Synthesis, structure, and pesticidal activity of 2,4- and 2,5-disubstituted 3-oxo-2*H*-pyridazine-5- and -4-thiols

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Dedicated to Corresponding Member M. Zikmund, in honour of his 65th birthday

A synthesis of thirteen novel 2,4- and 2,5-disubstituted 3-oxo-2*H*-pyridazine-5- and -4-thiols by the reaction of 2-R-4-alkoxy-5-chloro- and 2-R-5-alkoxy-4-chloro-3-oxo-2*H*-pyridazines with sodium hydrogen sulfide in methanol is described. The structure of compounds prepared was proved by spectral methods. None of the compounds prepared showed the significant insecticidal, acaricidal, ovicidal, fungicidal, and herbicidal activity. In addition, it was found that by the reaction of 2-phenyl-4-acetamido- and 2-phenyl-4-diacetamido-5-chloro-3-oxo-2*H*-pyridazines and 2-phenyl-5-acetamido- and 2-phenyl-5-diacetamido-4-chloro-3-oxo-2*H*-pyridazines, respectively, with sodium hydrogen sulfide pyridazinethiols formed were cyclized into corresponding thiazolopyridazinones.

Описан синтез тринадцати новых 2,4- и 2,5-дизамещенных 3-оксо-2*H*-пиридазин-5- и -4-тиолов путем реакции 2-R-4-алкокси-5-хлор- и 2-R-5-алкокси-4-хлор-3-оксо-2*H*-пиридазинов с гидросульфидом натрия в метиловом спирте. Строение полученных соединений было доказано с помощью спектральных методов. Ни одно из полученных соединений не обладало значительной инсектицидной, акарицидной, овицидной, фунгицидной или гербицидной активностью. Кроме того, обнаружено, что пиридазинтиолы, образующиеся посредством реакции 2-фенил-4-ацетамидо- и 2-фенил-4-диацетамидо-5-хлор-3-оксо-2*H*-пиридазинов, или 2-фенил-5-ацетамидо- и 2-фенил-5-диацетамидо-4-хлор-3-оксо-2*H*-пиридазинов с гидросульфидом натрия, циклизуются в соответствующие тиазолопиридазиноны.

It is known [1] that by the reaction of 2-phenyl-4,5-dichloro-3-oxo-2*H*-pyridazine with potassium hydrogen sulfide in ethanol 2-phenyl-4-chloro-3-oxo-2*H*-pyridazine-5-thiol is formed. Similarly, by the reaction of 2-phenyl-4-chloro-5-methoxy-3-oxo-2*H*-pyridazine with sodium hydrogen sulfide in etha-

nol 2-phenyl-5-methoxy-3-oxo-2*H*-pyridazine-4-thiol as the main product is formed, the by-product in this reaction being 2,7-diphenyldipyridazo[4,5-*b*;4,5--*e*]-1,4-dithiine-1,6-dione [2]. By the reaction of 2-phenyl-4,5-dichloro-3-oxo--2*H*-pyridazine with phosphoric sulfide in pyridine 2-phenyl-3-oxo-2*H*-pyridazine-4,5-dithiol is formed [3].

The present work is devoted to the study of the reaction of 2-R^1-4,5-disubstituted 3-oxo-2*H*-pyridazines containing alkoxy, alkylthio, acetamido, and chloro groups, respectively, in positions 4 and 5, with alkaline hydrogen sulfide in methanol. The structure of compounds prepared was proved by IR, UV, ^{1}H NMR, and ^{13}C NMR spectrometry. Insecticidal, acaricidal, ovicidal, fungicidal, and herbicidal activities of the compounds prepared were determined.

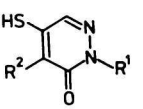
The yields of the prepared compounds (Table 1) were excepting compound *XV* high (70—90 %).

In the infrared spectra of compounds prepared (*IV—XVI*) (Table 2) the ν(C=O) intense bands are observed in the region of $\tilde{\nu} = 1635$—$1665\ \mathrm{cm}^{-1}$ belonging to the C=O groups in position 3 of the pyridazine ring and the ν(S—H) medium intense bands in the region of $\tilde{\nu} = 2492$—$2587\ \mathrm{cm}^{-1}$. In the ultraviolet spectra of compounds prepared (Table 2) three or four bands characteristic of pyridazinone derivatives are observed in the region of $\lambda = 220$—364 nm. In the ^{1}H NMR spectra of compounds prepared singlet signals of the S—H protons are observed in the region of $\delta = 3.86$—4.23 ppm (Table 2). In the ^{13}C NMR spectra of compounds prepared these signals can be seen:

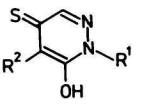
(*IV*) δ/ppm: 156.10 (C=O), 148.37 (C=N), 136.04 (=CH), 124.84 (C—S), 59.92 (CH_3O), 39.74 (CH_3N);

(*VIII*) δ/ppm: the pyridazinone ring carbons — 154.83 (C=O), 151.70 (C=N), 135.75 (=CH), 125.66 (C—S); the benzene ring carbons — 140.86 (C-1 —N), 128.58 (C-3=C), 127.91 (C-4=C), 124.84 (C-2=C).

