COAL-TAR-CHEMICAL β-PICOLINE FRACTION AS THE COMPLEX RAW MATERIAL IN THE MANUFACTURE OF HETEROCYCLIC MEDICINAL PREPARATIONS (REVIEW)

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The characteristics of the coal-tar-chemical β-picoline fraction and its composition are presented, and methods for the separation of its components by the application of chemical and physical methods are reviewed. The value of the β-picoline fraction as a raw material in the manufacture of pyridine, piperidine, and quinuclidine medicinal preparations with cardiovascular, neurotropic, and chemotherapeutic action is examined. Particular attention is devoted to the results of research conducted by Soviet specialists in the complex utilization of all of the components of the β-picoline fraction. The question of the need for the more nearly complete recovery of coal-tar-chemical gases and for the more efficient utilization of coal not only as a fuel and in the manufacture of coke but also as the most valuable complex raw material in the chemical and pharmaceutical-chemical industries is raised.

The products of conversion of coal to coke are the principal natural source of pyridine compounds. Except for the rather large-scale synthetic manufacture of 2-methyl-5-ethylpyridine, which is obtained from acetaldehyde and ammonia on the basis of the Chichibabin reaction [1], all of the remaining industrial pyridine compounds currently in use are prepared in our country from coal-tar-chemical raw material. The total synthesis of picolines and lutidines from lower aldehydes, ketones, and ammonia has, unfortunately, not yet progressed beyond the pilot-plant stage in our country.

In addition, the natural sources of pyridines are not inexhaustible, and the methods for the processing of coal presently in use are extremely imperfect from the point of view of sufficiently complete utilization of coal-tar-chemical raw material. The classic words of D. I. Mendeleev, who fought for full-fledged chemical utilization of petroleum, apply in full measure to the problems of coal-tar chemistry: "Burning petroleum as a fuel is tantamount to burning currency."

All of the considerations set forth above compelled us to examine in the present review the problems involved in the efficient harvesting and processing of the most important complex coal-tar-chemical pyridine raw material, viz., the β-picoline fraction, which is a mixture of substances with basic character that are used for the manufacture of a large group of medicinal preparations.

In coal from various fields in the USSR the percentage of nitrogen, which is included mainly in the composition of heterocyclic products, ranges from 1 to 3% [2]. During conversion to coke, which involves thermal transformations of the mass of the coal, the nitrogen bases are liberated with the coke-oven gas and the coal tar; the distribution of nitrogen between the products of thermal processing depends on the type of deposit, the degree of metamorphism, and the temperature at which the coal is converted to coke [3]. The "heavy bases" (quinoline, isoquinoline, indole, acridine, some of their homologs, etc.) are isolated in the form of coal tar [4]; the "light bases" (pyridine derivatives) remain primarily in the coke-oven gas, in which their content ranges from 0.3 to 0.1 g/m^3 [2]. According to data from gas–liquid chromatography (GLC), no fewer than 23 compounds are included in the composition of the "light pyridine bases," and the primary components are pyridine (38.6%), 2-methylpyridine (α-picoline) (12.6%), 3- and 4-methylpyridines (β- and γ-picolines) (10.8%), 2,6-dimethylpyridine (2,6-lutidine) (2.84%), and 2,4-dimethylpyridine (2,4-lutidine) (4.44%), as well as quinoline (11.6%) and aniline (8.59%) [5]. The ratio of the

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components of the "light pyridine bases" in the coke-oven gas depends on the type of coal, the coking conditions, and the conditions under which the products are isolated [6].

The "light pyridine bases" are usually extracted from the coke-oven gas with sulfuric acid and are isolated, after neutralization with ammonia, by distillation. Pyridine (bp 114-116°C), pyridine-solvent (bp 120-140°C), and a β-picoline (bp 138-146°C) fraction are obtained by primary rectification of the anhydrous mixture.

The chief components of the β-picoline fraction are γ-picoline (37.5-41%), β-picoline (29.5-31.5%), and 2,6-lutadine (18.0-23.5%). Each of them can be used for the preparation of the most diverse pyridine derivatives; the presence in the fraction of compounds with α-, β-, and γ-methyl groups opens up the possibility of the synthesis of substances that contain substituents in any of these three possible positions of the pyridine ring.

