PROTOBERBERINE ALKALOIDS: CHIROPTICAL PROPERTIES AND ABSOLUTE CONFIGURATION[1]

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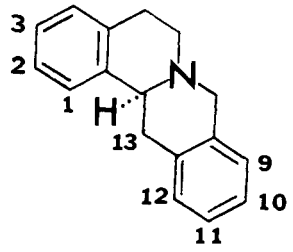
ABSTRACT.—Chiroptical properties of tetrahydroprotoberberines are reviewed. Previously proposed chirality rules for these compounds are discussed and difficulties in their application noted. Examination of the circular dichroism (cd) spectra of nine tetrahydroprotoberberine alkaloids and their hydrohalide salts shows that cd spectra can be used to distinguish between the two major substitution patterns and that the absolute configuration of the alkaloids can be assigned (independent of the substitution pattern) directly from the sign of the 280–290 nm Cotton effect of the hydrohalide salts. In addition, the sign of the intense 206–210 nm Cotton effect correlates directly with the absolute configuration and is independent of substitution pattern and of pH.

Tetrahydroprotoberberine alkaloids **1** occur widely in nature (1) and are usually oxygenated in the 2,3,9,10- or 2,3,10,11-positions, although a hydroxyl or methoxyl group may also be present at C–1.

The absolute configuration of tetrahydroprotoberberine alkaloids has been determined by chemical correlations (2) and may generally be inferred by comparison of optical rotations (3), since (for compounds of the same configuration) changes in the position of the oxygen substituents in the aromatic rings of **1** have little or no effect on the specific rotation at the sodium D line (3).



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However, to obtain maximum information concerning the influence of the substitution pattern on the sign of the Cotton effects (CE's) for a given absolute configuration, optical comparisons in a system of this complexity are best carried out in the absorption region of the compounds by means of optical rotatory dispersion (ord) or circular dichroism (cd) techniques which depend inherently upon the orientation of the electric transition dipoles of the molecules.

The ord (4) and cd (5–7) spectra of a few protoberberines have been reported. The most detailed study is that of Snatzke *et al.* (7). According to their treatment, the second sphere (comprised of the nonaromatic rings condensed with the benzenes) is chiral, and its chirality determines the sign of the CE associated with the ^1L_b band (7). In general, P helicity of the nonaromatic ring leads to a positive, and M helicity leads to a negative CE (8).

[1]Publication No. 31 in the series *Optical Rotatory Dispersion and Absolute Configuration.*

TABLE 1. Circular dichroism of tetrahydroprotoberberines in 95% ethanol.

Compound	Substituent at position						[α]D deg.[d]	Alkaloid	CD maxima: λ nm ([θ]·10⁻³)		
	1	2	3	9	10	11					
2.....		OMe	OMe	OMe	OMe		−291	Tetrahydropalmatine	280(+ 1.5)	232(−28.1)	206(−187.5)
2.HCl....									280(− 1.5)	230(−25.8)[a]	260(−182)
3.....		-O CH_2O-		-O CH_2O-			+310[e]	Stylopine	285(+ 0.96)	236(−19.2)	207(−150)
3.HCl....									288(− 2.3)	237(−15.0)	208(−122.8)
4.....		OH	OMe	OH	OMe		−295	Scoulerine	285(+ 1.9)	231(−18.4)	207(−172.2)
4.HCl....									280(− 1.5)	227(−16.2)[b]	210(−140.5)
5.....		OMe	OMe	OMe	OMe	OH		Stepharotine	280(− 1.8)	233(−38.8)	208(−125.6)
5.HBr....							−210		278(− 1.9)	233(−28.4)	209(−160)
6.....	OH	OMe	OMe	OMe	OMe		−285	Capaurine	280(− 4.7)	235(−12.3)[c]	208(−137.5)
6.HCl....									279(− 6.3)	233(−12.3)[c]	208(−169)
7.....	OH	OMe			OMe	OMe	−303	Caseadine	284(− 4.4)		207(−196)
7.HCl....									285(− 7.7)	231(−19.2)[c]	207(−282)
8.....	OMe	OH			OMe	OMe	−328	Caseamine	286(− 8.6)	230(−41.0)	207(−205)
8.HCl....									292(−11.1)	233(−39.0)	207(−248)
9.....		OMe	OMe		OMe	OMe	−280	Xylopinine	287(− 3.3)	235(−50.4)	207(−134.1)
9.HCl....									286(− 2.5)	238(−35.2)	210(−143)
10.....		OH	OMe		OMe	OH	−290	Coreximine	286(− 3.6)	235(−44.0)	207(−112)
10.HCl....									286(− 3.8)	237(−32.5)	209(−113.4)

[a]Additional CD maximum at 242 nm (+1.2).
[b]Additional CD maximum at 240 nm (+5.2).
[c]Shoulder.
[d]c=0.05–0.10, 95% ethanol.
[e]c=0.1, $CHCl_3$.

However, in (−)-tetrahydropalmatine both the nonaromatic rings were assigned M helicity, while the observed CE for the ^1L_b band was positive (4, 7). The explanation offered (7, 8) was that in *one* of the substituted isoquinoline moieties, due to a different substitution pattern of the aromatic ring, M helicity must be associated with a positive cd caused by a change in the direction of the transition moment vector for the ^1L_b band (7, 8). This shows that the influence of substitution pattern on the cd must be known before an unambiguous assignment of the net cd for purposes of correlation with the absolute configuration can be made using their treatment (7). The picture is further complicated by the experimental observation that in some tetrahydroberberines, e.g. stylopine (7), an unexpected inversion of the ^1L_b band cd occurs on protonation of the nitrogen.

