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The Electroreduction of Pyrazolone Glyoxalic Ester Derivatives in Aqueous Buffered Media

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Summary. The polarographic reduction of two series of pyrazolone derivatives in alcoholic buffered media indicated that these molecules predominate in the hydrazone form and are reduced via a $4e^-$ irreversible process. The main electrolysis products, 3,6-bis(pyrazoline-5-on-3yl)piperazine-2,5-dione (**3**), and 3,6-bis(1-phenyl-pyrazoline-5-on-3yl)piperazine-2,5-dione (**4**) were isolated and identified. A mechanism has been suggested and discussed.

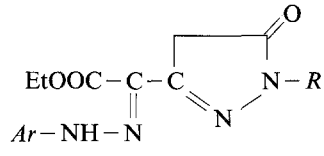
Keywords. Electroreduction; Pyrazolone derivatives.

Die Elektroreduktion von Pyrazolon-Glyoxalester-Derivaten in wäßrigem, gepuffertem Medium

Zusammenfassung. Die polarographische Reduktion zweier Serien von Pyrazolon-Derivaten in alkoholisch-wäßrigem, gepuffertem Medium zeigt, daß diese Moleküle bevorzugt in der Hydrazono-Form vorliegen und über einen irreversiblen $4e^-$-Prozeß reduziert werden. Die Hauptprodukte der Elektrolyse, 3,6-bis(pyrazolin-5-on-3-yl)piperazin-2,5-dion (**3**) und 3,6-bis(phenylpyrazolin-5-on-3-yl)piperazin-2,5-dion (**4**) wurden isoliert und identifiziert. Ein Mechanismus wird vorgeschlagen und diskutiert.

Introduction

The chemistry and biological activity of pyrazole functionality fused to heterocyclic ring system have attracted the attention of many workers, this led to the synthesis



1, $R = H$ **2**, $R = C_6H_5$

a $Ar = C_6H_5$
b $Ar = 4\text{-}Cl - C_6H_4$
c $Ar = 4\text{-}CH_3 - C_6H_4$
d $Ar = 4\text{-}OCH_3 - C_6H_4$

of a varity of pyrazole derivatives exhibiting bacteriostatic, bacteriocidal analgetic and antiinflammatory activities [1–6].

In the present work 3-[glyoxalicester-arylhydrazone]-5-pyrazolones (**1 a–d**) and 1-phenyl-3-[glyoxalicester-arylhydrazone]-5-pyrazolones (**2 a–d**) have been studied at a DME and Hg pool cathode.

Experimental

Synthesis

The arylamine azo-acetone dicarboxylic ester (0.01 mol) was added to hydrazine or phenyl hydrazine (0.01 mol) in cold acetic acid (25 ml [7]), the mixture was left overnight. The solid product was collected by filtration, washed with ethanol and crystallized from ethanol (cf. Table 1).

Instruments

The *i-E* curves were recorded on a Tacussel PRT 40 potentiostat EPLI recorder and PRG 3 pilot with a conventional three electrode system. The cell was a Tacussel RMO 4 cell. The capillary was Tacussel MTS 124 ($m = 0.33\,g\,s^{-1}$ for $h = 50\,cm$ and controlled by a hammer with the frequency of 1 Hz). The number of electrons was computed with a Tacussel type IG 3A electronic integrator in conjunction with the potentiostat. The absorption spectra were scanned on a PYE Unicam 500 Spectrophotometer within the wavelength range 550–200 mm. The ir spectra were recorded in KBr pellets on a Perkin Elmer 397 instrument. The half-wave potentials are expressed versus SCE (with an accuracy of ± 0.005 V). All measurements wre carried out at room temperature 25° ± 2 °C.

Solutions and Procedures

Stock solutions (10^{-3} mol dm^{-3}) were prepared in absolute *Et*OH. 1 ml stock solution was transferred into the cell containing the supporting electrolyte (Britton-Robinson modified universal buffers) [8] and the final concentration was 10^{-4} mol dm^{-3} of reactant in 50% by volume alcoholic buffer mixture. Finally the solution was deaerated with H_2 gas for about 5 min.

Coulometry and Preparative Electrolysis

After filling the cell with the proper electrolyte, dissolved oxygen was removed from the solution by bubbling through a stream of H_2 gas for 30 min. Prior to addition of the studied compound the e.m.f.

