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FREE RADICALS IN THE ELECTROCHEMICAL REDUCTION OF 1,2-DIHYDRO-3-NITROPYRIDINE DERIVATIVES

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The formation of primary radical anions of N-substituted 1,2-dihydro-3-nitropyridines was confirmed by the ESR method under conditions of electrochemical generation of free radicals, and their structure was established. The causes of the different ability of 1,2- and 1,4-dihydro-3-nitropyridines to form free radicals during electrochemical reduction that are stable enough to be studied by the ESR method are examined.

Despite the enormous importance of pyridine derivatives in the synthesis of drugs [1], the potentialities of this class of compounds have been far from entirely exhausted. Intensive searches for new drugs are continuing on the basis of these derivatives, including dihydropyridine derivatives, especially those whose molecule contains a nitro group [2-4].

In the course of the search for potential biologically active compounds, the ability of these compounds to participate in reductive and oxidative processes, as well as the detection and establishment of the structure of the particles formed in such processes, are being studied. We are systematically using electrochemical methods to model and study the course of redox processes. Thus, the structure of free radicals was studied by the ESR method during their electrochemical generation in the reduction or oxidation of the investigated compounds [5]. In series of dihydropyridine derivatives, radical cations of 1,2-dihydropyridines have been produced at reduced temperatures by these methods and have been studied [6]. However, the electrochemical generation and study of radical anions of dihydropyridine derivatives substituted with a nitro group can be accomplished more successfully. Nonetheless, for compounds where the nitro group is not directly bonded to the 1,4- or 1,2-dihydropyridine ring, little information on the state of the heterocycle itself in electrochemically generated free radicals has been obtained by the ESR method [7-11]. In turn, the study of electrochemically generated free radicals from derivatives of 1,4-dihydro-3-nitropyridines [12] and 1,4-dihydro-3,5-dinitropyridines [13] by cyclic voltammetry and by the ESR method has made it possible to judge not only the electronic state of the heterocycle but also its possible conversions in the course of the electrochemical process.

In this work we examined the results of a study of the course of the electrochemical reduction of 1,2-dihydro-3-nitropyridine derivatives I-VIII by polarography and cyclic voltammetry, as well as the electrochemical generation of free radicals and their study by the ESR method.

The electrochemical reduction of compounds I-VIII in DMFA on a dropping mercury electrode is complex and varied. Depending on the nature of the substituents, it proceeds in several steps (Table 1). For individual compounds, the number of observable steps of electrochemical reduction depends on the nature of the substituents R^1 and R^2. When the nitrogen atom of the pyridine ring is substituted, the four-step (in the case of compound III) or three-step (for compound VI) electroreduction process is reduced to two steps (compounds VIII, VII), which is evidence that a proton at the nitrogen atom of the heterocycle is involved in the initial stages of the electrochemical reduction of the molecule.

On the basis of the values of the limiting current of the polarographic waves, for which a current of 2.2 μA arbitrarily corresponds to the transfer of one electron, we can conclude that the total number of electrons consumed for the reduction of one molecule of the investigated compounds within the potential range under consideration is 2-6 or more.

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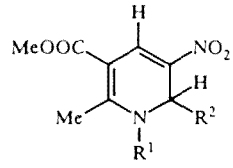
TABLE 1. Values of the Potential ($E_{1/2}$, V, relative to an aqueous saturated calomel electrode) and Standard Va'ues of the Limiting Current (i_{lim}, μA) of Polarographic Waves, Reversibility (+) of Electron Transfer at Individual Steps of Electrochemical Reduction at a Rate of Scanning of the Potential 50 mV/sec for Compounds I-VIII in Dimethylformamide [supporting electrolyte 0.1 M $(C_4H_9)_4NPF_6$]

