HETEROCYCLES, Vol. 9, No. 1, 1978

CONFORMATIONAL EQUILIBRIUM IN *cis*-OCTAHYDROCARBOSTYRILS

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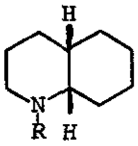
The proton magnetic resonance (^{1}H-NMR) studies on N-substituted *cis*-octahydrocarbostyrils have revealed a preference of the conformer ($\mathbf{2}_{eq}$) for the substituent methyl or benzyl and of the conformer ($\mathbf{2}_{ax}$) for the N-hydrogen compound. The positions of conformational equilibrium [$\mathbf{2}_{eq} \rightleftharpoons \mathbf{2}_{ax}$] in several other *cis*-octahydrocarbostyrils are also described.

Conformational studies on saturated heterocycles are in the foreground of recent researches.[1] Especially, Booth and coworkers[2] have widely examined the conformational analysis for equilibrium in a series of *cis*-decahydroquinolines, $\mathbf{1}[\mathbf{1}_{eq} \rightleftharpoons \mathbf{1}_{ax}]$, demonstrating that the conformer ($\mathbf{1}_{ax}$) is the predominant one for R=H or Me while the conformer ($\mathbf{1}_{eq}$) is preferred for R=CD_2CH_3 or CD_2CF_3.[2b] In the present communication we describe the conformational analysis for equilibrium in some *cis*-octahydrocarbostyrils, $\mathbf{2}[\mathbf{2}_{eq} \rightleftharpoons \mathbf{2}_{ax}]$, by use of the ^{1}H-NMR signal of their C-8a protons recorded at room temperature.



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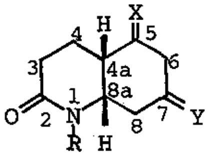

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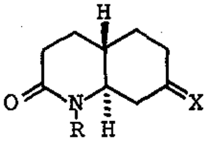

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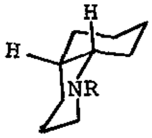
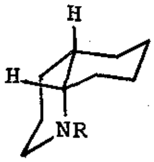
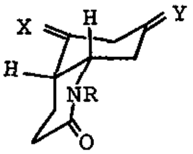


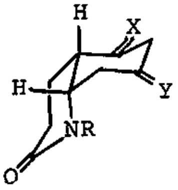
1_{eq}



1_{ax}



2_{eq}



2_{ax}

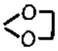
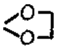
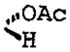
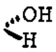
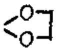
The C-8a proton signals for *cis*-octahydrocarbostyril derivatives (2a-2q), as summarized in Table I, appear in the downfield region with good separation from those of other ring protons.[3] The values of chemical shifts (δ *ca*. 3.2 ppm) and half-height width ($W_{1/2}$) (*ca*. 25 Hz) for the *trans* analogues (3: R=H, benzyl; X=O, ketal)[4] are almost constant while those for the *cis*-lactams (2) are widely varied depending on the conformational equilibrium in respective *cis*-lactams. Since the chemical shifts are affected not only by conformational circumstances but also by ring substituents, they are not suitable for diagnosis of the conformational equilibrium in substituted *cis*-octahydrocarbostyrils. On the other hand, values of $W_{1/2}$, or in other words splitting patterns, would be affected only by the position of conformational equilibria and therefore be utilizable to determine the position of the equilibrium.

If the $W_{1/2}$ values for the conformers (2_{eq} and 2_{ax}) are

$W_{1/2(eq)}$ and $W_{1/2(ax)}$, respectively, then the observed value of $W_{1/2}$ will be

$$W_{1/2(observed)} = N_{eq}\cdot W_{1/2(eq)} + N_{ax}\cdot W_{1/2(ax)} \qquad (I)^5$$

Table I. The C_{8a}-H signals in the ^{1}H-NMR spectra of cis-octahydrocarbostyrils (at 90 MHz, in $CDCl_3$, 35°C)

Compounds	R	X	Y	Chemical shifts(δ)	$W_{1/2}$(Hz)
2a	H	H_2	H_2	3.49	8.0*1
2b	Me	H_2	H_2	3.18	17.5
2c	$CH_2C_6H_5$	H_2	H_2	3.16	18.0
2d	H	O	H_2	4.06	9.5*1
2e	Me	O	H_2	3.65	15.5
2f	$CH_2C_6H_5$	O	H_2	3.40	17.5
2g	H		H_2	3.59	15.5*1
2h	Me		H_2	3.42	17.5
2i	$CH_2C_6H_5$		H_2	3.46	19.5
2j	H	H_2	O	3.96	8.0*1
2k	$CH_2C_6H_5$	H_2	O	3.57	20.0
2l	H	H_2		3.67	16.0*1
2m	$CH_2C_6H_5$	H_2		3.48	19.5*2
2n	Me		H_2	3.22	18.0
2o	Me		H_2	3.20	18.0
2p	$COPr^n$	H_2	H_2	4.37	19.0
2q	$CH_2CH{=}CH_2$	H_2		3.52	19.5

*1 The value on irradiation at NH signal.

