Polarography of Some Arylazothiohydantoin Derivatives

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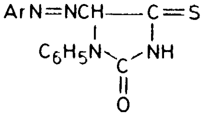
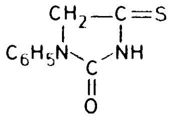
The polarographic behaviour of a series of arylazothiohydantoin derivatives has been investigated at a dropping mercury electrode. Two waves were displayed. The first and predominant one is due to the reductive splitting of the azo-linkage by a 4e irreversible process. The second is assumed to be for the reduction of the CONHCO group in the resulting molecule. A mechanism for the electrode process covering a wide range of pH is proposed, discussed, and clarified *via* model compounds, identification of the resulting products of electrolysis, pK_a determinations, and the interpretation of σ–$E_{\frac{1}{2}}$ plots.

AROMATIC azo-compounds have been the subject of many investigations during the last decade.[1-4] Recently heterocyclic azo-compounds have received attention.[5,6] However, a literature survey revealed the absence of polarographic data on arylazothiohydantoins, a class of compounds which have several interesting applications in the field of medicine since they contain the thiohydantoin ring.[7,8] In this paper the polarographic behaviour of 5-arylazo-1-phenyl-4-thiohydantoin (Ia) together with seven of its substituted derivatives (Ib—h) and a structurally related model compound, 1-phenyl-4-thiohydantoin (II), have been investigated in solutions of different hydrogen ion concentration covering a wide range of pH (2—12) in order to throw light on the possible electroreduction modes of such molecules at the dropping mercury electrode.



(I)



(II)

a ; Ar = C_6H_5
b ; Ar = *m* —$CH_3C_6H_4$
c ; Ar = *p* —$CH_3C_6H_4$
d ; Ar = *p* —ClC_6H_4
e ; Ar = *p* —BrC_6H_4
f ; Ar = *p* —$OCH_3C_6H_4$
g ; Ar = *p* —$CO_2HC_6H_4$
h ; Ar = *m* —$NO_2C_6H_4$

EXPERIMENTAL

Syntheses.—5-*Arylazo*-1-*phenyl*-4-*thiohydantoins* (Ia—h). An aromatic amine (0.006 8 mol), dissolved in concentrated hydrochloric acid (6 ml) and water (6 ml), was cooled to 0 °C and then treated with a cold solution of sodium nitrite (0.6 g) in water (6 ml). The diazotized amine was added gradually to an ice-cold solution of 1-phenyl-4-thiohydantoin[9] (II) (1.3 g) dissolved in ethanol (50 ml) containing sodium acetate (2.6 g). The mixture was then left aside in a cold chest for 1 h. The separated product was filtered off, washed with water, and recrystallized from acetic acid. Yields, m.p.s, and elemental analyses for the 5-arylazo-derivatives (Ia—h) are listed in Table 1.

Polarography.—(a) *Apparatus*. Polarographic curves were recorded with an LP60 polarograph (Laboratorni. Pristroge, Prague). A cell of our own design with a separated saturated calonel electrode was used. The capillary possessed the following characteristics in the H_2O open circuit: *t* 3 s drop^{-1}, *m* 2.15 mg s^{-1} for *h* 50 cm.

(b) *Solutions*. 10^{-3}M-Stock solutions were prepared by dissolving an accurately weighed quantity of material in the appropriate volume of absolute ethanol (n_D^{25} 1.359). Britton–Robinson modified universal buffers[10] (prepared from AnalaR grade chemicals) were used as supporting electrolyte.

(c) *Measurements*. All experiments were carried at 25 ± 2 °C. The half-wave potentials were measured graphically and expressed *versus* the saturated calomel electrode (s.c.e.) with an accuracy ± 0.005 V. The accuracy of the applied voltage was checked by recording polarograms of standard Tl^+ in 0.1M-KNO_3 solutions for different concentrations ($E_{1/2}$ −0.45 *versus* s.c.e.).

(d) *Procedure*. Ethanol and the appropriate buffer solution were introduced into the polarographic cell. The solution was then deaerated by bubbling a stream of hydrogen for 10 min. The calculated amount of stock solution was then introduced into the cell so that the final concentration was 10^{-4}M in 10 ml of 40% (v/v) ethanolic buffer.

