THERMAL HETEROCYCLIZATION OF METHYL ARYL KETAZINES.
2.* REACTIONS OF THE TAUTOMERIC ENEHYDRAZINE FORM

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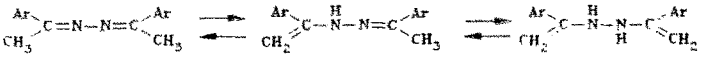
Over the temperature range 220-280°C the thermal reactions of methyl aryl ketazines (Ar = C_6H_5-, 4-CH_3C_6H-, 4-$CH_3OC_6H_4$-, and α-naphthyl-) proceed with their cyclization to give pyrazoline and benzodiazepine derivatives. With an increase in temperature to 320-350°C the subsequent transformations of these compounds lead to the formation of substituted pyrazoles, 1-methyl-1,2-diarylcyclopropanes isomeric olefins, low-molecular-weight aromatic hydrocarbons, and isoquinolines.

The present communication is a continuation of a series of publications [1-3] involving the experimental verification of the possibilities of the mass-spectrometric prediction of the thermal reactions of organic compounds. Considering the fact that thermolysis and mass-spectrometric fragmentation proceed with the formation of products with the same elementary compositions, the peculiarities of the dissociative ionization of methyl aryl ketazines make it possible to assume their cyclization under thermolysis conditions to give derivatives of pyridazine, pyrazole, phthalazine, benzodiazepine, and indazole [1,4]. We have previously shown [1] that over the temperature range 150-350°C the thermal transformations of azines I-IV are represented by reactions of the dienehydrazine tautomer, the initial step of which is the formation of substituted pyrroles and pyridazines.



I Ar=C_6H_5, II Ar=4-$CH_3C_6H_4$, III Ar=4-$CH_3OC_6H_4$, IV Ar=α-naphthyl

The appearance of new compounds in the compositions of the pyrolyzates of ketazines I-IV is observed over a narrower temperature range (220-350°). Among them we identified pyrazolines (I.18, I.15), pyrazoles (I.11, I, III, IV.12, I.23), cyclopropanes (I, II.14), the isomeric olefins (I, II.10), cyclopropanes (I, II.16), aromatic hydrocarbons (I-IV.1-7, I, II.8 9, I, II.13), and, as an individual group of products, N-methylbenzodiazepines (I, II, IV.22) and isoquinoles (I.17, I.19, I, II, IV.20, I.21; see Table 1).† The experimental method was previously described in [1]. The enumerated compounds were identified primarily by comparison of their chromatographic and mass-spectrometric characteristics with those of standards [1-3,5].

The principles of formation of the compositions of the products established in the course of analysis of pyrolyzate samples selected at various temperatures over the range 220-350°C reveal two consecutive reactives that determine the formation of all of the enumerated products. Since the established structures of these compounds are explained by known reac-

*See [1] for Communication 1.

†The order of numbering of the compounds corresponds to the sequence of their appearance in the compositions of the pyrolyzates with an increase in the temperature.

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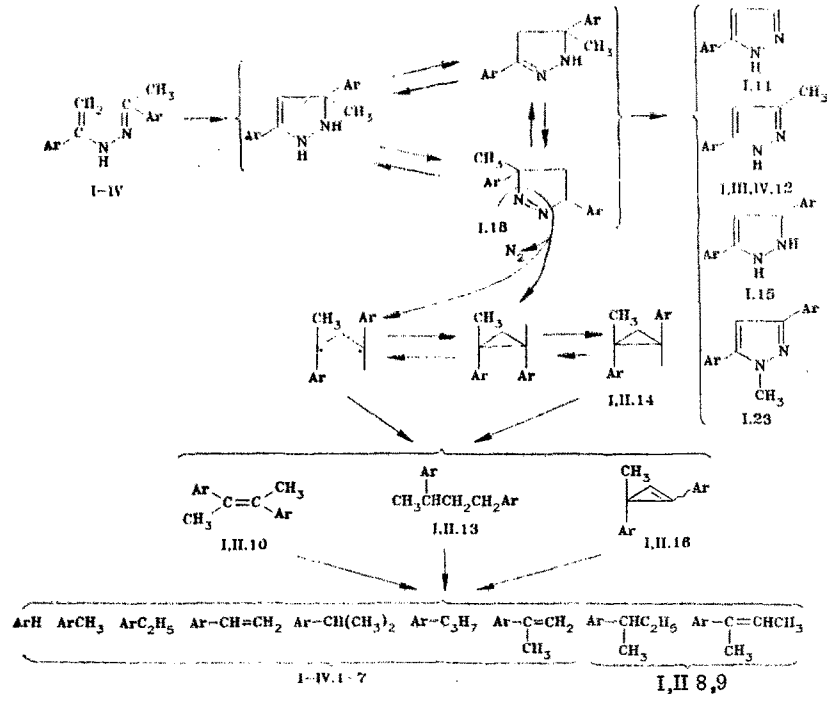
tions of hydrazones [5], we link their formation with the reactivity of the enehydrazine, one of the possible tautomeric forms of methyl aryl ketazines.

