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# Furo-, Thieno-, and Pyrrolo-[2,3-*d*] Pyrimidines

R.G.Melik-Ogandzhanyan, V.E.Khachatryan, and A.S.Gapoyan

The methods of synthesis and the chemical and biological properties of furo-, thieno-, and pyrrolo-[2,3-*d*] pyrimidines are described.
The bibliography includes 201 references

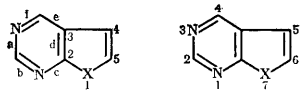
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## I. INTRODUCTION

Furo-, thieno-, and pyrrolo][2,3-*d*]pyrimidine derivatives occupy an important place among various heteroatomic bicyclic systems because they include compounds with different types of biological activity. Furthermore, these bicyclic compounds represent to a greater or lesser extent the structural analogues of biogenic purines and from this standpoint can be regarded as potential antimetabolites in nucleic acid metabolism. These data have served and continue to serve as a basis for the synthesis of a wide variety of derivatives of furo-, thieno-, and pyrrolo-[2,3-*d*]pyrimidines in order to discover physiologically active substances among them.

The IUPAC nomenclature and the numbering for these bicyclic systems, which we shall henceforth employ in the present review, are given below.



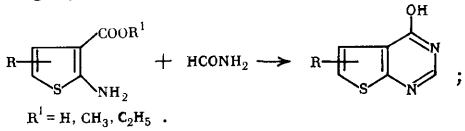
X = O, S, NH

Although the first communication on the synthesis of pyrrolo[2,3-*d*]pyrimidine appeared as early as 1911,[1] systematic studies on furo-, thieno-, and pyrrolo-[2,3-*d*]pyrimidines were begun 20–25 years ago. The methods of synthesis of these compounds can be divided into two groups: from derivatives of a five-membered heterocycle (furan, thiophen, and pyrrole) and from derivatives of a six-membered heterocycle (pyrimidine, oxazole, and thiazole).

## II. METHODS OF SYNTHESIS

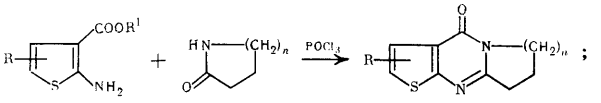
### 1. Methods of Synthesis from a Five-membered Heterocycle

Derivatives of 2-aminofurans, 2-aminothiophens, and 2-aminopyrroles containing the carbonyl or cyano-group in the 3-position in the five-membered ring have been widely used as the starting compounds for the synthesis of the bicyclic derivatives under consideration. Thus, when 2-aminothiophen-3-carboxylic acid or its esters are heated with formamide, 4-hydroxythieno[2,3-*d*]pyrimidines are formed in high yields:[2-8]



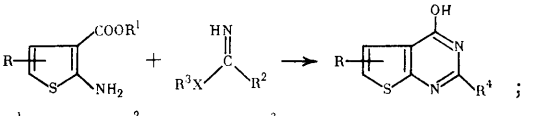
$R^1$ = H, $CH_3$, $C_2H_5$ .

Other workers[9] used the corresponding lactams instead of formamide; the yield of thienopyrimidine was 40–90%:



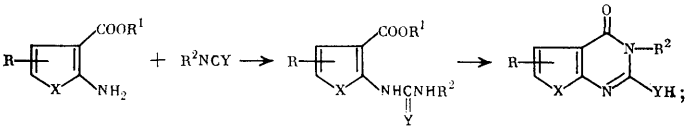
$R^1$ = H, $C_2H_5$; $n$ = 1, 2, 3 .

The esters of 2-aminothiophen-3-carboxylic acid react with urea,[6,10] thiourea,[11] and iminoesters[11,13] to form the corresponding 2-substituted 4-hydroxythieno[2,3-*d*]pyrimidines:



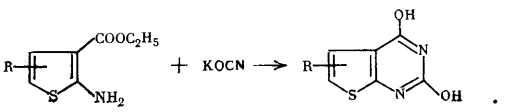
$R^1$ = $CH_3$, $C_2H_5$; $R^2$ = $NH_2$, Alk, Ar; $R^3$ = H, $C_2H_5$; $R^4$ = OH, SH, Alk, Ar; X = O, S .

The reactions of 2-amino-3-ethoxycarbonylthiophen with isocyanates,[14,15] isothiocyanates[11,16-25] and isoselenocyanates[26] lead to the formation of intermediate 3-ethoxycarbonyl-2-thienylureas (and the corresponding thioureas and selenoureas), which cyclise in an alkaline medium to the corresponding 2-substituted 3-alkyl(aryl)-4-hydroxythieno-[2,3-*d*] pyrimidines. An analogous reaction with isocyanate is known for 2-amino-3-methoxycarbonylfuran[27] and the corresponding pyrrole:[28]

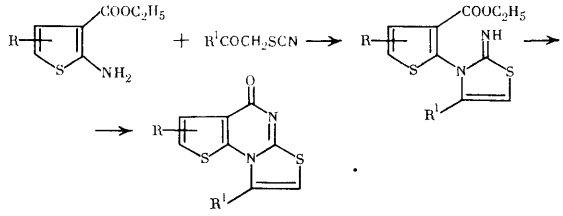


$R^1$ = $CH_3$, $C_2H_5$; $R^2$ = Alk, Ar; X = O, S, NH; Y = O, S, Se .

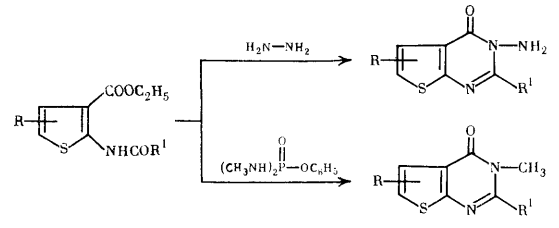
In an aqueous solution of potassium cyanate 2-amino-3-ethoxycarbonylthiophen cyclises 2,4-dihydroxythieno-pyrimidine in 70% yield:[29]



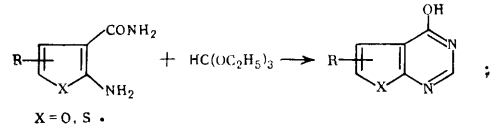
There is an interesting reaction between 2-amino-3-ethoxycarbonylthiophen and α-thiocyanatoacetone[30] or the corresponding acetophenone,[31] which results in the formation of the bicyclic thiazolothienopyrimidine system:



The interaction of 2-acylamino-3-ethoxycarbonylthiophen with hydrazine hydrate[32] or phenyl *NN*-dimethylphosphorodiamidate[33] results in the formation of 2-alkyl-3-amino- or 2-alkyl-3-methyl-4-oxo-thieno[2,3-*d*]pyrimidines respectively:

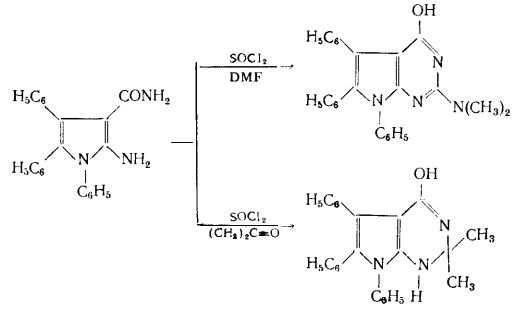


The 3-carbamoyl derivatives of the five-membered heterocycles can also participate in the cyclisation reactions. Thus 2-amino-3-carbamoylfurans[34,35] and the corresponding thiophens[5] react with orthoformic ester or with the acid itself[6] to form the corresponding 4-hydroxy-derivatives:

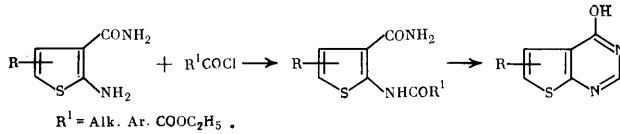


X = O, S.

On treatment with thionyl chloride in dimethylformamide (DMF), 2-amino-3-carbamoyl-1,4,5-triphenylpyrrole cyclises to 4-hydroxy-2-dimethylaminopyrrolo[2,3-*d*]pyridimine, while in acetone it cyclises to 2,2-dihydro-4-hydroxy-2,2-dimethylpyrrolopyrimidine:[36]

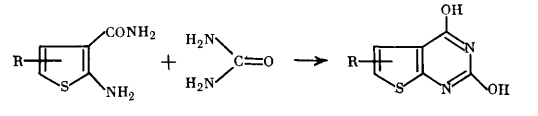


2,3-Substituted 4-hydroxythienopyrimidines can be synthesised from 2-acylamino-3-carbamoylthiophens:[6,37-39]

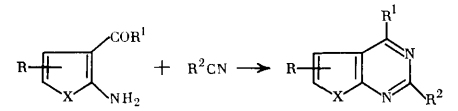


$R^1$ = Alk, Ar, $COOC_2H_5$.

When 2-amino-3-carbamoylthiophen is heated with urea, 2,4-dihydroxythieno[2,3-*d*]pyrimidine is formed in 40% yield:[6]

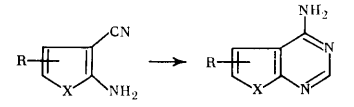


2-Amino-2-carbamoyl-, 2-amino-3-ethoxycarbonyl, and 2-amino-3-benzoyl-furans and the corresponding thiophens and pyrroles react with various nitriles to form the corresponding bicyclic compounds in 50–85% yields:[40]



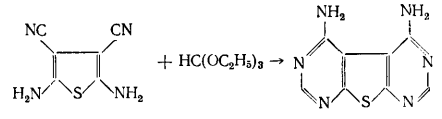
X = O, S, NH; $R^1$ = $NH_2$, $NHCH_3$, $OC_2H_5$, $C_6H_5$; $R^2$ = Alk, Ar.

