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REACTION OF DIAROYLETHYLENES WITH Ortho-PHENYLENEDIAMINE AND ITS DERIVATIVES

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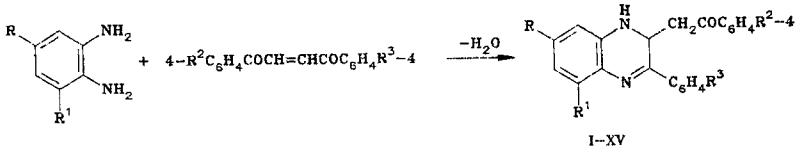
UDC 547.553:1'572.6'
863.19.07:543.422

Derivatives of 1,2-dihydroquinoxaline were synthesized. The direction of the reaction of unsymmetrical diaroylethylenes with o-phenylenediamine was shown by chemical and spectral methods and the reaction mechanism was discussed.

A number of studies have been devoted to the reaction of o-phenylenediamine (PDA) with dibenzoylethylene (DBE) [1-5] but only Bass et al. [5] convincingly demonstrated that the products formed upon heating PDA and DBE at reflux in glacial acetic acid are 1-(2-aminophenyl)-2,5-diphenylpyrrole, 2-phenylquinoxaline, and 2-phenacylidene-3-phenyl-1,2-dihydroquinoxaline. Brindra and LeGoff [2] and Trattner et al. [3, 4] carried out the reaction under milder conditions (in ethanol) and obtained only 2-phenylquinoxaline, while Bass et al. [5] subsequently managed to isolate the intermediate of this synthesis, which was found to be 2-phenacyl-3-phenyl-1,2-dihydroquinoxaline.

In the present communication, we studied the controlled formation of 1,2-dihydroquinoxaline in the reactions of derivatives of PDA and DBE.

Symmetrically substituted DBE ($R^2 = R^3$) and PDA even upon heating at reflux for 10 min in methanol form the desired products I, III, VI, VIII, and XI in good yields (Table 1). Under these conditions, the other diketones form dihydroquinoxalines only in trace amounts since the secondary elimination of the acetophenone fragment leads to 2-arylquinoxalines as the major reaction products. An exception was found for VII, which was obtained in 45% yield. The same results are obtained when the reaction is carried out at room temperature. On the other hand, stirring of benzene solutions of the starting compounds at 40-50°C for 3-4 h gave dihydroquinoxalines I-XV in good yields, although the formation of small amounts of 2-arylquinoxalines occurs under these conditions. This secondary reaction is especially pronounced in the synthesis of IV and X.



I—XI R=H; XII—XV R=Cl; I—XIII R^1=H; XIV—XV R^1=Cl; I R^2=R^3=H; II R^2=H, R^3=CH_3; III R^2=R^3=CH_3; IV R^2=Cl, R^3=H; V R^2=Cl, R^3=CH_3; VI R^2=R^3=Cl; VII R^2=Br, R^3=H; VIII R^2=R^3=Br; IX R^2=Br, R^3=CH_3; X R^2=NO_2, R^3=H; XI R^2=R^3=NO_2; XII, XIV R^2=R^3=H; XIII, XV R^2=R^3=CH_3

The formation of I-XV was shown by IR, UV, PMR, and mass spectroscopy and supported by the nitrogen content determined. The purity of these compounds was also indicated by thin-layer chromatography (see Tables 1-4). We should note that the formation of two isomeric structures is possible in the reactions of unsymmetrical diaroylethylenes ($R^2 \neq R^3$) with PDA. Isomers may also be obtained in the synthesis of XII-XV. Thus, an important problem was resolution of the question of the direction of the synthesis of II, IV, V, VII, IX, X, and XII-XV.

A. M. Gor'kii Kharkov State University, Kharkov. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5 pp. 656-661, May, 1986. Original article submitted January 28, revision submitted May 12, 1985.

