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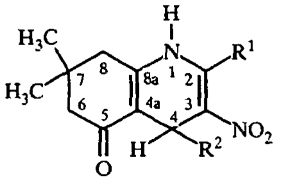
EPR SPECTRA OF FREE RADICALS GENERATED BY ELECTROCHEMICAL REDUCTION OF 3-NITROHEXAHYDROQUINOL-5-ONES AND 4-NITROHEXAHYDROISOQUINOL-8-ONES*

R. Gavars, L. Baumane, J. Stradins, B. Vigante, J. Ozols, and G. Duburs

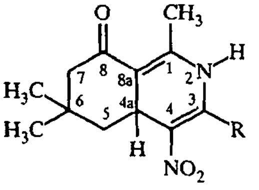
The polarographic characteristics (potentials, number of electrons, reversibility) of the electrochemical reduction of 7,7-dimethyl-3-nitro-1,4,5,6,7,8-hexahydroquinol-5-ones and 1,6,6-trimethyl-4-nitro-2,4a,5,6,7,8-hexahydroisoquinol-8-ones in DMF are determined. Secondary anion-radicals have been proved to arise during the electrochemical reduction and the hyperfine structure and coupling constants of their EPR spectra are established.

Derivatives of 7,7-dimethyl-3-nitro-1,4,5,6,7,8-hexahydroquinol-5-ones and 1,6,6-trimethyl-4-nitro-2,4a,5,6,7,8-hexahydroisoquinol-8-ones possess a nitrosubstituted 1,4-dihydropyridine moiety. Therefore, they are potential cardiovascular agents. EPR was used [1] to show that free radicals of various structure are formed during the electrochemical reduction of 3-nitro-1,4-dihydropyridines.

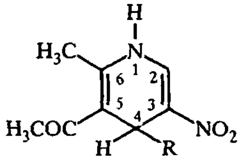
In the present work features of the electrochemical generation of free radicals formed during the electrochemical reduction of derivatives of 7,7-dimethyl-3-nitro-1,4,5,6,7,8-hexahydroquinol-5-ones (I-III) and 1,6,6-trimethyl-4-nitro-2,4a,5,6,7,8-hexahydroisoquinol-8-ones (IV and V) are studied. In addition, their structures are determined by EPR. These same characteristics are found for 3-nitro-1,4-dihydropyridines (VI and VII), which act as models for the dihydropyridine moiety in I-V.



I-III



IV, V



VI, VII

I R^1 = CH$_3$, R^2 = CH$_3$; II R^1 = H, R^2 = CH$_3$; III R^1 = H, R^2 = C$_6$H$_5$;
IV R = CH$_3$; V R = H; VI R = CH$_3$; VII R = C$_6$H$_5$

The examined compounds are polarographically reduced in three or four stages. The condensed bicyclic ketones I-V behave similarly to 1,4-dihydropyridines VI and VII during the electrochemical reduction (Table 1). This argues in favour of the hypothesis that the keto groups in the quinolones and isoquinolones I-V are not reduced in the examined potential range and that the electrochemical process is limited to the reduction of the 1,4-dihydropyridine moiety. Nevertheless, the presence of a cyclohexanone moiety in I-V changes the reduction

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* Dedicated to Professor Henk van der Plas on his 70th birthday.

Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: rgavars@osi.lanet.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 510-515, April, 1999. Original article submitted October 5, 1998.

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TABLE 1. Half-wave Potentials of Polarographic Waves *vs.* Aqueous Saturated Calomel Electrode, Relative Number of Transferred Electrons (*n*) and Reversibility (+) of Separate Stages of Electrochemical Reduction [Potential Scan Rate 100 mV·sec^{-1}, DMF, 0.1 M $(C_4H_9)_4NPF_6$]

Compound	$-E_{1/2}$, V			
	First wave	Second wave	Third wave	Fourth wave
I	1,36(0,8; -)*	1,94(0,4; -/+)	2,36(1,8; -/+)	
II	1,23(0,7; -)	2,05(0,3; -)	2,46(1,0; -)	
III	1,20(0,8; -)	1,74(0,3; +)	2,08(1,0; -)	2,66(3,3; -)
IV	1,12(1,0; -)	1,86(0,5; -)	2,15(2,0; +)	
V	1,15(0,8; -)	1,68(0,4; -/+)	2,02(1,2; +)	2,67(2,0; -)
VI	1,17(1,0; -)	1,67(0,3; -/+)	2,02(1,5; -/+)	2,62(2,0; -)
VII	1,12(0,8; -)	1,70(0,3; -/+)	2,10(1,5; -)	2,54(2,4; -)

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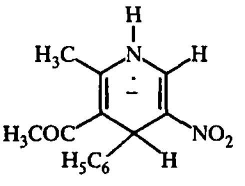
* Values of *n* and reversibility are given in parentheses.

