Chemistry of Heterocyclic Compounds, Vol. 38, No. 11, 2002

STUDY OF OXIDATION–REDUCTION PROPERTIES AND NO-DONOR ABILITY OF DIENEDIAMINES IN THE INDOLE, PYRROLE, AND THIOPHENE SERIES

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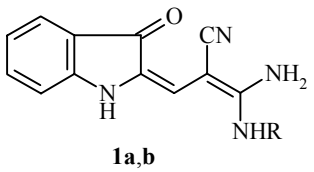
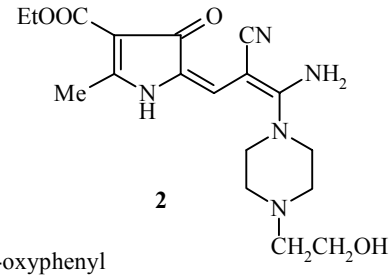
We have conducted an electrochemical study of the oxidation–reduction properties of synthesized dienediamines: derivatives of indole, pyrrole, and thiophene. We have established that reduction of the indicated compounds occurs with successive transfer of two electrons, the first transfer being reversible. We consider the effect of structural factors and the nature of the heterocycle on the ease of reduction of the given compounds. We present the results of an initial study of the NO-donor ability of the compounds upon oxidation.

Keywords: dienediamines of the 4,5-dihydrothiophen-4-one series, 2-indolinones and 3-indolinones, 2-pyrrolin-4-one, NO-donor ability, oxidation–reduction properties, synthesis, electrochemical study.

Earlier we developed a general method for synthesis of dienediamines **1** and **2**, derivatives of indole and pyrrole, based on reaction of different 2-(β,β-dicyanovinyl)-3-hydroxyheterocycles with amines [1-3].



1a,**b**



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1a R = CH_2Ph, **b** R = *o*-oxyphenyl

Using a similar scheme, we obtained dienediamines of a number of N-substituted oxindoles **3** [4], which are distinguished from compounds of type **1** by the fact that they do not contain a ketone group but rather have a cyclic amide group, conjugated with the diene moiety.

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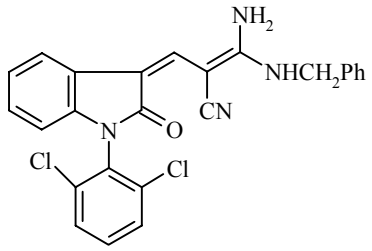

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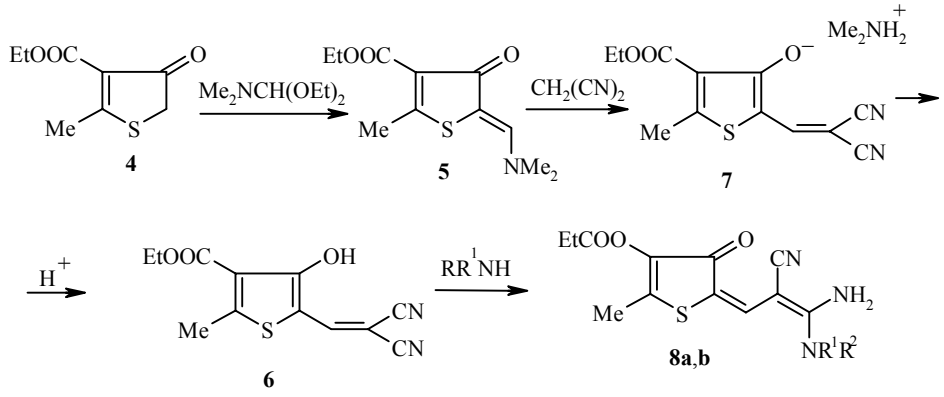
In this paper, the indicated method is extended to thiophene derivatives. Using the general scheme, we synthesized dienediamines of this series from 3-ethoxycarbonyl-2-methyl-4,5-dihydro-4-thiophenone (**4**) [5]. The latter condenses with diethylacetal DMF to form the 5-dimethylaminomethylene derivative **5** [6], from which upon reaction with malonodinitrile we obtain 5-β,β-dicyanovinyl-3-ethoxycarbonyl-4-hydroxy-2-methylthiophene (**6**), first isolated in the form of salt **7**. Then we react thiophene derivative **6** with amines, as a result of which thiophene analogs of compounds **1, 2** are formed: dienediamines **8a,b**.



