ELECTROCHEMICAL REDUCTION OF 1,4-DIHYDROPYRIDINE-3,5-DICARBOXYLIC ACID DERIVATIVES IN AN APROTIC MEDIUM

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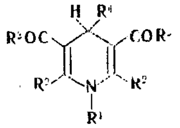
The polarographic reduction of 1,4-dihydropyridine-3,5-dicarboxylic acid derivatives in dimethylformamide was studied. It is shown that the first diffusion waves of these compounds are irreversible one-electron waves and correspond to electrical reduction of the C=C bond of the conjugated system of the 1,4-dihydropyridine ring to give a tetrahydro derivative. In the case of pyridine-3,5-dicarboxylic acid esters partial dimerization of the resulting free-radical products occurs along with electron transfer. It is shown that the introduction of alkoxycarbonyl substituents in 2,6-methyl and 3,5-methoxycarbonyl groups and in the 4 position and of a carboxyl group in the 4 position facilitates the electrical reduction of the 1,4-dihydropyridine ring. The introduction of a methyl group in the 4 position hinders reduction of the ring.

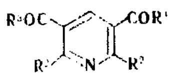
1,4-Dihydropyridine-3,5-dicarboxylic acid derivatives, particularly the 4-unsubstituted derivatives, have strong reductive properties that are responsible for their biological activity. The electrochemical oxidation of these compounds has therefore been studied quite thoroughly [1-3]. At the same time, conjugation of the β-carbonyl groups with the 1,4-dihydropyridine divinylamine system hinders nucleophilic attack of the carbonyl groups [4] in these molecules. It therefore seemed of value to also characterize the peculiarities of the electrochemical reduction of these compounds.

2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid esters can be regarded as potential intermediates in the reduction of esters of carboxylic acids of the pyridine series (for example, XVIII and XIX), since it has been shown that in the case of pyridine [5] and some of its derivatives related to esters of pyridinecarboxylic acids, particularly nicotinamide [6], the first overall step in electrochemical reduction in aqueous media leads to the formation of a dihydro product.

In the present research we used a polarographic method to study 1,4-dihydropyridine-3,5-dicarboxylic acid derivatives (I-XVII, Table 1) and some corresponding heteroaromatic compounds — esters of the pyridine series (XVIII and XIX).



I-XVII



XVIII, XIX

In view of the fact that these compounds are insoluble in water, we selected anhydrous dimethylformamide (DMF) as the solvent in the present research. This choice of medium also made it possible to exclude the influence of side effects, particularly protonation, on the first electrochemical step and to avoid the formation of catalytic waves.

It should be noted that only a small amount of data on the polarographic behavior of pyridine and its derivatives in DMF is available. In [7] it was shown that pyridine gives a two-electron wave for reduction to dihydropyridine ($E_{1/2}$ = −2.01 V relative to the mercury pool), and the $E_{1/2}$ value presented in [8] for the wave of pyridine in DMF in a tetraethylammonium perchlorate inert electrolyte is −2.6 V (relative to a saturated calomel electrode).

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TABLE 1. Half-Wave Potentials ($E_{1/2}$) and Limiting Currents (i_{lim}) for 1,4-Dihydropyridine-3,5-dicarboxylic Acid Derivatives in DMF in a 0.1 N Tetrabutylammonium Perchlorate Inert Electrolyte

Compound	R^1	R^2	R^3	R^4	First wave		Second wave	
					$-E_{1/2}$, V	i_{lim}, μA	$-E_{1/2}$, V	i_{lim}, μA
I	H	CH_3	OC_2H_5	H	2,33	0,77	—	—
II	H	CH_3	OC_2H_5	CH_3	2,39	0,80	—	—
III	H	CH_3	OC_2H_5	COOH	2,03	0,89	—	—
IV	H	CH_3	OC_2H_5	$COOCH_3$	2,21	0,73	2,76	1,06
V	H	CH_3	OC_2H_5	$COOCH(CH_3)_2$	2,22	0,67	2,78	0,95
VI	H	CH_3	OC_2H_5	C_6H_5	2,31	0,75	2,76	0,85
VII	H	CH_3	OC_2H_5	C_6H_4Cl-*p*	2,25	0,82	2,74	2,60
VIII	H	CH_3	OC_2H_5	$C_6H_4N(CH_3)_2$-*p*	2,36	0,77	—	—
IX	CH_3	CH_3	OC_2H_5	H	2,38	1,02	Weakly expressed	
X	CH_3	CH_3	OC_2H_5	CH_3	2,40	1,20		
XI	CH_3	CH_3	OC_2H_5	C_6H_5	2,30	1,10	2,63	0,82
XII	H	CH_3	$OCH_2CO_2C_2H_5$	H	2,15	0,80	Weakly expressed	
XIII	H	$CH_2CO_2C_2H_5$	OC_2H_5	H	2,17	0,63	2,68	1,10
XIV	H	CH_3	NHC_6H_5	H	2,35	0,79	2,72	0,53
XV	H	CH_3	OC_6H_5	H	2,10	0,45	2,51	3,80
XVI	H	CH_3	$OC_6H_4OCH_3$-*p*	H	2,14	0,90	2,62	2,20
XVII	H	CH_3	$OC_6H_4OCH_3$-*m*	H	2,12	0,70	2,58	2,20
XVIII	—	CH_3	OC_2H_5	—	1,95	1,07	—	—
XIX	—	CH_3	$OCH_2CO_2C_2H_5$	—	1,82	1,20	2,27	0,58

