Asian Journal of Chemistry; Vol. 26, No. 18 (2014), 6127-6130

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16826

Synthesis, Crystal Structures and Antimicrobial Activities of *N*'-[4-(Dimethylamino)benzylidene]-2-hydroxy-3-methylbenzohydrazide Monohydrate and *N*'-(4-Nitrobenzylidene)-2-hydroxy-3-methylbenzohydrazide Monohydrate

PEIFENG YIN

School of Biology and Food Engineering, Chuzhou University, Chuzhou 239000, Anhui Province, P.R. China

Corresponding author: E-mail: ypf197912@126.com

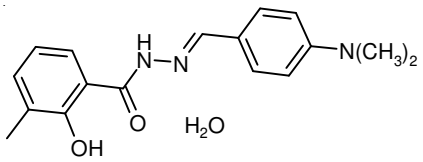
Received: 6 December 2013; *Accepted*: 28 April 2014; *Published online*: 1 September 2014; AJC-15867

Two structural similar hydrazone compounds, *N*'-[4-(dimethylamino)benzylidene]-2-hydroxy-3-methylbenzohydrazide monohydrate (**1**) and *N*'-(4-nitrobenzylidene)-2-hydroxy-3-methylbenzohydrazide monohydrate (**2**), have been synthesized and structurally characterized by elemental analysis, IR spectra, ^{1}H NMR and X-ray single crystal structure determinations. Both compounds crystallize in monoclinic space group $P2_1/c$. X-ray crystallography reveals that each compound consists of a hydrazone molecule and a water molecule of crystallization. The molecule of each compound has E configurations with respect to the C=N double bond and C-N single bond. The water molecules are linked to the hydrazone molecules through intramolecular O-H···O and O-H···N hydrogen bonds. In the crystal structures of both compounds, molecules are linked through intermolecular O-H···O and N-H···O hydrogen bonds, forming layers parallel to ac plane. Antimicrobial activities against *Bacillus subtilis*, *Escherichia coli*, *Staphyloccocus aureus* and *Bacillus magaterium* were studied.

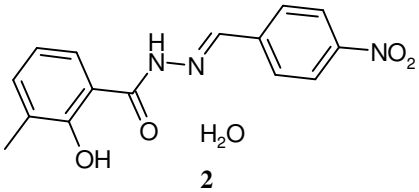
Keywords: Synthesis, Crystal structure, Hydrazone, Hydrogen bonds, Antimicrobial activity.

INTRODUCTION

Hydrazone compounds are readily synthesized by reaction of aldehydes with hydrazides[1-3]. These compounds have been demonstrated to possess effective biological activities, such as antibacterial and antitubercular activities[4-6]. Hydrazone compounds derived from salicylhydrazide have been widely investigated. However, no hydrazone compounds derived from 3-methylsalicylhydrazide have been reported so far. As an extension of work on structures and antimicrobial activities of such compounds, in this paper, two new structural similar compounds, *N*'-[4-(dimethylamino)benzylidene]-2-hydroxy-3-methylbenzohydrazide monohydrate (**1**) and *N*'-(4-nitrobenzylidene)-2-hydroxy-3-methylbenzohydrazide monohydrate (**2**) (**Scheme-I**), have been synthesized and characterized. The antimicrobial activities of the compounds against *Bacillus subtilis*, *Escherichia coli*, *Staphyloccocus aureus* and *Bacillus magaterium* have been studied.



1



2

Scheme-I: Hydrazone compounds

EXPERIMENTAL

3-Methylsalicylhydrazide, 4-dimethylaminobenzaldehyde and 4-nitrobenzaldehyde were analytical pure grade from Aldrich Chemical Co., Milwaukee, Wisconsin and used without further purification. Other reagents were also analytical pure grade and obtained from Beijing Reagent Factory, used without further purification. IR spectra were recorded on a Nicolet IR-470 spectrometer with KBr pellets in the range 4000-400 cm^{-1}. C, H, N analyses were carried out using a Perkin-Elmer model 240 analyzer. ^{1}H NMR spectra were recorded on Bruker AVANCE 500 MHz spectrometer with tetramethylsilane as the internal reference.