When 2-amino-3-cyanofurans and the corresponding thiophens or pyrroles are used in the syntheses, it is possible to obtain systems containing the amino-group at the C(4) atom of the pyrimidine ring. Thus the corresponding 4-amino-derivatives have been obtained by heating 2-amino-3-cyanofuran and the corresponding thiophen or pyrrole with formamide,[41-44] orthoformic ester in the presence of ammonia,[45-49] or formamidine acetate:[50,51]

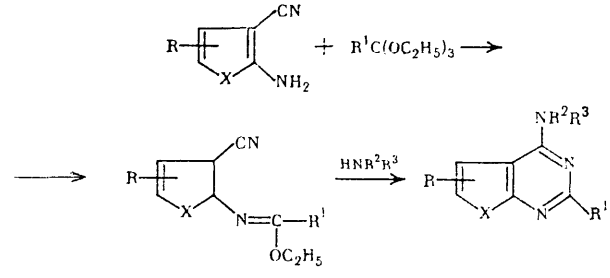


X = O, S, NH.

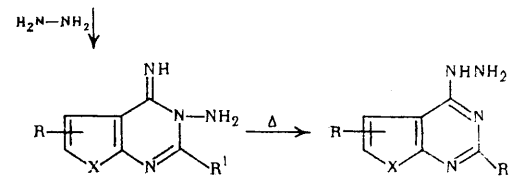
2,5-Diamino-3,4-dicyanothiophen reacts with orthoformic ester in the presence of ammonia and cyclises to 4,4'-diaminothieno[2,3-*d*;2',3'-*d*]dipyrimidine:[48]



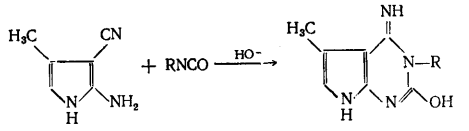
The first stage of the reaction of the corresponding furan or thiophen with orthoformic ester in the presence of ammonia usually involves the formation of 2-alkoxyethyleneimino-3-cyanofuran(or thiophen), which can be made to react with hydrazine[52] or substituted amines[53-56] to form the corresponding 4-amino-derivatives:



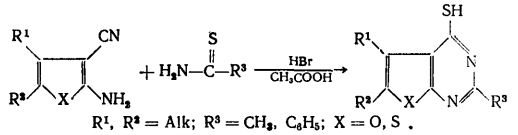
X = O, S; $R^1$ = H, Alk; $R^2$, $R^3$ = H, Alk, Ar;



2-Amino-3-cyanopyrrole cyclises on treatment with isocyanates in an alkaline medium to 3-alkyl-4-amino-2-oxopyrrolo[2,3-*d*]pyrimidine:[28]

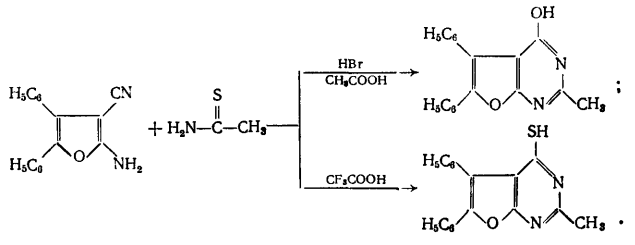


A study of the reaction of 2-amino-3-cyanofurans and the corresponding thiophens with thioamides established that the 4,5-dialkyl derivatives of these heterocycles in an acid medium give rise to 2-mercaptofuro- and 4-mercaptothieno-pyrimidines:[57]

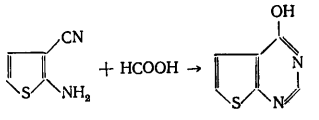


$R^1$, $R^2$ = Alk; $R^3$ = $CH_3$, $C_6H_5$; X = O, S.

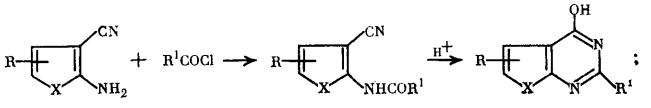
Under the conditions indicated above, 2-amino-3-cyano-4,5-diphenylfuran reacts with thioacetamide to form 4-hydroxyfuropyrimidine, while in the presence of trifluoro-acetic acid it cyclises to 4-mercaptofuropyrimidine:



It is noteworthy that, on treatment with formic acid in the presence of sodium acetate, 2-amino-3-cyanothiophen also cyclises to 4-hydroxythieno[2,3-*d*]pyrimidine:[6]

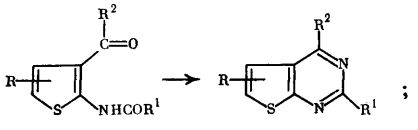


In an acid medium 2-acylamino-3-cyanofuran and the corresponding thiophens give rise to the corresponding 4-hydroxy-derivatives:[57]



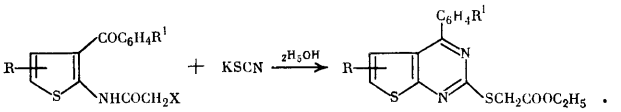
X = O, S; $R^1$ = $CH_3$ $C_6H_5$.

2-Aminothiophen-3-carbaldehydes and the corresponding ketones have found an application in the syntheses of thieno-[2,3-*d*]pyrimidines. In the presence of ammonium acetate, ammonia, or formamide they cyclise to 2,4-dialkyl(aryl)thieno-pyrimidines:[6,58–62]

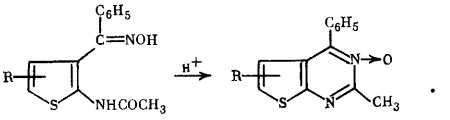


$R^1$ = Alk, Ar; $R^2$ = H, $C_6H_5$.

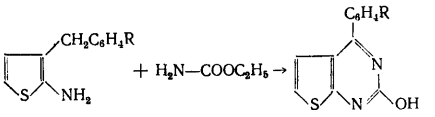
The reaction of 3-benzoyl-2-α-halogenoacylaminothiophen with potassium thiocyanate leads to the formation of 2-alkylthio-4-phenylthieno[2,3-*d*]pyrimidine:[63]



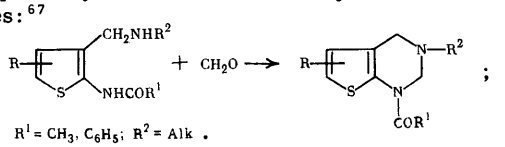
The oximes of 2-acylamino-3-benzoylthiophens cyclise in an acid medium to the corresponding *N*-oxides:[64,65]



In conclusion one may quote non-standard reactions whereby thiophens and pyrroles can be converted into thieno- and pyrrolo-pyrimidines. Thus 2-hydroxy-4-phenylthienopyrimidines have been obtained by heating 2-amino-3-benzylthiophen with urethane:[66]

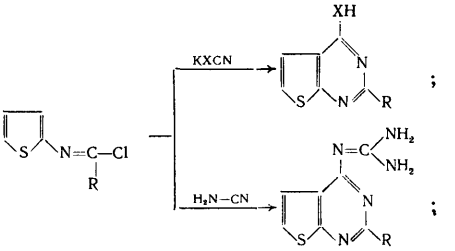


On treatment with formaldehyde, 2-acylamino-3-aminomethylthiophens cyclise to 1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidines:[67]



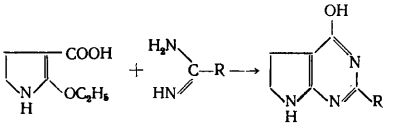
$R^1$ = $CH_3$, $C_6H_5$; $R^2$ = Alk.

The study of the reaction of *N*-(2-thienyl)chloroformamidines with isocyanates and cyanamide led to the synthesis of a series of 2-amino-4-substituted thienopyrimidines:[68]



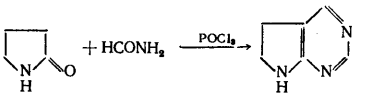
X=O, S, Se; R=N($CH_2$)$_4$, N($CH_2$)$_5$, N($CH_2CH_2$)$_2$O.

3-Carboxy-2-ethoxy-4,5-dihydropyrrole reacts with urea, thiourea, or acetamidine to form the corresponding pyrrolo-pyrimidines, the yield of the product varying in the range from 5 to 70% depending on the character of the reactant:[69,70]

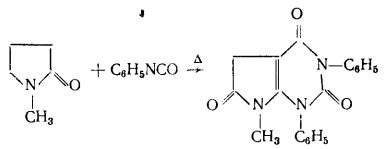


R=OH(4%); H(71%); $SCH_3$(5%), $NH_2$(59%); $CH_3$(40%).

