Synthesis of Original Benzo[*g*]quinoxaline-5,10-diones by Bis-$S_{RN}1$ Methodology

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A new heterocyclic bioreductive bis-alkylating agent, 2,3-bis(chloromethyl)benzo[*g*]quinoxaline-5,10-dione, was prepared in a four-steps synthesis. It was shown to react under electron transfer conditions with 2-nitropropane anion by an bis-$S_{RN}1$ mechanism to give three *C*-alkylation products in excellent yields. Extension of this bis-$S_{RN}1$ reaction to various nitronate or malonate anions and *S*-centered anions led to a new class of potentially active benzo[*g*]quinoxaline-5,10-dione derivatives.

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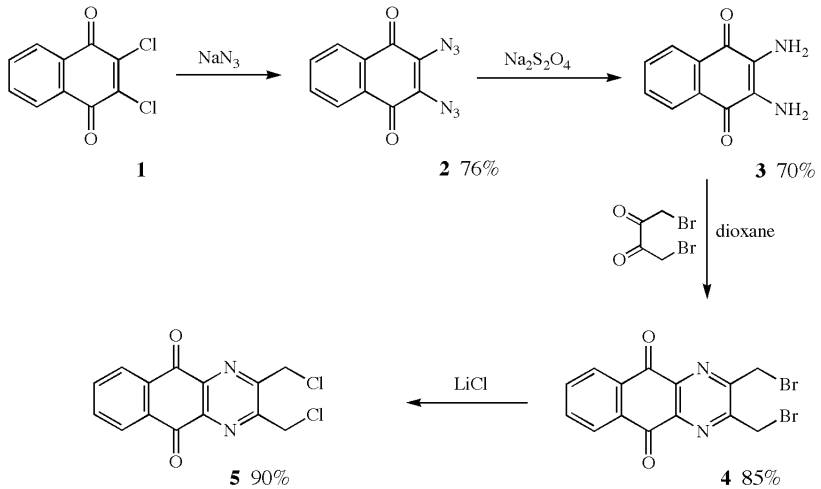
The importance of quinoxalines as pharmaceutical agents is manifested by the recent marketing of brimonidine [5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-quinoxalinamine] as an antiglaucoma agent [1]. Many drugs candidates bearing quinoxaline core structures are in clinical trials in antiviral [2], anticancer, antibacterial [3], and CNS (central nervous system) therapeutic areas. Studies on the activity of heterocyclic quinones containing nitrogen such as quinolinedione showed that the number and the position of nitrogens are considerably important for the cytotoxicity [4]. Thus the diazanaphthoquinones were proved to be the most active compounds in comparison with naphthoquinone and quinolinedione. It was published that 5,8-quinoxalinediones that have one additional nitrogen in the different nucleus from quinolinedione showed antitumor activity [5]. Another structural requirement for the antitumor activity is the *p*-quinone moiety in the nonheterocyclic ring, whereas *o*-quinone gave decreased activity [6]. The electron-withdrawing groups at the 6 and 7 positions of quinolinediones also contributed to the activity [7], Giorgi-Renault prepared benzoquinoxalinediones and pyridoquinoxalinediones, which are quinoxalinediones fused with benzene or pyridine, and examined their cytotoxic properties [8].

In continuation to our studies directed toward the synthesis of new nitroheterocyclic or quinonic bioreductible alkylating agents [9] using single electron transfer reactions, we have investigated the reactivity of 2,3-bis-(chloromethyl)benzo[*g*]quinoxaline-5,10-dione (**5**) with various aliphatic or cyclic nitronate anions, malonate and *S*-centered anions in order to prepare original benzo[*g*]-quinoxaline-5,10-dione derivatives.

