SYNTHESIS OF ETHYLAMINOPYRIDINES BY THE REACTION OF ISOMERIC BENZALDEHYDE PYRIDYLHYDRAZONES WITH SODIUM ETHOXIDE

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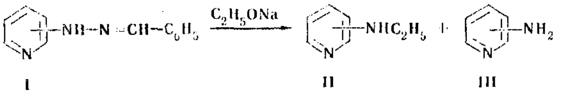
The reaction of isomeric benzaldehyde pyridylhydrazones with alkali metal alkoxides gave 2-, 3-, and 4-ethylaminopyridines. The effect of temperature and reaction time on the yields of products was investigated.

A new type of cleavage of the N–N bond to form 4-alkylaminopyridines and the sodium derivatives of the corresponding carbonyl compounds was observed in [1] during a study of the indolyzation of 4-pyridylhydrazones under the influence of alkali metal alkoxides. In order to establish how general this reaction is, in the present paper we consider the reaction of isomeric benzaldehyde 2-pyridyl-, 3-pyridyl-, and 4-pyridylhydrazones (I) with sodium ethoxide. The use of benzaldehyde as the carbonyl component of the isomeric pyridylhydrazones makes it possible to exclude the normal Fischer reaction and to direct the process to favor the formation of only ethylaminopyridines (II) and aminopyridines (III).



The mechanisms of the formation of II and III differ. While the formation of ethylaminopyridines II can be represented as attack by sodium ethoxide on the pyridylhydrazones and subsequent transformations of the cyclic transition state [1], the isomeric aminopyridines are apparently obtained as a result of the thermal decomposition of I without the participation of the alkali metal alkoxide. On the basis of previous investigations [1], it could be assumed that the temperature and reaction time should have different effects on the course of the two competitive processes.

In this connection, we studied the effect of temperature (from 190 to 300°C) and reaction time (from 15 min to 6 h) on the reaction of benzaldehyde 2-pyridyl-, 3-pyridyl-, and 4-pyridylhydrazones (Ia-c) with sodium ethoxide. This made it possible to find the optimum conditions for the synthesis of the isomeric ethylaminopyridines (II). All of the reactions were carried out with gas-chromatographic monitoring of the products formed. The yields of the substances, determined by gas-liquid chromatography (GLC), for the optimum conditions were confirmed by the results of preparative isolation of the products and are presented in Table 1.

An analysis of the results demonstrates that the ease of cleavage of the N–N bonds in the isomeric pyridylhydrazones differs. The process occurs most readily in the case of the 4-pyridylhydrazone (Ic), with somewhat greater difficulty for the Ib isomer, while the most severe conditions are required for the 2-substituted pyridine (Ia). The dependence of the yield of the isomeric ethylaminopyridines and aminopyridines on the temperature for a reaction time of 15 min is apparent from Table 1. The maximum amounts of 4-ethylaminopyridine (IIc) are formed under these conditions at 230°, while the maximum yield of 3-ethylaminopyridine (IIb) is obtained at 240°. As the temperature is raised further, the yields of IIb and IIc fall due to competitive reactions involving the formation of aminopyridines (IIIb,c). Benzaldehyde

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TABLE 1. Reaction of Isomeric Benzaldehyde Pyridylhydrazones with Sodium Ethoxide

Starting material	Reaction conditions		Yield, %		
	temp., °C	time	II	III	I
Ia	140	15min	—	—	100
	210	15min	1	1	89
	240	15min	3	3	87
	250	15min	5	4	59
	260	15min	11	44	9
	280	15min	27	41	4
	300	15min	58	25	—
Ia	240	2 h	4	3	34
	240	3 h	17	3	31
	240	4 h	28	8	30
	240	5 h	24	8	3
	240	6 h	5	8	3
Ib	210	15 min	5	12	67
	220	15 min	8	18	8
	240	15 min	83	8	—
	250	15 min	72	14	—
	260	15 min	56	27	—
Ib	190	1 h	6	12	65
	190	3 h	17	15	50
	190	6 h	12	20	10
Ic	190	15 min	—	—	95
	200	15 min	26	1	70
	220	15 min	72	2	18
	230	15 min	90	2	—
	250	15 min	72	27	—

2-pyridylhydrazone (Ia) reacts with sodium ethoxide in 15 min on heating above 250°, where processes involving the thermal cleavage of the N−N bond to form 2-aminopyridine IIIa and products of more profound destruction of the compound already begin to play a substantial role. The maximum amount of 2-ethylaminopyridine is isolated at 300°, where the process is accompanied by considerable resinification.

In this connection, we undertook a study of the reaction as a function of time at a lower temperature (240°) (Table 1). In this case, the maximum amounts of IIa are formed after 4 h, after which the yield of IIa decreases because of decomposition processes. A similar dependence on time is also observed for the yield of 3-ethylaminopyridine at 190°. The amounts of isomeric aminopyridines IIIa,b formed under these conditions are insignificant but increase regularly with time.

