POLAROGRAPHY OF HETEROCYCLIC COMPOUNDS

II.* HETEROETHYLENE AND HETEROPARAFFIN COMPOUNDS. EFFECT OF SUBSTITUENTS IN THE SIDE CHAIN ON PARAMETERS FOR THE ELECTROREDUCTION OF HETEROCYCLIC COMPOUNDS (REVIEW)

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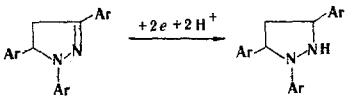
The literature data on the principles of the electrochemical reduction of heteroethylene and heteroparaffin compounds (pyrazoline, diazepine, diaziridine, pyran, pyridazone, aziridine, oxaziridine, and other derivatives), cyclic anhydrides, imides, and hydrazides of acids on a dropping mercury electrode are correlated. In addition, the effect of substituents attached to the heterocyclic ring on the polarographic behavior of heterocycles is analyzed.

Heteroethylene Systems

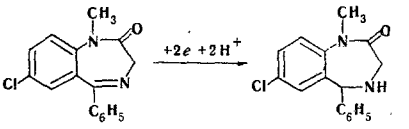
Considerably less study has been devoted to heteroethylene systems than to heteroaromatic compounds in a polarographic respect. Electrochemical reduction consists either in saturation of a double bond – usually the C=N bond – or in the reduction of an electrically active group, which may also be conjugated with the ring double bond, attached to the heteroring. The presence of a sufficient number of conjugated bonds or high polarizability of the molecule is necessary to confer electrochemical activity on the heteroring. We refer to Δ^2-pyrazoline derivatives as an example of polarographically active heteroethylene compounds.

Pyrazolines that are unsubstituted in the 3 position or substituted with a methyl group do not have polarographic activity. The introduction of a phenyl group or of heteroaromatic groups into the 3 position leads to the appearance of a wave for the reduction of the azomethine bond at –2.0 V with the consumption of two electrons [2-4].



Like 1,3,5-triphenyl-Δ^2-pyrazoline, all of its heterocyclic analogs have polarographic activity. The investigated heteroaromatic residues are electron acceptors with respect to the pyrazoline ring, and their electron-acceptor properties increase in the order α-furyl, α-thienyl, α-selenienyl; this is manifested in a decrease in the reduction potential of the corresponding pyrazoline derivatives (–2.14, –2.07, and –2.03 V). Because of its remoteness from the reaction center, a substituent in the 5 position has a weak effect on the reduction of the C=N group, and only its inductive effect is the deciding factor in this case [3].

The polarographic reduction of 1,4-benzodiazepines also apparently consists in saturation of the C=N bond [5]. The reduction proceeds with the addition of two electrons and two protons, for example:



*See [1] for part I of this review.

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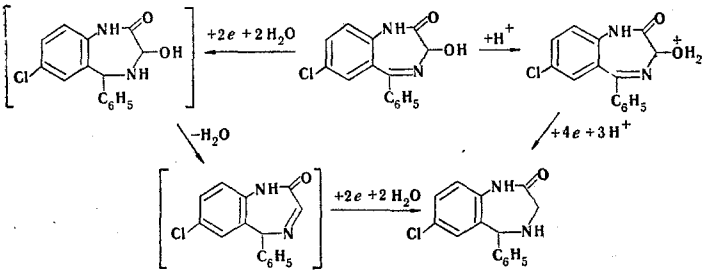
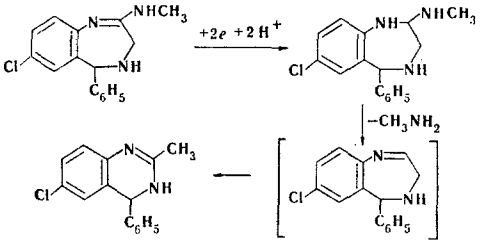
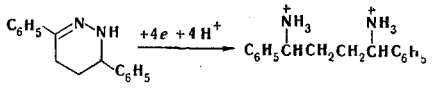
The reduction of 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one ("oxazepam") has been studied more thoroughly [6]. The half-wave potential ($E_{1/2}$) lies in the interval −1.0 to −1.2 V. In acidic media, oxazepam is reduced with the addition of four electrons to 7-chloro-5-phenyl-1,3,4,5-tetrahydro-1,4-benzodiazepin-2-one. In alkaline media, it undergoes 2e reduction to the 4,5-dihydro derivative:



One 2e wave ($E_{1/2}$ −1.45 V), which is ascribable to reduction of the C=N bond, is observed in the reduction of 7-chloro-2-methylamino-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine [7]. As a result of this reduction, the ring undergoes contraction to give 6-chloro-2-methyl-4-phenyl-3,4-dihydroquinazoline:

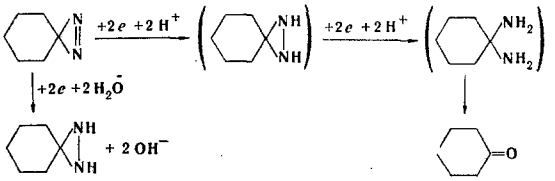


Cleavage of the N−N bond of the heteroring is responsible for the electrochemical activity of 3,6-diphenyl-2,3,4,5-tetrahydropyridazine [8, 9] in acidic media:



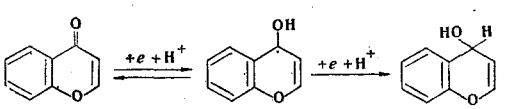
The electroreduction of 3,3-pentamethylenediazirine in alkaline media at −1.5 V consists in 2e saturation of the N=N bond to give the corresponding diaziridine [10].

However, in acid media (at −1.3 V) this compound undergoes 4e reduction. Cyclohexanone and ammonia were isolated in the hydrolysis of the products of the electrochemical reaction:



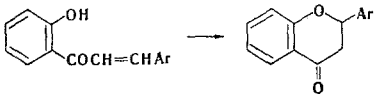
Of the heteroethylene derivatives, those in which the double bonds of the heteroring are conjugated with the carbonyl group seem of greatest interest.

γ-Pyrone [11] and chromone [12] are reduced irreversibly with the consumption of two electrons, and the corresponding alcohol is apparently formed:



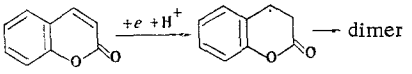
Benzopyrones, particularly flavones, give, at −0.9 to −1.3 V, a reversible 1e wave with subsequent dimerization of the resulting free radical; a second reduction wave is also observed at higher pH values, and both waves sometimes merge into an overall 2e wave [13-15].

Flavanones give a 2e wave at somewhat greater negative potentials than flavones, and this wave is also due to reduction to the alcohol. Isoflavones are reduced irreversibly with the consumption of two electrons. The more negative (than in the case of flavones) reduction potentials (from −1.1 to −1.5 V) and the distinctly expressed competition between the electroreduction waves of the protonated and unprotonated carbonyl groups in the medium pH range make it possible to polarographically distinguish isoflavones from flavones [14]. A polarographic method was used to follow the isomerization of o-hydroxychalcone to choromanone (i.e., into flavanone and its heterocyclic analogs containing furan, thiophene, pyrrole, and pyridine residues), since the $E_{1/2}$ values of the starting compounds and final isomerization products differ substantially from one another [15]:

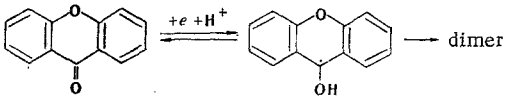


Ar		
phenyl	−0.69 V	−1.08 V
α-thienyl	−0.61 V	−1.07 V
α-furyl	−0.67 V	−1.10 V

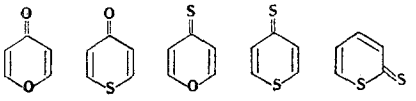
Since substituted flavones and isoflavones are encountered in the plant world in the form of glucosides and have high physiological activity, polarographic methods for the determination of compounds of this series have been developed (for example, see [16]).



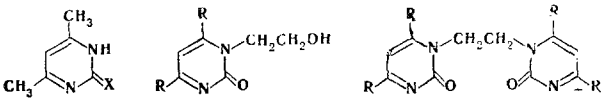
Coumarin is reduced [12, 17-21] at $E_{1/2}$ −1.53 V with the consumption of one electron and subsequent dimerization. Controlled-potential electrolysis gives two high-melting lactones, which are probably the meso- and d*l* -dimers [18]. β-Hydroxycoumarin is polarographically inactive, while β-methoxycoumarin gives a 2e wave with saturation of the C=C bond (probably because of steric hindrance to the dimerization reaction [12]). Xanthone is reduced in a 1e reversible process at $E_{1/2}$ −0.91 V with subsequent dimerization of the radical [22].



The thio and thia analogs of γ-pyrones also have polarographic activity. However, no linear correlation between the corresponding $E_{1/2}$ values and the energies of the lower vacant MO was detected [22]; this indicates different reduction mechanisms and different adsorption characteristics of the individual representatives of the series.

