POLAROGRAPHIC REDUCTION OF SUBSTITUTED PIPERIDINO BENZAMIDRAZONES. STRUCTURE-REACTIVITY RELATIONSHIPS[+]

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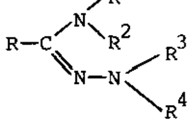
Dedicated to Professor Tetsuji Kametani

Abstract – Polarographic reduction of a series of substituted piperidino benzamidrazones, **2a**-**2h**, along with the unsubstituted benzamidrazone **3** has been investigated in 40% (vol.) ethanolic Britton-Robinson buffers. For the sake of comparison, also the polarographic reduction of benzaldehyde phenylhydrazone **4**, benzaldehyde *p*-nitrophenylhydrazone **5**, and benzamidine **6** has been studied under similar conditions. The assignment of the waves and the reduction scheme are outlined. The $E_{1/2}$ values of the polarographic waves were correlated with the Hammett substituent constants.

INTRODUCTION

Although there are numerous studies devoted to the chemistry of amidrazones (**1**),[1] their polarographic behavior has not yet been explored except for our recent study of the electroreduction of amidrazones containing the morpholine ring.[2] On the other hand, the polarographic reactivity of various other types of compounds containing the azomethine grouping (Schiff bases, oximes, hydrazones, semicarbazones, etc.) has been extensively studied.[3-11]



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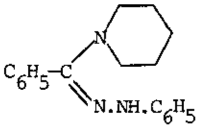
The present report summarizes the results of our study of the polarographic reduction of a series of N^3,N^3-disubstituted amidrazones, **2a**-**2h**. The polarographic reduction of the unsubstituted amidrazone **3**, benzaldehyde phenylhydrazone **4**, benzaldehyde *p*-nitrophenylhydrazone **5**, and benzamidine **6** was also studied under similar conditions for the sake of comparison. Due to their poor solubility in water, all these compounds (**2**-**6**) were studied in ethanolic aqueous buffer solutions containing 40% (vol.) of ethanol.


2

a, X = H
b, X = *p*-Me
c, X = *p*-OMe
d, X = *p*-Br
e, X = *p*-Cl
f, X = *o*-Cl
g, X = 2,4-Cl_2
h, X = *m*-NO_2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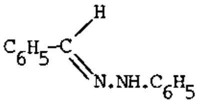
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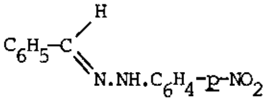
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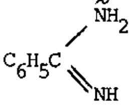
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RESULTS AND DISCUSSION

Polarographic current-potential curves of the amidrazones **2a**-**2h** show the following general characteristics. Below pH 3.6, each compound exhibits only one well-defined six-electron wave, i_a, and at 3.8 < pH < 6.85, an additional two-electron wave, i_b, at more negative potentials. Above pH 6.85, a third four-electron wave, i_c, appears and the wave i_b starts to disappear. Typical polarograms of the amidrazone **2a** in the pH range 2.4-11.4 are given in Fig. 1. The behavior of the amidrazone **3** is similar to that of the amidrazone **2a** except that its polarograms do not exhibit the wave i_a (Fig. 2). The amidrazone **2h** exhibits an additional four-electron wave i_d which persists throughout the whole pH range studied. The polarographic data obtained for the amidrazones **2a**-**2h** and **3** at pH 7.8 are given in Table 1.

