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Synthesis of 4-Aryl-1,5-benzodiazepine-2-carboxamides

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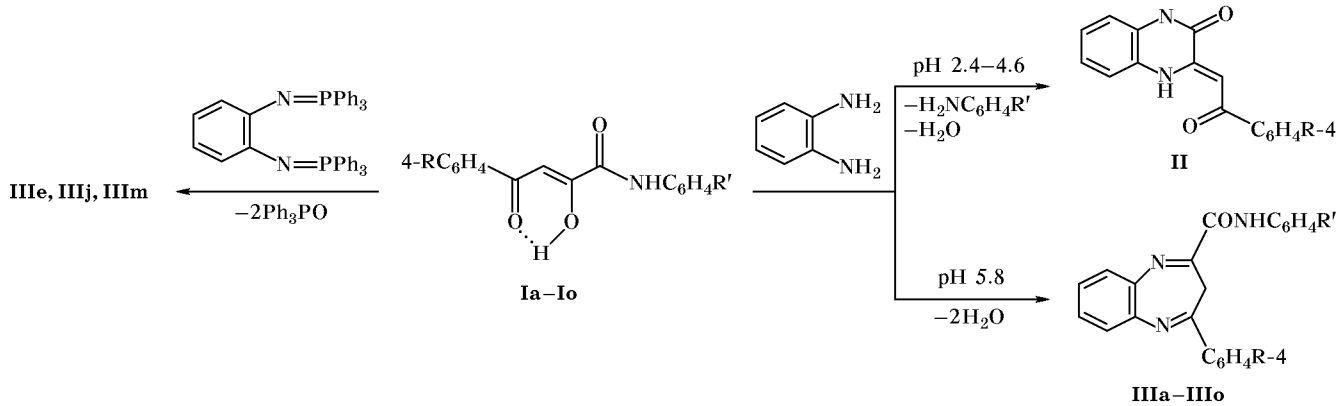
Abstract—4,*N*-Diaryl-1,5-benzodiazepine-2-carboxamides were synthesized by acid-catalyzed reaction of (*Z*)-4,*N*-diaryl-2-hydroxy-4-oxo-2-butenamides with *o*-phenylenediamine or *N*,*N*′-bis(triphenylphosphoranediyl)-*o*-phenylenediamine. The reaction mechanism is discussed.

The reaction of *o*-phenylenediamine with β-dicarbonyl compounds underlies a traditional procedure for preparation of 1,5-benzodiazepine derivatives. However, 4-aryl-2,4-dioxobutanoic acids and esters derived therefrom react with *o*-phenylenediamine in inert solvents to give exclusively 3-phenacylidene-3,4-dihydroquinoxalin-2-ones [1–3]. According to Andreichikov *et al.* [3], 4,*N*-diaryl-2,4-dioxobutanamides **I** do not react with *o*-phenylenediamine, but fusion of these reactants leads to formation of quinoxalin-2-ones **II** and 4-aryl-1,5-benzodiazepine-2-carboxylic acid arylamides **III**. The dual reactivity of arylamides **I** was revealed previously [4], and the kinetics of their reaction with *o*-phenylenediamine were studied in detail at pH 2.4–4.6 [5], i.e., under conditions which ensure formation of only quinoxalin-2-ones **II**. The goal of the present work was to develop a procedure for the synthesis of 1,5-benzodiazepine derivatives starting from arylamides **I**.

We studied the reaction of arylamides **Ia**–**Io** with *o*-phenylenediamine (*o*-PDA) over a wide range of pH. When the reaction was carried out in aqueous alcohol at pH 5.8, the products were 4-aryl-1,5-benzodiazepine-2-carboxamides **IIIa**–**IIIo** which were formed in 70 to 92% yield (method *a*; Scheme 1, Tables 1, 2).

Scheme 1.



I, **III**, R = H, R′ = 4-CH_3O (**a**), 4-CH_3 (**b**), 4-Cl (**c**), 3-NO_2 (**d**), 2-CH_3OCO (**e**), 4-C_2H_5OCO (**f**); R = Br, R′ = H (**g**), 4-CH_3O (**h**), 2-CH_3OCO (**i**), 4-C_2H_5OCO (**j**); R = Cl, R′ = H (**k**), 2-CH_3OCO (**l**), 4-C_2H_5OCO (**m**); R = CH_3, R′ = 2-CH_3OCO (**n**), 4-C_2H_5OC (**o**).

