Chemistry of Heterocyclic Compounds, Vol. 39, No. 3, 2003

METHODS FOR THE SYNTHESIS OF HYDRAZINOPYRIDINES AND SOME OF THEIR CHARACTERISTICS. (REVIEW)

K. I. Kobrakov, A. G. Ruchkina, and I. I. Rybina

Data on the synthesis of hydrazinopyridines, their properties, and their application in various fields over the last 30 years are reviewed.

Keywords: biologically active derivatives of pyridine, hetarylpyridines, hydrazinopyridine, hydrazones of hydrazinopyridines, pyridyl-containing azo dyes, pyridyldiazonium salts, heterocyclization.

Hydrazinopyridines with the general formula Py–NH–NH_2 have been actively investigated as precursors in the synthesis of products having biological activity. The presence of the highly reactive hydrazine group in the molecule makes it possible to insert the pyridine fragment into complex molecular structures, which are of interest, in particular, as effective chemical pharmaceutical products and pesticides. For example, products obtained on the basis of hydrazinopyridines have anti-inflammatory, antiulcer, and other types of activity [1-6]. Hydrazinopyridines and their derivatives have been recommended as herbicides, plant growth regulators, and fungicides [7-10]. According to literature sources, the peak of the interest in derivatives of hydrazinopyridines came in the seventies, probably with the release in certain countries of 2-hydrazinopyridine as a commercial product.

1. SYNTHESIS OF HYDRAZINOPYRIDINES

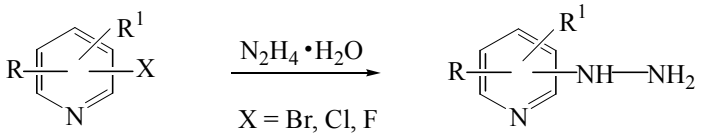
Hydrazinopyridines with the general formula Py–NH–NH_2 can be obtained by several methods, two of which (substitution of halogens by a hydrazino group and reduction of the corresponding diazonium salts) can be considered the main methods.

1.1. Nucleophilic Substitution of Halogen Atoms in Pyridines or their N-Oxides by Reaction with Hydrazine Hydrate

An effective method for the production of substituted hydrazinopyridines is the fairly well studied reaction of halopyridines with hydrazine hydrate [10-14].

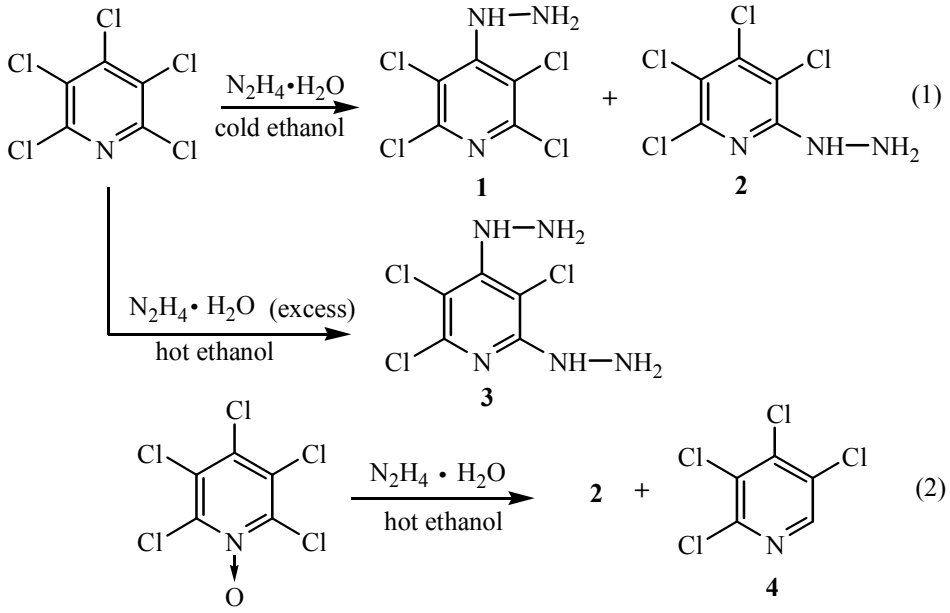
A. N. Kosygin State Textile University, Moscow 119991, Russia; e-mail: office@msta.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 323-349, March, 2003. Original article submitted November 19, 2001.

0009-3122/03/3903-0283$25.00©2003 Plenum Publishing Corporation



As a rule the reaction is carried out in a solvent (pyridine, dioxane, ethanol, acetonitrile, THF, DMF, methylene chloride) in the range of 0-150°C. The temperature conditions are determined by the structure of the initial halogen-substituted pyridine.

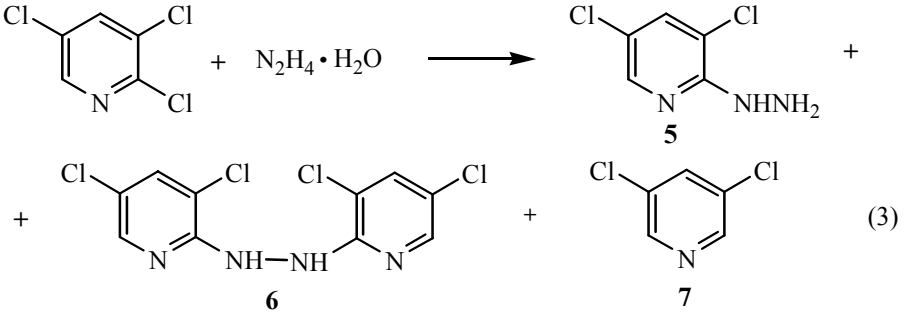
The reactions of polyhalopyridines with hydrazine hydrate usually give the product from substitution at position 4 or 2 with a preference for the former. With an excess of hydrazine hydrate the disubstitution products 2,4-dihydrazinopyridines can be obtained:



The products of reaction (1) **1** and **2** are formed in a ratio of 4:1 with yields of 60-70%. Triethylamine is sometimes added to the reaction mixture as acceptor of HCl [15].

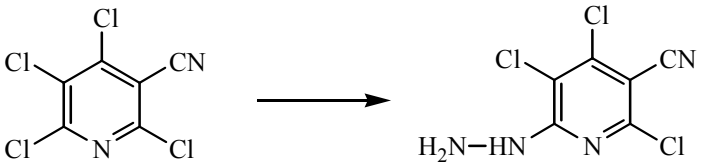
In the reaction of pentachloropyridine N-oxide with hydrazine hydrate [reaction (2)] the yield of 2-hydrazinotetrachloropyridine after recrystallization amounts to 36%. The side product **4** is probably formed as a result of intramolecular reduction of the N-oxide with simultaneous decomposition of the hydrazino group or as a result of the reduction of the chlorine atom at position 2 [12].

When 2,3,5-trichloropyridine is boiled with hydrazine hydrate (halopyridine–$N_2H_4 \cdot H_2O$ molar ratio 1:4) for 4 h without a solvent 3,5-dichloro-2-hydrazinopyridine (**5**) is formed with a yield of 90-96%. N,N'-Disubstituted hydrazine **6** and 3,5-dichloropyridine (**7**) were isolated as side products [16].



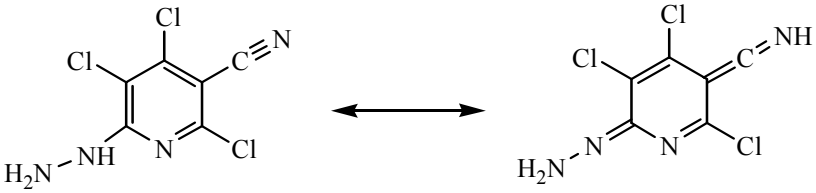
The reaction of tetrachloronicotinic acid with hydrazine hydrate leads to 2,5,6-trichloro-4-hydrazinonicotinic acid [17].

In the reaction of tetrachloronicotinonitrile with hydrazine hydrate the authors considered the possibility of the formation of seven products with various structures [18]. However, in the case of reaction at room temperature or with cooling to 0 to -10°C in dioxane, THF, DMF, or methylene chloride even with an excess of $N_2H_4 \cdot H_2O$ only the monosubstitution product **8** was isolated, and nucleophilic substitution took place exclusively at position 6.



8

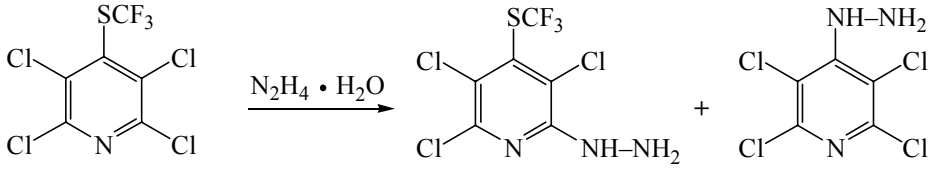
The data from X-ray crystallographic analysis make it possible to conclude that compound **8** exists in two tautomeric forms:



The authors explained the occurrence of the reaction at position 6, in contrast to the isomeric tetrachloropicolinonitrile where the reaction takes place at position 4 [19], by additional stabilization of the negative charge with participation of the CN group in a σ-complex of tetrachloropicolinonitrile and by the absence of such a possibility in the σ-complex of tetrachloropicolinonitrile.

The reaction of 4-aryl-2-chloro-3,5-dicyano-6-methoxypyridines with hydrazine hydrate takes place under mild conditions and leads to the respective 4-aryl-3,5-dicyano-2-hydrazino-6-methoxypyridines [20].

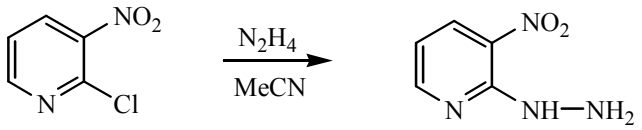
If the polyhalogenopyridine molecule contains an SCF_3 group capable of undergoing nucleophilic substitution, contact between such a substrate and hydrazine hydrate for 24 h at room temperature leads to a mixture of compounds **9** and **10** (2:1) [21]:



9 **10**

The authors explained the observed result by a marked decrease in the reactivity of the SCF_3 group toward N-nucleophiles, whereas it is readily substituted during attack by O- and S-nucleophiles [21].

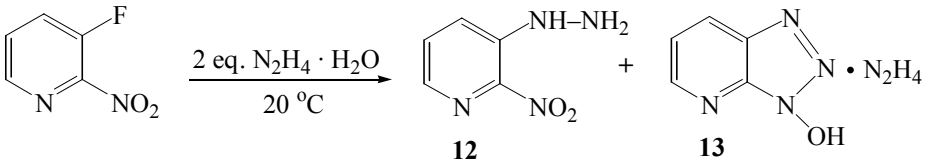
2-Hydrazino-3-nitropyridine (**11**) was obtained with a yield of more than 80% by the reaction of 2-chloro-3-nitropyridine with hydrazine in an anhydrous medium [22, 23]:



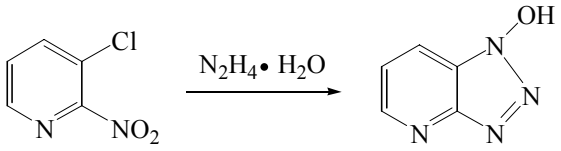
11

3-Nitro-4-hydrazinopyridine was obtained according to the same scheme from the corresponding chloronitropyridine [24].

In [25] it was indicated that substitution of the halogen atom in the reaction of 3-chloro(fluoro)-2-nitropyridine with hydrazine hydrate is complicated by cyclization as a side reaction:



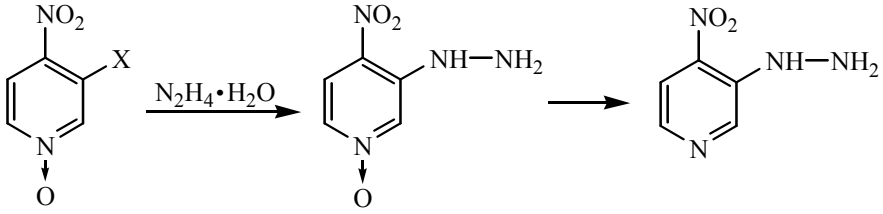
12 **13**



14

An excess of hydrazine hydrate promotes full transformation of the hydrazinopyridine **12** into a salt of pyridotriazole **13**.

