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# COMPARATIVE ELECTROCHEMICAL STUDIES ON SUBSTITUTED BENZOYL INDOLIZINE-1-CARBOXYLATES

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Indolizine derivatives have been used in medicine and pharmacology due to their biological activity and have also found application in modern sensors manufacturing technologies due to their capacity to form surface films. This work is devoted to the electrochemical study of ethyl 3-(4-bromobenzoyl) indolizine-1-carboxylate, ethyl 3-(4-chlorobenzoyl) indolizine-1-carboxylate and ethyl 3-(4-methylbenzoyl) indolizine-1-carboxylate by cyclic voltammetry (CV) and differential pulse voltammetry (DPV). The redox processes for each compound are established, analyzed and assessed to the particular functional groups at which they take place. The corresponding reaction mechanisms are formulated. The comparison between the electrochemical behaviour of the three compounds was connected to the similarities and differences in their structures.

## INTRODUCTION

This paper is the second of a series related to indolizines-1-carboxilates.[1] In recent years, the synthesis of macrocyclic compounds, which can reversibly respond to external actions (thermal, photochemical, electrochemical, pH, etc.) by changing important properties and characteristics (cavity size, surface shape, electronic structure, complexing ability, etc.) due to the specially introduced functional groups or fragments, has taken a special place in supramolecular chemistry.[2] Such "sensitive" heterocyclophanes containing redox-active biindolizine systems can serve as molecular switches[3] and membrane carriers[4] and are of great interest in the design of new sensors for modern technologies based on molecular processes. Unlike redox-active compounds (ferrocenes,[5-6] tetrathiafulvalenes,[7-8] and quaternized 4,4′-bipyridines[9-10]), biindolizines have found little use as active moieties, which make cyclophanes able to respond to external actions, in spite of the fact that biindolizines are quite stable two step redox systems, the electrochemical behaviour of which has been studied in sufficient detail.[11-16] Indolizines are π-rich compounds, which are readily oxidized (~0.2-0.3 V relative to $Fc/Fc^+$) to form radical cations.[11-15] The stability and subsequent transformations of radical cations are determined primarily by the presence of hydrogen atoms in the pyrrole ring of the indolizine system. The radical cations and dications of 3,3′-biindolizines, in which all hydrogen atoms in the five-membered ring are replaced by alkyl or aryl groups, are quite stable and can be isolated and characterized as perchlorates.[13] The electrochemical behaviour of two diastereomers of macrocyclic biindolizines, in which both heterofragments are linked at positions 3,3′ and, through a bridge, at positions 1,1′, is different.[14] Thus, the diastereomer having the *anti* configuration is oxidized to form stable radical cations and dications, whereas the oxidation of the diastereomer having the *syn* configuration is followed by the intramolecular cyclization with the involvement of the C(5) and

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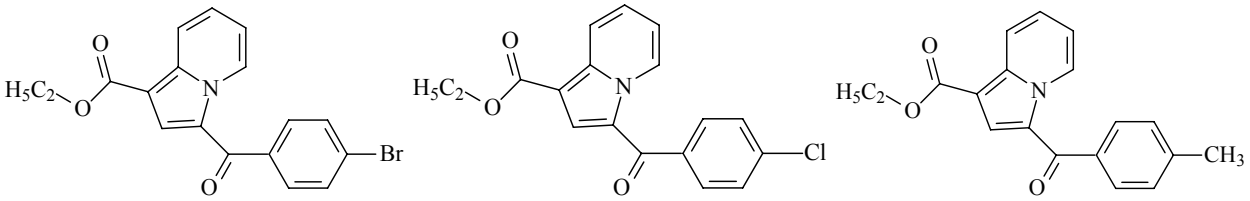
C(5′) atoms of the pyridine rings of the indolizine system having a favourable spatial arrangement.[17]

Indolizine derivatives possess valuable biological activity and have been studied for their psychotropic, anti-inflammatory, analgesic, antimicrobial, antiexudative and hypoglycemial effects.[18-21] Certain 1-indolizinols are easily oxidized to stable free radicals.[22] Therefore, oxygen-protected indolizinols may act as stable precursors for highly potent antioxidants, and it was found high inhibitory activity against lipid peroxidation *in vitro* for esters, ethers, carbonates, carbamates and sulfonates of indolizines as well as azaindolizines.[23] In order to establish the mechanism through which these antioxidant properties act, the electrochemical behaviour of several indolizine derivatives, esters, ethers, tolysilates, sulfonates and azaindolizines has been investigated by cyclic voltammetry and preparative electrolysis. The cyclic voltammetry data obtained were sensitive to the identities of the substituents and were used to characterise the principal oxidation process that took place in each case.[21] There are also some patents that stress the therapeutical effect of certain indolizine derivatives (1-glyoxylamide indolizines) in treating lung and ovarian cancer.[24]

