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FUSED 1,2,5-THIADIAZOLES AND SELENADIAZOLES

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Abstract -- Syntheses of aromatic and azaaromatic fused 1,2,5-thia- and selenadiazoles are described as well as the examples of their chemical reactivity are given.

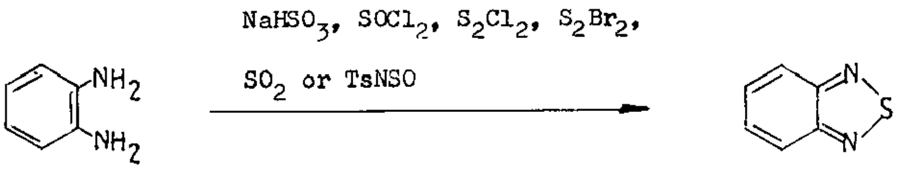
I. INTRODUCTION

The present paper, a continuation of our review[1], is dealing with heterocycles containing thiadiazole or selenadiazole ring condensed with aromatic system[2].
These compounds are interesting for their biological activity; they are used as drugs[3-6], herbicides[7,8] or radioprotective agents[9,10].
An attention ought to be paid to thia- and selenadiazoles fused with azaaromatic, especially pyrimidine ring, these compounds being analogs of purines and pteridines[11-19].
Fused thia- and selenadiazoles can be classified into two groups, according to the incorporated aromatic or azaaromatic system.

II. FUSED THIADIAZOLES

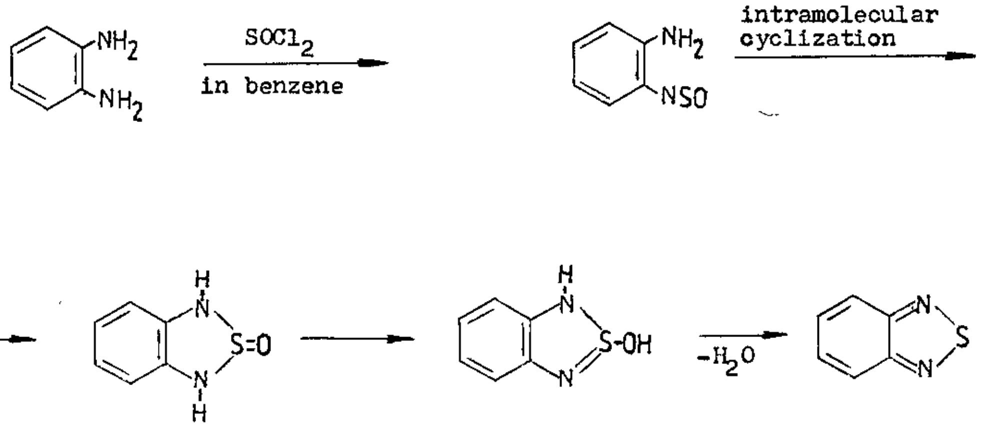
1 Syntheses

The parent compound of thiadiazoles condensed with aromatic ring is 2,1,3-benzothiadiazole, available from o-phenylenediamine in following reactions[20-26]:



In an analogous manner thiadiazoles containing azaaromatic ring /pyridine, pyrimidine, pyrazine/ can be prepared and the appropriate o-diaminoheterocycles are used as starting materials[27].

In the reaction of o-phenylenediamine with thionyl chloride, the initially formed 2-amino-N-sulfinylaniline undergoes the intramolecular cyclization to give 1 . Rearrangement of 1 and the following water elimination yields benzothiadiazole[28].



