ELECTROCHEMICAL OXIDATION OF SUBSTITUTED 3,4-DIHYDRO-2-PYRIDONES AT A ROTATING GRAPHITE ELECTRODE WITH A RING

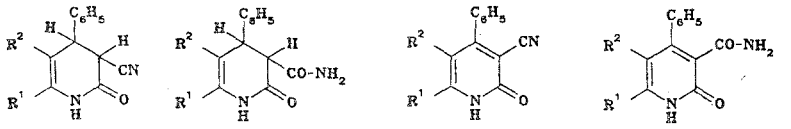
V. P. Kadysh, Ya. P. Stradyn', Ya. V. Ogle,
Yu. É. Pelcher, and G. Ya. Dubur

UDC 541.138.2:547.824

Using the method of a rotating disk (graphite) electrode with a ring, UV spectroscopy, and prolonged electrolysis, it has been shown that the first stage of the electrochemical oxidation of substituted 3,4-dihydro-2-pyridones in anhydrous acetonitrile corresponds to a two-electron process taking place by an ECE mechanism and leads to the formation of the corresponding substituted 2-pyridones. The potentials of the electrochemical oxidation of the 3-cyano and 3-carbamoyl derivatives of the reduced forms and the potentials of the electroreduction of the corresponding oxidized compounds have been determined.

3,4-Dihydro-2-pyridones exhibit membrane-protective activity in the peroxide oxidation of mitochondria, and it therefore is important to give a quantitative characterization of their capacity for undergoing oxidation. There is information in the literature on the chemical oxidation of these compounds to the corresponding 2-pyridones, but the direct oxidation reactions take place under fairly severe conditions and have not been characterized by kinetic results [1].

To obtain a quantitative characterization of the capacity of these compounds for undergoing oxidation, in the present investigation we have determined the potentials of the electrochemical oxidation of the 3,4-dihydro-2-pyridones (I) and (II) in an aprotic medium — acetonitrile — by the method using a rotating disk electrode with a ring. On the basis of an analysis of the volt–ampere curves obtained, and also of the results of controlled-potential electrolysis and of UV spectroscopy, an attempt has been made to determine the total course of the process of electrochemical oxidation.



I a,b II a,b III a,b IV a,b

I—IV a $R^1=C_6H_5$, $R^2=H$; b $R^1=CH_3$, $R^2=COOC_2H_5$

The study of the electrochemical oxidation of the dihydropyridones (I) and (II) at a rotating platinum disk electrode proved to be impossible because of the formation of ill-defined unreproducible waves due to the presence of surface oxides of platinum sharply changing the adsorption and catalytic properties of its surface [2]. The work was therefore performed on an electrode the disk of which was made of graphite and the ring of platinum.

It must be mentioned that compounds (I) and (II) can exist in pyridine in two tautomeric forms — as derivatives of 2-oxo-1,2,3,4-tetrahydropyridine and of 2-hydroxy-3,4-dihydropyridine; they can also exchange the protons at the carbon atoms in the positions 3 and 4 of the ring and at the nitrogen atom, the mobility of which is high [1, 3]. However, the IR spectra and NMR spectra taken in dimethyl sulfoxide have shown that compounds (I) and (II) exist in the 2-oxo form. The NMR spectra taken in anhydrous acetonitrile show that under the experimental conditions that we selected for the electrochemical study the compounds exist, at least in the bulk solution, in the undissociated oxo form.

Institute of Organic Synthesis, Academy of Sciences of Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 87-91, January, 1984. Original article submitted July 19, 1983.

