Communications to the Editor

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Fritillarizine, a New *Fritillaria* Alkaloid isolated from the Aerial Part of Mature *Fritillaria verticillata*

Fritillarizine (22S,25S)-cev-5-enine-3α,20β-diol, a new *Fritillaria* alkaloid was isolated from the hydrolysis products of aerial part extracts of mature *Fritillaria verticillata* and its structure and absolute configuration were determined by conversion from verticinone.

Keywords——Liliaceae; *Fritillaria verticillata*; a new *Fritillaria* alkaloid; alkaloid from aerial part; an epimer of veraflorizine; biogenesis of *Fritillaria* alkaloid; Δ^5-cevanine alkaloid; synthesis from verticinone

In our previous work on *Fritillaria* alkaloids isolated after acid hydrolysis of a glycoalkaloid fraction from a mature plant of *Fritillaria verticillata* WILLD. var. *Thunbergii* BAKER, Liliaceae, three new alkaloids, baimonidine (**2a**), isobaimonidine (**3**), and isoverticine (**4**) were identified, in addition to those already isolated: verticine (**5**), verticinone (**6**), solanidine and hapepunine. These three alkaloids are the diastereoisomers of **5**, concerning the configuration of the hydroxyl groups at C-3 and C-6. It is also of interest to note here that the 3α-hydroxyl epimers **4**, and **5**, mainly accumulated in the bulb.[1,2] In the continuation of our work on the separation of alkaloids from the aerial part of the mature plant, a new cevaine alkaloid named fritillarizine (**1a**) was isolated.

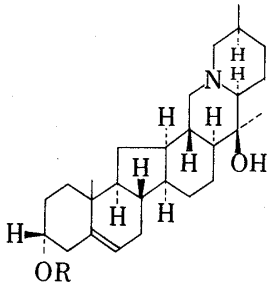
Fritillarizine (**1a**), mp 141.5—143° (uncorr.); $[\alpha]_D$ −18.6° (c=1.0, $CHCl_3$); $C_{27}H_{43}NO_2$ (high resolution MS); m/z: 413 (M^+, 9%), 398, 395, 112 (100%), 111, 98; ^{1}H-NMR ($CDCl_3$, 100 MHz, TMS); δ 1.02 (6H, s), 1.08 (3H, d, J=7 Hz), 4.02 (1H, m, $W_{1/2}$=8 Hz), 5.41 (1H, m, olefinic proton); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3550—3100, 2780, 1645, 1030, 805. On acetylation in pyridine **1a** gave O-monoacetate (**1b**), ^{1}H-NMR ($CDCl_3$, 100 MHz, TMS as internal standard): δ 2.01 (3H, s, -OAc), 5.01 (1H, m, $W_{1/2}$=8 Hz); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100, 1715, 1250, 1020.

Its empirical formula, the presence of two tertiary and one secondary methyl group (^{1}H-NMR) and *trans*-quinolizidine moiety (MS and IR),[3,4] suggested that **1a** was a steroidal alkaloid having cevanine skeleton. One of the two oxygen functions in **1a** was shown to be secondary hydroxyl by the conversion of **1a** into O-monoacetate (**1b**) and the hydrogen on the carbon bearing hydroxyl group in **1a**, multiplet centered at δ 4.02 (1H), shifted downfield to 5.01 in **1b**. A double bond, whose presence was revealed in the ^{1}H-NMR spectrum of **1a** (olefinic proton at δ 5.41), was found to be located in the proximity of the alcohol function by Oppenauer oxidation that converted **1a** into an α,β-unsaturated oxo-derivative (**1c**), UV λ_{max}^{EtOH} 236 nm (ε 16200); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100, 1645, 1610, 1070.

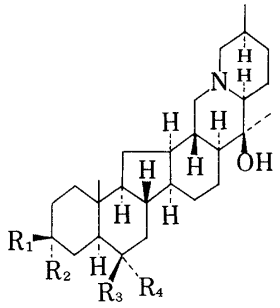
Since the chemical shift and half height width of the hydrogen on the carbon bearing hydroxyl group in **1a** were similar to those of 3β-H in **2a**, (δ 4.24, $W_{1/2}$=8 Hz), they were compared with those of two related compounds, veraflorizine (**7**)[5] and epicholesterol(**8**).[6] As shown in Fig. 2, ^{1}H-NMR spectral data were similar in **1a** and **8**, but not in **1a** and **7**. All of these considerations support the presence of the α-axial hydroxyl group at C-3 in **1a**.

