PECULIARITIES IN THE FISCHER CYCLIZATION OF 2,6-DICHLORO-4-PYRIDYLHYDRAZONES

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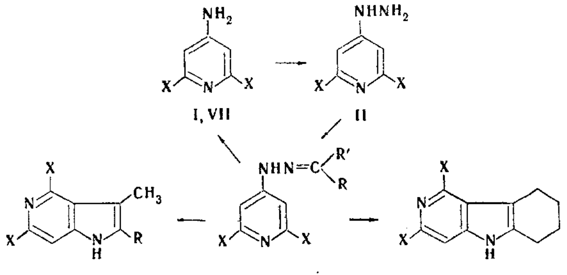
The peculiarities of the Fischer cyclization of 2,6-dichloro-4-pyridylhydrazones were examined. It is shown that the introduction of chlorine atoms into the α,α' position of the pyridine ring in all cases reduces the deactivating effect of the electron-acceptor pyridine nitrogen in this reaction and the Arbuzov modification ("catalytic method"). During thermal indolization, the process is shifted to favor the primary formation of 2,6-dichloro-4-aminopyridine.

The Fischer cyclization, which proceeds through a step involving electrophilic substitution – the semibenzidine rearrangement – is readily accomplished with various arylhydrazones, but difficulties are encountered in the case of pyridylhydrazones. The presence in the pyridine ring of a heteroatom with a high electron density and the decrease in the electron density on the carbon atoms under the influence of the cyclic nitrogen are responsible for the difficulty in constructing azaindole systems (as compared with indole systems) and induce a large number of side processes [1].

In addition, as we demonstrated in the course of previous investigations [2], the introduction of halogen atoms into the 2 and 6 positions of the pyridine ring suppresses the electron-acceptor effect of the heterocyclic nitrogen and, in their properties, 2,6-dihalopyridines approach compounds of the benzene series.

In this connection, it seemed of interest to study the Fischer cyclization of 2,6-dichloro-4-pyridylhydrazones, for which one might have expected greater ease in carrying out the process than for the corresponding dehalogenated compounds.

The previously undescribed 2,6-dichloro-4-pyridylhydrazine (II) was synthesized from 2,6-dichloro-4-aminopyridine (I) [3] by diazotization and subsequent reduction of the diazonium salt with stannous chloride in hydrochloric acid. The Fischer reaction was studied in the case of cyclohexanone 2,6-dichloro-4-pyridylhydrazone (IIIa), methyl ethyl ketone 2,6-dichloro-4-pyridylhydrazone (IIIb), and propionaldehyde 2,6-dichloro-4-pyridylhydrazone (IIIc). For comparison, we examined the results of cyclization of the corresponding 4-pyridylhydrazones (IVa-c) [4] under the same conditions. In each case, the reactions were



I, VII

II

V, VI b,c

III, IV a-c

V, VI

I-III X = Cl; IV, VII X = H; a R-R' = -$(CH_2)_5$-; b R = CH_3, R' = C_2H_5; c R = H, R' = C_2H_5;
V X = Cl; b R = CH_3; VI X = H; c R = H

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TABLE 1. Yields of Reaction Products in the Cyclization of 4-Pyridyl- and 2,6-Dichloro-4-pyridylhydrazones in the Presence of Various Catalysts

Catalyst	Starting 4-pyridylhydrazones																	
	IVa			IIIa			IVb			IIIb			IVc			IIIc		
	Yield, %																	
	VIa	VII	Other substanc.	Va	I	Other substanc.	VI	VII	Other substances	Vb	I	Other substanc.	VIc	VII	Other substances	Vc	I	Other substances
Zinc chloride	96			98			61			97			38	12	42*	55	25	6*
Cuprous chloride	42	55		55	26	7*	2	76	15*	54	28		3	76	12*	5	66	9*
p-Toluenesulfonic acid	66	32	2 †	69	31		8	85	5 ‡	52	39		9	34	40*	23	76	
Sulfosalicylic acid	40	37	8 †	70	30		6	45	20*, 12 ‡	55	32		7	82		12	86	
Polyphosphoric acid	49	41		82	18		4	40	30*, 20 ‡	52	43		8	57	34*	29	53	12*
Conc. hydrochloric acid	47	3	33 †	27	36	15*	2	10	80*	25	26	32*	6	88		11	68	19*
Diethylene glycol	83	2		—	90	3*	58	12		5	56	37*	—	—	100*	6	11	81*

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*Starting hydrazone.

