THE PROBLEM OF THE RELATIVE EFFECTIVENESS OF FISCHER REACTION CATALYSTS

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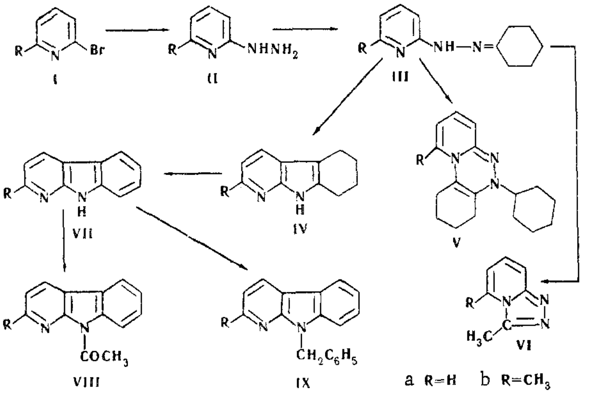
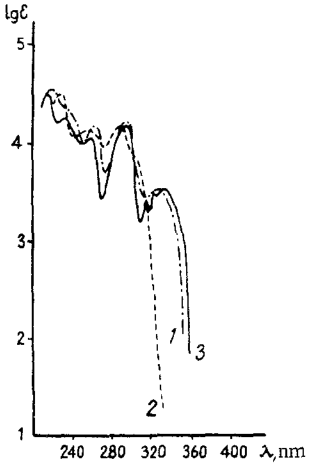
A study is made of the effectiveness of Fischer catalysts (zinc chloride, cuprous chloride, boron trifluoride, polyphosphoric, hydrochloric, sulfosalicylic, and p-toluenesulfonic acid) for the cyclization of cyclohexanone pyridyl-2-hydrazone and 6-methylpyridyl-2-hydrazone. The great effectiveness of mineral and sulfonic acids as compared with Lewis acids is shown. The possibility is shown of changing the course of the process by introducing an electron-donating substituent into the pyridine ring. 1-Acetyl and 1-benzyl derivatives of α-carboline are synthesized.

Numerous papers dealing with the synthesis of indole compounds from arylhydrazones describe the use of various catalysts in the Fischer reaction, mineral and organic acids, Lewis acids, etc. [1, 2]. Furthermore, the literature is practically lacking in information about the relative effectivenesses of Fischer reaction catalysts or about conversion of the various hydrazones by the various catalysts.

In the course of the work applying the Fischer reaction to synthesizing 7-azaindole derivatives, not only was a study made of the effect of various compounds on this reaction, but also of the possibility of altering the course of the reaction by introducing substituents into the pyridine ring of the pyridyl-2-hydrazones.



The selected subjects of study were cyclohexanone pyridyl-2-hydrazone (IIIa) whose conversion to 9,10,11,12-tetrahydro-α-carboline (IVa) by heating with phosphoric acid [3] or refluxing with ethylene glycol [4] has been described, and cyclohexanone 6-methylpyridyl-2-hydrazone (IIIb) whose Fischer cyclization has not been investigated previously. The condensing agents chosen were strong mineral or organic acids, polyphosphoric acid, concentrated hydrochloric acid, sulfosalicylic acid, and p-toluene sulfonic acid, as well as Lewis acids zinc chloride, cuprous chloride, and boron trifluoride.



UV spectra: 1) α-carboline (VII); 2) 1-acetyl-α-carboline (VIII); 3) 1-benzyl-α-carboline (IX).

The electron-accepting effect of nitrogen is known to cause a decrease in density of electrons in the β position of the pyridine ring, which leads to hindrance of electrophilic substitution in pyridines compared with the like reactions for the benzene ring. So the Fischer reaction, involving electrophilic substitution processes, takes place either considerably less readily than with the corresponding phenylhydrazones,

