239. C. Eaborn, J. Chem. Soc., 4858 (1956).
240. O. R. Pierce, G. W. Holdbrook, O. K. Johannson, and J. C. Sayer, Abstracts of Papers, No. 136, American Chemical Society Meeting, 1959.
241. K. P. Grinevich, N. E. Rodzevich, G. V. Odabashyan, and V. A. Ponomarenko, Zhur. Prikl. Khim., 957 (1960).
242. J. F. Hyde, U. S. P. 2629725 (1953); Chem. Abs., 47, 5720 (1953).
243. C. M. Blow and R. C. Cox, Rubber J., 133, No. 21, 738 (1957).
244. G. M. Konkle, Rubber Age, 84, No. 16, 975 (1959); Khimiya i Tekhn. Polimerov, No. 10, 63 (1959).
245. P. A. J. Gate and J. E. Monaghan, Rubber J. and Internat. Plast., 135, No. 21, 804 (1958).
246. T. D. Talcott, U. S. P. 2759904 (1956); Chem. Abs., 51, 4750 (1957).
247. G. C. Gainer, Ind. Eng. Chem., 46, 2355 (1954).
248. B. P. 812252 (1959); Chem. Abs., 53, 19880 (1959).
249. W. Postelnek, Ind. Eng. Chem., 50, 1602 (1958).
250. F. T. Buckley, U. S. P. 2746945 (1956); Chem. Abs., 50, 12542 (1956).
251. F. T. Buckley, U. S. P. 2528337 (1950); Chem. Abs., 45, 2267 (1951).
252. F. J. Sowa, U. S. P. 2449335 (1948); Chem. Abs., 42, 9005 (1948).
253. F. J. Sowa, U. S. P. 2610949 (1952); Chem. Abs., 47, 1872 (1953).
254. F. J. Sowa, U. S. P. 2769702 (1956); Chem. Abs., 51, 6076 (1957).

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ADVANCES IN THE SYNTHESIS OF ALKYLPYRIDINES

L.I. Vereshchagin and I.L. Kotlyarevskii

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I. INTRODUCTION

By virtue of their valuable properties the pyridine bases are acquiring an increasing importance in chemical industry. Pyridine and its homologues are widely used as solvents, and in the synthesis of rubber, plastics, and drugs. Interest in the synthesis of pyridine bases has been stimulated by the discovery that α-vinylpyridine, 2-methyl-5-vinylpyridine, and other vinylpyridines may act as valuable copolymers in the manufacture of synthetic rubber and plastics[1-11]. For instance, copolymers of butadiene and 2-methyl-5-vinylpyridine, and tripolymers of butadiene, styrene, and 2-methyl-5-vinylpyridine are used as latex for the impregnation of tyre cord because they increase the strength of the resin bond with the cord by 80–100%. Nicotinic and isonicotinic acids are of special significance. The former is a constituent of vitamin PP, which prevents and cures pellagra, and fortifies the nervous system. The latter is the main starting material in the synthesis of a series of antitubercular preparations of the isoniazid type[12].

Wider application of pyridine bases in organic synthesis is limited by the fact that the starting alkylpyridines are difficult to obtain.

The preparation of alkylpyridines has not been discussed in sufficient detail, although there are several reviews on the chemistry of pyridine derivatives[13-19]. We have therefore undertaken to describe systematically all the most important methods for the synthesis of alkyl- and aryl--pyridines which had appeared up to 1959. We divided these methods into two groups: (1) synthesis of pyridine bases from compounds not containing a pyridine ring; (2) synthesis from compounds containing a pyridine ring.

Compounds of the pyridine series can also be obtained by pyrolysis. Pyrolysis of coals and shales yields tar containing small quantities of a complex mixture of alkylpyridines which are difficult to separate. Although methods for the separation of individual compounds from the mixture of bases have been studied for many years[20], the problem is still not completely solved, and the practical use of mixtures of pyrogenic pyridines is still out of the question.

II. SYNTHESIS OF PYRIDINE BASES FROM COMPOUNDS NOT CONTAINING A PYRIDINE RING

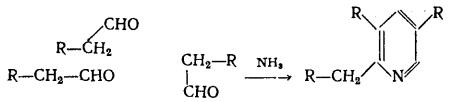
1. Synthesis Based on the Chichibabin Reaction

In 1869 Baeyer[21,22] carried out one of the first syntheses of pyridine, by passing acrolein through an aqueous solution of ammonia. He identified β-picoline in the reaction products by means of chloroplatinate. Dürkopf[23-25] carried out an analogous reaction, at almost the same time, by heating a mixture of aliphatic aldehydes and ammonium acetate in sealed tubes to 200°, and obtained a mixture of pyridine bases. He obtained the best results using paraldehyde, when he isolated 2-methyl-5-ethylpyridine from the mixture of reaction products.

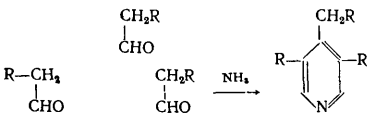
Chichibabin and his collaborators carried out a good deal of work in this field. They synthesised pyridine by two methods: (1) heating aldehydes with aqueous ammonia in sealed tubes; (2) passing a mixture of aldehyde vapours and ammonia over a dehydration catalyst. Using the first method[27-30] they obtained α- and γ-methylpyridines and

2-methyl-5-ethylpyridine from acetaldehyde and ammonia, and 3,5-dimethyl-2-ethylpyridine as the main product from propionaldehyde and ammonia. The preparation of 2-methyl-5-ethylpyridine from acetaldehyde in 70–80% yield[31-39] stimulated an interest in the further development of the Chichibabin reaction with a view to its use in industry. Of special interest in this respect was the work of Farberov and his associates[9], who found a suitable catalyst, giving high yields of 2-methyl-5-ethylpyridine from paraldehyde and ammonia, and thus succeeded in applying this process on an industrial scale.

From a mass of experimental data Chichibabin managed to establish certain definite principles governing this reaction. He showed that saturated aldehydes of the type of acetaldehyde and its monosubstituted homologues can react in two ways:

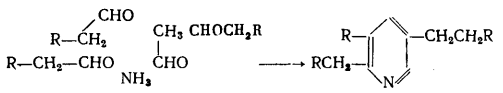


(1)

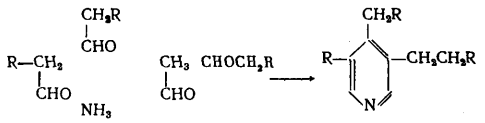


(2)

By using different aldehydes the reaction can be made to proceed according to the following schemes:

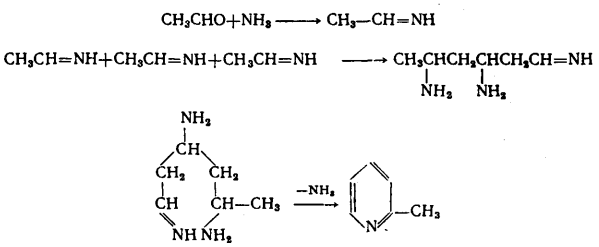


(3)

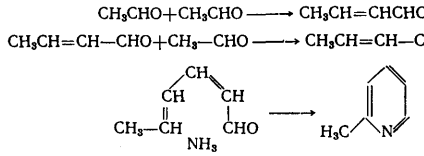


(4)

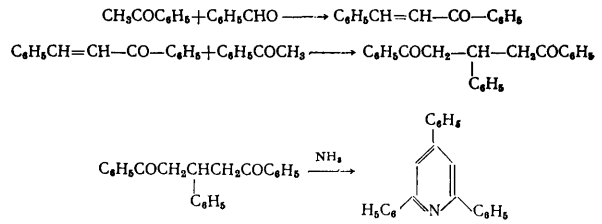
Although the mechanism of these reactions was studied by Chichibabin[27] and by other research workers[40-43], it has still not been completely elucidated. Opinions regarding the course of the reaction are rather controversial. Some[42] consider that aldehyde reacts primarily with ammonia, whereby the resulting imine undergoes an aldol condensation followed by an intramolecular cyclisation to pyridine bases. For instance, the formation of α-picoline from acetaldehyde is described by the following scheme:



Others think that acetaldehyde is first condensed to crotonaldehyde, which undergoes a 1,4-addition followed by ring closure with the participation of nitrogen. They do not think that ammonia plays any part in the first stage of the reaction[40-43]:

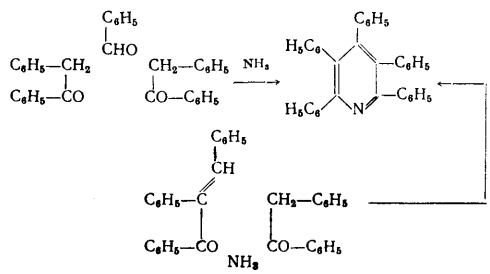


This reaction was later extended to the preparation of arylpyridines from aromatic aldehydes[41,44] or from a mixture of aldehydes and ketones[46,47]. Weiss[46] showed that by simultaneously using aromatic aldehydes and ketones the reaction can be carried out simply by boiling with ammonium acetate in acetic acid solution. Individual products are obtained in good yields. For instance, acetophenone and benzaldehyde gave 70% of 2,4,6-triphenylpyridine. Weiss considers this reaction to proceed by the following scheme:



Weiss has failed as yet to extend this method to alkylpyridines.

Frank and Seven[40] obtained pentaphenylpyridine by boiling benzaldehyde and phenyl benzyl ketone with ammonium acetate, or benzaldeoxybenzoin and phenyl benzyl ketone with ammonium acetate. Equal yields of pentaphenylpyridine in the two cases indicate that an aldol mechanism operates:



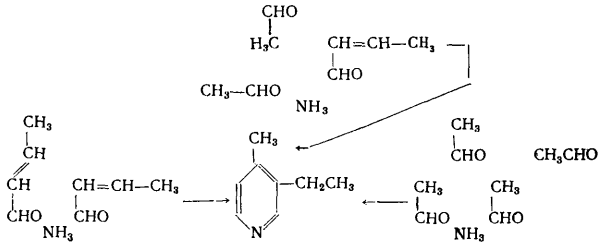
Eliel *et al.*[41] pointed out that the synthesis of arylpyridines from aromatic aldehydes does not proceed according to the Chichibabin reaction scheme. For instance, instead of the expected 2-benzyl-3,5-diphenylpyridine, the main reaction products from phenylacetaldehyde are 3,5-diphenylpyridine and toluene. In their opinion the Chichibabin mechanism for the anomalous condensations in the aliphatic series does not apply to aromatic compounds, and is also doubtful in the case of aliphatic aldehydes. They account for the formation of 3,5-diphenylpyridine by the splitting off of toluene in the course of reaction from the primary reaction product, *viz.* 2-(or 4-)benzyl-3,5-diphenylpyridine.

Chichibabin showed in his later studies[45,48] that the condensation of aldehydes with ammonia can be carried out in the gas phase using various catalysts. Here it is somewhat more difficult to control the course of the reaction than if the synthesis is carried out in an aqueous

medium. The reaction usually results in a complex mixture of products in small yields. Only by careful selection of the reaction conditions can the main reaction product be obtained in satisfactory yield. For instance, by passing a mixture of acetaldehyde and ammonia over alumina at 300°–330°, a mixture of pyridine bases consisting of 28% α-picoline, 30% γ-picoline, 33% 2-methyl-5-ethylpyridine, and 6% 4-methyl-3-ethylpyridine is obtained[48] in 60% yield. It should be noted that in aqueous medium 2-methyl--5-ethylpyridine is the main reaction product, while the gas phase reaction yields this material accompanied by an equal quantity of γ-picoline. The formation of 4-methylpyridine and 4-methyl-3-ethylpyridine can be accounted for by the reaction schemes (2) and (4) given above, where R = = H. The condensation of propionaldehyde with ammonia over alumina at 310°–320° gave 40% of a mixture of pyridine bases, from which 2-ethyl-3,5 dimethylpyridine (60%), small quantities of 4-ethyl-3,5-dimethylpyridine, and 18% of 3,5-dimethylpyridine were isolated[39].

To prepare 3,5-dimethylpyridine Chichibabin and Oparina treated propionaldehyde with formaldehyde and ammonia in the presence of an alumina catalyst[50]. The condensation of butyraldehyde with ammonia over silica at 300°–330° gave 3,5-diethylpyridine and 2-propyl-3,5-diethylpyridine[51]. The condensation of two moles of propionaldehyde and 1 mole of acetaldehyde in the presence of alumina at 330°–340° yielded 2,3,5-trimethylpyridine[49]. When aromatic aldehydes are used, aryl-substituted pyridine bases are obtained[45,52].

