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2,6-Dialkylpiperazines. III. (1) NMR Spectra of the Geometrical Isomers of 4-Phenyl-2,6-dimethylpiperazine

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The *cis* and *trans* configurations of the two geometrical isomers of 4-phenyl-2,6-dimethylpiperazine are assigned by NMR spectroscopy.

In the previous paper (1) the synthesis of 4-phenyl-2,6-dimethyl-3-ketopiperazine, whose NMR spectrum showed that the product was a mixture of the geometrical *cis* and *trans* isomers, was described. Also 4-phenyl-2,6-dimethylpiperazine, obtained by reduction with lithium aluminum hydride, was a mixture of two isomers, which were then isolated in the pure state. In the present paper the *cis* and *trans* configurations are assigned by NMR studies to the two isomers of 4-phenyl-2,6-dimethylpiperazine, indicated as I and II. The chart contains the most reasonable conformations (2a,3) for the two isomers of 4-phenyl-2,6-dimethylpiperazine, based upon comparison with the cyclohexane series (4,5). The *trans* isomer was obtained as a racemate and no attempt was made to resolve it.

The NMR analysis is based on the assumption that the *trans* isomer may exist in two chair forms "ea" and "ae" of equal energy, which, at room temperature, are interconverting at such a rate that the NMR signals are averaged. Upon cooling, the interconversion rate decreases and if the conformational "freezing" is obtained, separate NMR signals will be observed, corresponding to the conformationally fixed species. The *cis* isomer is expected to exist only in the "ee" conformation, because the diaxial conformation is to be considered much less stable (2b). This rigid isomer, containing several differently situated ring-hydrogen atoms in the fixed conformation, will show a more complex spectrum than the *trans* isomer, in which the NMR signals are averaged. Moreover, the NMR spectrum of the *cis* isomer will not change by lowering the temperature. Similar investigations have been reported for various compounds (6), among them dimethylcyclohexanes (7), cyclohexanediols (8), cyclohexyl halides (9,10) and *NN'*-dimethylpiperazine (5). As far as the nitrogen inversion in the piperazine ring is concerned, it has been assumed (4,5) that the inversion frequency in a six-membered ring is of the same order of that in ammonia and therefore will not interfere with the studies in question (11).

The NMR spectra at room temperature of the isomers I and II of 4-phenyl-2,6-dimethylpiperazine are reported in Figures 1 and 2. The absorptions due to the ring-hydrogen atoms in the spectrum of isomer I are more complex than those of isomer II and consequently the *cis* configuration is the more probable for the isomer I and the *trans* configuration for the isomer II. The NMR spectra of the two isomers have been examined also at lower temperatures and are reported in Figures 3 and 4. The NMR spectrum of I does not change in the temperature range 25° to -75°C, whereas the spectrum of II undergoes significant changes in this temperature region. Consequently, in agreement with the results at room temperature, the *cis* configuration with the diequatorial orientation of the methyl groups is assigned to the isomer I and the *trans* configuration with the equatorial-axial orientation of the methyl groups to the isomer II. It is noteworthy that the temperature reached (-75°C) has not been sufficiently low to permit a complete resolution of the two conformers of the *trans* isomer but only a broadening of the methyl resonances was observed. The broadening of the signal is due to the overlapping of the axial and equatorial methyl doublets, possessing a different chemical shift.

In a previous paper (12) the synthesis of 4-benzyl-2,6-dimethyl-3,5-diketopiperazine, obtained as the *cis* form only, was described. That assignment, based on the greater stability of the diequatorial *cis* isomer, is now confirmed by comparing the NMR spectrum at room temperature of *cis*-4-phenyl-2,6-dimethylpiperazine with that of *cis*-4-benzyl-2,6-dimethylpiperazine, obtained by reduction of the mentioned diketone.

