FISCHER CYCLIZATION OF 5-SUBSTITUTED PYRID-2-YL-HYDRAZONES OF CYCLOHEXANONE

L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov

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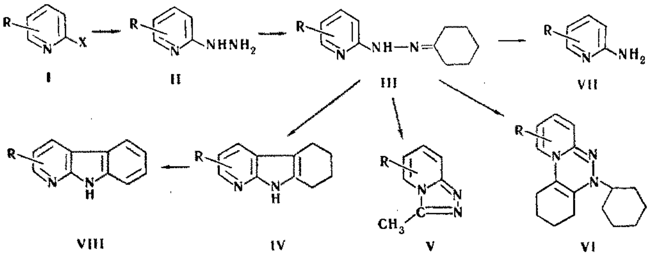
The effect has been studied of the nature of the substituent (methyl, chloro, nitro group) on the Fischer cyclization of 5-substituted pyrid-2-yl-hydrazones of cyclohexanone under the action of different catalysts: Lewis acids and strong mineral and arylsulfonic acids.

In previous communications [1, 2] we have described the effect of different catalysts on the Fischer cyclization of pyrid-2-yl-hydrazones and also the case where the reaction proceeds "anomalously" with formation of derivatives of sym-triazolo-[4, 3-a]pyridine and of pyrido-[2, 1-c]-asym-triazine. At the same time it was shown that introduction of a methyl group into position 6 of the pyridine nucleus enabled the process to be directed towards "normal" Fischer reaction products and led to an increase in their yield.

In this communication the effect on the course of the Fischer reaction of substituents in position 5 of the pyridine nucleus of pyrid-2-yl-hydrazones of cyclohexanone (III) is examined. In a similar way to the 6-methyl group, the electron-donating methyl radical in position 5 of the pyridine molecule shifts the process toward formation of a "normal" Fischer reaction product, i.e., a derivative of 5, 6, 7, 8-tetrahydro-α-carboline (IV).



R= a 5-CH_3; b 5-Cl; c 5-NO_2; d H; e 6-CH_3*; X=Cl, Br

Also as seen from the table, changing from the 6-methyl to the 5-methyl derivative of cyclohexanone pyridylhydrazone considerably facilitates the course of the Fischer reaction where Lewis acids were used as catalysts.

Yields of Fischer Reaction Products

Catalyst	Precursor							
	IIId		IIIe		IIIa		IIIb	
	Reaction products							
	IVd	Vd (VId)	IVe	Ve (VIe)	IVa	Va (VIa)	IVb	Vb (VIb)
Zinc chloride	—	—	26	—	42.2	—	29	—
Cuprous chloride	—	—	22.8	—	43.5	—	—	37*
Boron trifluoride	—	45	27.6	67	21.8	66.3	57.3	18.9
Conc HCl	20.2	(36.6)	66.1	(26.8)	67.4	(26.6)	29	(45.5)
Polyphosphoric acid	62	—	78	—	67.3	—	81.7	—
Sulfosalicylic acid	51.6	—	59.6	—	60.1	—	69	—
p-Toluenesulfonic acid	72	—	85	—	98	—	81	—

*Reaction product: 5-chloro-2-aminopyridine (VIIb).

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*Positions of substituent are indicated in accordance with the numbering in I.

The effect of a chlorine atom in position 5 of the pyridine nucleus is more complex than the effect of an alkyl substituent. Apparently in this case the halogen causes a stronger change in the basicity of the pyridine nitrogen and in the stability of the bonds in the hydrazine part of the molecule. These changes appear to the greatest extent in reactions catalyzed by Lewis acids. As seen from the table, with boron trifluoride etherate in acetic acid, the main reaction product is a derivative of 5, 6, 7, 8-tetrahydro-α-carboline IVb. With cuprous chloride the formation of 2-amino-5-chloropyridine (VIIb) occurs, i. e., there is cleavage of the N—N bond of the hydrazone, which did not take place in the previous reactions that we carried out with pyrid-2-yl-hydrazones. The 5, 6, 7, 8-tetrahydro-α-carboline derivative (IVb) was not detected among the reaction products by paper chromatography. In order to monitor the course of the reaction and the purity of the products, descending paper chromatography was used, the mobile phase being light petroleum. Below are given the R_f values of the compounds (in brackets the color of the complex with Dragendorff's reagent): IIIa, 0.91 (yellow); IIIb, 0.86 (brown); IVa, 0.58 (orange); IVb, 0.62 (orange); Va, 0.00 (orange); Vb, 0.00 (orange); VIa, 0.99 (orange); VIb, 0.98 (orange). On UV irradiation IIIa and IIIb absorbed, and the other compounds had a blue luminescence.

