THE ROLE OF pH IN THE SYNTHESIS OF DIAZIRIDINES

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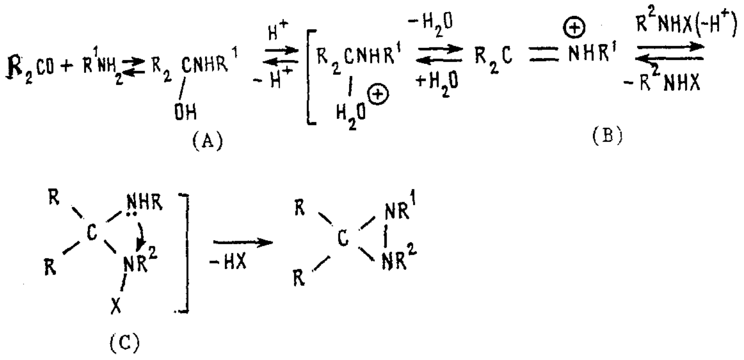
The greatest yield in the synthesis of diaziridines from carbonyl compounds, amines, and aminating reagents in water is achieved at a specific pH, which shifts to less alkaline values with increasing -I effect of the substituents in the carbonyl compound and with decreasing pK_{BH^+} value of the amine. The role of pH is related to the conditions for the generation of an immonium from the intermediate α-aminocarbinol. The nuclear Overhauser effect was used to determine the orientation of the substituents in several diastereomers of the didikyldiaziridines obtained.

The yield of 3,3-dialkyldiaziridines from ketones, ammonia, and chloramine in water depends on the pH. Azines or hydrazones are formed at pH > 12.5, while diaziridines are formed at pH < 12 [1]. On the other hand, 1,2-dialkyldiaziridines are formed from CH_2O, RNH_2, and NaOHal in highly alkaline media [2, 3]. In the present work, we clarified the effect of pH in the synthesis of diaziridines by these reactions.

The formation of the diaziridine ring is explained by intramolecular nucleophilic substitution in intermediate aminal C [4, 5]. The formation of C occurs through an aminomethylation reaction (scheme 1), whose result depend on the pH of the medium [6, 7].



(1)

X = Hal, OSO_3H.

If this scheme were valid, the step determining the rate of formation of C, as in the aminomethylation reaction, would be the conversion of α-aminocarbinol A into immonium cation B, which reacts with an aminating reagent to give C. Hence, we might expect that a decrease in the pH toward less alkaline values is necessary for diaziridine formation upon the introduction of electron-withdrawing substituents into the starting compounds.

In order to check this hypothesis, we studied the synthesis of diaziridines from carbonyl compounds and amines containing substituents with different -I effects at different fixed pH of the medium. The effect of the substituents in the amines was evaluated relative to their pK_{HB^+} values, while this effect in the carbonyl compounds was evaluated relative to the sum of the Taft induction constants $\Sigma\sigma^*$ of the substituents at the carbonyl group. Hydroxylamine-O-sulfonic acid (HASA) and N-chloro- and N-bromo-alkylamines were used as the aminating agents. The results are given in Tables 1 and 2 and Figs. 1 and 2.

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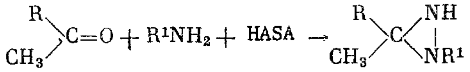
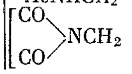
TABLE 1. Starting Compounds, pH_{opt}, and Diaziridine Yields in Reaction (2)


(2)

Experiment series	Diaziridine obtained	Carbonyl compound		Amine		pH_{opt}	Yield at pH_{opt}[a]
		R	Σσ* [9]	R^1	pK_{BH^+}		
1	–	Me	–0,98	Me	10,6 [10]	11,5–12,0	80(93)
2	(VI)	Me	–0.98	$HO(CH_2)_2$	9,5 [10]	11,0–11,3	80
3	(VIII)	Me	–0,98	$AcNH(CH_2)_2$	9,0[b]	10,5–11,0	77
4	–	H	–0,49	Me	10,6	11,0–11,5	60(78)
5	(VII)	H	–0.49	$HO(CH_2)_2$	9.5	10.0–11.0	81
6	(X)	$AcNHCH_2$	0–0,1	Et	10.6 [10]	10,25–10,7	73
7	(XI)	$AcNHCH_2$	0–0,1	$HO(CH_2)_2$	9,5	9,5–10,0	50
8	(XII)	$AcNHCH_2$	0–0,1	$AcNH(CH_2)_2$	9,0	9,0–9,3	50
9	(XVII)		0,8	Me	10,6	9,8–10,0	40

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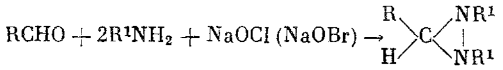
[a] The yields were not optimized relative to other parameters. The yields obtained with an increased amount of carbonyl compound are given in parentheses.

