rophile. A mixture of **17** (20 mmol), **24** (1.93 g, 20 mmol), and a dipolarophile [methyl acrylate (15 mL, 167 mmol) or styrene (10 mL, 87 mmol)] was refluxed in metahnol (80 mL) for 4 h with stirring in the presence of a small amount of hydroquinone. Evaporation of the solvent and an excess amount of the dipolarophile from the reaction mixture by rotary evaporation gave a generally crystalline mass, which was filtered with acetone (30 mL) to give analytically pure pyrazolidinium chlorides **34**, **35**, and **35′** in the yields shown in the text.

Compound **34**: mp 195 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.1 (s, 3 H), 3.7 (s, 3 H), 3.8 (s, 3 H), 3.7–4.6 (m, 3 H), 5.1–5.4 (m, 1 H), 7.3 (s, 5 H), 8.4 (br, 1 H, NH); IR (Nujol) 3100, 3300 (NH), 1725 (COO) cm^{-1}; SIMS, m/e 505 (2M – Cl), 235 (M – Cl), 149 (M – Cl – dipolarophile). Anal. Calcd for $C_{13}H_{19}N_2O_2Cl$: C, 57.67; H, 7.07; N, 10.34. Found: C, 57.44; H, 7.07; N, 10.26.

Compounds **35** and **35′** (mixture of two stereoisomers): mp 223 °C dec; ^{1}H NMR ($CDCl_3$) (one isomer) N-CH_3 [δ 2.75 (s) and 3.73 (s)], (the other isomer) N-CH_3 [δ 3.33 (s) and 3.50 (s)] (in 1:4 ratio); SIMS, m/e 541 (2M – Cl), 253 (M – Cl), 149 (M – Cl – dipolarophile). Anal. Calcd for $C_{17}H_{21}N_2Cl$: C, 70.70; H, 7.33; N, 9.70. Found: C, 70.45; H, 7.40; N, 9.81.

Reaction of 2 with 1,2-Dimethylhydrazine Dihydrochloride (39). General Procedure. A mixture of **2** (5 mmol) and **39** (5 mmol) was refluxed in ethanol (80 mL) for 3 h with stirring. After the mixture was cooled to room temperature, triethylamine (1.0 g, 10 mmol) was added to the reaction mixture, and the mixture was further stirred for 1 h at the temperature. Evaporation of the solvent from the reaction mixture gave a crystalline residue, which was dissolved with chloroform and washed with water several times. The chloroform layer was dried over anhydrous sodium sulfate, from which the solvent was evaporated to give crude product. Crystalline crude products obtained from the reaction using aldehydes **2b–d** were recrystallized from ethanol to give pure 3-substituted 1,2-dimethyl-1,2,3,3a,4,11c-hexahydronaphtho[1′,2′:5,6]pyrano[4,3-c]pyrazoles **41b–d** in the yields shown in the text. The oily product **40g** obtained from the reaction of **2g** with **39** was purified by distillation.

Compound **41b**: mp 48–51 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 3 H, J = 6 Hz), 2.33 (s, 3 H), 2.63 (s, 3 H), 2.3–3.0 (m, 2 H), 4.0 (dd, 1 H, J = 3.5, 11.5 Hz), 4.25 (dd, 1 H, J = 4, 11.5 Hz), 4.4 (d, 1 H, J = 8 Hz), 6.95–7.9 (m, 5 H), 8.1 (d, 1 H, J = 8 Hz); MS, m/e calcd for $C_{17}H_{20}N_2O$ (M^+) 268.1571, found 268.1566. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.02; H, 7.47; N, 10.18.

Compound **41c**: mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 2.8 (s, 3 H), 2.5–3.1 (m, 1 H), 3.82 (d, 1 H, J = 9 Hz), 3.9 (dd, 1 H, J = 3, 11.5 Hz), 4.2 (dd, 1 H, J = 3, 11.5 Hz), 4.5 (d, 1 H, J = 8 Hz), 6.95–7.85 (m, 10 H), 8.1 (d, 1 H, J = 8 Hz); MS, m/e calcd for $C_{22}H_{22}N_2O$ (M^+) 330.1731, found 330.1733. Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.84; H, 6.69; N, 8.23.

Compound **41d**: mp 117–120 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.17 (s, 3 H), 2.77 (s, 3 H), 3.4–3.9 (m, 1 H), 3.93 (d, 1 H, J = 8 Hz), 4.15 (dd, 1 H, J = 2.5, 12 Hz), 4.45 (dd, 1 H, J = 3, 12 Hz), 4.7 (d, 1 H, J = 7.5 Hz), 6.9–8.1 (m, 6 H); MS, m/e calcd for $C_{17}H_{17}N_3O$ (M^+) 279.1368, found 279.1366. Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 72.95; H, 6.10; N, 14.88.

Compound **40g**: bp 138 °C (1.8 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.2–3.0 (m, 2 H), 2.47 (s, 3 H), 2.6 (s, 3 H), 3.3–3.7 (m, 1 H), 3.5 (d, 1 H, J = 7 Hz), 4.05 (d, 2 H, J = 6 Hz), 6.75–7.3 (m, 4 H); MS, m/e calcd for $C_{12}H_{16}N_2O$ (M^+) 204.1259, found 204.1263. Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.33; H, 7.71; N, 13.55.

Reaction of 17 with 39 in the Presence of a Dipolarophile. General Procedure. A mixture of **17** (20 mmol), **39** (2.66 g, 20 mmol), and a dipolarophile [methyl acrylate (15 mL, 0.17 mol) or styrene (10 mL, 0.09 mol)] was refluxed in methanol (or ethanol) (80 mL) for 3 h with stirring in the presence of a small amount of hydroquinone. Evaporation of the solvent and an excess amount of the dipolarophile from the reaction mixture by rotary evaporation gave an oily residue, which was dissolved with chloroform (80 mL) and to which triethylamine (4.0 g, 40 mmol) was added at room temperature, and then the mixture was washed with water several times. The chloroform layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to give an oily residue. The oily residue was distilled in vacuo to give pure 1,2-dimethylpyrazolidines **42–44′**. Products obtained by the distillation are the mixture of two or three stereo- and regioisomers. Boiling points, mass spectral data, and elemental analyses of the mixture are as follows.

Compounds **42**, **43**, and **43′**: bp 110–120 °C (0.9 mmHg); MS, m/e calcd for $C_{13}H_{18}N_2O_2$ (M^+) 234.1346, found 234.1374. Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.56; H, 7.71; N, 11.84.

Compounds **44** and **44′**: bp 138–146 °C (0.5 mmHg); MS, m/e calcd for $C_{17}H_{20}N_2$ (M^+) 252.1622, found 252.1627. Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.90; H, 7.99; N, 11.05. Separation of the mixture into their components was effected by chromatography (silica gel; chloroform). **44**: 60% yield; ^{1}H NMR ($CDCl_3$) δ 2.3 (t, 2 H, J = 8.5 Hz), 2.4 (s, 6 H), 3.6 (t, 2 H, J = 8.5 Hz), 7.15–7.6 (m, 10 H). **44′**: 3% yield; ^{1}H NMR ($CDCl_3$) δ 2.1–3.1 (m, 2 H), 2.37 (s, 6 H), 4.1 (dd, 2 H, J = 7 and 9.5 Hz), 7.15–7.6 (m, 10 H).

Reaction of 2c with 11c in the Presence of Concentrated HCl. To an ethanol solution (50 mL) of **2c** (0.48 g, 1.66 mmol) and **11c** (0.5 g, 1.66 mmol) was added concentrated HCl (0.17 g, calcd for HCl: 1.66 mmol), and the mixture was refluxed for 3 h with stirring. After the mixture was cooled to room temperature triethylamine (0.2 g) was added to the reaction mixture, and then, crystals that precipitated directly from the mixture were filtered and recrystallized from ethanol to give pure **5c** in 79% yield.

Cycloaddition Routes to Azaanthraquinone Derivatives. 2. Use of Aza Dienes[1]

Kevin T. Potts,* Eileen B. Walsh, and Debkumar Bhattacharjee

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

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Azanaphthoquinones and 1-(dimethylamino)-3-methyl-1-azabuta-1,3-diene (methacrolein N,N-dimethylhydrazone) underwent extremely facile cycloaddition to aza- and polyazaanthraquinones after elimination of dimethylamine from the initial 1:1 cycloadduct and its subsequent oxidation. Introduction of a basic side chain into the 8-position of the azaanthraquinone occurred readily with primary amines and the 8-(tosyloxy) derivative, but more complex substitution patterns resulted with 5,8-bis(tosyloxy) derivatives and primary amines.

