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ORIGINAL PAPER

Synthesis and Crystal Structures of *o*-[(Phenyl/*p*-methoxyphenyl)carbamoyl]benzene Sulfonamides

**Waseeq Ahmad Siddiqui · Saeed Ahmad ·
Hamid Latif Siddiqui · Tanvir Hussain ·
Masood Parvez**

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Abstract *o*-[(Phenyl/*p*-methoxyphenyl)carbamoyl]benzene sulfonamides were synthesized in a straightforward manner utilizing directly saccharin and aniline/*p*-anisidine as starting material and their crystal structures have been determined. ($C_{13}H_{12}N_2O_3S$): Mr = 276.31, monoclinic, $P2_1/c, a = 10.277(6), b = 7.501(2), c = 16.261(10)$ Å, $\beta =$ 96.37(2)°, $V =$ 1,245.8(11) Å^3, $Z = 4$. (C_{14} H_{14} N_2 O_4 S): Mr = 306.33, monoclinic, $P2_1/c$, $a = 10.381(5)$, $b =$ $7.861(2), c = 16.837(9)$ Å, $\beta = 93.43(2)°, V =$ 1,371.5(10) Å^3, $Z = 4$. In both structures the phenyl rings are inclined at 47.09(7) and 39.88(5)° with respect to each other and the structures are characterized by extensive inter and intramolecular hydrogen bonds.

Keywords Sulfonamides · *o*-[(Aryl)carbamoyl]benzene sulfonamides · Biological activities · Crystal structure

W. A. Siddiqui
Department of Chemistry, University of Sargodha,
Sargodha, Pakistan

S. Ahmad
Department of Chemistry, University of Science
and Technology, Bannu, Pakistan

H. L. Siddiqui · T. Hussain
Institute of Chemistry, University of the Punjab,
Lahore, Pakistan

M. Parvez (✉)
Department of Chemistry, University of Calgary,
2500 University Drive, N.W. Calgary,
AB T2N 1N4, Canada
e-mail: parvez@ucalgary.ca

Introduction

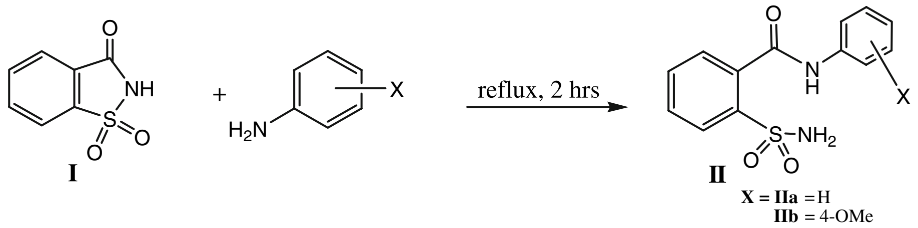
Saccharin derivatives have been of interest due to their widespread applications [1, 2], particularly their open ring benzene sulfonamide derivatives have shown cyclooxygenase-2 (COX-2) inhibitory action to act as analgesic and anti-inflammatory agents [3]. The crystal structure and convenient straightforward synthesis of the very first derivative of this important molecule has recently been reported by our research group [4]. Earlier, synthesis of only two unsubstituted *o*-cyclohexyl and *o*-phenylcarbamoyl benzene sulfonamide derivatives was reported utilizing indirectly *N*-vinylsulfobenzimide as starting material [5]. While continuing our research on the synthesis of *o*-carbamoyl benzene sulfonamide derivatives [6, 7], we have devised a simple and straightforward synthesis of the title compounds *o*-[(phenyl/*p*-methoxyphenyl)carbamoyl]-benzene sulfonamides (IIa) and (IIB), utilizing directly saccharin as starting material. Herein, we report the synthesis and crystal structures of these derivatives.

