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REACTION OF 3-BENZOYL-2,3-DIBROMO-PROPIONIC ACID WITH SUBSTITUTED *ortho*-PHENYLENEDIAMINES

N. N. Kolos, T. V. Berezkina, V. D. Orlov, Yu. N. Surov, and I. V. Ivanova

3-Benzoyl-2,3-dibromopropionic acid reacts with 4-substituted o-phenylenediamines to give 3-aryl-2-carboxymethylene-1,2-dihydroquinoxalines.

Keywords: 3-aryl-2-carboxymethylene-1,2-dihydroquinoxalines, 3-benzoyl-2,3-dibromopropionic acid, 4-R-*o*-phenylenediamines.

In continuation of our work on the reaction of polyelectrophilic systems with bidentate nucleophiles [1], we have studied the reaction of 3-benzoyl-2,3-dibromopropionic acid (**1**) with 4-substituted *o*-phenylenediamines **2a-g**. By refluxing the starting reagents in alcohol in the presence of triethylamine as dehydrobrominating agent acid **1** gives the geminally activated olefins **3** and **4** and these can act as polyfunctional building units in reaction with diamines **2a-g**. This can result in the possible formation of a series of reaction products, the most likely of which are dihydroquinoxalines **5**, benzodiazepines **6**, and quinoxalines **7**.

A negative test for the diazotropylium cation in the reaction products (absence of a violet coloration upon treatment with concentrated sulfuric acid) allows one to exclude the diazepine structure **6**. Phenacylidenequinoxaline **7** ($R^1 = R^2 = H$) has been prepared before [2] from benzoylpyruvic acid and *o*-phenylenediamine but its parameters (mp, ^{1}H NMR data) do not agree with the parameters for compound **5a** (Tables 1 and 2).

The combined spectroscopic data for the obtained products (Table 2) allows us to assign them the structure of dihydroquinoxalines **5**.

In their ^{1}H NMR spectra (measured in DMSO-d_6 solutions) a singlet for the C=CH group proton, two singlets at 12.0 and 13.0 ppm which disappear in conditions of deuterium exchange and which we assign to the NH and OH group signals respectively, and also multiplets for the aromatic protons at 7.0-8.1 ppm are observed.

The presence of substituents in the molecules of diamines **2b-g** suggests the formation of isomeric 6- and 7- substituted dihydroquinoxalines **5b-k**. In fact, the ^{1}H NMR spectra of the products obtained from diamines **2b-d,f** show a doubling of the signal for the =CH group proton and for the signals of the OH and NH group protons.

The isomeric ratio was calculated by a comparison of the integrated intensities of these signals and also integration of the signals for the aromatic protons in positions 5 and 8 of the indicated products. It did not prove possible to separate the isomeric dihydroquinoxalines **5b** and **5h**, **5c** and **5i**, **5d** and **5j**, or **5f** and **5k** using the TLC method. The reaction of acid **1** with diamine **2e** led to only the 5-nitro isomer **5e**.

V. N. Karazin National University, Kharkov 61077, Ukraine; e-mail: orlov@univer.kharkov.ua.
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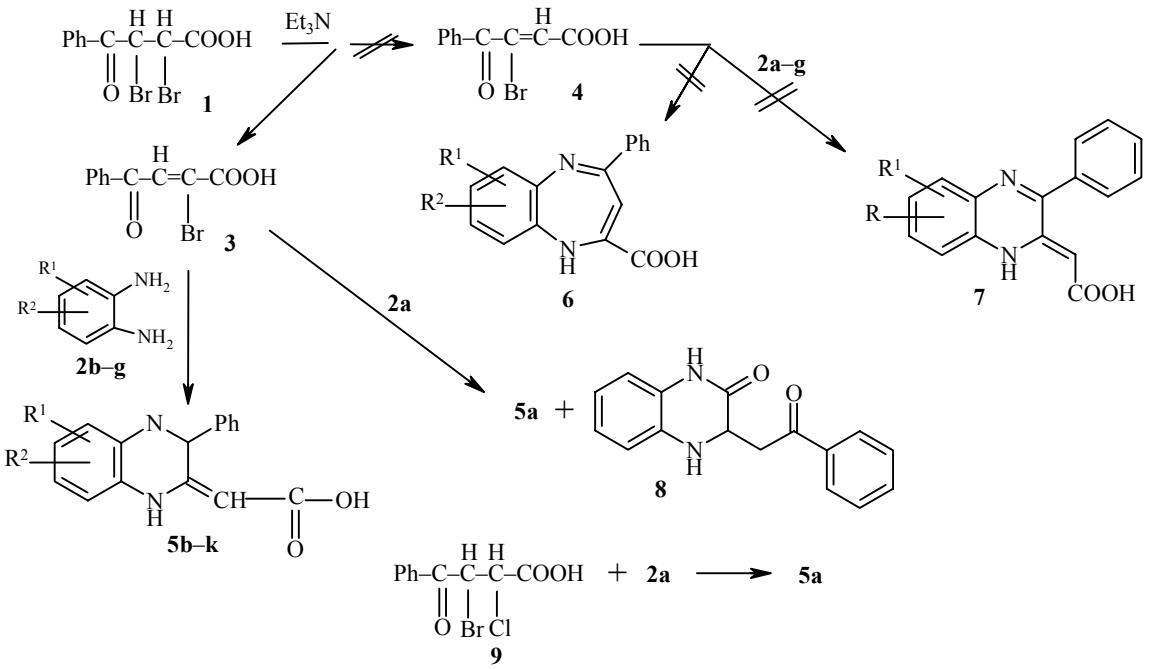


