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Synthesis of pteridines fused to heterocycles

A V Gulevskaya, A F Pozharskii

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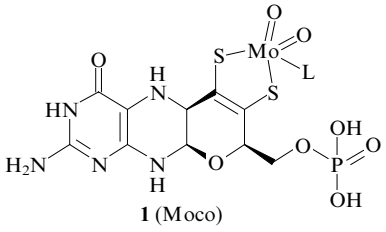
Abstract. The known methods for the synthesis of pteridines fused to other heterocycles, including natural compounds, are reviewed. The data are systematized according to the type of the fused ring. The bibliography includes 155 references.

I. Introduction

Pteridines fused to a heterocylic ring are a very important, but surprisingly little studied group of pteridines. Compounds of this class perform many important functions in biochemistry. Thus the molybdenum complex **1** (Moco) with the molybdopterin dianion **2** (ene-1,2-dithiolate) as the main ligand is a co-factor of numerous molybdenum-containing enzymes.[1,2] Molybdenum enzymes directly participate in redox reactions and catalyze transformations, the net effect of which is to transfer an oxygen atom from (or to) a water molecule to (or from) a substrate molecule X.

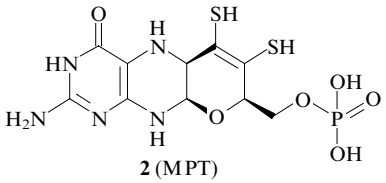
$$X + H_2O \rightleftharpoons XO + 2H^+ + 2e^-.$$

Most of the 50 known molybdenum enzymes are of bacterial origin. But only very few occur in higher organisms (*e.g.* xanthine dehydrogenase, sulfite oxidase, nitrate-eductase, aldehyde oxidase and amidoxime reductase). Some hyperthermophilic *Archaea* contain metalloenzymes with the tungsten ions coordinated to molybdopterin.[1]

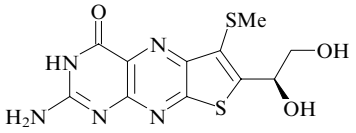


1 (Moco)

L = O^-, H_2O, S (Cys).

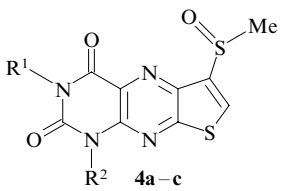


2 (MPT)



3a

In contrast with most of the known co-factors, Moco is extremely unstable and undergoes rapid degradation being devoid of protective enzyme environment. Thienopteridine **3a** (urothione) is one of the Moco metabolites found in human urine.[3] This tricyclic heterosystem is also a component of hirudinoidines A, B, C (**4a** – **c**) isolated recently from



4a – **c**

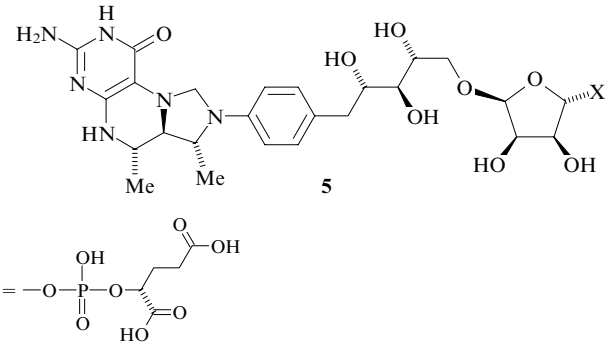
$R^1 = R^2 = Me$ (**a**), H (**c**); $R^1 = H$, $R^2 = Me$ (**b**).

A V Gulevskaya, A F Pozharskii Department of Chemistry, Southern Federal University, prosp. Zorge 7, 344090 Rostov-on-Don, Russian Federation. Fax (7-863) 297 51 51, tel. (7-863) 297 51 46, e-mail: agulevskaya@sfedu.ru (A V Gulevskaya), apozharskii@sfedu.ru (A F Pozharskii)

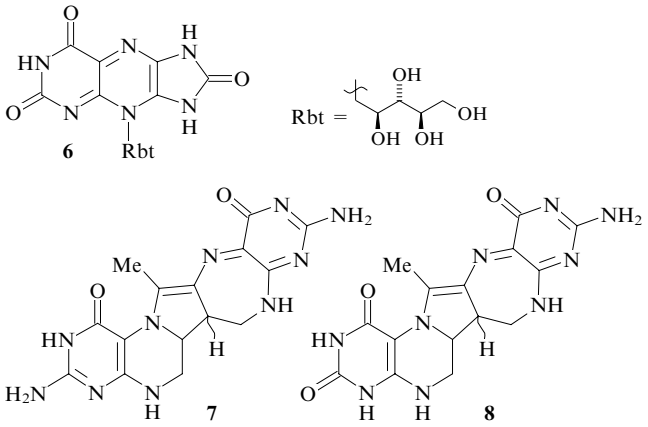
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Uspekhi Khimii **80** (6) 523 – 557 (2011); translated by V E Kotzuba

leeches *Hirudo nipponica* Whitman, used in traditional Chinese medicine to stimulate blood circulation.[4]

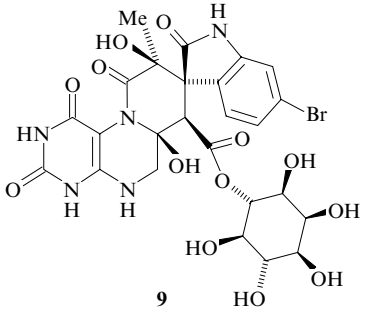
One of the co-enzymes involved in methanogenesis (biosynthesis of methane) is a derivative of 5,10-methylene-5,6,7,8-tetrahydromethanopterin **5**. The following substrates can be converted to methane by *Archea*: methanol, methylamines, methyl sulfides and CO_2.[5] The annual production of methane by microorganisms is estimated as 5×10^{14} g.



Pteridines fused to heterocycles are generally bright-coloured and occur in nature as pigments. For instance, fluorescent pigment russupteridine yellow IV (**6**) was isolated from the fungi *Russulae*.[6,7] The red colour of *Drosophila melanogaster* fruit-fly eyes is due to drosopterin and its enantiomer, isodrosopterin (**7**), and also minor pigments aurodrosopterin and isoaurodrosopterin (**8**).[8–10]



Pyrido[1,2-*f*]pteridine **9** (surugatoxin) was isolated from the toxic Japanese ivory shell *Babylonia japonica*.[11] Surugatoxin itself is not poisonous, it is prosurugatoxin and neosurugatoxin not belonging to the pteridine family present in the same mollusk that are the real toxins.

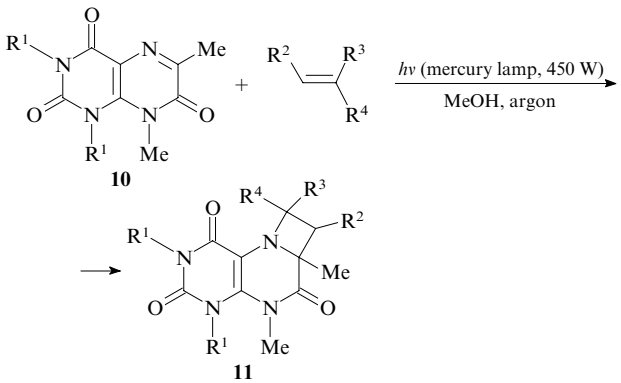


The progress in the biochemistry and pharmacology of pteridines fused to heterocycles has stimulated studies aimed at the development of the methods for their synthesis. The results of these studies are presented in part in the reviews[12–15] that mostly cover the general aspects of the pteridine chemistry. In the present review we tried to give comprehensive systematization of the methods of synthesis of pteridines fused to heterocycles. Some of the results discussed in the present review were obtained in our laboratory. We considered it reasonable to present data on the biosynthesis of several pteridines fused to heterocycles.

The known methods of the synthesis of pteridines fused to heterocycles can be formally divided into four groups: (1) syntheses based on pteridine derivatives (fusion of a heterocycle to the pteridine system); (2) syntheses based on pyrimidine derivatives (subsequent fusion to pyrazine and some other heterocycles); (3) syntheses based on pyrazine derivatives (subsequent fusion to pyrimidine and some other heterocycles); (4) syntheses based on hetero-annulated pyrimidines or pyrazines. In general, these methods are not versatile, and therefore it seems most rational to classify the data according to the type of the heterocyclic system.

II. Pteridines fused to four-membered heterocycles

Currently, only one report[16] describes synthesis of such pteridines. Thus prolonged photolysis of methanolic solutions of pteridine-2,4,7-triones **10** and electron-deficient alkenes (acrylonitrile, methyl metacrylate, metacrylonitrile, fumaronitrile, cynnamonitrile, dimethyl fumarate, 1,1-diphenylethylene) leads to the formation of azetidino[1,2-*f*]pteridines **11** in 25% – 95% yields.[16] [2 + 2] Cycloaddition involving the C=N bond proceeds regiospecifically. However, in some cases stereoisomers **11** were isolated from the reaction mixture. The spatial structures of these compounds have not been completely elucidated.

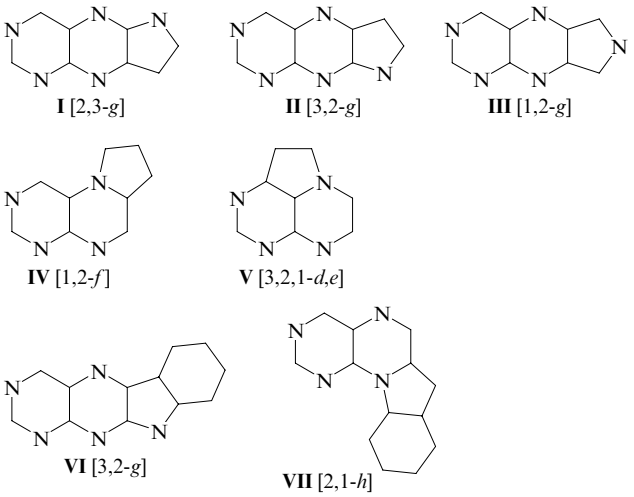


R^1 = Me, Ph; R^2 = H, CN, CO_2Me, Ph; R^3 = H, Me, Ph; R^4 = CN, CO_2Me, Ph.

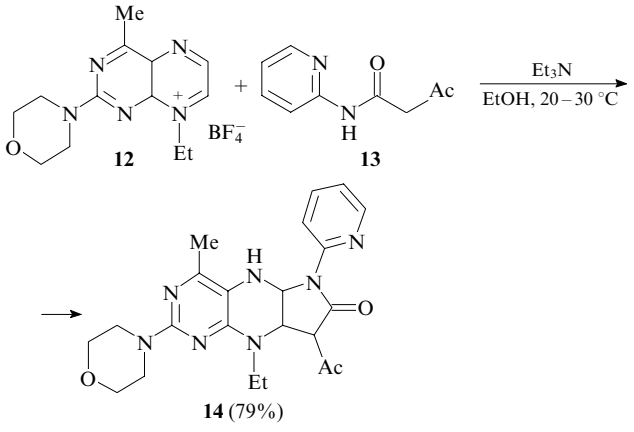
III. Pteridines fused to five-membered heterocycles

1. Pyrrolo- and indolopteridines

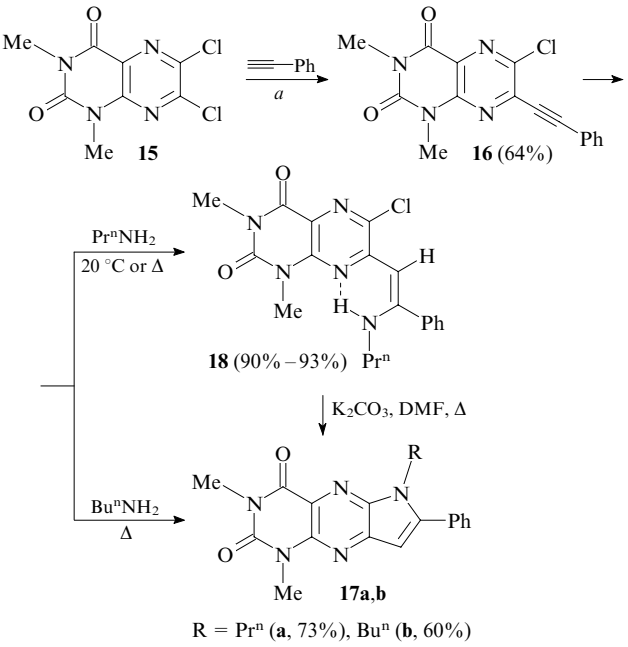
Pyrrolopteridines belonging to the structural types **I** – **V** and indolopteridines of the types **VI** and **VII** have been synthesized.



The published procedures of the synthesis of pyrrolo[2,3-*g*]- and pyrrolo[3,2-*g*]pteridines make use of the pteridine derivatives with electrophilic sites at C(6) and C(7) as bifunctional building blocks . Here the annulation of the pyrrole ring can result from either the reaction of the pteridine with C,N-dinucleophile or the consecutive introduction of C- and N-nucleophiles in positions 6 and 7 of the pteridine system. For example, the reaction of 8-ethylpteridinium cation **12** with acetoacetic acid arylamide **13** in the presence of triethylamine leads to pyrrolo[2,3-*g*]pteridine **14**.[17] The heterocyclization **12** → **14** is a tandem process of the A_N-A_N type, here cation **12** plays the role of a dielectrophile and the acetoacetamide (in the form of the C-anion) plays the role of a dinucleophile.

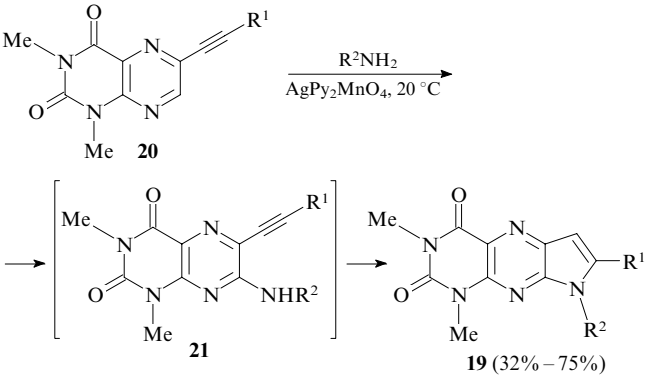


In a more general approach to the synthesis of pyrrolo[2,3-*g*]pteridines, the starting compound is the easily accessible 6,7-dichlorolumazine **15**, and the pyrrole ring closure is the result of a two-reaction sequence including the Sonogashira coupling of *ortho*-dichloride **15** with phenylacetylene and heating of the resulting alkynyl derivative with primary alkylamines.[18, 19] Note that in some cases the cyclization of 7-alkynyl-6-chlorolumazine **16** into pyrrolopteridine **17** under the action of amine is preceded by the formation of a sufficiently stable enamine rather than the expected product of chlorine substitution in posi tion 6. Thus the reaction of compound **16** with propylamine at ambient temperature or under reflux affords only enamine **18**. The latter undergoes cyclization into pyrrolopteridine **17a** upon brief heating with K_2CO_3 in dimethylformamide. At the same time, refluxing of **16** with butylamine furnishes directly compound **17b**. The described method obviously allows variations of both N- and C-substituents in the pyrrole ring.



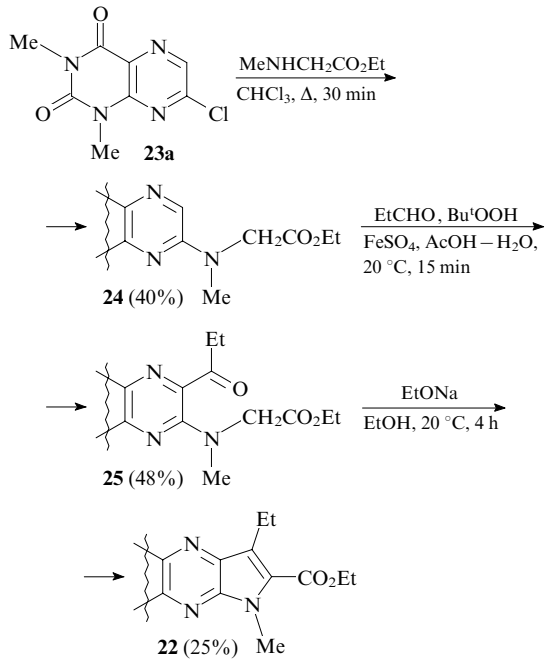
(*a*) $Pd_2(dba)_3$ (dba is dibenzylideneacetone), PPh_3, K_2CO_3, CuI, DMF, argon, 20 – 30 °C.

The ability of pteridines with unsubstituted C(6) or C(7) atoms to undergo nucleophilic aromatic hydrogen substitution can be used to synthesize the isomeric pyrrolo[3,2-*g*]-pteridines **19**. Thus the oxidative alkylamination of 6-alkynyllumazines **20** is accompanied by spontaneous pyrrole ring closure in the intermediate 7-alkylamino derivatives **21** and formation of pyrrolo[3,2-*g*]pteridines **19**.[19, 20] The reaction is sensitive to steric hindrance: a significant decrease in the product yield is observed in the case of *tert*-butylamine. Treatment of trimethylsilylacetylene derivatives **20** with alkylamines in the presence of an oxidant leads to pyrrolopteridines **19** unsubstituted at C(2) (R^1 = H).



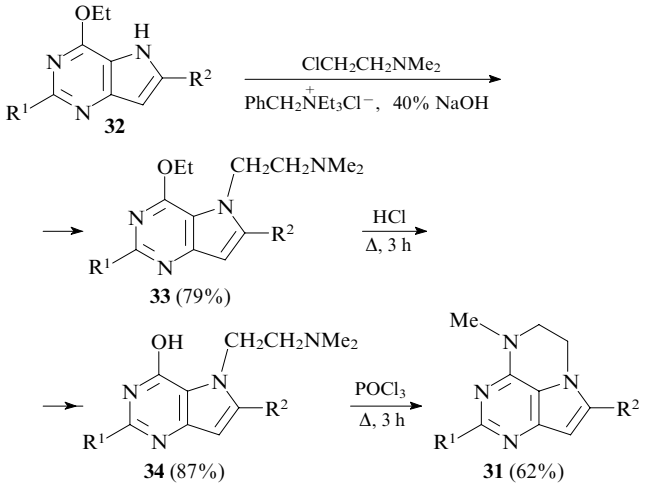
R^1 = Ph, $SiMe_3$, n-C_6H_{13}; R^2 = Pr^n, Pr^i, Bu^n, Bu^t.

Pyrrolo[3,2-*g*]pteridine **22** can be obtained from 7-chloro-1,3-dimethyllumazine (**23a**), the reaction includes the substitution of ethyl sarcosinate for the chlorine atom, homolytic acylation of 7-amino derivative **24** at the C(6) atom and intramolecular base-catalyzed condensation (**25** → **22**).[21]



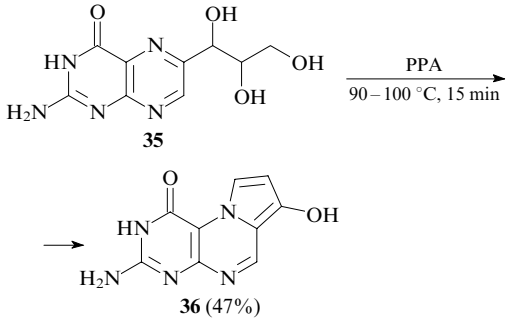
Pyrrolo[3,4-*g*]pteridines **26** have a notable structural resemblance with methotrexate.† They can be synthesized by consecutive annulation of the pyrrole and pyrimidine rings to the pyrazine ring.[22] Ethyl 6-amino-3-chloromethyl-5-cyanopyrazine-2-carboxylate (**27**), which has been obtained by condensation of 4-chloro-2-hydroxyimino-3-oxobutyrate with 2-cyanoacetamide followed by deoxygenation of the resulting *N*-oxide **28**, served as the starting compound. Classical cyclization of *o*-aminocyanoarenes with guanidines (**29** → **26**) is employed for the construction of the pyrimidine ring, and the pyrrole ring closure is the result of the reaction of 1,4-dielectrophilic four-carbon synthon with an N-nucleophile (**27** → **30** → **29**) (Scheme 1).

Bridged pyrrolo[3,2,1-*d*,*e*]pteridines **31** are synthesized from 4-ethoxypyrrolo[3,2-*d*]pyrimidine derivatives **32** in three steps. Alkylation of the pyrrole nitrogen atom of compounds **32** with β-(*N*,*N*-dimethylamino)ethyl chloride under conditions of the phase-transfer catalysis and the subsequent hydrolysis of the ethoxy group of compounds **33** afford pyrrolopyrimidines **34**. Heating of the latter with phosphorus oxychloride leads to pyrazine ring closure and the formation of pyrrolopteridines **31**. Presumably, compounds **34** are first transformed to the corresponding chloro derivatives; the subsequent intramolecular nucleophilic attack by the dimethylamino group on the carbon atom bearing chlorine completes the cyclization.[23] Compounds **31** exhibit anti-tumour activity against the Jensen sarcoma (in mice and rats, the tumour growth is suppressed by 39% – 52%), carcinoma 755 (39% – 77%) and melanoma B_{16} (54% – 62%). The lethal dose for a single intra-abdominal administration of the compound is 40 mg kg^{-1}.



$R^1 = R^2 = H$; $R^1 = Me$, $R^2 = Ph$.

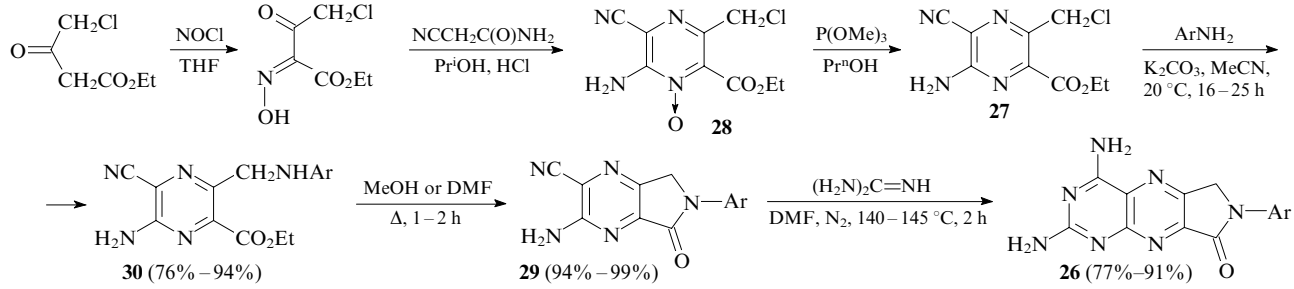
Upon brief heating of neopterin (**35**) in polyphosphoric acid (PPA), pyrrolo[1,2-*f*]pteridine **36** is formed in moderate yield.[24]



Another procedure involves the conversion of compound **35** into its cyclic acetal **37**, acylation of its OH

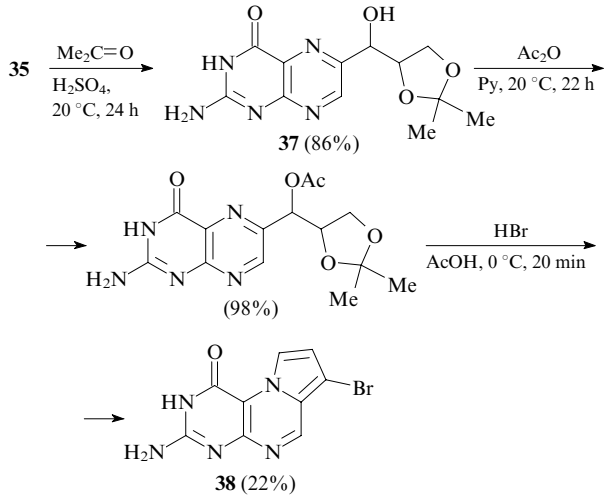
† Methotrexate, (2*S*)-2-[(4-{[(2,4-diaminopteridin-6-yl)methyl](methyl)-amino}benzoyl)amino]pentanedioic acid, is a cytostatic drug of the antimetabolite group, folic acid antagonists. It manifests pronounced immunosuppressive action and is employed in treatment of oncological diseases.

Scheme 1

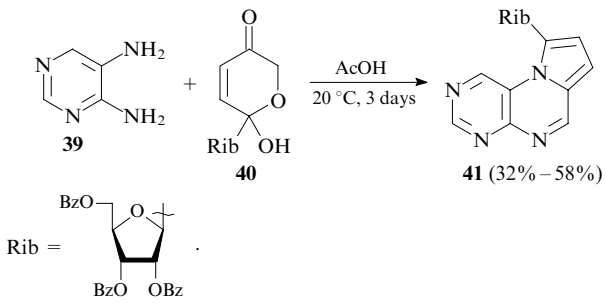


Ar = $C_6H_4CO_2Me$-4, $C_6H_4CO_2H$-4.

