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Polarographic Behaviour of Some Potential Antineoplastic Benzothiazolylazopyrazoles

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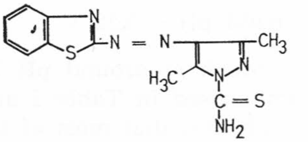
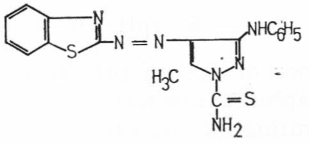
The present paper summarises the electrochemical behaviour of 4-benzothiazolylazo-*N*-thiocarbamoyl-3,5-dimethyl pyrazoles. The reduction of above compounds takes place in a single 2e wave at d.m.e. corresponding to the reduction of azo group. All the compounds give irreversible waves at pH values $pH > 3.0$ and reversible waves at pH values $pH < 3.0$. All waves are diffusion controlled and half-wave potentials pH dependent. The effect of substituents has been determined quantitatively by the application of Hammett equation. A plausible mechanism has been suggested for the electrodeprocess. Furthermore, the effect of ionic-strength, cations, anions and solvent composition has been studied in terms of the changed electrical double layer.

Keeping in mind the great importance of potential antineoplastic 4-benzothiazolylazo-*N*-thiocarbamoyl-3,5-dimethyl pyrazoles (I) from the electrochemical point of view, as they have an azo group attached to both sides with heterocyclic rings, polarographic reduction of substituted 4-benzothiazolylazo-*N*-thiocarbamoyl pyrazoles (having different substituents at the 3 and 5 positions of pyrazole ring) I, II and III has been investigated in this paper. Studies were carried out particularly from the point of view of azo group reduction mechanism and the effect of substituents on the reduction process.



(I)



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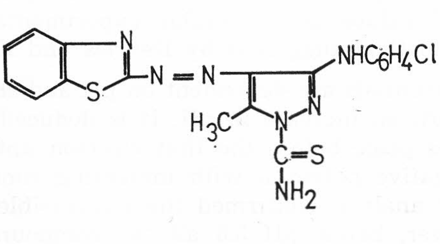


(III)

EXPERIMENTAL

4-benzothiazolylazo-*N*-thiocarbamoyl-3,5-dimethyl pyrazoles I, II and III were prepared by the method developed in this laboratory.[1]

Apparatus

D. C. polarographic curves were recorded on an ELICO DC CL 25 recording polarograph. The capillary characteristics were as follows: $m = 1.25$ mg s^{-1} and $t = 2.6$ s, $m^{2/3}t^{1/6} = 1.360$ mg$^{2/3}$ S$^{1/2}$ at a zero applied potential vs S.C.E. in 1.0 M KCl solution at $h = 110$ cm. The temperature of the solution was maintained at 25 ± 1 °C by keeping the polarographic cell in a thermostatic bath. The pH metric studies were made on an ELICO LI-15 expanded scale pH meter fitted with a glass electrode, and SCE was used as the reference electrode.

Solutions and Procedure

Stock solutions of concentration 1.0×10^{-3} M of all the compounds (Table I and II) were prepared in purified[2] *N,N*-dimethylformamide (AnalR). Britton-Robinson buffers[3] in the pH range 2.0 to 11.0, 0.1 N NaOH, 1.0 M KCl, KBr, KI, KNO_3, NaCl, LiCl and $(CH_3)_4NBr$ were prepared in doubly distilled water using AnalR grade chemicals. Solutions for polarographic measurements were prepared by mixing 1.0 ml of the compound, 3.0 ml of D.M.F. (which was necessary to keep the compound in solution), 1.0 ml of KCl (1.0 M) and 5.0 ml of the appropriate Britton-Robinson buffer. Dissolved oxygen was removed from the solution by passing the purified nitrogen gas for about 10 minutes and corrections for residual current were made in all the cases. The number of electrons *n* involved in the reduction process was determined for the parent compound (I) by the method of Devries and Kroon[4] using a mercury pool cathode. The temperature coefficient was calculated by Nejedly's[5] method.

RESULTS AND DISCUSSION

In the pH range 2.0 to 12.0 all the compounds (Table I and II), except the 6-NO_2 derivative, were reduced in a single 2-e process. In the case of 6-NO_2 derivative one more 4-e wave at a more positive potential for the reduction of nitro group was observed. For all the waves the limiting current was found to be diffusion controlled, as evident by the linear plots[6] of i_d vs. h and the low temperature coefficient (below $1.56\,^{0}/_{0}$ K^{-1}). Let the dependence of $E_{1/2}$ on pH for the parent compound be represented by the equation:

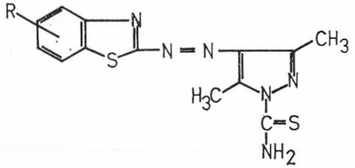
$$-E_{1/2}\,(\text{pH } 2.0\text{—}8.0) = 0.055 \text{ pH} + 0.22 \text{ V}$$

The dependence of $E_{1/2}$ on pH showed a break at around pH 8.0 (Figure 1). The polarographic characteristics are summarised in Table I and II. A comparison of limiting currents (i_d, Table I) indicates that most of the compounds studied are reduced by the same number of electrons. The number of electrons involved in the electrode process was found to be 2 by comparison with compounds of known *'n'* values under similar experimental conditions and by the millicoulometric method suggested by Devries and Kroon.

