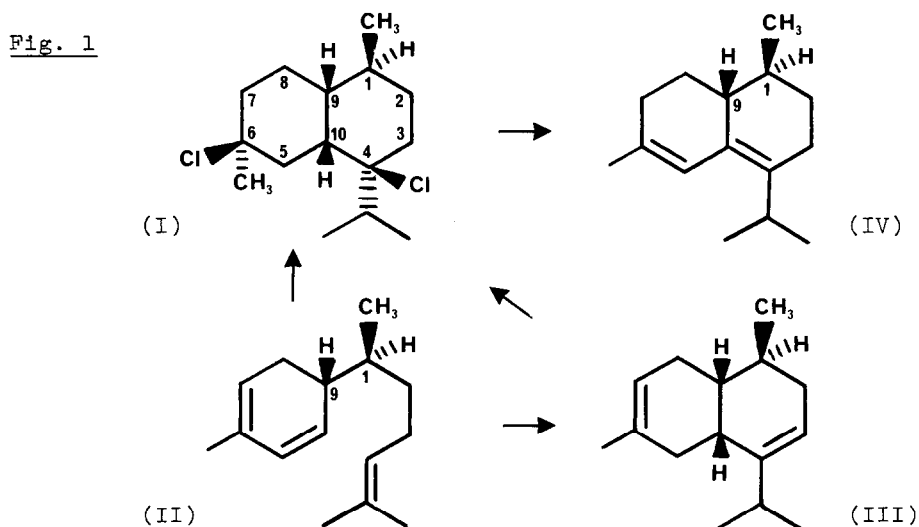


THE TOTAL STEREOSTRUCTURE OF (-)-ISOZINGIBERENE DIHYDROCHLORIDE

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**Abstract:** The stereochemistry and absolute configuration of (-)-isozingiberene dihydrochloride have been determined and the latter has been correlated with the cadalenic sesquiterpene, (-)-epizonarene.

Isozingiberene dihydrochloride (I)<sup>1</sup> is the characteristic crystalline derivative (Fig. 1) of both the monocyclic sesquiterpene, zingiberene (II), and the dicyclic sesquiterpene, "isozingiberene" (III)<sup>2</sup>. The gross structure of the dihydrochloride was established in 1944<sup>1</sup>, but its stereochemistry could be inferred only at C<sub>1</sub> and C<sub>9</sub> from its chemical correlation with that of zingiberene<sup>3</sup>. The present investigation establishes the stereochemistry at all five asymmetric centers by chemical, spectral and x-ray methods, and in addition correlates isozingiberene dihydrochloride with the cadalenic sesquiterpene, (-)-epizonarene (IV)<sup>4a,b,c</sup>. Our results confirm the chiral



identities of members of this series and establish the relationship between the monocyclic sesquiterpene, zingiberene, and sesquiterpenes of the cadalenic type possessing cis decalin systems<sup>5</sup>.

Isozingiberene dihydrochloride (I) was found to be stable under the conditions ( $\text{HCl}$  in  $\text{CH}_3\text{COOH}-\text{CHCl}_3$ ) which are reported<sup>6</sup> to result in the equilibration of chlorines in the 3-chloro-3-methylcholestanes from equatorial to the more preferred axial positions. These results suggested that the chlorines in (I) were axial. The IR data (KBr pellet) supported the axial configuration of the chlorines<sup>7</sup>, with absorption maxima observed for the carbon-chlorine bonds at 430, 470, 540, 575 (tertiary C-Cl bonds of the type  $T_{\text{HHH}}$  at  $C_6$ ) and at 630 and 660 (tertiary C-Cl bonds of the type  $T_{\text{CCH}}$  at  $C_4$ )  $\text{cm}^{-1}$ . The 220-MHz  $^1\text{H}$  NMR spectrum of (I) confirmed the gross structure previously assigned<sup>1</sup> to this compound, with peaks observed down-field from TMS for the  $C_1$ -methyl group at  $\delta$  0.89 (3H, doublet,  $J = 6.5$  Hz), for the  $C_4$ -isopropyl group at  $\delta$  1.02 and 1.03 (both 3H, doublets,  $J = 6.0$  Hz each), and for the  $C_6$ -methyl group at  $\delta$  1.62 (3H, singlet) ppm.

The conversion of (-)-isozingiberene dihydrochloride (I) to (-)-epizonarene (IV) of known stereochemistry and absolute configuration<sup>4a</sup> established in (I) the chiralities at  $C_1$  and at  $C_9$ . The dihydrochloride (I) was refluxed with ethanolic KOH to give a mixture of alkenes (b.p. 82-83°/1 mm)<sup>1,8</sup>. The latter was equilibrated with formic acid in *n*-decane at 100° for 5 hrs<sup>4a</sup>. The resulting mixture absorbed strongly in the UV and was found to consist, by gc analysis (25% Carbowax 20M/150°), of two major components. The compound corresponding to the peak with the longer retention time (59 min) was identified as (-)-epizonarene (IV,  $\lambda_{\text{max}}^{\text{MeOH}}$  246-247 nm,  $\epsilon$  18900;  $^1\text{H NMR}^{\text{CDCl}_3}$   $\delta$  0.97, 1.78, 6.22 ppm;  $[\alpha]_{\text{D}}^{23}$  -130°). The infrared spectrum of the diene (IV) was found to be superimposable with that reported for epizonarene (10  $\alpha$  H-muuroloa-4,6-diene) by Andersen and coworkers<sup>4a</sup>.

