Chemistry of Heterocyclic Compounds, Vol. 40, No. 2, 2004

INVESTIGATION OF THE OXIDATION-REDUCTION CHARACTERISTICS OF HETEROCYCLIC QUINONES

E. Yu. Khmel'nitskaya, N. B. Grigoriev, V. M. Lyubchanskaya, T. I. Mukhanova, and V. G. Granik

An electrochemical investigation was undertaken into the oxidation–reduction characteristics of heterocyclic quinones including derivatives of indazole, benzimidazole, benzofuran, benzothiazole, and isoquinoline. It was established that the compounds are reduced with the successive irreversible transfer of two electrons. The effect of structural factors and the nature of the heterocycle on the ease of reduction of the compounds is examined.

Keywords: heterocyclic quinones, oxidation–reduction characteristics, polarographic investigation.

Many derivatives containing a quinone fragment exhibit significant biological activity. Their role as cytotoxic agents resulting from enzymatic reduction and followed by oxidation by atmospheric oxygen with the formation of a superoxide radical-anion, peroxynitrite, and the initial quinone (the so-called redox cyclization) is well known.

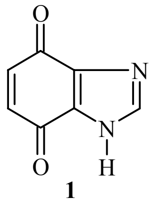
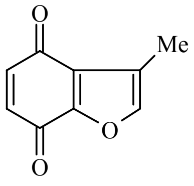
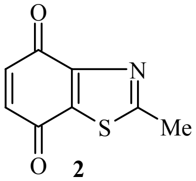
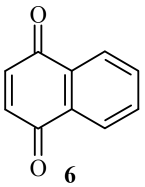
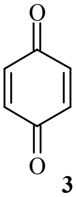
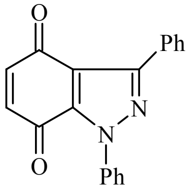
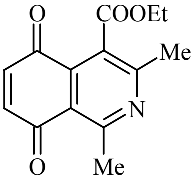
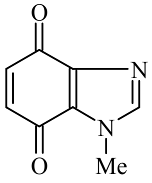
The mechanism of the Nenitzescu reaction (the reaction of quinones with enamines) [1, 2] includes a whole series of oxidation–reduction stages resulting from the redox characteristics of the quinones and hydroquinones and the various quinone- and hydroquinone-containing intermediates (e.g., hydroquinone and quinone adducts, quinoneimmonium derivatives, etc.) formed in the course of the reaction. Investigation of the Nenitzescu reaction is one of the promising directions in the development of the chemistry of heterocyclic compounds, since it can be used to produce 5-hydroxybenzofurans and, particularly, 5-hydroxyindoles and their derivatives, which include the neuromediator serotonin. The discovery of the role of serotonin has led to considerable progress in neuropharmacology. The 5-hydroxyindole derivatives include a whole group of biologically highly active compounds such as melatonin, indopan, etc., and interest in the mechanism of the Nenitzescu reaction is therefore constantly increasing. As a result it seems quite natural to investigate the polarographic behavior of the initial quinones in order to examine further their possible transformations under the influence of various nucleophilic agents, including enamines.

Recently a new direction, based on the use of heterocyclic quinones in condensation with enamines, was discovered in the development of the Nenitzescu reaction. In view of the fact that the electrochemical characteristics of the derivatives of benzo- and naphthoquinones have been studied in great detail while heterocyclic quinones have been investigated little in this respect, in the present work we studied the polarographic behavior of indazole-, benzimidazole-, benzothiazole-, and isoquinolinequinones, for which

---

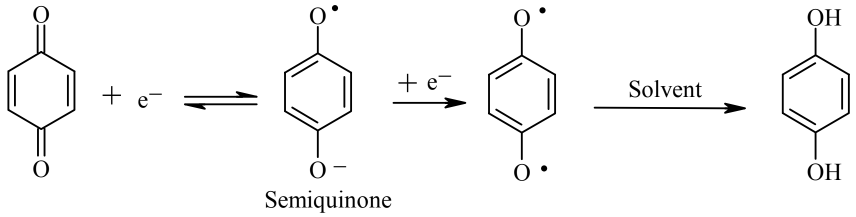
Federal State Unitary Undertaking State Scientific Center NIOPIK, Moscow 101999, Russia; e-mail: makar-cl@ropnet.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 195-200, February, 2004. Original article submitted October 24, 2001.

TABLE 1. The Half-Wave Potentials (E) of the Quinones in Anhydrous Dimethylformamide

Compound	$E_{1/2}$, V, of first wave	$E_{1/2}$, V, of second wave	Compound	$E_{1/2}$, V, of first wave	$E_{1/2}$, V, of second wave
 **1**	-0.39	-1.20	 **5**	-0.57	-1.32
 **2**	-0.46	-1.23	 **6**	-0.61	-1.28
 **3**	-0.49	-1.31	 **7**	-0.62	-1.37
 **4**	-0.52	-1.29	 **8**	-0.66	-1.38

information on the paths for their condensation with enamines is already available. A list of the investigated compounds and their half-wave potentials are given in Table 1.

