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Synthesis and Reactivity of 4-Hydroxy-5-methyl-2-(2-oxo-2*H*-chromen-3-yl)-6*H*-1,3-oxazin-6-ones

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Abstract—4-Hydroxy-6*H*-1,3-oxazin-6-ones with a coumarin fragment in position *2* of the oxazine ring were synthesized. Their hydrolysis, alcoholysis, and hydrazinolysis afforded a number of new coumarin derivatives containing malonamic acid and 1,2,4-triazole residues. The low stability of the title compounds toward oxygen-centered nucleophiles was interpreted by quantum chemical calculations.

Keywords: 4-Hydroxy-6*H*-1,3-oxazin-6-one, coumarin, malonamic acid, 1,2,4-triazole, quantum chemical calculations

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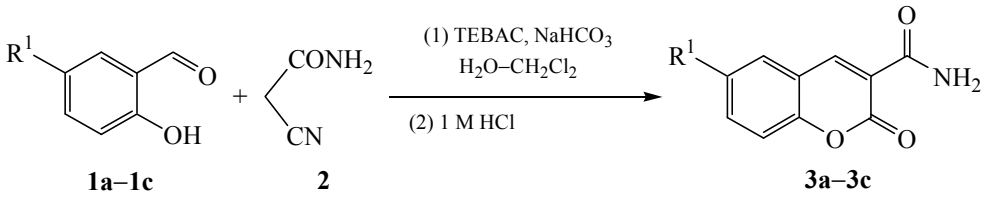
Coumarin derivatives constitute an abundant group of natural and synthetic compounds, many of which exhibit important pharmacological activities. In particular, a number of indirect anticoagulants (e.g., warfarin) are 4-hydroxycoumarin derivatives. Nowadays, extensive search for biologically active substances is performed among coumarin derivatives containing an amide or hydrazide moiety, as well as nitrogen heterocycle residues, in the 3-position [1–4]. Such compounds were found to possess antitubercular [1], antitumor [2, 3], and many other kinds of biological activity [4].

On the other hand, 4-hydroxy-6*H*-1,3-oxazin-6-ones are known to react with nucleophiles to give various acyclic (malonamic acid derivatives [5]) and heterocyclic systems (azoles [6], azines [7]). Herein, we report the synthesis of 1,3-oxazines containing a coumarin fragment and their reactions with nucleophiles with the goal of obtaining new biologically active compounds.

A convenient procedure for the synthesis of 4-hydroxy-6*H*-1,3-oxazin-6-ones is based on the well studied reaction of the corresponding carboxylic acid amides with malonyl chlorides [5, 7]. The required coumarin-3-carboxamides **3a**–**3c** were prepared by a modified known procedure [8, 9] (Scheme 1). According to published data, the Knoevenagel condensation of salicylaldehydes **1a**–**1c** with cyanoacetamide (**2**) is carried out in a two-phase system water–methylene chloride (9 : 1) in the presence of a phase-transfer catalyst. The subsequent acidification of the reaction mixture leads to closure of pyran ring with formation of coumarin-3-carboxamides **3a**–**3c** in 84–90% yield. Instead of cetyl(trimethyl)ammonium bromide [8] or Katamin AB [9], as phase-transfer catalyst we used more accessible benzyl(triethyl)-ammonium chloride (BTEAC). In this case, the yields of the target products did not decrease, and the experimental procedure was not complicated. Addition of methylene chloride to the reaction mixture made it possible to accomplish the reaction with solid 5-bromo- and 5-methylsalicylaldehydes **1a** and **1c**. The melting point and ^{1}H NMR spectrum of **3b** coincided with published data for 2-oxo-2*H*-chromene-3-carboxamide [9]. Apart from aromatic proton signals, the ^{1}H NMR spectrum of **3b** characteristically showed two broadened singlets due to protons of the NH_2 group (δ 7.91 and 8.08 ppm) and 4-H signal at δ 8.86 ppm. The structure of **3a**–**3c** was also confirmed by ^{13}C NMR spectra and elemental analyses (Tables 1, 2).

Amides **3a**–**3c** were reacted with methylmalonyl chloride (**4**) in aprotic solvents such as carbon

Scheme 1.



1a–1c **2** **3a–3c**

R^1 = Br (**a**), H (**b**), Me (**c**).

tetrachloride, benzene, 1,2-dichloroethane, and acetonitrile at the boiling point. Acetonitrile turned out to be the best solvent; it ensured reaction completion in 2–3 h, and the yield of 1,3-oxazines **5a**–**5c** was 76–84% (Scheme 2). 1,2-Dichloroethane was less efficient: the reactions were complete in 4–6 h, and the yields were slightly lower (70–78%). Insofar as initial amides **3a**–**3c** are poorly soluble in carbon tetrachloride and benzene, the reaction time in these solvents increased to 8–10 h, and the yield of **5a**–**5c** decreased to 20–24%, which may be due to polymerization of methylmalonyl chloride on prolonged heating.

