

FALCONERICINE AND FALCONERIDINE: TWO NEW ALKALOIDS FROM *ACONITUM FALCONERI* STAPF.

Haridutt K. Desai and S. William Pelletier*

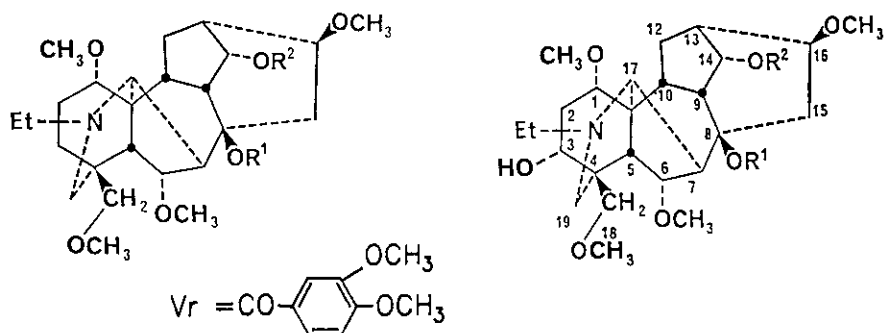
Institute for Natural Products Research and the School of Chemical Sciences,
The University of Georgia, Athens, Georgia 30602, USA

Abstract- Two new C_{19} -diterpenoid alkaloids, falconericine (1) and falconeridine (2) have been isolated from the roots of *Aconitum falconeri* Stapf. and their structures deduced by spectroscopic methods and chemical correlation with alkaloids of established structures. A third alkaloid, falconeridinine (3) is likely an artefact of the isolation conditions. It has been synthesized by refluxing a solution of falconerine-8-acetate in ethanol.

In previous studies we have reported the isolation and structures of seven alkaloids from the roots of *A. falconeri* Stapf.^{1,2,3} In continuation of our efforts to isolate the alkaloid bishatisine⁴ from the roots of the Indian crude drug *Mitha telia*^{5,6}, we have isolated two new alkaloids designated as falconericine (1) and falconeridine (2). The crude base extracted by the procedure described by Singh *et al.*⁴ was dissolved in dilute sulfuric acid and precipitated as Mayer's complex.³ The alkaloids were liberated by passing the methanolic solution of the Mayer's complex through Amberlite-IRA-400 (OH form) and were separated by vacuum liquid chromatography (vlc)⁷ on alumina by elution with chloroform and its gradient with methanol. The chloroform fraction was further fractionated on an alumina rotor of a "Chromatotron".⁸ The separating bands were visualized under a uv lamp (λ 254 nm).

Falconericine (1) was isolated as a white amorphous solid, $[\alpha]_D^{24} +16.7^\circ$ ($c = 0.336$, CHCl_3). Its molecular formula $\text{C}_{36}\text{H}_{51}\text{NO}_{10}$ was derived from its mass spectral data, EIMS m/z 657 (M^+) and carbon-13 nmr data (Table 1). The presence of fifty-one protons in the molecule was apparent from its DEPT spectra which showed 8 singlets, 13 doublets, 7 triplets and 8 quartets. Its ir spectrum (nujol) indicated the absence of -OH group in the molecule and showed absorptions at ν_{max} 1711 (ester carbonyl), 1598 (aromatic), 1512, 1292, 1270, 1218, 1175, 1090, 1020 and 763 (ortho disubstituted benzene) cm^{-1} . The ^1H nmr (CDCl_3) spectrum exhibited the following signals at δ 1.03 (3H, t, $J = 6.7$ Hz, NCH_2CH_3), 1.33 (3H, s, OCOCH_3), 3.10, 3.30 (each 3H, s, 2x OCH_3), 3.20 (6H, s, 2x OCH_3), 3.83 (6H, s, 2x aromatic OCH_3), 4.93 (1H, t, $J =$

4.5 Hz, C(14)- β -H), 6.23-7.56 (aromatic protons). The ^{13}C nmr spectrum showed 34 lines for the 36 carbon atoms of the molecule. The pattern of the chemical shifts obtained is similar to those reported for falconerine and falconerine-8-acetate³ and other C_{19} -diterpenoid alkaloids that contain a C(14) veratroyl ester group.^{1,2} The chemical shifts assignments for falconericine (1) (Table 1) were made by studying its DEPT spectra and comparing them with those reported for other related C_{19} -diterpenoid alkaloids.⁹



