STEREOCHEMISTRY OF HETEROCYCLIC COMPOUNDS

COMMUNICATION 2. GEOMETRIC ISOMERS OF 1-CYCLOHEXYL-
AND 1-PHENYL-2,5-DIMETHYL-4-PHENYLPIPERIDOLS-4

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In previous work on the synthesis of 2,5-dimethylpiperidone-4 derivatives, it was shown that by condensation of propenyl isopropenyl ketone with cyclohexylamine and aniline it is possible to isolate pure hydrochlorides of 1-cyclohexyl and 1-phenyl-2,5-dimethyl piperidones-4, respectively [1, 2]. In view of the method by which they were prepared and isolated, these isomers apparently should have the methyl groups in the energetically more favorable trans-diequatorial position. The corresponding bases were obtained by careful liberation from the hydrochlorides and on treatment with phenyllithium each of them gave only one pure isomer of 1-cyclohexyl- and 1-phenyl-2,5-dimethyl-4-phenylpiperidol-4, respectively [3, 4]. In this stereoselective synthesis with phenyllithium, these N-substituted piperidones differ from 1,2,5-trimethylpiperidones-4 studied previously [5].

\[ \text{R} \cdot \text{HCl} \quad \text{R} \]

where \( \text{R} = \text{C}_6\text{H}_{11} \) or \( \text{C}_6\text{H}_{5} \)

A more detailed study of the pure crystalline 1-cyclohexyl-2,5-dimethylpiperidone-4 (m. p. 72-73\(^\circ\)) made it possible to confirm its trans-configuration and to prepare the second isomer of this piperidone, which apparently had methyl groups in the cis-position. It was found that analogous to the conversion observed previously for 1,2,5-trimethylpiperidone, heating the crystalline trans-piperidone (I) with alumina at 100\(^\circ\) formed an equilibrium mixture of the two geometric isomers (I) and (II), from which the starting trans-isomer separated on cooling. The remaining liquid isomerization product was the second isomer (II) in an almost pure state and in accordance with its configuration, by treatment with hydrogen chloride it was converted practically quantitatively into the hydrochloride of the more stable trans-isomer (I). Heating this cis-piperidone (II) with alumina again led to an equilibrium mixture of the two geometric isomers, from which crystalline 1-cyclohexyltrans-2,5-dimethylpiperidone-4 (I) was readily isolated on cooling.

As has already been mentioned above, the reaction of the crystalline trans-piperidone (I) with phenyllithium proceeded stereospecifically and gave only one geometrical isomer of 1-cyclohexyl-trans-2,5-dimethyl-4-phenylpiperidol-4 (III). In accordance with general conformational rules, the phenyl group in the product formed should occupy the more energetically favored equatorial position; as a result of this and with the axial hydroxyl, in this isomer there could have been favorable steric conditions for trans-diaxial elimination. In actual fact, the isomer (III) was found to undergo dehydration and treatment with thionyl chloride at room temperature with subsequent hydrolysis gave a good yield of an unsaturated product with m. p. 98-100\(^\circ\) (apparently IV), whose structure, however, was not studied in more detail.
The reaction of phenyllithium with the isomeric cis-piperidone (II) also proceeded stereospecifically. In this case we obtained a good yield of only one isomer of 1-cyclohexyl-2,5-dimethyl-4-phenylpiperidol-4 (V), which at the same time confirmed that the starting liquid 1-cyclohexyl-cis-2,5-dimethylpiperidone-4 (II) was quite pure.

As was pointed out previously [5], in the case of isomeric phenylpiperidols with the methyl groups in the cis-position, the demonstration of the configuration may not be based solely on elimination or esterification reactions. However, certain experimental facts give us grounds for considering that the isomeric phenylpiperidol (V) obtained from the cis-piperidone (II) has the configuration with the phenyl and methyl groups in the cis-position. Thus, it was found that the phenylpiperidol (V) was dehydrated with comparative difficulty and treatment of the dehydration product with hydrogen bromide with subsequent hydrolysis gave a new isomeric 4-phenylpiperidol (VI), which differed from the other two. The cis-position of the methyl groups was apparently retained in the third isomer as it was shown previously that such elimination and hydration reactions lead predominantly to epimerization at C₄ as a result of the axial phenyl group moving into the energetically more favorable equatorial position.

If this is actually so, as a result of cis-addition of hydrogen, which could occur from both sides of the molecule, the catalytic hydrogenation of 1-cyclohexyl-2,5-dimethyl-4-phenyl-Δ⁵-dehydropiperidol-4 (VII) should lead to a mixture of geometric isomers (III) and (V).

The procedure described previously [6] was used to prepare the unsaturated phenylpiperidol (VII) from 1-cyclohexyl-trans-2,5-dimethylpiperidone-4 (I), but unfortunately we were unable to isolate it in a pure state. Bromination of the trans-piperidone (I) with dehydrobromination and subsequent treatment with phenyllithium yielded an uncrystallizable mixture of products; however, after catalytic hydrogenation of this mixture it was possible to isolate small amounts of only the isomeric phenylpiperidones (III) and (V), which may serve as definite confirmation of the accuracy of the configurations proposed for them.

During a study of the stability of 1-phenyl-2,5-dimethylpiperidone-4, which was isolated previously [2], it was found that it also gave an equilibrium mixture of isomers when heated with alumina. However, in this case both possible isomeric trans- and cis-piperidones (VIII) and (IX) were found to be liquid and could not be isolated in pure states.