CYCLOADDITION REACTIONS OF 2,3-DIPHENYLQUINOXALINE-5,8-DIONE. SYNTHESIS OF NOVEL PYRAZOLO[3,4-g]QUINOXALINEQUINONE, ISOXAZOLO[4,5-g]QUINOXALINEQUINONE AND PYRROLO-[3,4-g]QUINOXALINEQUINONE

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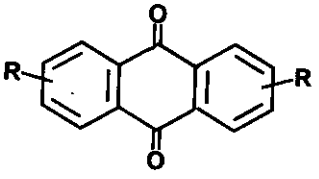
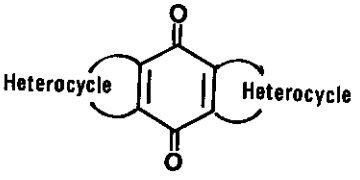
Abstract - 2,3-Disubstituted quinoxalinequinones were prepared. Synthesis of pyrazolo[3,4-g]quinoxalinequinones 4 and 5, isoxazolo[4,5-g]quinoxalinequinone 7 and pyrrolo[3,4-g]quinoxalinequinone 10 using dipolar cycloaddition reactions of quinoxalinequinones 3 with respective dipoles are reported.

Anthraquinone derivatives of the formula A were found to be active against Entamoeba histolytica infections in experimental animals[1-2]. They exhibited a gamut of antiprotozoal activities. In connection with our programme to find novel amoebicides, we were interested in synthesising a few new heterocyclic quinones of the type B[3] similar to anthraquinones A. Herein we report the synthesis of pyrazolo[3,4-g]quinoxalinequinone, isoxazolo[4,5-g]quinoxalinequinone and pyrrolo[3,4-g]quinoxalinequinone using dipolar cycloaddition reactions of quinoxalinequinones 3. Though there are a few reports on the [4 + 2] cycloaddition reactions of quinoxalinequinones[4-6], there is no report on the 1,3-cycloaddition reactions of quinoxalinequinones as described in this paper.



A



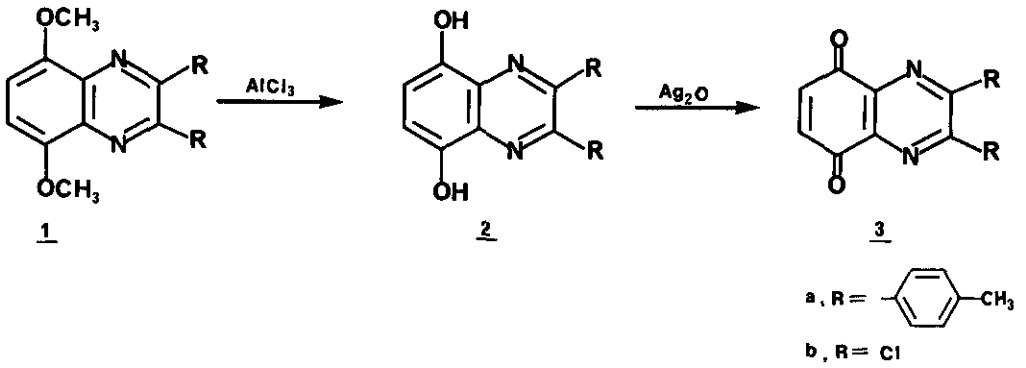
B

R = Amidines

$= CH_2N\begin{matrix}R_1\\R_1\end{matrix}$

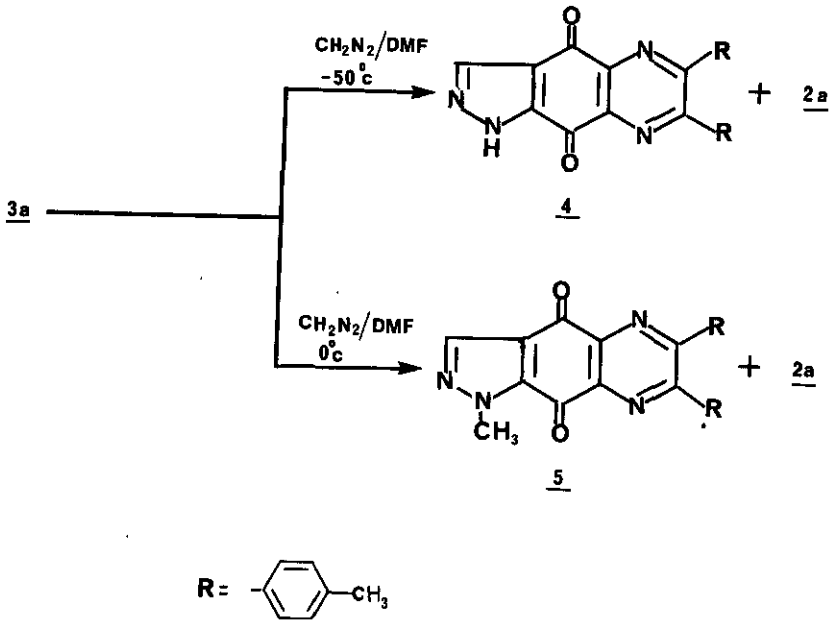
2,3-Diarylquinoxalinequinones 3a, b were synthesised from the corresponding dihydroxyquinoxalines 2 as shown in Scheme I.

