Polish J. Chem., **75**, 1661–1687 (2001) **REVIEW ARTICLE**

Approaches to Fused Pyrimidine Derivatives by the Pyrimidine Ring Construction and Their Application to Synthesis of Purines

by S. Ostrowski

[a)]*Institute of Chemistry, University of Podlasie, ul. 3-Maja 54, PL-08-110 Siedlce, Poland*
fax: (+48)-25-643-1069, e-mail: stan@ap.siedlce.pl
[b)]*Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52,*
PL-01-224 Warszawa, Poland; fax: (+48)-22-632-6681, e-mail: stan@icho.edu.pl

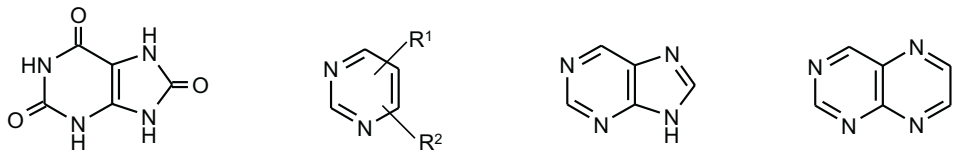
(Received September 29th, 2000; revised manuscript May 25th, 2001)

Fused pyrimidines can be easily synthesized from the corresponding *ortho*-aminobenzylamine derivatives or their heteroanalogues. *ortho*-Nitrobenzaldehydes, *ortho*-aminobenzaldehydes, anthranilic acid derivatives, *ortho*-isocyanatobenzoates, *ortho*-aminobenzonitriles, *ortho*-isocyanatobenzonitriles, *N*-substituted anilines, *ortho*-halobenzoates, benzenediazonium salts, (2-nitroaryl)methylisocyanides, and derivatives of the all above compounds were also used for this purpose. Often the limiting factor for the above syntheses is the difficulty encountered in obtaining the key intermediates or their precursors. Recently, this problem was successfully solved in several ways by the use of Vicarious Nucleophilic Substitution of Hydrogen (VNS). As a result, many quinazolines and new bicyclic and tricyclic heteroaromatic compounds and their mono-*N*-oxides were obtained, when starting from aromatic nitro compounds. These approaches were also successfully applied to the synthesis of purines with the use of 4-nitroimidazole derivatives.

Key words: fused pyrimidines: purines, quinazolines, perimidines, pteridines; *N*-oxides; Vicarious Nucleophilic Substitution

1. Introduction

Fused pyrimidine chemistry began in 1776, when Scheele isolated uric acid (**1**) (K.W. Scheele, *Opuscula,* **2**, 73 (1776)). However, more systematic investigations were undertaken around 100 years later, when the works of well-known chemists such as Bischler, Riedel, Niementowski, Gabriel, and Bogert established significant progress in this field [1]. Particularly, numerous papers on chemistry of pyrimidines (**2**) and purines (**3**) have been published since the discovery of the presence of some purine bases in double-stranded nucleic acids.



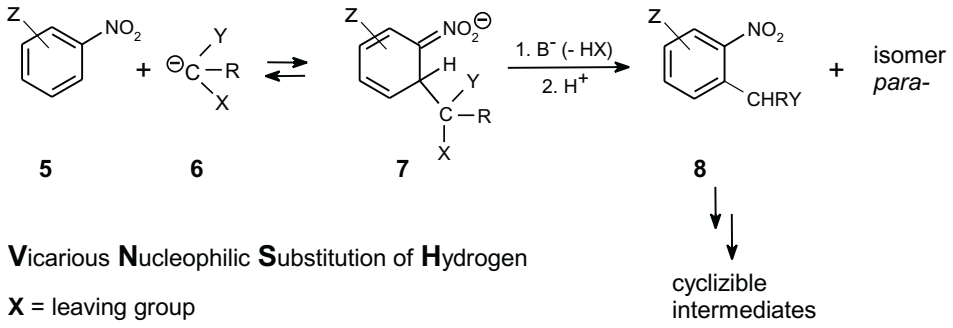
1 **2** **3** **4**

Figure 1

Since the early years of this century several studies on the synthesis and structure-activity relationships of pyrimidine derivatives have been reported [1–8]. Among them, chemical and biological aspects of purines were successfully developed. The most important preparation methods of these compounds, by the pyrimidine ring construction, include their synthesis from *ortho*-nitrobenzaldehydes, *ortho*-aminobenzaldehydes, *ortho*-aminobenzylamine derivatives, anthranilic acid derivatives, *ortho*-isocyanatobenzoates, *ortho*-aminobenzonitriles, and *N*-substituted anilines. However, because of the incessant interest in this field, new efficient syntheses of these compounds are still sought. Thus, the investigations described in the second part of this review (Chapter 4) [9–15] were also undertaken.

This problem can be successfully solved in several ways by the use of Vicarious Nucleophilic Substitution of Hydrogen (VNS, Scheme 1) [16,17]. The efforts described in that chapter *via* the VNS were oriented towards the synthesis of fused pyrimidines, particularly en route to the synthesis of purines.

Scheme 1



2. Fused pyrimidines – a short review on synthesis and biological activity

The pyrimidine nucleus is embedded in a large number of alkaloids, drugs, antibiotics, agrochemicals, and antimicrobial agents [5]. Many simple fused pyrimidines such as purines (**3**) and pteridines (**4**) are biologically active by themselves [2,3], or are essential components of very important naturally occurring substances (*i.e.*, nucleic acids). Some pteridine derivatives are also used as anti-leukemic drugs [18,19], or potassium-conserving diuretics [18,20]. In addition, several quinazoline alkaloids exhibit hypnotic [7,21,22], bronchodilatory [21,23], and antimalarial [8,21,24] activity. Some fused thieno[3,2-*d*]pyrimidines serve as anti-allergy drugs, some act as fungicides.

A very important biologically active pteridine system (fused pyrazino[2,3-*d*]pyrimidine) is present in folic acid (**12**), as well as in several antibiotics and diuretics [7]. Pteridine was also found in riboflavin (6,7-dimethyl-9-(D-1-ribityl)isoalloxazine, vitamin B_2; **13**) [7], a growth-regulator for microbes and animals. Examples of some biologically active pyrimidine derivatives are listed in Figure 2.

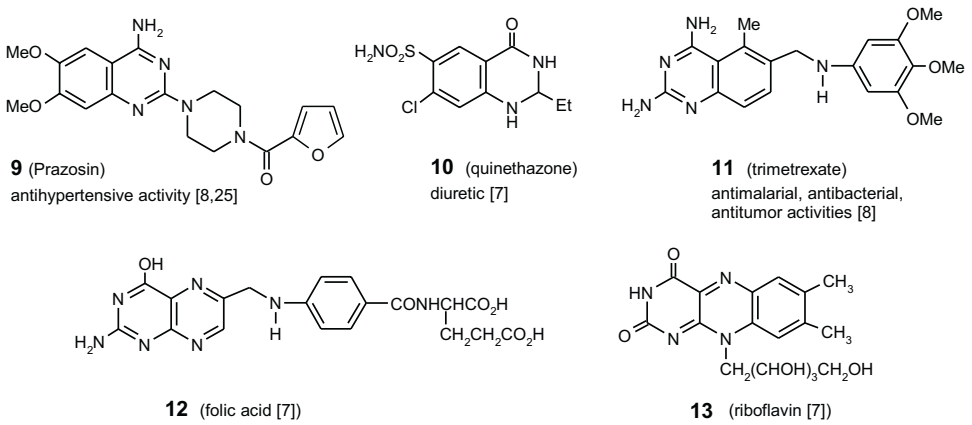
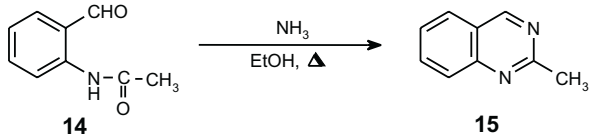


Figure 2

Of particular importance is the bioorganic chemistry of fused pyrimidine derivatives, hence substantial attention should be paid to their synthetic methods. From the historical point of view, three general methods are well known in the literature – Bischler's, Riedel's, and Niementowski's [1–4].

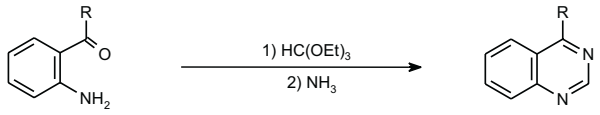
2.1. Synthesis from the *ortho*-aminobenzaldehyde and from the *ortho*-nitrobenzaldehyde derivatives. *The Bischler's synthesis*. In this method, 2-methylquinazoline (**15**) was prepared by heating *ortho*-acetamidobenzaldehyde (**14**) with alcoholic ammonia in a sealed tube at 100°C. According to Katritzky classification [8], this is an *N3 insertion* type synthesis.

Scheme 2



This reaction (first described by Bischler) is of general character and gives high yields. It has been widely used for obtaining 2-, 4- and 2,4-substituted quinazoline, and also for derivatives substituted in the benzene ring [1,26]. The use of related ketones as substrates in the reaction with ammonia [27] or with hydrazine [28] also leads to the desired products in high yield. Reactions of aminoketones (**16**), with orthoesters and ammonia, are transformations of a similar type, and undergo step-by-step process to form quinazolines. The *C2* and *N3* components were herein added separately. First, a reaction with orthoesters (in MeOH, r.t., 15 h) gave imidates. The subsequent reaction, with NH_3, led to the quinazoline type product (**17**) [29].

Scheme 3

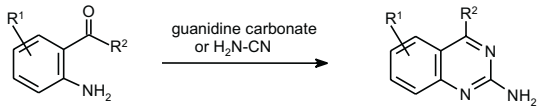


16 **17**

On the other hand, *ortho*-aminoacetophenone derivatives could also react in one step to give cyclic products. These ketones and amide synthons (*e.g.* $HCONH_2/BF_3xEt_2O$, 130°C) *via C2-N3 insertion* lead to quinazoline, substituted with methyl (alkyl) group in position 4- [30].

