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Reactivity of 6-Chloro-4- and 5-Hydrazino-2-phenyl-3(2*H*)-pyridazinones with Vilsmeier Reagent

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Abstract: Reactions of 6-chloro-4- and 5-hydrazino-2-phenyl-3(2*H*)-pyridazinones (**1–3**) with dimethylformamide/phosphorus oxychloride afforded the pyrazolo[3,4-*d*]pyridazinones (**4–6**). Concurrently the formation of acyclic 6-chloro-4- and 5-(*N*,*N*-dimethylaminomethylidenehydrazino)-2-phenyl-3(2*H*)-pyridazinones (**7–9**) has been observed. A mechanism of these reactions is proposed. Compound **8** is shown to form unsolvated and inclusion compounds, both characterized by X-ray diffraction.

Introduction

Pyridazine is a valuable system for obtaining various pharmaceutically and biologically active compounds, and biological activity of pyrazolopyridazinones has already been demonstrated: a recently synthesized pyrazole substituted pyridazinone derivative *in vitro* was shown to have bacteriostatic activity both on *Gram*(+) and *Gram*(−) bacteria [1]. The synthesis of pyrazolo[3,4-*d*]pyridazines either start from pyrazole or from the pyridazine [2]. The synthesis starting from pyrazole is well described in literature, and the usual method of synthesising pyrazolopyridazinones is based on 1,3-dipolar cycloaddition of diazoalkanes to pyridazinone or pyridazine systems [3, 4, 5, 6, 7]. Considerably fewer methods based on intramolecular cyclization through the Vilsmeier–Haack reaction are described and they are rarely used [8]. For example Kaji *et al.* [8] showed that the fusion of pyrazole ring to the pyridazine system with Vilsmeier reagent is possible. The Vilsmeier–Haack reaction is an efficient method for introducing one carbon unit into aromatic [9] or heteroaromatic rings [10], which was demonstrated by convenient syntheses of pyrazolo[3,4-*d*]pyridazines from 5-(1-methylhydrazino)-3(2*H*)-pyridazinones [8]. The structure of the pyrazolo[3,4-*d*]pyridazines was confirmed by comparison with an authentic specimen prepared from substituted 2-alkylidenehydrazino-3(2*H*)-pyridazinones by photochemical cyclization earlier described by Kaji *et al.* [11]. The Vilsmeier–Haack reaction of acetylhydrazinopyridazine derivatives under

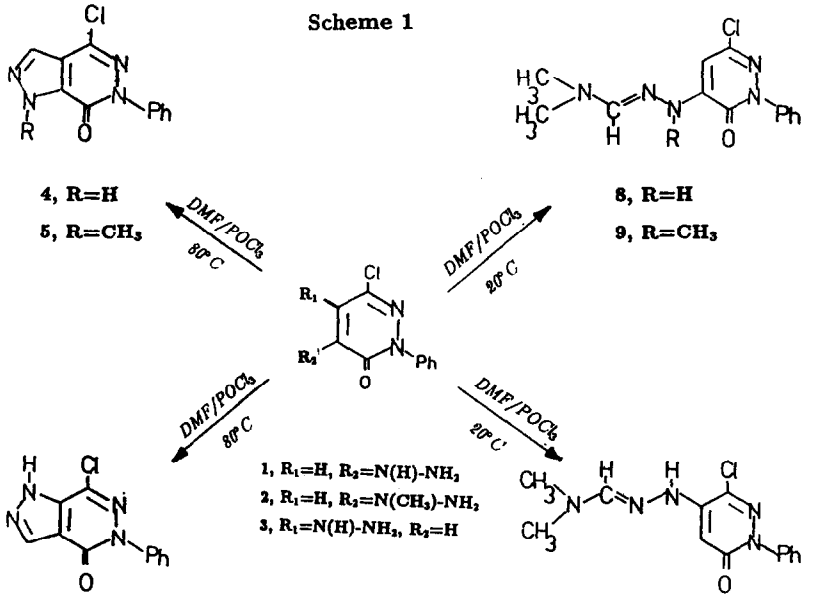
similar reaction conditions also afforded the novel concurrent formations: vinyl derivatives of pyrazolo-[3,4-*d*]pyridazine, obtained in good yields [11].

