

## *N,N*-Diethyl-2,6,6-trimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide

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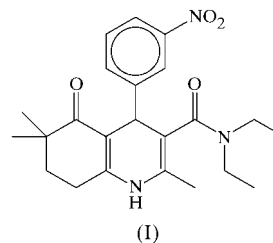
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The title compound, C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>, has potential calcium modulatory properties. The conformation of the 1,4-dihydropyridine ring is unusual in that it is planar, instead of the usual shallow boat. The 3-nitrophenyl substituent is in the synperiplanar orientation with respect to the dihydropyridine ring plane. The oxocyclohexene ring has a distorted envelope conformation, with the out-of-plane atom being disordered on opposite sides of the ring plane. The molecules are linked into chains by intermolecular hydrogen bonds.

### Comment

Calcium-channel blocking agents inhibit smooth muscle contraction and are used as antihypertensive drugs (Flaim & Zelic, 1982; Janis & Triggle, 1984). Although these drugs are represented by a diverse group of compounds, 1,4-dihydropyridine (1,4-DHP) derivatives are a well known class. Nifedipine is the most popular 1,4-DHP-based drug and many modifications are being made to the nifedipine molecule in attempts to obtain more active drugs. Active compounds have been produced by the introduction of the 1,4-DHP moiety in condensed systems and the replacement of the ester group in the nifedipine molecule with various carbonyl-containing groups, such as amides, nitriles and the acetyl group (Loev *et al.*, 1974; Rose, 1989, 1990*a,b*; Rose & Dräger, 1992; Ogawa *et al.*, 1993; Şafak *et al.*, 1995). Those derivatives that contain a chiral centre at the 4-position of the 1,4-DHP ring of the molecule also possess calcium modulatory properties. The activity depends on an axial aromatic ring, the plane of which bisects the N1...C4 axis of the 1,4-DHP ring, as well as on the conformation of the 1,4-DHP ring itself, which is usually that of a shallow boat (Goldmann & Stoltefuss, 1991; Linden *et al.*, 1998). The activity may be agonist or antagonist and varies with stereochemical changes in the molecule. The title compound, (I), has been prepared as a further potentially active 1,4-DHP derivative. Its structure was confirmed by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and elemental analyses, but the deter-

mination of its three-dimensional conformation is important in order to obtain further insight into the structure–activity relationships of these compounds.



The 1,4-DHP ring in the structure of (I) is planar; the r.m.s. deviation of the six atoms of the ring from their mean plane is 0.010 Å and the maximum deviation is 0.016 (2) Å for atom C2. The conformations of 4-aryl-1,4-DHP rings have been discussed previously (Goldmann & Stoltefuss, 1991; Linden *et al.*, 1998; Şimşek *et al.*, 2000) and it is usual for the ring to have a shallow boat conformation. In (I), even when atoms N1 and C4 are excluded from the plane calculation, they deviate from the mean plane defined by the other four atoms by 0.022 (4) and −0.014 (5) Å, respectively, which demonstrates that even the shallowest of boat conformations is not present. The Cambridge Structural Database (CSD, April 2002 Release; Allen & Kennard, 1993) currently contains 124 entries with the 4-aryl-1,4-DHP moiety, excluding 4,4-disubstituted derivatives. Even though these entries show that there can be considerable variation in the shallowness of the boat conformation, only three structures have an essentially planar 1,4-DHP ring (Pastor *et al.*, 1994; Duque *et al.*, 2000; Low *et al.*, 2001). A comparison of these three structures with (I) failed to reveal any obvious similarity in the substituents, either on the 1,4-DHP ring or on the 4-aryl group, that might explain the tendency for planarity.

Another measure of the planarity of 1,4-DHP rings is the sum of the magnitudes of the six intra-ring torsion angles, *P*, around the ring (Fossheim *et al.*, 1988). For compound (I), *P* is 10 (1)°. The value of *P* for the 124 entries in the CSD ranges from 4 to 130°, although only four structures have *P* < 28° and the mean value is 77 (2)°. For nifedipine itself, *P* is 72° (Miyamae *et al.*, 1986). Only one other reported structure has a smaller value of *P* than that for (I) (4.4°; Duque *et al.*, 2000). Such a severe flattening might have significant implications for the pharmacological potency of (I) as a calcium channel antagonist, because it has been suggested (Fossheim *et al.*, 1982, 1988) that the most active compounds in the nifedipine and nisoldipine series possess the shallowest boat conformations. The calcium modulatory activity of (I) will be reported later.