[b] The pK_{HB^+} value was determined according to Albert [11].

TABLE 2. Starting Compounds, pH_{opt}, and Diaziridine Yields in Reaction (3)


(3)

Experiment series	Diaziridine obtained	Carbonyl compound		Amine		Halogenating agent	pH_{opt}	Yield at pH_{opt}, %
		R	Σσ* [9]	R^1	pK_{BH^+} [10]			
1	–	H	0	Et	10,6	NaOCl	11.2–12,1	75
2	(XV)	H	0	$AcNH(CH_2)_2$	9.0	NaOCl	9.6–10,2	61
3	(V)	Me	–49.0	Me	10,6	NaOCl	11,5–11,9	85
4	(V)	Me	–49.0	Me	10,6	NaOBr	11.6–12,0	70
5	–	Me	–49.0	Et	10.6	NaOCl	11.6–11,9	80
6	(XIV)	Me	–49.0	$AcNH(CH_2)_2$	9,0	NaOCl	10,25–11,0	67

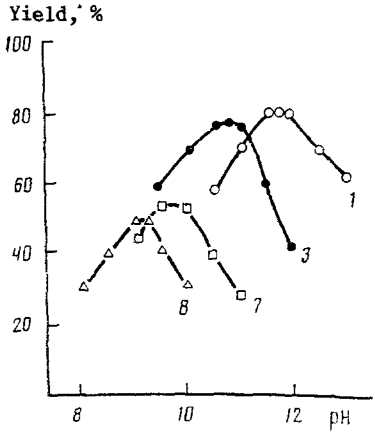


Fig. 1. Dependence of the diaziridine yield on the pH of the reaction mixture in reaction (2). The numbers correspond to the experiment series in Table 1.

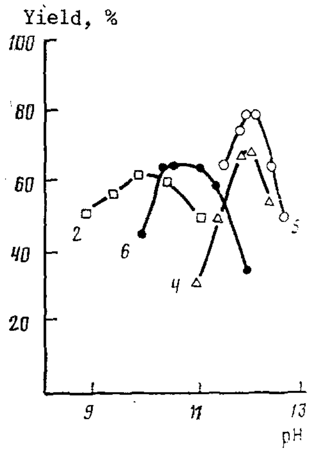
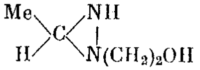
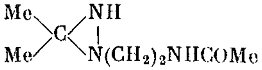
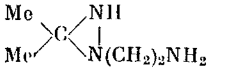
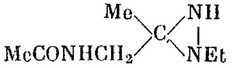
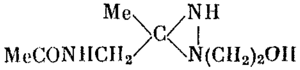
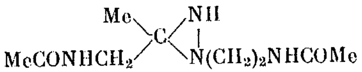
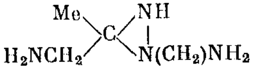
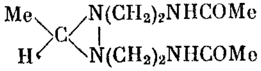
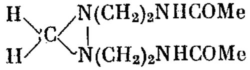
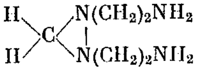
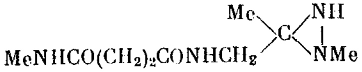


Fig. 2. Dependence of the diaziridine yield on the pH of the reaction mixture in reaction (3). The numbers correspond to the experiment series in Table 2.

In experiments with the same carbonyl compound and amines with different pK_{HB^+}, the pH_{opt} value decreases proportionally to the decrease in the pK_{HB^+} of the amines, while in experiments with different carbonyl compounds and amines with the same pK_{HB^+}, the pH_{opt} decreases proportionally to an increase in $\Sigma\sigma^*$ of the substituents at the carbonyl group. This behavior is observed for HASA and N-haloalkylamines and the pH_{opt} is the same for N-chloro- and N-bromoalkylamines in the same reaction.