Two tautomeric forms *a* and *b* can be considered with compounds *IV—XIV*



a



b

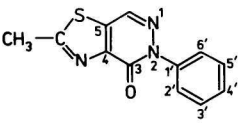
In the infrared spectra of these compounds the ν(S—H) and ν(C=O) bands are observed, the ν(O—H) bands are not observed, which proves that the compounds studied exist in solvents used exclusively in the thiol form *a*.

By the reaction of 2-phenyl-4-acetamido-5-chloro-3-oxo-2*H*-pyridazine and 2-phenyl-5-acetamido-4-chloro-3-oxo-2*H*-pyridazine with sodium hydrogen sulfide corresponding thiols were not isolated, only corresponding thiazolopyridazinones.

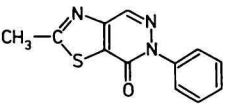
Table 1

Characterization of the prepared 2-R^1-4-R^2-5-R^3-3-oxo-2*H*-pyridazines

Compound	R^1	R^2	R^3	Formula	M_r	w_i(calc.)/% w_i(found)/% N	S	Yield %	M.p. °C
IV	CH_3	CH_3O	SH	$C_6H_8N_2O_2S$	172.18	16.27 16.01	18.62 18.37	81.2	88—90
V	CH_3	C_3H_7O	SH	$C_8H_{12}N_2O_2S$	200.22	13.99 14.11	16.01 16.22	90.1	52—53
VI	CH_3	$(CH_3)_2CHS$	SH	$C_8H_{12}N_2OS_2$	216.28	12.95 13.23	29.65 30.01	73.2	47—49
VII	C_6H_{11}(cyclo)	CH_3O	SH	$C_{11}H_{16}N_2O_2S$	240.30	11.66 11.73	13.35 13.58	80.2	40—42
VIII	C_6H_5	CH_3O	SH	$C_{11}H_{10}N_2O_2S$	234.25	11.96 11.85	13.69 13.38	86.8	140—142
IX	C_6H_5	C_2H_5O	SH	$C_{12}H_{12}N_2O_2S$	248.27	11.28 11.42	12.91 13.04	84.6	104—106
X	C_6H_5	C_3H_7O	SH	$C_{13}H_{14}N_2O_2S$	262.29	10.67 10.81	12.22 12.37	91.4	78—80
XI	C_6H_5	C_2H_5S	SH	$C_{12}H_{12}N_2OS_2$	264.33	10.59 10.68	24.25 23.95	71.2	108—111
XII	3-CH_3—C_6H_4	CH_3O	SH	$C_{12}H_{12}N_2O_2S$	248.27	11.28 11.39	12.91 12.74	87.9	116—119
XIII	3-Cl—C_6H_4	CH_3O	SH	$C_{11}H_9ClN_2O_2S$	268.59	10.42 10.30	11.93 12.19	78.5	147—149
XIV	3-CF_3—4-Cl—C_6H_3	CH_3O	SH	$C_{12}H_8ClF_3N_2O_2S$	336.59	8.32 8.50	9.52 9.68	80.6	97—100
XV	CH_3	SH	CH_3O	$C_6H_8N_2O_2S$	172.18	16.27 16.31	18.62 18.76	41.2	107—109
XVI	CH_3	SH	C_2H_5S	$C_7H_{10}N_2OS_2$	202.15	13.85 13.75	31.70 31.47	70.2	79—81

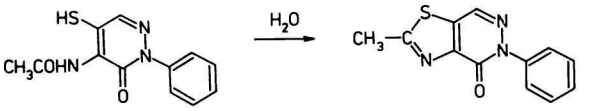


XVIII



XIX

The structure of these compounds was proved by spectral methods, namely by ^{13}C NMR spectrometry (the observation of the signal at $\delta \approx 20$ ppm pointing to the presence of the CH_3—C= grouping). The formation of these compounds can be explained by cyclization of the corresponding thiols



XVIII

In the infrared spectra of both compounds (*XVIII* and *XIX*) the ν(S—H) and ν(N—H) bands are not observed. The structure of these compounds was also proved by the infrared spectrum of the model compound — 2-phenyl-4-chloro--5-acetamido-3-oxo-2*H*-pyridazine in which the ν(N—H) band at $\tilde{\nu} = 3300\ cm^{-1}$ and the ν(C=O) bands at $\tilde{\nu} = 1670\ cm^{-1}$ and $\tilde{\nu} = 1720\ cm^{-1}$ are observed.

