CHCl$_3$ (900 ml). The CHCl$_3$ was concentrated to a homogeneous syrup, 1.2 g (78%). An analytical sample was prepared by preparative layer chromatography on silica gel (Merck 60F-254) using EtOAc–Et$_2$O–hexane (1:1:1, three times). The plate was extracted with EtOAc and 19 was crystallized from EtOAc–Et$_2$O: mp 88–89°; uv λ_{max} 230 nm (ϵ 14,000); ir (CHCl$_3$) 1776, 1751, 1680 cm^{-1}; NMR (CDCl$_3$) δ 1.83 (3 H, s), 2.92 (2 H, m, J = 2.5, 7.5), 4.38 (2 H, t, J = 7.5), 6.37 (1 H, d, J = 5.5), 7.3 (2 H, m); mass spectrum (low resolution) m/e 210 (weak, M$^+$), 97 (strong, methylbutenolide fragment, C$_5$H$_5$O$_2$). See Table I for additional data.

Bis(α-methylene-γ-butyrolactones) (21a–d). Activated zinc,[27] 2.75 g (20 mesh, Mallinckrodt AR), was placed in a dry round-bottomed flask equipped with a magnetic stirrer, N$_2$ inlet, and addition funnel. A septum was attached to the addition funnel and in sequence (through septum via syringe) a solution of 0.02 mol of dialdehyde (20a–d)[13] in 25 ml of dry (distilled from LiAlH$_4$) THF followed by 0.042 mol of bromomethylacrylic ester was added. About 1 ml of the mixture was then added into the flask and the flask was warmed with a small flame. On initiation of the reaction, stirring was initiated and the solution was added at a rate which maintained the temperature of the reaction mixture at 40–45°. The mixture was stirred for an additional 2 hr in a water bath (40–43°), then poured into ice-cold dilute H$_2$SO$_4$, and extracted with EtOAc. The EtOAc was washed with a cold, dilute solution of NaHCO$_3$ and water, dried (Na$_2$SO$_4$), and evaporated to a syrup. Chromatography on a column of Florisil using hexane–ether (8:2) mixtures followed by preparative layer chromatography on silica gel plates (Merck 60, F254) using hexane–ether–EtOAc (1:1:1) gave the pure dilactones 21a–d. Data on the individual compounds are given in Tables I and III.

