FREE RADICALS IN ELECTROCHEMICAL REDUCTION OF 1-(NITROPHENYL)-3,5-DICARBETHOXY-4-PHENYL-1,4-DIHYDROPYRIDINES

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In the primary electrochemical reduction of 1-(nitrophenyl)-3,5-dicarbethoxy-4-phenyl-1,4-dihydropyridine in DMF, free radicals of nitrophenyl type are formed; these are the products of a one-electron reduction of cathode-protonated molecules of the original compound. In alkaline DMF, where cathodic protonation of the initial compound is retarded, anion-radicals of the starting material are generated in addition, together with p-nitrophenol free radicals.

Derivatives of 1,4-dihydropyridine, substituted by a nitrophenyl group, have a certain electrochemically active reaction centers liable to reduction (the nitrogroup, carbonyl groups, double bonds in the heterocycle). In the course of electrochemical reduction of such compounds one would expect a mutual transformation of these centers in the anion-radical state with retention of the unchanged nitrogroup (as was noted for compounds with nitrofuran groupings studied previously [1, 2]). However, in the electrochemical reduction of dihydropyridines substituted with nitrophenyl groups in positions 2, 4, and 6, such mutual transformations have not been detected [3-5]. Relatively stable anion-radicals of nitrophenyl type have been detected in the first stage of the reduction of these compounds. Further electrochemical reduction at more negative potentials does not involve the dihydropyridine ring but only the nitrophenyl fragment — the second electrochemical stage of the reduction corresponds to the formation of an N-phenylhydroxylamine derivative which, in the reverse electrochemical process, is oxidized to a nitrosophenyl derivative of dihydropyridine [3-5], and this is reduced in its turn to a free radical of nitrosophenyl type. Consequently, from the point of view of electrochemical reduction, 1,4-dihydropyridine compounds substituted with a nitrophenyl group behave like nitrobenzene substituted with a 1,4-dihydropyridine residue.

We have extended the study of free radicals formed in the electrochemical reduction of dihydropyridines substituted with a nitrophenyl group in the direction of the electrochemical generation [6] of free radicals of 1-nitrophenyl-3,5-diethoxycarbonyl-4-phenyl-1,4-dihydropyridine I and of amino derivatives of nitrobenzene II.

Using polarography and cyclic voltammetry, we have established that compounds Ia-c in nonaqueous media (DMF, acetonitrile) are reduced in stages. The first stage of the one-electron electroreduction, partially reversible, takes place in the potential region of −1.0 V relative to a saturated aqueous calomel electrode. The difference between the potentials of the first and second stages of the electroreduction is 0.9-1.0 V. On the cyclic voltammetry curve with a sweep rate of 20-500 mV/sec over the potential range 0 to −1.2 V, the formation of a new redox system was not observed; however, in recording the analog curves in the interval from 0 to −2.0 V a new redox system was observed at higher positive potentials than the redox system characteristic for primary electroreduction (Fig. 1, *1, 2*). The new redox system was more clearly expressed at high rates of potential scanning which points to the instability of the particles composing it. A similar redox system has been detected previously for dihydropyridines substituted with nitrophenyl in positions 2, 4, and 6 of the heterocycle. Its appearance was explained by the formation of nitrosocompounds in the course of the electrochemical process [3-5].

I-III a–c

I-III a 4-R, b 3-R, c 2-R; I R=N

H   COOEt

H   COUEt

H
Ph

; II R=NH₂; III R= CH=CH₂
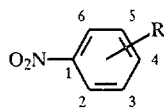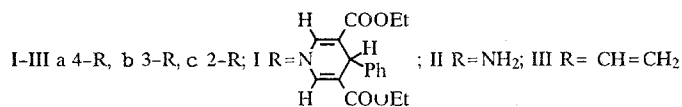
During the electrochemical generation of free radicals of compound I in DMF at potentials of the first polarographic wave, the ESR spectra of the free radicals were recorded. The hyperfine structure of these spectra provided evidence of the formation of free radicals of nitrophenyl type. For example, the hyperfine structure of the ESR spectrum (Fig. 2) of the free radical of compound Ia had the character $3_N \times 3_H \times 4_H \times 3_N$, i.e., in the ESR spectrum there appeared a coupling of an unpaired electron with the nucleus of one nitrogen atom with a hyperfine structure constant (0.828 mT; DMF) characteristic in value for the nitrogen atom of a nitro group in anion-radicals of substituted nitrobenzene [7]. The spectrum also showed equivalent hyperfine structure constants for the coupling of an unpaired electron with the protons in the ortho- (0.307 mT) and meta-positions (0.098 mT) of the nitrophenyl ring and a constant of 0.029 mT resulting from the coupling of an unpaired electron with the nucleus of a nitrogen of the heterocycle. However, besides the couplings referred to, characteristic for nitrobenzene-type anion-radicals, couplings were observed between an unpaired electron and one more proton which did not correspond with the assumed structure of the initial compound. For the primary anion-radical of Ia one would have expected a coupling of the unpaired electron with two protons in positions 2 and 6 of the dihydropyridine but not with the individual protons because the protons are distributed symmetrically relative to the p-nitrophenyl ring.

