2-Substituted 1-Aryl-7-methyl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines (IIa-e). Dry hydrogen chloride is introduced into a solution of 10 mmoles Ia-e in 40 ml anhydrous ethanol for 1.5 h and then, the reaction solution is heated for 0.5 h on a water bath. After cooling, the precipitate is filtered off and treated with aqueous sodium acetate. Crystallization from ethanol gives IIa-e.

1-Aryl-2-acetonyl-7-methyl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines (IIIa and IIIb). A solution of 10 mmoles 2-arylamino-6-methylnicotinamide (IVa or IVb) or 10 mmoles IIa or IIb and 0.7 g (8 mmoles) anhydrous sodium acetate in 10 ml acetic anhydride is heated at reflux for 10 h and poured into water. The residue is crystallized to yield IIIa or IIIb.

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ELECTROCHEMICAL REDUCTION OF HYDROGENATED 2-PYRIMIDONES ON A GRAPHITE ELECTRODE

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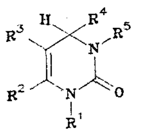
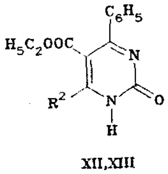
A rotating disk—ring graphite electrode was used to show that the first step in the electrochemical oxidation of substituted 2-oxo-1,2,3,4-tetrahydropyrimidines in anhydrous acetonitrile corresponds to a two-electron process and leads to the formation of the corresponding substituted 2-oxo-1,2-dihydropyrimidines. The electroreduction wave of 2-oxo-1,2-dihydropyrimidines on the ring electrode which appears at about −1.0 V is related to the reduction of the protonated oxidized species arising in the electrolysis. The electrochemical oxidation potentials of 11 hydrogenated 2-pyrimidones and electrochemical reduction potentials of two 2-pyrimidines were determined.

In a continuation of a study on the electrochemical oxidation of hydrogenated azines [1, 2], we investigated hydrogenated 2-pyrimidones in order to elucidate their capacity to undergo oxidation and to compare the electrochemical behavior of these compounds with that of previously studied 2-pyridones [3].



I-XI



XII,XIII

Table 1 shows that I-XI give a well-pronounced electrooxidation wave on a graphite disk in acetonitrile. The halfwave potentials lie in the range from 0.8 to 1.2 V. The linear de-

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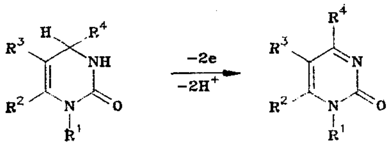
pendence of I_c on the square root of the angular rotational velocity of the disk ($\sqrt{\omega}$) and the direct proportionality of the concentration of the electrochemically active compound are retained for these waves, indicating the diffusional nature of the current. The wave is irreversible and the number of electrons (n) varies in the range from 1.5 to 1.9 (with the exception of pyrimidone VII which does not have a hydrogen atom at N-3 and requires one electron for oxidation). The value for n is only slightly dependent on change in the rate of disk rotation and decreases from 1.9 to 1.7 with an increase in the rotational velocity from 1000 to 7000 rpm for II.

Three waves are observed in the reverse electroreduction (on the ring) of the products of electrooxidation at the disk potential corresponding to the area of the limiting current of the first wave. The first of these waves which appears at from −0.3 to −0.5 V is assigned, as in our previous work [4], to the reduction of hydrogen ions formed in the oxidation of the compound studied on the disk. For some compounds (see Table 1), this wave is indistinct and elongated in shape; its height cannot be measured precisely. The nature of the second wave, which appears in the vicinity of −1.0 V, will be examined below. The third wave, which appears at −2.0 V, is close in potential to the reduction wave of oxidized forms of compounds taken as models (XII and XIII) and obtained as a result of the chemical oxidation of hydrogenated 2-pyrimidones. However, this wave is very small in height and becomes significant for some compounds only at high rotational velocities; the precise determination of $E_{1/2}$ is difficult.