Judging from experimental results[53], the reaction in the gaseous phase proceeds *via* the intermediate formation of β-unsaturated aldehydes. This reaction scheme is confirmed by the fact that identical reaction products are obtained from acetaldehyde and crotonaldehyde[53,54]:

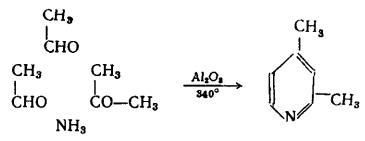


Similarly, the reaction of α,β-unsaturated aliphatic aldehydes with ammonia at 300°–350° in the presence of Al_2O_3, BPO_4, etc. gave various alkylpyridines[55,56]. For example, α-methylacrolein and ammonia, heated at 325°–370° over boron phosphate, gave mainly 3,5-dimethylpyridine, while α-ethylacrolein yielded 3,5-diethylpyridine under the same conditions[57].

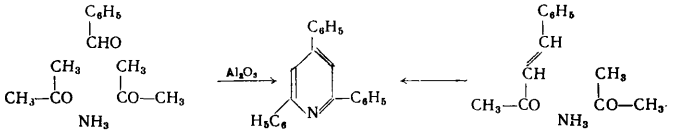
In view of the importance of β-picoline, the catalytic preparation of this compound from acrolein and ammonia, first carried out by Baeyer[21], has been studied in great detail. With the aim of applying this method to industrial preparation, special studies were undertaken, in which β-picoline was obtained in 45% yield[58,59].

The reaction of ammonia with allylamine[60], glycerol[61], or allyl alcohol[62-64] instead of acrolein, also yields β-picoline. The alcohols are evidently dehydrogenated to acrolein, or allylamine is formed and subsequently undergoes ring--closure to form a pyridine ring.

The catalytic reaction of aldehydes with ketones and ammonia affords pyridine by a series of reactions similar to the above. For instance acetaldehyde and acetone, heated at 340° in the presence of alumina, yield 2,4-dimethylpyridine[65].



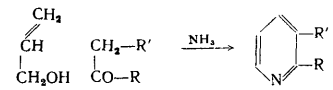
Similarly, the catalytic reaction of 2 moles of acetone and 1 mole of acetaldehyde with ammonia yields symmetrical collidine[66]. Oparina showed that the simultaneous condensation of formaldehyde and acetone (or methyl ethyl ketone) with ammonia yields 2,6-dimethylpyridine (or 2,3,5,6-tetramethylpyridine)[65,67]. A mixture of 2-methyl-4-phenylpyridine and 4-methyl-2-phenylpyridine was obtained[68] by passing acetaldehyde and acetophenone over alumina at 400°. Chichibabin synthesised 2,6-dimethyl-4-phenylpyridine in two ways: (a) from ammonia and benzaldehyde and acetone, and (b) from ammonia, benzylideneacetone, and acetone[45]. This was another confirmation of the reaction mechanism:



Heating a mixture of acetaldehyde, methyl-t-butyl ketone and ammonia with alumina at 310° results in the formation of 2,6-di-t-butyl-4-methylpyridine[69].

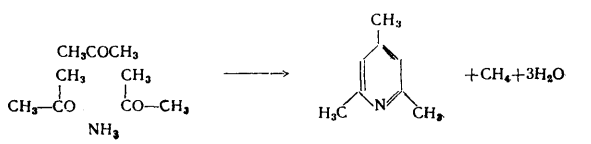
The recent publications of Ishiguro and his coworkers[70,71] showed that pyridines could be obtained by passing over a catalyst a mixture of various ketones with allyl alcohol and ammonia, the allyl alcohol being transformed into acrolein in the course of reaction. They showed that better yields of pyridine bases are obtained if a cadmium phosphate catalyst is used[70].

Similarly, by the catalytic reaction of various alkyl and alkylaryl ketones with allyl alcohol and ammonia, Ishiguro obtained a series of alkyl- and aryl-pyridines in 20–25% yield according to the scheme:



where R′ = alkyl or H; R = alkyl or aryl. 5,6,7,8-Tetrahydroquinoline was synthesised similarly from allyl alcohol, cyclohexanone, and ammonia.

Certain ketones, acetone[72] and acetophenone[73] in particular, react with ammonia to form 2,4,6-trimethylpyridine and 2,4,6-triphenylpyridine respectively. The reaction with acetone was carried out at 110°–140° in the presence of zinc chloride, but the yield of collidine was small and some methane was liberated. This reaction proceeds in the gas phase[74] over a SiO_2/Al_2O_3 catalyst at 400°–500°.

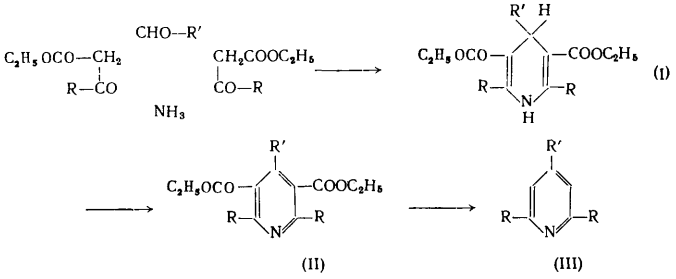


The reaction of acetophenone with ammonia over $Ti(VO_3)_4$ at 370°–380° gave 35% of 2,4,6-triphenylpyridine[73]. Various alkyl- and aryl-pyridines can thus be prepared by the reaction of aldehydes with ammonia, or of aldehydes and ketones with ammonia, in liquid or gas phase over different catalysts.

Since it yields mixtures of pyridines which are difficult to separate, the Chichibabin reaction has found very limited application in the preparation of pyridine bases of specified structure.

2. Synthesis Based on the Hantzsch Reaction

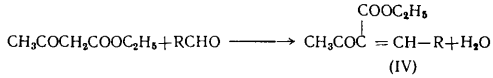
The most widely used synthetic methods for the preparation of individual pyridine derivatives start from 1,5-diketones or dialdehydes, or from compounds which yield 1,5-dicarbonyl derivatives in the course of reaction. The first method of this type was described by Hantzsch[75] in 1882. It consisted in the condensation of one mole of ammonia, two moles of a β-keto-ester and one mole of aldehyde to form a dihydropyridine (I), which was subsequently oxidised by nitric acid to form a 3,5-diethoxycarbonylpyridine (II):



(I)

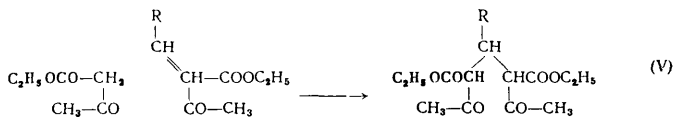
(II) (III)

The conversion of 3,5-diethoxycarbonylpyridines into alkylpyridines (III) is readily accomplished quantitatively by the usual methods. 2,6-Lutidine was obtained by this method in 30–36% yield from formaldehyde and acetoacetic ester[76]. The mechanism of the Hantzsch reaction, like that of the Chichibabin reaction, is still not completely clear. The two most probable reaction schemes are similar, and differ only in the sequence of reaction stages. According to the first, only one molecules of acetoacetic ester first reacts with the aldehyde, forming an alkylidene--(or arylidene-)acetoacetic ester (IV):



(IV)

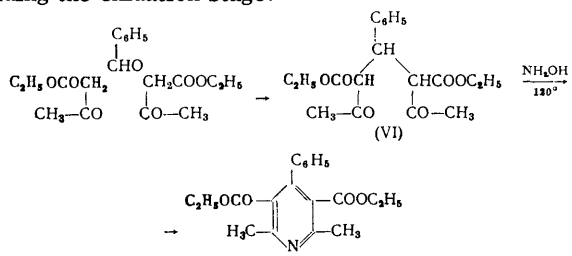
Compound (IV) undergoes Michael condensation with another molecule of acetoacetic ester, forming a 1,5-diketone (V):



(V)

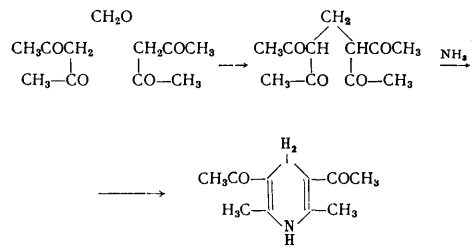
A number of authors[77-82] have confirmed that ring--closure of 1,5-diketones to form a dihydropyridine derivative (I) is possible. At this stage the 1,5-diketone evidently reacts in the enolic form.

Knoevenagel[83,84] modified the original Hantzsch synthesis. He isolated the intermediate product (VI) of the condensation of acetoacetic ester and aldehyde, and treated it with hydroxylamine in aqueous solution at 120°. Three molecules of water were split off to give the pyridine, thus avoiding the oxidation stage:

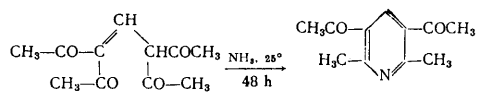


(VI)

The substitution of acetoacetic ester by acetylacetone[85] makes no difference to the course of the reaction. Acetylacetone, formaldehyde, and ammonia react according to the Hantzsch scheme to form 2,6-dimethyl-3,5-diacetyldihydropyridine:

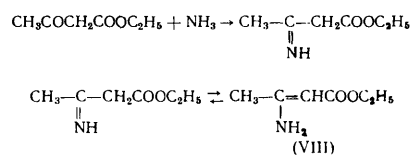


By amination of the tetraketone (VII) with concentrated ammonia at room temperature, Claisen[77] obtained 2,6-dimethyl-3,5-diacetylpyridine:



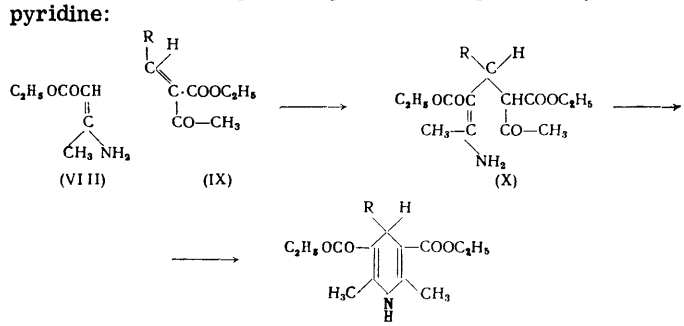
(VII)

The alternative is equally probable. Here, one molecule of acetoacetic ester is supposed to react first with ammonia, to form β-aminocrotonic ester (VIII):



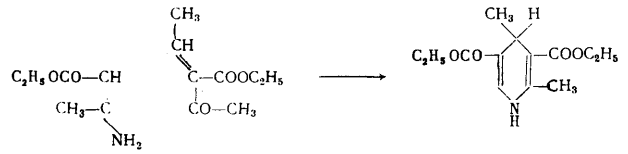
(VIII)

The alkylidene- (or arylidene-)acetoacetic ester (IX) formed in the Hantzsch reaction enters into the Michael condensation with aminocrotonic ester. The resulting ketoamine (X) undergoes ring-closure to give a dihydropyridine:

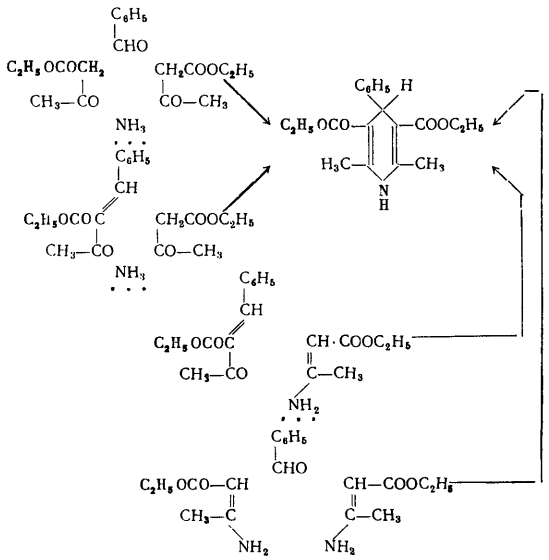


(VIII) (IX) (X)

The formation of compound (X) was confirmed by the work of Collie[86], who succeeded in adding β-aminocrotonic ester to alkylideneacetoacetic ester. Knoevenagel[87] showed that heating β-aminocrotonic ester with ethylideneacetoacetic ester yields a dihydropyridine derivative:

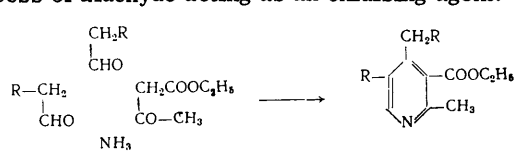


The above data support the second mechanism for the Hantzsch reaction. The reaction may, however, proceed simultaneously by both paths, yielding the same reaction product. This suggestion seems to be the most likely one, since 2,6-dimethyl-4-phenyl-3,5-diethoxycarbonyl--1,4-dihydropyridine may be obtained from the products of preliminary amination, as well as by the subsequent amination of 1,5-diketones[87]:

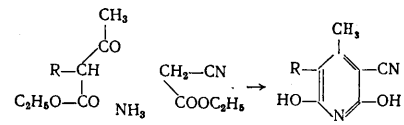


The Hantzsch synthesis is the classical method for the preparation of individual pyridine bases of strictly determined structure and in satisfactory yields. The main feature of the Hantzsch synthesis and all its modifications is the use of compounds containing active hydrogen atoms. By appropriate selection of β-keto-esters (or other 1,3-dicarbonyl compound) and aldehydes, this method can yield a great variety of pyridine derivatives[88].

