CROATICA CHEMICA ACTA CCACAA **59** (2) 463—473 (1986)

YU ISSN 0011-1643
CCA-1659 UDC 543.253
Original Scientific Paper

A Spectrophotometric and Polarographic Investigation of Some New Precursors of Potential Antineoplastic Compounds

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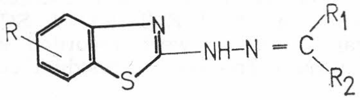
Received December 13, 1984

The present paper summarises the electrochemical behaviour of 2-benzothiazolylhydrazono-1-(*N*-phenylamino)-1,3-butane diones with special reference to the effect of substituents, ionic-strength and solvent composition on their redox mechanism. The reduction of the hydrazones takes place in a single 4e wave at D.M.E. All the compounds gave a single, well defined, irreversible, diffusion controlled reduction wave whose $E_{1/2}$ is pH-dependent. A plausible mechanism is also suggested on the basis of the number of protons involved in the rate determining step and the number of electrons involved in the reduction. The effect of substituents is interpreted in the terms of the Hammett equation. The *pK* values were calculated by polarographic and spectrophotometric methods.

INTRODUCTION

A review[1,2] of the electrochemistry of some biologically interesting organic molecules provides an excellent illustration of how modern electrochemical techniques can provide biological significant information. The ongoing studies of McCreery and co-workers on the electrochemistry of phenothiazene tranquilizer drugs[3–7], on polarographic analysis of corticosteroids[8,9] and antibacterial drugs used in the treatment of gram negative urinary tract infections viz., Nalidixic acid[10], represent a few examples of the biologically relevant information which can be deduced from electrochemical studies. The underlying rationale for our studies on the electrochemical reduction of biological important *N*-heterocyclic molecules is that such studies can lead to information on the reaction routes and mechanisms of biological redox reactions.

Keeping this in mind and to broaden the knowledge of the electrochemistry and possibilities of electroanalytical assays, it was considered worthwhile to study critically the electrochemical behaviour of some precursors of antineoplastic compounds[11] viz., (*Ia-Ij, II, III* and *IV*) at d. m. e.



Where R represents various substituents:

$$\left.\begin{array}{l} R_1 = CONHC_6H_5 \\ R_2 = COCH_3 \end{array}\right\} I;$$

$$\left.\begin{array}{l} R_1 = COCH_3 \\ R_2 = COCH_3 \end{array}\right\} II;$$

$$\left.\begin{array}{l} R_1 = COOCH_3 \\ R_2 = COOCH_3 \end{array}\right\} III;$$

The polarographic reduction of substituted 2-benzothiazolylhydrazono-1-(*N*-phenylamino)-butane-1,3-diones reported in this paper, particularly from the point of view of evaluating the reduction mechanism and the effect of substituents on the reduction process. Such substituent effects were first treated quantitatively by the electronegativity rule by Shikata and Tachi.[12] More recently, a linear free energy relationship was used for the quantitative treatment of modified Hammett equation[13-15] $\Delta E_{1/2} = \rho\sigma x$.

EXPERIMENTAL

Spectrophotometry

A UV-VIS Carl Zeiss Specord Spectrophotometer was used for spectral measurements. Solutions were prepared by diluting the appropriate amount of stock solutions in dimethylformamide with an aqueous Britton Robinson buffer of the desired pH values to give a concentration of 1.0×10^{-4} M of hydrazono derivatives and 40% DMF. The pK_a values were evaluated by making use of the equation.[16]

$$pK_a = \text{pH} + \log \frac{(A_{\min} - A)}{(A - A_{\max})} \qquad (1)$$

where A is absorbance at a given pH value, $A_{\max}$ is the maximum absorbance, *i. e.,* that corresponding to the absorbance of the cations, $A_{\min}$ is the minimum absorbance of the free base; all values were measured at the same wavelength. A fast scan-speed was used, and the instrument reference beam passed through a blank containing buffer solution with the same concentration of dimethylformamide as in the samples.

