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2,3,3-Trimethylene-2-hydroxy-5-pyrrolidone was obtained by the method in [3]. The PMR spectra of the compounds were recorded with an R-20A spectrometer at 34°C. The effective rate constants in 50% aqueous pyridine with the addition of sodium bicarbonate were obtained by dynamic NMR spectroscopy by the method described in [4]. In experiments with the addition of hydrochloric acid the constants were obtained from the time change with time in the integral intensities of the signals of the corresponding tautomeric forms. The reaction was begun with the chain tautomer and was first-order in both the tautomer and bicarbonate. The ρ constants in the Hammett equations at various temperatures were calculated by the method of least squares; the correlation coefficients ranged from 0.960 to 0.996.

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STRONG BASE-CATALYZED THERMAL REARRANGEMENTS OF AZINES OF BENZYL ALKYL KETONES

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Azines of benzyl alkyl ketones undergo cyclization in the presence of strong basic catalysts to give mixtures of compounds of the pyrrole and pyrazole series. The formation of pyrazole products probably proceeds via the scheme of the Fischer reaction taking into account the concept of a [3,3] sigmatropic shift. However, the presence of nitriles and hydrocarbons among the products of the reaction of pyrazole derivatives indicates the ambiguous character of the proposed scheme. The rearrangement of azines to pyrazole compounds probably proceeds through a step involving the formation of a carbanion, while the formation of nitriles and hydrocarbons can be explained by radical processes. The dependence of the ratio of the pyrolysis products (pyrrole/pyrazole) on the amount of catalyst and its basicity (LiH, NaH, KH, NaOH, KOH, PhOK, and CH_3OK) makes it possible to assume that the occurrence of the reaction through a step involving a [3,3] shift is realized thermally and that small amounts of the catalyst promote the realization of this reaction pathway; however, a high percentage of the catalyst and the use of the most basic catalysts lead to an increase in the yields of the pyrazole products.

One of us has previously proposed that the Fischer reaction and some related processes (e.g., the synthesis of pyrroles from azines under the influence of acidic agents) be regarded as sigmatropic [3,3] rearrangements [1]. We were later able to confirm this assumption for the Fischer reaction experimentally [2, 3].

An examination of the mechanism of the Piloty reaction from the point of view of a sigmatropic [3,3] shift and recognition of the decisive role in this reaction of tautomeric

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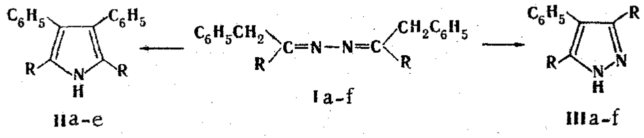
TABLE 1. Product Ratios in the Cyclization of Alkylbenzylketazines (Gas—Liquid Chromatography, Mole%)

Azine	Azine/NaH ratio (mole/mole)	Pyrazole	Pyrrole	Diphenylethane	Toluene	Nitrile
Ia	Thermolysis without NaH	28	7	65	42	58
Ia	20 : 1	16,5	50	33,5	52	48
Ia	10 : 1	7,5	85	7,5	58	42
Ia	5 : 1	6,5	80	13,5	63	37
Ia	2 : 5	36	59	5	100	—
Ia	1 : 1	61	35,5	3,5	100	—
Ib	5 : 1	36,5	46,5	17	64	36
Ic	5 : 1	44	32	24	55	45
Id	5 : 1	51,5	28,5*	20	42	58

*Identified only by chromatography.

conversion of the azine to a dienehydrazine make it possible to assume that this reaction may also proceed under alkaline catalysis conditions, i.e., alkaline catalysts, by accelerating the tautomeric conversion via the standard scheme that is analogous to enolization of carbonyl compounds, should, like acid catalysts, lead to pyrrole compounds.

