5,8-Isoquinolinediones. II. (1a) Chemical and Electrochemical Behavior of the 5,8-Isoquinolinedione System (1b)

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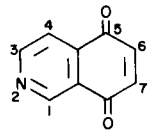
Dedicated to Professor Allan R. Day

We have devised two general synthetic schemes to 5,8-isoquinolinediones and have investigated the chemical and electrochemical behavior of these compounds. The 1,4-addition reactions of these quinones with amines was shown to occur at the 7-position and a number of 7-amino-5,8-isoquinolinediones were synthesized. The 1,4-addition of hydrogen bromide was also studied. The ethylenic double bond of the 5,8-quinone system underwent Diels-Alder additions to yield the oxidized forms of the adducts. The nucleophilic displacement of the methoxy group in 7-methoxy-5,8-isoquinoline was accomplished with both potassium hydroxide and morpholine. A polarographic study of the half-wave potentials of substituted 5,8-isoquinolinediones showed a linear correlation between the change in the half-wave potential of the quinone system ($\Delta E^{\circ}_{1/2}$) resulting from the introduction of different substituents, and the substituent constants ($\sigma_{p\text{-}x}$).

Heterocyclic analogs of 1,4-naphthoquinones such as 5,8-quinolinediones (3a-d) and 5,8-quinoxalinediones (4a-d) are well-known systems which have been thoroughly investigated. The closely related 5,8-isoquinolinedione (**1**) had not been synthesized (1a) until recently although picrates of some substituted 5,8-isoquinolinediones had been reported (5).



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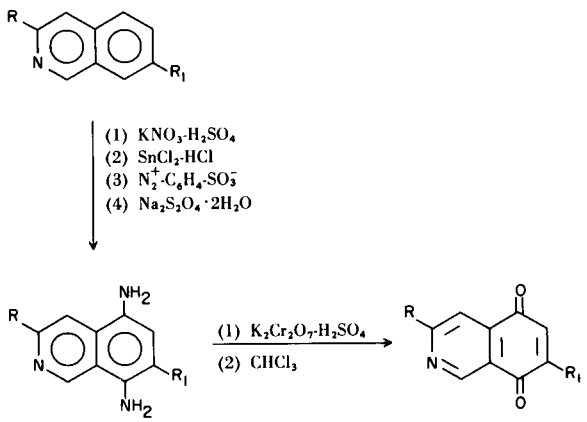
The potential biochemical importance of this system and its chemical similarity to the 1,4-naphthoquinone system prompted us to improve its synthesis and to study its reactivity. Although preliminary tests showed some antitumor activity for certain of these quinones, much work should be done before the biological activity of these compounds is established. On the other hand, the chemical reactivity of this quinone system was of theoretical interest because of the unsymmetrical nature of the ring and the possibility of obtaining isomeric mixtures. In addition, quantitative information on the effect of substituents and the effect of the nitrogen atom in the ring could be obtained from the redox potentials of these compounds.

RESULTS AND DISCUSSION

Synthetic Methods.

The preparation of **1** was reported in a previous publication (1a). The same route was used successfully to prepare 3-methyl-5,8-isoquinolinedione (**2**) from 3-methyl-5,8-diaminoisoquinoline (**3**) and 7-methoxy-5,8-isoquinolinedione (**4**) from 7-methoxy-5,8-diaminoisoquinoline (**5**) (Scheme I).

SCHEME I

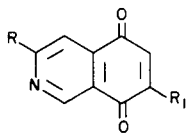


3, R = CH_3, R_1 = H **2**, R = CH_3, R_1 = H
5, R = H, R_1 = OCH_3 **4**, R = H, R_1 = OCH_3

A more direct route to **2** is shown in Scheme II. In this scheme, 3-methyl-5-nitroisoquinoline was electrolytically reduced by the Gatterman method (6) according to known

