Preparation and Study of Reactions of the 5-Substituted 4-Oxo-4*H*-pyran-2-carboxylic Acid

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The paper presents a study of oxidations of the primary alcohol group in position 2 of 5-substituted 4-oxo-4*H*-pyran ring. Some reactions of created carboxylic acids were investigated as well.

Previous papers described creation of 5-hydroxy-4-oxo-4*H*-pyran-2-carboxylic acid (comenic acid) during isolation of opium alkaloids [1], or by using of *Arthrobacter ureofaciens* K-I [2] or by oxidation of primary alcohol group or aldehyde in position 2 of γ-pyranone ring by different oxidation agents.

Preparation of 5-hydroxy-4-oxo-4*H*-pyran-2-carboxylic acid by oxidation of free 5-hydroxy-2-hydroxymethyl-4-oxo-4*H*-pyran in the stream of oxygen in the presence of palladium as catalyst was performed [3, 4].

Oxidation of 5-substituted 2-hydroxymethyl-4-oxo-4*H*-pyran was carried out according to the literature procedures [5—8].

Preparation of 5-hydroxy-4-oxo-4*H*-pyran-2-carboxylic acid by oxidation of appropriate aldehyde with Ag_2O as oxidation reagent [9] was described by *Becker* [10] in 1961 and *Looker* and *Shaneyfelt* [11] in 1962.

Some 5-benzyloxy derivatives of 5-hydroxy-4-oxo-4*H*-pyran-2-carboxylic acid can advantageously be used for preparation of cephemcarboxylates as antibiotic analogues [12]. *Jakopčic et al.* [13] observed a new nonphotochemical ring contraction of 5-hydroxy-4-oxo-4*H*-pyran-2-carboxylic acid methyl ester. Since hydroxypyran compounds have been reported to possess antimicrobial activity, *Kalyanam et al.* [14] synthesized 4,5-dihydropyran-2-carboxylic acid from 5-benzyloxy-4-oxo-4*H*-pyran-2-carboxylic acid which was obtained from 5-benzyloxy-2-hydroxymethyl-4-oxo-4*H*-pyran.

Garkusha and *Kutornenko* described preparation of some comenic acid esters but in relatively low yields [15].

This paper describes preparation of 5-methyl- and 5-benzyl-substituted comenic acid by several oxidation methods and preparation of some comenic esters and amides (Scheme 1).

Use of the Jones reagent was proved as the most efficient method for obtaining comenic acid (Table 1).

Structures of synthesized compounds were determined and confirmed by the elemental and the spectral analysis.

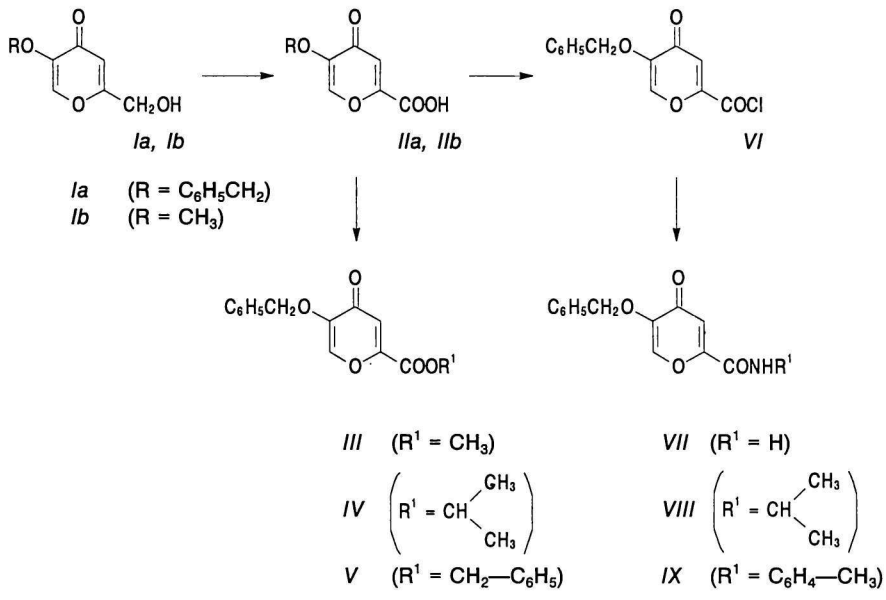
IR spectra of the prepared derivatives showed stretching vibrations as follows: ν(C=O) intense band in the $\tilde{\nu}$ region 1630—1740 cm^{-1}, ν(C—O—C) at $\tilde{\nu}$ = 1210—1310 cm^{-1}, ν(C=C) intense bands at $\tilde{\nu}$ = 1490—1580 cm^{-1}. The oxidation of the hydroxymethyl group resulted in appearing of a new band at $\tilde{\nu}$ = 1740 cm^{-1} belonging to ν(C=O) of created carboxylic acid. Stretching vibrations ν(OH) were observed at $\tilde{\nu}$ = 3340 cm^{-1} and 3380 cm^{-1} for derivatives *IIa*, *IIb* (Table 1). Vibrations at $\tilde{\nu}$ = 3320 cm^{-1} belong to ν(NH) with derivatives *VII—IX* (Table 1).

