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SYNTHESIS OF PYRIDINE BASES BY THE CHICHIBABIN METHOD (REVIEW)

R. S. Sagitullin, G. P. Shkil', I. I. Nosonova, and A. A. Ferber

Published data on the synthesis of pyridine bases from carbonyl compounds or acetylene and ammonia by the Chichibabin method are summarized.

INTRODUCTION

Many of the compounds containing a pyridine ring in their molecule are of considerable interest in organic chemistry. Such alkaloids as nicotine and anabasine are widely found in the plant world. Other compounds, such as vitamins of the B group (pyridoxine, nicotinic acid, etc.), play an important role in the metabolism of living organisms.

A special position among the compounds containing a pyridine ring is occupied by alkylpyridines. On account of their specific reactivity and physiological activity, they have found wide use in various branches of industry. The main users of alkylpyridines are the polymer, chemical, and pharmaceutical industries. In particular, α-picoline (2-methylpyridine), γ-picoline (4-methylpyridine), and 2-methyl-5-ethylpyridine are used as raw materials in the production of 2-vinylpyridine, 4-vinylpyridine, and 2-methyl-5-vinylpyridine, which are used in the manufacture of latexes for the impregnation of tire cord, ion-exchange resins, cine and photo materials, etc. In a number of cases pyridine bases are the only raw materials for recently instituted economically important processes, including chemical means for the protection of plants against weeds, pests, and various diseases. Thus, 2-picoline is used as the basis of nitropyrine (known as N-serve), which is an inhibitor of the nitrification of nitrogen fertilizers [1, 2].

Extractants, metal corrosion inhibitors, solvents, surfactants, vulcanization accelerators, and other products have been synthesized on the basis of substituted pyridines. However, the widespread industrial application of these compounds has been delayed by the absence of cheap and convenient methods for their production, since the amount of pyridine bases produced from coal tar is completely insufficient. Here it should be mentioned that the separation and identification of the individual compounds from coal tar raw material is an extremely laborious and complicated task [1, 3, 4].

All this has given rise to the development of synthetic methods for the production of pyridine and its simplest homologs, the cost of which is significantly lower than the cost of the substances isolated from the products of the coal-tar industry [5-7]. The synthesis of pyridine bases was first realized by Dürkopf [8, 9]. Systematic researches into the gas-phase synthesis of alkylpyridines from carbonyl compounds and ammonia were first undertaken under the leadership of Chichibabin [10-12], and this reaction was subsequently known by his name (sometimes called the Chichibabin–Bayer reaction). Modern technological syntheses of alkylpyridines by the gas-phase condensation of carbonyl compounds with ammonia only differ from the method developed by Chichibabin in the use of more effective catalytic systems and in the use of a fluidized bed.

However, in spite of the widespread use, including industrial use, of the Chichibabin reaction for the production of alkylpyridines, there have been no sufficiently complete reviews of this reaction. It is true, monographs and reviews that appeared in the press a few years back contained individual sections on this subject [13-25]. In the present paper an attempt is made to classify published data on the synthesis of pyridine bases by the Chichibabin and related methods. We were interested, primarily, not in the target products of these syntheses but in the side products and, in particular, the possibilities of producing, isolating, and identifying substances of neutral nonbasic character, especially as substances no less interesting

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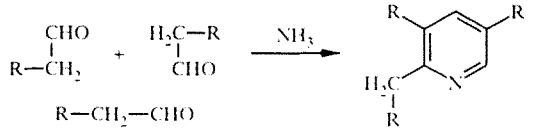
than the pyridines themselves can be found among these compounds. Investigations in this direction can provide additional information on the mechanism of the Chichibabin reaction.

MODERN THEORIES ABOUT THE MECHANISM OF THE CHICHIBABIN REACTION

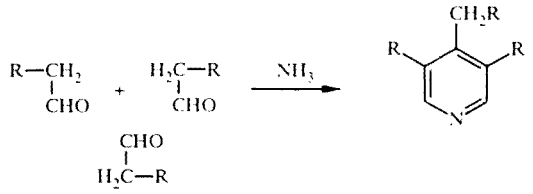
One of the first syntheses of pyridine was realized in 1869 by Baeyer [26], who passed acrolein into an aqueous solution of ammonia. An analogous reaction was developed almost simultaneously by Dürkopf [8, 9, 28]; by heating a mixture of aliphatic aldehydes and ammonium acetate to 200°C in sealed tubes, he obtained a mixture of pyridine bases. The best results were obtained with paraldehyde; 2-methyl-5-ethylpyridine was isolated from the mixture of products as the main product.

