LITERATURE CITED

1. D. Anderson and A. Hassner, Synthesis, No. 8, 483 (1975).
2. F. Fowler, Heterocycl. Chem., 13, 47 (1971).
3. H. Heimgartner, Isr. J. Chem., 21, 151 (1981).
4. H. Heimgartner, Chimia, 33, 111 (1979).
5. S. Chaloupka, P. Vittorelli, H. Heimgartner, K. Bernauer, and W. Oberhänsli, Helv. Chim. Acta, 60, 2476 (1977).
6. H. Link, K. Bernauer, S. Chaloupka, H. Heimgartner, and H. Schmid, Helv. Chim. Acta, 61, 2116 (1978).
7. H. Link, K. Bernauer, and J. J. Daly, Helv. Chim. Acta, 64, 49 (1981).
8. H. Link, Helv. Chim. Acta, 61, 2419 (1978).
9. P. Vittorelli, H. Heimgartner, H. Schmid, P. Hoet, and L. Chosez, Tetrahedron, 30, 3737 (1974).
10. J. A. Hyatt, J. Org. Chem., 46, 3953 (1981).
11. P. Chandrasekhar, H. Heimgartner, and H. Schmid, Helv. Chim. Acta, 60, 2270 (1977).
12. P. Cahndrasekhar, V. Schmid, R. Schmid, H. Heimgartner, and H. Schmid, Helv. Chim. Acta, 58, 1191 (1975).
13. M. Rens and L. Chosez, Tetrahedron Lett., No. 43, 3765 (1970).
14. P. Vittorelli, H. Heimgartner, H. Schmid, P. Hoet, and L. Chosez, Tetrahedron, 30, 3740 (1974).
15. M. B. Robin, F. A. Bovey, and H. Basch, in: The Chemistry of Amides, J. Zabisky, ed., Interscience, London—New York (1970), p. 7.

MECHANISM OF THE FISCHER REACTION. EFFECT OF ELECTRONIC FACTORS ON THE KINETICS OF THE REARRANGEMENT OF m-SUBSTITUTED CYCLOHEXANONE ARYLHYDRAZONES TO TETRAHYDROCARBAZOLES

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

UDC 547.759.1'556.8'594:541.127

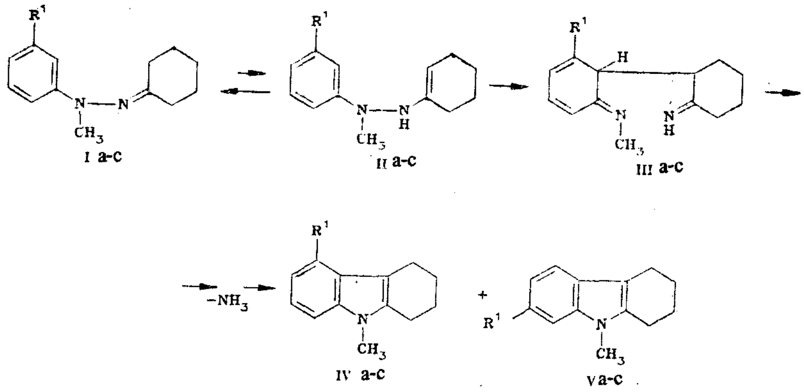
The kinetics of the thermal and acid-catalyzed Fischer indolization of m-substituted cyclohexanone arylhydrazones were studied. It was shown that substituents with different natures ($-CH_3$, $-Cl$) and the polarity of the solvent have little effect on the rate of the rearrangement. The results obtained were interpreted within the framework of a concerted mechanism for the formation of the carbon—carbon bond ([3,3]-sigmatropic rearrangement).

In a previous paper we reported the results of kinetic [in the case of cyclohexanone N-methylphenylhydrazone and N,N'-di-methyl-N-phenyl-N'-(1-cyclohexenyl)hydrazine] and quantum-chemical (for the model compound divinylhydrazine) investigations of the mechanism of the Fischer reaction [1]. It was shown that both the experimental data for the thermal and acid-catalyzed indolization of the indicated arylhydrazone and enehydrazine and theoretical calculations satisfactorily describe the mechanism in terms of the concerted formation of a carbon—carbon bond ([3,3]-sigmatropic rearrangement for step II → III in scheme 1). In addition, the data obtained from quantum-chemical calculations predicted an increase in the rate of the I → IV + V rearrangement when electron-donor substituents are introduced into the molecule undergoing cyclization and slowing down of the reaction when electron-acceptor substituents are present [1].

