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FUMSCHLEICHERINE, AN ALKALOID OF *FUMARIA SCHLEICHERI*

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Key Word Index—*Fumaria schleicheri*; Fumariaceae; structural elucidation; alkaloids; fumschleicherine; hydrated fumaramine; ^{1}H NMR; ^{13}C NMR.

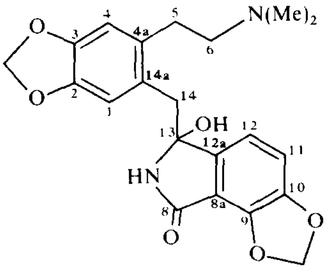
Abstract—The structure of fumschleicherine has been elucidated by spectroscopic methods and confirmed by its conversion to fumaramine.

Fumschleicherine (**1**) has been recently isolated from *Fumaria schleicheri* Soy-Will by Kiryakov and co-workers (unpublished results). The IR of **1** in nujol shows a peak at 3180 cm^{-1} attributed to NH absorption and at 1705 cm^{-1} attributed to carbonyl, present, as later revealed, in a 5-membered lactam. The MS of **1** provided the first clue to its overall structure. There is an intense peak at *m/e* 380 ($C_{21}H_{20}N_2O_5$) in the high mass region of the spectrum but the most intense peak appears at *m/e* 58. The latter peak suggested the presence of the fragment ion $CH_2{=}\overset{+}{N}(Me)_2$ and therefore of the structural unit $-CH_2-N(Me)_2$ in **1**. The peaks at *m/e* 380 and 58 are also intense peaks in the spectrum of fumaramine (**2**) and indeed the MS of the two compounds are very similar. Other properties of the two compounds are, however, quite different and this led to a closer examination of the MS of **1**. We found that there is a weak but reproducible peak at *m/e* 398 in **1** that is absent in the spectrum of **2**. This suggested that, in part, **1** was undergoing loss of H_2O either thermally or by electron impact prior to major fragmentation and that the probable formula of **1** was $C_{21}H_{22}N_2O_6$. A combustion analysis was compatible with this conclusion.

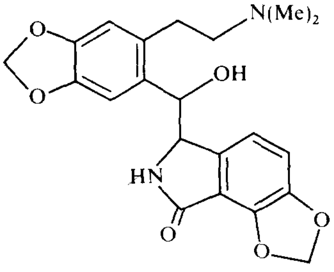
Treatment of **1** with trifluoroacetic acid in chloroform solution gave a product that was identical with fumaramine [1, 2] prepared as described in Experimental. It was now evident that **1** must be represented by either structure **1(a)** or **1(b)**, leaving aside stereochemical considerations. A choice between the two structures was made from an examination of the ^{1}H and ^{13}C NMR spectra and a comparison of these with those of fumaramine.

The ^{1}H NMR spectrum was recorded in DMSO-d_6 at 220 MHz. In the aliphatic region of the ^{1}H spectrum of **1** there is a sharp singlet consisting of six protons at 2.08 ppm which was assigned to the two N—Me groups. At 2.41 and 2.13 ppm there are two broad triplets, $J = 8$ Hz. These two signals approximate an A_2X_2 system and were shown to be coupled by a double irradiation experiment. These data confirm the presence of the structural fragment, $-CH_2-CH_2-N(Me)_2$, with the triplet at 2.41 ppm corresponding to the methylene group bonded to the nitrogen; the other methylene group appears to be benzylic. The lowest field aliphatic signals are in the form of an AB quartet at 2.99 and 3.14 ppm with a geminal coupling constant of 14 Hz.