Experimental

Synthesis of *o*-[(Phenyl/*p*-methoxyphenyl) carbamoyl]benzene Sulfonamides

A suspension of saccharin **I** (1.0 g, 5.46 mmol) and an excess of freshly distilled aniline (5 mL), whereas an exactly mole-equivalent quantity in case of *p*-anisidine (0.44 g, 5.46 mmol) in xylene (25 mL) was first stirred at room temperature (15 min.) and then under reflux (2 h). The reaction mixture was cooled to room temperature followed by ice-bath cooling (1 h), filtered and dried to obtain dark violet solid products (**IIa**) and (**IIb**). The

Scheme 1



products were crystallized from MeOH by slow evaporation at 313 K to obtain light violet crystals (yields = 78–83%).

IIa: IR (Neat, ν_{max}, cm^{-1}): NH and NH$_2$ 3304 (br) and 3234, CO 1626, SO$_2$1331 and 1160; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ: 7.00–7.25 (m, 3H, aromatic), 7.30–7.50 (m, 2H, aromatic), 7.60–7.85 (m, 3H + 2H, aromatic and NH$_2$), 7.90–8.05 (m, 1H, aromatic), 10.65 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ: 167.0, 140.7, 138.8, 135.1, 132.2, 130.2, 128.9, 128.7, 127.2, 124.0, 120.1. LRMS (ES$^+$): m/z: 276 [M]$^+$ (39.5%); m.p. 453–454 K.

IIb: IR (Neat, ν_{max}, cm^{-1}): NH and NH$_2$ 3357 (br) and 3274, CO 1632, SO$_2$1337 and 1162; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ: 3.76 (s, 3H, CH$_3$), 6.95–6.96 (m, 2H, aromatic), 7.15 (s, 2H, NH$_2$), 7.62–7.64 (m, 2H, aromatic), 7.70–7.75 (m, 3H, aromatic), 7.97–7.99 (m, 1H, aromatic), 10.56 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ: 166.7, 155.8, 140.7, 135.1, 132.2, 131.9, 130.2, 128.9, 127.1, 121.7, 113.8, 55.2. LRMS (ES$^+$): m/z: 306.4 [M]$^+$ (53.5%); m.p. 451–452 K (Scheme 1).

X-ray Structure Determination

A colorless needle crystal of (**IIa**) and a colorless prismatic crystal of (**IIb**) were coated with Paratone 8277 oil (Exxon) and mounted on glass fibers for data collection. All

Table 1 Crystal data and structure refinement for (**IIa**) and (**IIb**)

Compound	(**IIa**)	(**IIb**)
CCDC deposit No.	711413	711414
Empirical formula	$C_{13}H_{12}N_2O_3S$	$C_{14}H_{14}N_2O_4S$
Formula weight	276.31	306.33
Temperature	173(2) K	173(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system & space group	Monoclinic, P2$_1$/c	Monoclinic, P2$_1$/c
Unit cell dimensions		
a	10.277(6) Å	10.381(5) Å
b	7.501(2) Å	7.861(2) Å
c	16.261(10) Å	16.837(9) Å
β	96.37(2)°	93.43(2)°
Volume	1,245.8(11) Å^3	1,371.5(10) Å^3
Z	4	4
Density (calculated)	1.473 Mg/m^3	1.484 Mg/m^3
Absorption coefficient	0.265 mm^{-1}	0.254 mm^{-1}
F(000)	576	640
Crystal size	$0.26 \times 0.10 \times 0.07$ mm^3	$0.20 \times 0.12 \times 0.12$ mm^3
θ range for data collection	3.0–27.5°	3.5–27.5°
Reflections collected	4,680	5,556
Independent reflections	2,827 [*R*(int) = 0.035]	3,104 [*R*(int) = 0.034]
Completeness to $\theta = 27.5°$	98.7%	98.9%
Absorption correction	Multi-scan method	Multi-scan method
Max. and min. transmission	0.982 and 0.934	0.970 and 0.951
Data/restraints/parameters	2,827/0/181	3,104/0/200
Goodness-of-fit on F^2	1.10	1.03
Final *R* indices [$I > 2.0\ \sigma(I)$]	$R_1 = 0.049$, $wR_2 = 0.115$	$R_1 = 0.042$, $wR_2 = 0.097$
R indices (all data)	$R_1 = 0.069$, $wR_2 = 0.124$	$R_1 = 0.058$, $wR_2 = 0.108$
Largest diff. peak and hole	0.24 and −0.41 e.Å^{-3}	0.48 and −0.40 e.Å^{-3}

