This article was downloaded by:
On: *25 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Comparison of the reactivities of 2-mercaptoaniline and 2-hydroxyaniline with 2-chloronicotinoyl chloride

Marcus V. N. De Souza[a]; Solange M. S. V. Wardell[a]; James L. Wardell[bc]; Thatyana A. Vasconcelos[a]; Erika M. De Carvalho[a]
[a] Complexo Tecnológico de Medicamentos Farmanguinhos, Rio de Janeiro, RJ, Brazil [b] Department of Chemistry, University of Aberdeen, Old Aberdeen, Scotland [c] Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

To cite this Article De Souza, Marcus V. N. , Wardell, Solange M. S. V. , Wardell, James L. , Vasconcelos, Thatyana A. and De Carvalho, Erika M.(2006) 'Comparison of the reactivities of 2-mercaptoaniline and 2-hydroxyaniline with 2-chloronicotinoyl chloride', Journal of Sulfur Chemistry, 27: 3, 193 — 202
To link to this Article: DOI: 10.1080/17415990600708627
URL: http://dx.doi.org/10.1080/17415990600708627

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Journal of Sulfur Chemistry
Vol. 27, No. 3, June 2006, 193–202

Taylor & Francis
Taylor & Francis Group

Comparison of the reactivities of 2-mercaptoaniline and 2-hydroxyaniline with 2-chloronicotinoyl chloride

MARCUS V. N. DE SOUZA*†, SOLANGE M. S. V. WARDELL†,
JAMES L. WARDELL‡§, THATYANA A. VASCONCELOS†
and ERIKA M. DE CARVALHO†

†Complexo Tecnológico de Medicamentos Farmanguinhos, Av. Comandante Guaranys 447, Jacarepaguá - Rio de Janeiro, RJ, Brazil
‡Department of Chemistry, University of Aberdeen, Meston Walk, Old Aberdeen AB24 3UE, Scotland
§Instituto de Química, Universidade Federal do Rio de Janeiro, 21945-970 Rio de Janeiro, RJ, Brazil

Downloaded At: 12:06 25 January 2011

(Received 4 January 2006; in final form 15 March 2006)

The reaction between equimolar 2-chloronicotinoyl chloride and 2-mercaptopyridine in $ClCH_2CH_2Cl$, after 30 minutes refluxing in $ClCH_2CH_2Cl$ solution, produced pyrido[2,3,b][1,5]benzothiazepin-5(H)one **7**, and 6-[3-(2-benzothiazolyl)pyridin-2-yl)thio]-*N*-[3-(2-benzothiazolyl)pyridin-2-yl]aniline **8**. In contrast, the reaction using the same reaction conditions between equimolar 2-chloronicotinoyl chloride and 2-hydroxypyridine, produced the simple amide, 2-chloro-*N*-(2-hydroxyphenyl) nicotinamide **9**. 2-Chloro-*N*-(2-mercaptophenyl)nicotinamide was considered to be a common intermediate in the formation of **7** and **8**. The characterizations of **7–9** were achieved by X-ray crystallography. The conformations of **7** and **8** in the solid state can be described as "U" and "V"-shaped, respectively.

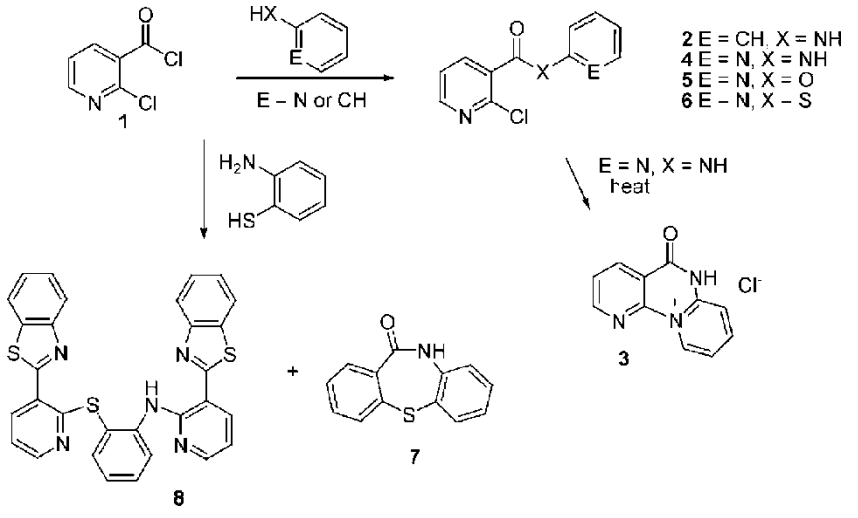
Keywords: 2-Benzothiazolyl derivatives; 2-Chloronicotinoyl chloride; X-ray crystallography; Pyrido[2,3,b][1,5]benzothiazepin-5(H)one

1. Introduction

Pyridine derivatives, due to their general wide ranging pharmaceutical uses, and in particular, their use in the treatment of current world wide diseases such as tuberculosis, attract much attention and study. The simple molecule, nicotinic acid (pyridine-3-carboxylic acid), also known as niacin and vitamin B_3, is found in various plants and animals and has vital roles in such biological processes as production of energy, signal transduction, regulation of gene expression and synthesis of fatty acids, cholesterol and steroids [1]. The derivative, 2-chloronicotinoyl chloride, 2-Cl-3-ClCO-pyridine, **1**, a di-electrophilic compound, has been found to be a particularly useful precursor of more complex pyridine derivatives. As expected, reactions of **1** with mono-nucleophiles such as simple amines, RNH_2 (R = alkyl or aryl), occur at the more reactive acyl chloride site to give amides, 2-Cl-3-RNHCO-pyridine **2** [2, 3].

