ELECTROCHEMICAL REDUCTION OF BENZOYL SUBSTITUTED BARBITURIC ACIDS IN ACID SOLUTIONS*

W.Pasek[a], J.Volke[b] and O.Manoušek[b]

[a] *Department of Organic Chemistry,*
School of Medicine, Kraków, Poland, and
[b] *J. Heyrovský Institute of Physical Chemistry and Electrochemistry,*
Czechoslovak Academy of Sciences, 118 40 Prague 1

In acid media the reduction of pharmacologically active benzoyl substituted barbituric acids at a dropping mercury electrode gives the corresponding barbituric acid and, depending on pH, benzyl alcohol or 1,2-dibenzyl glycol as final products. In coulometric measurements with a mercury pool electrode a value of n equal to 4 is obtained both in $0.1\text{N-H}_2\text{SO}_4$ and at pH 5·2. The polarographic wave in strongly acidic media corresponds to the uptake of 2 electrons whereas 4 electrons are consumed at pH 5·2. It follows both from this data and from the polarographic curves that an electrochemically inactive intermediate is the primary product which only in a chemical follow-up reaction yields benzaldehyde which can be further reduced. The rate of the follow-up reaction is pH-dependent.

The polarographic behaviour of some benzoyl derivatives of barbituric acid was described in a previous paper[1] but the investigations were carried out in buffered solutions only over a rather narrow pH-range from 5 to 7. It was established that during electrolysis at mercury electrodes a destructive reduction of the single C—N bond takes place. In this paper we present the results of an electrochemical investigation in acid media of the following substances: 1-benzoyl-5,5-diethylbarbituric acid (N-benzoylbarbital) (*I*), 1-benzoyl-5-ethyl-5-phenylbarbituric acid (N-benzoylphenobarbital) (*II*), 1-benzoyl-3-methyl-5-ethyl-5-phenylbarbituric acid (N-benzoylmebaral) (*III*), 1-benzoyl-3-methyl-5,5-diethylbarbituric acid (N-benzoylgemonil) (*IV*), 1-*p*-chlorobenzoyl-5,5-diethylbarbituric acid (N-*p*-chlorobenzoylbarbital) (*V*), 1-*o*-chlorobenzoyl-5,5-diethylbarbituric acid (N-*o*-chlorobenzoylbarbital) (*VI*), 1-acetyl-5,5-diethylbarbituric acid (N-acetylbarbital) (*VII*).

EXPERIMENTAL

Apparatus

Polarographic current–voltage curves were recorded with a LP 60 polarograph (Laboratorní přístroje, Prague) making use of a Kalousek cell with a separated calomel electrode (s.c.e.). The capillary had the following constants: $t_1 = 3.2$ s (at zero applied voltage), $m = 2.8$ mg . s^{-1},

$h = 65$ cm. The pH-values of the solutions were measured with a glass electrode (*vs* a saturated calomel electrode) making use of a Ridan PCR-68 s pH-meter. The controlled potential electrolysis and coulometric measurements were carried out in a cell devised by one of us (O.M.) (ref.[2]) in connection with a CMT 50 current integrator (Jaissle Elektronik, Neustadt) and a Tacussel potentiostat PRT-20-2Z (Tacussel, Lyon). In spectral measurements a Perkin-Elmer spectrophotometer 257 was used for the infrared region (solutions in Nujol) and a Unicam SP-800 for the ultraviolet spectra.

Chemicals

The barbituric acid derivatives were prepared by the first author according to literature[1]. Sulfuric acid used in the experiments was analytical reagent grade (Lachema, Brno, Czechoslovakia), the same holds true for the chemicals used for preparing the buffer solutions. The non-aqueous solvent, ethanol, was of spectral purity.