 0009-3122/86/2205-0538$12.50

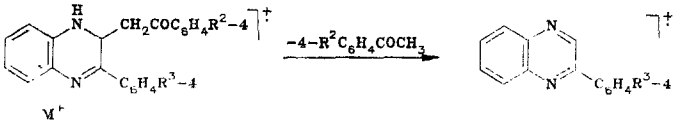
TABLE 1. Characteristics of I-XV

Compound	mp, °C	IR spectrum (KBr), cm^{-1}			Found N, %	Chemical formula	Calculated N, %	Yield,* %
		$\nu_{C=N}$	$\nu_{C=O}$	ν_{NH}				
I	124	1607	1668, 1678	3365	8,5	$C_{22}H_{18}N_2O$	8,6	61
II	135	1607	1679	3305	8,4	$C_{23}H_{20}N_2O$	8,2	51
III	136	1605	1663, 1654	3370	7,9	$C_{24}H_{22}N_2O$	7,9	55
IV	119	1605	1680	3364	7,9	$C_{22}H_{17}ClN_2O$	7,8	50
V	130	1608	1655	3356	6,1	$C_{23}H_{19}ClN_2O$	6,0	68
VI	122—123	1606	1656	3358	7,3	$C_{22}H_{16}Cl_2N_2O$	7,1	75
VII	131	1607	1680	3389	6,8	$C_{22}H_{17}BrN_2O$	6,9	60
VIII	134	1605	1652	3349	5,8	$C_{22}H_{16}Br_2N_2O$	5,8	81
IX	137	1608	1657	3361	6,8	$C_{23}H_{19}BrN_2O$	6,7	74
X	92—95 (decomp.)	1608	1690	3383	11,2	$C_{22}H_{17}N_3O_3$	11,3	69
XI	156	1604	1686	3339	13,5	$C_{22}H_{16}N_4O_5$	13,5	74
XII	116—117	1598	1650, 1658	3349	7,8	$C_{22}H_{17}ClN_2O$	7,8	58
XIII	143	1602	1654	3335	7,4	$C_{24}H_{21}ClN_2O$	7,2	52
XIV	132—133	1598	1672	3377	7.1	$C_{22}H_{16}Cl_2N_2O$	7,1	51
XV	144	1602	1676, 1658	3343	6,8	$C_{24}H_{20}Cl_2N_2O$	6,6	50

*For I, III, VI, VIII and IX, the yield of the product obtained according to method A is given while the yields of the other compounds obtained by method B are indicated.

The IR spectra of I-XV clearly show bands for the N–H (3305-3379 cm^{-1}), C=N (1598-1607 cm^{-1}), and C=O bonds (1650-1690 cm^{-1}). The slight sensitivity of these bands toward the electronic effects of substituents R-R^3 hinders the use of the IR spectra for the identification of isomers. Furthermore, the NH band in the IR spectra of I measured in CCl_4 in the concentration range from 10^{-4} to 10^{-2} mole/liter appears as a narrow peak with ν_{NH} 3422 cm^{-1} ($\Delta\nu_{1/2}$ = 27 cm^{-1}) independently of the concentration, which indicates the absence of hydrogen bonding between the NH and C=O groups. The electronic absorption spectra of I-XV (Table 2) are a function of the $NC_6H_4N{=}C_6H_4R^3$ chromophore group. A quantum mechanical analysis of this group was given in our previous work [6]. A feature of these spectra is the marked bathochromic shift upon introduction of electron-withdrawing R^3 groups, which permits us to resolve the question of the direction of the formation of IV, VII, IX, and X by the comparison of their spectra with those of dihydroquinoxalines I, III, VI, VIII and IX, in which the structure is unequivocally determined since $R^2 = R^3$. In all cases, the carbonyl group of the aroyl fragment containing the stronger electron-withdrawing substituent participates in the condensation with the amino group, i.e., the donor properties of R^3 are always greater than for R^2 in the dihydroquinoxalines obtained.

This conclusion was confirmed by analyzing the mass spectra of I-III and VII (Table 3). In all cases, greatest intensity is found for the 2-(4-R^3-phenyl)quinoxaline radical-ion peak, while the relative intensity of the molecular ion (M^+) peak is less than 5% and decreases with increasing sample inlet temperature.



Such fragmentation for II and VII permits the unequivocal identification of the position of the fragments containing the R^2 and R^3 substituents in the dihydroquinoxaline bicyclic system.

