ELECTROPHILIC SUBSTITUTION IN A SERIES OF ISOMERIC α-, β-, AND γ-HYDROXYPYRIDINES (REVIEW)

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The principles of orientation and the mechanism of electrophilic substitution in a series of isomeric 2-, 3-, and 4-hydroxypyridines are examined.

The differences in the properties of the three isomeric hydroxy derivatives of pyridine are due to the mutual orientation of the hydroxyl group and the heteroatom. As compared with the α and γ isomers, β-hydroxypyridine displays the greatest similarity to phenol with respect to its physicochemical properties, but, in contrast to the aromatic analog, the hydroxy form predominates only in solutions with low dielectric permeabilities. In other media, β-hydroxypyridine may be present in the dipolar form [1-4]. On the other hand, a type of tautomerism in which the dominant form is the N—H tautomer [5-9] is peculiar to α- and γ-hydroxypyridines.

The differences in the tautomerism of β-hydroxypyridine, on the one hand, and of the α- and γ-hydroxyisomers, on the other, have predetermined the features of the chemical behavior of the isomeric hydroxypyridines in substitution reactions and, in particular, in electrophilic substitution, and this is the subject of the present review.

Acidic and Basic Deuterium Exchange

The kinetic study of the acid- or base-catalyzed isotopic hydrogen exchange of isomeric hydroxypyridines (HP) has made it possible to ascertain the mechanism of electrophilic substitution of this class of compounds and to obtain a quantitative evaluation of the effect of protonation of the ring nitrogen atom and of diverse functional substituents on the reactivity of the hydroxy-substituted heteroring.

It has been established that 2- and 4-HP and some of their C- and N-methyl-substituted derivatives are deuterated in the 3 and 5 positions in the neutral oxo form [10]. An evaluation of the constants of acidic deuterium exchange of 4-HP and phenol in the neutral form has made it possible to establish that replacement of the m-CH grouping by the NH group lowers the exchange rate by a factor of 10^7, whereas the degree of deactivation is 10^{18} in the benzene—pyridine system. This confirmed the fact that electron-donor substituents have a large effect in electron-deficient substrates. A comparison of the rates of deuterium exchange of 2- and 4-HP in the neutral and protonated forms provided evidence that 4-HP is more reactive in the neutral form and that 2-HP is more reactive in the protonated form.

The exchange rates of 4-HP and its N-methyl-substituted derivative are identical [11].

It was found from a comparison of the rates of deuterium exchange of 4-nitrophenol and 4-HP in the cationic form that the NH group has $10^{3.5}$ times the deactivating effect of the nitro group. A similar tendency was revealed during a study of the acidic deuterium exchange of 3,5-dimethylphenol and its heterocyclic analogs (2.6-dimethyl-4-HP and its N- and O-methyl-substituted derivatives) [11]. The introduction of CH_3 groups in the 2 and 6 positions of 4-HP raised the rate of exchange of the protons in the 3 and 5 positions by factors of $\sim 10^2$ and $\sim 10^{4.5}$ for the neutral and protonated forms, respectively. Replacement of the hydroxy group by a methoxy group, on the other hand, lowered the rate of deuterium ex-

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change by a factor of $10^{1.8}$. It was found that the N-oxide group raises the reactivities of the 3 and 5 positions in 2,6-dimethyl-4-HP by two orders of magnitude during exchange involving the neutral form and lowers the reactivity by the same factor during exchange involving the protonated form [11].

Data from the acidic deuterium exchange of 3- and 5-methyl-2-HP indicated identical reactivities of the 3 and 5 positions both in the neutral and protonated forms.

An analysis of the results of the acidic exchange of 3-HP and methyl-substituted derivatives [12] provided evidence that the 2 position is the most reactive position in the hydroxypyridine ring and that the 4 position is the least reactive.

The introduction of an N-oxide group considerably increased the reactivity of the 2 position of the hydroxypyridine ring [13]. Thus, for example, 3-HP N-oxide is deuterated in the 2 position in the uncharged form, whereas 3-HP and its O-methyl ether do not undergo exchange under similar conditions. On the other hand, 3,5-dimethoxypyridine 1-oxide underwent exchange in both the 2 and 6 positions in the neutral or protonated forms, depending on the pD value of the medium. The ratio of the rates of deuterium exchange of the neutral and protonated forms was $\sim 10^{3.3}$; this clearly demonstrated pronounced deactivation of the pyridine ring when the ring nitrogen atom is protonated.

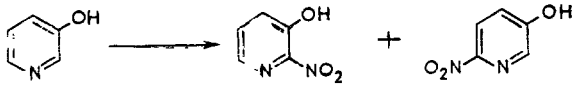
The transition from acidic to basic deuterium exchange of 3-HP was accompanied by a considerable increase in the rates; this was evidently due to participation of the latter in the most reactive (anionic) form in this type of substitution [14, 15]. Thus, whereas exchange of the protons of the β-pyridol ring was not observed under acid-catalysis conditions, exchange of the 2-, 6-, and 4-H protons in 3-HP is possible during basic deuterium exchange, depending on the conditions under which it is carried out [14]. The introduction of a CH_3 group in the 2 and, particularly, the 6 position increases the reactivity of the β-pyridol ring [14]. A comparison of the rate constants for exchange of the protons in 3-HP and its N-oxide showed that the introduction of an N-oxide group also accelerates the exchange of protons in the order 2-H > 6-H > 4-H. A similar pattern was also noted during a comparison of the data from deuterium exchange of 2-methyl-3-HP and its N-oxide [15]. A comparison of the data from basic deuterium exchange of 3-HP and its derivatives made it possible to establish that the rate of exchange of the 2-H proton is one order of magnitude higher than the rate of exchange of 6-H and approximately two orders of magnitude higher than the rate of exchange of 4-H.