In an earlier publication[2] the cycloaddition of 1- and 2-azanaphthoquinones and also 1,3- and 1,4-diazanaphthoquinones with a variety of alicyclic and cyclic dienes led to azaanthraquinones with nitrogen atoms in

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the 1- and 2-positions as well as in the 1,3- and 1,4-positions. With asymmetric dienes the regiochemistry of the cycloaddition was controlled by the position of the ring nitrogen atom relative to the quinone carbonyl groups, and this procedure allowed modification of substituents in both rings A and C of the azaanthraquinones. We now describe a complementary route to related azaanthraquinones involving cycloaddition of aza dienes with quinones and ring-fused azaquinones. These procedures, together with the recently described[3] route from 2,3-pyridinedicarboxylic anhydride, now make numerous substituted azaanthraquinones readily available.

Methacrolein *N,N*-dimethylhydrazone (**1**) has been shown[4] to undergo cycloaddition with acetylenic and olefinic dienophiles to yield a variety of substituted pyridines and dihydropyridines. Naphthoquinone (**2**; R = H) (2 equiv) and **1** gave[4] (CH_3CN, room temperature, 24 h) the fully aromatic system **4** (R = H), the intermediate 1:1 cycloadduct **3** (R = H) being oxidized by the excess of naphthoquinone (Scheme I).

Reaction of 1 with Azanaphthoquinones. 2,3-Dimethylquinoxaline-5,8-dione (**5**) and **1** underwent ready cycloaddition in benzene at room temperature. The first product isolated was the 9,10-dihydroxy tautomer **6** of the initial 1:1 cycloadduct less dimethylamine by 1,4-elimination, and it was unstable to protic solvents, slowly undergoing oxidation, but could be carefully recrystallized to give red needles from acetonitrile. Oxidation to 2,3,7-trimethyl-1,4,5-triazaanthraquinone (**7**) occurred in boiling ethanol. The isolation of the dihydroxy intermediate **6** establishes that the elimination of dimethylamine from the primary 1:1 cycloadduct is an extremely facile process that precedes oxidation. It was not possible in this reaction to determine whether elimination preceded tautomerization (Scheme II).

Quinoline-5,8-dione (**8**) and **1** also underwent cycloaddition in benzene at room temperature. The 9,10-dihydroxy tautomer of the initial 1:1 cycloadduct was not isolated. Instead, aerial oxidation of the crude reaction mixture in boiling ethanol resulted in formation of 3-methyl-1,8-diazaanthraquinone (**9**) in 74% yield. The cycloaddition was regiospecific, as **9** was the only isomer obtained. Structural assignment was based on the established regiochemistry of quinoline-5,8-dione[2] and the regioselectivity of the aza diene, which is controlled by the dimethylamino substituent.

Similar regiospecificity was observed in the cycloadditions of **1** with isoquinoline-5,8-dione (**10**) and 2-chloro-4-methylquinoline-5,8-dione (**11**), which afforded 3-methyl-1,6-diazaanthraquinone (**12**) and 2-chloro-4,6-dimethyl-1,8-diazaanthraquinone (**13**), respectively. The regiospecificity exhibited in these cycloadditions is consistent with the regiochemical control exerted by the position of the ring nitrogen atom relative to the carbonyl groups. Spectral data for all products can be found in Table I and are in agreement with these structural assignments.

Reaction of 1 with Substituted Naphthoquinones. Use of substituted naphthoquinones provides ready access

Table I. Di- and Triazaanthraquinones Obtained from Azanaphthoquinones and 1-(Dimethylamino)-3-methyl-1-azabuta-1,3-diene

compd	mp, °C (habit, solvent)	yield, %	mol formula[a]	M⁺·[b]	^{1}H NMR (200 MHz, $CDCl_3$): δ (*J*, Hz) 2	3	4	5	6	7	8	IR (KBr), cm^{-1}
6	210–212 dec (deep red needles, CH_3CN)	79	$C_{14}H_{13}N_3O_2$	255	2.82 (CH_3)	2.77 (CH_3)			8.77 ($J_{6,8}$ = 1.98)	2.60 (CH_3)	8.47 ($J_{8,6}$ = 1.98)	3740–3000 (OH)
7	238–240 dec (greenish yellow needles, EtOH)	93	$C_{14}H_{11}N_3O_2$	253	2.87 (CH_3)	2.86 (CH_3)			9.01 ($J_{6,8}$ = 2.15)	2.61 (CH_3)	8.52 ($J_{8,6}$ = 2.15)	1700 (C=O) 1690 (C=O)
9	>290 dec (greenish yellow needles, EtOH)	74	$C_{13}H_8N_2O_2$	224	9.01 ($J_{2,4}$ = 1.94)	2.61 (CH_3)	8.45 ($J_{4,2}$ = 1.94)	8.67 ($J_{5,6}$ = 7.97, $J_{5,7}$ = 1.75)	7.80 ($J_{6,7}$ = 7.97, $J_{6,5}$ = 4.67)	9.19 ($J_{7,6}$ = 4.67, $J_{7,5}$ = 1.75)		1690 (C=O) 1670 (C=O)
12	226–227 (pale yellow irregular prisms, EtOH, CH_2Cl_2)	60	$C_{13}H_8N_2O_2$	224	9.00 ($J_{2,4}$ = 2.15)	2.62 (CH_3)	8.47 ($J_{4,2}$ = 2.15)	9.60 ($J_{5,6}$ = 0.85)		9.18 ($J_{8,7}$ = 5.08)	8.21 ($J_{8,7}$ = 5.08, $J_{5,8}$ = 0.85)	1685 (C=O) 1670 (C=O)
13	252–254 (yellow needles, EtOH/CH_2Cl_2)	70	$C_{14}H_9ClN_2O_2 \cdot {}^1/_2H_2O$	272		7.58	2.90 (CH_3)	8.38 ($J_{5,7}$ = 2.18)	2.60 (CH_3)	8.97 ($J_{7,5}$ = 2.18)		1690 (C=O) 1665 (C=O)

[a] All compounds reported had acceptable analytical data (±0.4%) for C, H, N. [b] All 100% relative intensity.

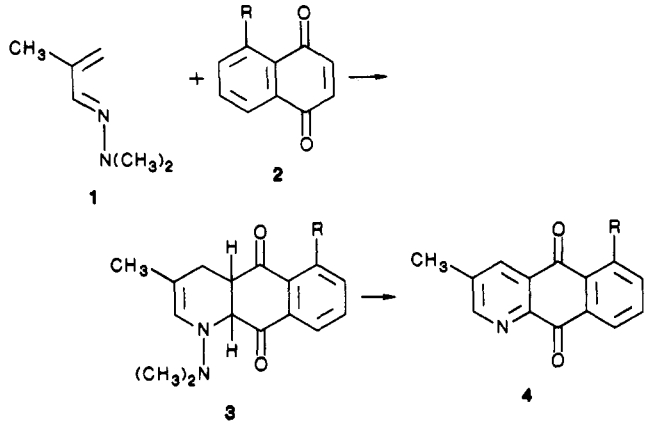
(1) (a) Partial financial assistance from USPHS Research Grant CA 27241 and from Lederle Laboratories is gratefully acknowledged; (b) Abstracted from the Ph.D. Thesis of E.B.W., Rensselaer Polytechnic Institute, 1985.

(2) Potts, K. T.; Bhattacharjee, D.; Walsh, E. B. *J. Org Chem.* **1986**, *51*, 2011.

(3) Krapcho, A. P.; Landi, J. J.; Hacker, M. P.; McCormack, J. J. *J. Med. Chem.* **1985**, *28*, 1124.

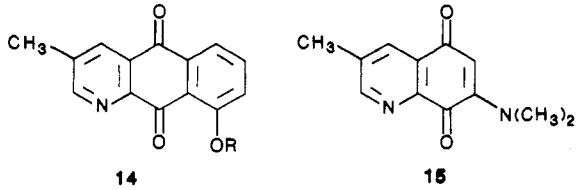
(4) Serckx-Poncin, B.; Hesbam-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, 3261.

