Electroreduction of a Series of 2-Benzoylamino-5-(1-cyano-2-arylvinyl)-1,3,4-thiadiazoles

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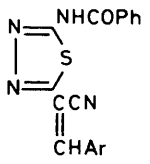
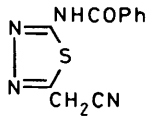
The electrochemical reduction of a series of 1,3,4-thiadiazoles in alcoholic buffered media has been investigated. The mechanism of the electrode processes is suggested and discussed. A cyclopentene carboxylic acid product is formed through a Ziegler–Throp reaction; the thiadiazole ring is inactive. Confirmation of the mechanism *via* c.p.e., spectrophotometric analyses, and the study of Hammett's relations is presented.

The 1,3,4-thiadiazole ring has received considerable attention due to its wide biological and pharmaceutical applications. Derivatives of this ring show antitumour, antitrypanosomal,[1] antibilharzial,[2] antibacterial, and tuberculostatic[3] activities and have been used in the treatment of leukaemia.[4] They cause ultrastructural changes of the thyroid gland,[5] inhibit stomach secretions,[6,7] and decrease the intraocular pressure of the eye.[8,9] Further, they form complexes to exert a direct effect on glycogenesis and glycogenolysis in the body, as they possess inhibitory power towards human C-type carbonic anhydrase (HCAC) enzyme.[8,10,11]

In the present investigation the polarographic behaviour of a series of 2-benzoylamino-5-(1-cyano-2-arylvinyl)-1,3,4-thiadiazole derivatives (**1a—d**) in alcoholic buffered media has been examined in order to elucidate the mechanism of electroreduction at the dropping-mercury electrode (d.m.e.). For comparison a model compound 2-benzoylamino-5-cyanomethyl-1,3,4-thiadiazole (**2**) was also studied under similar conditions.



(1)



(2)

a; Ar = Ph
b; Ar = *p*-Cl-C_6H_4
c; Ar = *p*-MeO-C_6H_4
d; Ar = *p*-NO_2-C_6H_4

Experimental

Syntheses.—Compounds (**1a—d**) and (**2**) were prepared according to literature procedures.[12] The precipitated products were filtered off and crystallized from the appropriate solvent as given in Table 1.

Polarography.—(a) *Apparatus.* Polarograms were recorded with a Metrohm Polarecord E506 with Polarography Stand E505 using Ag/AgCl reference electrode. The capillary possessed the following characteristics in 0.1 M-KNO_3 at zero applied potential: t = 3.9 s drop^{-1}, m = 1.54 mg s^{-1} for h = 52 cm. The pH measurements were carried out with an Iskra Kranj pH-meter MA5701.

(b) *Solutions and measurements.* In all experiments a final thiadiazole concentration of 10^{-4}M in 50% v/v ethanolic buffer was polarographed. Britton–Robinson buffers[13] were used as supporting electrolytes. The half-wave potentials ($E_{\frac{1}{2}}$) were measured graphically and expressed *versus* the Ag/AgCl reference electrode with an accuracy of ±0.005 V.

Determination of the Apparent Acid Dissociation Constants by Spectrophotometric Measurements.—Spectrophotometric measurements were carried out using a Pye–Unicam 1800 spectrophotometer supplemented with a program controller automatic linear recording unit. The runs in the u.v.–visible range were carried out on 4 × 10^{-5}M of the studied compound in 50% v/v alcoholic Britton–Robinson buffer solutions. Spectrophotometric measurement was recorded as a function of the pH of the solution. The pK_a was then calculated using the graphical correlation between pH and absorbance and using the appropriate equations.[14]

Following-up Controlled-potential Electrolysis (c.p.e.).—C.p.e. experiment on 10^{-4}M-(**1a**) was performed in acid medium (0.03

Table 1. Physical characteristics of compounds (**1a—d**) and (**2**)

