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Pyrido[2,3-*d*]pyrimidines

A.Sh.Oganisyan, A.S.Noravyan, and S.A.Vartanyan

The methods of synthesis and the chemical and biological properties of pyrido[2,3-*d*]pyrimidines are described. The bibliography includes 270 references.

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I. INTRODUCTION

In recent years investigators have shown much interest in pyrido[2,3-*d*]pyrimidines—heterocyclic systems with a broad spectrum of biological properties[1-4] some of which have found applications in medicine as medicinal preparations.[5,6] Only one review has been published on the synthesis of pyrido[2,3,*d*]pyrimidines, covering the literature data up to 1968 [7] including also recent information about their chemical reactions and biological properties.

As a result of the theoretical and practical interest in pyrido[2,3-*d*]pyrimidines, many publications devoted to new methods of synthesis, chemical reactions, and biological properties of compounds of this class have appeared during the last 15 years, so that it is of interest to survey and treat systematically the available literature data.

II. METHODS OF SYNTHESIS

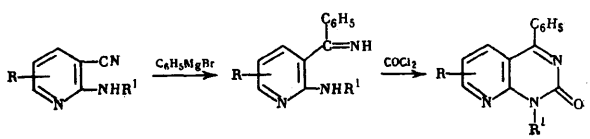
Condensed pyridopyrimidines can be synthesised from both pyridine and pyridimine derivatives.

1. Synthesis from Pyridines

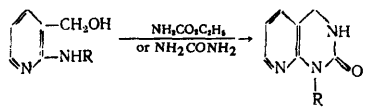
This section deals with the synthesis of pyrido[2,3-*d*]-pyrimidines with various functions group substituents in the pyrimidine ring from pyridines containing active groups in the 2- and 3-positions, which interact with the corresponding reactants, the reaction leading to closure of the pyrimidine ring.

(a) 2-Oxo-derivatives

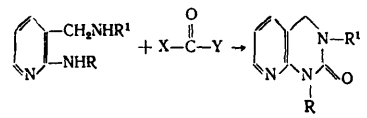
2-Oxo-4-phenyl-1,2-dihydropyrido[2,3-*d*]pyrimidines have been synthesised from 2-amino-2-cyanopyridines by reaction with a Grignard reagent and then with phosgene:[8-10]



Another method consists of the condensation of 2-amino-3-benzoylpyridines with urethane[9] or urea.[11] Under analogous conditions, 2-amino-3-hydroxymethyloyridines cyclise to the corresponding oxotetrahydropyrido[2,3-*d*]-pyrimidines:[12]

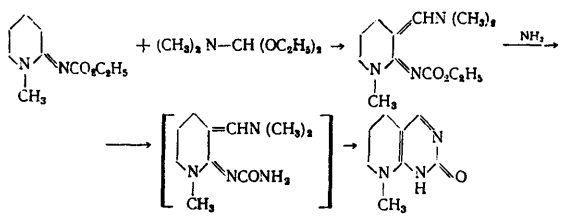


Analogues of these compounds containing substituents in the 3-position in the pyridine ring have been obtained by condensing 2-amino-3-aminomethylpyridines with various carbonic acid derivatives:[13]



X = halogen, alkoxy-group, amino-group; Y = halogen, alkoxy-group, trihalogenoalkyl.

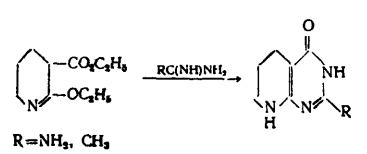
2,2-Dialkoxy-2-methylpiperidine has been used to synthesise *N*-methyl-2-oxohexahydropyridopyrimidines by its condensation with urethane to form an amidine. The reaction of the latter with dimethylformamide acetal yielded amino-methylene-ethoxycarbonyliminopiperidine whose treatment with aqueous ammonia led to the closure of the pyrimidine ring with the simultaneous elimination of dimethylamine:[14]



2-Oxodihydropyrido[2,3-*d*]pyrimidines have also been obtained by condensing 3-acetyl-2-pyridones with urea.[15]

(b) 4-Oxo-derivatives

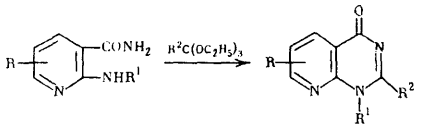
Methods of synthesis of 2-substituted 4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidines from 3-ethoxycarbonyl-2-ethoxy-3,4,5,6-tetrahydropyridine have been developed:[16]



R=NH_2, CH_3

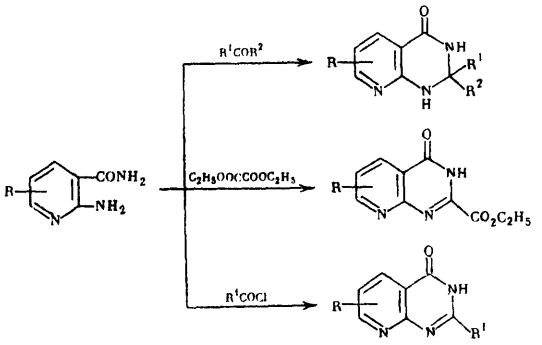
The methods of synthesis of analogous pyridopyrimidines containing alkyl groups at the nitrogen atom of the piperidine ring[17,18] and an angular substituent in the 10-position[16] have also been investigated.

2-Amino-3-carbamoylpyridines, whose condensation with orthoesters leads to the closure of the pyrimidine ring, are convenient starting materials for the synthesis of 1-substituted 4-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidines:[19–25]

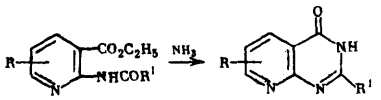


R^2=H, alkyl, phenyl

The reactions of 2-amino-3-carbamoylpyridines with aldehydes or ketones,[26] diethyl oxalate,[29] and acid chlorides[30] result in the formation of the corresponding 4-oxopyridopyrimidines:

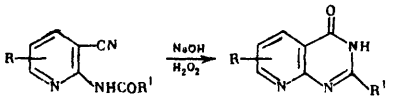


On treatment with alcoholic ammonia, 2-acylamino-3-ethoxycarbonylpyridines cyclise to form 2-substituted 4-oxodihydropyrido[2,3-*d*]pyrimidines:[30–32]

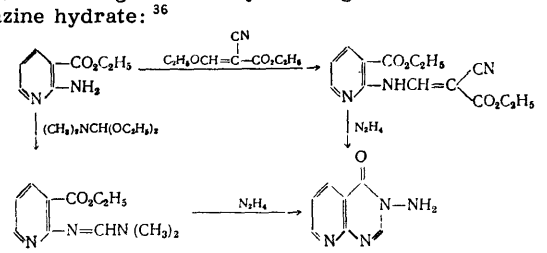


The hydrochlorides of various amines are used instead of ammonia as the cyclising agents for the synthesis of 2,3-substituted 4-oxodihydropyridopyrimidines from acylaminopyridines and the reaction is carried out in the presence of phosphorus pentoxide.[33]

