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Synthesis of Some Biologically Active Derivatives of 2-Hydroxymethyl-5-hydroxy-4*H*-pyran-4-one
II.* Synthesis and Biological Properties of *S*-Substituted 2-Thiomethyl-5-*O*-acyl Derivatives

M. VEVERKA**

Institute of Biotechnology, Slovak Technical University, CS-812 37 Bratislava

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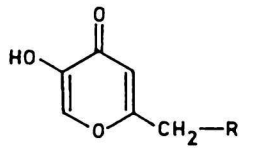
S-Substituted 2-thiomethyl-5-*O*-acyl-4*H*-pyran-4-ones were prepared by substituting bromine of 2-bromomethyl-5-hydroxy-4*H*-pyran-4-one by sulfur-containing nucleophiles and following acylation of the phenolic group. Products of this synthesis were active against bacteria and yeast and stimulate the growth of plants.

Kojic acid (2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one) reveals various pesticidal properties [1]. Our preceding paper concerned the preparation of a series of 5-*O*-acyl derivatives exhibiting interesting herbicidal and growth-regulating properties [2]. This paper presents a modification of the 2-hydroxymethyl group of some selected 5-*O*-acyl derivatives with the aim to investigate the change in transport properties in a biological system.

The substituted 2-thiomethyl-5-hydroxy-4*H*-pyran-4-ones (*I*; see formulas and Table 1) were obtained from 2-bromomethyl-5-hydroxy-4*H*-pyran-4-one (*Ia*) by displacement reaction with thiols [3—5]. Thus, 2-bromomethyl derivative *Ia* afforded on treatment with sodium salts of the respective thiols in an organic solvent (tetrahydrofuran, dimethylformamide) the corresponding sulfides *Ib—Ii*. Heteroaryl sulfides *Ij—In* were reacted in aqueous ethanol in the presence of potassium hydroxide. The 2-sulfomethyl derivative *Io* was synthesized from 2-bromomethyl derivative *Ia* and sodium sulfite.

Sommelet—Hauser rearrangement [6] is used for skeletal modification of 4*H*-pyran-4-one into 3-methylthiomethyl derivatives, but only 2-methylthiomethyl derivative *Ib* and unidentified tars instead of the expected compounds *IIIa*, *IIIb* were obtained when reacting 5-*O*-acylkojates with dimethyl sulfide.



I

R	
a	Br
b	CH_3S
c	$(CH_3)_2CHS$
d	$CH_3(CH_2)_2S$
e	$CH_3(CH_2)_4S$
f	$CH_3(CH_2)_7S$
g	$C_2H_5OCOCH_2S$
h	$HO(CH_2)_2S$
i	cyclohexylthio
j	2-methyl-1,3,4-thiadiazol-5-ylthio
k	2-benzimidazolylthio
l	2-benzthiazolylthio
m	2-pyridylthio
n	2-pyridylthio *N*-oxide
o	SO_3Na

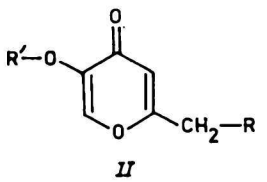
* For Part *I* see *Collect. Czechoslov. Chem. Commun. 55,* 833 (1990).

** *Present address:* Department of Inorganic Chemistry, Faculty of Chemical Technology, Slovak Technical University, CS-812 37 Bratislava.

Table 1. Characterization and ^{1}H NMR Spectral Data (δ) of the Substituted 2-Thiomethyl-5-hydroxy-4*H*-pyran-4-ones