The ^{1}H NMR spectra of **5a**–**5c** contained signals from aromatic protons of the coumarin fragment (δ 7.43–8.86 ppm), a singlet at δ 1.82–1.83 ppm from the

Table 1. Yields, melting points, and elemental analyses of compounds **3** and **5**–**10**

Comp. no.	R^1	R^2	R^3	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
						C	H	N		C	H	N
3a	Br	–	–	86	294–296	44.03	1.89	5.17	$C_{10}H_6BrNO_3$	44.81	2.26	5.23
3b	H	–	–	90	263–264	63.31	3.51	7.04	$C_{10}H_7NO_3$	63.49	3.73	7.40
3c	Me	–	–	84	218–220	64.77	4.12	6.76	$C_{11}H_9NO_3$	65.02	4.46	6.89
5a	Br	–	–	84	251–252	47.93	2.20	3.89	$C_{14}H_8BrNO_5$	48.03	2.30	4.00
5b	H	–	–	76	197–200	61.85	3.29	5.00	$C_{14}H_9NO_5$	62.00	3.34	5.16
5c	Me	–	–	79	205–207	63.01	3.65	4.72	$C_{14}H_{11}NO_5$	63.16	3.89	4.91
6a	Br	H	–	95	209–210	45.46	2.61	3.77	$C_{14}H_{10}BrNO_6$	45.68	2.74	3.80
6b	H	H	–	97	191–193	57.92	3.64	4.80	$C_{14}H_{11}NO_6$	58.14	3.83	4.84
6c	Me	H	–	95	194–195	59.33	4.12	4.49	$C_{15}H_{13}NO_6$	59.41	4.32	4.62
7a	Br	Et	–	87	173–174	48.44	3.51	3.47	$C_{16}H_{14}BrNO_6$	48.51	3.56	3.54
7b	H	Et	–	91	144–145	60.46	4.52	4.35	$C_{16}H_{15}NO_6$	60.57	4.77	4.41
7c	Me	Et	–	94	153–153	61.43	4.79	4.07	$C_{17}H_{17}NO_6$	61.63	5.17	4.23
8a	Br	–	H	69	288–290	41.98	2.35	6.91	$C_{14}H_{10}Br_2N_2O_2$	42.24	2.53	7.04
9a	Br	–	H	81	270–271	46.07	2.53	11.21	$C_{14}H_{10}BrN_3O_4$	46.18	2.77	11.54
9b	H	–	H	72	212–214	58.68	3.82	14.42	$C_{14}H_{11}N_3O_4$	58.95	3.89	14.73
9c	Me	–	H	85	210–211	59.93	4.17	13.86	$C_{15}H_{13}N_3O_4$	60.20	4.38	14.04
10a	Br	–	Ph	89	172–174	54.40	2.98	9.33	$C_{20}H_{14}BrN_3O_4$	54.56	3.21	9.54
10b	H	–	Ph	81	153–155	66.04	4.12	11.39	$C_{20}H_{15}N_3O_4$	66.48	4.18	11.63
10c	Me	–	Ph	83	158–159	66.97	4.36	10.97	$C_{21}H_{17}N_3O_4$	67.19	4.56	11.19

