Syntheses and crystal structures of two piperine derivatives

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Abstract

The title compounds, $C_{18}H_{21}NO_3$ and $C_{18}H_{21}NO_3$, are derivatives of piperine, which is known as a pungent component of pepper. Their geometrical parameters are similar to those of the three polymorphs of piperine, which indicate conjugation of electrons over the length of the molecules. The extended structure of (I) features N—H···O amide hydrogen bonds, which generate C(4) [010] chains. The crystal of (II) features aromatic π-π stacking, like two of three known piperine polymorphs.

Keywords: crystal structure, organic crystal, piperine, hydrogen bond

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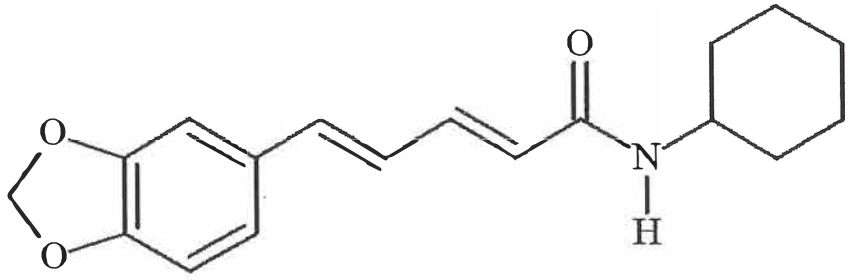

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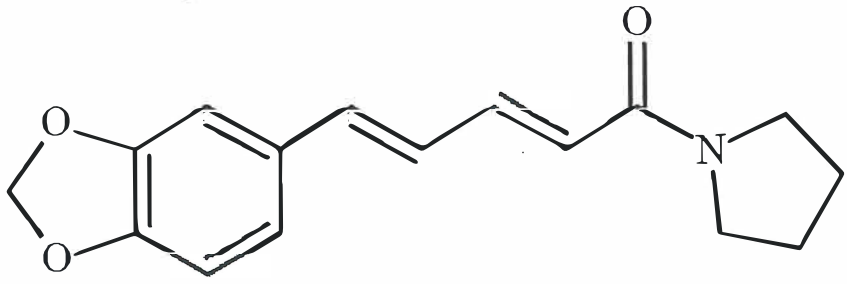

1. Chemical context

Piperine [(2*E*,4*E*)-1-[5-(1,3-benzodioxol-5yl)-1-oxo-2,4-pentadienyl]piperidine, $C_{17}H_{19}NO_3$, is the major pungent ingredient of piperaceae papper (piper nigrum). Piperine is an amide having a methylenedioxyphenyl grouping as a characteristic of its chemical structure (Fig. 1). Interestingly, when the amide group is in a near planar conformation, the conjugated state of the pentadiene chain of piperine has the property that electrons are easily donated and the stretching vibration of the amide carbonyl group is affected (Pfund *et al.*, 2015). As part of our studies in this area, we have already reported a complex using the poorly water-soluble piperine (log $P = 2.25$) and the cyclic polysaccharide cyclodextrin (Szejtli, 1998, Ezawa *et al.*, 2016). In addition, piperine has been evaluated for its inclusion mechanism and dissolution properties using various cyclodextrins (Ezawa *et al.*, 2018; Ezawa *et al.*, 2019). The synthesis of piperine derivatives was necessary to understand the inclusion mechanism of piperine and cyclodextrin and the detailed molecular behavior of piperine.

Therefore, the aim of this study was to synthesize the title compounds (2*E*,4*E*)-5-(2*H*-1,3-benzodioxol-5-yl)-*N*-cyclohexylpenta-2,4-dienamide, $C_{18}H_{21}NO_3$, (I) and (2*E*,4*E*)-5-(2*H*-1,3-benzodioxol-5-yl)-1-(pyrrolidin-1-yl)penta-2,4-dien-1-one, $C_{16}H_{17}NO_3$, (II) from piperine and to determine their X-ray crystal structures. Assessing the structural properties of the title compounds (crystal structure, geometry, intermolecular interactions, *etc.*) will help to evaluate the inclusion behavior of piperine with cyclodextrin.