Polarography

All the compounds having substituents viz., H, 4-CH_3, 5-CH_3, 6-CH_3, 4-Cl, 6-Cl, 6-NO_2, 6-OC_2H_5, 4-OCH_3, 5-OCH_3, 6-Br, 5-NO_2-6-CH_3 were prepared in this laboratory.[11] All the compounds were recrystallised from DMF-water mixture. Two more compounds viz., *II, III, IV* were also prepared for evaluating the effect of substituents when they are present at the other side of the benzothiazolyl ring. Stock solutions of all the compounds were prepared in DMF.

Direct current polarographic curves were recorded with an ELICO DC CL·25 polarograph equipped with a pen recorder. Saturated Calomel electrode was used as a reference in polarographic measurements. Potentiometric studies were carried out on an expanded scale pH meter with glass electrodes.

In a typical experiment, *e. g.,* when studying the influence of pH on the polarographic behaviour, a 10×10^{-4} M solution of these compounds containing 10% DMF + 30% DMF (to prevent precipitation) and appropriate B. R. buffer with KCL, as supporting electrolyte, was deaerated by a stream of nitrogen for about 10 min and then the *i-E* curves were recorded. The characteristics of d.m.e. were as follows: $m = 1.25$ mg s^{-1} and $t = 2.6$ s in 1.0 M KCL (O.OV, SCE) at $h = 110$ Cm. Unless otherwise stated, polarographic curves were recorded at $h = 110$ Cm and 25 °C. The current and potential were corrected for residual current and *IR* drop of the cell, respectively.

To determine the number of electrons involved in the reduction, the waves for the 1.0×10^{-4} M solution of parent hydrazono compound were compared with those for azobenzene in B. R. buffer at different pH by the method of Devries and Kroon[17], using a mercury pool cathode. The formula used was,

$$n_2 = n_1 \left[\frac{\Delta i_{\mathrm{d}} \text{ azobenzene}}{i_{\mathrm{d}} \text{ azobenzene}} \right] \left[\frac{i_{\mathrm{d}} \text{ substance}}{\Delta i_{\mathrm{d}} \text{ substance}} \right] \frac{V_1 C_1}{V_2 C_2}$$

where i_d azobenzene is the original diffusion current for azobenzene, V_1C_1 and Δi_d azobenzene are its volume, concentration and change in the diffusion current after electrolysis, i_d(sub), V_2C_2 and Δi_d(sub) are the corresponding quantities for the substance. The temperature coefficient was calculated by the Nejedlys method[18] and modified by Meites *et al.*[19] Moreover, the value of 'n' was also determined by controlled potential electrolysis.[20] In both cases electrolysis was carried out at a potential corresponding to the plateau of the wave. After completed electrolysis (~ 10 hours), the catholyte was subjected to product analysis.

Spectra and pK_a Determination

All the compounds (*Ia—Ij*) have almost similar electronic spectra. They exhibit two absorption maxima in acid media, one at 260 to 290 nm and one at 430 nm. With increasing pH the first maximum descreases to pH 10.0. At higher pH values, a pH independent spectrum with a diffuse peak at 430 to 435 nm is always obtained. With all these compounds Beer's law holds at any wavelength and pH over the concentration range from 10^{-5} M to 10^{-4} M. The molar absorptivities are 1.06×10^4 ($\lambda = 280$ nm, pH = 6.5) and 0.6×10^4 mol^{-1} cm^{-1} ($\lambda = 430$ nm, pH = 6.5).

The pK_a value of all these compounds, calculated according to eq (1), for absorbance measured at 430 nm was found to be 8.4—9.6, almost in the same range as evaluated by the polarographic method.

RESULTS AND DISCUSSION

Polarography

The compounds (*Ia-Ij*), *II*, *III*, and *IV*, listed in Table I and Table II, gave a single 4-e wave in B. R. buffer of pH range 2.0—12.0 and in H_2SO_4 in pH range 0.5—2.0, which was proved by mercury pressure to be diffusion controlled. Some typical polarograms are given in Figure 1. A comparison of limiting curents indicates that most of the compound studied are reduced by the same number of electrons. A very low value of temperature coefficient,[28] provided additional evidence for the fully diffusion controlled nature of the wave. The waves of the 4-OCH_3 derivative (*Ig*) were so affected by the maxima that measurement of the limiting current was not very accurate.