Nitration

The hydroxy group facilitates substitution in the pyridine ring and, in contrast to pyridine, the nitration of hydroxypyridines proceeds smoothly and gives the products in good yields.

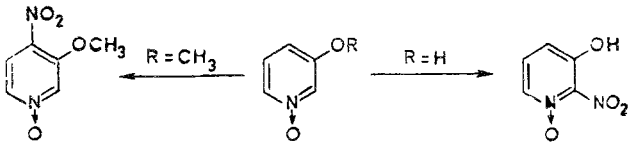
The position of the hydroxy group has a substantial effect on the ease and selectivity of substitution and also on the form in which the isomeric hydroxypyridines react.

The nitration of 3-HP proceeds exclusively in the 2 position, during which 3-HP reacts in the protonated form [16]. 2-Nitro-3-HP, the structure of which was proved by a series of chemical transformations [17], was initially obtained in the nitration of 3-HP. Later, the cis-nitro isomer was also isolated in negligibly low yield (1%) along with the 2-isomer (74%) [18].



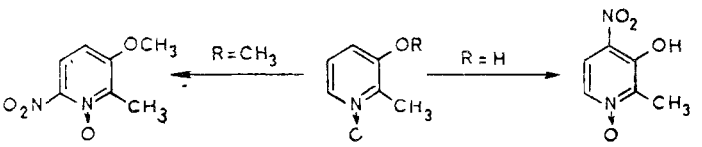
Depending on the nitration conditions, 3-alkoxypyridines form 2-nitro and 2,6-dinitro derivatives [19-21].

3-Hydroxypyridine 1-oxide is nitrated in the 2 position, and this constitutes evidence for the stronger orienting effect of the β-hydroxy group as compared with the para-directing effect of the N-oxide group [22]. In addition, the nitration of 3-alkoxypyridine N-oxides is directed exclusively to the 4 position, indicating the predominant para-orienting effect of the N-oxide group as compared with the alkoxy group [23, 24].



On the other hand, the nitration of 3,5-diethoxypyridine N-oxide proceeds in the 2 and 6 positions, despite the expected 4-substitution [25, 26].

Extremely interesting results were obtained during a study of the nitration of 2-alkyl- and 2-chloro-3-HP [18, 27] in which not only the 6 position but also the 4 position undergoes substitution, with predominant formation of the 4 isomer [28]. Exclusive nitration in the 4 position was also noted in the case of 2-methoxy-3-HP [29]. It has been assumed [28] that the primary direction of nitration in the ortho position relative to the hydroxy group in 2-alkyl- and 2-chloro-3-HP is due to the formation of a six-membered chelate complex in the transition state. This assumption was confirmed by the fact that primarily substitution of the 6 position occurs when nitration is carried out at higher temperatures, which give rise to weakening of the intramolecular hydrogen bond. At the same time, the nitration of 2-methyl-3-methoxypyridine, which is incapable of forming a hydrogen bond with the attacking nitronium ion, proceeds exclusively in the 6 position. The existence of only 6 substitution in the nitration of 2-nitro-3-HP is evidently a consequence of the impossibility of chelate formation because of the strong intramolecular bond between the nitro and hydroxy groups that is already present in the compound. The effect of chelate formation on the orientation of substitution was also confirmed in the case of nitration of 2-methyl-3-hydroxy- and 2-methyl-3-methoxypyridine N-oxides [30-31]. The nitration of 2-methyl-3-HP N-oxide was directed exclusively to the 4 position, whereas 2-methyl-3-methoxypyridine N-oxide was nitrated in the 6 position.



It is interesting to note that, in contrast to 3-methoxypyridine N-oxide, the nitration of 6-methyl-3-methoxypyridine N-oxide [31] also proceeds in the 2 position.

As one should have expected, the nitration of 6-methyl-3-HP [32] is directed to the 2 position.

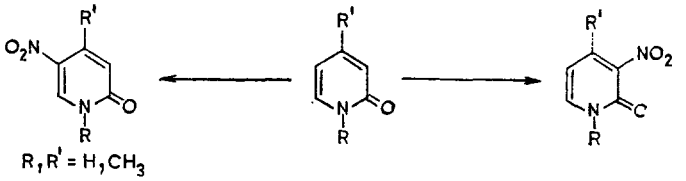
The presence of a nitro group in the β-pyridol ring does not prevent its further substitution. Thus, the corresponding 2,4- and 4,6-dinitro-3-HP were obtained by nitration of 6-methyl-2-nitro- and 2-methyl-6-nitro-3-HP [32]. In the nitration of 2-nitro-3-HP, 2,4,6-trinitro-3-HP is also formed along with the 2,6-dinitro derivative [33]. Thus, the data on the nitration of 3-HP provide evidence for the possibility of successive selective substitution of the 2, 6 and 4 positions of the β-pyridol ring.

In contrast to the 3 isomer, selectivity in the substitution of the 3 and 5 positions is not noted in the nitration of 2-HP.

A review of the earlier studies [34-36], despite their contradictory character, makes it possible to draw the conclusion that primarily the 3 position is nitrated, but the ratio of the 3- and 5-nitro- and 3,5-dinitro-2-HP to a great degree depends on the type of nitrating agent and the reaction conditions. A kinetic study of the nitration of 2-HP and its derivatives [37] showed that the direction of substitution is strongly dependent on three factors: the concentrations of the reagents, the temperature, and the acidity of the medium. The appropriate selection of these factors makes it possible to regulate the direction of substitution. Thus, primarily 3-nitro-2-HP are formed in high yields (75-85%) at high temperatures, high concentrations of the reaction substrate, and in relatively dilute sulfuric acid [37]. (See scheme on following page.)

