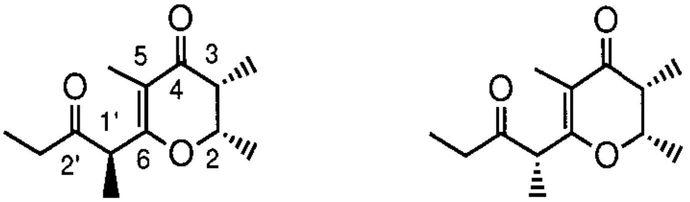
CONFORMATIONAL ANALYSES OF STEGOBINONE AND 1'-EPI-STEGOBINONE1)

Takashi Ebata*, Koshi Koseki, Kazuko Shimazaki, Hiroshi Kawakami,
Tatsuji Chuman, Hajime Matsushita, and Kenji Mori[†]
Life Science Research Laboratory, Japan Tobacco Inc., 6-2 Umegaoka,
Midori-ku, Yokohama, Kanagawa 227, Japan
[†]Department of Agricultural Chemistry, The University of Tokyo,
1-1-1, Yayoi, Bunkyo-ku, Tokyo 113, Japan

Abstract —— Conformational analyses of stegobinone **1**, the sex pheromone of the drugstore beetle, and 1'-epi-stegobinone **2** were performed by the combination of detail NOE measurements and molecular mechanics calculations.

Stegobinone [(2S,3R,1'R)-2,3-dihydro-2,3,5-trimethyl-6-(1'-methyl-2-oxobutyl)-4H-pyran-4-one] **1** is the sex pheromone produced by the female drugstore beetle, Stegobium paniceum L.2) As can be seen in Figure 1, it has a very unique structure with a tetrasubstituted dihydro-γ-pyron ring. We have previously reported the synthesis of stegobinone **1**3) and 1'-epi-stegobinone **2**.4) Very recently, Kodama et al. reported that 1'-epi-stegobinone **2** strongly inhibited the pheromone activity of stegobinone **1** in the male drugstore beetle.5) In order to investigate this



Stegobinone **1**

1'-*epi*-Stegobinone **2**

Figure 1. Structure of stegobinone **1** and 1'-*epi*-stegobinone **2**

inhibitional activity in detail, it is essential that both the three dimentional structures of stegobinone **1** and 1'-epi-stegobinone **2** are clarified. In this paper, we report the conformational analyses of these two compounds.

Conformation for the dihydro-γ-pyron ring As can be seen from the Figure 2, there are two possible conformers, (**A**) and (**B**), for the dihydro-γ-pyron ring of **1** and **2**. Up to the present, two groups have published papers on their work on the deduction of the conformation of the dihydro-γ-pyron ring of stegobinone **1**. In the earlier paper, Sakakibara et al. reported$^{6)}$ the comparision of ^{13}C-nmr data of racemic cis isomeric mixture and racemic trans isomeric mixture. They deduced that (**B**) was the more probable conformer based on the remarkable difference between both chemical shifts of C-2 methyl group. On the other hand, Hoffmann et al. reported$^{7)}$ another deduction based on the cd spectral analysis. In short, both of stegobinone **1** and 1'-epi-stegobinone **2** showed negative extrema due to the enone n-π* chromophore in the 350 nm region. They applied the Snatzke rule$^{8)}$ to this region and deduced that (**A**) was the more probable. However, neither of these deductions were based on decisive proof. In order to resolve this conformational ambiguity, we performed NOE experiments on **1** and **2** in detail. The results are shown in Figure 3. Remarkable enhancement of both the C-3 methine hydrogen signal and the C-2 methyl hydrogen signal of **1** and **2** was observed upon reciprocal irradiation experiments, while those of the C-2 methine hydrogen and C-3 methyl hydrogen were not observed. To explain these results without any inconsistency, both the C-2 methyl group and the C-3 methine hydrogen of **1** and **2** must occupy pseudoequatorial positions. That is to say, as a result of our studies, we concluded that conformer (**A**) is the correct one for the dihydro-γ-pyron ring.