The half-wave potentials of these compounds were dependent on pH and shifted towards more negative potentials with an increase in pH. The plots of $E_{1/2}$ versus pH were linear from pH 0.5 to pH 9.0 and after that there was little change in $E_{1/2}$. The irreversible nature of the waves was confirmed by log plots.[21] For checking the reversibility of the process, $E_{\mathrm{d.e.}}$ was plotted against log ($i/i_{\mathrm{d}} - i$) and it was found that the value of the slope of the above plots exceeded appreciably 59.2/n mV. Moreover, the numerical value of $E_{3/4} - E_{1/4}$ of the polarographic wave appreciably exceeded 56.4/n mV. These two facts confirmed the irreversible nature of the waves. Furthermore, values of $K^0_{\mathrm{f,h}}$ were found to be in the range 10^{-3} to 10^{-5} cm/s (Table I). Very low values of $K^0_{\mathrm{f,h}}$ clearly indicated the totally irreversible nature of the waves. The fact that $E_{1/2}$ shifted towards more negative potentials with increasing

TABLE I

Polarographic Characteristics of Some Substituted 2-Benzothiazolylhydrazono-1--(N-phenylamino)-1,3-butane Diones at pH 6.5

S. No.	R	$-E_{1/2}$, V	i_d, μA	αn_a	I	$\frac{dE_{1/2}}{dpH}$, $\frac{V}{pH}$	$\Delta E_{1/2}$, V	pK	$K^{o}_{f,h}$ (cm/s)
Ia	H	0.82	0.45	1.29	0.33	0.13	0.00	9.28	3.39×10^{-5}
Ib	4-CH_3	0.83	0.42	1.29	0.30	0.07	—0.01	9.38	3.42×10^{-4}
Ic	5-CH_3	0.81	0.35	1.29	0.25	0.08	+0.01	8.41	1.66×10^{-3}
Id	6-CH_3	0.88	0.42	0.86	0.30	0.06	—0.06	9.40	6.07×10^{-5}
Ie	4-Cl	0.79	0.33	1.29	0.24	0.09	+0.03	9.08	4.78×10^{-4}
If	6-Cl	0.83	0.42	0.86	0.30	0.09	—0.01	9.60	3.17×10^{-4}
Ig	4-OCH_3	0.80	0.30	1.03	0.22	—*	+0.02	9.20	1.30×10^{-4}
Ih	5-OCH_3	0.94	0.60	0.64	0.44	0.07	—0.12	9.12	5.56×10^{-4}
Ii	6-OC_2H_5	0.82	0.48	0.64	0.35	0.07	+0.04	8.96	1.16×10^{-4}
Ij	6-Br	0.78	0.48	0.86	0.35	0.08	0.00	9.30	1.13×10^{-4}
Ik	6-NO_2	0.94	0.45	0.73	0.33	0.06	—0.12	9.28	2.83×10^{-4}
Il	5-NO_2-6-CH_3	0.74	0.48	0.57	0.35	0.07	+0.08	8.95	3.80×10^{-4}

* Well defined waves were not realised at all pH.

TABLE II

Polarographic Characteristics of Some Coupled Products of 2-Amino Benzothiazoles with 2,4-Diketones/Esters at pH 6.5 when R_1 and R_2 are Different

S.	R	R_1	R_2	i_d, μA	αn_a	I	$\frac{dE_{1/2}}{dpH}$, $\frac{V}{pH}$	$\Delta E_{1/2}$, V	pK	$-E_{1/2}$, V	$K^{o}_{f,h}$ (cm/sec)
I	H	$CONHC_6H_5$	$COCH_3$	0.45	1.29	0.33	0.13	00	9.2	0.82	3.39×10^{-5}
II	H	$COCH_3$	$COCH_3$	0.42	0.86	0.30	0.09	00	8.62	0.81	6.77×10^{-5}
III	H	$COOCH_3$	$COOCH_3$	0.32	0.86	0.23	0.09	00	9.5	0.70	1.35×10^{-4}
IV	H	$CONHC_6H_4Cl$	$COCH_3$	0.51	1.29	0.37	0.18	00		0.71	4.40×10^{-3}

depolariser concentration further pointed towards the irreversible nature of the waves. The values of αn_a (product of transfer coefficient and number of electrons transferred in the rate determining step) and p (number of protons involved during the rate determining step of the reaction) were determined using the expression[21,22]

$$E_{1/4} - E_{3/4} = \frac{0.0517}{\alpha\, n_a}$$

$$\frac{dE_{1/2}}{dpH} = \frac{0.05915}{\alpha\, n_a}\, p$$

Since the half-wave potentials of these coupled products were pH dependent and the limiting current pH independent up to pH 9.0, it was concluded that both acidic and basic forms of the compounds reached the electrode

