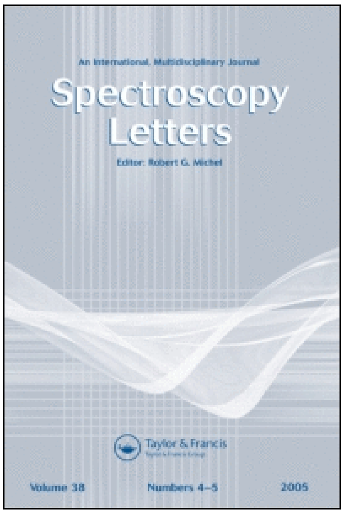

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Molecular Structure of Heterocycles: 4[#] NMR Spectroscopy, X-Ray Diffraction, and Semiempirical Mo Calculations of 3-Phenyl-5-Hydroxy- 5-Trichloromethyl-4,5-Dihydro-FH-Pyrazole-1-Carboxyamide

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MOLECULAR STRUCTURE OF HETEROCYCLES: 4[#] NMR SPECTROSCOPY, X-RAY DIFFRACTION, AND SEMIEMPIRICAL MO CALCULATIONS OF 3-PHENYL-5-HYDROXY-5-TRICHLOROMETHYL-4,5-DIHYDRO-*1H*-PYRAZOLE-1-CARBOXYAMIDE.

key words: 1H-Pyrazole-1-carboxyamides, NMR, X-ray Structure Investigation, MO calculations, AM1

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ABSTRACT

A new series of trichloromethylated- 4,5-dihydro-*1H*-pyrazoles has been studied. The molecular structure of 5-hydroxy-3-phenyl-5-trichloromethyl-4,5-dihydro-*1H*-pyrazole-1-carboxyamide (**2**), synthesized from the reaction of 4-methoxy -4-phenyl-1,1,1-trichloro-3-buten-2-one (**1**) with semicarbazide hydrochloride, was selected and determined by NMR spectroscopy, X-ray diffraction, and semiempirical MO calculations.

Proton and carbon-13 NMR data, as one set of signals, shown that only one pair of the

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[#]For Parts 1-3, see Ref. 10.

enantiomers was obtained. The AM1 calculations showed that **2a** (*1S5S/1R5R*) is the more stable enantiomers pair. The x-ray diffraction data confirmed that only the structure **2a** (*1S5S/1R5R*) was obtained.

This was explained by the existence of an intramolecular hydrogen bond between the hydroxy group at C(5) and the carbonyl group at N(1), with the formation a stable six-membered ring. Compound **2** ($C_{11}H_{10}Cl_3N_3O_2$, M_r = 320.98) crystallizes in the monoclinic space group $P2_1/c$ with the unit cell dimensions a = 6.495(1), b = 25.275(5) and c = 8.401(1) Å, β = 96.88(3)°, R = 3.00 % and wR_2 = 7.71 % for an F^2 refinement on 2012 observed reflections with [I>2σ(I)].

INTRODUCTION

Many trifluoromethylated *1H*-pyrazoles and derivatives are known to exhibit important biological activities in medicinal and agricultural scientific fields, therefore, much attention has been paid to the development of new methods for the synthesis of fluorine containing heterocycles [1-6] and considerable interest is being paid to the biological activities of trifluoromethylated *1H*-pyrazoles [2-6]. For example, a series of 3-trifluoroacetylamino-1-aryl-2-pyrazolines were prepared as antiinflammatories, analgesics, bactericides, fungicides, antiasthmatics, and / or allergy inhibitors [7].

In another recent study [8], a series was obtained of 5-amino-*1H*-pyrazole-1-carboximidine derivatives as Maillard reactions inhibitors. These compounds have been useful for the treatment and prevention of complications from diabetes mellitus. On the other hand, a few examples [9] of 5-hydroxy-4,5-dihydropyrazoles that contain substituents different from phenyl linked at the ring-nitrogen-1 are known. Thus, the intention of the experimental data of NMR spectroscopy and X-ray diffractometry of these compounds are very important for structural correlationships. The molecular structures of 5-trichloromethylated 4,5-dihydro-*1H*-pyrazole-1-carboxyamides (**2**), which present similar structures and may be expected to show potencial biological activity, were not reported so far.

As a part of our research program we have especially studied the molecular structure of a new heterocyclic compounds with chiral centers using ^1H and ^{13}C NMR spectroscopy, X-ray diffraction and semiempirical MO calculation tools [10].