*Corresponding author. Email: mvndesouza@click21.com.br

Journal of Sulfur Chemistry
ISSN 1741-5993 print/ISSN 1741-6000 online © 2006 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990600708627



SCHEME 1

Downloaded At: 12:06 25 January 2011

Table 1. Crystal data and structure refinement.

Compound	**7**	**8**	**9**
Empirical formula	$C_{12}H_8N_2OS$	$C_{30}H_{20}N_5S_3$	$C_{12}H_9ClN_2O_2$
Formula weight	228.26	546.69	248.66
Temperature, K	120(2)	120(2)	120(2)
Wavelength, Å	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P21/c	P21/a	C2/c
Unit cell dimensions			
a, Å	4.3210(2)	7.4539(3)	12.5286(3)
b, Å	25.8549(18)	24.0296(5)	7.9125(3)
c, Å	9.3805(7)	13.8094(5)	22.1185(7)
β,°	101.525(4)	101.0980(15)	97.3580(18)
Volume, Å^3	1026.85(12)	2427.20(14)	2174.61(12)
Z	4	4	8
Density (calculated), Mg/m^3	1.477	1.496	1.519
Absorption coefficient, mm^{-1}	0.291	0.338	0.341
F(000)	472	1132	1024
Crystal size, mm	0.18 × 0.10 × 0.04	0.25 × 0.15 × 0.04	0.45 × 0.30 × 0.10
Theta range for data collection, °	3.15 to 27.47.	2.95 to 27.57.	3.13 to 27.53.
Index ranges	−5 <= h <= 5; −33 <= k <= 32; −11 <= l <= 12	−9 <= h <= 8; −28 <= k <= 31 −17 <= l <= 17	−15 <= h <= 16; −10 <= k <= 10; −28 <= l <= 28
Reflections collected	9335	29813	13546
Independent reflections	2337 [R(int) = 0.0687]	5567 [R(int) = 0.0570]	2507 [R(int) = 0.0377]
Reflections observed (>2σ)	1728	4084	2102
Data Completeness	0.988	0.991	0.996
Absorption correction	None	None	None
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	2337 / 0 / 148	5567 / 0 / 349	2507 / 0 / 160
Goodness-of-fit on F^2	1.035	1.016	0.946
Final R indices [I > 2sigma(I)]	R1 = 0.0512 wR2 = 0.1122	R1 = 0.0423 wR2 = 0.0964	R1 = 0.0353 wR2 = 0.0943
R indices (all data)	R1 = 0.0796 wR2 = 0.1237	R1 = 0.0684 wR2 = 0.1074	R1 = 0.0464 wR2 = 0.1009
Largest diff. peak and hole, eÅ^{-3}	0.317 and −0.382	0.329 and −0.424	0.263 and −0.290

Other reports have indicated that reactions with di-nucleophiles, or sequentially, with two nucleophiles, can lead to fused heterocyclic products, due to reactions at both electrophilic sites [3,8]. Thus, with 2-aminopyridines, 2-H_2N-pyridine (X = Me or H), 5-oxo-5,6-dihydrodipyrido[1,2-a:3′,2′-e]pyrimidin-11-ium chlorides **3**, can be obtained *via* the intermediacies of 2-Cl-3-(X-pyridin-2-yl-NHCO)-pyridine **4**, (scheme 1) [4, 9, 10].

In contrast to the 2-aminopyridine reactions, both 2-hydroxypyridine and 2-mercaptopyridine, under similar reaction conditions as used for 2-H_2N-pyridine, only provided the non-cyclized ester, 2-Cl-3-(pyridin-2-yl-CO_2)-pyridine **5**, and thioester, 2-Cl-3-(pyridin-2-yl-SCO)-pyridine **6**, respectively [4].

Reaction of 2-chloronicotinoyl chloride, **1**, with 2-mercaptoaniline was initially reported by Hoffman and Faure using benzene as the solvent, in the presence of pyridine [11] using a reflux period of 3 hours: they reported the formation only of pyrido[2,3,b][1,5]benzothiazepin-5(H)one **7.** Other authors have also reported the formation of this benzothiazole [12–15]. We have reinvestigated the reaction of **1** with 2-mercaptoaniline using different reaction conditions [$ClCH_2CH_2Cl$ as solvent and a: 30 min. reflux period] and have found, as well as, **7** an additional product, 6-[3-(2-benzothiazolyl)pyridin-2-yl)thio]-*N*-[3-(2-benzothiazolyl)pyridin-2-yl]aniline **8**. Reaction of 2-hydroxyaniline, under the same conditions, merely produced the amido compound, 2-chloro- *N*-(2-hydroxyphenyl)nicotinamide **9**.

We now report our results, which include the crystal structures of **7**–**9**, products of the reactions between **1** and 2-mercaptoaniline and 2-hydroxyaniline in 1,2-dichloroethane (table 1).