UV spectra of the prepared derivatives showed two dominant absorption maxima in the λ_{max} region 220—280 nm, belonging to $\pi^* \leftarrow \pi$ transfer in the composition of γ-pyranone ring. A significant bathochromic shift to a higher wavelength band in the oxidation derivative of 5-benzyloxy-2-hydroxymethyl-4-oxo-4*H*-pyran was shown. The conjugation increases from the compound *Ia* (λ_{max}/nm 214, 263; log {ε} 4.22, 3.97) to the compound *IIa* (λ_{max}/nm 230, 281; log {ε} 4.30, 3.14).

All the synthesized derivatives possess characteristic singlet proton signals in positions 3 and 6 of γ-pyrone ring approximately at δ = 6.87—7.15 and 7.87—8.48, respectively (Table 2).

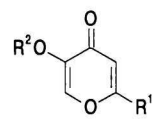
EXPERIMENTAL

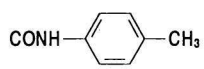
Infrared spectra were recorded on a Specord M 80 (Zeiss, Jena) instrument using the KBr technique. UV spectra were measured on a Specord M 40



Scheme 1

Table 1. Characteristic Data of Synthesized Compounds



Compound	R^1	R^2	Formula M_r	w_i(calc.)/% w_i(found)/% C	 H	Yield %	M.p. °C
IIa	COOH	$C_6H_5CH_2$	$C_{13}H_{10}O_5$ 246.2	63.42 63.40	4.09 4.08	23 (*A*) 45 (*B*) 61 (*C*) 18 (*D*)	187—190 188—189 189—191 190—192
IIb	COOH	CH_3	$C_7H_6O_5$ 170.1	49.42 49.54	3.55 3.50	31	280—281
III	$COOCH_3$	$C_6H_5CH_2$	$C_{14}H_{12}O_5$ 260.2	64.62 64.40	4.62 4.80	46	177—180
IV	COOPr-i	$C_6H_5CH_2$	$C_{16}H_{16}O_5$ 288.3	66.66 66.40	5.55 5.71	44	146—148
V	$COOCH_2Ph$	$C_6H_5CH_2$	$C_{20}H_{16}O_5$ 336.3	71.43 71.60	4.76 4.50	38	163—166
VI	COCl	$C_6H_5CH_2$	$C_{13}H_9ClO_4$ 264.7	58.86 59.00	3.39[a] 3.15	45	108—110
VII	$CONH_2$	$C_6H_5CH_2$	$C_{13}H_{11}NO_4$ 245.2	63.67 63.80	4.48[b] 4.32	38	159—160
VIII	CONHPr-i	$C_6H_5CH_2$	$C_{16}H_{17}NO_4$ 287.3	66.89 67.00	5.92[c] 5.72	40	162—164
IX		$C_6H_5CH_2$	$C_{20}H_{17}NO_4$ 335.4	71.63 71.42	5.11[d] 5.22	42	280—282

a)w_{Cl}(calc.)/%: 13.38, w_{Cl}(found)/%: 13.49; *b*)w_N(calc.)/%: 5.71, w_N(found)/%: 5.63; *c*)w_N(calc.)/%: 4.87, w_N(found)/%: 4.60; *d*)w_N(calc.)/%: 4.17, w_N(found)/%: 4.21.

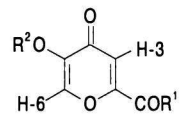
(Zeiss, Jena) spectrometer in methanol at the concentration 1×10^{-4} mol dm^{-3}. ^1H NMR spectra were taken on a Tesla BS 587 A spectrometer (80 MHz) in DMSO-d_6 using tetramethylsilane as internal standard.

5-Substituted kojic acid derivatives 5-benzyloxy-2-hydroxymethyl-4*H*-pyran-4-one (*Ia*) and 5-methoxy-2-hydroxymethyl-4*H*-pyran-4-one (*Ib*) were prepared according to the literature [16] and [17], respectively.

