carbon atoms participating in the reaction[58]. Thus on dehydration α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol yield the same 1, 2, 5-trimethyl-4-phenyl-Δ¹-tetrahydropyridine, so that in one case there is inversion at the asymmetric centre at C_4.

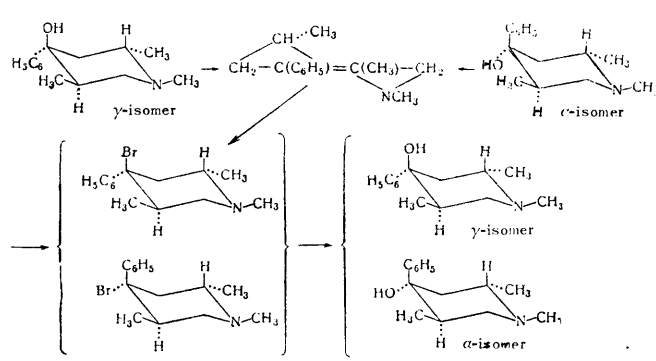
Study of the *N*-acyl → *O*-acyl rearrangement of α- and γ-1-acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol has shown that inversion occurs in the case of the α-isomer. This gives grounds for assuming that it is also the α-form which inverts when α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol are dehydrated. Consequently, α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol are dehydrated by different routes, and without kinetic investigation of the mechanism of the conversions, comparison of the quantitative results obtained in the dehydration of the piperidinol isomers under identical conditions is insufficient for any conclusions to be drawn in respect of their configuration.

Interconversions of α- and γ-1, 2, 5-Trimethyl-4-phenylpiperidin-4-ol

These have been studied in connection with the stereochemistry of promedol and α-promedol[57,59]. Treatment of γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol for 40 h with hydrogen bromide in glacial acetic acid at 100° and then with water gave the piperidinol dehydration product in 87% yield and a mixture of the α- and γ-piperidinols in 13% yield. This can give no definite information regarding the steric configuration of the initial piperidinol, because the reactions involve a number of successive stages the stereochemical nature of which is not yet known.

Heating γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol with hydrogen bromide or chloride causes dehydration, and it is important to note that the same 1, 2, 5-trimethyl-4-phenyl-Δ⁴-tetrahydropyridine is formed as when the α-piperidinol is dehydrated. The later reactions in the above series can thus give no indication of the steric configuration of the initial γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol.

The subsequent addition of hydrogen bromide to the 1, 2, 5-trimethyl-4-phenyl-Δ⁴-tetrahydropyridine may be *cis*- or *trans*-addition, and since the resulting bromides may undergo hydrolysis either with or without inversion at the asymmetric centre at C_4, the formation of a mixture of α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol is fully to be expected. It is known that in successive addition and elimination reactions only the occurrence of steric rearrangement in one of the steps can be established[60]:

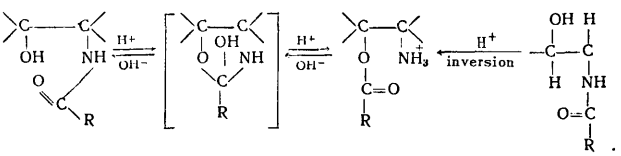


Consequently, the experimental results obtained in these conversions cannot be used to deduce the steric configuration of the γ- and α-piperidinols. Since α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol are dehydrated to form the same 1, 2, 5-trimethyl-4-phenyl-Δ⁴-tetrahydropyridine, the conversions can be regarded as those of γ-isomer to α-isomer, γ-isomer to γ-isomer, α-isomer to γ-isomer, and α-isomer to α-isomer.

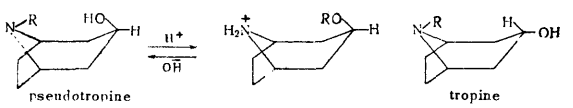
The observations of Cornubert and coworkers[61] on the reactions of *cis*- and *trans*-2-methylcyclohexanols illustrate the complexity of the processes taking place in the reaction of cyclic alcohols with hydrohalic acids. Heating the *trans*-alcohol with hydrochloric acid gave a mixture of 1-chloro-1-methylcyclohexane with *trans*- and *cis*-1--chloro-2-methylcyclohexanes, and also 1-methylcyclohexene and 3-methylcyclohexene. Under the same conditions the *cis*-alcohol gave as the main product (85%) 1-chloro-1-methylcyclohexane and 1-methylcyclohexene. It was suggested that dehydration of the methylcyclohexanol isomers first takes place, followed by addition of hydrogen chloride.

