procedure. An 18% yield of orange needles which melted at 247–249° was obtained. A nitrile band appeared at 2195 cm^{-1} in the infrared absorption spectrum. The nitrogen content was low, but the other analytical results agreed satisfactorily with those calculated for 2-pyridinium-3-(carboxamidocyanomethyl) quinoxaline (22) when corrected for 0.3% of residue.

Anal. Calcd for $C_{16}H_{12}ClN_5O$: C, 58.81; H, 4.01; N, 21.43. Found: C, 58.51; H, 4.50; N, 20.42.

When 42 ml of 3-picoline was used in place of the 42 ml of pyridine together with 24 ml of ethyl cyanoacetate in the foregoing procedure, orange needles which melted at 254° dec were obtained. The infrared absorption spectrum had a nitrile band at 2200 and a carbonyl band at 1715 cm^{-1}. The results of elemental analysis agreed satisfactorily with those calculated for 2-(3-picolinium)-3-(carbethoxycyanomethyl)quinoxaline.

Anal. Calcd for $C_{19}H_{17}ClN_4O_2$: C, 61.87; H, 4.64; N, 15.18. Found: C, 61.95; H, 4.92; N, 15.40.

Quinoxalinediones. III. 1,4-Addition Reactions of 2,3-Dimethyl-5,8-quinoxalinedione and a Study of the Influence of Substituents on the Polarographic Half-Wave Potential of This System[1,2]

WILSON F. GUM, JR.,[3] AND MADELEINE M. JOULLIÉ

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received June 8, 1966

The 1,4-addition reactions of 2,3-dimethyl-5,8-quinoxalinedione (1) with several amines and acids, in an aprotic solvent, were found to occur easily and to give higher yields of products than the corresponding reactions with 1,4-naphthoquinone. The higher yields may be attributed to the more desirable aprotic solvent used, 1,2-dimethoxyethane (1,2-DME). The polarographic half-wave potentials of the substituted 5,8-quinoxalinediones were measured and the two-step polarographic reduction mechanism of 1 was investigated. The polarographic reduction mechanism of 1 was found to be a composite of the known reduction mechanisms of quinones and quinoxalines. The effects of substituents on the $E^{\circ}{}_{1/2}$ of 1 could be determined quantitatively using a modified Hammett equation proposed by Zuman, thus testing the validity of this equation on this heterocyclic quinone system. A reaction constant, ρ, was determined and its value was analogous to the value obtained for the 1,4-naphthoquinone system which is the carbocyclic analog of 1. Some new substituent constants ($\sigma_{p\text{-}B}$) were assigned using this modified Hammett equation.

In the previous papers in this series, the synthesis and a study of the dienophilic properties of 2,3-dimethyl-5,8-quinoxalinedione (1) were described.[2,4] As part of a program investigating the physical and chemical properties of heterocyclic quinones and their potential pharmacological applications, we now report on the 1,4-addition reactions of 1 and on the oxidation–reduction potentials of the substituted quinones obtained from these reactions.

The synthesis of 1 was first reported in 1964 by Levy and Joullié.[4] In the present investigation the original synthetic route was used with some modifications (see the Experimental Section).

1,4-Addition Reactions.—Although most 2-alkylamino-1,4-naphthoquinones were obtained by nucleophilic displacements of 1,4-naphthoquinonesulfonate with amines,[5] Plimpton studied the action of ammonia and amines on 1,4-naphthoquinone using water and alcohol as solvents.[6] In these protic solvents, it was necessary to add the amines dissolved in neutral solutions of acetic acid to obtain the products in reasonable yields. Aniline reacted with the same quinone, in ethanol, to yield 2-anilino-1,4-naphthoquinone and 1,4-dihydroxy-naphthalene.[7] We have found that by using the aprotic solvent, 1,2-dimethoxyethane (1,2-DME), 1 undergoes 1,4-addition reactions with ammonia, aniline, and various primary and secondary amines (Scheme I).

Low yields of substituted quinones were obtained in the reaction of 1 with ammonia and methylamine owing to the decomposition of 1 in the alkaline reaction media. Quinone 1 decomposes readily above pH 8 to yield unidentifiable products while the substituted aminoquinones appear to be more stable to basic conditions. Since secondary amines react considerably faster with 1 than primary amines the decomposition of 1 does not have as much time to occur. The weak basic character of aniline causes negligible decomposition of 1.

When aziridine and ammonia were added to 6-chloro-2,3-dimethyl-5,8-quinoxaline dione (12), a 1,4-addition reaction occurred rather than the nucleophilic displacement of the chloro group as observed for certain halonaphthoquinones.[8] The corresponding aziridino (9), and amino (10) derivatives were obtained in good yields showing that the chloro group promoted the nucleophilic addition of these amines to the quinone ring by increasing the positive character of the 7 position. The isolation of the hydroquinone (2) in all of the reactions studied showed that all the reactions with amines involved product-starting material oxidation–reduction equilibration as expected for 1,4-addition reactions where electron-releasing groups are introduced.

Terentyev, Grinev, and Terentyev showed that quinones undergo 1,4-addition reactions with anhydrous halogen halides, in ether solution, to give the halogeno-substituted hydroquinones.[9] We have found that hydrogen halides add easily to 1, in 1,2-DME,

---

(1) Presented before the Division of Organic Chemistry, First Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 3, 1966, p 128.

(2) Paper II of this series: W. F. Gum, Jr., and M. M. Joullié, *J. Org. Chem.*, **30**, 2583 (1965).

(3) Abstracted in part from the Ph.D. dissertation of W. F. Gum, Jr., University of Pennsylvania, 1965.

(4) M. R. W. Levy and M. M. Joullié, *J. Heterocyclic Chem.*, **1**, 171 (1964).

(5) L. F. Fieser and M. Fieser, *J. Am. Chem. Soc.*, **57**, 491 (1935).