K. A. Timiryazev Moscow Agricultural Academy, Moscow 127550. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1207-1212, September, 1985. Original article submitted June 13, 1984.

0009-3122/85/2109-1002$09.50 © 1986 Plenum Publishing Corporation

Scheme 1



I—V a R^1=H; b R^1=CH_3; c R^1=Cl

Since a similar effect of substituents is also characteristic for an electrophilic (stepwise) mechanism for the formation of the C—C bond, a criterion that makes it possible to distinguish between these two mechanisms is the ratio of the rate constants for the indolization of hydrazones with donor and acceptor groups. In the case of a concerted mechanism this ratio ranges from 30 to 50, whereas it reaches several orders of magnitude for electrophilic substitution [2].

A great deal of literature data on the effect of substituents on the Fischer indolization of arylhydrazones is available; however, in the overwhelming majority of studies this effect was evaluated only on the basis of the percentage yields of the corresponding indoles [3-6; 7 (literature cited)]. The effect of substituents on the rate of the acid-catalyzed rearrangement of monosubstituted arylhydrazones of the I type to tetrahydrocarbazoles was examined in [8, 9]; however, the authors did not give an explanation of a number of contradictory results from a unified position. Let us also note that the conditions under which the reactions were carried out and the methods for the determination of the concentrations of the reacting substances used in [8, 9] differed appreciably, and this hinders the comparison and interpretation of the published data.

TABLE 1. Kinetic Parameters of the Fischer Reaction for Hydrazones Ia-c in Ethylene Glycol

Reaction conditions		Hydrazone	Reaction rate constants, $k \cdot 10^5$ sec^{-1}								Acceleration factor
			140°	130°	120°	110°	80°	60°	50°	40°	
Thermal		Ia	35,5	20,9	13,0	7,1	1,2				1
		Ib	79,4	44,7	28,2	17,8	3,2				2,2—2,7
		Ic	17,8	10,1	5,9	2,8	0,4				0,5—0,3
Acid-catalyzed*	H_2SO_4, 0,1 mole	Ia				44,7	7,9	2,0	0,9	0,4	1
		Ib				79,4	12,6	3,2	1,4	0,7	1,8
	H_2SO_4, 2 moles	Ia				56,2	10,0	2,5	1,1	0,6	1
		Ib				251,2	58,8	17,0	7,1	3,6	4,5—6,0
		Ic				39,8	6,3	1,4	0,6	0,3	0,7—0,5
	H_2SO_4, 20 moles	Ia					158,5	44,7	25,7	18,1	1
		Ib					562,3	199,5	125,9	70,8	3,5—3,9
	$(CH_3)_3CCOOH$, 2 moles	Ia			14,4	7,3	1,4	0,4			1
		Ib	112,2	70,8	44,7	25,9	4,5	1,1			3,1—2,8
CH_3ONa, 2 moles		Ia	50,1	28,2	17,8	8,9	1,5	0,4			1
		Ib	63,0	39,8	25,1	14,1	2,5	0,6			1,3—1,5
		Ic	10,0	5,6	3,2	1,6	0,2	0,04			0,2—0,1

---

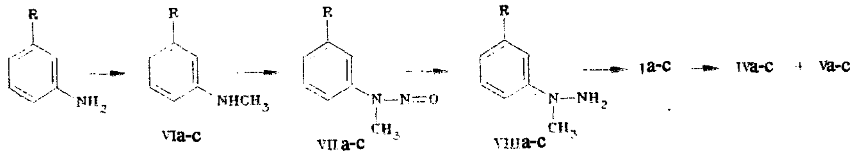
*The amount of acid or alkali in moles per mole of the hydrazone is given.

