Orthorhombic
$Pna2_1$
a = 12.5684 (9) Å
b = 14.4723 (10) Å
c = 6.1016 (9) Å
V = 1109.8 (2) Å^3
Z = 4
D_x = 1.354 Mg m^{-3}
D_m not measured

Cell parameters from 25 reflections
θ = 10.93–17.45°
μ = 0.077 mm^{-1}
T = 150 (2) K
Block
0.50 × 0.25 × 0.25 mm
Red

Data collection

Enraf–Nonius CAD-4T diffractometer
ω scans
Absorption correction: none
2782 measured reflections
1391 independent reflections
1260 reflections with $I > 2\sigma(I)$

R_{int} = 0.036
θ_{max} = 27.44°
$h = -16 \rightarrow 16$
$k = -18 \rightarrow 0$
$l = -7 \rightarrow 0$
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.089
S = 1.024
1391 reflections
163 parameters
H-atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0574P)^2 + 0.0850P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.183 e Å^{-3}
$\Delta\rho_{min}$ = −0.189 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected bond lengths (Å)*

C1—C15	1.383 (2)	C9—C10	1.406 (3)
C1—C2	1.394 (3)	C9—C17	1.488 (3)
C2—C3	1.383 (3)	C10—C16	1.354 (2)
C3—C4	1.406 (3)	C10—C11	1.396 (3)
C4—C5	1.383 (3)	C11—C12	1.380 (3)
C5—C15	1.431 (3)	C11—C18	1.491 (2)
C5—C6	1.487 (2)	C12—C13	1.444 (3)
C6—C7	1.387 (3)	C13—C14	1.383 (3)
C6—C16	1.406 (3)	C14—C16	1.404 (3)
C7—C8	1.448 (3)	C14—C15	1.491 (3)
C8—C9	1.385 (3)	C17—C18	1.362 (3)

The absolute structure was assigned arbitrarily. A check for additional higher symmetry with *ADDSYM* in *PLATON* (Spek, 1998) did not indicate any missed symmetry.

Data collection: locally modified *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *SET4* (Boer & Duisenberg, 1984). Data reduction: *HELENA* (Spek, 1997). Program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1997). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *PLATON*. Software used to prepare material for publication: *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1006). Services for accessing these data are described at the back of the journal.

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Methyl 1,4,5,6-tetrahydro-2-methyl-4-(2-nitrophenyl)-6-oxopyridine-3-carboxylate

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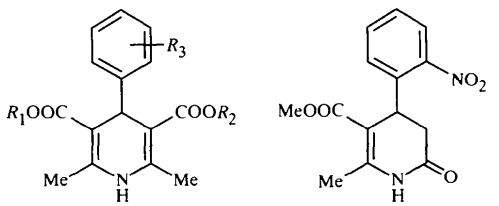
Abstract

The title compound, $C_{14}H_{14}N_2O_5$, represents a tetrahydropyridin-2-one analogue of 1,4-dihydropyridine-type calcium antagonists, and was selected for a crystal structure determination in order to clarify some aspects

of structure–activity relationships. The conformation of the central heterocyclic ring was found to be close to the flat-boat conformation characteristic of the similar ring in 1,4-dihydropyridines, the only difference being in the position and orientation of the NH moiety.

Comment

1,4-Dihydropyridines, (I), *i.e.* compounds having a substituted phenyl ring and one or two ester groups bonded to a 1,4-dihydropyridine nucleus, are known as the most potent class of calcium-channel antagonists widely used in clinical medicine. However, these compounds have a serious disadvantage, in that their plasma half-lives are relatively short, due to their rapid metabolic oxidation to inactive pyridines. In an effort to prolong the duration of action, new drugs based on some other heterocyclic rings have been developed (Rovnyak *et al.*, 1992; Kettmann *et al.*, 1996). Although the heterocyclic nucleus in such compounds was found to be stable against oxidation, their vasorelaxant activity was reported to be generally low compared with molecules (I). However, this was not the case for the tetrahydropyridin-2-one derivative, (II), which showed the same level of activity as the corresponding single-ester derivative of (I) in both *in vitro* and radio-ligand binding experiments (Kettmann *et al.*, 1996). To gain further insight into these structure–activity relationships, we undertook an X-ray analysis of the title compound, (II), and compared the results with those obtained previously for 1,4-dihydropyridines.



