SYNTHESIS OF PYRIDINE BASES FROM ALDEHYDES AND AMMONIA (REVIEW)

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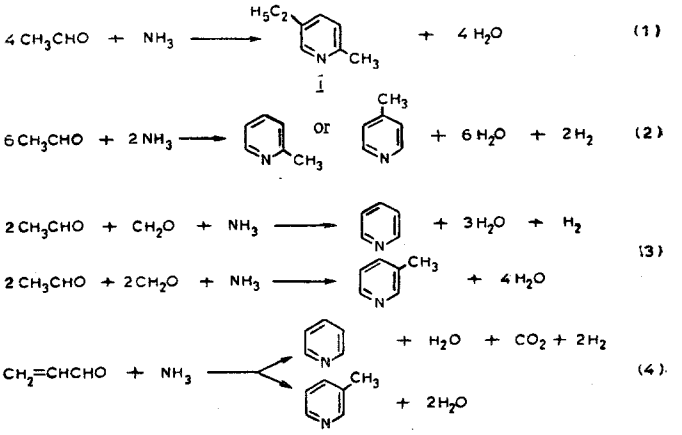
Research accomplished in the Yaroslav Polytechnic Institute on the synthesis of pyridine bases by the reaction of aliphatic aldehydes with ammonia is correlated.

Interest in synthetic methods for the preparation of individual pyridine bases has grown sharply in recent years. The pyridine bases of greatest significance as starting materials in the production of poly(vinylpyridine) polymers, pyridinecarboxylic acids, selective extracting agents, and acid-corrosion inhibitors are pyridine, picolines, and 2-methyl-5-ethylpyridines [1-8]. Until recently the only source of pyridine bases were coking side products, from which only ~0.1% pyridine derivatives can be isolated in the form of complex and difficult-to-separate mixtures.

The industrial production of some valuable pyridine bases on the basis of the Chichibabin reaction – the reaction of aliphatic aldehydes with ammonia – is presently being organized in various countries, including the USSR [1-3]. For a long time the Chichibabin reaction had no practical value [10-12], inasmuch as a complex mixture of pyridine bases with low yields of individual products was obtained under its conditions. The synthesis of 2-methyl-5-ethylpyridine (I), the production of which has been realized on an industrial scale [2, 9], was the simplest and most economically profitable reaction.

The synthesis of I [reaction (1)] is carried out in the liquid phase under pressure (80-100 atm) with paraldehyde and 50% ammonium hydroxide (with a molar ratio of paraldehyde to ammonia of 1:4) in the presence of catalysts (ammonium fluoride or acetate). The reaction proceeds quite vigorously at 225-250°C, and practically complete conversion of the paraldehyde is achieved after 20-90 min.



An advantage of this process is the rather high selectivity of the formation of base I (~70 mole %) and the possibility of practically complete utilization of all of the remaining pyridine derivatives.

Chichibabin also first realized the syntheses of isomeric picolines on the basis of the simplest aldehydes in the gas phase on heterogeneous catalysts [reactions (2) and (3)] [10-12]. These processes were subsequently improved technically through the use of more effective catalytic systems [4-8].

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TABLE 1. Principal Indexes of Processes for the Synthesis of Isomeric Picolines*

Reaction products	Starting aldehydes			
	formaldehyde–acetaldehyde molar ratio			acrolein
	0:1	1:1	3:1	
	yield based on the amount of acetaldehyde or acrolein passed through the system, mole %			
Pyridine	2,5	25,2	29,8	24,5
α-Picoline	22,0	2,6	—	3,2
β-Picoline	—	15,8	31,4	52,2
γ-Picoline	24,3	—	—	—
Lutidines	4,9	2,8	2,6	3,6
2-Methyl-5-ethylpyridine	4,8	3,2	8,2	5,9
Higher pyridine bases	29,2	5,3	1,5	—
Chemical losses	9,0	11,8	4,2	7.9

*The reaction temperature was 400°C, the total space velocity of the aldehydes was 0.25 liter/liter of catalyst particles, the molar acetaldehyde (acrolein)–ammonia ratio was 1 : 3, the catalyst was an aluminum silicate catalyst, and the conversion of acetaldehyde and acrolein was 78.0 and 97.3%, respectively.

