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


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.

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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-CH₃ and 3-CH₃ methyl groups are observed at δ 0.97 and 1.20 ppm, respectively, in the spectrum of a solution in CDCl₃. The signal of an axial 2-H proton (2.10 ppm, J₂a₂e = 13.5 Hz, J₂a₆a = 13.0 Hz) indicates an equatorial orientation of the 3-CH₃ group. This is also confirmed by the multiplicity of the 3-H signal (2.97 ppm, J₃a₂a = 13.0 Hz, J₃a₆a = 3.7 Hz, J₃a₆CH₃ = 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 J₅a₃e has a value on the order of 16 Hz, while J₅a₆ ≈ 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 J₃a₃e ≈ J₃a₂a ≈ J₃a₆a ≈ 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 J₆a₆e ≈ J₆a₃a ≈ 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-CH₃ 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 J₄a₃a ≈ J₄a₅a ≈ 10.0 Hz, J₄a₆e = 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, J₃a₃e ≈ J₃a₂a ≈ 11.6 Hz, J₃a₆a = 2.7 Hz), the methyl group in the 2 position is equatorially oriented, while the triplet at 3.00 ppm with J₆a₆e ≈ J₆a₃a ≈ 11.0 Hz of the 6-Ha proton proves the equatorial orientation of the methyl group in the 5 position.

The equatorial orientation of the substituents attached to C₂ and C₄ for the γ isomer of V in the PMR spectrum follows from the values J₃a₃e ≈ J₃a₂a ≈ J₃a₆a ≈ 11.5 Hz (1.40 ppm) of 3-H₂a. The 4-H multiplet at 3.84 ppm with J₄a₃a = 11.5 Hz and J₄a₆e ≈ J₄a₃e = 5.0 Hz makes it possible to establish that the 5-CH₃ 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.

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 was indicated in [1] and the presence of about 8% of the γ isomer in the mother liquor was indicated.