On treatment with formamide in the presence of phosphoryl chloride, 2-pyrrolidinone is converted into 5,6-dihydro-pyrrolo[2,3-*d*]pyrimidine:[71]

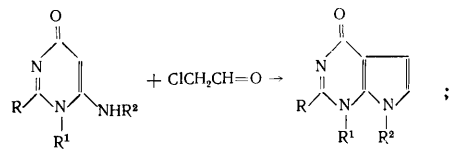


When 1-methyl-2-pyrrolidone is heated with phenyl isocyanate, 5,6-dihydropyrrolopyrimidine is formed:[72]



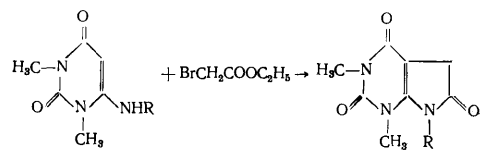
## 2. Methods of Synthesis from Six-membered Heterocycles

In this synthetic procedure, either pyrimidines without substituents at the C(5) atom but with different functional groups (hydroxy-, mercapto, and amino-groups) at the C(2), C(4), and C(6) atoms of the pyrimidine ring or the corresponding 5-substituted 6-hydroxy-, 6-amino-, and 6-mercapto-pyrimidines are usually employed. In the first case α-halogenocarbonyl compounds are used as the second component and the reaction with these substances can proceed both via the C(5) atom of the pyrimidine ring and via the 6-hydroxy-, 6-mercapto-, or 6-amino-group. Thus 2-substituted 6-amino-4-hydroxypyrimidines react with chloroacetaldehyde to form the corresponding pyrrolopyrimidines:[73-75]

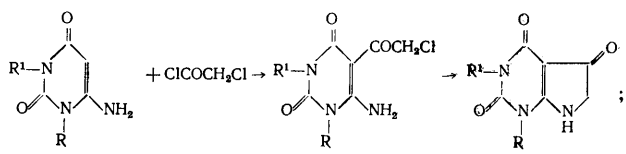


R=OH, SH, $SCH_3$, $NH_2$; $R^1$=H, $CH_3$; $R^2$=H, Alk.

On treatment with bromoacetic ester, 6-amino-1,3-dimethyluracil cyclises to 2,4,6-trioxopyrrolopyrimidine:[76]

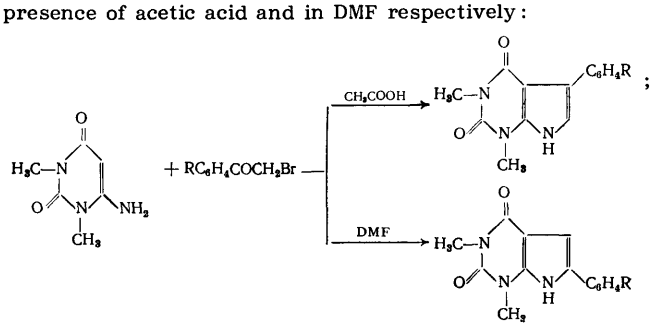


Chloroacetyl chloride also reacts with 6-aminouracils to form 5-acyl derivatives, which cyclise to 2,4,5-trioxopyrrolopyrimidines:[75,77]



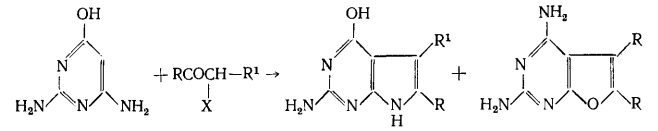
R=H, $CH_3$, $C_2H_5$, $C_6H_5$; $R^1$=H, $CH_3$.

Japanese workers[76,78] have shown that 6-amino-1,3-dimethyluracil reacts with phenacyl bromides via two different pathways depending on the conditions. 5-Phenyl- and 6-phenyl-pyrrolo[2,3-*d*]pyrimidines are formed in the presence of acetic acid and in DMF respectively:



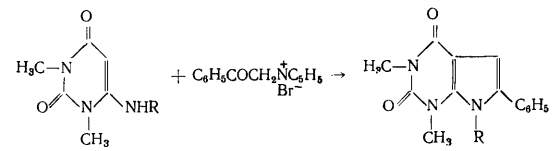
Evidently in the former case a molecule of hydrogen bromide is split off by reaction with the amino-group and in the latter case by reaction with the C(5)–H bond in the pyrimidine ring.

In the interaction of 2,4-diamino-6-hydroxypyrimidine with α-halogenoketones there is a possibility of the formation of both pyrrolo- and furo-[2,3-*d*]pyrimidines. Indeed, depending on the character of the ketone, either a mixture of these compounds or only one of the possible products is formed:[79]

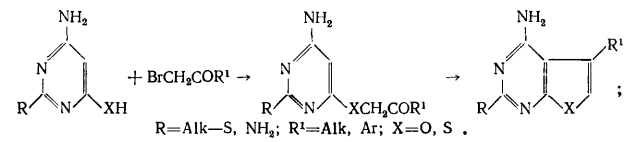


X=Cl, Br; R=H, $C_6H_5$, Alk; $R^1$=H, $CH_3$.

Instead of the α-halogenocarbonyl compounds, the corresponding pyridinium salts are sometimes employed. Thus 6-amino-1,3-dimethyluracil reacts with phenacylpyridinium bromide to form 6-phenylpyrrolopyrimidine:[80]

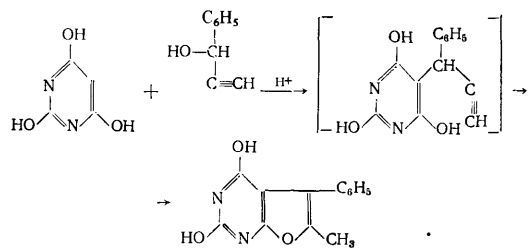


Certain 6-hydroxy- and 6-mercapto-pyrimidines can be alkylated at the hydroxy- and mercapto-groups with subsequent cyclisation to the corresponding furo-[81] or thieno-pyrimidine:[82,83]

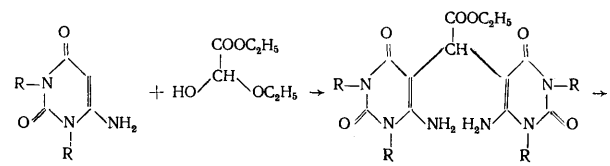


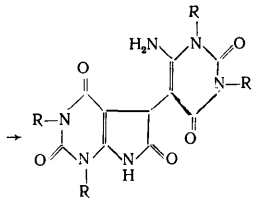
R=Alk—S, $NH_2$; $R^1$=Alk, Ar; X=O, S.

Instances of the employment of reactive hydroxy-compounds in the syntheses of furo- and pyrrolo-pyrimidines are known. Thus, when α-phenylpropargyl alcohol is heated with barbituric acid in the presence of sulphuric acid or boron trifluoride, 2,4-dihydroxy-6-methyl-5-phenylfuro[2,3-*d*]pyrimidine is formed in 75% yield:[84]



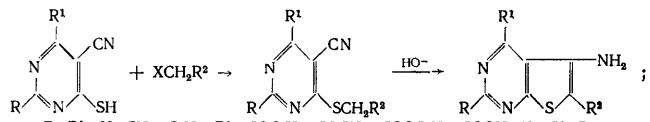
The reaction of ethyl glyoxalate with 6-aminouracils is of the type of aldol condensation and involves the formation of a bispyrimidine which cyclises under the influence of sodium bicarbonate to pyrrolo[2,3-*d*]pyrimidine:[85]





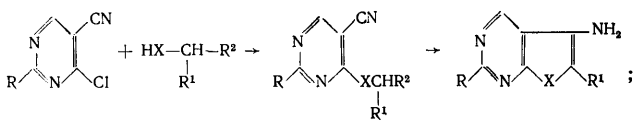
R=H, $CH_3$ .

Among the pyrimidines containing a substituent at the C(5) atom of the pyrimidine ring, the 5-cyano- and 5-ethoxycarbonyl derivatives are used in the syntheses of thieno- and pyrrolo-pyrimidines. Thus 5-cyano-6-mercaptopyrimidine can be alkylated by alkyl halides containing an active methylene group to form the 5-alkyl derivatives. The latter frequently cyclise in an alkaline medium to 5-aminothieno-[2,3-*d*]pyrimidines:[86,87]



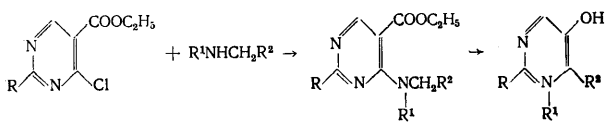
R, $R^1$=H, $CH_3$, $C_6H_5$; $R^2$=$COC_6H_5$, $COCH_3$, $COOC_2H_5$, COOH; X=Cl, Br .

When 6-chloro-5-cyanopyrimidines react with the corresponding mercapto- or amino-derivatives, intermediate 6-alkylthio- or 6-alkylamino-5-cyanopyrimidines are formed. These can be cyclised by a procedure analogous to that described above:[88,89]



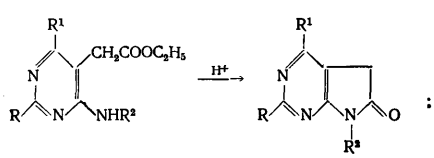
R=$CH_3$; $R^1$=$CH_2COOC_2H_5$; $R^2$=$COOC_2H_5$; X=S; R=$C_6H_5$; $R^1$=CN, $CONH_2$; $R^2$=H; X=NH, $NCH_3$ .

