

Conformational Analysis of Hexahydro-3*H*-oxazolo[3,4-*c*]pyridines by Carbon-13 Fourier-transform Nuclear Magnetic Resonance Spectroscopy

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Summary Comparison of the C(3), C(1), and C(8a) chemical shifts in hexahydro-3*H*-oxazolo[3,4-*c*]pyridine with those in anancomeric derivatives suggests its existence in solution at n.m.r. probe temperature as a *cis* ⇌ *trans* equilibrium mixture containing *ca.* 76% of the *trans*-fused conformation; ¹³C-H coupling constants involving the C(3) protons are dependent upon the orientation of adjacent lone pairs.

THE conformational analysis of the hexahydro-3*H*-oxazolo[3,4-*a*]pyridine system (1) has been studied¹ by ¹H n.m.r.

spectroscopy and, *inter alia*, on the basis of the n.m.r. parameters of the C(3) methylene group protons, compound (2) has been assigned a predominantly *trans*-fused ring conformation (2a) ($J_{gem} -0.8$ Hz, Δ_{ax-eq} 0.79 p.p.m.) and compound (3) the *cis*-fused ring conformation (3a) ($J_{gem} -5.0$ Hz, Δ_{ax-eq} 0.19 p.p.m.). Comparison of these values with those for compound (1) ($J_{gem} -2.4$ Hz, Δ_{ax-eq} 0.58 p.p.m.) show compound (1) to exist in solution at room temperature as an equilibrium (1a) ⇌ (1b) containing *ca.* 62—65% of (1a).

It has been suggested² however that J_{gem} and Δ_{ax-eq}

TABLE. ¹³C N.m.r. spectra of hexahydro-3*H*-oxazolo[3,4-*a*]pyridines^a

Compound	Chemical shifts (δ)								Coupling constants $J(^{13}\text{C}-\text{H})$					
	C(3)	C(1)	C(8a)	C(5)	C(6)	C(7)	C(8)	Me	C(1)	C(3)	C(8a)	C(5)	C(6)—(8)	Me
(1)	86.0	68.4	60.1	46.9	21.9	24.4	25.1	—	146	155	132	132	128	—
(2)	85.3	71.0	61.4	54.6	30.2	26.0	32.5	19.1	145	148, 158	130	132	128	125
(3)	87.8	63.7	57.3	54.4	30.1	22.5	27.5	19.3	146	157	136	135	128	125

^a Spectra obtained on Varian XL-100 FT Spectrometer with and without proton noise decoupling for solutions (50% v/v) in CDCl₃. Chemical shifts downfield from internal Me₄Si; coupling constants in Hz.

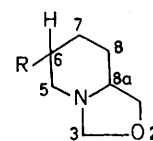
values for protons adjacent to heteroatoms in saturated heterocyclic systems are not suitable parameters on which to base quantitative estimates of conformational equilibria. With this in mind and in order to test the utility of ^{13}C n.m.r. chemical shifts and coupling constants in conformational problems the ^{13}C n.m.r. spectra of (1), (2), and (3) were obtained. The assignments shown in the Table are based on analogy with related compounds^{3,4} and the splitting pattern of the spectra recorded under non-decoupled conditions.

Application of the substituent chemical shifts derived for an axial and equatorial methyl group in methylcyclohexanes⁵ to the system (2a) \rightleftharpoons (2b) and (3a) \rightleftharpoons (3b), assuming the effect of the C(1) methylene in these compounds to be equivalent to that of the methyl group in methylcyclohexane, supports the adoption of conformations (2a) and (3a) by (2) and (3). Thus since δ C(6) values for (2) and (3) are almost identical these must exist either in conformations (2a) and (3a) or in (2b) and (3b). If the latter is the case, it is expected⁵ that C(7) and C(8) should be more shielded for (2) (in which the side chain is axial) than in (3) (in which the side chain is equatorial). Since the reverse is the case, the compounds (2) and (3) must exist in conformations (2a) and (3a).

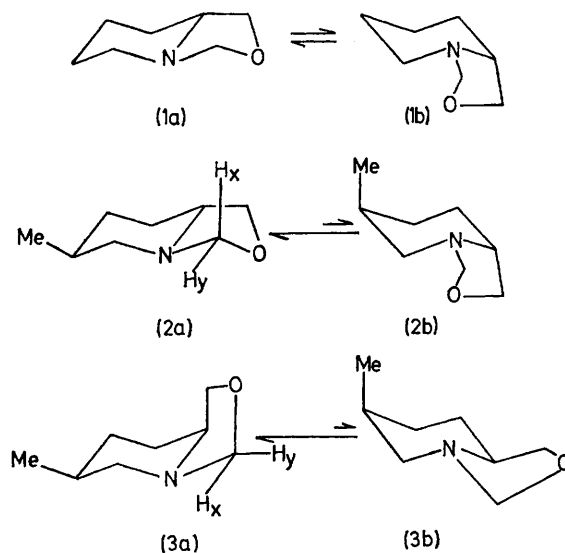
The ^{13}C chemical shifts of C(3), C(1), and C(8a) for (1) are intermediate between those for (2) and (3) and with the usual assumptions⁶ these figures give the proportions of 78, 74, and 76% of (1a) in the (1a) \rightleftharpoons (1b) equilibrium based on the C(3), C(1), and C(8a) chemical shifts, respectively. This result demonstrates the power of the ^{13}C n.m.r. method in the study of conformational problems and the position of equilibrium estimated by this method is not grossly different from that obtained previously.¹

Since $J(^{13}\text{C}-\text{H})$ is a function of the angular and polar environment surrounding the C-H bond⁷ $J(^{13}\text{C}-\text{H})$ is expected to reflect the stereochemistry of (1), (2), and (3). The most striking observation in the spectra of the compounds is the splitting pattern of C(3). In *cis*-fused (3a) the C(3) signal appears as a sharp triplet in the proton noise non-decoupled spectrum, indicating an equal coupling constant (157 Hz) for $^{13}\text{C}-\text{H}_x$ and $^{13}\text{C}-\text{H}_y$, while in the *trans*-fused (2a), the same carbon appears as a quartet with unequal coupling constants of 148 and 158 Hz. In (1), the C(3) signal is a triplet with a broadened central peak, consistent with its existence as a mixture of *cis*- and *trans*-fused conformations.

The origin of this large difference in coupling constants can be found in the relative geometry of H_x and H_y in



- (1) R=H
 (2) R=Me (*cis* to 8a-H)
 (3) R=Me (*trans* to 8a-H)



relation to the nitrogen lone pair. In (3a), the dihedral angle with the lone pair is much the same for C-H_x and C-H_y so that equal $J(^{13}\text{C}(3)-\text{H})$ values are expected. In (2a), however, H_x is almost *trans*-coplanar with the lone pair and H_y *gauche* and by analogy with results obtained⁸ on oxaziridines the couplings of 158 and 148 Hz in (2a) may be assigned to $J(^{13}\text{C}-\text{H}_x)$ and $J(^{13}\text{C}-\text{H}_y)$ respectively since overlap of the lone pair with C(3)-H will be more effective for H_x. The dihedral angles between the oxygen lone pairs and the C(3) methylene bonds are similar in (2a) and (3a). This stereochemical dependence of $J(^{13}\text{C}-\text{H})$ on lone pair-CH dihedral angle is a potentially powerful tool for the investigation of the conformation of compounds of this type.

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