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Synthesis of 5-Alkyl(aryl)-2-alkylsulfanyl(alkoxy)-4-hydroxy-6*H*-1,3-oxazin-6-ones

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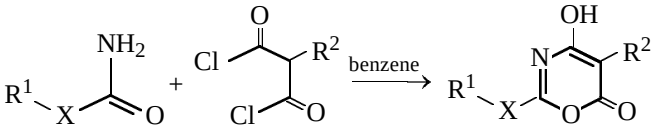
Abstract — Alkyl carbamates and *S*-alkyl thiocarbamates react with substituted malonyl dichlorides in boiling benzene to give the corresponding 2,5-substituted 4-hydroxy-6*H*-1,3-oxazin-6-ones. The reaction of *S*-methyl thiocarbamate with unsubstituted malonyl dichloride in boiling diethyl ether or benzene leads to formation of *S*-methyl (3-methylsulfanylaminocarbonyl-3-oxopropionyl)thiocarbamate and is not accompanied by cyclization, whereas in boiling toluene 4-hydroxy-2-methylsulfanyl-6*H*-1,3-oxazin-6-one is obtained.

It was previously shown [1, 2] that reactions of aromatic amides with substituted malonyl dichlorides provide a convenient synthetic route to 2-aryl- and 2-styryl-5-alkyl(aryl)-4-hydroxy-6*H*-1,3-oxazin-6-ones which exhibit a broad spectrum of biological activity: antimicrobial, antitumor, and anticoagulating [3–5]. Furthermore, these compounds can be used for the synthesis of difficultly accessible derivatives of malonamic acid and triazoles [6].

This study is devoted to on reactions of *S*-alkyl thiocarbamates **Ia**–**Ic** (which were prepared by acid hydrolysis of the corresponding alkyl thiocyanates [7]) and alkyl carbamates **Id**–**If** with malonyl dichlorides **IIa**–**IIe**. The reactions were carried out in boiling benzene or dichloroethane with reactant concentrations of 20–30%, and the products were the corresponding 5-alkyl(aryl)2-alkylsulfanyl(alkoxy)-4-hydroxy-6*H*-1,3-oxazin-6-ones **IIIa**–**IIIn** (Scheme 1); the yields were about 80%, regardless of the R^1 and R^2 substituents (Table 1).

Scheme 1.



Ia–**If** **IIa**–**IIe** **IIIa**–**IIIn**

X = S, R^1 = Me (**Ia**), Et (**Ib**), Pr (**Ic**); X = O, R^1 = Me (**Id**), Et (**Ie**), $EtO(CH_2)_2$ (**If**), R^2 = Me (**IIa**), Et (**IIb**), Bu (**IIc**), c-Hex (**IId**), Ph (**IIe**); X = S, R^1 = Me, R^2 = Me (**IIIa**), Et (**IIIb**), Bu (**IIIc**), *c*-Hex (**IIId**), Ph **(IIIe)**; R^1 = Et, R^2= Et (**IIIf**); R^1 = Pr, R^2 = Me (**IIIg**); X = O, R^1 = Me, R^2 = Me (**IIIh**), Et (**IIIi**), Bu (**IIIj**), *c*-Hex (**IIIk**), Ph (**IIIl**); R^1 = Et, R^2 = Et (**IIIm**), R^1 = $EtO(CH_2)_2$, R^2 = Me (**IIIn**).

The reaction of *S*-methyl thiocarbamate (**Ia**) with unsubstituted malonyl dichloride (**IIf**) in boiling benzene at reactant concentrations of 20–30% (i.e., under the same conditions as with substituted malonyl dichloride) led to formation of an intractable tarry material, presumably due to ready polymerization of malonyl dichloride at elevated temperature. When the reaction of **Ia** with **IIf** was performed in a dilute benzene solution (2–3%), the major product was *S*-methyl (3-methylsulfanylaminocarbonyl-3-oxopropionyl)thiocarbamate (**IV**) (yield 85%); also a small amount of the expected oxazine **IIIo** was formed. According to the ^{1}H NMR data, the ratio of products **IV** and **IIIo** was 10 : 1. Compound **IV** was formed as the only product when the reaction was performed in boiling diethyl ether, regardless of the reactant concentration. We made an attempt to raise the yield of oxazine **IIIo** having no substituent in position 5 of the heteroring