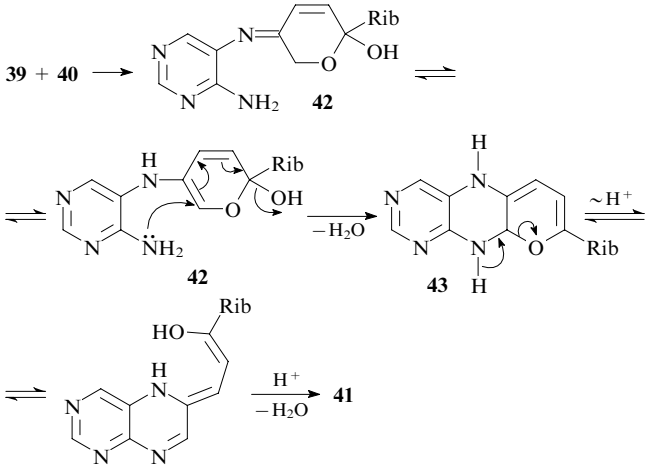
group and then cyclization into pyrrolopteridine **38** with HBr in acetic acid.[25]



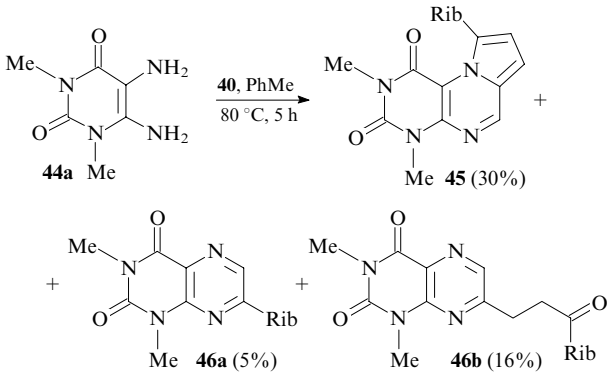
Pyrrolo[1,2-*f*]pteridine derivatives can be obtained by fusing the pyrazine and pyrrole rings to the pyrimidine one. Thus the reaction of 2,3-diaminopyrimidine (**39**) with 6-hydroxy-2*H*-pyran-3(6*H*)-one glycoside **40** in acetic (or trifluoroacetic) acid gives pyrrolo[1,2-*f*]pteridine **41**.[26]



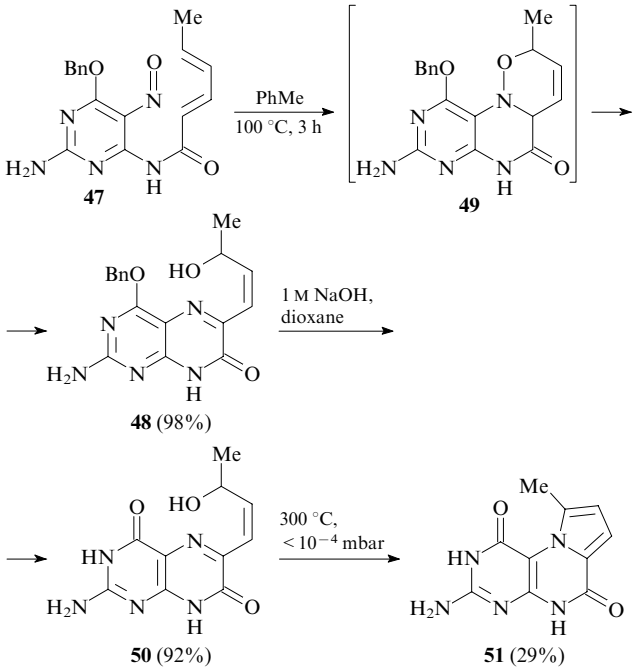
The mechanism of this heterocyclization includes the formation of azomethine **42**, its further transformation to pyranopteridine **43** and acid-catalyzed recyclization **43** → **41**.



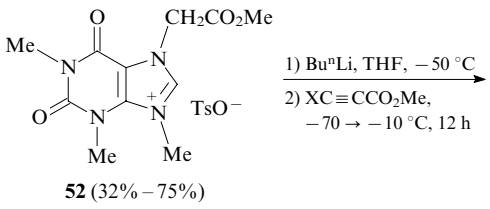
An analogous condensation of 5,6-diamino-1,3-dimethyluracil (**44a**) with glycoside **40** leads to pyrrolopteridine **45** along with lumazine derivatives **46a**,**b**.[27]

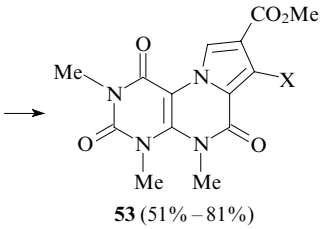


The classical syntheses of purines and pteridines make use of 4-amino-5-nitrosopyrimidines as typical starting compounds. Recently,[28] it has been shown that heating of 5-nitroso-4-(sorbylamino)pyrimidine **47** in toluene brings about the intramolecular Diels–Alder reaction, which results in 6-(3-hydroxybutenyl)pteridinone **48** *via* oxazinopteridine **49**. Alkaline hydrolysis of compound **48** affords compound **50**, which upon heating under reduced pressure undergoes dehydration and cyclization to pyrrolopteridine **51**.



Xanthinium salt **52** under the action of methyl propargylate or dimethyl acetylenedicarboxylate is transformed into pyrrolo[1,2-*f*]pteridines **53**.[29,30]

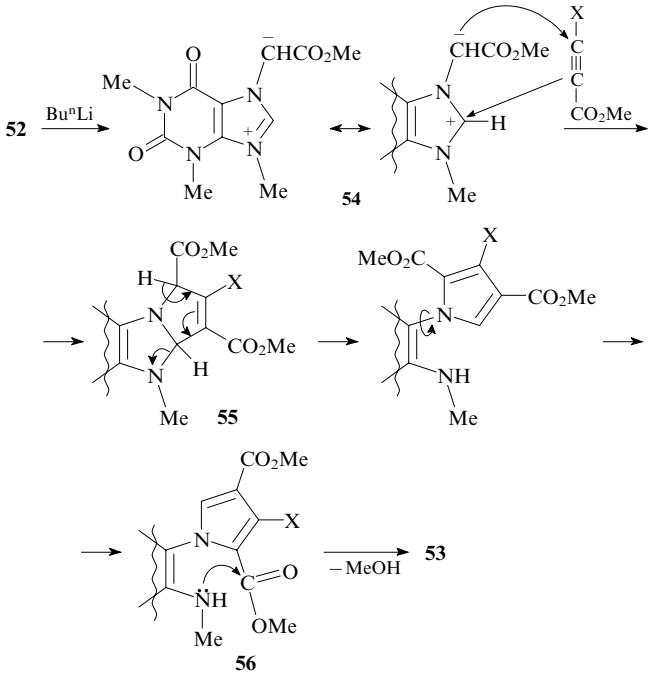




53 (51%–81%)

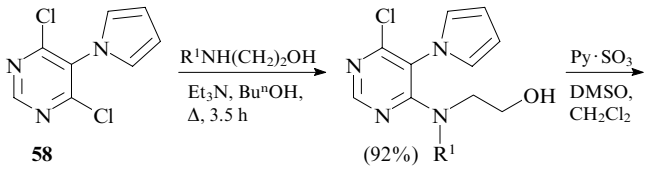
X = H, CO_2Me.

The main steps of this process are as follows: (1) the *in situ* formation of xanthinium ylides **54**, (2) 1,3-dipolar cycloaddition leading to unstable adducts **55**, (3) imidazole ring opening in compound **55** and finally (4) cyclization driven by nucleophilic addition of the methylamino group to the α-methoxycarbonyl group of the intermediate pyrrole **56**.

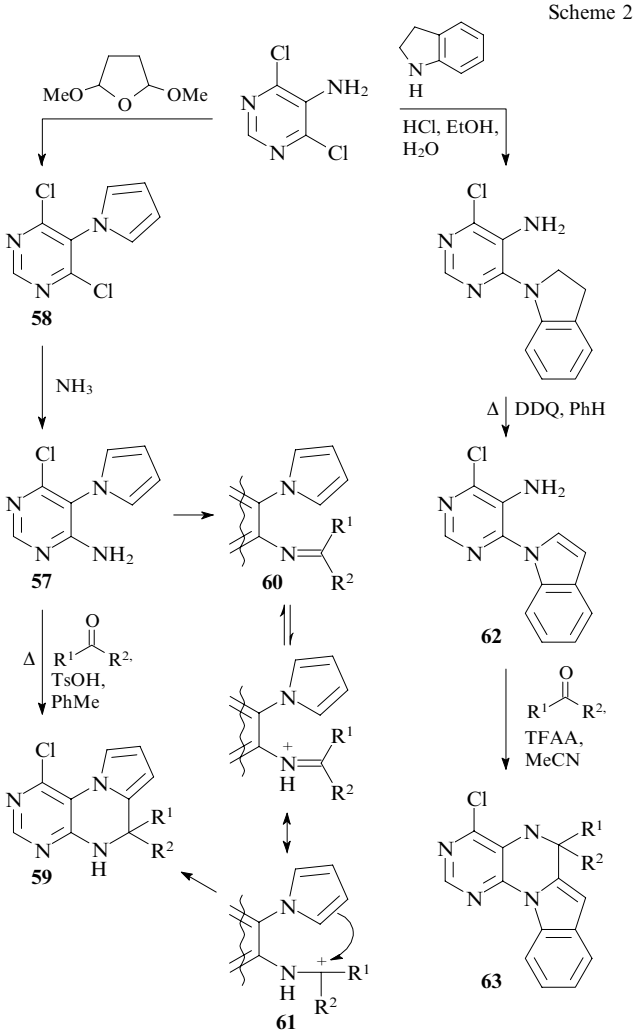


A very efficient methodology of construction of the pyrrolo[1,2-*f*]pteridine system was suggested by Chinese chemists (Scheme 2).[31] The starting 5-amino-4,6-dichloropyrimidine is transformed to 4-amino-5-(pyrrol-1-yl)pyrimidine **57** *via* intermediate **58**. The reaction of pyrrolylpyrimidine **57** with aldehydes or aliphatic ketones leads to the cyclization into 5,6-dihydropyrrolo[1,2-*f*]pteridines **59**. The reaction mechanism is alike to that of the Pictet–Spengler reaction and involves the formation of an imine intermediate **60**, its protonation and electrophilic cyclization (**61** → **59**). In a similar way, 5-amino-6-(indol-1-yl)pyrimidine **62** gave indolo[2,1-*h*]pteridines **63**.[32]

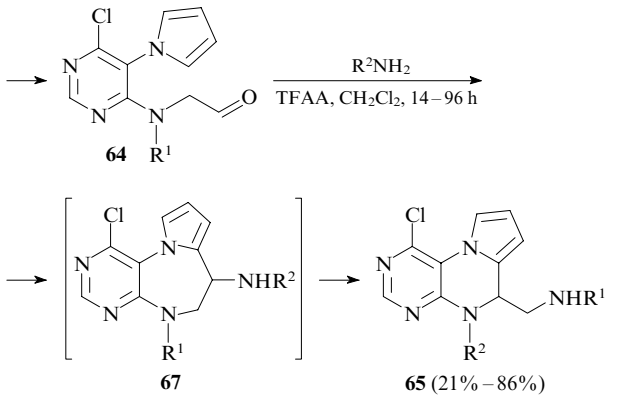
It was found that the long-term reaction of aldehydes **64** with primary alkyl- and arylamines in the presence of trifluoroacetic anhydride leads to 5,6-dihydropyrrolo[1,2-*f*]pteridines **65**.[33]



Scheme 2



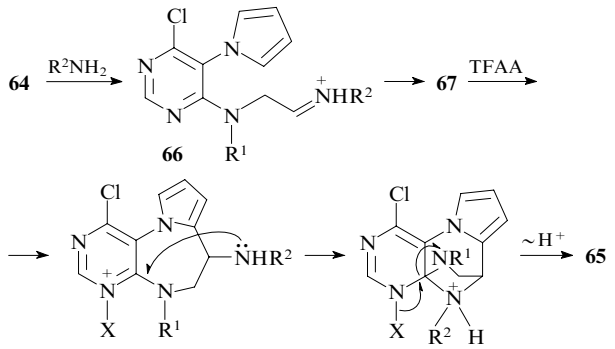
R^1 = H: R^2 = Et, Pr^n, Ph, 3,4-$Cl_2C_6H_3$, XC_6H_4 (X = 4-Me, 2-NO_2, 3-NO_2, 4-NO_2, 2-MeO, 2-Cl); R^1 = Me: R^2 = Et, Pr^n, Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$; R^1-R^2 = $(CH_2)_5$; DDQ is 2,3-dichloro-5,6-dicyanobenzoquinone, TFAA is trifluoroacetic anhydride.



65 (21%–86%)

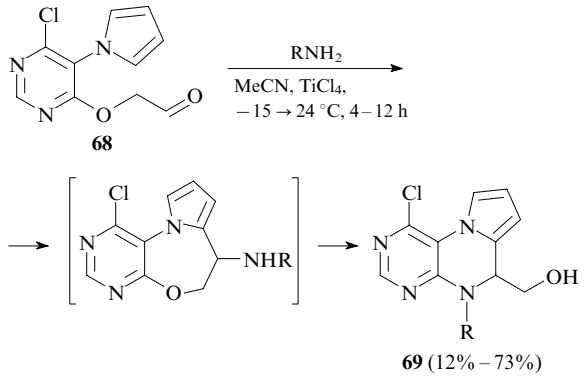
R^1 = Me, Bn; R^2 = Me, Pr^i, Bu^n, cyclo-C_6H_{11}, Bn, OBn, Ph, XC_6H_4 (X = 2-Me, 3-Me, 4-Me, 2-Cl, 3-Cl, 4-Cl, 2-NO_2, 4-NO_2, 4-F).

The reaction proceeds as the Smiles rearrangement of the expected cyclization products of the intermediate iminium salt **66**, *i.e.*, diazepines **67**.



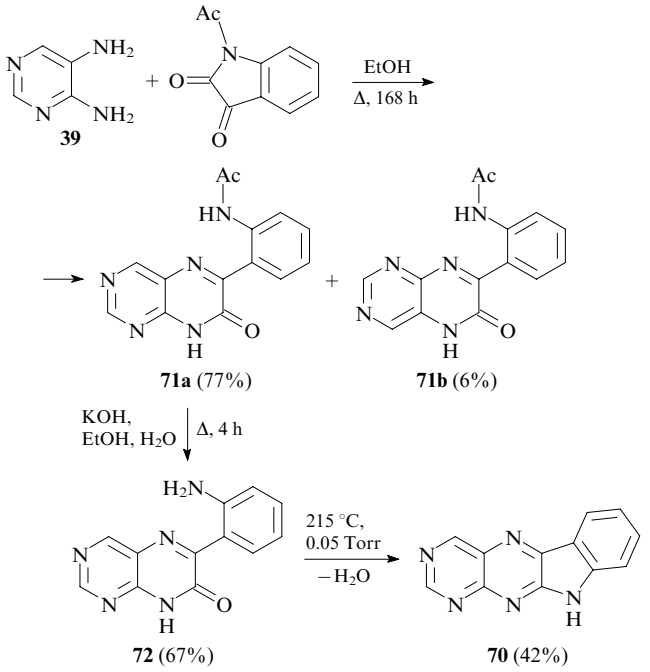
X = CF_3CO.

In an analogous reaction sequence, aldehyde **68** affords pyrrolo[1,2-*f*]pteridines **69**.[34]



R = H, Me, Pr^i, Bu^n, cyclo-C_6H_{11}, Bn, Ph, XC_6H_4 (X = 2-Me, 3-Me, 4-Me, 2-MeO, 4-MeO, 4-Cl, 4-F, 4-Br, 4-NO_2).

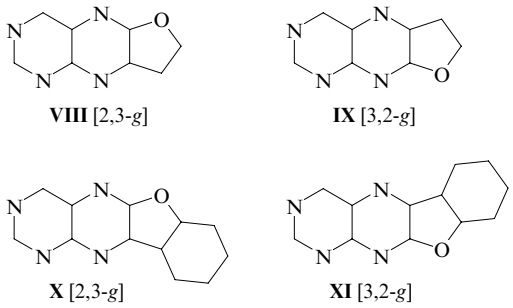
10*H*-Indolo[3,2-*g*]pteridine **70** is synthesized in three steps from 4,5-diaminopyrimidine and aminopyrimidine (**39**).[35] The diamine is first condensed with *N*-acetylisatin



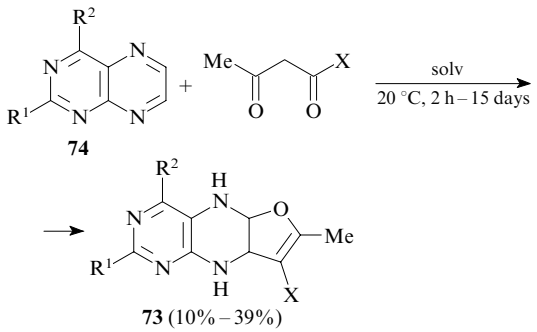
resulting in a mixture of isomeric arylpteridinones **71a**,**b**. Alkaline hydrolysis of the major reaction product **71a** and subsequent sublimation of the amino derivative **72** afford indolopteridine **70** in a moderate yield.

2. Furo- and benzofuropteridines

The currently known furo- and benzofuropteridine derivatives pertain to the heterosystems of the types **VIII**–**XI**.

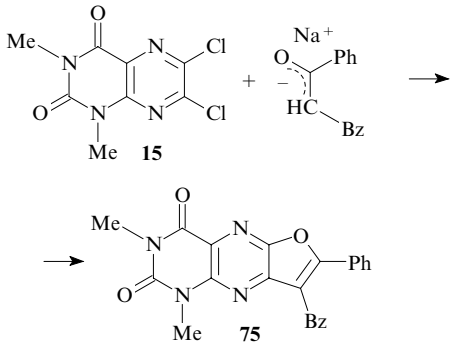


Furo[2,3-*g*]pteridines **73** are obtained in the reactions of acetylacetone or acetoacetates with pteridines **74** in neutral or basic media.[36,37] Presumably,[36,37] the dicarbonyl compound reacts in the enol or enolate ion form with addition of the more nucleophilic carbon of the latter to the more electron-deficient carbon atom C(7) of the pteridine.

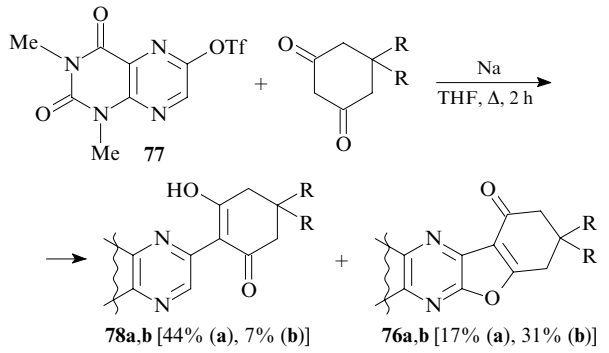


R^1, R^2 = H, Me; X = Me, OEt, OBn; solv = Et_3N–C_6H_6, THF, DMSO.

Similarly, the reaction of 6,7-dichloro-1,3-dimethyllumazine (**15**) with dibenzoylmethane sodium salt leads to furo[2,3-*g*]lumazine **75**.[38]

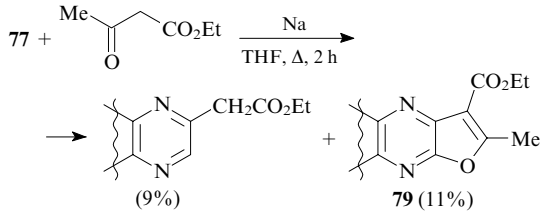


Isomeric furopteridines **76** of the [3,2-*g*]-series are prepared by the coupling of triflate **77** with cyclohexane-1,3-diones in the presence of metallic sodium.[39,40] Apparently, compounds **78** are intermediates in the heterocyclization **77** → **76**.

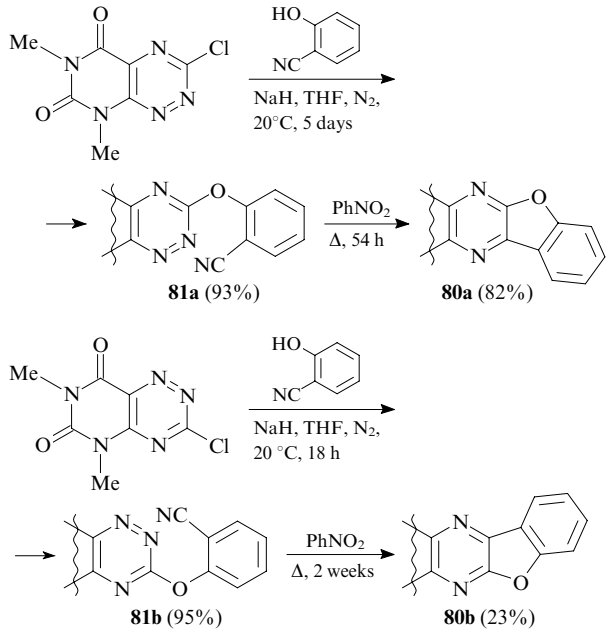


R = H (**a**), Me (**b**).

Ethyl acetoacetate was also used as the cyclization agent, whereupon triflate **77** transformed to furopteridine **79**.[39] Both reactions represent tandem processes of the $S_N^{ipso}-S_N^H$-type, atmospheric oxygen presumably taking part in the oxidation of the σ^H-adduct.

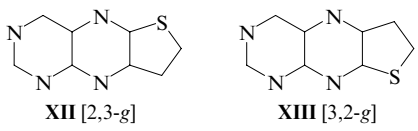


Synthesis of benzofuro[2,3-*g*]- (**80a**) and benzofuro-[3,2-*g*]pteridines (**80b**) is based on the intramolecular Diels–Alder reaction, where pyrimidotriazines **81a**,**b** serve as aza-dienes and the nitrile group of the lateral substituent serves as the dienophile.[41,42]

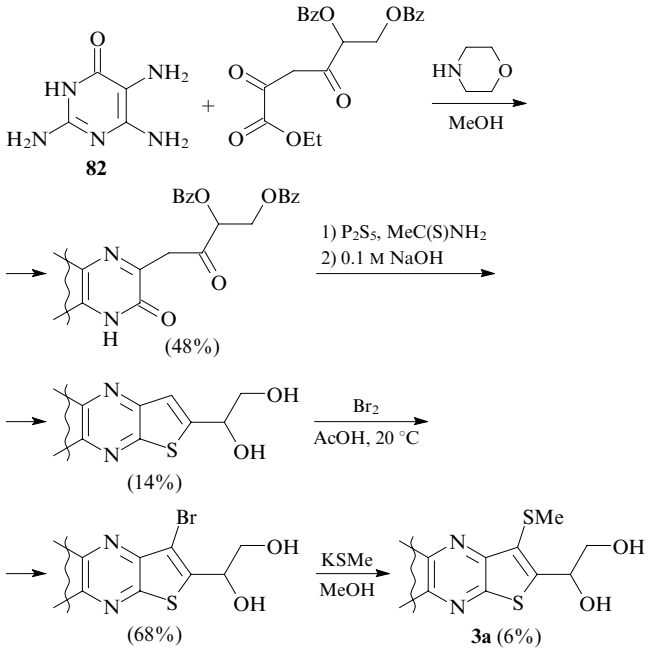


3. Thienopteridines

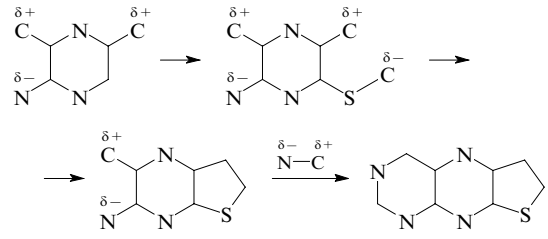
Thienopteridine derivatives of the structural types **XII** and **XIII** have been described, urothione (**3a**) belonging to the latter type.[43,44]



The total synthesis of urothione (**3a**) was first carried out by Japanese chemists;[45] this included consecutive annulation of pyrazine and thiophene rings to triaminopyrimidinone **82**.



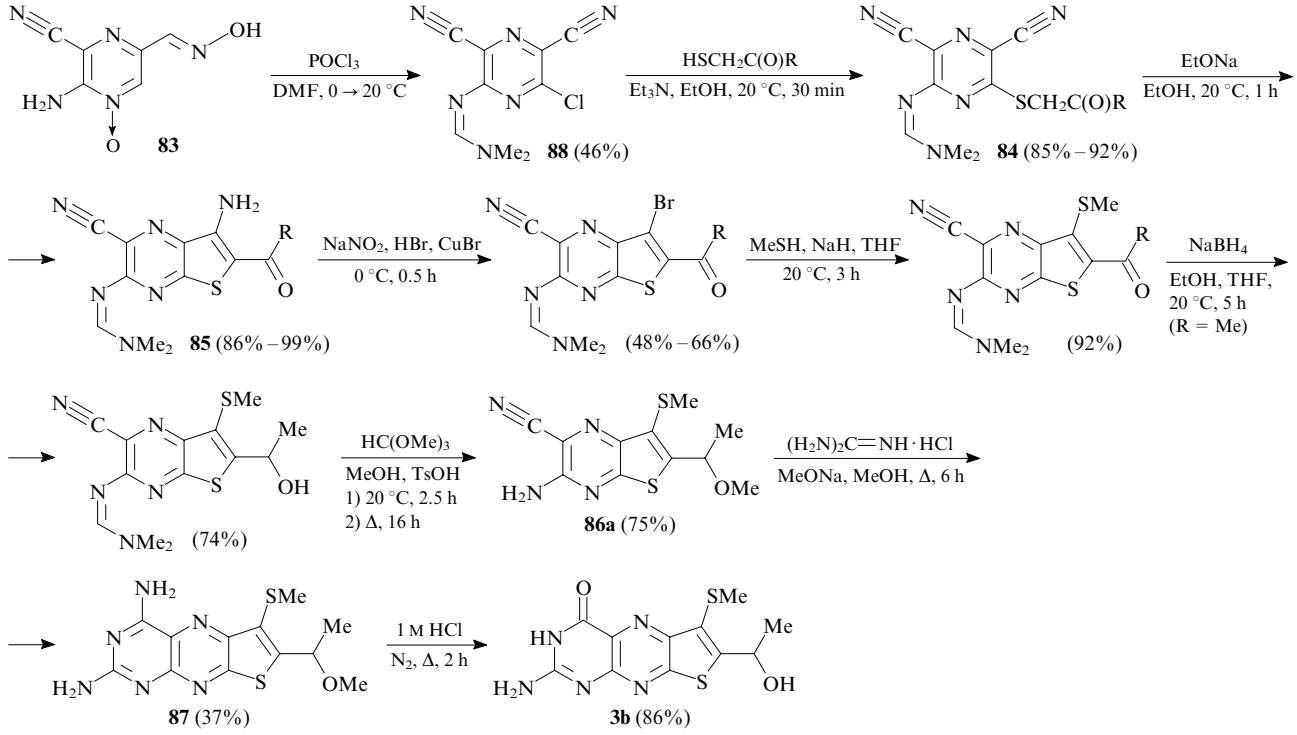
Other synthetic routes to urothione (**3a**) and deoxyurothione (**3b**) are based on the modification of available pyrazine derivatives according to the following cyclization scheme:



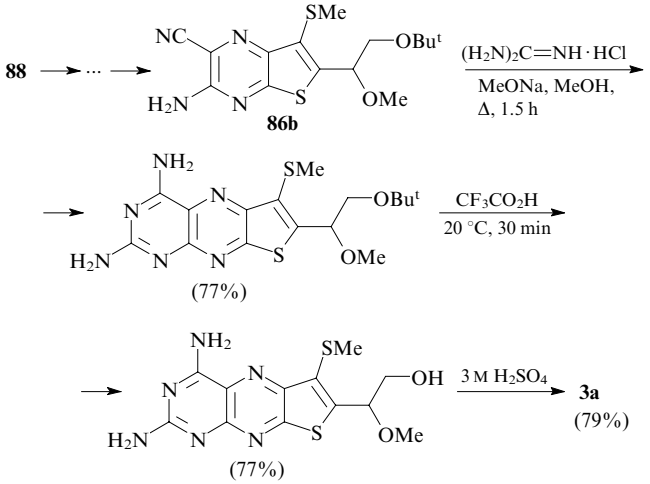
One of the protocols employs pyrazine *N*-oxide **83** (Scheme 3) as the starting compound.[46] The key steps of the synthesis are base-catalyzed cyclization of *o*-alkylthio(cyano)pyrazine **84** to thienopyrazine **85** and condensation of *o*-amino(cyano)thienopyrazine **86a** to thienopteridine **87** under the action of guanidine (see Scheme 3). Remarkable is the high efficiency of most of the synthetic steps. The total yield of deoxyurothione (**3b**) in the described transformation sequence is 9%.

