FISCHER CYCLIZATION OF 6-SUBSTITUTED PYRID-2-YLHYDRAZONES OF CYCLOHEXANONE

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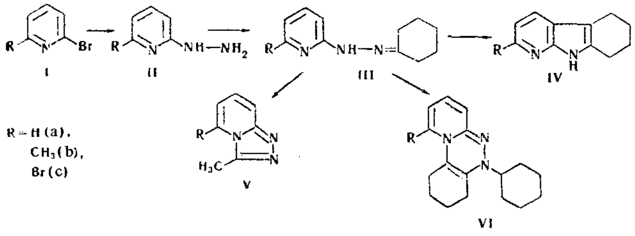
The influence of substituents in position 6 of the pyridine nucleus on the Fischer cyclization of cyclohexanone pyrid-2-ylhydrazones under the action of various catalysts has been studied. It has been established that the yields of the "normal" indolization products, derivatives of 5, 6, 7, 8-tetrahydro-α-carboline, increase regularly on passing from the unsaturated compound to the 6-methyl- and further to the 6-bromopyrid-2-ylhydrazones. The results obtained have been compared with the capacity of the pyridine nitrogen in the hydrazones mentioned for undergoing nucleophilic addition and substitution reactions.

In preceding papers [1–3] it has been shown that the results of the Fischer cyclization of pyrid-2-ylhydrazones depend markedly on the nature of the catalyst and also on the nature and position of substituents in the pyridine part of the molecule. These factors determine not only the yield of the normal indolization products but, in a number of cases, they even change the direction of the process [1].

The introduction of electron-donating groups into position 5 of the pyridine nucleus facilitates the "normal" Fischer reaction, while electron-accepting substituents hinder this process.

Preliminary experiments that we carried out earlier [2] showed that cyclohexanone 6-methylpyrid-2-ylhydrazone cyclizes more readily than the analogous compound without the methyl group. In view of this, it appeared of interest to make a more detailed study of the influence on the Fischer reaction of such substituents in position 6 of the pyrid-2-yl hydrazones as a methyl group and a halogen atom.

The appropriate comparative experiments on the indolization of unsubstituted cyclohexanone pyrid-2-ylhexanone (IIIa) and the analogous compounds containing a methyl group (IIIb) and a bromine atom (IIIc) in the pyridine part of the molecule were carried out with various catalysts: p-toluenesulfonic, sulfosalicylic, polyphosphoric, and hydrochloric acids, boron trifluoride etherate in acetic acid, excesses of zinc chloride, cuprous chloride, and boron trifluoride, and also by A. E. Arbuzov's method [4]—with catalytic amounts of cuprous chloride and zinc chloride.



The cyclization reactions with a given catalyst were carried out under the same conditions with all the pyrid-2-ylhydrazones. Column chromatography was used to separate the compounds in those cases where the process took place in more than one direction. The completeness of the separation and isolation and also the purity of the products were determined by paper chromatography. The analytical method of paper chromatography was also used to show that particular compounds (the initial hydrazone, the α-carboline derivative, etc.) were absent from the reaction products. Using descending chromatography with petroleum ether as the mobile phase, the R_f values of the compounds were as follows (the colors of the complexes with Dragendorff's reagent are given in brackets): IIIa, 0.53 (red); IIIb, 0.57 (red); IIIc 0.60 (orange); IVa, 0.83 (orange); IVb, 0.71, (orange); IVc, 0.56 (orange); Va–Vc, 0.00 (orange); VIa, 0.90 (orange); VIb, 0.93 (orange); VIc, 0.95 (orange); (on detection with UV irradiation, compounds IIIa–IIIc absorbed and the other substances possessed a blue fluorescence).