Compound	R^1	R^2	$-E_{1/2}$ (in parentheses – values of i_{lim} and reversibility of the reaction)
I	H	Ph	1,14 (1,9; -); 1,83 (1,3; -); 2,06 (4,6; -); 2,26 (5,1; -)
II	H	*p*-$MeOC_6H_4$	1,19 (1,9; -); 1,82 (1,1; -); 2,00 (0,4; +); 2,22 (8,4; -)
III	H	*p*-BrC_6H_4	1,12 (1,9; -); 1,82 (1,6; -); 2,04 (4,2; -); 2,27 (7,0; -)
IV	H	*m*-$O_2NC_6H_4$	0,90 (0,6; -); 1,05 (1,3; +); 1,22 (1,1; +); 2,02 (5,9; -)
V	H	*o*-$HF_2COC_6H_4$	1,10 (1,3; -); 1,82 (0,6; -); 2,16 (5,2; -)
VI	H	*o*-$MeOC_6H_4$	1,20 (1,4; -); 1,94 (0,8; -); 2,26 (6,2; -)
VII	Me	*o*-$MeOC_6H_4$	1,02 (1,3; +); 2,02 (3,8; -)
VIII	Me	*p*-BrC_6H_4	1,17 (2,8; +); 2,10 (7,6; -)



I–VIII

I—VI R^1 = H; VII, VIII R^1 = Me; I R^2 = Ph; II R^2 = *p*-$MeOC_6H_4$; III R^2 = *p*-BrC_6H_4; IV R^2 = m-$O_2NC_6H_4$; V R^2 = *o*-$HF_2COC_6H_4$; VI R^2 = *o*-$MeOC_6H_4$; VII R^2 = *o*-$MeOC_6H_4$; VIII R^2 = *p*-BrC_6H_4

The reaction site of the first step of electron transfer is apparently the nitro group, as the most electrophilic group in the molecules of the original compounds. A comparison of the potential of the first polarographic wave of the compounds studied (I, III, IV, VI) with the previously found values for the corresponding potentials of 3-nitropyridine [14] and 1,4-dihydro-3-nitropyridine [12] derivatives showed that 1,2-dihydro-3-nitropyridines are reduced with greater difficulty than 3-nitropyridines but more easily than 1,4-dihydro-3-nitropyridines. Such a change in the electron-acceptor properties of the nitro group is apparently due to the different degree of delocalization of the electron added by the nitro group over the pyridine ring. The possibilities of delocalization increase with expansion of the system of π-electrons conjugated with the nitro group, in the series: 1,4-dihydro-3-nitropyridine, 1,2-dihydro-4-nitropyridine, 3-nitropyridine, which agrees with the decrease in the potential of the first polarographic wave of the reduction of this series of compounds.

The limiting current of the first polarographic wave of the compounds investigated (with the exception of compound VIII) does not reach the one-electron level (2.2 μA). On the basis of the assumption that there is a one-electron reduction of the nitro group in the primary electrochemical process, we can conclude that part of the molecules are inaccessible for this process as a result of their transformation near the cathode into more difficultly reducible particles. In turn, in the one-electron process radical anions of N-unsubstituted 1,2-dihydropyridines I-VI formed are subjected to an immediate transformation to more difficult-to-oxidize particles, as indicated by the irreversibility of the initial reduction (Table 1). Thus, at this step of the reduction of compounds I-VI we should not expect the formation of primary radical ions sufficiently stable to be detected by the ESR method [5].

In contrast to the compounds discussed above, the initial reduction of N-substituted 1,2-dihydropyridines VII, VIII is reversible, and in this process we might expect the formation of primary radical ions accessible to investigation of their structure by the ESR method.

Partial reversibility of the electrochemical process is also observed at the third step of the reduction of compounds II, IV, and also at the second step of the reduction of compound IV.