The limiting currents, i_l, of the waves i_a through i_d are diffusion controlled. This can be seen from their linear dependence on the concentration and from the linearity of the plot log i_l vs. log *h* where *h* is the mercury column height. The slopes of the log i_l–log *h* plots are in the 0.53-

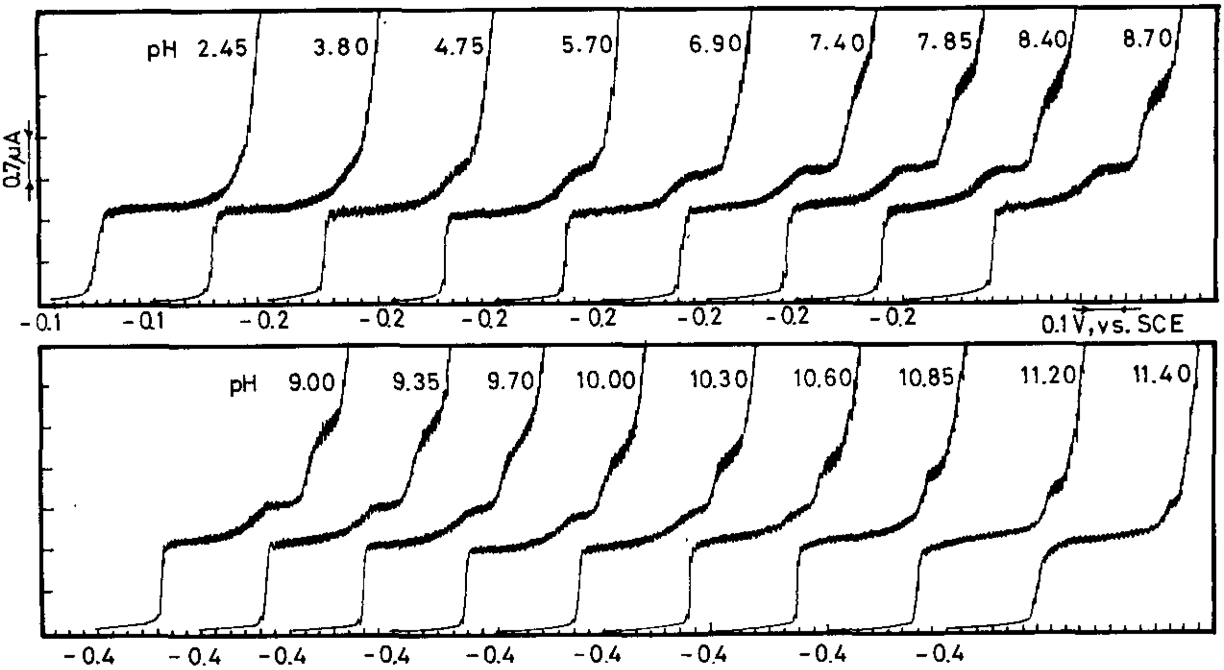


Fig. 1. Polarographic curves of benzamidrazone 2a (1.0×10^{-4}M) at different pH values.

0.55 range, the typical slope value for a diffusion-controlled polarographic wave being 0.50.[12] Logarithmic analysis of the waves i_a through i_d at different pH values suggests that they correspond to irreversible electrode processes. This is substantiated by the shift of the half-wave potentials towards more negative values as the concentration of the depolarizer increases.[13] The half-wave potentials of the waves i_a and i_b are pH-dependent whereas that of i_c is almost pH-independent (Fig. 3). The limiting current of the wave i_a was found to be pH-independent while the limiting currents of the waves i_b and i_c decrease with increasing pH in the form of a dissociation curve (Fig. 4).

On the basis of the above results, the wave i_a can be attributed to the reduction of the *p*-nitro group to the *p*-amino group. The identity of this wave in all respects with the wave involving the reduction of the *p*-nitro substituent in benzaldehyde *p*-nitrophenylhydrazone (Fig. 5) supports this assignment. The absence of this wave in the polarograms of the amidrazone 3 provides an additional evidence. The four-electron wave i_d of the amidrazone 2h is assumed to correspond to the reduction of the *m*-nitro group to the *m*-hydroxylamino group, in agreement with the fact that the *m*-nitro group in *m*-nitrobenzaldehyde arylhydrazones is reduced in a four-electron wave to the hydroxylamine stage.[14]

The waves i_b and i_c correspond to the reduction of the amidrazone grouping. A comparison of these