Starting with 2,3-dichloro-1,4-naphthoquinone (**1**), compound **5** could be easily prepared in a four-steps synthesis. Thus, **1** was first converted into the corresponding diazido derivative **2** using NaN_3 [10], followed by a reduction with $Na_2S_2O_4$ to form 2,3-diamino-1,4-naphthoquinone (**3**) [11]. The condensation of **3** with 1,4-dibromobutan-2,3-dione led to 2,3-bis(bromomethyl)benzo[*g*]-quinoxaline-5,10-dione (**4**) [8,12] which was converted into **5** by classical chlorination using lithium chloride (Scheme 1). The reaction of 2,3-bis(chloromethyl)benzo-

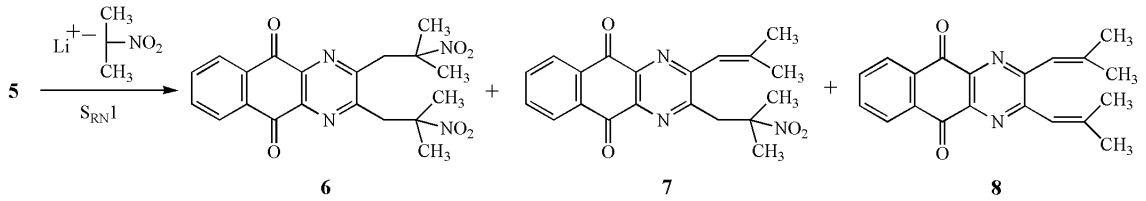
Scheme 1



[*g*]quinoxaline-5,10-dione (**5**) and 6 equivalents of 2-nitropropane anion under $S_{RN}1$ reaction conditions (inert atmosphere, light catalysis) gave the bis-*C*-alkylation product **6** and the ethylenic compounds **7** and **8**. These derivatives were obtained respectively *via* a single and a double base-promoted nitrous acid elimination of **6** (Scheme 2).

The bis-$S_{RN}1$ mechanism was confirmed by inhibition studies [13] under optimum conditions (Entry 8, Table 1): addition of *p*-dinitrobenzene as radical anion scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as radical trap, $CuCl_2$ or performing the reaction in the dark strongly decreased *C*-alkylation yield (Table 2).

Scheme 2



6 **7** **8**

Table 1

Entry [a]	M	Time	Equiv. of anion	Solvent	(%) Yield [b] 6	7	8	*C*-alk.
1	NBu_4	10 min	6	CH_2Cl_2/H_2O [c]	-	-	12	12
2	NBu_4	25 min	6	$C_6H_5CH_3/H_2O$ [c]	-	-	41	41
3	NBu_4	6 h	4	$C_6H_5CH_3/H_2O$ [c]	-	7	41	48
4	Li	1 h	6	CH_3OH	-	-	30	30
5	Li	45 min	8	CH_3OH	-	-	34	34
6	Li	2.5 min	6	DMSO	-	-	32	32
7	Li	2 h	6	H_2O [d]	25	45	5	75
8	**Li**	**24 h**	**6**	H_2O [d]	**20**	**34**	**36**	**90**
9	Li	24 h	8	H_2O [d]	17	13	22	52
10	Li	2 h	8	H_2O [d]	3	27	26	56

[a] All reactions were performed under argon and irradiation with a 300 W fluorescent lamp using one equivalent of **5**; [b] All yields refer to chromatographically isolated pure products and are relative to the electrophile; [c] Phase-transfer conditions with NBu_4OH 40% in water; [d] Reaction performed in refluxed water.

The best yield of bis-*C*-alkylated products was obtained in refluxed water with 6 equivalents of 2-nitropropane anion, during 24 hours under inert atmosphere and light catalysis (Entry 8, Table 1).

