

Research on methods for the preparation of hydrazinopyrimidines is reviewed. Ways to use hydrazinopyrimidines in the chemistry of pyrimidine and condensed systems that contain a pyrimidine ring and in the synthesis of polydentate ligands are examined.

Hydrazinopyrimidines constitute a vast class of heterocyclic compounds, interest in which is growing constantly [1]. Individual data on the synthesis and transformations of hydrazinopyrimidines are available in a number of reviews as, for example, in the book by Brown [2]. They are used as reducing agents in photography [3], as catalysts in processes for the preparation of polyurethane foams [4], as additives for epoxide resins [5], as reagents for metal cations [6, 7], as heterocyclic ligands [8-10] and intermediates in the synthesis of polydentate ligands [11-29], as biologically active compounds [30-53], and as intermediates in their synthesis [54-58]. Hydrazinopyrimidines and their derivatives and heterocyclic systems obtained on the basis of these compounds have anti-inflammatory [33, 59-64], antipyretic, pain-relieving [60-62], antibacterial [65], bactericidal [30, 66], and fungicidal [64] activity of the central nervous system [67], have a sedative and blocking effect on it [31], lower the arterial pressure [68], inhibit the enzymatic activity of DNA polymerase III [33, 36, 49, 50], are highly active mutagens [33], have antineoplastic properties and inhibit the growth of sarcoma [35], are preparations for the treatment of asthma and bronchitis [37], and are used as antibiotics [38] and anticancer and antitubercular preparations [37-44, 69-79].

Considering the variety of methods for the preparation of hydrazinopyrimidines, their value in the synthesis of various heterocyclic systems, their practical value, and the growing interest of researchers in this class of compounds, it is expedient to systematize the vast literature data on the chemistry of hydrazinopyrimidines.

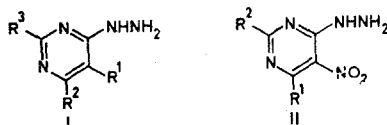
The review encompasses research published in the last 30 yr.

II. METHODS FOR THE PREPARATION OF HYDRAZINOPYRIMIDINES

1. Reaction of Halopyrimidines with Hydrazines

The most widely used method for the preparation of 2-, 4-, and 6-hydrazinopyrimidines consists in the action of hydrazines on chloropyrimidines in an alcohol medium. Thus 4-hydrazinopyrimidines (I) were obtained when 4-chloropyrimidines were refluxed with hydrazine hydrate for 15.5 h [80]. 4-Hydrazine-5- α -naphthyl- and 5-amino-4-hydrazino-6-methyl- [81], 4-hydrazino-2-methyl-6-[2-(5-nitro-2-furyl)vinyl]- [66-82], and other 4-hydrazinopyrimidines [37, 83-98] were synthesized under similar conditions, but the reagents were refluxed for 1-3 h.

In a number of cases 4-hydrazinopyrimidines are formed at room temperature [99-102], by brief heating [103], or at low temperatures [87]. For example, 2-alkylthio-4-hydrazino-6-methylpyrimidines are obtained by refluxing 0.01 mole of 2-alkylthio-4-chloro-6-methylpyrimidines with 0.03 mole of hydrazine hydrate in 10 ml of ethanol for 5 min [103], while 4-hydra-



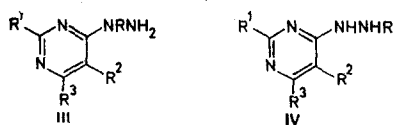
I $R^1 = C_1-C_7$ -alkyl, cyclohexyl, CF_3 , Cl; $R^2 = H$, CH_3 , $CH=CH_2$; $R^3 = C_1-C_5$ alkyl, $C_6H_5OCH_2CH_2$; II $R^1 = CH_3$, CH_3O ; $R^2 = CH_3$, Cl

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zino-5-nitropyrimidines (II) are obtained in 79-94% yields by the action of hydrazine hydrate on the corresponding 4-chloropyrimidines at -10 to -5°C for 40-90 min [87].

Butanol [104], dimethylformamide [101], water [99], and benzene or hydrazine hydrate [100, 105, 106] have also been used as solvents for this reaction. The yields of the desired products are generally greater than 60%.

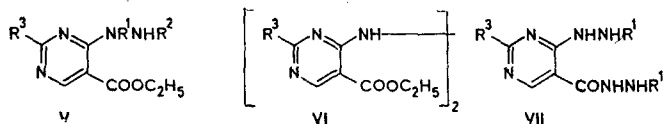
Severe conditions are required in some cases for the replacement of the chlorine atom by a hydrazino group. For example, to obtain 5-alkyl-2-dimethylamino-4-hydrazinopyrimidines the reaction is carried out in refluxing Cellosolve, while replacement of the chlorine atom in 2-chloro-4,6-bis(dimethylamino)pyrimidine is carried out at 140-150°C (for 10 h) in ethanol in the presence of copper bronze in a sealed tube [31]. The reaction of chloropyrimidines with monosubstituted hydrazines generally gives only one of the possible isomers, the structure of which depends on the nature of the substituent in the starting hydrazine, i.e., on the electron density on the nitrogen atoms of the hydrazine and on the steric hindrance that develops in the course of the reaction, which is also due to the presence of a substituent in the starting hydrazine. Thus the corresponding 4-(1-R-hydrazino)pyrimidines (III) are formed in the reaction of 5-amino- or 5-methylamino-4,6-dichloropyrimidine with methyl- or benzyl-hydrazine [99, 100, 107], while the corresponding 4-(2-R-hydrazino)pyrimidines (IV) are formed in the reaction of 5-amino-4,6-dichloropyrimidine with diphenylmethylhydrazine [108] or 4-chloro-5-carbethoxy-2-methylthiopyrimidine with phenylhydrazine [102].



III R=CH₃, C₆H₅CH₂; R¹=H; R²=NH₂, CH₃NH; R³=Cl; IV R=C₆H₅, 2-imidazolyl, R¹=H, CH₃; R²=Br, COOC₂H₅; R³=H

Hydrogen chloride, which is usually neutralized by excess hydrazine, is liberated in the reaction of chloropyrimidines with hydrazines. However, potassium carbonate [103, 109-111] or sodium ethoxide [108] is sometimes used to neutralize this acid.

When insufficient hydrazine is present, 1,2-dipyrimidinylhydrazines are formed along with hydrazinopyrimidines [102, 112, 113]. For example, the reaction of 4-chloro-5-carbethoxy-2-methylthio(or 2-amino)pyrimidine with hydrazine hydrate gives, in addition to the desired product V, the corresponding 1,2-di(4-pyrimidinyl)hydrazine (VI), which is the principal factor in decreasing the amount of hydrazine hydrate [102, 113]. 4-Hydrazinopyrimidine-5-carbohydrazide (VII) was isolated as a side product [113].



V-VII R³=CH₃, NH₂; V R¹=H, CH₃; R²=H, C₆H₅; VII R¹=H, C₆H₅

The reaction of 2-chloro-5-nitropyrimidine with hydrazine hydrate proceeds similarly [114].

It should be noted that in some cases the formation of 1,2-dipyrimidinylhydrazines occurs not only in the case of the appropriate reagent ratio but also in the case of a definite order of addition of the reagents. For example, if 4-chloro-2,6-dimethyl-5-nitropyrimidine is added to a solution of hydrazine hydrate at -5°C, 4-hydrazino-2,6-dimethyl-5-nitropyrimidine is obtained, while 1,2-bis(2,4-dimethyl-5-nitro-6-pyrimidinyl)hydrazine is obtained when the order of addition of the reagents is reversed [87].

