INDOLES

XXXV.* RATIO OF 4-NITRO- AND 6-NITROINDOLES FORMED IN THE FISCHER CYCLIZATION OF m-NITROPHENYLHYDRAZONES

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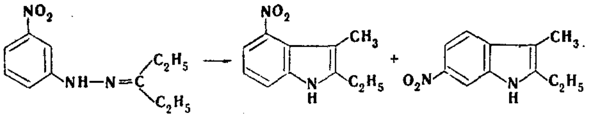
The cyclization of diethyl ketone m-nitrophenylhydrazone under different conditions always gives a mixture of the isomeric 4-nitro-3-methyl-2-ethylindole and 6-nitro-3-methyl-2-ethylindole, generally with a certain predominance of the former. The isomer ratio depends on the nature of the catalyst used. Only 6-nitro-2,3,3-trimethylindolenine is formed in the cyclization of methyl isopropyl ketone m-nitrophenylhydrazone.

We have previously formulated the problem of the quantitative investigation of the effect of substituents in the m-position of the ring of phenylhydrazones on the direction of the Fischer reaction. The isomer with a substituent in the 6 position of the indole ring predominates in all cases in the cyclization of m-alkyl-, m-alkoxy-, and m-haloarylhydrazones [2-4].

In a number of preceding studies of the cyclization of ketone m-nitrophenylhydrazones, the ratio of the isomers formed either was not determined at all or was constructed by means of separation on aluminum oxide, and the results obtained by various researchers were occasionally contradictory [5-12].

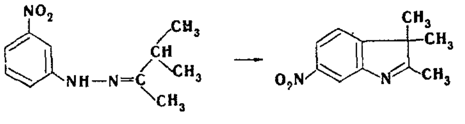
In the present paper we have studied the cyclization of diethyl ketone m-nitrophenylhydrazone to corresponding mixtures of nitroindoles under various conditions:



I II

The results obtained (Table 1) and the previous data [2-4] are in agreement with the intramolecular electrophilic substitution mechanism of the Fischer reaction [13]. Thus the nitro group has strong −I and −M effects. In electrophilic substitution reactions, the −I effect deactivates the o-position, but mesomeric polarization specifically deactivates the p-position [14].

It is necessary to note that the steric factors in the cyclization of m-substituted phenylhydrazones will always favor the formation of the 6-substituted isomer, regardless of the electronic nature of the substituent. This is particularly graphically displayed in the cyclization of methyl isopropyl ketone m-nitrophenylhydrazone, where cyclization proceeds entirely in the p-position relative to the substituent to give 6-nitro-2,3,3-trimethylindolenine:



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*See [1] for communication XXXIV.

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TABLE 1. Ratio of 4- (I) and 6-Nitro-3-methyl-2-ethylindoles (II) Obtained in the Cyclization of Diethyl Ketone m-Nitrophenylhydrazone

Catalyst	Ratio of I to II	
	gas-liquid chromatography	PMR
$ZnCl_2$	70 : 30	75 : 25
30% H_2SO_4	52 : 48	59 : 41
Conc. HCl	48 : 52	47 : 53
Polyphosphoric acid	64 : 36	73 : 27
$BF_3 \cdot (C_2H_5)O$	57 : 43	62 : 38

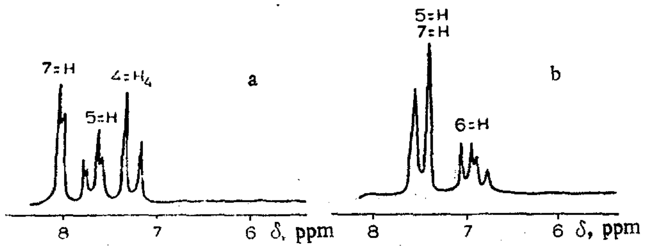

Fig. 1. PMR spectra of 6-nitro-3-methyl-2-ethylindole (a) and 4-nitro-3-methyl-2-ethylindole (b) (aromatic proton region).