In a previous work the synthesis of 5-hydroxy-3-aryl[alkyl]-5-trichloromethyl-4,5-dihydro-*1H*-pyrazole-1-carboxyamides from the reaction of 4-alkoxy-4-aryl-1,1,1-trichloro-3-buten-2-ones with semicarbazide hydrochloride, using methanol as solvent, was reported[11]. One of these reactions leads to compound **2** that contains two asymmetric atoms [*C(5)* and *N(1)*]. For compound **2** four stereoisomers were expected, among these, two pairs bear an enantiomeric relationship to one another and four pairs of diastereoisomers are present. The two pairs of enantiomers can be represented as following: [**2a** (*1S5S/1R5R*) and **2b** (*1S5R/1R5S*)], (**Scheme 1**).

The aim of this work is to study the molecular structure of 5-hydroxy-3-phenyl-5-trichloromethyl-4,5-dihydro-*1H*-pyrazole-1-carboxyamide (**2**) using ^{1}H and ^{13}C NMR spectroscopy, X-ray diffraction and semiempirical MO calculations. No experimental data on the molecular geometry of this compound in gaseous, liquid, or solid phases are available.

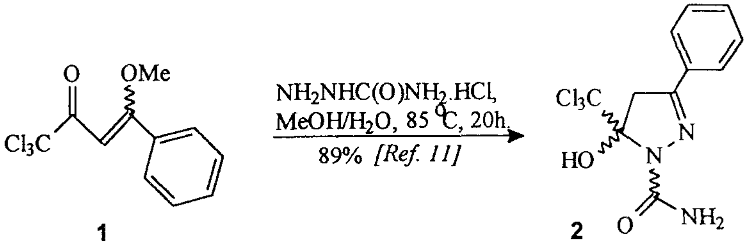
RESULTS AND DISCUSSION

Synthesis

The synthesis of 5-hydroxy-3-phenyl-5-trichloromethyl-4,5-dihydro-*1H*-pyrazole-1-carboxyamide (**2**) from the reaction of 4-methoxy-4-phenyl-1,1,1-trichloro-3-buten-2-one (**1**) with semicarbazide hydrochloride, in methanol as solvent, was developed[11] in our laboratories (**Scheme 1**).

NMR Spectroscopy

From the reaction described in **Scheme 1** the formation of four pairs of diastereoisomers and two pairs of enantiomers were expected for the compound **2**: [**2a** (*1S5S/1R5R*) and **2b** (*1S5R/1R5S*)]. If four pairs of diastereoisomers were formed both ^{1}H and ^{13}C NMR spectra should show two sets of signals. However, the NMR spectra showed only one set of signals which indicates that only one pair of enantiomers was obtained. ^{1}H NMR spectrum shows substantial nonequivalence for the diastereotopic protons H4a and H4b, as doublet (J = 20.0 Hz), singlets for -OH and -NH$_2$ and multiplet for the aromatic protons at the



Scheme 1

phenyl ring. The $^{13}C\{^1H\}$ NMR spectrum exhibits only one peak for each carbon. The selected NMR spectral data are presented in Table 1.

Semiempirical MO Calculations

The AM1 calculations[12] performed showed that **2a** (1*S*5*S*/1*R*5*R*) is the more stable structure. The bond lengths, bond angles and dihedral angles for compound **2a** obtained from the AM1 calculations[12] and X-ray diffraction (in monocrystal, see experimental part) are presented in Tables 2, 3, 4.

Tables 2, 3, 4 show that for most of the geometrical parameters, the AM1 calculations for **2a** furnished very close values to those determined in crystal, although to a certain extent of influence the intramolecular interactions appear in the X-ray values (mainly in bond angles measurements), which are not accounted in the AM1 calculation. Similar to other semiempirical methods[12], the AM1 calculation appears to overestimate some bond lengths (Table 2).

Simple linear regressions between experimental bond lengths, bond angles and dihedral angles acquired by X-ray and those calculated by AM1 were performed for **2a**. Excellent correlation coefficient [r = 0.996] was observed for dihedral angles, but correlation between experimental bond lengths and bond angles (X-ray) against the calculated (AM1) for **2a** exhibited good to regular correlation coefficients [r = 0.989 and r = 0.888, respectively].

TABLE 1

Selected ^1H and ^{13}C NMR data[a] of compound **2a**.