A convenient and satisfactory method for the synthesis of 2-amino substituted quinazolines (**19**) (Scheme 4) is the reaction of *ortho*-aminobenzaldehydes (or corresponding ketones; while reacting at higher temperature, >150°C) with guanidine carbonate or with cyanamide (*C2-N3 insertion*) [31].

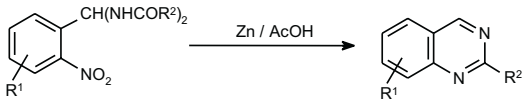
Scheme 4



18 **19**

The Riedel's synthesis. The reductive cyclization of bisformamido derivatives of *ortho*-nitrobenzaldehydes (**20**) leading to quinazoline ring system (**21**) is known as Riedel's synthesis [1] (*N1-C2 cyclization*). For years, a drawback to this preparation was the availability of the respective *ortho*-nitrobenzaldehydes.

Scheme 5



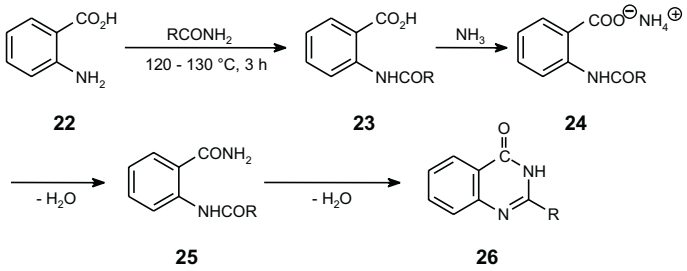
20 **21**

R¹, **R²** = alkyl [1,32]

2.2. Synthesis from the anthranilic acid derivatives. *The Niementowski's synthesis*. In 1895, Niementowski described the synthesis of quinazolin-4(3*H*)-one (**26**) by fusion of anthranilic acid (**22**) with formamide (S. Niementowski, *J. Prakt. Chem.*, **51 (2)**, 564 (1895)). High yields of the desired products were obtained from the anthranilic acid derivatives [33], as well from their esters [33,34]. In this condensation, starting materials such as acetamide, propionamide and isobutyramide can be also used to give the corresponding substituted products. However, those reactions required heating for long time at higher temperature [35]. The mechanism of this re-

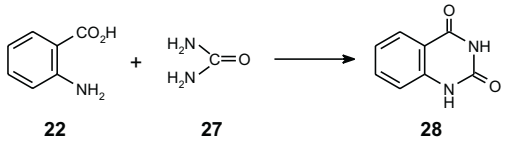
action was proposed by *Mayer & Wagner* [36] five decades later. In light of these investigations, it should be classified as a *C2-N3 cyclization*.

Scheme 6



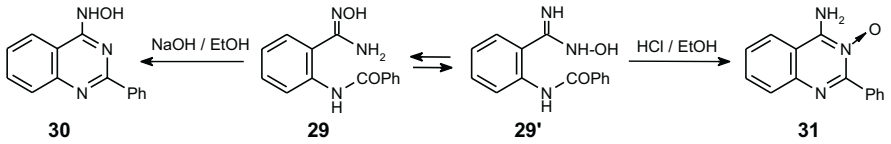
A particular case of this method is the condensation of anthranilic acid with urea, leading to quinazoline-2,4(1*H*,3*H*)-dione (**28**). This was described by Griess about thirty years before Niementowski's synthesis [1,8].

Scheme 7



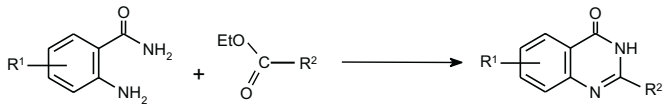
An extension of the above approaches is the synthesis from *ortho*-acylaminobenzamide oximes. These substrates (*e.g.* **29**/**29′**) gave 4-(hydroxyamino)-2-phenylquinazoline (**30**, 67%; in boiling dilute aqueous-ethanolic alkali), whereas the same substrate in boiling aqueous-alcoholic hydrochloric acid gave 4-amino-2-phenylquinazoline 3-oxide (**31**, 75% yield) [37,38] (Scheme 8).

Scheme 8



Amides of anthranilic acid (**32**) also react with a variety of other synthons to give the corresponding quinazolinones. In the reaction with carboxylic acids and their esters (*C2 insertion*), they resulted in the formation of 2-substituted quinazolin-4(3*H*)-ones in high yield (**34**; *e.g.* $R^2 = CO_2Et$, EtONa/EtOH, r.t., 95%) [39].

Scheme 9

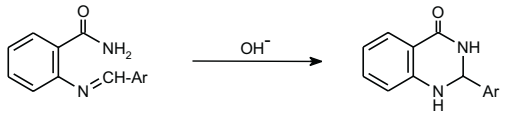


32 **33** **34**

The synthesis employing orthoesters [6,40], aldehydes [41,42], ketones [43], carboxylic acid halides and anhydrides [6], carboxamides [6,44] was also described in numerous papers. Other synthons, like carbon dioxide, carbon disulfide, phosgene, thiophosgene, alkyl chloroformate, dialkyl carbonates, urea, chloroformamidine, and cyanogen bromide in the reaction with anthranilamides were succesfully applied, as well [45].

Amides of anthranilic acid (upon conversion into *ortho*-[(arylmethylidene)amino]benzamides, *e.g.* **35**) results (with refluxing in alkali) in the formation of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-one **36** (55%) [46].

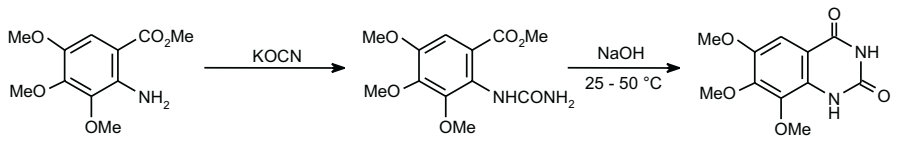
Scheme 10



35 **36**

Anthranilic acid, its esters, and amides can also be easily converted into derivatives of *ortho*-ureidobenzoic acid in the reaction with potassium cyanate. The intermediates obtained, *e.g.* **38**, are readily cyclized (*N3-C4 cyclization*) to quinazoline-2,4(1*H*,3*H*)-diones (**39**). Important application of this procedure include syntheses of quinazoline antihypertensive agents. For two of them (Prazosin and Trimazosin), the procedure was commercially developed on a kilogram-scale [25,47].

Scheme 11



37 **38** **39**, >90%

Anthranilic acid esters react also at elevated temperature with a variety of other reagents (ammonium thiocyanate, alkyl- and aryl- isothiocyanates, imidates) to give the same or similar quinazoline derivatives [8].

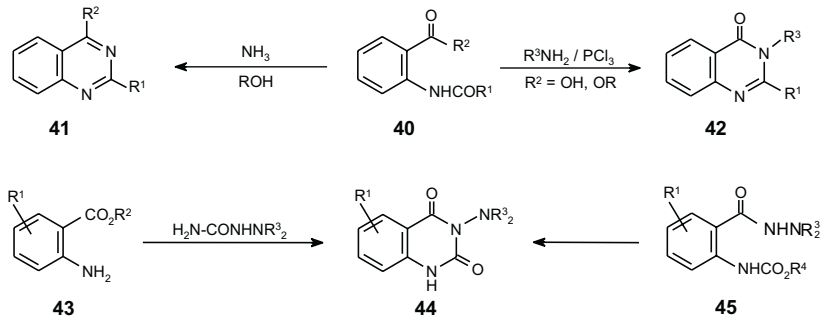
As previously mentioned, a general method for the preparation of quinazolines, substituted in the heterocyclic ring by aryl or alkyl groups (**41**, Scheme 12), is the re-

action of *ortho*-acylaminobenzaldehyde (**40**; R^2 = H; Bischler's synthesis), or the respective ketone (R^2 = alkyl, aryl), with ammonia or its salts (*N3 insertion*). On the other hand, *N3*-alkyl substituted quinazolin-4(3*H*)-ones (**42**) have been obtained in the reaction between acylaminobenzoic acid derivatives **40** (R^2 = OH, OR) and primary amines with phosphorus trichloride as the condensing agent [8]. 3-Aminoquinazolin-4(3*H*)-ones (**42**, $R^3 = NH_2$) are easily formed in high yields by *N3 insertion* when methyl or ethyl esters of the corresponding benzoic acid derivative (**40**, R^2 = OR) are heated with hydrazine in an alcohol [8].

In these widely used syntheses, either a primary amine or ammonia has been usually employed as the synthon in numerous reactions to supply the *N3* component [6,48,49]. Heating the starting material with anhydrous formic acid, ethyl orthoformate, or acetic anhydride effects the necessary acylation of the amino group in the above cases.

Synthesis of fused *N*3-aminated pyrimidines by *C2-N3 insertion* was realized in one step by heating of anthranilic acid esters (**43**) and semicarbazides to yield the corresponding quinazoline-2,4(1*H*,3*H*)-diones (**44**). The same effect can be achieved by thermal *C2-N3 cyclization* of *ortho*-(alkoxycarbonylamino)benzoylhydrazides (**45**) [8].

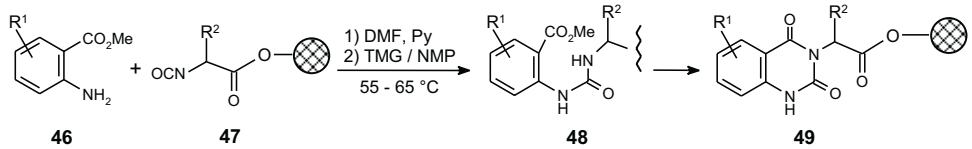
Scheme 12



41 **40** **42** **43** **44** **45**

Fused pyrimidine-2,4(1*H*,3*H*)-diones can also be generated by the reaction of *ortho*-amino aromatic carboxylic acid esters and isocyanates [50,51]. In a solid phase version of this synthesis the above dione of type **49** was obtained, *via* the urea derivative intermediate **48**, in the reaction of the ester **46** with amino-acid derived isocyanates (**47**), while immobilized on resin [52].