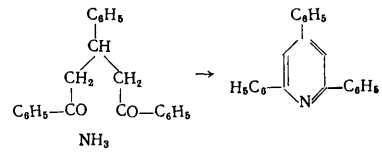
Subsequent modifications of this reaction were confined to improvements in the yields and extension of its scope[78-82,89,90]. For instance, if two moles of aldehyde and one mole of acetoacetic ester are made to react[91] instead of the usual two moles of the ester of a β-keto--acid and one mole of aldehyde, pyridines with substituents in the β-position can be obtained. It should be noted that in this case the dihydropyridine stage is bypassed and the pyridine derivative is obtained directly, the excess of aldehyde acting as an oxidising agent:



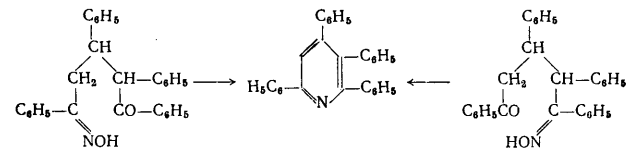
No aldehyde is used in the Guareschi–Thorpe modification of the Hantzsch reaction; its part is played by one of the keto groups in the ester of the keto-acid. This reaction yields hydroxycyano-pyridines, which can easily be converted to alkyl-pyridines[90,92,93].



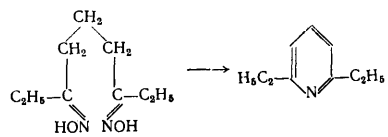
Substituted pyridines are obtained from 1,5-diketones, their oximes and other related compounds. The condensation of benzaldiacetophenone with ammonia or hydroxylamine in alcoholic solution yielded 2,4,6-triphenylpyridine[79,81]:



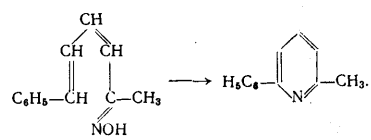
2,3,6-Phenylpyridine was synthesised in a similar manner[80]. By heating the mono-oximes of the 1,5-diketone to 80° with alcoholic hydrogen chloride, Knoevenagel[78] prepared 2,3,4,6-tetraphenylpyridine:



2,6-Diethylpyridine was obtained similarly in 60% yield[82]:

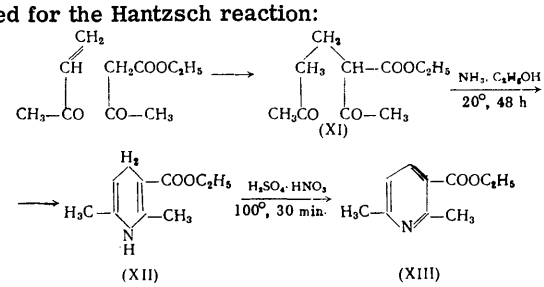


Scholtz prepared 2-methyl-6-phenylpyridine in 25% yield by the destructive distillation of the oxime of 6-phenol-3,5-hexadien-2-one[94]:



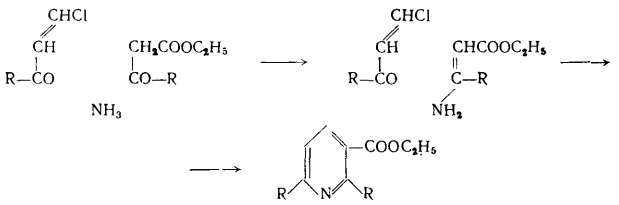
A series of other alkyl- and aryl-pyridines was obtained similarly[95].

Tanaka and Murata[96] synthesised 2,6-dimethylpyridine from acetoacetic ester and methyl vinyl ketone. This synthesis is a clear confirmation of one of the routes postulated for the Hantzsch reaction:



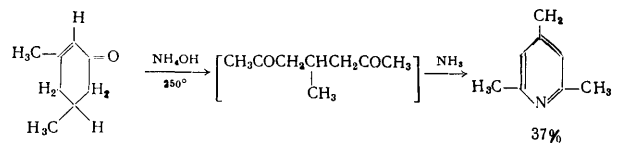
The first stage of this reaction yields 3-ethoxycarbonylheptane-2,6-dione (XI) by Michael condensation in aqueous-alcoholic solution. On standing for 48 h at room temperature with alcoholic ammonia, (XI) yields 2,6-dimethyl-3-ethoxycarbonyl-1,4-dihydropyridine (XII), which is oxidised by a mixture of sulphuric and nitric acid to 2,6-dimethyl-3-ethoxycarbonylpyridine (XIII).

Nesmeyanov and Kochetkov developed a preparative method for dialkylnicotinic acids and dialkylpyridines. By condensation of alkyl-β-chlorovinyl-ketones with esters of β-keto-acids in the presence of ammonia 50–75% yields of the esters of 2,6-dialkylnicotinic acids are obtained[97,98]:

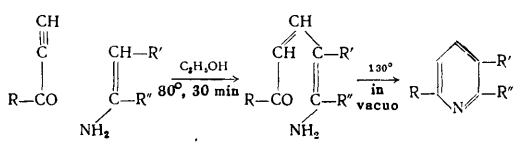


They showed that the reaction proceeds *via* the intermediate formation of the aminocrotonic ester, which subsequently condenses with an alkyl-β-chlorovinyl ketone into a pyridine base. 2,6-Dimethyl-3-ethoxycarbonylpyridine was thus obtained in 75% yield by heating methyl-β-chlorovinyl ketone and aminocrotonic ester at 25°, followed by heating on a water-bath.

An interesting modification of the Hantzsch synthesis[99,100] is afforded by heating alkylcyclohexen-2-ones to 250° in the presence of an aqueous solution of ammonia and ammonium acetate. Thus, 3,5-dimethyl-2-cyclohexen-1-one, 2-methyl-5-phenyl-2-cyclohexen-1-one, and 3-phenyl-2-cyclohexen-1-one yield 2,4,6-trimethylpyridine, 2,6-dimethyl-4-phenylpyridine, and 2-methyl-6-phenylpyridine respectively in yields up to 37%. The authors assumed that during the reaction the cyclohexene ring was cleaved at the double bond forming a 1,5-diketone intermediate. This subsequently underwent normal ring-closure with ammonia, forming a pyridine ring.

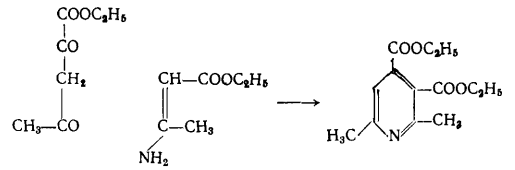


Quite recently Bohlman and Rahtz[101] synthesised pyridine derivatives from acetylenic carbonyl compounds and vinylamines:

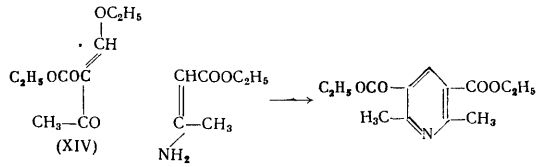


where R = H, R′ = $COOC_2H_5$, R″ = CH_3. Various pyridine bases were obtained in good yield by this general scheme.

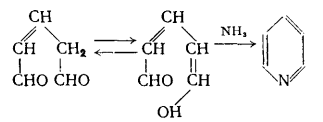
A particular case of the Guareschi–Thorpe synthesis is the condensation of β-aminocrotonic ester with the ester of acetylpyruvic acid. The reaction proceeds readily, giving good yields of 2,6-dimethyl-3,4-diethoxycarbonylpyridine[102]:



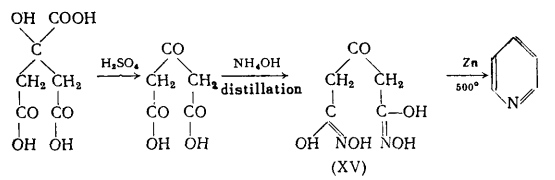
This modified method can also use ethoxymethyleneacetoacetic ester (XIV)[103]:



Finally, pyridine bases can also be obtained from glutaconic aldehyde, glutaconic acid, and their derivatives. Glutaconic aldehyde reacts with ammonia to form pyridine:



Pyridine is similarly formed from acetone dicarboxylic acid, prepared from citric acid[104].



Citric acid is first decarboxylated and oxidised by oleum to form acetone dicarboxylic acid. Upon distillation with aqueous ammonia the latter yields the di-imide (XV)† which is reduced by zinc at 500° to pyridine. The yield, referred to citric acid, is 35%. Heating oximes of glutaric aldehyde with an excess of hydrochloric and sulphuric acid also results in the formation of pyridine bases in 50–70% yields[105,106]. In spite of all their merits the Hantzsch method and its modifications have the disadvantage of starting, as a rule, from complex compounds difficult to obtain.

3. Synthesis from Acetylenic Hydrocarbons

The search for new starting materials for the preparation of pyridine bases has included compounds such as acetylenic hydrocarbons. There are data in the literature on the preparation of pyridines directly from acetylene and ammonia, in the presence of various catalysts at high temperature or in an autoclave under pressure.

In 1915 Chichibabin[107] carried out the first experiments on the synthesis of pyridine bases from acetylene and ammonia by passing their vapours over alumina at 300°–330°. In Chichibabin's own words "the bulk of the reaction product consisted of pyridine bases". He succeeded in isolating α- and γ-picoline, 2-methyl-5-ethylpyridine, and

† An error occurs in the original at this point (Ed. of Translation).

pyrrole. This communication was followed by a series (mainly patents) devoted to the catalytic preparation of pyridine bases from acetylene[108-123], which described in detail its condensation with ammonia. It was established that, depending on the conditions, pyridine bases or acetonitrile are formed. In all cases the reaction was carried out in a tube packed with granulated catalyst. A mixture of acetylene and ammonia of fixed molar ratio was passed over a layer of catalyst at 350°–500°, and the reaction products were isolated in the usual manner. The composition and the yield of the reaction products is influenced mainly by the catalyst. The oxides of heavy metals, *e.g.* molybdenum[121,123], tungsten[120,121,123], vanadium[123], chromium[119-121], zinc[110,111,119], cadmium[119-122], iron[107,111], and thorium[119], as well as aluminium oxide[107,111,119], were mainly used as catalysts. Catalysts were usually deposited on carriers such as pumice, fuller's earth, various clays, alumina or silica gel. Certain authors used various salts of heavy metals, *e.g.* $CdCrO_4$, $CdMoO_4$, $CdWO_4$, $Cd(VO_4)_2$, deposited on acid clay, or $Cd_3(PO_4)_2$ deposited on fuller's earth[117]. Others used mixed oxide catalysts, for example $ZnO/Cr_2O_5/Al_2O_3$,[118] or V_2O_5/Mo_2O_5/pumice[122]. Cadmium phosphate deposited on fuller's earth was found to be the most selective catalyst. Ishiguro[119] found that as compared with oxides of cadmium, zinc, aluminium, and chromium, the use of this catalyst considerably reduces the formation of acetonitrile in the reaction. For instance, passing a 1 : 1 mixture of acetylene and ammonia at 400° over zinc oxide gave up to 91% acetonitrile and 0.8% pyridine bases[124], whereas when $Cd_3(PO_4)_2$ deposited on fuller's earth was used as catalyst at 300°, only negligible quantities of acetonitrile were formed, the main reaction product being pyridine bases. The authors also observed that at temperatures above 350° the relative content of acetonitrile in the reaction products was increased[119].

In the course of reaction, the catalyst becomes covered by carbon and consequently inactivated. It can be regenerated by passing through it purified air or steam at 400°–500°.