2-Acylamino-3-cyanopyridines undergo an interesting reaction with sodium hydroxide and hydrogen peroxide, which yields 4-oxodihydropyridopyrimidines:[34,35]

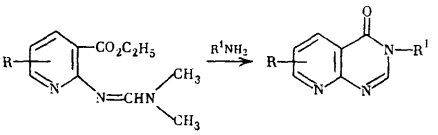


3-Amino-4-oxodihydropyrido[2,3-*d*]pyrimidine has been synthesised by condensing 2-amino-3-ethoxycarbonylpyridine with ethyl ethoxymethylenecyanoacetate or dimethylformamide acetal, this being followed by treating the intermediates with hydrazine hydrate:[36]

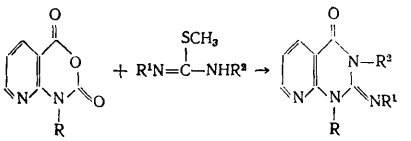


The reaction of 2-amino-3-hydrazinocarbonylpyridine with dimethylformamide diacetal gives an analogous result.[37]

On treatment of *N*-(2-pyridyl)amidines with various amines, intramolecular cyclisation takes place with formation of 3-substituted 4-oxodihydropyrido[2,3-*d*]pyrimidines:[38]

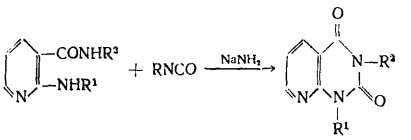


The reaction of thiourea derivatives with 1-substituted 2,4-dioxo-1,2-dihydro-4*H*-pyrido[2,3-*d*]1,3-oxazines, obtained by condensing aminopyridines with phosgene, has been used to synthesise various derivatives of 4-oxopyridopyrimidines:[39,40]



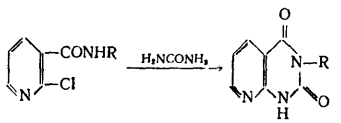
(c) 2,4-Dioxo-derivatives

One of the commonest methods of synthesis of 1,3-disubstituted 2,4-dioxotetrahydropyrido[2,3-*d*]pyrimidines is the condensation of derivatives of 2-amino-3-carbamoylpyridines with isocyanates in the presence of sodium amide:[41–45]

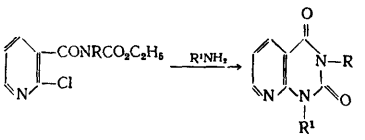


Analogous compounds have been obtained by cyclising aminocarbamoylpyridines with phosgene, chlorocarbonic acid ester or amide, and urea.[46–51]

The interaction of 2-chloro-3-carbamoylpyridines with urea afforded high yields of 3-substituted 2,4-dioxotetrahydropyridopyrimidines:[52,53]

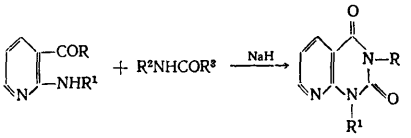


1,3-Disubstituted 2,4-dioxotetrahydro[2,3-*d*]pyrimidines can be synthesised from derivatives of 2-chloro-3-carbamoylpyridines containing the ethoxycarbonyl group at the nitrogen atom in the amide group condensing with amines:[54]



The synthesis of 1,3-disubstituted pyridopyrimidines from 2-chloro-3-carbamoylpyridines and isocyanates has been described.[55]

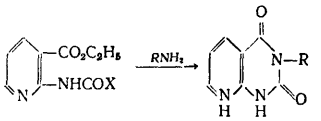
The corresponding 1,3-disubstituted dioxopyrimidines have been synthesised by condensing 3-substituted 2-halogenocarbamoylpyridines with carbamates in the presence of sodium hydride in dimethylformamide (DMF).[56] The interaction of the same carbamates with 2-amino-3-ethoxycarbonyl- or 2-amino-3-carbamoyl-pyridines results in the formation of analogous pyridopyrimidines with a different disposition of the substituents in the pyrimidine ring—in the 1- and 3-positions:[57]



$R = OC_2H_5$, NH_2; R^3 = halogen, heterocycle.

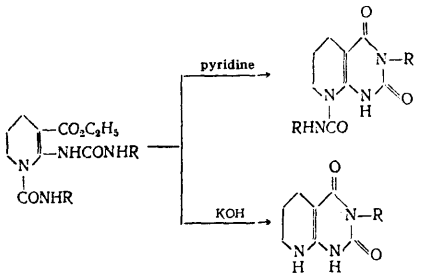
One of the ways of synthesising 2,4-dioxopyrido[2,3-*d*]-pyrimidines is condensation of 2-amino-3-carboxy- or 2-amino-3-ethoxycarbonyl-pyridines with urea, urethanes, or isocyanates.[58–65]

It has been shown that refluxing of 2-amino-3-ethoxycarbonylpyridine with chlorocarbonic esters or amide leads to the formation of 2-alkoxycarbonylamino- or ureido-derivatives of pyridine, which cyclise on treatment with amines to the corresponding dioxopyridopyrimidines:[66]



X = alkoxy-group, NH_2.

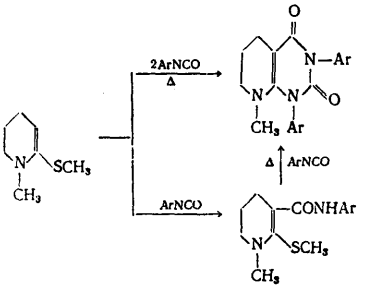
The interaction of 2-amino-3-ethoxycarbonyl-1,4,5,6-tetrahydropyridine with isocyanate yielded diureido-derivatives which cyclise in the presence of pyridine or potassium hydroxide to the corresponding 2,4-dioxo-octahydropyridopyrimidines:[67]



A novel method of synthesis of 3-butyl-2,4-dioxotetrahydropyrido[2,3-*d*]pyrimidine involves the refluxing of 2,3-dicarbamoylpyridine in DMF in the presence of palladium tetra-acetate:[68]



Single-stage and two-stage syntheses of 1,3-diaryl-2,4-dioxo-octahydropyridopyrimidines from 1-methyl-2-methylthiotetrahydropyridine and aryl isocyanates in accordance with the scheme

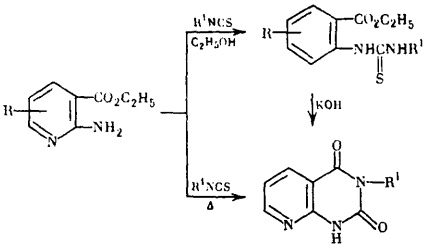


have been proposed.[69,70] The use of aryl isothiocyanates makes it possible to obtain the corresponding 2,4-dithiono-derivatives.[71]

