STRUCTURE OF THE PRODUCTS OF COUPLING OF SUBSTITUTED ETHYLIDENE MALONONITRILE WITH ARYLDIAZONIUM SALTS: POLAROGRAPHIC AND ACID DISSOCIATION MEASUREMENTS

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The structure of products of coupling of (α-ethoxycarbonyl-β-amino)ethylidene malononitrile (*Ia*) and (α-cyano-β-amino)ethylidene malononitrile (*Ib*) with aromatic diazonium salts could be established to be the corresponding hydrazone *IIa* (α-ethoxycarbonyl-α-phenylhydrazono-β-amino)ethylidene malononitrile and *IIb* (α-cyano-α-*p*-bromophenylhydrazono-β-amino)ethylidene malononitrile, via inspection of acid dissociation constants and the electrochemical behaviour of these products. *IIa* and *IIb* showed $pK_a \approx 6$ which is comparable to that of 2-phenylhydrazono-3-iminobutyronitrile (*IV*). The polarograms were found to be similar and consisted mainly of 4e reduction wave characteristic for hydrazones; also similar to the model hydrazone *IV*. The behaviour of 1-(*p*-methoxyphenyl)-3,5-dicyano-4-amino-6-iminopyridazine (*IIIb*) was found to be totally different. It did not reveal any potentiometrically traceable ionization step in aqueous media. Moreover its polarograms were totally different and consisted of two 2e waves. The more positive was $E_{1/2}$–pH dependent and the more negative was $E_{1/2}$–pH independent. Both waves were assigned for saturation of exocyclic and endocyclic C=N linkage. The mechanism of the electrode processes is also discussed.

Sometime ago Elnagdi et al.[1–6] reported the synthesis of pyridazines of type *III* via coupling of *I* with aromatic diazonium salts (Scheme 1) and subsequent cyclization of the coupling products. During this work they observed that the hydrazones *IIa* are resistant to cyclization. In light of this observation Mittelbach[7] has reported that *IIa* cyclizes as soon as it is formed in reaction medium to form *IIIa*. This suggestion was later rejected by Elnagdi et al.[8] based on ^{13}C NMR evidence. However, it seems to us that the reported ^{13}C NMR data do not permit unambiguous attribution to one of the two structures, *IIa* and *IIIa* as the reported data[8] for *IIa* can be interpreted for *IIIa*. For this

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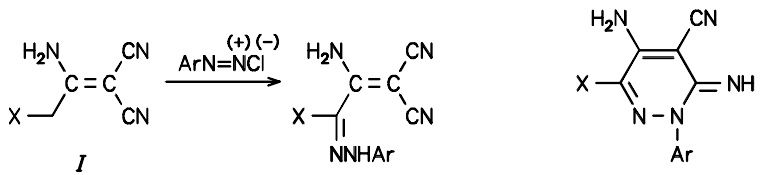
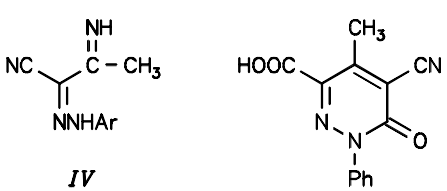
reason we have investigated the acidity and polarographic reduction of some derivatives of *II* and compared it to that of hydrazone *IV* and the pyridazines *IIIb* and *V*.



Ia, X = CO_2Et
Ib, X = CN

IIa, X = CO_2Et
IIb, X = CN, Ar = *p*-BrC_6H_4
IIc, X = CN, Ar = *p*-$CH_3OC_6H_4$

IIIa, X = CO_2Et
IIIb, X = CN, Ar = *p*-$CH_3OC_6H_4$



SCHEME 1

EXPERIMENTAL

Syntheses

Compounds *IV* and *V* were prepared utilizing reported procedures by Elnagdi et al.[1]. Compounds *IIa* and *IIb* were prepared via coupling of *Ia* and *Ib* with the appropriate aromatic diazonium salts utilizing procedures similar to those reported by Elnagdi et al.[1]. The characteristic of obtained products were found to be identical with those published earlier[8]. Compound *IIIb* was prepared via heating *IIc* in acetic acid as has been described earlier also by Elnagdi et al.[9].

