MICROBIOLOGICAL TRANSFORMATION OF PYRIDINE DERIVATIVES (REVIEW)

A. N. Kost and L. V. Modyanova

UDC 576.8

The pathways in the microbiological transformation of pyridine and its derivatives (alkylpyridines, hydroxypyridines, pyridinecarboxylic acids, alkaloids, and condensed systems with a pyridine ring) under the influence of various microorganisms and several enzyme systems are examined. It is noted that oxidation, reduction, hydrolysis, and destruction of the aromatic ring are the most characteristic processes.

In the last decades microbiological methods in organic chemistry have been undergoing intensive development for both the regiospecific and stereospecific synthesis of substances that are difficult to obtain [1] and as a result of the necessity for the purification of waste waters by removal of impurities [2]. In addition to this, a study of the pathways of metabolism under the influence of microorganisms makes it possible to draw conclusions regarding the transformations of medicinal compounds and pesticides in plants and animals, since many of the enzymes in them are similar [3].

Several reviews in Russian have been devoted to microbiological transformations (for example, see [4-6]), but they are general in character. There is virtually no information on the use of microorganisms in a recently published review on the application of isolated enzymes in the chemistry of heterocycles [7]. However, a great deal of material on pyridine and its derivatives has accumulated and deserves to be discussed, since these compounds are toxic waste products of a number of industries, and many of them have substantial significance in the lives of plants and animals.

Pyridine

In 1914 it was established that pyridine is decomposed rapidly by soil microorganisms. A number of bacteria (*Aerobacter aerogenes*, *Serratia marcescens*, and *Bacterium herbicola*) that are capable of growing in a medium containing 0.1-0.5% pyridine were isolated as a result of its use as a source of nitrogen, and several forms of microorganisms (*Proactinomyces*, *Actinomyces*, and *Pseudomonas*) have also assimilated carbon from the pyridine ring [8]. Although the maximum growth in the biomass was observed only after 70-90 days, it was found that it was possible to free waste waters of pyridine, present in concentrations of up to 0.3%, after only 16 h when an active slurry was used [9, 10].

It was later found that the above-indicated strains of bacteria and actinomycetes are capable of decomposing pyridine but have virtually no effect on 2- and 3-methylpyridines and do not assimilate the isomeric lutidines and collidines [11].

The primary reaction in the microbiological metabolism of the benzene ring is hydroxylation to give a dihydroxy compound with subsequent ring opening [12]. In the case of pyridine the reaction is a more complex process. For example, the *Nocardia* Z1 strain, which is capable of decomposing pyridine, has virtually no effect on various monohydroxy and dihydroxypyridines or on pyridine N-oxide. Correspondingly, pyridine did not undergo reaction in experiments with a hydroxylating system (ascorbic acid, Fe^{2+}, ethylenediaminetetraacetate, and oxygen [13]) that models the function of oxygenase [11].

The study of the pathway of pyridine degradation was complicated by the fact that cell-free extracts were found to be incapable of metabolizing pyridine even after the addition of various cofactors. Similarly, treatment of the cells with toluene, which disrupts cell permeability, leads to a loss in the ability to oxidize pyridine. It was found that it was possible to establish the products of ring opening only by means of several inhibitors. For

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1299-1313, October, 1978. Original article submitted November 21, 1977.

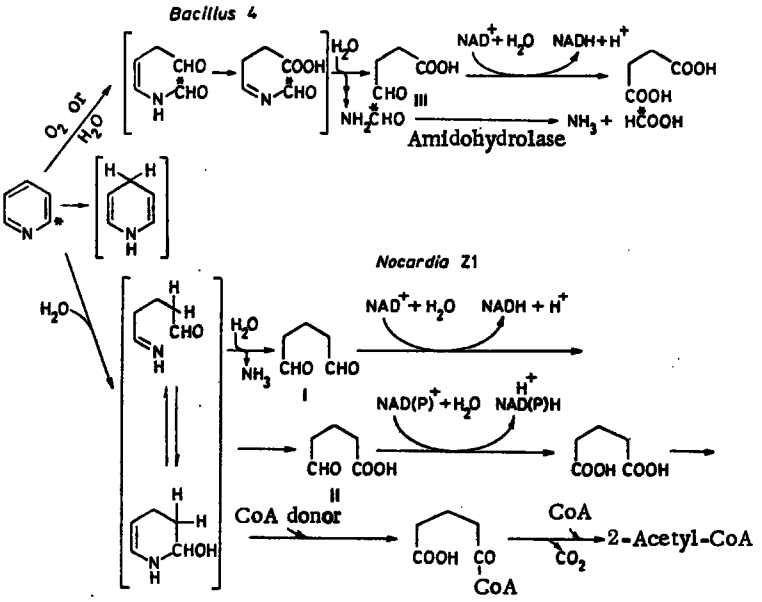
0009-3122/78/1410-1049$07.50

example, a decrease in the absorption of oxygen by a cell suspension of *Norcardia* Z1 and the formation of glutaric acid half-aldehyde semicarbazone (II) were observed when semicarbazide (a reagent for the keto group [14]) was introduced [15, 16].

When labeled 2,6-^{14}C-pyridine was used, it was established that the percentage of radioactivity included in aldehyde II was in agreement with the calculated value. The carbon skeleton of aldehyde II was consequently formed directly from the pyridine ring. This aldehyde is subsequently metabolized to glutaric acid. Dialdehyde I is also rapidly oxidized by cellular suspensions of *Nocardia* Z1 incubated in pyridine. However, it was not isolated, and the question as to whether aldehyde I is an intermediate in the metabolism of pyridine remained unanswered [16]. The formation of glutaryl-coenzyme A, which is finally converted to acetyl-coenzyme A, probably takes place during the subsequent metabolism of the products of oxidation of pyridine.

The metabolism of the pyridine ring proceeds in a different manner in the case of microorganisms that belong to various systematic groups. Thus, in contrast to *Nocardia* Z1, succinic acid half-aldehyde (III), which was isolated by the action of semicarbazide on a *Bacillus* B3 mutant strain, was identified as an intermediate in the degradation of *Bacillus* strain 4 [16]. This half-aldehyde is subsequently converted to succinic acid.

The formation of aldehyde III constituted evidence for cleavage of the pyridine ring between the 2-C and 3-C atoms. In fact, formamide, which is subsequently cleaved to formic acid and ammonia, also accumulates in the biomass [15]. The formation of formic acid from the 2-C atom of the pyridine ring was rigorously proved in the assimilation of 2,6-^{14}C-pyridine [16]. Similar data were obtained for *Corynebacterium* sp. and *Brevibacterium* sp. [17-19], but the rate of oxidation of aldehyde III by *Brevibacterium* sp. did not exceed 25-30% of the rate of oxidation of pyridine. Decomposition through a step involving half-aldehyde III probably plays only a minor role in this case, although other metabolites were not detected in the biomass [19].



Opening of the pyridine ring should have initially led to the formation of the corresponding unsaturated compounds; however, the presence of half-aldehydes constitutes evidence that reduction of pyridine is the primary process. Since 1,2,3,6-tetrahydropyridine and piperidine were not oxidized by cells grown in pyridine, it is completely likely that dihydropyridine is an intermediate in the degradation of pyridine. For comparison, let us note that nicotinamide is resistant to the action of ozone; however, ozonolysis to give 4-(N-formylmethylamino)buten-3-al proceeds readily after reduction to the 1,4-dihydro derivative.

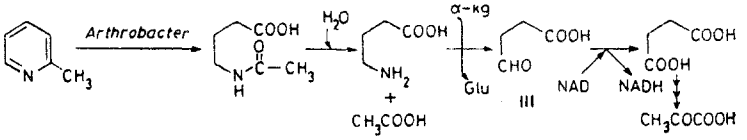
Alkylpyridines

It was shown relatively recently that the soil strains *Arthrobacter* and *Brevibacterium* can grow at the expense of 2-picoline, 2-ethylpyridine, 2,4-lutidine, and 2,4,6-collidine, during which they absorb air oxygen [21, 22]. These cultures display rigorous selectivity

with respect to the substrate on which they were isolated and usually do not affect other alkylpyridines. The optimum concentration of the base ranges from 0.15 to 0.20%; higher concentrations are toxic.