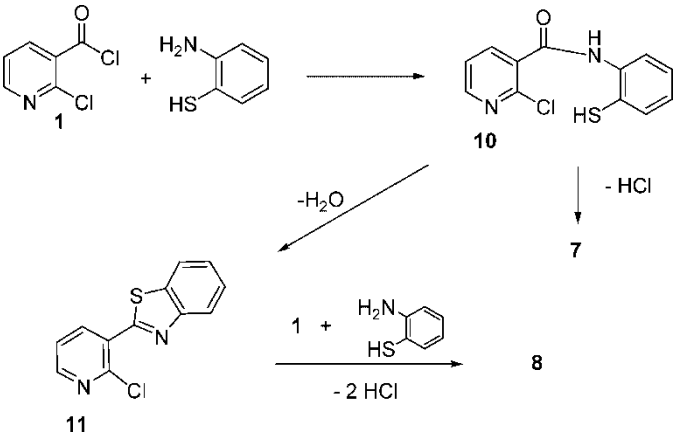
Downloaded At: 12:06 25 January 2011

2. Results and discussion

The reactions between equimolar **1** and 2-mercapto- and 2-hydroxyaniline were carried out, in this study, in $ClCH_2CH_2Cl$ solution with a 30 min. period of reflux. Products were isolated by fractional recrystallisation. With 2-mercaptoaniline, the products isolated were **7** as previously reported [11], and the new bis benzothiazole compound, 6-[3-(2-benzothiazolyl)pyridin-2-yl)thio]-*N*-[3-(2-benzothiazolyl)pyridin-2-yl]aniline **8**, see (scheme 1). Hoffman and Faure [11] carried out their reaction between 2-chloronicotinoyl chloride and 2-mercaptoaniline in benzene in the presence of pyridine with a 3 hour period of reflux.

We assume that the amide, 2-chloro-*N*-(2-mercaptophenyl)-nicotimamide, **10**, is the initial product and precursor of both **7** and **8**. The formation of compound **8** then is formed sequentially from **10** *via* formation of the benzothiazole, **11**, followed by reaction of two molecules of **11** with 2-$HSC_6H_4NH_2$ at both nucleophilic centres of the latter. Formation of **7** occurs simply by ring closure on reaction of the mercapto group with the chloro group (scheme 2).

There are various literature examples of the formation of benzothiazoles from 2-mercaptoanilines and acid halides [16,17]. Moreover, other carbonyl compounds, RCOX (X = OH, OR and H) and polymer-bound esters have also been used in the formation of benzothiazoles [18–20]. Reactions with acids and esters proceed readily in the presence of polyphosphoric acid, while syntheses of benzothiazoles from 2-mercaptoaniline and aldehydes, require a subsequent oxidative-cyclization of the initially formed Schiff bases [21–26]. While these reactions are general, specific reactions involving pyridine compounds include the following: in the patent literature, it has been reported that nicotinic acid and 2-$HSC_6H_4NH_2$ in the presence of ethyl polyphosphonate, produced 3-(2-benzothiazolyl)-pyridine [27] and reaction of 6-Cl-3-ClC(O)-pyridine with 2-$HSC_6H_4NH_2$ simply gave 6-Cl-3-(2-benzothiazolyl)pyridine, with the chloro group remaining unaffected [28].



SCHEME 2

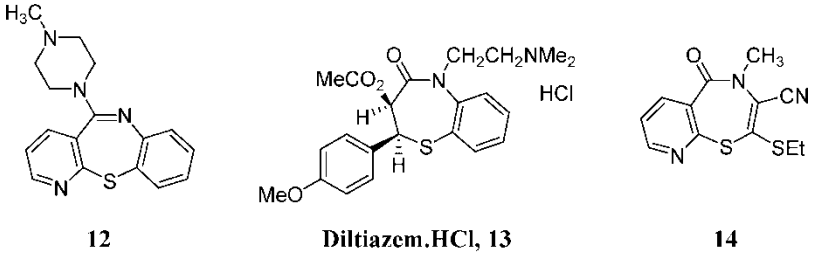


Figure 1. Structures of compounds with seven membered rings.

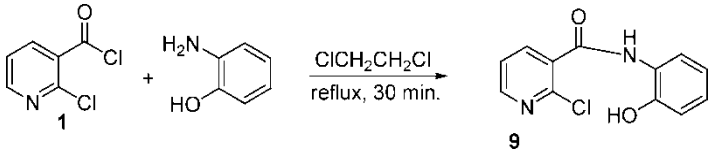
Downloaded At: 12:06 25 January 2011

Tricyclic benzazapine derivatives, such as **7** and related compounds, *e.g.*, **12** [29, 30] have been reported to have various useful biological properties, such as anti-histamine and anti-convulsive agents [11], HIV reverse transciptase inhibitors [31], and oxytocin and vasopressin antagonists [32] (figure 1). Similarly, compounds containing a fused benzene ring and the seven membered ring, as in diltiazem **13**, a calcium channel blocking agent, also have useful biological activites (figure 1).

Compound **8**, having two benzothiazole units, is of interest for further study of its biological activities and as a ligand for metal complexation. 2-Arylbenzothiazoles, in general, form a very important class of biological active compounds [33–35].

2.1 *Reaction with 2-hydroxyaniline*

It was found that from 2-hydroxyaniline, the sole reaction product isolated under the same conditions used for the 2-mercaptoaniline reaction, was the amido derivative 2-chloro-*N*-(2-hydroxypyridin-2-yl)nicotinamide **9**, (scheme 3).