An equimolecular mixture of α- and γ-picolines with an overall yield of up to 50 mole %, based on the amount of acetaldehyde passed through the system, and with practically complete conversion of the aldehyde was obobtained by condensation of acetaldehyde with a twofold excess of ammonia [reaction (2)] in a fluidized bed of an aluminum silicate catalyst at 380–400° [7, 8].

Under similar conditions, β-picoline was synthesized by condensation of ammonia with a mixture of formaldehyde and acetaldehyde [reaction (3)] or acrolein [reaction (4), Table 1] [4–6].

The molar ratio of the starting aldehydes has the greatest effect on the yield of β-picoline [reaction (3)]: A greater than twofold excess of formaldehyde insures the formation of β-picoline and the absence of isomeric picolines (Table 1). This fact is very important, inasmuch as it is difficult and costly to technically separate a mixture of close-boiling β- and γ-picolines. The development of this new extremely efficient method for the direct oxidation of ethylene to acetaldehyde leads to a substantial reduction in the cost of the acetaldehyde used in reactions (1-3).

The detailed investigation of reactions (1-4) has made it possible to expand concepts regarding the mechanism of the formation of the individual pyridine bases, about which there is as yet no unified opinion. The mechanism of the Chichibabin reaction has been discussed by many investigators [13-20]. Most researchers [13, 14, 17, 18] have represented this mechanism in the form of different schemes of mutual orientation of the starting reagents that, in their opinion, explain the formation of the individual pyridine bases. These investigators feel that the chief product of reaction (1) in the condensation of acetaldehyde with ammonia in the liquid phase is formed through crotonaldehyde. Similarly, the formation of the isomeric picolines is represented through a step involving the intermediate formation of α,β-unsaturated aldehydes – acrolein from formaldehyde and acetaldehyde [reaction (3)] [19, 20] and crotonaldehyde from acetaldehyde [reaction (2)] [8].

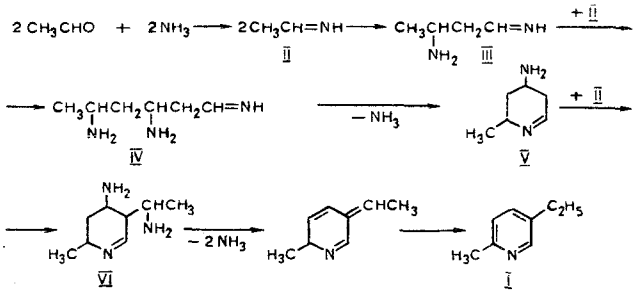
In our opinion, these schemes are not sufficiently convincing. Thus Chichibabin's data [12], which we have also confirmed, show that the use of crotonaldehyde in liquid-phase reaction (1) practically does not lead to the formation of individual pyridine bases; moreover, mainly a resin is obtained. Similarly, in an investigation of the condensation of formaldehyde and acetaldehyde with ammonia [reaction (3)] we showed that acrolein is not formed under the conditions of this reaction. In addition, it is seen from the experimental data (Table 1) that condensation of a formaldehyde–acetaldehyde mixture [reaction (3)] or of acrolein with ammonia [reaction (4)] leads to different ratios of the principal products – pyridine and β-picoline. The facts noted above confirm that the condensation of formaldehyde and acetaldehyde with ammonia evidently does not proceed through a step involving the intermediate formation of acrolein.

It is known [21] that the direct reaction of aldehydes with ammonia proceeds readily at moderate temperatures, and this reaction will therefore be the primary reaction at temperatures above 200° and in excess ammonia. It is precisely for this reason that it was found to be expedient in reaction (1) to use paraldehyde in place of acetaldehyde, which reacts with ammonia to form considerable amounts of resinification products [2]. This leads to a sharp decrease in the yield of the desired 2-methyl-5-ethylpyridine. However, paraldehyde, which is an unusual acetaldehyde "dispenser" in the reaction system, prevents the reaction of acetaldehyde

with ammonia even at reduced temperatures, at which the formation of the pyridine bases practically does not occur but the formation of aldehyde–ammonia resins is possible. At temperatures above 200°, paraldehyde slowly dissociates in ammonia to give acetaldehyde, which immediately reacts with ammonia to give the pyridine bases. Other acetaldehyde derivatives that are capable of dissociation at high temperatures to give free acetaldehyde (for example, acetals [17]) can also be used in place of paraldehyde.