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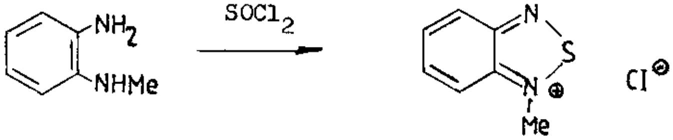
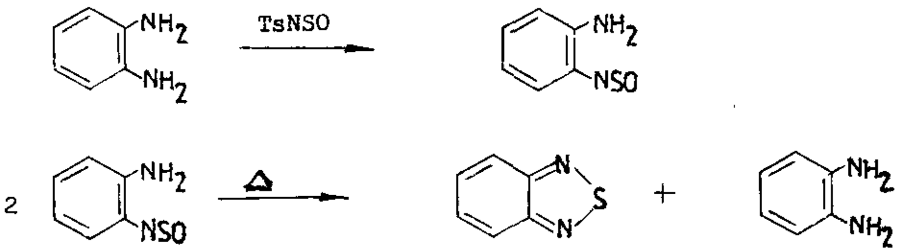
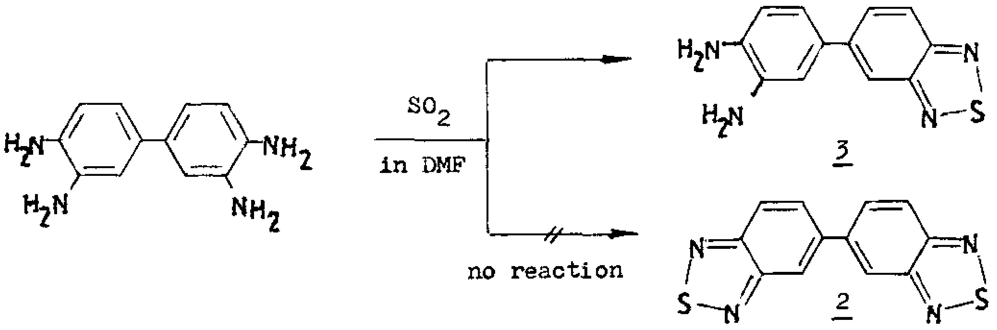
The interaction of N-metyl-o-phenylenediamine instead of o-phenylenediamine with thionyl chloride gives rise to benzothiadiazolium chloride[29]:



In the transsulfinylation reaction of o-phenylenediamine with TsNSO, the first step results in 2-amino-N-sulfinylaniline, which at higher temperatures undergoes a disproportionation to benzotiadiazole and o-phenylenediamine[30].



When 3,3'-diaminobenzidine was treated with sulfur dioxide in the DMF solution, 2 did not form, and the reaction resulted only in formation of 3 . This compound can be used as starting material in syntheses of heterocyclic steroide analogs[24].

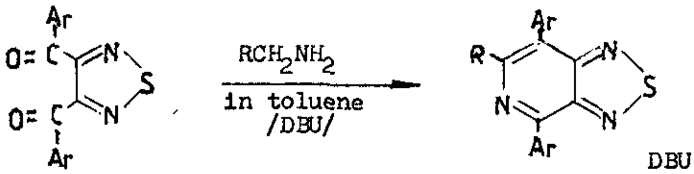


Among fused thiadiazole azaaromatics the thiadiazolopyridines should be mentioned. Harts obtained the following chloro and hydroxy derivatives of thiadiazolopyridines[16,31]:

X = H, Cl, OH

As the synthetic route the reaction of suitable o-diaminopyridines with thionyl chloride was used.

An other synthetic approach to thiadiazolopyridines, involving the pyridine ring formation, was described by Mataka and coworkers[32]. In this method, the 3,4-diaroyl-1,2,5-thiadiazoles are treated with amines in the presence of DBU catalyst:

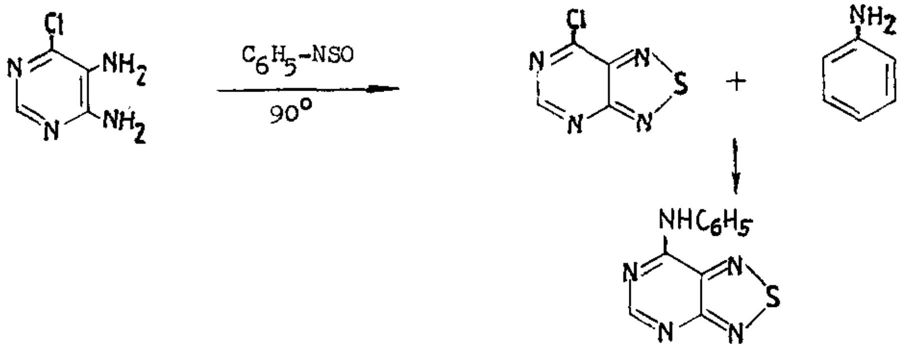


DBU = 1,8-diazabicyclo [5.4.0]undec-7-ene

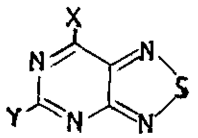
R = CH_2OH, COOEt, C_6H_5 Ar = C_6H_5, p-Me-C_6H_4