It is interesting that various components of the β-picoline fraction have attracted attention and have subsequently proved to be most valuable at various periods in the development of science and the economy. In the nineteen thirties and forties β-picoline, which can be readily oxidized to an antipellagric agent, viz., vitamin PP (nicotinic acid), was regarded as the most important raw material; γ-picoline and 2,6-lutidine had not yet found application. A method for the preparation of nicotinic acid from the β-picoline fraction was therefore developed in 1938 in the All-Union Scientific-Research Institute of Pharmaceutical Chemistry by O. Yu. Magidson and V. N. Sokolova and was modified in 1945 by A. M. Grigorovskii and Z. M. Kimen; according to this method, the γ-picoline and 2,6-lutidine contained in the raw material was converted completely to tar by condensation with formalin under severe conditions under pressure, and the β-picoline, which does not react with aldehydes, was oxidized to nicotinic acid [7].

The discovery in the nineteen fifties of the high antituberculous activity of isonicotinic acid hydrazine [8] and its derivatives [9] placed γ-picoline in the forefront as a pyridine raw material. The production of pyridine bases from coal was expanded substantially in the country, and in the All-Union Scientific-Research Institute of Pharmaceutical Chemistry M. V. Rubtsov, E. E. Mikhlina, E. S. Nikitskaya, V. Ya. Vorob'eva, and A. D. Yanina [10] studied various methods for the selective and most nearly complete oxidation of the γ-picoline contained in the β-picoline fraction to isonicotinic acid. A convenient and economically profitable method for the preparation of this compound was developed and has been in use industrially for ∿30 yr [11]. M. V. Rubtsev, L. N. Yakhontov, and S. V. Yatsenko developed and incorporated in industry a method for the isolation from the production of isonicotinic acid — a mixture of β-picoline and 2,6-lutidine — of crude β-picoline with conversion to nicotinic acid [12]. A simultaneous search was made for methods for the utilization of 2,6-lutidine [13] and conversion to isonicotinic acid of unsubstituted pyridine, a surplus of which developed in the country in connection with the general increase in the scale of the production of coal-tar-chemical pyridine bases.

The development at the end of the nineteen sixties of new herbicides and antibacterial agents on the basis of unsubstituted pyridine and α-picoline solved the problem of the utilization of low-boiling pyridine derivatives, while the creation and incorporation in industry in the nineteen seventies of an original method for the preparation of the antisclerotic preparation parmidin (Anginin) on the basis of 2,6-lutidine solved the problem of the complex utilization of all of the components of the β-picoline fraction; in this case the expansion of the scale of the production of parmidin required the most nearly complete utilization of 2,6-lutidine and placed on the agenda the need for a review of the sequence of isolation and processing of all of the components of the β-picoline fraction. This rather complex problem was the subject of a large number of studies over the entire range of the development of the chemistry of natural bases (see earlier reviews [14, 15]), and the methods for the separation of the components of the β-picoline fraction described in the literature can be combined in the following groups:

1. Chemical Methods

1.1. Methods based on differences in the reactivities of the methyl groups.

1.2. Methods involving different reactivities of the nitrogen atoms

1.2.1. Fractional precipitation of salts.

1.2.2. Complexing.

1.2.3. Ion exchange.

2. Physical Methods

2.1. Fractional freezing out.

2.2. Rectification.

2.3. Extractive rectification.

2.4. Extraction methods.

1.1. The methods that involve differences in the reactivities of α-, β-, and γ-methyl groups of the pyridine ring are based on the known decrease (due to the mesomeric and inductive effects of the pyridine nitrogen atom) in the lability of the hydrogen atoms of the methyl groups in the order $\gamma\text{-}CH_3 > \alpha\text{-}CH_3 \gg \beta\text{-}CH_3$, which has received quantitative characterization in the case of alkaline deuterium exchange, in which the reactivity indexes are, respectively, 1810:130:1 [16]. A large number of substances are used as reagents for the chemical isolation of the components of the β-picoline fraction: sulfur in the presence of oxides and hydroxides of alkaline earth metals [17] or zinc chloride [18], oxides, oxyhalides, and halides of sulfur or phosphorus [19, 20], ketene in the presence of BF_3, PCl_3, benzaldehyde, etc. [21, 22], selenium dioxide [23], air oxygen at high temperatures on catalysts containing vanadium, molybdenum, and cobalt oxides [24], phthalic anhydride [18, 25, 26], benzaldehyde [27, 28] in the presence of acetic anhydride or zinc chloride, furfural [29], and formaldehyde [11, 14, 15, 30-32] or formaldehyde together with secondary amines [33]. In all of these oxidation or condensation reactions one can carry out processes involving the methyl groups of α- and γ-methylpyridines and retain unchanged the bulk of the β-picoline, which, after alkalization, is removed from the reaction mass by distillation. In individual cases carrying out the process under milder conditions [11, 14, 15, 30] makes it possible to cause only γ-picoline to undergo reaction while leaving the mixture of 2,6-lutidine with β-picoline unchanged.