Scheme I



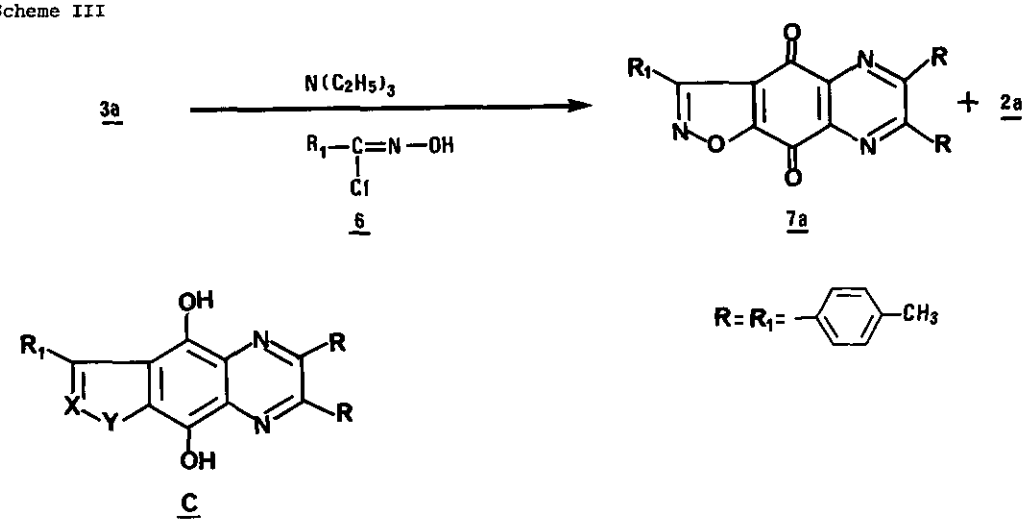
Treatment of quinoxalinequinone 3a with diazomethane in DMF at -50°C gave pyrazolo [3,4-g] quinoxalinequinone 4 [Mp > 300°C; 45%] and dihydroxyquinoxaline 2a [Mp 189-191°C; 45%] in 1:1 ratio. Dihydroxyquinoxaline 2a could be separated by column chromatography over silica gel and recycled. On the other hand, treatment of quinoxalinequinone 3a with diazomethane in DMF at 0°C afforded 1-methylpyrazolo [3,4-g]quinoxalinequinone 5 and 2a in 1:1 ratio (Scheme II). The compound 5 was analysed for $C_{24}H_{18}N_4O_2$. The ir (KBr) spectrum of the compound showed a strong peak at 1670 cm^{-1} (C=O). ^1H nmr of the compound showed a downfield shift for N-CH_3 at δ 4.3 and N = CH proton appeared at δ 8.0. On this basis the structure for the compound was assigned as 5.

Scheme II



Reaction of quinoxalinequinone 3a with 4-methylbenzohydroximinoyl chloride, 6[9] in the presence of triethylamine gave isoxazolo [4,5-g]quinoxalinequinone, 7a [Mp 258-260°C; 25%] and dihydroxyquinoxaline 2a in 1:1 ratio (Scheme III).

Scheme III



In all these dipolar cycloaddition reactions the initially formed cycloadduct C underwent oxidation by reacting with the starting quinone 3 and dihydroxyquinoxaline 2a was formed as a side product. In order to eliminate the formation of the side product and to increase the yield of isoxazoloquinoxalinequinone, use of silver oxide in place of triethylamine was made since silver oxide was found to act both as a base[10] and an oxidising agent. Treatment of quinoxalinequinone 3a with benzohydroximinoyl chloride 6 in the presence of silver oxide gave only isoxazolo [4,5-g] quinoxalinequinone, 7a in 63% yield. Similarly isoxazolo [4,5-g]quinoxalinequinones 7b, 7c and 7d were prepared (Scheme IV, Table I).