Fused thiadiazole systems, incorporating pyrimidine ring are interesting for their biological activity. These compounds are available from o-diaminopyrimidines in the reaction with thionyl chloride, sulfur dioxide or N-sulfinylaniline[16,28,31].

In the preparation of chlorothiadiazolopyrimidines, as in the case of their pyridine analogs, the nucleophilic substitution of the chlorine atom can occur:[33]

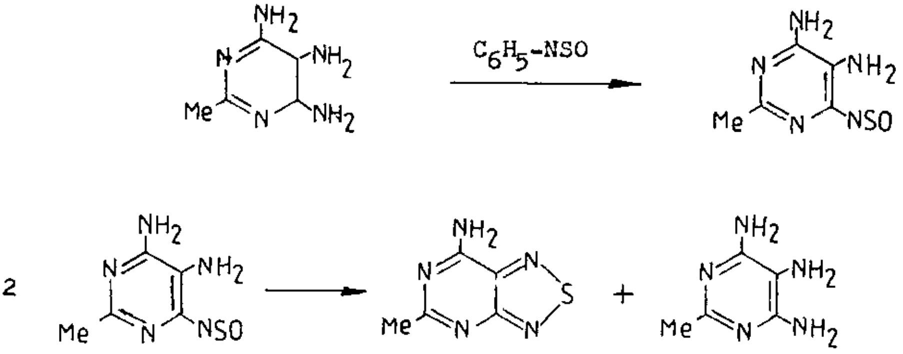


The use of N-sulfinylaniline in these syntheses is preferred over thionyl chloride because of the milder reaction conditions. In this way a series of substituted thiadiazolopyrimidines was obtained:[33]



X = NH_2, NMe_2, NHC_6H_5
Y = H, Me, SH, SMe

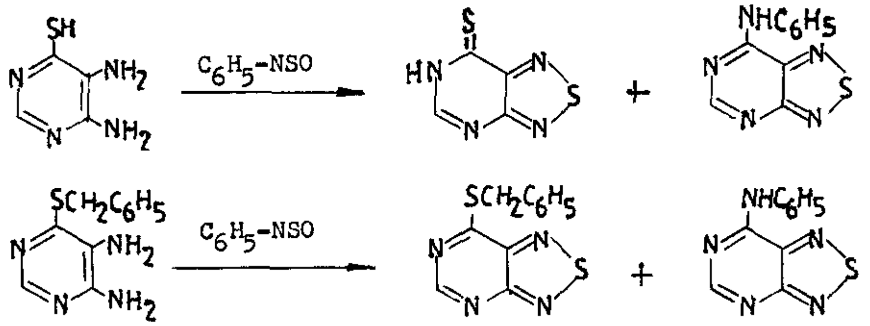
Carrying out reactions of o-diaminopyrimidines with N-sulfinylaniline derivatives, the influence of substituents on their reactivity was investigated.
If N-sulfinylaniline is substituted by electron-donating groups, the electropositive character of sulfur atom, and in turn, its reactivity is decreased; therefore such N-sulfinylanilines can be used in the transsulfinylation reaction of very reactive o-diaminopyridines[34].
In the syntheses carried out with N-sulfinylaniline, thiadiazolopyrimidines are formed in the disproportionation of the initially resulting 2-amino N-sulfinylanilines[33], e.g.:



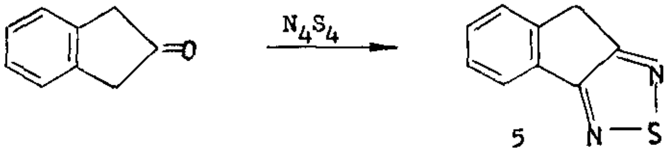
There were synthesized numerous thiadiazoloheterocycles, incorporating pyrimidine ring, analogs of adenine, guanine, xanthine or theophylline, as well as hypoxanthines and mercaptopurines[35,36]; for instance, the analog of theophylline 4 was obtained in the reaction:[35]

4

The thio-derivates of thiadiazolopyrimidines were produced in the following manner:[33]



Among so far not much studied thiadiazoles fused with polycyclic systems there ought to be mentioned the indene derivative 5 , obtained by Mataka and coworkers:[37]



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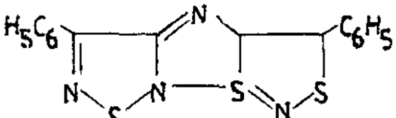
Compounds of the type 6 were synthesized by Tashiro and coworkers by the action of tetrasulfur tetranitride on phenylacetylene[38].



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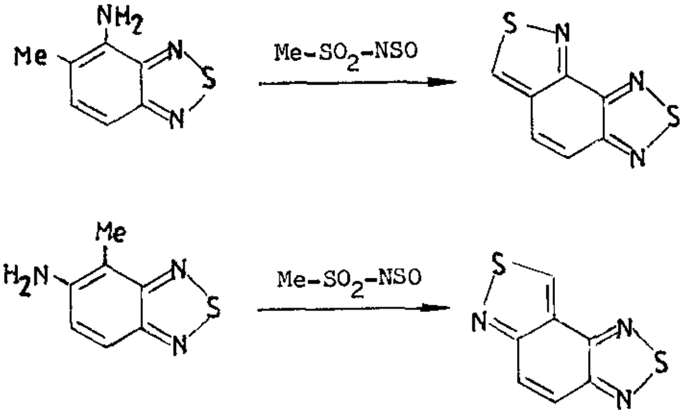
Danylec and Davis have carried out the following reactions:[39,40]



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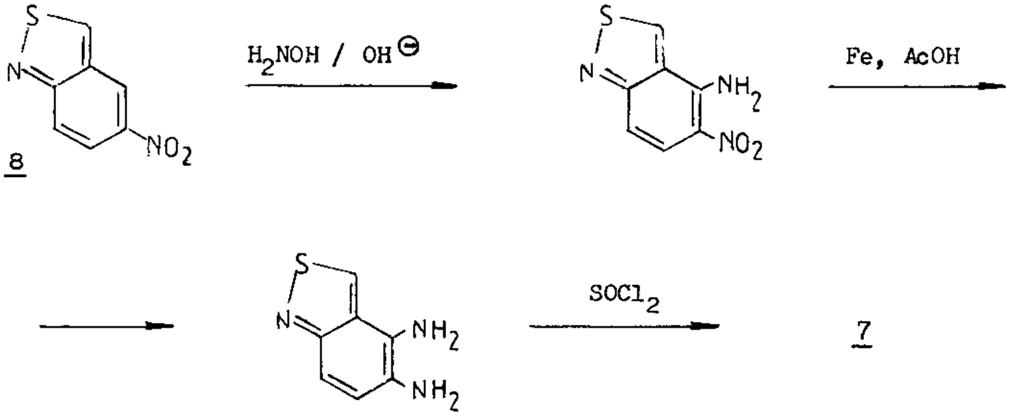
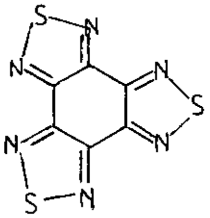
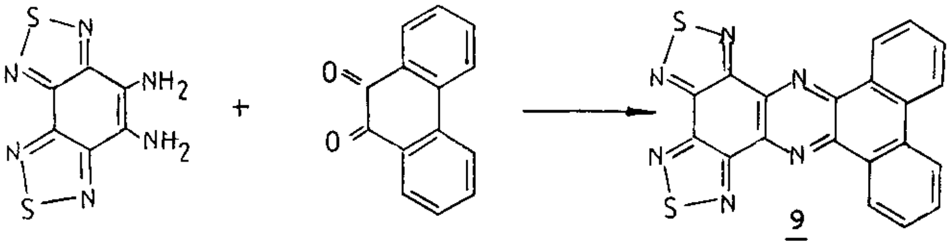
Compound 7 can also be obtained by the amination of 8, followed by reduction and cyclization with thionyl chloride:[40]