In the process of the electrochemical generation of free radicals of compounds Ib, c at potentials of the first stage of electroreduction, free radicals of nitrophenyl type are again obtained (Table 1). The hyperfine structure constants of the ESR spectrum of free radicals of Ic have averaged values, at least for the two rotational isomers of these radicals. Calculation of the barrier between the two most stable isomers formed by rotation about the C−N bond (phenyldihydropyridine) for the Ic
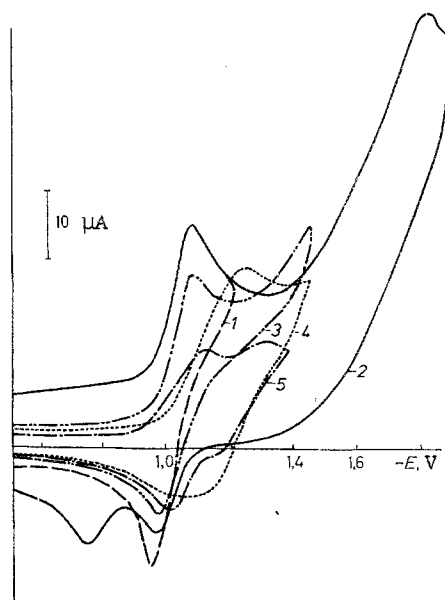

Fig. 1. Cyclic voltammetry curves recorded on a glassy carbon electrode for compound Ia: 1, 2) in DMF; 3, 4) in the same medium on control (3) and working (4) electrodes after prolonged electrolysis; 5) in alkaline DMF.

TABLE 1. Hyperfine Structure Constants (a, mT) in the ESR Spectra of Electrochemically Generated Free Radicals of Substituted Nitrobenzenes I-III

Substituent	Medium	$a_{N,1}$	$a_{H,2}$	$a_{H,3}$	$a_{H,4}$	$a_{H,5}$	$a_{H,6}$	a_N	a_H	a_H	a_H
4-DHP	MeCN	0,872	0,314	0,098	—	0,098	0,314	0,031	0,098		
	DMF	0,828	0,307	0,098	—	0,098	0,307	0,029	0,098		
	DMF+	0,855	0,320	0,098	—	0,098	0,320	0,029	0,098		
	OH⁻	1,050	0,312	0,098	—	0,098	0,312	0,025			
		1,287	0,287	0,074	—	0,074	0,287				
3-DHP	DMF	1,076	0,319	—	0,383	0,094	0,319	~0,01			
2-DHP	DMF	0,872	—	0,123	0,421	0,090*	0,328	0,053	0,025*		
4-NH$_2$	DMF	1,102	0,308	0,074	—	0,074	0,308	0,094	0,094	0,094	
3-NH$_2$	DMF	0,972	0,261	—	0,346	0,088	0,316	~0,03	~0,03	~0,03	
2-NH$_2$	DMF	1,157	—	0,045*	0,30	0,10*	0,30	0,08	0,045	0,045	
4-CHCH$_2$**	MeCN	0,872	0,323	0,129	—	0,129	0,323	—	0,120	0,239	0,239
3-CHCH$_2$**	MeCN	0,983	0,339	—	0,390	0,108	0,339	—	0,042	0,042	0,042
2-CHCH$_2$**	MeCN	0,959	—	0,113	0,312	0,113	0,305	—	0,367	0,152	0,044

*Assumed assignment of a_H value.
**Hyperfine structure constants taken from [8].

molecule, using the MOLDRAW method [9], gave a value of ~25 kcal · mole⁻¹ while for Ia and Ib the figure was around 5 kcal · mole⁻¹. In the absence of free radicals of compounds Ia and Ic, the ESR spectrum of compound Ib showed no coupling with an individual proton, but this does not exclude the possibility of the presence of such a proton because coupling with it could prove to be insignificant in the ESR spectrum on account of the low density of the unpaired electron in the meta-position of the nitrophenyl ring; evidence of this is the small value of a_N resulting from the coupling of an unpaired electron with the nitrogen of the dihydropyridine.