0009-3122/84/2001-0073$08.50

TABLE 1. Parameters of the Electrochemical Transformations of 3,4-Dihydro-2-pyridones at a Rotating Graphite Disk Electrode with a Ring in Acetonitrile [supporting electrolyte — tetrabutylammonium perchlorate (0.1 M); concentration — $5 \cdot 10^{-4}$ M]

Compound	Oxidation at the disk				n	Reduction at the ring[a]				Reduction at the ring[b]		Reduction at the disk		n
	first wave		second wave			first wave		second wave						
	$E_{1/2}$, V	i_{lim}, μA	$E_{1/2}$, V	i_{lim}, μA		$-E_{1/2}$, V	i_{lim}, μA[c]	$-E_{1/2}$, V	i_{lim}, μA	$-E_{1/2}$, V	i_{lim}, μA	$-E_{1/2}$, V	i_{lim}, μA	
Ia	1,26	470	1,50	245	1,8	0,31	(74)	1,74	(19)					
Ib	1,54	500	ill-defined		1,9	0,33	(68)	1,92	(8)					
IIa	0,95	440	1,49	320	1,7	0,32	(31)	1,92	(10)					
IIb	1,33	530	ill-defined		2,0	0,33	(48)	—	—					
IIIa										1,78	(49)	1,78	220	0,8
IIIb										1,94	(20)	1,91	210	0,8
IVa										1,90	(39)	1,90	215	0,8
IVb										—	—	2,13	210	0,8

[a] At the potential of the limiting-current plateau of the first wave. [b] At zero potential of the disk. [c] The values of the strength of the reduction current at the platinum ring given in parentheses are not completely reproducible, and therefore they cannot be compared with the corresponding values obtained at the graphite disk and be used for calculating the current yield of the substance at the disk.

As can be seen from Table 1, compounds (I) and (II) give two electrooxidation waves at the disk. The $E_{1/2}$ value of the first, well-defined, wave is in the range of 0.9-1.5 V, i.e., compounds of type (I) are oxidized with considerably greater difficulty than the 3,5-diethoxycarbonyl-1,4-dihydropyridines studied previously [4]. It is perhaps precisely the high values of $E_{1/2}$ for oxidation that explain the ill-defined antioxidant activity of compounds of type (I) and (II) in comparison with the 1,4-dihydropyridines.

For the first wave, a linear dependence of i_{lim} on the square root of the angular rate of rotation of the disk ($\sqrt{\omega}$) and a direct proportionality to the concentration of the electroactive substance are observed, which indicates a diffusional nature of the current. The process accompanying the first wave is two-electronic and irreversible (Table 1).

The second oxidation wave, however, is poorly reproducible, has maxima, and changes its form with a variation in the concentration. No direct proportionality of the height of the wave to the concentration is observed. Apparently, the processes taking place at the potentials of the second wave are strongly affected by the adsorption of the reaction products; for this reason, the nature of the second wave was not studied in more detail in the present investigations.

During reversible electroreduction at the ring of the products of electrooxidation at the potential disk corresponding to the limiting-current plateau of the first wave, a very well-defined wave was observed for the dihydropyridones (I) and (II) in the range of potentials from —0.30 to —0.35 V and a second wave in a more negative range (from —1.70 to —1.95 V).

The first of the waves at the ring can be ascribed to the reduction of the hydrogen ions H^+ formed as the result of the intermediate deprotonization of the cation radicals obtained in the electrooxidation of the compounds under investigation at the disk. This wave, like that observed earlier in the case of the electrochemical oxidation of 3,5-diethoxycarbonyl-1,4-dihydropyridines [4] was identified on the basis of the increase in its height after the addition of proton donors — standard solutions of sulfuric acid. At a concentration of the latter in the cell of $1 \cdot 10^{-3}$ M, the height of the hydrogen wave doubled (from 68 to 136 μA). An indirect confirmation of the occurrence of electrooxidation with the inclusion of a chemical reaction (ECE mechanism) is the linear fall in the magnitude $i_{lim}/\omega^{1/2} \cdot c$ as a function of $\sqrt{\omega}$ for the first oxidation wave (Fig. 1) [5]. This can be considered as an argument against the splitting out of a proton before the detachment of the first electron.