In the case of 3-halo-4-nitropyridine N-oxides the corresponding hydrazinopyridines are formed. The reaction can either end at the substitution stage or continue to reduction of the N-oxide [24]:



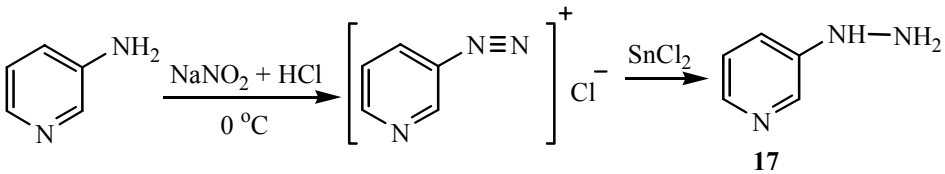
X = F, Br

15 **16**

1.2. Reduction of Diazonium Salts

The second main method for the production of hydrazinopyridines is based on the reduction of pyridinediazonium salts. Diazotization of the respective aminopyridines ($NaNO_2$ + HCl, 0°C) gives pyridinediazonium salts, which can be reduced to hydrazinopyridines by various methods [10, 26, 27].

Hydrazinopyridines with the hydrazino group at position 3, which is difficultly accessible for nucleophilic attack, were obtained by this method:



17

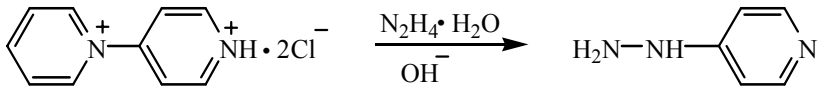
In certain cases reduction can be achieved with the sulfite anion [26]. The method is used for judicious reduction in cases where the aromatic ring contains groups that are reduced by the hydrogen at the moment of release and whose reduction is undesirable.

If the pyridinehydrazonium cation does not contain reducible fragments other than the diazo group, the corresponding hydrazinopyridine can be obtained using tin chloride and hydrochloric acid as reducing agent [27].

1.3. Other Methods for the Production of Hydrazinopyridines

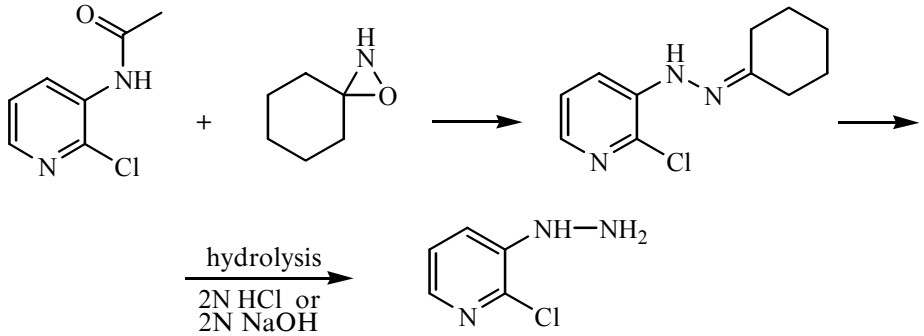
Some special methods for the production of 3- and 4-hydrazinopyridines are also described.

Unsubstituted 4-hydrazinopyridine (**18**) was obtained with a yield of 70% by the reaction of 4-pyridylpyridinium dichloride with hydrazine hydrate in a basic medium [28, 29].



18

It was proposed in [30] to produce 2-chloro-3-hydrazinopyridine **19** from 3-acetylamino-2-chloropyridine by the amination of 1-oxa-2-azaspiro[2,5]octane followed by hydrolysis of the obtained hydrazone:



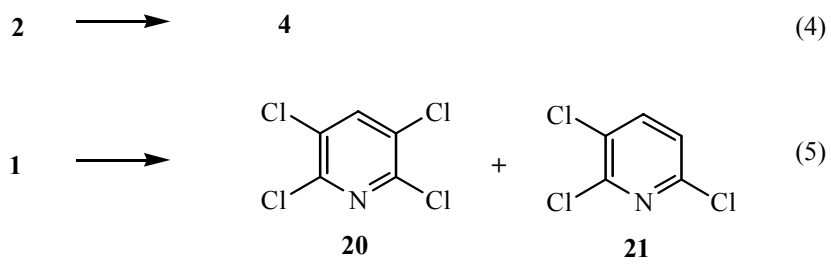
19 (62 %)

2. SOME CHEMICAL TRANSFORMATIONS OF HYDRAZINOPYRIDINES

2.1. Substitution of the Hydrazino Group

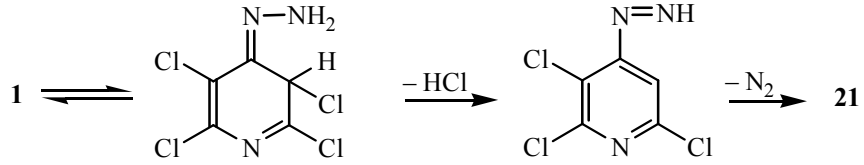
2.1.1. Substitution by Hydrogen. In the series of polyhalohydrazinopyridines substitution of the hydrazine group can be realized by treating the initial compounds with various types of reagents [12, 15, 17, 24, 31-33].

The action of oxidizing agents (an aqueous solution of $CuSO_4$ or alcoholic Ag_2O) on polyhalohydrazinopyridines at the boiling point of the solvent leads to the formation of the corresponding halogenopyridines:

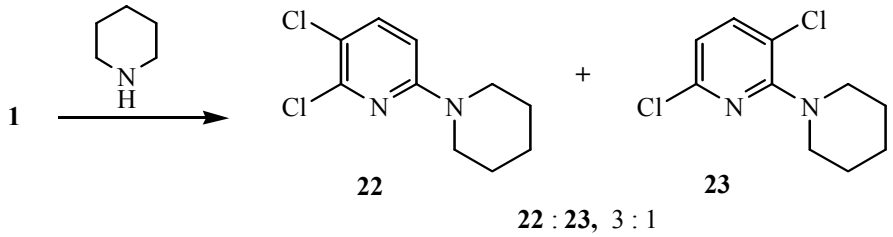


Only one compound **4** is obtained as a result of reaction (4).

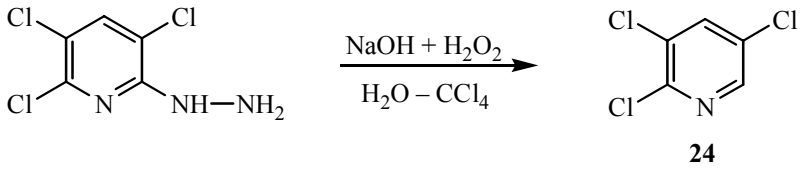
In reaction (5) the trichloropyridine **21** predominates. In the opinion of the authors [12], loss of the halogen at the *o* position to the hydrazino group is explained by the basic characteristics of the catalysts. (The basicity of Ag_2O is well known, while $CuSO_4$, being reduced to Cu_2O, begins to act as a base.) Apart from deamination, the action of basic reagents in the case of 4-hydrazinopyridines also leads to the elimination of HCl:



The reaction with piperidine takes place in the same way as in scheme (5) with the elimination of HCl [12]:

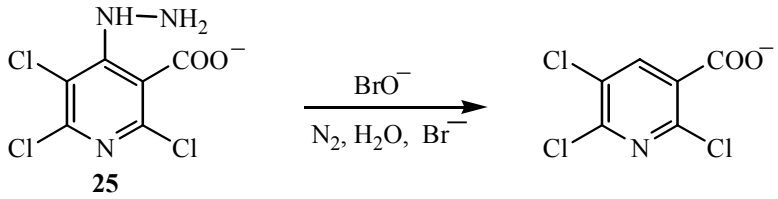


An almost theoretical yield (with 99.5% purity) of 2,3,5-trichloropyridine (**24**) can be obtained if the reaction of 3,5,6-trichloro-2-hydrazinopyridine with sodium hydroxide is carried out in the presence of hydrogen peroxide [31]:



A similar reaction occurs under the action of aqueous alkali in ethanol or 2-propanol (yield of pyridine **24** 83%) [32] or of NaOCl in CCl_4–H_2O [15] on 3,5,6-trichloro-2-hydrazinopyridine.

2,5,6-Trichloronicotinic acid was obtained with a good yield from 2,5,6-trichloro-4-hydrazinonicotinic acid (**25**) as a result of the following reaction [17]:



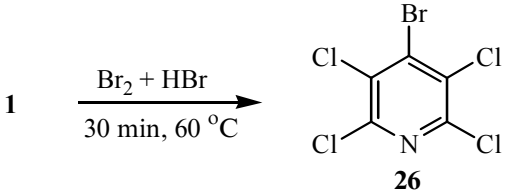
25

It must be emphasized that in almost all cases described above the substitution of the hydrazine group is one stage in the production of polychloropyridines with the chlorine atoms at specific positions in the ring with the aim of subsequently using these chloropyridines in the synthesis of effective herbicides [31].

The action of silver acetate or oxide or copper sulfate on hydrazinonitropyridines leads to oxidative cleavage of the hydrazino group with the formation of 3-nitropyridines [24].

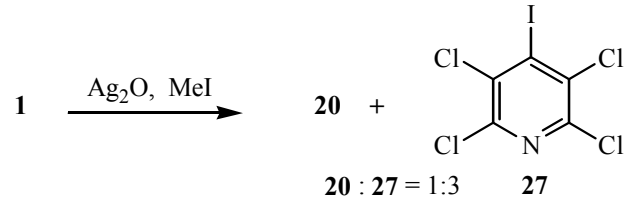
2.1.2. Substitution by Halogen. Substitution of a hydrazino group can be used for the introduction of halogen atoms into an aromatic ring.

Substitution by Br or I has been used to produce the corresponding polyhalogenopyridines with fairly high yields, whereas it is not possible by other methods (the reaction of pentachloropyridine with brominating or iodinating agents) to obtain a yield exceeding 30% [34]. Thus, in reaction with a Br_2–HBr mixture the hydrazino group in 2,3,5,6-tetrachloro-4-hydrazinopyridine is substituted by a bromine atom, and the yield of the desired product amounts to 68%:



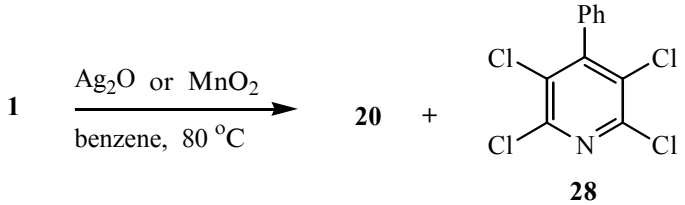
26

The reaction of the pyridine **1** with silver oxide and methyl iodide in an aprotic medium leads to substitution of the hydrazino group by hydrogen and iodine atoms (**20** and **27** respectively) [12]:



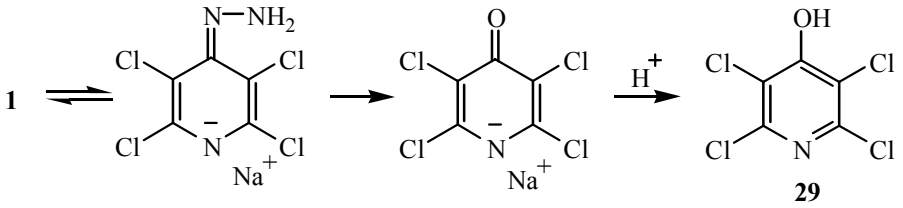
20 : **27** = 1:3 **27**

2.1.3. Substitution of a Hydrazino Group by a Phenyl Group. The action of Ag_2O or MnO_2 on 2,3,5,6-tetrachloro-4-hydrazinopyridine (**1**) in benzene gives a mixture of 2,3,5,6-tetrachloropyridine (**20**) and 2,3,5,6-tetrachloro-4-phenylpyridine (**28**) in a ratio of 1:1 [12]:



28

2.1.4. Substitution by a Hydroxyl Group. A hydrazino group is substituted by hydroxyl during the action of sodium hydroxide at 100°C. The reaction probably takes place through the formation of an imino-amine tautomer, which is clearly stabilized in the salt form:



The reaction with peroxytrifluoroacetic acid ($CF_3COOH + H_2O_2$) leads to the same result [12].