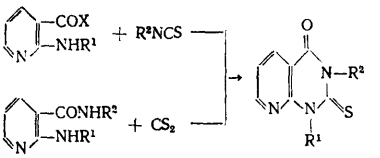
2,4-Dioxopyridopyrimidines can also be synthesised from dioxopyrido[2,3-*d*]-1,3-oxazine by treatment with amines and phosgene.[72,73]

(d) 4-Oxo-2-thionopyrido[2,3-d]pyrimidines

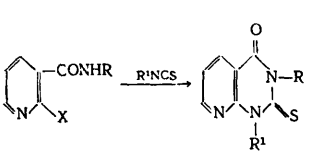
One of the convenient methods of synthesis of 4-oxo-2-thionotetrahydropyrido[2,3-*d*]pyrimidines involves the thermal cyclisation of 3-alkoxycarbonyl-2-aminopyridines by reaction with isothiocyanates with or without the isolation of the intermediate thioureidopyridines:[74–78]



1,3-Disubstituted compounds have been obtained from the esters or amides of 2-aminopyridine-3-carboxylic acids and various isothiocyanates[79] or carbon disulphide:[80,81]

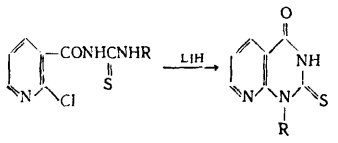


Analogous pyridopyrimides have been obtained by the reaction of 3-carbamoylpyridines, containing halogeno-, alkoxy-, alkylthio-, and sulphoxy-groups in the 2-position in the pyridine ring, with isothiocyanates:[82–84]



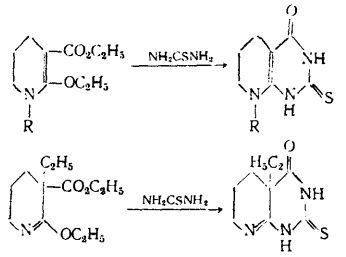
When 2-chloro-3-ethoxycarbonylpyridines are refluxed with thiourea derivatives in ethanol saturated with hydrogen chloride, the corresponding pyridopyrimidines are formed in low yields.[85–87]

1,3-Disubstituted 4-oxo-2-thionotetrahydropyridopyrimidines have been synthesised by cyclising 2-chloroicotinoylthioureas in the presence of lithium hydride: [88]



1,3-Diaryl-8-methyl-4-oxo-2-thiono-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidines have been obtained by the reaction of 3-arylcarbamoyl-1-methyl-2-methylthiotetrahydropyridine with aryl isothiocyanate. [69]

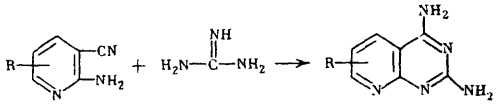
The esters of the lactim form of 3-ethoxycarbonylpiperidin-2-ones are convenient starting compounds for the synthesis of various pyrido[2,3-*d*]pyrimidines which cannot be synthesised in other ways: [16–18]



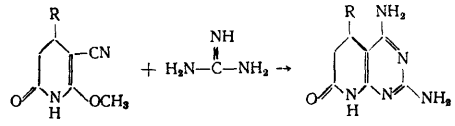
The synthesis of 4-imino-1,3-dimethyl-2-thionotetrahydropyrido[2,3-*d*]pyrimidine by condensing 2-chloro-3-cyanopyridine with *NN'*-dimethylthiourea has been reported. [89]

(e) 2,4-Diaminopyrido[2,3-d]pyrimidines and Other Derivatives

2-Amino-3-cyanopyridines readily react with guanidine to form derivatives of 2,4-diaminopyrido[2,3-*d*]pyrimidines: [90,91]

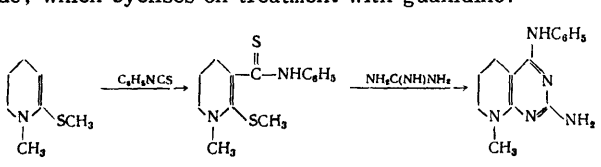


Another method of synthesis of 2,4-diaminopyridopyrimidines involves the reaction of 3-cyano-2-methoxypyridines with guanidine: [92]

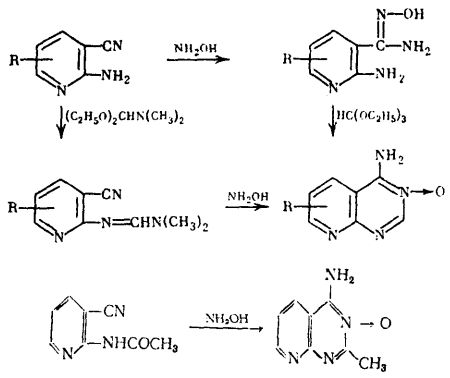


A pyridopyrimidine with an analogous structure has also been synthesised by condensing ethyl 4,4-dicyanobutyrate with guanidine. [93]

The reaction of 1-methyl-2-methylthiotetrahydropyridine with phenyl isothiocyanate afforded the corresponding thioamide, which cyclises on treatment with guanidine: [93]



The methods of synthesis of certain pyrido[2,3-*d*]pyrimidines, in particular the 3-*N*-oxides of 4-aminopyridopyrimidines, from 2-amino-3-cyanopyridines in accordance with the scheme [95,96]



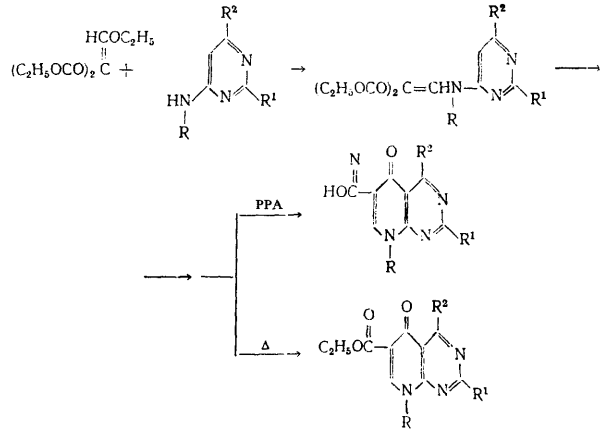
which have been described in the literature, are of interest.

