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Ipso and *cine* Substitution of Bromine in Pyridazinones

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Nucleophilic *ipso* and *cine* substitution of bromine in pyridazine derivatives has been investigated in several solvents, such as dry DMF, anhydrous ethanol and dry THF. The structures of obtained isomerie products have been monitored by chemical methods, X-ray diffraction and ^{1}H NMR spectra.

Key words: *ipso* and *cine* substitution, morpholine derivatives, pyridazine, crystal structure

Pyridazine derivatives exhibit a broad range of biological activity, for example bacteriostatic [1,2] or cytostatic [3,4]. They are also inhibitors in enzymatic processes [5]. This variety of pharmaceutical properties stimulates further studies on new pyridazine derivatives with potential medicinal applications. Substitution of bromine in 4- and 5-bromo-1-methyl-3,6-pyridazinediones in reactions with arenethiols or arenethiolates formed *cine* [6,7], *ipso* [6,8,9,10], or a mixture of *cine* and *ipso* substituted products. As a continuation of the studies on the nucleophilic substitution of bromine in 5-bromo-1-methyl-2-phenyl-3,6-pyridazinedione (**1**) and 5-bromo-6-methoxy-2-phenyl-3-pyridazinone (**2**) [9], their reactions with morpholine in such solvents as dry dimethylformamide (DMF), dry tetrahydrofurane (THF) and anhydrous ethanol (EtOH) have been examined.

Compounds **1** or **2** refluxed with morpholine in DMF gave only *ipso* substitution products: 1-methyl-5-morpholino-2-phenyl-3,6-pyridazinedione (**3**) or 6-methoxy-5-morpholino-2-phenyl-3-pyridazinone (**5**), respectively. In the ^{1}H NMR spectrum of compound **3** the signals of the hydrogen atoms from N-methyl group appear at 3.20 ppm and the signal of the hydrogen at C(4) at 5.95 ppm. In the ^{1}H NMR spectrum of compound **5** the proton signals of the methoxy group are found at 3.91 ppm and the signal of the proton at C(4) appears at 6.16 ppm.

Treatment of compounds **1** and **2** with morpholine in THF gave *ipso* substitution products **3** or **5** as precipitate, respectively. In anhydrous EtOH compounds **1** and **2** with morpholine produced a mixture of *ipso* and *cine* substitution products. Compound **3** and 1-methyl-4-morpholino-2-phenyl-3,6-pyridazinedione (**4**) or compo-

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und **5** and 6-methoxy-4-morpholino-2-phenyl-3-pyridazinone (**6**) were found in filtrate, respectively.

The ratio of *cine* and *ipso* isomers in the crude residue obtained from reaction mixtures were measured by ^{1}H NMR spectra based on separated singlets of the proton at C(4) or C(5) of the 5-morpholine or 4-morpholine derivatives. In the ^{1}H NMR spectrum of compound **4** the proton signal of C(5) appears at 6.01 ppm. The signal of the hydrogen at C(4) in the ^{1}H NMR spectrum of compound **3** appears at 5.95 ppm. In the ^{1}H NMR spectra of compounds **5** and **6** the signals of the protons at C(4) and C(5) appear at 6.16 ppm and 6.10 ppm, respectively.

In the reaction of compound **1** or **2** with morpholine in anhydrous ethanol were found 75% of **3** or 92% of **5** *ipso* isomers and 25% of **4** or 8% of **6** *cine* isomers, respectively. Compounds **1** and **2** with morpholine in dry THF or DMF yielded almost 100% of *ipso* and traces of *cine* substitution products, which were detected by TLC.

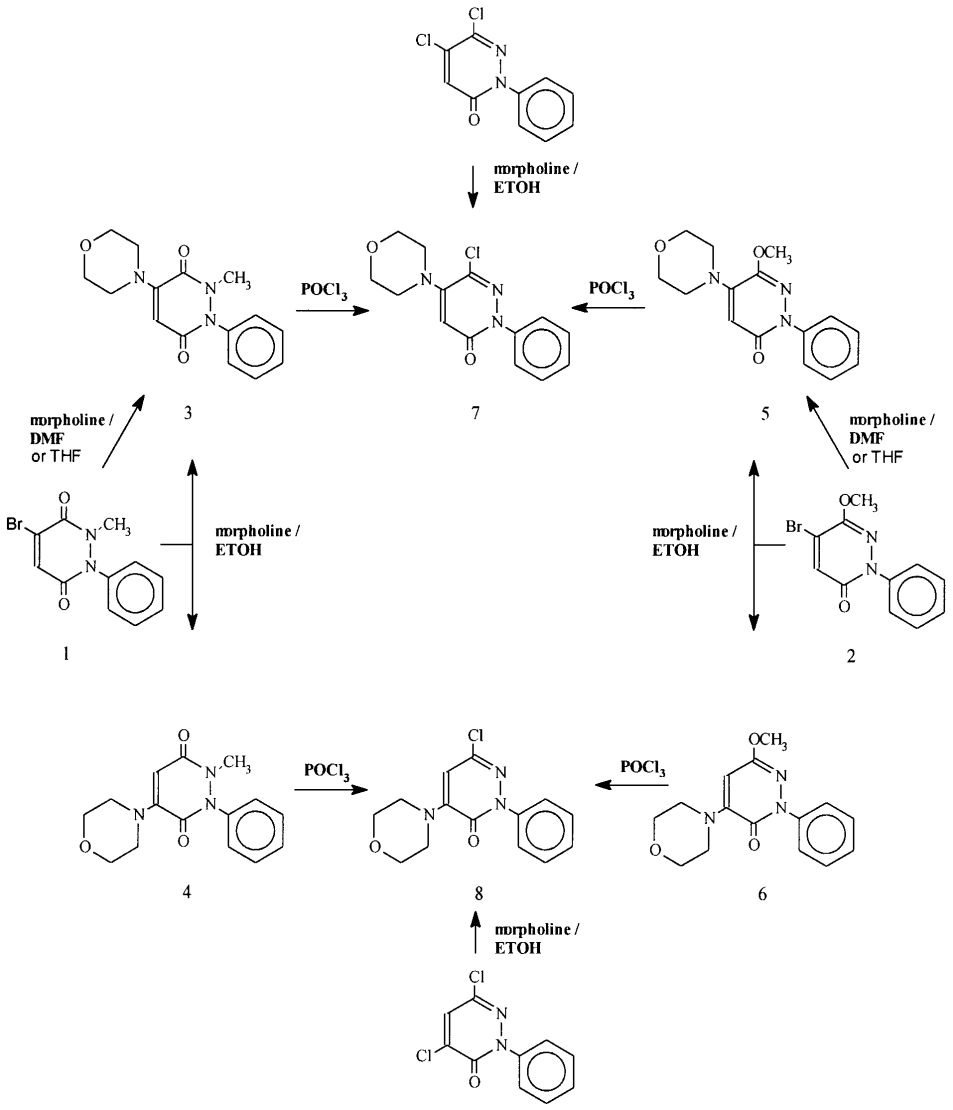
The isomers were isolated by a column chromatography. Their identity was confirmed by chemical transformations. Morpholine derivatives were refluxed with phosphorus oxychloride on a water bath. 6-Chloro-5-morpholino-2-phenyl-3-pyridazinone (**7**) was obtained from compounds **3** and **5**. Compounds **4** and **6** with $POCl_3$ have yielded 6-chloro-4-morpholino-2-phenyl-3-pyridazinone (**8**). The 4- and 5-morpholine derivatives of 6-chloro-3-pyridazinone (**7** and **8**) have been obtained also by treating 5,6- or 4,6-dichloro-2-phenyl-3-pyridazinone with morpholine (Scheme 1).

