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# Six new indole alkaloids from *Gelsemium sempervirens* Ait. f.

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**Abstract**—One new yohimbane and five new sarpagine-type indole alkaloids were isolated from the radix of *Gelsemium sempervirens* Ait. f., and their structures were determined by spectroscopic analysis, chemical conversion or total synthesis. It was found that 2-acyl sarpagine-type alkaloids possessing an $N_b$-methyl group take a keto–amino structure or a transannular form in solution depending on the solvent.


In our recent study, we proved that the original plant of 'Yakatsu,' one of the ancient medicines stored for more than 1250 years in Shosoin repository in Japan, was *Gelsemium elegans* Benth.[1] The genus *Gelsemium*, which belongs to Loganiaceae, comprises three species: *G. elegans* Benth., *G. sempervirens* Ait. f., and *G. rankinii* Small, from which more than fifty indole alkaloids have been isolated.[2–4] In the course of our chemical studies on *Gelsemium* alkaloids, we investigated the constituents in the radix of *G. sempervirens*, and this has resulted in the isolation of one new yohimbane alkaloid (**1**) and five new sarpagine-type alkaloids (**2**–**6**). In this paper, we describe the structure elucidation of the new alkaloids as well as an interesting spectroscopic observation in the new sarpagine-type alkaloids.

The dried radix of *G. sempervirens* Ait. f. (413.7 g), that was cultivated in the medicinal plant garden of our university, was extracted with hot MeOH to give the MeOH extract (50.2 g). The crude alkaloidal fraction (4.88 g) obtained by a conventional procedure from the MeOH extract was purified by $SiO_2$ column chromatography to afford six new alkaloids, sempervilam (**1**, 17.8 mg), gelsempervine-A (**2**, 20.7 mg), -B (**3**, 7.6 mg), -C (**4**, 49.0 mg), -D (**5**, 5.3 mg), and 19*Z*-16-*epi*-voacarpine (**6**, 1.7 mg) (Fig. 1).

The high-resolution (HR)-FAB-MS spectrum of new alkaloid (**1**)[5] gave a molecular ion peak at *m*/*z* 288.1272 $[M]^+$ that corresponded to the molecular formula $C_{19}H_{16}N_2O$ (*m*/*z* 288.1263). The UV spectrum of **1** was similar to that of sempervirine (**8**).[6] The $^1H$ NMR spectrum[5] that showed signals corresponding to seven aromatic protons including one singlet and eight aliphatic protons was very similar to that of sempervirine (**8**) that possessed two singlet aromatic protons. The $^{13}C$ NMR spectrum[5] showed 15$sp^2$ carbons, including one carbonyl carbon at $\delta$ 58.8 and four $sp^3$ methylenes. Heteronuclear multiple bond connectivity (HMBC) correlations between H-5 and the carbon at $\delta$ 58.8 revealed that the carbonyl function existed at

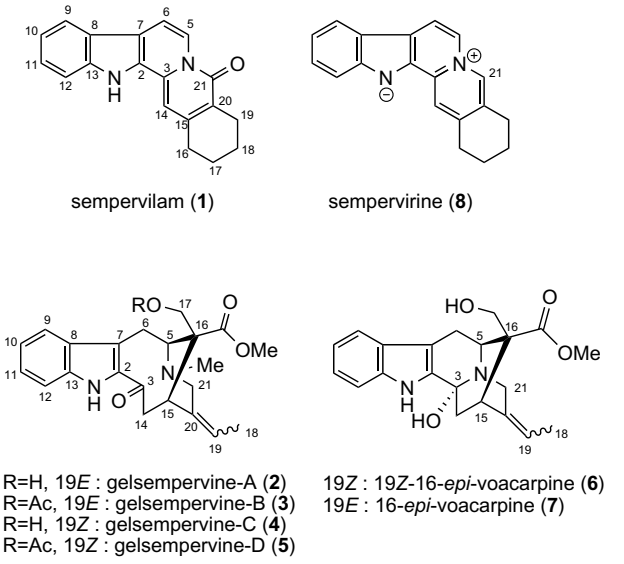


**Figure 1.** Structures of new alkaloids (**1**–**6**) and known alkaloids (**7**, **8**).

*Keywords*: Indole alkaloid; *Gelsemium*; Structure elucidation; NMR; Total synthesis; Isomerization; Solvent effect.
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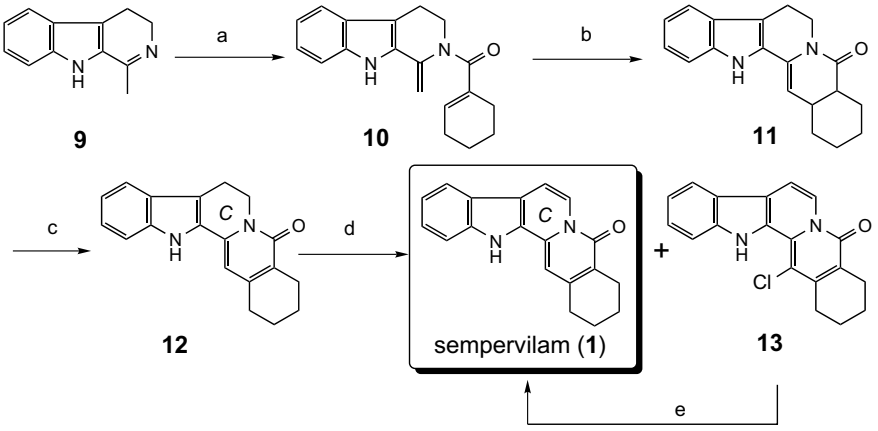
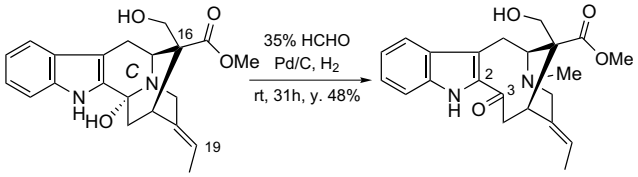