† Deceased.

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Table 1. Yields, melting points, and spectral parameters of 1,5-benzodiazepine derivatives **IIIa**–**IIIo**

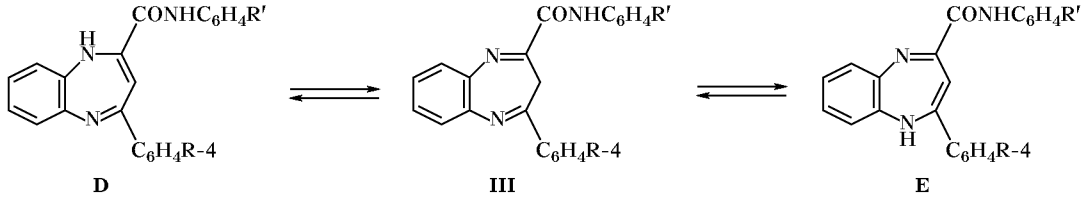
Comp. no.	Yield, %		mp, °C	IR spectrum, ν, cm^{-1}			^1H NMR spectrum, δ, ppm
	a	*b*		NH	COO, C=O	C=N, C=C	
IIIa[a]	83	42	179–180	3322	1685	1605	
IIIb[a]	83	63	201–202	3305	1680	1600	
IIIc	87	0	205–206	3348	1682	1615, 1595	3.59 s (2H, CH_2), 7.62 m (13H, C_6H_5, $2C_6H_4$), 10.42 s (1H, NHCO)
IIId	84		203–205	3305	1691	1595	
IIIe	80		194–195	3213	1699 br	1603	3.75 s (2H, CH_2), 3.97 s (3H, CH_3), 7.70 m (13H, C_6H_5, $2C_6H_4$), 8.75 s (1H, NH), 12.21 s (1H, NHCO)
IIIf	90		176–177	3330	1712, 1700	1610, 1595	
IIIg	85	0	240–241	3322	1699	1615 br	3.70 s (2H, CH_2), 7.55 m (13H, C_6H_5, $2C_6H_4$), 10.22 s (1H, NHCO)
IIIh[a]	85	44	207–208	3328	1685	1600 br	
IIIi	70		199–200	3263	1709, 1699	1590 br	
IIIj	89		229–231	3321	1717, 1691	1611, 1592	1.40 t (3H, CH_3), 3.73 s (2H, CH_2), 4.32 q (2H, CH_2), 7.70 m (12H, $3C_6H_4$), 10.35 s (1H, NHCO)
IIIk	86		242–244	3330	1680	1600 br	
IIIl	73		186–187	3305	1688	1590	
IIIm	88		238–239	3311	1718, 1689	1610, 1592	1.38 t (3H, CH_3), 3.72 s (2H, CH_2), 4.35 q (2H, CH_2), 7.75 m (12H, $3C_6H_4$), 10.41 s (1H, NHCO)
IIIn	82		197–199	3320	1710, 1685	1615, 1590	3.72 s (2H, CH_2), 3.92 s (3H, CH_3), 7.60 m (12H, $3C_6H_4$), 8.72 s (1H, NH), 12.51 s (1H, NHCO)
IIIo	92		205–207	3326	1709, 1700	1608, 1598	

[a] Compounds **IIIa**, **IIIb**, **IIIh** were reported in [4].

Table 2. Elemental analyses of compounds **IIIc**–**IIIg**, **IIIi**, **IIIj**, and **IIIl**–**IIIo**

