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## Chiroptical Properties of 1-Methyl-1,2,3,4-tetrahydroisoquinolines. A Semiempirical Quadrant Rule Based on One-Electron Theory<sup>1</sup>

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**Abstract:** Chiroptical properties of 1-methyl-1,2,3,4-tetrahydroisoquinolines are reviewed. Previously proposed empirical quadrant and segment rules for these compounds are discussed and some of the difficulties involved in their application pointed out. A semiempirical quadrant rule based on one-electron theory is developed, which is independent of the substitution pattern in the benzene ring. It is shown to apply correctly to twelve 1-methyltetrahydroisoquinolines of known absolute configuration, and is used to assign this in two cases where it is unknown.

The 1,2,3,4-tetrahydroisoquinolines comprise an important group of natural products<sup>2</sup> because of their biogenetic relationships to the morphine alkaloids. Many of the simple tetrahydroisoquinolines bear a substituent (usually methyl or benzyl) in the 1 position, and are optically active. Although ORD and CD spectra have been reported<sup>3</sup> for some of these compounds, there is no simple method which allows a correlation of chiroptical properties with their absolute configuration. Several quadrant and segment rules have been proposed,<sup>4-6</sup> utilizing different approaches, but none has, so far, proved to be generally applicable and independent of the substitution pattern in the benzene ring. The reasons for this are briefly discussed, and a semiempirical rule based on one-electron theory is outlined below.

**Ultraviolet Spectra.** Aromatic compounds usually show three major transitions between 180 and 300 nm; two strong absorption bands appear near 180 and 200 nm; and a weak band, usually showing considerable fine structure, appears at ~260 nm. These three transitions are designated <sup>1</sup>B<sub>a</sub>, <sup>1</sup>L<sub>a</sub>, and <sup>1</sup>L<sub>b</sub>, respectively, in the Platt notation.<sup>7</sup> Since the intensity of an electronic transition is proportional to the square of the transition dipole moment vector, for the symmetric benzene itself the intensity of the <sup>1</sup>L<sub>b</sub> transition is zero and is thus said to be "forbidden". Vibrational perturbations cause small distortions in the molecule resulting in a small net transition dipole moment, which accounts for the low intensity actually observed. The <sup>1</sup>L<sub>a</sub> transition is only partially forbidden, and its intensity is therefore ~10 to 100 times higher. <sup>1</sup>B<sub>a</sub> is an elec-

tronically "allowed" transition and is of far stronger intensity.

Substitution on the benzene ring results in changes of both the intensities and positions of the absorption bands. The simple tetrahydroisoquinoline alkaloids usually bear oxygen substituents at positions 6 and 7, and occasionally at 5 and 8. This substitution pattern results in a big change of the UV spectrum in comparison with benzene itself. Generally, the <sup>1</sup>L<sub>b</sub> transition is shifted to 280 nm (20-nm bathochromic shift), while the <sup>1</sup>L<sub>a</sub> transition is moved to 235 nm (35-nm bathochromic shift). Both shifts are accompanied by an increase in the extinction coefficient and loss of fine structure.

Theoretical studies<sup>8,9</sup> showed that such changes of intensity are caused by substitution perturbations so that the lower energy transitions mix with the allowed <sup>1</sup>B<sub>a</sub> transition. The resultant electronic contribution to the intensity is of the same order of magnitude as the vibrationally induced <sup>1</sup>L<sub>b</sub> intensity. Therefore, the effect is proportionately much greater for the <sup>1</sup>L<sub>b</sub> transition than for the <sup>1</sup>L<sub>a</sub> transition. The wavelength shift, however, is considered to arise from two different sources.<sup>8,9</sup> The first-order contribution comes from interactions of the lower energy transitions (<sup>1</sup>L<sub>a</sub> or <sup>1</sup>L<sub>b</sub>) with a higher energy "charge-transfer" state of the substituent, i.e., overlap of the π orbital of benzene with the nonbonding p orbital of oxygen, and this effect is larger for <sup>1</sup>L<sub>a</sub> than for <sup>1</sup>L<sub>b</sub>. The second-order contribution again comes from the mixing of the <sup>1</sup>B<sub>a</sub> transition with the <sup>1</sup>L<sub>a</sub> or <sup>1</sup>L<sub>b</sub> transition. In most cases, the net result is that the <sup>1</sup>L<sub>a</sub> shift is greater than the <sup>1</sup>L<sub>b</sub> shift and this is what

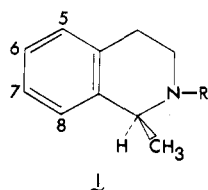
**Table I.** UV Spectra of 1-Methyl-1,2,3,4-tetrahydroisoquinolines in 95% Ethanol

