The aqueous solution was acidified to pH 3 with 5% HCl, and the precipitate was removed by filtration, washed with water until the wash waters were neutral, and crystallized from ethanol. Data on V, VI, and XX are presented in Table 5.

3-Indolylmethylmalonic Acid N-Phenylamide (VII). A 1.5-g sample of Raney nickel was added to a solution of 1.81 g (0.06 mole) of III in 300 ml of 0.05% alcohol solution of NaOH, and the mixture was hydrogenated until it became completely colorless (3.5-4 h). The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The resulting precipitate was removed by filtration, dissolved in the minimum amount of hot ethanol, and reprecipitated by the addition of water.

Data on VII are presented in Table 5.

LITERATURE CITED

- B. L. Moldaver and M. E. Aronzon, Khim. Geterotsikl. Soedin., No. 6, 804 (1970). 1.
- B. L. Moldaver, V. V. Zverev, M. P. Papirnik, M. E. Aronzon, and Yu. P. Kitaev, Khim. 2. Geterotsikl. Soedin., No. 3, 403 (1974).
- 0. Ya. Neiland and G. Ya. Vanag, Usp. Khim., <u>34</u>, 436 (1959). 3.
- P. Schuster, Öster. Chem. Zeit, <u>68</u>, 252 (1967). 4.
- N. N. Suvorov, V. S. Velezheva, and V. V. Vampilova, Khim. Geterotsikl. Soedin., No. 5, 5. 646 (1974).
- V. S. Velezheva, Yu. V. Erofeev, and N. N. Suvorov, Zh. Org. Khim., 9, 185 (1973). 6.
- P. Schuster, O. E. Polansky, and D. E. Wessely, Monatsh., 95, 53 (1964). 7.
- F. J. Kunz, P. Margaretha, and O. E. Polansky, Chimia, 24, 165 (1970). 8.

INDOLES

L.* m-MONOSUBSTITUTED DIARYLHYDRAZINES IN THE FISCHER INDOLE

SYNTHESIS (REACTION MECHANISM)

N. M. Przheval'skii, I. I. Grandberg, N. A. Klyuev, and A. B. Belikov

UDC 547.759.2.3:543.51

The cyclization of cyclohexanone m-monosubstituted α , α -diphenylhydrazones under the conditions of the Fischer reaction was studied. It is shown that in the case of both donor $(R = OCH_3)$ and acceptor (R = C1) substituents all three possible isomeric tetrahydrocarbazoles are formed as a result of the reaction. These data constituted an unambiguous confirmation of the concept of the occurrence of the principal step in the Fischer reaction (the step involving the formation of a carbon-carbon bond) via a sigmatropic [3,3]-rearrangement mechanism. The ratios of the tetrahydrocarbazoles in the reaction mixtures under various cyclization conditions were determined independently by PMR, IR, and mass spectrometry and gas-liquid chromatography. The structures of the products were proved by the set of spectral characteristics and by alternative synthesis.

In a previous communication we demonstrated that isomeric tetrahydrocarbazoles are formed in close ratios in the Fischer cyclization of cyclohexanone p-monosubstituted α , α diphenylhydrazones. These data served as a confirmation of our previously expressed concept of the occurrence of a step involving the formation of a carbon-carbon bond in the Fischer reaction via a [3,3]-sigmatropic rearrangement mechanism [2]. However, one could raise an objection regarding the relatively weak effect of substituents on the relative rates of electrophilic substitution in the meta position.

*See [1] for communication XLIX.

K. A. Timiryazev Moscow Agricultural Academy, Moscow 125008. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1349-1355, October, 1978. Original article submitted October 24, 1977.



Fig. 1. PMR spectrum (CC14) of a mixture of isomers IIa-IVa (experiment No. 1).

In the present research we investigated the cyclization of cyclohexanone m-monosubstituted diphenylhydrazones, in which a donor ($R = OCH_3$) or acceptor (R = C1) substituent in the m-substituted diarylhydrazone is located in the ortho or para position relative to the point of attack.