X-ray crystallographic analysis confirmed the amorphane-type structure for isozingiberene dihydrochloride (I)<sup>9</sup>. The latter was shown to possess a cis-decalin system<sup>10</sup>, with the  $C_4$ -isopropyl group trans and the  $C_1$ -methyl group cis to the bridgehead hydrogens, and the chlorines at  $C_4$  and  $C_6$  occupying axial positions (Fig. 2). The x-ray work also confirmed the absolute configuration of (-)-(I) as the enantiomorph shown in Fig. 1<sup>11a,b</sup>.

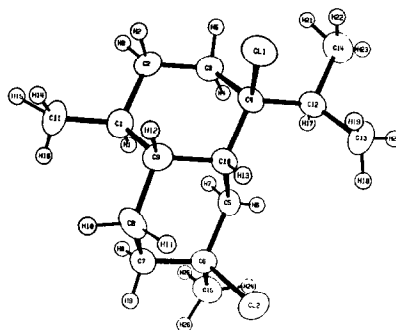


Fig. 2 ORTEP drawing of (-)-isozingiberene dihydrochloride (I).

Isozingiberene dihydrochloride (well-defined needles,  $[\alpha]_D^{22} -17^\circ$ , m.p.  $181-183^\circ$  with loss of HCl) belonged to the space group  $P2_12_12_1$  (orthorhombic), with unit cell dimensions  $a = 6.235(3)$ ,  $b = 14.809(4)$ ,  $c = 16.173(3)$  Å;  $\beta = 90^\circ$ ;  $V = 1493.3(5)$  Å<sup>3</sup>;  $\rho = 1.233$  g/cm<sup>3</sup>;  $Z = 4$ . The x-ray structure was solved by direct methods and refinement was carried out by the full matrix least squares method<sup>11a,b</sup>.

The deviation in the carbon-chlorine bond lengths from normal values in isozingiberene dihydrochloride was found to be similar to the deviations reported for both cadinene and muurolene dihydrochloride<sup>12,13</sup>. The carbon-chlorine bond distances in all these sesquiterpenoids are somewhat lengthened (found for isozingiberene dihydrochloride,  $C_4-Cl = 1.852(5)$  and  $C_6-Cl = 1.861(6)$  Å). The bond angles in (I), however, were found to deviate less appreciably from normal values compared to analogous bond angles reported for cadinene and muurolene dihydrochloride<sup>12,13</sup> (e.g., found for  $C_6-C_5-C_{10}$  in (I):  $114.3(5)^\circ$ ). The reduced strain in isozingiberene dihydrochloride and the favorable "non-steroidal" conformation of the *cis*-decalin system placing the alkyl substituents at  $C_1$ ,  $C_4$ , and  $C_6$  in preferred equatorial positions is consistent with the remarkable stability (compared to the lack of stability of muurolene dihydrochloride for instance<sup>14</sup>) observed in this study for this compound.

#### References and Footnotes

1. M. D. Soffer, C. Steinhardt, G. Turner and M. E. Stebbins, J. Am. Chem. Soc., **66**, 1520 (1944).
2. The dehydrochlorination product of isozingiberene dihydrochloride, which has been known as "isozingiberene" is actually a mixture of bond isomers (see ref. 8) of which the sesquiterpene III is the best characterized. Isozingiberene dihydrochloride is similarly derived from the "isozingiberene" prepared by direct cyclization ( $CH_3COOH-H_2SO_4$ ) of zingiberene.
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 b) G. Mehta and B. P. Singh, J. Org. Chem., **42**, 632 (1977).  
 c) V. K. Belavadi and S. N. Kulkarni, Indian J. Chem., **14B**, 901 (1976).
5. The cyclization of zingiberene resulting in the formation of a *cis*-decalin system may follow a mechanism similar to that proposed by Ohta and Hirose (Chem. Lett. 263 (1972)) for analogous cyclizations.
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8. The mixture from the dehydrochlorination consists of at least four clearly separable components (gc, 25% Carbowax 20M/150°). This mixture upon treatment with HBr readily formed isozingiberene dihydrobromide in high yield (m.p. 197-198°;  $[\alpha]_D^{20}$  -15.8°;  $\nu_{\max}^{\text{KBr}}$  482, 498, 570, 630, 648  $\text{cm}^{-1}$ ; 220-MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91 (3H, d,  $J = 6.0$  Hz), 1.04 (3H, d,  $J = 6.5$  Hz), 1.07 (3H, d,  $J = 6.5$  Hz), 1.84 (3H, s) ppm.
9. The x-ray analysis was carried out by the Molecular Structure Corporation in College Station, Texas.
10. It has been pointed out (L. Westfelt, Acta Chem. Scand., 20, 2852 (1966)) that  $\epsilon$ -muurolene and isozingiberene give the same tetrahydro derivative. It can be assumed from Westfelt's statement that isozingiberene, and therefore its dihydrochloride derivative, possess cis-decalin systems. However, structure assignments in this series which rely solely on correlations with tetrahydro derivatives are not unambiguous since the tetrahydro derivatives described in most cases consist of isomeric mixtures (see N. H. Andersen and M. S. Falcone, J. Chromatogr., 44, 52 (1969)). The cis nature of the ring junction in isozingiberene dihydrochloride was established in the present work for the first time directly, by the use of x-ray methods.
11. a) The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom. Any request should be accompanied by the full literature citation for this communication.  
b) Supplementary data available include bond distances, bond angles, standard deviations and structure factors. See announcement to authors, Tetrahedron Letters, 24, 5154 (1983).
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