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The Structure and Reactivity of 3-Hydroxypyridine Derivatives in Electrophilic Substitution

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The structure and reactivity of 3-hydroxypyridine and its derivatives in electrophilic substitution are considered and the problems concerning the mechanism and direction of electrophilic substitution in 3-hydroxypyridines are discussed as a function of the type of reaction, its conditions, and the nature of the substituent in the 3-hydroxypyridine ring. The reactivities of 3-hydroxypyridines are compared with the results of theoretical calculations by the Hückel molecular orbital and the Pariser - Parr - Pople method. Data for the biological activities of various 3-hydroxypyridine derivatives are presented.
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I. INTRODUCTION

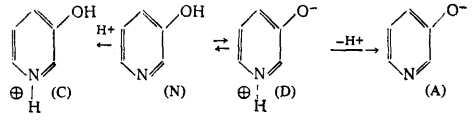
The number of studies dealing with the search for physiologically active compounds based on biogenic antioxidants has greatly increased in recent years. Academician N. M. Emanuel''s concept of the possibility of suppressing by non-toxing inhibitors undesirable free-radical reactions occurring in the organism in pathological states, in particular during malignant growth, radiation sickness, stress phenomena, and ageing, has served as a basis for the medico-biological application of these compounds[1-3]. Emanuel' suggested that phenol and polyphenol derivatives are suitable as inhibitors for this purpose. Numerous studies on the biological activity of these compounds showed that they exhibit pronounced antitumour properties and confer protection from radiation[4-6]. This stimulated further development of synthetic studies in this field. The structural difference between a number of the most effective phenolic antioxidants and the fragments of biochemical systems involved in cell metabolism, as a result of which the former are hydrophobic and possess a number of other undesirable properties, constituted an obstacle to their application in biology. In the attempts to overcome these obstacles, several ways were proposed for the synthesis of new phenolic compounds transformed as a result of the mono- and di-*ortho*-screening of the hydroxy-group. Substituted *p*-hydroxyphenylanilines, their decarboxylation products (tyramines and epinines) related to the alkaloid mescaline, *p*-hydroxybenzylamines structurally related to the precursor of the alkaloid capsaicin, and a number of arylaminobutyric acids and pyrrolidinones have been synthesised[7-10]. However, the amino-group, which ensures hydrophilic properties is as a rule also responsible for an increase in toxicity.

In order to find effective biogenic inhibitors, we undertook a study of heterocyclic hydroxy-derivatives. We chose for investigation 3-hydroxypyridine derivatives, the inhibiting properties of which might be due to the presence of the phenolic hydroxyl next to the conjugated cyclic bond system, and their structural similarity to compounds of the vitamin B_6 group (pyridoxine, pyridoxamine, and pyridoxal) ensured that the preparations synthesised were biogenic. Furthermore, the presence of the ring nitrogen atom together with the hydroxy-group made it possible to obtain water-soluble compounds as a result of salt formation. The synthesis of a large number of non-toxic and water-soluble inhibitors with biological activity was based on electrophilic reactions of 3-hydroxypyridine and its derivatives.

Attention is therefore concentrated in the present review on the characteristics of the structure and reactivity in electrophilic substitution of 3-hydroxypyridine and its derivatives.

II. ELECTRONIC STRUCTURE OF 3-HYDROXYPYRIDINE AND ITS DERIVATIVES

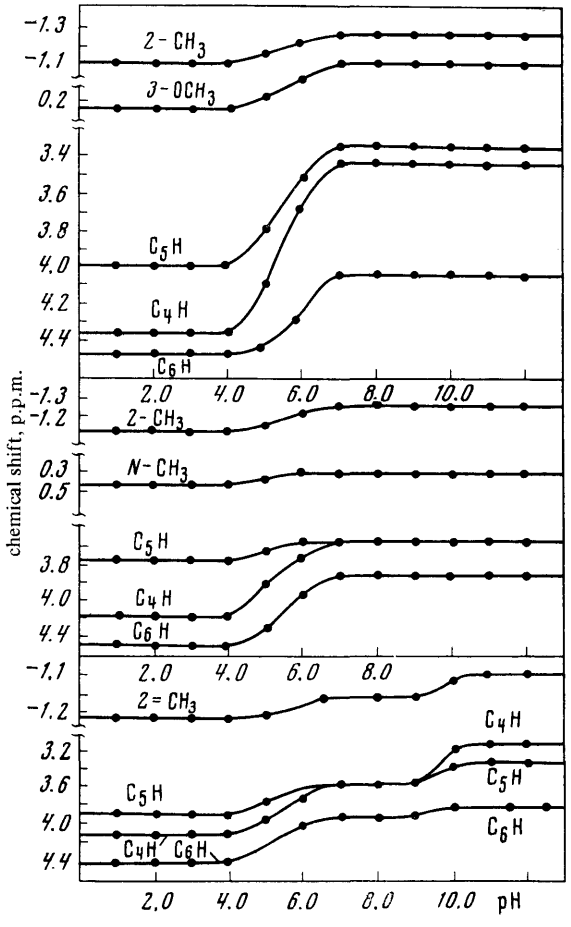
One of the characteristics of the 3-hydroxypyridine molecule, in contrast to aromatic phenols, is its ability to exist in four forms as a function of the pH of the medium: neutral (N), dipolar (D), cationic (C), and anionic (A), which is clearly reflected in the physicochemical properties and chemical behaviour of 3-hydroxypyridines in electrophilic substitution:



The presence of the dipolar form in a neutral medium was established by ultraviolet spectroscopy[11,12], potentiometric titration[13-15] as well as infrared spectroscopy and ^1H NMR.[16-18] It has been shown that in D_2O solution there is 54% of form (D) and 46% of form (N), while in pure dioxan form (D) is virtually absent[11].

The introduction of an alkyl, benzyl, or phenyl group into the 3-hydroxypyridine molecule does not decrease the possibility of the formation of all four forms. On the

contrary, the formation of the *N*-oxide of 3-hydroxypyridine has a significant influence on the acid–base equilibrium. The absence of form (D) of 3-hydroxypyridine *N*-oxide and a number of its derivatives in a neutral aqueous solution has been demonstrated by ultraviolet spectroscopy[19-20]. The limits of the existence of forms (A), (D), (N), and (C) of 3-hydroxypyridine and its derivatives were studied by ^{1}H NMR [18,21-22]—by investigating the dependence of the chemical shifts of the 3-hydroxypyridine ring protons on the pH of the medium†. The presence of three horizontal sections corresponding to the acid, neutral, and alkaline media (see Figure) has been noted and it has been shown that the ring nitrogen is fully protonated at pH < 4 and the ionisation of the OH group terminates at pH > 10.



Variation of the proton chemical shift (in p.p.m.) with the pH of the medium for different 3-hydroxypyridine derivatives: *a*) 3-hydroxy-2-methylpyridine; *b*) 3-hydroxy-2-methylpyridinium methiodide; *c*) 3-methoxy-2-methylpyridine.

† The results obtained for 3-hydroxy-2-methylpyridine are quoted as an example. The findings obtained for a large number of related compounds are similar.

The curves for aminomethyl derivatives of 3-hydroxypyridine in an acid medium have two horizontal sections due to the possibility of the protonation of two centres: the ring nitrogen and the nitrogen in the side chain.