SCHEME 3

Compared to 2-mercaptoaniline, 2-hydroxyaniline, clearly is a much less reactive compound, as shown by the formation of just the amide **9**. There was no evidence for further reaction, involving the HO group, either in formation of a benzo-oxazole or ring closure etc with the chloro group. Matsushita *et al.* [18] also found 2-$HOC_6H_4NH_2$ to be less reactive than *o*-$HSC_6H_4NH_2$ in reactions with polymer-bound esters, in the presence of a Lewis acid. The results can be explained by sulfur being a much more effective nucleophile than oxygen which renders a mercapto group more reactive than a hydroxyl group towards a halide.

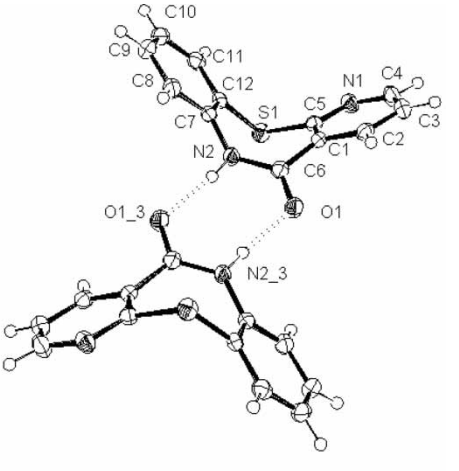
The only other compound isolated from the reaction mixture of **1** and 2-hydroxyaniline was a little 2-chloronicotinic acid, formed on hydrolysis of **1**.

2.2 *Crystal structure of pyrido[2,3,b][1,5]benzothiazepin-5(H)one (7)*

The crystal used in the X-ray structure determination was grown from ethanol solution. The atom numbering scheme and atom arrangements are shown in figure 2. The seven membered ring in **7** has a boat-shaped conformation, with S1, C6 and N2 atoms on the same side of the plane through the remaining ring atoms. Similar conformations have also been reported for the seven membered rings in **12** [30] and in 2-EtS-4-Me-5(4H)-oxopyrido [3,2-f][1,4]thiazepine-3-carbonitrile, **14** [36] (figure 1). The overall shape of the molecules of **7** is "U"-shaped. The angle between the planes of the pyridine and the phenyl rings is 64.26(7)°. Selected bond lengths and angles are listed in table 2. The N2-C7 and N2-C6 distances are significantly different in **7**, with N2-C7 [1.420(3) Å] slightly longer then a usual single bond [1.40 Å] and N2-C6 [1.348(3) Å] between a single and double bond lengths [1.24 Å]. The bonds, C12 and S1 [1.766(2) Å] and C5-S1 [1.773(2) Å] are close to the accepted C(sp^2)-S single bond length [1.76 Å]. The geometric parameters of the phenyl and pyridinyl rings are normal.

Hydrogen bonds involving the amido group lead to symmetrical dimers as shown in figure 2. In addition to these strong H-bonds, weaker C4-H4 – S1 hydrogen bonds are also present.

Downloaded At: 12:06 25 January 2011



symmetry operation : _3 = -x, 1-y, -z.

Figure 2. Atom arrangements and dimer formation in (**7**).

Table 2. Selected bond lengths [Å] and angles [°] for (**7**).

S1-C12	1.766(2)	S1-C5	1.773(3)
O1-C6	1.238(3)	N2-C6	1.348(3)
N2-C7	1.420(3)	N1-C4	1.335(3)
N1-C5	1.338(3)	C1-C5	1.391(3)
C12-S1-C5	98.98(11)	C1-C5-S1	120.89(18)
C5-C1-C6	124.3(2)	N2-C6-C1	121.5(2)
C6-N2-C7	130.2(2)	C12-C7-N2	122.1(2)
C7-C12-S1	121.15(19)		

Hydrogen bonding parameters

D-H – A	D-H (Å)	H – A (Å)	D – A (Å)	D-H – A (°)
N2-HN2 – O1^{i}	0.88(3)	1.97(3)	2.845(3)	171(2)
C4-H4 – S1^{ii}	0.95	2.76	3.593(3)	146

Symmetry operations: *i*: −x, 1 − y, −z; *ii*: −1 + x, 1/2 − y, −1/2 + z.

2.3 *Crystal structure of 6-[3-(2-benzothiazolyl)pyridin-2-yl)thio]-N-[3-(2-benzothiazolyl) pyridin-2-yl]aniline (8)*

The sample used in the X-ray crystallographic study was grown from $ClCH_2CH_2Cl$ solution. Atom numbering scheme and atom arrangements for **8** are shown in figure 3a. Selected bond