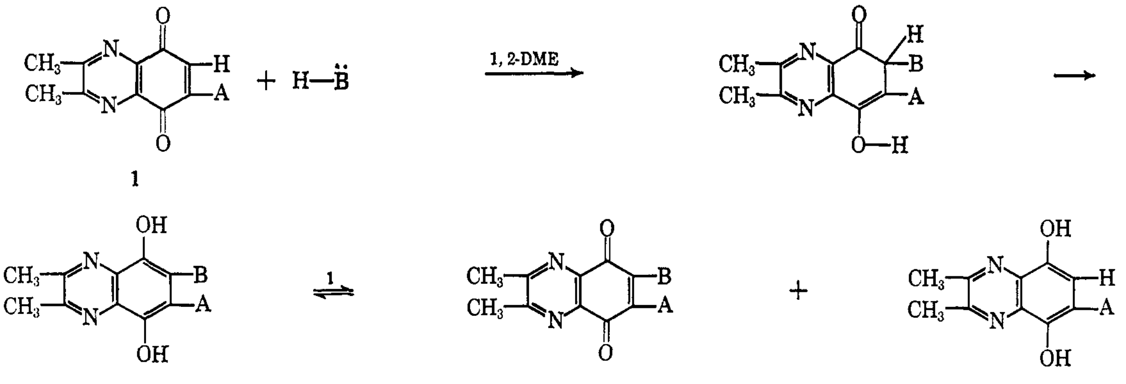
(6) R. T. Plimpton, *J. Chem. Soc.*, **37**, 633 (1880).

(7) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p 854.

(8) J. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **76**, 4148 (1954).

(9) A. P. Terentyev, A. N. Grinev, and A. B. Terentyev, *J. Gen. Chem. USSR*, **24**, 1415 (1954).

SCHEME I

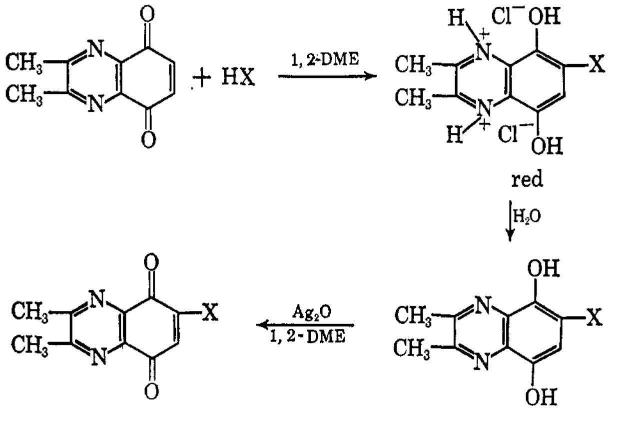


1

2

3, A = H; B = N◁
4, A = H; B = N(CH$_3$)$_2$
5, A = H; B = N⬡
6, A = H; B = NHCH$_3$
7, A = H; B = NHC$_6$H$_5$
8, A = H; B = NH$_2$
9, A = Cl; B = N◁
10, A = Cl; B = NH$_2$

SCHEME II



12, X = Cl
14, X = Br

11, X = Cl
13, X = Br

to form substituted hydroquinones which were oxidized to the corresponding quinones by silver oxide (Scheme II).

When anhydrous hydrogen chloride or bromide was bubbled into a 1,2-DME solution of **1**, a red dihydrochloride or dihydrobromide of **11** or **13** precipitated after a few minutes. These salts were rapidly hydrolyzed in water to give high yields of the respective substituted hydroquinones. A similar salt is formed when 2,3-dimethyl-5,8-dimethoxyquinoxaline is treated with anhydrous hydrogen chloride. Bennett and Willis have shown that 2,3-dimethylquinoxaline derivatives show halochromic effects when treated with acids.[10]

Kvalnes treated *p*-toluenesulfinic acid with 1,4-naphthoquinone, in methanol, to obtain the corresponding 2-*p*-toluenesulfonyl-1,4-naphthoquinone.[11] When **1** was treated with *p*-toluenesulfinic acid a substituted hydroquinone (**15**) was obtained as well as a dark red material which was not identified.

Polarography.—The polarographic reduction of **1** in aqueous McIlvaine buffer at pH 7.02 exhibited two well-defined cathodic waves at $E^{\circ}_{1/2} = -0.060$ and -0.759 v *vs.* saturated calomel electrode. The apparent diffusion current constant, $I = i_d/Cm^{2/3}t^{1/6}$, was $I = 3.72$ and 3.69 for the first and second waves, respectively. To establish that the second wave corresponded to the reaction of the heterocyclic moiety of **1**, 2,3-dimethyl-5,8-dimethoxyquinoxaline was reduced under identical conditions. A single cathodic wave at $E^{\circ}_{1/2} = -0.777$ v was observed. While this wave was shifted 0.018 v to a more negative potential from the second wave of **1** owing to the electron-releasing effects of the methoxy groups, it nevertheless established the first wave of **1** as being due to the reduction of the quinone moiety.

It is well known that the polarographic reduction of quinones in aqueous media involves a completely reversible electrode reaction which consumes two electrons and two protons to form the corresponding hydroquinone.[12,13] The reduction potential has a pH dependence of $\Delta E/\Delta\text{pH} = -0.058$ v.[14] The polarographic reduction of the quinoxaline ring to 1,4-dihydro-2,3-dimethylquinoxaline was studied by Furlani and was found to involve two electrons and two protons.[15] A pH dependence of $\Delta E/\Delta\text{pH} = -0.060$ v was observed.

In order to establish that the polarographic reduction of **1** is a composite of the known mechanisms of reduction of quinones and quinoxalines, it was necessary to establish the pH dependence of the $E^{\circ}_{1/2}$ of the two polarographic waves of **1** and to analyze logarithmically the current–voltage curves of the waves to determine the apparent number of electrons involved in the reduction.