In the case of reactions with such strong organic and mineral acids as p-toluenesulfonic, polyphosphoric, and others, changing from the 6-methyl to the 5-methyl and then to the 5-chloro derivatives of cyclohexanone pyrid-2-ylhydrazone did not materially effect the yield of the Fischer cyclization products.

Completely different results were observed on introducing into the pyridine molecule a strong electron-accepting substituent, the nitro group, at position 5. As was expected, the nitro group, sharply decreasing the electron density on the carbon atoms of the pyridine nucleus, made the "normal" Fischer reaction, which involves electrophilic substitution, impossible. Therefore with cyclohexanone 5-nitropyrid-2-ylhydrazone IIIc the formation of a derivative of 5, 6, 7, 8-hydro-α-carboline (IVc) was not observed even with such a strong catalyst as p-toluenesulfonic acid. The sole reaction product, isolated in 5% yield, was 5-nitro-2-aminopyridine (VIIc).

EXPERIMENTAL

5-Methylpyrid-2-ylhydrazine (IIa). A mixture of 66.35 g (0.38 mole) of 2-bromo-5-methylpyridine (Ia, X = Br) and 173 ml (3.5 mole) of hydrazine hydrate was boiled for 6 hr until there was complete mutual solubility of the layers. After cooling, 100 ml of ether was added. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried with magnesium sulfate and concentrated to afford 40.5 g (86%) of IIa as colorless crystals with mp 67–68° C (from light petroleum). The compound had poor solubility in light petroleum and good solubility in other organic solvents and was insoluble in water. Found, %: C 58.30; H 7.06; N 34.08. Calculated for $C_6H_9N_3$, %: C 58.51; H 7.36; N 34.13.

5-Chloropyrid-2-ylhydrazine (IIb). 1.3 g (0.01 mole) of 2, 5-dichloropyridine (Ib, X = Cl) and 13 ml (0.26 mole) of hydrazine hydrate were boiled for 3 hr. After working-up by the method described above, 0.92 g (73%) of IIb was obtained as colorless crystals, mp 123–125° C (from benzene). The compound had poor solubility in benzene and light petroleum and good solubility in other organic solvents and was insoluble in water. Found, %: C 41.80; H 4.34; Cl 25.03; N 29.26. Calculated, $C_5H_6ClN_3$, %: C 41.81; H 4.21; Cl 24.72; N 29.28.

Cyclohexanone 5-methylpyrid-2-ylhydrazone (IIIa). To 0.64 g (5.7 mM) of IIa was added 0.6 ml (6.1 mM) of cyclohexanone. The reaction mass heated up and became homogeneous. After standing 30 min it was distilled: bp 150° C (2 mm). Yield 1.15 g (quantitative). Colorless crystals, mp 56–57° C (from light petroleum). The compound had good solubility in the usual organic solvents and poor solubility in water. Found, %: C 71.04; H 8.39; N 20.65. Calculated for $C_{12}H_{17}N_3$, %: C 70.89; H 8.43; N 20.68.

Cyclohexanone 5-chloropyrid-2-ylhydrazone (IIIb), was prepared similarly. The yield of IIIb was quantitative. Colorless crystals, mp 54–55° C, bp 160° C (3 mm). The compound had good solubility in organic solvents and poor solubility in water. Found, %: C 59.20; H 6.15; Cl 15.55; N 18.46. Calculated for $C_{11}H_{14}ClN_3$, %: C 59.04; H 6.31; Cl 15.87; N 18.78.

