Synthesis of 5-Hydroxy-2-hydroxymethyl-4*H*-pyran-4-one Derivatives with Pesticide Activity

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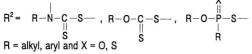
Synthesis of new 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (kojic acid) *via* reaction of its 2-halomethyl derivatives with salts of *N*,*N*-dialkyldithiocarbamic acid, *O*-alkyl esters, and *O*,*S*-dialkyl esters of dithiophosphoric acid is described. Biological screening of synthesized compounds was performed.

Many compounds active as bactericides and fungicides were prepared by substitution of hydroxyl group in position 7 of 4-pyranone skeleton [1—4]. Some organophosphorous compounds of kojic acid are active as insecticides and miticides [5].

Our paper deals with the preparation of compounds of the general formula

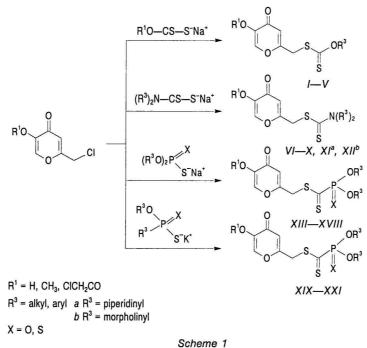


where $R^1 = H, CH_3, CICH_2CO$



These compounds were obtained by the reaction of 5-substituted 2-chloromethyl-4*H*-pyran-4-one derivatives with sodium salts of respective acids described in Experimental according to Scheme 1.

All synthesized compounds are characterized by elemental analysis and spectral methods. IR spectra of 4-pyranone derivatives (Table 1) exhibit characteristic absorption bands in the region $\tilde{v} = 1212$ —1275 cm⁻¹ (C—O—C) and a sharp band at $\tilde{v} = 1615$ —1720 cm⁻¹ (C—O), which in some derivatives is split. In the case of derivatives with hydroxyl group in position 5 (*I*—*V*, *IX*—*XIV*, *XVII*—*XXI*) absorption bands were observed at $\tilde{v} = 3410$ —3430 cm⁻¹ (OH). Ultraviolet spectra of title compounds displayed two absorption maxima: the first one at $\lambda = 216$ —222 nm, the second at $\lambda = 268$ —275 nm and derivatives



