ANOMALOUS TRANSFORMATIONS OF ACETALDEHYDE (2,6-DICHLORO-4-PYRIDYL)HYDRAZONE UNDER THE CONDITIONS OF THE FISCHER REACTION

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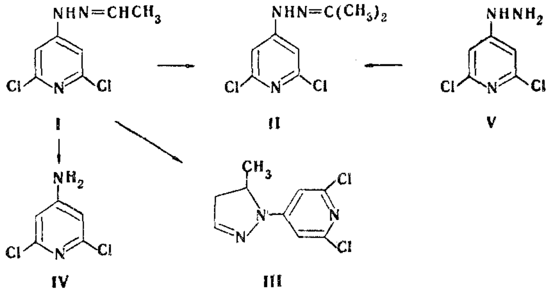
Instead of the usual indolization, when acetaldehyde (2,6-dichloro-4-pyridyl)hydrazone is heated with zinc chloride under the conditions of the Fischer reaction one observes the formation of acetone (2,6-dichloro-4-pyridyl)hydrazone, 1-(2,6-dichloro-4-pyridyl)-5-methylpyrazoline, and 2,6-dichloro-4-aminopyridine, the ratio between which depends on the temperature and duration of the reaction.

In our preceding communication [1], we considered the peculiarities of the Fischer cyclization of (2,6-dichloro-4-pyridyl)hydrazones and showed that the introduction of α,α'-chlorine atoms in all cases reduces the deactivating effect of the electron-acceptor pyridine nitrogen atom and makes it possible to appreciably raise the yields of normal indolization products. In a continuation of this research, we have studied the behavior of acetaldehyde (2,6-dichloro-4-pyridyl)hydrazone (I) under the conditions of the Fischer reaction. The reaction was carried out in the presence of zinc chloride, which has previously shown itself to be the best catalyst of the Fischer reaction for a number of pyridylhydrazones [2]. The temperature was varied from 220 to 270°C. The products of the transformations were analyzed by gas-liquid chromatography (GLC) and were then subjected to preparative separation by chromatography on aluminum oxide. All of the substances that were formed in yields above 5% were isolated and identified.

Acetaldehyde phenylhydrazone cannot be converted to indole under the usual conditions of the Fischer reaction [3], and this synthesis was realized only when a contact method [4] was used.

The normal indolization of I also does not occur in the reaction that we investigated. Depending on the temperature and time of heating of I with zinc chloride, we observed the formation of different ratios of products of anomalous transformations: acetone (2,6-dichloro-4-pyridyl)hydrazone (II), 1-(2,6-dichloro-4-pyridyl)-5-methylpyrazoline (III), and 2,6-dichloro-4-aminopyridine (IV).



The structures of II and III were established on the basis of elementary analysis and the PMR and mass spectra.

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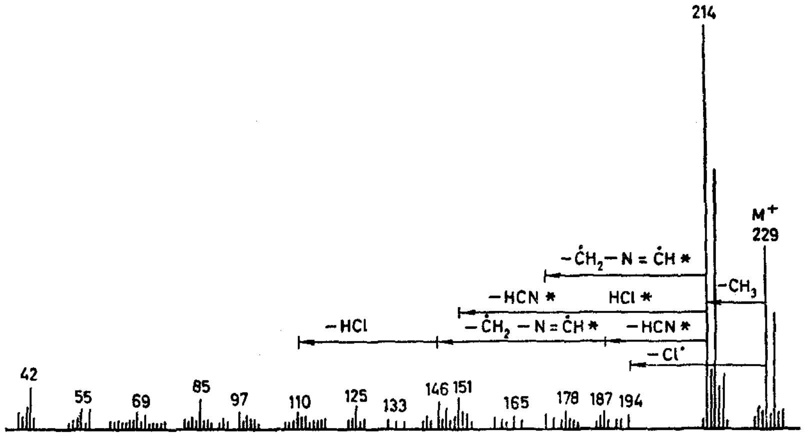
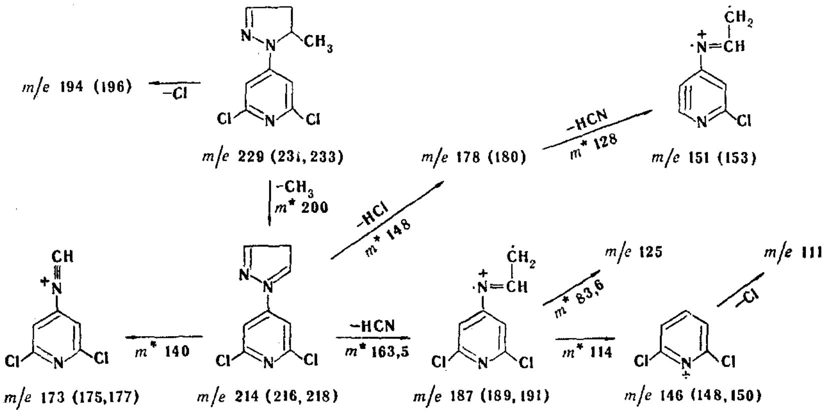


Fig. 1. Mass spectrum of 1-(2,6-dichloro-4-pyridyl)-5-methylpyrazoline.