Results Obtained

Catalyst	IIIa			IIIb		
	Reaction %			%		
	IVa	Va	VIa	IVb	Vb	VIb
Cuprous chloride,	—	—	—	22.8	—	—
Zinc chloride,	—	—	—	26	—	—
Boron trifluoride,	—	—	45	27.6	—	67
Conc. hydrochloric acid	20.2	36.6	—	66.1	26.8	—
Sulfosalicylic acid,	51.6	—	—	59.6	—	—
Polyphosphoric acid,	62	—	—	78	—	—
p-Toluenesulfonic acid	72	—	—	85	—	—

or else does not take place at all [3, 5]. Thus according to the results obtained by A. E. Arbuzov and coworkers [6, 7], the Fischer reaction with phenylhydrazones in the presence of catalytic amounts of zinc chloride or cuprous chloride, starts even at 180°–185° C and is completed at 210°–225° C. In the present experiments involving heating cyclohexanone pyridyl-2-hydrazone (**IIIa**) with zinc chloride or cuprous chloride for 1 hr at 230°–240° C, only the starting material was recovered. Here it is necessary to cast doubts on a statement by Kelly, McLeod, and Parrick [4], that conversion of **IIIa** to tetrahydro-α-carboline (**IVa**) by boiling in diethylene glycol (245° C) is an example of Fischer cyclization without a catalyst. Obviously, there the process was catalyzed by the diethylene glycol. The catalytic effect of hydroxylic solvents on analogous reactions has previously been recorded in the literature [8].

Boron trifluoride was also an insufficiently effective catalyst for Fischer cyclization of **IIIa** with an acetic acid solution of boronotrifluoride etherate under conditions which convert methylethyl ketone p-tolylhydrazone to an indole derivative in 80% yield [9], here gave only the starting pyridyl-2-hydrazone (**IIIa**). Heating **IIIa** with boron trifluoride and acetic acid at 180° C gave, instead of tetrahydro-α-carboline (**IVa**), the abnormal Fischer reaction product, 3-methyl-s-triazolo[4, 3-*a*]pyridine (**VIa**) [10].

The normal Fischer reaction took place when the catalysts for cyclizing **IIIa** were strong mineral acids and arylsulfonic acids (see table). When concentrated hydrochloric acid was used, there was obtained along with the normal Fischer reaction product (IVa) (yield 20.2%) an even higher yield (36.6%) of abnormal product, 1-cyclohexyl-7, 8, 9, 10-tetrahydro-1N-benz[1, 2-e]pyrido[2, 1-c]-as-triazine (Va) [10]. The highest yield (72%) of normal Fischer reaction product, 9, 10, 11, 12-tetrahydro-α-carboline (IVa) was obtained using p-toluenesulfonic acid.

In the case of cyclohexanone 6-methylpyridyl-2-hydrazone (**IIIb**) (see table) the relative order of effectiveness of catalyst found with cyclohexanone pyridyl-2-hydrazone is retained. Here, as would be expected, insertion of an electron-donating methyl group at position 6 in the pyridine ring increases the electron density at position 3. Hence all the Fischer cyclization reactions studied here using the 6-methyl derivative **IIIb**, take place more readily than in the case of the corresponding pyridyl-2-hydrazone unsubstituted at position 6 (**IIIa**). Examples which may be cited are formation of 4-methyl-9, 10, 11, 12-tetrahydro-α-carboline (**IVb**) using Lewis acids ($ZnCl_2$, Cu_2Cl_2, BF_3) under conditions such that **IIIa** did not react. Introduction of a methyl group at position 6 of cyclohexanone pyridyl-2-hydrazone also increases the extent of the normal Fischer reaction product, when the catalyst is concentrated hydrochloric acid, and enables the maximum yield of tetrahydrocarboline derivative (**IVa** and **IVb**) from 72 to 85% (for the reaction using p-toluenesulfonic acid).

The results secured show that it is possible to change the course of the process by inserting at position 6 in the pyridine ring substituents with various inductive effects.

9, 10, 11, 12-Tetrahydro-α-carboline (**IVa**) and its 4-methyl derivative (**IVb**) synthesized in the course of the present work, were used to prepare some substituted α-carbolines.

IVa and **IVb** were dehydrogenated by heating with palladium at 275° C. The process was checked spectrophotometrically.