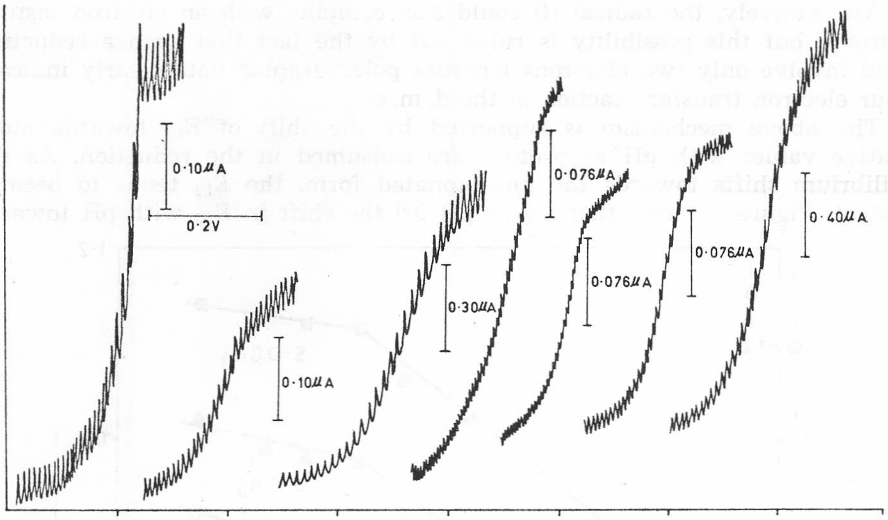
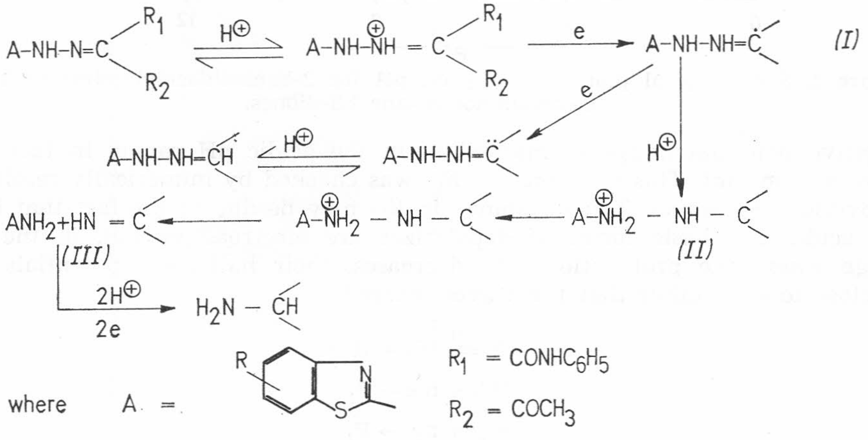


Figure 1. Some typical polarograms of 2-benzothiazolylhydrazono-1-(*N*-phenylamino)-butane-1,3-diones at various pH and concentrations (1) R = H at pH 6.5, Concn = 2.0×10^{-4} M; (2) R = H at pH 6.5, Concn = 1.0×10^{-4} M (3) R = 6 — CH_3 at pH 10.0, Concn = 2.0×10^{-4} M; (4) R = 6 — Br at pH 6.5, Concn = 1.0×10^{-4} M; (5) R = 4 — CH_3 at pH 7.9, Concn = 0.5×10^{-4} M; (6) R = 4 — CH_3 at pH 3.8, Concn = 1.0×10^{-4} M (7) R = 6 — Cl at pH 7.9 Concn = 2.0×10^{-4} M. Curves 1, 2 and 4 start at 0.6 V; 3 starts at 0.75 V; 5 starts at 0.68 V; 6 starts at 0.44 V and 7 starts at 0.7 V.

surface and were electroactive.[23,24] Thus, the proton transfer reaction preceded the electrode process in such cases. Out of the two general sequences[24,25] for the proton and electron addition, viz., $H^{\oplus}$, e, $H^{\oplus}$, e and e, $H^{\oplus}$, e, $H^{\oplus}$, the former sequence is more probable for these compounds in the light of their structural genesis. After the uptake of a proton and one electron, the radical (1) would accept a proton to form a protonated radical (II) which, after taking one electron, gets cleaved at nitrogen bond with the formation of aniline. The imine (*III*) formed gets further protonated and reduced (Scheme 1).