The halogen atom in the 4 or 6 position is primarily replaced by a hydrazino group in the action of hydrazine hydrate on polyhalopyrimidines. The halogen atom in the 5 position has the lowest reactivity. Thus 2,4-dichloro-6-(2-phenylhydrazino)pyrimidine is formed when phenylhydrazine is refluxed with 2,4,6-trichloropyrimidine in ethanol for 30 min [115]. A mixture consisting of 2-[1,1-bis(2-chloroethyl)hydrazino]-4,6- and 4-[1,1-bis(2-chloroethyl)hydrazino]-2,6-dichloropyrimidine (in 5 and 73% yields, respectively) was obtained by the action of 1,1-bis(2-chloroethyl)hydrazine on 2,4,6-trichloropyrimidine in dioxane in the presence of triethylamine at 70°C for 3-4 h [116]. The corresponding 4-hydrazinopyrimidines were ob-

tained in the reaction of 2,4-dichloropyrimidine or 2,4-dichloro-6-methoxypyrimidine with hydrazine hydrate [117-119] and formyl- or acetylhydrazine. The corresponding 2-hydrazino-5-bromo(or chloro)- or 4-hydrazino-5-bromopyrimidines are formed in the reaction of 5-bromo-2-chloropyrimidine [108], 5-bromo-4-chloropyrimidine [120, 121], or 2,5-dichloropyrimidine [122] with hydrazine hydrate [120-122] or 2-hydrazino-4,5-dihydroimidazole [108].

If the necessary amount of hydrazine is used, the corresponding dihydrazinopyrimidines are formed from 2,4- or 4,6-dichloropyrimidines [5, 99-101, 123-215].

It must be noted that in the action of hydrazines on 2-, 4-, or 6-chloropyrimidines that contain alkylthio [35, 45, 102, 100, 126], mercapto [110], hydroxy [93], alkoxy [5, 110, 126], dimethylamino [125], amino [127], or cyano [95, 96] groups primarily the chlorine atom is replaced by a hydrazino group.

2. Reaction of Thio- and Alkylthiopyrimidines with Hydrazines

The reaction of hydrazines with thio- and alkylthiopyrimidines is usually employed for the preparation of 2-hydrazinopyrimidines, since 2-thio- and 2-alkylthiopyrimidines are more accessible in some cases than the corresponding 2-chloropyrimidines. The reaction is generally carried out in alcohol. The reaction times and the yields of the desired products depend on the starting compounds and vary over wide ranges [111, 128-137]. For example, the corresponding 2-hydrazinopyrimidine is obtained in 82% yield when 4-methyl-2-methylthio-5-carbomethoxypyrimidine is heated with hydrazine hydrate in alcohol for 7 min [132]. The corresponding 2,4-dihydrazinopyrimidines are obtained in 55-70% yields under similar conditions from 2,4-dimercapto-6-phenyl(or benzyl)pyrimidine [136]. Less frequently, the reaction is carried out in butanol [135] or in anhydrous hydrazine [137]. In the latter case 4-amino-2-hydrazinopyrimidine-5-carboxylic acid amide was obtained in quantitative yield (after refluxing for 2 h in an argon atmosphere) from 4-amino-2-ethylthiopyrimidine-5-carboxylic acid amide.

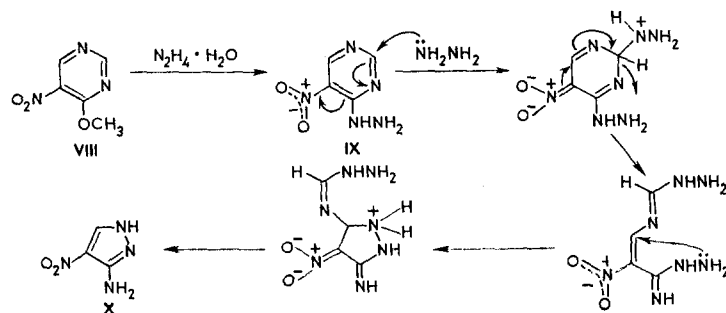
Ethyl 5-phenylazopyrimidine-2-thioacetate [138], 2-thiouracils [54, 56, 139], and 2-thio-barbituric acid [140] have also been used as starting compounds in this reaction. The yields of the corresponding 2-hydrazinopyrimidines reach 95%.

If the starting alkylthiopyrimidine contains an alkoxy group, as in the case of 2-alkylthio-4-methyl-6-methoxypyrimidines, primarily the alkylthio group is replaced by the action of hydrazine, whereas primarily the alkoxy group is replaced by a hydrazino group when thio and alkoxy groups are present in the molecule, as in the case of 5-amino-4-methoxy-6-thiopyrimidine [111].

It should be noted that in the preparation of 2-hydrazinopyrimidines from 2-thio- and 2-alkylthiopyrimidines and hydrazine hydrate the reaction may proceed with opening of the pyrimidine ring or with the formation of pyrazole derivatives. The direction of this reaction depends markedly both on the reaction conditions and on the substituents in the 4 and 6 positions [134, 140]. Hydroxy groups particularly promote transformation of the pyrimidine ring. Pyrimidine derivatives that do not contain hydroxy groups are generally resistant to the action of hydrazines. For example, 2-hydrazino-4,6-dimethylpyrimidine is formed in 35% yield when 2-methylthio-4,6-dimethylpyrimidine is heated with hydrazine hydrate in an autoclave at 150°C for 20 h, while 3-methyl-5-pyrazolone is obtained in 80% yield when 2-methylthio-4-methyl-6-hydroxypyrimidine is heated with hydrazine hydrate for 4 h. At the same time, 2-hydrazino-4-methyl-6-hydroxypyrimidine is obtained in good yield when the latter reaction is carried out for 10 min [134].

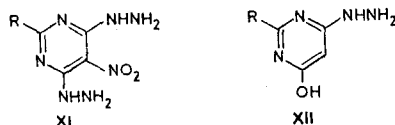
3. Reaction of Alkoxy- and Alkylthiopyrimidines with Hydrazines

The reaction of alkoxy- and alkylthiopyrimidines with hydrazines is used rather rarely as a method for the preparation of hydrazinopyrimidines. Nevertheless, it is of both practical [87, 141-147] and theoretical interest [145-149]. Thus the reactions of alkoxy-5-nitropyrimidines with hydrazines proceed via different pathways, depending on the reaction conditions. For example, a mixture of 2,4-dihydrazino- and 4-hydrazino-6-methyl-2-methoxy-5-nitropyrimidine was obtained when 2,4-dimethoxy-6-methyl-5-nitropyrimidine was refluxed with hydrazine hydrate in ethanol for 2 h [141]. 4-Hydrazino-6-methyl-5-nitro-2-propoxypyrimidine was obtained exclusively from 4-methoxy-6-methyl-5-nitro-2-propoxypyrimidine under similar conditions but with refluxing for 5 h [141].



4-Methoxy-5-nitropyrimidine (VIII) reacts with hydrazine at temperatures below 0°C to give 4-hydrazino-5-nitropyrimidine (IX) [87, 145-147], while 3-amino-4-nitropyrazole (X) is formed in 69% yield when excess hydrazine is used and the reaction is carried out at temperatures above 20°C [146, 147]. Temple and co-workers [144] have proposed a mechanistic scheme for this reaction (see above) that differs from the usual mechanism for the conversion of pyrimidines to pyrazoles [134, 140], according to which hydrazine adds to the 1-6 or 3-4 bond of the pyrimidine with the subsequent loss of an N₁-C₂-N₃ fragment.

Also of interest is the reaction of hydrazines with 4,6-dimethoxy-5-nitropyrimidines, which react rapidly with hydrazine to give 4,6-dihydrazino-5-nitropyrimidines (XI) in excellent yields [142, 143, 149], do not react with phenylhydrazine [149], and react with methylhydrazine, 1,2-dimethylhydrazine, and 1,1-diethylhydrazine to give, instead of the products of direct nucleophilic substitution of the methoxy group, products of more profound transformations, viz., 4-hydrazine-6-hydroxypyrimidines (XII) [142, 143, 148, 149], to which initially the 3-methyl-7-(1-methylhydrazino)-3H-triazolo[4,5-d]pyrimidine 1-oxide structure was erroneously assigned [139].