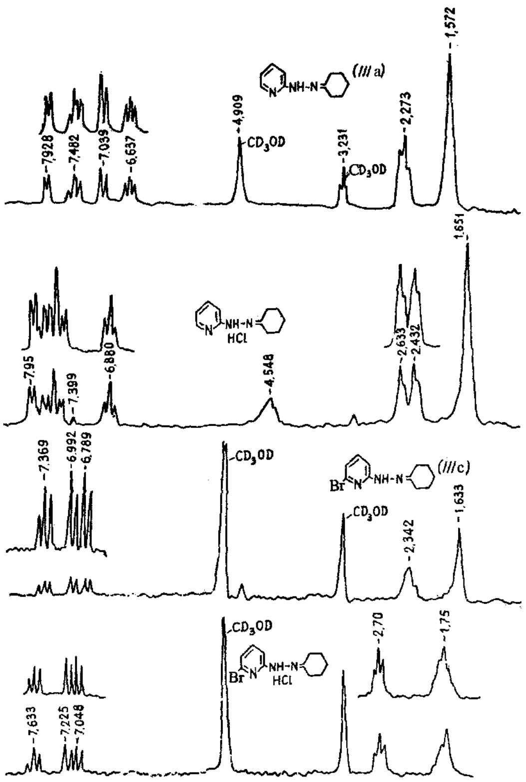
The results obtained in the Fischer reaction with cyclohexanone pyrid-2-ylhydrazone and some of its 6-substituted derivatives are given in Table 1.

As can be seen from Table 1, in almost all cases the yields of the "normal" products of the indolization of cyclohexanone pyrid-2-ylhydrazones, derivatives of 5, 6, 7, 8-tetrahydro-α-carboline (IV), rise uniformly on passing from the unsubstituted compound to the 6-methyl and further to the 6-bromo derivative. As has been observed previously for other pyrid-2-ylhydrazones [2], when strong mineral and organic acids are used as catalysts the highest indolization yields are obtained with p-toluenesulfonic acid and the lowest with hydrochloric acid. In the latter case, the process is accompanied by the side reaction of the formation of derivatives of 1 H-benz[1, 2-e]pyrido[2, 1-c]-asym-triazine (VI) through cyclization at the nitrogen of the pyridine nucleus [1]. It must be mentioned that the introduction of substituents (a methyl group and, particularly, bromine) into the α-position with respect to the pyridine nitrogen adversely affects the "anomalous" Fischer reaction and the yield of VI decreases from 36.6% in the case of the unsubstituted pyrid-2-ylhydrazone IIIa to 26.8% for the corresponding 6-methyl derivative (IIIb) and to 10.5% for the 6-bromo derivative (IIIc). Simultaneously, the yield of the "normal" cyclization products (IV) rise from 20.2 to 66.1 and 69.5%, respectively. The influence of substituents in the pyridine nucleus is shown to an even greater extent when boron trifluoride in acetic acid is used as the catalyst. Under these conditions no tetrahydro-α-carboline (IVa) is

Table 1

Yields of Substances (%) in the Fischer Reaction with Cyclohexanone Pyrid-2-ylhydrazone and Its 6-Substituted Derivatives

Catalyst	IVa	VIa (Va)	IVb	VIb (Vb)	IVc	VIc (Vc)
p-Toluene sulfonic acid	72		85		93.6	
Sulfosalicylic acid	51.6		59.6		77.9	
Polyphosphoric acid	62		73		71.3	
Hydrochloric acid	20.2	36.6	66.1	26.8	69.5	10.5
Zinc chloride (excess)	75		100		98	
Cuprous chloride (excess)	50.6		63		42.6	
Boron trifluoride (excess)	30		100		100	
Zinc chloride (catalytic amounts)	—		26		42.6	
Cuprous chloride (catalytic amounts)	—		22.8		32	
Boron trifluoride (in acetic acid)	—	(45)	27.6	(67)	58.5	(—)



PMR Spectra.

obtained from the unsubstituted pyrid-2-ylhydrazone IIIa: an "anomalous" reaction takes place and a derivative of asym-triazolo[4,3-a]pyridine (Va) is formed. In the case of the corresponding 6-bromo derivative (IIIc), on the other hand, the main reaction product is 2-bromo-5,6,7,8-tetrahydro-α-carboline (IVc), and cyclization at the nitrogen of the pyridine ring with the formation of Vc does not take place at all.

The suppression of the capacity of the pyridine nitrogen in 6-bromopyrid-2-ylhydrazine (IIc) for nucleophilic substitution reactions may also be judged from another reaction. When IIc is treated with acetic acid under the same conditions in which IIa is converted into a triazolopyridine derivative (Va) [5], it does not undergo cyclization and only the 6-bromopyrid-2-ylhydrazide of acetic acid (VII) is formed.