Cyclohexanone 5-nitropyrid-2-ylhydrazone (IIIc). A solution of 0.1 g (0.65 mM) of 5-nitropyrid-2-ylhydrazine (IIc) and 0.1 ml (0.97 mM) of cyclohexanone in 10 ml of ethanol was boiled for 3 min, cooled, and evaporated under vacuum. 0.15 g (100%) of IIIc was obtained as yellow crystals mp 127° C (from hexane). The compound had good solubility in alcohol, acetone, and chloroform and poor solubility in benzene and hexane, and was insoluble in water. Found, %: C 56.69; H 6.20; N 23.68. Calculated for $C_{11}H_{14}N_4O_2$, %: C 56.39; H 6.02; N 23.92.

3-Methyl-5, 6, 7, 8-tetrahydro-α-carboline (IVa). A) A mixture of 1 g (5.4 mM) of IIIa and 1.8 g (10.5 mM) of p-toluenesulfonic acid was heated in 10 min to 180° C. An exothermic reaction occurred and the temperature rose to 210° C. After cooling, 10 ml of a 50% potassium hydroxide solution was added to the reaction mixture, and extraction with ether gave 0.5 g of IVa, mp 209–210° C. The aqueous mother liquor was additionally extracted with chloroform, the compound was purified by chromatography on a column of alumina (diameter 2.2 cm, height 58 cm), and eluted with 500 ml of ether. 0.4 g of IVa was obtained, mp 211° C. Total yield of IVa, 0.9 g (98%). Colorless crystals, mp 211° C (from ethyl acetate). The compound had good solubility in chloroform, acetone, and alcohol and much poorer solubility in ether, benzene, and ethyl acetate, and it was insoluble in water. Found, %: C 77.10; H 7.48; N 15.16. Calculated for $C_{12}H_{14}N_2$, %: C 77.38; H 7.58; N 15.04. **The hydrochloride of IVa** formed colorless crystals, mp 259° C (from ethanol with acetone). The compound had good solubility in alcohol and water but poor solubility in acetone, benzene, and ethyl acetate. Found, %: C 64.50; H 6.95; Cl 15.99; N 12.37. Calculated for $C_{12}H_{14}N_2 \cdot HCl$, %: C 64.70; H 6.79; Cl 15.93; N 12.58.

B) A mixture of 1 g (5.4 mM) of IIIa and the polyphosphoric acid prepared from 0.9 ml of H_3PO_4 and 1.4 g of P_2O_5 was heated to 180° C and was worked up as in the previous experiment. Yield of IVa, 0.62 g (67.3%).

C) In a similar experiment, from 2 g (10.8 mM) of IIIa and 3.4 g (15.6 mM) of sulfosalicylic acid (reaction temperature 170° C) the yield of IVa was 1.1 g (60.1%).

D) By heating 1 g (5.4 mM) of IIIa with 0.01 g of freshly prepared cuprous chloride for 30 min at 230° C 0.4 g (43.5%) of IVa was obtained.

E) 0.98 g (4.8 mM) of IIIa and 0.01 g of zinc chloride were heated 30 min at 270° C; 0.38 g (42.2%) IVa was obtained.

3-Methyl-α-carboline (VIIIa). One gram (5.4 mM) of IVa and 2 g of palladium were heated for 30 min at 270° C. After cooling, the reaction mixture was dissolved in chloroform; the palladium was filtered off, the chloroform distilled off, the residue was sublimed under vacuum. 0.67 g (68.5%) of VIIIa was obtained as colorless crystals, mp 269–270° C (from ethyl acetate). The compound had good solubility in hot alcohol and chloroform and poor solubility in cold alcohol, chloroform, and benzene, and was insoluble in hexane and water. Found, %: C 79.27; H 5.80; N 15.18. Calculated for $C_{12}H_{10}N_2$, %: C 79.09; H 5.53; N 15.38. **The hydrochloride of VIIIa** formed colorless crystals, mp 258–260° C. It was readily soluble in water, poorly soluble in organic solvents. Found, %: Cl' 15.95. Calculated for $C_{12}H_{10}N_2 \cdot HCl$, %: Cl 16.23.

