Preparation and Study of Reactions of the 5-Substituted 4-Oxo-4H-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-4H-pyran ring. Some reactions of created carboxylic acids were investigated as well.

Previous papers described creation of 5-hydroxy-4-oxo-4H-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 y-pyranone ring by different oxidation agents.

Preparation of 5-hydroxy-4-oxo-4H-pyran-2-carboxylic acid by oxidation of free 5-hydroxy-2-hydroxymethyl-4-oxo-4H-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-4H-pyran was carried out according to the literature procedures [5—8].


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

Garkusha and Kutorenko 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: v(C=O) intense band in the v region 1630—1740 cm⁻¹, v(C—O—C) at v = 1210—1310 cm⁻¹, v(C=C) intense bands at v = 1490—1580 cm⁻¹. The oxidation of the hydroxymethyl group resulted in appearing of a new band at v = 1740 cm⁻¹ belonging to v(C=O) of created carboxylic acid. Stretching vibrations v(OH) were observed at v = 3340 cm⁻¹ and 3380 cm⁻¹ for derivatives Ia, Ib (Table 1). Vibrations at v = 3320 cm⁻¹ belong to v(NH) with derivatives VII—IIX (Table 1).

UV spectra of the prepared derivatives showed two dominant absorption maxima in the λmax region 220—280 nm, belonging to π* — π 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-4H-pyran was shown. The conjugation increases from the compound la (λmax/nm 214, 263; log [ε] 4.22, 3.97) to the compound IIa (λmax/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
Table 1. Characteristic Data of Synthesized Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Formula</th>
<th>$w_c$(calc.)/%</th>
<th>$w_c$(found)/%</th>
<th>Yield/%</th>
<th>M.p. °C</th>
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<tbody>
<tr>
<td>Ila</td>
<td>COOH</td>
<td>$C_6H_5CH_2$</td>
<td>$C_{13}H_{10}O_5$</td>
<td>63.42</td>
<td>4.09</td>
<td>23 (A)</td>
<td>187—190</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>246.2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IIb</td>
<td>COOH</td>
<td>$CH_3$</td>
<td>$C_2H_5O_5$</td>
<td>49.42</td>
<td>3.55</td>
<td>31</td>
<td>280—281</td>
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<td></td>
<td></td>
<td>170.1</td>
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<td>III</td>
<td>COOCH$_3$</td>
<td>$C_6H_5CH_2$</td>
<td>$C_{14}H_{12}O_5$</td>
<td>64.62</td>
<td>4.62</td>
<td>46</td>
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<td>260.2</td>
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<td>IV</td>
<td>COOPr-i</td>
<td>$C_6H_5CH_2$</td>
<td>$C_{16}H_{16}O_5$</td>
<td>66.66</td>
<td>5.55</td>
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<td>V</td>
<td>COOCH$_2$Ph</td>
<td>$C_6H_5CH_2$</td>
<td>$C_{16}H_{16}O_5$</td>
<td>71.43</td>
<td>4.76</td>
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<tr>
<td>VI</td>
<td>CONCI</td>
<td>$C_6H_5CH_2$</td>
<td>$C_{12}H_{11}ClO_4$</td>
<td>58.86</td>
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<td>284.7</td>
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<tr>
<td>VII</td>
<td>CONH$_2$</td>
<td>$C_6H_5CH_2$</td>
<td>$C_{13}H_{11}N_4O_2$</td>
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<td>4.48</td>
<td>38</td>
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<td>245.2</td>
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<tr>
<td>VIII</td>
<td>CONHPr-i</td>
<td>$C_6H_5CH_2$</td>
<td>$C_{16}H_{12}N_4O_2$</td>
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<td>5.92</td>
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<td>287.3</td>
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<tr>
<td>IX</td>
<td>CONH—$C_6H_5CH_2$</td>
<td>$C_6H_5CH_2$</td>
<td>$C_{26}H_{24}N_4O_2$</td>
<td>71.63</td>
<td>5.11</td>
<td>42</td>
<td>280—282</td>
</tr>
</tbody>
</table>

a)$w_c$(calc.)/%: 13.38, $w_c$(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 $1 \times 10^{-4}$ 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.

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

5-Benzylxy-4-oxo-4H-pyran-2-carboxylic Acid (Ila)

**Method A:** Mixture of Ia (0.01 mol) and KMnO$_4$ (0.07 mol) in water (47 cm$^3$) was tempered on

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-4H-pyran-2-carboxylate (IV) was prepared by analogous method.

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

Ila (1 mol) was added to benzyl alcohol (1.75 mol), p-toluenesulfonic acid (0.02 mol), and benzene (350 cm³). Water was removed by azeotropic distillation, catalyst from the reaction mixture was removed by rinsing with NaHCO₃ solution. Raw product after solvent evaporation was crystallized from chloroform.

**5-Benzyllox-4-oxo-4H-pyran-2-carboxylic Acid Chloride (VI)**

Mixture of Ila (0.1 mol) and PCl₅ (0.2 mol) was tempered for 1.5 h at 110 °C. POCl₃ 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 Al₂O₃ [20]. The chloride can be used directly in additional reactions.

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

10 cm³ 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-Benzyl-oxo-4-oxo-4H-pyran-2-carboxisopropylamide (VII)

VIII (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-4H-pyran-2-carboxylic acid (IX) was prepared by analogous method.

REFERENCES

1. Robiquet, A., Ann. 5, 95 (1833).

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

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3-Formylchromone $N$-arylo- 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 $N$-arylohydrazones 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-4H-1-benzyopyrans in their reactions with phenylhydrazine behave like $\alpha,\beta$-unsaturated ketones.