The plane of the 3-nitrophenyl ring of (I) is almost parallel to the N1...C4 axis, with an N1...C4—C15—C20 torsion angle of −12.3 (4)°. This is quite normal; the corresponding torsion angles in the 124 related structures in the CSD are clustered around 0° and rarely exceed ±30°. The nitro substituent lies above the C4—H bond in a synperiplanar orientation, and not over the 1,4-DHP ring. The carbonyl group of the amide substituent at C3 is far from being coplanar

with the 1,4-DHP ring and the C2=C3–C10=O10 torsion angle is 116.8 (3)°. This indicates that there is no significant  $\pi$ -electron conjugation between the C2=C3 bond and the carbonyl group. Instead, this carbonyl group conjugates with the lone electron pair on atom N10 in the normal fashion of amides, which gives rise to a planar geometry about N10. The CSD contains entries for seven structures that have an amide substituent at one or both of the 1,4-DHP ring C atoms adjacent to C4, and each of these structures shows a similar lack of coplanarity between the amide C=O and the ring C=C bonds. Conversely, coplanarity prevails when the carbonyl group is not part of an amide group (114 structures in the CSD).

The oxocyclohexene ring in compound (I) is disordered over two conformations. Each conformation is that of a slightly distorted envelope, with atom C7 or C7A as the envelope flap. The major conformation exists in 69.8 (6)% of the molecules and has the envelope flap, C7, on the opposite side of the fused ring plane to the 3-nitrophenyl substituent of the adjacent 1,4-DHP ring. The puckering parameters (Cremer & Pople, 1975) are  $Q = 0.447$  (4) Å,  $q_2 = 0.321$  (4) Å,  $q_3 = 0.311$  (4) Å,  $\theta = 45.9$  (5)° and  $\varphi_2 = 110.9$  (7)° for the atom sequence C5–C6–C7–C8–C8a–C4a, indicating that the envelope is distorted towards a half-chair conformation (Boeyens, 1987). Atoms C6 and C7 lie 0.134 (6) and –0.521 (8) Å, respectively, from the plane defined by atoms C4a, C5, C8 and C8a. The r.m.s. deviation of these latter four atoms from their mean plane is 0.023 Å and the maximum deviation is 0.030 (2) Å for atom C4a. In the minor conformation, the envelope flap, C7A, flips to the opposite side of the oxocyclohexene ring plane. The puckering parameters are  $Q = 0.423$  (9) Å,  $q_2 = 0.377$  (6) Å,  $q_3 = -0.192$  (6) Å,  $\theta = 117.0$  (9)° and  $\varphi_2 = 307.5$  (9)°, indicating that the envelope is distorted towards a screw-boat conformation. Atom C7A lies 0.664 (14) Å from the plane defined by atoms C4a, C5, C8 and C8a. It has been noted previously (Şimşek *et al.*, 2000) that C7 is always the out-of-plane atom in structures involving the 5-oxoquinoline or 1,8-dioxoacridine moieties. Of the 51 hits

(27 structures) for these moieties in the current release of the CSD, 43 have C7 on the same side of the ring plane as the substituent at C4 of the 1,4-DHP ring, so the major conformation of (I) belongs to the less common class in this respect.

Most of the bond lengths and angles in (I) have normal values. The C2=C3 bond is slightly shorter than the C4a=C8a bond, and the bond lengths about N1 are slightly asymmetric (Table 1). This may be an indication that N1 conjugates more strongly with the C4a=C8a bond than with the C2=C3 bond. An intermolecular hydrogen bond between the amine group and the carbonyl O atom of the oxocyclohexene ring of a neighbouring molecule (Table 2) links the molecules into infinite one-dimensional chains, which spiral parallel to the  $z$  axis and have a graph-set motif of  $C(6)$  (Bernstein *et al.*, 1995).

## Experimental

The title compound was synthesized by refluxing 4,4-dimethyl-1,3-cyclohexanedione (0.01 mol), *N,N*-diethylacetoacetamide (0.01 mol), 3-nitrobenzaldehyde (0.01 mol) and ammonium acetate (0.03 mol) in methanol for 8 h. The solution was then poured into water and the precipitate which formed was filtered off, dried and recrystallized from propan-2-ol (m.p. 465 K).

