INDOLES

XLIX.* DIRECT CONFIRMATION OF THE FISCHER SYNTHESIS OF INDOLES VIA A SCHEME INVOLVING A SIGMATROPIC [3,3]-REARRANGEMENT

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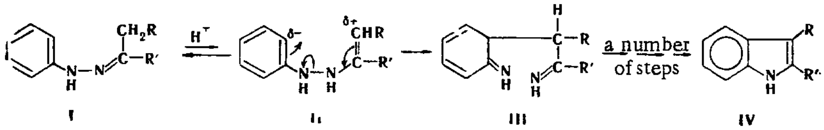
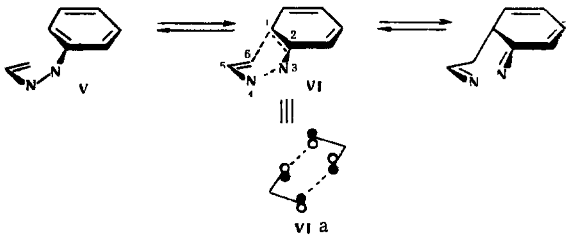
In a study of the Fischer cyclization of cyclohexanone mono-p-substituted α,α-diphenylhydrazones (in which the substituents were donor and acceptor groups) it was found that isomeric (formed during cyclization at the substituted and unsubstituted rings) indoles are formed in close ratios. The results were interpreted in terms of sigmatropic processes as a confirmation of the Fischer reaction via a scheme involving a sigmatropic shift.

The mechanism of the Fischer reaction first proposed by Robinson and Robinson in 1918 [2] has, of course, been subjected frequently to refinements and additions, but the principal step in the reaction – the formation of a carbon–carbon bond (II→III) – until most recently was considered from the point of view of electrophilic attack of the enehydrazine fragment on the aromatic ring [2-4].



An analysis of numerous experimental data on the Fischer reaction in [5-7] casts doubt on the electrophilic character of the second step in the synthesis of indoles and enabled us to earlier advance the hypothesis that the C–C bond is formed as a result of a sigmatropic [3,3]-rearrangement [5].



In order to experimentally confirm this concept we investigated the Fischer cyclization of cyclohexanone mono-p-substituted α,α-diphenylhydrazones.†

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* See [1] for communication XLVIII.

† We have previously published a brief communication regarding this [8].

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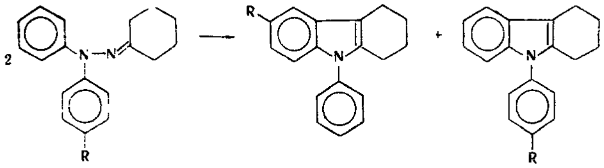


VII a, b　　VIII a, b　　IX a, b

VII-IX a R = OCH_3; b R = Cl

The above model scheme was selected on the basis of the following considerations.

One should have expected a strong effect of electron-donor and electron-acceptor substitutents in hydrazone VII on the direction of cyclization if the C – C bond is formed (II → III) via a scheme involving electrophilic substitution; in other words, practically only one of the tetrahydrocarbazoles (VIII if R is a donor, IX if R is an acceptor) should be formed.

An analogy to this sort of reaction is the electrophilic intramolecular acylation of monosubstituted β,β-diarylpropionic acids, as a result of which only one isomer is formed [9-11].

In addition, if one considers the II → III conversion from the position of the principle of retention of orbital symmetry, i.e., as a concerted process in which the six-membered transition state (VI) has the form of two upper occupied molecular orbitals of the allyl radical type (VIa), the effect of radical R in hydrazone VII is small in this case, and we should observe the formation of both possible isomers (VIII and IX) in close ratios.

A similar approach was used with great success in the discussion of the Claisen rearrangement, the rate of which changes only to a slight degree as a function of the nature of the substituent [12], and the generally accepted mechanism of this reaction is presently one involving a sigmatropic [3,3]-shift.

In an investigation of the cyclization of hydrazone VIIa, b under various conditions it was observed that a mixture of isomeric tetrahydrocarbazoles VIIIa, b and IXa, b in close ratios is always formed.