The reaction of 6-chloro-5-ethoxycarbonylpyrimidines with glycine derivatives leads to the formation of 5-hydroxypyrrolo[2,3-*d*]pyrimidines:[90-95]



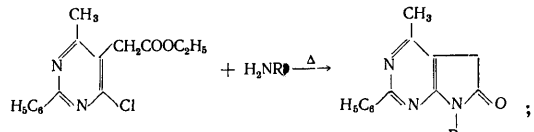
R=Alk, Ar; $R^1$=H, Alk; $R^2$=CN, $COOC_2H_5$ .

Derivatives of pyrimidine-5-acetaldehydes and pyrimidine-5-acetic acids are widely used in the synthesis of pyrrolo-[2,3-*d*]pyrimidines. As stated previously,[1] the first synthesis of pyrrolo[2,3-*d*]pyrimidine was achieved on the basis of 4-aminopyrimidine-5-acetic acid. Several other early investigations in this field have been described:[96-99]



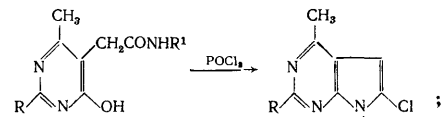
R=$CH_3$, $C_6H_5$, OH; $R^1$=H, OH; $R^2$=H, $CH_3$ .

When ethyl 6-chloropyrimidine-5-acetate is refluxed with amines, 6-oxopyrrolopyrimidines are also formed:[100,101]



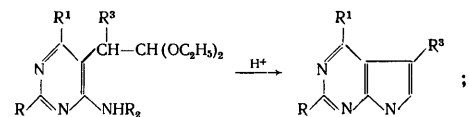
R=$CH_2CH_2OCH_3$, $CH_2C_6H_4Cl$-*p*, $NH_2$ .

6-Hydroxypyrimidine-5-acetamides cyclise on treatment with phosphoryl chloride to 6-chloropyrrolo[2,3-*d*]pyrimidines:[102-104]



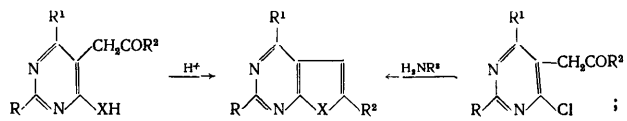
R=$CH_3$, $CH_2C_6H_4OCH_3$-*p*; $R^1$=Alk .

Many instances of the synthesis of pyrrolo[2,3-*d*]-pyrimidines from the acetals of 6-aminopyrimidine-5-acetaldehydes are described in the literature:[105-115]



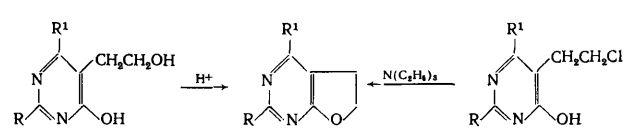
R=OH, SH, $NH_2$, H, Alk; $R^1$=H, OH, $NH_2$, Cl; $R^2$=H, Alk; $R^3$=H, $CH_3$ .

5-Acetonyl-6-hydroxypyrimidines and the corresponding 6-mercapto- and 6-amino-derivatives undergo an analogous reaction in an acid medium.[104,116-120] On the other hand, when 5-acetonyl-6-chloropyrimidines are heated with amines, pyrrolopyrimidines are formed:[118,121]



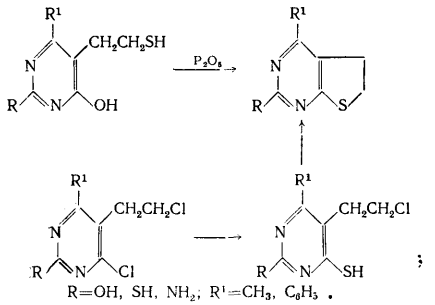
R=OH, SH, $NH_2$, $N(CH_3)_2$, H, $CH_3$, $C_6H_5$, $C_6H_5CH_2$; $R^1$=OH, Cl, $CH_3$, $C_6H_5$; $R^2$=$CH_3$, $C_6H_5$; $R^3$=Alk, Ar .

5-β-Hydroxy-, 5-β-halogeno-, and 5-β-mercapto-alkylamino-derivatives and 5-β-hydroxy-, 5-β-halogeno-, and 5-β-mercapto-ethyl derivatives of 6-hydroxy-, 6-amino-, or 6-chloro-pyrimidines have found applications in the syntheses of 5,6-dihydrofuro-, 5,6-dihydrothieno-, and 5,6-dihydropyrrolo-[2,3-*d*]pyrimidines. Thus, on treatment with thionyl chloride or sulphuric acid, 5-β-hydroxyethyl-6-hydroxypyrimidine cyclises to 5,6-dihydrofuropyrimidine.[122-127] The same compound can be obtained by treating 5-β-chloroethyl-6-hydroxypyrimidine with triethylamine:[128-130]



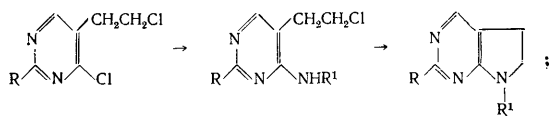
R=OH, SH, $NH_2$, $N(CH_3)_2$, $SCH_3$, H; $R^1$=OH, Cl, H, $CH_3$, $C_6H_5$ .

5,6-Dihydrothieno[2,3-*d*]pyrimidines have been obtained both from 6-hydroxy-5-β-mercaptoethylpyrimidine by treatment with phosphorus pentoxide and from 5-β-chloroethyl-6-chloropyrimidine by reaction with thiourea:[130-132]



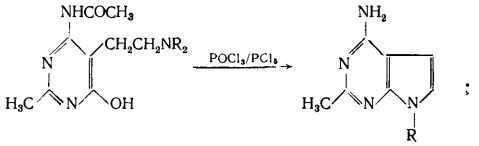
R=OH, SH, $NH_2$, $R^1$=$CH_3$, $C_6H_5$ .

5-β-Chloroethyl-6-chloropyrimidines can be made to react with amines to form the 6-amino-derivatives, which cyclise to 5,6-dihydropyrrolopyrimidines:[123,133–135]



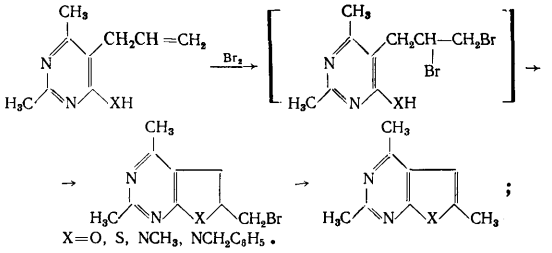
R=Cl, H, $CH_3$; $R^1$=Alk, Ar.

It is of interest to note that 7-alkylpyrrolo[2,3-*d*]-pyrimidine has been obtained by heating 5-β-dialkylamino-ethyl-6-hydroxypyrimidine with phosphoryl chloride and phosphorus pentachloride at 110 °C:[136]



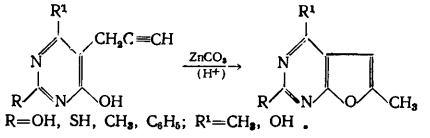
R=$CH_3$, $C_2H_5$ .

A convenient method of synthesis of furo-, thieno-, and pyrrolo-[2,3-*d*]pyrimidines from 5-allyl-6-hydroxy-, 5-allyl-6-mercapto-, and 5-allyl-6-amino-pyrimidines has been discovered recently.[137–139] When the above derivatives are brominated, 5-(2′,3′-dibromopropyl)pyrimidines are formed and then cyclise on refluxing in alcohol or DMF to the corresponding 6-bromomethyl-5,6-dihydro-derivatives. On treatment with sodium methoxide, these compounds give rise to 6-methylfuro-, 6-methylthieno-, and 6-methylpyrrolo-pyrimidines:



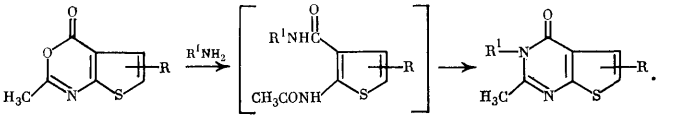
X=O, S, $NCH_3$, $NCH_2C_6H_5$ .

It is known[140] that 6-hydroxy-2,4-dimethyl-5-propargyl-pyrimidine and 6-hydroxy-2-phenyl-5-propargylpyrimidine are converted into 6-methylfuro[2,3-*d*]-pyrimidines on treatment with zinc carbonate. An analogous reaction has been observed for 5-propargylbarbituric acid and the corresponding thiobarbituric acid in the presence of sulphuric acid:

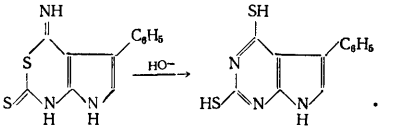


R=OH, SH, $CH_3$, $C_6H_5$; $R^1$=$CH_3$, OH .