TABLE 2. Nature and Constants of the Hyperfine Interaction with the Nuclei of Atoms in the Corresponding Positions of the Heterocycle (α_i, Gs) for Free-Radical Anions of 1,2-Dihydro-3-nitropyridines IV, VII, and VIII

Compound	R^1	R^2	Nature of HFS	a_i				
				a_1		a_3	a_4	a_6
				a_N	a_H			
IV	H	*m*-$O_2NC_6H_4$	$3_N \times 2_H \times 3_H \times 2_H \times 2_H$	$a_N = 9,77$; $a_H = 3,74$; $a_{2H} = 3,16$; $a_H = 0,94$; $a_H = 0,35$				
VII	CH_3	*o*-$H_3COC_6H_4$	$3_N \times 4_H \times 2_H \times 4_H \times 3_N$	1,10	1,43	8,58	4,67	6,16
VIII	CH_3	*p*-BrC_6H_4	$3_N \times 4_H \times 2_H \times 4_H \times 3_N$	1,10	1,43	7,59	4,40	6,27

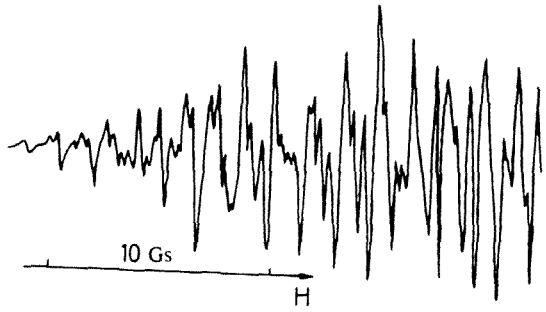


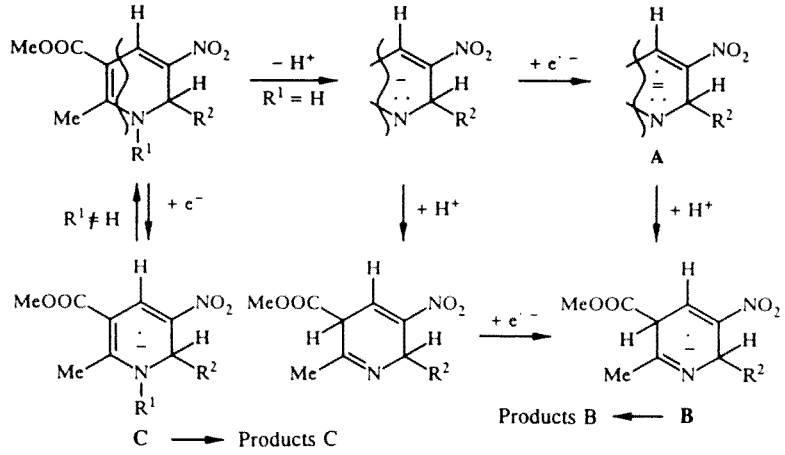
Fig. 1. Low-polar portion of the ESR spectrum of free radicals formed in their electrochemical generation during the reduction of compound VII.

As we should have expected from the results of a study of the electrochemical reduction of N-unsubstituted 1,2-dihydro-3-nitropyridines I-VI, in the course of electrochemical generation at the potentials of the first polarographic wave, free radicals could not be detected by the ESR method. Consequently, as a result of the initial addition of one electron to the original molecule, perhaps the radical anions formed undergo an immediate chemical or electrochemical conversion with a loss of paramagnetic properties. At higher potentials of generation of radicals of N-unsubstituted 1,2-dihydro-3-nitropyridines, with the exception of compound IV, ESR signals also were not observed.

In the case of compound IV at generation potentials close to -1.2 V relative to the Pt electrode, free radicals were detected, the hyperfine structure of whose ESR spectrum is due to interaction of an unpaired electron with the nucleus of a nitrogen atom, two equivalent protons, and three nonequivalent protons. The nature of the hyperfine structure and the values of its constants (Table 2) provide evidence of the fact that the detected radical has a structure similar to the radical anion of a meta-alkyl-substituted nitrobenzene [15, 16]. Consequently, after the first step of electrochemical reduction of compound IV, the 2-position of the heterocycle retains its initial state, and the instability of the radical anions formed in the initial process of one-electron reduction of N-unsubstituted 1,2-dihydro-3-nitropyridines may evidently be due to a rapid change in the state of the 1-position of the heterocycle and further accompanying chemical processes. Such a change in the state of the 1-position of the pyridine ring may be transition of the nitrogen atom of the heterocycle from the $1s^2 2s^2 \sigma^3$ state to the $1s^2 2s^2 p^2 \sigma^2$ or $1s^2 2s^2 \sigma^2 \pi^1$ state.

