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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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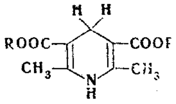
Twenty-two alkyl, alkoxyethyl, and aryl esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid were subjected to electrochemical oxidation on a rotating platinum microelectrode in acetonitrile. It was established that the effect of a change in the ester group on the E_p ($E_{1/2}$) value is 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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TABLE 1. Peak (E_p) and Half-Wave ($E_{1/2}$) Potentials in the Electrooxidation of 2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylic Acid Esters (DPDA esters)

Compound	R	E_p, V	$E_{1/2}$, V
I	C_3H_7-*n*	0,87	0,82
II	C_3H_7-*i*	0,88	0,82
III	C_4H_9-*n*	0,88	0,81
IV	C_4H_9-*i*	0,90	0,84
V	C_4H_9-*t*	0,88	0,82
VI	C_6H_{13}-*n*	0,85	0,78
VII	Cyclohexyl	0,86	0,79
VIII	C_7H_{15}-*n*	0,86	0,81
IX	C_8H_{17}-*n*	0,87	0,78
X	$C_{10}H_{21}$-*n*	0,86	0,82
XI	$C_2H_4OCH_3$	0,90	0,85
XII	$C_2H_4OC_4H_9$-*n*	0,90	0,84
XIII	$C_2H_4OC_6H_{13}$-*n*	0,89	0,84
XIV	$C_2H_4OC_6H_5$	0,90	0,84
XV	$CH_2COOC_2H_5$	0,99	0,94
XVI	$CH_2CH{=}CHC_6H_5$	0,90	0,83
XVII	C_6H_5	0,96	0,89
XVIII	$C_6H_4CH_3$-*p*	0,97	0,90
XIX	$C_6H_4OCH_3$-*p*	1,00	0,92
XX	C_5H_4OH-*p*	0,95	0,88
XXI	C_6H_4Cl-*p*	0,96	0,91
XXII	$C_6H_4NHCOCH_3$-*p*	0,98	0,90

undecyl, dodecyl, and other esters change slowly (undergoing oxidation to the corresponding pyridine derivatives) even under the prolonged influence of air oxygen, while some other DPDA esters such as, for example, the pentyl, isopentyl, hexyl (VI), and methoxyethyl (XI) esters change very rapidly. Considerable sensitivity to oxygen, which is sharply intensified under the influence of light, is characteristic for the latter compounds. This sort of difference might have been explained by the fact that the particles of the more stable DPDA esters are covered by a film of their oxidized form and their further oxidation is therefore retarded, whereas the less stable compounds, which have low-melting oxidized forms, are converted to liquids during oxidation, and this probably even promotes further oxidation. However, the different sensitivities of the DPDA esters to light and kinetic measurements of their reactivities on reaction with diphenylpicylhydrazyl [7] clearly speak in favor of the accelerating effect of a change in the length of alkyl group R. Consequently, despite the fact that the EO data on γ-substituted 1,4-dihydropyridines attest to the insubstantial effect of the ester group on the E_p values [2], we subjected γ-unsubstituted compounds of the DPDA ester series to EO.

Distinct voltampere curves with sufficiently satisfactorily reproducible peak potentials (E_p) and half-wave potentials ($E_{1/2}$) were obtained in most cases (Table 1). We were unable to uncover a clear dependence of the E_p values on the length and branched character of the alkyl chain of the ester grouping by comparison of the oxidation potentials of the alkyl esters (I-X): in all cases the E_p values ranged from 0.85 to 0.90 V.*

Because of the −I effect of the unconjugated phenoxy and alkoxy groups, the phenoxyethyl and alkoxyether esters (XI-XIV) are oxidized with somewhat more difficulty than the alkyl esters ($E_p \sim 0.90$ V), but the substituent effect lies almost within the limits of the experimental error. Replacement in the methyl ester [1] of one hydrogen atom by a styryl group (XVI) also has practically no effect on the E_p value, but the introduction of an ethoxycarbonyl group (XV), in view of the stronger electron-acceptor effect, which is transmitted through the methylene group, brings about a genuine increase in the EO potential ($E_p = 0.99$ V).