The cyclization was carried out by heating the appropriate starting reagents (diarylhydrazine and cyclohexanone) in isopropyl alcohol in the presence of acids, whereas thermal indolization was carried out in diethylene glycol.

The quantitative ratio of the resulting isomeric tetrahydrocarbazoles VIIIa, b and IXa, b was determined independently by gas – liquid chromatography (GLC), IR spectroscopy, and mass spectrometry. The three methods gave close results; they are presented in Table 1.

As seen from the data in Table 1, isomer IXa is formed in considerable amounts even in the case of a strong electron-donor substituent such as a methoxy group, i.e., a new C – C bond with the unsubstituted aromatic ring is formed.

When R = Cl, a large amount of isomer VIIIb is formed, but the VIIIb/IXb isomer ratio is still closer to unity than when R = OCH_3.

In addition, it is well known that the relative rates of electrophilic substitution reactions in anisole are ~ 10^{10} higher than in chlorobenzene (of course, in the ortho and para positions).

In our opinion, these data constitute a weighty confirmation of the correctness of the concept of the formation of a C – C bond in the second step of the Fischer reaction via a scheme involving a sigmatropic [3,3]-rearrangement rather than by electrophilic attack on the benzene ring.

TABLE 1. Quantitative Ratios of Isomeric Tetrahydrocarbazoles VIIIa, b and IXa, b

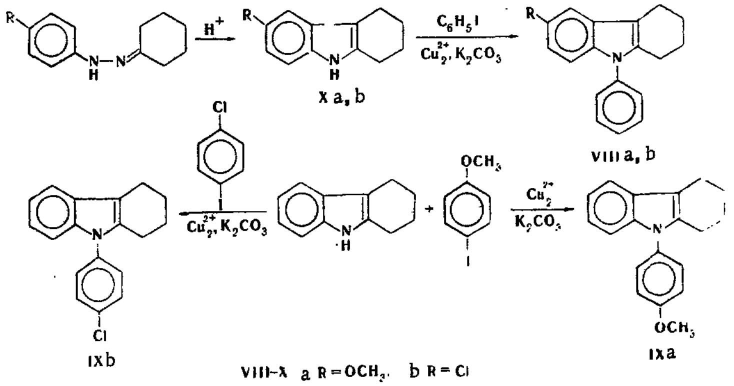
Reaction conditions	VIIIa, b/IXa, b isomer ratios						
	R = OCH_3			R = Cl			
	IR spectrometry	mass spectrometry	average	IR spectrometry	mass spectrometry	GLC	average
iso-C_3H_7OH, Saturated HCl	79 : 21	80 : 20	80 : 20	34 : 66	35 : 65	33 : 67	34 : 66
iso-$C_3H_7OH + H_2SO_4$ (1 mole)	76 : 24	78 : 22	77 : 23	32 : 68	33 : 67	30 : 70	32 : 68
Diethylene glycol (thermally)	62 : 38	62 : 38	62 : 38	32 : 68	32 : 68	31 : 69	32 : 68

TABLE 2. Analytical Ion Peaks. Coefficients of Relative Sensitivity, and Compositions of the Isomeric Mixtures (at an ionizing-electron energy of 50 eV)

Compound	Analytical ion peaks	Corresponding sensitivity coefficients (K)	Composition of reaction mixture formed in cyclization of VIIa, b in iso-C_3H_7OH saturated with HCl, %
IXa	258 230 107 249	0,3434 0,1607 0,1011 0,1080	IXa+VIIIa= =20+80
VIIIa	172 142 246	0,2160 0,0520 0,2815	
IXb	218 111 250	0,1810 0,1103 0,1116	IXb+VIIIb= =65+35
VIIIb	173 138	0,2093 0,1618	

A similar conclusion can also be drawn on the basis of an interpretation of the results obtained in other studies [13-15].

The structures of isomeric tetrahydrocarbazoles VIIIa, b and IXa, b were confirmed by alternative syntheses.



VIII–X a R=OCH_3, b R=Cl

The purity of all of the starting compounds and the reaction products was monitored by GLC.