References and Notes

(1) (a) Paper 4. Paper 1 is ref 18, paper 2 is ref 13, and paper 3 is submitted to *J. Pharm. Sci.* (b) Abstracted in part from the Ph.D. dissertation of Gary A. Howie.
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Potential Central Nervous System Antitumor Agents. Aziridinylbenzoquinones. 1
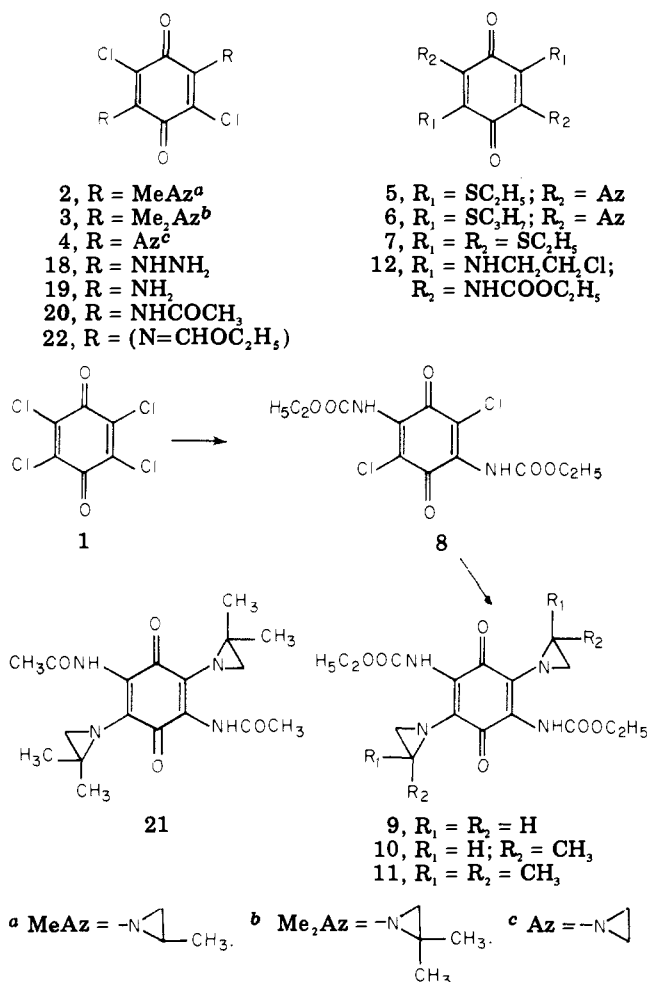
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A series of 3,6-substituted 2,5-diaziridinyl-1,4-benzoquinones was prepared as potential CNS antitumor agents. Activity was evaluated in the murine leukemia L1210 system. The diurethane derivative 9 was found to have significant activity in that system as well as in the intraperitoneal P388 and B16 tumor models. Marginal Lewis lung activity was observed. Reproducible activity was seen in the intracerebral L1210 and P388 systems. Multiple cures were observed in the murine ependymoblastoma brain tumor model. The effect of substituent type on aziridinylquinone activity is discussed.
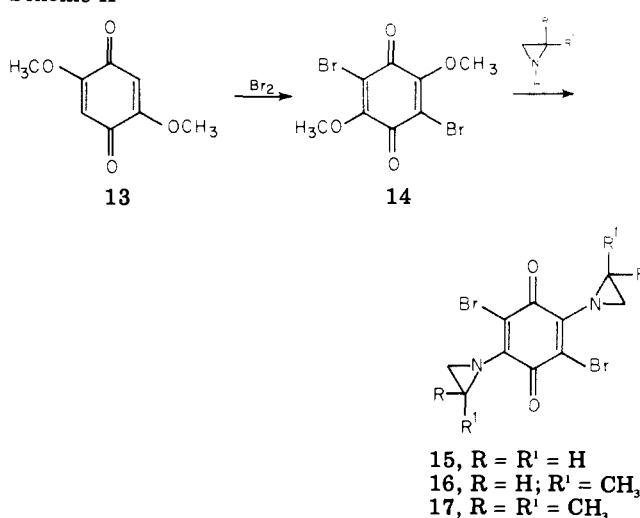
A recent analysis of murine antitumor test data obtained by the National Cancer Institute on quinone derivatives indicated that the aziridinylquinones, as a family, possessed significant activity against lymphoid leukemia L1210 as well as other test systems.[1] While the L1210 results were all obtained on an intraperitoneally implanted tumor, the molecular properties of the compounds appeared to fit some of the requirements suggested by Rall and Zubrod[2] as important for CNS penetration. Subsequent testing of these compounds at the NCI in several intracerebral (ic) tumor systems indicated that the aziridinylquinones possessed substantial ic antitumor activity.[3]

Scheme I

2, R = MeAz[a]
3, R = Me₂Az[b]
4, R = Az[c]
18, R = NHNH₂
19, R = NH₂
20, R = NHCOCH₃
22, R = (N=CHOC₂H₅)

5, R₁ = SC₂H₅; R₂ = Az
6, R₁ = SC₃H₇; R₂ = Az
7, R₁ = R₂ = SC₂H₅
12, R₁ = NHCH₂CH₂Cl;
R₂ = NHCOOC₂H₅

1 → 8

21

9, R₁ = R₂ = H
10, R₁ = H; R₂ = CH₃
11, R₁ = R₂ = CH₃

[a] MeAz = -N⟨ ⟩-CH₃.   [b] Me₂Az = -N⟨ ⟩-CH₃-CH₃.   [c] Az = -N⟨ ⟩

Scheme II

13   →Br₂→   14

15, R = R' = H
16, R = H; R' = CH₃
17, R = R' = CH₃

However, a major problem associated with almost all of the antitumor active aziridinylquinones is the very low aqueous solubility of the compounds. This has greatly complicated the preparation of a suitable parenteral dosage form. This work describes the first of several approaches directed toward the preparation of aziridinylquinones with optimized properties as CNS antitumor agents. Emphasis was placed on the study of the effect of nonionic functional groups, since ionic materials have difficulty penetrating the blood–brain barrier.[2]