 $I-IV = R = OCH_3$; b = CI

In the case of the realization of an electrophilic mechanism for the Fischer reaction only isomers IIa and IIIa ($R = OCH_3$) or IVb (R = Cl) should have been formed, since the rate of electrophilic substitution in the benzene ring increases three to four orders of magnitude when there is an o- or p-OCH₃ group present and decreases by the same degree when there is a chlorine atom in these positions [1].

In the case of a synchronous mechanism the reaction product should contain comparable amounts of all three possible isomers [1].

The data in Table 1 show that when there is a substituent ($R = OCH_3$) in the benzene ring, the ratio of the sum of tetrahydrocarbazoles IIa and IIIa to isomer IVa is 49:51 (the average value of experiments 1-3 in Table 1). However, if R = C1, the analogous (IIb + IIIb)/IVb ratio is 26:74.

Thus the formation of tetrahydrocarbazoles IIa, b-IVa, b in close ratios under various experimental conditions (the quantitative ratios were determined independently by PMR, IR, and mass spectrometry and GLC) indicates that the principal step in the Fischer reaction proceeds via a sigmatropic [3,3]-rearrangement mechanism.

The characteristic PMR spectrum of the products of cyclization of cyclohexanone m-methoxydiphenylhydrazone in isopropyl alcohol saturated with dry HCl is shown in Fig. 1. The assignment of the signals was made on the basis of the spectra of the individual isomers (see the experimental section) and the spectrum of a model artificial mixture of isomers IIa, IIIa, and IVa in a ratio of 3:2:1. The PMR spectra of a mixture of IIa-IVa was analyzed similarly.

The starting m-monosubstituted diarylhydrazines were synthesized via the following scheme:



. 1. Quantitative Katios of the Kesulting Isomeric Tetrahydrocarbazoles (IIa, b-IVa, b)	Ratio of isomers IIa, b + IIIa, b to IVa, b	R=CI	yíeld of the sum of iso- mers, %	20	20	40
			av. of three methods	17:83	27:73	35 : 65
			mass spec- trometry	(6+14):80	(15+25):60	(37+5):58
			IR spec- troscopy	(7+8):85	(8+11):81	(7+.15) : 78
			GLC	17:83	23:77	32:68
		R=OCH ₃	yield of the sum of iso- mers, %	85	06	48
			av. of three methods	.43:57	52:48	53:47
			mass spec- trometry	(14+27):59	(17+20):63	(15+30) : 55
			IR spec- troscopy	(23+24):53	(30+34):36	(12+44):44
			PMR	(20+32):48	(23+32):45	(19+40):41
	Reaction conditions			<i>i-C</i> ₃ H ₇ OH, saturated with HCl	<i>i</i> -C ₃ H ₇ OH + H ₂ SO ₄ (¹ mole)	Diethylene glycol (thermally)
		Fvnt	No.		7	en en

ε F 4 ć TABLE 1



Fig. 2. Aromatic portion of the PMR spectra of IXa and Xb.

Tetrahydrocarbazoles IIa, b-IVa, b were obtained by alternative synthesis:



II-IV a, VIII-X a $R = OCH_3$; b R = CI

Two isomeric tetrahydrocarbazoles IXa, b and Xa, b, which we were able to separate, are formed in the reaction of cyclohexanone m-substituted arylhydrazones VIIIa, b under the conditions of the Fischer reaction.

The aromatic portions of the PMR spectra of IXa, b and Xa, b are ABC and ABX systems, respectively, and this makes it possible to clearly distinguish the isomeric pairs.

The conversion of carbazoles IXa, b and Xa, b to N-arylated derivatives was accomplished by means of the Ullmann reaction.

