



SYNTHESIS AND CRYSTAL STRUCTURE OF ETHYL 1-(4-METHYLPHENYL)-4-(4-METHYLPHENYLAMINO)-2,6-BIS(4-NITROPHENYL)-1,2,5,6-TETRAHYDROPYRIDINE-3-CARBOXYLATE

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Keywords: Tetrahydropyridine ring; crystal structure; direct methods; intermolecular hydrogen bonding.

The title compound was synthesized by standard routes of synthesis and its structure was established by spectral and X-ray diffraction studies. The compound crystallizes in the triclinic space group P-1 with unit cell parameters $a=10.4395(6)$, $b=11.9493(6)$, $c=13.8651(7)$, $\alpha=108.958(5)$, $\beta=103.089(5)$, $\gamma=97.885(4)$, $Z=2$. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data collected at room temperature and refined by full-matrix least squares procedures to a final R -value of 0.0664 for 3330 observed reflections. In the title molecule, the tetrahydropyridine ring adopts a distorted boat conformation and both 4-nitro-phenyl substituents are in axial positions. The dihedral angle between the planes of the nitro-substituted rings is $45.5(1)^\circ$. The amino group and carbonyl O atom are involved in intramolecular hydrogen bonding and this interaction leads to the formation of a virtual-six membered ring. In the crystal, C-H...O intermolecular interactions stabilizes the crystal packing.

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Hence, investigation of the structural features of biologically relevant piperidine derivatives is demanding. In continuation of our structural studies of densely functionalized piperidines,^{13,14} we present the crystal structure of ethyl 1-(4-methylphenyl)-4-(4-methylphenylamino)-2,6-bis(4-nitrophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate, determined by X-ray diffraction.

Introduction

Functionalized piperidines are found to constitute a very important core in numerous natural products,^{1,2} synthetic pharmaceuticals,^{3,4} and a wide variety of biologically active compounds. In particular, 1,4-disubstituted piperidine scaffolds find useful applications as established drugs,^{5,6} and they exhibit a wide range of pharmacological activities including antibacterial,⁷ antimalarial,⁸ anticonvulsant, anti-inflammatory⁹ and enzyme inhibitory activity.^{10,11} Moreover a large number of compounds bearing piperidine scaffold have entered into preclinical and clinical trials over the last few years.¹²

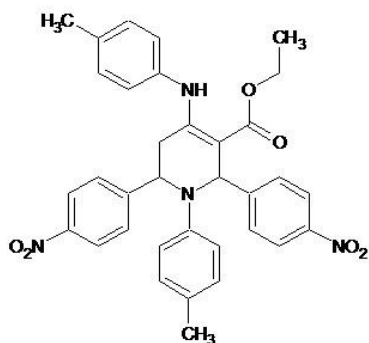


Figure 1. Chemical structure of the title compound

Experimental Methods

Synthesis

A mixture of ethyl acetoacetate (1 mmole), 4-methylaniline (2 mmole) and sulfamic acid (15 mol %) in 5 ml ethanol was stirred at RT for 15 min, then 4-nitro benzaldehyde (2 mmole) was added and stirring was continued at 78 °C till the completion of TLC. Then reaction mass gradually cools to RT, a solid precipitated out. The solid was filtered and washed with cold ethanol.

M.P.: 210-211 °C, Yield: 79 %. ¹H NMR (300 MHz, CDCl₃): δ = 1.45-1.50(t, 3H), 2.18(s, 3H), 2.29(s, 3H), 2.84-2.85(d, 2H), 4.31-4.53(m, 2H), 5.24(s, 1H), 6.30-6.33(d, 4H), 6.44(s, 1H), 6.90-6.98 (dd, $J=8.1$ Hz, 4H), 7.29-7.32(d, 2H), 7.51-7.53(d, 2H), 8.13-8.18(m, 4H), 10.25(s, 1H);

X-ray Data Collection, Crystal Structure Determination and Refinement

X-ray intensity data of 11409 reflections (of which 6077 unique) were collected on *X'calibur* CCD area-detector diffractometer equipped with graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å).¹² The crystal used for data collection was of dimensions 0.30 x 0.20 x 0.20 mm.