† 4-Hydroxypyridine.

‡ 1-(4'-Pyridyl)-3,5-diethyl-5-methylpyrazoline.

studied with various catalysts: strong mineral acids (hydrochloric and polyphosphoric), organic sulfonic acids (p-toluenesulfonic and sulfosalicylic), Lewis acids (zinc chloride and cuprous chloride). Thermal indolization in refluxing diethylene glycol was also investigated.

The yields of the products, determined by gas-liquid chromatography (GLC), were monitored from the results of preparative isolation of the compounds and are presented in Table 1. As seen from Table 1, when the Fischer reaction is carried out in the presence of acid catalysts, the yields of normal products of the indolization of 2,6-dichloropyridylhydrazones III are higher in all cases than the yields for the analogous pyridylhydrazones IV, which do not contain halogen. This provides a basis for asserting that the introduction of chlorine atoms into the α,α' positions of the pyridine ring of various 4-pyridylhydrazones to a certain degree reduces the deactivating effect of the electron-acceptor pyridine nitrogen on the course of the Fischer reaction.

It is interesting to note that the relationship is different in the thermal indolization of pyridylhydrazones in diethylene glycol without acid catalysts: the introduction of chlorine atoms into the 2 and 6 positions of the pyridine ring not only does not increase the yields of normal products of thermal indolization but shifts the process to favor the primary formation of 2,6-dichloro-4-aminopyridine. This is evidence for the different character of the effect of diethylene glycol on the course of the Fischer reaction as compared with the behavior observed with acid catalysts. It is possible that in this case the ease of solvation of the molecule has an important effect, and suppression of the basic properties of the pyridine ring hinders this process.

As demonstrated by the preceding investigations [5], in contrast to arylhydrazones, various pyridylhydrazones give low yields in the Arbuzov catalytic method of indolization; this was associated with the ability of the pyridine nitrogen (along with the nitrogen of the hydrazone portion of the molecule) to interact with Lewis acids and remove them from the reaction sphere.

It was natural to assume that in the case of 2,6-dichloropyridylhydrazones, in which the nucleophilic properties of the cyclic nitrogen and, consequently, its ability to tie up the Lewis acids are strongly suppressed, the Arbuzov catalytic indolization would proceed considerably more readily.

In this connection, we carried out comparative experiments on the indolization of IVa and its 2,6-dichloro derivative (IIIa) in the presence of catalytic amounts of zinc chloride at 240° for 7 min. In the first case, the yield of VIa was 8.2%, and about 90% of the starting IVa was recovered unchanged; in the second case, only 6.3% of the starting 2,6-dichloropyridylhydrazone (IIIa) did not undergo reaction, the yield of Va was 66%, and about 19% of the substance was converted to I.

Thus the greater ability of 2,6-dichloro-4-pyridylhydrazones, as compared with dehalogenated compounds, to undergo the Fischer reaction is apparently associated not only with the change in the electron density on the ring carbon atoms, but also with the different ease of salt formation at the pyridine nitrogen; this in turn affects the distribution of electron density and the energic favorability of the intermediates of the reaction.

