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CHIROPTICAL PROPERTIES OF 2-SUBSTITUTED PYRROLIDINES[1]

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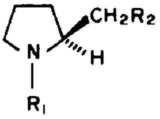
Abstract—The CD spectra of L-2-methylpyrrolidine, L-prolinol, and their N-methylated derivatives have been determined. As in the 2-substituted piperidines, N-methylation results in an inversion of the sign of the Cotton effects (CE). However, the sign of the long-wavelength CE does not follow the simple helicity rule found for 2-substituted piperidines, since the pyrrolidine ring is itself chiral and makes its own contributions to the observed CE's. The rotational contribution due to pyrrolidine ring chirality appears to be opposite in sign to and larger in magnitude than that due to the 2-substituent in both the secondary and the tertiary amines.

Saturated aliphatic and cyclic amines generally have a rather broad absorption band in the 200 nm region. Vapor phase measurements indicate that this band has its origin in two separate electronic transitions.[2,3] Thus, the gas phase spectrum of trimethylamine exhibits absorption bands at 227 nm (ϵ 900) and 199 nm (ϵ 3950),[2] hereafter referred to as bands I and II, respectively. However, the actual observation of two distinct absorption bands in this spectral region seems to be confined to only a few cases. For example, in triethylamine band I is completely obscured by band II, even in the gas phase,[2] and in pyrrolidine band I is present as a scarcely detectable shoulder.[3] However, 1 - methyl - 2 - n - butylpyrrolidine had λ_{max} 214 nm (ϵ 2300) in ether,[4] while N-methylpiperidine and quinolizidine showed λ_{max} 213 (ϵ 1600) and 215 nm (ϵ 3100) respectively in the same solvent.[4] Since bands I and II disappear in acid solution[2,3] the non-bonding electrons of introgen are involved in the corresponding transitions. In saturated aliphatic amines band I has been assigned[5] to a Rydberg transition ($n \rightarrow 3s$) whereas band II has been assigned either to an $n \rightarrow \sigma^*$ transition[3] or to a Rydberg $n \rightarrow 3p$ transition.[5]

Band I, although difficult to detect in the unpolarized UV spectrum, is readily observable in the CD spectra of chiral aliphatic and cyclic amines. (*R*)-3,3-Dimethyl-2-methylaminobutane in n-heptane showed a positive Cotton effect (CE) at 213 nm assigned to band I and a negative CE at 187 nm assigned to band II.[6] In the UV spectrum only the band at 187 nm was observed. The long-wavelength Cotton effect was shifted to 200 nm in methanol with a concomitant decrease in intensity,[6] an observation made also with 2-alkylpiperidines.[7] Although some ORD[8] and CD studies[7] on substituted piperidines have appeared, chiroptical data on pyrrolidines are extremely limited. A few 2-substituted pyrrolidines, investigated in hydrocarbon solvents, were found[9] to display a CD band around 220 nm, but attempts to observe this band in methanol solution were unsuccessful.[10]

It was therefore of interest to examine the chiroptical properties of 2-substituted pyrrolidines to establish if, as in the related 2-substituted piperidines,[7] N-methylation results in an inversion of the sign of the long-wavelength CE, and if the sign of this CE obeys the simple helicity rule found for the piperidine series.[7] The present study reports the CD spectra of L-2-methylpyrrolidine (**1**), L-prolinol (**2**) and their N-methyl derivatives (**3** and **4**) in 95% ethanol and (in two cases) also in hexane.



1: $R_1 = R_2 = H$
2: $R_1 = H, R_2 = OH$
3: $R_1 = CH_3, R_2 = H$
4: $R_1 = CH_3, R_2 = OH$

RESULTS AND DISCUSSION

The CD data for compounds **1–4** are given in Table 1.

The CD maxima of **1–4** in 95% ethanol are in the 194–203 nm region and can be ascribed to band I. However, in order to exclude the possibility that the 194 nm CD band of L-2-methylpyrrolidine (**1**) might have its origin in the absorption band II (observed[3] just below 200 nm for pyrrolidine in the gas phase), the CD spectra of **1** and of its tertiary analogue, **3**, were measured in hexane (Fig. 1). The 194 nm band of **1** showed the same solvent effect, i.e. a red shift of about 20 nm and a considerable increase in intensity[9] as the 203 nm band of **3** which indicates that these bands are correctly assigned to the long-wavelength absorption band (band I). This was moreover confirmed by the observation, in hexane,

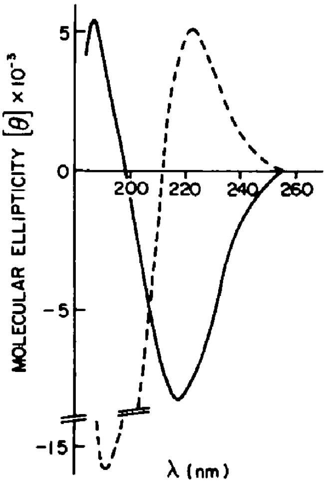


Fig. 1. Circular dichroism of L-2-methylpyrrolidine (—) and L-1,2-dimethylpyrrolidine (- - -) in hexane.