The aryl esters (XVII-XXII) are oxidized with greater difficulty (by ~ 0.1 V) than the alkyl esters. The −I effect of the unconjugated (with the carbonyl group) phenyl ring is apparently manifested in this case. However, no effect of the substituent in the phenyl ring on the EO potentials was detected.

Thus a change in the β-ester groups of the DPDA esters has practically no effect on the EO potential. The EO potentials are probably not a sufficiently sensitive indicator for the detection of the slight effect of the nature of the R group, especially since the EO potentials on solid electrodes depend not only on the electronic and steric effects of the substituents but also on the adsorbability and orientation of the electroactive molecules on the electrode surface.

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*Some of the E_p and $E_{1/2}$ values presented in [1] are somewhat too high; for example, $E_p = 0.90$ V and $E_{1/2} = 0.85$ V for the ethyl ester ($R = C_2H_5$).

On the basis of the available data on the structure of 1,4-dihydropyridines and the EO data obtained in this study, some assumptions regarding the EO process can be stated. The molecule of the compound undergoing oxidation should approach the anode with its most negatively charged center. Polarized β-carbonyl groups are centers of this type in the investigated 1,4-dihydropyridines. The presence of a substituent in the γ position may give rise to steric hindrance, and this should affect the E_p value. However, this does not clarify the question as to which site in the 1,4-dihydropyridine molecule is the EO reaction center — the conjugated aminovinylcarbonyl system (AVCS) or the carbon atom in the γ position. The ability of the dihydropyridines to split out a hydride ion provides evidence in favor of the latter [8].

Some assumptions regarding the reaction center can be stated on the basis of the EO potentials obtained in the present research and in earlier research [1, 2] and their correlation with the σ constants. It is known that when the reproducibility constants (ρ) in reaction series with an identical reaction center and an identical reagent (in this case the "reagent" is the platinum anode) are compared, the absolute value of ρ is lower, the more remote the substituents (identical substituents in both series) from the reaction center. In this case, $\rho_B : \rho_A = \pi'$ under identical reaction conditions, i.e., transmission factor π' is introduced [9].

Thus in the EO of dihydropyridines, one can compare the E_p values obtained during the oxidation of two series of compounds — the γ-aryl-substituted compounds [1, 2] and the β-aryloxycarbonyl derivatives (XVII-XXI). In the first case, a distinct linear correlation of the E_p values with the σ constants is observed ($\rho = 0.13$) [2], whereas in the second case, because of the subtle difference in the E_p values, the ρ value in the correlation, if such a correlation were to exist, would be close to zero. If it is assumed that the reaction center is the AVCS, the transmission factor (π') is 0.61 for β substituents attached to the oxygen atom of the ester grouping (the effect of a substituent through the oxygen atom, whereas $\pi' = 0.48$ — the effect through the carbon atom in the γ position — for the corresponding γ substituent), i.e., the ρ values for two completely different series should differ little from one another. However, it was actually established that the effect of the aryl substituent in the γ position is manifested considerably more markedly. However, if it is assumed that the reaction center is the carbon atom in the γ position, the effect of substituents in the ester group (β position) would be characterized by a transmission factor of $0.61 \cdot 0.43 \cdot 0.67 = 0.18$ (the effect of substituents through —O—, $\rangle C{=}O$ and the β carbon), while the effect of a substituent in the γ position in this case would be direct ($\pi' = 1$). Consequently, it may be supposed that in this case the effect of a γ-substituent will be approximately five times stronger than the effect of a substituent in the β position. As we have already stated above, this is in agreement with the experimental data. Thus correlation calculations on the basis of EO experimental data lend greater substantiation to the assumption that the reaction center during the EO of DPDA esters in the γ-carbon atom. The extremely facile oxidation of γ-carboxylate-substituted compounds [2] is also in agreement with this assumption.