XI, XII R=H, CH₃, C₆H₅

A detailed investigation of this reaction enabled Christensen and co-workers to propose a mechanism that includes reaction of the solvent with 4,6-dimethoxy-5-nitropyrimidine and subsequent transformation of the resulting salt [148].

4. Reaction of Methylsulfonylpyrimidines and Pyrimidinesulfonic

Acid Derivatives with Hydrazines

An investigation of the reaction of 5-methoxy-, 5-methoxycarbonyl-, 5-cyano-, and 5-fluoro-2-methylsulfonylpyrimidines with hydrazines showed that nucleophilic substitution in the 2-methylsulfonylpyrimidine series is controlled by the μ effect of the two heterocyclic nitrogen atoms and the substituent in the 5 position [150]. Depending on the substituent, the reaction time varies from 15 min to 3 h and the temperature ranges from 40-50°C. In this reaction nucleophilic substitution takes place in the 2 position, except for the 5-fluoro derivative, from which 5-hydrazine-2-methylsulfonylpyrimidine is formed [150]. It must be noted that in the reaction of 4-chloro-6-methyl-2-methylsulfonylpyrimidine with hydrazine primarily the chlorine atom is replaced to give 4-hydrazino-6-methyl-2-methylsulfonylpyrimidine [97]. 2-Methylsulfonylpyrimidines have also been used to obtain a number of other hydrazinopyrimidines [151].

Pyrimidine-2- and -4-sulfonic acids or their chlorides, amides, and hydrazides are sometimes used as starting compounds for the preparation of 2- and 4-hydrozinopyrimidines [152]. The reaction is usually carried out in lower alcohols, the reaction time is 30-60 min, and the yields of the desired products are usually higher than 90%. Pyrimidinesulfonic acids are usually employed in the form of their potassium salts, and the reaction is carried out in aqueous ethanol. This method has been used to obtain 2-hydrazino-5-methyl- and 4-hydrazino-2,6-dimethylpyrimidine in greater than 90% yields (from the corresponding sulfonyl fluorides), 2-hydrazino-4,6-dimethylpyrimidine (in 95% yield from the sulfonyl fluoride and in 41% yield from the potassium salt of the sulfonic acid), and 4-hydrazino-2,6-dimethylpyrimidine (in 41-46% yield from the potassium salt of the sulfonic acid). In the presence of a limited amount of hydrazine the products of this reaction are dipyrimidinylhydrazines [152].

5. Reaction of 2-Nitroaminopyrimidines with Hydrazines

2-Hydrazinopyrimidines are obtained by the action of hydrazines on 2-nitroaminopyrimidines in an aqueous medium or in hydrazine hydrate by brief heating of the reaction mixture. The yields range from 10 to 90%. This method has been used to obtain a large number of 2-hydrazino-4-R¹-5-R²-6-R³-pyrimidines [R¹ = H, CH₃, OH, NH₂; R² = H, Cl, Br, COOC₂H₅; R³ = H, CH₃, C₆H₅; R²-R³ = (CH₂)₃, (CH₂)₄] [42, 76, 153, 154]. From 2 to 28 moles of hydrazine hydrate per mole of 2-nitroaminopyrimidine are used in the preparation of 2-hydrazinopyrimidines from 2-nitroaminopyrimidines [21, 22, 42, 153, 154]. However, it was recently shown that higher yields of 2-hydrazino-4(3H)-pyrimidinones are obtained in the presence of a minimal excess of hydrazine hydrate and when the reaction is carried out in an aqueous medium [155]. The increase in the yields of 2-hydrazino-4(3H)-pyrimidinones in the latter case is evidently associated with suppression of a competitive reaction, viz., conversion of the pyrimidine ring to a pyrazole ring under the influence of hydrazine hydrate, which is well known in the chemistry of pyrimidine [54, 57, 134, 140].

6. Reaction of Aminopyrimidines and Trimethylpyrimidinylammonium

Salts with Hydrazines

Aminopyrimidines and trimethylpyrimidinylammonium salts are seldom used for the preparation of hydrazinopyrimidines; nevertheless, in certain cases they are useful and effective. For example, 4-amino-2,6-dihydrazinopyrimidine is obtained by refluxing 1 part 2-mercapto-4,6-diaminopyrimidine with 3 parts 80% hydrazine hydrate for 3 h [156], and 4-hydrazino-2(1H)-pyrimidinone is obtained in 41% yields by heating cytosine with hydrazine hydrate at 80°C for 1 h, whereas 1,2-bis(2-oxo-1,2-dihydro-4-pyrimidinyl)hydrazine is formed in 50% yield in the case of heating for 60 h [157].

2-Hydrazino-, 4-hydrazino-, and 2-hydrazino-5-nitropyrimidines are obtained in greater than 70% yields by the action of hydrazine hydrate on the corresponding trimethylpyrimidinylammonium chlorides at 20°C for 15 min. Such quaternary salts are 700-1000 times more reactive than the corresponding chloropyrimidines but five to eight times less reactive than methylsulfonylpyrimidines [158].

7. Other Methods for the Preparation of Hydrazinopyrimidines

2-Hydrazinopyrimidines are obtained by refluxing 2-benzylideneaminopyrimidines with hydrazine hydrate in an aqueous medium for 5-30 min. This method has been used to obtain 2-hydrazino-5-cyanopyrimidine [153, 154], 2-hydrazino-5-(2-hydroxyethyl)-4(3H)-pyrimidinone [76], and a number of other 2-hydrazinopyrimidines in 50-70% yields [76, 153].

A method for the preparation of 2-hydrazino-4(3H)-pyrimidinones by reduction of the corresponding nitroamino derivatives with zinc in acetic acid [6], as well as by electrochemical reduction on a tin cathode [159], has been described. However, these methods are inferior to the method examined above, which consists in the action of hydrazine hydrate on 2-nitroaminopyrimidines, both with respect to the yields of the desired products and the simplicity of the procedure.

1,2-Di(2-pyrimidinyl)hydrazines are obtained by condensation of biguanidine with 1,3-dicarbonyl compounds [160, 161] or by the reaction of 2-nitroaminopyrimidines with 2-hydrazinopyrimidines [153].

Hydrazinopyrimidines can be obtained by reduction of phenylazopyrimidines with sodium hydrosulfite in an alkaline medium at 0°C. This method has been used to obtain 6-(4-hydroxyphenylhydrazino)uracil, 6-(4-hydroxyphenylhydrazino)cytosine [162], and other 6-phenylhydrazinopyrimidines [65].

5-(1,2-Diethoxycarbonylhydrazino)pyrimidines are obtained by the reaction of diethyl azodicarboxylate with the corresponding pyrimidines, such as, for example, 6-amino-1,3-dimethyluracil [163] and 2,4-diamino-6-hydrazinopyrimidine [164].

Replacement of the cyano group by a hydrazino group, as, for example, in 6-cyano-1,3-dimethyluracil (after 30 min at 100°C, with 6-hydrazino-1,3-dimethyluracil as the product in 51% yield), has been described. However, 5-bromo-1,3-dimethyluracil-6-carboxylic acid amide was obtained by the action of hydrazine hydrate or methylhydrazine on 6-cyano-5-bromo-1,3-dimethyluracil under similar conditions [165]. The latter constitutes evidence that this method is useful only in special cases.

1. Action of Water, Acids, and Alkalis

Depending on the conditions and the nature of the substituents, hydrazinopyrimidines display different chemical behaviors under the influence of water, acids, and alkalis. Thus 2(or 4)-bis(2-chloroethyl)hydrazino-4(or 2),6-dichloropyrimidine is resistant to the action of hot hydrochloric acid and an aqueous methanol solution of sodium hydroxide [116], 4-hydrazino-2(1H)-pyrimidinone, and 1,2-bis[2(1H)-pyrimidin-4-yl]hydrazine under similar conditions are converted to uracil and hydrazine [157], and 2-(2-benzylhydrazino)-4,6-dimethylpyrimidine gives 2-hydrazino-4,6-dimethylpyrimidine and benzyl alcohol when it is refluxed in hydrochloric acid (for 30 min) [166].