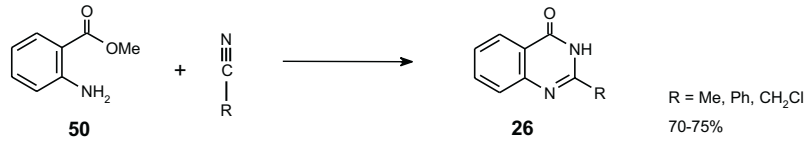
Scheme 13



46 **47** **48** **49**

Anthranilic acid esters can also react with nitriles to give quinazolin-4(3*H*)-ones (**26**) [6,53] (Scheme 14).

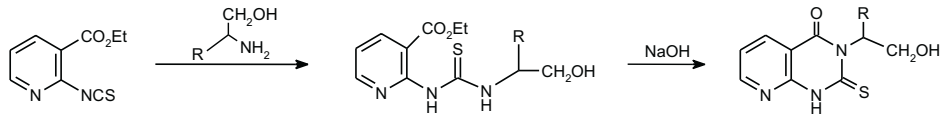
Scheme 14



50 **26**

In a similar reaction to that presented in Scheme 13, involving the thiourea intermediate **52**, the 2-thio-2,3-dihydroquinazolin-4(1*H*)-one can be obtained. Thus, 2-isothiocyanatopyridine-3-carboxylic acid ethyl ester (**51**) reacts with aminoalkohols to give the thiourea derivative, the treatment of which with sodium hydroxide solution led to the corresponding fused pyrimidine derivative **53** [54].

Scheme 15



51 **52** **53**

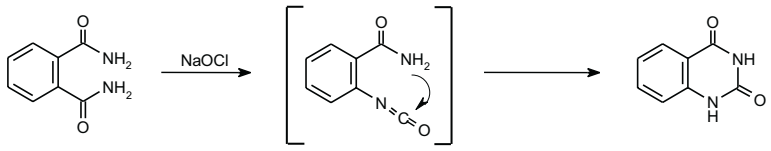
In this group of substrates, synthesis from the *ortho*-ureidobenzoyl chlorides should be mentioned. Conversion of the acid chloride of type **54** gives 3-substituted quinazoline-2,4(1*H*,3*H*)-dione (**55**) [55].

Scheme 16

54 **55**

Aromatic isocyanate intermediates (**57**), generated *in situ* by Hofmann type degradation of aromatic amides (*e.g.* **56**), can be trapped by the neighbouring nitrogen atom of $CONH_2$, $CSNH_2$ or CH_2NH_2 to give fused pyrimidine moieties, *e.g.* dione **28**

Scheme 17

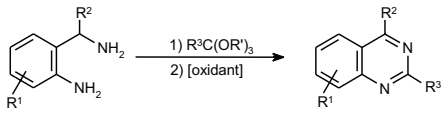


56 **57** **28**

(*C2-N3 cyclization*) [8] (Scheme 17). *ortho*-Isocyanatobenzoates, while reacting with amines (*via N3 insertion*) can give the same type of dione as a final product [56].

2.3. Synthesis from the *ortho*-aminobenzylamine derivatives. One of the best general synthetic methods for fused pyrimidines is synthesis based on the corresponding *ortho*-(aminomethyl)arylamines (**58**) [57,58]. These diamines upon condensation with carbonyl compounds or their derivatives, *i.e.*, orthoesters, gave 2-substituted fused pyrimidines **59** (Scheme 18) [1,59].

Scheme 18

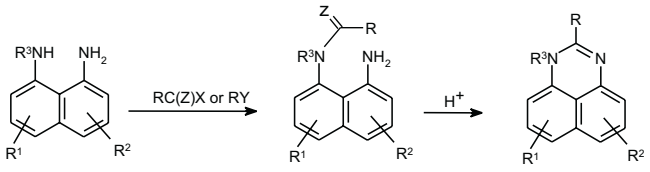


58 **59**

Heating of these compounds (**58**) with oxalic acid esters [60] led to the corresponding alkyl 3,4-dihydroquinazoline-2-carboxylate derivative, while heating with phosgene [1,6] led to 3,4-dihydroquinazolin-2(1*H*)-one. However, this synthesis also was limited by the availability of the respective starting materials [61], or their precursors [62].

Naphthalene-1,8-diamines can be regarded as diamines of this type, and, as such, they react by inserting a one-carbon atom *C2 unit* with carboxylic acids (or their equivalents), to give tricyclic fused pyrimidines (perimidines, in this case). Thus, naphthalene-1,8-diamine or its *N*-substituted derivatives react under heating by refluxing with formic acid to form the corresponding perimidine. Other substituted naphthalene diamines (**60**) and the use of various reagents, afforded perimidines **62**, substituted in all rings [8] (Scheme 19).

Scheme 19



60 **61** **62**

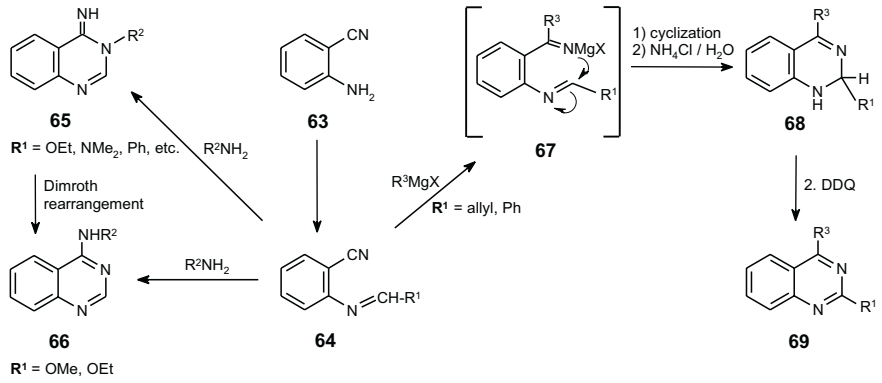
X = OH, OR^4, Cl, $OCOR^5$

R^1,R^2 = OH, Cl, Br, SO_3H **Y** = CN, $C(OR^6)$=NH, $C(NH_2)$=NH **Z** = O, NH

2.4. Synthesis from the *ortho*-aminobenzonitriles and their derivatives. *ortho*-Amino aromatic nitriles (**63**) are very useful and versatile substrates. They can act as precursors for the above diamino compounds (**58**), or they can be used, *via* methyleneamino intermediate of type **64**, in two alternative ways. Thus, the latter re-

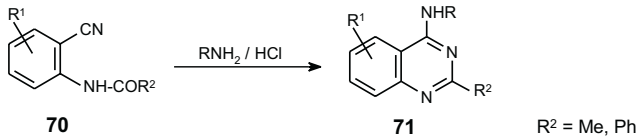
acts readily with nitrogen nucleophiles (ammonia or amino-type reagents) *via N3 insertion* to give 4-imino/amino quinazoline derivatives (**65**/**66**) [63–65]. On the other hand, selective addition of Grignard reagents (phenyl- and methylmagnesium bromide) to the cyano group of *ortho*-(methyleneamino)benzonitriles (**64**) leads to adducts **67**, cyclization of which (*C2-N3*) resulted in the formation of 2,4-disubstituted 1,2-dihydroquinazolines (**68**). Their oxidation by DDQ or O_2 gave the alkyl substituted, fully conjugated fused pyrimidines [66–68].

Scheme 20



Cyclizations with the use of acyl derivatives **70** of the above nitriles (**63**), on treatment with ammonia, or amine type reagents, in acidic conditions, gave also 4-quinazolinamine derivatives (**71**) [69,70].

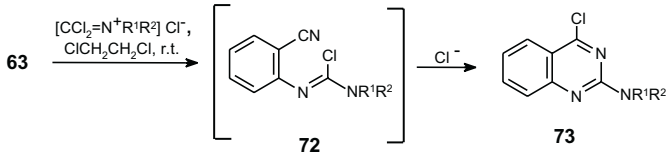
Scheme 21



In the reactions of the above *ortho*-aminobenzonitriles (**63**) with phosgeniminium chlorides, 2-alkylamino-4-chloroquinazoline (**73**) was obtained selectively by *C2 insertion*, followed by *C2-N3 cyclization* [71]. The product carries an amino group in the less electrophilic quinazoline 2-position, and a chlorine in the more electrophilic position 4-. Preparation of these particularly substituted quinazolines is usually a difficult task, and involves a multi-step synthesis.

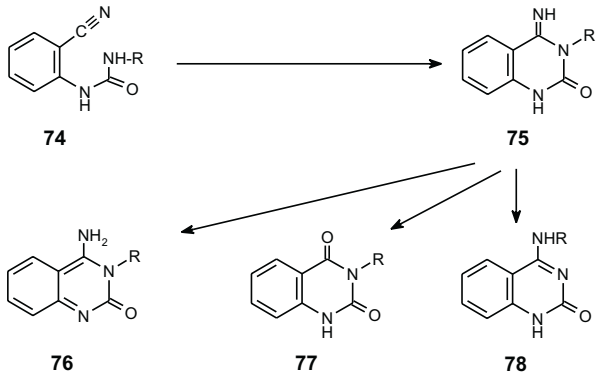
Synthesis from the *ortho*-ureidobenzonitriles should also be mentioned in this group of substrates. The cyclization of ureidobenzonitriles (**74**) proceeds by addition of the terminal NHR group to the triple bond of the cyano group, thus initially producing a 3-substituted 4-imino-3,4-dihydroquinazolin-2(1*H*)-one (**75**). This may tauto-

Scheme 22



merize to the 3-substituted 4-aminoquinazolin-2(3*H*)-one derivative (**76**), or, under reaction conditions, hydrolyze to a quinazoline-2,4(1*H*,3*H*)-dione **77** [72,73]. For R = alkyl, *etc*. it can also undergo Dimroth rearrangement to 4-(substituted-amino)-quinazolin-2(1*H*)-one (**78**) [74] (Scheme 23). The thioureido derivatives also cyclize, involving a cyano group in the *ortho*- position, to 4-aminoquinazoline-2(1*H*)-thiones [8].