Thus the formation of alkylaminopyridines during the reaction of isomeric pyridylhydrazones with alkali metal alkoxides is actually general in character. This reaction can be used for the preparative synthesis of 3- and 4-ethylaminopyridines in high yields. In the case of 2-ethylaminopyridine, this method does not have preparative advantages over the synthesis of IIa from 2-bromopyridine and ethylamine.

EXPERIMENTAL

4-Ethylaminopyridine (IIc). A 1.3-g (0.61 mmole) sample of benzaldehyde 4-pyridylhydrazone (Ic) [2] was added to 0.6 g of freshly prepared sodium ethoxide, and the reaction mass was heated at 230° for 15 min, cooled to room temperature, and dissolved in water. The aqueous solution was extracted with chloroform, and the extract was dried with potassium carbonate. The chloroform was removed by distillation, and the residue was vacuum-distilled at 110-112° (2 mm) to give 0.67 g (83%) of IIc with mp 98-99° (from cyclohexane). Found: C 68.8; H 8.1; N 22.6%. $C_7H_{10}N_2$. Calculated: C 68.8; H 8.2; N 22.9%.

3-Ethylaminopyridine (IIb). A 1-g (0.5 mmole) sample of benzaldehyde 3-pyridylhydrazone (Ib) [3] was added to 0.5 g of sodium ethoxide, and the mixture was heated at 240° for 15 min, cooled, and dissolved in 18% hydrochloric acid. The nonbasic substances were extracted with chloroform. The aqueous layer was made alkaline with 40% sodium hydroxide solution, and IIb was extracted with chloroform. The chloroform extract was dried with potassium carbonate and vacuum-evaporated. The residue was vacuum-distilled at 80-82° (3 mm) to give 0.46 g (74%) of IIb with n_D^{20} 1.5735. The product was quite soluble in the usual organic solvents and only slightly soluble in water. Found: C 68.5; H 8.1; N 22.9%. $C_7H_{10}N_2$. Calculated: C 68.8; H 8.2; N 22.9%.

2-Ethylaminopyridine (IIa). A mixture of 3 g (19 mmole) of 2-bromopyridine and 13 ml (200 mmole) of ethylamine was heated at 150° for 10 h in a glass beaker placed in a hermetically sealed steel bomb. The reaction mass was then dissolved in chloroform, and the chloroform solution was washed with water, dried with potassium carbonate, and vacuum-evaporated. The residue was distilled at 92-93° (12 mm) to give 1.3 g (56%) of IIa. The picrate was obtained as yellow crystals with mp 162-163° (from alcohol); the crystals were slightly soluble in ether, alcohol, and acetone and more soluble in water. Found: C 44.4; H 3.9; N 19.9%. $C_7H_{10}N_2 \cdot C_6H_3N_3O_7$. Calculated: C 44.4; H 3.7; N 19.9%.

The synthesized 2-ethylaminopyridine (IIa) and its picrate were identical to the corresponding substances obtained from benzaldehyde 2-pyridylhydrazone [4] via a method similar to that described above.

The synthesis of 2-ethylaminopyridine (IIa) from 2-aminopyridine by formylation, conversion of the 2-formylaminopyridine to the N-sodio derivative with subsequent N-alkylation with ethyl bromide, and removal of the formyl protective group was previously described in [5]. The overall yield of IIa with bp 79-82° (4 mm) obtained via this method was 20%.

The gas-chromatographic analysis of the products of the reaction of the isomeric benzaldehyde pyridylhydrazones with sodium ethoxide was carried out with a Pye Unicam series 104 gas-liquid chromatograph with a flame-ionization detector. The 2.1-mm by 4-mm column was filled with 10% SE-30 silicone elastomer on silanized diatomite S (100-200 mesh). The nitrogen flow rate was 29 ml/min with programmed temperature conditions from 160-245°. The initial period was 5 min, and the temperature rise was 32 deg/min. The retention times (in minutes) were as follows: 15 for Ia, 18 for Ib, 21 for Ic, 4.3 for IIa, 6 for IIb, 6.3 for IIc, 2.4 for IIIa, 3.2 for IIIb, and 4.2 for IIIc.

LITERATURE CITED

1. L. N. Yakhontov and M. F. Marshalkin, Dokl. Akad. Nauk SSSR, 199, 625 (1971).
2. E. Koenigs, W. Weiss, and A. Zscharn, Ber., 59, 317 (1926).
3. E. Mohr, Ber., 31, 2495 (1898).
4. A. E. Chichibabin and B. A. Razorenov, Zh. Russk. Fiz. Khim. Obshchestva, 47, 1286 (1915).
5. F. F. Blicke, and M. U. Tsao, J. Amer. Chem. Soc., 68, 905 (1946).