On the reduction of 1-aryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole 4-oxides

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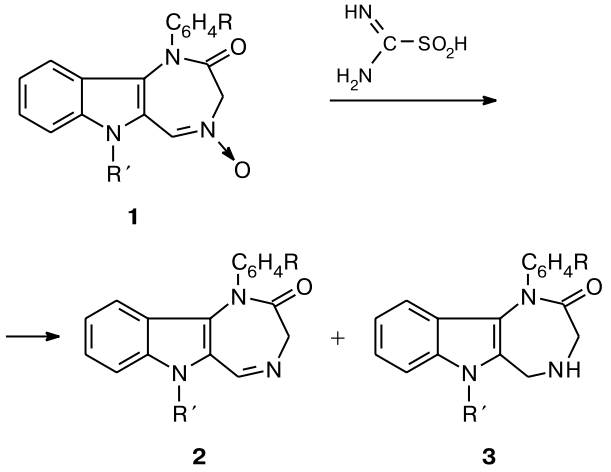
Electrochemical reduction of 1-aryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole 4-oxides, 2-oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole, and 2-oxo-1-phenyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole was studied. The results obtained were compared with previous data for the reduction of 4-oxides with formamidinesulfinic acid.

Key words: [1,4]diazepino[6,5-*b*]indole 4-oxide, formamidinesulfinic acid, electrochemical reduction.

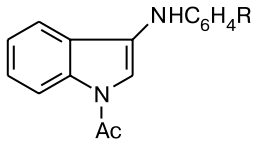
Recently,[1,2] we have developed a new approach to the synthesis of [1,4]diazepino[6,5-*b*]indole 4-oxides and studied their reduction with various agents, including formamidinesulfinic acid.

Both tetra- and hexahydrodiazepinoindoles can be obtained, depending on the reducing agent. Reduction of cyclic nitrones such as [1,4]diazepino[6,5-*b*]indole 4-oxides **1** with formamidinesulfinic acid (used for the first time for this purpose) afforded mixtures of tetrahydro- (**2**) and hexahydro[1,4]diazepino[6,5-*b*]indoles (**3**) (Scheme 1). It was found that the *para*-substituents R in the phenyl group bound to the N(1) atom noticeably affect the reaction outcome, although they are very distant from the reactive site. It was demonstrated[1,2] that the reduction of the N(4)=C(5) bond is favored by electron-withdrawing substituents but prevented by electron-donating ones. The significant role of the substituent was attributed to the known positive bridging effect[3,4] characteristic of compounds with two aromatic fragments (here, benzene and indole) bridged by an O, S, or N atom (as in our case). Such aromatic fragments have the tendency toward efficient p—π conjugation.[3,4]

Scheme 1



The reality of this effect in a system containing a 3-arylaminoindole fragment was proved by our ^{1}H NMR study[5] of deuterium exchange in 1-acetyl-3-arylaminoindoles (**4a,b**). The deuterium-exchange rate was higher for compound **4b** (R = 4-Cl): its ^{1}H NMR spectrum recorded in CD_3COOD immediately upon the dissolution showed no signal for the indole C(2)H proton. The slower deuterium exchange in indole **4a** than in **4b** is probably due to the electron-withdrawing effect of the NO_2 group, which weakens the electron-donating effect of the *exo*-NH fragment.



4a,b

R = 4-NO_2 (**a**), Cl (**b**)

Thus, the *para*-substituent R in the phenyl group affects the electron density at position 2 of the indole system even in 3-arylaminoindoles and we do not find it surprising that this effect extends to the C=N bond at position 2 of the indole fragment in diazepinoindoles **1**.

The goal of the present work was to compare the results obtained by chemical (with formamidinesulfinic acid) and electrochemical reduction of diazepinoindoles **1**.

