Chemistry of Heterocyclic Compounds, Vol. 33, No. 2, 1997

ELECTROCHEMICAL REDUCTION OF 4-(NITROPHENYL)-1,2- AND 4-(NITROPHENYL)-1,4-DIHYDROPYRIDINES AND THE ESR SPECTRA OF THE OBTAINED FREE-RADICAL PARTICLES

L. Baumane, R. Gavar, Ya. Stradyn', and G. Dubur

In the course of electrochemical generation the intermediate reaction products (free radicals of the nitro-and nitrosophenyl type, which appear on the cyclic voltammetric curves) were identified by ESR. The N-substituted derivatives are characterized by reduction of the dihydropyridine ring. The 4-nitrophenyl derivatives are characterized by the absence of intramolecular electron transfer during electrochemical reduction. In the case of the corresponding derivatives of 1,2-dihydropyridine intramolecular transfer of electrons and protons is possible under these conditions. Combined schemes of the primary and secondary chemical reactions involved in the electrochemical reduction of the investigated compounds are presented. It was established that the substances investigated with reference to the mechanism of the electrochemical transformations include the antihypertensive nifedipine (corinfar, fenigidine).

The interest in 1,4-dihydropyridine (DHP) derivatives has largely been due to the antioxidant properties of this type of compound, and special attention has therefore been paid to study of their electrochemical oxidation processes [1-5]. Among the dihydropyridines significant hypertensive activity is exhibited by the *ortho*-phenyl derivatives of 1,4-DHP [6], such as 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(*ortho*-nitrophenyl)-1,4-DHP (nifedipine, fenigidine, corinfar), widely used in medical practice.

The nitrophenyl derivatives of dihydropyridine are of interest from the standpoint of electrochemists as compounds containing electroactive groups capable of reduction and oxidation [7] and also from the standpoint of their use in pharmaceutical practice [8]. It is important to determine how the oxidation—reduction reactions occur and which processes determine the decomposition of these compounds.

The presence of a potential intramolecular redox system in the molecule lends urgency to the problem as to whether the application of an electrochemical potential induces the intramolecular transfer of electrons in the nitrophenyl-DHP molecules or only secondary redox systems are formed as a result of electron transfer. The question is more pertinent in that the introduction of an *ortho*-nitrophenyl substituent at position 4 of the heterocycle leads to photochemical reduction of these compounds [9].

The mechanisms of the electrochemical reduction of two series of 4-nitrophenyl derivatives of 1,4-DHP with 3,5-CN and 3,5-$COOC_2H_5$ groups respectively at positions 3 and 5 of the DHP ring were duly compared [10]. For a number of reasons data on the electrochemical reduction of the respective analogs of the 1,2-DHP series and the more detailed results on the electrochemical reduction of the 3,5-diethoxycarbonyl derivatives of 4-nitrophenyl-1,4-DHP and also nifedipine were only published in the preprint [11]. In view of the interest of researchers in the mechanism of the electrochemical transformations in the 4-(nitrophenyl) derivatives of DHP [12], we considered it essential to publish the existing data, bringing the previously obtained results to completion.

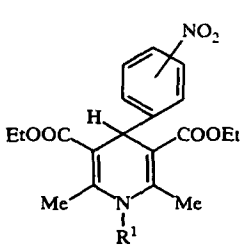
Latvian Institute of Organic Synthesis, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 219-233, February, 1997. Original article submitted October 14, 1996.

 0009-3122/97/3302-0190$18.00

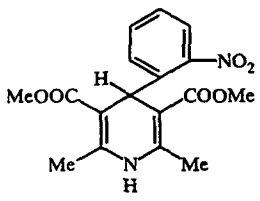
TABLE 1. Electrochemical Characteristics ($-E_{1/2}$, i) of Derivatives of DHP in DMFA at a Dropping Mercury Electrode with Reference to a Saturated Calomel Electrode with 0.1 M $(C_4H_9)_4NPF_6$ as Supporting Electrolyte

Compound	$-E_{1/2}^{I}$, V	$-E_{1/2}^{II}$, V	$-E_{1/2}^{III}$, V	$-E_{1/2}^{IV}$, V	i^{I}, μA	i^{II}, μA	i^{III}, μA	i^{IV}, μA
I(1a)	1,18	—	2,02	2,50	0,80	—	0,59	1,59
I(1б)	1,19	—	2,15	2,36	0,81	—	2,38	2,36
I(1в)	1,12	—	2,04	2,24	0,83	—	2,42	2,57
I(2a)	1,13	—	2,18	2,80	0,80	—	0,80	2,17
I(2б)	1,16	—	2,23	2,40	0,82	—	2,32	1,92
I(2в)	1,11	—	2,16	2,32	0,82	—	2,22	1,80
I(2г)	1,10	—	2,18	2,32	0,83	—	2,60	1,40
I(2д)	1,12	—	2,20	2,36	0,81	—	2,76	1,46
I(3a)	1,38	1,63	2,24	2,70	0,81	0,17	0,70	1,47
I(3б)	1,29	—	2,18	—	0,95	—	1,19	—
I(4)	1,39	1,64	2,20	2,65	0,81	0,08	0,63	1,72
I(5a)	1,15	—	1,75	2,30	0,80	—	0,87	2,50
I(5б)	1,18	—	2,20	2,70	0,87	—	1,57	2,50
I(5в)	1,27	—	1,98	2,48	0,87	—	1,57	0,78
I(6)	—	—	2,30	—	—	—	0,78	—
I(7)	—	—	2,14	2,60	—	—	0,79	1,27
I(8)	—	—	2,00	—	—	—	0,90	—
p-NO_2-Toluene [13]	1,15	—	2,1	—	4,0	—	10,0	—
m-NO_2-Toluene [13]	1,18	—	—	—	4,0	—	—	—
o-NO_2-Toluene [13]	1,26	—	2,1	—	4,6	—	9,8	—
o-NO_2-*tert*-Butyltoluene [13]	1,36	—	1,98	—	2,9	—	8,5	—

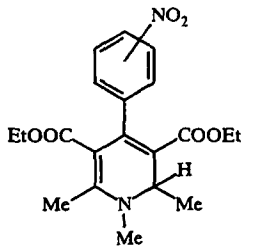
By polarography, cyclic voltammetry at a mercury drop and at platinum and glassy graphite electrodes, and ESR spectroscopy a systematic study was made of the mechanism of the electrochemical reduction of the 4-nitrophenyl derivatives of 1,4-DHP I(1-4) and the corresponding analogs of 1,2-DHP of series I(5):



I (1–3)



I (4)



I (5)

I(1) *p*-NO_2; a R^1 = H, b R^1 = CH_3, c R^1 = C_6H_5; I(2) *m*-NO_2; a R^1 = H, b R^1 = CH_3, c R^1 = C_6H_5, d R^1 = C_6H_4Br-*p*, e R^1 = $CH_2C_6H_5$; I(3) *o*-NO_2; a R^1 = H, b R^1 = CH_3; I(4) Nifedipine
I(5) a *p*-NO_2, b *p*-NO_2; c *o*-NO_2

As model compounds we studied 1,4-dihydropyridines not containing a nitro group in substituent 4: I(6), R^1 = CH_3, 4 = CH_3; I(7), R^1 = $C_6H_4CH_3$-*para*, 4 = C_6H_5; and 1,2-DHP I(8), 4 = C_6H_5.