Procedures

Polarography. Ethanolic solutions of investigated compounds ($2 . 10^{-4}$M in 40% ethanol) were diluted 1 : 1 with 0·1M citrate or phosphate buffers or with Britton–Robinson universal buffers, of appropriate pH-value. A solution of gelatin was added. The final concentration of depolariser was in most cases 10^{-4}M in 20% ethanol and with 0·001% gelatin. Dissolved oxygen was removed by a stream of nitrogen.
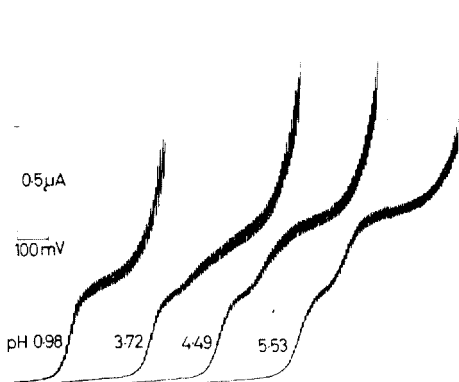

FIG. 1

Polarographic Reduction of Benzoylphenobarbital (*II*) as a Function of pH

1 . 10^{-4}M *II*; first curve with 0·2N-H_2SO_4, all other curves with Britton–Robinson buffers, 20% ethanol; from $-0·7$ V *vs* (S.C.E.).
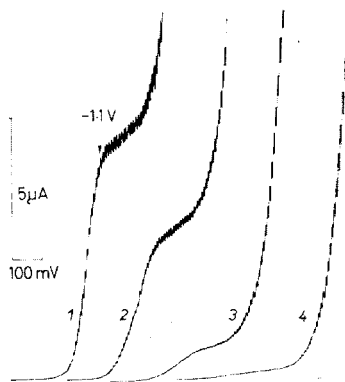
FIG. 2

Control of the Electrolysis of $3 . 10^{-3}$M Benzoylbarbital (*I*) in 0·1N-H_2SO_4

150 ml of the electrolyzed solution; 50% ethanol; from $-8·0$ V *vs* S.C.E.; time-intervals, t (min): 1 0; 2 9; 3 38; 4 65; area of the mercury-pool electrode: 20 cm², $s = 9·3 . 10^{-4}$ s^{-1}, E of electrolysis $-1·1$ V (*vs* S.C.E.).

Controlled potential electrolysis. Controlled potential electrolysis of N-benzoylphenobarbital (*II*) and of N-benzoylbarbital (*I*) was carried out in $0 \cdot 1 \text{N-H}_2\text{SO}_4$: 75 ml of an ethanolic solution of the compound were mixed with 75 ml $0 \cdot 2 \text{N-H}_2\text{SO}_4$. The concentration of the compound at the beginning of the electrolysis was usually $3 \cdot 10^{-3}$ M. A potential corresponding to the potential at the beginning of the limiting current of the reduction wave (Fig. 1) was applied to the stirred mercury pool cathode (as in our previous papers[3] the electrolyses were carried out with a three--electrode system). The course of electrolysis was checked by recording polarographic curves at certain time intervals until the reduction wave completely vanished (*cf.* Fig. 2). After electrolysis (in the above cases at $-1 \cdot 1$ V) 500 ml of water were added and the solution was extracted with four 100 ml portions of ether. Combined ethereal extracts were washed with water and dried over anhydrous sodium sulphate. Ether was distilled off and 10 ml of benzene were added to the oily residue. The separated precipitate was filtered, washed with benzene, dried and identified as barbital and phenobarbital, respectively. The IR and UV spectra (Fig. 3) as well as the mass-spectrum confirm this interpretation. The UV and IR spectra of the obtained products were identical with those of authentic samples; in addition to this the products did not lower the melting point in mixture (m.p. $190-191°C$ for barbital[4], and $173-174°C$ for phenobarbital[4] were in accordance with the data in the literature).