The variation of $E^{\circ}_{1/2}$ with pH for the two polarographic waves of **1** (B,D) is illustrated in Figure 1.

---

[10] G. M. Bennett and G. H. Willis, *J. Chem. Soc.*, 1960 (1928).

[11] D. E. Kvalnes, *J. Am. Chem. Soc.*, **56**, 670 (1934).

[12] O. H. Müller, *Chem. Rev.*, **24**, 95 (1939).

[13] O. H. Müller, *J. Am. Chem. Soc.*, **62**, 2434 (1940).

[14] A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. 1, Academic Press Inc., New York, N. Y., 1963, p 222.

[15] C. Furlani, *Gazz. Chim. Ital.*, **85**, 1668 (1955).

The $E°_{1/2}$ values were converted into the normal hydrogen electrode, $E°_{1/2}$ (nhe) = +0.246 v, in order to compare the extrapolated values at pH 0 with the oxidation–reduction potential values obtained by Fieser and Fieser[5] and Conant and Fieser[16] for *p*-benzoquinone (A) and 1,4-naphthoquinone (C) (points indicated by triangles in Figure 1). The variation of $E°_{1/2}$ with pH for quinones A, B, and C and for the quinoxaline ring of **1** (D) was calculated and found to be equal to −0.060 v per pH unit. This pH dependence is very similar to the values of −0.058 v expected for reductions involving two electrons and two protons.[17]

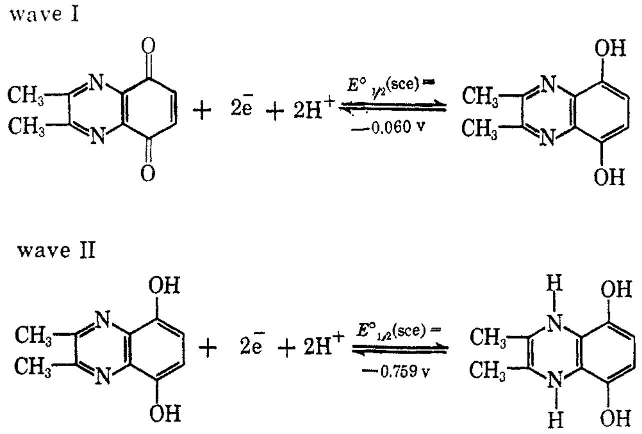
That two electrons are involved in each cathodic wave of **1** was further substantiated by a logarithmic analysis of the current–voltage curve of the first wave of I using the following equation[18]

$$Ec = E°_{1/2} - \frac{0.0591}{n} \log \frac{i}{i_d - i} \qquad (1)$$

where n = the number of electrons involved in the electrode reaction, i = the current, and i_d = the diffusion current. By plotting the applied voltage against the log $i/i_d - i$ term, a straight line was obtained with a slope of −0.029. From the above equation, an electrode reaction involving two electrons will give a slope of −0.030. Since the diffusion currents for waves I and II of **1** are identical one can assume a value of $n = 2$ for the second wave of the polarographic reduction of **1** as well.

In view of the demonstrated polarographic behavior of **1**, the following mechanism for the electrode reaction for the polarographic reduction is postulated in Scheme III.

Scheme III



Substituent Effects.—Zuman has demonstrated the applicability of the modified Hammett equation shown below to the quantitative treatment of substituent effects using polarography (eq 2).[19] In

$$\Delta E°_{1/2} = \rho_{\pi,Q}\sigma_{p\text{-B}} \qquad (2)$$

order to test the validity of this equation for the heterocyclic quinone system **1**, a series of half-wave potentials ($E°_{1/2}$) were determined for several 6-substituted derivatives of **1**. The results are shown in Table I along with the available $\sigma_{p\text{-B}}$ constants obtained from a compilation by McDaniels and Brown.[20]

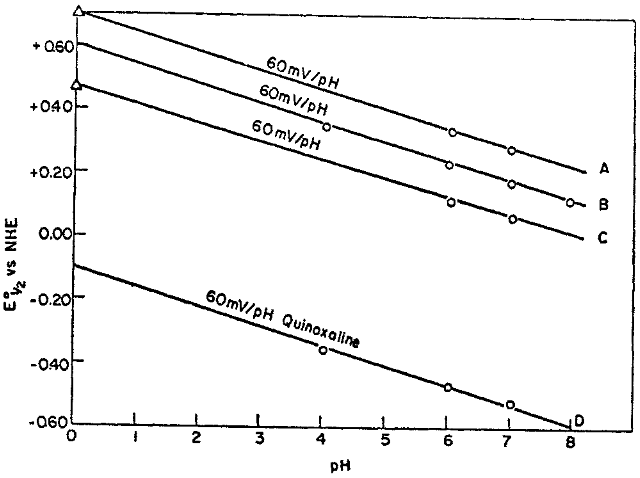
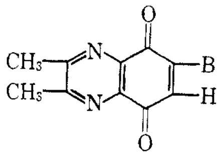
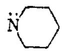
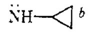
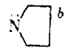


Figure 1.—Variation of $E_{1/2}$ with pH for some quinone systems: A, *p*-benzoquinone; B, wave I of **1**; C, 1,4-naphthoquinone; D, wave II of **1**.

Table I

Half-Wave Potentials in McIlvaine Buffer at pH 7.02



Compd	A	B	$E°_{1/2}$ (sce), quinone wave, v	$\Delta E°_{1/2}$	$\sigma_{p\text{-B}}$
1	H	H	−0.060	0.000	0.00
12	H	Cl	−0.055	+0.005	+0.23
14	H	Br	−0.055	+0.005	+0.23
..	H	CH_3[a]	−0.118	−0.058	−0.17
..	H	 [b]	−0.204	−0.144	...
5	H		−0.223	−0.163	...
7	H	$\ddot{N}HC_6H_5$	−0.240	−0.180	−0.59[c]
8	H	$\ddot{N}H_2$	−0.252	−0.192	−0.66
10	Cl	$\ddot{N}H_2$	−0.258	−0.198	...
4	H	$\ddot{N}(CH_3)_2$	−0.259	−0.199	−0.83
..	H	 [b]	−0.292	−0.232	...
6	H	$\ddot{N}IICH_3$	−0.306	−0.246	−0.84
..	H	 [b]	−0.318	−0.258	...

