MECHANISM OF FISCHER REACTION. DEPENDENCE OF THERMAL INDOLIZATION OF CYCLOHEXANONE ARYLHYDRAZONES ON NATURE OF SUBSTITUENT IN THE BENZENE RING

N. M. Przheval'skii, L. Yu. Kostromina,
and I. I. Grandberg

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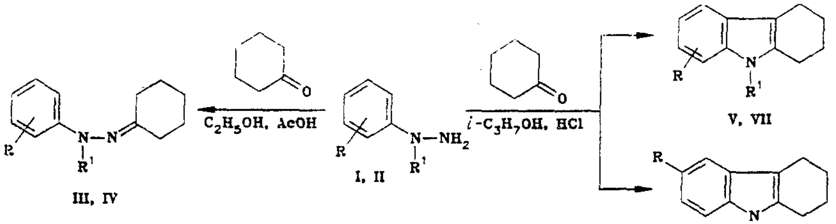
The kinetics of the Fischer thermal indolization of monosubstituted cyclohexanone arylhydrazones was studied by the spectrophotometric method. The enthalpy and entropy of activation of the reaction were calculated. The data obtained were interpreted in terms of a consistent mechanism of formation of a carbon-carbon bond (the [3,3]-sigmatropic shift). It was found that the influence of the electronic factors on the rate of the sigmatropic rearrangement is inappreciable.

The present work is a continuation of studies on the influence of electronic factors, nature of solvent and acidity of medium on the rate of the Fischer reaction [1-3]. Up until now, the influence of substituents on the course of the Fischer reaction could not always be satisfactorily explained, because of the drawbacks of the approach to the mechanism of this process from the point of view of electrophilic substitution, as well of absence of a sufficient experimental data, especially on thermal indolization [4].

As known [2, 5], the low sensitivity of consistent processes (in particular, of [3,3]-sigmatropic shift) to the effects of substituents is one of the criteria for the difference between these processes and stepwise processes (for example, S_E).

We have already shown [2, 3] that the inappreciable influence of alkyl groups and halogen atoms (R = p- and m-CH_3, p- and m-Cl) on the rate of indolization of arylhydrazones III, IV, correlates with the mechanism of the [3,3]-sigmatropic shift at the stage of formation of a carbon-carbon bond in the Fischer reaction.

We found it necessary to broaden the range of the systems studied, and therefore investigated the behavior of cyclohexanone arylhydrazones, containing electron-acceptor substituents (CN, $COOC_2H_5$, NO_2) and also Br and the OCH_3 group in the benzene ring, in the thermal Fischer reaction. These compounds and tetrahydrocarbazoles V-VIII were synthesized according to the following scheme



I, III, V, VI R^1=H; II, IV, VII, VIII R^1=CH_3

The kinetics of the thermal indolization of hydrazones III was studied spectrophotometrically in the temperature range of 110-150°C in ethylene glycol. The experimental data are reported in Table 1 (for the sake of convenience in the discussion, the data on the rates of rearrangements of arylhydrazones IIIa-e containing the CH_3 and Cl groups are also used). The following conclusions can be made from these data (Table 1).

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TABLE 1. Kinetic Parameters of Thermal Rearrangement of Cyclohexanone Arylhydrazones III*

Compound	R	Rate constants, $k \cdot 10^5$, sec^{-1}			Acceleration factor $f = k_R/k_H$
		150° C	130° C	110° C	
III a	H	25,1	7,9	2.5	1
III b	3-CH_3	43,7	15,4	5.6	1,7—2,3
III c	4-CH_3	50,1	17,8	6,3	2,0—2,5
III d	3-Cl	12,6	3,5	0,9	0,5—0,3
III e	4-Cl	17,8	5,0	1,3	0,7—0,3
III f	3-OCH_3	13,7	3,9	0,9	0,5—0,3
III g	4-OCH_3 †	—	—	—	—
III h	4-Br	9,0	2,2	0,4	0,4—0,08
III i	4-$COOC_2H_5$	2,5	0,4	0,06	0,1—0,02
III j	4-CN	1,3	0,2	0,02	0,05—0,01
III k	4-NO_2		Very slowly		

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*For compounds IIIa-e, the data of [3], and for IIIf-k the data of the present investigation are given.