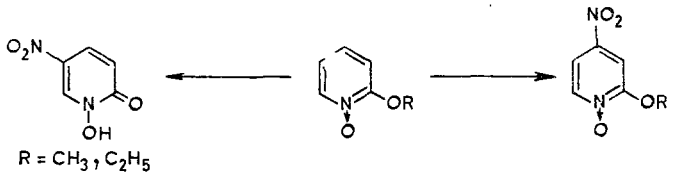
Primarily 5-nitro derivatives are formed in 60-75% yields at low temperatures, low substrate concentrations, and in concentrated sulfuric acid [37].

The nitration of 3-methyl- [38] and 5-methyl-2-HP [39] leads to the corresponding 5- and 3-mononitro derivatives.



As in the case of 3-HP, the presence of electron-acceptor nitro and carboxyl groups in the α-hydroxypyridine ring does not prevent further substitution. Thus, the 3,5-dinitro derivative is formed in the nitration of 3- and 5-nitro-2-HP [40, 41], whereas the reaction of 6-hydroxynicotinic acid with fuming HNO_3 in acetic anhydride at 50° gives 6-hydroxy-5-nitronicotinic acid [42], whereas 3,5-dinitro-2-HP is formed under more severe conditions [42]. The nitration of 2-HP was also successful when two deactivating groups were present [43, 44].

In contrast to the base, 2-HP N-oxide on nitration in acetic acid gives only the 5-nitro isomer [24, 25], which on further reaction can be converted to 3,5-dinitro-2-pyridine 1-oxide [24, 46]. As in the case of 3-HP, the N-oxide group does not have a para-orienting effect in the nitration of 2-HP, whereas 2-methoxy- and 2-ethoxypyridine N-oxides are nitrated exclusively in the 4 position [23, 24].



The nitration of 2-alkoxypyridines [47, 48] is directed primarily to the 5 position. The explanation of the absence of 3-nitro isomers in the nitration of 2-alkoxypyridines and their presence in the case of 2-HP with "chelate-forming" positions was assumed to be unlikely in view of the substitution of 2-HP in the neutral oxo form [37], which excludes the formation of a hydrogen bond with the attacking nitronium ion.

In contrast to 2- and 3-HP, the nitration of 4-HP proceeds under more severe conditions [49-53]. The reduced reactivity of 4-HP is evidently due to its primary existence in the pyridine ring with respect to aromatic substitution. The electronegative character of the NHCO fragment was demonstrated in the case of its intensifying acidic effect on the OH and COOH groups additionally present in the pyridine ring [54-56]. Nevertheless, the ease of nitration of 2- and 4-HP can be explained by the electromeric effect of the heteroatom.

Depending on the reagent ratio and the reaction conditions, 4-HP forms 3-nitro [51-53] and 3,5-dinitro derivatives [49, 50].

Similarly, 4-HP 1-oxide is nitrated to give 3-nitro and 3,5-dinitro derivatives [57]. 4-Methoxypyridine forms only the mononitro compound [58, 59]. As in the case of 2,6-dihydroxypyridine and its O-methyl ether [16, 62], the nitration of 2,4-dihydroxypyridine [60, 61] proceeds under milder conditions. In this case, 2,4-dihydroxypyridine forms 3-nitro-2,4-dihydroxypyridine; this is apparently a consequence of the existence of the hydroxy group in the 2 position in the enol form.

Similarly, 6-methoxy-2-HP, which in nonpolar solvents exists mostly in the hydroxypyridine form [16], is nitrated in the ortho position relative to the hydroxy group.

The nitration of isomeric 2-, 4-, and 3-HP was also studied in detail within a kinetic framework in order to ascertain the mechanism of this reaction. The rate profiles of the nitration of 4-HP, 4-methoxypyridine, and the 2,4,6-trimethylpyridinium cation were found to be similar, indicating that they are nitrated in the protonated form [59]. It was similarly shown that 2-methoxy-3-methylpyridine is nitrated in the protonated form, whereas the substitution of 3-nitro-4-HP, 3- and 5-methyl-2-HP, and 1,5-dimethyl-2-HP proceeds through a low concentration of the uncharged form.

At lower sulfuric acid concentrations (65-85%), the nitration of 4-HP also proceeds in the uncharged form; this is also noted during acidic deuterium exchange [63], during which the ratio of the rate constants of nitration of 4-HP in the neutral and protonated forms

was found to be 10^9, which attests to pronounced deactivation of the hydroxypyridine ring by the $\overset{+}{N}H$ group.

Evaluation of the effect of the NHCO and NMeCO fragments in 2-HP and N-methyl-2-HP shows that in nitration they deactivate the β position by a factor of 10 [59], whereas in the case of acidic deuterium exchange they activate it by a factor of 10^5 [64].

A comparison of the partial rate factors in the nitration of the cations of 4-hydroxy- and 2- and 4-methoxypyridines (10^{-10} 10^{-12}), on the one hand, and of anisole (150), on the other, made it possible to establish that the deactivating effect of the $\overset{+}{N}H$ group in this system is 10^{13} [59]. In the case of the nitration of pyridines it was shown that the compounds with pK_a 1.5 react in the uncharged form and that 4-HP (pK_a 3.27) is nitrated in the uncharged form when $H_0 > 8.2$ and in the cationic form at higher acidities.