Compd.	Molecular formula	M.p. (°C)	Solvent of crystallization	Yield (%)	Analysis (%) Found C	H	N	S	Calculated C	H	N	S
(**1a**)	$C_{18}H_{12}N_4OS$	265—268	AcOH	80	64.9	3.5	16.6	9.4	65.1	3.6	16.8	9.6
(**1b**)	$C_{18}H_{11}ClN_4OS$	>290	AcOH	76	58.5	3.1	15.3	8.5	58.7	3.0	15.2	8.7
(**1c**)	$C_{19}H_{14}N_4O_2S$	275	DMF–Ethanol	83	62.9	3.8	15.4	8.9	63.0	3.9	15.5	8.8
(**1d**)	$C_{18}H_{11}N_5O_3S$	>300	DMF	82	57.3	2.8	18.4	8.6	57.3	2.9	18.6	8.5
(**2**)	$C_{11}H_8N_4OS$	235	AcOH	85	53.9	3.4	22.6	12.7	54.1	3.3	22.9	13.1

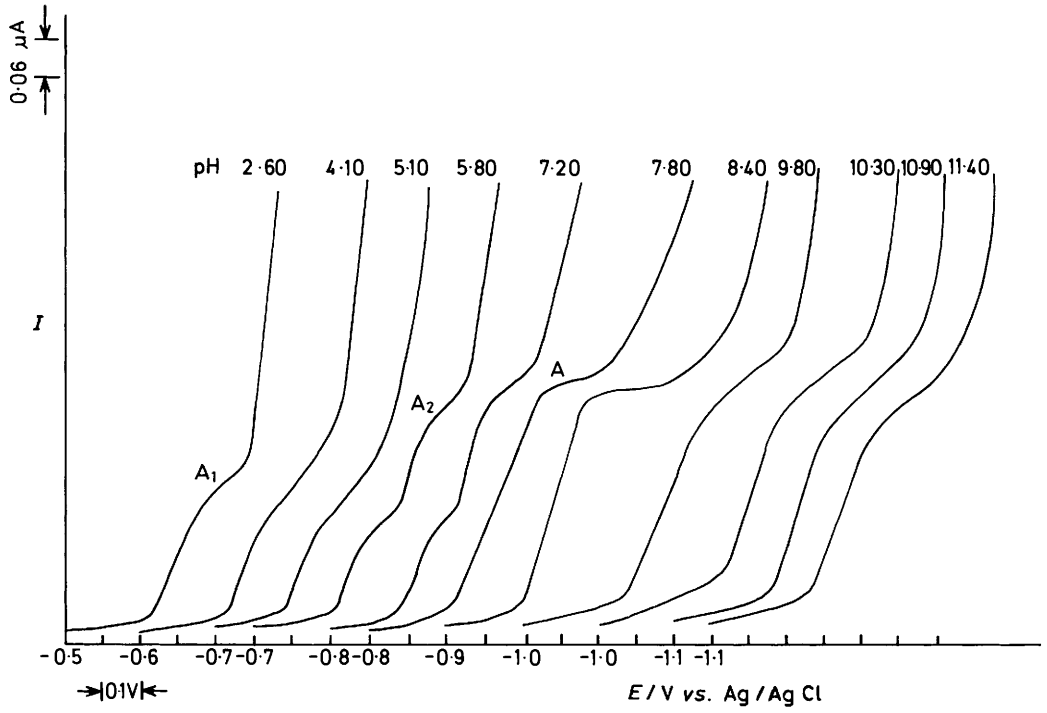


Figure 1. Polarograms of 10^{-4}M-(**1a**) in 50% (v/v) ethanolic Britton–Robinson buffers

M-HCl). The recorded curves show two waves, A_1 and a more negative wave, with $E_{\frac{1}{2}}$ values equal to -0.75 V and -1.01 V respectively. The electrolysis was carried out at a fixed potential of -0.81 V *vs.* Ag/AgCl, *i.e.* on the limiting-current plateau of the first wave A_1. The potential was controlled by a Tutorial T6 transistorized potentiostat. The ratio i_1/i_2 of the first and second wave was found to decrease as the electrolysis proceeds. Since the polarograms of this compound in buffered solutions did not show the second more negative wave, with a pH-independent i_1, it was assumed that this wave is due to hydrogen evolution. Moreover, this second wave cannot be a characteristic reduction wave of (**1a**) as with time no hydrolysis of this compound occurred. The limiting current of wave A_1 decreases as the electrolysis proceeds until it reaches its minimum value after 30 min.

