J Chem Crystallogr (2010) 40:428–431
DOI 10.1007/s10870-009-9672-3

ORIGINAL PAPER

Synthesis, Characterization and Antibacterial Activity of *N*-(*N*-Acetic Acid-yl-Phthalimide-5-yl) Maleamic Acid Dihydrate

Jian Li

Received: 10 March 2009 / Accepted: 3 December 2009 / Published online: 19 December 2009

Abstract The compound *N*-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid ($C_{14}H_{10}N_2O_7$, $M_r = 318$) was synthesized and its structure was characterized by elemental analysis, ^{1}H NMR and IR spectra. The single crystal of the title compound ($C_{14}H_{14}N_2O_9$, $M_r = 354.27$) was cultured and its structure was determined by single crystal X-ray diffraction. The crystal belongs to monoclinic system, space group $P21/c$ with $a = 14.3859(19)$, $b = 12.5835(18)$, $c = 8.6934(15)$ Å, $\beta = 102.824(2)°$, $V = 1534.5(4)$ Å^3, $Z = 4$, $D_c = 1.534$ g cm^{-3}, μ(Mo $K\alpha$) = 0.131 mm^{-1}, $F(000) = 736$. The final refinement gave $R = 0.0652$, $wR(F^2) = 0.1239$ for 2,703 observed reflections with $I > 2\sigma(I)$. X-ray diffraction analysis reveals that the asymmetric unit of the title compound contains one *N*-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid molecule and two water molecules. One of the two water molecules is disordered. The phthalimide group is essentially planar. The crystal structure of the title compound is stabilized by N–H…O and O–H…O hydrogen bonds interactions. The compound *N*-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid possesses moderate antibacterial activity.

Keywords *N*-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid dihydrate · Synthesis · Crystal structure · Characterization · Antibacterial activity

J. Li (✉)
Department of Chemistry and Chemical Engineering, Weifang University, 261061 Weifang, China
e-mail: ljwfu@163.com

Introduction

Nitrogen heterocycle is an important part of the chemical structures of many natural and synthetic products with a variety of properties and applications in medicine. Among the bicyclic non-aromatic nitrogen heterocycles, phthalimides are an interesting class of compounds with a large range of applications [1]. Phthalimides have served as starting materials and intermediates for the synthesis of many types of alkaloids and pharmarcophores [2]. The phthalimide group has provided the classical means for direct introduction of the masked amino functions as well as for *N*-protection of amino acids, amino sugars and simple amino alcohols [3]. Recently, phthalimide and some of its derivatives have proved to have important biological effects, similar or even hihger, than known pharmacological molecules, and so their biological activity is being a subject of biomedical research [4–6]. However, 5-amino-*N*-aminoacidlyphthalimide and their derivatives have never been reported so far. Investigation of their structures and antibacterial properties may help us to explore the interactions among the molecules, design and synthesize new phthalimide derivatives, as well as evaluate the potential medicinal applications. In this paper, the synthesis and antibacterial activities of *N*-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid (I) and the crystal structure of *N*-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid dihydrate (II) are reported.

Experimental Procedures

Reagents and Measurements

All reagents for synthesis and analyses were of commercially available analytical grade and were used as received

without further purification. *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *Staphylococcus aureus* were offered by College of Biological. Elemental analyses were performed on a Perkin–Elmer 240C elemental analyzer. Proton NMR spectra were obtained with a Varian INOVA300 spectrometer, using tetramethylsilane (TMS) as internal standard and $CDCl_3$ as solvent. IR spectra were measured on a TENSOR 27 (Bruker) FT-IR spectrometer with KBr pellets in the range 4,000–400 cm^{-1}.

Synthesis of the Compound (I) and (II)

According to the previous work [7, 8], 2-(1,3-Dioxoisoindolin-2-yl)acetic acid and 2-(5-Amino-1,3-dioxoisoindolin-2-yl)acetic acid was synthesized. The compound *N*-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid was prepared according to the literature [9].

To a solution of 2-(5-Amino-1,3-dioxoisoindolin-2-yl)acetic acid (5 mmol) in acetone (20 mL), maleic anhydride (5 mmol) in acetone (20 mL) was added drop by drop, the solution was stirred magnetically for 2 h at room temperature. The product was filtered and dried. Yield 65.3%. Anal. Calcd. (%) for $C_{14}H_{10}N_2O_7$: C 52.83, H 3.14, N 8.81. Found (%): C 52.02, H 3.24, N 8.75. ^{1}H NMR ($CDCl_3$): 4.57 (m, 2H, –CH_2–), 6.51 (d, 1H, = CH–), 6.80 (d, 1H, = CH–), 8.07–8.11 (d, 2H, ph-H), 8.51 (m, 1H, ph-H). All absorption bands in the IR data of the compound (I) appear as expected. ν(cm^{-1}): 3,408 cm^{-1} (O–H), 3,101 cm^{-1} (N–H), 1,743, 1,712 and 1,690 cm^{-1} (C=O), 1,511 cm^{-1} (N–C).