^1H NMR δ [J^2(H-H)] Hz				
H4a	H4b	-OH	NH_2	Ar-H
3.90 [20.0]	3.70 [20.0]	8.30	7.20	7.4 - 7.90

^{13}C NMR δ				
C3	C4	C5	CCl_3	C=O
152.60	46.30	100.80	104.60	157.60

[a] NMR-spectra were recorded on a BRUKER DPX-400(^1H at 400.13 MHz and ^{13}C at 100.62 MHz), 298 K, digital resolution ±0.01 ppm, in DMSO-d_6/TMS.

Part of the differences between the experimental bond lengths, bond angles and dihedral angles acquired by X-ray and those calculated by AM1 could be explained by the existence of intermolecular interactions, as showed by X-ray data (see experimental and Figure 1), which is not computed in MO calculations.

This evidence can be easily observed for the bond lengths [e.g., O(2)-H(5), N(3)-H(2)], bond angles [e.g., C(1)-N(3)-H(2),C(5)-O(2)-H(5), C(4)-C(5)-O(2)] and dihedral angles [e.g., N(1)-C(5)-O(2)-H(5), N(1)-C(1)-N(3)-H(2)] directly involved in the intermolecular interactions (Figure 1).

From the AM1 calculations it was also possible to observe that the most stable structure of compound **2** is that the sp^3 N(1) has the N-substituent *trans* to CCl_3 (**2a**). In this structure the steric interaction between the CCl_3 and N-substituent is minimized and the H(5)-O(1) hydrogen bond is favored.

TABLE 2

Selected bond lengths[a] calculated by AM1[b] and determined by X-Ray diffraction for compound **2a**.

Atoms	Bond Length (Å) Calcd. AM1 **2a** *(1S5S/1R5R)*	Bond Length (Å) X-Ray
N1-N2	1.3607	1.406(2)
N2-C3	1.3234	1.280(2)
C3-C4	1.5195	1.500(3)
C4-C5	1.5709	1.534(3)
C5-N1	1.5186	1.473(2)
C1-N1	1.4490	1.380(2)
C1-O1	1.2546	1.244(2)
C1-N3	1.3769	1.322(3)
N3-H1	0.9880	0.80(3)
N3-H2	0.9906	0.80(3)
C3-C6	1.4565	1.469(3)
C4-H3	1.1144	0.96(2)
C4-H4	1.1180	0.95(2)
C5-C2	1.5292	1.568(3)
C2-Cl1	1.7582	1.760(2)
C2-Cl2	1.7695	1.778(2)
C2-Cl3	1.7636	1.774(2)
C5-O2	1.4026	1.387(2)
H5-O2	0.9734	0.77(3)
H5-O1	2.0554	1.97(3)
H1-N2	2.6551	2.32(3)

[a] See Experimental.

[b] E=-2962.90 Kcal.mol^{-1}, gradiente 0.009 (Polak-Ribiere conjugated gradient (max. 0.01 Kcal.mol^{-1}).

X-Ray Diffraction Data

Figure 1 show the ZORTEP[14] plot of the molecular structure and atom labeling of **2a**. Selected bond lengths and angles are listed in Tables 2 and 3, respectively.

The lists of the observed and calculated structure factors, anisotropic thermal parameters and hydrogen atom coordinates are available from the authors upon request.

TABLE 3

Selected bond angles[a] calculated by AM1 and determined by X-Ray diffraction for compound **2a**.

Atoms	Bond Angle (degrees) Calcd. AM1 **2a** *(1S5S/1R5R)*	Bond Angle (degrees) X-Ray
N1-N2-C3	111.35	108.14(15)
N2-C3-C4	113.08	113.99(17)
C3-C4-C5	101.51	103.00(16)
C4-C5-N1	103.04	101.45(15)
C5-N1-N2	110.95	112.51(14)
N2-C3-C6	125.59	121.83(17)
N2-N1-C1	118.63	117.96(16)
N1-C5-O2	114.89	113.85(16)
N1-C5-C2	109.63	109.82(16)
N1-C1-O1	119.81	119.38(18)
N1-C1-N3	119.90	116.51(18)
C1-N3-H1	122.40	121(2)
C1-N3-H2	116.86	120(2)
C5-O2-H5	109.85	101.7(19)
O2-H5-O1	114.40	150(3)
H5-O1-C1	107.58	94.5(7)
C5-C2-Cl1	110.26	112.15(14)
C5-C2-Cl2	109.05	108.55(14)
C5-C2-Cl3	111.44	110.44(13)
C2-C5-O2	111.56	109.14(16)
C4-C5-O2	106.18	111.41(17)
C4-C5-C2	111.18	111.00(16)
H3-C4-H4	109.90	106.6(19)
H3-C4-C3	111.74	113.7(13)
H4-C4-C3	111.69	109.4(13)
N3-H1-N2	92.25	105(2)
H1-N2-N1	75.49	76.5(7)

[a] See Experimental.