However, the main researches in this direction were carried out by Chichibabin and his coworkers. They realized the synthesis of pyridines by two methods: 1) by heating aldehydes with ammonia in aqueous solution in sealed tubes; 2) by passing a mixture of the aldehyde and ammonia over a dehydrating catalyst in the vapor phase. In work on the first method, α- and γ-methylpyridines and 2-methyl-5-ethylpyridine were synthesized from acetaldehyde and ammonia [29-32]. The possibility of obtaining the latter with yields of 70-80% from acetaldehyde led to the development and study of the Chichibabin reaction with a view to industrial production.

On the basis of numerous experimental data, Chichibabin was able to establish the specific relationships of this reaction. He showed that two reaction paths are possible for saturated aldehydes of the type of acetaldehyde and its monosubstituted homologs:

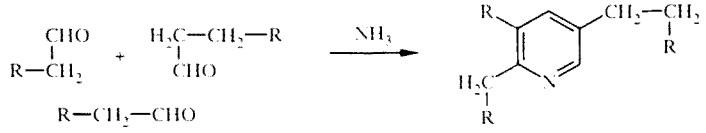


(1)



(2)

With various aldehydes the reaction can take place in the following way:



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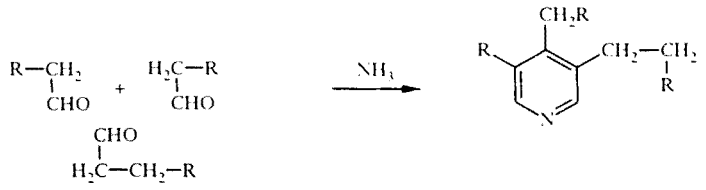
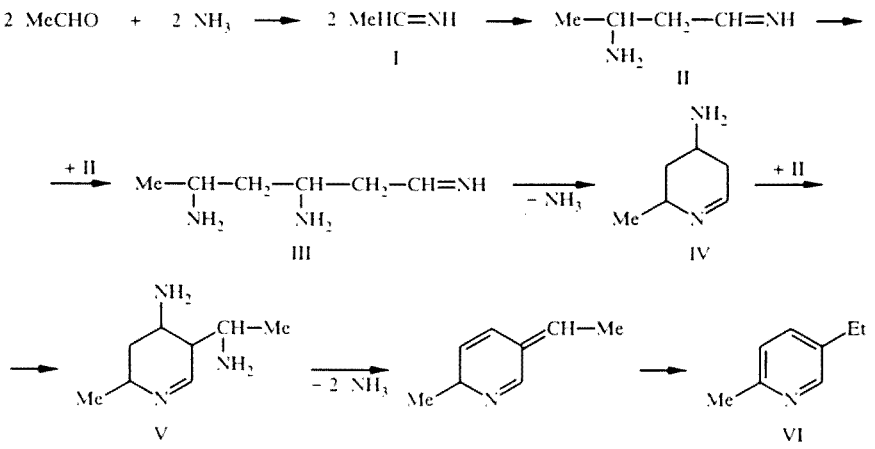