Scheme 1.

Alternatively, the radical (*I*) could also combine with an electron instead of proton but this possibility is ruled out by the fact that such a reduction would involve only two electrons whereas polarographic data clearly indicate a four electron transfer reaction at the d. m. e.

The above mechanism is supported by the shift of $E_{1/2}$ towards more negative values with pH as protons are consumed in the reduction. As the **equilibrium shifts towards** the unprotonated form, the $E_{1/2}$ tends to become constant. Figure 2 shows that above pH 9.0 the shift in $E_{1/2}$ with pH towards negative potential is not so marked as in the acidic pH range. In fact, $E_{1/2}$ becomes constant. This constancy in $E_{1/2}$ was checked by numerically resolving of overlapping waves. This constancy in $E_{1/2}$ may be due to the fact that both the acidic and basic forms of depolarizer are electroactive but, in the pH range where the protonation rate decreases, their half-wave potentials are so close to each other that the waves merge.[21]

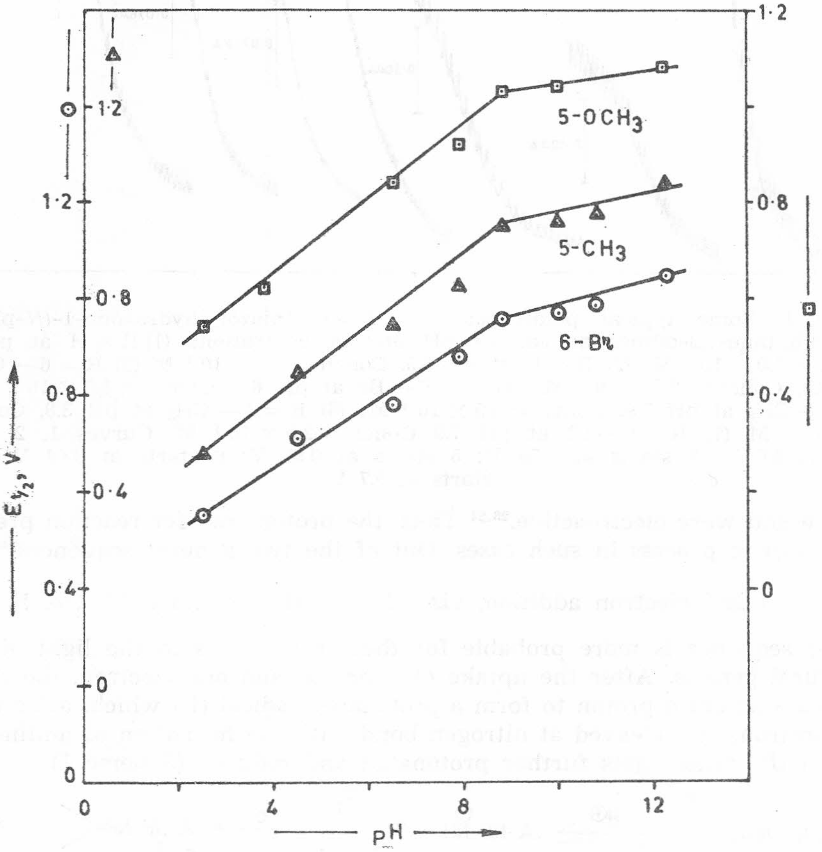


Figure 2. Some typical plots of $-E_{1/2}$ *vs.* pH for 2-benzothiazolylhydrazono-1-(*N*-phenylamino)-butane-1,3-diones.

