DUAL REACTIVITY OF 1,2-DISUBSTITUTED DIHYDRO-N-HETEROAROMATIC SYSTEMS.
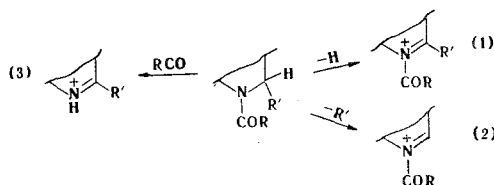
4.* FACTORS THAT AFFECT THE RATE OF AROMATIZATION OF SUBSTITUTED N-ACYLDIHYDROPYRIDINES

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The rate of dehydroaromatization of N-acyldihydropyridines under the influence of the 2,2,6,6-tetramethyl-1-oxopiperidinium cation increases in the case of electron-donor substituents and decreases in the case of electron-acceptor substituents in the acyl residue or in the α (γ) positions of the pyridine ring. The presence of an annelated benzene ring also decreases the rate of aromatization of dihydropyridines.

Substituted N-acyldihydropyridines (DHP) are converted to an aromatic system under the influence of various aromatizing agents via three pathways: as a result of detachment of hydrogen (1), a substituent (2), or an N-acyl group (3) [1-4].

The mechanisms of dehydroaromatization reactions (pathway 1) have recently become the subject of extensive discussion; however, the literature contains no information regarding the mechanisms of aromatization reactions via pathways 2 and 3 with cleavage of the C−N or C−C bonds or regarding the reasons for the ambident character of DHP and the factors that affect the selection of the pathway of these reactions. On the basis of the available data [1-4] we suppose that it is expedient to use the concept of charge- and orbital-controlled reactions [5] to predict the pathway of aromatization of 1,2-disubstituted dihydroaromatic systems. In orbital-controlled aromatization reactions the aromatizing agents interact with the upper occupied molecular orbital of the DHP to give π complexes with the subsequent detachment of one electron, i.e., in these reactions the aromatizing agents act essentially as oxidizing agents. Using the principle of hard and soft acids and bases [5, 6] one may assume that all "soft" electrophiles such as quinones, trinitrobenzene, etc., which have redox potentials that exceed the oxidation potentials of DHP, will be aromatizing agents of this type. In this case the intermediately formed DHP cation radicals are aromatized with the loss of a proton or an N-acyl cation and yet another electron and the formation of cations via scheme 1 or 3 [1]. In charge-controlled aromatization reactions "hard" electrophiles such as acetylium, triphenylmethylcarbenium, etc. cations evidently directly attack the sp³ carbon atom with heterolytic cleavage of the C−C bond and detachment of a substituent via a mechanism involving bimolecular electrophilic substitution. In these reactions DHP cation radicals are evidently not formed, for if they were, as demonstrated in [1], their fragmentation would lead to the formation of cations via pathways 1 and 3 rather than via pathway 2.

In the present research we studied the chemical aromatization of various DHP by means of 2,2,6,6-tetramethyl-1-oxopiperidinium perchlorate, which is a "soft" electrophile with a higher redox potential ($E_{1/2} = 0.62$ V) than DHP [1].
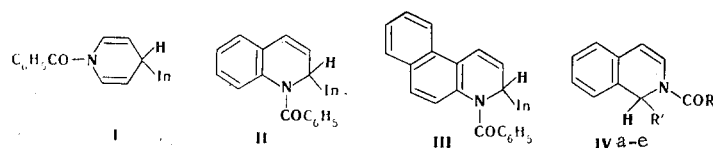
* See [1] for Communication 3.

