CIRCULAR DICHROISM OF APORPHINES[1]

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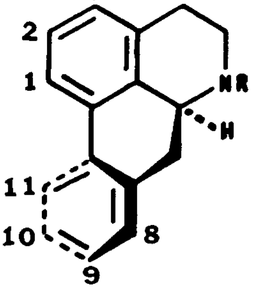
Abstract.—The circular dichroism (cd) spectra of nineteen aporphines of widely differing substitution patterns have been examined between 200 and 400 nm. Three major cd band systems exist, in the 220, 270–280, and 300 nm region. Two intense oppositely-signed Cotton effects (CE's) between 200 and 250 nm are substitution-independent and configuration-dependent, as is the third CE at 270–283 nm. In the region 293–327 nm, there are two further CE's which are substitution-dependent. In the case of symmetrically (1,2,10,11) substituted aporphines, the bands in the 300 nm region are split into two oppositely-signed CE's with a pattern similar to that observed for the 220 nm region.

In a preliminary survey (1) aporphine alkaloids were shown to possess a high-amplitude Cotton effect (CE) centered at 235–245 nm in their optical rotatory dispersion (ord) curves, from which the absolute configuration of the chiral center could be deduced. In view of the complex nature of the ord curve between 250 and 350 nm, it became evident that a number of additional optically active transitions existing in this region were probably largely obscured by the intense background due to the CE centered at 240 nm. An investigation of the circular dichroism (cd) curves was therefore required for the detection of these transitions, and for the elucidation of their relationship to the absolute configuration of the molecule.

The aporphine alkaloids contain a twisted biphenyl chromophore and resemble polyoxygenated 9,10-dihydrophenanthrenes possessing optical activity due to inherent dissymmetry. The special feature of the aporphine system is the correspondence between the absolute configuration of the chiral center and the sense of twist of the bridged biphenyl, resulting in the absolute configurations **I**(S) or **II**(R) (2).



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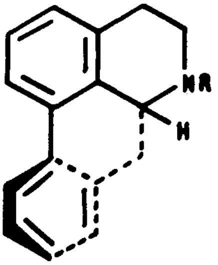

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[1] Publication No. 30 in the series *Optical Rotatory Dispersion and Absolute Configuration.*

The cd curves in 95% ethanol of a series of aporphines (table 1, **1**–**19**) of widely differing substitution patterns were examined in the 200–400 nm region and, as anticipated, much additional information was obtained compared to earlier ord data.

TABLE 1. Structure of aporphines examined.

Compound	Substituents at Position							R	Absolute Configuration	Ref.
	1	2	3	8	9	10	11			
1 Hernovine	OMe	OH				OH	OMe	H	S	5
2 Magnoflorine iodide	OH	OMe				OMe	OH	$(Me)_2$	S	20
3 Isocorydine	OMe	OMe				OMe	OH	Me	S	3
4 Catalpifoline	OMe	OMe				OMe	OMe	H	S	5
5 Nandigerine	$-OCH_2O-$					OH	OMe	H	S	20
6 Bulbocapnine	$-OCH_2O-$					OMe	OH	Me	S	3
7 Ovigerine	$-OCH_2O-$					$-OCH_2O-$		H	S	5
8 Boldine	OMe	OH			OH	OMe		Me	S	3
9 Laurotetanine	OMe	OMe			OH	OMe		H	S	3
10 N-Methyllaurotetanine·HBr	OMe	OMe			OH	OMe		Me	S	3
11 Dicentrine	$-OCH_2O-$				OMe	OMe		Me	S	3
12 Neolitsine	$-OCH_2O-$				$-OCH_2O-$			Me	S	19
13 Neolitsine·HCl	$-OCH_2O-$				$-OCH_2O-$			Me	S	19
14 Ocoteine	$-OCH_2O-$		OMe		OMe	OMe		Me	S	7
15 Cassyfiline	$-OCH_2O-$		OMe		OH	OMe		H	S	9
16 Leucoxine	$-OCH_2O-$			OH	OMe	OMe		Me	S	10
17 N,O-Diacetyl-O-Methyl-apocrotonosine	OMe	OAc				OMe		Ac	R	11
18 Apomorphine·HCl						OH	OH	Me	R	20
19 Nuciferine	OMe	OMe						Me	R	3

DISCUSSION

Three band systems, in the 220, 270–280 and 300 nm region, are generally (2, 3) observed in the electronic absorption spectra of aporphines. These bands have been assigned (4) respectively, to the $^1B_{ab}$, ^1L_a and ^1L_b bands of the benzene chromophores and are shifted to longer wavelengths due to substitution and conjugation between the aromatic nuclei. Since the band systems derive from the corresponding bands of the two benzene nuclei, there are in general two components to each of them, as evidenced by shoulders or band broadening within each absorption region.