The cell dimensions were determined by least-squares fit of angular settings of 2828 reflections in the θ range 3.90 to 27.83°. The intensities were measured by ω scan mode for θ ranges 3.70 to 26.00°. 3330 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz, polarisation and absorption factors. The structure was solved by direct methods using SHELXS97.¹³ All non-hydrogen atoms of the molecule were located in the best E-map. All the hydrogen atoms (except N2 H atoms) were geometrically fixed and allowed to ride on the corresponding non-hydrogen atoms with C-H = 0.93–0.98 Å, and $U_{\text{iso}} = 1.5U_{\text{eq}}$ of the attached C atom for methyl H atoms and $1.2U_{\text{eq}}$ for other H atoms. Full-matrix least-squares refinement was carried out using SHELXL97.¹³ The final refinement cycles converged to an $R=0.0663$ and $wR(F^2)=0.1723$ for the observed data. Residual electron densities ranged from -0.435 to $0.520 \text{ e}\text{\AA}^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4).

Table 1. Crystallographic data and other experimental details of (I).

CCDC deposition no.	990129
Crystal description	White block
Chemical Formula	C ₃₄ H ₃₂ N ₄ O ₆
Molecular weight(g mol ⁻¹)	592.64
Cell parameters	
<i>a</i> , Å	10.4395(6)
<i>b</i> , Å	11.9493(6)
<i>c</i> , Å	13.8651(7)
α , deg	108.958(5)
β , deg	103.089(5)
γ , deg	97.885(4)
Unit cell volume(Å ³)	1551.02(14)
Crystal system	Triclinic
Space group	P-1
Temperature (K)	293(2)
Number of molecules per unit cell	2
Radiation	MoK α
Wavelength (Å)	0.71073
F(000)	624
θ range for entire data collection	3.70< θ <26.00
Range of indices	-12 ≤ <i>h</i> ≤ 12, -12 ≤ <i>k</i> ≤ 14, -17 ≤ <i>l</i> ≤ 16
Number of measured reflections	11409
Number of unique reflections	6077
Number of observed reflections	3330
Number of parameters refined	404
Restraints	0
Refinement method	Full-matrix least squares on F^2
Final <i>R</i> -factor	0.0663
$wR^2(F^2)$	0.1723
Weight	$1/[\sigma^2(F_o^2)+(0.0932P)^2]$ + 0.3988], where $P=[F_o^2+2F_c^2]/3$
Goof(<i>S</i>) on (F^2)	1.029
Final residual electron density, Å ³	-0.435 < $\Delta\rho$ < 0.520
(Δ/σ) _{max} in the final cycle	0.001 (for tors H34A)

Scan mode	ω
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The crystallographic data are summarized in Table 1. CCDC - 990129 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

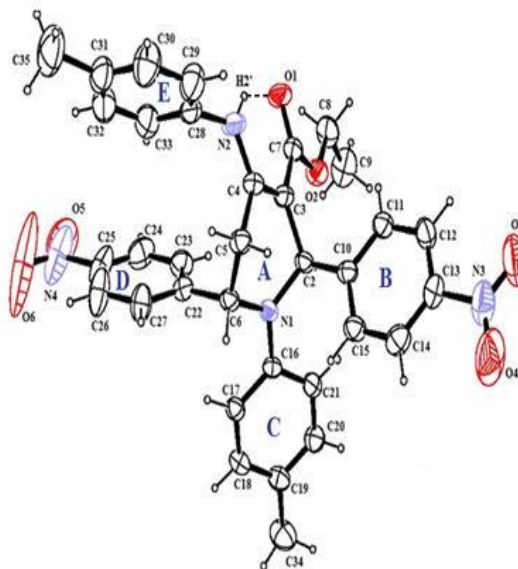


Figure 2. ORTEP view of the molecule with displacement ellipsoids drawn at the 50 % probability. H atoms are shown as small spheres of arbitrary radii

Results and Discussion

An ORTEP view of the title compound with atomic labeling is shown in Figure 2.¹⁴ The geometry of the molecule was calculated using the PLATON¹⁵ and PARST¹⁶ software. Crystal data, along with data collection and structure refinement details are summarized in Table 1. Selected bond lengths and angles are given in Table 2, while hydrogen bonds are presented in Table 3. In (I) (Fig.1), all bond lengths and angles are normal and correspond to those observed in related structures.^{17–20}