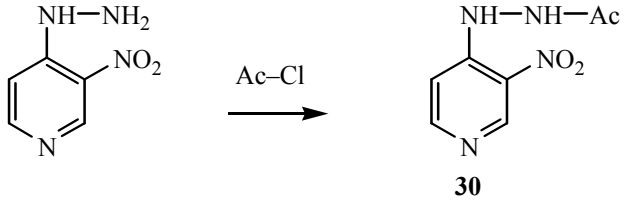
2.2. Reduction of the Hydrazino Group

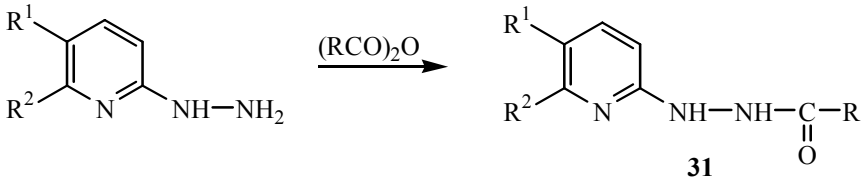
The hydrogenization of 2-hydrazino-3-nitropyridine in ethanol in the presence of nickel catalyst at room temperature for 5 h leads to the formation of 2,3-diaminopyridine [22].

During the pyrolysis of 4-hydrazinopyridine **1** at 160°C for 2 h 4-amino-2,3,5,6-tetrachloropyridine and 2,3,5,6-tetrachloropyridine are formed in a ratio of 7:1 [12].

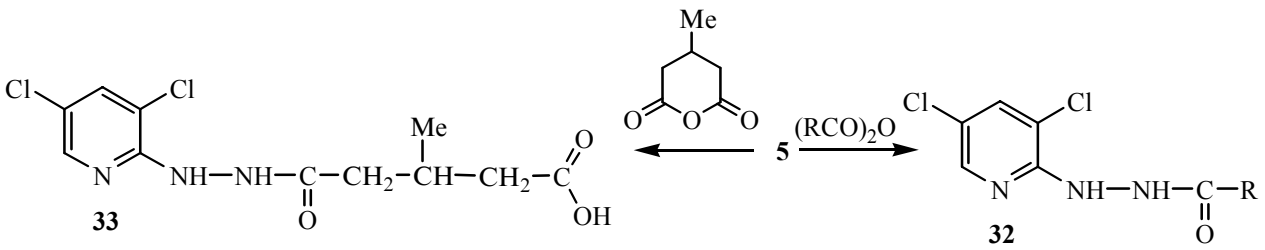
2.3. Substitution of a Hydrogen Atom in the Hydrazino Group

2.3.1. Acylation. Aliphatic carboxylic acids, their anhydrides, or their halides can be used as acylating agents for hydrazinopyridines. The reaction takes place in the absence of a solvent [35, 36] or in a solvent [16] at room temperature (or with gentle heating):

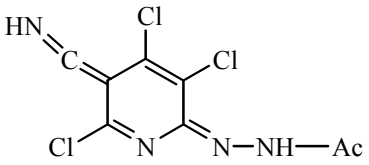




R^1 = H, R^2 = Cl, Br; R^1 = Cl, Br, R^2 = H; R = CF_3, Cl_2CH, F_2CH, MeCHBr



During the reaction of 3,4,6-trichloro-5-cyano-2-hydrazinopyridine (**8**) with acetic anhydride 2-(2-acetylhydrazono)-4-carbonimidoyl-3,4,6-trichloro-2,5-dihydropyridine (**34**) was isolated with an 11% yield together with the corresponding acetyl derivative [37]. (The latter was also obtained by an alternative method in the reaction of 2,4,5,6-tetrachloro-3-cyanopyridine with acetohydrazide.)

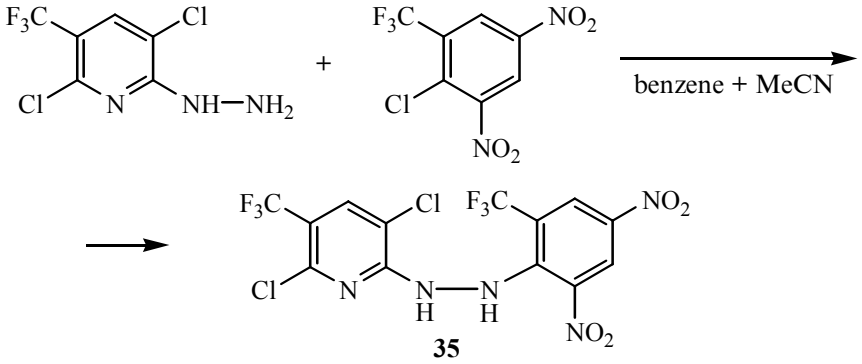


34

The authors attributed the formation of such an unusual compound to the tendency of the initial hydrazinopyridine to exist in the quinonoid form [18, 38], which is fixed in this case by the acetyl fragment.

Acylhydrazines can be obtained by the nucleophilic substitution of halogen atoms in the pyridine ring by the –NH–NH–COR group [39] during the action of the hydrazides of the respective acids.

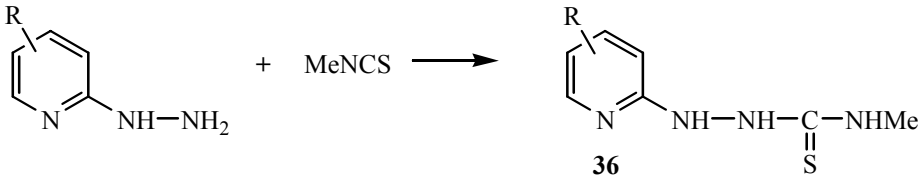
2.3.2. Arylation. The arylation product **35** was obtained with a small yield (<20%) in an aprotic medium [8]:



35

2.4. Addition of the Hydrazino Group at Multiple Bonds

2.4.1. Reaction with Methyl Isothiocyanate. A series of 3- and 4-(4-methylthiosemicarbazido)-pyridines **36** were obtained by treating substituted hydrazinopyridines with MeNCS [4]:



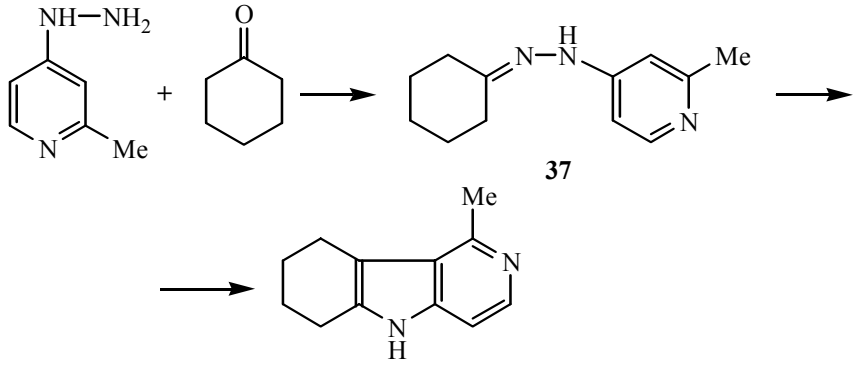
36

2.4.2. Reactions of Hydrazinopyridines with Carbonyl-containing Compounds. When equimolar amounts of 3,5-dichloro-2-hydrazinopyridine (**5**) and various carbonyl compounds or 1,2-naphthoquinone are boiled, the corresponding hydrazones or 1,2-naphthoquinone imine are formed [16].

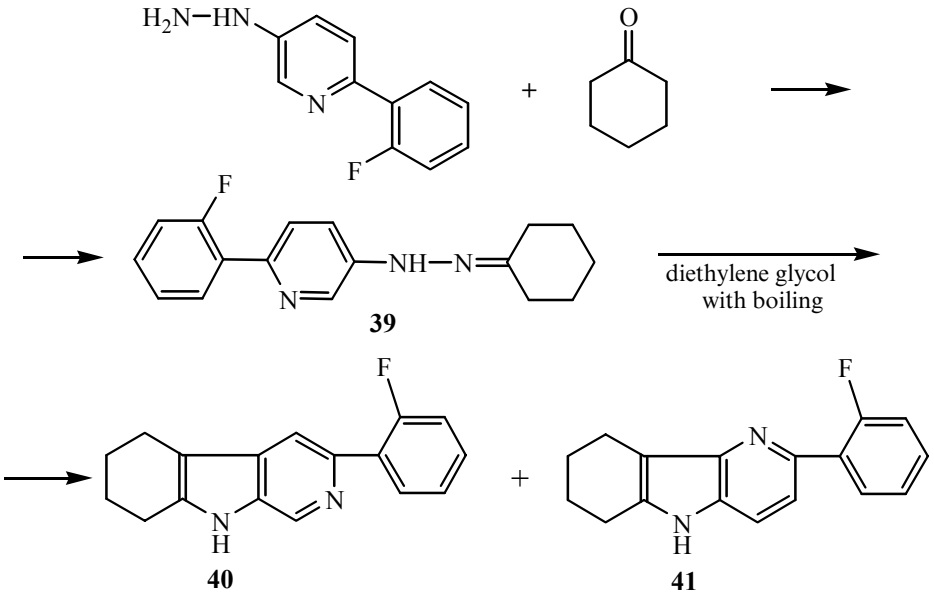
The reaction of 2,4,5-trichloro-6-hydrazinonicotinonitrile with a series of aliphatic, aromatic, and α,β-unsaturated aldehydes and ketones gave the corresponding hydrazones. The mass spectra of the products were studied, and paths for the fragmentation of their molecular ions under electron impact were proposed [40].

The pyridylhydrazones formed in the reactions are capable of entering into further chemical transformations. The most interesting in our opinion are the cyclization reactions, leading to heterocyclic derivatives of pyridines.

Such reactions include the indole cyclization of 2-pyridyl- and 4-pyridylhydrazones [41]. The widely used Fischer cyclization requires the use of $ZnCl_2$ as condensing agent, but there are data indicating that the cyclization of pyridylhydrazones according to this scheme is initiated not by acidic catalysts but by heat [42]. The 4-pyridylhydrazones of acetone, propionaldehyde, acetophenone, and cyclohexanone are converted into azaindoles in the Fischer reaction by heating in triethylene or diethylene glycol [41, 43, 44].

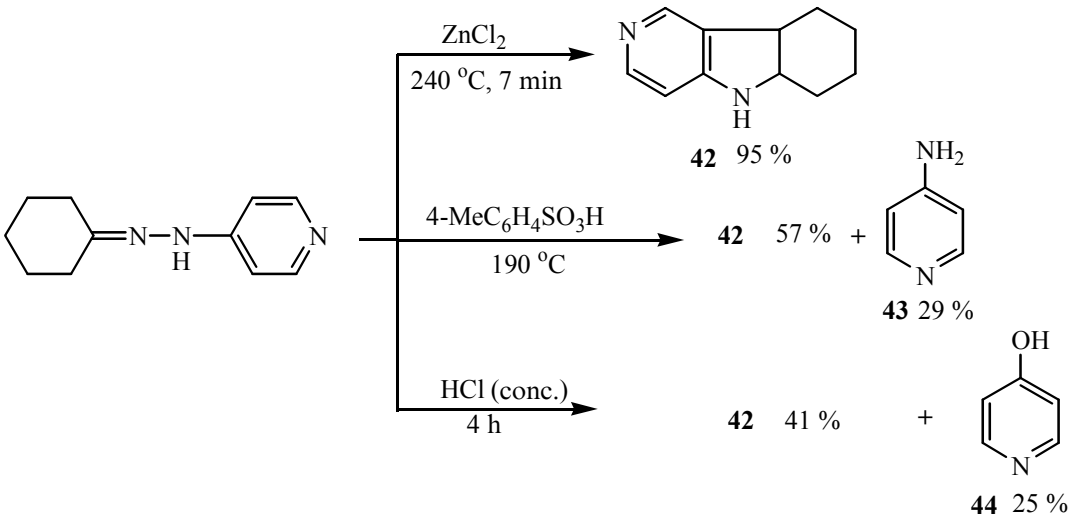


In the case of cyclohexanone two isomeric compounds **40** and **41** can be formed as a result of cyclization [45]:

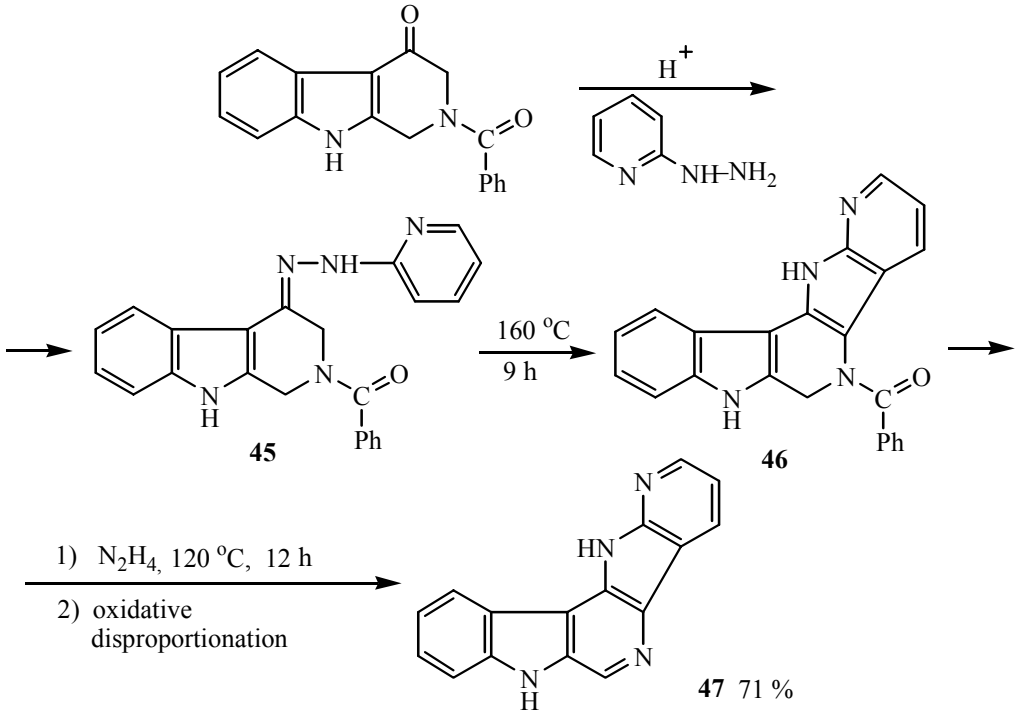


The authors point out that boiling in di- and triethylene glycol cannot be considered a noncatalytic reaction, since it is possible that these solvents have a catalytic effect at high temperature.

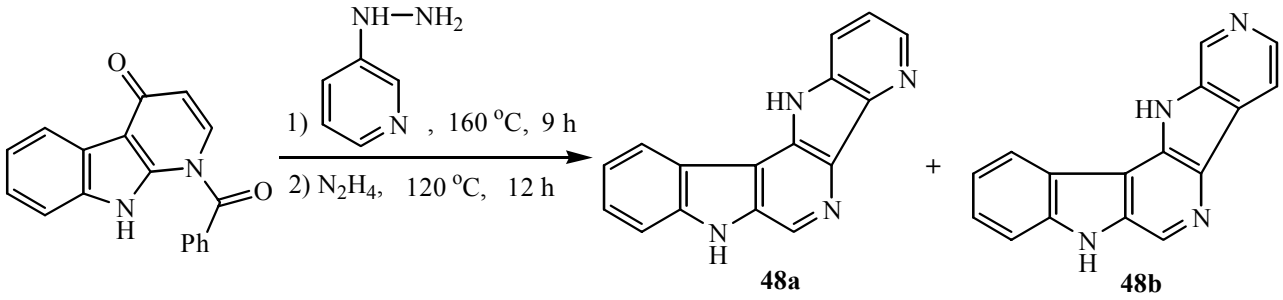
In certain cases it has been reported that various compounds have catalytic activity in the cyclization of pyridylhydrazones. Indolization of the 2-pyridylhydrazones of acetone and acetaldehyde is promoted by fluorinated Al_2O_3 [41]. Fischer cyclization of cyclohexanone 4-pyridylhydrazone takes place successfully in acidic media [42, 44]:



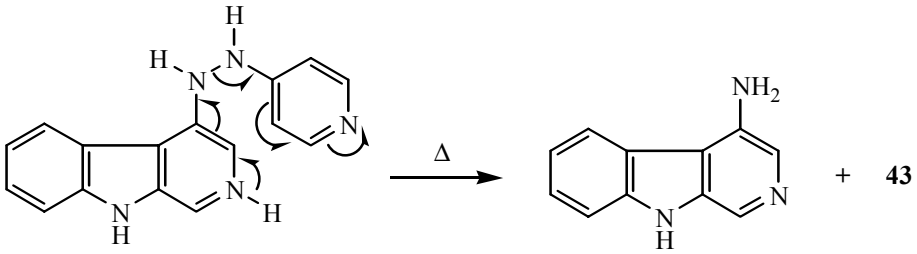
The reaction of pyridoindoles with hydrazinopyridine was investigated in the search for water-soluble ligands for benzodiazepine receptors. It was found that Fischer cyclization takes place successively with 2- and 3-hydrazinopyridines:



As expected, a mixture of isomers **48a** and **48b** was obtained in the case of 3-hydrazinopyridine:



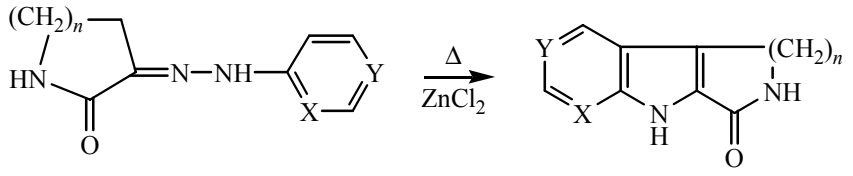
It was established that 4-hydrazinopyridine reacts according to a different scheme, leading to 4-amino-β-carboline (**49**) and 4-aminopyridine (**43**) [46]:



49

The authors explain such a reaction path by the fact that the nitrogen atom of the pyridine ring in this case promotes effective delocalization of the electron density of the transition state in the pyridine ring. This probably prevents cyclization and leads to the predominant formation of the 4-aminopyridine [27, 46].

The hydrazones of oxolactams, obtained by reaction with 2- or 4-hydrazinopyridine, undergo cyclization when heated in the presence of $ZnCl_2$ with the formation of the tricyclic compounds **50** [47]:

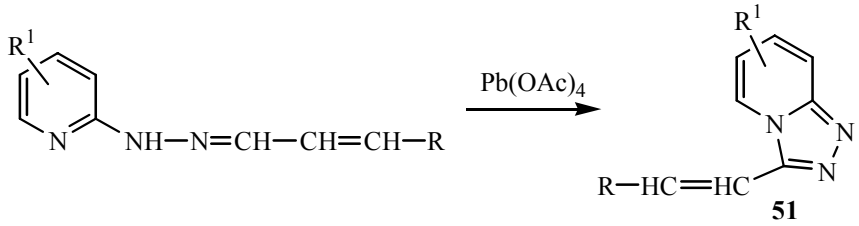


50 (74–100 %)

n = 2, 3; X = N, Y = CH; X = CH, Y = N

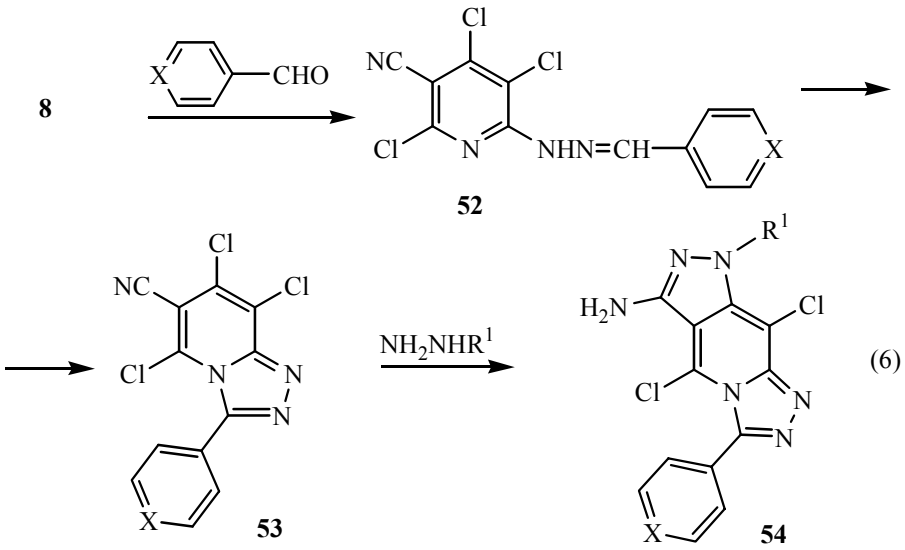
In the presence of certain catalytic systems the cyclization of 2-pyridylhydrazones of carbonyl compounds takes place with participation of the nitrogen atom of the pyridine ring. Thus, the action of hydrochloric acid and BF_3 etherate on cyclohexanone 2-pyridylhydrazones leads to the formation of either carbazole or triazine derivatives [41].

In the presence of lead tetraacetate the 2-pyridylhydrazones of aldehydes undergo cyclization to triazoles at the nitrogen atom of the pyridine ring [48] and not to the respective pyrazolines, as could be expected:



51

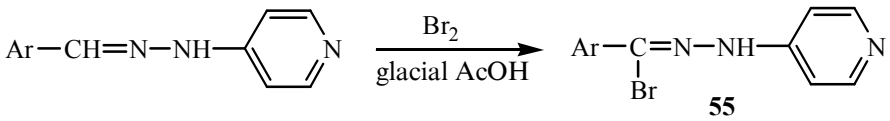
By analogy, under the influence of lead tetraacetate in acetic acid the series of *p*-substituted benzaldehydes and 4-pyridylaldehyde undergo oxidative heterocyclization to annellated 1,2,4-triazolo[4,3-*a*]-pyridines **53** with yields of 50-80% [reaction (6)] [49, 50]. It was noticed that the yields of the products of heterocyclization depend on the type of substituent at the *p*-position to the carbonyl group; the yield of the triazolopyridines increases with increase in the donating characteristics of the substituent [49]. During reaction of the products with hydrazines nucleophilic substitution takes place at position 4 of the pyridine ring and is accompanied by heterocyclization at the cyano group with the formation of annellated tricyclic systems **54** (yields 40-70%) [50]:



X = CR; R = OH, H, OMe, F, Cl; X = N; R^1 = H, Ph

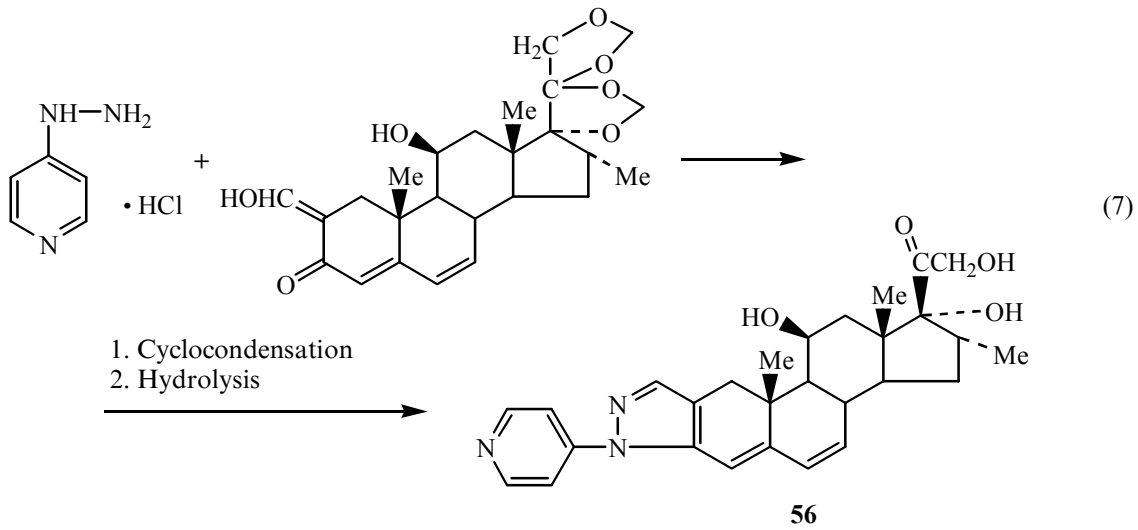
The authors explain the ease of oxidative heterocyclization by the existence of a favorable *cis* configuration in the hydrazone fragment, and this was confirmed by X-ray crystallographic analysis of the compounds [50]. (The same was observed earlier during the formation of tosyl-2-azetidines [51].)

