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4,4-Dinitro-5,6,7,8,9,10-hexahydro-4*H*-cyclonona[*d*]isoxazole

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.056
wR factor = 0.162
Data-to-parameter ratio = 20.8

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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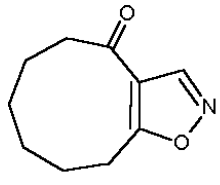
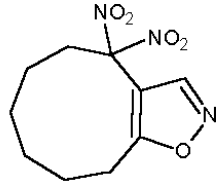
The title compound, $C_{10}H_{13}N_3O_5$, was designed as a potential endothelin receptor antagonist and as a probe of the structural requirements of the endothelin receptor binding site. The isoxazole ring is planar and the cyclononane moiety lies approximately in the plane of the heterocycle. The molecules are packed in the crystal structure by ionic and van der Waals interactions.

Comment

Recently, as a part of our ongoing project aimed at designing new therapeutic agents against cardiovascular disorders, we have focused our attention on the isoxazole family of subtype A selective endothelin (ET) receptor antagonists as potential drugs to treat hypertension and congestive heart failure (Murugesan *et al.*, 2003). The active analogues of this family have 4,5-disubstitution of the isoxazole ring by predominantly hydrophobic groups (which lie essentially in the plane of the isoxazole ring) but contain polar element(s) [usually hydrogen-bond acceptor(s)] in the vicinity of the 5-position of the heterocycle. On the basis of this knowledge, we were prompted to prepare compound (I), which meets the above-mentioned requirements for the ET(A)-receptor blocking activity. However, when the reaction mixture was left to stand for several weeks, single crystals of the 4,4-dinitro derivative, (II), as indicated by spectroscopic methods, appeared; obviously, the latter compound resulted from an oxidative rearrangement of an oxime of (I). Since, compared with (I), compound (II) has enhanced hydrogen-bond acceptor capacity, we selected the latter compound for a combined structural and biological investigation. In this communication, we report the crystal structure of (II).



(I)



(II)

The molecular structure and the atom-numbering scheme are shown in Fig. 1. As can be seen, X-ray analysis confirmed the spectroscopic assignments, *i.e.* the compound consists of a dinitro-substituted cyclononane moiety fused to an isoxazole ring. As expected, the isoxazole ring is planar within the limits of experimental error [r.m.s. deviation 0.002 (2) Å], and atoms C4 and C10 are displaced from this plane by 0.041 (4) and 0.056 (4) Å, respectively, on the same side of the ring. As

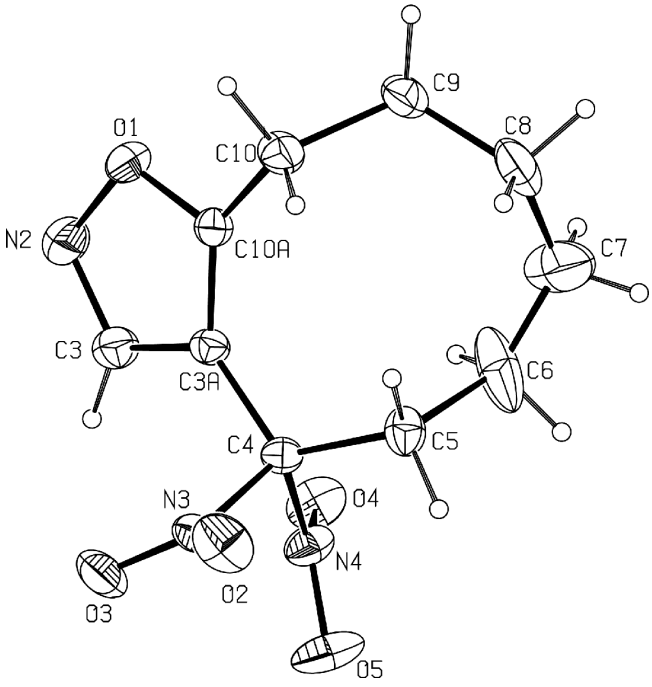


Figure 1
Displacement ellipsoid plot of (II), with the labelling scheme for the non-H atoms, which are drawn as 35% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary size.

estimated from the bond order *versus* bond length curves proposed by Burke-Laing & Laing (1976), the bonds in the heterocyclic ring are intermediate between single and double bonds, indicating π-electron delocalization in the ring. A similar pattern of bond lengths and angles has also been observed in other compounds containing the isoxazole substructure and bearing substituents not involved in conjugation with the heterocycle, as revealed by a search of the Cambridge Structural Database (Allen, 2002).

