Chem. Pharm. Bull.
33(7)2792—2797(1985)

Epimerization of 6-Protoilluden-8-one at C-3 and the Relative Thermodynamic Stabilities of Stereoisomeric 6-Protoilluden-8-ones[1)]

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(Received October 29, 1984)

Both 9-*epi*-6-protoilluden-8-one (**5**) and 6-protoilluden-8-one (**4**) underwent cyclobutyl-cyclopropylcarbinyl cation rearrangement on treatment with CF_3COOH(25%)–$CHCl_3$, to give 2,9-*cis*-2,3-*syn* 6-protoilluden-8-one (**6**). In order to elucidate the relative thermodynamic stabilities of these stereoisomeric enones (**4**—**7**), molecular mechanical calculations were carried out. The result showed that the *cis-syn* enone **6** is the most stable one. This is in good agreement with the experimental results.

Keywords——acid-catalyzed epimerization; stereoisomeric 6-protoilluden-8-one; relative thermodynamic stability; molecular mechanical calculation; cyclobutyl-cyclopropylcarbinyl cation rearrangement

Introduction

Basidiomycetes produce humulene-derived sesquiterpenes such as illudin-M, illudin-S, illudol, fomannosin, marasmic acid, illudalic acid, *etc.*[2)] In the biosynthesis of these sesquiterpenes, 6-protoilludene (**1**),[3)] and 6-protoilluden-8-ol (**2**) or 7-protoilluden-6-ol (**3**)[3)] are considered to play important roles as biosynthetic intermediates[4)] (Fig. 1). In connection with our studies on the biosynthesis of humulene-derived sesquiterpenes, syntheses of these hypothetical precursors **1**—**3** were carried out.[5)]

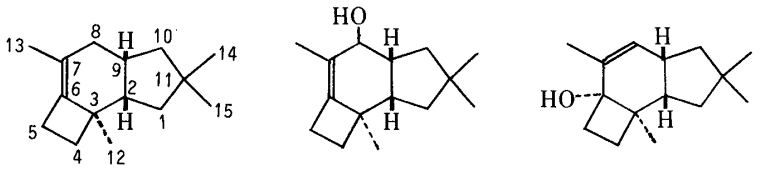
During the course of our synthetic studies, the intermediate **4** was found to be unstable under basic conditions, *e.g.*, 5% KOH–MeOH, and was readily epimerized to the 2,9-*trans*-2,3-*anti* enone **5**.[1)] In an attempt to isomerize **5** to **4** wirh CF_3COOH,[6)] we encountered unexpected epimerization of the *trans-anti* enone at the C-3 position, giving rise to the *cis-syn* enone **6** (Chart 1).

Although 6-protoilluden-8-one derivatives have been used as important synthetic intermediates in several protoilludane syntheses,[7,8)] their epimerization reactions have not been fully investigated and the relative stabilities of the stereoisomers remain to be clarified.

This paper describes the structure of **6** and the relative thermodynamic stabilities of the stereoisomeric enones **4**—**7**.[9)] Their stabilities were successfully explained by the results of molecular mechanical calculations.

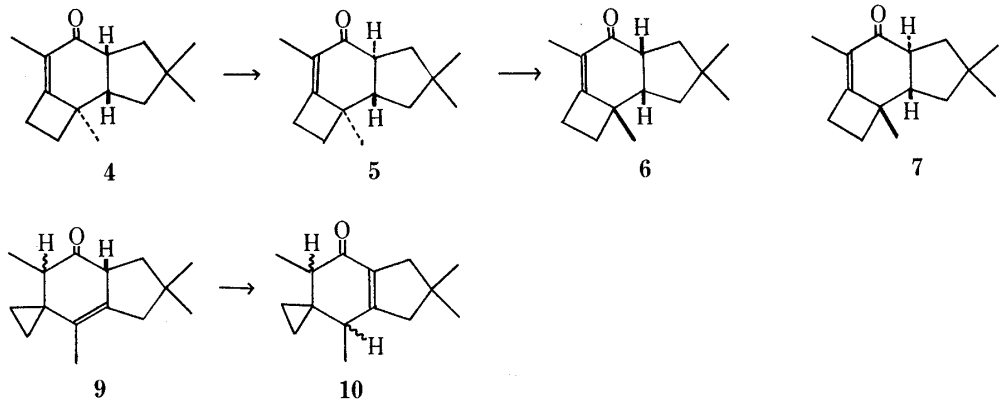
Epimerization of 6-Protoilluden-8-one at C-3: Formation of *cis-syn* 6-Protoilluden-8-one (6)

