REACTIONS OF N-ALKYLAZINIUM CATIONS. REACTION OF ACRIDINIUM SALTS WITH ENAMINES

O. N. Chupakhin, V. N. Charushin, and E. O. Sidorov

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The reaction pyridinium N-methylazinium salts and their benzo analogs — quinolinium, isoquinolinium, and acridinium ions — with enamines was investigated. Acridanyl-substituted enamines, their iminium salts, and the corresponding ketones were obtained by reaction of the N-methylacridinium salts with the enamines in dimethyl sulfoxide at room temperature. The quinolinium and isoquinolinium salts have lower activities; the N-methylpyridinium cation does not react at all under the indicated conditions.

Pyridinium and quinolinium cations generated by the action of acyl halides on heteroaromatic N-oxides (O-acyl derivatives of N-oxides) are capable of reacting with cycloalkenylamines [1-3]. The final products of these reactions are heteryl-substituted cycloalkyl ketones [1-3]. The reactions of other forms of azinium cations with enamines, particularly quaternary N-alkylazinium salts, have not been studied.

In an effort to study the possibility of such reactions we first of all attempted to subject quaternary acridinium salts (I), which are among the most active of the extensive series of azinium cations with respect to nucleophiles [4], to reaction with enamines.

It was established that the reaction of salts I with enamines in dimethyl sulfoxide (DMSO) at room temperature proceeds smoothly and quite vigorously with an appreciable exothermic effect and is complete a few minutes after the addition of excess enamine. Enamines II, which were obtained from cyclic ketones and cycloalkylimines, the enamine obtained from isobutyraldehyde and morpholine, and a heterocyclic enamine — 1,3,3-trimethyl-2-methylene-2,3-dihydroindole — were subjected to the reaction.

The addition of the enamines to the cation of I leads to the formation of iminium salts III. In the case of the reaction of perchlorate I with 1-pyrrolidinocyclohexene salt IIIa was found to be sufficiently stable and was obtained in high yield (Table 1). However, in the other cases iminium salts III are intermediates and split out a proton under the influence of excess enamine to give substituted enamines IVb-d or enamine VII in the reaction with indoline (Table 1). The second possible reaction pathway entails hydrolysis of ominium salts III, the tendency toward which depends on the nature of the enamine. Thus ketones V can be obtained by hydrolysis of salts III, while carbonyl compound VI is formed in 90% yield directly in the course of the reaction of I iodide with 1-morpholinoisobutene, evidently due to the water present in the DMSO. The deprotonation of iminium salts and their hydrolysis have been frequently noted in the literature for reactions of enamines with various electrophilic reagents [5, 6].

An intense peak of stretching vibrations of C=O groups at 1715-1740 cm^{-1} is present in the IR spectra of carbonyl compounds V and VI. The presence of a C=O group in Va was also demonstrated chemically by the formation of thiosemicarbazone VIII.

In the PMR spectrum of IVb presented in Fig. 1, the dihydroacridine fragment shows up as a singlet signal of $N-CH_3$ protons with δ 3.33 ppm and a multiplet of aromatic protons at 6.5-7.3 ppm. The splitting of the signal of the 9-H proton into a doublet (δ 4.44 ppm, J = 5 Hz) indicates that the acridine residue is not bonded to the double bond of the enamine. The signal of the proton of the double bond at δ 4.82 ppm is split into a triplet by the protons of the adjacent CH_2 group. The signal of the protons of the $N-CH_2$ group of the

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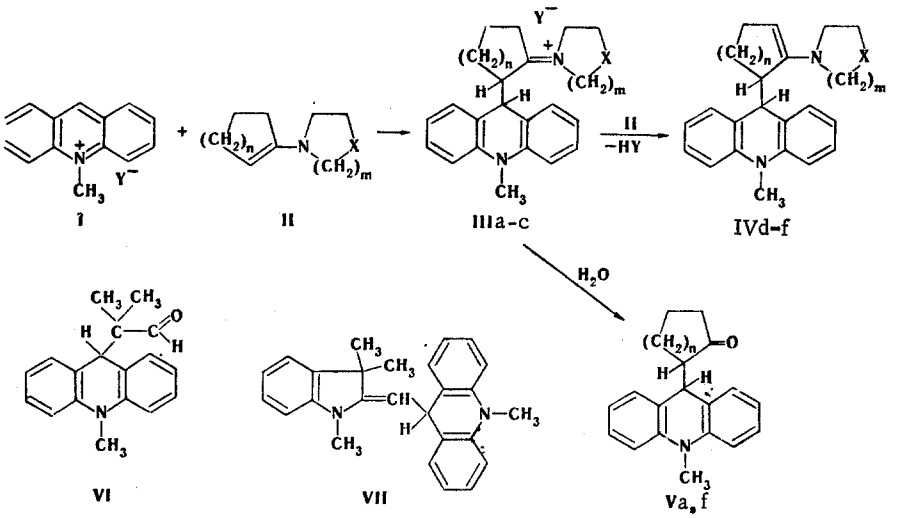

morpholine ring at δ 2.2-3.2 ppm is split into a complex multiplet which constitutes evidence in favor of nonequivalence of the axial and equatorial protons. The multiplet is simplified considerably in the case of suppression of the spin coupling with the protons of the O–CH_2 groups: In this case a doublet of axial (δ 2.45 ppm) and a doublet of equatorial (δ 2.97 ppm) protons with a geminal $J_{e,a}$ constant of 12 Hz are observed in the spectrum. A similar pattern was also noted in the spectra of IVc, d.

