EFFECT OF CATALYSTS ON THE FISCHER CYCLIZATION OF CYCLOHEXANONE 4-PYRIDYLHYDRAZONE

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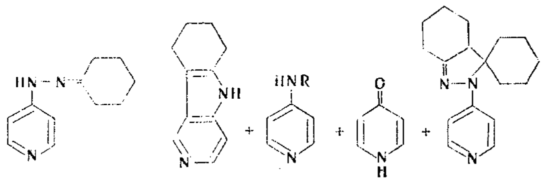
UDC 547.836.3:541.128.1

The peculiarities of the Fischer cyclization of cyclohexanone 4-pyridylhydrazone and the formation of 5,6,7,8-tetrahydro-γ-carboline, 4-aminopyridine, 4-ethylaminopyridine, 4-pyridone, and 2-(4-pyridyl)-3,3a,4,5,6,7-hexahydroindazole-3-spirocyclohexane under the conditions of this reaction are examined. In the case of I, as also for the isomeric 2-pyridylhydrazones, catalysts can be arranged in the following order with respect to their ability to increase the yield of the normal indolyzation product: cuprous chloride ≈ sulfosalicyclic acid < polyphosphoric acid < p-toluenesulfonic acid < zinc chloride. It was established that the indolyzation of I proceeds also without acid catalysts under the influence of sodium ethoxide.

In previous papers of this series [1-3], it was demonstrated that the character of the transformations and the yields of products in the cyclization of cyclohexanone 2-pyridylhydrazone and its analogs, substituted in the pyridine ring, depend to a considerable degree on the nature of the catalyst. Cyclization processes involving the pyridine ring nitrogen are one of the principal side reactions in this case [4]. In addition, systematic investigations of the Fischer cyclization of cyclohexanone 4-pyridylhydrazone (I), for which side reactions of this type are impossible, have not been made. Only the cyclization of I in the presence of zinc chloride, without any indication of the yield of the resulting 5,6,7,8-tetrahydro-γ-carboline (II) [5], and the thermal indolyzation of I, which gives technical-grade II in 95% yield [6], have been described in the literature.



I II III IV V

a R = H, b R = C_2H_5

In the present paper, we have examined the peculiarities of the cyclization of I as compared with the cyclization of cyclohexanone 2-pyridylhydrazone and have studied the effect of various catalysts – strong mineral acids (hydrochloric and polyphosphoric), organic sulfonic acids (p-toluenesulfonic and sulfosalicylic), Lewis acids (zinc chloride and cuprous chloride), and a catalyst of alkaline character (sodium ethoxide) – on this reaction. We also examined the thermal indolyzation of I in the absence of a catalyst. All of the reactions of I were carried out under the same conditions as those used in the case of cyclohexanone 2-pyridylhydrazone [1]: 4 h refluxing in hydrochloric acid, 7 min at 180° with polyphosphoric acid, 7 min at 190° with p-toluenesulfonic acid and sulfosalicylic acid, and 7 min at 240° with Lewis acids. The thermal indolyzation of I was accomplished in 18 h in refluxing diethylene glycol, while the reaction with sodium

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 508-513, April, 1972. Original article submitted January 25, 1971.

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TABLE 1. Yields of Products of the Transformations of Cyclohexanone 4-Pyridylhydrazone (I) as a Function of the Nature of the Catalysts

Catalyst	Yield, %				
	II	IIIa	IIIb	IV	V
Zinc chloride	95,6				
Cuprous chloride	42	54,5			
Conc. HCl	47	3		33	7
Polyphosphoric acid	49	41			
p-Toluenesulfonic acid	65,7	32		2,5	
Sulfosalicylic acid	40	37		8	9
Sodium ethoxide	42	5	35		
Thermal indolyzation	83	2			

TABLE 2. Yields of Tetrahydrocarbolines in the Cyclization of Pyridylhydrazones I and VI-X

Catalyst	Hydrazone					
	I	VI	VII	VIII	IX	X
Zinc chloride	95,6	75	100	100	98	100
p-Toluenesulfonic acid	65,7	72	85	98	93,6	81
Polyphosphoric acid	49	62	73	67,3	71,3	81,7
Sulfosalicylic acid	40	51,6	59,6	60,1	77,9	69
Cuprous chloride	42	50,6	63	54,5	42,6	56,6

ethoxide was accomplished at 240° in 7 min. The yields of substances, determined by gas-liquid chromatography, were monitored by means of the results of preparative isolation of the compounds (Table 1).