RESULTS

Except for N-acetylbarbital (*VII*) (where the carbonyl group is not conjugated with double bonds) all substances *I — VI* are reducible at the dropping mercury electrode. Whereas in strongly acidic media the substances *I — VI* are reduced in a single two-electron step (as follows from calculations with the help of the Ilkovič equation and from a comparison of the wave-heights with those of compounds having a molecule of similar size and a known electron consumption). With increasing pH-values either the wave -height of this 2-electron wave increases (*e.g.* with *VI*) until the total height at about pH 6 or higher corresponds to a 4-electron process, or a second, more negative wave develops (in case of the other derivatives) which again increases with
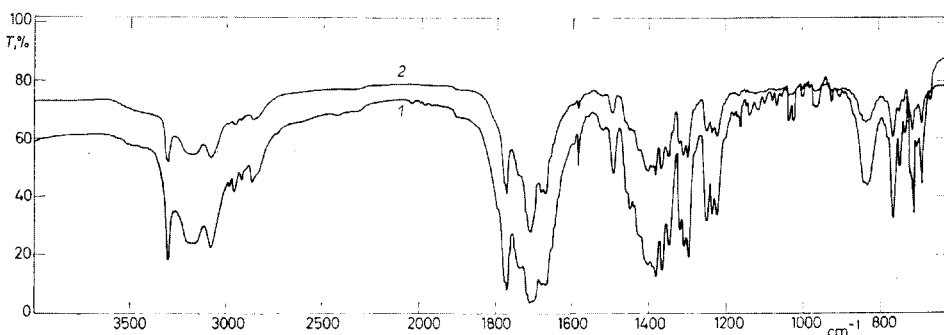

FIG. 3

Infrared Spectrum of Phenobarbital (*1*) and that of the Product (*2*) Isolated after the Reduction of Benzoylphenobarbital (*II*)
Both in potassium bromide.

increasing pH up to a value corresponding to $n = 2$. Thus the total consumption at pH 6—7 is again 4-electrons (Fig. 1) per molecule. Regardless of the fact whether a single 4-electron wave or two 2-electron waves result in approx. neutral media the broken log plots, $\log\left[i/(i_d - i)\right] = f(E)$, of the curves reveal that also the 4-electron reduction proceeds in two 2-electron steps.

The limiting currents of the waves of all reducible benzoyl barbiturates are a linear function of depolariser concentration over the region from 10^{-4} to $5 \cdot 10^{-4}$M in buffered solutions with 20% ethanol. Because of low solubility in this media, the behaviour at higher concentrations could not be studied. It follows from the dependence of the limiting currents on the height of the mercury head that all waves are diffusion-controlled. The dependence of the limiting current on temperature also points to the fact that the currents are controlled by diffusion because the temperature coefficients of i_1 lie in the region of $2 \cdot 1\%/^\circ$C except for substances V and VI for which values above $+1 \cdot 7\%/^\circ$C were obtained in $0 \cdot 1$N-H_2SO_4-solutions with 50% ethanol ($5 \cdot 10^{-4}$M depolariser) over the temperature range from 15°C to 55°C.

The half-wave potentials of the first 2-electron wave over the whole pH-area under investigation or of the combined 4-electron wave at higher pH-values of this region are a linear function of pH but the slopes $\Delta E_{1/2}/\Delta$pH of these dependences are somewhat different. The values for the individual compounds are as follows: I: $-0 \cdot 044$ V/pH; II: $-0 \cdot 042$ V/pH; III: $-0 \cdot 039$ V/pH; IV: $-0 \cdot 041$ V/pH; V: $-0 \cdot 041$ V/pH; VI: $-0 \cdot 041$ V/pH. The values of half-wave potentials are also different as the following figures exemplify ($0 \cdot 1$M citrate buffer):
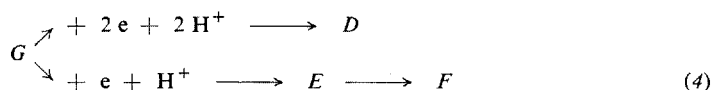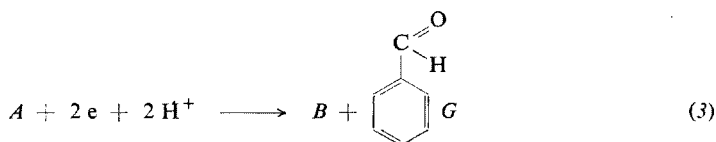
$-E_{1/2}$, V (pH): I $0 \cdot 95_5$ ($1 \cdot 04$); II $0 \cdot 87_5$ ($0 \cdot 98$); III $0 \cdot 91$ ($1 \cdot 04$); IV $0 \cdot 94$ ($1 \cdot 04$); V $0 \cdot 89$ ($1 \cdot 03$); VI $0 \cdot 87$ ($1 \cdot 03$).

