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Preparation of 5-Substituted 4-Oxo-4*H*-pyran-2-carbaldehydes and Their Condensation Reactions

[a]J. BRANSOVÁ, [b]M. UHER, and [a]J. BRTKO

[a]*Institute of Experimental Endocrinology, Slovak Academy of Sciences, SK-833 06 Bratislava*

[b]*Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, SK-812 37 Bratislava*

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Primary alcohol group oxidation in position 2 of kojic acid molecule (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one) to the corresponding aldehyde is described and a number of condensation reactions of 5-substituted kojic acid aldehyde (comenic aldehyde) with different agents is given.

5-Substituted 4-oxo-4*H*-pyran-2-carbaldehydes have been prepared *via* several alternative routes. *Becker* [1, 2] carried out the oxidation of hydroxymethyl group of kojic acid methyl ether by MnO_2 in benzene and in dioxane; *Thomas* [3] used $CHCl_3$ and authors in [4] 2-methyl-2-propanol as the solvent.

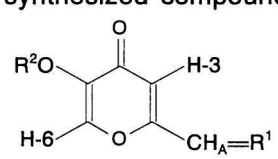
Condensation of *N*-alkylpyridinium salts with *p*-nitrosodimethylaniline (Kröhnke reaction) and following hydrolysis of arising intermediate was used for the synthesis of 5-methoxy-4-oxo-4*H*-pyran-2-carbaldehyde [5].

Since MnO_2 oxidations lead to yields of 5-substituted comenic aldehydes up to 20 %, the present paper describes use of SeO_2 in xylene for this purpose.

The reactivity of aldehydes prepared by this method was studied in condensation reactions with malonic acid and its derivatives, hydroxylamine, phenylhydrazine, thiosemicarbazide, and some aromatic amines (Table 1, *III*—*XV*).

While reactions with hydroxylamine or *o*-phenylenediamine proceeded in ethanol without catalysts, the other condensations required special conditions.

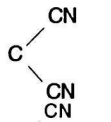
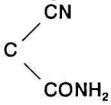
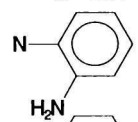
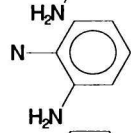
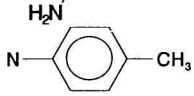
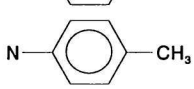
Structures of synthesized compounds



were determined and confirmed by the elemental and the spectral analysis. In selected compounds the confirmation of the structure was also supported by mass spectral analysis data.

IR spectra of the above synthesized kojic acid derivatives yielded stretching vibrations as follows: ν(C=O) intense band in the $\tilde{\nu}$ region 1620—1710 cm^{-1}, ν(C—O—C) at $\tilde{\nu}$ = 1190—1310 cm^{-1}, ν(C=C) intense bands at $\tilde{\nu}$ = 1480—1590 cm^{-1}. Derivative *IV* (Table 1) exerted a bright band of stretching vibrations ν(CN) at $\tilde{\nu}$ = 2220 cm^{-1}. Stretching vi-