4-Nitro- and 6-nitro-3-methyl-2-ethylindoles were isolated in individual form by separation with a column filled with aluminum oxide. The bands of the deformation vibrations (δ_{CH}) were observed at higher frequencies (810, 890 cm^{-1}) in the IR spectrum of 6-nitro-3-methyl-2-ethylindole than in the case of the 4-substituted isomer (740, 800 cm^{-1}); this unambiguously determined the type of substitution in the benzene ring. Characteristic differences were also observed in the aromatic portion of the PMR spectrum. The aromatic protons of 6-nitro-3-methyl-2-ethylindole form an ABX system (Fig. 1), and the 4-H doublet (δ 7.3 ppm) is found at strongest field. Because of the strong deshielding effect of the nitro group, the 5-H proton is observed at weaker field than the 4-H proton in the form of a quartet (δ 7.7 ppm), while the 7-H proton is seen at weakest field at 8.07 ppm as a doublet because of spin–spin coupling with 5-H. The aromatic protons of 4-nitro-3-methyl-2-ethylindole are observed as AA'B system (Fig. 1). The signals of the 5-H and 7-H protons are seen at weakest field at δ 7.47 ppm (doublet), while 6-H (quartet) is observed at δ 6.92 ppm with J = 9 Hz, which corresponds to J_{ortho} for aromatic protons. In addition, signals of the 3-CH_3 (2.18 ppm, singlet) and 2-C_2H_5 (1.25 ppm, triplet; 2.8 ppm, quartet) groups are observed in the spectra of both isomers.

The spectrum of 6-nitro-2,3,3-trimethylindolenine recalls the aromatic portion of the spectrum of 6-nitro-3-methyl-2-ethylindole.

The absorption characteristic for nitroindoles at 250-270 (log ε 3.7) and 400 nm (log ε 3.3) is observed in the UV spectra of 6- and 4-nitro-3-methyl-2-ethylindoles.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Jasco IRS spectrometer with an NaCl prism. The PMR spectra of 10% solutions in CD_3COCD_3 were recorded with a T-60 spectrometer with tetramethylsilane as the internal standard. The gas-liquid chromatographic analysis was performed with a Vanaco G-800 chromatograph with a column 2 m long and 4 mm in diameter. The carrier gas (H_2) flow rate was 60 ml/min, and the column temperature was 190°. Silicone SE-30 (5%) applied to Chezasorb AW-HMDS was used as the stationary phase. The retention volume of the nitroindoles was determined relative to indole. The isomer ratios were determined by weighing the chromatographic peaks.

Cyclization of Diethyl Ketone m-Nitrophenylhydrazone. A. A mixture of 0.2 g of the hydrazone [15] and 15 ml of concentrated hydrochloric acid or 30% sulfuric acid was heated for 2 h on a boiling-water bath. It was then diluted with water, and the precipitated indoles were removed by filtration and vacuum dried over P_2O_5. The yield was 40%.

B. A 0.15-g sample of $BF_3(C_2H_5)_2O$ was added to a solution of 0.2 g of diethyl ketone m-nitrophenylhydrazone in 15 ml of glacial acetic acid, and the mixture was heated on a boiling-water bath for 2 h. It was then diluted with water, and the indoles were removed by filtration and dried over P_2O_5. The yield was 45%.

C. A mixture of 0.16 g of zinc chloride and 0.2 g of the m-nitrophenylhydrazone was slowly heated to 180° on a Wood's metal bath and held at this temperature for 2 h. It was then diluted with 20 ml of water, and the precipitated crystals were removed by filtration and dried over P_2O_5. The yield was 18%.

D. A mixture of 0.2 g of diethyl ketone m-nitrophenylhydrazone and 0.34 g of polyphosphoric acid was heated on an oil bath at 130° for 2 h. At the end of the reaction, the mixture was diluted with 20 ml of water, and the indoles formed were removed by filtration and dried over P_2O_5. The yield was 50%.

