Communications to the Editor

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The Structures of Two Lycopodium Alkaloids, Lycothunine and Lycophlegmarine, and the Configuration of the C_3-C_4 Bond of Fawcettimine and Fawcettidine

The structures of two Lycopodium alkaloids, lycothunine and lycophlegmarine, were determined by an X-ray analysis. The configurations of C_3-C_4 bond of fawcettimine and fawcettidine were also established.

Keywords——lycopodium alkaloid; structure determination; lycothunine, lycophlegmarine; fawcettimine; fawcettidine; absolute configuration; X-ray analysis; benzoate rule

In this communication, we describe the structure of two new Lycopodium alkaloids and the configurational establishment of the C_3-C_4 bond of fawcettimine and fawcettidine which has been left behind.

In a previous paper,[1] we reported that lycothunine (**1**) isolated from *Lycopodium serratum* Thunbergii var. *serratum* f. *intermedium* Nakai is a tetracyclic alkaloid having an expanded formula $C_{10}H_{16}(>N-)(>C=O)(-CH=CH-)(>COH)(>CH-CH_3)$. Acetylation of lycothunine gave acetyllycothunine[2] (**2**) which was subjected to an X-ray analysis. Thus, acetyllycothunine (**2**) crystallized from pentane in the orthorhombic, space group $P2_12_12_1$, with eight molecules per unit cell of dimensions $a=14.509(8)$, $b=15.643(8)$, $c=14.349(6)$ Å, $Z=4$, and $Dx=1.24$ g/cm^3. A total of 2019 unique reflexions having $Fo>2\sigma(Fo)$ were measured on a Rigaku AFC-5 diffractometer using CuKα radiation. The structure was solved by direct methods using the program RASA-II.[3] The final refinement resulted in a minimum R of 0.107. Thus, the relative stereostructure of acetyllycothunine (**2**) was decided as shown in Fig. 1[4] and that of lycothunine, therefore, can be represented by the formula (**1**).

The structure of lycothunine (**1**) is closely related to that of fawcettimine (**3**).[5] Then, an attempt was made to establish the relative configuration of the C_3–C_4 bond of fawcettimine by correlating chemically lycothunine (**1**) with fawcettimine (**3**). Catalytic reduction of **1**