Apparatus

Polarographic curves were recorded with an E 506 pen-type recorder polarograph (Metrohm, Switzerland). The capillary possessed the following characteristics in H_2O open circuit: t = 4.8 s/drop, m = 1.42 mg/s for h = 40 cm. Constant voltage for controlled potential electrolysis was carried using potentiostat type Wenking (Germany).

Solution

Stock solutions (≈ 10^{-3} mol l^{-1}) were prepared by dissolving an accurately weighed quantity of material in the appropriate volume of absolute ethanol which in case of compounds *IIa*, *IIb* and *IV* is 2 vol.% in DMF. Britton–Robinson modified universal buffers were used as supporting electrolyte[10].

Measurements

All experiments were carried out at 25 ± 2 °C. The half-wave potentials were determined graphically and expressed vs SCE with an accuracy of ±0.005 V. The pH measurements were made using a digital pH meter (HANNA instruments 8519, Italy) and a combined glass electrode. The later was standardized using 40 vol.% ethanolic standard buffers.

Procedure

Ethanol (6 ml) and the appropriate buffer solution (12 ml) were introduced in the polarographic cell. The mixture was then deaerated by bubbling a stream of oxygen-free nitrogen for 12 min. Then 2 ml of ≈ 10^{-3} mol l^{-1} depolarizer solution were introduced into the cell so that the final concentration was ≈ 10^{-4} mol l^{-1} in 20 ml of 40 vol.% ethanolic buffer.

Coulometry and Determination of the Number of Electrons

The number of electrons transferred in the electrochemical reduction of compounds *IIa*, *IIIb*, *IV* and *V* was determined coulometrically following the method of Lingane[11] and using a cell similar to that described by Manousek and Zuman[12]. In each experiment 30 ml of solution (≈ 10^{-4} mol l^{-1} in depolarizer) containing 40 vol.% alcohol were electrolyzed for 90 min. For each of compounds *IIb*, *IIIb*, *IV* and *V*, the applied voltage was selected at the plateau of the more positive wave. The changes of the limiting current were determined by recording the polarograms at selected intervals. The number of electrons n was calculated using the equation:

$$n = \frac{i_0}{-2.303 \boldsymbol{F} c_0 V \dfrac{\mathrm{d} \log i}{\mathrm{d}t}} \,, \qquad (1)$$

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.

Determination of Apparent Dissociation Constants

The calculated volume from the prepared stock solution (≈ 10^{-3} mol l^{-1} in absolute ethanol) of *IIa*, *IIb*, *IIIb*, *IV* and *V* was diluted to 40 ml with doubly distilled water so that the final concentration was 5 . 10^{-4} mol l^{-1} in 40 vol.% aqueous ethanolic solution. The latter solution was titrated by standard carbonate free 5 . 10^{-3} mol l^{-1} aqueous NaOH solution (prepared by proper dilution) with continuous stirring at 25 ± 2 °C. The apparent pH values were read on and the pK_a values were calculated using the well known Henderson–Hasselbach equation[13] by plotting log ([A^-]/[HA]) vs pH values. Compounds *IIa*, *IIb*, *IV* and *V* gave well defined S-shaped pH-titration curves while *IIIb* did not show any acid character.

RESULTS AND DISCUSSION

The polarograms obtained for compounds *IIa*, *IIb*, *IIIa*, *IIIb*, *IV* and *V* in 40 vol.% ethanolic buffers in the whole pH range (pH 2 – 11) were analyzed. The experimental results representing $E_{1/2}$–pH and i_l–pH relations are graphically depicted in Figs 1 – 4. The respective polarographic data including equations of $E_{1/2}$–pH are compiled in Table I.

