

## The *ent*-*neo*-Clerodane Absolute Configuration of Ajuagarins

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**Summary** The absolute configurations of the caryoptins and ajuagarins are enantiomeric and both should be reversed from those previously proposed; the absolute configuration of the caryoptins can be correctly derived from the dibenzoate chirality method.

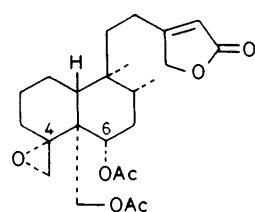
In our structural studies on the insect antifeedant ajuagarin-I ("1"),‡ we had converted it into the 6-keto derivative ("2") and compared the c.d. with that of a similar derivative ("4")<sup>2</sup> derived from clerodine ("3").<sup>1</sup> Since the c.d. of ("2") and ("4") were enantiomeric it was concluded<sup>1</sup> that the ajuagarins should be represented by ("1"), *i.e.*, an absolute configuration opposite to that of clerodine ("3"). On the

other hand, Hosozawa *et al.*<sup>2</sup> converted the antifeedant caryoptin ("5") into the 6-keto-3,4-acetonide ("6"), which exhibited a positive c.d. Cotton effect similar to that of ("4"); from this it was concluded<sup>2</sup> that the configuration of caryoptin was ("5"), namely, identical to that of clerodine, ("3") which in turn depended on an earlier heavy-atom X-ray study.<sup>3</sup>

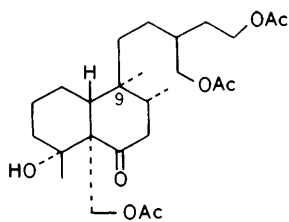
However, when it was found that the 3,6-bis-*p*-chlorobenzoate ("7") from caryoptin gave a negative split c.d. curve, *i.e.*, opposite to that predicted for ("7") on the basis of the exciton chirality method,<sup>4</sup> an intramolecular hydrogen bonding was invoked to account for this apparent exception.<sup>2</sup>

In order to resolve the c.d. enigma of the caryoptins, we have transformed 3-epicaryoptin (8) into the *N*-trichloroacetylurethane derivative (10) as follows.

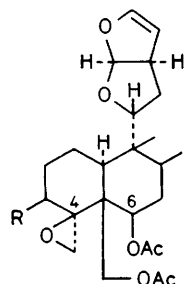
According to Hosozawa's method,<sup>2</sup> 3-epicaryoptin (8) was hydrogenated to its 14,15-dihydro-derivative which was further reduced and hydrolysed with LiAlH<sub>4</sub> to the 3,4,6,18-tetraol. The tetraol (5 mg) was selectively acetylated to give its 18-acetate (18- and 18'-H:  $\delta$  4.83 and 4.56, *J* 12.9 Hz).§ Treatment of the 18-acetate with *p*-bromobenzoyl chloride in pyridine at room temperature gave an isomeric mixture of bis-*p*-bromobenzoates which were



("1") Ajuagarin-I

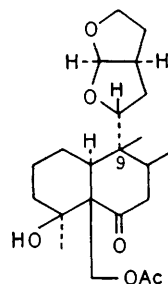


("2")  $\Delta \epsilon_{298} -3.41$

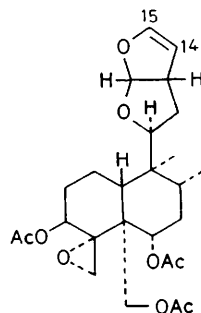


("3") R = H Clerodine

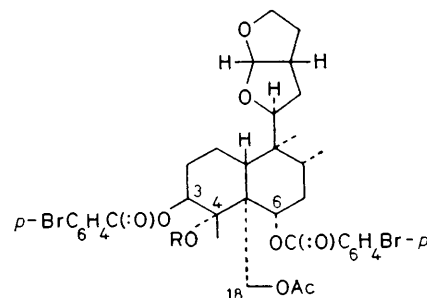
("5") R = OAc Caryoptin



("4")  $\Delta \epsilon_{302} +3.51$



(8) 3-Epicaryoptin



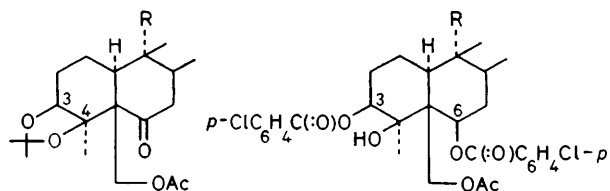
(9) R = H  $\Delta \epsilon_{252} +24.8$

$$\Delta \epsilon_{235} -11.6$$

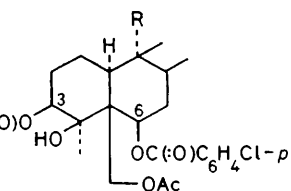
(10) R = CO·NH·COCCl<sub>3</sub>

$$\Delta \epsilon_{252} +18.1$$

$$\Delta \epsilon_{236} -7.2$$



("6")  $\Delta \epsilon_{301} +3.10$   
R: same as "4"