TABLE 2. Kinetic Parameters of the Fischer Reaction for Hydrazones Ia-c in Decane

Reaction conditions	Hydrazone	Reaction rate constants, $k \cdot 10^5$ sec^{-1}					Acceleration factor
		140°	130°	120°	110°	80°	
Thermal	Ia	31,6	17,8	13,8	6,3	1,1	1
	Ib	63,0	44,7	25,1	17,1	2,5	2—2,3
	Ic	2,2	1,0	0,4			0,07—0,03
$(CH_3)_3CCOOH$ (2 moles per mole of hydrazone I)	Ib	89,1	56,2	39,8	20,4	4,7	
	Ic	4,5	2,5	1,4	0,8	0,2	

In connection with the information set forth above, we undertook a systematic investigation of the effect of electronic factors on the rate of the Fischer reaction, for which we selected monosubstituted cyclohexanone arylhydrazones as model compounds. In this paper we present the results of a spectrophotometric study of the kinetics of the thermal and acid-catalyzed rearrangement of cyclohexanone N-methylphenylhydrazone (Ia), cyclohexanone N-methyl-N-(m-tolyl)hydrazone (Ib), and cyclohexanone N-methyl-N-(m-chloro-phenyl)hydrazone (Ic), which were synthesized via Scheme 2. The effects of the solvents, temperature, and acidity of the medium on the rate of indolization of hydrazones Ia-c were examined. The rate constants and enthalpies and entropies of activation of the process, as well as the acceleration factors as compared with the unsubstituted hydrazone, were calculated. The experimental data obtained are presented in Tables 1-3.

Scheme 2



I, IV—VIII a R=H; b R=CH3, c R=Cl

The rates of indolization of hydrazones Ia-c depend very little on the nature of the solvent over the temperature range from 80°C to 140°C under thermal conditions or in the presence of trimethylacetic acid (Tables 1 and 2). For example, the rate constants ($k \cdot 10^5$ sec^{-1}) for the thermal rearrangement of hydrazone Ia in ethylene glycol and in decane at 140°C are 79.4 and 63.0; in the presence of 2 moles of $(CH_3)_3CCOOH$ at the same temperature the rate constants for hydrazone Ib are 112 and 89, respectively. A somewhat greater difference in the reaction rates is observed for hydrazone Ic (at 140°C, 17.8 in ethylene glycol and 2.2 in decane).

It is apparent from the data in Tables 1 and 2 that the rates of all of the investigated acid-catalyzed reactions of hydrazones Ia-c are higher than the rates of the thermal transformations. This result is explained by the possibility of charge delocalization in the six-membered transition state in the case of realization of a charge-induced [3,3]-sigmatropic rearrangement [1]. A tendency for an increase in the reaction rate constants when the acid concentration is increased from 0.1 mole to 20 moles (per mole of the hydrazone) is also distinctly displayed.

In addition to this, the nature of the acid has a definite effect on the reaction rate. Thus the presence of 2 mmole of H_2SO_4 leads to a 10-fold to 20-fold increase in the rate of indolization of hydrazones Ia and Ib (at 80°C in ethylene glycol), whereas the weaker trimethylacetic acid accelerates the reaction by a factor of only 1.5-2 (hydrazones Ia and Ib, 80°C, ethylene glycol, Table 1) as compared with the thermal reaction. These data can be interpreted from the point of view of the reactivities of the intermediate enehydrazinium salts, the concentrations of which depend on the strength of the acid [1].

The thermal indolization (in ethylene glycol) of hydrazone Ib, which contains an electron-donor substituent (the CH_3 group) proceeds more rapidly under all of the investigated