Isomerization of *trans-anti* 13-acetoxyprotoilludan-8-ones to *cis-anti* 13-acetoxyproto-illudan-8-ones by treatment with a small amount of CF_3COOH in $CHCl_3$ was reported.[6)] The ratio of *trans-anti* derivatives to *cis-anti* isomers was reported to be 1/6 after a week at



1 2 3

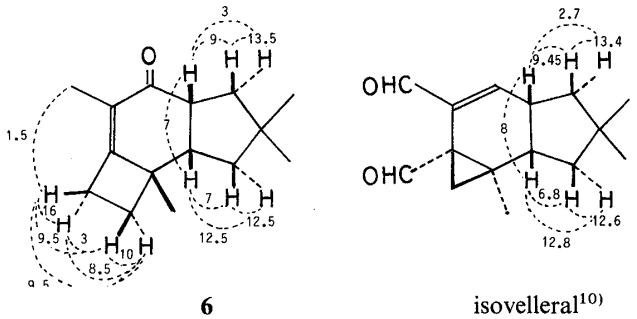
Fig. 1



4 5 6 7

9 10

Chart 1



6 isovelleral[10]

Fig. 2. ^{1}H-NMR Coupling Constants J_{HH} (Hz) of the Enone **6** and Isovelleral

TABLE I. ^{1}H-NMR Chemical Shifts (ppm) and Coupling Constants J_{HH} (Hz) of the Enone **6**

Proton	δ	J_{HH}
$H_{1\alpha}$	1.37	12.5, 12.5
$H_{1\beta}$	1.43	7, 12.5
H_2	2.33	7, 7, 12.5
$H_{4\alpha}$	2.13	8.5, 9.5, 10
$H_{4\beta}$	1.75	3, 9.5, 10
$H_{5\alpha}$	2.67	3, 8.5, 16
$H_{5\beta}$	2.76	1.5, 9.5, 9.5, 16
H_9	2.76	3, 7, 9
$H_{10\alpha}$	2.03	3, 13.5
$H_{10\beta}$	1.73	9, 13.5
H_{13}	1.63	1.5
H_{12}	1.45	
H_{14}	0.99	
H_{15}	0.96	

TABLE II. ^{13}C-NMR Chemical Shifts δ (ppm) of the Enone **6**

Carbon	
1	43.7
2	48.0
3	46.0
4	28.7
5	28.7
6	165.6
7	124.4
8	200.7
9	49.5
10	45.5
11	37.8
12	26.4
13	9.9
14	30.7
15	31.2

room temperature. In the case of our 6-protoilludenes, when the *trans-anti* isomer **5** was treated with CF_3COOH (25%) in $CHCl_3$ solution for several days at room temperature, a product which was not the *cis-anti* enone **4** but a third isomer, the enone **6**, was obtained. After 3 weeks, the isomerization reached equilibrium and the ratio of **5** to **6** was estimated to be 1/5. Compound **6** was purified by preparative gas chromatography (GC) to give a pure specimen. The proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) data for **6** are summarized in Fig. 2 and Tables I—II. Although the mass spectra (MS), infrared (IR) and ultraviolet (UV) characteristics of **6** were indistinguishable from those of **4** and **5**, the vicinal coupling constants J_{2-9} in the ^{1}H-NMR spectrum showed remarkable differences (11, 13 and 7 Hz for **4**, **5** and **6**, respectively). The coupling constants between protons around the cyclopentane ring in the enone **6** and isovelleral[10,11] which has a 5/6 *cis* marasmane-type skeleton are similar, suggesting the 5/6 ring junction in **6** to be *cis* (Fig. 2). The enone **4** was shown to have the *cis-anti* structure, so a *cis-syn* structure was assigned to the isomerized compound **6**.

Molecular Mechanical Calculations

In order to elucidate the relative thermodynamic stabilities of the enones **4**—**7**, we performed molecular mechanical calculations. The calculations on these four enones were carried out using Osawa's modification[12] of the MMPI program, which was developed by Allinger[13,14] to deal with molecules containing a delocalized π-system, based on the MMI force field. The program first calculates the bond lengths and force constants for the delocalized π-system, an α,β-unsaturated ketone in this case, by calculating the bond orders using the VESCF method, and then the steric energy is minimized according to the

TABLE III. Steric Energies (kcal/mol) of the Enones[a]

	4	5	6	7
Compression	2.84	2.87	2.83	3.01
Bending	30.71	28.27	28.39	30.35
Stretch-bend	−0.93	−1.24	−1.07	−1.24
Van der Waals 1,4	8.57	8.64	8.13	8.91
others	−4.43	−3.80	−4.12	−4.50
Torsional	9.38	6.76	7.39	11.18
Torsion bend	4.07	4.14	3.93	3.78
Dipole	−1.48	−1.54	−1.53	−1.45
Total energy	48.73	44.10	43.95	50.04

a) Only energy differences are significant to estimate the relative stabilities, not the absolute values.

