Chemistry of Heterocyclic Compounds, Vol. 36, No. 10, 2000

SPECIAL FEATURES OF THE ELECTROCHEMICAL OXIDATION OF SUBSTITUTED 4-CARBOXY-1,4-DIHYDROPYRIDINES*

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Electrochemical oxidation potentials of 1,4-dihydropyridines substituted with 4-COOH, 4-COOR, and 4-CONRR' groups have been determined in aprotic acetonitrile by the rotating ring-disk electrode method (RRDE). The electrochemical reduction potentials of the resulting products were also determined at the ring electrode. It was established that protonated pyridines are formed in the oxidation of derivatives with and without a substituent in position 4 of the heterocycle. In the case of 4-alkoxycarbonyl substituted compounds the substituent at position 4 is generally retained. 1,4-Dihydrogenated derivatives of isonicotinic acid as a rule loose the substituent at position 4 on oxidation, and both types of product were recorded for the corresponding 4-carbamoyl derivatives. The substituent at position 9 of the heterocycle was mainly retained on electrochemical oxidation of the 3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine derivatives studied.

Keywords: 4-carboxy-1,4-dihydropyridines, rotating ring-disk electrode method (RRDE), electrochemical reduction, electrochemical oxidation.

Derivatives of 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridine, including those containing various substituents at position 4 of the heterocycle, and also 1,4-dihydronicotinamides are considered as model compounds of the coenzyme NADH. The chemical basis of the NADH $\rightleftharpoons$ NAD^+ transformation is the oxidation of a 1,4-dihydropyridine structure to a pyridine [1]. The mechanism of this transition is interesting from the point of view of organic chemistry and medicinal biochemistry. On the other hand carbonyl derivatives of 1,4-dihydropyridine possess desirable pharmacological properties (for example, derivatives of 1,4-dihydronicotinoylamino acids are antiarrhythmics, neuroprotecting agents, and neuromodulators [2]). Depending on the oxidizing agent, the chemical structure of the reacting compounds, and the conditions of the medium, the routes of 1,4-dihydropyridines oxidation may be different and lead to different reaction products [3-6]. On electrochemical oxidation of 1,4-dihydropyridines [7-10] in protic media a *2e* process takes place as a result of which the corresponding pyridine is formed. In aprotic media the oxidation of 1,4-dihydropyridines occurs in stages, in certain cases with the formation of relatively stable primary products *viz*. cation-radicals, but the final product is the corresponding pyridinium salt (or pyridine in the case of N-unsubstituted 1,4-dihydropyridines). The overall electrochemical oxidation of 1,4-dihydropyridines may be represented as follows.

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* Dedicated to the clear memory of A. N. Kost, long-standing collaboration with whom deepened the understanding of heterocyclic chemistry in Latvia.

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N-Unsubstituted derivatives $PyH_2 - 2e^- - 2H^+ \rightarrow Py$

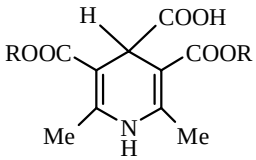
$PyH_2 - 2e^- - H^+ \rightarrow PyH^+$

N-Substituted derivatives $PyRH - 2e^- - H^+ \rightarrow PyR^+$

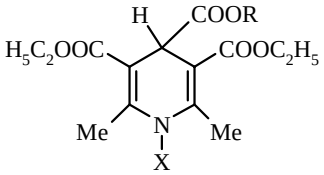
The electrochemical oxidation of dihydropyridines is one of the most frequently applied model methods for studying the above processes, and investigations are carried out on stationary (cyclic voltamperometry) or on rotating microelectrodes (using a disk electrode or a ring-disk electrode). Electrochemical reactions may be considered as models for understanding the mechanism (EC, CE or ECEC, EEC) of the step-wise fission of electrons and protons (or hydrogen atoms) in the process of oxidizing 1,4-dihydropyridines, and also as convenient reactions for detecting the structure of the oxidation products.

The chemical oxidation of 4-carbonyl substituted 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines in the case of compounds with 4-COOH and 4-CONRR' groups gives the corresponding 4-unsubstituted pyridine, but in the case of 1,4-dihydropyridines with a 4-COOAlk group a proton is split off in the majority of cases and the oxidized heterocycle retains the ester substituent at position 4 [11]. The same also applies to the polycyclic derivative 10,12-dioxo-5,10,11,12-tetrahydroindeno[1,2-*b*:2',1-*e*]pyridinecarboxylic acid, its ester, and amide [11]. However it was shown in [12] that the oxidation of these compounds under milder conditions, such as with the oxygen of the air at room temperature, the COOH substituent at position 4 of the heterocycle is retained.