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ompounds

Compound	R ¹	R ²	Formula <i>M</i> r	w _l (calc.)/% w _i (found)/%			Yield	M.p.	M⁺
				S	Ν	Р	%	°C	m/z
1	Н	C(S)OCH ₃	C ₈ H ₈ O₄S₂ 232.3	27.61 27.30	-	_	62	108	232
П	н	$C(S)C_2H_5$	C₃H₁₀O₄S₂ 246.3	26.30 26.40	-	_	70	112	246
111	н	C(S)OC ₃ H ₇	C ₁₀ H ₁₂ O₄S ₂ 260.3	24.63 24.50	-	_	61	111	260
IV	н	C(S)OC ₄ H ₅ -i	C ₁₁ H ₁₄ O ₄ S ₂ 274.3	23.37 23.61	_	_	80	94	274
V	н	C(S)OCH ₂ CH=CH ₂	C ₁₀ H ₁₀ O₄S₃ 258.3	24.82 25.02	-	_	74	172	258
VI	н	C(S)N(CH ₃) ₂	C ₉ H ₁₁ NO₃S₂ 245.3	26.14 26.12	5.71 5.80	-	79	156	245
VII	CICH₂CO	C(S)N(CH ₃) ₂	C ₁₁ H ₁₂ CINO₄S₂ 321.8	19.93 20.26	4.35ª 4.50	_	69	182	322
VIII	CH3	C(S)N(CH ₃) ₂	C ₁₀ H ₁₃ NO ₃ S ₂ 259.3	24.72 25.06	5.40 5.50	_	71	188	259
IX	н	$C(S)N(C_2H_5)_2$	C ₁₁ H ₁₅ NO ₃ S ₂ 273.4	23.45 23.09	5.12 5.08	-	69	116	273
x	н	$C(S)N(C_2H_5)(C_4H_9)$	C ₁₆ H ₁₉ NO ₃ S ₂ 301.4	21.28 21.49	4.64 4.70	-	81	104	301
XI	н	C(S)piperidinyl	C ₁₅ H ₁₅ NO ₃ S ₂ 285.4	22.47 22.61	4.90 5.21	_	79	200 decomp.	285
XII	н	C(S)morpholinyl	C ₁₄ H ₁₃ NO ₄ S ₂ 287.4	22.31 22.60	4.90 4.80	_	74	190	287
XIII	н	P(S)(OCH ₃) ₂	C ₁₈ H ₁₁ O₅PS₂ 282.3	22.72 22.48	_	10.97 10.70	68	165	282
XIV	н	$P(S)(OC_2H_5)_2$	C ₁₀ H ₁₅ O₅PS₂ 310.5	20.66 20.86	_	9.98 10.20	71	109	310
xv	CH ₃	P(S)(OCH ₃) ₂	C ₉ H ₁₃ O₅PS₂ 296.3	21.64 21.39	_	10.45 10.38	67	visc. liq.	296
XVI	CH3	$P(S)(OC_2H_5)_2$	C ₁₁ H ₁₇ O ₅ PS ₂ 324.3	19.76 20.07	_	9.55 9.78	76	visc. liq.	324
XVII	н	$P(S)(OC_5H_{11})_2$	C ₁₆ H ₂₇ O₅PS ₂ 394.5	16.26 16.41	_	7.85 8.05	84	47	394
XVIII	н	$P(S)(OC_6H_5)_2$	C ₁₈ H ₁₅ O ₅ PS ₂ 406.4	15.72 16.08	-	7.62 7.78	80	124	406
XIX	н	$P(S)(C_2H_5)(OC_2H_5)$	C ₁₀ H ₁₅ O₄PS₂ 254.3	21.78 22.08		10.52 10.68	69	110	294
xx	н	$P(S)(SC_2H_5)(OC_2H_5)$	C ₁₀ H ₁₅ O ₅ PS ₂ 310.3	20.68 21.04	-	9.49 9.79	69	149	310
XXI	н	P(O)(OC ₂ H ₅)(OC ₃ H ₇ -i)	C ₁₁ H ₁₇ O ₆ PS 308.3	10.40 10.61	Ξ	10.04 10.28	72	visc. liq.	308

a) w_{CI} (calc.) 11.02 %, w_{CI} (found) 11.30 %.

VI—*XII* (Table 1) show a small shoulder at $\lambda = 245$ —253 nm. The absorption maximum at the longer wavelength has been assigned to the $\pi \leftarrow \pi^*$ and $n \leftarrow \pi$ electron transition in the 4-pyranone skeleton, respectively. For verification of the 4-pyranone molecule protons H-3 and H-6 in the ¹H NMR spectra are important. The individual signals were found in the region $\delta = 6.37$ —6.44 (s, 1H, H-3) and 8.00—8.06 (s, 1H, H-6).

The results of tests for pesticide activity confirmed that compounds VI and VII of the group of alkyl esters of dithiocarbamic acid showed an effect on *Alternaria* species comparable to Dithian M-45, which was used as standard. Compound XXI belonging to the group of esters of organophosphonic acid showed in testing for contact insecticide activity on *Macrosiphoniella sanbornii* the activity of the same order as the standard (Metation E-50). Tests for acaricidal activity of derivatives XV and XIX confirmed their lower activity in comparison with the standard (Akarition E-20). No measurable herbicidal activity was observed at all tested compounds.

