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THE STEREOCHEMISTRY OF N-METHYL-3-(*P*-FLUORO-BENZOYL)-4-HYDROXY-4-(*P*-FLUOROPHENYL)PIPERIDINE[1]

M. D. Draper, F. J. Petracek, M. W. Klohs
Chemical Research Department, Riker Laboratories, Inc.
Northridge, California 91324, U. S. A.

Richard G. Parker and John D. Roberts[2]
Gates and Crellin Laboratories of Chemistry
California Institute of Technology
Pasadena, California 91109, U. S. A.

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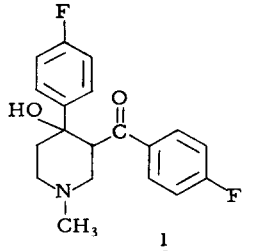
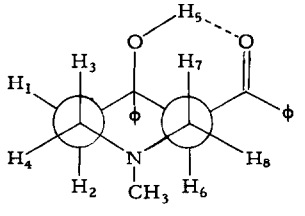
A rigorous assignment of the stereochemistry of substituted piperidines of the type 1 has not been reported. However, a paper by Unkovskii, et al.,[3] reporting infrared spectral studies of intramolecular hydrogen bonding in closely similar systems suggests that the bulky benzoyl and phenyl groups would be most energetically favored disposed in the trans-diequatorial configuration of the piperidine ring (chair form, 2). This evidence is, however, equivocal because such bonding is also possible in other conformations.



1

Because of current interest in N-methyl-3-(*p*-fluorobenzoyl)-4-hydroxy-4-(*p*-fluorophenyl)-piperidine as a potential antiinflammatory agent,[4] an unambiguous assignment of the stereochemistry was required to undertake a more sophisticated examination of the relationship between its structure and activity. This analysis was carried out with the aid of nmr spectra data at 60 and 220 MHz and an X-ray diffraction study. The method of synthesis of 1 has been reported elsewhere.[5] The 60-MHz spectrum of the free base (Figure 1A) permitted only the assignment of δ values for the N-CH_3, OH (H_5), and H_6 protons (partial Newman projection formula 2).



2

Deuterium exchange carried out in $CDCl_3$ with small amounts of D_2O enabled assignment of a doublet at 305 Hz to the H_5 proton. Dilution experiments showed only a very small (2 Hz) diamagnetic shift on extrapolation of the concentration versus H_5 frequency curve to infinite dilution, indicative of intramolecular hydrogen bonding. Also, the hydroxyl proton was shown to be coupled by 2.5 cps to some other proton, a point of special interest because this is a rather large value[6] for a long-range coupling to any of its neighboring ring protons. The N-CH_3 and H_6 signals were clearly identifiable by chemical shift and integration as a strong singlet at 144 Hz and a quartet at 258 Hz respectively. The remaining piperidine ring protons were identifiable only as two major groupings. The H_1 and H_2 group appeared at 95–135 Hz, and a second group consisting of H_3, H_4, H_7, H_8 were downfield from 155–190 Hz; but the complexity of these regions did not permit assignments of chemical shifts or coupling constants. Several 220-MHz spectra were then run on the free base in $CDCl_3$ before and after D_2O exchange (see Figure 1B). Although the 220-MHz spectra were not strictly first-order, it was possible on the basis of conformation 2 for the piperidine ring to arrive at approximate chemical shift and J values for all the H_{1-8} protons. More refined parameters were then obtained with the LAOCOON program[7] and these are summarized in Table I. The $^3J_{H-C-C-H}$ values were in reasonable agreement with those predicted from the Karplus equation[8]. A calculated spectrum corresponding to these parameters for the 60-MHz resonances of hydrogens at carbons 1, 2, 3, 4, 7 and 8 is also shown in Figure 1.

TABLE I

Chemical Shift and J Values for H_1–H_8 Protons of 1

H_1	Chemical shift, Hz at 220 MHz*	Protons	J, Hz*	$^3J_{HC-C-H}$, Hz, predicted from Karplus Eq.
N-CH_3	535	1,2	13.0	*gem*
1	401	1,3	2.2	1.7
2	461	1,4	2.2	1.7
3	617	2,3	13.0	10.0
4	609	2,4	4.5	1.7
5	–	3,4	14.0	*gem*
6	–	6,7	12.0	10.0
7	601	6,8	4.0	1.7
8	649	7,8	10.0	*gem*

* Refined values from LAOCOON analysis of 220-MHz pmr spectrum.