TABLE 4

Selected dihedral angles[a] calculated by AM1 and determined by X-Ray diffraction for compound **2a**.

Atoms	Dihedral Angle (Degrees) Calcd. AM1 **2a** *(1S5S/1R5R)*	Dihedral Angle (Degrees) X-Ray
N1-N2-C3-C4	-2.88	-3.2(2)
N2-C3-C4-C5	+2.12	+8.2(2)
C3-C4-C5-N1	-0.64	-8.9(2)
C4-C5-N1-N2	+0.90	+8.1(2)
C5-N1-N2-C3	-2.35	-3.5(2)
N1-N2-C3-C6	+176.23	175.98(16)
N1-C1-N3-H1	+3.08	0(2)
N1-C1-N3-H2	+170.25	+174(2)
O1-C1-N3-H1	-174.24	-179(2)
O1-C1-N3-H2	-7.07	-5(2)
N1-C5-O2-H5	+67.68	+37(2)
N1-C5-C2-Cl1	+54.75	+54.63(18)
N1-C5-C2-Cl2	+173.94	+173.99(12)
N1-C5-C2-Cl3	-66.24	-66.66(17)
N1-C5-C4-H3	-119.91	-131.8(14)
N1-C5-C4-H4	+117.72	+108.4(14)
O2-C5-C4-H3	+118.96	+106.7(15)
O2-C5-C4-H4	-3.41	-13.1(15)
C2-C5-C4-H3	-2.55	-15.1(15)
C2-C5-C4-H4	-124.93	-135.0(14)
H3-C4-C3-C6	-57.69	-49.1(15)
H4-C4-C3-C6	+65.88	+69.9(14)
N2-C3-C6-C7	-6.13	-11.4(3)
O1-C1-N1-N2	-149.56	-165.97(19)
O1-C1-N1-C5	-9.49	-12.9(3)
C1-N1-C5-C2	+97.76	+96.2(2)
C1-N1-C5-O2	-28.78	-26.5(3)

[a] See Experimental.

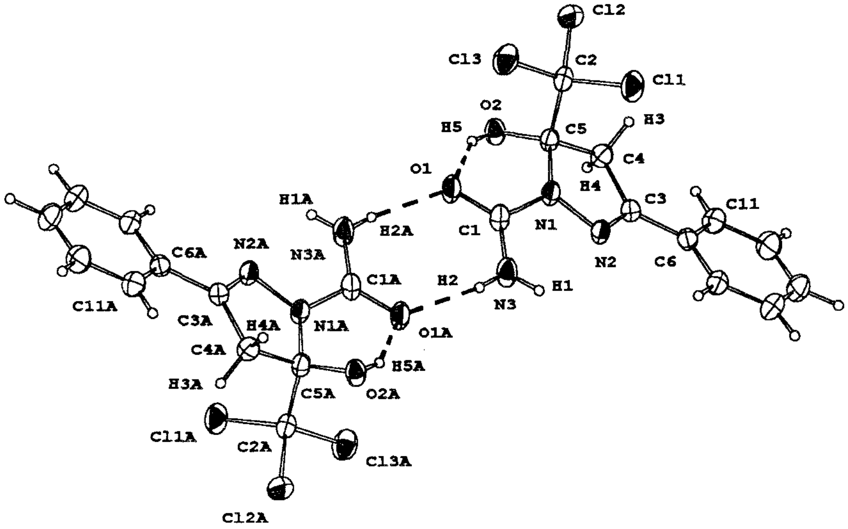


Figure 1. ZORTEP[14] plot with atom-labeling scheme of the structure of **2a** displacement ellipsoids at the 30% level. Symmetry related atoms generated by the operator -*x*-1, -*y*+1, -*z*-1. Intramolecular and intermolecular hydrogen bonds are indicated with dashed lines.