Comp. no.	Found, %				Formula	Calculated, %			
	C	H	N	Hlg		C	H	N	Hlg
IIIc	70.56	4.20	11.15	9.33	$C_{22}H_{16}ClN_3O$	70.68	4.28	11.25	9.51
IIId	68.58	4.12	14.56		$C_{22}H_{16}N_4O_3$	68.75	4.19	14.58	
IIIe	72.71	4.65	10.49		$C_{24}H_{19}N_3O_3$	72.54	4.79	10.57	
IIIf	72.62	5.21	10.25		$C_{25}H_{21}N_3O_3$	72.99	5.11	10.22	
IIIg	63.02	3.79	10.00	19.02	$C_{22}H_{16}BrN_3O$	63.16	3.83	10.04	19.14
IIIi	60.86	3.59	8.79	17.01	$C_{24}H_{18}BrN_3O_3$	60.51	3.81	8.82	16.77
IIIj	61.40	4.18	8.49	16.49	$C_{25}H_{20}BrN_3O_3$	61.22	4.08	8.57	16.32
IIIn	66.50	4.29	9.80	8.54	$C_{24}H_{18}ClN_3O_3$	66.74	4.17	9.73	8.22
IIIm	67.08	4.33	9.35	8.17	$C_{25}H_{20}ClN_3O_3$	67.34	4.48	9.43	7.97
IIIn	73.23	5.26	9.98		$C_{25}H_{21}N_3O_3$	72.99	5.11	10.22	
IIIo	73.14	5.48	9.83		$C_{26}H_{23}N_3O_3$	73.41	5.41	9.88	

Scheme 2.

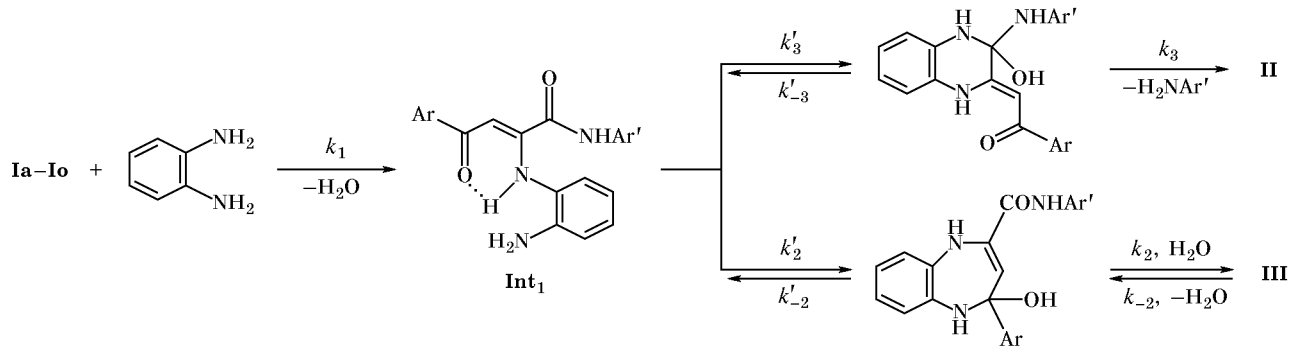


Compound **IIIa**–**IIIo** showed in the electron absorption spectra a strong maximum at λ 260–270 nm (log ε 4.75–4.90). Their IR spectra (Table 1) contained NH absorption band in the region 3350–3345 cm^{-1} and amide carbonyl band at 1680–1675 cm^{-1} (cf. [4]). In the ^1H NMR spectra of **IIIc**, **IIIe**, **IIIg**, **IIIj**, **IIIm**, and **IIIn** (Table 1), signal from the methylene protons appears as a singlet at δ 3.69–3.82 ppm. In the spectra of compounds **IIIc**, **IIIg**, **IIIj**, and **IIIm** this signal is strongly broadened, which is explained by inversion of the seven-membered ring, like that observed for both 1,4-benzodiazepines [6] and 4-methyl-1,2-dihydro-3*H*-1,5-benzodiazepin-2-one [7]. The presence of an electron-acceptor substituent in the *ortho*-position of the aromatic ring in the amide fragment (compounds **IIIe** and **IIIn**) induces a downfield shift of the amide proton signal relative to the corresponding signals of *para*-substituted amides **IIIj** and **IIIm** (Δδ 1.80–2.16 ppm). The spectrum contains the N^1H signal and signal from the methine proton in the aromatic region, and the intensity of the methylene proton signal corresponds to one proton. These data suggest tautomeric transformations of 1,5-benzodiazepines **III** (Scheme 2). However, the IR spectra of crystalline samples of **III** (in mineral oil) contain no signals assignable to tautomeric forms **D** and **E**.