Compd	Name of numbered compd	Substitution					$\lambda_{\max}$ , nm (log $\epsilon$ ) <sup>a</sup>						
		R	5	6	7	8							
1 HCl	1-Methyl-1,2,3,4-tetrahydroisoquinoline	H					208 (3.97)	251* (2.47)	256* (2.57)	264 (2.66)	267* (2.60)	271 (2.65)	285* (2.23)
2 HCl	1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline	Me					208 (3.98)	251* (2.25)	256* (2.38)	264 (2.48)	267* (2.39)	271 (2.44)	
3	Salsoline	H		OH	OMe		202 (4.94)	225 (4.25)	235* (4.02)	283 (3.84)			
4 HCl	<i>N</i> -Methylsalsoline	Me		OH	OMe		208 (4.59)	227 (3.85)	235* (3.74)	280 (3.35)	285 (3.36)		
5	Salsolidine	H		OMe	OMe		204 (4.57)	225 (3.85)	232* (3.82)	277* (3.44)	282 (3.53)	287 (3.53)	292* (3.44)
6 HCl	Carnegine	Me		OMe	OMe		203 (4.67)	224 (3.96)	232* (3.90)	275* (3.47)	282 (3.59)	286 (3.59)	291* (3.51)
8	<i>O</i> -Methylanhalonidine <sup>b</sup>	H		OMe	OMe	OMe	207 (4.61)	228* (3.97)	273 (3.09)	280 (3.11)			
7	Gigantine <sup>c</sup>	Me	OH	OMe	OMe		205 (4.8)						
10 HCl	Anhalonidine <sup>b</sup>	H		OMe	-OCH <sub>2</sub> O-		214 (4.67)	250* (3.43)	277 (2.99)	286* (2.94)			
11 HBr	Lophophorine <sup>b</sup>	Me		OMe	-OCH <sub>2</sub> O-		211 (4.63)	250* (3.47)	278 (3.03)	286* (3.98)			
12 HCl	Anhalonidine <sup>d</sup>	H		OMe	OMe	OH	230* (3.92)	271 (2.90)	280* (2.78)				
13 HCl	Pellotine <sup>e</sup>	Me		OMe	OMe	OH	230* (3.99)	271 (2.96)	281* (2.85)				
14 HCl	1,2-Dimethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline <sup>f</sup>	Me			OMe		199 (3.61)	227 (2.88)	279 (2.31)	287 (2.28)			

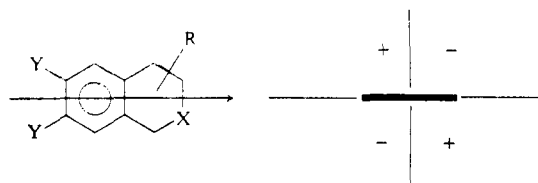
<sup>a</sup> Shoulder marked with asterisk. <sup>b</sup> Reference 10. <sup>c</sup> S. D. Brown, J. E. Hodgkins, J. L. Massingill, Jr., and M. G. Reinecke, *J. Org. Chem.*, **37**, 1825 (1972). <sup>d</sup> A. Bossi, F. Schenker, and W. Leimgruber, *Helv. Chim. Acta* **47**, 2089 (1964). <sup>e</sup> G. J. Kapadia, N. J. Shah, and T. B. Zalucky, *J. Pharm. Sci.*, **57**, 254 (1968). <sup>f</sup> R. P. K. Chan and J. C. Craig, unpublished work.

is observed here for the 1-methyltetrahydroisoquinoline alkaloids **1**. The total UV spectrum corresponds to an *o*-xylene chromophore ( $\lambda_{\max}$  210 nm ( $\epsilon$  8300) and 262.5 (300)) with the addition of oxygen substituents in the benzene ring (Table I).

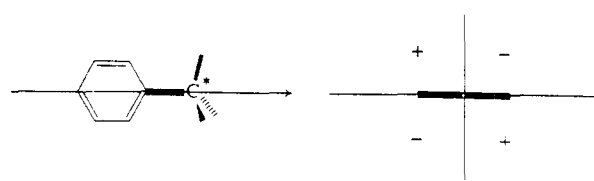
**CD and ORD Spectra.** On symmetry grounds, the <sup>1</sup>L<sub>b</sub> transition is considered as a formally forbidden transition. However, if the chromophore is situated in an asymmetric environment, the symmetry element is removed and the transition then becomes optically active. The CD spectra of 1-methyltetrahydroisoquinolines **1** are shown in Table II. CD



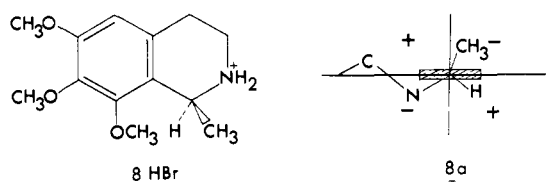
and ORD measurements on compounds with such an asymmetrically perturbed aromatic chromophore have led to the proposal of several empirical rules correlating Cotton effects with their absolute configurations. Kuriyama et al.<sup>4</sup> put forward a quadrant rule for the chiral <sup>1</sup>L<sub>b</sub> transition. The benzene chromophore is pictured along its C<sub>2</sub> axis of symmetry and the contribution of the group in each quadrant to the sign of the 290-nm Cotton effect is shown in Figure 1. However, it is clear that this rule applies only to those compounds symmetrically substituted at the 6 and 7 positions, i.e., those possessing C<sub>2</sub> symmetry. Kuriyama's rule therefore cannot be applied to compounds substituted at positions other than 6 and 7. De Angelis and Wildman<sup>5</sup> also proposed a quadrant rule. It is for the <sup>1</sup>L<sub>a</sub> transition and the compound under consideration has to have an asymmetric center adjacent to the aromatic ring (Figure 2) with the signs of the quadrants as shown. In the case