The formation of a pyrazoline (I.18), which provides the basis for a whole group of compounds observed in the compositions of the pyrolyzates, is associated with the existence of the enehydrazine tautomer (Scheme 1). Similar transformations of hydrazones under the influence of catalysts (carboxylic and mineral acids, Lewis acids, bases, and alkyl halides) or upon heating are well known [6, 7]. They also are not excluded for azines [8-12].

Because of the differences in the experimental conditions, the concepts regarding the mechanism of the formation of pyrazolines are not unambigous. The reaction schemes proposed by various authors in most cases reflect the nature of the catalyst; the temperature is regarded as a condition that is necessary to maintain the high rate of the process. Nevertheless, a number of publications contain conclusions regarding the sysnchronous character of the investigated reaction, classifying it as thermal disrotatory cyclization [13-15].

Thus the isomerization of methyl aryl ketazines to pyrazolines contradicts neither the chemical properties of these compounds nor the experimental conditions or the theoretical assumptions, and the very possibility of the subsequent tautomeric transformation to a dienehydrazine is demonstrated convincingly by the "pyrrole" cyclization that occurs [1].

Scheme 1



The formation of pyrazoline I.18 as an intermediate was previously proposed in the synthesis of geometrical isomers of 1,2-diarylcyclopropanes in the thermolysis of methyl aryl ketazines in the presence of bases [16-18]. The reaction scheme proposed by the authors thus also finds experimental confirmation under uncatalyzed thermolysis conditions, and this provides a basis for linking the origin of the trans-1,2-diarylcyclopropanes (I, II.14) with the thermal decomposition of pyrazoline I.18 (Scheme 1). A great deal of evidence for the formation of cycloalkanes upon heating cyclic azo compounds [18-21], including cyclopropanes from pyrazolines [8], confirms this conclusion.

Our experimental conditions and those described in [16-17] differ, and this is reflected in the compositions of the products: instead of cis- and trans-cyclopropanes, which are the

