CIRCULAR DICHROISM OF SOME BISBENZYLTETRAHYDROISOQUINOLINE ALKALOIDS

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The circular dichroism (CD) method has been used to study the stereochemistry of the bisbenzyltetrahydroisoquinoline alkaloids. A relationship has been established between the absolute configurations of the asymmetric centers and the parameters of the Cotton effects in the CD spectra. The changes in the CD spectra on protonation have been correlated with conformational rearrangements of the molecules due to the different attachment of the oxygen bridges.

With the aim of studying the stereochemical features of the bisbenzyltetrahydroquinoline alkaloids we have considered the circular dichroism (CD) spectra of hernandezine (I), O-ethyldihydrothalsimidine (II), O-ethyldihydroisothalsimidine (III), isohernandezine (IV), isotetrandrine (V), thalsimine (VI), thalsimidine (VII), O-methylthalicberine (VIII), thalisopine (IX), thalisopidine (X), thalmine (XI), base 2 (XII), base 3 (XIII), and thalfine (XIV) [1].

It was established from NMR and mass spectroscopic characteristics that bases 2 and 3 belong to the thalmine group and are structural isomers of thalbadensine [2].

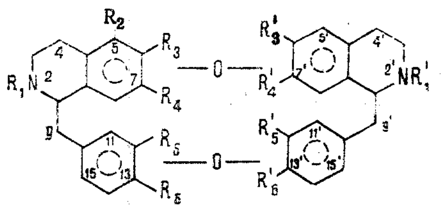
Analysis of the results obtained consisted essentially in a comparison of the changes in the CD spectra with the conformational rearrangements of the molecules connected with the different attachments of the oxygen bridges.

In the CD spectra of the compounds investigated in the 300-200 nm region a number of Cotton effects (CEs) were recorded which were due to $'L_b$, $'L_a$, and $'B_a$ aromatic transitions localized respectively in the 290, 240, and 200 nm regions. The results of the circular dichroism measurements are given in Table 1.

In the CD spectra of the bis-bases under consideration none of the characteristics established for the monobenzyltetrahydroisoquinolines [3] was observed. As is well-known, S-benzyltetrahydroisoquinolines are characterized by two positive Cotton effects in the 290 and 240 nm regions and the alkaloids of the R-series by negative Cotton effects in the same regions.

The optical rotations of the bis-bases do not obey the additivity rule, i.e., the rotation of a bis-base is not the sum of the rotations of the two monobenzyltetrahydroisoquinoline fragments. The parameters of the Cotton effects in the CD spectra of the bis-bases depend not only on the absolute configurations of the two asymmetric centers but also on the positions of the oxygen bridges and on the conformation of the internal dioxide ring.

According to the nature of the attachment of the ether bridges, the bisbenzyltetrahydroisoquinolines that we studied were subdivided into five types: type I (compounds I-VII), 8,7':12,13'-linkage; type II (VIII), 8,6':12,13'-linkage; type III (IX, X), 8,7':13,12'-linkage; type IV (XI-XIII), 5,7':13,12'-linkage; and type V (XIV), 5,8':12,13'-linkage.