The mononitration of 2,4- and 2,6-dimethoxypyridine proceeds in the 3 position in the protonated form, and secondary nitration occurs in the 5 position in the uncharged form [65], during which deactivation of the aromatic ring by the heteroatom amounts to 10^7, which is much smaller than the value observed for the benzene–pyridine system. This in turn was a consequence of the large activating effect of methoxy groups in the pyridine ring [65].

Like 2,6-dimethoxypyridine, its 3,5-isomer is nitrated initially in the 2 position in the protonated form, whereas nitration of 2-nitro-3,5-dimethoxypyridine in the 6 position proceeds through the neutral form [66]. A comparison of the rates of nitration of these compounds showed that the two symmetrical dimethoxypyridines have similar reactivities. On the other hand, 2,4-dimethoxynitrobenzene has a higher reactivity (a factor of $10^{3.17}$) than 3,5-dimethoxy-2-nitropyridine and 2,6-dimethoxy-3-nitropyridine (a factor of $10^{2.73}$) [66].

In contrast to 2,6-dimethoxypyridine, the nitration of 2,6-dihydroxypyridine and its 6-methyl ether proceeds in the uncharged form at a considerably higher rate [16].

It has been shown [67] that 2,6-dimethyl-4-methoxy-, 2,6-dimethoxy-, and 2,4,6-trimethoxypyridine 1-oxides undergo nitration in the protonated form. The mononitration of 3,5-dimethoxypyridine 1-oxide in the 2 position also proceeds in the protonated form [67], and it has a higher reactivity than 2,6-dimethoxy- and 2,4,6-trimethoxypyridine 1-oxides.

The nitration of 3-HP and its O-methyl ether proceeds in the protonated form, and the partial rate factors for the cation of 3-methoxypyridine were found to be $4 \cdot 10^{-1}$ and 10^{-10} for the 2 and 6 positions, respectively [16]. A comparison of these values with the partial factor for the 4-methoxypyridinium cation (10^{-12}) clearly indicated the higher reactivity of the β-pyridole ring during nitration in the cationic form. Analogous data for 2-methoxypyridine are unavailable, but the partial factor of $2.86 \cdot 10^{-10}$ found for 2-methoxy-3-methylpyridine also constitutes evidence for the higher reactivities of 2-alkoxypyridines as compared with 4-alkoxypyridines [16].

A comparison of the standard rates of nitration and isotopic hydrogen exchange of 2- and 4-HP showed that in the first case the 3 (20 times) and 5 (seven times) positions in 2-HP are more reactive, whereas 2- and 4-HP undergo acidic deuterium exchange at identical rates [68, 69].

Halogenation

The halogenation of hydroxypyridines has been studied in greatest detail.

It has been shown that 3-HP is substituted primarily in the 2 position. Bromination with an equivalent amount of bromine in pyridine [70], iodination with iodine in sodium carbonate solution [71], and chlorination with hydrochloric acid in the presence of hydrogen peroxide [71] all led to 2-halo-3-HP; the 4- and 6-halo derivatives of 3-HP were obtained only by an indirect method [70].

The iodination of 3-HP with excess iodine gives 2,6-diiodo and 2,4,6-triiodo derivatives [71]. Under the same conditions, 5-methyl-3-HP forms 2,6-diiodo-substituted compounds [72].

Similarly, bromination of 3-HP with a bimolecular amount of bromine in pyridine [70] gave the 2,6-dibromo compound, whereas 2,4,6-tribromo-3-HP is formed in the reaction with excess bromine water [70]. 2,4,5,6-Tetrabromo-3-HP was obtained by bromination of 5-bromo-3HP with excess bromine water [70].

The bromination of 3-HP N-oxide, like the bromination of the base, leads to the 2-bromo derivatives, which can be further brominated to 2,6-dibromo- and 2,4,6-tribromo-3-HP 1-oxide [73]. In contrast to this, the iodination of 3-HP 1-oxide in weakly alkaline solution gives only 4,6-diiodo-3-HP 1-oxide [74].

The 2,6-dibromo derivative is formed in the bromination of 3,5-diethoxypyridine in acidic media [75], whereas the 2-bromo-substituted compound was isolated as the principal product in pyridine.

The introduction of electronegative nitro and carboxyl groups does not prevent halogenation of the β-hydroxypyridine ring [76].

The halogenation of 2-hydroxy- and 2-alkoxypyridines proceeds extremely readily, is difficult to control in many cases, and usually gives 3,5-dihalo derivatives along with small amounts of the 5-monosubstituted compound [77-83]. This phenomenon is also characteristic for 1-methyl-2-pyridones [36, 84-90]. Thus, chlorination of 2-HP with chlorine in chloroform [91] gives a mixture of 5-chloro- and 3,5-dichloro-2-HP, and bromination with bromine water [92] and iodination with iodine monochloride [91] lead to the formation of 3,5-dihalo-2-HP. The bromination of 2-HP in glacial acetic acid also gives primarily 3,5-dibromo-2-HP [93]. The iodination of 2-HP in weakly alkaline solution [94] gave 5-iodo-2-HP (33.5%) along with the 3,5-diiodo derivative (26.5%).

N-Bromosuccinimide (NBS) reacts with 4,6-dimethyl-2-HP to give a mixture of products of bromination both in the ring and in the side chain [88].

It has been shown that N-methyl-2-HP is halogenated by chlorine [36], bromine [36, 95], and iodine monochloride in acetic acid [96] to give 3,5-disubstituted compounds.

Electronegative substituents have a weaker effect on the halogenation of 2-HP. The halogenation of 5-nitro-2-HP leads to 3-chloro and 3-iodo derivatives [97]. 6-Hydroxypicolinic acid readily forms a 2,5-diiodo-substituted compound in weakly alkaline solution [79].