Table 2. ^{1}H and ^{13}C NMR spectra (DMSO-d_6) of compounds **3** and **5–10**

Comp. no.	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	^{13}C NMR spectrum, δ_C, ppm
3a	7.44 d (1H, 8-H, *J* = 8.8), 7.86 d.d (1H, 7-H, *J* = 2.4, 8.8), 7.97 br. s (1H, NH), 8.04 br.s (1H, NH), 8.20 d (1H, 5-H, *J* = 2.4), 8.81 s (1H, 4-H)	117.0, 118.8, 120.8, 120.9, 132.5, 136.7, 146.9, 153.5, 160.3, 162.7
3b	7.43 t (1H, 6-H, *J* = 7.8), 7.48 d (1H, 8-H, *J* = 7.8), 7.74 t (1H, 7-H, *J* = 7.8), 7.91 br.s (1H, NH), 7.96 d (1H, 5-H, *J* = 7.8), 8.08 br.s (1H, NH), 8.86 s (1H, 4-H)	116.6, 118.9, 119.7, 125.5, 130.7, 134.5, 148.3, 154.5, 160.8, 163.0
3c	2.36 s (3H, CH_3), 7.34 d (1H, 8-H, *J* = 8.5), 7.52 d.d (1H, 7-H, *J* = 1.3, 8.5), 7.68 d (1H, 5-H, *J* = 1.3), 7.90 br.s (1H, NH), 8.08 br.s (1H, NH), 8.74 s (1H, 4-H)	20.7, 116.3, 118.6, 119.4, 130.1, 134.9, 135.5, 148.2, 152.6, 160.9, 163.0
5a	1.83 s (3H, CH_3), 7.45 d (1H, 8-H, *J* = 8.8), 7.90 d (1H, 7-H, *J* = 8.8), 8.25 s (1H, 5-H), 8.74 s (1H, 4-H), 12.66 br.s (1H, OH)	8.6, 91.6, 117.0, 118.9, 119.0, 120.3, 132.6, 137.2, 146.8, 153.8, 155.6, 158.0, 162.0, 165.5
5b	1.82 s (3H, CH_3), 7.46 m (2H, 6-H, 8-H), 7.76 t (1H, 7-H, *J* = 8.0), 7.97 d (1H, 5-H, *J* = 8.0), 8.78 s (1H, S^4N), 12.65 br. s (1H, OH)	8.5, 91.2, 116.6, 117.8, 118.4, 118.6, 125.5, 130.8, 135.1, 148.2, 154.5, 156.1, 158.4, 165.6
5c	1.83 s (3H, CH_3), 7.37 d (1H, 8-H, *J* = 8.5), 7.59 d (1H, 7-H, *J* = 8.5), 7.75 s (1H, 5-H), 8.69 s (1H, 4-H), 12.65 br.s (1H, OH)	8.4, 20.9, 90.5, 116.4, 118.7, 119.3, 130.4, 134.7, 135.6, 148.3, 152.5, 160.5, 162.2, 163.0, 165.6
6a	1.29 d (3H, *J* = 7.0, CH_3), 3.97 q (1H, *J* = 7.0, CH), 7.51 d (1H, *J* = 8.8, 8-H), 7.93 d.d (1H, 7-H, *J* = 2.4, 8.8), 8.23 d (1H, 5-H, *J* = 2.4), 8.71 s (1H, 4-H), 11.30 s (1H, NH), 12.81 br.s (1H, COOH)	13.6, 48.0, 117.3, 119.1, 120.5, 122.1, 132.6, 137.2, 146.3, 153.5, 159.4, 162.3, 171.1, 171.7
6b	1.31 d (3H, CH_3, *J* = 7.2), 4.01 q (1H, CH, *J* = 7.2), 7.48 t (1H, 6-H, *J* = 7.5), 7.54 d (1H, 8-H, *J* = 8.3), 7.80 t (1H, 7-H, *J* = 8.3), 7.98 d (1H, 5-H, *J* = 8.3), 8.83 s (1H, 4-H), 11.29 s (1H, NH), 12.73 br.s (1H, COOH)	13.6, 48.1, 116.8, 118.6, 120.1, 125.9, 130.9, 135.3, 148.5, 154.4, 160.2, 162.1, 171.2, 171.8.
6c	1.31 d (3H, CH_3, *J* = 7.3), 4.03 q (1H, CH, *J* = 7.3), 7.40 d (1H, 8-H, *J* = 8.4), 7.58 d (1H, 7-H, *J* = 8.4), 7.71 s (1H, 5-H), 8.74 s (1H, 4-H), 11.28 s (1H, NH), 12.71 br.s (1H, COOH)	13.6, 20.6, 48.2, 116.5, 118.4, 119.7, 130.3, 135.3, 136.2, 148.7, 152.7, 160.3, 162.0, 171.1, 171.8.
7a	1.19 t (3H, C**H**$_3$CH$_2$, *J* = 7.0), 1.32 d (3H, CH_3, *J* = 7.3), 4.06 m (3H, CH_3C**H**$_2$, CH), 7.50 d (1H, 8-H, *J* = 8.8), 7.91 d (1H, 7-H, *J* = 8.8), 8.22 s (1H, 5-H), 8.71 s (1H, 4-H), 11.33 s (1H, NH)	13.5, 14.4, 48.0, 61.3, 117.3, 119.1, 120.5, 121.9, 132.7, 137.2, 146.6, 153.5, 159.4, 162.3, 170.2, 170.7
7b	1.14 t (3H, C**H**$_3$CH$_2$, *J* = 7.0), 1.29 d (3H, CH_3, *J* = 7.2), 3.99 q (1H, CH, *J* = 7.2), 4.10 q (2H, CH_3C**H**$_2$, *J* = 7.0), 7.49 t (1H, 6-H, *J* = 7.5), 7.55 d (1H, 8-H, *J* = 8.3), 7.78 t (1H, 7-H, *J* = 7.8), 7.98 d (1H, 5-H, *J* = 7.8), 8.74 s (1H, 4-H), 11.22 s (1H, NH)	13.6, 14.4, 48.1, 61.5, 116.7, 118.7, 120.2, 125.8, 130.8, 135.2, 148.5, 154.4, 160.1, 162.2, 171.1, 172.8
7c	1.19 t (3H, C**H**$_3$CH$_2$, *J* = 7.0), 1.30 d (3H, CH_3, *J* = 7.3), 4.00 q (1H, CH, *J* = 7.3), 4.11 q (2H, CH_3C**H**$_2$, *J* = 7.0), 7.42 d (1H, 8-H, *J* = 8.4), 7.59 d (1H, 7-H, *J* = 8.4), 7.70 s (1H, 5-H), 8.72 s (1H, 4-H), 11.32 s (1H, NH)	13.6, 14.4, 20.8, 48.2, 61.4, 116.6, 119.2, 120.8, 120.9, 132.4, 137.6, 146.3, 152.3, 159.7, 162.2, 170.8, 172.6
8a	6.97 d (1H, 3-H, *J* = 8.8), 7.53 d. d (1H, 4-H, *J* = 2.0, 8.0), 7.90 d (1H, 6-H, *J* = 2.0), 8.93 s (1H, CH=N), 11.18 br. s (1H, OH)	111.0, 119.4, 121.1, 132.0, 135.9, 158.2, 161.1
9a	1.49 d (3H, CH_3, *J* = 7.3), 3.92 q (1H, CH, *J* = 7.3), 7.45 d (1H, 8-H, *J* = 8.8), 7.82 d.d (1H, 7-H, *J* = 2.3, 8.8), 8.22 d (1H, 5-H, *J* = 2.3), 8.76 s (1H, 4-H), 12.24 br. s (1H, NH), 13.87 br.s (1H, COOH)	16.4, 39.3, 117.0, 117.1, 118.8, 121.1, 131.9, 135.6, 141.1, 151.1, 152.7, 158.1, 161.5, 173.8
9b	1.48 d (3H, CH_3, *J* = 7.1), 3.90 q (1H, CH, *J* = 7.1), 7.43 t (1H, 6-H, *J* = 7.4), 7.50 d (1H, 8-H, *J* = 8.2), 7.70 t (1H, 7-H, *J* = 7.8), 7.99 d (1H, 5-H, *J* = 7.8), 8.81 s (1H, 2-H), 12.85 br.s (2H, NH, COOH)	16.4, 39.3, 115.8, 116.6, 119.2, 125.4, 130.1, 133.4, 142.5, 150.4, 153.7, 158.6, 161.9, 173.9
9c	1.48 d (3H, CH_3, *J* = 7.3), 3.91 q (1H, CH, *J* = 7.3), 7.39 d (1H, 8-H, *J* = 8.3), 7.51 d.d (1H, 7-H, *J* = 1.5, 8.3), 7.75 d (1H, 5-H, *J* = 1.5), 8.72 s (1H, 4-H), 12.33 br.s (1H, NH), 13.90 br.s (1H, COOH)	16.4, 20.8, 39.4, 115.7, 116.4, 118.9, 129.6, 134.4, 134.7, 142.5, 150.0, 151.9, 158.8, 162.0, 173.8