Table 2

Entry [a]	Scavenger	(%) Yield [b] 6	7	8	*C*-alk.
8	-	20	34	36	90
11	*p*-dinitrobenzene (0.1 equiv.)	30	17	-	47
12	*p*-dinitrobenzene (1 equiv.)	12	12	-	24
13	Dark	9	33	15	57
14	$CuCl_2$ (0.1 equiv.)	3	5	38	46
15	$CuCl_2$ (1 equiv.)	37	18	Traces	56
16	TEMPO (1 equiv.)	5	-	-	5

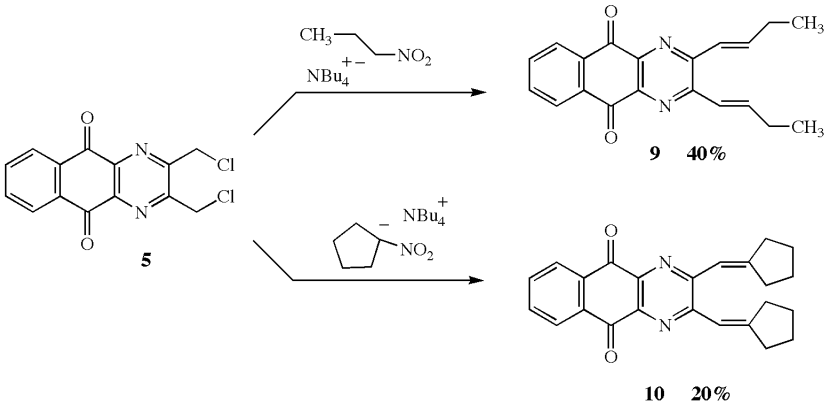
[a] All reactions were performed under argon and irradiation with a 300 W fluorescent lamp during 24 hours at refluxed water using one equivalent of **5**; [b] All yields refer to chromatographically isolated pure products and are relative to the electrophile.

All these experimental data provide good evidence for assigning the bis-$S_{RN}1$ mechanism to the reaction of 2,3-bis(chloromethyl)benzo[*g*]quinoxaline-5,10-dione (**5**) and 2-nitropropane anion.

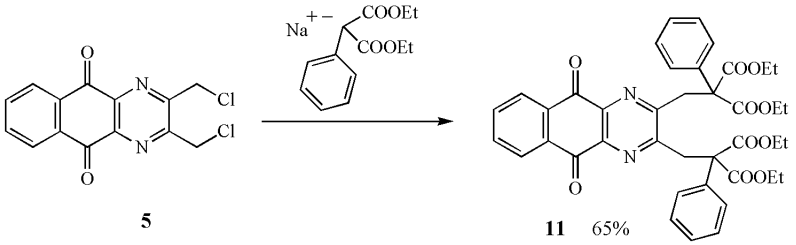
The understanding of the relationship between the nucleophile and the substrate in single electron transfer reaction is useful in order to increase the selectivity and the yield of the reaction [14], thus we have investigated the reactivity of **5** with other nitronate anions (aliphatic or cyclic). The precursors of the nitronate anions were commercially available or obtained by oxidation of the corresponding amines with *m*-chloroperbenzoic acid [15]. The reaction of **5** with primary nitronate anion such as 1-nitropropane anion, in refluxed water conditions (Entry 8, Table 1) led to untractable tarry matters. So, we have treated **5** in the mild operating conditions of Entry 3 (Table 1). In these conditions, we have only isolated the corresponding bis-ethylenic product **9** (*E,E* isomer) in 40% yield (Scheme 3). This selectivity may be explained by favored conformations of the bis-*C*-alkylated derivative. By reacting **5** with nitrocyclopentane anion in operating conditions of Entry 3 (Table 1), the corresponding bis-ethylenic compound **10** was also isolated in 20% yield (Scheme 3). These ethylenic compounds **8**, **9** and **10** present a great synthetic potential because they offer the possibility of further functionalizations. For example, such alkenes may be converted into polycyclic systems *via* a ring-closure process [16].

In continuation of our study on the generalization of the reactivity of 2,3-bis(chloromethyl)benzo[*g*]quinoxaline-5,10-dione (**5**) in single electron transfer conditions, we have performed the reaction of **5** with malonate derivatives such as anion of 2-phenylmalonic acid diethyl ester. The reaction of **5** with 2-phenylmalonic acid diethyl ester and sodium hydride in dimethylsulfoxide (appropriate conditions of reactions with malonate anions) led to the bis-*C*-alkylated product **11** (Scheme 4) in 65% yield. The

Scheme 3



Scheme 4



same reaction with 1 équivalent TEMPO added to the reaction mixture, led only to 10 % of product **11**. This inhibition data shows that as with nitronate anions, the bis-chloride **5** reacts with malonate anions according to an bis-$S_{RN}1$ mechanism.