In glacial acetic acid 4-pyridylhydrazones are capable of a different type of reaction. It was shown [52] that substitution of the methine proton is possible in reaction with Br_2:

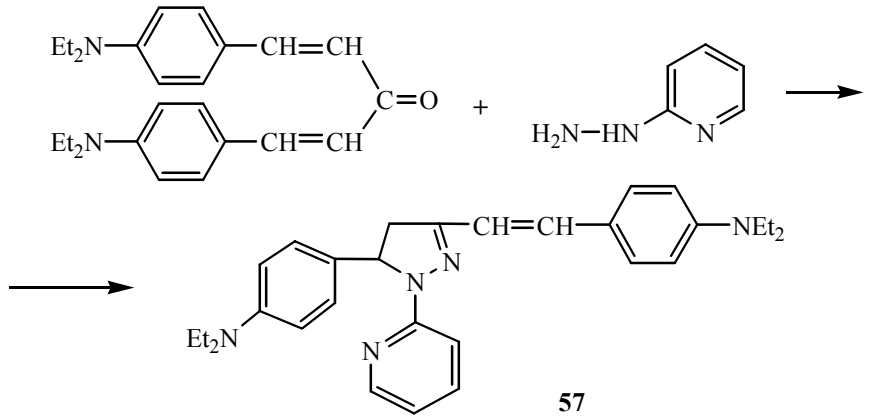


It was established that the stage determining the reaction rate is isomerization of the predominant *E* isomer to the active *Z* isomer.

The use of pregnadienones in the synthesis of hydrazones based on 4-hydrazinopyridine leads to the production of pregnatrienopyrazole **56**, which exhibits activity toward granuloma and is a resorption and anti-inflammatory agent [5, 53, 54]:

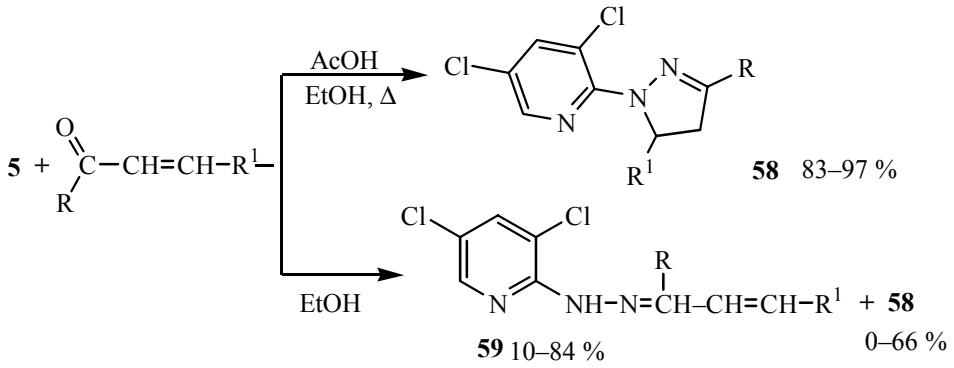


The respective pyrazolines can be obtained in the reaction of hydrazinopyridines with α,β-unsaturated carbonyl compounds. Thus, the reaction of 2-hydrazinopyridine with bis(*p*-diethylaminostyryl) ketone in ethanol in the presence of acetic acid gave the pyridyl-substituted pyrazoline **57** with a yield of 35% [55]:



57

The respective pyrazolines were also obtained with high yields (83-97%) by boiling a mixture of the hydrazinopyridine **5** with α,β-unsaturated aldehydes and ketones [56]:



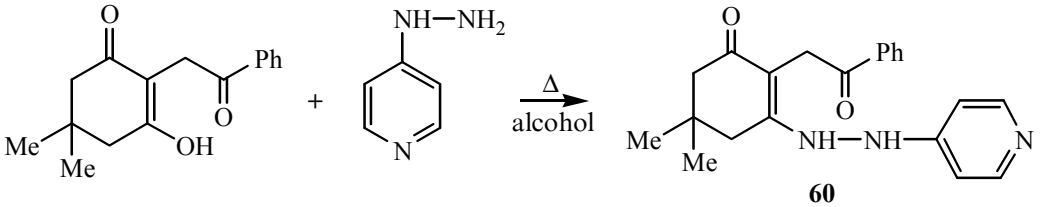
59 10–84 %

58 83–97 %

0–66 %

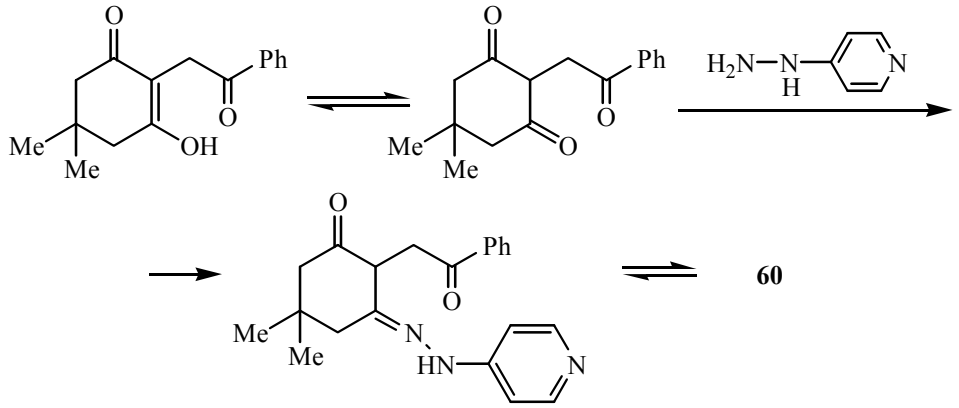
In the case of the reaction at room temperature a mixture of linear **59** and cyclic **58** products is formed. Their yield and ratio depend on the type of substituents in the carbonyl component [56].

During the development of methods for the production of products acting on the central nervous system [57] a series of reactions of polyfunctional carbonyl compounds with monosubstituted hydrazines and, in particular, with 4-hydrazinopyridine were carried out. In contrast to the formation of the corresponding hydrazone and subsequent cyclization usually observed in such cases, a good yield of the noncyclic product **60** from substitution of the hydroxy group was obtained:

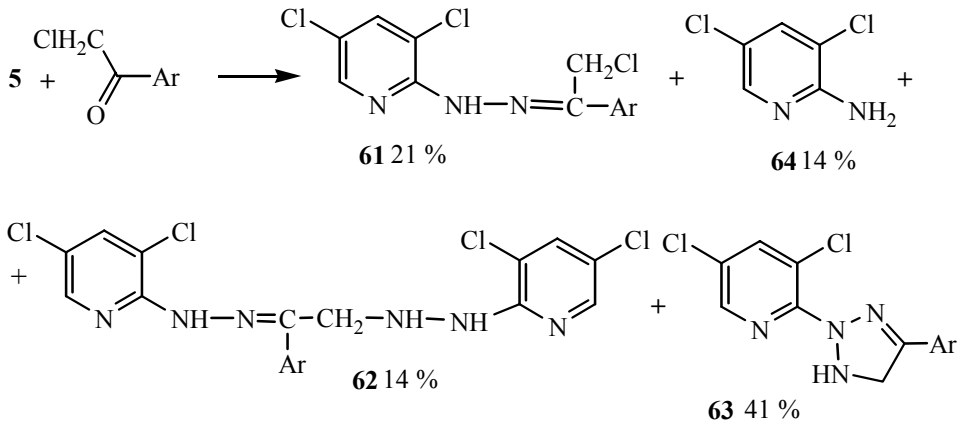


60

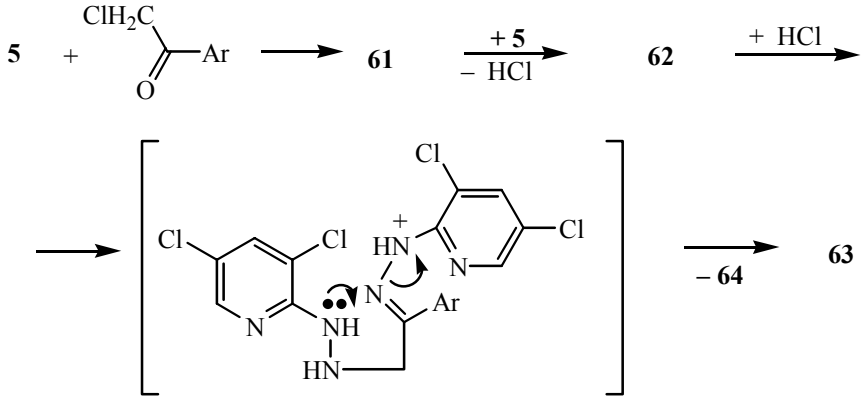
The reasons for the unexpected course of the reaction were not discussed by the authors. However, the structure of compound **60** was confirmed by the required analyses and spectral data. It can be supposed that the reaction takes place through the formation of a hydrazone with the tautomeric form of the polyfunctional carbonyl compound:



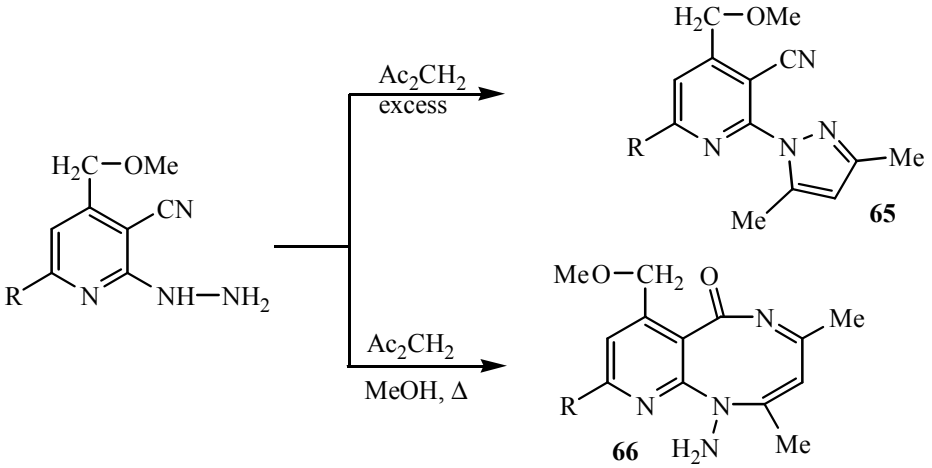
An unusual reaction between hydrazinopyridine **5** and 2-chloro-3',4'-dihydroxyacetophenone, leading to the formation of three other products **62**-**64** in addition to the required hydrazone **61**, was discovered [58]:



The authors suggested the following scheme for the formation of the indicated compounds in [58]:



In the case of the reaction with dicarbonyl compounds the direction of the process is affected by the structure of the initial hydrazinopyridine and by the reaction conditions [59]. It was established that the condensation of 4,6-disubstituted 3-cyano-2-hydrazinopyridines with acetylacetone without a solvent in an excess of the β-dicarbonyl compound leads to the 2-(1-pyrazolyl)pyridine **65**. At the same time cyclization in boiling methanol leads to the aminodiazepine **66**:

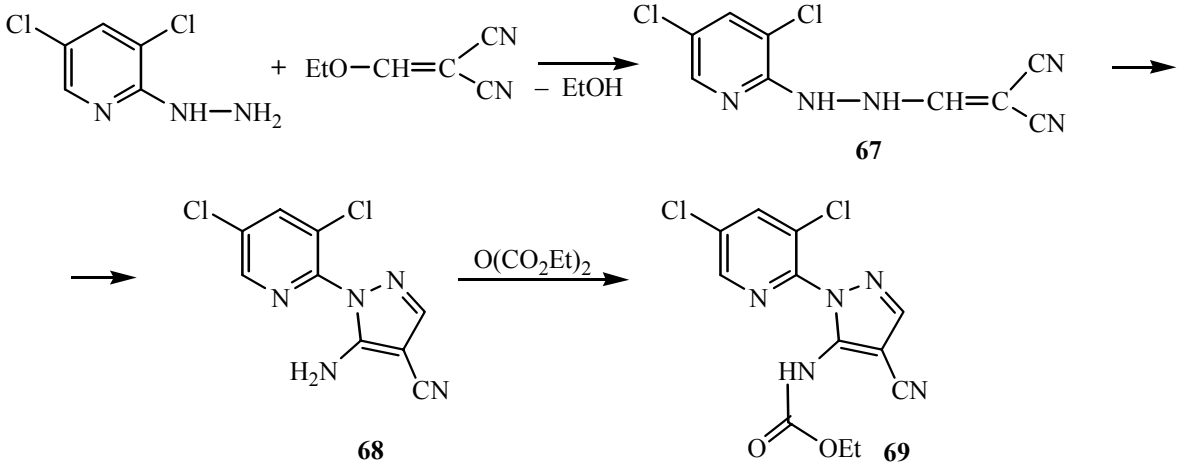


When the hydrazinopyridine **5** is boiled with acetylacetone and dibenzoylmethane in ethanol in the presence of acetic acid the corresponding 1-(3,5-dichloro-2-pyridyl)pyrazoles are formed [56]. A pyridyl-substituted pyrazolone is produced similarly by the reaction of compound **5** with acetoacetic ester [56].

