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STUDY OF THE MECHANISM OF THE POLAROGRAPHIC REDUCTION OF N-ACYLSYDNONEIMINES

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UDC 543.253 : 547.793.4

The polarographic reduction of the N-phenylcarbamoyl derivative of 3-(β-phenylisopropyl)-sydnoneimine ("sidnokarb") in aqueous alcohol media was investigated. It is shown that, depending on the protonation rate of both the starting depolarizer and the intermediates in the reduction of sidnokarb, six or four electrons may be consumed to give, in the first case, a derivative of the amino acid amide and ammonium ions and, in the second case, the corresponding hydrazine derivative.

The polarographic behavior of N-exo-acyl derivatives of sydnoneimines have received little study — the effect of the pH on the limiting current and $E_{1/2}$ has been investigated, and, in analogy with sydnones and sydnoneimine salts, preliminary considerations relative to the possible mechanism of the reduction of N-acylsydnoneimines have been expressed [1]. Insofar as the polarography of N-carbamoyl derivatives is concerned, there are not data except the $E_{1/2}$ values of several compounds [2] in the literature. Considering that N-acylsydnoneimines have recently attracted the attention of researchers in connection with the high pharmacological activity of representatives of this class of compounds [3-5], it was of interest to make a more detailed study of their polarographic reduction. The N-phenylcarbamoyl derivative of 3-(β-phenylisopropyl)sydnoneimine (I, "sidnokarb"), which is a medicinal preparation that is a highly effective central nervous system (CNS) stimulator [5], was selected as the subject of the investigation. We have recently made a detailed study [6] of the polarography of the salt of the corresponding 3-(β-phenylisopropyl)sydnoneimine, and a comparison of the behavior of the latter compound on a dropping mercury electrode with that of sydnoneimine I makes it possible to evaluate the effect of an N-exocyclic grouping.

The study of the polarographic behavior of sidnokarb I was carried out in buffered and unbuffered media containing 50% ethanol. One distinctly expressed polarographic wave, the limiting current of which decreases somewhat as the pH increases, is observed in the reduction of sidnokarb in acidic media. At pH 3-6, in addition to the principal wave, an additional wave with a voltage drop, the height of which depends markedly on the pH of the medium,* appears prior to the discharge current. The $E_{1/2}$ value of the principal reduction wave of sidnokarb itself depends on the pH of the medium and is shifted to negative potentials as the pH increases. At

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*This wave has the properties of a surface catalytic wave of hydrogen evolution and is determined by protonation of the intermediates, absorbed on the mercury electrode, in the reduction of sidnokarb; a similar phenomenon has been observed in the reduction of the 3-(β-phenylisopropyl)sydnoneimonium cation [6].
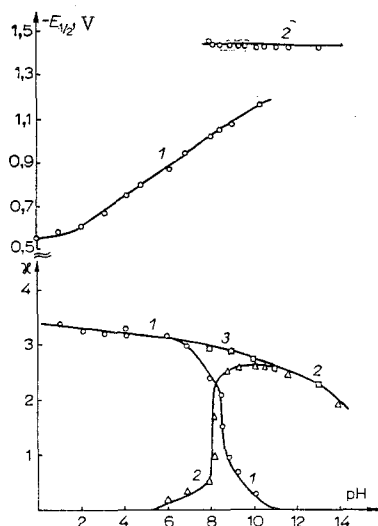

Fig. 1. Relationship between $\varkappa = i_{lim}/C$ and $E_{1/2}$ of sidnokarb and the pH of the medium: 1) first wave; 2) second wave; 3) overall waves.
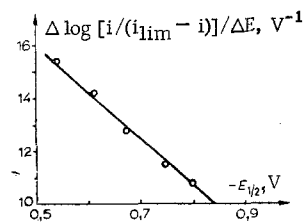
Fig. 2. Relationship between $\dfrac{\Delta \lg \frac{i}{i_{lim}-i}}{\Delta E}$ and $E_{1/2}$ (at pH 1-5).