These results are in accord with scheme 1 for the formation of intermediate C. Indeed, the shift of pH_{opt} to less alkaline values upon the introduction of substituents

TABLE 3. Indices of Diaziridines

Compound		Bp, °C (mm)	Mp, °C	n_D^{20}	R_f	IR spectra ν, cm^{-1}	Elemental analysis, Found/Calculated, %		
							C	N	H
	(VII)	75(3)	–	1,464	0,52	750, 860, 1030, 1200, 1400, 1630, 2920, 3210, 3350	47,5 47,1	9,6 9,8	27,8 27,4
	(VIII)	125(1) (dec.)	70–71 After distillation	–	0,50	750, 1100, 1280, 1370, 1550, 1650, 2930, 3070, 3280	53,8 53,5	9,8 9,6	26,3 26,7
	(IX)	75(15)	–	1,468	0,24	720, 910, 1120, 1330, 1380, 1450, 1640, 2910, 3200, 3310	52,4 52,2	11,8 11,3	36,1 36,5
	(X)	105(1)	–	1,477	0,57	590, 750, 1100, 1280, 1350, 1510, 1620, 2960, 3060, 3250	53,0 53,5	10,0 9,6	26,5 26,7
	(XI)	[a]		1,498	0,53	600, 750, 1080, 1310, 1400, 1550, 1640, 2940, 3270	48,3 48,6	8,4 8,7	25,0 24,3
	(XII)	[a]		1,506	0,48	560, 700, 1070, 1250, 1330, 1400, 1510, 1600, 3060, 3200	50,8 50,5	8,1 8,4	25,8 26,2
	(XIII)	90(1)	–	1,490	0,23	720, 920, 1030, 1280, 1360, 1420, 1620, 2910, 3330	46,5 46,1	10,5 10,8	43,5 43,1
	(XIV)	[a]		1,491	0,53	750, 930, 1100, 1290, 1380, 1440, 1540, 1630, 3030, 3080, 3280	52,3 52,6	8,5 8,8	25,0 24,6
	(XV)	–	131–134 from acetone	–	0,5	520, 650, 790, 1110, 1220, 1550, 1590, 2840, 3050, 3280	50,0 50,5	8,7 8,4	27,0 26,8
	(XVI)	80(1)	–	1,491	0,16	750, 860, 1050, 1150, 1350, 1580, 2910, 3330	46,5 46,4	10,5 10,7	43,0 43,1
	(XVII)	–	91–94 (from CHCl$_3$)	–	0,47	700, 1180, 1400, 1550, 1640, 2920, 3100, 3300	50,2 50,5	9,0 8,8	26,5 26,2

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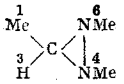
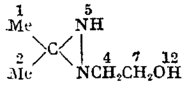
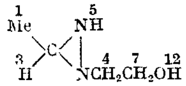
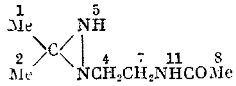
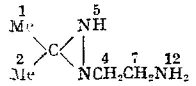
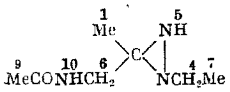
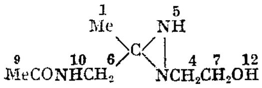
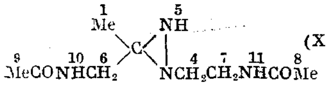
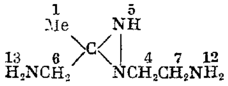
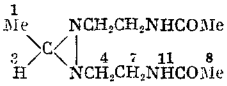
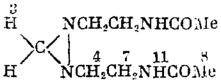
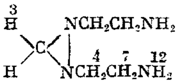
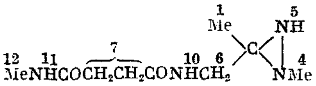
[a] Nondistillable liquid.

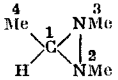
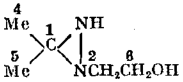
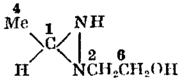
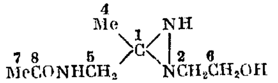
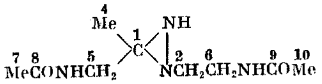
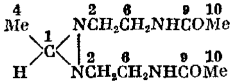
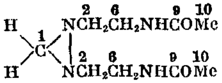
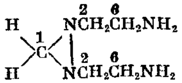
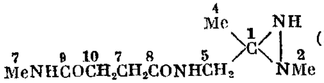
TABLE 4. PMR Spectra of Diaziridines