8 a $R^1R^2 = –CH_2–CH_2–O–CH_2–CH_2–$, **b** $R^1 = H$, $R^2 = CH_2CH_2OH$

This work was devoted to study of the polarographic behavior of some of the indicated derivatives, and an initial study of the NO-donor ability of these compounds upon oxidation. We selected dienediamines **1a,b, 2, 3,** and **8a,b** as the objects of investigation.

The model compounds were 2-dimethylaminomethylene-3-indolinone (**9**), 3-dimethylaminomethylene-2-indolinone (**10**), 1,4-naphthoquinone (**11**), phenalenone (**12**) (for the polarographic behavior of compounds **9** and **10, 11, 12**, see [7, 8, 9] respectively). The structures of the studied compounds contain carbonyl groups conjugated with carbon–carbon double bonds. We know [8] that polarographic reduction of such compounds occurs by means of attack by an electron on the carbonyl group, followed by addition of a proton to form radical (**A**), which then again adds an electron and a proton, as a result of which saturated ketones are formed:

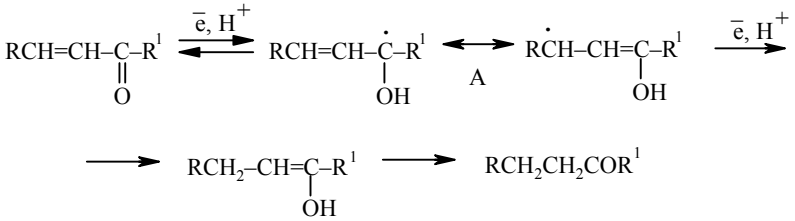
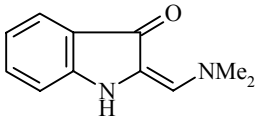


TABLE 1. Polarographic Characteristics of Studied Compounds

Compound	$\frac{i'}{C \cdot 10^3}$, μA, m	$E'_{1/2}$, V	$\frac{i''}{C \cdot 10^3}$, μA, m	$E''_{1/2}$, V	Compound	$\frac{i'}{C \cdot 10^3}$, μA, m	$E'_{1/2}$, V	$\frac{i''}{C \cdot 10^3}$, μA, m	$E''_{1/2}$, V
1a	0.73	-1.68	1.15	-2.24	**8b**	0.75	-1.61	1.14	-2.12
1b	—	—	—	—	**9**	1.2	-2.0		-2.66
2	0.64	-1.71	1.17	-2.48	**10**	1.33	-2.31	—	—
3	1.41	-1.97	—	—	**11**	1.4	-0.7	1.4	-1.42
8a	0.57	-1.56	0.9	-2.13	**12**	1.3	-1.2	1.3	-1.98

In [7], we studied the polarographic behavior of cyclic enaminoketones and enaminoamides: derivatives of 2-aminomethylene-3-indolinone and 3-aminomethylene-2-indolinone. We established that representatives of the first group of compounds (ketones of type **9**) are reduced in two steps, the first of which is a one-electron step and reversible, while derivatives of enaminoamides of type **10** are reduced in a single one-electron step.



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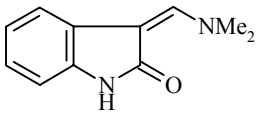

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The results of polarographic reduction of the compounds **1a, 2, 8a,b, 3** studied in this work are shown in Table 1. Compound **1b** is extremely easily oxidized in solution, and we were unable to take its polarogram. The derivatives **1a, 2, 8a,b** in anhydrous DMF are reduced in two steps. Based on comparison of the values of the proportionality coefficient in Ilkovic's equation for the first waves of the studied compounds and the first waves of the model compounds **9-12** and also controlled potential microcoulometry data, we established that the first electrochemical reduction step corresponds to transfer of ~0.5 electrons per molecule. In this case, the waves are diffusion-controlled and their slope corresponds to a reversible process.

