Synthesis of Heterocyclic Nitrogen Derivatives from Aryl-1,4-benzoquinones

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Treatment of 2-aryl-3,6-bis(arylamino)-1,4-benzoquinones **2a-h** with different acid chlorides, namely acetyl, phenylacetyl and chloroacetyl chloride yields 3a,7a-dihydropyrrolo[2,3-*f*]indole-2,6-dione **3**, 5-(*N*-phenylacetylarylamino)-3-phenylindole-2,6-dione **4** and 3-chloro-5-(*N*-chloroacetylarylamino)indole-2,6-dione **5** respectively. Stirring 2-aryl-1,4-benzoquinones (**1**) with ethylenediamine and/or *o*-phenylenediamine in methylene chloride gives pyrazino[2,3-*g*]quinoxalines derivative **6** and/or tetrapentacene derivative **7** respectively. The products 5-aryl- and 6-aryl-1*H*-indazole-4,7-diones **8** and **9** were obtained in the 1,3-dipolar cycloaddition of diazomethane to (**1**).

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Owing to the importance of quinones which posses a wide spread application in various fields including use as fungicides [1-3], antibacterial [4-6], antimalarial [7] and as antitumoral [8], we decided to synthesize some new heterocyclic quinones starting with aryl-1,4-benzoquinones (**1**) [9] hoping that such compounds would have certain required biological effects or other industrial applications.

In extension of the work by one of us on the synthesis of heterocyclic quinones, naphtho[2,3-*d*]imidazole-4,9-diones [10], the action of aromatic amines on **1a-c** followed by acetylation in order to synthesize pyrroloindoles and indoles now has been investigated. Thus, when **1a-c** were treated with aromatic amines namely aniline, *p*-toluidine and *p*-anisidine in absolute ethanol, 2-aryl-3,6-bis(arylamino)-1,4-benzoquinones **2a-h** were obtained.

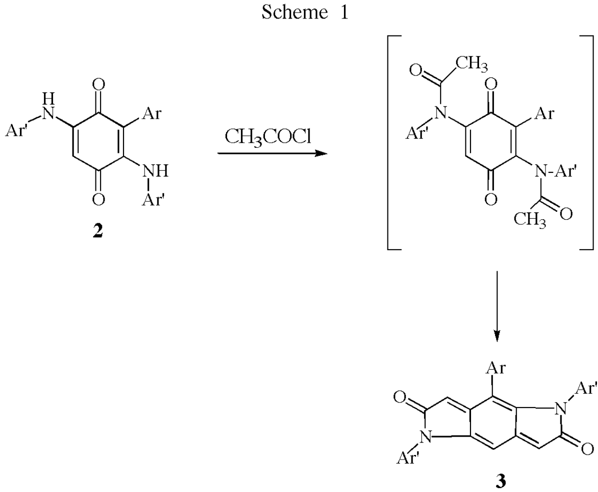
The structures of these products were supported by their spectral and elemental data. IR spectra for **2a-h** revealed the presence of corresponding bands at 3350-3250 cm^{-1} due to ν NH and the presence of strong absorption bands at 1650-1710 cm^{-1} which are characteristic for ν CO of quinones. ^{1}H-nmr data showed two broad bands peaks at δ 8.2-8.4 which are characteristic of the presence of two NH groups and a singlet peak at δ 6.1-6.3 corresponding to the (H_5) in the quinone ring. Some of the physical and spectroscopic data of compounds **2** are summarized in Tables 1 and 2.

The reaction of **2** with acetyl chloride in dry benzene in the presence of triethylamine gives 1,4,5-triaryl-3a,7a-dihydropyrrolo[2,3-*f*]indole-2,6-dione **3a-c**. The structures of these compounds were established by their spectra. IR spectra showed the disappearance of any absorption band characteristic for NH, and showed a strong absorption band at 1700-1685 cm^{-1} characteristic of the amide carbonyl group (*cf*. Table 2).

Formation of compounds **3** are assumed to proceed *via* (i) acetylation of both NH groups in **2** and (ii) a cyclocondensation reaction between the activated methyl groups and the carbonyl groups of quinone (Scheme 1).