(±)-Urothione (**3a**) was obtained in a similar way from dicyanopyrazine **88**, modifications concerning only conditions of several reaction steps.[47]

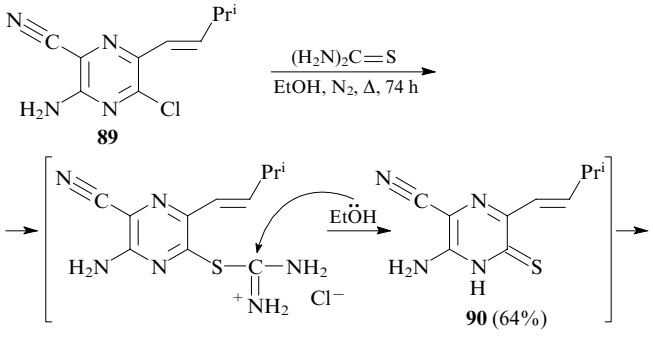
Scheme 3

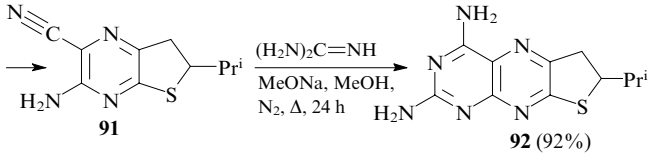


R = Me, OEt.



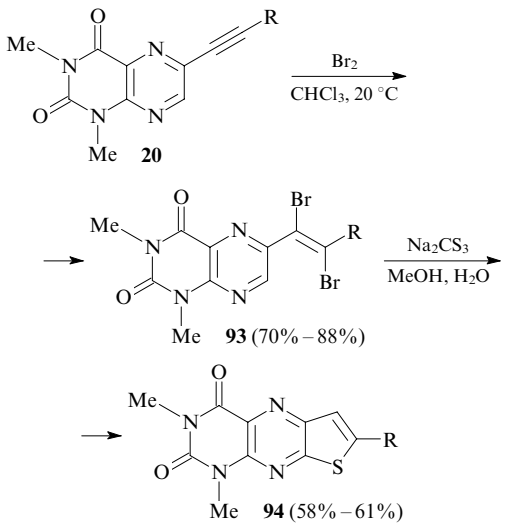
A related strategy of the construction of thieno[3,2-*g*]pteridines starting form vinylpyrazine derivative **89** makes use of the nucleophilic addition of the mercapto group to the *ortho*-vinyl group (**90** → **91**), which





leads to the thiophene ring closure; the pyrimidine ring is annulated, as described above, by way of condensation with guanidine (**91** → **92**).[48]

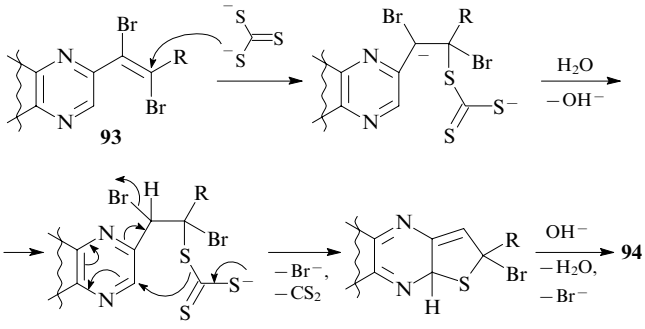
Fusion of the thiophene ring to the side *g* of the pteridine system starting from 6-alkynyllumazines **20** is described.[49] The addition of bromine to the triple bond with subsequent vicarious hydrogen substitution in com-



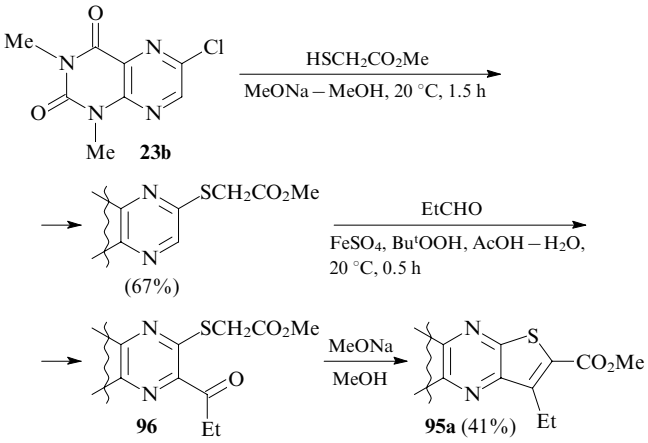
R = Ph, n-C_6H_{13}, $SiMe_3$.

pound **93** under the action of sodium trithiocarbonate lead to thieno[3,2-*g*]pteridines **94**.[19,20]

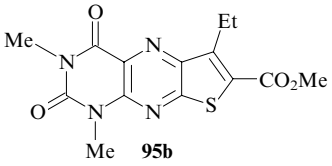
The final step of this synthesis can be represented as follows:



Thieno[2,3-*g*]pteridine **95a** is synthesized in three steps from 6-chloro-1,3-dimethyllumazine (**23b**).[21] Nucleophilic substitution of the alkylthio group for chlorine and subsequent free radical-induced acylation afford 6,7-disubstituted lumazine **96**, which undergoes cyclization to thienopteridine **95a** under the action of sodium methoxide.

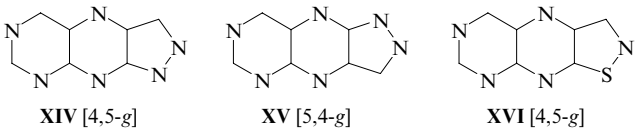


Isomeric thieno[3,2-*g*]pteridine **95b** is synthesized in a similar way from 7-chloro-1,3-dimethyllumazine **23a**.[21]



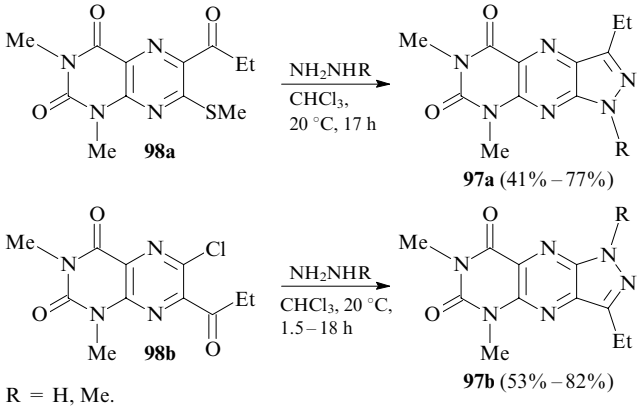
4. Pyrazolo- and isothiazolopteridines

Pteridines fused to a pyrazole or isothiazole ring are currently represented only by derivatives of heterocyclic systems of types **XIV**–**XVI**.



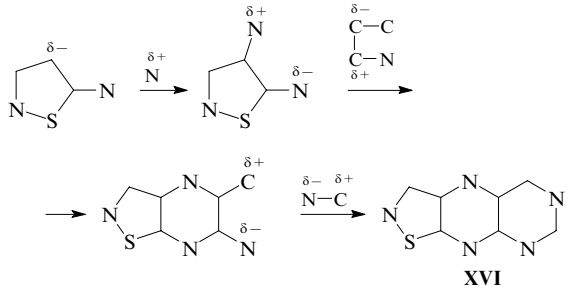
XIV [4,5-*g*] **XV** [5,4-*g*] **XVI** [4,5-*g*]

Pyrazolopteridines **97a**,**b** are obtained upon treatment of 6(7)-propionyl-7(6)-X-lumazines **98a**,**b** [X = SMe (**a**), Cl (**b**)] with hydrazine or methylhydrazine. Obviuosly, hydrazones are the intermediates in the corresponding transformation.[21]

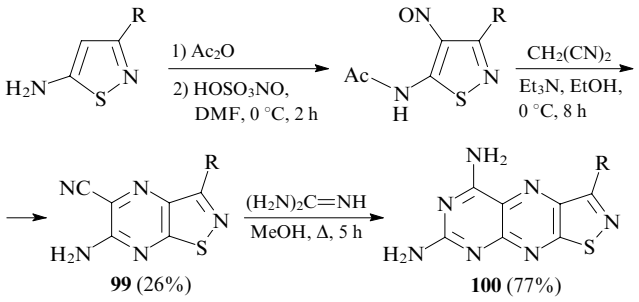


R = H, Me.

Isothiazolopteridines of the type **XVI** are synthesized from isothiazole derivatives by consecutive annulation of the pyrazine and pyrimidine rings.[50]

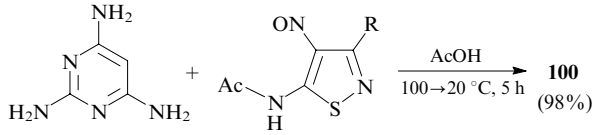


The starting 5-aminoisothiazoles are acylated and then nitrosated at C(4). The nitroso derivatives are then coupled with malononitrile in the presence of triethylamine to afford isothiazolopyrazines **99**. The latter are converted to isothiazolopteridines **100** under the action of guanidine.



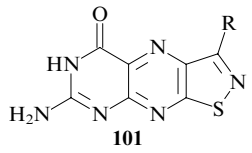
R = Me, SMe.

Compounds **100** were also obtained by condensation of 2,4,6-triaminopyrimidine with 5-acetylamino-4-nitrosoisothiazoles.[50]



R = Me, SMe.

Isothiazolopteridines **101** are synthesized in an analogous manner employing 2,6-diaminopyrimidin-4(3*H*)-one instead of triaminopyrimidine.[50]

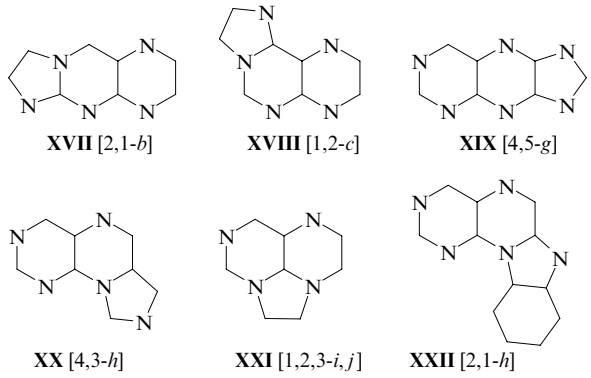


101

R = Me, SMe.

5. Imidazo- and benzimidazopteridines

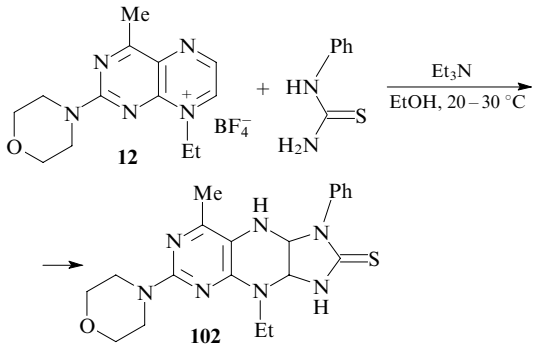
Syntheses of imidazo- and benzimidazopteridine derivatives belonging to structural types **XVII**–**XXII** have been described.



XVII [2,1-*b*] **XVIII** [1,2-*c*] **XIX** [4,5-*g*]

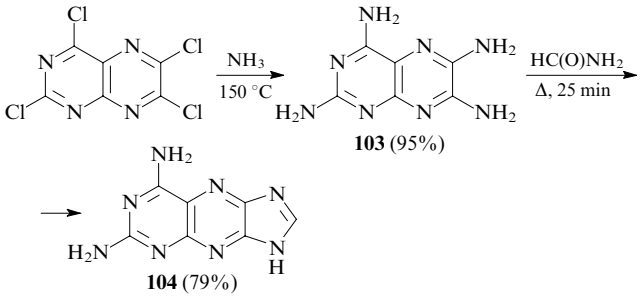
XX [4,3-*h*] **XXI** [1,2,3-*i*,*j*] **XXII** [2,1-*h*]

The majority of publications are devoted to the synthesis of imidazo[4,5-*g*]pteridines (*e.g.*, compound **102**), because of this heterocyclic system is the core of the natural pigment russupteridine yellow (**6**). Thus annulation of an imidazole ring to the side *g* of pteridine occurs in the tandem A_N-A_N-reaction of pteridinium cation **12** (dielectrophilic substrate) with *N*-phenythiourea (dinucleophile).[17]



12 **102**

6,7-Diaminopteridines are the accessible precursors of imidazo[4,5-*g*]- and imidazo [5,4-*g*]pteridines. Imidazole ring closure results from their reactions with one-carbon electrophilic agents. For example, heating of tetraaminopteridine **103** with formamide affords imidazo[4,5-*g*]pteridine **104**.[51]

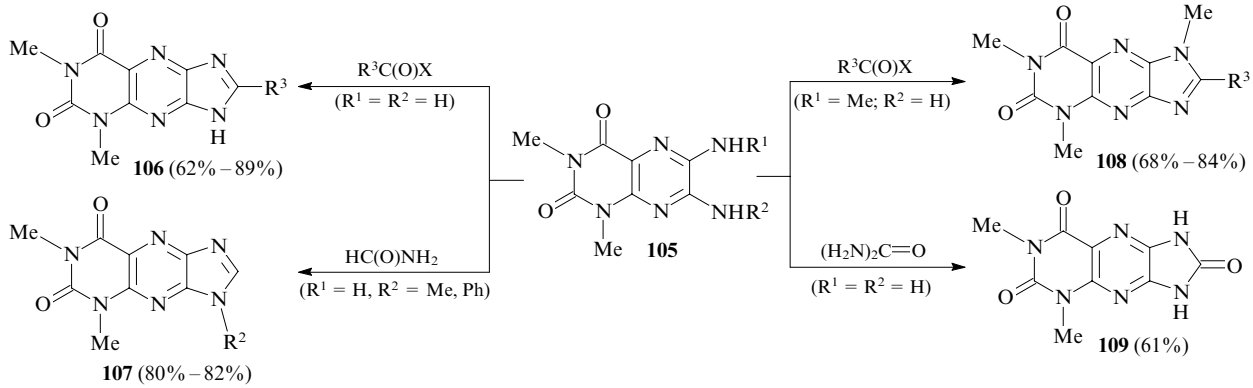


103 (95%) **104** (79%)

Condensation of 6,7-diaminolumazines **105** with formamide, acetic anhydride, aroyl chlorides or urea affords various imidazopteridines **106**–**109** in good yields (Scheme 4).[52]

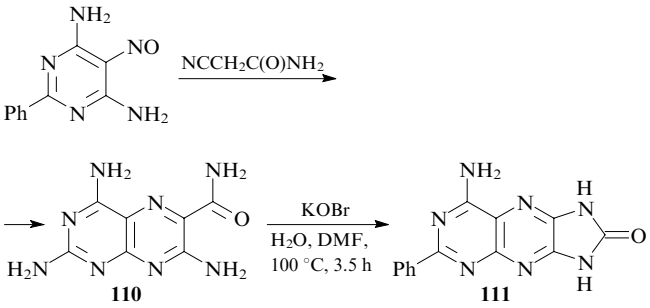
7-Aminopteridine-6-carboxamide **110** formed upon condensation of 4,6-diamino-5-nitroso-2-phenylpyrimidine with cyanoacetamide undergoes the Hoffmann rearrangement under the action of potassium hypobromite in aqueous DMF, the subsequent cyclization leads to imidazo[4,5-*g*]pteridine **111**.[53]

Scheme 4



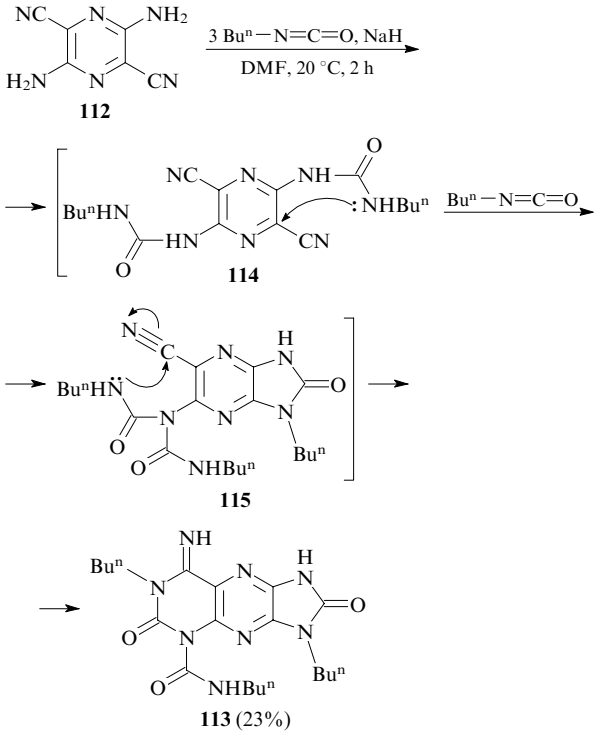
106 (62%–89%) **107** (80%–82%) **105** **108** (68%–84%) **109** (61%)

For **106**, **108**: X = Cl: R^3 = Ph, C_6H_4Y (Y = 4-Cl, 3-Cl, 2-Cl), $C_6H_3Y_2$ (Y_2 = 2,4-Cl_2, 3,4-Cl_2); X = NH_2, R^3 = H; X = OAc, R^3 = Me.



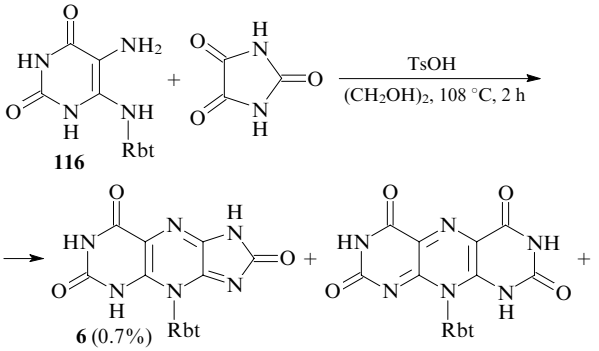
110 **111**

Heating of commercially available 2,5-diamino-3,6-dicyanopyrazine (**112**) with butyl isocyanate in the presence of sodium hydride affords imidazopteridine **113**, albeit in low yield.[54] Diureide **114** is the intermediate in this transformation. The intramolecular nucleophilic attack of the amino group leads to displacement of one nitrile group and closure of the imidazole ring. Annulation of the pyrimidine ring is the result of the nucleophilic attack of the terminal amino group of the ureide moiety on the *ortho*-cyano group of compound **115**.

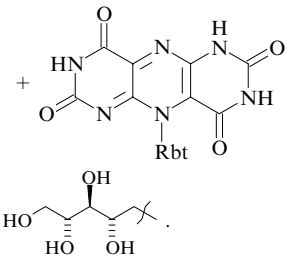


112 **114** **115** **113** (23%)

The pigment russupteridine yellow IV (**6**) is a minor condensation product of ribityl-5,6-diaminouracil **116** with parabanic acid in the presence of *p*-toluenesulfonic acid.[7]

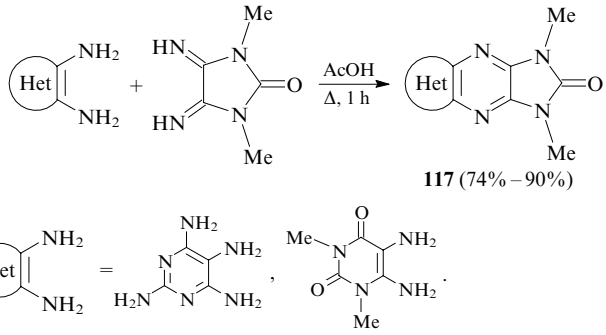


116 **6** (0.7%)



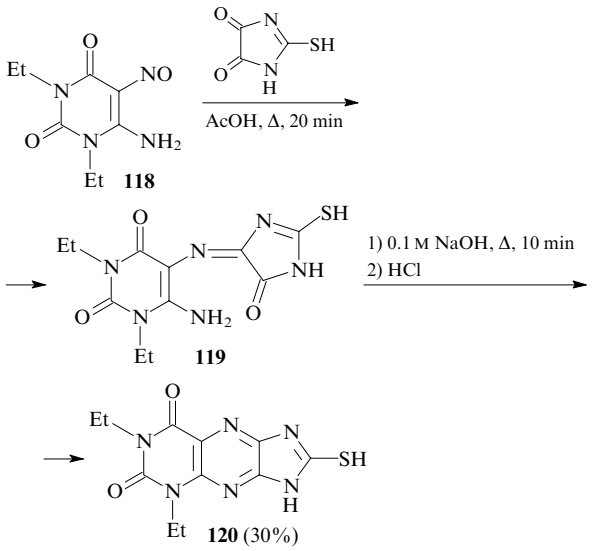
Rbt = HO, HO, OH, OH.

Condensation of *o*-diaminopyrimidines with 4,5-diimino-1,3-dimethylimidazolidin-2-one in acetic acid proceeds more efficiently, the yield of imidazopteridines **117** exceeds 74%.[55]



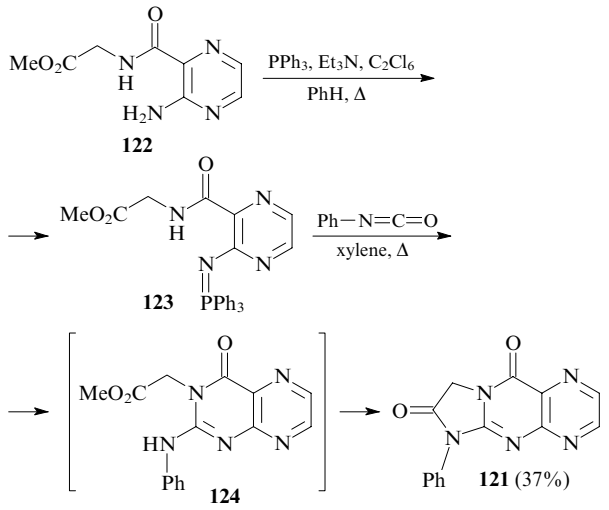
117 (74% – 90%)

6-Amino-5-nitrosouracil **118** reacts with 2-thiohydantoin giving rise to azomethine **119**, which undergoes cyclization to imidazo[4,5-*g*]pteridine **120** upon refluxing in an aqueous alkali.[56]

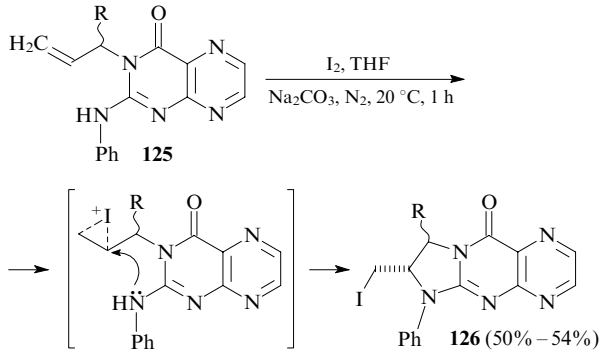


118 **119** **120** (30%)

The known methods of the synthesis of imidazo[2,1-*b*]-pteridines involve fusion of the pyrimidine and imidazole rings to pyrazine. Thus a two-step procedure giving rise to heteroannulated imidazolidinone **121** from 3-aminopyrazine-2-carboxamide **122** was suggested. The latter is converted into the aza-Wittig reagent **123** and then treated with phenyl isocyanate upon heating in xylene. The intermediate pteridine **124** undergoes spontaneous cyclization into imidazopteridine **121**.[57]



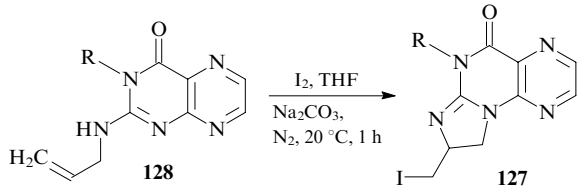
Electrophile-catalyzed nucleophilic addition of the amino group to the allylic C=C bond is the basis for yet another method of synthesis of imidazo[2,1-*b*]pteridines. Treatment of 3-allylpteridines **125** with iodine in THF affords imidazopteridines **126**.[57]



R = H, Me.

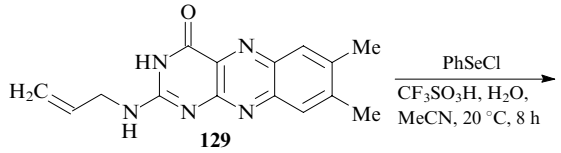
(for R = Me mixture of isomers 1 : 1)

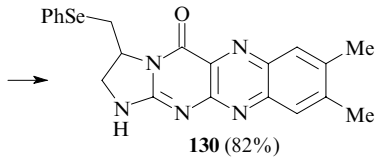
Imidazopteridines **127** of the isomeric [1,2-*a*]-series are isolated in quantitative yields upon cyclization of 2-allylamino-3-arylpteridin-4(3*H*)-ones **128** under similar conditions.[58]



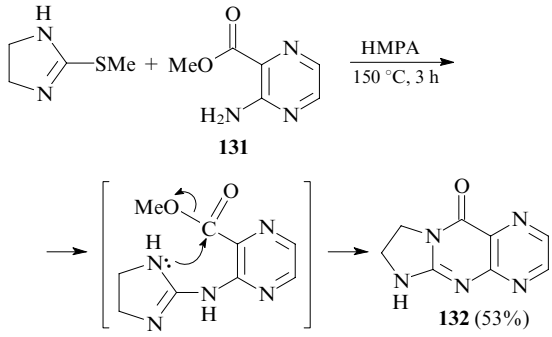
R = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$.