$$HA \overset{pK_1}{\rightleftharpoons} A^{\ominus} + H^{\oplus}$$

$$HA + n_1e \rightarrow P_1$$

$$A^{\ominus} + n_2e \rightarrow P_2$$

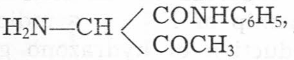
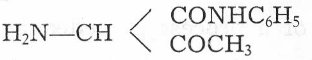
The half-wave potentials in the pH region defined by $(pK_1 + 1) < \mathrm{pH} <$ $< (pK_1 - 1)$ are shifted towards more negative values. The plot of $E_{1/2}$ against pH in the region is linear and corresponds to eq.

$$E_{1/2} = C - \frac{RT}{\alpha\,nF} \ln K_1 + \frac{RT}{\alpha\,nF} \ln \mathrm{H}\oplus$$

At $\mathrm{pH} > (pK_1 + 1)$ the half-wave potential of the acidic form is pH independent and practically equal to the $E_{1/2}$ of the basic form.

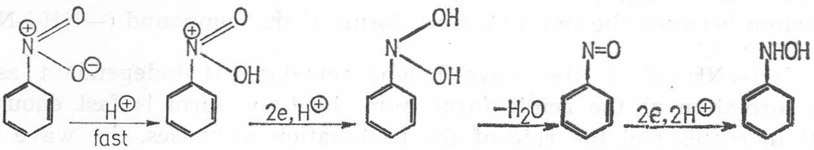
$$(E_{1/2})_{\mathrm{HA}} = C - \frac{RT}{2\,\alpha\,nF} \ln K_1 - \frac{RT}{\alpha\,nF} \ln 0.886/K_1 t_1 - \frac{RT}{\alpha\,nF} \ln K_1 \approx (E_{1/2})\ \mathrm{A}^-$$

The plot of $E_{1/2}$ *vs.* pH is composed of two intersecting linear segments and the pH at the point of intersection of its two linear parts is $\approx pK_1$. Similar steps for the reduction of hydrazono group involving cleavage of the —N—N— bond have also been proposed by other workers.[26,27] Due to an acid base equilibrium between the two structural forms of the compound ($\mathrm{-NH-N{=}C-} \rightleftharpoons \mathrm{-NH-\overset{\oplus}{N}H{=}C-}$), the wave height remains pH independent as long as the formation of the acidic form from the basic form is fast enough. As the pH increases and the rate of the protonation decreases, the wave height decreases as well.

UV spectra of the solution during electrolysis were recorded at different time intervals, $\varepsilon_{\max}$ at 430 nm due to —HN—N=C— grouping showed a decrease in the peak height after each interval of time and finally the wave disappeared, confirming the above reduction mechanism. After complete controlled potential electrolysis (~ 10 hrs.), the catholyte was subjected to product analysis. The electrolysed solution on separation by TLC gave two products. One of the products was identified as 2-aminobenzothiazole on the basis of R_f values identical with the authentic sample. Furthermore, the identical nature of IR and NMR spectra of the product and the authentic samples, *i. e.* 2-aminobenzothiazole, confirmed the presence of 2-aminobenzothiazole as a product of electroreduction. The IR spectrum of the second product gave primary amino stretching bands at 3050 and 3140 cm^{-1}, C—H linkage at 2680 cm^{-1} and a peak for CO group at 1620 cm^{-1}. All these bands point towards structure  $\mathrm{H_2N{-}CH}\left\langle \begin{array}{l}\mathrm{CONHC_6H_5}\\ \mathrm{COCH_3}\end{array}\right.$, as proposed in the above mechanism. Moreover, elemental analyses for C, N and H also indicate the above structure for the second product. The mass spectrum of the compound registered the molecular ion peak at *m/e* 192, which strongly supports the above structure of the aliphatic amine. This aliphatic amine viz.,  $\mathrm{H_2N{-}CH}\left\langle \begin{array}{l}\mathrm{CONHC_6H_5}\\ \mathrm{COCH_3}\end{array}\right.$ is quite an interesting synthetic intermediate and this method may be used for its synthesis. However, a detailed study of the electroorganic synthesis of such intermediates will be the subject matter of a separate communication.[28] Our results are also in agreement with the mechanism proposed by other workers[26,27] for the reduction of the hydrazono group at d. m. e.