The unsubstituted 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine has been obtained by condensing 2-piperidinone with formamide in the presence of phosphoryl chloride. [97,98]

2. Synthesis from Pyrimidines

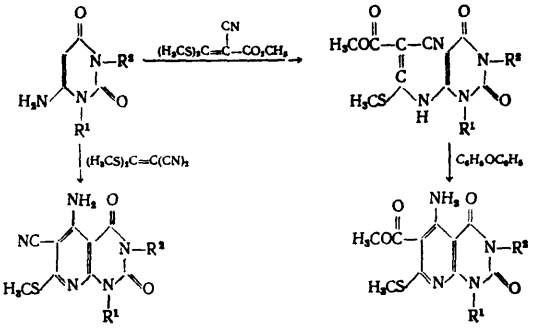
The methods described in this Section make it possible to obtain pyridopyrimidines with various substituents in the pyridine ring by forming the pyridine ring from pyrimidines with functional group substituents.

One of the commonest methods of synthesis of pyrido[2,3-*d*]pyrimidines involves the condensation of 4-aminopyrimidines with ethoxymethylenemalonic ester with subsequent cyclisation of the resulting compounds by treatment with phosphoryl chloride [99,100] or by refluxing in diphenyl ether. [101–105] Cyclisation in polyphosphoric acid (PPA) results in the formation of pyridopyrimidines with a carboxy-group in the pyridine ring: [106]

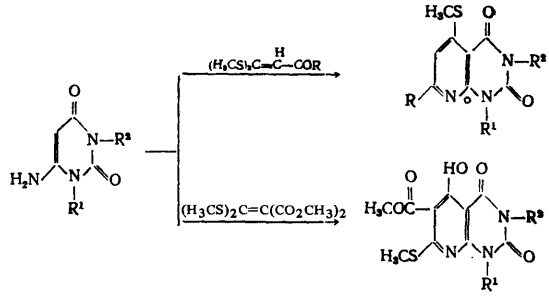


The reaction of 4-aminopyrimidines with cyanoethoxymethyleneacetic acid esters afforded the corresponding methyleneaminopyrimidines whose cyclisation is achieved in ethyl phosphate with subsequent hydrolysis by sodium hydroxide. [107] The condensation of 1,3-disubstituted 6-aminouracils with 2-cyano-3,3-bis(methylthio)acrylonitrile results in the formation in a single stage of 1,3-disubstituted 5-amino-6-cyano-7-methylthio-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines. However, the reaction of the same 6-aminouracils with 2-cyano-3,3-bis(methylthio)acrylate under analogous conditions is accompanied by the formation of intermediates the heating of which in diphenyl ether also

leads to the formation of pyridopyrimidines:[108]



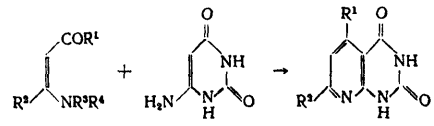
Other pyrido[2,3-*d*]pyrimidines containing various substituents in the pyridine ring were synthesised in the same study from 6-aminouracils in accordance with the scheme



New derivatives of pyridopyrimidines have been obtained by refluxing aminouracils with dimethyl acetylenedicarboxylate in protic solvents.[109,110]

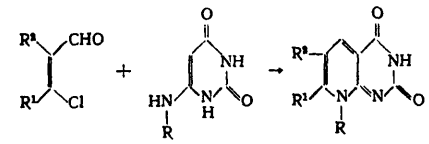
The reaction of 6-amino-1,3-dimethyluracil with unsaturated diketones also proceeds with formation of the pyridine ring.[111]

It has been shown that tetrahydropyrido[2,3-*d*]pyrimidines can be obtained in high yields by the reaction of 6-aminouracils with β-aminovinyl ketones:[112,113]

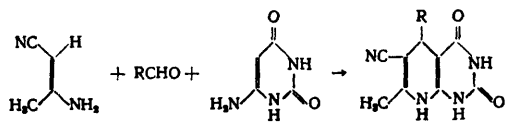


The cyclisation of 6-amino-1,3-dimethyluracil by reaction with unsaturated carbonyl compounds is carried out in the presence of basic or acid catalysts.[114]

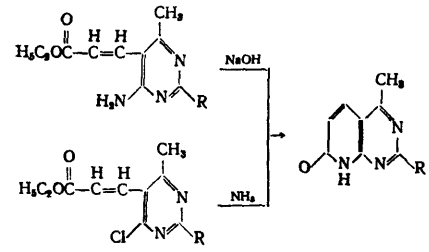
Heating of 6-aminouracils with β-chloro-substituted αβ-unsaturated carbonyl compounds in DMF leads to the formation of 6,7,8-trisubstituted pyridopyrimidines:[115]



A novel method of synthesis of certain pyridopyrimidine derivatives involves the interaction of 6-aminouracils with bisacetonitrile and aldehydes:[116]

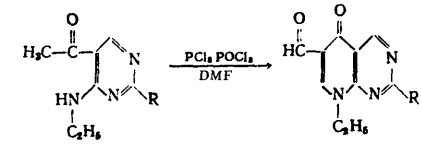


Methods of synthesis of 2-substituted 4-methyl-7-oxopyridopyrimidines based on the reaction of 2-substituted 4-amino-5-iodo-6-methyl- and 5-iodo-6-methyl-4-oxo-pyrimidines with ethyl acrylate in accordance with the scheme

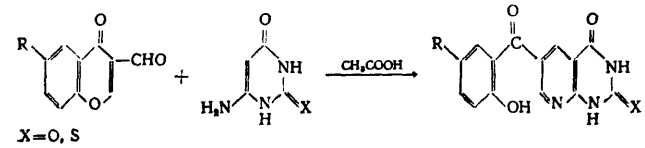


have been described.[117] Derivatives of 7-oxopyridopyrimidines can also be obtained by condensing 6-aminouracils with ethyl acrylate.[118]

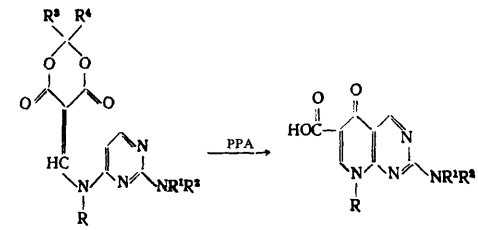
6-Formylpyridopyrimidines have been synthesised by the reaction of 2,4-diaminopyridines with DMF in the presence of phosphorus trichloride or phosphoryl chloride.[119] Other derivatives of 6-formylpyrido[2,3-*d*]pyrimidines have been synthesised under analogous conditions from 5-acetyl-4-ethylaminopyrimidines:[120,121]



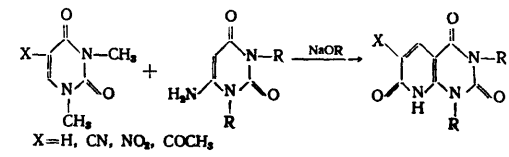
A method of synthesis of 6-(2-hydroxybenzoyl)tetrahydropyrido[2,3-*d*]pyrimidines involves the cyclisation of 4-aminouracils by reaction with chromene derivatives in acetic acid:[122]



