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Synthesis, crystal structure, and molecular modeling (AM1) of Methyl 6-chloro-4-(2-chlorophenyl)-5-formyl-2-methyl-1, 4-dihydropyridine-3-carboxylate

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The synthesis and structural characterization of Methyl 6-chloro-4-(2-chlorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate is described. The structure was refined to $R_1 = 0.0470$ for 2665 reflections (with $I > 2\sigma(I)$). Crystal data: $C_{15}H_{13}C_{12}NO_3$, monoclinic, space group $P2_1/c$, $a = 11.163(9)$, $b = 14.484(8)$, $c = 9.422(7)$ Å, $V = 1512.9(19)$ Å^3, $Z = 4$. The results of crystallographic and molecular modeling (AM1) were compared. The Cl atom attached to the phenyl group has two possible orientations, having 75% (*sp*) and 25% (*ap*) occupancy, respectively. The molecules in the crystal are held together by means of intermolecular hydrogen bonds of the type N—H···O and by C—H···O interactions.

KEY WORDS: Crystal structure; AM1; x-ray diffraction; dihydropiridines.

Introduction

Much effort has been devoted to the study of 1,4-dihydropyridines (1,4-DHPs) due to their calcium antagonist effect useful in the treatment of cardiovascular diseases.[1] It is well established that the fundamental requirement for the pharmacological activity of the members of this family is the presence in the 1,4-DHP ring of an aromatic substituent at position 4, alkyl groups (preferably methyl) attached at the 2 and 6 positions, ester groups on C3 and C5 atoms and an H atom on N1.[2–4] Recently, we have developed the experimental and theoretical structural study of 2-pyridyl- and 4-hydroxyphenyl-1,4-dihydropyridine derivatives[5] by X-ray analysis and semiempirical (AM1) calculations and both methods show a boat conformation for the 1,4-dihydropyridine ring with a pseudoaxial orientation of the aryl group in position 4. The conformational features reported for 1,4-DHP calcium modulators are preserved for these compounds.

In spite of the widely developed chemistry of the 1,4-DHPs,[6,7] much less is known about the structure of 1,4-DHPs bearing substituent other than hydrogen atoms or alkyl groups in C2 and C6.[8] In this paper we report the x-ray structure of methyl 6-chloro-4-(2-chlorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**II**). The title compound (**II**) was obtained as a crystalline solid in good yield from 4-(2-chlorophenyl)-6-methyl-3, 4-dihydropyridone-5-carboxylate (**I**)[9] (see Scheme 1) and has proved to be an excellent intermediate in the synthesis of other heterocyclic fused 1,4-DHPs like pyrazolo[3,4-*b*]pyridines[10] and thieno[2,3-*b*] pyridines.[11]

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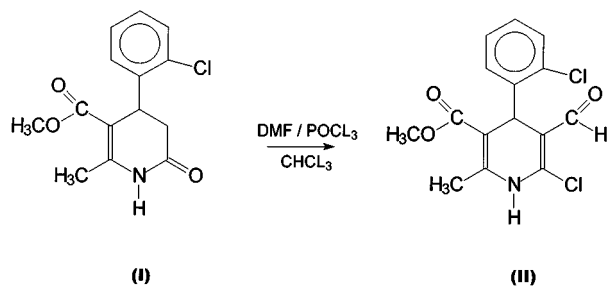
Experimental

*Synthesis of methyl 6-chloro-4-(2-chlorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**II**)*

A solution of anhydrous *N*,*N*-dimethylformamide (40 mmol, 3.1 mL) in dry chloroform (10 mL) was added dropwise to a stirred solution of phosphorus oxychloride (40 mmol, 3.85 mL) under a nitrogen atmosphere at room temperature. After 30 min a solution of 4-(2-chlorophenyl)-6-methyl-3, 4-dihydropyridone-5-carboxylate (**I**) (10 mmol)[11] in 40 mL of dry chloroform was added. After 18 h stirring at room temperature, a solution of sodium acetate (40 g) in water (60 mL) was slowly added. After 0.5 h, the mixture was partitioned between water and chloroform, and the aqueous phase was extracted with ethyl acetate. The organic phases were mixed and dried with anhydrous magnesium sulphate. The organic solvent was removed *in vacuum* and the solid recrystallized from ethanol (yield 80%), m.p. 197–198°C.