TABLE 3. Thermodynamic Parameters of the Fischer Reaction for Hydrazones Ia-c

Thermodynamic parameter	Hydrazone	Ethylene glycol						Decane	
		thermal	H_2SO_4, 0,1 mole	H_2SO_4, 2 moles	H_2SO_4, 20 moles	$(CH_3)_3CCOOH$, 2 moles	CH_3ONa, 2 moles	thermal	$(CH_3)_3CCOOH$, 2 moles
Enthalpy of activation $\Delta H^{\neq}$ ± 0.2, kcal/mole	Ia	16,8	15,9	15,9	13,2	16,2	15,9	16,8	
	Ib	15,0	14,1	14,1	10,6	15,0	15,0	15,0	14,1
	Ic	18,6		16,8			18,6	25,6	16,8
Entropy of activation $\Delta S^{\neq}$, eu	Ia	−34,2±0,8	−32,9±0,6	−32,6±0,8	−34,6±0,5	−35,6±0,6	−36,1±0,8	−34,4±0,4	
	Ib	−37,1±0,8	−36,4±0,6	−34,1±0,4	−39,1±0,4	−36,3±0,4	−37,5±0,5	−37,2±0,3	−39,1±0,4
	Ic	−31,2±0,6		−30,8±0,3	−33,5±0,2		−32,3±0,6	−18,6±0,3	−38,6±0,5

temperature conditions than the indolization of of unsubstituted hydrazone Ia (for example, at 110°C acceleration factor $f_{110°} \sim 2.5$). The rearrangement of hydrazone Ic, which has a deactivating substituent (R^1 = Cl), is realized more slowly than in the case of hydrazone Ia ($f_{110°} \sim 0.4$). The f_{Ib}/f_{Ic} ratio shows that hydrazone Ib reacts six times faster than hydrazone Ic at 110°C in ethylene glycol. The same principle is manifested in a comparative analysis of the rate constants for the thermal rearrangement of hydrazones Ia-c in decane (Table 2). The maximum difference in the rates of formation of tetrahydrocarbazoles from hydrazones Ib and c (in decane) is observed for the thermal reaction at 120°C (f_{Ib}/f_{Ic} = 62).

The effect of electronic factors on the acid-catalyzed indolization of hydrazones Ia-c is basically similar to the effect observed for the thermal process. Thus hydrazone Ib undergoes rearrangement more rapidly in ethylene glycol at 80°C in the presence of 2 moles of H_2SO_4 ($f_{80°} \sim 5.9$), whereas hydrazone Ic undergoes rearrangement more slowly ($f_{80°} \sim 0.6$) than unsubstituted hydrazone Ia. In this case the Fischer proceeds nine times faster for hydrazone Ib than for hydrazone Ic. Similar data on the effect of substituents on the rate constants for the rearrangement of monosubstituted cyclohexanone arylhydrazones in the presence of a large excess of acid in aqueous methanol solution were presented in [9].

A study of the rearrangement of arylhydrazones Ia-c in ethylene glycol in the presence of 2 moles of CH_3ONa with respect to 1 mole of the hydrazone showed that the alkaline agent does not have a substantial effect on the rate, which remains close to the rate of the thermal reaction. Thus the rate constants ($k \cdot 10^5$ sec^{-1}) for hydrazone Ia at 110°C are 7.1 (for the thermal process) and 8.9 (in the presence of CH_3ONa); the corresponding values for hydrazone Ib are 17.8 and 14.1, as compared with 2.8 and 1.6, respectively, for hydrazone Ic.

The thermodynamic parameters (particularly the $\Delta S^{\neq}$ values) for the indolization of hydrazones Ia-c are also an argument in favor of the concept of the concerted character of the step involving the formation of the C—C bond in the Fischer reaction. It is apparent from the data in Table 3 that the entropies of activation have rather high negative values, viz., from —19 eu to —39 eu, whereas the enthalpies of activation do not exceed 25 kcal/mole.

Thus the data obtained on the effect of electronic factors on the rates of indolization of hydrazones Ia-c via the Fischer method indicate that the principal step in this reaction is realized via a mechanism involving [3, 3]-sigmatropic rearrangement.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Bruker WH-90 MHz spectrometer with tetramethylsilane (TMS) as the internal standard. The IR spectra were obtained with a UR-20 spectrometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in a benzene—ether system (5:1) with development by iodine. The UV spectra of solutions in isopropyl alcohol, ethylene glycol, and decane were recorded with a Hitachi EPS-3T spectrophotometer. The kinetic data were obtained by spectrometry with the same apparatus. The method used to make the kinetic measurements was described in [1].

