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BICUCULLINIDINE, AN ALKALOID OF *FUMARIA SCHRAMMII*

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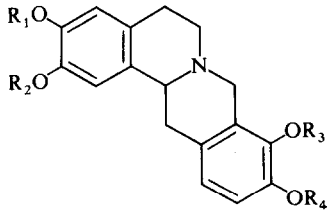
Key Word Index—*Fumaria schrammii*; Fumariaceae; alkaloid; structural elucidation; bicucullinidine; NMR.

Abstract—The structure of bicucullinidine has been established as 5-[[2-[2-(dimethylamino)ethyl]-4,5-dimethoxyphenyl]oxoacetyl]-1,3-benzodioxole-4-carboxylic acid by comparison of its spectroscopic properties with those of alkaloids of similar structure.

INTRODUCTION

Kiryakov *et al.* have recently examined *Fumaria schrammii* for its alkaloid content [1]. They isolated nine alkaloids of established structure, (−)-stylopine (**1**), (±)-sinactine (**2**), (−)-adlumine (**3**), protopine (**4**), fumschleicherine (**5**), adlumidiceine (**6**), adlumiceine (**7**), bicucullinine (**8**), (+)-fumariline (**9**) and a new alkaloid, designated bicucullinidine (**10**). Here we report studies on the alkaloid **10** that have led to the elucidation of its structure by spectroscopic methods.



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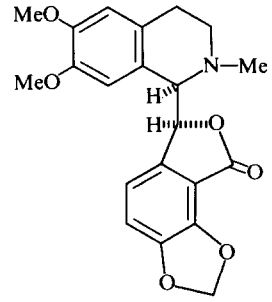

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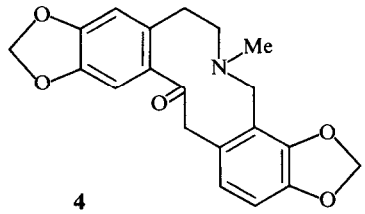

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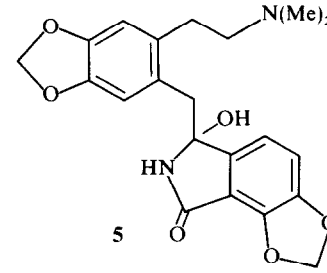

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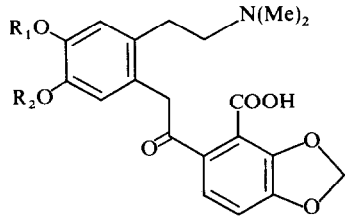
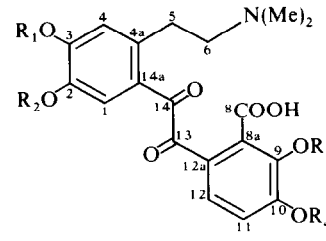


6 $R_1 + R_2 = -CH_2-$
7 $R_1 = R_2 = Me$



8 $R_1 + R_2 = R_3 + R_4 = -CH_2-$
10 $R_1 = R_2 = Me$; $R_3 + R_4 = -CH_2-$
11 $R_1 + R_2 = -CH_2-$; $R_3 = R_4 = Me$

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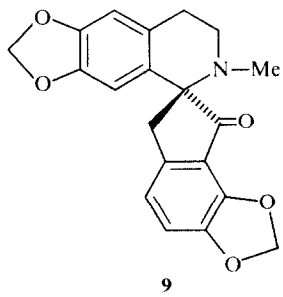

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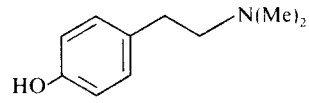

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RESULTS AND DISCUSSION

The mass spectrum of bicucullinidine provided the first clue to its overall structure. The most intense peak appears at *m/z* 58, suggesting the presence of the fragment ion, $CH_2{=}N^+(Me)_2$, and therefore of the structural unit, $CH_2N(Me)_2$, in **10**. An intense peak at *m/z* 411 ($C_{22}H_{21}NO_7$) in the high mass region is not the M^+ but a fragment, produced by the loss of water (either thermally or by electron impact) from the very weak M^+ at *m/z* 429. This is a fragmentation also observed in bicucullinine (**8**) [2], adlumiceine (**7**) and adlumidiceine (**6**) [3,4], and therefore it was reasonable to assume that **10** should have a similar structure to **6**, **7** and **8**. The elemental composition of **10** ($C_{22}H_{23}NO_8$) suggested that bicucullinidine was a homologue of bicucullinine (**8**). The increase of 16 mu observed in bicucullinidine relative to **8** led to the conclusion that bicucullinidine could be either oxo-*N*-methylhydrasteine (**11**) or have structure **10**. The ions at *m/z* 236 ($C_{13}H_{18}NO_3$) and *m/z* 192 in the spectrum of bicucullinidine originate by rupture of the bond between C-13 and C-14 and provide the clue to the substitution pattern, suggesting that structure **10** would be more likely.