TABLE 1. Products of the Thermolysis of Methyl Aryl Ketazines I-IV

Compound	Exit time, min	Amt.,* %	Mass spectrum*	M^+meas	Elementary composition	Lit. data
1	2	3	4	5	6	7
ArH hydrocarbons						
I	1,3	Traces	50 (16), 51 (18), 52 (18), 76 (5), 77 (14), 78 (100)	78,0470	C_6H_6	[30]
II	3,1	Traces	50 (8), 51 (14), 63 (9), 91 (100), 92 (60)	92,0628	C_7H_8	[30]
III	2,4	0,9	65 (61), 78 (56), 79 (11), 93 (11), 108 (100)	108,0576	C_7H_8O	[30]
IV	1,6	Traces	52 (5), 65 (18), 102 (7), 103 (5), 127 (10), 128 (100)	128,0623	$C_{10}H_8$	[30]
$ArCH_3$ hydrocarbons						
I	3,2	Traces	50 (6), 51 (13), 63 (10), 65 (20), 91 (100), 92 (60)	92,0624	C_7H_8	[30]
II	6,1	Traces	65 (10), 77 (15), 79 (11), 91 (100), 105 (24), 106 (50)	106,0771	C_8H_{10}	[30]
III	4,2	2,0	58 (96), 65 (23), 66 (19), 77 (38), 79 (31), 82 (42), 91 (23), 94 (77), 107 (35), 121 (46), 122 (100)	122,0732	$C_8H_{10}O$	[30]
IV	4,0	Traces	115 (20), 139 (10), 141 (78), 142 (100)	142,0783	$C_{10}H_{11}$	[30]
ArC_2H_5 hydrocarbons						
I	5,8	1,7	51 (20), 65 (14), 91 (100), 92 (8), 106 (28)	106,0776	C_8H_{10}	[30]
II	9,2	1,0	63 (6), 65 (10), 77 (15), 79 (15), 91 (13), 105 (100), 120 (25)	120,0939	C_9H_{12}	[30]
III	6,4	3,2	65 (7), 77 (15), 91 (11), 121 (100), 122 (12). 136 (28)	136,0886	$C_9H_{12}O$	[30]
IV	6,4	1,0	115 (13), 141 (100), 142 (12), 155 (5). 156 (52)	156,0937	$C_{12}H_{12}$	[30]
$ArCH{=}CH_2$ hydrocarbons						
I	6,8	1,8	51 (78), 77 (33), 78 (53), 103 (46), 104 (100)	104,0625	C_8H_8	[30]
II	10,0	1,0	51 (16), 63 (13), 65 (12), 91 (33), 103 (12), 115 (30), 117 (91), 118 (100)	118,0783	C_9H_{10}	[30]
III	7,2	0,7	65 (27), 77 (23), 91 (47), 107 (14), 108 (15), 119 (48), 134 (100)	134,0732	$C_9H_{10}O$	
IV	7,6	Traces	127 (35), 128 (55), 153 (78), 154 (100)	154,0782	$C_{12}H_{10}$	

TABLE 1 (continued)

Compound	Exit time, min	Amt., %	Mass spectrum*	M_{meas}	Elementary composition	Lit. data
1	2	3	4	5	6	7
			$ArCH(CH_3)_2$ hydrocarbons			
I	8,1	1,7	51 (13), 77 (13), 91 (5), 105 (100), 106 (9), 120 (26)	120,0940	C_9H_{12}	[30]
II	11,3	0,8	91 (23), 103 (4), 115 (6), 119 (100), 120 (10), 134 (28)	134,1098	$C_{10}H_{14}$	[30]
III	7,6	2,0	65 (6), 77 (8), 105 (19), 135 (100), 136 (8), 150 (24)	150,1046	$C_{10}H_{14}O$	[30]
IV	8,6	1,0	101 (15), 127 (15), 141 (8), 155 (100), 170 (25)	170,1095	$C_{13}H_{14}$	
			ArC_3H_7 hydrocarbons			
I	9,1	Traces	78 (9), 91 (100), 92 (10), 105 (5), 120 (20)	120,0938	C_9H_{12}	[30]
II	12,3	Traces	57 (18), 77 (24), 79 (10), 91 (9), 105 (100), 106 (11), 134 (13)	134,1097	$C_{10}H_{14}$	
III	8,4	0,9	77 (17), 91 (9), 107 (88), 121 (100), 122 (29), 150 (15)	150,1044	$C_{10}H_{14}O$	
IV	9,4	Traces	115 (33), 141 (100), 142 (12), 155 (7), 170 (23)	170,1096	$C_{13}H_{14}$	
			$ArC(CH_3)=CH_2$ hydrocarbons			
I	9,6	2,0	51 (28), 57 (25), 58 (11), 58,5 (10), 77 (25), 78 (37), 91 (22), 103 (57), 115 (19), 117 (63), 118 (100)	118,0784	C_9H_{10}	[30]
II	12,9	1,0	91 (22), 115 (27), 116 (9), 117 (100), 131 (21), 132 (63)	132,0940	$C_{10}H_{12}$	
III	9,6	1,0	77 (16), 79 (10), 103 (8), 105 (11), 106 (8), 133 (68), 148 (100)	148,0889	$C_{10}H_{12}O$	
IV	10,1	1,2	76 (10), 83 (50), 85 (61), 151 (10), 153 (100), 167 (32), 168 (52)	168,0937	$C_{13}H_{14}$	
			$ArCH(CH_3)C_2H_5$ hydrocarbons			
I	11,3	2,3	76 (20), 77 (20), 91 (19), 105 (100), 119 (5), 134 (13)	134,1095	$C_{10}H_{14}$	
II	15,8	Traces	77 (19), 90 (11), 91 (36), 105 (13), 116 (15), 117 (31), 120 (9), 133 (100), 148 (11)	148,1253	$C_{11}H_{16}$	
			$ArC(CH_3)=CHCH_3$ hydrocarbons			
I	11,6	Traces	91 (29), 103 (24), 115 (37), 117 (100), 118 (44), 131 (17), 132 (48)	132,0940	$C_{10}H_{12}$	[30]
II	15,8	Traces	91 (62), 92 (31), 115 (47), 116 (25), 117 (71), 119 (16), 128 (10), 129 (13), 131 (100), 132 (12), 134 (5), 146 (87)	146,1097	$C_{11}H_{14}$	

