QUINOXALINE N-OXIDE ION RADICALS.

2.* STRUCTURES OF ANION RADICALS OF N-OXIDES OF HYDROXYMETHYL DERIVATIVES OF QUINOXALINE AND PRODUCTS OF THEIR ELECTROCHEMICAL REDUCTION

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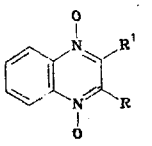
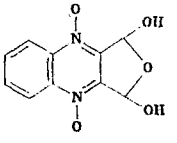
The redox properties of 1,4-dioxides of hydroxymethyl and formyl derivatives of quinoxaline were studied by means of EPR spectroscopy and polarography. The electrochemical reduction of the 1,4-dioxides proceeds in several steps with successive deoxidation and the formation of dianions of substituted quinoxalines and is also accompanied by an intramolecular redox process. The experimentally observed hfs constants in the EPR spectra of the anion radicals formed in the reduction are in agreement with the corresponding values calculated by the INDO method.

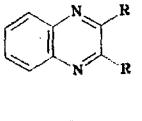
We have previously shown [1] that the electrochemical reduction of 2,3-dimethylquinoxaline 1,4-dioxide leads to the formation of unstable anion radicals, which are converted to the more stable 2,3-dimethylquinoxaline anion radicals (AR) when the applied voltage is increased. On the basis of a polarographic investigation it was established that the reduction is a stepwise process and that the final product is the 2,3-dimethylquinoxaline dianion. The subject of the present investigation was the study of the electrochemical reduction of the 1,4-dioxides of hydroxymethyl and formyl derivatives I-IV as compared with the corresponding unoxidized quinoxalines V-VII.



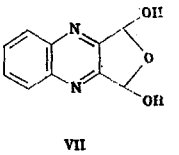
I-III



IV



V-VI



VII

I, II, V R=CH_2OH; III, VI R=CHO; I R^1=CH_2OH; II, III R^1=H

One of these compounds, viz., 2,3-bis(hydroxymethyl)quinoxaline (dioxidin) (I), is an effective medicinal preparation that is used in medical practice in the treatment of acute bacterial infections [2, 3].

It is known that N-oxides of α-hydroxyalkyl derivatives of azines display the ability to undergo redox reactions of various types [4, 6]. It has been shown [5] that dioxidin I in the presence of alkaline reagents undergoes redox transformations leading to the formation of 2-hydroxymethyl-3-formylquinoxaline 1-oxide, which is isolated in the form of the cyclic hemiacetal; in the presence of excess alkaline reagent it is converted to 2,3-diformylquinoxaline cyclic hemiacetal (VII). In this connection, it seemed of interest to ascertain if the dioxides (I, II) of α-hydroxymethyl derivatives of quinoxaline display the ability to undergo intramolecular redox transformations under the conditions of electrochemical reduction in an aprotic medium.

*See [1] for communication 1.

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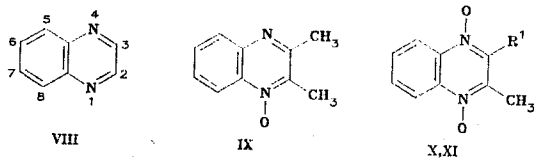
The results of a polarographic investigation are presented in Table 1. The electrochemical reduction of all of the investigated compounds on a mercury cathode proceeds in several steps. Two reduction steps are observed for unoxidized 2,3-substituted quinoxalines V-VII: transfer of one electron to the neutral molecule to give AR is realized in the first step, and the addition of a second electron to give dianions is realized in the second step. The reduction of 1,4-dioxides I-IV takes place in four steps, and the first step is a one-electron and reversible process (tan β = 55-60 mV); this constitutes evidence for the formation of AR of the starting compounds. The $E^1/_2$ values of the first reduction waves of the 1,4-dioxides are shifted to the positive region relative to V-VII. This is in agreement with the fact that the electron affinities are greater for the 1,4-dioxides of quinoxalines V-VII and the fact that the first antibonding molecular levels are lower than for the corresponding quinoxalines.

The structures of the AR formed in the electrochemical reduction of I-VII were studied by EPR spectroscopy. The EPR spectra of the AR of I-VII have complex and incompletely resolved hyperfine structures (hfs) because of the large number of nuclei with a half-integral spin that enter into the conjugation chains. The EPR spectra in this study were interpreted on the basis of a comparison of the experimentally observed hfs constants with the values calculated by the INDO method with Pople parametrization [7] for model compounds VIII-XI.



