REACTION OF ACRIDINIUM SALTS WITH PHENYLHYDRAZONES AND PHENYLHYDRAZIDES

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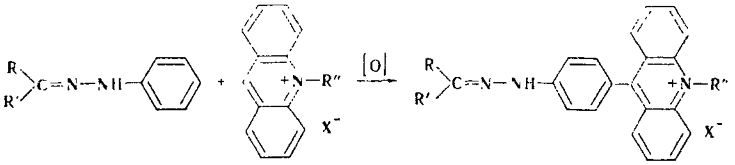
4-(9-Acridinyl)phenylhydrazones and phenylhydrazides were obtained by condensation of the phenylhydrazones of aromatic aldehydes and ketones and the phenylhydrazides of carboxylic acids with acridinium salts in the presence of an oxidizing agent.

In developing our research on the oxidative condensation of acridine with nucleophiles [1-3] we studied its reaction with phenylhydrazones and phenylhydrazides.* These compounds have not been used for introduction into heterocyclic systems, and there is no information regarding their use as arylating agents in any other cases.

We found that in the presence of an oxidizing agent the phenylhydrazones readily react with both quaternary and protic acridinium salts to give the corresponding p-acridinylphenylhydrazones.



The reaction can be carried out in a melt with sulfur, but better results are obtained when a polar solvent and air oxidation are used.

The reaction is a general one and is extended to the phenylhydrazones of aromatic aldehydes, ketones, and heterocyclic carbonyl compounds, and the cyclic analog of phenylhydrazone — N-phenylpyrazoline — can also be used.

The introduction of donor substituents into the aldehyde fragment of the hydrazone molecule facilitates the reaction, and this affects the yields of products (Table 1). Acceptor substituents that have —I and —M effects, for example, the nitro group, deactivate the phenylhydrazone molecule, and such compounds do not react with acridinium salts. Thus p-nitrobenzaldehyde phenylhydrazone is unreactive even at 170°. A nitro group located in the phenylhydrazine portion of the molecule has the same effect.

The electronic spectra of the compounds obtained in this research have the characteristic acridine spectrum with λ_{max} 250 and 350 nm. The presence of two nucleophilic centers in the phenylhydrazone molecule makes possible the formation of two products of the reaction with acridine — products p-substituted [2] into the phenylhydrazone portion of the molecule and products substituted at the CH=N group. The reaction at CH is completely likely, inasmuch as phenylhydrazones are capable of coupling, for example, with the diazonium cation [5], which is close to the acridinium ion with respect to electrophilic character; on the other hand, the capacity for oxidative coupling of CH with active com-

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*9,9'-Diacridanyls are formed in the reaction of phenylhydrazine with acridines [4].

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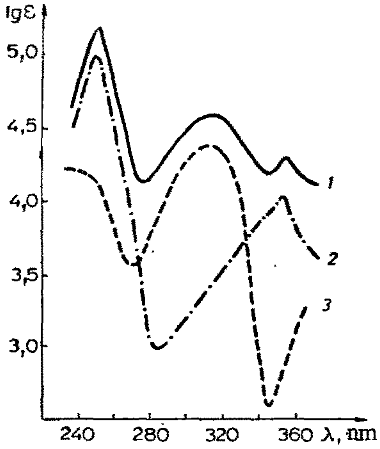

Fig. 1. UV spectra in alcohol: 1) 2-phenyl-5-(9-acridinyl)indole (XVIII); 2) acridine; 3) 2-phenylindole.

pounds is known [3]. In order to establish the structures of the compounds obtained we subjected them to hydrolysis. Acridinyl-substituted phenylhydrazones are hydrolyzed by refluxing in aqueous dimethylformamide (DMFA) solutions of the acid. We were unable to isolate the corresponding hydrazine in pure form. However, when excess p-nitrobenzaldehyde was added to the reaction mixture, p-nitrobenzaldehyde 4-(9-acridinyl)phenylhydrazone (XVII) was obtained. This unambiguously indicates the reaction of the phenylhydrazones with acridinium salts at the para position with respect to the hydrazone residue.

The hydrazone structure is retained during the reaction with acridine. In conformity with this, acetophenone 4-(9-acridinyl)phenylhydrazone (XII) undergoes Fischer cyclization to 2-phenyl-5-(9-acridinyl)indole (XVIII) when it is heated with polyphosphoric acid. The UV spectrum of indole XVIII differs from the spectrum of the starting hydrazone and contains the absorption bands of acridine (λ_{max} 255, 355 nm) and 2-phenylindole (λ_{max} 315 nm) (see Fig. 1), and this confirms its structure.

The phenylhydrazides of carboxylic acids of both the aromatic and aliphatic series are also capable of undergoing reaction with acridinium salts under similar conditions to give condensation products in 70-80% yields. When the phenylhydrazide is considered to be an N-substituted arylamine, it is difficult to expect the production of a compound other than a 4-(9-acridinyl)phenylhydrazide. In fact, the UV spectrum contains absorption typical for the acridine system (λ_{max} 250 and 355 nm). The characteristic (for secondary amides) absorption bands of "amide I" C=O stretching vibrations at 1656 cm^{-1} and of "amide II" N-H deformation vibrations at 1550 cm^{-1} are present in the IR spectra.

