and Bristol-Myers-Squibb for financial support of this work.

Registry No. 3, 128778-92-7; 8, 128778-93-8; 8·HCl, 128778-95-0; 9, 2688-77-9; 9·HCl, 6392-34-3; 11, 85611-40-1; 12, 475-81-0; 13, 128778-94-9; 15, 128709-13-7; $PhCH_2Cl$, 100-44-7; 3,4-$(MeO)_2C_6H_3CH_2Cl$, 7306-46-9; 3,4-$(MeO)_2C_6H_3(CH_2)_2I$, 64728-23-0.

Synthesis of 1,4-Dinitroanthracene-9,10-dione. Stepwise Substitution of the Nitro Groups by Diamines Leading to 1-[(Aminoalkyl)amino]-4-nitroanthracene-9,10-diones and Unsymmetrical 1,4-Bis[(aminoalkyl)amino]anthracene-9,10-diones

A. Paul Krapcho* and Kenneth L. Avery, Jr.

Department of Chemistry, The University of Vermont, Burlington, Vermont 05405

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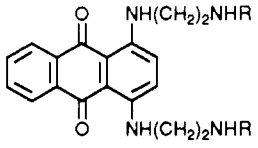
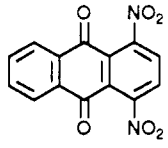
In connection with the synthesis of analogues related to **1** for antitumor evaluations,[1,2] we report preparative pathways to 1,4-dinitroanthracene-9,10-dione (**2**) and a study of the displacements of the nitro groups of **2** by various diamines.



1

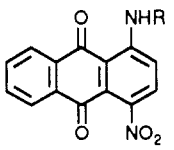


2

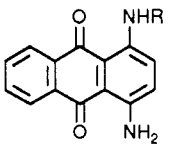
The regiospecific substitution of a nitro group by a nucleophile from an activated benzenoid substrate is a useful preparative route.[3-10] One preparative drawback to this procedure is the competitive reduction of the nitro group to an amino functionality which has been found in a few cases.[5,9] Anion-radical intermediates have been proposed as precursors in the substitution of some nitro benzenoid substrates.[10-12]

Substitutions of the nitro group of 1-nitroanthracene-9,10-diones have been utilized in the preparation of azido,[13,14] amino,[15-21] and alkoxyanthracene-9,10-diones.[22-24] In the substitution of 1-chloro- and 1-nitroanthracene-9,10-dione, the nitro group is displaced by amines such as piperidine about 50 times faster than the chloro group.[16,18] As in the nitro benzenoid substrates, evidence has been presented for an anion-radical intermediate in the substitution (or reduction) of 1-nitroanthracene-9,10-dione.[22]

The synthesis of **2** has been previously reported by a Japanese group[25] using a two-step oxidation [$(NH_4)_2S_2O_8$ followed by CrO_3] of 1-amino-4-nitroanthracene-9,10-dione (**3a**) in a 14% yield.



3a: R = H
b: R = $(CH_2)_2N(CH_3)_2$
c: R = $(CH_2)_2NH(CH_2)_2OH$
d: R = $(CH_2)_2NH_2$



4a: R = H
b: R = $(CH_2)_2N(CH_3)_2$
c: R = $(CH_2)_2NH(CH_2)_2OH$
d: R = $(CH_2)_2NH_2$

However, all attempts by our group to repeat this procedure have been unsuccessful. On the other hand, treatment of **3a** with trifluoroacetic acid and hydrogen peroxide (90%)[26] readily leads to **2** in a good yield. Although **3a** can be prepared from 1-aminoanthracene-9,10-dione via a four-step sequence,[27] we have also found that treatment of the commercially available 1,4-diaminoanthracene-9,10-dione (**4a**) with trifluoroperacetic acid (prepared by mixing trifluoroacetic anhydride with 90% hydrogen peroxide) leads to high yields of **2** (84%).

With **2** being readily available, we then investigated the displacements of the nitro groups with several diamino substrates. Some representative substitutions of **2** are tabulated in Table I.

The data presented in Table I indicates that good yields of the monosubstitution products related to **3** (entries 1, 3, and 4) can be obtained from the reactions performed for short periods in neat diamine or dioxane as the solvent. A small amount of the reduction of the nitro group to an amino group was found in the reaction of **2** with 1,2-diaminoethane (entry 4). Reduction and bis-substitution occurred in the reaction performed for longer periods (entry 2).