3-Dimethyl-sym-triazolo[4,3-a]pyridine (Va). A) A mixture of 1 g (5.4 mM) of IIIa, 0.7 g of boron trifluoride etherate, and 30 ml of glacial acetic acid was heated in a sealed glass tube for 6 hr at 200° C. The reaction mixture was concentrated, the residue was made alkaline with 50% potassium hydroxide solution and was extracted with chloroform, and the extract was dried with potassium carbonate evaporated under vacuum. The residue was transferred to a column of alumina (diameter 2.2 cm, height 58 cm), and eluted with 1.5 *l* of ether to afford 0.2 g (21.8%) of IVa. After the separation of the IVa, elution was continued with chloroform. From 1.5 *l* of chloroform eluate was obtained 0.48 g (66.3%) of Va as colorless crystals, mp 141° C (from benzene). The compound did not depress the melting point on admixture with a known sample of Va [1].

B) A solution of 0.7 g (3.8 mM) of IIa in 20 ml of glacial acetic acid was boiled for 9 hr. and then the reaction mixture was evaporated in vacuum. The residue was made alkaline with 50% potassium hydroxide solution and extracted with chloroform. The extract, dried with sodium sulfate, was evaporated under vacuum 0.78 g (93%) Va was obtained, mp and mixed mp with a sample of Va, 140–141° C [6].

2-Cyclohexyl-9-methyl-3, 4, 5, 6-tetrahydro-2H-benz[e]pyrido[2, 1–c]-asym-triazine (VIa). Five grams (2.46 mM) IIIa was boiled for 4 hr with 125 ml of conc HCl. After cooling, the reaction mixture was made alkaline with ammonia. The precipitate was filtered off and washed with ether and chloroform. 1.8 g of IVa was obtained. The aqueous alkaline solution and the ether and chloroform after the separation of the IVa were combined. After the separation of the layers, the alkaline solution was additionally extracted with ether. For purification the substance was chromatographed on a column of alumina (diameter 4 cm, height 57 cm) and eluted with 2.7 *l* of light petroleum. 0.93 g (26.6%) of VIa was obtained as colorless crystals mp 98–99° C (from heptane). The substance had good solubility in benzene, acetone, and chloroform much poorer solubility in heptane, light petroleum, and alcohol, and it was insoluble in water. Found, %: C 75.93; H 9.04; N 14.91. Calculated for $C_{18}H_{25}N_3$, %: C 76.28; H 8.89; N 14.83. On subsequent elution of the column with 1.25 *l* of ether an additional 1.46 g of IVa were obtained. Total yield of IVa, 3.26 g (67.4%).

3-Chloro-5, 6, 7, 8-tetrahydro-α-carboline (IVb). A) A mixture of 1 g (4.5 mM) of **IIIb** and 1.64 g (9.5 mM) of p-toluenesulfonic acid was heated to 180° C. The temperature rose sharply to 210° C. After cooling, the reaction mass was dissolved in 20 ml of 17% HCl, and the solution was filtered and made alkaline with ammonia. The precipitate of **IVb** was filtered off and dried in air; yield, 0.75 g (81%) as colorless crystals mp 215–216° C (from ethyl acetate). The substance had good solubility in alcohol, ether, acetone, and chloroform, less good in benzene and ethyl acetate and poor solubility in light petroleum, and it was insoluble in water. Found, %: C 63.82; H 5.12; Cl 16.92; N 13.55. Calculated for $C_{11}H_{11}ClN_2$, %: C 63.91; H 5.36; Cl 17.17; N 13.55.

B) A mixture of 1 g (4.5 mM) of **IIIb** and the polyphosphoric acid prepared from 1.27 g of P_2O_5 and 0.83 ml of H_3PO_4 was heated to 210° C and worked up as in the previous experiment. Yield of **IVb**: 0.76 g (81.7%), mp 215–216° C.

C) In a similar experiment, from 1 g (4.5 mM) of **IIIb** and 1.55 g (7.5 mM) of sulfosalicylic acid (reaction temperature 170° C) the yield of **IVb** was 0.64 g (69%).

D) 1 g (4.5 mM) of **IIIb** was heated with 0.01 g of zinc chloride for 30 min at 270° C. The reaction mixture was dissolved in 5 ml of chloroform and chromatographed on a column of alumina (diameter 2.2 cm, height 58 cm). It was eluted with 500 ml ether. Yield of **IVb** 0.27 g (29%).