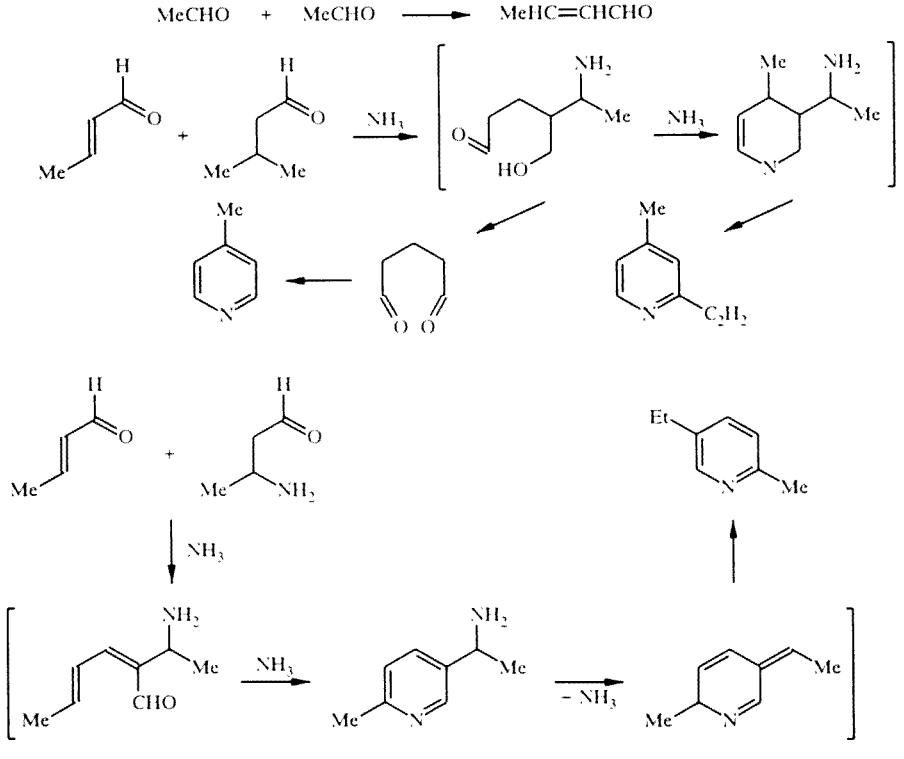
(4)

The mechanism of these reactions was studied by many other authors, but there is still no common opinion. Most of the authors [33-36] represented this mechanism in the form of various schemes of mutual arrangement of the initial reagents, which in their opinion explained the formation of the individual pyridine bases.

In [24, 37] the authors consider that their experimental data confirm the theory put forward by Strain [38] about the reaction mechanism:



In their opinion, the initial product of this reaction is the aldimine (I), which is capable of entering into a condensation similar to an aldol condensation with the formation of the aminoimine (II). The latter adds the next aldimine unit by the same mechanism and forms the diaminoimine (III), which readily undergoes cyclization with the loss of ammonia, forming the intermediate tetrahydropyridine (IV). Compound (IV), which also has a mobile hydrogen atom, then reacts with a molecule of the aldimine, forming the diamine (V). The latter rearranges with the loss of two molecules of ammonia, giving the main reaction product 2-methyl-5-ethylpyridine (VI).

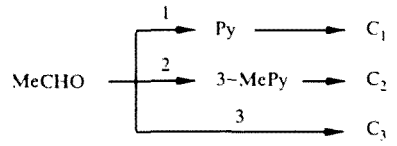


As considered by other authors [36, 39, 40], the first stage of the process is the formation of acrolein, which then reacts with a second molecule of the acetaldehyde by a mechanism of the crotonic condensation or Michael type.

Retroaldol cleavage of the intermediates can lead to the formation of 2- and 4-methylpyridines.

Kinetic investigations are needed in order to define the mechanism of the formation of the bases more precisely. This presents great difficulty on account of the nonstationary nature of the process, the multistage nature of the overall reaction,

and so forth. In [41] kinetic data are given for the synthesis of pyridine bases from acetaldehyde, formaldehyde, and ammonia in the presence of an aluminosilicate catalyst. With a threefold excess of formaldehyde and ammonia, the rate of transformation of acetaldehyde can be described by a first-order equation. The kinetics correspond to the parallel–consecutive reactions:



where C_i represents the side products of the reaction.

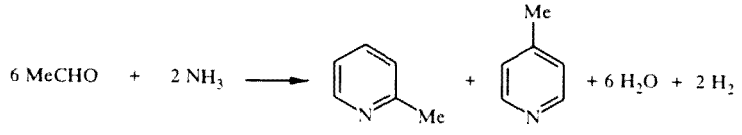
It is necessary to mention the paper [42], which was devoted to study of the conditions for the selective production of various alkylpyridines. The composition of the final products is affected by the temperature, the delivery rate of the mixture of aldehydes, and their ratio.