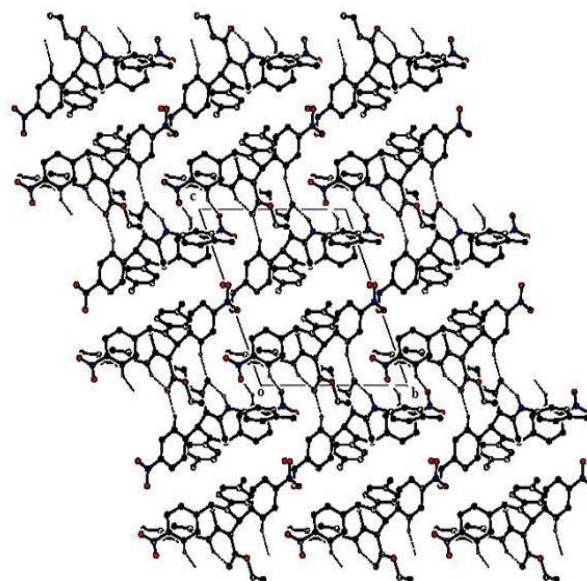


Figure 3. The crystal packing viewed down the a-axis is shown

Table 2. Selected bond lengths (Å) and angles (°) for (I).

Bond lengths, Å		Bond angles, °		Bond angles, °	
N1-C16	1.392(3)	C16-N1-C6	120.2(2)	C33-C28-N2	120.2(3)
N1-C6	1.453(3)	C16-N1-C2	120.5(2)	C29-C28-N2	121.2(3)
N1-C2	1.459(3)	C6-N1-C2	119.1(2)	C12-C13-N3	118.9(3)
O2-C7	1.344(3)	N1-C16-C21	122.0(2)	C14-C13-N3	119.5(3)
O2-C8	1.449(3)	N1-C16-C17	121.2(2)	O2-C8-C9	107.7(3)
O1-C7	1.215(3)	C7-O2-C8	117.6(2)	O3-N3-O4	123.1(4)
N2-C4	1.353(4)	N1-C2-C3	110.6(2)	O3-N3-C13	119.4(4)
N2-C28	1.433(4)	N1-C2-C10	113.6(2)	O4-N3-C13	117.5(4)
C13-N3	1.470(5)	C4-N2-C28	125.8(3)	C24-C25-N4	118.6(5)
N3-O3	1.193(4)	N1-C6-C22	114.8(2)	C26-C25-N4	119.0(5)
N3-O4	1.205(5)	N1-C6-C5	110.2(2)	O6-N4-O5	124.0(5)
O5-N4	1.214(6)	N2-C4-C3	124.4(2)	O6-N4-C25	118.1(6)
C25-N4	1.486(6)	N2-C4-C5	119.6(3)	O5-N4-C25	117.6(5)
N4-O6	1.155(7)	O1-C7-O2	122.1(3)	O2-C7-C3	112.5(2)
		O1-C7-C3	125.3(3)		

Table 3. Hydrogen bonding parameters (Å, °) for (I).

D-H	H...A	D...A	D-H...A	Symmetry Code
N2-H2'-O1	0.91(4)	1.92(4)	2.688(3)	141(4)
C11-H11...O1	0.93	2.44	3.255(3)	147
C24-H24...O5	0.93	2.56	3.340(7)	142
				-x+2,-y+2,-z+1
				-x+1,-y,-z

In the title molecule, the tetrahydropyridine ring (A) adopts distorted boat conformation with best mirror plane passing through the atoms C2 and C5 and bisecting the bonds C3-C4 and N1-C6 with asymmetry parameters [$\Delta C_s(C2)=9.53$] and [$\Delta C_s(C3-C4)=13.58$].²¹ The two nitrophenyl rings (B and D) are attached to the tetrahydropyridine ring in a *trans* orientation. Both the nitrophenyl rings are inclined to one another by 45.5(1)°, while for the 4-tolyl rings the dihedral angle is 46.2(1)°. The dihedral angle between nitrophenyl ring B and 4-tolyl ring C (B/C) is 69.7(1)°, ring B/E is 82.3(1)°, ring C/D is 85.6(1)° and ring D/E is 42.4(1)°. The amino group and carbonyl O atom are involved in an intramolecular N-H...O hydrogen bonding. This interaction leads to the formation of S(6) motif comprising atoms O1, C7, C3, C4, N2 and H2'. The double bond C7=O1 is confirmed by its respective distance of 1.215(3) Å. The length of the double bond C7=O1 is larger than the standard value for carbonyl group (1.192 Å) and lengthening of the C7=O1 double bond is due to strong intramolecular hydrogen bond between N2 and O1.

