3-ARYL-1,2-DIHYDROQUINOXALINES

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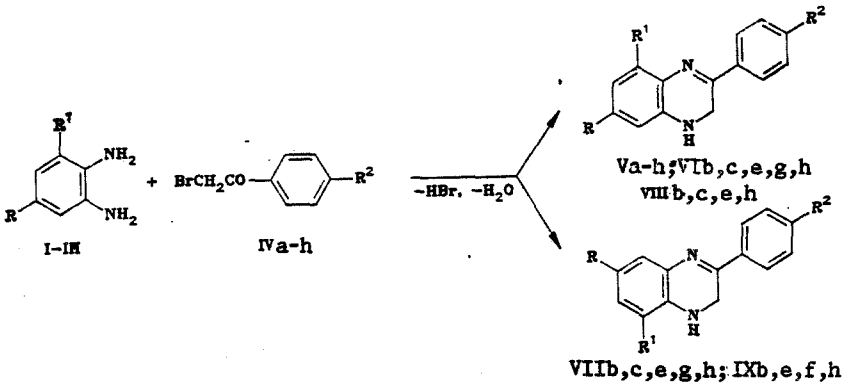
The reaction between o-phenylenediamine and its 4-chloro- and 3,5-dichloro-derivatives and 4-substituted ω-bromoacetophenones gives 1,2-dihydroquinoxalines. It has been found that the preferred course of the reaction under basic catalytic conditions involves the more basic of the amino groups of the diamine in condensation with the keto group. Anomalies have been found in the spectral-luminescent properties of the dihydroquinoxalines, owing to specific interactions with protic solvents.

1,2-Dihydroquinoxalines comprise a little-known group of compounds, probably owing to their high tendency to undergo oxidation [1]. The synthesis of a number of aryl derivatives of this heterocycle has been described [4-6], and the spectral and chemical properties of some compounds have been reported [2].

The object of the present study was to synthesize and examine some 3-aryl-1,2-dihydroquinoxalines. The compounds were obtained by reacting o-phenylenediamine and its 4-chloro- and 3,5-dichloro-derivatives with p-substituted ω-bromoacetophenones in methanol, with anhydrous sodium acetate as catalyst, in an inert gas medium provided by CO_2 or methane.



I, V $R=R^1=H$; II, VI, VII $R=Cl$, $R^1=H$; III, VIII, IX $R=R^1=Cl$; IV—IX a $R^2=H$, b $R^2=CH_3$, c $R^2=OCH_3$, d $R^2=OC_2H_5$, e $R^2=C_6H_5$, f $R^2=Cl$, g $R^2=Br$, h $R^2=NO_2$

The compounds obtained (V-IX) were identified by IR, PMR, and UV spectroscopy, and by elemental analysis (Tables 1 and 2). The $\nu_{C=N}$ values were little influenced by the substituents R^2 introduced into the aromatic ring, exceptions being (Vh-IXh) as a result of the considerable electron-acceptor influence of the nitro group. In the PMR spectra, singlets for the CH_2 protons, a broadened signal for the imino group, and signals for the 6-, 7-, and 8-protons of the annelated aromatic ring are readily identified. The UV absorption spectra of the dihydroquinoxalines (V-IX) are typical of compounds the basic chromophoric system of which is the fragment o-$N{-}C_6H_4{-}N{=}C{-}C_6H_4R$ [7], characterized by the presence in the near UV of three of four clearly apparent bands, the intensities of which decrease regularly as the wavelength increases.

