

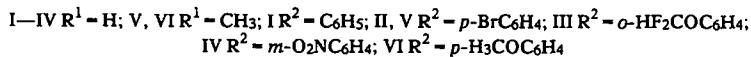
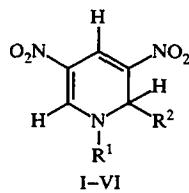
FREE RADICALS IN THE ELECTROCHEMICAL REDUCTION OF DERIVATIVES OF 3,5-DINITRO-1,2-DIHYDROPYRIDINE

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The characteristics (potentials, limiting currents, reversibility) of the electrochemical reduction of 3,5-dinitro-1,2-dihydropyridines were determined by cyclic voltammetry and polarography. It was established by ESR that the free radicals formed in these processes have a radical-dianion structure in the case of both the N-unsubstituted and the N-substituted dihydropyridines. The hyperfine coupling constants of the interaction between the unpaired electron and the nuclei of the atoms at various positions of the heterocycle were determined.

An important part of researches into the mechanisms of the electrochemical transformations of promising types of compound in the search for medical properties (dihydropyridines) is determination of the structure of the intermediate particles formed during the transformations. A method combining electrochemical generation of the particles and their simultaneous detection by ESR [1, 2] was used to produce and study the radical-cations of 1,2-dihydropyridines [3], the radical-anions of nitrophenyl-substituted 1,4- and 1,2-dihydropyridines [4-8], and the radical-anions of 3-nitro-1,4- [9], 3-nitro-1,2- [10], and 3,5-dinitro-1,4-dihydropyridines [11] formed in such processes.

In a continuation of research into the free radicals formed during the electrochemical reduction of the nitro derivatives of dihydropyridine compounds the characteristics of the electrochemical reduction of 3,5-dinitro-1,2-dihydropyridines (I-VI) were determined by polarography and cyclic voltammetry. The electrochemical generation [2] of the respective free radicals was also realized, and the hyperfine structure of their ESR spectra was recorded.



The polarographic reduction of compounds (I-IV) in DMFA at a dropping mercury electrode takes place in not less than three stages (Table 1). This probably also applies to the N-substituted compounds (V, VI), since the second stage of their reduction consists of at least two difficultly distinguishable stages. In the case of 3,5-dinitro-3-(*m*-nitrophenyl)-1,2-dihydropyridine (IV) it is possible to distinguish four stages of electrochemical reduction. This is probably explained by additional reduction of the nitrophenyl substituent. Starting from the limiting currents of the polarographic waves, for which a current of 2.2 μ A corresponds nominally to the transfer of one electron, it can be concluded that the total number of electrons used on the reduction of one molecule in the investigated range of potentials ranges from six [compound (I)] to 18 or more [compound (IV)].

The reaction center of the initial electron transfer is probably the nitro group as being the most electrophilic center in the investigated molecules. The first reduction potential of the investigated compounds depends on the donor-acceptor

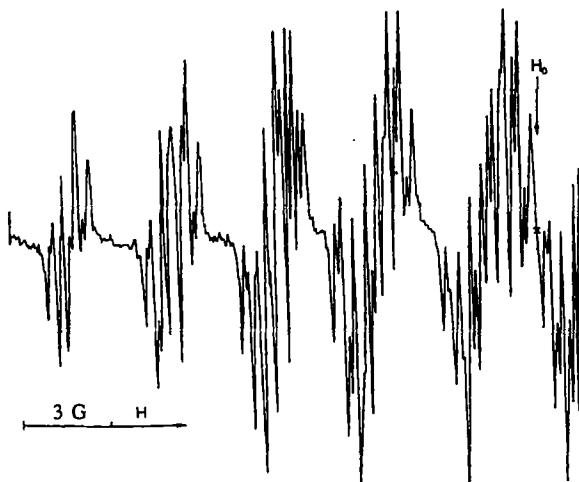


Fig. 1. ESR spectrum of the free radicals formed during their electrochemical generation in the course of the electrochemical reduction of compound (III) in DMFA.

characteristics of the substituents in the heterocycle. Reduction is impeded by substitution of position 1 in 1,2-dihydropyridine by methyl and facilitated by substitution by a more electrophilic substituent at position 2. Comparing the reduction potentials of 3-nitro-1,2-dihydropyridine [10] and 3,5-dinitro-1,2-dihydropyridines we see that the initial reduction of the latter takes place in the range of more positive potentials. The dependence of the ease of initial reduction on the degree of possible delocalization of the unpaired electron from the reaction center (the nitro group) in the π system of the molecule is preserved in the 3,5-dinitro-1,2-dihydropyridines. Thus, the investigated 3,5-dinitro-1,2-dihydropyridines are reduced in the initial process at more positive potentials than 3-nitro-1,2-dihydropyridines. The latter also applies to 3,5-dinitropyridines [12], the reduction of which takes place at even more positive potentials than for 1,3-dinitro-1,2-dihydropyridines.