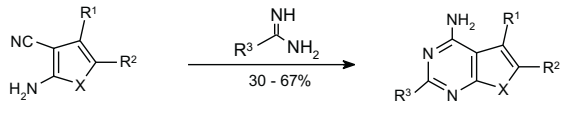
Scheme 23



The same type of cyclocondensation occurs in the reaction with ammonia or amine of *ortho*-isocyanatobenzonitriles [6,75]; however, these substrates have not been widely used for this purpose.

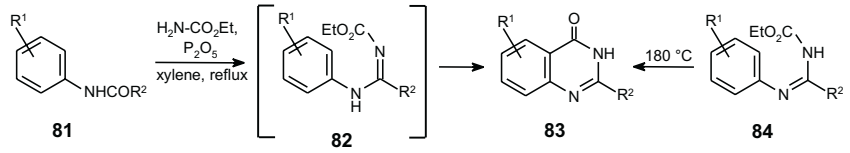
Another example of the use of aromatic *ortho*-amino- aromatic-carbonitriles is their reactions with amidines [76], leading to fused amino-pyrimidines (*e.g*. **80**). The reactions of amidines with some five-membered heterocycles, *e.g*. the 2-amino-4,5-dialkyl-3-furonitrile (**79**; X = O), *via* unexpected ring transformation, gave rise to 7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (**80**, X = NH, $R^3 = NH_2$) [77].

Scheme 24



2.5. Electrocyclic reactions. Synthesis from aniline derivatives. A large number of the elegant synthetic methods of fused pyrimidines can be characterized as approaches involving electrocyclic reactions. The necessary substrates in these methods are usually prepared from the aniline derivatives by simple transformations of NH_2 group. For example, quinazolin-4(3*H*)-one (**83**) was obtained from the anilide and urethane in the presence of phosphorus pentoxide on heating in xylene. The last step of this transformation is the thermal cyclization (*C4-C4a*) of the reactive intermediate, ethoxycarbonyl amidine **82**. The same *C4-C4a* thermal cyclization was achieved with *N*-ethoxycarbonyl-*N*′-aryl phenylformamidine (**84**) (R^2 = Ph) [8,78].

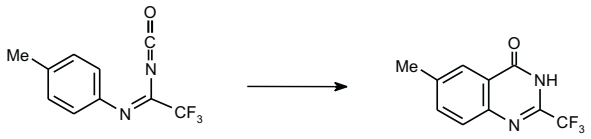
Scheme 25



81 **82** **83** **84**

Electrocyclic ring closure also allows the isocyano group in the β-position of the side chain of aromatic ring to give the fused heteroaromatic moiety. By this method, the preparation of the 2-trifluoromethyl-quinazolin-4(3*H*)-one derivative (**86**) was demonstrated [79] (Scheme 26). Isothiocyanato analogues allow the synthesis of quinazoline-4(3*H*)-thiones (*m*-xylene, reflux, 40%) [80,81].

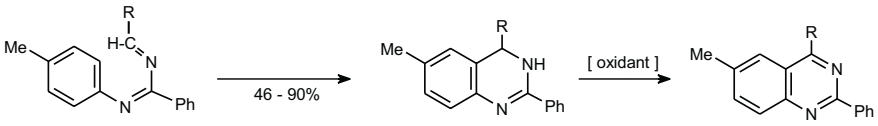
Scheme 26



85 **86**

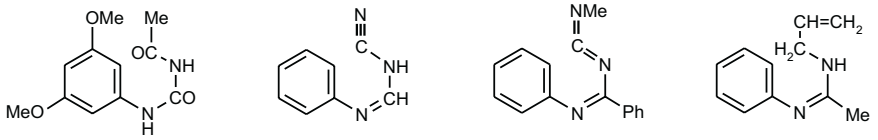
In the same type of six-electron electrocyclic ring closure, 1-aryl-1,3-diazadienes (**87**) (prepared from *N*-imidoyliminotriphenyl phosphorane and the corresponding aldehyde) can enter this cyclization in boiling xylene [82,83], to give 3,4-dihydroquinazolines **88**, which, under reaction conditions, may aromatize spontaneously to quinazolines **89**. This was realized for R = alkyl, aryl, as well as for R = NMe_2 [84].

Scheme 27



87 **88** **89**

All the above cyclizations are thermal electrocyclizations in which (*C4-C4a*)-bond formation occurred. Cyclizations can also be applied in the synthesis of fused pyrimidines *via N*-acyl (**90**) [85], nitrile (**91**) [86], methylene (**92**) [87], and methyl groups (**93**) [88] (*e.g.* compounds below, **90–93**; Figure 3).

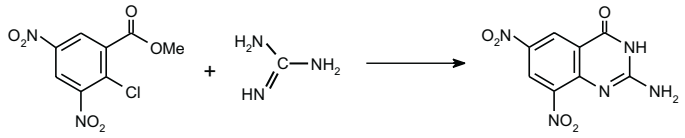


90 **91** **92** **93**

Figure 3

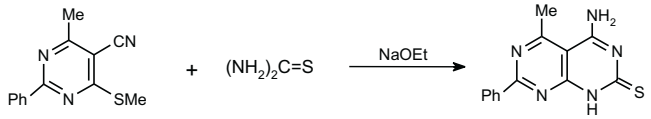
2.6. Other methods. It is worth mentioning the construction of fused pyrimidine ring by means of the *N1-C2-N3* component. Aromatic benzoates and carbonitriles bearing the nucleophugal group in the *ortho*-position are very valuable intermediates for this synthesis. The first case usually is a reaction between electrophilic *ortho*-halobenzoates and amidines (Scheme 28, eq. 1) [6]. In the next, aromatic carbonitriles (*e.g.*, 4-methyl-6-(methylsulphanyl)-2-phenylpyrimidine-5-carbonitrile, **97**), in which the SMe substituent can be easily exchanged by the NH_2 group of an amide type moiety, reacts step by step with thiourea to give 4-amino-5-methyl-7-phenylpyrimido[4,5-*d*]pyrimidine-2(1*H*)-thione derivative (**99**), in good yield [89]. In both cases, the molecules exhibit high electrophilic properties, being activated either by the strong electron-withdrawing NO_2 groups or heteroatoms in the rings.

Scheme 28



(1)

94 **95** **96**

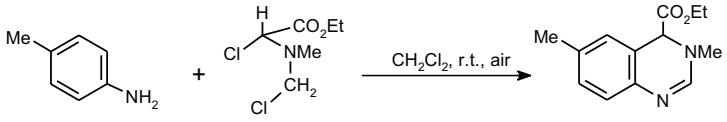


(2)

97 **98** **99**

The syntheses of fused pyrimidines from the aniline derivatives also involve preparation with the use of *C2-N3-C4* building blocks (or combination of synthons thereof). This method is not extensively used. However, it allows one to obtain the product from the aniline derivatives in one step. One example is the reaction between *para*-toluidine and the corresponding dichloro-derivative of type **101** [90] (Scheme 29).

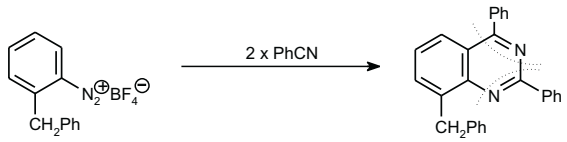
Scheme 29



100 **101** **102**, 37%

Finally, there are known syntheses in which the *N1-C2-N3-C4* component is supplied. These attempts are limited to a few examples, *e.g.*, benzenediazonium salts [91] (Scheme 30).

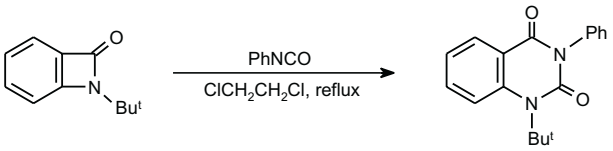
Scheme 30



103 **104**, 53%

An interesting synthetic method is the *C2-N3 insertion via* 4-membered ring expansion. It can be exemplified by the reaction of benzazetine type substrate with isocyanate. Thus, *tert*-butyl-benzazetinone **105** reacts with phenyl isocyanate, in refluxing 1,2-dichloroethane, to give 1-*tert*-butyl-3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**106**), in high yield [92].

Scheme 31



105 **106**

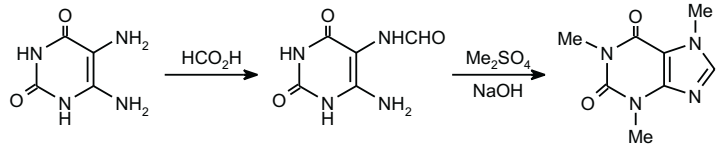
3. Purines – a particular case of fused pyrmidines. Synthesis and biological activity

Among fused pyrimidines, probably the most important class of compounds are purines. Many structures containing a purine moiety show high biological activity [93,94]. They usually have potential healing properties. There are dozens of papers concerning their antitumor [95,96], anti-HIV [97,98], antiviral [96,99,100], anticonvulsant [101,102], and bronchodilator [103] activity. They can serve as plant growth regulators [104,105] or herbicides [105]. Purines are also components of nucleotides that are monomeric building blocks of the DNA or RNA nucleic acid

poly-chains. Therefore, the synthesis and chemical modifications of purines are still of substantial interest.

The various methods of purine synthesis are described in numerous papers. In the majority of cases, the syntheses start from the 4,5-diaminopyrimidine derivatives (the Traube synthesis), and are well documented [106,107]. The cyclocondensation of these diamines with formic acid, carbonyl derivatives, or orthoesters leads to the purine moiety. However, direct closure to the purine ring is more often the exception than the rule, and two-step synthesis is generally executed (Scheme 32). A good example of this method is the formation of caffeine (**109**) in the reaction of a diaminopyrimidine derivative (**107**) with formic acid. The addition of a methylating agent in alkali before cyclization leads to the desired product **109** [108].