N(3)-Unsubstituted 2-allylaminobenzopteridines **129** undergo cyclization into benzimidazo[2,1-*b*]pteridines **130** under the action of phenylselenenyl chloride.[59]



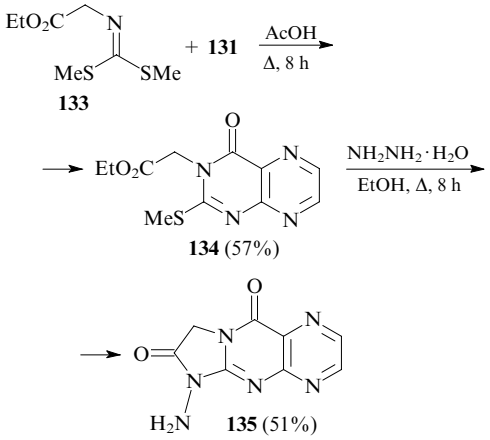


The reaction of 3-aminopyrazine-2-carboxylate **131** with 2-methylthioimidazoline results in simultaneous annulation of a pyrimidine and an imidazole rings to the starting heterocycle affording 7,8-dihydroimidazo[2,1-*b*]pteridin-10(6*H*)-one (**132**) in 58% yield.[60] The heterocyclization mechanism includes nucleophilic substitution of the amino group of compound **131** for the methylthio group of methylthioimidazoline and subsequent intramolecular acylation.

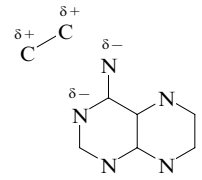


HMPA is hexamethylphosphorotriamide.

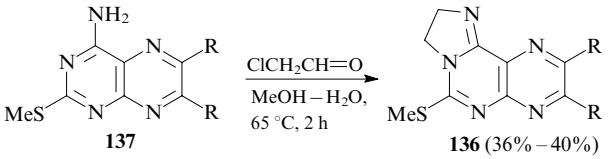
Coupling of compound **131** with 2-[bis(methylthio)methylideneamino]acetate **133** gives pteridine **134**; its reaction with hydrazine hydrate affords imidazopteridine **135**.[60]



The design of imidazo[1,2-*c*]pteridines **136** is based on the following kind of cyclization:[61]



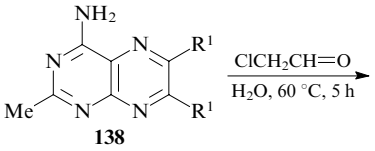
Chloroacetaldehyde in this cyclization plays the role of the bifunctional electrophile and 4-aminopteridine **137** acts as the 1,3-N,N-dinucleophile.



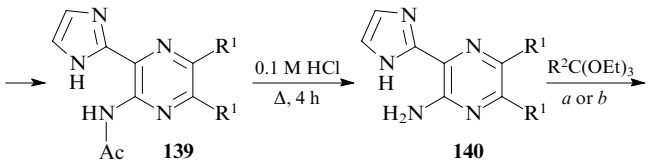
137 **136** (36%–40%)

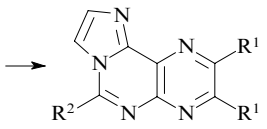
R = H, Me.

It is of note that the reaction of 4-aminopteridine **138** with chloroacetaldehyde under similar conditions results in pyrimidine ring opening and formation of (imidazol-2-yl)pyrazine **139** instead of the expected imidazopteridine.[62] However, acid hydrolysis of compound **139** and subsequent treatment of the amino derivative **140** with orthoesters give rise to imidazo[1,2-*c*]pteridines **141** in good yields.



138

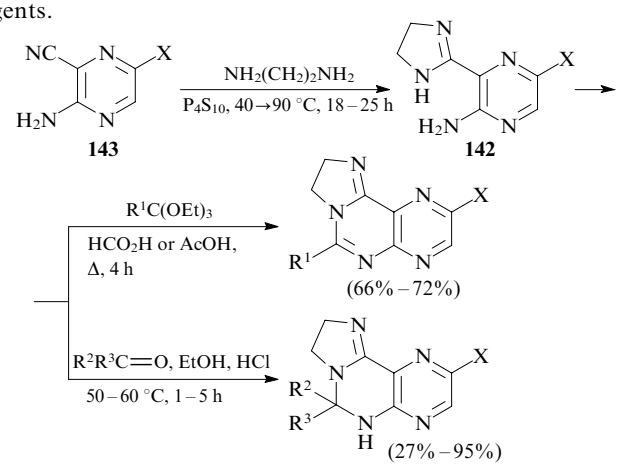




141

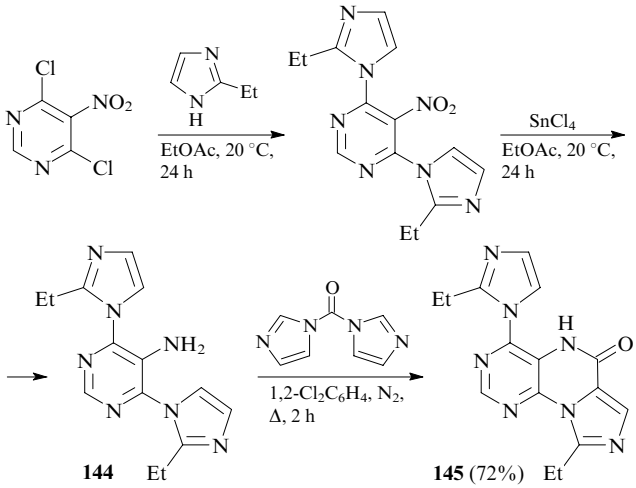
R^1 = H, Me; R^2 = H, Me, Et; (*a*) PhMe, Δ, 9–24 h; (*b*) CF_3CO_2H, Δ, 2.5–7 h.

A similar approach to the construction of the imidazo[1,2-*c*]pteridine system was described.[63] The key dihydroimidazolylpyrazine **142** was synthesized by condensation of cyanopyrazines **143** with ethylenediamine. Orthoesters, aldehydes or ketones served as the cyclization agents.



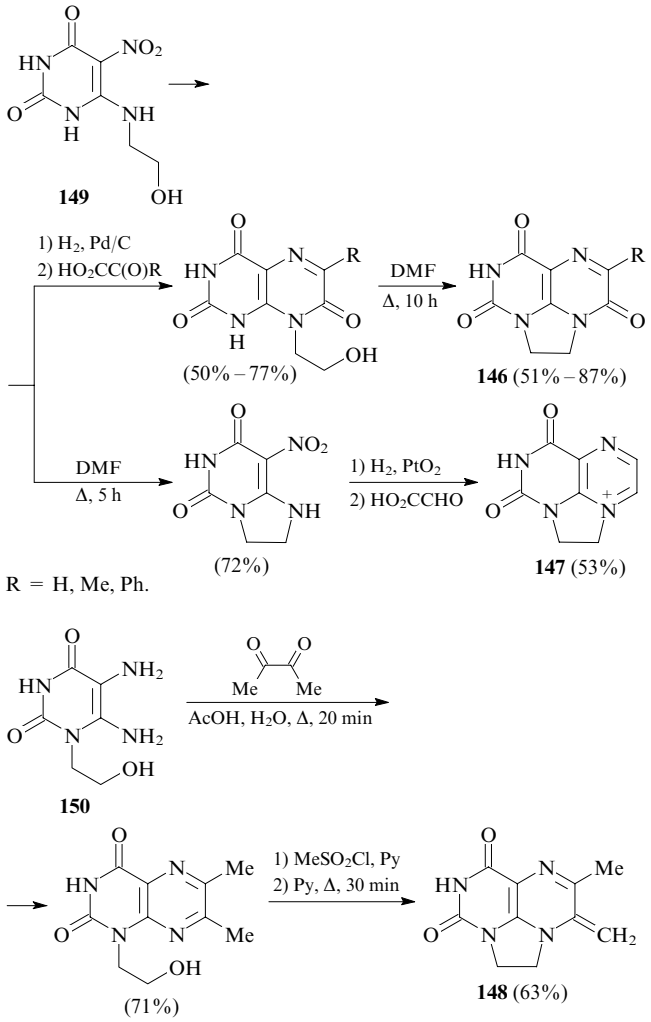
X = H, Br; R^1 = H, Me; R^2, R^3 = H, Me, Et, Ph, 4-$NO_2C_6H_4$; $R^2–R^3$ = $(CH_2)_5$.

5-Amino-4,6-bis(imidazol-1-yl)pyrimidine **144** undergoes cyclization under the action of *N*,*N*′-carbonyldiimidazole to form imidazo[4,3-*h*]pteridine **145**. Compound **144** is obtained from commercially available 4,6-dichloro-5-nitropyrimidine.[64]



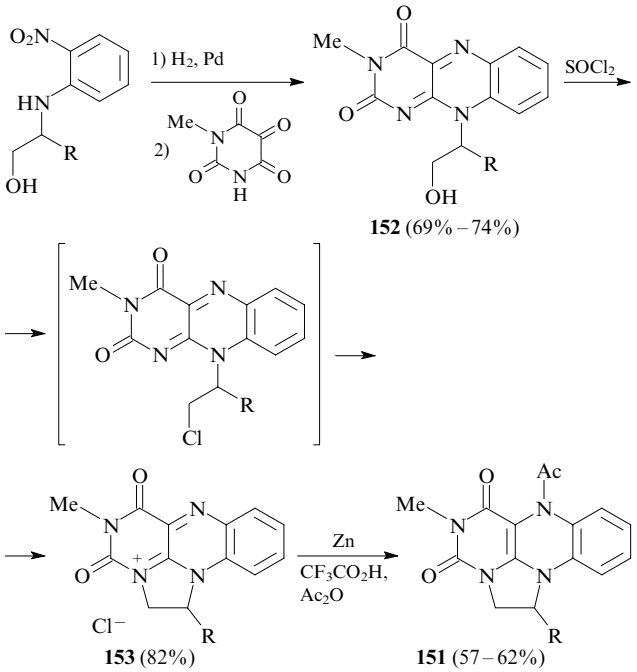
144 **145** (72%)

Imidazo[1,2,3-*i*,*j*]pteridine derivatives **146**–**148** can be synthesized from aminouracil derivatives **149** and **150**.[65]



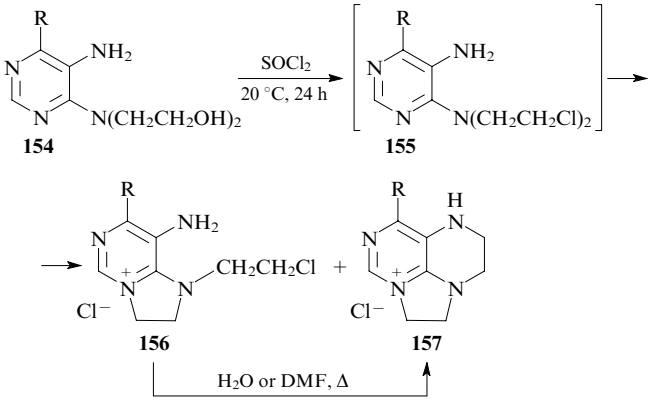
1,2-Dihydrobenzo[*g*]imidazo[1,2,3-*i*,*j*]pteridinones **151** are synthesized similarly to compounds **148**.[66] The key step of the synthesis, *viz*., chlorination of 10-(2-hydroxyethyl)benzopteridine derivatives **152** with thionyl chloride

is accompanied by intramolecular quaternization leading to pteridinium salts **153**. The latter can be smoothly reduced to benzimidazopteridines **151** with zinc in a mixture of trifluoroacetic acid and acetic anhydride.



R = H, Me.

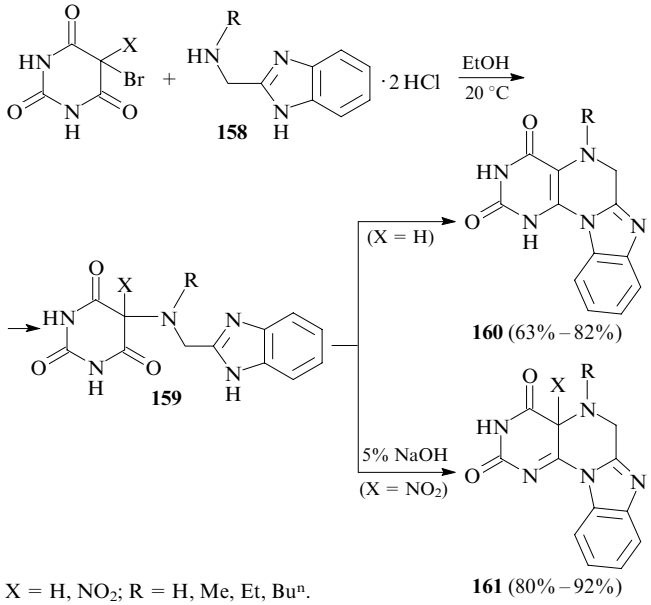
Treatment of 5-amino-4-[bis(β-hydroxyethyl)amino]pyrimidines **154** with thionyl chloride gives bis(β-chloroethyl)-amino derivatives **155**, which undergo spontaneous cyclization into imidazopyrimidines **156** and imidazo[1,2,3-*i*,*j*]pteridines **157**.[67] Compounds **156** can be converted into imidazopteridines by heating in water or DMF.



R = H, Cl.

Virtually the only one known procedure for the synthesis of benzimidazopteridines involves condensation of 2-(alkylaminomethyl)benzimidazoles **158** with 5-bromo- or 5-bromo-5-nitrobarbituric acid.[68] The primary aminodebromination products **159** undergo either spontaneous (**159** → **160**, X = H), or thermally-induced (**159** → **161**, X = NO_2) cyclization into benzimidazo[2,1-*h*]pteridines.

The heterocyclization **159** → **161** occurs also upon heating of compounds **159** (X = NO_2) in 5% NaOH solution.

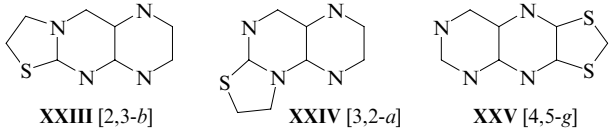


X = H, NO_2; R = H, Me, Et, Bu^n.

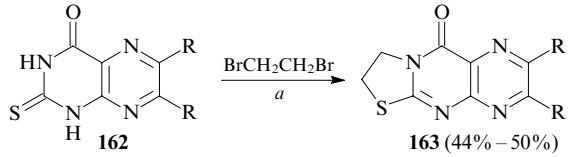
We should note that the heterocyclic system of imidazo[1,5-*f*]pteridine underlying the structure of 5,10-methylene-5,6,7,8-tetrahydrohydromethanopterin **5**, has been beyond the attention of synthetic chemists. No data on the synthesis of imidazo[1,5-*f*]pteridine derivatives seem to have been reported.

6. Thiazolo- and 1,3-dithiolopteridines

The known compounds of this group belong to the heterocyclic systems of the types **XXIII** – **XXV**.

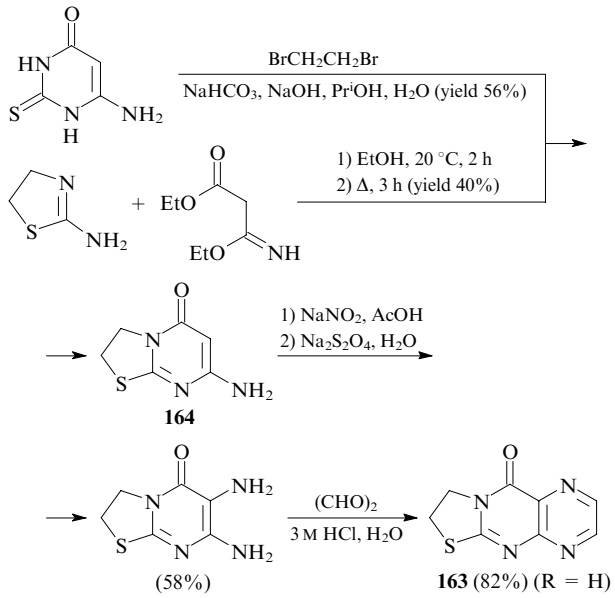


The reaction of 2-thiolumazines **162** with 1,2-dibromoethane in a basic medium gives thiazolo[2,3-*b*]pteridines **163** in moderate yields.[69, 70]



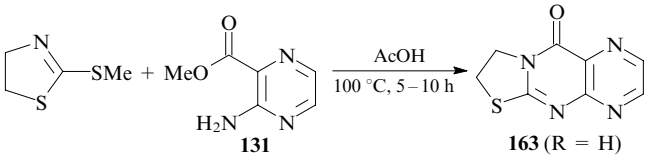
R = H, Me, Ph; (*a*) 1) NaOH, $NaHCO_3$, Pr^iOH, H_2O, Δ, 1 h; 2) 1 M NaOH, 20 °C, 96 h; 3) K_2CO_3, DMF, 85 °C, 6 h.

An alternative route is based on the use of 6-amino-2-thiouracil as the starting compound to which, first, the thiazole ring and then the pyrazine ring are annulated.[69] Compound **164** can be isolated in a somewhat lower yield by coupling of 2-amino-2-thiazoline with ethyl ethoxycarbonylacetimidate.[69]

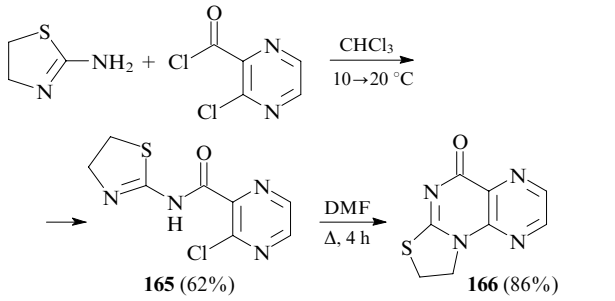


164

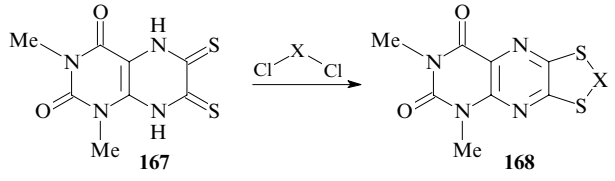
The formation of thiazolo[2,3-*b*]pteridine **163** (R = H) can also result from the condensation of methyl 3-aminopyrazine-2-carboxylate (**131**) with 2-methylthiothiazoline.[60]



Thiazolopteridines of the isomeric [2,3-*a*]-series are synthesized in two steps from 3-chloropyrazine-2-carbonyl chloride and 2-aminothiazoline.[69] Heating of the intermediate pyrazinecarboxamide **165** in DMF leads to pyrimidine ring closure and the formation of thiazolopteridine **166**.



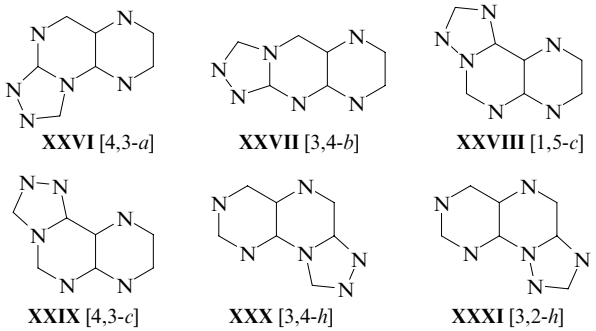
The reaction of lumazine-6,7-dithione **167** with phosgene, thiophosgene or dichloromethane leads to 1,3-dithiolopteridines **168**.[38, 71]



X = C=O, C=S, CH_2.

7. 1,2,4-Triazolopteridines

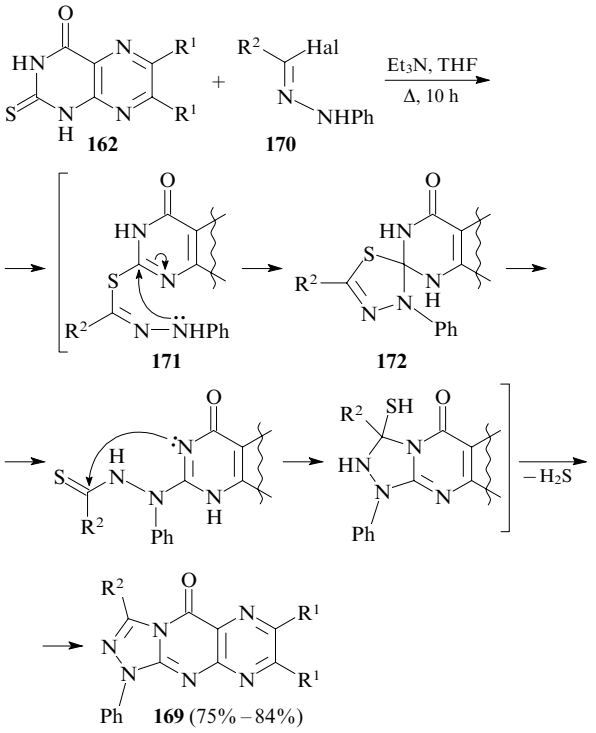
Pteridines fused to a [1,2,4]triazole ring are described in literature as six isomeric heterocyclic systems **XXVI**–**XXXI**.



XXVI [4,3-*a*] **XXVII** [3,4-*b*] **XXVIII** [1,5-*c*]

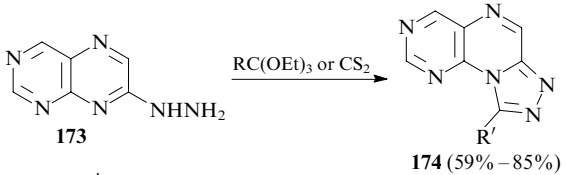
XXIX [4,3-*c*] **XXX** [3,4-*h*] **XXXI** [3,2-*h*]

1,2,4-Triazolo[3,4-*b*]pteridines **169** are obtained by cyclocondensation of lumazine-2-thiones **162** with hydrazonoyl halides **170** in the presence of triethylamine.[72, 73] The mechanism of this reaction includes nucleophilic substitution of the arylthio group for halogen, spiro-cyclization of the intermediate compound **171** into spirothiadiazoline **172** and re-cyclization of the latter with elimination of H_2S.



R^1 = H, Me, Ph; R^2 = Ac, Bz, CO_2Et, Ph, CH=CHPh.

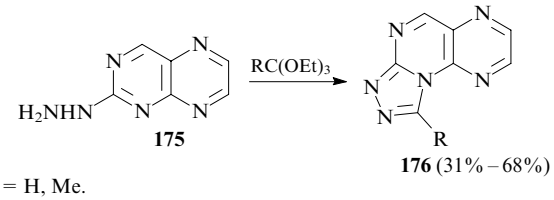
Hydrazinopteridines serve most often as the starting compounds in the synthesis of thiazolopteridines. Thus brief heating of compound **173** with one-carbon electro-



R = H, Me; R′ = H, Me, SH.

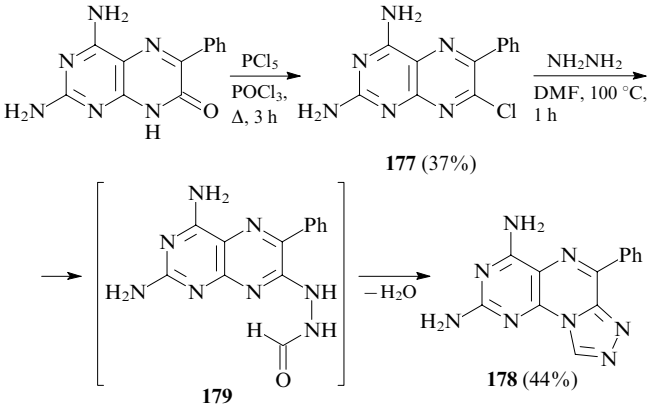
philes (orthoesters, carbon disulfide) in dioxane or pyridine leads to 1,2,4-triazolo[3,4-*h*]pteridines **174**.[74]

In an analogous manner, starting from 2-hydrazinopteridine **175**, triazolo[4,3-*a*]pteridines **176** are obtained.[74]



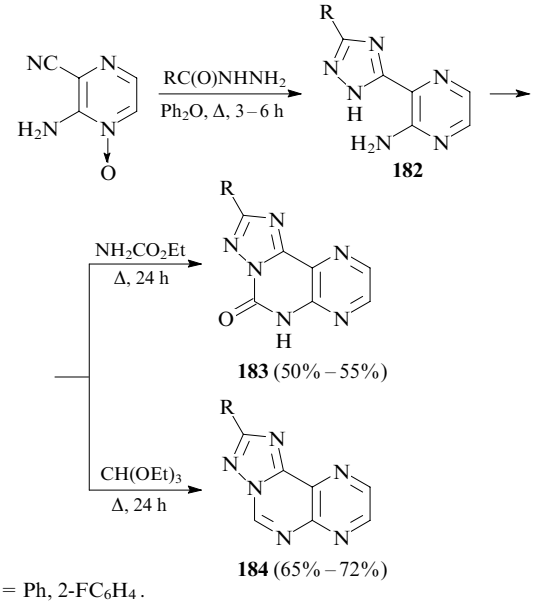
R = H, Me.