*2 The value of the width between outer lines.

where N_{eq} and N_{ax} are the mole fractions of the conformers ($\mathbf{2}_{eq}$ and $\mathbf{2}_{ax}$), respectively. The values of $W_{1/2(eq)}$ and $W_{1/2(ax)}$ could be given as 20 and 4.5 Hz from the C-8a proton signals for the corresponding conformers ($\mathbf{2}_{eq}$ and $\mathbf{2}_{ax}$), respectively, in the ^{1}H-NMR of N-methyl-cis-octahydrocarbostyril (**2b**) measured at -61°C. The relation between the observed $W_{1/2}$ and the position of conformational equilibrium is also shown in Fig. 1. Low temperature ^{1}H-NMR measurements for **2a** and **2b**, where the exact

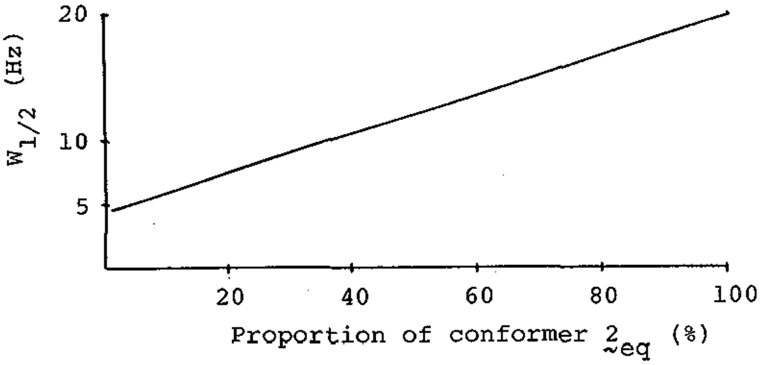


Fig. 1. The relation between the $W_{1/2}$ values of C_{8a}-H signals and the position of the equilibrium [$\mathbf{2}_{eq} \rightleftharpoons \mathbf{2}_{ax}$]

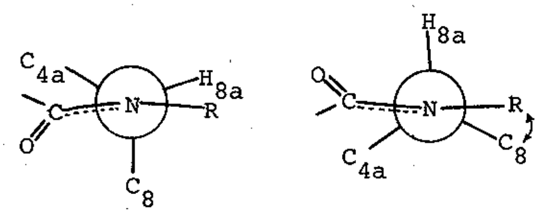
Table II. The position of conformational equilibrium in cis-octahydrocarbostyrils using the equation (I) and low temperature ^{1}H-NMR spectra

Compounds	Proportion of conformer $\mathbf{2}_{eq}$ (%)	
	calcd. from equation (I)	calcd. from low temp. NMR spectra
2a	23	19^{*1}
2b	84	86^{*2}

*1 The value at -48°C. δ(C_{8a}-H): 3.37 (for $\mathbf{2}_{eq}$) and 3.55 (for $\mathbf{2}_{ax}$). *2 The value at -61°C. δ(C_{8a}-H): 3.22 (for $\mathbf{2}_{eq}$) and 3.52 (for $\mathbf{2}_{ax}$).

proportions of two conformers are given by determining the signal areas for the corresponding C-8a protons, demonstrate that the equation (I) is well applicable to the conformational analysis for equilibrium in cis-octahydrocarbostyrils (Table II).[6]

The results show a preference for conformer $\underset{\sim}{2}_{ax}$ when R=H[7] and for conformer $\underset{\sim}{2}_{eq}$ when R=Me or benzyl. This tendency is somewhat different from that for decahydroquinolines[2b] and would be interpreted in terms of the severe repulsive interaction, between the N-substituent and the C-8 methylene in conformer $\underset{\sim}{2}_{ax}$, derived from the contribution of sp^2 character of the nitrogen valences (Fig. 2).



$\underset{\sim}{2}_{eq}$ $\underset{\sim}{2}_{ax}$

Fig. 2. Newman projections of $\underset{\sim}{2}_{eq}$ and $\underset{\sim}{2}_{ax}$ for a view along the N-C_{8a} bond

The position of the equilibrium in other cis-octahydrocarbostyrils ($\underset{\sim}{2}$c-$\underset{\sim}{2}$q) can also be estimated either from the equation (I) or from the slope of the $W_{1/2}$ vs. conformer proportion plots shown in Fig. 1.

From the above results, the $W_{1/2}$ values for the C_{8a}-H signals in ^{1}H-NMR of cis-octahydrocarbostyril derivatives measured at room temperature are found to be useful as a tool for conformational analysis concerning the equilibrium [$\underset{\sim}{2}_{eq} \rightleftarrows \underset{\sim}{2}_{ax}$]. Application of the method to configurational determination in other cis-octahydrocarbostyrils is in progress.

REFERENCES AND NOTES

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2. a) H. Booth and A.H. Bostock, *J.C.S. Perkin II*, 1972, 615; b) H. Booth and D.V. Griffiths, *ibid.*, 1975, 111; c) H. Booth, D.V. Griffiths, and M.L. Jozefowicz, *ibid.*, 1976, 751.
3. The signals for *cis*-decahydroquinolines are found to be often masked with C-2 proton signals.[2a]
4. T. Momose, S. Uchida, M. Kinoshita, and T. Imanishi, *Chem. Pharm. Bull.*, 1977, **25**, 1797.
5. A similar equation concerning the δ values is found in the literature: E.L. Eliel, *Chem. Ind. (London)*, 1959, 568.
6. The small deviation of the values calcd. from equation (I) from those based on the low temp. NMR spectra in Table II would be associated with the phenomenon that the contribution of minor conformers becomes smaller at lower temperature. Such a phenomenon has been described in many literatures: see, for example, ref. 1d.
7. For **2g** or **2l**, conformer $\mathbf{2}_{eq}$ is preferred because of an 1,3-repulsive interaction between the ketal oxygen and the C_3-C_4 or C_{8a}-N bond in conformer $\mathbf{2}_{ax}$.

Received, 24th September, 1977