Pergamon

Tetrahedron Letters 39 (1998) 407–410

TETRAHEDRON LETTERS

Cherinonaine, a Novel Dimeric Amide from the Stems of *Annona cherimola*

Chung-Yi Chen, Fang-Rong Chang and Yang-Chang Wu*

Graduate Institute of Natural Products, Kaohsiung Medical College, Kaohsiung, Taiwan, R.O.C.

Received 15 July 1997; revised 26 August 1997; accepted 7 October 1997

Abstract: Cherinonaine (**1**), a novel *Annona* dimeric amide, has been isolated from *Annona cherimola*, and its structure was determined on the basis of spectroscopic analysis. Amide **1** consists a unique ether bridge between two monomeric amides which are composed from ferulic acid and 6-methoxyl-7-hydroxyl amphetamine.

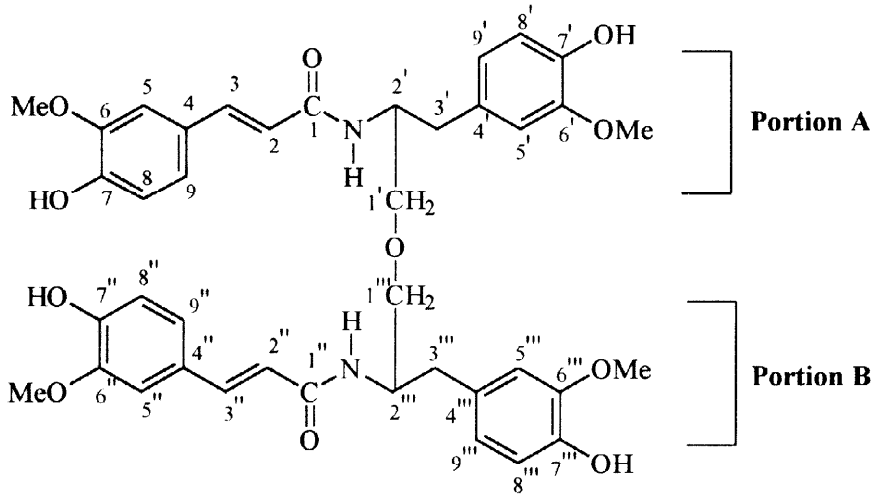
In the course of screening for biologically and chemically novel agents from Formosan Annonaceous plants, we found that *Annona cherimola* (Annonaceae) producing a novel dimeric amide named cherinonaine (**1**). Previously, we have isolated a novel alkaloid, cherimoline, [1] and twenty-one alkaloids, four kauranes, two amides, one purine, one lactam amide and six steroids from this plant. [2] In this paper, we report the isolation and structural elucidation of this new compound (**1**).

A number of Annonaceae and *A. cherimola* in particular have been described as cytotoxic.[3] They are used in the folk medicine of some tropical countries to treat various tumours and cancers.[4] The fresh stems of the plant were extracted with MeOH. The extracts was concentrated *in vacuo* and partitioned between $CHCl_3$ and water. The organic layer was separated by silica gel column chromatography using gradient elution of $CHCl_3$-MeOH. Further purification by preparative TLC on silica gel with hexane-EtOAc (1:4) afforded a white powder of 10 mg cherinonaine (**1**).

Cherinonaine (**1**), was obtained as white amorphous powder with $[\alpha]_D = \pm 0°$ (c 0.13, MeOH). The UV spectrum with strong absorptions maxima at 220, 290 and 317 nm, and the IR spectrum absorption at λ 1690 cm^{-1} revealed an α, β-unsaturated amide carbonyl functionality.[5-10] The structure determination commenced with the molecular formula of $C_{40}H_{44}N_2O_{11}$ established by HRFABMS at m/z $[M+H-CH_3]^+$ 714.2786 (Δ0.3 mmu). The ^1H NMR spectrum of **1** showed an ABX pattern at δ 7.20 (1H, d, J=8.0), 7.31 (1H, dd, J=8.0, 2.0) and 7.39 (1H, d, J=2.0) for H-8, H-9 and H-5 in the ferulic acid moiety, respectively. A downfield doublet at δ