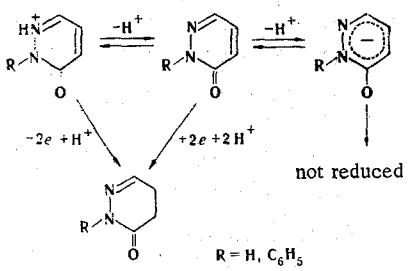


Pyrimidones and thiopyrimidones in aqueous methanol media give a wave in the interval −1.0 to −1.7 V, depending on the pH, with transfer of one electron, after which there is rapid dimerization of the resulting radicals [23, 24]. In a number of cases, anomalous waves associated with adsorption on the dropping mercury electrode (DME) of the dimeric electroreduction products appear. The introduction of electron-donor groups into the 4 position in principle hinders electroreduction, but, because of the possibility of surface protonation, 6-amino-2-pyrimidone (cytosine) and the corresponding nucleotides and nucleosides are reduced on the DME surface [24-27] (see part I of this review). On the other hand, uracil does not give a reduction wave. 6-Azauracil and 6-azauridine are reduced in the protonated form at −1.3 to −1.4 V, and the wave decreases and gradually becomes a kinetic wave as the pH increases [28, 29]. The possibilities of polarography in the study of heterocyclic bases of nucleic acids were examined in a paper by Berg and co-authors [30].

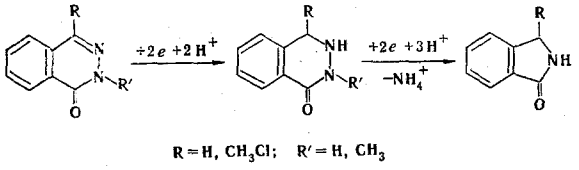


X = O, S; R = H, CH_3

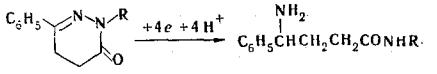
In acidic media, 6-methyl-3-pyridazone is reduced in two 2e stages (at −0.7 and −0.9 V, respectively), which in the medium pH range merge into one 4e wave; in alkaline media, the compound gives only one 2e wave [31]. The first 2e step leads to 6-methyl-4,5-dihydro-3-pyridazone, while the second wave, in the opinion of Pflegel and Wagner [31], is due to ring opening (cleavage of the N−N bond). However, the problem of the cleavage of the N−N bond in the pyridazone ring is still an open question, at least for 6-pyridazones that do not have an electron-acceptor substituent in the 4 and 5 positions of the ring, if they are investigated on a short-period DME. The following scheme for the electroreduction of substituted 6-pyridazones was substantiated in [32]. This sort of mechanism is observed in both protogenic and aprotic solvents. The polarographic method can be used for the analytical determination of the herbicide phenazone (pyramine, chlorazone) [33, 34].



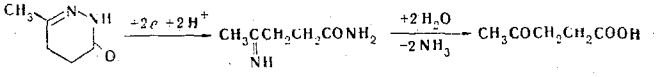
1(2H)-Phthalazinones and the potential primary products of their electroreduction – 3,4-dihydro-1(2H)-phthalazinones – which are reduced in acidic media to phthalimidines with the formation of two 2e waves, have been more thoroughly studied. 2-Phenyl-substituted derivatives give only the first stage of reduction [35].



5-Phenylpyridazinones are reduced with ring opening [9]:

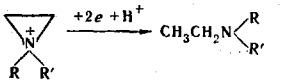


The same thing is also observed in the case of 6-alkylpyridazinones, only here the azomethine derivative formed in the first step undergoes hydrolysis [9]:

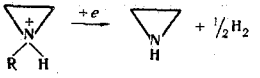


Saturated Heterocycles (Heteroparaffin Compounds)

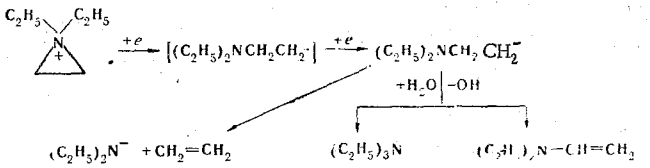
Of the saturated heterocycles, only single representatives, for example, ethyleneimine (aziridine) derivatives, have polarographic activity. In the opinion of Mantsavinos and Christian [36], the electroreduction waves observed in the interval −1.1 to −1.2 V are due to 2e reductive cleavage of the aziridine ring to give a trialkylamine:



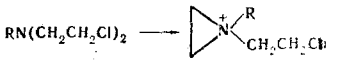
However, one cannot exclude the possibility that the waves are due to catalytic evolution of hydrogen via the following scheme [37]:



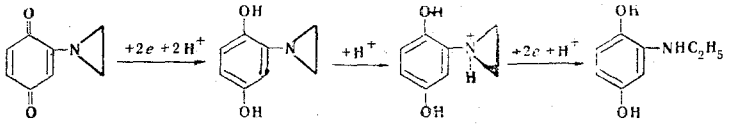
It has been shown in [38] that N,N-diethylaziridinium perchlorate is reduced in aqueous solution in one 2e step at about −1.5 V. One-electron cleavage of the aziridine ring to give a free radical, which is then reduced to a carbanion, apparently occurs initially. The resulting carbanion can either react with water (or with unreduced aziridinium ion) or decompose to give a diethylamine anion and ethylene:



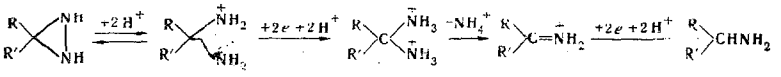
Polarography was used to study the cyclization of β-chlorodiethylamines, which is responsible for the development of the cytostatic activity of this series of compounds [39]:



Cytostatic agents containing a quinone group along with an aziridine ring give the reduction wave of the quinone ring and, in addition – at greater cathode potentials – a wave for the reduction of the aziridine ring, which has kinetic character, determined by the rate of protonation of the aziridine ring [40-44]. Under certain conditions, the second wave is due to catalytic evolution of hydrogen.



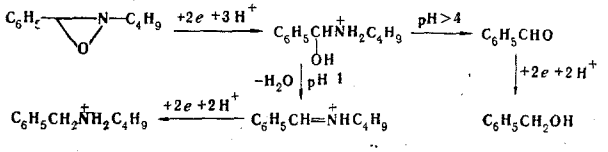
Diaziridines are reduced on a DME in two 2e steps (at −0.4 to −1.0 V and at −1.3 to −1.5 V, respectively) [45].



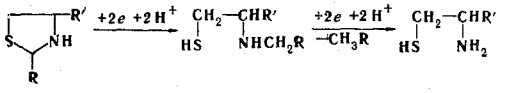
The dication formed as a result of cleavage of the N−N bond is extremely unstable and decomposes rapidly to give an imine, which is reduced in the second step to an amine. The isohydrazones of cyclohexanone and methyl ethyl ketone [45] are reduced specifically via this scheme [45].

It follows from a comparison of the $E_{1/2}$ values of diaziridines with the $E_{1/2}$ values of some substituted hydrazines and hydrazones that the electrochemical cleavage of the N−N bond in a three-membered ring occurs considerably more readily (by 200 mV) than in a noncyclic structure. The corresponding waves are markedly complicated by adsorption of the components of the electrochemical reaction.

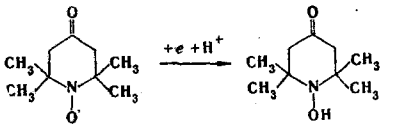
Oxaziridines are readily reduced on a DME [46], and their polarographic waves are begun by the wave for the dissolving of mercury. 2-tert-Butyl-3-phenyloxaziridine gives three waves. The first wave (about −0.3 V) corresponds to reduction to the gem-amino alcohol, which is dehydrated at low pH values to give a Schiff base, but is deaminated at higher pH values to give a carbonyl compound. Both products can be reduced further.



In a study of pyridoxine derivatives [47, 48] it was shown that the product of condensation of pyridoxal with cysteine – 2-(2-methyl-3-hydroxy-5-hydroxymethyl-4-pyridyl)thiazolidine-4-carboxylic acid – is reduced in two 2e steps at −0.5 to −0.7 V and −1.1 to −1.4 V, respectively, as a result of which the thiazolidine ring is opened.



The distinct 1e polarographic waves at sufficiently positive potentials (about −0.3 V) give stable iminoxyl free radicals, which are irreversibly reduced on a DME to the corresponding hydroxylamine derivatives [49].

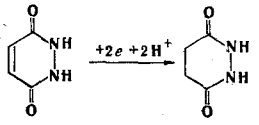


Cyclic Anhydrides, Imides, and Hydrazides of Acids

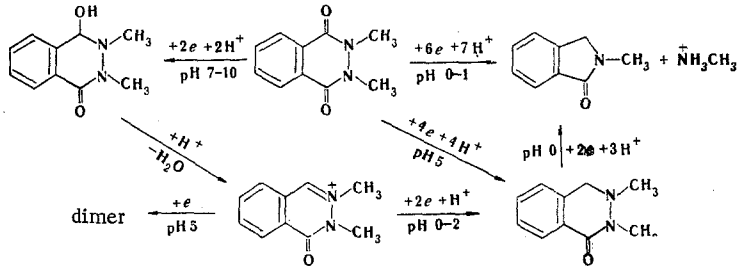
Formally speaking, cyclic anhydrides, imides, and hydrazides of dibasic acids can also be classified as heterocyclic compounds. The electroreduction of maleic, phthalic, and pyromellitic anhydrides, etc., in aprotic media leads to anion radicals with transfer of one electron [15]. The C=C bond is saturated in aqueous media [51].