RESULTS AND DISCUSSION

The reactivity of 5-bromo-1-methyl-2-phenyl-3,6-pyridazinedione (**1**) and 5-bromo-6-methoxy-2-phenyl-3-pyridazinone (**2**) with morpholine has been investigated. These results have corroborated the mechanism of *ipso* and *cine* substitution suggested previously [10]. The different paths of substitution reactions observed in ethanol and aprotic solvents suggest that the good availability of protons is essential for the formation of *cine* substitution products. The aprotic medium (DMF, THF) promotes the *ipso*-substitution path. It is as a result of the nucleophilic attack on the carbon bonded to the bromine atom and then elimination of the bromine anion. In the protogenic medium (ethanol) both competitive *ipso* and *cine* substitutions are realized. Substitution *cine* is initiated by an addition of nucleophile to the carbon atom adjacent to the carbon with bromine, subsequent addition of the proton to the resulting anion and final elimination of hydrogen bromide.

X-Ray analyses confirmed the molecular structures of compounds **3**, **5**, **7** and **8**, and revealed their conformations and distortions induced in the pyridazine ring by substituents. The ring bonds are strongly conjugated, and *e.g.* formally single bonds C(5)–C(6) change their length by nearly 0.1 Å between compounds **3** and **8** (see Table 1). A characteristic feature of the pyridazine ring in **8** is angle N(2)–N(1)–C(6) – considerably smaller than 120° – somewhat less acute angles were observed in the non-solvate and inclusion compound crystals of 6-chloro-4-(N,N-dimethylamine-methylidenohydrazine)-2-phenyl-3-pyridazinone [11]. The valency angles at the N

Scheme 1



atoms vary by over 10° between different pyridazine derivatives and they are very sensitive to the N-substitution or protonation, as is clearly seen from the ring geometry in maleic hydrazide polymorphs [12,13]. It is apparent that these angles play a major role for accommodating strains in the ring and for the modification of its electronic structure. The molecular conformations of **3**, **5**, **7** and **8** can be characterized by the torsion angles of the pyridazine-phenyl and pyridazine-morpholine junctions, but also by small distortions from planarity of the pyridazine ring (Table 2). The largest distortions, exceeding 8°, are observed in the least-aromatic 3,6-pyri-

dazinedione ring of **3**. As expected, the phenyl rings are planar and the morpholine rings are in the chair conformation. The phenyl rings are inclined by over 50° to the pyridazine rings in **5**, **7** and **8**, and at slightly larger angle to the more distorted pyridazinedione ring in **3**. Similar inclinations are observed between the pyridazine and morpholine rings. The conformation of **5** is different than those of **3**, **7** and **8** in this respect that the phenylpyridazine and pyridazinemorpholine junction are twisted in the same direction (both clockwise or both anti-clockwise in the centre-of-symmetry related molecules in the centrosymmetric space group C2/c of **5** – see Table 3), whereas the sense of turns about the phenyl-pyridazine and pyridazine-morpholine junctions are opposite, one clockwise and the other anticlockwise (or *vice versa* for the centre-of-symmetry images), in molecules **3**, **7** and **8** (compare Figures 1, 2, 3 and 4). At the absence of H-donors no hydrogen bonds are formed in structures **3**, **5**, **7** and **8**.

Table 1. Selected bond lengths [Å] and angles [°] for **3**, **5**, **7** and **8**.