The aim of the present work was to clarify what products are formed in the electrochemical oxidation of 4-carbonyl-substituted 1,4-dihydropyridines in an aprotic medium. The studied 2,6-dimethyl-1,4-dihydropyridine derivatives containing at position 4 of the dihydropyridine ring carboxyl, (compounds **1a-d**), ester (compounds **2a-e**), or amide groups (compounds **3a-d**), and various alkoxycarbonyl substituents at positions 3 and 5 of the heterocycle, are hydrogenated derivatives of isonicotinic acid. For comparison, an investigation was carried out on compounds with a more complex heterocyclic structure, *viz*. 3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridines (compounds **4a-c**), also having ester, amide, or carboxyl groups at position 9 of the heterocycle.



1a–d

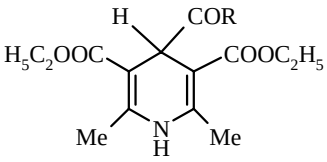


2a–e

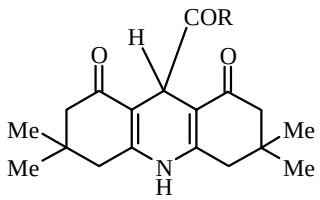
1 a R = Me; **b** R = C_2H_5; **c** R = C_3H_7; **d** R = $CHMe_2$;

2 a R = Me; **b** R = Me; **c** R = C_2H_5; **d** R = $CHMe_2$; **e** R = CMe_3;

2 a X = Me; **2b–e** X = H



3a–d

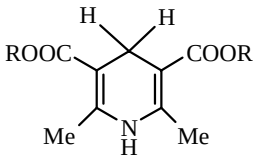


4a–c

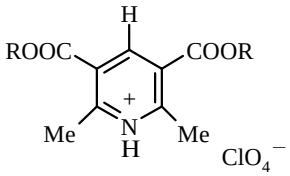
3 a R = NH_2, **b** R = NHMe, **c** R = NMe_2; **d** R = $N(C_2H_5)_2$;

4 a R = OH; **b** R = OMe; **c** R = NH_2

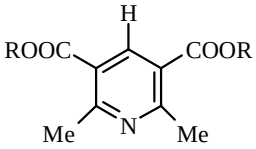
To clarify the structures of the products reduced at the ring electrode the corresponding 4-unsubstituted 1,4-dihydropyridines (compounds **5a-d**), pyridinium salts (compounds **6b,d**), and pyridines (compounds **7b,d**) were studied, in addition to the oxidized forms, *viz*. pyridinium salts (compounds **8b,d** and **9**) and pyridine **10** containing a substituent at position 4. Model compounds of polycyclic structure, dihydro-, protonated, and neutral forms without substituent at position 9 of the heterocycle (**11, 12, 13** respectively) and the protonated and neutral oxidized forms containing a COOH substituent (**14** and **15** respectively) were also investigated.



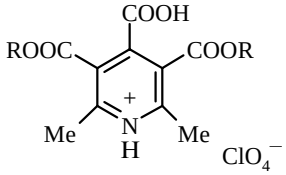
5a–d



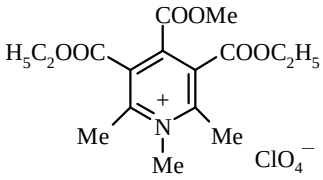
6b,d



7b,d



8b,d



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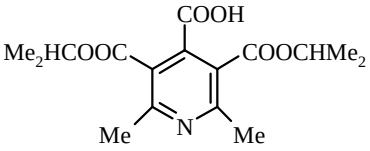
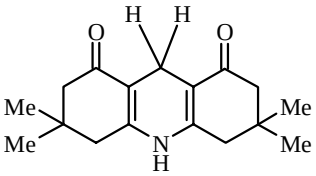


10

5–8 a R = Me, **b** R = C_2H_5, **c** R = C_3H_7, **d** R = $CHMe_2$



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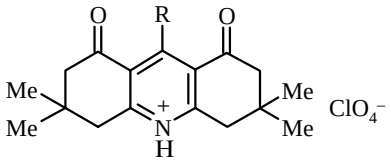
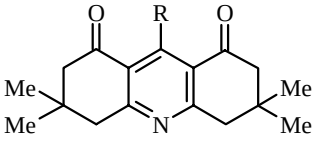


12, 14



13, 15

12, 13 R = H; **14, 15** R = COOH

The electrochemical investigations of dihydropyridines were carried out in acetonitrile. Electrooxidation was carried out on a rotating disk electrode and electroreduction of the products formed at a ring electrode (oxidation/reduction potentials and the number of electrons consumed in the course of the electrochemical reaction are given in the Tables).