1.2. The second group of methods involves the different reactivities of the free electron pairs of the pyridine nitrogen atoms in the components of the β-picoline fraction. It is known that owing to the inductive effect of the methyl groups, the electron density on the pyridine nitrogen atom of 2,6-lutidine is greater than that in β- and γ-picolines. In addition, α,α'-substituents create definite steric hindrance that is not displayed in protonation processes but increases substantially in complexing reactions [34-36] on passing to Lewis acids — as the size of the reagent increases, the corresponding reactions of 2,6-lutidine are more hindered than the analogous transformations of γ- and β-picolines. Both of the indicated factors or a combination of them are used in various processes involving the fractional precipitation of salts, complexing, and ion exchange. Thus the corresponding salts of 2,6-lutidine usually precipitate first, followed by the salts of γ-picoline and, lastly, the salts of β-picoline, in the fractional precipitation of salts — benzoates [37], phthalates [38, 39], oxalates [39-41], salicylates [14, 15, 42], and hydrochlorides [43]. The principal difficulty encountered in this type of separation is the selection of conditions that make it possible to realize the indicated processes most nearly completely and selectively. On the other hand, complexes of γ- and β-picolines are formed more readily and are more resistant to hydrolysis in the case of fractional precipitation of complex salts with zinc chloride [14, 15] and copper chloride and sulfate [14, 15, 44, 45]. Various methods for the isolation of β-picoline from mixtures with 2,6-lutidine and the sum of the β- and γ-picolines from the unseparated β-picoline fraction are based on this. The separation of complexes of γ- and β-picolines is a finer and more complex process. In these cases the complexes of γ-picoline, the electron density on the nitrogen atom of which is somewhat higher, are usually somewhat more stable. In particular, there have been reports [15, 46] of the preponderant formation of complexes of γ-picoline with cobalt, nickel, iron, calcium, and manganese chlorides, as well as with copper bromide and calcium iodide. These reactions are used for the isolation and purification of γ-picoline. The complexes of γ-picoline with the thiocyanates of divalent metals (for example, nickel) in the presence of organic substances (benzene, toluene, etc.) that form clathrates with tetrakis(γ-picoline) complexes are also used for the same purposes [47]. Similar processes also take place when esters of boric acid and phenols (for example, o- or p-cresol) are used [48, 49].

A method for the separation of 2,6-lutidine from monomethylpyridines, which in the case of refluxing of the β-picoline fraction with ethyl p-toluenesulfonate [50, 51] or with

2,4-dinitrochlorobenzene [52] are converted to quaternary salts, is also based on the steric effects of the α,α'-methyl groups in 2,6-lutidine. The unchanged 2,6-lutidine was removed from the mixture of quaternization products by distillation.

In addition, it should be noted that 2,6-lutidine forms complexes with mercuric chloride [14, 15], boron trifluoride [53], and urea [54-59] more easily than γ- and β-picolines, whereas in the case of β-picoline the addition of copper salts takes place more readily than for γ-picoline [57]. As in the case of isolation through their salts, the principal problem in the separation of pyridine products through complexes is the degree and selectivity of precipitation.

1.2.3. A number of publications have been devoted to the separation of the components of the β-picoline fraction by means of ion-exchange resins: In particular, studies have been devoted to the separation of 2,6-lutidine from a zeolite [60] or a mardenite in the NH_4^+, H^+, Ag^+, and K^+ forms [61], as well as to the isolation of β-picoline from the β-picoline fraction by passing an aqueous solution of the fraction through KU 2 × 8 ion-exchange resin in the Cu^{2+} form [62].

2.1. The fractional freezing out of the components of the β-picoline fraction is based on the differences in the melting point of γ-picoline (+3.65°C), 2,6-lutidine (−6.20°C), and β-picoline (−18.20°C) [63, 64]. Important conditions are the complete absence of moisture and numerous fractional crystallizations over a long period of time at a temperature below the melting points of the purified samples [64-66]; this makes it possible to obtain bases with a high degree of purity. Fractional freezing out has also been used for the separation of 2,6-lutidine and β-picoline hydrochlorides [67, 68]. Low efficiency, low yields, and the formation of eutectic mixtures are disadvantages of these methods.