TABLE 2. Calculation of the Number of Electrons (n) by Means of Electrolysis at a Controllable Potential (ECP) (E is the potential of the limiting current plateau at which ECP was carried out)

Compound	*n*	E, V
I	1,05 1,11*	−2,6
XII	1,27	−2,5
XVIII	1.05 1,35*	−2,5
XIX	1,75	−2,2

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*Calculated from the Ilkovič equation.

Very little data on the polarographic reduction of dihydropyridines are available. The only available indications by Kuthan and co-workers [9, 10] are contradictory. Thus in [9] it is asserted that I in a 50% aqueous ethanol acetate buffer solution (pH 6.1) gives a polarographic wave with $E_{1/2} = -1.2$ V, whereas in [10] it is noted that this compound does not undergo reduction over the investigated pH range under similar conditions. Compounds I-XIX have not been studied at all in aprotic media.

Electrical Reduction of 3,5-Bis(alkoxycarbonyl)pyridines

Compound XVIII gives one polarographic wave in DMF, whereas XIX gives two polarographic waves (Table 1).

The dependence of the height of the wave of pyridine XVIII and the first wave of pyridine XIX on the depolarizer concentration and the square root of the height of the mercury column provides evidence for the diffusion character of both waves; however, the height of the wave of pyridine XIX is somewhat greater than the height of the wave of XVIII.

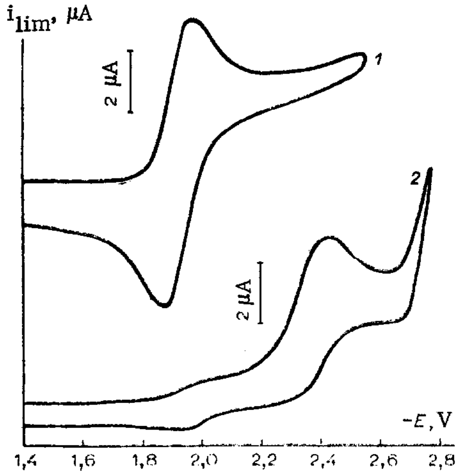

Fig. 1. Volt—ampere curves recorded on a hanging mercury drop in DMF in a 0.1 N $(C_4H_9)_4NClO_4$ inert electrolyte: 1) for 2,6-dimethyl-3,5-bis(ethoxycarbonyl)-pyridine (XVIII); 2) for 2,6-dimethyl-3,5-bis(ethoxycarbonyl)-1,4-dihydropyridine (I) (the depolarizer concentration was $5 \cdot 10^{-4}$ mole/liter, and the potential-scanning rate was 1 V/sec).

Coulometric studies made during electrolysis at a controllable potential (ECP) at potentials corresponding to the limiting current plateaus showed that the reduction wave of pyridine XVIII is a one-electron wave and that the first wave of XIX is close to a two-electron wave (Table 2). The cyclical volt—ampere curves showed that the waves are partially reversible (Fig. 1).

It might be assumed that the addition of the first electron leads to the formation of a free radical, which in the case of XVIII turned out to be stable enough to be recordable by ESR spectrometry. However, the spectra are too poorly expressed to establish the nature of the free-radical particles and the spin-density distribution in them.

The first step in the transfer of electrons is accompanied by simultaneous dimerization of the intermediate free-radical product. The linearity of the graph of the dependence of log $[i^{2/3}/(i_d - i)]$ on E, which is characteristic for reversible electrode processes complicated by a bimolecular chemical reaction that proceeds simultaneously with electron transfer [11], may serve as a confirmation of the latter (Fig. 2).

In contrast to pyridine XVIII, XIX has a limiting current that is more in keeping with a two-electron process and involves close to two electrons (Tables 1 and 2). It is possible that dimerization is impeded in this case because of steric hindrance and that the reduction goes more nearly to completion.