In addition to the fact of the formation of aldehyde–ammonias, in technological designing one must also take into account the gas-phase processes in the synthesis of isomeric picolines: Separate feeding of the starting aldehydes and ammonia in order to avoid the formation of aldehyde–ammonias is provided for in the realization of reactions (2-4) [4-7].

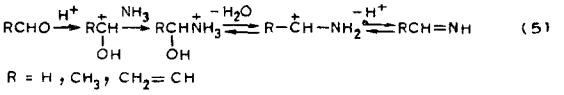
Thus, on the basis of the experimental data from the liquid-phase synthesis of 2-methyl-5-ethylpyridine (I) [reaction (1)], as first proposed by Strain [15, 16], Farberov and co-workers [2] supposed that the primary product of this reaction is aldimine II, which is capable of undergoing a condensation similar to an aldol condensation to give amino imine III:



The latter adds a subsequent aldimine link via the same mechanism to give diamino imine IV, which is readily cyclized with loss of ammonia to give intermediate tetrahydropyridine V. Tetrahydropyridine V, which also has a labile hydrogen atom, subsequently reacts with an aldimine molecule to give diamine VI. The latter undergoes rearrangement with the loss of two ammonium molecules to give the chief reaction product, 2-methyl-5-ethylpyridine.

During reaction (1), the authors also detected and identified a number of other pyridine derivatives formed principally from intermediate tetrahydropyridine V [2].

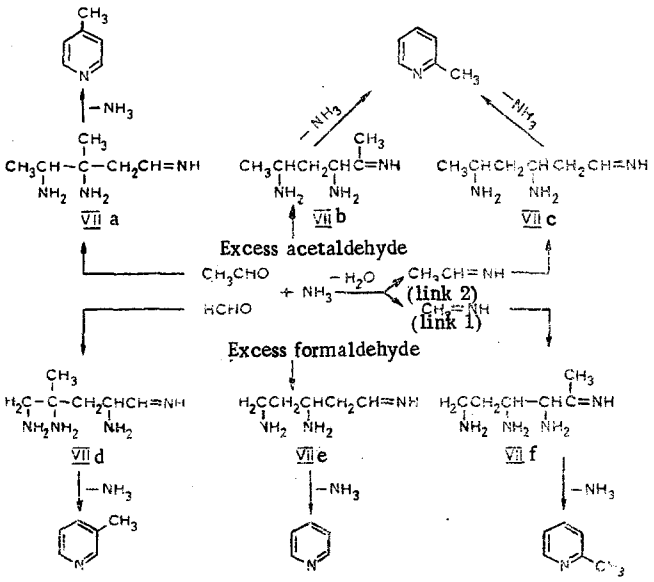
In order to obtain a more reliable experimental basis for the mechanism of the formation of pyridine bases under the conditions of the Chichibabin reaction, in our subsequent studies [4] we made detailed kinetic investigations of reactions (3) and (4) in the gas phase on various catalysts (aluminum oxide, aluminum silicate, and a bifunctional catalyst based on zinc oxide and aluminum). In these studies we noted an increase in the activity of the catalyst as the apparent values of their acidity functions increased. One may then expect the following sequence of reactions, through the formation of a carbonium ion [reaction (5)], on catalysts of the acid type:



Formaldehyde imine molecules, which do not contain hydrogen atoms in the α position relative to the carbon–nitrogen double bond, cannot undergo typical "aldol" condensation under the conditions of reaction (3): In fact, we did not detect pyridine bases during contact of formaldehyde with ammonia. However, the acetaldimine molecules formed during the reaction of acetaldehyde with ammonia [reaction (2)] or reaction of excess (with respect to formaldehyde) ammonia [reaction (3)] undergo condensation to give three structures (VIIa-c) from three acetaldimine molecules. Inasmuch as these pathways are apparently equivalent in the condensation, equimolecular amounts of α- and γ-picolines should be formed in the cyclization of amino imines VII, and this is in agreement with the experimental data (Table 1) [7]. However, in the reaction of the formaldehyde–acetaldehyde mixture with ammonia [reaction (3)] one might expect the formation of amino imine structure VIId with alternation of formaldimine (link 1) and acetaldimine (link 2) molecules (1, 2, 2, 1) when a considerable excess of formaldehyde is present. Amino imine structure VIIe becomes predominant when the percentage of formaldehyde in the starting mixture is reduced. These amino imines undergo cyclization to give the principal products

of reaction (3) – pyridine and β-picoline – as confirmed by the experimental data (Table 1). The amino imine VIIf structure with alternation of links 2, 1, 1, 2 is apparently less likely, and the formation of only insignificant amounts of α-picoline was therefore noted in reaction (3).

