Synthesis, spectral properties, and pesticidal activity of 4,5-dichloro-2-R-3-oxo-2*H*-pyridazines

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A synthesis and infrared and ultraviolet spectra of 4,5-dichloro-2-R-3-oxo-2*H*-pyridazines are reported. All the compounds prepared were tested on inhibition of the cholinesterase activity but none of them reached the activity of the used standard. The fungicidal activity of all compounds was measurable or very high mainly against fungi *T. foetida*. In the test on the inhibition of the Hill reaction 2-cyclohexyl-4,5-dichloro-3-oxo-2*H*-pyridazine, 2-phenyl-4,5-dichloro-3-oxo-2*H*-pyridazine, and 2-(*m*-tolyl)-4,5-dichloro-3-oxo-2*H*-pyridazine showed 5—10 times higher herbicidal activity than the Pyramin standard.

Приведены метод синтеза и ИК и УФ спектры 4,5-дихлор-2-R-3-оксо-2*H*-пиридазинов. У всех полученных соединений была исследована способность ингибировать холинэстеразную активность, однако ни одно из них не достигало значений использованного стандарта. Фунгицидная активность всех соединений была измеряема или очень высока главным образом по отношению к грибкам *T. foetida*. В тесте по ингибированию реакции Хилла 2-циклогексил-4,5-дихлор-3-оксо-2*H*-пиридазин и 2-(*m*-толил)-4,5-дихлор-3-оксо-2*H*-пиридазин проявили 5—10-кратную гербицидную активность по сравнению с Пираминовым стандартом.

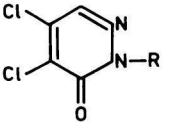
The studied 2-substituted 4,5-dichloro-3-oxo-2*H*-pyridazines are known as starting compounds for the preparation of pesticides [1—5]. One of the most used starting compounds is 4,5-dichloro-2-phenyl-3-oxo-2*H*-pyridazine affording with ammonia 5-amino-2-phenyl-4-chloro-3-oxo-2*H*-pyridazine which under the name Pyramin (Burex) belongs to the most used herbicides by cultivating of the sugar beet [6].

In the present paper a synthesis, spectral properties, and pesticidal activity of 2-substituted 4,5-dichloro-3-oxo-2*H*-pyridazine are described.

The i.r. spectra of the prepared compounds (Table 1) showed in the region $\tilde{\nu} = 1670—1700\ cm^{-1}$ very intense $\nu(C=O)$ bands of the pyridazine ring, the wavenumber being influenced by the substituents. The lowest wavenumbers of the $\nu(C=O)$ bands are observed in the spectra of compounds *XI*, *XII*, and *XIX*, which in the case of compounds *XII* and *XIX* can be explained by the presence of the intramolecular hydrogen bonding between the OH and C=O groups.

Table 1

Spectral data of compounds



Compound	R	IR $\tilde{\nu}/cm^{-1}$		UV λ_{max}/nm (log {ε})	
		$\tilde{\nu}(C=O)$	$\tilde{\nu}(C=N)$		
I	H	1700	1587	213.6 (4.55)	297.4 (3.78)
II	Cl	1711	1589	214.6 (4.48)	298.8 (3.75)
III	Br	1701	1590	213.0 (4.49)	297.7 (3.70)
IV	CH_3	1678	1588	215.9 (4.46)	300.0 (3.73)
V	C_2H_5	1673	1583	216.8 (4.45)	301.8 (3.77)
VI	C_3H_7	1675	1589	216.2 (4.50)	302.0 (3.77)
VII	$(CH_3)_2CH$	1674	1581	216.8 (4.44)	300.0 (3.77)
VIII	C_4H_9	1674	1583	217.7 (4.39)	302.0 (3.68)
IX	C_5H_{11}	1674	1587	216.7 (4.36)	301.8 (3.70)
X	C_6H_{13}	1674	1587	217.8 (4.42)	301.5 (3.71)
XI	C_6H_{11}(cyclo)	1671	1584	217.5 (4.58)	302.0 (3.80)
XII	CH_2OH	1671	1583	213.6 (4.46)	297.1 (3.69)
XIII	CH_2Cl	1697	1589	216.1 (4.44)	299.0 (3.82)