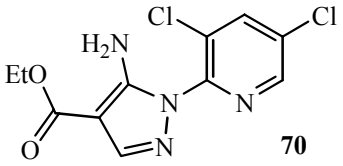
2.5. Synthesis of Nitrogen Heterocycles Based on Hydrazinopyridines

In addition to the examples of the production of pyridyl-substituted heterocycles based on the reaction of hydrazinopyridines with carbonyl compounds described above, which are essentially further transformations of the corresponding initially formed hydrazones, the literature contains a series of syntheses of hetarylpyridines with substrates whose functional groups are capable of reacting with the hydrazine fragment.

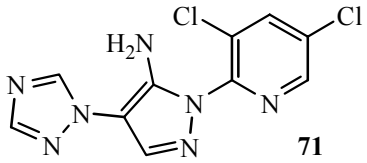
In 1984-1985 effective herbicides synthesized according to the following scheme were patented [10, 13, 60, 61]:



Acylation was used to enhance the herbicidal characteristics of the obtained compounds [60].
The pyrazolylpyridines **70** [10, 13] and **71** [61] were obtained by an analogous reaction:

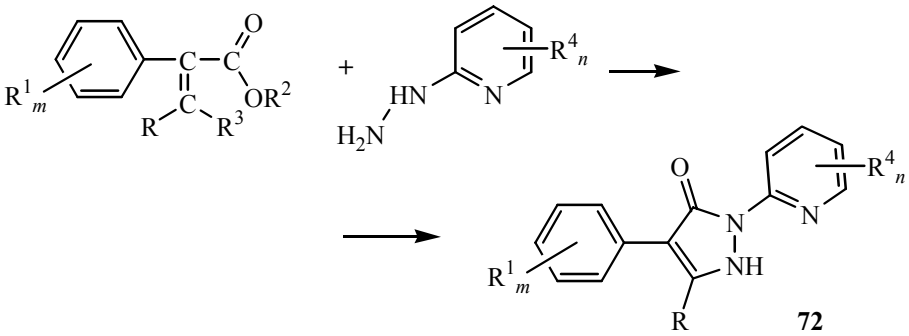


70



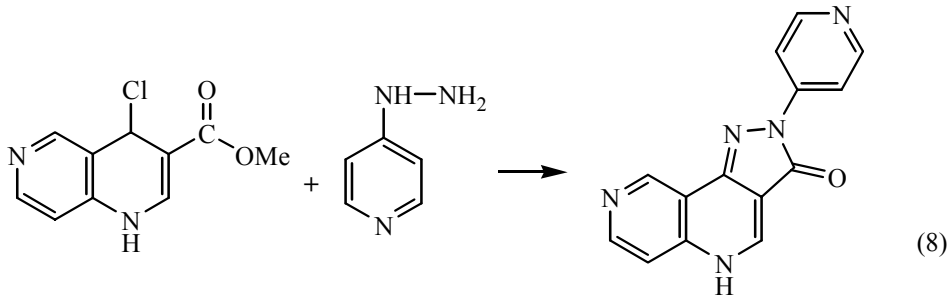
71

The pyridylpyrazolones **72** were obtained by the reaction of hydrazinopyridines with α-aryl-substituted esters of α,β-unsaturated carboxylic acids [62]:



72

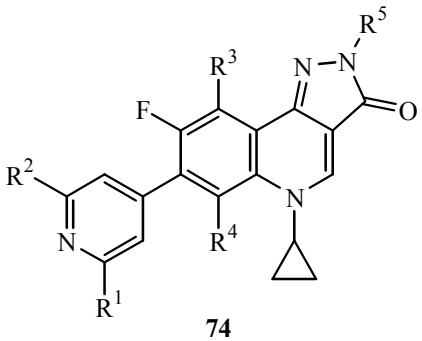
The polyheterocyclic compound **73**, containing three pyridine and pyrazoline fragments, was obtained according to scheme (8) [63]:



(8)

73

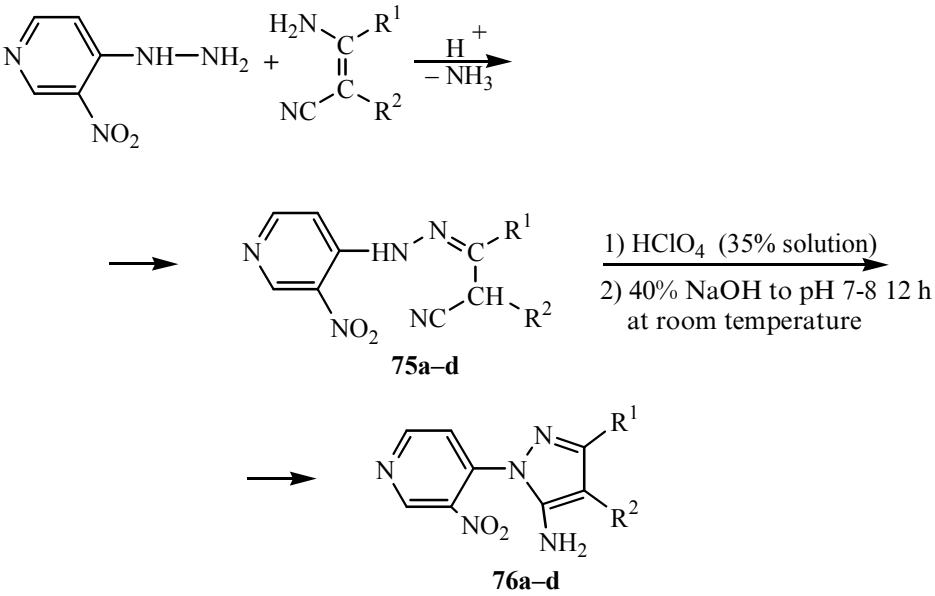
Pyrazole compounds with the following structure were obtained in a similar way [2]:



74

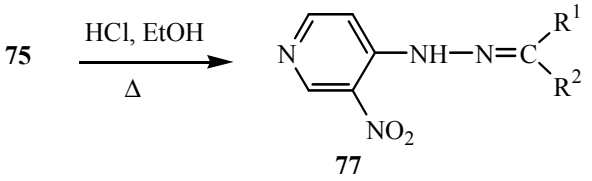
R2 = 2-pyridyl or 4-pyridyl

During cyclization of the hydrazones of β-keto acids **75**, formed in the reaction of 3-nitro-4-hydrazinopyridine with α,β-unsaturated β-amino nitriles, the corresponding aminopyrazoles **76** were obtained [64]:

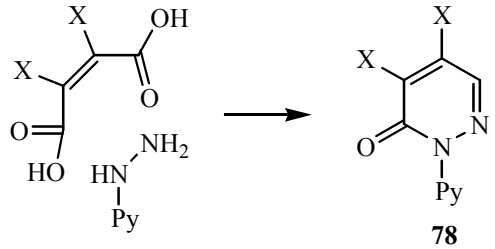


a R^1 = Me, R^2 = H; **b** R^1 = Ph, R^2 = H; **c** R^1 = Et, R^2 = Me; **d** R^1 = Ph, R^2 = Me

It is interesting to note that treatment of the hydrazones **75** with hydrochloric acid in ethanol does not lead to the formation of aminopyrazoles **76**. In the authors' opinion the reason for this may be the electron-withdrawing characteristics of the nitro group, as a result of which the electron density at the –NH– group is reduced, and with harsher reaction conditions the nitrile group is eliminated with the formation of the hydrazones **77** [64]:

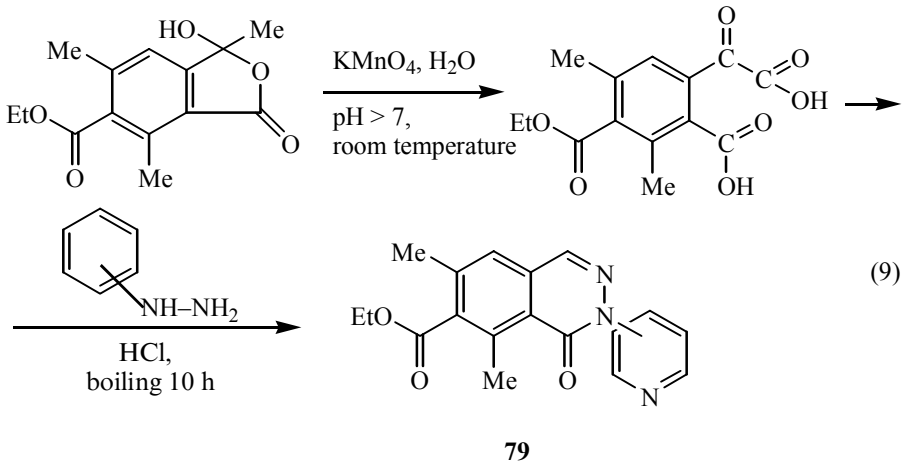


The synthesis of the pyridylpyridazines **78** with yields of ~90% by the reaction of hydrazinopyridines with derivatives of 2-butenedioic acid was described in [65]:



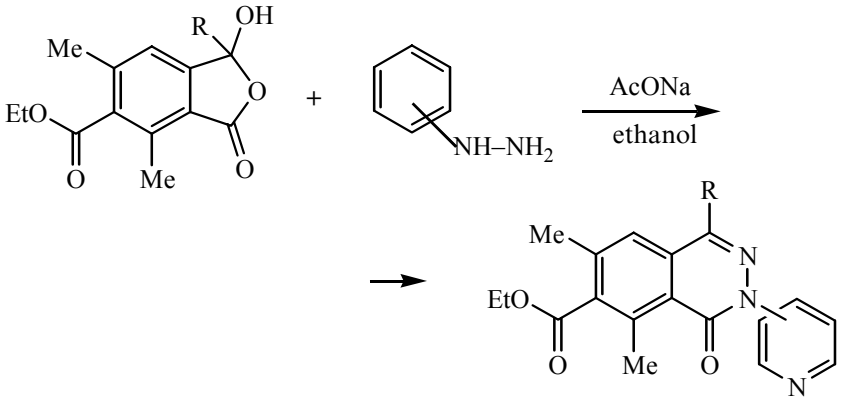
Py = 2-pyridyl, 3-pyridyl, 4-pyridyl, X = Cl, Br

The pyridylphthalazones **79** and **80** were obtained according to schemes (9) and (10) by the reaction of 2- and 3-hydrazinopyridines with the respective substrates [66, 67]:



(9)

79

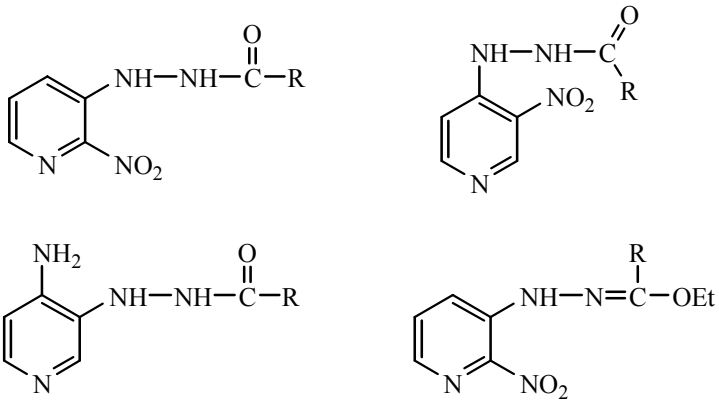


(10)