The IR spectrum of **1b** showed that broad hydroxyl absorption at 3550—3100 cm^{-1} due

1) K. Kaneko, M. Tanaka, K. Haruki, N. Naruse, and H. Mitsuhashi *Tetrahedron Lett.*, **1979**, 3737.
2) K. Kaneko, N. Naruse, K. Haruki, and H. Mitsuhashi, *Chem. Pharm. Bull.*, **28**, 1345 (1980).
3) F. Bohlman, *Chem. Ber.*, **91**, 2157 (1958).
4) H. Budzikiewicz, *Tetrahedron*, **20**, 2267 (1964).
5) K. Kaneko, N. Kawamura, T. Kuribayashi, M. Tanaka, H. Mitsuhashi, and H. Koyama, *Tetrahedron Lett.*, **1978**, 4801.
6) L.P.L. Piacenza, *J. Org. Chem.*, **42**, 3778 (1977).



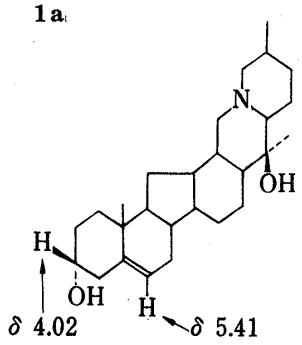
1a: R=H fritillarizine
1b: R=Ac
1d: R=Bz



		R_1	R_2	R_3	R_4
2a:	baimonidine	H	OH	OH	H
3:	Isobaimonidine	H	OH	H	OH
4:	Isoverticine	OH	H	OH	H
5:	verticine	OH	H	H	OH
6:	verticinone	OH	H	=O	

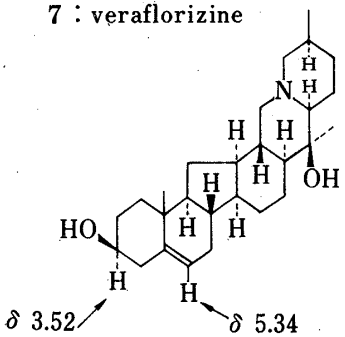
Fig. 1

1a



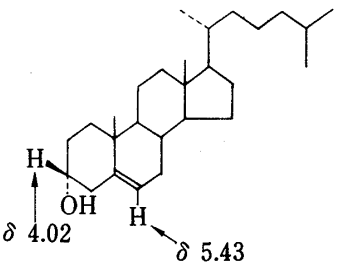
δ 4.02
δ 5.41
$W_{1/2}$=8 Hz

7 : veraflorizine



δ 3.52
δ 5.34
$W_{1/2}$=24 Hz

8 : epicholesterol



δ 4.02
δ 5.43
$W_{1/2}$=8 Hz

Fig. 2

to the other hydroxyl group, and that this absorption in $CHCl_3$ remained unchanged at high dilution. Due to the fact that the hydroxyl group at C-20 in cevanine alkaloids possesses a 1,3-diaxial relationship with a lone pair of nitrogen,[7] this hydroxyl group in **1a** was estimated as a β-axial configuration at C-20, based on analogy with other cevanine alkaloids.

In order to establish stereochemistry of **1a**, **6** was converted into **1a**. **6** was reduced with $NaBH_4$ in EtOH to give **4**, ^{1}H-NMR ($CDCl_3$, 100 MHz, TMS): δ 1.03 (6H, s, 19-H_3 and 21-H_3), 1.09 (3H, d, J=7 Hz, 27-H_3), 3.85 (1H, m, $W_{1/2}$=8 Hz, 6α-H), 3.63 (1H, m, $W_{1/2}$=24 Hz, 3α-H). **4** was converted into baimonidine 3-monobenzoate (**2b**), MS m/z: 535 (M^+, 3%), 112 (100%); ^{1}H-NMR: δ 3.80 (1H, m, $W_{1/2}$=8 Hz, 6α-H), 5.41 (1H, m, $W_{1/2}$=8 Hz, 3β-H), 7.36—8.10 (5H, m); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1270, following the method previously reported.[1] The β-axial hydroxyl group at C-6 in **2b** was mesylated with MsCl in anhydrous pyridine to give baimonidine 3-benzoate 6-mesylate (**2c**), ^{1}H-NMR: δ 3.00 (3H, s, -OMe), 4.81 (6α-H), 5.41 (3β-H); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1360—1320, 1165. Thus resulted **2c** was reacted with Li_2CO_3 in DMF to give cev-5-enine-3α,20β-diol 3-monobenzoate (**1d**), ^{1}H-NMR: δ 5.31 (2H, m, 3β-H and 6-H); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 805. **1d** was then saponified in methanolic KOH to yield **1a** (overall yield, 44%). The physical constants of **1a** were identical with those of the natural product. The identity was also confirmed by mixed melting point experiment.

