DUAL REACTIVITIES OF 1,2-DISUBSTITUTED DIHYDRO-N-HETEROAROMATIC SYSTEMS.

3.* ELECTROCHEMICAL AROMATIZATION OF SUBSTITUTED N-ACYLDIHYDROPYRIDINES AND IMIDAZOLES

I. I. Sosonkin, A. K. Sheinkman,
Z. M. Skorobogatova, G. N. Strogov,
and T. P. Ikher

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The principal pathway in the fragmentation of the cation radicals of N-acyl-α (γ)-substituted 1,4-dihydropyridines and 1,2-dihydroisoquinolines, as well as 1,2-dihydroimidazoles and 1,2-dihydrobenzimidazoles, that are formed in the electrochemical oxidation of the indicated N-acyldihydro-N-heteroaromatic systems is the loss of a proton and the subsequent loss of another electron or detachment of an N-acyl residue in the form of a cation and subsequent detachment of an electron to give the corresponding γ (α)-substituted heteroaromatic cations.

The "aromatization" of cyclic or heterocyclic dihydro derivatives is usually understood to mean their conversion to aromatic compounds with the loss of hydrogen, i.e., essentially "dehydroaromatization." Moreover, in the case of substituted N-acyl-1,2-dihydrobenzopyridines (DHP) it has been shown [1-3] that aromatization may occur not only as a result of dehydrogenation but also as a result of splitting out of geminal substituents from the α (or γ) position of the heterocyclic ring (a reaction that is the reverse of hetarylation [4]).

There are two alternative points of view regarding the mechanism of dehydroaromatization, which may be a stepwise process with the detachment of two electrons and a proton from the DHP in various sequences [5-9] or may be a one-step process with heterolytic cleavage of the C−H bond and splitting out of a hydride ion [1, 10]. Similar mechanisms are also evidently realized in reactions involving the aromatization of DHP with the detachment of a substituent. These mechanisms have been the subject of a great deal of published studies and continuous discussion; however, none of them explains the reasons for the different pathways in the aromatization of DHP, which depend on many factors, chief among which are the nature of the aromatizing agent, the magnitude of the electron density on the sp^3 carbon atom in the DHP, and the nature of the leaving group.

In order to exclude the effect of the nature of the aromatizing agent on the direction of aromatization we carried out the electrochemical oxidation of a series of DHP (Ia-VIIIa, Table 1) and established the structures of the resulting compounds.

Despite the fact that studies devoted to the electrochemical dehydrogenation of heterocyclic compounds have been recently published [5, 7, 8, 11], very little study has been devoted to the behavior of substituted N-acyl derivatives of dihydropyridines [12]. In addition, it seemed of interest to ascertain how replacement of the N-alkyl group in the dihydroheterocyclic compound [5, 7, 8] by an N-acyl group and the presence of an α (γ) substituent affect the character of the fragmentation of the cation radicals of the starting compounds, which are formed in the first step of the electrochemical oxidation.

Prior electrolytic oxidation of Ia-VIIIa in acetonitrile showed that this process is accompanied by adsorption of the reaction products on the electrode, which gives rise to blocking of the electrode surface, as a result of which the limiting currents of the oxidation waves are decreased and in individual cases are not observed at all when the oxidation wave is re-recorded.

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*See [1] for Communication 2.

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TABLE 1. Results of the Electrochemical Oxidation of N-Acyl Derivatives of Dihydropyridines and Other Model Systems (Ia-VIIIa) on a Rotating Platinum Disk Electrode with a Ring in Dimethylformamide (DMF)