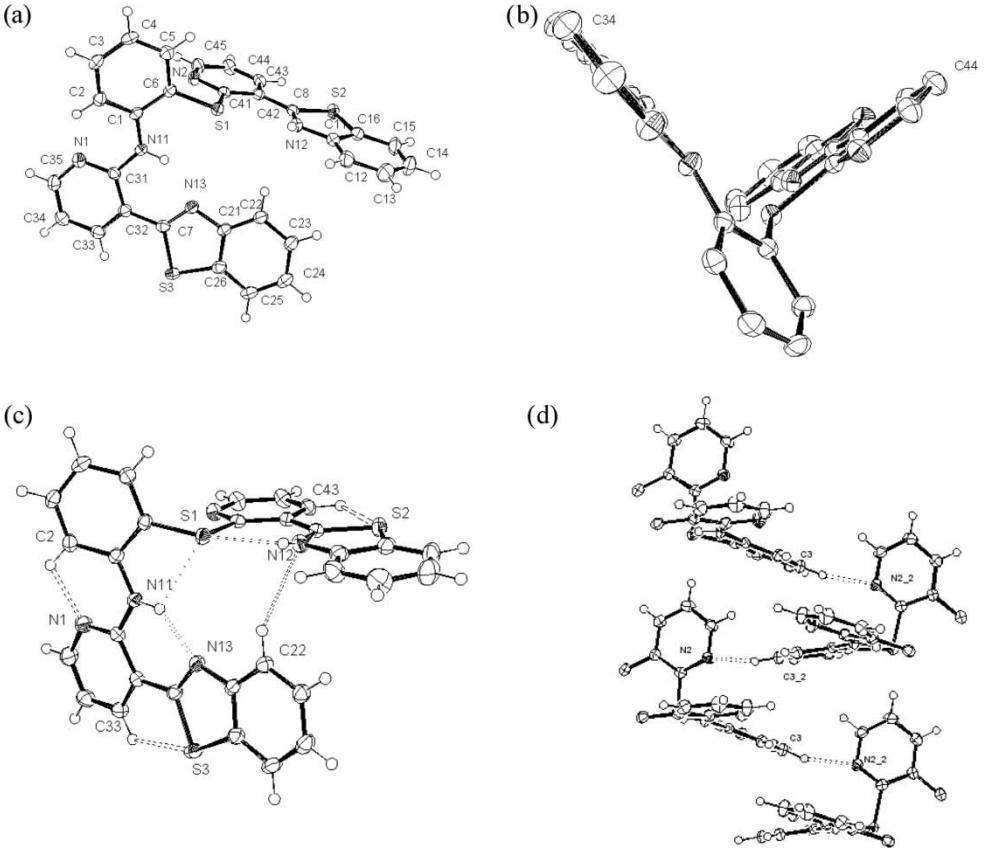


Figure 3. (a) Atom arrangements in **(8)**; (b) the V-shape conformation of **(8)**; (c) Intramolecular H-bonds in **(8)**; (d) Chain of molecules of 8 linked by a C-H – N hydrogen bond: the benzothiazole moieties have been omitted for clarity.

Downloaded At: 12:06 25 January 2011

Table 3. Selected bond lengths [Å] and angles [°] for compound (**8**).

S1-C41	1.771(2)	S1-C6	1.7791(19)
S2-C16	1.733(2)	S2-C8	1.763(2)
S3-C26	1.735(2)	S3-C7	1.762(2)
N11-C31	1.372(3)	N11-C1	1.396(3)
N12-C8	1.285(3)	N12-C11	1.392(3)
N13-C7	1.297(3)	N13-C21	1.391(2)
N1-C35	1.339(3)	N1-C31	1.339(3)
N2-C45	1.335(3)	N2-C41	1.337(3)
C41-S1-C6	101.39(9)	C16-S2-C8	89.04(10)
C26-S3-C7	89.23(10)	C31-N11-C1	129.64(17)
C8-N12-C11	112.21(18)	C7-N13-C21	111.59(17)
C35-N1-C31	118.56(18)	C45-N2-C41	118.72(17)

Hydrogen bonding parameters

D-H – A	D-H (Å)	H – A (Å)	D – A (Å)	D-H – A (°)
N12-H2N – S1	0.70(3)	2.63(3)	2.8390(18)	101(2)
N11-H11N – S1	0.88(2)	2.61(2)	3.0421(17)	111.5(18)
N11-H11N – N13	0.88(2)	1.94(2)	2.701(2)	144(2)
C2-H2 – N1	0.95	2.30	2.880(3)	119
C3-H3 – N2^{i}	0.95	2.59	3.312(3)	133
C22-H22 – N12	0.95	2.60	3.440(3)	148
C33-H33 – S3	0.95	2.64	3.079(2)	109
C43-H43 – S2	0.95	2.59	3.043(2)	110

Symmetry operation: *i*: 1/2 + x, 3/2 − y, z

Downloaded At: 12:06 25 January 2011

lengths and angles are listed in table 3. The conformation of **8**, like that of **7**, is unexpectedly V-shaped, (figure 3b). Each of the two 3-(2-benzothiazole)-pyridinyl moieties are essentially planar: the atom most out of the best plane (plane A) through the atoms, C31-C35, N2, C21-C26, S3,C7 is C33 [at 0.1044(19) Å] and that most out of the best plane (plane B) through C11-C16, N12, C42, C8, S2, C41-C45, N2 is C44 [at 0.0399(19) Å], with an angle between these best planes of 84.53(3)°. Furthermore, plane A is near orthogonal to the phenyl ring, C1-C6, actual angle being 89.83(5)°, compared to the angle of 25.43(5)°, which plane B makes with the phenyl ring. This arrangement allows the formation of numerous intramolecular H-bonds (figure 3c). With this solid state conformation, compound **8** has several donor atoms arranged in an ideal manner to make polydentate interactions with metallic species within the V-shaped cavity. This possibility is being investigated.

In addition to these intramolecular hydrogen bonds, there is a weak intermolecular C(3)-H(3) – N(2) hydrogen bond, which results in the formation of chains (figure 3d).