2. Structural commentary

Compound (I) (Fig. 2) crystallizes in the monoclinic space group $P2_1/c$ with four molecules per unit cell. The C1–C6 cyclohexyl ring adopts a chair conformation with the exocyclic C5—N1 bond in an equatorial orientation. The C7–C12/O2/O3 fused-ring system is almost planar (r.m.s. deviation = 0.020 Å) and subtends a dihedral angle of 21.57 (4)° with the cyclohexyl ring. The bond distances and angles (amide, pentadiene and methylenedioxyphenyl moieties) of (I) are not significantly different from the equivalent data for the three polymorphs of piperine (Pfund *et al.*, 2015) (Table 2).

Compound (II) (Fig. 3), also known as piperilyn, crystalizes in the orthorhombic space group *Pbca* with eight molecules per unit cell. The C13–C16/N1 ring is well described as being twisted with C14 and C15 deviating from C13/N1/C16 by 0.205 (2) and −0.382 (2) Å, respectively. The C9/O2/C10/O3/C11 ring has a clear tendency towards an envelope conformation [deviation of C10 from the other four atoms = −0.216 (2) Å]. The dihedral angle between the C13–C16/N1 and C6–C12/O2/O3 rings (all atoms) is 12.29 (10)°. As with (I), the key bond-distance data for (II) are comparable to those of piperine (Table 2).

Thus, we may conclude that the title compounds show intramolecular resonance from the amide group to the ether O atoms of the methylenedioxyphenyl moiety, similar to piperine.

3. Supramolecular features

Piperine crystalizes in three polymorphs: form I (CCDC refcode: PIPINE10) and form II (PIPINE12) in space group $P2_1/n$ and form III (PIPINE13) in space group $C2/c$ (Table 2) (Pfund *et al.*, 2015). The packing for forms II and III feature aromatic π-π stacking interactions, while that of form I does not.

The crystal structure of (I) does not feature π-π stacking interactions, which is similar to piperine form I. Compound (I) possesses an N—H grouping, which forms a classical N1—H···O1 hydrogen bond (Table 3) between the amide-bond sites to generate [010] C(4) chains (Fig. 4) with adjacent molecules related by simple translation. The unit-cell packing for (I) is illustrated in Fig. 5.

The structure of (II) does feature π-π stacking with the closest intermolecular contacts being C9···C9 = 3.268 (3), C9···C12 = 3.322 (3) and C11···C12 = 3.287 (3) Å (Fig. 6). The overall packing for (II) can be described as undulating sheets propagating in the (010) plane (Fig. 7).

4. Synthesis and crystallization

Piperine was purchased from Fujifilm Wako Pure Chemical Co., Ltd. The synthesis of piperine derivatives was performed using a previously reported procedure (Takao *et al.*, 2015). After dissolving piperine in ethanol, hydrolysis was performed by stirring for 20 h in the presence of KOH. After evaporating the solvent under vacuum, the resulting reaction mixture was suspended in water and acidified with 4 *M* HCl to pH < 1. The resultant pale brown precipitate was collected by filtration, washed with cold water and recrystallized from methanol solution to give piperic acid. The piperic acid (1.0 mmol) was dissolved in CH_2Cl_2 (5 ml) and oxalyl chloride (10 mmol) was added and the mixture was stirred at room temperature for 3 h. The solvent and excess oxalyl chloride were then evaporated under reduced pressure.

To prepare (I), the crude acid chloride generated was dissolved in CH_2Cl_2 (2 ml) and cyclohexylamine (1.2 mmol) and Et_3N (8 mmol) were added, and the mixture was stirred at 0 °C for 5 h. Ice-cold water was added to the mixture, followed

by extraction with chloroform (5 ml). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (eluent hexane:etyl acetate 1:1 *v*/*v*) to give (I) in the form of xxxx. Light yellow needles of (I) were recrystallized from xxxx solution.