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|---|---|---|---|
| 1 | $\text{R}^1 = \text{Ac}; \text{R}^2 = \text{Vr}$ | 3 | $\text{R}^1 = \text{CH}_2\text{CH}_3; \text{R}^2 = \text{Vr}$ |
| 2 | $\text{R}^1 = \text{H}; \text{R}^2 = \text{Vr}$ | 6 | $\text{R}^1 = \text{Ac}; \text{R}^2 = \text{Vr}$ |
| 4 | $\text{R}^1 = \text{CH}_2\text{CH}_3; \text{R}^2 = \text{Vr}$ | 7 | $\text{R}^1 = \text{CH}_2\text{CH}_3; \text{R}^2 = \text{CO}-\text{C}_6\text{H}_3(\text{OCH}_3)_2$
and C(13)- β (OH) |
| 5 | $\text{R}^1 = \text{R}^2 = \text{H}$ | 8 | $\text{R}^1 = \text{CH}_2\text{CH}_3; \text{R}^2 = \text{H}$ |

The positions of the veratroyl ester and the acetyl groups at C(14) and C(8), respectively, in falconericine (1) are supported by the following facts. C_{19} -Diterpenoid alkaloids bearing a C(8)-OAc and C(14)-aromatic ester show ^{13}C carbonyl absorption at 169.7 and 166.1 ppm, respectively, and absorption for the methyl protons of the C(8)-OAc at δ 1.25-1.45 ppm.⁹ Alkaloids with the reverse arrangement, i.e. C(8)-aromatic ester and C(14)-OAc groups such as anisoezo-chasmaconitine and ezochasmaconitine, display carbonyl absorption at 164.4 and 171.1 ppm, respectively, and absorption for the methyl protons of the C(14)-OAc at δ 1.76 ppm.⁹ Since in falconericine the carbonyl carbons of the acetate and the veratroyl ester appear at 169.7 and 166.1 ppm, respectively, and the methyl protons of the acetate at δ 1.33 ppm, clearly falconericine has the arrangement shown in structure 1.

A solution of falconericine (1) in absolute ethanol was refluxed overnight on a steam bath when 8-ethoxy-14-veratroylchasanine (4) was formed in a quantitative yield. The structure of the compound 4 was supported by its EIMS m/z 643 (M^+ , $C_{36}H_{53}NO_9$), 1H nmr ($CDCl_3$) δ 0.71 (3H, t, $J = 7.5$ Hz, OCH_2CH_3), 1.08 (3H, t, $J = 7.5$ Hz, NCH_2CH_3), 3.26, 3.28, 3.30, 3.35 (each 3H, s, 4x OCH_3), 3.95 (6H, s, 2x aromatic OCH_3), 4.97 (1H, t, $J = 4.3$ Hz, C(14)- β -H), 6.83-7.68 (aromatic protons) and its ^{13}C nmr spectrum (Table 1). The formation of an 8-ethoxy compound by replacement of the 8-acetyl group by boiling in ethanol is a known reaction for C_{19} -diterpenoid alkaloids bearing an 8-acetyl group.¹⁰

The structure of falconericine (1) was further confirmed by alkaline hydrolysis to chasanine (5). The hydrolysis product was identified by comparison of its tlc and mixture mp, and its ir, 1H nmr and ^{13}C nmr spectra with those of an authentic chasanine sample.