2.4 *Crystal structure of 2-chloro-N-(2-hydroxypyridin-2-yl)nicotinamide (9)*

The sample used in the X-ray crystallographic study was grown from EtOH solution. The atom numbering scheme and atom arrangements for **9** are shown in figure 4a. All bond lengths and angles are in the normal ranges. The central fragment, C8, N2, C7, O1, C3 is essentially planar with the pyridinyl and phenyl rings making angles of 19.58(9) and 9.04(9)°, respectively with this central fragment. As can be seen in table 4 and figure 4a, intramolecular hydrogen bonds, both strong, N2-H2 N – Cl1 and N2-H2 N – O2, and weak, C13-H13 – O1, are present. Intermolecular hydrogen bonds, again both strong and weak also arise. Figure 4b shows the chain formed from the strong O2-H2O – O1^{i} interaction; symmetry operation: *i* 1/2+x, 1/2+y, z.

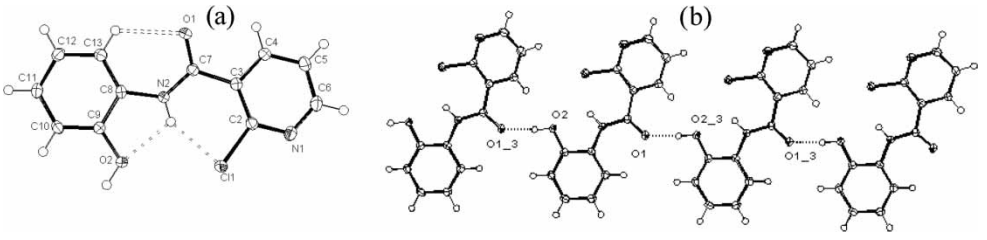


Figure 4. (a) Atom arrangements and intramolecular hydrogen bonds in (**9**); (b) chain of molecules of (**9**) linked by a O-H – O hydrogen bond.

Table 4. Selected bond lengths [Å] and angles [°] for compound (**9**).

N1-C6	1.339(2)	N2-C7	1.338(2)
N2-C8	1.4179(19)	N1-C2	1.324(2)
N2-C7-C3	117.76(14)	C7-N2-C8	128.94(14)
O1-C7-N2	122.10(14)		

Hydrogen bonding parameters

D-H – A	D-H (Å)	H – A (Å)	D – A (Å)	D-H – A (°)
N2-H2 N – Cl1	0.87(2)	2.29(2))	2.9922(14)	137.7(17)
N2-H2 N – O2	0.87(2)	2.11(2)	2.5716(19)	112.5(17)
O2-H2O – O1^{i}	0.94(2)	1.71(2)	2.6429(17)	174(2)
C4-H4 – O2^{ii}	0.95	2.47	3.323(2)	149
C6-H6 – Cl1^{iii}	0.95	2.82	3.7411(18)	165
C13-H13 – O1	0.95	2.33	2.9038(19)	118

Symmetry operations: *i*: $1/2 + x, 1/2 + y, z$; *ii*: $-1/2 + x, -1/2 + y, z$; *iii*: $1/2 - x, -1/2 + y, 1/2 - z$.

Downloaded At: 12:06 25 January 2011

3. Experimental section

3.1 *General*

Melting points were measured on a Melt-TempII instrument. Infrared spectra were obtained in KBr pellets at room temperature on a Nicolet Magna 760 FT-IR instrument, with 4 cm^{-1} resolution.

3.2 *Preparation of pyrido[2,3,b][1,5]benzothiazepin-5(H)one (7) and 6-[3-(2-benzothiazolyl)pyridin-2-yl)thio]-N-[3-(2-benzothiazolyl)pyridin-2-yl]aniline (8)*

A solution of 2-chloronicotinoyl chloride, **1**, (0.880 g, 5 mmol) and 2-mercaptoaniline (0.625, 5 mmol) was refluxed in 1,2-dichloroethane for 30 min, cooled and rotary evaporated to leave a solid residue. This was dissolved in 1,2-dichloroethane and 6-[3-(2-benzothiazolyl)pyridin-2-yl)thio]-*N*-[3-(2-benzothiazolyl)pyridin-2-yl]aniline, **8**, 0.86 g, precipitated on slow evaporation as fine crystals. After collection of **8**, the mother liquor was rotary evaporated and the residue was taken up in EtOH. Crystals of **7**, 0.41 g, appeared on slow evaporation of the solution.

3.2.1 Pyrido[2,3,b][1,5]benzothiazepin-5(H)one (7). m.p. 263–264 °C (sealed tube). Lit. m.p. 260 °C [11]. IR (KBr): 3280, 3164, 3082, 3030, 2963, 2906, 1659, 1573, 1573, 1481, 1451, 1398, 1384, 1299, 1253, 1237, 1154, 1127, 1073, 1033, 957, 913, 823, 791, 758, 726,

670, 651, 618, 545, 520, 506, 465, 439 cm^{-1}. Anal. Calcd for $C_{12}H_8N_2OS$: C, 63.16; H, 3.53; N, 12.27. Found: C, 63.28; H, 3.61; N, 12.13.

