Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Three methoxy-substituted diethyl 4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate compounds

Sara K. Metcalf and Elizabeth M. Holt*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078, USA
Correspondence e-mail: betsy@biochem.okstate.edu

Received 29 October 1999
Accepted 27 July 2000

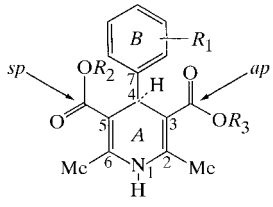
Diethyl 4-(2,5-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, $C_{21}H_{27}NO_6$, (I), diethyl 4-(3,4-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, $C_{21}H_{27}NO_6$, (II), and diethyl 2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate, $C_{22}H_{29}NO_7$, (III), crystallize with hydrogen-bonding networks involving the H atom bonded to the N atom of the 1,4-dihydropyridine ring and carbonyl O atoms in (I) and (II). Unusually, (III) shows O atoms of methoxy groups serving as hydrogen-bond acceptors.

Comment

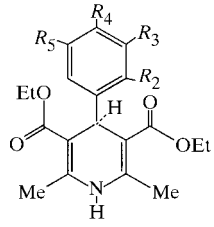
1,4-Dihydropyridine compounds (DHPs) are widely prescribed for treatment of hypertension and heart defibrilation. Their activity is believed to arise from binding with a receptor site located in the α_1 subunit of the L-type voltage gated channels present in skeletal and cardiac muscle (Tanabe *et al.*, 1987).

Early molecular modeling work involving *SYBYL* (Tripos Scientific, 1982) did not permit conformational flexibility of the drug or the receptor site. A static molecule was fitted into a static receptor site. Newer software (*FlexiDocK*; Tripos Scientific, 1998; *GOLD*; Jones *et al.*, 1997) permits rotation about specified bonds of both drug and receptor site groups, however, results using the newer programs do not agree with each other nor do they support the results of docking studies carried out with *SYBYL*. Thus, one seeks a knowledge of DHP interactions with polar environments as a basis for evaluation of the molecular modeling results. For DHP molecules (see Scheme), structure–activity relationship studies (Triggle *et al.*, 1989) have indicated specific conformational details which correlate with high binding efficiency. (i) The *A* ring should be in a flattened boat form (the total planarity achieved by making ring *A* aromatic is detrimental to activity; Rowan & Holt, 1995, 1996*a*). (ii) The *B* ring should be in a pseudo-axial position relative to the floor of the boat. (iii) Rings *A* and *B* should display an orthogonal relationship. (iv) Electron-withdrawing substituents on the *B* ring improve activity in the order *o*>*m*>>*p*. (v) Substituents on the *B* ring should be in the 'prow' position and not projecting backwards over the *B* ring. Furthermore, the conformation of the carbonyl groups of the ester moieties at C3 and C5 of ring *A* may be either *ap* or *sp* relative to the near double bond of the DHP ring (Scheme).

The conformation of a molecule in the crystal structure does not represent *a priori* the conformation of the molecule in its receptor site. The environment in the crystalline solid is surely different from that of the molecule in its receptor site. However, the process of crystallization, of maximizing hydrogen bonding, dipole–dipole and van der Waals type interactions within the solid must mimic the behavior of a molecule approaching its docking site. Both are processes of molecular recognition. Thus it is worthwhile to examine patterns of molecular interaction in the crystal as a guide to what to expect of the docked molecule. Particularly useful to this end are examinations of series of structures containing similar *B* ring substituents because they offer multiple observations of the molecule adapting to its environment. We have synthesized three DHP molecules with multiple methoxy groups substituted on the *B* ring: (I), (II) and (III).