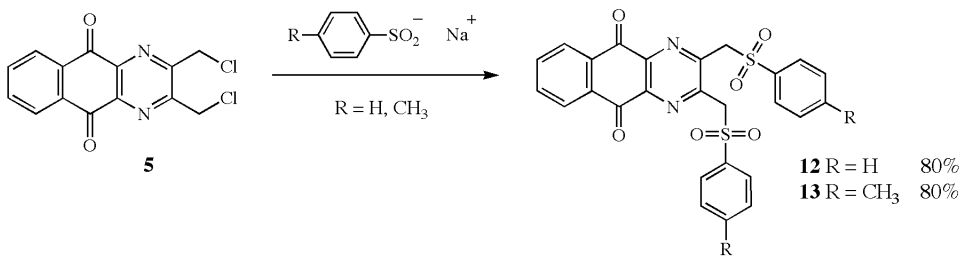
The extension of the reactivity to *S*-centered anions was realized from benzene- and toluenesulfinic acid anions. These two reactions treated in optimized conditions (Entry 8, Table 1) led to the corresponding bis-*S*-alkylated compounds **12** and **13** in 80% yields (Scheme 5). The inhibition experiments showed that the formation of products **12** and **13** was not sensitive to the presence of classical inhibitors of $S_{RN}1$ reactions. So, these bis-*S*-alkylations underwent an ionic S_N2 mechanism instead of the bis-$S_{RN}1$ mechanism.

In conclusion, we have demonstrated in this paper that this methodology, based on electron transfer reactions, was a general method for the preparation of new class of potentially active benzo[*g*]quinoxaline-5,10-diones under mild operating conditions. Moreover, we have showed that the bis-chloride **5** reacts with *S*-centered anions such as sulfinic acid anions according to an S_N2 mechanism.

EXPERIMENTAL

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3. Both ^1H and ^{13}C nmr spectra were determined on a Bruker ARX 200 spectrometer. The ^1H chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvents peaks: deuteriochloroform (76.9 ppm) or dimethylsulfoxide-d_6 (39.6 ppm). Absorptions are reported with the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets.

Scheme 5



Flash column chromatography was performed on silica gel 60 (Merck, particle size 0.063-0.200 mm, 70-230 mesh ASTM) and aluminium oxide (Fluka, type 507 C neutral, 100-125 mesh). Thin layer chromatography was performed on 5 x 10 cm aluminium plates coated with silica gel 60 F-254 (Merck) in an appropriate solvent.

2,3-Diazido-1,4-naphthoquinone (**2**).

This compound was obtained from reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with NaN_3 in 76% yield, mp 137 °C [10].

2,3-Diamino-1,4-naphthoquinone (**3**).

This compound was obtained from reaction of 2,3-diazido-1,4-naphthoquinone (**2**) with $Na_2S_2O_4$ in 70% yield, mp 230 °C [11].

2,3-Bis(bromomethyl)benzo[*g*]quinoxaline-5,10-dione (**4**).

This compound was obtained from reaction of 2,3-diamino-1,4-naphthoquinone (**3**) with 1,4-dibromobutan-2,3-dione in 85% yield, mp 185 °C [8].

2,3-Bis(chloromethyl)benzo[*g*]quinoxaline-5,10-dione (**5**).