The present paper is focused on the electrochemical behaviour of three benzoyl indolizine carboxylates with similar structure, which have a bromo, a chloro, and, respectively, a methyl substituent connected to the benzoyl fragment. The studied compounds were ethyl 3-(4-bromobenzoyl) indolizine-1-carboxylate (**I1**), ethyl 3-(4-chlorobenzoyl) indolizine-1-carboxylate (**I2**) and ethyl 3-(4-methylbenzoyl) indolizine-1-carboxylate (**I3**), Fig. 1. The compound **I3** was presented in a previous paper,[1] and was used for comparison.




**I1** **I2** **I3**

Fig. 1 – Structural formula of the investigated indolizines.

## Materials and methods

Acetonitrile ($CH_3CN$) and tetrabutylammonium terafluoroborate ($TBABF_4$) from Fluka were used as received as solvent and supporting electrolyte. The investigated compounds have been obtained by general procedure for synthesis of indolizines based on 1,3-dipolar cycloaddition reactions of heterocyclic-N-ylides with electron-deficient alkynes or alkenes, according to literature data.[25-26]

The experiments were carried out by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) using a PGSTAT12 AUTOLAB potentiostat and a three-compartment cell. The working electrode was a glassy carbon disk (diameter of 3 mm). The active surface was polished before each determination with diamond paste (200 μm). The Ag/10 mM $AgNO_3$ in $CH_3CN$ and 0.1 M $TBABF_4$ was used as reference electrode. The potential was referred to the potential of the ferrocene/ferricinium ion couple ($Fc/Fc^+$) which in our experimental conditions was +0.07 V. A platinum wire was used as auxiliary electrode. The determinations were performed at 25ºC under argon atmosphere.

Anodic and cathodic curves were recorded individually, starting from the stationary potential. CV and DPV curves were obtained for various concentrations (0 - 3mM) of the studied compounds. The CV curves were generally recorded at 0.1V/s or at various rates (0.05 - 1V/s) – when studying the influence of the scan rate and on various scan domains. DPV curves were recorded at 0.01V/s with a pulse height of 0.025V and a step time of 0.2s.

## RESULTS AND DISCUSSION

### Study of **I1**

The CV and DPV curves for increasing concentrations of the indolizine **I1** are presented in Fig. 2. There are observed three anodic (1a - 3a) and four cathodic (1c - 4c) processes, which are seen both

in CV and DPV. They were denoted in the order in which they appear in the voltammograms.

The influences of the scan rate and scan domain on the CV curves are presented in Fig. 3. The inset in Fig. 3a shows the dependence of the peak currents of 1a and 1c on the scan rate. The peak 2c presents a corresponding counterpeak 2c' in the reverse scan (Fig. 3b, c); all other processes do not show clear counterpeaks. The investigations were performed at a slower (0.1V/s) and a faster scan rate (1V/s) (Fig. 3b, 3c, respectively) in order to see if there are marked differences in the electrochemical reversibility of each process.

The linear dependences of 1a and 1c peak currents ($i_p$) and potentials ($E_p$) on the scan rate (v) are listed in Table 1. The nature of the peaks 1a and 1c, corresponding to the first electron transfers, is further examined in detail in order to establish the characteristic features. The other peaks appear to be electrochemically irreversible processes, as part of more complex mechanisms, and will be assigned further.

