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Hydrogen-bonding and C—H···π interactions in ethyl 4-acetyl-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylate monohydrate

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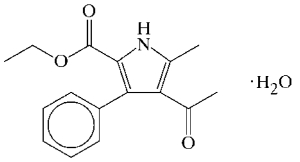
In the title compound, $C_{16}H_{17}NO_3{\cdot}H_2O$, the pyrrole ring is distorted slightly from ideal C_{2v} symmetry. Three strong hydrogen bonds link the substituted pyrrole and water molecules to form infinite chains, in which the hydrogen bonds form rings and chain patterns. Two intermolecular C—H···π interactions maintain the internal cohesion between these chains. The molecular structure differs slightly from that of the isolated molecule calculated by *ab initio* quantum-mechanical calculations. In the latter model, the non-H substituent atoms share the plane of the pyrrole ring, except for the phenyl group, which lies almost perpendicular to this plane.

Comment

Pyrroles are important compounds in many fields of research, from materials to pharmaceutical sciences. They are precursors of porphyrins and related macrocycles (Baltazzi & Krimen, 1963; Chadwick, 1990), and are also suitable for the assembly of Langmuir–Blodgett films when substituted with amphiphilic chains (Ramos Silva *et al.*, 2002*a*). In the pharmaceutical sciences, 2-(alkoxycarbonyl)pyrrole derivatives have attracted much interest, as they display a broad spectrum of biological activities, including analgesic, spasmolytic and even anti-HIV-1 activity (Artico *et al.*, 1996; Gribble, 1996). Some pyrrole alkaloid derivatives show anticancer properties because of their DNA-cleaving capabilities (Fürstner *et al.*, 2002). Following our work on the synthesis and structure determination of several substituted pyrroles (Paixão *et al.*, 2002; Ramos Silva *et al.*, 2000, 2002*a*,*b*), which are intended for incorporation at the β-pyrrole ring of porphyrins, the title compound, (I), was synthesized and an X-ray diffraction study was undertaken to clarify the conformation of the molecule. The results are presented here.



(I)

The weighted average of the absolute torsion angles of the pyrrole ring of (I) is 0.42 (6)°, indicating that the heterocyclic ring is almost perfectly planar. The internal ring angles range from 106.38 (10) to 110.47 (10)°, showing a small distortion from C_{2v} symmetry. The acetyl group at C4 and the ethoxycarbonyl group at C2 influence the π-electron distribution within the pyrrole ring, which results in a shortening of the C4—C15 and C2—C6 bond distances with respect to the usual value found for Csp^2—$C_{\rm aryl}$ bonds [1.483 (15) Å; Allen *et al.*, 1987]. The same effect accounts for the asymmetric nature of the two N—C bonds within the heterocyclic ring [usual average value 1.372 (16) Å; Allen *et al.*, 1987].

Atoms C15, C17 and C6 are approximately coplanar with the pyrrole ring and deviate by only −0.003 (2), −0.044 (2) and 0.046 (2) Å, respectively, from the least-squares plane of the pyrrole ring. On the other hand, atoms O1, O2 and O3 are tilted out of the ring plane by 0.219 (2), −0.137 (3) and 0.265 (3) Å, respectively. The angle between the least-squares planes of the phenyl and pyrrole rings is 76.93 (5)°. The ethoxycarbonyl group adopts an *anti* conformation with respect to the heterocyclic N atom. In this group, the C6—O2—C7—C8 torsion angle is 161.41 (15)°, which shows that atom C8 does not share the plane defined by atoms O1, C6, O2 and C7. The acetyl group is oriented so as to minimize the steric interaction between the C16 and C17 methyl groups.

Three strong hydrogen bonds link the molecules of (I) together into infinite one-dimensional chains and exhaust all donor sites of the substituted pyrrole and water molecules

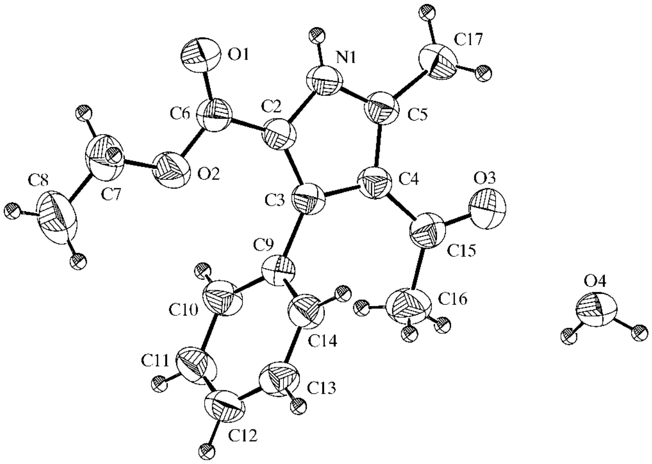


Figure 1
A view of the molecule of (I). Displacement ellipsoids are drawn at the 50% probability level.