The half-wave potentials are dependent on pH and shift towards the more negative potential with an increase in pH. It is deduced from this behaviour that protonation takes place before the first electron uptake. The shift of $E_{1/2}$ toward the more negative potential with increasing concentration of depolarizer and logarithmic analysis confirmed the irreversible[6] nature of the electrode process. However, below pH 3.0 all the compounds listed in Table I showed a reversible nature of the wave. The number of protons involved per

TABLE I

Polarographic Characteristics of Some Substituted 4-Benzothiazolylazo-N-thiocarbamoyl-3,5-dimethyl Pyrazoles at pH 6.5



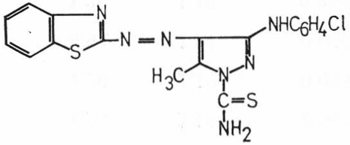
S. NO.	R	$-E_{1/2}$/V	$E_{3/4}-E_{1/4}$	i_d/μA	αn	P	$\frac{dE_{1/2}/V}{dpH/pH}$	$\Delta E_{1/2}$/V	I	$RT/\alpha n_a$/V	$K^0_{f,h}$/(cm/s)
Ia	H	0.56	0.040	0.36	1.26	1.19	0.055	0.00	0.26	1.917	5.04×10^{-4}
Ib	4-CH_3	0.57	0.040	0.45	1.26	1.19	0.055	—0.01	0.32	1.917	4.30×10^{-4}
Ic	5-CH_3	0.56	0.040	0.36	1.26	1.19	0.050	0.00	0.26	1.917	2.54×10^{-4}
Id	6-CH_3	0.54	0.040	0.36	1.26	1.19	0.055	0.02	0.26	1.917	2.46×10^{-4}
Ie	4-OCH_3	0.59	0.040	0.30	1.26	1.19	0.055	—0.03	0.21	1.917	1.79×10^{-4}
If	5-OCH_3	0.57	0.045	0.33	0.94	1.01	0.050	—0.01	0.24	2.169	3.91×10^{-4}
Ig	6-Cl	0.52	0.040	0.36	1.26	1.19	0.055	0.04	0.26	1.917	1.33×10^{-3}
Ih	6-Br	0.51	0.040	0.36	1.22	1.19	0.050	0.05	0.26	1.917	2.30×10^{-4}
Ii	6-OC_2H_5	0.56 0.64*	— 0.040*	— 0.24*	— 1.33*	— 0.98*	— 0.045	— 0.00	— 0.17*	— 1.917*	— 2.07×10^{-3}*
Ij	6-NO_2	1** 0.43 2 0.58	0.040 0.035	0.57 0.33	1.08 1.35	1.26 1.24	0.058 0.057	— 0.02	0.41 0.24	1.917 1.674	6.27×10^{-4} 1.63×10^{-4}

1** for the reduction of nitro group

* at pH 7.9

TABLE II

Polarographic Characteristics of Some Substituted 4-Benzothiazolylazo-N-thiocarbamoyl Pyrazoles at pH 6.5



S. NO.	R_1	R_2	$-E_{1/2}/V$	$i_d/\mu A$	$E_{3/4} - E_{1/4}/V$	αn	I	$\frac{dE_{1/2}/V}{dpH/pH}$	$RT/\alpha n_a/V$	$K^0_{f,h}/(cm/s)$
Ia	CH_3	CH_3	0.56	0.36	0.04	1.260	0.26	0.055	1.917	5.04×10^{-4}
II	CH_3	NHC_6H_5	0.76	0.48	0.06	0.813	0.35	0.150	2.870	3.43×10^{-4}
III	CH_3	NHC_6H_4Cl	0.53	0.54	0.02	2.380	0.39	0.045	0.956	8.26×10^{-3}