	3	**5**	**7**	**8**
N(1)–N(2)	1.407(3)	1.379(3)	1.373(12)	1.390(5)
N(2)–C(3)	1.381(3)	1.386(4)	1.385(13)	1.385(5)
C(3)–C(4)	1.424(4)	1.430(4)	1.45(2)	1.479(6)
C(4)–C(5)	1.351(3)	1.351(4)	1.341(13)	1.366(6)
C(5)–C(6)	1.485(3)	1.453(4)	1.430(13)	1.386(6)
N(1)–C(6)	1.350(3)	1.283(4)	1.362(12)	1.289(6)
N(1)–C(7)	1.467(3)	–	–	–
N(2)–C(1′)	1.433(3)	1.438(4)	1.384(12)	1.440(6)
N(3)–O(3)	1.228(3)	1.239(3)	1.25(2)	1.233(5)
C(4)–N(1″)	–	–	–	1.385(5)
C(6)–O(6)	1.232(3)	1.357(3)	–	–
O(6)–C(7)	–	1.445(3)	–	–
C(6)–Cl(6)	–	–	1.725(10)	1.746(4)
C(6)–N(1)–N(2)	123.7(2)	117.4(3)	118.5(8)	112.8(4)
C(3)–N(2)–(N1)	119.9(2)	123.9(3)	124.4(9)	127.3(4)
N(2)–C(3)–C(4)	117.2(2)	115.0(3)	114.3(12)	115.1(4)
C(5)–C(4)–C(3)	123.9(2)	123.4(3)	123.5(10)	116.9(5)
C(4)–C(5)–C(6)	117.8(2)	114.5(3)	117.5(9)	120.0(5)
N(1)–C(6)–C(5)	117.1(2)	125.5(3)	121.5(9)	127.9(5)
C(6)–N(1)–C(7)	118.4(2)	–	–	–
N(2)–N(1)–C(7)	115.6(2)	–	–	–
C(3)–N(2)–C(1′)	119.1(2)	122.5(3)	124.4(10)	119.9(4)
N(1)–N(2)–C(1′)	116.9(2)	113.3(3)	111.3(8)	112.8(4)
O(3)–C(3)–N(2)	119.1(2)	120.5(4)	118.8(11)	119.8(5)
O(3)–C(3)–C(4)	123.7(2)	124.5(3)	126.9(9)	125.1(5)
C(4)–C(5)–N(1″)	124.2(2)	124.8(3)	122.9(9)	–

Table 1 (continuation)	**3**	**5**	**7**	**8**
N(1″)–C(5)–C(6)	117.5(2)	120.4(3)	119.5(9)	–
O(6)–C(6)–N(1)	119.4(2)	119.8(3)	–	–
O(6)–C(6)–C(5)	123.4(2)	114.7(3)	–	–
O(6)–O(6)–C(7)	–	117.4(3)	–	–
N(1)–C(6)–Cl(6)	–	–	114.5(7)	114.4(4)
O(5)–C(6)–Cl(6)	–	–	123.9(8)	117.6(4)
N(1″)–C(4)–C(5)	–	–	–	125.1(5)
N(1″)–C(4)–C(3)	–	–	–	117.7(4)

Table 2. Selected torsion angles (°) for **3**, **5**, **7** and **8**.

	3	**5**	**7**	**8**
pyridazine ring				
N(1)–N(2)–C(3)–C(4)	–1.1(3)	–4.4(5)	2.1(16)	–2.9(7)
N(2)–C(3)–C(4)–C(5)	5.6(4)	0.1(6)	–5.8(16)	0.3(7)
C(3)–C(42)–C(5)–C(6)	–8.3(4)	3.0(5)	6.7(16)	1.5(7)
C(4)–C(5)–C(6)–N(1)	6.6(3)	–2.6(6)	–4.0(14)	–1.3(8)
C(5)–C(6)–N(1)–N(2)	–2.7(3)	–1.3(6)	0.6(13)	–0.9(8)
C(6)–N(1)–N(2)–C(3)	0.0(3)	5.0(5)	0.2(15)	3.1(7)
exocyclic torsions at pyridazine				
C(7)–N(1)–N(2)–C(3)	162.3(2)			
C(7)–N(1)–N(2)–C(1')	–40.5(3)	–	–	–
O(3)–C(3)–C(4)–C(5)	–172.4(2)	179.1(4)	172.6(12)	179.9(5)
C(7)–N(1)–C(6)–O(6)	12.1(3)	–	–	–
N(2)–N(1)–C(6)–O(6)	173.9(2)	–178.4(3)	–	–
C(7)–N(1)–C(6)–C(5)	–164.5(2)	–	–	–
C(4)–C(5)–C(6)–O(6)	–169.8(2)	174.7(3)	–	–
N(1)–N(2)–C(3)–O(3)	177.0(2)	176.6(4)	–176.4(10)	177.5(4)
N(1)–C(6)–O(6)–C(7)	–	–3.0(5)	–	–
C(5)–C(6)–O(6)–C(7)	–	179.5(3)	–	–
N(2)–N(1)–C(6)–Cl(6)	–	–	–175.9(7)	179.2(3)
C(4)–C(5)–C(6)–Cl(6)	–	–	172.1(7)	178.5(4)
N(1″)–C(5)–C(6)–Cl(6)	–	–	–5.0(12)	–
pyridazine-phenyl junction				
C(3)–N(2)–C(1′)–C(6′)	–69.5(3)	–52.1(5)	55.5(19)	–52.0(7)
N(1)–N(2)–C(1′)–C(6′)	133.1(2)	133.8(4)	–125.4(14)	127.4(5)
C(3)–N(2)–C(1′)–C(2′)	108.8(3)	126.3(4)	–116.4(12)	130.4(5)
N(1)–N(2)–C(1′)–C(2′)	–48.6(3)	–47.9(5)	62.7(13)	–50.3(6)
C(6)–N(1)–N(2)–C(1′)	157.2(2)	179.1(4)	–178.9(9)	–176.1(5)
C(1′)–N(2)–C(3)–O(3)	20.2(3)	3.0(6)	2.6(18)	–3.3(7)
C(1′)–N(2)–C(3)–C(4)	–157.8(2)	–177.9(4)	–178.9(10)	176.4(5)
N(2)–C(1′)–C(2′)–C(3′)	–178.3(2)	–179.4(3)	178.2(11)	177.3(5)
N(2)–C(1′)–C(6′)–C(5′)	177.0(2)	178.3(4)	–176.4(12)	–176.9(5)

