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Pyridazines with Heteroatom Substituents in Position 3 and 5, Part 1 [1]: 5-Hydroxy-3(2*H*)-pyridazinone and Its Derivatives

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Summary. The synthesis of the title compound **7** was achieved starting with mucochloric acid *via* the pyridazinones **1**, **2** and **6**. The electrolytic ionisation constants for **7** were found to be 4.81 (± 0.03) and − 0.3 (± 0.3). Crystal structure analyses were performed for **7** and its "fixed" derivatives **6** and **9**.

Keywords. Synthesis of 5-methoxy- and 5-hydroxy-3(2*H*)-pyridazinones; pK_a Values of 5-hydroxy-3(2*H*)-pyridazinone; Crystal structure of 3(2*H*)-pyridazinones.

Pyridazine mit Heteroatomsubstituenten in Stellung 3 und 5, Teil 1 [1]: **5-Hydroxy-3(2*H*)-pyridazinon und seine Derivate**

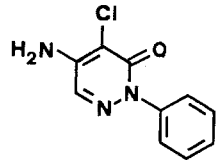
Zusammenfassung. Die Synthese der Titelverbindung **7** *via* **1**, **2** und **6** ausgehend von Mucochlorsäure wird beschrieben. Die *pK*-Werte von **7** sind 4.81 (± 0.03) und − 0.3 (± 0.3). Kristallstrukturanalysen von **7**, **6** und **9** wurden bestimmt.

Introduction

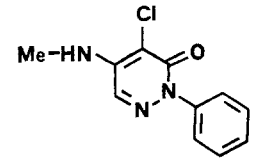
The literature on the chemistry of pyridazines functionalized in position 3 and 6 is well documented [3], because this class of compounds is easily derived from "maleic hydrazides". On the other hand, there are only few reports on pyridazines substituted with heteroatoms (such as halogen, oxygen, sulfur, and nitrogen) in positions 3 and 5, although several pyridazine nucleosides with this substitution pattern have been synthesized [4, 5], and some pyridazines from this series are used as herbicides, like chloridazone [6, 7], norflurazone [9, 10], BAS 44521 [8], pyridate [11–13] (Fig. 1).

5-Hydroxy-3(2*H*)-pyridazinone (**7**) represents one of the basic structures in this series. This compound is of special interest because it contains a malonyl moiety (an

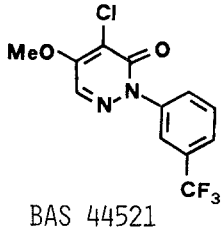
** See Ref. [2]
*** Dedicated to Prof. Dr. Hans Junek on the occasion of his 60th birthday



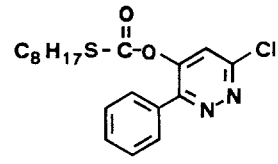
CHLORIDAZONE



NORFLURAZONE



BAS 44521



PYRIDATE

Fig. 1. In position 3 and 5 functionalized pyridazines used as herbicides

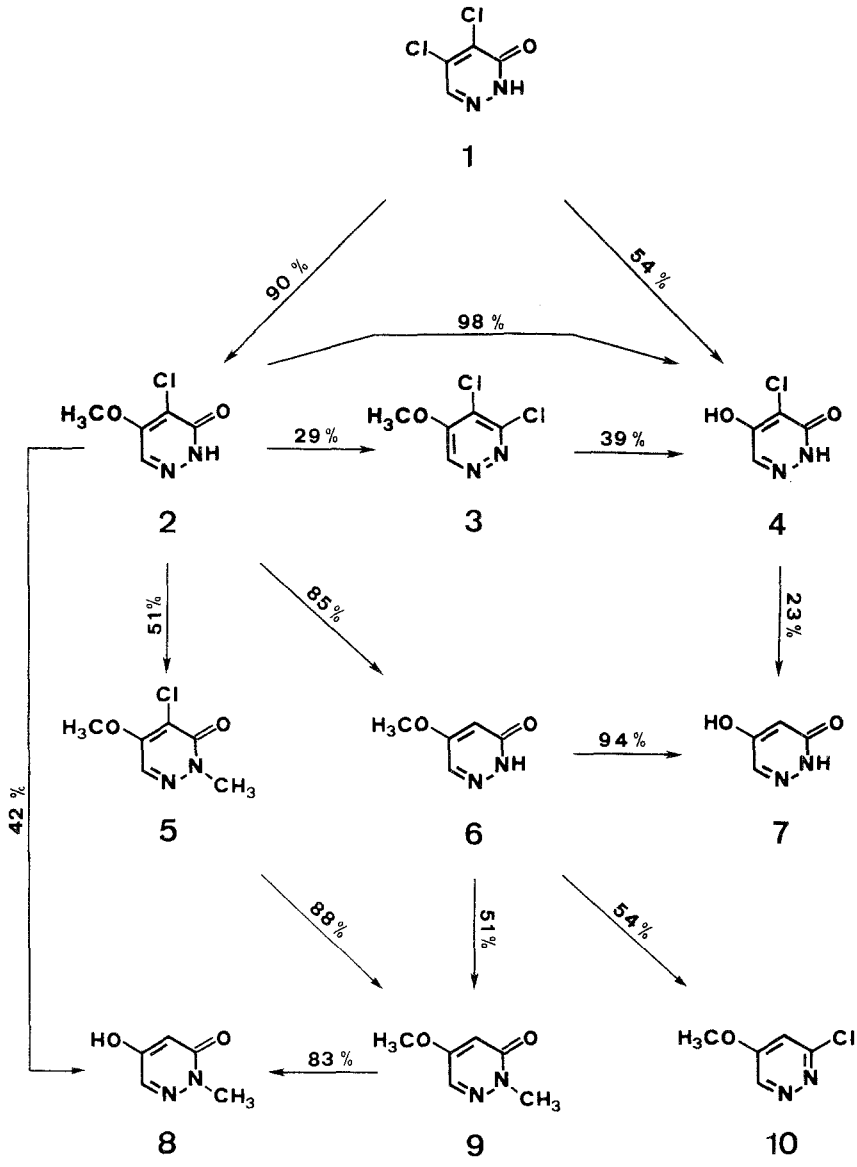
enolized β-dicarbonyl system), which is also present in many other "malonyl heterocycles", such as 4-hydroxy-coumarins, 4-hydroxy-2(1*H*)-quinolones, 4-hydroxy-2(1*H*)-pyridones, 4-hydroxy-2-pyrones (for example "triacetic acid lactone"), 6-hydroxy-4(3*H*)-pyrimidones, and barbituric acids. The enolized (or not enolized) β-dicarbonyl system in these compounds permits several electrophilic substitution reactions (e.g. halogenation, nitration, formylation, azo-coupling, etc.) at the center carbon atom of the malonyl moiety, yielding valuable starting materials for subsequent transformations. Therefore, we have focussed our interest primarily on the hydroxy-pyridazinone **7**. In this paper we describe an easy access to this compound starting with commercially available chemicals, such as "mucochloric acid" and report on some physical and spectroscopic properties of **7**.