Table 1 (Continued)

Compound	R	IR $\tilde{\nu}$/cm^{-1}		UV λ_{max}/nm (log {ε})	
		$\tilde{\nu}$(C=O)	$\tilde{\nu}$(C=N)		
XIV	CH_2Br	1693	1589	216.1	303.8
		1686*	1591*	(4.32)	(3.78)
XV	CH_2OCH_3	1688	1612	216.0	297.4
				(4.53)	(3.80)
XVI	$CH_2OC_2H_5$	1686	1609	215.9	296.4
		1674*	1611*	(4.52)	(4.33)
XVII	$CH_2SC_2H_5$	1684	1589	213.4	305.0
				(4.25)	(4.09)
XVIII	$CH_2N(C_2H_5)_2$	1669	1585	216.0	300.2
				(4.39)	(4.18)
XIX	CH_2CH_2OH	1670	1589	216.4	303.7
				(4.43)	(3.77)
XX	$CH_2CH=CH_2$	1679	1588	216.6	308.6
				(4.61)	(3.91)
XXI	$CH_2C\equiv CH$	1684	1584	215.9	300.0
				(4.46)	(3.80)
XXII	C_6H_5	1688	1585	209.0	316.5
		1678*	1587*	(4.48)	(3.86)
XXIII	3-$CH_3C_6H_4$	1687	1583	206.1	317.7
				(4.50)	(3.84)
XXIV	3-ClC_6H_4	1687	1582	208.8	315.4
				(4.66)	(3.90)
XXV	3$CF_3C_6H_4$	1688	1586	204.0	313.9
		1681*	1588*	(4.49)	(3.88)
XXVI	4-$NO_2C_6H_4$	1693	1613	214.8	324.6
		1681*	1617*	(4.47)	(4.05)
XXVII	3-CF_3-4-ClC_6H_3	1690	1587	204.6	316.7
				(4.48)	(3.92)
XXVIII	$CH_2C_6H_5$	1676	1583	211.5	300.0
				(4.49)	(4.28)
XXIX	SO_2CH_3	1699	1586	213.9	294.5
				(4.38)	(3.73)

* Measured in chloroform.

Additional infrared bands: *I*: $\tilde{\nu}$(NH) = 3437 cm^{-1}; *XII*: $\tilde{\nu}$(O – H) = 3388 cm^{-1} and 3550 cm^{-1}; *XIX*: $\tilde{\nu}$(O – H) = 3480 cm^{-1} and 3616 cm^{-1}; *XXI*: $\tilde{\nu}$(HC≡C) = 3310 cm^{-1}; *XXVI*: $\tilde{\nu}_{as}(NO_2)$ = 1349 cm^{-1}, $\tilde{\nu}_s(NO_2)$ = 1530 cm^{-1}; *XXIX*: $\tilde{\nu}_s(SO_2)$ = 1192 cm^{-1}, $\tilde{\nu}_{as}(SO_2)$ = 1390 cm^{-1}.

Additional ultraviolet bands [λ_{max}/nm (log {ε})]: *XIII*: 251.0 (3.64); *XIV*: 252.5 (3.63); *XV*: 262.5 (3.85); *XVI*: 251.3 (4.27); *XVII*: 239.0 (4.26); *XVIII*: 232.0 (sh); *XXV*: 250.7 (3.75); *XXVI*: 267.9 (4.00); *XXVII*: 260.0 (3.80).

The highest wavenumbers of the $\nu(C=O)$ bands are observed in the spectra of compounds having electron-withdrawing groups (compounds *XIII*, *XIV*, *XXIV—XXVII*, and *XXIX*). The $\nu(C=N)$ bands are observed in the region $\tilde{\nu} = 1582—1612\ cm^{-1}$ and their wavenumbers are less influenced by substituents as compared with those of the $\nu(C=O)$ bands. In the spectrum of *I* the $\nu(N—H)$ band is at $3430\ cm^{-1}$ The $\nu(O—H)$ bands in the spectra of *XII* and *XIX* at $3388\ cm^{-1}$ and $3550\ cm^{-1}$ and at $3480\ cm^{-1}$ and $3612\ cm^{-1}$, respectively, indicate that the OH groups are involved in hydrogen bonding.