TABLE 1 (continued)

Compound	Exit time, min	Amt., %	Mass spectrum*	M^+ meas	Elementary composition	Lit. data
1	2	3	4	5	6	7
			$Ar(CH_3)C=CAr(CH_3)$ hydrocarbons			
I	27,6	2,0	77 (36), 78 (13), 91 (68), 105 (98), 115 (100), 116 (21), 129 (26), 130 (37), 165 (21), 178 (40), 179 (33), 193 (77), 194 (25), 207 (29), 208 (75)	208,1250	$C_{16}H_{16}$	
II	31,4	1,0	77 (15), 91 (24), 105 (34), 115 (16), 117 (13), 129 (100), 130 (13), 144 (9), 206 (18), 221 (50), 236 (34)	236,1566	$C_{18}H_{20}$	
			5-Arylpyrazoles			
I	27,9	Traces	51 (16), 63 (9), 77 (17), 89 (11), 90 (14), 115 (25), 117 (16), 143 (14), 144 (100)	144,0687	$C_9H_8N_2$	[31]
			3-Methyl-5-arylpyrazoles			
I	29,6	Traces	77 (35), 78 (12), 89 (12), 90 (10), 91 (72), 103 (11), 104 (16), 105 (48), 115 (25), 117 (11), 118 (32), 119 (40), 128 (11), 129 (14), 130 (12), 157 (34), 158 (100)	158,0845	$C_{10}H_{10}N_2$	[31]
III	27,0	0,8	65 (10), 77 (11), 91 (7), 94 (7), 121 (19), 145 (44), 158 (10), 173 (75), 174 (10), 188 (100)	188,0950	$C_{11}H_{12}N_2O$	
IV	27,3	Traces	115 (6), 127 (11), 141 (13), 147 (12),153 (25), 155 (29), 165 (18), 167 (14), 178 (18), 179 (20), 180 (18), 207 (78), 208 (100)	208,1001	$C_{14}H_{12}N_2$	
			1,3-Diarylbutanes			
I	29,9	Traces	77 (32), 91 (64), 92 (31), 105 (69), 115 (72), 119 (16), 128 (11), 129 (26), 130 (64), 131 (16), 165 (13), 178 (37), 179 (20), 193 (100), 194 (14), 207 (15), 208 (75), 209 (14), 210 (46)	210,1410	$C_{16}H_{18}$	
II	34,0	Traces	77 (21), 91 (39), 105 (49), 115 (21), 119 (50), 129 (100), 143 (27), 144 (26), 206 (11), 221 (66), 222 (16), 236 (43), 238 (20)	238,1720	$C_{18}H_{22}$	
			trans-1-Methyl-1,2-diarylcyclopropanes			
I	30,2	3,0	77 (23), 91 (46), 103 (14), 105 (23), 115 (100), 129 (22), 130 (28), 131 (10), 178 (28), 179 (18), 194 (64), 207 (13), 208 (64)	208,1254	$C_{16}H_{16}$	[16]
II	34,6	1,4	77 (18), 91 (33), 105 (41), 117 (19), 119 (7), 129 (100), 143 (23), 144 (16), 206 (19), 221 (100), 222 (25), 236 (45)	236,1566	$C_{18}H_{20}$	[16]