pH > 6.2 this wave begins to decrease with respect to the "dissociation curve," acquiring kinetic character, and vanishes in the media at pH ~ 10. Simultaneously with the decreases in this wave, a second wave, which increases as the pH increases, appears at more negative potentials. However, the sum of these waves at pH 8-10 remains almost constant (Fig. 1). Thus in acidic media the protonation step preceeds reduction of sidnokarb, whereas in alkaline media (pH > 10) the unprotonated depolarizer participates in the reduction (the $E_{1/2}$ value of sidnokarb in these media is independent of the pH and amounts to -1.37 V). The height of the wave of sidnokarb in alkaline media is substantially lower than in acidic media, and a drop in the limiting current is observed at pH > 12 as the hydroxide ion concentration increases. The limiting current of the reduction wave of sidnokarb in acidic media (first wave) and in alkaline media (second wave) is linearly dependent on the depolarizer concentration over rather wide limits. The height of the sidnokarb wave in a 0.1 N HCl base electrolyte as the ethanol concentration changes from 10 to 50% decreases in conformity with the change in the viscosity of the medium, and $i_{lim} \cdot \eta^{1/2} = $ const. The temperature coefficient of the limiting current of the first wave of sidnokarb in acidic media and of the second wave in alkaline media amounts to 2.2% at 7-55°C. All of this information constitutes evidence for the diffusion character of the observed waves in strongly acidic and alkaline media.

The number of electrons determined coulometrically during electrolysis at the potential of the limiting current of the sidnokarb wave in 0.1 N $HClO_4$ and in a buffer solution with pH 11.6 was found to be 5.1 and 3.9, respectively; the products of reduction of sidnokarb in alkaline media are capable of undergoing oxidation on a dropping mercury electrode and form an anode wave, the $E_{1/2}$ value of which is -0.26 V, whereas the anode wave is not observed after electrical reduction of sidnokarb in acidic solutions.

Similarly, an anode peak appears at -0.46 V on the cyclical voltamperograms of sidnokarb recorded in a buffer solution with pH 11.6 during scanning of the potential in the anode direction from the potentials of the limiting current of the reduction wave, whereas an anode peak is absence when curves of this sort are recorded from solutions of in 0.1 N $HClO_4$.

The data presented above constitute evidence that the polarographic behavior of sidnokarb has features in common with those in the reduction on a dropping mercury electrode of sydnones [7, 8] and sydnoneimine salts [6].

In an alkaline media the $E_{1/2}$ value of the second wave of sidnokarb is independent of the pH, i.e., as we have already stated above, the neutral molecule undergoes reduction without a prior protonation step. The re-
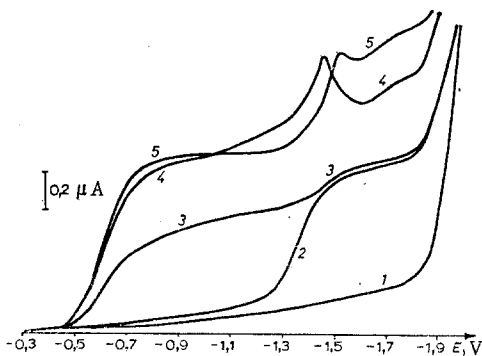
Fig. 3

Fig. 4

Fig. 3. Polarograms of a 0.3 mM solution of sidnokarb in a base electrolyte consisting of a 50% aqueous alcohol solution of 0.1 M KCl (2) at various HCl concentrations: 2) c = 0; 3) c = 0.385 mM; 4) c = 0.741 mM; 5) c = 0.909 mM (curve 1 is the residual base electrolyte current in a 50% aqueous alcohol solution of 0.1 M KCl).

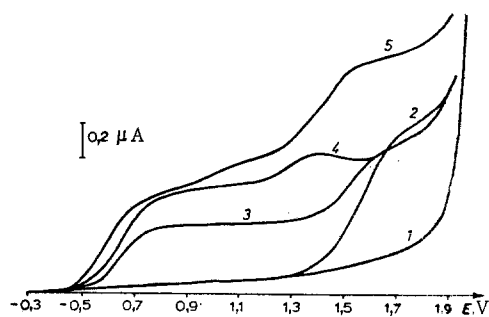Fig. 4. Polarograms of sidnokarb in a 0.5 mM HCl base electrolyte in a 50% aqueous alcohol solution of 0.1 M KCl (2). Sidnokarb concentration: 3) 0.095 mM; 4) 0.182 mM; 5) 0.461 mM. The residual current of the base electrolyte in a 50% aqueous alcohol solution of 0.1 M KCl is depicted by curve 1.

duction wave is irreversible, since the reciprocal of the slope of this four-electron wave in semilogarithmic coordinates is 65 mV. As one should have expected for irreversible discharge of a neutral depolarizer [9], a tenfold increase in the ionic strength of the solution on passing from 0.1 M LiOH to 1.0 M LiOH shifts $E_{1/2}$ by 60 mV to the positive-potential region. As in the reduction of sydnone [7, 8], transfer of four electrons apparently leads to the formation of the corresponding hydrazine derivative (III), which is capable of undergoing oxidation on the mercury electrode.

