Conformational Analysis by Carbon-13 Nuclear Magnetic Resonance Spectroscopy. Part I.[1] Hexahydro-3*H*-oxazolo[3,4-*a*]pyridines

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Comparison of the C(3), C(1), and C(8a) chemical shifts in hexahydro-3*H*-oxazolo[3,4-*a*]pyridine with those in methyl substituted derivatives suggests its existence in solution at n.m.r. probe temperature as a *cis* ⇌ *trans* equilibrium mixture containing 73—78% of the *trans*-fused conformation; ^{13}C–H coupling constants involving the C(3) protons are dependent upon the orientation of adjacent heteroatom lone pairs.

^{1}H N.M.R. spectroscopy has been used extensively in the conformational analysis of cyclic compounds [2] and ^{13}C n.m.r. spectroscopy [3] is now providing additional information. The ^{13}C n.m.r. technique, however, as applied to conformational problems, is largely based on the magnitude of the chemical shifts [4] and although the value of these parameters can never be overestimated, the amount of information obtainable from n.m.r. data should be greatly increased by the availability of values for the coupling constants.

In natural abundance ^{13}C n.m.r. spectroscopy, the spectra are normally recorded with proton-noise decoupling to increase the peak intensity by combining otherwise split peaks. This enhancement is, however, achieved at the expense of valuable ^{13}C–^{1}H coupling constant data. This difficulty has now been considerably, if not completely, overcome by the development of the ^{13}C Fourier transform n.m.r. technique.[5] The purpose of this paper is to demonstrate the utility of ^{13}C n.m.r. parameters to conformational problems.

The compounds selected for this purpose are hexahydro-3*H*-oxazolo[3,4-*a*]pyridine (1) and some of its monomethyl derivatives (2)—(5). Compound (1) is expected to exist as an equilibrium mixture of the *trans*- and *cis*-ring fused conformers (1a and b). For monomethyl derivatives, *e.g.*, 6-methylhexahydro-3*H*-oxazolo[3,4-*a*]pyridine, two racemic epimers, *trans*-(6-*H*,8a-*H*)- (2) and *cis*(6-*H*,8a-*H*)-6-methylhexahydro-3*H*-oxazolo[3,4-*a*]pyridine (3), are possible, and each epimer may exist as an equilibrium mixture of *cis*- and *trans*-fused species. For the 7-methyl and 8-methyl derivatives, only one of the epimers, *i.e.* *cis*(7-*H*,8a-*H*)-7-methyl- (4) and *cis*(8-*H*,8a-*H*)-8-methyl-hexahydro-3*H*-oxazolo[3,4-*a*]pyridine (5), will be discussed.

The conformational analysis of these compounds has been studied [6] by ^{1}H n.m.r. spectroscopy and *inter alia* on the basis of the n.m.r. parameters of the 3-methylene protons (2) has been assigned a predominantly *trans*-fused ring conformation (2a) (J_{gem} —0·8 Hz, $\Delta_{ax'-eq'}$ 0·79 p.p.m.) † and (3) a predominantly *cis*-fused ring conformation (3a) (J_{gem} —5·0 Hz, $\Delta_{ax'-eq'}$ 0·19 p.p.m.).

† J_{gem} is assumed to be negative. $\Delta_{ax'-eq'}$ is the difference in chemical shift between the pseudoaxial and pseudoequatorial protons on C(3).

Whereas (2) adopts almost exclusively the *trans*-fused conformation (3) appears to exist in solution at room temperature as *ca.* 80% *cis*-fused ring conformation (3a) in equilibrium with (3b) since a J_{gem} for the 3-methylene protons of —6·0 Hz is the most reasonable value for

(1a)   (1b)

(2a)   (2b)

(3a)   (3b)
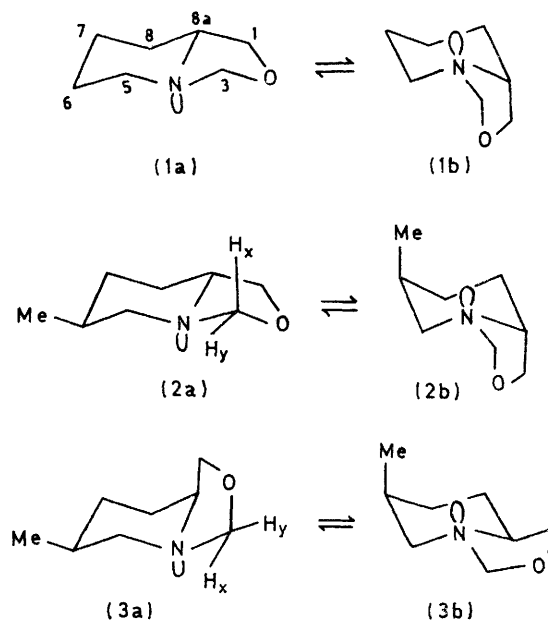
(3a).[7] Comparison of these values with those for compound (1) (J_{gem} —2·4 Hz, $\Delta_{ax'-eq'}$ 0·58 p.p.m.) shows (1) to exist in solution at room temperature as an equilibrium (1a) ⇌ (1b) containing *ca.* 68% (1a). A similar analysis of ^{1}H n.m.r. parameters of (4) and (5) reveals that (4) adopts predominantly the *trans*-fused ring conformation while (5) adopts the *cis*-fused ring one; thus compounds (2)—(5) all exist predominantly in conformations in which the methyl group occupies an equatorial position.