2 a R^1 = H, **b** R^1 = 4-Cl, **c** R^1 = 4-Br, **d** R^1 = 4-CN, **e** R^1 = 3-NO_2, **f** R^1 = 4-Me, **g** R^1 = 4-Me, **a-f** R^2 = H, **g** R^2 = 5-Me;
5 a R^1 = H, **b** R^1 = 6-Cl, **c** R^1 = 6-Br, **d** R^1 = 6-CN, **e** R^1 = 5-NO_2, **f** R^1 = 6-Me, **g** R^1 = 6-Me, **h** R^1 = 7-Cl,
i R^1 = 7-Br, **j** R^1 = 7-CN, **k** R^1 = 7-Me, **a-f**, **h-k** R^2 = H, **g** R^2 = 7-Me

The UV spectra of compounds **5a,e,g** and the mixtures of isomers **5b,h**, **5c,i**, and **5f,k** were measured in 2-propanol and showed intense absorption bands at 270-440 nm (Table 2). Dihydroquinoxalines **5** obtained luminesce in methanol solutions and in the solid phase but, in contrast to 3-aryl-1,2-dihydroquinoxalines [3], they are stable on storage in air.

The IR spectra of compounds **5** (KBr tablets) show bands for a C=CH group near 1620, carbonyl group in the region of 1680-1695, and a broad band at 3000-3100 cm^{-1} which we assign to an associated hydroxyl group. In CCl_4 solutions they show bands for the secondary amino group (see Table 2) as well as three bands in the region for carbonyl absorption. The high-frequency band in the latter is assigned to the free carboxyl group while that at low frequency is very likely related to the formation of dimeric associates in the products **5a-k**.

It should be noted that the IR spectrum of acid **1** in CCl_4 shows bands for the free and bound hydroxyl groups (ν_{OH}^{free} 3538, ν_{OH}^{bound} (br.) 3066 cm^{-1}) as well as three bands for the carbonyl absorption at 1679 (benzoyl fragment absorption), 1709, and 1743 cm^{-1} (carboxyl group cyclic dimer and monomer respectively). These data point to the retention of the carboxyl group in the molecules **5a-k**. The presence of a certain amount of the monomer form in the solution is confirmed by the appearance of absorption band due to stretching vibrations for a free hydroxyl group in compounds **5a, 5b,h, 5c,i,** and **5e**. Thus, from the IR spectroscopic data for compounds **5a-k** follows that they are characterized by the formation of dimers at the carboxyl group (structure **A**) and not intramolecular associates (**B**). This shows that the compounds obtained are in the *E*-isomer form.