In acidic media the protonation step precedes reduction, and the $E_{1/2}$ value is determined by the pH of the medium. In aqueous alcohol media the pK_a value of sidnokarb is 3.36; in strongly acidic media (pH < 1) the sidnokarb in the volume of the solution is also present in the protonated form, and the half-wave potential should be independent of the pH (on passing from 0.1 N HCl to 1.0 N HCl the $E_{1/2}$ value is shifted to the positive-potential region by only 10 mV). In strongly acidic media the reduction wave of sidnokarb is observed immediately in the vicinity of the zero-charge point, and it therefore can be assumed that sidnokarb is adsorbed on the mercury electrode. In fact, in these media the wave has its maximum slope. However, sidnokarb adsorption decreases as the pH of the medium increases as the reduction wave becomes farther from the zero-charge point, and the wave becomes more of a sloping wave; in this case a linear relationship is observed between the slope of the wave and the $E_{1/2}$ value, in conformity with theory [10] (Fig. 2). The absence of anode peaks after electrolysis of acid solutions of sidnokarb and during the recording of cyclical voltamperograms, as well as the considerable increase in the current on passing from alkaline to acidic media, makes it possible to conclude that, as in the reduction of sydnones [7, 8], the principal process is six-electron reduction of sidnokarb to give amino acid derivative IVa.

In [7, 8] it is postulated that the limiting current of sydnones is determined by the form of the depolarizer that undergoes the electrode reaction: reduction in the protonated form proceeds with the consumption of six electrons, whereas the unprotonated depolarizer forms a four-electron wave. Considering that the investigated polarographic reduction process is complicated and should obligatorily include a definite sequence of electrochemical and chemical steps, in our opinion, not only the rate of prior protonation of the starting depolarizer but also the rate of protonation of the reduction intermediates may play a substantial role in the determination of the mechanism. Moreover, of no small importance is the fact that a large number of protons (up to eight in the case of complete six-electron reduction of sidnokarb) are consumed in the reduction, and alkalization of the solution may occur as the current in the immediate vicinity of the electrode surface increases even in solutions with sufficient buffer capacity, and this may affect the rate of protonation of the reduction intermediate. In order to make a more detailed investigation of the indicated processes, we used the method of latent limiting currents of hydrogen ions [11].