The Stereoisomers α- and γ-2, 5-Dimethyl-4-phenylpiperidin-4-ol, α- and γ-1-Acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol, and α- and γ-1, 2, 5-Trimethyl-4-phenylpiperidin-4-ol. *N*-Acyl ⇌ *O*-Acyl and *N*-Acyl → *O*-Acyl Rearrangements of γ- and α-1-Acetyl-2, 5-dimethyl-4--phenylpiperidin-4-ol

A method based on stereospecificity has been used in the study of the structure of certain tropane alkaloids and *cis*- and *trans*-amino-alcohols[62]. It is known that "N → O migration of an acyl group proceeds readily and reversibly with the *cis*-isomer, but in the case of the *trans*-compound this process takes place only with simultaneous inversion of configuration of the carbon atom carrying the hydroxy--group. With O → N migration such inversion cannot occur"[63]:



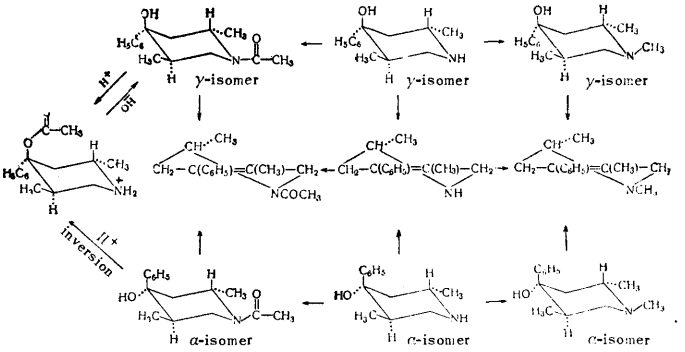
In this way, by studying the *N*-acyl ⇌ *O*-acyl rearrangement of *N*-acyl derivatives of nortropine and norpseudotropine, Fodor and Nador obtained data on the steric configuration of tropine and pseudotropine[64]:



The *cis*-position of the nitrogen bridge and the equatorial hydroxy-group in pseudotropine, and consequently their *trans*-relationship in tropine[65] have also been demonstrated by other methods, *e.g.* by measuring the rates of hydrolysis of their esters[66], and by comparison of the calculated and experimental dipole moments of tropine and pseudotropine[67].

Fodor[68] and others[69] consider the N → O acyl migration process to pass through the intermediate formation of a cyclic compound of the ortho-acid derivative type.

To use this method of conformational analysis for studying the structures of α- and γ-1, 2, 5-trimethyl-4--phenylpiperidin-4-ol, the isomers α- and γ-2, 5-dimethyl--4-phenylpiperidin-4-ol were prepared[31]. Their methylation and acetylation gave two series of genetically related stereoisomers: α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and 1-acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol.



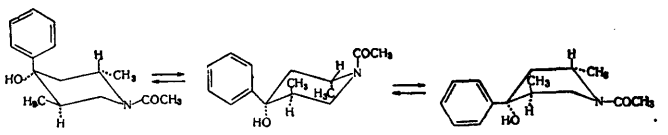
γ-1-Acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol, the steric configuration of which is identical with that of the γ-isomers of 1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and 2, 5-dimethyl-4-phenylpiperidin-4-ol, readily undergoes *N*-acyl ⇌ *O*-acyl rearrangement, which indicates the *syn*-position of the hydroxy-group relative to the nitrogen atom of the piperidine ring, *i.e.* the axial position of the hydroxy-group. The reversibility of the rearrangement indicates the absence of inversion at C_4 during the process.

Under more severe conditions α-1-acetyl-2, 5-dimethyl--4-phenylpiperidin-4-ol undergoes *N*-acyl → *O*-acyl rearrangement, but the same 2, 5-dimethyl-4-phenylpiperidin--4-ol acetate is formed (as the hydrochloride) as in the *N*-acyl → *O*-acyl rearrangement of the γ-isomer. The reverse *O*-acyl → *N*-acyl rearrangement with the formation of the initial α-1-acetyl-2, 5-dimethyl-4-phenylpiperidin--4-ol does not occur: the γ-isomer is formed. Consequently, in the case of the *N*-acyl → *O*-acyl rearrangement of the α-isomer, there is inversion of the configuration at C_4.