### Crystal data

C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>  
 $M_r = 411.50$   
 Trigonal,  $R3c$   
 $a = 28.2157$  (11) Å  
 $c = 14.2592$  (4) Å  
 $V = 9831.2$  (6) Å<sup>3</sup>  
 $Z = 18$   
 $D_x = 1.251$  Mg m<sup>-3</sup>

Mo  $K\alpha$  radiation  
 Cell parameters from 3851 reflections  
 $\theta = 2.0$ – $25.0^\circ$   
 $\mu = 0.09$  mm<sup>-1</sup>  
 $T = 160$  (1) K  
 Needle, yellow  
 $0.25 \times 0.05 \times 0.02$  mm

### Data collection

Nonius KappaCCD area-detector diffractometer  
 $\varphi$  and  $\omega$  scans with  $\kappa$  offsets  
 27 763 measured reflections  
 3733 independent reflections  
 2571 reflections with  $I > 2\sigma(I)$

$R_{int} = 0.106$   
 $\theta_{max} = 25^\circ$   
 $h = 0 \rightarrow 33$   
 $k = -28 \rightarrow 0$   
 $l = -16 \rightarrow 16$

**Table 1**

Selected geometric parameters (Å, °).

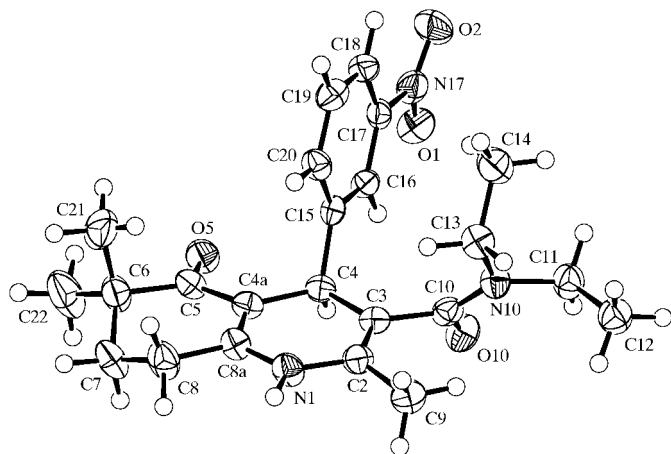
|             |           |            |           |
|-------------|-----------|------------|-----------|
| O10–C10     | 1.242 (3) | C3–C10     | 1.487 (4) |
| N1–C2       | 1.401 (4) | C3–C4      | 1.518 (4) |
| N1–C8a      | 1.345 (4) | C4–C4a     | 1.517 (4) |
| N10–C10     | 1.353 (4) | C4a–C8a    | 1.365 (4) |
| C2–C3       | 1.339 (4) |            |           |
| C2–N1–C8a   | 122.3 (2) | C2–C3–C4   | 122.7 (3) |
| C10–N10–C11 | 119.5 (2) | C3–C4–C4a  | 111.3 (2) |
| C10–N10–C13 | 123.9 (3) | C4–C4a–C8a | 121.7 (3) |
| C11–N10–C13 | 116.3 (2) | N1–C8a–C4a | 121.6 (3) |
| N1–C2–C3    | 120.4 (3) |            |           |

**Table 2**

Hydrogen-bonding geometry (Å, °).

| $D-H \cdots A$                 | $D-H$    | $H \cdots A$ | $D \cdots A$ | $D-H \cdots A$ |
|--------------------------------|----------|--------------|--------------|----------------|
| N1–H1 $\cdots$ O5 <sup>i</sup> | 0.84 (3) | 2.04 (3)     | 2.856 (3)    | 163 (3)        |

Symmetry code: (i)  $x, x - y, z - \frac{1}{2}$ .



**Figure 1**

The molecular structure of (I), showing the major conformation of the disordered oxocyclohexene ring, 50% probability displacement ellipsoids and the atom-labelling scheme. H atoms are drawn as small spheres of arbitrary radii.

## Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.047$   
 $wR(F^2) = 0.090$   
 $S = 1.00$   
 3730 reflections  
 311 parameters  
 H atoms treated by a mixture of  
 independent and constrained  
 refinement

$$w = 1/[\sigma^2(F_o^2) + (0.0233P)^2]$$

where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} = 0.001$   
 $\Delta\rho_{\max} = 0.15 \text{ e } \text{Å}^{-3}$   
 $\Delta\rho_{\min} = -0.15 \text{ e } \text{Å}^{-3}$   
 Extinction correction: *SHELXL97*  
 (Sheldrick, 1997)  
 Extinction coefficient: 0.00120 (9)