The results presented point to the probability of the hypothesis that in the electrochemical generation of free radicals from compounds Ia-c one obtains not the initial anion-radicals of these compounds but radicals corresponding to their transformation products. The comparatively small constants a_N of the nitro group of the free radicals of compounds Ia, c also bear this out; these are characteristic of nitrophenols with substituents having strong electron-acceptor properties.

In order to verify the correctness of such a hypothesis, we electrochemically generated anion-radicals of the nitrophenylamines IIa-c. The hyperfine structure constants in the ESR spectra of these anion-radicals are given in Table 1 where, for comparison, are quoted also the hyperfine structure constants of the ESR spectra of anion-radicals formed in the reduction of nitrostyrenes IIIa-c [7]. From a comparison of the constants resulting from the coupling of the unpaired electron with the nitrogen atom of the nitro group, one can establish that the nitrogen atom as a substituent in the nitrophenyl of compounds Ia, c displays strong electron-acceptor properties rather than electron-donor or weak electron-acceptor properties, as would be expected for a nitrogen atom in dihydropyridine. This property of the substituent is not evident as changes in the constant a_N of the nitro group for meta-substituted nitrobenzenes.

Such a representation of the structure of the free radicals formed is not, at first glance, always in agreement with the cyclic voltammetry curves for compounds Ia-c which show that the primary processes of electroreduction of compounds I are reversible and have one-electron character (the difference between the potentials of the reduction and oxidation peaks on a stationary mercury drop amounts to 59 mV) which is typical of the formation of anion-radicals of compounds I. However, these radicals probably fail to register on the ESR spectrum during electrochemical generation. The recorded free radicals of nitrobenzene type have a substituent the electrophilicity of which proved to be enhanced in comparison with the electrophilicity of the original compound. If one assumes that the free radicals were formed as a result of chemical transformation of the anion-radicals of the original compound then their formation must be accompanied by the cyclic voltammetry curves by the appearance of a new redox system at higher positive potentials corresponding to the recorded free radicals, since an increase in the electrophilicity of the substituent will facilitate the electroreduction of the nitro group on the phenyl ring [8]. We have carried out prolonged electrolysis of compound Ia in DMF at the potential of the first polarographic wave on a platinum electrode. To monitor the formation of reduction products of any sort in the solution during the electrolysis, a second cathode was placed in the cell and was connected to the polarograph only while recording cyclic voltammetry curves. It was found that on the curves
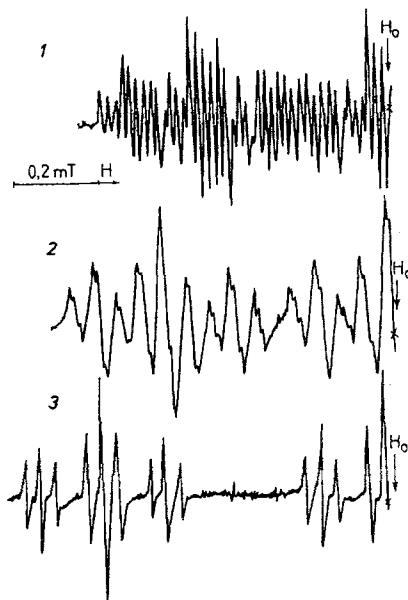
Fig. 2. ESR spectra of electrochemically generated free radicals of compound Ia: 1) in DMF; 2, 3) in alkaline medium.

recorded on the control electrode over the potential range 0-1.5 V, even after prolonged (up to 5 h) electrolysis, no new reduction or oxidation peaks were recorded. However, if the cyclic voltamperograms were recorded over the same range of potentials but on the same cathode as that on which the electrolysis was carried out, then a new redox system was detected at a more negative potential than that of the first redox system (Fig. 1, 3).