Table 1 (continuation)	**3**	**5**	**7**	**8**
phenyl ring				
C(1′)–C(2′)–C(3′)–C(4′)	1.1(5)	1.4(6)	–4.5(20)	0.2(9)
C(2′)–C(3′)–C(4′')–C(5′)	–0.8(5)	–0.8(7)	1.8(21)	–0.5(9)
C(3′)–C(4′)–C(5′)–C(6′)	–0.5(5)	–0.2(7)	–0.5(22)	0.9(9)
C(4′)–C(5′)–C(6′)–C(1′)	1.5(5)	0.7(7)	1.8(24)	–1.0(9)
C(2′)–C(1′)–C(6′)–C(5′)	–1.2(4)	–0.1(6)	–4.1(21)	0.8(8)
C(6′)–C(1′)–C(2′)–C(3′)	–0.1(4)	–1.0(6)	5.4(18)	–0.4(8)
pirydazine-morpholine junction				
C(4)–C(5)–N(1′′)–C(6′′)	1.7(4)	–7.6(6)	–11.0(3)	–
C(6)–C(5)–N(1′′)–C(6′′)	–169.5(2)	166.9(3)	166.0(8)	–
C(4)–C(5)–N(1′′)–C(2′′)	–140.6(3)	127.0(4)	115.1(11)	–
C(6)–C(5)–N(1′′)–C(2′′)	48.2(3)	–58.5(5)	–67.9(11)	–
C(5)–C(4)–N(1′′)–C(2′′)	–	–	–9.9(8)	
C(3)–C(4)–N(1′′)–C(2′′)	–	–	–	163.3(5)
C(5)–C(4)–N(1′′)–C(6′′)	–	–	–	134.9(6)
C(3)–C(4)–N(1′′)–C(6′′)	–	–	–	–51.8(7)
C(5)–N(1′′)–C(2′′)–C(3′′)	–160.1(3)	169.9(3)	174.5(9)	–
C(5)–N(1′′)–C(6′′)–C(5′′)	158.8(3)	–169.4(4)	–176.7(8)	–
C(3)–C(4)–C(5)–N(1′′)	–179.5(2)	177.9(4)	–176.3(9)	–
N(1′′)–C(5)–C(6)–O(6)	2.0(3)	–0.4(5)	–	–
N(1′′)–C(5)–C(6)–N(1)	178.4(2)	–177.7(4)	178.9(8)	–
C(3)–C(3)–N(4)–N(1′′)	–	–	–	6.1(8)
N(2)–C(3)–C(4)–N(1′′)	–	–	–	173.5(4)
N(1′′)–C(4)–C(5)–C(6)	–	–	–	–174.8(5)
C(4)–N(1′′)–C(2′′)–C(3′′)	–	–	–	–157.7(5)
C(4)–N(1′′)–C(6′′)–C(5′′)	–	–	–	159.0(5)
morpholine ring				
C(6′′)–N(1′′)–C(2′′)–C(3′′)	54.9(4)	–53.0(4)	–55.9(10)	54.2(8)
N(1′′)–C(2′′)–C(3′′)–O(4′′)	–58.1(5)	55.9(5)	60.1(11)	–55.8(8)
C(2′′)–C(3′′)–O(4′′)–C(5′′)	59.1(5)	–57.0(5)	–59.3(11)	57.0(8)
C(3′′)–O(4′′)–C(5′′)–C(6′′)	–57.7(4)	57.6(5)	57.1(11)	–57.9(8)
C(2′′)–N(1′′)–C(6′′)–C(5′′)	–55.0(4)	52.7(5)	54.2(10)	–54.4(7)
O(4′′)–C(5′′)–C(6′′)–N(1′′)	56.5(4)	–56.5(5)	–56.1(11)	56.8(7)

Table 3. Crystal data and structure refinement for **3**, **5**, **7** and **8**.

Compound:	**3**	**5**	**7**	**8**
Empirical formula	$C_{15}H_{17}N_3O_3$	$C_{15}H_{17}N_3O_3$	$C_{14}H_{14}ClN_3O_2$	$C_{14}H_{14}ClN_3O_2$
Formula weight	287.32	287.32	291.73	291.73
Temperature (K)	297(2)	297(2)	297(2)	297(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic

Table 1 (continuation)		**3**	**5**	**7**	**8**
Space group		*C*2/c	*C*2/c	$P2_1$	$P2_1/c$
Unit cell dimensions:	*a* (Å)	26.381(5)	13.814(3)	4.2780(10)	6.1010(10)
	b (Å)	8.425(2)	13.632(3)	9.329(2)	23.121(5)
	c (Å)	12.699(3)	14.950(3)	17.053(3)	9.986(2)
	β (°)	90.62(3)	95.14(3)	93.50(3)	100.77(3)
Volume ($Å^3$)		2822.3(11)	2803(10)	679.3(2)	1383.8(5)
Z		8	8	2	4
Density (calculated) (g/cm^3)		1.352	1.361	1.426	1.400
$\mu(MoK_\alpha)$ (mm^{-1})		0.096	0.097	0.286	0.281
F(000)		1216	1216	304	608
Crystal size (mm)		0.32 × 0.22 × 0.15	0.45 × 0.25 × 0.10	0.25 × 0.15 × 0.02	0.28 × 0.12 × 0.04
θ range for data (°)		2.54–29.49	3.56–28.97	3.24–29.56	3.74–29.27
Ranges of indices h, k, l		–22/22, –8/11, –15/17	–18/10, –17/6, –17/14	–4/5, –12/12, –20/23	–8/7, –29/30, –5/13
Reflections collected		6413	2729	4531	5711
Independent reflections/R_{int}		2774/0.0353	1877/0.0809	3269/0.0766	3097/0.1097
Data/parameters		2774/258	1877/208	3269/196	3097/196
Goodness-of-fit on F^2		1.093	1.146	0.880	1.167
Final R/wR2 indices ($I > 2\sigma I$)		0.0590/0.1277	0.0636/0.0583	0.0771/0.1690	0.0908/0.0643
R/wR2 indices (all data)		0.1206/0.1532	0.1573/0.0741	0.1897/0.2097	0.1925/0.0844
Extinction coefficient		0	0.0032(2)	0.21(2)	0.0008(4)
Max/min ΔF ($eÅ^{-3}$)		0.166/0.247	0.109/–0.112	0.830/–0.371	0.223/–0.235