The influence of the amount of catalyst used is extremely characteristic for the indolization of pyrid-2-ylhydrazones with Lewis acids. As is well known, in the case of a number of aryl hydrazones the course of the Fischer reaction is closely linked with the reaction of the nitrogen of the hydrazine part of the molecule and the catalyst. In these circumstances, fairly small amounts of catalyst are adequate for the reaction, which permitted A. E. Arbuzov to develop the "catalytic method" for the indolization of aryl hydrazones [4]. In the case of the pyridyl hydrazones, besides the hydrazone nitrogens the molecule has a new competing reaction center—the nitrogen atom of the pyridine nucleus, which is also capable of complex-formation. As a result, when catalytic amounts of Lewis acids are used the latter are bound completely by the nitrogen of the pyridine nucleus and are removed from the sphere of the reaction. Consequently, as has been reported previously [2], in contrast to the aryl hydrazones the indolization of various pyrid-2-ylhydrazones by Arbuzov's catalytic method takes place with low yields or not at all. Only the use of large excesses of Lewis acids ensures that they react with the hydrazone nitrogen and give high yields of the normal indolization products.

In addition to this, on passing from the unsubstituted pyrid-2-ylhydrazones to compounds containing a halogen atom in position 6, the capacity of the heterocyclic nitrogen for taking part in nucleophilic addition reactions decreases. As a result, the extent to which the catalyst is removed from the sphere of the reaction through complex-formation at the nitrogen of the pyridine nucleus is reduced. Consequently, unlike the halogen-free compound IIIa, which does not form 5,6,7,8-tetrahydro-α-carboline with catalytic amounts of Lewis acids, cyclohexanone 6-bromopyrid-2-ylhydrazone (IIIc) is converted into the normal indolization product under these conditions.

To characterize the comparative capacity for nucleophilic addition of the nitrogen atoms of the pyridine nucleus and of the hydrazone residue of cyclohexanone pyrid-2-ylhydrazone and its 6-bromo derivative, the PMR spectra of these compounds and of their hydrochlorides were recorded (see figure)*.

In the PMR spectrum of cyclohexanone pyrid-2-ylhydrazone (IIIa), the signals of the four protons of the pyridine nucleus can be seen clearly; in the spectrum of its hydrochloride there is a marked shift of the signals into a weaker field together with their partial fusion, while the signals of the protons of the cyclohexane moiety of the molecule undergo practically no change. The situation is different in the case of cyclohexanone 6-bromopyrid-2-ylhydrazone (IIIc) and its hydrochloride. Here the change in the signals of the pyridine protons is very slight, while the signals of the protons of the cyclohexane moiety change considerably on passing from the base to the hydrochloride—they become more diffuse. On the basis of these facts, it may be stated that in IIIa protonation takes place primarily at the nitrogen of the pyridine nucleus, while in the 6-bromo derivative IIIc, because of the influence of the bromine atom, which greatly reduces the basicity of the pyridine nitrogen, it takes place in the hydrazone part of the molecule. Hence it becomes understandable that the addition of Lewis acids to IIIa, which is analogous to protonation, takes place primarily at the nitrogen of the pyridine nucleus, which excludes the possibility of the indolization of the compounds, while in the case of IIIc this addition of Lewis acids takes place at a hydrazone nitrogen, which favors the formation of a 5,6,7,8-tetrahydro-α-carboline derivative.

It is also interesting that the use in the Fischer reaction of a large excess of Lewis acids, instead of catalytic amounts, enables the yields of tetrahydro-

Table 2

Yield of Substances (%) in the Fischer Reaction with Lewis Acids

Catalyst	3-Methyl-5,6,7,8-tetrahydro-α-carboline		3-Chloro-5,6,7,8-tetrahydro-α-carboline	
	amounts of Lewis acids		amounts of Lewis acids	
	catalytic	excess	catalytic	excess
Zinc chloride	42	100	29	100
Cuprous chloride	43.5	54.5	—	56.6
Boron trifluoride	21.8	82	18.3	100

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*We consider it our pleasant duty to express our thanks to Yu. N. Sheinker and L. M. Alekseeva for recording the PMR spectra and for a discussion on their interpretation.

α-carboline derivative to be markedly increased in other cases besides the unsubstituted and 6-substituted cyclohexanone pyrid-2-ylhydrazones. As can be seen from Table 2, similar results are found for the corresponding 5-substituted derivatives: the 5-methyl- and 5-chloropyrid-2-ylhydrazones of cyclohexanone.