The reaction of **2** with other acid chlorides, namely phenylacetyl chloride and chloroacetyl chlorides, were carried out under a similar condition to afford

Scheme 1



Scheme 2

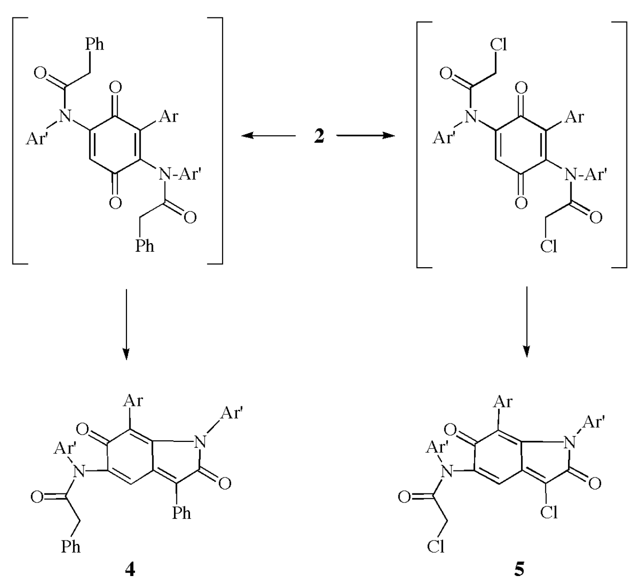


Table 1

Physical and Analytical Data of Compounds **2, 3, 4, 5, 6** and **7**

Compound No.	Ar	Ar'	Yield (%)	Appearance	mp (°C)	Molecular Formula	Elemental Analysis Found/(Calcd.) C	H	N
2a	C_6H_5	C_6H_5	55	red crystals	201-202	$C_{24}H_{18}N_2O_2$ (366.4)	78.62 (78.67)	4.93 (4.96)	7.62 (7.69)
2b	C_6H_5	*p*-$C_6H_4CH_3$	58	red crystals	202-204	$C_{26}H_{22}N_2O_2$ (394.5)	79.09 (79.15)	5.60 (5.63)	7.12 (7.10)
2c	C_6H_5	*p*-$C_4H_4OCH_3$	60	reddish brown crystals	208-209	$C_{26}H_{22}N_2O_4$ (426.5)	73.20 (73.21)	5.19 (5.21)	8.54 (8.57)
2d	*p*-$C_6H_4CH_3$	C_6H_5	60	red crystals	233-234	$C_{25}H_{20}N_2O_2$ (380.5)	78.89 (78.90)	5.30 (5.31)	7.32 (7.36)
2e	*p*-$C_6H_4CH_3$	*p*-$C_6H_4CH_3$	62	red crystals	207-208	$C_{27}H_{24}N_2O_2$ (408.5)	79.45 (79.38)	5.69 (5.93)	6.84 (6.86)
2f	*p*-$C_6H_4CH_3$	*p*-$C_6H_4OCH_3$	68	violet crystals	208-209	$C_{27}H_{24}N_2O_4$ (440.5)	73.58 (73.61)	5.52 (5.50)	6.38 (6.36)
2g	*p*-C_6H_4Cl	C_6H_5	63	violet crystals	230-232	$C_{24}H_{17}N_2O_2Cl$ (400.41)	71.95 (71.99)	4.30 (4.29)	7.01 (7.00)
2h	*p*-C_6H_4Cl	*p*-$C_6H_4CH_3$	60	brown crystals	254–256	$C_{26}H_{21}N_2O_2Cl$ (428.47)	72.75 (72.88)	4.90 (4.95)	6.58 (6.54)
3a	C_6H_5	C_6H_5	44	bluish violet micro crystals	118-120	$C_{28}H_{18}N_2O_2$ (414.46)	81.26 (81.14)	4.29 (4.39)	6.70 (6.76)
3b	*p*-$C_6H_4CH_3$	C_6H_5	38	blue micro crystals	98-100	$C_{29}H_{20}N_2O_2$ (428.49)	81.44 (81.28)	4.60 (4.71)	6.42 (6.54)
3c	*p*-$C_6H_4CH_3$	*p*-$C_6H_4CH_3$	39	blue micro crystals	100-102	$C_{31}H_{24}N_2O_2$ (456.55)	81.62 (81.55)	5.23 (5.31)	6.09 (6.14)
4a	C_6H_5	C_6H_5	25	reddish violet fine crystals	108-110	$C_{40}H_{28}N_2O_3$ (584.67)	82.32 (82.17)	4.77 (4.84)	4.80 (4.79)
4b	C_6H_5	*p*-$C_6H_4CH_3$	27	reddish violet fine crystals	95-96	$C_{42}H_{32}N_2O_3$ (612.70)	82.38 (82.33)	5.19 (5.26)	4.70 (4.57)
5a	C_6H_5	C_6H_5	44	violet fine crystals	183-185	$C_{28}H_{18}N_2O_3Cl$ (500.45)	67.06 (67.20)	3.56 (3.63)	5.52 (5.60)
5b	*p*-$C_6H_4CH_3$	C_6H_5	42	violet micro crystals	100-102	$C_{29}H_{18}N_2O_3C$ (514.48)	67.79 (67.70)	3.87 (3.93)	5.42 (5.45)
5c	*p*-$C_6H_4CH_3$	*p*-$C_6H_4CH_3$	40	violet micro crystals	142-144	$C_{31}H_{24}N_2O_3Cl_2$ (542.54)	68.48 (68.62)	4.39 (4.47)	5.08 (5.16)
6a	*p*-$C_6H_4CH_3$	(H)	55	yellow crystals	99-101	$C_{17}H_{14}N_4$ (274.35)	74.30 (74.42)	5.06 (5.15)	20.34 (20.43)
6b	*p*-C_6H_4Cl	(H)	58	yellow crystals	114-115	$C_{16}H_{11}N_4Cl$ (294.31)	65.17 (65.29)	3.69 (3.77)	18.97 (19.44)
7a	C_6H_5	(H)	40	yellow needles	173-175	$C_{24}H_{16}N_4$ (360.44)	79.94 (79.97)	4.53 (4.48)	15.50 (15.55)
7b	*p*-$C_6H_4CH_3$	(H)	32	yellow needles	115-117	$C_{25}H_{18}N_4$ (374.74)	80.14 (80.18)	4.69 (4.85)	14.88 (14.97)
7c	*p*-C_6H_4Cl	(H)	42	yellow needles	102-103	$C_{24}H_{15}N_4Cl$ (394.76)	73.23 (73.02)	4.03 (3.83)	13.98 (14.19)