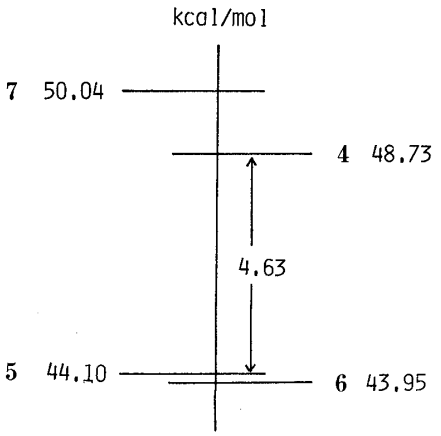


Fig. 3. Relative Stabilities of the Enones **4**, **5**, **6** and **7** from MMPI Calculation

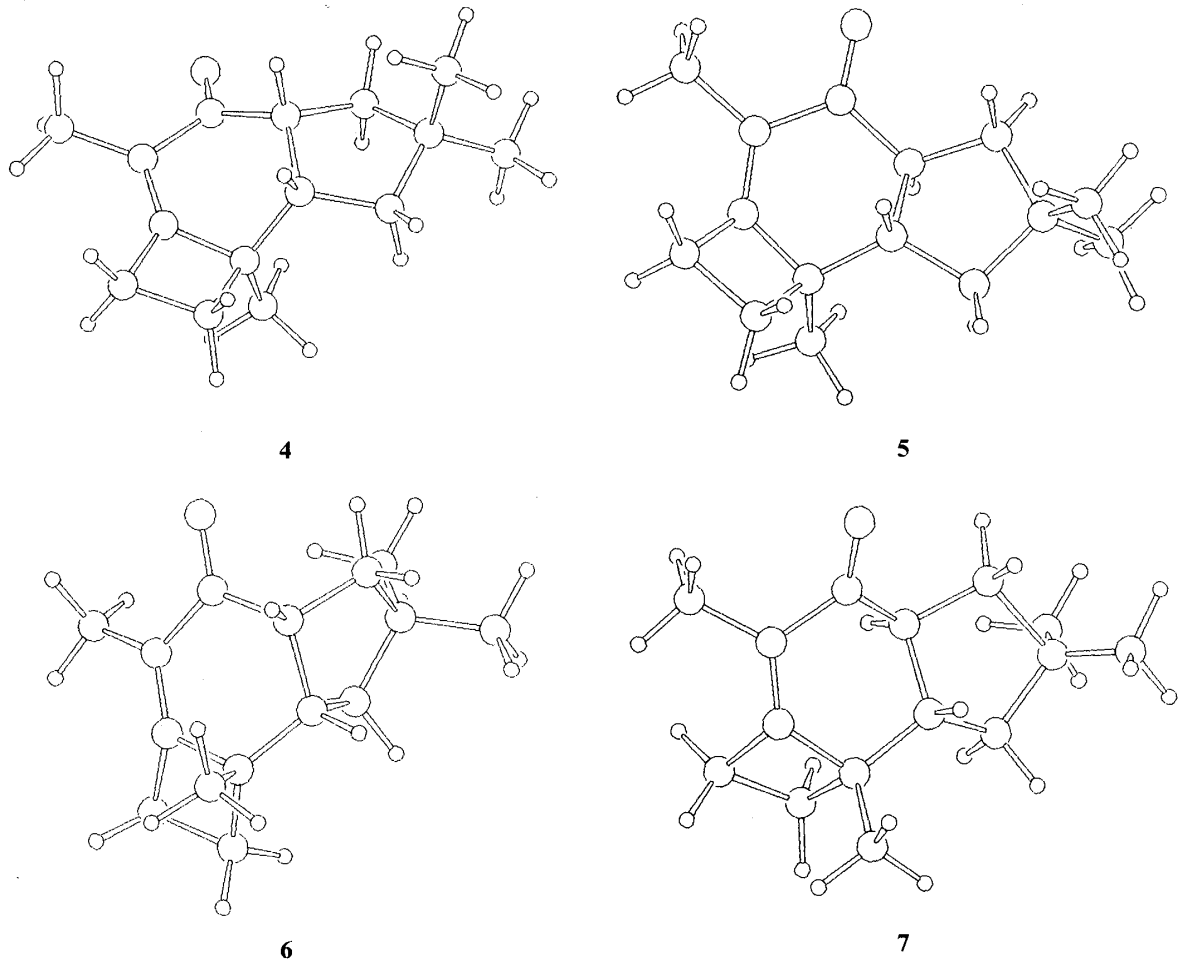


Fig. 4. Computer-Generated Drawings of the Optimized Structures of the Enones **4**, **5**, **6** and **7**