This paper describes the reactivity of 6-chloro-4-hydrazino-2-phenyl-3(2*H*)-pyridazinone (**1**), 6-chloro-4-(1-methylhydrazino)-2-phenyl-3(2*H*)-pyridazinone (**2**), and 6-chloro-5-hydrazino-2-phenyl-3(2*H*)-pyridazinone (**3**), with Vilsmeier reagent prepared instantaneously from dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$).

Results and discussion

A solution of compounds **1** or **2** was heated with phosphorus oxychloride ($POCl_3$) in an excess of dimethylformamide (DMF) at 80°C for 3h, followed by treatment with water, to afford 4-chloro-6-phenyl-1,7*H*-pyrazolo[3,4-*d*]-pyridazin-7-one (**4**) or 4-chloro-1-methyl-6-phenyl-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (**5**) (in 44% and 35% yields, respectively) [12]. The reaction of compound **3** with DMF/$POCl_3$ under similar reaction conditions afforded the 7-chloro-5-phenyl-1,4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (**6**) in 78% yield (Scheme 1).

Scheme 1



The reactions of compounds **1–3** with DMF/$POCl_3$ were also carried out at room temperature and revealed differences in reactivity of the substrates. Thus, the reaction of compound **3** with DMF/$POCl_3$ at 20°C gave 6-chloro-5-(*N*,*N*-dimethylaminomethylidenehydrazino)-2-phenyl-3(2*H*)-pyridazinone (**7**) (minor product, 26% yield), as well as the cyclized compound **6** (major product, 68% yield), while the reactions of compounds **1** and **2** gave only the acyclic derivatives **8**, **9** (62% yield in each case) and

the pyrazolopyridazinone derivatives were not formed (Scheme 1). Compounds **7** and **8** have been separated from the reaction mixtures as hydrochlorides **7a** and **8a**, but compound **9** did not yield a solid hydrochloride under the same conditions.

The molecular structure of compound **8** has been confirmed by X-ray diffraction study, carried out to determine the conformation of the molecule and its intermolecular interactions. Two crystalline forms of **8** have been identified: an unsolvated form and an inclusion compound with water. In the two crystals the molecules have nearly identical conformation, and form nearly identical hydrogen bonds linking the molecules into dimers, as shown Figure 1 [13].

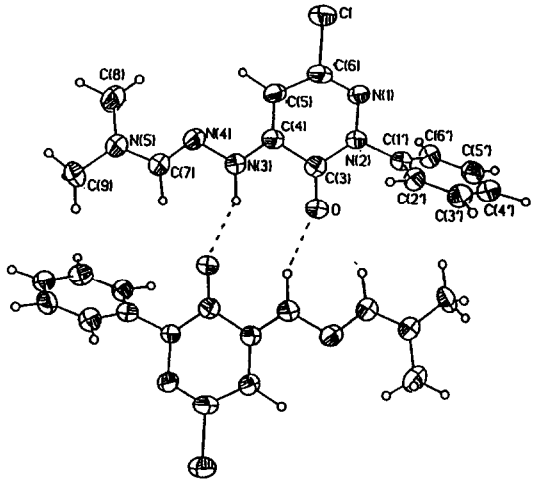
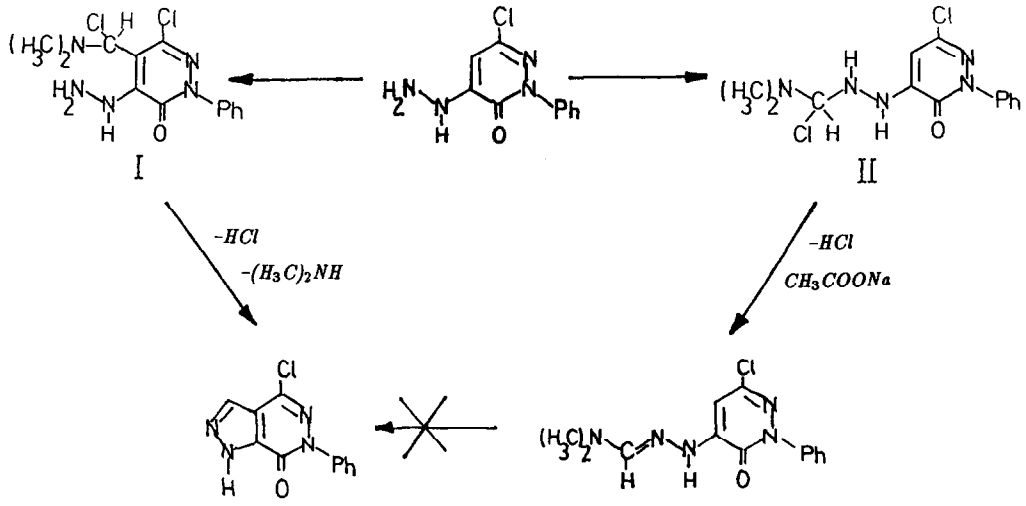