In a two-necked flask equipped with a drying tube, a solution of 5 g (12.60 mmoles) of **4** and 6.42 g (151.20 mmoles) of lithium chloride in anhydrous tetrahydrofurane was stirred at room temperature and under inert atmosphere for 48 hours. Then, 100 ml of dichloromethane was added. The organic layer was washed twice with water, dried over anhydrous magnesium sulfate and removed under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from isopropyl alcohol gave 2,3-bis(chloromethyl)benzo[*g*]quinoxaline-5,10-dione (**5**); mp 173 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 5.10 (s, 4H), 7.89-7.92 (m, 2H), 8.40-8.43 (m, 2H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 42.7 (2xCH_2), 128.1 (2xCH), 132.9 (2xC), 135.4 (2xCH), 143.6 (2xC), 156.3 (2xC), 180.4 (2xC).

Anal. Calcd for $C_{14}H_8Cl_2N_2O_2$: C, 54.75; H, 2.63; N, 9.12. Found: C, 54.47; H, 2.68; N, 9.02.

Bis-S_{RN}1 Reaction of **5** with 2-Nitropropane Anion (Entry 8, Table 1).

Under nitrogen atmosphere, a solution of 0.4 g (1.30 mmoles) of 2,3-bis(chloromethyl)benzo[*g*]quinoxaline-5,10-dione (**5**) in water (25 ml) was stirred at 100 °C. A solution of 2-nitropropane lithium salt (7.80 mmoles) in water (10 ml) was added and the mixture was stirred for 24 hours at 100 °C under nitrogen and irradiation with a 300 W fluorescent lamp. The aqueous layer was poured into ice water and extracted with chloroform (3 x 10 ml), dried over anhydrous magnesium sulfate and removed under reduced pressure. Purification by chromatography on silica column eluting with chloroform/ethyl acetate (9/1), and recrystallization from isopropanol gave the three products (**6-8**).

2,3-Bis(2-methyl-2-nitropropyl)benzo[*g*]quinoxaline-5,10-dione (**6**).

This compound was obtained as a yellow solid recrystallized from ethanol; mp 201 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.85 (s, 12H), 3.67 (s, 4H), 7.84-7.87 (m, 2H), 8.33-8.36 (m, 2H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.8 (4xCH_3), 42.9 (2xCH_2), 87.0 (2xC), 127.7 (2xCH), 132.9 (2xC), 135.0 (2xCH), 141.7 (2xC), 156.4 (2xC), 180.7 (2xC).

Anal. Calcd for $C_{20}H_{20}N_4O_6$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.07; H, 4.88; N, 13.59.

2-(2-Methyl-2-nitropropyl)-3-(2-methylpropenyl)benzo[*g*]quinoxaline-5,10-dione (**7**).

This compound was obtained as a yellow solid recrystallized from isopropanol; mp 200 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.80 (s, 6H), 2.09 (s, 3H), 2.22 (s, 3H), 3.69 (s, 2H), 6.49 (s, 1H), 7.83-7.86 (m, 2H), 8.34-8.37 (m, 2H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 20.8 (CH_3), 26.6 (2xCH_3), 28.3 (CH_3), 43.6 (CH_2), 86.8 (C), 118.6 (CH), 127.6 (CH), 127.7 (CH), 133.0 (C), 133.1 (C), 134.7 (CH), 134.8 (CH), 140.5 (C), 142.4 (C), 152.5 (C), 154.9 (C), 156.4 (C), 180.9 (C), 181.6 (C).

Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.50; H, 5.25; N, 11.50.

2,3-Bis(2-methyl-propenyl)benzo[*g*]quinoxaline-5,10-dione (**8**).

This compound (extremely unstable) was obtained as a yellow solid recrystallized from isopropanol; mp 210 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 2.06 (s, 6H), 2.20 (s, 6H), 6.51 (s, 2H), 7.81-7.84 (m, 2H), 8.34-8.37 (m, 2H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 20.7 (2xCH_3), 28.8 (2xCH_3), 120.1 (2xCH), 127.5 (2xCH), 133.2 (2xC), 134.5 (2xCH), 141.1 (2xC), 150.2 (2xC), 155.3 (2xC), 181.7 (2xC).

Inhibition Reactions of **5** with 2-Nitropropane (Table 2).

