SYNTHESIS AND CONFIGURATION OF DIASTEREOMERIC 1-(β-DIMETHYLAMINOETHYL)-2,5-DIMETHYL-4-PIPERIDOLS

E. S. Nikitskaya, E. I. Levkoeva,
T. F. Vlasova, Yu. N. Sheinker,
and L. N. Yakhontov

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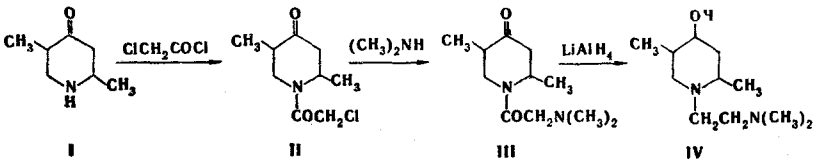
Diastereomeric 1-(β-dimethylaminoethyl)-2,5-dimethyl-4-piperidols were synthesized and their configurations were studied. The spatial orientation of the substituents in the α, β, and γ isomers of 2,5-dimethyl-4-piperidol was established, and the stereochemistry of the reduction of 2,5-dimethyl-4-piperidone with sodium in alcohol, with lithium aluminum hydride, and by catalysis on Raney nickel was studied by PMR spectroscopy. A series of transformations at the nitrogen atom of the piperidine ring do not change the configuration of 2,5-dimethyl-4-piperidols, but the stereochemistry of the reduction of the keto group in 2,5-dimethyl-4-piperidones with lithium aluminum hydride depends markedly on the character of the substituent attached to the piperidine nitrogen.

In order to study the pharmacological activity of substituted dialkylaminoalkylaminoalkanols in which the aminoalkanol portion is fixed as a cyclic residue, we synthesized a previously undescribed class of compounds – 1-dialkylaminoalkyl-2,5-dimethyl-4-piperidols. 2,5-Dimethyl-4-piperidone (I) was used as the starting compound. The synthesis led to a mixture of diastereomeric piperidols with three asymmetric centers. We studied the stereochemistry of the processes in greater detail in the case of 1-(β-dimethylaminoethyl)-2,5-dimethyl-4-piperidol (IV), and this paper is devoted to the synthesis and establishment of the configurations of the diastereomers of IV.*



2,5-Dimethyl-4-piperidone (I) was acylated with chloroacetyl chloride in the presence of triethylamine, and the resulting 1-chloroacetyl-2,5-dimethyl-4-piperidone (II), without isolation in pure form, was converted to 1-dimethylaminoacetyl-2,5-dimethyl-4-piperidone (III), the yield of which was 60% in two steps. As in the case of 2,5-dimethyl-4-piperidone [1] or its 1-substituted derivatives [2], the mixture of diastereomeric III cannot be separated. Reduction of the keto and amide groups simultaneously with lithium aluminum hydride gave IV in 64% yield as a mixture of close-boiling diastereomeric compounds. It was necessary to have individual diastereomeric compounds for the analysis of the composition of this mixture by PMR spectroscopy and for the establishment of their configurations. In connection with the fact that the separation of IV into stereo isomers seemed quite complicated to us, the synthesis of the latter was accomplished from the individual diastereomers of 2,5-dimethyl-4-piperidols by acylation of them with chloroacetyl chloride and subsequent treatment with dimethylamine and reduction of the amide function with lithium aluminum hydride.

*The synthesis of other representatives of this class of substances and their esters and the pharmacological properties of all of the compounds will be described separately.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow.
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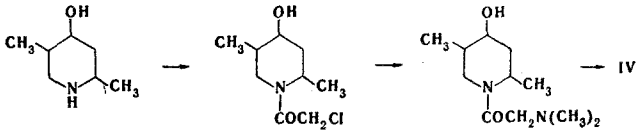

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We used the method in [1] to obtain the three individual diastereomers (α, β, and γ). The use of PMR spectroscopy enabled us to determine the configurations of all three isomers and to make a more detailed investigation of the stereochemistry of the various processes involved in the reduction of the keto group in I.

