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2,5-Dibromo-3,6-(dihydrazino or diphenylhydrazino)-1,4-benzoquinone **1a,b** reacts with active methylene reagents to give some new functionally substituted pyridazino cinnoline derivatives.

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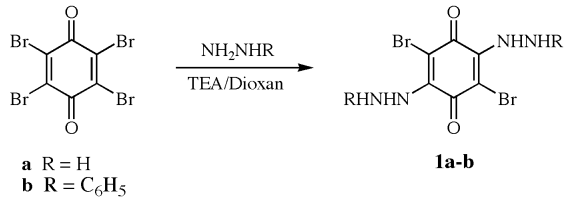
Heterocyclic annulated pyridazines continue to attract considerable attention which mainly arises from the large variety of interesting pharmacological activities observed with pyridazine derivatives [1-3]. On the other hand, many drugs, which are used in cancer chemotherapy, contain a quinone nucleus in their structures [4-6].

Recently, we have reported the use of tetrabromoquinone in the synthesis of some heterocyclic systems [7-9]. In the present study we report the synthesis of Cinnoline derivatives by the reaction of 3,6-dibromo-2,5-dihydrazino-1,4-benzoquinone **1a** or 3,6-dibromo-2,5-diphenylhydrazino-1,4-benzoquinone **1b** with some active methylenes.

The starting materials **1a,b** are prepared by a dropwise addition of hydrazine and phenylhydrazine, respectively, to tetrabromoquinone in the presence of Et_3N as catalyst and dioxan as solvent. The addition was carried out over a 20 minute period with stirring and cooling, followed by stirring at room temperature for further two hours (Scheme 1).

Scheme 1



a R = H
b R = C_6H_5

1a-b

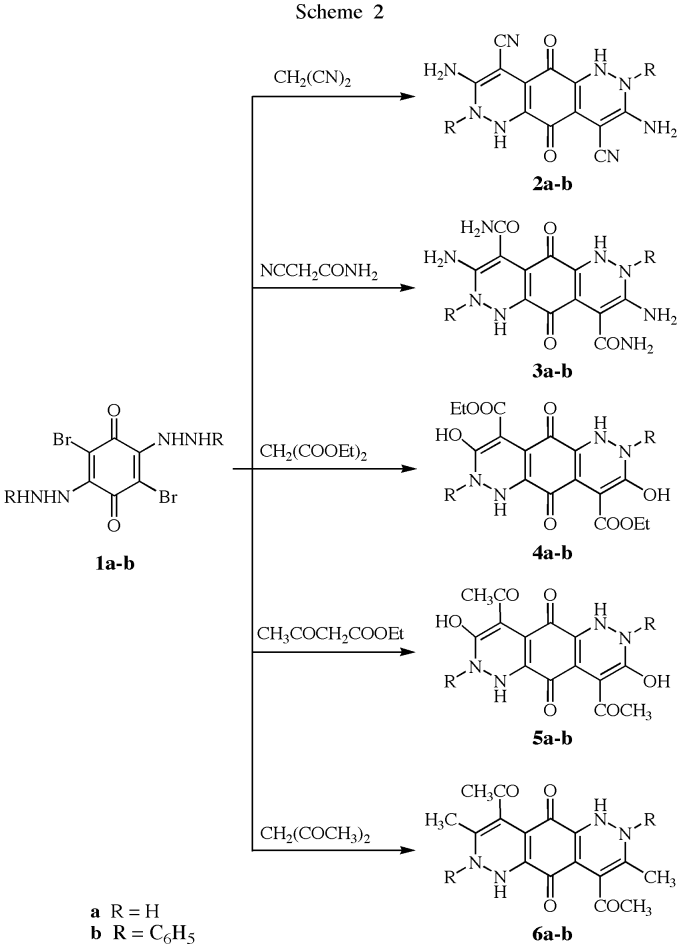
The compounds **1a,b** were allowed to react with a series of active methylene compounds in DMF as solvent and in the presence of Et_3N in 2:1:2 ratio. The reaction mixture was stirred for about one hour and then refluxed over different periods of time (1-3 hours, *c.f.* Table I) to give the corresponding polyfused ring systems (Scheme 2).

