Re-revision of the Stereo Structure of Piperidine Lactone, an Intermediate in the Synthesis of Febrifugine

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The stereo structure of piperidine lactone (3), an intermediate of the antimalarial agent febrifugine ((+)-1) prepared by a synthetic method, was re-revised to the *cis*-form from the *trans*-form.

Key words febrifugine; piperidine lactone; structure determination

Febrifugine ((+)-**1**) and isofebrifugine ((+)-**2**) are antimalarial agents that were isolated from *Dichroa febrifuga* and *Hydrangea umbellate*, respectively (Fig. 1).[1—4] The plane structure[5] of (+)-**1** and (+)-**2** was first proposed in 1950. Subsequently, their relative[6] and absolute[7] structures were proposed, based on Baker's synthetic work.[8—10] The relative configuration[11] of (+)-**1** was corrected in 1973 and then the absolute structures[12,13] of (+)-**1** and (+)-**2** were corrected in 1999. Currently, dramatic medical[14—17] and synthetic[18—25] studies of (+)-**1** are in progress.

Historically, Barringer *et al.*[11] corrected the configuration of febrifugine to the *trans*-form from the *cis*-form in 1973, based on the ^{1}H-NMR data of an intermediate, piperidine lactone (**3**), which Baker *et al.* synthesized.[9] Each proton on the bridge-head of **3** was observed at δ 4.69 and 5.15 ppm with a coupling constant of 8.5 Hz (Table 2). Recently, Kobayashi *et al.* synthesized dimethyl derivatives of *trans*-**3** in which each proton on the bridge-head was observed at δ 3.09 and 4.09 ppm with a coupling constant of 10.4 Hz.[26,27] From these directly opposing results, we thought that the structure of **3** could not be determined from the coupling constant.

In a molecular calculation, *cis*-**3** afforded two optimized conformers with similar heats of formation, but differing chair (*cis*-**3a**) and boat (*cis*-**3b**) forms of the piperidine ring (Table 1). The dihedral angle between H_{3a}–C_{3a}–C_{7a}–H_{7a} involving the bridge-head protons of *cis*-**3b** was smaller than in *cis*-**3a**. These results showed that even if the configuration of **3** was *cis*, the coupling constant between H_{3a}–H_{7a} would reasonably be 8.5 Hz. Since this result strongly supports our hypothesis, we discuss the exact structure of **3** synthesized by Baker *et al.* and corrected by Barringer *et al.*

cis-Piperidine lactone (*cis*-**3**), an intermediate of (±)-isofebrifugine (±-**2**), was prepared from *cis*-2-allyl-3-hydroxypiperidine derivatives (**4**) using our previously reported method[18,19] (Chart 1). Ozonolysis of **4**, followed by PCC oxidation afforded cis-piperidine lactone (*cis*-**5**) with a cbz group. Hydrogenolysis and benzoylation of *cis*-**5** gave *cis*-**3**, which has the same ^{1}H-NMR spectrum as reported by Barringer *et al.*[11] Each proton on the bridge-head of *cis*-**3** in the ^{1}H-NMR (60 MHz) spectrum was observed at δ 4.69 and 5.15 ppm, with a coupling constant of 7.7 Hz (Table 2).

The configuration of piperidine lactone (**3**) synthesized by

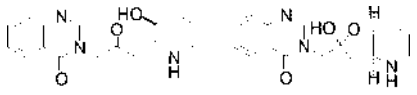
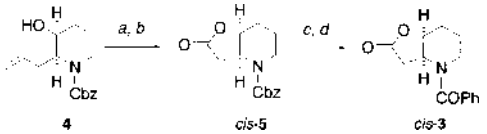


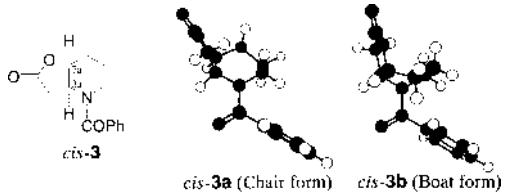
Fig. 1. The Final Corrected Structures of (+)-**1** and (+)-**2**



Reagents and conditions: *a*, i) O_3, MeOH, −78 °C, 2 h; ii) Me_2S, room temperature (rt), 1 h; *b*, PCC, AcONa, CH_2Cl_2, rt, 3 h, 55%; *c*, H_2, $Pd(OH)_2$/C, acetone, rt, 24 h; *d*, PhCOCl, Et_3N, $CHCl_3$, rt, 1 h, 32%.