Scheme 32



107 **108** **109** (caffeine)

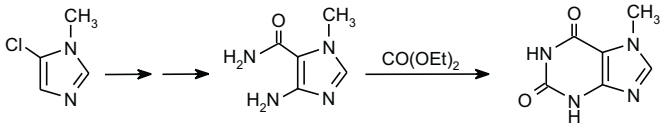
Although the greatest number of purines synthesised to date have been derived from pyrimidine precursors, the use of alternative intermediates is of growing importance. However, the synthesis of purines from acyclic substrates or from imidazole derivatives has not, thus far, been investigated in detail [2,107,109–111]. This was probably due to the difficulty in accessing key intermediates. Researchers in the nucleoside field, for whom this approach offered preparation of some glycosides not readily accessible by other methods, showed renewed interest therein.

Syntheses from acyclic substrates are of minor importance, but the methods dealing with the preparation from imidazole derivatives can be of substantial interest. Most of the methods reviewed in Chapter 2, by the pyrimidine ring construction, could also be applied herein, and important representative examples of them will be presented shortly in this paragraph. However, these syntheses are usually limited by the availability of the respective starting materials.

Sarasin and Wegmann described the first synthesis of a purine by this route in 1924 [2]. In a multi-step process, they obtained the amide of 4-amino-1-methyl-1*H*-imidazole-5-carboxylic acid (**111**), which was subsequently converted to 7-methyl-7*H*-xantine (**112**) in the reaction with diethyl carbonate (*C2 insertion*).

This route allows the formation of a wide range of purines. A cyclization of the 5-carbamoyl derivative of type **111** with formic acid [2,107,112], with esters [113] and orthoesters [2,107,114], with urea [2,107], with cyanates, or isothiocyanates [2], was also successfully applied. Little use has been made of this 5-carbamoyl type of intermediate (**111**) in the condensation with diethyl carbonate, and with carbon

Scheme 33



110 **111** **112**

disulfide, leading to the 7-alkyl-substituted xantine derivative, or to 2-thio-7*H*-purin-6-ones, respectively [2,107].

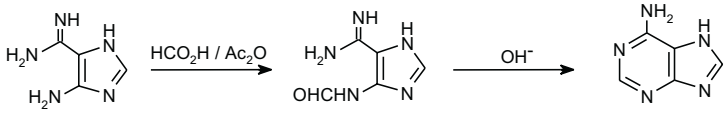
Synthesis from 1*H*-imidazole-4,5-dicarboxamides (**113**), with the use of alkaline potassium hypobromite, can be considered as a process of similar type to the one described above. In the first step, the substrate undergoes a Hofmann rearrangement to the isocyanato intermediate, from which the xantine derivative is obtained in good yield [115] by subsequent *C2-N3 cyclization*.

113 **122**

Figure 4

Instead of an imidazole-4-carboxamide derivative **111**, an amidinoimidazole **114** can be also used. Its formylation with a mixture of formic acid and acetic anhydride followed by treatment of the intermediate **115** with aqueous alkali, provides a useful method for the synthesis of adenine-type products (**116**) [2,107]. This cyclization (*C2-N3*) occurs more readily than it does with carbamoyl compounds **111**.

Scheme 34

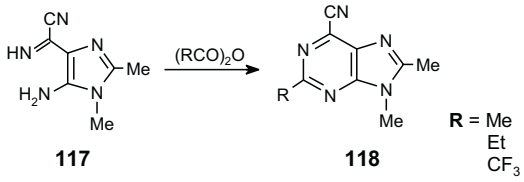


114 **115** **116**

In recent years, the synthesis from (5-amino-1*H*-imidazol-4-yl)(imino)acetonitrile derivatives (**117**) was described [107,116]. They react exothermically with an excess of carboxylic acids anhydrides (*C2 insertion*), giving substituted 9*H*-purine-6-carbonitriles (**118**), in good yield.

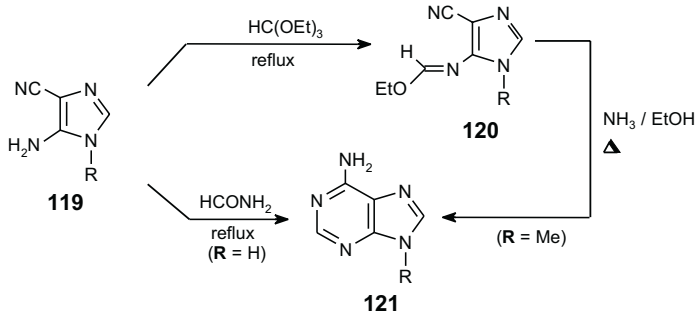
A distinct advantage over the above-mentioned amidinoimidazole reactions is demonstrated by the approach to adenine from 5(4)-amino-1*H*-imidazole-4(5)-carbonitriles (**119**). This advantage is due to a much wider range of availability of the latter. Cyclocondensation involving orthoesters (*N3 insertion*) [117], or its reactions

Scheme 35



with amide-like reagents (*C2-N3 insertion*) [118], resulted in the formation of the desired purine ring system **121** (Scheme 36).

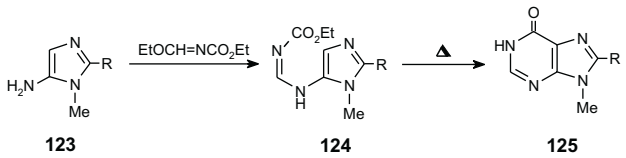
Scheme 36



Esters of aminoimidazole-5-carboxylic acid of type **122** (Figure 4) also can be used for the synthesis of purines. They undergo cyclization in the reaction with cyanates, isocyanates and ureas to give directly purines or their 2-thio analogoues [2,107].

Recently reported novel routes to purines starting from imidazole precursors are thermal electrocyclizations. One of the most representative examples is an approach to adenine or hypoxantine, which consists of the high-temperature intramolecular cyclization of imidazole intermediates **124** [107,119]. First, the reaction of 5-aminoimidazole **123**, with ethoxymethylideneuretane (EtOCH=NCO_2Et), results in the formation of **124**, which, on fusion, give 8,9-dialkyl hypoxantine **125**, in excellent yield (> 90%) (*C5-C6 cyclization*).

Scheme 37



This short review shows that purines can be synthesised from imidazoles in a variety of ways. Yet, there is still an open question regarding the availability of the appropriate intermediates. Convenient methods for their preparation are sought, as well.

4. New and efficient approaches to fused pyrimidine ring systems *via* Vicarious Nucleophilic Substitution of Hydrogen

The chemistry, biological activity, and physical properties of fused pyrimidines is thoroughly reviewed in many articles and monographs [1–4,6–8,107]. Generally – *ortho*-amino(aminomethyl)aromatics of type **58** would be the best starting materials for their synthesis. However, the limiting factor in the preparative methods presented in the above two paragraphs is the availability of the key intermediates, which are usually obtained in multi-step transformations from commercially available chemicals. So, of significant importance is to offer a useful tool for synthesis of intermediates from easily obtainable starting materials, or from inexpensive commercially available reagents.

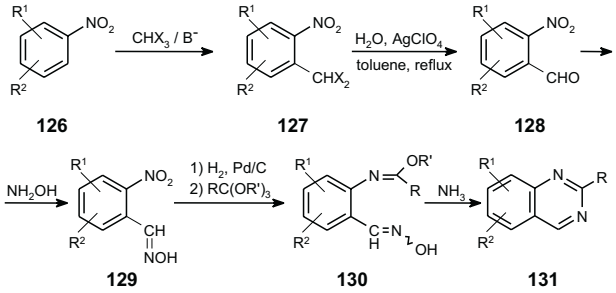
In the past years, several papers were published concerning new and efficient approaches to fused pyrimidines [10–15] with the use of Vicarious Nucleophilic Substitution of Hydrogen (VNS) [16,17] (Scheme 1), and they are shortly reviewed in this chapter. The preparation methods of many fused pyrimidines structured on carbocyclic (benzene, naphthalene) and heterocyclic (quinoline, thiophene, imidazole) rings were described. Starting materials for these syntheses were aromatic or heteroaromatic nitrocompounds. In this methodology, among others, the appropriate nitroaromatic compounds were transformed into the desired *ortho*-substituted derivatives, and the crucial step of these syntheses was realized by VNS. The use of this reaction has been found to be an excellent tool for the introduction of the dihalomethyl group [120] and the isocyanomethyl group [12,121], which can give an opportunity for transformations leading to the cyclizible intermediates.

These approaches to pyrimidine ring construction can be also applied to the synthesis of purines. The starting material in this case is commercially available 4-nitroimidazole. The presence of the nitro group in this compound allows for introduction of the desired substituents at the hydrogen-bearing carbon atom in position 5-. Many compounds of this type, obtained *via* VNS with appropriate carbanions, were described in publication [9]. The possible purine syntheses were presented in papers [10–13].

4.1. Synthesis of fused pyrimidines *via* oximes and Schiff bases. As starting material in this methodology, the corresponding nitroaromatic compounds are used. The principal intermediates in this approach to the fused pyrimidine rings are the *ortho*-dihalomethyl (the dichloromethyl, in this case) derivatives of nitroarenes, which are efficiently prepared *via* the VNS with haloforms [9,120].

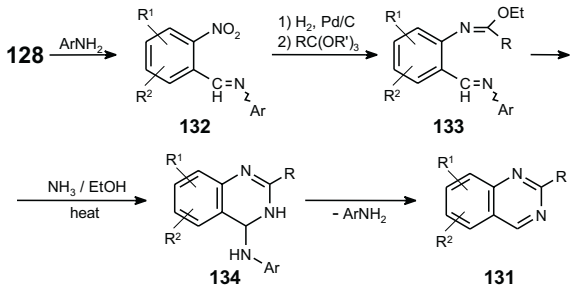
The hydrolysis of the CHX_2 substituent in compounds **127** to aldehydes and subsequent transformations into oximes **129** gave the desired intermediates for this synthesis. Standard transformations of **129**, followed by cyclocondensation with ammonia (*N3 insertion*), led to the fused pyrimidine ring system **131** (Scheme 38) [14].

Scheme 38



Alternatively, aldehydes **128** can be transformed into Schiff bases **132**. Selective reduction of the nitro group in **132**, followed by condensation with various orthoesters, resulted in the formation of imidates **133**. Heating of these imidates in a sealed tube with alcoholic ammonia yields quinazoline derivatives **131** [15] (*N3 insertion*).

