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OPTICAL ROTATORY DISPERSION AND ABSOLUTE CONFIGURATION—XII

THE ARGEMONINE ALKALOIDS*

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Abstract—ORD and CD measurements have been carried out on the alkaloids of the argemonine series, and have been related to the UV absorption and absolute configuration of these compounds. Of the 6 known argemonine alkaloids, five are configurationally identical.

(−)-ARGEMONINE (Ia) is one of several related alkaloids found in plants of the *Argemone* species.[1] Others are norargemonine (Ib)[1,2] and bisnorargemonine (Ic),[3] and recently the closely analogous eschscholtzine (Id)[4] and eschscholtzidine (Ie)[5] were isolated from *Eschscholtzia californica.*

The structural identity of (−)-argemonine and racemic N-methylpavine[6] has been rigidly established,[7] and its absolute configuration is of considerable interest in view of its possible biogenesis from reticuline.[8]

Both Ic and Ib gave (−)-argemonine on methylation[2,3] and Ie afforded the same material on demethylenating followed by methylation,[5] but the configurations of Ia and Id had not been chemically interrelated.

Since our work was completed, the isolation of the alkaloids crychine, caryachine, and (+)-0-methylcaryachine was reported[9] from *Cryptocaria chinensis.* The published physical constants of crychine appear to agree with those of eschscholtzine, and caryachine (If or Ig) on methylation gave a product with the physical properties of eschscholtzidine, while (+)-0-methylcaryachine appears to be the optical antipode of eschscholtzidine.

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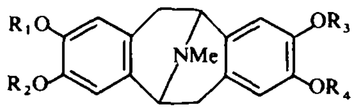
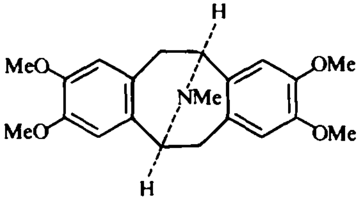


Ia: ($R_1 = R_2 = R_3 = R_4 = Me$)
Ib: ($R_1 = R_3 = R_4 = Me; R_2 = H$)
Ic: ($R_1 = R_3 = H; R_2 = R_4 = Me$)
Id: ($R_1R_2 = R_3R_4 = CH_2$)
Ie: ($R_1R_2 = CH_2; R_3 = R_4 = Me$)
If: ($R_1R_2 = CH_2; R_3 = Me; R_4 = H$)
Ig: ($R_1R_2 = CH_2; R_3 = H; R_4 = Me$)



II

Argemonine is a molecule showing a high degree of symmetry, as evidenced by its NMR spectrum,[4b, 7a] and possesses a chromophore which can be regarded as made up of two identical 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline moieties. In fact, the UV spectrum of argemonine (Table 1) shows absorption bands at 205, 230 and 287 mμ which are the local excitation bands of a 4,5-dialkylcatechol dimethyl ether together with the $p \rightarrow \pi$ electron transfer transition of the catechol system in the 226–230 mμ region. This spectrum is closely similar, but with twice the absorption intensity for each peak, to that of the 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolines[10] which show UV maxima at 204, 232 and 285 mμ (log ε 4·67, 3·85 and 3·56). This situation is analogous to the case of 1,2-diphenylethane and toluene (or ethylbenzene),[11] where the absorption curve of the first-named compound is almost identical with that of the last two but with about twice the intensity at 260 mμ.

The absolute configuration of the two asymmetric centers in argemonine must, from stereochemical requirements, be identical. Thus, if the biogenetic precursor of (−)-argemonine is S-(+)-reticuline,[8] then the absolute configuration of (−)-argemonine must be 1S,5S as shown in II.

