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# FREE ANION-RADICALS IN THE ELECTROCHEMICAL REDUCTION OF DERIVATIVES OF 1,4-DIHYDRO-3,5-DINITROPYRIDINE

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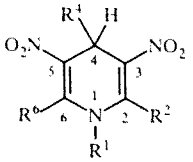
*The method of EPR under conditions of the electrochemical production of free radicals of N-unsubstituted derivatives of 1,4-dihydro-3,5-dinitropyridine was utilized to confirm the formation of dianion-radicals, and their structure was established. The methods of polarography and cyclic voltamperometry were utilized to show the possible formation of anion-radicals of the N-substituted derivative of 1,4-dihydro-3,5-dinitropyridine which, however, could not be registered by the method of EPR due probably to the π-dimeric diamagnetic state of these species.*

In the investigation of mechanisms of electrochemical conversions of compounds of the dihydropyridine class, which is very promising in the search for medicinal agents, the detection and structural study of intermediate species formed in the course of the conversions indicated comprise an important area. For this purpose, the method of the electrochemical production of free radicals [1,2] was utilized both in the course of oxidation of the π-electron system of dihydropyridines [3, 4], and in the reduction of the π-electron system of the substituents unconjugated with this nucleus, being mainly of the nitroaryl type [5-9]. In contrast to cation-radicals of dihydropyridine, in which the unpaired electron is delocalized in the dihydropyridine system and where the method of EPR can be utilized to obtain information on the structure of the dihydropyridine framework, such information is not readily available for anion-radicals of nitroaryl-substituted derivatives of dihydropyridine since the unpaired electron in these radicals does not interact with the nuclei of the atoms of the heterocyclic ring. Compounds are isolated favorably where the center of reduction is conjugated with the π-electron system of dihydropyridine. It was established in work which we started on the electrochemical production of anion-radicals of such a type using examples of compounds of the 1,4-dihydro-3-nitropyridine series that some intermediate species having free-radical character of differing structure may be formed in the course of their electrochemical reduction; the EPR method performed on the intermediate species successfully provides information on the state of the dihydropyridine framework [10].

The present work led to identification of the structure of the free radicals formed by the electrochemical reduction of 1,4-dihydropyridines substituted by two nitro groups conjugated with the π-electron system of dihydropyridine, namely derivatives of 1,4-dihydro-3,5-dinitropyridine (I)-(VII).



I–VII

I, III—VII $R^1 = H$, II $R^1 = C_6H_5$; I, II, IV, VII $R^2 = CH_3$, III, V, VI $R^2 = H$; I—III $R^4 = C_6H_5$, IV $R^4 = o\text{-}CHF_2OC_6H_4$, V $R^4 = p\text{-}BrC_6H_4$, VI $R^4 = m\text{-}O_2NC_6H_4$, VII $R^4 = H$; I, II, IV, VII $R^6 = CH_3$, III, V, VI $R^6 = H$

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TABLE 1. Values of the Potential ($E_{1/2}$, V, relative to the aqueous saturated calomel electrode) and Standard Values of the Limiting Current ($i_{lim}$, μA) of Polarographic Waves and the Reversibility (+) of the Transfer of Electrons at Separate Stages of Electrochemical Reduction with the Scanning Rate of the Potential of 50 mV·sec$^{-1}$ for the Compounds (I)-(VI) in Dimethylformamide [the Background Electrolyte 0.1 M $(C_4H_9)_4NPF_6$]