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(Table 2). Looking at the conventional hydrogen-bonding pattern, one can recognize the formation of chains and rings which can be characterized using Etter's graph-set analysis (Bernstein *et al.*, 1995). At the basic binary level are centrosymmetric rings which can be described by the $R_4^4(14)$ motif and which involve the pyrrole N—H atom and one water H atom as donors, and the water and ethoxycarbonyl O atoms as acceptors. A larger ring is formed at the binary level when both of the water H atoms act as donors, thereby involving four molecules in the sequence water–substituted pyrrole–water–substituted pyrrole. This pattern has a graph-set motif of $R_4^4(20)$. Finally, chains with the motif $C_2^2(8)$ are formed by the N1—H1···O4$^{\rm i}$ and O4—H42···O3$^{\rm ii}$ hydrogen bonds [symmetry codes: (i) $1 - x, -y, 1 - z$; (ii) $-x, -y, 1 - z$].

Two C—H···π intermolecular interactions can also be observed in (I), thereby exhausting the capacity of the pyrrole π electrons to act as acceptors. In one of the interactions, phenyl atom C10 acts as the donor, while in the other, one of the methyl H atoms bonded to atom C17 is the donor. The H···*Cg* (*Cg* is the centroid of the pyrrole ring) distances are 2.84 and 2.90 Å, and the C—H···π angles are 147.3 and 150.6°, for the two types of bonds, respectively. The angles of approach of the H···*Cg* vector to the plane of the aromatic ring are 76.0 and 80.4°, respectively, and the perpendicular projections of the H atoms onto the pyrrole ring plane are 0.69 and 0.49 Å, respectively, from the centroid of the ring. In the former interaction, the H atom lies above the centre of the ring, with the C—H bond pointing towards a pyrrole ring C atom. This corresponds to a type III interaction, according to the classification of Malone *et al.* (1997). The latter interaction corresponds to a type I interaction, with the classical T-shaped geometry. It has been recognized that these weak C—H···π interactions play an appreciable role in determining the conformations of organic compounds (Umezawa *et al.*, 1999).

To investigate the effect of these intermolecular interactions on the conformation of the molecule of (I), we have carried out an optimization of the geometry of the isolated molecule by *ab initio* quantum-mechanical molecular orbital Hartree–Fock (MO-HF) calculations using the computer program *GAMESS* (Schmidt *et al.*, 1993). The atomic wave functions were expanded on a standard 3-21G basis set. The optimization was conducted starting from the experimental crystal structure geometry without imposing any symmetry constraints on the molecule. Each self-consistent field calculation was iterated until a $\Delta\rho$ of less than 10^{-5} bohr^{-3} was achieved. The final equilibrium geometry at the minimum energy had a maximum gradient in the internal coordinates of 10^{-5} Hartree bohr^{-1} or Hartree rad^{-1}. These results reproduce well the observed asymmetry in the pyrrole ring of (I). However, the minimum energy of the isolated molecule occurs for a geometry where the non-H substituent atoms are practically in the ring plane, except for the phenyl group, which lies perpendicular to the heterocyclic ring (C2—C3—C9—C14 = 88.9°; *cf.* Table 1). The twists observed in the solid state are therefore probably due to the hydrogen bonding with the water molecule and to the C—H···π intermolecular interactions.

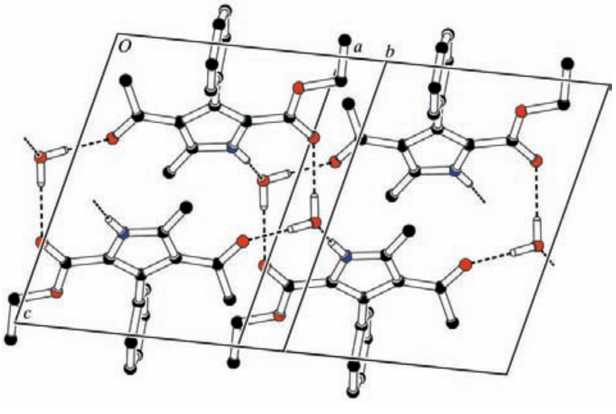

Figure 2
A view of the unit-cell packing in (I), with the hydrogen-bonding scheme shown as dashed lines. H atoms not participating in the hydrogen bonding have been omitted for clarity.

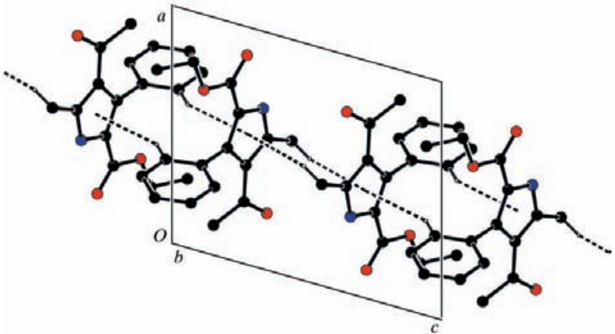

Figure 3
A view of the unit-cell packing in (I), with the C—H···π bonding scheme shown as dashed lines. H atoms not participating in the C—H···π interactions have been omitted for clarity.

