Voltammetric Studies on Some Substituted 5-Arylidene-2-Thiohydantoin in non Aqueous Medium

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Summary. Differently substituted 5-arylidene-2-thiohydantoins (**2 a — f**) were studied electrochemically in benzonitrile with 0.1 M tetra-n-butylammonium-perchlorate as supporting electrolyte using DC-, cyclic voltammetry (CV), coulometry and controlled potential electrolysis (CPE). These compounds are oxidized in a one two-electron transfer process or in irreversible two successive one-electron processes to the corresponding diradical, which simaltaneously reacts with the solvent to regenerate the starting species. On the other hand the reduction products are the 5-arylidene-4-imidazolidinone-2-thiols.

Keywords. 5-Arylidene-2-thiohydantoin; DC-Voltammetry; Cyclic voltammetry; Coulometry, Non aqueous medium.
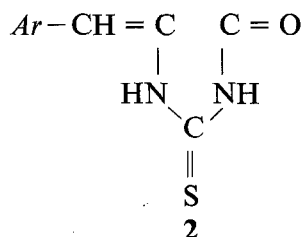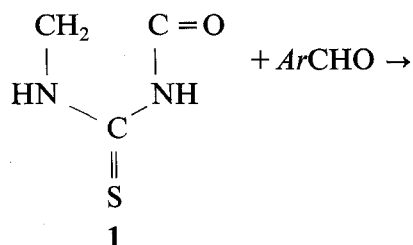
Voltammetrische Untersuchungen einiger substituierter 5-Aryliden-2-thiohydantoine in nichtwäßrigem Medium

Zusammenfassung. Es wurden verschieden substituierte 5-Aryliden-2-thiohydantoine (**2 a — f**) in Benzonitril mit 0.1 M Tetra-n-butylammoniumperchlorat als Leitsalz elektrochemisch untersucht, wobei DC-, Cyclische Voltammetry (CV), Coulometrie und kontrollierte-Potential-Elektrolyse (CPE) eingesetzt wurden. Die Verbindungen wurden entweder in einem Zweielektronen-Transferprozeß oder in zwei irreversiblen Prozessen aufeinanderfolgender Einelektronen-Stufen zum entsprechenden Diradikal oxidiert, welches simultan mit dem Solvens unter Regenerierung der Startspezies reagiert. Andererseits sind die Reduktionsprodukte die 5-Aryliden-4-imidazolidinon-2-thiole.

Introduction

5-Arylidene-2-thiohydantoin derivatives have been recommended for use in several cases of anoxia resulting from altitudes, in treatment of epilepsy, and as anticonvulsants and antiasthmatic [1 — 5]. However, literature survey revealed the absence of voltammetric data on this class of compounds in non aqueous media. Recent attemps to study the polarographic reduction of some thiohydantoin derivatives in aqueous media at the *DME* were described in literature [6 — 8]. The polarographic reduction of 5-substituted-4-thiohydantoins has been studied in ethanol/buffer media [8]. The reduction proceeds via a ECEC mechanism in acid media with the

formation of 5-benzyl-4-thiohydantoin and other products. In the following paper it was thought worthwhile to investigate the electrochemical redox characteristics of 5-arylidene-2-thiohydantoin derivatives (2 a − f) in benzonitrile using DC, cyclic voltammetry and coulometry at a rotating platinum disc electrode.

$$\begin{array}{ccc} CH_2 & C=O \\ | & | & +\text{\textit{Ar}CHO} \rightarrow \\ HN \diagdown \underset{C}{} NH \\ \| \\ S \\ \mathbf{1} \end{array}$$

$$\textit{Ar}-CH=C \quad C=O$$
$$| \quad |$$
$$HN \diagdown \underset{C}{} NH$$
$$\|$$
$$S$$
$$\mathbf{2}$$

2 a, $Ar = C_6H_5$
  b, $C_6H_4-OCH_3-p$
  c, $C_6H4-Cl-p$
  d, $C_6H_4-N(CH_3)_2-p$
  e, $C_6H_4-NO_2-m$
  f, $C_6H4-OH-p$