TABLE 1 (continued)

Compound	Exit time, min	Amt., %	Mass spectrum*	M_{meas}	Elementary composition	Lit. data
1	2	3	4	5	6	7
3,5-Diaryl-Δ^2-pyrazolines						
I	31,1	Traces	77 (34), 79 (25), 91 (40), 103 (20), 106 (26), 115 (25), 116 (10), 118 (21), 119 (18), 131 (10), 144 (9), 180 (9), 193 (8), 194 (8), 222 (14)	222,1160	$C_{15}H_{14}N_2$	[31]
1-Methyl-1,2-diaryl-Δ^2-cyclopropenes						
I	32,1	Traces	77 (38), 91 (87), 102 (19), 103 (20), 115 (20), 127 (23), 128 (45), 129 (24), 178 (8), 191 (77), 205 (19), 206 (100)	206,1095	$C_{16}H_{14}$	
II	33,4	Traces	77 (11), 91 (47), 105 (51), 115 (31), 129 (18), 132 (43), 204 (12), 219 (72), 233 (20), 234 (100)	234,1409	$C_{18}H_{18}$	
1,2,3,4-Tetrahydroisoquinolines						
I	33,4	0,5	77 (27), 91 (100), 105 (25), 115 (17), 117 (13), 118 (40), 132 (99), 133 (71)	133,0892	$C_9H_{11}N$	[32]
3-Methyl-3,5-diarylpyrazolines						
I†	35,1	0,8	77 (51), 91 (44), 103 (17), 104 (11), 105 (79), 118 (18), 119 (32), 120 (22), 131 (29), 132 (100), 133 (18), 193 (22), 220 (11), 221 (17), 236 (26)	236,1316	$C_{16}H_{16}N_2$	[31]
3-Aryl-1,2,3,4-tetrahydroisoquinolines						
I	35,6	0,8	77 (84), 78 (17), 91 (66), 103 (15), 105 (100), 115 (10), 117 (20), 118 (33), 119 (20), 120 (14), 131 (18), 132 (62), 209 (18)	209,1207	$C_{15}H_{15}N$	[32]
1-Methyl-3-aryldihydroisoquinolines†						
I	36,3	3,5	77 (54), 78 (11), 91 (16), 104 (24), 105 (24), 115 (34), 117 (13), 130 (12), 144 (12), 206 (11), 220 (100), 221 (51)	221,1207	$C_{16}H_{15}N$	[32]
II	40,9	2,0	91 (31), 105 (11), 115 (14), 117 (26), 118 (19), 119 (13), 131 (11), 234 (22), 235 (33), 248 (100), 249 (34)	249,1518	$C_{18}H_{19}N$	
IV	28,2	1,0	127 (35), 152 (100), 153 (92), 167 (15), 168 (37), 279 (27), 280 (17), 306 (35), 320 (40), 321 (45)	321,1520	$C_{24}H_{19}N$	

TABLE 1 (continued)

Compound	Exit time, min	Amt., %	Mass spectrum*	M^+ meas	Elementary composition	Lit. data
1	2	3	4	5	6	7
			3-Arylisoquinolines			
I	37,8	1,5	77 (20), 101,5 (11), 102 (52), 102,5 (23), 117 (11), 176 (15), 203 (14), 204 (68), 205 (100)	205,0831	$C_{15}H_{11}N$	
			1,3-Dimethyl-4-aryl-4,5-benzo[d]diazepines			
I	39,7	4,2	77 (67), 91 (14), 95,5 (22), 102 (29), 103 (22), 105 (76), 108,5 (53), 109 (16), 109,5 (32), 115 (36), 116 (15), 144 (86), 218 (17), 219 (54), 220 (47), 233 (21), 247 (10), 248 (50)	248,1315	$C_{17}H_{16}N_2$	[33]
II	43,8	1,5	91 (30), 115 (17), 117 (19), 118 (20), 119 (69), 158 (71), 159 (11), 246 (22), 247 (100), 248 (25), 261 (11), 276 (34)	276,1625	$C_{19}H_{20}N_2$	
IV	35,1	5,5	127 (51), 152 (22), 153 (28), 165 (20), 168 (17), 304 (19), 305 (16), 319 (100), 320 (67), 333 (26), 348 (32)	348,1627	$C_{25}H_{20}N_2$	
			3-Methyl-4,5-diarylpyrazoles			
I	44,2	4,4	77 (37), 103 (15), 104 (19), 115 (27), 116 (23), 165 (14), 189 (22), 191 (15), 219 (100), 234 (62)	234,1158	$C_{16}H_{14}N_2$	[31]