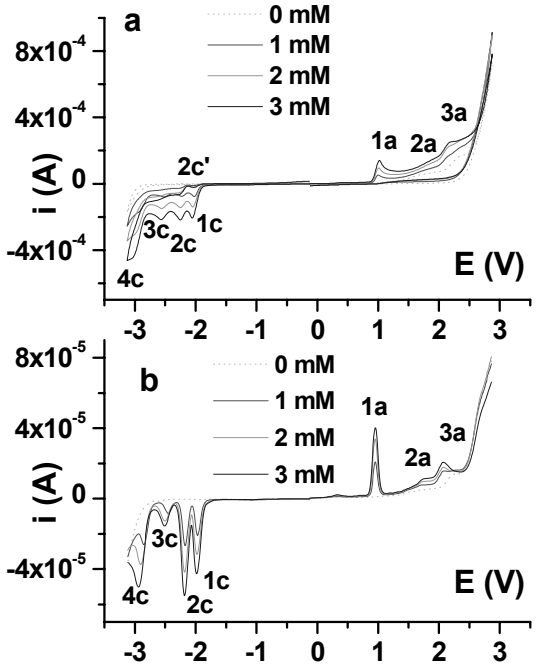



Fig. 2 – (a) DPV and (b) CV curves for various concentrations of **I1** in 0.1M $TBABF_4$, $CH_3CN$.

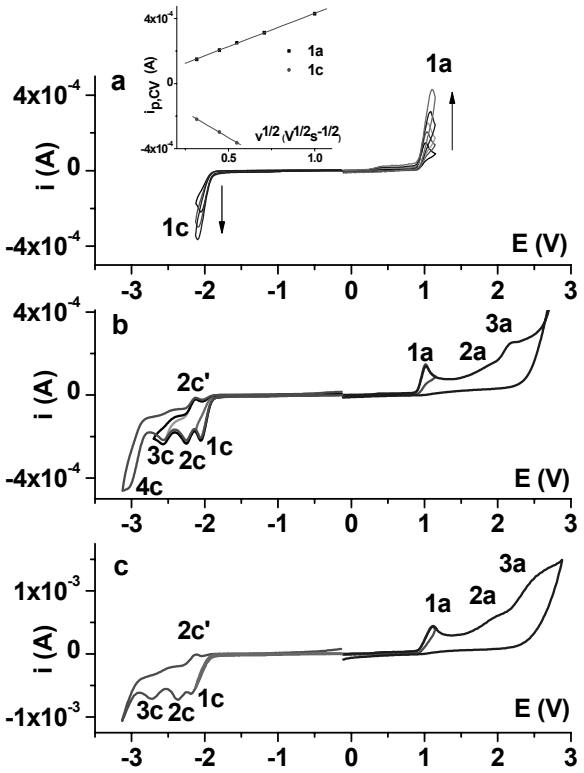



Fig. 3 – CV curves for various scan rates: 0.1; 0.2; 0.3; 0.5; 1V/s (a) and scan domains at 0.1V/s (b) and 1V/s (c) for **I1** (3mM) in 0.1M $TBABF_4$, $CH_3CN$.

*Table 1*

Linear CV peak currents and potentials dependences on scan rate for **I1**

| Peak | $i_p$, CV | $E_p$, CV |
|---|---|---|
| | Y (i, A); X ($v^{1/2}$, $(V/s)^{1/2}$) | Y (E, V); X (log (v, V/s)) |
| 1a | Y = 2.273E-5 + 4.085E-4 X $R^2$ = 0.999 | Y = 1.105 + 0.094 X $R^2$ = 0.963 |
| 1c | Y = -2.168E-5 - 6.210E-4 X $R^2$ = 0.999 | Y = -2.151 - 0.094 X $R^2$ = 0.976 |

## Study of **I2**

Fig. 4 shows the CV and DPV curves obtained for increasing concentrations of **I2**. There are observed two anodic (1a, 2a) and four cathodic processes (1c - 4c), which are correlated using the corresponding CV and DPV curves. The peaks 1c and 2c overlap in the CV curve, but DPV has the capacity to show them more separated.

The influences of the scan rate and scan domain on the CV curves are presented in Fig. 5. The inset in Fig. 5a shows the dependence of the peak current of 1a on the scan rate. The peak 2c presents a corresponding counterpeak 2c' in the reverse

scan; all other processes do not show clear counterpeaks. The investigations were performed again at two different scan rates (0.1V/s and 1V/s) in order to see if there are marked differences in the electrochemical reversibility of each process.

The linear dependence of 1a peak current and potential on the scan rate is given in Table 2. The peak 1a corresponds to the first electron transfer; its nature is further examined in order to establish its characteristic features. Since 1c and 2c overlap, the data for 1c cannot be read and processed properly. Except for 2c, all peaks appear to be electrochemically irreversible processes, as part of more complex mechanisms, and will be assigned further.

