Journal of Molecular Structure 998 (2011) 84–90

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Synthesis, tautomeric forms, specific intermolecular interactions, and lipophilicity of methylated 6-hydroxypyridazine-3-carboxylic acid and its 4,5-dihydro analogs

Anna Katrusiak [a,*], Paweł Piechowiak [a], Andrzej Katrusiak [b]

[a] Department of Organic Chemistry, Poznan University of Medical Sciences, Grunwaldzka 6, 60-780 Poznań, Poland
[b] Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland

ARTICLE INFO

Article history:
Received 8 April 2011
Received in revised form 10 May 2011
Accepted 10 May 2011
Available online 14 May 2011

Keywords:
Pyridazine–carboxylic acids
Lactam–lactim tautomers
Methylation
Lipophilicity
Crystal structure

ABSTRACT

Effects of methylation for intermolecular interactions and lipophilicity have been studied for a series of methylated 4,5-dihydro-6-hydroxypyridazine-3-carboxylic and 6-hydroxypyridazine-3-carboxylic acids (**1** and **2**). In solution they exist in equilibrium of the lactam and lactim tautomers, with the reverse preferences for analogs **1** and **2**, which affect the syntheses of their methylated derivatives. Carboxylic acid **2** preferably crystallizes as a hydrate, built of carboxylate anions and hydronium cations $\mathbf{2}^{-}\cdot H_3O^+$, hydrogen bonded into catemeric patterns involving both ions. In methyl 4,5-dihydro-6-oxopyridazine-3-carboxylate (**4A**) the molecules are NH···O hydrogen bonded into chains. In both structures $\mathbf{2}^{-}\cdot H_3O^+$ and **4A**, there are relatively strong CH···O hydrogen bonds, arranging the molecules into sheets. The increased lipophilicity of the methylated derivatives has been correlated with the formation of CH···O bonds.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Pyridazine derivatives exhibit biological activity of a broad spectrum, such as anticonvulsant and sedative, which stimulates research on reactivity and properties of this group of compounds [1]. Pyridazinone and its derivatives can transform between lactam and lactim tautomers, also characteristic of many organic substances. Their chemical and biological properties are associated with these tautomeric forms. It also applies to 6-hydroxypyridazine-3-carboxylic acid derivatives, exhibiting tautomeric transformations, which in turn affect their methylation and lipophilicity. 6-Hydroxypyridazine-3-carboxylic acid (**2**) was described in 1909 by Gabriel [2] who obtained it by treating α-ketoglutaric acid with hydrazine sulfate. The Gabriel's synthesis of **2** was a multistep reaction: condensation of α-ketoglutaric acid with hydrazine hydrate was the first step leading to 4,5-dihydro-6-hydroxypyridazine-3-carboxylic acid (**1**), which in the second step was treated with bromine in acetic acid, yielding **2**. In 1948 Homer et al. [3] synthesized **2** by the oxygenation of 6-methyl-3-pyridazinone with either diluted HNO_3 or $K_2Cr_2O_7/H_2SO_4$ [3]. The lipophilicity of **1** and **2** is low compared to the values of drugs penetrating into the nervous system. Therefore it has been undertaken to obtain new methylated derivatives of **1** and **2** and to investigate the role of methylation site for the lipophilicity of these compounds. The methylation sites in the products can be also used for studying the lactam and lactim tautomers of **1** and **2** present in the reaction solution and stabilized in the reactions of methylation.

2. Results and discussion

2.1. Tautomers of *1* and *2* as anchored by methylation

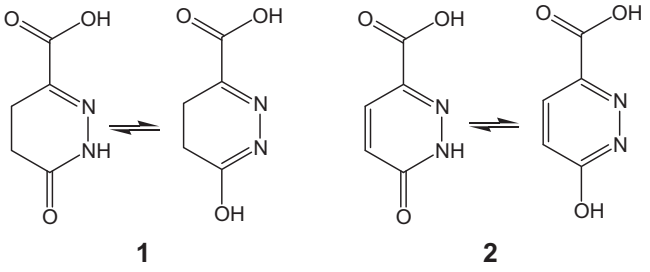
Both compounds **1** and **2** exhibit lactam–lactim tautomers resulting from the hydrogen atom migration between nitrogen N1 in pyridazine ring to O (C6) shown in Scheme 1. However, the X-ray diffraction analysis of compound **2** (see below) revealed that it preferably forms a hydrate, where the molecule dissociates into the ionic complex $\mathbf{2}^{-}\cdot H_3O^+$.

The substitution of the acidic proton by an alkyl group was performed as an attempt of anchoring one of the lactam–lactim forms. It was shown [4,5] that methyl group can be introduced by using either of the following methods: (i) treatment with dimethyl sulfate at 140–150 °C; (ii) treatment with methyl iodide in dry DMF at room temperature; and (iii) treatment with dimethyl sulfate in 20% aq. natrium carbonate at room temperature. It was further established [4,5] that methylation method (i) anchors the lactam form, so N-methyl pyridazinone arises. However, method (iii) leads to the lactim form and O-methyl derivatives are obtained.