Controlled Potential Electrolysis and Identification of the Products.—Mercury pool electrolysis was carried out 50% v/v ethanol–10^{-2}M-HCl solution (200 ml) and substance (Ia) (200 mg) taken as a typical example. The electrolysis cell was a 250-ml conical flask in which the reference, auxiliary electrodes, and the gas inlet were added by means of a cork. The potential was controlled by a Tutorial T6 transistorized potentiostat at −0.8 V *versus* s.c.e. (*i.e.* on the limiting current plateau of wave A). The progress of the electrolysis was followed by recording the decrease in current with time and the number of electrons was computed from *i*–*t* curves following the procedure outlined by Lingane[11] and found to be 4e. After disconnecting the electrolysis cell from the circuit, 1 ml of the resulting solution was withdrawn and the presence of aniline in this solution was revealed by a standard spot test.[12] The remaining reaction mixture was partially evaporated on a water-bath to half its volume, then allowed to cool to room temperature and extracted with ether. The ether layer was in turn evaporated. The oil obtained was treated with a few ml of ethanol and crystals separated and were recrystallized from diluted ethanol, m.p. 120 °C, $\nu_{max.}$ (KBr) 3 300 (NH_2), 3 130 (ring NH_2), 2 960 (CH), 1 770 (CO), 1 720 (CO), and 1 600 (NH) cm^{-1} (Found: C, 56.55; H, 4.7; N, 22.0. $C_9H_9N_3O_2$

requires C, 56.54; H, 4.71; N, 21.98%). The compound obtained was identified as *5-amino-1-phenylhydantoin*.

Determination of the Acid Dissociation Constants by Potentiometry.—The pK_a of our compounds (Table 2) were determined conventionally[13] by titrating a 5×10^{-4}M solution (50 ml; 1 : 1 C_2H_5OH–H_2O) of each compound against a standard 2×10^{-2}M-NaOH solution with a Pye–Unicam model 292 MK2 pH meter.

TABLE 1

5-Arylazo-1-phenyl-4-thiohydantoin derivatives (Ia—h)

			Analysis (%)							
			C		H		[N]		[S]	
Compound	M.p. (°C)	Yield (%)	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
(Ia)	261	90	60.8	60.9	4.05	4.0	18.9	19.0	10.8	10.7
(Ib)	263	91	62.0	61.9	4.5	4.6	18.05	18.0	10.3	10.3
(Ic)	250	90	62.05	61.8	4.5	4.4	18.05	18.1	10.3	10.4
(Id) *	265	92	54.45	54.4	3.35	3.4	16.95	16.9	9.7	9.7
(Ie) †	260	85	48.0	48.1	2.95	2.9	14.95	14.9	8.55	8.4
(If)	220	80	58.9	58.8	4.3	4.3	17.15	17.2	9.8	9.8
(Ig)	300	88	56.45	56.5	3.55	3.5	16.45	16.5	9.4	9.5
(Ih)	270	82	52.8	52.7	3.2	3.3	20.5	20.4	9.4	9.4

* Cl: calc. 10.74; found, 10.8%. † Br: calc. 21.33; found, 21.4%.

TABLE 2

Acid dissociation constants of 5-arylazo-1-phenyl-4-thiohydantoin derivatives (Ia—h) and 1-phenyl-4-thiohydantoin (II)

Compound	pK_a	Compound	pK_a
(Ia)	7.55	(Ie)	7.77
(Ib)	7.88	(If)	7.98
(Ic)	7.60	(Ig)	7.10
(Id)	7.53	(Ih)	7.30
		(II)	8.45

RESULTS AND DISCUSSION

Polarographic Behaviour of (Ia—g).—The polarograms of 10^{-4}M-(Ia—g) in 40% v/v ethanolic buffers are represented by those of (Ia) taken as typical example in Figure 1. In acid solutions of pH < 4 compounds (Ia—g) displayed a well defined polarographic wave a (*i ca.* 1.1 μA) the height of which was practically constant within the whole pH range (2—12). At pH > 4 a more negative wave b appeared with an i_l value equal to half that of wave a (i_l *ca* 0.55 μA); with further increases in pH the limiting current of wave b decreased in the form of a well defined dissociation curve[14] and vanished completely at pH ⩾ 8. The half-wave potential $E^a_{\frac{1}{2}}$ of wave a shifted towards negative potential values with the increase in pH of the solution. This shift is described by two linear segments as shown for compound (Ia), taken as a typical example, in Figure 2. The shifts of $E_{\frac{1}{2}}$ with pH for compounds (Ia—h) are compiled in Table 3 in the form of linear equations. The $E_{\frac{1}{2}}$–pH plots of the second wave *b* also revealed two linear segments intercepting at pH *ca.* 6 a value which is accord with the pK' values[14] (apparent polarographic dissociation constant, *i.e.* pH value corresponding to $i_l/2$) obtained for the i_l–pH curves (Figure 3). The half-wave potential of wave b in the first segment is little influenced by a change in hydrogen ion concentration and thus is practically independent of pH variation ($dE_{\frac{1}{2}}$/dpH *ca.* 0). Shifts of $E_{\frac{1}{2}}$ with the increase in pH for the second segment are given in Table 3. The more positive wave a is diffusion-controlled as shown by the linear dependence of i_l on concentration (0.5—3 × 10^{-4}M) at various pH values, and by the values x = 0.45—0.55 in $i_l = kh^x$ (h = mercury column height). Similarly, wave b was proved to be diffusion-controlled in the pH range in which i_l was