I, IV, V. $R_1 = R_1' = CH_3$; $R_2 = R_3 = R_4 = R_6 = R_3' = OCH_3$

II, III. $R_1 = CH_3$; $R_1' = H$; $R_2 = OC_2H_5$; $R_3 = R_4 = R_6 = R_3' = OCH_3$

VIII. $R_1 = R_1' = CH_3$; $R_2 = H$; $R_3 = R_4 = R_6 = R_4' = OCH_3$

IX. $R_1 = R_1' = CH_3$; $R_2 = OH$; $R_3 = R_4 = R_3' = R_6' = OCH_3$

X. $R_1 = R_1' = CH_3$; $R_2 = R_6' = OH$; $R_3 = R_4 = R_3' = OCH_3$

XI. $R_1 = R_1' = CH_3$; $R_3 = OH$; $R_4 = R_3' = R_6' = OCH_3$

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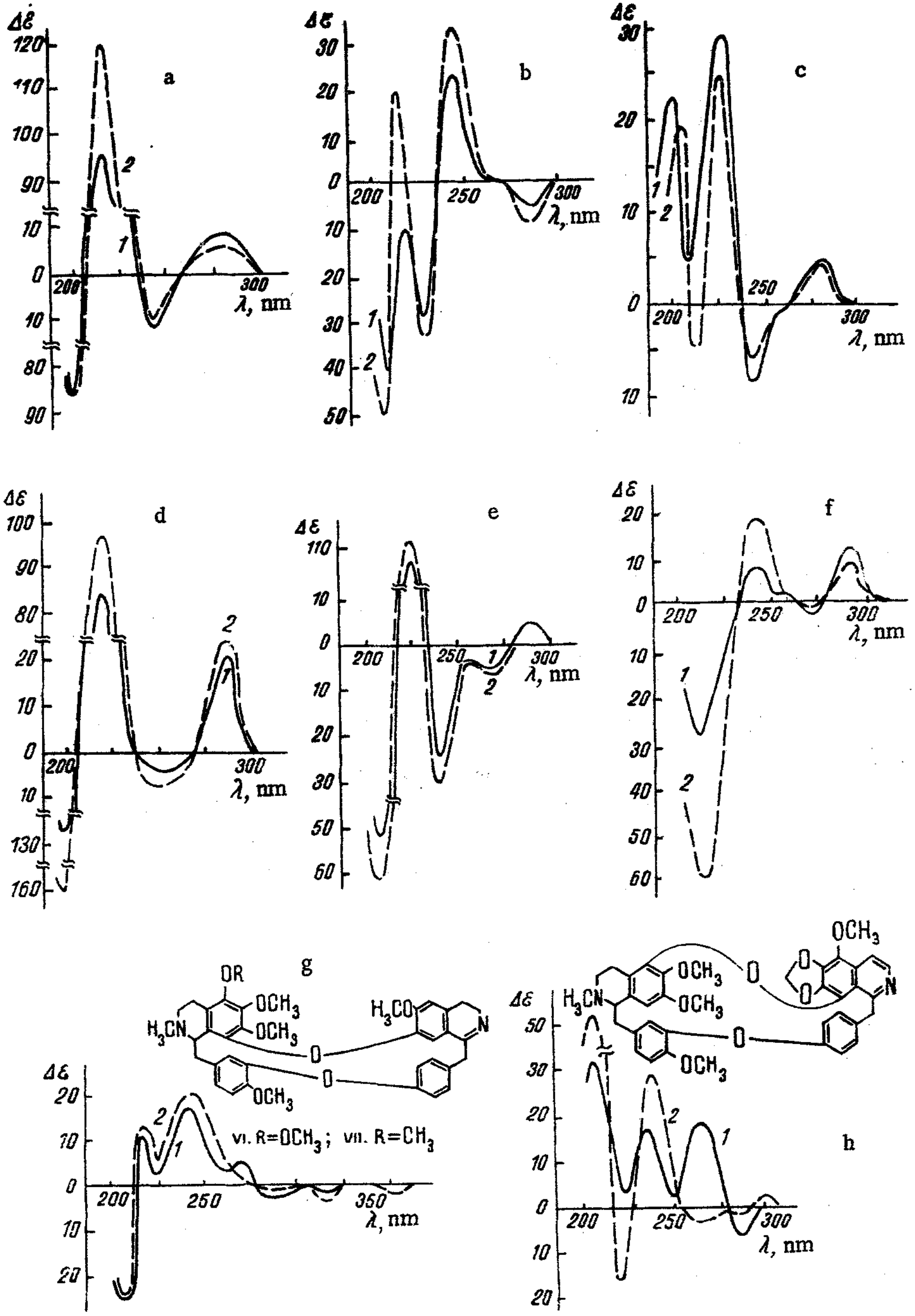

Fig. 1. CD spectra of hernandezine (a), isohernandezine (b), isotetrandrine (c), O-methylthalicberine (d), thalisopine (e), thalmine (f), thalsimine (g), and thalfine (h) in CH_3OH (1) and CH_3OH + HCl (2).