More profound transformations of hydrazinopyrimidines to give 1,2,4-triazoles are observed in some cases [126, 167]. For example, 1-phenyl-1,2,4-triazol-3-ylacetamide is formed when 6-phenylhydrazinouracil is refluxed in formic acid [126]. 4,6-Dihydrazinopyrimidine is converted to 3-methyl-1(2H)-1,2,4-triazole when it is heated in water at 210°C [126].

2. Reduction and Oxidation

The reduction of hydrazinopyrimidines and their derivatives is widely used in the chemistry of pyrimidine to obtain the corresponding aminopyrimidines [84, 106, 109]. The reduction is carried out in the presence of Raney nickel, or the compounds are hydrogenated with hydrogen over Raney nickel; better results are obtained in the latter case [106]. Sodium hydrosulfite is used as the reducing agent less frequently [84]. Lithium aluminum hydride is used for the selective hydrogenation of the substituents of hydrazinopyrimidines, since the hydrazino group is not affected in this case [168].

The oxidation of hydrazinopyrimidines is usually employed to obtain pyrimidines that are unsubstituted in the corresponding position. Silver oxide [123, 145] and acetate [121, 127, 169], silver nitrate [120], and copper(II) sulfate [94, 117] are used as the oxidizing agents. When silver oxide is used as the oxidizing agent, the reaction is carried out in methanol at 40-50°C, while when silver acetate or nitrate is used, the reaction is carried out in an aqueous medium with refluxing of the reaction mixture. Higher yields are obtained when silver salts are used.

4-Phenylazopyrimidines are obtained by the oxidation of 4-(2-phenylhydrazino)pyrimidines. Lead tetraacetate, iron(III) chloride, and mercury(II) oxide are used as the oxidizing agents in this case [115].

3. Synthesis of Hydrazinopyrimidine Derivatives

Hydrazinopyrimidines undergo all of the reactions that are characteristic for arylhydrazines, and either their derivatives or products of more profound transformations of the latter are formed.

(2-Acylhydrazino)pyrimidines are formed in the acylation of hydrazinopyrimidines with acid anhydrides [88, 103, 170] or acid chlorides [31, 106, 170, 171] in pyridine at room temperature or by brief refluxing. In some cases acylation is carried out in ethyl acetate [31] or in an organic acid [170].

A considerable number of papers has been devoted to the reactions of hydrazinopyrimidines with aldehydes and ketones [75, 77, 86, 103, 110, 125, 171-176], as a result of which a broad spectrum of hydrazones that are of interest as complexing reagents [15, 18, 26], potential biologically active compounds [171], and anticancer [75] and antitubercular [78] preparations, as well as intermediates in the synthesis of formazans [177-179] and condensed heterocyclic systems, was obtained. The reaction is usually carried out in ethanol [75, 172, 173] or acetone [120], but is sometimes carried out in the presence of hydrochloric acid [77, 103] at room temperature or by heating.

The reaction of 2- and 4-hydrazinopyrimidines with acetoacetic ester [180], ketene dimer [180], diethyl ethoxymethylenemalonate [181], or 1,1-dichlorobutan-3-one [182] gives hydrazino derivatives, heating of which in an alkaline medium gives various 2- and 4-(1H-pyrazol-1-yl)pyrimidines. However, 2(1H-pyrazol-1-yl)pyrimidines are most often obtained in one step by refluxing 2-hydrazinopyrimidines with ethylacetoacetic ester in methanol in the presence of sodium hydroxide or sodium methoxide [60, 61] or with 1,3-diketones in aqueous, aqueous alcohol,

or alcohol media [11, 21, 69, 74, 76, 79, 105, 183-186]. In the latter case better results are obtained when the reaction is carried out in an aromatic hydrocarbon in the presence of an acidic catalyst with removal of the water by azeotropic distillation [17]. 2-(1H-Pyrazol-1-yl)pyrimidines are also obtained by the reaction of 2-hydrazinopyrimidines with ethyl bromoacetate, ethyl 2-hydroxycyclopentanecarboxylate, ethyl 2-hydroxycyclohexanecarboxylate, ethoxymethyleneethylacetoacetic ester [153], ethoxymethylenecyanoacetic ester [63, 154], methoxymethylenemalonodinitrile [187], crotonic acid [188], 1,1-dimethoxybutan-3-one [189], (2-methyl-2-buten-4-yl)acetoacetic ester [190], and acylthioacetic esters [191].

Derivatives of 2- and 4-(1H-pyrazol-1-yl)pyrimidine are of interest as pharmacological preparations [60-62, 68-73, 76, 79, 153, 180-182, 188-191]. For example, 4-methyl-6-methoxy-2-(3-methyl-5-methoxy-1H-pyrazol-1-yl)pyrimidine (mepirizole) [192-196] has anti-inflammatory, antipyretic, and pain-relieving action.

When 2-hydrazinopyrimidines are refluxed with cyanoguanidine [154] or dicyanamine [197], they are converted to the corresponding 2-(1H-1,2,4-triazol-1-yl)pyrimidines, which are used to lower blood pressure, while 4-methyl-6-methoxy-2-[6-carboxy-3-hydroxymethylene-4(1H)pyridazinon-1-yl]pyrimidine was obtained by the reaction of hydrazinopyrimidines with calcium dioxoglucanate in aqueous pyridine in the presence of acetic acid at 5°C (for 4 days) [198].

The reaction of 4-hydrazinouracil and 6-hydrazinocytosine with 1,4-benzoquinone gave the corresponding 4-(4-hydroxyphenylazo)pyrimidines, which were converted to the corresponding 4-(2-arylhydrazino)pyrimidines, which have antibacterial properties [49, 50, 65, 162, 199].

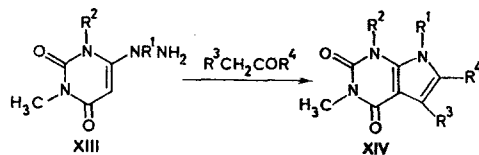
The action of sodium nitrite on 4,6-dihydrazinopyrimidine in 5% hydrochloric acid at room temperature gave 4,6-diazidopyrimidine (77%), which was reduced to 4,6-diaminopyrimidine [124]. Under similar conditions 4-hydrazino-6-(cycloalkylamino)pyrimidines gave 4-azido-6-(cycloalkylamino)pyrimidines, which, depending on the substituent in the 6 position, have an azide or tetrazole structure [200].

The corresponding pyrimidinyl-substituted semicarbazides [176, 201], thiosemicarbazides [88, 176], and aminoguanidines [202] were obtained by the reaction of hydrazinopyrimidines with isocyanic acid or isocyanates, isothiocyanic acid or isothiocyanates, and methylisothiurea sulfate.

4. Synthesis of Heterocyclic Systems That Contain a Pyrimidine

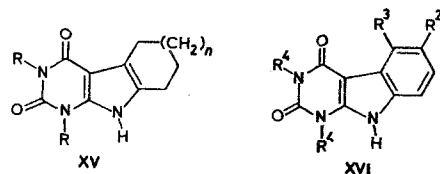
Ring

4.1 Pyrrolo[2,3-d]pyrimidines. 4-Hydrazinopyrimidines and their derivatives are used for the preparation of pyrrolo[2,3-d]pyrimidines and their analogs [67, 203-207] via the following scheme:



XIII, XIV R¹=H, CH₃; R²=CH₃, C₆H₅; XIV R³=H, CH₃; R⁴=CH₃, C₆H₅

Analogues of pyrrolo[2,3-d]pyrimidine (XV) were obtained by the reaction of 6-hydrazinouracils with piperidine, azepinedione [208], and α-hydroxycaprolactam and its enamines [206, 209] with subsequent thermal or catalytic cyclization of the resulting hydrazones.