Preparative Electrolysis.—Mercury-pool electrolysis was carried out on *ca.* 22 mg of (**1a**) in the appropriate supporting electrolyte (90 ml) of pH 2.60 [dimethylformamide (45 ml)–EtOH (15 ml)–M-HCl (30 ml; 0.031 M)]. The potential was adjusted at -0.81 V *vs.* Ag/AgCl. After complete reduction, the reaction mixture (pH 2.16) was evaporated *in vacuo* until dryness. The residue was dissolved in water then extracted with $CHCl_3$, which was by turn evaporated to give a brown powder, which was washed several times with light petroleum (b.p. 60—80 °C) to give a crystalline compound (9.46 mg, 43%), m.p. 160 °C; $\nu_{max.}$(KBr) 3 380br, 3 130 (NH), 2 900 (CH), and 1 650 (CO) cm^{-1}; *m/z* 685, 401, 334, 294, 245, 201, 122, 105, and 91.

Presentation of Data

The polarograms of 10^{-4}M-(**1a**) are illustrated in Figure 1. A single polarographic wave A_1 appears at pH < 5.5, and as the pH of the solution increases, another wave A_2 of approximately equal height appears in the pH range 5.5—7.5. The two waves merge near pH 7.5 to form a pH-dependent wave A whose diffusion current nearly equals the sum of those of waves A_1 and A_2. At pH ≥ 8.8 the i_1 of wave A starts to decrease in the form of a dissociation curve. The variation of $E_{\frac{1}{2}}$ and i_1 with pH is given in Figures 2(a) and 2(b) respectively. Half-wave potentials of waves A_1, A_2, and A are pH dependent, shifting towards more negative potentials with increasing pH. This shift of $E_{\frac{1}{2}}$ with pH for compounds (**1a**—**d**) is compiled in Table 2. Plots of $E_{\frac{1}{2}}$–pH showed mainly one segment for waves A_1 and A_2, in which $E_{\frac{1}{2}}$ is sensitive to a change in pH, while two segments for A indicate that only the first one is sensitive to pH change. The pH values at the intersection point of the segments of A_1 and the first segment of A are practically equal to the pK_a values obtained spectrophotometrically (see Table 3). Segments 1 and

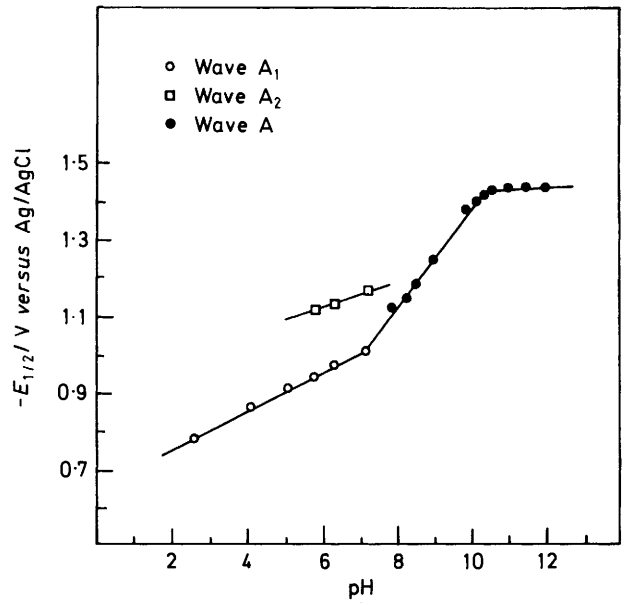


Figure 2(a). $E_{\frac{1}{2}}$–pH plots of the polarographic waves of 10^{-4}M-(**1a**) in 50% (v/v) ethanolic Britton–Robinson buffers

Table 2. Linear representation of $E_{\frac{1}{2}}$–pH dependence for waves A_1, A_2, and A of 2-benzoylamino-5-(1-cyano-2-arylvinyl)-1,3,4-thiadiazoles (**1a**—**d**)

	$\Delta E_{\frac{1}{2}}/\Delta$pH (mV/pH)		
Compd.	Wave A_1	Wave A_2	Wave A
(**1a**)	$E_{\frac{1}{2}} = -0.650 - 0.050$ pH	$E_{\frac{1}{2}} = -0.95 - 0.031$ pH	$E_{\frac{1}{2}} = -0.140 - 0.123$ pH
(**1b**)	$E_{\frac{1}{2}} = -0.665 - 0.043$ pH	$E_{\frac{1}{2}} = -0.78 - 0.050$ pH	$E_{\frac{1}{2}} = -0.320 - 0.095$ pH
(**1c**)	$E_{\frac{1}{2}} = -0.740 - 0.050$ pH	$E_{\frac{1}{2}} = -0.725 - 0.071$ pH	$E_{\frac{1}{2}} = -0.280 - 0.115$ pH
(**1d**)*			$E_{\frac{1}{2}} = -0.100 - 0.140$ pH

* The *p*-NO_2 derivative shows only wave A ($A_1 + A_2$).