From the previously obtained mass spectra of individual isomers IIa, b-IVa, b we selected the specific ion peaks (or the ratios of the intensities of the peaks) that were used for the quantitative evaluation of the percentages of tetrahydrocarbazoles IIa, b-IVa, b in the reaction mixtures. The general criteria of the selection of the indicated ion peaks and the calculations of the number of components in the mixture were analogous to those presented in [1]. For additional monitoring the mixtures were also analyzed by means of calibration graphs constructed for each isomer (the graphs were the dependences of the intensity of the peak of a specific ion or the ratio of the intensities of the ion peaks on the sample weight). The reproducibility of the results by both methods was 10 relative %. We selected the following peaks as the analytical peaks in our examination of the fragmentation processes of the molecular ions (M^+) of IIa-IVa: m/e 204 and 273 for IIa, 119 and 214 for IIIa, and 249 and 277 for IVa.

We used the ratios of the intensities of the ion peaks with m/e 217, 241, 253, 277, and 281 (4.8:1.0:2.3:2.0:7.3 for IIb, 1.5:4.5:1.0:2.3:4.0 for IIIb, and 1.0:2.0:4.0:3.8:12.0 for IVb) as the analytical characteristics for the determination of the components in the mixture. The formation of the indicated characteristic ions is described in the general case by the following scheme for the fragmentation of M⁺ (in the case of IIIa and IIIb):



EXPERIMENTAL

The mass spectra were recorded with a Varian MAT-311 spectrometer at an ionizing voltage of 70 V, a cathode emission current of 300 μ A, and an accelerating voltage of 31 kV. The temperature of the admission system and the ion source was 250°C (in the case of recording through the cylinder) or 70°C (in the case of recording by the direct introduction technique). The PMR spectra of solutions of the compounds in CDCl₃ or CCl₄ were recorded with a JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard. The UV spectra of solutions of the compounds in ethanol were recorded with a Hitachi EPS-3T spectrophotometer. Gas-liquid chromatography was carried out with a Khrom-4 chromatograph with a 3-m long column with a diameter of 4 mm: the solid support was Chromaton N-AW with a particle diameter of 0.125-0.160 mm, the stationary phase was SE-30 silicone (5% of the support), the carrier gas was nitrogen, the flow rate was 80 ml/min, the thermostat temperature was 260°C, and the vaporizer temperature was 320°C. Thin-layer chromatography (TLC) was carried out on activity II aluminum oxide. Quantitative analysis of the mixtures of isomers IIa, b-IVa, b by IR spectroscopy was carried out as in [1]; the following characteristic absorption frequencies (in reciprocal centimeters) for the isomers were selected: 1050 for IIIa, 960 for IIIb, 910 for IVa, and 1300 for IVb. The percentages of isomers IIa, b in the mixture were found from the difference $100 - \Sigma IIIa$, b + IVa, b.

<u>m-Methoxydiphenylamine (Va)</u>. This compound, with mp 70-71°C [from benzene-petroleum ether (1:1)], bp 157-159°C [160-162°C (2 mm) [3]], and R_f 0.40 [benzene-petroleum ether (1:1)], was obtained in 60% yield from m-anisidine by Ullmann arylation with iodobenzene.

<u>m-Chlorodiphenylamine (Vb)</u>. This compound, with bp 149-152°C (2 mm) [4] and R_f 0.37 [benzene-petroleum ether (1:2)], was similarly obtained in 50% yield from m-chloroaniline.

<u>N-Nitroso-m-methoxydiphenylamine (VIa)</u>. This compound, with mp 74-75°C (from methanol) and R_f 0.63 [ether-hexane (2:1)], was obtained in 88% yield by the method in [5] from amine Va. Found: C 68.9; H 5.3%. $C_{13}H_{12}N_2O_2$. Calculated: C 68.4; H 5.3%.

<u>N-Nitroso-m-chlorodiphenylamine (VIb)</u>. This compound, with bp 134-136°C (2 mm) and R_f 0.57 [benzene-petroleum ether (2:1)], was obtained in 85% yield by the method in [5] from amine Vb. Found: C 62.3; H 4.2%. C12H9N2OC1. Calculated: C 61.9; H 3.9%.