Scheme 3

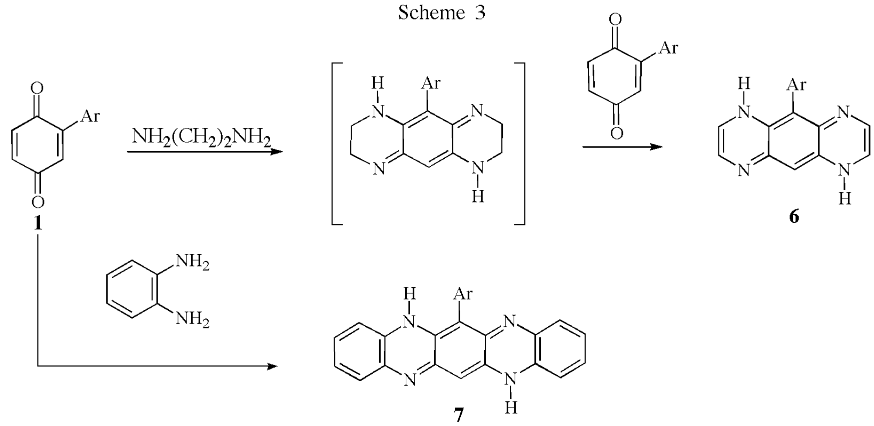


Table 2

Spectroscopic Data of Compounds **2, 3, 4, 5, 6** and **7**

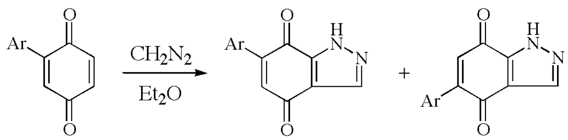
Compound No.	Ar	Ar'	MS m/e base peak (%)	IR (cm^{-1}) (NH,CO)	^{1}H-NMR (δ ppm) ($CDCl_3$)
2a	C_6H_5	C_6H_5		3330 1660	8.2, 8.4 (2s, 2H, 2NH), 6.5-7.5 (m, 15H, Ar), and 6.2 (s, 1H, H5 qu.).
2b	C_6H_5	*p*-$C_6H_4CH_3$		3250 1700	8.4, 8.6 (2s, 2H, 2NH), 6.7-7.6 (m, 13H, Ar), 6.1 (s, 1H, H5 qu.) and 2.1, 2.3 (2s, 6H, $2CH_3$).
2c	C_6H_5	*p*-$C_4H_4OCH_3$		3250 1670	8.2, 8.4 (2s, 2H, 2NH), 6.4-7.4 (m, 13H, Ar), 6.0 (s, 1H, H5 qu.) and 3.6, 3.8 (2s, 6H, $2OCH_3$).
2d	*p*-$C_6H_4CH_3$	C_6H_5	380 ($M^{+\cdot}$, 100)	3250 1660	8.2, 8.4 (2s, 2H, 2NH), 6.6-7.5 (m, 14H, Ar), 6.1 (s, 1H, H5 qu.) and 2.1 (s, 3H, CH_3).
2e	*p*-$C_6H_4CH_3$	*p*-$C_6H_4CH_3$		3250 1710	8.2, 8.4 (2s, 2H, 2NH), 6.4-7.4 (m, 12H, Ar), 6.1 (s, 1H, H5 qu.) and 2.1, 2.3, 2.4 (3s, 9H, $3CH_3$).
2f	*p*-$C_6H_4CH_3$	*p*-$C_6H_4OCH_3$		3300 1680	8.1, 8.3 (2s, 2H, 2NH), 6.3-7.4 (m, 12H, Ar), 6.0 (s, 1H, H5 qu.), 3.7, 3.9 (2s, 6H, $2OCH_3$) and 2.2 (s, 3H, CH_3).
2g	*p*-C_6H_4Cl	C_6H_5		3250 1650	8.1, 8.3 (2s, 2H, 2NH), 6.2-7.2 (m, 14H, Ar) and 6.1 (s, 1H, H5 qu.).
2h	*p*-C_6H_4Cl	*p*-$C_6H_4CH_3$	428 ($M^{+\cdot}$, 31.4) 36 (100)	3300 1660	8.2, 8.4 (2s, 2H, 2NH), 6.4-7.3 (m, 12H, Ar), 6.1 (s, 1H, H5 qu.) and 2.2, 2.4 (2s, 6H, $2CH_3$).
3a	C_6H_5	C_6H_5	414 ($M^{+\cdot}$, 27.7) 281(100)	1685	6.5-7.9 (m, 15H, Ar), 6.1 (s, 1H, H8) and 4.1 (s, 2H, H3 + H7).