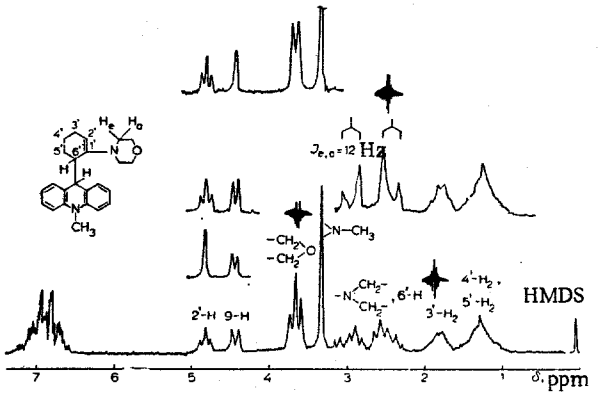

Fig. 1. PMR spectra of IVb in CCl_4.

TABLE 1. Dehydroacridines III-VIII

Compound*	n	m	X	mp, °C†	UV spectrum (in ethanol), λmax, nm (log ε)	R_f‡	Found, % C	Found, % H	Found, % N	Empirical formula	Calc., % C	Calc., % H	Calc., % N	Yield, %
IIIa	2	1	CH_2	188—190 (dec.)	282 (3,84), 322 (3,08)	—	64,7	6,7	6,4	$C_{24}H_{29}ClN_2O_4$	64,8	6,6	6,3	72
IVb	2	2	O	143	283 (4,06)	—	79,8	7,9	8,0	$C_{24}H_{28}N_2O$	80,0	7,8	7,8	75
IVc	2	2	CH_2	138—140	285 (4,03), 318 (3,43)	—	83,5	8,5	7,7	$C_{25}H_{30}N_2$	83,7	8,4	7,6	43
IVd	1	2	O	173—175	283 (4,36), 318 (3,75)	—	80,0	7,7	8,1	$C_{23}H_{26}N_2O$	79,7	7,6	8,1	75
Va	2	—	—	130	284 (4,17)	0,70	82,9	7,0	4,7	$C_{20}H_{21}NO$	82,4	7,3	4,8	62
Vd	1	—	—	110	287 (4,32)	0,71	82,5	7,0	5,1	$C_{19}H_{19}NO$	82,3	6,9	5,1	70
VI	—	—	—	228	282 (4,15)	0,73	81,5	7,3	5,3	$C_{18}H_{19}NO$	81,5	7,2	5,3	90
VII	—	—	—	167	283 (4,60)	—	85,2	7,1	7,8	$C_{26}H_{26}N_2$	85,2	7,1	7,6	36
VIII	—	—	—	220	275 (4,64)	0,79	69,3	6,6	15,4	$C_{21}H_{24}N_4$	69,2	6,6	15,4	—

*Compound IIIa is the perchlorate. Carbonyl stretching vibrations: Va 1717, Vd 1740, and VI 1715 cm^{-1}. †Compounds IIIa, IVb-d, Va, d, and VII were crystallized from ethanol, while VIII was crystallized from ethanol–dimethylformamide (1:1). ‡In chloroform on Silufol UV-254 plates.

Having established the reactivities of the acridinium salts with respect to enamines, we attempted to subject N-alkyl salts of other monoazines — pyridine and its benzo analogs, viz., quinoline and isoquinoline — to these reactions. The experiments carried out under these conditions showed that the N-alkylazinium cations, as one should have expected [7], are less active than the O-alkyl derivatives of N-oxides. Thus a mixture of N-methylpyridinium iodide with N-1-cyclohexenylmorpholine remains chromatographically and spectrally (PMR) unchanged after prolonged standing. According to the data from PMR spectroscopy and thin-layer chromatography (TLC), the N-methylquinolinium and isoquinolinium cations are reactive but form mixtures of substances that we have not yet been able to separate. However, these preliminary data show that, as in the case of reactions with other nucleophiles [7, 4], N-alkylpyridinium salts are not active in this case either. The benzoannelation of pyridine leads to an increase in the activity of the hetarenonium cation.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in deuterochloroform and CCl_4 were recorded with a Perkin–Elmer R-12B spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. Thin-layer chromatography was carried out on activity II aluminum oxide and on Silufol UV-254 plates with elution by chloroform.

Starting Enamines. The starting enamines were obtained by condensation of the corresponding carbonyl compounds with cycloalkylimines by heating in dry benzene with removal of the water by azeotropic distillation [6]. The boiling points and n_D values of the products were in agreement with the data in [8].