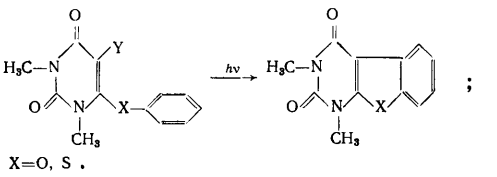
Only a few instances of the synthesis of thienopyrimidines from thieno[2,3-*d*]oxazines are described in the literature.[141–145] The intermediate 2-acylamino-3-carbamoylthiophens, which cyclise to thienopyrimidines on treatment with phosphoric acid, have sometimes been isolated in this process:



On treatment with alkali, 4-imino-5-phenyl-2-thiono-pyrrolo[2,3-*d*]thiazine rearranges to 2,4-dimercapto-6-phenylpyrrolo[2,3-*d*]pyrimidine:[146]

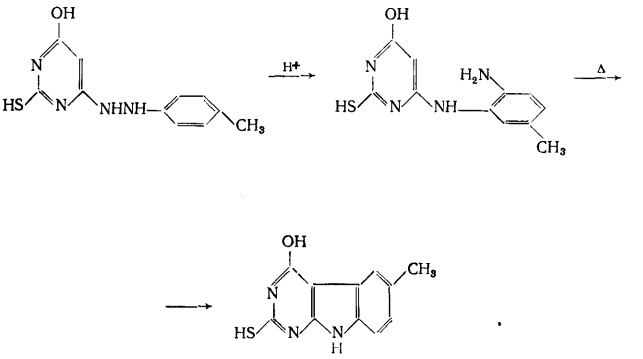


It has been observed[147] that the photolysis of 5-iodo-1,3-dimethyl-6-phenoxyuracil leads to the formation of a furo-pyrimidine in 1% yield, but the 6-phenylthio-analogue cyclises to the corresponding thienopyrimidine in 42% yield:

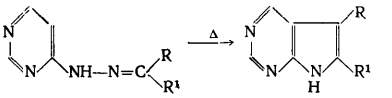


X=O, S .

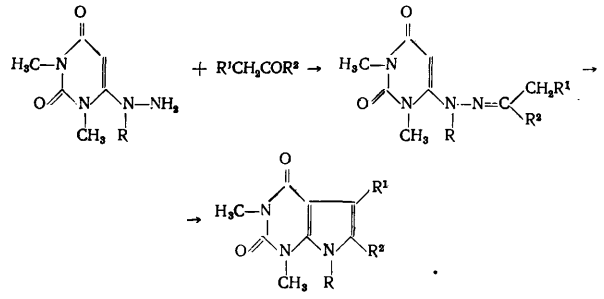
Mention should also be made of the method of synthesis of pyrrolopyrimidines from pyrimidinylhydrazines and hydrazones by analogy with the Fischer indole synthesis. Thus, on treatment with acids, 2-mercapto-6-*p*-tolylhydrazinouracil, gives rise to the stable 6-*o*-aminoanilino-2-mercaptouracil, which undergoes intramolecular cyclisation:[148]



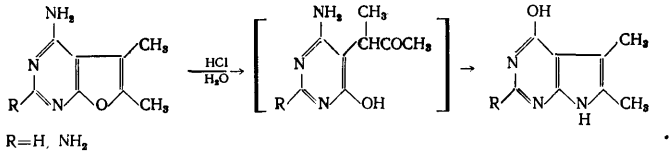
4-Pyrimidinylhydrazones undergo an analogous reaction on refluxing in ethylene glycol, but the yields are then low:[149]



The interaction of 6-hydrazino-1,3-dimethyluracil with ketones in ethylene glycol also affords pyrrolo[2,3-*d*]-pyrimidine:[150,151]



When an attempt was made to hydrolyse 4-aminofuro[2,3-*d*]-pyrimidine to the 4-hydroxy analogue with hydrochloric acid, 4-hydroxypyrrolo[2,3-*d*]pyrimidine was obtained.[152] Evidently the furan ring is opened during the reaction with the subsequent closure of the pyrrole ring. 2,4-Diamino-5,6-dimethylfuro[2,3-*d*]pyrimidine undergoes the same reaction:[79]

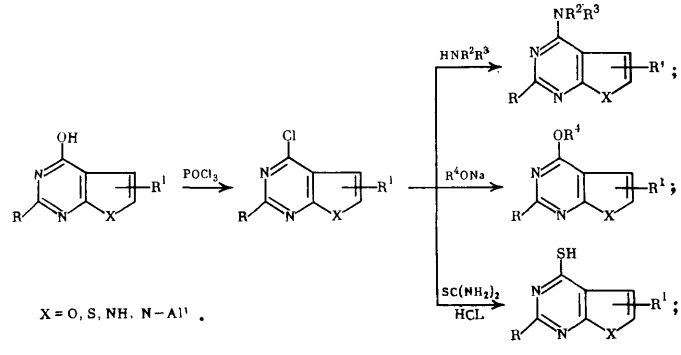


R=H, $NH_2$

## III. CHEMICAL REACTIONS

Consideration of the electronic structures of furo-, thieno-, and pyrrolo-[2,3-*d*]pyrimidines shows that the pyrimidine ring in thse compounds is capable of nucleophilic substitution, while the C(5) and C(6) atoms of the five-membered rings are susceptible to attack by electrophiles.

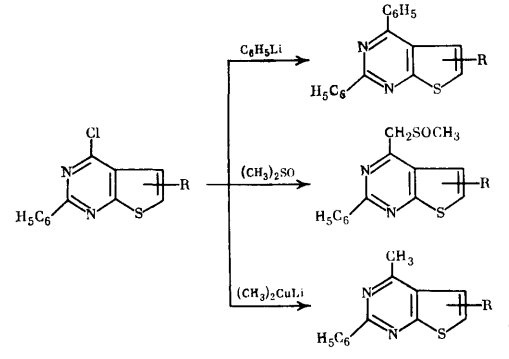
Thus the pyrimidine component of the molecule readily enters into reactions characteristic of pyrimidines. 4-Hydroxyfuro-, 4-hydroxythieno- or 4-hydroxypyrrolo-pyrimidines are readily converted into the 4-chloro-derivatives on treatment with phosphoryl chloride.[4,8,13,16,34,38,73,97,106-109,117-119,121,153-157] Next it is possible to obtain the 4-amino-, 4-hydrazino-, 4-alkoxy-, and 4-mercapto-derivatives of furo-, thieno-, and pyrrolo-[2,3-*d*]pyrimidines from these compounds by standard methods:[4,10,13,16,34,38,106,107,117-119,121,153-158,163,164]



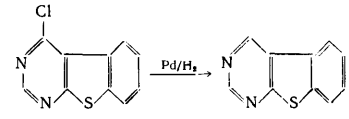
X = O, S, NH, N–Alk .

2,4-Dihydroxythieno[2,3-*d*]pyrimidines react with phosphoryl chloride to form 2,4-dichloro-derivatives, which are converted into a mixture of 4-amino-2-chloro- and 2-amino-4-chloro-thieno[2,3-*d*]pyrimidines on treatment with an alcoholic solution of ammonia at 100 °C.[156]

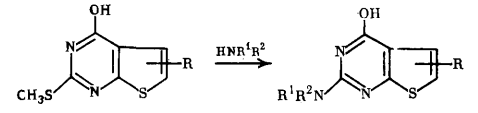
4-Chloro-2-phenylthieno[2,3-*d*]pyrimidine reacts with phenyl-lithium to form 2,4-diphenyl derivatives in 65% yield, the reaction with dimethyl sulphone affords the 4-methanesulphinylmethyl derivative (80%), and the reaction with lithium dimethylcuprate gives rise to the 4-methyl derivative (82%):[16]



On treatment with [hydrogen and] a palladium catalyst, 4-chlorobenzothieno[2,3-*d*]pyrimidine loses a chlorine atom and is reduced to benzothieno[2,3-*d*]pyrimidine:[8]

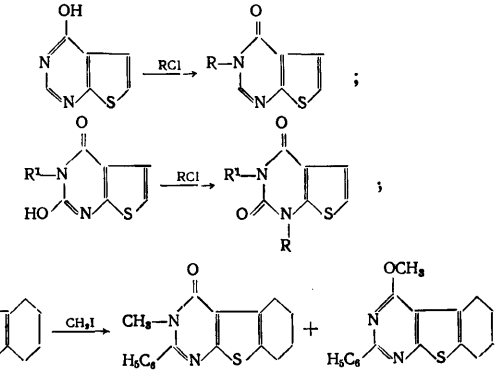


When 4-hydroxy-2-methylthiothieno[2,3-*d*]pyrimidine is acted upon by various amines, the corresponding 2-amino-derivatives are obtained:[165]



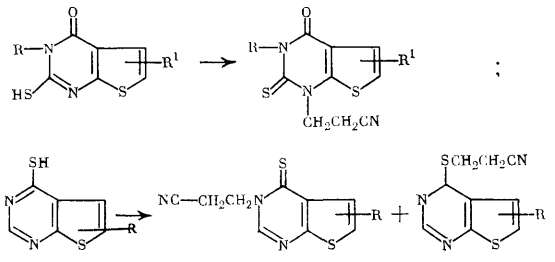
$-NR^1R^2 = N(CH_2)_5$, $N(CH_2CH_2)_2O$, $N(CH_2CH_2)_2NCH_3$, $NH(CH_2)_2OH$, $NHNH_2$ .