Results and Discussion

Syntheses

It has been reported previously that the halogen atoms in 4,5-dichloropyridazinone **1** are susceptible towards nucleophilic replacement reactions [4, 5, 13–19]. In fact, the title compound 5-hydroxy-3(2*H*)pyridazinone (**7**) has already been synthesized starting with **1** *via* **4** [19]. However, the yield in the dehalogenation step was only 8.8%.

Our synthetic experiments starting with **1** are summarized in the formula scheme. The starting 4,5-dichloro-3(2*H*)-pyridazinone (**1**) is readily available from mucochloric acid and semicarbazide [17, 20]. It is obvious from the scheme that the target compound **7** is best prepared *via* the route **1** → **2** → **6** → **7**. Although we could increase the yield in the catalytic dehalogenation over Pd/C of **4** to **7** up to 23% the reduction of **2** to the methoxypyridazinone **6** occurs with 85% yield, and the latter compound is easily cleaved with hydrobromic acid to produce **7** in 94% yield.



"Fixed derivatives" play an important role in the study of tautomerism of heterocycles [21]. Therefore, we have prepared (besides **6**) the 2-methyl-5-methoxy-pyridazinone **9** by methylation of **6** with methyliodide in *DMF*, or in toluene with dimethylsulfate; or alternatively *via* hydrogenolytic dehalogenation of **5**, which was in turn made from **2** by methylation with dimethylsulfate in aqueous sodium hydroxide solution. The site of methylation is proved by the X-ray structure determination of **9** (theoretically, a methylation at N-1 would produce a zwitterionic compound, cf. the methylation of 3-hydroxy-pyridin [21]). The 2-methyl-5-hydroxy-3(2*H*)-pyridazinone (**8**) is available through ether cleavage with hydrobromic acid of **9**. Alternatively, methylation of **2** with dimethylsulfate in strong sodium hydroxide solution and subsequent hydrogenation over palladium gives **8** in 42% yield.

pK_a Values and Spectroscopic Properties

"Malonyl heterocycles" (such as mentioned in the introduction) are acidic compounds, with pK_a values usually ranging between 4.0 and 6.0 [22]. We have determined the ionisation constants of the title compound **7** by the UV-method [23]. The UV absorption spectra of 5-hydroxy-3(2*H*)-pyridazinone (**7**) in water solution at seven representative *pH* values are shown in Fig. 2. From these measurements (and additional ones at other *pH* values) the ionization constants of **7** are $pK_a1 = 4.81 \pm 0.03$ (proton loss), and $pK_a2 = -0.3 \pm 0.3$ (proton gain). Protonation of **7** occurs in the expected *pH* region (compare for instance the value of 0.75 for 2-pyridone, -0.31 for 2-quinolone [24]) (Fig. 3).

Besides structure **K1**, the alternate structures **K2** or **K3** (or a tautomeric mixture of the two) can be envisaged for the protonated form of **7**.

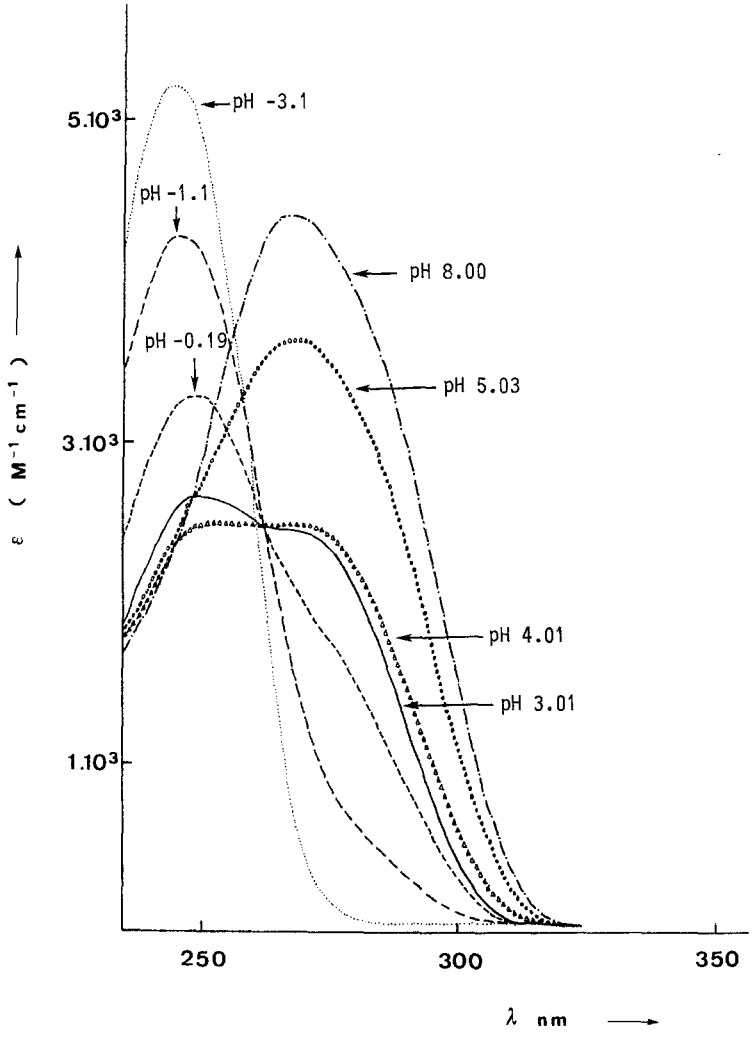
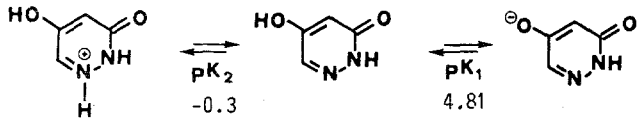
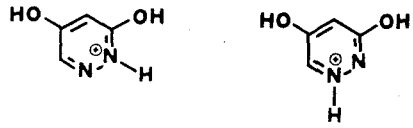