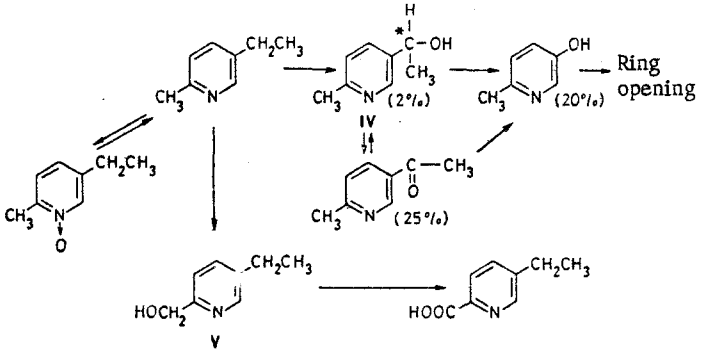
Data that make it possible to present the principal scheme for the metabolism are available for some alkylpyridines. For example, hydroxylation is not the primary process in the degradation of 2-picoline by means of *Arthrobacter* sp. [23], since this culture does not assimilate either 2-picoline N-oxide or one of the isomeric hydropyridines, particularly 2-hydroxy-6-methylpyridine. Picolinic acid is also not an intermediate, since *Arthrobacter* does not oxidize the α-methyl group.

Pyruvic acid and aldehyde III, which is subsequently readily oxidized to succinic acid, were identified as intermediates when some metabolic inhibitors were used.



N-Acetyl-γ-aminobutyric acid and γ-aminobutyric acid are evidently precursors of aldehyde III, since these compounds are readily metabolized by *Arthrobacter* cells, and enzymes responsible for the hydrolysis of N-acetyl-γ-aminobutyric acid and the metabolism of γ-aminobutyric acid are present in the cell-free extracts of this culture grown in 2-picoline. As in the case of the degradation of pyridine, the presence of fully reduced intermediates makes it possible to assume that reduction of the ring precedes ring opening; however, the nature of the hypothetical intermediate could not be established [23].

The fungi *Penicillium pusillum* and *Aspergillus terreus* are capable of utilizing up to 40% 2-methyl-5-ethylpyridine [24].



In contrast to 2-picoline, the primary process here was oxidation of the alkyl groups, particularly subterminal oxidation of the ethyl group to a carbinol (IV), the oxidation of which to 2-methyl-5-acetylpyridine and subsequent replacement of the acetyl group by a hydroxy group give 2-methyl-5-hydroxypyridine, which is a probable intermediate in opening of the pyridine ring [25].

The oxidation of the methylene group in 2-methyl-5-ethylpyridine by *P. pusillum* proceeds stereoselectively to give the levorotatory isomer of IV. However, if racemic 2-methyl-5-(1-hydroxyethyl)pyridine (IV) is used as the substrate, the fungus selectively oxidizes only the (−) form, leaving the dextrorotatory antipods untouched [26]. Thus it was found to be possible to obtain both the dextrorotatory and levorotatory isomers of carbinol IV by means of the same microorganism. The fungus *P. pusillum* also oxidizes the α-methyl group of 2-methyl-5-ethylpyridine to give 2-hydroxymethyl-5-ethylpyridine (V) and also forms the N-oxide; however, these pathways lead no further, since the N-oxide is reduced under the influence of the enzymes of the fungus to the starting base, and the 2-hydroxymethyl derivative V, although it is oxidized further, does not lead to 5-ethylpicolinic acid, which is toxic to the fungus, and this brings the metabolism to a halt.

Some of the intermediates in the metabolism of alkylpyridines or the products of their chemical transformation are worthy of special attention. Thus γ-aminobutyric acid is used as a regulator of the central nervous system. The dimethylaminoethyl esters of pyridylcarbinols have antihistamine activity [27], and the (−) isomers are more active [28]. 2-Methyl-5-hydroxypyridine is of interest as a "geroprotector" (a substance which retards the aging process) [29] (see an earlier review [30] for the chemistry of 3-hydroxypyridines).

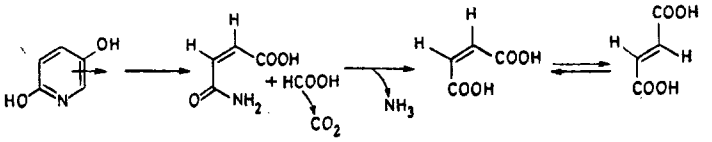
A co-oxidation method [31], which has been used for the oxidation of alkylbenzenes [32, 33], has been successfully used for the partial rearrangement of the alkylpyridine molecule with retention of the pyridine ring. Thus some *Nocardia* and *Arthrobacter* strains oxidize the methyl group of 3-methylpyridine to a carboxyl group to give nicotinic acid (up to 80% when hexadecane is added) [34, 35]. As in the case of p-xylene [36], the process occurs through a step involving the alcohol, i.e., 3-hydroxymethylpyridine [37]. The co-oxidation method was also found to be successful in the preparation of picolinic acid from 2-methylpyridine [38].

The extension of the co-oxidation method to disubstituted pyridines led to unexpected results. Thus cultures of some paraffin-oxidizing microorganisms (*Brevibacterium* sp. 180, *Nocardia* sp. 279, *Candida tropicalis* 63, etc.) inthe presence of n-hexadecane oxidized 2,6-dimethylpyridine to the N-oxide [39] (the side chains were not affected). However, this N-oxide did not accumulate (the yield was 0.04%) but was subsequently utilized by the microorganisms (in amounts up to 70% or higher) with complete destruction of the pyridine ring.

Hydroxypyridines

As stated above, the assumption by Houghton, Wright, and Cain [40] that hydroxypyridines are intermediates in the bacterial metabolism of the pyridine ring (in analogy with the oxidation of benzene derivatives [41]) was unwarranted. Nevertheless, hydroxypyridines can be used by a number of microorganisms as the sole source of carbon and nitrogen [40, 42]; the initial step in this process is hydroxylation to give dihydroxypyridines. For example, the oxidation of both 2- and 3-hydroxypyridines by *Achromobacter* gives 2,5-dihydroxypyridine [11, 40]. *Achromobacter* strain 7N is capable of accumulating large amounts (up to 43%) of 2,5-dihydroxypyridine in the medium, and this fact may be of preparative value [11]. The direction of hydroxylation of 2- and 3-hydroxypyridines by *Achromobacter* generally corresponds to the processes that take place in a model (monooxygenase) system [13].

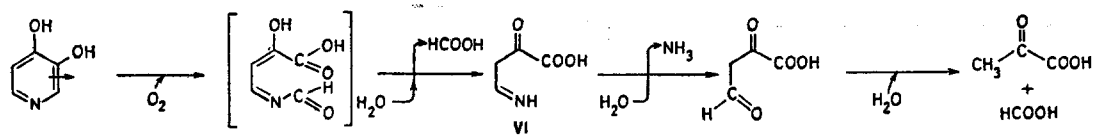
All of the strains that form 2,5-dihydroxypyridine from 2- and 3-hydroxypyridines degrade it further [43]. The presence of intermediate compounds could be demonstrated only by the use of individual fractions of the degraded cells. These fractions converted 2,5-dihydroxypyridine to formic acid and maleic acid half-amide and catalyzed the hydrolysis of the latter to ammonia and maleic acid, which was subsequently converted to fumaric acid:



The enzyme that opens the dihydroxylated pyridine ring was isolated and partially purified [43].