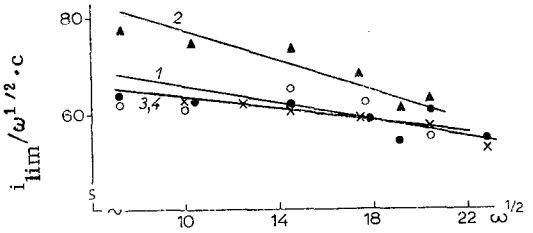


Fig. 1. Dependence of the reduced limiting current on the rate of rotation for 3-cyano-4,6-diphenyl-3,4-dihydro-2-pyridone (1), 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-2-pyridone (2), 3-carbamoyl-4,6-diphenyl-3,4-dihydro-2-pyridone (3), and 3-carbamoyl-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-2-pyridone (4) in acetonitrile on a support of 0.1 N tetrabutylammonium perchlorate.

The second electroreduction wave at the ring, appearing in the interval from −1.70 to −1.95 V corresponds to the potentials of the reduction of the oxidized forms of the compounds — 3-cyano-4,6-diphenyl-2-pyridone (IIIa), 3-cyano-5-ethoxycarbonyl-6-methyl-4-phenyl-2-pyridone (IIIb), and the corresponding 3-carbamoyl derivatives (IVa and IVb) — obtained as the result of the chemical oxidation of the dihydropyridones (I and II) [6]. These products were available to us as model compounds.

The prolonged electrolysis of compounds (I) and (II) carried out at the potentials of the limiting-current plateaus of the first waves with recording of the UV spectra of the solutions before and after electrolysis showed that the final products of the electrolysis of the nitriles (Ia) and (IIa) had long-wave absorption maxima at 367 nm, which are characteristic for the oxidized forms (IIIa) and (IVa).

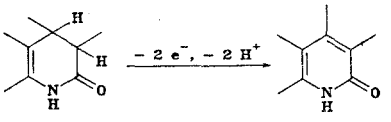
In the course of the prolonged electrolysis of compound (Ia), after predetermined intervals of time not only oxidation waves at the disk but also the reduction waves at the ring were recorded. It was found that with time the height of the second wave, due to the electroreduction of the pyridone (IIIa), rose, which is connected with its accumulation in the solution as electrolysis proceeded.

The prolonged electrolysis of compounds (Ib) and (IIb) did not give such unambiguous results as in the cases of (Ia) and (IIa), since, because of certain features of these compounds (perhaps a greater adsorbability of them themselves or of the products of electrochemical oxidation on the surface of the electrode), after each successive cleaning of the electrode the current strength rapidly fell to zero, i.e., electrolysis practically ceased (the potentials of the limiting-current plateaus at which electrolysis proceeded for compounds (Ib) and (IIb) lay in the higher positive region than for (Ia) and (IIa)).

However, the reduction wave of the oxidized form (IIIb) corresponding to the presumed end product of the electrochemical oxidation of the dihydropyridone (Ib) appeared at the ring at the same potentials as the second reduction wave at the ring for (Ib) (at a potential of the disk corresponding to the limiting-current plateau of the first oxidation wave). The reduction wave of the oxidized form (IVb) could be recorded at the disk in an excessively negative region (−2.13 V), and therefore the second reduction wave of the products of electrochemical oxidation at the ring corresponding to it could not be detected for the dihydropyridone (IIb) (it fused with that of the separation of the supporting electrolyte).

On the basis of the facts given above, it may be assumed that the electrochemical oxidation of compounds (I) and (II) takes place monotypically. This is also confirmed by the influence of substituents on the value of $E_{1/2}$ for electrooxidation in accordance with their electron-accepting properties.

The overall equation of the first stage of electrooxidation can be written in the form



The electrochemical results obtained do not permit an unambiguous judgment either of the position of the first detachment of an electron or of the sequence of detachment of protons and electrons from the various positions of the ring of the hydrogenated 2-pyridones. An elucidation of the stagewise mechanism of the electrooxidation process requires a study of model substances with a fixed structure and the separate identification of the products of preparative electrolysis: This will be the object of our further investigations.