Table 1. Characteristic Data of Synthesized Compounds

Compound	R^1	R^2	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	S	Yield %	M.p. °C
III	CH—COOH	$C_6H_5CH_2$	$C_{15}H_{12}O_5$ 272.26	66.17 66.10	4.41 4.53	– –	– –	71	182—183
IV		$C_6H_5CH_2$	$C_{16}H_{10}N_2O_3$ 278.27	69.06 69.30	3.59 3.30	10.07 10.10	– –	63	195—197
V		$C_6H_5CH_2$	$C_{16}H_{12}N_2O_4$ 296.28	64.86 65.00	4.05 4.01	9.45 9.49	– –	70	198—199
VI	N—NH—C_6H_5	$C_6H_5CH_2$	$C_{19}H_{16}N_2O_3$ 320.35	71.23 71.25	5.03 5.05	8.74 8.72	– –	71	186—188
VII	N—OH	$C_6H_5CH_2$	$C_{13}H_{11}NO_4$ 245.23	63.67 63.52	4.48 4.30	5.71 5.80	– –	64	163—164
VIII	N—OH	CH_3	$C_7H_7NO_4$ 169.14	49.72 49.75	4.17 4.15	8.28 8.31	– –	62	160—161
IX		$C_6H_5CH_2$	$C_{19}H_{16}N_2O_3$ 320.35	71.25 71.40	5.00 4.90	8.75 8.90	– –	68	203—205
X		CH_3	$C_{13}H_{12}N_2O_3$ 244.25	63.93 63.69	4.90 4.94	11.47 11.80	– –	62	139—141
XI		$C_6H_5CH_2$	$C_{20}H_{17}NO_3$ 319.36	75.23 75.40	5.32 5.15	4.39 4.50	– –	46	123—125
XII		CH_3	$C_{14}H_{13}NO_3$ 243.26	69.13 69.40	5.35 5.21	5.76 5.60	– –	32	128—130
XIII	N—C_6H_5	$C_6H_5CH_2$	$C_{19}H_{15}NO_3$ 305.33	74.75 74.60	4.92 5.00	4.59 4.32	– –	38	141—142
XIV	N—NH—CS—NH_2	$C_6H_5CH_2$	$C_{14}H_{13}N_3O_3S$ 303.34	55.44 55.20	4.29 4.40	13.86 13.60	10.56 10.20	65	199—201
XV	N—NH—CS—NH_2	CH_3	$C_8H_9N_3O_3S$ 227.24	42.27 42.30	3.99 4.00	18.48 18.46	14.10 14.15	60	243—245

brations ν(NH) were observed at $\tilde{\nu}$ = 3350—3390 cm^{-1} for derivatives *IX, X, XIV, XV* (Table 1).

UV spectra of synthesized derivatives showed two dominant absorption maxima in the region of 216—243 nm and 264—298 nm, belonging to $\pi^* \leftarrow \pi$ or $\pi^* \leftarrow n$ transfer in the composition of γ-pyranone ring. A significant bathochromic shift to a higher wavelength band in the condensation derivatives of 5-benzyloxy-4-oxo-4*H*-pyran-2-carbaldehyde was shown. This is due to an increased conjugation of the molecule. The conjugation increases from the compound *IIa* (λ_{max}/nm 264, log {ε} 3.82) to the compound *V* (292, 3.01) and next to the compound *IV* (298, 3.25).

All the synthesized derivatives possess characteristic singlet proton signals in positions 3 and 6 of γ-pyrone ring approximately at δ = 6.50—7.06 and 7.92—8.65, respectively (Table 2). ^{1}H NMR spectra of derivative *III* prove *trans* conformation of the double bond. Coupling constant *J* = 15 Hz.

Selected kojic acid derivatives (*IIa, IIb, III, IV, V, VII*) were screened for their biological properties, *i.e.* herbicidal, antifungal as well as growth-regulation activity. No herbicidal effect of these derivatives was confirmed. Antifungal activity was tested both *in vitro* and *in vivo*, by employing an agar diffusion test and on testing pair (pathogen—host) in the greenhouse. The antifungal activity of 5-benzyloxy- and 5-methoxy-4-oxo-4*H*-pyran-2-carbaldehydes (*IIa, IIb*, Table 1) when tested *in vitro*, on *Phytophthora infestans* was found (data not presented).

EXPERIMENTAL

Infrared spectra were recorded on a Specord M 80 (Zeiss, Jena) instrument using the KBr technique. UV spectra were measured on a Specord M 40 (Zeiss, Jena) spectrometer in methanol at concentration 1×10^{-4} mol dm^{-3}. ^{1}H NMR spectra were taken on a Tesla BS 587 A spectrometer (80 MHz) in DMSO-d_6 using tetramethylsilane as internal standard. Mass spectra were measured on an MS 902-S (AEI Manchester) model; direct inlet, ionizing electron energy 70 eV, electron current 100 μA, ion source temperature 110—170 °C.