Unfortunately, the reduced form of II corresponds completely to only model compound XII. Thus, II was specifically taken for carrying out prolonged electrolysis, accumulation of the final product, and identification of this product. The electrolysis at controlled potential was carried out at the potential corresponding to the area of the limiting current of the oxidation wave of II (1.5 V) over 4 h. A thin-layer chromatographic study of the electrolysate showed that the oxidized form II is indeed the final product of the electrolysis of XII. The final electrolysis product has a long-wavelength maximum at 320 nm characteristic for XII. We should note that the concentration of XII increases during the prolonged electrolysis and the wave for its reduction thus becomes pronounced. These results indicate that the electrochemical oxidation of I-XI on a rotating disk electrode (with the exception of VII) proceeds in one two-electron step as follows:



The oxidation of VI also occurs with the consumption of two electrons, apparently due to the loss of a proton and acetyl group. Thus, the general scheme for the electrochemical oxidation of hydrogenated 2-pyrimidones is analogous to the oxidation of hydrogenated 2-pyridones studied in our previous work [3]. However, a significant difference is found in the appearance of a second diffusional electroreduction wave on the ring at about −1 V for hydrogenated 2-pyrimidones. The height of this wave upon the introduction of 0.1 N H_2SO_4 as a proton donor in gradually increasing concentration from $1 \cdot 10^{-4}$ to $4 \cdot 10^{-4}$ mole/liter hardly changes.

For hydrogenated 2-pyrimidones, the dependence of the current yield of the second electroreduction wave on the ring (N_i^k) on the angular rotational velocity is very weak, indicating considerable stability of the corresponding electrochemical oxidation product. Thus, this wave cannot be assigned to the reduction of an intermediate radical-cation. In our opinion, this wave was likely the reduction wave of the protonated oxidized form. In order to check this hypothesis, we studied the electrochemical reduction of a model compound, namely, the oxidized pyrimidone form XII both with and without proton donors.

One reduction wave at from −1.4 to −2.0 V is observed in the reduction of XII on a graphite disk electrode and also on the ring (for disk potential (E_d) equal to zero) in acetonitrile not containing proton donors. However, upon the addition of a proton donor (0.1 N H_2SO_4) in gradually increasing concentration from $1 \cdot 10^{-4}$ to $4 \cdot 10^{-4}$ mole/liter, the height of this wave drops and a second wave at about −1.0 V concurrently increases. This wave corresponds

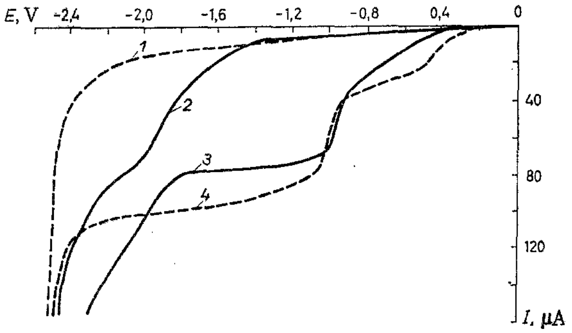
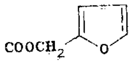


Fig. 1. Current—potential curves for the electroreduction taken on the ring electrode (m = 2000 rpm) in acetonitrile with 0.1 N $(C_4H_9)_4NClO_4$ as the base electrolyte for depolarizer concentration $5 \cdot 10^{-4}$ mole/liter with II at E_d = 0 (1) and 1.4 V (4) (potential corresponding to the area of the limiting current of the electro-oxidation wave) and XII without acid (2) and with the addition of $3 \cdot 10^{-4}$ M H_2SO_4(3).

TABLE 1. Parameters for the Electrochemical Transformations of I-XIII on a Graphite Rotating Disk—Ring Electrode in Acetonitrile (m = 2000 rpm, $5 \cdot 10^{-4}$ mole/liter depolarizer concentration; values for $E_{1/2}$ given relative to an $Ag/AgNO_3$ (0.2 N) electrode)