In order to prove this assumption, we studied the thermolysis of azines of carbonyl compounds that contain a relatively easily enolized benzyl group at 250°C in the presence of sodium hydride. Under these conditions, azines I undergo cyclization to mixtures of compounds of the pyrrole (II) and pyrazole (III) series:

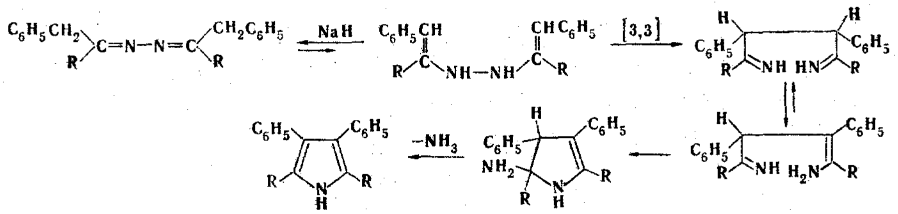

IIa-e

Ia-f

IIIa-f

I–III a $R=CH_3$; b $R=C_2H_5$; c $R=C_3H_7$; d $R=i\text{-}C_3H_7$; e $R=C_6H_5$; I, III f $R=H$

The investigated rearrangement of azines to pyrrole compounds can be explained on the basis of the scheme of the Fischer reaction, taking into account the concept of a [3,3] sigmatropic shift [1].



As in the case of the Fischer reaction, the azine is converted to a dienehydrazine in the first step of the cyclization. This conversion is reversible, and the equilibrium is shifted to favor the formation of the azine, for it is known that in the case of compounds that are capable of forming tautomeric forms of the ketone—enol and lactim—lactam type the tautomeric equilibrium under ordinary conditions is shifted markedly to favor the form in which the proton is bonded to the less electronegative atom of the tautomeric triad. An alkaline catalyst, while not shifting the equilibrium itself, appreciably increases the rate of the tautomeric conversion. A phenyl group also promotes an increase in the acidity of the hydrogen atom of the adjacent methylene group and increases the probability of the formation of the enehydrazine tautomer. The formation of a dienehydrazine evidently proceeds via an E_1 cleavage mechanism similar to the mechanism of enolization of O-phenyl oximes of unsymmetrical carbonyl compounds to benzofurans via the scheme of the Fischer reaction [4].

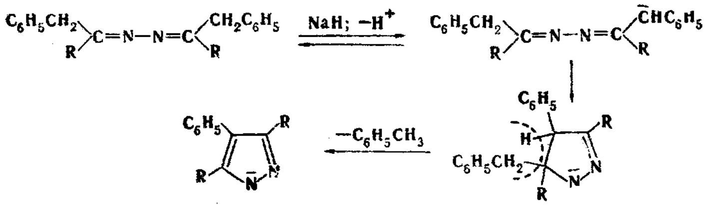
A sigmatropic [3,3] shift occurs in the next step, after which (after several steps accompanied by the elimination of ammonia) the pyrrole derivative is formed. The probability of the occurrence of the step involving the formation of a carbon—carbon bond as a sigmatropic [3,3] shift is confirmed by the very fact of the formation of a pyrrole compound when the thermolysis is carried out without a catalyst but at 300°C.

TABLE 2. Cyclization of the Azine of Methyl Benzyl Ketone in the Presence of Various Alkaline Catalysts (Ratios of the Pyrrole and Pyrazole Cyclization Products According to GLX, Mole%)

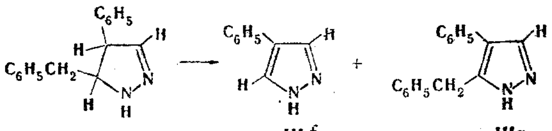
Catalyst	Pyrazole	Pyrrole	Overall yield of the mixture, %
LiH	20	80	27
NaH	31	69	26
KH	22	78	32
NaOH	4	96	42
KOH	2	98	36
PhOK	5	95	28
CH_3OK	17	83	31

The detection of nitriles and hydrocarbons among the reaction products along with pyrroles and pyrazoles (the mechanism of their formation will be discussed below) indicates the ambiguous character of the proposed scheme. The formation of these compounds can be explained by radical processes: Homolytic cleavage of the C—C and N—N bonds leads to the development of radical particles that form nitriles and hydrocarbons through recombination, decomposition, and disproportionation.

The rearrangement of azines to pyrazole compounds probably proceeds via a mechanism that includes the formation of a carbanion. Subsequent attack on the C=N bond by the carbanion center leads to the formation of the pyrazoline ring. The pyrazoline is subsequently stabilized by splitting out of a molecule of toluene and conversion to the pyrazole.



In the case of azine If the pyrazoline is stabilized via two pathways: by splitting out of toluene with the formation of a 4-phenylpyrazole (IIIf) and by splitting out of hydrogen with the formation of 3(5)-benzyl-4-phenylpyrazole (IIIg).