As for the remaining part of the molecule, the bond lengths C6—C7 and C7—C8 are considerably shorter than 1.533 Å (Bartell, 1959); similarly, the C—C—C bond angles around atoms C6 and C7 are much larger than normal tetrahedral values. As described below, this discrepancy is caused by unresolved disorder of atoms C6 and C7. Other bond distances and angles are close to those generally expected.

From the biological point of view, it is important that the hydrophobic volume of the cyclononane moiety lies approximately in the plane of the isoxazole ring (Fig. 1); as mentioned above, this is one of the steric requirements of a compound to act as an endothelin receptor antagonist.

As the title compound has no potential hydrogen-bond donor(s), the molecules are held together by dipolar and van der Waals interactions.

Experimental

The synthetic procedure for the title compound, (II), will be described in detail elsewhere (Marko *et al.*, 2005). In short, to 2-anilinomethylene-1,3-cyclononandione (2 mmol), prepared freshly from commercially available 1,3-cyclononandione by standard methods (Marko *et al.*, 2005), were added ethanol (7 ml), anhydrous potassium carbonate (2.7 mmol) and hydroxylamine hydrochloride (4.4 mmol). After the reaction mixture was stirred for 3 h, the carbonate was filtered off and the filtrate was set aside to crystallize, providing analytically pure (II) after several weeks. Crystals of (II) (m.p. 374–376 K) suitable for an X-ray analysis were selected directly from the sample as prepared.

Crystal data

$C_{10}H_{13}N_3O_5$
$M_r = 255.23$
Monoclinic, $P2_1/n$
$a = 8.735$ (2) Å
$b = 16.569$ (4) Å
$c = 8.764$ (2) Å
$\beta = 113.81$ (4)°
$V = 1160.5$ (5) Å^3
$Z = 4$
$D_x = 1.461$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20 reflections
$\theta = 7$–20°
$\mu = 0.12$ mm^{-1}
$T = 293$ (2) K
Prism, colourless
0.30 × 0.20 × 0.15 mm

Data collection

Siemens *P*4 diffractometer
$\omega/2\theta$ scans
3583 measured reflections
3383 independent reflections
1421 reflections with $I > 2\sigma(I)$
$R_{int} = 0.039$
$\theta_{max} = 30.0°$
$h = 0 \rightarrow 12$
$k = 0 \rightarrow 23$
$l = -12 \rightarrow 11$
3 standard reflections
every 97 reflections
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.056$
$wR(F^2) = 0.162$
$S = 0.91$
3383 reflections
163 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0694P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.29$ e Å^{-3}
$\Delta\rho_{min} = -0.33$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C10*A*	1.352 (3)	C4—N3	1.549 (3)
O1—N2	1.408 (3)	N3—O2	1.198 (2)
N2—C3	1.289 (3)	N3—O3	1.220 (2)
C3—C3*A*	1.413 (3)	N4—O4	1.202 (2)
C3*A*—C10*A*	1.360 (3)	N4—O5	1.214 (2)
C4—N4	1.547 (3)		
C10*A*—O1—N2	109.97 (16)	C10*A*—C3*A*—C3	104.18 (19)
C3—N2—O1	104.29 (19)	O1—C10*A*—C3*A*	108.2 (2)
N2—C3—C3*A*	113.3 (2)		

As an analysis of the principal mean square atomic displacements indicated possible twofold disorder for atoms C6 and C7, the structure was initially refined using a two-site model and restraints on corresponding bond distances and anisotropic displacement parameters. However, the structure was found to diverge during the least-squares refinement and hence it was finally refined by using an unrestrained ordered model; this, of course, led to anomalies in the bond lengths and angles involving atoms C6 and C7. H atoms were refined with fixed geometry, riding on their carrier atoms (C—H) = 0.93 and 0.97 Å), with U_{iso}(H) set to 1.2 times U_{eq} of the parent atom.

Data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLUTON* (Spek, 1992); software used to prepare material for publication: *SHELXL97*.

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References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388..
Bartell, L. S. (1959). *J. Am. Chem. Soc.* **81**, 3497–3498.
Burke-Laing, M. & Laing, M. (1976). *Acta Cryst.* B**32**, 3216–3224.
Marko, M., Milata, V., Kada, R. & Ilavský, D. (2005). *Collect. Czech. Chem. Commun.* In preparation.
Murugesan, N., Gu, Z., Spergel, S., Young, M., Chen, P., Martur, A., Leith, L., Hermsmeier, M., Liu, E. C.-K., Zhang, R., Bird, E., Waldron, T., Marino, A., Koplowitz, B., Humphreys, W. G. *et al.* (2003). *J. Med. Chem.* **46**, 125–137.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Siemens (1991). *XSCANS*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Spek, A. L. (1992). *PLUTON92*. University of Utrecht, The Netherlands.