Characterization and spectroscopy

Melting points were determined in a capillary tube in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker DPX300 spectrometer (300 MHz-^{1}H and 75.47 MHz-^{13}C). Chemical shifts are given as δ values against tetramethylsilane as the internal standard and J values are given in Hz. The IR spectra were measured with a Shimadzu FTIR 8300 instrument as potassium bromide pellets. Microanalyses were performed in a Perkin Elmer 2400 CHN by *Servicio de Microanálisis, Universidad Complutense de Madrid*. The reactions were monitored by TLC and performed on silica-gel plates (Merck $60F_{250}$) using hexane: ethyl acetate (8:2) as the eluent. Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification. Aromatic aldehydes were distilled before used.



(I) (II)

Scheme 1

*Methyl 6-chloro-4-(2-chlorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**II**)*

IR (KBr, cm^{-1}): 3250 (NH), 2850 (CO), 1712 (CO), 1612 (C=C); ^{1}H NMR (DMSO−d6): δ 10.36 (s, 1H, NH, deuterium oxide exchangeable), 9.65 (s, 1H, HCO), 7.30-719 (m, 4H, aromatics), 5.27 (s, 1H, CH), 3.49 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR δ 187.3 (HC=O), 167.3 (C=O), 145.7 (C2), 144.2 (C5), 144.1 (C2′), 132.7 (C1′), 132.1, 130.1, 128.9, 128.1, (C3′, C4′, C5′, C6′), 111.6 (C3), 105.3 (C6), 51.7 (OCH_3), 37.6 (C4), 18.4 (CH_3); *Anal.* Calculated C: 55.23, H: 4.02, N: 4.02; Found C: 55.31, H: 4.10, N: 4.41.

Crystallography

Suitable crystals were obtained from slow evaporation in ethanol at room temperature. The structures were solved by direct methods and Fourier synthesis using the program SHELXS97[12] and refined on F^2 with SHELXTL97[13] with scattering factors from *International Tables*.[14] Other programs used: DIF4[15] for computing data collection and cell refinement, REDU4[15] and EMPIR[15] for data reduction; DIAMOND[16] for computing molecular graphics, PLATON[17] for computing publication material. Non-H-atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times U_{eq} of their parent atoms. The Cl atom attached to the phenyl group was located from the ΔF map and found to be in two possible positions (Cl2a and Cl2b), with 75% and 25% occupancy respectively. Crystallographic data for compound **II** is given in Table 1; final atomic coordinates are in Table 2; and a comparison of geometrical parameters for the observed and calculated structure of **II** is given in Table 3.

Molecular modeling

Full energy minimization *in vacuo* was carried out using semiempirical AM1 calculations[18] with the aid of the MOPAC[19] molecular orbitals set. The

Table 1. Crystal Data and Structure Refinement Details for (**II**)

Compound	$C_{15}H_{13}C_{l2}NO_3$
CCDC no.	CCDC-141913-1003/5852
Color/shape	Colorless/prism
Chemical formula	$C_{15}H_{13}Cl_2NO_3$
Formula weight	326.16
Temperature	293(2)
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions $a = 11.163(9)$ Å $b = 14.484(8)$ Å $\beta = 96.71(6)^\circ$ $c = 9.422(7)$ Å, (from 24 reflections, $15 < \theta < 25$)	
Volume	1512.9(19) Å^3
Z	4
Density (calculated)	1.432 Mg m^{-3}
Absorption coefficient	0.437 mm^{-1}
Diffractometer/scan	Stoe STADI4/ω
Radiation/wave length	0.71073 Å
$F(000)$	672
Crystal size	0.53 × 0.38 × 0.15 mm
θ range for data collection, deg	1.84 to 25
Index ranges	$-13 \le h \le 13, -17 \le k \le 2, -2 \le l \le 11$
Reflections measured	4185
Independent/observed reflections	2665 ($R_{\text{int}} = 0.024$)/1645[$I > 2\sigma(I)$]
Absorption correction	Semi-empirical from ψ-scans[30]
Range of rel. transm. factors	0.833/0.924
Data/restraints/parameters	2665/48/0/203
Goodness-of-fit on F^2	1.020
SHELXL97 weight parameters	0.0457, 0.5257
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0470$, $wR_2 = 0.1021$
R indices (all data)	$R_1 = 0.1027$, $wR_2 = 0.1183$
Largest diff. Peak/hole	0.28/−0.21

