

**POLAROGRAPHIC REDUCTION
OF α -(4-ETHYLBENZOYL)- α , β -DIBROMOPROPIONIC ACID
ON MERCURY DROPPING ELECTRODE**

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A mechanism of the electrochemical reduction of β -(4-ethylbenzoyl)- α , β -dibromopropionic acid is suggested based on the results of classical polarography and polarography with Kalousek's switch and on the identification of the polarographically active intermediate products. The substance converts to β -4-ethylbenzoylacrylic acid on the electrochemical elimination of the bromine atoms, and the latter acid is reduced further to β -4-ethylbenzoylpropionic acid. The most negative polarographic wave corresponds to the reduction of the carbonyl group in the benzoyl part of the last acid.

β -(4-Ethylbenzoyl)- α , β -dibromopropionic acid (*I*) has been isolated as an intermediate product during the preparation of an antineoplastically active substance — γ , γ -bis(4-ethylphenyl)- α , β -dibromoisocrotonic acid (Edikron)¹ (*II*). The structure of *I*, suggested based on its elemental analysis and mass, infrared, and NMR spectra, is corroborated also by the mechanism of its electrochemical reduction on a mercury dropping electrode.

EXPERIMENTAL

The polarographic measurements were performed on a polarograph LP-60 (Laboratorní přístroje Prague) using mercury dropping electrode whose drop time was measured in 0.1M-KCl without the voltage applied. As the reference electrode served a saturated calomel electrode (s.c.e.) or a saturated mercurousulfate electrode (s.m.e.). The variations of the polarographic curves in dependence on the pH were examined in Britton-Robinson buffers containing 30% ethanol. The formation of bromides as the products of the electrochemical reduction in acidic medium was proved by using a Kalousek's switch². The measurements were performed in a connexion such that in the production stage at the auxiliary potential E_{aux} products were generated, which were then studied in the recording stage with a potential sweep. Since the method is designed for the detection of bromides, a saturated mercurousulfate electrode was employed as the reference electrode. The constant auxiliary potential, chosen at the limiting current of the most positive cathodic wave, was -0.4 V (s.m.e.). The application of this technique was restricted to acidic medium, since at higher pH values the bromides studied did not afford measurable anodic waves.

The acid *I* was isolated from the mother liquor after the separation of the crude acid *II* by co-

lumn chromatography on Kieselgel Merck applying benzene as the eluting agent; melting point after recrystallization from ethanol 169–170°C. For $C_{12}H_{12}Br_2O_3$ calculated: 39.58% C, 3.32% H 43.90% Br; found: 39.79% C, 3.32% H, 43.64% Br.

The 1H -NMR spectrum was measured on a spectrometer Tesla BS 487C (80 Hz) in DMSO- d_6 with TMS as the internal standard. 1H -NMR spectrum: δ 8.05 (d, $J = 8.5$ Hz, 2 H, p -subst. Ar, o to C=O), 7.38 (d, $J = 8.5$ Hz, 2 H, p -subst. Ar, o to C_2H_5), 5.90 (d, $J = 11.0$ Hz, 1 H, Ar. COCHBr—), 4.72 (d, $J = 11.0$ Hz, 1 H, —CHBrCOOH), 2.70 (q, $J = 7.0$ Hz, 2 H, ArCH $_2$ —), 1.21 (t, $J = 7.0$ Hz, 3 H, CH $_2$ CH $_3$). The IR spectrum was measured on a spectrophotometer Unicam SP 200 G. IR spectrum (KBr; cm^{-1}): 2600 (COOH), 1710 (COOH), 1671 (ArCO). 1600, 1565, 1505 (Ar—H), 850 (p -subst. Ar). The UV spectrum was scanned on a spectrophotometer Unicam SP 8000 in methanol. The substance is characterized by an absorption band at 269 nm, $\log \epsilon = 4.1740$. The mass spectrum was measured on a spectrometer MS 902 AEI. The spectrum confirms the suggested structure $C_{12}H_{12}Br_2O_3$.

