JOURNAL OF APPLIED ELECTROCHEMISTRY 15 (1985) 145–150

Electrochemical synthesis of pyrido[1,2-a]pyrimidine derivatives. II. Electrochemical reduction of 2,6-dimethyl-3-ethyl-4-oxo-4H-pyrido[1,2-a]pyrimidine in aqueous media

E. SZEBÉNYI-GYŐRY

Department of Applied Chemistry, Technical University of Budapest, PO Box 1521, Hungary

V. KOVÁCS-MINDLER, I. HERMECZ, B. PODÁNYI

Chinoin Pharmaceutical and Chemical Works Ltd, Budapest, PO Box 110, Hungary

J. BRLIK

Institute for General and Analytical Chemistry, Technical University of Budapest, PO Box 1521, Hungary

Received 27 March 1984; revised 21 May 1984

The electrochemical reduction of 2,6-dimethyl-3-ethyl-4-oxo-4*H*-pyrido[1,2-a]pyrimidine (base and HCl salt) was investigated by polarography and controlled potential electrolysis in aqueous buffered solutions at different pH values on a dropping mercury electrode and a mercury pool cathode. Controlled potential electrolyses performed in methanolic borate buffer solution (pH = 9, 10) at the first polarographic wave (1.45 V vs SCE) gave a stable C-8-coupled hydrodimer (III) in a one-electron process with a product yield of 52%. Reduction performed in alkaline methanolic solution (pH = 13.4), at the second polarographic wave (− 1.86 V vs SCE) showed a dihydromonomer (IV) formation with a product yield of 87%, in a two-electron process.

The structures of the reduction products were demonstrated by ^{1}H and ^{13}C NMR spectroscopy as well as by mass spectrometric (MS) data.

Two different routes were suggested for the reduction mechanism; a one-electron process involving a neutral radical intermediate formation accompanied by a rapid dimerization and one involving the primarily-formed neutral radical by a second electron uptake and protonation to give the dihydroderivative.

1. Introduction

Attempts to synthesize new organic compounds in our laboratories by electrochemical means have drawn attention to the biologically active pyrido[1,2-a]pyrimidines [1]. In our previous communication we described a new route to a C-8 dimerized product by the electrochemical reduction of the HCl salt of the analgetic 2,6-dimethyl-3-ethyl-4-oxo-4*H*-pyrido[1,2-a]pyrimidine in nonaqueous media [2].

The present report concerns the electrochemical reduction of the same compound in different buffered aqueous solutions. Emphasis has been placed on product identification in order to verify electrode mechanisms deduced from electrochemical and chemical data.

2. Experimental procedure

2.1. *Materials*

The base (I) and HCl salt (II) of 2,6-dimethyl-3-ethyl-4-oxo-4*H*-pyrido[1,2-a]pyrimidine were pre-

0021–891X/85 $03.00 + .12

Table 1. Composition of the buffer solutions

Name of the buffer	*pH**	*Composition for 1 dm³ aqueous solution*
Hydrochloric acid	0.80	Concentrated HCl (333 cm³) + water
Citrate	3.10	Citric acid (3.15 g) + KOH (28.5 g)
Acetate	4.90	Acetic acid glacial (90 cm³) + KOH (28.5 g)
Phosphate	6.88	KH_2PO_4 (102 g) + $Na_2HPO_4 \cdot 2H_2O$ (44.5 g)
Borate	9.10	Boric acid (72 g) + KOH (13 g)
Potassium hydroxide	13.40	KOH (112 g)

*pH values measured in the solution to be polarographed.

pared by the method described earlier [3–5]. The crude products were recrystallized from ethanol. Elemental and spectrophotometric analysis and chromatographic assay showed the compound to be of sufficient purity for polarographic study, i.e. the purities exceeded 98–99% and the polarographic waves for each compound failed to indicate any electroactive impurity. Aqueous methanolic (1 : 1) stock solutions for the polarographically-active compound were stable, as evidenced by the constancy of their reduction currents with time. Melting points of the compounds studied were: (I) – 133–4° C; (II) – 235–6° C. Buffer solutions (Table 1) were prepared from analytical reagent grade chemicals. The nitrogen used for deoxygenating was purified and equilibrated by bubbling it successively through alkaline pyrogallol solution, sulphuric acid and distilled water. The mercury and nitrogen were purified by standard techniques.

