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STRUCTURAL REVISION OF FRANCHETINE AND VILMORISINE, TWO NORDITERPENOID ALKALOIDS FROM THE ROOTS OF *ACONITUM* SPP.

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Key Word Index—*Aconitum hemsleyanum* var. *pengshiese*; Ranunculaceae; norditerpenoid alkaloids; franchetine; vilmorisine.

Abstract—The structural revision of franchetine (*Aconitum franchetii* and *A. hemsleyanum* var. *pengshiese*) and vilmorisine (*A. vilmorinianum*) have been carried out on the basis of chemical and ^{1}H, ^{13}C, ^{1}HCOSY, HETCOR, LOC, 1D-and 2D-NOE NMR spectral studies. They are the novel norditerpenoid alkaloids having a unique mixed *N*, *O*-acetal [*N*-C(17)-*O*-C(6)] moiety with a $\Delta^{7(8)}$-double bond.

INTRODUCTION

Sung *et al.* [1] first isolated franchetine from the roots of *Aconitum franchetti* Fin. et Gagnep and reported its structure as **1** based only on 1D ^{1}H and ^{13}C NMR spectra. After 10 years, in the course of our study on *Aconitum hemsleyanum* Pritz var. *pengshiese* W. J. Chang et G. H. Chen (*Ranunculaceae*), franchetine was reisolated from the roots of this plant. Its structure was revised as **2** on the basis of chemical correlation [2]. Vilmorisine **3**, which is very similar to franchetine, was isolated from the roots of *A. vilmorinianum* Kom, and its structure was proposed only on the basis of the 1D-NMR spectra and comparison of behaviour on TLC with hydrolytic alkamines from vilmorisine and franchetine [3]. In this paper we describe in detail the structural revision of both franchetine and vilmorisine.

RESULTS AND DISCUSSION

Extraction of the total alkaloids from the roots of *A. hemsleyanum* var. *pengshiese* using ion exchange resin [4], followed by repeated column chromatography, gave an alkaloid. On the basis of comparison of the melting points, R_f value on TLC, optical rotation, 1D ^{1}H and ^{13}C NMR data, this alkaloid was identified as franchetine, the structure of which was assigned as given in ref. [1].

Franchetine, white amorphous powder (HRMS *m/z*: 523.2891, $C_{31}H_{41}NO_6$ requires 523.2904). The ^{1}H NMR (400 MHz) spectrum showed the presence of an *N*-ethyl (δ 1.01, 3H, *t*, J = 7 Hz), three methoxyls (δ 3.25, 3.29, 3.36, each 3H, *s*) and a benzoyl group [δ 7.43 (2H, *t*, J = 7.6 Hz), 7.54 (1H, *t*, J = 8 Hz), 8.02 (2H, *d*, J = 7.2 Hz)]. Its ^{1}H and ^{13}C NMR spectra also showed the characteristic mixed *N*,*O*-acetal moiety (δ_H 4.40, *d*, J = 5.2 Hz; 4.39, *s*; δ_C 74.8 *d*, 92.2 *d*) and the presence of a trisubstituted double bond (δ_H 5.77, *d*, J = 5.2 Hz; δ_C 128.7 *d*, 136.8 *s*). The ^{13}C NMR spectrum of franchetine in combination with the DEPT spectrum revealed the presence of four methyl, seven methylene, 13 methine and five quaternary carbons. The characteristic basic peak at *m/z* 492 (M-OCH_3) was attributed to the methoxyl group at C-1 [5] and one-proton doublet (H-6, J = 5.2 Hz) signal at δ 4.40 to be assigned to one of the signals for the mixed *N*,*O*-acetal moiety in the ^{1}H NMR spectrum. Thus, the possibility of structure **5** may be ruled out, resulting in consideration of two possibilities, **1** or **2**. On the other hand, if we only considered the rings B, D and F, there are two additional possibilities (**6** or **7**) derived from an alternative arrangement for the double bond in the molecule of franchetine.

The 1D NOE (Fig. 1) and NOESY (Table 2) spectral data of franchetine showed the NOE relationships between the H-6 (δ 4.40) and H_2-18 (δ 3.00, 3.18), H-6 and H-5 (δ 4.1), H-6 and H-7 (δ 5.77), H-7 and H_2-15 (δ 2.50, 2.90) as well as H-17 (δ 4.39) and H_2-12 (δ 1.52, 2.02). This evidence rules out the possibilities of structures **1**, **5**, **6** and **7**. In addition, observation of the correlation between H_2-15 (δ 2.50, 2.90) and C-8