TABLE I

Substituted 5,8-Isoquinolinediones

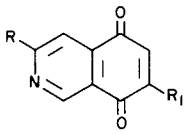


Compound Number	R	R_1	M.p. °C (a)	% Yield	Formula	Analysis, % Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
2	CH_3	H	142-144	66	$C_{10}H_7NO_2$	69.36	4.07	8.09	69.36	4.20	8.00
4	H	OCH_3	215-216	35	$C_{10}H_7NO_3$	63.49	3.73	7.40	63.70	3.81	7.51
7	H		158-160	65	$C_{13}H_{12}N_2O_3$	63.93	4.95	11.47	64.10	5.11	11.50
8	CH_3		168-170	72	$C_{12}H_{10}N_2O_2$	67.28	4.71	13.08	67.16	4.90	12.97
9	CH_3	NCH_3	255-258	77	$C_{11}H_{10}N_2O_2$	65.34	4.98	13.85	65.53	5.21	13.75
10	CH_3	$NHCH_2CH_3$	208-210	40	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95	66.59	5.78	12.86
11	CH_3	$NH(CH_2)_2CH_3$	165-166	68	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	67.60	6.05	12.21
12	CH_3	$NH(CH_2)_3CH_3$	172-173	60	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	68.80	6.66	11.22
13	CH_3	$NH(CH_2)_4CH_3$	173-174	74	$C_{15}H_{18}N_2O_2$	69.74	7.02	10.84	69.77	7.13	11.02
14	CH_3	$NH(CH_2)_2N(C_2H_5)_2$	120-122	39	$C_{16}H_{21}N_3O_2$	66.88	7.37	14.62	66.39	7.59	14.37
15	CH_3	$NH(CH_2)_3N(C_2H_5)_2$	101-102	57	$C_{17}H_{23}N_3O_2$	67.75	7.69	13.94	67.64	7.76	13.84
16	CH_3	$NHCH_2C_6H_5$	222-223	75	$C_{17}H_{14}N_2O_2$	73.37	5.07	10.07	73.63	5.15	10.05
17	CH_3	NHC_6H_5	252-253	46	$C_{16}H_{12}N_2O_2$	72.72	4.58	10.60	72.55	4.71	10.44
18	CH_3		89-90	32	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93	70.11	6.42	10.72
19	CH_3		193-195	50	$C_{14}H_{14}N_2O_2$	69.41	5.82	11.56	69.23	6.02	11.46
20	CH_3		237-239	83	$C_{13}H_{12}N_2O_2$	68.41	5.30	12.27	68.43	5.39	12.12
21	CH_3		168-170	67	$C_{14}H_{14}N_2O_3$	65.11	5.46	10.85	65.18	5.64	10.86
24	CH_3	Br	150	30	$C_{10}H_6BrNO_2$ (b)	47.65	2.39	5.55	47.57	2.40	5.44
27	H	OH	275	90	$C_9H_5NO_3$	61.72	2.88	8.00	61.91	3.02	8.13

(a) Decomposition point. (b) Calcd: Br, 31.70. Found Br: 31.99.

TABLE II

Ultraviolet Spectra and Infrared Carbonyl Absorption Bands of Substituted 5,8-Isoquinolinediones

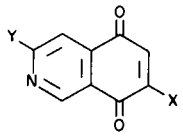


Compound Number	R	R_1	Infrared Absorption (a), cm^{-1} (intensity (b))		Ultraviolet Absorption Bands (c), mμ (log ε)			
2	CH_3	H	1602 (s)		340 (3.52)	254 (4.17)	236.5 (4.34)	
4	H	OCH_3	1650 (s),	1680 (s)	307 (3.63)	255 (3.97)	240 (4.03)	
7	H		1640 (s),	1674 (s)	324 (3.54)	284 (4.05)	251 (4.21)	
8	CH_3		1644 (m),	1670 (s)	325 (3.87)	261.5 (4.13)	232 (4.21)	
9	CH_3	$NHCH_3$	1680 (s)		322 (3.70)	276 (4.21)	235 (4.24)	
10	CH_3	$NHCH_2CH_3$	1620 (m),	1680 (w)	320 (3.72)	277 (4.23)	240 (4.24)	
11	CH_3	$NH(CH_2)_2CH_3$	1610 (m),	1681 (s)	321 (3.78)	276.5 (4.34)	236 (4.35)	
12	CH_3	$NH(CH_2)_3CH_3$	1625 (m),	1670 (w)	320 (3.74)	276.3 (4.29)	234 (4.33)	
13	CH_3	$NH(CH_2)_4CH_3$	1630 (s),	1677 (s)	320 (3.77)	277 (4.30)	236 (4.33)	
14	CH_3	$NH(CH_2)_2N(C_2H_5)_2$	1685 (s)		322 (3.67)	277 (4.19)	235 (4.23)	
15	CH_3	$NH(CH_2)_3N(C_2H_5)_2$	1625 (s),	1670 (s)	320 (3.68)	277.5 (4.21)	237.5 (4.26)	
16	CH_3	$NHCH_2C_6H_5$	1628 (s)		322.5 (3.79)	275 (4.34)	232.5 (4.46)	
17	CH_3	NHC_6H_5	1615 (m),	1675 (s)	327.5 (3.86)	268 (4.45)		
18	CH_3		1625 (m),	1665 (w)		279 (4.07)	245 (4.16)	
19	CH_3		1612 (m),	1678 (m)	295 (3.64)	250 (4.05)	245 (4.06)	
20	CH_3		1678 (m)		324 (3.57)	275 (4.01)	258 (4.01)	236 (4.13)
21	CH_3		1643 (m),	1672 (s)	325 (3.64)	275 (4.01)	242.5 (4.10)	
24	CH_3	Br	1670 (s)		309 (3.77)	263 (4.05)	247.5 (4.07)	
27	H	OH	1635 (s),	1680 (s)	295 (3.64)	250 (4.04)	245 (4.05)	

(a) As potassium bromide discs. (b) Intensity: s = strong, m = medium, w = weak. (c) In acetonitrile.

