SYNTHESIS OF 3-ARYL-2-BENZYL-1,2-DIHYDROQUINOXALINES THROUGH THE REACTION BETWEEN 1,2-DIAMINO-4,5-DIMETHYLBENZENE AND 1,2-DIAMINO-4-METHYLBEZENE WITH 2-BROMO-1,3-DIARYL-1-PROPANONES

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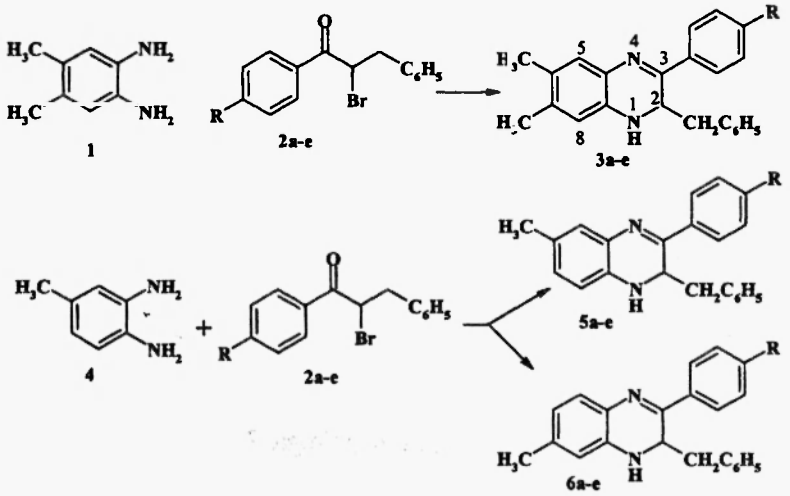
Abstract: Reaction of 1,2-diaminobenzenes (**1,4**) with substituted 2-bromo-1-aryl-3-phenyl-1-propanones (**2a-e**) was studied. The structures of 2-benzyl-3-aryl-1H-quinoxalines (**3, 5/6**) obtained was corroborated by ^{1}H-nmr and mass spectra data.

Introduction

1,2-Dihydroquinoxaline derivatives belong to a kind of unexplored compounds owing to their high tendency to oxidation [1]. For that, there are few reports about these substances. Besides their fluorescent properties, some dihydroquinoxalines have shown interesting chemiotherapeutic characteristics [2,3], moreover their usefulness like virucides [4]. The investigation on the reaction between ω-bromoacetophenones and 4-chloro- and 3,5-dichloro derivatives of 1,2-phenylenediamine let us to elucidate the isomeric composition of the respective products through ^{1}H-nmr and to study the effect of the substituents on the reaction velocity and electronic absorption and emission properties of the obtained products [5]. The reaction of 1,2-phenylenediamines with asymmetric trans-diaroylethylenes afforded specific information about the orientation of the reaction through electronic absorption and mass spectra of the obtained compounds [6]. On the other hand, Orlov *et al.* reported the synthesis of stable dihydroquinoxalines *via* the reaction of 1,2-phenylenediamine with 2-bromo-1,3-diaryl-1-propanones [7].

Results and Discussion

The goal of this work is to study the reaction of 1,2-diamino-4,5-dimethylbenzene (**1**) and 1,2-diamino-4-methylbenzene (**4**) with 2-bromo-1-aryl-3-phenyl-1-propanones (**2a-e**). Unsymmetrically substituted 1,2-diaminobenzene (4) led to a regiospecific cyclocondensation reaction. We carried out these reactions in methanol and sodium acetate under inert atmosphere and controling by tlc (Scheme 1).



