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Synthesis and X-ray Structure of a New Pyrrolo[1,2-b]-pyridazine Derivative

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Abstract: The synthesis, characterization and X-ray crystal structure of 2-(4-chloro-phenyl)-7-methylpyrrolo[1,2-b]pyridazine are reported. The compound crystallizes in the space group $P2_1/c$ (No.14) with a =3.8568(1), b = 11.0690(3), c = 26.4243(7) Å, β = 92.777(1)° and Z = 4. Accurate molecular parameters for the novel heterocyclic system were obtained from intensity data collected at 113K. The molecule assumes a planar conformation in the crystal and the packing is based on π-π stacking with interplanar spacing 3.400 Å, typical of aromatic molecules with potential for displaying useful optical properties.

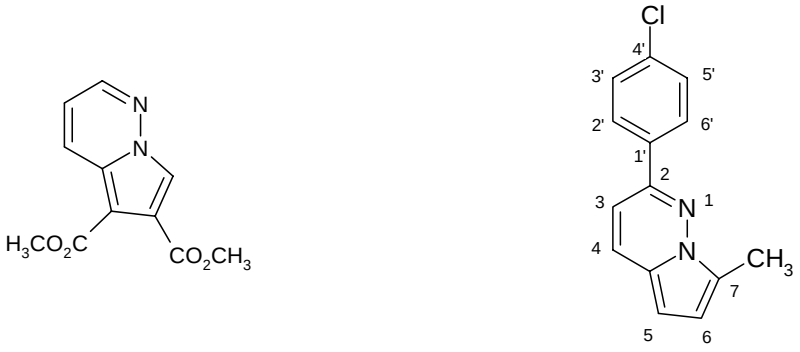
Keywords: Pyrrolo[1,2-b]pyridazine, crystal structure, π-π stacking

Introduction

The fused heterocyclic rings resulting from the condensation of pyridazine with a pyrrole [1,2] or oxazole [3] ring have interesting optical properties, offering new strategies and feasible ways to obtain stable light-emitting organic compounds. These condensed heterocycles are highly fluorescent in the solid state and in solution. Pyrrolo[1,2-b]pyridazine derivatives have also attracted attention in recent years due to their biological activity [4-10]. To our knowledge, only one X-ray structure of a

substituted pyrrolo[1,2-b]pyridazine has been reported to date, namely that of compound **1** [2], shown in Scheme 1.

Scheme 1. Structures of pyrrolo[1,2-b]pyridazines **1** [2] and **4** (present study)



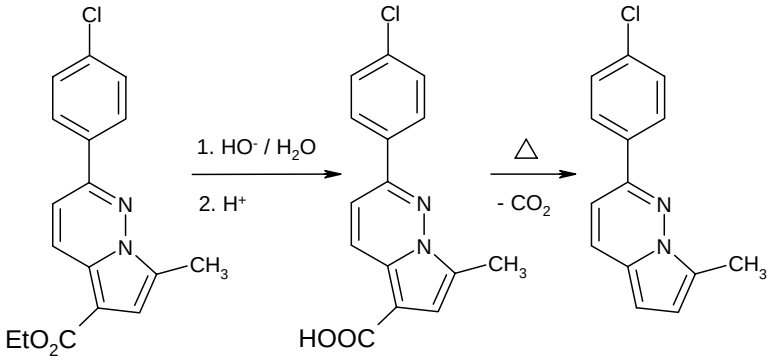
1 **4**

As suggested [2], the expansion of the π-electron system could have strong influences on the fluorescent properties of the compounds under discussion and represents the key step in the design of novel optically active materials. It is also known that π-π stacking interactions in the solid state are needed in order to have an extended π system, thus enabling electron mobility in the material. Such interactions are present in conjugated planar structures and to verify this hypothesis, the X-ray structure of **4** was determined.

Results and Discussion

2-(4-Chlorophenyl)-7-methylpyrrolo[1,2-b]pyridazine (**4**) was prepared from the ester **2** [11], under basic conditions, followed by thermal decarboxylation of the corresponding acid **3**.