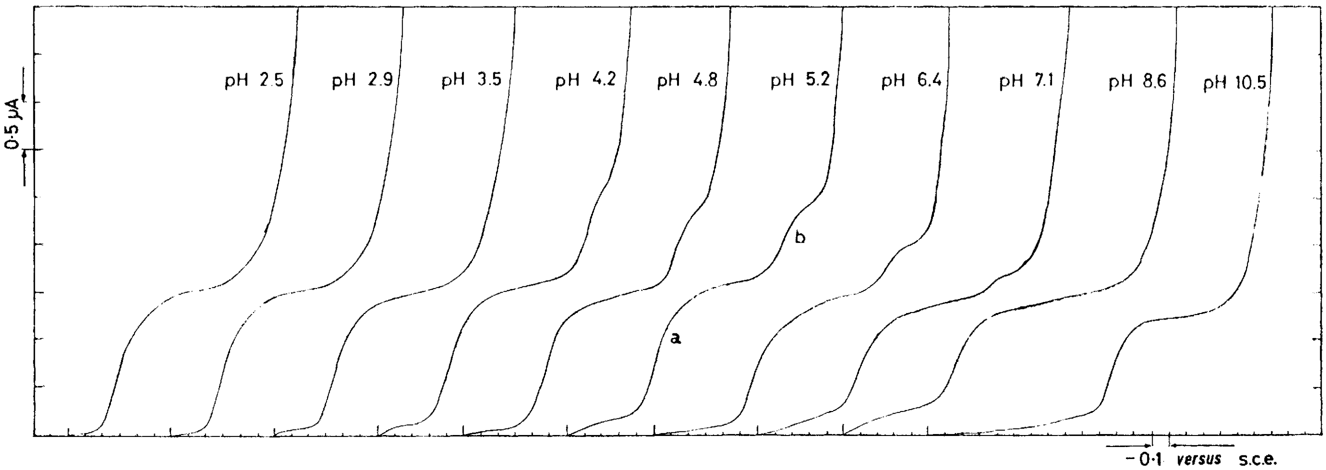


FIGURE 1 Schematic representation of the polarograms of 10^{-4}M-5-phenylazo-1-phenyl-4-thiohydantoin in 40% v/v ethanolic Britton–Robinson buffers. All curves start from zero potential

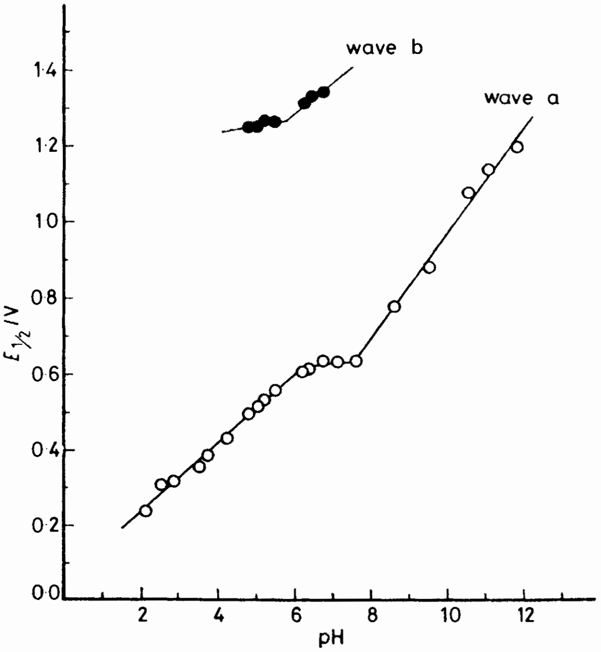


FIGURE 2 $E_{\frac{1}{2}}$–pH plot for the polarographic wave of 5-phenylazo-1-phenyl-4-thiohydantoin

practically constant (*i.e.* pH independent). Above pH 5 this wave was partly kinetically controlled (x 0.45). Logarithmic analysis of waves a and b at different pH values using the fundamental equation for polarographic waves [15] indicated that the two electrode processes proceed irreversibly; the slopes obtained are compiled in Table 3.