The procedure was similar to the general procedure except that the inhibitor was immediately added to the reaction mixture prior to the chloride **5**. The experiment performed in the dark needed to wrap the flask in aluminium foil.

General Procedure for the Reaction of **5** with Nitronate anions.

Under nitrogen atmosphere, a solution of tetrabutylammonium hydroxide (40% in water, 4.26 ml, 6.52 mmoles) was stirred at room temperature with nitroalkane (6.52 mmoles) for 1 hour. A solution of 2,3-bis(chloromethyl)benzo[*g*]quinoxaline-5,10-dione (**5**) (0.5 g, 1.63 mmoles) in toluene (40 ml) was added and the mixture was stirred for 6 hours at room temperature under nitrogen and irradiation with a 300 W fluorescent lamp. The organic layer was separated and the aqueous layer was extracted with chloroform (3 x 10 ml). The combined organic layers were washed twice with water (30 ml), dried over anhydrous magnesium sulfate and removed under reduced pressure. Purification by chromatography on silica column eluting with dichloromethane and recrystallization from appropriate solvent gave the required products.

Reaction of **5** with 1-Nitropropane.

(*E*,*E*)-2,3-(Dibut-1-enyl)benzo[*g*]quinoxaline-5,10-dione (**9**).

This compound was obtained as a yellow solid in 40% yield; mp 149 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.16 (t, 6H, J = 7,4 Hz), 2.37-2.47 (m, 4H), 6.81 (td, 2H, J_{trans} = 15.3 Hz, J = 1.4 Hz), 7.40 (td, 2H, J_{trans} = 15.3 Hz, J = 6.7 Hz), 7.83-7.86 (m, 2H), 8.36-8.39 (m, 2H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 12.8 (2xCH_3), 26.6 (2xCH_2), 122.4 (2xCH), 127.6 (2xCH), 133.2 (2xC), 134.6 (2xCH), 142.4 (2xC), 147.8 (2xCH), 151.8 (2xC), 181.5 (2xC).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.31; H, 5.68; N, 8.87.

Reaction of **5** with Nitrocyclopentane.

2,3-Bis(cyclopentylidenemethyl)benzo[*g*]quinoxaline-5,10-dione (**10**).

This compound was obtained as a green solid in 20% yield,

recrystallized from ethanol; mp 207 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.71-1.86 (m, 8H), 2.62 (t, 4H, J = 6.5 Hz), 2.99 (t, 4H, J = 6.5 Hz), 6.79 (s, 2H), 7.81-7.84 (m, 2H), 8.34-8.36 (m, 2H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 25.6 (2xCH_2), 26.9 (2xCH_2), 33.6 (2xCH_2), 37.2 (2xCH_2), 114.6 (2xCH), 127.4 (2xCH), 133.3 (2xCH), 134.4 (2xCH), 140.7 (2xC), 154.3 (2xC), 165.0 (2xC), 181.9 (2xC).

Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.75; H, 5.94; N, 7.50.

Reaction of **5** with Phenylmalonate Anion.

