Communications to the Editor

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EQUILIBRATION OF 2-CHLORO-1,2-DIHYDROSANTONIN CONFORMERS; A THEORETICAL APPROACH USING X-RAY DIFFRACTION AND MO CALCULATIONS[1)]

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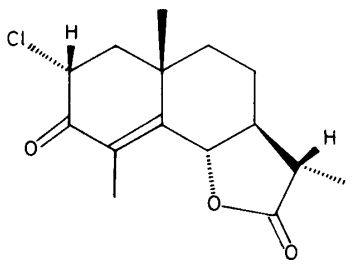
2α-Chloro-1,2-dihydro-ℓ-α-santonin (1) with the cyclohexenone A-ring of the ordinary half-chair form and the 2β-chloro isomer (2) with that of the unique half-boat form were found to equilibrate through acid-catalyzed epimerization and thermodynamic conformational change. In this, the former was favored over the latter by a free energy difference of 0.7 - 1.0 kcal/mol. The crystal structure and the half-chair conformation of the molecule of 1 were confirmed by X-ray diffraction methods. Semi-empirical (MNDO and CNDO) and ab initio molecular orbital calculations of these chloroenone conformers using input parameters obtained from their X-ray analytical data reproduced the observed conformational energy.

KEYWORDS——2α-/2β-chloro-1,2-dihydro-ℓ-α-santonin; half-chair/half-boat form; conformer; acid-catalyzed equilibration; stabilization energy; heat of formation; total energy; X-ray diffraction; MO calculation (MNDO/CNDO/ab initio)

During the course of our medico-chemical investigation of 2-chloro-1,2-dihydro-ℓ-α-santonins, we succeeded in isolating a new isomer with respect to the configuration of chlorine atom adjoining the carbonyl in the A-ring cyclohexenone with a unique half-boat form, i.e. 2β-chloro-4-en-3-one (2), together with another isomer, i.e. 2α-chloro-4-en-3-one (1) by the treatment of 4α,5α-epoxy-tetrahydro-ℓ-α-santonin with concentrated hydrochloric acid.[1)] Their structures and conformation were deduced on



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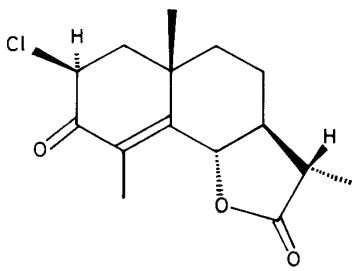

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the basis of IR, ^{1}H-NMR, MS and CD spectroscopic data for both isomers and established by X-ray crystallographic analysis for 2β-chloroenone (2).[1] In contrast to the energetically less favorable isomer (2) with the half-boat cyclohexenone A-ring, 2α-chloroenone (1) was considered to take the half-chair form, because 2 could be converted to 1 in the equilibration through the epimerization of the C_2 quasi-equatorial chlorine atom to the unfavorable quasi-axial orientation followed by the spontaneous inversion of the A-ring, and vice versa.[1,2] This paper describes the confirmation of the half-chair A-ring conformation and the configuration at C_2 of 2α-chloroenone (1) by X-ray diffraction methods, and the equilibration between these two isomers. The observed free energy difference is well supported by the two different semi-empirical and one ab initio molecular orbital (MO) calculations mentioned below.

Chlorination of 1,2-dihydro-ℓ-α-santonin with sulfuryl chloride in ether at 0°C afforded a mixture of 1 and 2, from which neither isomer was isolated by recrystallization or conventional column chromatography, but they were separated successfully by reversed phase high pressure liquid chromatography (HPLC) on μ-bondapak C_{18} using MeOH-H_2O-MeCN (10:10:3) or by ordinary HPLC on μ-porasil with n-hexane-$CHCl_3$ (1:1) as the solvent system. It is of interest to note that the ratio of 1 to 2 was always about 4:1 after several hours and even after 6 days. This suggests that α-chloroenone is apparently more stable than the β-isomer if the above reaction conditions achieved a thermodynamic control. In order to confirm the half-chair A-ring conformation in 1, we analysed it by X-ray crystallography. The resulting paramerters were used for the energy calculation discussed later. The crystal data for the colorless prism of 1 obtained by recrystallization from ethyl acetate are as follows: $C_{15}H_{19}O_3Cl$ (1), M.W. 282.8, orthorhombic, a = 8.347(2), b = 25.504(3), C = 6.191(9) Å, U = 1473.4 Å^3, z = 4, Dc = 1.2749 gcm^{-3}, space group $P2_12_12_1$. Intensities were measured with a four-circle diffractometer with graphite monochromated Cu-Kα radiation (λ = 1.5418 Å). The crystal structure and the molecular conformation were solved by the same method as mentioned previously,[1,3] to give a final R value of 0.079. Fig. 1 shows stereoviews of α-chloroenone (1) and β-chloroenone (2).