4-Hydroxypyridine is hydroxylated by an *Agrobacterium* sp. culture to give 3,4-dihydroxypyridine [40, 42]. Under conditions of restricted aeration this compound accumulates in amounts sufficient for its identification. A washed cellular suspension of *Agrobacterium* also oxidizes 4-hydroxypyridine to the 3,4-dihydroxy compound, during which 1 mole of oxygen per mole of substrate is absorbed, in conformity with the monooxygenase reaction [44]. Experiments with $^{18}O_2$ and $H_2{}^{18}O$ confirm these data. In addition, oxygen absorption by cell-free extracts during the oxidation of 4-hydroxypyridine occurs only in the presence of reduced nicotinamide-adenine nucleotide [45].

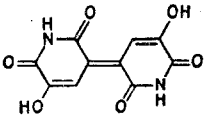
Pyruvic acid, formic acid, and ammonia were identified as the final products of the degradation of 3,4-dihydroxypyridine by cell-free extracts of *Agrobacterium* [42, 46]. Formic acid (1 mole) and 3-formyliminopyruvic acid (VI) were isolated at pH 8.5 [46].



The enzyme responsible for opening of the pyridine ring is similar to oxygenases that participate in the opening of the dihydroxylated benzene ring [47].

The metabolism of hydroxypyridines proceeds in a different manner in some cases. For example, an *Arthrobacter crystallopoietes* culture, which uses 2-hydroxypyridine as the only

source of nitrogen and carbon, decomposes the ring, and crystals of a blue pigment accumulate as the side product [48]. Other forms of *Arthrobacter* form a similar pigment when they are grown in 2-hydroxypyridine [49, 50]. This pigment probably has a structure of the azaquinone type (VII) and is apparently the product of autooxidation of 2,3,6-trihydroxypyridine [51, 52].

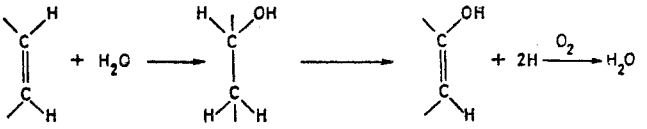


VII

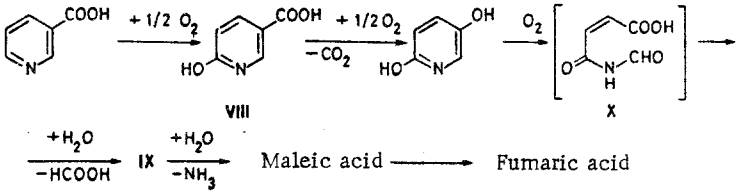
Nicotinic Acid

Nicotinic acid in 0.2-0.4% concentrations can sustain the growth of many microorganisms [53-55]. The first step for *Pseudomonas fluorescens* is hydroxylation of the pyridine ring to give 6-hydroxynicotinic acid (VIII) [56]. It is interesting that a suspension of cells of *Ps. fluorescens* also oxidizes 5-fluoro-, 2-fluoro-, and 5-chloro-substituted nicotinic acids in addition to nicotinic acid; the initial step in all cases is hydroxylation of the pyridine ring both in work with both the whole cells and the cell-free preparations [57].

The mechanism of the hydroxylation of nicotinic acid [58] differs substantially from the mechanism of hydroxylation of hydroxypyridines. When cell-free extracts of *Pseudomonas fluorescens* and labeled $^{18}O_2$ and $H_2{}^{18}O$ are used, product acid VIII becomes labeled only when the source of ^{18}O is $H_2{}^{18}O$ rather than oxygen [59]. The reaction consequently includes covalent hydration and subsequent dehydrogenation:



The latter is evidently associated with the cytochrome system of terminal oxidation, since the cytochromes are reduced in the case of the oxidation of nicotinic acid [60]. The hydroxylase responsible for the oxidation of nicotinic acid to 6-hydroxy derivative VIII was isolated from the cells of *Pseudomonas fluorescens* [61]. The terminal oxidase of nicotinic acid, isolated from *Pseudomonas ovalis*, has also been studied [62]. The cells of *Ps. fluorescens* grown in nicotinic acid rapidly (without a lag period) oxidize acid VIII further. By means of metabolic inhibitors or by work with individual fractions of the degraded cells it has been established that oxidative decarboxylation to give 2,5-dihydroxypyridine occurs in this case. The 2,5-dihydroxypyridineoxidase isolated from the cells rapidly oxidized 2,5-dihydroxypyridine to formic acid and maleic acid half-amide (IX) [60, 63].

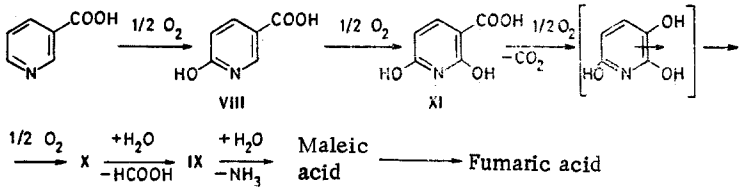


VIII X

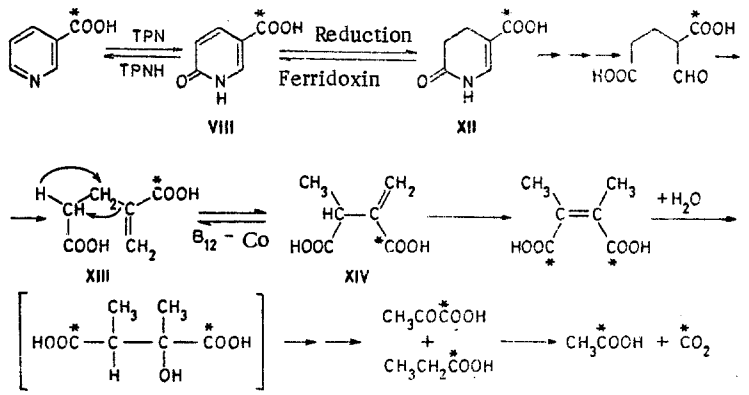
Maleic acid → Fumaric acid

The participation of dioxygenase in the step involving opening of the pyridine ring is confirmed by the fact that labeled reaction products are formed in the oxidation of 2,5-dihydroxypyridine in an $^{18}O_2$ atmosphere [64]. The hypothetical product (X) of the dioxygenase reaction could not be isolated. The problem of the structure of this compound still remains unsolved [65].

Only the first step — the formation of acid VIII — is similar in the degradation of nicotinic acid by other microorganisms (for example, *Bacillus* sp. [66]). 2,6-Dihydroxynicotinic acid (XI) [66], the product of the metabolism of which is evidently 2,3,6-trihydroxypyridine, which readily forms a blue pigment, was isolated as a subsequent intermediate. As in the case of *Pseudomonas*, the products of opening of the pyridine ring in this case are probably half-amide IX and maleic acid.



As in the case of the aerobic process, 6-hydroxynicotinic acid (VIII) is formed in the anaerobic metabolism [67] of nicotinic acid by *Clostridium* [68, 69]. The mechanism of hydroxylation is evidently related, since the entering oxygen atom comes from water. The subsequent conversion of acid VIII by *Clostridium* proceeds in a more complex manner than in the case of aerobic processes [70, 71]. Thus acid VIII vanishes in the reaction of pyruvic acid with cell-free extracts of *Clostridium*, and 1,4,5,6-tetrahydro-6-oxonicotinic (XII) and α-methyleneglutaric (XIII) acids accumulate. α-Methyleneglutaratemutase and methylitaconateisomerase, which catalyze the conversion of acid XIII to methylitaconic acid (XIV) and isomerization of the latter to methylmaleic acid [72, 73], were isolated from cells of *Clostridium*. These acids were isolated and identified on the basis of the mass spectra [74]. Propionic, acetic, and pyruvic acids and CO_2 are formed as the final products of the metabolism of nicotinic acid.

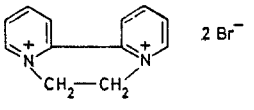


Correspondingly, *Clostridium* extracts brought about the fermentation of 7-^{14}C-nicotinic acid to $^{14}CO_2$ and a mixture of volatile and nonvolatile acidic substances, among which ^{14}C-XIII, ^{14}C-XIV, and ^{14}C-dimethylmaleic acid were determined, whereas labeled propionic and acetic acids and CO_2, respectively, were formed in the fermentation of labeled α-methyleneglutaric (XIII) and dimethylmaleic acids [75].