conventional molecular mechanical procedures.[15] The VESCF-minimization cycle is repeated until total self-consistency is reached. For these rather highly-strained compounds, the "non-planar" facilities were applied to allow distortion of the π-system. This method was proved to give good results for a conjugate diene or polyene system, but for an α,β-unsaturated ketone system, it is not yet established. As starting coordinates, we took the coordinates from the X-ray analysis[16] for **5**, while for **4**, **6** and **7**, we used roughly measured coordinates from Dreiding models. All the parameters including the four-membered ring used here were those stored in the program, and the energy values for bending seem to be unnecessarily large. The steric energy E was minimized to obtain the final steric energy and the optimized coordinates in each case. The final energies are listed in Table III and the relative stabilities of the enones **4**—**7** are shown in Fig. 3. The optimized structures are illustrated in Fig. 4. These results indicate that the *cis-syn* enone **6** is thermodynamically most stable and that the enone **7**, which has not yet been synthesized, is most unstable among the four isomeric enones. Table III shows that the torsional energy contribution is the predominant contributor to the total energy of the enones.

Possible Mechanism of the Acid-Catalyzed Isomerization of the Enones

As described above, the *trans-anti* enone **5** was isomerized to the *cis-syn* enone **6** on treatment with CF_3COOH in $CHCl_3$ solution. When the *cis-anti* enone **4** was treated similarly, isomerization to the enone **6** also occurred. In the latter case, it required only 10 min to reach a ratio of **4** to **6** of 1/20.[17]

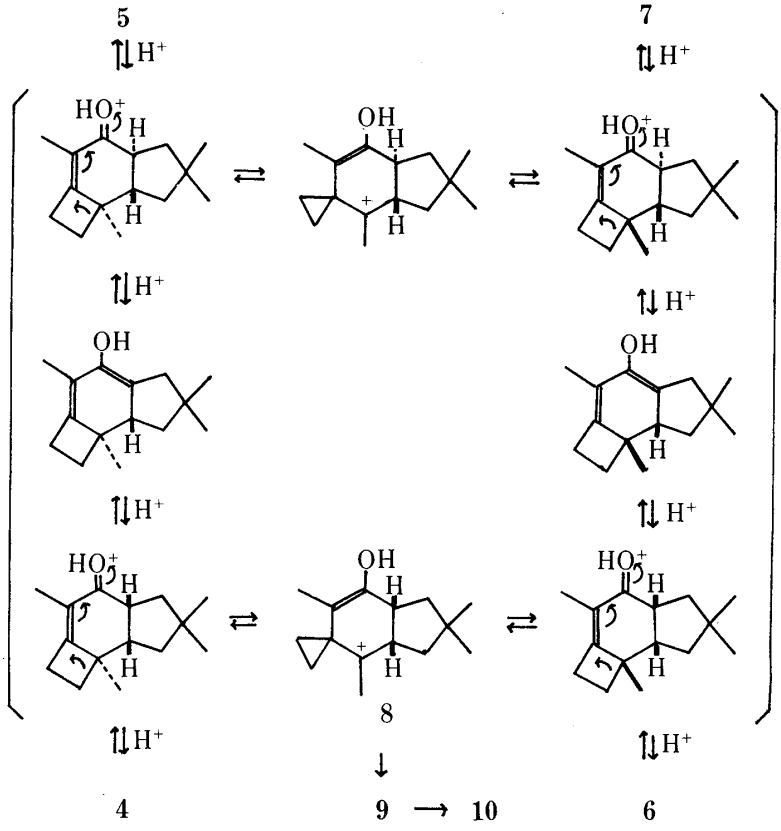


Chart 2

A possible mechanism of the acid-catalyzed isomerization of the enones **4** and **5** to **6** is shown in Chart 2. In acidic solution, the enone **4** might undergo cyclobutyl-cyclopropylcarbinyl cation rearrangement through **8**, giving rise to the energetically more stable enone **6**. The configuration of the methyl group at C-3 was inverted in the rearrangement.

In the conversion of the enone **5** to **6**, a small amount of the illudane-type compound **10**[1)] was found to be formed. This formation of **10** supports the proposed mechanism of the rearrangement through the protoilludene C-3 cation.