A 20 mg of the compound (I) was dissolved in 95% ethanol–water (95%) of 20 mL. The single crystal suitable for X-ray determination was obtained by evaporation at room temperature from the solution after a week.

X-Ray Single Crystal Structure Determination

A light yellow crystal with dimensions of 0.38 mm × 0.27 mm × 0.09 mm was selected for X-ray diffraction. The reflection data were collected on a Bruker Smart Apex II CCD area diffractometer with graphite monochromatized Mo-$K\alpha$ radiation ($\lambda = 0.71073$ Å) at 298 (2) K. A total of 7,878 reflections were collected in the range of $1.45 < \theta < 25.01$ by using ω scans mode. And a total of 2,703 observed reflections with $I > 2\sigma(I)$ were used in structure solution and refinement. 1,061 independent reflections and $R_{int} = 0.1307$. *LP* corrections were applied to the data.

The structure was solved by direct methods using SHELXL-97 [10] and expanded using Fourier techniques. All non-hydrogen atoms and hydrogen atoms were refined anisotropically and isotropically, respectively. The final refinement by full-matrix least squares method was converged at $R = 0.0680$, and $wR = 0.1605$ ($w = 1/[\delta^2(F_o^2) + (0.0157P)^2 + 0.0000P]$, $P = (F_o^2 + 2F_c^2)/3$), $S = 1.020$, $(\Delta/\sigma)_{max} = 0.000$. The largest peak in the final difference Fourier map is 0.240 e Å^{-3} and the minimum peak is −0.260 e Å^{-3}. Molecular graphics were drawn with the program package SHELXS-90 [11].

Antibacterial Activity Tests

Antibacterial tests were performed according to the literature [12, 13]. The media required for the preparation of test organism inocula are made from pancreatic digest of casein (15.0 g), papaic digest of soybean meal (5.0 g), sodium chloride (5.0 g), agar (15.0 g) and water (1,000 mL). The compound (I) 0.5 g was dissolved in 100 mL of Sodium Chloride Injection. Several pieces of filter paper (the diameter is 5 mm) were put into the solution and then sterilized at 121 °C for 20 min. Preparation of the bacteries solution was according to Edition 2005 Pharmacopoeia of PRC.

The medium (20 mL) was paced in Petri dishe with the required number and hardened into a smooth base layer with uniform depth. The bacteries medium (5 mL) was added and the plate was tilted back and forth to spread the inoculum enenly over the surface, and then allowed it to harden. Four pieces of test paper were attached to the surface of the medium in every dish, and the plates were covered to avoid contamination. The plate was incubated at 35 °C for 16 h. The diameter of each zone of growth, inhibition to the nearest 0.1 mm, was measured and recorded, and the averages of the three values were calculated.

Results and Discussion

Synthesis Scheme of the Compound (I)

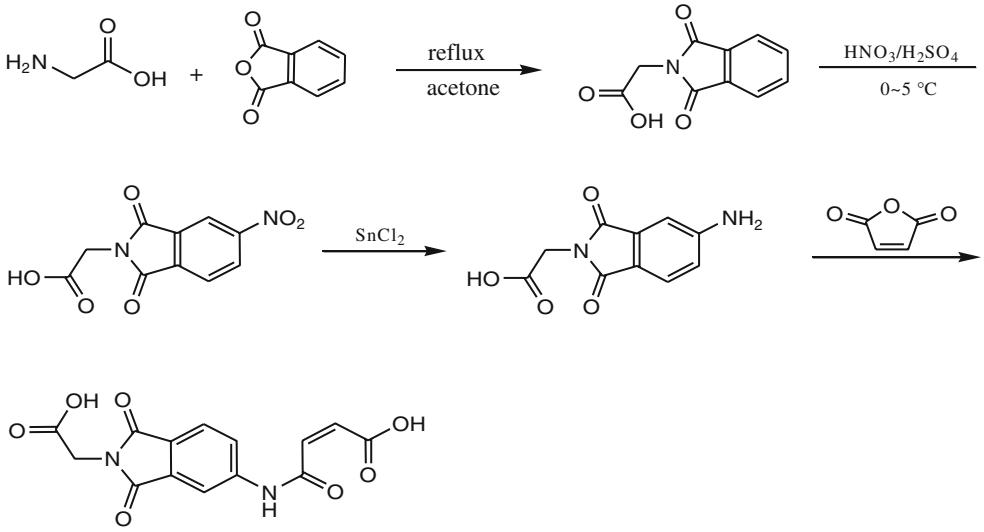
N-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid (I) was prepared by four steps in higher yield from 2-amino-acetic acid and isobenzofuran-1,3-dione, the synthesis process is shown in Scheme 1.