A decrease in the ethanol concentration from 50% to 20% causes a shift of $E_{1/2}$ to more positive values by about 60—80 mV. Neither the half-wave potential of the reduction wave nor the limiting current depend on the concentration of sulphuric acid.

The reduction in the more positive wave in sulphuric acid-solutions ($0 \cdot 1$N-H_2SO_4) is evidently irreversible since for these 2-electron waves the slopes of the log plots $dE/d\log\left[i/(i_d - i)\right]$ are almost equal for substances $I - VI$ and vary from 40 to 43 mV.

Coulometric Measurements

Coulometric measurements were carried out with a stirred mercury-pool electrode for I and II. As supporting electrolyte we used $0 \cdot 1$N-H_2SO_4 (where the 2-electron wave is observed) and $0 \cdot 1$M phosphate buffer pH $5 \cdot 2$ (where in classical polarography 4 electrons are consumed). The following values of n were obtained (corrected for the blank solution) for $0 \cdot 1$N-H_2SO_4 and for pH $5 \cdot 2$: I $4 \cdot 2$, $4 \cdot 3$; II $4 \cdot 3$, $4 \cdot 3$.

Since the formation of benzaldehyde could be expected as a result of the primary reduction step we compared the polarographic behaviour of I and that of benzaldehyde both separately and in mixtures (Fig. 4). It follows from this that at pH 5·1 benzaldehyde must be actually an intermediate of the two-step four-electron reduction. On the other hand in strongly acidic solutions such as $0·1\text{N-}H_2SO_4$ the 2-electron wave is not followed by the wave of benzaldehyde. Since free benzaldehyde gives a clear-cut reduction wave in such a solution it follows from this observation that in this media benzaldehyde is not set free from the primary reduction product during the drop-life of the polarographic measurement. Nevertheless, there is no difference in the electron consumption from coulometric measurements obtained both $0·1\text{N-}$ $-H_2SO_4$ and in buffers at pH 5·2.

DISCUSSION

The above experimental results have shown that the main and final reduction product, corresponding to an uptake of 4 electrons, is always the barbituric acid which has lost the benzoyl group. The second main product, obtained by the reductive splitting of the $C-N$ bond between the benzoyl group and the barbituric acid, which should be either benzyl alcohol or 1,2-dibenzylglycol (depending on the pH-value of the solution) was not searched for.

$$(1)$$

$$(2)$$

$$A + 2e + 2H^+ \longrightarrow B + \underset{\text{(benzaldehyde)}}{\boxed{}}\ G \qquad (3)$$

$$G \underset{\searrow}{\overset{\nearrow}{}} \begin{array}{l} + 2e + 2H^+ \longrightarrow D \\[6pt] + e + H^+ \longrightarrow E \longrightarrow F \end{array} \qquad (4)$$

