VOLTAMPEROMETRY OF 1,4-DIHYDROPYRIDINE DERIVATIVES

II.* ELECTRONIC AND STERIC EFFECTS IN THE ELECTROOXIDATION OF 4-SUBSTITUTED 1,4-DIHYDROPYRIDINES

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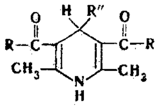
Thirty-nine γ-substituted 1,4-dihydropyridine derivatives were subjected to electrochemical oxidation on a rotating platinum microelectrode in acetonitrile, and the E_p ($E_{1/2}$) values were measured. A satisfactory linear correlation between the E_p and Taft σ^* constants of the substituents in the γ position was observed. A linear correlation of the E_p values with the σ^0, σ– and σ^- constants also exists.

In a preceding paper [1] we described the electrochemical oxidation (EO) of 1,4-dihydropyridine derivatives on a platinum microanode and studied the effect of substituents in the various positions of the dihydropyridine ring on the change in the EO potentials.

In the present research we have studied the EO anode curves of 1,4-dihydropyridines with various substituents in the γ position, i.e., I-XXXIX.



I–XXXIX

(See Tables 1 and 2 for the R, R', and R'' substituents)

A number of regularities are exposed when the experimental results are examined.

A change in the structure of the alkoxy group in the β-carbalkoxy group has little effect on the oxidation potentials: the EO potentials of the methyl, ethyl, alkoxyethyl, isopropyl, and benzyl esters are practically the same.

Replacement of one β-ethoxycarbonyl group of 2,6-dimethyl-4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridine [1] by a benzoyl group (XXXI) shifts E_p to the cathode side by 30 mV, while replacement of both groups (XXXII) gives rise to an even greater shift in the potential (Table 2). This is in agreement with data [1] that β-benzoyl derivatives of 1,4-dihydropyridine are oxidized more readily than β-ethoxycarbonyl derivatives.

When weaker electron-acceptor β substituents are present, the 1,4-dihydropyridines are oxidized more easily. Replacement of the β-ethoxycarbonyl groups by amide groups apparently markedly facilitates EO. 3,5-Diphenylcarbamoyl derivatives of 1,4-dihydropyridine (XXXIII-XXXVIII) are oxidized considerably more easily (by ~200 mV) than the corresponding 3,5-diethoxycarbonyl derivatives [1]. Our preliminary observation [1] that γ-unsubstituted dihydropyridines are oxidized more easily than γ-substituted dihydropyridines (and among the latter, the γ-methyl derivatives are oxidized more easily than the γ-phenyl derivatives) is once more confirmed in this series of compounds. The introduction in the γ position of any

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*See [1] for communication I.

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TABLE 1. Peak (E_p) and Half-Wave ($E_{1/2}$) Potentials in the Electrochemical Oxidation of 4-Substituted Esters of 2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylic Acid

Compound	R=R′	R″	Synthetic method	E_p, V	$E_{1/2}$, V
I	OC_3H_7-*i*	CH_3	*	0,98	0,92
II	OC_3H_7-*i*	C_6H_5	*	1,07	1,02
III	$OCH_2C_6H_5$	CH_3	*	0,97	0,89
IV	OC_2H_5	C_6H_4F-*m*	†	1,14	1,10
V	OC_2H_5	C_6H_4F-*p*	†	1,12	1,07
VI	OC_2H_5	C_6H_4Cl-*o*	5	1,07	1,03
VII	OC_2H_5	C_6H_4Cl-*m*	5	1,10	1,06
VIII	OC_2H_5	C_6H_4Br-*m*	†	1,14	1,08
IX	OC_2H_5	C_6H_4Br-*p*	†	1,11	1,05
X	OC_2H_5	C_6H_4J-*m*	†	1,16	1,09
XI	OC_2H_5	C_6H_4J-*p*	†	1,14	1,07
XII	OC_2H_5	$C_6H_4NO_2$-*o*	6	1,11	1,06
XIII	OC_2H_5	$C_6H_4NO_2$-*p*	7	1,22‡	1,17
XIV	OC_2H_5	$C_6H_4NO_2$-*m*	7	1,21	1,13
XV	OCH_3	$C_6H_4NO_2$-*o*	6	1,16	1,08
XVI	OCH_3	$C_6H_4NO_2$-*p*	6	1,18	1,12
XVII	OCH_3	$C_6H_4N(CH_3)_2$-*p*	6	0,65 1,18	0,60 1,13
XVIII	OC_2H_5	C_6H_4OH-*p*	5	1,07 1,30	1,01 1,22
XIX	$OC_2H_4OC_2H_5$	C_6H_5	8	1,11	1,06
XX	$OC_2H_4OC_2H_5$	$C_6H_4OCH_3$-*p*	8	1,08	0,99
XXI	$OC_2H_4OC_2H_5$	C_6H_4Cl-*p*	8	1,13	1,05
XXII	$OC_2H_4OC_2H_5$	$C_6H_4NO_2$-*m*	9	1,18	1,13
XXIII	$OC_2H_4OC_2H_5$	$C_6H_4NO_2$-*p*	8	1,20	1,10
XXIV	$OC_2H_4OC_4H_9$	$C_6H_4NO_2$-*m*	8	1,20	1,14
XXV	$OC_2H_4OC_4H_9$	$C_6H_4NO_2$-*p*	8	1,20	1,14