Pyridine bases obtained by the catalytic process consist mainly of α- and γ-picoline and 2-methyl-5-ethylpyridine. For instance, by passing 1000 litres of acetylene–ammonia mixture in 1 : 1 molar ratio over $Cd_3(PO_4)_2$ on acid kaolin at 300°–350°, 750–900 ml of product was obtained, from which were isolated 48.4–52.2% crude α-picoline, 15.2–23.2% crude γ-picoline, and 7.3–10.9% 2-methyl-5-ethylpyridine fraction[125]; when $ZnO(Cr_2O_3)Al_2O_3$ was used as catalyst, in addition to the above compounds, small quantities of 2,4-dimethylpyridine, 2,4,6-trimethylpyridine, 2-methyl-4-ethylpyridine, and other nitrogen bases were also obtained[118].

Thus, the pyridine bases obtained from acetylene and ammonia are the same as those obtained under the same conditions from acetaldehyde and ammonia. It is probable, as Chichibabin[107] first suggested, that acetylene is hydrated first to acetaldehyde, which is subsequently condensed with ammonia to yield α- and γ-picoline and 2-methyl-5-ethylpyridine. The main drawback of this method is the formation of a mixture of pyridine bases which are difficult to separate. This method can be extended by using in addition to acetylene and ammonia other organic compounds, containing one to three carbon atoms, *e.g.* CH_3OH, CH_2O, CH_3CHO or acetone, when the reaction product includes, beside α- and γ-picoline, other alkylpyridines whose structure depends on the structure of the compound introduced[60,125-127]. Various salts of cadmium, *e.g.* $Cd_3(PO_4)_2$,[60,125,127] $CdCrO_4$,[60,127,128] $CdWO_4$,[60,127] $CdTiO_3$, $Cd(VO_3)_3$,[127] $CdMoO_4$,[128] and of other metals, *e.g.* $PbCrO_4$ and $Zn_3(PO_4)_2$,[128] $ZnCl_2$ [126] on various carriers like fuller's earth, alumina, pumice, and acid clay, were tested as catalysts. The catalytic reaction was carried out under the same conditions as the reaction between acetylene and ammonia. By passing an equimolar mixture of acetylene, methanol, and ammonia over zinc phosphate, deposited on acid clay, at 400° about 65% of pyridine bases was obtained, containing about 25.4% of acetonitrile, 31.2% of pyridine, 19.3% of picoline isomers, and 14.5% of a mixture of 3,5-dimethylpyridine and 2-methyl-5-ethylpyridine[125].

Cislak[128] made a thorough study of the catalytic reaction of acetylene, methanol, and ammonia, and established the correlation between the qualitative and quantitative composition of the reaction products and the relative quantity of methanol in the mixture of reactants. The results of his experiments, carried out over ZnF_2/Al_2O_3 at 425°, are collected in the table. The molar ratio of acetylene to ammonia was 1 : 1 in all cases.

The reaction between formaldehyde, acetylene, and ammonia over $ZnCl_2/Al_2O_3$ seems to follow a similar course, yielding α- and γ-picolines in the reaction mixture[125,126]. Methylamine, acetylene, and ammonia react over cadmium phosphate at 400° forming a mixture of pyridine, α-, β-, and γ-picolines, as well as acetonitrile and high-boiling pyridine bases[125]. Addition of acetone sharply changes the composition of the products. The catalytic reaction of a mixture of acetone, acetylene, and ammonia over zinc phosphate at 400° yields 38% of a mixture of pyridine bases, consisting mainly of 2,4,6-trimethylpyridine[60,125,126]. There are grounds for supposing that in this case it is the hydration product of acetylene which enters the reaction. This is confirmed by the fact that α- and γ-picolines are obtained by the condensation of crotonaldehyde with acetylene and ammonia[126].

Of special interest is the liquid-phase catalytic condensation of acetylene with ammonia, which yields 2-methyl-5-ethylpyridine, a valuable industrial product. The reaction is carried out in an autoclave at high pressure and temperature, and salts of cadmium[129-131], mercury and copper[129], cobalt, nickel, and titanium[132] are used as catalysts.

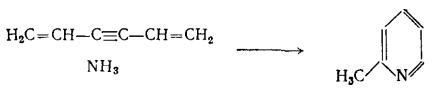
Reppe[132] patented the preparation of 2-methyl-5-ethylpyridine from acetylene and aqueous ammonia at 140° in the presence of $CoCl_2$. A mixture of pyridines containing 75% of the main product is obtained. Nozu[131] showed that in addition to 2-methyl-5-ethylpyridine the liquid-phase condensation over CdO/Al_2O_3 also yields acetonitrile, α-picoline, γ-picoline, 4-methyl-5-ethylpyridine, and a small amount of ethylamine. The reaction can proceed[133] in the presence of acetic acid at 180°–190° at 20 atm.

TABLE.

CH_3OH content in reactant mixtures, moles	Content of pyridines in the mixture of bases			
	pyridine	β-picoline	α-picoline	γ-picoline
2	14.5	22.5	4.5	0.0
1	21.0	18.0	9.5	traces
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

In 1877 Ramsey[134] obtained traces of pyridine by passing a mixture of acetylene and hydrocyanic acid through a hot tube. Meyer[135] later succeeded in repeating this experiment.

The synthesis of pyridine bases from acetylene derivatives has only been discussed in two papers, one of which has already been mentioned[101]. The other publication was a patent which only disclosed that "by passing a vapour-phase mixture of divinylacetylene and ammonia over a freshly prepared catalyst consisting of lead or cadmium deposited on alumina, α-picoline was obtained containing small admixtures of other products"[136].

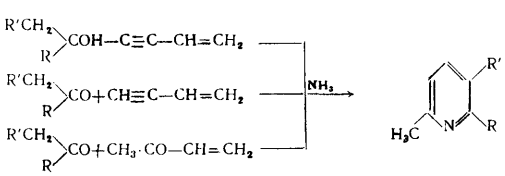


Finally, Cairns[137] demonstrated the possibility of preparing pyridines by the reaction of acetylene with benzonitrile:

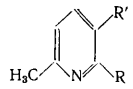


The reaction is carried out by treating benzonitrile with metallic potassium in an autoclave followed by passing in acetylene. The reaction temperature is kept at 175°–200°, and the pressure at 8 atm. The yield of 2-phenylpyridine is 1.8%; 29% of 2,4-diphenylpyridine is also obtained.

The authors of this review have recently developed[138-143] a new method for the synthesis of pyridine bases of specified structure consisting of the catalytic condensation of tertiary vinylacetylenic alcohols of general formula $R'CH_2C(R)OH-C\equiv CCH=CH_2$ with ammonia. 2-Methyl--5-R'-6-R-pyridines, where R = alkyl or aryl, R' = alkyl or hydrogen, were obtained as main reaction products. The yields were not above 32% of the theoretical. The reaction is carried out in the presence of aromatisation or hydration catalysts based on alumina-supported chromic oxide or cadmium salts at 350°–450°. Thus, dimethylvinylethynylcarbinol and methylphenylvinylethynylcarbinol gave with ammonia 2,6-lutidine (about 10%) and 2-methyl--6-phenylpyridine (14.4%) respectively. This method was used for the preparation of various dialkyl- and alkylaryl--pyridines. The reaction mechanism has been studied. It was shown that at 350°–450° tertiary vinylacetylenic alcohols decomposed under the influence of the hydration catalyst into a ketone and vinylacetylene, and that the latter, in the presence of the catalyst and water, was hydrated to form methyl vinyl ketone, which in its turn reacted with the ketone and ammonia yielding pyridine bases:



Knowledge of the reaction mechanism has made possible the synthesis, from ammonia and either vinylacetylene and a ketone or methyl vinyl ketone and methylketones, of pyridine bases in yields far higher than those obtained from vinylacetylenic alcohols. From various ketones, vinylacetylene, and ammonia over a cadmium phosphate/alumina catalyst, at 400°, pyridine bases of the following general formula were thus obtained in 29–49% yields:

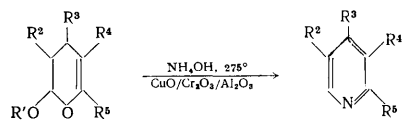


where R = alkyl or aryl, R' = hydrogen or alkyl. Similarly, cyclohexanone and cyclopentanone gave with vinylacetylene and ammonia 2-methyl-5,6,7,8-tetrahydroquinoline and 2-methyl-6,7-dihydropyridine, in 25% and 15.5% yields respectively.

The same pyridine bases were obtained similarly from methyl vinyl ketone, aliphatic and aromatic ketones, and ammonia.

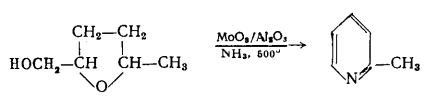
4. Synthesis from Heterocyclic Compounds

Pyridines can be obtained by chemical transformations of various heterocyclic compounds. However, most of these reactions are of theoretical importance only. Passing 2-alkoxy-3,4-dihydro-2H-pyrans with ammonia in the presence of steam at 275° over a copper–chromium catalyst deposited on alumina results in the formation of pyridine bases[144]. For example, pyridine of high purity was obtained from 2-ethoxy-3,4-dihydro-2H-pyran:



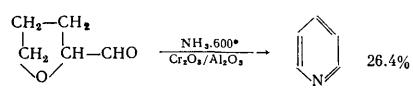
where R' = alkyl, R^2–R^5 = H or alkyl.

Hydrofurylcarbinols and ammonia over a molybdenum catalyst at 450°–500° gave 45–55% of pyridine bases[145], *e.g.*:



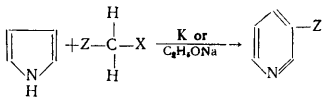
One German patent[146] claims the preparation of pyridines from furfural (or its hydrogenation products) and hydrogen and ammonia at 200° under pressure, in the presence of hydrogenation catalysts such as platinum, nickel, cobalt, or copper compounds. Kline and Turkevich[147], however, did not succeed in obtaining pyridines from furfural and ammonia, either in liquid or the vapour phase, over Cr_2O_3/Al_2O_3.

Pyridine can be synthesised[147,148] from tetrahydrofurfural over Cr_2O_3/Al_2O_3 at 600°.



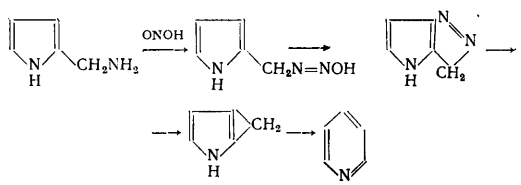
In 1904 Pictet[149] found that by passing 1-methylpyrrole through a heated tube, small quantities of pyridine are formed, in addition to 2-methylpyrrole. It was shown later that *N*- and α-substituted pyrroles are transformed into pyridine bases on heating[150]. Pyridine bases were later obtained by heating alkyl halides with pyrrole in the presence of alkali[151]. Alexander[165] made a thorough study of the ring-enlargement of pyrrole by the action of $CHCl_3$ and $CHBr_3$ on pyrrole-potassium or pyrrole[152-164] in the presence of alkali and found that the yield of β-substituted pyridines depends

on the nature of the halide and alkali used in the reaction. He suggested the following general reaction scheme:

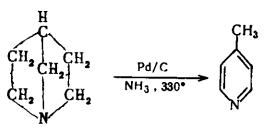


where Z = halogen, hydrogen, or phenyl.

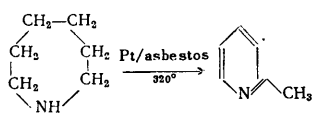
Putokhin[166] studied the oxidation of α-pyrrolylmethylamine by nitrous acid and found that at high dilution, in the cold, ring-enlargement occurred and pyridine was formed. He gave the following reaction scheme for the formation of pyridine from α-pyrrolylmethylamine:



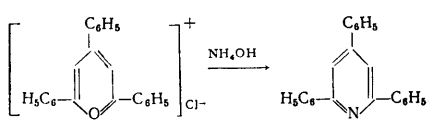
On being heated with palladium on activated charcoal, or with selenium, the bicyclic compounds of type 1-azabicyclo-(2,2,1)-heptane and 1-azabicyclo-(2,2,2)-octane gave γ-methylpyridine and γ-ethylpyridine respectively[167].



The dehydrogenation of hexamethylenimine on platinised asbestos at 320° yielded α-picoline[168].



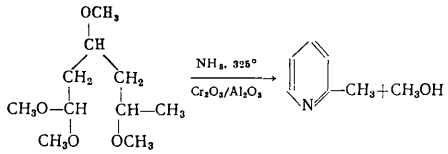
Pyridine can also be obtained in good yields by the ammonolysis of pyrylium salts[169].