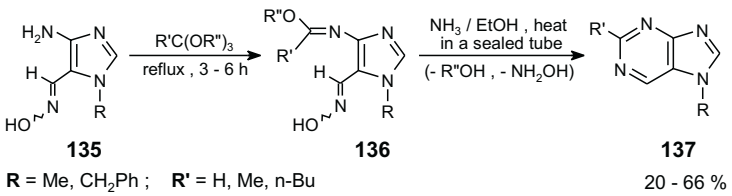
Scheme 39



The application of these methods is limited, due to moderate overall yields [14,15]. However, this type of cyclization was later successfully optimized for the synthesis of purines, giving high yields of the desired products [10,13].

7-Substituted purines can be also efficiently obtained from the 4-amino-1*H*-imidazole-5-carbaldehyde oximes (**135**) (easily prepared from 4-nitroimidazole [9,10]). Condensation of the amino group in oximes **135** with orthoesters resulted in the formation of iminoethers **136**. The cyclocondensation of the *ortho*-neighbouring iminoether and oxime groups with ammonia (*N3 insertion*), thus far unknown, led to the purine ring system **137** from imidates in good overall yield.

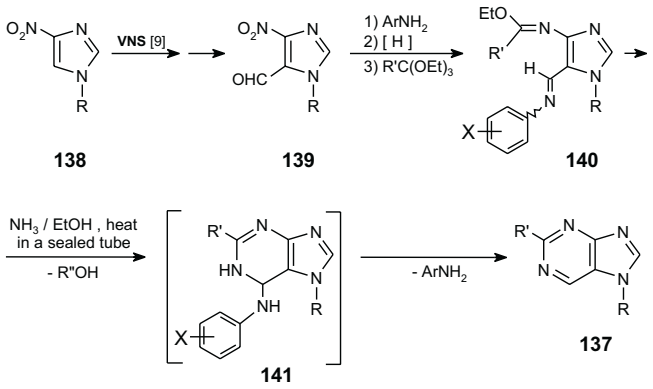
Scheme 40



Transformation, in the known manner, of the aldehydes **139**, with the use of arylamine, results in the formation of imidates **140**, and the subsequent cycloconden-asation with an excess of ammonia (in a sealed tube, over 100°C) gives purines **137** (Scheme 41).

If this postulated reaction sequence operates as drawn on Scheme 41, then the last step of this transformation should be the elimination of aryloamino- moiety from the dihydro-intermediate **141**. Generally, the yields were rather poor. However, for the reactions of X-substituted anilines $ArNH_2$, a moderate influence of substituent X on the yield was observed.

Scheme 41



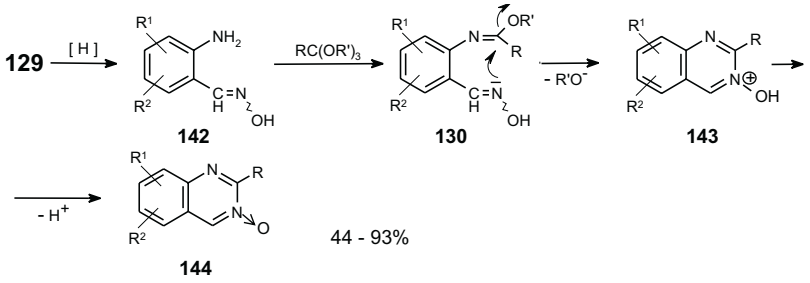
This problem was investigated on model compounds, and it was found that the strong electron-withdrawing groups (**X** = CN, SO_2Ph, 2,4-difluoro, *etc*.) increased the reactivity of the imine >C=N double bond, hence in the applied reaction conditions a competitive processess occurred, thus decreasing the overall yields [15].

For the synthesis of purines, the best results were obtained in the case of the moderate electron-withdrawing group **X** = *para*-Br, and the optimization of this reaction increased the yields up to 47% [13].

4.2. Selective synthesis of fused pyrimidine mono-*N*-oxides. The oximes of type **129** are also proper key intermediates for the synthesis of fused pyrimidine mono-*N*-oxides [122–125]. These substrates, upon reduction of the NO_2 group, can easy cyclize to *N*-oxides, the preparation of which would be a difficult task, and practically impossible to realize by direct *N*-oxidation of the corresponding heterocyclic bases. However, only a few examples of application of this method (or its modifications) have been described in the literature [123–129] – probably because of the limited availability of the proper starting *ortho*-amino-aromatic carboximes.

Improved access to these intermediates now [9,10] allows us to utilize this very useful cyclization for the synthesis of many heterocyclic systems [11]. The cyclization reaction of aminocarboximes with the use various orthoesters (*C2 insertion* before *C2-N1 cyclization*) led to the corresponding fused pyrimidine mono-*N*-oxides.

Scheme 42



This method allows not only the selective introduction of the N→O function into the desired position in the target compounds having more than one nitrogen atom, but can be also used for the preparation of compounds in which some substituents are present (*e.g.*, alkyl, aryl, halogens, or low valent sulphur moieties sensitive to oxidation). Examples of bicyclic and tricyclic fused pyrimidine mono-*N*-oxides are given in Figure 5.

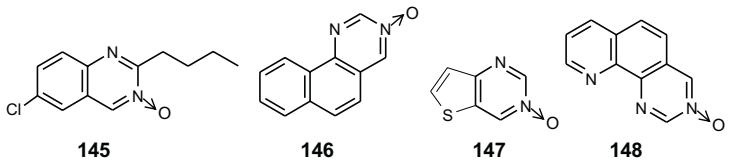
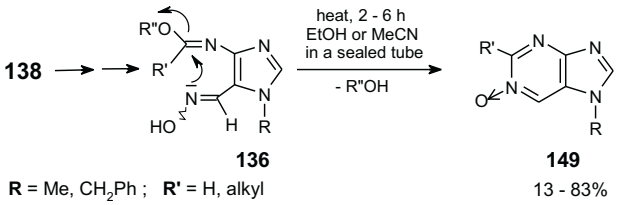


Figure 5

The synthesis of purine mono-*N*-oxides from 4-nitroimidazole derivatives by this method is also possible, and, for the first time, selective introduction of the N→O function into the 1-position in the target purine was achieved [11,13] (Scheme 43). However, for purine derivatives, this cyclization gives variable yields, because a few competitive reactions were observed. Thus, for each case of the purine *N*-oxide preparation, the optimization of the conditions was necessary (100–200°C in EtOH or CH_3CN, heating in a sealed tube).

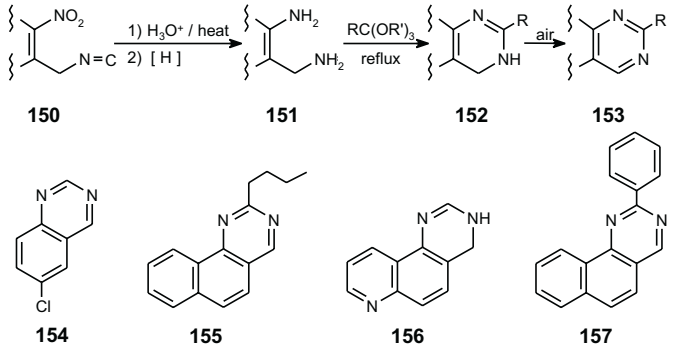
Scheme 43



4.3. Synthesis of fused pyrimidines *via* isocyanides. This approach is based on nitroarylmethyl-isocyanides (**150**) (Scheme 44), which are readily prepared *via* VNS with the use of nitroarenes and phenylthiomethylisocyanide, $PhSCH_2NC$ [121]. A practical application of the above method for the synthesis of fused pyrimidines is reported in [12].

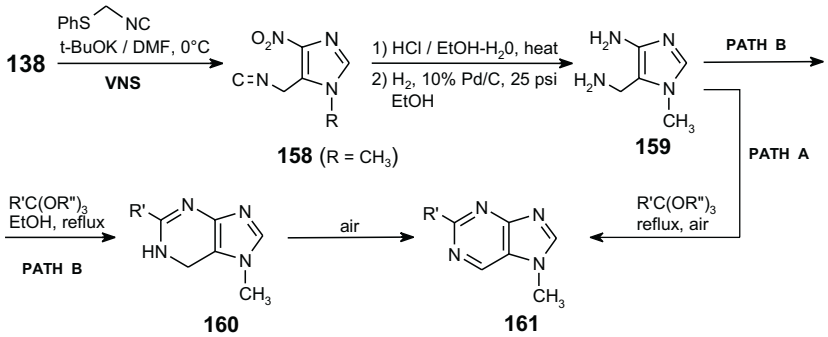
The exhaustive hydrolysis of **150**, and subsequent hydrogenation on a palladium catalyst, gave rise to the diamine derivative **151**, which was converted by treatment with an orthoester into the fused pyrimidine **153** (*C2 insertion*). The last step – an aromatization of the dihydro-derivative **152** – usually occurred spontaneously. In addition to its simplicity, this efficient pathway allowed functionalization at C-2 by using diverse orthoesters, as well as to stop the condensation at the stage of the dihydro-compound **152** (*via* lower temperature and dilution of the reaction mixture with ethanol). Some of the synthesised products (**154–157**) are listed below in Scheme 44.

Scheme 44



This approach, *via* the 5-(isocyanomethyl)-4-nitro-1*H*-imidazole derivative **158**, gave purines **161** in *ca* 20% overall yields. An aromatization of the dihydro-derivative (**160**, while exposed to air), occurred spontaneously as well (path A) [13].

Scheme 45



When the condensation with orthoesters (**159**→**160**) was carried out in boiling ethanol (to assure lower temperature, and to avoid the degradation of the unstable diamino compound **159** [130,131]), considerable higher yields (for R′ = H, Me) of the dihydro-purine **160** were obtained (40–60%, path B).

4.4. Summary. The methods presented in Chapter 4 yield intermediates, which are valuable for the synthesis of many fused pyrimidines. The development of several new and efficient approaches to these compounds was illustrated in papers [10–15].