Scheme IV

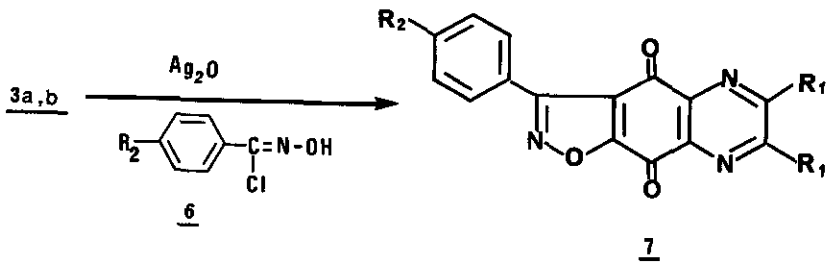
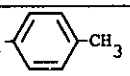
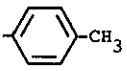
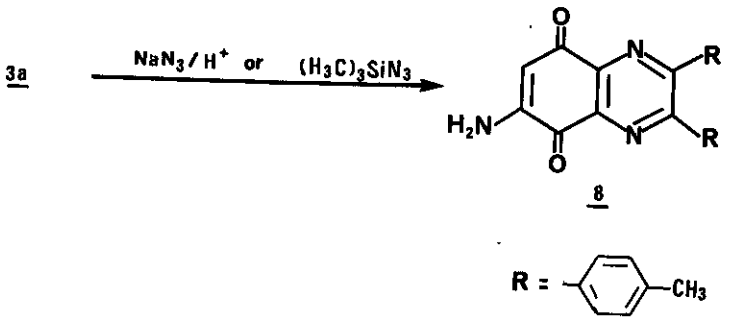


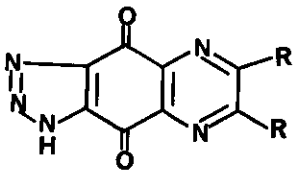
Table I

No.	R_1	R_2	Yield %	Mp°C	Analysis							
					Calculated (%)				Found (%)			
					C	H	N	Cl	C	H	N	Cl
7a		CH_3	63	258-260	76.42	4.49	8.91		75.91	4.73	9.24	
7b		H	63	223-225	76.14	4.19	9.19		75.98	4.10	8.82	
7c	Cl	NO_2	18	262-264	46.05	1.03	14.32	18.15	46.20	1.13	14.36	18.26
7d	Cl	H	27	238-240	52.03	1.46	12.14	20.51	52.38	1.25	12.49	20.80

Though the reaction of trimethylsilyl azide with olefin is reported to give triazoles[12], attempt to get quinoxalinequinone 9 by the treatment of quinoxalinequinone 3a with either sodium azide and acetic acid or trimethylsilyl azide furnished only 6-aminoquinoxalinequinone 8. In both the reactions, presumably any initially formed azidoquinone lost nitrogen followed by prototropic shift gave the aminoquinone 8 similar to the reaction of 1,4-naphthoquinone with hydrazoic acid[11]. (Scheme V).

