생 약 학 회 지
Kor. J. Pharmacogn.
26(3) : 273 ~ 275 (1995)

Two Phenolic Amides from *Cocculus diversifolius*

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Abstract—Two phenolic amides were isolated from the stem of *Cocculus diversifolius* (Menispermaceae) and identified as *N-trans*-feruloyl tyramine and *N-trans*-feruloyl 3-methyldopamine by spectroscopic methods.

Keywords—*Cocculus diversifolius* · Menispermaceae · phenolic amides · *N-trans*-feruloyl tyramine · *N-trans*-feruloyl 3-methyldopamine

The genus *Cocculus* contains compounds with a wide range of medicinal properties and its extracts are used in many countries.[1,2] From extensive previous phytochemical studies, many alkaloids have been isolated, including isoquinoline, benzylisoquinoline, bisbenzylisoquinoline, *Erythrina*, proaporphine, dibenz[d, f]azonine, quaternary, and morphinandienone alkaloids.[3] This paper describes two phenolic amides isolated from the MeOH extract of *C. diversifolius* DC (Menispermaceae).

Experimental

General Experimental Procedures - Mp's were determined on a Kofler hot-stage apparatus and are uncorrected. Uv spectra were obtained in EtOH on a Beckman DU-50 spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Unity 400 spectrometer at 400 and 100.57 MHz, respectively. DEPT, ^{1}H-^{13}C HETCOR and HMBC experiments were performed on the same spectrometer, using standard Varian pulse sequences. Flash chromatography was performed using silica gel Merck G60 (230-400 mesh) and Sorbsil RP-18 (Phase Separations Ltd). Sephadex LH-20 (Sigma) was employed for gel permeation chromatography.

Plant Material - The plant material was collected in California in March 1986 ; a voucher specimen has been deposited at the Herbarium of the National Arboretum, Agricultural Research Service, USDA, Washington DC.

Extraction and Isolation - Dried pulverized *C. diversifolius* (1.5 kg) was extracted sequentially with MeCOEt and MeOH. The MeOH extract (24.2 g) was partitioned between *n*-BuOH and H_2O. The *n*-BuOH-soluble extract (7.5 g) was partitioned between *n*-hexane and 80% aqueous MeOH. H_2O was added to the aqueous MeOH fraction until a 60% aqueous MeOH mixture was achieved, and this was extracted thoroughly with CHCl3 to afford 4.2 g of $CHCl_3$-soluble extract. This extract was subjected to gel permeation chromatography on Sephadex LH-20, eluting initially with $CHCl_3$-MeOH (1:9), followed by MeOH to obtain a total of 4 fractions.

Fraction 2 (750 mg) was loaded onto a silica gel column with elution by EtOAc followed by EtOAc-MeOH (9:1). The second of 4 combined fractions (171 mg) was separated by reversed-phase C-18 column chromatography using 60% aqueous MeOH as eluent. The first fraction (56 mg) from this column was further purified on a

Table I. ^{1}H- and ^{13}C-NMR data for **1** and **2** in Me_2CO-d_6

Position	1			2		
	δH^a	δC^b		δH^a	δC^b	
Feruloyl						
1	-	166.55	s	-	166.29	s
2	6.51 (1H, d, 15.6)	119.92	d	6.49 (1H, d, 15.6)	120.07	d
3	7.45 (1H, d, 15.6)	140.45	d	7.44 (1H, d, 15.6)	140.26	d
1′	-	128.19	s	-	128.26	s
2′	7.14 (1H, d, 2.0)	111.23	d	7.14 (1H, d, 2.0)	111.19	d
3′	-	148.57	s	-	148.56	s
4′	-	149.11	s	-	149.04	s
5′	6.82 (1H, d, 8.2)	116.05	d	6.82 (1H, d, 8.2)	116.04	d
6′	7.03 (1H, dd, 8.2, 2.0)	122.53	d	7.03 (1H, dd, 8.2, 2.0)	122.48	d
MeO	3.85 (3H, s)	56.17	q	3.86 (3H, s)	56.17	q
Amine						
1	3.49 (2H, m)	41.93	t	3.49 (2H, m)	41.76	t
2	2.74 (2H, t, 7.0)	35.71	t	2.75 (2H, t, 7.2)	36.15	t
1′	-	131.04	s	-	131.78	s
2′	7.05 (1H, d, 8.4)	130.47	d	6.84 (1H, d, 2.0)	113.07	d
3′	6.75 (1H, d, 8.4)	116.05	d	-	148.18	s
4′	-	156.70	s	-	145.83	s
5′	6.75 (1H, d, 8.4)	116.05	d	6.73 (1H, d, 8.0)	115.67	d
6′	7.05 (1H, d, 8.4)	130.47	d	6.66 (1H, dd, 8.0, 2.0)	121.96	d
MeO	-	-		3.81 (3H, s)	56.16	q

a: Multiplicity and apparent coupling constant(s) (*J*) in Hz in parentheses.

b: Assignments were confirmed by HETCOR and HMBC experiments, and carbon types were assigned by a DEPT experiment.

silica gel column with elution by hexane-EtOAc (1:4) to yield *N-trans*-feruloyl tyramine (**1**, 25 mg) and *N-trans*-feruloyl 3-methyldopamine (**2**, 7 mg).