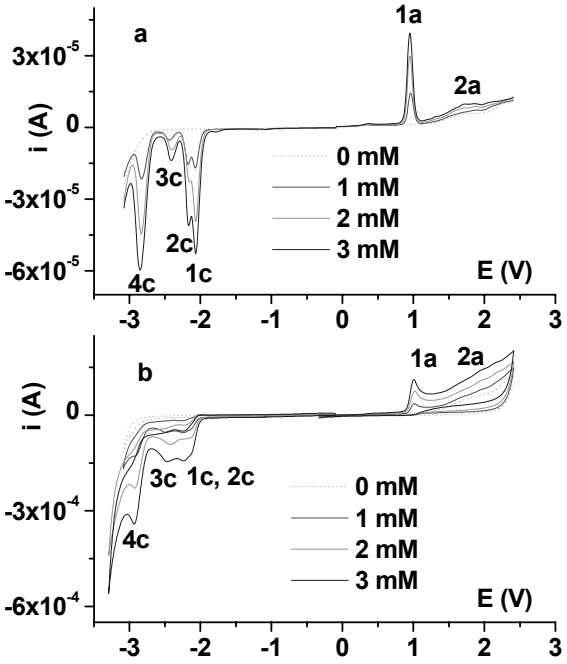



Fig. 4 – (a) DPV and (b) CV curves for various concentrations of **I2** in 0.1M $TBABF_4$, $CH_3CN$.

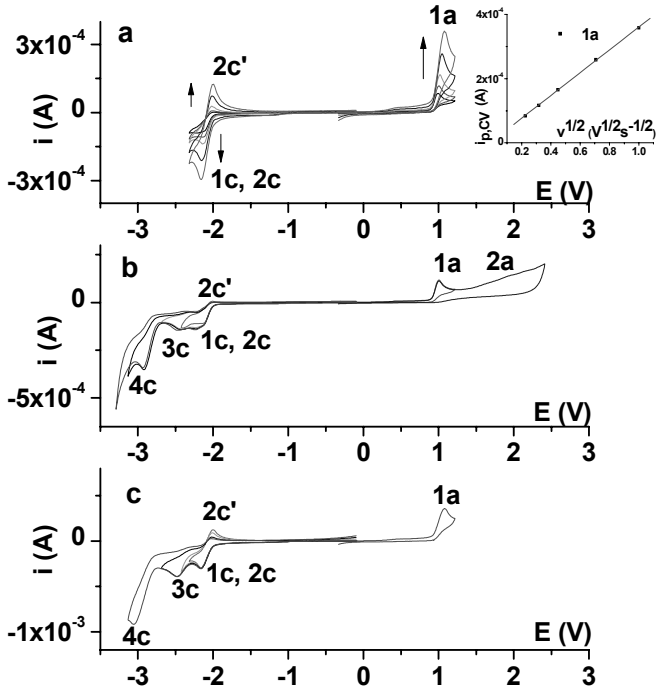



Fig. 5 – CV curves for various scan rates: 0.05; 0.1; 0.2; 0.5; 1V/s (a) and scan domains at 0.1V/s (b) and 1V/s (c) for **I2** (3mM) in 0.1M $TBABF_4$, $CH_3CN$.

*Table 2*

Linear dependence of 1a peak current and potential on scan rate for **I2** in CV

| Peak | $i_p$, CV | $E_p$, CV |
|---|---|---|
| | Y (i, A); X ($v^{1/2}$, $(V/s)^{1/2}$) | Y (E, V); X (log (v, V/s)) |
| 1a | Y = 5.583E-6 + 3.546E-4 X $R^2$ = 0.999 | Y = 1.070 + 0.064 X $R^2$ = 0.959 |

## Comparison between **I1**, **I2** and **I3**

### *Nature of first electron transfers*

Among the electrochemical processes that are observed when scanning, the processes 1a and 1c are the most important from the reaction mechanism point of view. They correspond to the first steps of electrochemical oxidation and reduction, respectively, that occur for the investigated compound. As in the case of any organic substrate, these steps lead to the formation of the radical cation and radical anion. The electrochemical nature of these processes was analyzed separately, for each compound, by taking into account several specific criteria, derived from the theories exposed by Bard,[27] Nicholson and Shain.[28] These criteria are expressed for the general case of a reduction process. For oxidation processes, the corresponding approach was used.