Scheme I



to 1-azaanthraquinones with control over the position of the substituent in the benzene ring. Reaction of 5-methoxy-1,4-naphthoquinone (2; R = OMe) with the aza diene 1 in benzene (room temperature, 24 h) followed by air oxidation in ethanol gave 5-methoxy-3-methyl-1-azaanthraquinone (4; R = OCH_3) in 62% yield. The regiospecificity of this cycloaddition can be attributed to two effects: the electron-donating influence of the 5-methoxy group[5] in the naphthoquinone 2 (R = OCH_3) making the C-3 carbon atom more electron deficient; the established directional effect exerted by the dimethylhydrazonyl group in 1.

Although 5-acetoxynaphthoquinone (2; R = OAc) would be expected to behave with the same regiospecificity[5] in its reactions with 1, reaction in benzene at room temperature followed by air oxidation in ethanol gave two products, the 5-hydroxy isomer 4 (R = OH) (52%) and the 8-hydroxy isomer 14 (R = H) (32%). No acetate was detected in the crude reaction mixture. This isomer formation may be readily rationalized in terms of removal of the acetoxy group by the dimethylamine eliminated from the initial 1:1 cycloadduct both before and after the cycloaddition. Thus, conversion of 2 (R = OAc) into 2 (R = OH) would result in a naphthoquinone in which hydrogen bonding of the 5-hydroxyl group to the adjacent carbonyl group of the quinone results in an electron-withdrawing effect, making carbon 2 the more electron-deficient carbon of the dienophilic system.[5] In support of this rationalization, the reaction of 2 (R = OH) with 1 gave 14 (R = H) exclusively in 84% yield. To obtain additional



spectral characterization data, 14 (R = H) was converted into 14 (R = CH_3) with methyl iodide and silver oxide[6] in 95% yield. Table II shows spectral data for all these isomers which, then considered together, are consistent with the structural assignments and in accord with the spectral data for other azaanthraquinones reported earlier.[2]

(5) Manning, W. B. *Tetrahedron Lett.* **1979**, 661. Krohn, K. *Tetrahedron Lett.* **1980**, 3557. Trost, B. M.; Waduchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554. Savard, J.; Brassard, P. *Tetrahedron Lett.* **1979**, 4911. Boeckman, R. K.; Dolak, J. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.

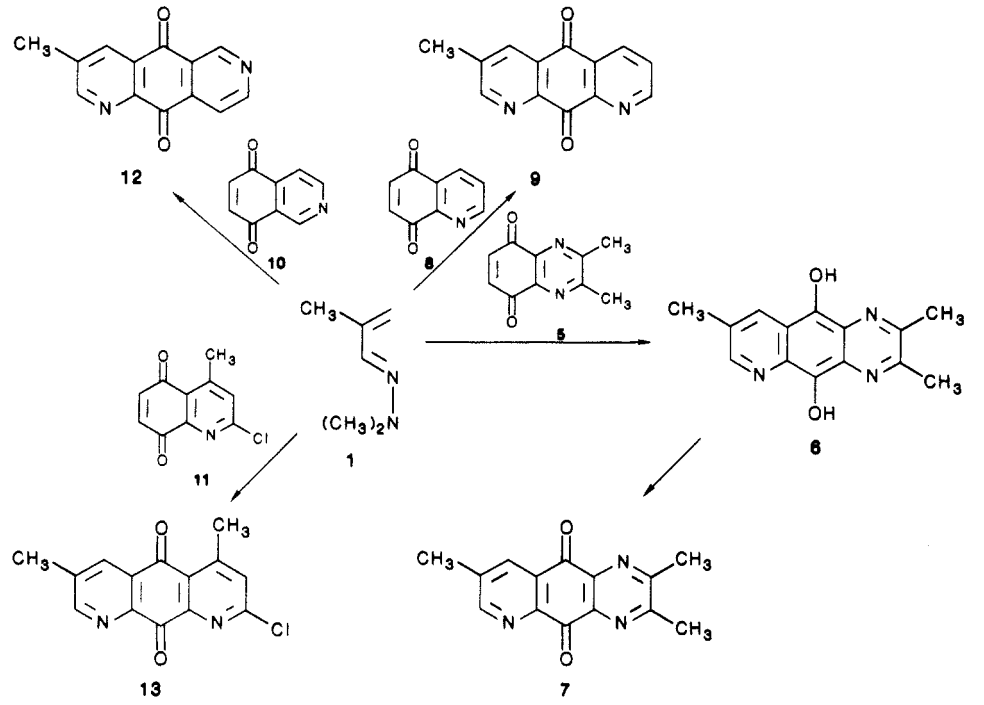
(6) Gorden, J. F. *J. Chem. Soc.* **1957**, 2483; *Tetrahedron Lett.* **1980**, 2629.

Table II. Azaanthraquinones Formed by Cycloaddition of Aza Dienes and 1,4-Naphthoquinones

compd	mp, °C (habit, solvent)	yield, %	mol formula[a]	$M^{+\cdot}$ [b]	^1H NMR (200 MHz, $CDCl_3$): δ (J, Hz) 2	3	4	5	6	7	8	IR (KBr), cm^{-1}
4 (R = OCH_3)	198–200 (yellow microneedles, MeOH)	62	$C_{15}H_{11}NO_3$	253	8.88 ($J_{2,4}$ = 2.12)	2.56 (CH_3)	8.38 ($J_{4,2}$ = 2.12)	4.08 (OCH_3)	7.39 ($J_{6,7}$ = 8.42, $J_{6,8}$ = 0.93)	7.78 ($J_{7,6}$ = 8.42, $J_{7,8}$ = 7.67)	8.08 ($J_{8,7}$ = 7.67, $J_{6,8}$ = 0.93)	1670 (C=O) 1665 (C=O)
4 (R = OH)	261–263 (orange needles, EtOAc/hexanes)	52	$C_{14}H_9NO_3$	239	8.95 ($J_{2,4}$ = 2.22)	2.59 (CH_3)	8.44 ($J_{4,2}$ = 2.22)		7.36 ($J_{6,7}$ = 8.43, $J_{6,8}$ = 1.10)	7.74 ($J_{7,6}$ = 8.43, $J_{7,8}$ = 7.53)	7.96 ($J_{8,7}$ = 7.53, $J_{8,6}$ = 1.10)	3700–3045 (OH) 1675 (C=O) 1630 (C=O)
14 (R = H)	225–226 (orange needles, EtOH)	84	$C_{14}H_9NO_3$	239	8.97 ($J_{2,4}$ = 2.05)	2.57 (CH_3)	8.43 ($J_{4,2}$ = 2.05)	7.87 ($J_{5,6}$ = 7.67, $J_{5,7}$ = 1.46)	7.74 ($J_{6,5}$ = 7.67, $J_{6,7}$ = 7.67)	7.39 ($J_{7,6}$ = 7.67, $J_{7,5}$ = 1.46)		3700–3100 (OH) 1675 (C=O) 1635 (C=O)
14 (R = CH_3)	184–185 (yellow needles, MeOH)	95	$C_{15}H_{11}NO_3$	253	8.29 ($J_{2,4}$ = 2.22)	2.57 (CH_3)	8.34 ($J_{4,2}$ = 2.22)	7.97 ($J_{5,6}$ = 8.01, $J_{5,7}$ = 1.09)	7.76 ($J_{7,6}$ = 8.01, $J_{6,7}$ = 8.01)	7.40 ($J_{7,6}$ = 8.01, $J_{7,5}$ = 1.09)	4.07 (OCH_3)	1655 (br, C=O)
18 (R = H)	216–217 (dark red granules, EtOH/CH_2Cl_2)	67	$C_{14}H_9NO_4$	255	9.00 ($J_{2,4}$ = 2.05)	2.64 (CH_3)	8.50 ($J_{4,2}$ = 2.05)		7.51 (s)	7.51 (s)		3275 (OH) 1625 (C=O)

[a] All compounds reported had acceptable analytical data (±0.4%) for C, H, N. [b] All 100% relative intensity.