In acidic media, phthalimides are reduced with the consumption of two electrons, while in alkaline media the 2e wave is split into two 1e waves [52, 53]. It is assumed that the result of the process is reduction to hydroxyphthalimidine, although the possibility of saturation of the C=C bond of the phthaloyl ring has also been discussed [52]. The polarographic activity of phthalimides was used for the study of the kinetics of hydrolytic cleavage of the phthalimide ring in numerous derivatives of this type [54-56].

Cyclic maleic hydrazide (pyridazinedione) is reduced to succinic acid hydrazides with the formation of several waves at −0.8 to −1.8 V, depending on the pH. The absence of an anode oxidation peak indicates that there is no diazahydroquinone in solution and that it cannot be formed [57, 58].



The corresponding cyclic phthalylhydrazides, according to the data in [59], are polarographically inactive, since conjugation with the phenylene ring stabilizes them. However, Lund has found that they are reduced in a 6e process to phthalimidine in acidic media at $E_{1/2}$ = −1.0 V [60].

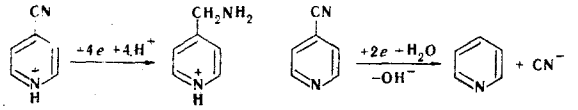


Heteroaromatic Compounds with an Electroactive Functional Group in the Side Chain

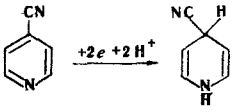
Heterocyclic compounds, in the course of the polarographic reduction of which an electrically active substituent added to the heteroring rather than the heteroring itself is involved, undoubtedly constitute the most important group of compounds of the greatest diversity. This classification includes diverse heteroaromatic aldehydes, ketones, amides, hydrazides, aldimines, ketimines, halo derivatives, nitro compounds, azo compounds, disulfides, etc., and derivatives of not only π-deficient (electroactive) heteroaromatic systems (such as pyridine, quinoline, pyrimidine, purine, etc.) but also derivatives of π-surplus (inactive in a polarographic respect) heteroaromatic systems (such as pyrrole, furan, thiophene, thiazole, imidazole, etc.). In general, the assumption noted in the review in [1] that polarographically active groups attached to a heteroaromatic ring behave like polarographically active groups attached to aromatic (benzene) rings, i.e., they are reduced approximately in the same ranges of electrode potentials and via the same chemical mechanism, is generally justified, but one cannot overlook a number of specific complicating factors.

First of all, the change in the nature of the heteroaromatic ring owing to purely electronic effects somewhat shifts the electrochemical reduction potential of this group to one or another side as compared with the potential of the same group attached to an aromatic ring. Although this change in the $E_{1/2}$ value usually does not exceed 0.1-0.2 V, nevertheless it sometimes may transfer the electroreduction process to a different region of the electrocapillary curve, where adsorption of the depolarizer molecules and the effect of the electrical double layer are manifested differently, and a result of this may be a change in the mechanism of the electrochemical process.

Second, heteroaromatic compounds, particularly nitrogen- and sulfur-containing heterocycles, are adsorbed on the electrode surface considerably more strongly than the corresponding benzene derivatives, thereby intensifying the effect of adsorption factors on the course of the electrochemical process. In the case of heteroaromatic compounds, adsorption forewaves, surface kinetic points (drops on the polarograms) etc., often appear.



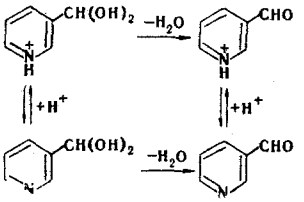
Third, owing to the specific effect of the heteroring, those substituents which, because they are added to the aromatic ring, are incapable of electroreduction, acquire polarographic activity. Thus, in contrast to inactive benzoic acids, all of the isomeric pyridinecarboxylic acids are reduced on a DME in the accessible range of potentials. In contrast to the polarographically inactive benzonitrile, 4-cyanopyridine and 2-cyanopyridine are reduced on a DME, and in this case a 4e process occurs in acidic media, while 2e cleavage of the C–CN bond occurs in basic media [61, 62]. Of course, the opinion that we are dealing here with electroreduction of the pyridine ring [63] via the following scheme has been expressed:



In contrast to N-phenylhydroxylamine, which is polarographically inactive in the unprotonated form, waves corresponding to reduction of the unprotonated hydroxylamino group [64] appear on the polarograms of 2-nitrofuran derivatives with electron-acceptor substituents.