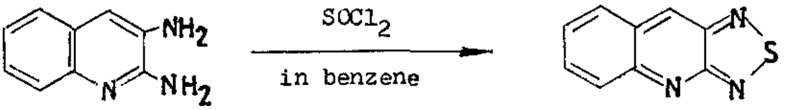
Benzotristhiadiazole has been described by Komin and Carmack:[41]

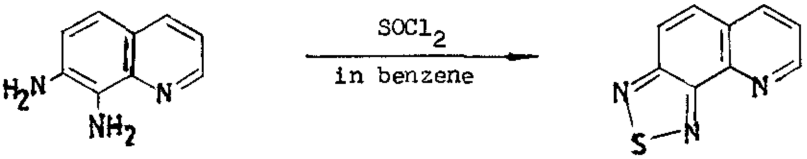


The heptacyclic system 9 can be obtained in the following condensation reaction:[41]

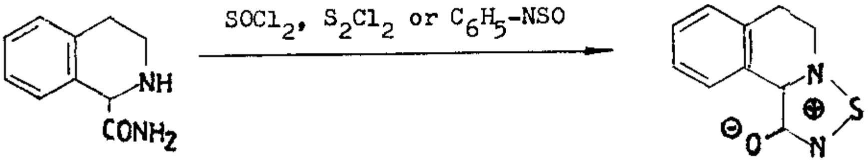


The synthesis of thiadiazoloquinolines was reported by Sharma and coworkers:[12]





To heterocycles containing thiadiazole ring can be included also the mesoionic compound 10 prepared by Masuda and coworkers:[42]



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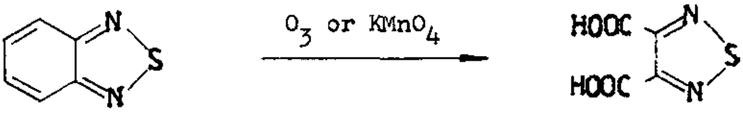
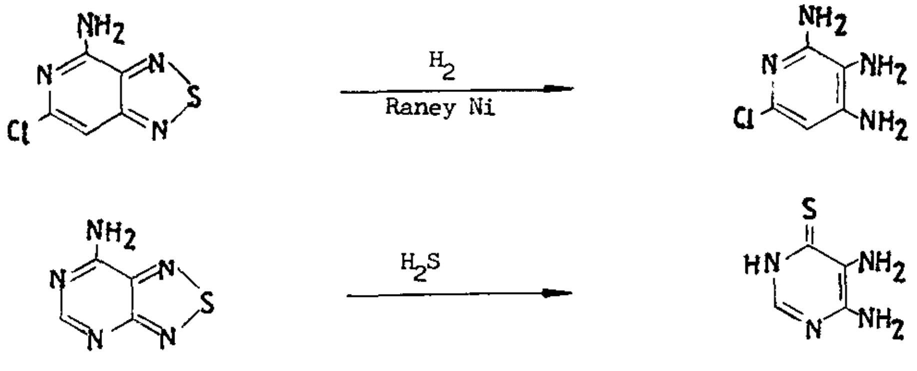
2 Chemical reactivity

The redox behaviour of benzothiadiazoles has been determined using mercury and platinum electrode.[43]

The oxidation of aromatic fused thiadiazoles results in the formation of dicarboxylic acid, e.g.:[44]



In the reduction of fused aromatic thiadiazoles o-diamines are formed; an analogous reductive cleavage was observed in the case of thiadiazolopyridines and -pyrimidines; the action of hydrogen sulfide however gave rise to the thio derivative 11. These reactions are useful in the structure elucidation of condensed aromatic thiadiazoles.[31,33]



