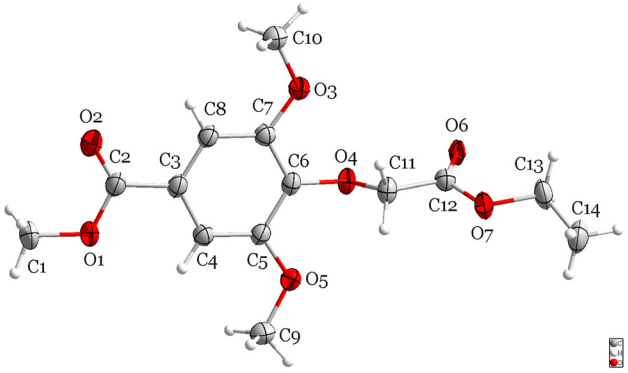
Xiao-ming Shang, Ying Luo, Nuo Chen, Zong-de Wang and Hai Luo*

Synthesis and crystal structure of methyl 4-(2-ethoxy-2-oxoethoxy)-3,5-dimethoxybenzoate, $C_{14}H_{18}O_7$



https://doi.org/10.1515/ncrs-2024-0387
Received October 1, 2024; accepted October 25, 2024;
published online November 14, 2024

Abstract

$C_{14}H_{18}O_7$, orthorhombic, $P2_12_12_1$ (no. 19), a = 4.3538(6) Å, b = 12.7630(19) Å, c = 26.493(4) Å, V = 1,472.2(4) Å^3, Z = 4, $R_{gt}(F)$ = 0.0414, $wR_{ref}(F^2)$ = 0.1043, T = 296(2) K.

CCDC no.: 2393676

Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colorless block
Size:	0.19 × 0.15 × 0.13 mm
Wavelength:	Mo *Kα* radiation (0.71073 Å)
μ:	0.11 mm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
θ_{max}, completeness:	25.5°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	11,557, 2,748, 0.039
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 1960
$N(param)_{refined}$:	194
Programs:	Bruker,[1] SHELX,[2,3] Diamond[4]

1 Source of materials

The mixture of methyl 4-hydroxy-3,5-dimethoxy-benzoate (2.12 g, 0.01 mol), ethyl bromoacetate (2.03 g, 0.012 mol), K_2CO_3 (2.76 g, 0.02 mol) and acetone (15 mL) was reacted at 70 °C for 24 h. After the reaction was completed (monitored by TLC), colorless crystals were obtained by slow cooling. The product was filtered, and washed with water 3 times respectively. Yield 90 % (based on methyl 4-hydroxybenzoate). **Elemental Anal. Calcd.** (%) for $C_{14}H_{18}O_7$ (298.29): C, 56.37; H, 6.08. Found (%): C, 55.53; H, 6.16.

2 Experimental details

All H atoms were included in calculated positions and refined as riding atoms, with C–H = 0.90–0.97 Å with U_{iso}(H) = 1.5 U_{eq}(C) for methyl H atoms and 1.2 U_{eq}(C) for all other H atoms.

3 Comment

Syringic acid, 4-hydroxy-3,5-dimethoxybenzoic acid, is a phenolic acid of benzoic acid categorie, which has anti-bacterial activities, sedative activities and local anesthetic effects.[5–8] Methyl syringate is considered as a symbolic component of Manuka honey, and it is also a functional

***Corresponding author: Hai Luo**, East China Woody Fragrance and Flavor Engineering Research Center of National Forestry and Grassland Administration, Jiangxi Provincial Key Laboratory of Improved Variety Breeding and Efficient Utilization of Native Tree Species, College of Forestry, Jiangxi Agricultural University, Nanchang, 330045, People's Republic of China and The Key Laboratory of State Forestry and Grassland Administration on Highly-Efficient Utilization of Forestry Biomass Resources in Southwest China, Kunming, 650224, People's Republic of China, E-mail: luohai87@126.com. https://orcid.org/0009-0001-1608-4339
Xiao-ming Shang, Ying Luo, Nuo Chen and Zong-de Wang, East China Woody Fragrance and Flavor Engineering Research Center of National Forestry and Grassland Administration, Jiangxi Provincial Key Laboratory of Improved Variety Breeding and Efficient Utilization of Native Tree Species, College of Forestry, Jiangxi Agricultural University, Nanchang, 330045, People's Republic of China