*The synthesis will be published separately.

†See the experimental section for the synthesis.

‡The value given in [1] is inaccurate.

TABLE 2. Peak (E_p) and Half-Wave ($E_{1/2}$) Potentials in the Electrochemical Oxidation of 3,5-Dicarbonyl-2,6-dimethyl-1,4-dihydropyridine Derivatives

Compound	R	R′	R″	Synthetic method	E_p, V	$E_{1/2}$, V
XXVI	CH_3	CH_3	COOH	10	0,63	0,60
XXVII	CH_3	CH_3	$COONH_4$	10	0,63	0,60
XXVIII	CH_3	CH_3	$CON(CH_2CH_2)_2O$	11	1,08	0,88
XXIX	OC_2H_5	OC_2H_5	$COONH_4$	10	0,72 1,30	0,65 1,22
XXX	C_6H_5	CH_3	C_6H_5	12	1,03	0,98
XXXI	C_6H_5	OC_2H_5	C_6H_5	12	1,04	0,98
XXXII	C_6H_5	C_6H_5	C_6H_5	12*	0,99	0,92
XXXIII	NHC_6H_5	NHC_6H_5	H	13	0,66	0,62
XXXIV	NHC_6H_5	NHC_6H_5	CH_3	14†	0,77	0,70
XXXV	NHC_6H_5	NHC_6H_5	C_6H_5	13	0,85	0,76
XXXVI	NHC_6H_5	NHC_6H_5	$C_6H_3Cl_2$-2,4	13	0,86	0,81
XXXVII	NHC_6H_5	NHC_6H_5	$C_6H_4NO_2$-*m*	13	0,95	0,88
XXXVIII	NHC_6H_5	NHC_6H_5	C_6H_4Cl-*p*	13	0,88	0,82
XXXIX	CH_3	CH_3	$C_6H_4NO_2$-*m*	15	1,15	1,08

*The PMR spectra did not confirm the previously proposed [12] structure (3-acetyl-5-benzoyl-2,4-diphenyl-6-methyl-1,4-dihydropyridine) for this compound.

†This compound was obtained from β-aminocrotonic acid anilide and had mp 219-222° (dec.).

(even an electron-donor substituent, except for a dissociated carboxyl group) hinders the oxidation of the 1,4-dihydropyridine. It is possible that this is associated with the effect of steric factors. The apparent facilitation of the oxidation of γ-(p-dimethylaminophenyl)-substituted dihydropyridines (XVII; also see [1]) is evidently explained by prior EO of the dimethylamino group. The presence of a second EO wave (E_p 1.18 V), the numerical value of the potential of which corresponds to the E_p values of dihydropyridines with a strong electron-acceptor substituent in the γ position, constitutes evidence in favor of this assumption.

On comparison of the E_p values of γ-carboxyl derivatives of 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (XXVI) and 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine [1] and their ammonium salts

TABLE 3. Parameters of the Correlation of the E_p Values with the σ Constants of γ Substituents R" for Reaction Series in Which R = R' = OC_2H_5 or NHC_6H_5

No.	R=R′	No. of compounds*	Correlation equation	ρ, V	r	ΔS	Notes
1a	OC_2H_5	17	$\Delta E_p = \rho^* \cdot \sigma^*$	0,13	0,95	0,006	The γ-unsubstituted compound is not included in the linear correlation.
1b		15		0,15	0,98	0,004	
2a	OC_2H_5	14	$\Delta E_p = \rho \cdot \sigma^\circ$	0,15	0,91	0,006	The o-phenyl-substituted compounds are not included in the correlation.
2b		13		0,16	0,95	0,005	
3a	OC_2H_5	14	$\Delta E_p = \rho \cdot \sigma$	0,13	0,89	0,006	The o-phenyl-substituted compounds are not included in the correlation.
3b		12		0,13	0,95	0,005	
4a	OC_2H_5	9	$\Delta E_p = \rho \cdot \sigma^-$	0,09	0,93	0,007	Only the p-phenyl-substituted compounds are correlated.
4b		8		0,09	0,97	0,005	
5	OC_2H_5	9	$\Delta E_p = \rho \cdot \sigma^+$	0,08	0,83	0,011	Only the p-phenyl-substituted compounds are correlated.
6	NHC_6H_5	4	$\Delta E_p = \rho^* \cdot \sigma^*$	0,13	0,97	—	The γ-unsubstituted compound is not included in the correlation.