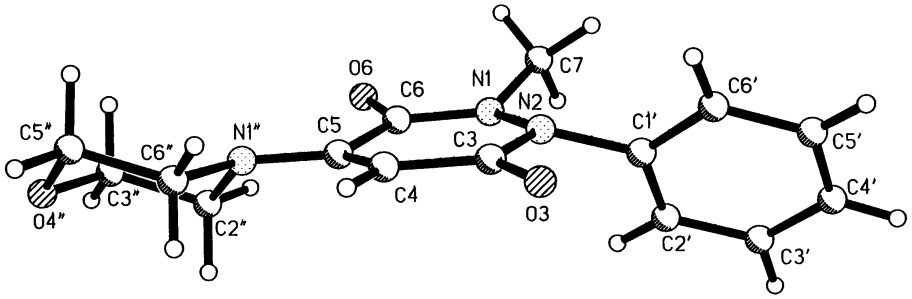


Figure 1. View of molecule **3**.

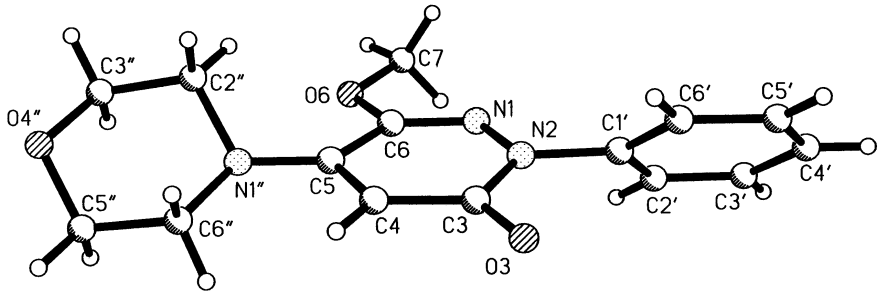


Figure 2. View of molecule **5**.

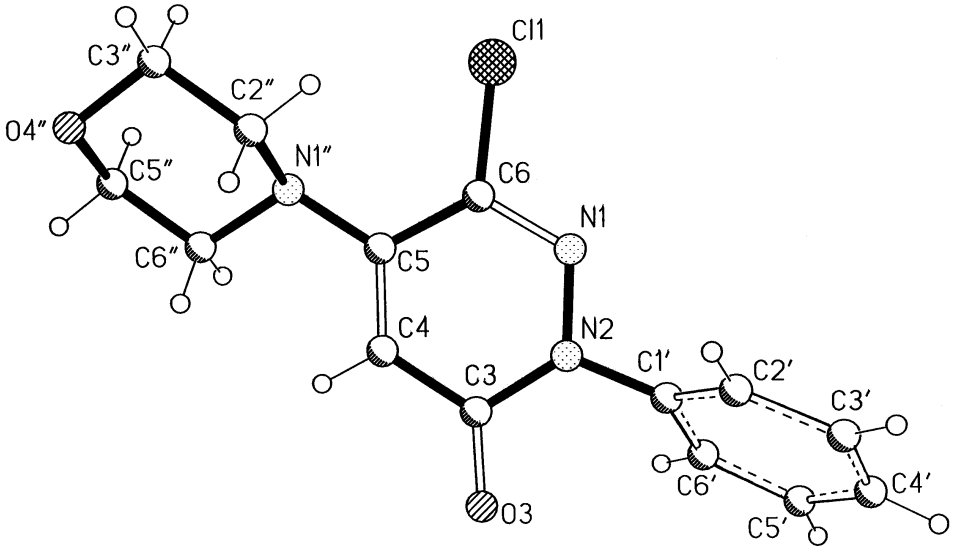


Figure 3. View of molecule **7**.

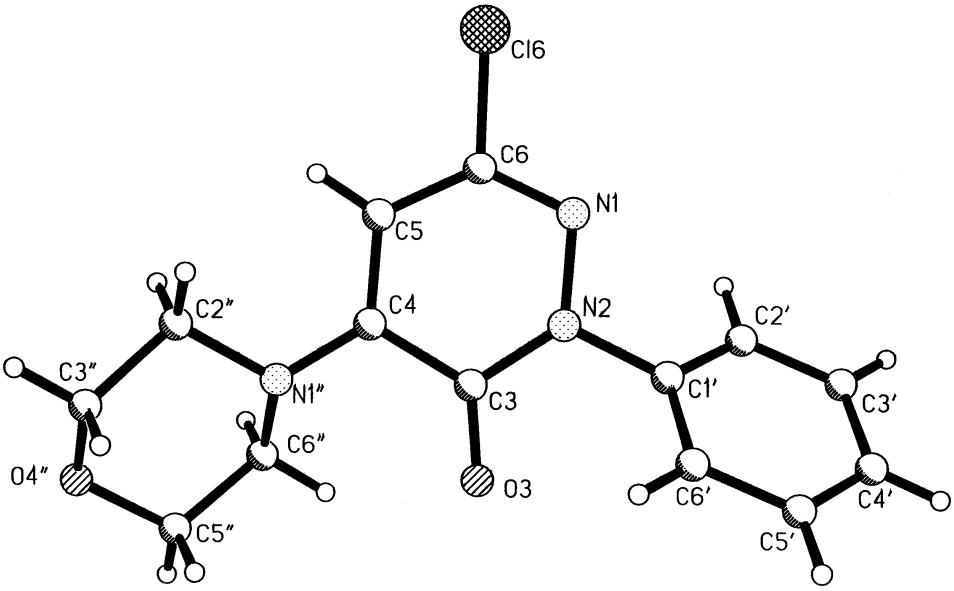


Figure 4. View of molecule **8**.