The ^{1}H NMR spectrum was recorded in DMSO-d_6 at 80 MHz. The aliphatic region shows four distinct signals: a sharp singlet at 2.66 ppm (6 H) generated by the two N–Me groups, a broad multiplet between 3.0 and 3.3 ppm integrating for four protons assigned to the two methylene units at C-5 and C-6, two singlets in the low field aliphatic region consisting of three protons each at 3.78 and 3.86 ppm, assigned to the two methoxy groups. At 6.18 ppm, a singlet of two protons is attributed to the methylendioxy group. Four protons resonate in the aromatic region of the spectrum. There is an AB quartet at 7.03 and 7.16 ppm (J_{AB} = 8.1 Hz) and two singlets at 7.0 and 7.73 ppm. This pattern is characteristic of two aromatic nuclei substituted at 1,2,3,4 and 1,2,4,5, respectively.

Except for the change in substituents, the spectrum is similar to that of bicucullinine (**8**) [2] and oxo-*N*-methylhydrasteine (**11**) [5]. It is interesting that the ^{1}H NMR spectrum of **10** in CD_3CO_2D is quite different from that in DMSO-d_6 as outlined in Table 1. This difference is caused by a change in charge distribution in the molecule resulting from the change in pH of the solution. This effect is also observed with bicucullinine **8** (D. B. MacLean and J. P. Ruder, unpublished results); the spectra of **8** in CD_3CO_2D and DMSO-d_6 are also recorded in Table 1.

A consideration of all these data leads to the conclusion that **10** is the most likely structure of bicucullinidine. As a homologue of bicucullinine, it is appropriately named bicucullinidine — 5-[[2-[2-(dimethylamino)ethyl]-4,5-dimethoxyphenyl]oxoacetyl]-1,3-benzodioxole-4-carboxylic acid.

Confirmation of structure **10** came from examination of its ^{13}C NMR spectrum. When the spectrum was recorded in CD_3CO_2D four signals were observed in the aliphatic region corresponding to a benzylic methylene (28.5 ppm), the dimethylamino group (42.2 ppm), two methoxy groups (54.8 ppm) and the methylene adjacent to nitrogen (57.6 ppm). These assignments were confirmed by comparison with chemical shifts observed in other *N,N*-dimethylphenylethylamines such as **5** [6], **6** [2], **7** (D. B. MacLean and J. P. Ruder, unpublished results), **8** (D. B. MacLean and J. P. Ruder, unpublished results) and **12** [7]. The methylendioxy group resonates characteristically at 102.7 ppm. Between 109 and 134 ppm there are eight aromatic carbon atoms either protonated or carbon-substituted, while peaks between 146 and 154 ppm can be definitely assigned to aromatic carbons with oxygen substituents. The three lowest field signals at 167.7, 187.1 and 190.7 ppm can be assigned to the carbon atom of the acid function, and the two carbonyl carbon atoms, respectively.

By recording the ^{13}C NMR spectrum in other solvents, one observes again a change in chemical shifts as outlined

Table 1. ^{1}H NMR chemical shifts of bicucullinidine (**10**) and bicucullinine (**8**) in different solvents in δ (ppm from TMS)

	10		**8**	
Proton	DMSO-d_6	CD_3CO_2D	DMSO-d_6	CD_3CO_2D
$N(Me)_2$	2.66 *s*	3.03 *s*	2.69 *s*	3.03 *s*
H-5, H-6	3.0–3.3 *m*	3.43 *br*	3.0–3.3 *m*	3.39 *br*
OMe	3.78 *s*, 3.86 *s*	3.89 *s*, 4.00 *s*	—	—
OCH_2O	6.18 *s*	6.27 *s*	6.17 *s* (4 H)	6.14 *s*, 6.26 *s*
H-4	7.00 *s*	7.06 *s*	7.01 *s*	6.99 *s*
H-11, H-12	7.03, 7.16 (J_{AB} = 8.1 Hz)	7.12, 7.46 (J_{AB} = 8.1 Hz)	7.05, 7.08 poor resol.	7.11, 7.43 (J_{AB} = 7.9 Hz)
H-1	7.73 *s*	7.67 *s*	7.71 *s*	7.58 *s*

Table 2. ^{13}C NMR chemical shifts of bicucullinidine (**10**) and bicucullinine (**8**) in δ (ppm from TMS)