The oxocyclohexene ring is disordered over two envelope conformations, with the methylene group at C7 occupying two positions, and, as a consequence, the dimethyl substituents at C6 are also disordered. The site-occupancy factors of the disordered atoms were refined, while constraining their sum for the two conformations to 1.0. The major conformation was found to be present in 69.8 (6)% of the molecules. Mild bond-length restraints were applied to all bonds involving the disordered atoms so as to maintain reasonable geometry. The position of the amine H atom was determined from a difference Fourier map and refined freely along with its isotropic displacement parameter. The methyl H atoms were constrained to an ideal geometry (C–H = 0.98 Å), with  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ , but were allowed to rotate freely about the C–C bonds. All remaining H atoms were placed in geometrically idealized positions (C–H = 0.95–1.00 Å) and constrained to ride on their parent atoms, with  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ . The space-group symmetry dictates that the compound is racemic, yet the structure possesses a polar axis. Due to the absence of any significant anomalous scatterers in the compound, attempts to confirm the absolute structure by refinement of the Flack parameter (Flack, 1983) in the presence of 1792 sets of Friedel equivalents led to an inconclusive value (Flack & Bernardinelli, 2000) of  $-0.6$  (12) for this parameter. Therefore, the absolute direction of the polar axis was assigned arbitrarily. Friedel opposites were not merged before the final refinement because the nature of the asymmetric unit in space group *R3c* means that doing so leads to a severe paucity of unique reflections and, for this structure, the subsequent refinement of the structure was less stable.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2002).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1560). Services for accessing these data are described at the back of the journal.

## References

- Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 1, 31–37.
- Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
- Bernstein, J., Davis, R. E., Shimon, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
- Boeyens, J. C. A. (1987). *J. Cryst. Mol. Struct.* **8**, 317–320.
- Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
- Duque, J., Pomés, R., Suárez, M., Ochoa, E., Verdecia, Y., Ponte, G. & Echevarría, G. (2000). *Z. Kristallogr. New Cryst. Struct.* **215**, 361–362.
- Flack, H. D. (1983). *Acta Cryst.* **A39**, 876–881.
- Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.
- Flaim, S. F. & Zelic, R. (1982). Editors. *Calcium Blockers: Mechanisms of Action and Clinical Applications*. Baltimore: Urban & Schwarzenberg.
- Fossheim, R., Joslyn, A., Solo, A. J., Luchowski, E., Rutledge, A. & Triggle, D. J. (1988). *J. Med. Chem.* **31**, 300–305.
- Fossheim, R., Svarteng, K., Mostad, A., Rømming, C., Shefter, E. & Triggle, D. J. (1982). *J. Med. Chem.* **25**, 126–131.
- Goldmann, S. & Stoltefuss, J. (1991). *Angew. Chem. Int. Ed. Engl.* **30**, 1559–1578.
- Janis, R. A. & Triggle, D. J. (1984). *Drug Dev. Res.* **4**, 257–274.
- Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
- Linden, A., Şafak, C. & Şimşek, R. (1998). *Acta Cryst.* **C54**, 879–882.
- Loev, B., Goodman, M. M., Snader, K. M., Tedeschi, R. & Macko, E. (1974). *J. Med. Chem.* **17**, 956–965.
- Low, J. N., Cobo, J., Noguera, M., Sánchez, A., Quiroga, J. & Mejía, D. (2001). *Acta Cryst.* **C57**, 1356–1358.
- Miyamae, A., Koda, S. & Morimoto, Y. (1986). *Chem. Pharm. Bull.* **34**, 3071–3074.
- Nonius (2000). *COLLECT*. Nonius BV, Delft, The Netherlands.
- Ogawa, T., Nakazato, A., Tsuchida, K. & Hatayama, K. (1993). *Chem. Pharm. Bull.* **41**, 108–116.
- Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
- Pastor, A., Alajarin, R., Vaquero, J. J., Alvarez-Builla, J., Fau de Casa-Juana, M., Sunkel, C., Priego, J. G., Fonseca, I. & Sanz-Aparicio, J. (1994). *Tetrahedron*, **50**, 8085–8098.
- Rose, U. (1989). *Arzneim. Forsch. (Drug Res.)*, **39**, 1393–1398.
- Rose, U. (1990a). *Arch. Pharm. (Weinheim)*, **323**, 281–286.
- Rose, U. (1990b). *J. Heterocycl. Chem.* **27**, 237–242.
- Rose, U. & Dräger, M. (1992). *J. Med. Chem.* **35**, 2238–2243.
- Şafak, C., Özkanlı, F., Erol, K. & Aktan, Y. (1995). *Arzneim. Forsch. (Drug Res.)*, **45**, 1154–1156.
- Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
- Şimşek, R., Linden, A. & Şafak, C. (2000). *Acta Cryst.* **C56**, 351–353.
- Spek, A. L. (2002). *PLATON*. University of Utrecht, The Netherlands.