On electrochemical oxidation of derivatives with the dihydropyridine structure at the disk electrode generally one polarographic wave was detected the height of which was close to the two-electron level. Branching of this wave was observed in the case of compounds containing a carboxyl group in position 4 of the heterocycle, however this wave was also close to the two-electron level in overall height (compounds **1a-d**). This may be caused by the dissociation of a proton from the carboxyl group, consequently two equilibrium forms of the compound are subject to oxidation. A comparison of the results given in Tables 1 and 2 shows that the introduction of a carboxyl, alkoxycarbonyl, or carbamoyl residue into position 4 of the heterocycle hinders the electrochemical oxidation and shifts the potential by 100-200 mV towards positive values compared with the electrooxidation of 4-unsubstituted 1,4-dihydropyridines. The electrochemical reduction of both the hydrogenated initial compounds and the products of heteroaromatic structure on introducing a carboxyl group proceeds more readily. The first reduction wave on the voltamperometric curve corresponding to the reduction of 4-carbonyl-substituted pyridinium salts was displayed in the range from -0.9 to -1.2 V relative to a $Ag/AgNO_3$ reference electrode, of pyridines from -1.8 to -2.0, and of 1,4-dihydropyridines from -2.0 to -2.4 V. Model 4-unsubstituted dihydropyridines, pyridines,

and pyridinium salts were reduced with more difficulty and the potential was shifted by 200-400 mV towards negative values (see Table 2). On electrochemical oxidation of N-unsubstituted derivatives of 1,4-dihydroisonicotinic acid and of the N-substituted compound reduction waves were detected at the ring electrode for the protonated forms of pyridine, but not for neutral pyridines, the formation of which was proposed in the case of N-unsubstituted 1,4-dihydropyridine derivatives [9]. There are several possibilities for the formation of a pyridinium salt in the *2e* process for the oxidation of 1,4-dihydropyridines. Firstly, the oxidation reaction may proceed by an ECE mechanism with retention of the proton on the nitrogen atom similar to the electrochemical oxidation of N-substituted 1,4-dihydropyridines. Secondly, the pyridine molecule formed after removal of two electrons and two protons is subject to protonation. To clarify this process the electrochemical oxidation of compound **1d** was carried out with addition of the corresponding pyridine **10** to the initial solution. At unchanged concentration of dihydropyridine being oxidized the height of the reduction wave for the pyridinium salt **8d** was increased with an increase in the concentration of pyridine **10** in the initial solution. This indicates that the neutral pyridine molecule is reduced at the ring in the form of pyridinium cations and consequently if neutral pyridine molecules are formed initially on electrooxidation then they are converted on the way from the disk to the ring electrode and are detected at the ring as pyridinium cations.

In order to identify the products formed, the half-wave potentials recorded at the ring electrode, for products of the electrochemical oxidation at the disk electrode of hydrogenated compounds, were compared with the potentials of model compounds recorded under analogous conditions, and also with the values of the reduction potentials of the 1,4-dihydropyridines being studied.