The limiting current of the first polarographic wave of the N-unsubstituted 1,2-dihydropyridines [with the exception of compound (IV)] does not reach the one-electron level ($2.2 \mu\text{A}$). On the basis of the idea that at least one electron adds to the molecule of the nitro compounds (I-III) at the first stage of electrochemical reduction, it can be concluded that part of the molecules are unsuitable for this process on account of their transformation near the cathode into more difficultly reduced particles. In turn, the radical-anions of the N-unsubstituted 1,2-dihydropyridines (I-IV) formed in the one-electron process undergo rapid irreversible transformation into particles with different structure, as demonstrated by the irreversibility of the initial reduction (Table 1). The nature of the first wave and the corresponding electrochemical processes were not studied in greater detail in the present work. By analogy with the electrochemical reduction of other heteroaromatic nitro compounds, however, it can be supposed that the corresponding wave appears as a result of electrochemical reduction of the protonated particles. Protonation is realized either by the HA particles themselves ("autoprotonation") or as a result of proton-donor side processes. In both cases only an insignificant part of the depolarizer molecules probably undergo electrochemical reduction in the protonated form to the derivatives of N-hydroxylamine in aprotic media. Thus, the formation of primary radical-anions or other radical-anions sufficiently stable for detection by ESR must not be expected at this stage of the reduction of N-unsubstituted dihydropyridines (I-IV) [2].

At more negative potentials, i.e., at the second stage of the reduction of the N-unsubstituted compounds (I-IV), and also at the third stage of the reduction of compound (IV) reversible addition of electrons is observed. This may indicate that radical-ions are formed in these processes.

Substitution at the nitrogen atom of the heterocycle radically changes the reduction path of 3,5-dinitro-1,2-dihydropyridines. Thus, instead of the irreversible initial reduction of compounds (I-IV) the N-substituted compounds (V, VI) are reduced reversibly at the first stage. This probably indicates the possibility of the formation of radical-anions sufficiently stable for investigation by ESR.

According to data on the electrochemical reduction of N-unsubstituted 3,5-dinitro-1,2-dihydropyridines (I-IV), it was not possible to detect free radicals during electrochemical generation at the potentials of the first polarographic wave by ESR. Consequently, as a result of the initial addition of one electron to the initial molecule the radical-anions that form undergo

TABLE 1. Potentials ($E_{1/2}$, V) with Reference to a Saturated Aqueous Calomel Electrode and the Limiting Currents (i_{lim} , μ A) of the Polarographic Waves, the Reversibility (+) of Electron Transfer at the Individual Stages of Electrochemical Reduction at a Potential Sweep Rate of 50 mV/sec for Compounds (I-VI) in Dimethylformamide [Supporting Electrolyte ($C_4H_9)_4NPF_6$]

Com- ound	$-E_{1/2}$ (the i_{lim} values and the reversibility of the reaction)
I	0.84(1,4; -); 1,34(1,7; +); 2,55(3,0; -)
II	0.80(1,7; -); 1,32(1,9; +); 2,55(3,2; -)
III	0.80(1,8; -); 1,28(1,8; +); 2,27(2,6; -)
IV	0.72(2,2; -); 1,15(2,2; +); 1,32(2,2; +); 2,36(12,0; -)
V	0.89(2,6; +); 1,55(7,1; -)
VI	0.92(2,6; +); 1,57(5,7; -)

fast chemical or electrochemical transformation with the loss of free radical character. The formation of free radicals was detected by ESR during electrochemical generation at potentials corresponding to the second polarographic stage in the reduction of the N-unsubstituted compounds (I-IV). Thus, free radicals were detected in the case of compound (IV), containing an *m*-nitrophenyl substituent at position 2 of the heterocycle, at the second stage of reduction at electrochemical generation potentials close to -1.2 V with reference to a platinum electrode. The hyperfine structure in their ESR spectra was due to coupling of the unpaired electron with the nucleus of the nitrogen atom, two equivalent protons, and three nonequivalent protons. The values of the constants and the nature of the hyperfine structure in the ESR spectrum (Table 2) indicate that the detected radical has a structure similar to the radical-anion of *m*-alkyl-substituted nitrobenzene [13, 14]. Its structure indicates that after the first stage of electrochemical reduction of compound (IV) the carbon atom at position 2 of the heterocycle retains the initial $1s^22\sigma^4$ state. Consequently, the retention of the proton at position 2 of 3,5-dinitro-1,2-dihydropyridine after the second stage of reduction confirms the idea that at the first stage molecules incapable of being reduced are formed as a result of the elimination of a proton at the nitrogen atom of the heterocycle and not at the carbon atom at position 2 of the heterocycle. The eliminated proton is probably used for protonation at the first polarographic stage in the reduction of the radical-anions that form. Such protonated radical-anions of nitro compounds are subsequently reduced easily to particles free of paramagnetic properties [1]. This explains the absence of free radicals recordable by ESR during their generation at the first stage in the reduction of the molecule of compounds (I-IV).

