REACTIONS OF SUBSTITUTED PHENAZINE SALTS WITH NUCLEOPHILIC REAGENTS

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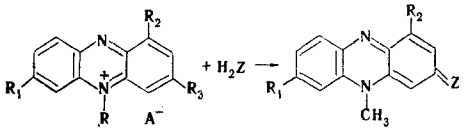
The condensation of 1-chloro-, 1-phenyl-, 3-chloro-, 3-cyano-, and 3,7-dimethoxy-substituted phenazinium salts with malonic and cyanoacetic esters, N-methylrhodanine, 2-methylbenzothiazolium and quinaldinium salts, aniline, and morpholine was studied. The absorption spectra of the synthesized dyes are described.

Quaternary phenazine salts display high reactivity in reactions with nucleophilic reagents – amines, ketomethylene compounds, and quaternary salts of nitrogen heterocycles with active methyl groups [1-4]. The quaternary salts of phenazine and the products of their reaction with amines are being widely used in histochemical investigations as active acceptors under conditions of oxygen starvation and, particularly, in nitrite poisoning [5].

The nucleophilic substitution reactions of quaternary salts of unsubstituted phenazine have been described, but there is only limited information regarding the reactions of quaternary salts of phenazine derivatives.

We have studied the nucleophilic substitution reactions of phenazinium salts (I) containing substituents – a chlorine atom in the 1 position (Ia) or in the 3 position (Ib), a cyano group in the 3 position (Ic), a phenyl group in the 1 position (Id), and a methoxy group in the 3 and 7 positions (Ie).



I II

R=CH$_3$; a R_1=R_3=H, R_2=Cl; b R_2=R_3=H, R_1=Cl; c R_2=R_3=H, R_1=CN; d R_1=R_3=H, R_2=C_6H_5; e R_2=H, R_1=R_3=OCH_3

The reactions of salts Ia and Ib with nucleophilic reagents gave products containing chlorine; this provides a possibility for assuming oxidative substitution without the halogen exchange characteristic for the unsubstituted salts [1]. The 1-chlorophenazinium salt (Ia) apparently reacts at the 3 rather than the 7 position, since the introduction of halogens into the aromatic ring usually activates it with respect to nucleophilic reactions. Salts Ib and Ic can react only at the 7 position. The reactions of salt Ie proceed with replacement of one methoxy group (Table 1).

The condensation of salts I with N-methylrhodanine give merocyanine dyes II (Z = 3-methyl-5-rhodanylidene) (Table 2). Very deeply colored cyanine dyes are obtained in the reaction of salts I with the quaternary salts of 2-methylbenzothiazole and quinaldine (Table 3).

The oxidative amination of salts I, which we studied in the case of reactions with aniline and morpholine, gives reaction products of the I type, where R_3 is an anilino or morpholino group (Table 4).

In all of the described reactions, it can be assumed that 3-cyanophenazinium salts are much more active than the unsubstituted salts, as is readily judged from the yields of the reactions. Chloro-substituted

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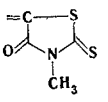
TABLE 1. Products of the Condensation of II with Quaternary Phenazine Salts (I, R = CH_3) with Ketomethylene Compounds

R_1	R_2	Z	mp, °C	Empirical formula	N, % found	N, % calc.	Spectrum λ_{max}, nm	Spectrum lg ε	Yield, %
H	Cl	$=C(COOC_2H_5)_2$	170 (Dec.)	$C_{20}H_{19}ClN_2O_4$	7,4	7,2	426 604	3,59 4,31	50
Cl	H		158 (Dec.)	$C_{20}H_{19}ClN_2O_4$	7,2	7,2	560* 596 650*	4,1 4,16 3,93	60
CN	H		211	$C_{21}H_{19}N_3O_4$	11,2	11,1	560* 600 650*	4,16 4,23 4,25	70
H	Cl	$=C(CN)COOC_2H_5$	240 (Dec.)	$C_{18}H_{14}ClN_3O_2$	12,5	12,4	412 436 594* 640 694*	3,78 3,78 4,23 4,4 4,25	70
Cl	H		261 (Dec.)	$C_{18}H_{14}ClN_3O_2$	12,4	12,4	420 586* 628 682*	3,79 4,35 4,49 4,34	68
CN	H		257—259	$C_{19}H_{14}N_4O_2$	17,1	17,0	580* 638 680*	4,08 4,25 4,17	80
H	Cl	$=CHCOC_6H_5$	above 300	$C_{21}H_{15}ClN_2O$	8,0	8,1	636	3,68	57
Cl	H		115—116	$C_{21}H_{15}ClN_2O$	8,3	8,1	624	3,72	65
CN	H		172	$C_{22}H_{15}N_3O$	12,2	12,4	626	3,94	70

* Shoulder on the absorption curve.