3b	*p*-$C_6H_4CH_3$	C_6H_5	428 ($M^{+\cdot}$, 6) 281 (100)	1790	6.6-7.5 (m, 14H, Ar), 6.1 (s, 1H, H8), 4.2, 4.4 (2s, 2H, H3, H7) and 2.0 (s, 3H, CH_3).
3c	*p*-$C_6H_4CH_3$	*p*-$C_6H_4CH_3$	456 ($M^{+\cdot}$, 9.2) 274 (100)	1690	6.4-7.8 (m, 12H, Ar), 6.2 (s, 1H, H8), 4.2 (s, 2H, H3 + H7) and 2.0, 2.1, 2.3 (3s, 9H, $3CH_3$).
4a	C_6H_5	C_6H_5		1690 1710	6.7-7.8 (m, 26H, Ar + H4) and 3.1-3.2 (d, 2H, CH_2).
4b	C_6H_5	*p*-$C_6H_4CH_3$		1690 1710	6.8-7.8 (m, 24H, Ar + H4), 3.0-3.1 (d, 2H, CH_2) and 1.24, 1.25 (2s, 6H, $2CH_3$).
5a	C_6H_5	C_6H_5	500 ($M^{+\cdot}$,5.56,Cl^{35}) 504 ($M^{+\cdot}$,1.41,Cl^{37})	1680 1695	6.6-7.6 (m, 15H, Ar), 6.3 (s, 1H, H4) and 3.9-4.0 (d, 2H, CH_2).
5b	*p*-$C_6H_4CH_3$	C_6H_5		1680 1700	6.7-7.5 (m, 14H, Ar), 6.3 (s, 1H, H4), 3.9-4.0 (d, 2H, CH_2) and 2.4 (s, 3H, CH_3).
5c	*p*-$C_6H_4CH_3$	*p*-$C_6H_4CH_3$		1685 1695	6.5-7.4 (m, 12H, Ar), 6.2 (s, 1H, H4), 3.9-4.0 (d, 2H, CH_2) and 2.2, 2.3, 2.4 (3s, 9H, $3CH_3$).
6a	*p*-$C_6H_4CH_3$	(H)		3300 3350	6.9-7.4 (m, 4H, Ar), 6.55 (m, 3H, H3 + H8+ H10), 6.4 (dd, 2H, H2 + H7), 2.5 (s, 2H, 2NH) and 2.3 (s, 3H, CH_3).
6b	*p*-C_6H_4Cl	(H)		3300 3360	7.2-7.4 (m, 4H, Ar), 6.7 (m, 3H, H3 + H8 + H10), 6.6 (dd, 2H, H2, H7) and 2.7 (s, 2H, 2NH).
7a	C_6H_5	(H)		3300 3380	8.0, 8.1 (2s, 2H, 2NH), 7.5-7.6 (m, 5H, Ar), 7.1-7.3 (m, 8H, H1-H4 + H8-H11) and 6.7 (s, 1H, H13).
7b	*p*-$C_6H_4CH_3$	(H)		3320 3400	8.0, 8.1 (2s, 2H, 2NH), 7.25-7.35 (m, 4H, Ar), 6.7-6.9 (m, 9H, H1-H4 + H8-H11+H13) and 2.4 (s, 3H, CH_3).
7c	*p*-C_6H_4Cl	(H)		3330 3400	7.9, 8.0 (2s, 2H, 2NH), 7.1-7.3 (m, 4H, Ar) and 6.6-6.8 (m, 9H, H1-H4 + H8-H11 + H13).