The microorganism *Neurospora crassa* deaminates nicotinamide to nicotinic acid and ammonia [76].

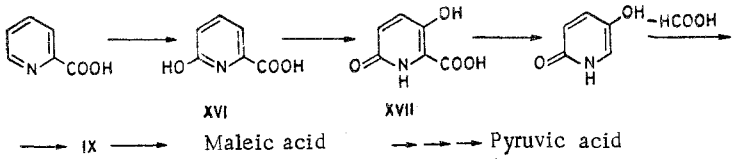
Picolinic and Dipicolinic Acid

Picolinic acid is an inhibitor of the sporulation of bacteria and, like its amide, was isolated as the product of photolytic decomposition of one of the most valuable herbicides — diquat (XV) — which is resistant to biological degradation and accumulates in the soil [77].



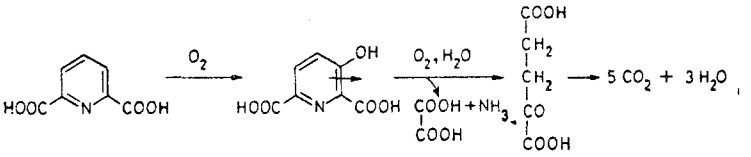
The initial step in the transformation of picolinic acid by *Aerococcus* QA, *Rhodotorula* M. R., and *Bacillus* sp. microorganisms proceeds in the same way as in the oxidation of nicotinic acid and leads to 6-hydroxypicolinic acid (XVI), which was isolated in the case of inhibition of the process by sodium arsenite [78, 79]. The mechanism of hydroxylation of picolinic acid is evidently related to the mechanism for nicotinic acid [58].

Hydroxylase, which catalyzes the inclusion of the hydroxyl group of water in the 6 position of picolinic acid, was isolated from the cells of *Arthrobacter picolinophilus* [80]. A second (minor) product of fermentation was 3,6-dihydroxypicolinic acid (XVII) [79]. 2,5-Dihydroxypyridine, and maleic and fumaric acids were recorded in the mixture by chromatography. The final degradation products — α-ketoglutaric and pyruvic acids — were isolated using semicarbazide as an inhibitor.



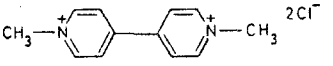
In general, the same intermediate compounds as in the case of picolinic acid were identified in the metabolism of picolinic acid amide by Gram-negative bacilli isolated from soil [81, 82].

The metabolism of dipicolinic acid proceeds in a different manner [83]. The primary reaction that is realized by *Achromobacter* soil bacteria is hydroxylation to the 3-hydroxy derivative (XVIII). This is followed by opening of the pyridine ring between the 2-C and 3-C atoms. However, of the intermediates, only α-ketoglutaric and oxalic acids were isolated and identified.

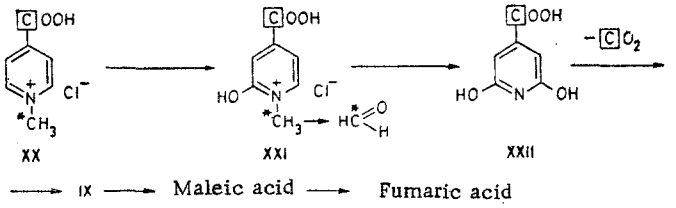


Metabolism of Paraquat

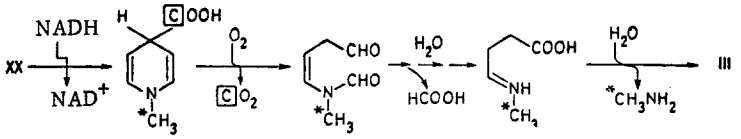
Researchers became interested in the microbiological decomposition of the herbicide paraquat (XIX) 10 yr ago [84] because of the fact that it is difficult to



remove from the soil. Microorganisms isolated from soil previously treated with paraquat that can use this compound as the sole source of carbon and nitrogen have been found; some of these microorganisms, such as, for example, *Corynebacterium fasciens* and *Clostridium pasteurianum* decompose 20-40% of the herbicide in 3 weeks. *Lipomyces starkeyi* yeasts utilize even 95% of the available paraquat in 2 weeks [84, 85]. During the degradation of paraquat, one of the pyridine rings is opened to give acid XX, which is also obtained by photochemical decomposition of paraquat [86, 87]. The next pathway in the metabolism of acid XX depends on the microorganism. In the case of degradation by Gram-positive 4C1 bacilli isolated from soil [88, 89] the pyridine ring is hydroxylated to give acid XXI, which then undergoes demethylation to 2-hydroxyisonicotinic acid. The methyl group is converted to formaldehyde, as confirmed by experiments with N-$^{14}CH_3$-isonicotinic acid methylchloride (XX). 2-Hydroxy acid XXI is then hydroxylated by cell-free extracts to 2,6-dihydroxyisonicotinic acid (XXII). Maleic acid half-amide and maleic and fumaric acids were identified as the final compounds in the metabolism of acid XX [89]:



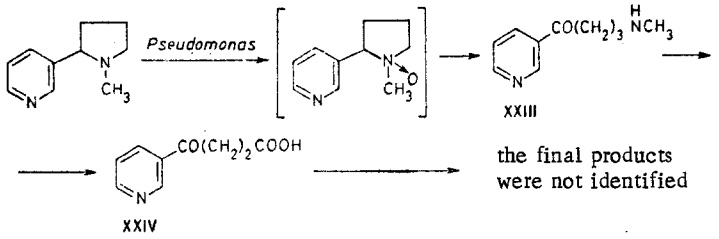
The metabolism of acid XX by another strain (4C2) [89] and by *Achromobacter* D [90-92] proceeded in a different manner. The necessity of NADH and O_2 during the assimilation of acid XX, which is typical for oxygenase reactions, and the absence of hydroxylation indicated the possibility in this case of direct oxidative opening of the partially reduced pyridine ring. However, no products of direct ring opening or intermediate whatsoever were detected. Methylamine and succinic and formic acids were identified as the final products, in addition to CO_2. It was established that decarboxylation precedes the formation of methylamine and succinic acid. Wright and Cain [92] were able to isolate the precursor of succinic acid — aldehyde III — by using an inhibitor (for example, semicarbazide).



In the case of the degradation by *Achromobacter* D of labeled acid XX it was demonstrated that the $^{14}O_2$ is formed from the 4-carboxy group and that the methylamine is formed from the N-methyl group [93]. Labeled formic and succinic acids were formed from N-methyl-2,3-$^{14}C_2$-isonicotinic acid.

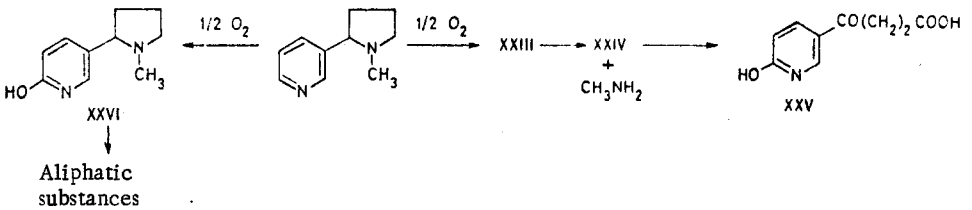
Nicotine and Other Pyridine Alkaloids

Soil bacteria are also capable of degrading nicotine. The pathways of the metabolism of this alkaloid differ for various microorganisms and depend on the conditions. For example, some forms of *Pseudomonas*, which utilize up to 60% nicotine, attack primarily the pyrrolidine ring to give a number of intermediates, some of which have been identified [94]:

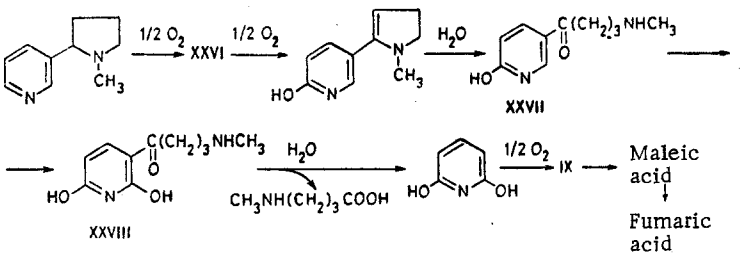


Other forms of *Pseudomonas* (for example, *Ps. nicotinophaga* [95]) affect not only the pyrrolidine ring but also the pyridine ring to give, in addition to pseudohydroxynicotine (XXIII) and 3-succinoylpyridine (XXIV), 6-hydroxy-3-succinoylpyridine (XXV), which in individual cases [96] accumulated in up to 12% yields.