Packing view of the molecules in the unit cell viewed down the a-axis is shown (see Figure 2). The title molecule is stabilized by N-H...O intramolecular interactions and C-H...O intermolecular interactions are responsible for the stability of crystal structure (see Table 3).

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References

- Desai, M. C., Lefkowitz, S. L., Thadeio, P. F., Longo, K. P., Sridar, R. M., *J. Med. Chem.*, **1992**, *35*, 4911–4913.
- Pinder, A. R., *Nat. Prod. Rep.*, **1992**, *9*, 491–504.
- Breman, J. G., Egan, A. and Keusch, G. T., *Am. J. Trop. Med. Hyg.*, **2001**, *64*, iv–vii.
- Watson, P. S., Jiang, B. and Scott, B., *Org. Lett.*, **2000**, *2*, 3679–3681.
- Targum, S., Zboroaski, J., Henry, M., Schmitz, P., Sebree, T., Wallin, B., *Eur. Neuropsychopharmacol.*, **1995**, *5*, 4–71.
- Schotte, A., Janssen, P. F. M., Gommeren, W., Luyten, W. H. M. L., van Gompel, P., Lasage, A. S., De Loore, K. and Leysen, J. E., *Psychopharmacol.*, **1996**, *124*, 57–73.
- Zhou, Y., Gregor, V. E., Ayida, B. K., Winters, G. C., Sun, Z., Murphy, D., Haley, G., Bailey, D., Froelich, J. M., Fish, S., Webber, S. E., Hermann, T., Wall, D., *Bioorg. Med. Chem. Lett.*, **2007**, *17*, 1206–1210.
- Misra, M., Pandey, S. K., Pandey, V. P., Pandey, J., Tripathi, R., Tripathi, R. P., *Bioorg. Med. Chem.*, **2009**, *17*, 625–633.
- Bin, H., Crider, A. M. & Stables, J. P., *Eur. J. Med. Chem.*, **2001**, *36*, 265–286.
- Agrawal, A. G., Somani, R. R., *Mini Rev. Med. Chem.*, **2009**, *9*, 638–52.
- Dekus, J. A., Epperson, J. R., Charles, P. S., Joseph, A., C., Deextraze, P., Qian- Cutrone, J., Gao, Q., Ma, B., Beno, B. R., Mattson, G. K., Molski, T. F., Krause, R. G., Taber, M. T., Lodge, N. J., Mattson, R., *Bioorg. Med., Chem. Lett.*, **2007**, *17*, 3099–3104.

- ¹²Kamei, K., Maeda, N., Katswagi-Ogino, R., Koyamaa, M., Nakajima, M., Tatsuoka, T., Ohno, T., Inoue, T., *Bioorg. Med. Chem. Lett.*, **15**, 2990–2993.
- ¹³Sambyal, A., Bamezai, R. K., Razdan, T. K., Gupta, V. K., *J. Chem. Crystallogr.*, **2011**, *41*, 868–873.
- ¹⁴Brahmachari, G., Das, S., *Tetrahedron Lett.*, **2012**, *53*, 1479–1484.
- ¹²Oxford Diffraction **2010**, CrysAlis PRO. Oxford Diffraction Ltd, Yarnton, Oxfordshire, England.
- ¹³Sheldrick, G. M., *Acta Cryst.* **2008**, *A64*, 112.
- ¹⁴Farrugia, L. J., *J. Appl. Cryst.* **2012**, *45*, 849.
- ¹⁵Spek, A. L., *Acta Cryst.* **2009**, *D65*, 148.
- ¹⁶Nardelli, M., *J. Appl. Cryst.*, **1995**, *28*, 659.
- ¹⁷ Anthal, S., Brahmachari, G., Das, S., Kant, R., Gupta, V. K., *Acta Cryst.* **2013b**, *E69*, o299-300.
- ¹⁸Anthal, S., Brahmachari, G., Das, S., Kant, R., Gupta, V. K., *Acta Cryst.*, **2013c**, *E69*, o373-374.
- ¹⁹Anthal, S., Brahmachari, G., Das, S., Kant, R., Gupta, V. K., *Acta Cryst.*, **2013d**, *E69*, o454-455.
- ²⁰Anthal, S., Brahmachari, G., Das, S., Kant, R., Gupta, V. K., *Acta Cryst.*, **2013a**, *E69*, o506-507.
- ²¹Duax, W. L., Norton, D. A., *In Atlas of Steroid Structures*, Vol. 1. New York: Plenum Press, **1975**.

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