crystallographic coordinates were used as starting geometry for calculations. Previously, the molecular geometry was optimized using Allinger's Molecular Mechanics[20] with PCMODEL program.[21] The structures with lowest energies following the AM1 optimization were used for comparison with the X-ray structures. Calculations were performed on an IBM-RS6000 workstation.

Discussion

We have previously confirmed that semiempirical calculations at the AM1 level (see experimental section) reproduce adequately the geometry of 3,4-dihydropyridones.[11,22] Therefore, we have used the AM1 method to find out the stability of the several conformers of the title compound (**II**). The semiempirical (AM1) calculations for (**II**) resulted in eight possible conformers within the range of less than 2 Kcal (Scheme 2). The most stable by about 0.3 Kcal/mol, is presented in Fig. 1. The crystal structure with the atomic numbering scheme and showing the Cl atom attached to the phenyl group with the two possible orientations (Cl2a and Cl2b, with 75% and 25% occupancy, respectively), is shown in Fig. 2.

Semiempirical AM1 method showed that the 1,4-dihydropyridine ring adopts a flattened boat conformation, in which the carbon atoms of the olefinic double bonds are in the same boat main plane and the aryl substituent on C4 in a pseudoaxial disposition (see Fig. 1).

The calculated heats of formation for this compound, using the AM1 semiempirical method, revealed that conformer *sp* (synperiplanar) is slightly more stable (0.15 kcal/mol) than conformer *ap* (antiperiplanar). In the crystal both conformers are present with a distribution population of 75% for *sp*

Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Compound (**II**)

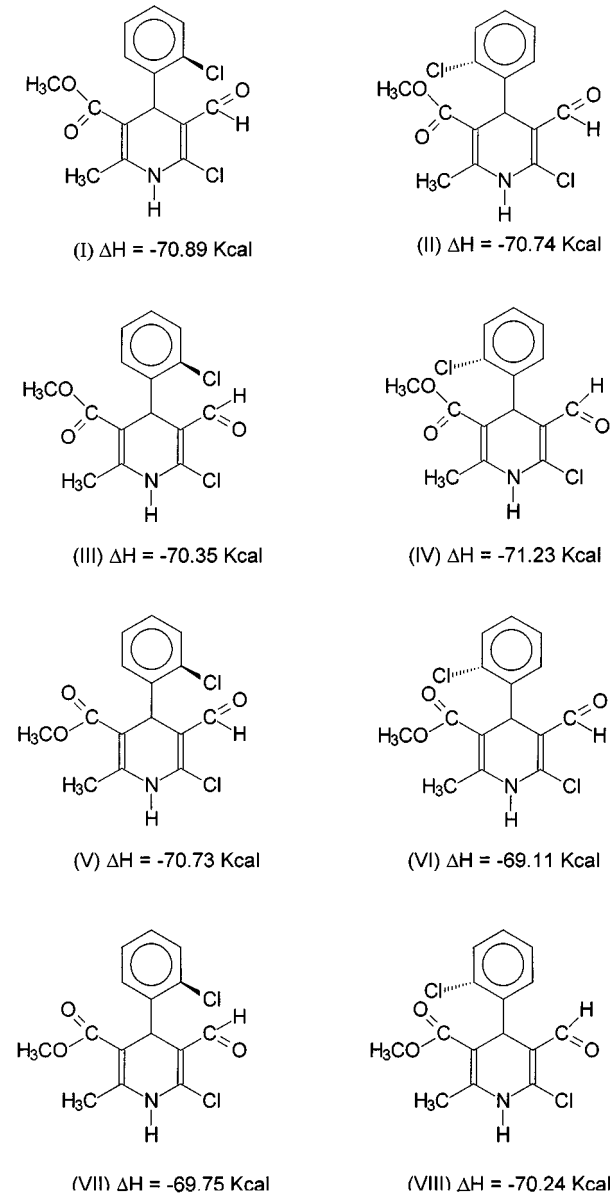
	x	*y*	*z*	U(eq)[a]
Cl1	5929(1)	6054(1)	1349(1)	72(1)
Cl2a	2111(1)	5546(1)	736(1)	58(1)
Cl2b	2925(4)	3012(2)	5066(4)	75(1)
N1	4234(2)	6631(2)	2761(3)	52(1)
O3	4975(2)	3423(2)	3002(3)	66(1)
O5	1372(3)	6417(2)	5390(4)	110(1)
O7	1990(2)	4988(2)	5801(2)	67(1)
C2	4800(2)	5849(2)	2415(3)	48(1)
C3	4502(2)	5000(2)	2854(3)	44(1)
C4	3437(2)	4877(2)	3706(3)	42(1)
C5	2949(3)	5806(2)	4147(3)	43(1)
C6	3333(3)	6617(2)	3665(3)	47(1)
C7	2036(3)	5794(2)	5150(4)	55(1)
C8	1098(4)	4889(3)	6774(4)	83(1)
C9	2937(3)	7566(2)	4017(4)	69(1)
C10	5183(3)	4195(2)	2571(4)	55(1)
C1′	2459(3)	4276(2)	2897(3)	44(1)
C2′	1852(3)	4517(2)	1576(3)	47(1)
C3′	991(3)	3948(3)	850(4)	62(1)
C4′	705(3)	3128(3)	1446(5)	73(1)
C5′	1276(4)	2871(2)	2744(5)	73(1)
C6′	2140(3)	3430(2)	3461(4)	57(1)