5. Miscellaneous Methods for the Formation of the Pyridine Ring

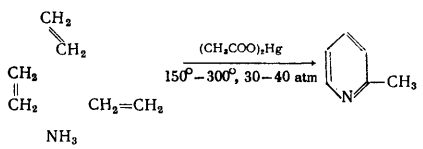
In addition to the above methods for the preparation of pyridine bases there are a number of others. One of them is the diene synthesis using nitriles, by the Diels–Alder method[170,171]. This reaction proceeds in the vapour phase over various oxide catalysts, the most successful being Cr_2O_3/Al_2O_3.[172,173] By passing a butadiene–benzonitrile mixture over alumina at 400°, 50–60% of 2-phenylpyridine was obtained. 2-Ethylpyridine, 2-methyl-6-phenylpyridine, 2-phenyl-4-methylpyridine, and 2-phenyl-4,6-dimethylpyridine were obtained in a similar manner.

Passing a 1,1,3,5-tetra-alkoxypentane, containing identical or different lower alkoxy groups (CH_3O, C_2H_5O, etc.), or an alkoxypentane substituted in position 5 by an alkyl or alkoxyl radical, with ammonia, over a dehydration catalyst (Al_2O_3, Cr_2O_3, silica gel, etc.) at 300°–350° resulted in the formation of 60% of pyridine or α-substituted pyridines[174].



Similar liquid-phase syntheses of pyridine from alkoxypentanes have been patented[175,176]. Treatment of 1,1,3,5,5-pentaethoxypentane with ammonia in a solution of ammonium chloride at 80°–90° gave 54% of pyridine.

α-Picoline (60%) was obtained by the reaction of ethylene and 25% aqueous ammonia in the presence of mercuric acetate at 150°–300° and at 30–40 atm.[177]



A number of patents have recently appeared dealing with the synthesis of 2-methyl-5-ethylpyridine from alkyl vinyl ethers and ammonia[178-181]. This reaction is carried out in the liquid phase, at elevated temperature and pressure, and in the presence of various catalysts [CuS, $Cu_3(PO_4)_2$, Cu_2Cl_2, NiI_2, NH_4F, etc.].

Some methods for the preparation of individual pyridine bases may also be mentioned. Thus, at 130°, vinyl acetate, methanol, and ammonia gave 2-methyl-5-ethylpyridine[182]. The treatment of isobutylene with formaldehyde and ammonium chloride at 107°, followed by dehydrogenation of the reaction products, gave γ-picoline[183]. Passing butadiene and ammonia vapours over a nickel or cobalt catalyst resulted in the formation of pyridines and nitriles[184]. The vapour-phase catalytic reaction of methanol with ammonia over CdO/Al_2O_3 also gave pyridine bases[185,186]. The vapour-phase reaction of butanediol with ammonia over alumina catalyst gave lutidines in addition to indole and tetramethylpyrazine[187]. The reaction of methyl vinyl ketone with ammonia at 120°–140° resulted in small amounts of 2,3,4-trimethylpyridine[188].

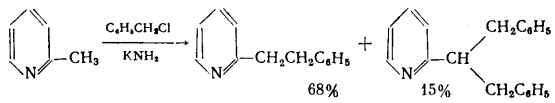
III. SYNTHESIS FROM COMPOUNDS CONTAINING A PYRIDINE RING

Pyridines can also be obtained by the chemical transformation of compounds already containing a pyridine ring. These reactions are generally similar to reactions in the benzene series, although some are specific for the pyridine ring.

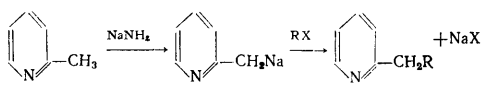
1. Alkylation Methods

Although the Friedel–Crafts synthesis is the chief method for alkylations in the aromatic series, it is entirely inapplicable to pyridine compounds. The most important and most widely used methods for alkylation in the pyridine series involve the use of organometallic compounds. The first synthesis of alkylpyridines using sodamide was carried out

in 1936 by Chichibabin[189]. To alkylate α- and γ-picolines he used mostly the higher alkyl halides. In alkylations of α- and γ-methylpyridines, *viz.* compounds containing an active methyl group, the action of alkyl halides results in the extension of the methyl group by the number of carbon atoms contained in the alkyl halide. Sodium, potassium, and lithium amides can be used as condensing agents in this reaction[203]. For instance, the treatment of α-picoline by potassamide and an alkyl (or aryl) halide gives rise to the substitution of a hydrogen in the methyl group of picoline by an alkyl or aryl radical, as in the case of benzyl chloride, when 1-phenyl-2-(α-pyridyl)ethane is formed. Since the resulting compound contains further active hydrogen atoms, the reaction can continue, yielding, in the presence of an excess of potassamide, 1,3-diphenyl-2-(α-pyridyl)propane:



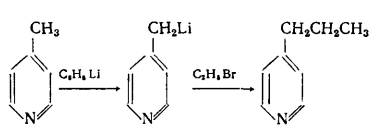
The reaction of α-picoline with sodamide consists in the substitution of a methyl hydrogen atom by sodium, *viz.* in the formation of picolylsodium. Picolylsodium reacts with an alkyl halide, yielding the alkylpyridine:



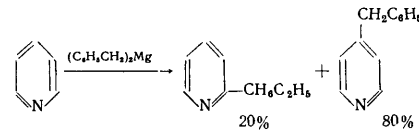
Using this method, many different α- and γ- alkyl- and aryl-pyridines were prepared in good yields from the lower pyridines (picolines, lutidines, etc.), which are relatively easy to obtain, and alkylaryl halides[195-197]. Alkylcyclohexyl halides gave alkylcyclohexylpyridines[198]. Notwithstanding their low reactivity, aryl halides also react with picolines. Thus, as shown by Bergstrom, in the presence of potassamide chlorobenzene reacted with α-picoline to form 24% of benzylpyridine[191].

For a long time it was thought that this method did not apply to β-substituted alkylpyridines, since the methyl group in β-picoline does not contain active hydrogen atoms. Only recently was it shown[192,199-202] that β-alkylpyridines, like the α- and γ-substituted derivatives, readily undergo alkylation with potassium or sodium amides, with yields reaching 70%. For the alkylation of pyridines Ziegler and Zeiser[203,204] used organolithium compounds. They prepared 2-butylpyridine by treating pyridine with butyllithium in benzene solution at 90°–100° and then adding water to the reaction mass.

This reaction was at first used only for the synthesis of α-substituted pyridine bases[205-209], but the method was later extended to γ-alkylpyridines. Thus, the reaction of γ-picoline with phenyllithium, followed by treatment with ethyl bromide, gave γ-propylpyridine as the main product[210]:

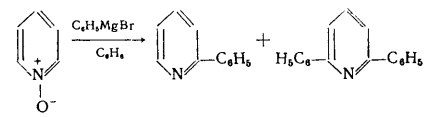


Walters[207] obtained 40% of 2-phenylpyridine by heating phenyllithium with pyridine in a sealed tube. The application of Grignard reagents has extended the possibilities for the preparation of pyridine compounds, and simplified the experimental procedure. In 1932 Bergman and Rosenthal[211] found that benzylmagnesium bromide reacts with pyridine in ether solution forming 2-benzylpyridine. It was later shown[212-215] that the alkylation of pyridine with organomagnesium compounds mainly yielded a mixture of α- and γ-substituted alkylpyridines (40–50%). Benzylpyridines can readily be prepared using dibenzylmagnesium in dioxane[213].



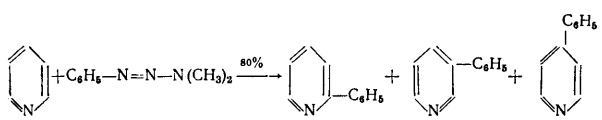
The mixture contains 80% of the γ-isomer. 2-Ethylpyridine was also obtained by heating ethylmagnesium bromide with pyridine in an autoclave[215].

Ochiai and Arima[216] showed that 2-phenylpyridine and a small amount of 2,6-diphenylpyridine are obtained by treating phenylmagnesium bromide with pyridine 1-oxide:

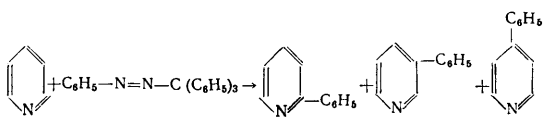


One of the older methods for the alkylation of the pyridine ring is that devised by Ladenburg[217,218]. He obtained mixtures of α- and γ-alkylpyridines by heating the simple pyridine alkyl halides in a sealed tube to 300°. Chichibabin[219] improved this reaction and found that cuprous chloride or bronze catalyse the Ladenburg rearrangement and increase the yield of benzylpyridines. As a result, this method has become widely used in the laboratory for the preparation of substituted pyridines.

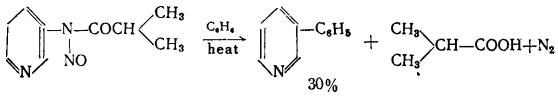
A number of methods for the preparation of alkyl- and aryl-pyridines are based on free-radical reactions. Thus, arylpyridines can be obtained by arylation with aryldiazonium salts. As early as 1893 a mixture of phenylpyridine isomers, containing 18% of α-phenylpyridine, was obtained by the reaction of benzenediazonium chloride with pyridine[220]. Chichibabin[221] later obtained "a very small" yield of a phenylpyridine mixture by adding to acetic acid a mixture of aniline, sodium nitrite, and pyridine. Heilbron[222-224] recently extended this reaction to the synthesis of various arylpyridines. The reaction is usually carried out by running an aryl diazonium chloride into pyridine, followed by heating and distilling off the unchanged pyridine. The yield of the mixture of three arylpyridine isomers sometimes reaches 80%, the α-isomer predominating in the mixture. The preparation of an arylpyridine from 1-aryl-3,3-dimethyltriazenes[225] or benzeneazotriphenylmethane proceeds likewise[226]:



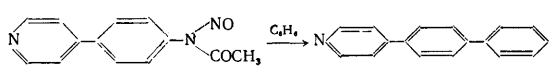
In contrast to the previous reactions, the α-isomer is here a minor product.



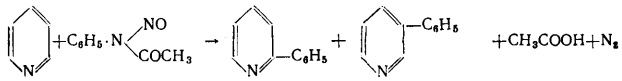
The Gomberg reaction can also be used for the preparation of pyridine bases. An example consists of heating *N*-(3-pyridyl)-*N*-nitrosoisobutyramide with benzene to form β-phenylpyridine [227].



4-γ-Pyridylbiphenyl was prepared similarly [224]:



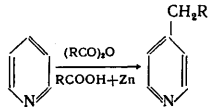
The reaction of nitrosoacetanilide with pyridine yielded a mixture of phenylpyridine isomers [228].



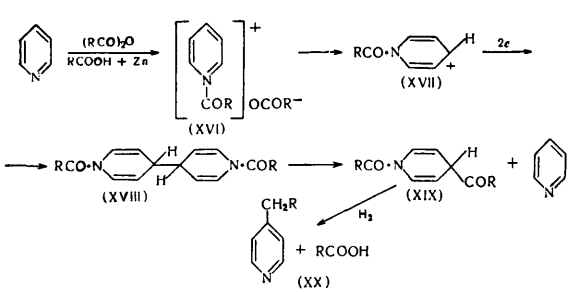
By electrolysis of various aliphatic acids in pyridine solution α- and γ-alkylpyridines, containing small amounts of 2,4-dialkylpyridines, were obtained at the platinum cathode [229]. 2-Methyl-, 2-ethyl-, and 2-propyl-pyridine were obtained by this method from pyridine and acetic, propionic and butyric acids, respectively, together with small quantities of the corresponding γ-isomers and α,γ-derivatives. Benzoyl peroxides and pyridine gave a mixture of α- and γ-phenylpyridines [229,230].

A mixture of α- and γ-pyridines is obtained by the reaction of diacylperoxides with pyridines [231], *e.g.* α- and γ-phenylpyridines were obtained by heating dibenzoyl peroxide with pyridine [232]. Heating a mixture of pyridine with the lead salts of organic acids to 80°–120° gave α- and γ-alkylpyridines [233]. For instance, pyridine and lead acetate in acetic acid solution gave a mixture of α- and γ-picolines. Heated to 110° with Pb_3O_4 in acetic acid, 3-butylpyridine gave in 45% yield a mixture of 2-, 4-, and 6-methyl-3-butylpyridines and 2,6-dimethyl-3-butylpyridine, with 2-methyl-3-butylpyridine predominating [234].

