

ELECTROCHEMICAL CONVERSIONS OF 5-OXO-1,4-DIHYDROINDENO[1,2-b]PYRIDINE DERIVATIVES

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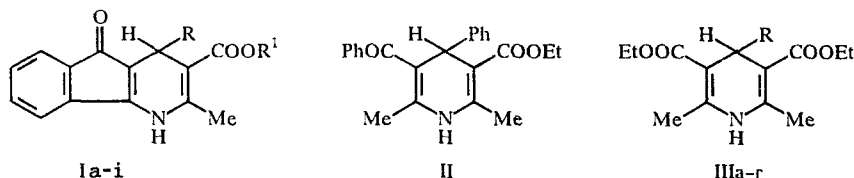
The electrochemical oxidation and reduction potentials of 9 derivatives of 5-oxo-1,4-dihydroindeno[1,2-b]pyridine in acetonitrile on a glassy graphite disk electrode have been established. Indenodihydropyridines are oxidized with considerably greater difficulty and reduced considerably more easily than the corresponding 3,5-diethoxycarbonyl derivatives of 1,4-dihydropyridines which is explained by the presence of the cyclopentane fragment which ensures the coplanarity of the carbonyl groups with the aminovinyl system of the heterocycle. The mechanism of electrooxidation has been studied by the rotating disk electrode with a ring method which revealed the reasons for the process.

Derivatives of 1,4-dihydropyridine are a very promising class of compounds for searching for new physiologically active compounds, for example effective antioxidants, radiation protectors to shield the skin, and cardiovascular drugs. Derivatives of 5-oxo-1,4-dihydroindeno[1,2-b]pyridine are polycyclic analogs of 1,4-dihydropyridines but their biological activity has been very little studied. However high antioxidant [1] and radiation protective [2] activity occurs in a series of compounds of this class and they are of considerable interest for practical work. This has led to the need for a more intense chemical study of this class of compounds and a knowledge of the physicochemical characteristics of the 5-oxo-1,4-dihydroindeno[1,2-b]pyridines.

One of the most important indicators for compounds with antioxidant activity is the oxidation potential, measured electrochemically. No studies of the electrochemical oxidation of 5-oxo-1,4-dihydroindeno[1,2-b]pyridines have been yet carried out (preliminary results on the electrochemical oxidation of some compounds have been reported [3]) and consequently it is not possible to compare these potentials and the mechanism of oxidation of these compounds with the corresponding results for the 3,5-diethoxycarbonyl derivatives of 1,4-dihydropyridine which have been studied in detail [4-6]. There are also no results for the electrochemical reduction of these compounds, although a systematic study of their catalytic reduction has begun [7, 8].

A systematic study of the electrochemical conversions of derivatives of 1,4-dihydroindeno[1,2-b]pyridine (Ia-i) has been carried out in acetonitrile by the rotating electrode with a ring method.

The molecules of compounds Ia-i have several electroactive centers: the dihydropyridine unit, which is capable of both electrooxidation and electroreduction, the cyclopentane fragment, and in compounds If-i the nitro group in the phenyl substituent on the dihydropyridine ring is capable of electroreduction. It is necessary first of all to ascribe the potentials to the electrochemical conversion of one group or another or to the conjugated system as whole.



Ia R = H, R¹ = Et; b R = Ph, R¹ = Et; c R = Ph, R¹ = C₅H₁₁; d R = Ph, R¹ = isobornyl; e R = Ph, R¹ = 1-adamantanyl; f R = C₆H₄NO₂-o, R¹ = menthyl; g R = C₆H₄NO₂-o, R¹ = bornyl; h R = C₆H₄NO₂-o, R¹ = C₆H₁₁; i R = C₆H₄NO₂-p, R¹ = Et; IIIa R = Ph; b R = C₆H₄I-p; c R = C₆H₄NO₂-p; d R = C₆H₄NO₂-o.