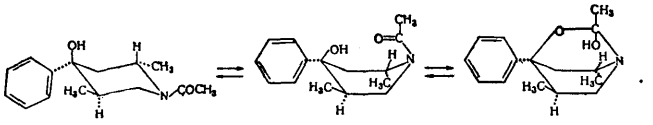
An analogous inversion of configuration of α-isomer to γ-isomer is found in the reaction of α- and γ-1-acetyl-2, 5--dimethyl-4-phenylpiperidin-4-ol with acetyl bromide[31]. These conversions of α- and γ-1-acetyl-2, 5-dimethyl-4--phenylpiperidin-4-ol indicate that the hydroxy-group is equatorial in the α-isomer and axial in the γ-isomer, and that the hydroxy-group has the same configuration in the genetically related α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and 2, 5-dimethyl-4-phenylpiperidin-4-ol.

A necessary condition for the *N*-acyl → *O*-acyl rearrangement is the close proximity of the 4-hydroxy-group to the *N*-acyl radical. This condition is realised if the 4-hydroxy-group is axial and the *N*-substituent equatorial. This must be kept in mind, since under the conditions of N → O acyl migration α-1-acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol may be in various conformations. Of course the *N*-acyl → *O*-acyl rearrangement is only possible in the conformation with an axial hydroxy-group. However, in this conformation of the α-isomer the *N*-acyl group must be axial, on the opposite side of the ring to the hydroxy-group, so that in the boat form produced from this conformer of the α-piperidinol, the hydroxy- and acetyl groups are also at a considerable distance from one

another, and the necessary conditions for *N*-acyl → *O*-acyl rearrangement are not realised:



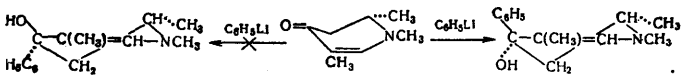
With γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol the spatial disposition of the hydroxy- and acyl groups is such as to facilitate N ⇌ O acyl migration:



Preparation of α-1, 2, 5-Trimethyl-4-phenylpiperidin-4-ol by the Catalytic Hydrogenation of 1, 2, 5-Trimethyl-4--phenyl-Δ⁵-tetrahydropyridin-4-ol

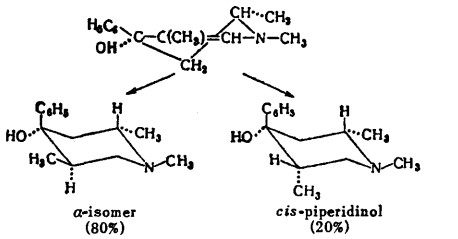
Shvetsov and Kucherov[57] have described the preparation of α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol from 1, 2, 5-trimethyl-Δ⁵-tetrahydropyrid-4-one. Reaction of this pyridone with phenyllithium gave only one of the possible isomers of 1, 2, 5-trimethyl-4-phenyl-Δ⁵-tetrahydropyridin--4-ol. From the steric point of view, this reaction should give predominantly or only the isomer of 1, 2, 5-trimethyl--4-phenyl-Δ⁵-tetrahydropyridin-4-ol having the 4-phenyl and 2-methyl radicals in the *trans*-position. In the 1, 2, 5-trimethyl-Δ⁵-tetrahydropyrid-4-one molecule all the atoms except C_2 lie almost in one plane.

The steric factor which determines the direction of attack of phenyllithium on the carbonyl group is the presence of the 2-methyl group; the *trans*-position relative to this methyl group is naturally less sterically hindered to the entry of the phenyl radical:

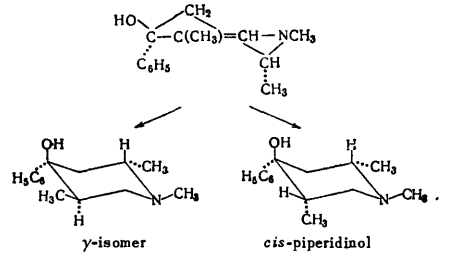


The structure of the 1, 2, 5-trimethyl-4-phenyl-Δ⁵-tetrahydropyridin-4-ol obtained was not given. Catalytic hydrogenation of the tetrahydropyridinol gave two isomers of 1, 2, 5-trimethyl-4-phenylpiperidin-4-ol: the α-isomer is known to have *trans*-methyl groups, and the β-isomer to have *cis*-methyl groups. The hydrogenation was found to give 80% of the α-isomer and 20% of the β-isomer, undoubtedly because of steric factors which influence the adsorption of the initial tetrahydropyridinol by the catalyst and the direction of addition of the hydrogen.