EXPERIMENTAL

The EO potentials were determined by a previously described method [1] with an LP-60 automatic polarograph. A rotating platinum microanode (with a diameter of 1 mm, a rotational rate of 1400 rpm, and a polarization rate of 400 mV/min) served as the polarized electrode. Acetonitrile with an 1 M $LiClO_4$ base electrolyte, the decomposition potential of which was 1.9-2.1 V, served as the experimental medium. The experimentally found E_p and $E_{1/2}$ values, which were measured relative to a saturated calomel electrode with an accuracy of +40 mV, are presented in Table 1. The compounds were synthesized by the methods in [3, 4].

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COMPLEXES OF 2-AMINOPYRIDINE AND ITS SUBSTITUTED DERIVATIVES WITH IODINE

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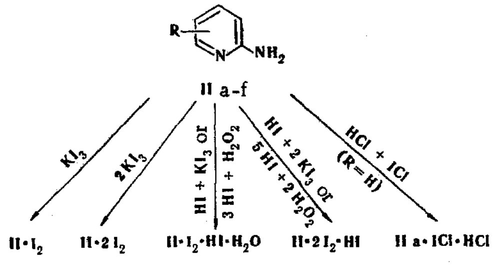
Depending on the amount of halogen used, 2-aminopyridine and its ring-substituted derivatives form complexes with 1 or 2 moles of iodine. In the presence of hydriodic acid, one equivalent of acid is included in the complex. 2-Amino-3,5-dibromopyridine forms a complex with 1 mole of iodine even in the presence of excess iodine or in the presence of HI. According to the IR spectra, the iodine in the complexes is coordinated with the ring nitrogen atom.

A large amount of research has been devoted to the study of complexes of pyridine and its alkyl-substituted derivatives (I) with iodine; however, information on complexes of 2-aminopyridine (IIa) is extremely limited. According to [1], base IIa forms a complex of the IIa $\cdot I_2$ type on reaction with a solution of KI_3 or of hydrogen peroxide in a solution of hydriodic acid. The UV spectrum of this complex is presented in [2]. Complexes of base IIa with ICl [3] and Pt^{2+} [4.6], Ag^+, and Cu^{2+} [7] salts have also been described.

We have found that IIa and its ring-substituted derivatives (IIb-f) react with iodine to give complexes of several types, which are shown in the scheme in Table 1. The complexes were obtained by the action of KI_3 on base II in water (method A) or in hydriodic acid (method B) and also by the action of hydrogen peroxide on solutions of the bases in hydriodic acid (method C).

The composition of the complex depends on the amount of iodine used in the reaction, the ring substituents, and the character of the medium. Complexes of the general type II $\cdot I_2$ are formed in all cases in the reaction of an equimolar amount of iodine by method A, whereas excess iodine leads to II $\cdot 2I_2$ complexes. However, in the case of 2-amino-3,5-dibromopyridine (IIe) the IIe $\cdot I_2$ complex is obtained even when 3 moles of iodine are used.

In hydriodic or hydrochloric acid solutions base IIa reacts with KI_3 solution to give IIa $\cdot I_2 \cdot HI \cdot H_2O$ or IIa $\cdot 2I_2 \cdot HI$ complexes depending on the amount of iodine used, monohalo-substituted IIc and IId form complexes only of the II $\cdot I_2 \cdot HI \cdot H_2O$ type even in the presence of excess iodine, and dibromo substituted IIe forms a IIe $\cdot I_2$ complex.



II a $R=H$; b $R=3\text{-}CH_3$; c $R=5\text{-}I$; d $R=5\text{-}Cl$; e $R=3{,}5\text{-}Br_2$; f $R=6\text{-}NH_2$

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