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Synthesis of 2-Aryl(Hetaryl)-4*H*-1,3,4-oxadiazine-5,6-diones

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Abstract — Aromatic and heteroaromatic acid hydrazides reacted with oxalyl chloride in benzene or chloroform to give previously unknown 2-aryl(hetaryl)-4*H*-1,3,4-oxadiazine-5,6-diones whose structure was confirmed by the NMR, IR, and mass spectra. According to the spectral data and the results of quantum-chemical calculations, the products exist mainly in the lactam form.
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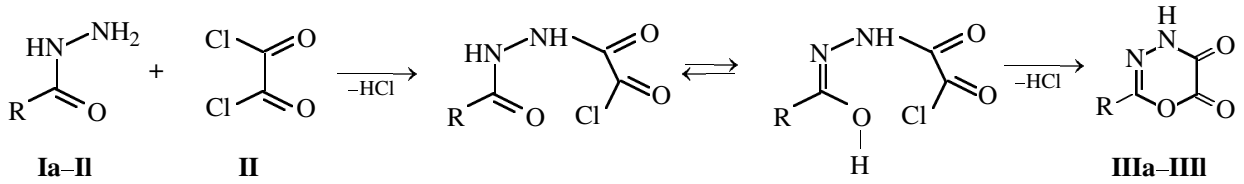
First representatives of 4*H*-1,3,4-oxadiazine-5,6-diones were synthesized in the first half of the XXth century by reaction of oxalyl chloride with N'-substituted benzo- and acetohydrazides [1–3]. The products were 2-alkyl(aryl)-4-aryl-4*H*-1,3,4-oxadiazine-5,6-diones. However, we have found no published data on 4*H*-1,3,4-oxadiazine-5,6-diones having no substituent in the 4-position.

In this study we examined reactions of oxalyl chloride with carboxylic acid hydrazides with unsubstituted NH_2 group. The reactions were carried out in boiling benzene, chloroform, or carbon tetrachloride using 15% excess of oxalyl chloride, the reactant concentration being 5–10%; the reaction mixtures were heterogeneous because of poor solubility of the initial hydrazides in the above solvents. The reactions were exothermic and were accompanied by vigorous evolution of hydrogen chloride. When chloroform was used as solvent, hydrazides **Ia**–**Il** were added in portions, otherwise the reaction mixture boiled up almost instantaneously. The progress of reactions was monitored by TLC. As a result, we isolated 1,3,4-oxadiazines **IIIa**–**IIIl** (Scheme 1).

Scheme 1.



Ia–**Il** **II** **IIIa**–**IIIl**

R = Ph (**a**), 3-$O_2NC_6H_4$ (**b**), 4-$O_2NC_6H_4$ (**c**), 3,5-$(O_2N)_2C_6H_3$ (**d**), 3-ClC_6H_4 (**e**), 4-ClC_6H_4 (**f**), 3-BrC_6H_4 (**g**), 2,4-$Cl_2C_6H_3$ (**h**), 3-$MeOC_6H_4$ (**i**), 4-$MeOC_6H_4$ (**j**), 2-furyl (**k**), 2-thienyl (**l**).

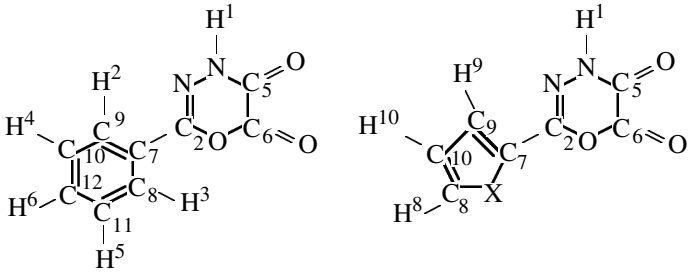
Compounds **IIIa**–**IIIl** are colorless substances poorly soluble in water, benzene, toluene, chloroform, methylene chloride, carbon tetrachloride, and ethyl acetate and readily soluble in THF and dioxane (on heating). Their yields, melting points, and analytical data are given in Table 1. The structure of oxadiazines **IIIa**–**IIIl** was confirmed by the ^1H and ^{13}C NMR, UV, and IR spectra (Tables 2, 3). In the ^{13}C NMR spectra of **IIIa**–**IIIl** in DMSO-d_6 we observed a signal at δ_C 143.5–146.8 ppm, which was assigned to the sp^2-hybridized C^2 atom. The C^5 and C^6 signals appeared at δ_C 150–153 ppm. Carbon nuclei in the substituent on C^2 resonated in the δ_C region 114.1–160.4 (**IIIa**–**IIIj**) or 112.2–142.2 ppm (**IIIk**, **IIIl**). The ^1H NMR spectra of oxadiazines **IIIa**–**IIIl** in DMSO-d_6 contained a signal from the NH proton at