VIII IX X,XI

X R^1=H; XI R^1=CH_3

The selection of the model compounds was due to the fact that the difference in the hfs constants of 2,3-dimethylquinoxaline [1] and 2,3-bis(hydroxymethyl)quinoxaline (V) is small (Δa ~ 0.1 Oe). The results of the calculations are presented in Table 2. The calculations showed that N oxidation of quinoxalines has a significant effect on the nitrogen hfs constants. The transition from quinoxaline (VIII) to N-monoxide IX leads to a pronounced redistribution of the spin density in the pyrazine ring: the hfs constants of the oxidized and unoxidized nitrogen atoms differ by a factor of two [$a_{N_{(1)}} \cong 2a_{N_{(4)}}$] The close values of the $a_{N_{(1)}}$ and $a_{N_{(4)}}$ hfs constants for the AR of X and XI mean that the introduction of a second methyl group into the pyrazine ring has almost no effect on the distribution of the spin density.

The EPR spectra of the primary AR could be recorded for I and V-VII at a value of the applied voltage that exceeds the $E_{1/2}$ value of the first reduction wave by 0.1-0.2 V. Primary quintet splitting with an intensity ratio of 1:2:3:2:1, which can be explained by coupling of the unpaired electron with two equivalent nitrogen nuclei, is characteristic for them. Further splitting of the lines of the quintet signal due to coupling of the unpaired electron with the 2,3-H and 5,8-H protons is also observed. The nitrogen splitting constants and the constants from the 2,3-H protons (see Table 3) show that the unpaired electron is delocalized primarily in the pyrazine ring. The experimentally observed a_N values for the AR of 1,4-dioxide I and the corresponding V differ by 1 Oe, which is in good agreement with the results of the calculations.

In the case of II-IV we were unable to record the spectra of AR formed in the first step of the reduction, evidently as a consequence of their instability. The EPR spectra of the products of the reduction of II and IV were recorded at a value of the applied voltage that is close to the $E_{1/2}$ value of the second reduction wave. The principal splitting observed for the spectrum of the product of reduction of 1,4-dioxide IV is triplet splitting with an intensity ratio of 1:1:1; this indicates the presence of two nonequivalent nitrogen atoms in the AR. This character of the splitting and the values of the nitrogen hfs constants [$a_{N_{(1)}}$ = 8.2 Oe and $a_{N_{(4)}}$ = 3.4 Oe] correspond to the formation of AR of the N-monoxide of VII in the reduction of IV. In fact, the spectrum of AR of VII was recorded in the case of prolonged electrolysis. The data obtained make it possible to conclude that the electrochemical reduction of 2,3-diformylquinoxaline cyclic hemiacetal 1,4-dioxide (IV), as in the case of 2,3-dimethylquinoxaline 1,4-dioxide [1], is a stepwise process with the successive splitting out of oxygen atoms of the N→O groups and the formation of AR of the corresponding N-monoxide as an intermediat

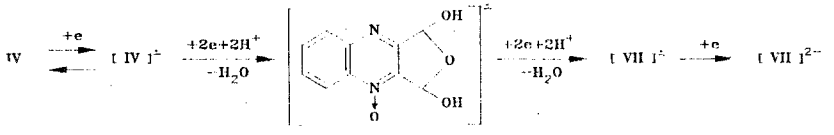


TABLE 1. Reduction Potentials ($-E_{1/2}$, V) of I-VII

Compound	$-E_{1/2}$I*	i_d †	$-E_{1/2}$II*	i_d	$-E_{1/2}$III*	i_d	$-E_{1/2}$IV*	i_d
I	1,53 (55)	1,24	2,10 (70)	2,06	2,45 (85)	2,48	2,87 (100)	1,36
II	1,63 (60)	1,28	2,18 (90)	2,04	2,56 (85)	2,28	2,91 (95)	1,52
III	1,12 (60)	1,44	1,52 (80)	2,35	1,90 (110)	2,37	2,15 (100)	1,52
IV	1,59 (55)	1,76	1,74 (30)	1,78	1,94 (86)	3,14	2,30 (95)	1,92
V	2,10 (66)	1,84	2,44 (80)	1,28				
VI	1,85 (80)	1,48	2,29 (118)	2,16				
VII	1,83 (70)	1,92	2,23 (100)	2,08				

*The tan β values in millivolts are presented in parentheses; $\tan \beta = \Delta E/\{\Delta \log [i/(i_d - i)]\}$.
†The symbol "i_d" is the limiting current in microamperes.