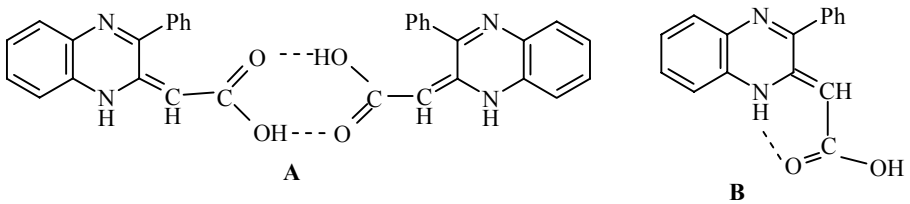


TABLE 1. Characteristics for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %	mp, °C	Yield, %
5a	$C_{16}H_{12}N_2O_2$	10.57 / 10.59	222-224	45*
5b+5h	$C_{16}H_{11}ClN_2O_2$	9.39 / 9.38	283-285	62
5c+5i	$C_{16}H_{11}BrN_2O_2$	8.18 / 8.16	228-230	64
5d+5j	$C_{17}H_{11}N_3O_2$	14.52 / 14.53	288-290	60
5e	$C_{16}H_{11}N_3O_4$	13.59 / 13.59	259-260	56
5f+5k	$C_{17}H_{14}N_2O_2$	10.09 / 10.07	282-284	40
5g	$C_{18}H_{16}N_2O_2$	9.58 / 9.58	270-272	48

* Yield using method A.

According to the data in Table 2, electron acceptor substituents in position 6 cause a related shift to low field for the vinyl bond C=CH protons whereas the opposite effect is observed for the hydroxyl group proton signals. Donor substituents raise the acidity of the carboxyl group and acceptors lower it, while for the 7-isomers the acidity is lower (Table 2). This can be explained by a competitive interaction of the imino nitrogen atom with two π-electronic fragments: the substituted phenyl ring and the C=CH–COOH group. Hence the introduction of acceptor substituents into the aromatic ring leads to a weakening of the interaction of the nitrogen atom unshared electron pair with the multiple bond and this is accompanied by a lowering of the acidity.

The yields of the products **5a-k** are low and, in the case of diamine **2a**, 3-phenacylquinoxal-2-one (**8**) was obtained along with compound **5a**. The compound **8** was identified by comparison with characteristics of a previously reported product [1]. We associate its formation with the reduction of the intermediate bromoolefin to benzoylacrylic acid in the presence of triethylamine which takes part as a reductant (as is known for activated olefins [4]).

The formation of olefin **3** in the reaction of acid **1** with diamines **2a-g** points above all to the high regioselectivity of the dehydrobromination process. A conjugative addition at the β-position of the olefin **3** is subsequently observed with cyclization and dehydrobromination leading to dihydroquinoxalines **5a-k**. Such a route for the dehydrobromination process is confirmed by the formation of compound **5a** also in the reaction of 3-bromobenzoyl-2-chloropropionic acid with diamine **2a** where the intermediate compound is 3-benzoyl-2-chloroacrylic acid.

The possibility of *ipso*-substitution in the intermediate bromoolefin **3** is, to us, less likely on the basis of the values of the charges on the carbon atoms of the ethylene fragment and the LUMO energy values as obtained by the AM1 method (Table 3).

Product **5a** is also formed under conditions of direct nucleophilic substitution (the reaction being carried out at 20-25°C without triethylamine). Evidently, in this case, substitution of the bromine atom in the β-position of acid **1** occurs with subsequent cyclization.

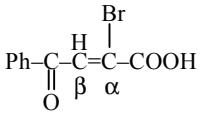
Hence, in the reaction discussed, a change in the direction of the nucleophilic addition of aromatic amine is observed when compared with the direction in the reaction previously studied by us for amines and benzoylacrylic acid [1] and this is due to the increased electrophilicity of the β-carbon atom in the intermediate olefin **3**.

TABLE 2. Spectroscopic Characteristics for the Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}						UV spectrum, propan-2-ol, λ_{max}, nm ($\varepsilon \cdot 10^{-4}$)	^{1}H NMR spectrum, δ, ppm				Isomer content, %	
	C=C (KBr)	C=O		N–H	OH			OH, s	NH, s	=CH, s	H arom., m	**6**	**7**
		(in KBr)	(in CCl_4)	(in CCl_4)	(in KBr)	(in CCl_4)							
5a	1615	1687	1682, 1702, 1742	3403	3086	3566	439 (14.9); 416 (17.1); 254 (9.2)	13.67	12.08 br.	6.83	7.16-8.00	—	—
5b+5h	1610	1691	1684, 1702, 1743	3399	3099	3528	438 (19.1); 415 (22.5); 270 (7.8)	13.53, 13.38	12.10 br.	6.85, 6.83	7.10-8.00	45	55
5c+5i	1610	1692	1687, 1701, 1747	3402	3112	3533	439 (14.0); 416 (16.4); 270 (5.9)	13.51, 13.37	12.12 br.	6.85, 6.83	7.26-8.00	30	70
5d+5j	1620	1692	1682, 1702, 1742	3393	3085		428 (17.1); 407 (20.1); 264 (7.9)	13.33, 13.26	12.30, 12.16	6.91, 6.86	7.19-8.10	20	80
5e	1618	1695	1687, 1712, 1742	3343	3118	3523	440 (19.2); 385 (12.9); 283 (17.1)	13.43	11.10	6.88	7.28-8.00	*	—
5f+5k	1610	1692	1682, 1702, 1742	3402	3113		448 (15.4); 423 (17.9); 272 (6.4)	13.71, 13.80	12.02	6.82, 6.78	6.97-8.00	25	75
5g	1615	1683	1677, 1700, 1742	3403	3098		454 (22.9); 428 (26.7); 253 (12.9)	13.83	11.94	6.77	6.91-7.90	—	—

