## Communications to the Editor

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# A NOTE ON THE A-RING CONFORMATION IN 2-CHLORO-1,2-DIHYDROSANTONINS[1)]

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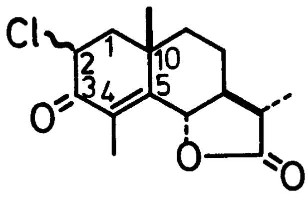
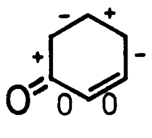
The half-chair and half-boat conformations observed by X-ray analysis for the A-ring of 2α- and 2β-chloro-1,2-dihydro-l-α-santonin 1, respecitvely, should be regarded as a deformed sofa conformation based on molecular mechanics.

KEYWORDS——2α- and 2β-chloro-1,2-dihydro-l-α-santonon;sofa conformation; molecular mechanics calculation; 2-cyclohexen-1-one

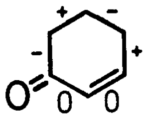
Recent syntheses and X-ray analyses of 2α- and 2β-chloro-1,2-dihydro-l-α-santonin 1[2)] revealed unusual conformations of the A-ring: half-chair in the former and half-boat in the latter. In polycondensed alicyclic systems including steroids, the component six-membered ring usually retains one of the energy-minimum conformations of the isolated ring.[3)] Since the parent structure of the A-ring, namely 2-cyclohexen-1-one, is known to exist only in sofa (2 or 2'),[4)] an intriguing question arises: do the observed A-ring conformations of 1 represent new conformers of 2, or are they merely 'wall' conformations that actually 'belong' to the sofa domain?



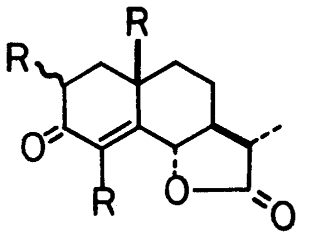
1



2



2'



3: R = H or Me

We applied the molecular mechanics technique[5] to this question. Allinger's MM2 force field[6] was used throughout this work.[7] When the cyclohexenone ring was cut out of the crystal coordinates of 2α- and 2β-Cl-**1**, and subjected to energy minimization, the one from the former optimized itself into sofa **2**, while that from the latter turned into the enantiomeric sofa **2'**. In fact, comparison of the endocyclic dihedral angles of the A-ring in **1**, **2** and **2'** (Table I) indicates close similarities between 2α-Cl-**1** and **2**, and between 2β-Cl-**1** and **2'**.

Table I. Endocyclic Dihedral Angles in 2-Cyclohexen-1-one **2** and **2'**, and along A-Rings of 2-Cl-1,2-dihydrosantonins **1**, and 1,2-Dihydrosantonin Homologues **3**[a]

| | Substituent at | | | Dihedral angle, deg[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compd. | $C_2$ | $C_4$ | $C_{10}$ | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $C_{10}$ |
| | Half-chair | | | − | + | − | 0 | − | + |
| | Half-boat | | | + | − | + | + | 0 | − |
| | Sofa | | | − | + | 0 | 0 | − | + |
| | Inverted sofa | | | + | − | 0 | 0 | + | − |
| **1** | α-Cl | Me | Me | (-65) | ( 49) | (-15) | ( -2) | (-12) | ( 45) |
| **1** | β-Cl | Me | Me | ( 64) | (-50) | ( 13) | ( 13) | ( 1) | (-40) |
| **2** | H | H | H[c] | -53 | 29 | -1 | -1 | -25 | 50[c] |
| **2'** | H | H | H[c] | 53 | -29 | 1 | 1 | 25 | -50[c] |
| **3a** | α-Me | Me | Me | -51 | 28 | -3 | 2 | -26 | 50 |
| **3b** | β-Me | Me | Me | 55 | -41 | 7 | 12 | 5 | -38 |
| **3c** | α-Me | Me | H | -55 | 33 | -5 | -1 | -22 | 49 |
| **3d** | β-Me | Me | H | 55 | -37 | 4 | 8 | 12 | -43 |
| **3e** | α-Me | H | Me | -51 | 27 | -2 | 0 | -24 | 48 |
| **3f** | β-Me | H | Me | 51 | -36 | 8 | 5 | 11 | -39 |
| **3g** | H | Me | Me | -51 | 26 | -2 | 3 | -28 | 50 |
| **3h** | H | Me | Me | 54 | -39 | 6 | 11 | 7 | -39 |
| **3i** | α-Me | H | H | -54 | 33 | -4 | -2 | -20 | 47 |
| **3j** | β-Me | H | H | 51 | -34 | 6 | 4 | 15 | -42 |
| **3k** | H | Me | H | -54 | 32 | -4 | -1 | -22 | 48 |
| **3l** | H | Me | H | 54 | -35 | 3 | 8 | 14 | -43 |
| **3m** | H | H | Me | -51 | 26 | -1 | 1 | -25 | 49 |
| **3n** | H | H | Me | 50 | -34 | 7 | 4 | 13 | -39 |
| **3o** | H | H | H | -53 | 31 | -3 | -1 | -22 | 47 |
| **3p** | H | H | H | 50 | -32 | 5 | 3 | 16 | -41 |