2.2. *Apparatus and procedure*

All polarograms were obtained with an OH-105 Universal Polarograph (Radelkis) with a two-electrode arrangement. The capillary characteristics of the dropping mercury electrode (DME) used for polarography were $m = 1.98$ mg s^{-1}; drop time, $t = 4.2$ s (1 M KCl). Direct current (DC) polarography was carried out in a Kalousek cell in a 2.4×10^{-3} M solution of (I) and (II). The solution to be polarographed (25 cm³) contained methanolic stock solution of (I) or (II) (2 cm³), aqueous buffer solution (5 cm³), methanol (10 cm³), saturated KCl (0.5 cm³) and water. The concentration of the stock solution of (I) and (II) was 5×10^{-3} M.

In macro-scale controlled potential electrolyses (c.p.e.) a Radelkis Model OH-405 potentiostat with an associated coulometer Model-404/C (Radelkis) were used. In these tests an H cell similar to that described by Lund [6] was employed using a mercury pool working electrode (area: 12 cm²) and a carbon rod auxiliary electrode, the latter separated from the main compartment by two coarse sintered glass discs. Stirring was accomplished by using a magnetic stirrer bar, as well as by degassing with nitrogen gas during the electrolysis. Both in the polarographic and in the macro-scale c.p.e. all the reported potential values were referred to a saturated calomel electrode (SCE). All experiments were carried out at room temperature.

In a typical run 1.0 g (about 5×10^{-3} M) (I) or (II) was dissolved in methanol (25 cm³) and aqueous buffer solution (25 cm³). This solution served as catholyte. The anodic compartment of the H-cell contained the same solution without (I) or (II).

The preparative electrolyses were carried out at the potential region of the polarographic limiting currents at different pH values. Usually the electrolysis took about 3 h to go to completion, as inferred from the complete disappearance of the reduction wave of the starting material and from the constant value of the current equal to that obtained at the same potential in a solution containing only the supporting electrolyte.

2.3. *Analysis*

The c.p.e. were followed up by thin layer chromatography (t.l.c.) as well as by DC-polarography. T.l.c. was performed on Kieselgel $60_{F\,254}$ (Merck) plates with 0.25 mm thickness of the layer using $CHCl_3 : CCl_4 : CH_3OH = 8 : 5 : 1$ as developing solvent. The t.l.c. spots were detected under UV light.

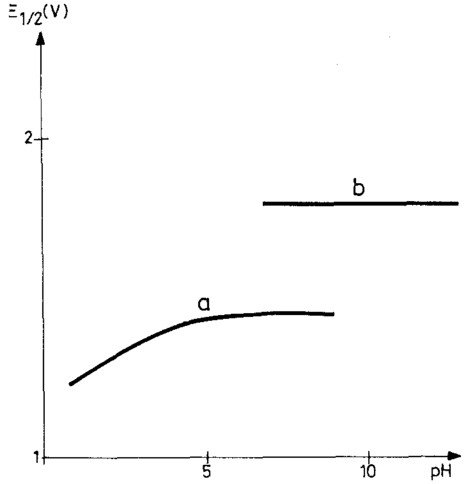

Fig. 1. Dependence of half-wave potentials on pH.

The MS spectra were recorded by a JEOL-01SG-2 type mass spectrometer. The ^{1}H NMR spectra were obtained at 80 Hz and the ^{13}C NMR spectra at 20.1 MHz on a Bruker WP-80 FT NMR spectrometer in $CdCl_3$ solution (in a 5 mm tube) using TMS as internal standard. The number of attached protons to carbons were gained from single-frequency off-resonance decoupling and/or gated spin-echo experiments.