The elimination of acetophenones with the formation of 2-arylquinoxalines is also observed upon heating methanolic solutions of I-XV with added mineral acids. This process (in addition to oxidation to 2-phenacylidene-3-phenyl-1,2-dihydroquinoxalines [5]) also occurs upon the storage of these extremely unstable compounds. Upon identifying the 4-R^2-acetophenones by their dinitrophenylhydrazones (DNPH) and the 2-arylquinoxalines by the comparison of their properties with those of compounds obtained by convergent syntehsis from arylgloyoxals and PDA, support was found for the conclusion concerning the structure of the dihydroquinoxalines with $R^2 \neq R^3$ made on the basis of their UV and mass spectra.

TABLE 2. Absorption and Luminescence Spectra of I-XV

Compound	λ_{max} for absorption, nm ($\varepsilon \cdot 10^{-3}$)		λ_{max} for luminescence, nm (Stokes shift, cm^{-1})	
	in methanol*	in toluene	in methanol	in toluene
I	395	395 (5,96)	571 (7800)	516 (5940)
II	391	392 (6,44)	584 (8450)	499 (5470)
III	391	392 (6,87)	560 (7720)	520 (6280)
IV	392	395 (4,22)	560 (7650)	525 (6270)
V	397	397 (3,99)	555 (7170)	533 (6430)
VI	402	403 (5,00)	590 (7928)	535 (6122)
VII	394	396 (5,85)	575 (7990)	510 (5650)
VIII	403	403 (4,76)	593 (7950)	524 (5730)
IX	393	397 (6,97)	584 (8320)	535 (6500)
X	390	390 (9,02)	—	—
XI	446	443 (6,34)	—	—
XII	400	397 (6,72)	584 (7880)	510 (5580)
XIII	392	390 (9,02)	553 (7430)	490 (5230)
XIV	397	397 (7,19)	558 (7270)	518 (5880)
XV	397	397 (7,49)	545 (6840)	518 (5880)

*The determination of the molar extinction coefficients for I-XV in methanol is complicated by the instability of these compounds.

TABLE 3. Mass Spectra of I-III and VII

Compound	m/z value* (intensity of the ion peaks as % of the maximum)
I	326 (1,2), 207 (22), 206 (100), 205 (8), 180 (8), 179 (61), 178 (15), 152 (7), 105 (27), 104 (10), 103 (25), 102 (8), 77 (36), 76 (55), 75 (15), 74 (6)
II	340 (1,4), 222 (13), 221 (87), 220 (100), 219 (36), 207 (8), 205 (16), 194 (16), 193 (7), 192 (46), 179 (12), 178 (11), 165 (24), 120 (54), 119 (19), 116 (27), 110 (32), 106 (12), 105 (99), 103 (19), 102 (13), 91 (44), 90 (22), 89 (27), 78 (39), 77 (98), 76 (72), 75 (23), 74 (17)
III	354 (1,8), 222 (15), 221 (76), 220 (100), 219 (54), 218 (6), 205 (21), 194 (25), 193 (82), 192 (87), 191 (13), 166 (10), 165 (37), 135 (8), 134 (82), 120 (35), 119 (89), 118 (25), 116 (59), 110 (12), 105 (13), 103 (35), 102 (24), 92 (50), 91 (97), 90 (70), 89 (89), 78 (16), 77 (68), 75 (44), 74 (23)
VII	208 (7), 207 (48), 206 (100), 205 (7), 200 (14), 198 (15), 185 (64), 183 (66), 180 (12), 179 (73), 178 (18), 157 (31), 153 (33), 152 (9), 151 (7), 149 (9), 104 (14), 103 (29), 102 (11), 89 (7), 78 (5), 77 (31), 76 (84), 75 (37)

*The M^+ peaks and ion peaks with intensity greater than 5% are given.