The redox properties of *N*-oxides of aromatic heterocycles, tertiary amines, and azomethine derivatives have been documented.[6,7] The effect of the nature of the substituent on the half-wave potential ($E_{1/2}$) of the reduction

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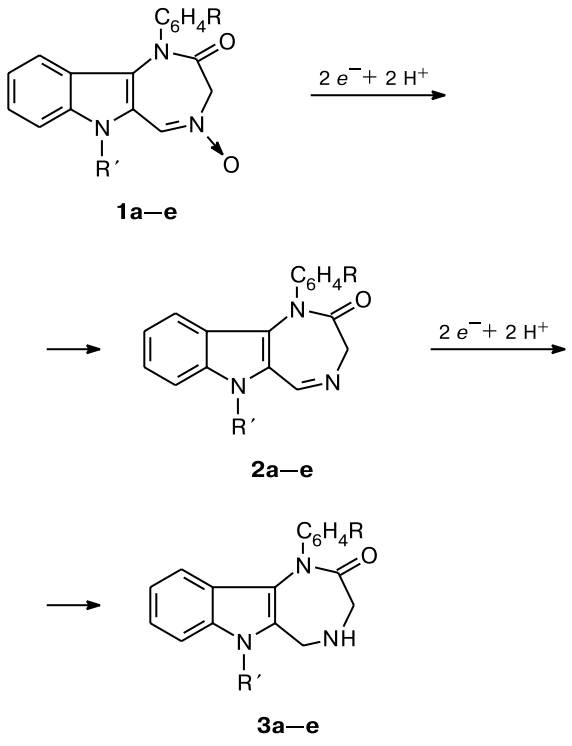
of the *N*-oxide group was studied for aromatic heterocyclic *N*-oxides.[6,7] It was found that the reduction of *N*-oxide group is hindered by electron-donating substituents ($E_{1/2}$ is shifted in the negative direction) but facilitated by electron-withdrawing groups and more benzene rings fused with the heterocycle.

Structurally, [1,4]diazepino[6,5-*b*]indole *N*-oxides **1** are cyclic nitrones. Because of this, it was of interest to investigate their reducibility by polarography and study the role of the substituent in the reduction of the *N*-oxide group and the C=N bond. The data obtained would be used to estimate the degree of conjugation between the aryl substituent and the N→O and C=N groups.

1-Aryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole 4-oxides (**1a**—**e**) and **1f** (R = 4-NO_2, R′ = H), 2-oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole (**2a**), and 2-oxo-1-phenyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (**3a**) were studied by polarography (Scheme 2).

Scheme 2



R = H (**a**), 4-OEt (**b**), 4-CN (**c**), H (**d**), 4-Cl (**e**)
R′ = H (**a—c, e**), Me (**d**)

In anhydrous DMF with $LiClO_4$ or $Bu_4N^+ClO_4^-$ as supporting electrolytes, the *N*-oxide groups of oxides **1a**—**f** are polarographically inactive. Aliphatic nitrones behave analogously.[6] Under these conditions, only a one-electron polarographic wave for the NO_2 group in compound **1f** was recorded. Addition of weak proton donors such as phenol or citric acid to anhydrous DMF did not activate the N→O group of these compounds. A different pattern was obtained only in the presence of strong mineral acid ($HClO_4$): one approx. four-electron wave was recorded for compounds **1a**—**f**, the $E_{1/2}$ of which depends on the concentration of the acid. Such a pattern can be due to the weak basicity of the N→O group in the compounds under consideration.

The four-electron process was divided into two two-electron ones in a mixed aqueous-organic solvent in the presence of a buffer (CH_3COONa—HCl, pH 1.90). Potentials $E_{1/2}$ were measured in two series: in DMF—ethanol—buffer (15 : 35 : 50) and acetonitrile (AN)—buffer (50 : 50).

In both cases, two irreversible two-electron waves were recorded for compounds **1a**—**e**. The irreversibility of these waves was concluded from the slope of the plot

$$\log[i/(i_d - i)] \textit{ vs. } E$$

(i_d is the diffusion current) and from the half-width of the peak in the differential pulse polarogram.[9]

The number of transferred electrons was calculated by the Ilkovic equation and compared with that for phenalenone and benzanthrone, which are close in molecular size and hence diffusion coefficient (the sum of their two waves in mixed aqueous-organic solvents corresponds to the transfer of two electrons[10]).

The diffusion character of both waves was determined from the slope of the plot of their amplitude *vs.* the mercury column height and from the temperature dependence of the limiting currents (1.7 to 2.5% per °C).