Of significant importance are: (**a**) The hitherto unknown cyclocondensation of the *ortho*-neighbouring iminoether and oxime groups (in imidazole ring) with ammonia, leading to purine rings [10,13] (or other fused pyrimidine derivatives [14]). (**b**) The selective introduction of the N→O functionality into the desired position in target heterocyclic compounds having more than one nitrogen atom [11,13], which has a wide range of applications in this selective synthesis. This demonstrates the general character of the presented method: any other process cannot obtain the newly prepared purine 1-oxides [13]. (**c**) The use of *ortho*-isocyanomethyl nitro-aromatic/heteroaromatic compounds in the synthesis of fused pyrimidines [12]. Many quinazolines, as well as various bicyclic and tricyclic new heteroaromatic compounds, were obtained by this method.

Starting materials in the above syntheses were either commercially available or very easily obtainable aromatic nitro compounds. The first synthetic step, the Vicarious Nucleophilic Substitution of Hydrogen reaction, can serve for the introduction of appropriate substituents into the position *ortho*- to the nitro group. This creates opportunities for transformations to the cyclizible intermediates. If one takes into account the extensive spectrum of available starting nitroarenes, the outcome of these methods will considerably broaden the frontiers of the synthesis of these biologically important compounds.

5. Conclusions

Many fused pyrimidines, such as purines, pteridines, or quinazolines, belong to the most important heterocyclic systems, and there are numerous synthetic preparative methods for these compounds. In this short review the well-known methods by the pyrimidine ring construction are presented. However, in some cases, difficult access to key intermediates, or to their precursors, was a serious limitation for the above syntheses. For this reason, the synthesis of purines from imidazole precursors has not so far been investigated in detail.

New perspectives in this chemistry open the possibilities of reactions involving the nucleophilic substitution of hydrogen, in which the starting materials are the easily obtainable aromatic or heteroaromatic nitrocompounds. Surreptitiously, it also allows the selective preparation of fused pyrimidine mono-*N*-oxides with the N→O functionality (in the target moiety) in the desired position.

Acknowledgment

The author's fee was financed by the Association for Author Rights Collective Administration of Scientific and Technical Works KOPIPOL with a seat in Kielce from the remuneration collected on the basis of Art. 20 of the Law on Author Right and Related Rights.

REFERENCES

1. Armarego W.L.F., in *The Chemistry of Heterocyclic Compounds, Fused Pyrimidines*, Part I: "Quinazolines", Brown D.J., ed.; vol. 24/1, Interscience Publishers: NY - London - Sydney, 1967.
2. Lister J.H., in *The Chemistry of Heterocyclic Compounds, Fused Pyrimidines*, Part II: "Purines", Brown D.J., ed.; vol. 24/2, Wiley - Interscience: NY - London - Sydney - Toronto, 1971.
3. Brown D.J., in *The Chemistry of Heterocyclic Compounds*, *Fused Pyrimidines*, Part III: "Pteridines", Taylor E.C., ed.; vol. 24/3, J. Wiley & Sons: NY - Chichester - Brisbane - Toronto - Singapore, 1988.
4. Delia T.J., in *The Chemistry of Heterocyclic Compounds*, *Fused Pyrimidines*, Part IV: "Miscellaneous Fused Pyrimidines", Taylor E.C., ed.; vol. 24/4, J. Wiley & Sons, Inc.: NY - Chichester - Brisbane - Toronto - Singapore, 1992.
5. Brown D.J., in *The Chemistry of Heterocyclic Compounds*, *The Pyrimidines*, Taylor E.C., ed.; vol. 23, J. Wiley & Sons: NY - Chichester - Brisbane - Toronto - Singapore, 1994.
6. Brown D.J., in *The Chemistry of Heterocyclic Compounds*, *Quinazolines*, Supplement I, Taylor E.C., ed.; vol. 55, J. Wiley & Sons, Inc.: NY - Chichester - Brisbane - Toronto - Singapore - Weinheim, 1996.
7. Katritzky A.R. and Rees C.W., *Comprehensive Heterocyclic Chemistry*, vol. 1, part 1, Meth-Cohn O., ed.; Pergamon Press: Oxford, 1984, pp. 143–199.
8. Katritzky A.R., Rees C.W. and Scriven E.F.V., *Comprehensive Heterocyclic Chemistry II*, vol. 6, Boulton A.J., ed.; Pergamon Press: Oxford - NY - Tokyo, 1996, pp. 195-231.
9. Ostrowski S., *Polish J. Chem*., **68**, 2237 (1994).
10. Ostrowski S., *Synlett*, 253 (1995).
11. Ostrowski S., *Heterocycles*, **43**, 389 (1996).
12. Ostrowski S., *J. Chem. Res.* (**S**), 14 (1998); (**M**), 0180–0187 (1998).
13. Ostrowski S., *Molecules*, **4**, 287 (1999).
14. Ostrowski S., unpublished results.
15. Ostrowski S. and Wolniewicz A.M., *Chem. Heterocycl. Compounds*, 806 (2000).
16. Mąkosza M. and Winiarski J., *Acc. Chem. Res*., **20**, 282 (1987).
17. Mąkosza M. and Wojciechowski K., *Liebigs Ann./Recueil*, 1805 (1997).
18. Ref. [3], pp. 358–360.
19. Albert A., in *Selective Toxicity: The Physico-Chemical Basis of Therapy*, 7th ed., Chapman N.B. and Hall J.E., eds.; London, 1985, p. 347.
20. Weinstock J., Wilson J.W., Wiebelhaus V.D., Maass A.R., Brennan F.T. and Sosnowski G., *J. Med. Chem*., **11**, 573 (1968).
21. Ref. [1], pp. 490–518.
22. Bough R.G., Gurd M.R., Hall J.E. and Lessel B., *Nature*, **200**, 656 (1963).
23. Mehta D.R., Naravane J.S. and Desai R.M., *J. Org. Chem.*, **28**, 445 (1963).
24. Baker B.R., Schaub R.E., McEvoy F.J. and Williams J.H., *J. Org. Chem.*, **17**, 132 (1952).
25. Constantine J.W. and Hess H.-J., *Eur. J. Pharmacol*., **74**, 227 (1981).
26. Armarego W.L.F. and Smith J.I., *J. Chem. Soc. (C)*, 234 (1966).
27. Madding G.D., *J. Org. Chem.*, **37**, 1853 (1972).
28. Derieg M.E., Fryer R.I., Hillery S.S., Metlesics W. and Silverman G., *J. Org. Chem.*, **36**, 782 (1971).
29. Haider N., Heinisch G. and Moshuber J., *Arch. Pharm. (Weinheim, Ger)*, **325**, 119 (1992).
30. Byford A., Goadby P., Hooper M., Kamath H.V. and Kulkarni S.N., *Indian J. Chem.,* **27B**, 396 (1988).
31. Ref. [8], pp. 211–212.
32. Armarego W.L.F., *J. Chem. Soc.*, 561 (1962).
33. LeMahieu R.A., Carson M., Nason W.C., Parrish D.R., Welton A.F., Baruth H.W. and Yaremko B., *J. Med. Chem*., **26**, 420 (1983).

34. Nixon W.J., Jr., Garland J.T. and Blanton C.D., Jr., *Synthesis*, 56 (1980).
35. Ref. [1], pp. 74–78.
36. Mayer J. and Wagner E., *J. Org. Chem.*, **8**, 239 (1943).
37. a) Korbonits D. and Kolonits P., *J. Chem. Res.* (**S**), 209 (1988); (**M**), 1652 (1988); b) *ibid*. (**S**), 328 (1989).
38. Korbonits D. and Kolonits P., *Acta Chim. Hung.*, **127**, 795 (1990); *C.A.,* **115**, 71523 (1991).
39. Nakanishi S. and Massett S.S., *Org. Prep. Proced. Int*., **12**, 219 (1980).
40. Taylor E.C., McKillop A. and Vromen S., *Tetrahedron*, **23**, 885 (1967).
41. Bonola G., Da Re P., Magistretti M.J., Massarani E. and Setnikar I., *J. Med. Chem*., **11**, 1136 (1968).
42. Cantarelli G., *Farmaco, Ed. Sci.*, **25**, 770 (1970).
43. Field G.F., Zally W.J. and Sternbach L.H., *J. Org. Chem.*, **36**, 777 (1971).
44. Manhas M.S. and Amin S.G., *J. Heterocycl. Chem*., **14**, 161 (1977).
45. Ref. [6], pp. 44–49.
46. Yale H.L. and Kalkstein M., *J. Med. Chem.*, **10**, 334 (1967).
47. Hammen P.D. and Allen D.J.M., *J. Heterocycl. Chem.*, **24**, 1701 (1987).
48. Wolfe J.F., Rathman T.L., Sleevi M.C., Campbell J.A. and Greenwood T.D., *J. Med. Chem*., **33**, 161 (1990).
49. Cho N.S., Song K.Y. and Párkányi C., *J. Heterocycl. Chem*., **26**, 1807 (1989).
50. Combs D.W. and Rampulla M.S., *J. Heterocycl. Chem*., **26**, 1885 (1989).
51. Peet N.P., Sunder S. and Barbuch R.J., *J. Heterocycl. Chem*., **17**, 1513 (1980).
52. Gordeev M.F., Hui H.C., Gordon E.M. and Patel D.V., *Tetrahedron Lett*., **38**, 1729 (1997).
53. Shishoo C.J., Devani M.B., Ananthan S., Jain K.S., Bhadti V.S., Mohan S. and Patel L.J., *Indian J. Chem., Sect. B*, **28**, 1039 (1989).
54. Urleb U., *J. Heterocycl. Chem*., **35**, 693 (1998).
55. Beam Ch.F., Heindel N.D., Chun M. and Stefanski A., *J. Heterocycl. Chem*., **13**, 421 (1976).
56. Canonne P., *Heterocycles*, **36**, 1305 (1993).
57. Bell S.C. and Childress S.J., *J. Org. Chem*., **27**, 1691 (1962).
58. Goto T, Kishi Y., Takahashi S. and Hirata Y., *Tetrahedron*, **21**, 2059 (1965).
59. Albert A., in *Advances in Heterocyclic Chemistry*, Katritzky A.R., ed.; **31**, 2 (1982).
60. Baker B.R. and Almaula P.I., *J. Org. Chem*., **27**, 4672 (1962).
61. Kano S., Tanaka Y., Sugino S. and Hibino S., *Synthesis*, **1980**, 695.
62. Tomioka Y., Ohkubo K. and Yamazaki M., *Chem. Pharm. Bull*., **33**, 1360 (1985).
63. Hosmane R.S., Lim B.B., Summers M.F., Siriwardane U., Hosmane N.S. and Chu S.S.C., *J. Org. Chem*., **53**, 5309 (1988).
64. Brown D.J. and Ienaga K., *J. Chem. Soc., Perkin Trans. 1*, **1975**, 2182.
65. Foster Ch.H. and Elam E.U., *J. Org. Chem*., **41**, 2646 (1976).
66. Schofield K., *J. Chem. Soc*., **1952**, 1927.
67. Bergman J., Brynolf A., Elman B. and Vuorinen E., *Tetrahedron*, **42**, 3697 (1986).
68. Strekowski L., Cegła M.T., Harden D.B., Mokrosz J.L. and Mokrosz M.J., *Tetrahedron Lett*., **29**, 4265 (1988).
69. Desai K.R. and Desai P.H., *J. Indian Chem. Soc*., **65**, 804 (1988).
70. Nielsen K.E. and Pedersen E.B., *Chem. Scr*., **18**, 242 (1981).
71. Kokel B., Menichi G. and Hubert-Habart M., *Tetrahedron Lett*., **25**, 1557 (1984).
72. Ref. [6], pp. 21–22.
73. Shiau C.-Y., Chern J.-W., Liu K.-C., Chan C.-H., Yen M.-H., Cheng M.-C. and Wang Y., *J. Heterocycl. Chem*., **27**, 1467 (1990).
74. Pazdera P. and Pichler J., *Chem. Pap*., **45**, 517 (1991).
75. Zinner G., Klein H. and Kahnert H., *Chem.-Ztg*., **111**, 341 (1987); *C.A.,* **109**, 128939 (1988).
76. Taylor E.C. and McKillop A., *The Chemistry of Cyclic Enamino-nitriles and ortho-Amino-nitriles*, Wiley-Interscience: NY, 1970.
77. Taylor E.C., Patel H.H. and Jun J.-G., *J. Org. Chem.*, **60**, 6684 (1995).
78. Dean W.D. and Papadopoulos E.P., *J. Heterocycl. Chem*., **19**, 171 (1982).
79. Uneyama K., Yamashita F., Sugimoto K. and Morimoto O., *Tetrahedron Lett.*, **31**, 2717 (1990).
80. Golomolzin B.V. and Postovskii I.Y., *Khim. Geterotsikl. Soedin*., **1970**, 855.
81. Stankovský Š, Dérer T. and Špirková K., *Monatsh. Chem*., **124**, 733 (1993).