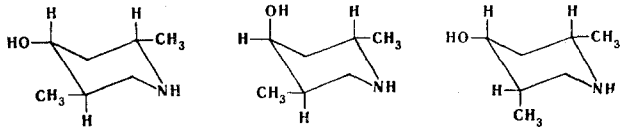
According to the PMR spectrum, piperidone I is a configurationally individual compound. Two doublets of the 6-CH_3 and 3-CH_3 methyl groups are observed at δ 0.97 and 1.20 ppm, respectively, in the spectrum of a solution in $CDCl_3$. The signal of an axial 2-H proton (2.10 ppm, $J_{2a2e} = 13.5$ Hz, $J_{2a3a} = 13.0$ Hz) indicates an equatorial orientation of the 3-CH_3 group. This is also confirmed by the multiplicity of the 3-H signal (2.97 ppm, $J_{3a2a} = 13.0$ Hz, $J_{3a2e} = 3.7$ Hz, $J_{3a,CH_3} = 6.5$ Hz). The signals of the axial and, respectively, equatorial 5-H protons are situated at 3.36 and 2.57 ppm. It follows from the structure of these signals that J_{5a5e} has a value on the order of 16 Hz, while $J_{5a6} \approx 10$ Hz; this corresponds to an equatorial orientation of the methyl group in the 6 position. Thus both methyl groups are equatorial in starting piperidone I. This is in agreement with the reported indication [1] regarding the preparation of only one – apparently the trans form – form of 2,5-dimethyl-4-piperidone.

In examining the PMR spectrum of the α isomer of V, the values $J_{3a3e} \approx J_{3a2a} \approx J_{3a4a} \approx 11.5$ Hz of the signal of the axial 3-H proton (1.32 ppm) make it possible to conclude that the substituents in the 2 and 4 positions of the piperidine ring are equatorial. The triplet at 2.26 ppm with $J_{6a6e} \approx J_{6a5a} \approx 11.6$ Hz is affiliated, according to the magnitude of the shift and the character of the splitting, with the axial 6-H proton and attests to an equatorial orientation of the 5-CH_3 group. The data presented on the spatial orientation of the substituents in the α isomer of V are also confirmed by the multiplicity of the low-field signal itself in the spectra (3.30 ppm) – the 4-H signal with $J_{4a3a} \approx J_{4a5a} \approx 10.0$ Hz, $J_{4a3e} = 4.5$ Hz.

The weakest-field multiplet (3.95 ppm), which is affiliated with the 4-H proton, in the PMR spectrum of the β isomer of V has a width of 9.0 Hz; this corresponds to an equatorial orientation of this proton and, correspondingly, to an axial orientation of the 4-OH group. In accordance with the character of the splitting of the 3-H axial proton (1.32 ppm, $J_{3a3e} \approx J_{3a2a} \approx 11.6$ Hz, $J_{3a4e} = 2.7$ Hz), the methyl group in the 2 position is equatorially oriented, while the triplet at 3.00 ppm with $J_{6a6e} \approx J_{6a5a} \approx 11.0$ Hz of the 6-H_a proton proves the equatorial orientation of the methyl group in the 5 position.

The equatorial orientation of the substituents attached to C_2 and C_4 for the γ isomer of V in the PMR spectrum follows from the values $J_{3a3e} \approx J_{3a2a} \approx J_{3a4a} \approx 11.5$ Hz (1.40 ppm) of 3-H_a. The 4-H multiplet at 3.94 ppm with $J_{4a3a} = 11.5$ Hz and $J_{4a3e} \approx J_{4a5e} \approx 5.0$ Hz makes it possible to establish that the 5-CH_3 group is axial and that the hydroxyl group is equatorial.

Thus it follows from the PMR spectral data that the α isomer of V is a compound with equatorial orientation of all of the substituents, the methyl groups in the β isomer of V are equatorial and the hydroxyl group is axial, and the methyl group in the 5 position of the γ isomer of V is axial and the hydroxyl group and the methyl group in the 2 position are equatorial.



α-isomer β-isomer γ-isomer

The use of PMR spectroscopy also made it possible to perform a quantitative analysis of the α, β, and γ isomers directly in the reaction mixtures after reduction of I by various methods and thereby to evaluate the stereochemistry of the processes involved in reduction of the keto group more accurately than was previously done [1] on the basis of preparative separation of the diastereomers. Thus, for example, in the reduction of I with sodium in absolute ethanol by the method in [1] we obtained (in 95% yield) a product that, according to PMR spectroscopy, proved to be the pure α isomer of V, while the isolation (in 56% yield) of the α isomer is described in [1] and the presence of about 8% of the γ isomer in the mother liquor was indicated.

In the reduction of I in alcohol on a nickel catalyst by the method in [1] we isolated (preparatively) the γ isomer in the same yield (21%) as described in the literature, but analysis of the mixture of products by PMR spectroscopy showed the presence of approximately equal amounts of the α, β, and γ isomers of V; the isolation of the benzoate of the γ isomer in 50% yield was previously described in [1], but the percentage of α isomer in the reaction products was not indicated.

The formation of the α and γ isomers of V in a ratio of about 3 : 1 in the reduction of I with lithium aluminum hydride in benzene–ether was shown by PMR spectroscopy.