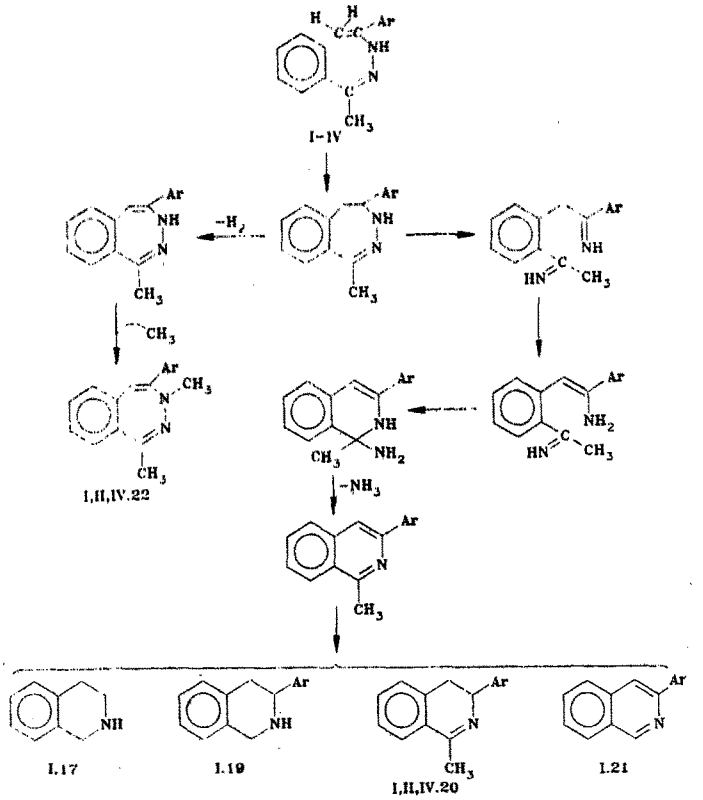
*The peaks of ions with intensities of 5% are presented.
†The position of the double bond was not established.

principal products in the published experiments, we observe the formation of only trans-cyclopropanes (I, II.14), the isomeric olefins (I, II.10), cyclopropanes (I, II.16), and a large group of aromatic hydrocarbons (Scheme 1, Table 1).

The formation of cyclopropanes via Scheme 1 is confirmed by independent investigations of the thermolysis of cis- and trans-1-methyl-1,2-diphenylcyclopropanes and a mixture of these geometrical isomers.*

The decomposition of the Δ^1-tautomeric form of pyrazoline to nitrogen and cyclopropane is not the only reaction. An independent pathway in the decomposition of pyrazoline, which is evidently determined by another tautomeric form, is the elimination of hydrocarbons (CH_4 or ArH) and the formation of, respectively, 3-methyl-5-aryl- or 3,5-diarylpyrazoles (Scheme 1). Subsequent hydrogenation, radical substitution, and N-methylation of these compounds lead to the actual compositions of the products. The enumerated processes are observed at high temperatures and do not exclude the possibility of an alternative origin of products of the pyrazole series. In this connection, it should be noted that numerous studies of the thermolysis of azines [23-26] explain the formation of pyrazoles by means of radical reactions.

Scheme 2



Above we examined the thermal reactions of methyl aryl ketazines, the initial step of which is isomerization of the tautomeric enehydrazine form to a pyrazoline. An alternative direction of cyclization of the enehydrazine leads to the formation of a benzodiazepine (Scheme 2). The chemical transformations of this compound in the ensuing steps are determined by either dehydrogenation and N-methylation or by decomposition with the elimination of a molecule of ammonia and the formation of isoquinolines. The indicated reactions take place at high temperatures at which radical processes make an appreciable contribution to the formation of the compositions of the products. This hinders the identification of some of the products indicated in Scheme 2.