[a] ( ): X-ray analysis. Other values are based on optimized structures obtained by MM2 calculation. Common to each pair, the upper line corresponds to the conformer having the A-ring in half-chair or sofa, and the lower line to that having the A-ring in half-boat or inverted sofa. [b] $C_1$, $C_2$.... corresponds to the second atom of a four-atom dihedral angle system in A-ring counted counterclockwise on the structure drawing. E.g., $C_1$ means the $C_{10}$-$C_1$-$C_2$-$C_3$ system. [c] Pertains to $C_6$ of the isolated cyclohexenone ring.

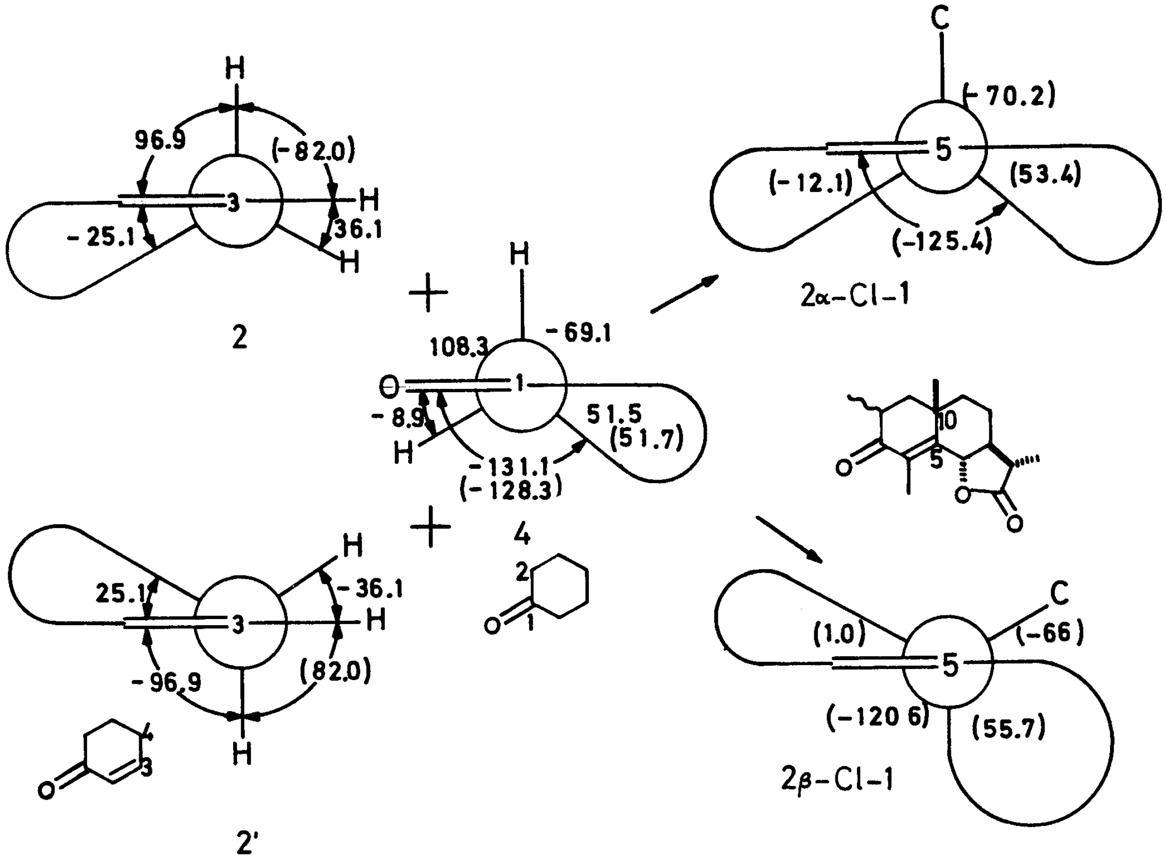


Fig. 1. Illustration of changes in dihedral angles in degrees during hypothetical fusion of two component rings to give the A/B-ring part of **1**. Newman projections are shown along $C_3$-$C_4$ bond of **2** and **2'**, along $C_1$-$C_2$ bond of cyclohexanone **4**, and along $C_5$-$C_{10}$ bond of 2α- and 2β-Cl-**1**. Unparenthesized angles refer to the calculated values and parenthesized to experimental.

There are, however, three problems regarding dihedral angles that argue against the straightforward assertion of the A-ring conformation: (A) Absolute values at $C_3$-$C_4$ in **1** are too large. (B) That of $C_4$-$C_5$ in 2β-Cl-**1** is also too large. These values should be near zero for the sofa conformation. (C) Absolute values at $C_5$-$C_{10}$ in **1** are too small, especially so for 2β-Cl-**1**, which should be about 25° for sofa.

Calculations of hydrocarbon analogues **3a-p** as model structures provide useful information (Table I). In these calculations, all possible combination patterns of methyl substitution at $C_2$, $C_4$, and $C_{10}$ are included, and the crystal coordinates of the ring skeletons of 2α- and 2β-Cl-**1** were used as the starting inputs for the pairs, **3a**/**3b**, **3c**/**3d**,...**3o**/**3p**, attaching the 2-methyl group at the equatorial position when it was present. None of the absolute value of $C_3$-$C_4$ dihedral angle is larger than 8°. Hence the observed large rotation of $C_3$-$C_4$ bond in **1** (the problem A) must be the result of substituents, probably the repulsion of α,β-unsaturated carbonyl with the neighboring C-Cl bond dipole.