An analysis by PMR spectroscopy of the α and β isomers of IV, synthesized from the individual α and β isomers of V by introduction of substituents into the 1 position without involvement of the asymmetric centers showed that the individual α and β isomers of IV are actually obtained as a result of the reactions. The quartet in the spectrum of the α isomer of IV, which is affiliated with the 3-H_a proton at 1.50 ppm with $J_{3a3e} \approx J_{3a2a} \approx J_{3a4a} \approx 12$ Hz, proves the equatorial orientation of the hydroxyl group and the methyl group attached to C_2, while the 4-H multiplet at 3.20 ppm confirms the axial orientation of 4-H and determines the equatorial position of the 5-CH_3 group. The 3-H_a signal in the spectrum of the β isomer of IV is a multiplet with $J_{3a3e} \approx J_{3a2a} \approx 10.5$ Hz and $J_{3a4e} = 3.5$ Hz, while the 4-H signal is observed at 3.85 ppm and has a width of no more than 9 Hz; this corresponds to an axial orientation of the hydroxyl group. Thus, as in the case of the α isomer of V, all of the substituents in the α isomer of IV are equatorial, while in the case of the β isomer of IV, as in the case of the β isomer of V, the hydroxyl group is axial and both methyl groups are equatorial, i.e., the configuration of the substituents does not change during the reactions under consideration.

Analysis by PMR spectroscopy of the mixture of diastereomeric IV obtained by reduction of keto amide III with lithium aluminum hydride showed that the spectral interval 1.6-2.8 ppm is extremely difficult to interpret because of the superimposition of a large number of signals, but there are three groups of signals in the weak-field region at 3.1, 3.6, and 3.9 ppm, which can be assigned, respectively, to the 4-H protons of the α, γ, and β isomers. Two doublets at 0.90 and 1.21 ppm, which are affiliated with the third (γ) isomer, are observed in the region of methyl groups in addition to signals of the α and β forms at 0.98-1.15 ppm. The ratio of the intensities of the signals of the methyl groups makes it possible to establish the ($\alpha + \beta$ isomer) to γ isomer ratio as 7 : 3. Thus, when there is predominant formation of alcohols with an equatorial hydroxyl group in the reduction of 4-piperidones with lithium aluminum hydride [2], the ratios and even the quantity of isomers obtained apparently depend to a considerable degree on the character of the substituents attached to the piperidine nitrogen.

EXPERIMENTAL

The PMR spectra of pyridine solutions were obtained with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

1-Dimethylaminoacetyl-2,5-dimethyl-4-piperidone (III). A solution of 5 g (44 mmole) of chloroacetyl chloride in 5 ml of anhydrous benzene was added dropwise to an ice-cooled solution of 5 g (39 mmole) of 2,5-dimethyl-4-piperidone and 4.46 g (44 mmole) of triethylamine in 45 ml of anhydrous benzene. At the end of the addition the mixture was stirred in an ice bath for 30 min and at room temperature for 2 h. The precipitated triethylamine hydrochloride was removed by filtration and washed with benzene. The benzene filtrates were combined, washed with 20% potassium carbonate solution, and dried. The solvent was removed by distillation to give 5.85 g (74%) of 1-chloroacetyl-2,5-dimethyl-4-piperidone (II). Without purification, it was dissolved in 15 ml of 20% alcoholic dimethylamine, and the solution was refluxed for 5 h. The alcohol was removed by distillation, and the residue was treated with an excess amount of 50% potassium carbonate solution and extracted with ether. The extract was dried, and the ether was removed by distillation to give 5.05 g (60%, based on 2,5-dimethyl-4-piperidone) of III as a viscous colorless liquid with bp 130-131° (3 mm). Found,%: C 62.3; H 9.5; N 13.1. $C_{11}H_{20}N_2O_2$. Calculated,%: C 62.2; H 9.5; N 13.2.

1-Dimethylaminoethyl-2,5-dimethyl-4-piperidol (IV). A 4.8-g (22 mmole) sample of III was reduced with 1.72 g (45 mmole) of lithium aluminum hydride in ether–benzene to give 2.9 g (64%) of IV as a viscous colorless liquid with bp 106-107° (2 mm). Found,%: C 65.7; H 12.0; N 14.2. $C_{11}H_{24}N_2O$. Calculated,%: C 66.0; H 12.1; N 14.0.

Reduction of 2,5-Dimethyl-4-piperidone (I) with Sodium in Alcohol. A 35-g (1.52 g-atom) sample of sodium was added in pieces with stirring to a solution of 12.7 g (0.1 mole) of I in 350 ml of absolute ethanol.