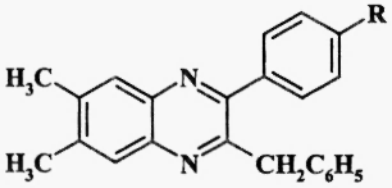
Scheme 1

All products, 3-aryl-2-benzyl-6,7-dimethyl-1,2-dihydroquinoxalines (**3a-e**), 3-aryl-2-benzyl-6-methyl-1,2-dihydroquinoxalines (**5a-e**) and 3-aryl-2-benzyl-7-methyl-1,2-dihydroquinoxalines (**6a-e**) were identificated by their ^{1}H-nmr, mass-spectra and elemental analysis. As characteristics, the ^{1}H-nmr spectra showed for both (**3** and **5/6**) three double doublets which belong to CH-CH_2 fragment, while the N-H group exhibited a singlet (see Table 1). ^{1}H-nmr spectroscopy allowed also to determine the isomeric composition of the products **5** and **6** formed due to unequivalence of NH_2 groups of compound **4**. In ^{1}H-nmr spectra of dihydroquinoxalines, the proton at the position 8, by influence of 1-NH group, has a chemical shift at higher field than the others aromatic protons, and is easily identificated. The signal of this proton showed a doublet with J = 8 Hz (*orto* constant for the isomer **5**) and J = 2 Hz (*meta* constant for the isomer **6**) [9]. When the proton signals were integrated it was possible to know the ratio of **5** and **6**. The efectivity of this spectral analysis, to know the isomeric composition of the heterocycles obtained, has been previously proved for 2,3-dihydro-1H-1,5-benzodiazepine isomeric mixtures [10], and confirmed by HPLC [11].

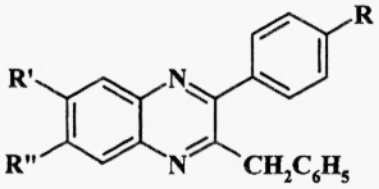
Table 1. ^{1}H-nmr data (δ values in $CDCl_3$, TMS as internal standard, 300 MHz)

Comp.	NH (s)	CH (dd)	CH_2 (dd)	8-H (s or d)	6-CH_3 (s)	7-CH_3 (s)	Aryl-H (m)
3a	4.13	4.70	2.82	6.47	2.39	2.17	7.0-8.2
3b	4.12	4.69	2.82	6.47	2.40	2.20	7.3-8.1
3c	4.03	4.68	2.81	6.48	2.52	2.30	6.9-8.2
3d	4.32	4.59	2.78	6.48	2.28	2.23	7.0-8.0
3e	4.21	4.67	2.83	6.49	2.60	2.35	7.1-8.2
5a	4.11	4.72	2.83	6.50	2.34	--	6.4-8.3
5b	4.11	4.71	2.81	6.50	2.44	--	6.6-8.2
5c	4.03	4.68	2.78	6.61	2.58	--	6.5-8.0
5d	4.32	4.68	2.80	6.51	2.38	--	6.5-8.1
5e	4.21	4.69	2.81	6.52	2.37	--	6.4-8.0
6a	4.12	4.71	2.79	6.49	--	2.35	6.3-8.3
6b	4.12	4.72	2.77	6.54	--	2.34	6.4-8.1
6c	4.02	4.68	2.69	6.60	--	2.42	6.4-8.0
6d	4.33	4.68	2.69	6.49	--	2.11	6.4-8.1
6e	4.23	4.67	2.77	6.54	--	2.23	6.4-7.9

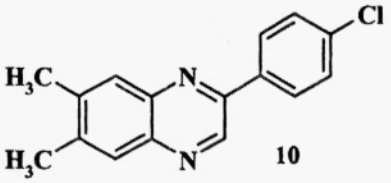
When the reaction mixtures were refluxed for more than 8 hours, the aromatized 3-aryl-2-benzyl-6,7-dimethylquinoxalines (**7a,b**), 3-aryl-2-benzyl-6-methylquinoxalines (**8a,b**), and 3-aryl-2-benzyl-7-methylquinoxalines (**9a,b**) were obtained as only products (Scheme 2). In a particular case, when the compound **3d** was recrystallized from methanol and left in solution for a week, 6,7-dimethyl-2-(4-chlorophenyl)quinoxaline **10** was obtained (Scheme 2).