A new method of synthesising derivatives of 6-carboxypyridopyrimidines via the scheme[123–125]

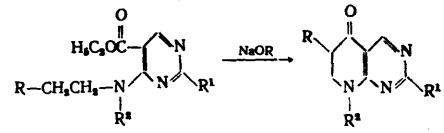


has been developed. A single-stage synthesis of pyridopyrimidines from two molecules of substituted uracils has been proposed:[126,127]



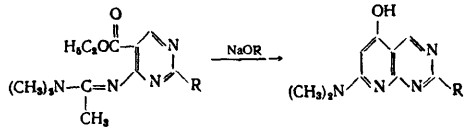
4-(2-Cyanoethyl)- or 4-(2-ethoxycarbonylethyl)-amino-5-ethoxycarbonyl pyrimidines, obtained by the reaction of 4-chloro-5-ethoxycarbonylpyrimidines with the nitriles or esters of 3-aminopropionic acids, cyclise on treatment with

sodium alkoxides or hydride with formation of the corresponding 5-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines:[128-141]



When 4-amino-5-ethoxycarbonylpyrimidines are acylated with the chloride of the monoethyl ester of malonic acid in the presence of alkoxide, intramolecular cyclisation takes place with formation of 5,7-dioxo-5,6,7,8-tetrahydropyridopyrimidines.[142-144]

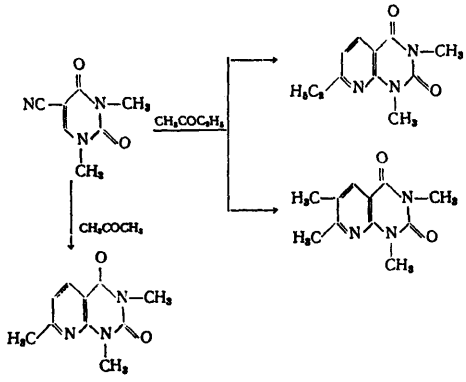
The amines formed as a result of the condensation of 4-amino-5-ethoxycarbonylpyrimidines with the diethyl acetal of dimethylacetamide in the presence of sodium alkoxide cyclise to 5-hydroxypyridopyrimidines:[145,146]



The condensation of 4-amino-5-methoxycarbonylpyrimidines with butenal, which led to the synthesis of *N*-substituted 5-oxo-6-vinyl-5,6-dihydropyridopyrimidine, has also been investigated.[147]

The reaction of 4-aminopyrimidines containing the formyl group in the 5-position with aryl acetonitriles, ketones, and cyanoacetamides yields the corresponding pyrido[2,3-*d*]-pyrimidines.[148-153]

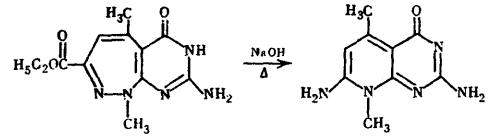
The condensation of 5-cyano-1,3-dimethyluracil with acetone involves the closure of the pyridine ring with formation of the trimethyl derivative, while treatement with butanone under the same conditions yields a mixture of the two isomeric dioxotetrahydropyrido[2,3-*d*]pyramidines:[154]



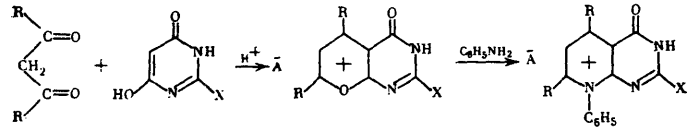
The reaction with malonodinitrile results in the formation of 7-amino-6-cyanodioxotetrahydropyrido[2,3-*d*]pyrimidine.[154]

Various derivatives of 2-thionopyridopyrimidines have been obtained by condensing arylidenethiobarbituric acid with malonodinitrile, ethyl cyanoacetate, and ethyl acetoacetate in the presence of ammonium acetate.[155]

An interesting condensation of 2-amino-4-(1-*N*-methylhydrazino)pyrimidine with ethyl 3-acetylpyruvate takes place with formation of 8-amino-3-ethoxycarbonyl-1,5-dimethyl-6-oxo-6,7-dihydropyrimido[4,5-*c*]-1,2-diazepine, whose treatment with potassium hydroxide leads to 2,7-diamino-5,8-dimethyl-4-oxo-4,8-dihydropyrido[2,3-d]pyrimidine:[156]



The synthesis of 8-phenylpyrido[2,3-*d*]pyrimidinium salts from 4,6-dihydroxypyrimidines and diketones via salts of pyrylio[2,3-*d*]pyrimidines in accordance with the following scheme has been reported:[158]



X = OH, SH, NH_2, SCH_3; A = ClO_4, H_2PO_4, CF_3COO

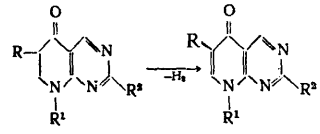
Treatment of pyrano[2,3-d]pyrimidine with aqueous ammonia solution leads to the replacement of the pyran ring by the pyridine ring, which results in the formation of 2,4-dioxopyridopyrimidine.[158]

III. CHEMICAL REACTIONS

The chemical reactions of condensed pyridopyrimidines can be carried out selectively, via the pyridine or pyrimidine ring, which makes it possible to obtain a large number of new derivatives of this series. The chemical reactions of pyridopyrimidines involving the opening of the pyrimidine ring have also been studied.

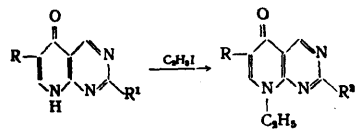
1. Reactions Via the Pyridine Component of the Molecule

It has been shown that 2,8-disubstituted 6-alkoxycarbonyl-5-oxo- or 6-cyano-5-oxo-tetrahydropyrido[2,3-*d*]pyrimidines are dehydrogenated on treatment with various dehydrogenating agents:[132,159-163]



An analogous result has been obtained on brominating 2,8-disubstituted 5-oxotetrahydropyridopyrimidines with subsequent dehydrobromination of the products.[131,133,137]

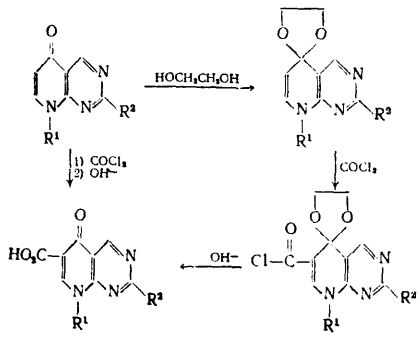
5-Oxopyridopyrimidines are readily alkylated with ethyl iodide to form the corresponding 8-ethyl derivatives:[102-104,164,165]