Thus, by studying the accumulated experimental data it is possible to come to a common view about the mechanism of the Chichibabin reaction.

SYNTHESIS OF ALKYL- AND ARYLPYRIDINES

Reactions of Aliphatic Aldehydes and Ketones with Ammonia

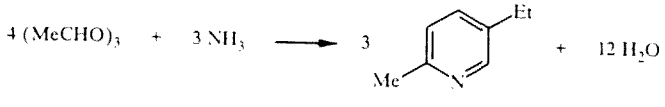
The condensation of aldehydes with ammonia can also be conducted in the gas phase, using various catalysts. The direction of the reaction in this case only changes a little compared with the aqueous phase. Complex mixtures are usually obtained as a result of the reaction. With careful choice of the conditions, however, it is possible to obtain a satisfactory yield of the main reaction product. Thus, if a mixture of acetaldehyde and ammonia is passed over Al_2O_3 at 300-330°C, a mixture of 2- and 4-methylpyridine is formed [43, 44] with an overall yield of up to 65%.



2-Methyl-5-ethylpyridine, 3-ethyl-4-methylpyridine, and other compounds are formed as side products. The formation of 4-methyl- and 4-methyl-5-ethylpyridine can be explained by the schemes (2) and (4) given earlier, where R = H.

A characteristic feature of the gas-phase synthesis of alkylpyridines is the fact that the reaction products contain compounds of nonpyridine type [45, 46]. Thus, 20-25% of neutral compounds were found in the crude condensate from the synthesis of α- and γ-picoline [47].

The production of 2-methyl-5-ethylpyridine from synthetic pyridines was first introduced by the American firm Philips Petroleum [48].

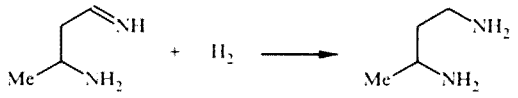


The synthesis was based on the liquid-phase condensation of the acetaldehyde trimer paraldehyde and ammonia in the presence of a catalyst: Ammonia was brought into the reaction in an excess of no less than threefold compared with the stoichiometric ratio. The pressure in the reaction mixture was kept at such a level that the reagents were in the liquid phase at the reaction temperature of 200-290°C. According to the patents [49-52], the fluorides of metals and boron, organic bases, sulfonic acids,

and other compounds can be used as catalysts. However, on account of the cherrystone of these compounds, ammonium acetate is usually employed as catalyst [53].

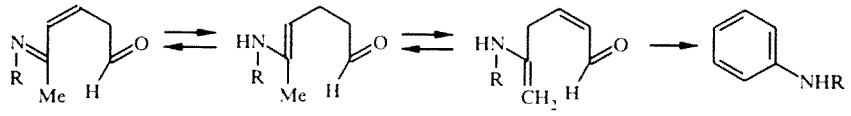
The side products of the reactions, which usually amount to about a third of the substances formed, are 2- and 4-picolines, 3-ethyl-4-methylpyridine, 2-propyl-3-ethylpyridine, and other high-boiling alkylpyridines [34, 54-56], and also quinoline and isoquinoline bases [57, 58]. Since hydrogenation and hydration occur here [59], it can be supposed that the products from reduction of the reagents and the intermediates by the released hydrogen are formed, i.e., alcohols can be formed from the carbonyl compounds, while aldehyde ammonias can be reduced to the corresponding amines:

$$CH_3CH{=}NH + H_2 \rightarrow CH_3CH_2NH_2;$$
$$CH_3CHO + H_2 \rightarrow CH_3CH_2OH \quad \text{etc.}$$



A 1,3-diamine can be obtained during the reduction of the iminoamine formed from the aldehyde and ammonia [60, 61].

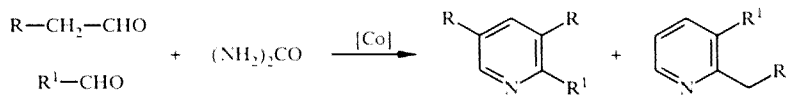
The amines formed in this way can enter into reaction with acetaldehyde and its derivatives, leading to the N-alkylated intermediates, which are not capable of closure to pyridine derivatives but can undergo cyclization to aniline derivatives [62].