TABLE 1. Parameters of the Electrochemical Conversions of Compounds I-III at a Rotating Graphite Disk Electrode with a Ring in Acetonitrile (supporting electrolyte 0.1 tetrabutylammonium perchlorate, depolarizer concentration $5 \cdot 10^{-4}$ mol/liter)

Com- pound	Oxidation on the disk			Reduction on the ring											
	$E_{1/2}^{ox}, V$	$i_{pr}, \mu A$	$i_{pr}, \mu A$	first wave			second wave			third wave			fourth wave		
				$-E_{1/2}, V$	$i_{pr}, \mu A$	$-E_{1/2}, V$	$i_{pr}, \mu A$	$-E_{1/2}, V$	$i_{pr}, \mu A$	$-E_{1/2}, V$	$i_{pr}, \mu A$				
Ia	0,51	425	425	0,47	22	1,44	14	1,71	26	2,23	32	2,23	32		
Ib	0,78	455	455	—	—	1,44*	13	1,68*	46	2,24*	36	2,24*	36		
Ic	0,80	450	450	—	—	1,50	10	1,71	45	2,10	30	2,10	30		
				—	—	1,46*	15	1,68*	80	2,20*	40	2,20*	40		
				0,55	40	1,40	30	1,59	35	2,17	65	2,17	65		
				—	—	1,35*	Poorly expressed	1,56*	70	2,09	50	2,09	50		
Id	0,76	420	420	0,56	30	1,60	35	—	—	2,20	60	2,20	60		
				—	75	1,54*	75	—	—	2,07*	37	2,07*	37		
Ie	0,73	442	442	0,60	45	1,47	30	1,73	35	2,33	57	2,33	57		
				—	—	1,36*	20	1,71*	60	2,23	35	2,23	35		
If	0,79	420	420	0,60	40	1,53	195	1,82	52	2,19	25	2,19	25		
				—	—	1,57*	185	1,86*	22,5	2,16*	30	2,16*	30		
Ig	0,79	390	390	0,57	42	1,43	87	1,80	80	Poorly expressed	—	Poorly expressed	—		
				—	—	1,46*	55	1,83*	65	—	—	—	—		
Ih	0,81	425	425	0,61	45	1,51	135	1,87	30	2,21	25	2,21	25		
				—	—	1,54*	135	1,83*	40	2,18*	40	2,18*	40		
Ii	0,86	425	425	0,50	57	1,48	125	1,76	Poorly expressed	—	—	—	—		
II	0,70	400	400	0,36	11	1,46*	95	1,77*	45	—	—	—	—		
IIIa	0,75	—	—	—	—	1,32	30	—	—	2,06	20	2,06	20		

* $E_D = 0$.

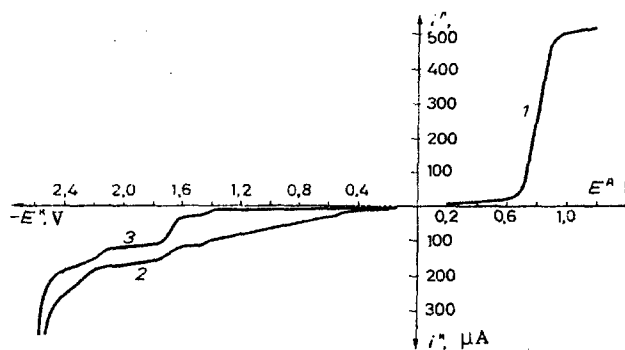


Fig. 1. Voltamperograms for the electrooxidation of compound Ib at the disk electrode (1) and electroreduction of the products at the ring electrode with $E_D = 1.2$ V (2) and $E_D = 0$ V (3). Rate of rotation of the electrode is 2000 rpm.

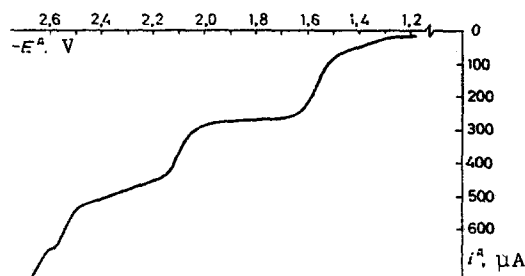


Fig. 2. Voltamperogram for the reduction of compound Ib at the disk electrode. Rate of rotation of the electrode 2000 rpm.

Electrooxidation of 5-oxo-1,4-dihydro[1,2-b]pyridines. Compounds Ia-i gave a well expressed single irreversible diffusion oxidation wave in the potential range from 0.50 to 0.86 V (Table 1) on a graphite disk electrode.