The preparation of unsymmetrically substituted 1,4-bis[(aminoalkyl)amino]anthracene-9,10-diones by sequential displacements of the nitro substituents by diamines was then examined.

Treatment of **2** with *N*,*N*-dimethylethylenediamine (8

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Table I. 1-[(Aminoalkyl)amino]-4-nitroanthracene-9,10-diones Prepared by Displacement of a Nitro Group from 2

diamine	reaction conditions	products (% yield)
$NH_2(CH_2)_2N(CH_3)_2$	neat, 2 h	**3b** (60)
$NH_2(CH_2)_2N(CH_3)_2$	neat, 48 h	**3b** (31), **4b** (34), **5a** (35)
$NH_2(CH_2)_2NH(CH_2)_2OH$	dioxane, 6 equiv of diamine, 6 h[a]	**3c** (76)
$NH_2(CH_2)_2NH_2$	dioxane, 6 equiv of diamine, 6 h	**3d** (70), **4d** (18)

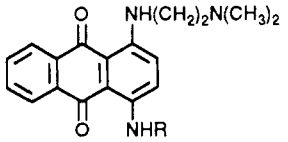
[a] On refluxing for 5 h, **4c** (28%) could be isolated.

Table II. Unsymmetrically Substituted 1,4-Bis[(aminoalkyl)amino]anthracene-9,10-diones Prepared by Displacement of 3b with Diamines in DMSO as Solvent[a]

diamine	products (% yield)
$NH_2(CH_2)_2NH_2$	**5c** (38), **4b** (2), **7d** (7)
$NH_2(CH_2)_2NH_2$[b]	**5c** (33), **4b** (37), **7d** (22)
$NH_2(CH_2)_4NH_2$	**5d** (73)
$NH_2(CH_2)_2NH(CH_2)_2OH$	**5b** (48), **4b** (6)

[a] DMSO, 8–11 equiv of diamine, 40 °C, 2–3 days. [b] Neat.

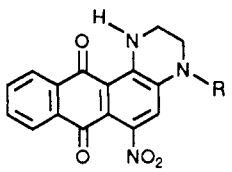
equiv) in DMSO at room temperature or at reflux led mainly to the monosubstituted reduced compound **4b** along with some of the bis-substitution product **5a**.



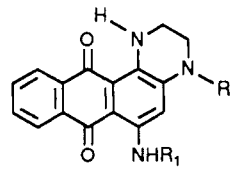
5a: R = $(CH_2)_2N(CH_3)_2$
b: R = $(CH_2)_2NH(CH_2)_2OH$
c: R = $(CH_2)_2NH_2$
d: R = $(CH_2)_4NH_2$

On the other hand, treatment of **2** with 2-[(2-aminoethyl)amino]ethanol or 1,2-diaminoethane in DMSO (8 equiv of either diamine) at room temperature for 5 days led to numerous products detectable by TLC. The mono- and bis-substituted tetrahydroquinoxalines were isolated by chromatography in small amounts and identified by ^1H NMR analysis. The diamine, 2-[(2-aminoethyl)amino]-ethanol, gave **6a** and **7a** while 1,2-diaminoethane led to **6b** and **7b**.

Compound **3c** on treatment with *N,N*-dimethylethylenediamine yielded **5b** (37%) and the tetrahydroquinoxaline **7c** (36%).



6a: R = $(CH_2)_2OH$
b: R = H



7a: R = $(CH_2)_2OH$; R_1 = $(CH_2)_2NH(CH_2)_2OH$
b: R = H; R_1 = $(CH_2)_2NH_2$
c: R = $(CH_2)_2OH$; R_1 = $(CH_2)_2N(CH_3)_2$
d: R = H; R_1 = $(CH_2)_2N(CH_3)_2$

Substitutions using **3b** were then examined in DMSO as the solvent using 8–11 equiv of the appropriate diamine. The results of these studies are tabulated in Table II.

As can be seen from the data in Table II, the displacement of the nitro group of **3b** is a useful synthetic route to unsymmetrically substituted bis[(aminoalkyl)amino]-anthracene-9,10-diones. When the reactions are performed in neat ethylenediamine (entry 2), some reduction of the nitro group and tetrahydroquinoxaline formation also occurred.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Proton NMR were obtained on a Bruker WP270SY or WM-250 pulsed Fourier transform spectrometer. TLC precoated silica gel or alumina sheets (Eastman Chromagram sheets with fluorescent indicator) were used to monitor the reactions. Chromatography was performed on a preparative centrifugally accelerated, radial thin-layer Model 7924 Chromatotron (Harrison Research, 840 Moana Court, Palo Alto, CA) using plates of Merck silica gel 60 PF 254 containing gypsum. Baker analyzed 80–200-mesh silica gel was utilized for column chromatography. Microanalyses were performed by Robertson Laboratories, Madison, NJ. Mass spectra were run on a Finnigan MAT 4610 spectrometer.