3. Results and discussion

3.1. *Polarography*

The polarograms were recorded over the entire pH range for selecting the best medium and pH values for c.p.e. Compound (I) and (II) showed one single polarographic wave both in acidic and strong alkaline media. Between pH values of about 7–9, two waves could be seen on the polarograms. The $E_{1/2}$ values of the first polarographic wave (a) shifted to more negative potentials with an increase of pH up to 5. At pH higher than 5, the half wave potentials of both waves (a) and (b) have been found to be nearly independent of pH (Fig. 1). Table 2 shows the $E_{1/2}$ values as well as the heights (h) of the polarographic waves. It can be seen that the wave heights of the first polarographic wave decreased and that of the second wave (b) increased with increasing pH. The $E_{1/2}$ values, indicated in Table 2, were selected for c.p.e.

The results of the polarographic tests suggest that in the pH interval 7–9 there is a possibility of obtaining different products by performing c.p.e. at different potentials.

3.2. *Preparative experiments*

On carrying out c.p.e. at the first polarographic wave in two buffered aqueous solutions (pH 6.88 and 9.10) using compound (I) or (II) as starting material, the main electrolysis product in each case was a pale yellow crystalline compound (III) whose R_f value was 0.63 and whose melting point was 134–6° C. The best product yield of (III) could be achieved if c.p.e. were performed in methanolic borate buffer (1 : 1; pH = 9.1) solution at − 1.45 V vs SCE. In this case (III) precipitated from the catholyte during electrolysis after about 1 F mol^{-1} of electricity was consumed. The precipitate was filtered and washed with water and dried in vacuo. The product yield of (III) (as a precipitate) was 32–5%, i.e. about 10–5% of the total amount of (III) remained soluble in the catholyte. The latter part of (III) could be separated from the filtrate by extracting the catholyte with benzene and then by preparative t.l.c. Although the total number of electrons (n_{app}) involved in the reduction at the first wave (obtained by macroscale

Table 2. Half-wave potentials and wave heights of the polarograms of compounds (I) and (II)

pH of the solution	$E_{1/2}$ *(V)*		*wave heights (μA)*		*Selected potentials for c.p.e.*
0.80	1.23		2.80		
3.10	1.34		1.90		
4.90	1.42		1.90		
6.88	1.45	1.76	1.10	0.95	1.45
9.10	1.44	1.86	0.70	1.15	1.86
13.40	–	1.78	–	2.15	

Table 3. ${}^1H$ NMR data of the electroreduction products (III) and (IV) (in $CDCl_3$, TMS = 0.00 ppm)

Product (III)	*Product (IV)*
5.55 m (2H); 7H and 7'H	5.65 tq (1H) 7H
3.1–2.3 m (6H); 8H and 8'H; $9H_2$ and $9'H_2$	2.77 m (2H) $9H_2$
2.50 q (4H); 1.07 t (6H); $3CH_2CH_3$ and $3'CH_2CH_3$	2.51 q (2H); 1.11 t (3H) 3Et; 2.33 d (3H) $6CH_3$
2.33 s (6H); $6CH_3$ and $6'CH_3$	2.27 s (3H) $2CH_3$
2.26 s (6H); $2CH_3$ and $2'CH_3$	2.20 m (2H) $8H_2$
	${}^3J_{7H,8H_2} = 5.4$ Hz
	${}^4J_{7H,6Me} = 1.5$ Hz

s, d, t, q: respectively singlet, doublet, triplet and quartet single-frequency, off-resonance multiplicities.

c.p.e.) was 1.39–1.42, it was more advantageous not to let the reaction go to completion, therefore the electrolyses were interrupted after 1 F mol^{-1} of electricity was consumed. This way the total yield for (III) was 52%.

A solution of compounds (I) and (II) electrolysed at the second polarographic wave in alkaline buffered solutions gave a stable product (IV) in a two-electron process.The R_f value of (IV) was 0.84. The best product yield for (IV) (87%) could be achieved when c.p.e. were performed in methanolic–KOH (pH = 13.4) solution at − 1.86 V vs SCE. Product (IV) could be isolated by extracting the catholyte with benzene. The extract was then column chromatographed, the column containing Kieselgel 40, grain size 0.063–0.200 nm (70–230 mesh ASTM) using $CHCl_3$: CCl_4: CH_3OH = 8 : 5 : 1 as eluent. After evaporation of the eluent in vacuo, (IV) appeared as a yellowish oily liquid.