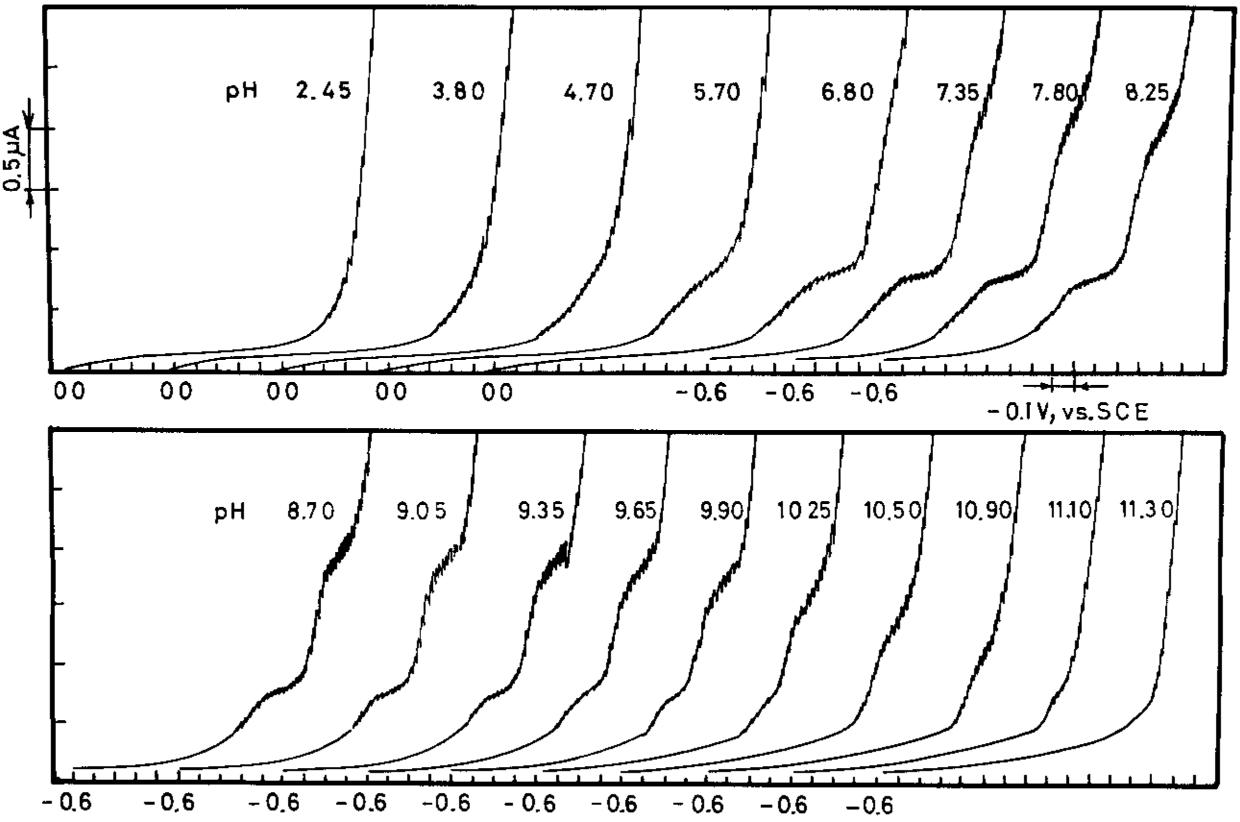
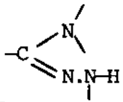


Fig. 2. Polarographic curves of benzamidrazone **3** ($1.0 \times 10^{-4}\underline{M}$) at different pH values.