The 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline alkaloids show a positive Cotton effect between 270 and 290 mμ for compounds of the S-configuration both for the N-acylated derivatives[12] and for the free bases and their salts.[13] In the

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case of the closely related 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline alkaloids, the UV spectrum of which is very similar to that of the 1-methyl analogues,[10] the compounds of S-configuration again possess a positive Cotton effect and circular dichroism maximum at ca. 280 mμ for the free bases, their salts, and their quaternary derivatives.[10]

TABLE 1. UV ABSORPTION OF ARGEMONINES

Compound	λ_{max} mμ (log ε)					
Argemonine* (Ia)	230 sh (4·15)	250 min (2·47)	276 sh (3·79)	282 (3·91)	287 (3·93)	292 (3·89)
Norargemonine* (Ib)	230 sh (4·12)	251 min (2·71)	278 sh (3·81)	283 (3·92)	287 (3·93)	293 (3·92)
Bisnorargemonine (Ic)	230 sh (4·07)	250 min (2·59)	279 sh (3·83)	285 (3·92)	288 (3·93)	294 (3·89)
Eschscholtzine (Id)	235 sh (3·80)	253 min (2·35)	275 sh (3·93)	281 (4·03)	296 (4·04)	307 sh (3·96)
Eschscholtzidine (Ie)	235 sh (4·01)	252 min (3·07)		282 sh (3·88)	290 (3·97)	303 (3·72)

* 205 sh (4·94).

The ORD curves of the argemonine alkaloids Ia–Ie were almost superimposable, and showed three Cotton effects centered at ca. 280, 235 and 206 mμ, in agreement with their UV absorption peaks, and confirmed by the positions of the CD maxima. The curves for (−)-argemonine (Ia) and (−)-eschscholtzidine (Ie) are shown in Figs. 1 and 2, respectively. The close similarity of all five curves indicates that the alkaloids Ia–Ie possess the same absolute configuration, identical with that of crychine and caryachine, while (+)-0-methylcaryachine must have the opposite configuration.

The large values of the molecular ellipticity for the "allowed" transitions between 200 and 240 mμ, and particularly that for the 206 mμ band ([θ] = ca. 250,000) in the argemonines suggest some degree of dissymmetry, possibly due to the twisted diphenylethane system in the molecule. Such enhancement of the CD of this region does not occur in the 1-methyl- and 1-benzyl-tetrahydroisoquinolines. For this reason, only the Cotton effect due to the long-wavelength (280 mμ) band, which is polarized in the molecular plane of the tetrahydroisoquinoline chromophore,[14] can be used for configurational comparison between the argemonines and the 1-substituted tetrahydroisoquinolines. The CD of the 280 mμ band in argemonines is, in fact, about twice the intensity as that for the same band in its 1-benzyltetrahydroisoquinoline isomer laudanosine,[10] so that the CD *per tetrahydroisoquinoline asymmetric center* is the same for this transition in both series.

As in the case of both the 1-methyl- and the 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines, protonation of the nitrogen in the argemonines showed little effect on the ORD curves or the UV spectrum, both of which closely resembled those of the parent base. The same was true for argemonine methiodide (Experimental).

The close correspondence between the sign of the 280 mμ Cotton effect and the absolute configuration of the asymmetric center in the 1-methyl- and 1-benzyl compounds, where all substances of S-configuration showed a positive Cotton effect and CD maximum at 280 mμ for the bases, salts, and methiodides, suggests that the identically substituted argemonine alkaloids, made up of two configurationally identical tetrahydroisoquinoline moieties and also showing the same rotatory behavior at 280 mμ for bases, salts, and methiodides, similarly belong to the S-series, and that (−)-argemonine therefore has the 1S,5S configuration.

This conclusion agrees with its proposed biogenesis[8] from S-(+)-reticuline, and with a calculation based on a non-empirical analysis[14] of the CD maximum of the 280 mμ band of this compound at 80°K. Since the completion of this work, we have been informed by Professor Battersby[15] that he has obtained the 1S,5S configuration for (−)-argemonine by chemical degradation. The conclusion based on ORD and CD methods is thus in agreement with the chemical evidence.