Compounds (V-IX) are oxidized to the quinoxalines extremely rapidly, especially in solution. This tendency to aromatization is in some cases so pronounced that, for instance, the sole products of the reaction of the diamines (II) and (III) with ω-bromoacetophenone (IVa) are the quinoxalines. For this reason, the dihydroquinoxalines were stored in sealed ampuls under CO_2, and the preparation of these compounds for study was preferably carried

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TABLE 1. 3-Aryl-1,2-dihydroquinoxalines (V-IX)

Compound	T_{mp}, °C	IR spectrum, cm^{-1}		δ Values, ppm[b,c] (in $CdCl_3$)					Found, N, %	Empirical formula	Calculated, N, %	Yield, %
		$\nu_{C=N}$	ν_{NH}	1-H	2-CH	6-H	7-H	8-H				
Va	121–122[d]	1615	3376	3,90	4,47	6,73 m	6,97 m	6,58 q	13,5	$C_{14}H_{12}N_2$	13,5	55
Vb	125–127	1608	3381	3,90	4,38	6,72 m	6,96 m	6,49 q	12,5	$C_{15}H_{14}N_2$	12,6	60
Vc	138–139[d]	1606	3355	3,93	4,48	6,82 m	7,08 m	6,61 q	11,8	$C_{15}H_{14}N_2O$	11,8	66
Vd	147–149	1606	3385	3,91	4,28	6,84 m	7,05 m	6,53 q	11,2	$C_{16}H_{16}N_2O$	11,2	66
Ve	123–124	1612	3371	3,92	4,51	6,79 m	7,04 m	6,60 q	9,9	$C_{20}H_{16}N_2$	9,9	76
Vf	137–138	1606	3353	3,86	4,40	6,75 m	7,01 m	6,59 q	11,6	$C_{14}H_{11}ClN_2$	11,5	73
Vg	139–141[d]	1606	3377	3,88	4,40	6,75 m	7,00 m	6,52 q	9,7	$C_{14}H_{11}BrN_2$	9,8	81
Vh	163–165[d]	1598	3361	3,97	4,46	6,75 m	7,00 m	6,56 q	16,7	$C_{14}H_{11}N_3O_2$	16,6	91
VI[b] (60)					4,46	6,73 m	—	6,55 d_1				
VII[b] (40)	114–116	1606	3403	3,98	4,46	6,73 q	6,98 q	6,50 d_2	11,0	$C_{15}H_{13}ClN_2$	10,9	52
VIc (60)					4,33	6,82 q	—	6,47 d_1				
VIIc (40)	109–111	1606	3383	3,96	4,35	—	6,93 q	6,47 d_2	10,4	$C_{15}H_{13}ClN_2O$	10,3	55
VIe (60)					4,48	6,74 q	—	6,54 d_1				
VIIe (40)	81–83 (decomp.)	1606	3363	3,97	4,48	—	6,99 q	6,49 d_2	8,7	$C_{20}H_{15}ClN_2$	8,8	65
VIg (65)					4,43	6,74 q	—	6,51 d_1				
VIIg (35)	104–106	1606	3379	3,96	4,43	—	7,00 q	6,50 d_2	8,8	$C_{14}H_{10}BrClN_2$	8,7	68
VIh (55)					4,51	6,76 q	—	6,57 d_1				
VIIh (45)	132–134	1596	3391	4,05	4,51	—	7,04 q	6,52 d_2	14,7	$C_{14}H_{10}ClN_3O_2$	14,6	81
VIIIb, IXb	126–128	1601	3327	4,03					9,7	$C_{15}H_{12}Cl_2N_2$	9,6	40
VIIIc, IXc	118–120	1606	3409	4,05					8,7	$C_{15}H_{12}Cl_2N_2O$	8,7	48
VIIIe (100)	89 (decomp.)	1606	3425	4,07	4,42	6,74 d_1		6,68[d] d_1	8,0	$C_{20}H_{14}Cl_2N_2$	7,9	58
IXe (0)												
VIIIf (66)	140–142	1616	3407	4,00	4,32	6,76 d_1	—	6,33 d_1	8,9	$C_{14}H_{10}Cl_3N_2$	9,0	60
IXf (34)					4,44	—	7,04 d_1	—				
VIIIh (63)	172–174	1596	3405	3,99	4,50	6,80 d_1	—	6,44 d_1	12,9	$C_{14}H_{10}Cl_2N_3O_2$	12,8	74
IXh (37)					4,62	—	7,08[d] d_1					