Table 2. (Contd.)

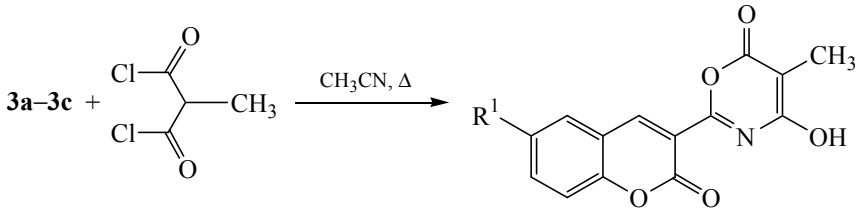
Comp. no.	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	^{13}C NMR spectrum, δ_C, ppm
10a	1.54 d (3H, CH_3, *J* = 7.3), 4.07 q (1H, CH, *J* = 7.3), 7.42 d (1H, 8-H, *J* = 8.9), 7.62 m (5H, Ph), 7.80 d. d (1H, 7-H, *J* = 2.4, 8.9), 8.23 d (1H, 5-H, *J* = 2.4), 8.73 s (1H, 4-H), 12.96 br.s (1H, COOH)	16.2, 37.5, 116.7, 118.7, 119.3, 121.1, 126.0, 130.0, 130.1, 131.7, 135.3, 137.2, 141.7, 153.00, 155.9, 156.5, 156.8, 172.3
10b	1.55 d (3H, CH_3, *J* = 7.3), 4.07 q (1H, CH, *J* = 7.3), 7.40 t (1H, 6-H, *J* = 7.5), 7.45 d (1H, 8-H, *J* = 8.3), 7.63 m (6H, Ph, 7-H), 7.96 d (1H, 5-H, *J* = 7.5), 8.75 s (1H, 4-H), 12.81 br.s (1H, COOH)	16.2, 37.3, 116.4, 119.1, 119.2, 125.2, 126.1, 130.0, 130.1, 130.3, 133.2, 137.0, 143.0, 153.5, 155.8, 156.3, 156.8, 172.4
10c	1.54 d (3H, CH_3, *J* = 7.3), 4.06 q (1H, CH, *J* = 7.3), 7.36 d (1H, 8-H, *J* = 8.2), 7.50 d.d (1H, 7-H, *J* = 1.5, 8.2), 7.63 m (5H, Ph), 7.73 d (1H, 5-H, *J* = 1.5), 8.68 s (1H, 4-H), 12.78 br.s (1H, COOH)	16.2, 20.8, 37.4, 116.2, 118.7, 119.1, 125.9, 129.3, 130.0, 130.2, 134.1, 134.5, 137.1, 142.9, 153.3, 155.6, 156.4, 156.6, 172.2