The u.v. spectra of investigated compounds (Table 1) showed two or three bands. The position of the bands at the shortest wavelengths ($\lambda = 204—217$ nm) is relatively little influenced by substituents. The bands at the longest wavelengths

Table 2

Characterization of the synthesized compounds

Compound	Formula	M_r	w_i(calc.)/w_i(found)		Yield	M.p./°C B.p./°C (p/Pa) n_D^{20}
			% N	% Cl	%	
VI	$C_7H_8Cl_2N_2O$	207.1	13.52	34.23	48.6	97 (53.2)
			13.57	34.29		1.5522
IX	$C_9H_{12}Cl_2N_2O$	235.1	11.91	30.16	29.8	126 (53.2)
			22.60	30.10		1.5380
X	$C_{20}H_{14}Cl_2N_2O$	249.1	11.24	28.46	51.4	120 (13.3)
			11.16	28.21		1.5320
XIV[a]	$C_5H_3BrCl_2N_2O$	257.9	10.86	27.49	95.1	75—76
			10.99	27.51		
XV	$C_6H_6Cl_2N_2O_2$	209.0	13.40	33.92	70.1	115—117
			13.29	34.17		
XVI	$C_7H_8Cl_2N_2O_2$	223.0	12.56	31.79	90.5	101—102
			12.88	31.99		
XVII[b]	$C_7H_8Cl_2N_2OS$	239.1	11.71	29.65	81.2	94—96
			12.01	29.73		
XX	$C_7H_6Cl_2N_2O$	205.1	13.66	34.57	89.9	46—48
			13.52	34.60		
XXI	$C_7H_4Cl_2N_2O$	203.0	13.80	34.93	59.0	83—85
			14.01	34.94		
XXVI	$C_{10}H_5Cl_2N_3O_3$	272.1	15.45	26.06	70.3	227—229
			15.49	26.31		
XXVII[c]	$C_{11}H_4Cl_3F_3N_2O$	343.5	8.15	30.97	66.4	115—116
			8.26	31.06		
XXIX[d]	$C_5H_4Cl_2N_2O_3S$	243.1	11.52	29.17	36.2	163—165
			11.60	28.98		

w_i(calc.)/w_i(found): *a*) 30.98/31.16 % Br; *b*)13.41/13.60 % S; *c*) 16.59/16.69 % F; *d*)13.19/ /13.31 % S.

are, excepting compounds having the phenyl group directly attached to the nitrogen atom of the pyridazine ring (compounds *XXII—XXVII*), in the region $\lambda = 296—308$ nm. A survey of novel compounds is given in Table 2.

Table 3

Relative fungicidal activity and IHR of 2-substituted 4,5-dichloro-3-oxo-2*H*-pyridazines

Compound	Relative fungicidal activity				IHR
	Tilletia foetida	*Botrytis cinerea*	*Fusarium avenaceum*	*Alternaria alternata*	
I	2	1	1	1	0.001
II	3	1	1	1	0.005
III	3	1	1	1	0.01
IV	2	1	1	1	0.001
V	2	1	1	1	0.001
VI	2	1	1	1	0.001
VII	2	1	1	1	0.05
VIII	2	1	1	1	0.5
IX	2	1	1	1	0.05
X	2	1	1	1	0.05
XI	2	1	1	1	10.0
XII	3	1	1	1	0.1
XIII	3	3	1	1	0.001
XIV	2	1	1	1	0.001
XV	2	1	1	1	0.01
XVI	2	1	1	1	0.01
XVII	2	1	1	1	0.05
XVIII	3	1	1	1	0.1
XIX	2	1	1	1	0.001
XX	3	1	1	1	0.05
XXI	2	1	1	1	0.01
XXII	2	1	1	1	5.0
XXIII	2	2	2	2	5.0
XXIV	1	1	1	1	0.05
XXV	2	2	2	2	0.1
XXVI	1	1	1	1	0.01
XXVII	2	2	2	1	0.1
XXVIII	2	1	1	1	0.5
XXIX	3	1	2	1	0.001
Standards:					
Vitavax	4	—	—	—	—
Euparen	—	4	—	—	—
MDR	—	—	4	—	—
Kaptan	—	—	—	4	—

IHR — inhibition of the Hill reaction, Pyramin standard (PCA) = 1.