To elucidate the nature of electrochemical processes behind the recorded waves, compounds **2a** (containing no *N*-oxide group) and **3a** (with the reduced double bond in the diazepine ring) were studied under the above conditions. The data obtained were compared with those for the reduction of *N*-oxides **1**. The polarogram of compound **2a** ($E_{1/2}$ = −0.70 eV) shows one two-electron wave at the potential of the second wave for compounds **1a**—**e**. Compound **3a** is polarographically inactive in the potential range studied. Therefore, the second wave for compounds **1a**—**e** corresponds to reduction of the double bond in the diazepine ring, while the first wave is due to reduction of the *N*-oxide group.

As with other *N*-oxides, the two-electron wave (in contrast to the case of anhydrous DMF) for NO_2-containing compound **1f** in acidic aqueous-organic solutions appears at the potential of the polarographic waves for the N→O group in compounds **1a**—**e**. For this reason, this wave should be assigned to the reduction of the N→O group of *N*-oxide **1f**. Unlike oxides **1a**—**e**, this compound gives a four-electron second wave corresponding either to complete reduction of the NO_2 group or its partial reduction with parallel hydrogenation of the double bond of the diazepine ring.

Table 1. Polarographic data for compounds **1a—f**

Compound	$-E_{1/2}$/V (pH 1.90)			
	DMF—ethanolic buffer		AN—buffer	
	wave I	wave II	wave I	wave II
1a	0.55	0.78	0.47	0.72
1b	0.54	0.78	0.50	0.78
1c	0.54	0.75	0.50	0.73
1d	0.52	0.70	0.45	0.63
1e	0.54	0.76	0.54	0.76
1f	0.55	0.76	0.48	—

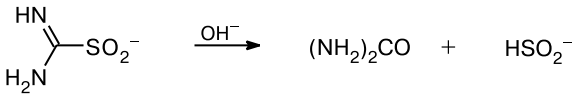
Polarographic data are summarized in Table 1. One can see that the $E_{1/2}$ values for the reduction of *N*-oxide groups are not affected by the substituents in the aryl ring, which suggests the absence of noticeable conjugation between the aryl and N→O groups.

Thus, the data obtained in the reduction of *N*-oxides **1a—f** with formamidinesulfinic acid and our polarographic data are in conflict. According to the former, the nature of the *para*-substituent in the benzene ring exerts a small but distinct effect on the degree of reduction of *N*-oxides **1a—f**. According to the latter, as shown above, the substituent does not affect the half-wave potential ($E_{1/2}$) due to the reduction of the *N*-oxide group and the C=N bond.

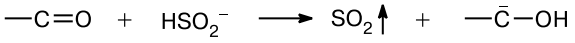
Formamidinesulfinic acid is known to be a rather strong reducing agent; it was also repeatedly reported that the true reducing agent is the HSO_2^- anion formed upon its decomposition in alkaline medium[11] (Scheme 3).

The tentative mechanism of the reduction of carbonyl-containing compounds[8] involves transfer of the hydride ion to the carbonyl O atom (Scheme 4).

Scheme 3



Scheme 4



Under the assumption that such a process limits the reduction rate of *N*-oxides **1a—e**, the reaction mechanism can be represented by Scheme 5.

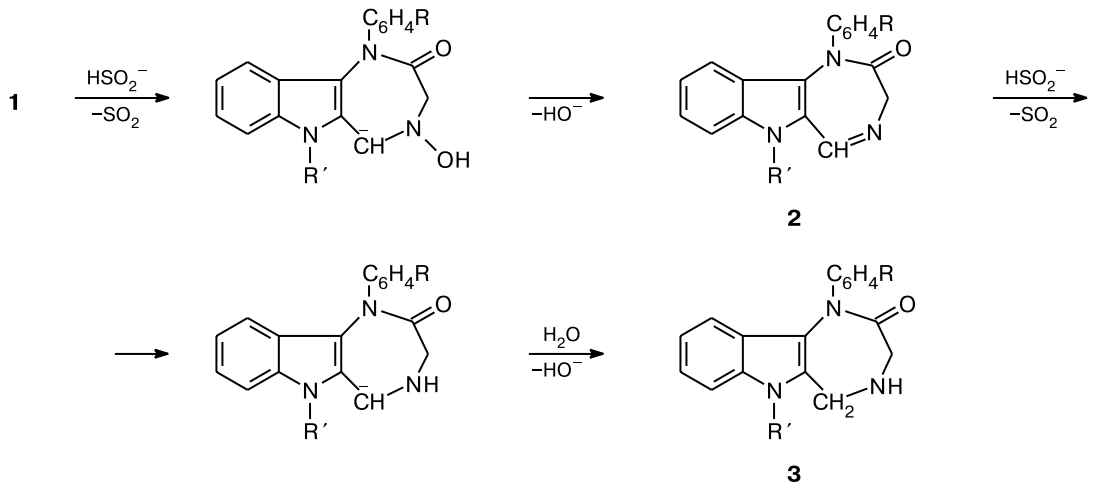
The fundamental difference between chemical reduction with formamidinesulfinic acid and electrochemical reduction is that the former requires strongly alkaline medium, while polarographic reduction exclusively occurs only in the presence of strong acids. The latter circumstance suggests that preprotonation of the starting depolarizer in electrochemical reduction should be taken into account.