The α-carbolines prepared (**VIIa** and **VIIb**) acylated unambiguously and, for example, gave practically quantitative yields of the 1-acetyl derivatives (**VIIIa** and **VIIIb**). Alkylation of α-carboline, even by reacting the N-sodio derivative in liquid ammonia gives a complex mixture of products, obviously due to addition of alkyl groups to nitrogen atoms at various parts of the molecule. Thus for example when α-carboline (**VIIa**) was benzylated, chromatographing on alumina led to isolation of 1-benzyl-α-carboline (**IXa**) in only 22% yield. The position of the benzyl group in **IXa** was confirmed spectrophotometrically, by comparing the UV spectra of **VIIa**, **VIIIa**, and **IXa** (figure).

EXPERIMENTAL

6-Methylpyridine-2-hydrazine (IIb). 48 g (0. 39 mole) 2-Bromo-6-methylpyridine (**Ib**) [11] was boiled with 125 ml hydrazine hydrate for 5 hr. All the **Ib** dissolved. After cooling **IIb** was extracted with ether. The ether solution was dried over Na_2SO_4 and evaporated under vacuum. The residue was distilled at 102°–103° C (20 mm). Yield of **IIb** 23. 33 g (70%). The compound was recrystallized, colorless crystals, mp 54°–56° C (ex hexane). The compound was not very soluble in water and hexane, but was readily soluble in ether, benzene, EtOH, acetone, AcOEt, and hot water. Found: C 58. 51; H 7. 36; N 34. 13%, calculated for $C_6H_9N_3$: C 58. 20; H 7. 29; N 34. 00%.

Cyclohexanone 6-methylpyridyl-2-hydrazone (IIIb). 1. 1 ml (0.0106 ml) Cyclohexanone was added to 1.35 g (0. 0067 mole) **IIb**, when the mixture warmed up. It was stirred for 30 min, then vacuum distilled, to give 1. 19 g (97%) **IIIb** bp 155° C (2 mm). The substance was recrystallized, colorless crystals mp 81°–82° C (ex hexane). Readily soluble in ether, EtOH, and benzene, slightly soluble in hexane. Found: C 70. 67; H 8. 20; N 20. 33%, calculated for $C_{12}H_{17}N_3$, C 70. 89; H 8. 44; N 20. 67%.

Reaction with zinc chloride. 1 g (0. 0049 mole) **IIIb** was heated for 1 hr with 0. 01 g fused $ZnCl_2$ at 240° C, then the products vacuum distilled at 1 mm, bath temperature 160° C, to give 0. 24 g (26%) **IVb**, colorless crystals, mp 183°–184° C (ex benzene). The compound was readily soluble in acetone, ether, alcohols, and $CHCl_3$, soluble with difficulty in benzene, insoluble in water. λ_{max} nm (lg ε)*: 234 (4. 38), 298 (3. 96). Found C 77. 04; H 7. 81; N 14. 89%, calculated for $C_{12}H_{14}N_2$: C 77. 38; H 7. 58; N 15. 04%.

In a similar reaction with 1 g **IIIa**, 0. 67 g (67%) starting material was recovered. **IVa** was not detected chromatographically in the reaction products.**

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*All UV spectra were observed in EtOH, using a SF-4 spectrophotometer.

Descending chromatogram on paper impregnated with formamide. The mobile phase was petrol ether. Visualization was by UV light (IIIa** and **IIIb** absorb; **IVa**, **IVb**, **Va**, **Vb**, **IXa** blue luminescence) and with Dragendorf 's reagent (**IIIa**, **IIIb** red complexes; **IVa**, **IVb**, **VA**, **Vb**, and **IXa** orange). R_f **IIIa** 0. 53; **IIIb** 0. 57; **IVa** 0. 83; **IVb** 0. 71; **Va** 0. 90; **Vb** 0. 93; **IXa** 0. 94.

Reaction with cuprous chloride. A mixture of 1 g (0.0049 mole) **IIIb** and 0.01 g freshly-prepared CuCl was heated at 230° C. The substance was vacuum sublimed at 160° C (1 mm). The sublimed material was chromatographed on a column of 140 g alumina. It was eluted with 500 ml petrol ether and 1 *l* ether–petrol ether (1:3). Yield 0.21 g (22.8 %) **IVb**.

In a similar run using 1 g **IIIa**, 0.76 g (76%) starting material was recovered. Chromatography did not reveal **IVa** in the reaction products.* Reaction of **IIIa** and **IIIb** with boron trifluoride etherate in acetic acid, and with conc HCl has previously been described [10].