5-methyl group, and a broadened singlet of the hydroxy proton at δ 12.65–12.66 ppm. In the ^{13}C NMR spectra of these compounds, the 5-CH_3 and C^5 carbon nuclei resonated at δ_C 8.4–8.6 and 90.5–91.6 ppm, respectively, and signals of C^2, C^4, and C^6 of the oxazine ring were located in the downfield region (δ_C 156.1–165.6 ppm). The structure of **5a**–**5c** was also confirmed by elemental analyses (Tables 1, 2) and by the high-resolution mass spectrum of **5b**.

While determining the structure of we have noticed their anomalously low hydrolytic stability. Compounds **5a**–**5c** underwent partial or complete hydrolysis via cleavage of the C^6–O bond during recording their NMR spectra in DMSO containing traces of water. The hydrolysis products were *N*-acylmalonamic acids **6a**–**6c**. Complete hydrolysis of **5a**–**5c** with quantitative formation of **6a**–**6c** was also observed on exposure to atmospheric moisture for 10–12 days. Further studies showed that oxazines **5a**–**5c** equally readily (at room temperature) reacted with another O-nucleophile, ethanol, to form malonamic acid esters **7a–7c** which were isolated in 87–94% yield (Scheme 3).

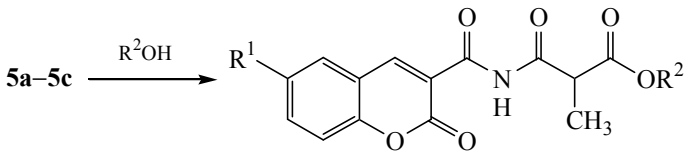
It should be noted that such hydrolytic stability is not typical of 2-aryl- and 2-styryl-substituted 4-hydroxy-5-methyl-6*H*-1,3-oxazin-6-ones [6]. The latter do react with O-nucleophiles to give products of oxazine ring cleavage at the C^6–O bond [5, 6], the corresponding malonamic acids or their esters analogous to **6** and **7**. However, these reactions occur under more severe conditions, on heating in aqueous

Scheme 2.



4 **5a–5c**

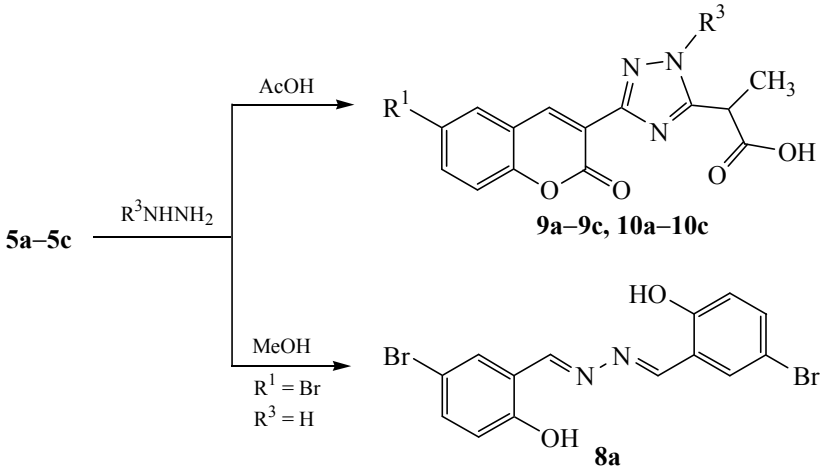
Scheme 3.



6a–6c, **7a–7c**

R^2 = H (**6a–6c**), Et (**7a–7c**).

Scheme 4.



R^3 = H (**9**), Ph (**10**).

acetonitrile or in alcohols at the boiling point for 1–2 h.