Heating of 7-chloropteridine **177** with hydrazine in DMF results in 1,2,4-triazolo[3,4-*h*]pteridine **178**, which is supposingly formed *via* the intermediate formylhydrazino derivative **179**.[75]



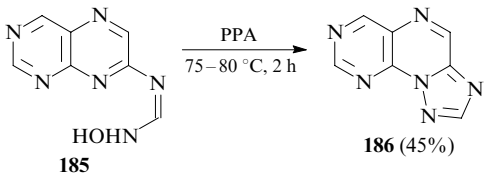
1,2,4-Triazolo[4,3-*c*]pteridines **180** are obtained in several steps from 3-amino-6-phenylpyrazine-2-carbonitrile. The pyrimidine ring is annulated to the pyrazine ring first. The triazole ring is closed as the result of the reaction of the intermediate 4-hydrazinopteridine **181** with orthoesters (Scheme 5).[76]

Despite high yields in all the steps of this synthetic route, another method is more efficient, which involves the transformation of 3-aminopyrazine-2-carbonitrile *N*(4)-oxide into triazolyl derivative **182** under the action of an acylhydrazine. The reaction of **182** with ethyl carbamate or orthoformate results in closure of the pyrimidine ring and formation of triazolopteridines **183**, **184**.[77]



R = Ph, 2-FC_6H_4.

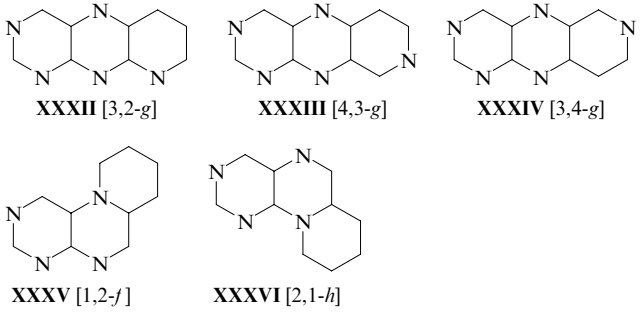
Heating of *N*-hydroxyformamidine **185** in polyphosphoric acid brings about cyclization into 1,2,4-triazolo[3,2-*h*]pteridine **186**.[74]



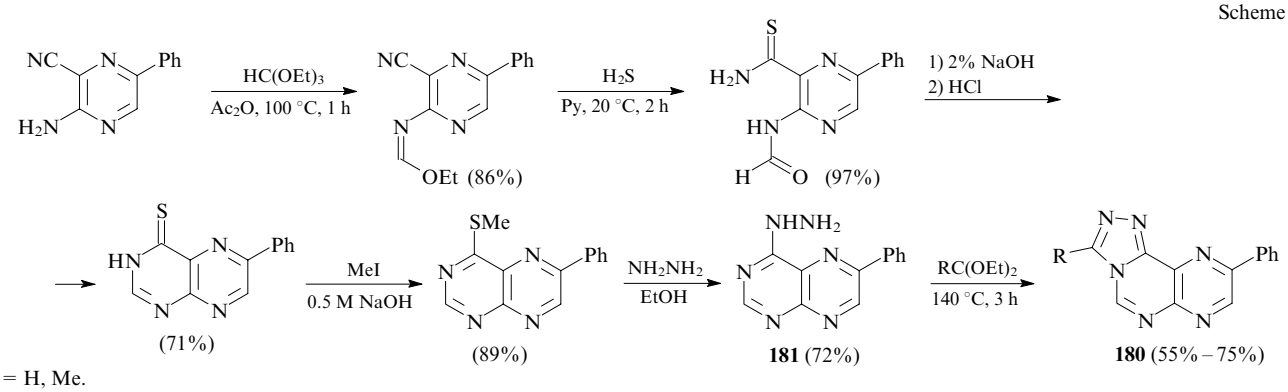
IV. Pteridines fused to six-membered heterocycles

1. Pyridopteridines

The data on the synthesis of pyridopteridines are scarce. They refer to the heterocyclic systems of the types **XXXII** – **XXXVI**.

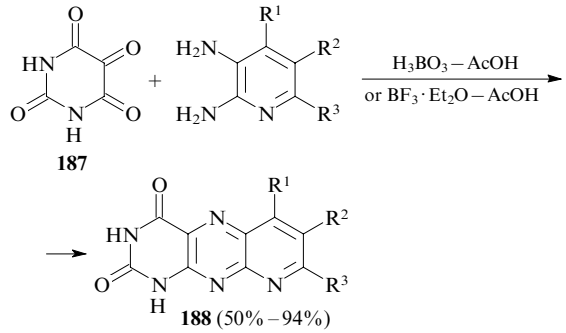


Scheme 5



R = H, Me.

[*g*]-Fused pyridopteridines are aza-analogues of alloxazine and isoalloxazine, the structural cores of the flavin coenzymes. It is this fact that is the reason for the increased attention to their synthesis and studies of biological activity.[78–83] A general method of the synthesis of [*g*]-fused pyridopteridines is the coupling of alloxane derivatives with *o*-diaminopyridines. Thus the reaction of alloxane (**187**) with 2,3-diaminopyridines in the system H_3BO_3–AcOH or $BF_3 \cdot Et_2O$–AcOH results in pyrido[3,2-*g*]pteridines **188**.[78,79] The regioselectivity of the reaction is remarkable: no pyrido[2,3-*g*]pteridines isomeric to compounds **188** are formed.

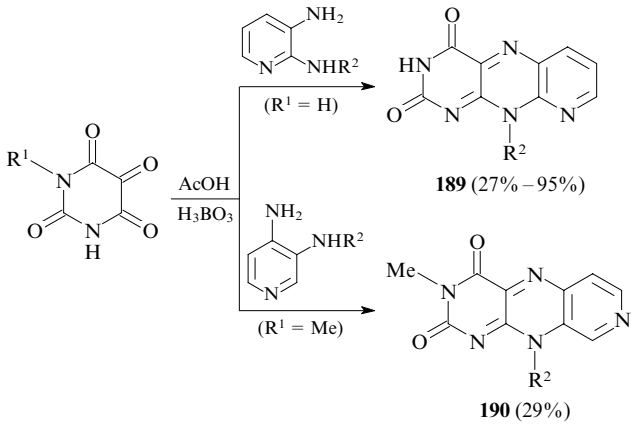


187

188 (50%–94%)

R^1, R^3 = H, Me; R^2 = H, Cl, Br.

A similar condensation of substituted alloxanes with *o*-amino[alkyl(aryl)amino]pyridines gives pyridopteridines **189** and **190**.[80–83]

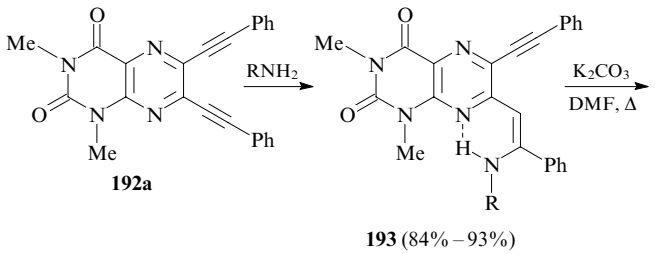


189 (27%–95%)

190 (29%)

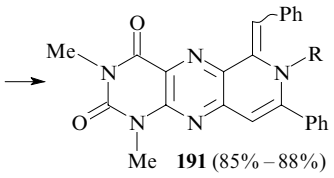
R^1 = H, Me; R^2 = Me, Pr^n, cyclo-C_6H_{11}, Ph, $(CH_2)_nOH$ (n = 2, 3, 5, 6), $CH_2CH(OH)Me$, $CH_2CH(OH)CH_2OH$, $(CH_2)_3N(CH_2CH_2OH)_2$, *etc*.

A two-step synthesis of pyrido[3,4-*g*]pteridines **191** from 6,7-dialkynyllumazine **192a** was described.[18,19] Compound **192a** is first treated with an excess of an alkylamine giving rise to enamine **193** stabilized by the intramolecular hydrogen bond. Heating of the latter with K_2CO_3 in DMF leads to closure of the pyridine ring.



192a

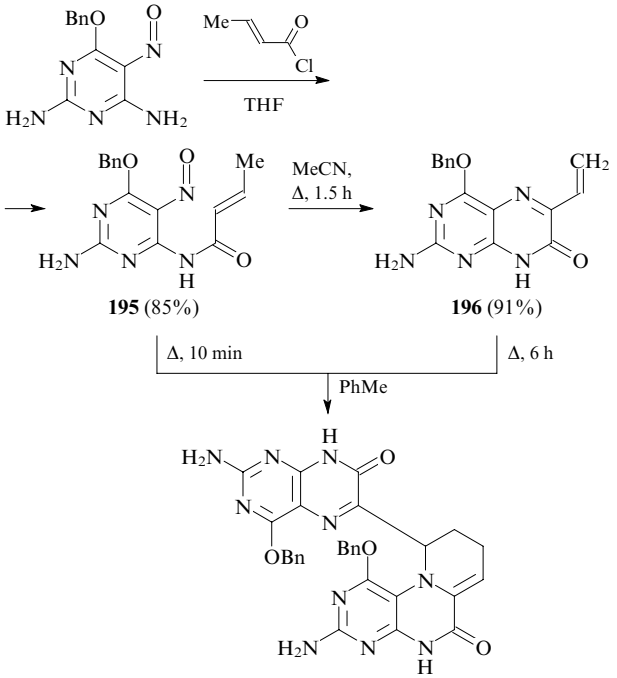
193 (84%–93%)



191 (85%–88%)

R = Pr^n, Bu^n.

4-Amino-5-nitrosopyrimidines are the starting compounds in the synthesis of pyrido[1,2-*f*]pteridines **194**. For example, heating of compound **195** in acetonitrile leads to 6-vinylpteridine **196**.[28] Refluxing of the latter in toluene results in the Diels–Alder reaction where the *cis*-diene fragment N(5)=C(6)–CH=CH_2 of one starting molecule and the vinyl group of another molecule are involved. This reaction affords pyrido[1,2-*f*]pteridine **194**, which can also be synthesized by heating **195** in toluene.



195 (85%)

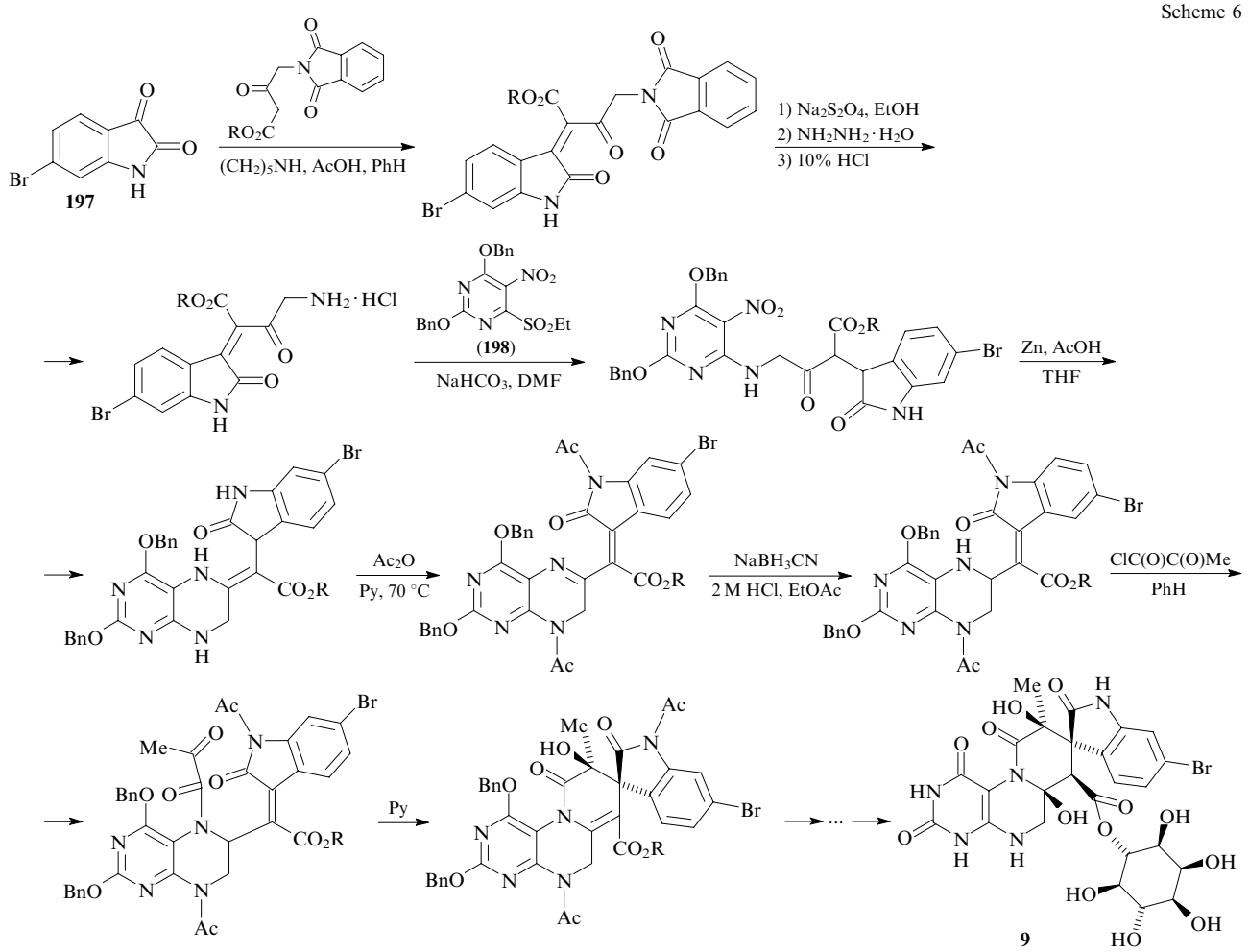
196 (91%)

194 (96% from compound **195**, 98% from compound **196**)

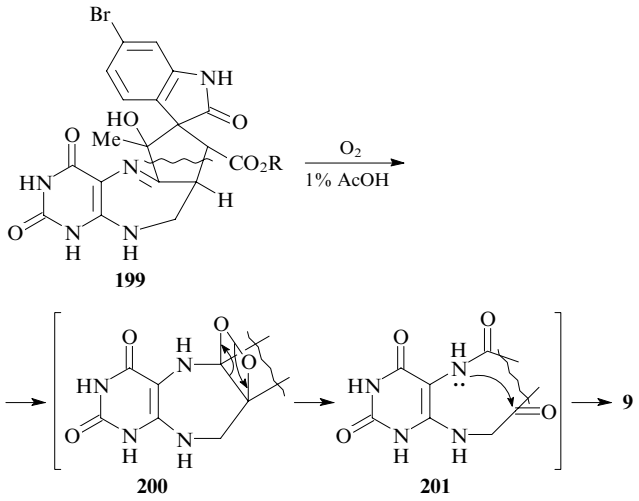
As has been mentioned above, one of pyrido[1,2-*f*]pteridine derivatives, surugatoxin (**9**), occurs in nature. Its total synthesis was accomplished starting from 6-bromoisatin **197** and nitropyrimidine **198**.[84] The key steps of the synthesis demonstrate yet another route to the pyrido[1,2-*f*]pteridine system (Scheme 6).

Prosurugatoxin **199** isolated from the shellfish *Babylonia japonica* is converted into surugatoxin (**9**) on storage in 1% acetic acid for several days.[85] Atmospheric oxygen is involved in the process giving the intermediate dioxetane **200**, which then undergoes isomerization into 10-membered lactam **201**, the precursor of compound **9**.

Scheme 6



R = CH_2CH_2SMe.

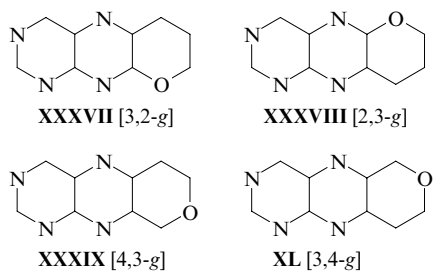


R is 6-myoinosityl.

On irradiation of aqueous solutions of pyridinium salts **202a–c** with visible light they transform into pyrido[2,1-*h*]pteridines **203a–c** (Scheme 7).[86,87] In the course of the reaction, the imidazole fragment of the starting molecule undergoes hydrolytic cleavage (**202** → **204** → **205**) with subsequent cyclization into betain **203**. Nucleosides **203**, in particular 2,3,5-tri-*O*-acetylluminarozine, possess strong fluorescence and belong to the few nucleosides that both absorb and emit visible light. This feature, along with the chemical stability, makes compounds **203a–c** very promising fluorescence probes for nucleic acids and other biomolecules.[88–90] Depending on the reaction conditions, hydrolysis of nucleosides **203a–c** leads to deacetyl derivative **203d** (luminarozine) or its aglycon **203e** (luminarine).

2. Pyranopteridines

Pyranopteridine derivatives belonging to the type **XXXVII–XL** systems have been synthesized.

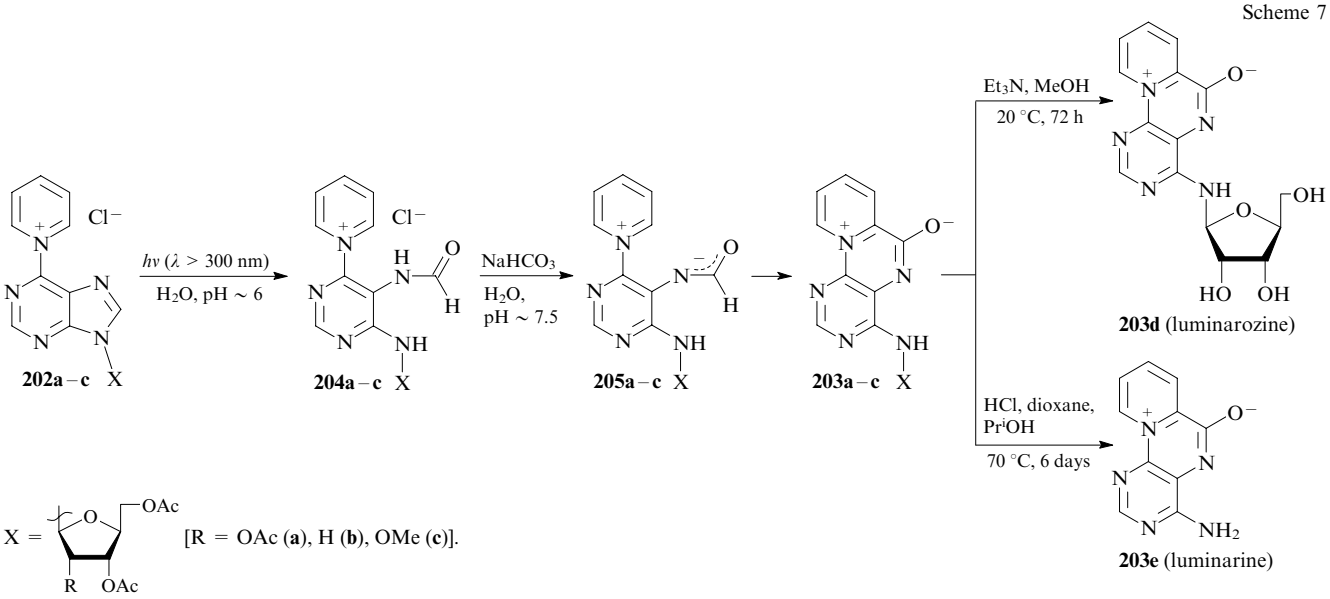


XXXVII [3,2-*g*] **XXXVIII** [2,3-*g*]

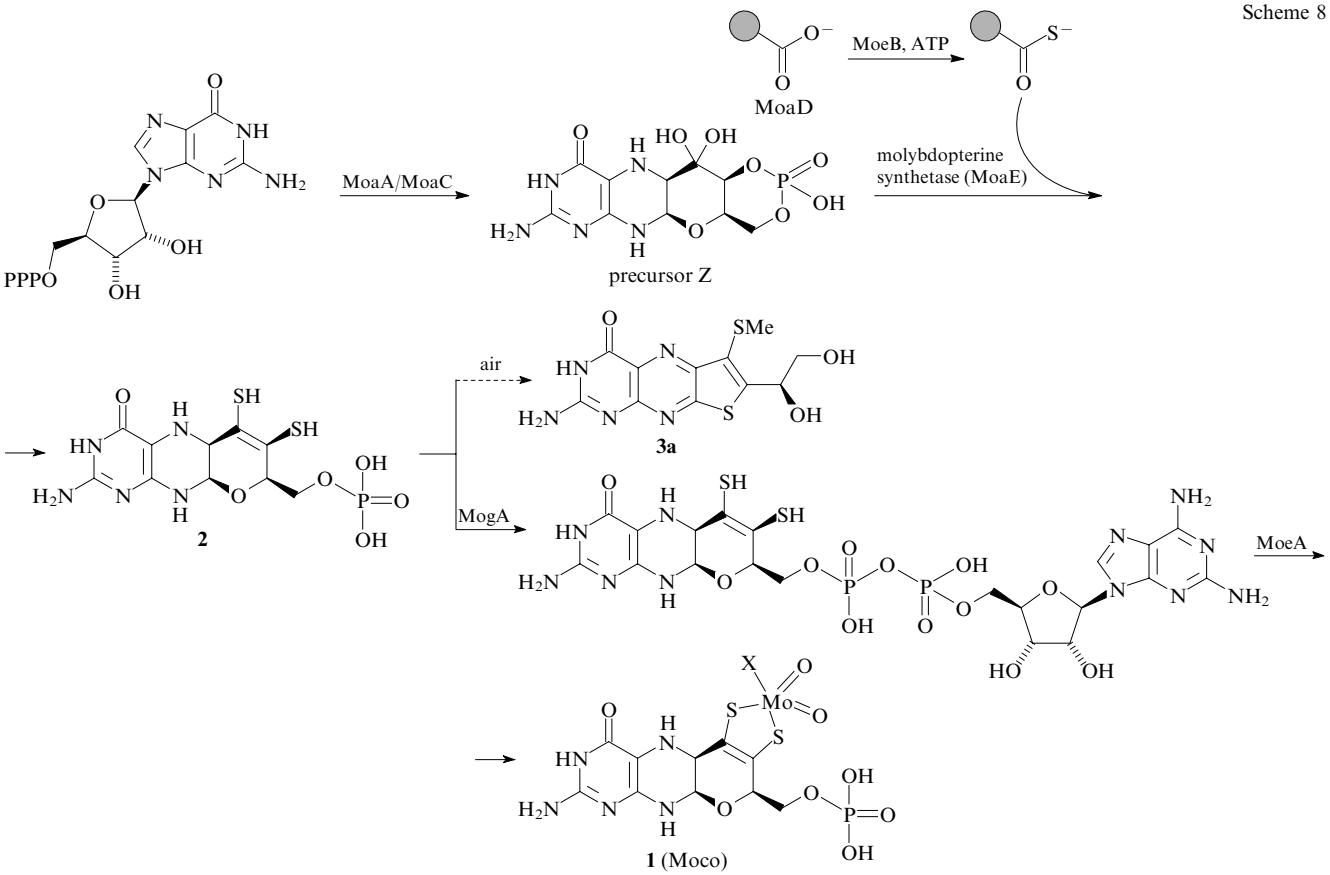
XXXIX [4,3-*g*] **XL** [3,4-*g*]

As has been noted above, the heterocyclic system of pyrano[3,2-*g*]pteridine **XXXVII** is the core fragment of molybdopterin (**2**) and co-factor Moco (**1**). Biosynthesis of Moco begins[1,3,91,92] with guanosine triphosphate (Scheme 8). Two enzymatic reactions convert this triphosphate into pyranopterin cyclophosphate (the so called precursor Z). Three subsequent enzymatic reactions accomplish the construction of an enedithiolate fragment and the

Scheme 7



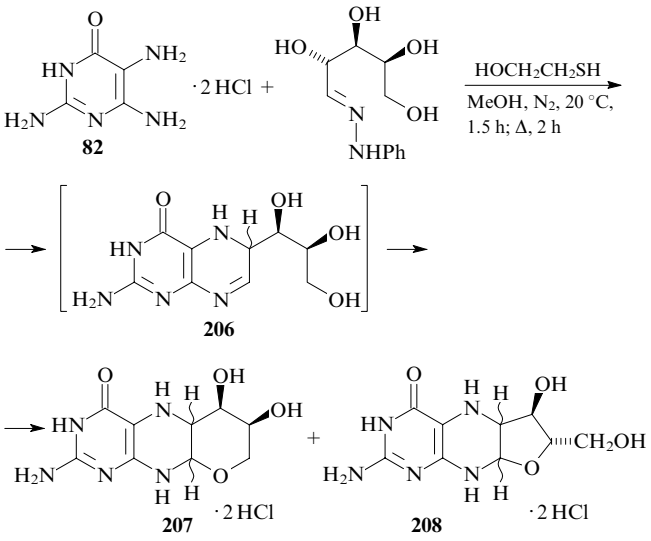
Scheme 8



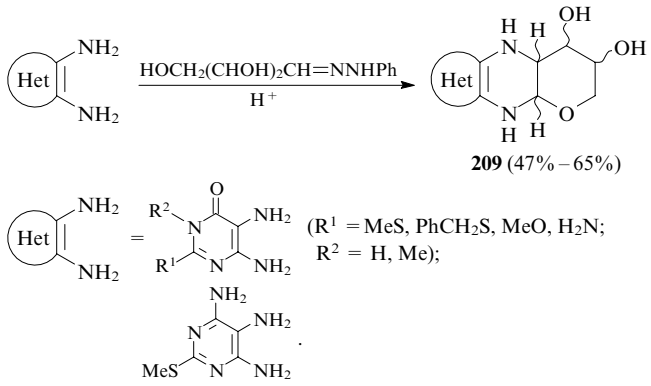
MoaA, MoaC, MoaD, MoaE, MoeA, MoeB, MogA are *E. coli* enzymes; ATP is adenosine triphosphate; PPP is triphosphate.

formation of molybdopterin (**2**). The monophosphate fragment of molybdopterin is then adenylated, which activates it towards binding of molybdenum (in the form of the molybdate anion) and formation of Moco.