| Compound | $R^1$ | $R^2$ | $R^4$ | $R^6$ | $-E_{1/2}$ (in the brackets are given the values of $i_{lim}$ and the reversibility of the reaction) |
|---|---|---|---|---|---|
| I | H | $CH_3$ | $C_6H_5$ | $CH_3$ | 1,04 (1,5; -) 1,44 (2,0; +);<br>2,47 (9,6; -) |
| II | $C_6H_5$ | $CH_3$ | $C_6H_5$ | $CH_3$ | 1,03 (2,2; +); 1,45 (1,9; +);<br>1,70 (0,9; +); 2,13 (0,5; -) |
| III | H | H | $C_6H_5$ | H | 0,90 (1,7; -); 1,27 (1,7; +);<br>2,22 (4,9; -) |
| IV | H | $CH_3$ | *o*-$CHF_2OC_6H_4$ | $CH_3$ | 1,03 (1,7; -); 1,38 (1,5; +);<br>2,28 (5,6; -) |
| V | H | H | *n*-$BrC_6H_4$ | H | (0,86; -); 1,18 (1,4; +);<br>2,02 (4,6; -) |
| VI | H | H | p- $O_2NC_6H_4$ | H | 0,81 (1,9; -); 1,08 (1,8; +);<br>1,31 (1,5; +); 2,20 (8,6; -) |

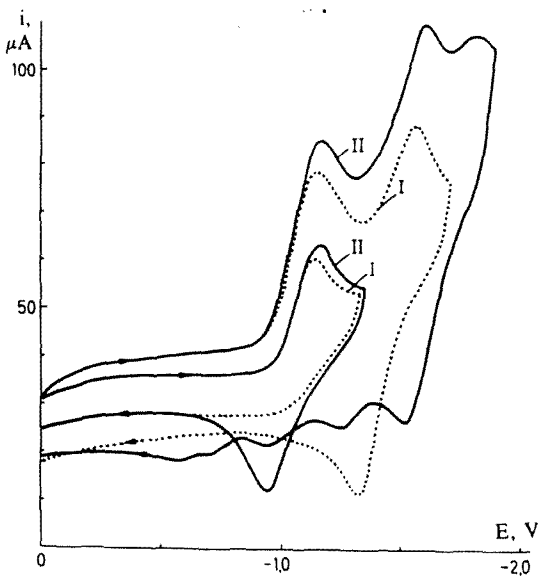


Fig. 1. Cyclic voltampere curves (V = 100 mV/sec) of the electrochemical reduction, on a glass-graphite electrode, of 1,4-dihydro-2,6-dimethyl-3,5-dinitro-4-phenylpyridine (I) and 1,4-dihydro-2,6-dimethyl-3,5-dinitro-1,4-diphenylpyridine (II) in dimethylformamide.

The investigated compounds (I)-(VI) in dry DMF [11] are reduced on a dropping mercury electrode in stages with the formation of three or more polarographic waves (Fig. 1). The potential of the first reduction of the investigated compounds depends mainly on the properties of the substituent at the position 4 of the heterocycle. For the N-unsubstituted derivatives of dihydropyridine, such a dependence, although with the reverse trend, is also observed approximately for values of the limiting current for the polarographic wave of the first reduction. For these compounds, the values of $i_{lim}$ do not reach the single-electron level ($i_{lim}$ = 2.2 μA), whereby the more difficult the reduction of the molecule, the lower is the portion of the molecules existing in solution which participates in the first process of electrochemical reduction (Table 1). The N-substituted compound (II) does not comply with the last trend. Although the substitution by phenyl at the nitrogen atom of the heterocycle does not significantly change the potential of the first reduction, the limiting current changes sharply and reaches a value corresponding with the single-electron process. This may indicate the participation of all the molecules of the investigated compound (II) in the first process of electrochemical reduction.

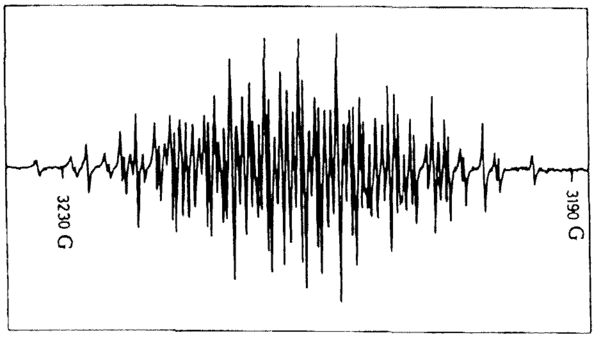


Fig. 2. EPR spectrum of the free radicals formed by electrochemical production in the course of the electroreduction of 1,4-dihydro-3,5-dinitro-4-p-bromophenylpyridine (V) in dimethylformamide.