2.2. The separation of the components of the β-picoline fraction by distillation is complicated to a great extent by the close boiling points of 2,6-lutidine (144.05°C), β-picoline (144.4°C), and γ-picoline (145.36°C) [63, 64]. *In vacuo* at a residual pressure of 200-300 mm, the boiling point of 2,6-lutidine is 20°C lower than that of β- and γ-picolines, and this can be used for its rough separation but not for the preparation of pure products [69]. In this connection various attempts have been made to extend the boiling range of the components of the β-picoline fraction by means of azeotrope formers. Azeotropes with water [63, 64, 70-74], with water in the presence of ammonium hydroxide [75-78], sulfur dioxide [79-81], methanol [82] or formaldehyde [15], with acetic, formic, and propionic acids [63, 64], and with phenol, halophenols, and cresols [83], and rectification of the hydrochlorides or hydrobromides, for which the difference in the boiling points is 5-7°C [68, 84], have been used for these purposes. The principal disadvantages of these methods are the necessity for the establishment of high-efficiency columns, the low efficiency of the processes, the high heat consumption, the formation of significant amounts of intermediate fractions, and (in the case of azeotropes) the necessity for the additional isolation of the pyridine bases from mixtures.

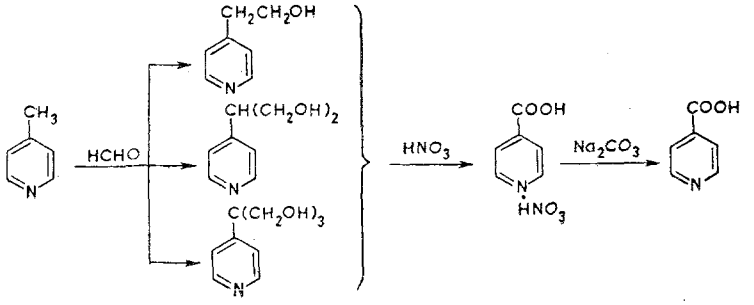
2.3. The efficiencies of columns can be increased in the separation of the components of the β-picoline fraction by extractive rectification [85-87]. Strongly polar substances with boiling points no lower than 180°C that usually contain several hydroxy groups (glycerol, triethanolamine, ethylene glycol, propylene glycol, and 1,2-propanediol) and are capable of forming strong hydrogen bonds with the pyridine nitrogen atom and, as a result of this, are capable of substantially changing the relative volatilities of the compounds are usually employed as the extractants. The general disadvantages of the methods are the need for carrying out the process at high temperatures, the significant consumption of raw material, and the low yields of pyridine bases.

2.4. The extraction methods for the separation of the components of the β-picoline fraction are based on the differences in the coefficients of their distribution between the water-immiscible organic solvents and aqueous solutions of the acids or inorganic salts; this is associated to a certain extent with the difference in the ease of hydrolysis of the salts or complexes, which increases in the order β-picoline < γ-picoline < 2,6-lutidine [14, 88-92]. Chloroform, aromatic or paraffin hydrocarbons, and mixtures of them have been used as the organic solvents, and inorganic acids (sulfuric and hydrochloric), sodium phosphate, nickel chloride, and potassium thiocyanate have been used as additives for the aqueous phase.

Differences in the distribution between solid or liquid and gaseous phases have also been used in addition to distribution between two immiscible liquid phases for the separation of the components of the β-picoline fraction. For example, the separation of a mixture of β- and γ-picolines by their contact in the vapor phase at 200°C with molecular sieves and subsequent desorption by pyridine [93] and the separation of 2,6-lutidine from monomethylpyridines by preparative GLC [94] have been described.

Despite the large number of variants for the separation of the components of the β-picoline fraction, the search for efficient methods for the realization of this process that are sufficiently simple, technologically convenient, and economical and that ensure high yields and a high degree of purity of the pyridine bases continues to be an urgent problem for the chemical and medicinal branches of industry. The urgency of the problem is especially great, since the β-picoline fraction is a complex raw material for the manufacture of a large number of valuable medicinal preparations; many of these are high-tonnage industries.

At the present time the complex utilization of the β-picoline fraction is realized via the following scheme in the pharmaceutical chemical industry of the USSR.