EXPERIMENTAL

The electronic spectra of alcohol solutions of the compounds were recorded with an SF-4A spectrophotometer. The IR spectra of chloroform solutions and mineral-oil suspensions were obtained with a UR-20 spectrometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in chloroform-alcohol (11:1).

4-(9-Acridinyl)phenylhydrazone Hydrochlorides (I-III, Table 1). A mixture of 2.15 g (0.01 mole) of acridine hydrochloride, 0.01 mole of the appropriate phenylhydrazone, and 15 ml of DMFA was heated at 120° for 2 h as air was bubbled through it at 20-30 ml/min. It was then cooled, and the resulting precipitate was removed by filtration and crystallized from DMFA.

For the isolation of the bases (IX-XV, Table 2), the hydrochloride was dissolved in alcohol, the solution was neutralized with NH_4OH and diluted with water, and the resulting precipitate was removed by filtration. Hydrazones IX, XI, XII, and XIV were crystallized from xylene, and X, XIII, and XV were crystallized from xylene-heptane (1:1).

Quaternary Salts of 4-(9-Acridinyl)phenylhydrazones (IV-VIII, Table 1). As in the preceding experiment, 3.2 g (0.01 mole) of N-methylacridinium iodide was subjected to reaction with 0.01 mole of the phenylhydrazone. The cooled reaction mixture was poured into 200 ml of benzene, and the resulting dark-violet precipitate of the quaternary salt was removed by filtration and crystallized from alcohol.

N-[p-(N-Methyl-9-acridinium)]phenylpyrazoline Iodide (XVI). As in the preceding experiment, 3.2 g (0.01 mole) of N-methylacridinium iodide was subjected to reaction with 1.6 g (0.01 mole) of N-phenylpyrazoline in 10 ml of DMFA. The mixture was poured into 250 ml of benzene, the benzene was decanted after 30 min, and the resinous precipitate was triturated with ether and crystallized from amyl alcohol to give violet prisms with mp 234-237°. Found: C 59.6; H 4.6%. $C_{23}H_{20}N_3$. Calculated: C 59.6; H 4.5%.

Hydrolysis of Benzaldehyde 4-(9-Acridinyl)phenylhydrazone (IX). A mixture of 1.5 g (0.004 mole) of hydrazone IX, 60 ml of DMFA, 20 ml of water, and 1 ml of concentrated HCl

TABLE 1. Protic and Quaternary Salts of 4-(9-Acridinyl)phenylhydrazones

Compound	R	R′	R″	X	mp, °C	Empirical formula	Found, %			Calc., %			Electronic spectra, λ_{max}, nm (log ε)	Yield, %
							C	H	N	C	H	N		
I	H	C_6H_5	H	Cl	283—285	$C_{26}H_{19}N_3 \cdot HCl$	75,9	4,3	10,3	76,2	4,9	10,2	250 (5,10); 310 (4,28); 355 (4,52); 410 (3,94); 545 (3,61)	46
II	H	4-Cl—C_6H_4	H	Cl	254—256	$C_{26}H_{18}N_3Cl \cdot HCl$	70,1	4,5	9,5	70,3	4,3	9,7	250 (4,87); 310 (4,15)*; 355 (4,58); 410 (3,90)*; 535 (3,95)	55
III	H	4-Br—C_6H_4	H	Cl	†	$C_{26}H_{18}N_3Br \cdot HCl$	63,8	4,0		63,9	3,9		250 (4,85); 310 (4,13)*; 355 (4,52); 410 (3,87); 540 (3,86)	30
IV	H	C_6H_5	CH_3	I	277—279	$C_{27}H_{22}N_3I$	62,9	4,3	8,2	62,9	4,3	8,2	260 (5,42); 355 (5,05); 410 (4,33); 555 (4,59)	82
V	H	4-Cl—C_6H_4	CH_3	I	243—245	$C_{27}H_{21}N_3ClI$	58,7	3,9	7,6	59,0	3,9	7,6	260 (4,74); 360 (4,43); 420 (3,40); 445 (3,32); 560 (3,87)	58
VI	CH_3	C_6H_5	CH_3	I	284—285	$C_{28}H_{24}N_3I \cdot H_2O$	62,8	4,5	7,8	62,5	4,7	7,8	260 (4,74); 330 (4,25); 360 (4,16); 420 (3,41); 570 (3,78)	57
VII	H	4-Br—C_6H_4	CH_3	I	250—252	$C_{27}H_{21}N_3BrI$	54,6	3,5	7,0	54,6	3,7	7,1	255 (4,82); 360 (4,69); 415 (3,70)*; 445 (3,57); 560 (4,04)	59
VIII	H	3,4-$(CH_3O)_2$—C_6H_3	CH_3	I	†	$C_{29}H_{26}N_3O_2I$	60,4	4,9	7,3	60,5	4,5	7,3	260 (5,16); 355 (4,85); 420 (3,81)*; 580 (4,22)	50

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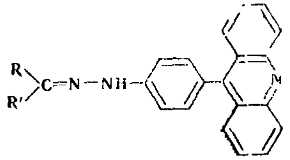
*Shoulder.