Polarographic Behaviour of (Ih).—In addition to waves a and b in the polarograms of (Ia—g), compound (Ih) showed an additional 4e irreversible diffusion-controlled wave c lying between waves a and b. The effect of pH on $E_{\frac{1}{2}}$ of the different waves is shown in Figure 4. The behaviour of the additional wave can be described by the linear equation (1). The data for the two other waves

$$E_{\frac{1}{2}} = -0.18 - 0.08 \text{ pH} \qquad (1)$$

are compiled in Table 3. Since the behaviour of this wave is comparable to that known for a m-nitro-group,[16] it is not unreasonable to attribute this extra wave to the reduction of the nitro-group to a hydroxylamine [equation (2)].[16]

$$-NO_2 + 4e^- + 4H^+ \xrightarrow{E_{\frac{1}{2}}} -NHOH + H_2O \qquad (2)$$

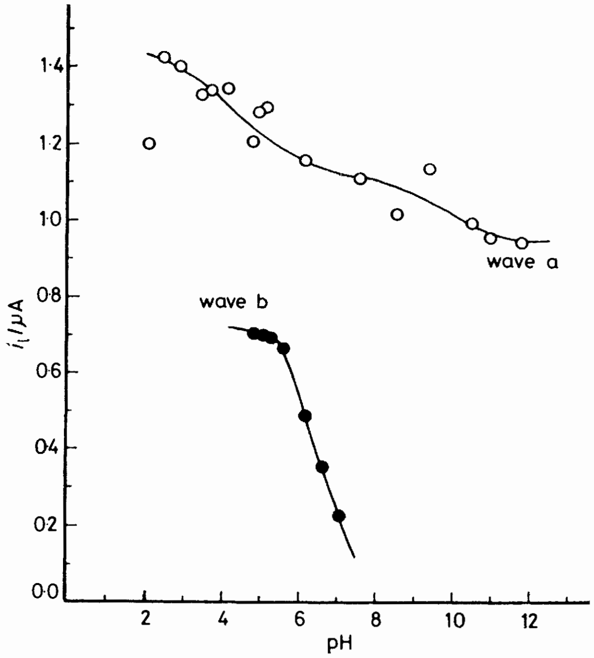


FIGURE 3 i_l–pH plot for the polarographic wave of 5-phenylazo-1-phenyl-4-thiohydantoin

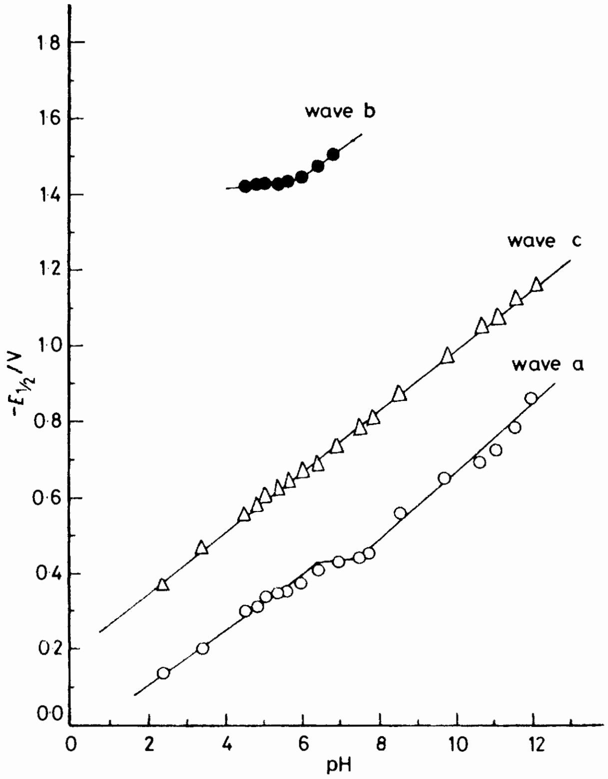


FIGURE 4 $E_{\frac{1}{2}}$–pH plots for the polarographic waves of 5-(m-nitrophenylazo)-1-phenyl-4-thiohydantoin

Polarographic Behaviour of Model Compound (II).—Under similar experimental conditions model compound (II) showed no polarographic wave in acid media of pH < 7.5. At pH values greater than 7.5 a wave started to appear which increased in height with the increase of pH and became well defined at pH > 10. As is clear from Figure 5, $E_{\frac{1}{2}}$ of this wave is pH-independent in the range of its appearance. The i_l–pH plot for this compound is illustrated in Figure 6. The increase of i_l with the increase of pH is in the form of a dissociation curve with a pK' value of 8.7.