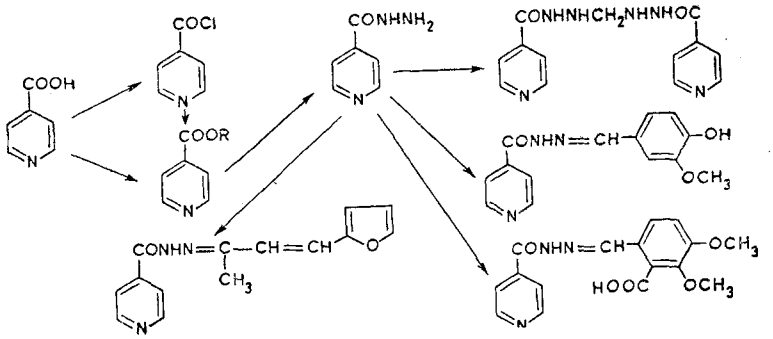


The most nearly complete utilization of β-picoline is achieved by treatment of the unseparated β-picoline fraction with a 38% solution of formaldehyde at 98-100°C for 18 h [11]; the γ-picoline contained in the fraction is converted almost completely to methylol derivatives, and the β-picoline and 2,6-lutidine, which do not react with formalin under these conditions, are removed by steam distillation and collected. The methylol derivatives of γ-picoline, which are obtained as a mixture of the mono-, di-, and trisubstituted compounds, are oxidized at 98-100°C with 60% nitric acid, and the resulting isonicotinic acid is isolated from a solution of its nitrate by means of calcined sodium carbonate [95].

Isonicotinic acid is the principal intermediate in the high-tonnage production of a number of antitubercular preparations of the isonicotinic acid hydrazide group, psychotropic drugs, and 3-quinuclidone, from which the industrial synthesis of various quinuclidine medicinal preparations is realized.

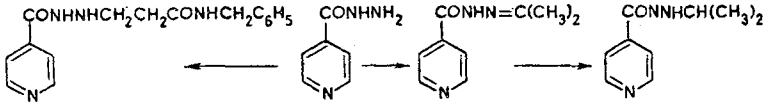
For the manufacture of antitubercular medications isonicotinic acid is converted through the chloride or by direct esterification to the corresponding ester [96, 97], which reacts with hydrazine hydrate to give isonicotinic acid hydrazide [95]; the latter is known as isoniazid (Tubazid, Rimifon, eutizon, rimitsid, etc.) in practical medicine [98]. Isoniazid has high tuberculostatic activity with respect to tuberculosis mycobateria and is used as a first-order preparation for the treatment of all forms and localizations of active tuberculosis in adults and children. The preparation is particularly effective in the case of fresh acute processes. The reaction of isonicotinic acid hydrazide [95, 99] with formalin gives bis(isonicotinoylhydrazino)methane, its reaction with vanillin gives isonicotinic acid 3-methoxy-4-hydroxybenzylidenehydrazide [100], its reaction with opianic acid gives isonicotinic acid 2-carboxy-3,4-dimethoxybenzylidenehydrazide [95, 100], and its reaction with furfuralacetone gives furfuralacetone isonicotinoylhydrazone [102]. The compounds listed above are original Soviet antitubercular preparations that are widely used in the chemotherapy of tuberculosis under the names metazid [99], ftivazid [9, 101], saluzid [9, 100], and larusan [95], respectively.

Saluzid in the form of the diethylammonium salt is used under the name saluzid soluble [95, 100] for injection into the cerebrospinal canal in tuberculous meningitis, for injection into lymph nodes, for irrigation of fistular passages with various localizations, for introduction into the genitourinary tract, for the irrigation of cavities in purulent serositis tuberculosis of the upper respiratory tract, and in tuberculous disease of the eyes.



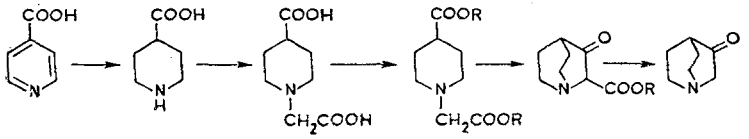
Isonicotinic acid hydrazide also lies at the foundation of the manufacture of psychotropic preparations such as iprazid [95, 103] and nialamide [95, 104], which are antidepressants that inhibit monoamine oxidase (MAO). Substances of this type were originally synthesized among diverse other N-substituted isonicotinoylhydrazides as antitubercular agents; iprazid has even been recommended as a promising preparation for the treatment of nonpulmonary tuberculosis. However, significant side effects made it necessary to discontinue its use in the chemotherapy of tuberculosis, while a study of the mechanism of the side action made it possible in the case of N-substituted isonicotinic acid hydrazides to ascertain considerable activity with respect to monoamine oxidase, which is of interest to psychiatry; iprazid is one of the most active irreversible monoamine oxidase inhibitors. A peculiarity of the antidepressive action of iprazid consists in the combination of a thymoleptic effect with a stimulating effect, which makes its application in depressions accompanied by retardation most expedient. The preparation is used in psychiatry chiefly for the treatment of protracted severe depressions that are resistant to other forms of therapy [98]. Nialamide has a somewhat weaker effect on monoamine oxidase. It is used in psychiatry in various forms of depression and as a psychostimulator in apathicoabuliac states, motor retardation, and asthenia, as well as in cardiology for decreasing the frequency and intensity of the paroxysms of stenocardia [98].