This suggestion is supported by the discovery of quinolines in the products from the synthesis of 2-methyl-5-ethylpyridine [57, 58]; the quinolines can be obtained from anilines and α,β-unsaturated ketones by a reaction of the Skraup type [63].

The formation of anilines by the recyclization of picolines is unlikely, since picolines are very stable and do not undergo such secondary reactions as decomposition, isomerization, and polycondensation [59]. According to data in [57, 61], isoquinolines were also found in the reaction products.

In the patent and scientific and technical literature, many methods have been described for the production both of individual alkylpyridines and of their mixtures from aldehydes, ketones, and ammonia. All these reactions can be represented by schemes (1)-(4) (see [148, 149]). Data on the synthesis of pyridine bases from aldehydes are summarized in Table 1.



R = Et, Bu, C_5H_{11}, C_6H_{13}; R^1 = Ph

The production of alkylpyridines from aldehydes and urea at 20°C with a cobalt catalyst is also known [83].

Pyridine bases can also be obtained by the catalytic ammonolysis of ketones. Thus, 2,4,6-collidine was obtained with a good yield from acetone and ammonia over aluminum oxide at 360-440°C [84, 85].

There are data on the use of a calcium–nickel–phosphate catalyst for the ammonolysis of acetone, methyl ethyl ketone, diethyl ketone, and propyl ketone [86].

Papers on the catalytic synthesis of alkylpyridines by the ammonolysis of ketones in the presence of acetylene are known [87, 88]. However, these methods have been studied little, and there are hardly any published data on the reaction mechanism.

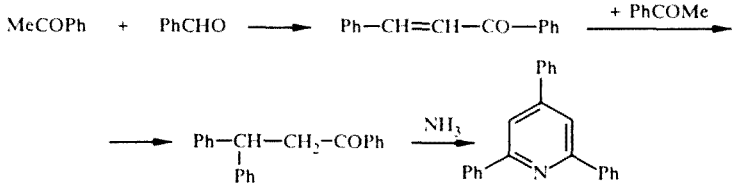
Reactions of Unsaturated and Aromatic Aldehydes and Ketones with Ammonia

The synthesis of pyridine bases from the industrially accessible crotonaldehyde (a side product in the production of acetaldehyde by the hydration of acetylene) is extremely promising.

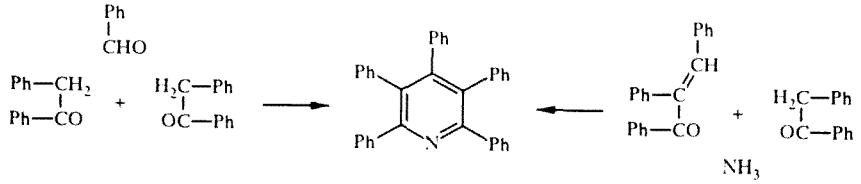
A catalytic synthesis of β-picoline (one of the mostly widely used pyridine bases in industry) from acrolein and ammonia, first carried out by Baeyer [89], has been developed in detail. For the industrial application of this method, special trials were carried out in which β-picoline was obtained with a 45% yield [90, 91]. The synthesis of pyridine bases from unsaturated aldehydes is summarized in Table 2.

The Chichibabin reaction was extended to the synthesis of aryl-substituted pyridines from aromatic aldehydes [108, 109] or from a mixture of aldehydes and ketones [110, 111].

With the simultaneous use of aromatic aldehydes and ketones, it is possible to simplify the experiment by heating them with ammonium acetate in acetic acid [110]. Thus, 2,4,6-triphenylpyridine was obtained from acetophenone and benzaldehyde with a yield of 70% probably according to the following scheme:



Pentaphenylpyridine was obtained by heating benzaldehyde and phenyl benzyl ketone with ammonium acetate or by heating benzylidenedeoxybenzil with phenyl benzyl ketone and ammonium acetate [112]. The identical yield of pentaphenylpyridine in both cases probably indirectly confirms the aldol mechanism of the reaction:



It has been suggested [108] that the synthesis of arylpyridines from aromatic aldehydes does not fit into the Chichibabin scheme. For example, 3,5-diphenylpyridine and toluene were obtained from phenylacetaldehyde as the main reaction products instead of the expected 2-benzyl-3,5-diphenylpyridine. In the opinion of the authors, the mechanism of anomalous condensations in the aliphatic series proposed by Chichibabin does not apply to aromatic compounds. The authors [108] explain the formation of 3,5-diphenylpyridine during the reaction by the elimination of toluene from the 2- or 4-benzyl-3,5-diphenylpyridine that forms.

