SYNTHESIS OF SOME BIOLOGICALLY ACTIVE DERIVATIVES OF 2-HYDROXYMETHYL-5-HYDROXY-4*H*-PYRAN-4-ONE

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Received April 24, 1989
Accepted August 24, 1989

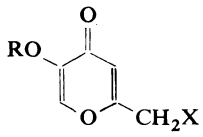
Depending on reaction conditions, acylation of the phenolic and primary alcoholic group in 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one leads to mono- or disubstituted products. Also described is acylation of the phenolic group in 2-chloromethyl- or 2-bromomethyl-5-hydroxy-4*H*-pyran-4-one as well as the nucleophilic replacement of the halogen by azide group. The prepared derivatives exhibit herbicidal and growth regulatory activity.

One of the possible ways in the search for more selective and safer pesticides consists in preparation of modified traditional structures by partial synthesis from natural material. 2-Hydroxymethyl-5-hydroxy-4*H*-pyran-4-one (kojic acid) and its derivatives exhibit pesticidal activities[1] and they undergo an easy microbial degradation to nontoxic products[2]. In the present study we modified the phenolic and primary alcoholic group in 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one and its derivatives by bonding to herbicidally active residues of carboxylic acids in order to improve transport properties of the desired structures in the plant system.

Depending on the conditions, treatment of 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one with reactive derivatives of carboxylic acids affords monoacyl or diacyl derivatives. Reaction with benzoyl chloride or acetic anhydride in an excess of pyridine leads to acylation of both groups[3]. Benzoylation in the presence of a small excess of aqueous alkali affords the 5-O-benzoyl derivative whereas with large excess of the alkali the reaction gives the 5,7-dibenzoyl derivative[3]. The 7-O-monoacetate was prepared by treatment of the 5,7-O-diacetate with aluminium chloride[4] or by reaction with hydroxylamine hydrochloride in pyridine[3]. Benzoylation in the absence of a hydrogen chloride acceptor results in formation of the 5-O-benzoyl derivative[5]. Selective benzoylations are described by Poonia[6].

In our work, the phenolic group of the title compound and its 2-halogenomethyl and 2-azidomethyl derivatives was acylated with acyl chlorides in aqueous acetone in the presence of sodium hydroxide, or in acetone with triethylamine as the base (*I*–*IV*). The yields of these reactions are given in Table I. Further, we tried to prepare derivatives *I*–*IV* under conditions described in the literature[5] (in the absence

of base). Whereas at room temperature the reaction of 2-hydroxymethyl-5-hydroxy--4*H*-pyran-4-one with 2-methyl-4-chlorophenoxyacetyl chloride in toluene did not proceed at all, at reflux both the phenolic and primary alcoholic groups were acylated (compound *V*).



I—*V*

I	X	R
a	OH	CH_3CH_2OCOCO
b	OH	$(CH_3)CCO$
c	OH	2,4-$Cl_2C_6H_3CO$
d	OH	2-naphthoxyacetyl
e	OH	2-CH_3,4-$ClC_6H_3OCH_2CO$
f	OH	2,4-$Cl_2C_6H_3OCH_2CO$
g	OH	2-CH_3,4-$ClC_6H_3OCH(CH_3)CO$
h	OH	2,4-$Cl_2C_6H_3OCH(CH_3)CO$
i	OH	2,3,6-$Cl_3C_6H_2CO$
j	OH	$CH_3(CH_2)_{14}CO$
k	OH	Cl_2CHCO

II	X	R
a	Cl	2,4-$Cl_2C_6H_3CO$
b	Cl	2-naphthoxyacetyl
c	Cl	2-CH_3,4-$ClC_6H_3OCH_2CO$
d	Cl	2,4-$Cl_2C_6H_3OCH_2CO$
e	Cl	2-CH_3,4-$ClC_6H_3OCH(CH_3)CO$
f	Cl	2,4-$Cl_2C_6H_3OCH(CH_3)CO$
g	Cl	$CH_3(CH_2)_{14}CO$
h	Cl	Cl_2CHCO