In its general features, the proposed scheme resembles the peculiarities of the formation of products of the pyrrole and pyridazine series [1]. As an additional argument in substantiation of this sequence of reactions one should point out examples of the synthesis of benzodiazepines and isoquinolines from hydrazones [6], as well as direct evidence for thermal transformations of benzodiazepines to isoquinolines with the elimination of a molecule of NH_3 [27-29].

*The results of this research are being prepared for publication.

EXPERIMENTAL

The synthesis and principal physicochemical characteristics of methyl aryl ketazines I-IV are described in [16].

The thermolysis was carried out under conditions of linear raising of the temperature. The starting compounds were heated in a sealed glass ampul from 20°C to 350°C at a constant rate of 5°C/min.

The temperature range of 220-350°C, which corresponds to the examined reactions, was determined beforehand by derivatographic analysis (see [1]).

The structural identification and quantitative analysis of the thermolysis products (Table 1) were carried out with a Varian MAT-311 mass spectrometer (USA) with the aid of low- and high-resolution mass spectrometry [ΔM/M 15000, polyphosphoric acid (PPA) standard] and gas-liquid chromatographic mass spectrometry. The ionizing-electron energy was 70 eV, the cathode emission current was 1 mA, the accelerating voltage was 3 kV, the ion-source temperature was 150°C, and the amplifier voltage was 2 kV. The chromatograph was a Varian Aerograph 3700 (USA), and the capillary column was an Aerograph OV-101 (USA) with a length of 25 m and an inner diameter of 0.25 mm; the injector temperature was 300°C. The rate of heating of the column over the ranges 40-240°C (for I), 40-260°C (II), and 60-260°C (III, IV) was 5°C/min; the times of the initial and final isothermal periods were 3 and 30 min, respectively, and the carrier gas was helium (1.5 ml/min).

The relative percentage of the thermolysis products were evaluated from the readings of an I-02 digital integrator (USSR) assuming equal sensitivity coefficients for all of the pyrolyzate components being separated.

The structures of the compounds indicated in Table 1 were confirmed by reference substances (by comparison of the exit times and the mass spectra) and/or by the mass spectra published in the cited literature.

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RESEARCH ON IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES. 22.* SYNTHESIS OF 2,3-DIHYDROIMIDAZO[1,2-a]BENZIMIDAZOLES STARTING FROM 2-IMINO-3-(2-HYDROXYETHYL)BENZIMIDAZOLINES

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A β-elimination reaction with the formation of 2-imino-3-vinylbenzimidazolines occurs simultaneously with intramolecular alkylation and the formation of an imidazoline ring in the action of alcoholic alkali on 2-imino-3-(2-chloroethyl) benzimidazolines. The thermolysis of 3-chlorethyl-substituted imines without a solvent or in an inert solvent leads exclusively to 2,3-dihydroimidazo[1,2-a] benzimidazoles. An attempt to obtain the latter directly from 2-imino-3-(2-hydroxyethyl)benzimidazolines by the action of a mixture of thionyl chloride and acetic anhydride on them also leads to ambiguous results.

One of the most widely spread methods for the formation of a condensed imidazoline ring in systems with a bridged nitrogen atom consists in the successive action of thionyl chloride and alcoholic alkali on N-β-hydroxyethyl-substituted nitrogen heterocycles in which there is an amino group in the α position relative to the heteroring nitrogen atom [2,3]. This method was used in 1967 to obtain 9-ethyl-2,3-dihydroimidazo[1,2-a]benzimidazole, the first representative of this hydrogenated system [4,5]. However, it does not always give good results, and the yields of 9-benzyl- [6] and 9-phenyl-substituted compounds [7] synthesized via a similar scheme were only 27% and 36%, respectively. We turned to an investigation of this reaction in order to establish the reasons for the low yields of 2,3-dihydroimidazo-[1,2-a]benzimidazoles and to find more acceptable cyclization conditions, especially since little study has been devoted to the chemical and, particularly, pharmacological properties of this heterosystem [6, 7].

*See [1] for communication 21.

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