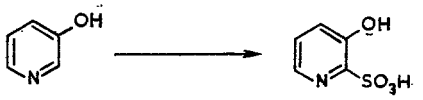
Like the 2 isomer, 4-HP also is readily halogenated to give primarily 3,5-disubstituted compounds. Thus, 3,5-dibromo- and 3,5-diiodo-4-HP are formed in the bromination of 4-HP with bromine water [98] and iodination with iodine monochloride in xylene [99]. Similarly, the 3,5-diiodo derivative was obtained in quantitative yield by heating 2,6-dimethyl-4-HP with iodine monochloride in hydrochloric acid [100]. 3-Iodo-4-HP was isolated in the iodination of 4-HP in weakly alkaline solution [94]. The presence of a carboxyl group does not prevent halogenation of 4-HP. Thus, 4-hydroxypicolinic acid forms 3,5-dihalo derivatives in the case of chlorination and iodination in alkali or bromination with bromine water [99].

2,4-Dihydroxypyridine is brominated to give both 3-bromo [60] and 3,5-dibromo derivatives [101], depending on the reagent ratio.

Sulfonation

Less study has been devoted to the sulfonation of hydroxypyridine than to other electrophilic reactions because of the low reactivity of the hydroxypyridine ring in this reaction.

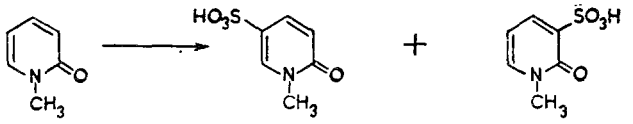
3-Hydroxypyridine is sulfonated under extremely severe conditions to give 3-hydroxypyridine-2-sulfonic acid in low yield [102, 103].



Similarly, 3-HP N-oxide is sulfonated in the 2 position [104].

In contrast to the 3 isomer, 2-HP does not undergo sulfonation at all, and the corresponding 5-sulfonic acid was obtained by diazotization of 2-aminopyridine-5-sulfonic acid [105, 106]. The latter is formed when quaternary salts of N-methyl-2-pyridone and 2-ethoxypyridine are heated with dimethyl sulfate at 200° [106, 107].

A mixture of 3- and 5-sulfonic acids is formed when 1-methyl-2-pyridone is heated with fuming sulfuric acid [108].



However, only the 5-sulfonic acid is obtained in high yield in the sulfonation of 1-methyl-2-pyridone with chlorosulfonic acid [108]. Chlorosulfonic acid was also used for the sulfonation of 1-methyl-5-nitro-2-pyridone in the 3 position.

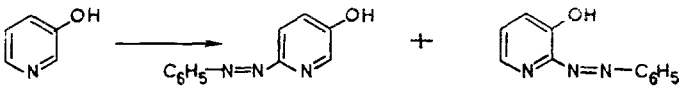
4-Hydroxypyridine is sulfonated by fuming sulfuric acid in the 3 position, but the yield was not indicated, and proof for the structure of the sulfonic acid obtained was not presented [109].

2,5-Di-tert-butyl-4-ethoxypyridine is sulfonated in the 3 position when sulfur trioxide is used as the sulfonating agent [110].

Diazo Coupling

As in the case of phenol, the diazo coupling of hydroxypyridine proceeds with the same ease and takes place primarily in the para position relative to the hydroxy group. Thus, the principal product of diazo coupling of 3-HP with benzenediazonium chloride is 6-phenylazo-3-HP (81%), along with a small amount of the 2-isomer (3%) [111]. Initially only the 2-azo derivative was isolated in the reaction of 3-HP with p-nitrobenzene diazonium chloride in weakly acidic solution [112]. A subsequent study of this reaction made it possible to establish the formation of 2- and 6-azo derivatives of 3-HP in different amounts [113].

On the other hand, the primary formation of the para isomer was noted when the indicated reaction was carried out under weakly alkaline conditions; the yield of the ortho isomer in this case was 13%.



Like 3-HP, diazo coupling of its N-oxide [114] in weakly acidic solution was directed to the 6 position.

A mixture of the o- and p-azo derivatives in equal amounts is formed in the diazo coupling of 5-phenyl-4-methyl-3-HP with benzenediazonium chloride [113]. The diazo coupling of 2- and 6-methyl-3-HP and their N-oxides gave only the 6- and 2-azo derivatives, respectively [115].

The absence of 4-substitution was common to the diazo coupling of both the 2- and 6-methyl derivatives and 2,6-dimethyl-3-HP with benzenediazonium chloride [115]. However, the introduction of an N-oxide group made it possible to effect smooth diazo coupling at the 4 position in the case of 2,6-dimethyl-3-HP 1-oxide [114].

The diazo coupling of 2-HP is directed to the para position relative to the OH group [116], whereas 2,6-dihydroxypyridine [117] and 4-methyl-2,6-dihydroxypyridine [118] are substituted in the 3 position. The diazo coupling of 2,3- and 2,5-dihydroxypyridine, as well as 2-methoxy-3-HP and N-methyl-3-hydroxy-2-pyridone, is directed to the 6 position [119]. This indicates that the β-hydroxy group is the principal orienting group in substitution in all of the compounds.

Aminomethylation

Hydroxypyridines in the anionic form undergo a number of reactions with weak electrophiles that are characteristic for phenolic compounds. Here one should primarily include aminomethylation, hydroxymethylation, and carboxylation.

The aminomethylation of isomeric hydroxypyridines clearly revealed the features of their chemical behavior due to the differences in the tautomeric equilibria of the indicated compounds.

3-Hydroxypyridine, which retains its phenolic properties to the maximum degree, readily undergoes Mannich condensation [120-122] with dialkylamines, arylalkylamines, and heterocyclic amines.