two waves with the characteristic waves observed for the hydrazones **4** (Fig. 6) and **5** (Fig. 5) reveals a difference in the reduction course of the >C=N–NH– grouping in amidrazones and in hydrazones. The absence of the waves $\underline{i}_b$ and $\underline{i}_c$ in acid media with pH <3.6 indicates that the amidrazones, unlike the hydrazones, are converted into polarographically inactive species under such conditions. This assumption was supported by the observation that dissolution of amidrazone **3** in acetic acid (pH ∼ 3) resulted in a facile cleavage of the piperidino group and the formation of 1-benzoyl-2-phenylhydrazine which is polarographically inactive. Similar treatment of all other amidrazones **2a**-**2h** resulted in the corresponding hydrazides. This conclusion is further supported by the observation that the polarograms of an authentic sample of 1-benzoyl-2-$\underline{p}$-nitrophenylhydrazine are similar to those of amidrazone **2a** at pH < 3.6 and have only the reduction wave $\underline{i}_a$ (Fig. 7). However, the absence of waves $\underline{i}_b$ at pH <3.6 (and $\underline{i}_c$ at pH <6.5) can be due not only to hydrolysis but also to a simple overlap of the waves by the hydrogen evolution current.



Amidrazone grouping

Table 1. Typical Polarographic Data for Benzamidrazones 2a-2h and 3 in 40% (vol.) Ethanolic Britton-Robinson Buffer (pH 7.85)[a]

Compound	Wave i_a			Wave i_b			Wave i_c		
No.	$-E_{1/2}$ (V)	i_l (μA)	αn	$-E_{1/2}$ (V)	i_l (μA)	αn	$-E_{1/2}$ (V)	i_l (μA)	αn
2a	0.78	1.41	1.00	1.35	0.54	0.51	1.77	1.13	0.96
2b	0.72	1.40	1.06	1.38	0.51	0.53	1.80	1.10	0.97
2c	0.71	1.42	1.11	1.40	0.52	0.62	1.79	1.10	1.07
2d	0.71	1.46	1.10	1.28	0.50	0.62	1.65	1.08	0.95
2e	0.72	1.43	1.15	1.28	0.51	0.59	1.66	1.13	1.05
2f	0.76	1.33	1.14	1.54	0.46	0.69	1.82	1.03	0.94
2g	0.72	1.22	1.20	1.41	0.43	0.68	1.67	1.05	1.02
2h	0.70	1.27	1.08	1.37	0.45	0.65	1.78[b]	0.98[b]	1.00[b]
3	—	—	—	1.39	0.47	0.47	1.76	1.01	0.98

[a] Wave i_d for compound 2h, $E_{1/2}$ (V), -0.56; i_l (μA), 0.91. The transfer coefficients, αn, were determined from the slopes of the logarithmic analysis plots. [b] At pH 8.40.

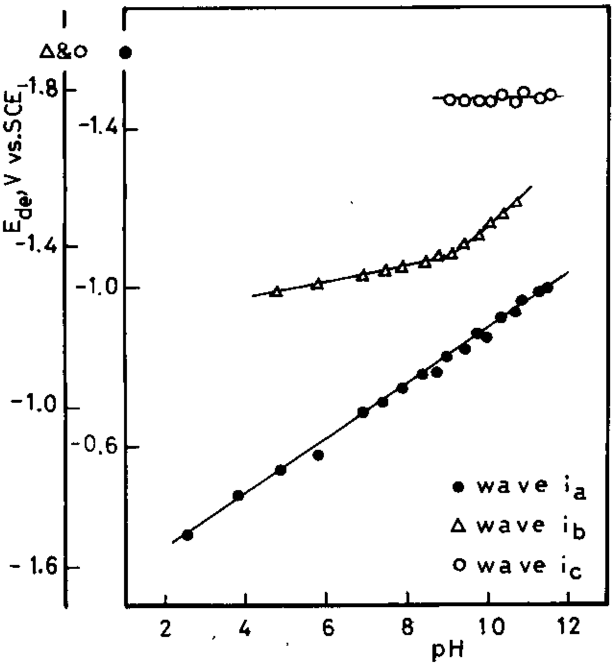


Fig. 3. Dependence of the half-wave potentials of the polarographic waves of benzamidrazone 2a on pH.