Apparently, the electrochemical reduction mechanism can be represented by Scheme 6.

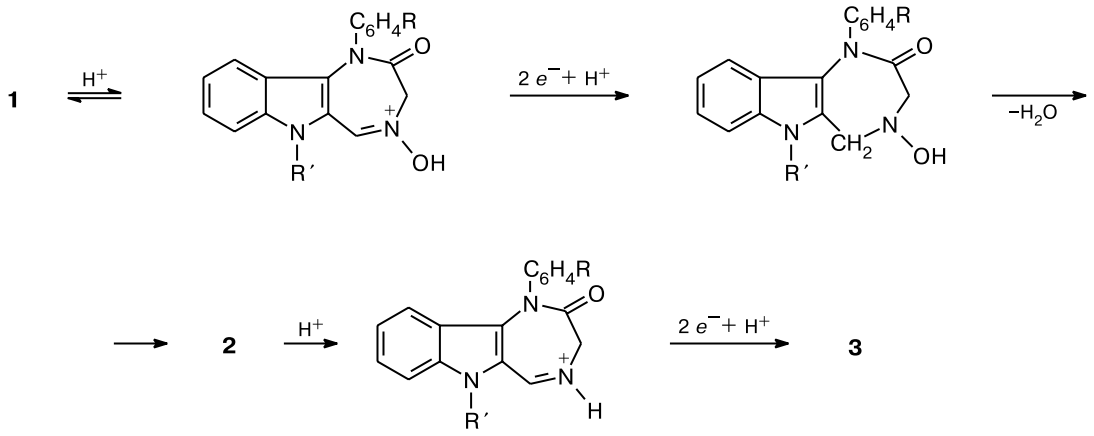
Schemes 5 (chemical reduction) and 6 (electron transfer in polarographic study) differ as follows: in the reduction with formamidinesulfinic acid, an integer negative charge is localized at the C(5) atom, while in the electrochemical reduction, the more electronegative N(4) atom bears a partial positive charge.

Obviously, the C(5) atom is the reactive site involved in an electron interaction with the *para*-substituents R in the 1-aryl group. Hence, the effect of these substituents will be more pronounced in the reduction with formamidinesulfinic acid. In this case, the interaction of

Scheme 5



Scheme 6



the substituent R with the negatively charged C(5) atom is much stronger than the effect of the substituent R on the uncharged C atom. It was because of this that the substituent had a certain effect on the course of the chemical reduction: as noted above, electron-withdrawing substituents favor the deeper reduction, while electron-donating ones act in an opposite way.

At the same time, the weaker interaction of the substituent with the reactive site under polarographic conditions confines possible differences between the compounds within the experimental error.

Experimental

Compounds **1a**—**f**, **2a**, and **3a** were synthesized as described earlier.[1,2] Polarographic measurements were carried out in a temperature-controlled cell (25±0.1 °C). The working electrode was a dropping mercury electrode (mass flow rate of Hg 2.9 mg s^{-1}, drop lifetime 3.5 s). The reference electrode was a saturated calomel electrode (sat.c.e.) connected to the test solution by an electrolytic bridge. An acetate buffer solution with pH 1.9 was used as a blank electrolyte. The potentials of the compounds studied were referenced to sat.c.e. in the "standard" potassium scale. Polarograms were recorded on a PU-1 polarograph. Dimethylformamide was distilled *in vacuo*; acetonitrile (special purity grade) was used without additional purification.

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