**Figure 1.** Quadrant rule of Kuriyama et al.<sup>4</sup> for <sup>1</sup>L<sub>b</sub> band CD.



**Figure 2.** Quadrant rule of De Angelis and Wildman<sup>5</sup> for <sup>1</sup>L<sub>a</sub> band CD.



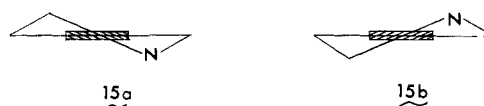
of (*S*)-(+)-*O*-methylanhalonidine hydrobromide (**8 HBr**), both the absolute configuration and conformation are known from x-ray data.<sup>10</sup> When the rule of De Angelis and Wildman is applied to this compound (**8a**), it predicts a negative Cotton effect for the <sup>1</sup>L<sub>a</sub> band, whereas the experimentally observed Cotton effect is positive from the CD spectrum (Table II). Similar discrepancies also occur in the case of other compounds, e.g. **3**, **4**, **5**, **6**, etc.

Table II. CD Spectra of 1-Methyl-1,2,3,4-tetrahydroisoquinolines in 95% Ethanol

Compd	Substitution				$[\alpha]_D$ , deg <sup>a</sup>	<sup>1</sup> L <sub>b</sub> band, [ $\theta$ ] <sub>max</sub> , nm	<sup>1</sup> L <sub>a</sub> band, [ $\theta$ ] <sub>max</sub> , nm				
	R	5	6	7				8			
<b>1</b> <sup>c</sup>	H				-66.2 <sup>b</sup>	+800 (273)	-2100 (221)				
<b>1</b> HCl <sup>c</sup>						+360 (272)	-1620 (219)				
<b>2</b> <sup>c</sup>	Me				-51	+1000 (273)	-9290 (220)				
<b>2</b> HCl <sup>c</sup>					-0.17	+320 (272)	-3180 (217)				
<b>2</b> MeI <sup>c</sup>					-2.7	+190 (269)					
<b>3</b> <sup>d</sup>	H	OH	OMe			+1910 (283)	+4210 (225), +3650 (235)				
<b>3</b> HCl									-27 <sup>e</sup>	+1800 (282)	+7020 (217), +5050 (235)
<b>4</b>	Me	OH	OMe			+1560 (280)	+2070 (220), +4150 (233)				
<b>4</b> HCl									+9.7	+1250 (282)	+5190 (213), +6220 (235)
<b>4</b> MeI									+10.3	+1400 (286)	+6090 (219), +10970 (235)
<b>5</b>	H	OMe	OMe			+1970 (281)	+3990 (220), +3990 (237)				
<b>5</b> HCl									-24 <sup>g</sup>	+1850 (279)	+6300 (215), +7760 (235)
<b>6</b>	Me	OMe	OMe			+2630 (280)	+8500 (200), +5100 (232)				
<b>6</b> HCl									+6 <sup>p</sup>	+2210 (280)	+8500 (212), +13 600 (234)
<b>6</b> MeI									+9.8	+2520 (280)	+6000 (212), +13 180 (235)
<b>7</b>	Me	OH	OMe	OMe		+28.7 <sup>i</sup>	-310 (276)				
<b>7</b> HCl									+8	+210 (283)	+870 (240)
<b>8</b>	H	OMe	OMe	OMe		+24 <sup>j</sup>	+130 (280)				
<b>8</b> HCl									+34.6	+170 (285)	+2930 (233)
<b>9</b> <sup>k</sup>	Me	OMe	OMe	OMe		+16	+310 (277)				
<b>9</b> HCl									+80 (284)	+930 (233), -100 (246)	
<b>10</b>	H	OMe	-OCH <sub>2</sub> O-			-340 (275)	-4910 (221) +2240 (240)				
<b>10</b> HCl									+110 (290)	-640 (275)	+3540 (240)
<b>11</b>	Me	OMe	-OCH <sub>2</sub> O-			-34.7 <sup>m</sup>	-450 (277)				
<b>11</b> HCl									+50 (290)	-920 (282)	+6430 (242.5)
<b>12</b> <sup>q</sup>	H	OMe	OMe	OH		-21.2 <sup>o</sup>	+9810 (225), -3680 (253)				
<b>12</b> HCl <sup>q</sup>									-0.7 <sup>o</sup>	-1340 (278)	+2100 (235)
<b>13</b> <sup>q</sup>	Me	OMe	OMe	OH		-1.1 <sup>o</sup>					
<b>13</b> HCl <sup>q</sup>									-0.7 <sup>o</sup>		
<b>13</b> <sup>r</sup>	Me	OMe	OMe	OH		-11.1 <sup>o</sup>	-1020 (277)				
<b>13</b> HCl <sup>r</sup>									-7.8 <sup>o</sup>	-1020 (277)	-1825 (235!)
<b>14</b> <sup>c</sup>	Me		OMe			-7.2	+510 (271)				
<b>14</b> HCl <sup>c</sup>									+500 (277)	-415 (230!)	
									-185 (290)		
									+510 (275)		
				-230 (289)	-740 (232!)						