The concentrations were calculated by a nomographic method [10], and the rate constants were calculated from the first-order kinetic equation (the error was ≤ 3%). The purity of all of the starting amines was monitored by gas-liquid chromatography (GLC). The solvents for the kinetic measurements were purified by standard methods.

N-Methyl-m-toluidine (VIb). This compound, with bp 63-65°C (2 mm) (bp 206-207° [12]), was obtained from the p-toluenesulfonamide derivative of m-toluidine by methylation with $(CH_3)_2SO_4$.

N-Methyl-m-chloroaniline (VIc). This compound, with bp 234-235°C (by 235°C [13]), was similarly obtained from m-chloroaniline [11].

N-Methyl-N-nitroso-m-toluidine (VIIb). This compound, with bp 104-106°C (2.5 mm) and R_f 0.78, was obtained in 88% yield from 30 g (250 mm) of amine VIb by the method in [14]. PMR spectrum: 2.29 (s, 3H, m-CH_3), 3.28 (s, 3H, N—CH_3), and 7.04-7.24 ppm (m, $4H_{arom}$). IR spectrum (film): 1480 cm^{-1} (N=O). UV spectrum, λ_{max} (log ε): 212 (4.07) and 275 nm (3.86). Found: C 63.8; H 6.8%. $C_8H_{10}N_2O$. Calculated C 63.5; H 6.7%.

N-Methyl-N-nitroso-m-chloroaniline (VIIc). This compound with mp 33-34°C (from ether) and R_f 0.76, was obtained in 75% yield from 35 g (250 mm) of amine VIc by the method in [14]. PMR spectrum: 3.41 (s, 3H, N—CH_3) and 7.27-7.60 ppm (m, $4H_{arom}$). IR spectrum (KBr): 1480 cm^{-1} (N=O). UV spectrum, λ_{max} (log ε): 217 (4.20) and 275 nm (3.85). Found: C 49.5; H 4.1%. $C_7H_7ClN_2O$. Calculated: C 49.1; H 4.1%.

N-Methyl-N-(m-tolyl)hydrazine (VIIIb). This compound, with bp 83-85°C (2 mm) and R_f 0.30, was obtained in 43% yield from 10 g (67 mmole) of VIIb by the method in [15]. IR spectrum (film): 1500 (N–N) and 1610 and 3350 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 252 (3.96) and 292 nm (sh) (3.23). Found: C 69.8; H 8.6%. $C_8H_{12}N_2$. Calculated: C 70.4; H 8.8%.

N-Methyl-N-(m-chlorophenyl)hydrazine (VIIIc). This compound, with bp 95-97°C (2.5 mm) and R_f 0.45, was similarly obtained in 44% yield from 15 g (88 mmole) of VIIc. IR spectrum (film): 1500 (N–N) and 1600 and 3360 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 256 (4.13) and 290 nm (sh) (3.47). Found: C 53.7; H 5.6%. $C_7H_9ClN_2$. Calculated: C 53.9; H 5.8%.

Cyclohexanone N-Methylphenylhydrazone (Ia). This compound was obtained from N-methylphenylhydrazine (VIIIa) and cyclohexanone via the method in [1]. UV spectrum (ethylene glycol), λ_{max} (log ε): 252 (3.94) and 290 (3.43).

Cyclohexanone N-Methyl-N-(m-tolyl)hydrazone (Ib). A solution of 1.5 g (15.4 mmole) of cyclohexanone in 5 ml of 30% ethanol was added dropwise to a solution of 2.0 g (14.8 mmole) of hydrazine VIIIb in 12 ml of 50% acetic acid. After 10 min, the reaction mixture was extracted with ether, and the extract was washed twice (two 25-ml portions) with 10% acetic acid and then with water. It was then dried with $MgSO_4$, the solvent was removed by distillation, and the substance was purified with a column (35 cm by 2 cm) packed with activity II Al_2O_3 by elution with benzene to give a product with R_f 0.45 in 72% yield. PMR spectrum: 1.69 (m, 6H), 2.31 (s, 3H, m-CH_3), 2.46 (m, 4H), 2.97 (s, 3H, N–CH_3), 6.60-6.70 (m, 2-, 4-, and 6-H_{arom}), and 7.13 ppm (t, $J_{45} = J_{56} = 9$ Hz, 5-H). IR spectrum (film): 1500 (N–N and 1640 cm^{-1} (N=C). UV spectrum, λ_{max} (log ε): 254 (4.16) and 292 nm (3.68). Found: C 77.9; H 9.5%. $C_{14}H_{20}N_2$. Calculated: C 77.7; H 9.3%.