The Wibaut–Arens reaction, which consists in heating pyridine with acid anhydrides in the presence of zinc powder, can also be used for the preparation of the γ-derivatives of pyridine



The authors made a thorough study of the mechanism of the formation of γ-alkylpyridines [235]. They established that in acid media pyridine forms a salt (XVI), which, reacting in the 1-acyl-1,4-dihydropyridine form (XVII), yields *N*,*N*-diacyltetrahydro-4,4-dipyridyl (XVIII)

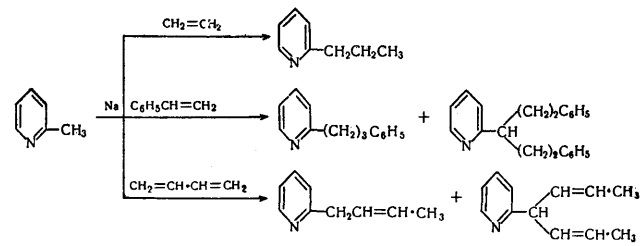


On being heated (XVIII) yields 1,4-diacyl-1,4-dihydropyridine (XIX), which is subsequently converted to 4-alkylpyridine (XX).

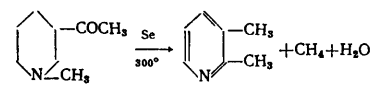
3-Methyl-4-ethylpyridine was obtained in 45% yield by treating a mixture of acetic anhydride and 3-picoline with zinc powder at 35°–40°, followed by boiling. Various 4-alkylpyridines were prepared similarly [236,238-240]. In the synthesis of 4-ethylpyridine iron powder could be used instead of zinc [241].

By passing a mixture of 2-methylpyridine and formaldehyde over alumina at 400°–550° high yields of 2-ethylpyridine and a little 2-vinylpyridine are formed [237].

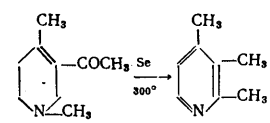
2-Methylpyridine gave higher alkylpyridines [242-244] on being alkylated with olefines in the presence of sodium at 120°–130° and elevated pressure.



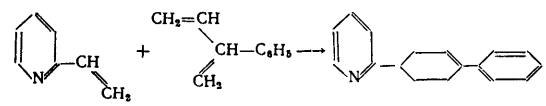
An interesting reaction is observed on heating 3-acetyl-1-methylpiperidines with selenium to 300° in a sealed tube, when a high yield of 2,3-dimethylpyridine results [245].



Similarly, 1,4-dimethyl-3-acetyl-1,2,5,6-tetrahydropyridine gave 88.5% of 2,3,4-trimethylpyridine [246]:



A complex mixture of isomeric picolines and lutidines is obtained by passing pyridine and methanol vapours over activated alumina at 400°–500°. [247] Cyclohexylpyridines were obtained by the Diels–Alder reaction of vinylpyridines with diene hydrocarbons. For example, xylene solutions of α- and γ-vinylpyridines and butadiene, heated in sealed tubes to 170°, gave 60% of α-cyclohexenylpyridine and 44% of γ-cyclohexenylpyridine respectively [249,250]. 2-(4-Phenylcyclohex-3-enyl)pyridine was also obtained from α-vinylpyridine and 2-phenyl-1,3-butadiene in the presence of phenyl-β-naphthylamine [251].



2. Miscellaneous Methods for the Preparation of Pyridine Bases

Methods such as the hydrogenation of unsaturated oxygen- and halogen-containing compounds, the decarboxylation of acids, the dehydrogenation of hydropyridines, and

finally, the dealkylation of alkyl derivatives play a significant part in the synthesis of various alkylpyridines.

The hydrogenation of alkenylpyridines is usually carried out over Raney nickel catalyst, in alcoholic solution, at room temperature, and small hydrogen pressure. Yields of alkylpyridines are nearly theoretical. Unsaturated pyridine bases can sometimes be reduced with iodine and red phosphorus. For instance, 2-styrylpyridine was reduced to 1-phenyl-2-(α-pyridyl)ethane[252]. The reduction of alkyl pyridyl ketones is best carried out by the Wolff–Kishner method, giving 80% yields[248,253-257]. The reaction is carried out in the usual manner by heating a mixture of alkyl pyridyl ketone and hydrazine in alcoholic-alkaline media.

In his comparative study of various methods for the reduction of 2-acetylpyridine Furst[258] obtained the best yields of ethylpyridine using the Clemmensen method.

Pyridine bases containing a hydroxyl group in the side-chain can readily be reduced by boiling in aqueous solution with hydroiodic acid and red phosphorus[259,260]. 4-Isopropylpyridine was obtained in this way from dimethyl-(γ-pyridyl)carbinol[261]. Another general method for the synthesis of pyridine is the catalytic reduction of 2- and 4-chloroalkylpyridines, using as a catalyst either palladium on activate charcoal[262-266], barium sulphate, or calcium carbonate[267], or Raney nickel[268,269]. The yields of the reaction products are nearly theoretical.

The preparation of pyridinecarboxylic acids followed by decarboxylation is another important method for obtaining pyridine bases. Pyridinecarboxylic acids can be obtained not only by the oxidation of alkylpyridines, but also from arylpyridines and benzylpyridines and in various other ways. Although many pyridine alkaloids are readily oxidised to pyridinecarboxylic acids, the oxidation of nicotine to yield nicotinic acid is alone of any preparative importance.

Decarboxylation of pyridinecarboxylic acids is widely used for the synthesis of pyridine bases because these acids are easy to obtain and the reaction itself is very simple. For instance, carboxyl groups in positions α and γ are decarboxylated on heating, the α-carboxyl group being eliminated at 180°, and γ-carboxyl groups at 240°. Nicotinic acid is decarboxylated by heating with soda-lime. The ease of decarboxylation of picolinic and isonicotinic acid is explained by the shift of the electron cloud and the lower electron density at positions 2 and 4 of the pyridine ring. For the same reason 2-pyridylacetic acid is easily decarboxylated (at 90°), while 3-pyridylacetic acid is stable at 180°.[270]

Dehydrogenation of various hydropyridines is often used in the synthesis of pyridines. Dehydrogenation of piperidines and other hydropyridines is carried out over palladium[41,271-273] or platinum[274], on asbestos, activated charcoal, or alumina. Selenium can also be used[275]. The dehydrogenation is usually carried out by heating the hydropyridine with the catalyst to 250°–300°, and the yields can be as high as 90%. The dealkylation of alkylpyridines is also a method of great potential importance: it consists in passing an alkylpyridine at 300°–660° over a catalyst of the nickel/alumina type[276], or Zelinskii's nickel catalyst[277]. For instance, passing the vapours of α-picoline and water over Ni/Al_2O_3 at 415° yields 50% of pyridine. High-temperature dealkylation of picolines and 2,6-lutidine at 595°–666° and at high hydrogen pressure has also been carried out[278]. The pyrolysis of α-picoline at 800° in a stream of hydrogen containing some hydrogen sulphide yields 21% of pyridine[279]. The catalytic oxidation of alkylpyridines by air over a vanadium oxide/molybdenum oxide catalyst deposited on pumice, at 580°, results in the formation of 15.3% of pyridine[280].

In addition to the methods discussed above, there are a large number of particular multistage syntheses, which are only applicable to individual pyridine bases[262-264,267,281-287].

1. N. Gumlich, Rubber Plastics Age, 39, 126 (1958).
2. O. Litvin, "Sovremennoe Proizvodstvo Sinteticheskikh Kauchukov za Rubezhom" (Present-Day Manufacture of Synthetic Rubbers Abroad), VINITI, Moscow, 1958.
3. G. Bachman and D. Micucci, J. Amer. Chem. Soc., 70, 2381 (1948).
4. M. Koton and O. Surina, Dokl. Akad. Nauk SSSR, 113, 1063 (1957).
5. P. Culhane and G. Rothrock, U. S. P. 2 636 023, (1954); Ref. Zhur. Khim., 24 573 (1954).
6. B. P. 735 715 (1955); Ref. Zhur. Khim. 16 262 (1958).
7. J. Pritchard *et al.*, Ind. Eng. Chem., 863 (1955).
8. C. Wheelock, Ind. Eng. Chem., 49, 1929 (1957).
9. M. Farberov *et al.*, Izv. Vys. Ucheb. Zaved. Khim. i Khim. Tekhnol., No. 5, 92 (1952).
10. Byull. Tekh. Ekon. Informatsii, No. 3, p. 15 (1959).
11. I. R. Haws, Rubber Chem. Technol., 30, 1387 (1957).
12. M. Shchukina *et al.*, Dokl. Akad. Nauk SSSR, 84, 981 (1952).
13. P. Bergstrom, Chem. Rev., 35, 79 (1944).
14. G. Ghiusoli, Chimica e Industria, 36, 699 (1954).
15. A. Morton, "The Chemistry of Heterocyclic Compounds", McGraw-Hill, New York, 1946.
16. H. Maier-Bode and J. Altpter, Das Pyridin und seine Derivate, Wilhelm Knapp Hall, Saale, 1934.
17. M. Ferles and J. Jizba, Chemie pyridinu, Praha, 1957.
18. I. A. Gautier and I. Renault, Bull. Soc. chim. France, No. 4, 588 (1955).
19. A. E. Chichibabin, Uspekhi Khim., 5, 481 (1936).
20. L. Fisher, and I. Kalechits, Trudy Vost.-Sib. Akad. Nauk SSSR, Ser. Khim., No. 3, 72 (1955).
21. A. Baeyer, Ber., 2, 398 (1869); Annalen, 155, 281, 294 (1870).
22. E. Ador and A. Baeyer, Annalen, 155–156, 296 (1870).
23. E. Dürkopf, Ber., 21, 444 (1887).
24. E. Dürkopf and M. Schlaugh, Ber., 21, 832 (1888).
25. E. Dürkopf and H. Göttsch, Ber., 23, 685 (1890).
26. L. Haskelberg, Chem. and Ind., 261 (1935).
27. A. E. Chichibabin, Zhur. Russ. Fiz.-Khim. Obshch., 54, 204 (1924).
28. A. E. Chichibabin and M. Oparina, Zhur. Russ. Fiz.-Khim. Obshch., 54, 428 (1923).
29. A. E. Chichibabin and M. Oparina, J. prakt. Chem., 107, 145 (1924).
30. A. E. Chichibabin and M. Oparina, Zhur. Russ. Fiz.-Khim. Obshch., 54, 420 (1924).
31. H. Narasaki and H. Suruki, Tokyo Kogyo Shikensho Hôkoku, 52, 8 (1957); Chem. Abs., 51, 12 089 (1957).
32. B. P. 749 718 (1956); Chem. Abs., 51, 11 396 (1957).
33. I. Dunn, B. P. 706 816 (1954); Ref. Zhur. Khim., 5787 (1957).
34. W. Bamford, U. S. P. 2 769 007 (1956); Chem. Abs., 51, 6704 (1957).
35. C. Becker, U. S. P. 2 745 835; Chem. Abs., 41, 2052 (1947).
36. J. Mahan and C. Stoops, U. S. P. 2 749 348 (1956); Ref. Zhur. Khim., 58 465 (1958).
37. R. Frank, F. Piligrim, and E. Riener, Org. Synth., 30, 41 (1950).
38. R. Frank *et al.*, J. Amer. Chem. Soc., 68, 1368 (1946).

