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INVESTIGATION OF THE OXIDATION–REDUCTION TRANSFORMATIONS OF DERIVATIVES OF DIPYRIMIDO-[4,5-*b*][4′,5′-*e*][1,4]THIAZINE

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The oxidation–reduction characteristics of both the free radical and the reduced forms of dipyrimido[4,5-b][4′,5′-e][1,4]thiazine derivatives were studied by polarography. It was found that these compounds can participate in oxidation–reduction reactions, such as the oxidation of thiols and ascorbic acid (the radical form) and the reduction of oxygen (the reduced form). This makes it possible to regard them as a system capable of modelling certain oxidation–reduction processes that take place in the living organism.

Derivatives of tricyclic systems containing the structural fragment of uracil are being studied intensively in connection with the ability of some of them to take part in oxidation–reduction reactions [1-3]. In [4, 5] we showed that derivatives of 6,8-dimethyl-7,9-dioxodipyrimido[4,5-*b*][4′,5′-*e*][1,4]thiazine can exist in the form of stable free radicals and enter into one-electron oxidation–reduction. In the present article, the ability of this type of compound to participate in the oxidation of compounds containing a thiol group, the oxidation of ascorbic acid, and the reduction of oxygen (Schemes 1-3) was studied for the case of 4-dimethylaminopyrimido[4,5-*b*][4′,5′-*e*][1,4]thiazines [their free radical (I, II), and reduced (III, IV) forms] using the polarographic method.

In order to obtain data on the electron-accepting characteristics of compounds (I, II), we investigated their electrochemical reduction at a dropping mercury electrode.

In view of the very poor solubility of compounds (I, II) it is extremely important during the production of the polarographic data to find the optimum composition of the supporting electrolyte and most of all to select a solvent that satisfies the usual conditions of polarography, i.e., a sufficiently wide range of ideal polarizability of the mercury electrode and a depolarizer concentration corresponding to its concentration in the solution in the range of 10^{-3}-10^{-5} M. Such widely used and almost universal solvents as dimethylformamide and acetonitrile do not fully satisfy the demands, while the use of chloroform is not always convenient on account of its electrochemical reduction at potentials more negative than −1.0 V (saturated calomel electrode). We obtained the most accurate and reproducible results in formic acid, which as known is used in polarographic practice and particularly during investigation of the processes involved in the electrochemical reduction of transition metals [6]. It was found that two waves with half-wave potentials ($E_{1/2}$) of −0.35 and −1.1 V were observed on the cathodic polarograms of the methylamino and dimethylamino derivatives (I, II) in formic acid, and the wave heights were approximately the same in both cases. For the first wave, the linear dependence of the limiting diffusion current on the concentration is preserved over the whole measured range of concentration (from 10^{-5} to 10^{-3} M). The value of α_n (α is the transfer coefficient, n is the number of electrons taking part in the electrochemical reaction), determined from the $\log[i/(i_{lim} - i)] - E$ relation, is approximately 140 mV, which corresponds to an irreversible one-electron process. The irreversibility of this cathodic reaction is also confirmed by cyclic voltammetry; the difference in the potentials of the cathodic and anodic peaks on the polarograms amounts to 150 mV. With change in the pH of the solution from 0.3 (1:1 formic acid–water) to 2.85 (a mixture of aqueous formic acid with sodium hydroxide solution) $E_{1/2}$ moved toward the negative side ($dE_{1/2}/d\text{pH} = 100$ mV), which confirms that H_3O^+ cations take part in the electrochemical process. All this makes it possible to propose the following reaction scheme:

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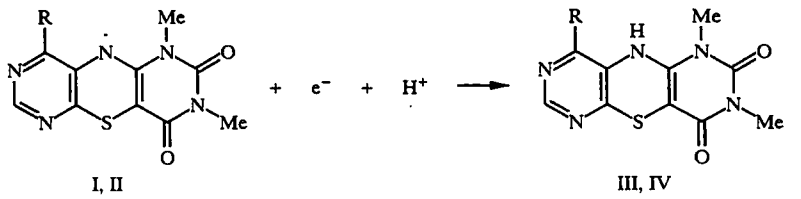
Scheme 1



I, II III, IV

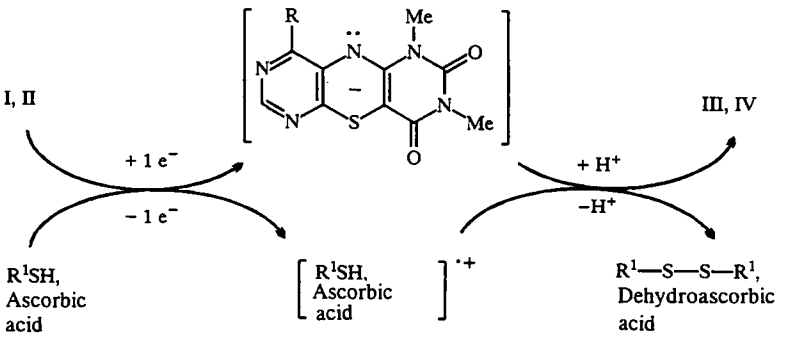
I, III R = NHMe; II, IV R = NMe_2

As a result of the decrease in the solvating capacity of the molecules of the thiazinyl radicals (I, II), the formation of their dimers could be expected in solution. However, the absence of additional reduction waves of the dimer on the polarograms and also the independence of the form of the reduction wave of the radicals in the range of temperatures between 6 and 25°C make it possible to rule out the presence of dimers in the solution. In addition, calculation of the concentration of the paramagnetic centers from the ESR data [4] shows that the investigated compounds exist almost completely in the form of monomeric radicals (I, II) in solution.

