

# CHIROPTICAL PROPERTIES OF 2-SUBSTITUTED PIPERIDINES

## A SIMPLE HELICITY RULE<sup>1</sup>

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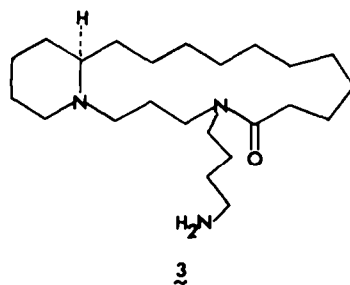
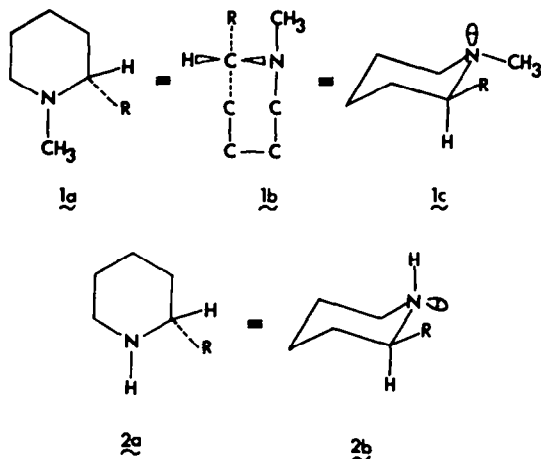
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**Abstract**—The CD spectra of fifteen 2-substituted piperidines **2** and their N-methylated derivatives **1** have been determined. The sign of the Cotton effect observed for the  $n \rightarrow \sigma^*$  transition of nitrogen is shown to be correlated, for a given absolute configuration, with the axial or equatorial orientation of the nitrogen lone pair, and to be determined by the screw sense of the helicity between the nitrogen lone pair and the 2-substituent R in **1** and **2**: for compounds of the absolute D configuration, a positive helicity gives a positive CD and vice versa.

The longest wavelength transition of saturated aliphatic and heterocyclic amines is the  $n \rightarrow \sigma^*$  transition involving a nonbonding orbital of nitrogen and the  $\sigma^*$  orbital of the C-N bond. This transition, which is located near 200 nm, disappears on protonation.<sup>2,3</sup> Early ORD<sup>4</sup> measurements on coniine and 2-methylpiperidine showed that the  $n \rightarrow \sigma^*$  transition of piperidines is optically active, and subsequent work on the absolute configuration of several piperidine alkaloids<sup>5</sup> demonstrated for the first time that the Cotton effect (C.E.) of the  $n \rightarrow \sigma^*$  transition of nitrogen could be observed directly by CD.

The present study reports the CD spectra of fifteen optically active 2-substituted piperidines **2a** and their N-Me derivatives **1a**, and a simple helicity rule.

in the Fischer protection **1b**. Since the  $n \rightarrow \sigma^*$  transition requires the presence of a lone pair of electrons on nitrogen, the CD in every case vanished completely on protonation. Measurements were made in 95% alcohol and (in a few cases) also in cyclohexane. The alcohol **1a**, R =  $n$ -(CH<sub>2</sub>)<sub>11</sub>OH is derived from the macrocyclic spermidine alkaloid oncinotin<sup>7</sup> **3** and was employed to assign the absolute configuration of **3** as L by chiroptical correlation with 1-methylconiine. It had been demonstrated earlier<sup>4,5</sup> that the OH function did not interfere in this assignment.



Like the  $n \rightarrow \pi^*$  transition of the CO chromophore,<sup>6</sup> the  $n \rightarrow \sigma^*$  transition of nitrogen shows a prominent blue shift of about 20 nm on going from a non-polar (cyclohexane) to a polar (95% alcohol) solvent, with a concomitant decrease in intensities (Fig. 1). In the case of the  $n \rightarrow \pi^*$  transition, the polar solvent tends to stabilize the nonbonding orbital more than the antibonding orbital, resulting in a blue shift of the spectrum,<sup>6</sup> and the same argument may be applied to the  $n \rightarrow \sigma^*$  transition of the cyclic amines **1** and **2**.