Behaviour of Nitro Group

The behaviour of nitro substituted benzothiazolyl hydrazones, viz., 6-NO_2(*Ik*) and 5-NO_2-6-CH_3(*Il*) were studied in order to investigate the effect of strongly electron attracting substituents on the reduction of hydrazono group. Other nitro substituted compounds could not be studied due to their non-availability. In the nitro compounds, reduction of the nitro group itself occurred in a single 4e wave at a more positive potential and didnt interfere with the measurement of —NH—N=C— waves. The wave due to the nitro group reduction was found to be diffusion controlled and the limiting current was equal to that of a normal reduction wave. The irreversible nature of the nitro group wave was confirmed by the shift of $E_{1/2}$ towards a more negative potential with the increasing concentration of depolarizer and by log plot. The following mechanism for the reduction of nitro group, as given for other nitro compounds,[29,30] can also be proposed for the reduction of these compounds.



Structural Effects

For the application of the modified Hammett equation for the treatment of polarographic $E_{1/2}$ for meta and para substituted compounds the process involved in the electroreduction of all compounds must be identical.[25,31] In the present series of compounds this is indicated by almost the same slopes of the plots of $E_{1/2}$ *vs.* pH and the degree of irreversibility (α) (Table I). Since in compounds *Ia-Il* the values of αn_a and $dE_{1/2}/d$pH are practically constant, it seemed worthwhile to correlate the $E_{1/2}$ of these compounds with the Hammett substituent constant (σ).[25] When the half wave potentials of these compounds were plotted against the Hammett substituent constant[32] (σ), a linear relationship was obtained. Only 5-OCH_3 and 6-NO_2 derivatives deviate significantly from the linear plot. The specific reaction constant (ρ) was found to be 0.12 and its positive sign indicated the nucleophilic nature of the electrode process. Furthermore, this value of specific reaction constant (ρ) is in good agreement with the values reported in the literature for similar systems.[32] The observed linear relationship of $E_{1/2}$ *vs.* σ indicated that the substituents appreciably affected the reduction of hydrazono group by polar and mesometric effects through the benzothiazolyl ring. From Figure 3 it is evident that the plot of $\Delta E_{1/2}$ *vs.* σ gave a better correlation.

Effects of Ionic Strength

The effect of double layer structure on the $E_{1/2}$ of a process preceded by protonation is given by equation.[33]

$$\Delta E_{1/2} \approx \Delta\psi \frac{\alpha n_a - Z}{\alpha n_a} - \frac{\partial E_{1/2}}{\partial \mathrm{pH}\ 2.30\ RT} \qquad (2)$$

where φ, is the variation in the double layer potential, α the transfer coefficient, n_a the number of electrons transferred in the rate determining step and