EXPERIMENTAL

Melting points have been determined on a Boetius apparatus and are uncorrected. DMF was dried by azeotropic distillation with benzene and stored over molecular sieves. Dry THF was stored over solid KOH. ^{1}H NMR spectra were recorded on a Varian spectrometer at 300 MHz in $CDCl_3$ with TMS as the internal standard. The reactions were monitored by TLC. The isomers were separated by a column chromatography on silica gel 230–400 mesh ASTM using chlorophorm:acetone mixture (30:1). The starting

products of 5-bromo-1-methyl-2-phenyl-3,6-pyridazinedione (**1**) and 5-bromo-6-methoxy-2-phenyl-3-pyridazinone (**2**) were obtained by methylation of 5-bromo-6-hydroxy-2-phenyl-3-pyridazinone with dimethyl sulfate [9]. 5,6-Dichloro-2-phenyl-3-pyridazinone was obtained from 5-bromo-6-hydroxy-2-phenyl-3-pyridazinone using $POCl_3/PCl_5$ [14], and analougsly 4,6-dichloro-2-phenyl-3-pyridazinone was obtained from 6-hydroxy-2-phenyl-3-pyridazinone [15].

1-Methyl-5-morpholino-2-phenyl-3,6-pyridazinedione (3): a) 1.0 g (0.003 mol) of 5-bromo-1-methyl-2-phenyl-3,6-pyridazinedione (**1**) was refluxed for 2 h with threefold excess of morpholine (0.90 cm^3, 0.010 mol) in dry DMF. After cooling the reaction mixture was poured into water and extracted with chloroform. The extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue was crystallized from ethanol. Yield 0.74 g (74%), m.p. 178–9°C. Analysis: For $C_{15}H_{17}N_3O_3$ (287.32) – Calcd.: 14.63% N, 62.70% C, 5.98 % H; found 14.57% N, 62.72% C, 6.00% H. IR (KBr, cm^{-1}), ν_{max}: 1620 (CO); ^{1}H NMR: 3.20 (3H, CH_3, s), 3.43–3.88 (8H, morpholine, m), 5.95 (1H, C-4, s), 7.33–7.54 (5H, phenyl, m). b) 1.0 g (0.003 mol) of comp. **1** with treefold excess of morpholine (0.90 cm^3, 0.010 mol) was refluxed for 2 h in dry THF. The reaction mixture was cooled. The precipitate was solvable in water and identified as morpholine hydrobromine, m.p. > 360°C. Analysis: For C_4H_9NOBr (167.03) – Calcd.: 8.39% N, 28.76 % C, 5.44H; found 8.40% N, 28.20% C, 5.50% H. ^{1}H NMR: 3.11–3.81 (8H, morpholine, m). The filtrate was evaporated, and the residue identified as compound **3**. Yield 0.52 g (52%).

Analogously was obtained:

6-Methoxy-5-morpholino-2-phenyl-3-pyridazinone (5): a) from 1.0 g (0.003 mol) of 5-bromo-6-methoxy-2-phenyl-3-pyridazinone (**2**). Yield 0.68 g (68%), m.p. 142–4°C. Analysis: For $C_{15}H_{17}N_3O_3$ (287.32) – Calcd.: 14.63% N, 62.70% C, 5.98% H; found 14.60% N, 62.65% C, 6.04% H. IR (KBr, cm^{-1}), ν_{max}: 1620 (CO); ^{1}H NMR: 3.91 (3H, CH_3, s), 3.17–3.87 (8H, morpholine, m), 6.16 (1H, C-4, s), 7.32–7.70 (5H, phenyl, m). b) from 1.0 g (0.003 mol) of comp. **2**. Yield 0.35 g (35%).

1-Methyl-5-morpholino-2-phenyl-3,6-pyridazinedione (3) and 1-Methyl-4-morpholino-2-phenyl-3,6-pyridazinedione (4): 1.0 g (0.003 mol) of comp. **1** with threefold excess of morpholine (0.90 cm^3, 0.010 mol) was refluxed for 2 h in anhydrous ethanol. The reaction mixture was cooled. The precipitate was crystallized from ethanol and identified as comp. **3**. Yield 0.41 g (41%).

The filtrate was evaporated. The residue was isolated by a column chromatography. The fractions were collected, evaporated and identified as compounds **3** and **4**. Identification of comp. **4**: m.p. 122–4°C. Yield 0.25 g (25%). Analysis: For $C_{15}H_{17}N_3O_3$ (287.32) – Calcd.: 14.63% N, 62.70% C, 5.98% H; found 14.67% N, 62.62% C, 6.01% H. IR (KBr, cm^{-1}), ν_{max}: 1620 (CO); ^{1}H NMR: 3.20 (3H, CH_3, s), 3.43–3.88 (8H, morpholine, m), 6.01 (1H, C-5, s), 7.33–7.54 (5H, phenyl, m).

Analogously was obtained:

6-Methoxy-5-morpholino-2-phenyl-3-pyridazinone (5) and 6-methoxy-4-morpholino-2-phenyl--3-pyridazinone (6): From 1.0 g (0.003 mol) of comp. **2** in anhydrous ethanol. Yield of comp. **5**: 0.83 g (83%). Identification of comp. **6**: m.p. 135–7°C. Yield 0.10 g (10%). Analysis: For $C_{15}H_{17}N_3O_3$ (287.32) – Calcd.: 14.63% N, 62.70% C, 5.98% H; found 14.59% N, 62.68% C, 5.96% H. IR (KBr, cm^{-1}), ν_{max}: 1620 (CO); ^{1}H NMR: 3.91 (3H, CH_3, s), 3.17–3.87 (8H, morpholine, m), 6.10 (1H, C-5, s), 7.32–7.70 (5H, phenyl, m).