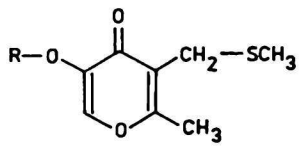
Compound	Formula M_r	Yield %	M.p. °C	H-3 (s)	H-6 (s)	CH_2 (s)	Other signals
Ib[a]	$C_7H_8O_3S$ 172.2	52	142—144	6.45	7.86	3.50	2.14 (s, 3H, CH_3)
Ic	$C_9H_{12}O_3S$ 200.2	75	72—74	6.44	8.01	3.71	1.27 (d, 6H, 2 x CH_3), 2.1 (q, 1H, CH)
Id	$C_9H_{12}O_3S$ 200.2	52	76—77	6.41	8.01	3.66	0.97 (t, 3H, CH_3), 1.04 (q, 2H, CH_2)
Ie	$C_{11}H_{16}O_3S$ 228.3	78	85—87	6.41	7.98	3.64	0.86 (t, 3H, CH_3), 1.32 (m, 4H, 2 x CH_2)
If	$C_{14}H_{22}O_3S$ 270.4	82	65—70	6.42	7.83	3.51	0.87 (t, 3H, CH_3), 1.25 (m, 12H, 6 x CH_2)
Ig	$C_{10}H_{12}O_5S$ 244.3	65	40—44	6.41	8.01	3.80	1.25 (t, 3H, CH_3), 3.39 (s, 2H, CH_2)
Ih	$C_8H_{10}O_4S$ 202.2	75	54—55	6.38	8.05	3.67	2.58 (t, 2H, CH_2), 3.51 (m, 2H, CH_2)
Ii	$C_{12}H_{16}O_3S$ 272.4	85	75—80	6.38	7.84	3.56	1.23—2.67 (m, 11H, cyclohexyl)
Ij	$C_9H_8N_2O_3S_2$ 256.3	75	128—130	6.52	8.01	4.51	2.74 (s, 3H, CH_3)
Ik	$C_{13}H_9N_2O_3S$ 273.3	75	103—104	6.58	7.96	4.58	7.20, 7.45 (q, 4H, H_{arom})
Il	$C_{13}H_9N_2O_3S_2$ 291.3	68	139—140	6.62	8.02	4.64	7.45—8.00 (m, 4H, H_{arom})
Im	$C_{11}H_9NO_3S$ 235.3	72	85—88	6.65	7.99	4.42	7.15—7.67 (m, 3H, H_{arom})
In	$C_{11}H_9NO_4S$ 251.3	78	225—228	6.55	8.05	4.29	7.23—8.36 (m, 4H, H_{arom})
Io	$C_6H_5O_6SNa \cdot 2H_2O$ 264.2	52	176—180	6.31	7.98	3.68	3.69 (bs, OH – exchangeable proton)

a) Mass spectrum, *m/z*: 172 (M^+).



II

	R	R´
a	$(CH_3)_2CHS$	2-CH_3-4-$ClC_6H_3OCH_2CO$
b	$(CH_3)_2CHS$	2,4-$Cl_2C_6H_3OCH_2CO$
c	$(CH_3)_2CHS$	Cl_2CHCO
d	$(CH_3)_2CHS$	2,3,6-$Cl_3C_6H_2CO$
e	$(CH_3)_2CHS$	2,4-$Cl_2C_6H_3OCH(CH_3)CO$
f	$CH_3(CH_2)_2S$	2-CH_3-4-$ClC_6H_3OCH_2CO$
g	$CH_3(CH_2)_2S$	2,4-$Cl_2C_6H_3OCH_2CO$
h	$CH_3(CH_2)_7S$	2-CH_3-4-$ClC_6H_3OCH_2CO$
i	$CH_3(CH_2)_7S$	2,4-$Cl_2C_6H_3OCH_2CO$
j	$C_2H_5OCOCH_2S$	2-CH_3-4-$ClC_6H_3OCH_2CO$
k	$C_2H_5OCOCH_2S$	2,4-$Cl_2C_6H_3OCH_2CO$
l	2-methyl-1,3,4-thiadiazol-5-ylthio	2-CH_3-4-$ClC_6H_3OCH_2CO$
m	2-pyridylthio	2-CH_3-4-$ClC_6H_3OCH_2CO$
n	2-pyridylthio	2,4-$Cl_2C_6H_3OCH(CH_3)CO$
o	H	2-CH_3-4-$ClC_6H_3OCH_2CO$
p	H	2,4-$Cl_2C_6H_3OCH_2CO$



III

	R
a	2-CH_3-4-$ClC_6H_3OCH_2CO$
b	2,4-$Cl_2C_6H_3OCH_2CO$

Phenolic group of sulfide derivatives was acylated with the appropriate acyl chlorides in acetone in the presence of triethylamine as a hydrogen chloride acceptor. Synthesis of substituted 2-thiomethyl-5-*O*-acyl-4*H*-pyran-4-ones *IIa—IIn* proceeded in high yields (Table 2). Dethio derivatives *IIo*, *IIp* were prepared from allomaltol by analogous procedure with the aim to examine the relation of the structure to biological effect.