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.2531 (12)	0.3586 (3)	−0.03413 (10)	0.0820 (13)
H1A	0.0477	0.3582	−0.0473	0.123*
H1B	0.3596	0.2970	−0.0454	0.123*
H1C	0.3591	0.4198	−0.0459	0.123*
C2	0.0917 (9)	0.4383 (2)	0.04178 (12)	0.0579 (9)
C3	0.1012 (8)	0.4357 (2)	0.09784 (10)	0.0474 (8)
C4	0.2571 (8)	0.3577 (2)	0.12362 (10)	0.0468 (8)
H4	0.3544	0.3041	0.1060	0.056*
C5	0.2670 (7)	0.3602 (2)	0.17595 (10)	0.0441 (7)
C6	0.1262 (7)	0.4418 (2)	0.20184 (10)	0.0417 (7)
C7	−0.0367 (8)	0.5184 (2)	0.17540 (11)	0.0458 (8)
C8	−0.0497 (8)	0.5149 (2)	0.12334 (10)	0.0489 (8)
H8	−0.1591	0.5655	0.1056	0.059*
C9	0.5440 (10)	0.1986 (3)	0.18127 (12)	0.0674 (10)
H9A	0.3864	0.1596	0.1643	0.101*
H9B	0.6408	0.1550	0.2061	0.101*
H9C	0.6943	0.2215	0.1572	0.101*
C10	−0.3476 (9)	0.6719 (2)	0.17966 (12)	0.0619 (9)
H10A	−0.2196	0.7096	0.1564	0.093*
H10B	−0.4303	0.7197	0.2041	0.093*
H10C	−0.5126	0.6391	0.1616	0.093*
C11	−0.0880 (7)	0.4045 (2)	0.28092 (10)	0.0500 (8)
H11A	−0.0901	0.3292	0.2758	0.060*
H11B	−0.2820	0.4326	0.2691	0.060*
C12	−0.0486 (8)	0.4284 (2)	0.33539 (11)	0.0471 (8)
C13	−0.2301 (10)	0.3800 (3)	0.41709 (10)	0.0693 (11)
H13A	−0.3647	0.4389	0.4239	0.083*
H13B	−0.0278	0.3963	0.4302	0.083*
C14	−0.3509 (11)	0.2845 (3)	0.44159 (12)	0.0866 (13)
H14A	−0.5495	0.2683	0.4279	0.130*
H14B	−0.3682	0.2962	0.4773	0.130*
H14C	−0.2134	0.2271	0.4355	0.130*
O1	0.2427 (6)	0.35965 (16)	0.02034 (7)	0.0672 (7)
O2	−0.0373 (9)	0.5048 (2)	0.01778 (8)	0.1019 (12)
O3	−0.1698 (6)	0.59389 (17)	0.20468 (7)	0.0590 (6)
O4	0.1574 (5)	0.44972 (15)	0.25340 (7)	0.0471 (5)
O5	0.4110 (6)	0.28758 (16)	0.20538 (7)	0.0570 (6)
O6	0.0991 (8)	0.4973 (2)	0.35315 (8)	0.0834 (9)
O7	−0.2130 (6)	0.36104 (16)	0.36309 (7)	0.0593 (6)

component of its antioxidant and antibacterial activity.[9–11] It also is an effective bacterial and fungal laccase phenol medium and an agonist of TRPA1.[12] Because of its strong activities and its wide applications, the synthesis and application of syringic acid derivatives have attracted much attention.[13,14] Saeed et al. have reported the synthesis and crystal structure of methyl 4-acetoxy-3,5-dimethoxybenzoate.[15] Nie et al. have reported the synthesis and crystal structure of methyl 4-acetoxy-3,5-dimethoxybenzoate.[16] We still focused on the synthesis and antibacterial activities of preservatives.

In the molecules of the title structure bond lengths and angles are very similar to those given in the literature.[15–17] In the title structure, the part of methyl 4-hydroxy-3,5-dimethoxybenzoic acid is approximately planar. The dihedral angle formed by the C3–C8 plane with the carboxlate group O1–C2–O2 plane is 2.5°. The torsion angles of C4–C5–O5–C9 and C8–C7–O3–C10 are −4.5(4)° and 3.2(4)°. The part of 2-ethoxy-2-oxoethoxy group is perpendicular to methyl 4-hydroxy-3,5-dimethoxybenzoic acid and the torsion angles of C5–C6–O4–C11, C6–O4–C11–C12 and C12–O7–C13–C14 are −95.6(3)°, −173.5(2)° and −165.8(3)°. The dihedral angle formed by the C3–C8 plane with the carboxylate group O6–C12–O7 plane is 71.218(107)°.