Scheme 2. Synthesis of compound **4**



2 **3** **4**

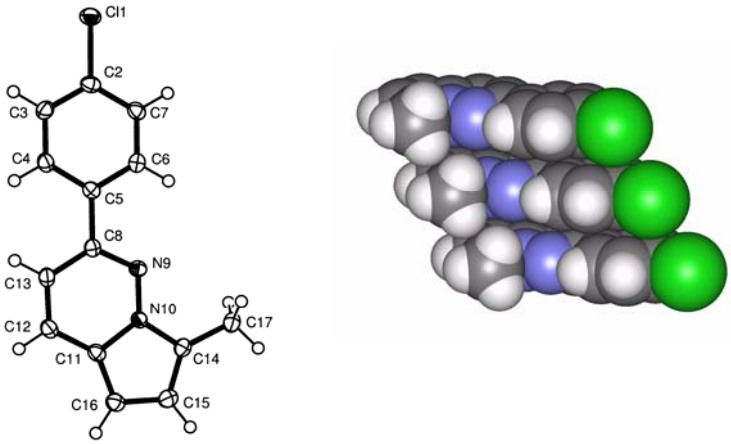
The structure of the pyrrolo[1,2-b]pyridazine **4** was confirmed by elemental analysis and NMR spectroscopy. In its ^{1}H-NMR the methyl group (δ = 2.62 ppm) appeared as a doublet (J = 0.7 Hz) due to the coupling with H-6. The H-5 proton (δ = 6.67 ppm) appeared as a doublet with coupling constant

J = 4.3 Hz, whereas H-6 (δ = 6.47 ppm) gave a double quartet with coupling constants of 4.3 and 0.7 Hz corresponding to the coupling with H-5 and methyl protons. The H-3 and H-4 protons from the pyridazine moiety gave two doublets at 6.82 and 7.72 ppm (J = 9.3 Hz). Also, the protons from the benzene ring appeared as two doublets with J = 8.6 Hz.

The ^{13}C-NMR data for compound **4** were in agreement with the structure assignment. The chemical shifts of tertiary carbon atoms were established by the HETCOR experiment. In turn, the chemical shift from 148.2 ppm was attributed to the C-2 atom due to its vicinity with the N-2 atom.

Figure 1 shows the molecular structure of **4** in the crystal. The maximum deviation of any atom from the least-squares (LS) plane including the nine non-H atoms of the pyrrolopyridazine moiety is 0.016(3) Å (for atom C16). This system is practically coplanar with the chlorophenyl residue (dihedral angle between LS planes 2.4(1)º).

Figure 1. Molecular structure of **4** showing (left) atomic numbering and thermal ellipsoids drawn at the 50% probability level [12] and (right) π-π stacking in the crystal

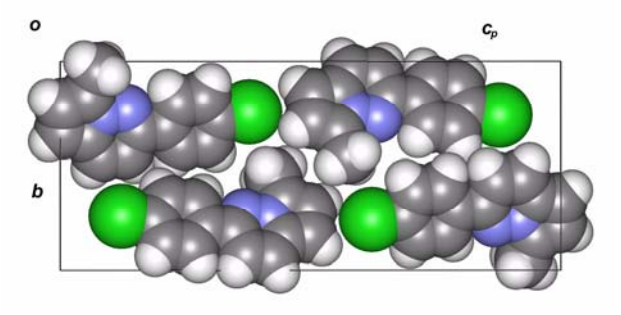


Salient geometrical parameters for the heterocyclic system were compared with those in **1** [2]. While both crystal structures were determined from low temperature intensity data (113 K for **4**, 100 K for **1**), it is noteworthy that the standard deviations in bond lengths for **4** (0.003-0.004 Å) are an order of magnitude smaller than those reported for **1** (0.037 Å [2]), justifying our reported analysis and allowing a more precise description of this heterocyclic system. The N-N bond length in **4** is 1.359(3) Å and the length C8-N9 is 1.314(3) Å. Given the relative standard deviations, these values overlap those quoted for **1** [2]. The carbon-carbon bonds in the 5-membered ring of **4** nominally span a narrower range (1.378(4)-1.396(5) Å) than that observed in **1** (1.383-1.426 Å). This is attributed to very significant electronic effects operating in **1** owing to the presence of two methyl ester substituents (Scheme 1). The asymmetry of the pyridazine ring of **4** is evident in Figure 1. In particular, the endocyclic angles subtended at N9 and C11 are equal (115.8(2), 115.7(3)º respectively) and significantly smaller than that subtended at N10 (126.1(2)º). Ring conjugation is reflected in the C5-C8 length of 1.490(4) Å, typical of e.g. biphenyls.

The likelihood of graphitic-type π-π stacking of these aromatic molecules in the crystal (Figure 1, right) was originally inferred from observation of the very short unit cell a-axis of 3.8568(1) Å. Molecules of **4** stack by translation along the x-direction forming columns. Crystal packing viewed

parallel to the stacking direction is shown in Figure 2. Because of their steep inclinations to the *bc*-face of the unit cell, molecules of **4** stack in an offset face-to-face mode (Figure 2, right) with an interplanar separation of 3.400 Å (i.e. significantly < *a*). This distance matches those reported in crystals of **1** and related heterocyclic aromatic systems (range 3.31-3.39 Å), for which it has been suggested that the strength of π stacking is sufficient for applications requiring high electron mobility [2]. The stacking offset in **4** results in the shortest centroid···centroid distance (3.635 Å) being that between the pyridazine ring of a molecule at *x, y, z* and the pyrrole ring of the translated molecule at *1+x, y, z*. The presence of only weak π-π stacking interactions in crystals of **4** is consistent with its low melting point of 54-55ºC. The X-ray analysis thus shows conclusively that the preparation and crystallization of **4** have achieved the desired goal in the solid state, namely extension of the π-electron system of the pyrrolo[1,2-b]pyridazine.