The wavelength of the 270–280 nm absorption band is particularly sensitive to alterations in the position of substituents in the biphenyl nucleus. Thus, in 1,11-dioxygenated aporphines (e.g. **1**–**7**), the effect of decreasing conjugation between the aromatic rings results in a shift of λ max down to about 270 nm, while in the absence of a C–11 substituent (e.g. **8**–**13**) λ max is shifted back to about 280 nm (2). Substitution at C–3 and C–9 (e.g. in **14** and **15**) has a bathochromic effect, while decreasing substitution (e.g. **18** and **19**) results in an expected hypsochromic shift of the 270–280 nm band.

Aporphines with similar substitution patterns also exhibit very similar cd curves (table 2). For example, in the 1,2,10,11-substituted aporphines (**1**–**7**), typified by ovigerine (fig. 1), it is apparent that not one, but two, cd maxima of opposite sign exist in the 200–250 nm region. According to the rule mentioned earlier (1), the high-intensity positive CE at about 235 nm shows these compounds

TABLE 2. Circular dichroism of aporphines in 95% ethanol.

Compound	[α]D, deg[a]	CD, maxima: λ nm ([θ] 10^{-3})[b]				
1	+266[c]	322(+ 1.7)	299(−18.2)	274(−19.5)	234(+329.8)	212(− 69.4)
2	+201[d]	315(+10.4)	297(− 5.9)	272(−56.3)	236(+245.0)	218(− 19.3)
3	+196[c]	322(+ 1.9)	302(− 4.7)[i]	272(−41.9)	234(+314.2)	215(− 23.4)
4	+220[f]	314(+15.6)	294(−11.6)[i]	270(−26.1)	235(+399.4)	216(− 56.3)
5	+248[f]	323(+10.7)	293(− 8.8)	270(−32.4)	234(+236.5)	214(− 30.0)
6	+237[c]	322(+27.9)	295(−14.5)	272(−38.6)	235(+255.4)	216(− 47.8)
7	+177[g,h]	327(+32.8)	299(−14.4)	272(−44.8)	234(+238.8)	203(−110.0)
8	+112[f]	316(−18.2)	303(−14.4)[i]	280(−20.1)	240(+259.0)	214(−139.1)
9	+125[c]	315(−14.9)	301(−16.7)	281(−20.5)	242(+213.9)	218(−144.2)
10	+ 73[f]	314(−26.1)	303(−27.4)	283(−22.4)	242(+211.3)	219(−149.2)
11	+ 56[f]	310(−18.7)		280(− 9.3)	237(+149.2)	216(− 67.1)
12	+ 57[e]	320(−16.6)	307(−12.6)	282(− 8.7)	234(+153.0)	215(− 93.8)
13		323(−24.8)	312(−24.5)	280(−13.0)	236(+ 94.3)	215(− 82.5)
14	+ 43[c]	313(−27.3)	301(−31.5)	283(−21.0)	242(+115.4)	218(− 94.4)
15	+ 24[e]	312(−26.2)	301(−21.1)	282(−22.2)	241(+120.9)	218(−115.9)
16	+ 81[f]	323(+ 5.2)	299(−17.3)	270(−24.5)	238(+358.8)	218(−138.0)
17	−397[d]	315(− 3.1)	294(+10.5)	273(+40.9)	238(−220.0)	219(+ 47.1)
18	− 48[g]		300(+ 3.5)	272(+49.1)	232(−226.3)	217(+ 26.2)
19	−215[f]	308(− 6.4)		272(+37.0)	233(−295.9)	213(+148.0)

[a] c 0.2–1.5, [b] Molecular ellipticity, [c] 95% ethanol, [d] methanol, [e] chloroform, [f] ethanol, [g] water, [h] As the hydrochloride, [i] Shoulder.