*The E_p values were taken from Tables 1 and 2 and an earlier paper [1]. All of the investigated compounds for which the appropriate σ constants are available [4] are included in correlation series "a."

(XXVII and XXIX) with the E_p values of 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine ($E_p = 0.90$ V [1] and 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine ($E_p = 0.93$ V [1]) and their 4-methyl and 4-phenyl derivatives ($E_p = 0.97$; 1.13 and 1.00 and 1.07 V, respectively [1]), the facile oxidation of 2,6-dimethyl-3,5-diacetyl-1,4-dihydroisonicotinic acid (XXVI, $E_p = 0.63$ V) may appear unexpected. However, this phenomenon is explained by the fact that XXVI, in contrast to the corresponding β-ethoxycarbonyl derivative ($E_p = 1.24$ V [1]) undergoes electrolytic dissociation under the experimental conditions and is consequently oxidized on the electrode in the form of the carboxylate anion. The ammonium salt of this acid (XXVII), like the salt of 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydroisonicotinic acid (XXIX), is oxidized very easily ($E_p = 0.63$ and 0.73 V, respectively). However, the second wave ($E_p = 1.30$ V) on the EO voltampere curve of XXIX evidently corresponds to the EO potential of the undissociated acid. The morpholides of both acids are oxidized with greater difficulty than the dissociated acids ($E_p = 1.08$ and 1.11 V [1]).

As we have already stated above, the introduction of an electron-acceptor group in the γ position of 1,4-dihydropyridine shifts the E_p value to more anodic potentials. In an examination of the effect of substituents in the phenyl ring in the γ position of 1,4-dihydropyridine (IV-XXV and XXXV-XXXVIII) it was found that a p- or m-nitro group hinders EO on the average by an E_p value of 0.12 V as compared with unsubstituted γ-phenyl derivatives. o-Substituted compounds (XII and XV) are oxidized more easily than p- and m-substituted compounds as a consequence of the possibility of the formation of an intramolecular bond. The well-known intramolecular photochemical disproportionation of these compounds to give γ-nitrosophenyl derivatives of the corresponding pyridines [2] constitutes evidence in favor of this. The introduction of a halogen in the phenyl ring (IV-XI, XXI, XXXVI, and XXXVIII) hinders oxidation but to a lesser extent than the introduction of a nitro group.

The appearance of a second wave ($E_p = 1.30$ V) on the EO voltampere curves of XVIII can evidently be explained by oxidation of the p-hydroxyphenyl substituent [3].

The effect of γ substituents on the EO potentials of 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine derivatives was studied by correlation-statistical analysis. The oxidation potentials (E_p) were correlated with various types of σ constants [4] (Table 3). It was found that the E_p values give the best linear correlation with the Taft σ^* constants. The E_p values of 15 representatives of this series lie on a correlation line having the following parameters: $\rho^* = 0.15$ V, $r = 0.98$, and $\Delta s = 0.004$ (Fig. 1). A satisfactory linear correlation of the E_p values of the p-phenyl substituted compounds with the σ^- constants is also observed, but the linearity of the correlation with the σ^+ constants is extremely doubtful. This circumstance probably constitutes evidence for the irreversibility of the EO of 1,4-dihydropyridines, as a consequence of which the intermediate state of the molecule undergoing oxidation (presumably a cation radical) does not affect the ease of detachment of the first electron.

The regularities uncovered in this study made it possible to assume that a similar correlation exists between the E_p and Taft σ^* constants of the γ substituents also in the case of a number of 1,4-dihydro-

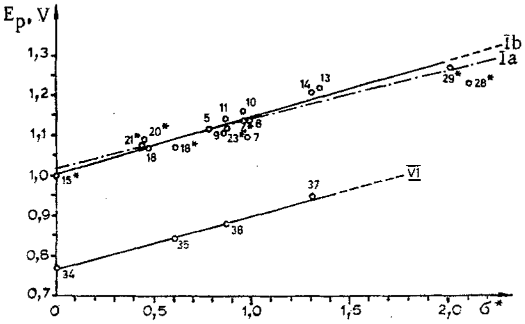

Fig. 1. Correlation of the E_p values with the σ* constant of the substituents: Ia) 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine derivatives; Ib) the same without allowance for VII and XXVIII*; VI) 2,6-dimethyl-3,5-di(phenylcarbamoyl)-1,4-dihydropyridine derivatives (the E_p values for the compounds whose numbers bear an asterisk were taken from [1]).