The X-ray structure analysis demonstrate clearly and unambigously the (1*S*5*S*/1*R*5*R*) conformation for **2a**. The observed planarity of the tetrasubstituted pyrazol ring (rms deviation of 0.0414 Å), can be attributed to the strain established by the double bond between the atoms N(2) and C(3) [N(2)···C(3) = 1.280(2) Å]. Consequentely, the sum of the internal angles of the N(1)N(2)C(3)C(4)C(5) ring is 539.09° which deviates slightly from the ideal value of 540°, while the atom N(1) assumes a sp^2-character so that the bond angles C(1)-N(1)-N(2) and C(1)-N(1)-C(5) are opened up to 117.96(16)° and 124.55(16)°, respectively. As expected, the phenyl ring C(6)-C(11) is planar (rms deviation of 0.0020 Å) with an interplanar angle of 13.8(1)° with the pyrazol ring. This deviation from coplanarity has a weakened effect on the p_{π}-p_{π} interaction between the phenyl ring and the C(3)-N(2)-N(1) fragment of the pyrazol ring. Table 5 lists the distances and angles related to the intramolecular and intermolecular hydrogen bonds observed in the crystal structure of **2a**. Figure 1 shows that the intramolecular hydrogen bond between the atoms O(2) and O(1) generates a six membered ring [C(1)N(1)C(5)O(2)H(5)O(1)] which possesses a twist conformation according to the torsion angle between the atoms O(1)-C(1)-C(5)-O(2) [-35.27(17)°]. Two molecules of **2a** generated by the symmetry operator -*x*-1 , -*y*+1 , -*z*-1 in Figure 1, point out the intermolecular hydrogen bonds between the symmetry related amine and carbonyl groups. The sites of the atoms O(1), C(1) and N(3) are converted to the sites of the atoms O(1A), C(1A) and N(3A) through the inversion center located in the planar eightlr membered ring [O(1)C(1)N(3)H(2)O(1A)C(1A)N(3A)H(2A)]. The hydrogen bond lengths and angles, the crystal data, the structure refinement and the final positioned parameters for non-hydrogen atoms of **2a** are given in Tables 5, 6 and 7.

EXPERIMENTAL

Compound

The 5-hydroxy-3-phenyl-5-trichloromethyl-4,5-dihydro-1H-1-pyrazolcarboxyamide (2) was synthesized from the reaction of 4-methoxy-4-phenyl-1,1,1-trichloro-3-buten-2-one with *semicarbazide hydrochloride in methanol*[11].

NMR Spectroscopy

^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DPX-400 (^{1}H at 400.13 MHz and ^{13}C at 100.62 Mhz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6/TMS.

AM1 Calculations

The calculations were carried out by the Austin Model 1 (AM1) semiempirical method[12], implemented in the HyperChem 4.5 package (1995)[13]. Geometries were completely optimized without fixing any parameter, thus bringing all geometric variables to their equilibrium values. The energy minimization protocol employs the Polak-Ribiere algorithm, a conjugated gradient method[13]. Convergence to a local minimum is achieved when the energy

TABLE 5

Hydrogen bond lengths and angles for **2a**.

Bond distances (Å)		Bond angles	(degreees)
H(5)·····O(1)	1.971	O(2)–H(5)·····O(1)	150(3)
H(2)·····O(1A)	2.091	N(3)–H(2)·····O(1A)	171(3)

Symmetry transformation used to generate equivalent atom: -x-1 , -y+1 , -z-1

gradient is ≤ 0.01 kcal.mol^{-1}. The calculations were performed on a PC Pentium-166MHz Megatropic computer equipped with an ink jet Epson Stylus Color II (720 dpi) printer.

X-Ray Diffraction

Crystals of **2a** were obtained by diffusion of a *n*-hexane layer into a concentrate tetrahydrofurane solution of **2a**. An additional slow evaporation of the solvents yielded the crystal of compound **2a**. A transparent colorless crystal of **2a** with approximate dimensions 0.50 x 0.33 x 0.23 mm^3 was mounted on a glass fiber and used for intensity data collection at 293(2) K. The unit cell dimensions and the orientation matrix for the data collection resulted from a least square fit of 25 reflections in the range of 17.94° to 20.64°.

The automatic intensity search and indexing method indicated a cell possessing monoclinic crystal system with a *P* lattice. Diffractometric intensity data were collected on an automatic four circles diffractometer (Enraf-Nonius CAD4)[15] using graphite-monochromatic Mo-K_α radiation and ϖ-2θ scans with a scan speed of 30 sec./reflection. Every 60 min., the intensity and orientation of three standard reflections were measured; the observed intensity decay was 2.0% over the data collection. A total of 2789 reflections were collected involving one quarter of the Ewald sphere. From the Bravais lattice and observed reflections conditions, the space group was chosen to be $P2_1/c$. Lorentz and polarization correction were made on the intensity data. After merging of the equivalent reflections ($R_{int.}$ = 1.55%), 2559 reflections were

TABLE 6

Crystal data and structure refinement for **2a**, with e.s.d.'s in parenthesis.