The potentials and the heights of the polarographic waves for the electrochemical reduction of all the investigated compounds are given in Table 1. The hyperfine structure constants in the ESR spectra of all the detected free-radical products formed in the reduction process I(1-5) are given in Table 2.

The electrochemical reduction of the 4-nitrophenyl derivatives I(1-5) in DMFA includes several electrochemical and chemical stages. In the case of both 1,4-DHP and 1,2-DHP the *para*- and *meta*-nitrophenyl-substituted derivatives are reduced by a common mechanism, whereas the *ortho* derivatives behave somewhat differently.

For the nitrophenyl derivatives of 1,4-DHP and the derivatives of 1,2-DHP the first stage of the reduction is one-electron and reversible and leads to the formation of the relatively stable radical-anions II (Scheme 1).

Scheme 1

$$[M] \underset{-e^-}{\overset{+e^-}{\rightleftharpoons}} [M]^{-\cdot}$$

I (1–5) II (1–5)

where [M] is the initial molecule of 1,4- or 1,2-DHP, and $[M]^{-\cdot}$ is the corresponding initial radical-anion. Here there is no substantial difference in the electrochemical reduction potentials and the reversibility of the process in relation to the substituent R^1 and the position of the nitro group in the benzene ring (Table 1). The potentials of the first reduction wave are close to the corresponding values of nitrotoluenes [13]. The exception is the N-substituted *ortho*-nitrophenyl derivatives I(3b) and I(5c), for which the first wave exceeds the 1e level in height. On the cyclic voltammogram it corresponds to two close-lying peaks with cathodic potentials of −1.23 and −1.33 V for I(3b) and −1.27 and −1.32 V for I(5). An oxidation peak and, hence, process reversibility are only observed for the more negative reduction stage. The reduction path is identical during reduction both at mercury drop and at a glassy graphite electrode. During a repeated potential sweep the first peak on the cyclic voltammetric curve remains if the sweep rate is low (0.05 V/sec), but at a high rate (0.5 V/sec) only the second reversible peak remains. This indicates either that a fast chemical reaction, leading to the formation of a different more stable product, occurs at the first stage of the reduction of the initial compounds I(3b) and I(5c) or that the initial compound is present in two forms, e.g., steric isomers, reduced at different potentials.

By ESR it was possible to detect the spectra of the initial radical-anions II(1-5) for all the investigated compounds except I(3b) and I(5c). To judge from the ESR spectra all the radical-anions have the structure of substituted nitrobenzene. Consequently, during initial electrochemical reduction the unpaired electron is largely delocalized in the nitrobenzene fragment of the molecule. In all cases splitting is observed at the nitrogen atom of the nitro group and at all the protons of the benzene ring (Table 2). In addition, for the derivatives of 1,4-DHP additional coupling appears with the proton at position 4 of the dihydropyridine ring. This indicates that the dihydropyridine skeleton is retained in the radical-anions II(1-4) of 1,4-DHP. In the ESR spectra of the radical-anions of the N-unsubstituted *ortho*-nitrophenyl derivatives of 1,4-DHP II(3a, 4) additional coupling was found between the unpaired electron ($a_{6H} \sim 0.1$ G) and the protons of the methyl groups in the substituents at positions 3 and 5 of the heterocycle [10]. During a check on other 4-*ortho*-nitrophenyl-1,4-DHP derivatives containing the substituents $COOCH_3$, $COCH_3$, and CN at positions 3 and 5 additional coupling, leading to splitting into seven components with a binomial intensity ratio in the case of $R^3 = R^5 = COOCH_3$ or $COCH_3$ and five components with a binomial intensity ratio in the case of $R^3 = R^5 = CN$, was observed. The value of these constants is about 0.1 G and is poorly distinguishable. However, from the total width of the overall signal and by simulation of the ESR spectrum it is possible to establish that for various $R^3 = R^5$ the value of the additional hfs constant decreases in the order $COOC_2H_5 > COOCH_3 > COCH_3$. Such additional coupling of the unpaired electron, which is largely delocalized in the nitrobenzene fragment of the molecule, with the substituents at positions 3 and 5 of the heterocycle may be due to their steric proximity to the nitro group in the phenyl ring [14]. It is interesting to note that additional coupling was not observed in the case of the N-substituted *ortho*-nitrophenyl derivatives I(3b) and I(5c).

In all cases the potentials of the first stage of reduction and the hfs constants are close to the values for the corresponding nitrotoluenes [15, 16]. However, the $a_{H,4}$ constant is significantly lower than for the protons of the methyl group and depends substantially on the substituent R^1 at the nitrogen atom in the DPH ring, whereas the hfs constants of the nitrobenzene fragment remain practically unchanged. Since there is no direct conjugation between positions 1 and 4 of the heterocycle in 1,4-DHP, the electronic effect of the substituent R^1 on the proton at position 4 is probably transmitted through space.

For the radical-anions of the 4-nitrophenyl derivatives, in contrast to the 1,4-DHP analogs, a substantial decrease is observed in the hfs constants. This is due to the nitrogen atom of the nitro group and is brought about by the inclusion of the ethoxycarbonyl groups at positions 3 and 5 and also the methyl group at position 6 of the heterocyclic part of the molecule in the conjugated π-electron system. As a result the density of the unpaired electron is redistributed onto the heterocycle, although in no case were additional hfs constants detected. This merely indicates that the main part of the density of the unpaired electron is concentrated on the ethoxycarbonyl groups in the heterocycle.