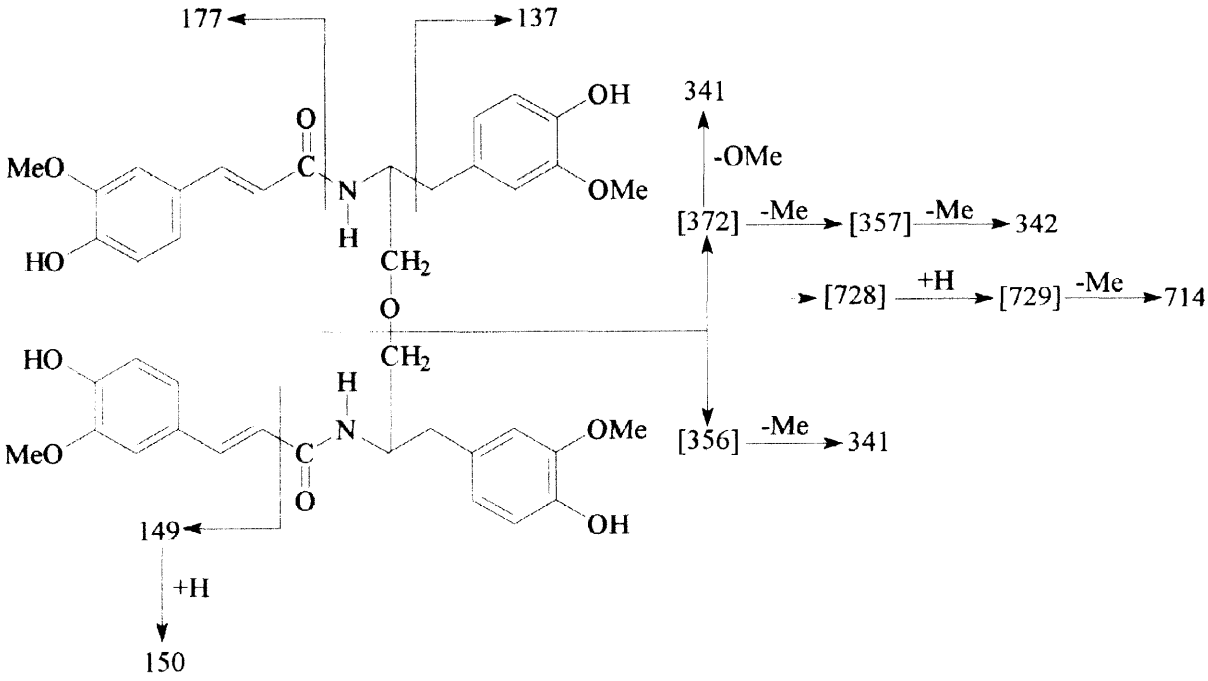
0040-4039/98/$19.00
PII: S0040-4039(97)10534-2

8.05 (J=16.0 Hz) was assigned to be the C-3 olefinic proton showing *trans*-coupling with the C-2 olefinic proton which appeared as a doublet at δ 6.80 (J=16.0 Hz). Another ABX pattern at δ 6.92 (1H, dd, J=8.0, 1.6), 7.00 (1H, d, J=1.6) and 7.20 (1H, d, J=8.0) for H-9', H-5' and H-8' in the 6-methoxy-7-hydroxyl amphetamine moiety, respectively. This was assigned as the C-2' methine proton due to the coupling with the neighbor C-3' and C-1' methylene protons which appeared as two double doublet at δ 2.92 (J=14.0, 7.6 Hz), δ 3.06 (J=14.0, 6.8 Hz) and δ 4.57 (J=11.4, 5.2 Hz) and δ 4.80 (J=11.4, 6.0 Hz), respectively. The ^{13}C NMR (Table 1) and DEPT experiments of **1** showed twenty resonance lines consisting of two methyls, two methylenes, nine methines, and seven quaternary carbons (including a carbonyl signal at δ 167.2).