It has been suggested,[8] however, that J_{gem} and $\Delta_{ax'-eq'}$ values for protons adjacent to heteroatoms in saturated

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[3] J. B. Stothers, ' Carbon-13 N.M.R. Spectroscopy,' Academic Press, New York, 1972, chs. 5 and 7.

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heterocyclic systems are not suitable parameters on which to base quantitative estimations of conformational equilibria. With this in mind, and in order to obtain independent evidence for the conformational preferences

(4)   (5)
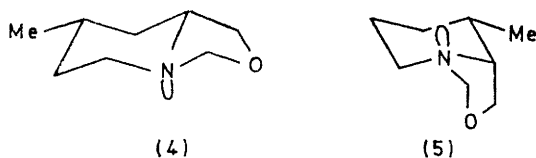
of these compounds, [13]C n.m.r. spectra of (1)—(5) were determined with proton-noise decoupling (to assess chemical shifts) and without (to assess coupling constants).

Assignment of C(1), C(3), C(5), *and* C(8a) *Signals.*— The chemical shifts (δ from Me$_4$Si) and '^1J' values (line separations) recorded for (1)—(5) are given in Table 1. The assignments were made as follows. It is known [9] that carbon nuclei adjacent to nitrogen

of (2) and (3) since these two compounds constitute a diastereoisomeric pair. The value of δ[C(6)] is the same for (2) and (3) since the effect of the side chain at C(8a) is negligibly small.[11] In addition, the effect of the side chain attached to nitrogen is expected to be equal for (2) and (3) whatever ring fusion is adopted, because this side chain is always equatorial to the piperidine ring. On the other hand, the effects of axial and equatorial methyl groups upon the carbon to which the methyl is bonded are significantly different. Thus, in the case of the methylpiperidines, Booth [9] has proposed chemical shift parameters * α_e (3) and α_a (3) of 5·3 and 1·9 respectively. Thus, the identity of δ[C(6)] for (2) and (3) indicates the same orientation of the methyl groups in both compounds; (2) and (3) must exist in either conformations (2a) and (3a) or (2b) and (3b).

Perhaps the most remarkable features of the undecoupled spectra of (2) and (3) are the differences in the

<div style="text-align:center">TABLE 1</div>

<div style="text-align:center">[13]C N.m.r. parameters of hexahydro-3H-oxazolo[3,4-a] pyridines (1)—(5)</div>

	δ^a								$^1J^b$			C(6)—C(8)		
	C(1)	C(3)	C(5)	C(6)	C(7)	C(8)	C(8a)	Methyl	C(1)	C(3)	C(5)	C(8)	C(8a)	Methyl
(1)	68·4	86·0	46·9	24·4	21·9	25·1	60·1		146	155	132	128	132	
(2)	71·0	85·3	54·6	[30·2]^c	32·5	26·0	61·4	19·1	148	148 / 158	132	128	130	125
(3)	68·7	87·8	54·4	[30·1]	27·5	22·5	57·3	19·3	148	157	135	128	136	126
(4)	70·8	85·2	46·8	32·4	[30·1]	34·8	61·2	18·9	149	149 / 159	133	128	129	125
(5)	61·2	87·5	46·8	24·1	27·2	[29·5]	63·0	17·5	148	157	135	128	136	125

^{a} In p.p.m. from Me$_4$Si. ^{b} Line separations (Hz). ^{c} Square brackets indicate substituted carbon.

absorb at lower field, and exhibit higher values of ^1J than in all-carbon analogues. These effects are expected to be larger for carbon nuclei adjacent to oxygen; in fact δ and ^1J values for C(3) and C(2) in morpholine are 67·2 and 45·7 and 140 and 132 Hz [10] in contrast with the corresponding values, δ 27·7 and J 125·0 Hz, for cyclohexane.[3] Thus values of both δ and ^1J are expected to lie in the order C(3) > C(1) > C(5), C(8a), and C(5) and C(8a) may be differentiated since the signals arising from these appear as a triplet and a doublet, respectively, in the undecoupled spectrum. For compounds (2)—(5), the carbon atom carrying a methyl group will absorb as a doublet, and the methyl carbon itself as a quartet, when undecoupled. Thus C(1), C(3), C(5), and C(8a) may be assigned unambiguously. For C(6)—C(8), however, the situation is not so clear, and this will be discussed later.