Compounds IIa, IIb

The polarograms of these compounds were found to be identical. Figure 1 illustrates $E_{1/2}$–pH and i_l–pH relation as exemplified by *IIa*. The polarograms showed two well defined diffusion controlled waves. The more positive 4e wave *A* is assigned to reduction of the hydrazone linkage by well known mechanism of cleavage followed by saturation[14] while the more negative 2e wave *B* is assigned to saturation of the >C=C< linkage. This assignment is based on the following facts:

a) Hydrazone linkage is known to be reduced at much more positive potential than the olefinic >C=C< bond[15,16].

b) Mostly reduction of hydrazones proceeds in 4e wave, while saturation of the >C=C< is 2 electron wave[14–16].

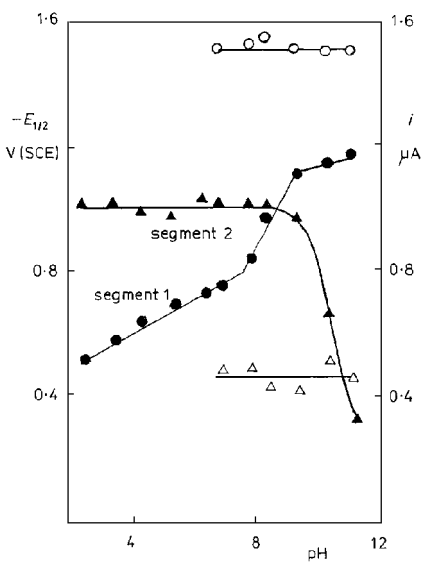


FIG. 1
Dependence of $E_{1/2}$ (❍,●) and i_l (Δ,▲) on pH for *IIb*: ●, ▲ wave *A*; ❍, Δ wave *B*

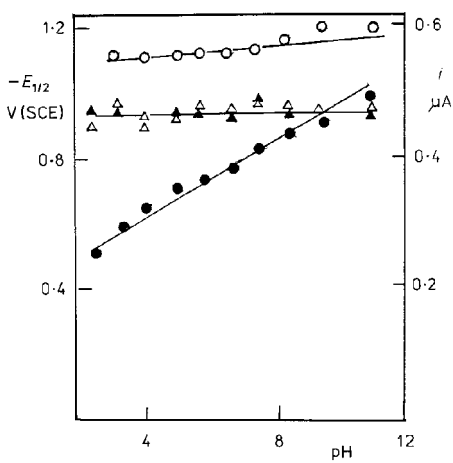


FIG. 2
Dependence of $E_{1/2}$ (❍,●) and i_l (Δ,▲) on pH for *IIIb*: ●, ▲ wave *A*; ❍, Δ wave *B*

c) Hydrazones are known to be reduced in the protonated form (particularly in acid and moderately alkaline buffers) which is the case with wave *A* which showed two $E_{1/2}$–pH dependent segments with $dE_{1/2}/dpH = 0.055$ and 0.170 respectively, while wave *B* is practically pH independent[14,15] (cf. Fig. 1 and Table I). The (H^+, e) reduction sequence followed in wave *A* is thus inverted to (e, H^+) for wave *B*. The i_l–pH relation for wave *A* followed the pattern of the well known dissociation curve[17] with $pK' \approx 10.5$ compared with the potentiometric pK_a (6.39). From the difference between polarographic pK' and potentiometric pK_a it is possible to calculate the value of the rate constant K_r, consequently the dissociation rate constant K_d for the equilibrium

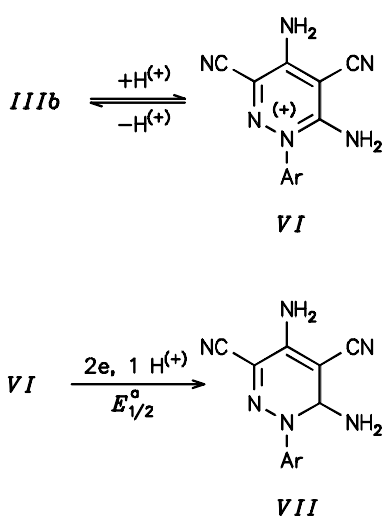
$$\mathrm{HA} \underset{K_r}{\overset{K_d}{\rightleftharpoons}} \mathrm{H^+} + \mathrm{A^-}$$