Structural Description

The molecular structure of the title compound is shown in Fig. 1 and the crystal packing of the compound is depicted in Fig. 2. The selected bond lengths and angles are given in Table 1.

As seen from Fig. 1, the asymmetric unit of the title compound contains one *N*-(*N*-acetic acid-yl-phthalimide-5-yl) maleamic acid molecule and two water molecules. One of the two water molecules is disordered. The *N*-(*N*-acetic

Scheme 1 Synthesis of the compound (I)



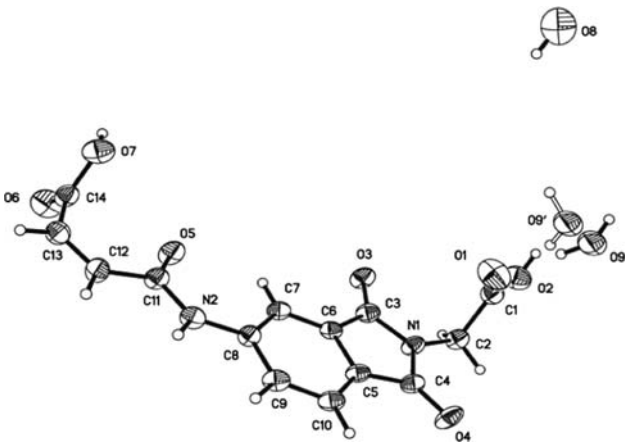


Fig. 1 Molecular structure of the title compound at 30% probability thermal ellipsoids

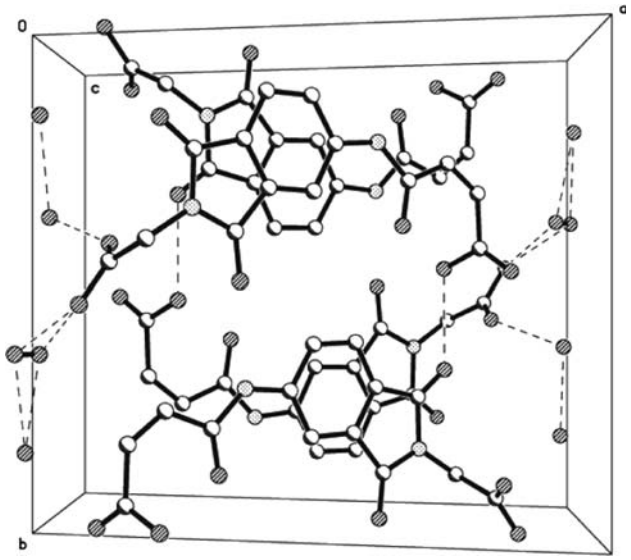


Fig. 2 Crystal packing of the title compound

Table 1 Select bond lengths (Å) and bond angles (°)

Bond	Distance	Bond	Distance	Bond	Distance
N(1)–C(3)	1.380(5)	N(2)–C(8)	1.402(5)	O(4)–C(4)	1.190(5)
N(1)–C(4)	1.410(5)	O(1)–C(1)	1.183(5)	O(5)–C(11)	1.223(4)
N(1)–C(2)	1.449(5)	O(2)–C(1)	1.296(5)	O(6)–C(14)	1.174(5)
N(2)–C(11)	1.356(5)	O(3)–C(3)	1.221(5)	O(7)–C(14)	1.344(6)
Bond	**Angle (°)**	**Bond**	**Angle (°)**	**Bond**	**Angle (°)**
C(3)–N(1)–C(4)	111.4(4)	O(3)–C(3)–N(1)	122.7(4)	C(7)–C(8)–N(2)	122.9(4)
C(3)–N(1)–C(2)	123.8(3)	O(3)–C(3)–C(6)	130.2(4)	O(5)–C(11)–N(2)	123.0(4)
C(4)–N(1)–C(2)	124.4(4)	N(1)–C(3)–C(6)	107.1(3)	O(5)–C(11)–C(12)	122.7(4)
C(11)–N(2)–C(8)	129.9(3)	O(4)–C(4)–N(1)	123.7(4)	N(2)–C(11)–C(12)	114.3(4)
O(1)–C(1)–O(2)	125.1(5)	O(4)–C(4)–C(5)	131.4(4)	O(6)–C(14)–O(7)	124.4(4)
O(1)–C(1)–C(2)	122.8(5)	N(1)–C(4)–C(5)	104.9(4)	O(6)–C(14)–C(13)	124.6(6)
O(2)–C(1)–C(2)	112.0(5)	C(9)–C(8)–N(2)	117.0(4)	O(9)–C(14)–C(13)	110.9(5)
N(1)–C(2)–C(1)	110.0(4)				