None of the compounds prepared reached the insecticidal, acaricidal, ovicidal, fungicidal, and herbicidal activity of the standards used.

Experimental

Infrared spectra of compounds prepared were recorded with a Specord IR 75 (Zeiss, Jena) instrument. The wavenumber calibration was checked against the spectrum of polystyrene. The spectra were recorded in tetrachloromethane and trichloromethane ($c \approx 0.04\ mol\ dm^{-3}$). Ultraviolet spectra were recorded with a Specord UV VIS (Zeiss, Jena) instrument using solution concentrations of 1×10^{-5}—$5 \times 10^{-5}\ mol\ dm^{-3}$ in methanol. ^1H NMR spectra were recorded with a Jeol FX-60 (60 MHz) instrument in trichloromethane using tetramethylsilane as an internal standard, ^{13}C NMR spectra with a Jeol FX-100 instrument (25 MHz) in deuteriotrichloromethane, mass spectra with an AEI MS 902 S instrument at 70 eV, ionization chamber temperature 105 °C. Pesticidal activity of compounds prepared was followed after the published methods [4—6].

Fungicidal activity was tested by both the *in vitro* and *in vivo* methods. Inherent activity was investigated by the glass slide method on spores of fungi *Sclerotinia fructicola* (WINT.) and by the Sharvell method using captan (3a,4,7,7a-tetrahydro-2-[(trichloromethyl)thio]-1*H*-isoindole-1,3(2*H*)-dione) as standard on *Aspergillus niger* TIEGH. and *Cladosporium cucumericum* ELL. *et* ARTH. Antipowdery mildew activity was followed

Table 2

Infrared, ultraviolet, and ^{1}H NMR spectral data of compounds prepared

Compound	$\tilde{\nu}$/cm^{-1}		λ_{max}/nm (log (ε/(m^2 mol^{-1})))				δ(S—H)/ppm
	ν(C=O)	ν(S—H)					
IV	1650	2585	230	(3.12),	255	(2.79),	3.95
			285	(2.72)			
V	1651	2585	234	(3.18),	262	(3.19),	3.96
			293	(2.96),	342	(2.79)	
VI	1652	2493	245	(3.18),	263	(3.15),	3.85
			300	(2.82),	325	(2.93)	
VII	1647	2584	231	(3.11),	248	(3.02),	3.91
			287	(2.78),	326	(2.76)	
VIII	1663	2585	230	(3.20),	263	(3.02),	3.86
			290	(2.91),	344	(2.76)	
IX	1663	2585	230	(3.22),	265	(3.04),	—
			290	(2.89),	340	(2.70)	
X	1662	2585	234	(3.18),	262	(3.19),	4.03
			293	(2.96),	342	(2.79)	
XI	1665	2492	224	(3.90),	253	(3.03),	4.16
			272	(2.99),	317	(2.90)	
XII	1663	2585	233	(3.18),	265	(3.24),	—
			292	(2.94),	342	(3.00)	
XIII	1665	2583	238	(3.16),	267	(3.16),	—
			295	(2.99),	349	(3.06)	
XIV	1665	2582	240	(3.22),	268	(3.19),	—
			296	(3.05),	351	(2.99)	
XV	1635	2520[a]	225	(3.10),	314	(2.78),	4.16
			357	(2.56)			
XVI	1647	2493	208	(3.02),	257	(3.11),	—
			302	(2.70),	349	(2.81)	

a) Additional band at $\tilde{\nu} = 2492\ \text{cm}^{-1}$.