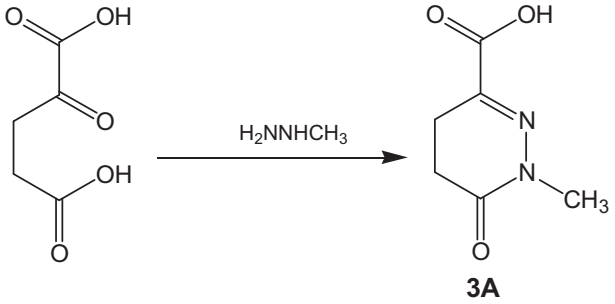
Methods (i) and (ii) applied for the methylation of **1** and **2** yielded a mixtures of compounds difficult to separate. Only method (iii) gave well crystallized methylated products of **1** and **2**. The course of reaction was controlled by TLC. The MS spectrum of the reaction **1** product showed that only one methyl group was introduced. Three mono-methylated derivatives could be formed:

* Corresponding author.
E-mail address: akatrus@ump.edu.pl (A. Katrusiak).

0022-2860/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2011.05.016



Scheme 1. Lactam and lactim molecular H-tautomers of **1** and **2**.



Scheme 3. Alternative direct synthesis of standard **3A**.

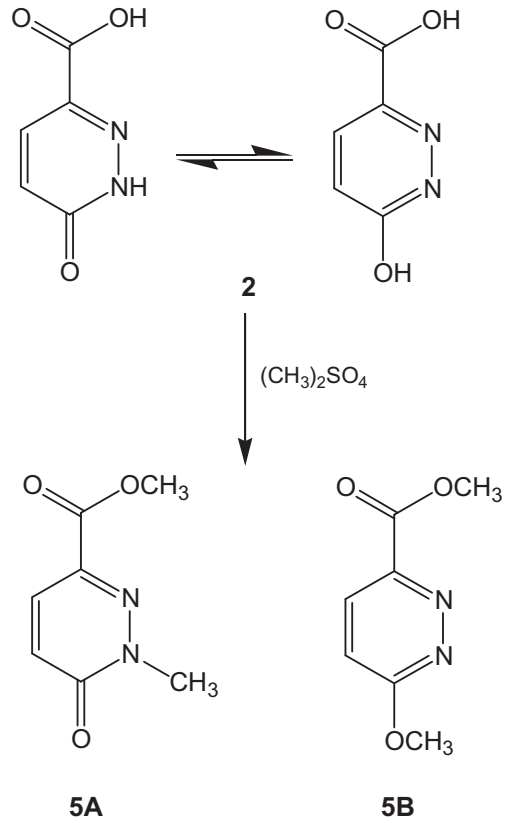
4,5-dihydro-1-methyl-6-oxopyridazine-3-carboxylic acid (**3A**), 4,5-dihydro-6-methoxypyridazine-3-carboxylic acid (**3B**) and methyl 4,5-dihydro-6-oxopyridazine-3-carboxylate (**4**), all shown in Scheme 2.

In order to identify the structure of obtained methylated product of **1**, we synthesized **3A** by treating α-ketoglutaric acid with methylhydrazine in 10% HCl (Scheme 3).

Then the isolated methylation product of **1** treated with dimethyl sulfate was compared to methylated the lactam form **3A** and showed that compound **3A** has not been stabilized by method (iii). The melting points, ^{1}H NMR spectra and TLC of both samples were compared where compound **3A** synthesized according to Scheme 3 was used as a standard. In the ^{1}H NMR spectrum of **3A**, the signal of the methyl group was observed at 3.27 ppm. Four protons at C4 and C5 appear at about 2.46 and 2.75 ppm as triplets. The carboxylic proton gives a wide signal at about 12.94 ppm.

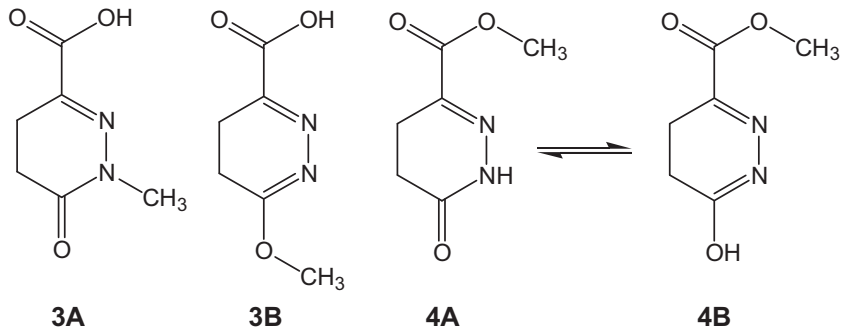
It was difficult to discriminate between products **3B** and **4** basic only on their ^{1}H NMR spectra, because the chemical shift of O-methyl protons at carboxylic group (**4**) is similar to that of O-methyl protons at hydroxylic group (**3B**). Therefore it has been studied by X-ray diffraction and established that methyl 4,5-dihydro-6-oxopyridazine-3-carboxylate (**4A**) was synthesized during the methylation of **1**. The signals in ^{1}H NMR spectrum of **4A** have been assigned to the methyl protons at 3.74 ppm, and C4/C5 protons at about 2.40 and 2.75 ppm.

In the analogous way as the C4–C5 saturated pyridazinone acid **1**, also unsaturated acid **2** has been treated with dimethyl sulfate at room temperature in 20% aq. natrium carbonate. A mixture of two products, methyl 1-methyl-6-oxopyridazine-3-carboxylate **5A** and methyl 6-methoxypyridazine-3-carboxylate **5B**, was obtained (Scheme 4). The identity of isolated products, separated by column chromatography, was determined by MS, ^{1}H NMR and ^{13}C NMR. The MS spectrum of the products of the methylation of **2** was consistent with two methyl groups introduced to the molecule. In the ^{1}H NMR spectrum of **5A**, a pair of doublets from protons at C4 and C5 at approximately 7 ppm (J = 9.6 Hz) were observed. The N-methyl protons were shifted to 3.36 ppm, while O-methyl protons



Scheme 4. Methylation method (iii) of **2** with dimethyl sulfate.

signaled their presence at 3.85 ppm. In the ^{1}H NMR spectrum of **5B**, apart from a pair of doublets (H–C4 and H–C5), also signals of two



Scheme 2. Three mono-methylated derivatives of 4,5-dihydropyridazinecarboxylic acid (**1**): only the ester exhibits lactam **4A** and lactim **4B** tautomers.

methyl groups were present. The signal of the methyl protons in methoxy group at C6 was close to the signal of methyl protons at the ester group: 3.78 ppm and 3.86 ppm, respectively.