Table 1. Circular dichroism of NH-pyrrolidines and N-methylpyrrolidines

Compound[a]	$[\alpha]_D^b$	CD, $[\theta]^c$ (λ, nm)	
		95% Ethanol	Hexane
L-2-Methyl-pyrrolidine (1)	-20°	-4860 (194)	-8220 (217) +5450 (187)
L-Prolinol (2)	+2.9°	-1230(202)	
L-1,2-Dimethyl-pyrrolidine (3)	-65.4°	+3120 (203)	+5148 (223) -15840 (191)
L-1-Methyl-prolinol (4)	-35.3°	+3550 (202)	
D-Conanine[d] (9)		-2475 (212)	-3960 (225) +20460 (196)

[a] Compounds 1 and 3 have R-configuration, 2, 4 and 9 S-configuration.

[b] Measured in 95% ethanol (c 0.8 - 2.2).

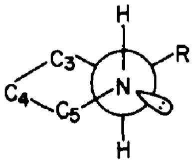
[c] Molecular ellipticity.

[d] Refers to the configuration at the 2-position in the pyrrolidine ring.

of a second CE of opposite sign at shorter wavelength (187 and 191 nm, respectively) which must clearly be assigned to band II. The CD spectra of the hydrochlorides in 95% ethanol followed the baseline down to 195 nm, showing that the observed CE's were due to the non-bonding electrons of nitrogen.

In order to minimize the eclipsing strain 5-membered rings usually assume different puckered forms as shown in the thorough studies of cyclopentane and its derivatives.[11] Cyclopentane itself has no single preferred ring-conformation and zero barrier to pseudorotation. However, in methylcyclopentane the increased torsional barrier about the bonds to the substituted carbon favors the C_s symmetric (envelope) conformation of the ring. In pyrrolidine the lower barrier for rotation about the C–N bonds relative to those about the C–C bonds favors the C_2 (half-chair) form with maximum puckering occurring at C_3 and C_4. Although these considerations on monosubstituted cyclopentanes were extended[12] to a 2-substituted pyrrolidine (proline) we do not feel that a similar approach[12] is applicable to a prediction of the ring conformations in compounds 1–4. However, on the basis of the above results,[11,12] it can be assumed that the pyrrolidine ring in 1–4 adopts a chiral rather than an achiral conformation. As in the case of the related 2-substituted piperidines, we will direct our attention to the possible conformations about the N–C_2 bond in 1–4.

For the secondary amines (1 and 2) four staggered conformations about the N–C_2 bond may be depicted depending on whether the nitrogen lone pair and the 2-substituent occupy a *trans*-(5 and 6) or a *cis*-(7 and 8) position relative to the main plane of the pyrrolidine ring. Conformers 6 and 8 should be less populated than 5 and 7 due to the 1,3-diaxial interactions of the quasi-axial R group and ring hydrogens. According to Brunck and Weinhold's analysis[13] of the forces responsible for internal rotation barriers in ethane-like molecules, the strength of the *trans*-interactions between the nitrogen lone pair and the C_2–C_3 and C_4–C_5 bonds in 5 may be greater (i.e. more stabilizing) than that of the corresponding *trans*-interactions between the lone pair and the C_2–H and C_5–H bonds in 7, suggesting that conformer 5 is more stable than 7.



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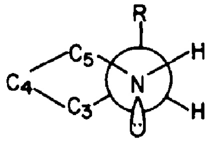

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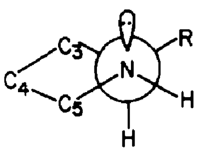

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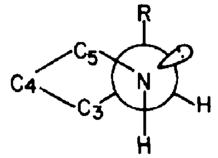

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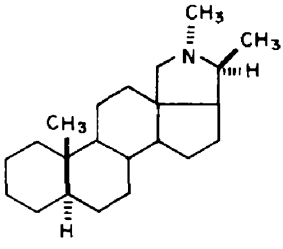
While nitrogen inversion in secondary amines generally is rapid, tertiary amines invert more slowly.[14] Thus the α-proton resonance of N-methylpyrrolidine separated into two groupings corresponding to protons *cis* and *trans* to the nitrogen lone pair at − 100°, whereas the NMR spectrum of pyrrolidine was unchanged down to − 150°.[14] In the case of conanine (9) the protons of the CH_2 group adjacent to nitrogen are non-equivalent at ambient temperatures and it was shown[15] that the preferred configuration of the nitrogen is such that the two neighboring methyl groups are *trans* to each other. Since 1,2-dimethylpyrrolidine shows a similar non-equivalence of the α-CH_2 protons[15] and since the volume requirement of the nitrogen lone pair is considerably smaller than that of a Me group[16] it can be assumed that in compounds 3 and 4 the N-Me group and the 2-substituent are also mainly *trans* to each other. Accordingly only two staggered conformations (10 and 11) about the N–C_2 bond need be considered for 3 and 4. Conformer 10



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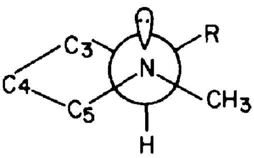
having the N-Me and the R-group in a quasi-equatorial position should be preferred over **11** with the same groups quasi-axial, due to the unfavorable 1,3-diaxial interactions expected if both the N-Me and the R group are axial.