The strong electron-acceptor effect of the ring nitrogen atom, which considerably reduces the electron density in the aromatic ring, particularly in the 2, 4, and 6 positions, leads to a decrease in the reactivity of 3-HP in the Mannich condensation as compared with phenols. Thus, in contrast to phenol, which readily forms a trisubstituted Mannich base, 3-HP is aminomethylated [122] only in the 2 and 6 positions. In addition, the combination, in a single molecule, of a hydroxy group attached to a conjugated cyclic system of bonds and a ring nitrogen atom changes the sequence of substitution from ortho-ortho-para, as in the case of phenols, to ortho-para-ortho in the case of 3-HP.

The success observed in the aminomethylation of 3-HP depends markedly on the pH of the medium [123]. Whereas phenols are readily aminomethylated in both acidic and weakly alkaline media, the highest yields of Mannich bases in the case of 3-HP are obtained when the reaction is carried out in weakly alkaline media.

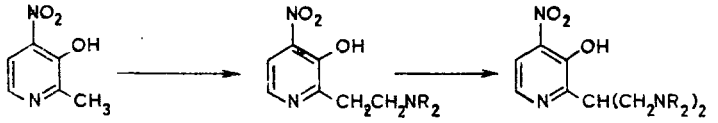
The different reactivities of the 2, 6, and 4 positions of the β-pyridol ring in the Mannich condensation make it possible to realize their successive selective substitution.

4-Aminomethylation is possible only for 3-HP containing an alkyl [124-126] or alkoxy group [127] in the 2 position and, in a number of cases, requires the application of more severe reaction conditions. An attempt to obtain 4-substituted compounds by aminomethylation of 6-alkyl-2-dialkylaminomethyl- and 2,6-bis(dialkylaminomethyl)-3-HP did not give positive results. This made it possible to conclude that the presence in the ortho position relative to the hydroxy group of a substituent that forms a strong intramolecular bond with the OH group sharply reduces the reactivity of the 4 position in the Mannich condensation.

The introduction of an N-oxide group did not affect the orientation of aminomethylation but somewhat increased the reactivity of the β-pyridol ring [128].

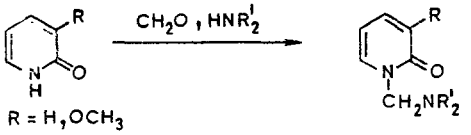
The presence of a nitro group in the 2 position of the β-pyridol ring did not hinder 6-aminomethylation of 2-nitro-3-HP [129].

However, aminomethylation of 4-nitro- and 2-nitro-6-methyl-3-HP was directed to the side chain rather than to the ring [130]. Thus, 2- and 6-(β-dialkylaminoethyl) derivatives, the subsequent aminomethylation of which led to Mannich double bases involving the methyl group, have been synthesized [130].



In contrast to the 3 isomer, 2-HP displays phenolic properties to an even lesser degree. This was reflected in the different character of the aminomethylation of 2-HP. The corresponding N-substituted Mannich bases, which were readily decomposed on refluxing with water with the evolution of formalin [131], were obtained by heating 2-HP with an equimolar mixture of secondary amine and paraformaldehyde in a sealed tube.

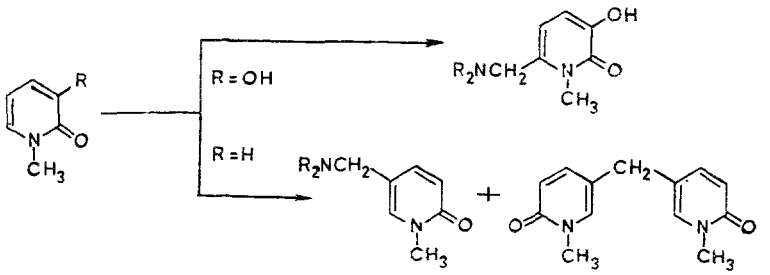
Similar results were also obtained in the aminomethylation of 3-methoxy-2-HP.



On the other hand, a 6-monosubstituted base is initially formed in the aminomethylation of 2,3-dihydroxypyridine [131] and 2-methoxy-3-HP [127], after which a 4,5-substituted double Mannich base is formed [127]; this indicates the decisive role of the β-hydroxy group in the orientation of substitution.

The aminomethylation of N-methyl-2-HP occurred with the formation of a 5-monosubstituted Mannich base in low yield (11%), along with 5,5-methylenebis(1-methyl-2-pyridone) (22%). In this case, 60% unchanged N-methyl-2-HP was isolated [132].

The aminomethylation of N-methyl-3-hydroxypyridone [133], like that of 2,3-dihydroxypyridine, proceeds under mild conditions in quantitative yield and is directed to the 6 position [133].



Like 2,3-dihydroxypyridine, the β-hydroxy group, which directs aminomethylation to the 6 position, is also the principal orienting group of electrophilic substitution in 2,5-dihydroxypyridine [133]. Attempts to realize 4,6-bis(aminomethylation) were unsuccessful.

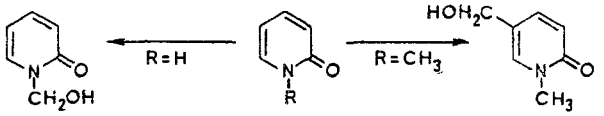
As we have already noted, 4-HP exists in the pyridone form to an even greater extent than the 2 isomer. This fact should evidently explain the unsuccessful attempts to aminomethylate 4-HP.

Hydroxymethylation

The ready controllability of hydroxymethylation of 3-HP, in contrast to the rapid polymerization of phenols under similar conditions, served as yet another graphical example of the deactivating effect of a ring nitrogen atom on the reactivity of the aromatic ring.