The reaction of **1a,b** with malononitrile gave, respectively, 3,8-diamino-4,9-dicyano-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione **2a** and 3,8-diamino-4,9-dicyano-2,7-diphenyl-1,2,6,7-tetrahydropyridazino-[3,4-*g*]cinnoline-5,10-dione **2b**. With cyanoacetamide the reaction of **1a,b** gave respectively 3,8-diamino-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione-4,9-dicarboxamide **3a** and 3,8-diamino-2,7-diphenyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione-4,9-dicarboxamide **3b**. These reactions occured *via* HBr eliminations from **1a,b** followed by nucleophilic additions of the hydrazine groups to the cyano groups of the resultant adducts and then tautomerization.

When compounds **1a,b** reacted with diethylmalonate they gave diethyl 3,8-dihydroxy-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione-4,9-dicarboxylate **4a**, and diethyl 3,8-dihydroxy-2,7-diphenyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione-4,9-dicarboxylate **4b**, respectively, while with diethylmalonate, they gave 4,9-diacetyl-3,8-dihydroxy-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione **5a** and 4,9-diacetyl-3,8-dihydroxy-2,7-diphenyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione **5b** ,respectively.

In this case the reaction mechanism involves eliminations of HBr from **1a,b** followed by nucleophilic additions of the hydrazine groups to the carbonyl of the ester groups

Scheme 2



a R = H
b R = C_6H_5

of the resultant adducts with a subsequent loss of ethanol.

The reaction of **1a,b** with 2,4-pentandione gave, respectively, 4,9-diacetyl-3,8-dimethyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione **6a** and 4,9-diacetyl-3,8-dimethyl-2,7-diphenyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione **6b**. The reaction mechanism involves eliminations of HBr from **1a,b** followed by nucleophilic additions of the hydrazine groups to the carbonyl groups of the resultant adducts with a subsequent loss of water and cyclization. The structures of the obtained products were assigned by elemental analysis, IR and ^{1}H-NMR spectra.

Table 1

Physical and Analytical Data of the Prepared Compounds

Prod. No.	T Hr.	Yield[a] %	M.P.(°C) Cryst.Solv.	M.Form. (M.Wt.)	Analytical data Calc./Found C%	H%	N%	Br
1a	2	72	255	$C_6H_6N_4O_2Br_2$	22.11	1.86	17.19	49.03
			EtOH	325.95	22.49	2.06	16.81	49.33
1b	2	68	240	$C_{18}H_{14}N_4O_2Br_2$	45.21	2.95	11.72	33.42
			EtOH	478.13	45.38	3.00	11.50	33.66
2a	2	63	283	$C_{12}H_8N_8O_2$	48.65	2.72	37.83	
			EtOAc	296.26	48.90	2.86	37.45	
2b	2.5	61	277	$C_{24}H_{16}N_8O_2$	64.28	3.60	24.99	
			EtOAc	448.49	64.08	3.45	24.79	
3a	2.5	76	270	$C_{12}H_{12}N_8O_4$	43.37	3.64	33.72	
			THF	332.27	43.56	3.84	33.40	
3b	3	51	295	$C_{24}H_{20}N_8O_4$	59.52	4.16	23.14	
			Dioxan	484.48	59.82	4.33	22.86	
4a	3	62	230	$C_{16}H_{16}N_4O_8$	48.98	4.11	14.28	
			THF	392.33	49.26	4.30	14.00	
4b	3	57	300	$C_{28}H_{24}N_4O_8$	61.76	4.44	10.29	
			EtOAc	544.51	61.60	4.34	10.01	
5a	2.5	56	215	$C_{14}H_{12}N_4O_6$	50.60	3.64	16.87	
			Dioxan	332.28	50.92	3.86	16.59	
5b	3	52	310	$C_{26}H_{20}N_4O_6$	64.46	4.16	11.57	
			EtOAc	484.46	64.76	4.32	11.32	
6a	3	55	307	$C_{16}H_{16}N_4O_4$	58.53	4.91	17.07	
			THF	328.33	58.30	4.85	16.75	
6b	3	50	298	$C_{28}H_{24}N_4O_4$	69.98	5.03	11.66	
			EtOAc	480.51	70.26	5.23	11.32	

[a] Yield of pure and crystallized products.