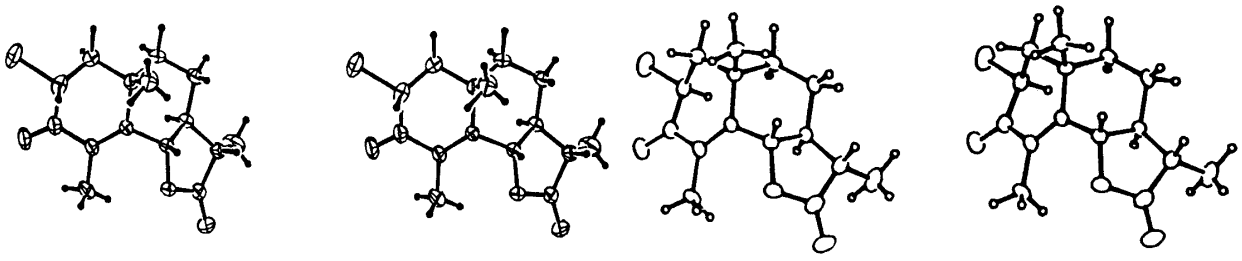

Fig. 1. Stereoviews of α-Chloroenone (1) (Left) and β-Chloroenone (2) (Right)

The α-chloroenone (1) with the more stable half-chair conformtaion epimerized at C_2 in the presence of hydrogen chloride, probably involving either its intermediary unfavorable 2β-axial-like chlorine epimer or 2α-quasi-axial half-boat conformer, to give an equilibrium mixture with its 2β-equatorial-like chlorine isomer with the less stable half-boat conformation (2). Starting from 2, the same equilibrium mixture with 1 through the identical intermediates was obtained in the same manner. Since the decomposition of both chloroenones was considerably decreased at 25°C in comparison

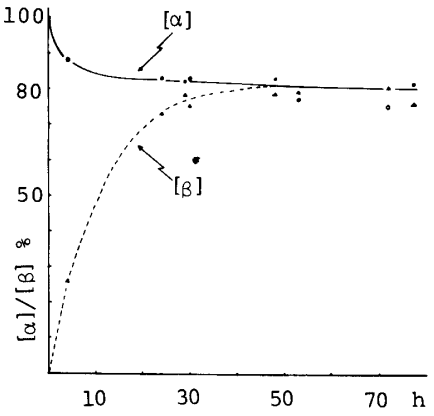

Fig. 2. Time Course of Equilibration for α- (1) and β-Chloroenone (2) at 25°C

with that at elevated temperatures (40°C and 80°C), the equilibration was regarded to be attained in an optimum condition at 25°C. The ratio of 1 to 2 in this reaction mixture was determined by the HPLC method mentioned above, at ambient temperature. Fig. 2 illustrates the time course of the equilibration between 1 and 2, where the compositions are achieved from each isomer as plotted against the reaction time. The equilibrium composition of 1 and 2 was determined to be 4:1. It is deduced from this equilibration experiment that α-chloroenone (1) is more stable than the β-isomer (2), and the rate of equilibration is faster for the former than for the latter. The enthalpy difference between 1 and 2 calculated by the equation $\bar{K} = [\alpha]/[\beta] = -\exp(\Delta H - T\Delta S)/RT$ ($\Delta S = 0$, $R = 1.987$ cal·mol^{-1}·K^{-1}, $T = 298$°K) was shown to be 0.7 - 1.0 kcal/mol (25°C).

While the observed higher stability of 1 than 2 is almost obvious, we intended to quantify the reason. The semi-empirical MO calculations using MNDO[4] and CNDO[5] as well as the ab initio MO calculation by STO-3G basis set,[6] were carried out for 1 and 2 to determine the total energy for comparison with the above results. The MNDO and ab initio MO calculations for the compound of this size containing the chloroenone moeity are rare. Internal coordinates obtained from the X-ray crystallographic analysis for 1 and those for 2 described previously,[1] were used as the input structure parameters for the MNDO calculations, and all the structural parameters were optimized. The optimized parameters resulting from the MNDO calculations were used as the input for the CNDO and the ab initio calculations. The results of the three calculations agree well with each other as shown in Table I. It can be seen that α-

Table I. Total Energies of α-Chloroenone (1) and β-Chloroenone (2) [kcal/mol]

T. E.	1	2	[α]-[β][a]
MNDO[b]	-80,862.80	-80,862.50	-0.30
CNDO	-121,110.27	-121,108.15	-2.12
ab initio[c]	-618,118.93	-618,116.50	-2.43

a) The stabilization energy of 1 relative to 2. b) Heats of formation: (1) -107.61, (2) -107.31 kcal/mol. c) STO-3G.

chloroenone (1) was consistently calculated to be more stable than β-chloroenone (2) and that the experimental stabilization energy (0.7 - 1.0 kcal/mol) falls among the values determined by the MNDO calculation, 0.30 kcal/mol, the CNDO calculation, 2.12 kcal/mol and the ab initio calculation, 2.43 kcal/mol. It has been reported that the absolute errors in energy with the MNDO calculation are within approximately 5 kcal/mol[7a] and that the errors with the CNDO calculation are 16 times greater than with the MNDO calculation.[7b] In our calculation, errors inherent in the approximation used must have been cancelled out by taking relative energy. Nevertheless, the agreement in the differences of very large figures among the three independent methods exceeds our expectation. However, examination of higher lying occupied MO's revealed no significant difference between 1 and 2, as expected.

Further studies on the origin of the conformational energy difference is now in progress and will be reported in a following paper.

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