The electronic structure of 3-hydroxypyridine has been the subject of a detailed study using quantum-chemical calculations and ^{1}H NMR data. Calculations of the electronic structure parameters of 3-hydroxypyridine [the energy of π-electron delocalisation E_π^d, the energies of the highest occupied and lowest vacant molecular orbitals (HOMO and LVMO), and the energy differences ΔE between them, the electronic charges, and bond lengths] were performed using the simple and extended molecular orbital methods[23-25] as well as the Pariser–Parr–Pople method[26]. The calculated values of E_π and E_π^d of forms (N), (A), (D), and (C) differ comparatively little from one another (Table 1). As was to be expected, the values of E_π^d for the forms containing exocyclic anionic oxygen are somewhat higher than for the hydroxy-forms.

Table 1. The energy characteristics of the electronic structure of 3-hydroxypyridine.

Form	E_π	E^d	E_{HOMO}	E_{LVMO}	ΔE
Neutral	11.975	1.917	0.564	0.894	1.458
Dipolar	10.960	2.199	0.459	0.785	1.244
Anionic	10.438	2.169	0.487	0.894	1.381
Cationic	12.482	1.988	0.630	0.786	1.416

The interaction of exocyclic oxygen with the pyridine ring is indicated by the C–O bond order, which is 0.295–0.394, and the π-electronic charge (+0.082–+0.146). The conjugation of the oxygen in the anionic form is much more marked than that of the hydroxyl oxygen: the PyC–O$^-$ bond order is 25% greater than the PC–OH bond order and the π-electronic charge on the anionic oxygen is almost twice as high as on the phenolic oxygen. The conclusion that the exocyclic oxygen interacts with the aromatic ring agrees with X-ray diffraction data, according to which the C–O bond length in phenol derivatives (1.37 Å) is smaller by approximately 0.1 Å than in saturated compounds (1.47 Å).[27] The calculated bond orders in the pyridine ring are high and similar, which may be attributed to the high degree of aromaticity of the ring and equalisation of its bonds. The interatomic distances in the four forms of 3-hydroxypyridine agree well with the available experimental lengths of the C⋯C bonds in benzene (1.397 Å), the C–N bonds in pyridine (1.34 Å), and the C–O bonds in phenols (1.37 Å) as well as the bond lengths in the ring of nicotinic acid as a model compound[28]: r_{CN} = 1.34 Å and r_{CC} = 1.39 Å.

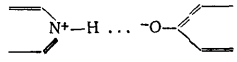
The π-electron density distribution in the 3-hydroxypyridine ring is non-uniform largely because of the presence of the ring nitrogen atom and the exocyclic oxygen atom. In consequence of the high electronegativity of the nitrogen atom (3.0) compared with that of carbon (2.5), a considerable negative π-electronic charge (–0.192) is concentrated on the nitrogen atom of the phenolic and anionic forms. As was to be expected, protonation of the nitrogen atom leads to a marked increase of the negative π-electronic charge on the nitrogen atom (–0.394) and its corresponding decrease on the carbon atoms.

Quantum-chemical calculations by the Pariser–Parr–Pople method were also used for a quantitative interpretation of the electronic absorption spectra of 3-hydroxypyridine[29,30]. All the observed absorption bands were assigned to $\pi-\pi^*$ transitions. A satisfactory correlation has been observed between the calculated and experimental absorption bands for both neutral and anionic forms.

The influence of the substituent on the electronic structure of the 3-hydroxypyridine ring was studied by ^{1}H NMR and quantum-chemical calculations of the electronic structure of alkyl and aminomethyl derivatives of 3-hydroxypyridine[23]. The distribution of electron density in the 3-hydroxypyridine ring was found to have the following characteristics.

1. In an inert medium the electron density at the carbon atoms increases in the sequence $C_{(6)} < C_{(2)} < C_{(4)} < C_{(5)}$.
2. In an aqueous medium the sequence remains the same.
3. In an alkaline medium the electron density increases in the sequence $C_{(5)} < C_{(6)} < C_{(2)} < C_{(4)}$, while in an acid medium the sequence becomes $C_{(4)} < C_{(6)} < C_{(2)} < C_{(5)}$.
4. On passing from inert and aqueous media to an acid medium, the electron density at the carbon atoms diminishes, the decrease becoming more pronounced in the sequence $C_{(5)} < C_{(2)} \leq C_{(6)} < C_{(4)}$.
5. On passing from an inert to an alkaline medium, the electron density increases. The most marked increase is observed for $C_{(6)}$ and then for $C_{(2)}$, $C_{(4)}$, and $C_{(5)}$.

Comparison of the experimental data for an inert medium with the charges calculated by the LCAO-MO method showed that the best agreement is achieved with the results of calculations for molecules in an uncharged form, where the charge increases in the sequence $C_{(6)} \leq C_{(2)} < C_{(4)} < C_{(5)}$. The calculation for the dipolar form led to another sequence: $C_{(4)} < C_{(6)} < C_{(5)} < C_{(2)}$, which agrees well with the sequence of the chemical shifts calculated for the dipolar form in an aqueous medium. This shows that in solutions in inert solvents (dimethyl sulphoxide and dioxan) the 3-hydroxypyridine molecules exist mainly in the uncharged form. However, in concentrated solutions, association complexes of the type



may make a major contribution in view of the existence of powerful intermolecular hydrogen bonds.

Direct comparison of the chemical shifts and the calculated charges for the entire series of test compounds revealed a very approximate agreement. The reason for the observed discrepancy is, apart from the approximate nature of the Hückel method, the influence on screening by factors such as dipole moments and the anisotropy of the diamagnetic susceptibility of the C–N, C–O, C–CH_3, and other bonds. However, in calculations on the electronic structure of 3-hydroxypyridine by the extended Hückel method[25] a satisfactory agreement was obtained between the chemical shifts and the calculated charges in the above series of compounds. Since the mode of electrophilic substitution reactions of heterocyclic compounds is determined by the state of the electron cloud in the molecule, as for aromatic compounds, the application of the molecular orbital theory made it possible to predict the substitution sites in the pyridine series and its derivatives. The reactivity indices for 3-hydroxypyridine were calculated both for the isolated molecule (π-electron densities, boundary electron densities, free valence index) and the reacting molecule (localisation energy) approximations[24]. Analysis of the calculated reactivity indices of 3-hydroxypyridine in the four forms (A), (D), (N), and (C) showed that the best agreement with experiment is observed for the localisation energies L_e. According to the values of L_e, electrophilic attack on the 3-hydroxypyridine molecule in acid and alkaline media should occur in the sequence $C_{(2)} > C_{(6)} > C_{(4)}$. Comparison of the values of L_e for forms (A) and (C) indicates a greater reactivity of the former.

III. ELECTROPHILIC REACTIONS OF 3-HYDROXYPYRIDINE DERIVATIVES

1. Acid- and Base-catalysed Deuterium Exchange

The electrophilic deuteration reaction of nitrogen-containing heterocycles has been widely used to elucidate the mechanism of electrophilic substitution in these compounds and also to obtain a quantitative estimate of the influence of the ring nitrogen and of a wide variety of functional substituents on the reactivity of the heteroaromatic ring[31–37].