5-(*N*-phenylacetylarylamino)-1,7-diaryl-3-phenylindole-2,6-dione **4a,b** and 5-(*N*-chloroacetylarylamino)-1,7-diaryl-3-chloroindole-2,6-dione **5a-c** respectively.

The compounds **4** and **5** were formed by acylation of NH groups followed by cyclocondensation occurring at the more electrophilic carbonyl group at C-4 whose polar resonance form is stabilized by the aromatic substituent. Attempts to convert **4** and **5** into the pyrroloindole derivatives showed that these products were extremely stable. The analytical and spectroscopic data were in full agreement with the assigned structures (Tables 1 and 2).

We completed our investigation by examining the behavior of 2-aryl-*p*-benzoquinones (**1**) toward 1,2-diamines. The dehydrogenated products 5-aryl-1,6-dihydropyrazino[2,3-*g*]quinoxalines **6a,b** were synthesized by stirring of **1b,c** with ethylenediamine in methylene chloride. On the other hand, the reaction of **1** with *o*-phenylenediamine in glacial acetic acid or by stirring at room temperature in methylene chloride afforded 6-aryl-5,12-dihydro-5,7,12,14-tetrazapentacenes **7a-c**. The ir spectra of compounds **6** and **7** revealed the absence of ν CO of the quinone and the

Scheme 4



8: Ar = C_6H_5
9: Ar = p-$C_6H_4CH_3$

presence of the NH band at 3400-3200 cm^{-1}. Analytical and spectroscopic data of compounds **6** and **7** are listed in Tables 1 and 2.

The cycloaddition of 1,3-dipoles, such as diazoalkanes, azides, nitrilimines and nitrile oxides, to 1,4-quinone dipolarophiles provides an excellent one step synthesis of heterocyclic nitrogen quinones [11]. 1,3-Dipolar cycloaddition of monosubstituted *p*-benzoquinones with diazomethane, gives rise to two possible regioisomeric products [12]. Treatment of **1a** and **1b** with 3 equivalent ethereal diazomethane at 0-5 ºC afforded a mixture of undistinguished isomers 5-aryl- and 6-aryl-1*H*-indazole-4,7-diones (**8**, 35% overall yield 2:1 and **9,** 38% overall yield 3:1) as evidenced by the 300 MHz ^{1}H-nmr spectra in which the integration of the protons at position 3 and of methyl in **9** were used to find the percentage ratio. All attempts to separate the two isomeric products using preparative tlc, column chromatography, and fractional crystallization were unsuccessful. All the analytical and spectral data (ir, nmr and ms) were in full agreement with the proposed isomeric structures.

EXPERIMENTAL

Melting points were determined on an electric melting points apparatus (Gallenkamp) and were uncorrected. The ir spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The ^{1}H-nmr spectra were recorded by 300 MHz Varian NMR spectrometer and chemical shifts are reported in ppm with TMS as an internal standard. Electron impact mass spectra were obtained at 70 eV using a GCMS sp. 1000 Shimadzu at Cairo University. Elemental analysis was carried out at the Microanalysis Unit at Assiut University.

2-Aryl-3,6-bis(arylamino)-1,4-benzoquinone (**2a-h**).

To (0.01 mole) of **2** in 50 ml absolute ethanol was added (0.02 mole) of pure primary aromatic amine, the reaction mixture was then refluxed for 3-5 hours. The precipitate formed after cooling was collected and recrystallized from benzene to give **2a-h**. Yields, melting points and analytical data are summarized in Table1.