<u>m-Methoxydiphenylhydrazine (VIIa)</u>. This compound, with mp 46°C and R_f 0.50 [etherhexane (2:1)], was obtained in 33% yield by the method in [5] from VI. PMR spectrum (CC14),

1097

δ: 3.62 (s, 3H), 3.85 (s, 2H), and 6.20-7.30 ppm (m, 8H). Found: C 73.4; H 6.7; N 12.5%. C₁₃H₁₄N₂O. Calculated: C 72.9; H 6.6; N 13.1%. The hydrochloride of VIIa had mp 120-121°C (dec., from ethanol). Found: C 62.2; H 6.1; N 11.1%. C₁₃H₁₄N₂O'HCl. Calculated: C 62.3; H 6.0; N 11.2%.

<u>m-Chlorodiphenylhydrazine (VIIb)</u>. This compound, with bp $171-174^{\circ}C$ (1 mm) and R_f 0.20 [benzene-petroleum ether (2:1)], was obtained in 75% yield from VIb by the method in [6]. Found: C 66.1; H 5.1%. C₁₂H₁₁ClN₂. Calculated: C 66.0; H 5.10%.

<u>5- and 7-Methoxy-1,2,3,4-tetrahydrocarbazoles (IXa and Xa)</u>. These compounds were obtained from m-methoxyphenylhydrazine VIIIa [bp 120-121°C (2 mm)] and cyclohexanone by the general method of the Fischer reaction in isopropyl alcohol saturated with dry HCl. The combined yield of isomers IXa and Xa (for 0.01 M hydrazine) was 72%. Preparative separation of the total amount of the mixture of crude isomers was carried out with a column (1 m) filled with activity II aluminum oxide [elution with benzene-petroleum ether (1:1)]. Isomers IXa and Xa were eluted successively. The course of the separation was monitored by TLC on Al₂O₃ in a benzene-petroleum ether system (3:1). Isomers IXa and Xa were obtained in a ratio of 3:7. Carbazole IXa had mp 130°C (from hexane) and Rf 0.44 [benzene-petroleum ether (3:1)]. PMR spectrum, δ : 1.79 (m, 4H), 2.75 (m, 4H), 3.79 (s, 3H), 6.38 (d, J_{7,8} = 8 Hz, H₈), 6.75 (d, J_{6,7} = 8 Hz, H₆), and 6.95 ppm (t, J_{6,7} = J_{7,8} = 8 Hz, H₇). Found: C 77.1; H 7.5%. C₁₃H₁₃NO. Calculated: C 77.6; H 7.5%. Carbazole Xa had mp 85-86°C (from benzene) [7] and Rf 0.24 (with the system used for IXa). The PMR spectrum was in agreement with the structure and coincided with the spectrum presented in [7].

<u>5- and 7-Chloro-1,2,3,4-tetrahydrocarbazoles (IXb and Xb)</u>. These compounds were obtained from m-chlorophenylhydrazine [bp 122°C (4 mm)] by the method used to prepare carbazoles IXa and Xa. The combined yield of isomers IXb and Xb (for 0.15 M hydrazine) was 55%. Two crystallizations from hexane gave isomer IXb with mp 178-179°C and R_f 0.42 [benzene-petroleum ether (1:1)]. The residue was crystallized from methanol to give isomer Xb with mp 149-150°C and R_f 0.44 (in the same system). PMR spectrum of isomer IXb (CDCl₃), δ : 1.82 (m, 4H), 2.62 (m, 4H), 6.90 (d, $J_{7,8} = 9$ Hz, $J_{6,8} = 2.4$ Hz, H_6), 7.08 (t, $J_{6,7} = 9$ Hz, H_7), and 7.20 ppm (d, $J_{6,7} = 9$ Hz, H_6). PMR spectrum of isomer Xb (CDCl₃), δ : 1.84 (m, 4H), 2.63 (m, 4H), 6.95 (d, $J_{5,6} = 9.0$ Hz), 7.12 (s, $J_{6,8} = 2.4$ Hz), and 7.26 ppm (d, $J_{5,6} = 9$ Hz). Found: a) for isomer IXb, C 69.8 and H 5.8%; b) for isomer Xb, C 70.0 and H 5.9%.