The comparative yields of tetrahydrocarboline derivatives in the cyclization of I, of cyclohexanone 2-pyridylhydrazone (VI), and of 6-methyl- (VII), 5-methyl- (VIII), 6-chloro- (IX), and 5-chloro-2-pyridylhydrazone (X) of cyclohexanone [1-3] are presented in Table 2.

As seen from Tables 1 and 2, the relative activities of the catalysts remain fundamentally the same, in the case of cyclohexanone 4-pyridylhydrazone (I), as in the cyclization of the various 2-pyridylhydrazones (VI-X). The greatest yields of normal indolyzation products are observed with excess zinc chloride. The use of p-toluenesulfonic acid reduces the yields somewhat. The successive transition to polyphosphoric acid, sulfosalicylic acid, and cuprous chloride increases the yields of side products.

As in the case of 2-pyridylhydrazones, the reduced capacity of the pyridine ring of I for reaction with electrophilic agents is manifested by the necessity to use high temperatures to carry out the reaction. Thus, for example, in the reaction of I with cuprous chloride, reducing the temperature from 240 to 160°, even on prolonged heating (3 h), was responsible for the isolation of 98% of the unchanged starting I.

A characteristic difference between the 2-pyridylhydrazones and the 4-pyridylhydrazones is the different distances between the pyridine nitrogen and the hydrazone grouping in the molecules of these compounds. The cyclization processes with participation of the pyridine nitrogen that are characteristic for 2-pyridylhydrazones [1,4] are sterically impossible in the case of I. Side products of a different character are therefore realized for 4-pyridylhydrazones (I).

One should first of all note the formation of 4-aminopyridine (IIIa) under the influence of different catalysts. The formation of the latter is associated with cleavage of the N—N bond without the subsequent semidine rearrangement that is necessary for normal indolyzation, which is hindered by the electron density deficit on the carbon atoms of the pyridine ring. The yields of IIIa vary from 2% during thermal indolyzation* to 54.5% when cuprous chloride is used. In all cases, raising the temperature shifts the process to favor 4-aminopyridine (IIIa). Thus, for example, the yield of IIIa at 190° and 250°, respectively, is 37% and 71% with sulfosalicylic acid. The amounts of II decrease simultaneously from 40 to 14%. In the case of p-toluenesulfonic acid, the yield of IIIa increased from 32 to 70% as the temperature was raised from 190° to 245°, while the yield of II decreased from 65.7 to 23%.

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*The formation of IIIa in the thermal indolyzation of I was not detected in [6].

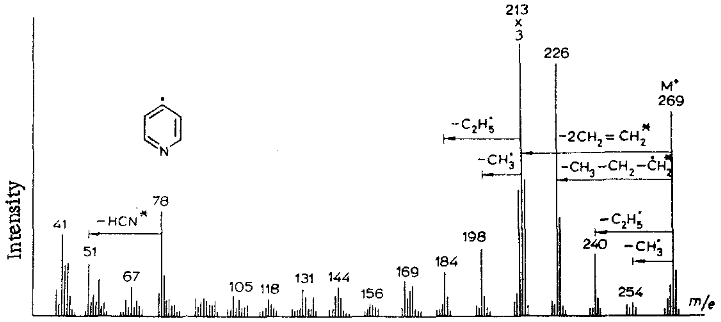


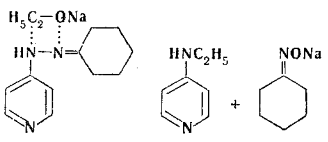
Fig. 1. Mass spectrum of 2-(4-pyridyl)-3,3a,4,5,6,7-hexahydroindazole-3-spirocyclohexane.

A second side product, which is formed in the indolyzation of I with organic sulfonic acids of hydrochloric acid, is 4-pyridone (IV). The yields of IV vary from 2.5 to 33%, depend primarily on the nature of the catalyst, and undergo little change as the reaction temperature is varied over broad limits.