Table 3. Spectrophotometric and polarographic data of compounds (**1a**—**d**) and (**2**)

	Spectrophotometric data						Polarographic data				
	Maxima/nm			Isosbestic point/nm			Intersection (1)	Intersection (2)	Number of protons		
Compd.						pK_a	pH	pH	Wave A_1	Wave A_2	Wave A
(**1a**)	294	342	386	312	360	6.0	7.10	10.40	1.10	0.98	1.11
(**1b**)	298	342	390	314	361	6.08	7.0	10.90	0.98	1.02	0.97
(**1c**)	314	366	394	332	382	6.1	7.10	10.60	1.02	—	1.23
(**1d**)	—	358	410	—	382	6.43	—	10.20	—	—	—
(**2**)	270	310	—	288	—	6.375	—	—	—	—	—

Table 4. Polarographic characteristics of 2-benzoylamino-5-(1-cyano-2-arylvinyl)-1,3,4-thiadiazoles (**1a**—**d**)

Compd.	pH	$-E_{\frac{1}{2}}$/V *vs.* Ag/AgCl	i_d/μ A	$RT/\alpha nF$	n	$D \times 10^{-6}$ cm^2/s
(**1a**)	7.80	1.13	0.378	0.1125	2	2.5440
	8.20	1.15	0.378	0.118	2	2.5440
	8.40	1.175	0.372	0.108	2	2.4639
(**1b**)	7.60	1.065	0.320	0.106	2	1.8232
	7.95	1.080	0.340	0.110	2	2.0582
	8.30	1.110	0.355	0.100	2	2.2438
(**1c**)	7.80	1.195	0.310	0.096	2	1.7110
	8.20	1.21	0.310	0.096	2	1.7110
	8.40	1.22	0.300	0.092	2	1.6024
(**1d**)	7.40	1.17	0.363	0.048	2	2.3461
	9.70	1.48	0.400	0.070	2	2.8487
	10.00	1.50	0.373	0.063	2	2.4771

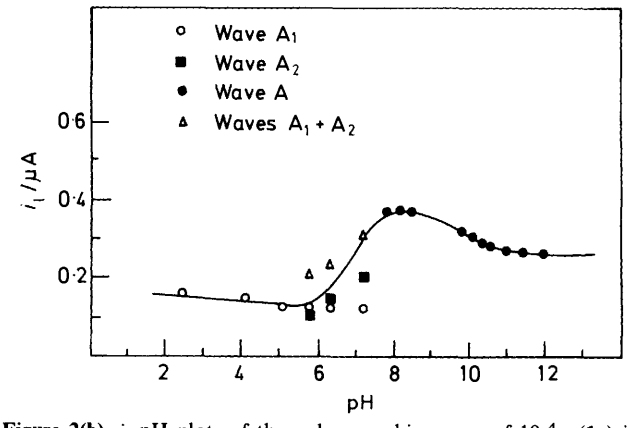


Figure 2(b). i_l–pH plots of the polarographic waves of 10^{-4}M-(**1a**) in 50% (v/v) ethanolic Britton–Robinson buffers

2 of wave A intercept at pH values equal to pK'. Cyclic voltammograms on the different waves at different pH values indicated that the processes are irreversible in nature (Figure 3). Analysis of the waves through the study of the effect of varying concentration and mercury-height on the limiting current (i_l) indicated that they are mainly controlled by diffusion in the range where i_l is practically pH independent. In contrast compound (**1d**) showed, in addition to wave A displayed in the polarograms of (**1a**—**c**), two additional four- and two-electron irreversible diffusion-controlled waves B and C respectively. Wave B appears at less negative potentials while C at more negative potentials as compared to wave A. The behaviour of these two additional waves can be described by the following linear equations:

$$E^{B}_{\frac{1}{2}} = +0.04 - 0.056 \text{ pH}$$

$$E^{C}_{\frac{1}{2}} = +0.10 - 0.135 \text{ pH}$$

Since the behaviour of wave B is similar to that of the well known *p*-nitro group,[15] it is reasonable to attribute this extra wave to the reduction of the nitro group to give the hydroxylamine[16] [equation (1)]. Wave C can be attributed to further reduction of the hydroxylamine to give the amino group[15] [equation (2)].