We have therefore examined the cd spectra in 95% ethanol of a series of tetrahydroprotoberberines (all of *S*-configuration) of widely differing substitution pattern, recorded both for the free bases and for the hydrochloride salts (table 1, **2–10**) specifically in order to establish whether a simple correlation can be found which would permit, *independent of the substitution pattern* of the compound, the assignment of the absolute configuration of the chiral center in **1** from the sign of the ^1L_b CE alone.

DISCUSSION

The uv absorption spectra of **2–10** in 95% ethanol showed a maximum at 281–289 nm (log ϵ 3.63–3.94)[2], a shoulder at 228–237 nm (log ϵ 3.96–4.33) and a second maximum at 203–205 nm (log ϵ 4.84–4.99). The long-wavelength absorption band and the shoulder were assigned (7) to the ^1L_b and ^1L_a transitions and the high intensity 205 nm absorption to a ^1B transition (5) of the aromatic chromophores. Although the uv spectra of tetrahydroprotoberberines are sufficiently characteristic for the ring system to be differentiated from many others, it is not possible to decide between the most frequently encountered substitution patterns (i.e., 2,3,9,10- and 2,3,10,11-tetraoxygenation) from uv absorption data alone (9). However, the cd spectra of **2–10** (table 1) allow such distinctions to be made. Thus for the S-configuration the three 2,3,9,10-substituted bases **2–4**, as well as the similarly-substituted (−)-canadine (7), show a *positive* CE within the 285 nm absorption band which becomes *negative* on protonation of the nitrogen atom. On the other hand, for the S-configuration the 2,3,10,11-substituted alkaloids **9** and **10** (as well as the 1-oxygenated **6**, **7** and **8** and the pentasubstituted compound **5**) display a negative CE for both the base and the hydrochloride. Another feature in the cd spectra which serve to distinguish between the 2,3,9,10- and 2,3,10,11-substitution patterns is the larger (approximately 2x) magnitude of the second CE (at about 235 nm) in compounds **9** and **10** with the latter substitution pattern.

Apart from the utility of the cd spectra for the distinction of 2,3,9,10- and 2,3,10,11-substitution, table 1 also shows that *all* tetrahydroprotoberberines of the S-configuration give a negative CE for the ^1L_b band of the protonated species (hydrohalide salt), independent of the substitution pattern in the aromatic rings. A similar inversion of sign of the ^1L_b CE on protonation has been observed (10, 11) in 1-benzyl- and 1-methyl-1,2,3,4-tetrahydroisoquinolines, where it was shown (10) that the sign of the ^1L_b CE of the hydrochloride salt gave the correct configurational assignment in all cases and was independent of the substitution pattern.

[2]As previously noted (9), capaurine **6** exhibits a slightly different spectrum with λ max 275 nm (log ϵ 3.39).

Thus, in the case of the phenolic base (−)-1-(4',5'-dimethoxy-2'-hydroxybenzyl)-7-methoxy-2-methyltetrahydroisoquinoline obtained by liquid ammonia reduction of (+)-cularine (12), the positive ^1L_b CE observed for the hydrochloride ($[\theta]_{290}$ +4600) (11) gives the absolute configuration as *S* in agreement with the recently reported X-ray structure determination of (+)-cularine (13).

Tetrahydroprotoberberines unsubstituted at C–1 or C–13 exist in the *trans*-quinolizidine conformation with rings B and C as half chairs (14). With a substituent at C–1 but C–13 unsubstituted (e.g. **6–8**), mixtures of *cis*- and *trans*-conformations can exist (14). However, except for the appearance of the 230 nm band as a shoulder on the very intense 205 nm band, the cd spectra of the 1-substituted compounds **6–8** (table 1) do not differ appreciably from those of compounds **2–5**, **9** and **10**. The nature of the B/C ring junction thus does not affect the sign of the ^1L_b CE for tetrahydroprotoberberines.

Table 1 also shows that the sign (and to a large extent also the magnitude) of the CE at 206–210 nm of all *bases* and *salts* is independent of the substitution pattern, of the nature of the B/C ring junction, and of nitrogen protonation. The high intensity of the CE (negative for the *S*-configuration) and its position at slightly longer wavelength than the absorption maximum suggest that it actually constitutes the long-wavelength branch of a bisignate pair resulting from electric-dipole coupling (15) of the transition moments of the ^1B transitions of the two aromatic rings. The expected CE of opposite sign has actually been observed below 200 nm (5) in the cd spectra of several tetrahydroprotoberberines. The sign of the 206–210 nm CE thus depends on the helicity between the coupling transition moment vectors, i.e., on the angle between the two planes formed by the aromatic rings, which in turn is dependent on the absolute configuration of the chiral center. The high intensity (average $[\theta] = 150{,}000$) of this CE permits the determination of the absolute configuration of tetrahydroprotoberberines on submilligram quantities.

EXPERIMENTAL

Cd spectra were measured in 95% ethanol on a JASCO ORD–CD 5 spectropolarimeter at 20°. Uv spectra were recorded in 95% ethanol with a Cary 14 instrument.

Received 25 July 1980

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