INDOLES

XXVI.* RATIO OF INDOLE ISOMERS FORMED DURING THE FISCHER CYCLIZATION OF META-SUBSTITUTED DIETHYL KETONE PHENYLHYDRAZONES

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UDC 547.751:542.952.1:541.67:543.422.4

The cyclization of m-$RC_6H_4NHN{=}C(C_2H_5)_2$ (R = C_2H_5, OCH_3, Cl) under various conditions always gives a mixture of 4-R-3-methyl-2-ethylindole and 6-R-3-methyl-2-ethylindole isomers with predominance of the latter. The ratios of the isomers formed depend on the catalyst used.

We have set for ourselves the general task of making a quantitative investigation of the effect of substituents in the meta position of the benzene ring of phenylhydrazones on the direction of the Fischer reaction. We previously studied the cyclization of m-tolylhydrazones of diethyl ketone and cyclohexanone [2] and established that the character of the symmetrical ketone component (cyclohexanone and diethyl ketone) has virtually no effect on the ratio of the isomers formed, and the isomer with a methyl group in the 6-position of the indole ring predominated in all cases.

In this research we have studied the cyclization of meta-substituted diethyl ketone phenylhydrazones to the corresponding indoles under various conditions.

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

No.	Cyclization conditions	Temp., °C (time, h)	R=C_2H_5		R=OCH_3		R=Cl	
			I : II	overall yield, %	I : II	overall yield, %	I : II	overall yield, %
1	$ZnCl_2$ (catalytic amount)	180 (2)	1 : 1	17	1 : 1	14	1 : 0,9	10
2	$ZnCl_2$ (molar amounts)	180 (2)	1 : 1,2	22	1 : 1	16	1 : 0,8	23
3	10% H_2SO_4 in C_2H_5OH	100 (0,5)	1 : 1,6	55	1 : 1,8	43	1 : 1,3	37
4	Polyphosphoric acid	120 (0,5)	1 : 1,5	41	1 : 1,8	35	—	19
5	10% sulfosalicyclic acid in 50% C_2H_5OH	100 (0,5)	1 : 1	91	1 : 1,8	98	—	12
6	$BF_3 \cdot (C_2H_5)_2O$ in glacial CH_3COOH	100 (0,5)	1 : 1,2	62	1 : 1,6	52	1 : 1,5	48
7	Hydrazine salt and ketone in dimethylformamide*	100 (2)	1 : 1,2	91	1 : 1,1	84	—	43
8	Saturated solution of HCl (gas) in C_2H_5OH	100 (0,5)	1 : 1,8	30	1 : 5,4	95	1 : 1,3	71

*A mixture of 0.025 mole of m-$RC_6H_4NHNH_2 \cdot HCl$, 0.027 mole of diethyl ketone, and 15 ml of dimethylformamide was refluxed for 2 h on a water bath, and the solvent was removed in vacuo. The residue was poured into 40 ml of 1 N hydrochloric acid, and the indole was extracted with benzene.

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*See [1] for communication XXV.

K. A. Timiryazev Moscow Agricultural Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1204-1208, September, 1971. Original article submitted September 22, 1970.

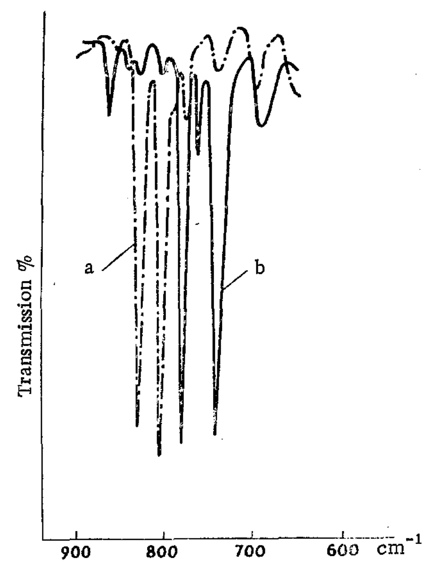
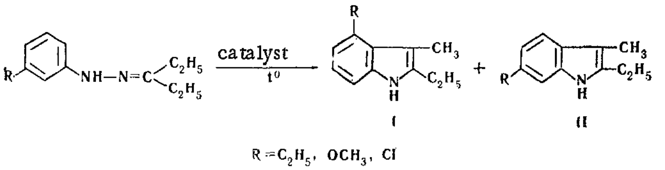


Fig. 1. IR spectra: a) 6-methoxy-3-methyl-2-ethylindole; b) 4-methoxy-3-methyl-2-ethylindole.



Our results, which are presented in Table 1, are in agreement with a mechanism involving intramolecular electrophilic substitution [3,4].