<sup>a</sup> Rotations were measured in 95% ethanol (*c* 0.1–1.0) unless otherwise indicated. All compounds except **12** and **13** have the *S* configuration. <sup>b</sup> Lit.<sup>s</sup> -71.5°. <sup>c</sup> Table I, ref. *f*. <sup>d</sup> Natural (*R*)-(+)-salsoline was used; the (-) enantiomer is reported here for consistency. <sup>e</sup> Measured in H<sub>2</sub>O (lit.<sup>t</sup> 40° (H<sub>2</sub>O)) for the (*R*)-(+)-compound. <sup>f</sup> Lit.<sup>t</sup> -63°. <sup>g</sup> Lit.<sup>u</sup> -23.4°. <sup>h</sup> Lit.<sup>u</sup> -25°. <sup>i</sup> Lit.<sup>w</sup> 27.1° (CHCl<sub>3</sub>). <sup>j</sup> Measured in MeOH (lit.<sup>v</sup> 20.5°). <sup>k</sup> *O*-Methylpeltoline. <sup>l</sup> Lit.<sup>x</sup> -56.3° (CHCl<sub>3</sub>). <sup>m</sup> Lit.<sup>x</sup> -47.3° (CHCl<sub>3</sub>). <sup>n</sup> Lit.<sup>x</sup> -16.3° (H<sub>2</sub>O). <sup>o</sup> Compounds **12** and **13** have the *R* configuration. <sup>p</sup> Lit.<sup>u</sup> 6.6°. <sup>q</sup> Natural.<sup>32</sup> <sup>r</sup> From natural anhalonidine. <sup>s</sup> L. Leithe, *Monatsh. Chem.*, **53**, 960 (1929). <sup>t</sup> N. Proskurnina and A. Orekhoff, *Bull. Soc. Chim. Fr.*, [5] **4**, 1265 (1937). <sup>u</sup> A. R. Battersby and T. P. Edwards, *J. Chem. Soc.*, 1214 (1960). <sup>v</sup> E. Späth and J. Bruck, *Chem. Ber.*, **70**, 2446 (1937). <sup>w</sup> J. E. Hodgkins, S. D. Brown, and J. L. Massingill, Jr., *Tetrahedron Lett.*, 1321 (1967). <sup>x</sup> E. Späth and F. Keszler, *Chem. Ber.*, **68**, 1663 (1935).

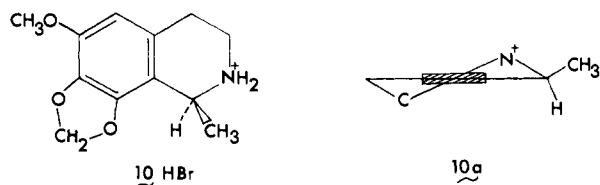
Snatzke et al.<sup>6</sup> took a somewhat different approach. They rationalize the experimental results for the <sup>1</sup>L<sub>b</sub> band by taking into account both the effect of the substitution pattern of the benzene ring and chiral contributions from the second and third spheres.<sup>6</sup> For a tetrahydroisoquinoline, the aromatic ring forms the first sphere (achiral), the piperidine ring forms the second, and groups or rings attached to this second sphere comprise the third sphere. The piperidine ring can assume two conformations referred to,<sup>6</sup> respectively, as P helicity (**15a**) and M helicity (**15b**). When the benzene ring is not further substituted, P helicity gives rise to a positive, and M helicity to a negative sign of the <sup>1</sup>L<sub>b</sub> CD band.<sup>6</sup> To determine the influence of the substituents in the benzene ring on the CD sign,



spectroscopic moments<sup>11</sup> are used in this treatment as illustrated in Figure 3. This shows the relationship<sup>12</sup> between the direction of the sum of the spectroscopic moments and the sign of the sectors for third sphere contributions, together with the sign of the second sphere contribution for P helicity.

As both the absolute configuration and conformation of (*S*)-(-)-anhalonine hydrobromide (**10** HBr) have been established by x-ray crystallography,<sup>10</sup> a test of Snatzke's rule

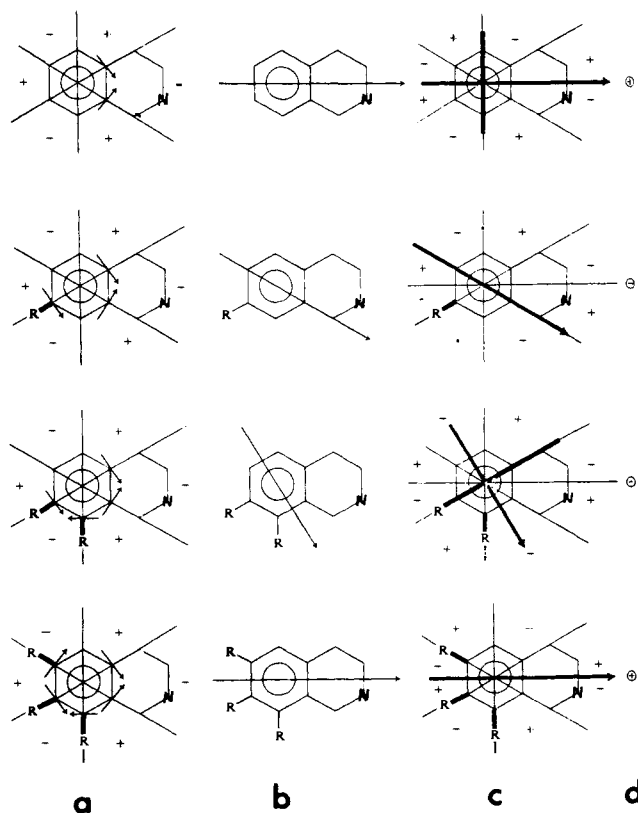
is possible on the basis of actual experimental data. Compound **10** HBr is a 6-methoxy-7,8-methylenedioxy-substituted tetrahydroisoquinoline. As shown in Figure 3, since the second sphere of **10** HBr adopts an M helicity (**10a**), it should lead to