<u>5-Methoxy-9-phenyl-1,2,3,4-tetrahydrocarbazole (IIa)</u>. A mixture of 1 g (0.005 mole) of carbazole IXa, 1 g (0.005 mole) of iodobenzene, 2.8 g (0.02 mole) of anhydrous potassium carbonate, and 0.3 g of copper powder was triturated in a porcelain mortar, and the triturated mixture was transferred to a flask equipped with a reflux condenser and a thermometer. A 0.1-g sample of CuI was added, and the mixture was heated on a Woods metal bath at 190-200°C for 6 h. The solid was then removed by filtration and washed on the filter with benzene. The benzene was removed from the filtrate by evaporation, and the residue was purified with a column filled with Al₂O₃ to give 0.7 g (50%) of carbazole IIa as a light-yellow oil with Rf 0.60 [benzene-petroleum ether (1:1)]. PMR spectrum (CCl₄), δ : 1.76 (m, 4H), 2.70 (m, 4H), 3.77 (s, 3H), and 6.20-7.40 ppm (m, 8H). IR spectrum: 700, 1490, and 1600 cm⁻¹. UV spectrum, λ_{max} (log ϵ): 224 (4.30), 244 (4.18), 277 (inflection, 4.08), and 286 nm (4.12). Found: C 82.8; H 6.6%. C_{1.9}H_{1.9}NO. Calculated: C 82.3; H 7.0%.

<u>7-Methoxy-9-phenyl-1,2,3,4-tetrahydrocarbazole (IIIa)</u>. This compound was similarly obtained in 52% yield as a yellow oil with R_f 0.50 (with the system used for carbazole IIa) from carbazole Xa. PMR spectrum (CC1₄), δ : 1.79 (m, 4H), 2.47-2.65 (m, 4H), 3.62 (s, 3H), and 6.54-7.42 ppm (m, 8H). IR spectrum: 700, 1050, 1500, and 1600 cm⁻¹. UV spectrum, λ_{max} (log ε): 230 (4.58), 248 (shoulder, 4.29), and 290 nm (shoulder, 4.08). Found: C 82.7; H 6.8%. C₁₉H₁₉NO. Calculated: C 82.3; H 7.0%.

<u>9-(m-Methoxyphenyl)-1,2,3,4-tetrahydrocarbazole (IVa)</u>. This compound was similarly obtained in 58% yield as a light-yellow oil with Rf 0.73 [benzene-petroleum ether (1:1)] from 1,2,3,4-tetrahydrocarbazole [mp 115-116°C (from methanol)] and m-iodoanisole [bp 110-111°C (11 mm)]. PMR spectrum (CCl₄), δ : 1.85 (m, 4H), 2.58-2.63 (m, 4H), 3.72 (s, 3H), and 6.69-7.40 ppm (m, 8H). IR spectrum: 700, 910, 1490, and 1600 cm⁻¹. UV spectrum, λ_{max} (log ε): 222 (4.76), 266 (4.23), 286 (4.21), and 293 nm (inflection, 4.20). Found: C 81.8; H 6.9%. C₁₉H₁₉NO. Calculated: C 82.3; H 7.0%.