EXPERIMENTAL

6 Bromopyrid-2-ylhydrazine (IIc). A mixture of 10 g (42.2 mM) of 2, 6-dibromopyridine (Ic) and 9 ml (182 mM) of hydrazine hydrate in 500 ml of butanol was boiled for 5 hr. Then the reaction mixture was evaporated in vacuum and the residue was dissolved in ether. The ethereal solution was filtered and acidified to Congo Red with an ethanolic solution of hydrogen chloride. The hydrochloride of IIc that deposited was filtered off, washed with ether, and dissolved in water. The aqueous solution was made alkaline with potassium carbonate, and the liberated base IIc was extracted with ether. The ethereal extract was dried with sodium sulfate and evaporated in vacuum. The yield of IIc was 5.31 g (67%). Light yellow crystals, mp 117.5° C (from hexane). The substance is readily soluble in ether, chloroform, benzene, and ethanol, less readily in hexane and petroleum ether, and sparingly in water. Found, %: C 32.13; H 3.45; Br 42.45; N 22.36. Calculated for $C_6H_6BrN_3$, %: C 31.93; H 3.22; Br 42.50; N 22.35. Hydrochloride of IIb, colorless crystals, mp 172-173° C (decomp.).

Cyclohexanone 6-bromopyrid-2-ylhydrazone (IIIc). 0.14 ml (1.33 mM) of cyclohexanone was added to 0.25 g (1.33 mM) of IIc. After a day at room temperature, the partially crystalline mass was washed with water, and the crystals were dried in the air. This gave 0.36 g (100%) of IIIc. Yellow crystals, mp 112° C, bp 150-151° C (0.9 mm). The substance is readily soluble in chloroform, ethanol, and benzene, sparingly soluble in hexane, and insoluble in water. Found, %: C 49.39; H 5.37; Br 29.93; N 15.38. Calculated for $C_{11}H_{14}BrN_3$, %: C 49.25; H 5.26; Br 29.82; N 15.67. Hydrochloride of IIIc, yellow crystals, mp 114.5-115° C. Found, %: C 42.91; H 4.80; Br 25.88; Cl' 11.59; N 13.81. Calculated for $C_{11}H_{14}BrN_3 \cdot HCl$, %: C 43.35; H 4.96; Br 26.25; Cl' 11.65; N 13.79.

Fischer cyclization of IIIc. A) With p-toluenesulfonic acid. A mixture of 1 g (3.74 mM) of IIIc and 1.36 g (7.9 mM) of p-toluenesulfonic acid was heated to 160° C. A vigorous reaction began, with the evolution of heat and the formation of gaseous products. After cooling, the reaction mixture was dissolved in 50 ml of water, and the solution was made alkaline with potassium carbonate and extracted with ether. The ethereal extract was dried with sodium sulfate and evaporated in vacuum, giving 0.88 g (93.6%) of 2-bromo-5, 6, 7, 8-tetrahydro-α-carboline (IVc). Colorless crystals, mp 231-232° C (from benzene). The substance is readily soluble in chloroform and alcohols, less readily in benzene, ethyl acetate, and ether, and insoluble in water. Found, %: C 52.34; H 4.16; Br 32.01; N 10.97. Calculated for $C_{11}H_{11}BrN_2$, %: C 52.59; H 4.41; Br 31.85; N 11.15.

B) With sulfosalicylic acid. A mixture of 1 g (3.74 mM) of IIIc and 1.3 g (5.97 mM) of sulfosalicylic acid was heated to 135° C. A vigorous reaction took place and the temperature rose spontaneously to 175° C. Treatment of the reaction mixture was carried out as in the preceding experiment, giving 0.73 g (77.9%) of IVc.

C) With polyphosphoric acid. A mixture of 1 g (3.74 mM) of IIIc and the polyphosphoric acid obtained from 1.06 g of P_2O_5 and 0.69 ml of H_3PO_4 was heated at 180° C for 3 min. The reaction mixture was worked up as in the preceding experiment. The yield of IVc was 0.67 g (71.3%).