In order to confirm structure **5A**, this product has been obtained directly in another chemical reaction. Acid **2** was treated with selectively methylated N,N-dimethylformamide dimethyl acetal (DMF–DMA). In this way 6-hydroxy-1-methylpyridazine-3-carboxylic acid (**6**) was synthesized. Compound **6** was also obtained in the reaction of **3A** treated with bromine in acetic acid, however its yield was very small. The ^{1}H NMR spectrum of **6** consists of a pair of doublets from the protons at C4 and C5 and N-methyl group at 3.32 ppm. Compound **6** was methylated under typical reaction conditions and **5A** was obtained with a small yield (Scheme 5).

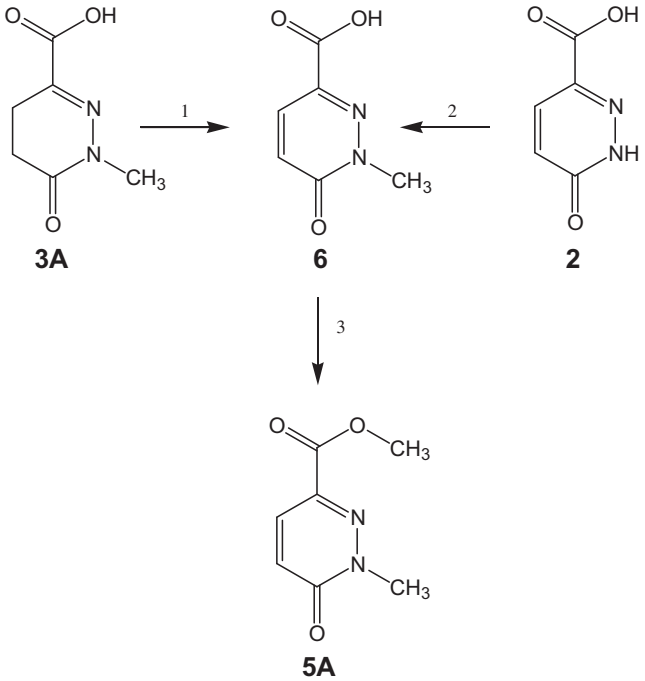
2.2. Heat of formation of lactam and lactim forms

The heat of formation (HOF) of tautomers **A** and **B** of compounds **1–5** have been calculated by the molecular orbital AM1 procedure with the standard parameters implemented in the MOPAC program in the precise mode [6]. The calculated HOF magnitudes have been compiled in Table 1. The HOF magnitudes of saturated acids **1**, **3**, **4** in lactam tautomers **A** are smaller than of their lactim form **B**, indicating that the lactam forms are more stable than the lactim tautomers. The calculations indicate that the reverse HOF energy preference applies to the unsaturated acid derivatives **2** and **5**. Their HOF magnitudes are smaller for the lactim tautomers **B**.

2.3. Crystal structures

The structures of **2** and methyl 4,5-dihydro-6-oxopyridazine-3-carboxylate **4A** have been determined by single-crystal X-ray diffraction.

Acid **2** preferably crystallizes as a hydrate, and in the crystalline state it transforms into the ionic form $\mathbf{2}^{-}\cdot H_3O^+$, as shown in Fig. 1. The $\mathbf{2}^-$ and H_3O^+ ions are hydrogen bonded (Table 2) into pairs by a short hydrogen bond O(1w)–H(1w)···O(1) of 2.498(2) Å. The hydronium cation forms further H-bonds O(1w)–H(2w)···N(2^{i}) of



Scheme 5. Reaction 1: Br_2/CH_3COOH, small yield; reaction 2: DMF–DMA, good yield; reaction 3: $(CH_3)_2SO_4/Na_2CO_3$/rt, small yield.

Table 1
Heats of formation HOF (kcal/mole) of the lactam **A** and lactim **B** tautomers of **1–5**.

Compound	HOF	Compound	HOF
1A	−91.49	**1B**	−48.02
2A	−38.15	**2B**	−72.42
3A	−83.44	**3B**	−43.58
4A	−83.37	**4B**	−45.26
5A	−30.75	**5B**	−53.14

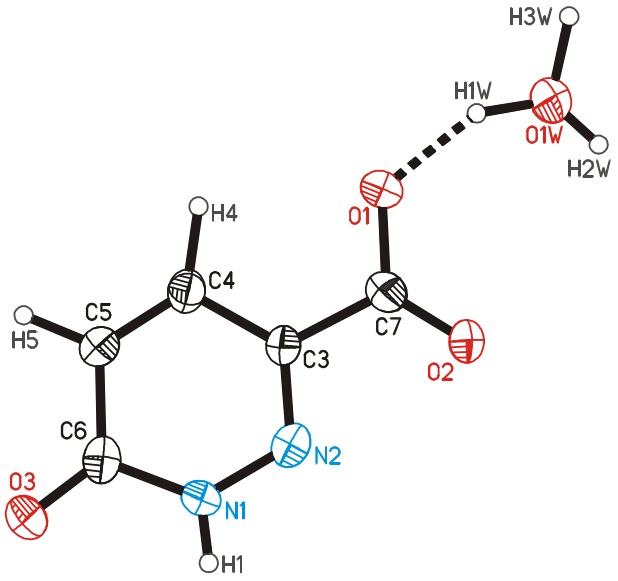


Fig. 1. The formula unit of hydrate $\mathbf{2}\cdot H_2O$, in the ionic form of $\mathbf{2}^{-}\cdot H_3O^+$ constituting an asymmetric part of the crystal. The thermal ellipsoids have been drawn at the 50% probability level, and the H-bond has been indicated by the dashed line.