	10			**8**
Carbon	CD_3CO_2D	DMSO-d_6	D_2O/NaOD	CD_3CO_2D
C-5	28.5	26.6	30.7	28.7
C-6	57.6	57.3	59.7	57.5
C1, C-4, C-4a, C-8a, C-11, C-12, C-12a, C-14a	109.5	108.1	108.0	109.5
	114.4	113.9	*	111.3
	116.3	114.7	*	112.4
	123.5	122.3	122.5	125.1
	125.1	123.4	122.8	125.6[c]
	125.6	127.3	127.7	
	129.2	132.0	*	129.2
	133.5	133.2	*	135.4
C-2, C-3, C-9, C-10	146.9	145.3	145.2	146.1
	147.1	145.8	146.0	147.0
	152.1	150.8	152.7	151.5
	153.1	151.2	153.0	152.1
C-8	167.7	168.1	171.2	*
C-13, C-14	187.1	188.8	*	190.1†
	190.7	192.3	*	
N(Me)	42.2	‡	43.8	42.1
OMe	54.8	55.6	56.1	–
OCH_2O	102.7	101.9	102.8	102.0
				102.7

* Signal obscured by background.
† Presumably two carbons.
‡ Signal hidden by solvent.

in Table 2. Similar shifts are also observed in the spectrum of **8** (Table 2 and [2]). Bicucullinidine (**10**) is another example of new bases related to the phthalideisoquinolines [8]. They all contain the dimethylaminoethyl chain derived from opening of ring B of the phthalideisoquinoline system.

EXPERIMENTAL

^1H NMR spectra were recorded on a Fourier transform spectrometer at 35°. Sample concn was *ca* 0.025 M. The solvents were used as int. standards at 2.10 ppm (CD_3CO_2D) and 2.56 ppm (DMSO-d_6). Spectra were obtained in 12 scans using a pulse width of 3.5 μsec. The sweep width was 1000 Hz (4.096 sec acquisition time). ^{13}C NMR spectra were also recorded on a Fourier transform spectrometer at 20.115 MHz and 35°. Sample concns were *ca* 0.025 M using as int. references CD_3CO_2D (18.25 ppm), DMSO-d_6 (39.56 ppm) and dioxane in D_2O/NaOD (66.6 ppm). Spectra were recorded over 6024 Hz sweep width with 30 000–56 000 scans (pulse width 1.8 μsec.) MS were determined at an ionizing voltage of 70 eV and a source temp. of 250°. HRMS were recorded on the same spectrometer, connected to a data system using 5000 static resolutions. IR were recorded in a KBr pellet and UV spectra in MeOH, MeOH/HCl and MeOH/NaOH.

Isolation of bicucullinidine (**10**). The title compound was isolated from *Fumaria schrammii* Vel collected in Bulgaria as described in ref. [1]. Recrystallization from $CHCl_3$–EtOH gave a sample, mp 265–266°. IR ν_{max}^{KBr} cm^{-1}: 1037, 1202, 1250 and 1272 (phenol ether and (CO)–O); 1591, 1616, and 1670 (C=O). UV λ_{max}^{MeOH} nm (log ε): 328 (3.78), 294 (3.69); $\lambda_{max}^{MeOH/HCl}$ nm (log ε): 334 (3.85), 283 (3.69), 222 (4.11) sh; $\lambda_{max}^{MeOH/NaOH}$ nm (log ε): 326 (3.81), 288 (3.76). MS (probe) 300° 70 eV, *m/z* (rel. int.): 429 [M^+] (<0.5), 411 [$M^+ - H_2O$] (10), 236 [$C_{13}H_{18}NO_3$] (1), 234 [$C_{13}H_{16}NO_3$] (6), 192 [$C_9H_4O_5$] (6), 58 [C_3H_8N] (100).

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REFERENCES

1. Kiryakov, H. G., Mardirossian, Z. H. and Panov, P. P. (1981) *C.R. Acad. Bulg. Sci.* (in press).
2. Rodrigo, R. G. A., Manske, R. H. F., Holland, H. L. and MacLean, D. B. (1976) *Can. J. Chem.* **54**, 471.
3. Preininger, V., Šimánek, V., Gašić, O., Šantavý, F. and Dolejš, L. (1973) *Phytochemistry* **12**, 2513.
4. Preininger, V., Veselý, J., Gašić, O., Šimánek, V. and Dolejš, L. (1975) *Collect. Czech. Chem. Commun.* **40**, 699.
5. Forgacs, P., Provost, J., Tiberghien, R., Desconclois, J.-F., Buffard, G. and Pesson, M. (1973) *C.R. Acad. Sci. Ser. D* **276**, 105.
6. Kiryakov, H. G., Mardirossian, Z. H., Hughes, D. W. and MacLean, D. B. (1980) *Phytochemistry* **19**, 2507.
7. Srinivasin, P. R. and Lichter, R. L. (1976) *Org. Magn. Reson.* **8**, 198.
8. Shamma, M. and Moniot, J. L. (1978) *Isoquinoline Alkaloid Research* 1972–1977, p. 307. Plenum Press, New York.