7a R=H
7b R=CH_3



8a R=H. R' = CH_3, R" =H
8b R=CH_3, R'=CH_3, R"=H
9a R=H, R' = H, R" =CH_3
9b R=CH_3, R'=H, R"=CH_3



10

Scheme 2

Besides of the CH_3-groups, ^{1}H-nmr spectra of quinoxalines **7**, **8** and **9** exhibited a singlet at 4.2-4.8 ppm, for the two protons of the benzyl group and signals for aromatic protons. The structure of compound **10** was confirmed by X-ray crystallography (Figure 1).

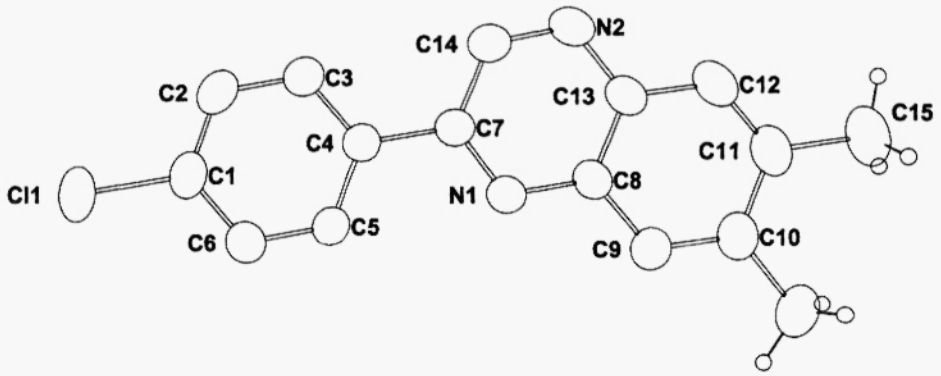


Figure 1

Conclusion

The reaction of 1,2-diaminobenzenes (**1,4**) with 2-bromo-1-aryl-3-phenyl-1-propanones (**2a-e**) constitutes a convenient synthetic route to the hitherto 2-benzyl-3-aryl-1H-quinoxalines. By integration of individual proton signals it was possible to determine the ratio of **5** and **6** formed from the diamine **4**. Aromatized quinoxalines (**7-10**) were obtained from the reaction by prolonged times of reflux or by long exposure to the solvent of crystallization, which reflects the relative stability of these compounds.

Experimental

Melting points are uncorrected. The ^{1}H-nmr were determined on a Bruker 300 in $CDCl_3$. Mass-spectra were obtained on a Finnigan-Mat 1020C spectrometer operating at 70 eV. The elemental analysis were obtained using a LECO CHNS-900 equipment.

2-Benzyl-3-(4-R-phenyl)-6,7-dimethyl-1,2-dihydroquinoxalines 3a-e and 2-Benzyl-3-(4-R-phenyl)-6(7)-methyl-1,2-dihydroquinoxalines 5(6)a-e

General Procedure.

A solution of 1,2-diamino-4,5-dimethylbenzene (1 mmol), 2-bromo-1-aryl-3-phenyl-1-propanone (1 mmol) and sodium acetate (2 mmol) in 20 mL of ethanol absolute was heated at 60 °C under inert atmosphere (N_2) for 4 hours. The reaction mixture was cooled and the solid formed was filtered. In some cases an oily residue was obtained which was crystallized from ethanol.

2-Benzyl-3-phenyl-6,7-dimethyl-1,2-dihydroquinoxaline **3a**

This compound was obtained according to general procedure as pale yellow crystals, mp 118 °C, yield 45 %. MS: (70 eV) m/z (%) = 328 (1), 326 (1), 325 (1), 324 (3), 323 (5), 237 (10), 236 (14), 235 (100), 234 (9) 103 (6), 91 (19), 77 (4).

Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84.66; H, 6.75; N, 8.59. Found: C, 84.52; H, 6.69; N, 8.66.