Total synthesis of compounds **1** and **2** has not been accomplished yet. However, potential precursors of molybdopterin have been synthesized. Thus condensation of triaminopyrimidinone dihydrochloride **82** with L-arabinose phenylhydrazone leads to triol **206**, which then undergoes cyclization into hexahydropyrano[3,2-*g*]pteridine **207** (the major product) and hexahydrofuro[3,2-*g*]pteridine **208**.[93]



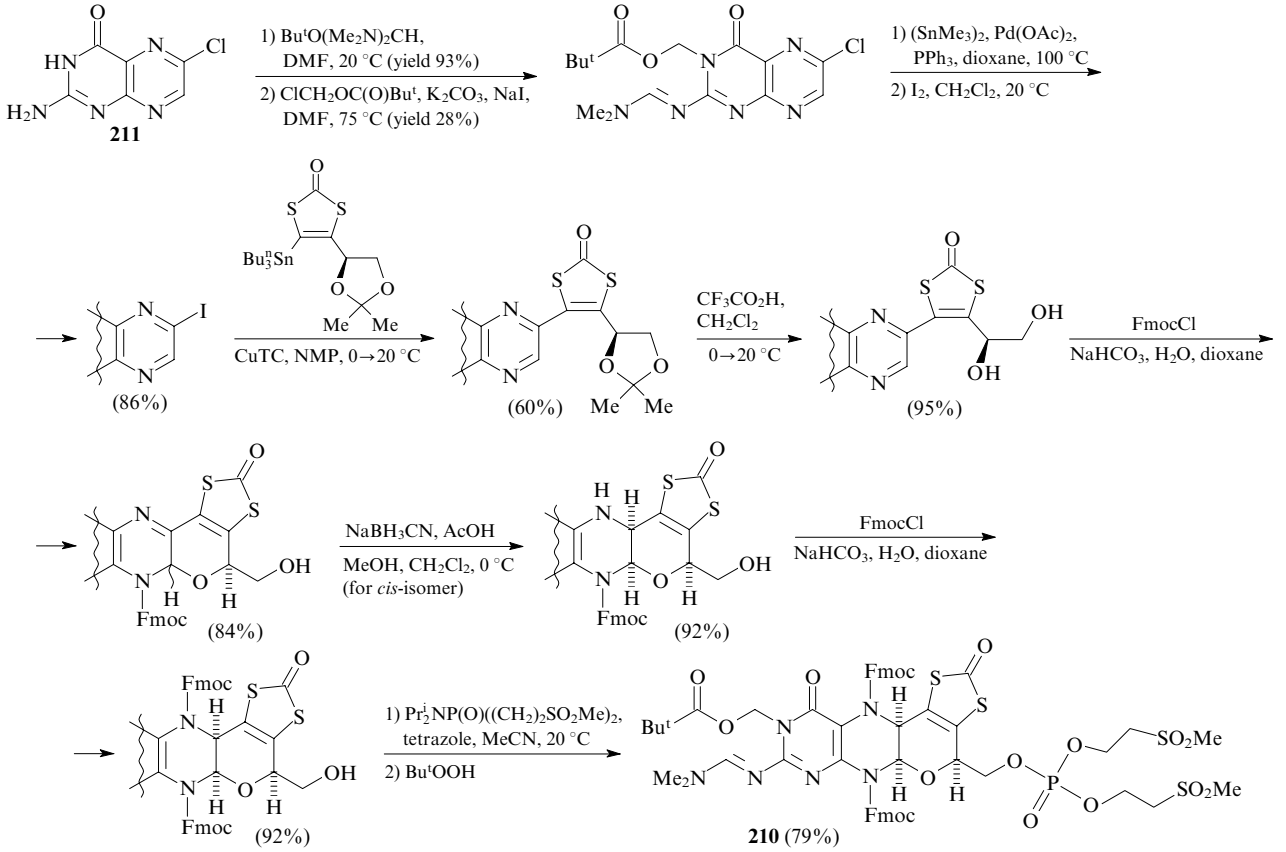
Similar cyclizations can involve other 5,6-diaminopyrimidines and phenylhydrazones of other L- and D-pentoses. Pyrano[3,2-*g*]pteridines **209** are obtained as diastereomeric mixtures.[94–97]



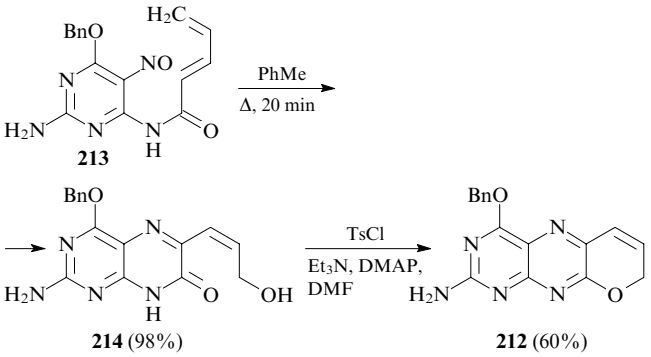
An analogue of MPT (**2**) with the protected functional groups (compound **210**) was synthesized from 6-chloropterin **211** by a multi-step procedure, which includes the introduction of protecting groups, cross-coupling reactions and redox reactions (Scheme 9).[98–100]

Pyrano[3,2-*g*]pteridine **212** was obtained in two steps from 6-amino-5-nitrosopteridine derivative **213**.[101,102] The intramolecular Diels–Alder reaction involving the nitroso group and the *cis*-diene fragment of compound **213** affords (*Z*)-6-hydroxypropenylpteridin-7(8*H*)-one **214**. Treatment of the latter with *p*-toluenesulfonyl chloride in the system Et_3N–DMAP leads to pyran ring closure and the formation of pyranopteridine **212**.

Scheme 9



CuTC is copper(I) thiophene-2-carboxylate, FmocCl is 9*H*-fluorenylmethyoxycarbonyl chloride.

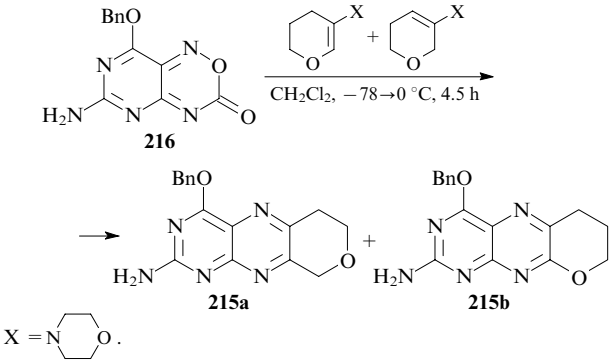


213

214 (98%) **212** (60%)

DMAP is 4-(dimethylamino)pyridine.

There are only a few examples of the synthesis of heterocyclic systems isomeric to pyrano[3,2-*g*]pteridine. Thus pyrano[4,3-*g*]pteridine **215a** and its [3,2-*g*]-isomer **215b** form in a very low yield in the [4 + 2] cycloaddition reaction involving pyrimido-1,2,5-oxadiazinone **216** and a mixture of dihydropyranylmorpholines.[102]

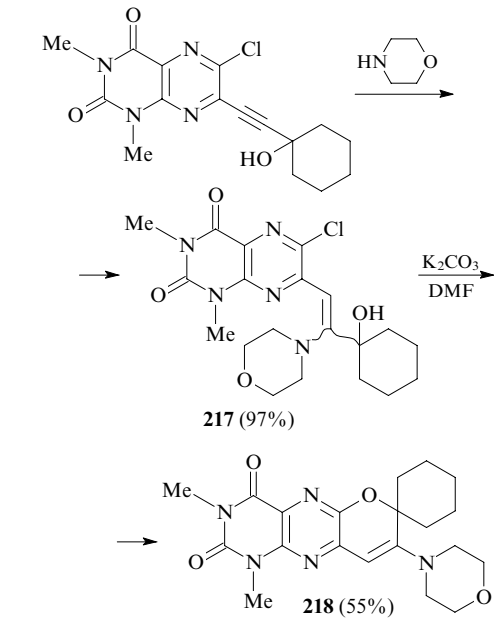


216

215a **215b**

X = N O .

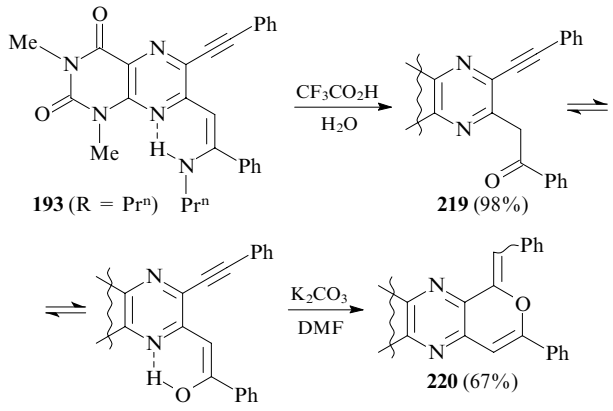
Reaction of 6-chloro-7-[(1-hydroxycyclohexyl)ethynyl]-lumazine with morpholine leads to enamine **217** in quantitative yield, which upon heating with K_2CO_3 in DMF undergoes cyclization into spiro(cyclohexane-1,7′-pyrano[2,3-*g*]pteridine) **218**.[18, 19]



217 (97%)

218 (55%)

Acid hydrolysis of enamine **193** (R = Pr^n) and subsequent base-catalyzed intramolecular nucleophilic addition of the hydroxy group of the enol form of ketone **219** to the *ortho*-C≡C bond afford 6-benzylidene-1*H*-pyrano[3,4-*g*]pteridine **220**.[18, 19]

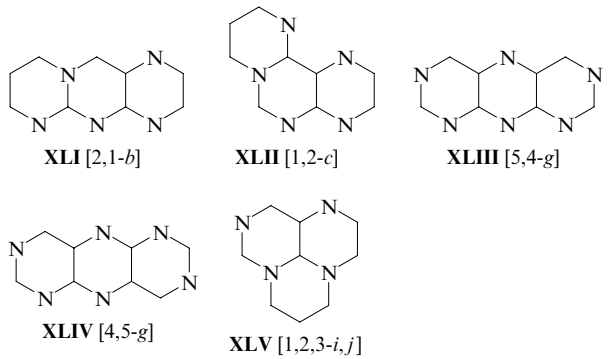


193 (R = Pr^n) **219** (98%)

220 (67%)

3. Pyrimidopteridines

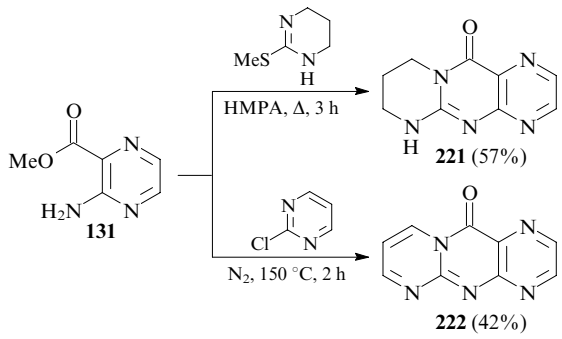
The known pyrimidopteridines are derivatives of five isomeric heterocyclic systems **XLI**–**XLV**.



XLI [2,1-*b*] **XLII** [1,2-*c*] **XLIII** [5,4-*g*]

XLIV [4,5-*g*] **XLV** [1,2,3-*i,j*]

The representatives of the system **XLI**, compounds **221** and **222**, are obtained by condensation of methyl 3-aminopyrazine-2-carboxylate (**131**) with 2-methylthio-1,4,5,6-tetrahydropyrimidine or 2-chloropyrimidine.[60] The mechanism of the cyclization is similar to that for the transformation **131** → **132** described earlier in Section III.5.

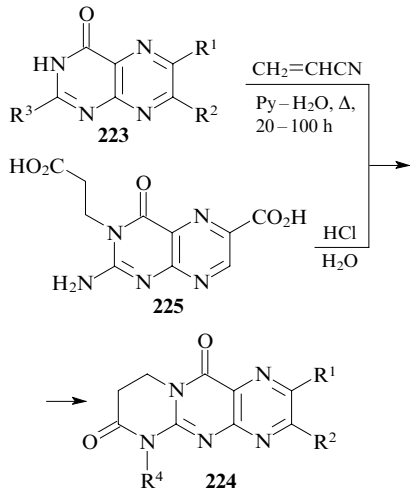


131

221 (57%)

222 (42%)

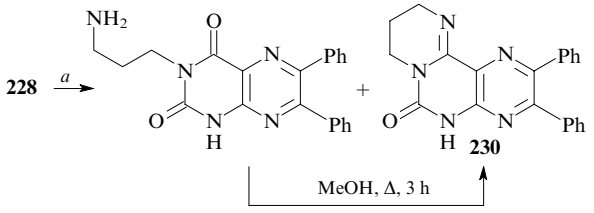
2-Amino- and 2-methylthiopteridin-4-ones **223** react with an excess of acrylonitrile in aqueous pyridine to give pyrimido[2,1-*b*]pteridines **224** in 33%–90% yields.[103] Obviously, the cyclization is preceeded by the N-cyanoethylation reaction and subsequent hydrolysis of the nitrile group into the amide. One of pyrimidopteridines **224** ($R^1 = R^4 = H$, $R^2 = CO_2H$) is obtained from **225** upon brief heating in an acidic medium.[103]



R^1 = Me, CO_2H; R^2 = H, Me;
R^3 = NH_2, SMe, NHX (X = Me, $CH_2CH_2CO_2H$); R^4 = H, X.

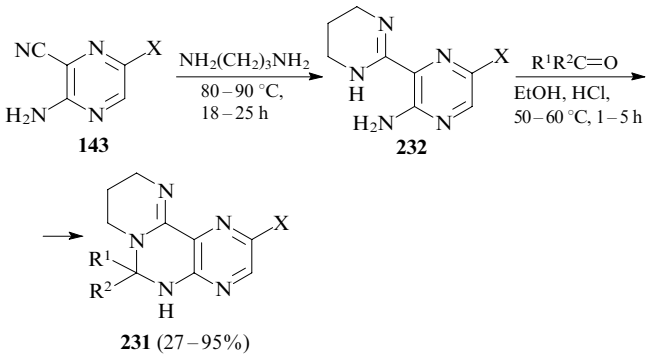
A similar procedure of construction of the pyrimido[2,1-*b*]pteridine system has been reported.[104] Treatment of (3-hydroxypropyl)pterin **226** with triphenylphosphine in carbon tetrachloride affords a mixture of o-chloropropyl derivatives **227a**,**b** (Scheme 10). In the presence of THF, the same reaction selectively affords 3-(3-chloropropyl)pterin **227b**. Under the action of alkali in aqueous ethanol, compound **227b** undergoes cyclization into pyrimido[2,1-*b*]pteridine **228**, which can be synthesized from pterin **226** through two other intramolecular reactions: 1) the base-catalyzed Dimroth rearrangement (**226** → **229**); 2) substitution of chlorine for the hydroxy group and intramolecular N-alkylation (**229** → **228**).

When pyrimido[2,1-*b*]pteridine **228** is heated in an alkaline medium, it is converted into a very unstable pyrimido[1,2-*c*]pteridine **230**.[104]



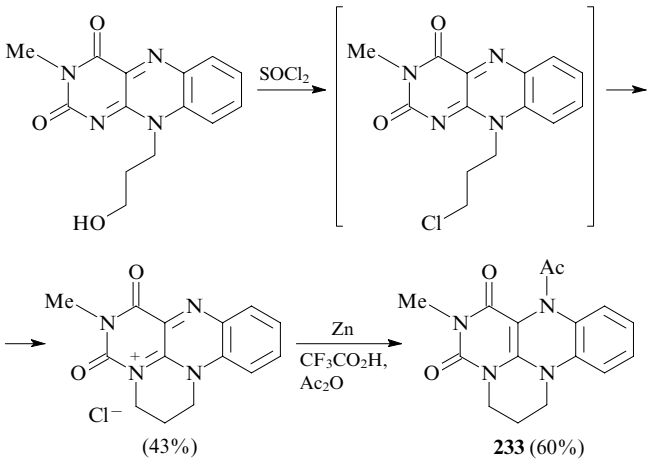
(*a*) KOH, H_2O, MeOH, Δ, 5.5 h.

Pyrimido[1,2-*c*]pteridines **231** are synthesized in two steps from 2-amino-3-cyanopyrazines **143**. The reaction of compounds **143** with 1,3-diaminopropane furnishes tetrahydropyrimidinylpyrazines **232**. The reaction of the latter with ketones in the presence of HCl leads to pyrimidopteridines **231**.[63]



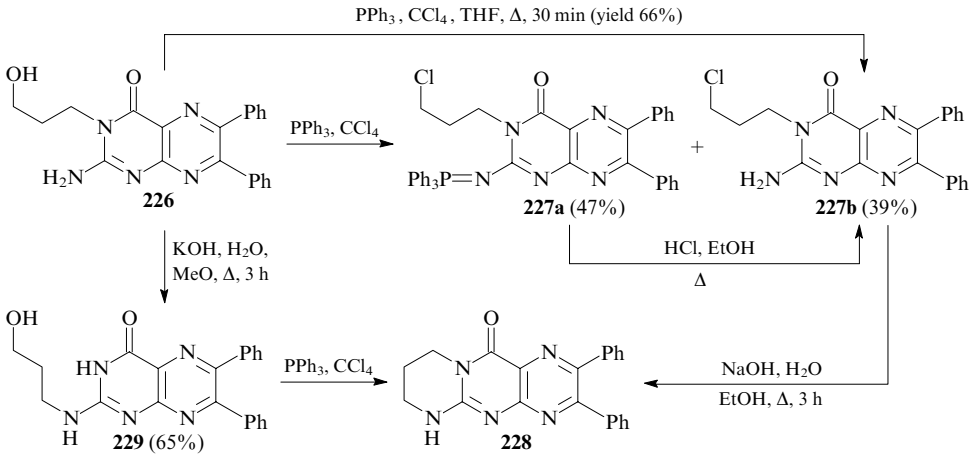
X = H, Br; R^1, R^2 = Me, Et, Ph, 4-$O_2NC_6H_4$; R^1-R^2 = $(CH_2)_5$.

Benzo[*g*]pyrimido[1,2,3-*i*,*j*]pteridine-5,7(6*H*,8*H*)-dione **233** is synthesized similarly to benzo[*g*]imidazo[1,2,3-*i*,*j*]pteridine-4,6(5*H*,7*H*)-diones **151**.[66]



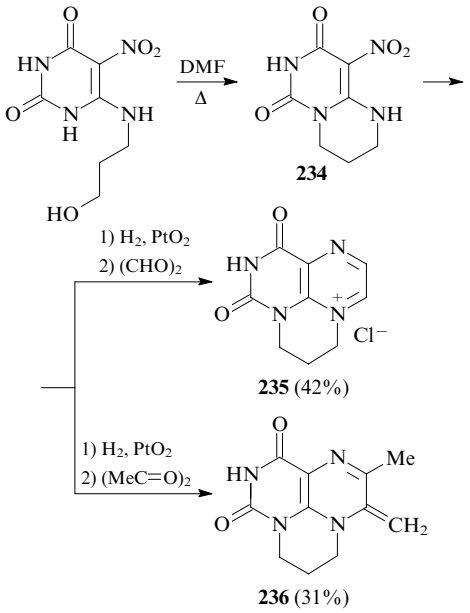
Heating of 6-(γ-hydroxypropylamino)-5-nitrouracil in DMF gives rise to pyrimidopyrimidines **234**, which is then converted into *peri*-fused pyrimido[1,2,3-*i*,*j*]pteridines **235**, **236** by consecutive reduction of the nitro group and

Scheme 10



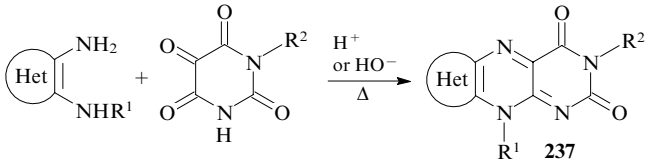
(65% from compound **227b**; 20% from compound **229**)

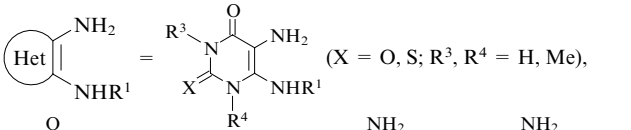
condensation of the formed *ortho*-diamine with 1,2-dicarbonyl compounds.[65]



The majority of publications of the 1950–1980s are devoted to pyrimido[5,4-*g*]- and pyrimido[4,5-*g*]pteridines. These heterocyclic systems are regarded as flavin models, their redox properties were studied.

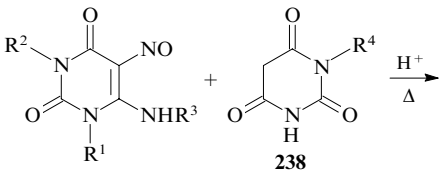
A general route to pyrimido[5,4-*g*]pteridines **237** is the condensation of the corresponding diaminopyrimidines with alloxanes. The reaction is both acid- and base-catalyzed. In some cases, together with compound **237**, small amount of its [4,5-*g*]-isomer is formed.[105–113] Instead of alloxane, 5,5-dihalobarbituric acids and 2-amino-5,5-dichloropyrimidine-4,6(3*H*,5*H*)-dione.[108]

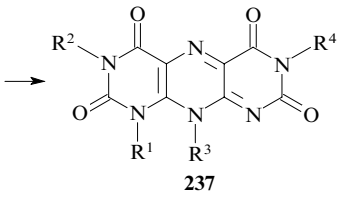




R^1 = Me, Et, CH_2CH_2OH, D-ribityl, D-mannityl, D-sorbityl;
R^2 = H, Me.

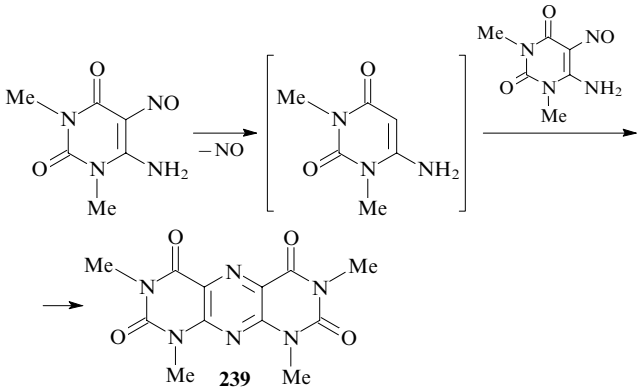
Pyrimido[5,4-*g*]pteridines are also formed in the reaction of 6-amino-5-nitrosouracils with barbituric acids **238**.[108, 109, 112]



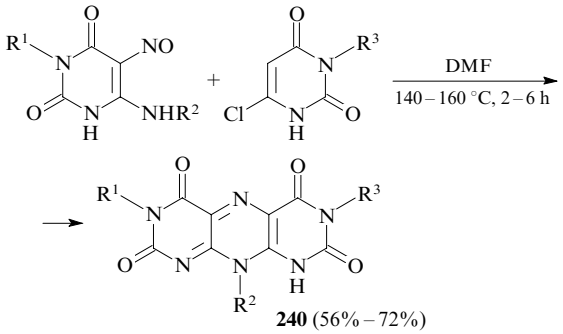


R^1, R^2, R^4 = H, Me; R^3 = H, Me, CH_2CH_2OH.

On melting, 6-amino-1,3-dimethyl-5-nitrosouracil affords tetramethylpyrimido[5,4-*g*]pteridine **239**.[114]

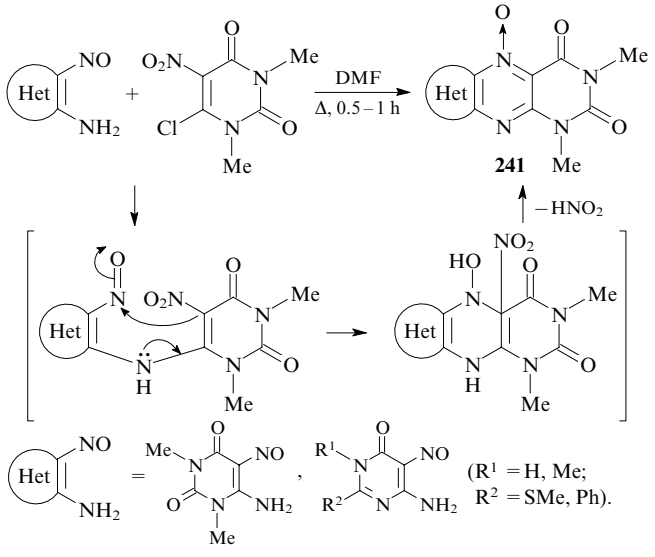


The reaction of 6-alkylamino-5-nitrosouracils with 6-chlorouracils results in pyrimidinopteridines **240**.[115]



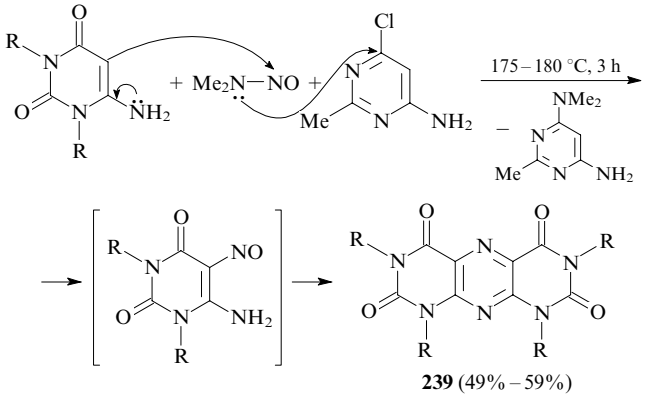
R^1, R^3 = H, Me; R^2 = Me, Pr^n, Bu^n, n-C_8H_{17}, n-$C_{12}H_{25}$.

The condensation of 6-amino-5-nitrosopyrimidinones with 6-chloro-1,3-dimethyl-5-nitrouracil affords pyrimidopteridine *N*(10)-oxides **241**.[116] It was suggested that the



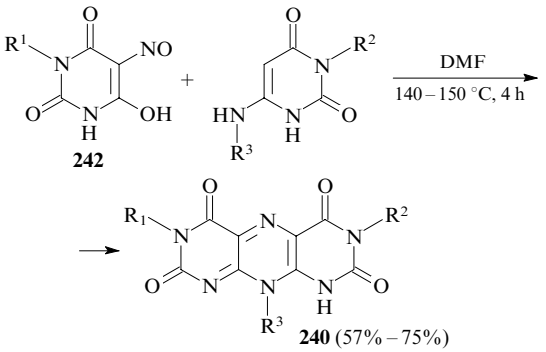
reaction mechanism includes aminodehalogenation with subsequent intramolecular nucleophilic attack at the nitroso group with elimination of HNO_2.