Thus, at the first stage of electrochemical reduction the effect of the DHP part of the molecule shows up with the substituent at the *para*, *meta*, or *ortho* position of nitrobenzene. In all cases the position of the heterocyclic residue in relation to the nitro group has an identical effect on the change in the electron affinity of the molecule — it increases in the order *ortho* > *para* > *meta* (Tables 1 and 2). From analysis of the electrochemical reduction potentials and the hfs constants of the *ortho*-,

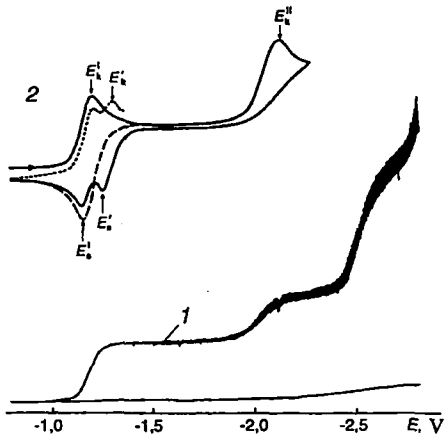


Fig. 1. Classical polarogram at a dropping mercury electrode (1) and the cyclic voltammograms at a sus-pended mercury drop (2) with a potential sweep rate of 0.2 V/sec for 4-*para*-nitrophenyl-1,4-DHP I(1a) in DMFA with reference to a saturated calomel electrode.

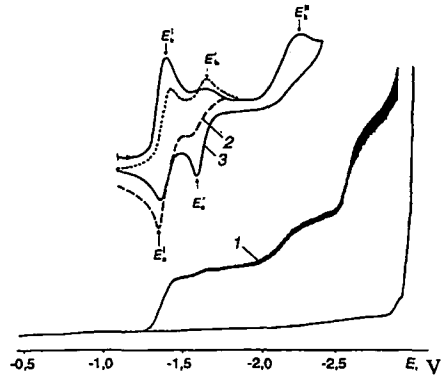


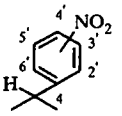
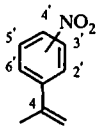
Fig. 2. Classical polarogram at a dropping mercury electrode (1) and the cyclic voltammograms at a suspended mercury drop for nifedipine I(4) in DMFA with reference to a saturated calomel electrode at a potential sweep rate of 0.2 V/sec from −1.1 to −1.7 V (2) and from −1.1 to −2.4 V (3).

meta-, and *para*-substituted nitrobenzenes [17] it emerges that such an order is characteristic of electron-donating substituents. Accordingly, in the compounds that we investigated the 1,4-DHP ring, like the 1,2-DHP ring, has electron-donating characteristics in relation to the nitrobenzene residue.

The further reduction of the radical-anions II depends substantially on the structure of the molecule; the process is affected by the substituent at the nitrogen atom in the heterocycle, by the position of the nitro group in the benzene ring, and by the structure of the DHP ring itself (i.e., whether it is 1,4- or 1,2-DHP).

In the case of the N-unsubstituted 4-*para*- and 4-*meta*-nitrophenyl-1,4-DHP the second polarographic wave is close in height to the one-electron level. This stage is irreversible. However, on the anodic branch of the cyclic voltammetric curve apart from the peak for the oxidation of the initial radical-anion E_a^I a new E_a^I peak is observed at a more negative potential, while the corresponding cathodic peak E_c^I is observed on the repeated cycle (Fig. 1). Consequently, during the addition of the second electron a product capable of forming a reversible redox system at a more negative potential than the potential of the radical-anion/initial molecule redox system appears.

TABLE 2. Hyperfine Structure constants in the ESR Spectra of the Free-Radical Products Formed during the Electrochemical Generation of Compounds I(1-5) in DMFA

Compound	Product	ECG potential	a, G					
			$a_{2'}$	$a_{3'}$	$a_{4'}$	$a_{5'}$	$a_{6'}$	$a_{H,4}$
I(1a)	II(1a)	-1,2	1,05	3,35	9,85	3,35	1,05	1,05
	IV(1a)	-2,1	1,10	3,30	10,70	3,30	1,10	1,30
I(1b)	II(1b)	-1,3	1,10	3,35	9,85	3,35	1,10	1,90
	IX/X(1b)	-3,0	1,10	3,55	10,30	3,55	1,10	2,45
	(1b)	-1,1	1,05	3,95	7,65	2,90	1,05	1,95
I(1c)	II(1c)	-1,1	1,10	3,40	9,90	3,40	1,10	2,35
	IX/X(1c)	-2,1	1,10	3,35	10,20	3,35	1,10	2,95
I(2a)	II(2a)	-1,2	3,25	9,50	3,25	1,05	3,70	0,40
	IV(2a)	-2,2	3,20	10,20	3,20	1,05	3,55	0,45
I(2b)	II(2b)	-1,2	3,30	9,85	3,30	1,05	3,95	0,65
	IX/X(2b)	-2,3	3,30	10,20	3,30	1,05	3,50	0,20
	VIII(2b)	-0,9	3,55	7,15	2,70	1,00	3,75	0,50
I(2c)	II(2c)	-1,2	3,15	9,80	3,15	1,05	3,90	0,40
	IX/X(2c)	-2,0*						
	VIII(2c)	-0,9*						
I(2d)	II(2d)	-1,1	3,20	9,80	3,20	1,05	3,80	0,35
	IX/X(2d)	-2,1*						
	VIII(2d)	-0,8*						
I(2e)	II(2e)	-1,3	3,20	9,60	3,20	1,00	3,95	0,55
	IX/X(2e)	-2,0*						
	VIII(2e)	-0,9	3,75	7,25	3,75	0,95	2,75	0,95
I(3a)	II(3a)	-1,4	9,70	3,10	1,00	4,00	1,00	0,90 > 0,1(6H)
	IV(3a)	-1,6	10,40	3,10	1,00	8,30	1,15	0,90 0,15(6H)†
I(3b)	IX/X(3b)	-1,4	9,95	3,35	1,20	4,00	1,20	1,50
I(4)	II(4)	-1,4	10,15	3,10	1,00	4,00	1,00	1,00 > 0,1(6H)
	IV(4)	-1,7	10,85	2,60	1,00	4,00	1,00	0,65 > 0,1(6H)
I(5a)	II(5a)	-1,2	1,00	3,20	8,85	3,20	1,00	—
	XI(5a)	-1,8	1,05	3,35	10,15	3,35	1,05	—
	XV/XVII(5a)	-0,9*						
I(5b)	II(5b)	-1,2	3,40	9,80	3,40	1,10	4,00	—
	XI(5b)	-1,8	3,20	11,10	3,20	1,10	3,80	—
	XV/XVII(5b)	-0,9	3,75	7,55	3,75	1,00	3,05	—
I(5c)	XI(5c)	-1,3	8,90	3,35	0,85	4,05	0,85	—

*The hfs constants were not determined on account of the strong overlap of the signals in the ESR spectra and the impossibility of identifying the individual components. †The hfs constants were determined by simulation of the ESR spectra (see [33]).