The available data allow the following conclusions which are presented in Scheme 1. Furthermore, the following information is available. The two-electron process does not yield the hydrazone which makes the cleavage of the C-piperidine bond in i_b improbable. Aniline and piperidine were detected among the products obtained from the controlled-potential electrolysis of the amidrazone at pH 6.1. It is assumed that in acid media, the N-N bond is reduced in a two-electron wave (i_b) and that this leads to the amidine and aniline derivatives. The $E_{1/2}$ of the wave i_b is pH-dependent due to the preceding acid-base equilibrium. In neutral to alkaline media, the amidine intermediate can be further reduced in a four-electron step (wave i_c) to the corresponding amine and piperidine. An authentic sample of the amidine 6 exhibits a four-electron reduction wave identical in all respects with the wave i_c recorded for the amidrazone 3 under the same experimental conditions. This finding excludes all the possible schemes involving a hydrazone intermediate. The above conclusion is further supported by the observation that the hydrazones 4 and 5 are reduced in a four-electron process in acid media to give amines and, unlike the amidrazones under study, they give no waves in solutions with pH > 8.

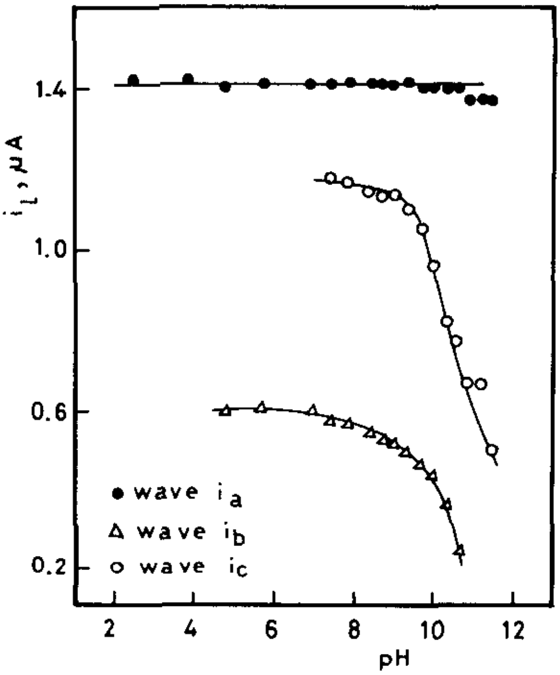
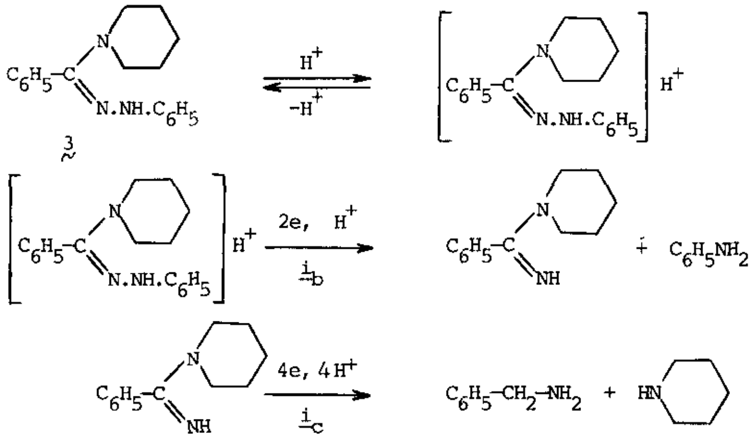


Fig. 4. Dependence of the polarographic limiting currents of the waves of benzamidrazone 2a on pH.