D) With hydrochloric acid. A mixture of 5 g (18.6 mM) of IIIc and 95 ml of conc HCl was boiled for 4 hr. After cooling, the reaction mixture was diluted twofold with water, made alkaline with ammonia, and extracted with ether. The ethereal extracts were dried with sodium sulfate and evaporated in vacuum. The residue was dissolved in petroleum ether and chromatographed on alumina. Elution was carried out first with 250 ml of petroleum ether and then with a mixture of ether and petroleum ether (1 : 3). Evaporation of the first eluate gave 0.34 g (10.5%) of VIc. Colorless crystals, mp 129-130° C (from ethanol). The substance is readily soluble in ether, acetone, and chloroform, less readily in ethanol and hexane, and insoluble in water. Found, %: C 58.33; H 6.30; Br 23.32; N 11.87. Calculated for $C_{17}H_{22}BrN_3$, %: C 58.61; H 6.37; Br 22.96; N 12.06. Evaporation of the second eluate in vacuum gave 3.25 g (69.5%) of IVc.

E) With an excess of zinc chloride. A mixture of 1 g (3.74 mM) of IIIc and 2.3 g (16.9 mM) of zinc chloride was heated to 240° C. There was a vigorous evolution of gaseous products, and the reaction mixture darkened. The reaction product was purified by chromatography on alumina with ether elution. The yield of IVc was 0.92 g (98%).

F) With an excess of cuprous chloride. A mixture of 1 g (3.74 mM) of IIIc and 3 g (15.1 mM) of freshly-prepared cuprous chloride was heated to 340° C and the reaction products were worked up in the same way as in the preceding experiment. This gave 0.4 g (42.6%) of IVc.

G) With an excess of boron trifluoride. A mixture of 1 g (3.74 mM) of IIIc and 2.5 g (17.6 mM) of boron trifluoride etherate was heated in a sealed tube at 200° C for 6 hr. After cooling, the reaction mixture was made alkaline with 50% potassium carbonate solution and extracted with chloroform. The residue after the distillation of the solvent was chromatographed on alumina with ether elution. This gave 0.94 g (100%) of IVc.

H) With catalytic amounts of zinc chloride. A mixture of 1 g (3.74 mM) of IIIc and 0.01 g (0.07 mM) of zinc chloride was heated to 240° C. The reaction mixture was worked up as in experiment E). The yield of IVc was 0.4 g (42.6%).

I) With a catalytic amount of cuprous chloride. A mixture of 1 g (3.74 mM) of IIIc and 0.01 g (0.05 mM) of freshly-prepared cuprous chloride was heated to 240° C. The reaction mixture was worked up as described in experiment F), giving 0.3 g (32%) of IVc.

J) With boron trifluoride in glacial acetic acid. A solution of 1 g (3.74 mM) of IIIc and 0.53 g (3.74 mM) of boron trifluoride etherate in 30 ml of glacial acetic acid was heated in a sealed tube at 180-200° C for 6 hr. After cooling, the reaction mixture was evaporated in vacuum. The residue was made alkaline with 50% potassium carbonate solution and extracted with chloroform. The chloroform solution, dried with sodium sulfate, was evaporated to a volume of 30 ml and was deposited on a column of alumina. Elution was carried out with 500 ml of ether, giving 0.55 g (58.5%) of IVc.

The Fischer reaction with IIIa and IIIb in the presence of various catalysts was carried out in a similar manner to the experiments described above with IIIc. The results obtained are given in Table 1.

The Fischer reactions for cyclohexanone 5-methyl- and 5-chloropyrid-2-ylhydrazones using various amounts of Lewis acids were carried out in a similar manner to experiments (E)-(J) described above. The results obtained are given in Table 2. The analytical characteristics of the starting materials and end products of the reaction for all these cases have been given in preceding papers [1-3].

6-Bromopyrid-2-ylhydrazide of acetic acid (VII). A mixture of 1 g (5.3 mM) of IIc and 30 ml of glacial acetic acid was boiled for 10 hr. The solution was evaporated in vacuum, and the solid residue obtained was titurated with ether. The yield of VII was 1 g (82%). Colorless crystals, mp 202-204° C. The substance was sparingly soluble in ether and hexane and readily soluble in acetic acid. Found, %: C 36.60; H 3.66; Br 35.00; N 18.02. Calculated for $C_7H_8BrN_3O$, %: C 36.53; H 3.50; Br 34.76; N 18.26.

REFERENCES

1. L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, DAN, 169, 361, 1966.

2. L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, KhGS [Chemistry of Heterocyclic Compounds], 3, 687, 1967.
3. L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, KhGS [Chemistry of Heterocyclic Compounds] (in press).
4. A. E. Arbuzov and A. P. Friaufa, ZhRKhO, 45, 695, 1913.
5. K. T. Potts and H. R. Burton, J. Org. Chem., 31, 251, 1966.

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