TABLE 1

Compound	Configuration	CH_3OH		$CH_3OH+HCl$	
		λ_{max}, nm	Δε	λ_{max}, nm	Δε
Type I, 8,7':12,13'-linkage					
1. Hernandezine	*SS*	282	+7,79	283	+6,12
		244	−12,6	244	−11,7
		216	+96,4	215	+120,6
		197	−87,2	197	−87,2
2. O-Ethyldihydrothalsimidine	*SS*	282	+4,99	288	+3,96
		246	−9,94	246	−8,55
		216	+52,4	213	+64,4
		196	−57,0	197	−57,0
3. O-Ethyldihydroisothalsimidine	SR	282	−2,28	282	−3,42
		243	+5,79	242	+12,4
		228	−5,09	228	−6,15
		215	+5,71	215	+16,2
		203	−24,1	201	−26,8
4. Isohernandezine	*SR*	285	−7,20	283	−9,52
		245	+23,3	243	+33,5
		228	−30,6	228	−35,0
		—	—	215	+19,7
		207	−43,3	204	−50,5
5. Isotetrandrine	*RS*	282	+3,56	282	+3,56
		242	−8,22	242	−6,24
		225	+28,8	226	+24,4
		—	—	215	−5,86
		200	+22,1	203	+19,9
6. Thalsimine	*S*	—	—	360	−0,98
		318	−0,91	318	−2,17
		289	−2,58	293	−1,30
		269	+4,95	—	—
		240	+16,8	246	+19,8
		217	+11,4	216	+13,4
		206	−23,0	204	−23,0
7. Thalsimidine	*S*			370	−0.41
		323	−0,57	318	−2,71
		290	−2,80	282	−2,22
		274	+4,30	—	—
		251	−1,86	245	+14,5
		220	+25,4	212	+29,0
		200	−41,0	201	−42,0
Type II, 8,6':12,13'-linkage					
8. O-Methylthalicberine	*SS*	286	+21,2	286	+23,3
		250	−4,31	250	−6,80
		215	+85,3	215	+98,4
		197	−129,0	195	−162,0
Type III, 8,7':13,12'-linkage					
9. Thalisopine	*SS*	289	+3,87	—	—
		270	−5,91	268	−6,3
		241	−25,1	240	−31,7
		224	+38,0	221	+42,9
		208	−55,0	207	−62,1
10. Thalisopidine	*SS*	290	+3,51	—	—
		272	−6,90	272	−6,90
		241	−22,9	241	−27,1
		224	+34,4	221	+39,4
		209	−69,7	210	−77,7
Type IV, 5,7':13,12'-linkage					
11. Thalmine	*SS*	292	+10,8	292	+7,50
		274	−3,31	275	−2,58
		242	+8,23	243	+18,5
		207	−28,9	209	−60,0

TABLE 1 (continued)

12. Base 2	*SS*	293	+6,11	297	+3,98
		276	−1,56	274	−0,92
		240	+4,48	242	+10,3
		210	−16,3	208	−32,0
13. Base 3	*SS*	293	+10,4	293	+6,92
		275	−4,33	276	−1,90
		240	+6,92	240	+19,2
		208	−28,1	209	−78,7
	Type V, 5,8':12,13'-linkage				
14. Thalfine*	*S*	—	—	298	+1,40
		288	−7,52	284	−1,18
		262	+17,7	259	−2,59
		232	+16,5	237	+29,4
		—	—	220	−16,5
		207	+32,0	207	+52,3

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*In the CD spectrum of thalfine two bands of very low intensity ($\Delta\varepsilon \sim 0.2$) are observed in the 362-320 nm region.

We have considered the CD spectra of eight alkaloids with the SS-configuration belonging to types I-IV and three alkaloids with the SR- and RS-configurations belonging to type I. Figure 1 shows CD spectra of alkaloids belonging to types I-V.