Characteristic singlets of H-3 and H-6 protons in the ^{1}H NMR spectrum (Tables 1 and 2) were at δ = 6.31—6.65 and 7.78—8.48, respectively. A broader interval for signals of thiomethyl group at

δ = 3.42—4.64 is due to a different nature of substituents. Selected IR spectral data are in Table 3.

The antibacterial activity was tested against gram-positive and gram-negative strains (Table 4). Testing the selected substances against phytopathogenic moulds we obtained the following ID_{50}/(g mol^{-1}) values: *A. alternata: Id* 1.41 x 10^{-4}, *Ie* 1.78 x 10^{-4}, *If* 1.12 x 10^{-4}; *B. cinerea: Id* 7.08 x 10^{-5}, *Ie* 1.12 x 10^{-4}; *F. nivale: Id* 7.08 x 10^{-5}, *Ie* 7.08 x 10^{-5}, *If* 5.01 x 10^{-5}.

Derivatives *IIa—IIp* tested for herbicidal and growth-regulating effects by standard methods showed activity comparable with references

Table 2. Characterization and ^{1}H NMR Spectral Data (δ) of the Substituted 2-Thiomethyl-5-acyloxy-4*H*-pyran-4-ones

Compound	Formula M_r	Yield %	M.p. °C	H-3	H-6	CH_2	H_{arom}	Other signals
IIa	$C_{18}H_{19}ClO_5S$ 382.9	68	Solidifying oil	6.49	8.31	3.75	7.13—7.19 (m, 3H)	1.25 (d, 6H, 2 x CH_3), 2.31 (m, 1H, CH), 2.26 (s, 3H, CH_3)
IIb	$C_{17}H_{16}Cl_2O_5S$ 403.3	72	Solidifying oil	6.50	8.33	3.70	7.13—7.14 (m, 3H)	1.25 (d, 6H, 2 x CH_3), 2.28 (m, 1H, CH), 5.2 (s, 2H, CH_2)
IIc	$C_{11}H_{12}Cl_2O_4S$ 311.2	51	Solidifying oil	6.64	7.85	3.60		1.31 (d, 6H, 2 x CH_3), 2.11 (q, 1H, CH), 6.01 (s, 1H, CH)
IId	$C_{16}H_{13}Cl_3O_4S$ 407.7	85	74—77	6.56	8.48	3.78	7.61—7.79 (d, 2H)	1.34 (d, 6H, 2 x CH_3), 2.11 (m, 1H, CH)
IIe	$C_{18}H_{18}Cl_2O_5S$ 417.3	62	65—70	6.56	7.91	3.76	7.61—7.79 (d, 2H)	1.29 (d, 6H, 2 x CH_3), 1.73 (d, 3H, CH_3), 3.07 (q, 1H, CH)
IIf	$C_{18}H_{19}ClO_5S$ 382.9	65	69—71	6.48	8.33	3.72	7.14—7.19 (m, 3H)	0.98 (t, 3H, CH_3), 1.59 (m, 2H, CH_2), 2.26 (s, 3H, CH_3)
IIg	$C_{17}H_{16}Cl_2O_5S$ 403.3	75	Solidifying oil	6.50	8.33	3.72	7.01—8.01 (m, 3H)	0.97 (t, 3H, CH_3), 1.62 (m, 2H, CH_2), 5.21 (s, 2H, CH_2)
IIh	$C_{23}H_{29}ClO_5S$ 452.9	78	70	6.49	7.78	3.51	6.63—7.12 (m, 3H)	1.48—1.62 (m, 2H, CH_2), 0.88 (t, 3H, CH_3), 4.99 (s, 2H, CH_2)
IIi	$C_{21}H_{26}Cl_2O_5S$ 461.4	74	71—75	6.50	7.85	3.50	6.63—7.12 (m, 3H)	0.92 (t, 3H, CH_3), 1.48—1.62 (m, 14H, 7 x CH_2), 4.99 (s, 2H, CH_2)
IIj	$C_{19}H_{19}ClO_7S$ 426.9	59	60—65	6.48	8.32	3.84	7.19 (m, 3H)	1.24 (t, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.42 (s, 2H, CH_2), 4.14 (q, 2H, CH_2)
IIk	$C_{18}H_{16}Cl_2O_7S$ 447.3	61	Solidifying oil	6.49	8.34	3.42		1.24 (t, 3H, CH_3), 3.82 (s, 2H, CH_2), 4.15 (s, 2H, CH_2), 5.2 (s, 2H, CH_2)
III	$C_{18}H_{15}ClN_2O_5S$ 438.1	83	60—62	6.60	8.01	3.84		2.25 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 4.56 (s, 2H, CH_2)
IIm	$C_{20}H_{16}ClNO_5S$ 417.9	78	97—99	6.56	8.30	4.47	7.38—8.52 (m, 7H, H_{arom}, $H_{heteroarom}$)	2.24 (s, 3H, CH_3), 5.07 (s, 2H, CH_2)
IIn	$C_{20}H_{15}Cl_2NO_5S$ 452.3	78	90—95	6.52	7.99	4.42	7.00—7.99 (m, 7H, H_{arom}, $H_{heteroarom}$)	1.67 (d, 3H, CH_3), 4.95 (q, 1H, CH)
IIo	$C_{15}H_{13}ClO_5$ 308.7	82	110—113	6.31	8.24	–		2.26 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 5.08 (s, 2H, CH_2)
IIp	$C_{14}H_{10}Cl_2O_5$ 329.1	79	68—70	6.32	8.26	–		2.35 (s, 3H, CH_3), 5.20 (s, 2H, CH_2)