IIIf IIIg

An analysis of the products of thermolysis of the azines made it possible to establish the existence of a certain correlation between the yields of the pyrrole and pyrazole thermolysis products and the length of the carbon chain of the alkyl substituent: An increase in the length from C_1 to C_3 is accompanied by an increase in the yield of the pyrazole product from 6.5 to 51.5 mole% vis-à-vis a simultaneous decrease in the pyrrole product from 80 to 28.5 mole% (Table 1). To ascertain the effect of the amount of alkaline catalyst on both pathways for cyclization of the azines we carried out the thermolysis of the azine (Ia) of methyl benzyl ketone in the presence of variable amounts of sodium hydride. The relative molar ratios of the principal thermolysis products — pyrazole and pyrrole derivatives and 1,2-diphenylethane in the reaction mixture, and toluene and acetonitrile in the forerun — were established by gas—liquid chromatography (GLC). The results of analysis by GLC are presented in Table 1.

The occurrence of the reaction through a step involving a sigmatropic [3,3] shift is evidently realized even thermally. In fact, thermolysis at 300°C without a catalyst leads to a pyrrole product (in 7% yield). The addition of small amounts of sodium hydride to the azine promotes the realization of this pathway to an even greater extent: The yield of the pyrrole increases to 50% in the case of an azine/NaH ratio of 20:1 and reaches the maximum

TABLE 3. Constants of the Azines

Azine	bp, °C (mm), [mp, °C]	R_f*	M (by mass spectrometry)	UV spectrum		IR spectrum (C=N), cm^{-1}
				λ_{max}, nm	lg ε	
Ia	160—162 (1)	0,38	264	216, 237, 269	4,07; 3,93; 3,12	1640
Ib	184—186 (2)	0,39	292	218, 241, 269	4,36; 4,04; 3,21	1640
Ic	189—191 (2)	0,50	320	218, 269	4,39; 3,15	1625
Id	[162—163]	0,69	388	278, 305	4,23; 4,27	1650
Ie	172—174 (1)	0,60	328	218, 269	4,40; 3,14	1630
If	175—177 (1)	0,35	236	248, 285, 296, 310	3,77; 3,58; 3,57; 3,51	1625
IV	[163—165] (1)	0,52	292	216, 238, 258, 265, 269	4,58; 4,11; 3,84; 3,04; 2,95	1640
V	[115—116]	0,58	416	242, 269	3,90; 3,19	1650

*On activity II aluminum oxide; benzene—petroleum ether (7:2) was used for elution of Ia-f, and petroleum ether—diethyl ether (1:1) was used for elution of IV and V.

value of 85% when this ratio is 10:1. This is evidently associated with an increase in the rate of formation of the enehydrazine.

It follows from the data in Table 1 that in the case of truly catalytic amounts of the catalyst the reaction is similar to the thermal reaction and proceeds through a step involving a sigmatropic [3,3] shift leading to the pyrrole compound: The process that leads to pyrazoles predominates in the case of equimolar amounts of the catalyst, and sodium hydride manifests its deprotonating ability in this case by facilitating the detachment of one of the acidic hydrogen atoms of the benzyl methylene group.

In order to verify the effect of the basicity of the catalyst on the pyrrole/pyrazole ratio we carried out the thermolysis of azine Ia in the presence of various catalysts of the basic type. The results of analysis of the reaction mixtures by GLC are presented in Table 2. It should be noted that the yields of pyrazoles are higher for the more basic catalysts.

We studied the thermolysis of the azines (IV and V, respectively) of 3-phenyl-2-butanone and 1,1-diphenyl-2-propanone, in which one of the hydrogen atoms of the methylene group is replaced by an alkyl or aryl group. The formation of pyrrole compounds is not observed in these cases. 3,5-Dimethyl-4-phenylpyrazole was detected among the products of thermolysis of azine IV. Its formation is completely within the limits of the proposed scheme of the pyrazole cyclization of azines. The thermolysis of azine V is evidently realized via a radical mechanism as a result of decomposition of the azine at the C—C, C=N, and N—N bonds and subsequent radical reactions. The isolation and identification of 1,1,2,2-tetraphenylethane, benzene, and diphenylmethane confirm this.