†This compound does not have a distinct melting point.

TABLE 2. 4-(9-Acridinyl)phenylhydrazones



Compound	R	R′	mp, °C	R_f	Empirical formula	Found, %			Calc., %			Electronic spectra, λ_{max}, nm (log ε)	Yield, %
						C	H	N	C	H	N		
IX	H	C_6H_5	238—240	0,55	$C_{26}H_{19}N_3$	83,8	5,2	11,3	83,6	5,1	11,2	250 (5,15); 310 (4,21)*; 345 (4,47); 410 (4,12)	46
X	H	4-Cl—C_6H_4	260—262	0,42	$C_{26}H_{18}N_3Cl$	76,4	4,4	10,1	76,5	4,4	10,3	250 (5,17); 310 (4,25); 355 (4,59); 410 (4,23)*	55
XI	H	4-$N(CH_3)_2$—C_6H_4	180—182	0,48	$C_{28}H_{24}N_4$	80,6	5,8		80,7	5,8		252 (5,23); 325 (4,50); 360 (4,68); 430 (4,16)	60
XII	CH_3	C_6H_5	278—280	0,49	$C_{27}H_{21}N_3$	80,4	5,5	10,9	83,7	5,5	10,8	251 (5,11); 310 (4,26)*; 340 (4,35); 385 (4,02)	49
XIII	H	3,4-$(CH_3O)_2$-C_6H_3	185—187	0,36	$C_{28}H_{23}N_3O_2$	77,4	5,3	9,3	77,6	5,3	9,7	250 (5,15); 310 (4,34)*; 355 (4,58); 420 (4,17)	60
XIV	H	4-CH_3O-3HO-C_6H_3	263—265	0,27	$C_{27}H_{21}N_3O_2$	77,4	5,4	9,9	77,3	5,0	10,0	250 (4,90); 315 (4,23)*; 350 (4,47); 425 (3,99)	58
XV	H	2-Furyl	205—207	0,52	$C_{24}H_{17}N_3O$	79,6	4,8	11,6	79,4	4,7	11,6	250 (5,08); 300 (4,14); 345 (4,48); 455 (4,15)	50

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*Shoulder.

was refluxed for 30 min, after which 6.2 g (0.04 mole) of p-nitrobenzaldehyde was added, and the mixture was refluxed for another hour. It was then cooled, and the resulting precipitate was removed by filtration, neutralized with NH_4OH, and crystallized from xylene to give 1.2 g (71%) of red prisms with mp 256-257°. Found: C 75.0; H 4.5; N 13.5%. $C_{26}H_{18}N_4O_2$. Calculated: C 74.6; H 4.3; N 13.4%.

Similar results were obtained in the hydrolysis of X and XII.

2-Phenyl-5-(9-acridinyl)indole (XIII). A mixture of 3.9 g (0.01 mole) of hydrazone IX and 4.6 g of polyphosphoric acid was heated to 180° and maintained at this temperature for 10 min. It was then cooled and diluted with 50 ml of water, the resulting precipitate was removed by filtration and neutralized with NH_4OH to give 2 g (70%) of light-yellow prisms with mp 293-295° [xylene-heptane (1:1)]. Found: C 87.4; H 5.0; N 7.5%. $C_{27}H_{18}N_2$. Calculated: C 87.5; H 4.9; N 7.6%.

Acetic Acid 4-(9-Acridinyl)phenylhydrazide (XIX). A mixture of 2.15 g (0.01 mole) of acridine hydrochloride, 1.8 g (0.015 mole) of acetic acid hydrazide, and 10 ml of DMFA was heated to 120° and air was bubbled through it for 2 h. It was then diluted with 100 ml of water and neutralized with NH_4OH. The base was removed by filtration, washed with water, and dried to give 2.3 g (70%) of yellow prisms with mp 238-240° (from xylene). UV spectrum, λ_{max}, nm (log ε): 250 (4.88), 355 (4.04), and 380 (3.91). Found: C 77.2; H 5.5; N 12.9%. $C_{21}H_{17}N_3O$. Calculated: C 77.0; H 5.2; N 12.9%.

Benzoic Acid 4-(9-Acridinyl)phenylhydrazide (XX). This compound [2.7 g (70%)], with mp 220-222° [from xylene-heptane (1:1)], was obtained from 2.15 g (0.01 mole) of acridine hydrochloride and 2.12 g (0.01 mole) of benzoic acid phenylhydrazide via the method described above. UV spectrum, λ_{max}, nm (log ε): 250 (4.81), 355 (3.86), and 480 (3.74). Found: C 79.5; H 5.5; N 10.7%. $C_{26}H_{19}N_3O$. Calculated: C 80.2; H 4.9; N 10.8%.

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