where $K = K_d/K_r$, using the relation[17]:

$$\log K_r = 2\,pK' - pK_a - 2\log 0.886 - \log t \quad . \qquad (2)$$

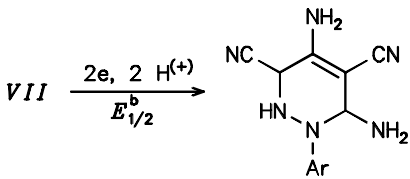
Compound IIIb

In fairly acid media the compound showed two successive 2e waves. $E_{1/2}$–pH and i_l–pH relations are shown graphically in Fig. 2. The more positive wave *A* is $E_{1/2}$–pH dependent ($dE_{1/2}/dpH = 0.062$) and is attributed to reduction of protonated >C=NH moiety which should exist in the more aromatic form (*VI*). Saturation of this linkage by reduction in wave *A* yields *VII*. The following Scheme 2 can intelligably represent the reaction at electrode surface.



SCHEME 2

The unsaturated linkage at ring N2 and C3 in *VI* is not now part of an aromatic conjugate system and is thus susceptible for reduction which occurred at more negative potentials in the 2e pH-independent wave *B*. Scheme 3 thus can properly represent the electrode process at this stage.



SCHEME 3

Compound IV

This compound is reduced in one 4e diffusion controlled wave. Figure 3 represents graphically $E_{1/2}$–pH and i_l–pH relations. The reduction wave of this compound (as reflected from $E_{1/2}$–pH and i_l–pH relations) is assigned to reduction of the hydrazone linkage since it showed practical identity with wave *A* of compound *IIa* (Fig. 1). The very small differences in $E_{1/2}$ and i_l values of this wave and that of wave *A* of compounds *IIa*, *IIb* is normally due to the differences in the molecular dimensions, diffusion coefficients and orientation of the two compounds at the surface of the electrode[18].

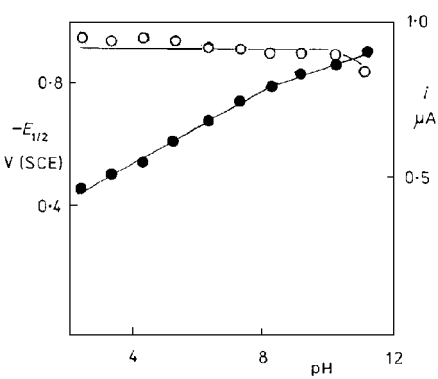


FIG. 3
Dependence of $E_{1/2}$ (●) and i_l (❍) on pH for *IV*

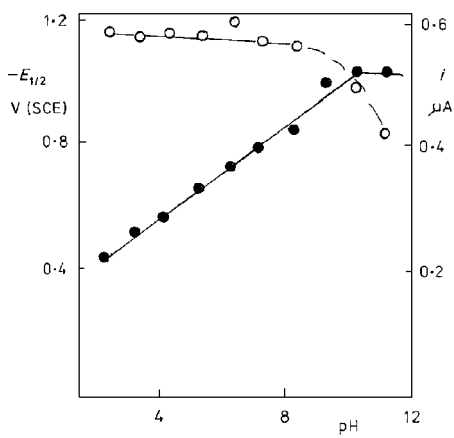


FIG. 4
Dependence of $E_{1/2}$ (●) and i_l (❍) on pH for *V*

The polarographic inactivity of the azamethine linkage CH_3–C=NH is probably due to the ready hydrolysis to the corresponding ketone[19]. As this compound is readily ionizable (pK_a = 6.80) self-protonation can thus initiate the hydrolysis.

Compound V

As reflected from Fig. 4 compound *V* is reduced in the whole pH range of study (pH ≈ 2 – 11) in one diffusion controlled 2e wave; also $E_{1/2}$ is pH dependent (d$E_{1/2}$/dpH = 0.080). This wave is assigned to reduction of the carbonyl >C=O group to the corresponding hydroxy compound >CH–OH. Ease of reduction (e.g., at pH 2.05, $E_{1/2}$ = –0.44 V) excludes any other reduction possibility in the molecule such as –C=N or saturation of the heterocyclic –C=N– double bond which are known to be reduced at more negative potentials[15].