The antitumor properties of aziridinylquinones, especially against the Ehrlich and Yoshida ascites tumor systems, have been recognized for over 20 years.[4-8] More recently, activity in the L1210 system has been studied, especially for carbazilquinone and its analogs.[1,9-11]

Chemistry. The chemistry used in the synthesis of the compounds described here is based mainly on the reactions of tetrachlorobenzoquinone (chloranil). Routes leading to aziridinylquinones from chloranil[6,7,12-16] and corresponding bromo[6,7,17] and alkoxy[18-20] intermediates have been described. Reactions between fluoranil and aziridine recently have been summarized.[21]

Chloranil (1) reacted with aziridine and its analogs to produce the disubstituted compounds 2, 3, and 4 by a patent procedure[6] (Scheme I). Compound 4 was converted to the corresponding ethyl (5) and propyl (6) mercapto derivatives.[7,13] It was possible to replace all the chlorine atoms in chloranil with ethylmercapto groups (7). Chloranil also reacted with the sodium salt of urethane to produce 8, a key intermediate. Attempts to react chloranil with methyl carbamate, urea, thiourea, and diethyl malonate in a similar manner were not successful. The

diaziridinylbenzoquinone urethanes 9-11 were prepared from 8. The aziridine rings of 9 were opened with HCl to give the bis(2-chloroethylamino) derivative 12.

The dibromodiaziridinylbenzoquinones 15-17 were prepared in a three-step synthesis starting from benzoquinone (Scheme II). Reaction of 1,4-benzoquinone with anhydrous zinc chloride in methanol gave 13 which was brominated to yield 14. Aziridine replaced the methoxy groups rather than the halogen atoms in accord with the reported relative reactivities of tetrasubstituted benzoquinones.[12,22]

Ammonia[23] and hydrazine reacted with chloranil to produce 18 and 19. These compounds were unreactive toward other nucleophiles because of ring deactivation by the electron-donating amino groups. Reactivation of the ring[12] by acetylation[23] produced 20 which then reacted with 2,2-dimethylaziridine to give 21. The monomethyl and unsubstituted aziridine analogs of 21 had previously been prepared and tested.[1] Compound 19 also reacted with diethoxymethyl acetate to give 22 but this compound was unreactive toward aziridine. Physical and chemical data for these compounds are summarized in Table I.

Antitumor Activity. Compounds 1, 4, 14, 19, and 20 had had prior testing[1] and were inactive in the L1210 system. Compounds 2, 3, 5–12, 15–18, 21, and 22 were tested during this study in the lymphoid leukemia L1210 system by standard NCI protocols on the Q4D (day 1, 5, 9) and the QD1-9 treatment schedules.[27] Among these compounds, only 9 was active (T/C > 125%).[27]

The optimum dose and activity (T/C, %) for 9 on the Q4D schedule was 6.25 mg/kg (154%). Compound 9 had greater L1210 activity on the QD1-9 schedule, however (Table II). The compound had an aqueous solubility of ~0.5 mg/ml. Using the assumptions and constants of Freireich et al.[28] and an optimum dose of 2 mg/kg in the mouse, an average human maximum tolerated dose of 10 mg per dose can be approximated. Since only 20 ml of water would be required to dissolve this amount of 9, the solubility of this compound appears to be in the acceptable range.

Because of its activity in the L1210 system, 9 was tested in some additional intraperitoneal and intracerebral tumor models. Biological data are shown for the L1210 (QD1-9 schedule) and P388 leukemia systems plus the B16 melanocarcinoma and Lewis lung solid tumor systems in Table II. Central nervous system antitumor activity is given in Table III for the intracerebrally implanted L1210, P388, and ependymoblastoma tumor systems. The criterion for minimum activity is defined here as follows:
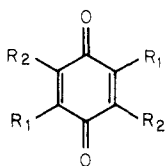
Table I. Physical and Chemical Data