General Procedure for the Reaction of 2-Aryl-3,6-bis-(arylamino)-1,4-benzoquinone (**2**) with Acids Chlorides.

Compound **2** (0.01 mole) was dissolved in 50 ml dry benzene then the proper acid chloride (0.03 mole) was added in the presence of a catalytic amount of triethylamine (0.03 mole). The reaction mixture was refluxed with continuous stirring for 8-12 hours, then filtered hot to separate the precipitated triethylamine hydrochloride. Reflux was then continued for a further 4 hours, where a stable reddish violet solution was obtained. The solvent was removed on vacuo and the solid residues were purified by using preparative thin layer chromatograph (benzene:light petroleum, 7:3). The fastest migrating dark zone was extracted with chloroform and the crude product obtained on evaporation of the extracts was rechromatographed with the same eluent to give **3, 4** and **5**. Yields, melting points, analytical and spectroscopic data are listed in Tables 1 and 2.

5-Aryl-1,6-dihydropyrazino[2,3-*g*]quinoxalines (**6a,b**).

To (0.02 mole) of **1** in 50 ml methylene chloride, (0.02 mole) of ethylenediamine was added and the reaction mixture was stirred at room temperature for 48 hours. The precipitate formed was collected and recrystallized from methylene chloride to give **6**. For yields, melting points, analytical and spectroscopic data see Tables 1 and 2.

6-Aryl-5,12-dihydro-5,7,12,14-tetrazapentacenes (**7a-c**).

o-Phenylenediamine (2.16 g, 0.02 mole) was added to a solution of **1** (0.01 mole) in methylene chloride (30 ml) at room temperature and the reaction mixture was stirred for 48 hours. The precipitate formed was collected and recrystallized from methylene chloride to give **7a-c**. Yields, melting points, analytical and spectroscopic data are listed in Tables 1 and 2.

General Procedure for the Preparation of 5-Aryl- and 6-Aryl-1*H*-indazole-4,7-diones (**8** and **9**).

A solution of diazomethane in ether (10 mL, 0.03 mole) was added dropwise to a cold stirred solution of 2-aryl-1,4-benzoquinone (**1**) (0.01 mole) in ether/acetone (10:1). The reaction mixture was transformed into a brown solution after the diazomethane solution had been completely added; the solution was stirred for 2 hours at 0-5 ºC. The mixture was chromatographed on tlc plates using benzene as an eluent. The upper yellow zone was extracted with acetone, which evaporated under vacuum and the solid formed was crystallized from benzene to yield the desired yellow isomeric products **8** and **9**.

5-Phenyl- and 6-Phenyl-1*H*-indazole-4,7-diones (**8a,b**).

This compound was obtained by reaction of 2-phenyl-*p*-benzoquinone (**1a**) (0.01 mole, 1.84 g) with diazomethane (10 mL, 0.03 mole, 1.26 g) as yellow crystals (0.8 g, 35% overall yield); mp 170-180 ºC (dec); ir: 3350 (NH), 1670 (CO qu.) cm^{-1}; ^{1}H-nmr (deuteriochloroform): 7.82, 7.94 (2d, 2H, H-3 of **8a, 8b,** J = 8 Hz), 7.00-7.55 (m, 12H, 10H Ar + H-5 + H-6) and 6.7, 6.8 (2d, 2H, 2NH, J = 8 Hz).

Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.57; N, 12.50. Found: C, 69.55; H, 3.59; N, 12.49.

5-(*p*-Tolyl)- and 6-(*p*-Tolyl)-1*H*-indazole-4,7-diones (**9a,b**).

This compound was obtained by reaction of 2-(*p*-tolyl)-*p*-benzoquinone (**1b**) (0.01 mole, 1.98 g) with diazomethane (10 mL, 0.03 mole, 1.26 g) as yellow fine crystals (0.9 g, 38 % overall yield); mp 214-230 ºC (dec); ir: 3320 (NH), 1690 (CO qu.) cm^{-1}; ^{1}H-nmr (deuteriochloroform): 8.25, 8.35 (2d, 2H, H-3 of **9a, 9b**, J = 8 Hz); 7.0-7.50 (m, 8H, Ar); 6.85, 6.95 (2s, 2H, H-5 and H-6); 6.6, 6.7 (2d, 2H, 2NH, J = 8 Hz) and 2.3, 2.45 (2s, 6H, $2CH_3$); ms: 238 ($M^{+\cdot}$, 100 %).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.24; N, 11.76. Found: C, 70.51; H, 4.18; N, 11.75.

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