When there is a methoxy group in the meta position of the phenyl ring of the arylhydrazone, its coordinated –I and +E effects lead to predominance of the 6-substituted isomer.

In the case of the m-chlorophenylhydrazone, the chlorine has a greater –I effect and a smaller +E effect than the methoxy group, and the predominance of the 6-isomer over the 4-isomer is diminished. In addition, in this case, as expected, the yields of the corresponding indoles are lower than when R = C_2H_5 and OCH_3.

When there is an ethyl group in the meta position of the arylhydrazone, its +I effect activates the ortho position more strongly than the para position in electrophilic substitution reactions; however, the considerable steric hindrance on the part of the bulky ethyl group probably leads to the formation of the 4-isomer in smaller amounts than the 6-isomer.

It must be noted that the steric factors in the cyclization of meta-substituted phenylhydrazones will always favor the formation of the 6-isomer, regardless of the electronic nature of the substituent.

These results were qualitatively confirmed in [5-8].

In examining the effect of the catalyst on the ratio of reaction products formed, it should be noted that when Lewis acids ($ZnCl_2$, for example) are used, the tendency for the formation of the 4-isomer increases as compared with what is observed when proton catalysts are used, although the overall yield decreases. Thus a small predominance of the 4-isomer was observed even in the cyclization of diethyl ketone m-chlorophenylhydrazone. This is probably associated with the effect of the catalyst on the structure of the complexes formed between the catalyst and the arylhydrazone.

The composition of the products of the cyclization of diethyl ketone m-ethyl- and m-methoxyphenylhydrazones was studied by gas-liquid chromatography. In the case of diethyl ketone m-chlorophenylhydrazone, we could not achieve good chromatographic separation of the isomers, and their ratio was determined by PMR spectroscopy from the relative intensity of the signals of the 3-CH_3 group.

3-Methyl-2,6-diethylindole and 6-chloro-3-methyl-2-ethylindole were isolated from reaction mixture 8 (see Table 1) after two crystallizations from pentane in yields of 20 and 18%, respectively. 3-Methyl-2,4-diethylindole and 4-chloro-3-methyl-2-ethylindole could not be isolated in pure form and were identified only by spectroscopy. It should be noted that 3-methyl-2,6-diethylindole is very readily converted to 3-hydroperoxy-3-methyl-2,6-diethylindolenine in air, particularly in solution.

The 6- and 4-methoxy-3-methyl-2-ethylindoles were separated by means of preparative gas-liquid chromatography.

The structures of all of the indoles obtained were established by IR, UV, and PMR spectra. The band of the deformation vibrations of the C–H bonds of the aromatic ring in the IR spectrum of the 6-substituted indole was observed at higher frequencies than in the case of the 4-isomer (Fig. 1). Characteristic differences were also observed in the aromatic portion of the PMR spectrum (Fig. 2), which made it possible to unambiguously determine the position of the substituent; in addition, in the case of the 4-isomer, the signal of the CH_3 group in the 3-position of the indole ring is always shifted to weaker field as compared with the 6-isomer. The absorption band characteristic for this class of compounds is observed at ~300 nm ($\log \varepsilon \sim 3.80$) in the UV spectra of the indoles obtained.

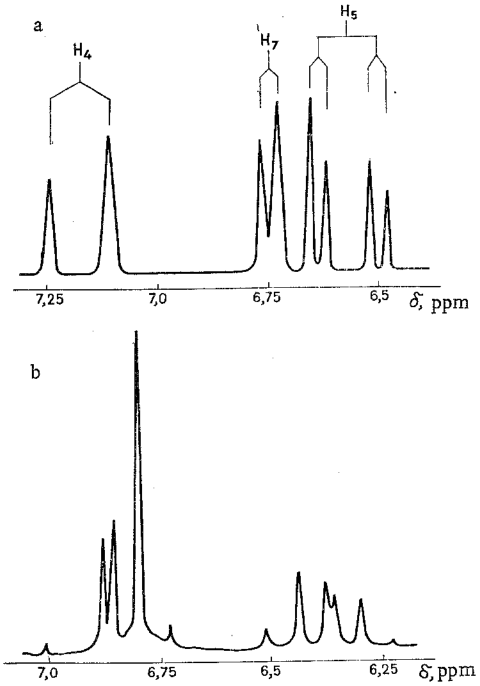
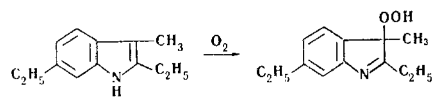


Fig. 2. PMR spectra (aromatic proton region): a) 6-methoxy-3-methyl-2-ethylindole; b) 4-methoxy-3-methyl-2-ethylindole.