Fig. 2. UV-Absorption spectra of 5-hydroxy-3(2*H*)-pyridazinone (**7**)



K1 N A

Two more tautomeric structures of the cation can be envisaged:



K2 K3

Fig. 3. Electrolytic ionisation of 7

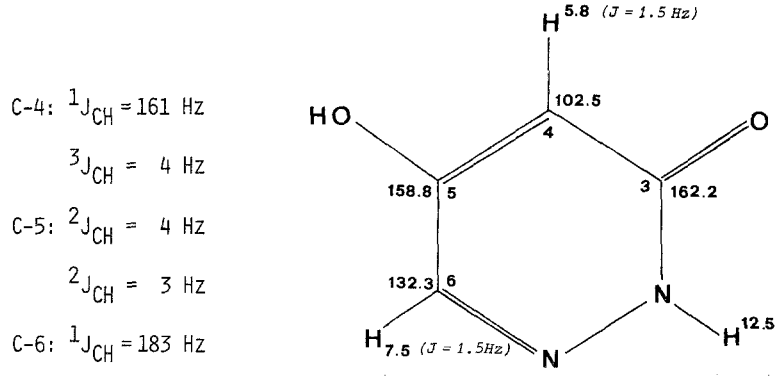


Fig. 4. ^{1}H- and ^{13}C-NMR data for 7

The *infrared spectra* of the "fixed" amine pyridazinones **5**, **8** and **9** show carbonyl absorption bands between 1 660 and 1 635 cm^{-1} (see experimental). The N-unsubstituted pyridazinones **2**, **4** and **6** have also sharp amide bands between 1 665 and 1 650 cm^{-1}; only the title molecule **7** shows a very diffuse carbonyl absorption in this region. However, this can be explained by the crystal packing, which involves strong hydrogen bonds between NH and O and between O and OH, as shown by the X-ray analysis. ^{1}H and ^{13}C *nuclear magnetic resonance spectra* for **7** in *DMSO* solution reveal also the existence of the 5-hydroxy-3(2*H*)-pyridazinone structure. The ^{1}H- and ^{13}C-NMR data for **7** are summarized in Fig. 4 (^{13}C-NMR of the 5-methoxyderivative and ^{1}H-NMR data for all other compounds see experimental).

X-Ray Crystal Structure Analyses

Crystal structure analyses have been performed for the title compound **7** as well as for the 5-methoxy derivative **6** and the 5-methoxy-N-methyl derivative **9**. Low temperature analyses for **6** and **9** were performed at 98 K and 95 K, respectively. The structure analyses for **7** could only be carried out at room temperature, since the crystals were destroyed at lower temperature due to phase transition. Room temperature data of **6** and **9** were also collected, and they are described in the thesis of U. G. Wagner [2].

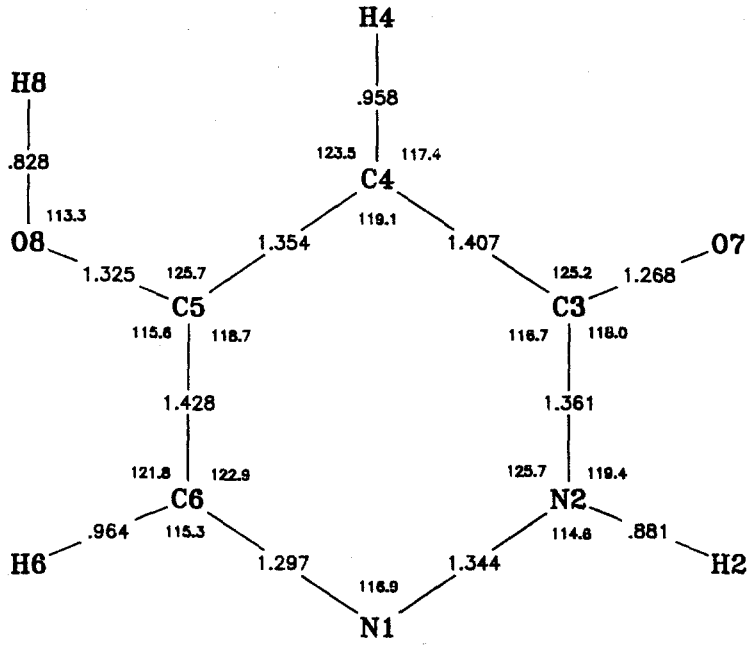


Fig. 5. Bond lengths and angles of **7**. Standard deviations: C—C 0.004 Å, C—N 0.004 Å, C—O 0.004 Å, N—N 0.005 Å, C—H 0.03–0.034 Å, O—H 0.042 Å, N—H 0.04 Å, C—C—C 0.3°, C—C—H 1.8–2.0°

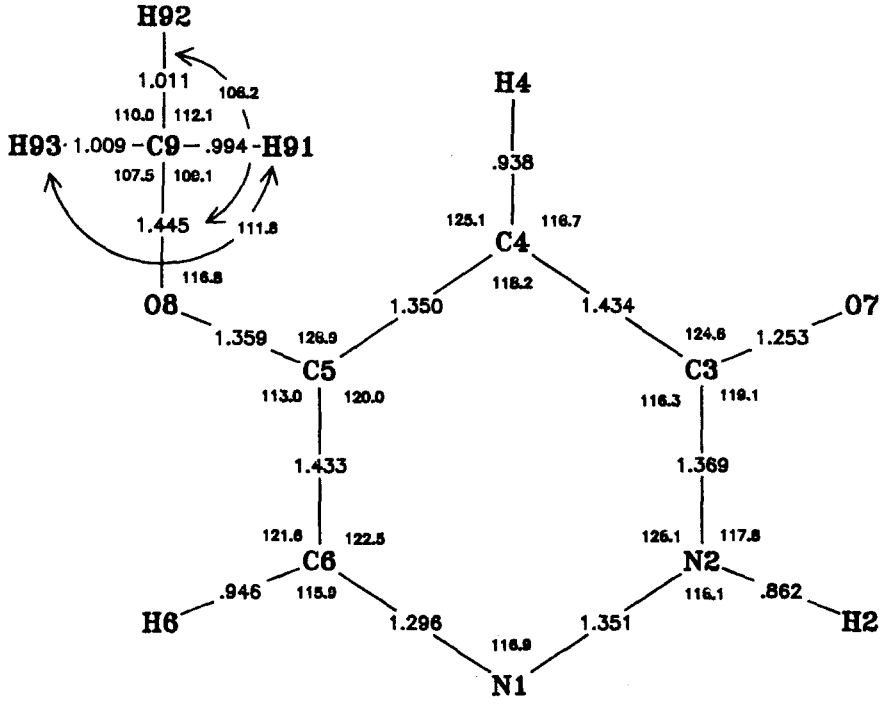


Fig. 6. Bond lengths and angles of **6**. Standard deviations: C—C 0.003–0.004 Å, C—N 0.004–0.005 Å, C—O 0.004–0.005 Å, N—N 0.004 Å, C—H 0.04–0.047 Å, N—H 0.037 Å; C—C—C 0.2°, C—C—H 1.4–2.1°