Table 1. Data of compounds **1 a–d** and **2 a–d**

Compound no.	Molecular formula[a]	M.P./°C	Yield %
1 a	$C_{13}H_{14}O_3N_4$	170	85
1 b	$C_{13}H_{13}O_3N_4Cl$	196	88
1 c	$C_{14}H_{16}O_3N_4$	187	90
1 d	$C_{14}H_{16}O_4N_4$	207	85
2 a	$C_{19}H_{18}O_3N_4$	138	87
2 b	$C_{19}H_{17}O_3N_4Cl$	177	85
2 c	$C_{10}H_{20}O_3N_4$	171	80
2 d	$C_{20}H_{20}O_4N_4$	136	85

[a] Elemental analysis of C, H, N, and Cl gave results which were equal to those calculated within experimental error

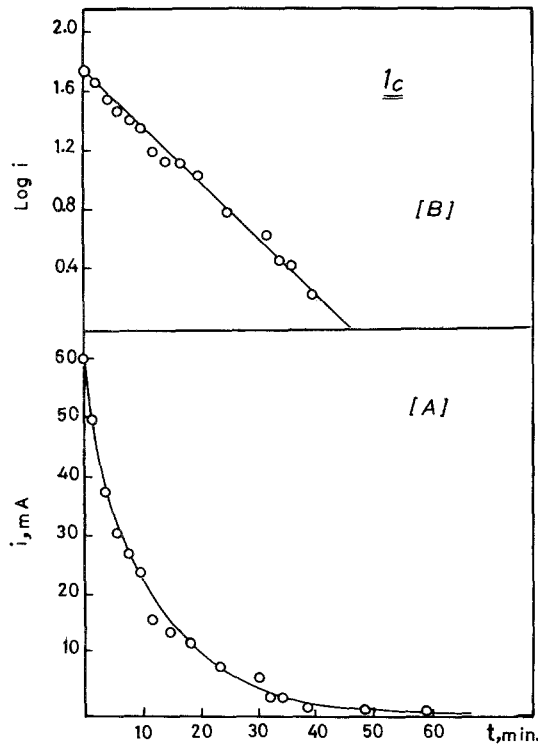


Fig. 1. Controlled potential electrolysis plots of compound **1c**; *A*: *i-t* plot., *B*: log *i-t* plot

was adjusted and controlled by the potentiostat at a value of -0.2 V more negative than the characteristic $E_{1/2}$ of the wave of the compound under investigation. The applied e.m.f. was then adjusted to the half-wave potential value. A known weight of the depolarizer was then added into the cell. The progress of electrolysis was followed by recording the decrease in current, when the current reached a constant value of few microampers, the electrolysis was stopped. The number of electrons "*n*" was computed electronically for these compounds using an electronic integrator connected to the main potentiostatic unit and found to be $4e^-$ in acid medium. In addition, using the classical Lingane [9] method, "*n*" was also calculated from log *i-t* plots of the following-up CPE experiments on 350 mg of **1c** at *pH* 1.85 and on 280 mg of **2c** at *pH* 1.55 (Fig. 1), by applying equation

$$\log i_t = \log i - \frac{(K)}{2.303} \cdot t,$$

i_0 and K values were computed to be $60 \cdot 10^{-3}$ A, $14.5 \cdot 10^{-4}$ and $44 \cdot 10^{-3}$ A, $14.17 \cdot 10^{-4}$ for **1c** and **2c**, respectively. From these values the quantity of electricity "*Q*" was calculated using $Q = i_0/K$ and found to be 41.18 and 31.05 for **1c** and **2c**, respectively. Substituting these latter values in equation

$$Q = nF(W/M)$$

gave values of 4.11 and 4.18 electron per molecule for the two compounds respectively.

Controlled Potential Electrolysis (CPE). Separation and Identification of Electrolysis Products

One compound from series **1** and another one from series **2**, namely 3-[glyoxalicester-phenyl-hydrazone]-5-pyrazolone (**1a**) and 1-phenyl-3-[glyoxalicester-(4-chlorophenyl-hydrazone)]-5-pyrazolone (**2b**) were taken as typical representative examples.

Preparative electrolysis procedure. CPE was carried out with 250 mg of the compound. The solution (199 ml ethanol + 70 ml 10 *N* HCl) was introduced into the electrolysis cell. Prior to electrolysis, H_2

gas was bubbled in the solution for 15 min. The potential was then adjusted to − 0.90 V vs. SCE and electrolysis was started (max. electrolysis current recorded at the starting point was 80 mA) and stopped after complete electrolysis (when the current reached a steady value of 3 mA). The solution was removed and the *pH* was checked to be 0.60. The solution was then evaporated to approximately half of its original volume, adjusted with concentrated NaOH to *pH* 6 and then extracted with ether the ethereal layer was then evaporated.