6-Chloro-5-morpholino-2-phenyl-3-pyridazinone (7): a) 1.0 g (0.003 mol) of comp. **3** or comp. **5** with 10.0 cm^3 (0.06 mol) in phosphorus oxychloride was refluxed for 1 h on the water bath. The reaction mixture was poured into water with ice and extracted with chloroform. The extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue was crystallized from ethanol. Yield 0.34 g (34%) or 0.31 g (31%) respectively, m.p. 173–6°C. Analysis: For $C_{14}H_{14}ClN_3O_2$ (291.74) – Calcd.: 14.40% N, 57.63% C, 4.84% H; found 14.47% N, 57.72 % C, 4.62% H. IR (KBr, cm^{-1}), ν_{max}: 1670 (CO); ^{1}H NMR: 3.20–3.91 (8H, morpholine, m), 6.33 (1H, C-4, s), 7.36–7.60 (5H, phenyl, m). b) 1.0 g (0.003 mol) of 5,6-dichloro-2-phenyl-3-pyridazinone with threefold excess of morpholine (0.90 cm_3, 0.010 mol) was refluxed for 2 h in anhydrous ethanol. The reaction mixture was cooled. The precipitate was crystallized from ethanol. Yield 0.86 g (86 %).

Analogously was obtained:

6-Chloro-4-morpholino-2-phenyl-3-pyridazinone (8): a) from 1.0 g (0.003 mol) of comp. **4** or comp. **6**. Yield 0.28 g (28%) or 0.26 g (26%) respectively, m.p. 108–10°C. Analysis: For $C_{14}H_{14}ClN_3O_2$ (291.74) – Calcd.: 14.40% N, 57.63% C, 4.84% H; found 14.35% N, 57.65% C, 4.63% H. IR (KBr, cm^{-1}), ν_{max}:

1660 (CO); ^{1}H NMR: 3.19–3.99 (8H, morpholine, m), 6.31 (1H, C-5, s), 7.35–7.61 (5H, phenyl, m). b) from 1.0 g (0.003 mol) of 4,6-dichloro-2-phenyl-3-pyridazinone. Yield 0.92 g (92%).

X-Ray diffraction analysis: Crystals **3**, **5**, **7** and **8** were obtained by slow evaporation from saturated ethanol solutions. Crystals **3**, **7** and **8** were plates; crystals **5** formed both plates and needles with well developed faces – several crystals of these two forms were investigated by X-ray diffraction and the same structure was found despite the diffrent crystal habits. The X-ray diffraction studies were carried out on a Kuma KM-4-CCD diffractometer, equipped with a graphite monochromator. The structures were straightforwordly solved by direct methods and refined with SHELXL-93 [16]. All H-atoms were located from molecular geometry, and then included in the refinements. Crystals **7** were twinned, hence lower accuracy of the final results. The experimental details are listed in Table 3, and the final atomic coordinates in Table 4. The structural data have been deposited with the Cambridge Crystallographic Database Center as supplementary publications No. CCDC152562, CCDC152563, CCDC152564 and CCDC153714, respectively.

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic temperature factors (Å$^2 \times 10^3$) for **3**, **5**, **7** and **8**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

3	x	y	z	U_{eq}
N(1)	2577(1)	1269(2)	3560(1)	37(1)
N(2)	2922(1)	781(2)	4349(1)	39(1)
C(3)	2757(1)	–149(3)	–5172(2)	41(1)
O(3)	3066(1)	–620(2)	5830(1)	59(1)
C(4)	2232(1)	–546(3)	5185(2)	42(1)
C(5)	1901(1)	–178(3)	4403(2)	36(1)
C(6)	2081(1)	881(3)	3550(2)	39(1)
O(6)	1797(1)	1469(2)	2879(1)	56(1)
C(7)	2742(1)	2610(3)	2911(2)	46(1)
C(1′)	3447(1)	752(3)	4077(2)	38(1)
C(2′)	3603(1)	37(3)	3164(2)	48(1)
C(3′)	4111(1)	–12(4)	2933(3)	63(1)
C(4′)	4458(1)	626(4)	3621(3)	67(1)
C(5′)	4302(1)	1332(4)	4533(3)	65(1)
C(6′)	3794(1)	1416(3)	4760(2)	52(1)
N(1″)	1397(1)	–546(3)	4414(2)	46(1)
C(2″)	1130(1)	–1081(5)	3460(3)	62(1)
C(3″)	572(1)	–838(6)	3601(4)	85(1)
C(4″)	383(1)	–1650(3)	4483(3)	93(1)
C(5″)	638(1)	–1122(5)	5405(3)	76(1)
C(6″)	1197(1)	–1350(5)	5339(3)	61(1)
5	x	y	z	U_{eq}
N(1)	4296(2)	–188(2)	6249(2)	41(1)
N(2)	3691(2)	–992(2)	6267(2)	39(1)
C(3)	4018(3)	–1952(2)	6337(3)	45(1)
O(3)	3436(2)	–2636(2)	6392(2)	57(1)
O(4)	5045(3)	–2071(2)	6325(3)	42(1)
C(5)	5664(3)	–1314(2)	6253(3)	35(1)

Table 4 (continuation)

