

## Circular Dichroism Spectra of 1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocines

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Circular dichroism curves of levorotatory 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol derivatives have been determined and correlated with stereochemical features. Compounds with the *rectus* configuration at C-6 were found to exhibit negative extrema for the long wavelength phenolic  $\pi \rightarrow \pi^*$  transition. The remaining Cotton effects have been ascribed to specific aromatic  $\pi \rightarrow \pi^*$  transitions.

The analgetic activity of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines (1) has been correlated with the relative configuration at C-6 and C-11 as well as the absolute configuration of the molecule (2). Levorotatory enantiomers, depicted in Table I, have been found to be more potent (2). Since optical rotatory dispersion (ORD) and circular dichroism (CD) data can be used to correlate stereochemical features of optically active molecules (3), the ORD and CD curves of compounds I-VI were recorded to determine whether these measurements could be used for assigning absolute configurations to hexahydro-2,6-methano-3-benzazocine derivatives. Our discussion will be confined to CD results, since these spectra proved to be more readily discernible.

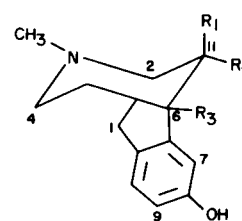
The absolute configuration of (-)-1,2,3,4,5,6-hexahydro-6,11 $\alpha$ -diethyl-3-methyl-2,6-methano-3-benzazocin-8-ol, II, (4) and (-)-1,2,3,4,5,6-hexahydro-3,11 $\beta$ -dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol, V (5), were shown to be related to that of (-)-morphine. The remaining levorotatory compounds in Table I provided CD curves similar to that obtained with II and V and therefore are assigned the same absolute configuration.

A diagnostic feature of the CD curves of compounds I-VI is the presence of two negative maxima in the 280-295 nm region (Figures 1 and 2). These extrema correspond to the ultraviolet absorption bands observed in the same region and are associated with the  $\pi \rightarrow \pi^*$  transition of the phenolic chromophore (6,7). Two bands are observed as a result of vibrational fine structure associated with this  ${}^1A_{1g} \rightarrow {}^1B_{2u}$  aromatic transition (7-9). Since it is to be expected that the stereochemistry at an asymmetric carbon atom adjacent to an absorbing chromophore would exert an influence on the sign of a Cotton effect (3), it is worthwhile to note that compounds I-VI, all of which have the *rectus* configuration at C-6, exhibit a negative maximum for this low energy Cotton effect.

The 6,11-diethyl compounds, I and II, contain only the phenolic chromophore. The *trans* (I) (10) and *cis* (II)

(4,11) isomers differ in configuration at the remote C-11 site and would therefore be expected to provide similar CD curves. This is found to be the case above 250 nm, with only minor differences in amplitude being apparent (Figure 1). However, important differences are noted in the rotational strengths of Cotton effects in the far ultraviolet region. The *trans* isomer shows a negative extremum at 204 nm ( $[\theta] = -11,500$ ) for the  ${}^1A_{1g} \rightarrow {}^1E_{1u}$  benzene transition, while the *cis* isomer exhibits a stronger negative maximum at 199 nm for this transition ( $[\theta] = -50,000$ ). A smaller difference in amplitude is observed for the 230 nm bands assigned to the  ${}^1A_{1g} \rightarrow {}^1B_{1u}$  aromatic transition, where the *trans* isomer, I, exhibits a more intense Cotton effect.

TABLE I



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Form
I	C <sub>2</sub> H <sub>5</sub>	H	C <sub>2</sub> H <sub>5</sub>	base
II	H	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	base
III	H	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	HCl salt
IV	H	H	C <sub>6</sub> H <sub>5</sub>	base
V	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	base
VI	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	HCl salt

A comparison of the ORD curves of the corresponding *cis*- and *trans*-6,11-dimethyl-2,6-methano-3-benzazocines has been reported by Casy and Parulkar (12). They concluded on the basis of measurements between 240 and