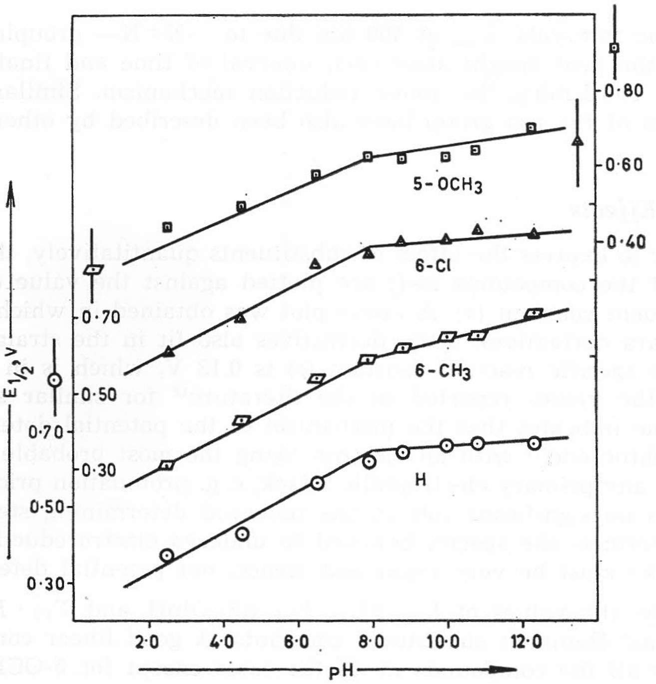
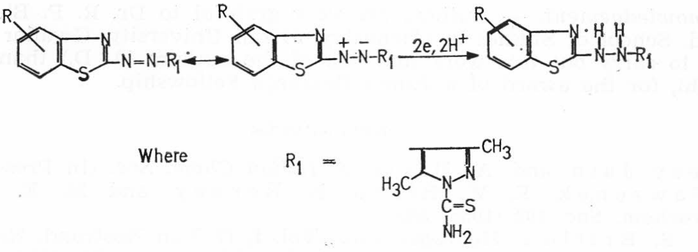


Figure 1. Some typical plots of $-E_{1/2}$ vs pH for 4-benzothiazolylazo-*N*-thiocarbamoyl-3,5-dimethyl pyrazoles in B. R. buffer

molecule of reactant in the rate determining step was calculated by the literature[6,7] method and found to be one (Table I).

As the number of electrons involved in the reduction is 2 and the number of protons involved in the rate determining step is one, the following mechanism can be proposed for the reduction of these compounds at d.m.e.



Scheme I

The above mechanism (Scheme I.) is supported from the increase of $E_{1/2}$ with pH as proton is consumed first. When the depolarizer solution was tested after controlled potential electrolysis, it did not give the dye test, thereby showing that —N=N— group is reduced to —NH—NH— and further reduction of —NH—NH— grouping to amine does not take place. Furthermore, UV-Vis. spectra of the solution during electrolysis were recorded at different time intervals. λ_{max} at 400 nm due to —N=N— grouping showed a decrease in the peak height after each interval of time and finally the wave disappeared, confirming the above reduction mechanism. Similar results for the reduction of the azo group have also been described by other workers[8-10] at d.m.e.

Structural Effects

In order to express the effect of substituents quantitatively, the half-wave potentials of the compounds Ia-Ij are plotted against the value of the Hammett substituent constant (σ). A linear plot was obtained in which, along with meta and para derivatives, ortho derivatives also fit in the straight line. The value of the specific reaction constant (ρ) is 0.13 V, which is in good agreement with the values reported in the literature[12] for similar systems. The positive value indicates that the mechanism of the potential determining step is a nucleophilic one,[11] with an electron being the most probable nucleophilic agent. Thus, any primary electrophilic attack, e. g. protonation prior to electron transfer, has no significant role in the potential determining step. Since the protonated form is the species believed to undergo electroreduction, the first proton uptake must be very rapid and, hence, not potential determining.

Similarly, the values of $E_{1/2}$, $\alpha E_{1/2}$, $E_{1/2} \cdot dE_{1/2}/dpH$ and $E_{1/2} \cdot RT/\alpha nF$ were plotted against Hammett substituent constants. A good linear correlation was obtained for all the compounds in all the cases except for 5-OCH_3 derivative which deviate from the regression line. In these cases the values of regression coefficient (ρ) were 0.13 V, 0.11 V, 0.14 V and 0.28 V, respectively.

When the methyl group in the pyrazole moiety was replaced by the aminophenyl group, a marked shift in $E_{1/2}$ towards negative value was observed in the former case (Table II). This shift may be due to the presence of the electron pair at the nitrogen, resulting in the increased electron density at the reduction site. However, when the chloro group was introduced in the phenyl ring, a shift in $E_{1/2}$ towards positive potential was observed. This shift may be due to the electron withdrawing nature of the chloro group.

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SAŽETAK

Polarografsko ponašanje nekih benzotiazolilazopirazola kao potencijalnih antineoplasta

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Istražena je polarografska redukcija nekih supstituiranih derivata 4-benzotiazolilazo-*N*-tiokarbamoilpirazola s obzirom na njihov značaj kao potencijalnih antineoplasta. Pretpostavljen je mehanizam te redukcije i ispitan je utjecaj supstituenata na taj mehanizam u području $2 < \mathrm{pH} < 12$.