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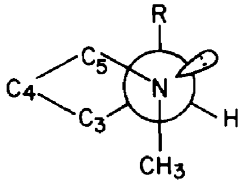

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The most noticeable feature in the CD spectra of **1–4** is the inversion of the sign of the Cotton effects for the secondary and the corresponding tertiary amines with the same (L)-configuration at C_2. The same observation was made for 2-alkylpiperidines and their N-Me analogues.[7] In the piperidine series the sign reversal of the CD was explained[7] by the different orientation of the nitrogen lone pair with regard to the 2-substituent in the secondary and tertiary amines. Moreover, a simple helicity rule could be deduced linking the sign of the observed CE to the screw sense of the helicity between the nitrogen lone pair and the 2-substituent. Thus positive helicity (right-handed screw) gave a negative CE and *vice versa.*[17,18]

The sign of the helicity between the symmetry axis of the lone pair lobe and the bond from the chiral carbon to the R-group in **5** and **10** is negative and positive, respectively. Since the observed CE's for the secondary amines (**1**, **2**) are negative and those for the tertiary amines (**3**, **4**) positive, the simple helicity rule found earlier[7] for the conformationally more defined (cyclohexane chair) piperidines apparently does not apply to the conformationally mobile pyrrolidines.

A possible explanation of the divergent behavior of the pyrrolidines is based on similar findings[19] among cycloalkanones. In cyclopentanones the chiroptical properties are considered to be associated mainly with twisting (and inherent chirality) of the cyclopentanone ring itself.[19] Substituent effects, predominating in cyclohexanones, are usually relatively small[19] in cyclopentanones.

It has been established that the piperidine system exists in a nearly perfect cyclohexane chair conformation.[20] 2-Substituted piperidines therefore have local C_s symmetry in the piperidine ring itself and the chiroptical behavior mainly reflects the perturbational influence of the 2-substituent on the nitrogen chromophore. On the other hand, in the pyrrolidines the ring is chiral (*vide supra*) and makes its own contribution to the observed CE. The results of the present study imply that the contribution due to ring chirality may be opposite in sign to and larger in magnitude than that due to the 2-substituent in both secondary and tertiary pyrrolidines.

The CD spectrum of conanine[21] (**9**, Table 1), having the D-configuration at C_2 in the pyrrolidine ring, is essentially enantiomeric to that of L-1,2-dimethylpyrrolidine, which suggests that the pyrrolidine rings in the two compounds have opposite chirality and hence that this chirality is linked to the absolute configuration at C_2. Therefore the R(= D) configuration assigned to the chiral center of the pyrrolidine ring in the Orchidaceae alkaloid dendroprimine[22,23] (5,7-dimethyloctahydroindolizine) on the basis of the negative CE ($[\theta]_{208} \sim -1600$ in methanol) observed for its degradation product (+)-1-methyl-2-(2′-methylpentyl)pyrrolidine[22] is in agreement with the results reported in the present study.

EXPERIMENTAL

CD measurements were carried out on a Jasco J-500A spectropolarimeter or a Roussel–Jouan Mark II dichrograph at 20°. Optical rotations at the sodium D line were measured in a 1-dm tube with a Perkin–Elmer 141 polarimeter.

L-2-*Methylpyrrolidine* **1** was obtained as previously described,[24] b.p. 96–97°, $[\alpha]_D^{20}$ −20° (*c* 0.8, 95% EtOH). Lit.[24] b.p. 96–97°, $[\alpha]_D^{22}$ −15.8° (*c* 1.0, H_2O).

L-*Prolinol* **2** was prepared as described,[9] b.p. 75–76.5°/3 mm, $[\alpha]_D^{25}$ +2.9° (*c* 1.9, 95% EtOH), yield 77%. Lit.[9] b.p. 69–72°/2 mm, $[\alpha]_D^{20}$ +3.4° (*c* 5.4, MeOH).

L-1,2-*Dimethylpyrrolidine* **3** was obtained from **1** as described,[9] b.p. 89–90°, $[\alpha]_D^{20}$ −77° (*c* 1.0, hexane), yield 69%. Lit.[9] b.p. 88–89°, $[\alpha]_D^{20}$ −63.4° (*c* 1.0, hexane).

L-1-*Methylprolinol* **4** was prepared from L-1-methylproline methyl ester as described[25] for the racemic compound, b.p. 66/12 mm, n_D^{20} 1.4689, $[\alpha]_D^{20}$ −35.3° (*c* 2.2, 95% EtOH), yield 53%.

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