# Phenolic Compounds from *Viburnum cylindricum*

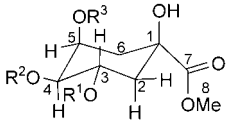
by **Xiangdong Zhu**, **Xujun Dong**, **Yifeng Wang**, **Peng Ju**, and **Shide Luo***

State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, China
(phone +86 871-5223097; e-mail: shideluo@hotmail.com)

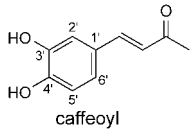
Three novel quinic acid esters, *i.e.*, neochlorogenic acid methyl ester (**1**), cryptochlorogenic acid methyl ester (**2**), and chlorogenic acid methyl ester (**3**), were isolated from *Viburnum cylindricum*. Their structures were determined by spectroscopic analysis.

**Introduction.** – The genus *Viburnum* (Caprifoliaceae) comprises over 200 species distributed from South America (Peru) to Southeast Asia (Philippines, Malaysia) [1], 80 of which are distributed in China [2]. Several phytochemical investigations have shown that *Viburnum* species characteristically contain iridoids, triterpenoids, coumarins, and flavones [3–7].

*Viburnum cylindricum* is distributed in tropical Asia, which has been used as folk medicine to treat different diseases, such as cough, diarrhea, rheumatoid arthritis, and tumefaction [8]. A literature search revealed that no previous phytochemical and pharmacological study has been undertaken of this species. As part of ongoing phytochemical and pharmacological investigations of the genus *Viburnum*, we collected the stems and leaves of *V. cylindricum* from Kunming in Yunnan province. From the AcOEt extract, three new quinic acid esters besides several known compounds were isolated: neochlorogenic acid methyl ester[1]) (**1**), cryptochlorogenic acid methyl ester[1]) (**2**), and chlorogenic acid methyl ester[1]) (**3**). All the structures were elucidated by spectroscopic methods. The assignments of the NMR data of compounds **1**–**3** were established by 2D NMR experiments.




**1**[1]) $R^1 = R^2 = H$, $R^3$ = caffeoyl
**2** $R^1 = R^3 = H$, $R^2$ = caffeoyl
**3** $R^1$ = caffeoyl, $R^2 = R^3 = H$




**Results and Discussion.** – Compound **1** showed a base peak at *m*/*z* 368 in the FAB-MS (negative-ion mode), corresponding to the molecular formula $C_{17}H_{20}O_9$, which was

[1]) For convenience **1** is numbered like **2** and **3** (see formula); for systematic names, see *Exper. Part.*

also confirmed by the $^{13}$C-NMR and DEPT data (*Table*). The $^{1}$H-NMR spectrum exhibited signals belonging to a caffeic acid (=(2*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid) moiety, a quinic acid (=*rel*-(1$\alpha$,3*R*,4$\alpha$,5*R*)-1,3,4,5-tetrahydroxycyclohexanecarboxylic acid) moiety, and a MeO group. The IR spectrum of **1** indicated the presence of OH (3441, 1118 cm$^{-1}$) and carboxylate groups (1725, 1631 cm$^{-1}$). Further spectral data established that the structure of **1** is that of neochlorogenic acid methyl ester.

Table 1. *$^{13}$C-NMR Data* (100 MHz,$CD_3OD$) *of Compounds* **1**–**3**

| | **1** | **2** | **3** |
|---|---|---|---|
| C(1) | 75.3 | 76.4 | 75.8 |
| C(2) | 40.8 | 42.1 | 37.9 |
| C(3) | 68.6 | 65.6 | 72.0 |
| C(4) | 73.8 | 78.5 | 72.4 |
| C(5) | 72.6 | 69 | 70.2 |
| C(6) | 36.3 | 37.7 | 38.3 |
| *C*OOMe | 176.4 | 175.6 | 175.4 |
| COO*Me* | 52.8 | 52.9 | 52.9 |
| C(1′) | 127.9 | 127.5 | 127.8 |
| C(2′) | 115.1 | 115.2 | 115.2 |
| C(3′) | 146.7 | 146.8 | 146.7 |
| C(4′) | 149.4 | 149.6 | 149.5 |
| C(5′) | 116.4 | 116.6 | 116.6 |
| C(6′) | 122.9 | 122.9 | 122.9 |
| *C*H=CHCO | 146.8 | 147.1 | 147.1 |
| CH=*C*HCO | 115.7 | 115.2 | 115.1 |
| CH=CH*C*O | 168.9 | 168.9 | 168.2 |