Since **1a** was also detected in an unsaponified basic fraction from the same plant, it appears to be a genuine alkaloid. It is also the first *Fritillaria* alkaloid having a cevanine skeleton with Δ^5-3-ol moiety.

7) S.M. Kapchan and A.W. By, "The Alkaloids," Vol. X, edited by R.H.F. Manske, Academic Press, New York, 1968, p. 193.

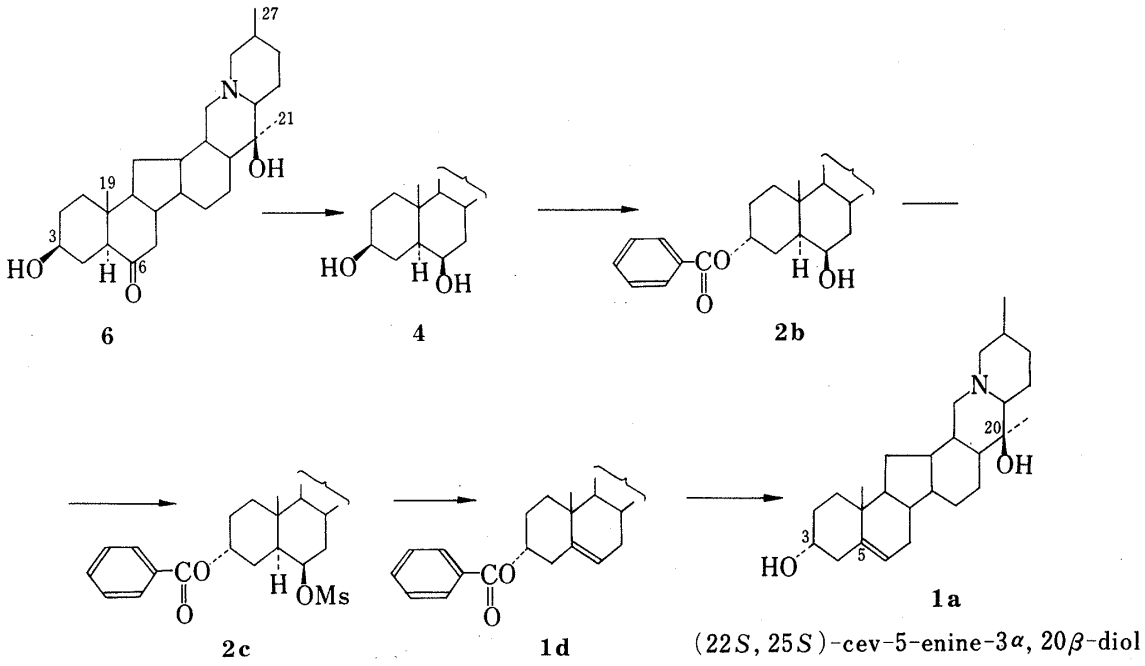


Chart 1

On the basis of fact that **1a** was isolated only from the aerial part, in addition to **2a** and **3**, it seems reasonable to suggest that **1a** and 5α-cevanine alkaloids having a 3α-hydroxyl group, such as **2a** and **3**, are synthesized through quite a similar biogenetic pathway at the aerial part of this plant.

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Revised Structures of Chebulinic Acid and Chebulagic Acid

The structures of chebulinic acid and chebulagic acid, which were previously formulated as dicarboxylic acids, Ib and IIb, have been revised to monocarboxylactones, Ic and IIc, respectively, on the basis of spectral and chemical evidences.

Keywords——myrobalans; *Terminalia chebula*; Combretaceae; chebulinic acid; chebulagic acid; revised structure; ^{13}C NMR; deuterium-induced differential isotope shift (DIS)

Chebulinic acid (I) and chebulagic acid (II) are the main tannins of myrobalans [fruit of *Terminalia chebula* (Combretaceae)]. Their structures were firstly formulated as Ia and