Some ketones and acetophenone, in particular, react with ammonia, forming 2,4,6-triphenylpyridine [113].

4-Phenylpyridine, derivatives of which are used in agriculture as herbicides, is obtained with a good yield [114] from benzaldehyde and acetaldehyde at a phosphate catalyst.

Reaction of Unsaturated Hydrocarbons with Ammonia

Investigations into the heterocyclization of acetylene with ammonia began with the papers of Meier, Dewar, and Ramsay [115, 116], who obtained a mixture of pyridine compounds by passing a mixture of acetylene with ammonia through a heated tube. By the reaction of acetylene with ammonia over a catalyst containing aluminum, iron, and cadmium oxides, Chichibabin and coauthors obtained a mixture containing 2- and 4-methylpyridine, pyrrole, 2,4-dimethylpyridine, 2-methyl-5-ethylpyridine, and other compounds [12]. Subsequently, in the presence of copper, mercury, zinc, cadmium, and iron salts on supports it was possible to obtain pyridine homologs with a yield of 65% from acetylene and ammonia [117]. Much time has passed since the discovery of the reaction of acetylene with ammonia, but it has only been widely developed in recent years.

TABLE 1. Synthesis of Pyridine Bases from Aliphatic Aldehydes

Reagents	Molar ratio	Phase in which reaction was conducted	Catalysts	Temperature, °C	Yield of pyridine bases	References
Paraldehyde, ammonia	1 : 1...8	liquid	Metal, boron, and ammonium fluorides, ammonium acetate, copper salts	200...290	2-methyl-5-ethylpyridine 61...81, 2-picoline 5...30, 4-picoline 1...32	[63–73]
Acetaldehyde, ammonia	1 : 17...29	gas	Metal phosphates on support, SiO_2, Al_2O_3, halides, Cd, Zn, F_2, HF, active silica gel	300...510	2-methyl-5-ethylpyridine up to 70, 2-picoline 20,4...85, 3-picoline 24...30, 4-picoline 15...28, pyridine 20...24	[74–79]
Paraldehyde, ammonia, benzene	2,5 1 1	liquid	CH_3COONH_4	–	2-methyl-5-ethylpyridine 49	[80]
Acetaldehyde, formaldehyde, ammonia	1 1...2,0 20...4,0	gas-liquid	ACK, NH_4I/ACK	400...460	pyridine 20...24, 3-picoline 24...30, 3,5-lutidine 33	[76–78]
Isobutyraldehyde, ammonia	1 2	gas	Fe_2O_3	400...425	2,3,4-collidine 10	[81]
Paraldehyde, ammonium sulfate (urea)	–	liquid	ACK/Zn, Fe, Co, Ni, Cr, Pd	200...220	2-methyl-5-ethylpyridine 80	[82]