Figure 1. Two molecules of **8** hydrogen–bonded into a dimer viewed perpendicular to its average plane. The hydrogen bonds are indicated by dashed-lines. The thermal ellipsoids are drawn at 50% probability level [14], the hydrogen atoms are shown as small circles of arbitrary size.

The mechanism of cyclization of the pyrazole to the 3-pyridazinone ring (**1–3** → **4–6**) consists in electrophilic substitution of the mesomeric carbo–cation $[(CH_3)_2N–CHCl]^+$ formed from $DMF/POCl_3$. It has been postulated that an intermediate compound **I** is formed in these reactions, and the hydrogen chloride and dimethylamine are eliminated from **I** to afford the pyrazolopyridazinone (Scheme 2). In this reaction cyclization competes with the formation of acyclic compounds **7–9**. The mechanism of formation of the latter consists in an attack of mesomeric carbo–cation at the hydrazine nitrogen atom. Intermediate **II** is formed, and β–elimination of the hydrogen chloride from **II** yields acyclic compounds **7–9** (Scheme 2). To support the hypothesis of two competing reactions it was attempted to carry out a cyclization of compounds **7–9**, **7a** and **8a** to the pyrazolopyridazine by heating in DMF. The solutions of the isolated acyclic compounds **7**, **8**, **9**, **7a** and **8a** were heated with $DMF/POCl_3$ at 80°C. When no cyclic products were found by thin-layer chromatography the mixture was heated again to 140°C, but no transformation to cyclic compounds could be detected. A similar procedure of heating to 80°C and 140°C

of the unisolated reaction mixtures obtained from reactions of compounds **1–3** with Vilsmeier reagent at room temperature did not lead to pyrazolopyridazine derivatives. It implies that the acyclic compounds (**7–9**) are not intermediates in the formation of the fused derivatives. The proposed reaction pathways are shown in Scheme 2.

Scheme 2



A significant difference in susceptibility between attack of the electrophilic agent on C(4) and C(5) has been observed. To explain this difference we carried out quantum-chemistry calculations of electric-charge distribution in compounds **1** and **3** using a MNDO program [15] (Figure 2). The calculations have been based on crystallographically determined molecular dimensions [16] and have shown that the negative charge at C(5) in compound **1**, of -0.298e, is somewhat smaller in value then that of -0.332e at C(4) in compound **3**. It is plausible that this difference may contribute to the greater susceptibility of atom C(4) to attack of mesomeric carbo-cation.

1 **3**

Figure 2. Net atomic charges at C(4) in compound **1** and at C(5) in compound **3**.

Conclusion

The mechanism of fusing one pyrazole ring to the pyridazinone system has been discussed. Treatment of hydrazino-3(2*H*)-pyridazinone **1–3** with the Vilsmeier reagent gave the corresponding pyrazolopyridazinones **4–6**. The observed cyclization of the pyrazole ring of 5-hydrazino-3(2*H*)-pyridazinone (**3**) at room temperature confirms the greater susceptibility of atom C(4) to attack of mesomeric carbo-cation $[(CH_3)_2N\text{-}CHCl]^+$. It has been postulated that the cyclization reaction competes with the formation of acyclic compounds **7–9**. It has been shown that the acyclic compounds **7–9, 7a** and **8a** are not intermediates in the formation of the fused derivatives. The proposed mechanism of the reactions explains why the formation of pyrazolopyridazinones from acyclic compounds is difficult to achieve.