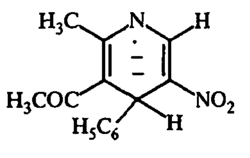
potentials of these compounds. Thus, the quinolones I-III are reduced at potentials markedly more negative than the isoquinolones IV and V or the 1,4-dihydropyridines VI and VII. The nitro group, which is the most electrophilic center of these molecules, is reduced first. The electrophility of the first unoccupied level of the π-system, which determines the first reduction potential of the compound, depends on the electrophility of the π-system of the cyclohexanone moiety conjugated to it. The differences in the first reduction potentials of quinolones I-III and the 1,4-dihydropyridines VI and VII are consistent with conjugation of the double bonds of the dihydropyridine moiety within the π-system. One of the conjugated bonds of the dihydropyridine ring of I-III is also a component of the second ring condensed with it. The tendency of the latter to adopt an energetically favorable conformation can sterically weaken the conjugation of the quinolone double bond between the 4a- and 8a-atoms and the double bond of the dihydropyridine moiety between the 2- and 3-atoms, thus decreasing the electrophility of all π-system of the dihydropyridine part. This in turn diminishes the electrophility of the π-system of the conjugated nitro group, what results in more negative potentials for the first electrochemical reduction of the molecule as a whole. For the isoquinolones (IV and V), where the double bond of the dihydropyridine is not a part of the fused ring, such an increase in the first reduction potential is not necessary (Table 1).

Although the polarographic results indicate that the first electrochemical reductions of I-V are close to one-electron processes, the reversibility characteristics and the number of electrons in the individual reduction stages (Table 1) neither provide unambiguous evidence that free radicals can be formed, nor much less provide their structures. Thus, free radicals were generated electrochemically and detected by simultaneous recording of their EPR spectra [2, 3].

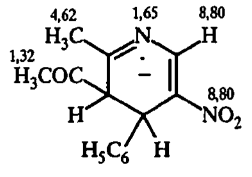
Only one type of free radical was produced during the electrochemical generation for each of I-VII (Table 2 and Fig. 1). Free radicals were detected for VII at a generation potential of -3.8 V (*vs.* a Pt reference electrode). The EPR spectrum of these has rather complicated hyperfine structure due to coupling of the unpaired electron to a single proton, two nonequivalent nitrogen atoms, and two different groups of three equivalent protons $(2_H \times 3_N \times 4_H \times 3_N \times 4_H)$. Three possible structures can be postulated for such a hyperfine structure in the EPR spectrum. These are a primary anion-radical (VIIa), its dianion-radical (VIIb), and the anion-radical (VIIc), which is an isomer of the anion-radical VIIa.



VIIa



VIIb



VIIc

TABLE 2. Potentials of Electrochemical Generation, Hyperfine Couplings, HF Coupling Constants of Unpaired Electrons with Nitrogen and Hydrogen Nuclei in Free Radicals Obtained from Reduction of I-VII

Compound	-*E*, V	HF Couplings	^{a}N	^{a}3H	^{a}3H	^{a}H	^{a}H	^{a}N	^{a}H	^{a}H
I	2,3	$3_N\times4_H\times2_H\times2_H\times3_N\times2_H$	8,80	8,58	—	8,58	2,85	1,82	1,10	—
II	2,7	$3_N\times2_H\times2_H\times2_H\times3_N\times2_H$	8,80	—	—	8,80	8,25	1,65	2,86	1,65
III	2,3	$2_H\times3_N\times2_H\times2_H\times3_N\times2_H$	8,36	—	—	10,01	7,37	1,54	2,75	1,54
IV	3,4	$3_N\times4_H\times4_H\times3_N\times2_H\times2_H$	8,58	8,58	4,29	1,54	0,55	1,92	—	—
V	3,1	$2_H\times3_N\times4_H\times2_H\times3_N\times2_H$	8,36	4,45	—	10,56	2,09	1,54	0,66	—
VI	3,0	$2_H\times3_N\times4_H\times3_N\times2_H$	8,80	4,51	1,32	10,45	—	1,54	—	—
VII	3,8	$2_H\times3_N\times4_H\times3_N\times2_H$	8,80	4,62	1,32	8,80	—	1,65	—	—