Compound	Diastereomer ratio			
		H^1	H^2	H^3
 (V)		0,99d (^3J=5,5)		2,31q (^3J=5,5)
 (VI)		1,09 s	1,14s	
 (VII)		1,41d (^3J=5,8)		2,66 d.q (^3J=8,1) (^3J=5,8) 2,87 m
 (VIII)		1,14s	1,20s	
 (IX)		1,07s	1,12s	
 (X)	6 : 1	1,07s: 1,12s		
 (XI)	4 : 1	1,08 s 1,12 s		
 (XII)	5 : 7; 4 : 1 (6 months at 20°)	1,30 s 1,36 s		
 (XIII)	6 / 1	0,92s: 1,03s		
 (XIV)		1,34d (^3J=5,8)		2,74 q (^3J=5,8)
 (XV)				2,56 s
 (XVI)				2,52 s
 (XVII)	4 : 1	1,31 s: 1,35 s		

δ ppm., J, Hz, $CDCl_3$

H^4	H^5	H^6	H^7	H^8	H^9	H^{10}, H^{11}	H^{12}, H^{13}
2,21s		2,18 s					
2,18d.t (^2J=13,5 ^3J=4,5) 2,58 m	1,98s		3,49 m				4,30 br.s
2,29d.t (^2J=13,0 ^3J=4,8) ~2,87m	1,85d (^3J=8,1)		3,77m				4,10 br.s
2,19m 2,62m	1,81 s		3,24m	1,80s		6,75br.s	
2,21d.t (^2J=12,1 ^3J=5,5) 2,57m	1,62 br.s		2,76 m				1,62 br.s
2,23m (^2J=12,50 ^3J=7,5)	2,10 s	2,87 d.d (^2J=14,0 ^3J=4,35) 3,32 d.d (^3J=7,32)	0,83 t (^3J=7,50)		1,71s	7,0 br.s	
2,23m 2,50 m	2,30 s	2,98 d.d (^2J=8,0 ^3J=2,4) 3,26 d.d (^3J=3,2)	3,48m		1,72 s	7,25br.s	4,4 br.s
2,59m 2,63m	2,32 s	3,50 m	3,50 m	1,95 s; 1,965 s		6,83 t 6,90 t	
2,64m	1,87 s	3,21 d.d (^2J=12,0 ^3J=4,5) 3,75 d.d (^3J=6,2)	3,36 m	1,955 s; 1,99 s		6,15 br.s 6,30 br.s	
2,0m 2,26m	1,24br.s	2,22; 2,57 2 d (^2J=13,5)	2,46m				1,24 br.s
2,21 d.t (^2J=13,0 ^3J=4,85) 2,44d.t (^2J=11,2 ^3J=4,8) 2,88m			3,42m	1,98s 2,92s		7,48 m	
2,18m 2,83m			3,46 m	2,02s		6,85br.s	
2,2 d.t (^2J=12,3 ^3J=5,0) 2,63m			2,89m				1,44 br.s
2,41 s	2,40 s	3,13d.d (^2J=15,0 ^3J=3,5) 3,64 d.d (^3J=8,30)	2,51 m			6,82 br.s 6,62br.s	2,74 d (^3J=5,0)

TABLE 5. ^{13}C NMR Spectra of Diaziridines

Compound	δ ppm, J, Hz, $CDCl_3$								
	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8 C^9	C^{10}
 (V)	60,08d	37,27q	46,17q	10,32q					
 (VI)	55,78s	54,16t (^1J=134)		16,22q (^1J=127)	26,15 q (^1J=127)	54,44t (^1J=142)			
 (VII)	57,30d (^1J=173)	61,46t (^1J=142)		19,73q (^1J=127) (^2J=4,88)		63,59t (^1J=137)			
 (IX)	55,70s	55,69t (^1J=133) (^2J=3,4)		27,39q (^1J=130) (^3J=3,4)	16,76 q (^1J=127) (^3J=3,0)	41,02 t (^1J=138) (^2J=3,7)			
 (XI)	57,89s	54,38t 54,18t		14,47q	45,14 t 39,82 t	60,91 t	22,75q 23,39 q	171,46s	
 (XII)	57,79s	51,55t		14,08 q	45,66 t	38,63	22,67q	170,57; 171,42s	22,85 q
 (XIV)	50,10d	58,71 t	59,47t	11,33q		37,76t 38,31t,		169,88 s	22,05 q
 (XV)	55,25 t (^1J=176)	58,53t (^1J=137) (^2J=3,7)				37,56 t (^1J=138) (^2J=3,4)		170,94s	20,65 q (^1J=128)
 (XVI)	54,57t	62,22 t				39,51 t			
 (XVII)	57,74s	37,55q 39,59q	25,76q	12,83 q 13,50 q	45,37 q		30,61 t	173,07s; 172,08s	31,06t