Scheme 1

Reduction of amidrazone 3

To shed more light on the reduction mechanism of the amidrazones 2a-2h, the $E_{1/2}$ values of the waves i_b and i_c observed for these compounds were correlated with the Hammett substituent constants σ and σ^{0}.[15] The transfer coefficient, αn, remains practically constant within the reaction

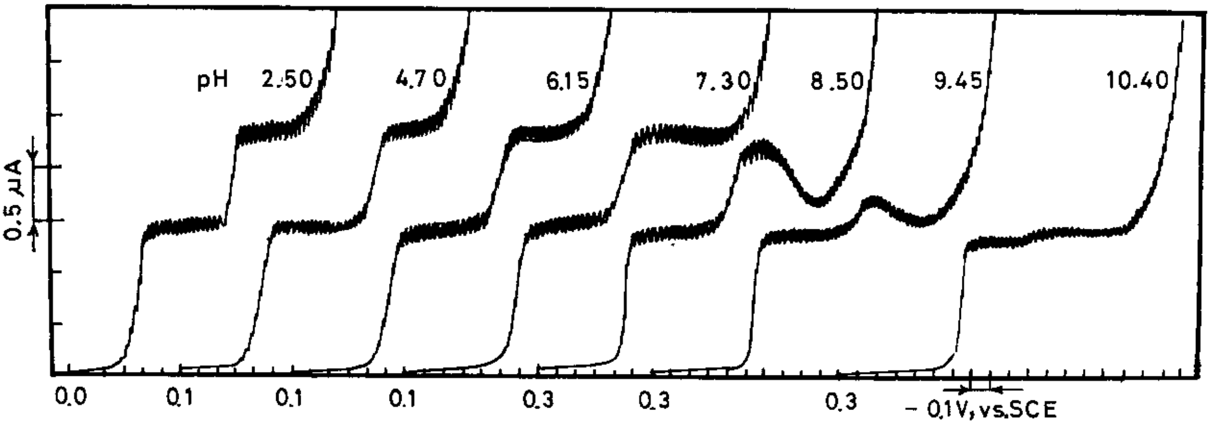


Fig. 5. Polarographic curves of benzaldehyde p-nitrophenylhydrazone (1.0×10^{-4} M) in 40% (vol.) ethanolic buffer solutions at different pH values.

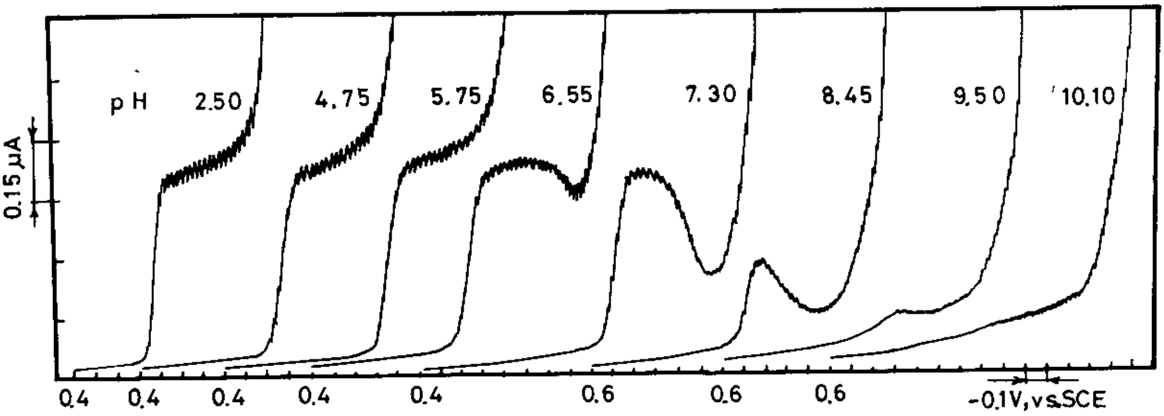


Fig. 6. Polarographic curves of benzaldehyde phenylhydrazone (2.0×10^{-4} M) in 40% (vol.) ethanolic buffer solutions at different pH values.

series as ascertained by the observation that the $E_{1/2}$ vs. pH plots for the compounds under study were practically parallel (cf. Table 1). This is the necessary condition for a quantitative correlation. The results of a statistical treatment of the data at pH 7.85 using the least squares method are summarized in Table 2. It can be seen from the values of the correlation coefficients that the $E_{1/2}$ values are better correlated with the σ^0 rather than the σ constants. This finding suggests that the conjugation of the substituent with the amidrazone moiety is not important enough to produce a noticeable effect.