(I) (II)

The molecular structure of (II) is depicted in Fig. 1. As shown in Table 1, the N1—C2 bond [1.343 (4) Å] is considerably shorter than the N1—C6 bond [1.392 (4) Å], indicating that the lone pair of electrons on N1 is involved in conjugation with the carbonyl group, as is typically found in amides. Other bond lengths correspond to pure single and double bonds, *i.e.* they are not affected by conjugation.

As noted above, the aim of this study was to explore the structural basis for the equipotency of the present compound, (II), with the corresponding single-ester derivative of (I). It is known that the activity is dependent on the relative disposition of the key pharmacophoric elements, *i.e.* the NH moiety, the 4-phenyl ring and the ester group(s), which in turn are determined by the conformation of the central heterocyclic ring (Goldmann & Stoltefuss, 1991). Therefore, it is of interest to compare the conformation of the heterocyclic ring in compounds (I) and (II).

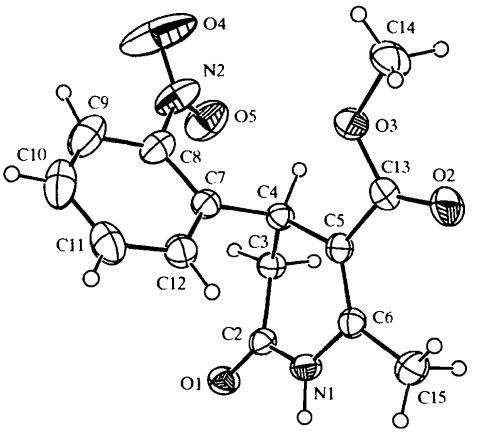


Fig. 1. View of the title molecule, showing the labelling of the non-H atoms. Displacement ellipsoids are shown at the 35% probability level and H atoms are drawn as small circles of an arbitrary radius.

As revealed by a number of X-ray structure determinations (Goldmann & Stoltefuss, 1991; Allen & Kennard, 1993), the dihydropyridine ring in molecules (I) exists in a flat-boat conformation, with N1 and C4 as the out-of-plane atoms. In the title molecule, (II), the heterocyclic ring is puckered in such a manner that the four atoms, C4, C5, C6 and N1, are coplanar to within 0.014 (2) Å, and the atoms C2 and C3 are displaced from this plane on the same side, with out-of-plane displacements of 0.251 (4) and 0.743 (4) Å, respectively. However, to make the comparison of the two molecules more feasible, it is advantageous to treat the conformation of the ring in terms of the 'boat' terminology; thus, calculation of the least-squares plane through atoms C2, C3, C5 and C6 has shown that these atoms are 'coplanar' to within 0.133 (2) Å, and the atoms N1 and C4 are displaced from this plane by 0.018 (3) and 0.519 (4) Å, respectively. Thus, the conformation of the ring at the C4 side in (II) resembles that found in molecules (I); as a result, one would expect similar disposition of the phenyl and ester groups in molecules (I) and (II). Indeed, due to the pseudoaxial position of the nitrophenyl substituent (Fig. 1), the phenyl ring is oriented perpendicularly with respect to the tetrahydropyridine ring [dihedral angle 89.5 (2)°]. The conformation of the 4-(2-nitrophenyl) substituent on the exocyclic C4—C7 bond is synperiplanar, *i.e.* the nitro group is on the same side as the H atom on C4. The ester group (atoms C13, O2, O3, C14) lies approximately in the plane of the C5=C6 double bond [torsion angle C6—C5—C13—O2 = 14.0 (5)°], with the carbonyl bond oriented *cis* with respect to this double bond. Similar features have also been observed for compounds (I) (Goldmann &

Stoltefuss, 1991). Thus, owing to the 'flattening' of the heterocyclic ring at the N1 side in molecule (II), the only difference between (I) and (II) concerns the position and orientation of the N—H bond relative to the other pharmacophoric elements. Obviously, in view of the pharmacological equivalency of molecules (I) and (II), such a small distortion of the NH moiety can be easily accommodated at the receptor site. The crystal packing is dominated by a hydrogen bond at N1—H1···O1($2-x$, $1-y$, $-z$) [N···O 2.867 (3), H···O 1.96 Å, N—H···O 171°]. Thus, the molecules associate in pairs to form hydrogen-bonded dimers across the centre of symmetry at $(0,\frac{1}{2},0)$. The dimers are packed by van der Waals interactions.