Another significant difference in the behavior of the N-substituted compound (II) and the N-unsubstituted compounds in the first electrochemical reduction is, as was established by the method of polarography and cyclic voltamperometry, that the latter are reduced irreversibly in the first stage. Therefore, the formation of free radicals of the compounds (I) and (III)-(VII) which are sufficiently stable for investigation of their structure by the method of EPR should not be expected at this stage of electrochemical reduction. On the other hand, the formation of primary anion-radicals can be expected in the case of compound (II) for which there is characteristic reversibility of the first electrochemical reduction.

For the second stage of electrochemical reduction, in contrast to the first, there is characteristic reversibility of the transfer of the electron. This gives some expectation of registering free radicals by the method of EPR at this stage, at least in the reduction of N-unsubstituted derivatives of dihydropyridine. However, it is impossible to confirm this in relation to the N-substituted compound (II), since the formation of anion-radicals, for which the single-electron reduction at the second stage should lead to a diamagnetic compound, is proposed for the last in the process of the first reduction. Starting from the stated points, as well as the evaluation of the limiting current for the first two stages of the electrochemical reduction of N-unsubstituted dihydropyridines, it can be concluded that free radicals can be formed at the second stage of reduction as a result of the single-electron reduction of chemically altered molecules, not participating in the first process of reduction of the investigated compounds.

Based only on the reversibility of the processes, the formation of free radicals can be expected in the course of the electrochemical reduction of all the investigated compounds. In the case of the compounds (II) and (VI), several free radicals of differing structure are possible for each compound. For compound (VI), such a feature can also be determined by the reduction of the nitrophenyl substituent.

As should be expected from the results of the electrochemical reduction of N-unsubstituted derivatives of 1,4-dihydro-3,5-dinitropyridine, free radicals could not be registered in the course of the electrochemical production at potentials of the first polarographic wave by the method of EPR. Consequently, anion-radicals formed as a result of the primary addition of one electron to the initial molecule possibly undergo immediate electrochemical alteration with the loss of paramagnetic properties. However, at more negative potentials of production, the EPR signals of the free radicals are registered nevertheless. The stability of these radicals was found to be sufficient for their isolation in a sample at a concentration necessary for registering the EPR spectra with well resolved hyperfine structure (Fig. 2). The hyperfine structure of the EPR spectra indicate that all the radicals of these compounds, with the exception of compound (VI), are monotypic (Table 2). The hyperfine structure in the EPR spectra of the radicals detected is determined by the interaction of the unpaired electron with the nuclei of the nitrogen atoms of the two nitro groups situated at equivalent positions in relation to the unpaired electron, protons or protons of the methyl groups of the same equivalent positions 2 and 6, the nucleus of the nitrogen atom of the heterocycle, as well as the proton at the position 4 of the heterocycle. In the hyperfine structure of the EPR spectra of the free radicals obtained, there is no appearance of the interaction of the unpaired electron with the proton at the nitrogen atom of the heterocycle; this indicates the cleavage of this proton and the formation of dianion-radicals. The delocalization of the unpaired electron at both nitro groups indicates the participation of the pair of electrons of the negatively charged nitrogen atom of the heterocycle in the system of $\pi$-electrons of these dianion-radicals. It follows from the comparison of the corresponding coupling constants that the dianion-radicals of the 1,4-dihydro-3,5-dinitropyridines (I) and (III)-(VII) and the 4-derivatives of 1,5-dinitro-