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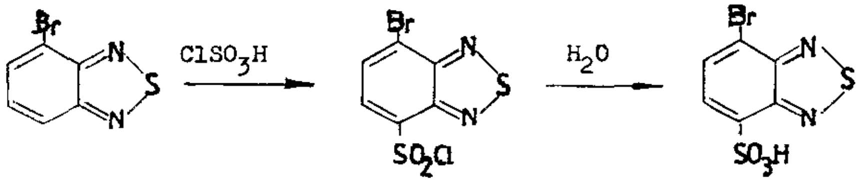
The interaction of 4-bromobenzothiadiazole with chlorosulfonic acid results in sulfochloride 12, which undergoes hydrolysis to give the sulfonic acid 13[44].



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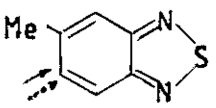
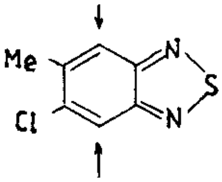
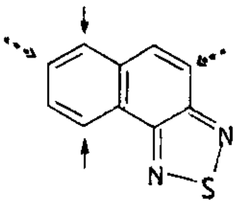
The quaternization reactions of benzothiadiazoles were examined by Davis and coworkers using dimethyl sulfate[45].

To investigate the reactivity of benzothiadiazoles their electrophilic substitution was studied. As examples of this reaction, the nitration and halogenation were performed in the benzene and naphthalene thiadiazole series[6,19,21,44,46,47].

Positions of the electrophilic attack are:



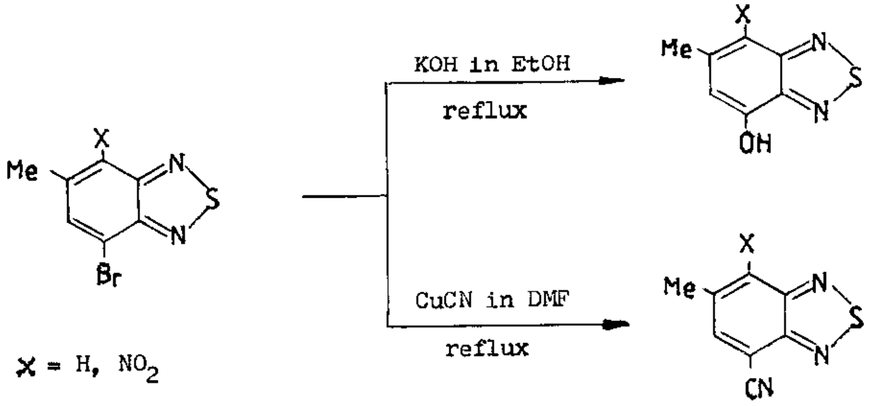




→ nitration

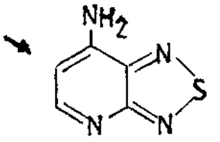
••> halogenation

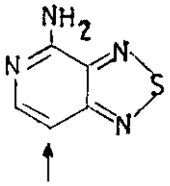
Nucleophilic substitution of the Br atom in bromobenzothiadiazoles was studied by Sharma:[19,21,30]

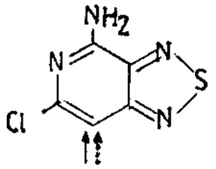


Thiadiazolopyridines undergo electrophilic substitution in a similar way as benzothiadiazoles. The thiadiazole ring for its electron-withdrawing properties makes the electrophilic substitution of the pyridine moiety difficult[30,31].