A three-component reaction leading to pyrimido[5,4-*g*]pteridines was described.[117] 6-Aminouracils, 4-amino-6-chloro-2-methylpyrimidine and *N*-nitrosodimethylamine serve as the starting compounds. The latter nitrosates the starting uracil and simultaneously aminates the chloropyrimidine. Two molecules of the resulting aminonitrosouracil then react with each other to form pyrimido[5,4-*g*]pteridine **239**.



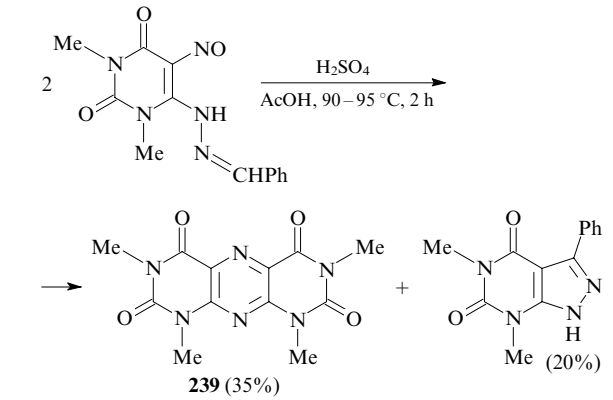
R = Me, Et.

6-Alkylamino- and 6-arylaminouracils react with 5-nitrosobarbituric acids **242** on heating in DMF giving rise to 10-substituted pyrimido[5,4-*g*]pteridines **240**.[118]

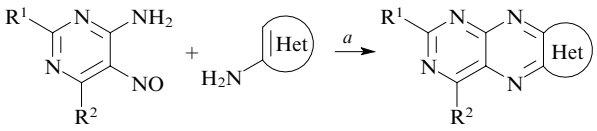


R^1, R^2 = H, Me; R^3 = Me, Pr^n, n-C_8H_{17}, n-$C_{12}H_{25}$, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-$HO_2CC_6H_4$, 2,4-$Me_2C_6H_3$.

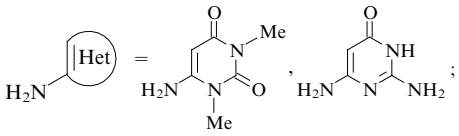
The major self-condensation product of 6-benzylidenehydrazino-1,3-dimethyl-5-nitrosouracil in acidic media is compound **239**.[119]



Pyrimidopteridines **243** of the isomeric [4,5-*g*]-series are obtained in the reaction of 4-amino-5-nitrosopyrimidines with 6-aminopyrimidinones.[120, 121]

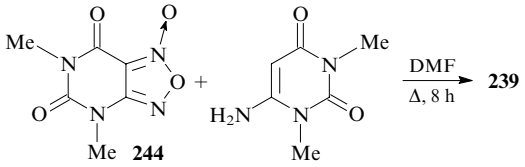


R^1 = NH_2, Me; R^2 = NH_2, OH;



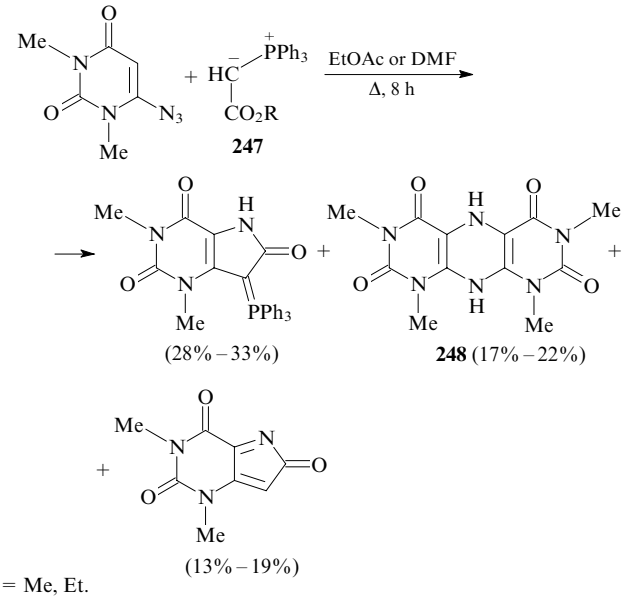
(*a*) AcOH, Δ, 3 h or TsOH–AcOH, 113 °C, 20 h.

Thermal cyclization of furazanopyrimidinedione *N*-oxide **244** with 6-amino-1,3-dimethyluracil affords 67% of pyrimido[5,4-*g*]pteridine **239**.[122]



Furoxane **244** undergoes self-condensation in the presence of alkyl- or arylamines or $Na_2S_2O_4$ to produce again compound **239**.[122–124] However, the reaction is not straightforward: along with pyrimidopteridine **239**, significant amounts of other products are formed (*e.g.*, compounds **245**, **246**) (Scheme 11).

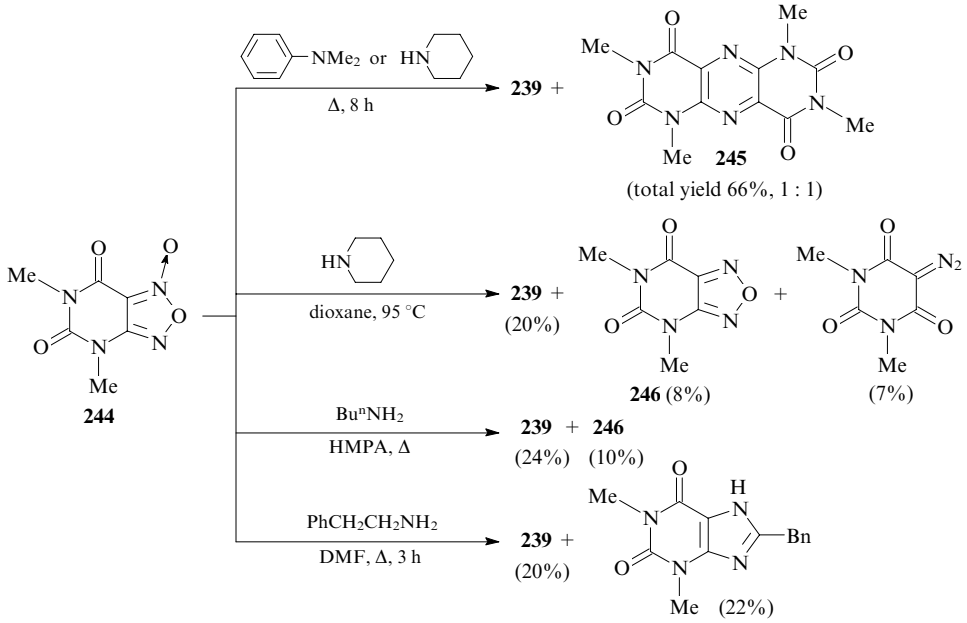
Compound **239** is also formed upon thermolysis of 6-azido-1,3-dimethyluracil.[125] Prolonged heating of this azide with the Wittig reagent **247** in ethyl acetate or DMF gives dihydropyrimidopteridine **248** as one of the products.[126]

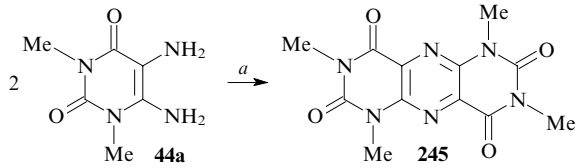


R = Me, Et.

5,6-Diaminouracil **44a** is transformed into pyrimido[4,5-*g*]pteridine **245** upon heating in an acidic medium.[127, 128]

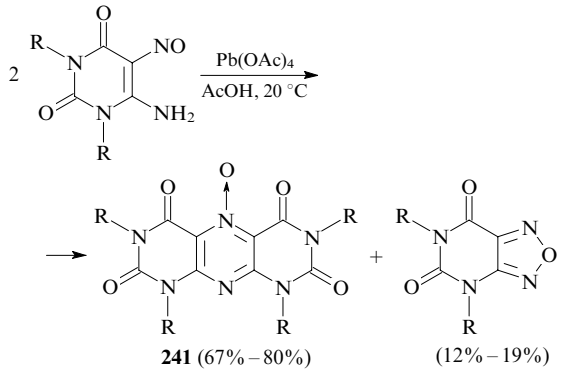
Scheme 11





(*a*) 1) HCl, H_2O, Δ, 12 h; 2) CCl_3CO_2H, DMF, Δ, 3 h; 3) 2-$NH_2C_6H_4CO_2H$, 200 °C, 1 h.

Oxidation of 6-amino-5-nitrosouracils with lead tetraacetate in acetic acid affords a mixture of pyrimido[5,4-*g*]pteridine *N*(10-)-oxides **241** and furazanopyrimidinediones.[129–131] The mechanism of this transformation was studied.[131] Compounds **241** possess unique properties among heterocyclic *N*-oxides: in photochemical processes, they can be acceptors of electrons, oxygen transfer agents or dehydrating agents depending on the nature of the substrate.[131] Many of them exhibit cytotoxic, antibacterial and other types of biological activity.[131]

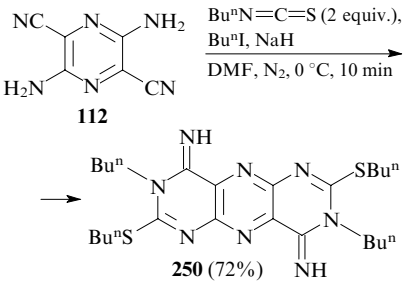


R = Me, Ph.

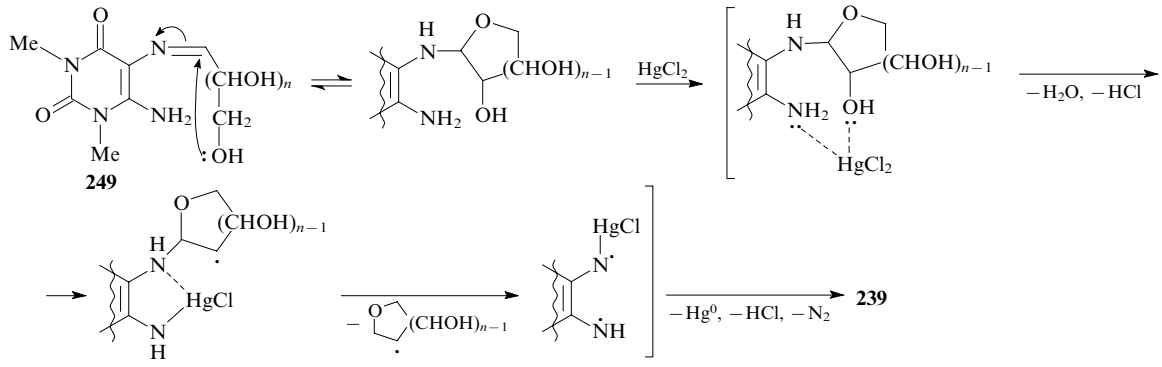
Oxidation of 5,6-diaminouracils with aqueous $FeCl_3$ gives compounds **239** devoid of the *N*-oxide group.[132]

Shiff bases **249**, derived from 5,6-diaminouracil **44a** and D-glucose, D- or L-arabinose, react with mercuric chloride in DMSO with the formation of compound **239** (Scheme 12).[133, 134] It was estimated that the reaction proceeds by a radical mechanism. The role of oxidant can be played by nickel peroxide.[135]

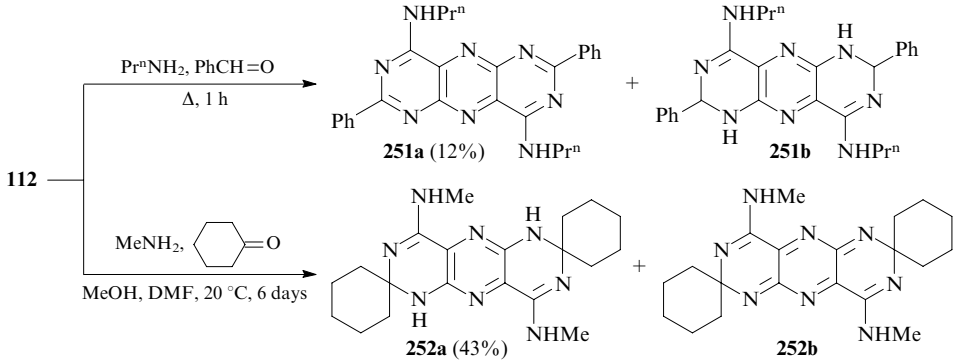
Pyrimido[4,5-*g*]pteridines are also synthesized from pyrazine derivatives. Treatment of 2,5-diamino-3,6-dicyanopyrazine (**112**) with butyl isothiocyanate in the presence of sodium hydride and butyl iodide results in pyrimido[4,5-*g*]pteridine **250**.[54]



Scheme 12



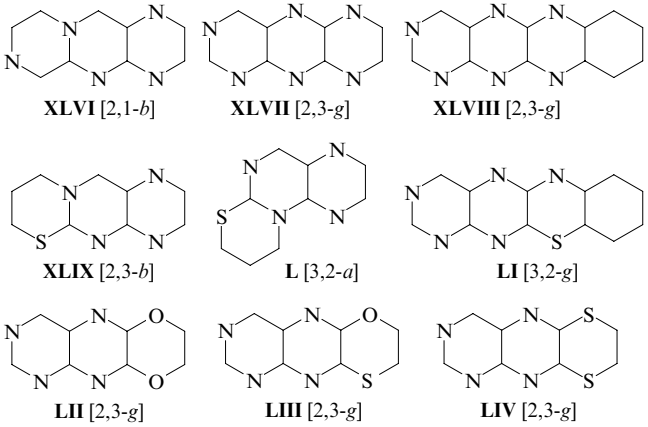
Scheme 13



In the reaction of pyrazine **112** with benzaldehyde and propylamine, a muxture of products **251a**,**b** is formed,[54] while cyclohexanone and methylamine give spiro compounds **252a**,**b** (Scheme 13).

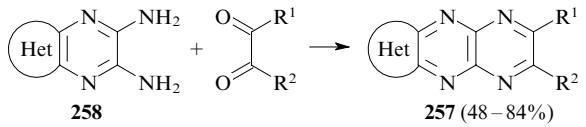
4. Pteridines fused to other six-membered heterocycles

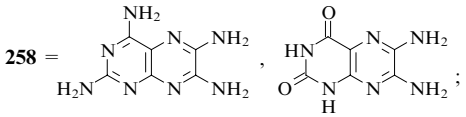
This Section contains a brief review of derivatives that belong to heterocyclic systems of the types **XLVI**–**LIV**.



A general method for the synthesis of pyrazino-, quinoxalino-, 1,4-dioxino-, 1,4-oxathiino- and 1,4-dithiino[2,3-*g*]pteridines **253**–**256** is based on the tandem addition reaction of bifunctional nicleophiles to C(6)- and C(7)-unsubstituted ethyl pteridine-4-carboxylate (Scheme 14).[136]

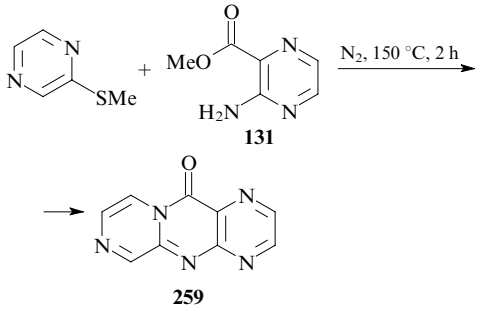
Pyrazino[2,3-*g*]pteridines **257** are obtained by fusion of 6,7-diaminopteridines **258** with 1,2-dicarbonyl compounds.[51,52] The reaction with *tert*-butylglyoxal is carried out by heating the reactants in aqueous ethanol in the presence of trifluoroacetic acid.[52]





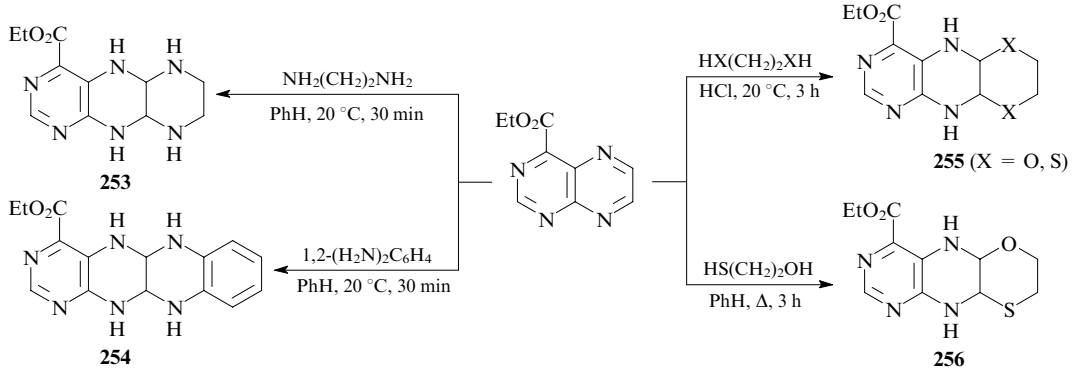
$R^1 = R^2 = OH, Cl, Ph; R^1 = H, R^2 = Bu^t; R^1 = OH, R^2 = CO_2Et.$

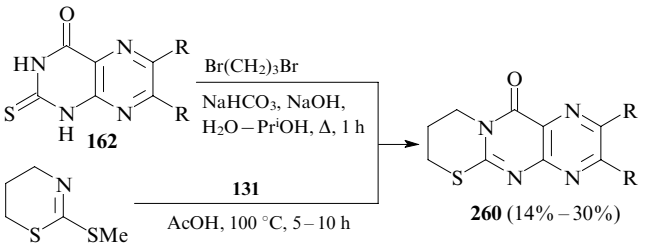
The reaction of 3-aminopyrazine-2-carboxylate **131** with 2-methylthiopyrazine leads to pyrazino[2,1-*b*]pteridine **259**.[60]



The base-catalyzed condensation of 2-thiolumazine **162** (R = H) with 1,3-dibromopropane affords 1,3-thiazino[2,3-*b*]pteridine **260**.[69,70] A similar reaction of compound **162** (R = Me) results in a mixture of isomeric 1,3-thiazino[2,3-*b*]- and 1,3-thiazino[3,2-*a*]pteridines, which are difficult to separate.[69] A more efficient route to thiazinopteridines **260** is the reaction of methyl 3-aminomethylpyrazine-2-carboxylate (**131**) with 2-methylthio-5,6-dihydro-4*H*-1,3-thiazine.[60]

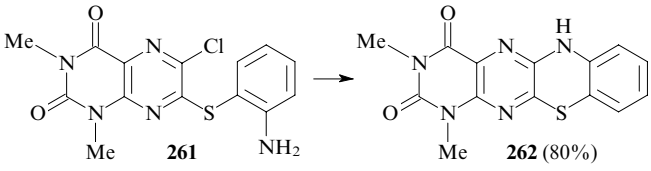
Scheme 14





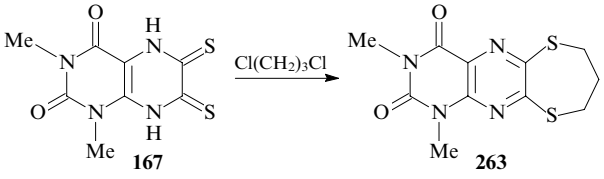
R = H, Me.

Heating of 7-(2-aminophenyl)thio-6-chlorolumazine **261** leads to intramolecular aminodehalogenation and formation of benzo-1,4-thiazino[3,2-*g*]pteridine **262**.[71]

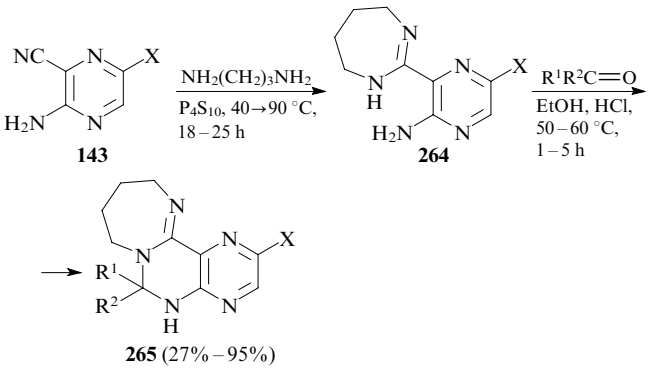


V. Pteridines fused to seven-membered heterocycles

Only two syntheses of seven-membered heterocycles fused to pteridines have been published. The action of 1,3-dichloropropane on 6,7-dithiolumazine **167** affords compound **263**.[38]



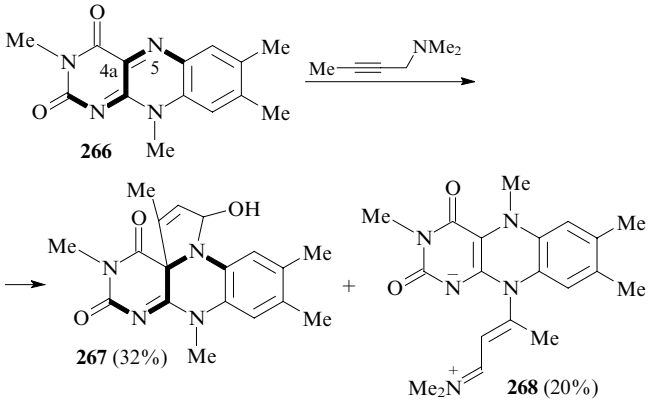
The condensation of *o*-aminocyanopyrazines **143** with 1,3-diaminopropane results in compounds **264**, which undergo cyclization into 1,3-diazepino[1,2-*c*]pteridines **265** when treated with ketones in acidic media.[63]



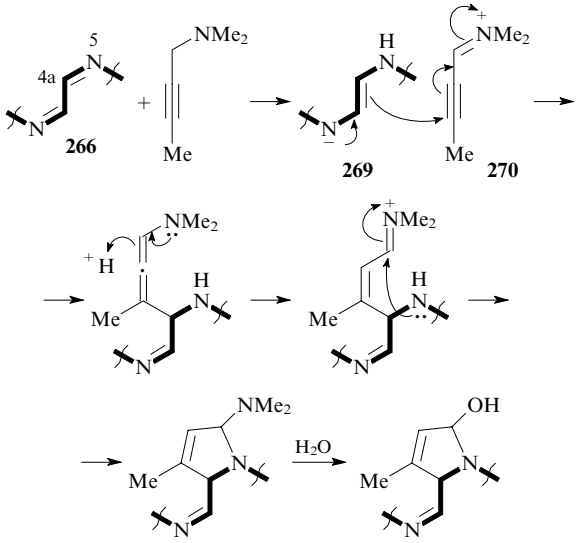
X = H, Br; R^1, R^2 = Me, Et, Ph, 4-$O_2NC_6H_4$, *etc.*

VI. Miscellaneous polyheterocyclic pteridine derivatives

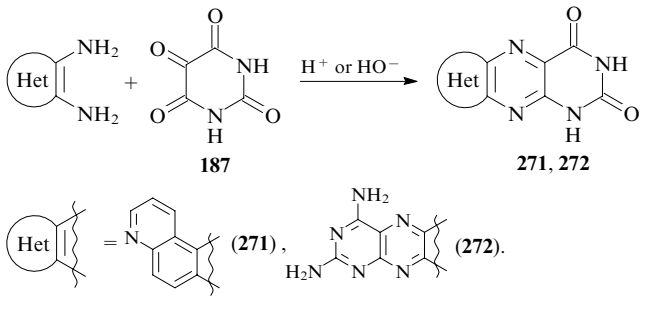
Besides indolo-, benzofuro-, benzimidazo-, quinoxalino- and benzothiazinopteridines described in the previous sections, syntheses of other polynuclear pteridines have been documented. For example, irradiation of a mixture of 3-methyllumiflavin (**266**) with *N*,*N*-dimethyl-2-butynylamine in acetonitrile in the presence of phosphate buffer (pH 7.2), affords pyrolloisoalloxazine **267** along with flavocyanine **268** (the fragments of compounds **266** and **267** that are considered below when discussing the reaction mechanism are highlighted in bold).[137]



The reaction begins with two-electron transfer from the tertiary amine to 3-methyllumiflavin (**266**) with subsequent proton migration and formation of the intermediate ions **269** and **270**. Nucleophilic addition of anion **269** to the C≡C triple bond of cation **270** results in pyrrole ring closure.

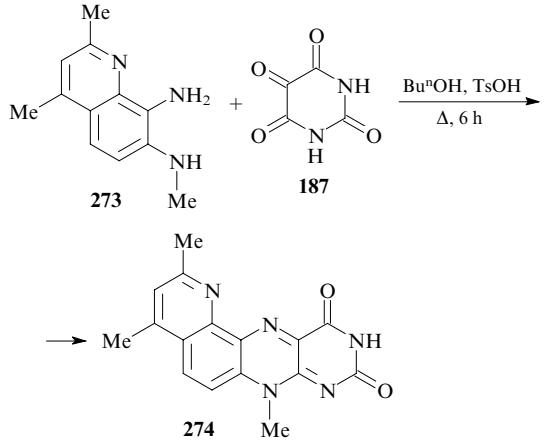


Condensation of *o*-diaminoarenes with alloxane (**187**) affords quinolino[5,6-*g*]pteridine-9,11(8*H*,10*H*)-dione (**271**)[138] and 7,9-diaminopteridino[6,7-*g*]pteridine-2,4(1*H*,3*H*)-dione (**272**).[51]

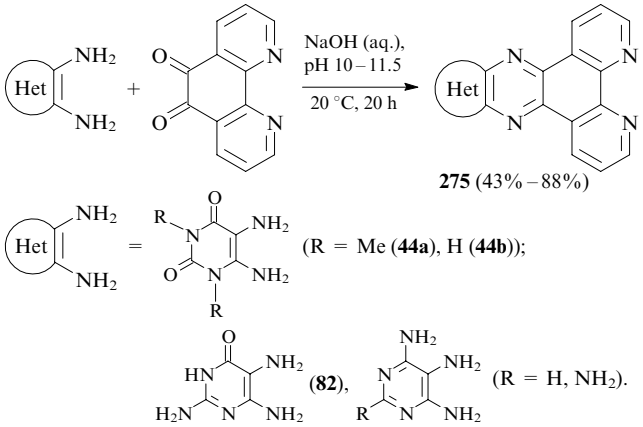


A similar reaction of 7,8-diaminoquinoline **273** with alloxane results in 2,4,7-trimethylquinolino[8,7-*g*]pteridine-

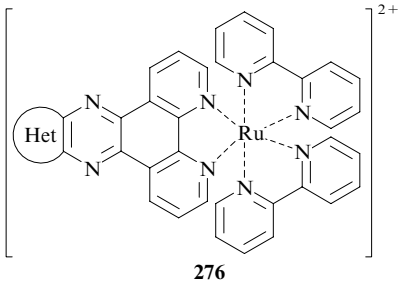
9,11(7*H*,10*H*)-dione (**274**).[139] Compound **274** and its 10-alkyl derivatives[140] contain an azaphenanthroline fragment and can form coordination compounds with metal ions. Such complexes can serve not only as models for metalloflavoproteins, but also can be employed as *in vitro* oxidation catalysts.



