ION RADICALS OF QUINOXALINE N-OXIDES.

1. EPR SPECTRA OF ANION RADICALS FORMED IN THE ELECTROCHEMICAL REDUCTION OF SOME QUINOXALINE 1,4-DIOXIDES

V. M. Kazakova, O. G. Sokol,
G. G. Dvoryantseva, I. S. Musatova,
and A. S. Elina

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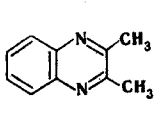
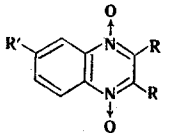
The anion radicals formed in the electrochemical reduction of 2,3-dimethylquinoxoline and its N,N'-dioxide, the 6-methoxy and 6-chloro derivatives of the N,N'-dioxide, and the preparation quinoxidine in DMF were studied. Polarographic analysis showed that the first step in the reduction is a one-electron step and is reversible for all of the compounds except quinoxidine. However, the EPR spectra of the primary anion radicals were recorded only for 2,3-dimethylquinoxaline and its 1,4-dioxide. For the remaining compounds we were able to obtain anion radicals of only the reduction products, the structures of which in a number of cases were established from the EPR spectra.

It is known that heterocyclic N-oxides have a tendency to undergo redox transformations [1], during which some of them may give rather stable ion radicals in the first step — the one-electron transfer step [2]. A study of the EPR spectra makes it possible to obtain valuable information regarding the electronic structures of these compounds and also facilitates elucidation of the mechanisms of the chemical reactions in which they participate.

Many derivatives of quinoxaline 1,4-dioxide have biological activity. 2,3-Bis(acetoxymethyl)quinoxaline (quinoxidine) and 2,3-bis(hydroxymethyl)quinoxaline (dioxidine) are original preparations with high antimicrobial action against strains of bacteria that are resistant to antibiotics and sulfanilamide preparations [3]. Data on the mechanism of the reduction of quinoxaline N-oxides are of interest for a study of the possible pathways of metabolism of the indicated preparations. In this connection we began a study of the EPR spectra of the anion radicals formed in the electrochemical reduction of a number of derivatives of quinoxaline N,N'-dioxides. To determine the optimal conditions of electrochemical generation of the anion radicals we made a polarographic analysis of the investigated compounds in dimethylformamide (DMF) on a dropping mercury electrode relative to a silver perchlorate electrode. Although the results of the polarographic measurements are subordinate in nature, in this case they are of independent interest and can be used to form a judgment regarding the electrochemical reduction process.



I



II–V

II–IV R=CH_3; V R=CH_2OCOCH_3; II, V R'=H; III R'=OCH_3; IV R'=Cl

There are two one-electron reduction waves separated from one another by 0.4 V on the polarogram of I. This provides a basis for the assumption that anion radicals of the starting compound are formed in the first step of the reduction. Three reduction waves are observed for quinoxaline N,N'-dioxide II, and $E_{1/2}^{I}$ of the first wave is shifted 0.4 V to the positive region as compared with the value for dimethylquinoxaline I. Since the polarographic analysis for I and II was carried out under identical conditions, a comparison

M. V. Lomonosov Moscow Institute of Fine Chemical Technology, Moscow 119831. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 376-380, March, 1980. Original article submitted July 24, 1978; revision submitted September 10, 1979.

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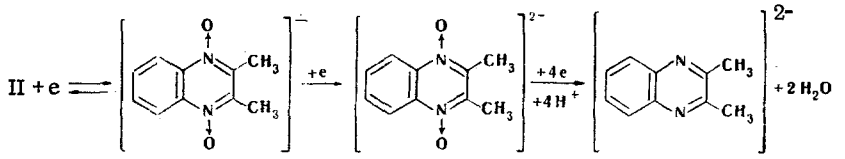
TABLE 1. Half-Wave Potentials (V) in the Reduction of Quinoxaline Derivatives in Volts

Compound	$-E_{1/2}^{I}$, $-\Delta E$[a]	$-E_{1/2}^{II}$, $-\Delta E$	$-E_{1/2}^{III}$, $-\Delta E$	$-E_{1/2}^{IV}$, $-\Delta E$	$-E_{1/2}^{V}$, $-\Delta E$
I	2,35 0,07	2,75 0,07			
II	1,94 0,06	2,28 0,07	2,7 —		
III	2,00 0,065	2,29 0,065	2,55 0,06	2,81 0,075	
IV	1,69 0,06	2,03 0,08	2,28 0,06	2,55 0,05	2,74 0,08
V	1,60 0,065	1,90 0,08	2,20[b] 0,06 2,37[c] 0,06	2,64 0,065	