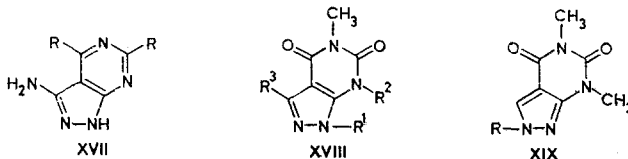
XV R=H, alkyl; n=1,2; XVI R¹-R⁴=H, CH₃

The cyclization of 6-arylhydrazinouracils by the Fischer method gives pyrimido[4,5-b]indoles (XVI), the yields of which depend on the substituents and the reaction conditions and range from 30 to 60% [207].

Let us note that pyrrolo[2,3-d]pyrimidine derivatives are formed only from uracil hydrazones and arylhydrazinouracils. However, other hydrazinopyrimidines and their hydrazones are evidently incapable of such cyclization.

4.2. Pyrazolo[3,4-d]pyrimidines. Pyrazolo[3,4-d]pyrimidines (XVII) are obtained in high yields by thermal cyclization of 5-cyano-4-hydrazinopyrimidines [95], while 4-hydroxy-1H-pyrazolo[3,4-d]pyrimidine derivatives are formed by heating 6-hydrazino-5-carbamoyl- or 6-hydrazino-5-carbethoxypyrimidines [102, 113, 210].

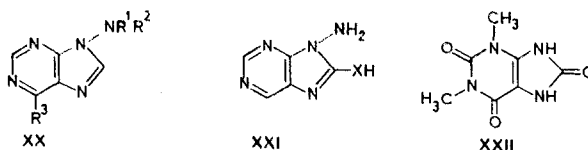
Other pyrazolo[3,4-d]pyrimidine derivatives (XVIII) are obtained by thermal oxidative cyclization of 6-arylidenehydrazinouracils [207, 211, 212].



XVII R = C₆H₅, 4-ClC₆H₄, 4-CH₃C₆H₄; XVIII R¹ = R² = H, CH₃; R³ = C₆H₅, 4-ClC₆H₄, 3,4-Cl₂C₆H₃, 4-CH₃OC₆H₄, 4-(CH₃)₂NC₆H₄; XIX R = alkyl

It was recently shown that pyrazolo[3,4-d]pyrimidine derivatives (XIX) can be obtained by heating 1,3-dimethyl-6-hydrazinouracil with dimethylformamide dialkylacetals [213].

4.3. Purines. 9-Aminopurines or their formyl derivatives (XX) are formed in the reaction of 5-amino-4-hydrazinopyrimidines with formic acid or ethyl orthoformate [81, 99, 100].



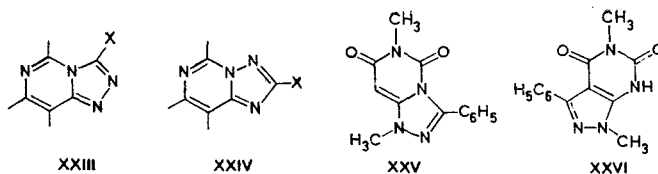
XX R¹ = H; R² = H, CHO; NR¹R² = N=CHC₆H₅; R³ = H, Cl, CH₃; XXI X = O, S

9-Benzylideneaminopurines (XX, NR¹R² = N=CHC₆H₅) are formed in the case of 5-amino-4-benzylidenehydrazinopyrimidines, while 9-aminopurin-8-ol and its thio analog (XXI) are obtained when phosgene or thiophosgene is used as the cyclizing agent [107, 142, 143].

1,3-Dimethyluric acid (XXII) is obtained by heating 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil with formic acid in formamide or in two steps by refluxing with formic acid or with Raney nickel and subsequent heating of the resulting 1,3-dimethyl-5-carbethoxyamino-6-aminouracil [163].

4-Chloro-8-ethoxypurine was obtained by the action of nitrous acid on 5-amino-6-chloro-4-hydrazinopyrimidine with subsequent reaction of the resulting 8-amino-7-chlorotetrazolo[1,5-c]pyrimidine with diethoxymethyl acetate and heating of the resulting 4-azido-6-chloro-5-ethoxymethyleneaminopyrimidine in an inert solvent [214].

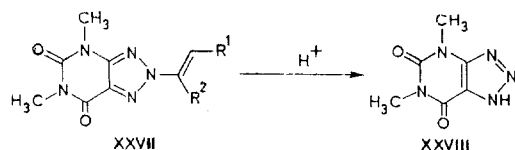
4.4. Triazolopyrimidines. The corresponding 1,2,4-triazolo[4,3-c]-(XXIII) or 1,2,4-triazolo[2,3-c]pyrimidine (XXIV) derivatives are obtained by the reaction of various 4-hydrazinopyrimidines with formic acid [216], cyanogen chloride (bromide) [37, 112, 176, 216], isocyanates and isothiocyanates [176], phosgene [106], carbon disulfide [88, 202], and alkylureas and guanidines [216]. Hydrazones of 5-substituted 4-hydrazinopyrimidines also are converted to the corresponding 1,2,4-triazolo[4,3-c]pyrimidines such as, for example, XXV, by the action of H₂SO₄-CH₃COOH-KNO₃. In the absence of KNO₃, pyrazolo[4,3-d]pyrimidine XXVI is formed in addition to XXV [217].



XXIII, XXIV X = H, NH₂, OH, SH, OR, SR, alkyl, etc.

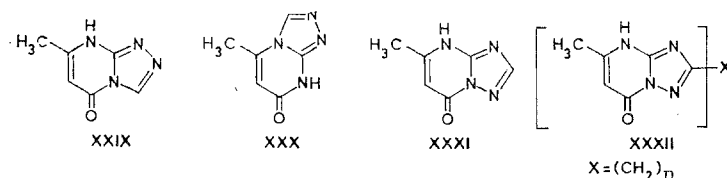
1,2,4-Triazolo[4,3-c]pyrimidines (XXIII) undergo recyclization to 1,2,4-triazolo[2,3-c]-pyrimidines (XXIV) either in the course of the reaction of 4-hydrazinopyrimidines with a cyclizing agent [176, 216] or when they are heated with strong acids or alkalis [106, 112].

4-Hydrazinopyrimidine derivatives are used in the synthesis of 1,2,3-triazolo[4,5-d]pyrimidines. For example, the reaction of 1,3-dimethyl-6-(α -methylalkylidenehydrazino)uracils with nitrosodimethylamine in the presence of phosphorus oxychloride gives the corresponding 1,2,3-triazolo[4,5-d]pyrimidines (XXVII), which are converted to 1,2,3-triazolo[4,5-d]pyrimidine (XXVIII) [218].



XXVII $R^1 = H, CH_3$; $R^2 = C_6H_5, 4-ClC_6H_4, 4-CH_3C_6H_4, CH_3, C_2H_5$

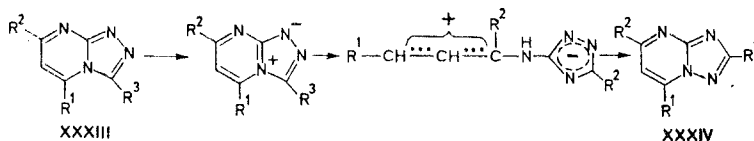
1,2,4-Triazolo[2,3-a]- (XXIX, XXX) and triazolo[4,3-a]pyrimidines (XXXI) are obtained by the action of formic acid or ethyl orthoformate on 2-hydrazino-6-methyl-4(3H)-pyrimidinone [219-223].