Scheme II

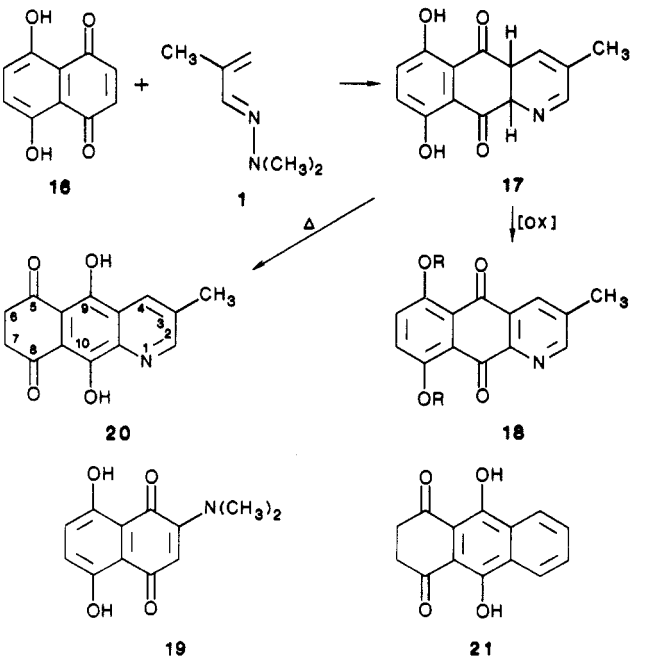


Dimethylamine eliminated in the overall cycloaddition prevented the formation of a bis cycloadduct from the aza diene **1** and benzoquinone. At room temperature and after oxidation of the crude reaction mixture, 6-(dimethylamino)-3-methylquinoline-5,8-dione (**15**) was obtained (44%). Addition of the dimethylamino group at C-6 is in accord with the influence of the ring nitrogen atom making the C-8 carbonyl group more electron deficient than that at the C-5 position. Attempts to remove the dimethylamine from the reation by various means to avoid the conjugate addition were unsuccessful.

An analogous addition of dimethylamine occurred in the cycloaddition of 5,8-dihydroxy-1,4-naphthoquinone (**16**) with the aza diene **1** in benzene at room temperature (Scheme III). The cycloadduct **17** was isolated, derived from the initial 1:1 cycloadduct by loss of dimethylamine, as well as the oxidized compound **18** (R = H) and 2-(dimethylamino)-5,8-dihydroxy-1,4-naphthoquinone (**19**). When argon was bubbled through the reaction mixture at 40–45 °C, the dimethylamine eliminated from the initial 1:1 cycloadduct was removed, eliminating formation of the byproduct, and the 1:1 cycloadduct **17** separated directly from the cooled reaction mixture (84%). Direct isolation of **17** from the reaction mixture as stable, dark blue needles in such a high state of purity is unique in these cycloadditions. On oxidation with Ag_2O (DME) it formed the deep red **18** (R = H), which was also obtained by boiling in ethanol or on heating with potassium carbonate in methanol and H_2O. On heating **17** in vacuo, oxidation was prevented, and the corresponding leuco compound, 9,10-dihydroxy-3-methyl-1-azaanthracene-5,8(6*H*,7*H*)-dione (**20**), resulted.

The potential for various tautomeric structures in the representation of **17** and **20** was of concern, and, for comparison, the spectral data of analogous leuco compounds were examined. The ^1H NMR spectrum of leuco quinizarin (**21**) lacks[7] the singlet aromatic resonance associated with the C-2 and C-3 hydrogens in the aromatic system. Instead, these hydrogens appeared as a sharp singlet at

Scheme III



δ 3.03 (methylene). The infrared spectrum of **21** showed[8] no hydroxyl frequency but a single carbonyl absorption at 1633 cm^{-1}. This suggests that leuco quinizarin exists as the nonaromatic tautomer **21**.

The ^1H NMR spectrum of **20** showed a sharp singlet at δ 3.11 for the C-6 and C-7 hydrogen atoms. The C-2 and C-4 hydrogens of the pyridine ring appeared as doublets in the aromatic region at δ 8.99 and 8.51 indicated by $J_{2,4}$ = 1.98 Hz. This suggests that the nonaromatic structure **20** is the best representation for this compound among the possible tautomers.

In the dihydroxy compound **17**, a strong hydroxy absorption at 3420–3100 cm^{-1} as well as weak carbonyl absorptions at 1680 and 1640 cm^{-1} were observed in its IR

(7) Bloom, S. M.; Hutton, R. F. *Tetrahedron Lett.* **1963**, 1993.

(8) Flett, M. St. C. *J. Chem. Soc.* **1948**, 1441.

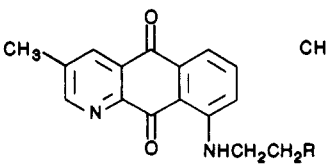
spectrum. Its ^1H NMR spectrum showed the C-6 and C-7 hydrogens as two doublets in the aromatic region at δ 7.09 and 7.25, distinguished by $J_{6,7}$ = 9.42 Hz. The C-2 and C-4 hydrogens appeared as complex multiplets upfield from the aromatic region centered at δ 6.76 and 5.95. The C-3 methyl group appeared at δ 1.70, which is significantly upfield from an aromatic methyl group; there was also a singlet at δ 3.27 corresponding to the ring junction hydrogens. These data suggest the intermediate product 17 is the 1:1 cycloadduct that has undergone 1,4-elimination of dimethylamine. This is the first instance in which the 1:1 cycloadduct of a naphthoquinone with the aza diene has been isolated in this system, which may be hindered by strong hydrogen bonding between the hydroxy groups and the adjacent carbonyl groups. Full spectral data for the products of these reactions can be found in Table II.

Synthesis of Substituted [(Aminoalkyl)amino]-azaanthraquinones. The reactions of 8-hydroxy- and 5,8-dihydroxy-3-methyl-1-azaanthraquinones (14 and 18, R = H) with *N*-alkyldiamines have the potential for introducing basic substituents at the 5,8-positions. 1,4-Bis(alkylamino)anthraquinones have usually been prepared by condensation of the appropriate primary amines with leucoquinizarin and subsequent oxidation[9] or with quinizarin[10] directly. In the latter instance a sufficient amount of carbonyl character must be present at the C-5 and C-8 positions for condensation to occur. This is possible by strong hydrogen-bonding interactions between the hydroxy and adjacent carbonyl groups.

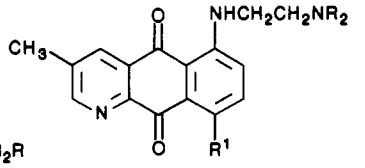
Zielske prepared[11] unsymmetrical 1,4-bis(alkylamino)-anthraquinones using alkylamines and 1,4-ditosylanthraquinone, and intermediate monoaminomonotosylanthraquinones were isolated by carrying out the reaction in refluxing methylene chloride. Unsymmetrical dialkylamines were obtained by subsequent treatment with a second amine in pyridine at 60–110 °C.

The reactions of 8-hydroxy-3-methyl-1-azaanthraquinone (14, R = H) with alkyldiamines of the type $H_2NCH_2CH_2NR_2$ under a variety of reaction conditions resulted in decomposition of the starting quinone. This may be due to the influence of the nitrogen heteroatom on the C-9 carbonyl moiety. The diminished electron density at this carbonyl group would be reflected in a reduction of the hydrogen bonding between this carbonyl group and the C-8 hydroxyl group. Less carbonyl character results at the C-8 position, decreasing its reactivity toward condensation with alkylamines.[12]

Treatment of 14 (R = H) with tosyl chloride and triethylamine in methylene chloride afforded 3-methyl-8-(tosyloxy)-1-azaanthraquinone (14, R = Ts). Reaction of 14 (R = Ts) with *N*-alkyldiamines in pyridine (60–70 °C, 16 h) afforded 8-[(aminoalkyl)amino]-3-methyl-1-azaanthraquinones **22a–c** as deep red crystalline products in good yields. ^1H NMR and mass spectral data confirmed the structural assignments; e.g., (in the ^1H NMR spectrum of **22a** a characteristic quartet splitting pattern of the methylene hydrogens adjacent to the NH group was centered at δ 3.44. These hydrogens are coupled to the β-methylene hydrogens that occur as a triplet at δ 2.69 distinguished by J = 6.32 Hz.