Protonation of the heteroatom has a peculiar effect on the $E_{1/2}$ value of a side group in the case of derivatives of nitrogen-containing heterocycles (pyridine, pyrrole, thiazole, etc.). Depending on the pH of the solution, the heteroring in the compound is in the protonated (salt) or unprotonated (base) form, each of which is reduced at definite potentials; this is responsible for the competitive electroreduction of the two different forms, the formation of kinetic waves, etc., which is not observed in the case of the corresponding derivatives of benzene or of heterocycles that do not have basic properties (furan, thiophene, etc.) (this should not be confused with the kinetic currents that arise because of the presence of a substituent in two different forms, for example, a protonated and unprotonated carbonyl group, an acid and its anion, etc.). The polarographic cleavage of the C–Hal bond in various monohalopyridines may serve as an example [65].

In addition, hydration of the carbonyl group is typical for a number of heteroaromatic aldehydes; this distinguishes them from the corresponding benzaldehydes and naphthaldehydes. The equilibrium between the electroactive unhydrated form of a heteroaromatic aldehyde and its inactive hydrated form is mobile, and the height of the waves is limited by the rate of dehydration of the aldehyde group, which is an acid–base catalyzed process, and, consequently, depends on the pH. This mechanism for dehydration, which precedes electroreduction, is characteristic for isomeric formylpyridines [66-69], formylimidazoles [70], 5-nitrofurfurals [64, 71], 2-formylthiazoles [68], etc., in aqueous media; the complex dependence of the wave height on the pH is responsible for it. For nitrogen-containing heterocycles, this mechanism is additionally complicated by acid–base equilibrium between the base and protonated form of the heteroring, which are distinguished with respect to their degree of hydration: the cation, owing to its positive charge, is usually hydrated more strongly than the free base. A complex set of equations arises because of all that was stated above. Protonation may show up in at least three different ways: its effect on the ring heteroatom, on the rate of dehydration, and on the surface protonation of the aldehyde group in the course of its electroreduction, for example [72]:



However, the general principles of polarographic reduction of aromatic carbocyclic compounds are applicable on the whole to the polarographic behavior of heteroaromatic compounds that have an electroactive functional group in the side chain. Moreover, these principles take on particular significance for the solution of the problems of the chemistry of heteroaromatic compounds, since the task in the interpretation of the structures of natural and synthetic biologically active substances with extremely diverse possibilities of structural isomerism, tautomeric forms, etc., very often is establishment of the presence and characterization of the fine electronic structure of one or another functional group. In this respect, polarography, together with more modern physical methods, can give valuable information. The determination of the concrete $E_{1/2}$ values in the chemistry of heterocyclic compounds also takes on more significance for the relative evaluation of the reactivities of one or another position in the heteroring, etc., which is not always easy to do with other methods, and also for modeling of the biochemical redox systems in which redox coenzymes of heteroaromatic structure, their model analogs, inhibitors, etc., often participate.

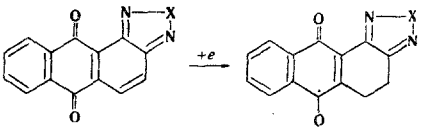
Insofar as the effect of the nature of the heteroring on the $E_{1/2}$ value of reduction of the heteroaromatic system bonded to it is concerned, one can particularly approximately use the rule that groups attached to heteroaromatic systems with a deficit of π electrons in the ring are reduced at more positive potentials, and groups bonded to π-surplus heteroaromatic systems are reduced at more negative potentials. In the first case, the electron density on the polarographically active group decreases, and this facilitates electroreduction, while the reverse occurs in the second case. The relative ease of reduction of a group depends also on its position with respect to the heteroatom. For example, if the ring nitrogen heteroatom in the pyridine molecule is considered to be a substituent with a strong negative mesomeric effect, electroactive groups in the 4 and 2 positions should be reduced considerably more readily than a substituent in the 3 position; this is experimentally observed [66, 73, 74]. Electroactive groups in the 2 position in furan, thiophene, and selenophene derivatives are reduced considerably more readily than the group in the 3 position; this was used, for example, for the analysis of the isomeric composition of the products of nitration of thiophene [75].

Imoto [76], Zuman [77, 78], Tirouflet [79], and other authors compared the relative ease of electroreduction with the so-called heteroring constants σ_F^-, which characterize the electronic effect (including the mesomeric effect) of a heteroaromatic ring (with respect to the phenyl ring). The investigated systems can be arranged in the following order with respect to the increase in the negative potentials of electrochemical reduction:

4-pyridyl	< 2-thiazolyl	< 2-pyridyl	< 3-pyridyl	< 2-thienyl	< 2-furyl
σ_F^- +1.86	+1.64	+1.5	+0.72	+0.24	+0.18

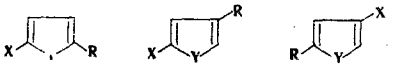
< phenyl	< 3-thienyl	< 2-pyridyl	< 3-pyridyl
σ_F^- 0	−0.09	−0.70	−1.68