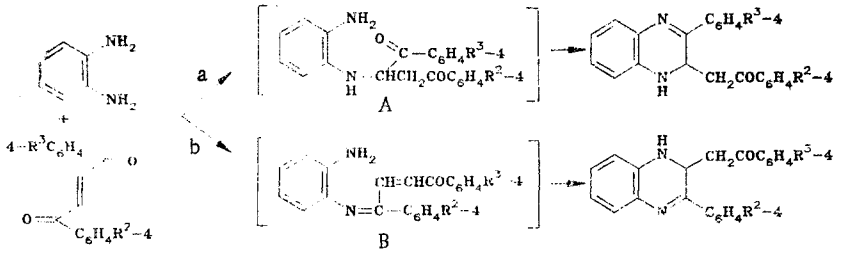
However, these methods do not answer the question of the direction of the reaction involving 4-chloro- and 3,5-dichloro PDA derivatives (XII-XV). A similar problem was encountered in the chemistry of dihydrodiazepines and solved by a PMR spectral method [7]. The PMR spectra of III, VIII and XII-XV in $CDCl_3$ (Table 4) display a septet and quartet for the CH_2—CH group protons and a broad imine proton singlet. The signals of the 8-H proton are readily identified in the aromatic proton region since they are shifted upfield by the effect of the electron-donor ortho amino group and are not overlapped by the signals of the other aromatic protons. The signals of this proton in the case of dihydroquinoxalines III and VIII (R = R^1 = H) are a quartet with J = 8 Hz (ortho) and J = 2 Hz (meta). On the other hand, the 8-H signals for XII-XV form a doublet with J = 2 Hz, which unequivocally indicates the presence of the chlorine atom at $C_{(7)}$. Such a structure for XII-XV indicates that, of the possible isomers, that, in which the less basic amino group adds at the double bond, is formed in the reactions of substituted o-phenylenediamines with diaroylethylenes.

The formation of heterocycles in the reactions of 1,2-diamines with α,β-unsaturated ketones may be achieved by two pathways differing in the sequence of addition and condensation [4, 8]. In the synthesis of I-XV, this can be illustrated by the following scheme:

TABLE 4. PMR Spectra of III, VIII, and XII-XV

Compound	δ, ppm				
	CH, q	CH_2*		NH, s	8-H
		H_A, q	H_B, q		
III	5,41	3,58	2,83	4,78	6,54 (q, J_{ortho} = 8 Hz, J_{meta} = 2 Hz)
VIII	5,35	3,53	2,76	4,75	6,51 (q, J_{ortho} = 8 Hz, J_{meta} = 2 Hz)
XII	5,46	3,56	2,91	4,93	6,50 (d, J = 2 Hz)
XIII	5,38	3,51	2,88	4,91	6,52 (d, J = 2 Hz)
XIV	5,48	3,56	2,93	5,07	6,48 (d, J = 2 Hz)
XV	5,43	3,48	2,88	5,03	6,44 (d, J = 2 Hz)

*The protons of the CH_2—CH group form an ABX system with the following coupling constants: J_{AB} = 9, J_{AX} = 5 and J_{BX} = 1.5 Hz (for III, VIII and XII-XV).



The experimental data on the reactions involving unsymmetrical diaroylethylenes indicate that the addition of the diamine proceeds at the carbon atom of the diketone in the β-position relative to the carbonyl group of the aroyl moiety with the more electron-withdrawing substituent, i.e., the direction of this reaction is a function of the polarization of the C=C bond in the starting diketone. This finding indicates that the formation of intermediate A is the first step in the reaction studied.

In our previous work [8], we established that the sequence of addition and condensation in such reactions may depend on the pH of the medium. Thus, we carried out the reaction for two unsymmetrical diaroylethylenes (R^3 = H, R^2 = Br or NO_2) in pure triethylamine and in methanol solutions containing Et_3N or HCl. The reaction course is not altered in basic media and VII and VIII are formed. On the other hand, the use of an acid catalytic agent led to the formation of a mixture of the two possible 2-arylquinoxalines and the corresponding acetophenones in approximately equal ratios. These results indicate that both isomeric dihydroquinoxalines are formed in the acid-catalyzed reaction and, thus, the reaction under these conditions loses its regioselectivity. In our opinion, this finding is a consequence of the competitive reaction of PDA with the diketones through pathway b.

The dihydroquinoxalines synthesized with the exception of the nitro derivatives X and XI have pronounced fluorescence in solution (see Table 2). We should note that the fluorescence spectra are much more sensitive to the solvent polarity than the absorption spectra. As a result, the Stokes shifts for the spectra taken in methanol are, on the average, 1800 cm^{-1} higher than the analogous values for the toluene solutions. This effect is characteristic for molecules whose excited state is more polar than their ground state [9]. The very high Stokes shifts observed in methanol solution also indicates a considerable specific interaction of the protic solvent with the dihydroquinoxaline molecules in their excited state.