A molecular ion with m/e 217 (here and elsewhere, the mass numbers for ions with a Cl^{37} isotope are presented) is observed in the mass spectrum of hydrazone II, while two singlets of methyl groups with δ 1.82 and 1.92 ppm and a singlet of two β protons of the pyridine ring (δ 6.83 ppm) are observed in the PMR spectrum (in CD_3OD).

The ratio of the intensities of the isotope peaks of the molecular ion in the mass spectrum of III demonstrates the presence in the molecule of two chlorine atoms. The most favorable process of disintegration of the molecular ion of III (m/e 229) is elimination of a CH_3 group with subsequent opening of the pyrazoline ring:



Disintegration of the pyrazoline ring leads to the appearance in the spectrum (see Fig. 1) of peaks with m/e 173, 187, and 146 and is confirmed by the presence of metastable transitions. The PMR spectrum of III (in CD_3COCD_3) contains the doublet of a methyl group at 1.24 ppm (J = 6 Hz), a multiplet of a CH_2 group at 2.60-3.45 ppm ($J_{44'}=18.7$ Hz, $J_{45}=9.7$ Hz, $J_{4'5}=3.7$ Hz, $J_{43}=J_{4'3}=1.9$ Hz), a multiplet at 4.5 ppm of the 5-H methylidyne proton, and a singlet at 6.89 ppm which is characteristic for two β protons of the pyridine ring, and a weakly resolved triplet of the 3-H proton at 7.14 ppm.

In addition, II was obtained by alternative synthesis from (2,6-dichloro-4-pyridyl)hydrazine (V) and acetone, while IV was identical to a sample of 2,6-dichloro-4-aminopyridine synthesized via a previously described method [5]. Increasing the reaction temperature from 220 to 245° and then to 270° (heating time 10 min) leads to a regular increase in the yields of III from 16% to 18% and further to 21%, respectively, while the yields of IV increase from 11% to 31% and then to 35%; the yield of II simultaneously decreases from 26% to 12% and then to 7%. The buildup of 2,6-dichloro-4-aminopyridine (IV) in the reaction mixture apparently occurs through thermal decomposition of pyridylhydrazones I and II. In particular, evidence for this is a comparison of the data presented above with the results of an experiment at 245° for 3 min, in which the yields of I, II, III, and IV were, respectively, 4%, 24%, 19%, and 1%. In addition, the pure acetone (2,6-dichloro-4-pyridyl)hydrazone (II) isolated from the reaction mixture proved to be an extremely stable compound that withstood heating with zinc chloride to 260° for 10 min. At 280° under the same conditions, up to 70% of II remained unchanged; considerable resinification was observed only at 300° (after 10 min), the amount of II (according to GLC) was reduced to 30%, and ~ 20% of IV was obtained.

The formation of acetone (2,6-dichloro-4-pyridyl)hydrazone (II) from acetaldehyde (2,6-dichloro-4-pyridyl)hydrazone (I) was unexpected and apparently can be explained by alkylation of I by methyl radicals formed during the high-temperature destruction of the substance.

As for the pyrazoline derivative III, we have observed the formation of similar types of compounds in the cyclization of cyclohexanone 4-pyridylhydrazones [2] and methyl ethyl ketone 4-pyridylhydrazone [6] in the presence of polyphosphoric acid and organic sulfonic acids. However, the capacity of zinc chloride to bring about closing of the pyrazoline ring on heating with 4-pyridylhydrazones has appeared for the first time in the case of I.

EXPERIMENTAL

The IR spectra of mineral oil suspension were recorded with a UR-10 spectrophotometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer at an ionizing voltage of 50 eV.

Acetaldehyde (2,6-Dichloro-4-pyridyl)hydrazone (I). A 1.78-g (10 mmole) sample of V [1] was stirred for 10 min with 4.4 g (100 mmole) of acetaldehyde until a homogeneous solution had formed, after which the excess acetaldehyde was removed by vacuum distillation. The residue was recrystallized from 33% aqueous methanol to give 1.79 g (88%) of I with mp 182-183°. The product was quite soluble in alcohol and chloroform and only slightly soluble in other organic solvents. Found: C 41.0; H 3.3; Cl 34.9; N 20.3%. $C_7H_7Cl_2N_3$. Calculated: C 41.2; H 3.4; Cl 34.8; N 20.6%.