a negative CD for the  $^1L_b$  band. The third sphere contribution, however, leads to a positive CD for that band. The net result thus depends upon the relative importance of these two opposite contributions. As in the case of the analogous tetrahydropalmatine,<sup>13</sup> the prediction of sign of the  $^1L_b$  CD band is complicated because of the presence of two oppositely signed rotational contributors in the molecule, and, without knowing the experimental result, it is impossible to make an unambiguous assignment. In fact, the experimental result shows **10** HBr to have a negatively signed  $^1L_b$  CD band (Table II). There appears therefore to be no consistent basis for assigning the relative importance of the spheres when they have oppositely signed contributions, to determine the sign of the resultant CD where it is unknown, and, although the approach of Snatzke et al. is an interesting one, it does not as yet permit an unequivocal assignment of the sign of the Cotton effect in such cases. What is required is a simple rule which would permit unequivocal sign assignment of tetrahydroisoquinolines independent of the substitution pattern in the benzene ring if the conformation is known. Such an approach is described below.

**Theoretical Background.** Optically active chromophores can generally be assumed to belong to one of the two limiting forms:<sup>14-16</sup> (i) inherently dissymmetric chromophores, or (ii) asymmetrically perturbed symmetric chromophores. However, as electron exchange between a chromophore and its surroundings becomes appreciable, the chromophoric system is accordingly enlarged. Thus, the latter limiting case smoothly passes over to the former through charge transfer and appreciable overlap between chromophore and environment. Examples of inherently dissymmetric chromophores are hexahelicene and certain other conjugated double-bond systems.<sup>17</sup> For the asymmetrically perturbed symmetric chromophores, two theories evolved at an early date, the coupled oscillator<sup>18</sup> and the one-electron<sup>19</sup> theories. In the coupled oscillator, or polarizability, theory the individual electric transition moments of different groups of the molecule are coupled by dipole-dipole interactions. For effective coupling one requires either large transition moments (strong absorption bands) or virtual contiguity of the two groups. Therefore, the Cotton effects of strong absorption bands are conventionally treated by this theory. The one-electron theory, on the other hand, proposes a model for optical rotation to arise from the static asymmetric perturbing field of the rest of the molecule (atoms other than the chromophore itself) and not from a reciprocal coupling mechanism. The application of this model is best known for its successful treatment of the optically active ketone transition, thus providing the best accepted theoretical basis for the ketone octant rule.<sup>20</sup>

As mentioned above, the aromatic  $^1L_b$  transition is a weak transition and the application of the coupled-oscillator theory is thus not suitable in the present case. Condon, Altar, and Eyring, in their original work, made an attempt to calculate the rotatory power of the phenyl band in methylphenylcarbinol nitrite.<sup>19</sup> This provides the first example applying the one-electron theory to the aromatic chromophore. The good agreement obtained between theory and experiment<sup>19</sup>



**Figure 3.** Effect of substitution pattern on sign of  $^1L_b$  band CD of tetrahydroisoquinolines:<sup>6</sup> a, Platt polarization diagrams; b, direction of sum vector of spectroscopic moments; c, sector rules for third sphere contributions; d, sign of CD for second sphere contributions for P helicity of piperidine ring.

prompted us to use a similar approach in exploring the Cotton effect of the  $^1L_b$  transition of the 1-substituted tetrahydroisoquinoline alkaloids which (like methylphenylcarbinol nitrite) have an asymmetric center adjacent to the benzene ring.

**One-Electron Theory.** Following the successful treatment of atomic spectra principally from one-electron transitions, the same procedure is usually adopted in interpreting most molecular spectra. Optical activity, being a phenomenon closely related to electronic transitions, may therefore be treated in the same way, i.e., using the one-electron theory of optical activity. The main features in this theory are that an electronic transition occurs in a fairly well-localized group in the molecule (the chromophoric group) and the electron which makes a transition is moving in a force field principally due to the immediate atoms to which it belongs and secondarily due to the fields set up by the effective charge distributions of the other atoms in the molecule. It is this secondary force field due to perturbation by the neighboring atoms which is responsible for the optical activity. The simplest model for discussion would be an anisotropic oscillator assuming an electron moves in a dissymmetric potential field in which the potential energy as a function of Cartesian coordinates  $X$ ,  $Y$ , and  $Z$  is given by eq 1.

$$V = \frac{1}{2}k_1X^2 + \frac{1}{2}k_2Y^2 + \frac{1}{2}k_3Z^2 + AXYZ \quad (1)$$

This is the equation of a twisted polarization ellipsoid.<sup>19</sup> The term in  $A$  is what produces the necessary dissymmetry. It is directly proportional to rotational strength and has sign and value defined as in eq 2

$$A = \frac{5}{2}e \sum_s e_s \frac{X_s Y_s Z_s}{R_s^7} \quad (2)$$

( $X_s$ ,  $Y_s$ ,  $Z_s$ ) is the position of a perturbing atom,  $s$ , with point charge  $e_s$  located at the center of each atom and  $R_s = (X_s^2 +$