TABLE 4. Characteristics of 4-Aryl-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridines ($R = R' = OC_2H_5$)

Compound	R″	mp, °C	Empirical formula	Found, %			Calc., %			UV spectrum, λ_{max}, nm (log ε)	Yield, %
				C	H	N	C	H	N		
IV	C_6H_4F-*m*	126--128	$C_{19}H_{22}FNO_4$	65,7	6,4	4,0	65,7	6,4	4,0	207 (4,16); 237 (4,28); 359 (3,86)	52
V	C_6H_4F-*p*	149—151	$C_{19}H_{22}FNO_4$	65,8	6,5	4,1	65,7	6,4	4,0	208 (4,17); 237 (4,23); 367 (3,85)	48
VIII	C_6H_4Br-*m*	118—120	$C_{19}H_{22}BrNO_4$	55,7	5,3	3,8	55,9	5,4	3,4	204 (4,39); 237 (4,37); 362 (3,92)	96
IX	C_6H_4Br-*p*	158—160	$C_{19}H_{22}BrNO_4$	55,4	5,5	3,3	55,9	5,4	3,4	203 (4,31); 241 (4,30); 360 (3,85)	64
X	C_6H_4J-*m*	117—118	$C_{19}H_{22}JNO_4$	50,1	5,1	3,0	50,1	4,9	3,1	205 (4,24); 227 (4,30): 362 (3,68)	79
XI	C_6H_4J-*p*	154—156	$C_{19}H_{22}JNO_4$	49,7	5,0	3,0	50,1	4,9	3,1	204 (4,30); 231 (4,29); 363 (3,81)	87

pyridines with other β substituents. Thus, for example, the E_p values of 3,5-di(phenylcarbamoyl)derivatives XXXIV-XXXVIII give a correlation line with an approximately equal slope (Fig. 1).

The γ-unsubstituted compounds are clearly not included in the linear correlation in all of the investigated cases. All of the γ-substituted 1,4-dihydropyridines, because of the passivating steric effect of the γ substituent, apparently form an individual series that differs from that of the γ-unsubstituted dihydropyridines.

EXPERIMENTAL

The EO potentials were determined by a previously described method with an LP-60 automatic polarograph in acetonitrile with an 1 M $LiClO_4$ background electrolyte with a rotating platinum microelectrode [1]. The experimentally found E_p and $E_{1/2}$ values, which were measured relative to a saturated calomel electrode, are presented in Tables 1 and 2. The compounds were synthesized by well-known methods (variations of the Hantzsch synthesis) indicates in Tables 1 and 2. The synthetic methods and physicochemical characteristics for the previously undescribed compounds are presented below. The UV spectra of ethanol solutions of the compounds were recorded with a Specord UV-Vis recording spectrophotometer (Table 4).

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VOLTAMPEROMETRY OF 1,4-DIHYDROPYRIDINE DERIVATIVES

III.* EFFECT OF ESTER GROUPINGS IN THE 3 and 5 POSITIONS OF γ-UNSUBSTITUTED 1,4-DIHYDROPYRIDINES ON THEIR ELECTROOXIDATION POTENTIALS

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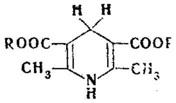
Twenty-two alkyl, alkoxyethyl, and aryl esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid were subjected to electrochemical oxidation on a rotating platinum microelectrode in acetonitrile. It was established that the effect of a change in the ester group on the E_p ($E_{1/2}$) value is insignificant. It is assumed that the γ-carbon atom is the possible center of primary detachment of an electron.

Continuing our investigation of the electrochemical oxidation (EO) of 1,4-dihydropyridines [1, 2], we have studied a number of 4-unsubstituted esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid (DPDA esters) of the general formula



Alkyl [3], alkoxyethyl [3], and aryl [4] esters were investigated (Table 1).

This group of 1,4-dihydropyridines is of special interest, inasmuch as electron-donor and hydrogen-donor properties are expressed more strongly by them than their γ-substituted analogs. These compounds are inhibitors of free-radical reactions [5] and represent a new group of antioxidants [6].

Studies of a large group of DPDA esters [3, 4] have shown that these compounds differ from one another not only with respect to their physical properties (melting points, lipophilicity, etc.) but also with respect to their chemical properties, for example, their stability on storage [3]. The methyl, ethyl, propyl,

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*See [2] for communication II.

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