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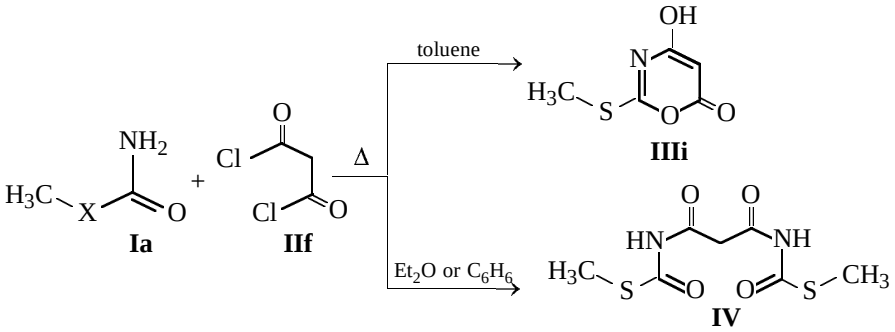
Table 1. Yields, melting points, R_f values, and elemental analyses of compounds **IIIa**–**IIIo** and **IV**

Comp. no.	mp, °C	Yield, %	R_f (ethyl acetate)	Found, %				Formula	Calculated, %			
				C	H	N	S		C	H	N	S
IIIa	149–151	81	0.51	41.42	3.99	8.18	18.59	$C_6H_7NO_3S$	41.62	4.05	8.09	18.50
IIIb	137–139	83	0.45	44.80	4.90	7.57	17.22	$C_7H_9NO_3S$	44.92	4.81	7.49	17.11
IIIc	104–106	80	0.50	50.38	6.17	6.57	14.68	$C_9H_{13}NO_3S$	50.23	6.05	6.51	14.88
IIId	141–143	79	0.57	54.89	6.15	5.75	13.21	$C_{11}H_{15}NO_3S$	54.77	6.22	5.81	13.28
IIIe	166–168	77	0.55	56.20	3.80	5.99	13.47	$C_{11}H_9NO_3S$	56.17	3.83	5.96	13.62
IIIf	120–122	83	0.41	47.59	5.41	6.93	15.81	$C_8H_{11}NO_3S$	47.76	5.47	6.96	15.92
IIIg	84–86	80	0.40	47.84	5.59	6.87	15.99	$C_8H_{11}NO_3S$	47.76	5.47	6.96	15.92
IIIh	150–152	75	0.50	45.73	4.49	9.01	–	$C_6H_7NO_4$	45.86	4.46	8.92	–
IIIi	142–144	76	0.44	49.18	5.36	8.23	–	$C_7H_9NO_4$	49.12	5.26	8.19	–
IIIj	100–102	78	0.49	54.35	6.45	6.94	–	$C_9H_{13}NO_4$	54.27	6.53	7.04	–
IIIk	182–184	73	0.56	62.61	7.23	6.53	–	$C_{11}H_{15}NO_4$	62.56	7.11	6.64	–
IIIl	186–188	79	0.47	64.56	4.50	6.92	–	$C_{11}H_9NO_4$	64.39	4.39	6.83	–
IIIm	100–103	75	0.50	51.95	6.03	7.63	–	$C_8H_{11}NO_4$	51.89	5.95	7.57	–
IIIn	104–106	77	0.54	50.57	5.72	6.64	–	$C_9H_{12}NO_5$	50.47	5.61	6.54	–
IIIo	121–123	82	0.50	37.84	3.22	8.94	20.23	$C_5H_5NO_3S$	37.74	3.14	8.81	20.13
IV	191–193	87	0.38	33.81	3.93	11.33	12.91	$C_7H_{10}N_2O_4S_2$	33.60	4.00	11.20	12.80

by carrying out the reaction in boiling anhydrous toluene (110°C). In this case (reactant concentration 2–3%; 4 h), compound **IIIo** was the only product (Scheme 2).