Acetone (2,6-Dichloro-4-pyridyl)hydrazone (II). A. A mixture of 0.5 g (2.4 mmole) of I and 1.5 g (10 mmole) of zinc chloride was heated at 230° for 10 min. It was then cooled and dissolved in 10 ml of 18% hydrochloric acid. The acid solution was extracted with three 50-ml portions of chloroform,* after which it was made alkaline to pH 10 with 20% sodium hydroxide, and the bases were extracted with three 75-ml portions of chloroform. The chloroform extract was dried with potassium carbonate and evaporated, and the residue was recrystallized from ether to give 0.07 g (14%) of II with mp 197-198°. The product did not depress the melting point of a sample obtained via method B. The IR spectra of the two samples were identical. Found: C 44.0; H 4.5; Cl 31.9; N 19.2%. $C_8H_9Cl_2N_3$. Calculated: C 44.3; H 4.2; Cl 32.2; N 19.4%.

B. A 10-ml sample of methanol and 3 ml (~ 50 mmole) of acetone were added to 0.9 g (5 mmole) of V, and the mixture was stirred for 5 min, after which it was vacuum-evaporated. The residue was recrystallized from 33% aqueous methanol to give 0.99 g (91%) of II with mp 197-198°. The product was quite soluble in alcohol and chloroform and only slightly soluble in other organic solvents.

Reaction of I and II with Zinc Chloride under the Conditions of the Fischer Reaction. A mixture of 10 mmole of I or II and 35 mmole of zinc chloride was heated at 220-300° for 3-10 min (the interval of temperature variations was 2-3°, while the interval of time variations was 1 min), after which the mixture was cooled and dissolved in 18% hydrochloric acid. The acid solution was made alkaline to pH 10 with 20% aqueous sodium hydroxide solution and extracted with chloroform. The extract was evaporated, and the residue was analyzed with a Pye-Unicam series 104 gas-liquid chromatograph with a flame ionization detector. The column (2.1 m by 4 mm) was filled with 10% silicone elastomer SE-30 on silanized diatomite (100-120 mesh). The nitrogen flow rate was 29 ml/min, the programmed temperature conditions ranged from 160 to 245°, and the initial period was 5 min. The temperature-rise rate was 32 deg/min. The retention times were as follows: 13.5 min for I, 14.5 min for II, 16 min for III, and 9 min for IV. The area of each peak was compared with the areas of the peaks of authentic samples of the pure compounds that were introduced under the same conditions. In addition, the results of analysis were compared with the results of preparative separation of the reaction mixtures by chromatography on aluminum oxide.

1-(2,6-Dichloro-4-pyridyl)-5-methylpyrazoline (III). A mixture of 1 g (4.9 mmole) of I and 3 g (21 mmole) of zinc chloride was heated at 245° for 3 min, after which it was cooled and dissolved in 10 ml of 18% hydrochloric acid. The acid solution was made alkaline with 20% aqueous sodium hydroxide and extracted with chloroform. The chloroform solution was dried with potassium carbonate and vacuum-evaporated. The residue was chromatographed with a column filled with aluminum oxide (h 60 cm, d 1 cm) with

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* A total of 0.03 g (8%) of IV with mp 171° passed into the extract. The substance was identified from the melting point of a mixture with a genuine sample and the IR spectrum [5].

ethyl acetate (100 ml) as the eluent. The ethyl acetate was removed by distillation, and the residue was reapplied to the same column filled with aluminum oxide; elution with 150 ml of ether gave 0.14 g (13%) of III with mp 103-104° (from 15% aqueous methanol). The product was quite soluble in ether, alcohol, and chloroform. Found: C 47.3; H 3.8; Cl 30.6; N 18.4%. $C_9H_9Cl_2N_3$. Calculated: C 47.0; H 3.9; Cl 30.8; N 18.2%.

LITERATURE CITED

1. L. N. Yakhontov and M. F. Marshalkin, Khim. Geterotsikl. Soedin., 1638 (1972).
2. L. N. Yakhontov, M. V. Marshalkin, and O. S. Anisimova, Khim. Geterotsikl. Soedin., 508 (1972).
3. N. N. Suvorov, V. P. Mamaev, and V. M. Rodionov, in: Reactions and Methods for the Investigation of Organic Compounds [in Russian], Vol. 9, Goskhimizdat (1959), p. 46.
4. V. Ya. Kanterov, N. N. Suvorov, N. E. Starostenko, and Yu. G. Oleinikov, Khim.-Farmats. Zh., 1583 (1970).
5. H. Meyer and E. Ritter, Monatsh., 36, 731 (1915).
6. M. F. Marshalkin and L. N. Yakhontov, Khim. Geterotsikl. Soedin., 1528 (1972).