Arthrobacter oxydans P-34 bacteria begin degradation of nicotine immediately with oxidation of the pyridine ring, namely, with 6-hydroxylation [97, 98] to 6-hydroxynicotine (XXVI). In a rapidly fissionable *Achromobacter nicotinophagum* culture nicotine is converted to aliphatic substances through the intermediately formed 6-hydroxynicotine (XXVI). However, the quiescent cells attack primarily the pyrrolidine ring to give XXIII, XXIV, and, finally, XXV, which is not metabolized further [99]:



The metabolism of 6-hydroxynicotine (XXVI) by *Arthrobacter oxydans* P-34 [100-102] leads to 6-hydroxypseudohydroxynicotine (XXVII), which is subsequently oxidized to 2,6-dihydroxypseudohydroxynicotine (XXVIII) [103]. The hydrolysis of this compound by the enzymatic fraction of *Arthrobacter oxydans* leads to 2,6-dihydroxypyridine and γ-methylaminobutyric acid. Both of these substances were oxidized further by *A. oxydans* [103].



Maleic acid half-amide (IX) was not isolated, but the pure compound is oxidized by *A. oxydans*. An oxidase that catalyzes the oxidation of 2,6-dihydroxypyridine was isolated from the cells of *A. oxydans* and purified [104]. Some forms of *Arthrobacter* convert nicotine to 6-hydroxynicotine (XXVI) [105, 106] in 50-83% yield. L-6-Hydroxynicotine and D-6-hydroxy-

nicotine, respectively, are formed (in 80% yields) from L- or D-nicotine during incubation with *Bacillus* sp. [107]. The enzymes of *A. oxydans* are responsible for the further oxidation of D- or L-6-hydroxynicotine to D- or L-6-hydroxypseudohydroxynicotine [108].

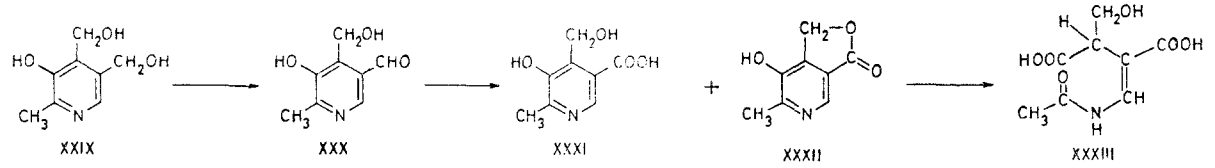
Some *Pseudomonas* strains are capable of separating racemic nicotine. For example, one of the strains that was unable to metabolize nicotine via the usual pathway decomposed approximately half of D,L-nicotine, and D-nicotine was isolated from the reaction mixture in 60-80% yield [109].

The initial steps in the metabolism of nornicotine and anabasine by forms of *Pseudomonas* are also dehydrogenation of the saturated ring and hydroxylation of the aromatic ring [96, 110].

Citric and fumaric acids were identified [112] as the final products of oxidation of anabasine by *Pseudomonas* Ch-23 [111]. The reader is referred to the book by Klyshev, Nurakhov, and Umirbaeva [113] for a more detailed discussion of the metabolism of anabasine.

Pyridoxine and Related Compounds

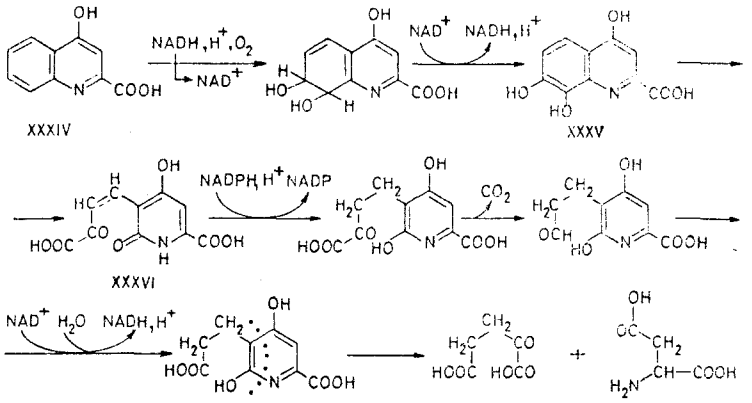
Oxidation reactions also predominate in the case of the metabolism of vitamin B_6 by forms of *Pseudomonas*. Thus *Pseudomonas* sp. 1A soil bacteria, which transform pyridoxine (XXIX) [114], first oxidize the 5-hydroxymethyl group [115] to give isopyridoxal (XXX), after which 5-pyridoxic acid (XXXI) and its lactone (XXXII) are obtained. The pyridine ring then opens to give α-hydroxymethyl-α'-(N-acetamidomethylene)succinic acid (XXXIII) [116].



Pseudomonas sp. M. A. [117, 118] metabolize pyridoxamine via a similar pathway to give α-(N-acetamidomethylene)succinic acid [25], which is converted to CO_2, NH_3, acetic acid, and succinic acid half-aldehyde by means of *Pseudomonas* sp. M. A. hydroxylase [119].

Other Compounds with a Pyridine Ring

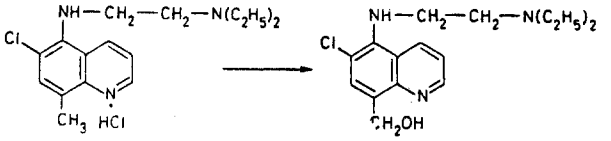
The dissimilation of tryptophan by forms of *Pseudomonas* includes anthranilic or kynurenic (4-hydroxyquinoline-2-carboxylic) acid as the intermediate [120, 121]. The metabolism of kynurenic acid (XXXIV) to the final products has been followed by various methods [122-124]:



Oxidation of the benzene ring leads to 7,8-dihydroxykynurenic acid (XXXV), after which the ring undergoes meta cleavage to give a substituted dihydroxypicolinic acid (XXXVI). Finally, the pyridine ring is cleaved to give α-ketoglutaric and L-aspartic acids. The individual steps of this conversion are realized not only by *Pseudomonas* but also by other microorganisms (for example, forms of *Aerococcus* [78]).

In the case of quinoline it is known that *Moraxella* microorganisms are capable of using it as the sole source of carbon and energy [125], during which 2-hydroxyquinoline accumulated. The whole cells of *Moraxella* oxidized not only 2-hydroxyquinoline but also 2,6-dihydroxyquinoline and 2,7,8-trihydroxyquinoline just as rapidly as quinoline itself, and this

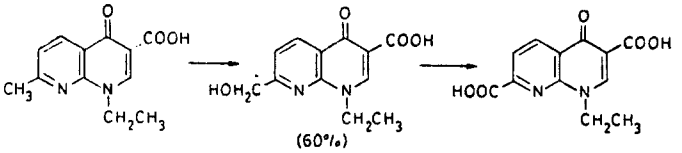
constituted evidence for the possible participation of these compounds as intermediates. Some soil *Pseudomonas* are also capable of utilizing 4-hydroxyquinoline [126] to initially give probably 4,7,8-trihydroxyquinoline. In some cases the quinoline ring is not affected by microorganisms, and only the substituents undergo conversion. For example, *Aspergillus sclerotiorum* selectively oxidize the methyl group in the antimalarial preparation XXXVII to a hydroxymethyl group [127]:



XXXVII

Sporotrichum sulfurescens fungi introduce a glycoside radical in substituted monohydroxy- and dihydroxyquinolines [128]. A number of microorganisms (*Escherichia coli*, *Candida utilis*, *Aspergillus niger*, etc.) reduce 4-nitroquinoline N-oxide. In this case both the N-oxide group and the nitro group are reduced to give 4-aminoquinoline [129]. Since the starting substrate has antimicrobial activity, this process should evidently be regarded as a detoxication process.