Apparent Dissociation Constant and pK_a for Compounds IIa, IIb, IIIb, IV and V

Statistical treatment of the pH vs log ([A^-]/[HA]) data was carried using Jaffe calculations[20]. Detailed calculations are summarized in Table I. The plots showed reasonable linearity and the intercept at log ([A^-]/[HA]) = 0 gave directly the pK_a (quoted in Table I). Compounds *IIa*, *IIb* and *IV* have practically the same pK_a (6.39 – 6.8) which could be expected since the acidity arises from the ionizable hydrogen of the hydrazone group >C=N–NH–. This is in contrast with compound *V* which behaved as a strong acid

TABLE I
Polarographic data and pK_a values of compounds *II* – *V*[a]

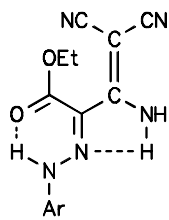
Compound	P^a	L^a	n^b	pH[c]	Polarographic pK' from i_l–pH	Polarographic pK' from $E_{1/2}$–pH	Potentiometric pK_a	*r*/*s*
IIa, *IIb*[d]								
Segment 1	–0.37	–0.055	1.194	3.62	10.5	8.2	6.39	0.991
Segment 2	–0.58	–0.170	–	–	–	9.5	–	0.073
IIIb[d]	–0.36	–0.062	1.250	6.01	–	–	no acidity	
IV	–0.31	–0.058	0.885	5.12	–	8.3	6.80	0.983
								0.116
V	–0.25	–0.080	1.125	4.04	11.5	10.2	3.42	0.990
								0.013

[a] Intercept *P* and slope *L* of the dependence: $E_{1/2} = P + L$ pH; *r* correlation coefficient, *s* standard deviation; [b] calculated from logarithmic analysis; [c] pH of logarithmic analysis; [d] wave *A*.

(pK_a = 3.42) where the acidity arises from the –COOH group; also the titration curve is even steeper than those for *IIa*, *IIb* and *IV*. No acidity has been traced for compound *IIIb*.

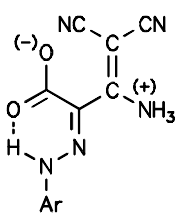
The obtained data clearly reveal that products of coupling *I* with aromatic diazonium salts exist in the hydrazone form suggested by Elnagdi et al.[6] and not in the cyclic pyridazine structure. Thus pK_a of *IIa* is similar to that of *IIb* and *IV* for both the hydrazone structure is well established. Furthermore, the pyridazine *IIIb* proved to have non-ionizable center as would be expected. Moreover, while the hydrazone linkage in *IIa*, *IIb* and *IV* behaved similarly on electroreduction (all revealed 4e reduction wave characteristic for hydrazones of similar structure)[19], the cyclic pyridazine *IIIb* behaved differently. Reduction of exocyclic >C=N bond in 2e wave precedes saturation of the endocyclic >C=N bond. This is in accordance with the structure of this product as prior to saturation the endocyclic >C=N is a part of an aromatic conjugate system and can thus only be reduced at more negative potential.

The stability of *IIa* on attempted cyclization in acid media may thus be due to existence in the strongly hydrogen bonded form *i*:

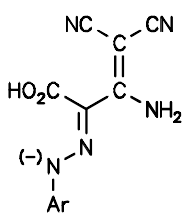


i

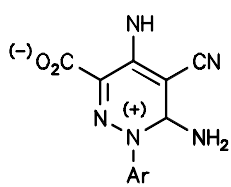
In this form the CN group is far from the >N–Ar moiety and for this reason cyclization could not be effected. On hydrolysis, the carboxylic acid group would then protonate the amino function affording the zwitterion *ii*. This then isomerizes into form *iii* in which the hydrogen linkage can rotate freely and thus cyclization into final isolable form *iv* can take place:



ii



iii



iv

This type of bonding cannot exist in *IIb* and for this reason it is cyclizable under mild conditions.

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