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CHUANBEINONE, A NOVEL D/E CIS-(22R,25S)-5α-CEVANINE ALKALOID FROM CHINESE HERBAL DRUG, CHUAN-BEI-MU

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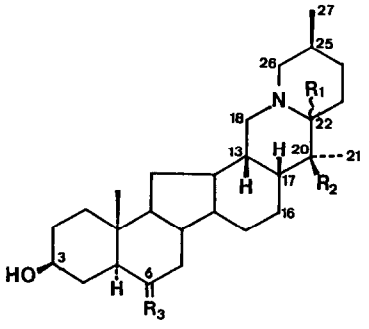
SUMMARY: A novel D/E cis (22R,25S)-20-deoxy-5α-cevanine alkaloid, chuanbeinone, was isolated from the herbal drug of Fritillaria plant ("chuan-bei-mu" in chinese), and its absolute configuration was confirmed by x-ray crystallographic analysis.

In the previous paper, we reported the structure elucidation of D/E cis (22S,25S)-20-deoxy-5α-cevanine alkaloids, delavine (**2**) and delavinone (**3**), which were isolated from Fritillaria delavayi Franch (Liliaceae)[1]. In a continuing study, a novel D/E cis (22R,25S)-20-deoxy-5α-cevanine alkaloid, chuanbeinone(**1**) (0.002% from dried bulb), was isolated together with imperialine (0.002% from dried bulb) from a chinese herbal drug, chuan-bei-mu (from some subspecies of F. delavayi Franch) which is commercially available on the chinese markets.



		R_1	R_2	R_3
Chuanbeinone	(1)	β-H	H	=O
Delavine	(2)	α-H	H	OH, H
Delavinone	(3)	α-H	H	=O
Imperialine		α-H	OH	=O

Chuanbeinone (**1**): crystallized from MeOH as colorless needles, mp 149-152°, $C_{27}H_{43}NO_2$ (M^+, obsd. m/z 413.3273, calcd. 413.3293), $[\alpha]_D$ -62.4° (c=0.5, $CHCl_3$), CD

$[\theta]_{295}$ - 5600 (neg. max., c=2.4X10^{-3}, MeOH) IR: $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3400(OH), 2800 and 2750(trans quinolizidine)[2], 1705(six-membered ring ketone), MS: m/z 413(45%), 398(9%), 395(7%), 112(46%), 111(base peak,100%), ^{1}H-NMR($CDCl_3$): δ 0.70(3H, s, 19-H), 0.84(3H, d, J=6Hz, 27-H), 0.98(3H, d, J=7Hz, 21-H) and 3.57(1H, m, $w_{\frac{1}{2}}$=23Hz, 3α-H). The appearance of two secondary methyl signals at δ 0.98 and 0.84 in the ^{1}H-NMR spectrum of **1** suggests the absence of any hydroxy group at C-20, similar to those of **2** and **3**[1], and the presence of an equatorial methyl group at C-25 respectively. The signal at δ 0.70 ascribable to 19-H in **1** was similar to that in imperialine[3]. The hydrogen on the carbon bearing a hydroxyl group observed at δ 3.57, and a six-membered ring ketone absorption was present in the IR spectrum of **1**. From these physical properties, chuanbeinone(**1**) was estimated to be 20-deoxy-5α-cevanine-3β-ol-6-on.

The absolute configuration of **1** was confirmed by the X-ray crystal structure elucidation of its hydroiodide (mp 303-306°). The structure of the molecule is shown in Fig. **1**. The crystal of chanbeinone-hydroiodide belongs to the orthorhombic system with space group $P2_12_12_1$, and the cell dimensions a=14.977(6), b=22.199(7), c=7.852(3)Å, v=2611(2)Å^3, d(calcd.)=1.38g cm^{-3}, d(obsd.)=1.34g cm^{-3}(flotation), z=4. Three-dimensional intensity data were collected on Rigaku AFC-5 diffractometer and 2635 independent reflections were measured for θ≤25° by the θ-2θ scan technique with Mo-Kα radiation. The structure was solved by a conventional heavy-atom method and refined by a block-diagonal anisotropic least-squares technique to R=0.026 for 2273 reflections.

