THE EFFECT OF THE STRUCTURE OF THE SUBSTITUENT IN POSITION TEN ON THE VOLTAMMETRIC BEHAVIOUR OF PHENOTHIAZINE DERIVATIVES*

Naďa ZIMOVÁ[a], Ivan NĚMEC[a], Miroslava EHLOVÁ[a] and Karel WAISSER[b]

[a] Department of Analytical Chemistry, Charles University, 128 40 Prague 2 and
[b] Department of Inorganic and Organic Chemistry, 501 65 Hradec Králové

Dedicated to Professor Otto Exner on the occasion of his 65th birthday.

The electrochemical oxidation of seven derivatives of phenothiazine substituted in position 10 on the phenothiazine skeleton has been studied in acetonitrile, using a platinum disc electrode. The electron donor properties of the derivatives that depend on the substituent structure and the presence of nucleophiles in acetonitrile were followed. The diffusion coefficients for the formation of the radical cations were from 10^{-5} to 10^{-6} cm^2 s^{-1} and depended on the concentration of the acid in acetonitrile medium. A determination of these substances has been proposed, using differential pulse voltammetry, with a detection limit of $1 . 10^{-7}$ mol l^{-1}.

The versatile utility of phenothiazine and its derivatives has caused that many substances of this type have been synthesized. Electrochemical studies permit determination of a number of important parameters of the test substances and thus contribute to clarification of the mechanism of their oxidation processes.

The present work continues in the previous studies dealing with anodic reactions of phenothiazine and its derivatives on a platinum electrode in an acetonitrile medium (AN)[1-5]. Attention is centred on the structure of the substituent in position 10 on the phenothiazine skeleton and on the effect of the presence of nucleophiles on the electrochemical oxidation. The basic electrochemical data can be utilized for the determination of the studied substances. All the studied derivatives belong to potential antiarhythmics.

EXPERIMENTAL

Materials

The studied phenothiazine derivatives were synthesized at the Faculty of Pharmacy, Charles University, Hradec Králové, using a method simpler than described earlier in the literature[6-8]:

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To phenothiazine (10 mmol) in anhydrous dimethylformamide (150 ml), NaH (12·5 mmol) was added with stirring, an alkyl bromide (10 mmol) or alkyl iodide (10 mmol) was added drop-wise and the reaction mixture was maintained at 70°C for two hours. The solvent was evaporated at a reduced pressure, the residue was dissolved in ethyl ether, the etherial layer washed with water, dried with Na_2SO_4 and the ethyl ether was distilled off. The raw product was dissolved in benzene, passed through silica gel and crystallized from a benzene–petroleum ether or petroleum ether–methanol mixture. The yield amounted to 35—65%. The samples were repeatedly recrystal-lized and dried for 20 hours over P_2O_5, at 40°C and 2·5 kPa. The experimental melting points of the prepared substances were in agreement with the literature[6−9]. The synthesis of 10-iso-butylphenothiazine was not described in the literature. For $C_{16}H_{17}NS$ (255·4) calculated: 75·25% C, 6·71% H, 5·49% N, 12·55% S; found: 75·13% C, 6·68% H, 5·17% N, 12·63% S. The experimental melting point was 133°C.
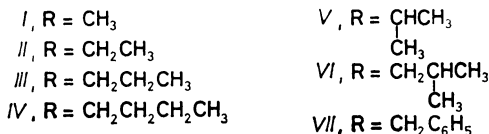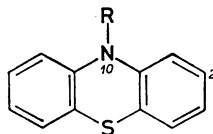
Voltammetric Measurements

The electrolytic vessel and the procedure have been described elsewhere[1,2]. The measurements were performed on a Universal modular polarograph Bruker E-310 (Belgium) and on a PA 3 Polarographic analyzer (Laboratorní Přístroje, Czechoslovakia). The voltammograms were recorded using an XY 4103 plotter (Laboratorní Přístroje, Czechoslovakia) and a 1 201 storage oscilloscope (Hewlett Packard, U.S.A.). A dual chart recorder TZ 4200 from Laboratorní Přístroje was further used. The platinum disc electrode (active surface area 0·033 cm^2, 0·111 cm^2 and 0·288 cm^2) was used as a stationary indicator electrode for cyclic voltammetry (CV) and differential pulse voltammetry (DPV) or as a rotating disc electrode (RDE) for DC voltammetry ($\omega = 679$, 970, 1 226, and 2 100 rpm). The reference electrode was a silver foil immersed in a solution of 0·01M-$AgNO_3$ in 1M-$NaClO_4$ in AN. A platinum spiral was used as a counter and generation electrode.