Various methods of synthesis of derivatives of condensed pyridopyrimidines containing the carboxy-group in the 6-position have been developed.[102-104,132,133,166-174] Thus it has

been shown that the hydrolysis of 6-ethoxycarbonylpyridopyrimidines leads to 6-carboxypyridopyrimidines in high yields.[102–104,132,133,166] 6-Formyl and 6-acyl derivatives of pyridopyrimidines are oxidised on treatment with various oxidants to the corresponding carboxypyridopyrimidines.[167,169] Heating of 6-oxazolidinylpyridopyrimidines in hydrochloric acid leads to the same result.[170]

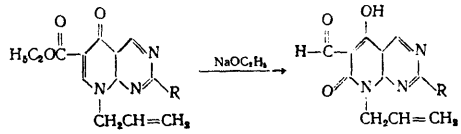
6-Carboxy-derivatives have been obtained in one or three stages from 8-alkyl-5-oxo-5,8-dihydropyridopyrimidines and phosgene:[171–173]



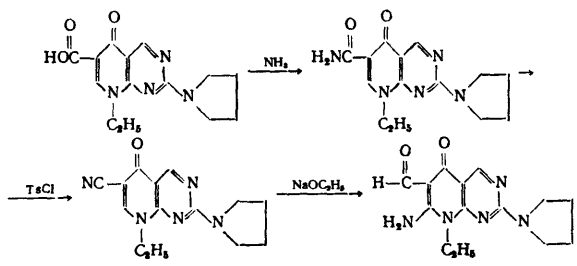
5-Alkylamino-6-carboxypyrido[2,3-*d*]pyrimidines can be obtained by hydrolysing 6-alkoxycarbonyl-5-alkylaminopyridopyrimidines.[174] Other workers established[147] that the oxidation of 6-vinylpyridopyrimidine with potassium permanganate leads to its 6-carboxy-derivative.

The alkylation of 8-alkyl-6-cyano- or 6-alkoxycarbonyl-8-alkyl-5-oxopyridopyrimidines has been investigated and it has been shown that the alkyl group enters the 6-position in the presence of sodium alkoxide.[132,136]

In the presence of sodium alkoxide, derivatives of 6-ethoxycarbonyl-5-oxo-5,8-dihydropyridopyrimidines are converted into the corresponding 6-formyl-5-hydroxy-7-oxopyrido-[2,3-*d*]pyrimidines:[175]



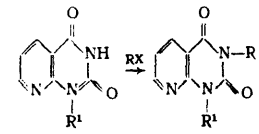
In the sams study the authors proposed the synthesis of 7-amino-8-ethyl-6-formyl-5-oxo-2-(1-pyrrolidino)-5,8-dihydropyrido[2,3-*d*]pyrimidine from 6-carboxypyridopyrimidine:



The oxo-group is substituted by chlorine atome when 5-oxopyridopyrimidines are treated with phosphoryl chloride. The subsequent interaction of 5-chloropyridopyrimidines with alcohols and amines leads to 5-alkoxy- and 5-amino-derivatives.[146]

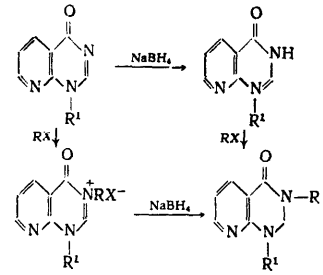
2. Reactions Via the Pyrimidine Component of the Molecule

The alkylation of monosubstituted dioxotetrahydropyridopyrimidines has been investigated and it has been shown that, regardless of the alkylating agents used, 1,3-disubstituted derivatives are obtained in high yields:[47,176–181]



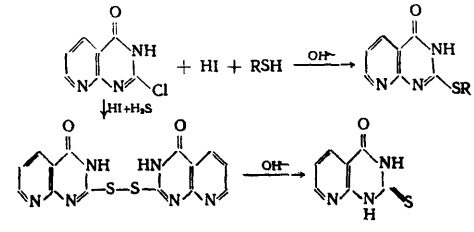
The alkylation of 1-substituted 2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines also takes place readily.[182–184]

The interaction of 1-substituted 4-oxo-1,4-dihydropyridopyrimidines with alkyl halides and dialkyl sulphates results in the formation of the corresponding salts of the 3-*N*-alkyl derivatives, whose treatment with sodium tetrahydroborate is accompanied by the reduction of the C=N double bond in the pyrimidine ring.[185] The same workers[186] proposed another method for the 3-*N*-alkylation of pyridopyrimidines, which involves essentially the initial reduction of the C=N double bond in the initial pyridopyrimidines with subsequent alkylation of the products:

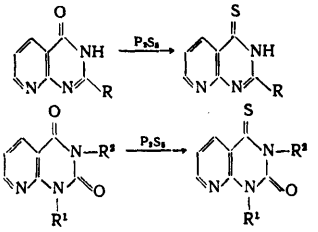


One of the important reactions of 2-oxo-, 4-oxo-, and 2,4-dioxo-pyrido pyrimidines is their conversion by treatment with phosphoryl chloride into the 2-chloro-, 4-chloro-, and 2,4-dichloro-derivatives—the starting materials for the synthesis of many pyridopyrimidine derivatives by the nucleophilic substitution of the chlorine atom. Thus the interaction of chloropyridopyrimidines with alcohols, amines, and ketones yielded the corresponding alkoxy-, amino-, and oxomethyl derivatives.[32,187–192]

The interaction of 2-chloro-4-oxodihydropyridopyrimidine with alkanethiols in the presence of hydrogen iodide afforded the corresponding 2-alkylthio-derivatives, while the reaction with hydrogen sulphide under the same conditions leads to the formation of the disulphide, which is converted into the 2-thiono-derivative as a result of hydrolysis:[193]

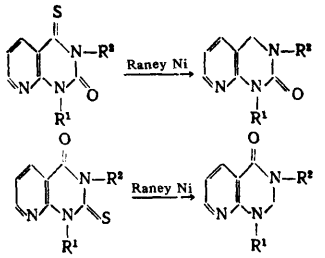


4-Oxodihydro- and 2,4-dioxotetrahydro-pyridopyrimidines are converted into the corresponding 4-thionopyridopyrimidines in high yields on treatment with phosphorus pentasulphide: [187,194]



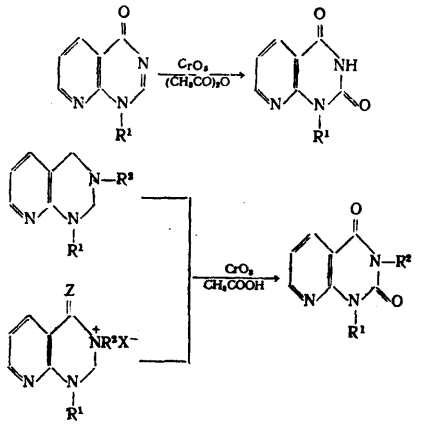
The conversion of thionopyridopyrimidines into oxopyridopyrimidines by oxidising the thiono-group with hydrogen peroxide is also possible. [195–197]