The alkaloid falconeridine (2) is an amorphous compound, $[\alpha]_D^{23} +50.8^{\circ}$ ($c = 0.191$, $CHCl_3$). Its molecular formula $C_{34}H_{49}NO_9$ was deduced from the mass spectral (EIMS m/z 615, M^+) and the carbon-13 nmr data. Ir (nujol): ν_{max} 3490 (OH), 1710 (ester) and 1600 (aromatic) cm^{-1} ; 1H nmr ($CDCl_3$) δ 1.07 (3H, t, $J = 7.0$ Hz, NCH_2CH_3), 3.21, 3.26 (each 3H, s, 2x OCH_3), 3.30 (6H, s, 2x OCH_3), 3.92 (6H, s, 2x aromatic OCH_3), 5.15 (1H, t, $J = 4.5$ Hz, C(14)- β -H) and 6.82-7.59 (aromatic protons). Its ^{13}C nmr spectrum showed 30 lines for the 34 carbon atoms of the molecule (Table 1) with seven quaternary carbons at 166.1, 153.1, 148.8, 123.1, 73.9, 50.4 and 39.3 ppm. The upfield chemical shifts at 39.3 and 50.4 are assigned to C(4) and C(11), respectively, and those appearing downfield at 123.1, 148.4, 153.1 and 166.1 ppm are due to the veratroyl ester carbons. The only oxygenated singlet at 73.9 ppm is assigned to C(8) which must bear a hydroxyl group.⁹ The pattern of the spectrum is similar to that reported for the aconitine-type C_{19} -diterpenoid alkaloids bearing a veratroyl group on C(14). The chemical shift assignments (Table 1) for falconeridine (2) were made by comparison with those reported for related alkaloids.^{1,2,3} Alkaline hydrolysis of falconeridine (2) furnished chasanine (5) (tlc, mixture mp, ir and 1H nmr spectra).

Falconeridinine (3) is a white, amorphous compound, and shows $[\alpha]_D^{24} +18.3^{\circ}$ ($c = 0.29$, $CHCl_3$). Its molecular formula, $C_{36}H_{53}NO_{10}$, was derived from its mass spectral (m/z 659, M^+) and its 1H nmr and ^{13}C nmr spectral data. Ir (nujol): ν_{max} 3460 (OH), 1710 (ester-CO), 1598 (aromatic), 1085 (ester) and 762 (ortho-disubstituted benzene) cm^{-1} . The 1H nmr spectrum exhibited the following signals: δ 0.71 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.05 (3H, t, $J = 7.0$ Hz, NCH_2CH_3), 3.23, 3.27, 3.29, 3.34 (each 3H, s, aliphatic OCH_3), 3.91 (6H, s, 2x aromatic OCH_3), 4.96 (1H, t, $J = 4.5$ Hz, C(14)- β -H), 6.81-7.74 (veratroyl protons). The 1H nmr and ^{13}C nmr (DEPT)

spectra suggested that falconeridinine is a C₁₉-diterpenoid alkaloid and the assignments of the carbon atoms (Table 1) agree with structure 3. A signal at 123.7 ppm, which was more intense than other signals in the vicinity, was assigned to two carbons of the veratroyl group. This signal resolved into two signals at 124.4 and 124.0 ppm when the spectrum was recorded in C₆D₆ (Table 1). The assigned structure (3) was confirmed by synthesis of falconeridinine by refluxing a solution of falconerine-8-acetate (6) in ethanol for 24 h. Since falconerine-8-acetate is present in this plant³ and the extraction was carried out using hot ethanol, falconeridinine (3) is likely an artifact resulting from replacement of the 8-acetate with an ethoxyl group.

The chemical shift assignment for the methylene carbon of the C(8) -OCH₂CH₃ group in falconeridinine (3) was difficult since the carbon-13 signals (DEPT series) for C(19), C(8)-OCH₂CH₃ and NCH₂CH₃ appear as only two lines instead of three triplets. Also there was no triplet around 55-58 ppm as reported for the seven C₁₉-diterpenoid alkaloids which bear a C(8)-OEt group (viz. columbidine and 14-acetylcolumbidine¹¹, aljesaconitine B¹², polyschistine A¹³, acoforine, acoforestine and acoforestinine¹⁰). The methylene carbons of C(19) and the NCH₂CH₃ group appear around 46-50 ppm when a -OH group is present on C(3) of the C₁₉-diterpenoid alkaloids.⁹ In alkaloids bearing an aromatic substitution on C(14) a shielding effect is observed on the substituent groups on C(8) in the ¹H nmr and the ¹³C nmr spectra of these compounds. A DEPT spectra for the alkaloid acoforestinine (7)¹⁰ did not show any triplet at 55.8 ppm as reported.¹⁰ The correct chemical shifts for compound 7 are given in Table 1.