22a: R = $N(CH_3)_2$
b: R = $N(C_2H_5)_2$
c: R = OH



23a: R = CH_3, R^1 = NHOH
b: R = Et, R^1 = NHOH
c: R = Et, R^1 = NH_2

The synthesis of 5,8-bis[(aminoalkyl)amino]-3-methyl-1-azaanthraquinones was also attempted under a variety of reaction conditions. The bis-substituted products were not obtained; instead, monoalkylamino derivatives were isolated corresponding to monosubstitution, or further reaction of the bis(alkylamino) compounds occurred leading to complex mixtures. Introduction of the amino groups is especially sensitive to reaction conditions, and in a recent report,[3] the reaction of 1-azaanthracene-9,10-dione and appropriate diamines in aqueous medium (reflux, 8 h) described the introduction of 5,8-bis(aminoalkyl)amino substituents in yields ranging only from 9 to 16%.

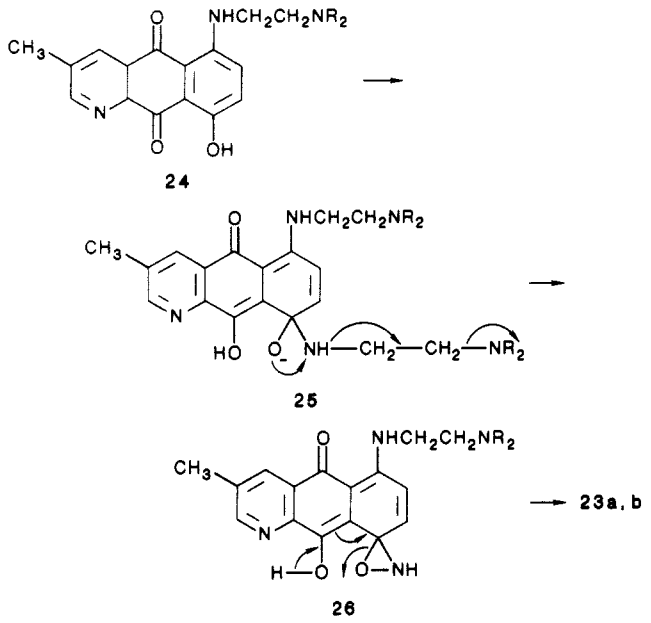
Reaction of 5,8-dihydroxy-3-methyl-1-azaanthraquinone (18, R = H) with an excess of *N,N*-dimethylethylenediamine afforded the substituted hydroxylamine 5-[[2-(dimethylamino)ethyl]amino]-8-(hydroxyamino)-3-methyl-1-azaanthraquinone (**23a**) as deep red needles in 55% yield. This product was separated and purified by extensive HPLC (silica gel, acetone) and was the predominant product of the reaction. Analytical data and high-resolution mass spectrometry[13] ($M^{\bullet+}$ 340.1526, calcd 340.1535) established the molecular formula of **23a** as $C_{18}H_{20}N_4O_3$. The presence of the [(dimethylamino)ethyl]amino side chain at position 5 was shown by the ^1H NMR spectrum (200 MHz), which showed the characeristic splitting pattern for this substituent with a quartet for the methylene hydrogens adjacent to the NH group, a triplet for the methylene hydrogens β to the NH group, and the NH proton as a broad singlet at δ 10.09. The retention of a 5,8-substitution pattern in this product was also evident from the chemical shifts of H_6 and H_7 which were at δ 7.72 and 6.98, respectively. This leaves only NH_2O to be accomodated in a structural assignment, as either ONH_2 or NHOH. The absence of two protons in **23a** assignable to an NH_2 group indicates that the remaining atoms are present as a hydroxylamine substituent. Initial displacement of the 5-hydroxy substituent is consistent with the influence of the 1-nitrogen atom on the carbonyl group at the 10-position, which is also exhibited in the reactions of other members of this series.

Reaction of 18 (R = H) with (*N,N*-diethylamino)-ethylamine resulted in **23b** obtained in 42% yield. Characterization data in agreement with this structure are consistent with that for **23a** above.

Introduction of a hydroxylamino substituent into the 8-position was also observed with other members of the 1-azaanthraquinones. Thus, reaction of the 1:1 cycloadduct 17 with (*N,N*-diethylamino)ethylamine under similar conditions to those above gave **23b**, although only in 7% yield. The leuco compound **20**, however, with an excess of (*N,N*-diethylamino)ethylamine in pyridine (60 °C, 16 h) gave **23b**, which separated directly from the reaction mixture in a relatively pure state in 59% yield.

(9) Zee-Cheng, R. K.; Cheng, C. C. *J. Med. Chem.* **1978**, *21*, 291. Greenhalgh, C. W.; Hughes, N. *J. Chem. Soc. C* **1968**, 1284.
(10) Zee-Cheng, R. K.; Prodrebarac, E. G.; Menon, C. S.; Cheng, C. C. *J. Med. Chem.* **1979**, *22*, 501.
(11) Zielske, A. G. *Abstracts of Papers*; 188th National Meeting of the American Chemical Society, Philadelphia, PA, Aug 1984; American Chemical Society: Washington, DC, 1984. We thank Dr. Zielske for this information prior to publication. Zielski, A. G. *J. Org. Chem.* **1987**, *52*, 1305.
(12) For example, see: Greenhalgh, C. W.; Hughes, N. *J. Chem. Soc. C* **1968**, 1284.
(13) Field dissorption and high-resolution mass spectral data were obtained by Steve Dorn, General Electric CRD, Schenectady, NY, whom we thank.

Scheme IV



Conversion of 18 (R = H) into its ditosylate 18 (R = tosyl), followed by reaction with (*N,N*-diethylamino)-ethylamine (pyridine, 70 °C, 16 h), resulted in two products. The 8-hydroxyamino derivative **23b** was obtained in 31% yield; this was accompanied by the 8-amino derivative **23c**, which was isolated in 21% yield by flash chromatography (silica gel, 20% $CHCl_3$ in acetone) as blue needles. Spectral data consistent with this structural assignment are described in the Experimental Section. We believe this amino compound **23c** is derived from **23b** by a reductive process under these reaction conditions.

Formation of the hydroxylamines **23a** and **b** can be readily rationalized in terms of the different reactivity of the 5- and 8-hydroxyl groups, resulting from the presence of a 1-nitrogen atom that influences the 9- and 10-carbonyl groups. Initial substitution occurs at C-5 to give the monosubstituted product **24**. Attack of the primary amino group on the C-8 position results in **25**, which form the oxaziridine **26** with loss of ethylene and dimethylamine. Tautomerization of **26** then results in opening of the oxaziridine ring to form **23a,b** (Scheme IV).

In support of this mechanism, it was found that the reaction of **18** (R = H) with (*N,N*-diethylamino)ethylamine under less vigorous conditions (pyridine, 55 °C, 1 h) resulted in monosubstitution only, **24** (R = Et) being isolated in 54% yield. A similar monosubstitution product was obtained with (*N,N*-dimethylamino)ethylamine and the 1:1 cycloadduct **17** (neat, 55 °C, 2 H) followed by aerial oxidation. This product was isolated in 6% yield and is represented by **24** (R = CH_3); a large amount of a bright blue product that could not be identified was also obtained.

Experimental Section[13]

The general procedures below illustrate those used for the cycloaddition of 1-(dimethylamino)-3-methyl-1-azabuta-1,3-diene (**1**).

Cycloaddition with 2,3-Dimethylquinoxaline-5,8-dione (5). (A) Formation of 2,3,7-Trimethyl-9,10-dihydroxy-1,4,5-triazaanthracene (6). Quinone **5** (0.90 g, 0.005 mol) and Diene **1** (1.0 g, 0.009 mol) in anhydrous benzene (50 mL) were heated under reflux for 24 h. A deep red precipitate slowly separated. After cooling, the benzene was evaporated and the residue recrystallized from CH_3CN, affording **6** as deep red needles: 0.97 g (79%); mp 210–212 °C dec (Table I).

(B) Oxidation of 6 to 2,3,7-Trimethyl-1,4,5-triazaanthracene-9,10-dione (7). Cycloadduct **6** (0.50 g, 0.002 mol) in 95% ethanol (50 mL) was heated on a steam bath for 2 h, during which time slow air oxidation of **6** occurred. Evaporation of the ethanol and recrystallization of the residue from ethanol gave **7** as greenish yellow needles: 0.46 g (93%); mp 238–240 °C (Table I).

Isolation of the 1:1 cycloadduct quinol tautomer **6** is not necessary. The residue from the benzene reaction can be oxidized directly by heating in ethanol for 2 h without diminution in yield. This direct procedure is most convenient for the preparation of the appropriate compounds in Table I.