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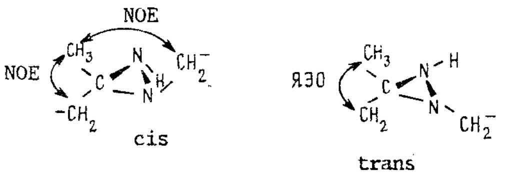
[a]Spectrum in CD_3OD. [The index "a" was omitted in the Russian original table - Editor.]

with an -I effect indicates difficulty in the conversion of A to B in less alkaline media due to a decrease in the basicity of A. Above the pH_{opt}, the reaction is apparently hindered and the diaziridine yield is reduced due to the decomposition of the aminating reagents in the alkaline medium [3, 12].

Below the pH_{opt}, the formation of B and, thus, of C is facilitated but a portion of the amine is removed from the reaction sphere under these conditions due to protonation, which leads to a reduction in the yield of the final products. Thus, the pH_{opt} obtained when the reaction medium still has a significant amount of free amine and the acidity facilitates the generation of immonium ion B.

The structures of these compounds were confirmed by comparison with authentic samples. The new diaziridines were characterized by elemental analysis and their spectral data (Tables 3-5). ABCD patterns were observed in the PMR spectra of (VI)-(IX) and (XI)-(XVI) for the CH_2—CH_2 fragments attached to the diaziridine nitrogen atom.

Products (X)-(XIII) and (XVII) were obtained as mixtures of two diastereomers. The diastereomer with the upfield signal for the Me—C(ring) group proved thermodynamically favored in all cases. Epimerization is observed for (XII) at 20°C (see Table 4). The orientation of the substituents in the diastereomers was determined for (XI), (XII), and (XVII) using the nuclear Overhauser effects (NOE), which are observed between close-lying protons and are rapidly extinguished with increasing distance (NOE $\approx I/R^6$) [13]. A nuclear Overhauser effect is observed upon irradiation of the Me—C(ring) group only for the signal of the CH_2N(ring) group of the predominant diastereomer, which indicates cis orientation of these substituents (Scheme 4). A nuclear Overhauser effect was observed for diastereomers relative to the signals of the CH_2C(ring) group. The magnitude of these effects was about 2%.



Hence, the thermodynamically preferred diastereomers of (X)-(XIII) and (XVII) have trans arrangement of the bulkiest substituents. Trans arrangement probably occurs in (VII), which was isolated as a single diastereomer.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr pellets for (VIII), (XII), (XV), and (XVII) and neat between KBr plates for the other samples. The PMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz relative to TMS as the internal standard. The ^{13}C NMR spectra were taken on a Bruker AM-200 spectrometer at 75.5 MHz relative to TMS as the internal standard. The thin-layer chromatography was carried out on Silufol UV-254 plates with development by I_2 vapor and, independently, spraying with diphenylamine in acetone with subsequent heating of the plate. The eluent was 95:4:1 methanol—water—NH_3. The diaziridine yields were determined by iodometric titration. The pH of the medium was monitored with an EV-74 pH-meter.

Synthesis of 1,3-Disubstituted and 1,3,3-Trisubstituted Diaziridines. General Procedure. A sample of 0.1 mole carbonyl compound was added to 0.1 mole amine in 30 ml water at 0-10°C. The required pH was established by the dropwise addition of 50% aq. sulfuric acid at 0-5°C. Then, 11.8 g (0.1 mole) 96% HASA was added, maintaining the given pH value by the concurrent dropwise addition of amine (Table 1, series nos. 1,2,4,5,6,7,9) or 20% aq. NaOH (Table 1, series nos. 3 and 8 and 1, 2, 4, and 5 in experiments with pH > 12). The reaction mixture was maintained for 12 h at 0-5°C, maintaining the given pH value, and 72 h at 20°C at pH 13-14. The precipitate formed was removed in the experiments in series nos. 3 and 8 and the experiments in series 1, 2, 4, and 5 with pH > 12 and the diaziridine yield was determined by iodometric titration of the reaction mixture.