39. A. Chichibabin and M. Oparina, Zhur. Russ. Fiz.-Khim. Obshch., 54, 428 (1924).
40. R. Frank and R. Seven, J. Amer. Chem. Soc., 71, 2629 (1949).
41. E. Eliel, R. McBride, and S. Kaufmann, J. Amer. Chem. Soc., 75, 4291 (1953).
42. H. Strain, J. Amer. Chem. Soc., 54, 1221 (1932).
43. I. Herzenberg and G. Boccato, Chimie et Industrie, 80, 248 (1958).
44. C. Farley and E. Eliel, J. Amer. Chem. Soc., 78, 3477 (1956).
45. A. Chichibabin and D. Orochko, Zhur. Russ. Fiz.-Khim. Obshch., 62, 1201 (1930).
46. M. Weiss, J. Amer. Chem. Soc., 74, 201 (1952).
47. R. Frank and E. Riener, J. Amer. Chem. Soc., 72, 4182 (1950).
48. A. E. Chichibabin, P. Moshkin, and L. Tyazhelova, Zhur. Russ. Fiz.-Khim. Obshch., 54, 413 (1924).
49. M. Oparina, Zhur. Russ. Fiz.-Khim. Obshch., 61, 2001 (1929).
50. A. Chichibabin and M. Oparina, J. prakt. Chem., (2), 107, 145 (1924).
51. M. Prostenik and L. Filipovik, Arhiv Kem., 21, 175 (1949); Chem. Abs., 45, 8520 (1951).
52. A. Chichibabin, Zhur. Russ. Fiz.-Khim. Obshch., 47, 711 (1915).
53. A. Chichibabin and M. Oparina, Ber., 60, 1877 (1927).
54. A. Chichibabin, Bull. Soc. chim. France, 4, 1826, 1831 (1937).
55. G. Hearne, U.S.P. 2520097 (1950); Chem. Abs., 44, 10738 (1950).
56. J. Mahan, U.S.P. 252380 (1950); Chem. Abs., 45, 1628 (1951).
57. G. Hearne, B.P. 654443; Chem. Abs., 46, 4575 (1952).
58. L. Sherman and F. Donald, Ind. Eng. Chem., 47, 789 (1955).
59. F. Stitz, Österr. Chem.-Ztg., 45, 159 (1942); Chem. Abs., 38, 2040 (1944).
60. T. Ishiguro and S. Kubota, J. Pharm. Soc. Japan, 74, 1100 (1954); Chem. Abs., 49, 11654 (1955).
61. N. Cullinane, S. Chard, and R. Meatyard, J. Soc. Chem. Ind., 67, 142 (1948); Chem. Abs., 42, 7297 (1948).
62. H. Hoog and N. Engel, Danish Pat. 59341 (1947); Chem. Abs., 41, 5905 (1947).
63. H. Hoog and W. Engel, U.S.P. 2605264; Chem. Abs., 47, 3352 (1953).
64. H. Hoog and W. Engel, U.S.P. 2603645; Chem. Abs., 47, 4376 (1953).
65. M. Oparina, Ber., 64, 569 (1931).
66. B. Shaw, J. Chem. Soc., 300 (1937).
67. M. Oparina, Zhur. Obshch. Khim., 19, 1351 (1949).
68. L. Musalo, Gazzetta, 62, 894 (1932).
69. H. Brown and B. Kanner, U.S.P. 2780626 (1957); Chem. Abs., 50, 9710 (1956).
70. T. Ishiguro, J. Morita, and K. Ikushima, J. Pharm. Soc. Japan, 77, 1501 (1957); Chem. Abs., 51, 16463 (1957).
71. T. Ishiguro, I. Morita, and K. Ikushima, J. Pharm. Soc. Japan, 77, 660 (1957); Chem. Abs., 51, 16463 (1957).
72. P. Riehm, Annalen, 238, 1 (1887).
73. A. Kagarlitskii, B. Suvorov, and S. Rafikov, Zhur. Obshch. Khim., 29, 157 (1959).
74. R. Zellner, U.S.P. 2796421 (1957); Chem. Abs., 51, 447 (1957).
75. A. Hantzsch, Annalen, 215, 1 (1882).
76. M. Oparina, A. Krasina, and B. Smirnov, Zhur. Prikl. Khim., 11, 965 (1938).
77. L. Claisen, Annalen, 297, 71 (1897).
78. E. Knoevenagel, Annalen, 281, 25 (1894).
79. K. W. Merz *et al.*, Arch. Pharm., 275, 294 (1937); Chem. Abs., 31, 7059 (1937).
80. C. Allen and N. Baker, J. Amer. Chem. Soc., 54, 736 (1932).
81. F. Newmann, Annalen, 302, 236 (1898).
82. E. Blaise and M. Montague, Compt. rend., 180, 1760 (1925).
83. E. Knoevenagel, Annalen, 288, 348 (1895); 281, 25 (1894).
84. E. Knoevenagel, Ber., 31, 738 (1898).
85. M. Scholtz, Ber., 30, 2295 (1897).
86. J. Collie, Annalen, 226, 297, 316 (1884).
87. E. Knoevenagel, Ber., 31, 738 (1898).
88. L. Hinkel, E. Ayling, and W. Morgan, J. Chem. Soc., 1835 (1931).
89. L. Hinkel and H. Cremer, J. Chem. Soc., 137 (1920).
90. B. Witkop, J. Amer. Chem. Soc., 70, 3712 (1948).
91. R. Michael, Ber., 18, 2020 (1885).
92. R. Ružicka and V. Fornasier, Helv. Chim. Acta, 12, 343 (1919).
93. F. Bergel and A. Cohen, B.P. 553097; Chem. Abs., 38, 4271 (1944).
94. M. Scholtz, Ber., 28, 1726 (1895); 43, 1861 (1910).
95. M. Häring, B. Prijs, and H. Erlenmeyer, Helv. Chim. Acta, 37, 147 (1954).
96. H. Tanaka and J. Murata, J. Chem. Soc. Japan, Ind. Chem. Sect., 1181 (1956); Ref. Zhur. Khim., 4606 (1958).
97. N. Kochetkov, A. Gonzales, and A. Nesmeyanov, Dokl. Akad. Nauk SSSR, 79, 609 (1951).
98. A. N. Nesmeyanov and N. K. Kochetkov, Dokl. Akad. Nauk SSSR, 77, 65 (1951).
99. E. Knoevenagel and A. Eler, Ber., 36, II, 2129 (1903).
100. R. Frank and R. Meikle, J. Amer. Chem. Soc., 72, 4184 (1950).
101. F. Bohlman and D. Rahtz, Chem. Ber., 90, 2265 (1957).
102. O. Mumm and O. Böhme, Ber., 54, 726 (1921).
103. L. Claisen, Ber., 26, 2729 (1893).
104. B. Dashevich and E. Orobchenko, Nauch. Zap. Uzhgorogsk. Univ., 12, 28 (1955).
105. W. Reppe, H. Pasedach, and M. Seefelder, German P. 952634 (1956); Ref. Zhur. Khim., 8946 (1955).
106. W. Reppe, H. Pasedach, and M. Seefelder, German P. 944250 (1956); Ref. Zhur. Khim., 42395 (1957).
107. A. Chichibabin, Zhur. Russ. Fiz.-Khim. Obshch., 47, 703 (1915).
108. A. Chichibabin and P. Moshkin, J. prakt. Chem., 107, 109 (1924).
109. German Pat. 365432 (1922); Chem. Zentr. II, 408 (1923); German Pat. 369731 (1923); Chem. Zentr., I, 1104 (1924); German Pat. 467220 (1928); Chem. Zentr., II, 1443 (1929); B.P. 326795 (1930); Chem. Zentr., II, 625 (1930).
110. L. Schlecht and H. Rötger, German Pat. 503133 (1927); Chem. Zentr., II, 2056 (1930).
111. O. Nicodemus and W. Schmidt, German Pat. 516765 (1928); Chem. Abs., 23, 4709 (1929).
112. German Pat. 477049 (1929); Chem. Zentr. II, 797 (1929).
113. H. Rötger, German Pat. 525652 (1928); Chem. Zentr. II, 770 (1931).
114. German Pat. 800499 (1936).
115. R. Hanmer and S. Swann, Ind. Eng. Chem., 41, 325 (1949).
116. T. Kiparenko, Thesis, Tbilisskii Gos. Univ. (1944).
117. S. Kunichika, Japanese Pat. 156434 (1943); Chem. Abs., 44, 2040 (1950).
118. F. Runge and H. Hummel, Chem. Tech. (Berlin), 3, 163 (1951).
119. T. Ishiguro, E. Kitamura, S. Kubota, and N. Tabata, J. Pharm. Soc. Japan, 72, 607 (1953); Chem. Abs., 47, 2685 (1953).
120. F. P. 684839; Chem. Abs., 24, 4363 (1953).
121. T. Ishigura, E. Kitamura, and N. Tabata, J. Pharm. Soc. Japan, 71, 556 (1951); Chem. Abs., 46, 504 (1952).
122. J. Utsumi, Japanese Pat. 6429 (1954); Ref. Zhur. Khim., 68489 (1958).
123. T. Ishiguro and J. Utsumi, J. Pharm. Soc. Japan, 72, 709 (1952).
124. T. Ishiguro *et al.*, J. Pharm. Soc. Japan, 72, 607 (1952); Chem. Abs., 47, 2685 (1953).

125. T. Ishiguro, Japanese Pat. 7319 (1954); Chem. Abs., 50, 9451 (1956).
126. O. Nicodemus, German Pat. 479 351 (1930); Chem. Zentr., II, 2575 (1930).
127. T. Ishiguro and S. Kubota, J. Pharm. Soc., Japan, 72, 899 (1952); Chem. Abs., 47, 6416 (1953).
128. F. Cislak and W. Wheeler, U. S. P. 2 744 904 (1956); Chem. Abs., 50, 1295 (1956).
129. S. Murahashi and S. Otuka, Mem. Inst. Sci. Ind. Res., Osaka Univ., 7, 121 (1950); Chem. Abs., 45, 9052 (1951).
130. K. Yamamoto, Japanese Pat. 503 (1951); Chem. Abs., 47, 3883 (1953).
131. R. Nozu, S. Kunitika, and E. Nisimura, J. Chem. Soc. Japan, 62, 179 (1941); Chem. Abs., 37, 4399 (1943).
132. W. Reppe, H. Krzikalla, and E. Woldan, German P. 858 399 (1952); Chem. Abs., 48, 12 810 (1954).
133. S. Murahashi, Japanese Pat. 3493 (1950); Chem. Abs., 47, 3352 (1953).
134. W. Ramsey, Phil. Mag. (5), 2, 269 (1876); 4, 24 (1877).
135. R. Meyer, Ber., 46, 3183 (1913).
136. A. Carter, U. S. P. 2 175 339 (1939); Chem. Abs., 34, 780 (1940).
137. T. Cairns, J. Saner, and W. Wilkinson, J. Amer. Chem. Soc., 74, 3989 (1952).
138. I. L. Kotlyarevskii and L. I. Vereshchagin, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 715 (1959).
139. L. I. Vereshchagin and I. L. Kotlyarevskii, Soviet Pat. 116 883 (1957).
140. I. L. Kotlyarevskii and L. I. Vereshchagin, Soviet Pat. 117 787 (1957).
141. L. I. Vereshchagin and I. L. Kotlyarevskii, Soviet Pat. 121 794 (1957).
142. L. I. Vereshchagin, E. K. Vasil'ev, A. S. Nakhmanovich, and I. L. Kotlyarevskii, Izv. Sib. Otd. Akad. Nauk SSSR, No. 6, 89 (1959).
143. I. L. Kotlyarevskii, E. K. Vasil'ev, and L. I. Vereshchagin, Izv. Sib. Otd. Akad. Nauk SSSR, No. 9, 52 (1959).
144. F. Young, U. S. P. 2 741 618 (1956); Ref. Zhur. Khim., 58 373 (1958).
145. L. Spillane and R. Tallman, U. S. P. 2 543 424 (1951); Chem. Abs., 45, 7153 (1951).
146. W. Schmidt, German Pat. 695 472 (1940); Chem. Abs., 35, 5520 (1941).
147. C. Kline, J. Turkevich, J. Amer. Chem. Soc., 66, 1710 (1944).
148. G. Natta, G. Mattei, and E. Bartoletti, Chimica e Industria, 81 (1942).
149. A. Pictet, Ber., 38, 1946 (1905).
150. A. Pictet and A. Rilliet, Ber., 40, 1166 (1907).
151. G. Ciamician and P. Silber, Ber., 20, 191 (1887).
152. G. Plancher and U. Fouti, Atti Accad. naz. Lincei, [5] 18, II, 469 (1909).
153. G. Plancher and C. Festoni, Atti Accad. naz. Lincei, [5] 10, I, 304 (1901).
154. G. Plancher and T. Zumbonini, Atti Accad. naz. Lincei, [5] 22, II, 712 (1913).
155. O. Bocchi, Gazzetta, 30, 89 (1899).
156. G. Ciamician, Gazzetta, 16, 140 (1886).
157. G. Ciamician, Gazzetta, 17, 11 (1887).
158. G. Ciamician, Gazzetta, 17, 476 (1887).
159. G. Plancher, Atti Accad. naz. Lincei, [5] 9, I, 218 (1900).
160. G. Plancher and O. Carrasco, Atti Accad. naz. Lincei, [5] 14, I, 162 (1905).
161. G. Plancher and O. Carrasco, Atti Accad. naz. Lincei, [5] 13, 3 (1904).
162. G. Ciamician and P. Silber, Ber., 18, 721 (1885).
163. G. Ciamician and J. Dennstedt, Ber., 14, 1154 (1881).
164. E. R. Alexander, A. B. Herrick, and T. M. Roder, J. Amer. Chem. Soc., 72, 2760 (1950).
165. E. Alexander, A. Herrick, and Th. Roder, J. Amer. Chem. Soc., 72, 2760 (1950).
166. N. Putokhin, Zhur. Russ. Fiz.-Khim. Obshch., 62, 2226 (1930).
167. V. Prelog and K. Balenovic, Ber., 74B, 1508 (1941).
168. M. Ehrenstein and J. Marggraff, Ber., 67B, 486 (1934).
169. G. Gastaldi, Gazzetta, 51, II, 289 (1921); Chem. Zentr. I, 1035 (1922).
170. C. Marvel and J. Hwa, J. Org. Chem., 15, 525 (1950).
171. G. Janz and W. McGulloch, J. Amer. Chem. Soc., 77, 3143 (1955).
172. G. Janz and W. McGulloch, Ind. Eng. Chem., 45, 1343 (1953).
173. P. Hawkins and G. Janz, J. Chem. Soc., 1479 (1949).
174. A. McLean and C. Hobbs, U. S. P. 2 780 627 (1957); Chem. Abs., 51, 15 597 (1957).
175. E. Kobayashi, Japanese Pat. 8029 (1954); Ref. Zhur. Khim., 61 927 (1958).
176. A. McLean and E. Parker, U. S. P. 2 740 789 (1956); Ref. Zhur. Khim., 82 630 (1958).
177. A. Gumboldt and H. Feichtinger, Z. Naturforsch., 46, 123 (1949); Chem. Abs., 44, 1506 (1950).
178. E. Kobayashi, Japanese Pat. 1134 (1956); Chem. Abs., 50, 5845 (1956).
179. J. Mahan, U. S. P. 2 706 730 (1955); Chem. Abs., 49, 2683 (1955).
180. H. Krzikalla and E. Woldan, German Pat. 890 957 (1953); Ref. Zhur. Khim., 40 881 (1956).
181. H. Krzikalla, German Pat. 896 648 (1953); Chem. Abs., 52, 9221 (1958).
182. S. Tsutsumi and M. Hasegawa, Technol. Reports Osaka Univ., 7, 185 (1957); Chem. Abs., 52, 10 081 (1958).
183. F. Boettner, U. S. P. 2 744 903 (1956); Chem. Abs., 51, 495 (1957).
184. E. Hook and P. Moss, U. S. P. 2 566 288 (1951); Chem. Abs., 46, 2563 (1952).
185. German Pat. 569 630 (1933); Chem. Zentr. I, 2747 (1933).
186. German Pat. 565 798 (1932); Chem. Zentr. I, 1018 (1933).
187. R. Guillaumin, Ann. Univ., Paris, 23, 328 (1953); Ref. Zhur. Khim., 34 172 (1954).
188. N. Murata and H. Arai, J. Chem. Soc. Japan, Ind. Chem. Sect., 58, 387 (1955); Ref. Zhur. Khim., 51 260 (1957).
189. A. Chichibabin, German Pat. 676 114 (1939); Chem. Abs., 33, 6345 (1939).
190. F. Bergstrom *et al.*, J. Chem. Soc., 452 (1945).
191. P. Dirstine and F. Bergstrom, J. Chem. Soc., 55 (1946).
192. A. Miller and R. Levine, J. Org. Chem., 22, 168 (1957).
193. A. Chichibabin, Bull. Soc. chim. France, [5], 429 (1938).
194. N. Sperber and D. Papa, U. S. P. 2 727 895 (1955); Chem. Abs., 49, 12118 (1955).
195. F. Brody and M. T. Bogert, J. Amer. Chem. Soc., 65, 1075 (1943).
196. G. Knight and B. Shaw, J. Chem. Soc., 682 (1938).
197. C. Barkovsky, Annalen, 19, 487 (1944).
198. F. Cislak, F. Karnatz, and K. Kelly, U. S. P. 2 505 461 (1950); Chem. Abs., 44, 6890 (1950).
199. H. Brown and W. A. Murphey, J. Amer. Chem. Soc., 73, 3308 (1951).
200. H. Lochte and F. Cheavens, J. Amer. Chem. Soc., 79, 1667 (1957).
201. E. Hardegger and E. Nikles, Helv. Chim. Acta, 40, 2421 (1957).
202. J. Wibaut and C. Hoogzand, Chem. Weekblad, 52, 357 (1956); Chem. Abs., 51, 3593 (1957).
203. K. Ziegler and H. Zeiser, Ber., 63B, 1847 (1930).
204. K. Ziegler and H. Zeiser, Annalen, 485, 174 (1931).
205. H. Brown and B. Kanner, J. Amer. Chem. Soc., 75, 3865 (1953).
206. H. Gilman and S. Broadbent, J. Amer. Chem. Soc., 70, 2809 (1948).