3.001(2) Å and O(1w)–H(3w)···O(3^{ii}) of 2.787(2) Å. Together with bonds N(1)–H(1)···O(2^{iii}) of 2.783(2) Å, two per one molecule, they connect the lactim nitrogen and carboxyl groups. These OH···O, OH···N and NH···O bonds link the ions into slightly corrugated tapes, shown in Fig. 2, along crystal direction [0 1 0]. These tapes are parallel to crystal planes (1 0 1). The tapes are further connected into sheets extending along planes (1 0 1), by C(4)–H(4)···O(5^{iv}) and C(5)–H(5)···O(1^{v}) of 3.337(3) Å and 3.501(3) Å, respectively (Fig. 3). The shortest contact between the sheets involves atoms C(3) and C(4^{vi}), the latter at ($x-1$, y, z), 3.332(4) Å apart. The hydronium cations are characteristic of very strong acids [7] and their hydrogen salts [8].

The molecular ring of 4,5-dihydro-6-oxopyridazine-3-carboxylate (**4A**) is in a strongly distorted half-chair conformation (Fig. 4), with the smallest torsion angle N(1)–N(2)–C(3)–C(4), and the largest one C(3)–C(4)–C(5)–C(6); the Cremer–Pople puckering parameters for the ring are: puckering amplitude q_2 = 0.3937(14) Å, and angles θ_2 = 111.58(19)° and φ_2 = 24.4(2)°. In the crystal structure molecules are arranged into sheets parallel to crystal plane (−1 0 1). Hydrogen bonds NH···O (Table 3) involve the lactim atoms and link the molecules into chains along crystal direction [0 1 0]. It is an unusual type of hydrogen bonding, because the lactim groups most frequently bind the maleic hydrazide molecules by a pair of NH···O bonds into dimers [9]. The ester groups form an aggregate resembling the catemers of carboxylic acids, but with the OH···O bonds replaced with OCH$_3$···O contacts (Table 3, Fig. 5).

2.4. Lipophilicity of methyl derivatives

The introduction of methyl groups increases the size of molecules and changes their interactions, which affects properties of

Table 2
Hydrogen bonds and short C–H···O contacts (Å and °) in the crystal structure of $\mathbf{2}^{-}\cdot H_3O^{+}$.

D–H···A	D–H	H···A	D···A	D–H···A	Symmetry code
N1–H1···O2	0.84(3)	1.95(3)	2.783(2)	168(3)	$1-x, y+0.5, 2-z$
O1w–H1w···O1	1.03(3)	1.56(2)	2.498(2)	149(3)	x, y, z
O1w–H2w···N2	0.85(2)	2.16(2)	3.001(2)	170(3)	$1-x, y-0.5, 2-z$
O1w–H3w···O3	1.09(2)	1.72(2)	2.787(2)	163(3)	$x, y-1, -z$
C4–H4···O3	1.11(3)	2.39(3)	3.337(2)	142(2)	$2-x, y-0.5, 1-z$
C5–H5···O1	1.06	2.47(3)	3.500(2)	163(3)	$2-x, y+0.5, 1-z$

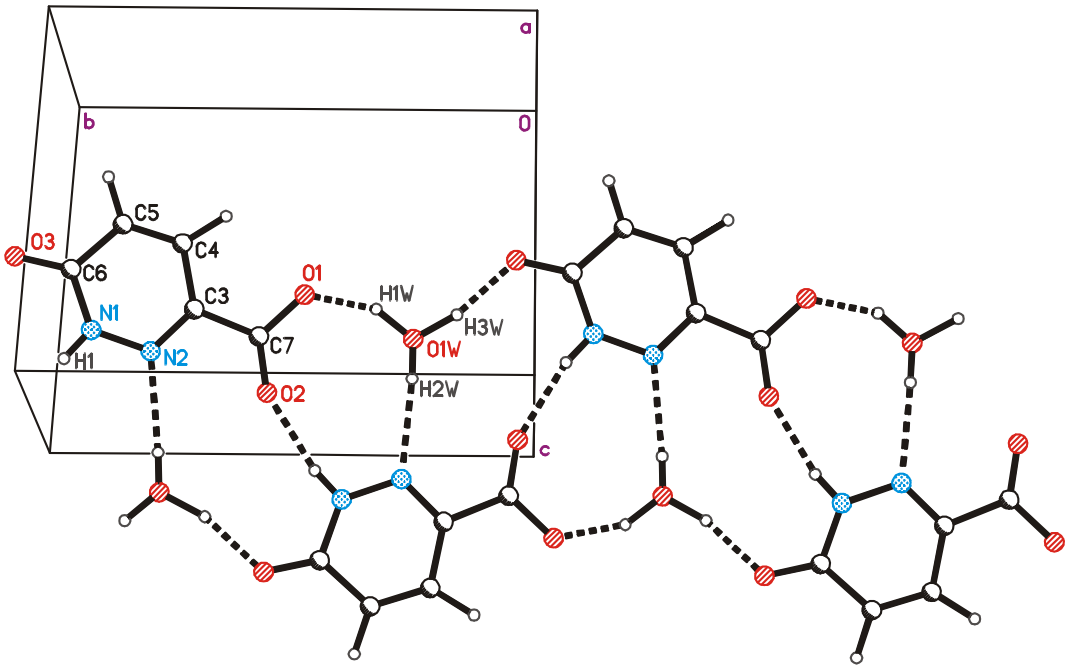


Fig. 2. The ionic aggregation within H-bonded sheets of $\mathbf{2}^{-}\cdot H_3O^{+}$.