Positions of the electrophilic attack are:







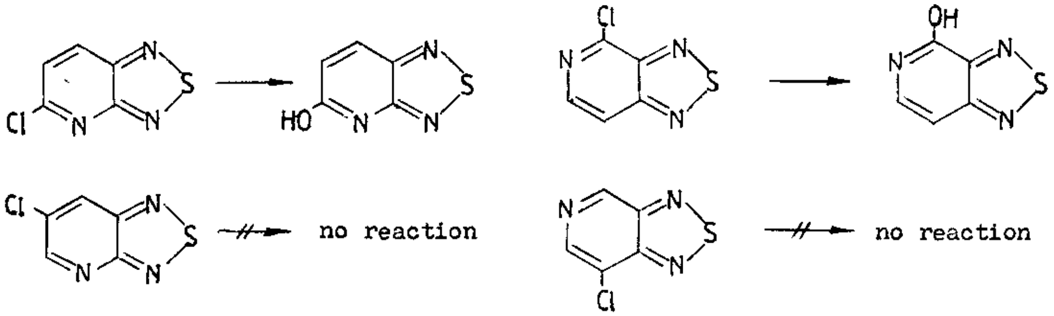
→ nitration

••> halogenation

The nucleophilic substitution of halogen in halogenothiadiazolopyridines is a useful synthetic approach to derivatives of thiadiazolopyridines[19,30,33]. In the chlorothiadiazolo[3,4-b]pyridines the 6-Cl, and in the [3,4-c] isomers the 7-Cl atoms do not undergo nucleophilic substitution, as is summarized in the following scheme[31,48].

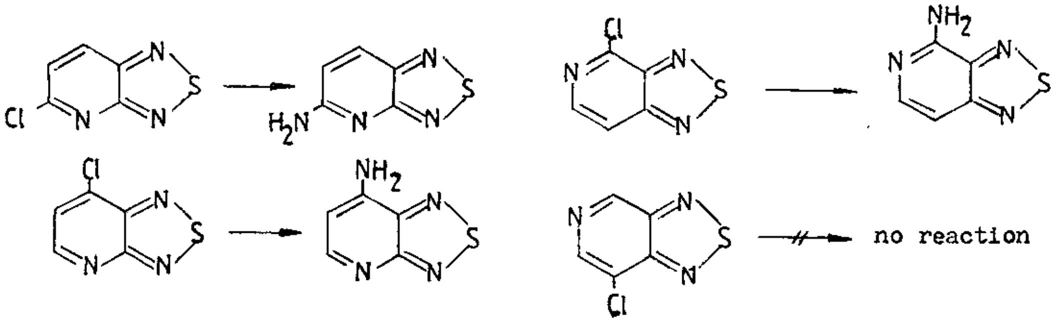
Hydrolysis

/ 5% AcOH, 2h, 100° /

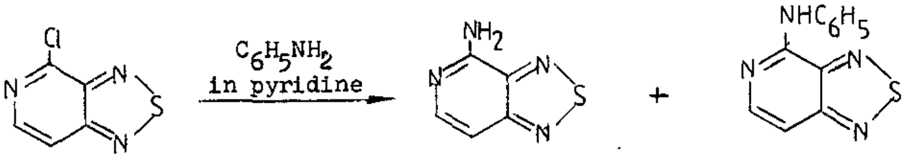


Ammonolysis

/ NH_3, 15h, 75° /

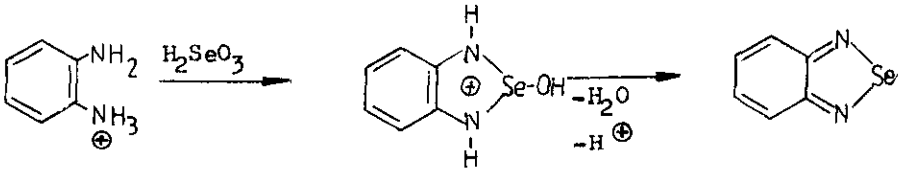


Heating of 4-chlorothiadiazolo[3,4-b]pyridine with aniline in pyridine gives rise to amino- and anilino derivatives:[31,49]

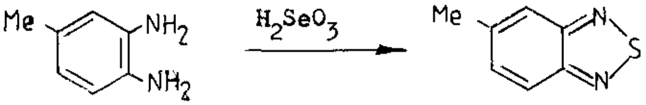


III. FUSED SELENADIAZOLES

Aromatic and azaaromatic selenadiazoles are not so much studied as their sulfur analogs. Benzoselenadiazoles are formed in the reaction of o-phenylenediamines with selenious acid or diselenium dichloride[50].