For example, four reduction waves were recorded at the ring electrode for the 1,4-dihydro derivative of substituted 4-isonicotinic acid **1b**. Two of them, at potentials of -2.34 and -2.68 V, may be assigned to the reduction of the initial 1,4-dihydropyridine **1b**, which is present in excess in solution. The value of the reduction potential for the first wave (-0.98 V) coincides with the value of the reduction potential for the corresponding model 4-substituted pyridinium salt **8b**. The following wave at a potential of -1.35 V corresponds to the reduction wave of another model compound, the 4-unsubstituted pyridinium salt **6b**, which is also formed on oxidation of the 4-unsubstituted 1,4-dihydropyridine derivative **5b**. The ratio of the wave heights and the character of the products reduced at the ring electrode did not in practice depend on whether electrolysis was carried out at the disk electrode at the potentials of the saturation current of the first or second oxidation wave of the 4-isonicotinic acid derivative **1b**. On electrochemical oxidation of compound **1d** a product with reduction potential -1.41 V was mainly formed, which indicates fission of the carboxyl group leading to the 4-unsubstituted pyridinium salt **6d**. The weakly expressed wave at -1.05 V corresponds to the product **8d**, a pyridinium salt with a carboxyl substituent in the heterocycle. Depending on the heights of the first two reduction waves it should be possible to judge the amount of one or other product. However it is difficult to realize a strict quantitative analysis, since neutral pyridines may be formed in addition to the protonated pyridines. These, such as the 4-substituted 1,4-dihydropyridine **1b** (-2.38 V) and the 4-unsubstituted pyridine **7b** (-2.34 V) are impossible to determine due to overlap of the reduction waves. It may therefore be concluded that both 4-substituted and 4-unsubstituted protonated pyridines **8b**,**d**, and **6b**,**d** may be formed as products of the electrochemical oxidation of compounds **1b** and **1d**. In the case of the electrooxidation of compounds **2a-e,** containing an ester group at position 4 of the heterocycle, the main product detected at the ring electrode was the 4-substituted protonated form of the pyridine. The half-wave potential value of the first wave on the reduction carried out for the product of electrochemical oxidation of the N-substituted compound **2a** (-0.99 V) corresponds to the half-wave potential for the reduction of model compound **9**. Since on electrochemical oxidation of the N-unsubstituted derivatives **2b-e** a reduction wave was also detected at this potential, it is highly probable that the N-unsubstituted derivatives **2b-e** are oxidized with retention of the substituent in position 4 of the heterocycle. However a second reduction wave was detected at the ring electrode at a potential of -1.35 V, which probably corresponds to the reduction of the 4-unsubstituted product **6b**. The height of this wave and consequently the quantity of product was significantly less than of the 4-substituted product (analog **9**), but for compound **2b** such a wave was completely absent. It is possible to analyze compounds for which model unsubstituted compounds are available in a similar manner. When such compounds are not available analogs close in structure may be used.

TABLE 1. Half-wave Potentials ($E_{1/2}^{ox}$, V) and Number of Electrons (n) in the Electrochemical Oxidation at the Disk Electrode, Half-wave Potentials ($E_{1/2}^{red}$, V) and Number of Electrons (n) in the Electrochemical Reduction at the Ring Electrode of 1,4-Dihydroisonicotinic Acid Derivatives **1-3**, the Polycyclic Analogs **4,** and of the Products Formed on Their Oxidation

Compound	Initial compound				Oxidation products									
					1st wave		2nd wave		3rd wave		4th wave		5th wave	
	$E_{1/2}^{ox}$, V	n	$E_{1/2}^{red}$, V	n	$E_{1/2}^{red}$, V	n	$E_{1/2}^{red}$, V	n	$E_{1/2}^{red}$, V	n	$E_{1/2}^{red}$, V	n	$E_{1/2}^{red}$, V	n
1a	0.82 1.05	1.1 0.8	-2.34 -2.70	1.1 0.3	-0.92	0.3	-1.32	1.3			-2.34	0.6	-2.70	0.3
1b	0.73 0.99	2.0 0.2	-2.38 -2.70	1.1 0.2	-0.98	0.4	-1.35	1.5			-2.37	0.6	-2.68	0.2
1c	0.84 1.06	0.8 0.8	-2.39 -2.8	1.1	-1.02	0.1	-1.35	1.3			-2.39	1.6	-2.68	0.4
1d	0.70 0.95	0.3 1.0	-2.46 -2.78	0.6 0.5	-1.05	0.1	-1.41	0.9	-1.81	0.1	-2.46	0.8	-2.78	0.5
2a	0.87	1.8	-2.61	1.9	-0.97 -1.22	1.6 0.5	-1.31	0.3	-1.99	0.3			-2.61	1.6
2b	0.90	2.0	-1.99 -2.58	0.3 1.2	-0.99	1.5			-1.99	0.4			-2.58	1.2
2c	0.93	2.0	-2.58	1.0	-0.99	1.3	-1.35	0.3	-1.98	0.6			-2.58	1.0
2d	0.93	2.0	-2.58	1.0	-0.99	1.4	-1.35	0.2	-1.90	0.5			-2.58	1.0
2e	0.91	1.6	-2.60	1.0	-1.01	0.8	-1.35	0.2	-1.98	0.5	-2.38	0.4	-2.63	1.2
3a	0.89	1.1	-2.61	0.8	-1.16	0.2	-1.38	0.4	-1.74	0.8			-2.63	0.9
3b	0.80	0.7	-2.59	0.5			-1.37	0.6	-1.69	0.5	-2.34	0.2	-2.59	0.5
3c	0.88	1.5	-2.57	1.0			-1.37	0.6	-1.75	0.6			-2.57	1.0
3d	0.89	1.1	-2.61	0.8	-1.20	0.2	-1.37	0.4	-1.73	0.8			-2.61	0.8
3e	0.91	1.4	-2.56	0.5			-1.37	0.5	-1.68	0.7	-2.32	0.1	-2.58	0.5
4a	1.12	1.2	-1.75 -2.35	0 8 1.0	-0.77	0.4	-1.24	0.1			-1.75	0.8	-2.35	1.0
4b	1.05	1.4	-1.97 -2.42	0.6 0.7	-0.54	0.7					-1.89	0.9	-2.42	0.7
4c	0.82	1.7	-1.91 -2.45	0.8 1.1	-0.58	0.3	-1.30	0.1			-1.94	1.0	-2.45	1.0