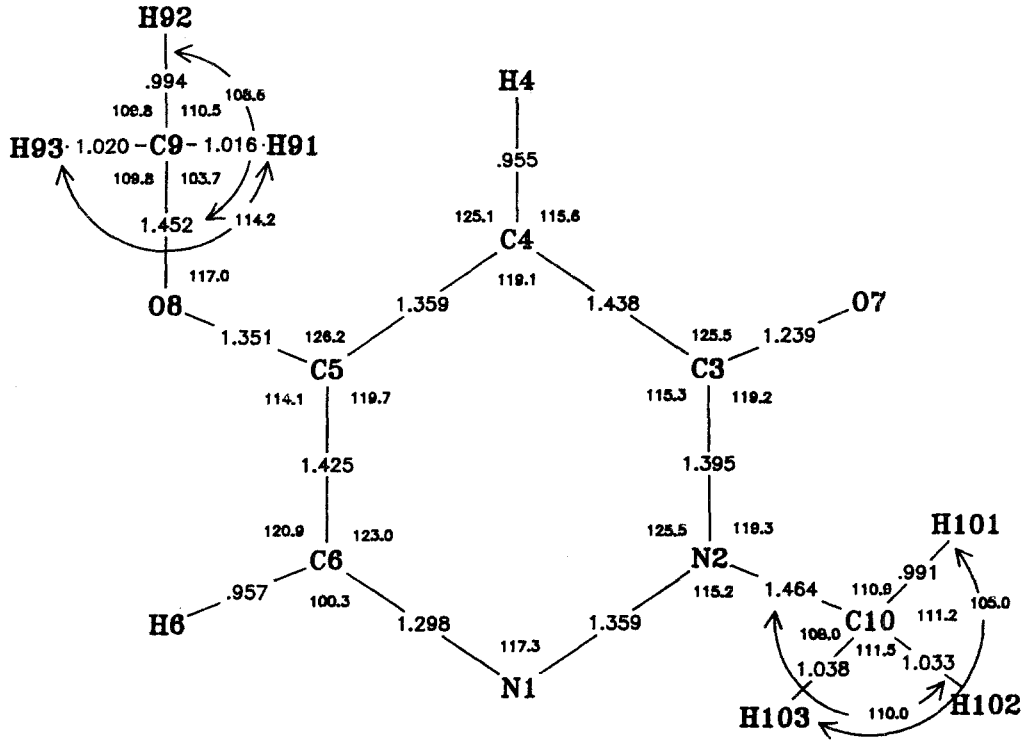


Fig. 7. Bond lengths and angles of **9**. Standard deviations: C—C 0.003–0.004 Å, C—N 0.003–0.004 Å, C—O 0.003 Å, N—N 0.003 Å, C—H 0.025–0.033 Å, C—C—C 0.2°, C—C—H 1.6°

Bond lengths and bond angles for **7**, **6** and **9** are presented in Figs. 5–7 and the corresponding ORTEP drawings [25] in Figs. 8–10 (Projection into the mean plane of the molecules). Atomic coordinates and thermal parameters for the three substances are given in Tables 1–3.

As expected, the pyridazine ring systems including the atoms directly bonded to the rings, are nearly planar. The highest deviation from a least square plane through the rings are 0.015(8) Å for **7**, 0.02(1) Å for **6** and 0.012(7) Å for **9**, and are not of statistical significance. Non-hydrogen atoms directly bonded to the rings show deviations up to 0.088 Å. The bonding geometry of **7**, **6**, and **9** is in good agreement with published data for pyridazinones as found in the Cambrdge Data File [26]. Best agreement exists with the closely related structure of 5-hydroxy-2-(*β-D*-ribofuranosyl)-pyridazin-3(2)-one (Refcode: HRFPZO) [26, 27]. From the chemical structure there are two hydrogen bonds possible in **7**, one in **6**, and none in **9**. The bond length of the carbonyl groups in the three pyridazinones is clearly dominated by the number of H-bonds: the two H-bonds in **7** lead to a C=O bond length of 1.268 Å (H-bond length 1.742 Å and 1.941 Å); one H-bond in **6** leads to a C=O bond length of 1.253 Å (H-bond length 1.965 Å). The absence of H-bonds in **9** leads to a C=O bond length of 1.239 Å.

The intermolecular hydrogen bonding capabilities have a dominating influence on the crystal packing (for stereoscopic packing diagrams see [2]). In the crystal structure of **7** there are two molecules connected by a pair of NH ... O bonds *via* a

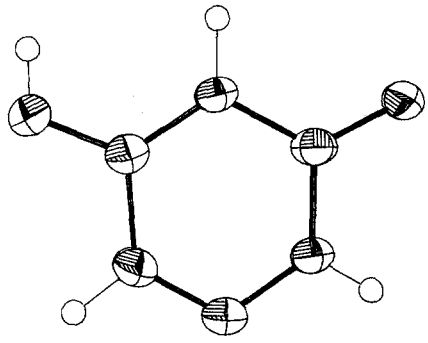


Fig. 8. ORTEP drawing (50%) [25] of the crystal structure of **7**

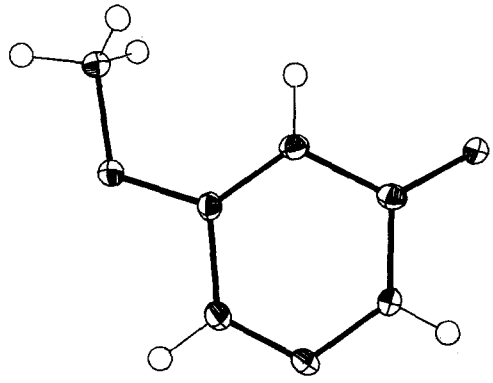


Fig. 9. ORTEP drawing (50%) [25] of the low temperature crystal structure of **6**