Cyclohexanone N-Methyl-N-(m-chlorophenyl)hydrazone (Ic). This compound, with R_f 0.59, was obtained in 78% yield from 5 g (34 mmole) of hydrazine VIIIc by a method similar to that used to prepare hydrazone Ib. PMR spectrum: 1.69 (m, 6H), 2.50 (m, 4H), 2.93 (s, 3H, N–CH_3), and 6.65-713 ppm (m, 4H_{arom}). IR spectrum (film): 1490 (N–N) and 1640 cm^{-1} (N=C). UV spectrum (ethylene glycol), λ_{max} (log ε): 258 (4.09) and 290 nm (3.74). Found: N 11.8%. $C_{13}H_{17}ClN_2$. Calculated: N 11.8%.

9-Methyl-1,2,3,4-tetrahydrocarbazole (IVa). This compound, with mp 50-51°C (from 60% ethanol) (mp 50-51°C [16]), was obtained from hydrazine VIIIa and cyclohexanone by the method in [16]. UV spectrum (ethylene glycol), λ_{max} (log ε): 234 (4.60) and 288 nm (3.87).

5,9- and 7,9-Dimethyl-1,2,3,4-tetrahydrocarbazoles (IVb and Vb). These compounds were obtained from 2.27 g (17 mmole) of hydrazine VIIIb and cyclohexanone via the general method of the Fischer reaction in isopropyl alcohol saturated with dry HCl. The mixture of isomers, with R_f 0.73 [petroleum ether–ether (5:1)], was obtained in 85% yield. IR spectrum of the mixture (KBr): 1380 cm^{-1} (C–N). UV spectrum of the mixture, λ_{max} (log ε): 234 (4.68), 288 (3.96), and 297 nm (sh) (3.92). Found: C 84.3; H 8.6%. $C_{14}H_{17}N$. Calculated: C 84.4; H 8.6%.

7,9-Dimethyl-1,2,3,4-tetrahydrocarbazole. This compound had mp 101-102°C (isolated from the mixture by three crystallizations from methanol). PMR spectrum of Vb: 1.87 (m, 4H), 2.47 (s, 3H, 7-CH_3), 2.67 (m, 4H), 3.57 (s, 3H, N–CH_3), 6.88 (d, 6-H, $J_{56} = 8.1$ Hz), 7.03 (s, 8-H), and 7.34 ppm (d, 5-H, $J_{56} = 8.1$ Hz). UV spectrum of Vb, λ_{max} (log ε): 234 (4.70), 288 (3.96), and 297 nm (sh) (3.90). According to [17], this isomer had mp 102-104°C.

5-Chloro- and 7-Chloro-9-methyl-1,2,3,4-tetrahydrocarbazoles (IVc and Vc). These compounds were obtained from 2.87 g (18 mmole) of hydrazine VIIIx and cyclohexanone by a method similar to that used to prepare carbazoles IVb and Vb. The mixture of isomers, with mp 72-77°C (from methanol) and R_f 0.61 [petroleum ether–ether (5:1)], was obtained in 89% yield. PMR spectrum: 1.87 (m), 2.68 (m), 3.08 (m, 1-H–4-H protons), 3.56 (s, N–CH_3), 3.57 (s, N–CH_3), and 6.95-7.39 ppm (m, H_{arom}). IR spectrum of the mixture (KBr): 1380 cm^{-1} (C–N). UV spectrum of the mixture (ethylene glycol), λ_{max} (log ε): 238 (4.56), 294 (3.82), and 300 nm (sh) (3.79). Found: C 71.3; H 6.4%. $C_{13}H_{14}ClN$. Calculated: C 71.1; H 6.4%.