The $^{1}$H-NMR signals of $H_{ax}$–C(3), $H_{ax}$–C(4), and $H_{eq}$–C(5) of the quinic acid moiety of **1** were assigned according to their multiplicity, their coupling constants, and $^{1}$H,$^{1}$H-COSY data[1]). The $^{1}$H,$^{1}$H-COSY showed the connectivity between H–C(3) ($\delta$ 4.11) and H–C(4) ($\delta$ 3.68), and the connectivity between H–C(4) and H–(5) ($\delta$ 5.34). The position of caffeoyl substitution and the location of the MeO group at the quinic acid moiety were confirmed as follows. The HSQC showed the connectivity between C(5) ($\delta$ 72.6) and H–C(5) ($\delta$ 5.34), C(3) ($\delta$ 68.6) and H–C(3) ($\delta$ 4.11 (*ddd*, $J$ = 3.5 Hz)), and C(4) ($\delta$ 73.8) and H–C(4) ($\delta$ 3.68 (*dd*, $J$ = 3.5, 7.6 Hz)). The HMBC spectrum showed a correlation between H–C(5) ($\delta$ 5.34) and a COO group ($\delta$ 168.9). The COO group correlated also with two *trans*-positioned olefinic protons, while a MeO group ($\delta$ 3.73) showed correlation with another COO group ($\delta$ 176.4). From these spectral data, the location of the caffeoyl substitution must be at C(5)[1]) of the quinic acid methyl ester moiety.

Compound **2**, an amorphous powder, showed a base peak at *m*/*z* 368 in its FAB-MS (negative-ion mode), corresponding to the molecular formula $C_{17}H_{20}O_9$, which also was confirmed by the $^{13}$C-NMR and DEPT data. The spectral data were very similar to those of **1**. The location of the caffeoyl substitution at the quinic acid methyl ester moiety was determined by the HMBC spectrum (correlation of $\delta$ 4.85 (H–C(4)) with $\delta$ 168.9 (COO)). These results established the location of the caffeoyl substitution at C(4) of the quinic acid methyl ester moiety. The structure of **2** is, therefore, that of cryptochlorogenic acid methyl ester.

Compound **3**, an amorphous powder, afforded also a base peak at *m*/*z* 368 in the FAB-MS (negative-ion mode), which was assigned to the molecular ion $C_{17}H_{20}O_9^-$ and

was in accord with the $^{13}$C-NMR and DEPT data. The spectral data were very similar to those of **1**. The location of the caffeoyl substitution at the quinic acid methyl ester moiety was determined by the HMBC spectrum (correlation of $\delta$ 5.3 (H–C(3)) with $\delta$ 168.2 (COO)). These results established the location of the caffeoyl substitution at C(3) of the quinic acid methyl ester moiety. The structure of **3** is that of chlorogenic acid methyl ester.

## Experimental Part

*General*. Column chromatography (CC): silica gel (200–300 mesh; *Qingdo Marine Chemical Inc.*, China), silica gel *H* (60 μm; *Qingdo Marine Chemical Inc.*, China), *Lichroprep RP$_{18}$* gel (40–63 μm; *Merck*, Darmstadt, Germany), and *Sephadex LH-20* (25–100 μm ). TLC: detection by spraying with 5% $H_2SO_4$ in EtOH followed by heating. Optical rotations: *Horiba SEPA-300* spectropolarimeter. UV Spectra: *Shimadzu 210A* double-beam spectrophotometer; $\lambda_{max}$ in nm. IR Spectra: *Bio-Rad FTS-135*-IR spectrophotometer; in cm$^{-1}$; KBr pellets. 1D- and 2D-NMR Spectra: *Bruker AM-400* and *DRX-500* instruments; $\delta$ in ppm, *J* in Hz. MS: *VG Auto-Spec-3000* spectrometer; in *m*/*z*.

*Plant Material*. Dried stems and leaves of *V. cylindricum* were collected at Kunming, Yunnan, China, in April 2004. The plant was identified by Dr. *Li Rong*. A voucher specimen (Kun No. 0085118) has been deposited in the Herbarium of the Department of Taxonomy, Kunming Institute of Botany, Chinese Academy of Sciences.

*Extraction and Isolation*. Dried stems and leaves of *V. cylindricum* (11.2 kg) were extracted with 90% EtOH (3 × at r.t. overnight, and the extract was filtered. After evaporation of the filtrate, the residue was suspended in $H_2O$ and extracted with petroleum ether, AcOEt, and BuOH. The AcOEt extract (510 g) was subjected to CC (silica gel (200–300 mesh), $CHCl_3$/MeOH 95:5 and 8:2): *Fractions 1–10*. *Fr. 10* (100 g) was subjected to CC (silica gel (200–300 mesh), $CHCl_3$/MeOH (9:1 → 8:2): *Fr. 10.1–10.8*. *Fr. 10.3–10.5* were subjected to CC (1. silica gel H; 2. *Sephadex-LH-20*, MeOH/$CHCl_3$ 1:1; 3. *RP$_{18}$*, MeOH/$H_2O$ 7:3): **1** (21 mg), **2** (18 mg), and **3** (19 mg).