Inspection of Table I reveals that the twist at $C_4$-$C_5$ double bond is larger than $10^o$ only for 2β-Cl-**1**, **3b** and **3h**, all having methyl groups at $C_4$ and $C_{10}$ on the *inverted sofa* A-ring. Further analysis$^{7)}$ indicates that this double bond also suffers from out-of-plane deformations causing large strain at this bond. Hence the problem B is also inherent to the substitution pattern of 2β-Cl-**1**.$^{8)}$

Figure 1 illustrates hypothetical fusion of enantiomeric *sofa* conformers of cyclohexenone (**2** and **2'**) with cyclohexanone **4** (as the model of the B-ring in **1**) to give A/B ring junctions. Smooth fusion may be expected to occur if the resulting endocyclic dihedral angles at the ring juncture do not change greatly from those of the starting component rings. The fusion of **2** with **4** corresponds to this case. In contrast, the fusion of **2'** involves dihedral angles of opposite sign (25.1 and -8.9$^o$), hence the new angle must approach zero. In the **3** series, the expectation is verified: $C_4$-$C_5$-$C_{10}$-$C_1$ dihedral angles are near -25$^o$ for the *sofa* series and near 10$^o$ for the *inverted sofa* series. For **1**, the signs are correct, but the absolute values are much smaller (the problem C), because of the anti-reflex effect$^{9)}$ from the increased puckering at $C_3$ to $C_5$.

In conclusion, the A-ring conformation of isomeric **1** should be regarded as the deformed *sofa*, and the empirical rule that the conformation of an isolated ring is essentially conserved in polycyclic systems appears to hold.

ACKNOWLEDGMENTS Calculations have been carried out at the Computing Centers of Hokkaido Univeristy and the Institute for Molecular Science.

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7) Details including parameterization will be given in the full account of this work.

8) The nature of the methyl effect on the double bond deformation is not yet clear.

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