Table 2. Results of the Statistical Treatment of the $E_{1/2}$ Data Using the σ^{ρ} and σ Constants

	Wave i_b					Wave i_c				
	ρ^a	$E_{1/2}^b$	s^c	r^d	n^e	ρ^a	$E_{1/2}^b$	s^c	r^d	n^e
σ^{ρ}	0.256	-1.34	0.006	0.993	6	0.367	-1.75	0.011	0.990	5
σ	0.222	-1.34	0.016	0.952	6	0.315	-1.75	0.025	0.957	5

[a] Reaction constant. [b] Intercept of the regression line. [c] Standard deviation in $E_{1/2}$. [d] Correlation coefficient. [e] Number of points.

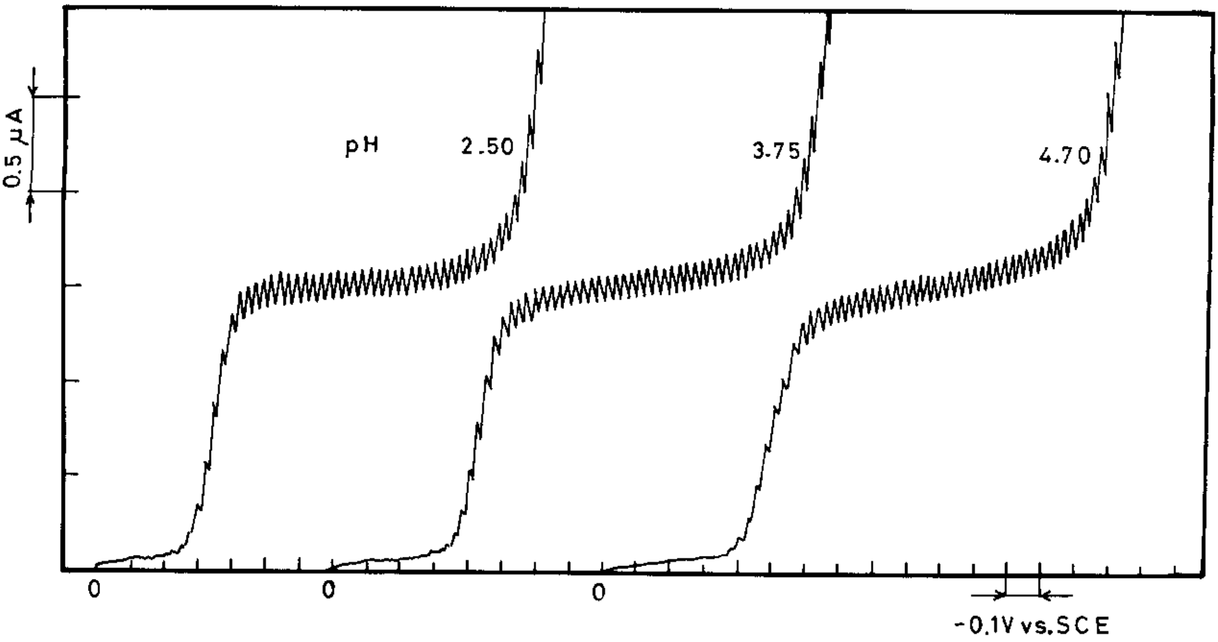


Fig. 7. Polarographic curves of 1-benzoyl-2-p-nitrophenylhydrazine (1.6×10^{-4} M) in 40% (vol.) ethanolic buffer solutions at different pH values.