†See Table 2.

TABLE 2. Kinetic Parameters of Rearrangement of Cyclohexanone Methoxyphenylhydrazones (ethylene glycol)

Compound*	Rate constants, $k \cdot 10^5$, sec^{-1}				Acceleration factor
	130 °C	110 °C	80 °C	60 °C	
	Thermal reaction				
IVa	56,2	20,0	—	—	2,5—3,3
IVc	20,9	7,1	—	—	1
	In presence of H_2SO_4 †				
IVa	—	794,3	167,8	50,1	14,1—20,5
IVc	—	56,2	10,0	2,5	1
IIb + cyclohexanone		482,8 (at 20 °C)			
Ig + cyclohexanone		44,9 (at 40 °C)			

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*For IVa R = 3-OCH_3, for IVc R = H, according to data in [1, 2].

†The concentration of the acid is 2 M per mole of hydrazone.

1. In general, the thermal indolization accelerates when electron-donor substituents are introduced into the rearranging molecule, and is inhibited when electron-acceptor groups are introduced. The acceleration factor for hydrazone IIIc (R = 4-CH_3) is equal to 2.0-2.5 [3], for hydrazones IIIi (R = 4-$COOC_2H_5$) and for IIIj (R = 4-CH) – 0.1 and 0.01, respectively.

2. The rates of the thermal rearrangement of m- and p-substituted arylhydrazones are similar, although a somewhat higher reactivity is always observed for the p-isomers (see the IIIb,c and IIId,e pairs Table 1).

3. The maximal ratio of the rate constants does not exceed 60-100 (except in the case of hydrazone IIIk, R = 4-NO_2, for which the rate could not be measured in the temperature range studied), which indicates a consistent mechanism of the rearrangement. Despite the fact that a similar influence of the substituents should be expected for the electrophilic (stepwise) mechanism of the formation of the C–C bond also, the latter is less probable, since in this case the ratio between the rate constants of the reaction of the compounds with the donor and acceptor groups reaches several orders of magnitude [5].

The data in Table 1 show that arylhydrazone IIIf, containing a methoxy group at the 3-position of the benzene ring, rearranges more slowly than the unsubstituted hydrazone IIIa (this agrees with [6, 7]). However, on transition to a hydrazone with a methyl group at the α-nitrogen atom, the process sharply accelerates (Table 2). Under the conditions of the thermal process, and also in the presence of sulfuric acid, the cyclohexanone N-methyl-m-

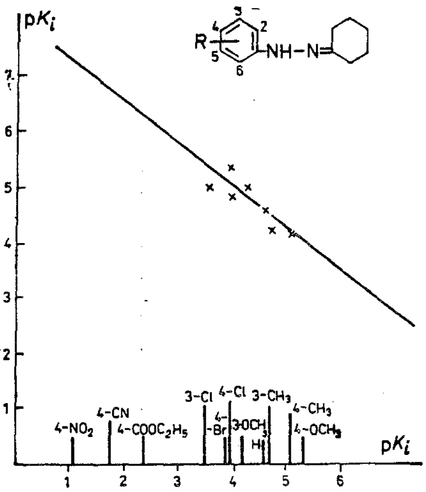

Fig. 1. Logarithmic dependence of rate constant of thermal rearrangements (pK = −log K) of cyclohexanone arylhydrazones on ionization constant (pK_a) of the corresponding substituted anilines at 100°C. $y = -0.74x + 7.93$; $r = 0.97$; $S = 1.07$.

methoxyphenylhydrazone IVa converts into carbazoles VIIa,b more rapidly than does the unsubstituted analog (Table 2).

Cyclohexanone p-methoxyphenylhydrazones cyclize at the highest rate (compared with unsubstituted aryl hydrazones).*

We should note that the indolization rate constant of hydrazone IVb could be measured only at room temperature (the rate of this process had not been recorded before [6]).