Among other condensed systems one should note the transformation of nalidixic acid (XXXVIII), an antibiotic used in diseases of the kidneys. *Penicillium adametzi* fungi selectively oxidize the methyl group in the α position of the pyridine ring of this acid to a hydroxymethyl group (in 60% yield). Acid XL was isolated in addition to carbinol XXXIX [130]:



XXXVIII XXXIX XL

A structural analog of nalidixic acid — 3-carboxy-7-methyl-1-ethyl-4-quinolone — undergoes a similar transformation [131].

A number of microbiological reactions are not a part of any metabolic pathway but arise in response to the presence of substrates that are toxic to microorganisms, and in this case processes of this sort can be regarded as detoxication reactions. For example, *Mycobacterium tuberculosis* strains that are sensitive and resistant with respect to isoniazid metabolize it to isonicotinic acid and 4-pyridylcarbinol [132, 133].

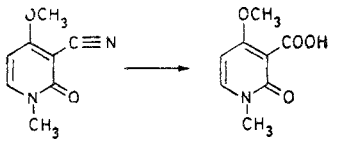
Similar results were obtained in the decomposition of nicotinic acid hydrazide by *M. tuberculosis* [134]. However, one should note here the microbiological reduction of pyridine N-oxides to the corresponding bases. The N-oxide of pyridine itself is reduced by ordinary baker's yeast to give pyridine (in 16% yield). The reaction proceeds specifically, since 4-picoline N-oxide was not reduced under the same conditions [135]. *Escherichia coli* 9723 [136] and *E. coli* 11303 [137] catalyze this reaction for substituted N-oxides.

Individual microbiological reactions are of interest, since they model processes involved in the conversion of a medicinal preparation that occur in the human organism. For example, the microorganism *Botryodiplodia theobromae Pat.* reduces ketone XLI (metirapon) to the corresponding alcohol (metirapol). The reaction proceeds stereospecifically and leads to the virtually optically pure levorotatory isomer of XLII in up to 90% yield [138].

XLI XLII

A similar process in the human organism leads to the formation of racemic alcohol XLII.

Individual forms of *Pseudomonas* grown in the alkaloid ricinine contain the enzyme ricininenitrilase, which catalyzes the hydrolysis of the nitrile group of ricinine [139, 140]:



It is important to note that the nitrile group of ricinine is very stable and is not hydrolyzed by ordinary methods and that the 4-alkoxy group is sensitive to the action of alkalis. However, the enzymatic hydrolysis proceeds smoothly without affecting the other substituents.

The examined literature data demonstrate the peculiarity of the transformations of pyridine compounds under the influence of the enzymatic systems of microorganisms; hydroxylation, reduction, hydrolysis, and opening of the aromatic ring are the most typical processes. The character and specificity of these transformations depend on the microorganism selected. Some of the processes have already shown promise for practical application.

LITERATURE CITED

1. A. Weissberger, Techniques of Chemistry. Application of Biochemical Systems in Organic Chemistry, Vol. 10, Part 1, Wiley — Interscience, New York—London—Sydney—Toronto (1976), pp. 49, 69.
2. M. N. Rotmistrov, P. I. Gvozdyak, and S. S. Stakovskaya, Microbiological Destruction of Synthetic Organic Substances [in Russian], Naukova Dumka, Kiev (1975).
3. R. V. Smith and J. P. Rosazza, Arch. Biochem. Biophys., 161, 551 (1974).
4. D. N. Kursanov, New Methods of Preparative Organic Chemistry [Russian translation], Inostr. Lit., Moscow (1950), p. 271.
5. G. Fonken and R. Johnson, Chemical Oxidations with Microorganisms, Marcel Dekker (1972).
6. G. K. Skryabin and L. A. Golovleva, Application of Microorganisms in Organic Synthesis [in Russian], Nauka, Moscow (1976).
7. K. L. Stuart, Heterocycles, 5, 701 (1976).
8. F. W. Moore, J. Gen. Microbiol., 3, 143 (1949).
9. A. Grunwald, Sb. Vys. Sk. Chem. — Technol. Praze, Technol. Vody, 13, 15 (1968); Chem. Abstr., 70, 70914 (1969).
10. D. A. Stafford and A. G. Callely, J. Gen. Microbiol., 63, No. 3, XIV (1970).
11. C. Houghton and R. B. Cain, Biochem. J., 130, 879 (1972).
12. E. K. Marr and R. W. Stone, J. Bacteriol., 81, 425 (1961).
13. S. Udenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie, J. Biol. Chem., 208, 731 (1954).
14. S. Dagley and D. E. Nicholson, Introduction to Metabolic Pathways, Wiley (1970).
15. G. K. Watson and R. B. Cain, Biochem. J., 127, 44 P (1972).
16. G. K. Watson and R. B. Cain, Biochem. J., 146, 157 (1975).
17. O. P. Shukla, Indian J. Exp. Biol., 11, 463 (1973).
18. O. P. Shukla and S. M. Kaul, Indian J. Biochem. Biophys., 11, 201 (1974).
19. O. P. Shukla and S. M. Kaul, Indian J. Biochem. Biophys., 12, 326 (1975).
20. J. B. Mudd, F. Leh, and T. T. McManus, Arch. Biochem., Biophys., 161, 408 (1974).
21. O. P. Shukla, Biochem. J., 128, 64P (1972).
22. O. P. Shukla, Indian J. Exp. Biol., 13, 574 (1975).
23. O. P. Shukla, Indian J. Biochem. Biophys., 11, 192 (1974).
24. A. N. Kost, P. B. Terent'ev, M. B. Kuplet-skaya, L. V. Modyanova, A. S. Demina, M. P. Khovrychev, and E. V. Shushenacheva, Dokl. Akad. Nauk SSSR, 214, 947 (1974).
25. L. G. Sparrow, P. K. Ho, T. K. Sundaram, D. Zach, E. J. Nyns, and E. E. Snell, J. Biol. Chem., 244, 2590 (1969).
26. P. B. Terent'ev, A. N. Kost, L. V. Modyanova, M. B. Kuplet-skaya, and E. V. Shushenacheva, USSR Inventor's Certificate No. 463670 (1974); Byull. Izobr., No. 10, 57 (1975).
27. C. H. Tilford, R. S. Shelton, and M. G. van Campen, J. Am. Chem. Soc., 70, 4001 (1948).
28. V. Barouh, H. Dall, D. Patel, and G. Hite, J. Med. Chem., 14, 834 (1971).
29. N. M. Émanuél', L. K. Obukhova, L. D. Smirnov, and T. V. Bunto, Dokl. Akad. Nauk SSSR, 226, 961 (1976).
30. L. D. Smirnov and K. M. Dyumaev, Khim. Geterotsikl. Soedin., No. 9, 1155 (1976).
31. E. P. Rozanova, Usp. Mikrobiologii, 10, 3 (1975).
32. J. B. Davis and R. L. Raymond, Appl. Mikrobiol., 9, 383 (1961).