[a] $U_{(eq)}$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 3. More Relevant Bond Distances [Å], Valence Angles [°] and Torsion Angles [°] for the More Stable Conformation of Compounds (**II**)

	AM1	X-ray
Bond distances		
N1−C2	1.397	1.355(4)
C2−C3	1.364	1.352(4)
C3−C4	1.507	1.520(4)
C4−C5	1.499	1.527(4)
C5−C6	1.372	1.347(4)
C6−N1	1.393	1.392(4)
C4−C1'	1.508	1.529(4)
C7−O5	1.232	1.221(4)
C7−O7	1.238	1.323(4)
C2−Cl1	1.712	1.727(3)
Valence angles		
C2−N1−C6	119.7	121.7(3)
C3−C4−C5	111.9	111.5(2)
O5−C7−C3	125.6	123.8(3)
O7−C7−C5	128.6	112.1(3)
Dihedral angles		
N1−C2−C3−C4	2.9	3.8(5)
C2−C3−C4−C5	−17.4	−8.8(4)
C3−C4−C5−C6	17.7	7.9(4)
C4−C5−C6−N1	−3.1	−1.8(4)
C5−C6−N1−C2	−13.5	−4.3(4)
C6−N1−C2−C3	13.7	3.3(5)
$\sum \lvert\rho\rvert$[a]	68.3	29.9(5)
O5−C7−C3−C2	22.8	176.7(3)
O7−C7−C5−C6	16.3	−163.3(3)
C2−C3−C4−C1'	106.4	117.4(3)
C3−C4−C1'−C2'	106.2	−61.7(3)

[a] $\sum \lvert\rho\rvert$ Sum of the modular values of internal dihedral angles of the dihydropyridine ring.[16]



Scheme 2

and 25% *ap*, respectively. The *cis* (*sp*) disposition between the endocyclic double bonds and the C=O at C3 was found more stable that the *trans* one by AM1. This is not the case of the crystal structure where this carbonyl group has a *trans* (*ap*) disposition, induced probably by packing interactions due to the fact that it is involved in an intermolecular hydrogen bond with the N1 of the neighboring molecule [N1···O3: 2.861(4) Å]. The ester group at C5 was found to be nearly coplanar with the nearest double bond in the DHP ring (both, in AM1 and in the crystal structure),