[a] Prepared by Levy and Joullié, ref 4. [b] Obtained through the courtesy of K. Heidere Ford, M.S. Thesis, University of Pennsylvania, 1966, pp 22, 24. [c] Determined by Zuman.[19]

When the $\Delta E°_{1/2}$ values ($\Delta E°_{1/2} = E°_{1/2(B)} - E°_{1/2(H)}$) shown in Table I were plotted against the known $\sigma_{p\text{-B}}$ constants (compounds **12** and **14** were excluded from plot for reasons that will become evident later in this discussion), a linear correlation was observed as shown in Figure 2. The best straight line through the points was determined by a least-squares analysis[21] performed on a computer where the inputs were the ordinate ($\Delta E°_{1/2}$) and abscissa ($\sigma_{p\text{-B}}$) values of the plotted data in Figure 2 and the output was the equation for a straight line

$$y = mx + b$$

---

[16] J. B. Conant and L. F. Fieser, *J. Am. Chem. Soc.*, **46**, 1858 (1924).

[17] W. A. Struck and P. J. Elving, *ibid.*, **86**, 1229 (1963).

[18] J. Heyrovsky and D. Ilkovič, *Collection Czech. Chem. Commun.*, **7**, 198 (1935).

[19] P. Zuman, *ibid.*, **27**, 2035 (1962).

[20] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

[21] The least-squares analysis was carried out on a JEOL (Japan Electron Optics Laboratory Co.) Model JNM-RA-1 computer.

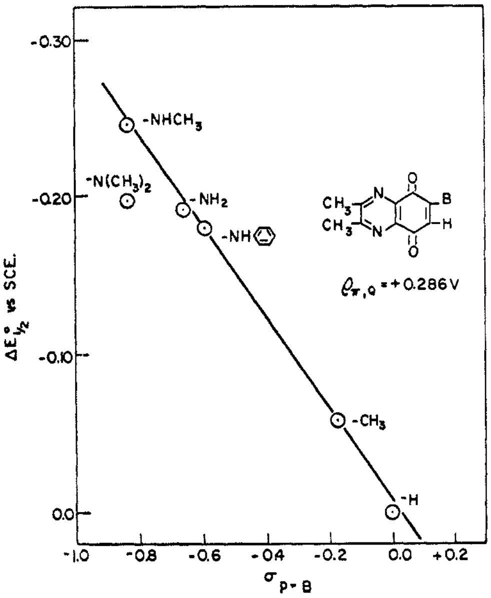


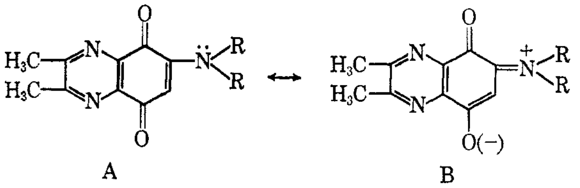
Figure 2.—Correlation between half-wave potentials expressed as shifts ($\Delta E°_{1/2}$) relative to the unsubstituted parent compound and substituent constants ($\sigma_{p\text{-}B}$).

where the slope $m = +0.286$ v, $y = \Delta E°_{1/2}$, $x = \sigma_{p\text{-}B}$, and the intercept $b = 0.000$.

The total polar reaction constant for eq 2 was assigned a value of $\rho_{\pi,Q} = +0.286$ v for the quinoxalinedione system **1**. This reaction constant was similar to the value of +0.28 v found by Zuman for the correlation of $\Delta E°_H$ *vs.* $\sigma_{p\text{-}X}$ for 2-substituted 1,4-naphthoquinones which are the carbocyclic analogs of **1**.[19] Thus, it appears that **1** has an identical susceptibility to substituent effects as 1,4-naphthoquinone, as one might expect from the symmetrical heterocyclic structure of **1**. However, **1** and its derivatives owing to the effect of the quinoxaline ring are constantly stronger oxidizing agents by 0.124 v than the corresponding 1,4-naphthoquinones.

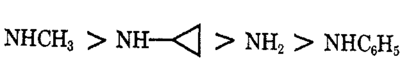
Compounds **10**, **12**, and **14** exhibited anomalous polarographic waves for the reduction of the quinone rings, while the waves for the reduction of the quinoxaline ring exhibited normal behavior. While the introduction of chloro and bromo groups into **1** should have substantially increased the $\Delta E°_{1/2}$ to more positive values, an almost negligible effect was observed. Zuman observed similar deviations for $\Delta E°_{1/2}$ determined in 75% aqueous ethanol for halogeno substituents in 1,4-naphthoquinones.[19] A similar behavior for these substituents was also observed by Peover for a number of quinone systems in hydroxylic solvents whereas in aprotic solvents normal behavior was observed. This anomalous behavior in aqueous media represents a departure from the expected electrode reaction mechanism. The similarity of the $E°_{1/2}$ to the parent system may be indicative of an electrode reaction which involves the loss of a halogen atom before the potential-determining step which would result in a $E°_{1/2}$ similar to the parent system.