Compound	Electrode	Constant potential, V	$E_{1/2}$, V	I_{lim}, μA	n
Ia	Disk	E_k 0	1,07	21,0	1,8
	Ring	E_D 1,25	−0,52	0,96	
			−0,72	1,64	
IIa	Disk	E_k 0,80	1,12	23,0	2,1
	Ring	E_D 0,80	1,04	0,024	
	Ring	E_D 1,30	−0,49	0,83	
			−0,71		
IIIa	Disk	E_k 0	1,07	17,8	1,8
	Ring	E_k 0,85	1,03	0,032	
	Ring	E_D 1,20	−0,40	0,84	
			−0,74	1,10	
IVa	Disk	E_k 0,60	1,13	19,7	1,8
	Ring	E_k 0,60	0,96	0,016	
	Ring	E_D 1,30	−0,49	0,88	
			−0,70	0,40	
Va	Disk	E_k 0	1,16	21,0	2,1
	Ring	E_k 0,90	0,97	0,034	
	Ring	E_D 1,35	−0,47	1,56	
VIa	Disk	E_k 0,90	1,22	18,6	1,8
	Ring	E_k 0,90	1,10	0,032	
	Ring	E_D 1,40	−0,48	1,27	
VIIa	Disk	E_k 0	0,99	19,6	2,0
	Ring	E_k 0,80	0,92	0,022	
	Ring	E_D 1,15	−0,50	1,0	
			−1,06	1,1	
VIIIa	Disk	E_k 0	1,30	18,0	1,9
	Ring	E_k 1,20	1,24	0,23	
	Ring	E_D 1,40	−0,50	1,18	
			−0,95	0,88	

TABLE 2. Electrochemical Reduction Potentials of the Cations on a Rotating Platinum Electrode

Cation	Solvent	$E_{1/2}$, V	i_{lim}, μA
Ic	DMF	−0,55	15,2
	CH_3CN	−0,58	23,4
IIb	DMF	−0,56	13,8
IIc	DMF	−0,48	13,9
IId	CH_3CN	−0,68	23,6
IIIb	CH_3CN	−0,47	23,2
IIIc	DMF	−0,39	5,6
		−0,71	3,4
IVc	DMF	−0,50	8,7
Vb	CH_3CN	−0,38	23,4
Vc	CH_3CN	−0,43	8,4
		−0,70	16,2
VIc	CH_3CN	−0,49	14,8

TABLE 3. Characteristics of 1,2-Dihydroisoquinolines IIIa and Va and the Corresponding Perchlorates IIIb, IVb, and IIIc, Vc

Compound	mp, °C	R_f	IR spectrum, cm^{-1}, C=O	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
IIIa	118—119 [a]	0,5	1600	80,0	5,0	7,7	$C_{25}H_{20}N_2O_2$	78,9	5,3	7,7	70
Va	169—171 [b]	0,47	1620	73,2	4,1	10,5	$C_{24}H_{17}N_3O_2$	72,9	4,3	10,6	80
IVb	130—133 [c]	—	1745	55,9	4,0	3,9	$C_{17}H_{14}ClNO_6$	56,1	3,9	3,9	81
Vb	201—203 [c]	—	1765	60,6	3,4	8,7	$C_{16}H_{11}ClN_2O_7$	60,3	3,5	8,8	70
IIIc	235—236 [c]	—	1737	62,7	3,7	6,2	$C_{25}H_{19}ClN_2O_6$	62,7	3,9	5,9	86
Vc	248—249 [c]	—	1755	58,7	3,3	8,5	$C_{24}H_{16}ClN_3O_7$	58,4	3,2	8,5	85

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[a] From methanol. [b] From n-butanol. [c] From acetonitrile.

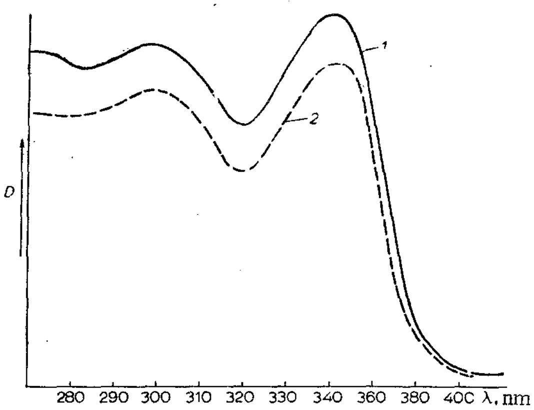
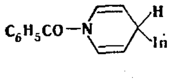
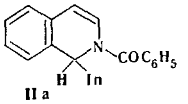


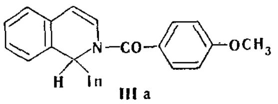
Fig. 1. Electronic spectra of perchlorate VIc obtained by electrochemical (1) and chemical (2) oxidation of dihydroisoquinoline VIa.