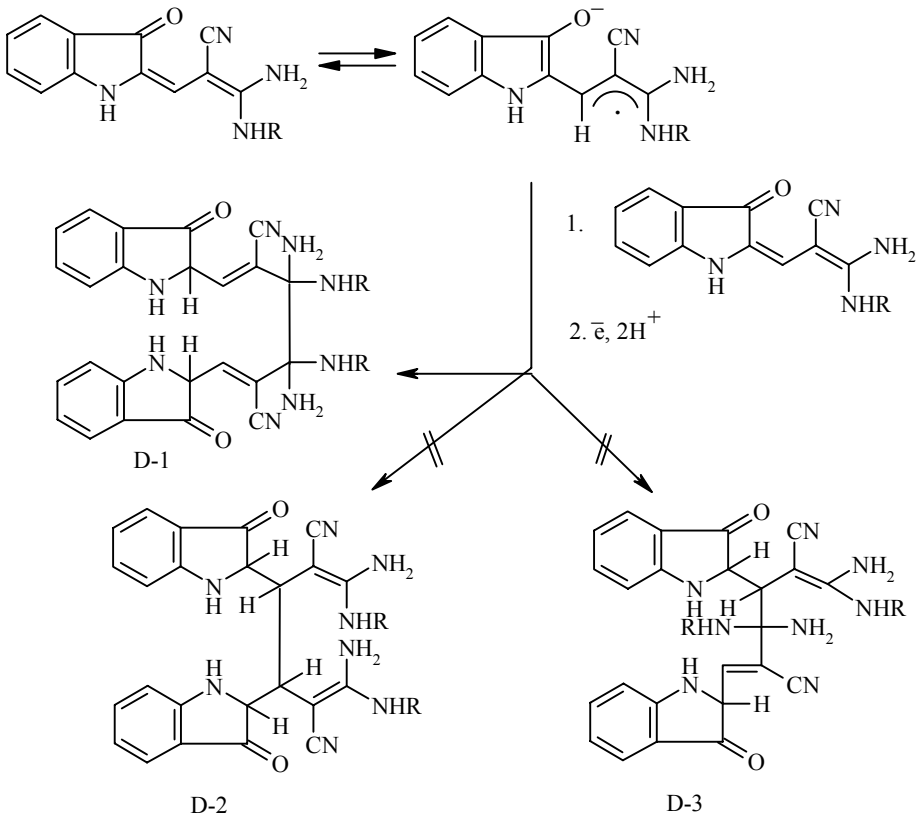
The second waves of compounds **1, 2, 8a,b** are one-electron, nonreversible waves. The nonintegral values of the determined number of electrons transferred in the first reduction step are probably explained by a rather fast chemical stage following the electron transfer involving reaction of the radical anion formed with a depolarizer molecule, evidence for which comes from the partially kinetic nature of the second wave. The dimer radical anion obtained in this way then picks up a second electron. Addition of a weak proton donor (phenol) to the solution of the polarographically active compound in an aprotic solvent leads to growth of the first wave to the one-electron level, i.e., the free radical formed upon protonation is so unstable that it can no longer react with the original depolarizer. The reduction scheme for the studied compounds can be supposedly represented by the Scheme 1.

Of the dimerization variants indicated on the scheme, the most likely from the steric standpoint (judging from construction of Dreiding and Stuart-Briegleb molecular models) is variant D-1. In the remaining cases (D-2 and D-3), steric hindrances arising upon formation of the dimer are much greater.

Comparison of the data from this polarographic study with literature data allows us to estimate the effect of individual structural moieties on the ease of electrochemical reduction of such systems in an aprotic solvent.

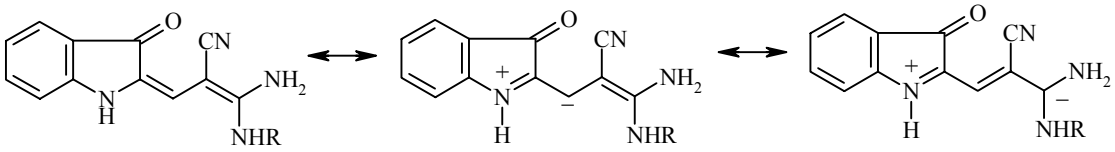
We know that extending the conjugated chain leads to more facile reduction [10]. Comparison of the polarographic characteristics of dienediamines with enamines **9** and **10** (see Table 1) supports this rule. It is important that the nature of the heterocycle also affects the ease of polarographic reduction. In our case, the

Scheme 1



compounds are arranged in the following sequence with regard to ease of reduction: thiophene > indole > pyrrole. This sequence agrees well with the maximum electron-acceptor effect of the sulfur atom in this series (and the corresponding ease of reduction) and coincides, for example, with the relative acidity of carboxylic acids of the same heterocycles: thiophene-2-carboxylic acid (p*K*a 3.52) is stronger than indole-2-carboxylic acid (p*K*a 3.75), and the lowest acidity appears in pyrrole-2-carboxylic acid (p*K*a 4.45) [11].