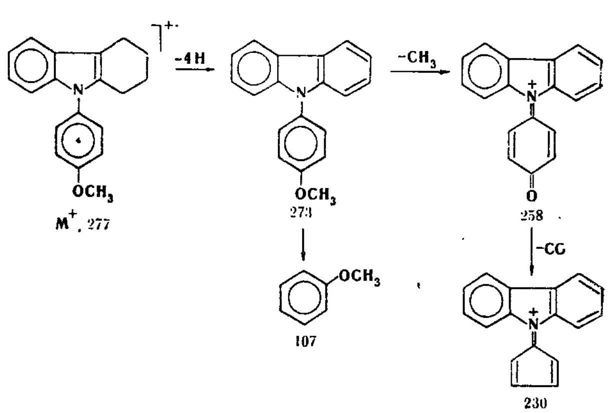
In the mass-spectrometric analysis of the mixture of tetrahydrocarbazoles VIIIa, b and IXa, b, formed as a result of Fischer cyclization, the mass spectra of individual isomers VIIIa, b and IXa, b were recorded initially, and the relative coefficients of sensitivity with respect to toluene were determined for each of them.

An examination of the mass spectra of VIIIa, b and IXa, b made it possible to ascertain the specific ion peaks. These peaks were selected on the basis of the general principles of mass-spectrometric analysis. The intensity of the fragment ion peaks (peaks caused by processes involving the dehydrogenation of the molecular ion were excluded) and their specific character in each concrete case were taken into account.

The true peak intensity (I) in the mass spectra of the mixtures was determined with allowance for the isotopic superimposition of the preceding (with respect to mass) fragment ion, and a correction for the magnitude of superimposition due to peaks of the other isomer was introduced.

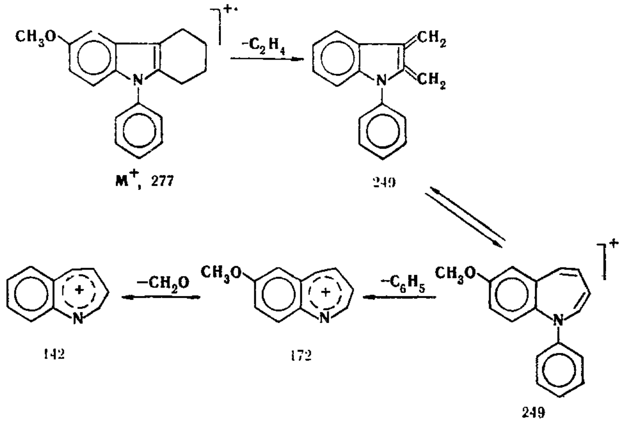
We exposed the specific peaks on the basis of the occurrence of processes involving fragmentation of the molecular ion (M^+). Thus, for example, in the fragmentation of M^+ of IXa we selected the fragment ion peaks (here and subsequently, the m/e values are presented) at 258, 230, and 107 (see Table 2).

Their formation is due to the characteristic dehydrogenation of M^+ to give the aromatic structure of carbazole [16] with subsequent successive processes involving the elimination of CH_3 groups and the ejection of a neutral CO particle (through the quinoid form).



The appearance of the ion peak at 107 in the spectrum is associated with the lability of the C–N bond in the system under consideration.

In the case of isomer VIIIa, fragmentation of M^+ at two β bonds with respect to the indole system with splitting out of an ethylene molecule, possibly with known rearrangement to give an ion with an azepinium structure [17], is extremely characteristic in the first stage of dissociative ionization.



The analytical ion peaks for isomers VIIIb and IXb (Table 2) were similarly selected.

The amount of a component in the mixture was calculated from the formula c = I/K (where c is the concentration of a certain isomer). In order to exclude the possible error in the determination of c in the case of inconstant sensitivity of the apparatus, the concentration of the isomer was determined from three independent peaks. The reproducibility of the results was 3 rel. %.

The isomer ratio in the cyclization of VIIa, b under other conditions was also calculated similarly.