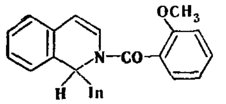
Ia



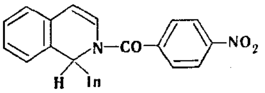
IIa



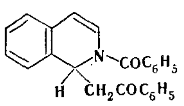
IIIa



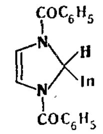
IVa



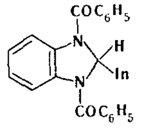
Va



VIa



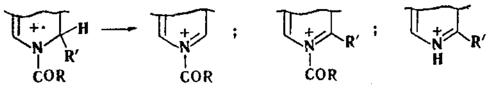
VIIa



VIIIa

In = 3-indolyl

In analogy with reactions involving the chemical aromatization of Ia-VIIIa [1, 3] one might have expected that the final products of the fragmentation of the cation radicals of these compounds would be the following cations:



b c d

To identify the cations formed on the disk with a ring we studied their electrochemical reduction and found that in DMF some of them are unstable, whereas they are quite stable in acetonitrile [3]. In addition to DMF, we therefore used acetonitrile as the solvent for these cations (Table 2).*

It follows from Table 1 that all of the dihydroheterocyclic compounds (Ia-VIIIa) that we investigated are oxidized formally in one two-electron step, as evidenced by the limiting diffusion current (i_{lim}) on the disk. To estimate the stabilities of the resulting cation radicals we recorded the volt–ampere graphs on a ring with a constant potential of the ring equal to the potential of the foot of the oxidation wave on the disk; the reduction waves of the cation radicals were observed in this case. The low values of the limiting currents of these waves constitute evidence for the low stability of the latter (Table 1). (The rate constants for monomolecular fragmentation estimated by the method in [14] are greater than 2000 sec^{-1}.) It is characteristic that replacement of the

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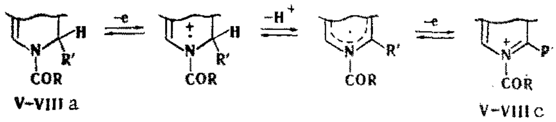
* The reduction potential of only one protic salt (IId) is presented in Table 2, since it is known [13] that N-protic salts of heterocyclic compounds are reduced on platinum with catalytic liberation of hydrogen at the same potential. The reduction potentials of cations VIIb, c and VIIIb, c were not measured, since we were unable to obtain them in the individual state; a difficult-to-separate mixture of cations VIIb, c or VIIIb, c was obtained in the aromatization of imidazolines VIIa and VIIIa under the influence of triphenylmethyl perchlorate.

N-methyl group in similar compounds [5, 7, 8] by an N-acyl group leads to a sharp increase in the oxidation potential of DHP and to a significant decrease in the stability of their cation radicals.

In order to identify the products formed from the cation radicals after they have gone into solution we recorded the volt–ampere graphs with potential scanning on a ring electrode; in this case the potential of the disk electrode was preset at a constant value equal to the start of the plateau of the limiting current for oxidation of the corresponding DHP. An overall approximately two-electron wave was observed for Va and VIa because of accidental coincidence of the reduction potentials of N-acyl cations Vc and IVc and the protons (−0.47 V, according to the data in [15]). In the case of Ia-IVa, in addition to the reduction wave of protons, we recorded another wave corresponding to the reduction of cations Id-IVd (compare Tables 1 and 2). Since, as we have already noted, we were unable to obtain the corresponding cations synthetically in the case of imidazolines VIIa and VIIIa, it may be assumed that the first wave on the volt–ampere graphs corresponds to the reduction of the proton, whereas the second wave corresponds to reduction of the N-acyl cations that retain the substituent in the 2 position (Tables 1 and 2).

The data obtained in this study show that, depending on the structure of the starting dihydro compound, electrochemical oxidation may lead to different products. The dehydroaromatization of Va-VIIIa probably proceeds via the following scheme:

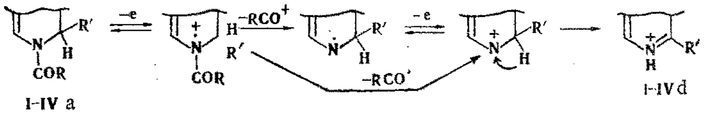


V-VIII a

V-VIII c

i.e., through the successive detachment of an electron, a proton, and an electron. The results obtained in the micropreparative electrolysis of dihydroisoquinoline VIa may serve as additional evidence for this scheme. It is apparent from Fig. 1 that the electronic spectrum of the reaction solution coincides completely with the spectrum of N-benzoyl-1-phenacylisoquinolinium perchlorate (VIc).

