# AZAINDOLE DERIVATIVES

## XL.* SYNTHESIS OF 3-METHYL- AND 2,3-DIMETHYL-5-AZAINDOLES

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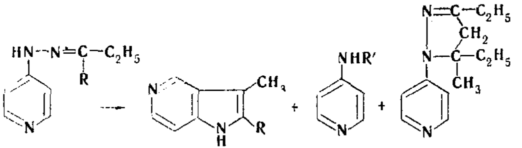
UDC 547.821.822.7'751.07

The peculiarities of the Fischer cyclization of the 4-pyridylhydrazones of propionaldehyde and methyl ethyl ketone, the formation of 3-methyl- and 2,3-dimethyl-5-azaindoles, 4-aminopyridine, 4-ethylaminopyridine, and 1-(4'-pyridyl)-3,5-diethyl-5-methylpyrazoline under these reaction conditions, and the effect of various catalysts on the direction of the process and the yields of products were examined.

The most rational method for the synthesis of 3-methyl- and 2,3-dimethyl-5-azaindoles (Ia, b) is the Fischer cyclization of the corresponding 4-pyridylhydrazones. The previously realized thermal indolyzation ("in the absence of catalysts") of the 4-pyridylhydrazones of propionaldehyde (IIa) and methyl ethyl ketone (IIb) gave Ia in 34.5% yield [2] and Ib in 51-52% yields [2-4].

In order to determine the effect of catalysts on these reactions, to verify how general in character the previously found regularities in the effect of catalysts are [5, 6] in the pyridylhydrazone series, to study the side products, and also to raise the yields of I, we investigated the indolyzation of the 4-pyridylhydrazones of propionaldehyde and methyl ethyl ketone under the influence of various catalysts – strong mineral acids (hydrochloric and polyphosphoric), organic sulfo acids (p-toluenesulfonic acid and sulfosalicylic acid), Lewis acids (zinc chloride and cuprous chloride), and a catalyst of basic character (sodium ethoxide). For comparison, we carried out the thermal indolyzation in refluxing diethylene glycol. In order to study the effect of the reaction temperature and time on the direction of the process and the yield of major products, we varied the indicated parameters over broad intervals.

The yields of substances, which were determined by gas-liquid chromatography (GLC), were checked by the results of preparative isolation of the compounds (Table 1).



IIa, b Ia, b IIIa, c IV

a R=H; b R=$CH_3$; c R=$C_2H_5$

As the data in Table 1 demonstrate, the relative activities of the catalysts during the cyclization of cyclohexanone 4-pyridylhydrazone, which were previously found in [6], are basically retained also for the indolyzation of the 4-pyridylhydrazones of aliphatic aldehydes and ketones. The highest yields of normal Fischer products (Ia, b) are observed with excess zinc chloride. Successive transition to p-toluenesulfonic acid, polyphosphoric acid, sulfosalicylic acid, and cuprous chloride regularly increases the yields of side products. The use of zinc chloride as a catalyst makes it possible to raise the yields of 2,3-di-

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*See [1] for communication XXXIX.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 652-655, May, 1972. Original article submitted March 16, 1971.

TABLE 1. Effect of Catalysts, Temperature, and Reaction Time on the Indolyzation of 4-Pyridylhydrazones of Propionaldehyde and Methyl Ethyl Ketone