Scheme 2.



The structure of compounds **IIIa**–**IIIo** was confirmed by the ^1H and ^{13}C NMR, UV, and IR spectra (Tables 2, 3). The ^{13}C NMR spectra of oxazines **IIIa**–**IIIo** in DMSO-d_6 contained a signal at δ_C 84.4–113.4 ppm, which may be assigned to the sp^2-carbon atom in position 5 of the heteroring. No such signal was observed in the spectrum of compound **IV**; instead, a signal at δ_C 45.8 ppm was present, which is typical of sp^3-hybridized methylene carbon atom in **IV**. The downfield carbon signals in the regions δ_C 145.4–147.1, 160.2–161.8, and 160.9–169.9 ppm were assigned to C^2, C^4, and C^6, respectively. In the spectrum of **IV**, signals from the carbonyl carbon atoms appeared at δ_C 166.2 and 169.3 ppm. The spectra of **IIIa**–**IIIo** and **IV** also contained upfield signals from carbon atoms of the alkyl groups.

Oxazines **IIIa**–**IIIo** displayed in the ^1H NMR spectra (DMSO-d_6) a downfield signal from the 4-hydroxy proton at δ 11.59–11.85 ppm. The signal at

Table 2. IR, UV, and ^{1}H NMR spectra of compounds **IIIa**–**IIIo** and **IV**

Comp. no.	IR spectrum, ν, cm^{-1}			UV spectrum, λ_{max}, nm (log ε)	^{1}H NMR spectrum (DMSO-d_6), δ, ppm		
	OH	C=O	C=N		OH	CH_2X	other protons
IIIa	3150	1780	1640	206 (3.84), 280 (4.09)	11.84 s	2.50 s	1.75 s (3H, CH_3)
IIIb	3150	1780	1630	207 (3.80), 280 (4.15)	11.83 s	2.49 s	0.98 t (3H, CH_3), 2.23 q (2H, CH_2)
IIIc	3150	1770	1650	205 (3.72), 281 (4.03)	11.81 s	2.49 s	0.88 t (3H, CH_3), 1.29 m (4H, $2CH_2$), 2.22 t (2H, CH_2)
IIId	3150	1780	1650	207 (4.28), 281 (4.12)	11.72 s	2.48 s	1.22–1.92 (11H, *cyclo*-C_6H_{11})
IIIe	3150	1770	1640	209 (4.37), 234 (4.23), 285 (4.21)	11.68 s	2.50 s	7.35 s (5H, Ph)
IIIf	3170	1780	1660	207 (3.98), 281 (4.25)	11.84 s	3.01 q	0.98 t (3H, CH_3), 1.31 t (3H, CH_3), 2.25 q (2H, CH_2)
IIIg	3150	1770	1640	206 (3.91), 281 (4.22)	11.85 s	3.02 t	0.98 t (3H, CH_3), 1.67 q (2H, CH_2), 1.77 s (3H, CH_3)
IIIh	3250	1780	1640	209 (3.41), 250 (4.20)	11.66 s	3.93 s	1.62 s (3H, CH_3)
IIIi	3200	1780	1640	210 (3.43), 250 (4.23)	11.67 s	3.94 s	0.96 t (3H, CH_3), 2.14 q (2H, CH_2)
IIIj	3150	1770	1650	209 (3.80), 251 (4.33)	11.66 s	3.93 s	0.84 t (3H, CH_3), 1.25 m (4H, $2CH_2$), 2.16 t (2H, CH_2)
IIIk	3200	1775	1660	209 (3.83), 251 (4.26)	11.59 s	3.92 s	1.19–1.67 (11H, *cyclo*-C_6H_{11})
IIIl	3150	1780	1655	208 (4.44), 250 (4.47)	11.69 s	3.94 s	7.38 s (5H, Ph)
IIIm	3150	1770	1640	209 (3.57), 251 (4.24)	11.64 s	4.31 q	0.84 t (3H, CH_3), 0.94 t (3H, CH_3), 2.15 q (2H, CH_2)
IIIn	3150	1780	1640	211 (3.06), 250 (4.19)	11.67 s	4.38 t	1.09 t (3H, CH_3), 1.64 s (3H, CH_3), 3.48–3.50 m (4H, $2CH_2$)
IIIo	3150	1780	1640	207 (3.84), 281 (4.09)	11.78 s	2.49 s	5.87 s (1H, C^5H)
IV	–	1650	–	207 (4.05), 233 (3.93), 270 (3.47)	–	2.22 s	3.36 s (2H, CH_2), 11.48 s (1H, NH)