[a] $\Delta E = E_{3/4} - E_{1/4}$. [b] $E_{1/4}^{III}$. [c] $E_{3/4}^{III}$.

of the $E_{1/2}^{I}$ values for them provides evidence that in the case of the N,N'-dioxide the first antibonding molecular level is lower than in the case of the corresponding unoxidized compound. The first two waves for N,N'-dioxide II are one-electron waves, and the third with respect to the current is higher by a factor of approximately four than each of the two preceding waves. An examination of these data taking into account the available literature data on the electrochemical reduction of 4,4'-azopyridine 1,1'-dioxide [4] makes it possible to propose the following scheme for the reduction of N,N'-dioxide II:



The anion radical of starting N,N'-dioxide II is formed in the first step, which is a one-electron step and is reversible, after which the dianion is formed by the subsequent addition of another electron. The third polarographic wave, which is a four-electron wave and is irreversible, constitutes evidence for the fact that the following steps in the reduction of the dianion of II correspond to irreversible chemical reactions of protonation and splitting out of the oxygen atoms of the N–O group and lead to the dianion of 2,3-dimethylquinoxoline.

In the case of III the first reduction wave is also a one-electron wave and is reversible, and $E_{1/2}^{I}$ is shifted 0.06 V to the negative region as compared with the $E_{1/2}^{I}$ value of N,N'-dioxide II because of the weak donor effect of the OCH_3 group. A total of four waves is observed on the polarogram, and the $E_{1/2}$ value of the last wave evidently corresponds to the formation of the dianion of 2,3-dimethyl-6-methoxyquinoxaline. In the polarographic reduction of N,N'-dioxide IV the first two waves successively correspond to the formation of the anion radical of IV and splitting out of a chloride ion. The third reduction wave (which is a two-electron wave with respect to the current) corresponds to the formation of the dianion of II. The polarogram of N,N'-dioxide IV contains a fourth and fifth wave, the half-wave potentials of which show that reduction to the dianion of 2,3-dimethylquinoxaline is also observed for IV.

The polarographic results obtained for the preparation quinoxidine (V) are of particular interest. The polarogram of quinoxidine V contains five reduction waves, and the $E_{1/2}$ potential of the first wave is shifted significantly (0.4 V) to the positive region as compared with the potential of II, although the ester group is isolated from the heteroaromatic system by a methylene link. It is possible that this phenomenon is associated with the fact that the protons of the CH_2 group of α substituents in quinoxidine have increased lability [5]. The polarographic properties of the medium in which the polarographic study was carried out should promote an increase in the lability of these protons. The fact that the first reduction wave is a two-electron wave with respect to the current also constitutes evidence in favor of this; this is in agreement with the presence in quinoxidine V of two labile protons. An examination of the $E_{1/2}$ potentials of all of the subsequent

TABLE 2. Parameters of the EPR Spectra of the Anion Radicals of Quinoxaline Derivatives

Compound	ΔH, Oe	Character of the splitting	Position	a constants, Oe
I	36,5	$5_N \times 7_H \times 3_H \times 3_H$	1,4 2,3 5,8 6,7	5,6 3,1 1,5 1,1
II	39,0	$5_N \times 7_H \times 3_H \times 3_H$	1,4 2,3 5,8 6,7	6,3 2,5 2,2 1,2
II[a]	36,5	$5_N \times 7_H \times 3_H \times 3_H$	1,4 2,3 5,8 6,7	5,6 3,1 1,5 1,1

[a]These data pertain to the product of reduction of II.

reduction waves provides a basis for the assumption that the last observed wave corresponds to the formation of the dianion of a 2,3-disubstituted quinoxaline also in the case of quinoxidine.

Using the data from the polarographic analysis we carried out the electrochemical reduction of I-V in DMF and studied the EPR spectra of the anion radicals that were formed in this case.