Analysis of the results obtained has permitted the following characteristic features to be established:

1. Regardless of the nature of the attachment of the oxygen bridges, alkaloids with the SS-configuration belonging to types I-IV have a positive Cotton effect in the 290 nm region and a negative one in the 200 nm region (Fig. 1a, d, e, f); and

2. Compounds of type I with the SR-configuration are characterized by negative Cotton effects in the 280 and 200 nm regions, and those with the RS configuration by positive CEs in analogous regions (Fig. 1b, c).

The bisbenzyltetrahydroisoquinolines form a conformationally mobile dihomoconjugated system. Both a change in the positions of the oxygen bridges causing a conformational rearrangement of the molecule and also protonation strongly affect the chirality of the homoconjugated chromophore, which is reflected in the CD spectra. Consequently, specific features of the CD spectrum are characteristic for each type of compound, and these we shall consider below.

On passing from linkage of type I to type II, the 18-membered inner dioxide ring becomes 19-membered and a marked rise in the intensity of the CE at 290 nm is observed. On protonation, in the case of alkaloids of type I with the SS-configuration, the intensity of the CE at 290 nm decreases, while for those of type II it increases (compare compounds (I), (II), and (VIII); Fig. 1a, d).

A change in the position of the lower bridge from 12,13' (type I) to 13,12' (type III) (the size of the inner dioxide ring does not change) causes the appearance of an additional CE at 270 nm. When compounds (IX) and (X) (type III) are protonated the CE in the 290 nm region decreases to zero (Fig. 1e).

The Cotton effect in the 270 nm region is obviously characteristic for bases with the 13,12'-position of the lower oxygen bridge, since it is also present in the CD spectra of the alkaloids (XI-XIII) (type IV).

In contrast to the alkaloids of the other three types, in the CD spectra of the SS-bases of type IV there is no CE in the 220 nm region, as is observed in the CD spectra of the SS-alkaloids belonging to types I-III (Fig. 1f).

In the dehydrogenated bis-bases (VI, VII, XIV) there is only one asymmetric center with a S-configuration. The CD spectra of these compounds differ both from the spectra of the S-monobenzyltetrahydroisoquinolines and from the spectra of the SS-bis-bases.

In the alkaloids of this type, overlapping of the π-orbitals of the aromatic ring and of the azomethine bond and the additional internal dyssymmetric chromophore formed substantially complicate the CD spectra of these compounds.

When the bases (VI, VII, and XIV) are protonated, one more positive CE appears in the long-wave regions of the CD spectra (Fig. 1g, h) which is probably due to the presence of a homoconjugated chromophore including a sp^2-hybridized nitrogen atom. In the case of thalfine, this CE is opposite in sign to the $'L_b$ CE at 288 nm, the intensity of which sharply decreases (Fig. 1h).

For compounds (VI) and (VII), the $'L_b$ CE is shifted bathochromically to 318 nm, and on protonation its intensity increases and a (—)-CE appears at 360 nm (Fig. 1g).

All these features of the CD spectra can be used to identify bisbenzyltetrahydroisoquinoline alkaloids.

EXPERIMENTAL

The CD spectra were recorded on a JASCO J=20 spectropolarimeter. The concentration of the solutions was 0.5-1 mg/ml and the cell thicknesses were 0.2, 0.05, and 0.01 cm. Methanol was used as solvent. On acidification, one drop of concentrated hydrochloric acid was added to 3 ml of a methanolic solution of the base. The CD measurements were performed 1 h after the addition of the acid.

SUMMARY

It has been established from the characteristics of the CD spectra that bisbenzyltetrahydroisoquinoline alkaloids with the SS-configuration belonging to linkage types I-IV are characterized by a positive CE in the 290 nm region and a negative one in the 200 nm region; compounds of type I with an SR-configuration have negative Cotton effects and those with an RS-configuration, positive effects in the 280 and 200 nm regions.

The interrelationship between the nature of the attachment of the oxygen bridges and changes in the CD spectra on the protonation of the bisbenzyltetrahydroisoquinolines has been elucidated.

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