$$-NO_2 + 4\bar{e} + 4H^+ \longrightarrow NHOH + H_2O \quad (1)$$

$$-NHOH + 2\bar{e} + 2H^+ \longrightarrow NH_2 + H_2O \quad (2)$$

Absorption Spectra of Compounds (**1a**—**d**) *and* (**2**).—In the pH range 1.99—5.34 the absorption spectra of compound (**1a**) (4×10^{-5}M) are characterized by a strong band with $\lambda_{max.}$ at 342 nm and a weak band with $\lambda_{max.}$ at 278 nm. These are due to the absorption of the non-ionized form, liable to exist at low pH values. In the pH range 5.34—7.20 a red shift occurs giving rise to a band with $\lambda_{max.}$ at 354 nm and a shoulder at *ca.* 294 nm. With increasing pH the two bands are further red-shifted, having $\lambda_{max.}$ at 386 and 294 nm respectively. The absorption spectra are characterized by the presence of two isosbestic points at 312 and 360 nm respectively within the whole pH range (see Table 3). The apparent ionization constant was calculated and the mean pK_a for each compound was compiled in Table 3. The absorption spectra of the model compound showed one band at 270 nm in the pH range 1.99—6.15. At pH 6.15—11.76 the band is red-shifted, acquiring a $\lambda_{max.}$ at 310 nm. One isosbestic point at 288 nm is observed within the whole pH range.

Table 5. Results of statistical treatment of $E_{\frac{1}{2}}$ data for 2-benzoylamino-5-(1-cyano-2-arylvinyl)-1,3,4-thiadiazole derivatives (**1a—d**)

pH	Wave	No. of points	r^a	ρ^b	s.d.^{c}	r	ρ	s.d.	r	ρ	s.d.
3	A_1	3	0.926	0.203	±0.020	0.795	0.219	±0.033	0.968	0.088	±0.014
5	A_1	3	0.969	0.212	±0.013	0.872	0.239	±0.027	0.993	0.090	±0.006
6.5	A_1	3	0.982	0.242	±0.012	0.898	0.278	±0.027	0.998	0.102	±0.004
	A_2	3	0.995	0.191	±0.005	0.933	0.224	±0.017	1.000	0.080	±0.001
7.5	A	4	0.935	0.145	±0.021	0.935	0.206	±0.021	0.974	0.075	±0.013
8.0	A	4	0.954	0.165	±0.020	0.941	0.245	±0.023	0.988	0.085	±0.010
8.5	A	4	0.971	0.188	±0.018	0.982	0.270	±0.014	0.984	0.095	±0.013
9.0	A	4	0.970	0.206	±0.020	0.989	0.298	±0.012	0.976	0.103	±0.018
9.5	A	4	0.967	0.225	±0.023	0.992	0.327	±0.012	0.967	0.112	±0.023
10.0	A	4	0.968	0.245	±0.024	0.994	0.356	±0.011	0.965	0.122	±0.026

^{a} Correlation coefficient. ^{b} Slope. ^{c} Standard deviation.