Synthesis of compound 1: 3-Methylsalicylhydrazide (0.1 mmol, 15.2 mg) and 4-dimethylaminobenzaldehyde (0.1 mmol, 14.9 mg) were dissolved in a sufficient volume of methanol and the mixture was refluxed for 2 h. The mixture was then allowed to cool, poured into a beaker and kept aside

for evaporation. The resulting crude sample was recrystallized twice from methanol. Colorless block crystals of compound **1** were then obtained. Yield: 21.3 mg (79.2 %). Analysis calcd. (%) for $C_{15}H_{15}N_3O_2$: C 66.9, H 5.6, N 15.6. Found: C 66.7, H 5.6, N 15.7. IR data (KBr, ν_{max}, cm^{-1}): 3450 (b, w), 3337 (s, w), 2937 (m), 2925 (w), 2853 (w), 2361 (m), 2340 (w), 1723 (m), 1640 (s), 1263 (s), 1153 (m), 751 (m). ^1H NMR data (DMSO-d_6, ppm): δ = 12.40 (s, 1H), 11.95 (s, 1H), 8.53 (s, 1H), 7.63 (d, 1H), 7.54 (d, 2H), 7.30 (d, 1H), 6.91 (t, 2H), 6.82 (d, 2H), 3.03 (s, 6H), 2.13 (s, 3H).

Synthesis of compound 2: 3-Methylsalicylhydrazide (0.1 mmol, 15.2 mg) and 4-nitrobenzaldehyde (0.1 mmol, 15.1 mg) were dissolved in a sufficient volume of methanol and the mixture was refluxed for 2 h. The mixture was then allowed to cool, poured into a beaker and kept aside for evaporation. The resulting crude sample was recrystallized twice from methanol. Colorless block crystals of compound **2** were then obtained. Yield: 26.5 mg (88.6 %). Analysis: calcd. (%) for $C_{15}H_{13}N_3O_4$: C 60.2, H 4.4, N 14.0. Found (%): C 59.9, H 4.5, N 14.2. IR data (KBr, ν_{max}, cm^{-1}): 3422 (b, w), 3345 (s, w), 2938 (m), 2925 (w), 2854 (w), 2360 (m), 2341 (w), 1725 (m), 1638 (s), 1341 (s), 1282 (s), 1167 (m), 749 (m). ^1H NMR data (DMSO-d_6, ppm): δ = 12.47 (s, 1H), 12.34 (s, 1H), 8.35 (d, 2H), 8.53 (s, 1H), 8.07 (d, 2H), 7.66 (d, 1H), 7.32 (d, 1H), 6.93 (t, 1H), 2.13 (s, 3H).

X-ray crystallography: X-ray single crystal structure determination was carried out at 298 (2) K on a Bruker Smart 1000 CCD area diffractometer equipped with a graphite-monochromatic MoK_α radiation (λ = 0.71073 Å) for data collection. Unit cell dimensions were obtained with least-squares refinements[7,8] and the structure were solved by direct methods with SHELXTL-97 package[9]. The final refinements were performed by full-matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. The water and amino H atoms in both compounds were located in difference Fourier maps and refined isotropically, with $U_{iso}(H)$ values fixed at 0.08 $Å^2$ and with N-H distance restrained to 0.90(1) Å, O-H distances restrained to 0.85(1) Å and H···H distance restrained to 1.37(2) Å. Other H atoms were placed in the calculated positions and constrained to ride on their parent atoms. Multi-scan absorption correction was applied by using the SADABS program[10]. Crystallographic data for the compounds are summarized in Table-1. Selected bond lengths and bond angles are listed in Table-2. Hydrogen bonding interactions are listed in Table-3.

RESULTS AND DISCUSSION

Both compounds were crystallized as colorless block-shaped crystals, soluble in common polar organic solvents, such as methanol, ethanol, acetonitrile and DMF, insoluble in water.

Crystal structure description: The molecular structures of compounds **1** and **2** are shown in Figs. **1** and **2**, respectively. Each compound consists of a hydrazone molecule and a water molecule of crystallization. The hydrazone molecules are approximately coplanar, with mean deviations from corresponding planes of 0.154(2) Å for compound **1** and 0.119(2) Å for compound **2**. Both hydrazone molecules have E configurations with respect to the C=N double bonds and C-N single bonds. The dihedral angles between the corresponding substituted benzene rings are 1.6(3)° for compound **1** and