In the second electrolysis, the potential was adjusted at a value of − 0.75 V vs. SCE. The electrolysis in this latter case was followed by recording the decrease in current with time (starting value 70 mA). After complete electrolysis (3 mA) the cell was disconnected from the circuit and the solution (*pH* 0.7) was evaporated to $^1/_3$ of its original volume, extracted with ether and finally the etheral layer was evaporated. From the mother liquors of both experiments aniline and *p*-chloroaniline were identified by the azo-dye test [10] which gave positive results.

Isolation and identification of the main electrolysis product of **1 a**. The resulting brownish product yield 60%; m.p. 139 °C; ir (KBr): 3 600–3 300 (NH), 1 650–1 630 (C=0), 1 480 (C=N) cm^{-1}ms, $m/z = 27 (M^+)$; elem. anal. C 43.2, H 3.6, N 30.31] was identified as 3,6-bis-pyrazoline-5-one-3-yl)-piperazine-2,5-dione (**3**).

Isolation and identification of the main electrolysis product of **2 b**. The obtained deep red compound [yield 60%; m.p. 128 °C; ir (KBr); 3 200–2 950 (NH), 1 740–1 660 (C=O), 1 490 (C=N) cm^{-1}; ms, $m/z = 430 (M^+)$; elem. anal. C 61.3, H 4.66, N 19.55] was identified as 3,6-bis-(1-phenylpyrazoline-5-one-3-yl)piperazine-2,5-dione (**4**).

Spectrophotometric Measurements and Determination of the Apparent Acid Dissociation Constants

Spectrophotometric measurements were carried out using a PYE Unicam 500 spectrophotometer supplemented with a program controller automatic linear recording unit. The runs in the visible and uv ranges were carried out on $2 \cdot 10^{-5}$ mol dm^{-3} of the studied compounds in 50% (*v*/*v*) alcoholic Britton-Robinson buffer solutions. The spectrophotometric measurements were recorded as a function of *pH* of solution. pK_a values were then calculated using the graphical correlation between *pH* and absorbance 11 (Tab. 1 and 2).

The spectra of series **1** and **2** are characterized by two absorption maxima at 430 and 390 nm and one absorption maximum at 400 nm.

Results and Discussion

The polarographic curves obtained with compounds **1 a** and **2 a** selected as typical examples for both studied series are reproduced in Fig. 2 for **1 a**. As revealed from Fig. 2 the polarograms of each compound displayed a four electron diffusion controlled irreversible wave. The effect of variation of *pH* on their half-wave potentials (*E*) and limiting current (i_e) are given in Fig. 3. *E* of this wave is *pH*-dependent shifting towards negative potential with increase of *pH*, this shift is described by two linear segments, and i_e of this wave decreases with increase of *pH* in the form of a well defined dissociation curve.

The characteristic data of series **1** are compiled in Table 2 (Fig. 3). Series **2** showed similar behavior as **1**. The characteristic data of **2** are compiled in Table 3.

Acid-Base Equilibrium and Mechanism of the Electrode Process

The substitution of the hydrogen atom of **1** in position "1" by a phenyl moiety to yield **2** will change the actual tautomerism in these molecules. The tautomeric forms

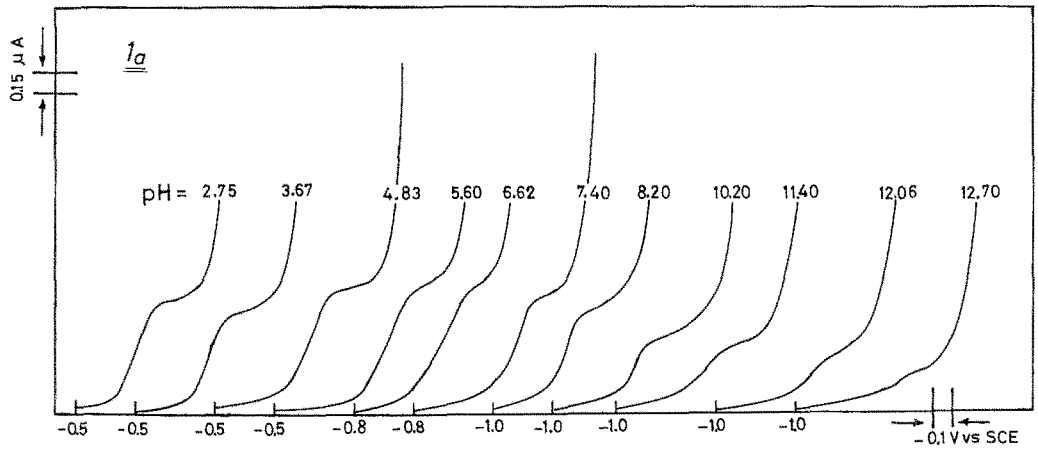


Fig. 2. Polarograms of 10^{-4} mol dm^{-3} compound **1 a** in 50% (*v*/*v*)ethanolic Britton-Robinson buffers