RESULTS AND DISCUSSION

β -(4-Ethylbenzoyl)- α,β -dibromopropionic acid (I) is reduced in the whole pH region. In strongly acidic medium the polarographic curves display two cathodic waves (i_1, i_2) of approximately equal height and slope, which are augmented with another wave i_3 at $pH > 3$. While the heights of the waves i_1 and i_2 remain in the region $pH 2-10$ practically constant, the height of the wave i_3 decreases in the medium pH range, and simultaneously a poorly developed more negative wave i'_3 rises. The height of the most positive cathodic wave i_1 in solutions $pH > 9$ drops gradually on account of basic hydrolysis, and in 0.1M-NaOH this wave is no more apparent on the polarographic curves. At $pH > 10$ the second two-electron step i_2 is divided, which evidences the occurrence of an acid-base equilibrium in the solution. From a comparison of the heights of the waves i_1 and i_2 with that of the two-electron reduction wave of β -4-methoxybenzoylacrylic acid³ it follows that the former waves correspond to two-electron reductions. The independence of the half-wave potential of the most positive cathodic wave i_1 of the pH gives evidence that this reduction, unlike the more negative steps i_2 and i_3 , proceeds without a participation of protons. The shifts of the half-wave potentials ($E_{1/2}$)₂ and ($E_{1/2}$)₃ with the pH and in comparison with the half-wave potentials of β -4-methoxybenzoylacrylic acid are shown in Fig. 1. The linear dependence of the heights of the waves on the concentration of the substance in question and on the square root of the mercury column height in acidic medium confirms the diffusion nature of the limiting currents, which for the wave i_3 converts to the kinetic one in the medium pH region.

When the Kalousek's switch was employed, the switched curves displayed an anodic wave on the switching on the limiting current of the most positive cathodic wave i_1 . The increase of this wave on an addition of potassium bromide gives evidence that the wave corresponds to the oxidation of the bromide ions formed on the electrode during the first reaction step i_1 (Fig. 2). In addition to bromide ions, another substance is formed and further reduced on the electrode. Based on the two-electron

nature of the first reduction stage and on the identification of the bromide ions in the solution it can be assumed that after the accepting of two electrons, either one of the bromine atoms in the molecule is substituted by a hydrogen atom, or both bromine atoms are eliminated with the formation of β -4-ethylbenzoylacrylic acid (III):

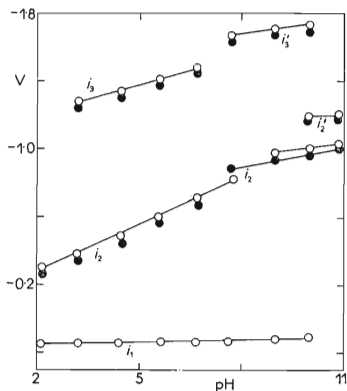
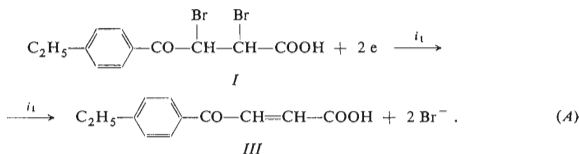


FIG. 1

The pH Dependence of the Half-Wave Potentials of $5 \cdot 10^{-4}\text{M}$ β -(4-Ethylbenzoyl)- α,β -dibromopropionic Acid (○) and $5 \cdot 10^{-4}\text{M}$ β -4-Methoxybenzoylacrylic Acid (●) i_1 C—Br; i_2 C=C—COOH; i_2' C=O—COO⁻; i_3 COH⁽⁺⁾; i_3' C=O

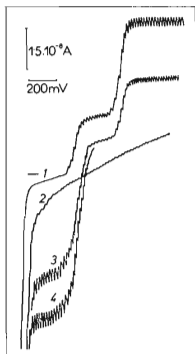


FIG. 2

Verification of the Formation of Bromide Ions During the Polarographic Reduction of β -(4-Ethylbenzoyl)- α,β -dibromopropionic Acid in $1\text{N-H}_2\text{SO}_4$ with 30% Ethanol

Kalousek's switch, $E_{\text{aux}} = -0.4\text{V}$ (S.M.E.), switching frequency 6.25 Hz, recording up from $+0.2\text{V}$ (S.M.E.); 1 $1.5 \cdot 10^{-3}\text{M}$ depolarizer, classical polarographic curve; 2 switched curve of the base electrolyte; 3 as sub 1, with the Kalousek's switch; 4 as sub 3, with an addition of KBr.

The accordance of the polarographic behaviour of the product of the first reaction step with that of β -4-methoxybenzoylacrylic acid (Figs 1, 3) proves unambiguously the elimination mechanism (A), indicated also by the independence of $(E_{1/2})_1$ of the pH. β -4-Ethylbenzoylacrylic acid (III) is further reduced in the two-electron wave i_2 , succeeded by the more negative wave i_3 , the latter converting to the wave i'_3 on a change of the pH. The dependence of $(E_{1/2})_2$ on the pH and the agreement of the polarographic behaviour of the product formed in the second reduction step with that of β -4-methoxybenzoylpropionic acid indicate that in the second two-electron wave i_2 the double bond in the aliphatic part of the molecule of β -4-ethylbenzoylacrylic acid is hydrogenated with the formation of β -4-ethylbenzoylpropionic acid (IV). This substance is formed on the electrode probably in its enol (IVa), polarographically inactive form, which by base as well as acid catalysis is converted to the polarographically active keto form (IVb) (refs.^{3,4}):