The reaction medium viscosity was measured by an Ubbelohde viscosimeter. The experiments were carried out at a constant temperature $25 \pm 0·1°C$.

RESULTS AND DISCUSSION

The electrochemical oxidation of 7 derivatives of phenothiazine substituted in posi-tion 10 was studied by RDE voltammetry, CV and potentiostatic coulometry and DPV.

I, R = CH$_3$

II, R = CH$_2$CH$_3$

III, R = CH$_2$CH$_2$CH$_3$

IV, R = CH$_2$CH$_2$CH$_2$CH$_3$

V, R = CHCH$_3$
         CH$_3$

VI, R = CH$_2$CHCH$_3$
          CH$_3$

VII, R = CH$_2$C$_6$H$_5$

In anhydrous AN, two step oxidation has been observed (Fig. 1) in agreement with the literature describing the oxidation of 10-methyl and 10-phenylpheno-

thiazine[4,5,11,12]. The calibration dependences are linear within $(0{\cdot}6 - 20) \cdot 10^{-5}$ mol .
. l^{-1} (the standard deviation of the linear regression did not exceed $1 \cdot 10^{-6}$ A),
the half-wave potentials are independent of the derivative concentration and are
determined by the structure of the substituent (Table I). The ratio of the convective-
-diffusional limiting currents for the first and the second anodic step is $i_1^1/i_1^2 = 0{\cdot}6$.
The degree of reversibility of the electrode processes was characterized by the CV
parameters[10] (Table II). The transport of the electroactive substance toward the
electrode was controlled by diffusion (DPV, CV) or convective diffusion (RDE).
In the first anodic step, one electron was exchanged quasireversibly (Table II, poten-
tiostatic coulometry and semilogarithmic analysis of the curves), with formation
of the radical cation, that was irreversibly (CV, v $0{\cdot}7 - 50$ V s^{-1}, Fig. 1, curve 1) or
quasireversibly (CV, v $50 - 270$ V s^{-1}, Fig. 1, curve 2), oxidized to the dication.
The dication is highly unstable and the reaction is considerably affected by the
interfering chemical reaction (Fig. 1). The reaction of the dication with the initial
derivative with formation of the radical cation is probable (the equilibrium constant
of this reaction obtained by CV is 10^{-11} to 10^{-12} in agreement with the literature[10]).
The formation of an unstable dimer of the C—C type is also possible.

At an acid concentration in AN higher than $5 \cdot 10^{-3}$ mol l^{-1}, the second anodic
wave or peak becomes split, in dependence on the acid concentration and the voltam-
metric method used (CV or DC on the RDE) and three or four-step oxidation is
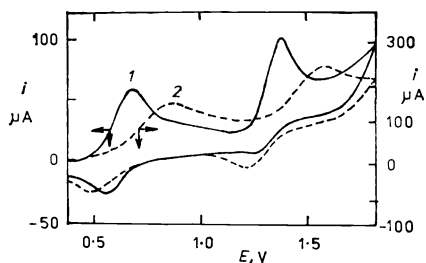observed (Fig. 2, curve 1). The effect of HClO$_4$ on the voltammetric behaviour was

FIG. 1

CV recording of the oxidation of I in $0{\cdot}1$M-
-NaClO$_4$ in AN; A $0{\cdot}033$ cm^2, $25°$C, 1st
cycle. 1 $8{\cdot}5 \cdot 10^{-4}$ mol l^{-1}, v 2 V s^{-1}; 2 $1{\cdot}3$.
. 10^{-3} mol l^{-1}, v 70 V s^{-1}
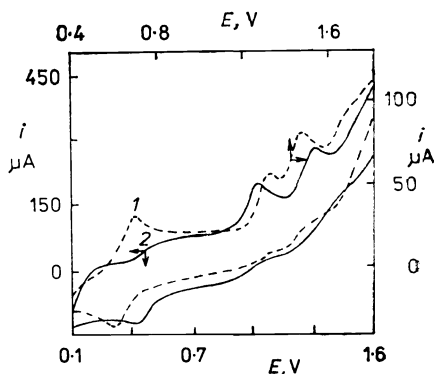
FIG. 2