Despite the fact that for I the first polarographic wave is a one-electron reversible wave and corresponds to the formation of anion radicals, we were able to record the EPR spectrum only at a potential corresponding to the second reduction wave, i.e., to the formation of dianions. However, there can be no doubt that the spectrum obtained belongs to the anion radicals of the starting compound, since the reconstruction of the spectrum with splitting constants close to the splitting constants in the spectrum of the anion radicals of quinoxaline [6] is in good agreement with the experimental data. Only the $a_{5,8}$ values differ appreciably; however, the anion radicals of quinoxaline were obtained in [6] by means of an alkali metal in an ether solvent, and some difference in the splitting constants is therefore possible. The fact that we were able to record the EPR spectrum of the anion radicals of I only at a potential close to $E_{1/2}$ of the second wave can be explained by the fact that it is difficult to accumulate a concentration of the anion radical sufficient for recording of the spectra at the $E_{1/2}$ potential of the first wave. At higher potentials, i.e., at the $E_{1/2}$ potential of the second reduction wave, the resulting dianions can undergo disproportionation with the unreduced molecules and give an anion radical concentration sufficient for recording of the EPR spectra. This phenomenon is observed in the reduction of some dinitro compounds [7].

In the case of the anion radicals of N,N'-dioxide II the EPR spectrum is also recorded at ∿2.5 V, i.e., after the second reduction wave. The anion radicals formed in this case are less stable than the anion radicals of dimethylquinoxaline I, whereas the EPR spectrum of the anion radical of I, i.e., the product of reduction of N,N'-dioxide II, is recorded when the potential is increased to 2.7 V. These results are in agreement with the polarographic data. The hyperfine splitting constants for the anion radical of N,N'-dioxide II (Table 2) are close to the hyperfine splitting constants of the anion radical of quinoxaline 1,4-dioxide [2].

We were unable to record an EPR spectrum in the electrochemical reduction of III for either primary anion radicals or for the anion radicals of the reduction products. In the case of N,N'-dioxide IV at E = 2.5-2.7 V we obtained a spectrum that corresponded to the EPR spectrum of the anion radical of dimethylquinoxaline I. In the case of quinoxidine V the EPR spectrum is also recorded only after prolonged electrolysis at E = 2.5-2.7 V and with respect to the character of the splitting proved to be very similar to the spectrum of the anion radical of dimethylquinoxaline I. It should be noted that it is difficult from the spectrum to form a judgment as to which changes occurred with the α substituents in quinoxidine. It is known from the literature data that the ester group under certain conditions can be reduced to an ether group. One should then expect a spectrum with

$5_N \times 5_H \times 3_H \times 3_H$ splitting character (instead of $5_N \times 7_H \times 3_H \times 3_H$ for the anion radical of 2,3-dimethylquinoxaline). The ratio of the splitting constants in the spectrum of this hypothetical compound. A decrease in the number of lines on the flanks to two or four lines should lead to a spectrum that has a silhouette that is close to that observed for the anion radical of I but with less overall spread. In fact, the total spread of the spectrum (ΔH) of the anion radical of the product of reduction of quinoxidine is somewhat less than that observed for the anion radical of dimethylquinoxaline I; this constitutes evidence in favor of the assumption of conversion of the ester groups of the α substituents of quinoxidine to ether groups. We are conducting additional studies to definitively ascertain the structure of the product of the reduction of quinoxidine.

EXPERIMENTAL

The polarographic measurements were made for solutions ($c = 5 \cdot 10^{-4}$ mole/liter) of the investigated substances in DMF; tetraethylammonium perchlorate was used as the supporting electrolyte. The polarograms were recorded with a PPT-1 recording polarograph in a thermostatted cell involving a three-electrode circuit with an internal reference electrode and an auxiliary electrode. A dropping mercury electrode with forced detachment of the drops was used. A silver perchlorate electrode was used as the reference electrode, and the mercury pool, contact with which was realized with a platinum wire isolated from the solution by means of a glass tube, served as the auxiliary electrode [8]. Air oxygen was removed from the investigated solutions by purging with argon that had been previously saturated with the solvent at 25°C. Pure-grade DMF was additionally purified by the method in [9] with certain changes described in [4]. The quality of the DMF was monitored by polarography [4].

The electrochemical generation of the anion radicals was realized in DMF with a polarized mercury drop in a cell placed directly in the resonator of an RÉ-1301 radiospectrometer. Oxygen was removed from the solutions prior to the experiments by repeated freezing and thawing at a residual pressure of 10^{-2}-10^{-3} mm (mercury column). The concentration of the investigated substances was $(3\text{-}5) \cdot 10^{-3}$ mole/liter. All of the investigated compounds were synthesized and purified by the methods in [10, 11].

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