LITERATURE CITED

1. N. M. Przheval'skii, M. B. Kletskii, I. I. Grandberg, and L. Yu. Kostromina, Khim. Geterotsikl. Soedin., No. 6, 779 (1985).

2. T. Gilchrist and R. C. Storr, Organic Reactions and Orbital Symmetry, Cambridge University Press (1972).
3. H. Robinson, Usp. Khim., 40, 1434 (1971).
4. Yu. P. Kitaev and T. V. Troepol'skaya, Khim. Geterotsikl. Soedin., No. 8, 1011 (1978).
5. I. I. Grandberg, Zh. Org. Khim., 19, 2439 (1983).
6. I. I. Grandberg and V. I. Sorokin, Usp. Khim., 43, 266 (1974).
7. N. N. Suvorov, V. N. Shkil'kova, and N. Ya. Podkhalyuzina, Zh. Org. Khim., 19, 2420 (1983).
8. P. I. Sheltus, "Kinetic investigations of the Fischer indole synthesis," Dissertation, Leiden (1959).
9. R. N. Elgersma, "Some aspects of the Fischer indole synthesis," Dissertation, Rotterdam (1969).
10. I. Ya. Bershtein and Yu. L. Kaminskii, Spectrophotometric Analysis in Organic Chemistry [in Russian], Khimiya, Leningrad (1975), p. 75.
11. Houben-Weyl, Methoden der Organischen Chemie, Vol. 4, Georg Thieme Verlag, Stuttgart.
12. B. Roberts and H. Vogt, Organic Syntheses, Vol. 4, Wiley, New York (1963), p. 420.
13. I. V. Braun and O. Kruber, Chem. Ber., 46, 3474 (1913).
14. R. O. Matevosyan, I. Ya. Postovskii, and A. K. Chirkov, Zh. Obshch. Khim., 29, 858 (1959).
15. R. H. Poirier and F. Benington, J. Am. Chem. Soc., 74, 3192 (1952).
16. P. Schiess and A. Greeder, Helv. Chim. Acta, 57, 2643 (1974).
17. N. F. Kucherova, V. P. Evdakov, and N. K. Kochetkov, Zh. Obshch. Khim., 27, 1049 (1957).

REGIOSELECTIVITY OF THE REARRANGEMENT OF PROPIONIC ACID N,N-DIARYLHYDRAZIDES UNDER THE CONDITIONS OF THE KOST REACTION

V. N. Barinova, V. G. Voronin, V. P. Zhestkov,
and Yu. N. Portnov

UDC 547.751'293'298.61:541.124

The transformation of propionic acid N,N-diarylhydrazides with electron-donor and electron-acceptor substituents in the aromatic rings under the conditions of the Kost reaction was studied. The ratios of the resulting isomeric N-aryl-2-aminoindoles were determined.

The question of the mechanism of the formation of the new C—C bond — the fundamental step in the scheme of the formation of indoles via the Fischer method — still remains open to discussion. The concept of Grandberg, who proposed that this step be regarded as a [3, 3]-sigmatropic rearrangement in all processes involving the formation of indole systems, viz., the Fischer and Brunner syntheses and the Kost reaction [1, 2], is finding increasing confirmation. As direct evidence that the indicated reactions proceed through a step involving [3, 3]-sigmatropic rearrangement the authors cite data on the slight, from their point of view, effect of the electronic nature of the substituents in the Fischer rearrangement of unsymmetrical N,N-diarylhydrazones of symmetrical carbonyl compounds on the ratios of the resulting arylindoles [3, 4]. The consideration of the conversion of arylacylhydrazines to 2-aminoindoles via the Kost reaction from these positions has not been experimentally confirmed.

The aim of the present research was to study the direction of the indolization of acid N,N-diarylhydrazides with different substituents in the aromatic rings and to investigate their relative orienting abilities with respect to this process. As the subjects of the investigation we selected propionic acid N,N-diarylhydrazides Ia-d, which contain, in the para

---

Branch of the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Kupavna 142450. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1213-1217, September, 1985. Original article submitted January 29, 1985.

0009-3122/85/2109-1008$09.50 © 1986 Plenum Publishing Corporation