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The IR spectra of liquid films, solutions in CCl_4 and $CHCl_3$, and KBr pellets of the compounds were recorded with Jasco IR-S (with an NaCl prism) and UR-20 spectrometers. The UV spectra of solutions of the compounds in isopropyl alcohol, ethanol, and dioxane were recorded with a Hitachi EPS-3T spectrophotometer. Analysis by GLC was carried out with Yanaco G-800T and Khrom-4 chromatographs with 2 m by 4 mm columns. Column I was filled with 5% SE-30 on Chromaton N-AW (0.125-0.160 mm particles), column II was filled with 7.5% neopentyl glycol succinate on acid-washed Chromosorb-G (0.2-0.3 mm particles), and column III was filled with 5% SE-30 on Chezasorb (0.25-0.30 mm particles). The vaporization temperature was varied from 150 to 320°C, and the column temperature was varied from 80 to 260°C, depending on the composition of the mixtures analyzed. The carrier-gas (N_2 or H_2) flow rate was varied from 40 to 80 ml/min, and a catharometer and a flame-ionization detector were used as detectors.

We determined the coefficients of sensitivity of the nitriles with respect to toluene for the quantitative calculation of the nitrile/toluene ratios in the foreruns. The quantitative calculation of the ratios of the pyrazoles, pyrroles, and 1,2-diphenylethane was made on the basis of the sensitivity coefficient relative to 1,2-diphenylethane. The ratio of only the pyrrole and pyrazole products was determined in a series of experiments with different catalysts. The melting points of the compounds were measured with a Mettler EP-5 apparatus.

TABLE 4. Constants of Pyrroles and Pyrazoles

Compound	mp, °C	R_f*	UV spectra		Found, %		Empirical formula	Calc., %		M (by mass spectrometry)
			λ_{max}, nm	lg ε	C	H		C	H	
IIa	149–150	0,30	222 i; 240; 276	4,21; 4,23 3,99	87,4	7,0	$C_{18}H_{17}N$	87,4	6,9	247
IIb[5]	147–148	0,50	239; 274	4,18; 3,91	86,9	7,7	$C_{20}H_{21}N$	87,2	7,7	275
IIc[5]	93–94	0,61	222 i; 240; 277	4,26; 4,27; 3,99	87,0	8,3	$C_{22}H_{25}N$	87,0	8,3	303
IIe[6]	213–214	0,58	248; 239	4,37; 4,38	90,5	5,8	$C_{28}H_{21}N$	90,5	5,7	371
IIIa	131–132	0,22	247	4,16	76,2	7,0	$C_{11}H_{12}N_2$	76,4	6,4	—
IIIb	106–107	0,30	237	3,98	77,3	7,9	$C_{13}H_{16}N_2$	77,8	8,0	201
IIIc	131–132	0,53	222 i; 270	3,86; 4,04	78,9	8,6	$C_{15}H_{20}N_2$	78,9	8,8	229
IIId	124–125	0,32	230; 240 i,	3,84; 3,79	78,9	8,8	$C_{15}H_{20}N_2$	78,9	8,8	229
IIIe[5]	266–267	0,28	238 i; 247	4,52; 4,54	84,6	5,6	$C_{21}H_{16}N_2$	85,1	5,4	296
IIIf[6]	232–233	0,34	248; 304 i	4,14; 3,11	73,9	5,6	$C_9H_8N_2$	74,5	5,6	144
IIIg[7]	120–121	0,27	243	4,13	81,4	6,0	$C_{16}H_{14}N_2$	82,0	6,0	234

*From TLC on activity II Al_2O_3; IIa-c,e were eluted with benzene–petroleum ether (1:1), and IIIa-g were eluted with benzene–acetone (6:1).

Synthesis of the Azines. The azines were obtained in a Dean–Stark apparatus from the corresponding ketones and hydrazine hydrate in molar ratios of 2:1 by refluxing in benzene with removal of the water by distillation. After isolation of the theoretical amount of water, the benzene was removed by evaporation with a rotary evaporator, and the residue was distilled in vacuo or recrystallized. The physical constants and spectral characteristics of the synthesized azines are presented in Table 3.

Standard Method of Thermolysis of the Azines. A 0.03-mole sample of the azine and 0.006 mole of sodium hydride in the form of a 30% suspension in mineral oil were placed in a 30 ml Claisen flask equipped with a capillary for introduction of dry N_2, a thermometer, a descending condenser, a vacuum adapter, and a receiver for the forerun; and the flask was placed in a Wood's metal bath heated to 180°C. The bath temperature was raised to 250°C in 15 min and maintained at that point for 6 h. The liberation of ammonia and a low-boiling forerun was observed during the thermolysis. The forerun was collected in the receiver and was analyzed by GLC with the use of appropriate standards. After heating was discontinued, the reaction mixture was extracted with hot benzene (three 30-ml portions) to free it from the catalyst; and the extract was washed with water, dried with magnesium sulfate, and concentrated with a rotary evaporator. The pyrroles and pyrazoles were isolated from the residues by vacuum distillation, crystallization in suitable solvents, or chromatography on Al_2O_3.