III	X	R
a	Br	2,4-$Cl_2C_6H_3CO$
b	Br	2-naphthoxyacetyl
c	Br	2-CH_3,4-$ClC_6H_3OCH_2CO$
d	Br	2,4-$Cl_2C_6H_3OCH_2CO$

IV	X	R
a	N_3	2-CH_3,4-$ClC_6H_3OCH_2CO$
b	N_3	2,4-$Cl_2C_6H_3OCH_2CO$
c	N_3	Cl_2CHCO

V, X = R = 2-CH_3,4-$ClC_6H_3OCH_2CO$

The nucleophilic substitution of the halogen with sodium azide in N,N-dimethylformamide took place irrespective whether 2-bromomethyl-5-hydroxy-4*H*-pyran-4--one or its 5-O-acyl derivatives *IV* were used as substrates.

The UV spectra of the prepared derivatives exhibit two strong absorption maxima in the regions 215–216 nm and 255–293 nm, corresponding to the respective $\pi \rightarrow \pi^*$ and $n - \pi^*$ transitions in the γ-pyron ring. The IR spectra display characteristic bands of the ν(C=O) vibrations in the region 1 780–1 650 cm^{-1} and of the ν(C=C) vibrations at 1 600–1 490 cm^{-1}. Characteristic singlets of the H-3 and H-6 protons in the ^{1}H NMR spectrum were found at 6·47–6·85 and 7·81–8·70 ppm. The broad interval for the H-6 proton signal is caused by the different character of substituents in position 5.

TABLE I

2-Hydroxymethyl-5-hydroxy-4*H*-pyran-4-one derivatives *I*– *V*

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found		
			% C	% H	% Cl
Ia	$C_{10}H_{10}O_7$ (242·2)	90–91 76	49·59 49·85	4·16 4·09	– –
Ib	$C_{11}H_{14}O_5$ (226·2)	81–84 69	58·4 57·69	6·24 6·15	– –
Ic	$C_{13}H_8Cl_2O_5$ (315·1)	176 68	49·55 49·26	2·56 2·44	22·50 22·17
Id	$C_{18}H_{14}O_6$ (326·3)	154–157 57	66·27 65·92	4·32 4·07	– –
Ie	$C_{15}H_{13}ClO_6$ (324·7)	135–138 85	55·48 55·12	4·04 4·54	10·92 11·25
If	$C_{14}H_{10}Cl_2O_6$ (345·1)	125–127 90	48·72 48·42	2·92 2·83	20·54 20·59
Ig	$C_{16}H_{15}ClO_6$ (338·7)	109–114 85	56·73 56·23	4·46 4·27	10·47 10·12
Ih	$C_{15}H_{12}Cl_2O_6$ (359·2)	77–81 79	50·16 49·82	3·37 3·13	19·74 19·27
Ii	$C_{13}H_7Cl_3O_5$ (349·6)	157–158 82	44·67 44·52	2·02 1·99	30·43 30·24
Ij	$C_{22}H_{36}O_5$ (380·5)	67–70 62	69·44 69·16	9·54 9·39	– –
Hk	$C_8H_6Cl_2O_5$ (253·0)	107–109 51	37·97 37·66	2·39 1·81	28·02 27·85
IIa	$C_{13}H_7Cl_3O_4$ (333·6)	103–108 72	46·81 46·44	2·12 2·08	31·89 31·35
IIb	$C_{18}H_{13}ClO_5$ (344·8)	132 43	62·71 62·13	3·80 3·57	10·28 9·98
IIc	$C_{15}H_{12}Cl_2O_5$ (343·2)	66–71 64	52·50 52·39	3·52 3·42	20·66 20·81
IId	$C_{14}H_9Cl_3O_5$ (363·6)	92–96 75	46·25 46·46	2·50 2·58	29·25 29·11
IIe	$C_{16}H_{24}ClO_5$ (357·2)	129–133 81	53·80 53·31	3·95 3·84	19·85 19·47
IIf	$C_{15}H_{11}Cl_3O_5$ (377·6)	76 74	47·71 47·18	2·94 2·73	28·17 27·88