207. L. Walters and S. McElvain, J. Amer. Chem. Soc., 55, 4625 (1933).
208. H. Gilman, J. Org. Chem., 22, 1169 (1957).
209. M. Birchenovgh, J. Chem. Soc., 1263 (1951).
210. J. Wibaut and J. Hey, Rec. Trav. chim., 72, 513 (1953); Chem. Abs., 47, 4540 (1953).
211. E. Bergman and W. Rosenthal, J. prakt. Chem., 135, 267 (1932).
212. W. Veer and S. Goldschmidt, Rec. Trav. chim., 65, 793 (1946); Chem. Abs., 41, 3100 (1947).
213. R. Benkeser and D. Holton, J. Amer. Chem. Soc., 73, 5861 (1951).
214. N. Goetz-Luthy, J. Amer. Chem. Soc., 71, 2254 (1949).
215. F. Bergstrom and S. McAllister, J. Amer. Chem. Soc., 52, 2845 (1930).
216. E. Ochiai and K. Arima, J. Pharm. Soc. Japan, 69, 51 (1949); Chem. Abs., 44, 1502 (1950).
217. Ladenburg, Ber., 16, II, 2059 (1883).
218. Ladenburg, Annalen, 247, 1 (1888).
219. A. Chichibabin, and P. Ryumshin, Zhur. Russ. Fiz.-Khim. Obshch., 47, 1297 (1915).
220. R. Möhbav and Barger, Ber., 26, 1994 (1893).
221. A. Chichibabin, Ber., 37, 1373 (1904).
222. E. Butterworth, J. Heilbron, and D. Hey, J. Chem. Soc., 355 (1940).
223. J. Haworth, J. Heilbron, and D. Hey, J. Chem. Soc., 358 (1940).
224. J. Heilbron *et al.*, J. Chem. Soc., 1279 (1940).
225. J. Elks and D. Hey, J. Chem. Soc., 441 (1943).
226. W. Adams and D. Hey, J. Chem. Soc., 3181 (1949).
227. H. Rapoport *et al.*, J. Amer. Chem. Soc., 74, 6293 (1952).
228. J. Haworth, J. Heilbron, and D. Hey, J. Chem. Soc., 351 (1940).
229. S. Goldschmidt and M. Minsinger, Chem. Ber., 87, 956 (1954).
230. D. Augood, D. Hey, and G. Williams, J. Chem. Soc., 2094 (1952).
231. D. Hey and E. Walker, J. Chem. Soc., 2213 (1948).
232. J. Overhott and G. Tilman, Rec. Trav. chim., 48, 993 (1929); Chem. Abs., 23, 5185 (1929).
233. W. Pieger, U. S. P. 2 503 174 (1950); Chem. Abs., 44, 5396 (1950).
234. E. Hardegger and E. Nikles, Helv. Chim. Acta, 40, 2421 (1957); Chem. Abs., 52, 9103 (1958).
235. J. Wibaut and J. Arens, Rec. Trav. chim., 60, 119 (1941).
236. J. Wibaut and S. Vromen, Rec. Trav. chim., 67, 345 (1948); Chem. Abs., 43, 1775 (1949).
237. F. Cislak, U. S. P. 2 786 846 (1957); Chem. Abs., 50, 13 941 (1956).
238. J. Arens and J. Wibaut, Rec. Trav. chim., 61, 59 (1942); Chem. Abs., 37, 5063 (1943).
239. S. Wavsonek and M. Nelson, J. Amer. Chem. Soc., 74, 2894 (1952).
240. T. Tkaczynsky, L. Grabowski, and W. Pietzak, Polish Pat. 39 565 (1957); Ref. Zhur. Khim., 20 455 (1959).
241. G. Wilbert, L. Reich, and L. Tenenbaum, J. Org. Chem., 22, 694 (1957).
242. F. Schneider, German Pat. 12 914 (1957); Ref. Zhur. Khim., 18 909 (1958).
243. G. Pieper and R. Wegler, German Pat. 831 099 (1952); Chem. Abs., 52, 9223 (1958).
244. R. Wegler and G. Pieper, Chem. Ber., 83, 6 (1950); Chem. Abs., 44, 5358 (1950).
245. V. Prelog, E. Moor, and J. Führer, Helv. Chim. Acta, 26, 846 (1943); Chem. Abs., 38, 1505 (1944).
246. V. Prelog, A. Komzak, and E. Moor, Helv. Chim. Acta, 25, 1654 (1942).
247. N. Cullinane *et al.*, J. Soc. Chem. Ind., 67, 142 (1948); Chem. Abs., 42, 7297 (1948).
248. A. Dornow and W. Schacht, Chem. Ber., 82, 117 (1949).
249. A. Petrov and V. Lyudvig, Zhur. Obshch. Khim., 25, 740 (1955).
250. A. Petrov and V. Lyudvig, Zhur. Obshch. Khim. 26, 51 (1956).
251. J. Meek, R. Merrow, D. Ramey, and S. Cristol, J. Amer. Chem. Soc., 73, 5563 (1951).
252. B. Shaw and E. Wagstaff, J. Chem. Soc., 80 (1933).
253. T. Fand and C. Lutomski, J. Amer. Chem. Soc., 71, 2931 (1949).
254. R. Lukes and P. Vaculik, Chem. Listy, 51, 1510 (1957); Chem. Abs., 52, 1163 (1958).
255. A. Dornow and H. Mochens, Ber., 73B, 355 (1940).
256. M. Prostenik and V. Balling, Arkiv Kemi, 18, 10 (1946); Chem. Abs., 42, 3399 (1948).
257. R. Zelinski and M. Benilda, J. Amer. Chem. Soc., 73, 696 (1951).
258. A. Furst, J. Amer. Chem. Soc., 71, 3550 (1949).
259. R. Lukes and J. Ernest, Coll. Czech. Chem. Comm., 15, 107 (1950).
260. R. Lukes and M. Pergal, Chem. Listy, 52, 68 (1958); Ref. Zhur. Khim., 4715 (1959).
261. G. Clemo and E. Hoggarth, J. Chem. Soc., 41 (1941).
262. A. H. Tracy, J. Chem. Soc., 63 (1941).
263. R. Mariella, J. Amer. Chem. Soc., 69, 2670 (1947).
264. R. Mariella, L. Peterson, and R. Ferris, J. Amer. Chem. Soc., 70, 1494 (1948).
265. P. Pickard and H. Lochte, J. Amer. Chem. Soc., 69, 14 (1947).
266. R. Mariella and R. Stansfield, J. Amer. Chem. Soc., 73, 1368 (1951).
267. K. Tsuda *et al.*, Pharm. Bull. (Japan), 1, 142 (1953); Chem. Abs., 50, 13 895 (1956).
268. R. Adams, J. Nine, and J. Campbell, J. Amer. Chem. Soc., 71, 387 (1949).
269. J. Wibaut, Rec. Trav. chim., 63, 141 (1944); Chem. Abs., 40, 4062 (1946).
270. U. S. P. 2 408 020 (1946); Chem. Abs., 41, 780 (1947).
271. C. Schmidle, J. Locke, and R. Mansfield, J. Org. Chem., 21, 1194 (1947).
272. J. Finkelstein and R. Elderfield, J. Chem. Soc., 365 (1939).
273. S. Horrobin, B. P. 744 928 (1956); Ref. Zhur. Khim., 43 341 (1959).
274. E. Ehrenstein, Ber., 64B, 1137 (1931).
275. V. Prelog and A. Komzak, Ber., 74B, 1705 (1941).
276. A. Balandin, L. Sovalova, and T. Slovokhotova, Dokl. Akad. Nauk SSSR, 110, 79 (1956).
277. L. Zykova, Uch. Zap. Saratov. Univ., 43, 89 (1956).
278. W. Betts and F. Popper, J. Appl. Chem., 8, 513 (1958).
279. T. Ishiguro, Japanese Pat. 178 745 (1949); Chem. Abs., 46, 540 (1952).
280. T. Ameniya, M. Suzuki, and K. Koguchu, Coal Tar, 4, 183 (1952).
281. C. Schmidle, J. Locke, and R. Mansfield, J. Org. Chem., 21, 1194 (1956).
282. R. Lukes and P. Vaculik, Chem Listy, 51, 1510 (1957); Chem. Abs., 52, 1163 (1958).
283. R. Lukes and M. Pergal, Chem. Listy, 52, 68 (1958); Chem. Abs., 52, 16 346 (1958).
284. G. Clemo and W. Gourlay, J. Chem. Soc., 478 (1938).
285. P. Karrer and S. Mainoni, Helv. Chim. Acta, 34, 2151 (1951).
286. H. Lochte, E. Thomas, and P. Trutt, J. Amer. Chem. Soc., 66, 550 (1944).
287. E. A. Coulson and J. Ditcham, J. Chem. Soc., 356 (1957).

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