Reaction with polyphosphoric acid. 1 g (0.0049 mole) **IIIb** was heated with 2.9 g polyphosphoric acid at 210° C. After cooling the products were dissolved in 100 ml 17% HCl. Non-basic impurities were extracted with ether. The aqueous solution was made alkaline with ammonia, and the base **IVb** precipitated was filtered off, yield 0.71 g (78%).

Similarly **IIIa** and polyphosphoric acid gave a 62% yield of **IVa**.**

Reaction with p-toluenesulfonic acid. a) 1 g (0.0053 mole) **IIIa** was heated with 1.7 g (0.01 mole) p-toluenesulfonic acid to 180° C, when the temperature rapidly jumped to 220° C. The cooled reaction mixture was dissolved in 100 ml 17% HCl and non-basic impurities extracted with ether. The HCl solution was made alkaline with ammonia, and the precipitate of **IVa** filtered off, yield 0.66 g (72%), colorless crystals, mp 154°–154.5° C (ex 70% EtOH) [3, 4], λ_{max} nm (lg ε): 232 (4.38), 295 (3.92). Found: C 76.68; H 6.97; N 16.50%, calculated for $C_{11}H_{12}N_2$: C 76.71; H 7.02; N 16.27%.

When the reaction was run at 240° C, there was marked tar formation, and the yield of **IVa** dropped to 45%. When the reaction was run for 3 hr in boiling BuOH, 92% of the starting **IIIa** was recovered.

b) 4 g (0.019 mole) **IIIb** was heated to 180° C with 7.2 g (0.043 mole) p-toluenesulfonic acid. The temperature jumped to 220° C, and gaseous products were vigorously evolved. The products were worked up as described below. Yield of **IVb** 3.14 g (85.5%).

Reaction with sulfosalicylic acid. a) 1 g (0.0053 mole) **IIIa** was heated at 180° C with 1.9 g (0.0087 mole) sulfosalicylic acid. The products were dissolved in 17% HCl, and non-basic impurities extracted with ether. The HCl solution was made alkaline with ammonia. The precipitate of **IVa** was filtered off, yield 0.47 g (51.7%). After isolating **IVa**, the mother liquor was extracted with ether, the extracts dried over Na_2SO_4, and evaporated, to give 0.3 g (30%) starting **IIIa**, mp 80°–82° C, undepressed mixed mp with known **IIIa**.

b) A mixture of 3 g (0.0148 mole) **IIIb** and 5.1 g (0.0234 mole) sulfosalicylic acid was heated at 180° C. The products were dissolved in 300 ml 17% HCl, and non-basic impurities extracted with ether. The HCl solution was made alkaline with ammonia. The precipitate of **IVb** was filtered off, and washed with petrol ether, yield 1.53 g (56%). Paper chromatography showed the petrol ether washings to contain **IVb**, and they were column chromatographed on alumina (145 g). Impurities were eluted with 3.6 *l* petrol ether, 1.25 *l* ether–petrol ether (1:9), and 2.5 *l* ether–petrol ether (1:3), and lastly **IVb** was eluted with 0.75 *l* ether. A further 0.1 g **IVb** was obtained. The total yield of **IVb** was 1.63 g (59.64%).

4-Methyl-α-carboline (VIIb). 0.5 g (0.0027 mole) **IVb** was heated with 0.5 g Pd for 30 min at 270°–280° C. After cooling the products were dissolved in hot $CHCl_3$, the catalyst filtered off, the solution evaporated, and the material recrystallized from benzene. Yield of **VIIb** 0.33 g (67%), colorless crystals, mp 241°–242° C (ex benzene). The substance was soluble in hot $CHCl_3$ and benzene, soluble with difficulty in water and cold organic solvents, λ_{max}, nm (lg ε): 215 (4.58), 234 (4.32), 261 (4.12), 297 (4.23), 326 (3.78). Found: C 79.45; H 5.90; N 15.05%, calculated for $C_{12}H_{10}N_2$.: C 79.09; H 5.55; N 15.38%.