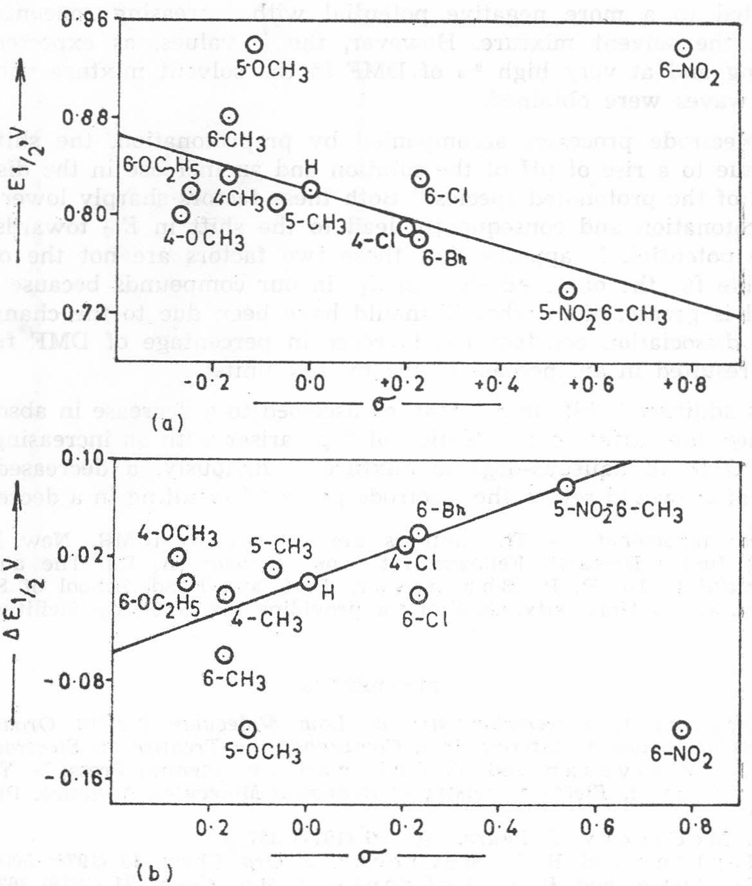


Figure 3. Plot of (a) $-E_{1/2}$ *vs.* σ (b) $\Delta E_{1/2}$ *vs.* σ for 2-benzothiazolylhydrazono-1-(*N*-phenylamino)-butane-1,3-diones in B. R. buffer at pH 6.5.

Z the charge of the particle being discharged. Undoubtedly, a marked effect of change in ionic strength of $E_{1/2}$ should be observed in cases where the depolarizer is in the ionic form. No such effect should be observed when it is in the non ionic form, *i. e.* when $Z = 0$. Since the second term in the bracket of equation (2) is nearly equal to 1 and $Z = 0$, $E_{1/2}$ will be almost independent of φ or of ionic strength. This was verified by carrying out experiments with varying concentrations of KCl (0.01 M and 0.25 M). The values of $dE_{1/2}/d$pH thus obtained fall in the range 0.060—0.10 V/pH and $E_{1/2}$ and i_d remained unaffected by the change in concentration of the supporting electrolyte.

Effect of Solvent Composition

First the polarograms of the compounds (*Ia-Il*) were recorded in the minimum amount of DMF (30%) necessary for dissolving the compound. The DMF percentage was then gradually increased from 30% to 70% to see the effect of solvent composition on the electrode process. It was observed that

$E_{1/2}$ shifted to a more negative potential with increasing concentration of DMF in the solvent mixture. However, the i_d values, as expected, go on decreasing and at very high % of DMF in the solvent mixture very poorly defined waves were obtained.

In electrode processes accompanied by preprotonation, the shift in $E_{1/2}$ can be due to a rise of pH of the solution and an increase in the dissociation constant of the protonated species.[34] Both these factors sharply lower the rate of preprotonation and consequently lead to the shift in $E_{1/2}$ towards a more negative potential. It appears that these two factors are not the only ones responsible for the observed shift in $E_{1/2}$ in our compounds because the shift observed is greater than what it should have been due to the change in pH and the dissociation constant (an increase in percentage of DMF from 30% to 60% resulted in an increase of pH by 1.01 units).

This additional shift in $E_{1/2}$ may be ascribed to a decrease in absorbability and, hence, the surface concentration of depolariser with an increasing percentage of DMF in aqueous-organic mixture.[35] Obviously, a decreased surface concentration would retard the electrode process[36] resulting in a decrease in i_d.

Acknowledgement. — The authors are grateful to ICMR, New Delhi for awarding Junior Research Fellowship to one of them (A. D.). The authors are also thankful to Dr. R. P. Bhatnagar, Prof. and Head, School of Studies in Chemistry, Jiwaji University, Gwalior for providing the necessary facilities.

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SAŽETAK

Spektrofotometrijsko i polarografsko istraživanje nekih novih preteča potencijalnih antineoplasta

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U ovom radu ispitano je elektrokemijsko ponašanje nekih 2-benzotiazolilhidrazono-1-(*N*-fenilamino)-1,3-butandiona. Istražen je utjecaj supstituenata, ionske jakosti i sastava otapala na mehanizme redoks-reakcija. Redukcija hidrazona na kapajućoj živinoj elektrodi odvija se u jednom stupnju u kojemu sudjeluju četiri elektrona. Polarografski valovi dobro su definirani, ireverzibilni i difuzijom kontrolirani, a poluvalni potencijal ovisan je o pH otopine. Vjerojatni mehanizam pretpostavljen je na temelju broja protona koji sudjeluju u najsporijem stupnju i broja elektrona koji sudjeluju u redukciji. Utjecaj supstituenata interpretiran je na temelju modificirane Hammettove jednadžbe. Spektrofotometrijskom i polarografskom metodom određene su *pK*-vrijednosti ispitivanih spojeva.