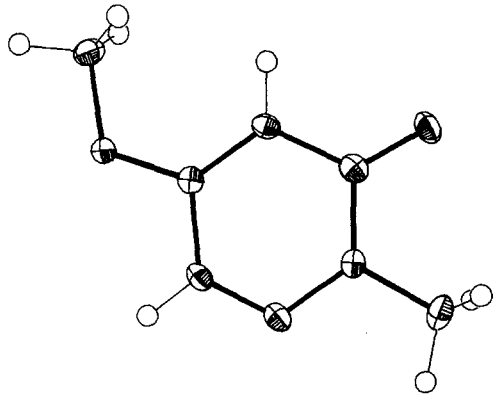


Fig. 10. ORTEP drawing (50%) [25] of the low temperature crystal structure of **9**

center of symmetry leading to the formation of coplanar dimers. With another center of symmetry (at 0, 0, ½) these dimers are laterally packed (antiparallel) which leads to nearly planar band in (1, 1, 0) direction. Along *c* there are alternate bands in (1, 1, 0) direction and ($\bar{1}$, 1, 0) direction, which are connected through C=O...HO hydrogen bonds.

Experimental Part

Melting points were determined on a Gallenkamp melting point apparatus, Mod. MFB-596 and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 298 spectrophotometer. ^{1}H-NMR spectra were obtained using a Varian EM 360 and a Varian XL-200 instrument. ^{13}C-NMR were

obtained with the Varian XL-200. UV spectra were recorded with a Perkin-Elmer Hitachi 200 spectrophotometer. Elemental analyses were performed with a C,H,N-Automat Carlo Erba 1106.

4-Chloro-5-methoxy-3(2H)-pyridazinone (**2**)

A mixture of methanolic sodium methoxide solution (prepared from 450 ml of methanol and 23 g of sodium) and 25.0 g (0.15 mol) of **1** [17, 20] was heated under reflux for 3 days. After evaporation *in vacuo* the residue was dissolved in water and neutralized with acetic acid. Filtration gave 21.8 g of **2**. Colorless prisms from methanol, m.p. 235°C (dec.). IR: 3 340–2 500 m, 1 655 s, 1 600 s cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): $\delta = 4.3$ (s, OCH_3), 8.4 (s, H at C-6), 13.5 (s, b, NH). $C_5H_5ClN_2O_2$ (160.5); calcd. C 37.41, H 3.14, N 17.45; found C 37.81, H 3.34, N 17.47.

3,4-Dichloro-5-methoxy-pyridazine (**3**)

A mixture of **2** (1.0 g, 6 mmol) and $POCl_3$ (15 ml) was heated under reflux for 15 min; then poured on ice and neutralized with potassium hydroxide solution. Yield 0.40 g (29%) of **3**; m.p. 100°C (from H_2O), Lit. [19] 100–101°C. IR: 3 030 w, 1 575 sh, 1 550 s cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): $\delta = 4.2$ (s, OCH_3), 9.3 (s, H at C-6).

4-Chloro-5-hydroxy-3(2H)-pyridazinone (**4**)

Method A. 4,5-Dichloropyridazinone **1** (2 g, 12 mmol) were refluxed in 20 ml of 8 *N* KOH for 6 h. After acidification with HCl the reaction mixture was concentrated *in vacuo* and **4** extracted with ethyl acetate; yield 0.69 g (54%).

Method B. A mixture of **2** (3.0 g, 19 mmol), 15 ml of glacial acetic acid, and 15 ml of HBr (47% in H_2O) was heated under reflux for 6 h. After addition of 30 ml of water the reaction mixture was evaporated to dryness and 10 ml water were added; yield 2.7 g (98%).

Method C. The pyridazinone **3** (1.0 g, 6 mmol) in 25 ml of conc. hydrochloric acid was refluxed for 48 h. After cooling the *pH* was adjusted to 2–3 with aqueous KOH; yield 0.30 g (39%).

Recrystallization from water yields colorless crystals, m.p. 267–272°C (from *DMF*), Lit. [15] 270–273°C. IR: 2 300–3 340 m, b, 1 650 m, 1 595 s, 1 555 sh cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): $\delta = 7.7$ (s, H at C-6), 12.9 (s, b, NH). $C_4H_3ClN_2O_2$ (146.5); calcd. C 32.78, H 2.06, N 19.12; found C 32.75, H 2.17, N 19.06.

4-Chloro-5-methoxy-2-methyl-3(2H)-pyridazinone (**5**)

To a stirred solution of 3 g NaOH and 10 g (60 mmol) **2** in 200 ml of water were added 17.7 ml (0.18 moles) of dimethylsulfate. Filtration after 48 h yielded 5.6 g (51%) of **5**, colorless needles from methanol, m.p. 159°C. IR: 3 025 w, 2 950 w, 1 630 s, 1 600 m cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): $\delta = 3.7$ (s, NCH_3), 4.1 (s, OCH_3), 8.2 (s, H at C-6). $C_6H_7ClN_2O_2$ (174.6); calcd. C 41.27, H 4.04, N 16.05; found C 41.00, H 4.02, N 16.07.

3-Methoxy-3(2H)-pyridazinone (**6**)

The pyridazinone **2** (15.0 g, 0.1 mol) was dissolved in 350 ml of water by the addition of 50 ml of 2 *N* NaOH. After the addition of 3 g of 10% Pd/C hydrogen was bubbled through the stirred solution for

19 h. The reaction mixture was heated and filtered still hot. Concentration *in vacuo* and filtration of the cold mixture afforded 10.1 g (85%) **6**. Colorless crystals from methanol, m.p. 246–249°C. IR: 3 320–2 300 m, b, 1 665 s, 1 610 m, 1 555 w cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ = 3.8 (s, OCH_3), 6.1 (d, J = 1 Hz, H at C-4), 7.5 (d, J = 1 Hz, H at C-6), 12.4 (s, b, NH). ^{13}C-NMR (*DMSO-d_6*): δ = 54.8 (CH_3O), 102.1 (C-4), 131.5 (C-6), 159.4 (C-5), 161.4 (C-3). $C_5H_6N_2O_2$ (126.1); calcd. C 47.61, H 4.80, N 22.22; found C 47.42, H 4.68, N 22.10.