TABLE 1. Rate Constants for the Aromatization of I-IV by the 2,2,6,6-Tetramethyl-1-oxopiperidinium Cation in Acetonitrile in Air at 25°C
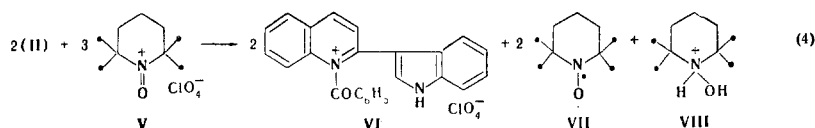
Compound	Initial DHP concn., $[I\text{-}IV]_0 \cdot 10^3$ moles/liter	Iminoxyl radical concn., $[VII]_0 \cdot 10^3$ moles/liter	$K \cdot 10^4$ sec^{-1}	$K \cdot 10^3$ liters/mole-sec	$E_{1/2}$, V [1]
I	0,3	1	10	1000	1,05
II			2,7	0,27	1,15
III	0,4	2	2,16	108	
	0,4	3	3,36	112	
	0,5	5	4,95	99	1,13
	0,5	10	11,50	115	
IVa			2,62	0,52	1,12
IVb	0,3	1	3,07	307	
	0,3	3	9,33	311	
	0,3	5	12,80	320	1,07
	0,3	5	15,05	301	
IVc	2	20	0,27±0,01	1,34±0,05	
	2	40	0,56±0,02	1,41±0,05	1,16
	1	60	0,76±0,03	1,26±0,05	
IVd	2	40	0,37±0,01	0,92±0,03	
	2	60	0,50±0,02	0,83±0,03	1,22
	1	80	0,73±0,02	0,92±0,03	
IVe	20	200	—	—	1,40

We also simultaneously made a quantitative study of the effect of the nature of R and R' and the number and position of annelated benzene rings in the DHP on the rate of this reaction:

IV a R=C_6H_5, R'=In; b R=p-C_6H_4—OCH_3, R'=In; c R=p-NO_2—C_6H_4, R'=In;
d R=C_6H_5, R'=$CH_2COC_6H_5$; e R=C_6H_5; R'=—CH—COOC$_6$H$_5$; In = 3-indolyl
                                                    |
                                                    CN

The kinetics of aromatization of I-IV were studied under standard conditions, viz., in air in spectrally pure and dry acetonitrile, in which the starting reagents and the reaction products are stable. As we have previously shown [4], 3 moles of 2,2,6,6-tetramethyl-1-oxopiperidinium cation V, of which 2 moles are reduced to piperidine oxyl radical VII and 1 mole is reduced to cation VIII, are consumed per 2 moles of converted DHP. Under these conditions the aromatization of I-IV takes place only via scheme 1 with formal detachment of a hydride ion and the formation of N-acyl heteroaromatic cations of the VI type [4]:

In conformity with the reaction equation, the rate was determined from the accumulation of piperidine oxyl radical VII, the concentration of which was measured by EPR spectroscopy, while the instantaneous concentrations of the reagents were calculated with allowance for the stoichiometry of reaction 4 from the difference in the initial concentrations of the reagents and the instantaneous concentrations of the reaction products.

As in the case that we previously described in [3], we found that in the presence of a large excess of one of the reagents the reaction proceeds in accordance with pseudo-first-order equations, and the pseudomolecular rate constants K are directly proportional to the concentrations of the reagent taken in excess amounts. Bimolecular rate constants $K_1 = k/[\stackrel{+}{=}N=O]_0 = \alpha k/[DHP]_0$ do not depend on the stoichiometry of the reaction and the initial concentrations of the reagents (Table 1).

It is apparent from Table 1 that the position and number of annelated benzene rings have a substantial effect on the rate of aromatization of I-IV. Thus the rates of dehydroaromatization drop sharply in the order dihydropyridine I to dihydrobenzopyridines II, III, and IV, which have identical substituents. The R' substituents bonded, along with a hydrogen atom, to the geminal node in the DHP have an even greater effect on the rate of

dehydrogenation. On passing from IVa to IVd the reaction rate constant decreases sharply as a consequence of replacement of electron-donor indole residue R' by an electron-acceptor phenacyl substituent.

Aromatization does not occur at all when an even stronger electron-acceptor substituent, viz., an ethyl cyanoacetate residue (IVe), is introduced; the starting reagents were isolated from the reaction mixture in unchanged form, and an EPR signal was not observed at 25 to 75° C.