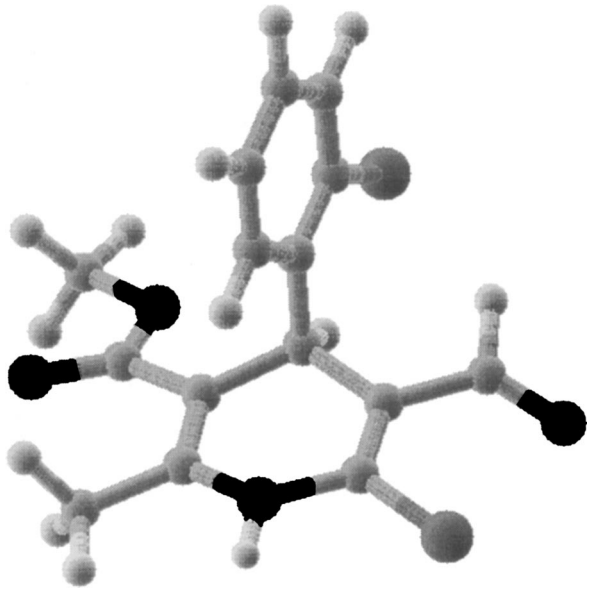


Fig. 1. Plot showing the lowest energy conformer for compounds (**II**) obtained by semiempirical calculations (AM1), $\Delta H = -71.23$ kcal/mol.

and having a *sp* orientation, as found in the majority of the more than 30 crystal structures of members of the nifedipine family.[2] It is thought that only the *sp* conformation of the ester group permits hydrogen bonding to the carbonyl O atom as acceptor atom when the drug binds to its receptor site.[4,23]

The geometrical features predicted for the minimum energy conformation of (**II**) calculated by AM1 along with the results obtained by X-ray crystallography analysis are listed in Table II, showing the most relevant bond distances, valence angles and dihedral angles. Most bond lengths and angles are in good agreement with values retrieved from the Cambridge Structural Database[24] (Version 5.18, October 1999). The torsion angles predicted by AM1 do not agree well with those in the crystal structure (Table II) showing clearly the differences in the conformations found in the solid state and by minimization *in vacuo*. The mean value of the C=C in the 1,4 DHP ring is 1.350(4) Å, which is closer to that found by Krajewski[25] in a related compound (1.365Å).

X-ray crystallography data shows that the 1,4 DHP ring has a slight twofold axis along C4 $\cdots$ N1 and can be described as being mainly in a boat-like conformation, a common feature for cyclohexa-1,4-dienes, with puckering parameters[26] $Q = 0.0873(3)$ Å, $\theta = 71.9(2)^\circ$ and $\phi = 8(2)^\circ$. This ring conformation represents 14% of puckering in ideal cyclohexane