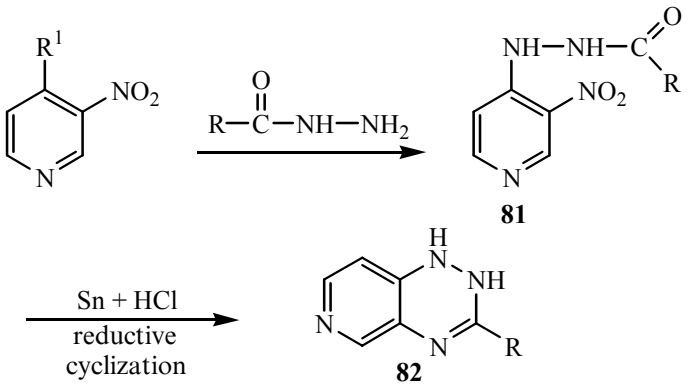
R = H, Alk, CH_2OH

80

Pyridines condensed with triazine rings were obtained from acylated hydrazinopyridines or hydrazones with the following structures:

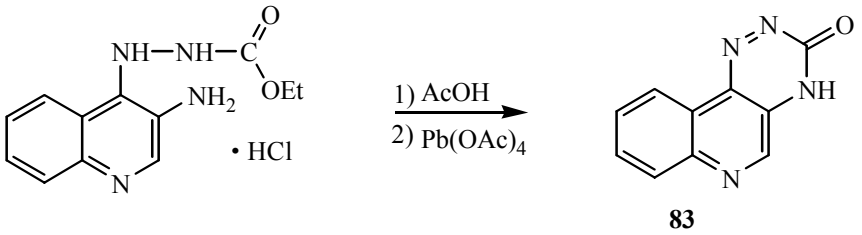


The desired reaction required the presence of an amino group or nitro group, which may be reduced either beforehand or during the cyclization process, at the *o*-position to the hydrazino group [35, 39, 68-70]. The hydrazino group can also be acylated before cyclization, or an acetylated hydrazino group can be introduced before cyclization by substitution of a halogen atom or an alkoxy group at the *o*-position to the nitro group:

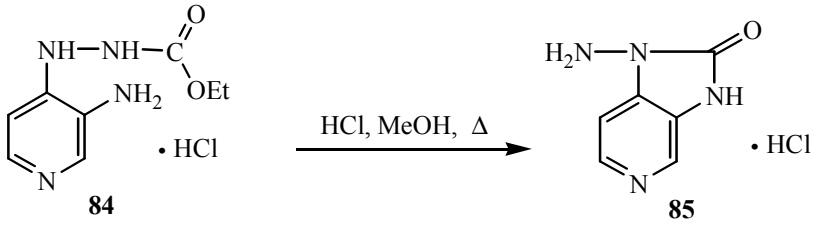


R^1 = Hal, OAlk

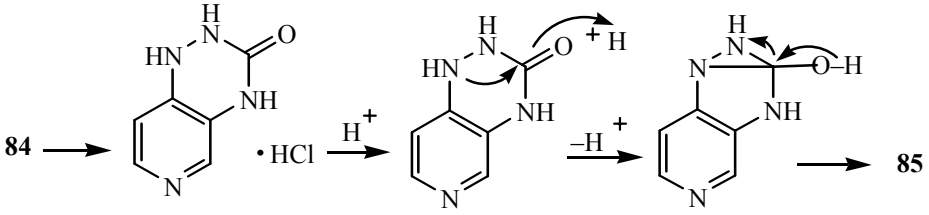
If there is a carboxylate group in the initial compound, the final cyclization product is the triazinone **83** [71]:



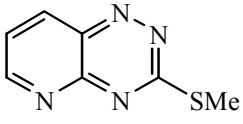
In the case of the pyridine **84** the use of HCl as catalyst leads to compound **85** [72].



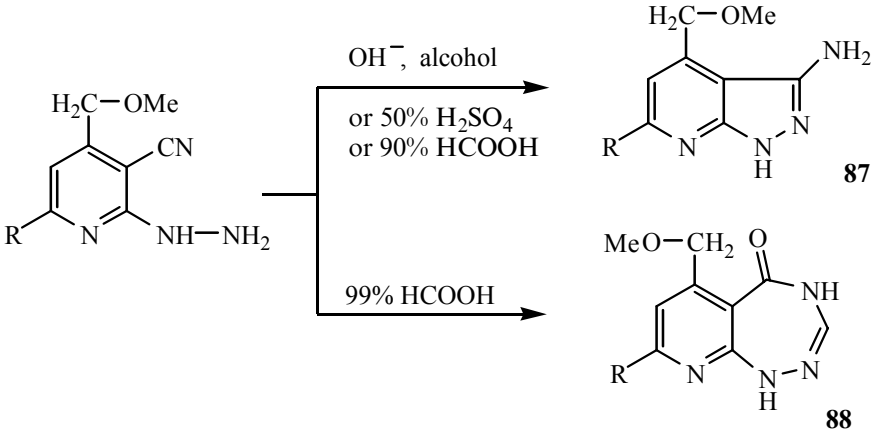
It was assumed that the 1-amino-1H-imidazo[4,5-*c*]pyridin-2(3H)-one (**85**) is formed according to the following scheme:



The pyridotriazine **86** was obtained with a yield of 50% from 2-amino-3-hydrazinopyridine by cyclization with CS_2 followed by methylation with methyl iodide [73]:



The presence of a nitrile group in the molecule of the initial hydrazinopyridine at the position adjacent to the hydrazino group promotes intramolecular cyclization [59], and the process takes place both in an acidic and in an alkaline medium. Thus, the action of an alcohol solution of alkali, 50% sulfuric acid, or 90% formic acid on 4,6-disubstituted 2-hydrazino-3-cyanopyridines leads to the formation of pyrazolo[4,5-*b*]pyridines **87**. With 99% formic acid the pyrido[5,6-*b*]triazepinones **88** are formed.

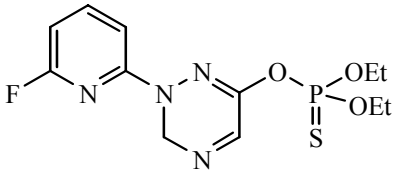


3. POSSIBLE REGIONS OF PRACTICAL APPLICATION OF HYDRAZINOPYRIDINES AND THEIR DERIVATIVES

As a rule hydrazinopyridines and also compounds based on them exhibit high biological activity, and they have therefore found practical use as herbicides, insecticides, fungicides, plant growth regulators, and pharmaceutical products for various purposes (ranging from antipyretics to products with cardiological, antitumor, and immunostimulant activity).

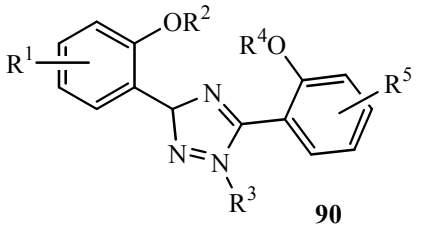
Thus, for example, compounds **69-71** were patented as new highly effective herbicides [10, 13, 60, 61], while according to trials the pyrazole **71** exhibited the highest activity among herbicides of its class [61]. Compound **35** has also been recommended as a herbicide [8].

Compound **89**, which represents a pyridylhydroxytriazine esterified with organophosphorus compounds, has insecticidal characteristics [7]:



89

The substituted 3,5-diaryl-1,2,4-triazoles **90**, which are capable of forming chelate compounds with metals, have been recommended for use as pharmaceutical agents [74]:



90

R^3 = pyridyl, alkylpyridyl

It was established that certain annellated hydrazinopyridines **31** exhibit antiswelling characteristics [36].

Some derivatives of hydrazinopyridine **8** exhibit anti-inflammatory, analgesic, antimicrobial, or antidepressant activity [75]. Some have an inhibiting or, conversely, activating effect on the transport function of the Ca–ATPase of sarcoplasmatic reticulum [76].

Compounds **36** and **74** exhibit antitumor activity [2, 4], and their possible use as antitumor agents has been discussed.

A mixture of the pyridoindoles **40** and **41** exhibits activity as ligands of GABA receptors of the brain [45].

The product of reaction (7) **56**, which exhibits resolving and antiinflammatory activity, was tested in comparison with hydrocortisone. Apart from the anti-inflammatory characteristics the product is capable of inhibiting granuloma, while a 1% solution is active with respect to psoriasis [54]. The authors remark that pyrazole derivatives based on 2-hydrazinopyridine and 3-hydrazinopyridine have insignificant therapeutic effect [5, 53, 54].

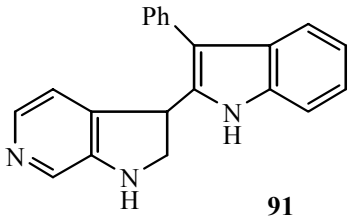
Tests have demonstrated the antidepressant characteristics of compound **60** [57].

The pyridylpyrazolones **72** were recommended for use as pharmaceutical products – inhibitors of lipoxygenase, useful for various diseases: respiratory, blood vessels, inflammatory processes, dermatological, and also as cytoprotectors in diseases of the gastrointestinal tract [62].

Derivatives of pyridylpyrazolones **73** exhibit inhibiting activity toward flunitrazepam [63].

Phthalazones, obtained by reactions (9) and (10). are recommended as antithrombotic agents [66, 67]. Polycyclic systems containing phthalazole fragments exhibit antiinfarction activity [77].

Dihydropyrrolopyridines are of interest as pharmaceutical products [1, 45]. For example, the derivative **91**, synthesized from 3-hydrazino-2-methoxypyridine, exhibits inhibiting activity with respect to H^+ and K^+, which is useful for the treatment of ulcerous complaints [1]:



91

Derivatives of hydrazinopyridines are also used in various regions of industry. In particular, compound **57** has been used to improve the formulas used in electrophotography [55].

The use of the hydrazones of hydrazinopyridine **5** as starting compounds in the synthesis of dyes with special characteristics (fungicides to confer biostability against molds in textile materials) has been described [16].

The presented data on the chemical characteristics of hydrazinopyridines and possible regions of practical application of their derivatives make it possible to regard them as highly reactive and promising raw materials. They can be used effectively in widely varying syntheses that make it possible to introduce a pyridyl fragment into complex organic structures.

REFERENCES

1. T. Takahashi, M Harigome, K. Momose, Sh. Nagai, N. Oshida, M. Sugita, K. Katsuyama, Ch. Suzuki, and K. Nakamaru, Jpn. Patent 06247967; *Chem. Abstr.*, **122**, 105862 (1995).
2. M. P. Wentland, US Patent 5334595; *Chem. Abstr.*, **121**, 230766 (1994).
3. J. E. Francis, K. J. Doebel, P. M. Schutte, E. F. Bachmann, and R. E. Detlefsen, *Can. J. Chem.*, **60**, 1214 (1982).