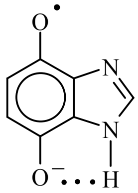
1,4-Benzoquinone (**3**) and 1,4-naphthoquinone (**6**) were used as models for comparison with heterocyclic quinones. In anhydrous DMF all the listed quinones are reduced in two stages – two waves of equal height are observed on the polarograms. By comparison of the proportionality factor in the Ilkovic equation for each waves of the investigated substances and model compounds it was established that both electrochemical stages correspond to the transfer of one electron. It is known that in aprotic solvents aromatic quinones form a semiquinone as a result of the transfer of one electron, and reduction takes place according to the following scheme [3]:



In electrochemical reduction the heterocyclic quinones that we investigated also go through a semiquinone stage. Here the waves have diffusion character, and their slope corresponds to an irreversible process. Aromatic quinones behave similarly in aprotic media. Thus, even Kolthoff found that a quinhydrone electrode is not reversible in nonaqueous solutions and anodic waves for the corresponding hydroquinones are not detected at the reduction potentials of the quinones [4, 5]. Similar results were obtained by cyclic voltammetry [6].

The obtained data are largely unexpected, e.g., the fairly large hindrance of the reduction of compound **8** compared with the derivative of thiazolequinone **2** or the high negative reduction potential of the indazolequinone **7**, which has phenyl substituents at positions 1 and 3. The latter is explained by the fact that the phenyl rings must be turned significantly from the plane of the bicycle for steric reasons. The previously mentioned [7] large difference between the half-wave potentials of the first stage in the reduction of the benzimidazolequinone **1** and its N-methyl derivative **8** can be explained by the presence in compound **1** of a hydrogen bond between the NH and C=O groups of the quinone fragment, which stabilizes the radical-anion (or transition state) to a greater degree than the initial molecule.

It is clear that such stabilization is impossible for compound **8**.



It is seen from the data in Table 1 that the difference in the half-wave potentials of the first stage of electrochemical reduction is appreciably larger that for the second, i.e., the stabilization of the dianion depends less on the nature of the annelated heterocycle.

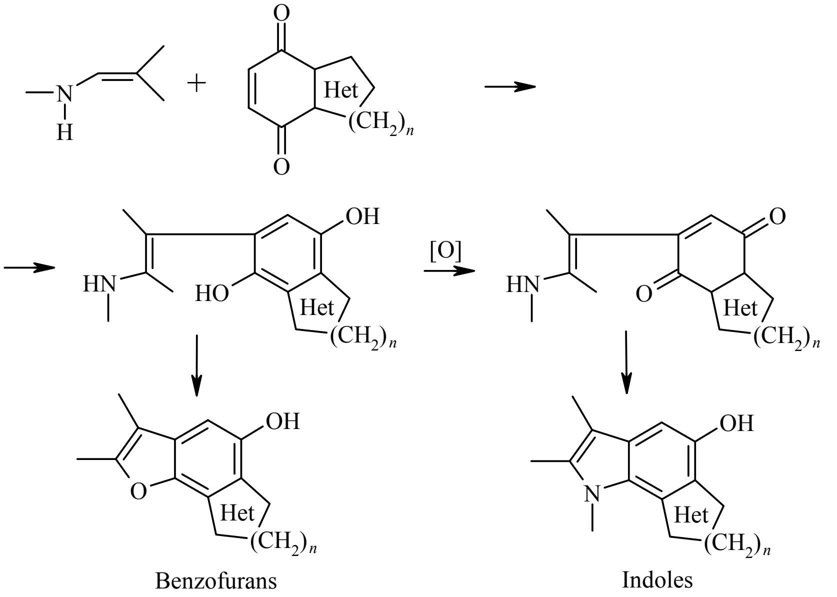
For the heterocyclic quinones that we investigated an analogy is also observed in the behavior with aromatic quinones after the addition of a proton donor to the aprotic medium. Phenol was used as proton donor. Here the second wave is shifted toward more positive potentials, and in the limit (in the transition to aqueous organic solvents) it merges with the first, forming one two-electron wave.

In 40% aqueous solutions of DMF, however, in a neutral medium with Bu_4NClO_4 as supporting electrolyte a difference in the behavior of the model and the investigated compounds is observed. For benzo- and naphthoquinones under these conditions one clear two-electron wave is obtained on the direct-current polarogram, and the corresponding peak is observed on the alternating-current curve. For all the investigated heterocyclic quinones the two-electron wave has a tendency to split, which appears on the alternating-current polarogram as two distinct peaks. It is only possible to eliminate such splitting in an acidic DMF–water medium at a pH of about 5. This means that the semiquinones of compounds **1**, **2**, **4**, **5**, **7**, and **8** are more stable than benzo- and naphthoquinones, and their complete protonation requires the presence of a stronger proton donor then water in the solution. The half-wave and peak potentials obtained in the DMF–water medium are given in Table 2.