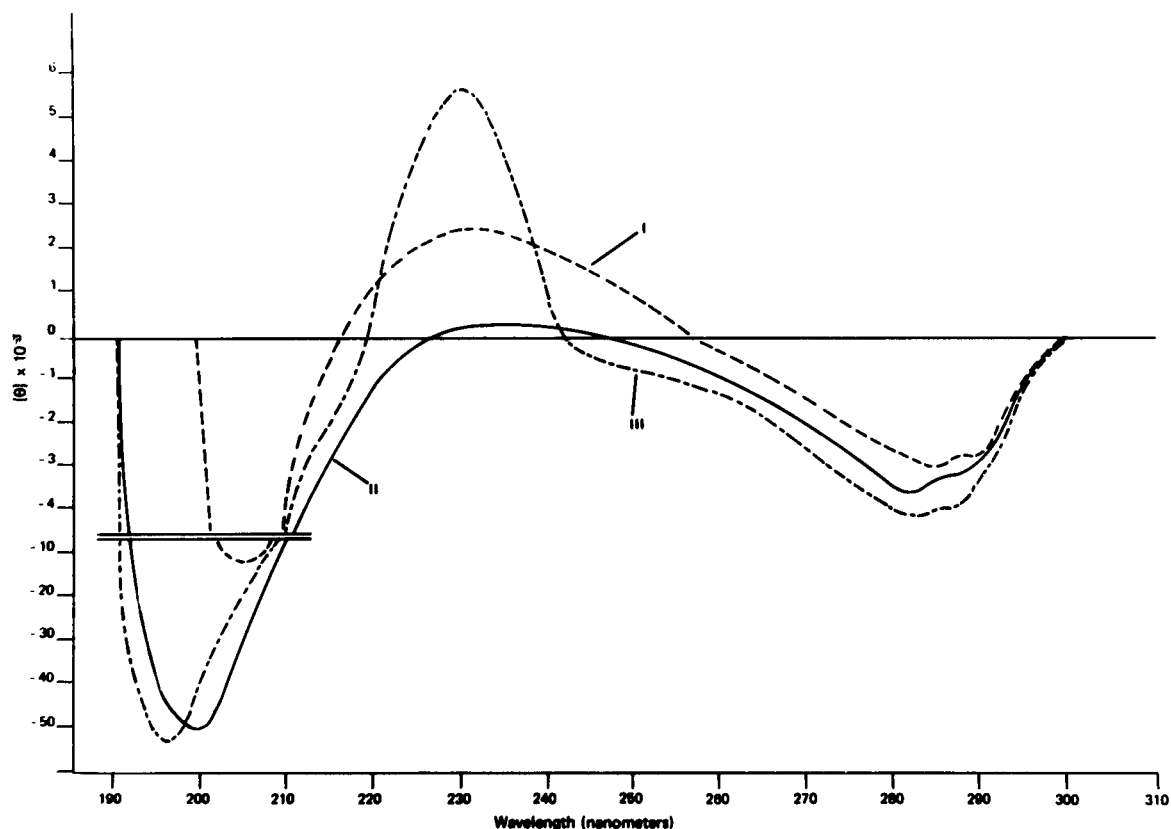


Figure 1: CD curves of *l*-1,2,3,4,5,6-hexahydro-6,11 $\beta$ -diethyl-3-methyl-2,6-methano-3-benzazocin-8-ol (I) (---), *l*-1,2,3,4,5,6-hexahydro-6,11 $\alpha$ -diethyl-3-methyl-2,6-methano-3-benzazocin-8-ol (II) (—), and *l*-1,2,3,4,5,6-hexahydro-6,11 $\alpha$ -diethyl-3-methyl-2,6-methano-3-benzazocin-8-ol hydrochloride salt (III) (-·-·-).

350 nm that the configuration at C-11 has a negligible effect upon the ORD characteristics of these compounds. However, as can be seen from Figure 1, substantial differences in amplitude and rotational strength occur below 240 nm in the CD curves when the geometry at C-11 is altered.

The CD curve of the *cis* hydrochloride salt, III is included in Figure 1. The short and long wavelength bands are similar to those obtained with the base II, while the 230 nm band shows approximately a tenfold enhancement in rotational strength.

Compounds IV-VI, containing a phenyl substituent at C-6 provide more complex CD curves due to the presence of two chromophores (Figure 2). In addition to the bands ascribed to the long wavelength  $\pi \rightarrow \pi^*$  phenolic transitions, three distinct negative Cotton effects are noted in the 250-270 nm region. They are attributed to overlapping  $^1A_{1g} \rightarrow ^1B_{2u}$  aromatic transitions of the phenyl substituent. The Cotton effects between 215 and 240 nm appear to be associated with the  $^1A_{1g} \rightarrow ^1B_{1u}$  aromatic

transitions, while the two lowest wavelength negative extrema appear in the region expected for  $^1A_{1g} \rightarrow ^1E_{1u}$  aromatic transitions (7). Phenolic compounds of the C-6 phenyl series exhibit very intense Cotton effects at 191 nm with molecular ellipticities of approximately -300,000.