Catalytic hydrogenation is known to effect *cis*-addition of hydrogen to a double bond. Hydrogenation of the 1, 2, 5--trimethyl-4-phenyl-Δ⁵-tetrahydropyridin-4-ol, which on theoretical grounds should be formed solely or predominantly in the phenyllithium synthesis (with the 4-phenyl and 2-methyl radicals in the *trans*-position), could produce two isomers of 1, 2, 5-trimethyl-4-phenylpiperidin-4-ol, the methyl groups being *trans* or *cis*:



It is not difficult to see that the adsorption of the initial 1, 2, 5-trimethyl-4-phenyl-Δ⁵-tetrahydropyridin-4-ol by the catalyst and the addition of hydrogen will be considerably hindered from the side of the ring carrying the large phenyl radical; the opposite side of the ring is not so hindered, and consequently the piperidinol with *trans*-methyl groups should be produced in predominant quantity, as was found experimentally. From this point of view, in the hydrogenation of the second, less probable isomer of 1, 2, 5--trimethyl-4-phenyl-Δ⁵-tetrahydropyridin-4-ol (having the 4-phenyl and 2-methyl radicals in the *cis*-position) the steric factors would favour the adsorption of the tetrahydropyridinol and the direction of addition of hydrogen such as to produce in predominant quantity the 1, 2, 5-trimethyl-4--phenylpiperidin-4-ol with *cis*-methyl groups; in this case conditions are unfavourable for the production of the piperidinol with *trans*-methyl groups. However, as indicated above, experiment showed the reverse.



In connection with these hydrogenation reactions of unsaturated tetrahydropyridinols, the observations of Plisov and Bogatskii on the hydrogenation of crotonic and isocrotonic acids are not without interest: *cis*-isocrotonic acid is hydrogenated more rapidly than *trans*-crotonic acid[70].

The data reviewed above confirm that α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol has an equatorial hydroxy--group.

Spectroscopic Study of the Isomeric α- and β-1, 3-Dimethyl--4-phenylpiperidin-4-ol

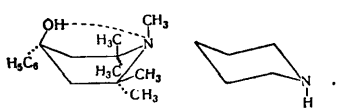
The only work which apparently contradicts the view put forward in this article on the structure of α- and β-prodine and hence of their analogues promedol and α-promedol, is that of Ziering *et al.*[49], who made a spectroscopic study of α- and β-1, 3-dimethyl-4-phenylpiperidin-4-ol (the piperidinols corresponding with α- and β-prodine) in the infra-red. The spectral characteristics in the region 3700–3510 cm^{-1} were used to estimate the degree of association of the alcohols. It was found that the α-isomer is more associated than the β-isomer. The data were interpreted by analogy with the results obtained by Smitt[71], who showed that

pentan-3-ol and 2-methylpentan-3-ol are associated to differing extents, the latter being considerably less associated than the former, and it was concluded that the presence of a methyl group adjacent the hydroxy-group limits the possible formation of an intermolecular hydrogen bond. Unfortunately, the orientation of the methyl radical relative to the hydroxy-group was not taken into account.

These considerations were used by Ziering *et al.* to determine the configurations of the α- and β-piperidinols from their degree of association. The more associated piperidinol, in their opinion, should have the 4-hydroxy- and 3-methyl groups in the relative positions which would preclude any screening effect by the methyl on the hydroxy--group, *i.e.* the *trans*-position. Assuming this α-1,3--dimethyl-4-phenylpiperidin-4-ol must contain an equatorial hydroxy-group and an axial phenyl radical. The β-isomer, which according to the results obtained is less associated, must have the reverse configuration at C_4. This contradicts numerous observations which have been made and are partially set out above.

It must be said that comparison of the abilities of aliphatic alcohols and cyclic amino-alcohols to associate (the comparison made by Ziering and coworkers) can only be relative. The association of aliphatic alcohols is due to the formation of intermolecular hydrogen bonds between the hydroxy-groups of different alcohol molecules, but with amino-alcohols the amino-nitrogen can also take part in hydrogen bonding. When considering cyclic amines, intramolecular association, *i.e.* the formation of an intramolecular bond between the hydroxy-group and the nitrogen of the piperidine ring, must also be taken into account. A necessary condition for this is for the hydroxy-group and the piperidine nitrogen to be in the *syn*-position. Intramolecular association is possible in the isomer of 1,3--dimethyl-4-phenylpiperidin-4-ol having an axial hydroxy--group. A second condition for this intramolecular association is the presence of the boat conformation. The ratio of the chair and boat conformations in piperidine derivatives is determined by the nature and position of the ring substituents. There has been a recent publication of data on the stereochemistry of 1,2,2,6,6-pentamethyl-4--phenylpiperidin-4-ol, which is an illustration of the case where the boat conformation of the piperidine ring is more stable than the chair conformation.