4. D. Twomey, *Proc. Roy. Ir. Acad., B*, **74**, 37 (1974).
5. Merck and Co. Inc., Austrian Pat. 318827; *Chem. Abstr.*, **83**, 10605 (1975).
6. G. Nadler, M. Martin, and R. Zimmermann, Eur. Pat. Appl. EP 351213; *Chem. Abstr.*, **113**, 59233 (1990).
7. Ch. E. Pawlowski, US Patent 4298602; *Chem. Abstr.*, **96**, 85744 (1982).
8. Sh. Shuitsu, I. Shigenara, S. Mizukoshi, T. Nakajima, Sh. Nishimura, and T. Oshima, Jpn. Patent 02104575; *Chem. Abstr.*, **113**, 115104 (1990).
9. R. Andree, U. Busse, R. Kirsten, H. J. Santel, K. Luerssen, and R. R. Schmidt, Ger. Patent DE 3917469; *Chem. Abstr.*, **114**, 164251 (1991).
10. O. Schallner, R. Gehring, and J. Stetter, Ger. Patent DE 3520330; *Chem. Abstr.*, **106**, 156458 (1987).
11. F. G. Mann, A. F. Prior, and T. J. Willcox, *J. Chem. Soc.*, 3830 (1959).
12. I. Collins, S. M. Roberts, and H. Suschitzky, *J. Chem. Soc., C*, 167 (1971).
13. O. Schallner, R. Gehring, J. Stetter, H.-J. Santel, and R. R. Schmidt, US Patent 4772312; *Chem. Abstr.*, **106**, 156458 (1987).
14. I. Collins and H. Suschitzky, *J. Chem. Soc., C*, 1523 (1970).
15. S. D. McGregor and D. Stanley, US Publ. Pat. Appl. B 537053; *Chem. Abstr.*, **85**, 46366 (1976).
16. K. I. Kobrakov, V. K. Korolev, I. I. Rybina, and V. I. Kelarev, *Khim. Geterotsikl. Soedin.*, 1066 (2000).
17. V. P. Danil'chuk and A. M. Sipyagin, in: *Chemistry and Technology of Pyridine-Containing Pesticides. Collection of Papers* [in Russian], No. 2, Chernogolovka (1988), p. 63.
18. E. G. Aliev, V. G. Kartsev, E. M. Gizatullina, S. V. Chapyshev, and L. O. Atovmyan, in: *Chemistry of Biologically Active Nitrogen Heterocycles. Collection of Papers of Interinstitute Colloquium* [in Russian], No. 1, Chernogolovka (1990), p. 28.
19. S. D. McGregor, US Patent 4087431; *Chem. Abstr.*, **89**, 109124 (1978).
20. I. I. Naumova, V. I. Promonenkov, and A. S. Petrovskii, in: *Chemistry and Technology of Pyridine-Containing Pesticides. Collection of Papers of All-Union Conference* [in Russian], (1988), p. 129.
21. A. M. Sipyagin, S. V. Pal'tsun, I. A. Pomytkin, and N. N. Aleinikov, *Khim. Geterotsikl. Soedin.*, 63 (1994).
22. J. B. Campbell, E. R. Lavagnino, and A. J. Pike, Eur. Pat. Appl. EP 159112; *Chem. Abstr.*, **104**, 148751 (1986).
23. A. Lewis and R. G. Shepherd, *J. Heterocycl. Chem.*, **8**, 41 (1971).
24. R. Gawinecki and D. Rasala, *Heterocycles*, **26**, 2727 (1987).
25. G. A. Mokrushina, Yu. A. Azev, and I. Ya. Postovskii, *Khim. Geterotsikl. Soedin.*, 1004 (1975).
26. Houben-Weyl, *Methoden der organischen Chemie*, Georg Thieme Verlag, Stuttgart, (1967), Vol. 10/2, p. 203.
27. M. J. Martin, M. L. Trudell, H. D. Arauzo, M. S. Alien, A. J. Laloggia, L. Deng, C. A. Schultz, Y.-Ch. Tan, Y. Bi, K. Narayanan, L. J. Dorn, K. F. Koehler, Ph. Skolnick, and J. M. Cook, *J. Med. Chem.*, **35**, 4105 (1992).
28. L. N. Yakhontov and M. F. Marshalkin, *Sintez Geterotsiklicheskikh Soedinenii*, No. 11, 21 (1979); *Chem. Abstr.*, **94**, 30516 (1981).
29. Z. N. Yakhontov and M. F. Marshalkin, USSR Inventor's Certificate 363700; *Chem. Abstr.*, **78**, 159442 (1973). [*Otkrytiya, Izobreteniya, Promyshlennye Obraztsy, Tovarnye Znaki*, **50**, No. 4, 58 (1973)].
30. S. Andreae and E. Schmitz, *Heterocycles*, **37**, 379 (1994).
31. H. Tajika, T. Tezuka, and K. Wada, Jpn. Kokai Tokkyo Koho JP 03200769; *Chem. Abstr.*, **116**, 59231 (1992).
32. S. D. McGregor, D. Stanley, and H. O. Sankbeil, US Patent No. 3947457; *Chem. Abstr.*, **84**, 180074 (1976).
33. S. D. McGregor and D. Stanley, US Patent No. 4127575; *Chem. Abstr.*, **90**, 103850 (1979).
34. A. G. Mark, H. Suschitzky, and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 1472 (1979).

35. P. Benko, A. Messmer, A. Gelleri, and L. Pallos, *Acta Chim. Acad. Sci. Hung.*, **90**, 285 (1976).
36. J. P. Dusza, US Patent No. 4260767; *Chem. Abstr.*, **95**, 132677 (1981).
37. E. M. Gizatullina and V. G. Kartsev, in: *Chemistry of Nitrogen Heterocycles. Abstracts of Interinstitute Colloquium* [in Russian], Chernogolovka (1995), p. 86.
38. V. G. Kartsev, E. M. Gizatullina, and Z. G. Aliev, *Khim. Geterotsikl. Soedin.*, 369 (1992).
39. P. Benko, L. Pallosh, A. Mishshmer, A. Gelleri, I. Sabo, L. Petech, P. Gereg, and A. Varga, USSR Patent 888823, *Otkrytiya, Izobreteniya, Promyshlennye Obraztsy, Tovarnye Znaky*, No. 45, 281 (1981); *Ref. Zh. Khim.*, 15O119P (1982).
40. P. A. Sharbatyan, U. A. Abdullaev, E. M. Gizatullina, V. and G. Kartsev, in: *Chemistry of Biologically Active Nitrogen Heterocycles. Collection of Papers of Interinstitute Colloquium* [in Russian], Chernogolovka (1990), p. 37.
41. Yu. P. Kitaev and B. I. Buzykin, *Hydrazones* [in Russian], Nauka, Moscow (1974).
42. B. Robinson, *The Fischer Indole Synthesis*, J. Wiley and Sons, Ltd., New York (1982), Chap. 2-5 and references cited therein.
43. A. Molina, J. J. Vaquero, J. L. Garcia-Navio, J. Alvarez-Builla, B. de Pascual-Teresa, F. Gago, M. M. Rodrigo, and M. Ballesteros, *J. Org. Chem.*, **61**, 5587 (1996).
44. L. N. Yakhontov, M. F. Marshalkin, and O. S. Anisimova, *Khim. Geterotsikl. Soedin.*, 508 (1972).
45. Ch. A. Blum, A. J. Hutchison, and R. F. Horvath, PCT Int. Appl. WO 94 25.461; *Chem. Abstr.*, **122**, 105865 (1995).
46. Yun-Chou Tan, M. L. Trudell, and J. M. Cook, *Heterocycles*, **27**, 1607 (1988).
47. L. N. Yakhontov, R. G. Glushkov, E. V. Pronina, and V. G. Smirnova, *Dokl. Akad. Nauk*, **212**, 389 (1973).
48. R. N. Butler, F. L. Scott, and T. A. F. O'Mahony, *Chem. Rev.*, **73**, 93 (1973).
49. E. M. Gizatullina, A. V. Piyuk, Z. G. Aliev, and V. G. Kartsev, in: *Chemistry of Biologically Active Nitrogen Heterocycles. Collection of Papers of Interinstitute Colloquium* [in Russian], No. 1, Chernogolovka (1990), p. 48.
50. V. G. Kartsev and E. M. Gizatullina, *Abstracts of Fifth All-Union Conference on the Chemistry of Nitrogen-Containing Heterocyclic Compounds* [in Russian], Part 1, Chernogolovka (1991), p. 50.
51. Z. G. Aliev, A. M. Sipyagin, V. G. Kartsev, and L. O. Atovmyan, *Izv. Akad. Nauk. SSSR. Ser. Khim.*, 134 (1986).
52. A. F. Hegarty, P. J. Maroney, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1466 (1973).
53. J. Hannah, Can. Patent 975 754; *Chem. Abstr.*, **85**, 21723 (1976).
54. J. Hannah, K. Kelly, A. A. Patchett, S. L. Steelman, and E. R. Morgan, *J. Med Chem.*, **18**, 168 (1975).
55. Sh. Ishikawa, Sh. Ohkawa, and Sh. Masubuchi, Ger. Patent DE 2935536; *Chem. Abstr.*, **93**, 115946 (1980).
56. K. I. Kobrakov, I. I. Rybina, V. I. Kelarev, and V. K. Korolev, *Khim. Geterotsikl. Soedin.*, in the press.
57. K. Nagarajan, J. David, and R. K. Shah, *J. Med. Chem.*, **19**, 508 (1976).
58. K. I. Kobrakov, I. I. Rybina, and V. I. Kelarev, *Khim. Geterotsikl. Soedin.*, 1567 (2000).
59. I. S. Arustamova and V. G. Piven', in: *Chemistry of Nitrogen Heterocycles. Abstracts of Interinstitute Colloquium* [in Russian], Chernogolovka (1995), p. 122.
60. K. Dickore, R. Gehring, K. Sasse, H. J. Santel, and R. R. Schmidt, Ger. Patent DE 3520327; *Chem. Abstr.*, **106**, 119882 (1987).
61. J. Stetter, O. Shallner, R. Gehring, M. Linding, H. J. Sautel, and R. R. Schmidt, Ger. Patent DE 3520328; *Chem. Abstr.*, **106**, 8460 (1987).
62. K. Sasse, M. Hammond, F. Seuter, E. Perzborn, B. Pelster, G. Sturton, and T. Abram, Ger. Patent DE 3443308; *Chem. Abstr.*, **105**, 153057 (1986).
63. N. Yokoyama, Eur. Pat. Appl. EP 115469; *Chem. Abstr.*, **101**, 211137s (1984).
64. S. Hauptmann, G. Blattmann, and W. Schindler, *J. Prakt. Chem.*, **318**, 835 (1976).

65. F. Sauter, P. Stanetty, A. Blaschke, and H. Vyplel, *J. Chem. Res., Synop.*, No. 4, 103 (1981); *Chem. Abstr.*, **95**, 97697 (1981).
66. M. Ishikawa, Jpn. Patent 8047678; *Chem. Abstr.*, **94**, 15756 (1981).
67. M. Ishikawa, H. Tanaka, Y. Eguchi, Sh. Ito, Y. Takashima, and M. Kobayashi, Ger. Patent DE 2932259; *Chem. Abstr.*, **92**, 215457 (1980).
68. N. Ple-Colombier, G. Queguiner, and P. Pastour, *J. Heterocycl. Chem.*, **10**, 1073 (1973).
69. E. Gy and T. Gyoguszervegyeszeti Gyar, Ger. Patent DE 2237073; *Chem. Abstr.*, **78**, 124640 (1973).
70. P. Benko, A. Geller, A. Messmer, and L. Pallos, *Magy. Kern. Foly.*, **82**, No. 4, 166 (1976); *Chem. Abstr.*, **85**, 123873 (1976).
71. G. C. Wright, J. E. Gray, and C.-N. Yu, *J. Med. Chem.*, **17**, 244 (1974).
72. G. C. Wright, *J. Heterocycl. Chem.*, **13**, 601 (1976).
73. I. Ya. Postovskii, Yu. A. Azev, and G. A. Mokrushina, *Khim. Geterotsikl. Soedin.*, 1140 (1976).
74. R. Lattman and P. Acklin, PCT Int. Appl. WO 97 49 395; *Chem. Abstr.*, **128**, 114953 (1998).
75. V. E. Kolla, I. I. Gradel', M. V. Pushkareva, G. V. Matveev, A. M. Sipyagin, E. M. Gizatullina, S. V. Pal'tsun, M. V. Eksanova, and V. G. Kartsev, in: *Chemistry of Biologically Active Nitrogen Heterocycles. Collection of Papers of Interinstitute Colloquium* [in Russian], No. 1, Chernogolovka (1990), p. 143.
76. L. V. Tat'yanenko, V. G. Kartsev, A. M. Sipyagin, E. M. Gizatullina, S. V. Pal'tsun, and I. V. Lisetskaya, in: *Chemistry of Biologically Active Nitrogen Heterocycles. Collection of Papers of Interinstitute Colloquium* [in Russian], No. 1, Chernogolovka, (1990), p. 169.
77. T. M. Bare, M. J. Chapdelaine, T. W. Davenport, J. R. Empfield, L. E. Garcia-Davenport, P. F. Jackson, J. A. McKinney, Ch. D. McLaren, and R. B. Sparks, PCT Int. Appl. WO 96 15 127; *Chem. Abstr.*, **125**, 142755 (1996).