| Starting hydrazone | Catalyst | Time, min | Temp, °C | Yield, % | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | I | II | IIIa | IIIc | IV |
| IIa | Zinc chloride | 7 | 240 | 38 | 47 | 12 | | |
| | " " | 60 | 240 | 34 | 13 | 49 | | |
| | Cuprous chloride | 7 | 240 | 3 | 12 | 76 | | |
| | Conc. HCl | 240 | Reflux | 6 | — | 88 | | |
| | Polyphosphoric acid | 10 | 180 | 8 | 34 | 57 | | |
| | p-Toluenesulfonic acid | 7 | 170 | 9 | 40 | 34 | | |
| | Sulfosalicylic acid | 7 | 190 | 7 | — | 82 | | |
| | Sodium ethoxide | 10 | 220 | — | 79 | 7 | 12 | |
| | " " | 40 | 270 | — | — | 15 | 74 | |
| | Thermal indolyzation in diethylene glycol | 18 h | Reflux | 3 | 88 | 7* | | |
| IIb | Zinc chloride | 7 | 200 | 86 | 2 | 6 | | |
| | " " | 7 | 240 | 61 | — | 31 | | |
| | Cuprous chloride | 7 | 240 | 2 | 15 | 76 | | |
| | Conc. HCl | 4 h | Reflux | 2 | 80 | 10 | | |
| | Polyphosphoric acid | 7 | 170 | 2 | 40 | 30 | | 25 |
| | " " | 180 | 170 | 2 | 16 | 62 | | 8 |
| | " " | 7 | 230 | 2 | 17 | 60 | | 12 |
| | p-Toluenesulfonic acid | 7 | 170 | 8 | 4 | 78 | | 4 |
| | Sulfosalicylic acid | 7 | 190 | 6 | 20 | 45 | | 12 |
| | Sodium ethoxide | 7 | 200 | — | 80 | 3 | 17 | |
| | " " | 20 | 270 | 3 | 5 | 2 | 85 | |
| | Thermal indolyzation in diethylene glycol | 18 h | Reflux | 58 | — | 12* | — | — |

*The formation of 4-aminopyridine (IIIa) during the thermal indolyzation of II was not detected in [2-4].

methyl-5-azaindole (Ib) to 86% and of 3-methyl-5-azaindole (Ia) to 38%. It should be noted that, on passing from cyclohexanone 4-pyridylhydrazone to derivatives of noncyclic aldehydes and ketones, which have a lower capacity for enolization, as also in the case of the corresponding 2-pyridylhydrazones [7], the yields of normal Fischer reaction products are lowered. The quantities of substances that are formed due to other transformations of II increase simultaneously.

Among such substances, one should first note 4-aminopyridine (IIIa), the yields of which in all cases increase as the reaction temperature increases and reach 85-88% under certain conditions.

When sodium ethoxide is used as the catalyst, the major product, as is the case for other 4-pyridylhydrazones [6, 8] is 4-ethylaminopyridine (IIIc), the yields of which amount to 74-85%.

The formation of a substance that contains a pyrazoline ring during the Fischer reaction in the presence of hydrochloric or sulfosalicyclic acid was first demonstrated in the case of cyclohexanone 4-pyridylhydrazone [6]. A similar product of the "anomalous" Fischer reaction – 1-(4'-pyridyl)-3,5-diethyl-5-methylpyrazoline (IV) – is formed in the cyclization of IIb in the presence of polyphosphoric, p-toluenesulfonic, and sulfosalicylic acids. In its properties, this substance proved to be extremely close to 1-(4'-pyridyl)-3,3a,4,5,6,7-hexahydroindazole-3-spirocyclohexane, which is obtained as a result of a side reaction from cyclohexanone 4-pyridylhydrazone [6]. The UV and mass spectra of the two compounds are similar.* The yield of IV decreases with increasing temperature and heating time, under which conditions the process is shifted to favor the formation of IIIa.

## EXPERIMENTAL

3-Methyl-5-azaindole (Ia). A 1.3 g (8.7 mmole) sample of IIa [2] was mixed with 3 g (21 mmole) of zinc chloride, and the mixture was heated at 230-240° for 7 min and dissolved in 30 ml of 18% hydrochloric acid. The solution was made alkaline to pH 9 with sodium hydroxide and extracted with chloroform. The

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*We are pleased to thank E. M. Peresleni, O. S. Anisimova, N. P. Kostyuchenko, and Yu. I. Pomerantsev for their assistance in carrying out the spectral investigations.

chloroform extract was dried with potassium carbonate and vacuum evaporated. The residue was washed with 150 ml of ether and crystallized from ether–alcohol (1:1) to give 0.36 g (31.2%) of I with mp 144-145° [2]. The ether filtrate was evaporated, and the residue was chromatographed with a column filled with aluminum oxide (d 2 cm, $Al_2O_3$ h 54 cm). The column with the applied substance was washed with 200 ml of heptane, after which 200 ml of ether eluted 0.08 g (9%) of IIIa with mp 168°, while 300 ml of ether eluted 0.51 g (43.5%) of IIa with mp 87-89°. The yield of Ia did not exceed 3% on many repetitions of the thermal indolyzation of IIa under the conditions in [2].