TABLE III

Half-Wave Potentials in McIlvaine Buffer at *p*H 7.02



Compound Number	X	Y	$E^{\circ}_{1/2}$ (SCE) (a) Quinone wave, V	$\Delta E^{\circ}_{1/2}$, V	$\sigma_{p\text{-}x}$ (b)
1	H	H	-0.063	0.000	-0.000
28 (c)	Cl	H	-0.041	+0.022	+0.227
4	OCH_3	H	-0.187	-0.124	-0.270
27	OH	H	-0.224	-0.161	-0.460 (d)
29 (c)		H	-0.305	-0.242	
7		H	-0.198	-0.135	
2	H	CH_3	-0.065	0.000	0.000
9	$NHCH_3$	CH_3	-0.339	-0.274	-0.84
10	$NHCH_2CH_3$	CH_3	-0.324	-0.259	
11	$NH(CH_2)_2CH_3$	CH_3	-0.323	-0.258	
12	$NH(CH_2)_3CH_3$	CH_3	-0.334	-0.269	
13	$NH(CH_2)_4\ H_3$	CH_3	-0.326	-0.261	
14	$NH(CH_2)_2N(C_2H_5)_2$	CH_3	-0.300	-0.235	
15	$NH(CH_2)_3N(C_2H_5)_2$	CH_3	-0.320	-0.255	
8		CH_3	-0.306	-0.241	
16	$NHCH_2C_6H_5$	CH_3	-0.317	-0.252	
17	NHC_6H_5	CH_3	-0.267	-0.202	-0.59 (e)
18		CH_3	-0.241	-0.176	
19		CH_3	-0.336	-0.271	

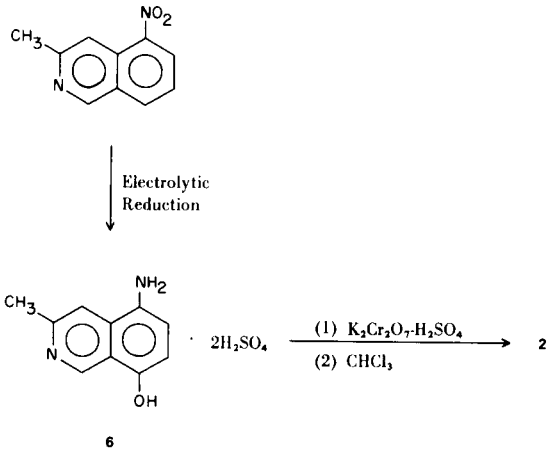
(a) All $E^{\circ}_{1/2}$ values are referred to the saturated calomel electrode at 25° ± 0.1°. (b) These substituent constants are based on the ionization constant of benzoic acids, D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958). (c) Reference 1a. (d) H. H. Jaffe, *Chem. Rev.*, 53, 191 (1953). (e) Reference 17.

directions (7). This reduction is believed to proceed through the reduction of the nitro compound to a hydroxylamine which undergoes an intramolecular rearrangement to give a *p*-aminophenol (8a,b). In the present study, 3-methyl-5-amino-8-hydroxyisoquinoline precipitated as the disulfate salt (**6**) in the cathode compartment of the electrolytic cell. Compound **6** was then dissolved in dilute hydrochloric acid and oxidized with potassium dichromate as in Scheme I.

1,4-Addition Reactions.

Since the 1,4-additions of amines to 1,4-naphthoquinones and 5,8-quinoxalinediones are well-known, similar reactions were tried with **1** and **2**. A number of aliphatic and aromatic amines gave fairly high yields of the corresponding monoaminoquinones. Yields were somewhat lower for the more basic amines because 5,8-isoquinolinediones decompose in alkaline medium (above *p*H 8). The introduction of electron-donating groups in a quinone system is known to yield substituted quinones with redox potentials below that of the parent quinone. Thus, oxidation-reduction equilibration of product and starting material has usually been observed. Addition of amines to **1** and **2** always yielded the substituted quinone. The

SCHEME II



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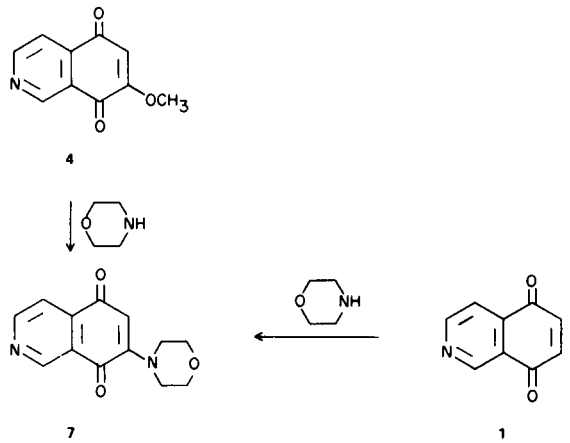
corresponding hydroquinone could never be isolated as a side product. Apparently these hydroquinones are so readily oxidized by air that the reactions go to completion. This is in agreement with the report that some aminoquinones may be obtained in better yields by mixing the amines with hydroquinone and allowing the mixture to stand in air rather than treating the quinone with amines (9a,b).