A second wave that increases with time appears in the electrolysis at a controllable potential of XVIII; the $E_{1/2}$ value of this wave (—2.33 V) coincides with the $E_{1/2}$ value of the corresponding 1,4-dihydropyridine (Fig. 3). The height of the new wave is half the height of the starting wave, and this also constitutes evidence in favor of dimerization of

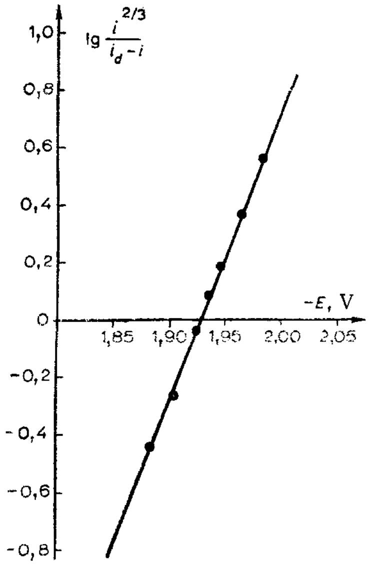

Fig. 2. Dependence of log $[i^{2/3}/(i_d - i)]$ on E for the wave of 2,6-dimethyl-3,5-bis-(ethoxycarbonyl)pyridine (XVIII) in DMF.

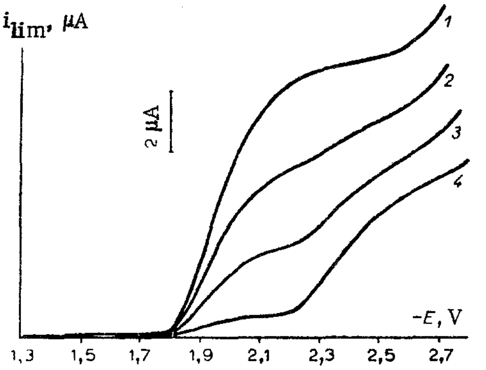

Fig. 3. Change in the polarographic waves of 2,6-dimethyl-3,5-bis(ethoxycarbonyl)-pyridine (XVIII) during electrolysis at a controllable potential (ECP): 1) form of the polarogram prior to ECP (starting concentration $1 \cdot 10^{-2}$ mole/liter); 2,3) polarograms recorded during ECP; 4) at the end of ECP.

the intermediate. The appearance of a new wave corresponding to the electrical reduction wave of 1,4-dihydropyridine is also evidence that the pyridine ring rather than the ester grouping is involved in electrical reduction.

The polarographic data on XVIII and XIX thus fit into the general scheme of the electrical reduction of pyridines — dihydro derivatives, which are subsequently reduced in the more negative region, are formed.

Electrical Reduction of 1,4-Dihydropyridine-3,5-dicarboxylic Acid Derivatives

The polarograms of almost all of the investigated 1,4-dihydropyridine derivatives (Table 1) contain two polarographic waves: the first is found at —2.0 to —2.4 V, and the second is located at —2.5 to —2.8 V. Because of the closeness of the reduction potentials of the second wave and the potential for discharge of the inert electrolyte, the limiting current plateau of the latter is expressed weakly in the polarograms of some compounds, and calculation of the accurate values of the limiting current is difficult.

The nature of the current and the reversibility of the first step of the electrochemical reduction of I and XII was investigated, and millicoulometric measurements were made. It was shown that the first waves of these compounds are irreversible (Fig. 1) one-electron waves (Table 2) and have diffusion character. The $E_{1/2}$ values, which were compared with the $E_{1/2}$ value of I, the parent compound of this series of compounds, and with one another, were obtained for the remaining compounds; this comparison made it possible to estimate the influence of electronic effects of substituents on the electrochemical reduction potentials of these compounds.

We were able to record free-radical products for some of the compounds (I, III, and XII) by ESR spectrometry; however, it should be noted that, for example, the ESR spectrum obtained for I is completely identical to the spectrum of the corresponding pyridine XVIII. The possibility that the compound underwent partial chemical oxidation in solution and that the recorded ESR spectrum is related to a secondary radical is not excluded.

The addition of a proton donor (water) to up to 40% by volume does not have a substantial effect on $E_{1/2}$ and i_{lim} of the wave of I.

The data obtained in this study make it possible to assume that the electrical reduction involves the $>C=C<$ bond of the conjugated system of the 1,4-dihydropyridine ring rather than the ester grouping in the side chain. In principle, this conclusion is in agreement with the conclusions in [10] that the heterocyclic ring rather than the acetyl group is primarily reduced in the electrical reduction of 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine in a protogenic medium. In the case of esters the polar character of the $>C=O$ bond is markedly weakened due to the addition of the OR group to the carbon atom, as a consequence of which esters of aliphatic acids are electrochemically inactive [12]. The ester grouping in the investigated compounds is in the β position with respect to the nitrogen atom of the dihydropyridine ring; because of conjugation, this makes its reduction much less likely. The alkyl esters of 1,4-dihydropyridine-3,5-dicarboxylic acid that we investigated can be compared with the esters of acrylic and methacrylic acids, the vinylene bond of which corresponds to the $>C=C<$ bond in the dihydropyridine ring. It has been demonstrated [13] for the latter that they undergo reduction directly at the C=C bond in DMF at potentials above —2 V and that the initial addition of an electron and a proton to the C=O group with subsequent keto—enol rearrangement is unlikely.