Alkaline hydrolysis of falconeridinine (3) gave 8-O-ethylezochasmanine (8), a new compound whose structure is supported by its mass spectrum (m/z 495, M⁺ for C₂₇H₄₅NO₇), ¹H nmr (CDCl₃) δ1.05 (3H, t, J = 6.5 Hz, NCH₂CH₃), 1.12 (3H, t, J = 6.5 Hz, OCH₂CH₃), 3.20, 3.29, 3.31, 3.34 (each 3H, s, 4x OCH₃), 4.10 (1H, t, J = 4.5 Hz, C(14)-β-H). Its ¹³C nmr chemical shifts (Table 1) are in agreement with structure 8. The methylene carbon of the 8-O-ethyl group appears as a triplet at its expected position (δ56.4 ppm), indicating that the shielding effect due to the veratroyl group on C(14) has disappeared. The methyl of the 8-O-ethyl group in 8 appears at δ1.12 ppm in contrast to the value of δ0.71 ppm for the parent compound (3), which reflects an upfield shift due to the shielding effect of the C(14) veratroyl group. This experiment demonstrates that in falconeridinine (3) the methylene, as well as the methyl of the 8-O-ethyl group, experiences the shielding effect of the C(14) veratroyl group.

Table 1. ^{13}C Nmr Chemical Shifts and Assignments for Falconericine (1), Falconeridine (2), Falconeridinine (3), Acoforestinine (7), 8-O-Ethylezochasmanine (8) and 8-O-Ethyl-14-verotryochasmanine (4).

Carbon	1	2	3	3 ^d	7*	4	8
1	85.0 d	85.5	83.3 d	83.9 ^a	83.9 d	85.7 d	83.5 d
2	26.4 t	26.4	33.2 t	34.2	33.4 t	26.4 t	33.5 t
3	34.8 t	35.0	72.0 d	71.3	71.5 d	35.0 t ^a	71.6 d
4	39.0 s	39.3	43.1 s	43.6 s	43.5 s	39.1 s	43.2 s
5	49.1 d ^a	47.0	45.0 d ^a	45.2	46.0 d	49.3 d	47.6 d
6	83.4 d	81.9	83.6d ^b	84.1 ^a	82.7 d ^a	83.4 d	82.7 d
7	45.0 d	53.9	45.2 d ^a	45.2 ^b	46.0 d	45.2 d	46.3 d
8	85.8 s	73.9 s	78.3 s	78.6 s	78.5 s	78.0 s	78.9 s
9	49.3 d ^a	49.9	48.7 d	49.1	48.8 d	45.2 d	48.7 d
10	43.9 d	49.1	45.6 d	45.6 ^b	41.6 d	45.2 d	45.3 d
11	50.3 s	50.5 s	50.9 s	50.9 s	50.9 s	50.9 s	50.6 s
12	28.8 t	29.2	28.7 t	28.9	35.8 t	29.5 t	29.2 t
13	39.2 d	37.2	38.8 d	39.2	75.4 s	38.8 d	39.9 d
14	75.3 d	76.7	76.0 d	76.1	79.3 d	76.0 d	75.3 d
15	37.9 t	41.5	36.4 t	36.9	37.6 t	36.3 t ^a	35.9 t
16	82.8 d	82.9	82.8 d ^b	83.0	83.2 d ^a	83.4 d	82.7 d
17	61.5 d	61.8	60.7 d	60.9	61.0 d	61.1 d	61.2 d
18	80.4 t	80.8	77.1 t	76.5	76.7 t	80.2 t	76.7 t
19	53.8 t	53.9	48.4 t ^c	48.8	48.7 t	54.0 t	48.6 t
N-CH ₂	48.9 t	45.3	47.8 t	48.1	47.6 t	48.9 t	47.8 t
CH ₃	13.4 q	13.6	13.3 q	13.5	13.4 q	13.5 q	13.3 q
1'	56.5 q	56.1	56.3 q	55.3	55.8 q	55.8 q	56.5 q
6'	57.8 q	57.6	58.5 q	58.4	58.8 q	58.7 q	58.7 q
16'	56.0 q	56.1	55.6 q	55.3	57.8 q	56.3 q	55.7 q
18'	59.0 q	59.2	59.1 q	58.7	59.1 q	59.1 q	59.1 q
C(8)-OCH ₂	-	-	48.5 t ^c	48.8	47.6 t	48.3 t	56.4 t
CH ₃	-	-	15.6 q	15.9	15.3 q	15.5 q	16.0 q
C=O	169.6 s	-	-	-	-	-	-
CH ₃	21.7 q	-	-	-	-	-	-
C=O	165.9 s	166.1 s	166.1 s	166.0 s	166.2 s	166.3 s	-
1	123.1 s	123.1 s	123.7 s	124.4 s	123.6 s	123.8 s	-
2	110.4 d	110.5	110.2 d	110.9	131.8 d	110.3 d	-
3	148.7 s	148.8 s	148.5 s	149.6 s	113.6 d	148.5 s	-
4	152.9 s	153.1 s	152.8 s	153.6 s	163.4 s	152.9 s	-
5	112.2 d	112.4	112.4 d	113.4	55.4 q	112.5 d	-
6	123.6 d	123.6	123.7 d	124.0	-	123.6 d	-
	55.9, 55.9 q	56.1, 56.1	55.9, 55.9 q	56.1, 55.9	-	55.9, 55.9 q	-