5-Benzyloxy-4-oxo-4*H*-pyran-2-carboxylic Acid (*IIa*)

Method A: Mixture of *Ia* (0.01 mol) and $KMnO_4$ (0.07 mol) in water (47 cm^3) was temperated on

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



Compound	δ			
	H-3	H-6	R^2	R^1
IIa	7.08 (s)	8.15 (s)	7.50 (s, Ph), 5.15 (s, CH_2)	10.95 (s, OH)
IIb	7.05 (s)	8.20 (s)	3.50 (s, CH_3)	10.85 (s, OH)
III	7.02 (s)	8.15 (s)	7.37 (s, Ph), 5.00 (s, CH_2)	3.65 (s, CH_3)
IV	6.92 (s)	7.87 (s)	7.18 (s, Ph), 4.81 (s, CH_2)	5.21 (m, CH), 1.28 (d, CH_3 + CH_3)
V	7.15 (s)	8.12 (s)	4.95 (s, CH_2)[a]	5.15 (s, CH_2)[a]
VI	7.00 (s)	8.13 (s)	7.40 (s, Ph), 5.13 (s, CH_2)	–
VII	6.90 (s)	8.48 (s)	7.26 (s, Ph), 4.50 (s, CH_2)	6.70 (bs, NH_2)
VIII	6.87 (s)	7.88 (s)	7.38 (s, Ph), 5.04 (s, CH_2)	5.28 (m, CH), 1.18 (d, CH_3 + CH_3)
IX	7.10 (s)	8.21 (s)	7.40 (s, Ph), 5.10 (s, CH_2)	6.94 (d), 7.18 (d, C_6H_4), 2.40 (s, CH_3)

a) 7.30—7.57 (m, 10H, C_6H_5 + C_6H_5).

water bath until the colour of the solution was changed. MnO_2 precipitate was filtered off. The filtrate was concentrated and mixed with HCl (2 cm^3) and the raw product crystallized from water.

Method B (Sarett reagent): *Ia* (0.006 mol) in pyridine (15 cm^3) was allowed to stand for 24 h after mixing with CrO_3 (0.024 mol) in pyridine (10 cm^3). Then 50 cm^3 of water was added, acidified and extracted with diethyl ether. Extract was evaporated and the raw product crystallized from petroleum ether.

Method C (Jones reagent): *Ia* (0.006 mol) was dissolved in minimum of dry acetone. Then oxidation reagent was dropped in [18], until developing of orange-brown colour (θ < 30 °C). The mixture was allowed to stand for 30 min at ambient temperature, then it was extracted with diethyl ether and after evaporating of the solvent the raw material was crystallized from ethanol.

Method D: Mixture of *Ia* (0.043 mol), MnO_2 (0.6 mol) [19], and CrO_3 (0.25 mol) in water (1000 cm^3) was stirred for 2 h at 60 °C. After extraction with diethyl ether and evaporation of the solvent, the raw product was crystallized from ethanol.

5-Methoxy-4-oxo-4*H*-pyran-2-carboxylic Acid (*IIb*)

Mixture of *Ib* (0.019 mol), HNO_3 (15 cm^3, ρ = 1.41 g cm^{-3}), and HNO_3 (3 cm^3, ρ = 1.52 g cm^{-3}) was allowed to stand for 70—80 h at ambient temperature. Reaction mixture was then mixed with 18 g of ice in 90 cm^3 of H_2O and filtered on Büchner funnel. Raw product was crystallized from ethanol.

Methyl 5-Benzyloxy-4-oxo-4*H*-pyran-2-carboxylate (*III*)

Solution of *IIa* (0.04 mol) in a mixture of concentrated H_2SO_4 (4 cm^3) and absolute methanol (3 cm^3) was stirred for 2 h at laboratory temperature, then it was mixed with water and extracted with diethyl ether. Product after evaporation was crystallized from chloroform.

Isopropyl 5-benzyloxy-4-oxo-4*H*-pyran-2-carboxylate (*IV*) was prepared by analogous method.

Benzyl 5-Benzyloxy-4-oxo-4*H*-pyran-2-carboxylate (*V*)

IIa (1 mol) was added to benzyl alcohol (1.75 mol), *p*-toluenesulfonic acid (0.02 mol), and benzene (350 cm^3). Water was removed by azeotropic distillation, catalyst from the reaction mixture was removed by rinsing with $NaHCO_3$ solution. Raw product after solvent evaporation was crystallized from chloroform.