In the case of Ia-IV, splitting out of an acyl group via one of the schemes presented below occurs along with dehydroaromatization:



I-IV a

I-IVd

These schemes differ in that in the first scheme the acyl group is split out in the form of a cation, whereas in the second it is split out in the form of a radical. Overall, the first process corresponds to the transfer of two electrons, while the second corresponds to the transfer of one electron. Since a two-electron wave is experimentally observed for Ia-IVa (Table 1), the first scheme is the most likely process.

Thus a study of the electrochemical oxidation of N-acyl derivatives of dihydropyridines has shown that parallel processes involving the splitting out of a proton and an acyl group, as a result of which the corresponding substituted N-acyl (c) and N-protic (d) salts are formed and the formation of unsubstituted salts (b) by detachment of the α (γ) substituent is not observed in a single case, are characteristic for the conversion of the cation radicals formed in the first step.

EXPERIMENTAL

The method used to purify the DMF, the construction and characteristics of the rotating platinum electrode with a ring, the method used to record the volt–ampere curves, and the calculation of the number of electrons transferred were described in [16]. Pure-grade acetonitrile was purified immediately prior to preparation of the solutions as in [17]. Prior electrolysis was realized in DMF by the method in [18]. A saturated calomel electrode served as the reference electrode in all cases. The number of electrons transferred on the disk electrode was calculated starting from the assumption that the coefficients of diffusion of the depolarizers are inversely proportional to the square root of the molecular mass. The concentrations of the compounds were $5 \cdot 10^{-4}$ M in the recording of the volt–ampere curves and 10^{-4} M in the case of prior electrolysis. The concentration of the inert electrolyte was 0.1 M in all cases.

The electronic spectra of solutions of the compounds in DMF were recorded with a Hitachi EPS-3T spectrophotometer. The IR spectra of KBr pellets of the compounds were obtained with a Perkin-Elmer spectrometer. Chromatography was realized in a loose thin layer of activity II aluminum oxide by elution with chloroform–benzene–hexane (30 : 6 : 1) and development with iodine vapors.

The N-acyl derivatives (Ia-IIIa, VIa-VIIIa) of dihydro-N-heteroaromatic compounds were obtained by hetarylation [4]; perchlorates Ib-d-VIb-d were obtained by the methods in [3].

N-o-Methoxybenzoyl-1-(3-indolyl)-1,2-dihydroisoquinoline (IVa). An 8.5-g (0.05 mole) sample of o-methoxybenzoyl chloride was added dropwise with vigorous stirring to a solution of 12.9 g (0.1 mole) of dry isoquinoline and 5.85 g (0.05 mole) of indole in 20 ml of dry benzene, the reaction mixture was refluxed for 2 h, and 50 ml of water and 50 ml of hexane were added. The precipitate was removed by filtration, washed with methanol, and recrystallized from n-butanol to give 10.9 g (73%) of a product with mp 208-210°C and R_f 0.36. IR spectrum: 1600 cm^{-1} (C=O). Found: C 78.5; H 5.3; N 7.8%. $C_{25}H_{20}N_2O_2$. Calculated: C 78.9; H 5.3; N 7.7%.

Compounds IIIa and Va were similarly obtained (Table 3).

N-o-Methoxybenzoyl-1-(3-indolyl)isoquinolinium Perchlorate (IVc). This compound was obtained by the method in [1] by the reaction of 0.02 mole of IVa and 0.03 mole of 2,2,6,6-tetramethyl-1-oxopiperidinium perchlorate in dry acetonitrile. The product, with mp 251-253°C (from acetonitrile) was obtained in 88% yield. IR spectrum: 174 cm^{-1} [sic]. Found: C 62.9; H 4.0; N 5.6%. $C_{25}H_{19}ClN_2O_6$. Calculated: C 62.7; H 3.9; N 5.9%.

Perchlorates IIIc and Vc (Table 3) were obtained under similar conditions.

N-o-Methoxybenzoylisoquinolinium Perchlorate (IVb). This compound was obtained by the method in [3] by the reaction of equimolar amounts of IVa and triphenylmethyl perchlorate in dry acetonitrile. The principal characteristics of perchlorate IVb and the similarly obtained perchlorate Vb are presented in Table 3.

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