Assignment of the Polarographic Waves of (Ia—h).—(1) In the more positive wave a the -N=N- moiety is the reduced species. (2) The more negative reduction step (wave b) corresponds to reduction of the molecule resulting from the reductive splitting of the -N=N- moiety. The following proof is given for these assignments. The shift of $E_{\frac{1}{2}}$ with increase of pH given in Table 3 is in good agreement with the reported values for the analogous azobenzene derivatives.[1-4] This is also confirmed by the fact that when c.p.e. experiments were carried out on this wave, the main products of electrolysis were 5-amino-1-phenylhydantoin (III) and aniline, a direct indication that the site attacked is the -N=N- group. The identification of the nitro-group in compound (Ih) as the source of the more negative wave is a further indication that the reducible species is in the azo and not in the hydrazone form. If this was not correct the nitro-wave would appear first (this is further confirmed by the Hammett relationship). That 5-amino-1-phenylhydantoin (III) is the product and not 5-amino-1-phenyl-4-thiohydantoin (IV) is reasonably explained by the fact that (IV) is hydrolysed under mild conditions to (III). This is confirmed by the fact that 2,4-dithiohydantoin derivatives are known to be easily hydrolysed at the 4-position in hydrochloric acid giving 2-thiohydantoin [17] derivatives thus indicating that the thiocarbonyl group in position 4 is very reactive. Scheme 1 provides an interpretation of these results.

TABLE 3

Polarographic data of 5-arylazo-1-phenyl-4-thiohydantoin derivatives (Ia–h)

	Wave a					Wave b [c]			
	$E_{\frac{1}{2}}$—pH					$E_{\frac{1}{2}}$—pH			
Compound	Segment 1 (pH 2—7)	Segment 2 (pH 8—12)	$RT/\alpha nF$ [a]	αn	pH [b]	Segment 2 (pH 5—7)	$RT/\alpha nF$	αn	pH [b]
(Ia)	$E_{\frac{1}{2}} = -0.06—0.091$ pH	$E_{\frac{1}{2}} = +0.57—0.143$ pH	0.150	0.394	6.4	$E_{\frac{1}{2}} = -0.78—0.088$ pH	0.066	0.895	6.2
(Ib)	$E_{\frac{1}{2}} = +0.08—0.091$ pH	$E_{\frac{1}{2}} = +0.75—0.143$ pH	0.161	0.367	6.3	$E_{\frac{1}{2}} = -0.60—0.100$ pH	0.098	0.603	5.7
(Ic)	$E_{\frac{1}{2}} = -0.18—0.077$ pH	$E_{\frac{1}{2}} = +1.18—0.200$ pH	0.170	0.348	5.9	$E_{\frac{1}{2}} = +0.53—0.100$ pH	0.071	0.832	6.4
(Id)	$E_{\frac{1}{2}} = +0.03 - 0.080$ pH	$E_{\frac{1}{2}} = +0.96—0.167$ pH	0.179	0.330	6.5	$E_{\frac{1}{2}} = -0.59—0.100$ pH	0.066	0.895	5.7
(Ie)	$E_{\frac{1}{2}} = +0.06—0.083$ pH	$E_{\frac{1}{2}} = +0.79—0.167$ pH	0.162	0.365	6.4	$E_{\frac{1}{2}} = -0.59—0.100$ pH	0.095	0.622	5.7
(If)	$E_{\frac{1}{2}} = -0.04—0.091$ pH	$E_{\frac{1}{2}} = +0.65—0.200$ pH	0.180	0.328	5.9	$E_{\frac{1}{2}} = -0.75—0.100$ pH	0.070	0.844	6.9
(Ig)	$E_{\frac{1}{2}} = +0.14—0.86$ pH	$E_{\frac{1}{2}} = +1.05—0.25$ pH	0.145	0.408	6.4	$E_{\frac{1}{2}} = -0.75—0.100$ pH	0.102	0.579	5.7
(Ih)	$E_{\frac{1}{2}} = +0.04—0.071$ pH	$E_{\frac{1}{2}} = +0.25-0.167$ pH	0.167	0.354	6.0	$E_{\frac{1}{2}} = -0.97—0.08$ pH	0.067	0.882	6.0

[a] Slope of logarithmic analysis. [b] Individual pH value at which logarithmic analysis was carried out. [c] $E_{\frac{1}{2}}$ in the first segemnt of wave b is pH-independent ($dE_{\frac{1}{2}}/d$pH *ca.* 0).