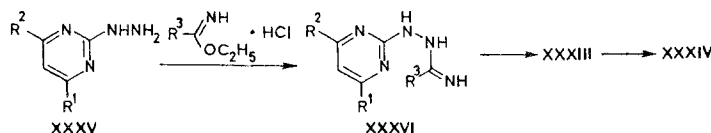
Diverse 2-hydrazinopyrimidines [126, 221, 223, 225] and (in addition to formic acid and ethyl orthoformate) acetic acid [220, 221], acetic anhydride [224], phenyl benzoate or ethyl orthobenzoate [223], carbon disulfide [223], and dicarboxylic acid esters [3] have been used as the starting compounds in the synthesis of these systems. In the latter case bis(5-methyl-7-hydroxy-1,2,4-triazolo[2,3-a]pyrimidines) (XXXII) were obtained. 2-(2-Acylhydrazino)pyrimidines [219, 221, 222] and various hydrazones of 2-hydrazinopyrimidines [139, 223, 226, 227] are also used in this reaction. In the latter case the hydrazones undergo oxidative cyclization under the influence of lead tetraacetate [139, 223, 226, 227] or air during illumination with UV light [227].

3-Amino-1,2,4-triazolo[4,3-a]pyrimidines are obtained by the reaction of 2-hydrazinopyrimidines with cyanogen chloride [228] or cyanogen bromide [160]. The reaction is carried out in acetic acid in the presence of sodium acetate at 0-10°C.

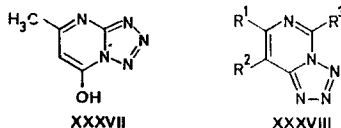
Most 1,2,4-triazolo[4,3-a]pyrimidines (XXXIII) undergo recyclization at high temperatures to give 1,2,4-triazolo[2,3-a]pyrimidines (XXXIV). The mechanism of this reaction can be represented by the following scheme [228].



1,2,4-Triazolo[4,3-a]pyrimidines are also obtained by the reaction of 2-hydrazinopyrimidines with dimethylformamide [229], N-cyanoethyl imidate [230], or ethyl imidate hydrochlorides [231]. In the latter case 1,2,4-triazolo[4,3-a]pyrimidines (XXXIII), 1,2,4-triazolo[2,3-a]pyrimidines (XXXIV), or amidrazones XXXVI ($R^1 = R^2 = R^3 = CH_3$) are formed, depending on the substituents in the 2-hydrazinopyrimidine (XXXV).

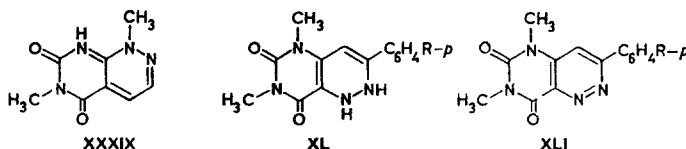


4.5. Tetrazolopyrimidines. The action of nitrous acid on 2- and 4-hydrazinopyrimidines gives azides, which undergo cyclization to, respectively, tetrazolo[1,5-a]- (XXXVII) [128, 166] and tetrazolo[1,5-c]pyrimidines (XXXVIII) [200, 203, 214]. The tetrazole structure exists, as a rule, in the crystalline state, whereas an equilibrium between tetrazole and azide structures exists in solutions [200].



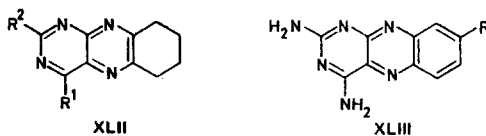
XXXVIII $R^1 = \text{Cl}, \text{OCH}_3$; $R^2 = \text{NH}_2, \text{CH}_3, \text{morpholino}, \text{piperidino}, \text{homopiperidino}, \text{pyrrolidino}$; $R^3 = \text{H}, \text{CH}_3$

4.6. Pyrimido[4,3-c]pyridazines. Pyrimido[4,3-c]pyridazine derivatives are formed in the reaction of 4-hydrazinouracils with 1,2-dicarbonyl compounds [91, 232] and ω -bromoacetophenone [233, 234]. For example, 1,6-dimethyl-1,5,6,7-tetrahydropyrimido[4,5-c]pyridazine-5,7-dione (XXXIX) was obtained by refluxing 3-methyl-6-(1-methylhydrazino)uracil with 40% aqueous glyoxal. Diacetyl, phenylpropane-1,2-dione [91], and α -keto esters such as diethyl ketomalonate or acetylformic acid esters [232] are also used as the 1,2-dicarbonyl compounds.



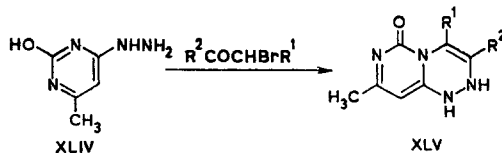
The reaction of 6-hydrazino-1,3-dimethyluracil with phenacyl bromide and its p-substituted derivatives gives, in addition to 1,2-dihydro derivatives, viz., pyrimido[4,5-c]pyridazine-5,7-diones (XL), the yields of which range from 32 to 50%, the corresponding pyrimido[4,5-c]pyridazine-5,7-diones (XLI) in 2-10% yields [233].

4.7. Pteridines. Hydrazinopyrimidine derivatives are used in the synthesis of pteridines. For example, benzopteridine derivatives XLII and XLIII were obtained by heating (at 250°C for 20 min) 4-amino-5-(1,2-diethoxycarbonylhydrazino)pyrimidines with cyclohexylmorpholine or aniline [164].



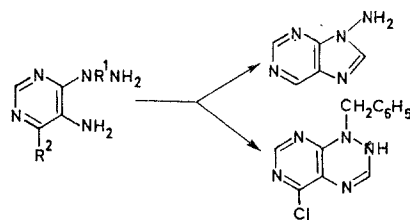
XLII $R^1 = \text{OH}, \text{NH}_2$; $R^2 = \text{NH}_2, \text{CH}_3$; XLIII $R = \text{H}, \text{Cl}$

4.8. Pyrimidotriazines. Pyrimido[4,3-c]triazines (XLV) are obtained by condensation of 4-hydrazinopyrimidines (XLIV) with α -bromo ketones [235].



XLV $R^1 = \text{H}, \text{CH}_3, \text{C}_6\text{H}_5$; $R^2 = \text{C}_6\text{H}_5, 4\text{-NO}_2\text{C}_6\text{H}_4$

The 4-, 5-, or 6-hydrazinopyrimidines are used considerably more often in the synthesis of pyrimido[5,4-e]-as-triazines. 5-Amino-4-hydrazino- [59, 84, 99, 100, 118, 119, 142, 143, 236, 237], 4-hydrazino-5-nitro- [87, 93, 98, 141, 145, 238], and 4-hydrazino-5-nitrosopyrimidines [239, 240], 5-unsubstituted 4-hydrazinopyrimidines [90, 104, 241, 242], 4-amino-5-hydrazinopyrimidines [243, 244], and 5,6-dihydrazinopyrimidines have been used as 4(6)-hydrazinopyrimidines, while carboxylic acids, ortho esters, imido esters, nitriles, phosgene, and thiophosgene have been used as cyclizing agents. Let us note that the corresponding pyrimido[5,4-e]-as-triazines or 9-aminopurines or both simultaneously are formed in the reaction of 5-amino-4(6)-hydrazinopyrimidines with carboxylic acids and their derivatives. The result of this reaction is determined by the nature of the starting reagents and the reaction conditions.



XLVI $R^1 = H, CH_2C_6H_5$, $R^2 = H, Cl$

Thus, for example, 9-aminopurine (XLVII) is obtained when 5-amino-6-hydrazinopyrimidine (XLVI) is refluxed in formic acid, while 1-benzyl-5-chloro-1,2-dihydropyrimido[5,4-e]-as-triazine (XLVIII) is obtained from 5-amino-4-(1-benzylhydrazino)-6-chloropyrimidine (XLVI, $R^1 = PhCH_2$) under similar conditions [100].