("7")  $\Delta \epsilon_{248} -28.8$   
 $\Delta \epsilon_{230} +7.5$   
R: same as "4"

separable on h.p.l.c. (Waters,  $\mu$ -Bondapak C<sub>18</sub>, 20% H<sub>2</sub>O in MeOH). The major product was characterized as the 3,6-bis-*p*-bromobenzoyl-18-acetate (9) and the minor product as the 3,18-bis-*p*-bromobenzoyl-6-acetate from the <sup>1</sup>H-n.m.r. spectra (18- and 18'-H:  $\delta$  5.04 and 4.77, *J* 12.5 Hz; and  $\delta$  5.25 and 4.98, *J* 12.5 Hz, respectively). The major dibenzoate (9),  $\lambda_{\max}$  243 nm,  $\epsilon$  3.5 × 10<sup>4</sup> (in MeOH) showed

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‡ The numerals in quotation marks, both in the text and in structural formulae, represent the earlier *enantiomeric* structures.

§ All <sup>1</sup>H n.m.r. spectra were measured in CDCl<sub>3</sub>.

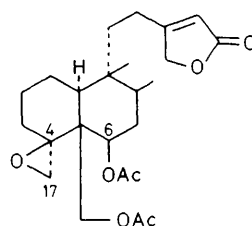
a positively split c.d. similar to that of the corresponding bis-*p*-chlorobenzoate reported by Hosozawa.<sup>2</sup>

Absence of the twisting of the benzoate transition moment by hydrogen bonding was inferred from the c.d. behaviour at elevated temperature (up to *ca.* 70 °C, in EtOH); only a 10% decrease in amplitude was observed at *ca.* 50 °C. In order to ascertain the absence of the effect of hydrogen bonding on the c.d., the dibenzoate (**9**) (*ca.* 50 μg) was treated with trichloroacetyl isocyanate<sup>5</sup> in dry CH<sub>2</sub>Cl<sub>2</sub> at room temperature to afford the dibenzoate urethane (**10**), λ<sub>max</sub> 245 nm, ε 2 × 10<sup>4</sup> (in MeOH); chemical ionization mass spectrum (methane): *m/e* 505, 507, 509, and 511 (9:10:3:1) [(*M*+1) - 2(BrC<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H) - (CH<sub>3</sub>CO<sub>2</sub>)]<sup>+</sup>; Fourier transform i.r. spectrum: (film on NaCl), ¶ 3500 and 3400 (NH), 1800 (w, shoulder on the strong 1740—1720 ester and urethane band), and 760 cm<sup>-1</sup> (C-Cl). The c.d. of the urethane (**10**) was positively split and unchanged from that of the dibenzoate (**9**). Thus it can be concluded that a hydrogen bond is not involved in the c.d. of dibenzoates (**9**) and (**10**); in view of the dibenzoate chirality, the absolute configuration of caryoptins therefore should be revised from ("5") to that shown in (**8**) for 3-epicaryoptin.

However, the fact that the c.d. signs of the 6-keto-compounds ("4") [from clerodin ("3")] and ("6") [from caryoptin ("5")] are the same<sup>2</sup> does not necessarily lead to the conclusion that the clerodin configuration should also be reversed. This is because the aforementioned comparison of the c.d. curves<sup>2</sup> of ("4") and ("6") is not conclusive: namely, the 3,4-acetonide group in ("6") falls into a front octant<sup>6</sup> and hence its contribution relative to that of the 4-hydroxy-group in ("4") cannot be estimated. However Harada and Uda<sup>7</sup> have recently shown that the caryoptin

and clerodin configurations should both be revised to those enantiomeric to ("3") and ("5"). The same conclusion was reached independently by Rogers *et al.*<sup>8</sup> who reinvestigated the crystal structures of 3-epicaryoptin and clerodin bromolactone.

The comparison of the c.d. curves of the 6-ketones ("2") and ("4") is valid since except for the side-chains, which should have no effect on the Cotton effect, the substituents on both nuclei have identical spatial relations. Since the c.d. curves are antipodal, it follows that the ajugarins should be represented by structures enantiomeric to those of the clerodin and caryoptin series ("neo-clerodanes"<sup>8</sup>);



(11) Ajugarin-I  
(12) Ajugarin-II (6-OH)  
(13) Ajugarin-III (4,17-diol)

therefore they should be depicted as (**11**)–(**13**) ('*ent*-neo-clerodanes'<sup>8</sup>). It is interesting to note that in spite of their enantiomeric absolute configurations, the ajugarins and clerodins/caryoptins both exhibit insect antifeedant activities.<sup>9</sup>

We thank Drs. N. Harada, D. Rogers, and S. V. Ley for discussions. The studies were supported by the National Institutes of Health.

(Received, 19th June 1979; Com. 652.)

¶ We are grateful to Dr. S. L. Chen, Lederle Laboratories, for this measurement with a Nicolet instrument. The frequencies quoted were also present in the spectrum of *N*-trichloroacetyl methylcarbamate.

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<sup>9</sup> S. Hosozawa, N. Kato, and K. Munakata, *Phytochem.*, 1973, 12, 1833; 1974, 13, 308.