INDOLES

XIX.* RATIO OF 5-METHYL- AND 7-METHYL-1,2,3,4-TETRAHYDROCARBAZOLES FORMED IN THE CYCLIZATION OF CYCLOHEXANONE m-TOLYLHYDRAZONE

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The Fischer cyclization of cyclohexanone m-tolylhydrazone under various conditions always gives a mixture of isomers (5-methyl- and 7-methyl-1,2,3,4-tetrahydrocarbazole) with predominance of the 7-methyl isomer.

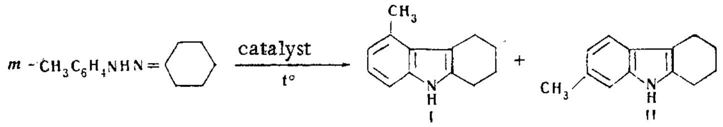
The formation of a mixture of isomeric reaction products should be expected in the cyclization of arylhydrazones of unsymmetrical ketones and meta-substituted arylhydrazones of ketones. It is likely that the ratio of isomers formed in the process will depend on a number of factors – the cyclization conditions, the nature of the meta substituent of the aromatic ring, and the structure of the carbonyl component.

This problem was previously investigated in [2-5], but the results obtained in them are disparate and often contradictory.

We have taken on the general task to carry out a quantitative investigation of the effect of substituents in the meta position of the phenyl ring of arylhydrazones and the structure of unsymmetrical ketones on the direction of the Fischer reaction under various conditions. The first of the results obtained are presented in this communication.

Cyclohexanone m-tolylhydrazone was taken as the object of the investigation and was cyclized in the presence of various catalysts (Table 1).

The composition of the reaction products was studied by means of gas-liquid chromatography. Since some overlapping of the peaks is observed on the chromatogram of isomers I and II and cannot be eliminated by changing the conditions, carrier, and composition of the liquid phase, the accuracy in estimating the yields does not exceed 5-10%.



Preparative gas-liquid chromatographic separation of isomers I and II was carried out to identify the chromatographic peaks and to prove the structures of the compounds corresponding to them.

PMR and IR spectroscopy indicated that the first peak on the chromatogram corresponds to 7-methyl-1,2,3,4-tetrahydrocarbazole (mp 118°), while the second peak corresponds to 5-methyl-1,2,3,4-tetrahydrocarbazole (mp 130°).

The IR spectrum of isomer I (Fig. 1a) contained the following bands: 777 and 750 cm^{-1} (δ_{CH}), 1510, 1575, and 1640 cm^{-1} (ν_{ring}), 2871 and 2941 cm^{-1} (ν_{CH}), and 3440 cm^{-1} (ν_{NH}). Two intense absorption bands

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*See [1] for communication XVIII.

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TABLE 1. Effect of the Cyclization Conditions on the Ratio of Isomers I and II*

Cyclization conditions	Temp. (time, h)	Yield, %	I : II
$ZnCl_2$ (catalytic amount)	180 (2)	63	1 : 1
$ZnCl_2$ (0,02 g)	180 (2)	83	1 : 1
Cu_2Cl_2 (0,02g)	250 (2)	28	1 : 1
10 % H_2SO_4 in C_2H_5OH (5 ml)	100 (0,5)	91	3 : 4
HCl in C_2H_5OH (5 ml)	100 (0,5)	40	5 : 9
Polyphosphoric acid (0.02 g)	120 (0,5)	16	5 : 8
10 % sulfosalicylic acid in 50% C_2H_5OH (5 ml)	100 (0,5)	84	1 : 1
$BF_3 \cdot (C_2H_5)_2O$ (0.15 g) in 5 ml of glacial CH_3COOH	100 (0,5)	59	5 : 6
In dimethylformamide†	100 (2)	60	1 : 1

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*The amount of hydrazone used in all of the experiments was 0.2 g.

†A mixture of 4 g (0.025 mole) of m-tolylhydrazine hydrochloride, 2.6 g (0.027 mole) of cyclohexanone, and 15 ml of dimethylformamide was refluxed for 2 h on a water bath, the solvent was removed by vacuum distillation, the residue was poured into 40 ml of 1 N hydrochloric acid, and the carbazole was extracted with benzene.

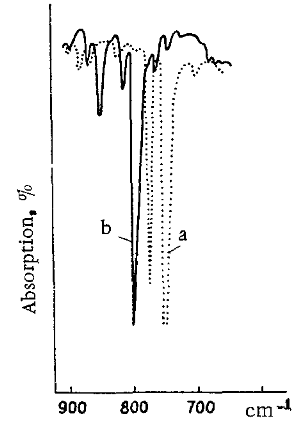

Fig. 1

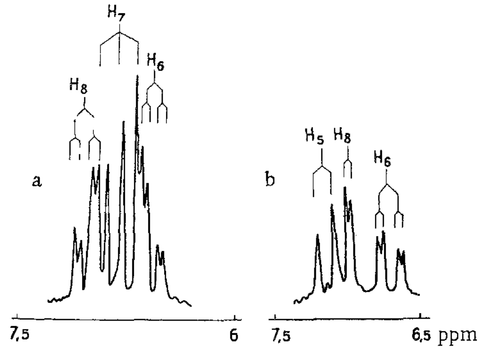

Fig. 2

Fig. 1. IR spectra: a) 5-methyl-1,2,3,4-tetrahydrocarbazole; b) 7-methyl-1,2,3,4-tetrahydrocarbazole.