TABLE 2. Half-wave Potentials ($E_{1/2}^{ox}$, V) and Number of Electrons (n) for the Electrochemical Oxidation at the Disk Electrode, Half-wave Potentials ($E_{1/2}^{red}$, V) and Number of Electrons (n) for the Electrochemical Reduction at the Ring Electrode of Model Compounds **5-15,** and of the Products Formed on Oxidation of the Dihydropyridine Forms **5** and **15**

Compound	Initial compound				Oxidation products					
					1st wave		2nd wave		3rd wave	
	$E_{1/2}^{ox}$, V	n	$E_{1/2}^{red}$, V	n	$E_{1/2}^{red}$, V	n	$E_{1/2}^{red}$, V	n	$E_{1/2}^{red}$, V	n
5a	0.60	2.0	-2.74	1.0	-1.32	1.5			-2.74	1.0
5b	0.64	2.0	-2.68	1.0	-1.35	1.5			-2.68	1.0
5c	0.71	2.0	-2.27	0.3	-1.40	1.4	-2.20	0.7	-2.76	0.8
			-2.76	0.8						
5d	0.55	1.3	-2.43	0.5	-1.41	1.3	-2.43	0.7	-2.76	0.8
			-2.76	0.8						
6b			-1.33	1.2						
			-2.35	1.2						
6d			-1.41	1.2						
			-1.80	0.2						
			-2.43	0.5						
			-2.76	0.4						
7b			-2.35	1.0						
7d			-2.27	0.8						
8b			-0.98	0.5						
			-1.90	0.8						
8d			-1.05	1.3						
			-1.50	0.2						
			-1.78	1.6						
9			-0.98	1.3						
			-1.72	1.3						
10			-1.82	0.8						
			-2.58	0.3						
11	0.67	1.6	-2.06	0.8	-1.40	1.4	-2.06	0.7	-2.53	1.5
			-2.53	1.5						
12			-0.87	1.5						
			-1.40	0.2						
			-2.10	0.8						
13			-1.98	1.1						
14			-0.77	1.3						
			-1.40	0.1						
			-2.37	0.9						
15			-1.75	1.4						

Both types of product were formed in almost all cases under conditions of electrochemical oxidation carried out for derivatives of 1,4-dihydroisonicotinic acid, i.e., the process occurs both with retention of the substituent at position 4 of the heterocyclic ring and with its removal. The structure of the substituent affects only the ratio of both reaction products. On electrochemical oxidation of isonicotinic acid esters the product with a substituent at position 4 predominates. Methyl ester **2b** gives the only product with a 4-$COOCH_3$ substituent, but in the case of compounds with a COOH group the product with the carboxyl group split off is generally detected. Transition from methoxyl to a more complex ester group in the substituent at position 4 facilitates fission (compounds **2b-e**). Lengthening of the alkyl chain in alkoxycarbonyl substituents at positions 3 and 5 of the heterocycle also leads to destabilization of the 4-COOH group (compounds **1a-d**). In the case of substituted amides of isonicotinic acid we failed to develop any reliable rules, possibly because these compounds are poorly soluble in aceto-nitrile and the waves of the reduced products are weakly expressed, and also due to the absence of model compounds containing an amide substituent.