The chair form of 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol is less favoured because the molecule has three opposed axial substituents (the 2- and 6-methyl groups and the 4-hydroxy-group), and it may therefore be assumed that the conversion of the chair form to the boat form has a low energy barrier. 1,2,2,6,6-Pentamethyl--4-phenylpiperidin-4-ol is exceptionally stable towards esterification and dehydration reactions. Its chemical properties and spectroscopic data indicate that in the solid form and also in solution 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol exists to a considerable extent in the boat form, stabilised by intramolecular hydrogen bonding[72]. An example of the opposite case is piperidine, for which the main configuration is the chair form.



Between these two extremes lie a series of intermediate cases, in which each conformation exists to a greater or lesser extent.

Smissman and West studied intramolecular hydrogen bonding in a number of β- and γ-piperidinols by infra-red spectroscopy[73], and showed that with piperidin-3-ol and 1-methylpiperidin-3-ol the bonded and non-bonded forms are in equilibrium, since only conformations with an axial hydroxy-group form intramolecular hydrogen bonds.

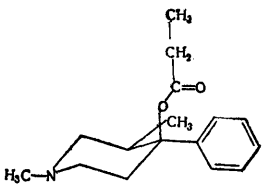
The spectrum of 1-methyl-3-phenylpiperidin-3-ol does not exhibit the frequency corresponding to a free hydroxy--group, since the preferred conformation has an axial hydroxy-group. In the case of 1-methylpiperidin-4-ol no intramolecular hydrogen bonding is observed, indicating that the hydroxy-group is equatorial.

Ziering and coworkers determined spectroscopically the total degree of association of the 1,3-dimethyl-4-phenylpiperidin-4-ol isomers; part of this is intramolecular association, but at the concentrations used (6.28% solution of piperidinol in chloroform) it is impossible to determine the intramolecular association by spectroscopic analysis, since this requires very low concentrations[74].

It may be assumed that of α- and β-1,3-dimethyl-4--phenylpiperidin-4-ol, the isomer which can form an intramolecular bond will be associated to a greater extent, *i.e.* the α-isomer, since this has an axial hydroxy-group.

X-Ray Structure Analysis of α-Prodine

A recent study dealing with the conformations of α- and β-prodine is that of Ahmed *et al.*[75], who studied single crystals of *dl*-α-prodine hydrochloride and hydrobromide by X-ray crystallography. They showed that the 3-methyl and 4-phenyl radicals are in the *trans*-position, and that the phenyl radical is equatorial and the propionoxy-group axial. The piperidine ring is in the chair form:



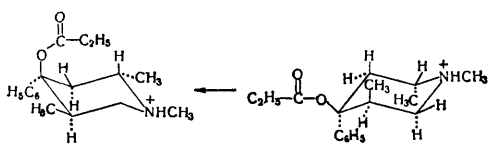
The X-ray structure data are a convincing proof that the conformations of α- and β-prodine and promedol and α-promedol determined from their chemical conversions are correct.

Anomalies in the Melting Points of Promenol and α-Promedol

Promedol (γ-1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine hydrochloride) is produced in quantitative yield by treating the piperidinol with propionyl chloride in benzene, preferably in molar ratio 1:2.5.[76] Usually one recrystallisation of the technical product from a mixture of acetone and alcohol gives crystals with a distinct melting point at 198°–199°. However, on further heating the melt solidifies and begins to melt again above 215° (usually at 217°–219°). If the product of m.p. 198°–199° is subjected to further crystallisations (heating in acetone or alcohol), promedol of m.p. 221°–222° is obtained. Analytically the samples melting at 198°–199° and 221°–222° are identical, both being 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine

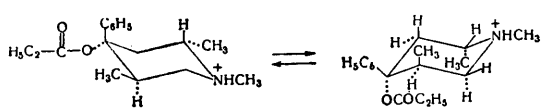
hydrochloride; on hydrolysis they yield γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol, and, what is particularly important, they all have identical analgesic activity and toxicity.

The reason for the anomaly in the melting point of promedol may be that in addition to the main conformation, with equatorial phenyl and methyl groups, there exists a considerably less stable conformer in which these groups are axial; on heating, this isomer is converted into the more stable form with equatorial phenyl and methyl radicals.