3.3. *Product analysis*

The structures of products (III) and (IV) were demonstrated by ${}^1H$, ${}^{13}C$ NMR and MS data.

Mass spectral characterization of the isolated electrolysis product (III)showed a hydrodimer formation with a molecular ion at $m/e = 406$ and of formula $C_{24}H_{30}N_4O_2$, that is, the mass number of product (III) is greater by two than that of the dimer of (I). This fact can be attributed to the addition of one mole of hydrogen. The mass spectral data (m/e, rel. in t %) are as follows: 406 (17.6); 204 (61.8); 203 (100); 189 (5.7); 159 (8.2); 133 (16.6); 92 (29.6); 67 (17.0); 41 (13.1). Since the base peak appeared as m/e 203, it gave evidence that (III) is a symmetric dimer.

${}^1H$ and ${}^{13}C$ NMR data for (III) (see Tables 3 and 4) showed the saturation of the C8–C9 double bond and that the coupling occurred in the C-8

Table 4. ${}^{13}C$ NMR data of the electroreduction products (III) and (IV) (in $CDCl_3$, TMS = 0.00 ppm)

Product (III)		*Product (IV)*	
C atoms	*Peak frequency*	*C atoms*	*Peak frequency*
C2 and 2'	156.1 s	C2	150.0 s
C3 and 3'	125.7 s	C3	125.6 s
C4 and 4'	160.8 s	C4	161.2 s
C6 and 6'	137.3 s	C6	136.5 s
C7 and 7'	119.6 d	C7	118.6 d
C8 and 8'	33.0 d	C8	19.0 t
C9 and 9'	35.8 t	C9	32.3 t
C8a	154.1 s	C9a	155.8 s
6 and $6'CH_3$	20.5^{a}q	$6CH_3$	20.1 q
2 and $2'CH_3$	20.7^{a}q	$2CH_3$	20.7 q
3 and $3'CH_2$	19.5 t	$3CH_2$	19.6 t
3 and $3'CH_2CH_3$	12.6 q	$3CH_2CH_3$	12.7 q

a: tentative assignment is also possible.
s, d, t, q: respectively singlet, doublet, triplet and quartet single-frequency, off-resonance multiplicities.

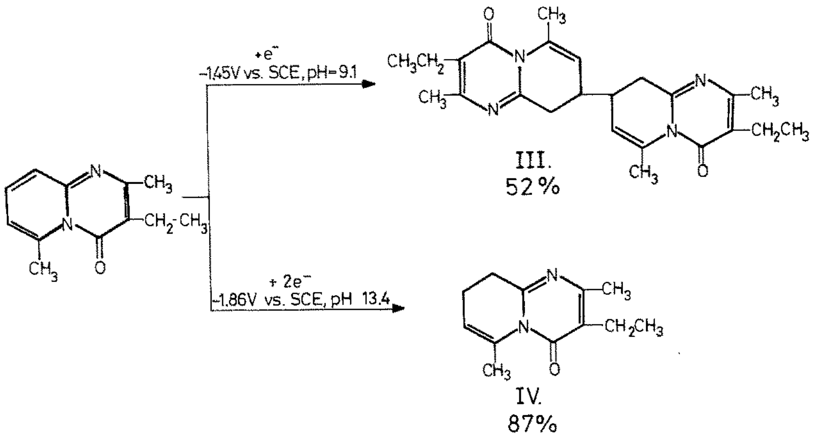

Fig. 2. Products of the controlled potential electrolysis in aqueous-alkaline buffered solution on a mercury pool cathode.

position. It was proved by the disappearance of the 8H and 9H signals from the aromatic region of the ^1H NMR spectrum and by the presence of the multiplet signal of 7H at 5.55 ppm with a half-width of 8 Hz. Additional evidence was given by the ^{13}C NMR spectra, namely while C7 gave a doublet signal in the 'off-resonance' spectrum at 119.6 ppm, C8 and C9 were found in the sp^3 region (doublet at 33.0 ppm and triplet at 35.8 ppm). Both in the ^1H and ^{13}C NMR spectra only one series of signals were detected, since the corresponding signals of the two coupled heterocycles, because of their symmetry, were found in the same place.