The markedly enhanced CD intensity observed (Table 2) for 2-methyl- and 2-ethylpiperidine (Fig. 1) in cyclohexane vs alcohol solution may be due to increased intermolecular H-bonding in the nonpolar solvent for these -NH compounds since this change does not seem

### RESULTS AND DISCUSSION

The CD data for 15 piperidines are given in Tables 1 and 2. These include a number of natural products<sup>4</sup> and their N-Me derivatives. All the compounds listed in Tables 1 and 2 are related to D-pipecolic acid, as shown

Table 1. Circular dichroism of N-methyl piperidines 1a

Compound	<u>1a</u> , R =	$[\alpha]_D^a$	$[\theta]_{\max}^a$	$\lambda_{\max}(\text{nm})^d$
D-(+)-1-Methylpipercoline (S)	CH <sub>3</sub>	+44.3°	+900	2051
D-(+)-1-Methyl-2-ethylpiperidine (S)	C <sub>2</sub> H <sub>5</sub>	+72.3°	+2880	1881
"	C <sub>2</sub> H <sub>5</sub>	+82.3° <sup>b</sup>	+3560 <sup>b</sup>	204
D-(+)-1-Methylconifine <sup>c</sup> (S)	n-C <sub>3</sub> H <sub>7</sub>	+74.9°	+3110	2001
D-(+)-1-Methyl-pipercolinol (R)	CH <sub>2</sub> OH	+14.7°	+1000	2001
D-(+)-1-Methyl-2-(11'-hydroxyundecyl)-piperidine <sup>c</sup> (S)	n-(CH <sub>2</sub> ) <sub>11</sub> OH	+21°	+4500	1971

<sup>a</sup>Measurements are in 95% alcohol unless otherwise stated (c, 0.2-2.0).

<sup>b</sup>Measured in cyclohexane

<sup>c</sup>Measured as the L-enantiomer. For consistency of presentation, the data given are for the D-form.

<sup>d</sup> signifies lowest measured wavelength (i.e. cutoff point).

Table 2. Circular dichroism of NH piperidines 2a

Compound	<u>2a</u> , R =	$[\alpha]_D^a$	$[\theta]_{\max}^a$	$\lambda_{\max}(\text{nm})^d$
D-(+)-Pipercoline (S)	CH <sub>3</sub>	+7.3°	+4670	1901
" (S)	CH <sub>3</sub>		+9075 <sup>b</sup>	2021
D-(+)-2-Ethylpiperidine <sup>a</sup> (S)	C <sub>2</sub> H <sub>5</sub>	+6.6°	-730	205
"	C <sub>2</sub> H <sub>5</sub>	+16.9° <sup>b</sup>	-4930 <sup>b</sup>	227
D-(+)-Conifine (S)	n-C <sub>3</sub> H <sub>7</sub>	+5.0°	-630	205
D-(+)-2-n-Butylpiperidine <sup>c</sup> (S)	n-C <sub>4</sub> H <sub>9</sub>	+7.5°	-860	204
D-(-)-Pipercolinol (R)	CH <sub>2</sub> OH	-16.9°	-1140	200
D-(+)-2-(2'-Hydroxyethyl)-piperidine <sup>c</sup> (R)	CH <sub>2</sub> CH <sub>2</sub> OH	+2.3°	-690	205
D-(-)-Sedridine (R)	(R)-CH <sub>2</sub> CH(OH)CH <sub>3</sub>	-27.5°	-518	205
D-(+)-Alloesdridine (R)	(S)-CH <sub>2</sub> CH(OH)CH <sub>3</sub>	+17.0°	-915	205
D-(-)-Conhydrine (R)	(R)-CH(OH)C <sub>2</sub> H <sub>5</sub>	-9.3°	-1917	198
D-(-)-Halosalina (R)	(R)-CH <sub>2</sub> CH(OH)C <sub>3</sub> H <sub>7</sub>	-19.5°	-548	209

<sup>a</sup>Measurements are in 95% alcohol unless otherwise stated (c, 0.2-2.0).

<sup>b</sup>Measured in cyclohexane

<sup>c</sup>Measured as the L-enantiomer. For consistency of presentation, the data given are for the D-form.

<sup>d</sup> signifies lowest measured wavelength (i.e. cutoff point).