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. IR spectra in KBr pellets were measured with an IR–71 spectrometer. ^1H NMR spectra were recorded on a Jeol MH–100 spectrometer at 100 MHz in $CDCl_3$ or DMSO, with TMS as an internal standard. **6-Chloro-4-hydrazino-2-phenyl-3(2*H*)-pyridazinone (1)** and **6-chloro-4-(1-methylhydrazino)-2-phenyl-3(2*H*)-pyridazinone (2)** were obtained from 5,6-dichloro-2-phenyl-3(2*H*)-pyridazinone using hydrazine hydrate or methylhydrazine, respectively [12]. **6-Chloro-5-hydrazino-2-phenyl-3(2*H*)-pyridazinone (3)** was prepared from hydrazine and 5,6-dichloro-2-phenyl-3(2*H*)-pyridazinone, but reaction of the latter with methylhydrazine failed [17].

4-Chloro-6-phenyl-1,7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (4)

A solution of 2.37 g (0.01 mol) of compound **1** in dry DMF (10 ml) was added in portions to the Vilsmeier reagent (prepared from 0.77 g of phosphorus oxychloride and 2.0 ml of dry DMF), and the whole was heated at 80°C for 3 h. 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 recrystallized from ethanol. Yield 44%, m.p. 284°C. IR (cm^{-1}): 3280 (NH), 1600 (CO), ^1H NMR ($CDCl_3$) δ: 5.37 (1H, NH, s)*, 6.45 (1H, C(3), s), 7.36-7.52 (5H, Ph, m). *Anal.* Calcd. for $C_{11}H_7ClN_4O$ (246.66): C, 53.56; H, 2.87; N, 22.72; Cl, 14.37. Found: C, 53.63, H, 2.50; N, 22.06; Cl, 14.41%.

Similarly were obtained:

4-Chloro-1-methyl-6-phenyl-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (5)

from 2.51 g (0.01 mol) of compound **2**. Yield 35%, m.p. 152°C. IR (cm^{-1}): 1610 (CO), ^1H NMR ($CDCl_3$) δ: 4.41 (3H, CH_3, s), 7.93 (1H, C(3), s), 7.42-7.58 (5H, Ph, m). *Anal.* Calcd. for $C_{12}H_9ClN_4O$ (260.69): C, 55.28; H, 3.49; N, 21.49; Cl, 13.59. Found: C, 55.32, H, 3.47; N, 21.01; Cl, 13.31%.

7-Chloro-5-phenyl-1,4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (6)

from 2.37 g (0.01 mol) of compound **3**. Yield 78%, m.p. 110°C. IR (cm^{-1}): 3210 (NH), 1650 (CO), ^1H NMR ($CDCl_3$) δ: 5.56 (1H, NH, s)*, 7.96 (1H, C(3), s), 7.41-7.54 (5H, Ph, m). *Anal.* Calcd. for $C_{11}H_7ClN_4O$ (246.66): C, 53.56; H, 2.87; N, 22.72; Cl, 14.37. Found: C, 53.32, H, 2.47; N, 22.01; Cl, 14.31%.

7-Chloro-5-phenyl-1,4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (6), 6-chloro-5-(*N,N*-dimethylaminomethylidenehydrazino)-2-phenyl-3(2*H*)-pyridazinone hydrochloride (7a,) and **6-chloro-5-(*N,N*-dimethylaminomethylidenehydrazino)-2-phenyl-3(2*H*)-pyridazinone (7)**

A solution of 2.37 g (0.01 mol) of compound **3** in dry DMF (10 ml) was added in portions to the Vilsmeier reagent, and the whole stirred at room temperature for 4 h. The separated product was collected and identified as **6**. Yield 68%. The fitrate was poured into water and extracted with chloroform. The extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue of compound **7a** was recrystallized from ethanol. Yield 29%, m.p. 225°C. IR (cm^{-1}): 1620 (CO), ^1H NMR (DMSO) δ: 3.19 (3H, CH_3, s), 3.99 (broad, NH), 6.34 (1H, C(4), s), 8.45 (1H, CH=N, s), 7.41-7.51 (5H, Ph, m). *Anal.* Calcd. for $C_{13}H_{15}Cl_2N_5O$ (328.22): C, 47.57; H, 4.62; N, 21.34; Cl, 21.60. Found: C, 47.48; H, 4.39; N, 21.02; Cl, 21.02%.