Empirical formula	$C_{11}H_{10}Cl_3N_3O_2$
Formula weight	322.57
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system / Space group	Monoclinic / $P2_1/c$
Unit cell dimensions (Å)	a = 6.495(1) b = 25.275(5) c = 8.401(1) β = 96.88(3)°
Volume (Å^3) , Z	1369.2(4) , 4
Density (calculated) (Mg/m^3)	1.565
Absorption coefficient (mm^{-1})	0.669
F(000)	656
Crystal size (mm^3) /Colour	0.50 x 0.33 x 0.23 / Colourless
No. of reflns. (lattice)	25
Theta range (lattice)	17.94° to 20.64°
Theta range for data collection (°)	2.57 to 25.57
Limiting indices	$-7 \leq h \leq 0$, $-30 \leq k \leq 0$, $-10 \leq l \leq 10$
Reflections collected	2789
Independent reflections	2559 [R(int) = 0.0155]
Reflections observed	2012
Criterion for observation	[I>2sigma(I)]
Absorption correction	Psi-scan
Max. and min. transmission (%)	96.42 and 90.08
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2559 / 0 / 203
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R_1 = 0.0300, wR_2 = 0.0771
Maximal (Δ/σ)	0.001
Extinction coefficient	0.0189(13)
Largest diff. peak and hole (e.Å^{-3})	0.268 and -0.262

TABLE 7

Atomic coordinates ($\cdot 10^4$) and equivalent isotropic displacement parameters ($Å^2 \cdot 10^3$) for **2a**, with e.s.d.'s in parenthesis.

Atom	*x*	*y*	*z*	U_{eq}
Cl(1)	2342(1)	5856(1)	-1064(1)	66(1)
Cl(2)	-109(1)	6632(1)	398(1)	63(1)
Cl(3)	-1693(1)	5586(1)	-243(1)	65(1)
O(1)	-4200(2)	5506(1)	-3588(2)	54(1)
O(2)	-3171(2)	6481(1)	-2559(2)	48(1)
N(1)	-1083(2)	5875(1)	-3867(2)	41(1)
N(2)	364(2)	5986(1)	-4941(2)	41(1)
N(3)	-2482(3)	5245(1)	-5649(3)	58(1)
C(3)	1121(3)	6446(1)	-4611(2)	37(1)
C(4)	180(3)	6725(1)	-3299(3)	42(1)
C(5)	-1182(3)	6296(1)	-2665(2)	38(1)
C(1)	-2686(3)	5533(1)	-4363(3)	44(1)
C(2)	-211(3)	6094(1)	-976(3)	45(1)
C(6)	2784(3)	6667(1)	-5451(2)	38(1)
C(11)	3355(3)	7194(1)	-5229(3)	48(1)
C(10)	4967(4)	7400(1)	-5979(3)	58(1)
C(9)	6011(4)	7085(1)	-6933(3)	63(1)
C(8)	5453(4)	6559(1)	-7168(3)	61(1)
C(7)	3850(3)	6351(1)	-6433(3)	49(1)

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

unique. Although the little observed linear absorption coefficient (0.669 mm^{-1}), a semi-empirical absorption correction based on *psi*-scans was performed.

The structure was solved using the direct methods employing SHELXS-97 program[16] and all non-hydrogen atoms were located by subsequent Fourier difference synthesis. For structure refinement the SHELXL-97 program[17] was employed and the full-matrix least-squares method minimized on $\Sigma w(F_o^2 - F_c^2)^2$ where w is a weighting scheme detailed below. All non-hydrogen atoms were refined using anisotropic thermal parameters. The positions of the hydrogen atoms were found in the Fourier difference map and the thermal displacement parameters were refined isotropically. For the final refinement of the structure an isotropic extinction correction was included. Scattering factors for all atoms were as in the SHELXL-97 program[17]. The final refinement including 203 parameters gave $R = 3.00\%$ and $wR_2 = 7.71\%$ with the weighting scheme, $w = 1/[s^2(F_o^2) + (0.0371P)^2 + 0.4689P]$ and $P = (F_o^2 + 2F_c^2)/3$ with a maximal shift/e.s.d. = 0.001. Table 6 summarizes the crystal data and structure refinement parameters for **2a**.

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