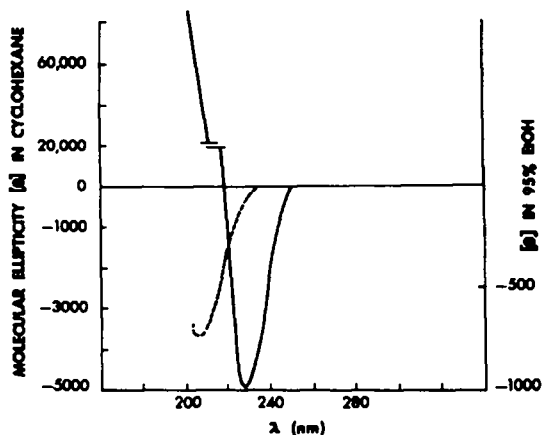


Fig. 1. CD spectra of D-(+)-2-ethylpiperidine in 95% ethanol (---) and cyclohexane (—).

to occur in the corresponding N-methyl-2-ethylpiperidine (Table 1).

It has been established by NMR<sup>9</sup> and several other physical methods<sup>10</sup> that the piperidine system exists in a nearly perfect cyclohexane chair conformation. Two processes may be operative in this system: ring reversal and inversion of nitrogen. As the proton NMR spectrum of piperidine-3,3,5,5-d<sub>4</sub> consists of two fairly sharp peaks at temperatures above -10°, both processes must be fast on the NMR time scale.<sup>11</sup>

For 2-alkylsubstituted piperidines of both types 1 and 2, the  $\alpha$ -substituents are generally assumed to occupy the equatorial position in order to minimize steric interactions between the neighboring ring substituents. This has been confirmed by several studies using both <sup>1</sup>H NMR<sup>12</sup> and <sup>13</sup>C NMR,<sup>13-15</sup> and the same has been shown for  $\alpha$ -substituents in the piperazine ring.<sup>16</sup> It has also been documented<sup>10,11,14,15,17,18,20,21,23</sup> by several different methods that the Me group in N-methylpiperidines has a decided preference for the equatorial position, with an axial lone pair of electrons as shown in Fig. 2, where the Newman projection is drawn looking at the asymmetric center and along the C-N bond.

All the N-methylpiperidines shown in Table 1 have a positive C.E. below 200 nm. Although the maximum could not be reached in 95% alcohol solution, use of cyclohexane as solvent made it possible to observe the CD maximum at 204 nm for the 1-methyl-2-ethyl compound. Assuming a solvent shift of ca. 20 nm, this would place the CD maximum in alcohol at ca. 185 nm, in agreement with the fact that this CD maximum was not reached at 188 nm.

Table 2 gives the CD data for the compounds of type 2 possessing an NH group. These [with the exception of D-(+)-pipercoline (2, R = Me)] show a negative C.E. with a maximum at ca. 205 nm Using cyclohexane, a similar solvent shift (ca. 20 nm) to longer wavelengths (227 nm) was observed for the 2-Et compound. In the case of D-(-)-pipercolinol and D-(-)-conhydrine, intramolecular

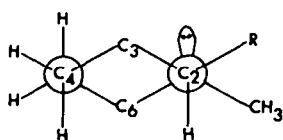


Fig. 2. Newman projection of 1.

H-bonding from the OH of the  $\alpha$ -OH substituted side-chain R to the amino group is probably responsible for the blue shift of the CD maximum (ca. 5 nm). This may be caused by the lowering of the ground state energy of the nonbonding orbital of nitrogen. The greater rigidity of the H-bonded structure also results in an increased value of the ellipticity for these two compounds.

The most favored conformation for the 2-substituted NH piperidines 2 will be that with an NH axial preference and an equatorial electron pair (Fig. 3). As in

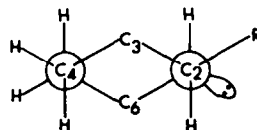


Fig. 3. Newman projection of 2.

piperidine itself<sup>10</sup> this form is favored both by the gauche effect<sup>24</sup> (the axial conformation maximizing the number of gauche interactions between the equatorial lone pair on N and the vicinal polar C-H bonds) and by attractive 1,3-axial N-H interactions.<sup>25</sup>

However, in 2-Me substituted piperidines, <sup>13</sup>C NMR evidence<sup>14-16</sup> indicates that both 2,6- and 2,5-dimethylpiperidine, and 2-methylpiperidine, possess an equatorial 2-Me group and an axial electron pair, as in quinolizidine.<sup>15,26</sup> No reasonable explanation of this anomaly has been advanced.