Table 3. Infrared Spectra ($\tilde{\nu}$/cm^{-1}) of Selected Compounds

Compound	ν(C=O)	ν(C=C)
Ic	1650	1610
Ig	1730, 1650	1625
Ij	1650	1610
Im	1655	1630
Io	1637	1618
IIg	1800, 1655	1625
IIi	1740, 1660	1605
IIk	1780, 1770, 1725	1640
III	1740, 1795	1625
IIm	1790, 1740	1630
IIn	1780, 1670	1630
IIp	1750, 1650	1610

MCPA (2-methyl-4-chlorophenoxyacetic acid) and Fluozifop-P ((2*R*)-(4-(5-trifluoromethyl-2-pyridyloxy)phenoxy)propionic acid) [7].

EXPERIMENTAL

The melting points are corrected, the ^{1}H and ^{13}C NMR spectra of deuterochloroform solutions of the prepared compounds containing tetramethylsilane as internal reference were measured with a Jeol IX-100 apparatus, the IR spectra were taken with a spectrophotometer PU 9800 FTIR (Philips Analytical) in KBr pellets and the mass spectra were run with an instrument 902 S (AEI, Manchester). Samples of products for analyses were dried over P_2O_5 at room temperature and pressure 60 Pa, others at room temperature in air. Solvents were removed by distillation under reduced pressure (2—2.5 kPa) at 25—30 °C. The reaction course was monitored by thin-layer chromatography on Silufol sheets (Kavalier, Votice) with detection by UV_{254} light or with iodine vapours. Silica gel (60—120 μm) in the carrier to substance ratio 30 : 1 was used for column chromatography. Deviation between the calculated and found values of analysis did not exceed 0.4 %.

Microdilution test with a binary dilution was employed for the basic antimicrobial and anti-yeast tests on a peptone culture medium at 37 °C with evaluation of turbidity after 24 h or on a Sabouraud soil at 24 °C with the evaluation after 48 h for bacteria and yeast, respectively. The inhibitory effect was judged on the basis of MIC exerting a 100 % inhibition against control. The fungicidal effect was estimated by a plate dilution method at cultivation temperatures 24 or 21 °C (*F. nivale*) on a 2 % glucose agar or 2 % malt wort agar (*F. nivale*). The curves were constructed from diameters of the growing colony. ID_{50} (concentration of a substance causing a 50 % inhibition against control) was estimated graphically [8]. The herbicidal effect after a pre-emergent application of a 5 % aqueous solution of the prepared derivatives on oat, millet, cress, and mustard seeds sown in rows in laboratory conditions (5 cm^3 of solution per 500 cm^2 of soil) was evaluated after 21 d employing the bonity grades 0—5 (0 = no effect, 5 = a total herbicidal effect).