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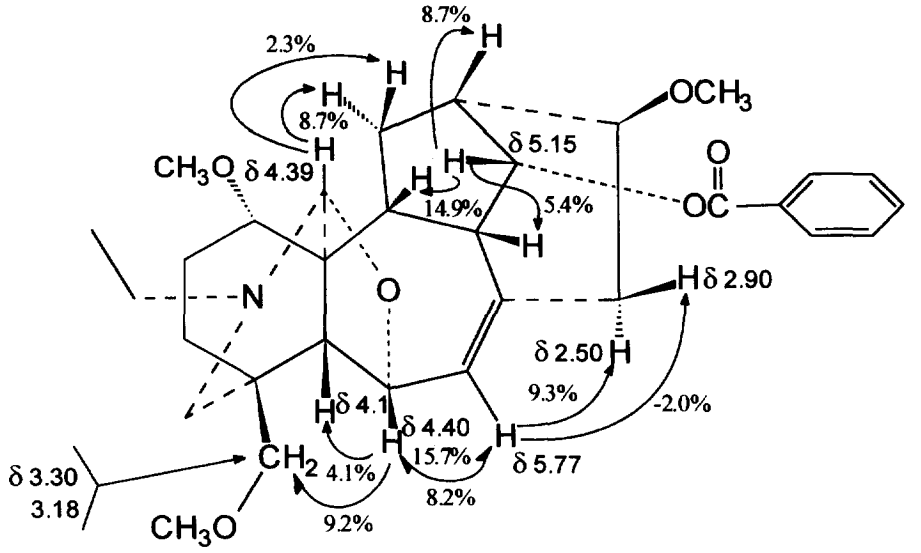
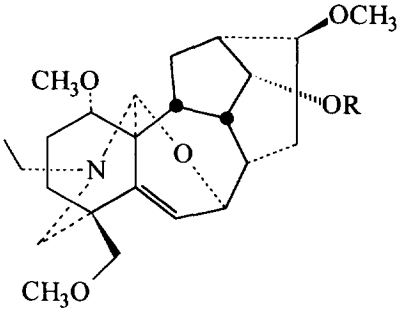


Fig. 1. 1D NOEs observed for franchetine **2** in $CDCl_3$ (400 MHz).

(^2J) in the COLOC spectrum of franchetine supports the deduction mentioned above. Therefore, the structure of franchetine has been revised to **2**, and all the ^1H and ^{13}C NMR data obtained for franchetine (Table 1) support this structure. Furthermore, we carried out the chemical correlations shown in Scheme 1. Treatment of franchetine with NaOAc–HOAc under reflux, followed by hydrolysis, afforded the known alkaloid foresticine (**8**) [6]. Evidently, the structure **1** will not afford foresticine (**8**).

Vilmorisine (**3**) was isolated from the roots of *A. vilmorinianum* by Ding *et al.* [3], and its structure was determined on the basis of comparison of the ^1H and ^{13}C NMR data with franchetine. The structure of vilmorisine should therefore be revised to **4**.

It is of interest to note that franchetine (**2**) and



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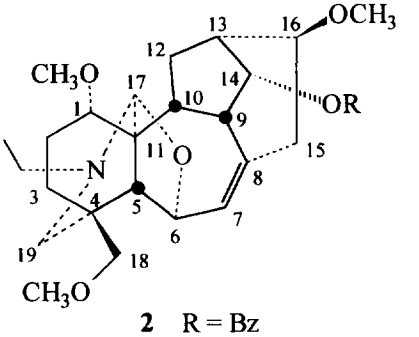
3 R = Ac



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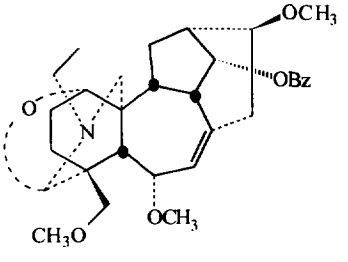

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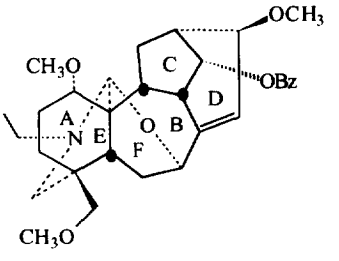

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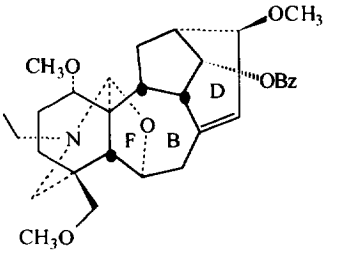

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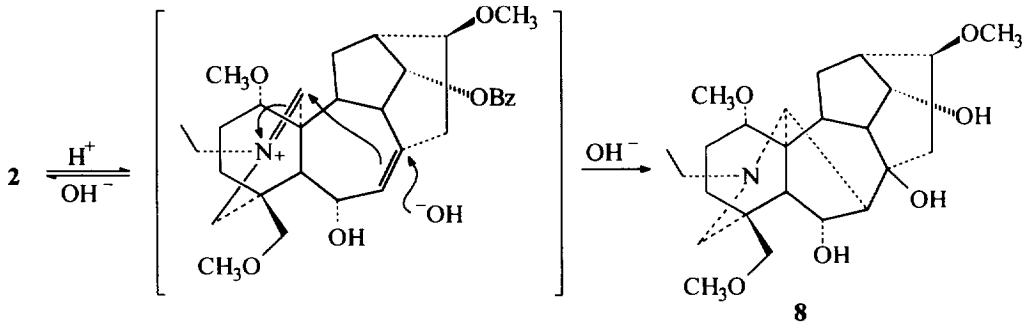
Table 1. NMR data for franchetine (**2**) in $CDCl_3$ (400 MHz for ^1H, 100 MHz for ^{13}C)