The chiroptical properties of D-(+)-pipercoline appear to confirm the NMR evidence. Not only does its CD have the opposite sign (Table 2), but also the CD maximum is shifted to shorter wavelengths (below 190 nm) in alcohol solution. This blue shift was also apparent in cyclohexane. It therefore appears to be the only compound in Table 2 which resembles in its CD properties the 1,2-disubstituted compounds of type 1 (Table 1). It should be noted that its N-nitroso derivative shows similar CD behavior (sign of C.E. opposite to that of all other  $\alpha$ -substituted N-nitroso compounds of the same configuration).<sup>19</sup> If compound 2, R = Me possesses an axial electron pair, it thereby falls into the group of 2-substituted piperidines shown in Fig. 2, explaining why its CD spectrum conforms in sign and wavelength with those shown in Table 1.

The CD maximum of 2-alkylpiperidines with an equatorial electron pair 2 is thus generally found at higher wavelength (205 nm) than that of those with an axial electron pair 1 (<200 nm). This also applies to 2-methylpiperidine which from other evidence is thought to have an axial electron pair, and in which  $\lambda_{max}$  is <200 nm for the CD. Although this means that the energy difference between the non-bonding orbital of nitrogen and the anti-bonding orbital of the C-N bond is greater for the  $n \rightarrow \sigma^*$  transition of that conformation in which the electron pair is axial compared with that in which the electron pair is equatorial, no theoretical interpretation of this fact is available.

Comparing Figs. 2 and 3, it can be seen that the relative positions of the lone pair electrons and the  $\alpha$ -substituent R are opposite for the two cases. In Fig. 2, if one draws an arrow from the lone pair to the  $\alpha$ -substituent, using the pathway with smaller dihedral angle, it traces out a clockwise (positive) screw sense, while in Fig. 3, it produces a counter clockwise (negative) screw sense. Empirically, for compounds of

absolute D-configuration, these screw senses may be correlated with the signs of the Cotton effect, i.e. a clockwise screw sense of the helicity indicating a positive Cotton effect, and a counter clockwise screw sense a negative Cotton effect.

It is of interest that, in spite of the fact that compounds of type 1 and 2 gave oppositely-signed CD maxima for the same absolute configuration (Tables 1 and 2), all compounds of the L-series give negative plain ORD curves below 225 nm in alcohol<sup>4,7</sup> whether they are of type 1 or 2. It should be noted that the ORD curve of L-(−)-coniine (R) in water shows a weak but distinct positive C.E. in the 200 nm region, confirming the positive CD maximum found at the same wavelength.<sup>22</sup> Thus, the absolute configuration of L-(−)-2-ethylpiperidine (R) was correctly established<sup>19</sup> by comparison of its ORD spectrum with L-(−)-2-methylpiperidine (R) as reference compound. The sign of the CD maximum of 1 and 2 in the 200 nm region, corresponding to the  $n \rightarrow \sigma^*$  transition of nitrogen, is therefore governed by the dihedral relationship between the lone electron pair on N and the  $\alpha$ -substituent R, and is related to the screw sense of the helicity in the manner shown above. Therefore, assuming the preferred equatorial position of the sidechain R in both 1 and 2, it will be the axial or equatorial nature of the lone electron pair (i.e. the conformation) which will be the deciding factor in the helicity and hence in the sign of the CD. While the CD is conformation-dependent, the ORD curve is the result of the summation of the total ( $\sigma \rightarrow \sigma^*$ ) rotational contributions below 200 nm, to which the lone pair of N does not contribute significantly, and in alcohol therefore appears to be independent of conformational changes.

#### EXPERIMENTAL

The CD and ORD measurements were carried out on a Roussel-Jouan Mark II dichrograph and on a Jasco ORD-CD5 at room temp. CD values are recorded as molecular ellipticity units [ $\theta$ ] and are given only for maxima or the lowest wavelengths measured.

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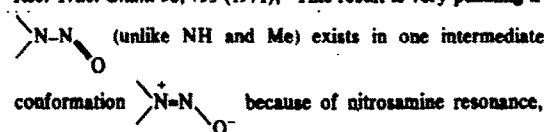
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and could involve some non-planarity of the N-NO group.

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