However, only one $>C=C<$ bond is reduced in the investigated 1,4-dihydropyridines, i.e., the compounds are reduced to the tetrahydro derivatives.

The increased i_{lim} values observed for the aryl esters (XV-XVII) evidently indicate that the ester grouping is also reduced during the electrical reduction of these representatives of the series.

The character of the effect of other functional groups on the electrochemical reduction potentials also constitutes evidence in favor of initial reduction of the $>C=C<$ bond in the dihydropyridine ring. Thus the introduction of a methyl group in the 4 position (compare I and II and IX and X) hinders the reduction of the dihydropyridine ring; this can be explained by both the electron-donor effect of the methyl group and the disruption of the conjugation of the 3,5-alkoxycarbonyl groups with the dihydropyridine ring, which lead to an increase in the electron density in the ring. This phenomenon is in agreement with the previously observed hypsochromic shift of the long-wave absorption maximum in the electronic spectra [14].

The introduction of a phenyl group in the 4 position (VI) does not have a substantial effect; this can be explained by two opposing factors — the weak electron-acceptor capacity of the phenyl group and the decrease in the electron-acceptor effect of the 3,5-alkoxycarbonyl groups.

A study of 1,4-dihydropyridine derivatives with substituents in the 4-phenyl ring shows that the electronic effect is transmitted to the dihydropyridine ring either through the σ bonds or through space (the field effect): An electron-acceptor substituent facilitates electrical reduction (VII), whereas an electron-donor substituent hinders reduction (VIII).

The introduction of electron-acceptor ethoxycarbonyl substituents in both the 2,6-methyl groups (XIII) and the 3,5-methoxycarbonyl groups (XII) facilitates electrical reduction as compared with I by 160 and 180 mV, respectively. The introduction of one alkoxycarbonyl group in the 4 position (IV, V) has approximately the same effect (110-120 mV).

A carboxyl group in the 4 position (III) has a strong activating effect, evidently because of the formation of an intramolecular hydrogen bond with the carbonyl group in the 3 position, which intensifies the electron-acceptor properties of the latter.

Aryl esters (XV and XVII) of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid are reduced at more positive potentials than alkyl esters ($\Delta E_{1/2}$ = 190-230 mV); this is in agreement with the increase in the electron-acceptor properties of 3,5 substituents.

The $E_{1/2}$ values of 3,5-bis(phenylcarbamoyl)-2,6-dimethyl-1,4-dihydropyridine (XIV) and I differ by only 20 mV, although one might have expected a large difference because of the weaker electron-acceptor properties of the carbamoyl group as compared with the alkoxycarbonyl group.

The electron-donor properties of the N-methyl group (IX-XI) are manifested only in the case of 4-unsubstituted IX, and the $E_{1/2}$ values of the 4-methyl- and 4-phenyl-substituted compounds (II and X and VI and XI) virtually coincide, although in the case of X and XI one might have expected a shift to the more negative region.

The data obtained in this research may also be of value for analytical chemists, since they show a fundamental possibility for the determination of the oxidized form (XVIII and XIX) in the presence of the reduced form without dilution of the components of the mixture.

EXPERIMENTAL

The polarographic study of I-XIX was carried out in anhydrous DMF. Tetrabutylammonium perchlorate, prepared by the method in [15], was used as the inert electrolyte. The depolarizer concentration in all cases was $5 \cdot 10^{-4}$ mole/liter, and the ionic strength of the solution was 0.1. The polarographic measurements were made with a Radiometer PO-4 polarograph at 25°C with a thermostatted cell. A dropping mercury electrode with forced detachment of the drops (with a spatula), $m = 0.31$ mg/sec, and $t = 0.25$ sec (open circuit) served as the working electrode; an aqueous saturated calomel electrode served as the anode.

The number of electrons (n) consumed in the electrical reduction of one particle of the depolarizer in the first step of the electrochemical reduction was determined by a millicoulometric method with a PAR-170 apparatus. In the case of I and XVIII the n values were also calculated from the Ilkovič equation. The diffusion coefficient for dihydropyridine I ($6.25 \cdot 10^{-6}$ cm^2/sec) was determined from pycnometric data with the Stokes–Einstein equation [12] and was used for the calculation of the n value for XVIII.

Cyclical volt–ampere curves were obtained with a stationary electrode–hanging mercury drop system with a surface area of 2.87 mm^2. Compounds I-XVIII were synthesized by previously described methods [4, 16-18], and their purity was monitored from their melting points.

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