CV recording of the oxidation of 1 I in
$0{\cdot}1$M-NaClO$_4$ in AN, with $0{\cdot}1$M-HClO$_4$, A
$0{\cdot}033$ cm^2, $25°$C, 1st cycle, c $7{\cdot}6 \cdot 10^{-4}$ mol .
. l^{-1}, v $2{\cdot}8$ V s^{-1}; 2 III in $0{\cdot}1$M-NaClO$_4$ in
AN, with $1{\cdot}0$M-HClO$_4$, A $0{\cdot}288$ cm^2, $25°$C,
1st cycle, c $8{\cdot}0 \cdot 10^{-4}$ mol l^{-1}, v $1{\cdot}36$ V s^{-1}

studied in AN containing 0.02 to $1.5 \, \text{mol} \, l^{-1}$ acid. The calibration curves of the studied derivatives were linear under the given conditions within a concentration range of $(0.6-20) \cdot 10^{-5} \, \text{mol} \, l^{-1}$ (the standard deviation of linear regression was not greater than $1 \cdot 10^{-6}$ A) and the half-wave potentials were determined by the substituent structure and the concentration of the acid (Table I). The first anodic step was controlled by diffusion (CV) or convective diffusion (RDE). Potentiostatic coulometry and semilogarithmic analysis of the curves indicate the exchange of a single electron in the first anodic step in presence of 0.02 to 1.5M-HClO_4 in AN, except for V with which one electron exchange was observed in presence of 0.02 to

TABLE I

Half-wave potentials for the anodic oxidation of the phenothiazine derivatives in AN, containing $0.1 \, \text{mol} \, l^{-1}$ NaClO_4, and varying concentration of HClO_4. A $0.111 \, \text{cm}^2$, $25°\text{C}$, ω 1 226 rpm, concentration of the derivatives $5 \cdot 10^{-5} \, \text{mol} \, l^{-1}$; the 1st, 2nd, 3rd anodic step, DC voltammetry at RDE

Compound	$E_{1/2}(V)$ at $c(\text{HClO}_4)$ (mol l^{-1})					
	0·00	0·05	0·10	0·50	1·00	1·50
I	0·40	0·43	0·44	0·45	0·46	0·46
	1·00	0·99	0·99	0·99	0·98	0·97
	—	1·15	1·18	1·22	1·23	1·23
II	0·37	0·45	0·46	0·49	0·49	0·49
	1·01	0·98	0·98	0·95	0·95	0·94
	—	1·16	1·18	1·21	1·21	1·21
III	0·37	0·43	0·43	0·45	0·47	0·47
	1·04	0·97	0·97	0·95	0·94	0·93
	—	1·15	1·16	1·19	1·21	1·22
IV	0·37	0·39	0·40	0·46	0·48	0·49
	1·01	0·96	0·95	0·95	0·94	0·94
	—	1·08	1·14	1·19	1·21	1·22
V	0·46	0·58	0·59	0·60	—	—
	1·08	0·98	0·98	0·97	0·96	0·95
	—	1·14	1·16	—	—	—
VI	0·43	0·42	0·43	0·47	0·49	0·49
	1·04	0·98	0·98	0·97	0·96	0·95
	—	1·16	1·17	1·22	1·24	1·24
VII	0·43	0·43	0·44	0·47	0·49	0·50
	1·09	1·01	1·01	1·00	0·99	0·98
	—	1·20	1·22	1·26	1·27	1·27

0.1M-HClO_4 in AN. The voltammetric parameters depended on the concentration of the acid (and thus also on the concentration of water because the acid was a 70% aqueous solution) and the derivative structure (Table I). Reversible or quasireversible exchange (Tables II, III, IV) of one electron yields the stable radical cation. Depending on the acid concentration, the potential scan rate and the derivative structure, the first anodic step was distorted and finally inhibited (Fig. 2, curve 2). This phenomenon was not observed in the cathodic part of CV recording and in DC voltammetry on the RDE (at ω $670-2\,100$ rpm), except for V with which the first step was not observed even in DC voltammetry at $0.5-1.5\text{M-HClO}_4$ and CV indicated inhibition already at v 1.3 V s^{-1} and 0.02M-HClO_4. This fact can be explained by a chemical reaction protonation, followed by dissociation of the protonated form prior to the electron-transfer reaction (the protonated form is electrochemically inactive). The effect of the preceding chemical reaction is thus perceptible at higher potential scan rates and depends on the substituent structure. The inhibition occurs in the order opposite to that of increasing half-wave potentials due to increasing acid concentration (I is oxidized most readily, inhibition occurs at v 170 V s^{-1} and 1.0M-HClO_4; V has the highest $E_{1/2}^1$ value, inhibition occurs at v 1.3 V s^{-1} and 0.02M-HClO_4).