No.	R_1	R_2	Mp, °C	Yield, %	$\lambda_{max}^{CH_3OH}$ (log ϵ)	Mol formula	Analyses
2	MeAz[a]	Cl	155[b]	52	347 (4.24)	$C_{12}H_{12}Cl_2N_2O_2$	C, H, N, Cl
3	Me₂Az	Cl	200	15	362 (4.30)	$C_{14}H_{16}Cl_2N_2O_2$	C, H, N, Cl
5	Az	SC₂H₅	135[c]	33	340 (6.18)	$C_{14}H_{18}N_2O_2S_2$	C, H, N, S
6	Az	SC₃H₇	159	44		$C_{16}H_{22}N_2O_2S_2$	C, H, N, S
7	SC₂H₅	SC₂H₅	88	13		$C_{14}H_{20}O_2S_4$	C, H, S
8	NHCOOC₂H₅	Cl	220	27	317 (4.06)	$C_{12}H_{12}Cl_2N_2O_6$	C, H, N, Cl
9	Az	NHCOOC₂H₅	230[d]	68	340 (4.17)	$C_{16}H_{20}N_4O_6$	C, H, N
10	MeAz	NHCOOC₂H₅	198	89		$C_{18}H_{24}N_4O_6$	C, H, N
11	Me₂Az	NHCOOC₂H₅	175	22	355 (4.23)	$C_{20}H_{30}N_4O_6$	C, H, N
12	NHCH₂CH₂Cl	NHCOOC₂H₅	215	68	340 (4.40)	$C_{16}H_{21}Cl N_4O_6$	C, H, N, Cl
15	Az	Br	181[e]	47	347 (4.15)	$C_{10}H_8Br_2N_2O_2$	C, H, N
16	MeAz	Br	160	69	357 (4.24)	$C_{12}H_{12}Br_2N_2O_2$	C, H, N
17	Me₂Az	Br	210	16	362 (4.26)	$C_{14}H_{18}Br_2N_2O_2$	C, H, N
18	NHNH₂	Cl	198	78	330 (3.59)	$C_6H_8Cl_2N_4O_2$	C, H, N, Cl
19	NH₂	Cl	360	72		$C_6H_4Cl_2N_2O_2$	C, H, N, Cl
21	Me₂Az	NHCOCH₃	205	73		$C_{18}H_{26}N_4O_4$	C, H, N
22	NCHOC₂H₅	Cl	148	76	320 (5.40)	$C_{12}H_{12}Cl_2N_2O_4$	C, H, N, Cl

[a] See footnotes in Scheme I for structure of Az, MeAz, and Me₂Az. [b] Lit.[6] mp 182°. [c] Lit.[19] mp 134°. [d] Lit.[15] mp 250°. [e] Lit.[6] mp 178°.

Table II. Antitumor Activity[a] of Compound 9

L1210 lymphoid leukemia[b]				P388 lymphocytic leukemia[b]				B16 melanocarcinoma[b]				Lewis lung carcinoma[c]			
Expt no.	Dose[d]	T/C[e]	T - C[f]	Expt no.	Dose	T/C	T - C	Expt no.	Dose	T/C	T - C	Expt no.	Dose	T/C	T - C
6942	12.50	T[g]	-5.0	4323	3.12	112	-3.6	267	6.25	T	-3.5	8	4.00	T	-0.1
	6.25	127	-4.1		1.56	238	-2.4		3.12	158	-1.9		2.00	138	+0.3
	3.12	213	-3.2		0.78	211	-2.4		1.56	138	-1.2		1.00	127	-0.1
									0.78	136	-1.4				
7140	4.60	98	-4.6	4328	6.25	T	-6.1	284	6.25	T	-4.4	9	4.00	T	+1.7
	3.12	128	-3.1		3.12	127	-4.1		3.12	143	-2.7		2.00	134	+1.6
	2.00	201	-3.6		1.56	235	-4.0		1.56	144	-3.6		1.00	89	+2.4
					0.78	199	-2.1		0.78	113	-2.2				
7262	1.30	160	-2.3	4387	3.12	100	-3.4	285	6.25	T	-3.5				
	0.88	132	-1.4		1.56	212	-2.1		3.12	170	-1.2				
					0.78	212	-1.4		1.56	158	-2.7				
									0.78	136	-1.1				
8095	4.60	151	-3.9												
	3.12	269	-4.1												
	2.00	225	-3.8												

[a] Protocols and tumor systems described in ref 27. [b] Ip tumor implantation, ip QD1-9 treatment schedule. [c] Subcutaneous tumor implantation, ip QD5-15 treatment schedule. [d] mg/kg/injection. [e] T/C = (treated survival ÷ control survival) × 100%. [f] T - C = average weight change of test group minus average weight change of control animals in grams on day 5. [g] T = toxic dose.

intraperitoneal and intracerebral L1210 leukemia, 125%; intraperitoneal and intracerebral P388 leukemia, 125%; B16 melanoma, 140%; Lewis lung carcinoma, 125%; and intracerebral ependymoblastoma, 140%.