Depending on the reproducibility of a given electroactive functional group to the effect of substituents, the corresponding increase or decrease in the half-wave potentials on passing from one heteroaromatic system to another may be considerable or less pronounced. Thus, on passing from the 4-pyridyl framework to the phenyl framework the $E_{1/2}$ values for electroreduction of bromo derivatives are shifted to the cathode side by about −1.1 V, compared with shifts of −0.5 V for aldehydes and ketones and −0.25 V for aldoximes and nitro compounds [78]. However, these data are only approximate in nature, since the values of the σ_F^- constants may vary over very wide limits, depending on the mesomeric interaction of the heteroaromatic ring with the electroactive group, while the electrochemical process depends also on the possibility of protonation of the heteroring, its adsorbability, etc. In the case of small electronic effects of the heteroring, the $E_{1/2}$ values may also change to the positive side – thus 5-nitrofuran is reduced more readily by 40-50 mV than 5-nitrothiophene, while the latter, just as 5-nitroselenophene, has approximately the same potential as nitrobenzene [71]. In addition, there is almost no research in which one author has studied, under identical (strictly compared) conditions, the polarographic behavior of the same electroactive group in various heteroaromatic systems.



An investigation of angular heterocyclic derivatives of anthraquinone of the anthraquinone-1,2,5-X-diazole type and related compounds gave interesting results [79-81]. Since the rings of 1,2,5-X-diazoles are strong electron acceptors, their introduction into a molecule increases the electron affinity of the quinone, which can be characterized by the $E_{1/2}$ value of the first wave for electroreduction of the quinone grouping in an aprotic solvent to a semiquinone anion radical. The corresponding $E_{1/2}$ values correlate linearly with the results of kinetic measurements [82] (Table 1).

The effect of an extraneous substituent (X) that is incapable of electroreduction on the $E_{1/2}$ value for polarographic reduction of an electroactive functional group (R) was studied quite thoroughly in a number of derivatives of furan, thiophene, and selenophene [78]:



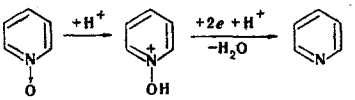
It was shown that, in general, the same principles as in the effect of substituent X on the electroreduction of group R in electrochemical reactions of the benzene series are observed here, and the $E_{1/2}$ values correlate linearly with the Hammett constants; the 2,5-position in these heterorings is approximately equivalent to the para position in the benzene ring, while the 2,4-position is approximately equivalent to the meta position [71, 83-85]. The ρ_π constants in a number of derivatives of these heteroaromatic rings differ somewhat from the corresponding values in the benzene series [78]. The decrease in transmission of the electronic effect of substituent X is also caused by interposition of the $-CH_2-$, $-CH=CH-$, etc., bridge groups [84-86]. It is interesting that a decrease in the $\Delta E_{1/2}/\Delta pH$ coefficients of various derivatives of the series [85] in the linear dependence on the Hammett substituent constants is observed in a number of 2-substituted derivatives of 5-nitrofuran on ordinary capillaries, and that this decrease is observed only on short-period capillaries in a number of nitrobenzene derivatives [87].

There are numerous data on the polarographic reduction of electroactive groups bonded to a heteroaromatic ring. The functional derivatives of pyridine [88-92], pyrrole [93, 94], furan [95, 96], thiophene [97, 98], imidazole [70, 99], thiazole [100], etc., particularly the corresponding carbonyl, nitro, and halo derivatives, and derivatives of pyridinecarboxylic acids (cyanides, hydrazides, amides, etc.) have been studied thoroughly. Many of these compounds – derivatives of nicotinic and isonicotinic acids, 2-nitrofuran, α-nitropyrrole, etc. – have high chemotherapeutic activity, and the possibility of their polarographic determination seems of substantial analytical interest.

N-Oxides occupy a special place among substituted derivatives of nitrogen-containing heterocycles; the polarographic behavior of N-oxides has been studied extremely intensely in view of their low polarographic reduction potentials, which are convenient for analytical work, and also because of the great importance that they have for the preparative chemistry of heterocycles. The N-oxides of pyridine, quinoline, piperidine, and a number of alkaloids give an irreversible 2e wave in acidic media at potentials from −0.7

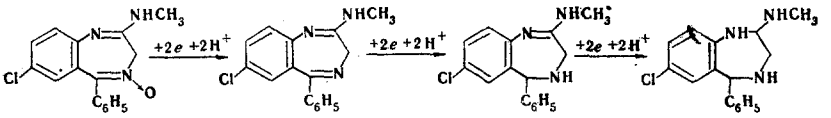
TABLE 1. $E_{1/2}$ Values (in Dimethylformamide) of 9,10-Anthraquinone and Anthraquinone-1,2,5-X-diazoles