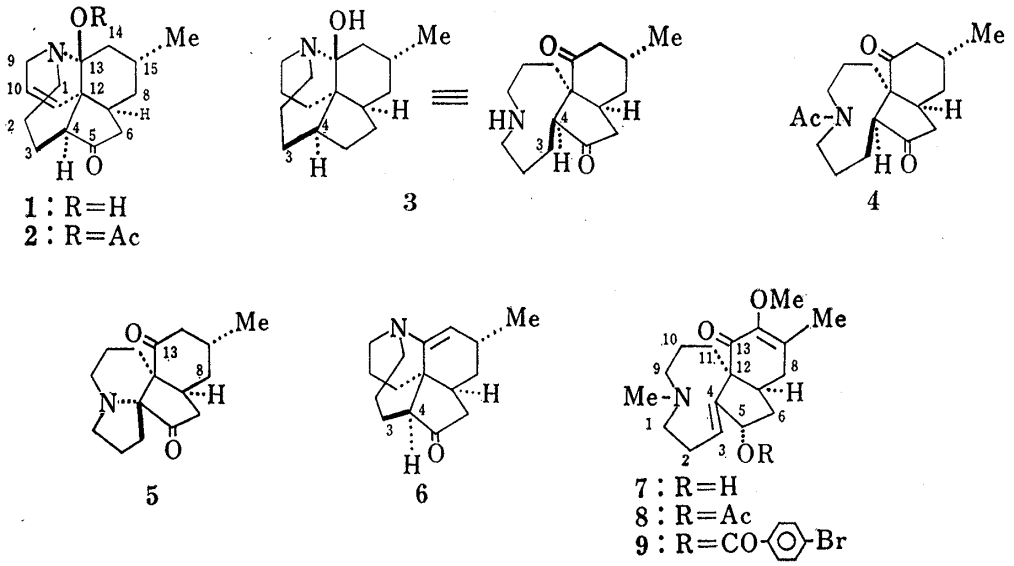

Chart 1

on PtO_2 gave the dihydro compound, which was identified with fawcettimine (**3**) by comparison of infrared (IR) spectra in $CHCl_3$ and CCl_4, and thin-layer chromatography behavior. N-Acetyldihydrolycothunine was also identical with N-acetylfawcettimine[6] (**4**) in all respects including the specific rotation. Therefore, the relative configuration of the C_3-C_4 bond of fawcettimine was determined as shown by the formula (**3**). Since the absolute configurations of these alkaloids (**1** and **3**), are not decided, we attempted to determine those of two alkaloids by chemical correlation of these alkaloids with 8-deoxy-13-dehydroserratinine[7] (**5**), the absolute configuration of which has been already established. Thus, treatment of **5** with Zn–Ac_2O under reflux afforded N-acetylfawcettimine (**4**). The specific rotation of N-acetyldihydrolycothunine (**4**) $[[\alpha]_D^{17}$ +114.1° (c=1.10, MeOH)], N-acetylfawcettimine (**4**) $[[\alpha]_D$ +109.2° (c=

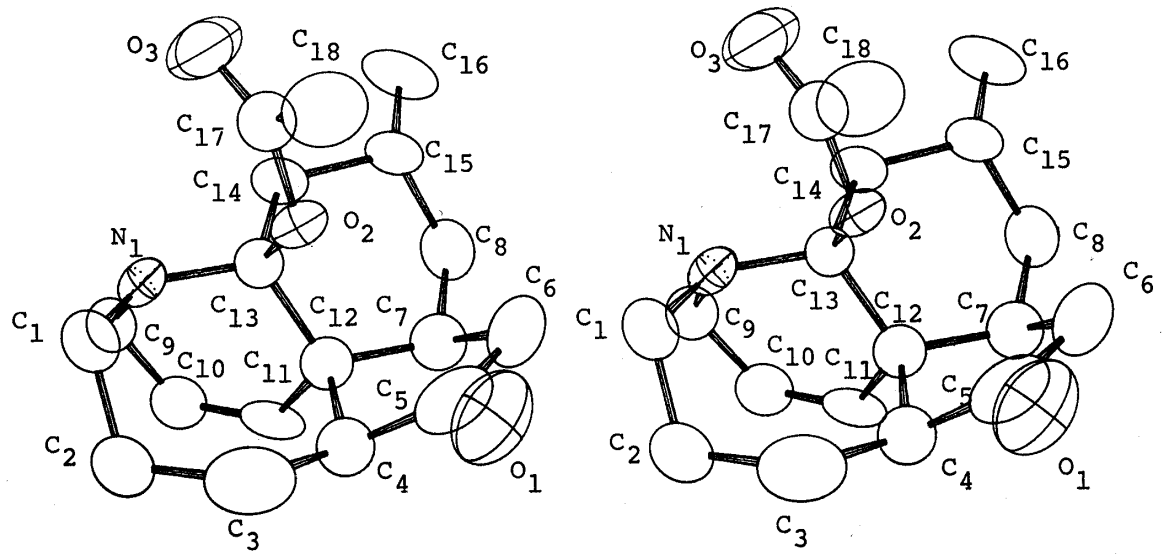

Fig. 1. Stereoscopic View of the Structure of Acetyllycothunine (**2**)