Preparation of 5,8-Dihydroxy-3-methyl-1-azaanthracene-9,10(4a*H*,9a*H*)-dione (17). 5,8-Dihydroxynaphthoquinone (**16**; 3.0 g, 0.016 mol) in anhydrous benzene (150 mL) was treated with the diene **1** (2.13 g, 0.02 mol) under an atmosphere of argon, the gas being bubbled rapidly through the reaction mixture. After 4 h at 40–50 °C, the reaction mixture was cooled and the separated product was collected and washed with hexane until the washings were colorless: 3.4 g (84%) of dark blue needles of **17**, crystallized from $EtOAc/CH_2Cl_2$; mp 166–167 °C, subliming to a red needle melting at 206–207 °C; IR (KBr) ν_{OH} 3420–3100 (s, br) ν_{CO} 1680 (w) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, 1, $J_{6,7}$ = 9.42 Hz, H_6 or H_7), 7.09 (d, 1, $J_{6,7}$ = 9.42 Hz, H_6 or H_7), 6.78 (br s, 1, H_2), 5.95 (br s, 1, H_4), 3.26 (s, 2, H_{4a} and H_{9a}), 1.70 (s, 1, CH_3); MS, m/z ($M^{\cdot+}$) 257 (100). Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.44. Found: C, 65.19; H, 4.36; N, 5.39.

Conversion of 17 into the Quinone 18 (R = H). Method A. Oxidation with Ag_2O. Cycloadduct **17** (3.0 g, 0.002 mol) in DME (200 mL) and Ag_2O[14] (5.4 g, 0.004 mol) were stirred together at room temperature in the dark for 4 h. The reaction mixture was filtered through a sintered glass funnel, the residue was repeatedly washed with hot $CHCl_3$, and the combined organic fractions were evaporated. The residue crystallized from $EtOAc/CH_2Cl_2$ as dark red granules: 2.1 g (72%); mp 216–217 °C (Table I).

Method B. Cycloadduct **17** (3.0 g, 0.002 mol) and potassium hydrogen carbonate (2.0 g, 0.020 mol) in methanol (20 mL) and H_2O (20 mL) were refluxed for 1 h. The solution was cooled and extracted with $CHCl_3$ (3 × 100 mL). The combined organic fractions were dried (anhydrous Na_2SO_4) and evaporated. Recrystallization from $EtOAc/CH_2Cl_2$ gave quinone **18**, 2.7 g (92%).

Conversion of 17 into Leuco Compound 20. Cycloadduct **17** (3.0 g, 0.012 mol) was heated to 100–120 °C in vacuo (10^{-2} mmHg). The compound slowly sublimed, affording leuco compound **20** as dark red granules: 2.6 g (87%); mp 209–211 °C; IR (KBr) ν_{OH} 3600–3100, ν_{CO} 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.99 (d, 1, $J_{2,4}$ = 1.98 Hz, H_2), 8.52 (d, 1, $J_{4,2}$ = 1.98 Hz, H_4), 3.11 (s, 4, 2 × H_6 and 2 × H_7), 2.62 (s, 3, CH_3); MS, m/z ($M^{\cdot+}$) 257 (9).

3-Methyl-8-(tosyloxy)-1-azaanthracene-9,10-dione (14, R = Ts). 8-Hydroxy-3-methyl-1-azaanthracene-9,10-dione (**14**, R = H) (1.5 g, 0.006 mol) was dissolved in dry CH_2Cl_2 (300 mL) containing triethylamine (1 g, 0.025 mol). The solution was stirred at room temperature, and purified tosyl chloride (2.4 g, 0.012 mol) was added. After 24 h, the organic solution was washed with water (3 × 100 mL), dried (anhydrous Na_2SO_4), and evaporated. The residue was stirred in CCl_4 (100 mL) for 2–3 h, and the solid that separated was filtered. Recrystallization from $CHCl_3$/petroleum ether gave the tosylate as pale yellow, irregular prisms: 1.7 g (69%); mp 226–228 °C; IR (KBr) $\nu_{C=O}$ 1690, 1680, ν_{SO_2} 1185 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.92 (d, 1, $J_{2,4}$ = 2.82 Hz, H_2), 8.35 (d, 1, $J_{4,2}$ = 2.82 Hz, H_4), 8.34 (dd, 1, $J_{5,6}$ = 6.70 Hz, $J_{5,7}$ = 1.40 Hz, H_5), 8.06 (d, 2, J = 8.36 Hz, $SO_2C{=}CH$), 7.86 (m, 2, H_6 and

(14) Spectral characterizations were carried out on the following instruments: infrared spectra, Perkin-Elmer Model 298 or 337 grating infrared spectrophotometer; ^1H NMR spectra, Varian XL-200 or Hitachi Perkin-Elmer R-600 Fourier transform spectrometer with Me_4Si as an internal standard; mass spectra, Hewlett-Packard GC–MS system Model 5987A spectrometer. All melting points were determined in capillaries on a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus and are unconnected. Evaporations were carried out under reduced pressure by using a Buchi Rotovap apparatus. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN, or Atlantic Microlab, Inc., Atlanta, GA. Anhydrous benzene, xylene, *n*-hexane, and diethyl ether were stored over metallic sodium and decanted in an inert atmosphere before use. Chromatographic separations were performed with silica gel in gravity or flash columns or a Waters Prep 500A HPLC system.

(15) Fisher-purified Ag_2O was found to be the most satisfactory.

H_7), 7.37 (d, 2, J = 8.36 Hz, $CH_3C{=}CH$), 2.56 (s, 3, $ArCH_3$), 2.43 (s, 3, p-CH_3); MS, m/z ($M^{\cdot+}$) 393 (9). Anal. Calcd for $C_{21}H_{15}NO_5S \cdot {}^1/_4H_2O$: C, 63.38; H, 3.86; N, 3.52. Found: C, 63.29; H, 3.96; N, 3.52.

3-Methyl-5,8-bis(tosyloxy)-1-azaanthracene-9,10-dione (18, R = Ts). By the same procedure as above, **18** (R = H) and 4 equiv of tosyl chloride resulted in isolation of the ditosylate **18** (R = Ts) as light tan irregular prisms from $CHCl_3$/petroleum ether: mp 212–215 °C (50%); IR (KBr) $\nu_{C=O}$ 1685, ν_{SO_2} 1180 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.87 (d, 1, $J_{2,4}$ = 2.22 Hz, H_2), 8.22 (d, 1, $J_{4,2}$ = 2.22 Hz, H_2), 8.01 (d, 1, $J_{6,7}$ = 8.36 Hz, H_6 or H_7), 7.87 (d, 1, $J_{6,7}$ = 8.36 Hz, H_6 or H_7), 7.82 (d, 2, J = 8.90 Hz, aromatic), 7.47 (d, 2, J = 8.90 Hz, aromatic), 7.37 (d, 4, J = 8.90 Hz, aromatic), 2.54 (s, 3, CH_3), 2.45 (s, 3, p-CH_3), 2.42 (s, 3, p-CH_3); MS, m/z ($M^{\cdot+}$) 563 (2).

Synthesis of 8-[(Aminoalkyl)amino]azaanthraquinones. A. 8-[[2-(Dimethylamino)ethyl]amino]-3-methyl-1-azaanthracene-9,10-dione (22a). 3-Methyl-8-(tosyloxy)-1-azaanthracene-9,10-dione (**14**, R = Ts; 0.50 g, 0.0013 mol) and *N,N*-dimethylethylenediamine (2 g, 0.023 mol) were heated in pyridine (15 mL) at 70 °C for 16 h. The solution slowly became dark red in color over a 2-h period. Excess pyridine and amine were removed under reduced pressure. The residue was subjected to column chromatography (silica gel), eluting with acetone and isolating a bright red fraction. Crystallization from ether gave the alkylamino compound as bright red needles: 0.32 g (81%); mp 155–156 °C; IR (KBr) $\nu_{C=O}$ 1650, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.89 (d, 1, $J_{2,4}$ = 2.22 Hz, H_2), 8.34 (d, 1, $J_{4,2}$ = 2.22 Hz, H_4), 7.62–7.57 (m, 2, H_5 and H_7), 7.11 (dd, 1, $J_{5,6}$ = 6.16 Hz, $J_{6,7}$ = 3.89 Hz, H_6), 3.44 (q, 2, J = 6.32 Hz, $NHCH_2$), 2.69 (t, 2, J = 6.32 Hz, CH_2CH_2), 2.53 (s, 3, $ArCH_3$), 2.35 [s, 6, $N(CH_3)_2$]; MS, m/z ($M^{\cdot+}$) 309 (11). Compounds **22b** and **22c** were also obtained by this procedure. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.83; H, 6.21; N, 13.56.