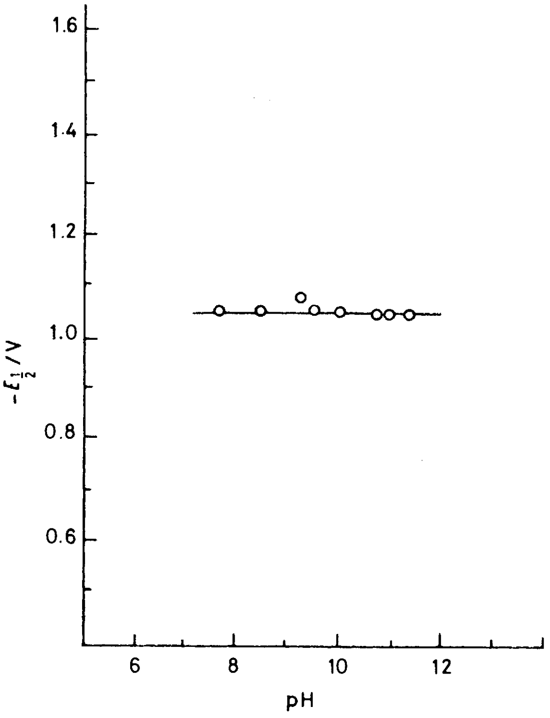


FIGURE 5 $E_{\frac{1}{2}}$–pH plot for the polarographic wave of the model compound 1-phenyl-4-thiohydantoin

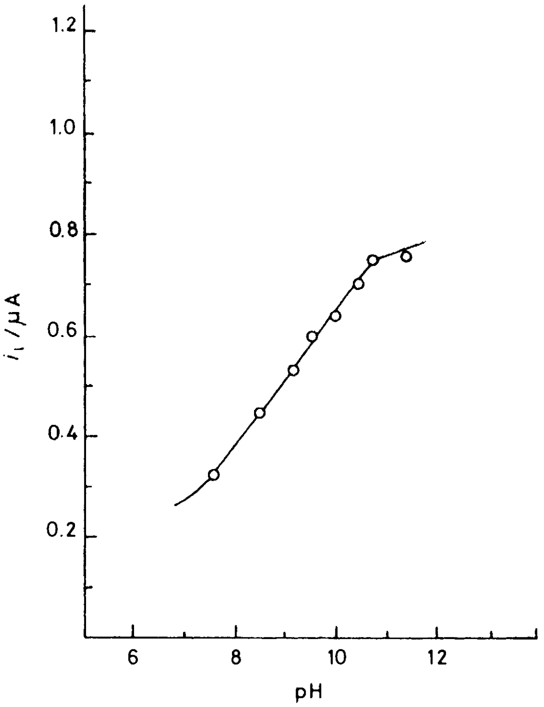
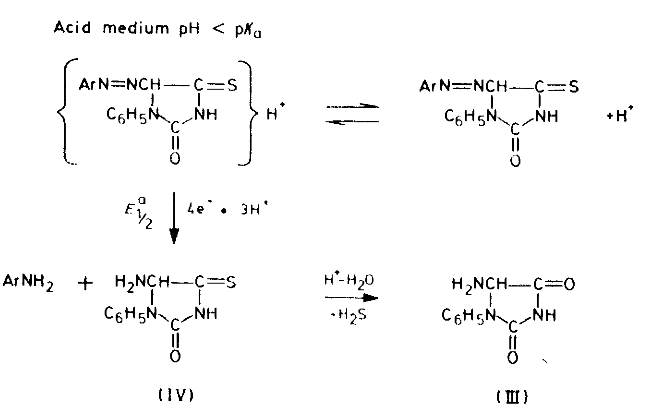