the compounds and can be significant for its pharmaceutical activity. Such modifications of molecular structure are termed as the methylene shuffle, and this method is often aimed at increasing the hydrophobicity of compounds. Larger lipophilicity, which represents the affinity of a molecule or a moiety for a lipophilic environment, facilitates penetration of drugs into the central nervous system. Therefore the lipophilicity control is essential in designing new active pharmaceutical ingredients. Lipophilicity has been measured for **1**, **2**, **3A**, **4A**, **5A**, **5B** and **6** by thin-layer chromatography (Table 4). Higher or positive R_M values are characteristic of the compounds more lipophilic than those exhibiting lower R_M magnitudes. A correlation between the lipophilicity and the number of methyl substituents in the acid derivatives is apparent. The unmethylated acids **1** and **2** have the lowest R_M value.

3. Conclusions

The lactam–lactim tautomers of 6-hydroxypyridazine-3-carboxylic acid (**1**) and its **4–5** saturated analog **2** have been methylated and the methylation products correspond to the tautomers of **1** and **2**. Acid **2** crystallized of aqueous solution forms hydrates, with the acidic proton transferred and hydronium cation formed: $\mathbf{2}^{-}\cdot H_3O^{+}$. In the crystal structures, the methylation leads to the replacement of strong OH···N and NH···O hydrogen bonds, with weaker CH···O interactions, which correlates with increasing lipophilicity of the methylated derivatives. This has been confirmed by the measurements of lipophilicity of the investigated compounds. It has been established, that the C4–C5 bond saturation reverses the preference of lactam–lactim tautomers. The methylation of tautomers of **1** and **2** can be used as alternative reactions for obtaining compounds **3A**, **4**, **5A**, **5B**, **6** that were described in literature [11–17]. Compound **3A** was obtained in 1961 by Kline and Cox obtained by treating α-ketoglutaric acid with methylhydrazine sulfate [11]. Synthesis of **4** was published by Teotino in 1959. It consisted in reaction between dimethyl 2-oxoglutarate and hydrazine with acid catalysis in refluxing methanol [12,13].

5A was synthesized by Homer in 1948 from methyl 6-oxopyridazine-3-carboxylate using methyl iodide [3]. **5B** is known also in literature [14–16]. It was obtained from ethyl 6-chloropyridazine-3-carboxylate with sodium methylat [14], or from 6-methoxypyridazine-3-carboxylic acid with thionyl chloride (stage 1) and methanol (stage 2) [15], or by cyclization of cis-phospharene [16].

Compound **6** was obtained by King and Mc Millan in 1952. This was prepared by 1:1 hydrochloric acid hydrolysis of a small amount of its ethyl ester [17]. It was also prepared by Homer, Gregory and Wiggins by oxidation of 2,6-dimethyl-3-pyridazinone [3].

4. Experimental

Melting points were determined on a Boetius apparatus and were uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ or DMSO with TMS as an internal standard and chemicals shifts are expressed as δ (ppm).