Discussion

The L1210, P388, and B16 test systems described in Table II utilize intraperitoneal (ip) tumor implantation and ip drug treatment while the Lewis lung system employs subcutaneous tumor implantation and ip treatment. All three CNS tumor models (Table III) use intracerebral (ic) tumor implantation and ip treatment.

Table II indicates that the diaziridinyldi(carboethoxyamino)benzoquinone 9 has reproducible activity in excess of T/C 200% in the standard ip L1210 test on the QD1-9 treatment schedule. The optimum dose (OD) is 2-3 mg/kg and a therapeutic ratio (TR, highest active dose divided by lowest active dose) of ~4 is seen. Similar activity results were observed in the P388 system at a

slightly lower OD (1-2 mg/kg). B16 melanoma activity was significant with activity as high as 170% observed at an OD of 3.12 mg/kg. Marginal activity was seen in the refractory Lewis lung tumor system. While insufficient low-dose testing was carried out to establish TI values in the last three systems, 9 might be characterized as a reasonably toxic material with a TR in the range of 3-4.

Antitumor activity was observed with compound 9 in all of the ic tumor systems studied (Table III). While only two dose response experiments were conducted in the ic L1210 and ic P388 systems, reproducible activity was seen in both cases. The activity of 9 in ic L1210 (T/C 179, 184% at OD 3.12 mg/kg) is noteworthy.

A third ic tumor model, the ependymoblastoma[24] system, was also studied. This system requires intracerebral implantation of a solid tumor fragment while the ic L1210 and ic p388 systems utilize ic inoculated ascites tumor fluid. All three use ip drug treatment, however. Compound 9 was very active in the ependymoblastoma ic tumor

Table III. Intracerebral Antitumor Activity[a] of Compound 9

Ic L1210 lymphoid leukemia[b]			Ic P388 lymphocytic leukemia[b]				Ic ependymoblastoma[c]				
Expt no.	Dose[d]	T/C[e]	T − C[f]	Expt no.	Dose	T/C	T − C	Expt no.	Dose	T/C	T − C	Cures[g]
28	6.25	110	−2.1	25	6.25	T[h]	−2.1	133	4.00	T	−3.0	
	3.12	184	−1.1		3.12	139	−0.1		2.00	449	−1.3	4/6
	1.56	151	−0.6		1.56	137	−0.6		1.00	448	−1.3	3/6
	0.78	116	+0.5		0.78	125	+1.0					
					0.39	107	+0.8					
29	6.25	103	−2.8	26	6.25	T	−2.8	136	8.00	T	−5.0	
	3.12	179	−2.1		3.12	131	−2.1		4.00	376	−2.4	4/6
	1.56	146	−0.5		1.56	151	−1.1		2.00	377	−1.1	5/6
	0.78	103	−0.5		0.78	125	−0.4		1.00	226	−0.2	1/6
					0.39	102	−0.7					
								144	4.00	T	−3.9	
									2.00	271	−2.7	5/6
									1.00	271	−2.1	5/6
									0.50	162	−1.8	
									0.25	130	−1.5	

[a] Protocols and tumor systems described in ref 27. [b] Ic tumor implantation, ip QD1-9 treatment schedule. [c] Ic tumor implantation, ip QD1-5 treatment schedule. [d] mg/kg/injection. [e] T/C = (treated survival ÷ control survival) × 100%. [f] T − C = average weight change of test group minus average weight change of control animals in grams on day 5. [g] Number of animals alive per six test animals on day of termination of experiment (day 99 for expt 133 and day 60 for expt 136 and 144). [h] Toxic dose.

model. Cures (survivors from the group of six mice on the last day of the experiment) are indicated. Experiments 136 and 144 were terminated on day 60. Since the number of cures was about the same, the differences in T/C values in these two experiments reflect differences in the life span of the two different sets of control animals. Experiment 133 was terminated on day 99 with a resulting higher activity value. A majority of the test animals were alive on day 99 at a dose of 2.0 mg/kg in this experiment. An optimum dose of 1–2 mg/kg is indicated for 9 in the ependymoblastoma system with a TR of 4–8.