Figure 2. [100] projection of the crystal structure of **4**



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Experimental

General

Melting points were determined on a Boëtius hot plate and are uncorrected. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. IR spectra were recorded with a UR-20 Carl Zeiss-Jena spectrometer.

Syntheses

2-(4-Chlorophenyl)-7-methylpyrrolo[1,2-b]pyridazine-5-carboxylate (**3**)

Ethyl 2-(4-chlorophenyl)-7-methylpyrrolo[1,2-b]pyridazine-5-carboxylate (**2**, 1 g, 3.2 mmoles) [11] was heated under reflux, under continuous stirring, for 4 hours, with 10 % NaOH (20 mL). After acidification with concentrated HCl, the precipitate was collected by filtration, washed with water and air dried. Recrystallization from DMF afforded white crystals with m.p. 279-281 ^{0}C. Yield 97 %. Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C 62.84, H 3.87, Cl 12.37, N 9.77. Found C 63.22, H 4.15, Cl 12.73, N

10.07; ^{1}H-NMR ($CDCl_3$ + TFA; δ, ppm; *J*, Hz): 2.63 (d, 3H, 0.8; 7-Me); 7.20 (q, 1H, 0.8; H-6); 7.42 (d, 1H, 9.4; H-3); 7.50 (d, 2H, 8.6, H-3', H-5'); 7.95 (d, 2H, 8.6, H-2', H-6'); 8.48 (d, 1H, 9.4; H-4); ^{13}C-NMR ($CDCl_3$ + TFA; δ, ppm): 11.0 (7-Me); 100.2 (C-5); 113.7, 115.1,127.8 (C-3, C-4, C-6); 128.3, 129.4 (C-2', C-3', C-5', C-6'); 129.2, 130.7, 133.9; 136.7 (C-4a, C-7, C-1', C-4'); 151.0 (C-2); 171.5 (COOH).

2-(4-Chlorophenyl)-7-methylpyrrolo[1,2-b]pyridazine (**4**).

Carboxylic acid **3** (0.5 g, 1.7 mmoles) was heated above its melting point (bath temperature 290-5 ºC) until evolution of CO_2 ceased (ca. 5 min.). After cooling, the crude product was dissolved in a minimum amount of dichloromethane and purified by column chromatography on neutral Al_2O_3 using CH_2Cl_2 as eluent. The solvent was evaporated, the residue crystallized from isopropanol affording yellow crystals of **4**, m.p. 54-5 ^{0}C. Yield 62 %. Anal. Calcd. for $C_{14}H_{11}ClN_2$: C 69.28, H 4.57, Cl 14.61, N 11.54. Found C 69.67, H 4.88, Cl 14.97 N 11.88. IR (CH_2Cl_2; cm^{-1}): 1100, 1490, 1520, 1590, 1615, 2905; ^{1}H-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 2.62 (s, 3H, 0.7; 7-Me); 6.47 (d, 1H, 4.3; H-5); 6.67 (dq, 1H, 4.3, 0.7, H-6); 6,82 (d, 1H, 9.3, H-3); 7.42 (d, 2H, 8.6, H-3', H-5'); 7.72 (d,1H, 9.3; H-4); 7.90 (d, 2H, 8.6, H-2', H-6'); ^{13}C-NMR ($CDCl_3$; δ, ppm): 11.2 (7-Me); 98.7 (C-5); 106.1 (C-3); 112.6 (C-6); 124.9, 125.9 (C-4a, C-7); 127.1 (C-4); 127.9, 128,8 (C-2', C-3', C-5', C-6'); 135.1, 135.6 (C-1', C-4'); 148,2 (C-2).

X-ray analysis of **4**

A small fragment was cut from a needle of **4** and mounted on a Nonius Kappa CCD four-circle diffractometer. Intensity data were collected using Mo-Kα radiation (λ = 0.71069 Å) with the crystal cooled in a stream of N_2 from a Cryostream cooler (Oxford Cryosystems, UK). The data-collection strategy (program COLLECT [13]) involved suitable combinations of 1.0° φ- and 0.60º ω-scans. Program DENZO-SMN [14] was used for cell refinement (15365 reflections in the θ-range 0.21-27.48°) and data reduction. The SADABS program [15] was used to apply absorption corrections. The structure was solved with the SHELXS86 program [16] and refined on F^2 with SHELXL97 [17], all non-hydrogen atoms being modelled anisotropically. All H atoms were located in difference electron-density maps and were included in idealized positions in a riding model with isotropic thermal parameters equal to 1.2 times those of their parent atoms. In the final cycles of refinement, least-squares weights of the form $w = 1/[\sigma^2(F_o)^2 + (aP)^2 + bP]$, $P = [\max(F_o^2, 0) + 2F_c^2]/3$ were employed. Molecular parameters were calculated with PLATON [18] and programs ORTEP-3 [12] and WebLab Viewer Pro3.7 [19] were used for illustrations. Crystallographic data for **4** are listed in Table 1. CCDC-254383 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK: fax: (internat.) +44-1223/336-033; Email: deposit@ccdc.cam.ac.uk].