The radical cation is oxidized irreversibly (for v $0.7-50$ V s^{-1}, CV) or quasireversibly at higher potential scan rates (for v $50-270$ V s^{-1}, CV), to the dication. The dication is more electrophilic and is stabilized by reaction with nucleophiles present. The third and fourth anodic steps satisfied criteria for totally irreversible systems (for v $0.47-270$ V s^{-1}). A protonated form of the sulphoxide (5-hydroxy-derivative) or sulphoxide was probably formed. The higher oxidation steps apparently correspond to the oxidation of sulphoxide at certain experimental conditions[5,12]. In this connection, the question is often discussed whether the radical cation or the dication preferentially reacts with nucleophiles. The reaction medium and the derivative structure play the predominant role. In our case, a disproportionation reaction of the radical cation with nucleophiles with formation of the sulphoxide is more probable.

The diffusion coefficients were determined for the formation of the radical cations from the Levich equation for the RDE voltammetry in anhydrous and acidic medium of AN, $0.02-1.5\text{M-HClO}_4$. They were in the range of $(0.5-1.9)\,.\,10^{-5}$ cm^2 s^{-1}, depending on the concentration of the acid.

The effect of water on some of the test derivatives was studied earlier[1], that on the other derivatives was analogous.

Base (diphenylquanine) distorted the voltammograms, especially the first anodic steps.

On the bases of the previous results, optimal conditions have been found for a DPV determination. The oxidation to the first step was utilized, with a platinum

TABLE II

Experimental and calculated data obtained by CV method in AN containing 0.1 mol l^{-1} $NaClO_4$; the 1st anodic step of 10-benzylphenothiazine (*VII*) (c $6 . 10^{-4}$ mol l^{-1}, A 0.111 cm^2, 25°C)

v^a $V s^{-1}$	E_p^a V	E_p^c V	ΔE_p V	$i_p^a . 10^6$ A	$i_p^c . 10^6$ A	i_p^a/i_p^c	$i_p^a/cv^{1/2}$	$i_p^c/cv^{1/2}$
							A mol^{-1} l V$^{-1/2}$ s$^{1/2}$	
0.7	0.71	0.63	0.080	22.0	12.0	1.8	0.044	0.024
5.0	0.71	0.61	0.100	47.5	35.0	1.4	0.036	0.026
10.0	0.72	0.60	0.120	67.5	47.5	1.4	0.036	0.026
50.0	0.75	0.57	0.180	155.5	110.0	1.4	0.037	0.026
71.4	0.76	0.56	0.200	180.0	140.0	1.3	0.036	0.028
167.0	0.80	0.54	0.260	290.0	220.0	1.3	0.038	0.029

^{a} $v = dE/dt$.

TABLE III

The effect of $HClO_4$ in AN medium containing 0.1 mol l^{-1} $NaClO_4$ on the anodic behaviour of 10-isobutylphenothiazine (*VI*) and 10-propylphenothiazine (*III*); A 0.111 cm^2, 25°C, v 0.47 V . . s^{-1}, the 1st anodic step, CV data

$c(HClO_4)$ mol l^{-1}	E_p^a V	E_p^c V	ΔE_p V	i_p^a/i_p^c	$i_p^a/cv^{1/2}$	$i_p^c/cv^{1/2}$
					A mol^{-1} l V$^{-1/2}$ s$^{1/2}$	
VI, $9.7 . 10^{-4}$ mol l^{-1}						
0.00	0.466	0.390	0.076	1.04	0.25	0.24
0.02	0.442	0.360	0.082	1.20	0.25	0.21
0.10	0.445	0.370	0.075	1.10	0.24	0.22
0.50	0.480	0.418	0.062	1.10	0.20	0.20
0.90	0.499	0.436	0.063	0.80	0.17	0.20
1.30	0.513	0.450	0.063	0.80	0.16	0.19
III, $7.8 . 10^{-4}$ mol l^{-1}						
0.00	0.410	0.321	0.089	1.04	0.20	0.19
0.02	0.424	0.340	0.084	1.00	0.19	0.19
0.10	0.465	0.385	0.080	1.00	0.18	0.18
0.50	0.510	0.425	0.085	0.85	0.15	0.18
0.90	—	0.436	—	—	—	—
1.30	—	0.436	—	—	—	—

disc electrode in AN containing $0·06M$-$HClO_4$. Optimum conditions for maximum sensitivity were: scan rate v $0·002$ V s^{-1}, modulation amplitude A' $0·05$ V, pulse frequency t' $0·2$ s; for a mixture of derivatives: A' $0·025$ V, v $0·02$ V s^{-1}, t' $0·2$ s. The concentration dependences for the studied derivatives were linear within the interval of $(0·2-7) . 10^{-6}$ mol l^{-1} (the standard deviation of linear regression did

TABLE IV

The effect of scan rate on the anodic behaviour of 10-isobutylphenothiazine (VI) (c $9·7 . 10^{-4}$ mol . l^{-1}) in AN medium, containing $0·1$ mol l^{-1} $NaClO_4$ and varying concentration of $HClO_4$. A $0·288$ cm^2, 25°C; the 1st step, CV data