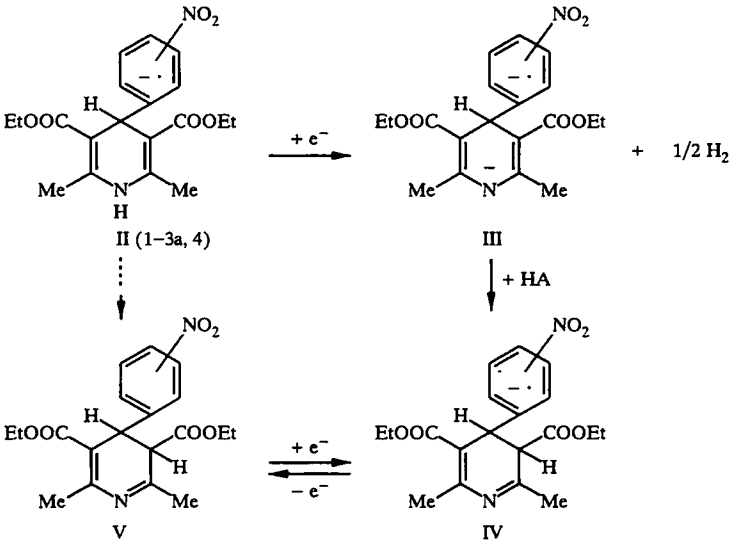
For the N-unsubstituted *ortho*-nitrophenyl derivatives of 1,4-DHP (3a, 4) an additional wave was noticed between the first and second main polarographic waves. On the cyclic voltammetric curve it corresponded to a reversible redox system E_a'/E_c', and the formation of a new product was detected. The amount of this product increased if the potential was brought up to the potential of the second polarographic wave (Fig. 2).

We tried to reproduce the conditions for the appearance of the new product in an electrochemical generation cell, placed in the resonance cavity of the ESR spectrometer, and to record the ESR spectra, since the presence of a reversible redox system indicates the possible formation of free-radical particles. For the *ortho*-nitrophenyl derivatives (3a, 4) the free-radical products were detected even at the potentials of the intermediate wave. For the *para*- and *meta*-nitrophenyl derivatives the ESR spectra were only obtained at the potential of the second polarographic wave. The values of the potentials at which the new redox systems were detected are given in Table 3. In structure the new radicals were also the radical-ions of the substituted nitrobenzene (Table 2), in which the proton at position 4 of the DHP ring was retained.

As demonstrated in the case of the 4-nitrophenyl-3,5-dicyano derivatives of 1,4-DHP [18], the idea that the radical-dianion of the initial compound is formed was not confirmed. In contrast to the 3,5-dicyano-substituted analogs, which both in an alkaline medium and during electrochemical reduction in aprotic DMFA give a relatively stable anionic form capable of being reduced to the radical-dianion [2,18], in the case of the 3,5-diethoxycarbonyl-substituted compounds, according to electronic spectroscopy, the anionic form is extremely unstable in an alkaline medium and is quickly transformed. It is known that the acidity of the N-unsubstituted 3,5-diethoxycarbonyl derivatives of 1,4-DHP is 3.4 pK units lower than that of the corresponding 3,5-dicyano derivatives [19]. The addition of up to 2% of water, the molecules of which would protonate the anions, to dry DMFA does not affect the yield and stability of the secondary radical recorded by ESR.

The following scheme is put forward as a possible explanation for the formation of the secondary radicals: At the second one-electron stage the proton at the nitrogen atom of the heterocycle is reduced [20], and the heterocycle is quickly protonated but in a different position (e.g., at position 3 of the DHP ring). As a result isomerization takes place by means of the anion (III) with the formation of the nitrophenyl radical-anion (IV) with a new structure (Scheme 2):

Scheme 2



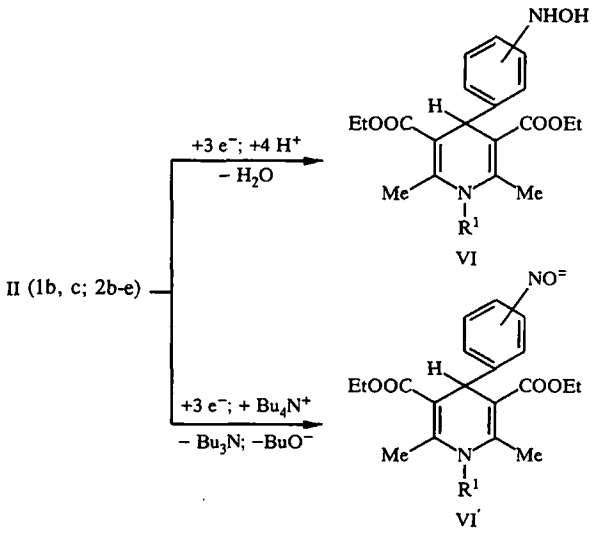
Such a radical-anion of 3,4-DHP (IV) must have stronger electron-donating properties in relation position 4 of the heterocycle compared with 1,4-DHP on account of rearrangement of the double bonds in the DHP ring. This shows up as a shift of the reduction potential toward more negative values and an increase in the value of the hfs constant $a_{H,4}$ in the ESR spectra. The results presented in Table 2 agree with the conclusion for the radical-anions of the *para*- and *meta*-nitrophenyl derivatives IV(1a, 2a). However, they are also not contradicted in the case of the *ortho*-nitrophenyl derivatives IV(3a, 4) if it is accepted that additional coupling between the unpaired electron and the methyl groups at positions 3 and 5 of the heterocycle exists in these radical-anions (Table 2).

The third reduction wave of the N-unsubstituted compounds I(1a, 2a, 3a, 4) is due to reduction either of the nitro group to hydroxylamine or of the double bond in the DHP ring (see further schemes 3 and 5). The appearance of new oxidation peaks or of new redox systems is not detected on the cyclic voltammetric curves during the potential sweep up to the third wave.