Under nitrogen atmosphere, a solution of 0.07 g (2.60 mmoles) of sodium hydride and 0.62 g (2.60 mmoles) of diethyl phenylmalonate in dimethylsulfoxide (8 ml) was stirred at room temperature for 1 hour. A solution of 2,3-bis(chloromethyl)benzo[*g*]-quinoxaline-5,10-dione (**5**) (0.2 g, 0.6 mmoles) in dimethylsulfoxide (5 ml) was added and the mixture was stirred for 3.5 hours under nitrogen at room temperature and irradiated with a 300 W fluorescent lamp. The reaction was stopped by addition of water. The aqueous layer was extracted with toluene (4 x 30 ml). The organic layer was washed twice with water (20 ml), dried over anhydrous magnesium sulfate, filtrated and removed under reduced pressure. Purification by chromatography on silica gel column eluting with dichloromethane/ethyl acetate (95/5), followed by recrystallization from cyclohexane gave 2-[3-(2,2-bis-ethoxycarbonyl-2-phenyl-ethyl)-5,10-dihydrobenzo[*g*]quinoxalin-2-ylmethyl]-2-phenyl-malonic acid diethyl ester (**11**) in 65% yield; mp 172 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.23-1.28 (m, 12H), 3.74 (s, 4H), 4.24-4.42 (m, 8H), 7.23-7.36 (m, 10H), 7.81-7.84 (m, 2H), 8.33 (m, 2H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 13.9 (4xCH_3), 41.8 (2xCH_2), 61.8 (2xC), 62.1 (4xCH_2), 127.5 (2xCH), 127.6 (2xCH), 127.7 (2xCH), 128.4 (2xCH), 133.0 (2xC), 134.5 (2xCH), 137.3 (2xC), 141.3 (2xC), 157.7 (2xC), 169.7 (2xC), 180.8 (2xC).

Anal. Calcd for $C_{40}H_{38}N_2O_{10}$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.04; H, 5.46; N, 3.82.

General Procedure for Reactions of **5** with *S*-centered Anions.

Under nitrogen atmosphere, a solution of 0.3 g (0.98 mmoles) of 2,3-bis(chloromethyl)benzo[*g*]quinoxaline-5,10-dione (**5**) in water (10 ml) was stirred at 100 °C. A solution of sulfinic acid sodium salts (5.88 mmoles) in water (10 ml) was added and the mixture was stirred for 1 hour at 100 °C under nitrogen and irradiation with a 300 W fluorescent lamp. The aqueous layer was frozen with ice, and extracted with dichloromethane (3 x 10 ml), dried over anhydrous magnesium sulfate, removed under reduced pressure. Recrystallization of the crude residue from ethyl acetate gave the required products.

2,3-Bis(benzenesulfonylmethyl)benzo[*g*]quinoxaline-5,10-dione (**12**).

This compound was obtained as a grey solid in 80% yield; mp 299 °C. ^{1}H nmr (dimethylsulfoxide-d_6, 200 MHz): δ 5.33 (s, 4H), 7.56-7.84 (m, 10H), 7.95-7.98 (m, 2H), 8.20-8.23 (m, 2H). ^{13}C nmr (dimethylsulfoxide-d_6, 50 MHz): δ 59.8 (2xCH_2), 127.1 (2xCH), 128.8 (2xCH), 129.5 (2xCH), 133.3 (2xC), 134.6 (2xCH), 135.0 (2xCH), 138.4 (2xC), 143.6 (2xC), 149.8 (2xC), 180.4 (2xC).

Anal. Calcd for $C_{26}H_{18}N_2O_6S_2$: C, 60.22; H, 3.50; N, 5.40. Found: C, 59.84; H, 3.40; N, 5.27.

2,3-Bis(toluene-4-sulfonylmethyl)benzo[*g*]quinoxaline-5,10-dione (**13**).

This compound was obtained as a grey solid in 80% yield; mp 278 °C. ^{1}H nmr (dimethylsulfoxide-d_6, 200 MHz): δ 2.39 (s, 6H), 5.24 (s, 4H), 7.38 (d, 4H, J = 8.6 Hz), 7.69 (d, 4H, J = 8.6 Hz), 7.96-7.99 (m, 2H), 8.22-8.25 (m, 2H). ^{13}C nmr (dimethylsulfoxide-d_6, 50 MHz): δ 21.3 (2xCH_3), 60.0 (2xCH_2), 127.1 (2xCH), 128.7 (4xCH), 130.0 (4xCH), 133.4 (2xCH), 135.0 (2xC), 135.7 (2xC), 143.7 (2xC), 145.2 (2xC), 149.8 (2xC), 180.5 (2xC).

Anal. Calcd for $C_{28}H_{22}N_2O_6S_2$: C, 61.52; H, 4.06; N, 5.12. Found: C, 61.14; H, 4.03; N, 5.20.

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