Acid-catalysed deuterium exchange involving 3-hydroxypyridine and its alkyl derivatives made it possible to determine the sequence and rates of substitution of various positions in the 3-hydroxypyridine ring[38]. It was found that the 2-position is the most reactive while the 4-position is the least reactive. The introduction of the *N*-oxide group greatly increases the reactivity of the 2-position. For example, it has been shown[33] that 3-hydroxypyridine *N*-oxide is deuterated in the 2-position in the uncharged form, whereas both 3-hydroxy- and 3-methoxy-pyridines are not involved in the exchange under analogous conditions. On the other hand, 3,5-dimethoxypyridine *N*-oxide enters into the exchange reaction and both the 2- and 6-positions in the neutral or protonated form are involved, depending on the acidity of the medium. The ratio of the rates of deuterium exchange involving the uncharged and protonated forms is 1000, which constitutes an excellent demonstration of the powerful deactivation of the pyridine ring on protonation of the ring nitrogen.

On passing from acid-catalysed to base-catalysed deuterium exchange involving 3-hydroxypyridine, there is an appreciable increase of the rate of exchange of the protons of the 3-hydroxypyridine ring, probably owing to the involvement of the latter in this type of substitution in the most reactive anionic form[39,40]. In contrast to acid-catalysed deuterium exchange, where the exchange of the 3-hydroxypyridine ring protons was not observed, in the base-catalysed process the $H_{(2)}$, $H_{(6)}$, and $H_{(4)}$ protons may be exchanged, depending on the conditions (Table 2). The introduction of the CH_3 group in the 2-position and particularly in the 6-position increases the reactivity of the 3-hydroxypyridine ring[39].

Comparison of the rate constants for the exchange of the ring protons of 3-hydroxypyridine and its *N*-oxide (Table 2) shows that the introduction of the *N*-oxide group also accelerates proton exchange in the sequence $H_{(2)} > H_{(6)} > H_{(4)}$. A similar behaviour was likewise observed when deuterium-exchange data were compared for 3-hydroxy-2-methylpyridine and its *N*-oxide[40]. Comparison of the results for base-catalysed deuterium exchange involving 3-hydroxypyridine and its derivatives established that the rate of exchange of the $H_{(2)}$ proton is higher by an order of magnitude than the rate of exchange of the $H_{(6)}$ proton and higher by approximately two orders of magnitude than the rate of exchange of the $H_{(4)}$ proton.

2. Nitration

The hydroxy-group facilitates substitution in the pyridine ring. In contrast to pyridine, the nitration of hydroxypyridine proceeds smoothly and in high yields. Nitration of 3-hydroxypyridine proceeds exclusively in the 2-position. 3-Hydroxypyridine reacts in the protonated form[41]. The first study of the nitration of 3-hydroxypyridine was carried out by Plazek and Rodgwald[42], who obtained 3-hydroxy-2-nitropyridine and demonstrated its structure by a series of chemical transformations. In a later investigation the 6-nitro-isomer was obtained in a negligible yield (1%) together with the 2-isomer (74%):[43]

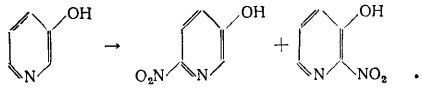
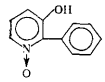
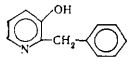
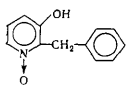
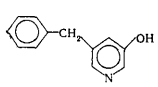
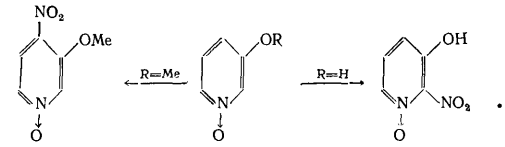


Table 2. The rate constants for the base-catalysed deuterium exchange involving 3-hydroxypyridine, its 2-methyl, 2-phenyl, 2-benzyl, and 5-benzyl derivatives, and their *N*-oxides at 160°C in 0.5*N* NaOD solution[40].

Compound	k_2, min^{-1}	k_6, min^{-1}	k_4, min^{-1}
	$1.1\cdot10^{-2}$	$1.2\cdot10^{-3}$	$5.1\cdot10^{-4}$
	$2.3\cdot10^{-2}$	$2.5\cdot10^{-3}$	$9.0\cdot10^{-4}$
	—	$3.7\cdot10^{-3}$	—
	—	$6.0\cdot10^{-3}$	$1.6\cdot10^{-3}$
	—	—	$7.8\cdot10^{-4}$
	—	$1.6\cdot10^{-3}$	$1.5\cdot10^{-3}$
	—	$4.6\cdot10^{-3}$	$1.0\cdot10^{-3}$
	$7.1\cdot10^{-3}$	$1.5\cdot10^{-3}$	$6.0\cdot10^{-4}$

Such selective substitution in the 2-position of the 3-hydroxypyridine ring is probably caused by the significant influence of the six-membered chelate complex of the hydroxy-group and the nitronium ion, formed in the transition state, on the site of substitution[44].

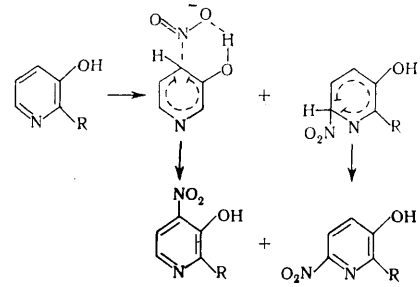
3-Hydroxypyridine *N*-oxide is nitrated similarly in the 2-position, which indicates a more powerful directing effect of the 3-hydroxy group than the *para*-directing effect of the *N*-oxide group[45]:



On the other hand 3-alkoxypyridine *N*-oxides are nitrated exclusively in the 4-position[46,47], which shows that the *para*-directing influence of the *N*-oxide group predominates.

In contrast to the base *N*-oxide, 3-methoxy-[48,49] and 3-ethoxypyridines[50] give rise to the 2-nitro- and 2,6-dinitro derivatives depending on the experimental conditions. 3,5-Diethoxypyridine *N*-oxide is also nitrated in the 2- and 6-positions instead of the expected 4-position[51,52].

Very interesting results were obtained in the nitration of 2-alkyl- and 2-chloro-3-hydroxypyridines[49,53]. It was found that in this case the 4-position as well as the 6-position is nitrated, the formation of the 4-isomer predominating[44]:



The authors suggested that the preferential nitration in the *ortho*-position relative to the hydroxyl in these compounds is due to the formation of a six-membered chelate complex in the transition state. This hypothesis is confirmed by the finding that, when the nitration is carried out at a higher temperature, which weakens the intramolecular hydrogen bond, the 6-position is preferentially substituted. On the other hand, nitration of 3-methoxy-2-methylpyridine, which cannot form a hydrogen bond with the attacking nitronium ion, proceeds exclusively in the 6-position.

The occurrence of 6-substitution only in the nitration of 3-hydroxy-2-nitropyridine can also be a consequence of the impossibility of the formation of a chelate when the nitronium ion attacks the 4-position because of the strong intramolecular hydrogen bond between the nitro- and hydroxy-groups already present in the compound. The influence of chelate formation on the direction of substitution has been confirmed also in the nitration of the *N*-oxides of 3-hydroxy-2-methyl- and 3-methoxy-2-methyl-pyridines[54,55]. The nitration of 3-hydroxy-2-methylpyridine *N*-oxide is directed exclusively to the 4-position, while 3-methoxy-2-methylpyridine is nitrated in the 6-position.

It is interesting to note that the nitration of 3-methoxy-6-methylpyridine[56] proceeds in the 2-position, in contrast to 3-methoxypyridine, while 3-hydroxy-2-methoxypyridine is nitrated exclusively in the 4-position. As expected, the nitration of 3-hydroxy-6-methyl- and 3-hydroxy-4-methyl-pyridines is directed to the 2-positions[57].