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

Comp. no.	mp, °C	Yield, %	R_f [a]	Found, %					Formula	Calculated, %				
				C	H	N	O	other		C	H	N	O	other
IIIa	241–243	82	0.22	56.61	3.21	14.81	25.37	–	$C_9H_6N_2O_3$	56.84	3.18	14.74	25.24	–
IIIb	282–284	75	0.34	45.91	2.20	17.88	34.01	–	$C_9H_5N_3O_5$	45.97	2.14	17.87	34.02	–
IIIc	280–282	77	0.40	46.04	2.22	17.90	33.84	–	$C_9H_5N_3O_5$	45.97	2.14	17.87	34.02	–
IIId	304–306	80	0.37	38.41	1.43	20.07	40.09	–	$C_9H_4N_4O_7$	38.58	1.44	20.00	39.98	–
IIIe	247–248	74	0.21	48.07	2.30	12.45	21.33	15.85 (Cl)	$C_9H_5ClN_2O_3$	48.13	2.24	12.48	21.37	15.78 (Cl)
IIIf	339–341	85	0.34	48.15	2.27	12.40	21.40	15.78 (Cl)	$C_9H_5ClN_2O_3$	48.13	2.24	12.48	21.37	15.78 (Cl)
IIIg	295 decomp.	81	0.28	40.20	1.90	10.60	17.73	29.57 (Br)	$C_9H_5BrN_2O_3$	40.17	1.87	10.42	17.84	29.70 (Br)
IIIh	254–256	80	0.24	41.67	1.59	10.85	18.42	27.47 (Cl)	$C_9H_4Cl_2N_2O_3$	41.73	1.56	10.81	18.53	27.37 (Cl)
IIIi	330–332	80	0.26	54.45	3.69	12.70	29.16	–	$C_{10}H_8N_2O_4$	54.55	3.66	12.72	29.07	–
IIIj	330–332	81	0.28	54.47	3.72	12.81	29.00	–	$C_{10}H_8N_2O_4$	54.55	3.66	12.72	29.07	–
IIIk	193–195	78	0.24	46.82	2.21	15.48	35.49	–	$C_7H_4N_2O_4$	46.68	2.24	15.55	35.53	–
IIIl	295 decomp.	82	0.33	42.98	1.99	14.22	24.54	16.27 (S)	$C_7H_4N_2O_3S$	42.86	2.06	14.27	24.47	16.34 (S)

[a] THF–AcOH–H_2O, 40 : 4 : 3.