3-Hydroxypyridine is efficiently hydroxymethylated on treatment with an alkaline solution of formaldehyde [134-136]. In this case one obtains a mixture of mono- and disubstituted products, the formation of which cannot be avoided, even when equimolar reagent ratios are used. Hydroxymethylation in the 6 and 2 positions, respectively, is observed in the case of 2- and 6-methyl-3-HP [124, 137]. 4-Substitution was not observed in a single case, even in the hydroxymethylation of 2,6-dimethyl-3-HP [123].

Like aminomethylation, the hydroxymethylation of 2-HP takes place at the ring nitrogen atom [138]. If a substituent (alkyl group) is attached to the ring nitrogen atom, hydroxymethylation is directed to the ring [139].



Information on the hydroxymethylation of 4-HP is not available in the literature.

Carboxylation

Hydroxypyridines in the anionic form also undergo the Kolbe reaction with CO_2 under pressure that is also characteristic for aromatic phenols. However, in contrast to phenol, which forms primarily o-substitution products, the carboxylation of 2- and 3-HP occurs primarily in the para position. Thus, 5-hydroxypicolinic acid is formed in 85-87% yield when 3-HP is heated with potassium carbonate in a ratio of 1:1.5 at an initial CO_2 pressure of 40 atm [112, 140]. Carboxylation of the sodium or potassium salt of 3-HP gives low yields of 3- and 5-hydroxypicolinic acids, and the sodium salt undergoes substitution primarily in the ortho position, whereas the potassium salt undergoes substitution primarily in the para position of the β-pyridol ring [112, 141]. 2-Methyl-3-HP [142] is carboxylated in the 6 position, whereas 5-methyl-3-HP forms an acid of unestablished structure [143].

Carboxylation of 2-HP with potassium carbonate and CO_2 at 50 atm and 200° leads to the p-substituted acid in 60% yield [144, 145].

Depending on the reaction conditions, 4-HP undergoes carboxylation to give 3-mono- and 3,5-dicarboxylic acids [146].

Other Reactions of Hydroxypyridines

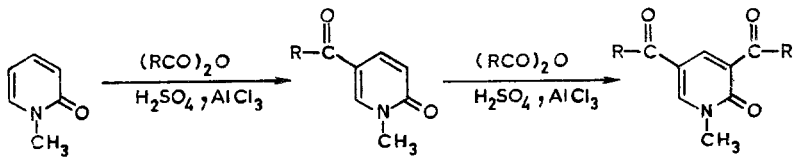
The mercuration of 2-, 3-, and 4-HP with mercuric acetate in water has been investigated [147]: 2-HP gives a 3,5-disubstituted derivative, 3-HP gives a 2-mercuriacetate, and 4-HP gives a 3-mercuriacetate.

2-Hydroxypyridine was efficiently arsenated when it was fused with arsenic acid. Brief heating (5 h) leads to the primary formation of the 5 isomer, whereas the 3 isomer is formed on prolonged fusion (24 h) [148, 149]. Fusion of 1-methyl-2-pyridone with arsenic acid at 210° gave the 3 isomer [149], whereas a number of other 1-substituted 2-pyridones gave the 5 isomers [150].

One of the confirmations of the pronounced deactivation of the aromatic ring by a heteroatom is the low reactivities of hydroxypyridines in Friedel–Crafts reactions, which are particularly sensitive to the deactivating effect of a ring nitrogen atom as compared with other electrophilic reactions. The possibility of benzylation and cyclohexylation of 2-HP, N-ethyl-2-pyridone, and 4-ethoxypyridine was demonstrated very recently. 2-Benzyloxy-3-benzylpyridine, along with N-benzyl-2-pyridone (52% yield), and 2-cyclohexyloxy-3-cyclohexylpyridine, along with N-cyclohexyl-2-pyridone (30% yield), respectively, are formed in the reaction of 2-HP with benzyl chloride or chlorocyclohexane in the presence of $AlCl_3$ at 180° [151, 152]. Under similar conditions, N-ethyl-2-pyridone forms a mixture of 3- and 5-benzyl-substituted products, whereas only the 3-benzyl-substituted product is formed on more prolonged heating [153].

4-Ethoxypyridine also reacts with benzyl chloride or chlorocyclohexane in the presence of $AlCl_3$ to give 3-benzyl-N-ethyl-4-pyridone (maximum yield 60%) or 3-cyclohexyl-4-ethoxypyridine (17% yield), respectively [154, 155].

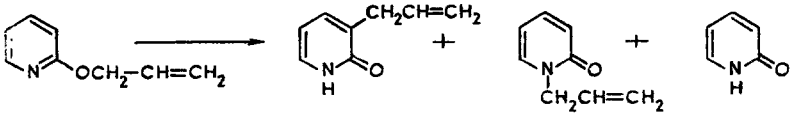
In contrast to alkylation, Friedel–Crafts acylation gave the desired result [156, 157] only with N-methyl-2-pyridone. Better yields of the acylation products were obtained when benzoyl [157] and cyclohexanecarbonyl chloride [156] were used; in this case a mixture of the 3 and 5 isomers and a small amount of 3,5-dibenzoyl-N-methyl-2-pyridone are formed (see Table 1). The yields of acylation products were also low in the case of acylation with acid anhydrides. However, acylated compounds were obtained in relatively high yields in the reaction of 1-methyl-2-pyridone with anhydrides in the presence of H_2SO_4 (Table 1) [156].