One of the possible explanations for the influence of the electronic factors on the rate of the rearrangement of cyclohexanone arylhydrazones is based on the difference in the basicity of the corresponding anilines. Already in [8] a relationship was noted between the rate of indolization of arylhydrazones in the acid medium and the basicity of the corresponding aniline. However, no quantitative dependence was established. We tried to find such a relationship for the Fischer reaction. We believe that it is justified to compare the rate of the rearrangement of cyclohexanone arylhydrazones with the basicity of the corresponding arylamine, since, irrespective of the nature of the radical in the benzene ring, these compounds differ from each other while containing one and the same cyclohexyliminium fragment, and in the series studied the additivity rule is retained. The determination of pK_a of arylhydrazones is complicated by the occurrence of the indolization reaction, while in the arylhydrazones there are two protonation centers, which hinders the evaluation of the ionization constants [9].

The literature data on the ionization constants of p- and m-substituted anilines [10, 11] were used to find a satisfactory correlation [$r = 0.97$ (110°C) and $r = 0.98$ (150°C)] between the pK_a and the logarithms of rate constants ($-\log k = pK_i$) of the rearrangement of hydrazones III (Fig. 1). The mean standard deviation (s) was 1.07 (110°C, 150°C), and the standard error of calculations (c) was equal to 0.18 (110°C) and 0.11 (150°C).

The observed correlation $pK_i = f(pK_a)$ shows that the rate of the thermal reaction is higher the more basic is the corresponding arylamine (Fig. 1). It is thus possible to explain the fact of the retardation of the rate of indolization due to the OCH_3 group (hydrazone IIIf), compared with the rate of indolization of unsubstituted hydrazone (IIIa), and also the increase in the reaction rate for compounds with p-substituents in the benzene ring,

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*Cyclohexanone p-methoxyphenylhydrazones IIIg and IVb are extremely unstable, and therefore the rate of the acid-catalyzed indolization during the reaction of arylhydrazines Ig and IIb with cyclohexanone (without isolation of hydrazones IIIg and IVb) were measured. This change in conditions is justified, since it was shown in [8] that the rate constants of the acid-catalyzed rearrangements of arylhydrazones and the arylhydrazine-carbonyl compound systems are practically the same.

TABLE 3. Physicochemical Characteristics of Cyclohexanone Arylhydrazones III, IV

Compound	R	Mp, °C	R_f (silufol benzene–ether, 5:1)	Found, %		Empirical formula	Calc., %		Yield, %
				C	H		C	H	
IIIf	OCH_3	Oil	0,67	71,8	8,1	$C_{13}H_{18}N_2O$	71,5	8,3	94
IIIh	4-Br	62—62 (hexane)	0,77	53,6	5,5	$C_{12}H_{15}BrN_2$	53,9	5,6	90
IIIi	$4\text{-}COOC_2H_5$	107—108 (hexane)	0,44	69,3	7,9	$C_{15}H_{20}N_2O_2$	69,2	7,7	85
IIIj	4-CN	181—182 (methanol)	0,43	73,6	7,2	$C_{13}H_{15}N_3$	73,2	7,1	95
IV	$3\text{-}OCH_3$	Oil	0,37	72,3	8,7	$C_{14}H_{20}N_2O$	72,4	8,7	68