Another goal of this work was to evaluate the feasibility of the studied dienediamines acting as nitrogen oxide donors. We know [12] that in a living organism, NO is formed through oxidation of *L*-arginine by isoenzymes of NO-synthase. The specificity of this enzyme with respect to *L*-arginine is probably not absolute, since many derivatives of this amino acid and a whole series of compounds containing a guanidine moiety also undergo oxidation *in vitro* and *in vivo*, releasing nitrogen oxide [12]. Hence we can assume that it is specifically the degree of saturation by electrons of the guanidine moieties that is responsible for the possibility of their oxidation to NO. Furthermore, it was established earlier that among compounds (including those studied in this work) including a dienediamine moiety, there are compounds with antihypertensive activity that activate the soluble guanylatecyclase enzyme. Accordingly, it was interesting to evaluate their NO-producing activity, especially since their structures presume creation of partial negative charges along the chain of atoms of the diene system.



With this objective, we used the polarographic procedure described previously in [13], based on oxidation of the studied compound by potassium ferricyanide. The nitrogen oxide formed in this case is determined by differential-pulsed or a.c. polarography in the form of the polarographically active sodium nitroprusside, obtained according to the following scheme:

$$X + [Fe(CN)_6]^{3-} \rightarrow Y + [Fe(CN)_6]^{4-} + NO$$

$$NO + [Fe(CN)_6]^{3-} \rightarrow NO^+ + [Fe(CN)_6]^{4-} \rightarrow [Fe(CN)_5NO]^{2-} + CN^-$$

Among the compounds we investigated, compounds **1a,b,** and **2** can generate ~2% nitrogen oxide. Derivatives of 2-indolinone and 4,5-dihydrothiophen-4-one (**3** and **8a,b**) did not exhibit NO-donor capability. The latter circumstance seems quite important and possibly suggests that a cyclic NH group must be present in the system, directly added to the diene moiety of the system.

EXPERIMENTAL

Polarographic determinations were performed on a PU-1 polarograph with a dropping mercury electrode. The electrode open-circuit characteristics were: drop time 3.5 s, mercury flow rate 2.9 mg/s in a 0.1 N KCl solution. As the supporting electrolyte, we used citrate-phosphate buffer solutions (pH 4-5) and aqueous solutions of $HClO_4$ with different DMF contents. When working in anhydrous DMF, the supporting electrolyte was a 0.1 M solution of Bu_4NClO_4 in DMF. The DMF was dried above calcined potash and then was distilled under vacuum. Bu_4NClO_4 was obtained by precipitation with hydrochloric acid from Bu_4NOH solutions followed by crystallization from ethanol. The half-wave potentials were reduced to the saturated calomel electrode scale by comparing with $E_{1/2}$ of the K^+ ion according to the Vlcek method [14].

The IR spectra were obtained on a Perkin-Elmer 457 spectrometer in the form of vaseline oil mulls; the mass spectra were obtained on a Varian MAT-112 spectrometer (70 eV) with direct injection of the sample into the ion source. The course of the reactions was monitored chromatographically on Silufol UV-254 plates in the system chloroform—methanol, 10:1.

2-[2'-Cyanoprop-2'-enylidene-3'-(*o*-oxyphenylamino)]-3-indolinone (1b) was obtained analogously to the synthesis of dienediamine **1a** [1, 3]. The nitrile of α-cyano-β-(3-acetoxy-2-indoline)acrylic acid [15] (1.63 g, 6.5 mmol) and *o*-aminophenol (1.77 g, 16.2 mmol) were refluxed in 2-propanol (100 ml) for 3 h. The dark red precipitate formed was filtered out and washed with 2-propanol. Obtained 0.73 g (35.3%) of compound **1b**; mp 217-219°C. M^+ 318. Found, %: N 17.7. $C_{18}H_{14}N_4O_3$. Calculated, %: N 17.7.