The reaction of triphenylchloromethane or triphenylcarbinol with 2-hydroxypyridine and its N-methyl-substituted derivative, as a result of which 5-triphenylmethyl-2-HP was obtained, has also been described [158].

Fries rearrangement of 2-HP o-benzoate gave 5-benzoyl-2-HP in only 1% yield [158].

Claisen rearrangement in the presence of a tertiary amine or in the absence of a solvent was studied in the case of 2-alkoxypyridines [159, 160].



Nitrosation, which is an example of a substitution reaction that is sensitive to the deactivating effect of electron-acceptor substituents, also does not occur with 2-, 3-, and 4-HP. In contrast to pyridines that contain one hydroxy group, dihydroxypyridines readily undergo nitrosation. The nitrosation of 2,5-dihydroxypyridine [113] is directed to the 6 position, whereas the nitrosation of 2,6-dihydroxypyridine [161] is directed to the 3 position.

4-Methyl-3-phenyl-2,5-dihydroxypyridine is nitrosated in the pyridine ring [113], and this constitues evidence for its higher reactivity as compared with the phenyl group.

Quantum-Chemical Calculations of the Reactivity Indexes of Hydroxypyridines

The application of molecular orbital theory has made it possible to predict the orientation of entering substituents in pyridine and its derivatives. Calculations of the

TABLE 1

R	Position of RCO	Yield of acylation product, %		
		$AlCl_3$, RCOCl	$AlCl_3$, $(RCO)_2O$	H_2SO_4, $(RCO)_2O$
CH_3	5	—	1,9	34,3
C_2H_5	5	4,4	2,8	66,4
	3,5	—	—	2,5
C_3H_7	3	6,0	—	—
	5	3,6	10,3	75,9
	3,5	—	2,0	7,4
C_4H_9	5	14,7	17,1	70,4
	3,5	—	2,3	3,0
C_6H_{11}	3	13,1	—	—
	5	32,8	—	—
$C_6H_5CH_2$	3	12,4	—	—
	5	30,9	—	—
	3,5	3,8	—	—

reactivity indexes (RI) of 2-, 3-, and 4-HP molecules have been carried out within the approximation of both isolated and reacting molecules [162-164]. An analysis of the calculated RI of the 3-HP molecule in four forms (anionic, dipolar, neutral, and cationic) showed that the best agreement with the experimental data was observed for localization energy L_e [162]. In accordance with the L_e, the electrophilic attack of the 3-HP molecule in acidic and alkaline media should proceed in the order 2 > 6 > 4. In addition, a comparison of the L_e values for the anionic and cationic forms provides evidence for the higher reactivity of the anionic form. The calculated localization energies for the carbon atoms of 2- and 4-HP indicate that electrophilic agents should attack the hydroxypyridine molecules in the 3 and 5 positions. In the case of 2-HP the 3 and 5 positions are not equivalent, and the 3 position is the most reactive.

A comparison of the localization energies of the oxo and hydroxy forms of 2- and 4-HP indicates that the corresponding localization energies of the hydroxy forms are substantially higher than for the oxo forms. It follows from this that hydroxypyridines in neutral media react to give a transition complex corresponding to the lactam form.

The results of calculations of the RI of the protonated forms of 2- and 4-HP indicate that, in conformity with the experimental data, the 3 and 5 positions are the sites of electrophilic attack.

The results of the calculation of the anionic forms of 2- and 4-HP indicate the same sequence of substitution and are also in agreement with the experimental data [93].

A comparison of the localization energies on the corresponding atoms of 2- and 4-HP in reactions of the same type provides evidence that all of the aromatic substitution reactions for 2-HP should proceed more readily than for 4-HP, i.e., the former is more aromatic than the latter. This is in complete agreement with data on the reactivities of the indicated compounds in acidic deuterium exchange and nitration [68, 69].

Agreement between the experimental results and the calculated localization energies was also noted for various forms of the 2,3- and 2,5-dihydroxypyridine molecules [165, 166] and 2-methyl- and 2-benzoyl-3-HP [167].

Thus, the results of calculation of the reactivities of hydroxypyridines by the Hückel MO method are in good agreement with the experimental data and can be used to predict the direction of as yet uninvestigated reactions of hydroxypyridines and their derivatives.

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LIQUID-PHASE FREE-RADICAL ISOMERIZATION OF CYCLIC ACETALS

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1,3-Dioxacyclanes are converted to esters in the presence of di-tert-butyl peroxide. The reaction is described by the kinetic equation of an unbranched chain reaction with quadratic chain termination. It is shown that five-membered acetals are more reactive than seven- and six-membered acetals. The introduction of hydrocarbon groups in the 2 position of the ring increases the reactivity. It is concluded that the primary site of attack by the alkyl radical is the methylene or methylidyne group adjacent to the two heteroatoms.

It has previously been shown [1] that 1,3-dioxane is converted to the isomeric propyl formate in the presence of di-tert-butyl peroxide (DTB) via a mechanism involving an unbranched chain reaction.

To study the effect of the ring size and the nature of the substituents on this reaction, we investigated the kinetics of the liquid-phase free-radical isomerization of a number of 1,3-dioxacyclanes.

Cyclic acetals I-VI are converted to the isomeric esters at rate W_{est} during which the $W_{est}/\sqrt{W_{alc}}$ ratio (W_{alc} is the rate of formation of tert-butyl alcohol, which reflects the rate of initiation) remains satisfactorily constant over the range of change in DTB concentrations from 0.05 to 0.70 mole/liter (Table 1). From this it follows that the esters are formed via an unbranched radical-chain mechanism with quadratic chain termination.

The rate of formation of the esters increases linearly as the substrate concentration increases (Fig. 1), and this indicates participation of one acetal molecule in the rate-

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