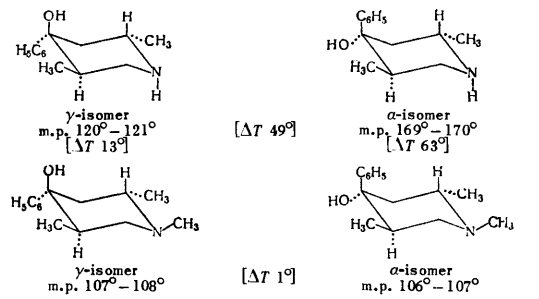
There is a particularly clear anomaly in the melting point of α-1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, *i.e.* α-promedol. Up to the present α-promedol has not been characterised by an accurate melting point. Samples prepared by the esterification of α-1,2,5-trimethyl-4-phenylpiperidin-4-ol with propionyl chloride in benzene usually have a low (in comparison with promedol) and diffuse melting point (98°–102°, 102°–106°, 104°–106°, 108°–112°, 132°–140°, 153°–154°). Unlike promedol, α-promedol is soluble in benzene and toluene; recrystallisation from benzene has given a sample of α-promedol melting at 153°–154°, but after being kept molten for some time, it later melted at 116°–123°.

As with promedol, the various samples of α-promedol are analytically identical, and on hydrolysis they all give α-1,2,5-trimethyl-4-phenylpiperidin-4-ol; they are all equivalent in analgesic activity and toxicity. In the same way as with promedol, with α-promedol there apparently exists, in addition to the conformation with equatorial methyl groups and an axial phenyl group, the inverse conformer with axial methyl groups and an equatorial phenyl radical. This conformation apparently exists to a greater extent in α-promedol than in promedol, and there is a state of dynamic equilibrium, which is not found with promedol. The large size of the phenyl radical in the axial position and its 1,3-interaction with the hydrogens at C_2 and C_6 favour the formation of the inverse conformer having an equatorial phenyl radical:



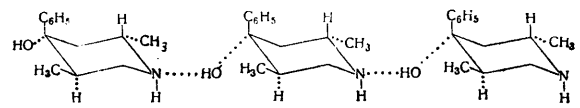
Structure and Melting Points of the Isomeric α- and γ-1,2,5-Trimethyl-4-phenylpiperidin-4-ol and 2,5-Dimethyl-4-phenylpiperidin-4-ol

α- and γ-1,2,5-Trimethyl-4-phenylpiperidin-4-ol have very close melting points (α-isomer, m.p. 106°–107°, γ-isomer, m.p. 107°–108°), but α- and γ-2,5-dimethyl-4-phenylpiperidin-4-ol melt at very different temperatures (α-isomer, m.p. 169°–170°, γ-isomer, m.p. 119°–121°), and there are also large differences in the melting points of the 2,5-dimethyl-4-*p*-tolylpiperidin-4-ol and 2,5-dimethyl-4-benzylpiperidin-4-ol isomers.



On passing from the piperidinols with a secondary amino-group to those with a tertiary nitrogen atom, there is a fairly large change in melting point in the α-series and a comparatively small change in the γ-series.

The higher melting point of α-2,5-dimethyl-4-phenyl piperidin-4-ol (and also of the analogous piperidinols of the α-series) in comparison with the γ-isomer may be due to this conformation, with an equatorial hydroxy-group and an unscreened piperidine nitrogen (the hydrogen on the nitrogen being axial), favouring intermolecular association, which is considerably more in evidence in the α-isomer than in the γ-isomer.



The steric configuration of the γ-isomer, with an axial hydroxy-group, hinders intermolecular association, and intramolecular association is evidently present only to a slight extent. This causes the large difference in melting point between these isomeric alcohols.

Intermolecular association due to hydrogen bonding between the hydroxy-group of one piperidinol molecule and the piperidine nitrogen of another is greatly weakened if the hydrogen on the nitrogen is replaced by an alkyl radical, and hence, there is a large change in melting point on passing from α-2,5-dimethyl-4-phenylpiperidin-4-ol to α-1,2,5-trimethyl-4-phenylpiperidin-4-ol. This is not observed in the analogous conversions in the γ-series.

From what has been said above, we may consider the question of the steric configuration of the efficient analgesics promedol and α-promedol to be solved. The task now is to obtain stereochemical analogues of α-promedol and β-prodine, which should prove to be highly effective analgesics.

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