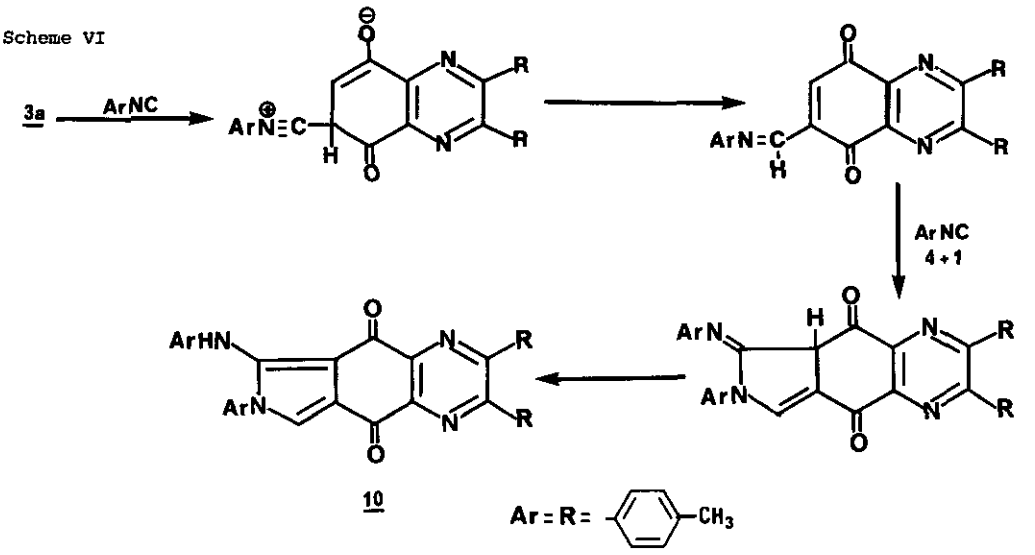
Scheme V





Reaction of quinoxalinequinone 3a with tolyl isocyanide[13] gave pyrrolo [3,4-g] quinoxaline-quinone 10 as only isolable product in 4% yield. (Scheme VI). The reaction course may follow the same pathways as reported[14] in the reaction of benzoquinone with tolyl isocyanide.

Scheme VI



EXPERIMENTAL

Melting points are uncorrected. Ir spectra were taken in KBr using a Perkin Elmer 157 Spectrophotometer. Chemical shifts (δ) are in parts per million relative to tetramethylsilane. Coupling constants (J values) are in Hertz (Hz). ^{1}H nmr spectra were run on a Varian T-60 spectrometer.

Preparation of 2,3-Ditolyl Quinoxaline-5,8-dione 3a and 2,3-Dichloroquinoxaline-5,8-dione 3b.

5,8-Dimethoxy-2,3-ditolyl quinoxaline 1a was prepared similar to the reported procedure[7] for the preparation of 5,8-dimethoxy-2,3-diphenylquinoxaline. Mp 184-186°C; Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.42; H, 5.79; N, 7.64%.

A pulvarised mixture of 5,8-dimethoxy-2,3-ditolyl quinoxaline 1 (21.3 g; 0.0576 mol) and anhydrous aluminium chloride (90 g; 0.675 mol) in dry benzene (500 ml) was refluxed for 8 h. The reaction mixture was cooled, poured into crushed ice and the product extracted with benzene. The organic layer was washed with water dried and solvent removed to yield a gummy solid. The crude product was passed through a column of silica gel and on elution with benzene gave 2,3-ditolyl-5,8- dihydroxyquinoxaline 2a (12.2 g; 62%). An analytical sample was prepared by crystallising from chloroform. Mp 189-191°C; Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found : C, 77.28; H, 5.53; N, 7.98%.

To a mixture of 2,3-ditolyl-5,8-dihydroxy quinoxaline 2a (3.3 g; 0.0096 mol), activated charcoal (1.5 g) and anhydrous sodium sulphate (8.0 g) in 150 ml of dry benzene, silver oxide (4.0 g) was added in portions at room temperature. The reaction mixture was stirred for 20 min. The insoluble solid was removed by filtration and the residue was washed with benzene.

The filtrate was concentrated to give 2,3-ditolylquinoxaline-5,8-dione 3a as a solid (3.08 g; 94%). An analytical sample was prepared by crystallising from dichloromethane-pet. ether (60-80°C). Mp 212°C; Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found : C, 77.25; H, 4.83; N, 8.38%.

Similarly, 2,3-dichloro quinoxaline-5,8-dione 3b was prepared from 2,3-dichloro-5,8-dihydroxyquinoxaline[8] Mp 204-206°C ($CHCl_3$/pet. ether 60-80°C). Anal. Calcd. for $C_8H_2Cl_2N_2O_2$: C, 41.93; H, 0.88; Cl, 30.99; N, 12.23. Found : C, 41.80; H, 0.79; Cl, 30.98; N, 11.93%.

Preparation of 6,7-Di-p-tolyl-1H-pyrazolo [3,4-g]quinoxaline-4,9-dione 4.