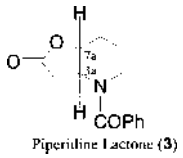
Chart 1

Table 1



Calculation method	Heat of formation (kcal/mol)		Dihedral angle (H_{3a}–C_{3a}–C_{7a}–H_{7a})	
	3a	**3b**	**3a**	**3b**
PM3	−98.19	−97.73	−22.9	−4.2
AM1	−86.63	−86.39	−22.5	−10.6
MNDO	−88.43	−89.06	−15.2	8.3

Table 2



Compound	mp (°C)	^{1}H-NMR	
		H_{3a}	H_{7a}
3	99—101	5.15 (q, J=8.5 Hz)[a]	4.69 (m, J=8.5, 8.5, 5.0 Hz)[a]
cis-**3**[d]	85—86	5.15 (q, J=7.7 Hz)[a]	4.69 (dt, J=7.7, 4.9 Hz)[a]
		5.09 (q, J=7.8 Hz)[b,c]	4.68 (dd, J=12.5, 7.5 Hz)[b,c]
trans-**3**[e]	133—134	3.24—3.65 (m)[a] 3.30—3.39 (m)[b]	3.97—4.08 (m)[a] 4.06 (ddd, J=11.0, 10.0, 4.0 Hz)[b]

a) 60 MHz. *b*) 500 MHz. *c*) 80 °C. *d*) NOE between H_{3a} and H_{7a} in NOESY spectrum was observed. *e*) NOE between H_{3a} and H_{7a} in NOESY spectrum was not observed.

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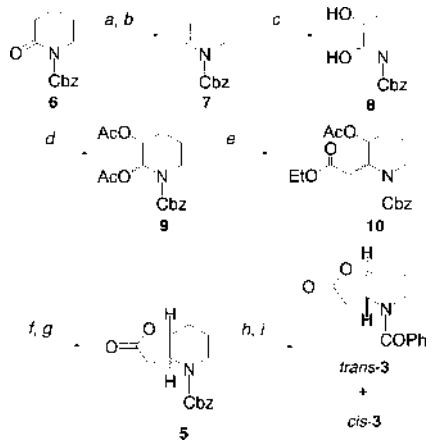

Reagents and conditions: *a*, $NaBH_4$, MeOH, 0 °C, 15 min; *b*, H_2SO_4, THF, rt, 1 h, 52%; *c*, Oxone®, acetone, K_2CO_3, H_2O, rt, 2 h, 76% (*trans* : *cis*=1 : 1); *d*, Ac_2O, Et_3N, DMAP, rt, 2 h, 88%; *e*, CH_2=C(OEt)OTMS, $Sc(OTf)_3$, CH_2Cl_2, rt, 13 h, 62%; *f*, 10% KOH, MeOH, H_2O, rt, 1.5 h; *g*, EDC, DMAP, CH_2Cl_2, rt, 3 h, 62% (*trans* : *cis*=41 : 58); *h*, H_2, $Pd(OH)_2$/C, acetone, rt, 18 h; *i*, PhCOCl, Et_3N, $CHCl_3$; rt, 1 h, 33% (*trans*-**3**)+44% (*cis*-**3**).

Chart 2

Baker *et al.* is *cis* based on the spectrum data. However, the difference in the melting points of **3** and *cis*-**3** was large. Consequently, we attempted to synthesis *trans*-**3** (Chart 2). Considering green chemistry, the key intermediate, piperidine-2,3-diol (**8**), was prepared by our new method using oxidation of 2,3-dehydropiperidine (**7**) with Oxone® instead of osmium reagent. *N*-Cbz-protected piperidine lactone (**5**) was prepared from **8** according to Kobayashi's method.[26,27] As they discussed, the reaction of **9** with non-substituted ketene silyl acetal has low diastereoselectivity. Deprotection followed by benzoylation of **5** afforded a separable mixture (3 : 4) of *trans*-**3** and *cis*-**3**.

The melting point and ^{1}H-NMR data of **3** reported by Barringer *et al.*, *cis*-**3**, and *trans*-**3** are summarized in Table 2. It is clear that **3** is *cis*-**3**, since the difference in the melting points of **3** and *trans*-**3** was larger than that between **3** and *cis*-**3**. Moreover, Burgess *et al.*, who reported another method of synthesizing febrifugine in 1996, used Barringer's result to determine the syn or anti configuration of a derivative of **4** prepared by the reaction of piperidine oxide with allyl silane.[28] This result should also be corrected.

Now, we know that the configuration of substituents on the piperidine ring in febrifugine is trans, without a doubt. Therefore, our result suggests that the isomerization of the *cis*-form to the *trans*-form occurs in the synthetic stage after **3** in Baker's synthesis of febrifugine. We are now in the process of determining at which stage in Baker's synthesis of febrifugine the isomerization occurs.

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