These data indicate that in all cases the annelated heterocyclic fragments stabilize the semiquinone radical-anions and hinder their protonation, i.e., exhibit distinct electron-accepting characteristics. The obtained results do not correlate entirely with the data for the Nenitzescu reaction. Apparently, the quinones that are most easily reduced should have the strongest oxidizing power, and their use (if they and not other intermediates are the oxidizing agents in the Nenitzescu reaction) should lead to an increase in the degree of indolization compared with benzofuran cyclization.

TABLE 2. The Peak and Half-Wave Potentials of Quinones **1-8** in 40% Dimethylformamide

Compound	φ, V, of first peak	φ, V, second peak	$E_{1/2}$, V, DMF–acetone buffer, pH ~5
	0.02 M Bu_4NClO_4		
1	-0.20	-0.58	Dissolution of Hg
2	-0.35	-0.58	-0.06
4	-0.30	-0.55	-0.05
5	-0.21	-0.43	Maximum
6	-0.49		
7	-0.41	-0.62	-0.16
8	-0.35	-0.58	-0.19



This agrees well with the results obtained for compounds **1** and **2**; in the first case the formation of only indole derivatives is observed, and in the second both indole and benzofuran derivatives are formed. However, for the most difficultly reduced indazolequinone **7** and for the derivatives of isoquinoline **4** and benzofuran **5** that exist in the middle range of potentials the picture remains uncertain, since for compounds **7** and **5** cyclization takes place in both directions (with the formation of 5-hydroxyindoles and 5-hydroxybenzofurans), while for the isoquinolinequinones only benzofuran cyclization is observed. Thus, the picture is more complicated when the Nenitzescu reaction occurs; the oxidizing agents are probably not only the initial quinones but also quinone-containing intermediates that are formed (and, possibly, also other active forms of oxygen that are formed), and this requires further investigations.

EXPERIMENTAL

Polarography was performed on a PY-1 polarograph with a dropping mercury electrode having the following characteristics: drop time 3.5 sec, mercury flow rate 2.9 mg/sec, 0.1 N potassium chloride solution, open circuit. The supporting electrolytes were 0.1 M solutions of Bu_4NClO_4 in DMF and acetate buffer solutions in mixture with DMF. The Bu_4NClO_4 was obtained by precipitation from solutions of Bu_4NOH with perchloric acid and was crystallized from ethanol. The DMF was dried over calcined potassium carbonate and was then distilled under vacuum. The half-wave potentials were reduced to the saturated calomel electrode scale by comparison with $E_{1/2}$ of the K^+ ion using Vlcek's method [8]. The investigated quinones were prepared by known methods: Compound **1** by the method [9], **2** [10], **4** [11], **5** [12], **7** [13], **8** [14].

The work was supported by grant No. 99-03-32973 from the Russian Fundamental Research Fund.

REFERENCES

1. G. R. Alien, *Organic Reactions*, Wiley Interscience, New York (1973), Vol. 20, p. 337.
2. V. G. Granik, V. M. Lyubchanskaya, and T. I. Mukhanova, *Khim.-Farm. Zh.*, No. 6, 37 (1993).
3. C. Mann and K. Barnes, *Electrochemical Reactions in Nonaqueous Systems* [Russian translation], Khimiya, Moscow (1974), p. 187.
4. S. Wawzonek, R. Berkey, and M. Blaha, *J. Electrochem. Soc.*, **103**, 456 (1956).
5. I. Kolthoff and T. Reddy, *J. Electrochem. Soc.*, **108**, 980 (1961).
6. B. Eggins and J. Chambers, *Coll. Czech. Chem. Commun.*, **34**, 232 (1969).
7. V. D. Bezuglyi, L. Ya. Kheifets, E. R. Zakhs, and L. S. Efros, *Zh. Org. Khim.*, **2**, 1103 (1966).
8. A. Vlcek, *Coll. Czech. Chem. Commun.*, **20**, 980 (1955).
9. L. Weinberger and A. R. Day, *J. Org. Chem.*, **24**, 1451 (1959).
10. K. Fries and H. Reitz, *Liebigs Ann. Chem.*, **527**, 53 (1936).
11. G. R. Alien and M. Weiss, *J. Org. Chem.*, **33**, 198 (1968).
12. Y. Jnouye and H. Kakisawa, *Bull. Chem. Soc. Jpn.*, **42**, 3318 (1969).
13. V. M. Lyubchanskaya, L. M. Alekseeva, and V. G. Granik, *Tetrahedron*, **53**, 15005 (1997).
14. W. Middleton, H. Monney, and J. Parrick, *Synthesis*, **9**, 740 (1984).