TABLE 2. Potentials of the Electrochemical Production (E, V, in relation to the Pt electrode) and the Character and Constants of the Hyperfine Interaction with the Nuclei of Atoms in the Corresponding Positions of the 1,4-Dihydropyridine Ring ($a_i$, G) of Free Radicals of the Compounds (I) and (III)-(VII)

| Compound | R¹ | R² | R⁴ | R⁶ | -E | Character of the HFI | $a_i$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | $a_1$ | $a_2$ | $a_3$ | $a_4$ | $a_5$ | $a_6$ |
| I | H | CH$_3$ | C$_6$H$_5$ | CH$_3$ | 1,2 | 7H×5N×3N×2H | 2,70 | 7,40 | 3,95 | 2,29 | 3,95 | 7,40 |
| III | H | H | C$_6$H$_5$ | H | 2,2 | 3H×5N×3N×2H | 2,54 | 7,13 | 4,10 | 2,95 | 4,10 | 7,13 |
| IV | H | CH$_3$ | $o$-CHF$_2$OC$_6$H$_4$ | CH$_3$ | 1,6 | 7H×5N×3N×2H | 2,69 | 7,70 | 4,16 | 2,69 | 4,16 | 7,70 |
| V | H | H | $n$-BrC$_6$H$_4$ | H | 1,4 | 3H×5N×3N×2H | 2,77 | 7,42 | 4,00 | 3,05 | 4,00 | 7,42 |
| VI | H | H | p- O$_2$NC$_6$H$_4$ | H | 1,2 | 3N×2H×3H×2H | $a_N$ = 9,88; $a_{2H}$ = 3,19; $a_H$ = 4,12; 0,90 | | | | | |
| | | | | | 1,3 | 3N×2H×3H×2H | $a_N$ = 10,54; $a_{2H}$ = 3,41; $a_H$ = 3,80; 0,99 | | | | | |
| | | | | | 1,4 | 3H×5N×3N×2H | 2,77 | 7,39 | 4,00 | 2,77 | 4,00 | 7,39 |
| VII | H | CH$_3$ | H | CH$_3$ | 1,4 | 7H×3H×5N×3N | 2,63 | 7,02 | 4,09 | 5,26 | 4,09 | 7,02 |

cyclohexanedienes [12] do not differ significantly in the structure of their frontal molecular orbitals occupied by the unpaired electron.

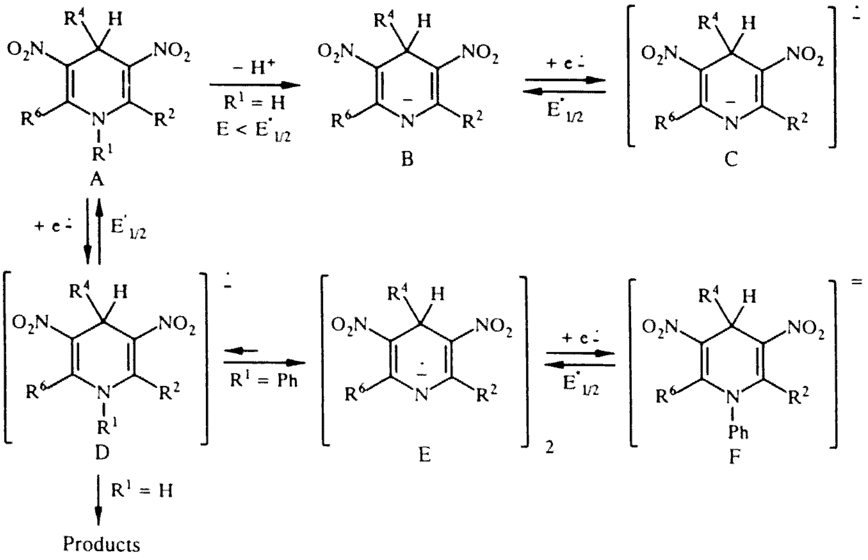
In the case of compound (VI) with the meta-nitrophenyl substituent, two kinds of free radicals of the nitrophenyl type, somewhat differing in the constants of hyperfine interaction (Table 2), were registered by the method of EPR at less negative potentials of electrochemical production besides dianion-radicals of the structure mentioned. In these free radicals, the unpaired electron is only delocalized along the $\pi$-electron system of the nitrophenyl group and, in contrast to the type of anion-radicals in similar compounds such as 1,4-dihydropyridines unsubstituted by the nitro group [8] or 1,4-dihydro-3-nitropyridines [10], it does not even interact with the proton situated at the position 4 of the heterocycle. The last indicates that this proton occurs in the plane of the phenyl ring. The difference in the constants of hyperfine interaction for these two radicals of the nitrophenyl type of compound (VI) may be determined by two stable steric positions of the nitro group of the meta-nitrophenyl substituent in relation to the $\pi$-electron system of 1,4-dihydro-3,5-dinitropyridine. It would also be possible to attempt an explanation of the formation of two kinds of free radicals of the nitrophenyl type by the different state of their dihydropyridine fragment, namely its occurrence in the state of the initial molecule and that of the corresponding anion. However, the hyperfine structure of the radicals does not give direct information on the state of this fragment; the state of the unchanged dihydropyridine fragment is impossible in the free radical since, at less negative potentials than the potentials of formation of free radicals of the nitrophenyl type, this fragment already undergoes irreversible reduction.