1,4-Dinitroanthracene-9,10-dione (2). Method 1. Trifluoroacetic anhydride (9.6 mL) was added dropwise over a 10-min period to a mixture of hydrogen peroxide (90%, 1.6 mL) in methylene chloride (30 mL). This mixture was allowed to stir for 1 h, and solid **4a** (2 g, 8.4 mmol) was added slowly so as to control the exothermic process. The reaction mixture which had changed to a yellow color was then heated at reflux for 2 h. The yellow precipitate of **2** was collected by filtration (2.11 g, 84%); mp 308–310 °C (lit.[25] mp 328.5–333.5 °C); ^1H NMR (DMSO-d_6) δ 8.48 (s, 2 H), 8.13 (m, 2 H), 7.95 (m, 2 H). Anal. Calcd for $C_{14}H_6N_2O_6$: C, 56.38; H, 2.03; N, 9.40. Found: C, 56.17; H, 2.04; N, 9.12.

Method 2. To a stirred solution of **3a** (500 mg, 1.86 mmol) in trifluoroacetic acid (40 mL) was added hydrogen peroxide (90%, 0.5 mL, 18.6 mmol). This mixture was heated at 60 °C for 1 h and allowed to cool and **2** was collected by filtration (361 mg, 65%).

1-[[2-(Dimethylamino)ethyl]amino]-4-nitroanthracene-9,10-dione (3b). Compound **2** (313 mg, 1.05 mmol) was dissolved in *N,N*-dimethylethylenediamine (5 mL, 4.0 g, 45.5 mmol), and the deep red mixture was stirred at room temperature for 2 h, poured into ice–water, and a reddish solid (255 mg) was collected by filtration. Chromatography (chromatotron, silica gel, 95% $CHCl_3$/5% MeOH) of this crude solid gave **3b** (212 mg, 60%). Recrystallization from MeOH yielded red needles: mp 151–152 °C; ^1H NMR ($CDCl_3$) δ 10.14 (s, 1 H), 8.26 (dd, 1 H), 8.15 (dd, 1 H), 7.77 (m, 2 H), 7.58 (d, 1 H), 6.98 (d, 1 H), 3.43 (q, 2 H), 2.69 (t, 2 H), 2.36 (s, 6 H). Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.70; H, 5.05; N, 12.39. Found: C, 63.58; H, 5.00; N, 12.09. The hydrochloride salt was prepared by passing HCl gas through a chloroform solution of **3b**, mp 226–227 °C.

1-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-4-nitroanthracene-9,10-dione (3c). A solution of dione **2** (132 mg, 0.44 mmol) and 2-[(2-aminoethyl)amino]ethanol (280 mg, 2.65 mmol) in dioxane (4.5 mL) was stirred at room temperature for 6 h. The red precipitate was collected by filtration and washed with water to yield **3c** (118 mg, 76%). The analytical sample was recrystallized from MeOH: mp 149–151 °C; ^1H NMR ($CDCl_3$) δ 10.39 (br s, 1 H), 8.27 (d, 1 H), 8.16 (d, 1 H), 7.71–7.88 (m, 2 H), 7.60 (d, 1 H), 7.01 (d, 1 H), 3.74 (t, 2 H), 3.43–3.55 (m, 2 H), 3.08–3.15 (m, 2 H), 2.89–2.95 (t, 2 H). Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.69; H, 4.63; N, 11.76.