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



Comp. no.	^{1}H NMR spectrum (DMSO-d_6), δ, ppm		UV spectrum, λ_{max}, nm	IR spectrum (KBr), ν, cm^{-1}			
	NH (H^1)	other protons		N–H	(O–)C=O	(NH)C=O	C=N
IIIa	12.21 s	7.82 m (2H, H^2, H^3), 7.54 m (2H, H^4, H^5), 7.52 m (1H, H^6)	203.5; 239; 290	3220	1800	1710	1640
IIIb	12.47 s	8.70 m (1H, H^2), 8.33 m (1H, H^3), 7.85 m (1H, H^5), 8.46 m (1H, H^6)	205; 217.5; 258.5	3200	1770	1700	1650
IIIc	12.51 s	8.12 s (2H, H^2, H^3), 8.37 s (2H, H^4, H^5)	205; 264.5	3210	1790	1690	1650
IIId	12.62 s	9.02 m (2H, H^2, H^3), 8.96 m (1H, H^6)	202; 237.5; 327.5	3225	1800	1705	1640
IIIe	12.38 s	7.91 m (1H, H^2), 7.76 m (1H, H^3), 7.67 m (1H, H^5), 7.56 m (1H, H^6)	205; 280	3210	1790	1715	1640
IIIf	12.31 s	7.85 d (2H, H^2, H^3), 7.50 d (2H, H^4, H^5)	206; 279	3215	1780	1720	1640
IIIg	12.37 s	7.89 m (1H, H^2), 7.81 m (1H, H^3), 7.74 m (1H, H^5), 7.49 m (1H, H^6)	207; 281	3200	1810	1700	1660
IIIh	12.43 s	7.71 m (1H, H^2), 7.80 m (1H, H^4), 7.56 m (1H, H^5)	208; 275	3150	1780	1710	1655

Table 2. (Contd.)

Comp. no.	^{1}H NMR spectrum (DMSO-d_6), δ, ppm		UV spectrum, λ_{max}, nm	IR spectrum (KBr), ν, cm^{-1}			
	NH (H^1)	other protons		N–H	(O–)C=O	(NH)C=O	C=N
IIIi	12.37 s	7.55 m (1H, H^2), 7.61 m (1H, H^3), 7.54 m (1H, H^5), 7.12 m (1H, H^6) 3.81 s (3H, CH_3)	207; 270	3200	1810	1700	1640
IIIj	12.19 s	7.06 d (2H, H^2, H^3), 7.75 d (2H, H^4, H^5), 3.83 s (3H, CH_3)	210; 258	3210	1780	1705	1645
IIIk	12.21 s	7.92 m (1H, H^8), 7.05 m (1H, H^9), 6.69 m (1H, H^{10})	207; 253.5	3230	1790	1705	1650
IIIl	12.20 s	7.55 m (1H, H^8), 7.62 m (1H, H^9), 7.28 m (1H, H^{10})	204; 249.5	3220	1790	1710	1640

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

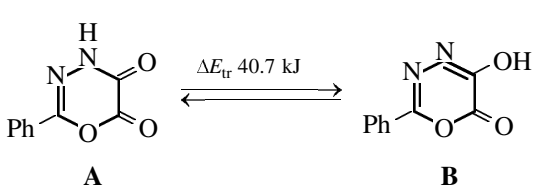
Comp. no.	Oxadiazine ring			Other signals
	C^2	C^5	C^6	
IIIa	145.8	151.0	152.3	131.1 (C^7), 125.6 (C^8, C^9), 128.2 (C^{10}, C^{11}), 128.9 (C^{12})
IIIb	143.9	151.1	151.9	120.2 (C^7), 133.9 (C^8), 128.4 (C^9), 148.3 (C^{10}), 131.1 (C^{11}), 130.6 (C^{12})
IIIc	144.1	151.1	152.0	131.3 (C^7), 137.9 (C^8, C^9), 123.9 (C^{10}, C^{11}), 149.6 (C^{12})
IIId	146.8	151.3	152.4	136.2 (C^7), 126.4 (C^8, C^9), 148.6 (C^{10}, C^{11}), 120.4 (C^{12})
IIIe	144.4	151.1	152.1	134.2 (C^7), 128.4 (C^8), 125.3 (C^9), 133.5 (C^{10}), 130.5 (C^{11}), 131.1 (C^{12})
IIIf	144.8	151.2	152.3	131.2 (C^7), 130.7 (C^8, C^9), 127.8 (C^{10}, C^{11}), 137.4 (C^{12})
IIIg	144.3	151.0	152.1	130.3 (C^7), 132.1 (C^8), 130.3 (C^9), 126.5 (C^{10}), 128.2 (C^{11}), 136.1 (C^{12})
IIIh	143.5	150.7	152.0	134.4 (C^7), 122.2 (C^8), 128.7 (C^9), 133.7 (C^{10}), 130.5 (C^{11}), 131.4 (C^{12})
IIIi	144.4	151.1	152.1	134.2 (C^7), 120.8 (C^8), 113.7 (C^9), 158.6 (C^{10}), 130.5 (C^{11}), 116.7 (C^{12}), 55.28 (CH_3)
IIIj	144.9	150.9	152.0	126.2 (C^7), 128.7 (C^8, C^9), 114.1 (C^{10}, C^{11}); 160.4 (C^{12}), 55.26 (CH_3)
IIIk	146.1	150.9	151.8	142.2 (C^7), 139.4 (C^8), 113.0 (C^9), 112.2 (C^{10})
IIIl	145.9	150.9	152.0	139.2 (C^7), 132.4 (C^8), 131.0 (C^9), 126.2 (C^{10})