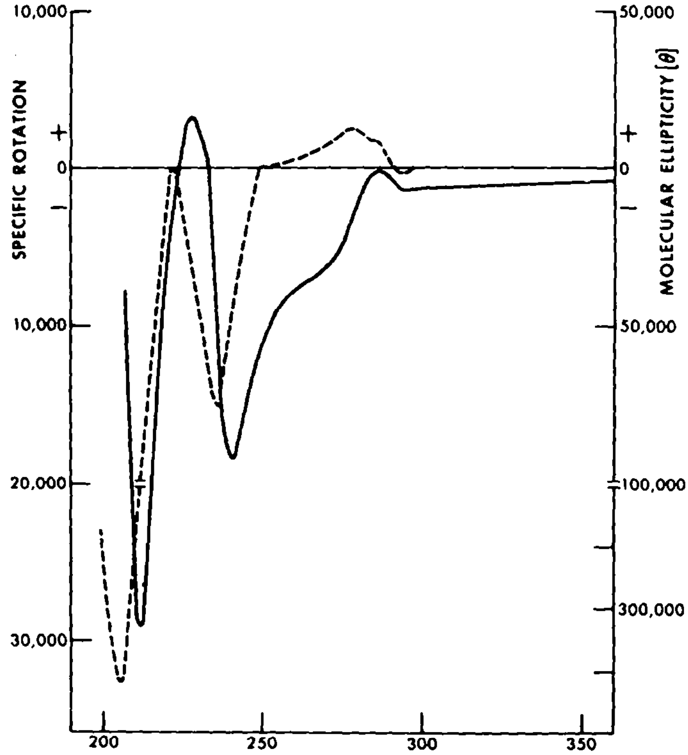

FIG. 1. Rotatory dispersion (———) and circular dichroism (------) curves of (−)-argemonine.

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[14] S. F. Mason, K. Schofield, R. J. Wells, J. B. Whitehurst and G. W. Vane, unpublished work. We thank Professor Mason for this information.

[15] A. R. Battersby, private communication. We thank Professor Battersby for informing us of his results before publication.

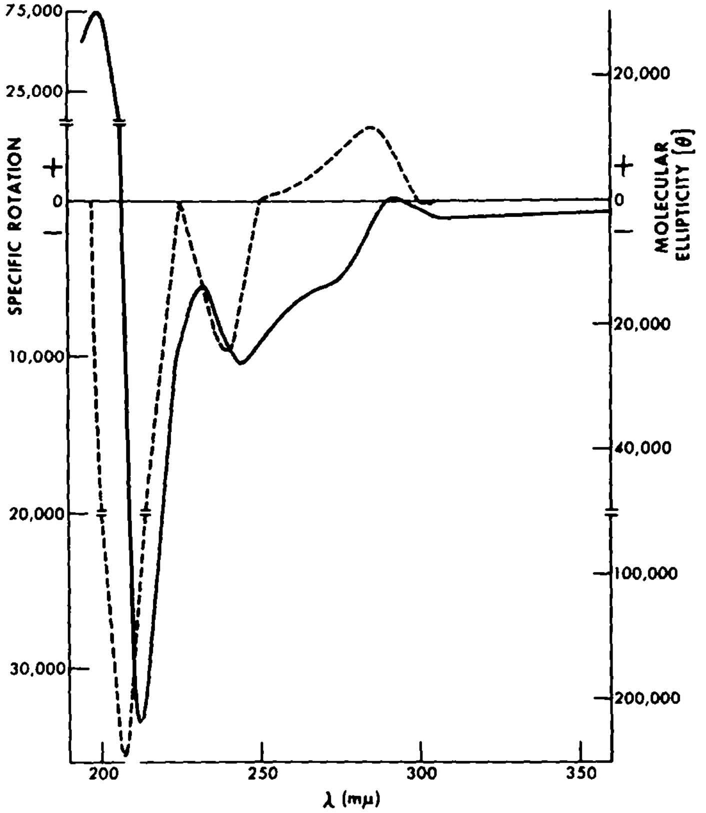

FIG. 2. Rotatory dispersion (———) and circular dichroism (– – – –) curves of (−)-eschscholtzidine.

EXPERIMENTAL

ORD and CD curves were determined on a Jasco ORD/CD-5 instrument in 95% EtOH at 25°. Rotations are given only for (1) the highest and lowest wavelengths measured, (2) peaks and troughs. CD is recorded in molecular ellipticity units [θ].[16]

(−)-*Argemonine.* $[\alpha]_D$ −214° (c 1·01, EtOH). ORD (c 0·12) $[\alpha]_{370}$ −779°, $[\alpha]_{294}$ −1353° (tr), $[\alpha]_{287}$ −123° (pk), $[\alpha]_{273}$ −5600° (sh), $[\alpha]_{241}$ −18,360° (tr), $[\alpha]_{228}$ +3280° (pk), $[\alpha]_{212}$ −29,100° (tr), $[\alpha]_{207}$ −7787°. CD $[\theta]_{298}$ 0, $[\theta]_{292\cdot5}$ −1344, $[\theta]_{291}$ 0, $[\theta]_{278}$ +12,680, $[\theta]_{251}$ 0, $[\theta]_{236}$ −74,890, $[\theta]_{223}$ 0, $[\theta]_{206}$ −415,000.