Finally, a third side product in the cyclization of I in concentrated hydrochloric acid or in the presence of sulfosalicylic acid is a substance that contains two cyclohexyl groups and apparently has the 2-(4-pyridyl)-3,3a,4,5,6,7-hexahydroindazole-3-spirocyclohexane (V) structure. The yields of V are 7-9%. The process involved in the development of this compound is similar to the "anomalous" Fischer reaction in the cyclohexanone 2-pyridylhydrazone series, which leads to 1-cyclohexyl-7,8,9,10-tetrahydro-1H-benzo[e]-pyrido[2,1-c]-as-triazine [4]. The difference consists only in the fact that the formation of a new ring in I proceeds without the participation of the spatially far-removed pyridine nitrogen but occurs exclusively through the hydrazone side chain.

Compounds IIIa, IV, and V were isolated in the pure form by means of column chromatography. Compounds IIIa and IV were identified by means of genuine samples of, respectively, 4-aminopyridine and 4-pyridone from mixed melting points and IR spectra. The structure of V is in agreement with the IR, UV, PMR, and mass-spectroscopic data. The IR spectrum of this compound contains an intense band at 1590 cm^{-1}, which is characteristic for C=C and C=N double bonds, and absorption is absent in the region of NH bands. In the UV spectrum, λ_{max} is found at 275 nm (log ε 4.29). Two doublets of the β and α protons of a 4-monosubstituted pyridine ring appear distinctly in the PMR spectrum at 7.17 ppm (2H) and 8.07 ppm (2H). In addition to these signals, the PMR spectrum contains only a complex multiplet of cyclohexane protons at 1.4-3.2 ppm (19H). An intense molecular ion peak with mass number 269 is observed in the mass spectrum of V. Other intense peaks with m/e 226 and 213 are characteristic for fragments formed from the molecular ions due to disintegration of the cyclohexane rings, and their origin is confirmed by the presence of metastable transitions. Further fragmentation of the molecule leads to the formation of particles with m/e 78, characteristic for the pyridine ring, with subsequent ejection of HCN and formation of a fragment with m/e 51 (Fig. 1).

Interesting results were obtained in the indolyzation of I in the presence of sodium ethoxide. The formation of 5,6,7,8-tetrahydro-γ-carboline (II) in this case demonstrates that, despite the generally accepted opinion [7], the participation of acid catalysts in the Fischer reaction is not compulsory. It should be noted that, in addition to II and IIIa, 4-ethylaminopyridine (IIIb), the structure of which was confirmed by direct comparison with an authentic sample obtained by alternative synthesis from pyridylpyridinium dichloride and ethylamine, is obtained in the reaction of I with sodium ethoxide. The formation of IIIb can be represented as the result of attack of I by sodium ethoxide, during which the ethyl group of the ethoxide reacts with a more nucleophilic nitrogen of the NH group, while the ONa grouping is tied up by the more electrophilic nitrogen attached to the double bond of the side chain of the hydrazone. Subsequent redistribution of the electron density in the four-membered transition state leads to cleavage of the N—N bond of the molecule under attack and of the C—O bond of the alkoxide to produce IIIb.



IIIb

Reducing the temperature of the reaction of I with C_2H_5ONa to 210° for 1.5 h leads to an increase in the yield of II to 62% with a simultaneous decrease in the yield of IIIa to 3% and of IIIb to 13%. Under these conditions, about 21% of the starting I is recovered unchanged. The use of aromatic aldehydes (benzaldehyde or cumaldehyde) instead of cyclohexanone and the carbonyl component makes it possible to direct the reaction exclusively to favor the formation of IIIb [8].

EXPERIMENTAL

4-Pyridylhydrazine. A 7.7-g (33 mmole) sample of pyridylpyridinium dichloride was mixed with 10 ml (200 mmole) of hydrazine hydrate, and the mixture was allowed to stand at room temperature for 18 h. It was then refluxed for 7 h and cooled. A total of 50 ml of 20% aqueous sodium hydroxide was added, and the mixture was immediately extracted repeatedly with chloroform. The extract was dried with potassium carbonate, the solvent was removed by vacuum evaporation, and the residual 4-pyridylhydrazine was distilled to give 2.8 g (76.5%) of a product with bp 188-188.5° (17 mm) and mp 30°.