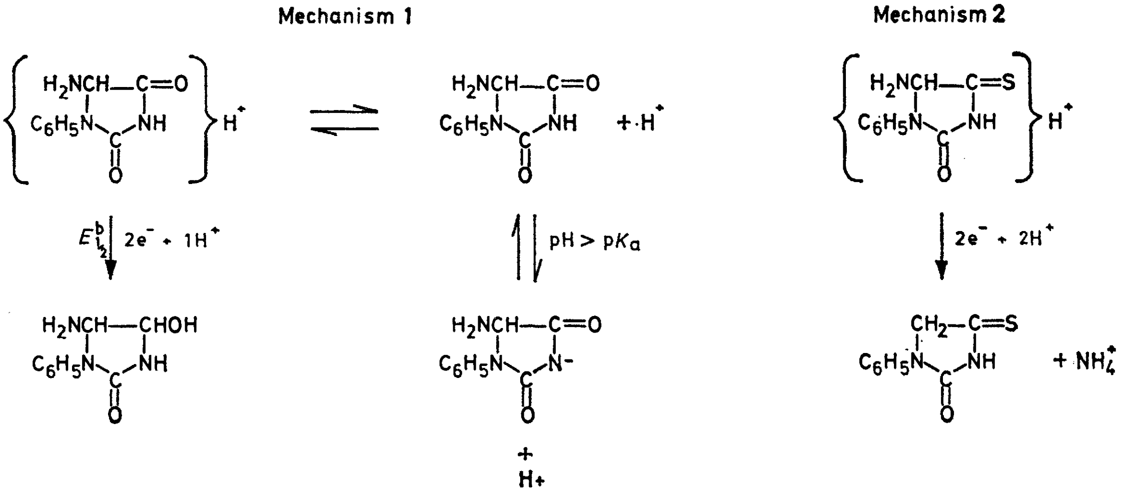
FIGURE 6 i_l–pH plot for the polarographic wave of the model compound 1-phenyl-4-thiohydantoin

At first glance two mechanisms 1 and 2 (Scheme 2) can be attributed to the electrode process occurring in wave b. Mechanism 2 is rejected for the following reasons. When c.p.e. was carried out on wave b no ammonia could be detected. Also, if mechanism 2 took place, compound (II) would be a main product of electrolysis and hence the polarograms will consist of three waves in alkaline media [*cf.* polarographic behaviour of (II)]. This is not the case since a third wave did not make an appearance. Thus mechanism 1 most probably explains the results for wave b. Compounds containing the –CO–NH–CO– structure have been reported to be reduced in a similar way.[18]



SCHEME 1

The fact that in alkaline medium, *i.e.* at pH > pK_a, only wave a is observed is because in these media compounds (Ia—h) exist as stabilized anions in which the negative charge is distributed over the CS, N, and CO functions rendering the molecule electron repelling. This also explains why wave b disappears in alkaline media. Additional support for our electroreduction scheme was found to be necessary. Thus it appeared mandatory to study the effect of substituents on the reaction site of these molecules. The constant value of the transition coefficient (αn),[19] a prerequisite for quantitative study of the effects of substituents, was ascertained by examination of the data in Table 3. The value was found to be practically constant at individual pH values. The most reliable $E_{\frac{1}{2}}$ values at selected pH have been correlated with different Hammett constants.[20] Statistical treatment of the data was carried out using Jaffé calculations[21] (Table 4). Representative $E_{\frac{1}{2}}$–σ plots are illustrated in Figure 7. As is clear from these plots and the data in Table 4 good linearity is obtained. Above pH *ca* 7 the correlation is weak probably due to the fact that at the vicinity of these pH values (*i.e.* approximate pK_a values) the studied compound is in the form of a



