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

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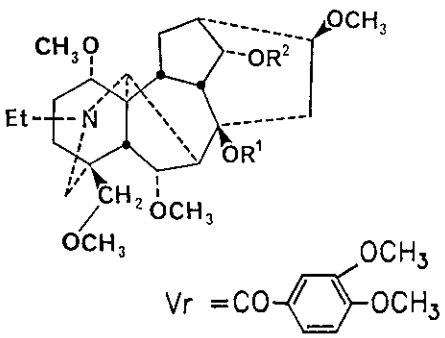
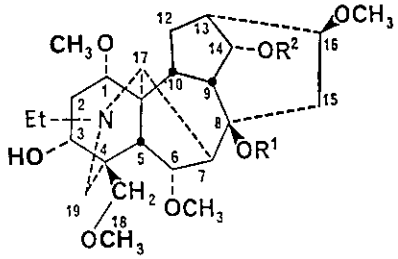
Abstract- Two new C_{19}-diterpenoid alkaloids, falconericine (1) and falconeridine (2) have been isolated from the roots of Aconitum falconeri Stapf. and their structures deduced by spectroscopic methods and chemical correlation with alkaloids of established structures. A third alkaloid, falconeridinine (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 bishatisine[4] 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° (c = 0.336, $CHCl_3$). Its molecular formula $C_{36}H_{51}NO_{10}$ 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 δ1.03 (3H, t, J = 6.7 Hz, $NCH_2\underline{CH_3}$), 1.33 (3H, s, $OCO\underline{CH_3}$), 3.10, 3.30 (each 3H, s, 2x $O\underline{CH_3}$), 3.20 (6H, s, 2x $O\underline{CH_3}$), 3.83 (6H, s, 2x aromatic $O\underline{CH_3}$), 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-acetate[3] 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]





1 R^1 = Ac; R^2 = Vr

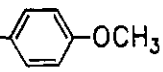
2 R^1 = H; R^2 = Vr

3 R^1 = CH_2CH_3; R^2 = Vr

4 R^1 = CH_2CH_3; R^2 = Vr

5 R^1 = R^2 = H

6 R^1 = Ac; R^2 = Vr

7 R^1 = CH_2CH_3; R^2 = CO-  -OCH_3 and C(13)-β(OH)

8 R^1 = CH_2CH_3; R^2 = 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 δ1.25-1.45 ppm.[9] Alkaloids with the reverse arrangement, i.e. C(8)-aromatic ester and C(14)-OAc groups such as anisoezochasmaconitine 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 δ1.76 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 δ1.33 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-veratroylchasmanine (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 ($CDCl_3$) δ0.71 (3H, t, J = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.08 (3H, t, J = 7.5 Hz, $NCH_2C\underline{H}_3$), 3.26, 3.28, 3.30, 3.35 (each 3H, s, 4x $OC\underline{H}_3$), 3.95 (6H, s, 2x aromatic $OC\underline{H}_3$), 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 replacment 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 chasmanine (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 chasmanine sample.

The alkaloid falconeridine (2) is an amorphous compound, $[\alpha]_D^{23}$ +50.8° (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 ($CDCl_3$) δ1.07 (3H, t, J = 7.0 Hz, $NCH_2C\underline{H}_3$), 3.21, 3.26 (each 3H, s, 2x $OC\underline{H}_3$), 3.30 (6H, s, 2x $OC\underline{H}_3$), 3.92 (6H, s, 2x aromatic $OC\underline{H}_3$), 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 chasmanine (5) (tlc, mixture mp, ir and ^1H nmr spectra).

Falconeridinine (3) is a white, amorphous compound, and shows $[\alpha]_D^{24}$ +18.3° (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: δ0.71 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.05 (3H, t, J = 7.0 Hz, $NCH_2C\underline{H}_3$), 3.23, 3.27, 3.29, 3.34 (each 3H, s, aliphatic $OC\underline{H}_3$), 3.91 (6H, s, 2x aromatic $OC\underline{H}_3$), 4.96 (1H, t, J = 4.5 Hz, C(14)-β-$\underline{H}$), 6.81-7.74 (veratryol protons). The ^1H nmr and ^{13}C nmr (DEPT)

spectra suggested that falconeridinine is a C_{19}-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 C_6D_6 (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 plant[3] 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) $-OCH_2CH_3$ group in falconeridinine (**3**) was difficult since the carbon-13 signals (DEPT series) for C(19), C(8)-$O\underline{C}H_2CH_3$ and $N\underline{C}H_2CH_3$ appear as only two lines instead of three triplets. Also there was no triplet around 55-58 ppm as reported for the seven C_{19}-diterpenoid alkaloids which bear a C(8)-OEt group (viz. columbidine and 14-acetylcolumbidine[11], aljesaconitine B[12], polyschistine A[13], acoforine, acoforestine and acoforestinine[10]). The methylene carbons of C(19) and the $N\underline{C}H_2CH_3$ group appear around 46-50 ppm when a -OH group is present on C(3) of the C_{19}-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 ^{13}C 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 $C_{27}H_{45}NO_7$), ^1H nmr ($CDCl_3$) δ1.05 (3H, t, J = 6.5 Hz, $NCH_2C\underline{H}_3$), 1.12 (3H, t, J = 6.5 Hz, $OCH_2C\underline{H}_3$), 3.20, 3.29, 3.31, 3.34 (each 3H, s, 4x $OC\underline{H}_3$), 4.10 (1H, t, J = 4.5 Hz, C(14)-β-H). Its ^{13}C 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-verotroylchasmanine (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	-
OMe	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 $CDCl_3$.
a,b,c These assignments may be interchanged in any vertical column.
* Revised assignments for acoforestinine (7).
d Spectrum recorded in C_6D_6.

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