Argemonine hydrochloride ORD (c 0·13, 95% ethanolic 0·1 N–HCl) $[\alpha]_{350}$ −918°, $[\alpha]_{303}$ −1229° (tr), $[\alpha]_{292}$ −862° (pk), $[\alpha]_{275}$ −4670° (sh), $[\alpha]_{244}$ −18,360° (tr), $[\alpha]_{233}$ +7787° (pk), $[\alpha]_{216}$ −17,200° (tr), $[\alpha]_{203}$ +7800°. CD $[\theta]_{300}$ 0, $[\theta]_{281}$ +8256, $[\theta]_{255}$ 0, $[\theta]_{240}$ −76,810, $[\theta]_{226}$ 0, $[\theta]_{215}$ 0, $[\theta]_{207}$ −375,000.

Argemonine methiodide. M.p. 273–274°. ORD (c 0·01) $[\alpha]_{360}$ −800°, $[\alpha]_{296}$ −1200° (tr), $[\alpha]_{288}$ −700° (pk), $[\alpha]_{274}$ −3000° (sh), $[\alpha]_{246}$ −11,400° (tr), $[\alpha]_{234}$ −5000° (pk), $[\alpha]_{211}$ −18,500° (tr), $[\alpha]_{202}$ −36,000° (pk), $[\alpha]_{195}$ −14,000°. CD $[\theta]_{299}$ 0, $[\theta]_{290}$ −1974, $[\theta]_{289}$ 0, $[\theta]_{278}$ +4600, $[\theta]_{255}$ 0, $[\theta]_{240}$ −62,200, $[\theta]_{229}$ 0, $[\theta]_{215}$ 0, $[\theta]_{208}$ −138,000, $[\theta]_{200}$ 0.

(−)-*Norargemonine.* $[\alpha]_D$ −154° (c 2·79), $CHCl_3$). ORD (c 0·10) $[\alpha]_{360}$ −750°, $[\alpha]_{289}$ +450°, $[\alpha]_{273}$ −6000° (sh), $[\alpha]_{241}$ −16,800° (tr), $[\alpha]_{228}$ −750° (pk), $[\alpha]_{212}$ −32,000 (tr), $[\alpha]_{205}$ +30,000°. CD $[\theta]_{298}$ 0, $[\theta]_{280}$ +14,630, $[\theta]_{250}$ 0, $[\theta]_{235}$ −58,520, $[\theta]_{220}$ −22,510, $[\theta]_{206}$ −225,000.

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Norargemonine hydrochloride. ORD (*c* 0·108, 95% ethanolic 0·1 N–HCl) $[\alpha]_{360}$ −550°, $[\alpha]_{294}$ +417° (pk), $[\alpha]_{275}$ −4810° (sh), $[\alpha]_{244}$ −14,420° (tr), $[\alpha]_{233}$ +5100° (pk), $[\alpha]_{212}$ −3240° (tr), $[\alpha]_{205}$ +27,500°. CD $[\theta]_{307}$ 0, $[\theta]_{214}$ 0, $[\theta]_{207}$ −205,000.

(−)-*Bisnorargemonine.* $[\alpha]_D$ −265·8° (*c* 0·158, MeOH). ORD (*c* 0·10) $[\alpha]_{260}$ −800°, $[\alpha]_{296}$ −1225° (tr), $[\alpha]_{288}$ +250° (pk), $[\alpha]_{270}$ −6800° (sh), $[\alpha]_{240}$ −16,400° (tr), $[\alpha]_{227}$ −5000 (pk), $[\alpha]_{212}$ −37,000° (tr), $[\alpha]_{208}$ −11,500°. CD $[\theta]_{300}$ 0, $[\theta]_{294}$ −1295, $[\theta]_{280}$ +13,810, $[\theta]_{250}$ 0, $[\theta]_{235}$ −47,470, $[\theta]_{224}$ −23,740, $[\theta]_{206}$ −287,500.