5-Benzyloxy-4-oxo-4*H*-pyran-2-carbonyl Chloride (*VI*)

Mixture of *IIa* (0.1 mol) and PCl_5 (0.2 mol) was temperated for 1.5 h at 110 °C. $POCl_3$ was distilled off and the remaining product was isolated by vacuum distillation at 110 °C (2 kPa), or the mixture was dissolved in absolute diethyl ether and separated by column chromatography on Al_2O_3 [20]. The chloride can be used directly in additional reactions.

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

10 cm^3 of dry diethyl ether was added to *VI* (0.0018 mol). The mixture was bubbled with dry ammonia and cooled simultaneously. The remainder after evaporation of solvent was dissolved in hot acetone, filtered and crystallized from benzene after distilling off the acetone.

5-Benzyloxy-4-oxo-4*H*-pyran-2-carboxisopropylamide (*VIII*)

VI (0.0018 mol) was dissolved in minimum of absolute acetone. Isopropylamine (0.16 cm^3) and triethylamine (0.27 cm^3) were added. Mixture was stirred at laboratory temperature for 1 h, then mixed with excess of water and extracted with benzene. Evaporation of solvent gave solid product. Raw material was crystallized from benzene.

N-(4-Methylphenyl) amide of 5-benzyloxy-4-oxo-4*H*-pyran-2-carboxylic acid (*IX*) was prepared by analogous method.

REFERENCES

1. Robiquet, A., *Ann. 5*, 95 (1833).
2. *Japan* 67, 1176 (1963); *Chem. Abstr. 66*, 84748y (1967).
3. *Belg*. 625, 114 (1963); *Chem. Abstr. 60*, 10651g (1964).
4. *Belg*. 651, 427 (1965); *Chem. Abstr. 64*, 9688f (1966).
5. Bowden, K., Heilbron, I. M., Jones, E. R. H., and Weedon, B. C. L., *J. Chem. Soc. 1946*, 39.
6. Weinhaus, H., *Ber. 47*, 322 (1914).
7. *Japan* 7005, 775 (1970); *Chem. Abstr. 72*, 132522t (1970).
8. Nakagawa, K., Konaka, R., and Nakata, T., *J. Org. Chem. 27*, 1597 (1962).
9. Campaigne, E. and Lesuer W. M., *J. Am. Chem. Soc. 70*, 1557 (1948).
10. Becker, H. D., *Acta Chem. Scand. 16*, 78 (1962).
11. Looker, J. H. and Shaneyfelt D. L., *J. Org. Chem. 27*, 1894 (1962).
12. *Eur*. 341, 948 (1989); *Chem. Abstr. 113*, 6031j (1990).
13. Jakopčic, K., Kojic, J., Orhanovic, Z., Stiplošek, Z., and Nagl, A., *J. Heterocycl. Chem. 29*, 107 (1992).
14. Kalyanam, N., Likhate, M. L., and Fuhrer, H., *Indian J. Chem., B 30*, 358 (1991).
15. Garkusha, G. A. and Kutornenko, G. A., *Zh. Obshch. Khim. 31*, 2573 (1961).
16. Thomas, A. F. and Marxer, A., *Helv. Chim. Acta 43*, 469 (1960).
17. Campbell, K. N., Ackerman, J. F., and Campbell, B. K., *J. Org. Chem. 15*, 221 (1950).
18. Curtis, R. G., Heilbron, I., Jones, E. R. H., and Woods, G. F., *J. Chem. Soc. 1953*, 457.
19. Fatiadi, A. J., *Synthesis 1976*, 67.
20. Keil, B., *Laboratorní technika organické chemie*. (Laboratory Technique of Organic Chemistry.) P. 430. Academia, Prague, 1954.

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Synthesis and Antimycobacterial Effect of 3-Formylchromone *N*-Aroyl- or *N*-Alkylcarbonylhydrazones

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3-Formylchromone *N*-aroyl- or *N*-alkylcarbonylhydrazones were prepared by condensation reaction of 3-formylchromones with hydrazine derivatives in ethanol and toluene-*p*-sulfonic acid as catalyst. Some of the prepared compounds were tested against typical and atypical *Mycobacterium tuberculosis*.

Biological activities of chromone derivatives render them of considerable pharmaceutical and chemical interest [1]. In this work we describe the synthesis of 3-formylchromone *N*-aroylhydrazones and 3-formylchromone *N*-alkylcarbonylhydrazones because many of hydrazide derivatives are of pharmacological importance [2], and also 3-formylchromones show interesting pharmacological activities [3—5], so we were interested to synthesize some new derivatives of chromones with prediction of new pharmacological activities.

4-Oxo-4*H*-1-benzopyrans in their reactions with phenylhydrazine behave like α,β-unsaturated ketones