At the end of the addition, the mixture was warmed until all of the sodium had dissolved. At the end of the reaction, the mixture was cooled and 100 ml of water was added. The mixture was acidified to pH 2 with hydrochloric acid, and the precipitated sodium chloride was removed by filtration. The mother liquor was vacuum evaporated to a small volume, and excess sodium hydroxide was added. The mixture was extracted with ether, and the extract was dried. The solvent was removed by distillation to give 12.3 g (95%) of a colorless crystalline substance with mp 97-98°, which, according to the PMR spectrum, was the α isomer of 2,5-dimethyl-4-piperidol (V).

Reduction of 2,5-Dimethyl-4-piperidone (I) with Hydrogen in the Presence of a Raney-Nickel Catalyst. A 0.5-ml sample of 20% sodium hydroxide solution and 1.5 g of Raney nickel were added to 10 g (79 mmole) of I in 50 ml of absolute alcohol, and the compound was hydrogenated at room temperature and a pressure of 20-30 cm (water column) until hydrogen absorption had ceased (about 2000 ml). The reaction was complete in 30 h. The catalyst was removed by filtration, and the solution was vacuum evaporated. The residue was dissolved in benzene, and the solution was dried with anhydrous potassium carbonate. The benzene was evaporated to give 9.76 g (96%) of oily crystals which, according to PMR spectroscopy, were a mixture of approximately equal amounts of the α, β, and γ isomers of V. Treatment of the mixture of isomers with anhydrous ether precipitated a colorless crystalline substance with mp 126°, which melted at 142° after recrystallization from ethyl acetate. The yield was 2.05 g (21%). According to PMR spectroscopy, the substance is the β isomer of 2,5-dimethyl-4-piperidol (V).

Reduction of 2,5-Dimethyl-4-piperidone (I) with Lithium Aluminum Hydride. A solution of 5 g (40 mmole) of I in 30 ml of anhydrous benzene was added to a suspension of 3 g (80 mmole) of lithium aluminum hydride in 30 ml of ether, and the mixture was stirred and refluxed for 1.5 h. It was then cooled with ice, and 6 ml of water was added. The base was extracted with benzene, and the benzene was removed by vacuum distillation to give 3.45 g (69%) of a colorless crystalline substance with mp 84°; the product, according to PMR spectroscopy, was a mixture of the α and γ isomers of V in a ratio of 3:1.

1-Dimethylaminoacetyl-2,5-dimethyl-4-piperidol (α Isomer). A solution of 3.85 g (34 mmole) of chloroacetyl chloride in 5 ml of benzene was added dropwise with stirring to an ice-cooled solution of 4 g (31 mmole) of the α isomer of 2,5-dimethyl-4-piperidol and 3.45 g (34 mmole) of triethylamine in a mixture of 40 ml of anhydrous benzene and 20 ml of dry dioxane. The mixture was worked up as in the preparation of III to give 2.0 g (30%) of a viscous colorless liquid with bp 149-150° (2 mm). Found,%: C 61.9; H 10.2; N 13.6. $C_{11}H_{22}N_2O_2$. Calculated,%: C 61.6; H 10.4; N 13.7.

1-(Dimethylaminoacetyl-2,5-dimethyl-4-piperidol (β Isomer). This isomer was similarly obtained from the β isomer of 2,5-dimethyl-4-piperidol in 30% yield as a viscous colorless liquid with bp 170-172° (3 mm). Found,%: C 61.8; H 10.2; N 13.8. $C_{11}H_{22}N_2O_2$. Calculated,%: C 61.6; H 10.4; N 13.7.

1-(β-Dimethylaminoethyl)-2,5-dimethyl-4-piperidol (α Isomer of IV). A 2-g (9.3 mmole) sample of the α isomer of 1-dimethylaminoacetyl-2,5-dimethyl-4-piperidol was reduced with 1.42 g (37 mmole) of lithium aluminum hydride in ether–benzene to give 1.05 g (57%) of a viscous colorless liquid with bp 109-111° (4 mm). Found,%: C 65.7; H 12.1; N 14.2. $C_{11}H_{24}N_2O$. Calculated,%: C 66.0; H 12.1; N 14.0.

1-(β-Dimethylaminoethyl)-2,5-dimethyl-4-piperidol (β Isomer of IV). This isomer was similarly obtained in 63% yield from the β isomer of 1-dimethylaminoacetyl-2,5-dimethyl-4-piperidol as a viscous colorless liquid with bp 105-108° (2 mm). Found,%: C 66.0; H 12.3; N 13.7. $C_{11}H_{24}N_2O$. Calculated,%: C 66.0; H 12.1; N 14.0.

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