The inactivity of the other compounds studied here is also noteworthy. Methyl substitution in the aziridine ring (10, 11, 21) abolished activity relative to 9 and a previously reported aziridinylacetylaminobenzoquinone.[1] All ring-halogenated aziridinylquinones (2–4, 15–17) were inactive. Although the diethylmercapto derivative 5 gave one marginally active test (T/C 130%, ip L1210, Q4D), the activity was not reproducible. The dipropylmercapto analog 6 was also inactive. These results are in contrast with the activities found (T/C 150%) for the corresponding alkoxy aziridinylbenzoquinone compounds.[1] When the aziridine rings of 9 were opened to the corresponding di(one arm mustard) derivative 12, activity was abolished.

In the compounds and test systems investigated here, the aziridine ring is necessary, but not sufficient, for antitumor activity. Whether the inactivity of the dihalodiaziridinyl compounds is due to an electronic effect (and resulting effect on the redox potential), a lipophilic transport effect, or steric effect (effect on the degree of coplanarity of the quinone and aziridine ring systems) cannot be answered with the derivatives presently available. More definitive answers are expected from a study of a series of di(alkylamino)diaziridinylbenzoquinone derivatives which is currently in progress. This study should also help answer the question of whether the carbamates, the amides,[1] their in vivo amino hydrolysis products, or both give rise to the high antitumor activity noted for these compounds.

Experimental Section

All melting points are uncorrected and recorded on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were performed by NIAMDD, NIH, Bethesda, Md.

Chloranil was obtained commercially. When several compounds were prepared by comparable procedures, only one representative example is included in this section. Reference should be made to Table I for supplementary information for each compound. New compounds were identified by NMR and ir spectroscopy. Satisfactory elemental analyses (±0.4% of calculated values) are indicated by elemental symbols in Table I.

2,5-Dichloro-3,6-di(2,2-dimethyl-1-aziridinyl)-1,4-benzoquinone (3). General Procedure for 2. To a stirred anhydrous ether solution of 2,2-dimethylethylenimine (5.0 ml, 0.08 mol) under nitrogen was added dropwise a solution of 15 ml (0.024 mol) of 1.6 *M* *n*-butyllithium–hexane solution in 100 ml of ether. After addition was completed (0.5 hr) stirring was continued for 1 hr and triethylamine (5 ml) was added. A solution of chloranil (10.0 g, 0.04 mol) in THF (250 ml) was added dropwise. Stirring was continued at room temperature for 16 hr. The resulting solid was filtered, stirred with ice water, collected, and dried to give 1.9 g (15%) of brown solid. Recrystallization from boiling ethanol gave brown needles. For physical data see Table I.

2,5-Dichloro-3,6-diaziridinyl-1,4-benzoquinone (4). General Procedure for 15, 16, and 17. This compound was prepared from chloranil on a 25-g scale (92%) by the patent method[6] to give brown needles: mp 215° dec (lit.[6] mp 185° dec). Anal. C, H, N, Cl.

2,5-Diaziridinyl-3,6-di(thiopropyl)-1,4-benzoquinone (6). General Procedure for 5. To a stirred, dry ice–acetone cooled solution of propanethiol (5 ml, 0.04 mol) in dry methanol (30 ml) was added sodium metal (1.0 g, 0.04 mol). 2,5-Diaziridinyl-3,6-dichloro-1,4-benzoquinone (1.0 g, 0.004 mol) was added to the above solution. The reaction mixture was stirred at 10° for 1 hr. Excess solvent was removed in vacuo and the resulting yellow solid was washed with ice-cold water and dried. Recrystallization from ethyl acetate gave 0.57 g (44%) of yellow prisms: mp 158–159°.