Table 4. Antibacterial and Anti-yeast Activities (MIC/(mol dm^{-3}))

Microorganism	*Id*	*Ie*	*If*	*Ii*
B. subtilis	1×10^{-3}	2.5×10^{-4}	1.56×10^{-5}	–
S. subflava	5×10^{-4}	5×10^{-4}	6.3×10^{-5}	–
S. aureus	1×10^{-3}	2.5×10^{-4}	6.3×10^{-5}	–
E. coli	1×10^{-3}	1×10^{-3}	1×10^{-3}	–
P. mirabilis	1×10^{-3}	1×10^{-3}	1×10^{-3}	–
C. albicans	–	1.25×10^{-4}		1.25×10^{-4}

Nucleophilic Displacements of 2-Bromomethyl-5-hydroxy-4*H*-pyran-4-one by Alkanethiols or Heteroarenethiols

Method A. Stepwise, the respective thiol (14 mmol) and after a 10 min stirring 2-bromomethyl derivative *Ia* (13 mmol) were added to sodium hydride (0.34 g; 14 mmol) in anhydrous tetrahydrofuran (70 cm^3) or dimethylformamide (50 cm^3, derivatives *IIf*, *IIi*). The mixture was stirred till the starting *Ia* was consumed (6 to 12 h, monitored by thin-layer chromatography), acidified with acetic acid and the solvent was distilled off. The residue was washed with water and crystallized from benzene. This method was applied for compounds *Ic—Ii*.

Method B. Solution composed of 2-bromomethyl derivative *Ia* (5.1 g; 25 mmol), the respective thiol (25 mmol) and potassium hydroxide (1.9 g; 30 mmol) in ethanol (80 %, 120 cm^3) was refluxed for 6 h. The mixture was then acidified with acetic acid, the solvent was distilled off and the solid residue was washed with water and purified either by crystallization from 2-propyl alcohol or by chromatography on silica gel, chloroform—acetone (φ_r = 6 : 1) being the eluent. This method was applied for preparation of compounds *Ij—In*.

2-Methylthiomethyl-5-hydroxy-4*H*-pyran-4-one (*Ib*)

2-Bromomethyl-5-(2,4-dichlorophenoxyacetoxy)-4*H*-pyran-4-one (4.04 g; 10 mmol) in chloroform (10 cm^3) and dimethyl sulfide (5.7 g; 60 mmol) were stirred under nitrogen atmosphere at room temperature for 12 h. The suspension was filtered off and treated with sodium methoxide (0.3 g Na)

in methanol (25 cm^3). This mixture was refluxed for 2 h, acidified with dilute (φ_r = 1 : 1) hydrochloric acid, the solvent was removed and the residue was washed with ethyl acetate and recrystallized from benzene—cyclohexane (φ_r = 2 : 1).

Sodium Salt of 2-Sulfomethyl-5-hydroxy-4*H*-pyran-4-one (*Io*)

Sodium sulfite (1.4 g; 11 mmol), *Ia* (2.05 g; 10 mmol), and water (7 cm^3) were heated till the solution became clear. The crude product, separating on standing in a refrigerator, was filtered off, washed with ether to remove the yellow colouration and crystallized from ethanol—water (φ_r = 5 : 1).

Acylation of Substituted 2-Thiomethyl-5-hydroxy-4*H*-pyran-4-ones

The respective acyl chloride (20 mmol) was added successively to a mixture of substituted 2-thiomethyl-5-hydroxy-4*H*-pyran-4-one or allomaltol (17 mmol) and triethylamine (2.8 cm^3, 20 mmol) in acetone (100 cm^3) at 5—10 °C. The mixture was stirred at room temperature for 2 h, the solid was filtered off, the filtrate was concentrated and the crude product *II* was either crystallized from benzene or chromatographed on silica gel, chloroform—acetone being the eluent (φ_r = 6 : 1).

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