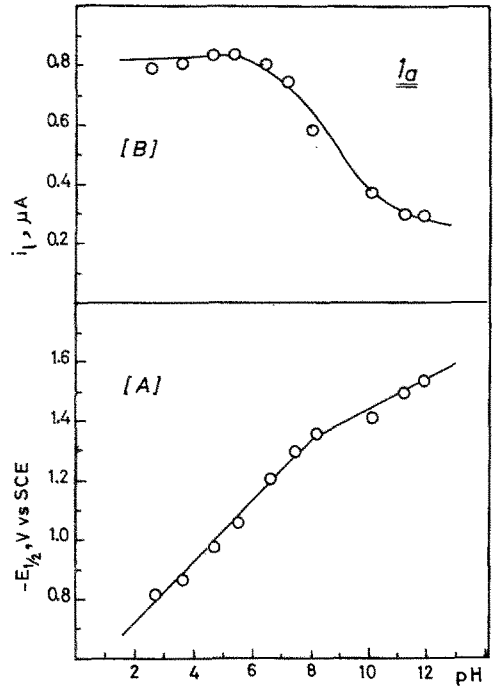
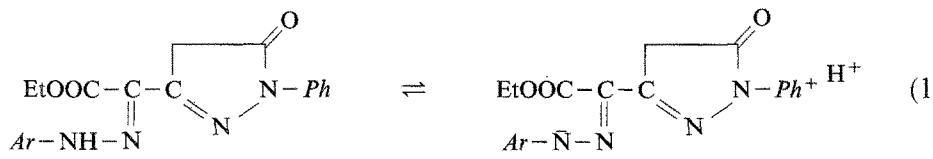


Fig. 3. *A*: $E_{1/2}$-, *B*: i_e-*pH* plots for the polarographic wave of compound **1 a**

of series **1** are illustrated in Scheme 1. While by blocking the labile hydrogen through phenyl substitution at N-1, the N-NH can only be involved in tautomerization as represented by equilibrium (1).



(1)

Table 2. Polarographic data of series **1**

Compound	$E_{1/2}-pH$	$RT^c/\alpha nF$	αn	pH^d	$pK_{a_1}{}^e$	$pK_{a_2}{}^e$
1a	$E_{1/2} = -0.53 - 0.102pH^a$	0.087	0.68	2.76	8.6	10.25
	$E_{1/2} = -0.93 - 0.050pH^b$	0.050	1.18	8.20		
		0.050	1.18	11.40		
1b	$E_{1/2} = -0.49 - 0.103pH^a$	0.067	0.88	2.90	8.35	10.1
	$E_{1/2} = -0.94 - 0.042pH^b$	0.083	0.71	7.20		
			0.04	11.48	10.50	
1c	$E_{1/2} = -0.48 - 0.120pH^a$	0.053	1.12	3.20	8.8	10.5
	$E_{1/2} = -1.02 - 0.048pH^b$	0.057	1.04	7.10		
		0.057	1.04	11.80		
1d	$E_{1/2} = -0.60 - 0.100pH^a$	0.069	0.68	2.40	9.10	10.9
	$E_{1/2} = -1.02 - 0.050pH^b$	0.049	1.21	6.30		
		0.052	1.14	8.00		

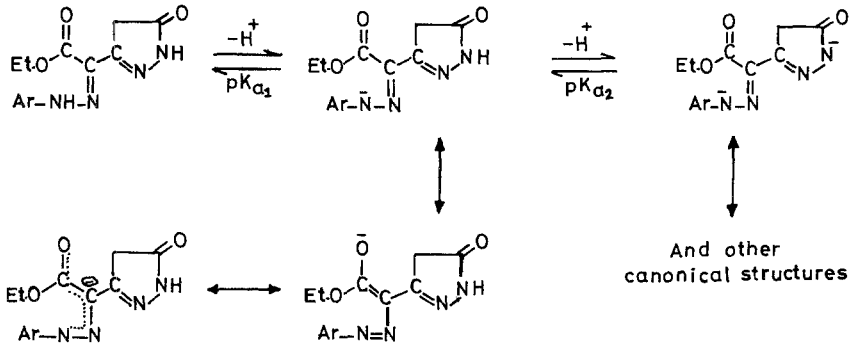
[a] Equation of first segment
[b] Equation of second segment
[c] Logarithmic analysis slope
[d] Individual *pH* value at which logarithmic analysis was carried out
[e] Spectrophotometric acid dissociation constant