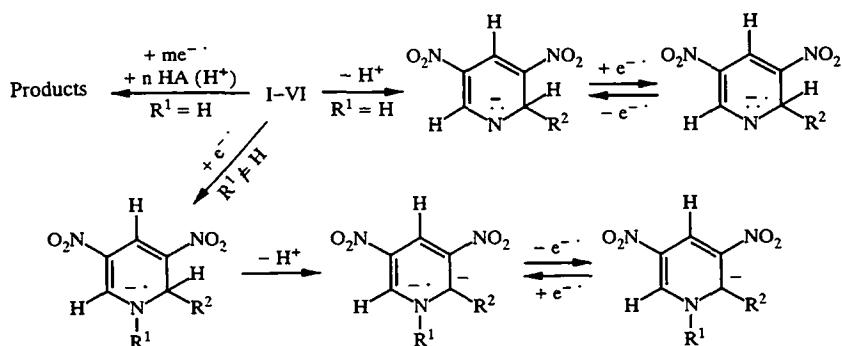
During electrochemical generation at potentials corresponding to the third stage of the polarographic reduction of compound (IV) free radicals of a different structure were detected by ESR. The hyperfine structure of their ESR spectra is due to the coupling of the unpaired electron with the nuclei of the nitrogen atoms of the nitro groups (situated at nonequivalent positions of the heterocycle) and also with the nitrogen atom of the heterocycle, with the protons at positions 4 and 6 of the heterocycle, and with the proton at position 1 or 2 of the heterocycle. The last proton is probably the hydrogen atom at position 2 of the heterocycle. This idea is supported by the fact that the radicals produced at the previous stage of the reduction contain a proton at position 2 of the heterocycle. It is also supported by the fact that the molecular products of transformation near the electrode without the expenditure of electrons, which are incapable of reduction at the potentials of the first wave, are probably reduced at the third polarographic stage. It follows from the ESR spectra of the free radicals produced at the potentials of the second polarographic stage of reduction that the initial stage of such a transformation may be the elimination of the proton at the nitrogen atom of the heterocycle near the cathode. The formation of such products shows up more clearly in the case of compounds (I-III), similar to compound (IV). For these compounds the limiting current of the first polarographic wave in no way reaches the one-electron level (Table 1). The ESR signals of the free radicals were also not detected in the course of the electrochemical generation of free radicals at the potentials of the first polarographic wave for the reduction of compounds (I-III). Consequently, in the course of such reduction in the initial process of the addition of one electron to the un-ionized molecules the radical-anions that are formed are also quickly transformed into different products with loss of the paramagnetic properties.

The electrochemical reduction of compounds (I-III) at the second polarographic stage [the potentials of which correspond to the third stage of the polarographic reduction of compound (IV)] also leads, according the reversibility of this process, to the formation of free radicals that can be studied by ESR. The nature of the hyperfine structure in the corresponding ESR spectra is the same as for the free radicals produced in the case of compound (IV) during reduction of the latter at the

potentials of the third stage of polarographic reduction (Table 1). In this sense the only difference is observed in compound (III) (Fig. 1), for the free radicals of which it was possible to determine the value of the additional constant for the significantly weaker interaction of the unpaired electron with another single proton. In our opinion, it applies to the hydrogen atom at the *o* position of the phenyl substituent. Further evidence for the fact that the investigated free radicals are formed from particles in which the proton is removed from position 1 of the heterocycle and not from position 2 is the course of the electrochemical generation of the free radicals of compound (V), for which removal of the proton at position 1 is not very likely.