TABLE 2. Syntheses of Pyridine Bases Based on Unsaturated Aldehydes

Reagents	Molar ratio	Phase in which the reaction occurs	Catalysts	Temperature, °C	Yield of pyridine bases, %	References
Acrolein, ammonia	1...1,3 1...5	gas	$(H_3BO_3 + H_3PO_4)$, $Mg(NO_3)_2$, Bi_2O_3, MgO, TeO_2, Zr_2O_3 / ACK	300...500	pyridine 20...43, 3-picoline 8...42	[92–98]
Acrolein, ammonium acetate	1 1, 14	liquid	Cu^{2+} or Fe^{3+} salts	95	3-picoline 12	[98]
Acrolein, butanal, ammonia	1 1 3	gas	Zeolites	400	3-picoline 16, 3-ethylpyridine 70	[99, 100]
Acrolein, propanal, ammonia	1...1,9 0,03...2,0 0,3...4,0	gas	SiO_2–Al_2O_3/Zn, Cd, Sn, Bi	–	3-picoline 10...61, pyridine 60, 3,5-lutidine 30	[101, 102]
Acrolein, acetone, ammonia	1 1 2...2,2	gas	ACK / Al_2O_3, PbF_2	400...440	2-picoline 20...25, 3-picoline 15...28	[103, 104]
Crotonaldehyde, acetone, ammonia	1 2	gas	SnO_2 / ACK	330...550	2,4-lutidine 19	[105]
Crotonaldehyde, monoethanolamine	1 1	gas	Zn, Cr, Al	340...400	4-picoline 26 pyridine 12, 2,5-lutidine 23	[108]
Allyl alcohol, monoethanolamine	1 1	gas	CdF_2, AlF_3 / ZnO, Cr_2O_3, Al_2O_3, Fe_2O_3	360...420	pyridine 30, 2-picoline 20	[107]

When an equimolar mixture of acetylene and ammonia is passed at 300-350°C, a catalyzate containing 2-methylpyridine, 4-methylpyridine, 2-methyl-5-ethylpyridine, acetonitrile, and other compounds is formed. The catalyst, for which the oxides of molybdenum, cadmium, tungsten, vanadium, chromium, zinc, iron, and aluminum were used, has a major effect on the composition and yield of the reaction products [118-121].

The condensation of acetylene with ammonia in the presence of cadmium pyrophosphate on aluminum oxide leads to 2- and 4-methylpyridines with yields of 15 and 10% respectively [122].

The effect of a series of factors (the composition and the properties of the catalysts, the reaction temperature, the volume ratio of ammonia and acetylene, and their overall volume rate) on the content of the reaction products was not finally resolved. It is considered [123] that the optimum temperature for the synthesis of 2- and 4-methylpyridine is 420-440°C with an ammonia–acetylene ratio of 2:1.

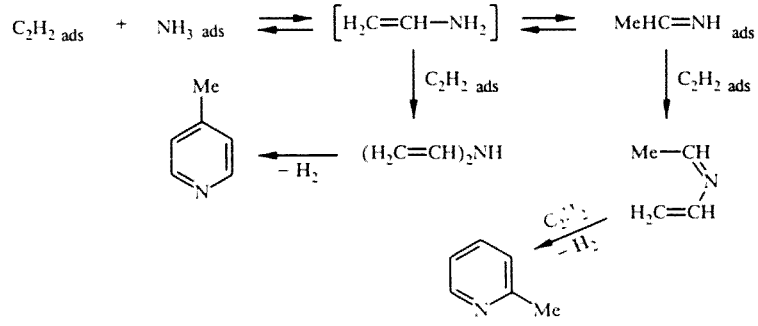
The addition of a third component (methanol) to the reaction zone directs the process toward the formation of pyridine and 3-methylpyridine [124].

More detailed investigations of simultaneous contact between acetylene, methanol, and ammonia made it possible to establish a relation between the quantitative and qualitative composition of the reaction products and the relative methanol content [125]. The results of the experiments, carried out over ZnF_2/Al_2O_3 as catalyst at 425°C, are given in Table 3.

The introduction of acetone into the reaction greatly changes the composition of the final products. Contact with a mixture of acetone, acetylene, and ammonia gave a mixture consisting mainly of 2,4,6-trimethylpyridine [81, 117].

At the present time there are two views in the literature on the mechanism of the formation of methylpyridines from acetylene and ammonia. According to Chichibabin [126], the pyridine bases are formed from acetaldehyde (as intermediate product from the hydration of the acetylene) and ammonia. However, the presence of water is not essential for the formation of the pyridine bases [115]. It was established that the ammonolysis of acetylene in the presence of water vapor is directed toward the formation of acetonitrile with a reduction in the yield of the pyridine bases.

A scheme was proposed for the formation of alkylpyridines, according to which the acetylene and ammonia are adsorbed on the surface of the catalyst, react with the formation of vinylamine and ethylenediamine, and then give divinylamine with a new molecule of acetylene [123].