The effect of R substituents in the N-acyl residues was similarly manifested: Electron-donor substituents increased the rate of aromatization of dihydroisoquinolines IVa–c, while electron-acceptor substituents decreased it. Thus the rate constant decreased by approximately two orders of magnitude when the methoxy group in IVb was replaced by a nitro group (IVc) (Table 1).

The rate constants for aromatization of I-IV obtained in this research correlate satisfactorily with the oxidation potentials of these compounds obtained during electrochemical oxidation [1]; this may constitute evidence in favor of the common character of the mechanisms of electrochemical and chemical dehydroaromatization of these substances under the influence of cation V.

EXPERIMENTAL

The starting N-acyldihydropyridines (I-IV) were obtained by the methods in [7] and were recrystallized twice from n-butanol. Oxopiperidinium salt V was obtained by the method in [8] and was crystallized from acetonitrile. The percentage of the 2,2,6,6-tetramethyl-1-oxopiperidinium cation in the perchlorate samples ($[=\overset{+}{N}=O]$) used for the kinetic measurements was 99.5 ± 0.3%, according to the results of iodometric titration. The IR spectra of mineral oil suspensions of the compounds were recorded with an RE-1306 radiospectrometer. Solutions of the reagents in spectrally pure and dry acetonitrile were mixed at 20° C (the temperature of the experiments was maintained with an accuracy of ± 0.5° C) and transferred to ampuls for EPR measurements. The concentration of piperidine oxyl VII in the reaction mixture was determined from the ratio of the intensities of the EPR signals of the reaction mixture and a solution of radical VII in the same solvent with a known concentration. The solutions to be analyzed and the standard solutions were placed in the same ampul with an inner diameter of 8 mm, and the EPR spectra were recorded under identical conditions. A linear dependence of I on $[=\overset{+}{N}-O]$ was strictly observed over the concentration range $5 \cdot 10^{-4} > [=\overset{+}{N}-O] \gg 10^{-5}$ mole/liter and at the uhf-energy and high-frequency modulation levels used. The accuracy in the determination of $[=\overset{+}{N}-O]$ was ± 3.5%.

Typical Method for the Reaction of I-IV with 2,2,6,6-Tetramethyl-1-oxopiperidinium Perchlorate. A 2-mmole sample of dihydrobenzopyridines I-IV was added in portions at 25°C in the course of 10 min to a solution of 3 mmole of perchlorate V in 15 ml of MeCN, after which the mixture was maintained at 20°C for 60 min. Dry ether (150 ml) was then added, and the precipitated crystals were separated and dried. Perchlorates of the VI type were obtained in 90-95% yields. This method was used to obtain the following compounds. a) 1-Benzoyl-2-(3-indolyl)benzo[f]quinolinium perchlorate, with mp 320-322° C, was obtained in 93% yield. IR spectrum: ν_{CO} 1760 cm^{-1}. Found: C 67.6; H 3.7; N 5.7%. $C_{28}H_{19}ClN_2O_5$. Calculated: C 67.4; H 3.8; N 5.6%; b) 2-(p-nitrobenzoyl)-1-(3-indolyl)isoquinolinium perchlorate, with mp 248-249° C, was obtained in 85% yield. IR spectrum: ν_{CO} 1635 cm^{-1}. Found: C 58.7; H 3.3; N 8.5%. $C_{24}H_{16}ClN_3O_7$. c) 2-(o-Methoxybenzoyl)-1-(3-indolyl)isoquinolinium perchlorate, with mp 251-253°C, was obtained in 88.8% yield. IR spectrum: ν_{CO} 1740 cm^{-1}. 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%.

The ether filtrate was evaporated, and the residual resin was extracted with pentane. The pentane was evaporated to give 1.9 mmole (95%) of piperidine oxyl, which was identical to a genuine sample with respect to its IR spectrum and melting point. The remaining N-acyl salts of the VIII type obtained in these reactions were described in [3].

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