82. Rossi E., Celentano G., Stradi R. and Strada A., *Tetrahedron Lett*., **31**, 903 (1990).
83. Rossi E., Calabrese D. and Farma F., *Tetrahedron*, **47**, 5819 (1991).
84. Robev S.K., *Tetrahedron Lett*., **24**, 4351 (1983).
85. Bandurco V.T., Schwender Ch.F., Bell S.C., Combs D.W., Kanojia R.M., Levine S.D., Mulvey D.M., Appollina M.A., Reed M.S., Malloy E.A., Falotico R., Moore J.B. and Tobia A.J., *J. Med. Chem*., **30**, 1421 (1987).
86. Gewald K., Schäfer H. and Mauersberger K., *Z. Chim*., **17**, 223 (1977).
87. Goerdeler J. and Eggers W., *Chem. Ber.*, **119**, 3737 (1986).
88. Partridge M.W. and Smith A., *J. Chem. Soc., Perkin Trans. 1*, **1973**, 453.
89. Erian A.W. and Abu-Shanab F.A., *Bull. Chem. Soc. Jpn*., **71**, 2387 (1998).
90. Huys F., Merényi R., Janousek Z., Stella L. and Viehe H.G., *Angew. Chem*., **91**, 650 (1979).
91. Schmidt R.R., Schneider W., Karg J. and Burkert U., *Chem. Ber.*, **105**, 1634 (1972).
92. Olofson R.A. and Meer R.K.V., *J. Org. Chem*., **49**, 3377 (1984).
93. Samokhvalov G.I., *Med. Prom. SSSR*, **11**, 10 (1957); *C.A*., **52**, 7334i (1958).
94. Glasby J.S., *Encyclopaedia of Antibiotics*, J. Wiley & Sons: Chichester - Brisbane - NY - Toronto, 1979.
95. Le Page G.A., Worth L.S. and Kimbal A.P., *Cancer Res*., **36**, 1481 (1976).
96. McCarthy J.R., Stemerick D.M., Prakash N.J., Edwards M.L. and Jarvi E.T., Eur. Pat. Appl. EP 365,849, 1990; *C.A*., **114**, 24495p (1991).
97. Jeong L.S., Schinazi R.F., Beach J.W., Kim H.O., Nampalli S., Shanmuganathan K., Alves A.J., McMillan A., Chu C.K. and Mathis R., *J. Med. Chem*., **36**, 181 (1993).
98. Barchi J.J., Jr., Marquez V.E., Driscoll J.S., Ford H., Jr., Mitsuja H., Shirasaka T., Aoki S. and Kelly J.A., *J. Med. Chem*., **34**, 1647 (1991).
99. Prabhakar Y.S. and Bhakuni D.S., *Indian J. Biochem. Biophys*., **27**, 342 (1990); *C.A*., **114**, 156594e (1991).
100. Nord L.D., Dalley N.K., Mc Kernan P.A. and Robins R.K., *J. Med. Chem*., **30**, 1044 (1987).
101. Effland R.Ch., Klein J.T., Davis L. and Olson G.E., Eur. Pat. Appl. EP 402,752, 1990; *C.A*., **114**, P247683z (1991).
102. Kelly J.L., Krochmal M.P., Linn J.A., McLean E.W. and Soroko F.E., *J. Med. Chem*., **31**, 606 (1988).
103. Merlos M., Gomez L., Vericat M.L., Bartroli J., Garcia-Rafanell J. and Forn J., *Eur. J. Med. Chem*., **25**, 653 (1990).
104. Strong F.M., Skoog F. and Miller C.O., Ger. Pat. 1,026,334, 1958; *C.A*., **54**, P18863h (1960).
105. Fischer K., Mayer H., Hamprecht G., Wuerzer B. and Westphalen K.O., Ger. Offen DE 3,921,271, 1991; *C.A*., **114**, P142981s (1991).
106. Ref. [2], pp. 31–90.
107. Lister J.H., in *The Chemistry of Heterocyclic Compounds*, *The Purines*; Supplement 1; Wiley-Interscience: NY - Chichester - Brisbane - Toronto - Singapore, 1996.
108. Bobrański B. and Synowiedzki Z., *J. Am. Pharm. Assoc., Sci. Edu*., **37**, 62 (1948).
109. Kadir K., Shaw G. and Wright D., *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2728.
110. Andersen K.E. and Pedersen E.B., *Liebigs Ann. Chem*., **1985**, 921.
111. Birkett P.R., King H., Chapleo Ch.B., Ewing D.F. and Mackenzie D., *Tetrahedron*, **49**, 11029 (1993).
112. Shaw G., *J. Org. Chem*., **30**, 3371 (1965).
113. Yamazaki A., Kumashiro I. and Takenishi T., *J. Org. Chem*., **32**, 3258 (1967).
114. Glushkov R.G. and Magidson O.Yu., *Khim. Geterotsikl. Soedin*., 85 (1965).
115. Baxter R.A. and Spring F.S., *Nature*, **154**, 462 (1944).
116. Booth B.L. and Proença M.F., *J. Chem. Soc., Chem. Commun*., 788 (1981).
117. Albert A., *J. Chem. Soc., Perkin Trans. 1*, 2659 (1973).
118. Prasad R.N. and Robins R.K., *J. Am. Chem. Soc*., **79**, 6401 (1957).
119. Al-Shaar A.H.M., Gilmour D.W., Lythgoe D.J., McClenaghan I. and Ramsden Ch.A., *J. Chem. Soc., Chem. Commun*., 551 (1989).
120. Mąkosza M. and Owczarczyk Z., *J. Org. Chem*., **54**, 5094 (1989).
121. Mąkosza M., Ostrowski S. and Kinowski A.J., *Synthesis*, 1215 (1993).
122. Katritzky A.R. and Lagowski J.M., in *Chemistry of the Heterocyclic N-oxides*, Blomquist A.T., ed.; Acad. Press: London - NY, 1971, pp. 19–141.
123. Adachi K., *Yakugaku Zasshi*, **77**, 507, 514 (1957); *C.A*., **51**, 14744i, 14745i (1957).

124. Sternbach L.H., Kaiser S. and Reeder E., *J. Am. Chem. Soc*., **82**, 475 (1960).
125. Sternbach L.H., Reeder E., Keller O. and Matlesics W., *J. Org. Chem*., **26**, 4488 (1961).
126. Schöpf C., Hartmann A. and Koch K., *Chem. Ber.*, **69**, 2766 (1936).
127. Hansen S.B. and Petrow V., *J. Chem. Soc*., 350 (1953).
128. Taylor E.C., Cheng C.C. and Vogl O., *J. Org. Chem*., **24**, 2019 (1959).
129. Cresswell R.M. and Brown G.-B., *J. Org. Chem*., **28**, 2560 (1963).
130. Bodor N., Dewar M.J.S. and Harget A.J., *J. Am. Chem. Soc*., **92**, 2929 (1970).
131. Al-Shaar A.H.M., Chambers R.K., Gilmour D.W., Lythgoe D.J., McClenaghan I. and Ramsden Ch.A., *J. Chem. Soc., Perkin Trans. 1*, 2779, 2789 (1992).