Consequently, the particles of the redox system formed can be recorded only in a changed medium such as the cathodic layer after prolonged electrolysis. With the object of carrying out, in the cathode layer, studies of conditions similar to those which were established on the cathode after prolonged electrolysis, solutions of compound Ia containing added acid or alkali were examined with the aid of cyclic voltammetry. It was discovered that after addition of alkali [$\sim 10^{-2}$ mole/liter $(C_4H_9)_4NOH$] to a solution of compound Ia in DMF, particles of two types were detected (Fig. 1, 5). It was observed that after adding alkali to the two solutions, two redox systems can into being: The first corresponded in terms of potentials to the primary product recorded in DMF, and the second to the product recorded on the working cathode after prolonged electrolysis (Fig. 1, 5). Addition of benzoic acid led to a many-electron process in the course of which free radicals were not detected by ESR.

For determining the structure of the new particles detected, free radicals of compounds of type I were generated electrochemically in alkaline DMF solution. As a result, three types of free radicals were detected by ESR spectroscopy. For example, for compound Ia the hyperfine structure in the ESR spectrum of one type of free radical corresponded to the free radical obtained in pure dimethylformamide (containing no alkali) ($3_N \times 3_H \times 4_H \times 3_N$) and a second to an anion-radical of the initial compound Ia ($3_N \times 3_H \times 4_H \times 3_N$) while the third radical had ($3_N \times 3_H \times 3_H$) character (Fig. 2, 3) and apparently was formed after more extensive chemical transformations of the compound examined, the nitro group here being retained. The hyperfine structure constants of this spectrum (Table 1) are close to those given in the literature [7] for p-nitrophenol free radicals in DMF. This makes it possible to suggest that in our case also the same nitrophenyl free radicals are formed in an alkaline medium as a result of the splitting by the OH- anion of the $C-N$ bond between the nitrophenyl and the nitrophenyl and the heterocycle in the excited free radical state.

The hyperfine structure of the ESR spectrum of the second radical provides evidence of the formation of anion-radicals of the initial compound: Its constant is closer to that for p-nitrophenyl anion-radicals than that for p-nitrostyrene (Table 1). It would be expected that in an alkaline medium the same radicals were formed also on reduction of compounds Ib and Ic but on account of the complexity of the hyperfine structure in the ESR spectra of these radicals and the overlapping of the ESR spectra of the free radicals of the three types for each of the compounds Ib and Ic it was not possible to establish the values of the hyperfine structure constants of the radicals. This is particularly characteristic for free radicals of compound Ic which can exist

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in the form of at least two rotational isomers. It was possible to establish only an approximate average value for the hyperfine structure constant of the ESR spectrum of the anion-radical of compound Ic resulting from the coupling of the unpaired electron with the nucleus of the nitrogen atom of the nitro group (~ 0.95 mT).

The results presented provide evidence that in DMF, as in acetonitrile, without the addition of alkali, it is not the initial compound, but a transformed form thereof, which participates in the primary process of electroreduction. The transformation of the molecule takes place not in the bulk of the sample but in the cathode layer. Evidence that the transformation does not take place in the bulk of the sample is provided by the fact that in the PMR spectrum of, for example, a solution of compound Ia in DMSO$-$D$_6$ no deviation is observed from the original molecular structure. At the same time, electrochemical generation of free radicals in solution in DMSO-D$_6$ at the potentials of the primary electroreduction leads to the formation of the same radicals with additional hyperfine structure constants as in DMF or acetonitrile.

One cannot unequivocally establish the structure of electrochemically generated free radicals in DMF from their ESR spectra. Taking into account only the character of the hyperfine structure of the spectra of the free radicals obtained as a result of a one-electron reduction of molecules of the initial compound transformed in the cathode space, it is theoretically possible to represent a few structures for these radicals as shown below for compound Ia in the form of free radicals IVa-VIIa:

$$\left[\ O_2N-\underset{1}{\overset{6}{\bigcirc}}\underset{3\ 4}{\overset{5}{}}-R\ \right]^{\cdot-}$$

IV–VIa

IVa $R=$ ... ; Va $R=$ ... ; VIa $R=$ ...
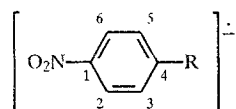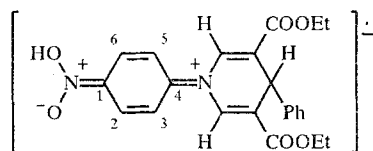
VIIa