Thionopyridopyrimidines are desulphurised in the presence of Raney nickel as catalyst: [198,199]

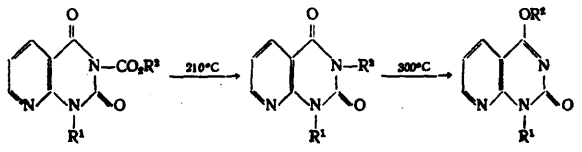


It has been shown that, on treatment with a 5% solution of sodium hydroxide, 2,4-diaminopyrido[2,3-*d*]pyrimidine is converted into 4-amino-2-oxo-1,2-dihydropyridopyrimidine. [91]

2,4-Dioxopyridopyrimidines are obtained by oxidising various pyridopyrimidine derivatives with chromium trioxide: [200–202]

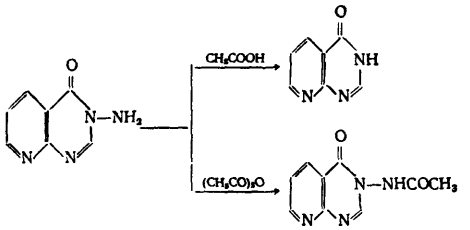


A study of the decarboxylation of 3-alkoxycarbonyl-2,4-dioxotetrahydropyridopyrimidines showed that different products are obtained depending on the temperature. Thus the corresponding 3-alkyl derivatives are formed at 210 °C, while on raising the temperature to 300 °C the alkyl group migrates from the nitrogen atom in the 3-position in the pyrimidine ring to the oxygen atom in the 4-position: [203,204]



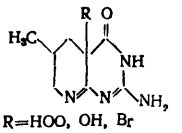
6-Substituted 8-ethyl-5-oxo-5,8-dihydropyrido[2,3-*d*]-pyrimidines, containing the 2-methylthio-, 2-methylsulphoxy-, and 2-chloro-substituents, undergo substitution reactions with amines, forming the corresponding amino-derivatives. [101, 121,205–210]

It has been shown that the interaction of 3-amino-4-oxo-3,4-dihydropyridopyrimidine with pentyl nitrite in the presence of acetic acid entails its deamination, while in the reaction with acetic anhydride the amino-group is acylated: [36]



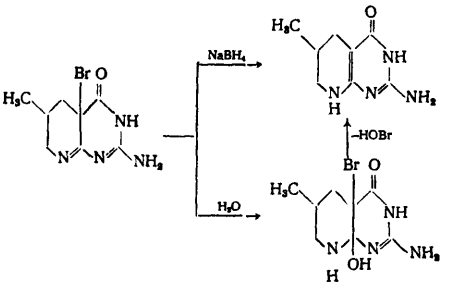
The 2-methyl-group in 1-substituted dioxopyridopyrimidines reacts with acid anhydrides and with aromatic aldehydes to form the corresponding 2-acylmethyl and 2-styryl derivatives. [211–213]

Various chemical reactions of 2-amino-6-methyl-4-oxohexahydropyridopyrimidine, in particular those making it possible to obtain new derivatives with angular substituents, have been investigated: [214,215]

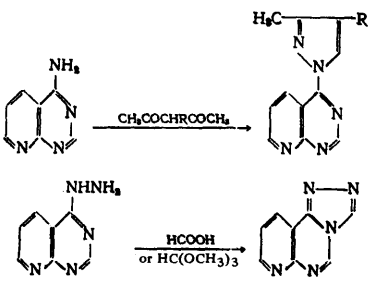


R=HOO, OH, Br

Hexhydropyridopyrimidine containing an angular bromine atom is converted by treatment with sodium tetrahydroborate into the initial pyridopyrimidine, while treatment with water entails an addition reaction which results in the formation of octahydropyridopyrimidine with two angular substituents (OH and Br), which readily splits off hypobromous acid: [215]



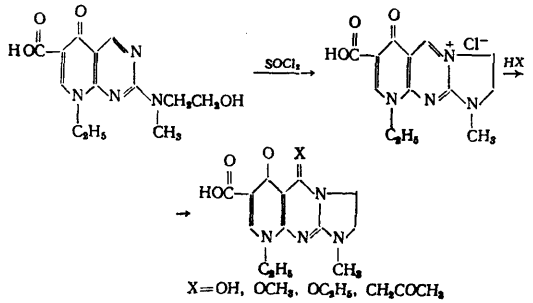
The reactions of substituted pyridopyrimidines via the substituents in the pyrimidine ring, which lead to the formation of tricyclic systems, are of great interest. Thus the condensation of 4-aminopyridopyrimidine with β-diketones and of 4-hydrazinopyridopyrimidine with formic acid or its orthoester afforded the corresponding 1-(4-pyrazolyl)pyridopyrimidine and triazolo[3,4-*f*]pyridopyrimidine: [216]



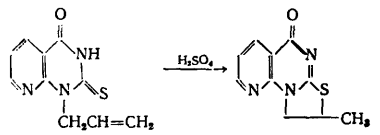
1-Subsituted 5-oxo[*H*]triazole[3,4-*f*]pyridopyrimidines have been obtained by an analogous procedure.[217]

The interaction of 2-amino-3-(5-tetrazolyl)pyridine with orthoesters leads to a condensed tricyclic system—pyrido-[2,3-*d*]tetrazolo[5,1-*f*]pyrimidine.[218,219]

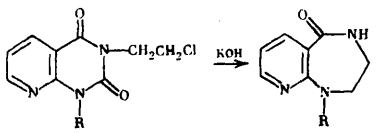
Imidazopyridopyrimidine has been synthesised by the reaction of 2-(β-hydroxyethylamino)pyridopyrimidine with thionyl chloride:[220]



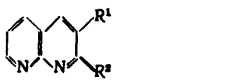
1-Allyl-4-oxo-2-thiono-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine undergoes intramolecular cyclisation in the presence of concentrated sulphuric acid with formation of the condensed thiazolidinopyridopyrimidine:[85]



One of the interesting reactions of 1-substituted 3-(β-chloroethyl)-2,4-dioxotetrahydropyridopyrimidines is their conversion into derivatives of pyrido-1,4-diazepines by treatment with an alcoholic solution of potassium hydroxide:[221]



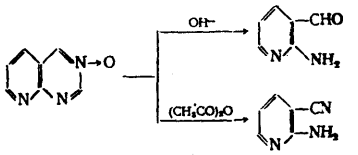
A number of reactions of pyridopyrimidine 3-oxide derivatives with ethyl cyanoacetate, ethyl acetoacetate, and malonodinitrile, leading to the corresponding 1,8-naphthyridines, have been carried out:[222]