EXPERIMENTAL

All m.p. are uncorrected, IR spectra were obtained (KBr discs) on a Nicolet 710 FT-IR spectrometer. ^{1}H- NMR spectra were obtained on a Varian EM 360 A at 60 MHz using TMS as an internal standard. The elemental analyses were carried out on an elemental analyzer model 240c.

3,8-Diamino-4,9-dicyano-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione (**2a**).

3,6-Dibromo-2,5-dihydrazino-1,4-benzoquinone **1a** (3.26 g, 10 mmol) and malononitrile (1.32 g, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise within about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 2 hours. After cooling the solid formed was isolated by filtration and recrystallized from EtOAc to yield **2a**.

3,8-Diamino-4,9-dicyano-2,7-diphenyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione (**2b**).

3,6-Dibromo-2,5-diphenylhydrazino-1,4-benzoquinone **1b** (4.78 g, 10 mmol) and malononitrile (1.32 g, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 2.5 hours. After cooling the solid formed was isolated by filtration and recrystallized from EtOAc to yield **2b**.

3,8-Diamino-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione-4,9-dicarboxamide (**3a**).

3,6-Dibromo-2,5-dihydrazino-1,4-benzoquinone **1a** (3.26 g, 10 mmol) and cyanoacetamide (1.68 g, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 2.5 hours. After cooling the solid formed was isolated by filtration and recrystallized from THF to yield **3a**.

Table 2
IR and NMR Spectra of the Prepared Compounds

Prod. No.	IR(KBr) ν(cm^{-1})	^{1}H- NMR (DMSO-d_6)
1a	3410, 3348, 3270($NHNH_2$), 1657 (CO).	8.20 (s, 2H, 2NH),4.00-4.40 (s,4H, $2NH_2$).
1b	3408(NH), 1656(CO).	8.40 (s, 2H, 2NH),8.00 (s, 2H, 2NH), 7.70- 7.20 (m, 10H, $2C_6H_5$).
2a	3443(NH), 3317, 3252, 3189(NH, NH_2), 2218(CN), 1659(CO).	12.90 (s, 4H, 4NH),6.03 (br, 4H, $2NH_2$)
2b	3441(NH), 3325, 3230(NH_2), 2006(CN), 1653(CO).	12.60 (s, 2H, 2NH),7.90-7.50 (m, 10H, $2C_6H_5$),6.00 (m, 4H, $2NH_2$).
3a	3439(NH), 3325, 3218, 3190(NH, NH_2), 2930(CH,aliph.),1690, 1659(CO).	12.80 (s, 4H, 4NH), 6.30 (br, 4H, $2CONH_2$),5.60 (br, 4H, $2NH_2$).
3b	3430(NH), 3325, 3220,(NH_2), 1685,1655(CO).	12.60 (s, 2H, 2NH), 7.70-7.30 (m, 10H, $2C_6H_5$),6.20 (br, 4H, $2CONH_2$), 5.30 (br, 4H, $2NH_2$).
4a	3440(NH), 3400(OH), 3325(NH) 2930(CH,aliph.), 1705, 1649 (CO).	13.10 (s, 4H, 4NH), 10.50 (s, 2H, 2OH), 4.40 (q, 4H, $2OCH_2$), 1.30 (t, 6H, $2CH_3$).
4b	3450(NH), 3420(OH), 2924(CH,aliph.), 1710, 1634(CO).	12.80 (s, 2H, 2NH), 10.3 (s, 2H, 2OH), 7.60-7.20 (m, 10H, $2C_6H_5$),4.30 (q, 4H, $2OCH_3$) 1.20 (t, 6H, $2CH_3$).
5a	3443(NH), 3398(OH), 3319(NH) 2925(CH,aliph.), 1700, 1651(CO).	13.10 (s, 4H, 4NH), 10.70 (s, 2H, 2OH), 3.65 (s, 6H, $2CH_3$).
5b	3428(NH), 3418(OH), 2915(CH,aliph.), 1690, 1655(CO).	12.80 (s, 2H, 2NH), 10.40 (s, 2H, 2OH), 7.80-7.30 (m, 10H, $2C_6H_5$), 3.60 (s, 6H, $2CH_3$).
6a	3448, 3320(NH), 2922(CH, aliph.), 1700, 1645(CO).	12.40 (s, 4H, 4NH), 3.50 (s, 6H, $2COCH_3$), 1.40 (s, 6H, $2CH_3$).
6b	3436(NH), 2930(CH,aliph.), 1705, 1649(CO).	12.20 (s, 2H, 2NH), 7.50-7.10 (m, 10H, $2C_6H_5$), 3.35 (s, 6H, $2COCH_3$), 1.30 (s, 6H, $2CH_3$).