2-Benzyl-3-(4-methylphenyl)-6,7-dimethyl-1,2-dihydroquinoxaline **3b**

This compound was obtained according to general procedure as pale yellow crystals, mp 125 °C, yield 46 %. MS: (70 eV) m/z (%) = 339 (2), 338 (9), 337 (11), 250 (40), 249 (100), 248 (27), 103 (9), 91 (28), 77 (6), 65 (7).

Anal. Calcd. for $C_{24}H_{24}N_2$: C, 84.71; H, 7.06; N, 8.24. Found: C, 84.77; H, 7.12; N, 8.14.

2-Benzyl-3-(4-methoxyphenyl)-6,7-dimethyl-1,2-dihydroquinoxaline **3c**

This compound was obtained according to general procedure as pale yellow crystals, mp 132 °C, yield 40 %. MS: (70 eV) m/z (%) = 355 (3), 354 (13), 353 (10), 266 (15), 265 (100), 264 (23), 250 (5), 249 (20), 235 (22), 222 (9), 105 (7), 103 (6), 91 (17), 77 (6).

Anal. Calcd. for $C_{24}H_{24}N_2O$: C, 80.90; H, 6.74; N, 7.87. Found: C, 80.82; H, 6.84; N, 7.81.

2-Benzyl-3-(4-chlorophenyl)-6,7-dimethyl-1,2-dihydroquinoxaline **3d**

This compound was obtained according to general procedures as pale yellow crystals, mp 137 °C, yield 53 %. MS: (70 eV) m/z (%) = 361 (4), 360 (23), 359 (44), 358 (80), 357 (78), 323 (5), 271 (29), 270 (19), 269 (100), 268 (12), 267 (7), 247 (18), 104 (6), 103 (17), 91 (20), 78 (9), 77 (11).

Anal. Calcd. for $C_{23}H_{21}N_2Cl$: C, 76.56; H, 5.83; N, 7.77. Found: C, 76.68; H, 5.89; N, 7.88.

2-Benzyl-3-(4-bromophenyl)-6,7-dimethyl-1,2-dihydroquinoxaline **3e**
This compound was obtained according to general procedure as pale yellow crystals, mp 119 °C, yield 55 %. MS: (70 eV) m/z (%) = 408 (3), 406 (6), 405 (7), 404 (32), 403 (34), 402 (29), 401 (27), 324 (7), 323 (11), 317 (6), 316 (16) , 315 (99), 314 (30), 313 (100), 312 (13), 247 (11), 235 (18), 234 (10), 233 (9), 217 (8), 150 (8), 124 (7), 104 (8), 103 (15), 102 (6), 91 (27), 78 (8), 77 (15), 65 (7), 51 (6), 50 (6).
Anal. Calcd. for $C_{23}H_{21}N_2Br$: C, 68.16; H, 5.19; N, 6.91. Found: C, 68.08; H, 5.16; N, 6.86.

2-Benzyl-3-phenyl-6(7)-methyl-1,2-dihydroquinoxaline **5(6)a**
The yield was 40 % (Ratio 5:6, 68:32), yellow crystals of mp 122 °C; MS: (70 eV) m/z (%) = 314 (4), 313 (22), 312 (6), 311 (6), 222 (29), 221 (100), 155 (7), 138 (11), 137 (20), 136 (23), 107 (7), 91 (7), 89 (5).
Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.62; H, 6.41; N, 8.97. Found: C, 84.56; H, 6.46; N, 8.91.

2-Benzyl-3-(4-methylphenyl)-6(7)-methyl-1,2-dihydroquinoxaline **5(6)b**
The yield was 42 % (Ratio 5:6, 62:38), yellow crystals of mp 97 °C; MS: FAB m/z 327 (M^++1).
Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84.66; H, 6.75; N, 8.59. Found: C, 84.56; H, 6.86; N, 8.51.

2-Benzyl-3-(4-methoxyphenyl)-6(7)-methyl-1,2-dihydroquinoxaline **5(6)c**
The yield was 39 % (Ratio 5:6, 64:36), yellow crystals of mp 91 °C; MS: FAB m/z 343 (M^++1).
Anal. Calcd. for $C_{23}H_{22}N_2O$: C, 80.70; H, 6.43; N, 8.19. Found: C, 80.66; H, 6.46; N, 8.11.