The addition of amines to **1** or **2** could yield 6- or 7-substituted products or a mixture of both. Studies of similar additions to substituted 1,4-naphthoquinones (10a-c) and 5,8-quinolinediones (3d) have shown that, in most cases, one isomer is formed. The more positive carbon is attacked preferentially by nucleophilic reagents. The aminoquinones obtained in this study were single compounds rather than mixtures as indicated by their sharp melting points and the sharp peaks of their nmr spectra. All attempts to separate some of these products into isomeric substances by chromatography failed. The formation of a 7-substituted quinone as the exclusive product was confirmed, in the case of morpholine, by an independent synthesis of 7-morpholine-5,8-isoquinolinedione from **4**. This product was found to be identical with the 1,4-addition product from **1** and morpholine (Scheme III).

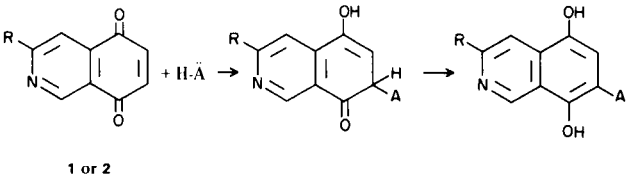
SCHEME III



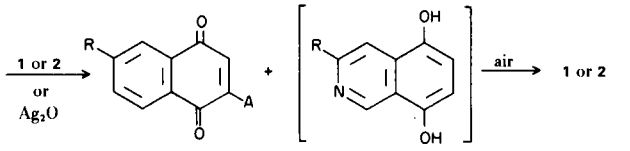
The formation of a 7-substituted product is best understood by comparing the two carbonyl groups at C_5 and C_8. The electron-withdrawing effect of the nitrogen atom in the adjacent ring is most strongly felt at C_5. Attack of a nucleophile at C_7 relieves this effect. In 5,8-quinolinedione the same effect is felt at C_8. Thus, it is best relieved by nucleophilic attack at C_6.

The general mechanism of a 1,4-type addition to **1** or **2** is shown in Scheme IV. Various amines could be added to **1** or **2** by this Scheme.

SCHEME IV



1 or 2



7, R = -H, A = -N O
8, R = $-CH_3$, A = -N
9, R = $-CH_3$, A = $-NHCH_3$
10, R = $-CH_3$, A = $-NHCH_2CH_3$
11, R = $-CH_3$, A = $-NH(CH_2)_2CH_3$
12, R = $-CH_3$, A = $-NH(CH_2)_3CH_3$
13, R = $-CH_3$, A = $-NH(CH_2)_4CH_3$
14, R = $-CH_3$, A = $-NH(CH_2)_2N(C_2H_5)_2$
15, R = $-CH_3$, A = $-NH(CH_2)_3N(C_2H_5)_2$
16, R = $-CH_3$, A = $-NHCH_2C_6H_5$
17, R = $-CH_3$, A = $-NHC_6H_5$
18, R = $-CH_3$, A = -N
19, R = $-CH_3$, A = -N
20, R = $-CH_3$, A = -NH
21, R = $-CH_3$, A = -N O
24, R = $-CH_3$, A = -Br

The 1,4-addition of hydrogen halides to **2** was also investigated. Compound **1** was already known to react with anhydrous hydrogen chloride to give, after oxidation, the corresponding chloroquinone (**28**) (1a). Hydrogen bromide and **2** yielded a substituted hydroquinone hydrobromide (**22**) which was converted to the free base (**23**) and then oxidized to the corresponding quinone (**24**) with silver oxide. The structure of this product was not established by an independent synthesis but assumed to be a 7-substituted compound. This is also true of the other amino derivatives.

TABLE IV

Calculated Substituent Constants from $\Delta E^{\circ}_{1/2}$ Data for Some Amino Groups

Substituent	$\Delta E^{\circ}_{1/2}$	$\sigma_{p\text{-}x}$
	-0.271	-0.835
$-NH(CH_2)_3CH_3$	-0.269	-0.825
$-NH(CH_2)_4CH_3$	-0.261	-0.800
$-NHCH_2CH_3$	-0.259	-0.795
$-NH(CH_2)_2CH_3$	-0.258	-0.790
$-NH(CH_2)_3N(C_2H_5)_2$	-0.255	-0.775
$-NHCH_2C_6H_5$	-0.252	-0.765
	-0.241	-0.725
$-NH(CH_2)_2N(C_2H_5)_2$	-0.235	-0.705
	-0.176	-0.480
	-0.135	-0.335