Cyclohexanone 4-Pyridylhydrazone (I). A 2.6-ml (26.5 mmole) sample of cyclohexanone was added to 2.8 g (26 mmole) of 4-pyridylhydrazine, and the mixture was stirred for 2-3 min until a homogeneous mass formed. In the process, the reaction mixture warmed up and thickened. The resulting I was washed with 50 ml of water to give 4.52 g (93%) of colorless crystals with mp 168-169°.*

5,6,7,8-Tetrahydro-γ-carboline (II). A mixture of 1 g (5.3 mmole) of I and 2 g (14 mmole) of zinc chloride was heated at 240° for 7 min. The mixture was dissolved in 100 ml of hot water and made alkaline to pH 9 with sodium hydroxide. Compound II was extracted with chloroform, and the chloroform extract was dried with potassium carbonate and vacuum-evaporated to give 0.85 g (95%) of II with mp 269°. According to gas-liquid chromatography, the product has one peak with a retention time of 17 min. Found: C 76.69; H 6.95; N 16.18%. $C_{11}H_{12}N_2$. Calculated: C 76.71; H 7.02; N 16.27%.

Reaction of I with p-Toluenesulfonic Acid. A mixture of 2 g (10.6 mmole) of I and 3.4 g (20 mmole) of p-toluenesulfonic acid was heated at 190° for 7 min, cooled, and dissolved in 50 ml of 18% hydrochloric acid. The acid solution was made alkaline to pH 9 with 20% aqueous sodium hydroxide. The resulting light-brown precipitate was extracted with chloroform. The solution was dried and vacuum-evaporated, and the residue was chromatographed with a column filled with aluminum oxide (d 2 cm, h 54 cm). The column was washed with 400 ml of heptane, after which elution with 600 ml of ether gave 0.29 g (29%) of IIIa with mp 168°. Elution with 300 ml of methanol then gave 1.03 g (57%) of II with mp 269°.

Reaction of I with Hydrochloric Acid. A 2-g (10.6 mmole) sample of I was dissolved in 30 ml of concentrated HCl, and the solution was refluxed for 4 h. The cooled solution was made alkaline to pH 9 with 20% aqueous sodium hydroxide and extracted with chloroform. The extract was dried with potassium carbonate and evaporated, and the residue was chromatographed with a column filled with aluminum oxide (d 2 cm, h 54 cm). Elution initially with 100 ml of ether gave 0.06 g of IIIa with admixtures of other side products, while subsequent elution with 250 ml of ether—methanol (1 : 1) gave 0.24 g (25%) of 4-pyridone (IV) with mp 148°. Subsequent elution with 300 ml of methanol gave 0.73 g (41%) of II with mp 269°.

Reaction of I with Sulfosalicylic Acid. A mixture of 4 g (21.2 mmole) of I and 8 g (42 mmole) of sulfosalicylic acid was heated at 190° for 7 min. The reaction mass was worked up as in the experiment involving the reaction of I with p-toluenesulfonic acid. The residue was chromatographed with a column filled with aluminum oxide (d 2 cm, h 60 cm) with monitoring by gas-liquid chromatography. The column was eluted with 500 ml of benzene—isopropyl alcohol (15 : 1), and the V-enriched fraction was selected. Evaporation of the eluate gave 0.45 g of a mixture of substances, which was again subjected to chromatographic separation with a column filled with aluminum oxide (d 1 cm, h 40 cm). Elution with 600 ml of ether gave 0.38 g (7%) of V as an oily substance that was quite soluble in ether, alcohols, and chloroform and only slightly soluble in benzene and heptane; n_D^{20} 1.3900. Found: C 75.80; H 8.56; N 15.68%. $C_{17}H_{23}N_3$. Calculated: C 75.83; H 8.55; N 15.61%.

4-Ethylaminopyridine (IIIb). A mixture of 4 g (17 mmole) of pyridylpyridinium dichloride and 2 g (25 mmole) of ethylamine hydrochloride was heated at 175° for 3 h, cooled, and made alkaline with 20% aqueous sodium hydroxide. Compound IIIb was extracted with chloroform, and the extract was dried with potassium carbonate and evaporated. The residue was vacuum-distilled with collection of the fraction with bp 110-112°

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*The synthesis of I from 4-pyridylhydrazine hydrochloride and cyclohexanone in the presence of sodium acetate in 70% yield is described in [5].