None of the structures similar to IVa-VIIa has previously been studied by ESR and hence none of them can be given preference on the basis of the hyperfine structure constants of their ESR spectra. It would be possible for a quinoid structure similar to VIIa to be formed but it is impracticable for free radicals of compound Ib for which the possibilities are either an anion-radical structure of the original molecule or one of the structures IVa-VIIa — an anion-radical protonated at the dihydropyridine ring of the Ib molecule. A factor pointing to the possible formation of anion-radicals of the initial compound Ib is the absence from their ESR spectra of any information on the coupling of the unpaired electron with a proton not directly bonded to the benzene ring. However, the absence of such coupling might also be due to the small density of an unpaired electron in the meta position of the nitrobenzene ring [7] which would make it difficult to detect this coupling because the value of its coupling constant with the nitrogen of the heterocycle in the free radical of compound Ib is not large (Table 1). At the same time, some (far from indisputable) support for the formation of structure VIIa for compounds Ia and Ic can be found in that, in contrast to them, after prolonged cathode electrolysis of compound Ib in DMF the formation of a new redox system on the first stage of the electroreduction is not observed, i.e., in the process of primary electroreduction of compound Ib in DMF which, in contrast to a similar process for compounds Ia and Ic is almost fully reversible, its anion-radicals are formed and evidence for such formation could be the comparatively high value of the hyperfine structure constant due to the nitrogen of the nitro group of this radical (Table 1).

What has been said, however, does not exclude the probability that prior to the electroreduction of compounds Ia and Ic, cathodic protonation takes place not at the nitro group but at the dihydropyridine. As a result of insufficient lowering of the potential of electrochemical reduction of compound Ib preliminary protonation of this molecule proves to be energetically unfavorable and on the first stage of the electroreduction anion-radicals of the initial compound Ib are formed.

Consequently, electrochemically generated free radicals of compounds Ia and Ic in DMF have one of the isomeric structures similar to IVa-VIIa, compound Ib one of the structures IVa-VIa or the structure of a primary anion-radical of compound Ib. The free radical state of the molecules Ia-c arising as a result of a one-electron reduction of these compounds, activates the C—N bond to splitting by OH⁻ ions and thus enables the formation of free radicals; such splitting is not observed for the initial compounds Ia-c.

EXPERIMENTAL

Free radicals were generated under stationary conditions on a platinum cathode in a cell located in a type H_{102} rectangular resonator of an ER-9 ESR spectrometer (Carl Zeiss) using the method described in [6]. Electrochemical generation potentials were measured on a three-electrode apparatus against a silver electrode.

ESR spectra were recorded with a magnetic field scan rate of 0.004 mT/sec with depth of high-frequency (100 kHz) modulation of the magnetic field 0.005-0.09 mT and a constant recording time of 0.45 sec. The magnetic field scan was calibrated on the ESR spectrum of the anion-radical of nitrobenzene [10]. For the electrochemical generation of free radicals 10^{-4} to $5 \cdot 10^{-3}$ mole/liter solutions of compounds I and II in DMF or acetonitrile were used; the solutions contained 0.1 mole/liter tetrabutylammonium perchlorate.

Polarograms of compounds Ia-c were recorded on a mercury electrode with induced separation of the drops (t = 0.5 sec), and the cyclic voltammetry curves on a stationary glassy carbon electrode (comparison electrode — saturated aqueous calomel electrode, auxiliary electrode — platinum wire) using a PAR-170 electrochemical system by the method of [4].

Compounds Ia-c were prepared by the method of [12]. Preparative chromatography was used to prepare the individual substances. Preparative TLC was effected on a loose layer of silica gel (40/100 μ, eluent: 9:1 hexane—isopropanol).

Results of elemental analysis of C, H, N in compounds Ia-c were in agreement with calculations.

1-(2'-Nitrophenyl)-3,5-diethoxycarbonyl-4-phenyl-1,4-dihydropyridine (Ic) was prepared by the method of [12] but with 8 h reaction time. Crystals from methanol, mp 142-144°C. IR spectrum (in Nujol): 1718, 1705, 1610 cm⁻¹. PMR spectrum (DMSO-D₆): 1.06 (3H, t, OCH₂CH₃), 3.93 (4H, q, OCH₂CH₃), 4.73 (1H, s, 4-H), 7.75 (2H, s, 2,6-H), 6.93-8.20 (9H, m, arom.). M⁺ 422. Yield 0.5 g (12%).

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