As in alkaline media, one wave corresponding to four-electron reduction of the unprotonated form of sidnokarb is observed in unbuffered KCl solutions, and the $\varkappa = i_{lim}/c$ value is 2.6. In the first series of ex-
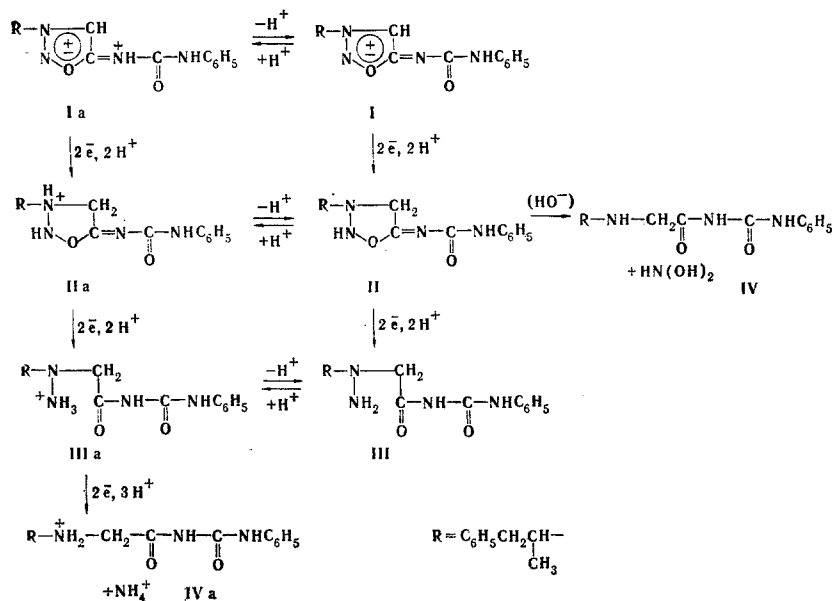
periments hydrochloric acid was added to a 0.3 mM solution of sidnokarb in a 0.1 M KCl base electrolyte while maintaining the sidnokarb concentration at a constant level. In the case of insufficient hydrochloric acid, in addition to the developing wave of protonation of the sidnokarb form, the wave of its basis form also remains. As a result of depletion of the protons in the near-electrode layer as the current of the first wave increases, this wave has more of a sloping form, and, in addition, a small additional wave with $E_{1/2} \approx -0.95$ V is observed (Fig. 3, curve 3). However, the increase in the overall current as the proton concentration increases is insignificant, i.e., the reduction wave of the protonated form of sidnokarb under the given conditions does not reach six electrons, whereas the wave with $E_{1/2} = -0.95$ V may correspond to reduction of an intermediate particle, for example, the unprotonated form of the product of two-electron reduction − the corresponding 2,4-dihydrosydnoneimine II. As the HCl concentration increases, the wave of the protonated form of sidnokarb becomes steeper, the current rise vanishes gradually at −0.95 V, and the reduction wave of the unprotonated form of sidnokarb vanishes. The wave of reduction of the protonated form of sidnokarb gradually approaches the height corresponding to transfer of six electrons only in the case of excess HCl, i.e., when the wave of discharge of H_3O^+ ions is also visible on the polarograms (the reduction wave of the protonated form of sidnokarb is higher by a factor of 1.43 in the presence ot 0.9 mM HCl than the reduction wave of sidnokarb in a 0.1 M KCl base electrolyte). It is interesting to note that prior to discharge of the H_3O^+ ions another apparently surface catalytic wave, which is also associated with reduction intermediates, develops. The behavior of this wave is rather complex, since, on the one hand, the proton-donor strength of the medium increases as the HCl concentration increases, and, on the other, the number of reduction intermediates (probably hydrazine derivative IIIa) decreases, since the concentration of these products decreases because of their reduction at the potentials of the first wave (see curves 4 and 5 in Fig. 3).

When a solution of sidnokarb is added to a 0.5 mM solution of HCl in 0.1 M KCl, in addition to the wave of H_3O^+ ions, a wave of protonation of the sidnokarb form develops on the polarograms. In this case, when the sidnokarb concentration is 0.095 mM, the height of the wave that appears is higher by a factor of 1.4 than the height of the wave at the same sidnokarb concentration in a 0.1 M KCl base electrolyte (Fig. 4, curve 3), i.e., it approaches the level corresponding to the transfer of six electrons. At a sidnokarb concentration of 0.18 mM, the analogous ratio of the wave heights decreases to 1.26. A further increase in the sidnokarb concentration does not affect the height of the wave of the protonated form, and a wave of reduction of the basic form of sidnokarb, the height of which depends linearly on its concentration, develops on the polarograms (as in the reduction of sidnokarb in a 0.1 M KCl base electrolyte, $\varkappa$ is 2.6). When the reduction wave of the protonated form of sidnokarb does not reach the level corresponding to the transfer of six electrons and H_3O^+ ions are still present in the near-electrode layer, a surface catalytic wave is also observed (Fig. 4, curve 4), whereas at high sidnokarb concentrations, there is an additional wave with $E_{1/2} \approx 0.95$ V, as well as waves of the acid and base forms of sidnokarb. The number of protons consumed in the reduction of sidnokarb, determined from the total currents, was found to be 4.07. Thus the data presented above constitute evidence that four electrons may be consumed in the reduction of sidnokarb in the protonated form and in the reduction of its basic form, and the height of the sidnokarb wave approaches the level corresponding to the transfer of six electrons only in the case of excess acid, when the rates of all of the intermediate protonation reactions are sufficiently high. At pH 8-10, where sidnokarb forms two reduction waves, the first wave also corresponds to the transfer of four electrons, since the total current is almost the same as in alkaline media (Fig. 1), and an anode peak of oxidation of hydrazine derivative III is present on the cyclical voltamperograms even in the case of application of a potential only up to the plateau of the limiting current of the first wave.