In contrast to the N-unsubstituted compounds, the N-phenyl-substituted compound (II) is reduced at the first stage in a single-electron reversible process (Fig. 1, Table 1); this indicates the formation of primary anion-radicals in this process. However, both in this stage, and in the two subsequent stages of electrochemical reduction which are also reversible, free radicals were not detected by the method of EPR in the course of electrochemical production.

The results obtained together allow the presentation of the following scheme for the electrochemical reduction of the derivatives of 3,5-dinitro-1,4-dihydropyridines, indicating the formation of free radicals in the initial stages of this process (Scheme 1).

Scheme 1

Reactions proceeding in the electrochemical reduction of the compounds studied



The course of the primary electrochemical reduction of derivatives of 1,4-dihydro-3,5-dinitropyridine is different for the N-unsubstituted compounds and N-substituted compounds (A). At the potentials of the first stage of reduction, the influence of the negatively charged cathode causes a proportion of the molecules of the N-unsubstituted dihydropyridines to be deprotonated and form the anions (B), which are not capable of undergoing further electroreduction at these potentials. At more negative potentials (the second stage), these anions are reduced with the outlay of one electron to the comparatively stable dianion-radicals (B) detected by the method of EPR. The (B) are more stable than similar radicals of N-unsubstituted derivatives of 1,4-dihydro-3-nitropyridine, which may be explained by the stabilizing influence of the second nitro group. This probably also explains the fact that the electrochemical reduction of these compounds does not lead to observation of the isomerization of the 1,4-dihydropyridine ring to the 4,5-dihydropyridine ring characteristic of N-unsubstituted derivatives of 3-nitro-1,4-dihydropyridine.

The electrochemical reduction of N-phenyl-1,4-dihydro-3,5-dinitropyridine (II) proceeds in a different way from that in the case of N-unsubstituted derivatives of 1,4-dihydro-3,5-dinitropyridine and 1,4-dihydro-3-nitropyridine, as well as the corresponding N-substituted compound of the last. The main difference for compound (II) is its ability to be reduced reversibly in the first single-electron process (Fig. 1, Table 1); this indicates the formation of anion-radicals (D) of this compound. Another distinctive feature of compound (II) is also the reversibility of the two other subsequent stages of the electrochemical reduction of this compound. Although the free radicals (D) were not detected by the method of EPR in the course of the first single-electron reversible stage of reduction, their formation can nevertheless not be excluded. The absence of the EPR signals may be explained by the conversion of the anion-radicals to the diamagnetic $\pi$-dimers of (E) in a rapid equilibrium process, strongly shifted in favor of the $\pi$-dimers. The reversibility of the second stage of electrochemical reduction of compound (II) may be explained by the single-electron reduction of anion-radicals of the equilibrium system "anion-radicals—their $\pi$-dimers" for (D)-(E) and the formation of diamagnetic species — dianions (F). The formation of similar $\pi$-dimers was already observed in solutions, e.g. for viologen [13], Wurster's blue [14], and porphyrins [15]. Such $\pi$-dimers, as well as $\pi$-stacks, were investigated as low-molecular analogs of polarons and bipolarons, responsible for electrical properties of the electric conductivity of polymers, organic salts with charge transfer [16]. It is known that, in the ground state, these structures of free radicals—$\pi$-dimers are diamagnetic [17]. In our case, on the basis of results of the study of free radical formation, the possible occurrence of such $\pi$-dimers ($\pi$-stacks) was only indirectly shown. The more detailed study of this possibility is the object of further investigations.