As a rule, pyrimido[5,4-e]-as-triazine derivatives are always formed when 5-amino-4-[1-alkyl(aralkyl)hydrazino]pyrimidines are used [99, 100].

The effect of the cyclizing agent under the conditions of this reaction can be demonstrated by the reaction of 5-amino-4-chloro-6-hydrazinopyrimidine with ethyl orthoformate in acetic anhydride in the presence of hydrochloric acid, as a result of which 5-chloro-1,2-dihydropyrimido[5,4-e]-as-triazine is obtained [99]. In the absence of hydrochloric acid the product is 9-acetamido-6-chloropurine [100].

The formation of pyrimido[5,4-e]-as-triazines from 5-amino-4-hydrazinopyrimidines and ortho esters is promoted by carrying out the reaction in the presence of hydrochloric acid [59, 84, 87, 99, 118, 119]. However, the formation of a mixture of 9-aminopurine and pyrimido[5,4-e]-as-triazine has been noted in some cases [236].

A study of the cyclization of 5-amino-4-chloro-6-hydrazino(or 1-methylhydrazino)pyrimidines with phosgene and thiophosgene has shown that 9-amino-6-chloropurin-8-ols and their thio analogs are formed from hydrazino derivatives, while the corresponding pyrimido[5,4-e]-as-triazines are formed from 1-methylhydrazino derivatives; it was established that 9-amino-6-chloropurin-8-ol is converted to the corresponding pyrimido[5,4-e]-as-triazine when it is refluxed with alcoholic HCl [142, 143].

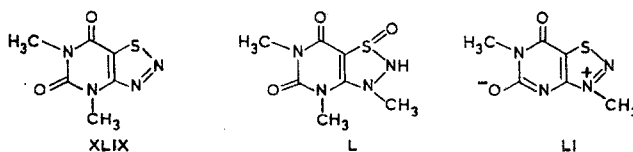
Pyrimido[5,4-e]-as-triazines are also formed in the 30-95% yields in the reductive cyclization of various 5-nitropyrimidine-4-hydrazone [87, 93, 98, 141, 145, 238].

Pyrimido[5,4-e]-as-triazine derivatives are also obtained by the reaction of 4-hydrazino-5-nitrosouracils with benzyl halides and phenacyl bromides [239] or with $Ph_3P=CHR$ [240] in 11-72% yields.

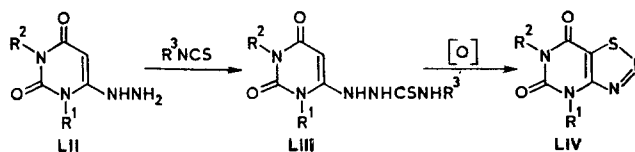
A method for the preparation of pyrimido[5,4-e]-as-triazines that consists in the reaction of various uracil-4-hydrazone with nitrous acid has become widely used [91, 104, 241, 242, 247, 248].

Analog of the natural antibiotics fervenulin and 2-methylfervenulin are obtained by cyclization of 4-amino-1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinopyrimidine in acetic acid in the presence of lead tetraacetate [163, 243] or 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinopyrimidine in the presence of sodium ethoxide or in an alcohol solution of potassium hydroxide [163, 244, 245].

4.9. 1,2,3-Thiadiazolo[4,5-d]pyrimidines. 1,2,3-Thiadiazolo[4,5-d]pyrimidines are obtained by cycloaddition of thionyl chloride to substituted 4-hydrazinouracils; 1,2,3-thiadiazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione (XLIX), S-oxide L, or hydroxide LI is formed, depending on the reaction conditions and the substituents [63, 249, 250].



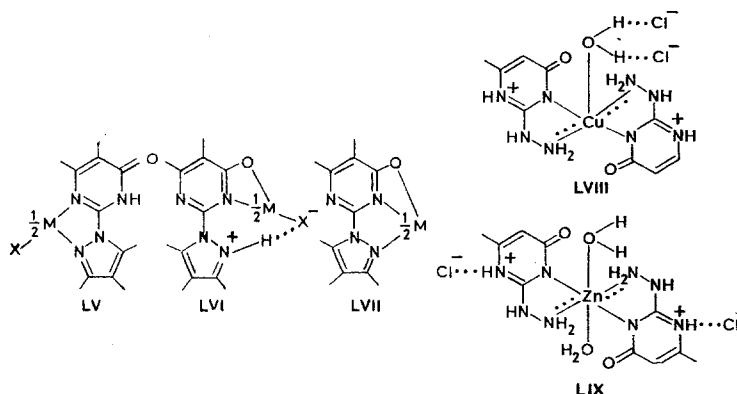
1,2,3-Thiadiazolo[5,4-d]pyrimidines (LIV) are also obtained in two steps by the reaction of hydrazine LII with thiocyanates and subsequent oxidation of the resulting thiosemicarbazides LIII [63].



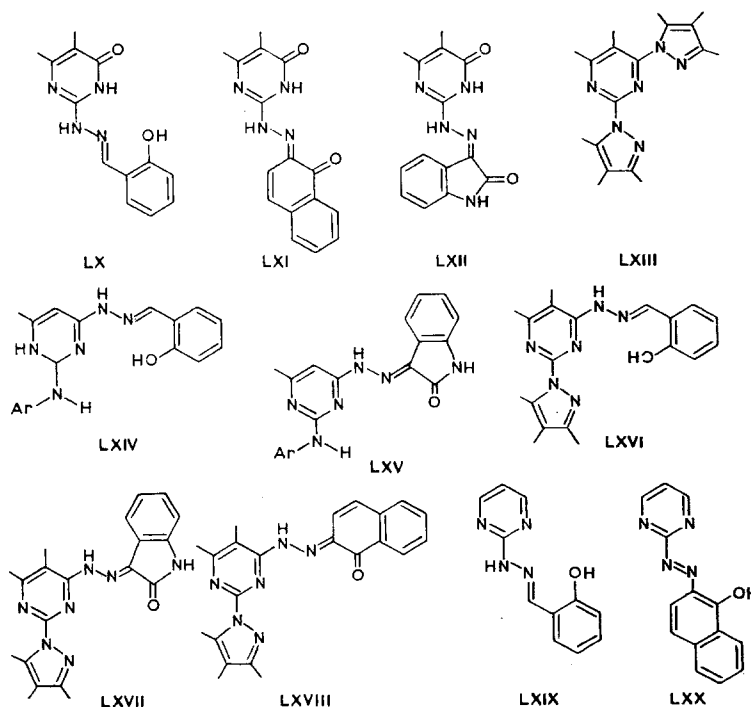
LII—LIV $R^1 = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_4\text{H}_9, (\text{CH}_3)_2\text{CHCH}_2, \text{cyclohexyl}$; $R^2 = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_4\text{H}_9, \text{cyclohexyl}$; LIII $R^2 = \text{alkyl, aryl, etc.}$

4.10. Ligands Based on Hydrazinopyrimidines. The chemistry of pyrimidine in general and of hydrazinopyrimidines in particular opens up virtually unlimited possibilities in the construction of various types of organic ligands and complexes based on them. This is confirmed by research conducted primarily in recent years, the results of which will be examined briefly in this section.

2-(1H-Pyrazol-1-yl)-4(3H)-pyrimidines, which are obtained by the reaction of 2-hydrazino-4(3H)-pyrimidinones with β -diketones [13, 16, 21, 251], are ambident ligands and, depending on the metal cation (M), the anion ligand (X), and the conditions of their reaction with metal salts (MX_2), form complexes with different coordination environments of the central metal ion such as, for example, LV–LVII [13, 18, 19, 23, 24]. A study of the complexing abilities of these ligands in extraction systems showed that they display selectivity with respect to some metal salts such as, for example, copper(II) salts [20, 252].