As in the case of the mechanism presented above, the two aldimine molecules formed in the reaction of acrolein with ammonia [reaction (4)] give the corresponding amino imine, cyclization of which gives primarily β-picoline; this is also in agreement with the experimental data (Table 1). In order to confirm the proposed mechanism for the formation of pyridine bases via reactions (2)-(4), a series of control experiments were carried out in order to ascertain the possibility of dealkylation of the alkylpyridines and isomerization of the picolines under the conditions of these reactions: Dealkylation products were not detected, and isomerization of the picolines was not observed. The formation of pyridine [reaction (4)] is therefore apparently explained by cracking of the amino imines at high temperatures and subsequent cyclization of them.



Thus the proposed mechanism for the formation of pyridine bases primarily through a step involving the initial formation of aldimines explains the observed facts and structures of the products detected in the processes underinvestigation [reaction (1-4)]. On the basis of this mechanism, one can also explain the formation of the pyridine compounds obtained by a number of other investigators [13-20] by reaction of diverse carbonyl compounds with ammonia in the liquid and gas phases.

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CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES

III.* SYNTHESIS OF BENZIMIDAZOLE AND BENZOTHIAZOLE ANALOGS OF ISOFLAVONES

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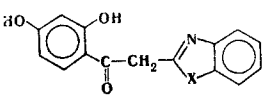
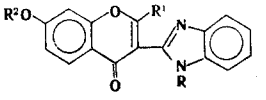
Condensation of cyanomethyl derivatives of benzimidazole and benzothiazole with resorcinol gave the corresponding 2,4-dihydroxy-α-hetarylacetophenones. The latter were converted to 3-hetarylchromones with methyl, trifluoromethyl, and ethoxycarbonyl groups in the 2 position or to chromones without substituents in this position.

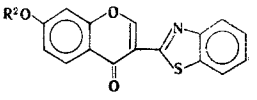
Continuing our study of chromones containing nitrogen heterorings in the 3 position [2, 3], we have synthesized benzimidazole and benzothiazole analogs of isoflavones (IV-XII). The starting α-hetaryl-2,4-dihydroxyacetophenones (I-III) were obtained by condensation of the appropriate 2-hetarylacetonitriles with resorcinol by the method in [2]. Boron trifluoride etherate, which also served as the solvent, was used as the catalyst.



I-III



IV-IX, XI



X, XII

I X=NH; II X=NCH_3; III X=S; IV R=R^2=H, R^1=CF_3; V R=CH_3, R^1=CF_3, R^2=H; VI R=R^2=H, R^1=$COOC_2H_5$; VII R=CH_3, R^1=$COOC_2H_5$, R^2=H; VIII R=R^1=CH_3, R^2=$COCH_3$; IX R=CH_3, R^1=R^2=H; X R^2=H; XI R=CH_3, R^1=H, R^2=$COCH_3$; XII R^2=$COCH_3$

Chromones IV-VII containing trifluoromethyl and ethoxycarbonyl groups in the 2 position were obtained by reaction of α-benzimidazolylacetophenones I and II with trifluoroacetic anhydride by our modification of the method in [4] or by reaction of ethoxyallyl chloride [5] in pyridine in the cold. The pyrone ring in the indicated reactions is formed considerably more readily than in the case of α-hetarylacetophenones with thiazole [2] and pyrazole [3] residues; this is apparently explained by the increased reactivity of the methylene group of ketones I and II. The activating effect of the benzimidazole rings shows up particularly clearly in reactions leading to 2-methylchromone derivatives. Thus, for example, the reaction of acetic anhydride with acetophenone II proceeds smoothly in pyridine at room temperature to give 2-methyl-7-acetoxychromone VIII, while prolonged heating at 120-150° in triethylamine (which is a stronger base than pyridine) is necessary for realization of the analogous cyclization of the above mentioned α-hetarylacetophenones [2, 3] and α-phenylbenzyl ketones [6]. Under these conditions acetophenone II gives a difficult-to-purify resinous product. Chromones IX and X, which

*See [1] for communication II.

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