 In ppm downfield from TMS. Spectra were taken in CDCl₃.

a, b, c These assignments may be interchanged in any vertical column.

* Revised assignments for acoforestinine (7).

 d Spectrum recorded in C₆D₆.

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REFERENCES

1. S. W. Pelletier, N. V. Mody, and H. S. Puri, *Chem. Comm.*, 1977, 12.
2. S. W. Pelletier, N. V. Mody, and H. S. Puri, *Phytochemistry*, 1977, 16, 623.
3. H. K. Desai, B. S. Joshi, and S. W. Pelletier, *Heterocycles*, 1986, 24, 1061.
4. N. Singh, G. S. Bajwa, and M. G. Singh, *Indian J. Chem.*, 1966, 4, 39.
5. Roots of the drug *Mitha telia* were collected from Ms. Santosh Ayurvedic Drug Supply Co., Bombay, India. This drug has been identified as *Aconitum falconeri* Stapf.⁶
6. R. N. Chopra, S. L. Nayar, and I. C. Chopra, *Glossary of Indian Medicinal Plants*, CSIR, New Delhi, 1956, p. 4.
7. S. W. Pelletier, H. P. Chokshi, and H. K. Desai, *J. Nat. Prod.*, 1986, 49, 892.
8. H. K. Desai, B. S. Joshi, A. M. Panu, and S. W. Pelletier, *J. Chromatogr.*, 1985, 322, 223.
9. S. W. Pelletier, N. V. Mody, B. S. Joshi, and L. C. Schram, "¹³C and Proton Nmr Shifts Assignments and Physical Constants of C₁₉-Diterpenoid Alkaloids", in *Alkaloids: Chemical and Biological Perspectives*, Vol. 2, S. W. Pelletier, editor, John Wiley and Sons, New York, (1984), 205-462.
10. S. W. Pelletier, B. S. Joshi, J. A. Glinski, H. P. Chokshi, S. Y. Chen, K. Bhandary, and K. Go, *Heterocycles*, 1987, 25, 365; S. Sakai, I. Yamamoto, K. Hotoda, K. Yamaguchi, N. Aimi, E. Yamanaka, J. Haginiwa, and T. Okamoto, *Yakugaku Zasshi*, 104, 222 (1984).
11. S. W. Pelletier, S. K. Srivastava, B. S. Joshi, and J. D. Olsen, *Heterocycles*, 1985, 23, 331.
12. H. Bando, K. Wada, M. Watanabe, T. Mori, and T. Amiya, *Chem. Pharm. Bull.* Japan, 1985, 33, 4717.
13. H. C. Wang, A. Lao, Y. Fujimoto, and T. Tatsuno, *Heterocycles*, 1985, 23, 803.

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