The second wave of the methylamino and dimethylamino derivatives (I, II) with $E_{1/2} = -1.1$ V is most likely due to the nonradical electrochemical hydrogenation of the pyrimidine ring of the molecule. We note that waves at the same potentials are also observed for reduced derivatives of type (III, IV). Investigation of the electrochemical properties of compounds (III, IV) is hindered to a significant degree as a result of the ease of their oxidation by atmospheric oxygen. In the solid state, the color of the reduced derivatives of type (III, IV) changes in the course of 3-4 days in air from yellow to blue-green, which indicates the formation of thiazinyl radicals (I, II) and demonstrates the instability of the reduced forms. Solutions of compounds (III, IV) change color after the first few minutes of dissolution. On the cathodic polarograms there are waves, the $E_{1/2}$ values of which correspond to electrochemical reduction of the respective radicals (I, II). The observed anodic oxidation waves of the reduced forms are nonreproducible in nature and cannot provide reliable information on the mechanism of the reaction on account of the fact that it is complicated by electrochemical oxidation of the mercury and chemical reaction between the adsorbed products from the electrochemical oxidation of mercury and compounds (III, IV).

If reducing agents, such as cysteine and ascorbic acid, are added to the solution of the thiazinyl radicals (I, II), the color of the solution changes from blue to greenish-yellow, indicating a change from the radical form to the reduced form. However, the cystine and dehydroascorbic acid formed as a result of the reaction give cathodic waves that mask the reduction wave of the radicals (I, II).

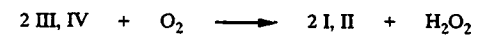
Scheme 2



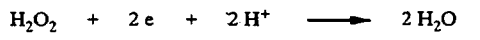
R^1SH = Cysteine

When the reduced forms of the dipyrimidothiazines (III, IV) are dissolved in deaerated aqueous dimethylformamide, the redox potential of the system corresponds to −0.180 V. If the solution is subsequently blown with air, the potential is shifted to −0.08 V. This shift is most likely due to the formation of hydrogen peroxide as a result of the reaction of compounds (III, IV) with atmospheric oxygen (Scheme 3):

Scheme 3

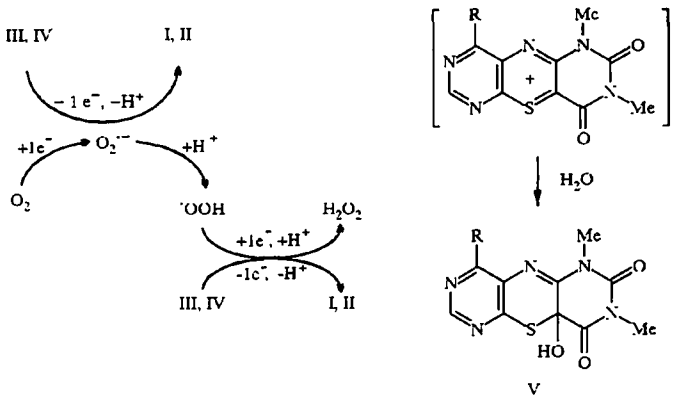


The hydrogen peroxide can be detected by means of its electrochemical reduction wave. In fact, on the polarograms of compounds (III, IV), the solutions of which were prepared with undeaerated distilled water, there was a two-electron wave with $E_{1/2} = -0.85$ V, which corresponds to the electrochemical reduction of hydrogen peroxide [7]:



Thus, study of the electrochemical characteristics of the derivatives of 7,9-dioxo-6,8-dimethyl-5H-6,7,8,9-tetrahydrodipyrimido[4,5-*b*][4′,5′-*e*][1,4]thiazine shows that they have fairly high reactivity in the oxidation of ascorbic acid and also of substrates containing thiol groups. In addition, it was discovered that they are capable of converting atmospheric oxygen into hydrogen peroxide under aerobic conditions. This provides grounds for regarding the free radical form of dipyrimidothiazines together with its reduced modification as a system capable of modelling certain oxidation–reduction processes in living organism, e.g., the first stage of the consecutive and reversible transformation of flavin coenzymes. At the same time, in spite of its unusual stability, the free radical form is capable not only of being reduced but also of undergoing oxidation, leading to the formation of the angular derivatives (V), which contain a hydroxyl at position 9a of the molecule (Scheme 4):

Scheme 4



The formation of compounds (V) is irreversible, and with an excess of the oxidizing agent the radical form can be completely removed from the system. The thia analogs of the alloxazines have a similar feature [5, 8], which distinguishes them from other structurally similar heterocyclic systems having oxidation–reduction characteristics.

EXPERIMENTAL

The polarographic measurements were made in a thermostated cell at 25 ± 0.1°C. A dropping mercury electrode with a spatula for enforced drop removal was used, and the reference electrode was a saturated calomel electrode. Before the measurements, the solutions were blown with nitrogen in order to free them from atmospheric oxygen. The supporting electrolyte was a solution of formic acid (1:1). The polarograms were recorded in the range of +0.2-1.3 V at a potential sweep rate of 10 mV/sec in a constant regime on a Radelkis ON-105 polarograph (Hungary). The cyclic voltammograms were recorded on a PAR electrochemical system at rates between 10 and 250 mV/sec.

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