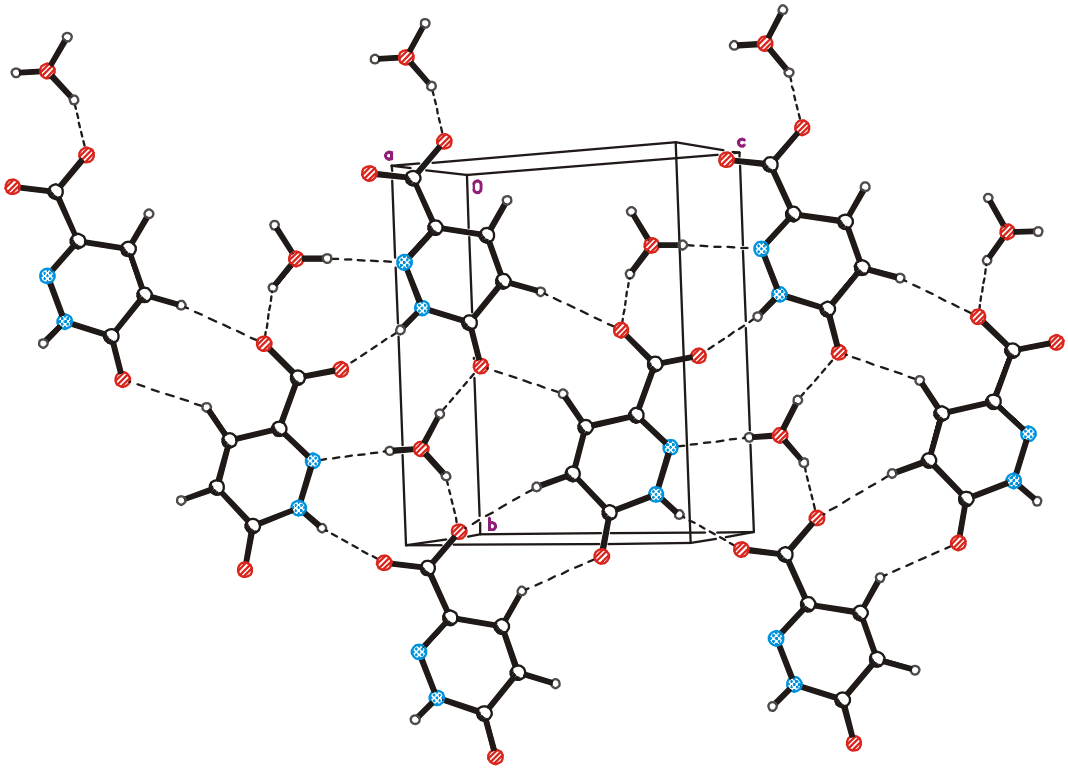


Fig. 3. The pattern of hydrogen bonds, including the CH···O bonds, in $\mathbf{2}^{-}\cdot H_3O^{+}$.

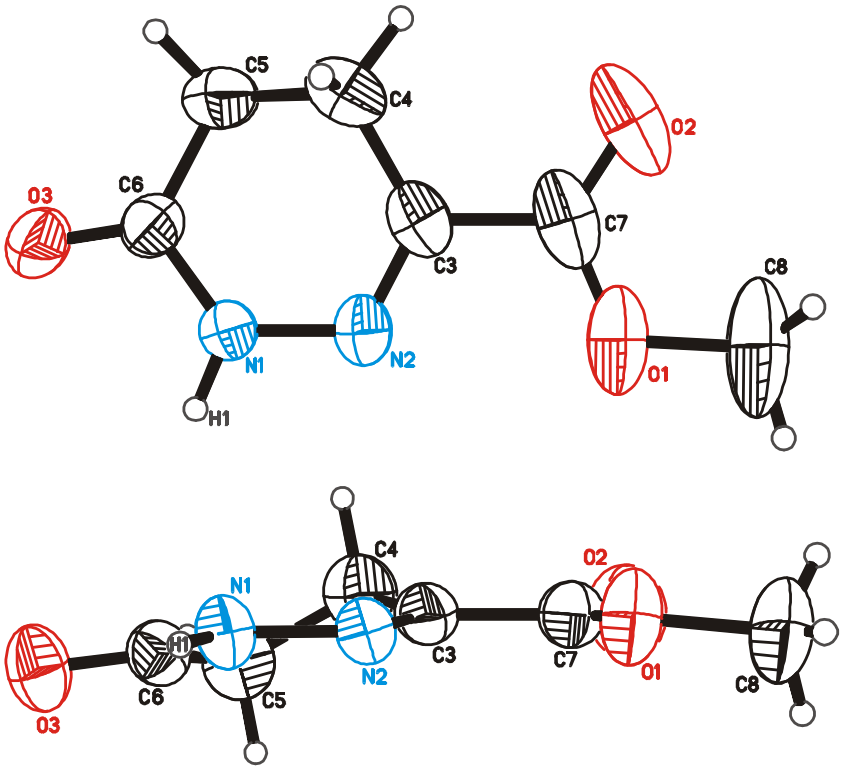


Fig. 4. Two perpendicular projections of methyl 4,5-dihydro-6-oxopyridazine-3-carboxylate (**4A**) molecule perpendicular to the N1-N2 bond. Thermal ellipsoids have been drawn at the 50% probability level.

The *J*-values are given in Hz. Mass spectra were obtained on an AMD 604 Inectra GmbH instrument. The products were separated by a column chromatography using as a mobile phase acetone/hexane mixture (3:2). The column was filled by silica gel (0.040–0.063 mm, 230–400 mesh ASTM, Merck). The lipophilicity measurement was done according to the literature [18]. Separation

Table 3
Hydrogen bonds and short contacts in methyl 4,5-dihydro-6-oxopyridazine-3-carboxylate (**4A**) (Å and °). Apart from the C8–H8*n*···O2 (*n* = 1, 2, 3) contacts involving the carboxyl methyl hydrogens and oxygen atoms, also the next shortest C–H···O contact dimensions have been given for comparison.

D–H···A	D–H	H···A	D···A	D–H···A	Symmetry code
N1–H1···O3	0.89(3)	1.91(3)	2.791(2)	168.6(3)	$1-x, y-0.5, 0.5-z$
C8–H81···O2	0.96	3.01	3.137(2)	88.9	$-x, y-0.5, -0.5-z$
C8–H82···O2	0.96	3.06	3.137(2)	85.6	$-x, y-0.5, -0.5-z$
C8–H83···O2	0.96	2.82	3.137(2)	100.5	$-x, y-0.5, -0.5-z$
C5–H51···O3	0.96	2.72(3)	3.593(2)	150.8(3)	$1-x, y+0.5, 0.5-z$

was carried out on precoated RP-TLC plated of RP-18F 254s (Merck, Darmstadt, Germany). The polar mobile phase was a mixture methanol/water (8:2). Each compound was dissolved in methanol (1 mg/mL) and the solution (5 μL) was applied onto the plate with aid of a HAMILTON syringe. After development, the plates were dried and the spots were localized in UV 254 nm.

*4.1. 4,5-Dihydro-1-methyl-6-oxopyridazine-3-carboxylic acid **3A***

1.46 g (10 mmol) of α-Ketoglutaric acid was dissolved in 10% HCl and 0.46 g (10 mmol) of methylhydrazine was added dropwise. Then the reaction mixture was refluxed for 3 h. After cooling the reaction mixture was extracted with dichloromethane. The extracts were washed with water, dried (anhydrous $MgSO_4$) and evaporated. Crude product was crystallized from ethanol. Yield 52%; m.p. 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 2.46 (t, J = 8.5 Hz, 2H), 2.75 (t, J = 8.5 Hz, 2H), 3.27 (s, 3H); ^{13}C NMR δ 25.8, 36.6, 39.0, 143.4, 164.3, 173.9. MS(*m*/*z*, M^+): 156.0 (100%). Anal. Calcd for $C_6H_8N_2O_3$ (156.14): C, 46.15; H, 5.16; N, 17.94. Found C, 46.03; H, 5.13; N, 17.52.