Conformational Analysis of Compounds (2)—(5).— For this purpose it is convenient to compare the spectra

values of $^1J[C(3)]$ and $^1J[C(8a)]$ † between the two compounds. The C(3) signals of (2) form a quartet, indicating two couplings of unequal magnitudes (148 and 158 Hz) to be involved while (3) shows a triplet, indicating two couplings of equal magnitudes (157 Hz). A remarkable difference (6 Hz) in the magnitude of $^1J[C(8a)]$ for (2) and (3) is also observed.

These observations are most reasonably explicable in terms of the difference in the dihedral angle between the nitrogen lone pair and the C–H bond involved. In aziridines,[12] imidazolidines,[13] and oxaziridines [14] where there is a large difference in ^1J depending on whether the proton involved is *cis* or *trans* to the nitrogen lone pair the larger coupling constant has been assigned to the proton *cis* to the lone pair. In the Figure, the geometrical relationships of the lone pair with 3-H and with 8a-H for the *trans*- and *cis*-ring fused conformers

* In the nomenclature of Dalling and Grant [11] α_e (3) is the effect on the shift of the carbon α to the substituent, caused by replacement of a 3-equatorial hydrogen by a methyl substituent.

† Throughout this paper ^1J refers to the observed J^{13}C–H splittings which may not equal the actual J values. This may explain the observation of triplets for the C(5) nuclei, since the differing orientations of H$_{5ax}$ and H$_{5eq}$ with respect to the nitrogen lone pair should result in different ^1J values. The values of the splittings have therefore not been used in the estimation of the position of conformational equilibrium (1a) ⇌ (1b).

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are illustrated.* In the *trans*-fused conformer, 3_x-H is *trans* to and near coplanar with the lone pair and 3_y-H is *cis*, while in the *cis*-fused conformer, both protons are *cis*. On this basis (2) may be assigned the predominantly *trans*-fused conformation (2a) with $^1J[\mathrm{C}(3) \cdots \mathrm{H}(3_x)]$ 148 and $^1J[\mathrm{C}(3) \cdots \mathrm{H}(3_y)]$ 158 Hz, and (3) the predominantly *cis*-fused conformation (3a) with $^1J[\mathrm{C}(3) \cdots \mathrm{H}(3_x)] = {}^1J[\mathrm{C}(3) \cdots \mathrm{H}(3_y)] = 157$ Hz. Similarly it can be concluded from the J values for C(3) and C(8a) that (4) adopts the *trans*-fused conformation

trans-
fused

cis -
fused
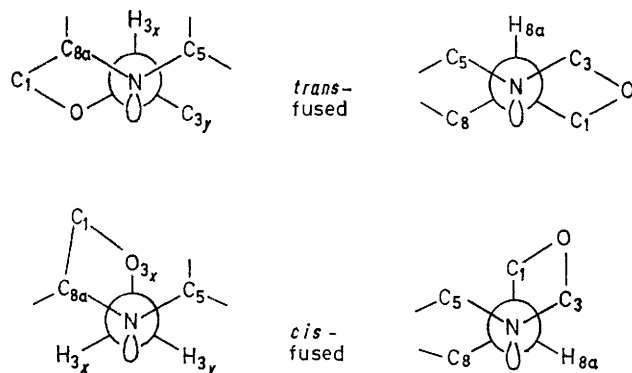
Relationships of the nitrogen lone pair with 3-H and with 8a-H for *trans*- and *cis*-fused hexahydro-3*H*-oxazolo[3,4-*a*] pyridine

(4a) and (5) the *cis*-fused one (5a). All the compounds (2)—(5) possess an equatorial methyl group in their most stable conformations. These conclusions are independent of, but in accord with, that obtained from ^{1}H n.m.r. spectroscopy.[6]