33. R. L. Raymond, V. W. Jamison, and J. O. Hudson, Appl. Microbiol., 15, 857 (1967).
34. L. A. Golovleva, G. K. Skryabin, A. N. Kost, and P. B. Terent'ev, USSR Inventor's Certificate No. 228688 (1967); Byull. Izobr., No. 32, 14 (1968).
35. G. K. Skryabin, L. A. Golovleva, and V. I. Krupyanko, Izv. Akad. Nauk SSSR, Ser. Biol., No. 5, 660 (1969).
36. R. L. Raymond, V. W. Jamison, and J. O. Hudson, Lipids, 6, 453 (1971).
37. G. K. Skryabin and L. A. Golovleva, Mikrobiol. Promyshlennost', No. 6, 53 (1970).
38. L. A. Golovleva, E. L. Golovlev, G. K. Skryabin, G. A. Sadyrina, and T. I. Anan'eva, USSR Inventor's Certificate No. 417468 (1974); Byull. Izobr., No. 8, 76 (1974).
39. A. N. Kost, L. I. Vorob'eva, P. B. Terent'ev, L. V. Modyanova, O. K. Shibilkina, and L. A. Korosteleva, Prikl. Biokhim. Microbiol., 13, No. 5, 696 (1977).
40. C. Houghton, K. A. Wright, and R. B. Cain, Biochem. J., 106, 51P (1968).
41. D. T. Gibson, G. Cardini, F. C. Maslles, and R. E. Kallio, Biochemistry, 9, No. 7, 1631 (1970).
42. C. Houghton, G. K. Watson, and R. B. Cain, Biochem. J., 114, 75P (1969).
43. R. B. Cain, C. Houghton, and K. A. Wright, Biochem. J., 140, 293 (1974).
44. O. Hayaishi, Ann. Rev. Biochem., 38, 21 (1969).
45. G. K. Watson, C. Houghton, and R. B. Cain, Biochem. J., 140, 265 (1974).
46. G. K. Watson, C. Houghton, and R. B. Cain, Biochem. J., 140, 277 (1974).
47. S. Dagley, Nature, 202, 775 (1964).
48. J. C. Ensign and S. C. Rittenberg, Arch. Microbiol., 47, 137 (1963).
49. P. E. Kolenbrander, N. Lotong, and J. C. Ensign, Arch. Microbiol., 110, 239 (1976).
50. R. C. Gupta and O. P. Shukla, Indian J. Biochem. Biophys., 12, 296 (1975).
51. M. J. Knackmuss, Angew. Chem., Int. Ed., 12, 139 (1973).
52. P. E. Holmes, S. C. Rittenberg, and H. J. Knackmuss, J. Biol. Chem., 247, 7628 (1972).
53. M. J. C. Allinson, J. Biol. Chem., 147, 785 (1943).
54. R. Dubos and B. F. Miller, J. Biol. Chem., 121, 429 (1937).
55. A. Pinsky and M. Michaelis, Biochem. J., 52, 33 (1952).
56. D. E. Hughes, Biochem. J., 60, 303 (1955).
57. E. J. Behrman and R. Y. Stanier, J. Biol. Chem., 228, 947 (1957).
58. W. C. Evans, Biochem. J., 103, 1P (1967).
59. A. L. Hunt, D. E. Hughes, and J. M. Lowenstein, Biochem. J., 69, 170 (1958).
60. E. J. Behrman and R. Y. Stanier, J. Biol. Chem., 228, 923 (1957).
61. A. L. Hunt, Biochem. J., 72, 1 (1959).
62. M. V. Jones and D. E. Hughes, Biochem. J., 129, 755 (1972).
63. J. J. Gauthier and S. C. Rittenberg, J. Biol. Chem., 246, 3737 (1971).
64. J. J. Gauthier and S. C. Rittenberg, J. Biol. Chem., 246, 3743 (1971).
65. E. J. Behrman, Arch. Microbiol., 110, 87 (1976).
66. J. C. Ensign and S. C. Rittenberg, J. Biol. Chem., 239, 2285 (1964).
67. I. Harary, Nature, 177, 328 (1956).
68. I. Harary, J. Biol. Chem., 227, 815 (1957).
69. I. Harary, J. Biol. Chem., 227, 823 (1957).
70. I. Pastan, L. Tsai, and E. R. Stadtman, J. Biol. Chem., 239, 902 (1964).
71. L. Tsai, I. Pastan, and E. R. Stadtman, J. Biol. Chem., 241, 1807 (1966).
72. H. F. Kung, S. Cederbaum, L. Tsai, and T. C. Stadtman, Proc. Nat. Acad. Aci. USA, 65, 978 (1970).
73. H. F. Kung and T. C. Stadtman, J. Biol. Chem., 246, 3378 (1971).
74. H. F. Kung and L. Tsai, J. Biol. Chem., 246, 6436 (1971).
75. H. F. Kung, L. Tsai, and T. C. Stadtman, J. Biol. Chem., 246, 6444 (1971).
76. T. K. Sundaram, K. V. Rajagopalan, and P. S. Sarma, Biochem. J., 70, 196 (1958).
77. P. Slade and A. E. Smith, Nature, 213, 919 (1967).
78. S. Dagley and P. A. Jonson, Biochem. Biophys. Acta, 78, 577 (1963).
79. O. P. Shukla and S. M. Kaul, Indian J. Biochem. Biophys., 10, 176 (1973).
80. R. L. Tate and J. C. Ensign, Can. J. Microbiol., 20, 695 (1974).
81. C. G. Orpin, M. Knight, and W. C. Evans, Biochem. J., 122, 57P (1971).
82. C. G. Orpin, M. Knight, and W. C. Evans, Biochem. J., 127, 819 (1972).
83. Y. Kobayashi and K. Arima, J. Bacteriol., 84, 759 (1962).
84. B. C. Baldwin, M. F. Bray, and M. J. Geoghegan, Biochem. J., 101, 15P (1966).
85. J. R. Anderson and E. A. Drew, J. Gen. Microbiol., 70, 43 (1972).
86. P. Slade, Nature, 207, 515 (1965).
87. A. D. McLaren and G. H. Peterson, Soil Biochemistry, Marcel Dekker, Inc., New York (1967), p. 336.