Strengthening of the electron-donating properties of the alkyls in the ester groups at positions 3, 5, and also 4 assists fission of the 4-carbonyl substituent. A similar property was noted in the chemical oxidation of 4-alkyl and 4-aralkyl derivatives of 1,4-dihydropyridine [5,13,14]. Fission of the 4-alkyl group from 1,4-dihydropyridine (in difference to 1,4-dihydropyridines with a 4-aryl group) was also observed on oxidation with cytochrome P-450, which acts as a 1*e* oxidizing agent [4,6,15].

Three polycyclic dihydro derivatives substituted with COOH, $COOCH_3$, and $CONH_2$ groups (compounds **4a-c**, Table 1), and some compounds modeling hydrogenated isonicotinic acid (see Table 2) were also studied by ring-disk method. Analysis of the results obtained indicates that the polycyclic analogs of 1,4-dihydropyridine were oxidized with more difficulty than the corresponding monocyclic compounds. The oxidation products formed were correspondingly reduced more readily. In the case of a methoxycarbonyl substituent in position 4, the substituent was completely retained during the oxidation process and a protonated product analogous to **14** was formed. All the model compounds for the possible oxidation products of the derivative with a COOH substituent **4a** were synthesized. In comparisons, it is seen that the reduction potential of the product (-0.77 V), the protonated form **14**, is displaced by 170 mV towards positive values compared with the reduction potential of the monocyclic analog **8b**, and by 100 mV compared with the reduction potential of the 4-unsubstituted polycyclic product **12**. On oxidizing compounds **4a** and **4c** a second weakly expressed wave at a half-wave potential of -1.3 V was recorded on the polarograms. Its assignment to a definite product was difficult since none of the studied model oxidation products possessed such a value of potential, but further reduction products such as **14** and **12** may occur in this region of potentials. However it may be said fairly confidently that on electrochemical oxidation of polycyclic analogs of 1,4-dihydroisonicotinic acid the substituent in position 4 is retained. This conclusion is in agreement with that stated for monocyclic 1,4-dihydropyridine derivatives and shows that the expressed electron-withdrawing properties at positions 3, 4, and 5 of tricyclic condensed cyclohexenone derivatives of 1,4-dihydropyridine hamper the fission of electrons [16] and on electrochemical oxidation display a stabilizing effect on the fission of a carbonyl substituent at position 4.

EXPERIMENTAL

The 4-carboxyl derivatives of 1,4-dihydropyridine **1a-d** were synthesized by the method of [17], the 4-alkoxycarbonyl derivatives **2a-e** as in [11], and the 4-carbamoyl derivatives **3a-d** as in [18,19]. The procedure for synthesizing compound **4a** was described in [20], and for compounds **4b,c** in [21,22]. N-Unsubstituted derivatives of 1,4-dihydropyridine **5a-d** were synthesized by the procedure given in [23]. Chemical oxidation and the general method for the synthesis of the oxidized forms of compounds **7** are given in [11]. Since the direct oxidation of 4-carboxyl derivatives of 1,4-dihydronicotinic acid occurs with decarboxylation, a more lengthy route was used to obtain dehydrogenated compounds of type **10**: 1) preparation of the methyl ester of 1,4-dihydroisonicotinic acid; 2) methylation at nitrogen (for the synthesis of N-methyl substituted compounds) by sequential treatment with sodium hydride in an anhydrous medium and methyl iodide according to [24]; 3) oxidation ($NaNO_2$+CH_3COOH; N_2O_3 in alcohol); 4) hydrolysis of the 4-$COOCH_3$ group with an equivalent of KOH in alcohol. Perchlorates of the pyridine derivatives were prepared from solutions of the corresponding pyridines in perchloric acid.

The electrochemical investigations were carried out by rotating disk electrochemical methods on equipment consisting of a PAR (USA) Model 636 Ring-Disk Electrode System and a Bruker model E-350 twin potentiostat. The disk and ring electrodes were made of glass–graphite. The calculated efficiency coefficient of the electrodes [25] was 0.39, and the electrode rotation rate was 2000 min^{-1}. All potentials were measured relative to a 0.1 N silver reference electrode ($Ag/AgNO_3$) in acetonitrile, the solvent being purified by the procedure of [26]. The depolarizer concentration for the majority of compounds was 5.10^{-4} M, and for poorly soluble compounds 1.10^{-5} M. Tetrabutylammonium hexafluorophosphate (1.10^{-1} M) was used as base electrolyte.

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