To a solution of 2,3-ditolylquinoxaline-5,8-dione 3a (4.0 g; 0.0118 mol) in dry dimethylformamide (150 ml), a precooled solution of diazomethane (0.55 g) in 60 ml of ether was added dropwise with stirring at -50°C. The mixture was stirred at -50°C for 45 min. Excess diazomethane was removed under vacuum at -50°C and then dimethylformamide was distilled off from the reaction mixture. The residue was extracted with dichloromethane, washed with water, dried and concentrated. The crude product was passed through a column of silica gel and on elution with chloroform gave 2,3-ditolyl-5,8-dihydroxyquinoxaline 2a (1.8 g; 44.74%), Mp 189-191°C. Further elution with chloroform : methanol (98:2) gave 6,7-di-p-tolyl-1H-pyrazole [3,4-g]quinoxaline-4,9-dione 4 as a solid. (2.0 g; 44.74%). An analytical sample was prepared by crystallising from dichloromethane/pet. ether (60-80°C). Mp > 300°C; ^1H nmr ($CDCl_3$) : δ 2.3 (s, 6H, CH_3), 7.0 (d, J = 8 Hz, 4H, Ar). 7.45 (d, J = 8 Hz, 4H, Ar), 8.4 (s, 1H, N = CH); ir (KBr) : 1670 cm^{-1}; Anal. Calcd. for $C_{23}H_{16}N_4O_2.0.5H_2O$: C, 70.94; H, 4.40; N, 14.39. Found : C, 71.06; H, 4.41; N, 13.96%.

Preparation of 6,7-Di-p-tolyl-1-methylpyrazolo [3,4-g]quinoxaline-4,9-dione 5.

To a solution of 2,3-ditolylquinoxaline-5,8-dione 3a (6.2 g; 0.0182 mol) in dry dimethylformamide (100 ml), a solution of diazomethane (1.76 g) in 175 ml of ether, was added dropwise at -20°C. The reaction mixture was stirred at -20°C for 1 h. Dimethylformamide was distilled off under vacuum and the residue was extracted with ethyl acetate, washed with water, dried and concentrated. The crude product was passed through a column of silica gel and on elution with benzene gave 2,3-ditolyl-5,8-dihydroxyquinoxaline 2a (2.6 g; 41.69%), Mp 189-191°C. Further elution with chloroform gave 6,7-di-p-tolyl-1-methyl pyrazolo [3,4-g]quinoxaline-4,9-dione 5 as a solid (3.0 g; 42%). An analytical sample was prepared by crystallising from dichloromethane/pet. ether (60-80°C), Mp 206-208°C; ir (KBr) 1670 cm^{-1}; ^1H nmr ($CDCl_3$):δ 2.3 (s, 6H, CH_3), 4.3 (s, 3H, NCH_3), 7.0 (d, J = 8 Hz, 4H, Ar), 7.5 (d, J = 8 Hz, 4H, Ar), 8.0 (s, 1H, N = CH-). Anal. Calcd. for $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.21. Found : C, 72.97; H, 4.33; N, 14.16%.

Preparation of 3,6,7-Tri(p-tolyl)isoxazolo[4,5-g]quinoxaline-4,9-dione 7a

Method I

To a solution of 2,3-di(p-tolyl)quinoxaline-5,8-dione 3a (1.0 g; 0.003 mol) in dimethylformamide (10 ml), triethylamine (0.4 ml ; 0.003 mol) was added and cooled to -50°C. To this cold solution 4-methylbenzohydroximinoyl chloride 6 (0.5 g; 0.003 mol) in dimethylformamide (2 ml) was added dropwise at -50°C. The reaction mixture was diluted with water and the solid thus precipitated was filtered. The crude product was passed through a column of silica gel. Elution with benzene/pet. ether (bp 60-80°C) (2:3) gave 5,8-dihydroxy-2,3-di(p-tolyl)quinoxaline (0.3 g; 30%, Mp 189-191°C). Further elution with benzene gave 3,6,7-tri(p-tolyl)isoxazolo[4,5-g]quinoxaline-4,9-dione 7a as an orange solid (0.35 g; 25%). An analytical sample was prepared by crystallising from dichloromethane and pet. ether (60-80°C). Mp 258-260°C; ir (KBr) 1670 cm^{-1}; ^1H nmr ($CDCl_3$ + 2 drops of d_6DMSO): δ 2.3 (s, 6H, CH_3), 2.4 (s, 3H, CH_3), 7.55 (m, 12H, Ar). Anal. Calcd. for $C_{30}H_{21}N_3O_3$: C, 76.42; H, 4.49; N, 8.91. Found : C, 76.01; H, 4.73; N, 9.24%.