In contrast to the N-substituted compounds (I-IV), in the case of compound (V) the reversibility of this process was detected by cyclic voltammetry at the first stage of reduction. According to such a property of compound (V), the formation of free radicals was detected at this stage of reduction by ESR. However, it was established by cyclic voltammetry that the concentration of the oxidized particles (radical-ions) increased with decrease in the potential sweep rate and with increase in the number of cycles, i.e., oxidation not of the initial radical-anion but of its transformed form takes place at the potentials of the negative current branch. The transformed form may be the radical-dianion formed as a result of the removal of a proton from position 2 of the heterocycle. The nature of the hyperfine structure in the ESR spectrum of the free radical generated electrochemically at these potentials also leads to the same idea. Coupling of the unpaired electron in the free radical with the three nuclei of the nonequivalent nitrogen atoms at position 1 and also at positions 3 and 5 of the heterocycle, with the two protons at the nonequivalent positions 4 and 6, and with the three protons of the methyl group at the nitrogen atom of the heterocycle was detected in the spectrum. The presence of the proton at position 2 of the heterocycle was not observed (Table 2). The formation of other free radicals was detected by ESR during the electrochemical generation of the free radicals of compound (V) at potentials ~ 0.2 V more negative than for the investigated radical-anions. It was not possible to establish the origin, nature, and structure of these free radicals (Table 2). Their formation was not detected by electrochemical methods (Table 1). The hyperfine structure of their ESR spectra indicates that the distribution of the density of the unpaired electron in this radical differs somewhat from that observed for the investigated radical-dianion, while the principal difference in these radicals lies in the fact that the nitrogen atom of the heterocycle in the new radical is ionized. (There is no coupling with the proton of the hydrogen atom or with the protons of the methyl group at this nitrogen atom.) Coupling with the proton of the hydrogen atom at position 2 of the heterocycle is also observed. The obtained free radical differs from the radical-dianion of compound (II), as shown by the different values of the hyperfine structure constants in their ESR spectra (Table 2).

Together the obtained results make it possible to determine certain stages in the electrochemical reduction of 3,5-dinitro-1,2-dihydropyridines (I-VI) connected with the formation of free radicals and to represent them in the following way:



Two processes take place simultaneously at the first stage of the electrochemical reduction of the N-substituted compounds. Some molecules are reduced to primary radical-anions or free radicals, which quickly undergo further electrochemical or chemical transformations with loss of the paramagnetic properties. By losing the proton at the nitrogen of the heterocycle in the region near the cathode, other molecules are converted into anions, which subsequently form radical-dianions at the second one-electron stage of electrochemical reduction.

Unlike the N-substituted 1,2-dihydro-3-nitropyridines, for which their primary radical-anions were recorded [12], in the case of the N-substituted 3,5-dinitro-1,2-dihydropyridine (V) the radical-anions possibly formed in the initial electrochemical reduction process are converted into its radical-dianions by eliminating the proton at position 2 of the heterocycle.

TABLE 2. Nature and the Hyperfine Coupling Constants (a_i , G) of the Unpaired Electron with the Nuclei of the Atoms at the Respective Positions of the Heterocycle for the Free Radical-Dianions of 3,5-Dinitro-1,2-dihydropyridines (I-V)

Compound	Nature of hfs	a_i					
		a_1		a_2	a_3	a_4	a_5
		a_N	a_{3H}				
I	$2H \times 3N \times 3N \times 2H \times 2H \times 3N$	0,28	—	0,30	6,77	8,01	3,98
II	$2H \times 3N \times 3N \times 2H \times 2H \times 3N$	0,35	—	0,40	6,93	8,12	4,02
III	$2H \times 3N \times 3N \times 2H \times 2H \times 3N \times 2H$	0,40	—	0,42; 0,16	7,01	7,91	3,90
IV	$3N \times 2H \times 3H \times 2H \times 2H$ $2H \times 3N \times 3N \times 2H \times 2H \times 3N$	$a_N = 10,23; aN = 3,85; a2H = 3,35; aH = 1,32; aH = 0,55$		0,44	—	7,34	8,30
V	$2H \times 3N \times 3N \times 3N \times 2H \times 4H$ $2H \times 3N \times 3N \times 2H \times 3N \times 2H$	2,0	0,16	—	6,9	6,9	5,7
		1,45	—	0,57	6,16	6,16	5,72
							1,45

EXPERIMENTAL

The electrochemical reduction of compounds (I-VI) was conducted in anhydrous dimethylformamide [15] ($C = 5 \cdot 10^{-4}$ M) with tetrabutylammonium hexafluorophosphate ($C = 10^{-1}$ M) as supporting electrolyte.

The free radicals were generated under standard conditions on the surface of a platinum electrode, placed in the cylindrical TM₁₁₀ resonance cavity of the SE/X 2547 ESR spectrometer, fitted with an MP-102 spectral analyzer (OPP Radiopan, Polish Academy of Sciences) by the method in [2]. A $5 \cdot 10^{-4}$ - 10^{-3} M solution of compounds (I-V) in anhydrous dimethylformamide was used for the electrochemical generation of the free radicals. The solutions contained 10^{-1} M of tetrabutylammonium hexafluorophosphate.

The procedure used for the synthesis of the 1,2-dihydro-3,5-dinitropyridines (I-VI) was described in [16].

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