2,3-Dimethyl-5-azaindole (Ib). A 2 g (12 mmole) sample of IIb [2] was mixed with 4 g (28 mmole) of zinc chloride, and the mixture was heated at 240° for 7 min. The reaction was exothermic and was accompanied by gas evolution. The reaction mixture was dissolved in 100 ml of hot water, and the solution was made alkaline to pH 9 with sodium hydroxide and extracted with chloroform. The extract was dried with potassium carbonate and vacuum evaporated, and the residue (1.85 g) was crystallized from ethyl acetate to give 1.4 g (79%) of Ib with mp 214-215° [2].

1-(4'-Pyridyl)-3,5-diethyl-5-methylpyrazoline (IV). A 2.8 g (17 mmole) sample of IIb was heated with polyphosphoric acid (prepared from 4 ml of orthophosphoric acid and 5 g of $P_2O_5$) at 170° for 45 min. The cooled reaction mass was dissolved in 50 ml of 18% hydrochloric acid, and the solution was extracted with chloroform. The extract was washed with 50% potassium carbonate solution, dried with calcined potassium carbonate, and evaporated to give 1.06 g (27%) of IV. The substance was vacuum distilled to obtain an analytical sample with bp 120-121° (3 mm) as a colorless liquid that was quite soluble in the usual organic solvents and poorly soluble in water; $n_D^{20}$ 1.5728. IR spectrum: intense band at 1590 $cm^{-1}$ (C=C, C=N), absence of absorption in the region of NH bond vibrations. UV spectrum: $\lambda_{max}$ 295 nm (log ε 4.36). PMR spectrum: two doublets at 6.91 (2 proton units) and 8.14 ppm (2 proton units) from the protons in the β and α positions of the γ-monosubstituted pyridine ring, singlet at 1.43 ppm (3 proton units) from a $CH_3-C$ group, two triplets at 0.74 and 1.11 ppm (3 proton units each), two quartets at 2.30 and 2.79 ppm (2 proton units each) from two $C_2H_5$ groups, and a multiplet at 1.5-2.0 ppm (2 proton units) from two protons in the 4 position of the pyrazoline ring. Found: C 72.18; H 8.75; N 19.12%. $C_{13}H_{19}N_3$. Calculated: C 71.90; H 8.75; N 19.35%.

The aqueous solution remaining after extraction of IV with chloroform was made alkaline to pH 9 with sodium hydroxide and was again extracted with chloroform. The extract was dried with potassium carbonate and vacuum evaporated. The residue was chromatographed with a column filled with aluminum oxide (d 2 cm, h 54 cm). The column with the applied substance was washed with 200 ml of heptane, after which 300 ml of ether eluted 0.46 g (31%) of IIIa with mp 168°, while 400 ml of ether eluted 0.64 g (24%) of the starting IIb with mp 124-125°, and 200 ml of ether–methanol (1:1) eluted 0.06 g (2.7%) of Ib with mp 214-215°. All of the isolated substances did not depress the melting points of authentic samples of IIIa, IIb, and Ib, respectively.

Reaction of Methyl Ethyl Ketone 4-Pyridylhydrazone (IIb) with Sodium Ethoxide. A 0.5 g (3 mmole) sample of IIb was mixed in a reaction flask with 0.3 g (4.5 mmole) of freshly prepared sodium ethoxide, and the mixture was heated at 270° for 20 min and cooled. Water (25 ml) was then added to the reaction mass, and the mixture was extracted with chloroform. The extract was dried with potassium carbonate and vacuum evaporated, and the residue was distilled to give 0.29 g (73%) of IIIc with bp 110-112° (2 mm) and mp 98-99°. The product did not depress the melting point of an authentic sample of IIIc.

The conditions used to carry out the remaining experiments and the results are presented in Table 1. Gas-liquid chromatography was carried out with a Pye-Unicam series 104 chromatograph with a flame-ionization detector and a 2.1 m × 4 mm column packed with 10% SE-30 silicone elastomer on silanized diatomite (100-120 mesh) with a nitrogen flow rate of 29 ml/min at a column temperature of 215°. The retention times (in minutes) were as follows: 8.0 for Ia, 7.0 for Ib, 5.8 for IIa, 6.0 for IIb, 1.0 for IIIa, 1.7 for IIIc, and 12.5 for IV.

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