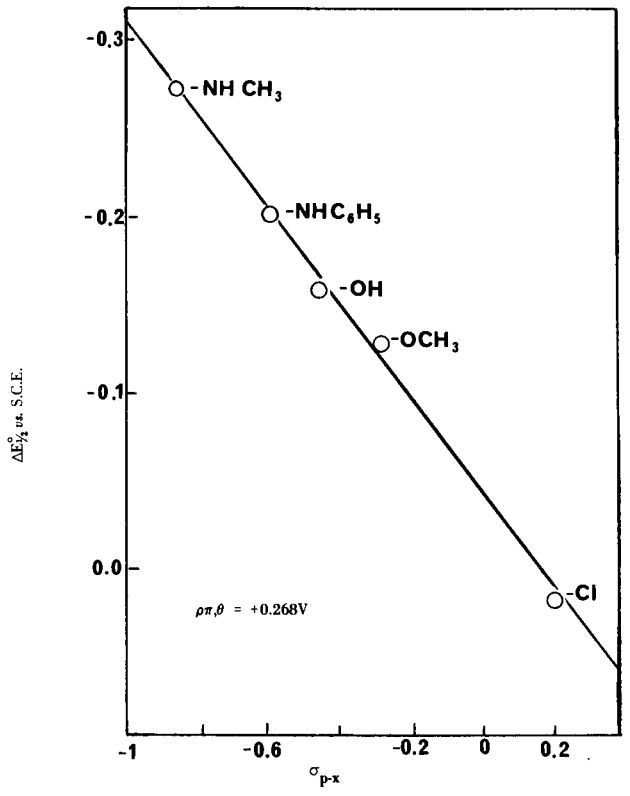
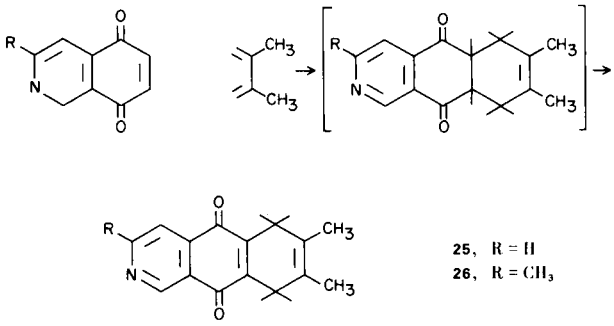


Figure 1. Correlation between the change in half-wave potentials ($\Delta E^{\circ}_{1/2}$) relative to the unsubstituted parent compound and substituent constants ($\sigma_{p\text{-}x}$).

Diels-Alder Reactions.

1,4-Naphthoquinone has been used as a dienophile to give an adduct with 2,3-dimethyl-1,3-butadiene in ethanol (11), in nitrobenzene (12), and in the absence of solvents using an excess of diene (13). When nitrobenzene was used, enolization, dehydrogenation and oxidation of the primary adduct occurred to give a substituted 9,10-anthraquinone. 2,3-Dimethyl-5,8-quinoxalinedione was shown to be more reactive than 1,4-naphthoquinone and several Diels-Alder adducts could be prepared from this quinone (4c). This behavior was not observed for the 5,8-isoquinolinediones which appeared to be considerably less active as dienophiles. When **1** was treated with 2,3-dimethylbutadiene in nitrobenzene a red adduct was formed but recrystallization from methanol caused its oxidation to the yellow 6,9-dihydro-7,8-dimethylbenzo-[*g*]isoquinoline-5,10-dione (**25**). When **2** was treated with the same diene and refluxed in ethanol, the corresponding oxidized form of the adduct, 6,9-dihydro-3,6,7-trimethylbenzo[*g*]isoquinoline-5,10-dione (**26**) was obtained (Scheme V).

SCHEME V



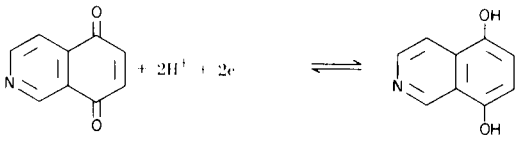
Nucleophilic Displacement of the Methoxy Group.

2-Methoxy-1,4-naphthoquinone (14a,b) and 6-methoxy-5,8-quinolinedione (3a) are vinylogs of an ester and the methoxy groups in these compounds are easily replaced by various nucleophiles. Similarly **4** is hydrolized rapidly at room temperature to give a red solution which yields 7-hydroxy-5,8-isoquinolinedione (**27**) quantitatively on neutralization. When **4** was treated with morpholine, it yielded **7** in high yield.

The physical constants and analytical data for the new quinones prepared in this investigation are shown in Table I. The main infrared and ultraviolet absorption bands of these compounds are shown in Table II.

Polarography.

The polarographic reduction of quinones in aqueous media is known to involve a completely reversible electrode reaction involving two electrons (15a,b). The polaro-



graphic reduction of several substituted 5,8-isoquinolinediones was carried out in 75% v/v aqueous ethanol acetate buffer at *p*H 6.5. To ascertain that a similar mechanism was involved in these reductions, a logarithmic analysis of the current voltage curve obtained from the polarogram for the reduction of **1** was carried out using the equation proposed by Heyrovsky and Ilkovic (16a,b). A straight line was obtained by plotting the applied voltage against $\log \frac{i}{id-i}$ with a slope of -0.03 which corresponds to a value n = 2, thus showing that two electrons were involved in the electrode reaction.