B. 8-[[2-(Diethylamino)ethyl]amino]-3-methyl-1-azaanthracene-9,10-dione (22b): bright red needles from ether; mp 127–128 °C (84%); IR (KBr) $\nu_{C=O}$ 1660, 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.89 (d, 1, $J_{2,4}$ = 1.83 Hz, H_2), 8.32 (d, 1, $J_{4,2}$ = 1.83 Hz, H_4), 7.14–7.09 (m, 2, H_5 and H_7), 7.11 (dd, 1, $J_{6,5}$ = 5.98 Hz, $J_{6,7}$ = 3.87 Hz, H_6), 3.42 (q, 2, J = 6.36 Hz, $NHCH_2$), 2.82 (t, 2, J = 6.36 Hz, CH_2CH_2), 2.64 (q, 4, J = 7.13 Hz, CH_2CH_3), 2.53 (s, 3, CH_3), 1.11 (t, 6, J = 7.13 Hz, CH_2CH_3); MS (CI), m/z [M + 1] 338 (3). Anal. Calcd for $C_{20}H_{23}N_3O_2 \cdot {}^3/_4H_2O$: C, 68.45; H, 7.04; N, 11.97. Found: C, 68.30; H, 7.01; N, 11.96.

C. 8-[(2-Hydroxyethyl)amino]-3-methyl-1-azaanthracene-9,10-dione (22c): dark red granules from CH_2Cl_2/EtOH; mp 250–252 °C (79%); IR (KBr) ν_{OH} 3550–3400, ν_{CO} 1665, 1635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.89 (d, 1, $J_{2,4}$ = 2.26 Hz, H_2), 8.34 (d, 1, $J_{4,2}$ = 2.26 Hz, H_4), 7.63–7.57 (m, 2, H_5 and H_7), 7.19 (dd, 1, $J_{6,5}$ = 7.41 Hz, $J_{6,7}$ = 2.85 Hz, H_6), 6.48 (s, 1, NH), 4.01–3.96 (m, 2, CH_2OH), 3.60 (q, 2, $HNCH_2$, J = 5.68 Hz), 2.54 (s, 3, CH_3); MS, m/z ($M^{\cdot+}$) 282 (33). Anal. Calcd for $C_{16}H_{14}N_2O_3 \cdot {}^1/_4H_2O$: C, 67.00; H, 5.10; N, 9.77. Found: C, 66.85; H, 5.16; N, 9.56.

5-[[2-(Dimethylamino)ethyl]amino]-8-(hydroxyamino)-3-methyl-1-azaanthracene-9,10-dione (23a). 5,8-Dihydroxy-3-methyl-1-azaanthracene-9,10-dione (**18**, R = H; 0.020 g, 0.005 mol) and *N,N*-dimethylethylenediamine (0.42 g, 0.003 mol) in pyridine (25 mL) were refluxed for 16 h. The reaction mixture immediately became dark blue upon addition of the amine and changed to dark red after 1 h. The mixture was poured into H_2O (150 mL) and extracted with $CHCl_3$ (4 × 100 mL). The organic fractions were combined, washed with H_2O, dried (anhydrous Na_2SO_4), and evaporated, affording an oily red residue. Column chromatography (TLC-grade silica gel) eluting with acetone isolated the hydroxylamine as bright red needles: 0.18 g (55%); mp 214–216 °C ($EtOAc/CH_2Cl_2$); IR (KBr) ν_{CO} 1630, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.15–10.03 (br s, HN), 8.69 (d, 1, $J_{2,4}$ = 1.84 Hz, H_2), 8.46 (d, 1, $J_{4,2}$ = 1.84 Hz, H_4), 7.72 (br s, 1, H_7), 6.98 (br s, 1, H_6), 5.79 (s, 1, $HNOH$), 3.28 (q, 2, J = 6.12 Hz, $NHCH_2$), 2.65 (t, 2, J = 6.12 Hz, CH_2CH_2), 2.56 (s, 3, CH_3), 2.32 [s, 6, $N(CH_3)_2$]; MS (FD), m/z [M + 1] 341 (100); high-resolution mass spectrum, exact mass calcd for $C_{18}H_{22}N_4O_3$ m/z 340.1535, found 340.1526. Anal. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.23; H, 5.97; N, 16.43.

5-[[2-(Diethylamino)ethyl]amino]-8-(hydroxyamino)-3-methyl-1-azaanthracene-9,10-dione (23b). Method A. 23b was prepared in the same manner as **23a** from *N,N*-diethylethylenediamine, affording the compound as dark red needles from EtOAc: mp 210–212 °C (42%); IR (KBr) ν_{CO} 1635, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.08–9.99 (br, s, 1 HN), 8.69 (d, 1, $J_{2,4}$ = 1.59 Hz, H_2), 8.47 (d, 1, $J_{4,2}$ = 1.59 Hz, H_4), 7.74 (br s, 1, H_6 or H_7), 7.07 (br, s, 1, H_6 or H_7), 5.79 (s, 1, $HNOH$), 3.22 (q, 2, J = 6.23 Hz, $NHCH_2$), 2.77 (t, 2, J = 6.23 Hz, CH_2CH_2), 2.61 (q, 2, J = 7.18 Hz, CH_2CH_3), 2.56 (s, 3, CH_3), 1.07 (t, 3, J = 7.18 Hz, CH_2CH_3); MS (FD), m/z [M + 1] 369 (100). Anal. Calcd for $C_{20}H_{24}N_4O_3 \cdot {}^3/_4H_2O$: C, 62.89; H, 6.73; N, 14.67. Found: C, 62.53; H, 6.30; N, 14.57.

Method B. A solution of the leuco compound, 9,10-dihydroxy-1-azaanthracene-5,8(6*H*,7*H*)-dione (**20**; 1.5 g, 0.006 mol) and *N,N*-diethylethylenediamine (3.0 g, 0.15 mol) in pyridine (25 mL) was heated to 60 °C for 16 h. Pyridine and excess amine were removed under reduced pressure. A small amount of ether was added to the residue, the suspension cooled, and the separated product filtered. Recrystallization from EtOAc afforded hydroxylamine identical with that obtained by the previous method; 1.3 g (59%).

Method C. 5,8-Dihydroxy-3-methyl-1-azaanthracene-9,10-(4a*H*,9a*H*)-dione (**17**; 2.0 g, 0.008 mol) and *N,N*-diethylenediamine (10.0 g, 0.105 mol) in pyridine (50 mL) were heated to 70 °C for 16 h. Pyridine and excess amine were removed under reduced pressure, and TLC showed multiple product formation. Column chromatography eluting with acetone afforded the hydroxylamine as the only isolable product; 0.2 g (7%).

5-[[2-(Diethylamino)ethyl]amino]-8-(hydroxyamino)-3-methyl-1-azaanthracene-9,10-dione (23b) and 8-Amino-5-[[2-(diethylamino)ethyl]amino]-3-methyl-1-azaanthracene-9,10-dione (23c). A solution of 5,8-bis(tosyloxy)-3-methyl-1-azaanthracene-9,10-dione (**18**, R = Ts; 3.0 g, 0.005 mol) and *N,N*-diethylethylenediamine (10.0 g, 0.086 mol) in pyridine (50 mL) was heated to 70 °C for 16 h. Pyridine and excess amine were removed under reduced pressure, and the resulting dark purple residue was dissolved in $CHCl_3$ (150 mL). The $CHCl_3$ solution was washed with H_2O (2 × 50 mL), dried (anhydrous Na_2SO_4), and evaporated. Flash column chromatography (silica gel) of the residue eluting with 20% $CHCl_3$ in acetone isolated the 8-hydroxylamine as bright red needles identical with that obtained previously [0.6 g (31%)] and the 8-amino compound as blue needles with a reddish reflection (0.4 g (21%)]: mp 149–150 °C (EtOAc); IR (KBr) ν_{NH} 3380–3200, $\nu_{C=O}$ 1640, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.72 (d, 1, $J_{2,4}$ = 1.90 Hz, H_2), 8.59 (d, 1, $J_{4,2}$ = 1.90 Hz, H_4), 8.26–8.10 (br, s, 2, NH_2), 7.37 (d, 1, $J_{6,7}$ = 10.08 Hz, H_6 or H_7), 7.19 (d, 1, $J_{6,7}$ = 10.08 Hz, H_6 or H_7), 3.63 (q, 2, J = 6.49 Hz, $HNCH_2$), 2.82 (t, 2, J = 6.49 Hz, NCH_2CH_2), 2.65 (q, 4, J = 7.13 Hz, CH_2CH_3), 2.56 (s, 3, $ArCH_3$), 1.09 (t, 6, J = 7.13 Hz, CH_2CH_3); MS (FD), m/z [M + 1] 353 (100). Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.13; H, 6.88; N, 15.86.