Synthesis of 1,2-Disubstituted and 1,2,3-Trisubstituted Diaziridines. General Procedure. A sample of 0.05 mole carbonyl compound (CH_2O as 20% aqueous solution and MeCHO as a 50% aqueous solution) was added dropwise to a solution of 0.1 mole amine in 30 ml water at 0-10°C. The required pH of the mixture was established by the dropwise addition of 15% hydrochloric acid when NaOCl was used and 15% hydrobromic acid when NaOBr was used. Then, 0.05 aqueous NaOCl or NaOBr was added dropwise at 0-5°C at a rate such that the given pH was maintained. The mixture was maintained for 24 h at 0°C, maintaining the given pH by the dropwise addition of 20% aqueous NaOH. Then, an additional 5 ml 20% aq. NaOH and the mixture was maintained for an additional 72 h at about 20°C. The diaziridine yield was determined by iodometric titration of the reaction mixture taking account of the results of a blank experiment.

Separation of 1,3,3-Trimethyl-, 1,3-Trimethyl-, 1,2-Diethyl-, 1,2,3-Trimethyl- (V), and 1,2-Diethyl-3-methyldiaziridines. General Procedure. The reaction mixture was saturated with NaOH at 20-30°C. The upper layer was separated and dried over NaOH. This fraction was thrice distilled, collecting the fraction with the corresponding boiling point. The indices of these compounds virtually were the same as those already reported [14].

Separation of Diaziridines (VI)-(VIII), (X)-(XII), and (XIV)-(XVII). General Procedure. The reaction mixture was brought to pH 7.0 at 0-5°C by the addition of 50% aqueous sulfuric acid and evaporated to half volume on a rotary evaporator. A fivefold excess of methanol was added to the residue and the mixture was maintained for 30 min at 0°C. The precipitate was filtered off and the solvent was evaporated. The precipitate was dissolved in chloroform and dried over K_2CO_3. The diaziridines were separated on a column packed with silica gel L40-100 using chloroform as the eluent. The solutions were washed twice with an equal volume of 25% aqueous NH_3. The indices of products (VI)-(XVII) are given in Tables 3, 4, and 5. The indices of (VI) are virtually identical to those described in our previous work [15].

Blank experiments: a) with RHNCl. A solution containing 0.05 mole NaOCl in water was added dropwise to a solution of 0.1 mole amine in 30 ml water at 0°C. The mixture was maintained at 0°C for 24 h and at ~20°C for 72 h. The concentration of RNHHal was determined by iodometric titration (usually 0-3% of the starting amount). b) with RNHBr. A solution of 0.05 mole NaOBr in water was added dropwise to a solution of 0.1 mole $MeNH_2$ in 30 ml water at 0°C and maintained for 1 h at ~20°C. Iodometric titration showed the absence of MeNHBr in solution. c) with HASA. A 5.9 g sample of 96% HASA was added dropwise to a solution of 0.1 mole amine in 30 ml water at 0°C and the mixture was brought to ~20°C (HASA decomposed with vigorous gas evolution). The reaction mixture was maintained for 0.5 h. Iodometric titration indicated the absence of HASA in solution.

Alkaline Hydrolysis of Diaziridines (VIII), (XII), and (XV). A solution of 0.05 mole diaziridine in 50 ml 20% aqueous KOH was maintained for 4-8 h at 70°C and monitored by thin-layer chromatography. The solution was saturated with KOH and the upper layer was separated. The lower layer was extracted with two 50-ml portions of CH_2Cl_2 cooled to 0°C. The extract was added to the separated upper layer and dried over K_2CO_3. The solvent was evaporated and the residue was distilled in vacuum, collecting the fraction with the corresponding boiling point (see Table 5). This procedure gave 4.0 g (69%) (IX), 0.1 g (15%) (XIII), and 2.4 g (37%) (XVI).