As can be seen from Figure 2, *l*-1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocin-8-ol, IV (13), the 11 $\beta$ -methyl derivative, V (5), and the 11 $\beta$ -methyl hydrochloride salt, VI, exhibit similar spectral characteristics with only small differences in peak position and amplitudes being apparent, in contrast to the effects noted with the 6,11-diethyl compounds.

#### EXPERIMENTAL

CD measurements were determined with a Durrum-Jasco Model J-20 spectropolarimeter at a sample compartment temperature of 26°. Sample cells of 0.1 and 1.0 mm fixed path length were employed, with a concentration range of approximately  $7.0 \times 10^{-4} M$  to  $8.0 \times 10^{-3} M$  in spectroquality methanol. Results are expressed as molecular ellipticities,  $[\theta] = \text{deg cm}^3/\text{decimeter mole}$ .

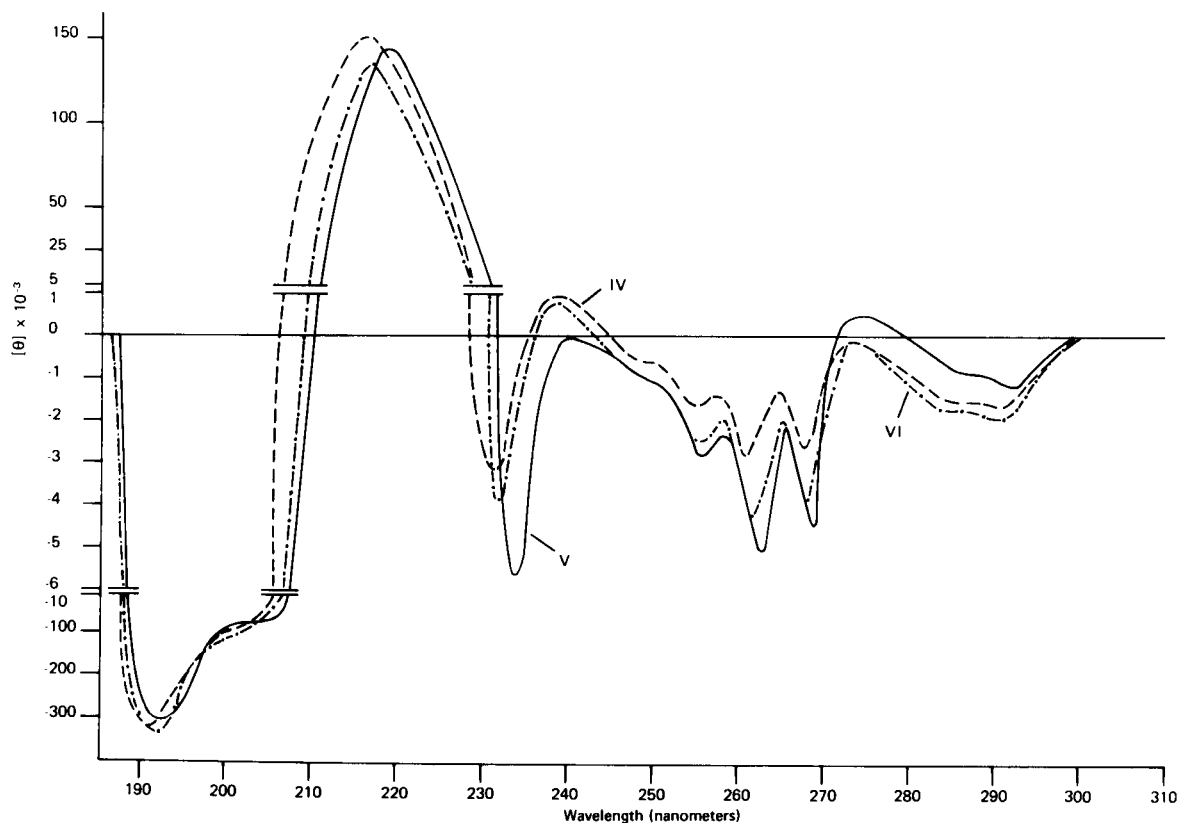


Figure 2: CD curves of *l*-1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (IV) (----), *l*-1,2,3,4,5,6-hexahydro-3,11 $\beta$ -dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (V) (—), and *l*-1,2,3,4,5,6-hexahydro-3,11 $\beta$ -dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol hydrochloride salt (VI) (-·-·-).

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