For the N-substituted *para*- and *meta*-nitrophenyl derivatives of 1,4-DHP I(1b, c, 2b-e) during further reduction of the radical-anions (II) two waves close in potential are observed in the region from −2.1 to −2.4 V. The height of the second reduction wave is close to the 3e level. The radical-anions of nitrotoluenes are reduced in this range of potentials in the aprotic medium DMFA {Table 1, compounds I(12-14) [13]}. By analogy it can be supposed that the second wave corresponds to the reduction of the radical-anions (II) to the hydroxylaminophenyl derivative of 1,4-DHP or to the dianion of the nitrosophenyl derivative of 1,4-DHP if the amount of proton donors in the electrolysis medium is insufficient (see Scheme 3 on following page).

However, the 1,4-DHP derivatives not containing a nitrophenyl substituent at position 4 of the heterocycle are also reduced in this region of potentials {see Table 1, compounds I(9), I(10), and [21]}. Consequently, it is impossible on the basis of the polarographic data to establish which of the above-named reduction processes (radical-anion or 1,4-DHP ring) takes place earlier.

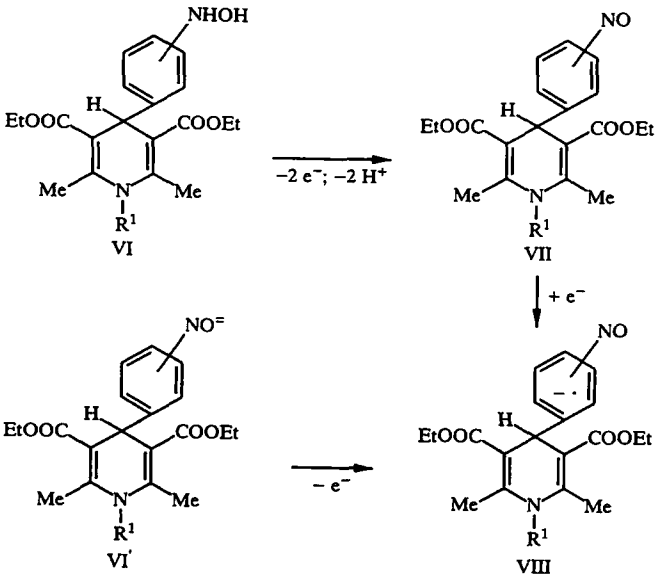
Scheme 3



On the cyclic voltammetric curves recorded for the N-substituted *para*- and *meta*-nitrophenyl derivatives of 1,4-DHP during reduction up to the second wave, in addition to the oxidation peak of the radical-anion, a new anodic peak is observed at more positive potentials (E_a = ~ −0.7 V) [10]. During a repeated potential sweep it corresponds to the reduction peak of this product (E_c = ~ −0.8 V). The potentials of the new redox system are given in Table 3 [product (VIII), scheme 4].

During electrochemical generation at the potential of the second polarographic wave there are additional ESR signals for these compounds. Their intensity increases significantly if the potential is greatly reduced (to 0 V) and then increased (to −0.8 V). Analysis of the hfs of the recorded spectra showed that they are the radical-anions of substituted nitrosobenzene [21]. The presence of the hfs constant $a_{H,4}$ indicates that the structure of the heterocycle in the 1,4-DHP is retained and excludes the possibility of intramolecular transfer of electrons and protons from the DHP part of the molecule to the nitrophenyl fragment. Consequently, at the second stage the radical-anion (II) is reduced further at the nitro group (Scheme 3). The radical-anions of the 4-nitrosophenyl derivatives of 1,4-DHP (VIII) appear during the reverse oxidation of (VI) through the formation of the nitrosophenyl derivative (VII), which can be reduced to the radical-anion (VIII), or during one-electron oxidation of the dianion (VI′) (Scheme 4):

Scheme 4



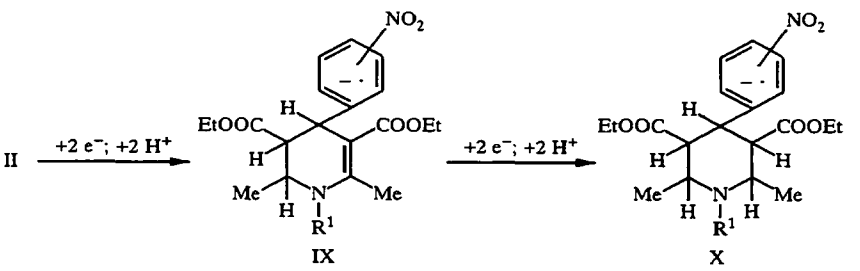
Since the last reaction takes place at significantly more negative potentials than the oxidation of (VI) [13], this may explain the appearance of the radical-anions of the nitrosophenyl derivative at the potential of the second polarographic wave.

The formation of nitrosobenzene was examined a long time ago [23]. However, the radical-anions of the nitrosophenyl derivatives still remain extremely exotic particles, since they are difficult to detect by ESR on account of their low stability. Only in [24] were data given on the formation of the relatively stable radical-anions of 2-nitroso-4-chloro-6-nitroanisole at the potential of the second polarographic wave in the electrochemical reduction of 2,6-dinitro-4-chloroanisole. For the N-substituted *ortho*-nitrophenyl derivative I(3b) neither the radical-ions of the nitrosophenyl derivative nor the formation of an additional redox system were detected on the cyclic voltammetric curves at the second stage of reduction.

The third polarographic wave for the N-substituted derivatives of 1,4-DHP [I(1b, c) and II(2b-e)] corresponds to the transfer of from two to four electrons. On the cyclic voltammetric curves during the potential sweep before the third stage of reduction on the reverse oxidation branch another redox system is observed, in addition to the primary radical-anion/initial molecule and nitrosophenyl derivative radical-anion/neutral molecule redox systems. This time it is in the range of potentials between the first and second stages of the reduction of the initial compound, i.e., at a more negative potential than the potential of the primary redox system (Table 3). During the electrochemical generation of these compounds at the potential of the third wave the ESR spectra of the corresponding free radicals (IX) or (X) were recorded (Scheme 5). They are formed with considerably greater difficulty than the N-unsubstituted derivatives of 1,4-DHP. It is practically impossible to isolate the second radical in the pure form. However, the hfs constants for some secondary radicals were determined by simulation and theoretical addition (subtraction) of the two ESR spectra (Table 2). According to the nature of the hyperfine structure, they are also radical-ions of substituted nitrobenzene with retention of the proton at position 4 of the heterocycle but with somewhat increased values for the hfs constants from the nitrogen atom of the nitro group and the proton at position 4 of the DHP ring.

