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A CARBON-13 MAGNETIC RESONANCE STUDY OF THE STEREOCHEMISTRY IN ISOMERIC 1,2,5-TRIMETHYL-4-PHENYLPIPERIDINE-4-OLS.

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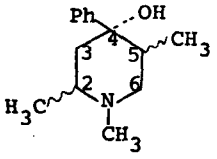
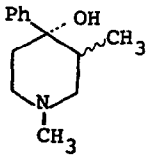
As part of our investigations concerning the application of carbon-13 magnetic resonance techniques to problems in conformational analysis[1,2] we have studied the tertiary alcohols (1) derived from 1,2,5-trimethyl-4-piperidone[2,3] and phenyllithium. Casy and McErlane[4], following Russian work[5], have described the isolation of three[5] diastereoisomers from this reaction along with their proton magnetic



(1)



(2)

resonance (pmr) spectra. Initial interpretation of the pmr spectral features suggested the configuration t-2-CH_3, c-5-CH_3, r-4-OH for the most abundant γ-isomer, t-2-CH_3, t-5-CH_3, r-4-OH for the β-isomer and c-2-CH_3, t-5-CH_3, r-4-OH for the α-isomer, though significant skew-boat populations were considered to contribute in the case of the α-isomer. The carbon-13 data we report provides evidence in agreement with the configuration suggested for the γ-isomer but the alternative configurations c-2-CH_3, t-5-CH_3, r-4-OH and c-2-CH_3, c-5-CH_3, r-4-OH must be proposed for the β and α-isomers, respectively. The latter configurations have more recently been confirmed by X-ray analysis[6] and the proton data may be reconciled with the new findings.

The carbon-13 data obtained for the γ,β and α-isomers and their corresponding hydrochlorides for solutions in deuterochloroform[7] are given in Table I. Assignment of the resonances to individual carbon atoms was made using additivity relationships derived for the 4-piperidones and by comparison with data for a variety of related compounds including the 3-methyl analogues (2) (α- and β-prodinol, see Table II), whose stereochemistry has been established.[8] The additive effects noted in the 4-piperidones upon protonation[2] were correspondingly noted in these systems and helped confirm the assignments.

TABLE I

	Carbon Position[a]											
Isomer	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-5'	C-q	C-o	C-m	C-p
γ	54.8_0	42.8_2	74.7_5	39.4_8	60.0_8	49.6_2	20.1_7	11.9_7	147.2_4	128.2_5	124.9_1	126.6_3
γ-hydrochloride	57.6_0	40.6_7	72.9_2	37.7_5	57.6_0	45.5_4	16.9_4	11.5_4	144.6_5	128.3_6	124.9_1	127.1_7
β	57.2_5	42.5_7	74.9_4	42.5_7	60.4_8	47.3_2	20.6_6	14.4_6	144.9_2	127.6_6	127.3_3	126.8_5
β-hydrochloride[b]	60.1_1	40.7_4	72.2_5	40.3_0	59.0_8	47.0_5	17.9_7	14.3_0	142.1_7	128.3_6	127.1_7	127.5_5
β-hydrochloride[b]	56.0_1	39.5_5	72.7_9	38.5_2	59.0_8	34.9_6	15.0_5	12.8_4	145.1_4	128.3_6	125.6_6	127.1_7
α	54.4_9	42.3_5	74.7_8	38.5_8	54.4_9	45.5_9	13.0_0	15.0_0	147.4_6	128.0_9	125.2_8	126.4_7
α-hydrochloride	56.1_1	40.4_7	72.5_7	38.0_4	50.6_1	41.8_7	13.0_6	11.5_5	145.6_8	128.1_4	125.2_8	126.8_5

[a] n' refers to ring atom to which substituent attached, C-q, C-o, C-m and C-p refer to phenyl ring carbons. C-o and C-m were distinguished from all other carbons by their double intensity but were not distinguished unequivocally from each other.

[b] Studied as a mixture of conformers.