TABLE 4. Spectral Characteristics of Cyclohexanone Arylhydrazones III, IV

Compound	R	UV spectrum (ethylene glycol) λ_{max}, nm (log ε)	IR spectrum, cm^{-1} (N—N, N=C)	PMR spectrum, δ, ppm
IIIf*	$3\text{-}OCH_3$	274 (4,19)	1500, 1620	1,65 and 2,25 [10H, m, $(CH_2)_5$]; 3,68 (3H, s, $3\text{-}OCH_3$); 6,26 (1H, dd, 6-H, $J_{56}=8{,}2$, $J_{46}=J_{26}=2{,}2$ Hz); 6,44 (1H, dd, 4-H, $J_{45}=8{,}2$, $J_{24}=J_{46}=2{,}2$ Hz.); 6,58 (1H, t. 2-H); 6,99 (1H, t, 5-H); 7,13 (1H, s NH)
IIIh	4-Br	284 (4,44)	1500, 1600	1,63 and 2,25 [10H, m, $(CH_2)_5$]; 6,84 (2H, d, 3-and 5-H, $J_{23}=J_{56}=9{,}0$ Hz); 7,26 (2H, d, 2 and 6-H); 7,57 (1H, s, NH)
IIIi	$4\text{-}COOC_2H_5$	231, (3,81), 324 (4,52)	1520, 1605	1,36 (t); 4,31 (5H, q, OC_2H_5, $J=7{,}0$ Hz); 1,65 and 2,30 [10H, m, $(CH_2)_5$]; 7,01 (2H, dd, 3- and 5-H, $J_{23}=J_{56}=8{,}9$, $J_{35}=J_{26}=2{,}8$ Hz); 7,91 (2H, dd, 2- and 6-H); 7,51 (1H, br.s NH)
IIIj	4-CN	220pl (4,07), 250 (4,51)	1510, 1603	1,73 and 2,38 [10H, m, $(CH_2)_5$]; 7,09 (2H, d, 3-and 5-H, $J_{23}=J_{56}=8{,}6$ Hz); 7,54 (2H, d, 2-and 6-H)
IIIk	$4\text{-}NO_2$	255 (4,29)	—	1,69 and 2,36 [10H, m, $(CH_2)_5$]; 7,00 (2H, d, 3- and 5-H, $J_{23}=J_{56}=8{,}4$ Hz); 8,08 (2H, d, 2 and 6-H); 7,71 (1H, br. s, NH)
IV	$3\text{-}OCH_3$	255 (4,14), 293 (3,81)	1500, 1610	1,68a and 2,46 [10H, m $(CH_2)_5$]; 2,98 (3H, s N—CH_3); 3,78 (3H, s, $3\text{-}OCH_3$); 6,38—6,48 (3H, m, 2-, 4-, 6-H); 7,15 (1H, t 5-H, $J_{45}=J_{56}=8{,}0$ Hz)

*The spectrum of hydrazone IIIf was measured on a Bruker WM-250 spectrometer.

compared with that of m-substituted analogs [cf. pK_a 4.73 (R = $3\text{-}CH_3$) and pK_a 5.08 (R = $4\text{-}CH_3$)]. Moreover, the presence of the $pK_i = f(pK_a)$ correlation indicates a proton transfer during the reaction, which in turn confirms the necessity of an aryl $\rightleftarrows$ enhydrazine isomerization stage.

We also calculated the thermodynamic parameters of the indolization reaction.* For cyclohexanone arylhydrazones containing electron-acceptor groups, the enthalpy of activation $\Delta H^{\neq}$ (kcal/mole) has relatively low values: 23.0 (IIIh), 28.9 (IIIi), 31.2 (IIIj), while the entropies of activation $\Delta S^{\neq}$ (e.u.) for these compounds have fairly high negative values: −23.4; −11.8; −7.7, respectively. These regularities are retained also in the case of hydrazines with m-methoxy groups: $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are equal to 20.6 and −28.5 (IIIf), 14.0 and −39.2 (IVa, thermal reaction), 13.0 and −34.6 (IVa, acid-catalyzed reaction).

Our experimental data on the influence of substituents in the benzene ring on the rate of thermal indolization of cyclohexanone arylhydrazones supplement the investigations already carried out [12, 13], which showed that the substituent in the carbonyl fragment of enhydra-

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*The calculation was carried out for reactions, when the rate was measured at 110°C, and the error in the values of the parameters did not exceed 3%.

zines has little influence on the rate of their thermal [3,3]-sigmatropic rearrangement into indoles.

All these data and also the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values indicate that the stage of formation of the C–C bond in the Fischer reaction can be regarded as a sigmatropic [3,3]-shift.

EXPERIMENTAL

The PMR spectra were run on a Bruker WH-90 spectrometer (in $CDCl_3$), using TMS as internal standard. The IR spectra were obtained on a UR-20 spectrophotometer, and UV spectra on a Hitachi EPS-3T spectrophotometer. The kinetic data were obtained spectrophotometrically on the same apparatus. The method of carrying out the kinetic measurements has been described in [1]. The concentrations were calculated nomographically [14], and the rate constants according to a first order kinetic equation (error $\leq 5\%$). The purity of the initial amines was controlled by GLC. The solvents were purified by standard procedures.

The physical constants of the arylhydrazines and 1,2,3,4-tetrahydrocarbazoles synthesized correspond to the literature data. The physicochemical and spectral characteristics of the arylhydrazones are listed in Tables 3, 4.

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