EXPERIMENTAL

2,6-Dichloro-4-pyridylhydrazine (II). A solution of 1.5 g (22 mmole) of sodium nitrite in 15 ml of water was added dropwise (initially) with stirring and cooling to −5° to 2 g (12 mmole) of I in 20 ml of concentrated hydrochloric acid, after which 15 g (81 mmole) of stannous chloride in 20 ml of concentrated hydrochloric acid was added and stirring was continued at 0 to −3° for 2.5 h. The precipitate was removed by filtration, and the filtrate was washed three times with 100 ml portions of chloroform and made alkaline with 40% sodium hydroxide solution. Compound II was extracted with chloroform in an extractor. The solvent was removed by distillation to give 1.67 g (76%) of colorless crystals of II with mp 209-210° (from methanol). The product was soluble in chloroform and hot alcohols but only slightly soluble in the other ordinary organic solvents and water. Found,%: C 34.2; H 3.0; Cl 39.3; N 23.5. $C_5H_5Cl_2N_3$. Calculated,%: C 33.9; H 2.8; Cl 39.5; N 23.7.

Cyclohexanone 2,6-Dichloro-4-pyridylhydrazone (IIIa). A 3-ml (30 mmole) sample of cyclohexanone was added to 1.5 g (8.8 mmole) of II. The reaction mass warmed up, became homogeneous, and solidified after 20 min. Compound IIIa was triturated with 20 ml of 70% aqueous methanol and removed by filtration to give 1.63 g (82%) of a product with mp 188-189° (from 80% aqueous methanol). Found,%: C 51.6; H 5.2; Cl 26.8; N 16.5. $C_{11}H_{13}Cl_2N_2$. Calculated,%: C 51.4; H 5.1; Cl 27.2; N 16.3.

A similar procedure was used to obtain methyl ethyl ketone 2,6-dichloro-4-pyridylhydrazone (IIIb) (81% yield, mp 161-162°. Found,%: C 46.7; H 5.1; Cl 29.9; N 18.0. $C_9H_{11}Cl_2N_3$. Calculated,%: C 46.6; H 4.8; Cl 30.0; N 18.1) and propionaldehyde 2,6-dichloro-4-pyridylhydrazone (IIIc) (80% yield, mp 137-138°. Found,%: C 44.3; H 4.3; Cl 32.2; N 18.9. Calculated,%: C 44.0; 4.1; Cl 32.5; N 19.3). All of the substances were quite soluble in acetone, less soluble in alcohol and chloroform, and only slightly soluble in the other organic solvents and water.

2,4-Dichloro-5,6,7,8-tetrahydro-γ-carboline (Va). A 0.4-g (1.5 mmole) sample of IIIa was heated at 240° with 1.2 g (8.1 mmole) of zinc chloride for 7 min, and the mixture was dissolved in 100 ml of water and made alkaline to pH 10 with 40% sodium hydroxide solution. Compound Va was extracted with chloroform, and the extract was dried with potassium carbonate and evaporated to give 0.36 g (98%) of Va with mp 287-288°. The product was quite soluble in acetone, less soluble in alcohols and chloroform, and only slightly soluble in other organic solvents and water. Found,%: C 54.6; H 4.4; Cl 29.1; N 11.9. $C_{11}H_{10}Cl_2N_2$. Calculated,%: C 54.8; H 4.2; Cl 29.4; N 11.6.

Reaction of IIIa with p-Toluenesulfonic Acid. A 0.5-g (1.8 mmole) sample of IIIa was heated at 190° with 1 g (6.2 mmole) of p-toluenesulfonic acid for 7 min. The mixture was cooled, dissolved in 50 ml of 18% hydrochloric acid, and made alkaline to pH 10 with 40% sodium hydroxide solution. The alkaline mixture was extracted with chloroform, and the chloroform was removed from the extract by distillation. The residue was chromatographed with a column filled with aluminum oxide (height 54 cm, diameter 2 cm). Ether (500 ml) eluted 0.08 g (26%) of I with mp 172-173°, and methanol (200 ml) eluted 0.26 g (63%) of Va with mp 287-288°.