TABLE-1
CRYSTAL DATA FOR THE COMPOUNDS STUDIED

Compound	**1**	**2**
Gross formula	$C_{17}H_{21}N_3O_3$	$C_{15}H_{15}N_3O_5$
M	315.37	317.30
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
T, K	298(2)	298(2)
a, Å	6.779(2)	14.978(3)
b, Å	19.143(3)	8.017(2)
c, Å	13.095(3)	12.796(2)
β, deg	100.387(3)	105.425(2)
V, $Å^3$	1671.5(5)	1502.1(4)
Z	4	4
D_c, g cm^{-3}	1.253	1.403
Crystal dimensions, mm^3	0.12 × 0.10 × 0.10	0.20 × 0.20 × 0.18
μ, mm^{-1}	0.087	0.107
Radiation λ, Å	0.71073	0.71073
T_{min}/T_{max}	0.990/0.991	0.979/0.981
Reflections measured	8349	8417
Total no. of unique data	2942	3250
No. of observed data, $I > 2\sigma(I)$	966	2245
No. of variables	221	220
No. of restraints	4	4
R_{int}	0.1097	0.0662
R_1, wR_2 $[I \geq 2\sigma(I)]$[a]	0.0511, 0.0898	0.0471, 0.1304
R_1, wR_2 (all data)[a]	0.1611, 0.1127	0.0652, 0.1423

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$

TABLE-2
SELECTED BOND LENGTHS (Å) AND ANGLES (°) FOR THE COMPOUNDS

1		2	
Bond lengths (Å)			
O1–C2	1.365(3)	O1–C2	1.356(2)
O2–C7	1.246(3)	O2–C7	1.244(2)
N1–C7	1.346(3)	N1–C7	1.345(2)
N1–N2	1.389(3)	N1–N2	1.378(2)
N2–C8	1.285(3)	N2–C8	1.270(2)
N3–C12	1.385(4)	N3–C12	1.470(2)
N3–C17	1.444(4)	O4–N3	1.213(2)
N3–C16	1.444(4)	O5–N3	1.223(2)
C3–C15	1.509(4)	C3–C15	1.501(2)
C8–C9	1.457(4)	C8–C9	1.463(2)
Bond angles (°)			
C7–N1–N2	118.4(2)	C7–N1–N2	118.4(2)
C8–N2–N1	114.6(3)	C8–N2–N1	115.7(2)
C12–N3–C17	121.3(3)	O4–N3–O5	123.6(2)
C12–N3–C16	120.7(3)	O4–N3–C12	118.3(2)
C17–N3–C16	117.8(3)	O5–N3–C12	118.2(2)
O1–C2–C3	117.0(3)	O1–C2–C3	116.8(2)
O1–C2–C1	120.4(3)	O1–C2–C1	121.9(2)
C4–C3–C15	122.2(3)	C4–C3–C15	122.0(2)
C2–C3–C15	120.3(3)	C2–C3–C15	120.0(2)
O2–C7–N1	120.7(3)	O2–C7–N1	121.0(2)
O2–C7–C1	121.1(3)	O2–C7–C1	121.3(2)
N1–C7–C1	118.1(3)	N1–C7–C1	117.8(2)
N2–C8–C9	122.3(3)	N2–C8–C9	120.5(2)
C13–C12–N3	121.1(3)	C13–C12–N3	119.1(2)
N3–C12–C11	121.1(4)	C11–C12–N3	118.5(2)

TABLE-3
HYDROGEN-BOND GEOMETRY OF THE COMPOUNDS

D–H···A	d(D–H) (Å)	d(H···A) (Å)	d(D···A) (Å)	∠(D–H···A) (°)
1				
O3–H3B···O1^{i}	0.85(2)	2.116(10)	2.960(3)	179(3)
O3–H3A···N2	0.86(2)	2.57(2)	3.239(3)	135(2)
O3–H3A···O2	0.86(2)	2.094(16)	2.887(3)	153(3)
N1–H1A···O3^{ii}	0.90(2)	2.131(13)	3.002(3)	162(3)
O1–H1···O2	0.82	1.75	2.493(3)	149
2				
O1–H1···O2	0.82	1.80	2.529(2)	168(2)
N1–H1A···O3^{iii}	0.90(2)	2.053(10)	2.939(2)	168(2)
O3–H3A···O2	0.86(2)	2.069(11)	2.884(2)	158(2)
O3–H3A···N2	0.86(2)	2.666(15)	3.333(2)	135(2)
O3–H3B···O1^{iv}	0.87(2)	2.080(10)	2.933(2)	166(2)