* 100% 5-Nitro isomer.

TABLE 3. Effective Charges on the Ethylene Carbon Atoms and LUMO Energies



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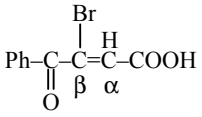

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Compound	Atom	Charge	LUMO Energy, a.u.
3	α	-0.139	-0.0506
	β	-0.106	
4	α	-0.110	-0.3678
	β	0.183	

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) instrument using DMSO-d_6 and TMS as internal standard. IR spectra were obtained on a Specord IR-75 spectrometer for KBr tablets and solutions in CCl_4. UV spectra were taken on a Hitachi U-3210 apparatus for solutions in propan-2-ol. Monitoring of the course of the reaction and the purity of the products was carried out using TLC on Silufol UV-254 plates in the system methanol–chloroform (1:3).

3-Benzoyl-2,3-dibromopropionic Acid (1). Solution of bromine (6.1 g, 38 mmol) in glacial acetic acid (10 ml) was added dropwise with stirring and at room temperature to solution of β-benzoylacrylic acid (6.8 g, 38 mmol) in glacial acetic acid (50 ml). Stirring was continued to full disappearance of the color. The reaction mixture was poured onto ice. The precipitate formed was filtered off and crystallized from toluene to give acid **1** (10.4 g, 80%); mp 143°C. IR spectrum (KBr tablet), ν, cm^{-1}: 3550 (OH), 1685 (C=O), 1670 (C=O).

3-Benzoyl-3-bromo-2-chloropropionic Acid (9). N-Bromosuccinimide (2.8 g, 17 mmol) and concentrated hydrochloric acid (3.4 ml) were added to solution of β-benzoylacrylic acid (3.0 g, 17 mmol) in acetic acid (40 ml). The mixture was stirred for 24 h, poured onto ice, and the precipitated product obtained was filtered off to give acid **9** (3.23 g, 66%); mp 137°C. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 8.17 (2H, d, *J* = 8.3, *o*-H_{Ph}); 7.75 (1H, *p*-H_{Ph}); 7.60 (2H, m, *J* = 8.3, *m*-H_{Ph}); 5.92 (1H, d, *J* = 10.5, CH); 4.86 (1H, d, *J* = 10.5, CH); 4.70 (1H, s, OH).

2-Carboxymethylene-3-phenyl-1,2-dihydroquinoxaline (5a). A. Solution of acid **1** (1.30 g, 3.8 mmol) and triethylamine (0.5 ml) in ethanol (12 ml) was refluxed for 20 min, diamine **2a** (0.42 g, 3.8 mmol) was then added, and the reaction mixture was held for 40 min on a water bath at 70-80°C. The precipitate formed was crystallized from ethanol–dimethylformamide to give the product **5a** (0.40 g). Evaporation of the mother liquor to one third gave 3-phenacylquinoxal-2-one (**8**) (0.33 g, 33%); mp 171°C (mp 171°C [1]). Compound **8** does not give a depression of melting point when mixed with a previously known sample.

Compounds 5b-k were prepared similarly.

B. Solution of acid **9** (0.61 g, 2.10 mmol) and diamine **2a** (0.23 g, 2.10 mmol) in ethanol (7-10 ml) was refluxed for 20 min. The precipitate formed was crystallized from ethanol to give the product **5a** (0.13 g, 26%).

C. Solution of acid **9** (1.0 g) and diamine **2a** (0.3 g) in ethanol (10 ml) was stirred for 2 h at room temperature using a magnetic stirrer and the reaction mixture was further held at the same temperature for 12-15 h to give compound **5a** (0.26 g, 34%).

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