Table 2 Atomic coordinates $(\times 10^4)$ and equivalent isotropic displacement parameters $(\text{Å}^2 \times 10^3)$ for (**IIa**)

Atom	x	y	z	U(eq)
S(1)	3,160(1)	3,417(1)	7,182(1)	24(1)
O(1)	941(2)	408(2)	6,784(1)	26(1)
O(2)	4,341(2)	4,403(3)	7,412(1)	38(1)
O(3)	2,123(2)	4,219(2)	6,648(1)	31(1)
N(1)	−691(2)	2,262(3)	7,113(1)	22(1)
N(2)	3,597(2)	1,629(3)	6,727(1)	27(1)
C(1)	2,504(2)	2,772(3)	8,101(1)	23(1)
C(2)	3,234(3)	3,095(3)	8,855(2)	29(1)
C(3)	2,749(3)	2,577(4)	9,580(2)	33(1)
C(4)	1,537(3)	1,778(4)	9,555(2)	31(1)
C(5)	782(3)	1,507(3)	8,804(2)	27(1)
C(6)	1,265(2)	1,973(3)	8,067(1)	21(1)
C(7)	493(2)	1,489(3)	7,255(1)	21(1)
C(8)	−1,567(2)	2,242(3)	6,370(2)	22(1)
C(9)	−1,181(2)	1,745(3)	5,611(2)	26(1)
C(10)	−2,051(3)	1,959(4)	4,903(2)	33(1)
C(11)	−3,297(3)	2,634(4)	4,946(2)	36(1)
C(12)	−3,686(3)	3,081(4)	5,707(2)	35(1)
C(13)	−2,832(2)	2,883(3)	6,422(2)	28(1)

U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor

Table 3 Atomic coordinates $(\times 10^4)$ and equivalent isotropic displacement parameters $(\text{Å}^2 \times 10^3)$ for (**IIb**)

Atom	x	y	z	U(eq)
S(1)	−3,164(1)	2,787(1)	7,741(1)	21(1)
O(1)	−991(1)	−164(2)	8,108(1)	23(1)
O(2)	−2,152(1)	3,504(2)	8,252(1)	27(1)
O(3)	−4,288(1)	3,786(2)	7,521(1)	30(1)
O(4)	3,797(1)	1,952(2)	10,582(1)	41(1)
N(1)	574(1)	1,735(2)	7,808(1)	21(1)
N(2)	−3,671(2)	1,126(2)	8,185(1)	26(1)
C(1)	−2,458(2)	2,177(2)	6,848(1)	20(1)
C(2)	−3,092(2)	2,571(2)	6,124(1)	25(1)
C(3)	−2,538(2)	2,130(2)	5,422(1)	28(1)
C(4)	−1,356(2)	1,324(2)	5,449(1)	29(1)
C(5)	−702(2)	964(2)	6,173(1)	24(1)
C(6)	−1,246(2)	1,383(2)	6,882(1)	19(1)
C(7)	−546(2)	920(2)	7,661(1)	19(1)
C(8)	1,381(2)	1,693(2)	8,523(1)	21(1)
C(9)	888(2)	1,391(2)	9,258(1)	26(1)
C(10)	1,693(2)	1,488(3)	9,945(1)	29(1)
C(11)	2,982(2)	1,883(2)	9,897(1)	29(1)
C(12)	3,478(2)	2,176(3)	9,168(1)	33(1)
C(13)	2,680(2)	2,079(3)	8,479(1)	28(1)
C(14)	3,528(2)	3,302(3)	11,087(1)	45(1)

U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor

measurements were made on a Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα radiation. Details of crystal data and structure refinement for both structures have been provided in Table 1. The data were corrected for Lorentz and polarization effects and for absorption using multi-scan method [8, 9]. The structures were solved by direct methods [10] and expanded using

Table 4 Selected bond lengths [Å] and angles [°] for (**IIa**) and (**IIb**)