Annelated heteroring	$E_{1/2}$, V	Annelated heteroring	$E_{1/2}$, V
9,10-Anthraquinone	−0,82		−0,43
	−0,57		
	−0,43		−0,42
	−0,57		−0,27



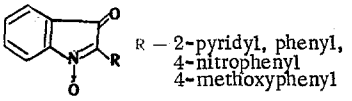
to −1.0 V, the $E_{1/2}$ value of which depends on the pH [101-110]. The height of the wave decreases with increasing pH, gradually takes on kinetic character, and finally disappears. This is associated with the fact that pyridine N-oxide itself is polarographically inactive but in the protonated form acquires the capacity for electroreduction, as shown above. The height of the wave corresponding to cleavage of the $\overset{+}{N}-O$ bond is limited by the protonation kinetics, which have volume character in the case of N-methylpiperidine and partially surface character with the participation of adsorbed N-oxide molecules in the case of pyridine [103].

In acidic media, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (chlordiazepoxide) gives three reduction waves. The first wave ($E_{1/2}$ −0.38 V) corresponds to 2e reduction of the N→O group, the second wave ($E_{1/2}$ −0.72 V) corresponds to 2e reduction of the C=N double bond in the 4,5 position, and the third wave ($E_{1/2}$ −1.2 V) corresponds to 2e reduction of the N=C double bond in the 1,2 position [109-112].

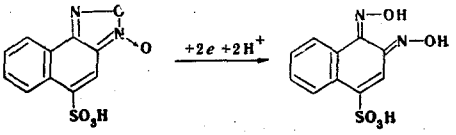


The effect of substituents on the $E_{1/2}$ values for reduction of N-oxides and the reduction of other electroactive groups contained in N-oxide molecules was examinedin [102, 104-106, 108, 109].

Isatogens, which are reduced like 1,4-quinones on a DME and consequently have quinoid character [113], are close to N-oxides:



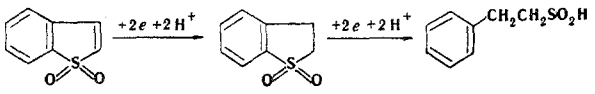
The mechanism of electroreduction of the N-oxides of 1,2,5-oxadiazoles (furoxans) is fundamentally different [114]. Depending on the pH, two or three waves are observed on the polarograms of 1,2-naphthofuroxan-4-sulfonic acid. The first wave at −0.1 to −0.2 V corresponds to 2e reduction to 1,2-quinodioxime-4-sulfonic acid. The next waves pertain to the reduction of the protonated and unprotonated forms of the dioxime. Eight electrons are consumed in the complete reduction to give the final product – 1,2-diaminonaphthalene-4-sulfonic acid. Thus cleavage of the ring bonds occurs more readily in the case of furoxan than splitting out of an exocyclic oxygen atom.



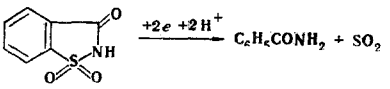
Two-electron and six-electron waves are observed separately in the reduction of naphthofuroxan in anhydrous dimethylformamide. The absence of a 1e step may be associated with weakening of the aromatic character of the molecule on passing from furazans to furoxans.

The S-oxides and S-dioxides of phenothiazine [115] and benzo- and dibenzophenothiazines are reduced on a DME in an alcohol solution of tetramethylammonium chloride at −1.7 to 2.3 V (relative to the mercury bottom). In acidic media (in hydrochloric, acetic, and nitric acids) the S-oxides undergo 1e reduction at −0.8 to −1.0 V. The mechanism of the electroreduction has not been adequately studied, but it is assumed that in this case the resulting phenothiazonium salts, which, by adding one electron, give stable semiquinones that are not reduced up to the point of discharge of the base electrolyte are reduced.

Benzothiophene 1,1-dioxide in benzene–methanol solution gives two reduction waves with $E_{1/2}$ −0.97 and −1.93 V, respectively [116]. On the basis of data in [116, 117], Lund proposes cleavage of the thiophene ring to give β-phenylethanesulfinic acid [118]:



Cleavage of the C–S bond is the primary electrode reaction in the reduction of saccharin; chemical reaction follows after primary electrochemical cleavage [118]:



Thus, abundant – and frequently the most diverse – variations of mechanisms of electrochemical reduction, which are far from being completely discovered, are manifested among the extremely diverse heterocyclic compounds. Not all of the literature data have been obtained under comparable conditions and cannot be correlated from a single position. However, the electrochemical material already available makes it possible to both expose the peculiarities of the reactivities of individual heterorings and to use the polarographic method for the quantitative analysis and evaluation of the reactivities of numerous heterorings.

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