The compounds in Table I are listed in order of increasing stability to the reduction of the quinone ring. This represents an increasing ability of the substituent to donate electrons to the quinone ring *via* a mesomeric effect. For the alkylamino substituents this involves the ability of the lone pair of electrons on nitrogen to overlap with the quinoid double bond leading to delocalization of the following type



in analogy to the behavior of enamines.[22] Similar resonance contributions were observed for half-wave potentials of the oxidation waves of substituted *p*-diethylaminoanilines.[19]

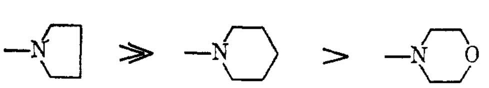
If one assumes that resonance form B is important and steric effects are negligible for amino and monoalkylamino groups, the following order would be expected and was observed (see Table I). This order



represents the decreasing ability of the group attached to nitrogen to stabilize inductively the positive nitrogen in resonance form B. If the stabilization of B were purely inductive, the dialkylamino substituted compounds would be expected to have more negative $E°_{1/2}$ potentials than the methylamino, but this is not observed.

Severe steric interactions between the methyl group of a dimethylamino substituent and the carbonyl group of the quinone should be expected in analogy with similar observations in enamine chemistry.[23,24] This steric interference to the coplanarity required by form B is demonstrated by the deviation shown by the dimethylamino group in Figure 2. A similar deviation for this substituent was observed by Zuman in the 1,4-naphthoquinone series.[19] Both deviations may be ascribed to the fact that the $\sigma_{p\text{-}B}$ constant used was obtained from the ionization constant data for *p*-dimethylaminobenzoic acid where no steric interactions are possible.[20]

However, steric factors cannot completely explain the order observed for the cyclic dialkylamino groups



and cannot adequately account for the magnitude of the differences in $E°_{1/2}$ observed for these groups. Alternatively, no apparent relationship can be observed between the basicities of the groups in question and the observed order and differences in $E°_{1/2}$. The data are best rationalized in terms of the decreasing contribution to form B as a function of the exocyclic double bond required in B. Application of the Brown, Brewster, and Shechter[25,26] rule (double bonds *exo* to five-membered rings are more stable relative to the saturated system than the related double bond *exo* to six-membered rings) to the 5,8-quinoxalinedione system would account for the observed data. The position of the morpholino substituent relative

---

[22] W. D. Gurowitz and M. A. Joseph, *Tetrahedron Letters*, 4433 (1965).

[23] S. K. Malhotra and F. Johnson, *ibid.*, 4027 (1965).

[24] F. Johnson and A. Whitehead, *ibid.*, **No. 50**, 825 (1964).

[25] H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

[26] H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

to the piperidino group reflects a further decrease in the stability of B due to the introduction of additional ring strain by the oxygen atom.

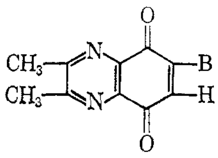
Since similar steric interactions and exocyclic double bonds stabilities for the dialkyl and cyclic dialkylamino substituents will be present in other 1,4-quinone systems, $\sigma_{p-\mathrm{B}}$ values may be assigned using eq 3 and the $\Delta E°_{1/2}$ data from Table I. These assignments

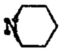
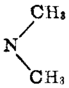
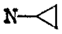
$$\Delta E°_{1/2} = +0.286 \text{ v } \sigma_{p-\mathrm{B}} \qquad (3)$$

are listed in Table II. The new assignment given to the dimethylamino group reflects the steric interference encountered by this group in quinone systems. This value brings the deviation observed by Zuman in the 1,4-naphthoquinone series more into line with his Hammett correlation.[19] However, it should be noted that the values listed in Table II are approximations and only applicable to linear correlations of substituent effects in 1,4-quinone systems.

Table II

Substituent Constants ($\sigma_{p\text{-}\mathrm{B}}$) for Some Alkylamino Groups



B	$\sigma_{p\text{-}\mathrm{B}}$
	−0.50
	−0.57
	−0.70
	−0.81
	−0.90

Experimental Section[27]

The yields and physical, and analytical data for all the compounds prepared are given in Tables III and IV. The infrared absorption bands in the 1750–1550-cm^{-1} region are shown in Table V. The data for compounds 12 and 14 are similar to those observed for the corresponding *p*-benzoquinones.[28]

2,3-Dimethyl-5,8-quinoxalinedione (1).—The nitration of 1,4-dimethoxybenzene was carried out as described by King, Clark, and Davis[29] to yield a mixture of 2,3- and 2,5-dinitro-1,4-dimethoxybenzenes, mp 155–178°, the 2,3-dinitro isomer being the predominant component. This mixture (10 g, 0.044 mole) was suspended in glacial acetic acid (150 ml), 10% palladium on carbon (0.8 g) was added to it, and the heterogeneous solution was hydrogenated in a Parr hydrogenator. The catalyst was removed by filtration and the filtrate was diluted with 150 ml of water and treated with 6 ml of diacetyl. The red solution was stirred for 5 min and poured into 500 ml of ice–water to yield a yellow precipitate of 2,3-dimethyl-5,8-dimethoxyquinoxaline (8.9 g, 94%) which was recrystallized from petroleum ether (bp 90–120°), mp 171–172° (lit.[30] mp 170°). Demethylation of this product was achieved with aluminum chloride as previously described[4] to yield 2,3-dimethyl-5,8-dihydroxyquinoxaline (2). The oxidation of 2 was accomplished using a modification of the procedure used by Levy and Joullié.[4] Compound 2 (12.6 g, 0.066 mole) was suspended in 400 ml of 1,2-dimethoxyethane and treated with purified silver oxide (18.8 g, 0.076 mole) for 4 hr at room temperature in the dark. Decolorizing carbon was added to the mixture and the solid material was removed by filtration from a hot solution. Concentration of the filtrate to one-third of its original volume yielded 12.3 g (98%) of long yellow needles of 1, mp 206–208° dec (lit.[4] mp 182° dec).

Addition of Amines to 1.—Two general procedures will be given, one for amines which are liquids, the other for amines which are gases at room temperature.