TABLE I
(*Continued*)

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found		
			% C	% H	% Cl
IIg	$C_{22}H_{35}ClO_4$ (399·0)	46—48 66	66·23 66·06	8·84 8·72	8·89 8·78
IIh	$C_8H_5Cl_3O_4$ (271·5)	105—107 49	35·39 35·03	1·86 1·78	39·18 38·88
IIIa	$C_{13}H_7BrCl_2O_4$ (378·0)	96 72	41·31 41·27	1·87 1·83	18·76 18·14
IIIb	$C_{18}H_{13}BrO_5$[a] (389·2)	127—132 49	55·49 54·97	3·37 3·13	— —
IIIc	$C_{15}H_{12}BrClO_5$ (387·6)	82—85 72	46·48 46·70	3·12 3·92	9·15 9·07
IIId	$C_{14}H_9BrCl_2O_5$ (408·0)	85—90 76	41·21 41·17	2·22 2·21	17·38 17·11
IVa	$C_{15}H_{12}ClN_3O_5$[b] (349·8)	95—98 76	51·52 51·49	3·46 3·79	10·14 10·03
IVb	$C_{14}H_9Cl_2N_3O_5$[c] (370·1)	87—92 70	45·43 45·48	2·45 2·49	19·16 19·15
IVc	$C_8H_5Cl_2N_3O_4$[d] (278·1)	158 82	34·56 34·33	1·81 1·72	25·50 25·14
V	$C_{24}H_{20}Cl_2O_8$ (507·3)	80—83 65	56·82 56·66	3·97 3·81	13·98 13·82

[a] % Br: calculated 20·53, found 20·01; [b] % N: calculated 12·02, found 11·91; [c] % N: calculated 11·35, found 11·28; [d] % N: calculated 15·11, found 14·97.

The synthesized derivatives *I*—*V* were tested as potential herbicides and plant growth regulators. The plant growth regulatory activity was determined[7] on subapical segments of wheat seed coleoptiles; at the chosen concentration of the tested compound (75 mg/l), the following inhibition % (related to the coleoptile segment elongation in the control after cultivation) and increase % (related to the coleoptile segment length prior to cultivation), using IAA (β-indolylacetic acid) as the positive control (37·5% and 38·4%, respectively), were found: *Id* 42·5, 40·1; *Ie* 71·3, 51·2; *If* 78·6, 42·1; *Ih* 75·5, 42·2; *Ii* 81·3, 56·4; *IIb* 28·7, 36·1; *IIc* 40·7, 39·5; *IId* 68·8, 41·2; *IIId* 72·8, 38·6.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Proton NMR spectra (Table II) were obtained with a BS 487 C TESLA instrument (80 MHz) in hexadeuteriodimethyl sulfoxide with hexamethyldisiloxane as internal standard. Infrared spectra (Table III) were recorded on a Specord 71 IR spectrometer (Carl Zeiss, Jena) by the KBr technique. Ultraviolet spectra (Table III) were measured in 10^{-4} mol l^{-1} solutions in the Mc Ilvain buffer (pH 4) on a Specord UV VIS instrument (Carl Zeiss, Jena) at room temperature. Samples of the obtained compounds were dried over phosphorus pentoxide at room temperature and 60 Pa or by simple exposure to air at room temperature. The extracts were dried over sodium sulfate and concentrated at 40–45°C under diminished pressure (2–2·5 kPa) on a rotatory evaporator. Thin-layer chromatography (TLC) was performed on Silufol sheets (Kavalier, Czechoslovakia) and spots were detected by UV light (254 nm). Column chromatography was carried out on silica gel (60–120 μm) using 30 g of the sorbent per 1 g of compound.