The capacity for oxidation of the anionic forms of compounds (Ia) and (IIa) was also estimated on the basis of calculations of the rate constants for the oxidation of these compounds by 2-benzylideneindane-1,3-dione [7]. It was found that the rate of oxidation of the dihydropyridone (IIa) ($k = 3.7 \cdot 10^{-4}$ sec^{-1}) was somewhat higher than that of the dihydropyridone (Ia) ($k = 3.1 \cdot 10^{-4}$ sec^{-1}), which can be explained by the electron-accepting influence of the nitrile group and is in harmony with the sequence of electrochemical oxidation potentials.

It must be mentioned that compounds (III) and (IV) can be reduced not only at the ring but also at the disk, the $E_{1/2}$ values in the two cases practically coinciding, but the shape of the wave at the graphite is expressed far better (Table 1). However, the presence of the strong electron-accepting ethoxycarbonyl group in position 5 does not facilitate the electroreduction of compounds (IIIb) and (IVb), as compared with (IIIa) and (IVa), as would have been expected. This "anomaly" is also retained in the reduction of compounds (III) and (IV) at a dropping mercury electrode. At the same time, these electroreduction waves, although they are one-electron waves in both cases, have different degrees of reversibility. Apparently, the introduction of an ester grouping into position 5 changes the mechanism of electrochemical reduction, which may be connected with a disturbance of the coplanarity of the substituents in positions 4 and 5 with the pyridone ring. However, at such high cathodic potentials the possibility is not excluded, either, of the electroreduction in the first stage of the ester groupings themselves in compounds (IIIb) and (IVb), while in the case of compounds (IIIa) and (IVa) it is the heterocycle that is reduced in the first stage.

EXPERIMENTAL

The electrochemical oxidation of compounds (I) and (II) was performed on a Bruker apparatus with a rotating disk electrode and a Pine Instrument ring. The disk was made from vitreous graphite ($S^d = 0.47$ cm^2) and the ring from platinum ($S^r = 0.06$ cm^2). The theoretical efficiency was $N = 0.183$. The speed of rotation was varied in the range from 500 to 5000 rpm. The comparison electrode was a silver electrode.

The investigations were carried out at room temperature in anhydrous acetonitrile, which was purified as described in the literature [8]. The concentration of depolarizer in all cases was $5 \cdot 10^{-4}$ M. The diffusion coefficient was determined from pycnometric figures by means of the Stokes–Einstein equation [9]. For the dihydropyridone (IIa) it proved to be $1.37 \cdot 10^{-5}$ cm^2/sec. The same value was used for calculating the number of electrons for the other compounds studied. The number of electrons consumed per molecule of compound undergoing oxidation was calculated from the equation of the limiting diffusion current at a rotating disk electrode [10]. As the supporting electrolyte we used tetrabutylammonium perchlorate (0.1 M). UV spectra were taken on an SP-1800 spectrometer with a cell thickness of 1 cm, the concentrations of the solutions of compounds (I) and (II) being $1 \cdot 10^{-4}$ M and of (III) and (IV) $6.25 \cdot 10^{-5}$ M.

Controlled-potential electrolysis was performed under the same experimental conditions: at a speed of rotation of 2000 rpm, for 2–2.5 h, and at potentials of 1.38 V and 1.20 V for the dihydropyridones (Ia) and (IIa) and 1.80 V and 1.48 V for (Ib) and (IIb), respectively. To decrease adsorption, the potential of the working electrode was switched to a value of −1 V every 5 sec (for a time of 2–2.5 sec), whereupon the substance was desorbed.

The NMR spectra, which were obtained on a Bruker WH-90 spectrometer, showed that compound (I) was a mixture of cis and trans isomers. The value $^4J_{NH,5-H} = 1.4$ Hz in both isomers shows a predominantly oxo form in acetonitrile solution. Also in harmony with these facts is the existence of a $^4J_{cis}$ coupling constant in the spectrum of the cis isomer (∿0.4 Hz). Compounds (IIa) and (IIb) exist in the trans form [3].