EXPERIMENTAL

Compounds. The amidrazones **2a**-**2h** and **3** were synthesized from the corresponding arenecarbohydrazonoyl bromides[16,17] and piperidine in ethanol. The compounds were crystallized from ethanol to a constant melting point. Their physical constants are given in Table 3. Stock solutions (10^{-3} M) were prepared in ethanol. The Britton-Robinson buffers were prepared as previously described.[18,19]

Polarography. The polarograms were recorded using a pen-recording LP-60 polarograph (Laboratorní

Table 3. Synthesized Benzamidrazones **2** and **3**

Compound No.	Mp, °C	Mol. formula	Nitrogen, %	
			Calcd.	Found
2a	147-148	$C_{18}H_{20}N_4O_2$[a]	17.27	17.19
2b	176	$C_{19}H_{22}N_4O_2$	16.55	16.60
2c	184-185	$C_{19}H_{22}N_4O_3$	15.81	15.77
2d	138-140	$C_{18}H_{19}BrN_4O_2$	13.89	13.88
2e	177	$C_{18}H_{19}ClN_4O_2$	15.61	15.48
2f	148-149	$C_{18}H_{19}ClN_4O_2$	15.61	15.54
2g	172	$C_{18}H_{18}Cl_2N_4O_2$	14.24	14.30
2h	179-180	$C_{18}H_{19}N_5O_4$	18.96	19.00
3	103	$C_{18}H_{21}N_3$[b]	15.04	15.01

[a] Anal. Calcd. (Found) C, 66.64 (66.54); H, 6.21 (6.00) %. [b] Anal. Calcd. (Found) C, 77.38 (77.40); H, 7.57 (7.53) %.

Přístroje, Prague, Czechoslovakia). A Prolabo Titrimeter pH-meter, model TS 4N, was used to measure the pH values. The pH-meter readings were calibrated before and checked after each measurement using standard aqueous buffers with pH's 4.01 and 7.00 ± 0.01.

Polarographic current-voltage curves were recorded in solutions placed in a cell with an immersed calomel electrode (surface area 12.5 cm^2) and a dropping mercury electrode with t = 3.75 sec and m = 2.18 mg/sec at a 57 cm height of the mercury reservoir and 0.00 V. The junction between the two half-cells was accomplished through a sintered glass disc (G4) in the wall of the polarographic cell.

Ethanolic buffer solution (9.0 ml, 33.3 % vol.) containing 1 ml of Thylose-SL 600 solution (0.005%) was transferred into the cell and deaerated by a stream of nitrogen for 2 min. The amidrazone stock solution (1.0 ml) was then added and, after additional deaeration for 2 min, the polarographic curve was recorded and the apparent pH value of the solution was measured.

Controlled-Potential Electrolysis. The number of electrons transferred in the electrode process was determined coulometrically following the method of Lingane[20] and using a cell similar to that described by Manoušek and Zuman.[21] In each run a 30% ethanolic buffer solution (31.5 ml) was stirred by nitrogen for 30 min, the emf was adjusted to a value 0.3 V more negative than the $E_{1/2}$ of the compound under study, and the electrolysis was continued for 20 min. The emf was readjusted to a value 0.1 V more negative than the $E_{\frac{1}{2}}$ of the wave to be studied, and 3.5 ml of the amidrazone stock solution were added. A stream of nitrogen was being passed through and the changes of the limiting current with time were determined by recording the polarograms at selected intervals during a period of 2 h. The number of electrons transferred, n, was calculated using the equation:

$$n = \frac{i_0}{-2.303\ F\ C_0\ V\ \frac{d\ \log\ i}{dt}}$$

where i_0 is the current at $t = 0$ when $C = C_0$; V is the volume of the solution in liters; and $d \log i/dt$ is the slope of the plot of $\log i$ *vs.* t. The number of electrons transferred in the electrode processes i_a, i_b, and i_c of the amidrazone **2a** was found to be approximately 6.0, 2.0, and 4.0, respectively.

Identification of Controlled-Potential Electrolysis Products. The solutions obtained after complete electrolysis of the amidrazone **3** in four runs were combined and concentrated to one tenth of their original volume. Aniline and piperidine were identified in the resulting mixture by standard spot tests.[22]

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