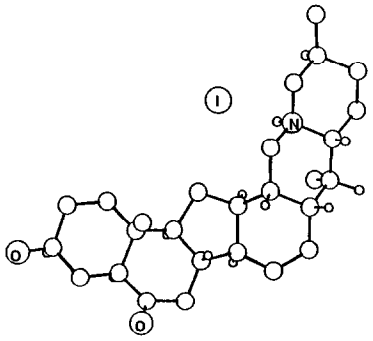


Fig. 1 A Molecular Perspective Drawing Showing the Absolute Configuration of Chuanbeinone Hydroiodide

The ring fusions in **1** are as follows: A/B trans, B/C trans, C/D cis, D/E cis and E/F trans. The configurations at the chiral centers have been settled as 3-OH β-equatorial, 10-Me β-axial, 20-Me α-axial, 22-H β-axial, 25-Me β-equatorial, and a lone pair of the nitrogen α-axial. The six membered rings A, B, E and F are in the chair conformations and ring D is in a boat one.

Table I ^{13}C-NMR Chemical Shifts of **1** and **3**[a)]

C-No.	1	3[1)]
1	37.6	37.6
2	30.6	30.6
3	70.9	70.9
4	30.3	30.3
5	56.4	56.7
6	211.1	211.0
7	46.8	47.0
8	38.2	39.7
9	54.8	56.7
10	38.2	38.3
11	32.0	30.0
12	36.6	39.5
13	37.7	39.3
14	43.3	41.0
15	24.4	26.8
16	24.8	17.1
17	48.0	46.9
18	65.7	59.3
19	12.4	12.7
20	37.4	35.7
21	11.4	15.6
22	66.9	62.4
23	30.1	24.9
24	33.6	30.4
25	31.1	28.4
26	59.9	61.8
27	19.8	18.3

a) In ppm relative to TMS in $CHCl_3$.

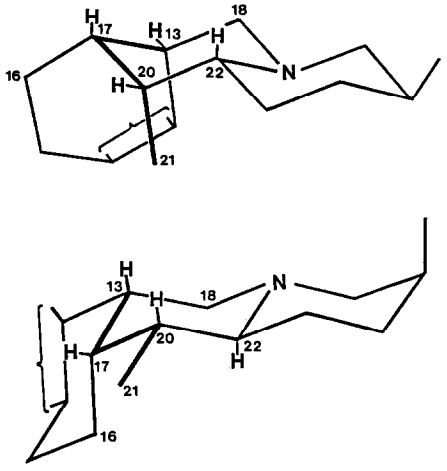


Fig. 2

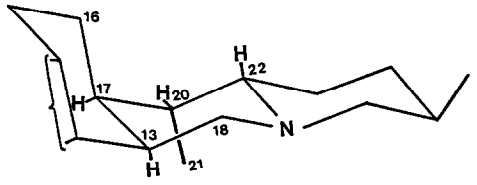


Fig. 3

In the ^{1}H-NMR spectrum of **1**, one of the two secondary methyls (21-H) was shifted downfield at δ 0.98 compared with that of **3** (δ 0.83) because of the deshielding effect on 21-H with the α-axial lone pair of the nitrogen atom. The another methyl signal (27-H) was shifted upfield compared with those of other (25S)-5α-cevanine alkaloids because of the equatorial orientation with shielding effect from the α-axial lone pair of the nitrogen atom. In the ^{13}C-NMR spectrum of **1** (Table I), the chemical shifts of C-18, C-22, which are carbons attached to the nitrogen atom, and C-16 were exhibited to be downfield at δ 65.7, 66.9 and 24.8 compared with those of **3** at δ 59.3, 62.4 and 17.1, respectively. This fact supports the absence of γ-gauche interaction between these carbons in **1**. The signal for C-21 shifted higher field at δ 11.4 ppm compared with **3** at δ 15.6 ppm because of the γ-gauche interaction of this carbon with C-13 (fig.2).[4)] However in the molecular model study, the mirror image correlation was established for E and F ring moiety between **1** and (20S,22S,25R) D/E

cis cevanine derivative (Fig.3). Therefore, we could not determine the absolute configuration of **1** on the basis of NMR study, but on the x-ray analysis instead.

Chuanbeinone (**1**) is the first alkaloid, with an unusual (22R)-trans quinolizidine moiety from Fritillaria sources. This compound has an interest in its biological activity[5], because of this unique structure. The main biological activities of chuanbeinone are as follows: coronary-dilator MIC 2.5μg/ml in guinea pig heart in vitro (reference; isoproterenol 0.1 μg/ml), cardiotropic MIC 10μg/ml in guinea pig heart in vitro (isoproterenol 0.01 μg/ml)and anti-serotonin MIC 10μg/ml in guinea pig ileum in vitro (promethazine 2 μg/ml).

References and Note

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