The presence of the nitro-group in the 3-hydroxypyridine ring does not preclude its further nitration. Thus nitration of 3-hydroxy-6-methyl-2-nitro- and 3-hydroxy-2-methyl-6-nitro-pyridines yielded the corresponding dinitro-derivatives[57]. Nitration of 3-hydroxy-2-nitropyridine results in the formation of 3-hydroxy-2,4,6-trinitropyridine together with the 2,6-dinitro-derivative[58]. When the 2- and 6-positions of the 3-hydroxypyridine ring were occupied by alkyl groups, the 4-position was substituted smoothly[57,59]. Thus the results presented indicate the possibility of the successive selective nitration of the 2-, 6-, and 4-positions of the 3-hydroxypyridine ring.

To elucidate the mechanism of the electrophilic substitution of the 3-hydroxypyridine ring, the kinetics of the nitration of 3-hydroxypyridine were studied[41]. Comparison of the variation of the rate of nitration with pH for 3-hydroxy- and 3-methoxy-pyridines with the results found previously for the 2,4,6-collidinium cation revealed their considerable similarity, which suggested the involvement of the 3-hydroxypyridine ring in nitration in the protonated form. The partial rate factors in the nitration of the 3-methoxypyridinium cation are 4×10^{-10} for the 2-position and 1×10^{-11} for the 6-position.

3. Halogenation

The halogenation of 3-hydroxypyridine has been studied in detail in many investigations. It has been shown that substitution proceeds primarily in the 2-position. Bromination with an equivalent amount of bromine in pyridine[60], iodination with iodine in sodium carbonate solution[61,62], and chlorination with hydrochloric acid in the presence of hydrogen peroxide[61] all lead to the formation of 2-halogeno-derivatives. The 4- and 6-halogeno-derivatives of 3-hydroxypyridine has been obtained only by an indirect procedure[60].

The iodination of 3-hydroxypyridine with an excess of iodine proceeds with formation of 2,6-diiodo- and 2,4,6-triiodo-derivatives[61]. Under these conditions, 3-hydroxy-5-methylpyridine gives rise to the 2,6-diiodo-derivative[63]. Similarly the bromination of 3-hydroxypyridine with twice the molar amount of bromine in pyridine yields the 2,6-dibromo-derivative and the reaction with an excess of bromine water results in the formation of 2,4,6-tribromo-3-hydroxypyridine[60]. The bromination of 5-bromo-3-hydroxypyridine with an excess of bromine water yielded 2,4,5,6-tetrabromo-3-hydroxypyridine[60].

The bromination of 3-hydroxypyridine *N*-oxide, like that of the non-oxidised base, leads to the 2-bromo-derivative, which can be brominated further to give the 2,6-dibromo- and 2,4,6-tribromo-3-hydroxypyridine *N*-oxides[64]. In contrast to this, the iodination of 3-hydroxypyridine *N*-oxide in a weakly alkaline solution leads to the formation of 3-hydroxy-4,6-diiodopyridine *N*-oxide as the only product[65]. The bromination of 3,5-diethoxypyridine in an acid medium results in the formation of 2,6-dibromo-3,5-diethoxypyridine, while in pyridine solution the main product isolated was 2-bromo-3,5-diethoxypyridine[66]. 2,3,4-Trihydroxypyridine gives rise to a monohalogeno-derivative of unknown structure[67].

The introduction of the electronegative nitro-group does not affect the halogenation process; the bromination of 3,5-diethoxy-2-nitropyridine yields 6-bromo-3,5-diethoxy-2-nitropyridine[66]. The iodination of 3-hydroxypicolinic acid with iodine in an alkaline medium proceeds with simultaneous decarboxylation and the formation of 3-hydroxy-2,6-diiodopyridine[68].

4. Sulphonation

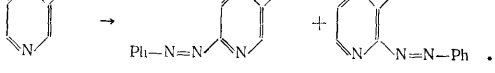
The sulphonation of 3-hydroxypyridine requires the use of extremely severe conditions and proceeds with formation (in a low yield) of 3-hydroxypyridine-2-sulphonic acid[69,70]. Similarly 3-hydroxypyridine *N*-oxide is sulphonated in the 2-position[71]. Comparison of the conditions for the sulphonation of pyridine and 3-hydroxypyridine indicates a lower reactivity of the latter in this reaction.

It has been suggested[71] that the sulphonation of pyridine and its derivatives proceeds via the initial formation of a complex of sulphur trioxide with the heterocycle, which rearranges to the corresponding sulphonic acid at a high temperature in the presence of catalysts. The rate-determining state of the reaction is the rearrangement of the complex, the ease of which is determined by the stability of the heterocycle–sulphur trioxide complex formed. The higher stability of the complex of 3-hydroxypyridine with sulphur trioxide compared with that formed by pyridine itself is probably the cause of its lower reactivity in sulphonation.

5. Azo-Coupling

The azo-coupling of 3-hydroxypyridine proceeds preferentially in the *para*-position relative to the hydroxy-group. Thus the main product formed in the interaction with benzenediazonium chloride is 3-hydroxy-6-(phenylazo)-pyridine (81%) together with a small amount (3%) of the 2-isomer[72].

On the other hand, the reaction of 3-hydroxypyridine with *p*-nitrobenzenediazonium chloride in a weakly acid solution led initially to the isolation of only the 2-azo-derivative[62]. Later studies demonstrated the formation of equal amounts of 2-azo- and 6-azo-derivatives[73]. On the other hand, when the above reaction was carried out under weakly alkaline conditions, the preferential formation of the *para*-isomer was observed; the yield of the *ortho*-isomer was 13% under these conditions:



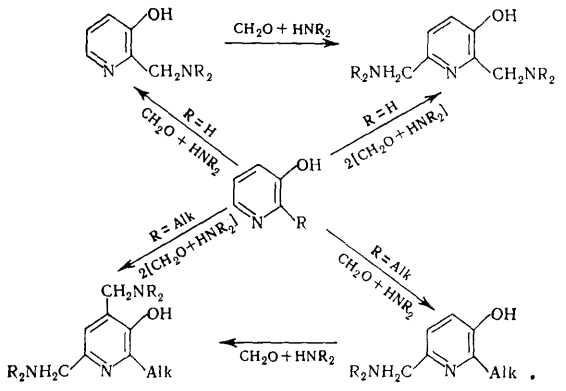
The azo-coupling of 3-hydroxypyridine *N*-oxide in a weakly alkaline solution, like that of 3-hydroxypyridine itself, involves the 6-position[74]. The azocoupling of 3-hydroxy-4-methyl-5-phenylpyridine with benzenediazonium chloride gives rise to a mixture of equal amounts of the *o*-azo- and *p*-azo-derivatives[73]. The azocoupling of 3-hydroxy-2-methyl- and 3-hydroxy-6-methylpyridines and their *N*-oxides proceeds with formation of only the 6-azo- and 2-azo-derivatives respectively[75]. The absence of 4-substitution proved to be general in the azo-coupling of both the 2- and 6-methyl derivatives and of the 2,6-dimethyl derivatives of 3-hydroxypyridine with benzene-diazonium chloride[75]. However, the introduction of the *N*-oxide group permitted a smooth azo-coupling in the 4-position of 3-hydroxy-2,6-dimethylpyridine *N*-oxide[74].