## EXPERIMENTAL

The electrochemical reduction of the compounds (I)-(VI) ($C = 5.10^{-4}$ M) was performed in dry DMF [11] with the background electrolyte of tetrabutylammonium hexafluorophosphate ($C = 10^{-1}$ M).

Free radicals were produced in the stationary regime on the surface of a flat platinum electrode placed in a cylindrical resonator of the type TM$_{110}$ of the SE/X 2547 EPR spectrometer fitted with the MP-102 spectral analyzer (OPP Radiopan, the Polish AN) according to the method described in the works [1, 2]. Resolution of the magnetic field was calibrated from the EPR spectrum of the anion-radicals of nitrobenzene [18]. For the electrochemical production of free radicals, $5.10^{-4}$-$10^{-3}$ M solutions of the compounds (I)-(VII) in dry DMF were utilized; the solutions contained $10^{-1}$ M tetrabutylammonium hexafluorophosphate.

The UV spectra were obtained on the Specord M 40 spectrophotometer — Carl Zeiss (in ethanol). The PMR spectra were obtained on the Bruker WH-90 spectrometer in DMSO-D$_6$. The discreteness of the substances synthesized was verified by the method of TLC on plates of Silufol UV-254 in the 9:7:2:1 solvent system of chloroform—hexane—acetone—ethanol.

The 1,4-dihydro-2,6-dimethyl-3,5-dinitropyridines (I), (IV), and (VII) were obtained by the Hantzsch reaction using known methods [19, 20]. The method of synthesis of the aryl derivatives unsubstituted at the positions 2 and 6 of 1,4-dihydro-3,5-dinitropyridines (III), (V), and (VI) has been published [21].

**1,4-Dihydro-2,6-dimethyl-3,5-dinitro-1,4-diphenylpyridine (II).** ($C_{19}H_{17}N_3O_4$). The mixture of 1.41 g (10 mmole) of the potassium salt of nitroacetone [22], 0.53 g (5 mmole) of benzaldehyde, and 0.47 g (5 mmole) of aniline in 40 ml of ethanol with the added 10 ml of glacial acetic acid is boiled for 10 h. The excess ethanol is removed *in vacuo*, and the residue is poured into 60 ml of water prior to the extraction with ethyl acetate (3 × 30 ml), the drying with anhydrous sodium sulfate, and the removal of the solvent *in vacuo*. The residue is chromatographed on a column with silica gel Silpearl, using the 9:7:2:1 mixture of chloroform—hexane—acetone—ethanol as the eluent. The bright yellow band is collected. After the extraction with acetone and the removal of the solvent *in vacuo*, the yellow oil is crystallized from dilute methanol. The yield of 0.75 g (42%) of compound (II), with the mp 206°C (from methanol), is obtained. The UV spectrum (in ethanol), given as the $\lambda_{max}$, is as follows: 208, 247, 317, and 429 nm. The PMR spectrum is as follows: 2.52 ppm (6H, s, 2,6-CH$_3$), 5.70 ppm (1H, s, 4-CH), and 7.0-7.2 ppm (10H, m, H$_{arom}$). Found, %: C 64.7, H 4.8, and N 12.0. $C_{19}H_{17}N_3O_4$. Calculated, %: C 65.0, H 4.9, and N 12.0.

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