Table 2 Hydrogen bond lengths (Å) and bond angles (°)

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠DHA
N(2)–H(2C)…O(3)[a]	0.86	2.150	2.975	161(2)
O(2)–H(2)…O(9′)[b]	0.82	1.718	2.495	157(2)
O(2)–H(2)…O(9)[b]	0.82	1.856	2.642	160
O(7)–H(7)…O(4)	0.82	1.932	2.750	176
O(8)–H(8C)…O(6)[c]	0.85	2.148	2.997	176
O(8)–H(8D)…O(9)[d]	0.85	1.750	2.600	180
O(8)–H(8D)…O(9′)[d]	0.85	2.004	2.801	156
O(9)–H(9C)…O(1)	0.85	1.921	2.997	178
O(9)–H(9D)…O(2)[b]	0.85	2.084	2.642	123
O(9)–H(9D)…O(1)[b]	0.85	2.465	3.315	179
O(9′)–H(9′C)…O(1)	0.85	1.990	2.812	163
O(9′)–H(9′D)…O(6)[c]	0.85	2.307	3.134	164

Symmetry codes: [a] $-x + 1$, $y + 1/2$, $-z + 3/2$; [b] $-x + 2$, $-y + 1$, $-z + 2$; [c] $-x + 1$, $-y + 1$, $-z + 1$; [d] $-x + 2$, $y - 1/2$, $-z + 3/2$

Table 3 Antibacterial activities tests of the title compound

Bacterial strain	Inhibitory zone (mm)	Bactericidal efficiency assay	Agar media
Escherichia coli	20.2	Positive	Negative
Pseudomonas aeruginosa	8.4	Positive	Negative
Salmonella typhi	17.3	Positive	Negative
Staphylococcus aureus	15.0	Positive	Negative

acid-yl-phthalimide-5-yl) maleamic acid molecule adopts an *Z* configuration about the C=C functional bond. The phthalimide group is essentially planar. All the bond lengths and bond angles in the title compound are within normal ranges and comparable to those in the similar compound [8]. The C–N bond lengths of 1.356(5)–1.449(5) Å conform to the value for a single bond. The crystal structure of the title compound is stabilized by N–H…O and O–H…O hydrogen bonds interactions (Fig. 2; Table 2).

Antibacterial Activity

The results of antibacterial activities tests were listed in Table 3. The preliminary antibacterial tests show that the compound, (I), exhibits moderate antibacterial activities against four bacteria: *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *Staphylococcus aureus*, with their corresponding inhibition zones of 20.2, 8.4, 17.3 and 15.0 mm.

Supplementary Material

Crystallographic data for the structure of the title compound have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-698464. These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/deposit. Telephone: (44) 01223 762910 Facsimile: (44) 01223 336033 Postal Address: CCDC, 12 Union Road, CAMBRIDGE CB2 1EZ, UK.

Acknowledgments This work was supported by the Natural Science Foundation of Shandong Province (No. 2009ZRA07019).

References

1. Ribeier da Silva MAV, Santos CPF, Monte MJS, Sousa CAD (2006) J Therm Anal Calorim 83:533
2. Luzzio FA, Zacherl DAP (1999) Tetrahedron Lett 40:2087
3. Debebham JS, Madsen R, Roberts C, Freiser-Reid B (1995) J Am Chem Soc 117:3302
4. Wang T, Zhang YH, Ji H, Chen YP, Peng SX (2008) Chinese Chem Lett 19:26
5. Sena VLM, Srivastava M, Silva RO, Luis VLM (2003) II Farmaco 58:1283
6. Lima LM, Brito FCF, Souza SD, Miranda ALP, Rodrigues CR, Fraga CAM, Barreiro EJ (2002) Bioorg Med Chem Lett 12:1533
7. Li J, Liang ZP (2006) Acta Cryst E62:o4195
8. Liang ZP, Li J (2006) Acta Cryst E62:o4126
9. Shi DX, Feng YQ, Li XF, Zhou LS (2003) Acta Cryst E59:o1068
10. Sheldrick GM, SHELXL97 (1997) Program for the Refinement of Crystal Structure. University of GÖttingen, Germany
11. Sheldrick GM, SHELXL97 (1990) Acta Crystallogr A46:467
12. You ZL, Zhu HL (2004) Z Anorg Allg Chem 630:2754
13. Li BL, Guo J, Zhang XQ, Lai YT, Hu HM (2007) Z Naturforsch 62b:244