Carbon	^{13}C	^1H	^1H-^1H COSY	COLOC(H → C)
1	86.5 *d*	3.30(H_2-1) *m*	2.41(H-2), 1.80(H-2)	
2	24.3 *t*	1.80 *m*(*β*)	2.41(H-2),	
		2.41 *m*(α)	3.30(H-1), 1.50(H-3), 1.80(H-2)	C_4, C_{11}
3	32.7 *t*	1.50 *m*(*β*)	2.41(H-2), 1.70(H-3)	
		1.70 *m*(α)	1.50(H-3), 2.41(H-2)	C_5
4	37.3 *s*	—	—	
5	47.9 *d*	2.31 *s*	—	C_6, C_{10}, C_{11}, C_{17}
6	74.8 *d*	4.40 *d*(5.2)	5.77(H-7)	C_{17}
7	128.7 *d*	5.77 *d*(5.2)	4.40(H-6)	
			2.95(H-15)	
8	136.8 *s*	—	—	—
9	42.9 *d*	3.05 *m*	2.40(H-10), 5.15(H-14)	C_{13}, C_{15}
10	49.4 *d*	2.40 *m*	2.02(H-12), 1.52(H-12)	C_{13}
11	50.1 *s*	—	—	—
12	29.7 *t*	1.52 *m*(*β*)	2.60(H-13)	C_{13}, C_{15}
		2.02 *m*(α)	2.60(H-13), 2.40(H-10)	C_9, C_{11}, C_{13}, C_{16}
13	38.3 *d*	2.60 *m*	5.15(H-14), 2.02(H-12)	C_{15}
14	78.7 *d*	5.15 *br s*	3.05(H-9)	
			2.60(H-13)	
15	38.5 *t*	2.50 (hidden)(α)	3.30(H-16)	C_8
		2.90 *t* (8.1)(*β*)	3.30(H-16)	C_8
16	85.4 *d*	3.30 *m*	2.90(H-15)	C_{14}, C_{16}
17	92.2 *d*	4.39 *s*	—	C_5, C_6, C_{11}
18	78.8 *t*	3.00 AB*q*(9)	3.18 ABq	C_{19}
		3.18	3.00	C_{19}
19	52.1 *t*	(a) 2.00 ABq	2.00 ABq	C_{18}
		(e) 2.42 (hidden)	2.42	C_{18}
NCH_2CH_3	49.0 *t*	2.19 *m*	1.01 (CH_3-22)	
		2.51 *m*		
NCH_2CH_3	13.0 *q*	1.01 *t*(7)	2.51(H-21)	
1′	57.6 *q*	3.25 *s*	—	
16′	55.9 *q*	3.36 *s*	—	
18′	59.3 *q*	3.29 *s*	—	
O=C	166.4 *s*	—	—	
1″	136.8 *s*	—	—	
2″, 6″	128.8 *d*	8.02 *d*(7.2)	7.43(3″, 5″)	C=O
3″, 5″	128.2 *d*	7.43 *t*(7.6)	8.02(2″, 6″), 7.54(4″)	$C_{2''}$, $C_{6''}$
4″	132.6 *d*	7.54 *t*(8.0)	7.43(3″, 5″)	$C_{2''}$, $C_{6''}$

Table 2. NOESY data for franchetine (**2**) in $CDCl_3$

protons	NOEs (NOESY)	protons	NOEs (NOESY)
H-1*β*	H-2*β*, H-3*β*, H-5, H-10	H-12α	H-16α, H-17
H-1α	H-2α	H-13	H-12*β*, H-14*β*, H-16α
H-2*β*	H-1*β*	H-14	H-9, H-10, H-13
H-2α	H-1α	H-15α	H-7, H-16α
H-3*β*	H-1*β*, H-5, H_2-18	H-15*β*	Aromatic protons
H-3α	H(e)-19 (*δ* 2.42)		(*δ* 7.43, 7.54, 8.02)
H-5	H-1*β*, H-3*β*, H-6	H-16α	H-12α, H-15α
	H-9, H_2-18	H-17	H-12α
H-6	H-5, H-7, H_2-18	H_2-18	H-3*β*, H-5, H-6, H(a)-19
	H(a)-19 (*δ* 2.00)	H(a)-19	H-6, H_2-18
H-7	H-6, H-15α (*δ* 2.54)	H(e)-19	H-3α, H_2-18, H(CH_3)-22
H-9	H-5	H_2-21	H_2-19
H-10	H-1*β*, H-14*β*	H(CH_3)-22	H_2-19



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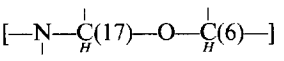
vilmorisine (**4**) are the only examples of the norditerpenoid alkaloids containing both a mixed *N,O*-acetal



and a $\Delta^{7(8)}$-double bond moiety.

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