5-[[2-(Diethylamino)ethyl]amino]-3-methyl-8-hydroxy-1-azaanthracene-9,10-dione (23, R = CH_2CH_3, R^1 = OH). A solution of 5,8-dihydroxy-3-methyl-1-azaanthracene-9,10-dione (**18**; R = H; 2.0 g, 0.008 mol) and *N,N*-diethylethylenediamine (10.0 g, 0.086 mol) was heated in pyridine (30 mL) at 55 °C for 1 h. Pyridine and excess amine were removed under reduced pressure. Flash column chromatography (silica gel) of the residue eluting with methanol afforded the monosubstituted compound as blue needles with a reddish reflection: 1.8 g (64%); mp 151–152 °C (EtOAc); IR (KBr) ν_{OH} 3650–3050, ν_{CO} 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.90 (d, 1, $J_{2,4}$ = 1.90 Hz, H_2), 8.34 (d, 1, $J_{4,2}$ = 1.90 Hz, H_4), 7.30 (s, 2, H_6 and H_7), 3.44 (q, 2, J = 6.86 Hz, $HNCH_2$), 2.85 (t, 2, J = 6.86 Hz, CH_2CH_2), 2.65 (q, 4, J = 7.38 Hz, CH_2CH_3), 2.55 (t, 6, J = 7.38 Hz, CH_2CH_3), 2.53 (s, 3, CH_3); MS (CI), m/z [M + 1] 345 (54), [M + 2] 355 (100). Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 68.06; H, 6.57; N, 11.87.

5-[[2-(Dimethylamino)ethyl]amino]-3-methyl-8-hydroxy-1-azaanthracene-9,10-dione (23, R = CH_3, R^1 = OH). 5,8-Dihydroxy-3-methyl-1-azaanthracene-9,10(4a*H*,9a*H*)-dione (**17**); 3.0 g, 0.0116 mol) and *N,N*-dimethylethylenediamine (11.0 g, 0.116 mol) were stirred in an argon atmosphere at 55 °C for 2 h. The reaction mixture was transferred to a three-neck 250-mL flask fitted with a gas inlet system, and ethanol (200 mL) was added. Dry air was bubbled through the solution, and the temperature

was maintained at 60–65 °C for 4 h. Ethanol was removed under reduced pressure to yield an oil blue residue. Ether (200 mL) was added; the mixture was stirred at room temperature for 1 h and filtered. This afforded 2.9 g of a bright blue precipitate that could not be characterized. From the ether filtrate a precipitate formed after 1 h and was filtered. Crystallization from hexanes/ethanol gave the monosubstituted compound as purple fluffy needles: 0.2 g (6%); mp 191–192 °C; IR (KBr) ν_{OH} 3420, ν_{CO} 1615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.92 (d, 1, $J_{2,4}$ = 2.33 Hz, H_2), 8.43 (d, 1, $J_{4,2}$ = 2.33 Hz, H_4), 7.29 (s, 2, H_6 and H_7), 3.53 (q, 2, J = 6.26 Hz, NCH_2), 2.68 (t, 2, J = 6.26 Hz, CH_2CH_3), 2.56 (s, 3, CH_3), 2.35 [s, 6, $N(CH_3)_2$]; MS (CI), m/z [M + 1] 326 (100). Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.44; H, 5.89; N, 12.92. Found: C, 66.38; H, 5.90; N, 12.90.

Notes

Nonacidic Nitration of Secondary Amines

Jeffrey C. Bottaro,* Robert J. Schmitt, and Clifford D. Bedford*†

Energetic Materials Program, Chemistry Laboratory, Physical Sciences Division, SRI International, Menlo Park, California 94025

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The N-nitration of secondary amines under neutral conditions poses a unique problem of N-nitrosation as a competing side reaction. When nitrogen dioxide,[1] nitryl chloride,[2] nitrogen pentoxide, nitryl fluoride, nitronium fluoroborate,[3] and tetranitromethane[4] are used in the N-nitration of amines, they all result in substantial yields (≥30%) of nitrosamine side products, which are extremely toxic and difficult to separate from the target nitramines. Nitramines are potentially useful as explosives, biocides, and pharmaceuticals, necessitating a high-yielding synthesis devoid of carcinogenic nitrosamine byproducts.

To overcome the problems associated with N-nitrosation, we studied a series of novel covalent nitrating agents and examined the effect of amine blocking groups on the outcome of the nitration reaction. The use of amine protecting groups on the nitro/nitrosamine product distribution proved futile. When the *N*-trimethylsilyl, *N*-trimethoxysilyl, *N*-trichlorosilyl, and *N*-difluoroboryl derivatives of piperidine (our model amine substrate) were treated with the conventional nitrating agents mentioned above, they all produced products contaminated with nitrosamine byproducts. Nitrations with nitryl fluoride were complicated by unavoidable contamination of NO_2F with NO_2, which occurred as a result of contact of NO_2F with glass, air, and organic solvents. This approach was abandoned in favor of developing novel nonacidic nitrating agents.

The production of nitrosamines is a result of the redox reaction between secondary amines and nitrating agent. We sought to attenuate the oxidizing power of the nitrating agent by varying the electronegativity of the leaving group. For example, when nitryl fluoride was reacted with secondary amines, it gave unacceptable yields of nitrosamines (≃50%). In our hands similar results were obtained with tetranitromethane, *N*-nitrocollidinium fluoroborate,[10] and nitryl chloride. In response to this problem, we chose to examine nitrating agents with leaving groups that were less electronegative than fluorine. Since ordinary nitrate esters failed to nitrate secondary amines at all, we concluded that the viable range of electronegativities for the nitro transfer reaction lay somewhere between alkoxide (the leaving group on a nitrate ester) and fluoride (the leaving group on nitryl fluoride). Thus, we examined a series of electron-deficient nitrate esters as our target category of neutral nitrating agents for secondary amines.

Scheme I. Amine-Induced Elimination of Nitrous Acid

$$CX_3CH_2ONO_2 + HNR_2 \rightarrow \begin{cases} CX_3CHO \xrightarrow{R_2NH} CX_3CH(OH)NR_2 \\ + \\ R_2NH_2^+NO_2^- \xrightarrow[\Delta]{} R_2NNO + H_2O \end{cases}$$

This approach was attempted by Emmonds and Freeman,[5] who studied some electron-deficient nitrate esters and found that acetone cyanohydrin nitrate[6,7] does indeed produce the nitration of amines at elevated temperatures. Unfortunately, this reagent releases acetone and hydrogen cyanide, which react with amines to give amino nitriles, rendering this method low yielding with respect to the amine substrate. The use of trichloroethyl nitrate[6] also did not solve this problem; the nitrate ester suffered an elimination of nitrous acid to give a mixture of dialkylammonium nitrite and trichloroacetaldehyde, which itself reacted with 1 equiv of the amine to form the hemiaminal side product (Scheme I).

We sought to design nitrating agents that could achieve the desired acyl transfer (here, acyl = nitro) without any undesirable side reactions. Our initial efforts focused on the use of polyfluoroalkyl nitrates. Hexafluoroisopropyl nitrate and trifluoroethyl nitrate were synthesized by direct nitration of the corresponding alcohols in fuming nitric/sulfuric acid. Treating these materials with piperidine, our preliminary test amine, yielded predominantly elimination products as depicted in Scheme I. In the case of trifluoroethyl nitrate, a small amount of nitramine was formed in competition with the elimination products. Only elimination products were detected in the case of hexa-

†Present address: Naval Surface Weapons Center, Code R-11, White Oak Laboratory, Silver Spring, MD 20910.

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