Iprazid is synthesized by the reaction of isonicotinic acid hydrazide with acetone and subsequent catalytic reduction of isonicotinic acid isopropylidene hydrazide [95]. The reaction of β-chloropropionic acid benzylamide with ioniazid is used for the production of nialamide [95].



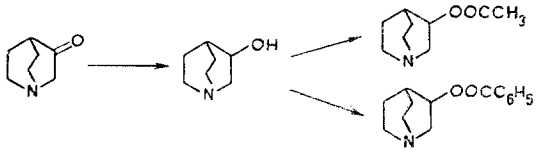
The industrial synthesis of 3-quinuclidone — the chief intermediate for virtually all quinuclidine medicinal preparations (except for temekhin and imekhin, the sources for the production of which are acetone and ammonia) [106] — is also realized on the basis of the isonicotinic acid obtained from the β-picoline fraction.

The industrial method for the preparation of 3-quinuclidone is based on a scheme developed in the All-Union Scientific-Research Institute of Pharmaceutical Chemistry [105]:



The reduction of 3-quinuclidone gives 3-hydroxyqunuclidine, which is the 1-azabicyclic analog of the biogenic amine choline. The structural analogy between 3-hydroxyquinuclidine and choline and the peculiarities of the quinuclidine bicyclic system, which are associated with the fixed structure, which restricts the conformational changes and fixes the distances between the reaction centers, the deshielding of the nodal nitrogen atom, which ensures the ease with which it approaches the electrophilic centers of the biochemical receptors, the stronger interaction with them and their more pronounced shielding — all of this constituted the theoretical foundation for the creation of new medicinal preparations that are active with respect to cholinergic systems [107, 108]. Among preparations of this type, the quinuclidine analog of acetylcholine, vis., the cholinomimetic preparation atseklidin

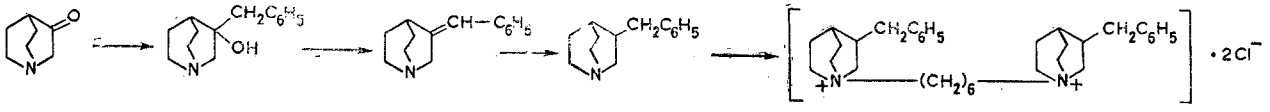
(3-acetoxyquinuclidine salicylate) [109, 110], which is used in ophthalmic practice as an agent that contracts the pupils and reduces intraocular pressure in glaucoma, in surgical, urological, and obstetrical-gynecological practice for the prevention and elimination of postoperative atony of the organs of the abdominal cavity, as well as in the case of depressed tone and subinvolution of the womb and to stop hemorrhage in the postnatal period [98].



Another medicinal preparation of this group, viz., 3-benzoyloxyquinuclidine hydrochloride, which has been called oksilidin [110, 111], is an agent that sedates the central nervous system in the same way as minor tranquilizers and combines sedative and hypotensive action. Oksilidin is used in neuroses and neurosislike states that are accompanied by agitation, stress, increased irritability, and insomnia and as an agent that lowers the blood pressure in hypertonia and improves the state of patients with disorders of the cerebral circulation due to hypertonic disease and cerebral atherosclerosis [98].

The original medicinal preparation fenkarol — 3-quinuclidinyldiphenylcarbinol hydrochloride — which was synthesized from 3-quinuclidone [112], is an antihistamine and antiallergic agent that differs from the known antiallergic preparations with respect to the mechanism of its action (it suppressed diamino oxidase) and is therefore particularly effective when other preparations have no effect. In contrast to the previously known antihistamine agents, fenkarol has no effect on the central nervous system and can be used to treat persons with active professions [98].