A study of the alkylation of hydroxythieno[2,3-*d*]-pyrimidines yielded the following results: 4-hydroxythieno- and 2-hydroxo-4-oxothieno-pyrimidines react with alkyl halides to form *N*-derivatives, but 4-hydroxy-2-phenylthieno-pyrimidine reacts with methyl iodide in the presence of sodium hydride to form a mixture of the *N*(3)- and *O*-methyl derivatives in proportions of 1 : 1:[6,16]

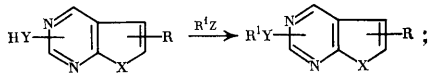


The cyanoethylation of 3-alkyl-2-mercapto-4-oxothieno-[2,3-*d*]pyrimidine proceeds via a nitrogen atom of the pyrimidine ring,[18] while 4-mercaptothienopyrimidine reacts

with acrylonitrile to form a mixture of *N*- and *S*-alkyl derivatives:[166]

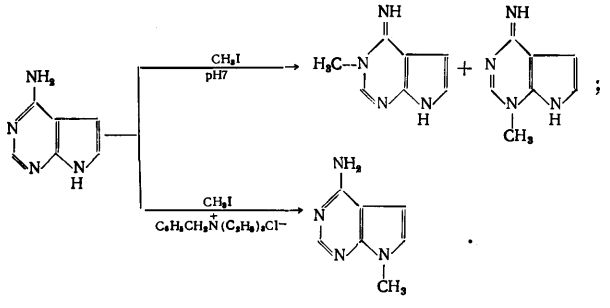


4-Mercaptothieno-, 2-mercaptothieno-, 2-selenothieno-, and 4-mercaptopyrrolo-[2,3-*d*]pyrimidines react with alkyl halides to form only the *S*(*Se*)-alkyl derivatives:[10,17,20,26,156,166–169]

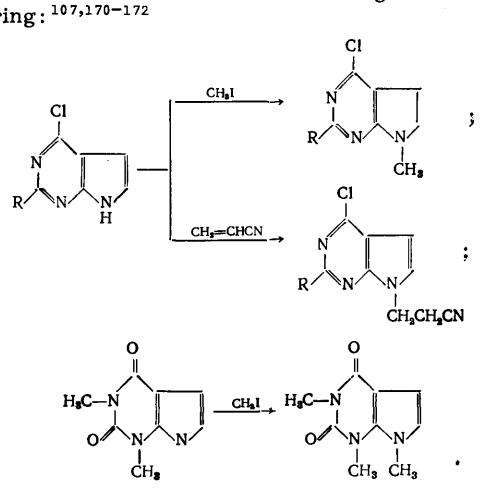


$R^1$ = Alk; X = S, NH; Y = S, Se; Z = Cl, Br, I.

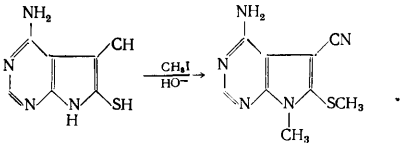
The study of the alkylation of 4-aminopyrrolo[2,3-*d*]-pyrimidine by methyl iodide yielded a 1 : 1 mixture of *N*(1)- and *N*(3)-methyl derivatives. However, the selective methylation of this compound involves the nitrogen atom of the pyrrole ring:[114]



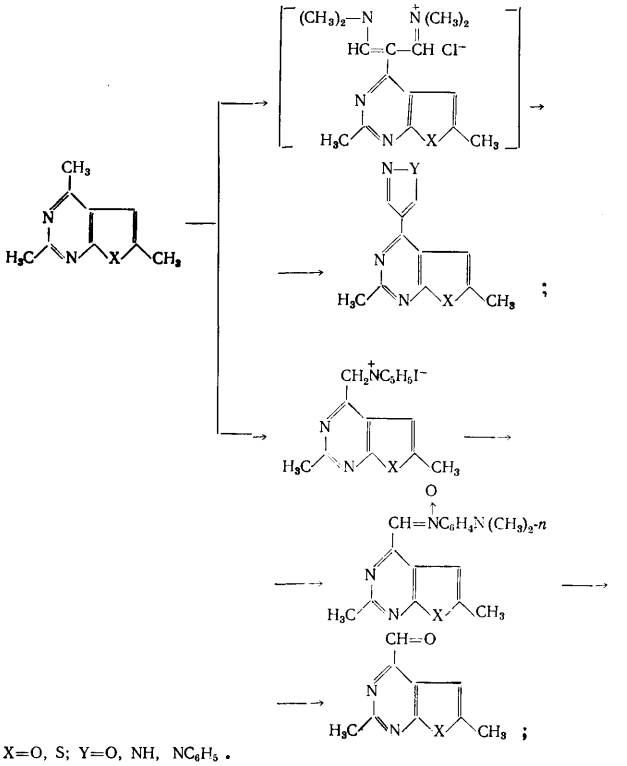
Like 2,4-dihydroxy-1,3-dimethylpyrrolo[2,3-*d*]pyrimidine, 4-chloropyrrolo[2,3-*d*]pyrimidine is methylated or cyanoethylated in an alkaline medium at the nitrogen atom of the pyrrole ring:[107,170–172]



The reaction of 4-amino-5-cyano-6-mercaptopyrrolo[2,3-*d*]-pyrimidine with methyl iodide results in the formation of 6-methylthio-7-methylpyrrolopyrimidine:[45]

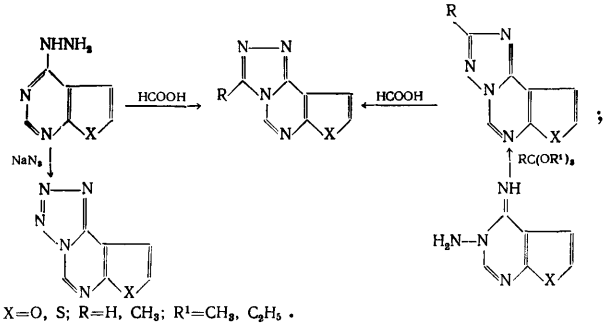


Certain reactions of the methyl group in 2,4,6-trimethyl-furo-, and 2,4,6-trimethylthieno-[2,3-*d*]pyrimidines have been investigated. Thus the corresponding pyrimidine-4-aldehydes have been obtained from these compounds by the Kröhnke method. It has been demonstrated by $^1$H NMR that the most reactive methyl group at the C(4) atom of the pyrimidine ring is oxidised as a result of this reaction. The same methyl group reacts with Vilsmeier's reagent to form an unstable derivative of malonodialdehyde, which cyclises to 2,6-dimethyl-4-(4′-oxazolyl)- or 2,6-dimethyl-4-(4′-pyrazolyl)-furo(thieno)[2,3-*d*]pyrimidine on treatment with hydroxylamine or hydrazine:[173]



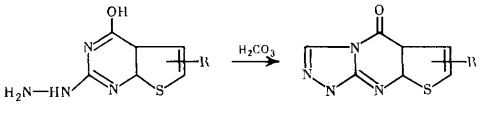
X=O, S; Y=O, NH, $NC_6H_5$.

Tricyclic systems can be obtained from certain furo- and thieno-pyrimidines by virtue of the presence of substituents in the pyrimidine ring. Thus, on treatment with formic acid or its ortho-ester, the 4-hydrazino-derivatives give rise to triazolothienopyrimidines,[10,38,52,156,174–176] while on treatment with sodium azide the products formed are tetrazolothieno-pyrimidines.[10,38,156,174,175] 3-Amino-4-iminofuropyrimidines and the corresponding thieno-derivatives cyclise on treatment with orthoformic or orthoacetic ester to the isomeric triazolo-derivatives, which undergo the rearrangement shown in the scheme below when acted upon by formic acid:[52,176]

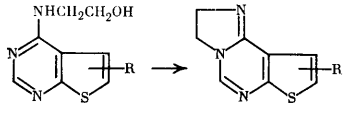


X=O, S; R=H, $CH_3$; $R^1$=$CH_3$, $C_2H_5$ .

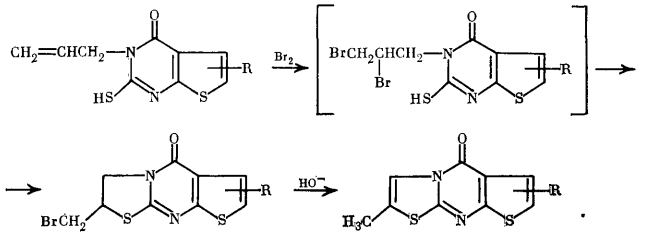
When acted upon by carbonic acid, 2-hydrazino-4-hydroxythieno[2,3-*d*]pyrimidine also cyclises to the corresponding triazolothienopyrimidine:[165]



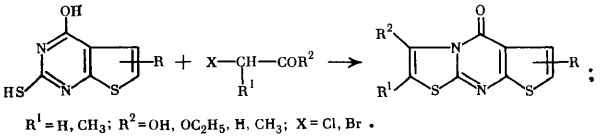
Imidazolinothienopyrimidine has been obtained from 4-β-hydroxyethylaminothieno[2,3-*d*]pyrimidine:[38,175]



3-Allyl-2-mercapto-4-oxothieno[2,3-*d*]pyrimidines are convenient starting materials in the synthesis of thiazolothienopyrimidines. On treatment with bromine, these compounds give rise to the corresponding tricyclic systems:[18,23-25,177,178]

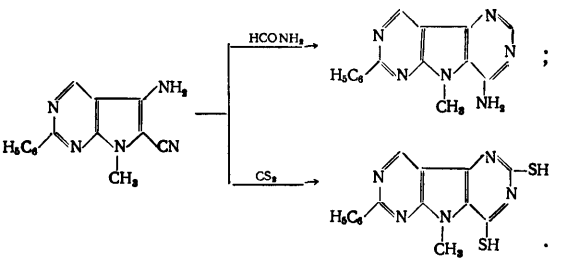


The same system can be obtained by the reaction of α-halogenocarbonyl compounds with 4-hydroxy-2-mercaptothieno[2,3-*d*]pyrimidines:[179]

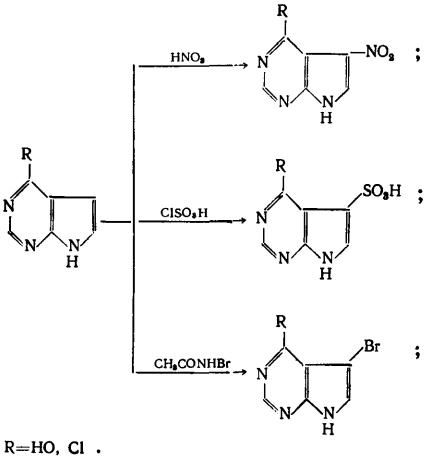


$R^1$=H, $CH_3$; $R^2$=OH, $OC_2H_5$, H, $CH_3$; X=Cl, Br .