We tried to explain the formation of such free radicals by the fact that the potentials of the second and third waves for the further reduction of the initial radical-anion (II) to the hydroxylaminophenyl derivative at the nitro group or at the double bonds of the heterocycle are extremely close. Depending on the orientation of the molecule, a certain part of (II) can be reduced at the double bonds without affecting the nitro group (Scheme 5):

Scheme 5



A heterocycle with reduced double bonds has more clearly defined donating characteristics than 1,4-DHP. This leads to redistribution of the density of the unpaired electron and to an increase in the values of the hfs constants, due to the nitrogen atom of the nitro group and the proton at position 4 of the 1,4-DHP ring. The alternative structure for the secondary radical (a substituted phenyl nitroxide or the protonated radical-anion of the nitrosophenyl derivative $-C_6H_4-NHO^{\cdot}$) is definitely excluded, since the value of the hfs constant $a_{H,4}$ from the proton not belonging to the phenyl ring is considerably smaller than the hfs constant from the nitrogen atom of the nitro group [e.g., see compound (I), Table 2]. This does not agree with abundant data on nitroxyl radicals [25], for which the proton constant in the $-NHO^{\cdot}$ group exceeds the nitrogen constant in numerical value.

The disagreement between the values of the hfs constants of the secondary radicals for the N-substituted and N-unsubstituted nitrophenyl-1,4-DHP derivatives indicates different transformations for the dihydropyridine part of the molecule during their electrochemical reduction.

For the N-substituted *ortho*-nitrophenyl derivative of 1,4-DHP I(3b) further reduction involves one irreversible stage. In contrast to the other N-substituted nitrophenyl-1,4-DHP derivatives, the second reduction wave of I(3b) at -2.18 V is only slightly above the one-electron level. The appearance of any new products capable of reverse reduction is not observed on the cyclic voltammetric curves. However, it must be remembered that the first reduction wave of I(3b) consists of two close waves

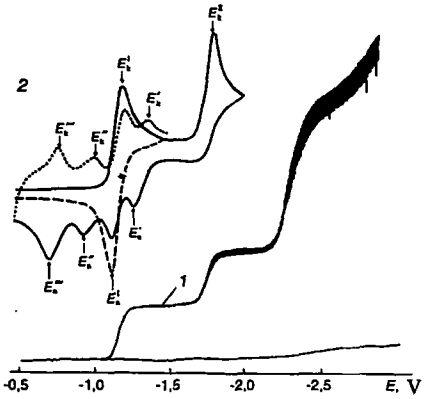


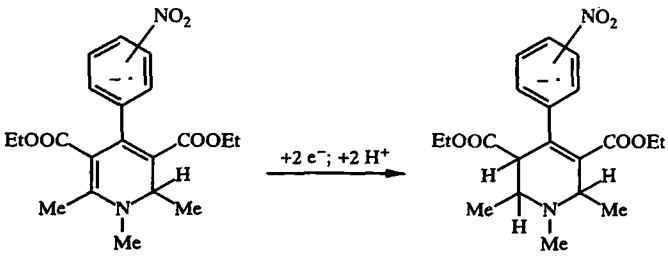
Fig. 3. Classical polarogram at a dropping mercury electrode (1) and the cyclic voltammograms at a suspended mercury drop (2) at a potential sweep rate of 0.2 V/sec for 4-*para*-nitrophenyl-1,2-DHP I(1a) in DMFA with reference to a saturated calomel electrode.

and the formation of the new product (IX) in this case may be a purely chemical process. As for the other N-substituted *para*- and *meta*-nitrophenyl derivatives of 1,4-DHP, the recorded ESR spectrum for this product indicates that the radical-anion that forms is an *ortho*-substituted nitrobenzene retaining the proton at position 4 (Table 2).

In the case of 4-nitrophenyl-1,2-DHP I(5a-c) further electrochemical reduction of the radical-anions (II) formed at the first stage (Scheme 1) takes place in two stages with the expenditure of 1-3 electrons (Table 1). For the *para*- and *meta*-nitrophenyl derivatives I(5a) and I(5b) the formation of three new reversible redox systems is observed on the cyclic voltammetric curves recorded before the second reduction wave (Fig. 3). One (E_a'/E_c') at a more negative potential than the initial reduction potential corresponds, according to the ESR data, to the formation of a product which, as in the case of N-substituted 1,4-DHP derivatives, is a substituted nitrobenzene with a more donating substituent in place of the 1,2-DHP ring. Two other reversible redox systems E_a''/E_c'' and E_a'''/E_c''' arise at potentials more positive (−0.7 V and −0.9 V) than the potential of the redox system in the initial reduction of the initial compounds. In interpretation and in the values of the hfs constants the recorded spectrum corresponds to the radical-anions of the *para*- or *meta*-substituted nitrosophenyl derivative of 1,2-DHP.

We suppose that the redox system at a more negative potential and the corresponding free radical product may arise as a result of reduction of the double bond in the heterocycle (Scheme 6):