Actually, in the case of N-substituted 1,2-dihydro-3-nitropyridines VII and VIII, for which such changes in the state of the nitrogen atom of the heterocycle and thereby the accompanying chemical processes are rather improbable, at the first step of their electrochemical reduction free radicals are detected, the hyperfine structure of whose ESR spectra may indicate the formation of primary radical anions (Table 2). Thus, for example, in the case of compound VII an ESR spectrum was obtained (Fig. 1) whose hyperfine structure was due to the interaction of an unpaired electron with two nuclei of nonequivalent nitrogen atoms, two nonequivalent groups of three equivalent protons, and a single proton. Both in the nature of the hyperfine structure and in the values of its constants, these radicals are similar to the radical anions of nitrodienes [17], which should also have been expected for primary radical anions of compound VII.

Hence, in contrast to 1,4-dihydro-3-nitropyridines [12], in the course of the electrochemical reduction of 1,2-dihydro-3-nitropyridines I-VIII, secondary free radicals with an unpaired electron delocalized over the heterocycle could not be detected by the ESR method, which prevents a reliable judgment of the mechanism of their electrochemical reduction. However, this does not rule out the possibility that in this case also the electrochemical reduction occurs schematically partially according to a mechanism similar to the electroreduction of 1,4-dihydro-3-nitropyridines [12]:



In our case the possibility of detecting primary free radicals C of N-substituted compounds VII and VIII is due to delocalization of the unpaired electrons from the nitro group over the system of four π-electrons of the diene fragment of the heterocycle, in contrast to similar free radicals of 1,4-dihydropyridines, which could not be detected [12], evidently as a result of their high reactivity, due to the relatively limited delocalization of the unpaired electron over the system of two π-electrons of the vinylene fragment of the heterocycle and thereby increased unpaired electron density on the nitro group. Similar factors were probably responsible for the possibility of detecting secondary free radicals by the ESR method. Thus, in the case of 1,4-dihydropyridines [12], secondary free radicals like B proved to be the most stable for them on account of delocalization of the unpaired electron over the system of four π-electrons of the diene fragment of the heterocycle, whereas in free radicals B for 1,2-dihydropyridines such delocalization is possible only over the two-electron system of π-electrons of the vinylene fragment of the heterocycle.

The instability of radicals B and their rapid transformation into products of further conversions may evidently be responsible for the reduced probability of formation of radicals of type A, and vice versa. This was also observed in the present work in the course of the electrochemical reduction of 1,2-dihydro-3-nitropyridines, and also earlier for 1,4-dihydroanalogs. For the latter the increased stability of free radicals of type A may also be due to the six-electron π-system formed by the nitrogen atom of the heterocycle in the $1s^2 2s^2 \sigma^2 \pi^2$ state, conjugated with two vinyl fragments [12]. In the case of 1,2-dihydro-3-nitropyridines, this atom in the $1s^2 2s^2 p^2 \sigma^2$ state, as an electron donor, can destabilize the free radical by increasing the unpaired electron density on the nitro group.

EXPERIMENTAL

The electrochemical reduction of compounds I-VIII was conducted in anhydrous DMFA [18] in tetrabutylammonium hexafluorophosphate ($C = 10^{-1}$ M).

Free radicals were generated in a stationary system on the surface of a platinum electrode placed in a cylindrical resonator of the TM_{110} type of an SE/X 2547 ESR spectrometer, equipped with an MR-102 spectrum analyzer (Radiopan OPP Polish Academy of Sciences) according to the procedure of [5]. For the electrochemical generation of free radicals, a $5 \cdot 10^{-4} \ldots 10^{-3}$ M solution of compounds I-VIII in anhydrous DMFA was used; the solutions contained 10^{-1} M tetrabutylammonium hexafluorophosphate.

The procedure of synthesis of 1,2-dihydro-3-nitropyridines I-VIII was presented in [19].

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