The electronic influence of the substituents present in the quinone were related to the half-wave potentials of the substituted quinones through a Hammett type relationship expressed by the equation (17), $\Delta E^{\circ}_{1/2} = \rho\pi\theta\ \sigma_{p\text{-}x}$ where $\Delta E^{\circ}_{1/2} = E^{\circ}_{1/2}(x) - E^{\circ}_{1/2}(H)$ and $\rho\pi\theta$ is a reaction constant which expresses the susceptibility of the quinone system to the substituent and $\sigma_{p\text{-}x}$ is the *para sigma* constants derived from substituted benzene derivatives.

The half-wave potentials obtained for the substituted 5,8-isoquinolinediones and the corresponding known $\sigma_{p\text{-}x}$ are shown in Table III. A well-defined reduction wave could not be obtained for 7-bromo-5,8-isoquinolinedione (**24**). Similar results have been observed in other quinone systems (18). When the $\Delta E^{\circ}_{1/2}$ values shown in Table III were plotted against the known $\sigma_{p\text{-}x}$ constants a straight line was obtained (Figure 1). The reaction constant obtained from the slope of the curve, ρ = +0.268 V was similar to that obtained for 5,8-quinoxalinediones (4c) (ρ = +0.286 V) and 1,4-naphthoquinones (17) (ρ = +0.28 V). Approximate *sigma* values were assigned to some substituents used in this study, utilizing the $E^{\circ}_{1/2}$ values shown in Table III. These values are shown in Table IV. The order obtained for the σ_p values of the cyclic dialkylamino groups, pyrrolidine ›› piperidine › morpholine, is the same as that observed in a similar study of the 5,8-quinoxalinediones (4c). The ability of the lone pair of electrons on nitrogen to interact with the quinone system appears to be the most important factor which determines the value of the substituent constant.

Biological Activity.

Some of the substituted 5,8-isoquinolinediones were tested for possible biological activity since 7-(1-aziridinyl)-5,8-isoquinolinedione had shown slight antitumor activity (1a). 5,8-Isoquinolinedione showed a significant degree of inhibitory activity in the *E. coli* bioassay system (19a). Compounds **7**, **8**, **9**, and **11** showed definite activity in the KB mamalian cell bioassay system (19a). Compounds **7**, **13**, **14**, and **17** were tested for antimalarial activity but showed none (19b).

EXPERIMENTAL

All melting points were determined with a Thomas-Hoover apparatus (capillary method) and are uncorrected. Elemental analyses were performed by Dr. A. Bernhardt, Max Plank Institute, 433 Mülheim (Ruhr), West Germany and by Galbraith Laboratories, Knoxville, Tennessee. Infrared spectra were determined on a Perkin-Elmer double beam 521 recording spectrophotometer as potassium bromide disks. Absorptions are given in cm^{-1}. Ultraviolet spectra were obtained in spectrograde acetonitrile on a Cary Model 14 recording spectrophotometer using 1 cm. quartz cells. The nuclear magnetic resonance spectra were determined at 60 Mc/sec. on a Varian model HR-60 spectrometer. Samples were run as 5-10% w/v solutions in deuteriochloroform or trifluoroacetic acid with tetramethylsilane as an internal reference standard. Chemical shifts are expressed in ppm (δ) (TMS = 0). Signals are expressed as s (singlet) or d (doublet). The polarographic data were obtained on a Sargent Model XV Polarograph.

5,8-Isoquinolinedione (**1**).

This compound was prepared from 5-nitroisoquinoline according to a previously described procedure (1a), yield 50% m.p. 135-138° dec. (lit. (1a) m.p. 135-138° dec.); nmr (deuteriochloroform) δ 9.38 (s, 1, H_1), 9.12 (d, 1, H_3), 7.87 (d, 1, H_4), 7.06 (s, 2, H_6, H_7); (trifluoroacetic acid) δ 9.65 (s, 1, H_1), 9.35 (d, 1, H_3), 8.78 (d, 1, H_4), 7.55 (s, 2, H_6, H_7).

3-Methyl-5,8-isoquinolinedione (**2**).

Method A.

The route used to synthesize **1** was followed (1a). 3-Methyl-5-nitroisoquinoline was prepared according to the previously described directions, yield 93%, m.p. 107-108° (lit. (20) m.p. 108-110°) and reduced with stannous chloride in 2 *N* hydrochloric acid to yield 3-methyl-5-aminoisoquinoline in 70% yield, m.p. 218-219° (lit. (20) m.p. 219.5-221°). This compound (15 g., 0.09 mole) was dissolved in a mixture of 200 ml. of 1 *N* acetic acid and 200 ml. of a saturated sodium acetate solution. A slurry of diazotized sulfanilic acid (21) (24.4 g., 0.14 mole) was added to the previous solution at 5-10°. After 30 minutes the product was salted out and collected. The moist azo dye was then dissolved in 600 ml. of water containing 16 g. of sodium hydroxide, treated with 60 g. of solid sodium hydrosulfite and heated to 60° for 30 minutes. The solution was then cooled, made alkaline with 30 g. of sodium hydroxide and extracted in a liquid-liquid extractor with ether for 2 days. Evaporation of the ether solution yielded 11 g. (67%) of 3-methyl-5,8-diaminoisoquinoline (**3**), m.p. 178-179°.