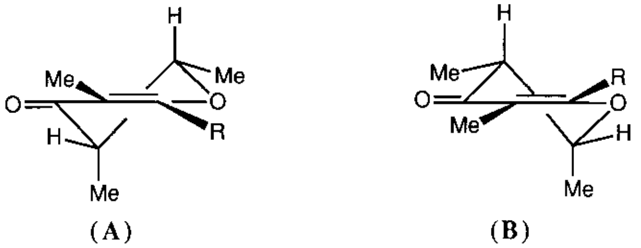
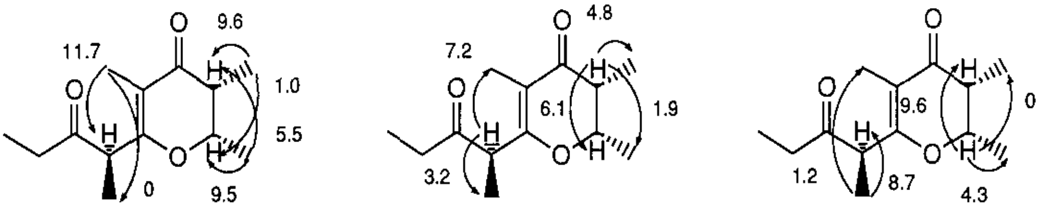
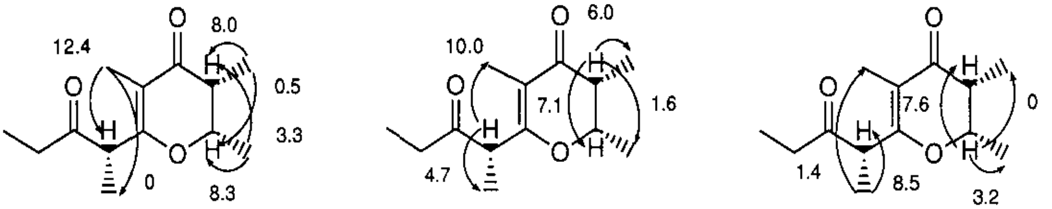


Figure 2. The possible conformers for the dihydro-γ-pyron ring



Stegobinone **1**



1'-*epi*-Stegobinone **2**

Figure 3. NOE value (%) of **1** and **2**

Direction of the C-6 side chain As can be seen from the Table I, there are significant differences in the cd spectral data of **1** and **2** in 250 to 300 nm region.

Table I. Cd spectral data of **1** and **2**

1		**2**	
λ(nm)	Δε	λ(nm)	Δε
360	-0.46	360	-0.88
345	-0.86	345	-2.18
332	-0.69	331	-2.34
290	-12.9	285	+13.4
262	+8.8	261	-10.9

If both the dihydro-γ-pyron rings of **1** and **2** have the conformation as described above, the cd value of this region would be greatly influenced by the C-1' chiral center. This suggests that significant conformational differences on C-6 side chain exist between **1** and **2**. Indeed, molecular mechanics calculations on **1** and **2** revealed that the C-6 side chains of the major conformers of **1** and **2** are on directly opposite sides to each other, as shown in Figure 4. These results were also confirmed by NOE experiments. A remarkable NOE enhancement of both the C-1' methine hydrogen signal and the C-5 methyl hydrogen signal of **1** and **2** was observed upon reciprocal irradiation experiments, while no NOE was observed between C-1' and C-5 methyl groups.(Figure 3) Consequently, we conclude that the perturbation of C-2' carbonyl group from opposite side raised these differences in the cd spectral data of **1** and **2**.

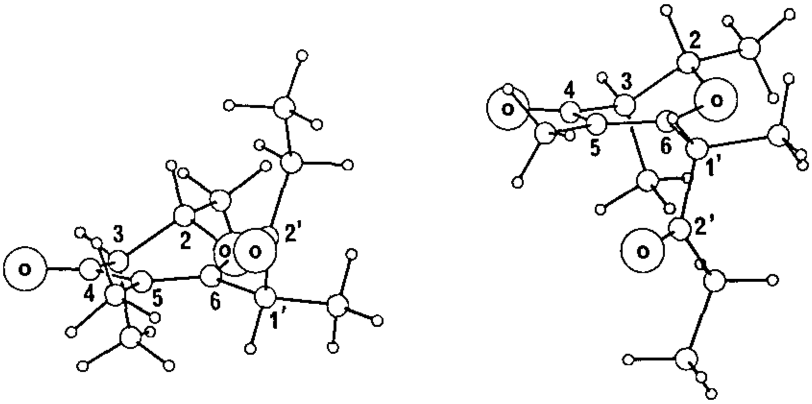


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Figure 4. Major conformer of **1** and **2** obtained from MM calculations

In conclusion, the three dimentional structures of stegobinone **1** and 1'-epi-stegobinone **2** have been clarified by detail NOE mesurements and molecular mechanics calculations.

General Methods

NOE mesurements NOE experiments were performed on a Bruker AM-500 instrument equipped with an Aspect 3000 computer. The Bruker program (NOE differences modified by us) was used with relaxation of 4s, NOE generation for 8s (ca. 3-5 x T1), repetitive cycling with accumulation of eight scans on and off resonance and four dummy scans to assure saturation. The differences were accumulated by 16-20 times. Enhancements are reported in percent relative to the irradiation signal.

MM calculations The molecular mechanics calculations were performed by CHARMM program (Polygen Corpolation, Waltham, MA, USA) on IRIS 4D/80GT work station. Stable conformations of stegobinone **1** and 1'-epi-stegobinone **2** were selected from all energy minima obtained by MM minimizations of each 72 initial conformations.

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