1

The structure **1** was also confirmed by 2D NMR experiments. A COSY correlation was observed between the H-2' and H-1' , and between H-2' and H-3'. The HETCOR experiment showed that the carbon signals at δ 64.7 for C-1', 40.9 for C-2' and 35.3 for C-3' were correlated to the proton signals at δ 4.80 and 4.57 for H-1', δ 2.66 for H-2' ,and δ 3.06 and 2.92 for H-3', respectively. Thus, these two portions of the dimeric amide were proved to be ether linked at the C-1' position of the A-portion and at the C-1''' position of the B-portion. The NOESY correlations between H-2' and H-3' and between H-2' and H-1' established the connective site as shown in structure **1**. This dimer structure was further confirmed by FABMS fragment at 341 $[M-C_{21}H_{25}O_6N]^+$ (Scheme 1). Compound **1** showed zero in optical rotation, suggested **1** as a *meso* compound. Alkaloids, which possess a dimeric structure, are a rare class of compounds except for the indole and the benzylisoquinoline alkaloids.[11] This is the first example of the dimeric *Annona* acid amide composed of ferulic acid and 6-methoxyl-7-hydroxy amphetamine.



Scheme 1. Ms fragment ions of **1** (m/z)

Table 1. ^{13}C **(100 MHz, methanol-d_4) and** ^{1}H **NMR (400 MHz, methanol-d_4) data of ferulic acid moiety of cherinonaine (1).**

C#	δ_C	δ_H	mult., *J* (Hz)	COSY	NOESY
1(1")	167.23				
2(2")	114.27	6.80	d, 16.0	H-3(3")	H-3(3")
3(3")	144.05	8.05	d, 16.0	H-2(2")	H-2(2")
4(4")	131.59				
5(5")	109.67	7.39	d, 2.0		6(6")-OMe
6(6")	148.45				
7(7")-OH	147.07	5.01	br s		H-8(8")
8(8")	114.94	7.20	d, 8.0	H-9(9")	H-9(9")
9(9")	123.01	7.31	dd, 8.0, 2.0	H-8(8")	H-8(8"), H-5(5")
6(6")-OMe	55.90	3.78			H-5(5")

Table 2. ^{13}C (100 MHz, methanol-d_4) and ^{1}H NMR (400 MHz, methanol-d_4) data of 6-methoxy-7-hydroxy amphetamine moiety of cherinonaine (1).

C#	δ_C	δ_H	mult., *J*(Hz)	COSY	NOESY
1'(1''')	64.42	1'(1''')a : 4.80	dd, 11.4, 6.0	H-2'(2''')	H-1'(1''')b, H-2'(2''')
		1'(1''')b : 4.57	dd, 11.4, 5.2	H-2'(2''')	H-1'(1''')a
2'(2''')	40.16	2.66	m	H-1'(1'''), H-3'(3''')	H-3'(3''')a, H-3'(3''')b, H-1'(1''')a
3'(3''')	35.22	3'(3''')a : 3.06	dd, 14.0, 6.8	H-2'(2''')	H-3'(3''')b
		3'(3''')b : 2.92	dd, 14.0, 7.6	H-2'(2''')	H-3'(3''')a, H-2'(2''')
4'(4''')	126.62				
5'(5''')	111.39	7.00	d, 1.6		6'(6''')-OMe
6'(6''')	146.60				
7'(7''')-OH	145.15	5.01	br s		H-8'(8''')
8'(8''')	115.00	7.20	d, 8.0	H-9'(9''')	H-9'(9''')
9'(9''')	121.67	6.92	dd, 8.0, 1.6	H-8'(8''')	H-8'(8'''), H-5'(5''')
6'(6''')-OMe	55.72	3.76			H-5'(5''')

Acknowledgment. This investigation was supported by a grant from the National Science Council, R.O.C. (NSC-87-2314-B-037-054-M 25) awarded to Y. C. Wu.

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