Scheme 6

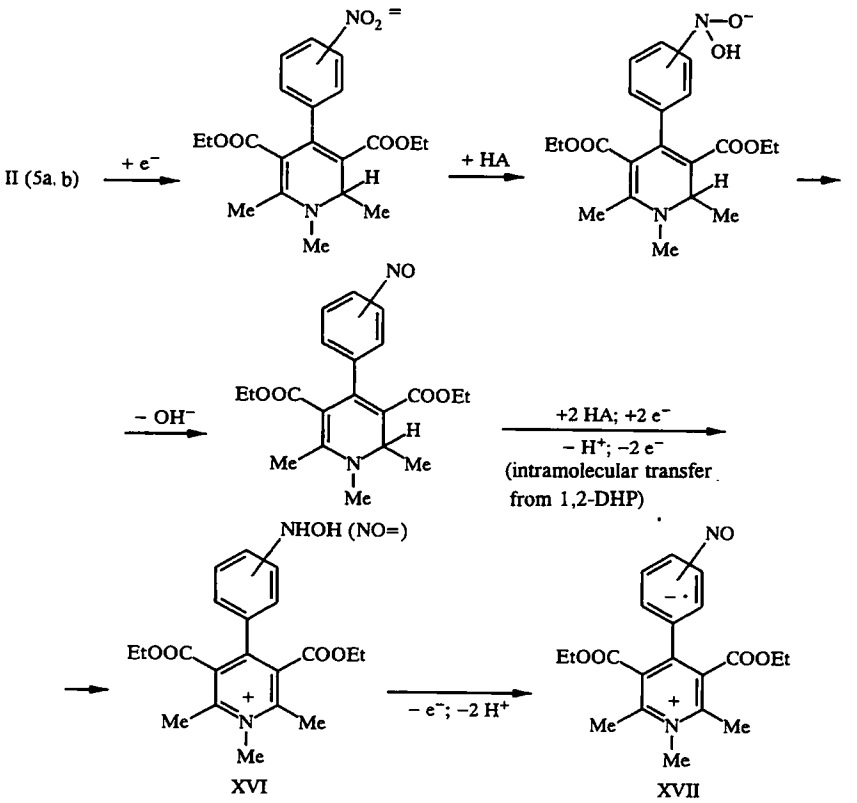


II (5a, b) XI

Radical-anions of the substituted nitrophenyl derivative can be formed during the reverse oxidation of the hydroxylaminophenyl derivative or the dianion of the nitrosophenyl derivative as for the derivatives of 1,4-DHP (scheme 4). In this case, however, it is impossible to assign the structure of the heterocyclic substituent unambiguously to these radicals of 1,2-DHP, since the absence of a proton at position 4 of the heterocycle and accordingly the hfs constant do not exclude the possibility of intramolecular transfer of electrons and protons. It can be supposed that with an insufficient amount of proton donors in the reaction mixture the protons and electrons required for reduction of the nitro group may be partly transferred from the 1,2-DHP ring with the formation of the pyridinium salt of the hydroxylaminophenyl or nitrosophenyl derivative (XVI).

The reduction of the nitro group near the electrode will be the combined process of chemical and electrochemical transformations, presented in Scheme 7:

Scheme 7



The probability of the formation of the pyridinium ion (XVI) confirms that the first reduction wave of the pyridinium part of the molecule during the electrochemical reduction of the pyridinium salts containing a nitrophenyl substituent at position 4 lies at more positive potentials than the reduction potential of the corresponding 1,2-DHP. For example, for the *para*-nitrophenyl-1,2,6-trimethyl-3,5-diethoxycarbonylpyridinium salt $E_{1/2} = -0.73$ V, whereas for the corresponding 1,2-DHP $E_{1/2} = -1.15$ V. Moreover, the probability of the intramolecular transfer of electrons and protons is indicated by the appearance of the radical-anions of the nitrosophenyl derivative at the potential of the second polarographic wave, particularly in the case of the *para*-nitrophenyl-substituted 1,2-DHP I(5a), for which this wave is one-electron (Table 1).

For the *ortho*-nitrophenyl-substituted derivative of 1,2-DHP I(5c) the poorly defined oxidation and reduction peaks of a new product were only recorded during the potential sweep before the third reduction wave. However, no additional free-radical products were detected by ESR.

The characteristics of the electrochemical reduction of the *ortho*-nitrophenyl derivatives of 1,4-DHP and 1,2-DHP appear both in the values of the potentials at the first stage of reduction and in the further reduction process. The shift of the potential of the first reduction wave of these compounds to the more negative region may be due to rotation of the nitro group about the C—N bond from the plane of the benzene ring as a result of the repulsion of the NO_2 groups in the phenyl and $COOC_2H_5$ groups in the DHP fragments of the molecule. As mentioned above, in no case were we able to record the ESR spectra of the *ortho*-nitrosophenyl derivatives characteristic of the *para*- and *meta*-nitrophenyl-substituted derivatives. In addition, it is necessary to mention the extremely low stability of the recorded primary radical-anions in the N-unsubstituted derivatives of 1,4-DHP. The initial reduction products probably undergo rapid electrochemical transformations with the formation of electrochemically inactive compounds.

It follows from the presented results that the nitrophenyl derivatives of 1,4-DHP are reduced electrochemically with retention of the 1,4-DHP structure of the heterocycle, and intramolecular transfer of electrons and protons from the DHP part to the nitrophenyl fragment does not occur in these compounds. The presence of the radical-anions of the nitrosophenyl derivative is due to the oxidation of the hydroxylamine group, and their relative stability is an extremely interesting feature

TABLE 3. Potentials (V) of the Secondary Redox Systems formed during the Electrochemical Reduction of Compounds I(1-5)

Compound	Product									
	IV		VIII, XV		IX, X		XI		XVII	
	$-E_K$	$-E_a$	$-E_K$	$-E_a$	$-E_K$	$-E_a$	$-E_K$	$-E_a$	$-E_K$	$-E_a$
I(1a)	1,31	1,25								
I(2a)	1,26	1,20								
I(3a)	1,64	1,56								
I(4)	1,63	1,59								
I(1b)			0,86	0,80	1,32	...				
I(1c)			0,88	0,80	1,28	...				
I(2b)			0,93	0,84	1,23	1,18				
I(2c)			0,95	0,84	1,34	1,28				
I(2d)			0,94	0,86	1,30	1,24				
I(2e)			0,95	0,86	1,33	1,26				
I(3b)			—	—	1,33	1,23				
I(5a)			0,97	0,90			1,35	1,27	0,76	0,70
I(5b)			0,96	0,88			1,35	1,29	0,74	0,68
I(5c)			—	—			1,32	1,23	—	—

of the reduction of these compounds. The presence of the fairly stable free radical particles formed in the electrochemical process must attract attention both during investigation of the toxicity of this type of compound [26] and during interpretation of the inhibition of the autooxidation of the nitrophenyl derivatives of DHP through the formation of nitroxyl radicals [27].

EXPERIMENTAL

The 1,4-DHP derivatives were obtained by the methods in [28, 29], and the 1,2-DHP derivatives were obtained by the method in [30]. Electrochemical reduction was conducted in anhydrous DMFA [31] with tetrabutylammonium hexafluorophosphate as supporting electrolyte (0.1 M). The classical polarograms and the cyclic voltammetric curves were recorded on a PAR-170 polarograph with a three-electrode cell. The cathode was a dropping mercury electrode with forced drop removal (t = 0.5 sec, m = 0.90 mg/sec). The anode was a platinum wire. The reference electrode was an aqueous calomel electrode provided with a bridge for working in nonaqueous solvents. The cyclic voltammetric curves were recorded at a suspended mercury drop or a glassy graphite electrode with a sweep rate of 0.2 V/sec.