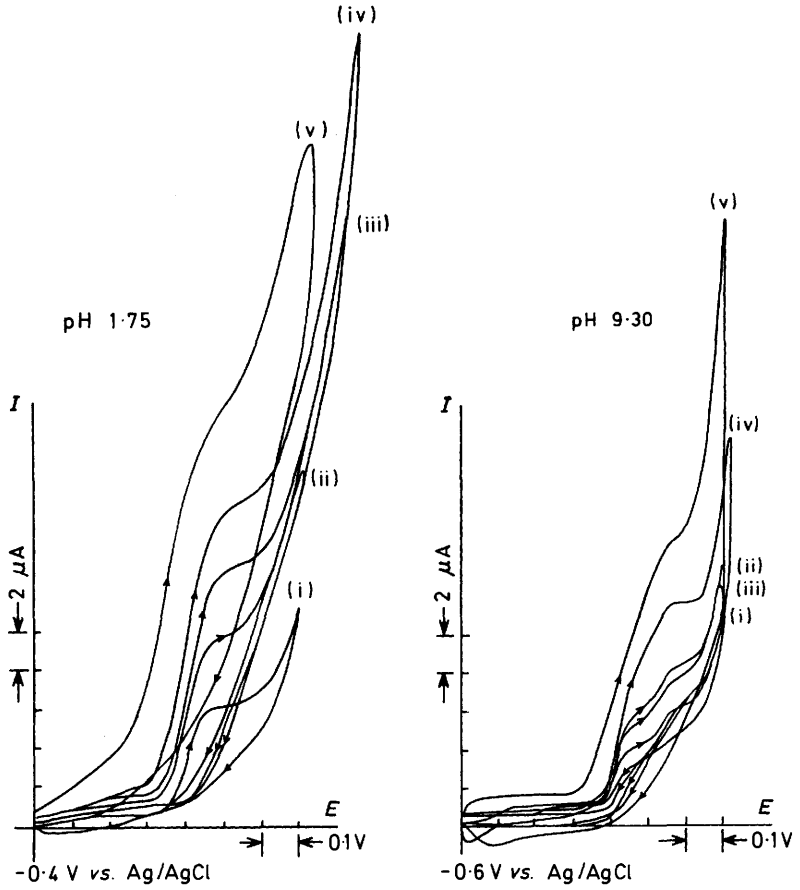
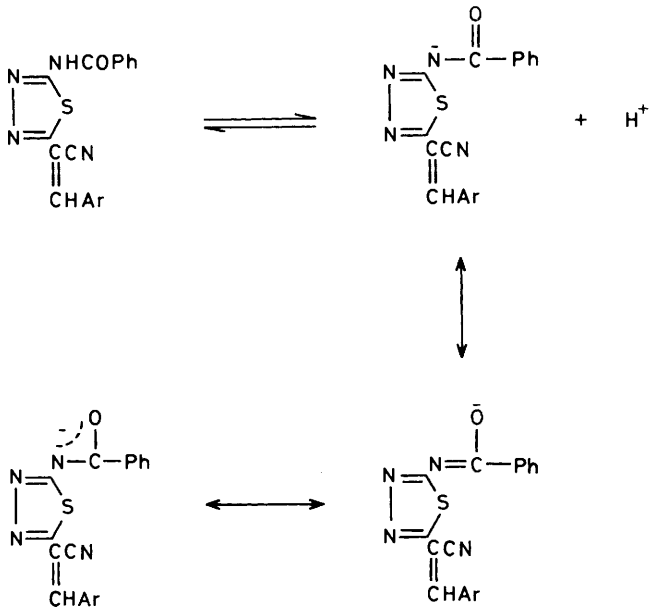


Figure 3. Cyclic voltammograms of 3.33×10^{-4}M-(**1a**). (i) 20 mV s^{-1}; (ii) 50 mV s^{-1}; (iii) 100 mV s^{-1}; (iv) 200 mV s^{-1}; (v) 500 mV s^{-1}

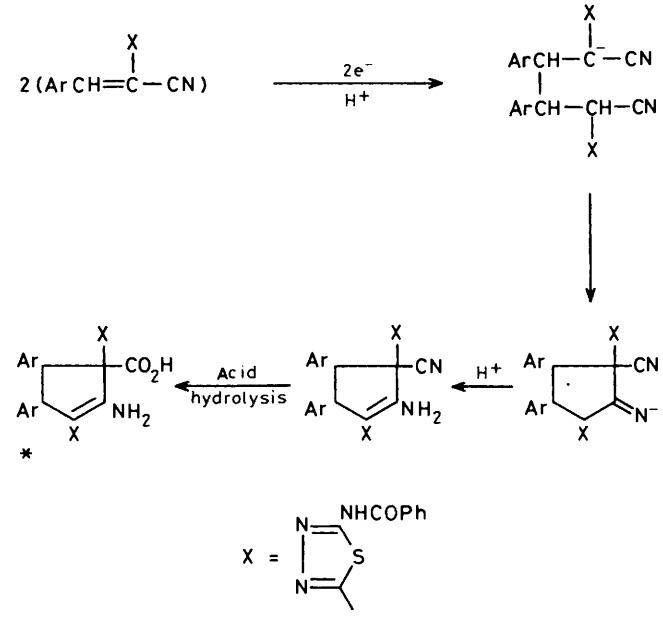
Since all the compounds (**1a—d**) have practically constant pK_a values ranging from 6.0—6.43 (see Table 3), it is clear that there is no dependence of ionization on substituent effects. Hence, the ionizable centre can be considered far from the aryl group, and this is confirmed through the fact that the model compound (**2**) gave the same pK_a value.