The azo-coupling of 2,3-dihydroxypyridine, 3-hydroxy-2-methoxypyridine, and 3-hydroxy-1-methyl-2-pyridone involves the 6-position[76]. This shows that the main directing group in all the compounds is the 3-hydroxy-group. The decisive directing influence of the 3-hydroxy-group was established also in the azo-coupling of 2,5-dihydroxypyridine, which involves the 6-position[76].

6. Aminomethylation

3-Hydroxypyridine in the anionic form enters into a number of reactions with weak electrophilic agents, which are characteristic of phenolic compounds. Among these one must include the aminomethylation, hydroxymethylation, and carboxylation reactions. The aminomethylation of 3-hydroxypyridine and its derivatives has been studied both with the aim of synthesising pyridoxine (vitamin B_6),[77] its analogues[78], and antagonists[79] and with the aim of studying the comparative reactivities of the 2-, 4-, and 6-positions in the 3-hydroxypyridine ring.

The pronounced electron-accepting influence of the ring nitrogen, which greatly reduces the electron density in the aromatic ring, particularly in the 2-, 4-, and 6-positions, leads to a reduced reactivity of 3-hydroxypyridine in the Mannich condensation compared with phenols. Thus, in contrast to phenol, which readily gives rise to a trisubstituted Mannich base, 3-hydroxypyridine is aminomethylated only in the 2- and 6-positions[80]. Furthermore, the combination in a single molecule of the hydroxy-group adjoining the conjugated ring system with the ring nitrogen atom alters the sequence of substitution from *ortho-ortho-para*, as in phenols, to *ortho-para-ortho* in 3-hydroxypyridine:



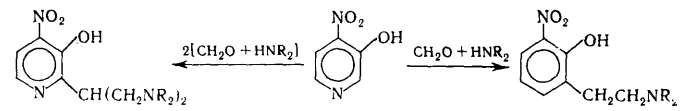
The success of the aminomethylation depends markedly on the pH of the medium[81]. Whereas phenols are readily aminomethylated in both acid and weakly alkaline media, the maximum yield of Mannich bases formed from 3-hydroxypyridines is achieved in weakly alkaline media. The different reactivities of the 2-, 6-, and 4-positions of the 3-hydroxypyridine ring in the Mannich condensation make it possible to synthesise the individual compounds. Both 2-dialkylaminomethyl- and 2,6-bis(dialkylaminomethyl)-3-hydroxypyridine can be readily obtained from 3-hydroxypyridine[80]. The mode of reaction can be controlled by an appropriate choice of reactant ratio. However, in all stages there is an initial attack on the 2-position and then on the 6-position. Under analogous conditions, 2-alkyl-3-hydroxy-[82] and 3-hydroxy-6-methylpyridines[80] are aminomethylated with formation of the corresponding 6- and 2-dialkylaminomethyl derivatives.

4-Aminomethylation is possible only for 3-hydroxypyridines containing an alkyl or alkoxy-group in the 2-position and in many instances requires the use of more severe conditions. 2,6-Dialkyl-4-dialkylaminomethyl-3-hydroxypyridine[83], 2-alkyl-3-hydroxypyridine[82,84], and 4,6-bis(dialkylaminomethyl)-3-hydroxy-2-methoxypyridine[85] were synthesised in this way. The attempt to obtain 4-substituted compounds by the aminomethylation of 6-alkyl-2-dialkylaminomethyl- and 2,6-bis(dialkylaminomethyl)-3-hydroxypyridines was unsuccessful. This led to the conclusion that the presence in the *ortho*-position with respect to the hydroxyl of a substituent forming a strong intramolecular bond with the OH group sharply reduces the reactivity of the 4-position in the Mannich condensation. It has been noted that the reduction of the acid properties of the OH group also affects the success of substitution at the $C_{(4)}$ atom[84].

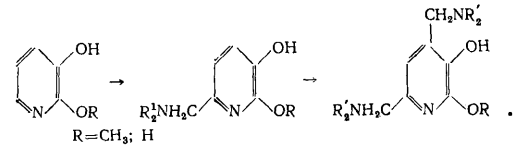
Furthermore, the course of aminomethylation is significantly influenced also by the structure of the secondary amine. Thus aminomethylation of 2,6-dialkyl-3-hydroxypyridines was unsuccessful when secondary amines such as diethylamine, diisopropylamine, and diallylamine were used, probably owing to the steric hindrance to the substitution of the 4-position[82].

The aminomethylation of 3-hydroxypyridine *N*-oxide and its 6-methoxy-2-methyl- and 2,6-dimethyl derivatives is characterised by the same sequence of the substitution of various positions of the 3-hydroxypyridine ring[86]. Comparison of the conditions for the aminomethylation of the oxidised and non-oxidised bases indicates a somewhat greater reactivity of 3-hydroxypyridine *N*-oxides[86].

Interesting results were obtained in a study of the aminomethylation of nitroderivatives of 3-hydroxypyridine. The presence of the nitro-group in the 2-position of the 3-hydroxypyridine ring does not prevent the 6-aminomethylation of 3-hydroxy-2-nitropyridine[87]. However, the aminomethylation of the 4-nitro- and 2-nitro-derivatives of 3-hydroxy-6-methylpyridine is not directed to the ring but to the side chain[88]. 2-(β-dialkylaminoethyl)-3-hydroxy-4-nitropyridines, the further aminomethylation of which leads to the formation of Mannich bis-bases via the methyl group, were synthesised in this way:



Similarly the aminomethylation of 3-hydroxy-6-methyl-2-nitropyridine yielded 6-(β-dialkylaminoethyl)-3-hydroxy-2-nitropyridines[88]. The aminomethylation of 2,3-dihydroxypyridine[89] and 3-hydroxy-2-methoxypyridine[85] leads to the initial formation of the Mannich 6-monobases and subsequently of the 4,6-bisbases, which indicates a definite role of the 3-hydroxy group in directing the substituent[85]:

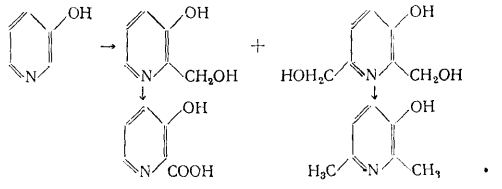


Comparison of the conditions for the aminomethylation of 2-alkyl-3-hydroxypyridines with those for 2-alkoxy- and 2-alkoxy-3-hydroxy-pyridines shows that the replacement of the alkyl group by alkoxy- and hydroxy-groups increases somewhat the reactivity of the 3-hydroxypyridine ring[85]. The aminomethylation of 3-hydroxy-1-methyl-2-pyridone proceeds, like that of 2,3-dihydroxypyridine, under mild conditions in a quantitative yield and involves the 6-position[90]. However, the attempts at 4,6-disubstitution of 3-hydroxy-1-methyl-2-pyridone were unsuccessful, which is caused, as for 3-hydroxy-2-nitropyridine and 2-dialkylaminomethyl-3-hydroxypyridine, by the presence of a strong intramolecular hydrogen bond between the 3-hydroxy-group and the *ortho*-substituent.

As in 2,3-dihydroxypyridine, the main directing group for electrophilic substitution in 2,5-dihydroxypyridine is the 3-hydroxy-group, which directs aminomethylation to the 6-position[90].