Another industrially produced (from 3-quinuclidone) original medicinal preparation, viz., kvalidil [113, 114] [1,6-hexamethylenebis(3-benzylquinuclidinium chloride)], which is synthesized via the scheme

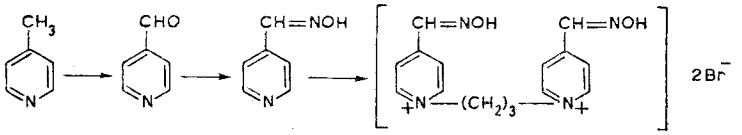


is an antidepolarizing muscle relaxant that is used for relaxing muscles and for controlling respiration during narcosis in the course of operations.

It should be noted that in the case of their action on cholinergic and histaminergic systems the transition from quinuclidine medicinal preparations to the analogous aliphatic, monocyclic, and other azabicyclic compounds leads to weakening or even to the complete loss of pharmacological activity: In all cases the most effective substances are precisely the quinuclidine preparations [108], the manufacture of which is based on the use of γ-picoline — a component of the β-picoline fraction.

The γ-picoline contained in the β-picoline fraction is used not only for conversion to isonicotinic acid and the products of its subsequent processing.

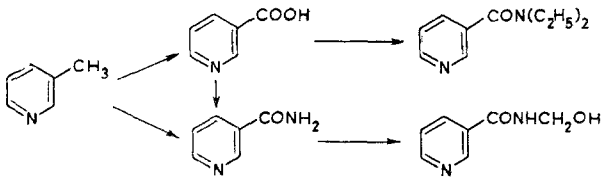
A contact method for the preparation of 4-formylpyridine with subsequent conversion through the oxime to 1,3-trimethylenebis(4-oximinomethylpyridinium bromide), which is known under the name dipiridoksim or trimedoksim as an effective cholinesterase reactivator [116], has been developed on the basis of γ-picoline isolated from the fraction. The synthesis of dipiridoksim is realized via the scheme



Dipiridoksim, inasmuch as it is a specific antagonist of organophosphorus compounds, finds application in poisoning by phosphorus-containing anticholinesterase agents, which have recently begun to be widely used in the economy, particularly as highly effective insecticides and medications. In addition to its therapeutic action, dipiridoksim also has prophylactic action [98].

After utilization of γ-picoline, the residual two components of the β-picoline fraction (β-picoline and 2,6-lutidine), which are removed from the methylol-γ-picolines by distillation, are subjected to separation by azeotropic rectification with water.

The isolated β-picoline is oxidized with potassium permanganate to nicotinic acid [12] or is converted by oxidative ammonolysis [117] to 3-cyanopyridine, which is hydrolyzed to nicotinamide [118]:



Analysis of various raw sources for the production of nicotinic acid and nicotinamide showed that precisely β-picoline is the most profitable raw material. The high-tonnage industrial production of the indicated products, which are widely used as vitamins in the medicinal, perfume, and food industries, as well as in agriculture, is therefore based chiefly on the use of β-picoline.

In addition, nicotinic acid and its amide are important intermediates that are necessary for the production of other medicinal preparations.

Nicotinic acid hydroxymethylamide, which is used under the name Nikodin (Bilamid, Nikoform, etc.) [95, 106] in the treatment of cholecystitis, hepatocholecystitis, infections of the urinary tract, and gastroenteritis as a cholagogue that has simultaneously bacteriostatic and bactericidal properties, is obtained industrially from nicotinamide by hydroxymethylation by means of formaldehyde. It is assumed that the effectiveness of the preparation is associated to a considerable extent with splitting out of formaldehyde in the organism and with the positive effect of nicotinamide (vitamin PP) on liver function [98].

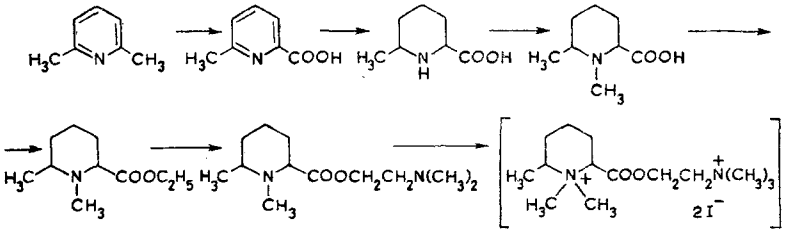
Another derivative of nicotinic acid, viz., nicotinic acid diethylamide, which is obtained industrially by treatment of this acid with phosphorus chloride and diethylamide [95], is used in medical practice in the form of a 25% aqueous solution under the name Cordiamin (Nikethamide, Corvitol, etc.). Cordiamin stimulates the central nervous system and the respiratory and vasomotor centers and is used in acute and chronic circulatory disorders, in reducing vascular tone and decreasing respiration, and in acute collapse, asphyxia, and shock states [98].