1-[(2-Aminoethyl)amino]-4-nitroanthracene-9,10-dione (3d). A solution of dione **2** (110 mg, 0.37 mmol) and ethylenediamine (0.15 mL, 133 mg, 2.2 mmol) in dioxane (4.5 mL) was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and the mixture was subjected to column chromatography (silica gel, gradient elution, 95% $CHCl_3$/5% MeOH to 80% $CHCl_3$/20% MeOH) to give **3d**. Recrystallization from methanol gave a red solid (81 mg, 70%), mp 170–172 °C. This compound had a tendency to form a water-soluble compound on exposure to air, which on treatment with a $NaHCO_3$ solution would regenerate the $CHCl_3$-soluble **3d**: ^1H NMR ($CDCl_3$) δ 10.20 (br s, 1 H), 8.20 (m, 1 H), 8.11 (m, 1 H), 7.76 (m, 2 H), 7.54 (d, 1 H), 7.03 (d, 1 H), 3.35–3.55 (m, 4 H), 3.12 (br s, 2 H). Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.49; H, 4.15; N, 13.32. A purple compound (lower R_f) was identified as **4d** (19 mg, 18%): ^1H NMR ($CDCl_3$) δ 10.81 (br s,

1 H), 8.35 (m, 2 H), 7.62 (m, 2 H), 7.20 (d, 2 H), 7.15 (br s, 2 H), 7.00 (d, 1 H), 3.50 (m, 4 H).

1-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-4-aminoanthracene-9,10-dione (4c). A solution of **2** (136 mg, 0.45 mmol) and 2-[(2-aminoethyl)amino]ethanol (285 mg, 2.73 mmol) in dioxane (4 mL) was refluxed for 5 h. Upon removal of the solvent on a rotary evaporator, the crude solid was subjected to column chromatography (silica gel, gradient elution using 90% $CHCl_3$/10% MeOH to 70% $CHCl_3$/30% MeOH). Collection of a major purple band gave **4c** (42 mg, 28%).[2]

1,4-Bis[[2-(dimethylamino)ethyl]amino]anthracene-9,10-dione (5a). A solution of **2** (50 mg, 0.17 mmol) in *N,N*-dimethylethylenediamine (1 mL) was stirred at room temperature for 48 h and then quenched into water. The water was saturated with NaCl and extracted with chloroform. After drying over magnesium sulfate, removal of the chloroform under reduced pressure gave a purple solid (95 mg). Column chromatography (silica gel, gradient elution from 95% $CHCl_3$/5% MeOH to 1:40:10 triethylamine/$CHCl_3$/MeOH) gave, in order of elution: a red band identified as **3b** (20 mg, 31%), a purple band identified as **4b** (30 mg, 34%) [^{1}H NMR ($CDCl_3$) δ 10.67 (br t, 1 H), 8.30–8.38 (m, 2 H), 7.67–7.74 (m, 2 H), 7.16 (d, 1 H), 7.11 (br s, 2 H), 7.00 (d, 1 H), 3.45–3.53 (m, 2 H), 2.67 (t, 2 H), 2.35 (s, 6 H)], and **5a** (blue, 43 mg, 35%) [^{1}H NMR ($CDCl_3$) δ 10.73 (br s, 2 H), 8.33 (m, 2 H), 7.68 (m, 2 H), 7.32 (s, 2 H), 3.52 (m, 4 H), 2.70 (t, 4 H), 2.38 (s, 12 H).[28]

1-[[2-(Dimethylamino)ethyl]amino]-4-[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthracene-9,10-dione (5b). (a) From 3b. Compound **3b** (595 mg, 1.75 mmol) and 2-[(2-aminoethyl)amino]ethanol (1.9 mL, 1.94 g, 18.6 mmol) in DMSO (10 mL) was stirred at 40 °C for 66 h. Workup as in **5a** gave a purple solid (684 mg). Column chromatography (silica gel, gradient elution from 10% $CHCl_3$/90% MeOH to 3:3:1 $CHCl_3$/MeOH/triethylamine gave the following products in order of elution: a little starting material, **4b** (33 mg, 6%) [^{1}H NMR ($CDCl_3$) δ 10.68 (br s, 1 H), 8.35 (m, 2 H), 7.71 (m, 2 H), 7.18 (d, 1 H), 7.12 (br s, 1 H), 7.00 (d, 1 H), 3.51 (q, 2 H), 2.70 (t, 2 H), 2.38 (s, 6 H)], and **5b** (331 mg, 48%): mp 117–118 °C (lit.[28] mp 115–116 °C); ^{1}H NMR ($CDCl_3$) δ 10.89 (br t, 1 H), 10.72 (br t, 1 H), 8.23–8.38 (m, 2 H), 7.62–7.72 (m, 2 H), 7.12 (s, 2 H), 3.67–3.79 (m, 2 H), 3.35–3.59 (m, 4 H), 2.98–3.08 (m, 2 H), 2.85–2.93 (m, 2 H), 2.61–2.71 (m, 2 H), 2.35 (s, 6 H).