	(**IIa**)	(**IIb**)
S(1)–O(3)	1.430(2)	1.436(1)
S(1)–O(2)	1.435(2)	1.433(1)
S(1)–N(2)	1.620(2)	1.609(2)
S(1)–C(1)	1.773(3)	1.777(2)
O(1)–C(7)	1.239(3)	1.244(2)
N(1)–C(7)	1.345(3)	1.337(2)
N(1)–C(8)	1.425(3)	1.425(2)
O(4)–C(11)	–	1.391(2)
O(4)–C(14)	–	1.398(2)
O(2)–S(1)–O(3)	119.55(13)	119.67(8)
O(3)–S(1)–N(2)	107.25(12)	106.26(9)
O(2)–S(1)–N(2)	106.06(12)	106.78(9)
O(3)–S(1)–C(1)	107.39(12)	107.40(9)
O(2)–S(1)–C(1)	108.09(12)	106.83(9)
N(2)–S(1)–C(1)	108.05(12)	109.69(9)
C(7)–N(1)–C(8)	128.0(2)	127.3(2)
C(11)–O(4)–C(14)	–	113.6(2)

Table 5 Hydrogen bonding geometry [Å and °]

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N(1)–H(1N)···O(1)$^{\#1}$	0.89(3)	2.14(3)	2.992(3)	160(2)
N(2)–H(21N)···O(2)$^{\#2}$	0.85(3)	2.11(3)	2.929(3)	162(3)
N(2)–H(22N)···O(1)	0.87(3)	2.13(3)	2.890(3)	146(3)
C(2)–H(2)···O(2)	0.95	2.49	2.891(4)	105
C(9)–H(9)···O(1)	0.95	2.32	2.911(3)	119
C(5)–H(5)···O(3)$^{\#3}$	0.95	2.54	3.451(4)	162
N(1)–H(1N)···O(1)$^{\#1}$	0.85(2)	2.13(2)	2.930(2)	158(2)
N(2)–H(21N)···O(1)	0.87(2)	2.24(2)	2.971(3)	142(2)
N(2)–H(22N)···O(3)$^{\#2}$	0.86(2)	2.16(2)	2.997(2)	164(2)
C(2)–H(2)···O(3)	0.95	2.49	2.887(3)	105
C(9)–H(9)···O(1)	0.95	2.41	2.933(3)	114
C(2)–H(2)···O(4)$^{\#3}$	0.95	2.50	3.324(3)	145

(**IIa**): Symmetry transformations used to generate equivalent atoms: #1 $-x, y + ½, -z + 3/2$ #2 $-x + 1, y - ½, -z + 3/2$ #3 $-x, y - ½, -z + 3/2$

(**IIb**): Symmetry transformations used to generate equivalent atoms: #1 $-x, y + ½, -z + 3/2$ #2 $-x - 1, y - ½, -z + 3/2$ #3 $x - 1, -y + ½, z - ½$

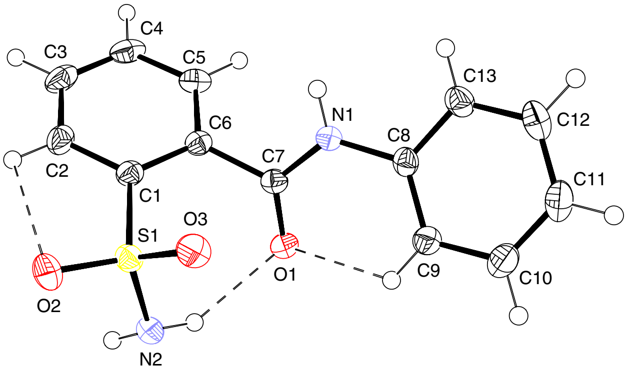


Fig. 1 ORTEP-3 [13] drawing of (**IIa**) with displacement *ellipsoids* plotted at 50% probability level; intramolecular hydrogen bonds are represented by *dashed lines*

Fourier techniques [11]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms bonded to C-atoms were included at geometrically idealized positions and were refined in riding model while H-atoms bonded to N-atoms were allowed to refine; isotropic temperature factors U_{iso} were allowed for all H-atoms times 1.2(U_{eq}) of the parent atoms. The structures were refined by full-matrix least-squares calculations using F^2 with the aid of SHELXL-97 [12]. The weighting schemes were based on counting statistics and the final difference Fourier maps were essentially featureless. The Figures were plotted with the aid of ORTEP-3 for Windows [13]. Atomic coordinates and equivalent isotropic displacement parameters have been provided in Tables 2 and 3 for (**IIa**) and (**IIb**), respectively, selected bond distances and angles in Table 4 and hydrogen bonding geometry in Table 5.