[a]The figure in brackets indicates the amount of the isomer in mixtures of (VI) with (VIII) and (VII) with (IX), %. [b]Type of spectrum: d – doublet (d_1 with J = 2 Hz, d_2 with J = 8 Hz), m – sextet. [c]Signals identified, 5-H, δ = 7.37 q (Vc), 7.27 q (Vh), and 7.28 d_1 (VII). [d]According to [2], mp (Va) 141-142°C, (Vc) 138-139°C, (Vg) 138-139°C, (Vh) 144-146°C.

TABLE 2. Absorption and Luminescence Spectra of (V)-(IX)

Compound	λ_{max}^{abs}, nm (ε·10⁻³)		λ_{max}^{lum}, nm (Stokes shift, cm⁻¹)	
	in methanol	in toluene	in methanol	in toluene
Va	392 (3,6), 292 pl.,258 (19,8)	392	601 (8870)	514 (6060)
Vb	389 (4,7), 292 pl., 267 (23,6)	388	593 (8840)	509 (6130)
Vc	388 (6,1), 297 (13,9), 277 (20,8)	385	466 (4300)	539 (7420)
Vd	388 (6,5), 306 (15,4), 279 (22,2)	385	494 (5530)	513 (6480)
Ve	427 (8,6), 301 (22,9), 259 (26,8)	400	467 (2000)	530 (6130)
Vf	405 (4,5), 294 pl., 265 (24,0)	400	606 (8200)	529 (6100)
Vg	405 (4,9), 296 (10,3), 270 (26,0)	400	617 (8500)	547 (6720)
Vh[a]	448 (4,9), 304 (11,2), 282 (17,0)			
VIb, VIIb	391 (4,7), 304 (8,4), 270 (23,0)	397	573 (8100)	510 (5580)
VIc, VIIc	390 (6,2), 308 (14,7), 286 (27,2)	389	475 (4600)	485 (5090)
VIe, VIIe	406 (5,9), 309 (21,4), 286 (27,2)	405	473 (3500)	543 (6270)
VIg, VIIg	406 (4,1), 307 pl., 268 (26,7)	405	596 (7850)	550 (6510)
VIh, VIIh[a]	455 (4,7), 305 (10,3), 286 (19,7)			
VIIIb, IXb	392 (6,6), 305 (9,4), 274 (24,2)	394	559 (7600)	503 (5500)
VIIIc, IXc	385 (9,2), 312 (14,5), 286 (22,0)	388	485 (5300)	546 (7460)
VIIIe, IXe	398 (7,5), 312 (21,5), 287 (27,8)	397	489 (4700)	525 (6140)
VIIIf, IXf	410 (3,9), 302 (8,7), 265 (23,7)	411	600 (7700)	532 (5530)
VIIIh, IXh[a]	438 (3,3), 344 (7,6), 286 (16,0)			

[a]Did not fluoresce.

out in an inert atmosphere. Even under these conditions, however, it was not possible to obtain the PMR specta of (VIIIb), (IXb), (VIIIc), or (IXc) (Table 1).

According to the literature [5], the introduction of substituents R^2 has little effect on the rates of either step (substitution and condensation) in the formation of dihydroquinoxalines. In fact, under the same synthetic conditions (concentrations of reactant and catalyst, temperature, and reaction time) the variation of yields of the dihydroquinoxalines is slight. Nevertheless, there is a tendency for the reaction rate to increase as the electron-acceptor properties of R^2 are increased. For example, (Vh) is obtained in a yield of 91% after 10-15 min. Introduction of chlorine atoms into the o-phenylenediamine molecule reduces the reaction rate and the yields of the products (VI-IX). This is in accordance with a report [8] of the influence of substituents on the rate of bimolecular substitution.

