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1,2,4- AND 1,2,5-OXADIAZOLES.

1. POLAROGRAPHIC REDUCTION OF METHYL- AND PHENYL-OXADIAZOLES IN ANHYDROUS DIMETHYLFORMAMIDE

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It is shown that the first step in the reduction of the investigated oxadiazoles on a dropping mercury cathode in dimethylformamide corresponds to two-electron cleavage of the N-O bond. The degree of reduction is determined by the nature and position of the substituents in the oxadiazole ring and by the rate of protonation of the intermediately formed particles.

There is no information in the literature regarding the polarographic behavior of oxadiazoles that have an N-O bond; only the polarography of condensed 1,2,5-oxadiazoles (furazans) has been described [1]. In the present research we investigated the reduction of 3,4-dimethyl-1,2,5- (I), 3,4-diphenyl-1,2,5- (II), 3,5-dimethyl-1,2,4- (III), 3,5-diphenyl-1,2,4- (IV), 3-phenyl-5-methyl-1,2,4- (V), and 3-methyl-5-phenyl-1,2,4-oxadiazole (VI) on a dropping mercury cathode in anhydrous dimethylformamide (DMF). From one to three waves are observed on the polarograms of the indicated compounds in a 0.05 M solution of tetrabutylammonium perchlorate (Table 1); in all cases the first wave corresponds to irreversible transfer of two electrons.

Since, from a formal point of view, the 1,2,4-oxadiazole ring includes fragments of oxazole and isoxazole rings, it is expedient to compare the polarographic reduction of the indicated heterocycles. We have previously established that phenylisoxazoles are capable of undergoing polarographic reduction in DMF and that the first step in the reduction is a two-electron process with cleavage of the N-O bond [2].

Oxazoles and 1,3,4-oxadiazoles can be reduced with the consumption of six electrons, i.e., with ring cleavage, or with the consumption of four electrons without ring cleavage [3]. However, the reduction of condensed 1,2,5-oxadiazoles proceeds with cleavage of both N-O bonds, but in DMF the first step is reversible and corresponds to the transfer of one electron with the formation of an anion radical [1].

TABLE 1. Half-Wave Potentials ($E_{1/2}$, V) and Current Diffusion Constants $\left(I=\frac{i_{\lim}}{c\cdot m^{2/3}t^{1/6}}\right)$ of Derivatives of 1,2,4- and 1,2,5-Oxadiazoles in DMF Containing 0.05 M Bu_4NClO_4 as the Base Electrolyte

		I	II	III	IV	V	VI	VII
$-E_{1/2}$, V	1	2,54	2,00	2,94	1,91	2,25	2,00	2,36
	2	2,97	2,53		2,75	2,93	2,92	2,53
	3		2,75					
I	1	4,37	3,46	3,64	3,34	3,95	3,13	1,28
	2	2,43	6,45		2,96	2,60	4,71	2,95
	3		3,34					
Sum of I		6,80	13,25	3,64	6,30	6,55	7,84	4,23

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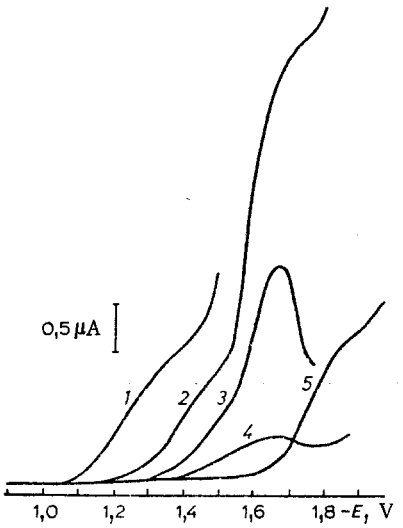

Fig. 1. Polarograms of 0.5 mM solutions of 3,5-diphenyl-1,2,4-oxadizol-2-ine in citrate-phosphate buffer solutions with pH 2.87 (1), 5.46 (2), 6.0 (3), 7.05 (4), and 3,5-diphenyl-1,2,4-oxadiazole at pH 7.05 (5).

To establish the nature of the first step in the reduction of the oxadiazoles presented in Table 1, we studied the polarographic behavior of 3,5-diphenyl-1,2,4-oxadiazol-2-ine (VII). In DMF this compound, like the corresponding oxadiazole IV, undergoes reduction in two steps. However, whereas the first wave of oxadiazoline VII is found at more negative potentials than the first wave of oxadiazole IV (Table 1), the subsequent reduction proceeds with greater difficulty in the case of oxadiazole IV. Thus oxadiazoline VII cannot be the product of the first step in the reduction of oxadiazole IV.