Method II

To a solution of 2,3-di(p-tolyl)quinoxaline-5,8-dione 3a (5 g; 0.015 mol) in dry dimethylformamide (40 ml), 4-methylbenzohydroximinoyl chloride (2.5 g; 0.015 mol) in dimethylformamide (20 ml) and silver oxide (0.68 g; 0.003 mol) were added simultaneously dropwise and portionwise respectively at 0°C. The reaction mixture was stirred at 0°C for 1 h. Additional amount of 4-methylbenzohydroximinoyl chloride (1 g) in dimethylformamide (2 ml) and silver oxide (1.5 g) were added. The reaction mixture was further stirred for 1 h at 0°C. The reaction mixture was filtered. The insoluble solid was washed with water and chloroform. The organic layer was separated from the filtrate dried and concentrated. The crude product was passed through a column of silica gel. Elution with benzene gave 3,6,7-tri(p-tolyl)isoxazolo[4,5-g]quinoxaline-4,9-dione 7a as an orange solid. Mp 258-260°C. TLC and spectral data of this compound were identical with those of the compound isolated by method I. Similarly 3-phenyl-6,7-di(p-tolyl) isoxazolo[4,5-g]quinoxaline-4,9-dione 7b, 3-(4-nitrophenyl)-6,7-dichloroisoxazolo[4,5-g] quinoxaline-4,9-dione 7c, 3-phenyl-6,7-dichloroisoxazolo[4,5-g]quinoxaline-4,9-dione 7d were prepared. (Table I).

Preparation of 6-Amino-2,3-di(p-tolyl)quinoxaline-5,8-dione 8.

Method I

To a warm solution of 2,3-(p-tolyl)quinoxaline-5,8-dione 3a (1.5 g; 0.0044 mol) in glacial acetic acid (30 ml), an aqueous solution of sodium azide (342 mg; 0.0053 mol) in water (3 ml) was added. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was filtered and the filtrate was concentrated. The crude product was passed through a column of neutral alumina and on elution with chloroform gave 6-amino-2,3-di(p-tolyl)quinoxaline-5,8-dione 8 as an orange red solid (690 mg; 46%). An analytical sample was prepared by crystallising from dichloromethane/pet. ether (60-80°C). Mp 270-272°C; ir (KBr) : 1670 cm^{-1}, 1580 cm^{-1}; ^1H nmr ($CDCl_3$ + d_6DMSO) : δ 2.3 (s, 6H, CH_3), 6.2 (s, 1H, HC = C-C), 6.6 (b.s., 2H, NH_2), 7.1 (d, J = 8 Hz, 4H, Ar), 7.5 (d, J = 8 Hz, 4H, Ar). Anal. Calcd. for $C_{22}H_{17}N_3O_2.0.5H_2O$ C, 72.51; H, 4.98; N, 11.53. Found : C, 72.61; H, 5.19; N, 12.10%.

Method II

To a solution of 2,3-di(p-tolyl)quinoxaline-5,8-dione 3a (0.3 g; 0.001 mol) in dichloromethane (5 ml), trimethylsilyl azide (0.12 ml, 0.001 mol) was added at 0-5°C. The reaction mixture was brought to room temperature and stirred at room temperature for 18 h. Solvent was removed under vacuum and the reaction product was diluted with water. A solid was precipitated and was filtered. The crude solid was passed through a column of silica gel and on elution with benzene gave 5,8-dihydroxy-2,3-(p-tolyl)quinoxaline 2a (0.1 g; 33%, Mp 189-191°C). Further elution with ethylacetate gave 6-amino-2,3-di(p-tolyl)quinoxaline-5,8-dione 8 as an orange red solid (0.12 g; 38%). The solid was recrystallised from dichloromethane/pet. ether (60-80°C). Mp 270-272°C; TLC and spectral data were identical with those of the compound prepared by method I.

Preparation of 2-p-Tolyl-3-(p-tolylamino)-6,7-di(p-tolyl)pyrrolo[3,4-g]quinoxaline-4,9-dione 10.

A mixture of 2,3-di(p-tolyl)quinoxaline-5,9-dione 3a (0.42 mg; 0.0012 mol) and tolyl isocyanide[13] (0.5 g; 0.0043 mol) in dry toluene (10 ml) was refluxed for 4 h. The solvent was removed under vacuum. The crude product was passed through a column of silica gel and on elution with chloroform gave pyrrolo[3,4-g]quinoxaline-4,9-dione 10 as a black solid (30 mg; 4%). An analytical sample was prepared by crystallising from dichloromethane/pet. ether (60-80°C). Mp > 300°C; ir (KBr) 1670 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.3 (s, 9H, CH_3), 2.4 (s, 3H, CH_3), 7.3 (m, 17H, Ar); Anal. Calcd. for $C_{38}H_{30}N_4O_2.0.5H_2O$: C, 78.19; H, 5.35; N, 9.60. Found : C, 77.81; H, 5.67; N, 9.38%.

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