The nature of the wave, the size of the halfwave potential ($E_{1/2}$) range and the height of the wave (i_d) correspond with the waves obtained earlier for the electrochemical oxidation of 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine and some of its derivatives [4-6]. The latter may be considered as model systems corresponding to the electrooxidation of the dihydropyridine fragments in the molecules of Ia-i. The approximate coincidence of the current characteristics for their electrochemical oxidations (compare Ib-i with II and III, Table 1) indicates that the oxidation of compounds Ia-i is also a two electron process. In this case, the mechanism of the electrochemical oxidation proceeds through formation of a cation radical with subsequent deprotonation. The latter process is indicated by the appearance for all these compounds of a reduction wave on the ring electrode in the potential range -0.5 to -0.6 V with a disk potential (E_D) corresponding to the limiting current field for the oxidation wave. This reduction wave had been previously identified as the wave for proton reduction characteristic for derivatives of 1,4-dihydropyridine [4].

From a comparison of the oxidation potentials of compounds Ib, II and IIIa, compound Ib is the most difficult to oxidize on the rotating disk electrode with a ring (0.78 V, 0.70 V, and 0.75 V respectively) (Fig. 1). This may be explained by the coplanarity of the 5-oxo group with the aminovinyl system in the 1,4-dihydroindeno[1,2-b]pyridines (I) in distinction from compound III where the ethoxycarbonyl group is strongly twisted out of the plane of the ring as shown by x-ray crystallographic results, quantum chemical calculations and the experimentally determined dipole moments and acidity constants [9, 10]. The coplanarity of the rings in the case of the dihydroindeno[1,2-b]pyridines increases the oxidation potential of the dihydropyridine fragment in comparison with the electrooxidation of compounds II and IIIa which also have sufficiently strong electron acceptor groups in positions 3 and 5 of the dihydropyridine ring. A similar effect is apparent in the pK_a values; the indenodihydropyridines are stronger NH acids than the monocyclic 1,4-dihydropyridine structures II and III [10].

It is clear from a comparison of compounds Ib and Ii (Table 1) that introduction of an NO_2 group in the para-position of the phenyl substituent on the dihydropyridine ring hinders the oxidation by 80 mV. A more precise estimate of the influence of the nitro group is difficult within the limits of the compounds studied since the electron acceptor effect of the nitro group

TABLE 2. Values of the Halfwave Potentials ($-E_{1/2}$, V) for the Electrochemical Reduction of Ia-i and II at a Graphite Rotating Disk Electrode in Acetonitrile (background electrolyte 0.1 M tetrabutylammonium perchlorate, depolariser concentration $5 \cdot 10^{-4}$ mol/liter)

Compound	1st wave	2nd wave	3rd wave	4th wave
Ia	1.40	1.68	2.20	2.56
Ib	1.50	1.67	2.19	2.61
Ic	Very small 1.50	1.69	2.21	2.63
Id	1.45	1.68	2.23	2.62
Ie	1.49	1.70	2.26	2.63
If	Split 1.53	1.86	Split 2.27	2.59
Ig	1.43	1.82	2.22	2.61
Ih	Split 1.50	1.82	2.24	Poorly expressed
Ii	1.33	1.57	2.28	—
II	—	Small wave 1.94	2.23	2.58

in the remaining compounds overlaps with the effects of the alkyl groups with varying electron donor properties in position 3, increasing in the order 1-adamantyl > bornyl > isobornyl > menthyl > cyclohexyl > ethyl. Nevertheless the change in the ease of oxidation of compounds Ib-i corresponds to the electronic effects of the substituents at position 3. Thus, the most readily oxidized compound, Ie ($E_{1/2} = 0.73$ V) has the strongly electron donating 1-adamantyl substituent, while the most difficult to oxidize, Ic ($E_{1/2} = 0.81$ V) has a weak electron donor (cyclohexyl) and a strong electron acceptor (nitro) substituent in the phenyl ring.

The cyclopentane unit, which facilitates the coplanarity of the carbonyl group with the aminovinyl system, considerably hinders the electrochemical oxidation process.

Electroreduction of 5-oxo-1,4-dihydroindeno[1,2-b]pyridines. As expected, the pattern of electrochemical reduction at the ring electrode for compounds Ia-i is complex. The first wave, which falls in the -0.4 to -0.6 V range, can be assigned with reasonable certainty to reduction of the proton eliminated during electrooxidation of the dihydropyridine group. However three other waves are observed for practically all of the compounds in the potential ranges of -1.4 to -1.6 V, -1.7 to -1.9 V, and above -2.0 V. These waves appear not only at values of E_D equal to the limiting current for oxidation at the disk but also with $E_D = 0$. Hence these waves may be reduction waves for oxidation products or for the starting materials themselves.