Assignment of C(6)—C(8) *Signals.*—As mentioned above, there remains some uncertainty in the assignment of C(6)—C(8) signals (except for the methyl-substituted carbon) in the spectra of (2)—(5). For example, two alternative assignments are possible for C(7) and C(8) of (2) and (3). One possibility is given in Table 1. If corrections for the effect of the methyl group are made with the aid of Booth's parameters[9] $\alpha_e(3) = 5\cdot3$, $\beta_e(3) = 7\cdot1$ (for 2-H), $\beta_e(3) = 8\cdot9$ (for 4-H), and $\gamma_e(3) = \delta_e(3) = 0$, considering compounds (1)—(5) as piperidine derivatives, the observed δ values for (2) are converted to 23·6 and 26·0 for C(7) and C(8) respectively. Such δ values are reasonable for (1a) which in turn should not differ greatly from the observed δ values of (1). On the contrary, if the assignments are reversed, *i.e.* if δ[C(7)] and δ[C(8)] are 26·0 and 32·5, respectively, the corrected δ values will be 17·1 and 32·5, which are out of the ' normal ' range for these carbon nuclei. Thus, with the assumption that if proper corrections are made for the effect of the substituent methyl group the corrected δ values of (2) and (4) should give δ values of (1a) while

* In reality the hexahydro-3*H*-oxazolo[3,4-*a*]pyridine ring system must be deformed compared with decalin so that the dihedral angles shown in the Figure will not be exactly π or π/3. Differing orientations of the oxygen lone pairs may also affect ^1J but ^{1}H n.m.r. work on this system suggests the influence of the nitrogen lone pair to be dominant.

those of (3) and (5) would lead to δ values of (1b), assignments should be made so that the observed δ values of (1) are weighted averages of the estimated δ values for (1a) and (1b), *i.e.*, the corrected δ values of (2) and (4) and (3) and (5), respectively. In a similar manner, assignments were made for (3) and (5) so that the corrected δ values fall in the ' reasonable ' range. These corrected values for C(5)—C(8) and C(8a) of (2)—(5) based on the assignments in Table 1 are summarised in Table 2 and the observed δ values for (1) are included for comparison purposes.

TABLE 2

Corrected δ values of C(5)—C(8) and C(8a) for (1)—(5)

	C(5)	C(6)	C(7)	C(8)	C(8a)
(1)	46·9	24·4	21·9	25·1	60·1
(2)	47·5	24·9	23·6	26·0	61·4
(3)	47·3	24·8	18·6	22·5	57·3
(4)	46·8	23·2	23·4	26·0	61·2
(5)	46·8	24·1	18·3	24·2	55·9

a Corrections were made with the aid of Booth's parameters.[9]

The corrected δ values for C(7), C(8), and C(8a) are seen to be dependent upon the conformation with δ values for these carbons always large for the *trans*-fused conformers. With the aid of these parameters, it is now possible to eliminate the remaining uncertainty in the assignment of signals in the spectrum of (1). Thus, the δ values of (1) should be identical with those of others [for C(6)] or, when δ values are conformationally dependent, the intermediate values of the *trans*- and *cis*-fused conformers [for C(7) and C(8)].

Conformational Analysis of Compound (1).—Comparison of δ and ^1J values of (1) with those of (2)—(5) clearly indicates that (1) is an equilibrium mixture of (1a) and (1b). With the usual assumptions, and accepting the ^{1}H n.m.r. result[7] of 80% (3a) in the (3a) ⇌ (3b) equilibrium, the population of (1a) in the equilibrium is estimated from the δ values of C(3), C(7), C(8), and C(8a). The results are summarised in Table 3. The conclusion that 73—78% of (1) is in the *trans*-ring fused conformation compares with the estimate based on ^{1}H n.m.r. spectroscopy[7] of 68%.

TABLE 3

Conformational equilibrium of hexahydro-3*H*-oxazolo-[3,4-*a*]pyridine (1) estimated by ^{13}C n.m.r. parameters

Parameter used	δ[C(3)]	δ[C(7)]	δ[C(8)]	δ[C(8a)]
trans-Conformation (%)	78	73	79	75

These results demonstrate the power of ^{13}C n.m.r. spectroscopy for the conformational analysis of compounds of this type, particularly when both δ and J values are available. Further work along these lines is in progress.

EXPERIMENTAL

The preparation of the hexahydro-3*H*-oxazolo[3,4-*a*]-pyridines (1)—(5) has already been described.[6]

The ^{13}C n.m.r. spectra of these compounds were obtained on a Varian XL-100-FT spectrometer operating at 25·2 MHz. Samples were dissolved in equal volumes of $CDCl_3$ which also acted as the internal lock signal. Spectral width 2500 Hz with 4096 memory points; acquisition time 0·8 s; pulse width 25 μs; number of pulses accumulated 100—500 (decoupled) or 10,000—16,000 (undecoupled).