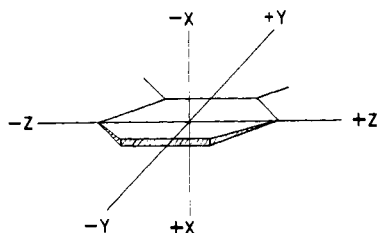
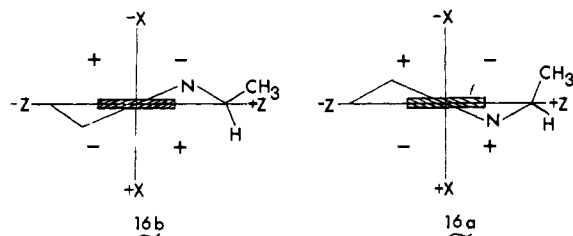


Figure 4. Coordinate system for calculation of sign of  $^1L_b$  CD band.

$Y_s^2 + Z_s^2)^{1/2}$ . Following the detailed discussion in ref 19, it is clear that the most important effects of the vicinal perturbers are the removal of the axes of symmetry and of the planes of symmetry possessed by the unperturbed polarization ellipsoid. For formal calculations, one has to know the angle of twist of the principal axes of this ellipse. In comparison to other chromophores, the  $\pi$  electrons of benzene are actually much more stiffly bound in the direction at right angles to the ring than in the other two directions, and will offer a certain amount of resistance to the tilting of its principal axes by the vicinal perturbers. The resultant tilting (while still of importance in causing the optical activity) is therefore small enough to be ignored for an approximate calculation of  $A$  by eq 2. Therefore one can take the three axes as they are in the unperturbed state and reduce the problem to the determination of  $A$  directly. (The same approximation has been used in all previously discussed empirical rules,<sup>4-6</sup> although this has not been explicitly stated.) Since the magnitude of vicinal interactions between atoms due to point charges is always small and falls off rapidly with increasing distance, it is clear that only first-order, i.e., coulombic, contributions to optical rotation are important. Atoms more than two bonds away from the asymmetric center may therefore be neglected in the calculation of  $A$  without affecting its qualitative picture. A right-handed coordinate system is set up with the origin at the center of the benzene ring (Figure 4). Vicinal charges on every atom involved, i.e., adjacent to the asymmetric center, may be calculated in such a way as to represent the observed values of the static dipole moments arising from each bond. The so-called "bond charge" has been defined<sup>21</sup> as a quantity which when multiplied by bond length gives the value of bond moment, and summation of all the bond charges relating to one atom gives the point charge on that atom. Once the coordinates and point charges are known,  $A$  can be determined easily according to eq 2.

For all the simple tetrahydroisoquinoline alkaloids studied, the chiral moiety (piperidine ring) always falls in the octants composed of  $+Y$  coordinates of Figure 4. From a molecular model, the piperidine ring may assume two conformations **16a** and **16b** with an opposite sense of helicity relative to the ben-



zene ring. When these two conformations are projected in the coordinate system provided, C(1) and C(4) are in the  $YZ$  plane; therefore they do not contribute to the optical activity in either case. The exclusion of possible contributions from C(1) and C(4) simplifies the calculation to a great extent; yet the remaining computation, especially the portion which concerns the calculation of  $XYZ/R^7$  for every atom, is still very time consuming. However, if it is only desired to obtain the sign of  $A$  in order to assign the absolute configuration or confor-

Table III. Calculation of Bond Charges from Bond Length and Bond Moment

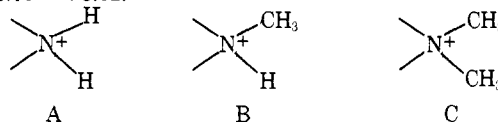
Bond	Bond length, Å	Bond moment, D	Bond charge, $e^a$
+ -			
H-C	1.09	0.4	0.07
C-N	1.49	0.45	0.06
H-N	1.00	1.31	0.27
$C_{sp^3}-C_{sp^3}$	1.54	0	0

<sup>a</sup> Bond charge ( $e$ ) = bond moment (D)/bond length (Å)  $\times 1/4.8$  esu where  $e = 4.8 \times 10^{-10}$  esu and  $D = 10^{-18}$  esu cm =  $10^{-10}$  esu Å.

Table IV. Calculation of Point Charge

Point charge for $>N-H^a$		Point charge for $>N-b$	
H(1)	+0.07	H(1)	+0.07
C(9)	$-0.07 \times 3 = -0.21$	C(9)	$-0.07 \times 3 = -0.21$
H(9)	+0.07	H(9)	+0.07
N	$-0.06 - 0.06 - 0.27 = -0.39$	N	$-0.06 - 0.06 - 0.06 = -0.18$
H(N)	+0.27	C(N)	$0.06 - 0.07 \times 3 = -0.15$
C(3)	$+0.06 - 0.07 \times 2 = -0.08$	C(3)	$+0.06 - 0.07 \times 2 = -0.08$

<sup>a</sup> In the case of A only the point charge of N is changed  $+1 - 0.39 = +0.61$ . <sup>b</sup> In the case of B or C only the point charge of N is changed  $+1 - 0.18 = +0.82$ .