δ 12.20–12.62 ppm, signals from protons in the aromatic and heterocyclic substituents on C^2, and singlets at δ 3.93–3.95 ppm from the methoxy protons of compounds **IIIi** and **IIIj**.

Compounds **IIIa**–**IIIl** showed in the IR spectra (KBr) absorption bands belonging to stretching vibrations of the carbonyl groups (C^6=O, 1770–1810 cm^{-1}; C^5=O, 1690–1720 cm^{-1}), C=N bonds (1640–1660 cm^{-1}), and NH bonds (3200–3250 cm^{-1}). The electronic spectra of solutions of **IIIa**–**IIIl** in ethanol contained absorption maxima at δ 202–209 and 270–290 nm; in the spectrum of **IIId**, the latter maximum was displaced to 327 nm. Compounds **IIIa** and **IIId** also displayed a maximum at δ 237–239 nm. In the spectra of **IIIk** and **IIIl**, the long-wave maximum appeared at δ 250–253 nm.

According to the PM3 semiempirical quantum-chemical calculations (HyperChem 7.0 software package), among two possible tautomeric forms **A** and **B**, the former (lactam) is energetically more favorable (Scheme 2).

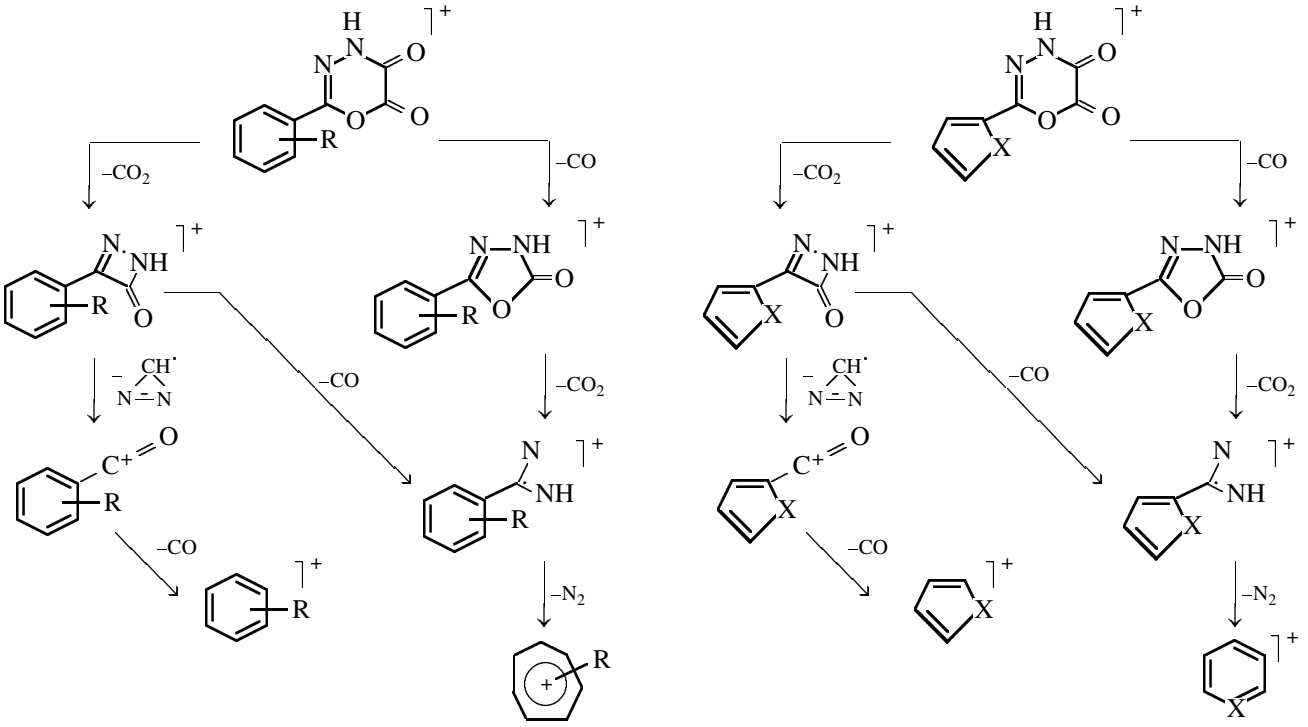
Scheme 2.