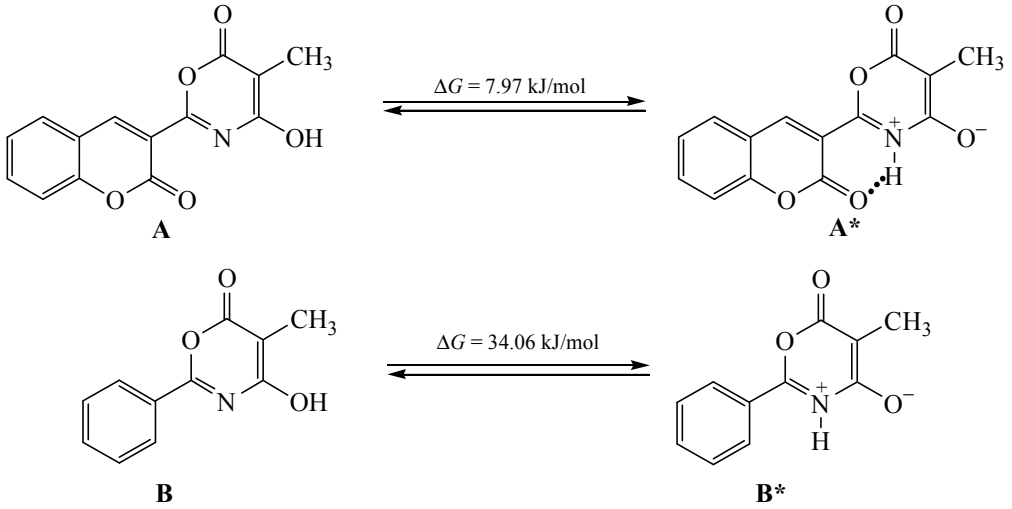
As shown previously [5, 6], reactions of 4-hydroxy-6*H*-1,3-oxazin-6-ones react with binucleophiles, such as hydrazines and guanidine, in methanol involve opening of the oxazine ring via cleavage of the C^2–O bond usually with subsequent recyclization to azole or azine heterocyclic system. Analogous reaction of **5a** with hydrazine in methanol resulted in decomposition of the pyran ring with formation of aldehyde azine **8a** as the major product (yield 69%; Scheme 4). Compound **8a** was identified by comparing its melting point and ^{1}H NMR data with those reported in [10] for 5-bromosalicylaldehyde azine. According to published data [10, 11], such behavior is typical of 3-acetylcoumarin and coumarin-3-carboxylic acid derivatives. Oxazines **5a**–**5c** can also be regarded as analogs of the latter. When the reactions of **5a**–**5c** with hydrazine and phenylhydrazine were carried out in glacial acetic acid, the nucleophilic attack was directed mainly at C^2 of the oxazine ring, and the final products were coumarin-containing 1,2,4-triazole derivatives **9a**–**9c** and **10a**–**10c** (yield 72–89%; Scheme 4).

The structure of **6a**–**6c**, **7a**–**7c**, **9a**–**9c**, and **10a**–**10c** was confirmed by elemental analyses and ^{1}H and ^{13}C NMR spectra (Tables 1, 2). Compound **9b** was also characterized by the high-resolution mass spectrum. In the ^{1}H NMR spectra of **6**, **7**, **9**, and **10** we observed two signals belonging to a CH_3CH fragment (a doublet at δ 1.29–1.54 ppm and a quartet at δ 3.90–4.07 ppm) instead of 5-CH_3 singlet typical of initial oxazines **5a**–**5c**: the corresponding carbon nuclei resonated in the ^{13}C NMR spectra at δ_C 13.4–16.2 (CH_3) and 37.5–48.2 ppm (CH). Malonamic acid derivatives **6** and **7** showed a singlet at δ 11.22–11.33 ppm in the ^{1}H NMR spectra due to the NH proton, and triazoles **9** and **10** showed a broadened singlet at δ 12.85–13.87 ppm due to hydroxy proton of the COOH group). Signals in the region δ_C 155.9–158.8 ppm were assigned to carbon atoms of the triazole ring.

Our results led us to conclude that the presence of a coumarin fragment in the 2-position strongly affects the chemical behavior of the 1,3-oxazine system. Presumably, the 2-substituent affects geometric parameters of the oxazine ring in **5a**–**5c**, which largely determine their reactivity toward O-nucleophiles. In order to evaluate the effect of the 2-substituent we performed B3LYP/6-31+G(*d*,*p*) quantum chemical calculations (GAUSSIAN 09 A.02 [12]) of the geometric parameters and free energies of tautomeric forms of 2-coumarinyloxazine (**A** and **A***) and 2-phenyloxazine (**B** and **B***). While optimizing the geometric parameters, stationary points on the potential energy surfaces were identified as energy minima by the absence of imaginary vibration frequencies in the corresponding Hessian matrices.