It is noteworthy that in the reaction of substituted ω-bromoacetophenones with 4-chloro- and 3,5-dichloro-1,2-diaminobenzenes, two isomeric products could be formed: 7- or 6-chloro- and 5,7- or 6,8-dichloro-3-aryl-1,2-dihydroquinoxalines (VI-IX). It will be seen from Tables 1 and 2 that substituents R and R^1 have little influence on the IR and UV spectra of dihydroquinoxalines, and it is therefore not possible to use them to locate the positions of the chlorine atoms. Checks for the purity of the compounds by TLC were in this instance also unreliable in view of the rapid oxidizability of (VI-IX). The isomeric composition of the compounds could only be resolved by PMR spectrometry.

In the PMR spectra, the signal for the proton in the 8-position of the bicycle is shifted to higher field than any of the other aromatic protons as a result of the influence of the electron-donor imino group, and is readily identified. The signal for this proton consists of a doublet with a coupling constant (J) of 2 Hz (meta-constant [9]) for 7-chloro- (VI) and 8 Hz (ortho-constant [9]) for the 6-chloro isomers (VII); the weak para-interaction with the 5-proton of the bicycle was not seen in these spectra. In the PMR spectra of (VIII), the doublet for the 8-proton (J = 2 Hz) is retained, whereas in the isomeric compounds (IX) this proton is totally absent. As will be seen from Table 1, the chemical shifts of the 6- and 7-protons are also highly characteristic, and provide further confirmation of the correctness of this assignment of the signals to these isomers. The effectiveness of such a spectral analysis of the isomeric composition of heterocycles derived from o-phenylenediamine has been demonstrated in the case of 2,3-dihydro-1H-1,5-benzodiazepines [10].

Having obtained the integral spectra of the relevant protons, we estimated the amounts of each isomer in the mixtures (VI)-(VII) and (VIII)-(IX) (Table 1). It was found that the ω-bromoacetophenones (IV) react with the diamine (II) to give mixtures of the isomers (VI)-(VII) in a ratio of 3:2 (on average), and with diamine (III) to give mixtures of (VIII) and (IX) (VIII predominating), or the pure compounds, for instance (VIIIe) (for the reasons

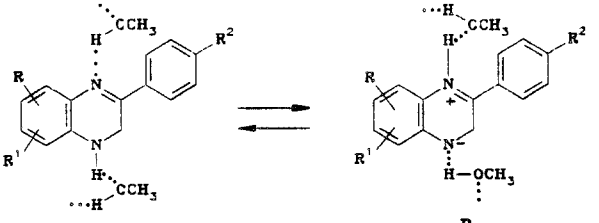
given above, it was not possible to determine the composition of mixtures (VIIIb)-(IXb) and (VIIIc)-(IXc)). The ratios of the isomers (VI) and (VII) indicate that there is little difference in the basicities of the amino groups in the diamine (II). Introduction of a second halogen atom (diamine III) increases this difference. The results obtained show that under basic catalytic conditions, the more basic amino group is preferentially involved in the formation of the azomethine bond, i.e., in the condensation reaction.

These results are in accordance with the findings of Kano et al. [11], who examined the reactions of a number of substituted o-phenylenediamines, including diamine (II), with ω-methylsulfinylacetophenone. In this reaction, 6- and 7-chloro-2-phenylquinoxalines (the intermediate dihydroquinoxalines were not isolated) were formed in a ratio of 1:3. When the 4-methoxy- and 4-nitro-derivatives of the diamine (I) were used in this reaction, only one of the possible isomeric phenylquinoxalines was obtained (the 7-methoxy- and 6-nitro-2-phenylquinoxaline, respectively), i.e., the more basic amino group is involved in replacement of the methylsulfinyl group. It should be noted that Kano et al. [11] used acidic catalysis, and therefore the difference in the course of the reaction of ω-methylsulfinylacetophenone and (IV) with diamines is to be expected in view of the change in the acidity of the medium.