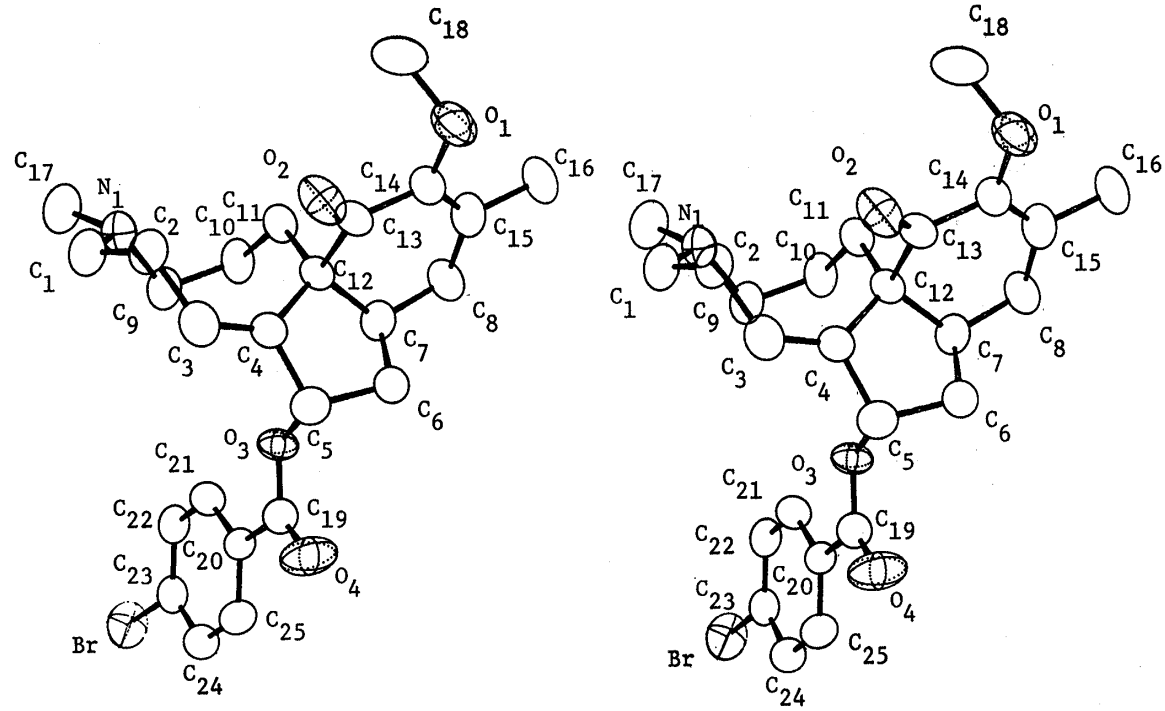

Fig. 2. Stereoscopic View of the Structure of *p*-Bromobenzoyllycophlegmarine (**9**)

0.39, MeOH)[8]], and the compound (**4**) derived from **5** [$[\alpha]_D^{17}$ +109.3° (c=0.92, MeOH)] was the same within experimental error. The absolute stereostructures of lycothunine and fawcettimine can be now represented by the formulae (**1** and **3**), respectively. Furthermore, the absolute configuration of the C_3-C_4 bond of fawcettidine[7] (**6**) should be β, because **6** has been correlated with fawcettimine[5] (**3**).

On the other hand, detailed examination of alkaloid components of *Lycopodium phlegmaria* L.[9] collected in Sri Lanka resulted in six new alkaloids and three known alkaloids. Lycophlegmarine (**7**) [oil, $C_{18}H_{27}NO_3$, $[\alpha]_D^{17}$ +258.5° (c=0.94, EtOH)] showed IR bands in $CHCl_3$ at 3300, 1665, and 1645 cm^{-1}, indicating the presence of the hydroxy and the α,β-unsaturated ketonic functions. Its ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum (100 MHz) showed signals at δ 1.88 (3H, s, vinylic CH_3), 2.32 (3H, s, NCH_3), 3.56 (3H, s, OCH_3), 4.36 (1H, br s, $W_{1/2}$=7 Hz, >CH–OH), and 5.94 (1H, dd, J=12 and 6 Hz, olefinic H). Acetylation of **7** gave the monoacetate (**8**) (oil, $C_{20}H_{29}NO_4$), which showed no hydroxy band in the IR spectrum and the signals at δ 2.02 (3H, s, $OCOCH_3$) and 5.41 (1H, br s, $W_{1/2}$=7 Hz, >CH–OAc) in the ^{1}H-NMR spectrum (60 MHz). The ^{13}C-NMR spectrum of **7** showed the presence of four sp^2 carbons at δ 147.22, 146.61, 139.70, and 131.83, and one carbonyl carbon at δ 195.12, indicating that lycophlegmarine is a tricyclic alkaloid. Lycophlegmarine was derived to its p-bromobenzoate (**9**) [mp 140—142°C, $C_{25}H_{30}BrNO_4$, $[\alpha]_D^{17}$ +133.5° (c=1.07, EtOH)], which was subjected to an X-ray analysis.

p-Bromobenzoyllycophlegmarine (**9**) crystallized from hexane in the tetragonal, space group $P4_1$, with four molecules per unit cell of dimensions $a=b$=7.890(3), c=37.582(8) Å, Z=4 and Dx=1.39 g/cm^3. A total of 2468 unique reflexions having $Fo>2\sigma(Fo)$ were measured on a Rigaku AFC-5 diffractometer using CuKα radiation. The structure was solved by heavy atom methods using the program RASA-II. The final refinement resulted in a minimum R of 0.049. The molecular structure, so derived is depicted in Fig. 2.[4] In order to determine the absolute stereostructure of **7**, the Brewster's benzoate rule[10] was applied to **7** and **9** [$[M]_D^{17}$ +651.5° (p-bromobenzoate)−$[M]_D^{17}$ +788.4° (OH)=−136.9°]. This result led to the conclusion that the absolute configuration at C_5 asymmetric center is the (S)-configuration. Consequently, the absolute stereostructure of lycophlegmarine can be represented by the formula (**7**).