3.2.2 6-[3-(2-Benzothiazolyl)pyridin-2-yl)thio]-N-[3-(2-benzothiazolyl)pyridin-2-yl] aniline (8). m.p. 171–173 °C. ^{1}H NMR (400.00 MHz, DMSO-d_6) δ: 11.70 (1H; s; NH); 8.52–7.02 (18H; m) ppm. IR (KBr): 3212–2994, 1596, 1580, 1547, 1523, 1404, 1459, 1434, 1393, 1336, 1313, 1296, 1257,1235, 1218, 1192, 1096, 1068, 1037, 1012, 860, 949, 938, 900, 788, 751, 736, 725, 698, 684 cm^{-1}. Anal. Calcd for $C_{30}H_{19}N_5S_3$: C, 66.03; H, 3.51; N, 12.83. Found: C, 66.21; H, 3.38; N, 12.98.

3.3 *Preparation of 2-chloro-N-(2-hydroxyphenyl)nicotinamide (9)*

A solution of 2-chloronicotinoyl chloride (0.880 g, 5 mmol) and 2-hydroxyaniline (0.545 g, 5 mmol) was refluxed in 1,2-dichloroethane for 30 min, cooled and rotary evaporated. The solid residue was crystallized from 1,2-dichloroethane to give crystals of **9**; 1.30 g, m.p. 135–137 °C. ^{1}H NMR (400.00 MHz, DMSO-d_6) δ: 9.87 (1H; s; NH); 8.50 (1H; dd; J = 1.6 and 4.8 Hz; H_6); 8.04 (1H; dd; J = 1.6 and 7.2 Hz; H_4); 7.85 (1H; dd; J = 1.2 and 7.6 Hz; $H_{6'}$); 7.53 (1H; dd; J = 4.8 and 7.2 Hz; H_5); 7.02 (1H; ddd; J = 1.4; 7.2 and 7.6 Hz; $H_{4'}$); 6.93 (1H; dd; J = 1.2 and 7.6 Hz; $H_{3'}$); 6.83 (1H; ddd; J = 1.2; 7.2 and 7.6 Hz; $H_{5'}$) ppm. ^{13}C NMR (100.0 MHz, DMSO-d_6) δ: 163.8; 150.2; 148.7; 146.5; 138.3; 133.0; 125.6; 125.5; 123.1; 123.0; 118.9; 115.7 ppm.

IR (KBr): 3358, 3300–2700, 1642, 1615, 1589, 1546, 1454, 1389, 1344, 1284, 1233, 1201, 1182, 1133, 1097, 1055, 960, 929, 902, 849, 827, 753, 644, 552, 506, 432 cm^{-1}. Anal. Calcd for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.65; N, 11.26. Found: C, 58.12; H, 3.78; N, 11.19.

3.4 *X-ray crystallography*

The crystals of **7** were grown from EtOH, those of **8** and **9** from $ClCH_2CH_2Cl$. The intensity data in each case were collected at 120K on a Nonius KappaCCD area detector system by the EPSRC X-ray crystallographic service at the University of Southampton, UK. The entire process of data collection, cell refinement and data reduction was accomplished by means of the programs DENZO [37] and COLLECT [38]. Correction for absorption was achieved in each case by a semi-empirical method based upon the variation of equivalent reflections with the program SORTAV [39]. The structures were solved by direct methods in SHELXS-97 [40] within the OSCAIL suite of programs [41] and refined in SHELXL-97 [42]. Approximate positions for H atoms were obtained from difference maps and were refined with a riding model. PLATON was used for the data analysis [43]. The program ORTEP-3 for Windows was used to obtain the figures [44]. Conformational and H-bonding analysis was performed using PLATON [38]. Crystal data and structure refinement details are listed in table 1. "CCDC 289911, 289910 and 289912 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif".

Acknowledgements

JLW acknowledges support by CNPq, Brazil. The authors thank the EPSRC X-ray Crystallographic Service, University of Southampton, England for the data collections.