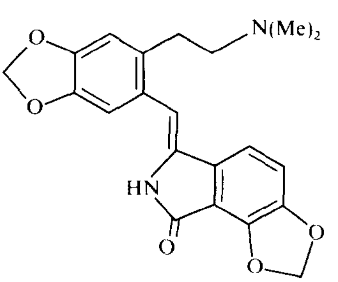
At 5.86 and 6.07 ppm there are two singlets integrating for two protons that are assigned to methylenedioxy groups. The singlet at 6.3 ppm was attributed to an OH group; it was found to undergo exchange when D_2O was added to the sample. This OH group must be present as a phenol or as a tertiary alcohol since no coupling was



1 (a)



1 (b)



2

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observed when dry DMSO-d_6 was used as solvent. Four protons resonate in the 6.0–7.1 ppm region of the spectrum. There are two singlets at 6.61 and 6.62 ppm and an AB quartet at 6.7 and 7.0 ppm ($J_{AB} = 8$ Hz). This pattern of signals in the aromatic region is compatible with structures **1(a)** or **1(b)**. The lowest field resonance at 10.14 ppm was assigned to the NH group and it too was exchangeable in D_2O. A consideration of these data, particularly the presence of the AB quartet at δ 2.99 and 3.14, leads to the conclusion that **1(a)** is the most likely structure of the alkaloid. The ^{1}H NMR data are summarized in Table 1.

Confirmation of structure **1(a)** came from an examination of the ^{13}C NMR. When the spectrum of **1** was recorded in DMSO-d_6 three peaks were observed in the aliphatic region corresponding to a benzylic methylene (30.3 ppm), the $N(Me)_2$ group (45.0 ppm) and the methylene adjacent to nitrogen (60.6 ppm). These assignments were confirmed by the off-resonance spectrum and correlated with chemical shifts observed in other *N*,*N*-dimethylphenylethylamines [3]. A quaternary carbon resonance was observed at 87.6 ppm. Signals at 100.5 and 102.4 ppm are characteristic of the methylenedioxy group. In the low-field region of the spectrum there are signals attributed to four protonated aromatic carbon atoms between 109 and 116 ppm. The remaining signals, which are attributed to substituted aromatic carbon atoms, can be divided into two groups. Those resonances, occurring at 113.8, 126.9 and 133.1 ppm, may be assigned to carbon-substituted aromatic carbon atoms while at least four of the five signals between 142 and 149 ppm can be definitely assigned to carbon atoms with oxygen substituents. The fifth carbon atom is most likely α to an electron-withdrawing substituent. The lowest field signal at 164.9 ppm may be assigned to the amide carbonyl.

One aliphatic carbon atom was not accounted for in the DMSO-d_6 spectrum and must be hidden under the solvent signal. By recording the ^{13}C NMR in a 3:2 mixture of DMSO and $CDCl_3$, it was possible to observe this signal at 37.0 ppm and it has been assigned to the methylene group at C-14. A comparison of the ^{13}C spectra of **1** and **2** is given in Table 2. The major points of difference appear as expected for the resonances at C-13 and C-14, at the sites of structural change, and at C-12a and C-14a, the sites adjacent to the structural change.

Fumschleicherine is another example of a growing number of alkaloids that are structurally related to the phthalideisoquinolines; these alkaloids are characterized by the presence of a dimethylaminoethyl group apparently derived from ring B of the phthalideisoquinoline system and a transformed phthalide function [4].

Table 1. 220 MHz ^{1}H NMR chemical shifts of fumschleicherine in DMSO-d_6

Proton	δ (ppm from TMS)
$N(Me)_2$	2.08
H-5	2.13 (*t*, $J = 8.0$ Hz)
H-6	2.41 (*t*, $J = 8.0$ Hz)
H-14	2.99, 3.14 ($J_{AB} = 14.0$ Hz)
OCH_2O	5.86, 6.07
C-13 OH	6.30*
H-1, H-4	6.61, 6.62
H-11, H-12	6.70, 7.00 ($J_{AB} = 8.0$ Hz)
NH	10.14*

*Both signals are removed when D_2O is added to the sample.