2-Benzyl-3-(4-chlorophenyl)-6(7)-methyl-1,2-dihydroquinoxaline **5(6)d**
The yield was 50 % (Ratio 5:6, 55:45), yellow crystals of mp 137 °C; MS: (70 eV) m/z (%) = 346 (6), 258 (5), 257 (48), 256 (37), 255 (100), 254 (9), 219 (5), 143 (5), 91 (12), 89 (7).
Anal. Calcd. for $C_{22}H_{19}N_2Cl$: C, 76.19; H, 5.48; N, 8.08. Found: C, 76.26; H, 5.53; N, 8.16.

2-Benzyl-3-(4-bromophenyl)-6(7)-methyl-1,2-dihydroquinoxaline **5(6)e**
The yield was 54 % (Ratio 5:6, 57:43), yellow crystals of mp 93 °C; MS: (70 eV) m/z (%) = 393 (18), 392 (9), 391 (24), 302 (27), 301 (100), 300 (34), 299 (90), 221 (13), 155 (10), 139 (5), 138 (13), 137 (23), 136 (33), 107 (9), 91 (10).
Anal. Calcd. for $C_{22}H_{19}N_2Br$: C, 67.52; H, 4.86; N, 7.16. Found: C, 67.58; H, 4.82; N, 7.26.

2-Benzyl-3-(4-R-phenyl)-6(7)-methylquinoxaline 7a,b and 8(9)a,b.

General Procedure
The method to obtain these compounds is the same for the synthesis of the compounds **3**, **5** and 6. In this case, the heating period was about 10 hours at reflux.

2-Benzyl-3-phenyl-6,7-dimethylquinoxaline **7a**
This compound was obtained according to general procedure as pale yellow crystals, mp. 154 °C (ethanol). Yield 67 %. MS:(70 eV) m/z (%) = 325 (17), 324 (84), 323 (100), 247 (13), 77 (6).
Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.19; H, 6.17; N, 8.64. Found: C, 85.25; H, 6.23; N, 8.51.

2-Benzyl-3-(4-methylphenyl)-6,7-dimethylquinoxaline **7b**

This compound was obtained according to general procedure as pale yellow crystals, mp. 140 °C (ethanol). Yield 61 %. MS:(70 eV) m/z (%) = 339 (21), 338 (92), 337 (100), 323 (26), 247 (17), 103 (9), 91 (8), 76 (9).

Anal. Calcd. for $C_{24}H_{22}N_2$: C, 85.21; H, 6.51; N, 8.28. Found: C, 85.26; H, 6.57; N, 8.15.

2-Benzyl-3-phenyl-6(7)-methylquinoxalines **8(9)a**

The yield was 61 %, yellow crystals of mp 119 °C; MS: (70 eV) m/z (%) = 311 (19), 310 (85), 309 (100), 233 (15), 91 (7), 89 (10).

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.16; H, 5.81; N, 9.03. Found: C, 84.99; H, 5.85; N, 9.11.

2-Benzyl-3-(4-methylphenyl)-6(7)-methylquinoxalines **8(9)b**

The yield was 62 %, yellow crystals of mp 98 °C; MS: (70 eV) m/z (%) = 325 (21), 324 (99), 323 (100), 310 (7), 309 (32), 233 (16), 91 (11), 89 (11).

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.19; H, 6.17; N, 8.64. Found: C, 85.25; H, 6.09; N, 8.62.

2-(4-Chlorophenyl)-6,7-dimethylquinoxaline **10**

From recrystallization of **3d**, mp. 142 °C (ethanol). Yield 58 %.

Anal. Calcd. for $C_{16}H_{13}N_2Cl$: C, 71.51; H, 4.84; N, 10.43. Found: C, 71.55; H, 4.79; N, 10.52.

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