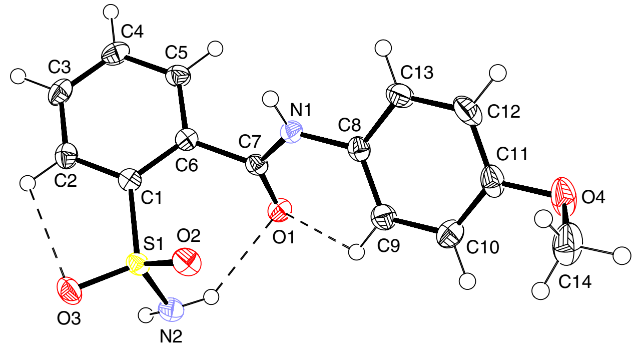


Fig. 3 ORTEP-3 [13] drawing of (**IIb**) with displacement *ellipsoids* plotted at 50% probability level; intramolecular hydrogen bonds are represented by *dashed lines*

Results and Discussion

The molecular structure of (**IIa**) is presented in Fig. 1. The mean-planes formed by the phenyl rings C(1)–C(6) and C(8)–C(13) are inclined at 47.09(7)° with respect to each other and are oriented at 62.92(11)° and 24.10(18)°, respectively, with respect to the carbamoyl group, C(7)/N(1)/O(1). The structure is characterized by classical intermolecular hydrogen bonds of the type N–H···O resulting in a three dimensional frame-work (Fig. 2). In addition, non-classical hydrogen bonding interactions, C(5)–H(5)···O3$^{\#3}$, link the molecules into sheets. The structure also exhibits intramolecular interactions, N(2)–H(22 N)···O(1), C(9)–H(9)···O1 and C(2)–H(2)···O(2) resulting in seven, six and five membered rings with S(7), S(6) and S(5) motifs, respectively [14]; details of hydrogen-bonding geometry have been provided in Table 5.

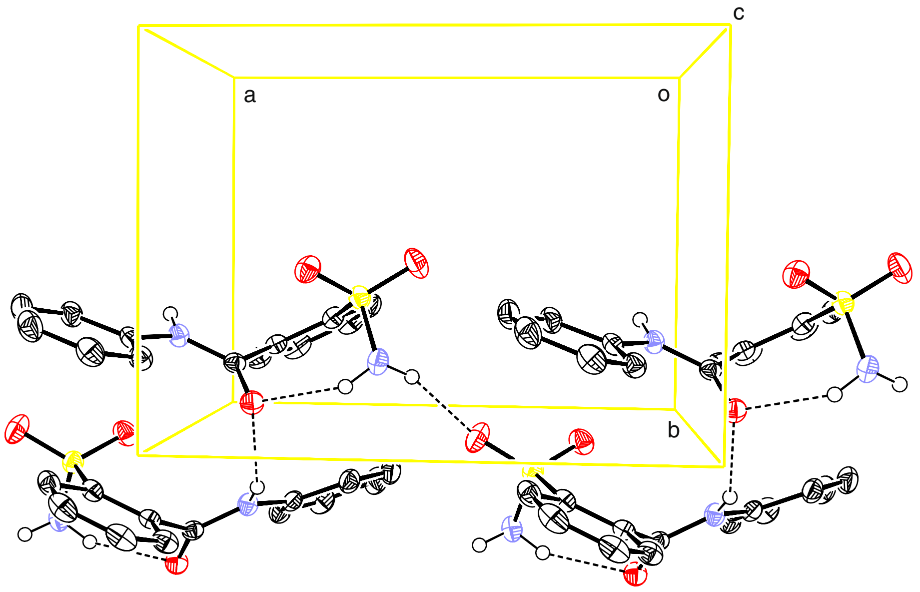


Fig. 2 Unit cell packing of (**IIa**) viewed down the *c*-axis showing N–H···O type hydrogen bonds