A third component of the β-picoline fraction, viz., 2,6-lutidine, which is purified in the form of a complex with urea through the hydrochloride or by azeotropic distillation with water, is the raw material for the high-tonnage production of the antisclerotic preparation parmidin (anginin) [119-121], which is bis(methylcarbamic acid) 2,6-pyridinediyldimethylene diester.

Parmidin decreases the deposition of cholesterol in the intima of arteries and reduces the manifestation of the atherosclerotic process, decreases the aggregation of thrombocytes and the change in the endothelium of arteries, improves microcirculation, weakens inflammatory reactions, and has antibradykinin action. Parmidin is used for the treatment of atherosclerosis of the vessels of the brain, the heart, and the extremities, in atherosclerotic and diabetic retinopathy, thrombosis of the veins of the retina, obliterative endoarteritis, and trophic ulcers of the extremities [98, 119].

In addition, the production of two piperidine medicinal preparations, viz., dimekolin [122-124] and nanofin [125], is realized in the medicinal industry on the basis of 2,6-lutidine.

The original ganglion-blocking preparation dimekolin is synthesized via the scheme



In practical medicine dimekolin is used in stage II and III of hypertonic diseases, hypertonic crises, spasms of the peripheral vessels and organs of the abdominal cavity, ulcerative disease of the stomach and the duodenum, and in obstetric practice as a labor-inducing agent [124].

Ganglion-blocking activity is displayed by not only dimekolin but also by the secondary amine 2,6-lupetidine (2,6-dimethylpiperidine), which is obtained by hydrogenation of 2,6-lutidine; in the hydrochloride form this substance is called nanofin, since it was first isolated as a natural alkaloid that is the primary nutrient of *Nanophyton erynoceum*. Synthetic nanofin obtained on the basis of the β-picoline fraction and used for the treatment of stage I and II hypertonia is presently used in practical medicine [98].

Thus it is apparent from this review that the coal-tar chemical β-picoline fraction serves as a complex raw material for the industrial production of an entire series of diverse medicinal preparations that are necessary for public health [106]. It should be emphasized that the β-picoline fraction is presently virtually the only source of pyridine raw material for the industrial production of these medications. The most important economic task of workers in the coal, metallurgy, coal-tar chemical, and medicinal industries is therefore the most nearly complete and economical accumulation and utilization of this valuable natural product and the complete utilization (rather than use as a fuel) of coking oven gases, which are an industrial source of the β-picoline fraction.

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CONVERSION OF 1,4-BUTANEDIOL TO FURAN COMPOUNDS ON COBALT CATALYSTS IN THE LIQUID PHASE

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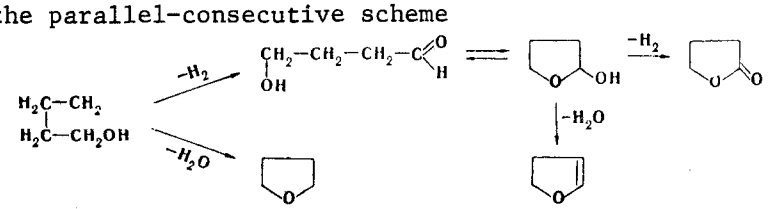
The transformation of 1,4-butanediol on cobalt catalysts applied to kieselguhr in the liquid phase under periodic and continuous conditions was investigated. When the reaction is carried out under periodic conditions, the principal reaction products are 2,3-dihydrofuran, tetrahydrofuran, and γ-butyrolactone. An increase in the selectivity of the formation of 2,3-dihydrofuran as the temperature is raised was established. 2,3-Dihydrofuran is obtained in 63-73 mole % yields under optimum conditions. 2,3-Dihydrofuran is converted to tetrahydrofuran when the process is carried out under continuous conditions on a tableted cobalt catalyst.

Relatively little study has been devoted to the catalytic transformations of 1,4-butanediol to furan compounds on cobalt-containing catalyst. It has been shown [1, 2] that 1,4-butanediol is converted to 2,3-dihydrofuran with high selectivity on such catalysts promoted by magnesium and zinc ions and by other additives in the liquid phase. The reaction proceeds via the parallel-consecutive scheme



The first parallel steps in the process are dehydration of 1,4-butanediol to tetrahydrofuran and dehydrogenation of 1,4-butanediol to γ-hydroxybutyraldehyde, which exists in equilibrium

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