Table 4
Lipophilicitiy of **1** and **2** and their methylated derivatives. The R_M values have been calculated from the experimental R_f values, according to formula $R_M = \log[1/R_f - 1]$.

Compound	**1**	**2**	**3A**	**4**	**5A**	**5B**	**6**
R_M	−1.28	−1.69	−1.06	1.56	0.31	0.75	0.27

4.1.1. General procedure of methylation reaction

To a stirred mixture of 10 mmol of acid **1** or **2** in 30 mL of 20% Na_2CO_3 13 mL of dimethylsulfate was added at room temperature. The reaction mixture was stirred for 2 h then poured into water and extracted with dichloromethane. The extracts dried with $MgSO_4$ and evaporated. Crude products were purified by column chromatography and crystallization from ethanol.

*4.2. Methyl 4,5-dihydro-6-oxopyridazine-3-carboxylate **4A***

Yield 67%; m.p. 115–118 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (t, J = 8.1 Hz, 2H), 2.75 (t, J = 8.1 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR δ 24.6, 37.8, 39.5,

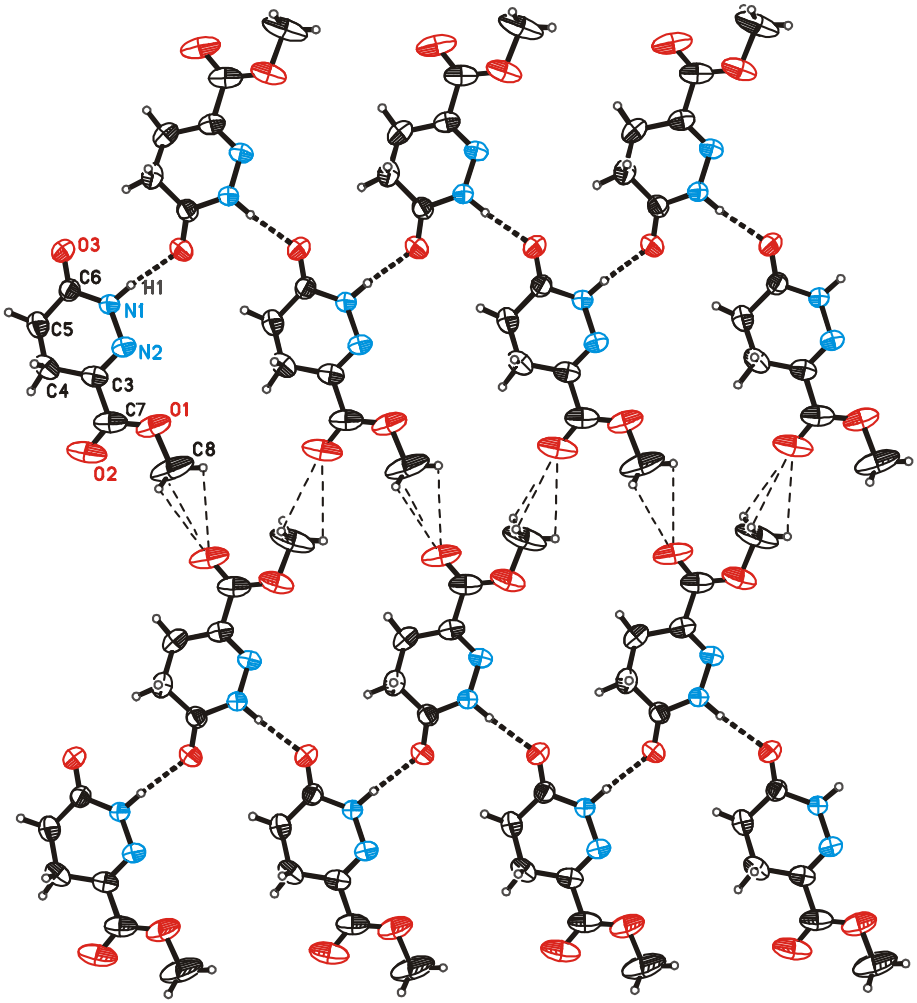


Fig. 5. Autostereographic projection [10] of the H-bonding pattern within the sheets in methyl 4,5-dihydro-6-oxopyridazine-3-carboxylate (**4A**) structure, viewed perpendicular to crystal plane (−1 0 1).

143.7, 159.6, 173.6. MS(*m/z*, M^+): 156.0 (100%). Anal. Calcd for $C_6H_8N_2O_3$ (156.14): C, 46.15; H, 5.16; N, 17.94. Found C, 45.92; H, 5.08; N, 17.34.

4.3. Methyl 1-methyl-6-oxopyridazine-3-carboxylate **5A** and methyl 6-methoxypyridazine-3-carboxylate **5B**

For **5A**: Yield 37%; m.p. 189–191 °C; ^{1}H NMR ($CDCl_3$) δ 3.36 (s, 3H), 3.85 (s, 3H), 6.97 (d, J = 9.9 Hz, 1H), 7.84 (d, J = 9.9 Hz, 1H); ^{13}C NMR δ 38.9, 52.6, 129.4, 132.1, 136.1, 160.6, 162.6. MS(*m/z*, M^+): 168.0 (7%). Anal. Calcd for $C_7H_8N_2O_3$ (168.15): C, 50.00; H, 4.80; N, 16.66. Found C, 49.95; H, 4.61; N, 16.34.