The considerations about the course of the reduction lead to the following two possibilities: The products which can actually be isolated after such a reaction are the same regardless of the fact whether mechanism A or mechanism B is operative. For this reason the interpretation must be based on polarographic and coulometric measurements. Since in coulometric measurements both in $0.1\text{N-}H_2SO_4$ and at pH 5·2 the same value of n, equal to 4, was obtained whereas the polarographic behaviour in these two media is different, *i.e.* a 2-electron wave in strongly acidic media and a 4-electron wave (in some derivatives in two 2-electron steps) at higher pH-values, an ECE mechanism must be postulated in which the rate of the chemical reaction is a function of pH. It follows from Fig. 5 that benzaldehyde is an intermediate in the reduction of benzoylbarbituric acids at pH 5·2; on the other hand its reduction wave does not appear on their polarograms recorded with $0.1\text{N-}H_2SO_4$ as supporting electrolyte. Hence, the assumed ECE mechanism is most probably as follows:

$$A + 2e + 2H^+ \longrightarrow B, \qquad (5)$$
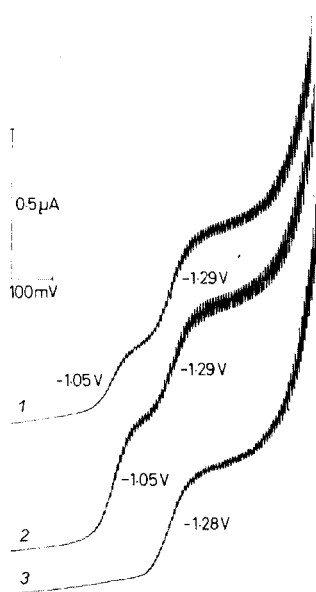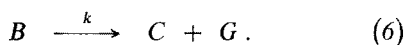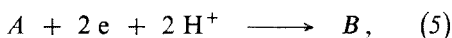
$$B \xrightarrow{k} C + G. \qquad (6)$$

FIG. 4

Comparison of the Polarographic Waves of Benzoyl-phenobarbital (*II*) with Those of Benzaldehyde on 0.1M Phosphate Buffer pH 5·1 (20% ethanol)

1 $5.10^{-5}\text{M }II$, 5.10^{-5} benzaldehyde; *2* $1.10^{-4}\text{M }II$; *3* 1.10^{-4}M benzaldehyde; from -0.8 V (*vs* S.C.E.).

In the next reduction steps benzaldehyde is reduced[5] according to equations in (2). The rate determining step which is decisive for obtaining the reduction-wave of benzaldehyde is reaction (6). In $0.1\text{N-H}_2\text{SO}_4$ the rate constant of the cleavage of the reduction intermediate in (6) is so low that no benzaldehyde forms during the drop-time t_1, in less acidic solutions, *e.g.* in the buffers of pH 5.2, the values of k are much higher (in accordance with the data in[6]) so that depending on the substituents R_1 and R_2-either two 2-electron waves are formed or a single 4-electron wave. The plot $\log i_e = f(t)$ for a controlled potential electrolysis in $0.1\text{N-H}_2\text{SO}_4$ is a straight line: consequently the value of k in (5) must be much higher than the first order electrolytic rate constant* s according to Meites[7] which in our case was equal to 9.3 . $. 10^{-4} \text{ s}^{-1}$. This means that a completion of the electrolysis to 99.9% would require about 2.05 hours. This value can be easily obtained making use of the equation

$$(C^0 - C_t)/C^0 = 1 - 1^{-st} ;$$

in this equation C^0 stands for the concentration at the beginning of electrolysis, C_t for that at time t.