Table 1. Crystallographic parameters for **4**

Chemical formula	$C_{14}H_{11}ClN_2$
Formula weight	242.71
Crystal Color, Habit	yellow, needle
Crystal Dimensions	0.08 x 0.12 x 0.18
Crystal System	monoclinic
Lattice Type	primitive
Space Group	$P2_1/c$ (#14)
Lattice Parameters	a = 3.8568(1) Å
	b = 11.0690(3) Å
	c = 26.4243(7) Å
	β = 92.777(1)°
Volume	1126.75(5) Å^3
Z value	4
D_{calc}	1.431 g/cm^3
F(000)	504
μ(MoKα)	0.314 mm^{-1}
Reflections/restraints/parameters	2460 / 0 / 156
Residuals: R1, wR2 [I > 2σ(I)]	0.0578, 0.1305
Goodness of Fit, S	1.158
Max. shift/error	< 0.001
Max. peak in final Δρ synthesis	0.49
Min. peak in final Δρ synthesis	-0.32

References

1. Cheng, Y.; Ma, B.; Wudl, F. *J. Mater. Chem.* **1999**, *9*, 2183-2188.
2. Mitsumori, T.; Bendikov, M.; Sedó, J.; Wudl, F. *Chem. Mater.* **2003**, *15*, 3759-3768.
3. Vasilescu, M.; Dumitrascu, F.; Lemmetyinen, H.; Tkachenko, N. *J. Fluorescence* **2004**, *14*, 443-450.
4. Ruxer, J. M.; Lachoux, C.; Ousset, J. B.; Torregrosa, J. L.; Mattioda, G. *J. Heterocycl. Chem.* **1994**, *31*, 409-417.
5. Ungureanu, M.; Mangalagiu, I.; Grosu, G.; Petrovanu, M. *Ann. Pharm. Fr.* **1997**, *55*, 69-72; [*Chem. Abstr.* **1997**, *126*, 303587].
6. Nassir, A. I.; Gundersen, L.-L.; Rise, F.; Antonsen, Ø.; Kristensen, T.; Langhelle, B.; Bast, A.; Custers, I.; Haenen, G. R. M. M.; Wikström, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1829-1832.
7. Østby, O. B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G. R. M. M. *Eur. J. Org. Chem.* **2000**, *9*, 3763-3770.
8. Ohtani, M.; Fuji, M.; Fukui,Y.; Adachi, M. *World Patent WO 9959999 A1*, **1999**; [*Chem. Abstr.* **2000**, *132*, 12318].
9. Østby, O. B.; Gundersen, L.-L.; Rise, F.; Antonsen, Ø.; Fosnes, K.; Larsen, V.; Bast, A.; Custers, I.; Haenen, G. R. M. M. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 21-24.

10. Pal, M.; Batchu, V. R.; Khanna, S.; Yeleswarapu, K. R. *Tetrahedron* **2002**, *58*, 9933-9940.
11. Dumitraşcu, F.; Mitan, C. I.; Dumitrescu, D.; Drăghici, C.; Căproiu, M. T.; Vasilescu, M., *Book of Abstracts*, *10th Blue Danube Symposium on Heterocyclic Chemistry*, PO-126, Vienna, Austria, September 3-6, **2003**
12. Farrugia, L. J. ORTEP-3 for windows - a version of ORTEP-III with a graphical user interface (GUI). *J. Appl. Crystallogr.* **2000**, *30*, 565.
13. COLLECT. *Nonius 2000*; Nonius BV: Delft, The Netherlands, **2000**.
14. Otwinowski, Z.; Minor,W. *Methods Enzymol.* **1997**, *276*, 307-326.
15. Sheldrick, G. M. *SADABS. Program for Empirical Absorption Correction of Area Detector Data*; University of Göttingen: Göttingen, Germany, **1996**.
16. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467-473.
17. Sheldrick, G. M. *SHELXL97*; University of Göttingen: Göttingen, Germany, **1997**,
18. Spek, A. L. *PLATON, A multipurpose Crystallographic Tool*, Version 10500 © **1980-2000**.
19. *WebLab ViewerPro Version 3.5*, Molecular Simulations Inc.: San Diego, CA, USA © **1999**.

Sample availability: Samples of compound **4** are available from the authors.