TABLE 2. Calculated hfs Constants (a, Oe) of the Anion Radicals of Quinoxaline (VIII) and Methylquinoxaline N-Oxides IX-XI

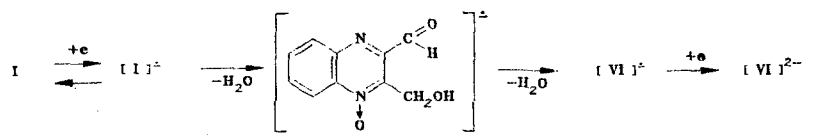
Compound	$N_{(1)}$	$N_{(4)}$	2-H	3-H	5-H	6-H	7-H	8-H
VIII	6,23	6,23	2,07	2,07	2,7	0,7	0,7	2,7
IX	8,59	3,94	2,16	3,7	1,49	0,9	0,1	2,76
X	7,15	7,23	1,18	0,9	2,22	0,3	0,4	2,1
XI	7,26	7,26	2,0	2,0	2,05	0,4	0,4	2,05

TABLE 3. Experimental Values of the hfs Constants (a, Oe) of the Anion Radicals Obtained in the Electrochemical Reduction of I-VII

Compound*	$N_{(1)}$	$N_{(4)}$	2-H	3-H	5-H	6-H	7-H	8-H
I	6,7	6,7	3,1	3,1	1,6	0,8	0,8	1,6
	[6,2]	[6,2]	[3,1]	[3,1]	[1,65]	[0,85]	[0,85]	[1,65]
II	(3,4)	(8,2)	(3,4)	(3,4)	(1,45)	(0,6)	(0,6)	(1,45)
III	(3,4)	(8,2)	(3,4)	(3,4)	(1,45)	(0,6)	(0,6)	(1,45)
	[6,0]	[6,0]	[3,5]	[3,5]	[2,4]	[1,5]	[1,5]	[2,4]
IV	(8,2)	(3,4)	(3,4)	(3,4)	(1,5)	(0,6)	(0,6)	(1,5)
	5,6	5,6	3,5	3,5	2,6	1,65	1,65	2,6
V	5,7	5,7	3,2	3,2	1,6	1,0	1,0	1,6
VI	6,2	6,2	3,1	3,1	1,65	0,85	0,85	1,65
VII	5,6	5,6	3,5	3,5	2,6	1,65	1,65	2,6

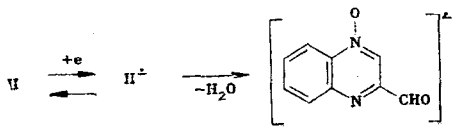
*The values of the AR of the starting compounds are presented) the values of the AR of the intermediate reduction products are given in parentheses, and the values of the AR of the deoxidated (at the nitrogen atom) reduction products are given in brackets.

The electrochemical reduction of the 1,4-dioxides (I and II) of α-hydroxymethyl derivatives of quinoxaline proceeds via a different scheme. If the reduction included deoxidation without a change in the structure of the side chains, the spectrum of AR of V would be observed in the case of prolonged electrolysis of a solution of dioxidin I. In fact, the spectrum of AR of 2,3-diformylquinoxaline (VI) is recorded with time during electrochemical generation. When the voltage is increased to the potentials of the third and fourth reduction waves, no products of transformation of VI are observed in the EPR spectra. An analysis of the data thus obtained with allowance for the ability of N-oxides of α-hydroxymethyl derivatives of quinoxaline to undergo redox transformations [5, 6] makes it possible to propose the following scheme for the electrochemical reduction of dioxidin I:



In the first step the products are AR of I, which then, via an intramolecular redox process, are converted to stable AR of VI; this rearrangement proceeds without the additional participation of electrons. The spectrum of the AR of VI is therefore recorded at potentials that are close to the $E_{1/2}$ value of the second reduction wave. The final product under the investigated conditions is the dianion of 2,3-diformylquinoxaline.

The proposed mechanism of the reduction of dioxidin I was confirmed by an analysis of the EPR spectra of the AR formed in the reduction of II and III. Equivalent triplet EPR signals, which can be assigned to the same reduction product rather than to the AR of the starting compounds, are recorded under the conditions of electrochemical generation of solutions of II and III (see Table 3). In the reduction of III these AR are formed at the potentials of the second reduction wave and correspond in structure to the product of deoxidation of III to give 2-formylquinoxaline 4-oxide. A quintet spectrum with a_N = 6.0 Oe, which corresponds to the AR of 2-formylquinoxaline, is recorded when the reduction potential is increased. In the case of 2-hydroxymethylquinoxaline 1,4-dioxide (II) AR of 2-formylquinoxaline 4-oxide are recorded at the first reduction wave, and their formation can be explained by an intramolecular redox process via the scheme



Thus, the electrochemical reduction of 2-formylquinoxaline 1,4-dioxide (III) and 2,3-formylquinoxaline hemiacetal 1,4-dioxide (IV) in an aprotic medium takes place in several steps with the successive splitting out of oxygen atoms of the N→O groups and the formation of dianions of the corresponding quinoxaline derivatives as the final products. The electrochemical reduction of α-hydroxymethyl derivatives of quinoxaline under the same conditions is accompanied by an intramolecular redox process with conversion of the hydroxymethyl groups to formyl groups.