Compound (II) was prapared by the same procedure with pyrrolidine (1.2 mmol) replacing the cyclohexylamine to give (II) in the form of xxxx. Colourless needles of (II) were recrystallized from xxxx solution.

5. Refinement

Crystal data, data collection and structure refinment details are summarized in Table 3. Hydrogen atoms for carbon atom were included in their calculated positions and refined as riding atoms with $U_{iso}(H) = 1.2U_{eq}(C)$. The hydrogen atom attached to N1 in (I) was located in a difference Fourier map and its position freely refined with $U_{iso}(H) = 1.2U_{eq}(N)$.

fig1.tif

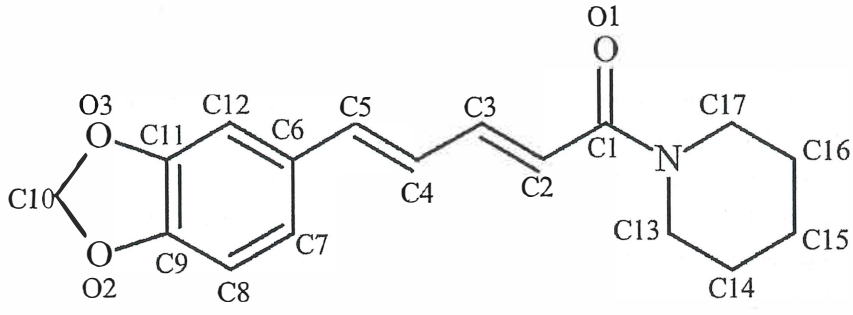

Figure 1

The chemical structure of piperine.

fig2.tif

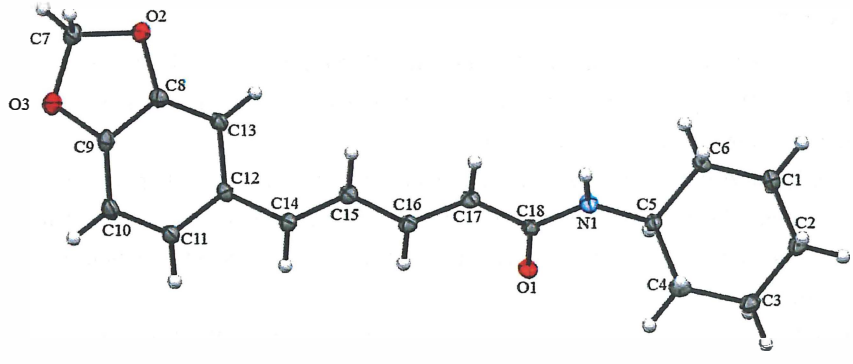

Figure 2

Displacement ellipsoid drawing at a 50% probability level of the asymmetric unit of (I).

fig3.tif

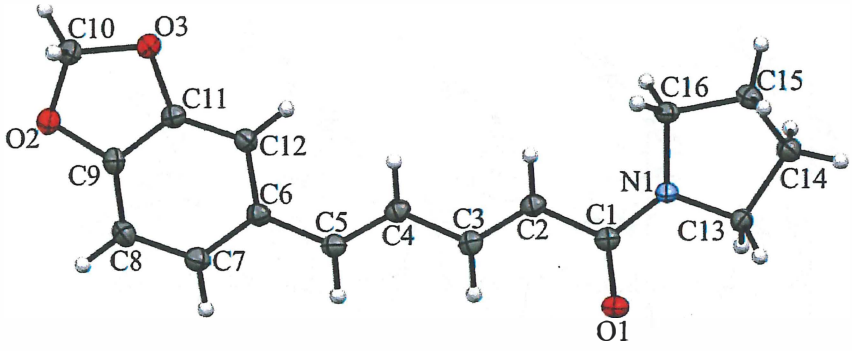

Figure 3

Displacement ellipsoid drawing at a 50% probability level of the asymmetric unit of (II).