EXPERIMENTAL

Except for the 4-chloro and 4-ethyl isomers, the IR spectra of which were obtained from liquid films, the IR spectra were recorded from KBr pellets (5 mg of compound per 0.5 g of KBr) with a Jasco JR-S spectrophotometer.

The PMR spectra were recorded from 10% solutions in CD_3COCD_3 with a T-60 spectrometer with tetramethylsilane as the internal standard.

The mixture of 6- and 4-methoxy-3-methyl-2-ethylindoles was separated with a Khrom-2 chromatograph equipped with a preparative adapter. The column was 0.8 m long and had an inner diameter of 18 mm. Chromosorb W, to which 4% KOH and 6% polyethylene glycol (mol. wt. 15,000) had been applied, was used as the stationary phase. The column temperature was 200°, and the gas-carrier (N_2) flow rate was 260 ml/min. The detector was a flame ionization device.

The ratio of the reaction products in the cyclization of the m-ethyl- and m-methoxyphenylhydrazones was studied with a Tswett-1 chromatograph. The column was 1 m long and had an inner diameter of 4 mm. Chromosorb A, to which 1.7% KOH and 10% polyethylene glycol (mol. wt. 15,000) had been applied, was used as the stationary phase. The column temperature was 170°, and the gas-carrier (N_2) flow rate was 110 ml/min. A flame-ionization detector was used. Only the yields of reaction products were determined in the case of 4- and 6-chloro-3-methyl-2-ethylindoles by chromatography. Chromosorb G, to which 5% 5F4É polyphenyl ether and 20% polyethylene glycol (mol. wt. 15,000) had been applied, served as the stationary phase. The column temperature was 220°, and the gas-carrier (N_2) flow rate was 144 ml/min. The yields of reaction products were determined by internal normalization. Benzene solutions of 3,4-dimethyl-2-ethylindole (R = C_2H_5), 2,3,5-trimethylindole (R = OCH_3), and 1-benzyl-2,3-dimethylindole (R = Cl) were used as the standards. The yields and percentage ratios of isomers formed (see Table 1) were determined by weighing the chromatographic peaks.

m-Ethyl-, m-Methoxy-, and m-Chlorophenylhydrazones. These were obtained by condensation of the appropriate hydrazines with diethyl ketone [9].

3-Methyl-2,6-diethylindole. This compound melted at 67-68°. IR spectrum, cm^{-1}: 813 δ_{CH} (H_7), 864 δ_{CH} ($H_{5,6}$); 1565, 1590, and 1625 ν_{ring}; 2860, 2931, and 2965 ν_{CH}; 3415 ν_{NH}. UV spectrum: λ_{max} 230, 289 nm (log ε 4.52 and 3.70). PMR spectrum*: 2-CH_3 1.20 t; 2- and 6-CH_2 2.70 q and 2.67 q, J = 7.5 Hz; 3-CH_3 2.15 s. Aromatic ring protons: H_4 7.27 d; H_5 6.75 q; H_7 7.0 d; $J_{4,5}$ = 7.5 Hz; $J_{5,7}$ = 1.8 Hz.

3-Methyl-2,4-diethylindole.† IR spectrum, cm^{-1}: 745 and 785 δ_{CH} ($H_{5,6,7}$); 1558 and 1590 ν_{ring}; 2810, 2870, and 2910 ν_{CH}; 3320 ν_{NH}. The UV spectrum was identical to the spectrum of 3-methyl-2,6-diethylindole. PMR spectrum: 2-CH_3 1.25 t, 2- and 4-CH_2 3.00 q and 2.97 q; J = 7.5 Hz; 3-CH_3 2.35 s. Aromatic ring protons: H_7 7.15 d; H_6 7.02 t; H_5 6.80 d; $J_{5,7}$ = 1.8 Hz; $J_{5,6}$ = $J_{6,7}$ = 7.5 Hz.

3-Hydroperoxy-3-methyl-2,6-diethylindolenine. A solution of 0.5 g of 3-methyl-2,6-diethylindole in 15 ml of hexane was allowed to stand for 6 h, and the precipitated crystals were removed by filtration and dried to give 0.41 g (71%) of 3-hydroperoxy-3-methyl-2,6-diethylindolenine with mp 120°. IR spectrum,

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*The chemical shifts (in parts per million) are given in the δ scale. The following abbreviations were used: s is singlet, d is doublet, t is triplet, and q is quartet.