We previously showed [13] by both theoretical and experimental methods that 4-hydroxy-1,3-oxazin-6-ones exist preferentially as 4-hydroxy-6-oxo tautomers (**A** and **B**) among four theoretically possible ones. One of the minor tautomers which could exist in equilibrium with the major form is dipolar ion **A*** or

Scheme 4.



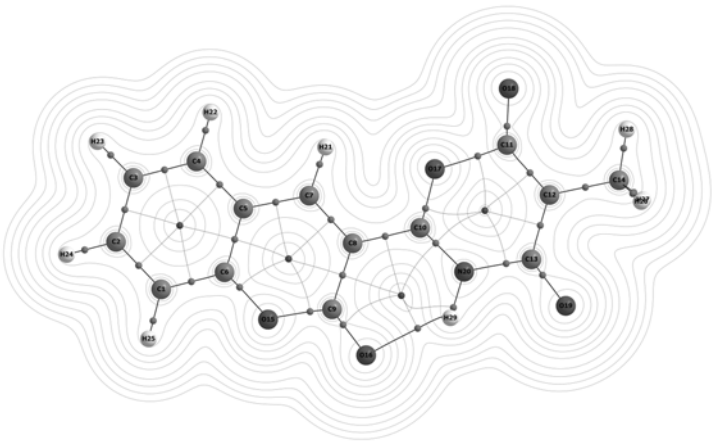
B*. On the basis of the calculated Gibbs energies we estimated the compositions of tautomeric mixtures **A**/**A*** and **B**/**B*** (χ, %) by the equation $\Delta G = -R T \ln K$ (Table 3). It is seen that the transformation of tautomer **A** of **5b** into structure **A*** should be relatively facile and that analogous transformation of 2-phenyloxazine is hindered. The equilibrium concentration of **A*** is 3.85%, whereas zwitterionic tautomer **B*** of 2-phenyloxazine is almost absent in the equilibrium mixture. This difference in the tautomeric compositions may be related to the effect of the oxo group in the coumarin fragment of **5b**, which stabilizes structure **A*** due to formation of hydrogen bond C=O···H–N (d = 1.962 Å). The formation of this hydrogen bond was confirmed by topological analysis of electron density distribution in tautomer **A*** by the atoms-in-molecules method [14] (AIMAll [15]) (see figure). A critical point of the (3, –1) type was found for tautomer **A***, which corresponded to N–H···O hydrogen bonding. The bond energy was determined from the potential energy density at the critical point according to the procedure described in [16], E_{HB} = 28.4 kJ/mol.

Assuming that reactions of 1,3-oxazines **5a**–**5c** with O-nucleophiles are favored by anomalously high concentration of dipolar structure **A***, we compared the reactivities of tautomers **A** and **A***. As we already noted, the hydrolysis and alcoholysis of 1,3-oxazines involves cleavage of the C^6–O bond. Its strength was quantitatively assessed by its length and order in structures **A**/**A*** and **B**/**B*** (Table 3). The bond orders were calculated according to Wiberg using the NBO (natural bond orbital) module implemented in Gaussian 09. The results showed that the transformation of **A** into **A*** is accompanied by appreciable elongation of C^6–O in **5b** (from 1.433 to 1.618 Å); simultaneously, the C^6–O bond order decreases. Analogous pattern was observed for tautomers **B** and **B*** of 2-phenyloxazine. Thus, dissociation of the C^6–O bond in dipolar tautomers **A*** and **B*** is much easier than in major 4-hydroxy-6-oxo tautomers **A** and **B**, and the low stability of **5a**–**5c** toward hydrolysis and alcoholysis is determined by the presence of dipolar tautomer **A*** which readily undergoes ring opening because of low strength of the C^6–O bond.

In summary, we have synthesized for the first time 4-hydroxy-6*H*-1,3-oxazin-6-one derivatives containing a coumarin fragment in the 2-position of the oxazine ring. These compounds react with with nucleophiles to give previously unknown coumarin derivatives possessing malonamic acid and 1,2,4-triazole fragments. Taking into account published data [1–4], the synthesized compounds attract interest as potential biologically active substances with antitumor, antitubercular, and other valuable therapeutic properties.

Table 3. Characterisitc of tautomers **A**/**A*** and **B**/**B***

Parameter	Oxazin **5b**		2-Phenyloxazine	
	A	**A***	**B**	**B***
Gibbs energy ΔG, kJ/mol	7.973		34.059	
Equilibrium concentration χ, %	96.15	3.85	99.9999	0.0001
Bond length C^6–O, Å	1.433	1.618	1.435	1.613
Bond order C^6–O	0.840	0.579	0.838	0.587



Topological analysis of tautomer **A***.