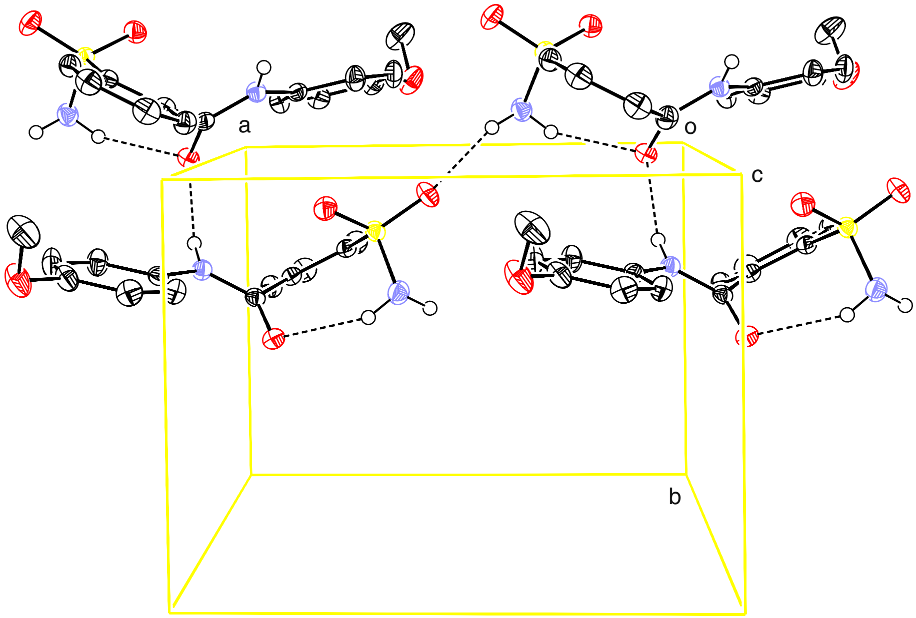


Fig. 4 Unit cell packing of (**IIb**) viewed down the *c*-axis showing N–H···O type H-bonds

In the structure of (**IIb**) (Fig. 3), the mean-planes formed by the phenyl rings C(1)–C(6) and C(8)–C(13) are inclined at 39.88(5)° with respect to each other and are oriented at 65.85(8)° and 31.95(11)°, respectively, with respect to the carbamoyl group, C(7)/N(1)/O(1). The methoxy group, C(11)/O(4)/C(14), forms an angle 67.31(16)° with the plane of the phenyl ring with which it is bonded. Like the structure of (**IIa**), the structure of (**IIb**) also shows classical intermolecular hydrogen bonds of the type N–H···O (Fig. 4). In addition, non-classical hydrogen bonding interactions, C(2)–H(2)···O2$^{\#3}$, link the molecules into sheets. The structure also exhibits intramolecular interactions, N(2)–H(22 N)···O(1), C(9)–H(9)···O1 and C(2)–H(2)···O(3) resulting in seven, six and five membered rings with S(7), S(6) and S(5) motifs, respectively [14]; details of hydrogen-bonding geometry have been provided in Table 5.

The bond distances and bond angles in both the structures, i.e., distances S–C 1.773(3) and 1.777(2), mean S=O 1.433(3) and 1.435(2) and S–N 1.620(2) and 1.609(2) Å, respectively, in the sulfonamide moieties of (**IIa**) and (**IIb**), and the rest of the dimensions are in agreement with the expected values for the corresponding dimensions [15]. The geometry around N2 atoms in both structures is tetrahedral with sum of the angles being 339 and 341° in (**IIa**) and (**IIb**), respectively. A search of the Cambridge Structural Database [16] for structures containing *o*-carbamoyl sulfonamide moiety revealed only one structure (refcode = XEPRUG) [17] wherein the geometry about N2 is also tetrahedral with sum of the angles equal to 342°.

Supplementary Material

CCDC-711413 and CCDC-711414 contain the crystallographic data for compounds (**IIa**) and (**IIb**), respectively, reported in this article. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK: fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk].

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