Table 3. Polarographic data of series **2**

Compound	$E_{1/2}-pH$	$RT^c/\alpha nF$	αn	pH^d	$pK_a{}^e$
2a	$E_{1/2} = -0.34 - 0.086pH^a$	0.063	0.94	2.90	7.6
	$E_{1/2} = -0.88 - 0.025pH^b$	0.056	1.06	7.40	
		0.063	0.94	11.05	
2b	$E_{1/2} = -0.47 - 0.067pH^a$	0.061	0.98	2.90	7.0
	$E_{1/2} = -0.84 - 0.010pH^b$	0.050	1.18	7.20	
		0.047	0.26	10.50	
2c	$E_{1/2} = -0.44 - 0.083pH^a$	0.046	1.29	2.90	7.8
	$E_{1/2} = -0.85 - 0.026pH^b$	0.048	1.23	6.90	
		0.083	0.71	8.00	
2d	$E_{1/2} = -0.44 - 0.071pH^a$	0.044	1.34	2.40	8.0
	$E_{1/2} = -0.89 - 0.024pH^b$	0.042	1.41	5.70	
		0.057	1.04	7.50	

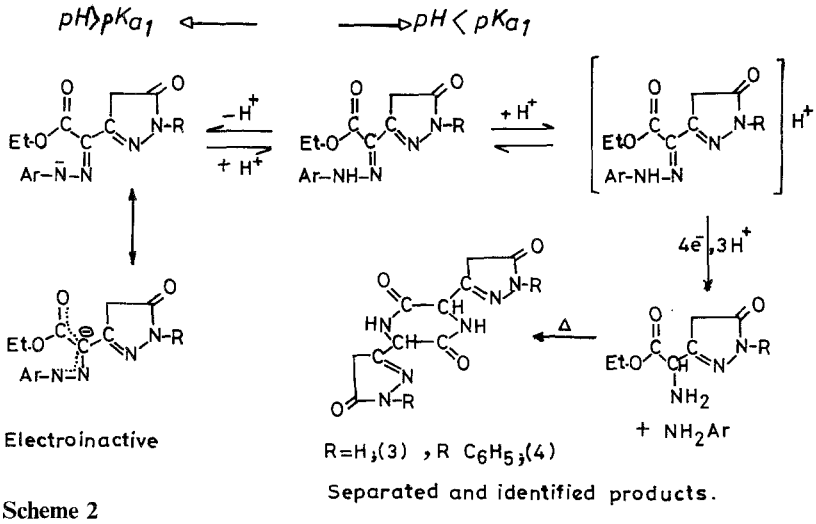
[a] Equation of first segment
[b] Equation of second segment
[c] Logarithmic analysis slope
[d] Individual *pH* value at which logarithmic analysis was carried out
[e] Spectrophotometric acid dissociation constant

Furthermore, in series **1** two pK_a values, pK_{a_1} and pK_{a_2} are obtained. In series **2** only one pK_a value is observed and these values are practically equal to those of pK_{a_1} of series **1**. Thus, it may be assumed that the ionization process (pK_{a_1}) is due to the N-NH of the hydrazone fragment. On the other hand, the second pK_a can only be attributed to the ionization of the hetero NH (Scheme 1).



Scheme 1

From these results one may conclude that the compounds of both series **1** and **2** are reduced in a single four electron irreversible wave. According to Mairanovskii [12], the slope of the first *pH*-dependent segment indicate that these molecules are reduced in the protonated form. Moreover, the slopes of the second segment could be considered very low i.e. practically *pH*-independent. This very low value of 10–26 mV per *pH* unit may be due to the high basicity of the pyrazolone ring. Based on the isolation and identification of CPE products, Scheme 2 can be suggested for the mechanism of the electrode process. Attempts to reduce the hydrazone in these compounds in order to prepare the amines failed. The unsuccessful isolation of the amino ester is due to the self condensation of the product during evaporation of the solvent. At $pH > pK_{a_1}$ values, series **1** and **2** will not afford a reduction wave due to the spreading of the negative charge all over the electroactive center rendering it negatively shielded and thus preventing further electroreduction.



Scheme 2

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