EXPERIMENTAL

The IR spectra of I-XV were taken in KBr pellets on a Specord IR-75 spectrophotometer. The electronic absorption spectra were taken on a Specord UV-vis spectrometer in methanol and toluene at $(3-4)\cdot10^{-5}$ mole/liter. The PMR spectra were taken on a Varian XL-100 spectrometer in $CDCl_3$ with TMS as the internal standard. The fluorescence spectra were taken in methanol and toluene on a unit consisting of a monochromator from an SF-4 spectrophotometer, FÉU-38 photodetector and DRSh-500 mercury lamp. The optical density at the excitation wavelength did not exceed 0.2. The mass spectra were taken on a Varian MAT CH-6 spectrometer with direct sample inlet into the ion source.

The purity of I-XV and the composition of the reaction mixtures were monitored by thin-layer chromatography on Silufol UV-254 plates with chloroform as the eluent.

2-Phenacyl-3-phenyl-1,2-dihydroquinoxaline (I). A. A solution of 0.5 g (2.1 mmoles) trans-dibenzoylethylene and 0.23 g (2.1 mmoles) o-phenylenediamine in 5 ml methanol was heated at reflux for 15 min and then cooled. The yellow-orange crystalline precipitate was filtered off to give 0.42 g (61%) I, mp 124°C (from hexane).

Products III, VI-VIII, and XI were obtained by analogous procedures.

B. A sample of 0.46 g (4.2 mmoles) PDA was added to a solution of 1 g (4.2 mmoles) dibenzoylethylene in 5 ml benzene and the mixture was stirred for 3-4 h at 40-50°C. The solution was cooled and filtered to give 0.75 g (57%) I, mp 124°C.

Products II-XV were obtained by analogous procedures (Table 1).

2-Phenylquinoxaline. A solution of 0.3 g I in 10 ml methanol with 0.3 ml hydrochloric acid was heated at reflux for 15 min, cooled to room temperature and added to a methanol solution of 0.5 g 2,4d-initrophenylhydrazine. The precipitate (0.18 g, 62%) is the NDPH of acetophenone (compared with an authentic sample, mp 237°C, λ_{max} 337 nm in methanol, and R_f 0.75). The excess hydrazine was eliminated by the addition of acetone and the filtrate obtained by removing the DNPH of acetone was neutralized with ammonia and diluted with 30-40 ml water. The precipitated oily product was crystallized from hexane to give 0.1 g (53%) 2-phenylquinoxaline, mp 76°C, λ_{max} 335 nm in methanol, R_f 0.6.

Reaction of 1-(4-Bromophenyl)-4-phenyl-2-butene-1,4-dione with PDA under Acid Catalysis Conditions. A solution of 1 g (3.2 mmoles) 1-(4-bromophenyl)-4-phenyl-2-butene-1,4-dione and 0.35 g PDA in a mixture of 30 ml methanol and 1 ml hydrochloric acid was heated at reflux for 30 min. The reaction mixture was then divided into two equal portions. The first portion was evaporated to 10 ml and cooled. Filtration gave 0.2 g (44%) 2-(4-bromophenyl)quinoxaline with mp 141°C (from hexane). The filtrate was diluted with 20 ml water and left at room temperature for 3-4 h and then 0.14 g (42%) 2-phenylquinoxaline with mp 76°C was filtered off. The second portion of the reaction mixture was treated with a methanolic solution of 1 g 2,4-dinitrophenylhydrazine and 0.25 g of a mixture of the dinitrophenylhydrazones of acetophenone, and 4-bromoacetophenone were filtered off. These derivatives were identified relative to authentic samples with R_f 0.75 and 0.6, respectively.

The reaction with 1-(4-nitrophenyl)-4-phenyl-2-butene-1,4-dione was carried out under analogous conditions to give 40% 2-(4-nitrophenyl)quinoxaline (mp 187°C), 46% 2-phenylquinoxaline (mp 76°) and a mixture of the dinitrophenylhydrazones of acetophenone (R_f 0.75) and 4-nitroacetophenone (R_f 0.5).

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