Tricyclic heteroatomic systems have also been synthesised with participation of substituents in the five-membered ring. Thus 5-amino-6-cyano-2-phenylpyrrolo[2,3-*d*]pyrimidine reacts with formamide to form the corresponding aminopyrrolo[2,3-*d*;4,5-*d'*]dipyrimidine, while the reaction with carbon disulphide yields the dimercapto-derivative:[89]

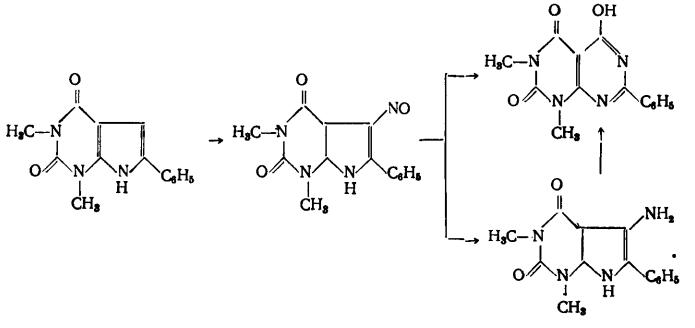


In considering reactions involving electrophilic substitution in the pyrrole ring, mention should be made of a study[157] in which 4-hydroxy- and 4-chloro-pyrrolo[2,3-*d*]pyrimidines were nitrated, chlorosulphonated, and brominated. In all cases the reaction involves the β-position in the pyrrole ring:



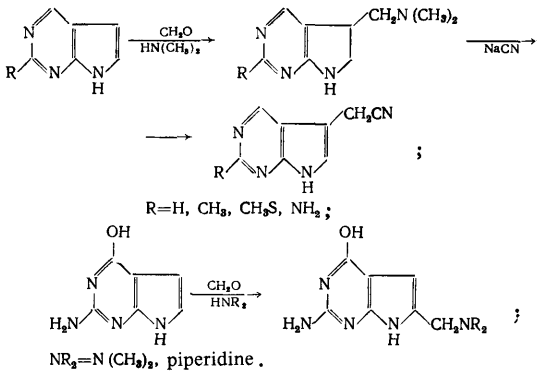
R=HO, Cl .

The nitrosation of 1,3-dimethyl-6-phenylpyrrolo[2,3-*d*]-pyrimidine also takes place in the β-position of the pyrrole ring.[78] Subsequently the 5-nitroso-derivative can undergo the Beckmann rearrangement with formation of a pyrimidopyrimidine. The reduction of the nitroso-group results in the formation of 5-aminopyrrolopyrimidine which also rearranges to a pyrimidopyrimidine on treatment with lead acetate:[180]

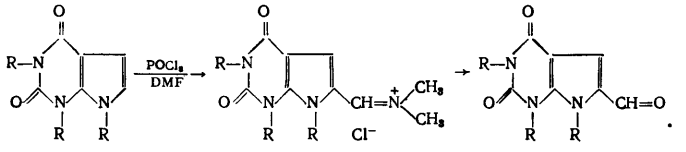


Pyrrolopyrimidines undergo the Mannich reaction, but the available literature data are somewhat contradictory. 2-Substituted pyrrolo[2,3-*d*]pyrimidines react with formaldehyde and dimethylamine in the presence of sodium acetate to form the 5-dimethylaminomethylene derivatives,[181] which can be converted into 5-cyanomethylenepyrrolopyrimidines. However, it has been reported[113] that 2-amino-4-hydroxypyrrolo-[2,3-*d*]pyrimidine reacts with formaldehyde and dialkylamines

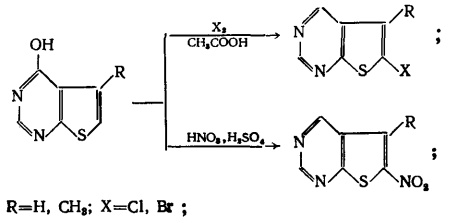
in the presence of acetic acid to form the 6-dialkylaminomethylene derivative:

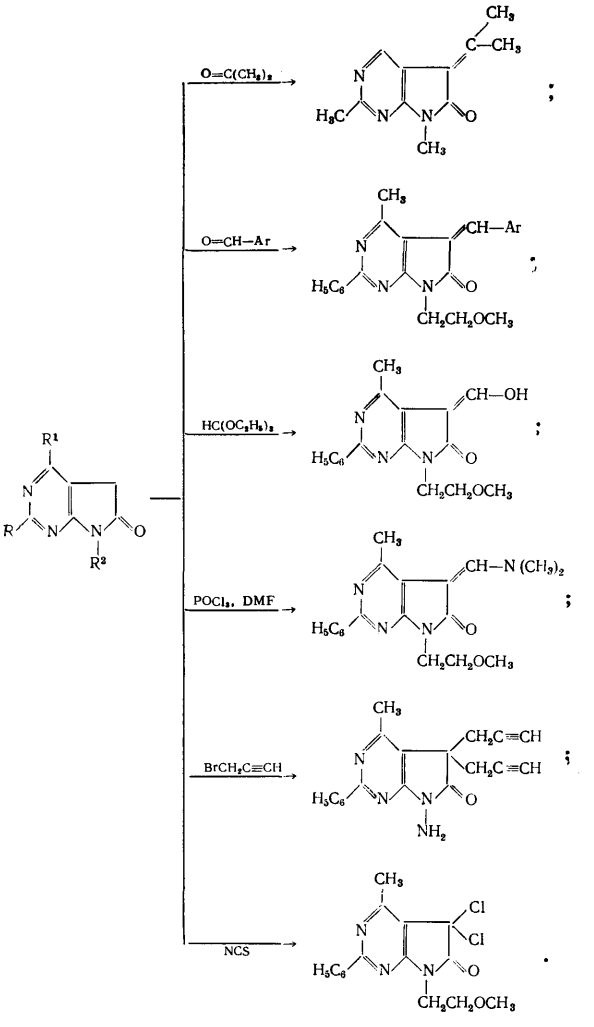



1,3,7-Trialkyl-2,4-dioxopyrrolo[2,3-*d*]pyrimidine reacts with Vilsmeier's reagent also in the α-position in the pyrrole ring to form the corresponding aldehyde:[182]



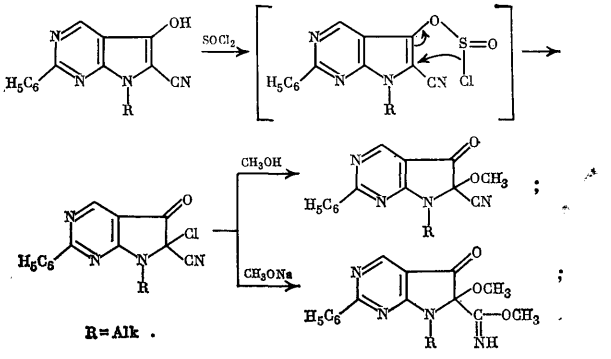

Certain electrophilic substitution reactions of 4-hydroxythieno[2,3-*d*]pyrimidines which involve the α-position in the thiophen ring, have been investigated:[6,61,174]



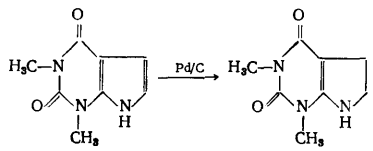




It has been observed that the methylene group in the pyrrole ring of 6-oxopyrrolopyrimidines is very reactive and reacts with aldehydes,[101] ketones,[98] propargyl bromide,[100] orthoformic ester, Vilsmeier's reagent, and *N*-chlorosuccinimide[101] to form the corresponding 5-substituted 6-oxopyrrolo[2,3-*d*]pyrimidines.