on *Erysiphe graminis* (on the living plants of spring barley, sort Dunajský trh) using dinocap (2-(1-methylheptyl)-4,6-dinitrophenyl (*E*)-2-butenoate) as standard and on tomatoes (*Phytophtora infestans* DE BY) using mancozeb (a complex of manganese(II) and zinc(II) 1,2-ethanediylbis(carbamodithioate) as standard. Herbicidal activity was investigated by the preemergent (into the soil) and postemergent (to the leaf) application methods using testing objects: *Avena sativa* L., *Polygonum persicaria* L., *Fagopyrum sagitatum* L., and *Sinapis alba* L. Contact insecticidal activity was followed on *Musca domestica*, *Sitophylus granarius*, and *Aphis fabae* SCOP using fenitrothion (*O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate) as standard. Systemic insecticidal activity was followed on *Macrosiphoniella sanbornii* THEOB., on *Chrysanthenum indicum* using thiometon (*S*-[2-(ethylthio)ethyl] *O*,*O*-dimethyl phosphorodithioate) as standard. Acaricidal activity was followed on females *Tetranychus urticae* KOCH and ovicidal activity on

eggs of *Tetranychus urticae* KOCH using carbophenothion (*S*-[[(4-chlorophenyl)-thio]methyl] *O,O*-diethyl phosphorodithioate) as standard.

2-Phenyl-4-acetamido-5-chloro-3-oxo-2H-pyridazine (I)

A mixture of 2-phenyl-4-amino-5-chloro-3-oxo-2*H*-pyridazine (50 g) and acetyl chloride (200 cm^3) was stirred for 2 h under reflux. After cooling to 0 °C the excluded solid was filtered off, purified by crystallization from ethanol. Yield = 43 g (71.60 %), m.p. = 181.4 °C. For $C_{12}H_{10}ClN_3O_2$ (M_r = 263.67) w_i(calc.): 54.66 % C, 3.82 % H, 13.44 % Cl, 15.94 % N; w_i(found): 54.71 % C, 3.91 % H, 13.60 % Cl, 15.81 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 1660 ν(C═O), 1705 ν(C═O), CH_3CON. ^1H NMR spectrum ($CDCl_3$), δ/ppm: 3.64 (s, 3H, CH_3N), 7.60 (s, 1H, ═CH).

2-Phenyl-4-chloro-5-acetamido-3-oxo-2H-pyridazine (II)

Compound *II* was prepared after the method used by the synthesis of compound *I*. Yield = 45 g (75 %), m.p. = 174 °C. For $C_{12}H_{10}ClN_3O_2$ (M_r = 263.67) w_i(calc.): 13.44 % Cl, 15.94 % N; w_i(found): 13.71 % Cl, 15.90 % N.

2-Phenyl-4-diacetamido-5-chloro-3-oxo-2H-pyridazine (III)

A mixture of 2-phenyl-4-amino-5-chloro-3-oxo-2*H*-pyridazine (50 g) and acetic anhydride (600 cm^3) was stirred for 8 h under reflux. Acetic anhydride was distilled off under reduced pressure and to the residue toluene (150 cm^3) was added, refluxed with active charcoal and filtered off. After cooling the excluded crystalline compound was filtered off, and crystallized from ethanol. Yield = 41 g (59 %), m.p. = 104 °C. For $C_{14}H_{12}ClN_3O_3$ (M_r = 305.71) w_i(calc.): 55.0 % C, 3.95 % H, 11.60 % Cl, 13.75 % N; w_i(found): 55.16 % C, 4.03 % H, 11.72 % Cl, 13.81 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 1658 ν(C═O), 1700 ν(C═O), $(CH_3CO)_2N$. ^1H NMR spectrum ($CDCl_3$), δ/ppm: 3.80 (s, 6H, $(CH_3)_2N$), 7.68 (s, 1H, ═CH).

2-Substituted 4-alkoxy-5-chloro-3-oxo-2*H*-pyridazines and 2-substituted 4-chloro-5--alkoxy-3-oxo-2*H*-pyridazines were prepared according to [7].

2-R¹-4-alkoxy(alkylthio)-3-oxo-2H-pyridazine-5-thiols (IV—XIV) and 2-R¹-5-alkoxy(alkylthio)-3-oxo-2H-pyridazine-4-thiols (XV and XVI)

To a suspension of 2-R^1-4-alkoxy(alkylthio, acetamido)-5-chloro-3-oxo-2*H*-pyridazine (0.1 mol) and 2-R^1-5-alkoxy(alkylthio, acetamido)-4-chloro-3-oxo-2*H*-pyridazine, respectively, in methanol (100 cm^3) a methanolic solution (9.2 mass %) of sodium hydrogen sulfide (0.2 mol) was added with stirring. The temperature of the reaction mixture spontaneously reached 42 °C and stirring was continued for 4 h at 20—30 °C. Then, methanol was distilled off under reduced pressure and to the distilled residue water (120 cm^3) was added, and filtrate. The filtrate was acidified (pH = 1) by hydrochloric

acid. After cooling to 5 °C the excluded compound was filtered off and crystallized from cyclohexane or toluene. Analytical data of compounds *IV—XVI* are summarized in Table 1.