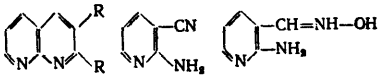
R^1=$CO_2C_2H_5$, R^2=NH_2; R^1=CN, R^2=NH_2; R^1=$CO_2C_2H_5$, R^2=CH_3

3. Reactions Involving the Opening of the Pyridine Ring

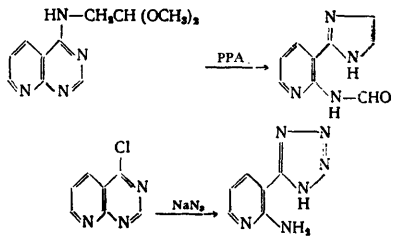
The pyramidine ring in pyrido[2,3-*d*]pyrimidines is known to be opened in the presence of both bases and acids. 2-Amino-3-carboxypyridines are obtained in the former case[87,223] and the 2-amino-3-formyl derivatives are formed in the latter case.[151] Treatment of 3-hydroxypyridopyrimidine with sodium or potassium hydroxide also leads to an aminoformylpyridine.[222] The opening of the pyrimidine ring by treatment with acetic anhydride has been described in the same study:



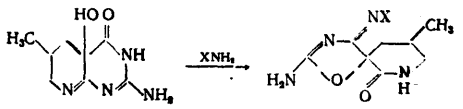
The condensation of 3-hydroxypyridopyrimidine with ketones has also been investigated and it has been established that a mixture of three compounds with the following structures is formed:[224]



The opening of the pyrimidine ring has been studied in the dimethyl acetal of 4-pyridopyrimidinylaminoacetaldehyde and 4-chloropyridopyrimidine when the latter are treated with polyphosphoric acid (PPA) and sodium azide respectively:[218,219]

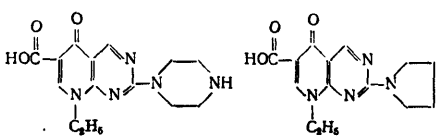


The condensation of the 2-amino-10-hydroxy-4-oxo-derivatives with methoxyamine and semicarbazide, which results in the formation of spiro-oxazolopiperidine derivatives, is also of interest:[215]



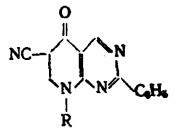
IV. BIOLOGICAL PROPERTIES

As mentioned above, derivatives belonging to the class of pyrido[2,3-*d*]pyrimidines exhibit a broad spectrum of biological activity, two representatives being used as effective antibacterial agents in medical practice under the names "pipemidic acid"[5,225–244] and "piromidic acid".[6,245–254]

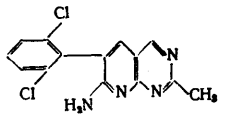


The study of the antibacterial activity of analogous derivatives containing various substituents in the 2-, 6-, and 8-positions showed that, for identical substituents in the 2- and 8-positions, the highest activity is shown by compounds with a carboxy-group in the 6-position. The most effective compounds are pyridopyrimidines with ethyl and amino-groups in the 2- and 8-positions respectively.[100,103,104,133–138,160,164,166,174,203,255–260] Furthermore, certain derivatives of this series exhibit anti-inflammatory analgesic,[206,261] and hypotensive[149,205] activities.

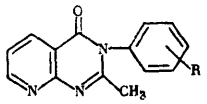
8-Substituted 6-cyano-5-oxo-2-phenyl-5,6,7,8-tetrahydropyridopyrimidines[128–130] exert a depressing activity on the central nervous system.



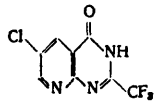
An effective hypotensive agent has been found among 2-substituted 7-amino-6-aryl derivatives:[3,149,150]



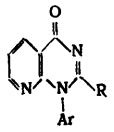
2-Substituted 4-oxodihydropyrido[2,3-*d*]pyrimidines exhibit antiallergic[25,29,262] and diuretic[26–28,30,263–265] activities. 3-Aryl-2-methyl-4-oxodihydropyridopyrimidines containing different substituents in the benzene ring are effective inhibitors of xanthine oxidase:[4]



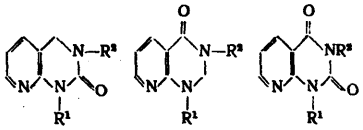
Among derivatives of 2-alkyl(or halogenoalkyl)-4-oxo-3,4-dihydropyridopyrimidines, containing various substituents in the pyridine ring, the 6-chloro-2-trifluoromethyl derivative with a strong herbicidal activity has been discovered:[2]



1-Aryl-4-oxotetrahydropyridopyrimidines exhibit diuretic, hypotensive anti-inflammatory, and tranquillising activities.[19–21] 2-Substituted derivatives of this series are also analgesics and depressants:[23,24,211,212]

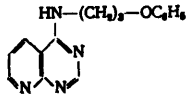


Almost all 2-oxo-derivatives,[12,13,182–184,209] 4-oxo-derivatives,[185,186,195,210,266] and 2,4-dioxo-derivatives[41,51,54–58,60–66, 176–181,196–201] of 1,3-disubstituted tetrahydropyrido[2,3-*d*]-pyrimidines show analgesic and anti-inflammatory activities and are depressants:



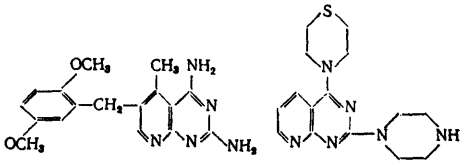
4-Oxo-2-thiono- and 2-oxo-4-thiono-tetrahydropyridopyrimidines possess the same properties[79–82,194] and some of them exhibit antihistamine[76] and diuretic[192] activities.

Whereas 4-chloropyridopyrimidines are neuroleptic substances,[187] the 4-alkoxy(or 4-amino)-derivatives are spasmolytic substances.[32,188] This series also includes a powerful antifungal agent—4-(3-phenoxypropylamino)pyrido[2,3-*d*]-pyrimidine:[267]



The series of 1-substituted 4,7-diaminopyridopyrimidines includes effective depressants of the central nervous system.[152,153]

Among derivatives of 2,4-diaminopyridopyrimidines, it is possible to distinguish two compounds: the first is an effective inhibitor of several enzymes[1] and the second inhibits the aggregation of thrombocytes:[268]



Antibacterial properties have been found in certain derivatives of pyridopyrimidines containing the penicillanic acid residue.[269,270]

In conclusion it should be stated that a more far-reaching study of the methods of synthesis and new derivatives of pyrido[2,3-*d*]pyrimidines, directed towards the development of other methods or the simplification of individual stages of existing methods of synthesis, is of great theoretical and practical interest for the preparation of new, hitherto unknown, biologically active compounds and medicinal preparations.

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Mndzhoyan Institute of
Fine Organic Chemistry,
Academy of Sciences of
the Armenian SSR, Erevan