**Scheme 1.** Reagents and conditions: (a) cyclohexene-1-carboxylic acid, HOAT, EDCI, $^{i}Pr_2NEt$, $CH_2Cl_2$, rt, 4 h, 87% ; (b) hν, benzene, rt, 1 h, 36%; (c) DDQ, 1,4-dioxane, reflux, 20 min, 74%; (d) (1) $^{t}BuOCl$, $Et_3N$, $CH_2Cl_2$, 0 °C, 1 h; (2) DBU, toluene, reflux, 2 h, **1**: 28%, **14**: 24%; (e) *n*-$Bu_3SnH$, AIBN, toluene, reflux, 5.5 h, 74%.

C-21. The spectroscopic data led to the elucidation of structure **1** for the new alkaloid, sempervilam.

To confirm the structure, we planned the total synthesis of **1** (Scheme 1). 3,4-Dihydroharman (**9**), which was prepared from tryptamine by acetylation and subsequent Bishler–Napieralski reaction, was condensed with cyclohexene-1-carboxylic acid using HOAT and EDCI to give amide **10** in 87% yield. Photocyclization[7] of **10** gave cycloadduct **11** in 36% yield together with the recovered starting material (14% recovery). Oxidation of **11** with DDQ gave pyridone **12** in 74% yield. Next, to aromatize the C-ring, **12** was treated with $^{t}BuOCl$ and then with DBU to afford **1** in 28% yield together with 14-chloro derivative **13** (24% yield), the latter of which was treated with *n*-$Bu_3SnH$ and AIBN to give **1** in 74% yield. The spectroscopic data ($^1H$ NMR, $^{13}C$ NMR, and UV) of synthetic compound **1** were completely identical with those of the natural product.

The HR-FAB-MS spectrum of new alkaloid (**2**),[8] named gelsempervine-A, gave a protonated molecular ion peak at *m*/*z* 383.1935 ($[MH]^+$) that corresponded to the molecular formula $C_{22}H_{27}N_2O_4$ (*m*/*z* 383.1971). The $^1H$ NMR spectrum (in $CDCl_3$) showed significant signals characteristic of an ethylidene group at δ 5.28 (ddd, H-19) and δ 1.71 (3H, d, $H_3$-18), together with four aromatic protons of the indole system [δ 7.69 (d, H-9), 7.37 (d, H-12), 7.31 (dd, H-11), 7.15 (dd, H-10)], an $N_b$-methyl group at δ 2.29 (3H, s) and a carboxymethyl group at δ 3.68 (3H, s). The $^{13}C$ NMR data of **2** and the known sarpagine-type alkaloid, 16-*epi*-voacarpine (**7**),[9] are highly similar but for two exceptions, namely, the spectrum of **2** shows a signal due to the $N_b$-methyl group at δ 42.0 and does not exhibit a signal at the C-3 position, which is indicative of the hemiaminal function in **7**. Taking the molecular formula into consideration, new alkaloid **2** was deduced to be the $N_b$-methyl derivative of **7**. To reveal the structure, including the stereochemistry at C-16 and the geometry of the ethylidene side chain, **7** was converted into the $N_b$-methyl derivative by treating with formalin in the




**Scheme 2.** Chemical conversion from 16-*epi*-voacarpine (**7**) to gelsempervine-A (**2**).

presence of catalytic Pd–C under $H_2$ atmosphere.[10] The product was completely identical with natural alkaloid, gelsempervine-A, demonstrating the 3-oxo, that is, 2-acyl indole structure of **2** (Scheme 2).

However, perusal of the UV spectrum of **2** revealed typical absorptions of the indole nucleus in MeOH ($\lambda_{max}$, 290.5, 282, 220.5 nm). The 2-acyl indole alkaloids are known to exhibit a characteristic absorption at around 310 nm.[11] In order to investigate this unusual observa-

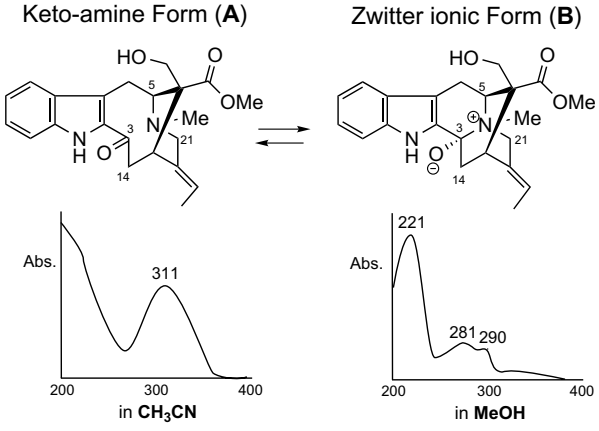



**Figure 2.** Two structural forms and UV spectra of gelsempervine-A (**2**).