Experimental

The title compound was synthesized by condensation of methyl acetoacetate with Meldrum's acid and 2-nitrobenzaldehyde in the presence of ammonium acetate, as described in detail elsewhere (Svetlík *et al.*, 1990). The reaction mixture was refluxed in ethanol for 6 h. The oily residue obtained after removal of the solvent was treated with methanol. Separated crystals were filtered off and recrystallized from methanol.

Crystal data

$C_{14}H_{14}N_2O_5$
$M_r = 290.27$
Triclinic
$P\bar{1}$
$a = 7.328\,(8)$ Å
$b = 8.729\,(9)$ Å
$c = 11.513\,(11)$ Å
$\alpha = 95.83\,(7)°$
$\beta = 107.27\,(8)°$
$\gamma = 97.34\,(7)°$
$V = 689.9\,(13)$ Å^3
$Z = 2$
$D_x = 1.395$ Mg m^{-3}
$D_m = 1.40\,(1)$ Mg m^{-3}
D_m measured by flotation in bromoform–hexane

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 15 reflections
$\theta = 8$–$19°$
$\mu = 0.108$ mm^{-1}
$T = 293\,(2)$ K
Prism
0.35 × 0.20 × 0.15 mm
Light yellow

Data collection

Syntex $P2_1$ diffractometer
$\theta/2\theta$ scans
Absorption correction: none
3345 measured reflections
3193 independent reflections
1612 reflections with $I > 2\sigma(I)$
$R_{int} = 0.031$

$\theta_{max} = 27.56°$
$h = 0 \rightarrow 9$
$k = -11 \rightarrow 11$
$l = -14 \rightarrow 14$
2 standard reflections
frequency: 100 min
intensity decay: none

Refinement

Refinement on F^2
$R = 0.060$
$wR = 0.123$
$S = 1.182$
3193 reflections
191 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.0838P)^2 + 0.0437P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = -0.005$
$\Delta\rho_{max} = 0.257$ e Å^{-3}
$\Delta\rho_{min} = -0.271$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.020 (6)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

N1—C2	1.343 (4)	C13—O2	1.194 (4)
N1—C6	1.392 (4)	C13—O3	1.331 (4)
C2—O1	1.209 (4)	N2—O5	1.184 (4)
C8—N2	1.458 (5)	N2—O4	1.189 (4)
C2—N1—C6	124.6 (2)	O2—C13—O3	122.2 (3)
O1—C2—N1	121.6 (3)	O2—C13—C5	127.3 (3)
O1—C2—C3	123.6 (3)	O3—C13—C5	110.5 (3)
N1—C2—C3	114.8 (3)	O5—N2—O4	122.9 (4)
C6—C5—C4	120.5 (3)	O5—N2—C8	119.2 (3)
C13—C5—C4	117.9 (2)	O4—N2—C8	117.7 (4)
C5—C6—N1	119.0 (2)		
C6—N1—C2—O1	−174.8 (3)	C2—N1—C6—C5	15.9 (4)
C6—N1—C2—C3	7.7 (4)	C5—C4—C7—C12	−31.9 (3)
C2—C3—C4—C5	49.7 (3)	C3—C4—C7—C12	91.3 (3)
C3—C4—C5—C6	−28.8 (3)	C6—C5—C13—O2	14.0 (5)
C4—C5—C6—N1	−3.2 (4)	C7—C8—N2—O5	41.0 (5)

All H atoms were located in difference maps and fixed during refinement, with U_{iso} set to 1.2 times the U_{eq} of the parent atom.

Data collection: Syntex $P2_1$ software. Cell refinement: Syntex $P2_1$ software. Data reduction: *XP*2$_1$ (Pavelčík, 1987). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1228). Services for accessing these data are described at the back of the journal.

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