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.37; H, 6.36; N, 24.28. Found: C, 69.49; H, 6.41; N, 24.15.

Compound **3** (11 g., 0.06 mole) was dissolved in 10 ml. of 12 *N* sulfuric acid and 300 ml. of water and treated with a mixture of 50 ml. of 12 *N* sulfuric acid and 200 ml. of potassium dichromate solution containing 10 g. of dichromate per 100 ml. of water. This mixture was extracted with chloroform. The chloroform solution was washed with saturated sodium chloride solution, then water, and dried over Drierite. After being treated with decolorizing carbon, this solution was reduced in volume and

poured into 500 ml. of petroleum ether (b.p. 30-60°) to yield the quinone (**2**) as a fine yellow powder (Table I); nmr (trifluoroacetic acid) δ 9.44 (s, 1, H_1), 8.56 (d, 1, H_4), 7.49 (s, 2, H_6, H_7), 3.12 (s, 3, CH_3).

Method B.

3-Methyl-5-nitroisoquinoline (100 g., 0.53 mole) was dissolved in 200 ml. of concentrated sulfuric acid and the solution was placed in a cylindrical vessel made of porous porcelain which was contained in a beaker filled with 80-90% sulfuric acid. A platinum electrode (5 cm. x 4 cm.) was introduced into the solution of the porcelain jar (cathode compartment). Another platinum electrode (3 cm. x 2 cm.) was introduced into the solution of the outer beaker (anode compartment). The current from a 6 V line was passed through the electrolytic cell. The current density increased from 1.5 amp to about 3 amp as the temperature rose to 60-70°. The reaction was completed in 24 hours and 3-methyl-5-amino-8-hydroxyisoquinoline disulfate (**6**) precipitated in the cathode compartment in 65% yield. Compound **6** darkens at 210° and melts with decomposition at 245-250°. It dissolves in water and the less soluble monosulfate precipitates from this solution shortly after.

Anal. Calcd. for $C_{10}H_{14}N_2O_9S_2$: C, 32.43; H, 3.81; N, 7.56; S, 17.32. Found: C, 32.58; H, 3.94; N, 7.71; S, 17.27.

This disulfate was dissolved in 20 ml. of concentrated hydrochloric acid and 200 ml. of water to form a water-soluble hydrochloride and this solution was oxidized by the same procedure described in Method A to yield **2** in 57% yield, m.p. 141-143°.

7-Methoxy-5,8-isoquinolinedione (**4**).

Compound **4** was prepared from 7-methoxyisoquinoline which was synthesized by the Fritsch method (22), yield 45%, b.p. 193-194° (50 mm.). This product was nitrated to 7-methoxy-8-nitroisoquinoline in 86% yield, m.p. 162-163° (lit. (23) m.p. 164-165°). The nitrated product was reduced with stannous chloride in 2 *N* hydrochloric acid to give 7-methoxy-8-aminoisoquinoline in 34% yield, m.p. 153-155° (lit. (23) m.p. 156-157°). This product was converted into 7-methoxy-5,8-diaminoisoquinoline (**5**) by the procedure described in Method A. Compound **5** was obtained in 50% yield, as a yellow solid which turned brown in air, m.p. 165-166°.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.21; H, 5.96; N, 22.04.

The oxidation of **5** was carried out as described under Method A to give quinone **4** as a bright yellow powder (Table I); nmr (trifluoroacetic acid) δ 9.65 (s, 1, H_1), 9.36 (d, 1, H_3), 8.81 (d, 1, H_4), 6.83 (s, 1, H_6), 4.10 (s, 3, OCH_3).

Addition of Amines.

The general procedure consisted of dissolving the quinone (0.006 mole) in 100 ml. of 1,2-dimethoxyethane and adding slowly to this solution an excess of the amine (0.02 mole) in 25 ml. of the same solvent with stirring. The resulting solution was stirred for 3-6 hours. If a black residue formed, it was removed by filtration. Usually the desired aminoquinone precipitated as a red solid. When a precipitate was not formed the solution was evaporated, the product was extracted with chloroform, and the extract was poured into an excess (200 ml.) of petroleum ether (b.p. 30-60°). The compounds prepared are listed in Table I.

Addition of Hydrogen Bromide to **2**. 3-Methyl-7-bromo-5,8-dihydroxyisoquinoline Hydrobromide (**22**).