According to quantum chemical calculations, high reactivity of coumarin-containing 1,3-oxazines toward O-nucleophiles is related to their partial existence as reactive zwitterionic tautomers.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in DMSO-d_6 on a Bruker Avance III spectrometer (400 and 100 MHz, respectively), using the residual proton and carbon signals of the solvent as reference. The elemental analyses were obtained on a LECO CHNS-932 analyzer. The mass spectra were recorded on a Bruker micrOTOF instrument (electrospray ionization, positive ion detection). The purity of the isolated compounds was checked, and the progress of reactions was monitored, by thin-layer chromatography on Silica gel 60 F254 plates (Merck) using ethyl acetate as eluent; spots were visualized under UV light. The solvents were purified and dried by standard methods. The yields, melting points, and analytical data of compound **5**–**10** are given in Table 1, and their spectral parameters are presented in Table 2.

6-Bromo-2-oxo-2*H*-chromene-3-carboxamide (3a). A mixture of 20 g (10 mmol) of 5-bromosalicylaldehyde (**1a**), 12.6 g (15 mmol) of cyanoacetamide (**2**), 2.3 g (1 mmol) of benzyl(triethyl)ammonium chloride, 5 g of sodium hydrogen carbonate, 450 mL of water, and 50 mL of methylene chloride was stirred for 3 h at 18–20°C. The mixture was acidified with 1 M aqueous HCl to pH 2–3 and heated for 2 h at 60–65°C. The mixture was then cooled, and the white solid was filtered off, washed with water, and dried at 50°C. Yield 23.0 g (86%).

Coumarin-3-carboxamides **3b** and **3c** were synthesized in a similar way.

4-Hydroxy-5-methyl-2-(2-oxo-2*H*-chromen-3-yl)-6*H*-1,3-oxazin-6-one (5b). A mixture of 1.5 g (8 mmol) of amide **3b** and 1.8 g (12 mmol) of methylmalonyl chloride (**4**) in 20 mL of anhydrous acetonitrile was refluxed for 2–3 h (until the initial amide disappeared according to the TLC data). The mixture was cooled, and the yellow precipitate was filtered off, washed with acetonitrile, and dried in a vacuum desiccator over phosphoric anhydride. Yield 1.7 g (76%). Mass spectrum (HRMS ESI): *m*/*z* 294.0377 $[M + Na]^+$; calculated for $C_{14}H_9NNaO_5$: 294.0374.

Oxazines **5a** and **5c** were synthesized in a similar way.

3-[(6-Bromo-2-oxo-2*H*-chromen-3-ylcarbonyl)-amino]-2-methyl-3-oxopropanoic acid (6a). Oxazine **5a**, 1.4 g (4 mmol), was kept on exposure to air for 10–12 days (TLC). Yield 1.4 g (95%).

N-Acylmalonamic acids **6b** and **6c** were synthesized in a similar way.

Ethyl 3-[(6-bromo-2-oxo-2*H*-chromen-3-ylcarbonyl)amino]-2-methyl-3-oxopropanoate (7a). A suspension of 1.4 g (4 mmol) of oxazine **5a** in 10 mL of ethanol was stirred for 3–4 h. When the reaction was complete, the precipitate was filtered off and dried in air. Yield 1.4 g (87%).

Esters **7b** and **7c** were synthesized in a similar way.

5-Bromosalicylaldehyde azine (8a). A mixture of 1.4 g (4 mmol) of oxazine **5a** and 200 μL (200 mg, 4 mmol) of hydrazine hydrate in 10 mL of methanol was stirred for 12 h until the initial oxazine disappeared (TLC). The precipitate was filtered off,

washed with methanol, and dried in air. Yield 0.55 g (69%), mp 288–290°C [10].

2-[3-(2-Oxo-2*H*-chromen-3-yl)-1*H*-1,2,4-triazol-5-yl]propanoic acid (9b). A mixture of 1.1 g (4 mmol) of oxazine **5b** and 200 μL (200 mg, 4 mmol) of hydrazine hydrate in 10 mL of glacial acetic acid was stirred for 2–3 days (TLC). The white solid was filtered off, washed with acetic acid, and dried under reduced pressure. Yield 0.9 g (72%). Mass spectrum (HRMS ESI): *m*/*z* 308.0640 $[M + Na]^+$; calculated for $C_{14}H_{11}N_3NaO_4$: 308.0642.

Triazoles **9a**, **9c** and **10a**–**10c** were synthesized in a similar way. In the synthesis of 1-phenyl-1,2,4-triazoles **10a**–**10c** phenylhydrazine was used instead of hydrazine hydrate.

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