The quantitative ratios of the principal thermolysis products – pyrazoles, pyrroles, toluene, nitriles, and 1,2-diphenylethane – were established by GLC, which was carried out separately for the reaction mixtures and for the foreruns. The degree of purity of the isolated compounds was monitored by GLC and thin-layer chromatography (TLC).

All of the compounds of the pyrazole and pyrrole series were identified from their IR and UV spectra. The fragmentation in the mass spectra and the information obtained from the PMR spectra were in agreement with the proposed structures. The constants are presented in Table 4. The composition of the gases that were liberated during the thermolysis was not established.

Thermolysis of the Azine of Phenylacetaldehyde. A forerun [0.2 g (7%)], which was identified as toluene by GLC, was obtained in a standard experiment from 7.0 g (0.03 mole) of the azine. Vacuum fractionation of the reaction mixture gave fraction A with bp 80-100°C (2 mm) and fraction B with bp 180-200°C (2 mm). Chromatography of fraction A on Al_2O_3 (elution with benzene) yielded 0.5 g (7%) of benzyl cyanide, which was identified by GLC.

Fraction B was dissolved in 20 ml of benzene, and 30 ml of diethyl ether was added to the solution to "precipitate" 1.3 g (30%) of 4-phenylpyrazole. The filtrate after isolation of the 4-phenylpyrazole was concentrated, and 0.7 g (10%) of 3(5)-benzyl-4-phenylpyrazole (IIIg) was isolated from the residue by crystallization from petroleum ether.

izer temperature of 150°C, and a carrier-gas (N_2) flow rate of 40 ml/min with a flame-ionization detector (see Table 1).

Effect of Various Catalysts of the Alkaline Type on the Thermolysis of the Azine of Methyl Benzyl Ketone. A 4-g (0.015 mole) sample of the azine was subjected to thermolysis in the presence of 0.003 mole of the catalyst. The catalyst was then removed from the reaction mixture, and the latter was chromatographed under the conditions indicated above. The pyrrole/pyrazole ratios in all of the chromatographed reaction mixtures were calculated with allowance for the coefficients of sensitivity of the detector to the given compounds, which were 1 and 0.57, respectively (Table 2).

Dependence of the Thermolysis of the Azines of Benzyl Alkyl Ketones on the Length of the Carbon Chain of the Alkyl Substituent. A 0.03-mole sample of the azine was subjected to thermolysis in the presence of 0.006 mole of sodium hydride. The quantitative ratio of the principal thermolysis products was determined by GLC (Table 1). The conditions for GLC of the products of thermolysis of azines Ia-c were similar to those described above, and the products of thermolysis of azine Ie were analyzed with a G-800 chromatograph [with a catharometer, column III, a column temperature of 240°C, a vaporizer temperature of 320°C, and a carrier-gas (H_2) flow rate of 40 ml/min].

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INDOLIZINES. 6.* RELATIVE REACTIVITIES OF ISOMERIC 6-, 7-, AND 8-ETHOXYCARBONYLINDOLIZINE DERIVATIVES

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G. G. Dvoryantseva, E. E. Mikhlina,
and L. N. Yakhontov

UDC 547.759.4

The kinetics of the alkaline hydrolysis of 2-phenyl-6-, -7-, and -8-ethoxycarbonylindolizines were studied. The rate constants for the hydrolysis of these compounds and the indexes of the dissociation constants of 2-phenylindolizine-6-, -7-, and -8-carboxylic acids were determined by spectrophotometry. The indexes of the electronic structures and reactivities of 2-methyl-6-, -7-, and -8-ethoxycarbonylindolizines were calculated from theory.

In our preceding communications of this series [1-5] we described the syntheses of isomeric 6-, 7-, and 8-ethoxycarbonyl-2-methyl(aryl)indolizines and a qualitative study of the reactivities these compounds in some electrophilic substitution processes and in reactions with nucleophilic reagents. From the point of view of a study of the mutual effect of the pyrrole and pyridine rings in condensed systems and of the reaction of the indolizine

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*See [1] for Communication [5].
†Deceased.

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