EXPERIMENTAL

The mass spectra were recorded with an MKh-1303 spectrometer at an ionizing voltage of 50 eV, a cathode emission current of 1.5 mA, and an accelerating voltage of 2 kV; the temperature of the inlet system and the ion source was 250°. Introduction of ions into the source was accomplished through the detector's inlet cylinder. The PMR spectra of CCl_4 solutions of the compounds were recorded with a JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with a Jasco IR-S spectrometer. The UV spectra of iso-C_3H_7OH solutions of the compounds were recorded with a Hitachi EPS-3T spectrophotometer.

Gas–liquid chromatography (GLC) was carried out with a Khrom-4 chromatograph with a 2-m long column; the support was Chezasorb AW-HMDS, the liquid phase was XE-60 silicone (5% of the support weight), the carrier gas was nitrogen, the flow rate was 60 ml/min, the thermostat temperature was 250°, and the vaporization temperature was 270°.

Thin-layer chromatography (TLC) was carried out on activity II aluminum oxide.

The IR spectra of the individual compounds were obtained for quantitative analysis of the mixtures of isomers VIIIa, b and IXa, b, and the analytical absorption frequencies (700 cm^{-1} for VIIIa and 715 cm^{-1} for

VIIIb) were selected. These frequencies were used to construct the corresponding calibration graph in coordinates of D (optical density) and $c_{mole/liter}$ (concentration of the component). The percentages of VIIIa, b and IXa, b in the mixture were then calculated from the formula D=2−log T, where T is the throughput percent or the peak intensity (see Table 1).

p-Methoxydiphenylhydrazine (VIIa). This compound, with mp 59-60° (from hexane), was obtained by the method in [18].

p-Chlorodiphenylhydrazine (VIIb). This compound, with bp 186-189° (1 mm), was obtained by the method in [19].

6-Methoxy-1,2,3,4-tetrahydrocarbazole Xa). This compound, with mp 96-97° (from methanol), was obtained from p-methoxyphenylhydrazine by the method in [20].

6-Chloro-1,2,3,4-tetrahydrocarbazole (Xb). This compound, with mp 143-144° (from methanol), was obtained from p-chlorophenylhydrazine by the method in [21].

6-Methoxy-9-phenyl-1,2,3,4-tetrahydrocarbazole (VIIIa). A mixture of 5 g (0.04 mole) of hydrazine Xa, 8.9 g (0.04 mole) of freshly distilled iodobenzene, 6.1 g (0.04 mole) of anhydrous potassium carbonate, and 0.3 g of powdered copper in 50 ml of nitrobenzene was heated at 195-200° in a flask equipped with a Dean-Stark trap for 5 h. The mixture was then filtered to remove the copper and potassium carbonate, and the nitrobenzene was removed from the filtrate by vacuum distillation (water aspirator). The residue was distilled to give 5.8 g (52%) of carbazole VIIIa with bp 192-195° (2 mm) and R_f 0.60 [benzene–petroleum ether (1:1), development with iodine]. Found: C 82.1; H 7.1%. $C_{19}H_{19}NO$. Calculated: C 82.3; H 7.0%. PMR spectrum, ppm: 3.75 (s, 3H), 1.80 (m, 4H), 2.55 (m, 4H), and 6.80-7.15 (m, 8H). IR spectrum, cm^{-1}: 700, 1520, and 1600. UV spectrum, λ, nm (log ε): 224 (4.20), 227 (3.98), and 299 (inflection, 3.74).

9-(p-Methoxyphenyl)-1,2,3,4-tetrahydrocarbazole (IXa). This compound, with mp 85-86° (from methanol), was obtained in 60% yield from 1,2,3,4-tetrahydrocarbazole [mp 115-116° (from methanol)] and p-iodoanisole (mp 51-52°) by the method presented above for the preparation of VIIIa. Found: C 82.6; H 7.0%. $C_{19}H_{19}NO$. Calculated: C 82.3; H 7.0%. The product had R_f 0.43 [benzene–petroleum ether (1:1), development with iodine]. PMR spectrum, ppm: 3.75 (s, 3H), 1.80 (m, 4H), and 6.76-7.16 (m, 8H). IR spectrum, cm^{-1}: 740, 1510, and 1610; no absorption bands at 700 cm^{-1}. UV spectrum, λ_{max}, nm (log ε): 225 (4.48) 261 (4.08), 285 (3.92), and 290 (inflection, 3.92).