TABLE 2. Products (II) of the Condensation of Quaternary Phenazine Salts (I, R = CH_3) with N-Methylrhodanine

R_1	R_2	Z	mp, °C (dec.)	Empirical formula	S, % found	S, % calc.	Spectrum λ_{max}, nm	Spectrum lg ε	Yield, %
H	Cl		225	$C_{17}H_{12}ClN_3OS_2$	17,0	17,2	412 688* 724	4,46 4,34 4,36	60
Cl	H		256	$C_{17}H_{12}ClN_3OS_2$	17,1	17,2	410 689	4,3 4,31	70
CN	H		267—268	$C_{18}H_{12}N_4OS_2$	19,5	19,6	408 694 714*	4,45 4,39 4,38	70

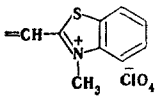
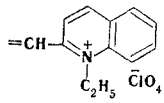
* Shoulder on the absorption curve.

phenazinium salts have approximately the same activity as unsubstituted salts. The introduction of electron-donor substituents into the quaternary phenazine salts lowers their reactivity with respect to nucleophilic reagents; for example, 3-(N-morpholino)phenazinium salt does not undergo condensation with quaternary salts and amines, while the reactions of 3-methoxyphenazinium salts with amines lead to products of replacement of a methoxy group by an amino group.

The major absorption maxima of the compounds that we obtained and of several dyes described in the literature are presented in Table 5. Dyes II, which are derivatives of cyanoacetic and malonic esters and acetophenone, are blue with absorption maxima at 596-620 nm. The dyes derived from cyanoacetic ester absorb more deeply than the derivatives of malonic ester.

Substituents (1-phenyl, 1-chloro, 3-chloro, 3-methoxy, and 3-cyano) have little effect on the color, but a considerable shift of the absorption band to the long-wave region is observed for 3-(N-morpholino)-

TABLE 3. Products (II) of the Condensation of Quaternary Salts of Phenazine (I, R = CH_3) with Quaternary Salts of Nitrogen Heterocycles

R_1	R_2	Z	mp, °C	Empirical formula	Cl, % found	Cl, % calc.	Spectrum λ_{max}, nm	Spectrum lg ε	Yield, %
H	Cl		292 (Dec.)	$C_{22}H_{17}Cl_2N_3O_4S$	14,3	14,4	462 626* 686 746	3,72 4,32 4,59 4,57	56
Cl	H		Above300	$C_{22}H_{17}Cl_2N_3O_4S$	14,6	14,4	402 634* 692 750	4,1 3,96 4,1 4,04	60
CN	H		232	$C_{23}H_{17}ClN_4O_4S$	7,2	7,4	446 624* 686 736	3,81 4,3 4,53 4,53	72
H	C_6H_5		225	$C_{28}H_{22}ClN_3O_4S$	6,5	6,7	466 626* 686 736	4,0 4,38 4,66 4,69	58
H	Cl		216	$C_{25}H_{21}Cl_2N_3O_4$	14,2	14,2	428 700 745	4,30 4,6 3,5	70
Cl	H		199 202	$C_{25}H_{21}Cl_2N_3O_4$	14,2	14,2	420 698 760	4,33 4,7 3,1	65
CN	H		247	$C_{26}H_{21}ClN_4O_4$	7,2	7,2	420 694 780	4,22 4,45 3,8	70
H	C_6H_5		200	$C_{31}H_{26}ClN_3O_4$	6,3	6,6	430 704 746	4,0 4,28 4,25	56

* Shoulder on the absorption curve.

TABLE 4. Aminated Quaternary Salts of Phenazine (I)