fig4.tif

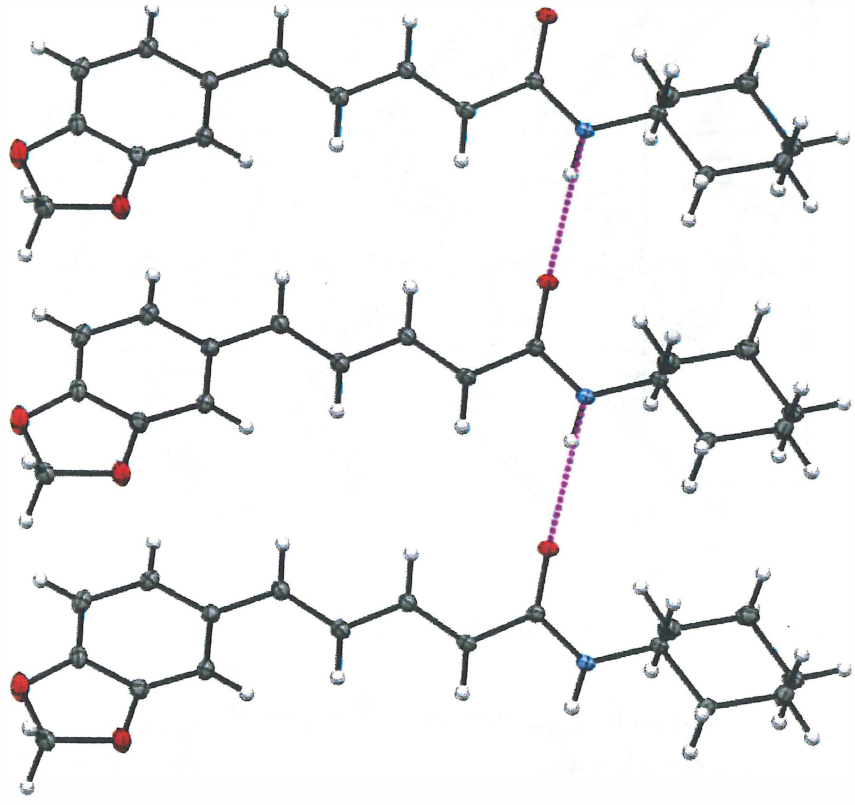

Figure 4

A view along the *c* axis direction of the crystal packing of (I). The N—H···O hydrogen bonds are drawn as dashed lines.