Experimental Part

Synthesis

A series of 5-arylidene-2-thiohydantoins (2 a − f) was synthesised. Compounds (2 a − c) were prepared according to reported procedures [9 − 11]. The new arylidene derivatives (2 d − f) were prepared as follows:

A mixture of 2-thiohydantoin (1) (0.01 mol), fused sodium acetate (2 g) and a slight excess (0.011 mol) of the appropriate aromatic aldehyde in 30 ml glacial acetic acid was refluxed for 2 h. During the reaction, the solution become dark brown in colour. The reaction mixture was cooled, poured into ice cold water, then the separated solid was filtered off, washed with water and recrystallised from acetic acid to give yellow crystals of 2 d − f (cf. Tables 1 and 2).

Reagents

Benzonitrile (*BN*) (Rotitainerm, W. Germany) was purified by a first distillation under vacuum from orthophosphoric acid, followed by repeated distillations from phosphorous pentoxide and a final fractional distillation from potassium metal.

The supporting electrolyte, tetra-*n*-butylammonium-perchlorate (*TBAP*) (Fluka-Swiss), was recrystallized several times from ethanol-water (9.1 *v/v*) mixture and dried in vacuum before use.

Table 1. 5-Arylidene-2-thiohydantoin derivatives **2 a − f**

Compound	M. p. (°C)	Yield (%)	Mol. formula	Analysis (%) calcd./found			
				C	H	N	S
2 a	260	85	$C_{10}H_8N_2OS$	58.82	3.92	13.72	15.68
				58.60	4.10	13.50	15.80
2 b	265	88	$C_{11}H_{10}N_2O_2S$	56.41	4.27	11.96	13.67
				56.60	4.50	12.20	13.50
2 c	272	82	$C_{10}H_7ClN_2OS$*	50.31	2.93	11.74	13.41
				50.50	3.10	11.90	13.50
2 d	251	80	$C_{12}H_{13}N_3OS$	58.29	5.26	17.00	12.95
				58.50	5.50	16.80	13.20
2 e	205	83	$C_{10}H_7N_3O_3S$	48.19	2.81	16.86	12.85
				48.00	3.10	16.60	13.00
2 f	293	88	$C_{10}H_8N_2O_2S$	54.54	3.63	12.72	14.54
				54.70	3.50	12.60	14.30

* Cl: calcd. 14.88, found 14.6

Table 2. IR and ^{1}H-NMR data of compounds **2 a − f**

Compound	IR (ν/cm^{-1})	^{1}H-NMR (δ/ppm)
2 a	3 370, 3 250 (2NH); 1 710 (C=O), 1 200 (C=S)	6.2 (s, 1 H, CH=C); 7.2 − 7.4 (m, 5 H, aromatic protons); 12.1, 10.8 (2 s, br, 2 H, 2 NH)
2 b	3 330, 3 190 (2 NH); 1 710 (C=O), 1 205 (C=S)	3.9 (s, 3 H, OCH₃); 6.5 (s, 1 H, CH=C); 7.1 − 7.4 (m, 4 H, aromatic protons); 11.9, 10.5 (2 s, br, 2 H, 2 NH)
2 c	3 400, 3 210 (2 NH); 1 720 (C=O), 1 210 (C=S)	6.3 (s, 1 H, CH=C); 7.2 − 7.5 (m, 4 H, aromatic protons); 11.5, 10.8 (2 s, br, 2 H, 2 NH)
2 d	3 350, 3 170 (2 NH); 1 700 (C=O), 1 200 (C=S)	2.7 (s, 6 H, 2 CH₃); 6.3 (s, 1 H, CH=C); 7.2 − 7.5 (m, 4 H, aromatic protons); 11.8, 10.3 (2 s, br, 2 H, 2 NH exchangeable with D₂O)
2 e	3 380, 3 240 (2 NH); 1 720 (C=O), 1 205 (C=S)	6.5 (s, 1 H, CH=C); 7.3 − 7.6 (m, 4 H, aromatic protons); 12.1, 10.5 (2 s, br, 2 H, 2 NH)
2 f	3 500 − 3 150 (OH, 2 NH), 1 710 (C=O), 1 210 (C=S)	