Experimental

Ethyl oximinobenzoylacetate was prepared by the dropwise addition of an acetic acid solution (8 ml) of ethyl benzoylacetate (5 ml, 0.0025 mol) to aqueous sodium nitrite (3.00 g, 0.0044 mol; in 20 ml water) and then stirring for 72 h at 293 K. A mixture of acetylacetone (2.50 g, 0.0025 mol), Zn dust (5.00 g, 0.00724 mol) and glacial acetic acid (35 ml) was placed in a 500 ml round-bottomed flask fitted with a reflux condenser and a silica guard tube. After the dissolution of all reactants, the oxime (ethyl oximinobenzoylacetate) was added slowly. The mixture was stirred and heated under reflux for 4 h. The hot reaction mixture was decanted from the zinc sludge before zinc acetate or a new compound could crystallize. To promote precipitation of the pyrrole, several volumes of water were added slowly to the reaction. After a few hours, the product was filtered off, washed thoroughly with water and recrystallized from hot *n*-hexane. Compound (I) was obtained in 14% yield (m.p. 326–328 K). Spectroscopic analysis, IR (ν, cm^{-1}): 1523 (aromatic C—C), 1662 (C=O), 2965 (aromatic C—H), 3508 (N—H); ^{1}H NMR (CDCl$_3$, δ, p.p.m.): 1.00 (*t*, 3H, CH$_3$–CH$_2$O, *J* = 7.00 Hz), 1.82 (*s*, 3H, position 4 COCH$_3$), 2.58 (*s*, 3H, position 5 CH$_3$), 4.09 (*q*, 2H, OCH$_2$–CH$_3$, *J* = 7.25 Hz), 7.37 (*m*, 5H, position 3 aromatic H), 10.0 (*sl*, 1H, NH).

Crystal data

$C_{16}H_{17}NO_3 \cdot H_2O$
$M_r = 289.32$
Monoclinic, $P2_1/c$
$a = 8.9102$ (4) Å
$b = 17.1911$ (10) Å
$c = 10.4861$ (10) Å
$\beta = 105.859$ (8)°
$V = 1545.08$ (19) Å^3
$Z = 4$

$D_x = 1.244$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 18.9$–$35.4°$
$\mu = 0.74$ mm^{-1}
$T = 293$ (2) K
Prism, yellow
0.46 × 0.27 × 0.18 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{\min} = 0.853$, $T_{\max} = 0.876$
6215 measured reflections
3048 independent reflections
2726 reflections with $I > 2\sigma(I)$

$R_{\rm int} = 0.035$
$\theta_{\max} = 72.5°$
$h = -11 \rightarrow 11$
$k = 0 \rightarrow 21$
$l = -12 \rightarrow 12$
3 standard reflections
frequency: 180 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.110$
$S = 1.05$
3048 reflections
202 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0573P)^2 + 0.2709P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.19$ e Å^{-3}
$\Delta\rho_{\min} = -0.20$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0073 (7)

Table 1
Selected geometric parameters (Å, °).

O1—C6	1.2122 (16)	N1—C2	1.3836 (15)
O2—C6	1.3255 (15)	C2—C6	1.4569 (18)
N1—C5	1.3371 (16)	C4—C15	1.4617 (18)
C5—N1—C2	110.47 (10)	C2—C3—C4	106.38 (10)
N1—C2—C3	108.09 (10)	C5—C4—C3	107.02 (11)
N1—C2—C6	118.96 (11)		
C3—C4—C5—N1	0.22 (13)	C2—C3—C9—C10	78.88 (16)
C5—C4—C15—O3	15.1 (2)	C4—C3—C9—C10	−104.56 (15)
C3—C4—C15—O3	−165.61 (14)	C2—C3—C9—C14	−101.68 (14)
C5—C4—C15—C16	−162.52 (14)	C6—O2—C7—C8	161.41 (15)
C3—C4—C15—C16	16.8 (2)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O4$^{\rm i}$	0.86	2.10	2.8966 (14)	155
O4—H42···O3$^{\rm ii}$	0.92 (2)	1.92 (2)	2.8386 (16)	173 (2)
O4—H41···O1$^{\rm iii}$	0.87 (2)	2.06 (2)	2.9077 (16)	167 (2)

Symmetry codes: (i) $1 - x, -y, 1 - z$; (ii) $-x, -y, 1 - z$; (iii) $x - 1, y, z$.

The methyl H atoms were constrained to an ideal geometry, with C—H distances of 0.96 Å and $U_{\rm iso}({\rm H}) = 1.5U_{\rm eq}({\rm C})$, but were allowed to rotate freely about the C—C bonds. All remaining H atoms were placed in geometrically idealized positions, with C—H distances in the range 0.93–0.97 Å and N—H distances of 0.86 Å, and constrained to ride on their parent atoms with $U_{\rm iso}({\rm H}) = 1.2U_{\rm eq}$(parent atom), with the exception of the H atoms of the water molecule, the positions and atomic displacement parameters of which were refined freely. Examination of the crystal structure with *PLATON* (Spek, 2002) showed that there are no solvent-accessible voids in the crystal lattice.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1152). Services for accessing these data are described at the back of the journal.

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