SCHEME 2

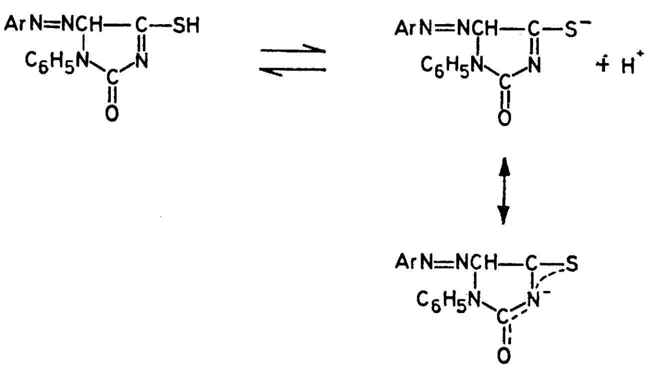


TABLE 4

Statistical treatment of $E_{\frac{1}{2}}$-σ data

	Wave a								
	σ			σ_0			σ^+		
pH	ρ	r	s.d.	ρ	r	s.d.	ρ	r	s.d.
4.8	0.266	0.807	±0.069	0.224	0.586	±0.096	0.207	0.836	±0.084
6.9	0.244	0.869	±0.050	0.239	0.736	±0.068	0.184	0.876	±0.0048
7.85	0.165	0.514	±0.098	0.268	0.722	±0.079	0.136	0.569	±0.094
	Wave b								
5.8	0.104	0.363	±0.069	0.163	0.383	±0.0681	0.072	0.377	0.068
6.6	0.091	0.357	±0.065	0.093	0.245	±0.0640	0.062	0.366	0.061

stabilized anion in which the negative charge is delocalized on the CO, N, and CS groups. That the half-wave potential values of wave b are weakly correlated and are practically independent of the substituent can be readly understood from the fact that wave b corresponds to reduction of the molecule resulting from the reductive cleavage of the azo-moiety (wave a), thus forming the heterocyclic molecule and a substituted aniline. In this way the substituent is separated from the reducible centre and has negligible effect on the reducible centre of the heterocyclic portion of the molecule. That the nitro-group is reduced after wave a is confirmed by the fact that the point for m-NO_2 lies on the $E_{\frac{1}{2}}$-σ curve but not that for m-NHOH, an indication that the reducible centre is influenced by a nitro- and not a hydroxylamine-group. The opposite is the case for wave b since the nitro-wave lies between the more positive wave a and the negative wave b.

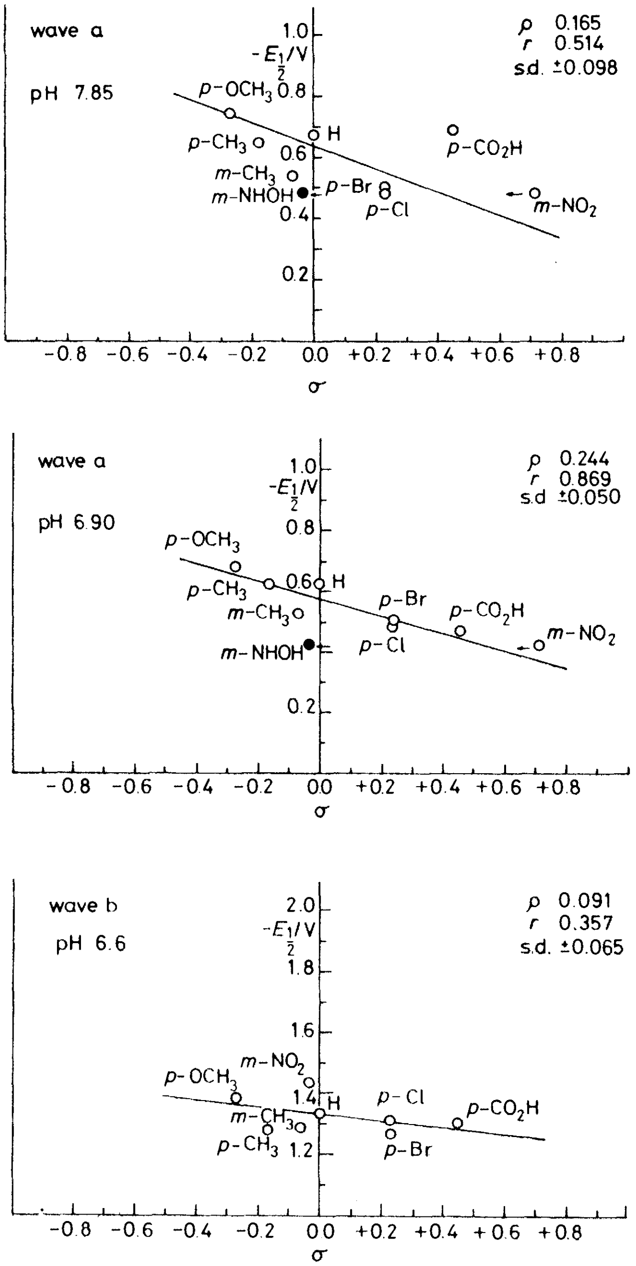


FIGURE 7 $E_{\frac{1}{2}}$-σ Relation for 5-arylazo-1-phenyl-4-thiohydantoin derivatives at different pH values

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