Table 2. ^{1}H NMR Spectra of the Prepared Compounds

Compound	δ				
	H-3	H-6	H_A	R^2	R^1
IIa	7.03 (s)	8.15 (s)	9.75 (s)	7.41 (s, Ph), 5.12 (s, CH_2)	–
IIb	6.97 (s)	8.06 (s)	9.73 (s)	3.76 (s, CH_3)	–
IIc	7.06 (s)	8.65 (s)	9.56 (s)	7.42 (d), 7.80 (d, C_6H_4), 3.26 (s, CH_3)	–
IId	6.50 (s)	8.10 (s)	9.35 (s)	3.34 (s, CH_3)	–
III	6.60 (s)	8.06 (s)	6.42 (d)	7.26 (s, Ph), 4.80 (s, CH_2)	10.60 (s, COOH), 7.13 (d, H_B)
IV	6.85 (s)	8.25 (s)	8.43 (s)	7.35 (s, Ph), 4.96 (s, CH_2)	–
V	6.90 (s)	8.43 (s)	7.85 (s)	7.37 (s, Ph), 4.97 (s, CH_2)	8.00 (bs, NH_2)
VI	6.53 (s)	7.94 (s)	7.56 (s)	5.10 (s, CH_2)[a]	2.87 (s, NH)[a]
VII	6.50 (s)	7.92 (s)	7.90 (s)	7.32 (s, Ph), 4.90 (s, CH_2)	9.26 (s, OH)
VIII	6.50 (s)	8.03 (s)	7.95 (s)	3.38 (s, CH_3)	9.21 (s, OH)
IX	6.81 (s)	8.18 (s)	7.67 (s)	5.12 (s, CH_2)[b]	2.81 (bs, NH_2)[b]
X	6.75 (s)	8.20 (s)	7.80 (s)	3.25 (s, CH_3)	7.20—7.55 (m, 4H, C_6H_4), 2.79 (bs, NH_2)
XI	6.87 (s)	8.37 (s)	8.07 (s)	5.11 (s, CH_2)[c]	2.35 (s, CH_3)[c]
XII	6.81 (s)	8.20 (s)	7.95 (s)	3.20 (s, CH_3)	7.23 (d), 7.48 (d, C_6H_4), 2.37 (s, CH_3)
XIII	6.71 (s)	8.22 (s)	7.77 (s)	4.90 (s, CH_2)[d]	[d]
XIV	6.85 (s)	8.06 (s)	7.74 (s)	3.63 (s, CH_3)	–
XV	6.95 (s)	8.00 (s)	7.90 (s)	7.40 (s, Ph), 5.20 (s, CH_2)	–

a) 7.23—7.41 (m, 10H, C_6H_5 + C_6H_5); *b*) 6.97—7.53 (m, 9H, C_6H_5 + C_6H_4); *c*) 7.25—7.41 (m, 9H, C_6H_5 + C_6H_4); *d*) 6.95—7.47 (m, 10H, C_6H_5 + C_6H_5).

Herbicidal, antifungal, and growth-regulation activities were tested as described in the literature [6—8].

5-Substituted kojic acid derivatives *Ia—Id* were prepared according to the literature as follows: 5-benzyloxy-2-hydroxymethyl-4*H*-pyran-4-one (*Ia*) [9], 5-methoxy-2-hydroxymethyl-4*H*-pyran-4-one (*Ib*) [10], 2-hydroxymethyl-5-(4-methylphenylsulfonyl)-oxy-4*H*-pyran-4-one (*Ic*) [11], 5-acetoxy-2-hydroxymethyl-4*H*-pyran-4-one (*Id*) [12].

5-Substituted 4-Oxo-4*H*-pyran-2-carbaldehyde Derivatives *IIa—IId*

Mixture of *Ia—Id* (0.015 mol) and SeO_2 (0.023 mol) in xylene (75 cm^3) was refluxed for 2 h, then cooled, filtered and the solvent evaporated. Raw product was crystallized from CCl_4 or benzene.