DHP



	R_2	R_3	R_4	R_5
(I)	OMe	H	H	OMe
(II)	H	OMe	OMe	H
(III)	H	OMe	OMe	OMe

DHP molecules with methoxy substituents on the *B* ring are not unknown in the literature. For example, the synthesis of (II) has been reported (Shirodkar & Varadarajan, 1996; Ohsumi *et al.*, 1995). However, the solid-state structures of (I), (II) and (III) are unreported. Previous work has shown that esterification groups should be small (Rowan & Holt, 1996*b*, 1997; Rowan, 1996) for optimum activity, thus we have synthesized molecules with ethoxycarbonyl groups at C3 and C5.

Compounds (I), (II) and (III) crystallize with the *A* rings in flattened boat form. The sum of the absolute values of the six successive torsional angles of the *A* ring may be used to quantify the flatness of these rings, the total being zero if the ring is totally flat and 240° if the six-membered ring is in classic boat form. The sums of the absolute values of the torsion angles for the *A* ring in (I), (II) and (III) are 91.0, 102.5 and 76.5°, respectively. Thus all three structures display significant flattening of the boat conformation of the *A* ring.

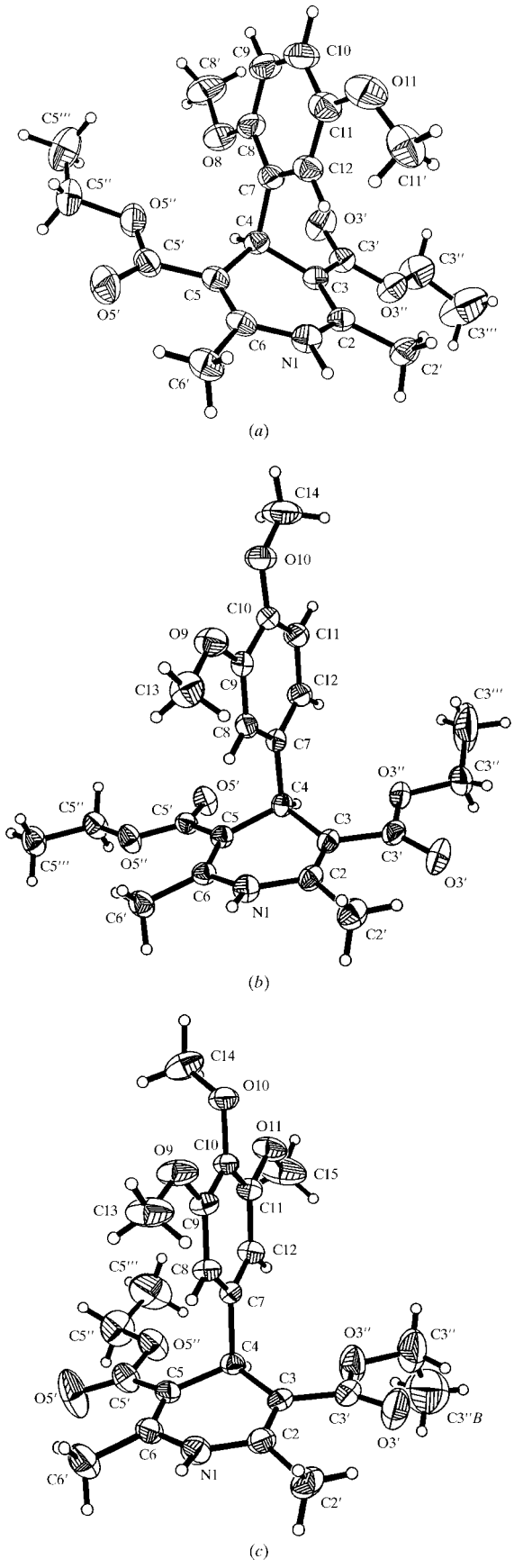


Figure 1
Projection views of compounds (*a*) (I), (*b*) (II) and (*c*) (III) (ellipsoids are shown at the 50% probability level).