5-Hydroxy-3(2H)-pyridazinone (**7**)

Method A. A mixture of 2 g (16 mmol) **6**, 20 ml of HBr (47% in water), and 20 ml of glacial acetic acid was refluxed for 10 h. After addition of 50 ml of water the mixture was taken to dryness. The resulting oil was triturated with 10 ml of water and the crystals thus obtained collected. Yield 1.7 g (94%).

Method B. The pyridazinone **4** (1.7 g, 10 mmol) are dissolved in 150 ml of water and 9 ml of 2 *N* NaOH. After addition of 1 g of 5% Pd/C the mixture is hydrogenated overnight at 1.8 kp/m^2. The reaction mixture is acidified with acetic acid, evaporated to a volume of 50 ml, and the precipitate collected by filtration. Yield 0.3 g (23%).

Colorless prisms from water, m.p. 274–276°C; Lit. [19]: m.p. 274–278°C. IR: 3 340–2 060 m, 1 720–1 510 s (1 635 sh, 1 535 sh) cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): 5.8 (d, J = 1.5 Hz, H at C-4), 7.5 (d, J = 1.5 Hz, H at C-6), 12.5 (s, broad, NH). ^{13}C-NMR (*DMSO-d_6*): 102.5 (C-4), 132.3 (C-6), 158.8 (C-5), 162.2 (C-3). $C_4H_4N_2O_2$ (112.1); calcd. C 42.86, H 3.60, N 25.00; found C 42.58, H 3.59, N 25.19.

5-Hydroxy-2-methyl-3(2H)-pyridazinone (**8**)

Method A. A mixture of 0.4 g (4 mmol) **9**, 10 ml of HBr (47% in water), and 10 ml of acetic acid was refluxed for 6 h. After dilution with 40 ml of water the reaction mixture was taken to dryness. Yield 0.3 g (83%).

Method B. A mixture of 5.0 g (30 mmol) **2**, 100 ml of water, 12 g NaOH, and 8.8 ml (90 mmol) dimethylsulfate was stirred for 12 h at room temperature. The reaction mixture was acidified with acetic acid and the precipitate collected. The dried precipitate was dissolved in 100 ml of water by the addition of 15 ml of 2 *N* NaOH and hydrogenated for 6 h after the addition of 5% Pd/C as catalyst. The reaction mixture was acidified with acetic acid and concentrated *in vacuo*. Yield 1.7 g (42%).

Colorless crystals from methanol, m.p. 176°C. IR: 3 400–2 500 m, b, 1 660 m, 1 610 s, 1 540 sh cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ = 3.7 (s, NCH_3), 6.6 (d, J = 2.5 Hz, H at C-4), 7.6 (s, J = 2.5 Hz, H at C-6), 8.4 (s, b, OH). $C_5H_6N_2O_2$ (126.1); calcd. C 47.61, H 4.80, N 22.22; found C 47.56, H 4.72, N 22.21.

5-Methoxy-2-methyl-3(2H)-pyridazinone (**9**)

Method A. A stirred mixture of 1.0 g (8 mmol) **6**, 3.5 g K_2CO_3, and 2 ml of methyl iodide was refluxed for 3 h. The inorganic material was removed by filtration, and the solution taken to dryness. The oily residue was dissolved in water and **9** extracted with dichloromethane. Yield 0.6 g (51%).

Method B. The hot solution of 1.2 g (7 mmol) **5** in 50 ml of water and 5 ml of 2 *N* NaOH is hydrogenated in the presence of 5 g of 5% Pd/C for 4 h. After removal of the catalyst the filtrate is concentrated *in vacuo*. Yield 0.9 g (88%).

Method C. A mixture of 1.0 g **6**, 3.0 g of K_2CO_3, and 0.7 ml of dimethylsulfate in 25 ml of toluene was refluxed for 8 h. The organic phase was taken to dryness. Yield 0.6 g (55%).

Colorless needles from toluene, m.p. 113°C. IR: 3 030 w, 1 650 s, 1 625 sh, 1 600 m, 1 550 sh cm^{-1}. ^{1}H-NMR (CF_3CO_2H): $\delta = 4.1$ (6H, s, NCH_3, OCH_3), 7.0 (d, $J = 1.5$ Hz, H at C-4), 8.2 (d, $J = 1.5$ Hz, H at C-6). $C_6H_8N_2O_2$ (140.1); calcd. C 51.42, H 5.76, N 20.00; found C 51.70, H 5.88, N 19.87.

3-Chlor-5-methoxy-pyridazine (**10**)

A solution of 1.2 g (9 mmol) **6** in 20 ml of $POCl_3$ was heated for 5 min under reflux, cooled and poured on ice. The solution was brought to *pH* 6 with aqueous KOH and extracted with ether. After evaporation of the ether the remaining material was crystallized from tetrachloromethane to afford 0.6 g (54%) brownish crystals, m.p. 101°C. IR: 3 030 sh, 3 025 m, 2 940 w, 1 570 s, 1 530 sh cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): 3.9 (s, OCH_3), 7.5 (d, $J = 1$ Hz, H at C-4), 9.0 (d, $J = 1$ Hz, H at C-6). $C_5H_5ClN_2O$ (144.6); calcd. C 41.54, H 3.49, N 19.38; found C 41.27, H 3.57, N 19.22.

Crystal Structure Analyses

Suitable crystals of **7** were obtained from water, **6** was crystallized from methanol, and **9** from toluene. A modified STOE 4-circle difractometer (MoKα-radiation, graphite monochromator, $\lambda = 0.71069$ Å) was used. Relevant experimental conditions and a summary of the results of structure refinement are given in Table 4.