Bisnorargemonine hydrochloride. ORD (*c* 0·108, 95% ethanolic 0·1 N–HCl) $[\alpha]_{360}$ −741°, $[\alpha]_{291}$ −370° (pk), $[\alpha]_{275}$ −4820° (sh), $[\alpha]_{243}$ −14,100° (tr), $[\alpha]_{230}$ +1850° (pk), $[\alpha]_{212}$ −38,450° (tr), $[\alpha]_{205\cdot5}$ +10,000°. CD $[\theta]_{304}$ 0, $[\theta]_{280}$ +9870, $[\theta]_{250}$ 0, $[\theta]_{238\cdot5}$ −47,520, $[\theta]_{225}$ 0, $[\theta]_{218}$ 0, $[\theta]_{207}$ −242,000.

(−)-*Eschscholtzine.* $[\alpha]_D$ −202° (*c* 1·00, MeOH). ORD (*c* 0·10 $[\alpha]_{360}$ −900°, $[\alpha]_{301}$ −1250° (tr), $[\alpha]_{292}$ +850 (pk), $[\alpha]_{275}$ −7200° (sh), $[\alpha]_{245}$ −15,600° (tr), $[\alpha]_{232}$ −4000° (pk), $[\alpha]_{215}$ −36,000°. CD $[\theta]_{306}$ 0, $[\theta]_{300}$ −2395, $[\theta]_{297}$ 0, $[\theta]_{286}$ +18,650, $[\theta]_{254}$ 0, $[\theta]_{240}$ −37,310, $[\theta]_{227}$ −17,050, $[\theta]_{205}$ −255,000.

Eschscholtzine hydrochloride. ORD (*c* 0·11, 95% ethanolic 0·1 N–HCl) $[\alpha]_{360}$ −720°, $[\alpha]_{293}$ −22·5 (pk), $[\alpha]_{280}$ −4505° (sh), $[\alpha]_{248}$ −12,210° (tr), $[\alpha]_{231}$ −2870° (pk), $[\alpha]_{215}$ −23,151°. CD $[\theta]_{310}$ 0, $[\theta]_{305}$ +427, $[\theta]_{300}$ 0, $[\theta]_{285}$ +11,760, $[\theta]_{257}$ 0, $[\theta]_{240}$ −30,500, $[\theta]_{220}$ −1600, $[\theta]_{206}$ −219,000.

(−)-*Eschscholtzidine.* $[\alpha]_D$ −194·2 (*c* 1·56, MeOH). ORD (*c* 0·10) $[\alpha]_{360}$ −750°, $[\alpha]_{292}$ +150° (pk), $[\alpha]_{275}$ −5200° (sh), $[\alpha]_{244}$ −10,400° (tr), $[\alpha]_{232}$ −5500° (pk), $[\alpha]_{212}$ −33,500° (tr), $[\alpha]_{199}$ +75,000° (pk), $[\alpha]_{195}$ +56,250. CD $[\theta]_{305}$ 0, $[\theta]_{301}$ −335, $[\theta]_{299}$ 0, $[\theta]_{285}$ +11,600, $[\theta]_{251}$ 0, $[\theta]_{240}$ −22,400, $[\theta]_{225}$ 0, $[\theta]_{207}$ −245,000, $[\theta]_{198}$ 0.

Eschscholtzidine hydrochloride. ORD (*c* 0·11, 95% ethanolic 0·1 N–HCl) $[\alpha]_{360}$ −741°, $[\alpha]_{293}$ −406° (pk), $[\alpha]_{278}$ −3960° (sh), $[\alpha]_{247}$ −9910° (tr), $[\alpha]_{235}$ −3150 (pk), $[\alpha]_{212}$ −36,950° (tr), $[\alpha]_{200}$ +74,200 (pk), $[\alpha]_{195}$ +34,600. CD $[\theta]_{309}$ 0, $[\theta]_{285}$ +7800, $[\theta]_{253}$ 0, $[\theta]_{243}$ −29,000, $[\theta]_{229}$ 0, $[\theta]_{218}$ 0, $[\theta]_{207}$ −234,800, $[\theta]_{200}$ 0.