For **5B**: Yield 67%; m.p. 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.98 (s, 3H), 6.97 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 9.6 Hz, 1H); ^{13}C NMR δ 40.5, 52.6, 128.4, 131.7, 135.3, 159.6, 162.3. MS(*m/z*, M^+): 168.0 (9%). Anal. Calcd for $C_7H_8N_2O_3$ (168.15): C, 50.00; H, 4.80; N, 16.66. Found C, 49.87; H, 4.72; N, 16.51.

4.4. 1-Methyl-6-oxopyridazine-3-carboxylic acid **6**

(a) To 1.56 g (10 mmol) of **3A** in acetic acid 0.79 g (10 mmol) of bromine was added dropwise. The reaction mixture was stirred for 2 h at 70 °C then poured into water, alkalized with NH_4OH and extracted with dichloromethane. The extracts dried with $MgSO_4$ and evaporated. Crude products were purified by crystallization from ethanol. Yield 7%; subl. 220 °C; m.p. 295 °C; ^{1}H NMR ($CDCl_3$) δ 3.32 (s, 3H), 6.95 (d, J = 9.8 Hz, 1H), 7.82 (d, J = 9.8 Hz, 1H); ^{13}C NMR δ 39.7, 128.4, 132.5, 139.7, 159.6, 162.3. MS(*m/z*, M^+): 154.1 (13%). Anal. Calcd for $C_6H_6N_2O_3$ (168.15): C, 46,76; H, 3.92; N, 18.18. Found C, 46.57; H, 3.76; N, 18.41.

(b) 1.40 g (10 mmol) of **2** and 1.19 g (10 mmol) of DMF–DMA in dry DMF were refluxed for 3 h then poured into water and extracted with dichloromethane. The extracts dried with $MgSO_4$ and evaporated. Crude products was crystallized from ethanol. Yield 62%.

4.4.1. X-ray diffraction

The single crystals of compounds $\mathbf{2}^-\cdot H_3O^+$ and **4A** for X-ray diffraction measurements were grown from the dichloromethane solution by evaporation. The diffraction data were recorded using a 4-circle KUMA KM4-CCD diffractometer. The structures were solved by direct methods with program Shelxs-97 and refined with Shelxl-97 [19]. The crystal data of $\mathbf{2}^-\cdot H_3O^+$ and **4A** have been listed in Table 2. The crystal structures have been also deposited with the Cambridge Crystallographic Database Centre as supplementary publications Nos. CCDC 771942 and CCDC 771943 copies can be obtained free of charge on request from www.ccdc.cam.ac.uk/data_request/cif. The crystallographic details of these structures are tabulated in Supplementary information, Tables S1–S12.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2011.05.016.

References

[1] C. Rubat, P. Coudert, J. Couquelet, P. Tronche, J. Bastide, P. Bastide, Farmaco Ed. Sci. 45 (1990) 331.
[2] S. Gabriel, Chem. Berichte 42 (1909) 654.
[3] R.F. Homer, H. Gregory, L.F. Wiggins, J. Chem. Soc. (1948) 2191.
[4] A. Katrusiak, A. Katrusiak, J. Mol. Struct. 694 (2004) 85.
[5] A. Katrusiak, S. Bałoniak, Acta Pol. Pharmaceut. – Drug Res. 51 (1994) 403.
[6] MOPAC is a Semi-empirical Quantum-mechanical Method: Quantum Chemistry Program Exchange, No. 455, Indiana University, USA.; J.J.P. Stewart, J. Comput. Chem. 10 (1983) 209–221.
[7] I. Olovsson, J.-O. Lundgren, in: P. Schuster, G. Zundel, C. Sndorfy (Eds.), The Hydrogen Bond, vol. II, North Holland Publishing Company, Amsterdam, New-York, Oxford, 1976, pp. 471–526.
[8] A. Katrusiak, M. Szafrański, Chem. Phys. Lett. 340 (2001) 302.
[9] A. Katrusiak, Acta Crystallogr. B 47 (2002) 697.
[10] A. Katrusiak, J. Mol. Graph. Model. 19 (2001) 363.
[11] G.B. Kline, S.H. Cox, J. Org. Chem. 26 (1961) 1854.
[12] U.M. Teotino, G. Cignarella, Gazz. Chim. Ital. 89 (1959) 1200.
[13] A.G. Olsen, O. Dahl, P. Nielsen, Biorg. Med. Chem. Lett. 14 (2004) 1551.
[14] T. Nagakome, R.N. Castle, J. Heterocycl. Chem. 5 (1968) 379.
[15] AstraZeneca AB, NPS Pharmaceuticals INC Patent US 2007/259862 A1 (2007).
[16] M.B. Supurgibekov, L. Hennig, B. Schulze, V.A. Nikolaev, Russ. J. Org. Chem. 44 (2008) 1840.
[17] J.A. King, F.H. Mc Millan, J. Am. Chem. Soc. 74 (1952) 3222.
[18] (a) G.L. Biagi, A.M. Barbaro, M.F. Gamba, M.C. Guerra, J. Chromatogr. 41 (1969) 371;
(b) G.E. Granero, M.M. Bertorello, M.C. Briñón, J. Liq. Chromatogr. Rel. Technol. 22 (1999) 229.
[19] G.M. Sheldrick, Acta Crystallogr. A 64 (2008) 112.