Table 1. Atomic coordinates and anisotropic (C, N) and isotropic (H) temperature coefficients and their e.s.d.'s ($\cdot 10^4$; *U*-values in Å^2). The isotropic temperature factor has the form $T = \exp[-(8\pi^2 u \sin^2\delta/\lambda^2)]$, the anisotropic temperature has the form $T = \exp[-2\pi^2(h^2 a^{*2} u_{11} + \ldots + 2hka^* 6^* u_{12} + \ldots)]$

Atom	*X*	*Y*	*Z*	*U*11	*U*22	*U*33	*U*23	*U*13	*U*12
N1	7763 *5*	1757 *3*	4762 *2*	385 *14*	376 *15*	387 *14*	58 *12*	−187 *11*	−34 *12*
N2	6141 *5*	2972 *3*	4689 *2*	423 *14*	293 *13*	348 *13*	24 *11*	−195 *11*	−21 *11*
C3	4346 *5*	3117 *3*	3882 *3*	325 *16*	315 *15*	332 *15*	−27 *13*	−124 *12*	33 *13*
C4	4107 *5*	1850 *3*	3094 *3*	356 *16*	305 *16*	335 *1*	−2 *13*	−169 *13*	−19 *12*
C5	5671 *5*	591 *3*	3161 *3*	301 *15*	332 *15*	340 *15*	−10 *14*	−88 *12*	−17 *14*
C6	7538 *6*	605 *4*	4022 *3*	324 *16*	342 *16*	453 *17*	55 *15*	−167 *13*	−9 *16*
O7	3030 *4*	4368 *2*	3898 *2*	546 *13*	286 *11*	564 *14*	119 *11*	−339 *11*	−105 *11*
O8	5645 *4*	−687 *3*	2487 *2*	440 *13*	379 *12*	531 *14*	100 *11*	−238 *11*	−154 *11*

Atom	*X*	*Y*	*Z*	U_{iso}
H2	6431 *71*	3769 *46*	5160 *35*	740 *132*
H4	2843 *62*	1938 *38*	2525 *30*	453 *86*
H6	8679 *55*	−268 *36*	4111 *25*	366 *84*
H8	4527 *76*	−667 *53*	2005 *36*	801 *140*

Table 2. Atomic coordinates and temperature coefficients of **6**

Atom	*X*	*Y*	*Z*	*U*11	*U*22	*U*33	*U*23	*U*13	*U*12
N1	5116 *5*	1474 *3*	7751 *2*	172 *11*	170 *11*	145 *11*	23 *9*	−10 *9*	51 *8*
N2	2920 *6*	1286 *3*	6511 *2*	175 *11*	109 *10*	137 *10*	1 *9*	−21 *8*	14 *8*
C3	1910 *6*	2634 *3*	5881 *2*	134 *12*	129 *11*	139 *12*	26 *10*	36 *10*	45 *9*
C4	3356 *6*	4411 *3*	6614 *3*	141 *13*	133 *12*	148 *12*	21 *10*	12 *10*	50 *10*
C5	5545 *6*	4619 *3*	7857 *2*	126 *12*	120 *11*	126 *11*	15 *9*	24 *9*	16 *9*
C6	6377 *7*	3085 *3*	8403 *3*	160 *13*	160 *12*	114 *12*	19 *10*	−9 *10*	30 *10*
O7	−183 *4*	2257 *2*	4736 *2*	202 *10*	117 *8*	134 *9*	2 *7*	−50 *8*	21 *7*
O8	7123 *4*	6173 *2*	8708 *2*	191 *9*	114 *8*	138 *8*	24 *7*	−27 *7*	15 *7*
C9	6267 *7*	7786 *3*	8278 *3*	171 *13*	118 *12*	180 *13*	25 *10*	−18 *11*	35 *10*

Atom	*X*	*Y*	*Z*	U_{iso}
H2	2150 *74*	221 *40*	6097 *30*	204 *75*
H4	2615 *68*	5325 *36*	6185 *28*	158 *69*
H6	7814 *73*	3174 *36*	9280 *30*	223 *74*
H91	7123 *66*	7886 *33*	7331 *28*	145 *63*
H92	7458 *73*	8774 *39*	9077 *29*	238 *73*
H93	3644 *72*	7713 *33*	8216 *26*	147 *64*

Table 3. Atomic coordinates and temperature coefficients of **9**

Atom	*X*	*Y*	*Z*	*U*11	*U*22	*U*33	*U*23	*U*13	*U*12
N1	6575 *5*	1947 *2*	1083 *1*	184 *11*	190 *12*	156 *11*	−1 *10*	−7 *9*	25 *9*
N2	5284 *5*	2308 *2*	194 *1*	186 *11*	179 *12*	136 *10*	3 *9*	22 *9*	−13 *8*
C3	3499 *6*	3290 *2*	−5 *2*	148 *12*	165 *14*	176 *13*	−42 *11*	34 *10*	37 *10*
C4	3159 *6*	3971 *2*	815 *2*	150 *13*	138 *14*	175 *12*	−9 *11*	21 *10*	33 *10*
C5	4477 *6*	3614 *2*	1702 *2*	111 *12*	154 *14*	152 *13*	−23 *10*	23 *9*	−3 *10*
C6	6160 *6*	2576 *2*	1807 *2*	181 *13*	166 *13*	139 *13*	−11 *11*	−4 *10*	40 *11*
O7	2364 *5*	3511 *1*	−847 *1*	262 *11*	229 *10*	133 *9*	−22 *8*	−33 *8*	24 *8*
O8	4393 *4*	4160 *1*	2537 *1*	216 *9*	153 *9*	133 *9*	31 *8*	19 *7*	1 *7*
C9	2755 *7*	5232 *2*	2481 *2*	230 *15*	149 *13*	219 *14*	21 *11*	51 *11*	−4 *11*
C10	5935 *8*	1591 *3*	−601 *2*	257 *16*	266 *16*	182 *13*	8 *13*	54 *11*	−67 *12*

Atom	*X*	*Y*	*Z*	U_{iso}
H4	1885 *63*	4635 *21*	684 *17*	104 *63*
H6	7034 *65*	2300 *21*	2429 *20*	148 *65*
H91	3273 *74*	5529 *23*	3160 *22*	316 *80*
H92	175 *79*	5152 *24*	2247 *20*	321 *82*
H93	3882 *68*	5692 *21*	2024 *19*	195 *71*
H101	7338 *74*	1972 *23*	−1045 *21*	290 *80*
H102	3612 *79*	1315 *24*	−959 *21*	330 *84*
H103	7478 *86*	944 *29*	−320 *23*	469 *96*