mation of a compound, eq 2 may be simplified for this purpose with two assumptions. (i) Atoms two bonds away from the asymmetric center are of negligible significance in causing the optical activity, and may therefore be neglected from consideration. (ii) If a formal charge,  $+e$ , is put on the N atom as in the salt or quaternary salt,  $X_s Y_s Z_s / R_s^7$  may be assumed to be of about the same magnitude for every atom under consideration. This numerical factor can then be taken out of the summation sign and eq 2 is reduced to eq 3

$$A \approx \frac{5}{2} e \frac{XYZ}{R^7} \sum_s e_s x_s^i y_s^j z_s^k \quad (3)$$

where  $x^i$ ,  $y^j$ , and  $z^k$  are unit coordinates with value  $\pm 1$  (see Table V). From the available data on bond moment<sup>22</sup> and bond length (Table III), the point charge on every atom can be calculated (Table IV). As indicated in Table IV, the substitution pattern of the N atom has a definite effect on the charge distribution. Combining these point charge data and coordinate dispositions of **16a** and **16b**, the sign of the  $^1L_b$  CD band can now be found by simple manipulation of  $\sum_s e_s x_s^i y_s^j z_s^k$  (Table V). The results show that, with similar charge distribution around the asymmetric center, the opposite sense of helicity of the heterocyclic ring from the plane of the benzene ring thus leads to the opposite sign of the  $^1L_b$  CD band.

It is known from x-ray data<sup>10</sup> that **8** HBr has the P conformation **16a** in the solid state. According to the prediction (Table V), this compound should have a positive CD for the  $^1L_b$  band. This is exactly what is observed in CD measurements (Table II). When adopting the P conformation, the 1-methyl group is in the pseudoaxial position which, with the presence of 1,3-diaxial steric interactions, would generally be less favored than the pseudoequatorial one. However, there are two other factors that would counterbalance this situation: (i) the steric interaction between a C(8) *O*-methyl and a C(1) methyl group is considerably greater; (ii) in occupying the pseudoaxial position, the C(1) methyl leaves the charged N more accessible

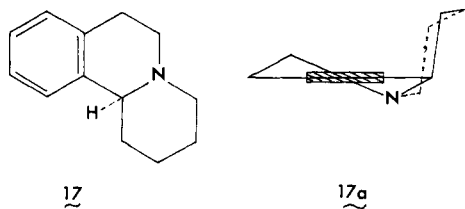
Table V. Calculation of Sign of  $^1L_b$  CD Band

A. For Secondary Amine Salts $>NH_2^+$							
Sign of $A$ for M helicity				Sign of $A$ for P helicity			
$s$	$e_s$	$x_s^i y_s^j z_s^k$	$e_s^i x_s^j y_s^k z_s^l$	$s$	$e_s$	$x_s^i y_s^j z_s^k$	$e_s^i x_s^j y_s^k z_s^l$
H(1)	+0.07	+1	+0.07	H(1)	+0.07	+1	+0.07
C(9)	-0.21	-1	+0.21	C(9)	-0.21	-1	+0.21
3[H(9)]	+0.21	-1	-0.21	3[H(9)]	+0.21	-1	-0.21
N <sup>+</sup>	+0.61	-1	-0.61	N <sup>+</sup>	+0.61	+1	+0.61
C(N <sup>+</sup> )	+0.27	-1	-0.27	H(N)	+0.27	+1	+0.27
C(3)	-0.08	-1	+0.08	C(3)	-0.08	+1	-0.08
$\sum_s e_s^i x_s^j y_s^k z_s^l = -0.73$				$\sum_s e_s^i x_s^j y_s^k z_s^l = +0.87$			
Result Negative CD				Result Positive CD			
B. For Tertiary Amine Salts $>NHMe^+$ and Quaternary Salts $>N(Me)_2^+$							
Sign of $A$ for M helicity				Sign of $A$ for P helicity			
$s$	$e_s$	$x_s^i y_s^j z_s^k$	$e_s^i x_s^j y_s^k z_s^l$	$s$	$e_s$	$x_s^i y_s^j z_s^k$	$e_s^i x_s^j y_s^k z_s^l$
H(1)	+0.07	+1	+0.07	H(1)	+0.07	+1	+0.07
C(9)	-0.21	-1	+0.21	C(9)	-0.21	-1	+0.21
3[H(9)]	+0.21	-1	-0.21	3[H(9)]	+0.21	-1	-0.21
N <sup>+</sup>	+0.82	-1	-0.82	N <sup>+</sup>	+0.82	+1	+0.82
C(N <sup>+</sup> )	-0.15	-1	+0.15	H(N)	-0.15	+1	-0.15
C(3)	-0.08	-1	+0.08	C(3)	-0.08	+1	-0.08
$\sum_s e_s^i x_s^j y_s^k z_s^l = -0.52$				$\sum_s e_s^i x_s^j y_s^k z_s^l = +0.66$			
Result Negative CD				Result Positive CD			

for the expected solvation from the polar solvent used (95% EtOH) than it would be in the pseudoequatorial position where there is appreciable hindrance from H(1) and H(3). (Both the salt and quaternary derivatives would be expected to be solvated by the strong Lewis base solvent.) The overall result must be that the conformation shown is the most stable one for **8** HBr.