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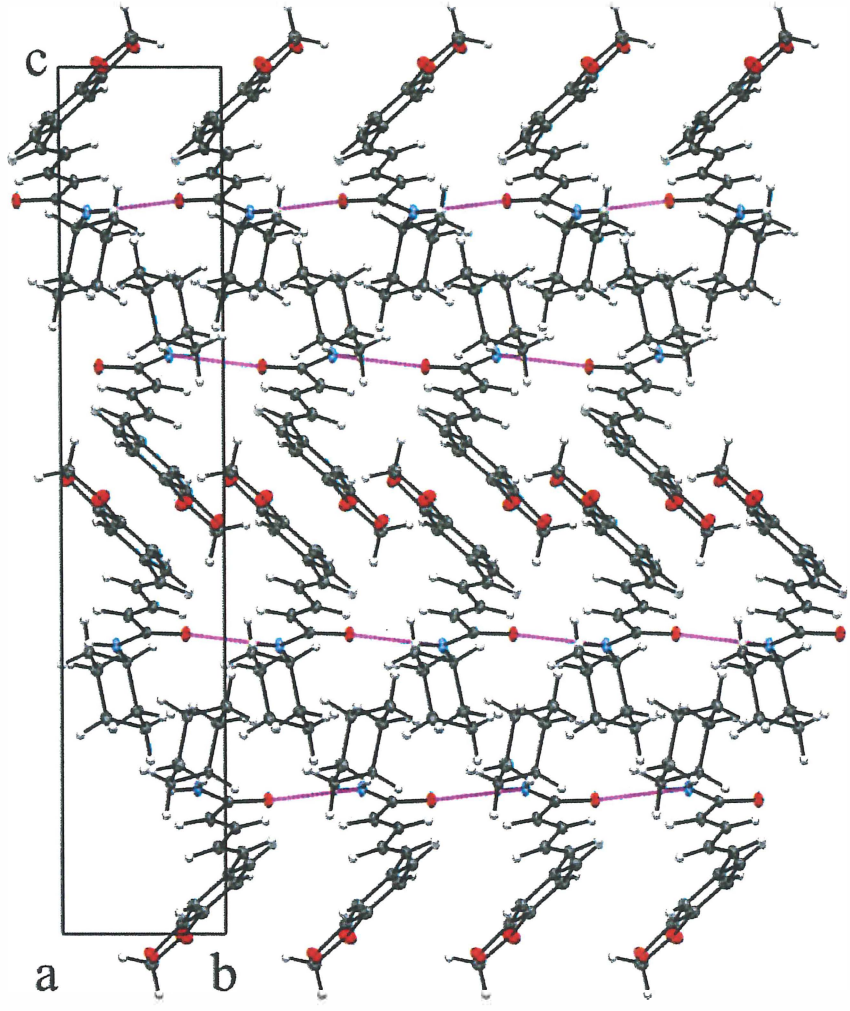

Figure 5

The unit cell packing for (I) viewed down [100] with hydrogen bonds drawn as dashed lines.

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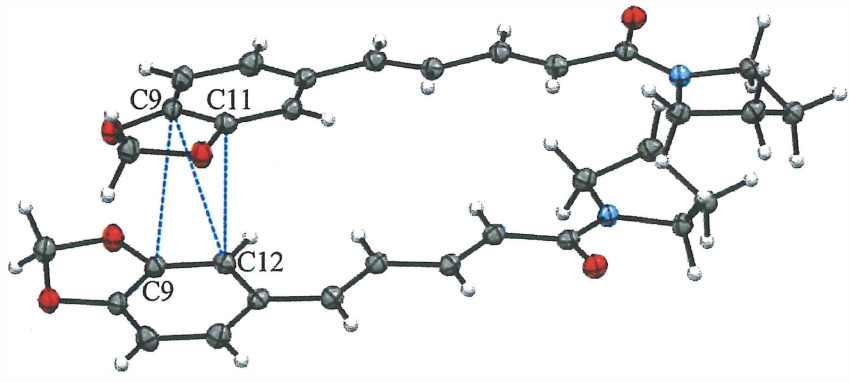

Figure 6

Fragment of the crystal of (II) showing close C···C contacts due to π-π stacking.

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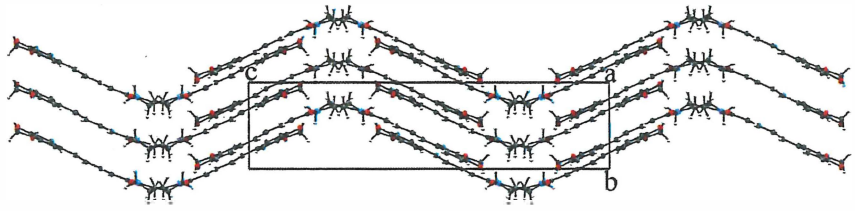

Figure 7

The unit cell packing for (II) viewed down [100].