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Faculty of Pharmaceutical Sciences,
Kyoto University
Yoshida Shimoadachi-cho,
Sakyo-ku, Kyoto, 606,
Japan

Yasuo Inubushi*
Takashi Harayama

Faculty of Pharmaceutical Sciences,
Chiba University
1-33, Yayoi-cho, Chiba, 260,
Japan

KEIICHI YAMAGUCHI
HISASHI ISHII

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Novel Type Secoiridoid Glucosides, Hydrangenosides B, C and D from *Hydrangea macrophylla*

Along with the known hydrangenoside A (**4**), new glucosides of the same series, hydrangenosides B (**1**), C (**2**) and D (**3**), have been isolated from *Hydrangea macrophylla* and their absolute structures have been established. These substances are considered to be formed by an aldol-type condensation of secologanin (**5**) with a shikimate–malonate derived moiety followed by decarboxylation. Hydrangenoside A (**4**) and B (**1**) are stereoisomers, while hydrangenoside C (**2**) and D (**3**) are their homologues containing one fewer acetate unit and also are stereoisomers.

Keywords——*Hydrangea macrophylla*; Saxifragaceae; secoiridoid glucosides with shikimate–malonate derived side chain; Hydrangenosides B, C and D; structure elucidation

We have previously isolated hydrangenoside A from *Hydrangea macrophylla* (Thunb.) Ser. var. *macrophylla* (Japanese name, Ajisai) and established[1] that it has the novel structure **4** consisting of secologanin (**5**) and a unit formed by the shikimate–malonate route, which are joined through a C–C bond.

In this paper we describe the structure elucidation of three new glucosides, hydrangenosides B (**1**), C (**2**) and D (**3**), isolated as the minor components from the same plant.

The ethyl acetate soluble portion of the aqueous extract of the overground parts of *Hydrangea macrophylla* was fractionated by sequential silica gel column chromatography, droplet counter current chromatography and high performance liquid chromatography, affording hydrangenosides B (**1**), C (**2**) and D (**3**), along with hydrangenoside A (**4**).

Hydrangenoside B (**1**) was obtained as a white powder, $C_{31}H_{40}O_{13}\cdot H_2O$, $[\alpha]_D$ −80.9° (MeOH). Its spectral data (infrared (IR), ultraviolet (UV) and ^1H nuclear magnetic resonance (NMR)) are in good accordance with those of hydrangenoside A (**4**), suggesting that **1** is closely related in structure to **4**. Acetylation of **1** gave a pentaacetate (**6**) whose ^1H NMR spectrum is similar to that of hydrangenoside A pentaacetate (**7**), except that the C-7 and C-15 protons of **6** resonate at higher field (δ 3.75 and 4.05) than those of **7** (δ 4.20 and 4.60, respectively). Additionally, the ^{13}C NMR signals of **6** are in agreement with those of **7**, except for the chemical shifts of C-7 and C-15 (δ 72.8 and 73.7). Thus, hydrangenoside B (**1**) is assumed to be a C-7 and/or C-15 stereoisomer of hydrangenoside A (**4**). In order to verify this assumption, **6** was subjected to the same chemical degradation as was **7**. Thus, **6** was converted, through $NaBH_4$ reduction, mesylation and 2,6-lutidine-induced elimination, into an olefinic mixture, which was hydrogenated over 10% Pd-C in AcOH to give the lactone (**8**), the 7-alcohol (**9**) and the tetrahydropyran (**10**).

The lactone (**8**) was identical to the 7*S*-isomer (whose ^1H NMR showed 11% nuclear Overhauser effect (NOE) between the C-5 and C-7 protons) of the two lactones[1] which had been synthesized by Grignard reaction of *p*-benzyloxyphenyloctanyl bromide (**11**) and secologanin tetraacetate (**12**). Since the conversion of **6** into **8** (*vide supra*) is expected to occur with