7. Hydroxymethylation

The ease of controlling the hydroxymethylation of 3-hydroxypyridine, in contrast to the rapid polymerisation of phenols under similar conditions, provide a clear example of the deactivating influence of the ring nitrogen on the chemical reactivity of the aromatic ring. 3-Hydroxypyridine can be effectively hydroxymethylated by treatment with an alkaline solution of formaldehyde[91]. This yields a mixture of mono- and di-substituted products[91,92], the formation of which cannot be avoided even when equivalent ratios of the reactants are employed[93]. The substitution of the 2-position was demonstrated by oxidising the product to 3-hydroxypicolinic acid[91] and that of the 6-position by converting the di(hydroxymethyl) compound into 3-hydroxy-2,6-dimethylpyridine[92]:



The hydroxymethylation of 3-hydroxy-2-methyl- and 3-hydroxy-6-methyl-pyridines[82,94] proceeds equally successfully with formation of the corresponding 6- and 2-isomers. 4-Substitution was not observed in either case (and also for 3-hydroxy-2,6-dimethylpyridine). The corresponding 4-hydroxymethyl derivatives of 3-hydroxy-2-methyl- and 3-hydroxy-2,6-dimethyl-pyridines were obtained indirectly from the 4-aminomethyl derivatives[82,95]. The hydroxymethylation of the 3-hydroxypyridine ring can be achieved successfully also in the presence of the electron-accepting carboxy-group in the 2-position. 5-Hydroxypicolinic acid forms the 2-hydroxymethyl derivative[96].

8. Carboxylation

Like phenol, 3-hydroxypyridine in the anionic form undergoes the Kolbe reaction with carbon dioxide under pressure. However, in contrast to phenol, the carboxylation of 3-hydroxypyridine is directed mainly to the *para*-position and not the *ortho*-position with respect to the hydroxy-group. Thus, when 3-hydroxypyridine was heated with potassium carbonate in proportions of 1 : 1.5, a quantitative yield of 5-hydroxypicolinic acid was obtained[97]. In the carboxylation of the sodium or potassium salt of 3-hydroxypyridine the formation of low yields of 3- and 5-hydroxypicolinic acids was noted, the sodium salt being substituted preferentially in the *ortho*-position and the potassium salt in the *para*-position relative to the hydroxy-group[98]. 3-Hydroxy-2-methyl-pyridine is carboxylated in the 6-position[99], while 3-hydroxy-5-methylpyridine forms an acid of unknown structure[100].

9. Other Reactions of 3-Hydroxypyridine

Other electrophilic reactions of 3-hydroxypyridine include mercuration with mercury acetate in the 2-position[101]. Vigorous attempts have been made to involve 3-hydroxypyridine in the Friedel–Krafts acylation and alkylation reactions but without success. This is probably because of the great sensitivity of these reactions to the deactivating influence of the nitrogen in the pyridine ring owing to complex formation and the corresponding change in the aromaticity of the ring. 3-Hydroxypyridine is not involved in the nitrosation reaction, which is also sensitive to the deactivating effect of electron-accepting substituents[72].

However, 2,5-dihydroxypyridine is readily nitrosated with formation of the 6-nitroso-derivative. The same position was also nitrosated in 2,5-dihydroxy-4-methyl-3-phenylpyridine[73].

IV. BIOLOGICAL PROPERTIES

3-Hydroxypyridine has been the subject of vigorous research with the aim of synthesising on its basis various biologically active compounds. Experimental studies have shown that 3-hydroxypyridine derivatives exhibit a wide spectrum of biological and pharmacological activity[102].

For example, the ethers of base-substituted 3-hydroxypyridines exhibit physostigmine-like, anticurare, and anticholinesterase activities[103]. The synthesis of a large number of 3-hydroxypyridine derivatives with bactericidal and anti-inflammatory activities has been reported[104,105]. 3-Hydroxypyridine derivatives can be used as depressants of the central nervous system[104]. Acylated 2-amino-3-hydroxypyridines have been suggested as anti-inflammatory compounds and for the treatment of cardiovascular diseases[106]. 2- and 6-Formyl-3-hydroxypyridine thiosemicarboazones exhibit a marked antileukaemic activity in both experimental and clinical tests[107]. Phosphate esters of 3-hydroxy-6-methylpyridine exhibit an insecticidal activity[108], while 3-hydroxy-2-nitropyridinium salts exhibit herbicidal activity[109]. Esters of 3-hydroxypyridines and of their nitro-derivatives have been used successfully in the synthesis of peptides and polypeptides having regular structures[110,111].

Relatively non-toxic and water-soluble radical process inhibitors with a wide spectrum of biological activity can be obtained from 3-hydroxypyridine[95]. The possibility of using inhibitors derived from 3-hydroxypyridine as agents conferring protection against radiation, discovered by Emanuel' and coworkers is of greatest interest[112,113]. 2,6-Dialkyl- and 2,4,6-trialkyl-3-hydroxypyridines exhibit the most effective anti-radiation activity. A study of the antiradiation properties of 3-hydroxypyridine derivatives and of inhibitors of other classes established a relation between the anti-radical activity of the inhibitor and its antiradiation activity[114,115]. 3-Hydroxypyridine derivatives can protect DNA molecules from radiation-induced depolymerisation[4] and also exhibit antileukaemic activity[116]. Apart from their use as prophylactic agents, alkyl-substituted 3-hydroxypyridines possess therapeutic activity against the effects of radiation and promote a more rapid recovery of the blood-forming system[116]. It has been noted that 2,6-dialkyl- and 2,4,6-trialkyl-3-hydroxypyridines possess cytogenic activity.

The mechanism of the biological action of 3-hydroxypyridine derivatives has been the subject of a detailed microbiological study on yeast cells as the biological test

object[117]. It was established that 3-hydroxypyridine inhibitors suppress the multiplication of yeast cells, which are incapable of synthesising inositol and pantothenic acid, by blocking these vitamins when the latter are introduced from outside. It has been suggested[117] that alkyl-substituted 3-hydroxypyridines function as specific inhibitors of cell division, acting primarily by arresting the division of the nuclei. It has been shown that individual alkyl-3-hydroxypyridines exhibit vitamin B_6-like activity[117].

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Thus systematic study of the structure of 3-hydroxypyridines and of their reactivity in electrophilic substitution using quantum-chemical calculations, spectroscopic methods, and the kinetics of the acid- and base-catalysed deuterium exchange made it possible to investigate the molecular sites involved in electrophilic reactions, to develop methods for the introduction of various substituents in different specific positions in the 3-hydroxypyridine ring, and to achieve on this basis the synthesis of a large number of relatively non-toxic and water-soluble inhibitors of radical chain processes with a wide spectrum of biological activity.