Although the piperidine ring was thus indicated to have the chair conformation, the *trans* disposition of the *p*-fluorophenyl and *p*-fluorobenzoyl groups was not definitely proven because the nmr shifts and couplings of the ring hydrogens would be expected to fit about as well for the structure with the 4-OH and 4-*p*-fluorophenyl reversed from that shown in 2. However, the *trans* arrangement is not only expected to be energetically more favorable, but also places the H_5 and H_2 protons in the so-called W-configuration which should be especially favorable for the large observed coupling for H_5.

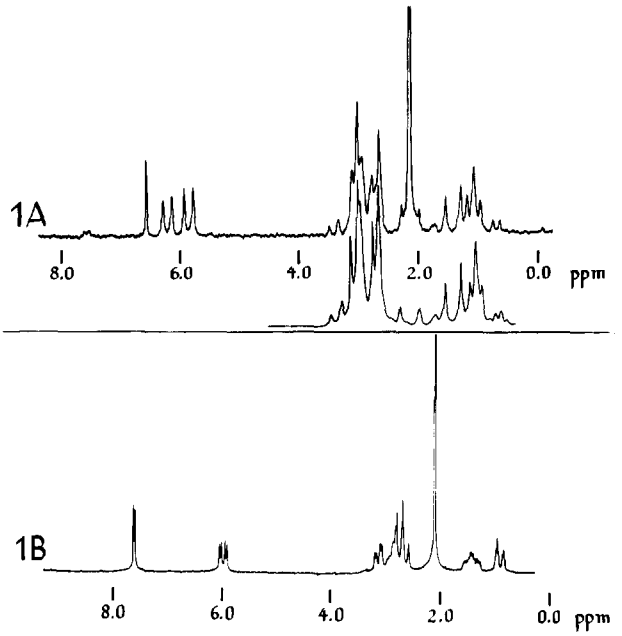


Figure 1. A, Proton nmr spectrum of 1 in $CDCl_3$ at 60 MHz and ambient temperature. Upper curve is the experimental spectrum and the lower curve was calculated using the chemical shifts and couplings in Table I. B, 220-MHz pmr spectrum of 1 in $CDCl_3$.

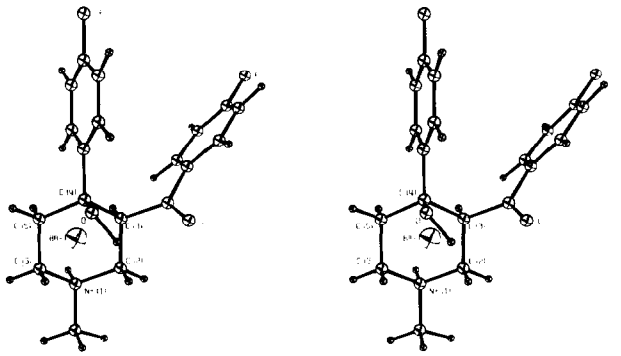


Figure 2. Stereoprojection of 1 as determined by X-ray diffraction.

The stereochemistry of 1 as the crystalline hydrobromide was established as based on conformation 2 by X-ray diffraction.[9] The hydrobromide crystallizes in a monoclinic space group $P2_1/c$ with four molecules in a unit cell of dimensions: a = 17.763, b = 7.198, c = 16.097 A and β = 113.11°. The intensity data (1819 reflections) were collected on a General Electric-Datex diffractometer, using Ni-filtered Cu radiation. The bromide ions were located by means of a Patterson map and the entire trial structure was revealed in the first Fourier map. The trial structure was refined to an R index of 7.2% by the method of least squares. The final refinement cycles contained the following parameters: coordinates, anisotropic temperature factors and scale factor. The hydrogen positions were calculated and added to the structure factor calculations but were not included in the refinement sycles. A stereoprojection of the structure is shown in Figure 2.

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1. The X-ray and nmr studies which were carried on at the California Institute of Technology were supported by the National Science Foundation.
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