Instruments

The voltammetric measurements were carried out with the following apparatus. Potential Source: Potential Scan Cenerator VSG 72. Potentiostate: Potential Control Amplifier PCA 72 C (Bank Elec-

tronic, Göttingen, W. Germany). X-Y Recorder: Servogor XY (Metrowatt, Nürnberg, W. Germany).
Digital Multimeter: T 2201 (Hartman & Braun, Frankfurt, W. Germany). Coulometry: (Bank Electronic, Göttingen, W. Germany).

The rotating platinum disc electrocle (RDE) was mounted to a rotating motor (750 rpm, Metrohm, Swiss).

Melting points are uncorrected. The IR spectra were recorded on a Pye Unicam SP-1100 spectrophotometer. ^{1}H-NMR spectra were measured in $DMSO$-d_6 on a Varian EM-360 90 MHz spectrometer, using TMS as internal standard and chemical shifts are expressed as δ/ppm. Elementary analyses were performed by the Microanalytical Centre, Cairo University.

Measurements

All measurements were carried out under nitrogen atmosphere in dry benzonitrile (BN) containing 0.1 M tetra-n-butylammonium perchlorate ($TBAP$) as supporting electrolyte. The voltammetric studies involved the use of DC voltammetry at RDE and CV at stationary platinum disc electrode. The number of electrons participating in each electrode process was obtained using controlled potential coulometry (CPC) at a platinum sheet electrode of large surface area.

The electrode potentials were measured against saturated Ag/AgCl/Cl$^-$ (BN) electrode, which was from time to time calibrated against the redox potential of the cobaltocinium/cobaltocen system [12]. The standard potential of Ag/AgCl/Cl$^-$ (BN) electrode against the normal hydrogen electrode (NHE) is -176 mV [13, 14].

Controlled Potential Electrolysis (CPE)

CPE experiments were carried out twice in dry benzonitrile and in acetonitrile containing lithium perchlorate as supporting electrolyte. The potential was controlled at -0.7 V (reduction) and $+1.9$ V (oxidation) vs. Ag/AgCl/Cl$^-$ (BN) electrode (i. e. on the limiting current plateau of compound 2a taken as a typical representitive example of the studied series). The progress of electrolysis was followed by recording periodically the decrease in current with time. After complete electrolysis, the cell was disconnected from the circuit and the solvent was evaporated in vacuo. The remaining residue (yield 80%) was crystallised from acetic acid as yellow crystals and identified.

The CPE oxidation product was 5-benzal-2-thiohydantoin (regenerated 2a). Anal. Calcd. C 58.82, H 3.92, N 13.72, S 15. 68; found C 58.68, H 4.00, N 13.47, S 15.8. IR (KBr, v/cm^{-1}): 3 370, 3 250 (2 NH); 1 710 (C=O) and 1 200 (C=S). ^{1}H-NMR (δ/ppm): 6.2 (s, 1 H, CH=C), 7.2−7.4 (m, 5 H, aromatic protons), and 12.1, 10.8 (2 s, br, 2 H, 2 NH).

The CPE reduction product was 5-benzal-4-imidazolidinone-2-thiol. Anal. Calcd. C 58.25, H 4.85, N 13.59, S 15.53; found C 58.43, H 4.92, N 13.47, S 15.53. IR (KBr, v/cm^{-1}): 3 370, 3 250 (2 NH); 2 240 (SH); 2 900 (sat. CH) and 1 710 (C=O). ^{1}H-NMR (δ/ppm): 4.3 (s, 1 H, CH), 4.8 (s, 1 H, SH), 6.2 (s, 1 H, CH=C), 7.2−7.4 (m, 5 H, aromatic protons), and 12.1, 10.8 (2 s, br, 2 H, 2 NH).