A **B**

Fragmentation of 1,3,4-oxadiazines **IIIa**–**IIIl** under electron impact generally follows Scheme 3. The mass

Scheme 3.



spectra of all compounds contain the molecular ion peak, and its subsequent decomposition involves ring contraction along two possible pathways: via successive elimination of CO and CO_2 or vice versa, CO_2 and CO (Table 4). Elimination of diazirenyl radical is also possible.

EXPERIMENTAL

The electronic absorption spectra were measured from solutions in ethanol on an SF-2000 spectrophotometer. The IR spectra were recorded in KBr on a Specord IR-75 instrument. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-500 spectrometer using DMSO-d_6 as solvent. The mass spectra (electron impact, 70 eV) were recorded on an MKh-1321 mass spectrometer. The progress of reactions was monitored by TLC on Sorbfil plates using THF–AcOH–H_2O (40 : 4 : 3) as eluent; spots were visualized under UV light or by treatment with iodine vapor. The melting points were determined by the capillary technique.

2-Aryl(hetaryl)-4*H*-1,3,4-oxadiazine-5,6-diones IIIa–IIIl *(general procedure).* Hydrazide **Ia–Il**, 0.020 mol, was added to a solution of 0.023 mol of oxalyl chloride (**II**) in 50 ml of anhydrous benzene or chloroform. When the exothermic reaction was complete, the mixture was heated for 2–3 h under reflux (TLC) and cooled, and the precipitate was filtered off, washed with chloroform and diethyl ether, and recrystallized from chlorobenzene or toluene.

Table 4. Mass spectra of compounds **IIa–IIl**, *m/z* (I_{rel}, %)

Comp. no.	M^+	$[M-CO]^+$	$[M-CO_2]^+$	$[M-CO-CO_2]^+$
IIIa	190 (100)	162 (89)	146 (5.4)	118 (87)
IIIb	235 (100)	207 (91)	191 (7.5)	163 (82)
IIIc	235 (100)	207 (94)	191 (4.4)	163 (78)
IIId	280 (100)	252 (88)	236 (4.8)	208 (75)
IIIe	224 (100)	196 (83)	180 (2.8)	152 (72)
IIIf	224 (100)	196 (74)	180 (3.1)	152 (69)
IIIg	269 (100)	241 (71)	225 (4.5)	197 (72)
IIIh	259 (100)	231 (80)	215 (3.4)	187 (91)
IIIi	220 (100)	192 (77)	176 (4.2)	148 (82)
IIIj	220 (100)	192 (59)	176 (1.8)	148 (65)
IIIk	180 (100)	152 (70)	136 (4.1)	108 (62)
IIIl	196 (100)	168 (72)	152 (3.5)	124 (71)

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