3-(5-Benzyloxy-4-oxo-4*H*-pyran-2-yl)propenoic Acid (*III*)

Pyridine solution (50 cm^3) containing malonic acid (0.004 mol), *IIa* (0.004 mol), and Dowex 1X2-100 (1.5 g) was stirred at room temperature for 48 h. After filtration pyridine was distilled off and the raw product was crystallized from ethanol.

2-(5-Benzyloxy-4-oxo-4*H*-pyran-2-ylmethylene)-propanedinitrile (*IV*)

Reaction mixture containing glycine (0.0004 mol), malonodinitrile (0.015 mol), *IIa* (0.004 mol), and 0.5 cm^3 of acetic acid in 50 cm^3 of absolute ethanol was refluxed for 2 h, then cooled to room temperature and stirred for additional 4 h. Solid particles of the product were filtered off and crystallized from ethyl acetate.

2-Cyano-3-(5-benzyloxy-4-oxo-4*H*-pyran-2-yl)-propenamide (*V*) and 5-benzyloxy-4-oxo-4*H*-pyran-2-carbaldehyde phenylhydrazone (*VI*) were prepared by analogous method.

VI: Mass spectrum, *m/z* (I_r/%): 320($M^{+\bullet}$) (30), 243 (30), 213 (55), 93 (25), 91 (100).

5-Benzyloxy-4-oxo-4*H*-pyran-2-carbaldehyde Oxime (*VII*)

IIa (0.002 mol) was added to hydroxylamine (0.015 mol) in 100 cm^3 of absolute ethanol and stirred at room temperature for 1 h. After removal of a solvent, filtration and crystallization from ethanol gave *VII*.

5-Methoxy-4-oxo-4*H*-pyran-2-carbaldehyde oxime (*VIII*) was prepared by the same method from *IIb*.

VIII: Mass spectrum, *m/z* (I_r/%): 169($M^{+\bullet}$) (100), 152 (16), 151 (24), 139 (18), 124 (16), 95 (71), 44 (10).

2-(2-Aminophenyliminomethyl)-5-benzyloxy-4*H*-pyran-4-one (*IX*)

IIa (0.002 mol) was dissolved at a minimal volume of dry ethanol. Then *o*-phenylenediamine (0.005 mol) in 10 cm^3 of dry ethanol was added and the reaction mixture was stirred for 30 min. Coloured

precipitate was filtered and crystallized from ethanol—benzene (φ_r = 1 : 1) mixture to obtain pure *IX*.

2-(2-Aminophenyliminomethyl)-5-methoxy-4*H*-pyran-4-one (*X*) was prepared by the similar method as *IX*.

2-(4-Methylphenyliminomethyl)-5-benzyloxy-4*H*-pyran-4-one (*XI*)

IIa (0.004 mol) was added to a solution of *p*-toluidine (0.005 mol) in 10 cm^3 of acetic acid. The mixture was stirred at room temperature for 1 h, then mixed with $CHCl_3$ and washed with Na_2CO_3. Organic layer of the mixture was dried in Na_2SO_4. Crystallization of the residue from ethyl acetate gave *XI*.

2-(4-Methylphenyliminomethyl)-5-methoxy-4*H*-pyran-4-one (*XII*) and 2-(phenyliminomethyl)-5-benzyloxy-4*H*-pyran-4-one (*XIII*) were prepared by the similar method as *XI*.

5-Benzyloxy-4-oxo-4*H*-pyran-2-carbaldehyde Thiosemicarbazone (*XIV*)

Solution of *IIa* (0.002 mol), thiosemicarbazide (0.005 mol), and sodium acetate (0.009 mol) in absolute ethanol was refluxed for 15 min, after cooling it a solid substance was recovered by filtration and crystallized from ethanol—benzene (φ_r = 1 : 1) mixture to give *XIV*.

5-Methoxy-4-oxo-4*H*-pyran-2-carbaldehyde thiosemicarbazone (*XV*) was prepared from *IIb* by the same method as *XIV*.

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