Compound*	R^2	R^3	Disk oxidation		n	Ring reduction						Disk reduction		Q, %
						first		second		third				
			$E_{1/2}$, V	I_C, V		$-E_{1/2}$, V	I_C, V	$-E_{1/2}$, V	I_C, V	$-E_{1/2}$,† V	I_C, V	$-E_{1/2}$, V	I_C, V	
I	H	$COOC_2H_5$	1,16	455	1,5	Indistinct		0,92	25,5	—	—			33,0
II	CH_3	$COOC_2H_5$	1,13	500	1,8	Indistinct		1,0	38	1,7	14			44,7
III	H	$COOC_2H_5$	1,21	470	1,7	Indistinct		0,89	63	1,9	6			78,8
IV	CH_3	$COOC_2H_5$	1,09	430	1,6	0,44	16	1,02	28	2,0	16			38,3
V	C_6H_5	$COOC_2H_5$	1,10	500	1,9	0,34	26	0,95	34	1,9	7			40,0
VI	CH_3	$COOC_2H_5$	1,36	420	1,6	0,41	30	0,85	37	—	—			51,8
VII	CH_3	$CONH_2$	0,85	255	0,9	Indistinct		1,19	32	1,8	6			73,8
VIII	CH_3	CN	1,14	510	1,8	0,35	23	0,86	30	1,8	8			34,1
IX	CH_3	$CONH_2$	1,01	437	1,6	Indistinct		1,09	26	—	—			35,0
X	CH_3		1,07	440	1,7	0,42	26	1,01	14	2,0	7			18,7
XI	CH_3	$COSC_2H_5$	1,08	430	1,6	0,42	18	1,02	26	2,0	9			35,6
XII	CH_3		—	—								1,80	180	
XIII	C_6H_5		—	—								1,68	145	

*I, II, R^1 = H, III-XI, R^1 = CH_3; I, R^4 = H, II-XIII, R^4 = C_6H_5; I-V, VIII-XIII, R^5 = H, VI = R^5 = $COCH_3$, VII, R^5 = CH_3.

†In light of the difficulty of obtaining a precise measurement, the values of $E_{1/2}$ are given with an error up to ±0.1 V.

to the second reduction wave on the ring for the product of the electrochemical oxidation of II (Fig.1). In addition, a wave in the range from —0.3 to —0.5 V arises and grows upon the addition of a proton donor. This wave is assigned to the reduction of hydrogen ions. Thus, it is convenient to assume that the electrochemical reduction of XII, similarly to that for the final product of the electrochemical oxidation of II, may proceed by two parallel pathways both with and without prior protonation.

In the reduction of model compound XII, the wave appearing at $E_{1/2}$ = —1.8 V corresponds to the reduction of the nonprotonated form. Upon the introduction of a proton donor and an increase in the proton donor concentration, reduction with prior protonation begins to predominate (appearance of a wave with $E_{1/2}$ = —1.0 V).

The reverse reduction of the oxidation product of II proceeds largely after prior protonation even in an aprotic medium such as acetonitrile. This is likely due to the formation of a sufficient proton concentration required for the protonation of the oxidized species arising on the surface of the disk upon the electrooxidation of the starting compound in the solution near the electrode and a further increase in the proton concentration by adding sulfuric acid does not affect the height of this wave.

Comparison of the electrochemical behavior of II and XII indicates that a proton adds to N-3 since II does not give a reduction wave on the disk even when protons are available in the solution.

On the other hand, in the case of 2-pyridones, in which the $>C{=}C<$ group is the reaction site in electrochemical reduction instead of the $>C{=}N{-}$ group, prior protonation is impossible and, thus, the corresponding reduction wave on the ring is absent.

Comparison of the halfwave potentials of I-XI indicates that the introduction of the electron-donor methyl group, as expected, facilitates the electrooxidation and the greatest shift of $E_{1/2}$ toward less positive potentials (by 160 mV) is found for IX, in which the methyl group is at N-3, i.e., adjacent to the reaction site (compare with VII). On the other hand, the introduction of the electron-withdrawing $COCH_3$ group at N-3 as in VI makes the electrooxidation more difficult (compare with IV).

The electrochemical oxidation of hydrogenated 2-pyrimidones and hydrogenated 2-pyridones proceeds at comparatively similar potential ranges, while derivatives of 1,2- and 1,4-dihydropyridine are oxidized much more readily (by an average of 400-500 mV) [4, 5]. This finding is in accord with the antioxidant properties of these compounds.