to be members of the S(or L)-series in agreement with known assignments for **2**, **3**, **5** and **6** (2, 3). The configuration of (+)-hernovine, (+)-catalpifoline and (+)-ovigerine (5) is now shown to be S also. A third CE (negative) is present at 270–274 nm, close to the position of the electronic absorption maximum of a 1,11-

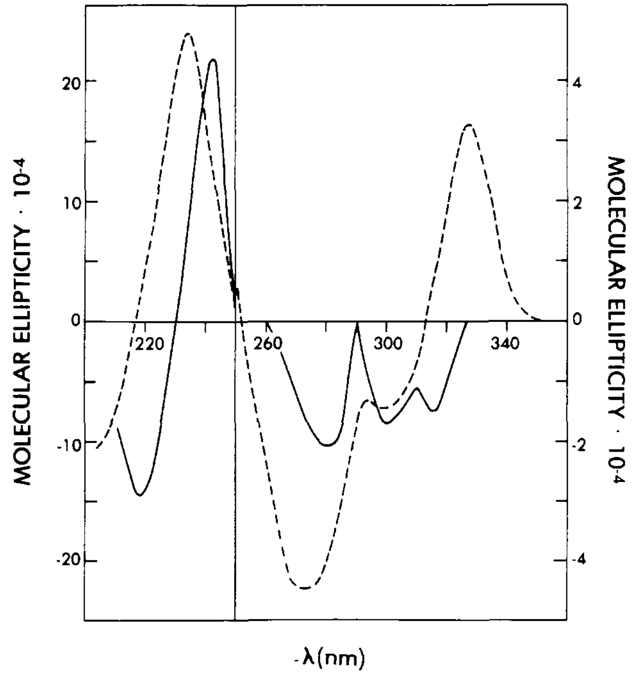

FIG. 1. Circular Dichroism Spectra in 95% ethanol of Laurotetanine (————) and Ovigerine (- - - - - -).

dioxygenated aporphine. In the 290–340 nm region there are two additional CE's of *opposite* sign. The cd curves are unaffected by methylation of the nitrogen since the tertiary **3** and **6** and quaternary (6) bases **2** give spectra which are very similar to those found for the secondary amines.

A change of the substitution pattern from 1,2,10,11-tetrasubstitution to 1,2,9,10-tetrasubstitution (**8–13**) is accompanied by some significant alterations in the cd spectra as typified by laurotetanine (fig. 1). The presence of a high-intensity positive CE in the 240 nm region and a negative CE around 215 nm confirm the configurational assignments for these aporphines. The negative cd band, found at 270–274 nm in the 1,2,10,11-oxygenated aporphines, is shifted to 280–283 nm with a concomitant decrease in intensity. However, the most noticeable change is the presence of two Cotton effects of the *same* sign in the long-wavelength region.

(+)-Ocoteine (7) **14** is an example a 1,2,3,9,10-substituted aporphine and has been shown to be identical with (+)-thalicmine (8). Its absolute configuration is clearly S. The closely related alkaloid (9) (+)-cassyfiline **15** is seen also to have the S-configuration; the identity of (+)-*O*,*N*-dimethylcassyfiline with (+)-ocoteine has been shown chemically (9). The position of the negative CE in **14** and **15** at 282–283 nm is in agreement with the corresponding uv absorption maxima of 3,9-oxygenated aporphines. Again the two long-wavelength CE's have the same sign.

(+)-Leucoxine **15** (10) was examined as an example of an aporphine oxygenated in the 8-position. The cd spectrum shows it to be a member of the S (or L)-series. It should be noted that as a result of oxygen substitution at C–8, the two long-wavelength CE's again have opposite signs, as in the 1,2,10,11-substituted aporphines **1–7**.

The absolute configuration of (−)-*N*,*O*-diacetyl-*O*-methylapocrotonosine (11) **17** has been deduced from that of its precursor (+)-crotonosine (12) assigned the R (or D)-configuration both by chemical correlation (11, 13, 14, 15) with D-(+)-pronuciferine and D-(−)-nuciferine and by cd comparison (16) with D-(+)-pronuciferine and D-(+)-stepharine (15). The R (or (D) configurational assignment is now confirmed by the negative cd observed for **17** at 238 nm. In addition, there are strong positive cd maxima at 219 and 273 nm and smaller cd bands at 294 and 315 nm. As expected, neither *N*- nor *O*-acylation has any measurable effect on the cd spectrum, since the weak (n→π*) transitions of the ester or amide chromophores in the 210–225 nm region are overshadowed by the intense aromatic absorption maxima (table 2).