6-Chloro-9-phenyl-1,2,3,4-tetrahydrocarbazole (VIIIb). This compound, with mp 105-106° (from ethanol), was obtained in 55% yield from Xb and iodobenzene by the method used to prepare VIIIa. Found: C 76.8; H 5.6%. $C_{18}H_{16}ClN$. Calculated: C 76.7; H 5.7%. The product had R_f 0.57 [benzene-petroleum ether (1:2), development with iodine]. PMR spectrum, ppm: 1.79 (m, 4H), 2.54 (m, 4H), and 6.84-7.30 (m, 8H). IR spectrum, cm^{-1}: 715, 1590, and 1520. UV spectrum, λ_{max} nm (log ε): 231 (4.58), 266 (4.19), 259 (4.00), and 302 (inflection, 3.92). GLC: retention time τ = 6.48 min.

9-(p-Chlorophenyl)-1,2,3,4-tetrahydrocarbazole (IXb). This compound, with mp 109-110° (from hexane), was obtained in 62% yield from 1,2,3,4-tetrahydrocarbazole and p-chloroiodobenzene (mp 56-57°) by the method used to prepare VIIIa. Found: C 76.6; H 5.9%. $C_{18}H_{16}ClN$. Calculated: C 76.7; H 5.7%. The product had R_f 0.56 [benzene–petroleum ether (1:2), development with iodine]. PMR spectrum, ppm: 1.76 (m, 4H) 2.50 (m, 4H, and 6.84-7.30 (m, 8H). IR spectrum, cm^{-1}: 1600 and 1490; no absorption band at 715 cm^{-1}. UV spectrum, λ_{max}, nm (log ε): 226 (4.57), 269 (4.15), 287 (inflection, 4.02), and 298 (inflection 3.90). GLC: retention time τ = 5.42 min.

Cyclization of Hydrazones VIIa, b under the Conditions of the Fischer Reaction. A mixture of 0.01 mole of VIIa or VIIb and 0.01 mole of cyclohexanone in 100 ml of isopropyl alcohol containing 0.01 mole of concentrated H_2SO_4 or saturated with dry HCl was refluxed for 4 h. At the end of the reaction, the alcohol was removed by distillation, and the residue was treated with aqueous potassium carbonate solution. The mixture was then extracted with benzene, and the benzene extract was washed with water and dried over magnesium sulfate. The benzene was evaporated, and the residue was dissolved in benzene–petroleum ether (1:1) and passed through a filter containing 50 g of activity II Al_2O_3 [elution with benzene–petroleum ether (1:1)] in order to separate the unchanged hydrazine. The solvent was then removed by distillation, and the resulting mixture was analyzed, without further purification, by IR spectroscopy, mass spectrometry, and GLC. According to the results of elementary analysis and the PMR spectra, the mixture contained only two isomeric tetrahydrocarbazoles. The sum of the yields of isomers VIIIa and IXa was 60% of the theoretical value, and the sum of the yields of isomers VIIIb and IXb was 70% of the theoretical value.

Thermal Indolization of Hydrazones VIIa, b. A mixture of 0.01 mole of VIIa or VIIb and 0.01 mole of cyclohexanone in 50 ml of diethylene glycol was heated at 240-245° for 8 h in a flask equipped with a reflux condenser. At the end of the reaction, the mixture was diluted with water and extracted with five 50-ml portions of benzene. The benzene was evaporated, and the residue was purified with a filter containing Al_2O_3 as described above. The sum of the yields of VIIIa and IXa was 40% of the theoretical value, and the sum of the yields of VIIIb and IXb was 55% of the theoretical value. The isomer ratios are given in Table 1. We were unable to separate the mixture of isomers VIIIa and IXa by GLC.

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