UV data for (III) are as follows: $(\lambda_{295}) \log \epsilon = 4.13$; $(\lambda_{220}) \log \epsilon = 4.37$.

Mass spectra of (IV) indicated the addition of one mole of hydrogen with a molecular ion appearing at $m/e = 204$ and of formula $C_{12}H_{16}N_2O$. The fragmentation patterns of the mass spectral data (m/e, rel. in t%) are as follows: 204 (100.0); 203 (29.9); 189 (91.9); 175 (7.6); 161 (28.2); 94 (8.8); 67 (18.5); 53 (14.2).

The ^1H and ^{13}C NMR data of (IV) (Tables 3 and 4) were similar to those of product (III), proving the saturation of the C8–C9 double bond. Strong evidence for the dihydromonomer structure of (IV) was the 1.5 Hz allylic-coupling of the olefinic 7H and $6CH_3$ determined in the ^1H NMR spectrum. UV data are as follows: (I) $(\lambda_{292}) \log \epsilon = 3.75$; (IV) $(\lambda_{222}) \log \epsilon = 4.04$.

Thus by MS, ^1H and ^{13}C NMR as well as by elemental analysis it was proved that the c.p.e. of (I) and (II) in buffered, aqueous alkaline media, on a mercury pool cathode gave two different main products (III) and (IV) on performing the electrolyses at different potentials (Fig. 2).

3.4. *Reaction mechanism*

On the basis of DC polarography, c.p.e. and product analysis, a reaction scheme has been proposed for the reduction of (I) and (II) in buffered alkaline, aqueous media at − 1.45 and − 1.86 V, respectively, vs SCE, on a mercury cathode.

This mechanism consists of an initial one-electron step which produces an anion radical ($R^{\cdot-}$):

$$R + e \longrightarrow R^{\cdot-} \qquad (1)$$

where R is (I) or (II).

Two alternative reaction paths are available for this anion radical:

$$\begin{tikzcd} R^{\cdot-} + H^+ \arrow[r] & RH^{\cdot} \arrow[r, "+e+H^+"] \arrow[d, "\text{dimerization}"] & RH_2 \\ & 1/2\ H\text{-}R\text{-}R\text{-}H & \end{tikzcd} \qquad (2)$$

When protons are present, the anion radical can be protonated to product a stable neutral radical which dimerizes. At more cathodic potentials, or if the reduction is not interrupted after about 1 F mol^{-1} of electricity consumed, the rate for addition of a second electron becomes competitive with the dimerization reaction and the yield of the

C8 coupled hydrodimer decreases through a dihydromonomer formation.

Indeed radical formation and dimerization have been previously indicated for a number of related systems including for example the reduction of N-alkyl pyridine derivatives [7] and 4-aminopyrimidine in aqueous media [8].

References

[1] Z. Mészáros, *Kém. Közl.* **50** (1978) 173.

[2] E. Szebényi-Győri, K. Koleszár, V. Kovács-Mindler, I. Hermecz, G. Horváth and G. Tóth, *Magy. Kém. Foly.* **88** (1982) 327.

[3] F. Fülöp, I. Hermecz, Z. Mészáros, Gy. Dombi and G. Bernáth, *J. Heterocycl. Chem.* **16** (1979) 457.

[4] J. Knoll, Z. Mészáros, I. Hermecz, F. Fülöp, G. Bernáth, S. Virág, G. Nagy and P. Szentmiklósi, German Patent No. 2 835 004 (see also *Chem. Abs.* **918** (1979) 5243.

[5] *Idem,* US Patent No. 4 291 036 (see also *Chem. Abs.* **96** (1982) 35295).

[6] H. Lund, *Österreich. Chem. Z.* **68** (1967) 43.

[7] H. H. Bauer, *Electrochim. Acta* **21** (1976) 753.

[8] B. Czochralska and P. J. Elving, *ibid.* **26** (1981) 1755.