All three structures show near orthogonality between the *B* ring and the base of the flattened boat. The atoms C7–C12 of ring *B* subtend angles of 88.3 for (I), 89.1 for (II) and 87.3° for (III) with the atoms C2, C3, C5 and C6 of the base of the boat conformation of the *A* ring.

The three structures show near coplanarity of the carbonyl C═O bonds with the conjugated double bond of the DHP ring. The torsion angles C6—C5—C5′—O5′ and C2—C3—C3′—O3′ are −0.2 (4) and −176.2 (3)° for (I), −168.1 (3) and 1.6 (5)° for (II), and 2.6 (8) and −15.5 (7)° for (III). These torsional angles reflect conformations at C5 and C3, respectively, of *sp, ap* for (I), *ap, sp* for (II) and *sp, sp* for the molecules of (III).

We have previously noted that carbonyl groups which are not involved in hydrogen bonding exist in *sp* conformation (Caignan & Holt, 2000; Caignan *et al.*, 2000), whereas the molecule responds to a hydrogen-bonding opportunity by rotating about the C3—C3′ or C5—C5′ bond involved to present the carbonyl group in *ap* conformation. We have observed as a general rule that carbonyl groups not involved in hydrogen bonding crystallize in *sp* conformation whereas those which do serve as hydrogen-bond acceptors are seen in *ap* conformation. Thus, in (I), the carbonyl group at C3 is seen in *ap* conformation, and is hydrogen bonded to the H atom of the amino group of an adjacent molecule [N1···O3′($x, \frac{1}{2}-y, -\frac{1}{2}+z$) 2.910 (3), H1*A*···O3′ 1.910 Å, N—H1*A*···O3′ 163.4°]. In (II), the carbonyl group C5′—O5′ is seen in *ap* conformation [N1···O5′($x, -1+y, z$) 3.048 (4), H1*A*···O5′ 2.153 Å, N—H1*A*···O5′ 172.6°]. Compound (III) displays *sp, sp* orientation and neither carbonyl O atom serves as an acceptor in a hydrogen bond. Instead, H1*A* is involved in a bifurcated hydrogen bond with the methoxy O atoms of the *para*- and *meta*-substituted methoxy groups of a neighboring molecule [N1···O9($-x, \frac{1}{2}+y, \frac{1}{2}-z$) 3.189 (5), H1*A*···O9 2.427 Å, N1—H1*A*···O9 142.6° and N1···O10($-x, \frac{1}{2}+y, \frac{1}{2}-z$) 3.219 (5), H1*A*···O10 2.415 Å, N1—H1*A*···O10 148.9°]. Our generalizations, thus, hold true for structures (I), (II) and (III) as a group. Electron pairs of the substituents on the aromatic *B* rings are involved in hydrogen bonding only for (III) in the crystal. Ether O atoms of the ester groups have not been observed to be involved.

The orientation of substituents on the *B* ring is of interest. For (I), the *ortho*-methoxy substituent is in the 'prow' position, directed away from the *A* ring. The *meta* substituent is thus over the *A* ring. In (II), the *meta* methoxy substituent is back over the *A* ring. In (III), the hydrogen-bonded *meta* substituent is back over the *A* ring, whereas the non-hydrogen-bonded substituent is in the 'prow' position. These observations suggest that *ortho* substituents on the *B* ring prefer a 'prow' position for spatial reasons whereas the *meta* substituents have no preference. The observation of hydrogen bonding to that methoxy O atom (and simultaneously to its *para* neighbor) in (III) is unexpected and at variance with the expectation that DHP molecules should dock with substituents involved in hydrogen bonding on the 'prow' side of the molecule for maximum hydrogen bonding with the receptor site.

Experimental

For (I), an ethanol solution (40 ml) of 2,5-dimethoxybenzaldehyde (6.4 g, 0.0386 mol), ethyl acetoacetate (10.036 g, 0.0772 mol), and ammonium hydroxide (2.027 g, 0.0579 mol) was refluxed for 6 h. Acetonitrile was added to the resulting immiscible liquids, following which all solvent was removed under reduced pressure. The remaining solid was recrystallized from methanol giving large yellow cubes.