The ESR spectra of the free radical particles produced by electrochemical generation [32] in a three-electrode system at the surface of a flat platinum electrode in a microcell in the resonance cavity were recorded on a Carl Zeiss (Jena) ER-9 radiospectrometer. The spectra were modelled on an HP 2116C minicomputer coupled with the radiospectrometer on line [33].

Part of the experimental work was conducted earlier at the J. Heyrovský Institute of Electrochemistry and Physical Chemistry, Academy of Sciences of Czechoslovakia with the participation of I. Volke, V. Volkova, and I. Klima, to whom we convey our sincere gratitude. We also express our gratitude to the synthetic chemists who provided the samples of the compounds. The final investigations were financed by the Latvian Scientific Council (Project No. 94-467).

REFERENCES

1. Ya. P. Stradyn', Yu. I. Beilis, Ya. R. Uldrikis, G. Ya. Dubur, A. É. Sausin', and B. S. Chekavichus, Khim. Geterotsikl. Soedin., No. 11, 1525, 1530 (1975).
2. V. Skala, J. Volke, V. Ohanka, and J. Kuthan, Coll. Czech. Chem. Commun.; **42**, 292 (1977).
3. J. Ludvik, J. Klima, J. Volke, A. Kurfürst, and J. Kuthan, J. Electroanal. Chem., **138**, 131 (1982).

4. Ya. V. Ogle, Ya. P. Stradyn', G. Ya. Dubur, V. K. Lusis, and V. P. Kadysh, Khim. Geterotsikl. Soedin., No. 9, 1263 (1980).
5. Ya. V. Ogle, L. Kh. Baumane, P. A. Gavar, V. P. Kadysh, Ya. P. Stradyn', V. K. Lusis, D. Kh. Mutsenietse, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 5, 651 (1984).
6. I. É. Kirule, D. Ya. Rubene, É. A. Bisenieks, G. D. Tirzit, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 3, 416 (1982).
7. Ya. V. Ogle, L. Kh. Baumane, Ya. P. Stradyn', G. Ya. Dubur, V. P. Kadysh, R. A. Gavar, and V. K. Lusis, Khim. Geterotsikl. Soedin., No. 8, 1099 (1985).
8. J. R. Prous, The Years News. Therapeutic Targets, Prous Science Publishers, Barcelona (1994).
9. J. A. Derson and E. Brown, J. Am. Chem. Soc., **77**, 447 (1955).
10. L. Baumane, J. Stradins, R. Gavars, and G. Duburs, Electrochim. Acta, **37**, No. 14, 2599 (1992).
11. Ya. P. Stradyn', I. Fol'ke, L. Kh. Baumane, V. Fol'kova, I. Klima, G. Ya. Dubur, and R. A. Gavar, Electrochemical Reduction of 4-(Nitroaryl)dihydropyridines. Cyclic Voltammetry and ESR Spectra of Electrochemically Generated Radical-Anions (Preprint) [in Russian], IOS Akad. Nauk LSSR (1985).
12. A. Alvarez-Lueje, L. J. Nunez-Vergara, and J. A. Squella, Electroanalysis, **6**, 259 (1994).
13. D. H. Geske, J. L. Ragle, M. A. Bambenek, and A. L. Balch, J. Am. Chem. Soc., **86**, 987 (1964).
14. A. M. Triggle, E. Scheffer, and D. J. Triggle, J. Med. Chem., **23**, 1442 (1980).
15. T. Fujinaga, Y. Deguchi, and K. Umemoto, Bull. Chem. Soc. Jpn., **37**, 822 (1964).
16. L. G. Lawless, D. E. Bartak, and M. D. Hawley, J. Am. Chem. Soc., **91**, 7121 (1969).
17. L. Hollek and D. Becher, J. Electroanal. Chem., **4**, 321 (1962).
18. L. Kh. Baumane, Ya. P. Stradyn', R. A. Gavar, A. P. Gaukhman, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 11, 1494 (1988).
19. B. A. Vigante, Ya. Ya. Ozols, M. I. Terekhova, É. S. Petrov, G. Ya. Dubur, É. É. Liepin'sh, and G. I. Rozentale, Khim. Geterotsikl. Soedin., No. 4, 491 (1986).
20. T. I. Vakul'ska, L. I. Larina, O. B. Nefedova, and V. A. Lopyrev, Khim. Geterotsikl. Soedin., No. 4, 523 (1982).
21. V. P. Kadysh, G. Ya. Dubur, Ya. P. Stradyn', and Ya. R. Uldrikis, Khim. Geterotsikl. Soedin., No. 5, 641 (1978).
22. R. B. Ayscough, F. P. Sargent, and R. Wilson, Zh. Strukt. Khim. B, 903 (1966).
23. W. Kemula and Z. Kublik, Roczn. Chem., **32**, 941 (1958).
24. V. F. Starichenko, V. A. Ryabinin, and S. M. Shein, Izv. Akad. Nauk. Ser. Khim., 520 (1976).
25. Landolt-Börnstein, Zahlenwerten und Funktionen aus Naturwissenschaften und Technik. Neue Serie, Springer Verlag, Berlin (1980), Gr. II, Vol. 9, Part d1, p. 538.
26. J. E. Biaglow, O. F. Nygaard, and C. L. Greenstock, Biochem. Pharmacol., **25**, 393 (1976).
27. G. D. Tirzit, I. É. Kirule, L. Kh. Baumane, R. A. Gavar, Ya. P. Stradyn', and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 8, 1120 (1984).
28. U. Eisner and J. Kuthan, Chem. Rev., **72**, 1 (1972).
29. A. É. Sausin', V. K. Lusis, G. Ya. Dubur, and Yu. I. Beilis, Khim. Geterotsikl. Soedin., No. 11, 1508 (1978).
30. D. Kh. Mutsenietse, V. K. Lusis, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 9, 1225 (1982).
31. Yu. M. Kargin, V. V. Kondranina, and N. I. Semakhina, Izv. Akad. Nauk. Ser. Khim., 178 (1971).
32. Ya. P. Stradyn', R. A. Gavar, and L. Kh. Baumane, Izv. Akad. Nauk Latv. SSR, No. 2, 73 (1986).
33. L. M. Baider, R. A. Gavar, B. Ya. Liberman, A. B. Rozenblit, Ya. P. Stradyn', P. É. Tomson, and M. B. Fleisher, Teor. Éksp. Khim., **15**, 588 (1979).