(b) From 3c. Compound **3c** (24 mg, 0.068 mmol) was dissolved in *N,N*-dimethylethylenediamine (4.5 mL, 3.61 g, 50.0 mmol), and the mixture was stirred for 44 h at room temperature. Workup as in **5b** above led to a purple solid which was separated by column chromatography (silica gel, gradient elution from 95% $CHCl_3$/5% MeOH to 40% $CHCl_3$/60% MeOH). A purple high R_f band was identified as **7c**: ^{1}H NMR ($CDCl_3$) δ 11.41 (br s, 1 H), 11.29 (br s, 1 H), 8.28–8.43 (m, 2 H), 7.58–7.75 (m, 2 H), 6.04 (s, 1 H), 3.85–3.95 (m, 2 H), 2.35 (s, 6 H), 3.34–3.48 (m, 2 H), 2.61–2.71 (m, 2 H), 2.35 (s, 6 H). Compound **5b** was also isolated and characterized.

1-[[2-(Dimethylamino)ethyl]amino]-4-[(2-aminoethyl)amino]anthracene-9,10-dione (5c). (a) DMSO as Solvent. Compound **3b** (604 mg, 1.78 mmol) and ethylenediamine (1.1 g, 17.8 mmol) were dissolved in DMSO (10 mL), and the mixture was stirred at 40 °C under nitrogen for 21 h. The mixture was poured into a saturated NaCl solution and extracted with chloroform, and the extracts were dried over $MgSO_4$. Removal of the solvent left a purple solid (641 mg). Column chromatography (silica gel, gradient elution from 5% $CHCl_3$/95% MeOH to 3:3:1 $CHCl_3$/MeOH/triethylamine gave the following products in order of elution: starting material (189 mg, 31%), purple **4b** (11 mg, 2%), the tetrahydroquinoxaline analogue **7d** (45 mg, 7%) [^{1}H NMR ($CDCl_3$) δ 11.18 (br s, 1 H), 10.95 (br s, 1 H), 8.25–8.32 (m, 2 H), 7.55–7.73 (m, 2 H), 6.11 (s, 1 H), 4.85 (s, 1 H), 3.33–3.71 (m, 6 H), 2.68 (t, 2 H), and 2.31 (s, 6 H)], and **5c** (237 mg, 38%) [^{1}H NMR ($CDCl_3$) δ 10.90 (br s, 1 H), 10.78 (br s, 1 H), 8.35 (m, 1 H), 7.60 (m, 1 H), 7.25 (dd, 2 H), 3.53 (m, 4 H), 3.09 (m, 2 H), 2.58 (t, 2 H), and 2.34 (s, 6 H).

(b) Neat. Compound **3b** (84 mg, 0.25 mol) was dissolved in ethylenediamine (8 mL), and the mixture was stirred under nitrogen for 22 h and then poured into ice water. Workup as in **5c** above gave a purple solid (100 mg). Column chromatography (silica gel, gradient elution from 95% $CHCl_3$/5% MeOH to 20% $CHCl_3$/80% MeOH, pure MeOH for the disubstituted material) gave in order of elution: **4b** (29 mg, 37%), **7d** (19 mg, 22%), and **5c** (28 mg, 33%).

1-[[2-(Dimethylamino)ethyl]amino]-4-[(4-aminobutyl)amino]anthracene-9,10-dione (5d). Compound **3b** (207 mg, 0.61 mmol) and 1,4-diaminobutane (430 mg, 4.8 mmol) were combined in DMSO, and the mixture was stirred at 40 °C under nitrogen for 72 h. Workup as in **5c** yielded a purple solid (230 mg). Column chromatography (silica gel gradient elution from 10% $CHCl_3$/90% MeOH to 3:3:1 $CHCl_3$/MeOH/triethylamine) with collection of a major blue band gave **5d**[29] (168 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 10.78 (br s, 2 H), 8.33 (m, 2 H), 7.68 (m, 2 H), 7.20 (s, 2 H), 3.25–3.60 (m, 4 H), 2.55–2.85 (m, 4 H), 2.33 (s, 6 H), 1.66–1.81 (m, 4 H).

(28) Getahun, Z. Ph.D. Thesis, University of Vermont, 1987.

(29) Landi, J. J., Jr. Ph.D. Thesis, University of Vermont, 1986.