REFERENCES

1. N. M. Emanuel', "Trudy Soveshchaniya Biokhimicheskie i Fiziko-Khimicheskie Osnovy Biologicheskogo Deistviya Radiatsii, Moskva, 1957" (Proceedings of the Conference on the Biochemical and Physicochemical Principles of the Biological Action of Radiation, Moscow, 1957).
2. N. M. Emanuel', "Puti Sinteza i Izyskaniya Protivoopukholevykh Preparatov" (Methods of Synthesis and Research on Antitumour Preparations), Medgiz, Moscow, 1962.
3. N. M. Emanuel', "Pervichnye Mekhanizmy Biologicheskiogo Deistviya Ioniziruyushchikh Izluchenii" (Primary Mechanisms of the Biological Action of Ionising Radiation), Izd. Akad. Nauk SSSR, Moscow, 1963, Vol. 7, p. 73.
4. N. M. Emanuel', K. E. Kruglyakova, N. A. Zakharova, and I. I. Sapezhinskii, Dokl. Akad. Nauk SSSR, **131**, 1451 (1960).
5. E. B. Burlakova and N. M. Emanuel', Dokl. Akad. Nauk SSSR, **135**, 599 (1960).
6. N. M. Emanuel', Symposium, "Penol'nye Soedineniya i Ikh Biologicheskie Funktsii" (Phenolic Compounds and Their Biological Functions), Izd. Nauka, Moscow, 1968, p. 311.
7. K. M. Dyumaev and G. A. Nikiforov, Neftekhimiya, **1**, 93 (1961).
8. G. A. Nikiforov, A. A. Volod'kin, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1661 (1964).
9. K. M. Dyumaev and I. S. Belostotskaya, Zhur. Obshch. Khim., **32**, 2661 (1962).
10. G. A. Nikiforov and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 721 (1963); 1075 (1964).
11. D. E. Metzlez and E. E. Snell, J. Amer. Chem. Soc., **77**, 2431 (1955).
12. A. Albert and J. N. Phillips, J. Chem. Soc., 1294 (1956).
13. A. Bryson, J. Amer. Chem. Soc., **82**, 4871 (1960).
14. S. F. Mason, J. Chem. Soc., 5010 (1957).
15. K. M. Dyumaev, B. A. Korolev, and R. E. Lokhov, Zhur. Obsch. Khim., **41**, 2520 (1971).
16. D. Heinert and A. E. Martell, J. Amer. Chem. Soc., **81**, 3933 (1959).
17. W. Korytnyk and R. P. Singh, J. Amer. Chem. Soc., **85**, 2813 (1963).
18. V. P. Lezina, L. D. Smirnov, K. M. Dyumaev, and V. S. Bystrov, Izv. Akad. Nauk SSSR, Ser. Khim., 25 (1970).
19. V. T. Grachev, B. E. Zaitsev, K. M. Dyumaev, and L. D. Smirnov, Khim. Geterotsikl. Soed., 92 (1974).
20. V. T. Grachev, B. E. Zaitsev, V. I. Kuz'min, K. M. Dyumaev, and L. D. Smirnov, Teor. Eksper. Khim., 532 (1973).
21. V. P. Lezina, N. A. Andronova, L. D. Smirnov, and K. M. Dyumaev, Khim. Geterosikl. Soed., 1546 (1971).
22. V. P. Lezina, N. A. Andronova, L. D. Smirnov, and K. M. Dyumaev, Khim. Geterosikl. Soed., 1540 (1971).
23. V. P. Lezina, V. F. Bystrov, L. D. Smirnov, and K. M. Dyumaev, Teor. Eksper. Khim., 281 (1965).
24. B. E. Zaitsev, V. T. Grachev, K. M. Dyumaev, V. P. Lezina, and L. D. Smirnov, Izv. Akad. Nauk SSSR, Ser. Khim., 2140 (1971).
25. C. T. Goralski and W. B. Neely, Theor. chim. Acta, **20**, 41 (1971).
26. F. A. Savin, N. P. Bazhulina, and Yu. V. Morozov, Mol. Biol., **7**, 674 (1973).
27. J. A. Robertson, Proc. Roy. Soc., **A157**, 79 (1936).
28. A. R. Katritzky (Editor), "Physical Methods in Heterocyclic Chemistry" (Translated into Russian), Izd. Khimiya, Moscow, 1966.
29. J. N. Kwiatkowski, Theor. Chim. Acta, **16**, 243 (1970).
30. M. Berndt and J. N. Kwiatkowski, Theor. Chim. Acta, **17**, 35 (1970).
31. P. Bellingham, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., 1226 (1967).
32. P. Bellingham, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc. (B), 866 (1968).
33. G. P. Bean, P. J. Brignell, C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, H. O. Tarhan, and A. M. White, J. Chem. Soc. (B), 1222 (1967).
34. V. P. Lezina, A. U. Stepanyants, L. D. Smirnov, N. A. Andronova, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 2092 (1972).
35. V. P. Lezina, A. U. Stepanyants, L. D. Smirnov, N. A. Andronova, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 2267 (1972).
36. V. P. Lezina, A. U. Stepanyants, L. D. Smirnov, N. A. Andronova, and K. M. Dyumaev, Khim. Geterosikl. Soed., 1647 (1972).
37. V. P. Lezina, A. U. Stepanyants, L. D. Smirnov, N. A. Andronova, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1224 (1972).
38. V. P. Lezina, A. U. Stepanyants, L. D. Smirnov, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1206 (1972).
39. V. P. Lezina, A. U. Stepanyants, L. D. Smirnov, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1208 (1972).
40. V. P. Lezina, A. U. Stepanyants, V. S. Zhuravlev, L. D. Smirnov, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1498 (1974).
41. A. R. Katritzky, H. O. Tarhan, and S. Tarhan, J. Chem. Soc. (B), 114 (1970).
42. E. Plazek and Z. Rodgewald, Roczniki Chem., **16**, 502 (1936).
43. R. C. De Selms, J. Org. Chem., **33**, 478 (1968).