2-Phenyl-4-methoxy-5-acetylthio-3-oxo-2H-pyridazine (XVII)

A mixture of 2-phenyl-4-methoxy-3-oxo-2*H*-pyridazine-5-thiol (2.3 g) and acetic anhydride (25 cm^3) was refluxed for 5 h. Then, acetic anhydride was distilled off under reduced pressure and the residue crystallized from ethanol. Yield = 1.8 g (66 %), m.p. = 99—101 °C. For $C_{13}H_{12}O_3N_2S$ (M_r = 276.28) w_i(calc.): 10.13 % N, 11.60 % S; w_i(found): 10.11 % N, 11.64 % S. ^{1}H NMR spectrum ($CDCl_3$), δ/ppm: 2.61 (s, 3H, CH_3CO), 3.90 (s, 3H, CH_3O), 7.12—7.75 (m, 5H, C_6H_5), 8.17 (s, 1H, =CH). IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 1660 ν(C=O), 1720 ν(C=O), CH_3COS. UV spectrum (CH_3OH), λ/nm (log (ε/(m^2 mol^{-1}))): 217 (3.22), 260 (3.18), 335 (2.97). Mass spectrum: M_r ($M^{+\bullet}$) = 276.

5-Methylthiazolo[4,5-d]-2-phenyl-3-oxo-2H-pyridazine (XVIII)

A mixture of 2-phenyl-4-diacetamido-5-chloro-3-oxo-2*H*-pyridazine (15.2 g; 0.05 mol) and sodium hydrogen sulfide in methanol (61 g, 9.2 mass %) was stirred for 4 h at 20 °C and then for 2 h at 40 °C. After cooling methanol was distilled off under reduced pressure. To the residue water (100 cm^3) was added and after dissolution acidified (to pH = 1) by hydrochloric acid. The excluded solid was separated and purified by crystallization from toluene. Yield = 6.9 g (57 %), m.p. = 174.5 °C. For $C_{12}H_9N_3OS$ (M_r = 243.27) w_i(calc.): 59.24 % C, 3.73 % H, 17.27 % N, 13.18 % S; w_i(found): 59.41 % C, 3.90 % H, 17.62 % N, 13.37 % S. IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 1665 ν(C=O). UV spectrum (CH_3OH), λ/nm (log (ε/(m^2 mol^{-1}))): 310 (3.25), 220 (3.78), 212 (3.78). ^{1}H NMR spectrum ($CDCl_3$), δ/ppm: 2.80 (s, 3H, CH_3), 7.17—7.83 (m, 5H, C_6H_5), 8.28 (s, 1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ/ppm: 172.20 (CH_3C=N), 154.95 (C=O), 141.39 (C-4), 136.25 (C-1), 131.90 (C-5), 128.30 (C-3′, C-5′), 127.61 (C-4′), 125.80 (C-2′, 6′), 19.32 (CH_3—C). Mass spectrum: M_r ($M^{+\bullet}$) = 243.

5-Methylthiazolo[5,4-d]-2-phenyl-3-oxo-2H-pyridazine (XIX)

A mixture of 2-phenyl-4-chloro-5-acetamido-3-oxo-2*H*-pyridazine (13.1 g; 0.05 mol) and sodium hydrogen sulfide in methanol (47 g, 12.0 mass %) afforded under equal conditions as by the preparation of compound *XVIII* a white crystalline compound (yield = 7.5 g (62 %), m.p. = 141.0 °C). For $C_{12}H_9N_3OS$ (M_r = 243.27) w_i(calc.): 59.24 % C, 3.73 % H, 17.27 % N, 13.18 % S; w_i(found): 59.62 % C, 3.81 % H, 17.30 % N, 12.96 % S. IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 1670 ν(C=O). UV spectrum (CH_3OH), λ/nm (log (ε/(m^2 mol^{-1}))): 305 (2.75), 235 (sh), 217 (3.33). ^{1}H NMR spectrum ($CDCl_3$), δ/ppm:

2.98 (s, 3H, CH_3), 7.30—7.70 (m, 5H, C_6H_5), 8.56 (s, 1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ/ppm: 176.02 (CH_3C=N), 155.83 (C=O), 152.30 (C-4), 141.13 (C-1′), 133.41 (C-5), 128.56 (C-3′, 5′), 128.01 (C-4′), 125.96 (C-2′,6′), 19.92 (CH_3—C). Mass spectrum: M_r ($M^{+\bullet}$) = 243.

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