6-(N-Aziridinyl)-2,3-dimethyl-5,8-quinoxalinedione (3).—The preparation of this compound is typical for all 1,4-addition reactions of liquid amines to quinones 1 and 12. Compound 1 (2.09 g, 0.011 mole) was dissolved in 140 ml of 1,2-DME under nitrogen. Dry nitrogen gas was bubbled through the solution while aziridine (1.6 g, 0.04 mole) dissolved in 20 ml of 1,2-DME was added with stirring to the solution of 1 over a period of 10 min. The reaction mixture was stirred for an additional 2 hr at room temperature. The solution was concentrated to one-half of its original volume and the solid formed removed by filtration to yield 1.0 g (82%) of 3 as a deep orange, crystalline solid. Further concentration of the filtrate yielded 0.65 g (64%) of 2 which was recrystallized from ethyl acetate to a constant melting point, 226–229°. This compound was identified by melting point determinations on a mixture of this product and an authentic sample of 2 and also by a comparison of their infrared spectra. Prolonged evaporation of the filtrate yielded a red material which did not melt above 300°. The infrared spectrum of this product suggested that it was a quinhydrone.

For the 1,4 addition of aniline to 1, the reaction mixture was refluxed for 48 hr after the addition of aniline, and air instead of nitrogen was bubbled through the reaction mixture. The order of product precipitation was reversed in this reaction, the hydroquinone being the less soluble. In the reaction of piperidine and 1, compounds 5 and 2 precipitated together and had to be separated by sublimation at 110° (3 mm). Compound 2 sublimed and compound 5 remained as a residue which was recrystallized from isooctane.

6-Dimethylamino-2,3-dimethyl-5,8-quinoxalinedione (4).—The preparation of this compound is typical for all 1,4-addition reactions of gaseous amines to 1. Compound 1 (1.0 g, 0.0053 mole) was dissolved in 75 ml of 1,2-DME. Dimethylamine was bubbled into this solution for 5 min with stirring. The red solution was stirred for 3 additional hr and then concentrated to yield 0.80 g of a solid A. The filtrate was treated with an equal volume of ether to yield an unidentified gelatinous precipitate which was removed by filtration. The filtrate was evaporated to dryness to yield 0.29 g of a solid B. Solids A and B were combined, dissolved in 1,2-DME, and treated with decolorizing carbon, and the carbon was removed by filtration from the hot solution. The filtrate was cooled and treated with three times its volume of ether. A bright red, crystalline precipitate formed and was removed by filtration to yield 0.48 g (40%) of 4. Concentration of the filtrate produced the hydroquinone (28%) which was identified as previously described.

In the reaction of methylamine with 1, the solution was stirred for 1 hr. A gelatinous precipitate and an insoluble, dark red solid which did not melt up to 250° were removed first. Concentration of the filtrate, followed by addition of ether, produced first the desired quinone, 6, and further concentration of the filtrate yielded 2. The addition of ammonia to 1 was carried out at 5° and stirring was continued for 0.5 hr.

Addition of Acids to 1.—The addition of anhydrous hydrogen halides will be illustrated by the reaction of 1 with hydrogen chloride.

6-Chloro-2,3-dimethyl-5,8-dihydroxyquinoxaline (11).—Compound 1 (1.0 g, 0.0053 mole) was dissolved in 150 ml of 1,2-DME and this solution was stirred at room temperature while anhydrous hydrogen chloride was slowly bubbled into it for 1 hr. The reaction was slightly exothermic and within 10 min a red precipitate formed. The solution was concentrated to approxi-

---

[27] Melting points were determined in a Thomas–Hoover capillary melting point apparatus. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and by Dr. A. Bernhardt, Max Planck Institute, 433 Mülheim (Ruhr), West Germany. The infrared spectra were determined on a Perkin-Elmer double-beam 521 recording spectrophotometer either as potassium bromide disks or in 0.211-mm sodium chloride cells using chloroform as a solvent.

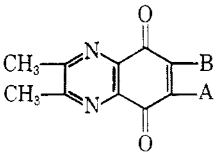
[28] J. F. Bagli, *J. Am. Chem. Soc.*, **84**, 177 (1962).

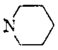
[29] F. E. King, N. G. Clark, and P. M. Davis, *J. Chem. Soc.*, 3012 (1949).

[30] S. Kawai, S. Tanaka, K. Ichikawa, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **75**, 40 (1954); *Chem. Abstr.*, **49**, 10315*a* (1955).

TABLE III

AMINO-SUBSTITUTED 2,3-DIMETHYL-5,8-QUINOXALINEDIONES



Compd	A	B	Mp, °C	Yield, %	Yield, % hydroquinone	Recrystn solvent	Formula	Calcd, % C	H	N	Found, % C	H	N
3	H	N◁	203–204 dec	41	32	1,2-DME	$C_{12}H_{11}N_3O_2$	62.87	4.84	18.33	62.77	4.98	18.50
4	H	$N(CH_3)_2$	194–195 dec	40	28	1,2-DME	$C_{12}H_{13}N_3O_2$	62.33	5.66	18.17	62.21	5.90	18.16
5	H		146–148 dec	44	42	Isooctane	$C_{15}H_{17}N_3O_2$	66.40	6.32	15.49	66.55	6.40	15.65
6	H	$NHCH_3$	220–221 dec	12	23	Sublimed, 120° at 1 mm	$C_{11}H_{11}N_3O_2$	60.82	5.11	19.34	61.11	5.30	19.23
7	H	NHC_6H_5	219–220 dec	44	33	benzene–Skellysolve H[a]	$C_{16}H_{13}N_3O_2$	68.81	4.69	15.04	68.97	4.73	14.83
8	H	NH_2	222–225 dec	16	49	1,2-DME–ether	$C_{10}H_9N_3O_2$	59.11	4.46	20.68	58.91	4.38	20.90
9	Cl	N◁	164–165 dec	34	20	1,2-DME–ether	$C_{12}H_{10}ClN_3O_2$[b]	54.66	3.82	15.94	54.58	4.07	16.16
10	Cl	NH_2	250–253 dec	47	23	1,2-DME–Skellysolve H	$C_{10}H_8ClN_3O_2$[c]	50.54	3.39	17.88	50.81	3.50	17.48

[a] A petroleum ether fraction (bp 70–74°) obtained from Skelly Oil Co., Kansas City, Mo. [b] Calcd: Cl, 13.45. Found: Cl, 13.75. [c] Calcd: Cl, 14.92. Found: Cl, 14.85.