44. L. D. Smirnov, R. E. Lokhov, V. P. Lezina, B. E. Zaitsev, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1567 (1969).
45. K. Lewicka and E. Plazek, Rec. Trav. chim., 78, 644 (1959).
46. H. J. den Hertog, C. R. Rolder, and W. Combe, Rec. Trav. chim., 70, 591 (1951).
47. H. J. den Hertog and M. van Ammers, Rec. Trav. chim., 74, 1160 (1955).
48. E. Koening, H. C. Gerdes, and A. Sirot, Ber., 61, 1022 (1928).
49. J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, J. Amer. Chem. Soc., 69, 1151 (1947).
50. H. J. den Hertog, C. Jouwersma, A. A. van der Wal, and E. C. C. Willebrands-Schogt, Rec. Trav. chim., 68, 275 (1949).
51. H. J. den Hertog, C. H. Heukens, and K. Dilz, Rec. Trav. chim., 72, 269 (1953).
52. M. van Ammers, H. J. den Hertog, and S. Shukking, Rec. Trav. chim., 74, 1171 (1955).
53. L. D. Smirnov, V. P. Lezina, B. E. Zaitsev, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1652 (1968).
54. K. M. Dyumaev, L. D. Smirnov, R. E. Lokhov, and B. E. Zaitsev, Izv. Akad. Nauk SSSR, Ser. Khim., 2599 (1970).
55. K. M. Dyumaev and R. E. Lokhov, Khim. Geterotsikl. Soed., 1003 (1971).
56. L. D. Smirnov, M. R. Avezov, V. P. Lezina, B. E. Zaitsev, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 845 (1971).
57. L. D. Smirnov, S. L. Orlova, V. P. Lezina, G. P. Kartasheva, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 2752 (1967).
58. W. Czuba and E. Plazek, Rec. Trav. chim., 77, 92 (1958).
59. H. Ban-Oganowska, Z. Skrowezewska, and J. Syper, Roczniki Chem., 40, 1215 (1966).
60. H. J. den Hertog, F. R. Scherpman, J. de Bruyn, and J. E. Thysse, Rec. Trav. chim., 69, 1281 (1950).
61. O. Shickh, A. Binz, and A. Schulz, Ber., 69, 2593 (1936).
62. H. Bojarska-Dahlig and T. Urbanski, Chem. Abs., 48, 1337 (1954).
63. H. Bojarska-Dahlig, Roczniki Chem., 30, 475 (1966).
64. K. Lewicka and E. Plazek, Roczniki Chem., 40, 405 (1966).
65. K. Lewicka and E. Plazek, Roczniki Chem., 40, 1875 (1966).
66. H. J. den Hertog and B. Mulder, Rec. Trav. chim., 67, 957 (1948).
67. A. Ost, J. prakt. chem., 19, 203 (1879).
68. H. Bojarska-Dahlig, Roczniki Chem., 30, 315 (1956).
69. E. Plazek, Roczniki Chem., 16, 403 (1936).
70. E. Plazek, Roczniki Chem., 17, 97 (1937).
71. K. M. Dyumaev and R. E. Lokhov, Khim. Geterotsikl. Soed., 813 (1973).
72. R. Urban and O. Schnidez, Helv. Chim. Acta, 47, 363 (1963).
73. J. A. Moore and F. J. Marascia, J. Amer. Chem. Soc., 81, 6049 (1959).
74. R. E. Lokhov, Candidate's Thesis, NIIOPiK, Moscow, 1971.
75. K. M. Dyumaev, R. E. Lokhov, B. E. Zaitsev, and L. D. Smirnov, Izv. Akad. Nauk SSSR, Ser. Khim., 2601 (1970).
76. B. E. Zaitsev, G. V. Sheban, L. D. Smirnov, and K. M. Dyumaev, Khim. Geterotsikl. Soed., 224 (1973).
77. L. A. Perez-Medina, R. P. Mariella, and S. M. McElvain, J. Amer. Chem. Soc., 69, 2574 (1947).
78. R. F. Brown and S. J. Miller, J. Org. Chem., 11, 388 (1946).
79. G. S. Martin, S. Avakian, and J. Moss, J. Biol. Chem., 174, 495 (1948).
80. L. D. Smirnov, V. P. Lezina, V. F. Bystrov, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 198 (1968).
81. K. M. Dyumaev, L. D. Smirnov, V. P. Lezina, and V. F. Bystrov, Teor. Eksper. Khim., 290 (1965).
82. L. D. Smirnov, V. P. Lezina, V. F. Bystrov, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1836 (1965).
83. K. M. Dyumaev, L. D. Smirnov, and V. F. Bystrov, Izv. Akad. Nauk SSSR, Ser. Khim., 883 (1962).
84. L. D. Smirnov, S. L. Orlova, V. P. Lezina, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1816 (1967).
85. K. M. Dyumaev, L. D. Smirnov, M. R. Avezov, and B. E. Zaitsev, Nauch. Trudy Sam. Gos. Univ., Collection No. II, 108 (1971).
86. K. M. Dyumaev and R. E. Lokhov, Zhur. Org. Khim., 416 (1972).
87. L. D. Smirnov, G. P. Kartasheva, V. P. Lezina, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 1942 (1967).
88. L. D. Smirnov, V. P. Lezina, G. P. Kartasheva, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 199 (1968).
89. Nakamura S. Kamiya, Chem. Pharm. Bull. (Tokyo), 16, 1466 (1968).
90. L. D. Smirnov, M. R. Avezov, V. P. Lezina, B. E. Zaitsev, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 2338 (1971).
91. T. Urbanski, J. Chem. Soc., 1104 (1946).
92. A. Stempel and E. C. Buzz, J. Amer. Chem. Soc., 71, 2969 (1948).
93. D. Heinert and A. Martell, Tetrahedron, 3, 49 (1958).
94. T. Urbanski, J. Chem. Soc., 132 (1947).
95. L. D. Smirnov, S. I. Sholina, K. E. Kruglyakova, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 899 (1963).
96. T. R. Gowinachari, N. S. Nazashimhan, and S. Rajaclurai, Chem. Ind., 33 (1956).
97. H. Bojarska-Dahlig, and T. Urbanski, Roczniki Chem., 26, 158 (1952).
98. O. Baine, G. F. Adamson, J. W. Barton, J. L. Fitch, D. R. Swayampati, and H. Jeskey, J. Org. Chem., 19, 510 (1954).
99. H. Rapoport and E. J. Volcheck, J. Amer. Chem. Soc., 78, 2451 (1956).
100. H. Bojarska-Dahlig, Roczniki Chem., 90, 475 (1956).
101. T. Takahashi and F. Yoneda, Chem. Pharm. Bull. (Tokyo), 6, 611 (1958).
102. W. C. Cutting, "Handbook of Pharmacology", 4th Edition, Appleton–Century–Crafts, New York, 1969, p. 545.
103. A. Stempel and J. A. Aeschimann, J. Amer. Chem. Soc., 74, 3323 (1952).
104. Mitsutaka Kawazu, Masahiko Seto, and Masao Watanabe, Japanese P. 7102, 019 (1971); Chem. Abs., 74, 99885e (1971).

105. Takio Shimamoto, Masyuki Ishikawa, Michiro Inoue, and Hisao Ishakawa, Japanese P. 7031, 185 (1970); Chem. Abs., 74, 53 553s (1971).
106. Philippe Jean (Ferlux), BRD P. 2 205 194 (1972). Chem. Abs., 77, 151 947e (1972).
107. E. Blanz and F. A. French, Cancer Research, 28, 2419 (1968).
108. D. Demosay, D. Pillon, and J. Ducret, BRD P. 1 959 418 (1970); Chem. Abs., 72, 111 304h (1970).
109. R. S. Deselms, US P. 3 630 714 (1969); Chem. Abs., 70, 57 663t (1969).
110. E. Taschner and B. Rzesznortarska, Angew. Chem., Intern. Ed., 4, 594 (1965).
111. V. A. Shibnev, K. M. Dyumaev, G. P. Chuvaeva, L. D. Smirnov, and K. T. Poroshin, Izv. Akad. Nauk SSSR, Ser. Khim., 1133 (1967).
112. E. B. Burlakova, V. D. Gaintseva, L. V. Slepukhina, N. G. Khrapova, and N. M. Emanuel', Dokl. Akad. Nauk SSSR, 157, 979 (1964).
113. E. B. Burlakova, N. G. Khrapova, V. N. Shtol'ko, and N. M. Emanuel', Dokl. Akad. Nauk SSSR, 169, 688 (1966).
114. L. D. Smirnov, K. M. Dyumaev, G. P. Zhizhina, K. E. Kruglyakova, and N. M. Emanuel', Symposium, "Svyaz' Stroeniya i Svoistv v Ryadu Azotsoderzhashchikh Geterotsiklicheskikh Soedinenii" (Relation Between Structure and Properties in the Series of Nitrogen-Containing Heterocyclic Compounds), Izd. Ural'sk. Politekh. Inst., Sverdlovsk, 1967, p. 185.
115. E. B. Burlakova, V. D. Gaintseva, K. M. Dyumaev, L. V. Slepukhina, L. D. Smirnov, N. G. Khrapova, and N. M. Emanuel', Symposium, "Svyaz' Stroeniya i Svoistv v Ryadu Azotsoderzhashchikh Geterotsiklicheskikh Soedinenii" (Relation Between Structure and Properties in the Series of Nitrogen-Containing Heterocyclic Compounds), Izv. Ural'sk. Politekh. Inst., Sverdlovsk, 1967, p. 184.
116. L. V. Slepukhina and E. B. Burlakova, Radiobiologiya (in the Press).
117. E. N. Odintsova, Dokl. Akad. Nauk SSSR, 176, 717 (1967).

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