C(6)	5209(3)	–352(2)	6235(3)	35(1)
O(6)	5838(2)	414(2)	6239(2)	46(1)
C(7)	5430(3)	1390(2)	6214(4)	54(1)
C(1′)	2685(3)	–734(2)	6297(3)	40(1)
C(2′)	2442(3)	–46(2)	6902(3)	45(1)
C(3′)	1482(3)	203(3)	6947(3)	55(2)
C(4′)	766(3)	–255(3)	6399(4)	68(2)
C(5′)	1003(3)	–949(3)	5800(4)	66(2)
C(6′)	1975(3)	–1191(3)	5743(3)	58(1)
N(1″)	6655(2)	–1400(2)	6267(2)	38(1)
C(2″)	7127(3)	–966(3)	5538(3)	44(1)
C(3″)	8215(3)	–964(3)	5730(3)	56(1)
O(4″)	8597(2)	–1912(2)	5919(2)	60(1)
C(5″)	8185(3)	–2312(3)	6645(4)	58(2)
C(6″)	7060(3)	–2370(2)	6484(3)	48(1)
7	x	y	z	U_{eq}
N(1)	–2716(23)	6766(11)	6850(5)	72(3)
N(2)	–4310(23)	7916(8)	7133(5)	56(2)
C(3)	–5172(35)	8043(15)	7900(5)	79(4)
O(3)	–6763(19)	9106(9)	8082(4)	79(3)
C(4)	–4150(24)	6869(11)	8407(6)	51(3)
C(5)	–2739(23)	5689(11)	8152(6)	49(3)
C(6)	–1923(20)	5669(10)	7351(5)	44(3)
Cl(6)	297(5)	4341(2)	6953(1)	45(1)
C(1′)	–4984(28)	8919(10)	6549(6)	51(3)
C(2′)	–6910(26)	8559(14)	5895(6)	68(3)
C(3′)	–7782(31)	9529(19)	5285(6)	83(4)
C(4′)	–6890(31)	10887(16)	5357(9)	83(4)
C(5′)	–5057(34)	11330(16)	6013(7)	88(4)
C(6′)	–4234(41)	10301(13)	6585(10)	93(5)
N(1″)	–1915(16)	4514(9)	8646(4)	45(2)
C(2″)	–3657(30)	3143(12)	8430(6)	60(3)
C(3″)	–2367(26)	1947(13)	8943(6)	60(3)
O(4″)	–2745(16)	2269(7)	9763(4)	63(2)
C(5″)	–1131(22)	3576(11)	9968(6)	50(3)
C(6″)	–2165(24)	4778(10)	9487(5)	52(3)
8	x	y	z	U_{eq}
N(1)	1410(7)	8085(2)	4890(4)	37(1)
N(2)	–236(7)	8101(2)	5682(4)	34(1)
C(3)	–1408(8)	7637(2)	6072(5)	33(1)

Table 4 (continuation)

O(3)	–2775(5)	7717(1)	6821(3)	49(1)
C(4)	–887(9)	7070(2)	5522(5)	30(1)
C(5)	678(9)	7064(3)	4706(5)	41(2)
C(6)	1732(8)	7573(3)	4456(4)	39(2)
Cl(6)	3762(2)	7533(1)	3438(1)	52(1)
N(1″)	–2143(7)	6608(2)	5756(4)	41(1)
C(2″)	–2068(13)	6098(3)	4922(6)	61(2)
C(3″)	–4129(14)	5745(3)	4917(7)	65(2)
O(4″)	–4449(7)	5592(2)	6234(4)	65(1)
C(5″)	–4523(12)	6098(3)	7005(6)	59(2)
C(6″)	–2481(11)	6463(3)	7122(6)	46(2)
C(1′)	–702(10)	8678(2)	6091(5)	31(2)
C(2′)	1039(11)	9025(3)	6676(5)	50(2)
C(3′)	667(13)	9521(3)	7032(6)	62(2)
C(4′)	–1480(13)	9800(3)	6793(7)	64(2)
C(5′)	–3231(12)	9451(3)	6200(6)	55(2)
C(6′)	–2859(11)	8884(3)	5853(5)	40(2)

REFERENCES

1. Bałoniak S. and Mroczkiewicz A., *Ann. Pharm*., **12**, 53 (1975).
2. Sayed G.H., Ismail A.A., El-Nagdy S. and Mohamed S.M., *Egypt. J. Chem*., **29**, 433 (1986).
3. Hładoń B., Szafarek P., Bałoniak S. and Mroczkiewicz A., *Pol. J. Pharm*., **33**, 145 (1981).
4. Biagi G., Dell Ommadorme G., Giorgi I., Livi O. and Scartoni V., *Farmaco*, **47**, 91 (1992).
5. Hasimoto F., Sugimoto C. and Hayashi H., *Chem. Pharm. Bull. Tokyo*, **40**, 795 (1992).
6. Druey J., Meier K. and Staechelin A., *Pharm. Acta Helv.*, **38**, 498 (1963).
7. Stam C., Zwinselman J., van der Plas H.C. and Bałoniak S., *J. Het. Chem*., **16**, 855 (1979).
8. Bałoniak S. and van der Plas H.C., *J. Het. Chem*., **18**, 1109 (1981).
9. Bałoniak S. and Ostrowicz A., *Polish J. Chem*., **64**, 741 (1990).
10. Bałoniak S. and Ostrowicz A., *Polish J. Chem*., **66**, 935 (1992).
11. Katrusiak A. and Katrusiak A., *J. Mol. Struct*., **374**, 251 (1996).
12. Katrusiak A., *Acta Cryst. C*, **49**, 36 (1993).
13. Katrusiak A., *Acta Cryst. B*, **57**, 697 (2001).
14. Meier K., Ringier B.H. and Druey J., *Helv. Chim. Acta*, **37**, 523 (1954).
15. Druey J., Meier K. and Staechelin A., *Helv. Chim. Acta*, **45**, 1485 (1962).
16. Sheldrick G. SHELXL-93. Program for crystal structure determination. University of Göttingen, 1993.