As regards the stability of the intermediate resulting in equation (1) it can be compared with the stability of substances formed in a reaction between aromatic aldehydes

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* The rate-constant s can be defined by 4 different equations:

$$s = i_0/nVC_0 \qquad (a)$$

or

$$s = DA/V\delta \qquad (b)$$

or

$$s = - \Delta \ln i/\Delta t \qquad (c)$$

or

$$s = - 1/t \ln Q_R/Q_\infty \qquad (d)$$

In these equations i_0 stands for the current at the beginning of the electrolysis, C_0 for the concentration at the same moment, V for volume, D for the diffusion coefficient, A for the electrode area, δ for the thickness of the diffusion-layer. Q_R is defined as follows:
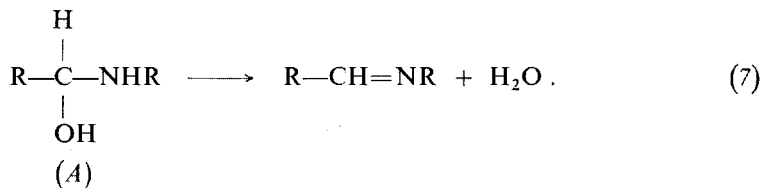
$$Q_R = \int_t^\infty i \, dt = Q_\infty - \int_0^t i \, dt = Q_\infty - Q_t . \qquad (e)$$

(Q_t and Q_∞ are the electric charges for times t and t_∞, respectively).
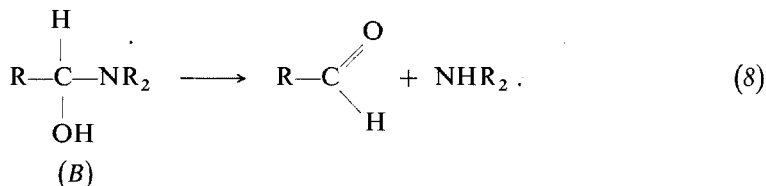
In our case we obtained the value of s by making use of equation (c), *i.e.* by plotting $\log i$ *vs* t since the above relation can be also expressed as follows:

$$i_t = i_0 . e^{-st} = snFVC_0 e^{-st} . \qquad (f)$$

and primary and secondary amines: The reaction with primary amines yields a hydroxyl-containing intermediate which loses a molecule of water in the next step:

$$
\underset{\underset{(A)}{\overset{\displaystyle |}{OH}}}{\overset{\overset{\displaystyle H}{|}}{R\!-\!C\!-\!NHR}} \longrightarrow R\!-\!CH\!=\!NR \; + \; H_2O \; . \tag{7}
$$

On reacting benzaldehyde with a secondary amine an intermediate results from which the water molecule cannot be split off. Consequently a fission of the intermediate occurs giving rise to free aldehyde again and to the original secondary amine:

$$
\underset{\underset{(B)}{\overset{\displaystyle |}{OH}}}{\overset{\overset{\displaystyle H}{|}}{R\!-\!C\!-\!NR_2}} \longrightarrow R\!-\!C\!\!\underset{H}{\overset{O}{\diagup}} \; + \; NHR_2 \; . \tag{8}
$$

This means that in (7) the equilibrium is strongly shifted to the left-hand side of the equation. The structure of our intermediate in Eq. (5) corresponds to (B) in (8) which is thus readily decomposed except for strongly acidic solutions[6]. The above considerations hold only for slightly acidic or neutral solutions because in strongly acidic media the reduction wave of benzaldehyde could not be observed as a second step of the polarographic reduction. Similar ideas have been developed by Lund[8] in interpreting the reduction mechanism of some amides.

REFERENCES

1. Kahl W., Pasek W.: Roczniki Chem. *44*, 2425 (1970).
2. Manoušek O.: Chem. listy, in press.
3. Manoušek O., Volke J.: J. Electroanal. Chem. *43*, 365 (1973).
4. *Czechoslovak Pharmacopoea*, 2nd Ed. Prague, 1954.
5. Pasternak R.: Helv. Chim. Acta *31*, 753 (1948).
6. *Organikum* (K. Schwetlick, Ed.), 12th Ed., p. 420. Deutscher Verlag der Wissenschaften, Berlin 1973.
7. Meites L.: *Polarographic Techniques*, 2nd Ed., p. 516. Wiley-Interscience, New York 1965.
8. Lund H.: Acta Chem. Scand. *17*, 2325 (1963).

Translated by the author (J. V.).