The electrochemical behavior at the ring using the rotating disk electrode with a ring method is confirmed by the pattern of electrochemical reduction of compounds I at the rotating graphite disk (Table 2, Fig. 2). Four reduction waves with halfwave potentials $E_{1/2}$ in the range from -1.4 to -2.6 V were observed for practically all of the compounds I. The $E_{1/2}$ values for the first three waves coincide completely with the $E_{1/2}$ values for the waves observed on the ring electrode. The fourth wave ($E_{1/2} -2.6$ V) of the voltamperometric curve obtained with the ring electrode is absent but it is quite likely that in this case it is close to the discharge of the background electrolyte and it is simply not resolved.

A completely reliable interpretation of the nature of the electrochemical reduction waves for compounds of type I is difficult. Three factors are mainly responsible: the presence of several electroactive groups in the compounds, the unsatisfactory nature of the model compounds, most clearly expressed in the electroreduction of the carbonyl group in the cyclopentane unit, and the possibility of protonation of both the carbonyl and other electroactive centers. Moreover the compounds studied are substantially absorbed on the surface of the solid electrodes.

The wave of compounds Ia-i which appears in the potential range -1.4 to -1.5 V may be assigned to the facile reduction of the coplanar system of the 5-oxo-1,4-dihydroindeno[1,2-b]pyridine molecules. It follows that a similar wave should not occur for compound II either on the ring electrode (at $E_D = 0$) or on the graphite electrode (see Table 2). In all likelihood compounds of type I are reduced as α,β -aminovinylcarbonyl systems in a similar manner to their catalytic reduction with Raney nickel [9]. Consequently, in contrast to the electrooxidation of 5-oxo-1,4-dihydroindeno[1,2-b]pyridines, their electroreduction occurs considerably more readily than the electroreduction of the corresponding 3,5-dialkoxycarbonyldihydropyridines which are reduced at potentials of about -2.30 to -2.40 V [11].

The wave for the electroreduction of the aromatic nitro groups in the p-nitrophenyl substituent on the dihydropyridine ring (compounds If-i) is superimposed on the wave for the reduction of the conjugated α,β -aminovinylcarbonyl group. However, another wave corresponding to the electroreduction of the nitro group is observed at a potential of -1.8 V [12, 13]. The third wave in the electroreduction of compounds Ia-i may be assigned to the reduction of the end product of the electrooxidation, the corresponding pyridine [11].

The systematic investigation of compounds I permits the confirmation in this series of the correlation between the antioxidant properties, the rate constant for chemical oxidation, and the potentials for the electrochemical oxidation of these compounds. The greater the antioxidant activity of a compound, the greater the rate of oxidation with chloranil [14], and the easier the process of electrochemical oxidation. For example, for Ia and Ib $k = 415 \times 10^{-2}$ and 82×10^{-2} liter $\text{mol}^{-1}\text{s}^{-1}$ while the values of $E_{1/2}^{\text{ox}}$ are 0.5 and 0.78 V respectively. A similar relation hold for diludin (III, R = H) and IIIa ($k = 450 \times 10^{-2}$ liter $\cdot \text{mol}^{-1}\text{s}^{-1}$ and 1.8×10^{-2} liter $\cdot \text{mol}^{-1}\text{s}^{-1}$, and $E_{1/2}^{\text{ox}} = 0.54$ [4] and 0.75 V respectively.

EXPERIMENTAL

The electrochemical oxidation of compounds I-III by rotating disk electrode with a ring was carried out in the complex apparatus described previously [15]. The disk (glassy and graphite) and ring (platinum) electrodes had active surfaces of 0.45 and 0.06 cm^2 respectively. Experimental values for the coefficient of effectiveness for the electrode was $N = 0.18$. All potentials were measured relative to a 0.2 M silver comparison electrode (Ag/AgNO_3) in acetonitrile. The acetonitrile was purified by a known method [16]. The concentration of the depolarizer was 5×10^{-4} mol/liter in all cases and 0.1 mol/liter tetrabutylammonium perchlorate was used as background electrolyte.

Compounds Ia [17], II [18], and Ib-i [19] were synthesized by known methods.

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