Coupling of 5,6-diaminopyrimidines with phenanthroline-5,6-dione yields pteridino[6,7-*f*]-1,10-phenanthrolines **275**.[141–144] Compounds **275**, like flavins, are reversibly reduced on a glassy carbon electrode in water (one- and two-electron reduction of the pyrazine ring) and are useful mediators of various electrochemical processes.



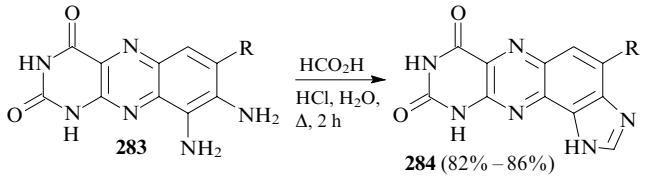
Ruthenium complexes of pteridinophenanthrolines **275**, *e.g.*, complex **276**, behave as intercalators and can be used as sensitive luminescent probes for DNA.[145]



The reaction of tetraaminopyrimidine with 17,18-dioxotetraarylporphyrin **277** results in pteridino[2,3-*b*]porphyrin **278**, which was studied as a model of a rigid non-covalent charge transfer (electron transfer) system (Scheme 15).[146]

Condensation of 5-aminocytidine with isatines **279** in aqueous ethanol with heating is accompanied by intramolecular nucleophilic addition of the OH group of intermediate **280** at the C(4) atom of the pyrimidine ring, which leads to 1,5,3-dioxazepino[3,2-*c*]indolo[3,2-*g*]pteridines **281**.[147–149] The latter are smoothly converted to compounds **282**, which exhibit moderate anti-leukemic activity (Scheme 16).

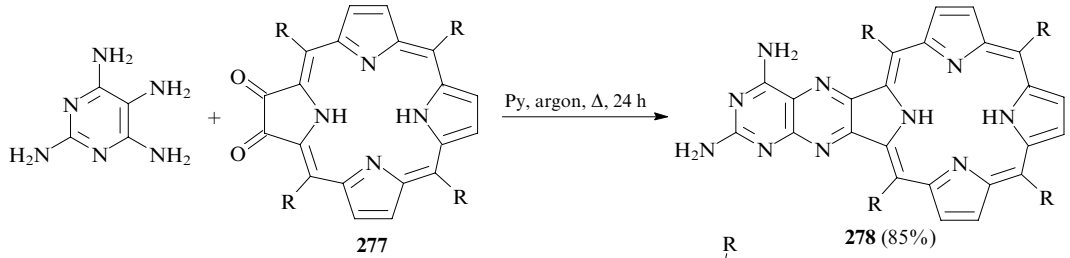
Diamines **283** upon heating in formic acid are transformed to imidazo[4,5-*j*]alloxazines **284**.[150]



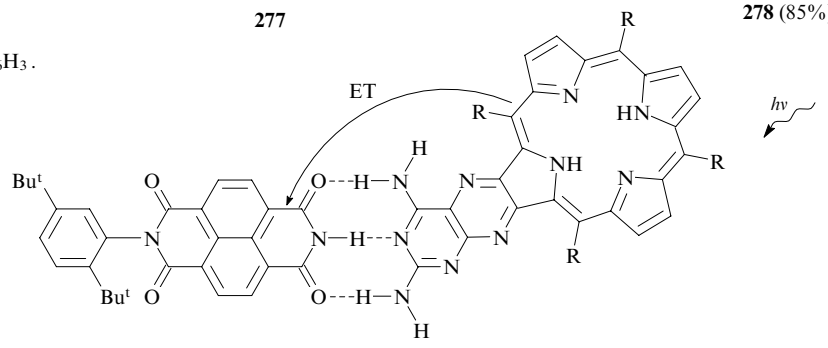
R = H, Me.

Lumazine-6,7-dithione (**167**) undergoes self-condensation in triethylamine resulting in a mixture of pentacyclic compounds **285a**,**b**.[38]

Scheme 15

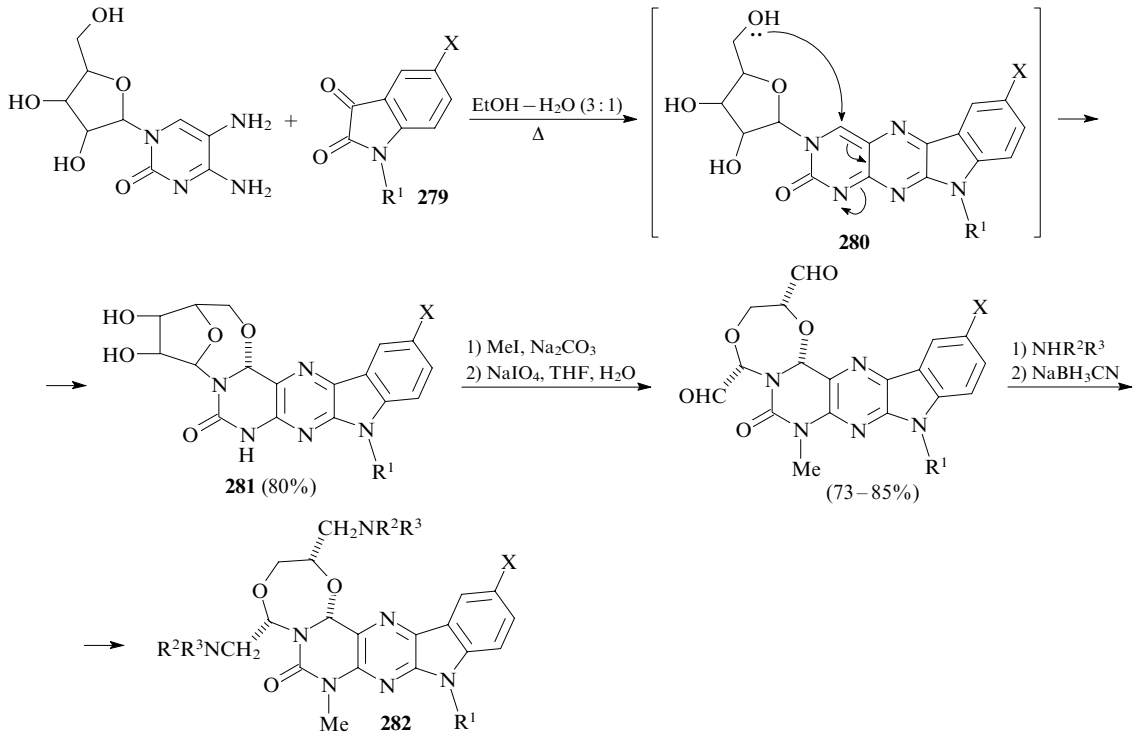


R = 3,5-$Bu^t_2C_6H_3$.

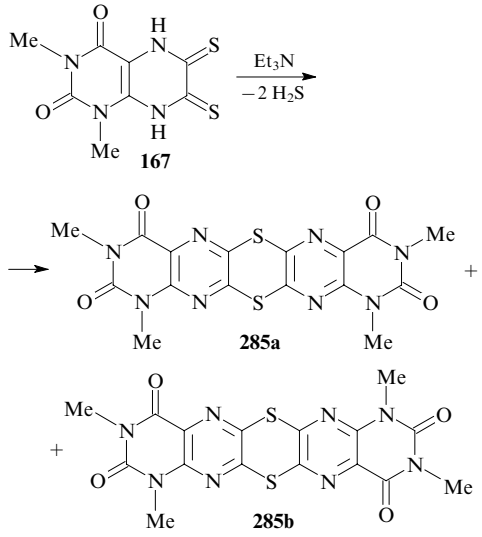


Model system of charge transfer

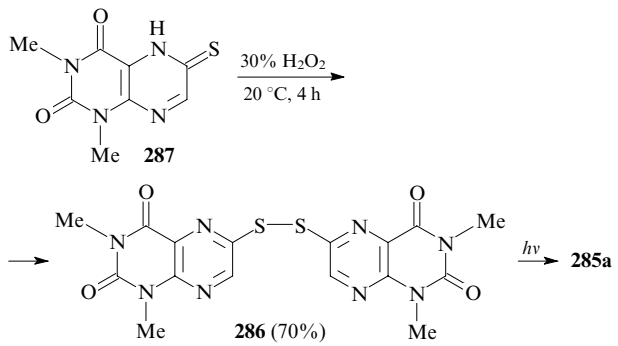
Scheme 16



R^1 = H, Me; X = H, F; NR^2R^3 = NEt_2, NNMe, $NMeR^4$ (R^4 = $(CH_2)_3NMe_2$, NNMe).

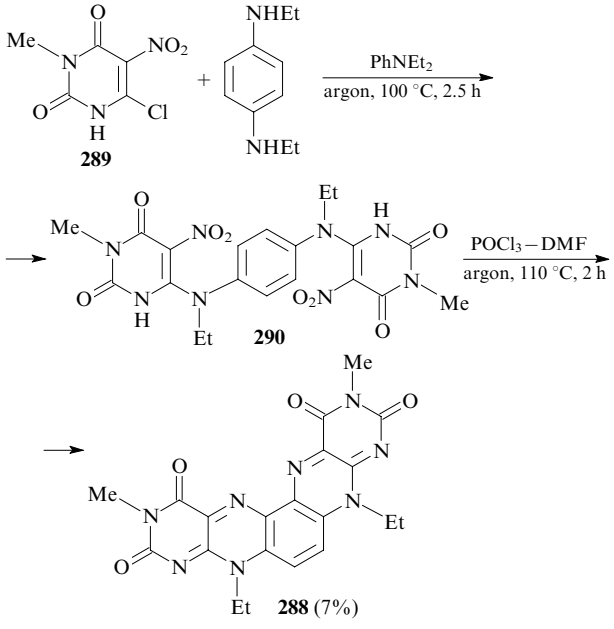


Compound **285a** is also formed when dipteridinyl disulfide **286** derived from thione **287** upon oxidation is exposed to prolonged irradiation.[151]



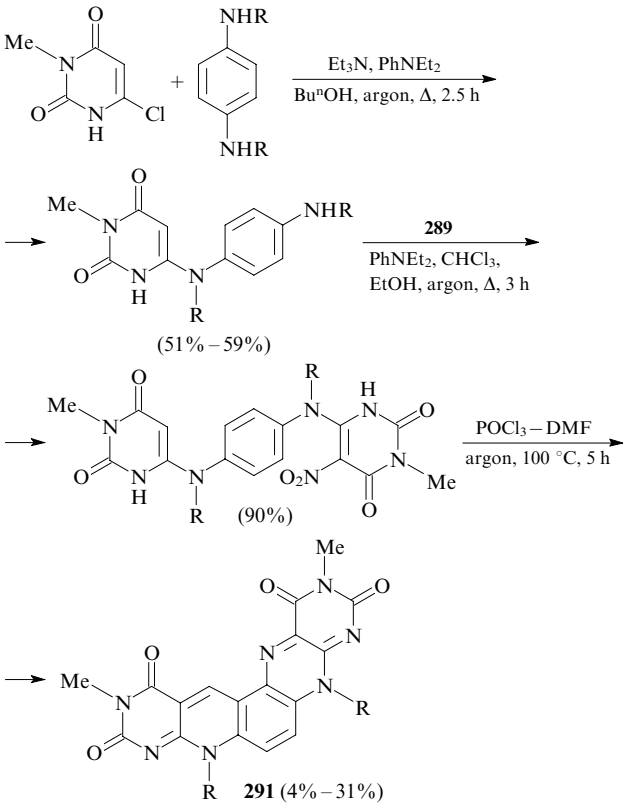
The isomeric lumazine-7-thione undergoes a similar cyclization giving rise to dithiinodipteridine **285b**.[151] 6,7-Dichloro-1,3-dimethyllumazine (**15**), when heated with thiourea in ethanol and then in DMF, gives a mixture of compounds **285a**,**b**.[151]

Pentacyclic angular benzodipteridines **288** were obtained in two steps from 6-chloro-5-nitrouracil **289** and *N*,*N*′-diethyl-*p*-phenylenediamine. Heating of compound **290**, which is formed in the first step, with a mixture $POCl_3$–DMF results in closure of two pyrazine rings and formation of benzodipteridines **288**.[152]



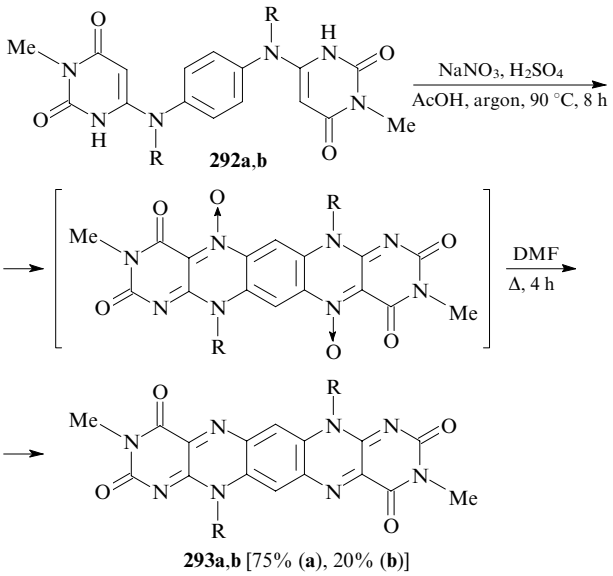
Deaza-derivatives of compound **288**, pentacycles **291**, are obtained in a similar way using 6-chlorouracil, *N*,*N*′-

dialkyl-*p*-phenylenediamine and chloronitrouracil **289** as the starting compounds.[152]



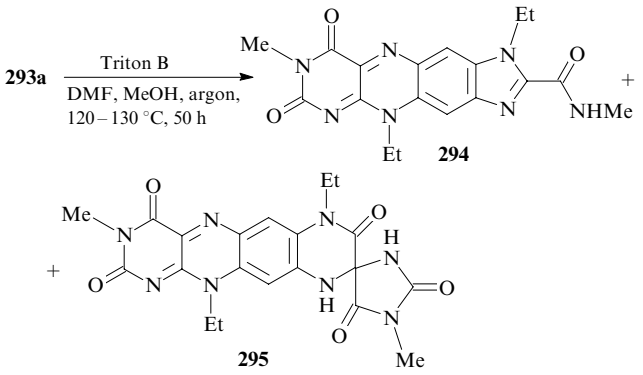
R = Et, n-C_8H_{17}, n-$C_{12}H_{25}$.

Nitration of diamines **292a**,**b** is accompanied by heterocyclization leading to linear benzodipteridines **293a**,**b**.[152]

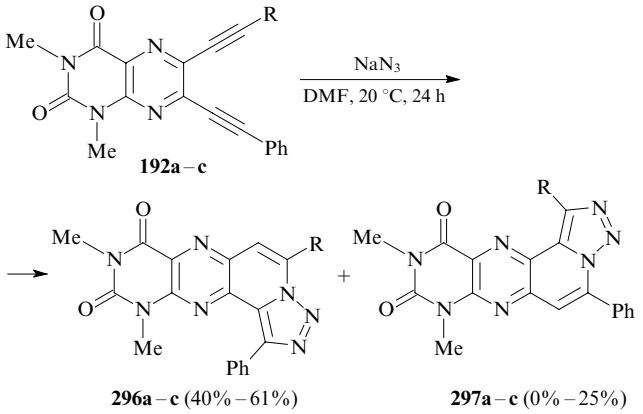


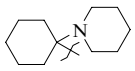
R = Et (**a**), n-C_8H_{17} (**b**).

Heating of benzodipteridine **293a** with Triton B in DMF results in recylization of one of the pyrimidine rings and formation of a mixture of compounds **294** and **295**.[152]

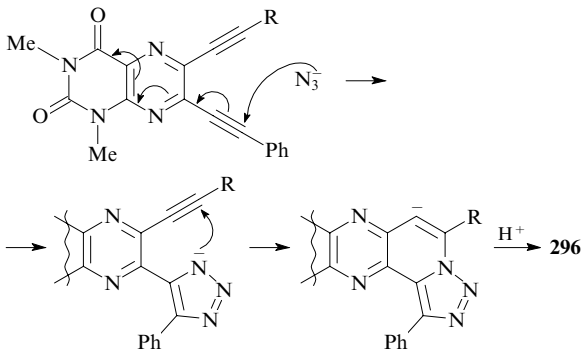


Treatment of 6,7-dialkyllumazines **192a**–**c** with sodium azide in DMF affords 1,2,3-triazolo-[1′,5′;1,2]pyrido[4,3-*g*]pteridines **296a**–**c** along with isomeric compounds **297a**–**c**.[153]



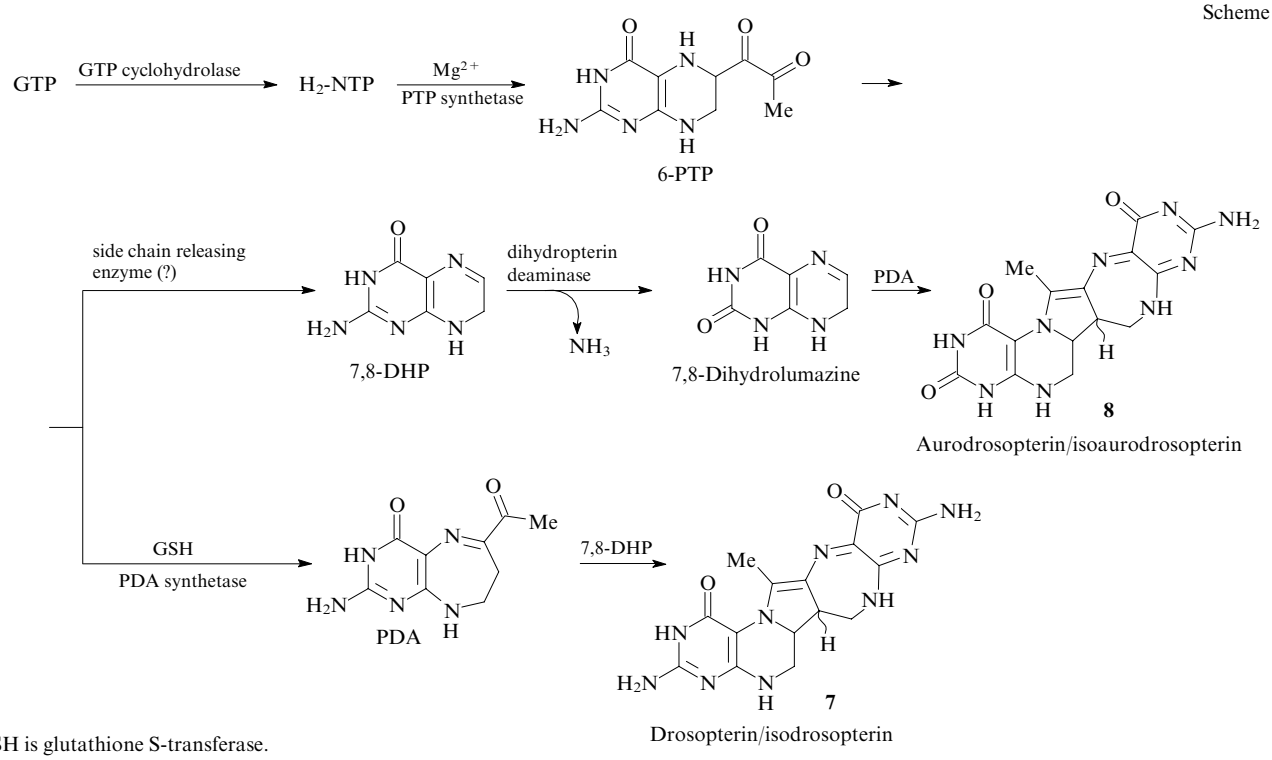
R = Ph (**a**), n-C_6H_{13} (**b**),  (**c**).

The mechanism of this tandem cyclization can be represented as follows:



The most complex of all fused structures of the pteridine series are probably the pigments of fruit-fly *Drosophila melanogaster* eyes mentioned in the Introduction, *i.e.*, drozopterin (**7**), aurodrozopterin (**8**) and their enantiomers.[8–10] Their biosynthesis[10] includes transformations of guanosine triphosphate (GTP) into 7,8-dihydroneopterin triphosphate (H_2-NTP) and then into 6-pyruvoyltetrahydropterin (6-PTP). One of the subsequent enzymatic reactions results in conversion of 6-PTP into pyrimidinodiazepine (PDA),

Scheme 17

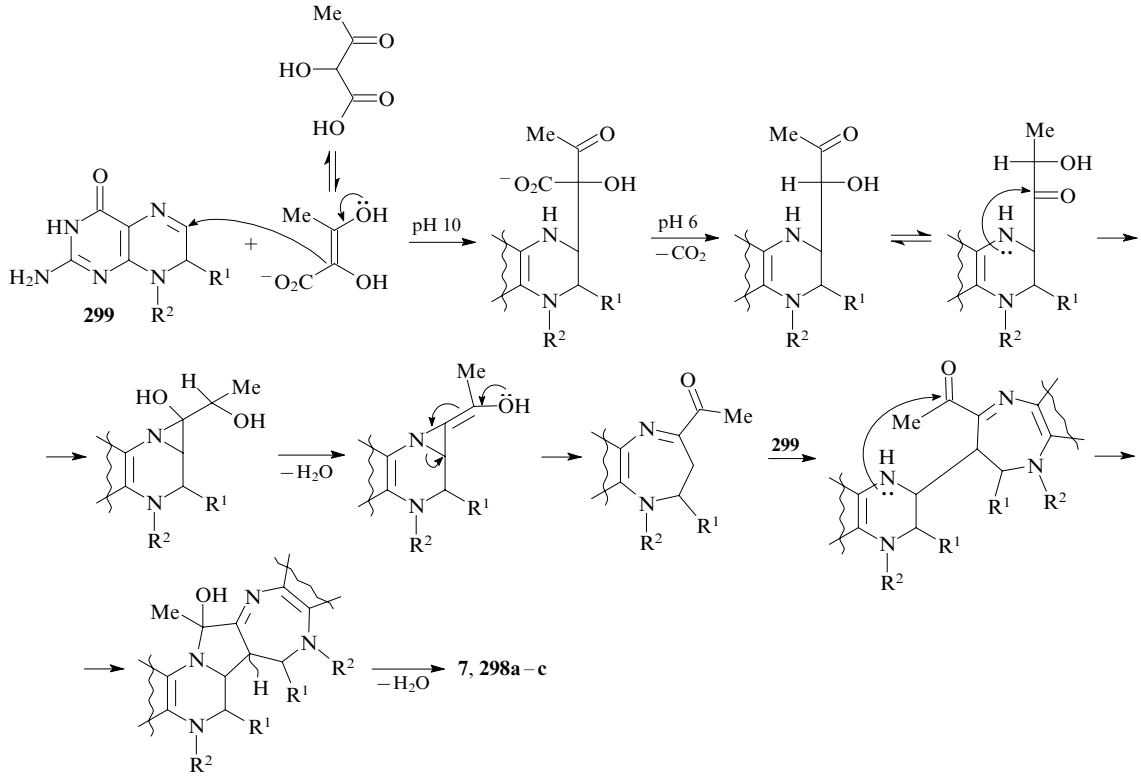


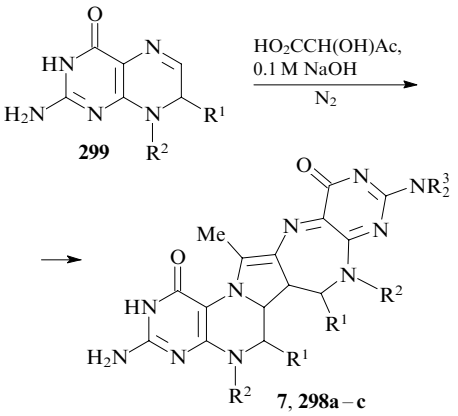
GSH is glutathione S-transferase.

and another one furnishes 7,8-dihydropterin (7,8-DHP). Non-enzymatic coupling of PDA with 7,8-dihydropterin results in drozopterin and its enantiomer isodrozopterin. The formation of aurodrozopterin and isoaurodrozopterin is preceeded by deamination of 7,8-dihydropterin. The reaction product is 7,8-dihydrolumazine, which then undergoes condensation with PDA giving the minor pigments aurodrozopterin and isoaurodrozopterin (Scheme 17).

It is truly amazing that compounds of such a complex structure, **7** and **298a**–**c**, can be synthesized by condensation of 7,8-dihydropterins **299** with 2-hydroxy-3-oxobutanoic acid in alkaline media.[8, 154]

Scheme 18





Compound	R^1	R^2	R^3	Yield (%)
7	H	H	H	45
298a	H	Me	H	5
298b	Me	H	H	3.6
298c	H	Me	Me	10

The supposed mechanism of this transformation is presented in Scheme 18.

The synthesis of aurodrozopterin (**8**) was carried out by condensation of 6-acetyl-2-amino-3,7,8,9-tetrahydro-4*H*-pyrimido[4,5-*b*]-1,4-diazepin-4-one with 7,8-dihydroalumazine in HCl at pH 3.[155]

* * *

To conclude this review, we should say that the studies in the pteridine chemistry are being more and more integrated with the studies of their biochemistry, pharmacology and medicinal applications. The development of various synthetic approaches to pteridines fused to heterocycles lays a firm basis for their practical application, in particular in medicinal chemistry.

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