For the diagnosis of an irreversible cathodic process in CV, the following criteria were tested:

1. Absence of the anodic peak;
2. $i_{pc} \sim v^{1/2}$ liniar dependence;

3. $E_{pc}$ shifts with $30/\alpha_c n_\alpha$ mV per decade of v (at 25°C);
4. $E_p - E_{p/2} = 47.7/(\alpha_c n_\alpha)$ mV.
In 1 - 4: $E_{pc}$ / $i_{pc}$ - cathodic peak potentials/currents; v - scan rate; $E_{p/2}$ - half-peak potential; $\alpha_c$ - cathodic charge transfer coefficient; ($\alpha_c \approx 0.5$ for monoelectronic processes); $n_\alpha$ - number of electrons transferred in the rate determining step.

The dependence of $i_{pc}$ on concentration and scan rate for an irreversible process can lead to the calculation of the diffusion coefficient of the oxidized species $D_O$ (in $cm^2/s$) at $25^0$C, according to eqn. (1).

$$i_p = (2.99*10^5)n(\alpha_c n_\alpha)^{1/2} A c_O^* D_O^{1/2} v^{1/2} \qquad (1)$$

where n - number of transferred electrons; A - electrode surface ($cm^2$); $c_O^*$ - concentration of the oxidized species in solution ($mol/cm^3$).

For the compound **I1**, the peaks 1a and 1c from CV have been analyzed against the above criteria. After examining the nature of the peaks 1a and 1c, it was concluded that they are both irreversible electrochemical transfers, since all relevant criteria are accomplished. The diffusion coefficient calculated from 1a data is $10.1\times10^{-5}$ $cm^2/s$. Although they do not overlap as in the case of **I2**, the peaks 1c and 2c are quite closely spaced; consequently, when calculating the diffusion coefficient from 1c data, the obtained value would be distorted with respect to the value obtained from 1a data.

For the compound **I2**, a similar analysis has been performed, but only for the peak 1a. It was concluded that 1a is again an irreversible electrochemical transfer, all relevant criteria being accomplished. The diffusion coefficient calculated from 1a data is $3.4\times10^{-5}$ $cm^2/s$. As already mentioned, 1c could not be analyzed since it overlaps with the subsequent peak.

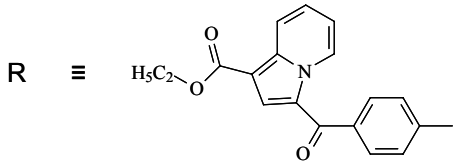
In Table 3, there are synthesized and compared the results for **I1** and **I2** discussed above with those obtained for **I3.**[1]

*Table 3*

Analysis of the nature of the first anodic and cathodic processes for **I1**, **I2** and **I3** in CV

| Compound | Structural formula | Peak | Electrochemical nature | $D_O \times10^5$ ($cm^2/s$) | Other parameters* |
|---|---|---|---|---|---|
| **I1** | R-Br | 1a | irreversible | 10.1 | - |
| | | 1c | irreversible | - | - |
| **I2** | R-Cl | 1a | irreversible | 3.4 | - |
| | | 1c | not yet established | - | - |
| **I3** | R-$CH_3$ | 1a | irreversible | 5.2 | - |
| | | 1c | reversible | 2.8 | $k_s$ = 0.029 cm/s; $k_c$ = 0.865 $s^{-1}$ |

* $k_s$ – rate constant of the electron transfer; $k_c$ – rate constant of the chemical reaction




It is observed that all 1a processes have a similar nature, while the processes 1c are different. These aspects are further discussed when assessing the processes to the functional groups at which they take place. The value of the diffusion coefficient obtained for the bromine substituted compound (**I1**) is, as expected, much higher than for the chlorine (**I2**) and methyl (**I3**) substituted compounds. Although it should be expected a slightly higher value of the diffusion coefficient for

**I2** than for **I1**, the last two are quite close, in the limit of experimental error.

*Assessment of the processes in CV*

By analyzing the results obtained for the three compounds in CV (Fig. 6), it was observed that **I1** presents three anodic and four cathodic processes (denoted 1a-3a and 1c-4c in Fig. 6). Except for 2c, which is reversible, all the other are electrochemically irreversible processes.

**I2** presents two anodic and four cathodic processes (denoted *1a-2a* and *1c-4c* with italic characters in Fig. 6). Except for *2c*, which is reversible, all the other are electrochemically irreversible processes.

**I3** presents two anodic processes (denoted 1a-2a and 1c-3c with underlined characters in Fig. 6). Except for 1c, which is reversible, all the other are electrochemically irreversible processes.