Results and Discussion

The electrochemical redox data of compounds 2a−f are summarised in Table 3. Figures 1 and 2a, b illustrate (as an example) the DC voltammogramm and their corresponding cyclic voltammograms.

As shown in Table 3 the compounds 2a−f show both oxidation and reduction characreristics. Compounds 2a−c behave identically in both oxidation and reduction processes. They are oxidised in a two-electron wave in the potential range $+1\,517$ mV to $+1\,652$ mV. The values of the slope of the logarithmic analysis and the differences ($E_{3/4} - {}_{1/4}$) show that the oxidation processes of these compounds are irreversible in nature. The cyclic voltammograms corresponding to the oxidation
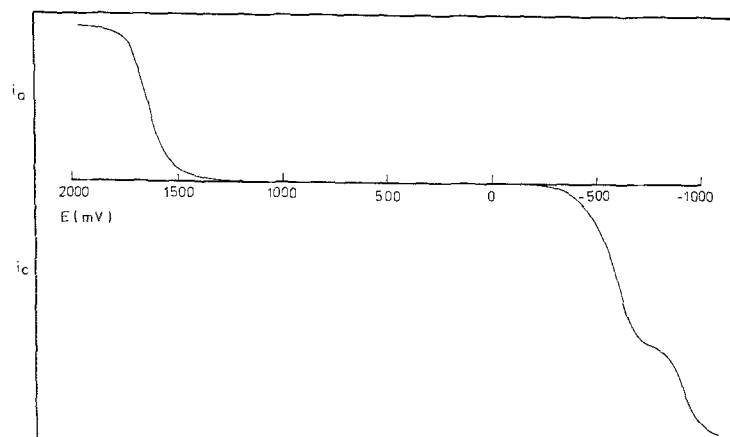
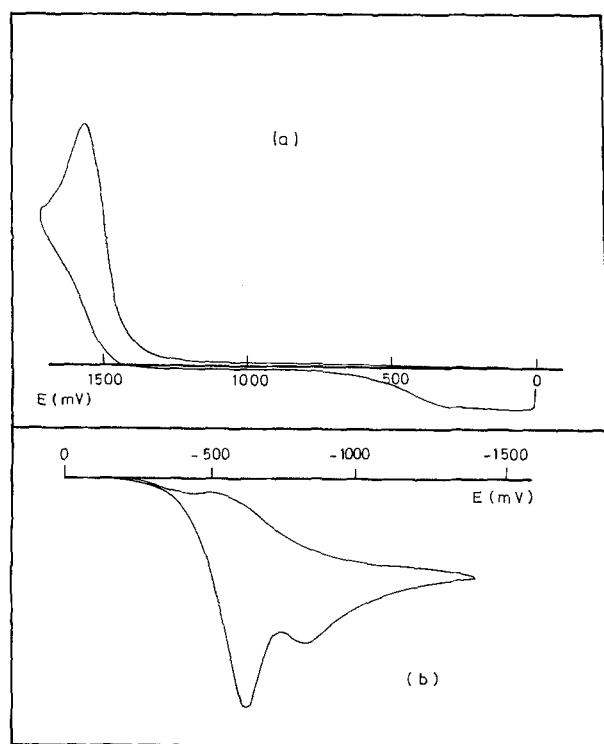**Fig. 1.** DC-volammogram of compound **2 b** in *BN*

Fig. 2. Cyclic voltammogram of compound **2 b** in *BN*. a) Oxidation. b) Reduction. Scan rate = 100 mV/
sec

show that the apparent irreversibility of the oxidation processes is due to a coupled
chemical reaction following the electron transfer process. This can be deduced from
the absence of the corresponding reverse peak to that of oxidation. The chemical
reaction product is electrochemically active and can be simultaneously reduced as
shown from the appearance of a reduction peak in the reverse CV cycle; i. e. the
oxidation process follows the well known ECE mechanism.