3,8-Diamino-2,7-diphenyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]-cinnoline-5,10-dione-4,9-dicarboxamide (**3b**).

3,6-Dibromo-2,5-diphenylhydrazino-1,4-benzoquinone **1b** (4.78 g, 10 mmol) and cyanoacetamide (1.68 g, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 3 hours. After cooling the solid formed was isolated by filtration and recrystallized from dioxan to yield **3b**.

Diethyl 3,8-Dihydroxy-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione-4,9-dicarboxylate (**4a**).

3,6-Dibromo-2,5-dihydrazino-1,4-benzoquinone **1a** (3.26 g, 10 mmol) and diethylmalonate (3.03 mL, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 3 hours. After cooling the solid formed was isolated by filtration and recrystallized from THF to yield **4a**.

Diethyl 3,8-Dihydroxy-2,7-diphenyl-1,6-dihydropyridazino[3,4-*g*]cinnoline-5,10-dione-4,9- dicarboxylate (**4b**).

3,6-Dibromo-2,5-diphenylhydrazino-1,4-benzoquinone **1b** (4.78 g, 10 mmol) and diethylmalonate (3.03 mL, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 3 hours. After cooling the solid formed was isoated by filtration and recrystallized from EtOAc to yield **4b**.

4,9-Diacetyl-3,8-dihydroxy-1,2,6,7-tetrahydropyridazino[3,4-*g*]-cinnoline-5,10-dione (**5a**).

3,6-Dibromo-2,5-dihydrazino-1,4-benzoquinone **1a** (3.26 g, 10 mmol) and ethylacetoacetate (2.55 mL, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 2.5 hours. After cooling the solid formed was isolated by filtration and recrystallized from dioxan to yield **5a**.

4,9-Diacetyl-3,8-dihydroxy-2,7-diphenyl-1,6-dihydropyridazino[3.4-*g*]cinnoline-5,10-dione (**5b**).

3,6-Dibromo-2,5-diphenylhydrazino-1,4-benzoquinone **1b** (4.78 g, 10 mmol) and ethylacetoacetate (2.55 mL, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 3 hours. After cooling the solid formed was isolated by filtration and recrystallized from EtOAc to yield **5b**.

4,9-Diacetyl-3,8-dimethyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]-cinnoline-5,10-dione (**6a**).

3,6-Dibromo-2,5-dihydrazino-1,4-benzoquinone **1a** (3.26 g, 10 mmol) and 2,4-pentandione (2.10 mL, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 3 hours. After cooling the solid formed was isolated by filtration and recrystallized from EtOAc to yield **6a**.

4,9-Diacetyl-3,8-dimethyl-2,7-diphenyl-1,2,6,7-tetrahydropyridazino[3,4-*g*]cinnoline-5,10-dione (**6b**).

3,6-Dibromo-2,5-diphenylhydrazino-1,4-benzoquinone **1b** (4.78 g, 10 mmol) and 2,4-pentandione (2.10 mL, 20 mmol) were dissolved in 25 mL of DMF. Et_3N (3 mL, 20 mmol) in 10 mL of DMF was added dropwise over about 15 minutes while the reaction mixture was stirred on an ice bath. Then the reaction mixture was refluxed for 3 hours. After cooling the solid formed was isolated by filtration and recrystallized from EtOAc to yield **6b**.

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