Reaction of the Acridinium Salts with Enamines. A 25-mmole (∿4 ml) sample of the corresponding enamine was added dropwise with stirring to a suspension of 0.01 mole of N-methylacridinium iodide or perchlorate in 5 ml of DMSO, during which the reaction mixture warmed up spontaneously and became colorless. Ethanol (15 ml) was then added, and the mixture was stirred for another 30 min. The resulting colorless precipitate was removed by filtration and crystallized from the solvent indicated in Table 1; depending on the nature of the enamine and the gegenion of starting salt I, either iminium salt IIIa or conjugate bases IVb-d and VII, the characteristics of which are presented in Table 1, were formed.

9-(2-Cyclohexanonyl)-10-methyl-9,10-dihydroacridine (Va). A 2-ml sample of a 30% aqueous solution of KOH was added to a solution of 1 g of iminium salt IIIa in 5 ml of DMF, and the mixture was heated on a water bath for 2 h. The precipitate that formed when the mixture was cooled was separated and crystallized from ethanol to give 0.4 g (64%) of a product with mp 130°C. PMR spectrum in deuterochloroform: 1.0-2.6 (m, 9H of the cyclohexane ring), 3.37 (s, NCH_3), 4.68 (d, 9-H, $J_{9,1}$ = 6.7 Hz), and 6.6-7.5 ppm (m, 8H of the benzene rings). The remaining characteristics of Va are presented in Table 1.

Ketone Va reacts with thiosemicarbazide when the components are heated in aqueous ethanol to give thiosemicarbazone VIII (Table 1).

9-(Formyl-2-isopropyl)-10-methyl-9,10-dihydroacridine (VI). A 3-ml sample of 1-morpholinoisobutene was added dropwise with stirring to a suspension of 3.2 g (10 mmole) of I iodide in 5 ml of DMSO, and the resulting precipitated colorless crystals of VI were removed by filtration and washed with ethanol to give 2.4 g (90%) of a product with mp 228°C. PMR spectrum in deuterochloroform: [s, $(CH_3)_2C$], 3.32 (s, NCH_3), 3.99 (s, 9-H), and 6.7-7.5 ppm (m, 8H of the benzene rings), and 9.27 (s, HC=O). The results of elementary analysis, the R_f values, and the UV and IR spectral data are presented in Table 1.

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RESEARCH ON AMINOMETHYLENE DERIVATIVES OF AZOLES. 23.* SYNTHESIS AND STRUCTURE OF FORMYL DERIVATIVES OF 1-PHENYL-5-HYDROXY(MERCAPTO)-IMIDAZOLES

I. Ya. Kvitko, R. V. Khozeeva, and A. V. El'tsov

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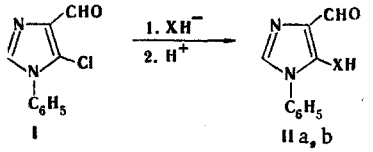
1-Phenyl-4-formyl-5-hydroxy(mercapto)imidazoles were obtained by replacement of the chlorine atom in 1-phenyl-4-formyl-5-chloroimidazole by hydroxy and mercapto groups, and their physicochemical properties and structures were studied. It was shown by a comparison of the electronic and IR spectra (and the PMR spectra in the case of the sulfur-containing compound) with the spectral characteristics of compounds that model the various possible tautomeric forms that 1-phenyl-4-formyl-5-hydroxy(mercapto)imidazoles exist primarily in the mesoionic form; this is associated with their high acidities and the presence of a sufficiently basic ring nitrogen atom.

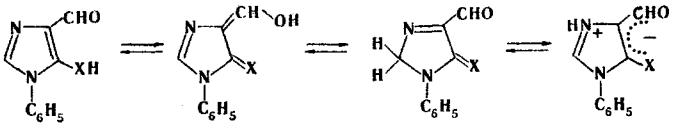
In a continuation of our studies of the tautomeric transformations of 4-formyl-5-hydroxypyrazoles [2] and 4-formyl-5-mercaptopyrazoles [3] it seemed of interest to study their corresponding imidazole derivatives. The latter were obtained from 1-phenyl-4-formyl-5-chloroimidazole (I) by replacement of the chlorine atom by hydroxy and mercapto groups.



I IIa, b

IIa X=O; b X=S

Compounds IIa, b are rather strong acids and have pK_a values of 5.68 ± 0.03 (X = O) and 4.63 ± 0.03 (X = S). These compounds, like 1-phenyl-3-R-4-acyl-5-pyrazolones [2] and 2-phenyl-4-acyl-5-oxazolones [4], may exist in several tautomeric forms:



A B C D

Because of the low solubilities of the investigated compounds in nonpolar solvents, their structures were investigated primarily by comparison of the data from the electronic and IR spectra with the data for compounds that model the most important tautomeric forms, viz., the hydroxy aldehyde (structure A, IIIa, b), hydroxymethylene (structure B, IVa, b), and mesoionic (structure D, Va, b) forms. Compound IIIa was obtained by replacement of the chlorine atom by a methoxy group, while IIIb was obtained by alkylation of imidazole IIb with methyl iodide. 1-Phenyl-4-dimethylaminomethylene-5-imidazolone (IVa)

*See [1] for Communication 22.

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