Table 4. Summary of experimental conditions

	7	**6**	**9**
Chemical formula	$C_4H_4N_2O_2$	$C_5H_6N_2O_2$	$C_6H_8N_2O_2$
Molecular weight	112.0	126.1	140.1
Crystal size [mm]	$0.3 \times 0.2 \times 0.1$	$0.4 \times 0.1 \times 0.1$	$0.3 \times 0.2 \times 0.1$
Temperature [K]	298(2)	98(1)	95(1)
Space group	$P2_1/n$	$P\bar{1}$	$P2_1/n$
Cell dimensions a[Å]	5.186(1)	3.855(1)	3.886(1)
b[Å]	8.547(1)	7.734(6)	12.198(3)
c[Å]	11.119(1)	9.616(6)	14.026(11)
α[°]		99.01(4)	
β[°]	84.25(1)	96.79(2)	97.05(1)
γ[°]		99.62(1)	
Number of molecules/unit cell	4	2	4
Density calcd. from room-temperature volume [g/cm³]	1.518(1)	1.446(1)	1.359(2)
Density found [g/cm³]	—	1.449(3)	1.358(1)
Number and Θ-range [°] of reflections used to refine cell constants	43	12	12
	8–28°	10–23°	22–24°
Limits for data collection [°]	$0 < \Theta < 50$	$0 < 2\Theta < 50$	$0 < 2\Theta < 50$
	$-6 < h < 6$	$0 < h < 4$	$0 < h < 4$
	$0 < k < 10$	$-9 < k < 9$	$0 < k < 14$
	$0 < l < 13$	$-11 < l < 11$	$-16 < l < 16$
Scan type/scan width [°]	ω-Θ/1.5	ω-Θ/1.5	ω-Θ/1.5
Number of obs. reflections	988	1 167	1 514
Number of indep. reflections	860	973	1 167
Number of reflections with $\lvert F_0 \rvert > 4\sigma(F_0)$	660	714	826
R-factors	0.043	0.033	0.036
Number of parameters	89	106	123
Number of observations	660	714	826
Highest peak/lowest through in final ΔF-Fourier synth. [eÅ^{-3}]	0.18/−0.2	0.4/−0.5	0.16/−0.3

References

[1] Part 2: Olesen P. H., Becher J., Kappe T. (1989) J. Heterocycl. Chem. (in press)

[2] From Wagner U. G. (1984) Diploma Thesis. University of Graz, Austria

[3] Tisler M., Stanovnik B. (1984) In: Katritzky A. R., Rees C. W. (eds.) Comprehensive Heterocyclic Chemistry, Vol. 3. Pergamon Press, Oxford, pp. 1–56

[4] Katz D. J., Wise D. S., Townsend L. B. (1982) J. Med. Chem. **25**: 813; Katz D. J., Wise D. S., Townsend L. B. (1983) J. Heterocycl. Chem. **20**: 369

[5] Yoon Y. J., Wise D. S., Townsend L. B. (1987) Bull. Korean Chem. Soc. **8**: 171

[6] Rapos P., Winternitz P. (1966) French Pat. 1.461.373 (Cl. C07d, A01n), Dec. 9, 1966; Appl. Mar. 17, 1965; (1967) Chem. Abstr. **67**: P 90824g

[7] Rapos P., Winternitz P. (1966) Czech. Pat. 120.858 (Cl. C07d, A01n), Dec. 15, 1966; Appl. Jul. 25, 1963; (1968) Chem. Abstr. **68**: P 78303z
[8] Badische Anilin- und Soda-Fabrik AG (1969) French Demande 2.001.700 (Cl. C07d, A01n), Sep. 26, 1969; Ger. Appl. Feb. 10, 1968; (1970) Chem. Abstr. **72**: P 111494v
[9] Ebner C., Schuler M. (Sandoz Ltd.) (1970) Swiss Pat. 482.684 (Cl. C07d, A01n), Jan. 30, 1970; Appl. Jan. 2, 1967; (1970) Chem. Abstr. **72**: P 121567k
[10] Ebner C., Schuler M. (Sandoz Ltd.) (1969) French Pat. 1.575.643 (Cl. C07d, A01n), Jul. 25, 1969; Appl. Mar. 28, 1968; (1970) Chem. Abstr. **73**: P 35389t
[11] Schönbeck R., Kloimstein E., Mayr H., Diskus A., Auer E. (Lentia GmbH) (1975) Ger. Offenl. 2.3331.398 (Cl. C07d, A01n), Jan. 23, 1975; Appl. P 23 31 398.6–44, Jun. 20, 1973; (1975) Chem. Abstr. **82**: P 156354x
[12] Schönbeck R., Kloimstein E., Diskus A., Auer E., Mayr H. (Chemie Linz AG) (1975) Austrian Pat. 326.137 (Cl. C07d), Nov. 25, 1975; Appl. 5661/73, Jun. 27, 1973; (1976) Chem. Abstr. **84**: P 59522j; Schönbeck R., Kloimstein E., Diskus A., Auer E., Mayr H. (1975) Austrian Pat. 326.406 (Cl. A01n), Feb. 15, 1975, Appl. Jun. 27, 1973; (1976) Chem. Abstr. **84**: 116939b
[13] Schönbeck R., Kloimstein E. (1984) Österr. Chem. Zeitschr. **85**: 185
[14] Drury K. (1965) Angew. Chem. Int. Ed. Engl. **4**: 292
[15] Konecny V. (1976) Chem. Zvesti **30**: 658
[16] Gomez-Gil M. C., Gomez-Para V., Sanchez F., Torres T. (1985) Liebigs Ann. Chem. **1985**: 1465
[17] Okafor C. O., Castle R. N. (1983) J. Heterocycl. Chem. **20**: 199
[18] Womack C. H., Martin L. M., Martin G. E., Smith K. (1982) J. Heterocycl. Chem. **19**: 1447
[19] Schönbeck R., Kloimstein E. (1968) Monatsh. Chem. **99**: 15
[20] Mowry D. T. (1953) J. Amer. Chem. Soc. **75**: 1909
[21] Katritzky A. R. (1970) Chimia **24**: 134
[22] Kappe T. (1984) Lect. Heterocycl. Chem. **7**: 107
[23] Albert A., Serjant E. P. (1971) The Determination of Ionisation Constants, 2nd edn. Chapman and Hall, London
[24] Albert A. (1962) Chemie der Heterocyclen. Verlag Chemie, Weinheim, p. 59
[25] German G., Main P., Woolfson M. M. (1971) Acta Cryst., Sect. A **27**: 368; Sheldrick G. M. (1976) Program SHELX 76. University of Cambridge, England; Johnson C. K. (1976) ORTEP report ORNL 5138. Oak Ridge National Laboratory, Oak Ridge, TN, USA; Motherwell S. (1976) Program PLUTO. University of Cambridge, England
[26] Allen F. H., Kennard O., Taylor R. (1983) Acc. Chem. Res. **16**: 146
[27] Graves B. J., Hodgson D. J., Wise D. S., Townsend L. B. (1978) Biochim. Biophys. Acta **520**: 229

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