Table 2. ^{13}C chemical shifts of fumschleicherine (**1**) and fumaramine (**2**)

Carbon	**1***	**2†**
1	109.2	108.6
2	144.7	146.8
3	145.7	147.5
4	110.8	110.3
4a	126.9‡	132.6§
5	30.3	31.5
6	60.6	60.3
8	164.9	166.0
8a	113.8	111.4
9	142.6‡	143.6
10	148.7	149.5
11	111.0	112.1
12	115.8	113.3
12a	142.2‡	133.7§
13	87.6	131.9§
14	37.0‖	102.6
14a	133.1‡	126.7§
2,3 OCH_2O	100.5	101.4
9,10 OCH_2O	102.4	103.1
$N(Me)_2$	45.0	45.2

*Solvent: DMSO-d_6.
†Solvent: $CDCl_3$.
‡Assignments may be reversed.
§Tentative assignment only.
‖Solvent: 60% DMSO and 40% $CDCl_3$.

EXPERIMENTAL

General. The ^{13}C NMR spectra were recorded on a Fourier transform spectrometer at 22.62 MHz. The probe temp. was +35. Sample concn ranged from 0.15 to 0.20 M in either DMSO-d_6 (using TMS as ext. ref.) or $CDCl_3$ (using TMS as int. ref.). Spectra were recorded over a 6 KHz sweep width using 16 K data points (1.359 sec acquisition time). A pulse width of 3.4 μs (15.6° pulse angle) was used. The 220 MHz ^{1}H NMR spectra were obtained at the University of Toronto, Toronto, Ontario. DMSO-d_6 and TMS were used as solvent and int. ref., respectively. Other ^{1}H NMR spectra were recorded at 90 MHz in $CDCl_3$ (using TMS as int. ref.) MS were determined at an ionizing voltage of 80 eV and a source temp. of 200–250°. The high resolution spectra were recorded on plates and accurate mass measurements were made by using PFK as marker [5]. The composition of all ions discussed in this paper have been checked by high resolution mass spectrometry and agree with calculated values within ±0.005 amu.

*Isolation of fumschleicherine** (**1**). The alkaloid was isolated from *F. schleicheri* collected in Bulgaria. The crude alkaloid mixture obtained from the plant by MeOH extraction and subsequent conventional work-up was dissolved in a mixture of

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*Full details of the isolation procedure and analysis of the alkaloid content of *F. schleicheri* will appear in a subsequent publication by H. G. Kiryakov, Z. H. Mardirossian and P. Panov.

hot $CHCl_3$ and EtOH. Compound **1** separated as crystals after the soln was cooled and allowed to evaporate slowly. Recrystallization from $CHCl_3$–EtOH gave a sample, mp 224–226°. IR ν_{max}^{nujol} cm^{-1}: 1705 (lactam), and 3180 (NH). UV λ_{max}^{EtOH} 294 and 314 nm; log ε = 3.6 and 3.5, respectively. Found, C, 62.9; H, 5.7. $C_{21}H_{22}N_2O_6$ requires: C, 63.3; H, 5.6%.

Dehydration of **1**. **1** (80 mg) was added to $CHCl_3$ (5 ml) containing 15–20 drops of TFA. The soln was gently warmed at 100° for *ca* 5 min during which time the soln turned yellow. The solvent was then removed under red. pres. the residue made alkaline and then repeatedly extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4), filtered and evapd to give the product as a yellow solid (~50–60 mg). The spectroscopic properties of the product were identical with those of fumaramine prepared as described below.

Transformation of bicuculline methiodide into fumaramine. The following procedure was adopted from methods described in refs. [6, 7]. To a stirred suspension of bicuculline methiodide (0.23 g, 0.45 M) in 8 ml of 95% EtOH was added 0.75 ml of 28% NH_4OH. This mixture was heated until gently refluxing at which point the bicuculline methiodide dissolved. An additional 2.5 ml of 28% NH_4OH was added in portions and the reaction mixture refluxed for 1 hr. The mixture was then allowed to stand at room temp. overnight. Solvent was removed under red. pres. and the residue refluxed for 2 min in 2–3 ml of H_2O–conc HCl (1:4). The mixture was made alkaline and repeatedly extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4), filtered and evapd to give a bright yellow solid (160–180 mg) with spectroscopic properties identical with those of fumaramine.

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