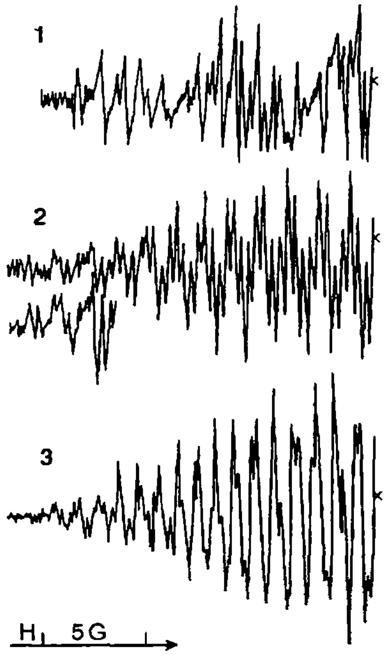
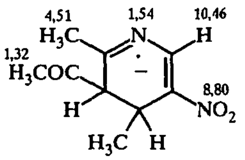


Fig. 1. EPR spectra of electrochemically generated free radicals in DMF (0.1 M tetrabutylammonium hexafluorophosphate supporting electrolyte): radical of II (1), radical of V (2), radical of VI (3).

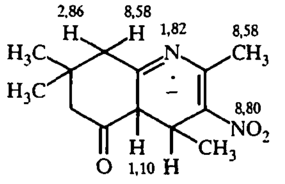
The anion-radical VIIa could be formed in the first reduction of VII. However, the polarographic data indicate that the first electron addition is irreversible. Therefore, the primary anion-radical should be unstable. Furthermore, the lack of a coupling constant for the unpaired electron with the proton at the nitrogen atom of the heterocycle in the hyperfine structure of the EPR spectrum indicates that the structure of the resulting free radical does not correspond to VIIa. The structure of the resulting free radical does not correspond to the dianion-radical VIIb because the hyperfine constant in the EPR spectrum of the radical due to the nitrogen atom of the nitro group (8.80 G) is significantly smaller than expected for VIIb (~15 G [1]) with the negatively charged nitrogen atom in the heterocycle. Thus, the most likely structure is VIIc.

The EPR spectrum (Fig. 1) recorded during the electrochemical generation of free radicals from VI at a potential of -3.0 V has the same hyperfine structure as that from VII. The corresponding constants also are similar. Like for VII, the EPR spectrum can be assigned to the anion-radical VIc:

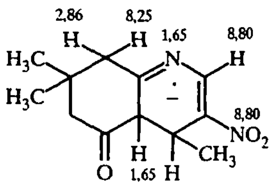


VIc

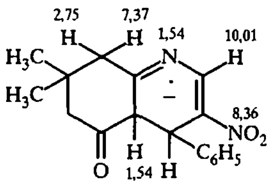
The EPR spectra obtained upon reduction of the quinolones I-III and the isoquinolones IV and V have a more complicated hyperfine structure (Table 2). Thus, the hyperfine structure of the EPR spectrum of free radical I is caused by coupling of the unpaired electron with nonequivalent nitrogen atoms of the nitro group and heterocycle, three equivalent protons of the methyl substituent, and three nonequivalent protons of the ring. The similarity of the hyperfine coupling constants caused by the nitrogen atoms of I-III and the corresponding model compounds VI and VII indicates that the free radicals of I-III contain a π-electron system similar to that observed for the corresponding radicals of VI and VII. Therefore, the structure of the free radicals obtained by electrochemical reduction of I-III can be represented as the anion-radicals Ic, IIc, and IIIc:



Ic

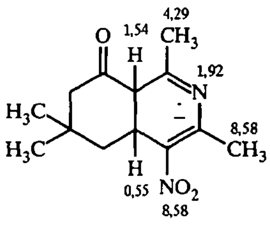


IIc

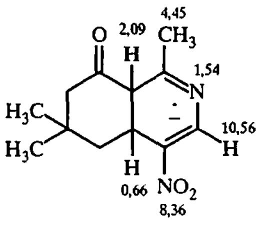


IIIc

Approximately the same distribution of unpaired electron density is observed in the free radicals generated by electrochemical reduction of the isoquinolones IV and V (Fig. 1). This is consistent with the similar hyperfine coupling constants in the EPR spectra of these radicals (Table 2). Therefore, the hyperfine coupling constants for the free radicals IVc and Vc can be related to nuclei of atoms corresponding to those for the radicals examined above.

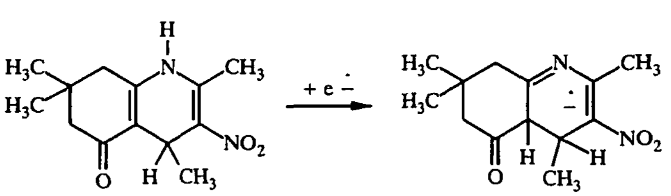


IVc



Vc

The results indicate that primary anion-radicals stable enough for study by EPR cannot be formed by one-electron electrochemical reduction of the nitrosubstituted quinolones I-III and isoquinolones IV and V in DMF. Neglecting preceding electrochemical and chemical reactions and reactions facilitating the isomerization of the 1,4-dihydropyridine ring, the nature of which is difficult to discern from the experimental results, the following irreversible transformation into the detected anion-radical can be proposed for I:



Undoubtedly these radicals are not formed by such a simple and direct route. Thus, they were not observed at the potentials of the first polarographic wave. Comparatively high cathodic reduction potentials in the range (-2) to (-4) V *vs.* a Pt electrode must be applied in order to generate them (Table 2). The formation of these radicals at such potentials is difficult to propose on the basis of the polarographic data (Table 1). Furthermore, the polarographic data contradict this because the changes in the potential for generating the free radicals is not a function of the structure of the molecule and the changes in the polarographic potentials. The free radicals of isoquinolones IV and V and 1,4-dihydropyridines VI and VII can be detected if they are generated at much more negative potentials than for quinolones I-III (Table 2). Moreover, the potentials of the first polarographic waves of I-III are more negative than those of IV-VII. The same can be said for the potentials of the succeeding polarographic waves, the value of which do not correlate with the potentials at which the free radicals are generated. This suggests that the free radicals are formed and accumulated upon electrochemical generation on a stationary electrode not at the cathode but in the bulk solution through reactions involving species formed at more negative potentials than that of the primary anion-radicals. Such a process in the bulk solution makes further cathodic reduction of the nitro group impossible and ensures that the free radicals formed are stable at such high generation potentials.

EXPERIMENTAL

Compounds I-VII ($c = 5 \cdot 10^{-4}$ mol·l^{-1}) were reduced electrochemically in anhydrous DMF [4] with tetrabutylammonium hexafluorophosphate ($c = 10^{-1}$ mol·l^{-1}). Classical polarograms and cyclic voltammograms were recorded on a PAR-170 polarograph using a three-electrode cell. The cathode was a dropping mercury electrode with forced drop detachment ($t = 0.5$ sec, $m = 0.90$ mg·sec^{-1}). The anode was a Pt wire. The reference electrode was an aqueous saturated calomel electrode equipped with a bridge for working in nonaqueous solutions. Cyclic voltammograms were recorded using a glassy carbon electrode at a scan rate of 0.1 V·sec^{-1}.

Free radicals were generated under steady-state conditions in the three-electrode cell on the surface of the Pt electrode. The cell was placed in the TM_{110} cylindric resonator of an SE/X 2547 (OPP Radopan) EPR spectrometer. The literature procedure was followed [2, 3]. The scan rate of the magnetic field was calibrated using the EPR spectrum of nitrobenzene anion-radicals generated electrochemically by the literature method [5]. Free radicals were electrochemically generated using $5 \cdot 10^{-4}$-10^{-3} M solutions of I-VII in anhydrous DMF with 10^{-1} M tetrabutylammonium hexafluorophosphate.

Compounds I-VII were synthesized by the literature method [6].

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