TABLE IV

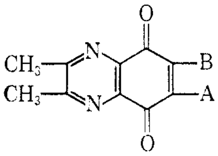
6-SUBSTITUTED HYDROQUINONES AND QUINONES

Compd	Mp, °C	Yield, %	Recrystn solvent	Formula	Calcd, % C	H	N	Found, % C	H	N
11	227–228 dec	97	Ethyl acetate	$C_{10}H_9ClN_2O_2$[a]	53.46	4.04	12.47	53.49	3.87	12.45
12	137–138 dec	85	Ethyl acetate	$C_{10}H_7ClN_2O_2$[b]	53.94	3.17	12.59	53.71	3.14	12.67
14	133–134 dec	81	Methanol–cyclohexane–ether	$C_{10}H_7BrN_2O_2$[c]	44.96	2.64	10.49	45.04	2.78	10.32
15	278–279 dec	52	Acetone–dimethylsulfoxide	$C_{17}H_{16}N_2O_4S$[d]	59.29	4.68	8.13	59.27	4.80	8.42

[a] Calcd: Cl, 15.78. Found: Cl, 15.92. [b] Calcd: Cl, 15.93. Found: Cl, 15.75. [c] Calcd: Br, 29.92. Found: Br, 30.33. [d] Calcd: S, 9.31. Found: S, 9.45.

TABLE V

INFRARED ABSORPTION BANDS IN THE 1750–1550-CM^{-1} REGION OF SOME 5,8-QUINOXALINEDIONES



Compd	A	B	Absorption bands,[a] cm^{-1} (intensity[b])
1	H	H	1685 (s), 1671 (vs), 1599 (m)
3	H	N◁	1684 (vs), 1642 (vs), 1588 (vs)
4	H	$N(CH_3)_2$	1683 (s), 1627 (vs), 1587 (vs)
5	H		1684 (vs), 1636 (vs), 1572 (s)
6	H	$NHCH_3$	1696 (s), 1600 (vs)
7	H	NHC_6H_5	1688 (s), 1635 (s), 1610 (vs), 1591 (vs)
8	H	NH_2	1696 (m), 1610 (vs)
9	Cl	N◁	1682 (s), 1662 (s), 1562 (vs)
10	Cl	NH_2	1703 (s), 1650 (m), 1595 (vs)
12	H	Cl	1693 (vs), 1667 (vs), 1590 (s)
14	H	Br	1691 (vs), 1666 (vs), 1583 (s)

[a] As KBr disks. [b] Intensity: s = strong, vs = very strong, m = medium.

mately 25 ml and the red precipitate was removed by filtration and treated with 60 ml of water. The aqueous solution was stirred for 10 min and the yellow precipitate was removed by filtration to yield 1.15 g (97%) of **11**.

6-Chloro-2,3-dimethyl-5,8-quinoxalinedione (**12**).—Compound **11** (6.4 g, 0.029 mole) was dissolved in 500 ml of 1,2-DME. Purified silver oxide (8.0 g, 0.0324 mole) was added to this solution and the mixture was stirred for 6 hr in the dark at room temperature. Decolorizing carbon was added and the solid material removed by filtration from the hot solution. Concentration of the filtrate yielded 5.4 g (85%) of **12**. Compound **13** was oxidized using similar conditions.

6-*p*-Toluenesulfonyl-2,3-dimethyl-5,8-dihydroxyquinoxaline (**15**).—Compound **1** (1.0 g, 0.0053 mole) was dissolved in 100 ml of 1,2-DME. *p*-Toluenesulfinic acid (0.90 g, 0.0058 mole), freshly prepared from sodium *p*-toluenesulfinate, dissolved in 36 ml of 1,2-DME was added to the solution of **1** over a period of 0.5 hr. The mixture was stirred for another hour and then left standing for 2 days. A yellow, crystalline precipitate was removed by filtration to yield 0.95 g (52%) of **15**. Concentration of the red filtrate gave an unidentified red solid.

Determination of Polarographic Half-Wave Potentials. Apparatus.—Polarograms were recorded automatically on a Sargent Model XV polarograph using the standard H-shaped cell of Lingane and Laitinen modified for rapid deaeration of the sample solution. The cell was maintained at 25.0 ± 0.1° in a constant temperature bath. A saturated calomel reference electrode[31] was used, and an agar plug[32] saturated with potassium nitrate separated the reference and dropping mercury electrode compartments. No recorder damping was used. The supporting electrolyte was McIlvaine buffer.[32] The capillary used had a flow rate of 1.89 mg/sec in McIlvaine buffer at pH 7.02 at a height of

---

[31] L. Meites, "Polarographic Techniques," 1st ed, Interscience Publishers, Inc., New York, N. Y., 1955, p 22.

[32] O. H. Müller, "The Polarographic Method of Analysis," Chemical Education Publishing Co., Easton, Pa., 1951, p 44.

46 cm, at 25°, and voltages of −0.150 (sce) or −0.850 v (sce) and a drop time of 4.3 sec. The cell resistance, measured with a Wayne-Kerr Model B 221 universal impedance bridge, was always less than 50 ohms in McIlvaine buffer, consequently the $E^{\circ}{}_{1/2}$ were not corrected for iR drop. The integrity of the reference calomel electrode was checked against a standard thallium sulfate solution. Using Triton X-100 as a maximum suppressor the average $E^{\circ}{}_{1/2}$ was −0.459 ± 0.003 v in exact accordance with the literature value.[33]

Procedure.—The quinones were dissolved in McIlvaine buffer solutions in 50-ml volumetric flasks and transferred to the H cell after the pH had been checked on a Beckman Expandomatic pH meter. Triton X-100 (3 or 4 drops of 0.1% solution) was added, and the solution was deoxygenated for about 10 min with purified nitrogen[34] and then polarographed. The polarograms were analyzed graphically to determine the $E^{\circ}{}_{1/2}$ and in certain cases the diffusion current (i_d) from the average of the recorder traces. The $E^{\circ}{}_{1/2}$ values are accurate to ±0.003 v.