The hydrochloride salt **7a** was dissolved in water and alkalized with sodium acetate. The separated product was collected and identified as **7** after recrystallization from ethanol. Yield 26%, m.p. 216°C. IR (cm^{-1}): 1610 (CO), ^1H NMR ($CDCl_3$) δ: 1.62 (1H, NH, s), 2.94 (3H, CH_3, s), 6.32 (1H, C(4), s), 8.45 (1H, CH=N, s), 7.43-7.59 (5H, Ph, m). *Anal.* Calcd. for $C_{13}H_{14}ClN_5O$ (291.76): C, 53.51; H, 4.85; N, 24.01; Cl, 12.15. Found: C, 55.35; H, 4.88; N, 23.90; Cl, 12.11%.

6-Chloro-4-(*N,N*-dimethylaminomethylidenehydrazino)-2-phenyl-3(2*H*)-pyridazinone hydrochloride (8a) and **6-chloro-4-(*N,N*-dimethylaminomethylidenehydrazino)-2-phenyl-3(2*H*)-pyridazinone (8)**

A solution of 2.37 g (0.01 mol) of compound **1** in dry DMF (10 ml) was added in portions to the Vilsmeier reagent, and the whole stirred at room temperature for 4 h. The separated product was collected, and identified as **8a**. Yield 75%, m.p. 189°C. IR (cm^{-1}): 1600 (CO), ^1H NMR (DMSO) δ: 3.16 (3H, CH_3, s), 4.38 (broad, NH), 6.67 (1H, C(5), s), 7.12 (1H, CH=N, s), 7.43-7.51 (5H, Ph, m). *Anal.* Calcd. for $C_{13}H_{15}Cl_2N_5O$ (328.22): C, 47.57; H, 4.62; N, 21.34; Cl, 21.60. Found: C, 47.58; H, 4.40; N, 21.12; Cl, 21.42%.

The hydrochloride salt **8a** was dissolved in water and alkalized with sodium acetate. The separated product was collected and after recrystallization from ethanol was identified as **8**, exclusively in the form of unsolvated crystals. Yield 62%, m.p. 206°C. IR (cm^{-1}): 1650 (CO), ^1H NMR ($CDCl_3$) δ: 1.25 (1H,

NH, s), 2.56 (3H, CH_3, s), 6.58 (1H, C(5), s), 7.69 (1H, CH=N, s), 7.41-7.55 (5H, Ph, m). *Anal.* Calcd. for $C_{13}H_{14}ClN_5O$ (291.76): C, 53.51; H, 4.85; N, 24.01; Cl, 12.15. Found: C, 55.45; H, 4.81; N, 23.93; Cl, 12.10%.

Two forms, the unsolvated and an inclusion compound with water, were obtained by slow recrystallization from acetone solution. The unsolvated form crystallized as long, very thin plates, their m.p. 206°C. The inclusion compound formed prisms of regular dimensions, decomposing and transforming into the unsolvated form at 145°C [13].

In the ^{1}H NMR spectrum of compounds **7a** and **8a** the signal of proton from hydrochloride could be with difficulty assigned to a broad signal at about 4.0 ppm.

6-Chloro-4-[2-(*N,N*-dimethylaminomethylidene)-1-methylhydrazino]-2-phenyl-3(2*H*)-pyridazinone (9)

A solution of 2.51 g (0.01 mol) of compound **3** in dry DMF (10 ml) was added in portions to the Vilsmeier reagent, and the whole was stirred at room temperature for 4 h. The reaction mixture was poured into water, alkalized with sodium acetate, and extracted with chloroform. The extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue was recrystallized from ethanol. The elemental analysis shows that compound **9** crystallizes with molecule of water.

Yield 62%, sublimation starts at 186°C, m.p. 220°C. IR (cm^{-1}): 1620 (CO), ^{1}H NMR ($CDCl_3$) δ: 2.98 (6H, $2CH_3$, s), 3.39 (3H, CH_3, s), 4.87 (H_2O, s), 6.57 (1H, C(5), s), 7.41-7.55 (5H, Ph, m), 7.79 (1H, CH=N, s). *Anal.* Calcd. for $C_{14}H_{16}ClN_5O$. H_2O (323.80): C, 51.93; H, 4.99; N, 21.63; Cl, 10.95. Found: C, 51.81; H, 4.20; N, 21.60; Cl, 10.31%.

* signals disappearing after deuteration with D_2O.

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