TABLE II

	Carbon Position											
Compound	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-q	C-o	C-m	C-p
α-prodinol	59.0_8	40.7_9	73.3_8	39.4_4	51.6_9	46.2_9	-	12.3_0	147.4_6	128.2_5	124.9_1	126.5_8
β-prodinol	58.1_4	40.2_3	72.7_0	31.5_0	51.5_6	46.4_9	-	16.2_9	147.2_4	128.0_4	125.6_6	126.9_6

In the α- and β-prodinols it has been established[8] that the piperidine ring adopts the chair conformation with the 4-phenyl substituent equatorial. In α-prodinol the methyl group C-3' is equatorial while in β-prodinol this group is axial. The carbon-13 chemical shifts (Table II) of these isomers exhibit the similarities and differences in configuration since the methyl (C-3') carbon in the β-isomer is deshielded 4 ppm by the lone pair[1] on the nitrogen and the 1,3-syn-axial interaction between the proton at C-5 and the axial methyl group results in an upfield shift (7.9 ppm) at C-5 compared with the α-isomer. The substituent shifts caused by the axial group are also clearly less[9] as indicated by the shifts at C-2,

C-3 and C-4 in the β- compared with the α-isomer. In the N-methyl-4-piperidones[2] it was established that the characteristic shift for equatorial 2-methyl substituents was 21.2±0.6 ppm. In the α-prodinols[8b] the characteristic shift for the equatorial methyl substituent (C-3') is 12.0±0.6 ppm and for the corresponding β-system the axial methyl group is characterised by the shift 15.6±0.6 ppm.

Taking the above analysis into consideration it is apparent from the observed methyl group shifts in the γ-isomer of 1,2,5-trimethyl-4-phenylpiperidin-4-ol that the C-2' and C-5' (equivalent to C-3') methyl groups are equatorial. All other shifts in this isomer agree with the configuration assigned in the pmr study[4]. In the carbon-13 spectrum of the β-isomer the absence of any appreciable shift at C-3 (syn-axial to C-5') removed the possibility that the C-5' methyl group is axial since in β-prodinol an upfield shift of 7.9 ppm was observed at this site. Furthermore, the correspondence in shifts at C-6 in the γ- and β-isomers suggests similar substitution at C-5 (β-additivity effect). The typical equatorial methyl shift of 20.7 ppm at C-2' establishes the configuration of this group. Consequently it is the orientation of the phenyl ring which must change. The upfield shift at C-q (2.4 ppm compared to the γ and α-isomers) is indicative of syn-axial interaction of this group with the protons at C-2 and C-6. However, downfield shifts of approximately 3.0 ppm are observed at C-2 and C-5 indicating ring distortion about the carbons C-3 and C-5 which would effectively reduce the steric interactions but would introduce strain into the ring. It is noteworthy that unlike the γ- and α-isomers the β-isomer forms a "chair" and a "boat" conformation in equal proportions on protonation.

The shifts observed at the C-2' and C-5' methyl carbon sites in the α-isomer are most significant, though in this isomer differentiation of these resonances is less certain[10]. These uncertainities do not, however, preclude the observation that the C-2 methyl group is axial since not only does the methyl resonance shift upfield (syn-axial to C-6H and C-4-OH) but also a concomitant upfield shift (5.5 ppm) occurs at C-6 compared with the γ-isomer. The magnitude of the latter shift is lower than noted at C-5 in β-prodinol but coupled with the observation that the N-methyl group, C-1', moves upfield (4.0 ppm, due to increased steric interaction with C-2') suggests ring flattening over these sites. Furthermore, the negligible shift at C-3 in the α-isomer compared with the corresponding sites in β-prodinol

again suggests that the methyl group C-5' is equatorial. The similarity in shifts for the phenyl ring carbon atom C-q in the γ- and α-isomers provides evidence for the equatorial configuration of the phenyl group.

We conclude that the β- and α-isomers are in distorted chair conformations with configurations c-2-CH_3, t-5-CH_3, r-4-OH and c-2-CH_3, c-5-CH_3, t-4-OH, respectively. We suggest that the above analysis indicates the significant contribution that carbon-13 magnetic resonance can make to the solution of structural problems involving conformation and configuration.

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