Mechanism of Reduction.—At first glance, the limiting current values showed that the overall process A is a two-electronic process. Consequently, it could be concluded that A_1 and A_2 are monoelectronic processes. However, it was found to be misleading to form conclusions from the general polarographic behaviour of these compounds, since the $E_{\frac{1}{2}}$ values, wave-shape, and position could lead to a variety of indications as to whether the carbonyl group is involved, the benzylidene linkage or the thiadiazole ring itself. Thus, it was necessary to run the polarograms of the model compound (**2**) under the same experimental conditions. It was found that no wave was displayed by (**2**), indicating that neither the carbonyl group nor the thiadiazole ring is electroactive.* From the foregoing results and based on the separated main c.p.e. product (*cf.* Experimental) one can propose that Scheme 2 represents the

* Conflicting scattered results based on assumptions and probabilities were traced in the literature.[18–20]



Scheme 1.



Scheme 2.

electroreduction of the 1,3,4-thiadiazole compounds in acid media. This mechanism is very similar to one previously reported by Wawzonek *et al.*[17].

The segmentation of $E_{\frac{1}{2}}$–pH plot [Figure 2(a)] indicates the participation of a proton in the acid–base equilibria prior to or in the electrochemical process itself. Thus, using the following equation:[21]

$$dE_{\frac{1}{2}}/dpH = 2.3pRT/\alpha nF$$

where p is the number of protons and αn is obtained from the slopes of logarithmic analysis. These values are determined for

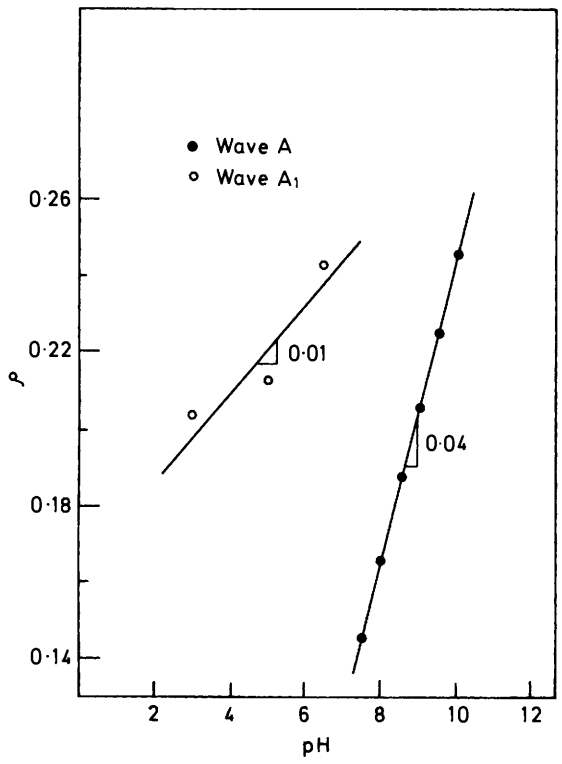


Figure 4. Variation of ρ with pH for (**1a**—**d**)

the first segments of waves A_1, A_2, and A. Accordingly, it is not unreasonable to assume a preprotonation of the molecule followed by its reduction in the sequence described in Scheme 2. Further confirmation of the proposed mechanism involved a study of Hammett's linear relationship of $E_{\frac{1}{2}}$ *versus* different σ sets[22,23] at various pH values. Statistical treatment of the data[24] indicated that the best correlations are those with σ, and σ^0 values (Table 5). From the slopes ρ one can deduce the strong dependence of $E_{\frac{1}{2}}$ on values for all sets of waves, confirming the fact that the substituted aryl group affects the reduction centre by both inductive and mesomeric effects. The variation of the reactivity parameter with pH is illustrated in Figure 4. The parameter ρ varies with an increase in pH and this can be rationalized by the fact that substituent effects predominate in alkaline medium due to the presence of compounds (**1a**—**d**) as anions in which the negative charge is delocalized over the entire molecule.

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Received 23*rd May* 1985; *Paper* 5/868