rel-*(1*R,*3*R,*4*S,*5*R*)-3-{[(2*E*)-3-(3,4-Dihydroxyphenyl)-1-oxoprop-2-enyl]oxy}-1,4,5-trihydroxycyclohexanecarboxylic Acid Methyl Ester* (= *Neochlorogenic Acid Methyl Ester*; **1**): Amorphous powder. $[\alpha]_D^{25} = +7.3$ ($c$ = 0.003, MeOH). UV (MeOH): 213, 328. IR (KBr): 3447, 1725, 1631, 1118. $^1$H-NMR ($CD_3OD$, 400 MHz)[1]: 2.01 (*m*, $H_{ax}$–C(6)); 2.22 (*m*, $H_{eq}$–C(6)); 2.02 (*m*, $H_{ax}$–C(2)); 2.09 (*m*, $H_{eq}$–C(2)); 4.11 (*ddd*, *J* = 3.5, H–C(3)); 3.68 (*dd*, *J* = 3.5, 7.6, H–C(4)); 5.34 (*ddd*, *J* = 3.5, H–C(5)); 3.73 (*s*, MeO); 6.29 (*d*, *J* = 15.9, CH=C*H*CO); 6.76 (*d*, *J* = 8.2, H–C(5′)); 6.94 (*dd*, *J* = 2.02, 8.2, H–C(6′)); 7.03 (*d*, *J* = 2.02, H–C(2′)); 7.58 (*d*, *J* = 15.9, C*H*=CHCO). $^{13}$C-NMR ($CD_3OD$, 100 MHz): *Table*. FAB-MS (neg.): 368 ($M^-$), 353 ([$M$ – Me]$^-$), 325 ([$M$ – 15 – 28]$^-$).

rel-*(1*α,*3*R,*4*α,*5*R*)-4-{[(2*E*)-3-(3,4-Dihydroxyphenyl)-1-oxoprop-2-enyl]oxy}-1,3,5-trihydroxycyclohexanecarboxylic Acid Methyl Ester* (= *Cryptochlorogenic Acid Methyl Ester*; **2**): Amorphous powder. $[\alpha]_D^{25} = -33.6$ ($c$ = 0.004, MeOH). UV (MeOH): 216, 329. IR (KBr): 3426, 1696, 1606, 1164. $^1$H-NMR ($CD_3OD$, 400 MHz): 2.04 (*m*, $H_{ax}$–C(6)); 2.20 (*m*, $H_{eq}$–C(6)); 2.05 (*m*, $H_{ax}$–C(2)); 2.24 (*m*, $H_{eq}$–C(2)); 4.27 (*ddd*, *J* = 3.5, H–C(3)); 4.84 (*dd*, *J* = 3.5, 8.6, H–C(4)); 4.29 (*ddd*, *J* = 3.5, H–C(5)); 3.73 (*s*, MeO); 6.38 (*d*, *J* = 15.9, CH=C*H*CO); 6.80 (*d*, *J* = 8.2, H–C(5′)); 6.99 (*dd*, *J* = 1.6, 8.2, H–C(6′)); 7.06 (*d*, *J* = 1.6, H–C(2′)); 7.65 (*d*, *J* = 15.9, C*H*=CHCO). $^{13}$C-NMR ($CD_3OD$, 100 MHz): *Table*. FAB-MS (neg.): 368 ($M^-$), 353 ([$M$ – Me]$^-$), 325 ([$M$ – 15 – 28].

rel-*(1*S,*3*R,*4*R,*5*R*)-3-{[(2*E*)-3-(3,4-Dihydroxyphenyl)-1-oxoprop-2-enyl]oxy}-1,4,5-trihydroxycyclohexanecarboxylic Acid Methyl Ester* (= *Chlorogenic Acid Methyl Ester*; **3**): Amorphous powder. $[\alpha]_D^{25} = +7.3$ ($c$ = 0.003, MeOH). UV (MeOH): 234, 329. IR (KBr): 3426, 1734, 1631, 1178. $^1$H-NMR ($CD_3OD$, 400 MHz): 2.03 (*m*, $H_{ax}$–C(6)); 2.24 (*m*, $H_{eq}$–C(6)); 2.02 (*m*, $H_{ax}$–C(2)); 2.04 (*m*, $H_{eq}$–C(2)); 5.29 (*dd*, *J* = 3.5, H–C(3)); 3.74 (*dd*, *J* = 3.5, 7.6, H–C(4)); 4.15 (*ddd*, *J* = 3.5, H–C(5)); 3.73 (*s*, MeO); 6.23 (*d*, *J* = 15.9, CH=C*H*CO); 6.80 (*d*, *J* = 8.1, H–C(5′)); 6.99 (*dd*, *J* = 1.6, 8.1, H–C(6′)); 7.08 (*d*, *J* = 1.6, H–C(2′)); 7.54 (*d*, *J* = 15.9, C*H*=CHO). $^{13}$C-NMR ($CD_3OD$, 100 MHz): *Table*. FAB-MS (neg.): 368 ($M^-$), 353 ([$M$ – Me]$^-$), 325 ([$M$ – 15 – 28]$^-$).

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