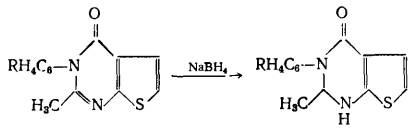
Kim and Santilli[183,184] investigated the reaction of thionyl chloride with 7-alkyl-6-cyano-5-oxo-2-phenylpyrrolo[2,3-*d*]-pyrimidines and established that it involves the oxicative chlorination at the α-position in the pyrrole ring:



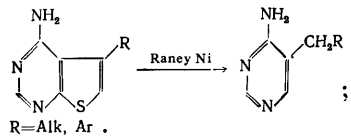
Several instances of the reduction of thieno- and pyrrolopyrimidines in the presence of various catalysts have been described in the literature. When 1,3-dimethyl-2,4-dioxopyrrolo[2,3-*d*]pyrimidine is treated with a palladium catalyst, the corresponding 5,6-dihydro-derivative is formed in 66% yield:[185]



Sodium tetrahydroborate reduces 2-methyl-4-oxo-3-phenylthieno[2,3-*d*]pyrimidine to the 1,2-dihydro-derivative:[186]

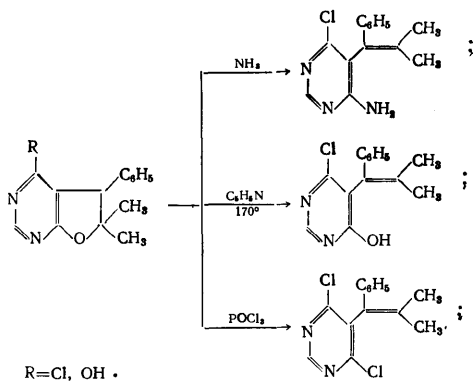


4-Aminothieno[2,3-*d*]pyrimidine containing a substituent in the 5-position in the thiophen ring gives rise to a 4-amino-5-substituted pyrimidine on treatment with Raney nickel:[47-49]



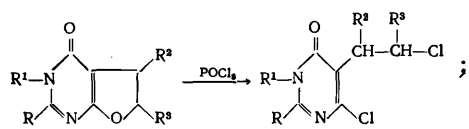
R=Alk, Ar .

Among other reactions involving the opening of the five-membered ring, mention may be made of the formation of 5-vinylpyrimidines from the corresponding 5,6-dihydro-6,6-dimethyl-5-phenylfuropyrimidines on treatment with ammonia or phosphoryl chloride:[34,187]



R=Cl, OH .

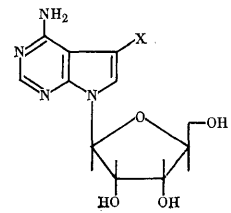
When acted upon by phosphoryl chloride, certain 5,6-dihydrofuropyrimidines give rise to 6-chlor-5-β-chloroethylpyrimidines:[130,188]



R=OH, $CH_3$; $R^1$=H, $C_6H_5$; $R^2$=$R^3$=H, $CH_3$ .

## IV. BIOLOGICAL PROPERTIES

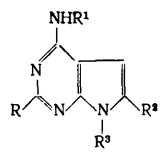
It was discovered in the 1960's that the antibiotics tubercidin, toyocamycin, and sangivamycin are derivatives of pyrrolo[2,3-*d*]pyrimidine:[51,189-191]



X = H (tubercidin)
X = CN (toyocamycin)
X = $CONH_2$ (sangivamycin)

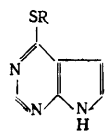
Toyocamycin actively inhibits the growth of various microorganisms,[192-194] tubercidin exhibits an analogous activity,[195,196] while sangivamycin shows a distinct antitumour activity, becoming involved in DNA and RNA synthesis.[191,197] There exists a good review on these antibiotics.[198]

4-Aminopyrrolo[2,3-*d*]pyrimidine is also an inhibitor of the growth of various micro-organisms[73] and its derivatives possess bactericidal,[111] hypotensive, anticonvulsant, and tranquilising properties[107,160] and exhibit an antimitotic activity.[121]



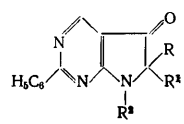
R=H, $CH_3$, OH, H, $NH_2$; $R^1$, $R^3$=H, Alk, Ar; $R^2$=H, $CH_3$

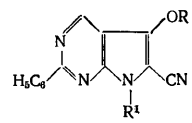
4-Mercaptopyrrolo[2,3-*d*]pyrimidine is the 5-deaza-analogue of the familiar antitumour preparation 6-mercaptopurine, but it does not exhibit a pronounced anticancer activity. Nevertheless 4-alkylmercaptopyrrolopyrimidines do possess antineoplastic properties.[167-169]



R=H, Alk, $(CH_2)_n CONHR^1$;
$R^1$ = aminoacid residue

Among 5-hydroxy-2-phenylpyrrolo[2,3-*d*]pyrimidines, compounds have been discovered which act on the central nervous system as depressants.[92-95,184]

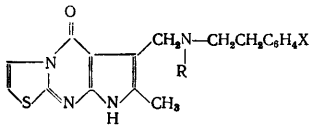


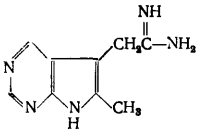


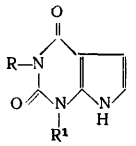
R=Cl, $OCH_3$, $OC_2H_5$, $OC_3H_7$-iso; R=H, $CH_3$, $SO_2C_6H_5$; $R^1$=$CH_3$, $R^1$=CN, $C(OCH_3)$=NH; $R^2$=Alk $C_2H_5$, $C_4H_9$

5-Alkylaminomethyl derivatives of thiazolopyrrolopyrimidines prevent the formation of blood clots,[199] while 5-amidinomethyl-6-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine has a powerful ganglion stimulating activity.[200]

It has also been reported that 1,3-dialkyl-2,4-dioxopyrrolo[2,3-*d*]pyrimidines exhibit sedative and antipyretic activities.[151]

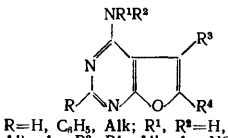




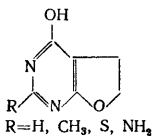


R, R¹=Alk

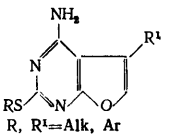
There are also biologically active compounds among furo-[2,3-*d*]pyrimidines. Thus 4-aminofuro[2,3-*d*]pyrimidines are muscle relaxants[119] and exhibit sedative, antihistamine, and diuretic properties.[53,54] 2-Substituted 4-hydroxy-5,6-dihydrofuropyrimidine reduces the cholesterol content in the blood,[127] while 2-alkylthio-4-aminofuro[2,3-*d*]pyrimidine shows an antiulcer activity:[81]



R=H, $C_6H_5$, Alk; $R^1$, $R^2$=H, Alk, Ar; $R^3$, $R^4$=Alk, Ar, $NO_2$.

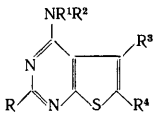


R=H, $CH_3$, S, $NH_2$



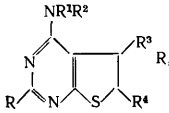
R, $R^1$=Alk, Ar

Numerous compounds with a wide variety of different types of physiological activity have been discovered among synthetic thienopyrimidines. Derivatives of 4-aminothieno[2,3-*d*]pyrimidines exhibit bactericidal, trichomonacidal,[13] antiradiation, antimalarial,[43] antihistamine,[153] acaricidal, insecticidal, and fungicidal properties[161,162] and prevent the formation of clots.[29]



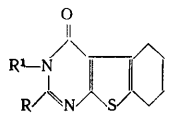
R=Ar, NH—Alk; $R^1$, $R^2$=H, $CH_3$, $(CH_2)_2$, NH—Alk, $SO_2C_6H_5$, $OC_6H_5$, Ar, Alk; $R^3$, $R^4$=H, $CH_3$, $(CH_2)_4$

4-Amino-5,6-dihydrothieno[2,3-*d*]pyrimidines possess sedative, diuretic, and antihistamine activities and function as muscle relaxants.[56,163,164]

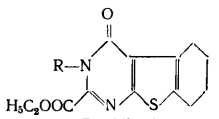


R, $R^1$, $R^2$, $R^3$, $R^4$=H, Alk, Ar.

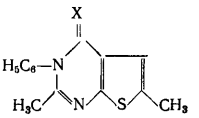
Depressants of the central nervous system, diuretics, and hypotensive, antipyretic,[144,145] analgesic, sedative,[30] antiallergic,[37,39] and hypnotic[201] substances have been discovered among 4-oxothienopyrimidines.



R=$CH_3$, $C_2H_5$; $R^1$=H, $CH_3$, $C_6H_5$.

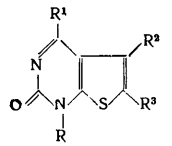


R=Alk, Ar

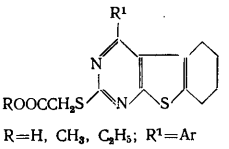


X=O, $NC_6H_5$

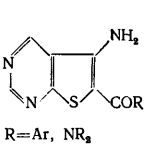
4-Aryl-2-oxothienopyrimidines also exhibit analgesic and diuretic activites;[58,66] 2-alkylthio-4-aryl derivatives show anticlotting, antipyretic, and analgesic activities and reduce the sugar content in the blood.[63] 5-Amino-6-carboxythieno-[2,3-*d*]pyrimidine exhibits bactericidal, analgesic, and diuretic activities and has an antipyretic effect.[86]



R=H, Alk; $R^1$=Ar; $R^2$=H, $CH_3$; $R^3$=H, $CH_3$, Cl, $NO_2$.



R=H, $CH_3$, $C_2H_5$; $R^1$=Ar



R=Ar, $NR_2$

Thus the foregoing findings permit the conclusion that derivatives of furo-, thieno-, and pyrrolo-[2,3-*d*]pyrimidines are of considerable interest as physiologically active substances, which has attracted the attention of numerous investigators to these compounds.

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