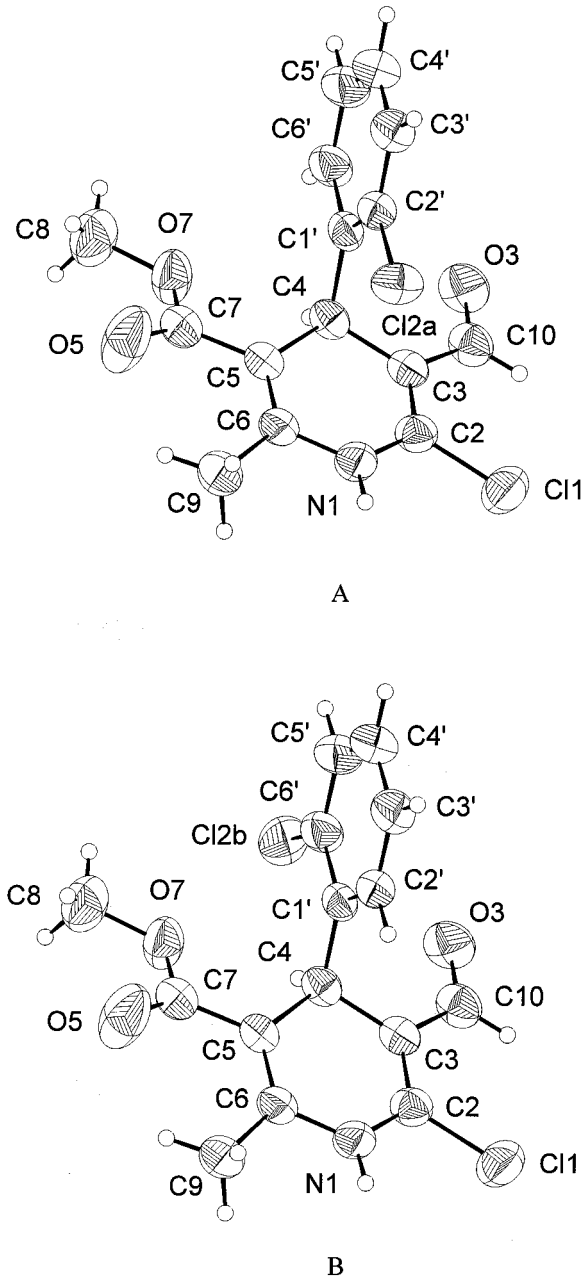


Fig. 2. Plot showing the atomic numbering scheme. The Cl atom attached to the phenyl group has two possible orientations (Cl2a and Cl2b), having 75% (A) and 25% (B) occupancy, respectively. Displacement ellipsoids are drawn at 50% probability level for non-H-atoms.

chair (20% chair with N1 pointing down, 21% twist boat with axis through C5 and C4 pointing up, 59% boat with bowsprit at N1 pointing up).[27]

When the plane of the aromatic ring attached to C4 is perpendicular to the pseudoplane of the

base of the DHP boat, activity of DHP's increases.[4,28] The torsion angle that describes this parameter is C3—C4—C1′—C2′. The bisection of the aromatic ring with respect to the DHP ring can be expressed as the difference between this torsion angle and the ideal value of 60°. This torsion angle shows that the plane of the phenyl ring is approximately bisecting the pyridine ring. The dihedral angle between their respective least-squares planes is 87.79(16)°. This inter-ring orientation is preferred because it minimizes the steric strain imposed by the *ortho* phenyl substituent. The value of the dihedral angle C1′—C4—C3—C2, lower than 120°, shows that the phenyl group is in axial position.

This compound exhibits a deviation of 1.7(3)° from the ideal value. The sum, $\Sigma|\rho|$, of the absolute values of the internal torsion angles of the DHP ring is a measure of its planarity (Table II). Published structure activity ratios indicate that increased planarity of this ring ($\Sigma|\rho|$ tending to zero) correlates with higher activity of the compound. Larger $\Sigma|\rho|$ values are observed, in general, for parent compounds with a nitro group in the *meta* position. Deviations from planarity in the DHP ring, defined as the sum of the numeric values of the six-intraring torsion angles, range from 52.1° to 112.5° in the investigated nifedipines derivatives.[29] Compound (**II**) exhibits a $\Sigma|\rho|$ value of 29.9(5)°, which is one of the lowest values ever found. However, it is difficult to justify in this case the activity comparing the degree of planarity of the ring in the solid state. Presumably, activity should be determined in solution. Besides, the crystal structure was obtained at room temperature, and there is a 75%/25% disordered chlorine atom on the phenyl group at C4 of the DHP ring, both of which may affect how "planar" this ring appears in the solid state.

For a series of compounds investigated by Triggle and coworkers,[4] the authors noted an apparent correlation between activity (as measured by IC_{50} for tonic CD response in guinea pig ileal longitudinal muscle) and the planarity of the DHP ring (as indicated by θ_{ave}, the average of the absolute value of the torsion angles C2—C3—C4—C5 and C3—C4—C5—C6). The value $\theta_{ave} < 15°$ corresponds to the most potent compounds in that series. In compound (II) θ_{ave} is 8.4(4)°, which is in the range of the most active compounds studied by Triggle's group.

The molecules in the crystal are held together by means of an intermolecular hydrogen bond [N1···O3: 2.861(4) Å, H1···O3: 2.01 Å and N1—H1···O3: 169° $(-x+1, -y+1/2, -z+1/2)$]. The C—H···O intramolecular interaction [C9···O5: 2.833(5) Å, H9a···O5: 2.14 Å, and C9—H9a···O5: 128°; and C10···Cl1: 3.081(4) Å, H10···Cl1: 2.67 Å, and C10—H10···Cl1: 107°] stabilizes the molecular conformation in the crystal.

Acknowledgments

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