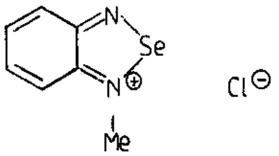


In a similar manner the substituted benzoselenadiazoles are obtained as follow[51,52].

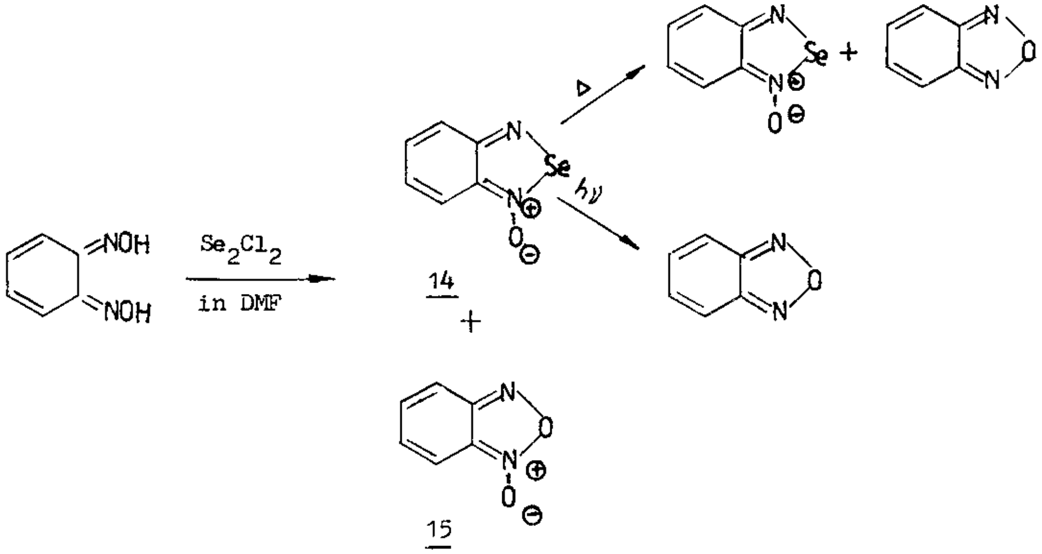


The reaction of o-diamines with selenious acid, resulting in fused selenadiazole systems can be useful as the photometric method of the selenium determination[53].

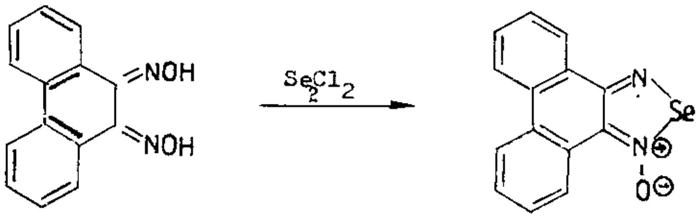
When in the reaction with selenious acid, instead of o-phenylenediamine its N-methyl derivative is used, the benzoselenadiazolium chloride is formed[29].



Pedersen treated 1,2-dioximes with diselenium dichloride to obtain in the first step N-oxides 14 and 15. The N-oxide 14 undergoes thermolysis to give benzoselenadiazole and benzooxadiazole, whereas in the photolysis only benzooxadiazole is formed[54,55].

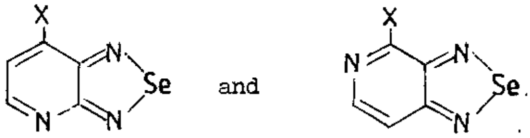


An other reaction of this kind proceeds as follows:[54]

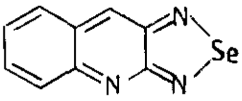


o-Diaminopyridines reacted with selenious acid to give selenadiazolopyridines:[16,31]

X = H, Cl, OH



In a similar way selenadiazoloquinolines 16 and 17 were synthesized[12].



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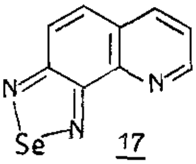

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The rates of quaternization of benzothiadiazoles were determined using dimethyl sulfate[45].

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