The HCl salts or methiodides of the tetrahydroisoquinoline alkaloids **1–9** and **14** shown in Table II are all known to have the *S* configuration and, like **8** HCl, all show a positive CD at 280 nm. They may therefore be assumed to possess the same, i.e., *P*, helicity as compound **8** HCl. The pseudoaxial conformation of the C(1) substituent in these tetrahydroisoquinoline alkaloids thus resembles that also found in the corresponding tetralins.<sup>23–25</sup>

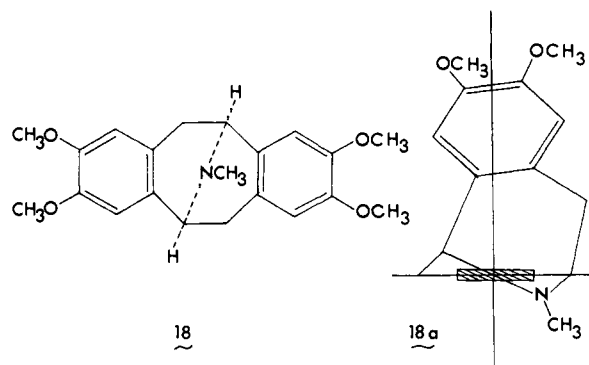
(*S*)-(-)-Benzoquinolizidine hydrochloride (**17**), a cyclic



analogue of 1,2-dimethyltetrahydroisoquinoline, also exhibits a positive  $^1L_b$  CD band at 280 nm.<sup>26</sup> This suggests a *cis* fusion at the ring junction and, of the two possible *cis* forms, it is the one with *P* helicity (**17a**) that is more favored when the possibility of solvation from the polar solvent used is considered.

The alkaloid (*S*)-(-)-argemonine (**18**) possesses two exactly identical chromophores which are the same as that of the simple tetrahydroisoquinoline alkaloids. It has been shown<sup>27</sup> to exhibit a positive CD for the  $^1L_b$  band at 280 nm. As NMR data<sup>28</sup> have confirmed that the piperidine ring possesses the *P* helicity (**18a**), this serves as another example of the existence of *P* conformation in the piperidine ring.

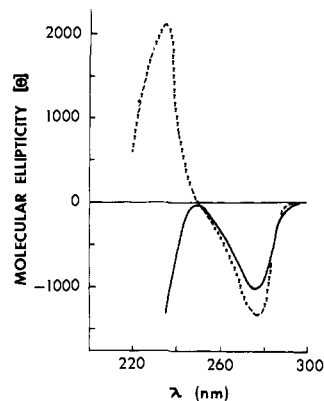
Molecular orbital calculations<sup>29</sup> have shown that there are two equivalent MOs localized on the ether oxygen atom (two lone-pair electrons), each projecting above and below the



C–O–C plane. In **10** HBr, the methylenedioxy linkage exerts such a strain that changes in bond angles and bond lengths of the benzene ring are caused, so that the ring is distorted, with *M* helicity (**16b**). From the x-ray data of **10** HBr, a negative  $^1L_b$  CD band can be predicted for the *S* configuration. The data shown in Table II verified that both **10** and **11** have the same negative CD owing to the methylenedioxy linkage at C(7) and C(8).

The above results indicate that most 1-methyltetrahydroisoquinoline alkaloids (specifically compounds **1–9** and **14**) normally exist in the *P* helicity. For these, Table V predicts that the absolute *S* configuration will correspond to a positive sign of the  $^1L_b$  CD band for the protium salt or quaternary salt. Such a conclusion is independent of the oxygenation pattern of the benzene ring and the position of the substituents. In the case of the 7,8-methylenedioxy compounds **10** and **11**, x-ray data indicate, and CD measurements confirm, that the compounds have *M* helicity with corresponding sign inversion of the  $^1L_b$  CD band.

**Absolute Configuration Assignment for Natural Anhalonidine and Pellotine.** In his original work, Späth reported<sup>30</sup> that the alkaloids anhalonidine and pellotine obtained from peyote were optically inactive. Later, Späth and Keszler<sup>31</sup> synthesized a pellotine sample with slight optical activity after tartaric acid resolution, which, however, rapidly racemized on standing. This suggests that the alkaloids may be optically active in the



**Figure 5.** CD spectra of (—)-anhalonidine hydrochloride (—) and (---)-pellotine hydrochloride (---).

plant but racemize during the extraction procedure. So far, optically active anhalonidine and pellotine have not yet been reported, and therefore no absolute configuration assignments have been made for these compounds. Out of a number of samples of natural anhalonidine and pellotine which we investigated, one preparation (isolated from the plant by Dr. Ara Paul, University of Michigan, by means of ion-exchange chromatography)<sup>32</sup> proved to be optically active. Natural (—)-anhalonidine hydrochloride showed a strong negative CD signal at 280 nm (Figure 5). Natural (—)-pellotine, however, possessed a weak rotation of only  $-1.1^\circ$  at the sodium D line. In order to obtain a better result for configurational assignment, natural anhalonidine was methylated with  $\text{NaBH}_3\text{CN}/\text{HCHO}$  to give (—)-pellotine,  $[\alpha]_D -11.1^\circ$ , showing a negative CD at 280 nm (Figure 5). This indicated that the sample of natural pellotine was only 9–10% optically pure, having racemized to an appreciable extent during isolation. Nevertheless, the conversion of natural (—)-anhalonidine into (—)-pellotine is sufficient to establish the configurational identity of these two alkaloids, here described for the first time in optically active forms. From the negative sign of the CD at 280 nm, both belong to the *R* series (assuming them to have the normal *P* conformation, analogous to compounds 1–9 and 14).

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