Table 1

Key geometrical parameters (Å) for the title compounds and piperine polymorphs

	(I)	(II)	PIPINE10	PIPINE12	PIPINE13
Amide	C18—N1 (1.344)	C1—N1 (1.350)	C1—N1 (1.331)	C1—N1 (1.363)	C1—N1 (1.353)
	C18—O1 (1.242)	C1—O1 (1.243)	C1—O1 (1.218)	C1—O1 (1.235)	C1—O1 (1.482)
	C14—C15 (1.346)	C4—C5 (1.345)	C4—C5 (1.312)	C4—C5 (1.330)	C4—C5 (1.347)
Pentadiene	C15—C16 (1.444)	C3—C4 (1.441)	C3—C4 (1.437)	C3—C4 (1.440)	C3—C4 (1.442)
	C16—C17 (1.342)	C2—C3 (1.341)	C2—C3 (1.311)	C2—C3 (1.332)	C2—C3 (1.341)
	C17—C18 (1.479)	C1—C2 (1.480)	C1—C2 (1.473)	C1—C2 (1.477)	C1—C2 (1.482)
	C8—C9 (1.390)	C6—C7 (1.397)	C6—C7 (1.387)	C6—C7 (1.399)	C6—C7 (1.403)
	C8—C13 (1.371)	C6—C12 (1.412)	C6—C12 (1.396)	C6—C12 (1.414)	C6—C12 (1.412)
	C9—C10 (1.374)	C7—C8 (1.403)	C7—C8 (1.393)	C7—C8 (1.395)	C7—C8 (1.393)
Methylenedioxyphenyl	C10—C11 (1.402)	C8—C9 (1.369)	C8—C9 (1.343)	C8—C9 (1.360)	C8—C9 (1.371)
	C11—C12 (1.399)	C9—C11 (1.385)	C9—C11 (1.357)	C9—C11 (1.377)	C9—C11 (1.381)
	C12—C13 (1.412)	C11—C12 (1.364)	C11—C12 (1.364)	C11—C12 (1.370)	C11—C12 (1.367)
	C8—O2 (1.371)	C9—O2 (1.378)	C9—O2 (1.373)	c9—O2 (1.383)	C9—O2 (1.378)
	C9—O3 (1.370)	C11—O3 (1.376)	C11—O3 (1.362)	C11—O3 (1.383)	C11—O3 (1.383)
π-stacking close contacts		C9···C9 (3.268)		C8···C8 (3.110)	C9···C12 (3.327)
		C9···C12 (3.322)		C8···C8 (3.303)	
		C11···C12 (3.287)			

Table 2

Experimental details

	(I)	(II)
Crystal data		
Chemical formula	$C_{18}H_{21}NO_3$	$C_{16}H_{17}NO_3$
M_r	299.36	271.30
Crystal system, space group	Monoclinic, $P2_1/c$	Orthorhombic, $Pbca$
Temperature (K)	90	90
a, b, c (Å)	11.4982 (7), 5.0086 (3), 26.7240 (16)	11.8747 (10), 7.2485 (6), 30.392 (2)
α, β, γ (°)	90, 97.683 (2), 90	90, 90, 90
V (Å^3)	1525.22 (16)	2616.0 (4)
Z	4	8
Radiation type	Mo $K\alpha$	Mo $K\alpha$

μ (mm^{-1})	0.09	0.10
Crystal size (mm)	0.58 × 0.07 × 0.07	0.28 × 0.06 × 0.06
Data collection		
Diffractometer	Bruker D8 goniometer	Bruker D8 goniometer
Absorption correction	Multi-scan *SADABS2016*/2	Multi-scan *SADABS2016*/2
T_{min}, T_{max}	0.580, 0.747	0.666, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	27741, 4862, 4204	41504, 3506, 2193
R_{int}	0.066	0.128
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.725	0.685
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.049, 0.121, 1.07	0.050, 0.143, 1.05
No. of reflections	4862	3506
No. of parameters	202	182
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.42, −0.26	0.28, −0.26

Computer programs: SHELXT 2014/5 (Sheldrick, 2014), *SHELXL2018*/3 (Sheldrick, 2018).

Table 3

Hydrogen-bond geometry (Å, °) for (I)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O1^{i}	0.874 (16)	2.086 (16)	2.9547 (12)	172.8 (14)

Symmetry code: (i) $x, y+1, z$.

Acknowledgements

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