The reduction and oxidation processes of the compounds **I1**, **I2** and **I3** can be assigned based on the examination of the chemical structures, taking into account the specific potential of activity for each functional group.[29-31]

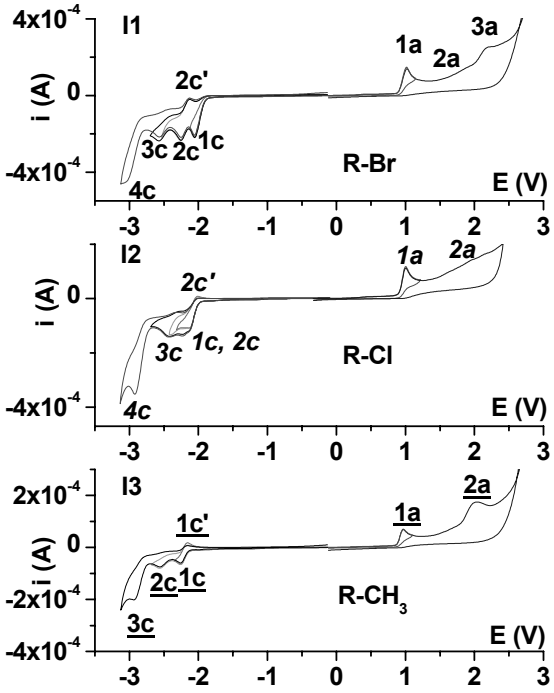
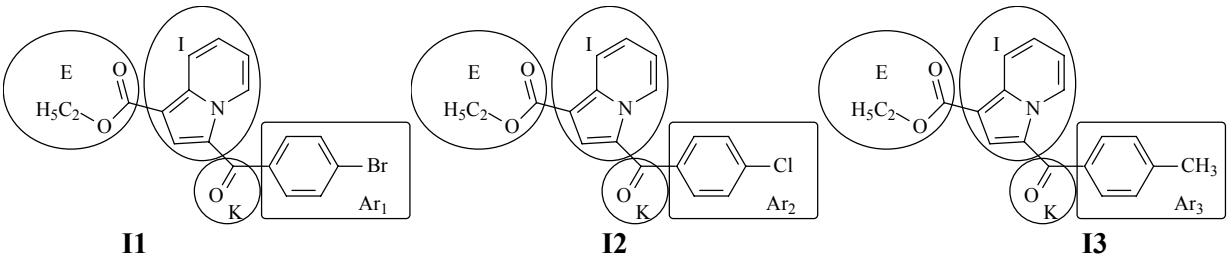



Fig. 6 – Comparison between the CV curves of the indolizines **I1**, **I2** and **I3** on all scan domains.