Separation of a Mixture of 4- and 6-Nitro-3-methyl-2-ethylindoles. A 2.2-g sample of the mixture of indoles in 20 ml of $CHCl_3$ was applied to a column (40 by 4 cm) containing activity IV Al_2O_3. The compounds were then eluted with petroleum ether–chloroform (1:3). The mixture separated distinctly into two zones in the chromatographic column: the lower zone was yellow and the upper zone was orange. The lower layer gave (after evaporation) orange crystals of 4-nitro-3-methyl-2-ethylindole (0.8 g), and the upper layer gave bright-red crystals of 6-nitro-3-methyl-2-ethylindole (0.7 g).

6-Nitro-3-methyl-2-ethylindole. This compound had mp 164.5°. IR spectrum: 740 cm^{-1} (δ_{C-N-O}), 810, and 890 cm^{-1} [δ_{CH} (4-, 5-, and 7-H)], 1320 cm^{-1} ($\nu_{NO_2}{}^{s}$), 1560 cm^{-1} ($\nu_{NO_2}{}^{as}$), 1470, 1590, and 1620 cm^{-1} (ν_{ring}), 2925, 2950, and 2980 (ν_{CH}), 3350 cm^{-1} (ν_{NH}). UV spectrum: λ_{max} 217, 251, and 402 nm (log ε 4.20, 3.72, and 3.30, respectively). R_f^{1}[*] 0.30, R_f^{2} 0.56, R_f^{3} 0.44. GLC: v_R^{rel} 5.1. Found: C 64.4; H 6.0%. $C_{11}H_{12}N_2O_2$. Calculated: C 64.7; H 5.9%.

4-Nitro-3-methyl-2-ethylindole. This compound had mp 175°. IR spectrum, cm^{-1}: 740 (broad) and 800 [δ_{CH} (5-, 6-, and 7-H)], 740 possibly also δ_{C-N-O}, 1335 $\nu_{NO_2}{}^{s}$, 1565 ($\nu_{NO_2}{}^{as}$), 1470, 1505, and 1570 (ν_{ring}), 2880, 2930, and 2980 (ν_{CH}), 3375 (ν_{NH}). UV spectrum: λ_{max} 218, 252, and 390 nm (log ε 4.11, 3.88, and 3.26). R_f^{1} 0.62, R_f^{2} 0.68, and R_f^{3} 0.52. GLC: v_R^{rel} 3.7. Found: C 64.7; H 5.9%. $C_{11}H_{12}N_2O_2$. Calculated: C 64.7; H 5.9%.

6-Nitro-2,3,3-trimethylindolenine. This compound was obtained in 56% yield by condensation of the corresponding hydrazone [15] in concentrated hydrochloric acid via a method similar to that used for diethyl ketone m-nitrophenylhydrazone. The product had mp 135°. IR spectrum, cm^{-1}: 740 (δ_{C-N-O}), 830 [δ_{CH} (4- and 5-H)], 890 [δ_{CH} (7-H)], 1340 ($\nu_{NO_2}{}^{s}$), 1530 ($\nu_{NO_2}{}^{as}$), 1575, 1610 (ν_{ring}), 1710 ($\nu_{C=N}$). PMR spectrum: δ 0.95 (singlet, 3-CH_3), 1.88 (singlet, 2-CH_3), 7.33 (distorted quartet, 4-H), 7.6 (quartet, 5-H, $J_{5,7}$ = 2.0 Hz, $J_{4,5}$ = 9 Hz), 7.8 (singlet, 7-H). UV spectrum: λ_{max} 215, 243 nm (log ε 4.23, 4.30). GLC: v_R^{rel} 4.3. Found: C 64.6; H 6.2%. $C_{11}H_{12}N_2O_2$. Calculated: C 64.7; H 5.9%.

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[*] Here and below, R_f^{1} was determined on activity IV Al_2O_3 [petroleum ether–chloroform (1:3)], R_f^{2} was determined on activity IV Al_2O_3 [benzene–methanol (10:1)], and R_f^{3} was determined on silufol UV 254 [benzene–methanol–water (4:1:2)].