EXPERIMENTAL

Polarographic reduction was carried out in solution in dimethylformamide (DMF) with a 0.1 M solution of $(n\text{-}C_4H_9)_4NClO_4$ as the inert electrolyte; a 0.1 M solution of $Ag/AgClO_4$ in acetonitrile [8] served as the reference electrode. The polarograms were recorded with a PPT-1 recording polarograph. The EPR spectra were recorded with RÉ-1306 and Radiopan SE/X2543 spectrometers. Electrochemical generation was realized with a polarized mercury drop in a cell mounted directly in the spectrometer resonator. The concentrations of the substances ranged from $1 \cdot 10^{-3}$ M to $5 \cdot 10^{-3}$ M. The pure-grade DMF was additionally purified and dried by the method in [8]. Compounds I-VII were synthesized and characterized (by means of the physicochemical constants) via previously described methods [5, 9-12].

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CYCLIZATIONS OF N-ALKYLAZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES. 19.* CRYSTAL STRUCTURE OF THE KINETIC PRODUCT OF THE REACTION OF N-METHYLQUINOXALINIUM IODIDE WITH THIOACETAMIDE

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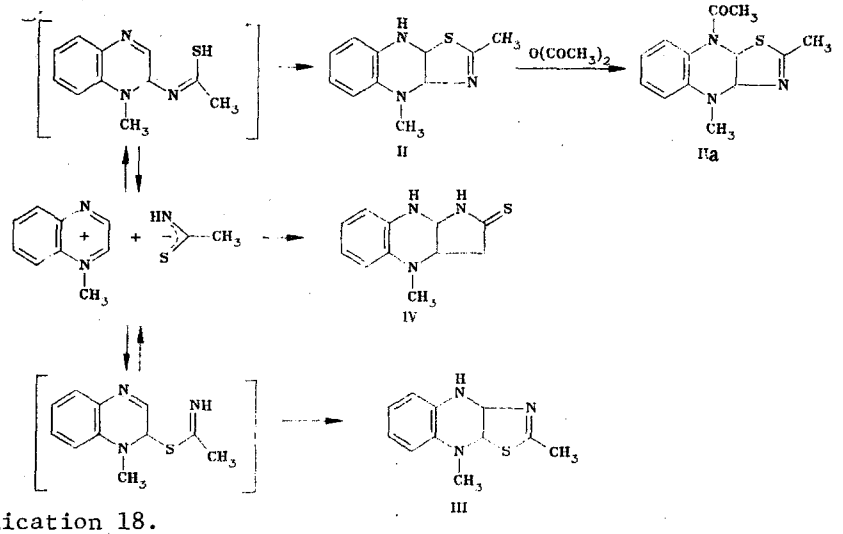
The mutual orientation of the heterorings and the three-dimensional structure of the kinetic product of the reaction of N-methylquinoxalinium iodide with thioacetamide were established by x-ray diffraction analysis of 2,4-dimethyl-9-acetyl-3α,4,9,9α-tetrahydrothiazolo[4,5-b]quinoxaline.

The ambident properties of thioamides in reactions with electrophilic reagents are well known [2]. The ratio of the N- and S-isomeric products depends on the nature of the electrophilic agent and on whether the reaction is carried out under conditions of kinetic or thermodynamic control. As a rule, the rate of S addition is higher, and reactions such as protonation and alkylation proceed primarily at the sulfur atom [2]. It is also known that N-acylated products are formed in the reactions of thioamides with acylating agents, although one cannot exclude the possibility that this takes place through kinetically controlled S acylation [2].

It has been previously shown [3, 4] that the reactions of the N-methylquinoxalinium cation (I) with thioamides proceed with the participation of both reaction centers (N and S) and lead to cyclic adducts, viz., thiazolo[4,5-b]quinoxalines; however, the regioorientation of the thiazole ring in the cyclization products may differ and depends on the reaction conditions. Structure II was assigned to the kinetic product of the reaction of cation I with thioacetamide on the basis of the ^1H and ^{13}C NMR spectra [3], whereas regioisomeric thiazolo[4,5-b]quinoxaline III and pyrrolo[2,3-b]quinoxaline-2-thione IV are formed under conditions of thermodynamic control [4].



*See [1] for communication 18.

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