For (II), an ethanol solution (40 ml) of 3,4-dimethoxybenzaldehyde (6.4 g, 0.0386 mol), ethyl acetoacetate (10.036 g, 0.0772 mol) and ammonium hydroxide (2.027 g, 0.0579 mol) was refluxed for 6 h. The resulting solid was collected by filtration and heated in acetonitrile. Cooling of the resulting solution yielded large yellow cubes.

For (III), a solution of 3,4,5-trimethoxybenzaldehyde (4.704 g, 0.024 mol), ethyl acetoacetate (6.24 g, 0.048 mol), and ammonium hydroxide (1.26 g, 0.036 mol) was refluxed in ethanol for 5 h and the solvent removed. The remaining solid was heated in ethanol and the solution allowed to cool to room temperature, whereupon large colorless rhombs formed.

Compound (I)

Crystal data

$C_{21}H_{27}NO_6$
$M_r = 389.4$
Monoclinic, $P2_1/c$
$a = 8.268\ (4)$ Å
$b = 17.802\ (7)$ Å
$c = 14.707\ (8)$ Å
$\beta = 93.32\ (2)^\circ$
$V = 2161\ (2)$ Å^3
$Z = 4$
$D_x = 1.196$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 33 reflections
$\theta = 4.4$–22.2°
$\mu = 0.087$ mm^{-1}
$T = 301$ K
Cube, yellow
0.1 × 0.1 × 0.1 mm

Data collection

Syntex $P4$ four-circle diffractometer
$\theta/2\theta$ scans
7927 measured reflections
6302 independent reflections
2411 reflections with $I > 2\sigma(I)$
$R_{int} = 0.059$
$\theta_{max} = 30.01^\circ$
$h = -1 \rightarrow 11$
$k = -25 \rightarrow 1$
$l = -20 \rightarrow 20$
3 standard reflections
every 97 reflections
intensity decay: <1%

Refinement

Refinement on F^2
$R(F) = 0.071$
$wR(F^2) = 0.250$
$S = 1.01$
6302 reflections
254 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1102P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.04$
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}

Compound (II)

Crystal data

$C_{21}H_{27}NO_6$
$M_r = 389.4$
Monoclinic, $P2_1/n$
$a = 8.462\ (6)$ Å
$b = 7.637\ (6)$ Å
$c = 33.44\ (2)$ Å
$\beta = 94.48\ (2)^\circ$
$V = 2154\ (3)$ Å^3
$Z = 4$
$D_x = 1.198$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 97 reflections
$\theta = 4.17$–12.72°
$\mu = 0.088$ mm^{-1}
$T = 301$ K
Cube, yellow
0.1 × 0.1 × 0.1 mm

Data collection

Syntex $P4$ four-circle diffractometer
$\theta/2\theta$ scans
8355 measured reflections
6261 independent reflections
2644 reflections with $I > 2\sigma(I)$
$R_{int} = 0.062$
$\theta_{max} = 30.09^\circ$
$h = -1 \rightarrow 10$
$k = -10 \rightarrow 1$
$l = -47 \rightarrow 47$
3 standard reflections
every 97 reflections
intensity decay: <1%

Refinement

Refinement on F^2
$R(F) = 0.085$
$wR(F^2) = 0.263$
$S = 1.01$
6261 reflections
253 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1016P)^2 + 1.0333P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max} = 0.21$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}

Compound (III)

Crystal data

$C_{22}H_{29}NO_7$
$M_r = 419.46$
Orthorhombic, $P2_12_12_1$
$a = 8.714\ (8)$ Å
$b = 16.167\ (14)$ Å
$c = 16.948\ (14)$ Å
$V = 2388\ (5)$ Å^3
$Z = 4$
$D_x = 1.164$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 46 reflections
$\theta = 4.08$–12.84°
$\mu = 0.087$ mm^{-1}
$T = 301$ K
Rhomb, colorless
0.3 × 0.2 × 0.2 mm