A very important property of the dihydroquinoxalines obtained is their fluorescence (with the exception of (Vh-IXh), which contain a nitro-group, Table 2). It has been shown [7] by quantum chemical calculations of the electronic spectra of molecules containing the N-arylidene-ortho-phenylenediamine chromophore that the long-wavelength absorption band may be correlated with the one-electron transition 0 → 1, localized at this chromophore. This transition is accompanied by transfer of electron density from the amino (or imino) group to the azomethine bond, as shown by the effects of the substituent R^2, which are seen clearly in the experimental spectra of (V)-(IX). Thus, the introduction of electron-acceptor groups R^2 (Cl, Br, NO_2) favors this transfer. The incorporation of the chromophore system into the flattened dihydroquinoxaline ring also results in the absorption of (V)-(IX) being strong as compared with their p, π-analogs (azirinoquinoxalines and dihydrobenzodiazepines [7]), and in the occurrence of fluorescence.

In examining the fluoresence and absorption spectra, obtained in methanol solution (Table 2), attention is drawn to their differing sensitivity to the electronic character of R^2, in consequence of which the Stokes shift varies from anomalously high (~8800 cm^{-1}) to extremely low values (2000 cm^{-1} for (Ve)). When the spectra were obtained in toluene, these anomalies were not seen, leading to the conclusion that the spectral behavior of the dihydroquinoxalines in methanol is due to solvation by the solvent. It is known [12] that if the excited state of a molecule is considerably more polar than the ground state, then an increase in the polarity of the solvent will stabilize the excited state to a greater extent than the ground state. Stabilization of the excited state will also facilitate specific interactions with the protic solvent.

Stabilization of the excited state in dihydroquinoxalines may occur as follows:



A B

Electron-donor substituents R^2 destabilize form B, resulting in a considerable hypsofluoric effect in the polar solvent, whereas when R^2 is an electron acceptor group, the opposite effect operates. Stabilization of structure B is much less in toluene than in methanol, and hence the effect of R^2 on fluorescence λ_{max} is largely evened out.

Worthy of special note is the fact that in carrying out the spectral measurements the stability of the quinoxalines to oxidation was very different in toluene and methanol. The spectra of (V-IX) in methanol remained virtually unchanged over periods of weeks, whereas the measurements in toluene required the prior deoxygenation of the solvent and rapid scanning.

EXPERIMENTAL

The IR specta of (V)-(IX) were obtained in KBr disks on a Specord IR-75 spectrometer, electronic absorption spectra in methanol and toluene at concentrations of $(2\text{-}3)\cdot10^{-5}$ mole/liter on a Specord UV-VIS spectrophotometer, and fluorescence spectra in the same solvents using an apparatus consisting of the monochromator from an SF-4A spectrophotometer, an FÉU-38 radiation detector, and a DRSh-500 mercury lamp as light source. The spectra obtained were corrected for the spectral sensitivity of the apparatus. The optical density at the excitation wavelength was not greater than 0.2. PMR spectra were obtained on Tesla BS-2487-B (80) and Varian XL-100 instruments, with TMS as internal standard.

3-Phenyl-1,2-dihydroquinoxaline (Va). A mixture of 1.1 g (10 mmole) of o-phenylenediamine, 2.0 g (10 mmole) of ω-bromoacetophenone, and 0.83 g (10 mmole) of sodium acetate in 50 ml of methanol was boiled under reflux for 2 h, while passing a stream of methane or carbon dioxide continuously through the solution. Inorganic salts were then removed by filtration, and the filtrate cooled in a chamber filled with carbon dioxide, which was also used to filter off the crystals of (Va) which separated, yield 1.14 g (55%), mp 121-122°C (from methanol).

Dihydroquinoxalines (V)-(IX) were obtained similarly, except that for (Vh)-(IXh) the reflux time was shortened to 20 min.

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