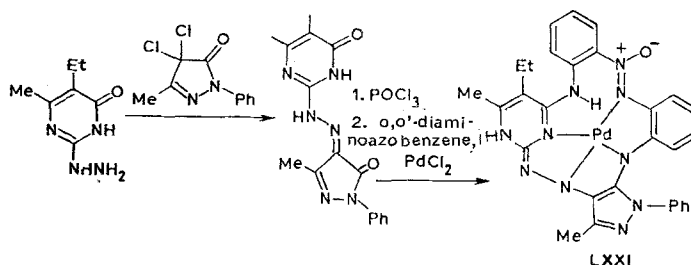
Let us note that 2-hydrazino-4(3H)-pyrimidinones – the starting compounds in the synthesis of 2-(1H-pyrazol-1-yl)-4(3H)-pyrimidines – and their structural analogs form complexes LVIII



and LIX and that localization of the coordinate bonds is realized only at the N₃ atom of the pyrimidine ring and the N₂ atom of the hydrazino group [9, 10].

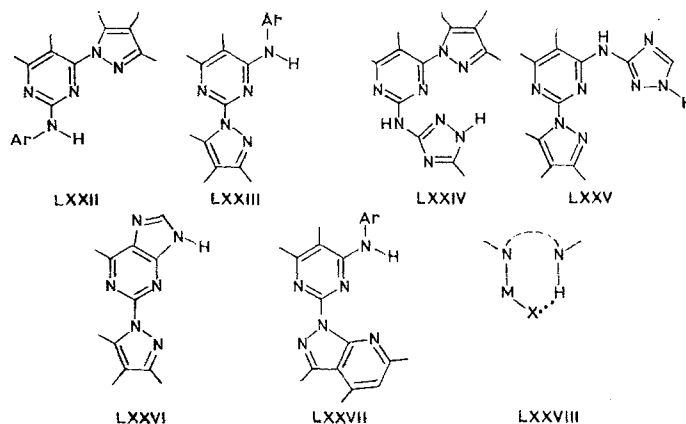
The condensation of hydrazinopyrimidines, which already are at least bidentate ligands [7-9], with carbonyl compounds, which have their own potential coordination nodes, makes it possible to obtain the most diverse polydentate ligands. For example, 2-hydrazino-4(3H)-pyrimidinones have been used to obtain some tetradentate ligands (LX-LXII) [14, 26]; tri- (LXIII-LXV) [14, 26] and tetradentate ligands (LXVI-LXVIII), [15, 17, 21, 26] with different constructions of the coordination nodes have been obtained by condensation of 4-hydrazinopyrimidinones with β -diketones, salicylaldehyde, isatin, and β -naphthoquinone. Simpler ligands (LXIX, LXX) were previously obtained on the basis of 2-hydrazinopyrimidine and salicylaldehyde [11] and naphthoquinones [12].

Hydrazinopyrimidines can also be used to obtain macrocyclic complexes, which in recent years have attracted the interest of researchers. Thus palladium complex LXXII has been obtained from 2-hydrazino-5-ethyl-6-methyl-4(3H)-pyrimidinone [253].



2-Arylamino-4-(1H-pyrazol-1-yl)pyrimidines (LXXII) [29], 4-arylamino-2-(1H-pyrazol-1-yl)-pyrimidines (LXXIII) [254], and derivatives of 3-(2-pyrimidinyl)amino-1(2)H-1,2,4-triazole (LXXIV) [255], 3-(4-pyrimidinyl)amino-1(2)H-1,2,4-triazole (LXXV) [256], 2-(1H-pyrazol-1-yl)-purine (LXXVI) [22], and 1-(2-pyrimidinyl)-1H-pyrazole[3,4-b]pyridine (LXXVII) [257] — ligands with different constructions of the coordination nodes that form complexes that are stabilized by metallocycles with intramolecular hydrogen bonds between the secondary amino group of the ligand and the anion ligand (LXXVIII) — have been obtained on the basis of 2- and 4-hydrazino-pyrimidinones [25, 27, 258, 259].

A study of the complexing ability of ligands of this type has made it possible to establish that stabilization of the complexes by metallocycles with intramolecular hydrogen bonds



leads to an increase in their stabilities in low-polarity organic solvents (as compared with complexes obtained on the basis of their structural analogs without stabilization by metallocycles of this type) and their extraction by these solvents from aqueous media (pH 1-3) [259, 260].

Ligands LXXII-LXXVII are potentially ambident species. However, in the investigated cases localization of the coordinate bonds in their complexes (complexes with Co²⁺ halides) is realized at the same coordination sphere that favors the formation of metallocycles with intramolecular hydrogen bonds. The latter makes it possible to carry out the purposeful synthesis of ligands on the basis of ambident systems that ensure the production of complexes with definite environments of the central metal ion due to stabilization of their metallocycles with intramolecular hydrogen bonds. It must be noted that ambident ligands are, as a rule, synthetically more accessible than ligands with the same yet unique construction of the coordination node.

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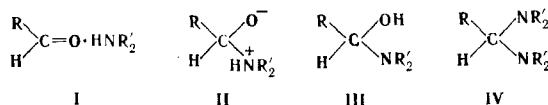
MECHANISM OF THE REACTION OF ALDEHYDES OF THE FURAN SERIES WITH SECONDARY AMINES IN METHANOL

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The reaction of 5-halofurfurals with piperidine and morpholine in methanol under various reaction conditions was investigated by means of spectrophotometry. The kinetics of the stepwise addition of the amine to the aldehyde function of the halofurfural were studied in the case of a dilute solution, while the conversion of the aldehyde to a 5-N,N-dialkylaminofurfurylidene-N,N-dialkylimmonium salt, for which two autocatalysis mechanisms were observed, was investigated in the case of a concentrated solution. Reaction intermediates, viz., 5-halofurfurylidene-N,N-bis(dialkylamines), were isolated preparatively and investigated.

Aldehydes of the furan series react with nitrogen bases that contain a primary amino group (phenylhydrazine [1, 2] and aniline [3]) with the intermediate formation of aminocarbinols, which subsequently lose water and are converted to the corresponding imines. The mechanism of the reaction of furfural derivatives with secondary amines has not been previously studied in detail. It is known [4] that furfural under mild conditions forms stable crystalline molecular compound I with morpholine; I undergoes disproportionation during storage to give the starting aldehyde and an aminal of the IV type. The latter can be obtained directly from the aldehyde by heating it with excess morpholine. Lidak and Giller [5] have investigated this reaction using ethyleneimine and piperidine, in addition to morpholine, as the bases and have expanded the number of aldehydes used. The reaction of the reagents in ethyl chloride at -40°C gave molecular complexes I in high yield, which retain the band of a carbonyl group in their IR spectra. In attempts to recrystallize them they were converted to aminals IV. Lidak and Giller [5] assumed the intermediate formation in this reaction of dipolar adducts II, which exist in equilibrium with aminocarbinols III.



5-Halofurfurals react with secondary amines to give ultimately products of substitution of both the aldehyde oxygen atom and the halogen atom by an amino group. This reaction is carried out preparatively in two variants — in one of them the aldehyde is converted to the corresponding Schiff base, which upon reaction with a secondary amine gives a 5-N,N-dialkylaminofurfurylidene-N,N-dialkylimmonium salt [6]; in the other variant the aldehyde is subjected directly to reaction with a secondary amine, and the same immonium salt is formed [7]. A study of the kinetics of the reaction [8-10] showed that nucleophilic attack by the amine at the aldehyde function and in the 5 position of the furan ring is involved in a complex manner. In a continuation of these studies we investigated the reaction of aldehydes of the furan series with secondary amines (piperidine and morpholine) in absolute methanol. By varying the concentrations of the reagents and by purposeful modification of the experimental method we found it possible to form a more valid judgment regarding the structures of the intermediates formed in this reaction and the reaction mechanism.

Kinetics of the Reaction in Dilute Solution

The electronic spectra of aldehydes of the furan series contain an intense band with an absorption maximum at 270-360 nm (its absorption depends on the nature of the substituent in

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