2,3,5,6-Tetrathioethyl-1,4-benzoquinone (7). To a stirred, dry ice–acetone cooled solution of ethyl mercaptan (200 ml, 3.2 mol) was dissolved sodium metal (5.0 g, 0.22 mol) under anhydrous conditions and chloranil (25.0 g, 0.10 mol) was added portionwise. After the addition was complete, the reaction mixture was stirred at room temperature for 5 hr. Excess solvent was removed and the resulting yellow solid was washed with ice-cold water and dried. Recrystallization from ethanol gave 4.5 g (13%) of yellow prisms: mp 88°.

Diethyl 2,5-Dichloro-3,6-diamino-1,4-benzoquinone-*N,N'*-dicarboxylate (8).[15] To a stirred suspension of urethane sodium salt prepared from ethylcarbamate (44.5 g, 0.5 mol) and sodium metal (11.5 g, 0.5 mol) in dry benzene (300 ml) was added chloranil (30.7 g, 0.12 mol). The reaction mixture was stirred overnight at 25–30°. The resulting dark brown solid was filtered and washed first with benzene and finally with a mixture of water

and acetic acid (250:30 ml) (*caution*). The dark residue was washed with cold methanol to give a yellow solid. Recrystallization from ethyl acetate gave 12.0 g (27%) of yellow needles: mp 220–221°. The yield has varied from 0 to 27%.

2,5-Diaziridinyl-3,6-bis(carboethoxyamino)-1,4-benzoquinone (9). General Procedure for 10, 11, and 21. A solution of 8 (1.5 g, 0.004 mol) in tetrahydrofuran (60 ml) was added dropwise to an ice-cold stirred solution of ethylenimine (1.0 ml, 0.03 mol) and triethylamine (2.5 ml) in THF (20 ml). After the addition was complete (0.5 hr), the reaction mixture was stirred at room temperature overnight (16 hr). Excess solvent was removed in vacuo and the resulting reddish-brown solid was washed with ice-cold water and dried over KOH pellets in vacuo. Recrystallization from ethanol gave 1.06 g (68%) of orange needles: mp 230° dec (lit.[15] mp 250°).

2,5-Di(2-chloroethylamino)-3,6-bis(carboethoxyamino)-1,4-benzoquinone (12). Dry HCl gas was passed through a hot solution of 9 (0.60 g, 0.002 mol) in methanol (250 ml) for 15 min. The solution was then stirred at room temperature for 16 hr. The solution was reduced in volume to 25 ml. Addition of ether caused a crystalline solid to precipitate which was filtered, washed with ether, and recrystallized from ethanol: mp 215°.

2,5-Dimethoxy-1,4-benzoquinone (13). This compound was prepared in 32% yield on a 25-g scale by the method of Knoevenagel and Buckel:[25] mp 306°. Anal. C, H.

2,5-Dibromo-3,6-dimethoxy-1,4-benzoquinone (14). This compound was prepared on a 25-g scale (48%) by the general method of Robinson and Vasey:[26] mp 153°. Anal. C, H.

2,5-Dichloro-3,6-dihydrazino-1,4-benzoquinone Dihydrochloride (15). A solution of 85% hydrazine hydrate (15 ml, 0.3 mol) in ethanol (220 ml) was added dropwise to a suspension of chloranil (10.0 g, 0.04 mol) in benzene (220 ml) over a 0.5-hr period. The reaction mixture was stirred at room temperature for 55 hr and the resulting white solid was filtered and washed with benzene. Recrystallization from ethanol gave 7.5 g (78%) of white needles: mp 197–198°.

2,5-Dichloro-3,6-diamino-1,4-benzoquinone (19). This compound was prepared on a 15-g scale in 73% yield by the method of Fieser and Martin:[23] mp >360° (no literature melting point given).

2,5-Dichloro-3,5-acetylamino-1,4-benzoquinone (20). This compound was prepared on a 1.0-g scale in 74% yield as a yellow solid by the method of Fieser and Martin:[23] mp 235° (lit. mp 253–254°).

2,5-Dichloro-3,6-bis(ethoxyformimino)-1,4-benzoquinone (22). Cold diethoxymethyl acetate (10 ml, 0.06 mol) was added to a stirred solution of 19 (1.0 g, 0.005 mol) in Me$_2$SO (10 ml). The reaction mixture was stirred at room temperature for 60 hr and the resulting grayish-white solid was filtered and washed with cold ethanol. Recrystallization from ethanol gave 1.17 g (76%) of white needles: mp 146–148°.

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