Similarly 0.5 g (0.0029 mole) **IVa** gave 0.4 g (81.6%) **VIIa**, mp 214°–215° C (ex benzene) [3]. λ_{max}, nm (lg ε): 215 (4.52), 234 (4.29), 258 (4.08), 297 (4.22), 329 (3.57).

1-Acetyl-α-carboline (VIIIa). 0.5 g (0.003 mole) **VIIa** was refluxed for 1 hr with 5 ml Ac_2O, and as reaction proceeded, the **VIIa** gradually dissolved. The products were evaporated under vacuum. Yield of **VIIIa** 0.63 g (100%), colorless crystals, mp 96°–97° C (ex hexane). The compound was readily soluble in ordinary organic solvents, soluble with difficulty in water and hexane. λ_{max}, nm (lg ε): 228 (4.51), 258 (4.14), 290 (4.18). IR spectrum: 1697 cm^{-1} ($CH_3CON<$).* Found C 74.40; H 4.75; N 13.59%, calculated for $C_{13}H_{10}N_2O$: C 74.27; H 4.79; N 13.33%.

1-Acetyl-4-methyl-α-carboline (VIIIb). Prepared similarly to **VIIIa** from 1 g (0.0055 mole) **VIIb** and 10 ml Ac_2O. Yield of **VIIIb** 1.22 g (100%). Colorless crystals, mp 110°–111° C (ex hexane). Readily soluble in ordinary organic solvents, soluble with difficulty in water and hexane. λ_{max}, nm (lg ε): 230 (4.48), 262 (4.12), 296 (4.18); IR spectrum 1702 cm^{-1} ($CH_3CON=$). Found: C 75.02; H 5.47; N 12.65%, calculated for $C_{14}H_{12}N_2O$: C 74.97; H 5.39; N 12.49%.

1-Benzyl-α-carboline (IXa). 1 g (0.006 mole) **VIIa** was added in portions to 0.17 g (0.0074 mole) Na in 20 ml stirred liquid ammonia. The mixture was stirred for 1 hr, then the ammonia evaporated off. 20 ml dry toluene was added and 0.94 g (0.0074 mole) benzyl chloride, and the whole refluxed for 3 hr. 10 ml 17% HCl was added, and the precipitate of hydrochloride plus hydrochloric acid solution separated off, washed with benzene to remove non-basic material, made alkaline with 50% K_2CO_3, and the base extracted with ether. Paper chromatography showed the ether extract to contain a complex mixture of products, and it was column chromatographed on 200 g alumina (64 cm long, 2.5 cm diam). Elution was with 400 ml ether–petrol ether (1:1). Yield 0.34 g (22%) **IXa**, colorless crystals, mp 107°–108° C (ex hexane). It was readily soluble in ordinary organic solvents, soluble with difficulty in hexane and water. λ_{max}, nm (lg ε): 220 (4.55), 234 (4.35), 262 (4.18), 297 (4.23), 314 (3.42), 322 (3.49), 334 (3.54). Found: C 83.40; H 5.34; N 10.86%, calculated for $C_{18}H_{14}N_2$: C 83.69; H 5.46; N 10.85%.

Hydrochloride. This formed colorless crystals, mp 187°–188°C, readily soluble in EtOH, $CHCl_3$, and water, soluble with difficulty in benzene, acetone, ether, and EtOAc. Found: C 73.20; H 4.88; N 9.45; Cl 11.81%, calculated for $C_{18}H_{14}N_2 \cdot HCL$: C 73.34; H 5.13; N 9.51; C 12.02%.

The other components of the mixture formed by benzylating **VIIa** were not isolated and investigated.

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*Descending chromatogram on paper impregnated with formamide. The mobile phase was petrol ether. Visualization was by UV light (**IIIa** and **IIIb** absorb: **IVa**, **IVb**, **Va**, **Vb**, **IXa** blue luminescence) and with Dragendorf's reagent (**IIIa**, **IIIb** red complexes; **IVa**, **IVb**, **VA**, **Vb**, and **IXa** orange). R_f **IIIa** 0.53; **IIIb** 0.57; **IVa** 0.83; **IVb** 0.71; **Va** 0.90; **Vb** 0.93; **IXa** 0.94.

**A 53% yield is reported by Okuda and Robinson [3].

*A UR-10 registering spectrophotometer was used to observe the IR spectra.

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