<u>5-Chloro-9-phenyl-1,2,3,4-tetrahydrocarbazole (IIb)</u>. This compound was similarly obtained in 45% yield as a light-yellow oil with R_f 0.57 [benzene-petroleum ether (1:2)] from carbazole IXb. PMR spectrum (CDCl₃), δ : 1.81 (m, 4H), 2.63 (m, 4H), and 6.90-7.42 ppm, (m, 8H). IR spectrum: 710, 860, 1490 and 1600 cm⁻¹. The GLC retention time (τ) of this compound was 13.6 min. Found: C 77.3; H 5.6%. C₁₈H₁₆ClN. Calculated: C 76.7; H 5.7%.

<u>7-Chloro-9-phenyl-1,2,3,4-tetrahydrocarbazole (IIIb)</u>. This compound was similarly obtained in 48% yield as a light-yellow oil with Rf 0.65 (with the system used for IIb) from carbazole Xb. PMR spectrum (CDCl₃), δ : 1.80 (m, 4H), 2.64 (m, 4H), and 7.02-7.54 ppm, (m, 8H). IR spectrum: 700, 960, 1500, and 1600 cm⁻¹. UV spectrum, λ_{max} (log ε): 242 (4.78), 260 (shoulder, 4.29), 290 (4.18), 299 (4.29), and 3.27 nm (3.68). The GLC retention time of this compound was 13.2 min. Found: C 77.0; H 5.5%. C₁₈H₁₆ClN. Calculated: C 76.7; H 5.7%.

<u>9-(m-Chlorophenyl)-1,2,3,4-tetrahydrocarbazole (IVb)</u>. This compound, with mp 86-87°C (from hexane) and R_f 0.75 [benzene-petroleum ether (1:2)], was similarly obtained in 46% yield from 1,2,3,4-tetrahydrocarbazole and m-chloroiodobenzene. PMR spectrum (CDCl₃), δ : 1.85 (m, 4H), 2.67 (m, 4H), and 7.00-7.50 ppm (m, 8H). The GLC retention time of this compound was 11.8 min. IR spectrum: 700, 1300, 1480, and 1590 cm⁻¹. UV spectrum, λ_{max} (log ϵ): 220 (4.71), 270 (4.27), 292 (inflection, 4.17), and 300 nm (shoulder, 4.13). Found: C 76.7; H 5.7%. CleHicClN. Calculated: C 76.7; H 5.7%.

<u>Cyclization of Hydrazones Ia, b under the Conditions of the Fischer Reaction</u>. The cyclization of hydrazones Ia, b in isopropyl alcohol containing concentrated H_2SO_4 or saturated with HCl, the thermal indolization in diethylene glycol, and the purification of the reaction products were carried out by the method presented in [1]. The combined yields of isomers IIa-IVa and IIb-IVb under various cyclization conditions are given in Table 1. PMR spectrum of the mixture of isomers IIa-IVa (CCl₄), δ : 1.79 (m, 4H), 2.53-2.69 (m, 4H), 3.62 (s, OCH₃, IIIa), 3.72 (s, OCH₃, IVa), 3.77 (s, OCH₃, IIa), and 6.50-7.30 ppm (m, 8H).

LITERATURE CITED

- N. M. Przheval'skii, I. I. Grandberg, and N. A. Klyuev, Khim. Geterotsikl. Soedin., No. 8, 1065 (1976).
- 2. I. I. Grandberg, Izv. Timiryazev. Sel'skokhoz. Khim. Akad., No. 5, 188 (1972).
- 3. I. Gruda and J. Braitburg, Polish Patent No. 54428 (Cl. CO7c), Jan. 20 (1968); Chem. Abstr., 70, 11329k (1969).
- 4. F. Ullmann, Ann., 355, 338 (1901).
- 5. R. O. Matevosyan, I. Ya. Postovskii, and A. K. Chirkov, Zh. Obshch. Khim., <u>29</u>, 858 (1959).
- 6. R. H. Poirier and F. Benington, J. Am. Chem. Soc., 74, 3192 (1952).
- 7. R. Iyer, A. Jackson, P. V. R. Shannon, and Naidoo Balakrishna, J. Chem. Soc., Perkin Trans., Part II, No. 6, 872 (1973).