Results

From the molecular mechanical calculation, it was concluded that the *cis-syn* enone **6** was thermodynamically the most stable among the four enones **4**—**7**. The *cis-anti* enone **4** was shown to be very unstable compared with the *trans-anti* enone **5** and the *cis-syn* enone **6**. These conclusions are in good agreement with the experimental results described in this paper and the preceding paper.

6-Protoilluden-8-ones underwent cyclobutyl-cyclopropylcarbinyl cation rearrangement in CF_3COOH–$CHCl_3$ solution. The formation of *cis-syn* protoilludenes such as **6** has not been reported previously.

Experimental

^{1}H-NMR spectra were measured on a JEOL GX-400 FT-NMR spectrometer (400 MHz for ^{1}H) and chemical shifts are reported in δ values relative to internal tetramethylsilane (TMS) ($\delta=0$) in $CDCl_3$. ^{13}C-NMR spectra were measured on the same spectrometer (100 MHz). IR spectra were measured on a JASCO DS-301 or A-102 instru-

ment, UV spectra on a Shimadzu UV-300 spectrometer, and MS on a Shimadzu-LKB 9000 machine at 70 eV. GC analysis were performed on a Shimadzu GC-4BP or GC-7AG apparatus.

Conversion of 9-*epi*-6-Protoilluden-8-one (5) to 3-*epi*-6-Protoilluden-8-one (6)——The enone **5** (100 mg) was dissolved in CF_3COOH(25%)–$CHCl_3$ and left at room temperature. The isomerization of **5** into **6** was followed by GC. After 10 d, the ratio of **5** to **6** was 1/1, and after 3 weeks, 1/5. Compounds **5** and **6** were separated by GC. For **6**, ^{1}H-NMR data are listed in Table I and Fig. 2, and ^{13}C-NMR data in Table II. MS *m/z* (218-100): 218 (M^+, 96%), 203 (M−15, 83%), 189 (M−29, 100%), 175 (45%), 161 (49%), 149 (90%), 147 (46%), 133 (35%), 119 (56%), 107 (44%), 105 (57%). IR ($CHCl_3$) ν: 1663 cm^{-1} (enone). UV (EtOH) λ: 250 nm (ε=6200). *Rf* values of **4**—**6** (precoated silica gel plate, benzene : acetone = 9 : 1) and relative retention times (Rt_R) of **4** and **5** with respect to **6** (GC: OV-17, 0.28 mm i.d., 30 m, 170 °C) were as follows.

	4	**5**	**6**
Rf	0.53	0.56	0.56
Rt_R	1.35	1.24	1.00

Conversion of 6-Protoilluden-8-one (4) to 6——The enone **4** was treated with CF_3COOH(25%)–$CHCl_3$ at room temperature. The ratio of **4** to **6** was 1/20 in 10 min.

Conversion of 6 to 5——The enone **6** was treated with CF_3COOH(25%)–$CHCl_3$ at room temperature. The ratio of **5** to **6** was 1/5 after 2 months.

Formation of 2(9)-Illuden-8-one (10)——A small amount of **10** was produced in the course of the reaction of **5** to **6** (after 40 d, **5** : **6** : **10** = 1 : 5 : 0.1; after 8 months, **5** : **6** : **10** = 1 : 5 : 0.5). Compound **10** might be formed from the cation **8** *via* **9**[1)] and then be accumulated in the acidic reaction media. Relative retention times of **6** and **10** were 1.00 and 1.03, respectively (OV-17: 0.28 mm i.d., 30 m, 130 °C). Quantitative analysis of **6** and **10** was done by ^{1}H-NMR measurement of the mixture of **6** and **10** obtained by preparative GC (OV-17: 1.5%, 1.5 m); under the preparative GC conditions, **6** and **10** were not separable.

References and Notes

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9) The enone **7** has not yet been synthesized.
10) G. Magnusson, S. Thoren and B. Wickberg, *Tetrahedron Lett.*, **1972**, 1105.
11) Bond angles and dihedral angles of the six hydrogen atoms on the cyclopentane ring of both the enone **6** and isovelleral are considered to be similar on the basis of Dreiding models.
12) We are grateful to Prof. E. Osawa, Hokkaido University, for the use of the modified MMPI program.
13) N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, **95**, 3893 (1973).
14) N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1 (1976).
15) Though the MM2P program would be preferable for this study because of the four-membered ring and improvements in the parameters of van der Waals interactions and torsional energies, it was not available to us.
16) The X-ray crystallographic analysis data are given in the preceding paper.
17) Acid-catalyzed isomerization of the enones **4** and **5** to yield enone **6** was also effected with BF_3–Et_2O in benzene.