Reaction of IIIb with cuprous chloride. A mixture of 1 g (4.5 mM) of **IIIb** and 0.01 g of cuprous chloride was heated for 20 min at 250° C. The reaction mass was dissolved in 30 ml of chloroform and chromatographed on a column of alumina (diameter 2.2 cm, height 58 cm), being eluted with 500 ml of ether, to give 0.3 g of a yellow crystalline substance which did not give a hydrochloride, did not develop a color with the Dragendorff reagent, and was not studied further. On subsequent elution with 2.25 *l* of ether, 0.35 g of a white crystalline substance with mp 110° C was obtained. After repeated chromatography on alumina and elution with a mixture (1 : 1) of ether and light petroleum, 0.21 g (37%) of pure 2-amino-5-chloropyridine (**VIIb**) was obtained, mp 133–135° C. Admixed with a known sample it gave no depression in melting point.

Reaction of IIIc with p-toluenesulfonic acid. Five grams (21.4 mM) of **IIIc** and 7.8 g (45 mM) of p-toluenesulfonic acid were heated to 180° C. A vigorous reaction occurred with considerable resinification. After cooling, the reaction mass was dissolved in 2 *l* of 17% HCl. The carbonized precipitate was separated off and the solution was made alkaline with ammonia. The base (0.84 g) which separated out was extracted with chloroform, and purified by chromatography on alumina, being eluted with 1.75 *l* of chloroform. 0.14 g (5%) of 2-amino-5-nitropyridine (**VIIc**) was obtained. The compound did not depress the melting point of a known sample.

2-Cyclohexyl-9-chloro-3, 4, 5, 6-tetrahydro-2H-benz[e]pyrido[2, 1–c]-asym-triazine (VIb). A mixture of 5 g (22.4 mM) of **IIIb** and 115 ml of conc HCl was boiled for 5 hr, cooled, and filtered. The filtrate was made alkaline with ammonia and extracted with chloroform. The chloroform solution was chromatographed on alumina (diameter of column 4 cm, height 57 cm) and eluted with 1 *l* of ether to afford 1.64 g (45.5%) of **VIb** as colorless crystals with mp 112.5–113.5° C (from heptane). The substance had good solubility in acetone, benzene, chloroform, and ethyl acetate and poor solubility in hexane, and it was insoluble in water. Found, %: C 67.37; H 7.19; Cl 11.93; N 14.00. Calculated for $C_{17}H_{22}ClN_3$, %: C 67.19; H 7.30; Cl 11.68; N 13.83. On further elution of the column with 1.5 *l* of ether–light petroleum (1 : 1), 1.27 g (29%) of **IVb** was obtained with mp 215–216° C. The substance did not depress the melting point of a known sample of **IVb**.

3-Methyl-6-chloro-sym-triazolo[4, 3–a]pyridine (Vb). A) One gram (7 mM) of **IIb** with 30 ml of glacial acetic acid was boiled for 9 hr, concentrated under vacuum, made alkaline with 50% potassium hydroxide solution, and extracted with choroform. After removal of the solvent, 1.14 g (100%) of **Vb** was obtained as colorless crystals with mp 131–132° C (from benzene). The compound had good solubility in chloroform, acetone, alcohol, hot benzene, and poor solubility in light petroleum and water. Found, %: C 50.23; H 3.62; Cl 21.48; N 24.84. Calculated for $C_7H_6ClN_3$, %: C 50.15; H 3.61; Cl 21.17; N 25.07.

B) A mixture of 1 g (4.5 mM) of **IIIb**, 0.64 g of boron trifluoride etherate, and 30 ml of glacial acetic acid was heated for 6 hr in a sealed tube at 200° C. The reaction mass was concentrated and the residue was made alkaline with 50% potassium hydroxide solution, extracted with chloroform, and chromatographed on a column of alumina (diameter 2.2 cm, height 58 cm); 0.5 *l* of ether eluted 0.17 g (18.3%) of **IVb**, mp 215–216° C; the following 2 *l* of ether gave 0.44 g (57.3%) of **Vb**.

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Ordzhonikidze All-Union Scientific-Research Institute of
Chemistry and Pharmacy, Moscow