LITERATURE CITED

1. British Patent No. 1,167,105 (1969); Chem. Abstr., 14904g (1970).
2. R. Ohme, E. Schmitz, and P. Dolge, Chem. Ber., 99, 2104 (1966).
3. V. V. Kuznetsov, N. N. Makhova, and L. I. Khmel'nitskii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2090 (1989).
4. E. Schmitz, Usp. Khim., 45, 54 (1976).
5. R. G. Kostyanovskii, G. V. Shustov, A. I. Mishchenko, and V. I. Markov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2026 (1976).
6. V. M. Belikov, Yu. N. Belokon', M. M. Dolgaya, and N. S. Martinkova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1721 (1967).
7. C. McDonald and R. N. Beaver, Macromolecules, 12, 203 (1979).
8. O. A. Tavrizova, Yu. I. Veitser, and Yu. A. Klyachko, Zh. Vses. Khim. Ova., 31, No. 1, 110 (1986).
9. A. N. Vereshchagin, Inductive Effect. Substituent Constants for Correlational Analysis [in Russian], Nauka, Moscow (1988).
10. H. K. Hall, J. Am. Chem. Soc., 79, 5441 (1957).

11. A. Albert and E. Sargent, Ionization Constants of Acids and Bases [Russian translation], Khimiya, Moscow (1964).
12. F. Sommer, O. F. Schulz, and M. Nassau, Z. Anorg. Allg. Chem., 147, 142 (1925).
13. Y. Nogge and R. E. Schirmer, Nuclear Overhauser Effect, Academic Press, London (1971).
14. R. Ohme, E. Schmitz, and L. Sterk, J. Prakt. Chem., 37, 257 (1968); A. A. Dudinskaya, A. E. Bova, L. I. Khmel'nitskii, and S. S. Novikov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1523 (1971); B. Carboni, F. Tonnard, and R. Carrie, Bull. Soc. Chem. Fr., No. 3, 525 (1987); M. Komatsu, N. Nishikaze, M. Sakamoto, Y. Ohshiro, and T. Agawa, J. Org. Chem., 39, 3198 (1954).
15. A. N. Mikhailyuk, N. N. Makhova, A. E. Bova, L. N. Khmel'nitskii, and S. S. Novikov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1566 (1978).

COMPLEXES OF LIQUID CRYSTAL o-HYDROXYAZO COMPOUNDS WITH Cu^{2+} AND Pd^{2+} IONS

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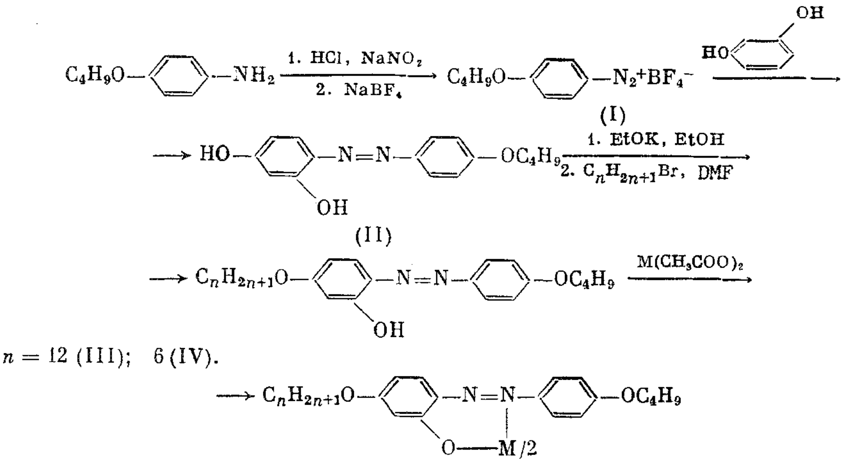
UDC 542.91:532.783:547.556

Liquid crystal o-hydroxyazo compounds were prepared and used to give complexes with Cu^{2+} and Pd^{2+} ions. The structures of these complexes were studied by ESR, IR, and UV spectroscopy. The relationship of the structures of these complexes and their mesogenic properties was examined.

A whole series of liquid crystal metal complexes has recently been obtained [1-4]. Such complexes derived from o-hydroxyazomethines (Schiff bases) [1, 2], many of which have mesogenic properties in a broad temperature range, have been studied rather thoroughly [1, 2]. Metal complexes of structurally similar o-hydroxyazo compounds presumably should also have liquid crystal properties.



$n = 12$ (III); 6 (IV).

M = Pd (2+), $n = 12$ (V); 6 (VII); M = Cu (2+), $n = 12$ (VI); 6 (VIII).

The structure of these compounds was indicated by PMR, IR, UV, and ESR spectroscopy. The finding of a singlet at 13.07 ppm for (III) is in accord with the analogous PMR data for o-hydroxyazo compounds [5], in which the o-hydroxy group participates in a strong intramolecular hydrogen bond. An analogous contribution may be drawn from the IR spectral

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