A similar conclusion can be drawn when one compares the polarographic behavior of IV and VII in protogenic media. In acidic citrate–phosphate buffer solutions containing 30% DMF the reduction wave of oxadiazole IV is hidden by the discharge current of the base electrolyte. At pH 7 this compound is reduced in one step (Fig. 1), during which $E_{1/2}$ is independent of the pH, i.e., the protons do not participate in the potential-determining step. The same pattern is also observed in the reduction in buffer solutions of oxadiazole II, but in this case the height of the wave is substantially greater than the height of the wave of oxadiazole IV.

On the other hand, the reduction of oxadiazoline VII can be detected only in acidic media. At pH 2.87 there is one reduction wave, which has diffusion character (Fig. 1), on the polarogram of this compound (Fig. 1). As the pH increases, this wave is shifted to the negative-potential region, and a second wave appears at pH 4 ahead of the discharge current of the base electrolyte. A drop in this wave, accompanied by a substantial decrease in its height, appears at pH 6.0, and the first wave takes on the form characteristic for the chemical waves with surface prior protonation at pH 7. A further increase in the pH of the medium leads to disappearance of the reduction waves of oxadiazoline VII. Thus, in these media oxadiazoline VII is capable of undergoing reduction only when there is a prior protonation step, and oxadiazole IV cannot be the reduction product.

It may be assumed that, as in the reduction of phenyloxazoles, the first step in the reduction of the investigated oxadiazoles is cleavage of the N-O bond. However, the degree of reduction is determined by the structure of the oxadiazoles and the rate of protonation of the intermediate particles. From a comparison of the diffusion current constants it may be concluded that eight electrons participate in the overall electrical reduction of oxadiazole II in DMF, while the electrical reduction of III in the accessible range of potentials is complete after the transfer of two electrons. Four electrons are consumed in the reduction of oxadiazoles I and IV-VI. As one should have assumed, the heterocyclic ring is more easily reduced in the aza analogs of isoxazole, which contain an acceptor "pyridine" nitrogen atom. In contrast to 3,5-dimethylisoxazole [2], dimethyloxadiazoles I and III are capable of undergoing reduction in DMF, although the reduction wave of oxadiazole III is observed only immediately ahead of the discharge current of the base electrolyte. Phenyl-substituted oxadiazoles are reduced substantially more easily; this is particularly true of diphenyl derivatives II and IV. The same order of the change in the $E_{1/2}$ values of the first wave of the process was also observed in the phenylisoxazole series [2]. Moreover, of the isomeric 1,2,4-oxadiazoles (V and VI), VI, which contains a phenyl group in the 5 position, is also reduced more easily. A relationship between the greater conjugation in this isomer [5] and

the more positive $E_{1/2}$ value of the first reduction wave, which we have previously noted for 5-phenylisoxazole [2], is also observed here. It is interesting to note that whereas oxadiazole I is reduced at potentials that are 400 mV more positive than the potentials of oxadiazole III, the picture is reversed in the case of diphenyl derivatives II and IV — 1,2,4-oxadiazole is reduced more easily (Table 1). This is evidently associated with the fact that as a result of steric hindrance both phenyl groups of oxadiazole II cannot be present simultaneously in the plane of the heteroring, i.e., conjugation is disrupted, while in the case of diphenyloxadiazole IV there is no hindrance whatsoever to conjugation. The conjugation in these diphenyloxadiazoles resembles the conjugation in 3-phenylisoxazole [6], except that in IV both benzene rings are conjugated independently with the multiple bonds of the heteroring [5], whereas only one is conjugated in this manner in isomer II [λ_{max} 242 nm (log ε 4.03)].

EXPERIMENTAL

The compounds were obtained by described methods, and their constants were in agreement with the literature data; chromatographically pure samples were used for the polarographic study. A capillary with a spatula for forced detachment of the drops and the following characteristics was used for the experiments carried out in aprotic media: m = 0.73 mg/sec, t = 0.30 sec, and $m^{2/3}t^{1/6} = 0.662$. A silver wire submerged in the test solution served as the anode. The half-wave potentials of the investigated compounds were scaled relative to a saturated calomel electrode on the "standard" (potassium) scale [7]. A capillary with forced detachment of the drops and the following characteristics were also used in aqueous media: m = 1.06 mg/sec, t = 0.305 sec, and $m^{2/3}t^{1/6} = 0.85$.

The polarographic measurements were made in a thermostatted cell (25 ± 0.1°C) with a PO-4 polarograph (Radiometer, Denmark). The oxygen was removed from the solutions to be polarographed with a stream of purified nitrogen. The DMF was dried with fused KOH and distilled in vacuo. The UV spectrum of a solution of II in alcohol was recorded with a Perkin–Elmer 402 spectrophotometer.

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