δ 11.48 ppm in the spectrum of **IV** belongs to the amide protons, while that located at δ 3.62 ppm corresponds to the methylene protons of the malonamide moiety. Protons of the methylsulfanyl group in compounds **IIIa**–**IIIg** and **IIIo** and methoxy group in **IIIh**–**IIIn** give rise to signals in the regions δ 2.49–2.53 and 3.93–3.95 ppm, respectively.

The most characteristic region in the IR spectra of oxazines **IIIa**–**IIIo** (KBr) was 1600–1800 cm^{-1}; it contained absorption bands due to stretching vibrations of the C=O, C=N, and C=C bonds. Absorption bands belonging to vibrations of the hydroxy group were located at 3150–3200 cm^{-1}.

Compounds **IIIa**–**IIIg** and **IIIo** showed in the UV spectra (recorded from solutions in ethanol) absorption maxima at λ 205–209 and 280–285 nm; the spectrum of **IIIe** contains an additional absorption maximum at λ 234 nm. Oxazines **IIIh**–**IIIn** in ethanol give rise to absorption maxima at λ 208–211 and 250–251 nm. Compound **IV** absorbs at λ_{max} 207, 233, and 270 nm. The yields, melting points, R_f values, and elemental analyses of compounds **IIIa**–**IIIo** and **IV** are given in Table 1.

Preliminary testing of the obtained compounds for biological activity showed that their acute toxicity in the Miller–Tainter assay in white mice (15–18 g) considerably depends on the structure. Extension of the alkyl group in position 2 or 5 of the oxazine ring reduces the toxicity only slightly (except for compound **IIIf**), whereas compounds having a phenyl or cyclohexyl group in position 5 are considerably less toxic. 2-Alkoxy oxazines exhibit a slightly lower toxicity as compared to the corresponding 2-alkylsulfanyl-substituted analogs (Table 4).

EXPERIMENTAL

The electronic absorption spectra were measured from solutions in ethanol on an SF-2000 spectrophotometer. The IR spectra were recorded on a Specord IR75 spectrometer from samples prepared as KBr pellets. The ^{1}H and ^{13}C NMR spectra were ob-

Table 3. ^{13}C NMR spectra (δ_C, ppm) of compounds **IIIa**–**IIIo** and **IV** in DMSO-d_6