According to the data of [4], electron-donor substituents in the aroyl moiety favor formation of benzodiazepine derivatives **III** on fusion of amides **I** with *o*-phenylenediamine (method *b*), whereas electron-acceptor groups favor formation of quinoxalin-2-ones **II**. In our procedure (method *a*) there is no effect of the substituent nature (both in the aroyl and in the amide moieties) on the yield of compounds **III**. The yields of products **III** obtained according to methods *a* and *b* are compared in Table 1. It should be noted that method *a* requires that the necessary reaction time was strictly met, otherwise (on prolonged reaction) quinoxalin-2-one derivatives accumulate in the reaction mixture. Compounds **IIIe**, **IIIj**, and **IIIm** were also synthesized by the action of *N*,*N*′-bis(triphenylphosphoranediyl)-*o*-phenylenediamine on arylamides **Ie**, **Ij**, and **Im** in toluene on heating (method *c*), but their yields were as poor as 21, 15, and 27%, respectively. The reason is that the isolation and purification of the products is accompanied by formation of quinoxalin-2-one derivatives **II**.

In the first reaction stage, nucleophilic attack by the amino group of *o*-phenylenediamine on the C^2 atom of the substrate and subsequent elimination of water give intermediate enamine $\mathbf{Int}_1$. Stabilization of the latter can take two pathways. In acid medium (pH 2.4–4.6), the rate constant k_3 is high in absolute value, even if the rates of formation of 1,5-benzodiazepine and quinoxalin-2-one derivatives are comparable ($k_2 \approx k_3$). Therefore, fast displacement of the equilibrium toward more stable product **II** should occur (thermodynamic control). As pH rises to 5.8, the rate of formation of benzodiazepine **III** is likely to exceed the rate of formation of quinoxalin-2-one **II** ($k_2 > k_3$), provided that nucleophilic attack by the free amino group in intermediate $\mathbf{Int}_1$ on the γ-carbonyl

Scheme 3.



group is less sensitive to acid catalysis than the attack on the amide carbonyl. This is quite probable, for resonance stabilization of the amide carbonyl undoubtedly requires stronger catalysis, as compared to the γ-carbonyl group. Correspondingly, when the reaction time is not long (0.5–1.0 h), compounds **III** can be isolated as kinetically controlled products. Increase of the reaction time to 5–6 h even at pH 5.8 leads to accumulation of quinoxalin-2-ones **II**, while benzodiazepines **III** cannot be isolated.

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord M-80 spectrometers in mineral oil. The ^{1}H NMR spectra were obtained on a Bruker WR-80-SY instrument (80 MHz) using HMDS as internal reference and chloroform-*d* and DMSO-d_6 as solvents. The UV spectra were measured on a Specord UV-Vis spectrophotometer in ethanol ($c = 1 \times 10^{-5}$ M). The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using the solvent system diethyl ether–benzene–acetone (10 : 9 : 1), development with iodine vapor.

4-Aryl-1,5-benzodiazepin-2-carboxamides IIIa–IIIo. *a.* A solution of 2.97 g (0.01 mol) of amide **Ia**, 1.08 g (0.01 mol) of *o*-phenylenediamine, 6 ml of acetate buffer (pH 5.8), and 0.8 ml of a 1.68 M alcoholic solution of HCl in 100 ml of ethanol was refluxed for 0.5 h. The solvent was evaporated, and the residue was recrystallized from acetonitrile. Yield 3.06 g. Compounds **IIIb**–**IIIo** were synthesized in a similar way.

b. A mixture of 0.297 g (1 mmol) of amide **Ia** and 0.108 g (1 mmol) of *o*-phenylenediamine was heated for 0.25 h at 120–130°C. The melt was heated in 15 ml of boiling acetonitrile, the mixture was filtered, the filtrate was cooled, and the precipitate of compound **IIIa** was filtered off and recrystallized. Yield 0.155 g. Compounds **IIIb** and **IIIh** were obtained in a similar way.

c. A solution of 0.325 g (1 mmol) of amide **Ie** and 0.629 g (1 mmol) of *N*,*N*′-bis(triphenylphosphoranediyl)-*o*-phenylenediamine in 7 ml of dry toluene was refluxed for 12 h. The solvent was removed, the residue was dissolved in 5 ml of alcohol, and the precipitate of compound **II** was filtered off. The filtrate was evaporated, and the residue was recrystallized from acetonitrile. Yield of compound **IIIe** 0.08 g (21%), mp 194–195°C. Compounds **IIIj** and **IIIm** were synthesized in a similar way.

The yields, melting points, and IR and ^{1}H NMR spectra of the products are collected in Table 1, and Table 2 contains their elemental analyses.

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