On the basis of the data obtained in this study, the reduction of sidnokarb in media with different proton-donor capacities can be represented by the scheme on the following page.

In acidic media, in which the rates of protonation of starting depolarizer I and of all of the intermediate reduction products are sufficiently high, the wave corresponds to the transfer, at once, of six electrons, and the final reduction products are the cation of the derivative of the amide of amino acid IVa and ammonium ions. The fact that the wave nevertheless may be somewhat smaller than in the case of six-electron reduction, whereas the coulometric n value is 5.1, is evidently associated with partial decomposition (hydrolysis) of the cation of the corresponding dihydrosydnoneimine IIa. If this phenomenon were associated with incomplete reduction of hydrazine derivative IIIa, we would have seen an anode wave of IIIa in acidic media. In alkaline media four-electron reduction leads to the base of hydrazine derivative III, which gives an anode wave; the decrease in the height of the wave at pH > 12.5 is apparently determined by partial alkaline hydrolysis of dihydrosydnoneimine II, and a possible product of this reaction is amino acid derivative IV. * Since only one reduc-

*The decrease in the height of the reduction wave of sidnokarb I in strongly acidic and strongly alkaline media is not associated with cleavage of starting I, since the height of the wave in 1% NaOH and HCl solutions remains practically unchanged for 24 h.

R—N——CH   R—N——CH
$\underset{N\diagdown O}{\overset{(+)}{\diagup}}$C=$\overset{+}{N}$H—C—NHC$_6H_5$ $\underset{+H^+}{\overset{-H^+}{\rightleftharpoons}}$ $\underset{N\diagdown O}{\overset{(+)}{\diagup}}$C=N—C—NHC$_6H_5$
          ‖   ‖
          O   O

I a   **I**

$\downarrow$ 2ē, 2H$^+$ $\downarrow$ 2ē, 2H$^+$

R—$\overset{H}{\underset{HN\diagdown O}{\overset{+}{N}}}$—CH$_2$ R—N——CH$_2$
  C=N—C—NHC$_6$H$_5$ $\underset{+H^+}{\overset{-H^+}{\rightleftharpoons}}$ $\underset{HN\diagdown O}{}$C=N—C—NHC$_6H_5$ $\overset{(HO^-)}{\longrightarrow}$ R—NH—CH$_2$C—NH—C—NHC$_6$H$_5$
          ‖   ‖   ‖   ‖
          O   O   O   O
                                           +HN(OH)$_2$

II a   **II**   **IV**

$\downarrow$ 2ē, 2H$^+$ $\downarrow$ 2ē, 2H$^+$

R—N——CH$_2$ R—N——CH$_2$
$\overset{+}{N}$H$_3$ C—NH—C—NHC$_6$H$_5$ $\underset{+H^+}{\overset{-H^+}{\rightleftharpoons}}$ NH$_2$ C—NH—C—NHC$_6$H$_5$
        ‖   ‖   ‖   ‖
        O   O   O   O

III a   **III**

$\downarrow$ 2ē, 3H$^+$

R—$\overset{+}{N}$H$_2$—CH$_2$—C—NH—C—NHC$_6$H$_5$ R = C$_6$H$_5$CH$_2$CH—
                  ‖   ‖ |
                  O   O   CH$_3$

+NH$_4^+$ **IV a**

tion wave is observed on the polarograms in strongly acidic and alkaline media, it can be concluded that the cations of intermediates IIa and IIIa are reduced more readily than the starting cation of sidnokarb Ia, whereas the dihydrosydnoneimine base II is reduced more readily than sidnokarb base I. In solutions with insufficient buffer capacity the IIa ⇌ II equilibrium in the near-electrode layer may be shifted to favor dihydrosydnone-imine II, and, as a result, its reduction wave appears at $^-$0.95 V, i.e., at less negative potentials than for sidnokarb base I and at more negative potentials than for sidnokarb cation Ia.

EXPERIMENTAL

The polarographic investigation was carried out in a thermostated cell at 25 ± 0.1°. The polarograms were recorded with a Radiometer PO-4 polarograph. A dropping mercury electrode with forced drop detachment was used (m = 0.75 mg/sec, t = 0.26 sec), and a saturated calomel electrode (sce) served as the anode. Cyclical voltamperometry and electrolysis at a controllable potential were accomplished by the method in [6]. Sidnokarb was obtained by the method in [5] and had mp 134–135°C.

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