Comp. no.	CX	Oxazine ring				Other signals
		C^2	C^4	C^5	C^6	
IIIa	12.70	147.0	160.7	105.3	161.3	9.59 (CH_3)
IIIb	12.62	147.0	160.9	111.2	160.9	12.01 (CH_3), 17.97 (CH_2)
IIIc	12.70	147.0	161.0	110.1	161.1	13.60 (CH_3), 21.77 (CH_2), 24.15 (CH_2), 29.39 (CH_2)
IIId	12.94	146.8	160.4	113.4	161.1	25.26–37.43 (*cyclo*-C_6H_{11})
IIIe	12.96	146.8	160,4	111.3	163.4	128.13–130.40 (Ph)
IIIf	24.70	147.1	160.4	105.7	161.3	9.66 (CH_3), 12.70 (CH_2)
IIIg	32.06	147,0	160.2	106.5	161.4	9.86 (CH_3), 12.74 (CH_2), 22.81 (CH_2)
IIIh	56.46	145.5	161.4	84.46	164.4	14.01 (CH_3)
IIIi	56.44	145.7	161.2	85.35	164.9	11.20 (CH_3), 14.70 (CH_2)
IIIj	56.30	145.6	161.2	85.50	164.9	13.50 (CH_3), 20.50 (CH_2), 23.50 (CH_2), 29.90 (CH_2)
IIIk	56.59	145.4	161.4	93.88	163.7	25.39–32.54 (*cyclo*-C_6H_{11})
IIIl	56.30	145.4	161.8	88.30	162.6	127.10–130.80 (Ph)
IIIm	65.91	145.6	161.0	91.22	164.0	11.60 (CH_3), 12.82 (CH_3), 14.88 (CH_2)
IIIn	69.03	145.6	161.0	85.64	164.4	6.39 (CH_3), 14.91 (CH_3), 65.48 (CH_2O), 67.47 (CH_2O)
IIIo	13.15	147.0	160.7	96.96	169.9	–
IV	11.76	–	–	–	–	45.8 (CH_2), 166.2 (C=O), 169.3 (C=O)

tained on a Bruker AM-500 spectrometer from solutions in DMSO-d_6. The progress of reactions was monitored by thin-layer chromatography on Sorbfil plates using ethyl acetate as eluent; spots were visualized by treatment with iodine vapor or under UV light. The melting points of compounds **IIIa**–**IIIo** and **IV** were determined in an open capillary.

5-Alkyl(phenyl)-2-alkylsulfanyl-4-hydroxy-6*H*-1,3-oxazin-6-ones IIIa–**IIIg** *(general procedure).* A mixture of 0.20 mol of *S*-alkyl thiocarbamate **Ia**–**Ic** and 0.22 mol of alkyl(phenyl)malonyl dichloride **IIa**–**IIe** in 30 ml of anhydrous benzene was heated for 3.5 h under reflux (until hydrogen chloride no longer evolved). After cooling, the precipitate was filtered off and recrystallized from benzene or toluene.

2-Alkoxy-5-alkyl(phenyl)-4-hydroxy-6*H*-1,3-oxazin-6-ones IIIh–**IIIn.** A mixture of 0.20 mol of alkyl carbamate **Id**–**If** and 0.22 mol of alkyl(phenyl)-malonyl dichloride **IIa**–**IIe** in 30 ml of anhydrous benzene was heated for 3.5 h under reflux (until hydrogen chloride no longer evolved). After cooling, the precipitate was filtered off and recrystallized from benzene or toluene.

4-Hydroxy-2-methylsulfanyl-6*H*-1,3-oxazin-6-one (IIIo). A mixture of 1.5 g of *S*-methyl thiocarbamate and 2.57 g of malonyl dichloride in 20 ml of anhydrous toluene was heated for 4 h under reflux (until hydrogen chloride no longer evolved). After cooling, the precipitate was filtered off and recrystallized from benzene or toluene.

Table 4. Acute toxicity of compounds **IIIa**–**IIIf, IIIh, IIIi, IIIk**, and **IIIl** according to Miller–Tainter

Comp. no.	LD_{50}, mg/kg	Comp. no.	LD_{50}, mg/kg
IIIa	152	**IIIf**	1230
IIIb	251	**IIIh**	250
IIIc	498	**IIIi**	348
IIId	1045	**IIIk**	1640
IIIe	1028	**IIIl**	1620

***S*-Methyl (3-methylsulfanylaminocarbonyl-3-oxopropionyl)thiocarbamate (IV).** A mixture of 1.5 g of *S*-methyl thiocarbamate and 1.28 g of malonyl dichloride in 100 ml of anhydrous benzene or diethyl ether was heated under reflux until hydrogen chloride no longer evolved (~2.5 h). The precipitate was filtered off, washed with benzene, and dried.

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