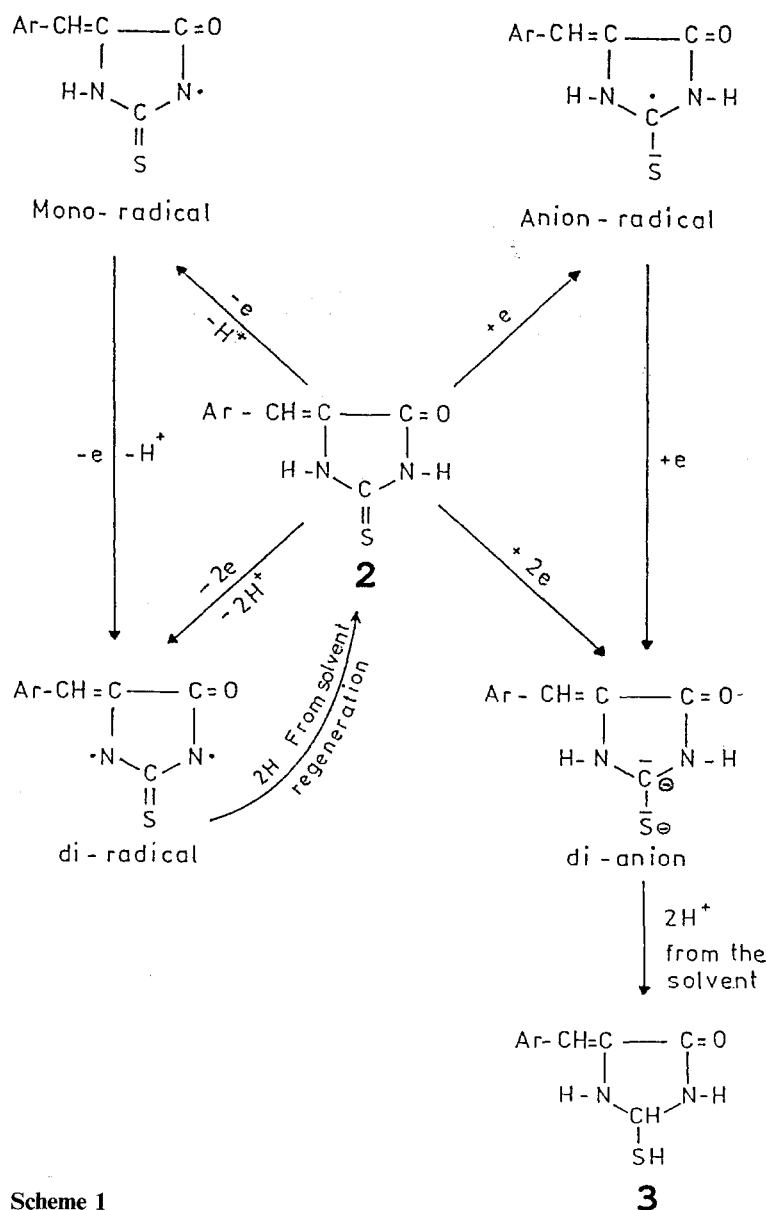**Table 3.** DC-Voltammetric data of compounds **2a–f**.
$S = \delta E / \delta(\log(i_d - i)/i)$

Compound	Process	$E_{1/2}$ (mV)	$E_{3/4} - E_{1/4}$	S
2a	O_I	1652	160	155.79
	R_I	−528	125	98.92
2b	O_I	1517	105	102.47
	R_I	−673	110	95.18
2c	O_I	1643	80	67.71
	R_I	−758	155	154.40
2d	O_I	867	120	103.00
	R_I	−793	150	175.46
	R_{II}	−1143	110	95.55
2e	O_I	−	−	−
	R_I	−588	110	129.88
	R_{II}	−1128	95	102.31
2f	O_I	1257	120	108.73
	O_{II}	2187	140	121.46
	R_I	−733	160	195.56