Data collection

Syntex $P4$ four-circle diffractometer
$\theta/2\theta$ scans
4844 measured reflections
4634 independent reflections
2616 reflections with $I < 2\sigma(I)$
$R_{int} = 0.041$
$\theta_{max} = 30.03^\circ$
$h = -12 \rightarrow 1$
$k = -22 \rightarrow 1$
$l = -1 \rightarrow 23$
3 standard reflections
every 97 reflections
intensity decay: <1%

Refinement

Refinement on F^2
$R(F) = 0.069$
$wR(F^2) = 0.220$
$S = 1.00$
4634 reflections
270 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1102P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.045$
$\Delta\rho_{max} = 0.34$ e Å^{-3}
$\Delta\rho_{min} = -0.28$ e Å^{-3}

For all three compounds, the H atoms on the C2′ and C6′ methyl groups display disorder over two sets of positions. Each set of H-atom positions was included in the final refinement with 50% occupancy. For (III), the terminal methyl C atom of the ethyl ester group at C3 displays disorder over two positions, C3′′*A* and C3′′*B*, which were treated as half-populated and isotropic. The tetrahedral methylene C3′′ atom has one ordered H atom clearly visible and a second one which is disordered over two sites depending upon which version of the terminal methyl C atom is present. This H atom was not located. H-atom positions were calculated using idealized geometry and a C—H distance of 0.97 Å.

For all compounds, data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* (Siemens, 1990); software used to prepare material for publication: *SHELXL*97.

SKM acknowledges the support of the Wentz Foundation in the form of a Wentz Undergraduate Research Fellowship.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1251). Services for accessing these data are described at the back of the journal.

References

Caignan, G. A. & Holt, E. M. (2000). *Z. Kristallogr.* **215**, 122–126.
Caignan, G. A., Metcalf, S. K. & Holt, E. M. (2000). *Z. Kristallogr.* Submitted.
Jones, G., Willett, P., Glen, R. C., Leach, A. R. & Taylor, R. (1997). *J. Mol. Biol.* **267**, 727–748.
Ohsumi, K., Ohishi, K., Morinaga, Y., Nakagawa, R., Suga, Y., Sekiyama, T., Akiyama, Y., Tsuji, T. & Tsuruo, T. (1995). *Chem. Pharm. Bull.* **43**, 818–828.
Rowan, K. R. (1996). PhD thesis, Oklahoma State University, USA.
Rowan, K. R. & Holt, E. M. (1995). *Acta Cryst.* C**51**, 2554–2559.
Rowan, K. R. & Holt, E. M. (1996*a*). *Acta Cryst.* C**52**, 1565–1570.
Rowan, K. R. & Holt, E. M. (1996*b*). *Acta Cryst.* C**52**, 2207–2212.
Rowan, K. R. & Holt, E. M. (1997). *Acta Cryst.* C**53**, 257–261.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Shirodkar, P. Y. & Varadarajan, S. (1996). *Indian J. Heterocycl. Chem.* **6**, 155–156.
Siemens (1990). *XP*. Version 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Siemens (1991). *XSCANS User's Manual.* Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Tanabe, T., Takeshima, H., Mikami, A., Flockerzi, V., Takahashi, H., Kangawa, K., Kojima, M., Matsou, H., Hirose, T. & Numa, S. (1987). *Nature*, **328**, 313–318.
Triggle, D. J., Langs, D. A. & Janis, R. A. (1989). *Med. Res. Rev.* **9**, 123–180.
Tripos Scientific (1982). *SYBYL*. Tripos Scientific, St Louis, USA.
Tripos Scientific (1998). *FlexiDocK*. Tripos Scientific, St Louis, USA.