(2 mm) to give 0.62 g (29%) of colorless crystals of IIIb with mp 98-99° (from cyclohexane). The product was quite soluble in water, alcohol, benzene, chloroform, and ethyl acetate and only slightly soluble in hexane and cyclohexane. Found: C 68.86; H 8.10; N 22.59%. $C_7H_{10}N_2$. Calculated: C 68.85; H 8.20; N 22.95%.

Reaction of I with Sodium Ethoxide. A 1-g (5.3 mmole) sample of I was mixed with 0.6 g (9 mmole) of freshly prepared sodium ethoxide, and the mixture was heated at 240° for 7 min. It was then cooled and dissolved in 50 ml of water. The basic substances were extracted with chloroform, and the chloroform extract was dried with potassium carbonate and vacuum evaporated. The residue (0.76 g) was triturated with 20 ml of 50% aqueous alcohol, after which it was recrystallized from 40 ml of 80% alcohol to give 0.48 g (28%) of II with mp 269°. The 50% aqueous alcohol mother liquor was vacuum evaporated, and the residue was distilled at 110-112° (2 mm) to give 0.19 g (29%) of 4-ethylaminopyridine (IIIb) with mp 98-99° (from cyclohexane). This product did not depress the melting point of the sample of IIIb described above, and the IR spectra and retention times in gas-liquid chromatography were in agreement.

Cumaldehyde 4-Pyridylhydrazone. A 2-g (18 mmole) sample of 4-pyridylhydrazine was mixed with 2.8 ml (18.5 mmole) of cumaldehyde, and the mixture was allowed to stand at room temperature for 30 min. The thickened reaction mass was crystallized from 25% aqueous methanol to give 4.13 g (94%) of a substance with mp 187-188°. Found: C 74.99; H 6.99; N 17.58%. $C_{15}H_{17}N_3$. Calculated: C 75.28; H 7.16; N 17.55%.

Reaction of Cumaldehyde 4-Pyridylhydrazone with Sodium Ethoxide. A 0.7-g sample of cumaldehyde 4-pyridylhydrazone was added to 0.3 g (45 mmole) of freshly prepared sodium ethoxide, and the mixture was heated at 240° for 20 min. It was then cooled, and 50 ml of ether and 5 ml of water were added. The mixture was acidified to pH 1 with hydrochloric acid, and cumaldehyde oxime was extracted with ether. The ether extract was dried with potassium carbonate, the solvent was removed by distillation, and the residue was sublimed at 95° and a residual pressure of 3 mm to give 0.28 g (60%) of the syn-oxime with mp 112°. Found: C 73.87; H 8.51; N 8.25%. $C_{10}H_{13}NO$. Calculated: C 73.59; H 8.03; N 8.59%. This product did not depress the melting point of a genuine sample [9]. The aqueous acid solution remaining after extraction with ether was made alkaline to pH 9 and extracted with chloroform. The chloroform extract was dried with potassium carbonate and vacuum-evaporated to give 0.18 g (63%) of IIIb with mp 98-99°.

The reaction products were studied by gas chromatography with a Pye-Unicam series 104 chromatograph with a flame ionization detector. A 2.1-m by 4-mm column filled with 10% SE-30 silicone elastomer on silanized diatomite (100-120 mesh) was used. The nitrogen flow rate was 29 ml/min, with programmed temperatures from 160 to 245°, an initial period of 5 min, and a temperature rise of 32 deg/min. The retention times (in minutes) were as follows: 1 for I, 17 for II, 4.2 for IIIa, 6.3 for IIIb, 15 for IV, and 40 for V.

The IR spectra of mineral-oil suspensions were recorded with a UR-10 spectrophotometer. The UV spectra of ethanol solutions were recorded with an EPS-3 spectrophotometer. The PMR spectra of CD_3OD solutions were recorded with a JNM-4H-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with an ionizing voltage of 50 eV. We thank N. P. Kostyuchenko, Yu. I. Pomerantsev, and E. M. Peresleni for their assistance in conducting the spectral investigations.

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