Symmetry codes: (i) – x, y, z; (ii) x, 3/2 – y, – z; (iii) x, 3/2 – y, 1 – z; (iv) – x, –1/2 + y, 1/2 – z

6.8(3)° for compound **2**. All the bond lengths in the compounds are within normal ranges[11] and comparable to each other. The C8=N2 bond lengths of 1.285(3) Å in compound **1** and 1.270(2) Å in compound **2** confirm them as double bonds. The C7-N1 bond lengths of 1.346(3) Å in both compound **1** and compound **2** are relatively short, suggesting delocalization in the acetohydrazide systems.

In the crystal structures of the compounds, water molecules are linked to the hydrazone molecules through intramolecular O-H···O and O-H···N hydrogen bonds. Adjacent molecules are further linked through intermolecular O-H···O and N-H···O hydrogen bonds, forming layers parallel to the ac plane (Fig. 3 for compound **1** and Fig. 4 for compound **2**).

Antimicrobial activity: Qualitative determination of antimicrobial activities of the compounds was done using the disk diffusion method[12,13]. The results are summarized in Table-4. It can be seen that compound **1** has moderate activities against *Bacillus subtilis*, *Escherichia coli* and *Staphyloccocus aureus*, but no activity against *Bacillus magaterium*. Compound **2** has moderate activities against *Escherichia coli* and *Staphyloccocus aureus* and no activity against *Bacillus subtilis*. It is notable that compound **2** has 100 % inhibition on *Bacillus magaterium*, which is even stronger than tetracycline. Considering the merely difference of the two compounds is the substituent groups of the aromatic rings, the existence of the nitro group

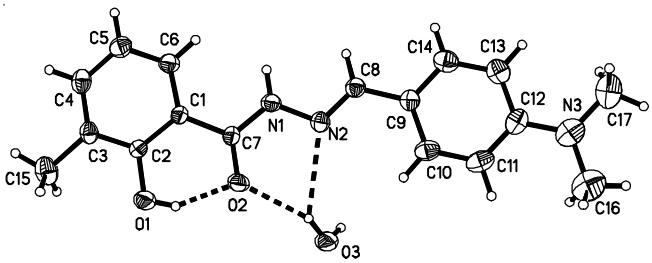


Fig. 1. Molecular structure of compound **1** with 30 % probability thermal ellipsoids. Intramolecular hydrogen bonds are shown as dashed lines

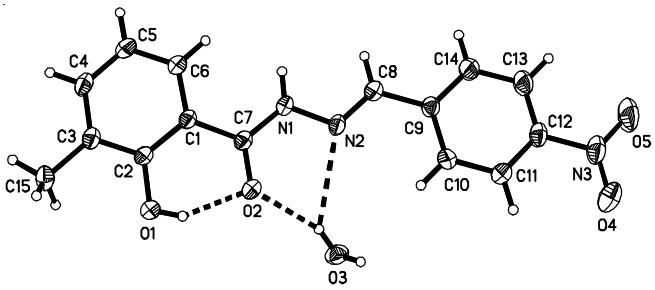


Fig. 2. Molecular structure of compound **2** with 30 % probability thermal ellipsoids. Intramolecular hydrogen bonds are shown as dashed lines

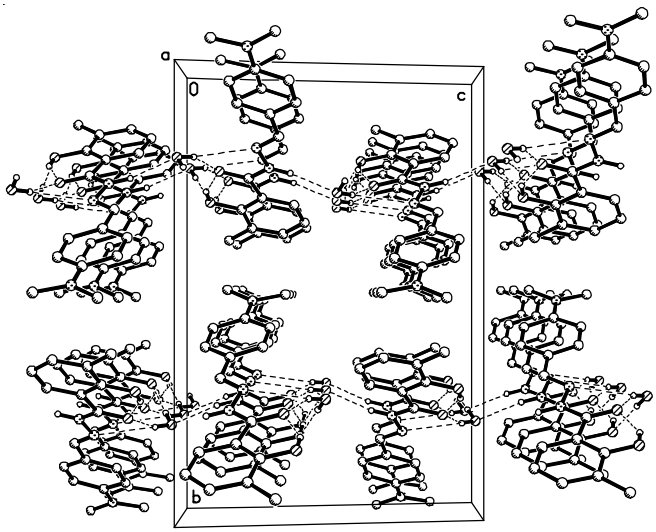


Fig. 3. Molecular packing of compound **1**, viewed along the a axis. Hydrogen bonds are shown as dashed lines