EXPERIMENTAL

Kojic acid was commercial chemical (LIKO,

Bratislava), 2-chloromethyl derivative of kojic acid was prepared according to the Kipnis reaction [5], 5-methoxy-2-chloromethyl-4H-pyran-4-one according to [6]. The following starting salts of the respective acids were synthesized by the published procedures: potassium salts of O-dialkyldithiocarbonic acid [7], sodium salts of dithiocarbamic acid [8], sodium salts of O,O-dialkyl(diphenyl)dithiophosphoric acid [9], and sodium salts of O,O-dialkylthiophosphoric acid [10]. Melting points (not corrected) were measured on a Kofler hot stage. Samples for elemental analysis were dried over phosphorous pentaoxide (30-50 °C; 2 kPa) for 8-10 h. Reaction course and purity of compounds were monitored by thin-layer chromatography (Silufol UV₂₅₄ sheets, Kavalier, Votice) using the solvent system toluene—acetone ($\varphi_r = 7$: 3). IR spectra (KBr pellets) were taken on the spectrophotometer Specord 80 (Zeiss, Jena), ultraviolet spectra of metanolic solutions were recorded on spectrophotometer M 20 (Zeiss, Jena). ¹H NMR spectra (DMSO- d_6) were measured on the spectrometer model BS 487 (Tesla) with HMSDO as an internal standard, MS spectra were recorded on spectrometer MS 902 (AS Kratos) using all-glass heated inlet system with the temperature of an ion source 90-120 °C. Electron energy was 70 eV, trap current 100 µA.

Pesticide activity was tested according to the published procedure [11—13].

Disodium Salt of O-Ethyl-O-isopropylthiophosphoric Acid

To the solution of NaOH (16 g; 0.4 mol) in water (100 cm³) dioxane (100 cm³) was added and under the stirring *O*-ethyl-*O*-isopropylchlorothiophosphate (40.5 g; 0.2 mol), too. Reaction mixture was stirred for 5 h at 60 °C. Dioxane and water were removed from the reaction mixture by distillation under the reduced pressure. Toluene (200 cm³) was added to the rest and traces of water were removed by azeotropic distillation. The separated NaCl was filtered off, to the filtrate cyclohexane (60 cm³) was added, white crystalline substance was filtered off, washed with cyclohexane and dried *in vacuo.* Yield = 31.9 g (75.2 %).

Sodium Salt of Ethyl-S-ethyldithiophosphoric Acid

NaOH (8 g; 0.2 mol) dissolved in water (80 cm³) was added to the stirred solution of *O*-ethylchlorodithiophosphate (20.5 g; 0.01 mol) in dioxane (60 cm³). Reaction mixture was stirred for 5 h at the temperature 60 °C. Next procedure is the same as in the preparation of sodium salt of *O*-ethyl-*O*-isopropylthiophosphoric acid. Yield = 18.6 g (89.4 %).

Potassium Salt of Ethyl-O-ethyldithiophosphonic Acid

To the stirred mixture of *O*-ethyldithiophosphonic acid (17 g; 0.1 mol) in dry benzene (100 cm³) potassium ethoxylate (3.9 gramatom K, 80 cm³ ethanol) was added at the temperature 15 °C. Ethanol was removed by azeotropic distillation with benzene, the reaction mixture was cooled, and the filtered salt was dried under reduced pressure. Yield = 15.8 g (75.8 %).

Synthesis of the Compounds I-XXI

To the stirred solution of the alkaline salt of corresponding acid (0.04 mol) in 80 cm³ of solvent (acetone, ethyl methyl ketone, acetonitrile) 5-hydroxy-2-chloromethyl-4H-pyran-4-one or its substituted derivative was added at once. The reaction mixture was stirred for 8 h under reflux in the used solvent. The reaction course was monitored by thin-layer chromatography. The solvent was removed from the reaction mixture under reduced pressure and water (100 cm³) was added to the rest under intensive stirring. If the product was solid and not soluble in water, it was filtered off and recrystallized. In the case that the product was insoluble in water, but liquid, chloroform (80 cm³) was added to the aqueous layer and the mixture was thoroughly extracted. Chloroform layer was separated, washed with water and dried. Chloroform and rests of solvents were distilled off in vacuo and the product was definitely dried at 80 °C and 13.3 Pa.

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