By testing the compounds for the relative fungicidal activity (Table 3) by the method *in vitro* it was found that all compounds excepting *XXVI* were in tests against *T. foetida* active in the same order as the used standard but none was more active. In tests against *B. cinerea* only compound *XIII* reached the activity of the used standard, however, also compounds *XXIII*, *XXV*, and *XXVII* showed a relatively good activity. Compounds *XXIII*, *XXV*, *XXVI*, and *XXIX* against *F. avenaceum* and compounds *XXIII* and *XXV* against *A. alternata* were as active as the used standards, however, none of them was better.

In herbicidal tests (Table 3) excellently active was 2-cyclohexyl-4,5-dichloro-3-oxo-2*H*-pyridazine (*XI*), its activity was 10 times higher than that of the used standard. The activity of compounds 2-phenyl-4,5-dichloro-3-oxo-2*H*-pyridazine (*XXII*) and 2-(*m*-tolyl)-4,5-dichloro-3-oxo-2*H*-pyridazine (*XXIII*) was 5 times higher than that of the used standard.

Compounds were treated as 50 % wettable powders and treatment of specimens on suspension property and sedimentation satisfied a condition of ON 655711. By this treatment conditions of equal application form were determined (these compounds were slightly soluble in the form of emulsion concentrates) as with the used standard Pyramin. In these tests surprising results were obtained.

None of the compounds showed measurable herbicidal activity in used concentrations, the used standard showed in tests high herbicidal activity with preservation of selectivity on the sugar beet.

Summarizing, it can be stated that with 2,4,5-substituted 3-oxo-2*H*-pyridazine derivatives there is no linear relation between inhibition of the Hill reaction and activity on living plants. By studying the effect on inhibition of cholinesterase activity none of the compounds showed comparable activity to the used standard.

Experimental

The i.r. spectra of the prepared compounds were recorded with a Specord IR-75 instrument (Zeiss, Jena) in carbon tetrachloride ($c = 0.02$—0.06 mol dm^{-3}, cell thickness 0.275 mm), the u.v. spectra with a Specord UV VIS apparatus (Zeiss, Jena) in methanol ($c = 1 \times 10^{-4}$—2×10^{-5} mol dm^{-3}, cell thickness 1.00 cm).

4,5-Dichloro-3-oxo-2*H*-pyridazine *I* was prepared according to [1] by the reaction of mucochloric acid with hydrazine; 2,4,5-trichloro-3-oxo-2*H*-pyridazine *II* and 2-bromo-4,5-dichloro-3-oxo-2*H*-pyridazine *III* according to [7] by the reaction of *I* with chlorine or bromine in an aqueous solution of alkaline hydroxide; 4,5-dichloro-2-methyl-3-oxo-2*H*-pyridazine *IV* according to [3] by the reaction of *I* with dimethyl sulfate; 2-cyclohexyl- and 2-aryl-4,5-dichloro-3-oxo-2*H*-pyridazines (*XI*, *XXII*—*XXVII*) by the reaction of mucochloric acid with appropriate substituted hydrazine according to [2]; 4,5-dichloro-2-hydroxymethyl-3-oxo-2*H*-pyridazine *XII* according to [5] by the reaction of

I with an aqueous solution of formaldehyde; 4,5-dichloro-2-chloromethyl-3-oxo-2*H*-pyridazine *XIII* according to [5] by the reaction of *XII* with thionylchloride; 4,5-dichloro-2-(*N*,*N*-diethylaminomethyl)-3-oxo-2*H*-pyridazine *XVIII* according to [5] by the reaction of *I* with diethylamine and formaldehyde. Physicochemical constants of the prepared compounds agreed with the data in literature.