LITERATURE CITED

1. J. Kuthan, P. Nesvadba, and Z. Donnerova, and P. Trška, Collect. Czech. Chem. Commun. 42, 2152 (1977).
2. B. B. Damaskin, O. A. Petrii, and V. V. Batrakov, The Adsorption of Organic Compounds on Electrodes [in Russian], Nauka, Moscow (1968), p. 246.

3. Z. A. Bomika, Yu. É. Pelcher, G. Ya. Dubur, A. A. Krauze, and É. É. Liepin'sh, Khim. Geterotsikl. Soedin., No. 10, 1377 (1979).
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. L. S. Marcoux, J. M. Fritsch, and R. N. Adams, J. Am. Chem. Soc., 89, 5766 (1967).
6. Z. A. Bomika, M. A. Andaburskaya, Yu. É. Pelcher, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 8, 1108 (1975).
7. N. M. Émanuél' and D. G. Knorre, A Course of Chemical Kinetics [in Russian], Vysshaya Shkola, Moscow (1974), p. 136.
8. S. Wawzonek and M. E. Runner, J. Electrochem. Soc., 99, 457 (1952).
9. S. G. Mairanovskii, Ya. P. Stradyn', and V. D. Bezuglyi, Polarography in Organic Chemistry [in Russian], Khimiya, Moscow (1975), p. 83.
10. Z. Galus, Fundamentals of Electrochemical Analysis, Ellis Horwood, Chichester (1976).

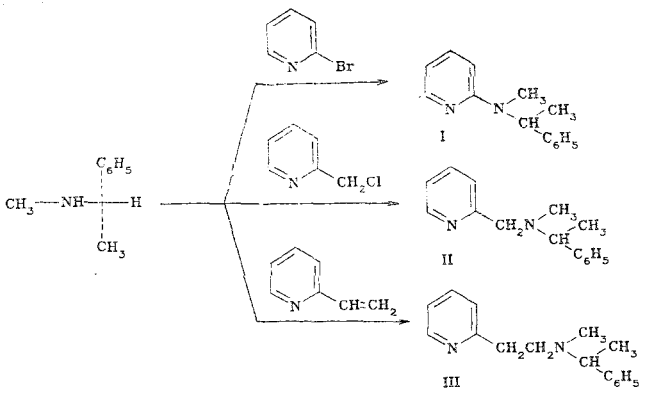
SYNTHESIS AND CHIROOPTICAL PROPERTIES OF SOME TERTIARY AMINES CONTAINING A PYRIDINE RING

V. M. Potapov, V. M. Dem'yanovich, and V. A. Khlebnikov

UDC 541.653:547.822.7.07:543.422

Tertiary amines of the pyridine series containing an α-phenylethylamine residue have been synthesized. The IR spectra and circular dichroisms of these amines have been measured in the 400-200 nm interval, and an assignment of the bands has been made. It is suggested that the long-wave absorption band in the 315 nm region for N-methyl-N-[2-(pyridin-2-yl)ethyl]-α-phenylethylamine and the Cotton effect corresponding to it are due to an intramolecular CTC.

Tertiary amines are catalysts of many acyl transfer reactions that are important from the synthetic point of view. Some derivatives of pyridine and, in particular, its dialkylamino derivative, have proved to be particularly effective in this role [1, 2]. In view of this it appears of interest to obtain chiral tertiary amine derivatives of pyridine in order to study them as chiral catalysts in reactions of this type. In the present investigation, from optically active N-methyl-α-phenylethylamine we have synthesized a number of tertiary amines of the pyridine series (I-III):



(S)(−)-N-methyl-α-phenylethylamine

The synthesis of N-methyl-N-(pyridin-2-yl)-α-phenylethylamine (I) in two stages from 2-fluoropyridine N-oxide has been described previously [3]. For this purpose we used the nucleophilic substitution of a halogen atom directly in the pyridine ring: The amine (I) was obtained

M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 92-96, January, 1984. Original article submitted June 29, 1983.

0009-3122/84/2001-0077$08.50