88. C. G. Orpin, M. Knight, and W. C. Evans, Biochem. J., 122, 58P (1971).
89. C. G. Orpin, M. Knight, and W. C. Evans, Biochem. J., 127, 833 (1972).
90. K. A. Wright and R. B. Cain, Soil Biol. Biochem., 1, 5 (1969).
91. K. A. Wright and R. B. Cain, Biochem. J., 118, 52P (1970).
92. K. A. Wright and R. B. Cain, Biochem. J., 128, 543 (1972).
93. K. A. Wright and R. B. Cain, Biochem. J., 128, 561 (1972).
94. E. Wada and K. Yamasaki, J. Am. Chem. Soc., 76, 155 (1954).
95. T. Tabuchi, Nippon Nogei Kagaku Kaishi, 29, 219 (1955); Chem. Abstr., 52, 20378 (1958).
96. E. Wada, Arch. Biochem. Biophys., 64, 244 (1956).
97. L. I. Hochstein and S. C. Rittenberg, J. Biol. Chem., 234, 151 (1959).
98. L. I. Hochstein and S. C. Rittenberg, J. Biol. Chem., 234, 156 (1959).
99. W. J. Hylin, Arch. Biochem. Biophys., 83, 528 (1959).
100. L. I. Hochstein and S. C. Rittenberg, J. Biol. Chem., 235, 795 (1960).
101. S. H. Richardson and S. C. Rittenberg, J. Biol. Chem., 236, 959 (1961).
102. S. H. Richardson and S. C. Rittenberg, J. Biol. Chem., 236, 964 (1961).
103. R. L. Gherna, S. H. Richardson, and S. C. Rittenberg, J. Biol. Chem., 240, 3669 (1965).
104. P. E. Holmes and S. C. Rittenberg, J. Biol. Chem., 247, 7622 (1972).
105. G. D. Griffith, R. U. Byerrum, and W. A. Wood, Proc. Soc. Exptl. Biol. Med., 108, 162 (1961).
106. W. C. Squires and L. E. Hayes, US Patent No. 3644176 (1972); Chem. Abstr., 76, 125444 (1972).
107. M. Gloger and K. Decker, Z. Naturforsch., B, 24, 140 (1969).
108. H. C. Reeves, L. Messmer, and K. Decker, Arch. Microbiol., 111(1-2), 111 (1976).
109. Y. Yamashita, S. Shimizu, and E. Tamaki, Nippon Nogei Kagaku Kaishi, 37(7), 385 (1963); Chem. Abstr., 63, 6033 (1965).
110. E. Wada, Arch. Biochem. Biophys., 72, 145 (1957).
111. D. B. Nurakhov, L. K. Klyshev, and S. Saryeva, Prikl. Biokhim. Mikrobiol., 7, 39 (1971).
112. L. K. Klyshev, D. B. Nurakhov, and B. Batyrbekov, Izv. Akad. Nauk Kaz. SSR, Ser. Biol., 8, No. 5, 12 (1970).
113. L. K. Klyshev, D. B. Nurakhov, and K. Zh. Umirbaeva, The Microbiological Oxidation of Anabasine [in Russian], Nauka, Alma-Ata (1977).
114. V. W. Rodwell, B. E. Volcani, M. Ikawa, and E. E. Snell, J. Biol. Chem., 233, 1548 (1958).
115. T. K. Sundaram and E. E. Snell, J. Biol. Chem., 244, 2577 (1969).
116. M. Ikawa, V. W. Rodwell, and E. E. Snell, J. Biol. Chem., 233, 1555 (1958).
117. R. W. Burg, V. W. Rodwell, and E. E. Snell, J. Biol. Chem., 235, 1164 (1960).
118. R. W. Burg and E. E. Snell, J. Biol. Chem., 244, 2585 (1969).
119. E. J. Nyns, D. Zach, and E. E. Snell, J. Biol. Chem., 244, 2601 (1969).
120. R. Y. Stanier and M. Tsuchida, J. Bacteriol., 58, 45 (1949).
121. R. Y. Stanier and O. Hayaishi, Science, 114, 326 (1951).
122. H. Taniuchi and O. Hayaishi, J. Biol. Chem., 238, 283 (1963).
123. S. Kuno, Tanabe Amino Acid Res. Found. Symp., 1, 116 (1964); Chem. Abstr., 63, 6041 (1965).
124. S. Dagley and D. E. Nicholson, Introduction to Metabolic Pathways, Wiley (1970).
125. D. J. W. Grant, and T. R. Al-Najjar, Microbios., 15(61-62), 177 (1976).
126. T. R. Al-Najjar, R. J. Grout, and D. J. W. Grant, Microbios. Lett., 1(3-4), 157 (1976); Chem. Abstr., 85, 106503 (1976).
127. S. Archer, D. M. Bailey, D. Rosi, and E. W. Dennis, UAR Patent No. 680816709 (1969); Chem. Abstr., 72, 65415 (1970).
128. K. Kieslich, H.-J. Vidic, K. Petzoldt, and G.-A. Hoyer, Ber., 109, 2259 (1976).
129. T. Okabayshi and A. Yoshimoto, Chem. Pharm. Bull. (Tokyo), 10, 1221 (1962).
130. P. B. Hamilton, D. Rosi, G. P. Peruzzotti, and E. D. Nielson, Appl. Microbiol., 17, 237 (1969).
131. K. Kieslich, H. Wieglepp, G.-A. Hoyer, and D. Rosenberg, Ber., 106, 2636 (1973).
132. J. Youatt, Austral. J. Exp. Biol. Med. Sci., 38, 245 (1960).
133. J. Youatt, Austral. J. Chem., 14, 308 (1961).
134. J. Youatt, Austral. J. Exp. Biol. Med. Sci., 40, 191 (1962).
135. A. May, Enzymologia, 18, 142 (1957).
136. P. T. Sullivan, M. Kester, and S. J. Norton, J. Med. Chem., 11, 1172 (1968).
137. M. Kester and S. J. Norton, Biochem. Biophys. Acta (E), 258, 709 (1972).

138. R. Howe and R. H. Moore, J. Med. Chem., 14, 287 (1971).
139. W. G. Robinson and R. H. Hook, J. Biol. Chem., 239, 4257 (1964).
140. R. H. Hook and W. G. Robinson, J. Biol. Chem., 239, 4263 (1964).

NEW REACTION FOR THE PREPARATION OF LOWER OXODIHYDROFURANS

L. A. Badovskaya

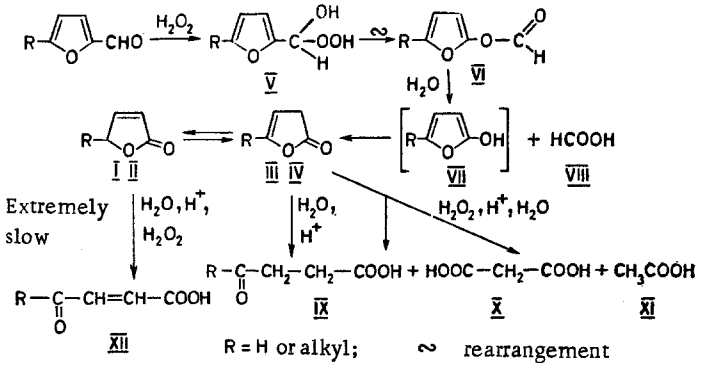
UDC 547.722.3'724.07

A reaction for the preparation of lower oxodihydrofurans by oxidation of formylfurans with hydrogen peroxide is proposed. The mechanisms of their formation and transformations are discussed.

Oxodihydrofurans are widely used in organic synthesis [1, 2] and to obtain polymers for special purposes [3, 4] and have high and diversified physiological activity [1, 2, 5].

Of the lower lactones, 2-oxo-5-methyl-2,3-dihydrofuran III (β,γ-angelica lactone) is the most readily available compound and has been the subject of the greatest study. It is obtained by dehydration of levulinic acid [6, 7]. The more simply constructed 2-oxo-2,5-dihydrofuran has been obtained from β,γ-dihalo- and hydroxyhalobutyric acids [8], from butyrolactone through bromobutyrolactone [9], by pyrolysis [10] of 2,5-diacetoxy-2,5-dihydrofuran, or by acid hydrolysis of 2-acetoxyfuran [11]; however, all of these methods are based on the use of a starting compound that is difficult to obtain and are laborious and give the products in low yields.

During an investigation of the oxidation of furfural with hydrogen peroxide we detected oxodihydrofurans I and IV in the intermediate reaction products; in the case of oxidation of 5-methylfurfural we detected 5-methyl-2-oxodihydrofurans II and III (see the scheme below, Figs. 1 and 2, and Table 1). The formation of I-IV during the oxidation of formylfurans with hydrogen peroxide occurs during the hydrolysis of ester VI [12], which is the product of rearrangement of hydroxyhydroperoxyfurfural V [13]. It is known [11] that acetoxyfuran is also hydrolyzed to give lactones I and IV. The immediate hydrolysis product — hydroxyfuran VII — could not be detected in the reaction mixture because of its instability [14, 15]. Methods for the preparation of the hydroxyfuran are indicated in the literature [16, 17], but other researchers have found that they could not reproduce them. It has been assumed that α-hydroxyfuran is formed in the radiative oxidation of the furan—water system (1:1000) [18]. The oxidation of formylfurans with hydrogen peroxide gives, in addition to VII, formic acid (VIII), which probably catalyzes the conversions of hydroxyfuran and its homologs of isomeric forms of oxodihydrofurans I-IV [13].



Thus hydroxyfurans of the VII type are present in the oxo form in the reaction mixture. This constitutes one of the differences between the peroxide oxidation of formylfurans and the oxidation of aromatic aldehydes. In the latter case the resulting phenols are stable

Krasnodar Polytechnic Institute, Krasnodar 350006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1314-1319, October, 1978. Original article submitted December 1, 1976; revision submitted March 31, 1978.

 0009-3122/78/1410-1062$07.50