R	R_1	R_2	R_3	mp, °C	Empirical formula	N, % found	N, % calc.	Spectrum λ_{max}, nm	Spectrum lg ε	Yield, %
CH_3	H	Cl	NHC_6H_5	240	$C_{19}H_{15}Cl_2N_3O_4$	10,2	10,0	552	4,27	30
CH_3	Cl	H	NHC_6H_5	204—205 (Dec.)	$C_{19}H_{15}Cl_2N_3O_4$	9,9	10,0	548	4,3	50
CH_3	CN	H	NHC_6H_5	250	$C_{20}H_{15}ClN_4O_4$	13,7	13,6	558	4,23	58
CH_3	H	C_6H_5	NHC_6H_5	259	$C_{25}H_{20}ClN_3O_4$	9,0	9,1	434 552	4,08 4,28	48
C_2H_5	OCH_3	H	NHC_6H_5	234	$C_{21}H_{20}ClN_3O_5$	9,6	9,8	548	4,34	53
CH_3	H	Cl	$N(CH_2CH_2)_2O$	263 264	$C_{17}H_{17}Cl_2N_3O_5$	10,3	10,1	406 566	3,61 4,19	40
CH_3	Cl	H	$N(CH_2CH_2)_2O$	215 (Dec.)	$C_{17}H_{17}Cl_2N_3O_5$	10,1	10,1	558	4,55	57
CH_3	CN	H	$N(CH_2CH_2)_2O$	210 212	$C_{18}H_{17}ClN_4O_5$	13,7	13,8	520* 562 606*	4,04 4,19 4,07	60
CH_3	H	C_6H_5	$N(CH_2CH_2)_2O$	267	$C_{23}H_{22}ClN_3O_5$	9,1	9,2	410 560	3,08 4,32	50
C_2H_5	OCH_3	H	$N(CH_2CH_2)_2O$	213	$C_{19}H_{22}ClN_3O_6$	9,8	9,9	404 530* 562	3,7 4,64 4,76	57

* Shoulder on the absorption curve.

substituted dyes [1]. This can be explained by conjugation of the electron-donor amino group with the electron-acceptor group of the dye.

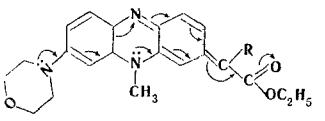
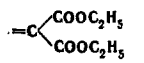
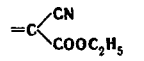
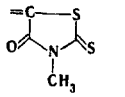
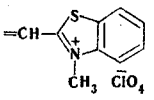
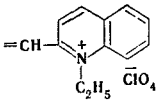


TABLE 5. Absorption Maxima of Cyanine Dyes I and II (nm)

Compound	Z for II or R_3 for I \ R_1, R_2	$R_1=R_2=H$	$R_1=H$, $R_2=Cl$	$R_1=H$, $R_2=C_6H_5$	$R_1=Cl$, $R_2=H$	$R_1=CN$, $R_2=H$	$R_1=OCH_3$, $R_2=H$	R_1= $R_2=H$
II		598[1]	604	600[1]	596	600	604[1]	620[1]
II		626[1]	640	628[1]	628	638	628[1]	640[1]
II		700[3]	724	720[1]	689	694	710[3]	—
II		688[2] 744	686 746	684 736	692 750	686 736	695[2] 727	—
II		702[2] 735	700 745	700 746	698 760	694 780	720[2] 775	—
I	$-NHC_6H_5$	548[4]	552	552	548	558	548	—
I	$-N(CH_2CH_2)_2O$	548[1]	566	560	558	562	562	

The analogous conjugation of the 7-methoxy group is much weaker, but a deepening of the color of dyes II is nevertheless noted. The electronegative 3-cyano group has little effect on the color of the dyes, except for amino-substituted dyes, in which it deepens the colors substantially.

The cyanine dyes that are derivatives of benzothiazole and quinoline are green and usually have two long-wave absorption bands, which change only slightly as a function of the type of substituent.

EXPERIMENTAL

1-Chloro-5-methylphenazinium chloride and 3-chloro-5-methylphenazinium chloride were obtained by the action of $POCl_3$ and PCl_5, respectively, on the red and blue N-alkylphenazinones [6]. 3-Cyano-5-methylphenazinium iodide was obtained from N-methylphenazinium methosulfate and NaCN via the method in [7]. The quaternary 1-phenylphenazinium salt was obtained by heating the base with dimethyl sulfate in nitrobenzene. 3,7-Dimethoxyphenazinium methosulfate was obtained from 7-methoxy-3-phenazinone by reaction with dimethyl sulfate.

The condensation of the quaternary salts of phenazine derivatives with ketomethylene compounds was carried out in absolute methanol with sodium methoxide [1]. The data on the reaction products are presented in Table 1.

The condensation of quaternary salts of phenazine derivatives with N-methylrhodanine and quaternary salts of nitrogen heterocycles was carried out in alcohol or aqueous solutions containing sodium acetate [2, 3]. The data on the reaction products are presented in Tables 2 and 3.

The condensation of the quaternary salts of phenazine derivatives with amines was carried out by air oxidation of a mixture of the amine and quaternary salt [4]. The data on the reaction products are presented in Table 4.

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