Compound **2d** behaves similarly upon oxidation, as **2a–c**. Thus **2d** is reduced in two successive irreversible one-electron waves. The difference in the half-wave potential values of these two waves is rather small (−793 mV and −1143 mV) which means that the -N(CH$_3$)$_2$ group stabilizes to some extent the product of the first electron transfer. On the other hand compound **2e** shows no oxidation characteristics but only two successive reduction waves are displayed. The first two-electron wave is simmilar to the above mentioned one for compounds **2a–c**, while the second two-electron wave has the known characteristic of the reduction wave of the nitro group in non aqueous benzonitrile. The difference in $E_{1/2}$-values of the two reduction waves (−588 mV and −1128 mV) is a further confirmation that the second wave is the characteristic reduction wave of the nitro group. Finally, it is worthy mentioning that the *p*-hydroxy derivative **2f** reduces similarly, differing only in its oxidation behaviour. It is reduced in two successive irreversible one-electron oxidation waves.

Based on the foregoing results one may conclude that these compounds are reduced in a two-electron process or in two successive one-electron transfers forming the anion-radical and the dianion respectively. This active dianion reacts chemically with the solvent through which it accepts two protons to form the corresponding thiol derivative (**3**) (main product) which has been isolated and identified in CPE experiments. It is conceivable that the dianion produced in the two-electron tranfer would be a base strong enough to abstract protons from the solvent [15, 16]. The effect of small quantities of water must be considered and hence very dry benzonitrile was used (< 0.4 mM water) for this work in order to ensure that, if protonation does occur, the protons come mainly from the solvent and not from residual water.

On the other hand the oxidation process is directly related to the reduction process. Thus these species are oxidised in a two-electron transfer or in two one-electron transfers resulting in the splitting of two protons and hence forming the mono-radical and the di-radical respectively. The formed di-radical reacts simultaneously with the solvent [15, 16] to regenerate the starting compound 2. This is confirmed through characterisation of the product of CPE as previously mentioned. The redox mechanism of series (2 a − f) is illustrated in Scheme 1.

Ar-CH=C ——— C=O
$\quad$ | $\qquad$ |
H-N$_{\diagdown}$$_{\text{C}}$$_{\diagup}$N•
$\qquad$ ||
$\qquad$ S

Mono- radical

Ar-CH=C ——— C=O
$\quad$ | $\qquad$ |
H-N$_{\diagdown}$$_{\text{C}}$$^{•}$N-H
$\qquad$ |
$\qquad$ S

Anion - radical

−e −H$^+$ $\qquad$ +e

Ar - CH=C ——— C=O
$\quad$ | $\qquad$ |
H-N$_{\diagdown}$$_{\text{C}}$$_{\diagup}$N-H
$\qquad$ ||
$\qquad$ S

2

−2e −2H$^+$ $\qquad$ +2e

2H$^+$ From solvent regeneration

Ar-CH=C ——— C=O
$\quad$ | $\qquad$ |
•N$_{\diagdown}$$_{\text{C}}$$_{\diagup}$N•
$\qquad$ ||
$\qquad$ S

di - radical

Ar- CH=C ——— C=O$^-$
$\quad$ | $\qquad$ |
H-N$_{\diagdown}$$_{\text{C}}$$^{\ominus}$N-H
$\qquad$ |
$\qquad$ S$\ominus$

di -anion

2H$^+$
from the solvent

Ar- CH=C ——— C=O
$\quad$ | $\qquad$ |
H-N$_{\diagdown}$$_{\text{CH}}$$_{\diagup}$N-H
$\qquad$ |
$\qquad$ SH

Scheme 1 $\qquad\qquad$ **3**

It is clear that both NH centers are vulnerable towards oxidation. C=S is more favoured over the activated C=O upon electroreduction, due to the stabilisation of the latter through conjugation and thus rendering the thio-keto moiety relatively less stable and hence the reducible moiety in non aqueous media.

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