Acknowledgments: X-ray data were collected at Instrumental Analysis Center Nanchang Hangkong University, Nanchang, 330063, People's Republic of China.
Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: This research was supported by the National Natural Science Foundation of China (Grant Number 32360365), the Key Laboratory of State Forestry and Grassland Administration on Highly-Efficient Utilization of Forestry Biomass Resources in Southwest China (Grant Number 2022–KF12).
Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

1. Bruker. *APEX2*, *SAINT* and *SADABS*; Bruker AXS Inc.: Madison, Wisconsin, USA, 2009.
2. Sheldrick, G. M. A Short History of *SHELX*. *Acta Crystallogr.* **2008**, *A64*, 112–122.
3. Sheldrick, G. M. Crystal Structure Refinement with *SHEXL*. *Acta Crystallogr.* **2015**, *C71*, 3–8.
4. Brandenburg, K. *DIAMOND. Visual Crystal Structure Information System. Ver. 4.0*; Crystal Impact: Bonn, Germany, 2015.
5. Liu, F.; Jiang, F. B.; Li, Y. T.; Liu, R. M.; Wu, Z. Y.; Yan, C. W. Cocrystallization with Syringic Acid Presents a New Opportunity for Effectively Reducing the Hepatotoxicity of Isoniazid. *Drug Dev. Ind. Pharm.* **2020**, *46*, 988–995.
6. Cordelia, M. J.; Sumathy, A. Syringic Acid (4-hydroxy-3,5-Dimethoxybenzoic Acid) Inhibits Adipogenesis and Promotes Lipolysis in 3T3–L1 Adipocytes. *Nat. Prod. Res.* **2020**, *34*, 3432–3436.
7. Wang, J. R.; Ma, L.; Li, W. F.; Tang, X. H.; Zhao, G.; Peng, L. X.; Zhao, J. L. Effect of Trace Elements on the Flavonoids and Phenolic Acids in Tartary Buckwheat Sprouts. *Acta Agric. Univ. Jiangxiensis* **2017**, *39*, 55–63.
8. Srinivasulu, C.; Ramgopal, M.; Ramanjaneyulu, G.; Anuradha, C. M.; Suresh, K. C. Syringic Acid (SA) – A Review of its Occurrence,

Biosynthesis, Pharmacological and Industrial Importance. *Biomed. Pharmacother.* **2018**, *108*, 547–557.
9. Main, E. N.; Huang, J. C.; Bowlin, G. L. Methyl Syringate: A Primary Driving Factor in Manuka Honeys Ability to Ameliorate Neutrophil Intracellular ROS Activity and NETosis. *Front. Biosci.* **2024**, *29*, 255.
10. Ahn, D.; Kwon, J. H.; Song, S. Y.; Lee, J. Y.; Yoon, S. Y.; Chung, S. J. Methyl Syringate Stimulates Glucose Uptake by Inhibiting Protein Tyrosine Phosphatases Relevant to Insulin Resistance. *Life* **2023**, *13*, 1372.
11. Elamine, Y.; Lyoussi, B.; Miguel, M. G.; Anjos, O.; Estevinho, L.; Alaiz, M.; Girón–Calle, J.; Martín, J.; Vioque, J. Physicochemical Characteristics and Antiproliferative and Antioxidant Activities of Moroccan Zantaz Honey Rich in Methyl Syringate. *Food Chem*. **2020**, *339*, 128098.
12. Park, J.; Shim, M. K.; Jin, M.; Rhyu, M. R.; Lee, Y. Methyl Syringate, a TRPA1 Agonist Represses Hypoxia-Induced Cyclooxygenase-2 in Lung Cancer Cells. *Phytomedicine* **2016**, *23*, 324–329. ISSN 0944–7113.
13. Zhou, X. L.; Huang, S. X.; Wang, P. C.; Luo, Q.; Huang, X.; Xu, Q.; Qin, J. K.; Liang, C. Q.; Chen, X. A Syringic Acid Derivative and Two Iridoid Glycosides from the Roots of Stachys Geobombycis and Their Antioxidant Properties. *Nat. Prod. Res.* **2017**, *31*, 681–686.
14. Chen, P. S.; Chen, H. M.; Zhang, G. F.; Chen, W. J.; Chen, W. X. Synthesis, Characterization and Interaction of Syringic Acid–Copper Complex with DNA. *Chin. J. Chem.* **2018**, *81*, 170–174.
15. Saeed, A.; Khera, R. A.; Bolte, M. Methyl 3,4,5-Trimethoxybenzoate. *Acta Crystallogr*. **2007**, *E63*, o4582.
16. Xiong, C. L.; Lan, Y. D.; Song, X. Y.; Xiong, W. M.; Nie, X. L. Crystal Structure of Methyl 4-Acetoxy-3,5-Dimethoxybenzoate, $C_{12}H_{14}O_6$. *Z. Kristallogr. N. Cryst. Struct* **2021**, *236*, 573–575.
17. Liu, S. J.; Guo, C. M.; Wang, G. S.; Li, W. J.; Nie, X. L. Crystal Structure of Methyl 4-(2-Ethoxy-2-Oxoethoxy)-3-Methoxybenzoate, $C_{13}H_{16}O_6$. *Z. Kristallogr. N. Cryst. Struct* **2024**, *239*, 129–130.