Fungicidal activity of the prepared compounds was examined by the method *in vitro* on spores of fungus: *Tilletia foetida, Botrytis cinerea, Fusarium avenaceum,* and *Alternaria alternata* according to the previously published methods [8]. The evaluation of the activity *a* was carried out according to the scale (*a*/%): 0—0, 1—25, 2—50, 3—75, and 4—100 using standards — Vitavax (2,3-dihydro-5-carboxanilido-6-methyl-1,4-oxathiin), Euparen (*N'*-dichlorofluoromethylthio-*N*,*N*-dimethyl-*N'*-phenylsulfamide), Kaptan (*cis*-*N*-[(trichloromethyl) thio]-4-cyclohexene-1,2-dicarboximide), and MDR (methylene rhodanide).

Herbicidal activity was investigated by the method *in vitro* on inhibition of the Hill reaction (IHR) [9]. The herbicidal effect was expressed as a relative activity a_r to Pyramin, the values of $a_r > 1$ and $a_r < 1$ stand for higher and lower activity, respectively, than that of Pyramin.

The most active compounds *XI*, *XXII*, and *XXIII* were tested on the living plants using a preemergence and postemergence application in doses 5.0 kg, 1.58 kg, 0.5 kg, and 0.158 kg of active compound per 1 ha [10]. In tests the following testing objects were used: *Avena fatua, Echinochloa cruss-galli, Panicum miliaceum, Fagopyrum vulgare, Sinapis alba, Lepidium sativum,* and *Beta vulgaris.* The evaluation of the activity was carried out according to the scale: 0 — normal plants, 1 — slightly attacked plants, 2 — significantly attacked plants (50 %), 3 — very attacked plants (75 %), 4 — heavy attacked plants (90 %), 5 — totally died plants (herbicidal activity = 100 %), N — not evaluated.

Insecticidal activity was investigated on inhibition of cholinesterase enzyme by the method *in vitro* according to the known method [11] using the standard Fenitrothion — *O*,*O*-dimethyl-*O*-(3-methyl-4-nitrophenyl) thiophosphate.

2-R-4,5-Dichloro-3-oxo-2H-pyridazines (R = alkyl, allyl, propargyl, benzyl, methanesulfonyl; V—X, XIX—XXI, XXVIII, and XXIX

To a potassium salt of 4,5-dichloro-3-oxo-2*H*-pyridazine (1.1 mol) in methyl ethyl ketone (800 cm^3), alkyl iodide, allyl bromide, propargyl bromide, benzyl bromide or methanesulfonyl chloride (1 mol) were added with stirring and the reaction mixture was mixed at reflux for 8 h. The excluded potassium halogenide was filtered off and from the filtrate methyl ethyl ketone was distilled off under reduced pressure. Then the residue was purified by distillation under reduced pressure or by crystallization from cyclohexane or heptane. Compound *XXIX* was purified by column chromatography on silicagel activated before use at 140 °C for 6 h using toluene with the addition of acetone (1—10 %) as eluent. The separation control was carried out by t.l.c. using the u.v. light ($\lambda = 254$ nm).

2-Bromomethyl-4,5-dichloro-3-oxo-2H-pyridazine (XIV)

To 4,5-dichloro-2-hydroxymethyl-3-oxo-2*H*-pyridazine (0.2 mol) in benzene (200 cm^3) phosphorus tribromide (0.1 mol) was added over 30 min with stirring. Stirring was con-

tinued 2 h at reflux. The benzene solution was decanted and dried with calcium chloride, benzene was distilled off under reduced pressure and the product purified by crystallization from toluene.

4,5-Dichloro-2-R-3-oxo-2H-pyridazines (R = methoxymethyl XV, ethoxymethyl XVI, ethylthiomethyl XVII)

To 4,5-dichloro-2-chloromethyl-3-oxo-2*H*-pyridazine (0.2 mol) in methanol or ethanol (200 cm^3), sodium methanolate in methanol sodium ethanolate or sodium ethanolate in ethanol were gradually added at 5—10 °C with stirring. Stirring was continued at 50 °C over 30 min. The excluded sodium chloride was filtered off and from filtrate alcohol was distilled off under reduced pressure. A distilled residue was dissolved in toluene (200 cm^3) washed with water, dried with anhydrous sodium sulfate and toluene distilled off under reduced pressure. The crude product was purified by crystallization from heptane.

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