EXPERIMENTAL

The electrochemical oxidation of I-XIII was carried out on a Bruker electrolyzer equipped with a Pine Instruments rotating disk—ring electrode, using a fiberglass disk (S^D = 0.47 cm^2) and platinum ring (S^R = 0.06 cm^2). The theoretical efficienty coefficient N = 0.183. The rotational velocity was varied from 1000 to 7000 rpm. The reference electrode was $Ag/AgNO_3$ (0.2 N) in acetonitrile with 0.1 N tetrabutylammonium perchlorate.

The studies were carried out at room temperature in anhydrous acetonitrile purified according to Clark et al. [6] after prior drying over calcium hydride for three days. The depolarizer concentration in all cases was $5 \cdot 10^{-4}$ mole/liter. The diffusion coefficients were found from pycnometric data using the Stokes—Einstein equation [7]. This coefficient was $1.40 \cdot 10^{-5}$ cm^2/sec for II. The number of electrons consumed per molecule of the oxidized compound was calculated using the equation for the limiting diffusion current on a rotating disk electrode [8].

A sample of 0.1 N tetrabutylammonium perchlorate was used as the base electrolyte. The UV spectra were taken on a Pye-Unicam SP-1800 spectrometer.

The electrolysis at controlled potential of II was carried out with 2000 rpm rotational velocity over 4 h at 1.5 V. The electrolysis product was identified using thin-layer chromatography on Silufol-254 plates using 9:7:1 chloroform—hexane—acetonitrile as eluent.

The PMR spectra were taken on a Bruker WH-90 spectrometer in DMSO-d_6 with TMS as the internal standard.

Compounds I-XI were prepared according to reported procedures [9-13].

Furfuryl Ester of 1,6-Dimethyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid (X). mp 134-136°C (from propanol). Yield, 74%. PMR spectrum: 8.0 (1H, d, NH), 7.24 (5H, m, C_6H_5), 7.69 and 6.26 (1H, and 2H, m, furan ring, H), 5.15 (1H, d, 4-H), 5.06 (2H, s, CH_2), 3.11 (3H, s, NCH_3), 2.46 ppm (3H, s, CH_2). Found: C 63.6; H 6.0; N 16.7%. Calculated for $C_{18}H_{18}N_2O_4$: C 63.6; H 6.4; N 17.1%.

S-Ethyl Ester of 1,6-Dimethyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-thiocarboxylic Acid (XI). mp 166-168°C (from ethanol). Yield, 85%. PMR spectrum: 8.16 (1H, d, NH), 7.33 (5H, s, C_6H_5), 5.24 (1H, d, 4-H), 2.98 (3H, s, NCH_3), 2.82 (2H, q, SCH_2CH_3), 2.44 (3H, s, CH_3), 1.02 ppm (3H, t, SCH_2CH_3). Found: C 62.4; H 6.3; N 9.1; S 11.5%. Calculated for $C_{15}H_{18}N_2O_2S$: C 62.1; H 6.2; N 9.6; S 11.0%.

Ethyl Ester of 4-Phenyl-6-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic Acid (XII) was obtained by the oxidation of I [14].

Ethyl Ester of 4,6-Diphenyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic Acid (XIII). A sample of 5.6 g (0.02 mole) PCl_5 was added to 3.36 g (0.01 mole) V and heated at reflux for 4 h in 20 ml $POCl_3$. After evaporation, 100 ml ice water was added and the mixture was extracted with three 40-ml portions of ether. Ether was evaporated and the precipitate was crystallized from ethanol to give 1.44 (45%) XIII, mp 266-267°C. PMR spectrum: 7.48 (10H, s, $2\text{-}C_6H_5$), 3.82 (2H, q, OCH_2CH_3), 0.71 ppm (3H, t, OCH_2CH_3). Found: C 71.3; H 5.1; N 8.3%. Calculated for $C_{19}H_{18}N_2O_3$: C 71.8; H 5.4; N 8.4%.

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