The formation of divinylamine is confirmed by the fact that in the presence of cadmium, zinc, or iron salts, diethylamine (the product from the hydrogenation of divinylamine) was found in the reaction products [126]. Other evidence can be obtained from the example with monoethanolamine, which gives the same pyridine bases when passed through the catalyst with acetylene under analogous conditions. By reacting with the next molecule of acetylene, the divinylamine is converted into 2- and 4-methylpyridines.

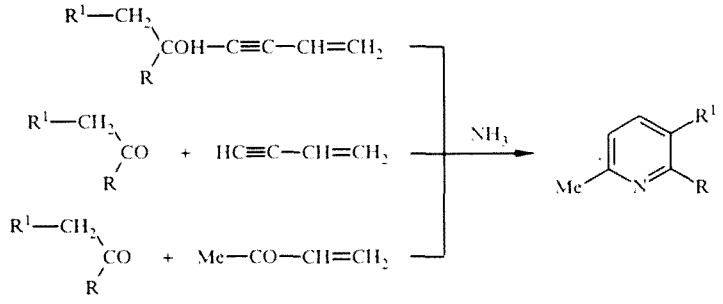
Related Reactions

In addition to the syntheses of pyridine bases described above, there is a series of related methods for the formation of the pyridine ring. Thus, tertiary vinylacetylenic alcohols with the general formula $R^1-CH_2-C(R)OH-C\equiv C-CH{=}CH_2$ can be used as carbonyl component [127-132]. Here the main reaction products are 2-methyl-5-R^1-6-R-pyridines (R = alkyl, aryl; R^1 = alkyl or hydrogen) and are obtained with yields not exceeding 32%. Study of the reaction mechanism showed that

TABLE 3

Content of CH_3OH in mixture, mole	Content of pyridines in mixture, moles			
	Pyridine	β-Picoline	α-Picoline	γ-Picoline
2	14,5	22,5	4,5	0,0
1	21,0	18,0	9,5	trace
0,5	14,5	17,5	16,0	17,5
0,25	11,0	17,0	24,5	17,0
0,0	0,0	0,0	32,0	28,0

such alcohols form a ketone and vinylacetylene during cleavage; in the presence of a catalyst and water, the vinylacetylene is hydrated to methyl vinyl ketone, which reacts with the ketone and ammonia with the formation of pyridine bases:



A series of patents describing the synthesis of 2-methyl-5-ethylpyridines from alkyl vinyl ethers and ammonia have been published [133-136]. The reaction is carried out in the liquid phase with various catalysts [CuS, $Cu_3(PO_4)_2$, Cu_2Cl_2, NiI_2, NH_4F, etc.] under pressure and at elevated temperature.

Some special methods for the production of pyridine bases should be mentioned. Thus, γ-picoline was obtained by the treatment of isobutylene with formaldehyde and ammonium chloride at 107°C [137]. During contact between butanediol vapor and ammonia over alumina, lutidines are formed at the same time as indole and tetramethylpyrazole [138].

In the present paper we have attempted to summarize known data on the Chichibabin reaction. In spite of the fact that a mixture of pyridine compounds is produced as a result of the reaction, the method is being more and more widely developed. In recent years a considerable number of papers have appeared on various aspects of the reaction, new catalysts have been proposed, the reaction mechanism has been discussed, and so forth.

Finally, in 1994 a review was published on the prospects for the use of homogeneous metal-complex catalysts [139]. Without referring to experimental data, the author reports that he has for the first time demonstrated the possibility of condensing acetaldehyde with ammonia under conditions involving the use of homogeneous metal-complex catalysts to produce the targeted methylethylpyridine with a yield of 95% under mild conditions (100-150°C). Soluble compounds of Co^{2+}, reduced by trialkylalanes or finely dispersed transition and nontransition metal powders, are used as catalysts. Examples are also given of the synthesis of compounds of the pyridine, quinoline, and phenanthroline series from carbonyl compounds and alcohols and ammonia, amines, and N-containing organic compounds.

Thus, the use of homogeneous Co-containing catalysts in the synthesis of substituted pyridines has made it possible not only to extend the application range of the Chichibabin reaction but also to achieve the condensation of carbonyl compounds with amines under milder conditions and to obtain higher yields of the required products.

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