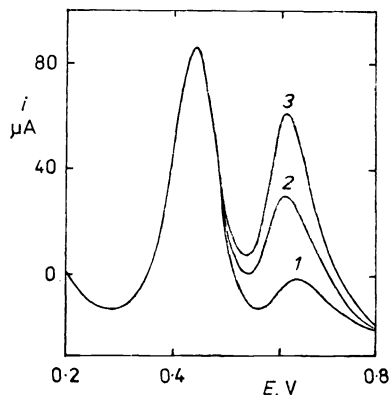| $c(HClO_4)$ mol l^{-1}	v V s^{-1}	E_p^a V	E_p^c V	ΔE_p V	$i_p^a . 10^6$ A	$i_p^c . 10^6$ A	i_p^a/i_p^c	$i_p^a/cv^{1/2}$ A mol^{-1} l V$^{-1/2}$ s$^{1/2}$	$i_p^c/cv^{1/2}$
0·02	0·46	0·442	0·360	0·082	164·1	140·6	1·2	0·25	0·21
	0·83	0·450	0·355	0·095	210·9	195·3	1·1	0·24	0·22
	5·00	0·474	0·330	0·144	468·8	438·1	1·1	0·22	0·20
	7·14	0·485	0·324	0·161	531·3	500·0	1·1	0·21	0·19
	10·00	0·490	0·312	0·178	593·8	593·8	1·0	0·20	0·20
	16·70	0·494	0·300	0·194	781·3	756·6	1·0	0·20	0·20
0·10	0·46	0·445	0·370	0·075	156·3	140·6	1·1	0·24	0·22
	0·83	0·450	0·360	0·090	210·9	195·3	1·1	0·24	0·22
	5·00	0·470	0·350	0·120	484·0	484·0	1·0	0·23	0·23
	7·14	0·474	0·342	0·132	500·0	531·3	0·9	0·20	0·21
	10·00	0·480	0·336	0·144	625·0	625·0	1·0	0·21	0·21
	16·70	0·494	0·325	0·169	812·5	828·1	1·0	0·21	0·21

FIG. 3

DVP recording of determination of a mixture of 10-ethylphenothiazine (II) (c $4 . 10^{-5}$ mol . l^{-1}) and 10-isopropylphenothiazine (V): 1 $2·6 . 10^{-5}$ mol l^{-1}; 2 $5·1 . 10^{-5}$ mol l^{-1}; 3 $7·6 . 10^{-5}$ mol l^{-1} in $0·1M$-$NaClO_4$ in AN, with $0·06M$-$HClO_4$, A $0·111$ cm^2, 25°C, A' $0·025$ V, v $0·002$ V s^{-1}, t' $0·2$ s

not exceed $0.04 \cdot 10^{-6}$ A). The peak potentials did not depend on the derivative concentration. (The relative standard deviations of the peak currents were max. 5%.) The detection limit amounted to $1 \cdot 10^{-7}$ mol l^{-1}. Fig. 3 depicts a possibility of determining the studied derivatives in a mixture. The use of DPV for determining the studied substances is relatively simple, rapid and sufficiently sensitive and permits determining in a mixture.

In addition to the principal voltammetric parameters the electron-donor properties of the studied derivatives were compared. The half-wave potentials of the studied derivatives confirm the fact observed earlier[1,2], that substitution in position 10 causes a deterioration in the electron donor properties due to a change in the molecular geometry and decreased participation of the heterocyclic hydrogen in delocalized system[13-15]. The difference in the half-wave potentials of the studied derivatives were too small to permit a mathematical correlation (mathematical relationships were sought for $E_{1/2}^1$ and σ^* and E_s). The oxidation proceeds more easily with straight carbon chain substituents than with branched ones and branching on C-1 causes a greater deterioration in the electron donor properties than that on C-2. Introduction of an aromatic ring into position C-2 has an effect analogous to branching on C-2. This behaviour can be explained by the effect of non-bonding interactions that are manifested by a change in the spatial arrangement of the heterocyclic phenothiazine system; the effect was strongest for V and also appeared with VI and VII. Analogous behaviour has also been observed with phenothiazine psychopharmaceuticals[2], with which an effect of alkylsubstituents containing nitrogen atoms has been demonstrated.

Summarizing the results obtained hitherto, we conclude that the electrochemical oxidation of the studied derivatives depends on the position and structure of the substituent and on the reaction medium, especially the presence of nucleophiles in AN. DPV is a suitable method for determination of derivatives of this type.

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