Compound **2** (2.0 g., 0.012 mole) was dissolved in 200 ml. of 1,2-dimethoxyethane. Anhydrous hydrogen bromide was slowly bubbled through the stirred solution. A brownish yellow precipitate formed which turned deep yellow after a few minutes. The flow of hydrogen bromide was continued for 3 hours. The yellow solid was collected, washed with ether and dried to yield 3 g. (76%) of **22**, m.p. 238-242° dec. The ir spectrum of **22** in Nujol showed a strong absorption for the -OH groups at 3405 cm^{-1}.

Anal. Calcd. for $C_{10}H_9Br_2NO_2$: C, 35.86; H, 2.70; N, 4.18; Br, 47.72. Found: C, 36.01; H, 2.91; N, 4.02; Br, 47.66.

When **22** (2.8 g., 0.008 mole) was dissolved in a minimum amount of water and the solution was treated with 50 ml. of a saturated sodium acetate solution, a deep red precipitate formed immediately. This solid was collected by filtration, washed with distilled water and dried to yield 2 g. (94%) of the free base **23**. This compound turned black when heated. It began to decompose at 150° but did not melt.

Anal. Calcd. for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51; Br, 31.44. Found: C, 47.05; H, 3.33; N, 5.45; Br, 31.57.

3-Methyl-5-bromo-5,8-isoquinolinedione (**24**).

Compound **23** (1 g., 0.004 mole) was suspended in 100 ml. of 1,2-dimethoxyethane and protected from light. Purified silver oxide (3.0 g., 0.012 mole) was added to this solution and the mixture was stirred for 12 hours. The solid which formed was removed by filtration, the solution was treated with decolorizing carbon and reduced to a small volume. It was then poured into 200 ml. of petroleum ether (b.p. 30-60°). The quinone (**24**) separated as a yellow precipitate (Table I); nmr (trifluoroacetic acid) δ 9.54 (s, 1, H_1), 8.62 (s, 1, H_4), 8.00 (s, 1, H_6), 3.17 (s, 3, CH_3).

Diels-Alder Additions.

6,9-Dihydro-7,8-dimethylbenzo[*g*]isoquinoline-5,10-dione (**25**).

Compound **1** (0.3 g., 0.002 mole) was dissolved in 50 ml. of nitrobenzene and treated with 2,3-dimethyl-1,3-butadiene (0.5 g., 0.006 mole); the mixture was stirred at 70-80° for 1 hour. The crude adduct (0.2 g., 44% yield) separated as a red precipitate and was collected by filtration. When this product was recrystallized from methanol it gave the corresponding oxidized product (**25**) as yellow needles, m.p. 255-256°. The ir spectrum of **25** showed a strong carbonyl band at 1665 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.32; H, 5.44; N, 5.99. Found: C, 75.53; H, 5.51; N, 6.10.

6,9-Dihydro-3,7,8-trimethylbenzo[*g*]isoquinoline-5,10-dione (**26**).

Quinone **2** was dissolved in 100 ml. of absolute ethanol and 2,3-dimethyl-1,3-butadiene (1 g., 0.01 mole) added to this solution. This mixture was refluxed for 12 hours, and then concentrated to a small volume. The yellow solid which separated (**26**) was recrystallized from absolute ethanol, m.p. 235°. The ir spectrum of **26** showed a strong carbonyl band at 1670 cm^{-1}. The uv spectrum showed λ max (acetonitrile) mμ (log ε): 316.5 (4.13), 277.5 (4.73), 271 (4.76) and 249 (4.47).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.64; H, 5.83; N, 5.63.

The nmr spectrum of this compound was measured in trifluoroacetic acid and in this solvent, **26** tautomerized to the corresponding aromatic form. The protons on the hydroxyl groups were masked by the solvent. Peaks were observed at δ 9.96 (s, 1, H_1), 9.73 (s, 1, H_4), 9.23 (s, 2 H_6, H_9), 3.15 (s, 3, 3-CH_3), 2.56 (s, 6, 7-CH_3 and 8-CH_3).

Nucleophilic Displacements. 7-Hydroxy-5,8-isoquinolinedione (**27**).

7-Methoxy-5,8-isoquinolinedione (**4**) (0.30 g., 0.0015 mole) was added to 3 ml. of 1 *N* potassium hydroxide. Quinone **4** dissolved in a few minutes to give a deep red solution. After ten

minutes, the solution was treated with 2 ml. of 2 *N* hydrochloric acid and cooled in ice. Compound **27** precipitated as golden yellow crystals (Table I).

Compound **4** (0.50 g., 0.0026 mole) was dissolved in a mixture of 200 ml. of absolute ethanol and 50 ml. of 1,2-dimethoxyethane and 0.3 g. (0.003 mole) of morpholine was added to this solution. The yellow solution slowly changed to red over a period of 2 hours and was refluxed for 12 hours. Evaporation of the solution gave a red residue which was redissolved in chloroform, dried and decolorized. The clear chloroform solution was reduced in volume and poured into an excess (100 ml.) of petroleum ether (b.p. 30-60°) to give a red precipitate (0.4 g., 62% yield) which was identical in every respect to the product obtained from 7-methoxy-5,8-diaminoisoquinoline (**5**).

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