Fig. 2. PMR spectra: a) 5-methyl-1,2,3,4-tetrahydrocarbazole (aromatic portion); b) 7-methyl-1,2,3,4-tetrahydrocarbazole (aromatic portion).

at 750 and 777 cm^{-1}, which correspond to out-of-plane deformation vibrations of the CH of the benzene ring, indicate the presence of three adjacent hydrogen atoms, which corresponds to 5-methyl-1,2,3,4-tetrahydrocarbazole.

The IR spectrum of isomer II (Fig. 1b) contains the following bands: 800, 820, and 860 cm^{-1} (δ_{CH}), 1640, 1575, and 1510 cm^{-1} (ν_{ring}), 2851 and 2931 cm^{-1} (ν_{CH}), and 3400 cm^{-1} (ν_{NH}). The bands at 800-860 cm^{-1}, which correspond to out-of-plane deformation vibrations of the CH of the benzene ring, indicate the presence of one isolated (800 cm^{-1}) and two adjacent (820 and 860 cm^{-1}) hydrogen atoms in the phenyl ring. This made it possible to assign the 7-methyl-1,2,3,4-tetrahydrocarbazole structure to compound II.

The PMR spectrum* of isomer I (Fig. 2a) contained the following peaks: 2.5-3.0 m (α-CH_2), 1.6-2.0 m (β-CH_2), 2.60 s (5-CH_3), aromatic ring protons at 6.65 q (H_6), 6.80 t (H_7), 7.02 q (H_8), $J_{6,7} = J_{7,8} = 7.5$ Hz, $J_{6,8} = 1.8$ Hz.

The PMR spectrum of isomer II (Fig. 2b) contained the following peaks: 2.5-2.7 m (α-CH_2), 1.8-2.0 m (β-CH_2), 2.39 s (7-CH_3), aromatic ring protons at 7.20 d (H_5), 6.77 q (H_6), 7.05 d (H_8), $J_{5,6} = 7.5$ Hz, $J_{6',8} =$ 1.9 Hz.

We obtained fundamental information regarding the structures of I and II on the basis of data on the multiplicity of the aromatic protons. The signal from the H_5 protons, followed by those from H_8, H_7, and H_6, are found at the weakest fields in the spectra of indoles. The spin-spin interaction of ortho protons is 7.5 Hz, while that of meta protons is 1.8-1.9 Hz. In accordance with the proposed formulas (I and II), the H_8 (7.02 ppm) and H_6 (6.65 ppm) signals in the spectrum of the 5-methyl isomer are split into quartets, while the H_7 (6.80 ppm) signal is split into a triplet.

In the spectrum of the 7-methyl isomer the H_5 (7.20 ppm) and H_6 (6.77 ppm) protons form an AB system, and the H_6 doublet is additionally split into a quartet by spin-spin interaction with the meta H_8 proton, which in turn is seen as a doublet at 7.05 ppm ($J_{6,8} = 1.5$ Hz). An additional confirmation of the proposed structures is the fact that the signal of the CH_3 group of the 5-methyl isomer is observed at weaker field (2.60 ppm) than that of the 7-methyl isomer (2.39 ppm), just as the H_5 signal is found at weaker field than the H_7 signal [6].

The identical UV spectra of isomers I and II with λ_{max} 230 and 289 nm (log ε 4.40 and 3.59) are in accordance with the spectrum of tetrahydrocarbazole.

It was found that the formation of the 7-methyl isomer prevails over the formation of the 5-methyl isomer in all cases (see Table 1). This is probably associated with the steric hindrance exerted by the methyl group on the direction of cyclization or with the electron-density distribution in the ring; detailed calculations of this sort will be presented in our next communication.

EXPERIMENTAL

The UV spectra in ethanol were obtained with an EPS-3T (Hitachi) UV spectrometer. The IR spectra of KBr pellets were obtained with a JASCO-IR-S spectrometer with a NaCl prism. The PMR spectra of 10% solutions in CD_3COCD_3 were obtained with a T-60 spectrometer with hexamethyldisiloxane as the internal standard.

The mixture of 7-methyl- and 5-methyl-1,2,3,4-tetrahydrocarbazoles was separated with a "Khrom-2" chromatograph equipped with a preparative adapter. The preparative column was 0.8-m long with a diameter of 18 mm. Chromosorb "G", to which 4.5% KOH and 7% polyethylene glycol (mol. wt. 15,000) was applied, was used as the stationary phase. The column temperature was 210°, and the gas-carrier (N_2) flow rate was 270 ml/min.

The ratio of reaction products was studied with a model 1-64 "Tsvet" analytical chromatograph. The column was 1-m long with a cross section of 4 mm. Neutral Chromosorb "A", to which 0.6% KOH and 5% polyethylene glycol (mol. wt. 15,000) were applied, served as the stationary phase, and the gas-carrier (N_2) flow rate was 60 ml/min.

The yields of the reaction products and the isomer ratios were determined by the internal normalization method. A solution of 0.05 g of 5,6-benzoquinoline in 2 ml of benzene was used as the standard. A definite amount of benzene (2 ml in the case of $ZnCl_2$ and Cu_2Cl_2, and 6 ml for the other catalysts) was added to the reaction mass after carrying out the cyclization (0.2 g of the hydrazone was used in all of the experiments). A "marker—test substance" mixture in a definite ratio was taken for analysis. The cyclization product yields and the percent ratios of the isomers formed (see Table 1) were determined by weighing the chromatographic peaks.

Cyclohexanone m-Tolylhydrazone. m-Tolylhydrazine [7] [3 g (0.025 mole)] and 3 g (0.031 mole) of cyclohexanone in 30 ml of benzene were refluxed for 30 min on a water bath, and the benzene was removed by vacuum distillation to give 3.18 g (65%) of crude product.

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*Here and elsewhere s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet; the chemical shifts in parts per million in the δ scale are given in parentheses.

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