Acylation of 2-Hydroxymethyl-5-hydroxy-4*H*-pyran-4-one and its 2-Halogenomethyl or 2-Azidomethyl Derivatives

A) The corresponding acyl chloride (17 mmol) was gradually added at 5–10°C to a solution of 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one or its 2-chloromethyl, 2-bromomethyl or 2-azido derivative (17 mmol) and sodium hydroxide (0·8 g, 20 mmol) in a mixture of acetone and water (50 ml, 3 : 1). The reaction mixture was stirred at room temperature for 2 h, the acetone was evaporated and the residue was extracted with ethyl acetate. The combined extracts were dried over sodium sulfate, the solvent was evaporated and the crude product was crystallized from benzene.

This method was employed for the preparation of compounds *Ia*, *Ib*, *If–Ik*, *IId–IIh*, *IIId* and *IVa–IVc*.

B) The corresponding acyl chloride (20 mmol) was gradually added at 5–10°C to a solution of 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one or its 2-chloromethyl or 2-bromomethyl derivative (17 mmol) and triethylamine (2·8 ml, 20 mmol) in acetone (100 ml). The reaction mixture was stirred for 2 h at room temperature, filtered and the filtrate was concentrated. The crude product was purified by crystallization from benzene or by column chromatography on silica gel in chloroform–acetone (6 : 1).

This procedure was used in the preparation of compounds *Ic–Ie*, *IIa–IIc* and *IIIa–IIIc*.

2-Azidomethyl-5-(2-methyl-4-chlorophenoxyacetoxy)-4*H*-pyran-4-one (*IVa*)

Sodium azide (0·36 g, 5·5 mmol) was added to a solution of 2-bromomethyl-5-(2-methyl-4-chlorophenoxyacetoxy)-4*H*-pyran-4-one (*IIIc*; 1·94 g, 5 mmol) in N,N-dimethylformamide (10 ml). After stirring for 3·5 h, the mixture was poured into water (70 ml) and the separated oil was extracted with ethyl acetate. The solvent was evaporated and the product was purified by column chromatography on silica gel in acetone–chloroform (1 : 10).

Compound *IVb* was prepared analogously from compound *IIId*.

2-(2-Methyl-4-chlorophenoxyacetoxymethyl)-5-(2-methyl-4-chlorophenoxyacetoxy)-4*H*-pyran-4-one (*V*)

A mixture of 2-methyl-4-chlorophenoxyacetyl chloride (2·39 g, 10 mmol), 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one (0·71 g, 5 mmol) and toluene (20 ml) was refluxed for 1·5 h. The solvent was distilled off and the crude product was crystallized from benzene–cyclohexane (2 : 1).

TABLE II

^{1}H NMR spectra of compounds *I*— *V*, in ppm (δ-scale), coupling constants in Hz

Compound	H-3 (s)	H-6 (s)	CH_2 (s)	H-arom.	Other signals
Ia	6·57	7·88	5·10		4·29 q, 2 H (CH_2, J = 7·2); 1·38 t, 3 H (CH_3, J = 7·2)
Ib	6·49	7·81	4·44		1·33 s, 9 H (CH_3)
Ic	6·49	8·57	5·13	8·03 s, 7·76 d, 7·59 d[c]	
Id	6·52	8·04	5·06	8·25—7·37[a]	5·18 s, 2 H (CH_2)
Ie	6·49	8·25	4·49	7·24 s, 7·14 d, 7·05 d[b]	5·06 s, 2 H (CH_2); 2·20 s, 3 H (CH_3)
If	6·47	8·55	4·39	7·60 d, 7·35 d, 7·28 s[c]	5·27 s, 2 H (CH_2)
Ig	6·75	8·07	4·95	7·20 s, 7·11 d, 7·01 d[b]	4·95 q, 1 H (CH, J = 6·6); 2·17 s, 3 H (CH_3) 1·72 d, 3 H (CH_3, J = 6·6)
Ih	6·48	8·02	4·48	7·48 d, 7·36 d, 7·28 s[c]	4·92 q, 1 H (CH, J = 6·6); 1·72 d, 3 H (CH_3, J = 6, 6)
Ii	6·53	8·47	4·52	7·54 d, 7·15 d[d]	
Ij	6·45	8·19	4·48		3·38 t, 2 H (CH_2, J = 6·1), 2·97—1·30 m, 26 H (CH_2); 0·83 t, 3 H (CH_3, J = 6·8)
Ik	6·70	8·06	5·25		6·56 s, 1 H (CH)
IIa	6·73	8·70	4·71	8·04 s, 7·79 d, 7·62 d[c]	