†Characterized in a mixture with 3-methyl-2,6-diethylindole.

cm^{-1}: 1600 $\nu_{C=N}$; 1110 ν_{C-O}; 980 ν_{O-O}; 3480 (broad) ν_{OH}. UV spectrum: λ_{max} 223, 228, and 266 nm (log ε 4.18, 4.26, and 3.46). PMR spectrum (in $CDCl_3$): 2-CH_3 1.15 t; 2- and 6-CH_2 2.60 q, J = 7.5 Hz; 3-CH_3 1.35 s; 3-OOH 10.4 s. The position of the peroxide grouping was unambiguously established from the signal of the 3-CH_3 group. The chemical shift of 1.35 ppm is peculiar to an aliphatic grouping. Aromatic ring protons: H_5 6.80 q; H_4 7.07 d; $J_{4,5}$ = 7.5 Hz; H_6 7.15 s. Found %: C 71.3, 71.2; H 7.7, 7.8. $C_{13}H_{17}NO_2$. Calculated %: C 71.2; H 7.7.

6-Methoxy-3-methyl-2-ethylindole. This compound had mp 101-102°. IR spectrum, cm^{-1}: 800 δ_{CH} (H_7), 825 δ_{CH} ($H_{4,5}$); 1500, 1575, and 1628 ν_{ring}; 2910 and 2960 ν_{CH}; 3440 ν_{NH}. UV spectrum: λ_{max} 229, 274, and 296 nm (log ε 4.42, 3.50, and 3.56). PMR spectrum: 2-CH_3 1.20 t; 2-CH_2 2.69 q, J = 7 Hz; 3-CH_3 2.15 s; 6-OCH_3 3.73 s. The aromatic protons are displayed as an ABX system, and a broad H_4 doublet at 7.18 (J = 8.4 Hz, $J_{4,7}$ = 0.8 Hz) is seen at weak field (determined from the half width of the signal). The H_7 signal is displayed as a broad doublet at 6.75 ($J_{5,7}$ = 2.4 Hz), while H_5 appears at 6.60 q. Found %: C 76.3, 76.5; H 7.8, 7.8. $C_{12}H_{15}NO$. Calculated %: C 76.2; H 7.9.

4-Methoxy-3-methyl-2-ethylindole. This compound had mp 76-77°. IR spectrum, cm^{-1}: 740 and 778 δ_{CH} ($H_{5,6,7}$); 1565, 1590, and 1615 ν_{ring}; 1920 ν_{CH}; 3410 ν_{NH}. UV spectrum: λ_{max} 226, 272, and 292 nm (log ε 4.66, 3.86, and 3.81). PMR spectrum: 2-CH_3 1.21 t; 2-CH_2 2.69 q, J = 7 Hz; 3-CH_3 2.35 s; 4-OCH_3 3.82 s. Two multiplets in the aromatic proton region with chemical shifts of 6.34 and 6.83 ppm represent a spectrum of the AA'B type. The stronger-field signal is related to the protons in the 5-position, while the weaker-field signal is related to the H_6 and H_7 protons. The observed J value (3.9 Hz) is close to the expected average value [$(J_o + J_m)$] [2].

6-Chloro-3-methyl-2-ethylindole. This compound had mp 114-115°. IR spectrum, cm^{-1}: 744 ν_{C-Cl}; 807 δ_{CH} (H_7); 845 δ_{CH} ($H_{4,5}$); 1557, 1610 ν_{ring}; 2860, 2920, and 2980 ν_{CH}; 3380 ν_{NH}. PMR spectrum: 2-CH_3 1.22 t; 2-CH_2 2.72 q, J = 7 Hz; 3-CH_3 2.15 s. The aromatic protons are displayed as an ABX system and, as always, a broad H_4 doublet is seen at weakest field (7.34), followed by H_7 at 7.29 q and H_5 at 6.96 q with $J_{4,5}$ = 8.4 Hz, $J_{5,7}$ = 2 Hz, and $J_{4,7}$ = 0.5 Hz. Found %: C 68.3, 68.6; H 6.0, 6.2. $C_{11}H_{12}ClN$. Calculated %: C 68.2; H 6.2.

4-Chloro-3-methyl-2-ethylindole.[*] IR spectrum, cm^{-1}: 745[†] and 772 δ_{CH} ($H_{5,6,7}$); 1550 and 1590 ν_{ring}; 2865, 2930, and 2970 ν_{CH}; 3420 ν_{NH}. PMR spectrum: the signal of the ethyl group coincides with the signals of the ethyl group of 6-chloro-3-methyl-2-ethylindole; 3-CH_3 2.42 s. Two multiplets in the aromatic proton region at 6.92 and 7.22 ppm represent a spectrum of the AA'B type. The signal at weaker field is related to the proton in the 7-position, while the signal at stronger field is related to the $H_{5,6}$ protons. The observed J value (3.4 Hz) is close to the expected average value [$(J_o + J_m)/2$].

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[*] Characterized in a mixture with 6-chloro-3-methyl-2-ethylindole.

[†] The band of the deformation vibrations of the CH bonds of the benzene ring (745 cm^{-1}) in this case coincide with the C−Cl stretching vibrations.