Finally, (−)-apomorphine **18** and (−)-nuciferine **19** were investigated as examples of aporphines substituted only in the 10, 11- and 1,2-positions, respectively. Both gave cd curves in agreement with their known absolute configurations and with earlier optical data (1, 16, 17).

From the results presented in table 2 several new findings emerge: (A) Aporphines exhibit *two* extremely intense cd maxima *of opposite* sign within the *shortest* wavelength absorption band (B band), and a single less intense cd maximum at higher wavelength (^1L_a band), all of which are *substitution-independent* and *configuration-dependent*. Thus for a compound possessing the S-configuration, the cd maximum at 240 nm is positive, while the two others are negative. The sign of the intense CE in the 234–242 nm region, characteristic of the absolute sense of twist of the dissymmetric biphenyl, dominates the visible region and provides a physical explanation for the generalization that aporphines of S-configuration have a positive rotation at the D-line (18). Even when the D-line rotation is small (e.g. **14** and **15**), the cd maximum at 242 nm still shows an ellipticity >100,000. (B) the sign of the two cd maxima within the *longest* wavelength absorption band (>293 nm, ^1L_b) is substitution-dependent and is, therefore, unsuitable for configurational assignment.

The empirical results obtained in the present study are fully supported by the theoretical interpretation of aporphine (4) and biaryl (21) optical activity proposed by Mason (4). Thus the two oppositely signed CE's between 200 and 250 nm in aporphines are considered (4) as arising from electric dipole coupling of the transition moments of the nearly degenerate ^1B_b transitions of the two aromatic rings. The directions of these moments, perpendicular to the pivotal bond of an unsubstituted biphenyl, are not very sensitive to the substitution pattern since the corresponding parent band of benzene is of high intensity, arising from a fully allowed transition with a large transition moment (4). The particular signs and frequency order of the two CE's then depend only on the chiral arrangement of the transition moment vectors, *i.e.*, on the sense of twist of the biphenyl system and thus also on the absolute configuration at the chiral center. However, the directions of the transition moments associated with the ^1L_a and especially the ^1L_b bands of the biphenyl system of an aporphine are sensitive to the nature and positions of the substituents, since the corresponding parent bands of benzene are of moderate or weak intensity, deriving from electronic transitions with small transition moments (4). The sign of the CE's arising from electric dipole coupling of the transition moments associated with the ^1L_b transitions of the two aromatic rings should therefore be strongly dependent on the substitution pattern (4). In the case of the symmetrically substituted aporphines 1–7, the transition moment vectors for the ^1L_b bands of the two aromatic rings lie in the same direction as those of the ^1L_b band (4) and, as can be seen in table 2, the circular dichroism of the ^1L_b region follows a pattern *similar to that observed for the* ^1B_b *region* with a positive band at longer wavelength and a negative band at shorter wavelength for the S-configuration.

Mason's treatment (4) also accounts for the appearance of only *one* CE within the ^1L_a band system of aporphines. As in the case of biaryls (21), this CE is probably generated by electric dipole coupling of the ^1L_a moment of one aromatic chromophore and the ^1B_b moment of the other. By analogy with the biaryls (21), the sign of the CE should be opposite to that of the longer-wavelength cd band in the bisignate pair resulting from the coupling of the two ^1B_b transition moments, and the rotational strength in the ^1L_a absorption region should be an order of magnitude smaller than that of the ^1B_b region. These expectations are observed in the cd spectra of aporphines (table 2).

In conclusion, the sign of the CE's associated with the short-wavelength absorption band is the more general and reliable guide to the absolute configuration of aporphines, as was found earlier on empirical grounds (1).

EXPERIMENTAL

Cd spectra were measured in 95% ethanol on a Roussel-Jouan Mark II dichrograph or a Jasco ORD-CD5 spectropolarimeter at 20°.

Received 1 August 1980.

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