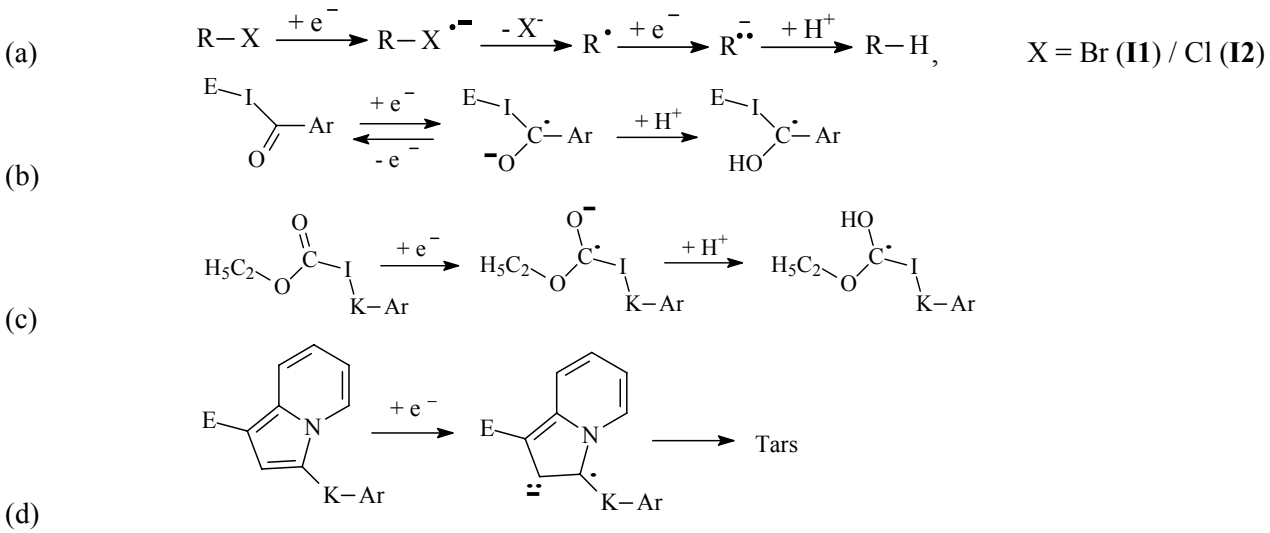



**I1** **I2** **I3**

Fig. 7 – Key fragments for the compounds **I1, I2** and **I3**: E - ester fragment; I - indolizine fragment; K - ketone fragment; $Ar_1$ / $Ar_2$ / $Ar_3$ - aryl fragments of **I1** / **I2** / **I3**.

When analyzing the structure of the compounds **I1** and **I2** (Fig. 7), it is observed that four reduction processes are most likely to occur at four particular functional groups, in the following order of increasing potential: the halogen groups (-Br / -Cl) in the aryl fragments ($Ar_1$ / $Ar_2$), the carbonyl groups from the ketone fragments (K), the carbonyl groups from the ester fragments (E) and the indolizine systems (I).[29-30] Consequently, the processes corresponding to the peaks 1c from **I1**

and *1c* from **I2** (Fig. 6) have been assigned to the irreversible reduction of the halogen groups through a reductive elimination mechanism[30-31] (Scheme 1a). The processes 2c of **I1** and *2c* of **I2** (Fig. 6) have been assigned to the reductions of the carbonyl groups from the ketone fragments (Scheme 1b). These reductions are reversible processes, which is also in agreement with the nature of the processes 2c of **I1** and *2c* of **I2**; this is why it was considered that the counterpeak that appears on the cathodic branch for **I2** corresponds to *2c'*. The peaks 3c of **I1** and *3c* of **I2** (Fig. 6), which appear to be electrochemically irreversible, could correspond to the irreversible reduction of the carbonyl groups from the ester fragments (Scheme 1c). Finally, the reductions that occurs at the most negative potentials for **I1** and **I2**, corresponding to peaks 4c and, respectively, *4c* (Fig. 6) could be attributed to the reductions that take place at the indolizine fragments (Scheme 1d), since such processes are destructive and can involve several electrons. These radical anions can further polymerize with tars formation. In the case of the compound **I3**, similar reduction processes occur; consequently, the process 1c-1c' (Fig. 6) was assigned to the reversible reduction of the carbonyl group from the ketone fragment (Scheme 1b); the peak 2c (Fig. 6) was assigned to the irreversible reduction of the carbonyl group from the ester fragment (Scheme 1c); the peak 3c (Fig. 6) was assigned to the destructive reduction of the indolizine system[1] (Scheme 1d). For all these processes, EC mechanisms were proposed (Scheme 1).

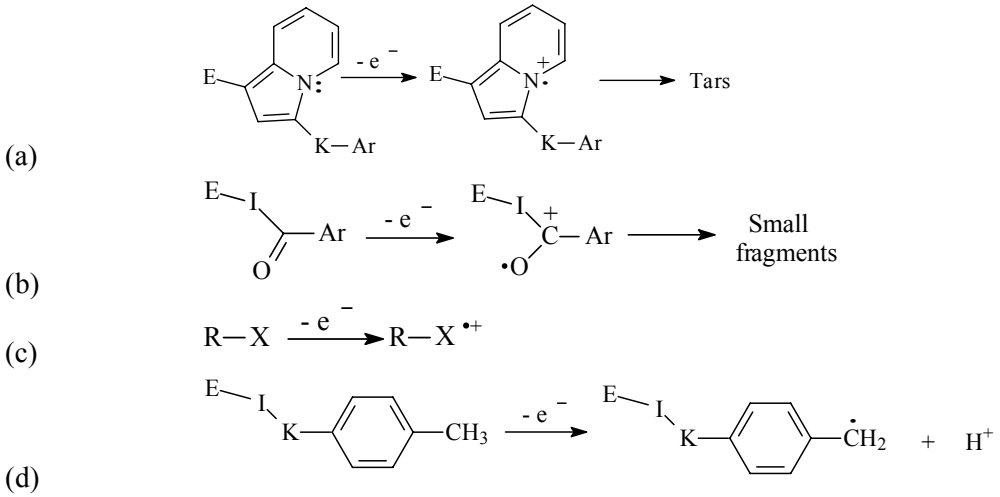



Scheme 1 – Reduction mechanisms.