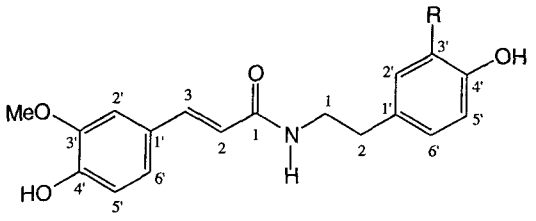
***N-trans*-feruloyl tyramine (1)** - Colorless powder; mp 140-142° [Lit. 4) mp 142-145.5°] ; UV, λ_{max}^{EtOH} nm 219, 296, 319 ; EIMS *m/z* (rel. int., %) 313 $[M]^+$ (0.7), 192 (25), 177 (27), 120 (22), 107 (100), 77 (47) ; Positive FABMS *m/z* (rel. int., %) 314 $[M+H]^+$ (100); ^{1}H- and ^{13}C-NMR: Table I.

***N-trans*-feruloyl 3-methyldopamine (2)** - Colorless oil; UV, λ_{max}^{EtOH} nm 219, 231, 287, 319; EIMS *m/z* (rel. int., %) 343 $[M]^+$ (1.6), 192 (13), 177 (38), 150 (100), 137 (18); ^{1}H- and ^{13}C-NMR: Table I.

Results and Discussion

The $CHCl_3$-soluble part of the MeOH extract from *C. diversifolius* was subjected to column chromatography on Sephadex LH-20, silica gel and reversed-phase C-18 to afford two compounds, which gave positive reactions when sprayed with the ferricyanide-ferric chloride and iodoplatinate reagents.

In the ^{1}H-NMR spectrum of compound **1**, signals of 2 methylene groups, 1 methoxyl group, a trans-olefin group, and 7 aromatic protons were observed (Table I). The ^{13}C-NMR spectrum with the help of a DEPT experiment showed the presence of 6 singlets, 9 doublets,



1 : R = H
2 : R = OMe

2 triplets, and 1 quartet (Table I). The mass spectrum of **1** revealed a molecular ion peak at *m/z* 313, together with fragment ion peaks at *m/z* 192, 177, and 107. These data suggested that compound **1** consist of a feruloyl moiety and a tyramine segment. Detailed analysis with the aid of HETCOR and HMBC techniques confirmed its identity as *N-trans*-feruloyl tyramine, and resulted in unambiguous assignments of ^{1}H- and ^{13}C-NMR spectra. Comparison of ^{13}C-NMR data of **1** with those of *N-trans*-feruloyl tyramine[5], isolated from *Actinodaphne longifolia*, gave good agreement except for the assignments of C-3′ and C-4′ of the feruloyl moiety. The methoxy protons at 3.85 ppm showed a cross peak with the carbon peak at 56.17 ppm in the HETCOR spectrum, and a 3-bond correlation peak at 148.57 ppm in the HMBC spectrum. The proton at 6.82 ppm (feruloyl H-5′) showed two 3-bond correlation peaks at 128.19 and 148.57 ppm in the HMBC spectrum. The protons at 7.14 (feruloyl H-2′) and 7.03 ppm (feruloyl H-6′) exhibited 3-bond correlation peaks with resonances at 122.53, 140.45, 149.11 ppm and 111.23, 140.45, 149.11 ppm, respectively. Based on these results, the chemical shifts of C-3′ and C-4′ of the feruloyl moiety of compound **1** are unambiguously established as 148.57 and 149.11 ppm, respectively. Therefore, the assignments of these carbons (C-3′, 149.1; C-4′, 148.6 ppm) in the literature require reversal. A strong inhibitory activity against platelet aggregation has been reported for compound **1**.[4]

By comparison of MS, ^{1}H- and ^{13}C-NMR spectra of **2** with those of **1**, the structure of **2** had an additional methoxyl group on the aromatic ring of the tyramine portion of compound **1**. Compound **2** was identified as *N-trans*-feruloyl 3-methyldopamine by comparison of physical and spectral data with literature values.[5] The ^{13}C-NMR spectral assignments in the literature require the same revision as those of compound **1**.

This is the first report of the isolation of phenolic amides from a *Cocculus* species.

Acknowledgements - We thank Mr. Kim Harich (Virginia Polytechnic Institute and State University) for mass spectra.

<Received 28 August 1995>

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