Acknowledgments.—The authors wish to thank Mrs. Kathleen Heidere Ford for supplying several substituted 5,8-quinoxalinediones and Dr. Vernon Sandel of the Eastern Research Laboratory, Dow Chemical Company, for the least-squares analysis. This investigation was supported by a grant (AM 07684-02) from the National Institutes of Health, U. S. Public Health Service.

---

[33] I. M. Kolthoff and J. J. Lingane, *Chem. Rev.*, **24**, 1 (1939).

[34] L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 299.

---

ortho Claisen Rearrangement of Allyloxy-Substituted Isoquinolines[1]

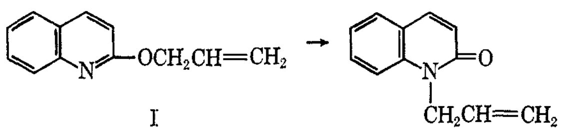
HTAIN WIN AND HOWARD TIECKELMANN

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

Received August 22, 1966

Thermal rearrangements of 3-allyloxyisoquinoline, 3-allyloxy-4-methylisoquinoline, and 1-allyloxyisoquinoline are reported. It is shown that the nature of the annular atoms adjacent to the allyloxy-substituted carbon in N-heteroaromatic allyl ethers does not play a significant role in the direction of the allyl group migration.

It has been observed that *ortho* Claisen rearrangements of 4-allyloxypyrimidines and 2-allyloxypyridines take place indiscriminately to the adjacent annular nitrogen and carbon.[2] Recently, Makisumi[3] reported that the thermal rearrangement of 2-allyloxyquinoline (I) gave N-allyl-2-quinoline (II) without a competing rearrangement to the 3 carbon.



I

II

In this reaction the behavior of 2-allyloxyquinoline is similar to that of a number of other condensed ring allyl ethers, which rearrange to give only one product. For example, 2-allyloxynaphthalene rearranges to give only 1-allyl-2-naphthol[4] and 7-allyloxyquinoline rearranges to 8-allyl-7-quinolinol as the exclusive product.[5] In these systems, when the preferred rearrangement terminus is blocked by an allyl group, rearrangement to the alternative adjacent carbon does not occur and decomposition results. Therefore, if 2-allyloxyquinoline is considered as a model to compare with 2-allyloxynaphthalene, its annular nitrogen has replaced the favored α carbon in the naphthalene ring as a rearrangement terminus.

In previous reports, rearrangement to the adjacent annular nitrogen has always been observed.[2] However, no examples are available in which a nitrogen by analogy with 2-allyloxynaphthalenes is in the unfavored β′ position as the rearrangement terminus. Allyloxyisoquinolines have this structural feature, and permit a comparison between the relative importance of nitrogen nucleophilicity and the naphthoid structural influence. For this reason it seemed pertinent to study the rearrangements of 1-allyloxyisoquinoline (III), in which the nitrogen occupies the favored position, 3-allyloxyisoquinoline (IV) in which the nitrogen is in an unfavorable ring position, and 3-allyloxy-4-methylisoquinoline (V) in which the potential carbon rearrangement terminus is blocked.

Results and Discussion

Allyloxyisoquinolines III, IV, and V were subjected to Claisen rearrangement conditions. Compound IV was prepared by treatment of 3-isoquinolinol[6] with allyl bromide and silver carbonate in dimethylformamide.[7] The isomeric alkylation product, N-allyl-3-isoquinolone, was not isolated using this method. Compound V was prepared from 3-amino-1-bromo-4-methylisoquinoline.[8] Hydrogenolysis employing palladium on charcoal followed by treatment with nitrous acid gave 3-hydroxy-4-methylisoquinoline which was converted into 3-allyloxy-4-methylisoquinoline by the method used for the preparation of IV. Compound III was prepared from 1-chloroisoquinoline[9] and sodium allyloxide.

Previous reports have shown that in 3-isoquinolinol and 1-methyl-6,7-dimethoxy-3-isoquinolinol, the amide structure predominates.[6,10] Spectral comparisons with 3-isoquinolinol and with 3-allyloxyisoquinoline indicate

---

[1] This investigation was supported by Public Health Service Research Grant No. GM-12112 from the National Institute of General Medical Sciences.

[2] (a) F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **28**, 1015 (1963); (b) F. J. Dinan and H. Tieckelmann, *ibid.*, **29**, 892 (1964).

[3] Y. Makisumi, *Tetrahedron Letters*, **No. 39**, 2833 (1964).

[4] L. Claisen, *Ber.*, **45**, 3157 (1912).

[5] E. Ochiai and K. Kokeguti, *J. Pharm. Soc., Japan*, **60**, 271 (1940).

[6] H. E. Baumgarten, W. F. Murdock, and J. E. Dirks, *J. Org. Chem.*, **26**, 803 (1961).

[7] These conditions were chosen because they have led to predominantly O alkylation of 2-pyridone with methyl iodide: G. A. Hopkins, Ph.D. Dissertation, State University of New York at Buffalo, Feb 1967.

[8] F. Johnson and W. A. Nasutavicus, *J. Org. Chem.*, **27**, 3953 (1962).

[9] N. I. Fisher and F. M. Hamer, *J. Chem. Soc.*, 1905 (1934).

[10] H. Plieninger, W. Müller, and K. Weinerth, *Chem. Ber.*, **97**, 667 (1964).