As for the oxidation processes of the compounds **I1** and **I2**, it is observed that the nitrogen atoms from the indolizine fragments (I) are the most oxidizable, followed by the carbonyl groups in the ketone fragments (K).[29-30] Consequently, in both cases, the processes corresponding to the peaks 1a from **I1** and *1a* from **I2** (Fig. 6) have been assigned to the formation of the radical cations at the nitrogen atoms. These radical cations can further polymerize with tars formation (Scheme 2a). The processes 2a from **I1** and *2a* from **I2** have been assigned to the oxidations of the carbonyl groups in the ketone fragments (Scheme 2b). The process 3a of **I1** was assigned to the oxidation of the bromine atom (Scheme 2c). The corresponding oxidation of the chlorine atom for **I2** cannot be observed, since it takes place at higher potentials.[29-31] In the case of the compound **I3**, similar oxidation processes occur; consequently, the process 1a has been assigned to the formation of the radical cation at the nitrogen atom (Scheme 2a). The oxidation of the ketone carbonyl cannot be observed, perhaps because the process 2a overlaps on 1a. The process corresponding to the peak 2a has been assigned to the oxidation of the methyl group (Scheme 2d). For all oxidation processes, EC mechanisms were proposed (Scheme 2).

The above assignments are verified since: (i) the peak potential of 1c from **I1** is slightly lower (in absolute value) than that of *1c* from **I2**, because the bromine substituent is easier to be eliminated than the chlorine substituent;[30] this fact also explains why in the case of **I2** the peak *1c* falls over *2c*, while for **I1** this does not happen (Fig. 6); (ii) the peak potentials of 2c from **I1**, *2c* from **I2**

and 1c from **I3** are very close, as they all correspond to the ketone reduction; (iii) the peak potentials of 3c from **I1**, *3c* from **I2** and 2c from **I3** are very close, as they all correspond to the ester reduction, (iv) the peak potentials of 4c from **I1**, *4c* from **I2** and 3c from **I3** are very close, as they all correspond to the reduction of the indolizine system; (v) the peak potentials of 1a from the compound **I1**, *1a* from the compound **I2** and 1a from the compound **I3** are very close, as they all correspond to the oxidation of the nitrogen atom from the indolizine fragment, and (vi) the peak potential of 2a from the compound **I1** and that of *2a* from the compound **I2** are very close, as they both correspond to ketone oxidation (Fig. 6, Table 4).




Scheme 2 – Oxidation mechanisms.

*Table 4*

Assignment of the redox processes for **I1**, **I2** and **I3** in CV and DPV

| Compound | I1 | | I2 | | I3 | | Functional group involved |
|---|---|---|---|---|---|---|---|
| Peak*[a]/Technique | DPV | CV | DPV | CV | DPV | CV | |
| 1c/*1c* | -1.984 | -2.053 | -2.065 | -2.122 | - | - | halogen |
| 2c/*2c*/1c | -2.181 | -2.253 | -2.164 | -2.235 | -2.203 | -2.259 | ketone |
| 3c/*3c*/2c | -2.507 | -2.557 | -2.395 | -2.485 | -2.499 | -2.558 | ester |
| 4c/*4c*/3c | -2.939 | -3.029 | -2.852 | -2.921 | -2.843 | -2.916 | indolizine system |
| 1a/*1a*/1a | 0.953 | 1.019 | 0.951 | 1.008 | 0.920 | 0.971 | indolizine nitrogen |
| 2a/*2a* | 1.759 | 1.820 | 1.733 | 1.800 | -*[b] | -*[b] | ketone |
| 3a | 2.080 | 2.154 | - | - | - | - | bromine |
| 2a | - | - | - | - | 1.904 | 2.007 | methyl |

*a – normal, italic and underlined characters for **I1**, **I2**, **I3**, respectively; *b – not possible to be read, overlapping

## CONCLUSIONS

The investigated indolizines present similar electrochemical characteristics. The differences in behaviour are attributed to the structure differences. However, the common functional groups present electron transfers around the same potentials.

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