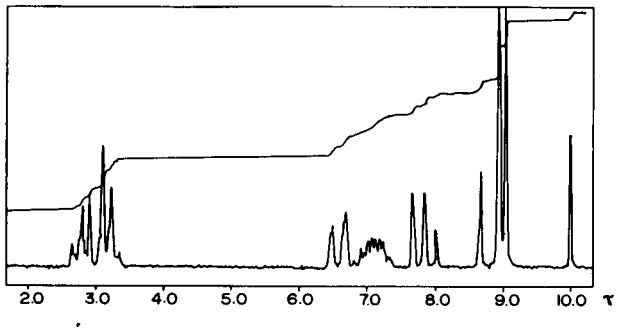
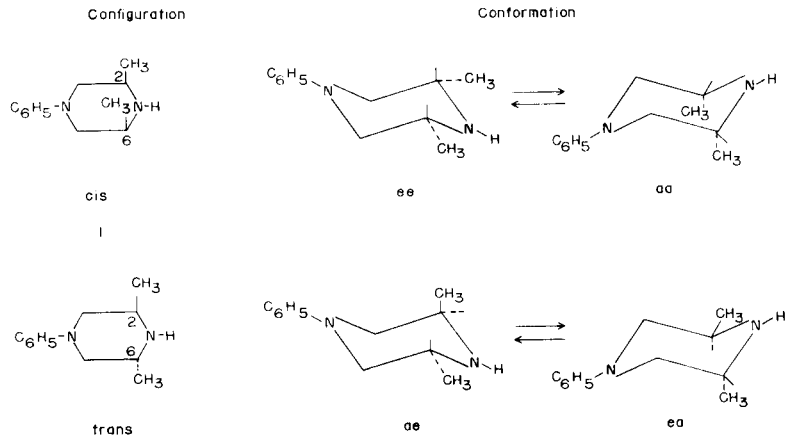


Fig. 1. NMR spectrum of the isomer I of 4-phenyl-2,6-dimethylpiperazine.



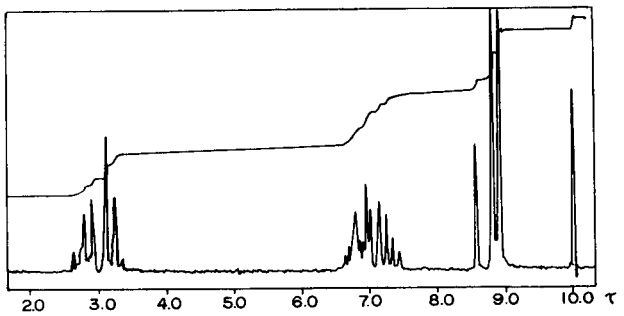


Fig. 2. NMR spectrum of the isomer II of 4-phenyl-2,6-dimethylpiperazine.

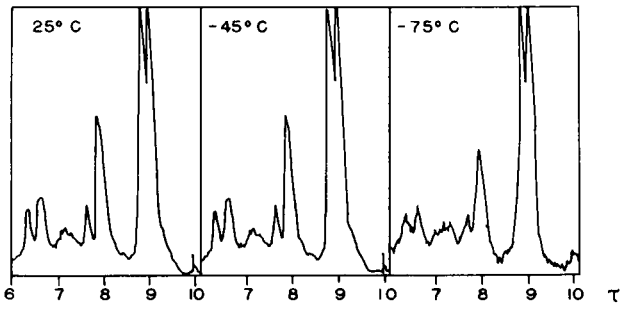


Fig. 3. NMR spectrum of the isomer I of 4-phenyl-2,6-dimethylpiperazine as a function of temperature.

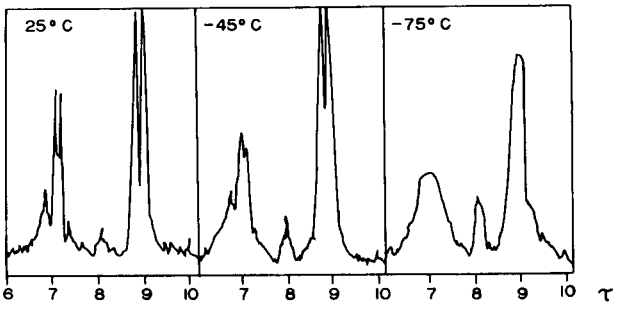


Fig. 4. NMR spectrum of the isomer II of 4-phenyl-2,6-dimethylpiperazine as a function of temperature.

EXPERIMENTAL

The spectra reported in Figures 1 and 2 were obtained with a Varian A-60 spectrometer (60 Mc/sec) in deuterochloroform, using TMS as internal reference (τ = 10 ppm). The spectra reported in Figures 3 and 4 were obtained with a Varian 4310-C spectrometer (40 Mc/sec) in hexadeuteroacetone, TMS as internal reference, by courtesy of Dr. A. Segre of the "Istituto di Chimica Industriale del Politecnico di Milano", to whom we are indebted.

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