5-{3'-Amino-2'-cyano-3'-[4-(β-hydroxyethyl)piperazino]}-3-ethoxycarbonyl-2-methyl-2-pyrrolin-4-one (2). A mixture of the nitrile of α-cyano-β-(3-ethoxycarbonyl-4-hydroxy-2-methylpyrrol-5-yl)acrylic acid [16] (0.5 g, 2 mmol) and N-(β-hydroxyethyl)piperazine (0.49 ml, 4 mmol) in 2-propanol (30 ml) was refluxed for 3 h. The mixture was allowed to stand for 16 h, then cooled using a water–ice mixture; the precipitate was filtered out, and 0.45 g (60%) of compound **2** was obtained; mp 211-213°C (methanol–dioxane, 1:4). M^+ 375. IR spectrum, ν, cm^{-1}: 3420, 3380, 2160, 1720, 1640. Found, %: C 57.9; H 6.9; N 18.9. $C_{18}H_{25}N_5O_4$. Calculated, %: C 57.7; H 6.7; N 18.7.

5-Dimethylaminomethylene-3-ethoxycarbonyl-2-methyl-4-oxo-4,5-dihydrothiophene (5) [6]. DMF diethylacetal (3.52 g, 24 mmol) was added dropwise to a solution of 3-ethoxycarbonyl-2-methyl-4-oxo-4,5-dihydrothiophene **4** [5] (3.8 g, 20 mmol) in high-boiling petroleum ether (10 ml). This was stirred for 7 h and cooled with ice. The precipitate was filtered out and 2.4 g (49%) of compound **5** was obtained; mp 123-125°C (petroleum ether–benzene, 1:1). M^+ 241. IR spectrum, ν, cm^{-1}: 1690, 1660. Found, %: C 54.9; H 6.4; N 6.0; S 13.2. $C_{11}H_{15}NO_3S$. Calculated, %: C 54.8; H 6.3; N 5.8; S 13.3.

Nitrile of α-Cyano-β-(3-ethoxycarbonyl-4-hydroxy-2-methylthiophen-5-yl)acrylic Acid (6). A solution of compound **5** (0.5 g, 2 mmol) and malonodinitrile (0.2 g, 3 mmol) in benzene (30 ml) was stirred for 3 h and allowed to stand for 16 h. The precipitate was filtered out, washed on the filter with cold ether; 0.5 g (82%) of the acid **6** dimethylamine salt (compound **7**) was obtained; mp 130-131°C (benzene). M^+ 307. IR spectrum, ν, cm^{-1}: 2190, 1720, 1570. Found, %: C 54.8; H 5.6; N 13.6; S 10.8. $C_{14}H_{17}N_3O_3S$. Calculated, %: C 54.7; H 5.6; N 13.7; S 10.4.

An HCl solution (1:1) was added to a solution of (0.65 g, 2 mmol) of the obtained salt **7** in 2-propanol (20 ml) while cooling with a mixture of water and ice until it tested acid according to a universal indicator. The mixture was held for 30 min. The precipitate was filtered out, washed with water; 0.45 g (86%) of compound **6** was obtained; mp 185-187°C (2-propanol). M^+ 262. IR spectrum, ν, cm^{-1}: 3200, 2210, 1670, 1570. Found, %: C 55.2; H 4.0; N 10.8; S 12.3. $C_{12}H_{10}N_2O_3S$. Calculated, %: C 55.0; H 3.8; N 10.7; S 12.2.

5-(3'-Amino-2'-cyano-3'-morpholinoprop-2'-enylidene)-3-ethoxycarbonyl-2-methyl-4-oxo-4,5-dihydrothiophene (8a) and 5-[3'-Amino-2'-cyano-3'-(β-hydroxyethylamino)prop-2'-enylidene]-3-ethoxycarbonyl-2-methyl-4-oxo-4,5-dihydrothiophene (8b) were obtained analogously to compound **2** from the nitrile of acrylic acid **6**, morpholine (for **8a**) and monoethanolamine (for **8b**). Yield of **8a** 98%; mp 210-211°C (methanol). M^+ 349. IR spectrum, ν, cm^{-1}: 3320, 2200, 1680. Found, %: C 55.3; H 5.5; N 11.7; S 9.4. $C_{16}H_{19}N_3O_4S$. Calculated, %: C 55.0; H 5.5; N 12.0; S 9.2. Yield of **8b** 75%; mp 151-153°C (methanol). M^+ 323. IR spectrum, ν, cm^{-1}: 3320, 2190, 1670. Found, %: C 52.0, H 5.4, N 13.1, S 9.8. $C_{14}H_{17}N_3O_4S$. Calculated, %: C 52.0; H 5.3; N 13.0; S 10.0.

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