2,3-Dimethyl-4,6-dichloro-5-azaindole (Vb). A 0.2-g (0.09 mmole) sample of IIIb was heated at 240° with 0.6 g (4 mmole) of zinc chloride for 7 min. The reaction mixture was dissolved in hot water, made alkaline to pH 10, and extracted with chloroform. The chloroform was evaporated from the extract to give 1.79 g (97%) of Vb with mp 283-284° (from methanol). The product was quite soluble in acetone, chloroform, and hot alcohols, but only slightly soluble in other organic solvents and water. Found,%: C 49.9; H 3.6; Cl 33.2; N 13.0. $C_9H_8Cl_2N_2$. Calculated,%: C 50.2; H 3.7; Cl 33.0; N 13.0.

Reaction of IIIb with Sulfosalicylic Acid. A 0.4-g (1.8 mmole) sample of IIIb was heated at 190° with 0.8 g (4.2 mmole) of sulfosalicylic acid for 7 min. The mixture was dissolved in 18% hydrochloric acid, made alkaline to pH 10, and extracted with chloroform. The chloroform was removed by distillation, and the residue was chromatographed with a column filled with aluminum oxide (height 54 cm, diameter 2 cm). A total of 400 ml of heptane–chloroform (1 : 5) eluted 0.75 g (27%) of I with mp 172-173°, 300 ml of chloroform then eluted 0.02 g of a mixture of I and Vb, and 800 ml of chloroform eluted 0.17 g (46%) of Vb with mp 283-284°.

3-Methyl-4,6-dichloro-5-azaindole (Vc). A 0.6-g (2.9 mmole) sample of IIIc was heated at 240° with 1.8 g (12 mmole) of zinc chloride for 7 min. The mixture was dissolved in 50 ml of 18% hydrochloric acid, made alkaline to pH 10 with 40% sodium hydroxide, and extracted with chloroform. The chloroform was evaporated, and the residue was recrystallized from methanol to give 0.23 g (42%) of Vc with mp 274-275°. The colorless crystals were quite soluble in acetone and hot alcohol and only slightly soluble in other ordinary organic solvents and water. Found,%: C 47.9; H 3.0; Cl 35.2; N 13.6. $C_8H_6Cl_2N_2$. Calculated,%: C 47.8; H 3.0; Cl 35.3; N 13.9.

The methanol mother liquor was evaporated to dryness, and the residue was chromatographed with a column filled with aluminum oxide (height 54 cm, diameter 2 cm). A total of 300 ml of heptane–chloroform (1 : 5) eluted 0.08 g (17%) of I with mp 173-174°, and 250 ml of chloroform then eluted 0.03 g (5%) of IIIc with mp 137-138°.

In order to study the reactions by means of gas-liquid chromatography, the process was carried out with 0.45 mmole of starting pyridylhydrazone IIIa-c or IVa-c under the following conditions: for 7 min at 240° with zinc chloride (1.13 mmole) and cuprous chloride (1.35 mmole), for 7 min at 190° with p-toluenesulfonic acid, sulfosalicyclic acid (0.9 mmole in each case), and polyphosphoric acid (prepared from 0.1 ml of phosphoric acid and 0.13 g of phosphorus pentoxide), refluxing for 4 h with concentrated hydrochloric acid (a 10-fold quantity by volume), and refluxing for 18 h in diethylene glycol (a 12-fold quantity by volume). All of the reaction products were converted to bases (in the case of hydrochloric acid and diethylene glycol, the mixtures were first evaporated), extracted with chloroform, and analyzed with a Pye-Unicam 104 chromatograph with a flame ionization detector and a 2.1 m by 4 mm column filled with 10% SE-30 silicone elastomer on silanized diatomite (100-120 mesh); the nitrogen flow rate was 29 ml/min, the program temperature conditions ranged from 160 to 245°, the initial period was 5 min, and the temperature rise rate was 32 deg/min. The retention times in minutes were as follows: 9 for I, 29 for IIIa, 16.5 for IIIb, 14 for IIIc, 33 for Va, 18 for Vb, and 16.5 for Vc. The retention times and chemical characteristics of IVa-c, VIa-c, and VII are presented in [4].

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