IIb	6·72	8·08	4·69	8·23–7·32[a]	4·95 s, 2 H (CH_2)
IIc	6·74	8·65	4·73	7·25 s, 7·14 d, 7·05 d[b]	5·15 s, 2 H (CH_2); 2·20 s, 3 H (CH_3)
IId	6·75	8·65	4·73	7·44 e, 7·35 d, 7·28 s[c]	5·28 s, 2 H (CH_2)
IIe	6·85	8·08	4·75	7·24 s, 7·14 d, 6·92 d[b]	5·09 q, 1 H (CH, J = 6·6); 2·19 s, 3 H (CH_3); 1·79 d, 3 H (CH_3, J = 6·6);
IIf	6·60	8·07	4·62	7·45 d, 7·32 d, 7·24 s[c]	5·03 q, 1 H (CH, J = 6·6); 1·69 d, 3 H (CH_3, J = 6·6)
IIg	6·66	8·48	4·69		3·40 t, 2 H (CH_2, J = 6·1); 2·50–1·25 m, 26 H (CH_2); 0·84 t, 3 H (CH_3, J = 6·8)
IIh	6·70	8·06	5·25		6·56 s, 1 H (CH)
IIIa	6·71	8·69	4·69	8·02 s, 7·78 d, 7·61 d[c]	
IIIb	6·58	8·04	4·59	8·25–7·32[a]	4·92 s, 2 H (CH_2)
IIIc	6·75	8·64	4·73	7·24 s, 7·14 d, 7·05 d[c]	5·11 s, 2 H (CH_2); 2·21 s, 3 H (CH_3)
IIId	6·75	8·65	4·73	7·61 d, 7·32 d, 7·28 s[c]	5·28 s, 2 H (CH_2)
IVa	6·48	8·04	4·42	7·17 s, 7·12 d, 6·89 d[b]	4·76 s, 2 H (CH_2); 2·21 s, 3 H (CH_3)
IVb	6·59	8·05	4·62	7·48 d, 7·32 d, 7·24 s[c]	4·88 s, 2 H (CH_2)
IVc	6·60	8·08	4·63		6·48 s, 1 H (CH)
V	6·49	7·99	4·74	7·17 s, 7·09 d, 6·81 d[b]	5·90 s, 2 H (CH_2); 4·90 s, 2 H (CH_2) 2·20 s, 3 H (CH_3); 2·18 s, 3 H (CH_3)

[a] m, 7 H (H-arom.); [b] $J(5', 6')$ = 9·0; [c] $J(5', 6')$ = 8·8; [d] $J(4', 5')$ = 8·8.

TABLE III

Infrared (wavenumbers in cm^{-1}) and ultraviolet (λ_{max}, nm; log ε, $m^2\ mol^{-1}$) spectra of selected compounds

Compound	ν(C=O)		ν(C=C)		log ε	λ_{max}	log ε
Ib	1 768	1 750	1 600	255	4·04	215	3·50
	1 657						
Id	1 778	1 652	1 595	275	3·68	226	3·86
If	1 741	1 653	1 589	280	3·79	225	3·54
Ii	1 770	1 652	1 490	255	4·10	216	3·53
Ik	1 765	1 652	1 595	268	3·90	226	3·70
IIb	1 748	1 653	1 600	275	4·04	226	4·12
IId	1 789	1 653	1 593	272	3·84	221	3·84
IIIb	1 725	1 653	1 590	293	4·00	225	4·15
IIId	1 788	1 654	1 580	280	4·06	223	4·00

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Translated by M. Tichý.