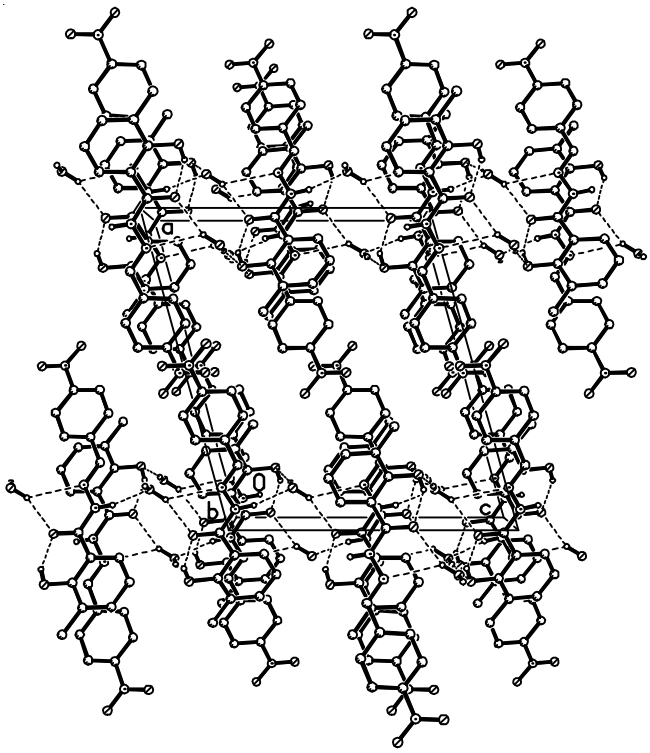


Fig. 4. Molecular packing of compound **2**, viewed along the b axis. Hydrogen bonds are shown as dashed lines

TABLE-4
ANTIMICROBIAL ACTIVITIES OF COMPOUNDS

Compound	Percentage of Inhibition			
	B. subtilis	*E. coli*	*S. aureus*	*B. magaterium*
1	24	12	26	0
2	0	14	16	100
Tetracycline	57	62	33	95

may be regarded as preferred functional groups for the search of antimicrobial agents for *Bacillus magaterium*.

ACKNOWLEDGEMENTS

The author greatly acknowledged Prof. Gang Wu for his help in synthesis and X-ray diffraction.

REFERENCES

1. N. Sari, D. Nartop, F. Karci and A. Disli, *Asian J. Chem*., **20**, 1975 (2008).
2. M.M. Hania, *Asian J. Chem*., **14**, 1074 (2002).
3. M. Zhang, D.-M. Xian, H.-H. Li, J.-C. Zhang and Z.-L. You, *Aust. J. Chem*., **65**, 343 (2012).
4. A. Cukurovali, I. Yilmaz, S. Gur and C. Kazaz, *Eur. J. Med. Chem*., **41**, 201 (2006).
5. S.G. Küçükgüzel, A. Mazi, F. Sahin, S. Ozturk and J. Stables, *Eur. J. Med. Chem*., **38**, 1005 (2003).
6. K.P. Deepa, K.K. Aravindakshan and F. Suhara, *Asian J. Chem*., **13**, 513 (2001).
7. J.-G. Yang and F.-Y. Pan, *Acta Crystallogr*., **E60**, o2009 (2004).
8. F. Magirius, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, **76**, 1980 (1993).
9. G.M. Sheldrick, SADABS Program for Empirical Absorption Correction of Area Detector, University of Göttingen, Germany (1996).
10. G.M. Sheldrick, SHELXTL V5.1. Software Reference Manual; Bruker AXS, Inc: Madison, Wisconsin, USA (1997).
11. F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. II*, S1 (1987).
12. A. Barry, Procedures and Theoretical Considerations for Testing Antimicrobial Agents in Agar Media, In: Lorian (Ed.), Antibiotics in Laboratory Medicine, Williams and Wilkins, Baltimore, edn. 5 (1991).
13. T. Rosu, M. Negoiu, S. Pasculescu, E. Pahontu, D. Poirier and A. Gulea, *Eur. J. Med. Chem*., 45, 774 (2010).