Downloaded At: 12:06 25 January 2011

References

[1] P. Guiot, M.A. Ryan, E.F.V. Scriven. *Chim. Oggi –Chemistry Today*, **14**, 55 (1996).
[2] B.P. Boyode, M. Sinet, A. Farese, M.A. Forestierroux, R. Condom, I.A. Ayi, A. Kirn, G. Moog, R. Guedj. *Antiviral. Chem. Chemotherapy*, **6**, 162 (1995).
[3] M. Valès, V. Lokshin, G. Pèpe, R. Guglielmetti, A. Samat. *Tetrahedron*, **58**, 8543 (2002).
[4] E.L. Fernandes, A. Magalhães, K.C. Paes, M.V.N. de Souza, T.R.A. Vasconcelos, J.L. Wardell, S.M.S.V. Wardell. *J. Chem. Res.*, 93 (2006).
[5] E.V. Nosova, G.N. Lipunova, V.N. Charushin. *Russ. Chem. Bull*., **53**, 1137 (2004).
[6] G.R. Newkome, T. Kawato, F.R. Fronczek, W.H. Benton. *J. Org. Chem.*, **45**, 5423 (1980).
[7] K.R. Prasad, M. Darbarwar. *Synth. Commun*., **22**, 2479 (1992).
[8] E. Belgodere, R. Bossio, R. Cencioni, S. Marcaccini, R. Pepino. *J. Heterocyclic. Chem*., **21**, 1241 (1984).
[9] A. Monge, V. Martinez-Merino, E. Cenarruzabeitia, B. Lasheras, E. Fernandez-Alvarez. *Eur. J. Med. Chem*., **20**, 61 (1985).
[10] A. Kamal, M.V. Rao, P.B. Sattur. *Heterocycles*, **24**, 3075 (1986).
[11] C. Hofman, A. Faure. *Bull. Soc. Chim. France*, 2316 (1966).
[12] S. Rudrawar, A. Kondskar, A.K. Chakraborti. *Synthesis*, 2521 (2005).
[13] E. Daltrozzo, A. Reiss. EP 1174430 (2002); *Chem. Abs*. **136**, 1184436 (2002).
[14] A. Brembilla, D. Roizard, P. Lochon. *Synth. Comm*., **20**, 3379 (1990).
[15] C.P. Chen, Y.T. Chen. *Tetrahedron Letters*, **45**, 113 (2004).
[16] K.C. Eapen, C. Tamborski. *J. Fluorine Chem*., **12**, 271 (1978).
[17] C. Chen, Y.-J. Chen. *Tetrahedron Letters*, **45**, 113 (2004).
[18] H. Matsushita, S.H. Lee, M. Joung, B. Clapham, K.D. Janda, *Tetrahedron Letters*, **45**, 313 (2004).
[19] A.K. Chakraborti, C. Selvem, C. Kaur, S. Bhagat, *Synlett*, 851 (2004).
[20] J.S. Yadav, G. Rajaiah, *Synlett*, 1537 (2004).
[21] J.B. Chang, K. Zhao, S.F. Pan, *Tetrahedron Letters*, **43**, 951 (2002).
[22] K.J. Duffy, A.T. Price, E. Delorme, S.B. Dillon, C. Duquenne, C. Erickson-Miller, L. Giampa, Y.F. Huang, R.M. Keenan, P. Lamb, N.N. Liu, S.G. Miller, J. Rosen, A.N. Shaw, H. Smith, K.J. Wiggall, L.H. Zhang, J.I. Luengo. *J. Med Chem*., **45**, 3576 (2002).
[23] X.F. He, C.M. Vogels, A. Decken, S.A. Westcott. *Polyhedron*, **23**, 155 (2004).
[24] R. Kumar, C. Selvam, G. Kaur, A.K. Chakraborti. *Synlett*, 1401 (2005).
[25] S. Rostamizadeh, S.A.G. Housaini. *Phosphorus, Sulfur, Silicon and Related Elements*, **180**, 1321 (2005).
[26] T. Itoh, K. Nagata, H. Ishikawa, A. Ohsawa. *Heterocycles*, **62**, 197 (2004).
[27] V.L. Narayanan, R.C. Angel. US Patent 3985885, **1976**.
[28] G. di Modica, P. Savarino. *Tinctoria*, **71**, 333 (1974); CA **82**, 1975, 113165u.
[29] C. Hoffmann, E. Bowley. US Patent, 4163785, **1979**.
[30] M. Sbit, L. Dupont, O. Dideberg, J.F. Líegeois, J. Delarge. *Acta Cryst.*, **C44**, 319 (1988).
[31] G. Schmidt, K.D. Hargrave. European Patent. Appl EP 90-116337, 19900827.
[32] J.D. Albright, F.W. Sum, X. Du. U. S. Patent. 94-254823, 199940613
[33] M. Yoshida, C. Hayakawa, N. Hayashi, T. Agatsuma, Y. Oda, F. Tanzawa, S. Iwasaki, K. Koyama, H. Furukawa, S. Kurakata, Y. Sugano. *Biorg. Med. Chem. Letters*, **15**, 3328 (2005).
[34] D.J. Skalitzky, J.T. Marakovits, K.A. Maegley, A. Ekker, X.H. Yu, Z. Hostomsky, S.E. Webber, B.W. Eastman, R. Almassy, J.K. Li, N.J. Curtin, D.R. Newell, A.H. Calvert, R.J. Griffin, B.T. Golding. *J. Med. Chem*., **46**, 210 (2003).
[35] G. Wells, J.M. Berry, T.D. Bradshaw, A.M. Burger, A. Seaton, B. Wang, A.D. Westwell, M.F.G. Stevens. *J. Med. Chem*., **46**, 532 (2003).
[36] W. Dölling, M. Biedermann, H. Hartung. *Eur. J. Org. Chem*., 1237 (1998).
[37] Z. Otwinowski, W. Minor. In *Methods in Enzymology: Macromolecular Crystallography, Part A*, C.W. Carter, R.M. Sweet (Eds), pp. 307–326, Academic Press, New York (1997).
[38] R.W.W. Hooft. *COLLECT*. Nonius BV, Delft, The Netherlands (1998).
[39] R.H. Blessing. *Acta Crystallogr. Sect. A*, **51**, 33 (1993), *J. Appl. Crystallogr*., **30**, 421 (1997).
[40] G.M. Sheldrick, *SHELXS-97. Program for the Solution of Crystal Structures*, University of Göttingen, Germany (1997).
[41] P. McArdle. *OSCAIL for Windows*, National University of Ireland, Galway, Ireland (2002).
[42] G.M. Sheldrick. *SHELXL-97. Program for the Refinement of Crystal Structures*, University of Göttingen, Germany (1997).
[43] A.L. Spek. *PLATON. Version of 2002*, University of Utrecht, The Netherlands (2002).
[44] L.J. Farrugia. *J. Appl. Crystallogr*., **30**, 565 (1997).

Downloaded At: 12:06 25 January 2011