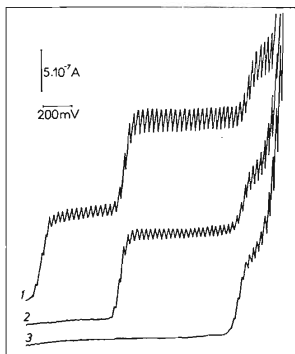
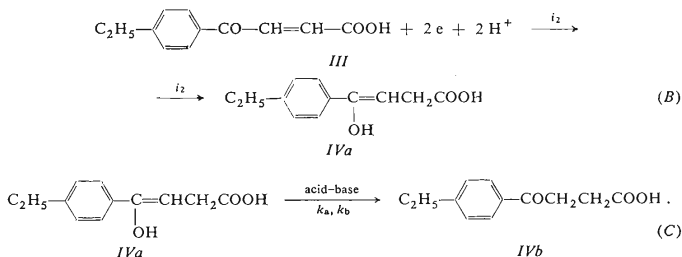
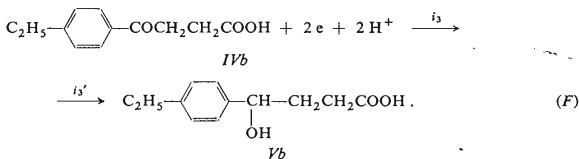
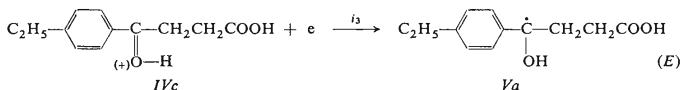
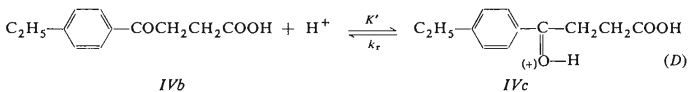


FIG. 3

Polarographic Reduction Waves

1 β -(4-Ethylbenzoyl)- α,β -dibromopropionic acid; 2 β -4-methoxybenzoylacrylic acid; 3 β -4-methoxybenzoylpropionic acid. 4. $\cdot 10^{-4}$ M depolarizer in Britton-Robinson buffer pH 4.40 with 30% ethanol. Up from +0.3 V (S.C.E.).

The more negative cathodic waves (i_3, i'_3) agree with the polarographic waves observed for β -4-methoxybenzoylpropionic acid as to their height and position changes with the pH and their half-wave potential values (Fig. 3). The wave i_3 , whose half-wave potential varies with the pH, can be attributed to the reduction of the protonized form of the carbonyl group (*IVc*). The wave height decreases at $\text{pH} > 5$ in the shape of a dissociation curve. Simultaneously with the decrease of the wave i_3 the two-electron wave i'_3 rises at more negative potentials, corresponding to the reduction of the unprotonated form of the carbonyl group (*IVd*). In analogy to the behaviour of other carbonyl compounds⁵⁻⁷, the half-wave potential of the more negative wave virtually does not depend upon the pH, since this reduction step is not preceded by a proton transfer.



The rate of the recombination reaction (*D*) possessing the rate constant k_r limits the wave height at $\text{pH} > 5$.

The curves recorded in solutions $\text{pH} > 10$ show that in alkaline medium hydrolytic elimination of the bromine atoms proceeds from the molecule of β -(4-ethylbenzoyl)- α, β -dibromopropionic acid (*I*), which in these solutions obviously occurs in the form of its anion. As follows from the above reaction mechanism, on accepting two electrons the acid *I* is converted to β -4-ethylbenzoylacrylic acid (*III*), which – apart from the substituent on the benzene ring – is identical with the intermediate products formed during the polarographic reduction of the *cis* form of the β -4-methoxybenzoyl- β -halogenoacrylic compounds which have been polarographically and spectroscopically examined during the study of the antineoplastic activity in relation to the chemical structure³.

β -4-Ethylbenzoylacrylic acid (*III*) can only be formed from the molecule of the substance under study by elimination of the bromine atoms, which — as indicated by the value of the half-wave potential of the first cathodic wave i_1 — proceeds very readily; this situation is not unusual, being found also for the electrochemical elimination of halogen atoms from the molecules of other substances⁸⁻¹¹. The subsequent electrochemical reduction of the acid proceeds at more negative potentials and its mechanism is in accordance with that suggested for similar compounds^{3,12}.

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