Synthesis and Properties of Diaza-, Triaza-, and Tetraazaphenothiazines

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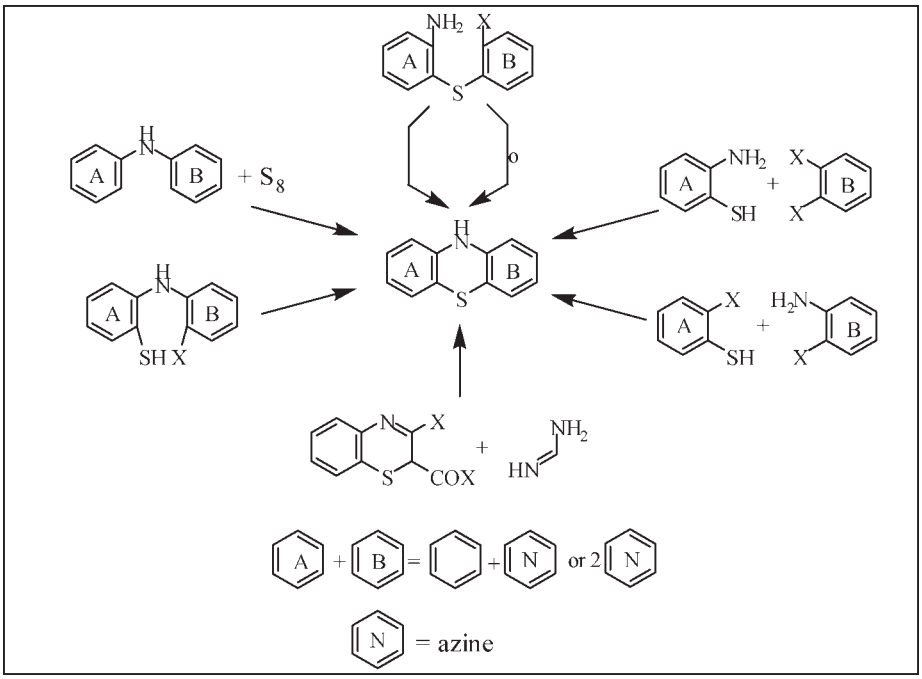

The review surveys the chemistry of diaza-, triaza-, and tetraazaphenothiazines and their benzo and dibenzo derivatives consisting of over 30 different heterocyclic systems.

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INTRODUCTION

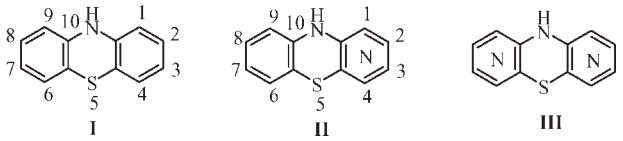
Phenothiazine (10*H*-dibenzo-1,4-thiazine, **I**) was obtained for the first time by Bernthsen in 1883 in the thionation of diphenylamine [1]. Since this moment over 5000 phenothiazine derivatives have been obtained and this class of organic compounds became very important because of their varied biological and chemical properties. Phenothiazines (mainly substituted at positions 2 and 10) exhibit valuable activities such as neuroleptic, antiemetic, antihistaminic, antipuritic, analgesic, and antihelmintic. At least 100 phenothiazines were used in therapy. Recent reports deal with anticancer, antiplasmid, and antibacterial activities, reversal of multidrug resistance and potential treatment in Alzheimer's and Creutzfeldt-Jakob diseases [2–6].

Modifications of the parent phenothiazine structure have been carried out by:

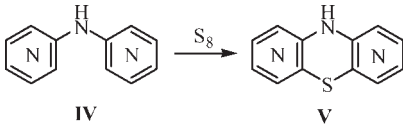
1. an introduction of a substituent at the thiazine nitrogen atom (at position 10),
2. an introduction of a substituent at the benzene ring (at positions 1–4 and 6–9, most often at position 2),
3. an oxidation of the sulfide function into sulfoxide and sulfone ones,
4. a substitution of one or two benzene rings with homoaromatic and heteroaromatic rings (most often azine rings).

Substitution with one or two azine rings led to new type of fused heterocyclic compounds being azinobenzo-1,4-thiazines II and diazino-1,4-thiazines III. Depending on the structure of an azine ring (pyridine, pyridazine, pyrimidine, pyrazine, quinoline, quinoxaline, and 1,2,4-triazine) they can form tri-, tetra-, and pentacyclic heterocycles. There has been known over 30 types of such heterocyclic systems. Okafor, Castle, and Wise synthesized a significant portion of these systems. As the azine rings contain one or more nitrogen atoms, these compounds are named as azaphenothiazines (monoaza-, di-, tri-, and tetraazaphenothiazines) (Scheme 1).

Scheme 1



Scheme 2



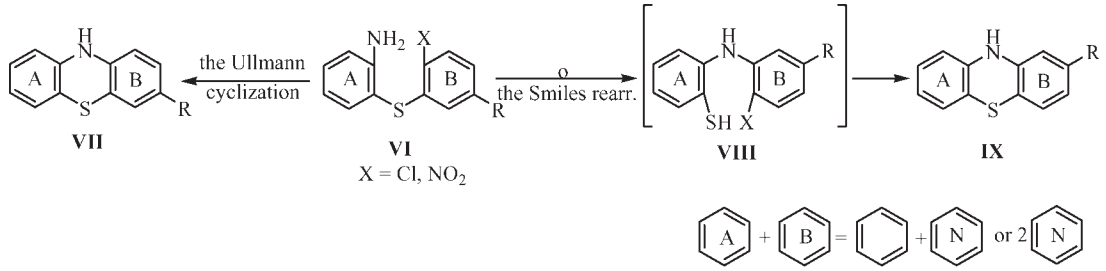
Synthesis of azaphenothiazines has been achieved by the following methods (generally outlined in Schemes 2–6):

1. thionation of diazinyl amines with elemental sulfur as a hydrogen atom substitution.
2. cyclization of phenyl azinyl sulfides or diazinyl sulfides proceeding directly as the Ullmann cyclization or with the Smiles rearrangement (the S→N type, phenyl or azinyl part migrates from sulfur atom to the nitrogen atom giving amine, not isolated) depending on the reaction conditions. The amino group might be attached to the phenyl ring and a leaving group X to an azinyl ring or inversely. Sometimes, it is impossible to state if a reaction goes with or without the rearrangement because the Ullmann's and Smiles's products are the same. The rearrangement proceeds under basic (most often) but also under acidic and neutral conditions.
3. cyclization of phenyl azinyl amines or diazinyl amines possessing a mercapto and good leaving groups (chlorine, nitro).
4. reactions of pairs of *ortho*-aminobenzenethiols or *ortho*-aminoazinethiols (or tautomers) with *ortho*-disubstituted azines, proceeding through formation of sulfides or amines which were not isolated during synthesis.
5. building of an azine ring to the benzo-1,4-thiazine moiety.

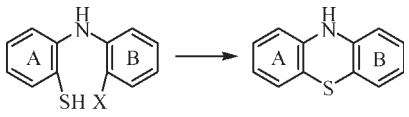
Phenothiazines were reviewed in the 50s and 70s [7–10] and exhaustively in a monograph edited by Gupta in the 80s [11]. Recently, a retrosynthetic approach to the synthesis of phenothiazines was described [12]. Syntheses and properties of monoazaphenothiazines were reviewed in 1990 in Polish based on 78 references [13]. Monoaza-, diaza-, triaza-, and tetraazaphenothiazines have already been reviewed by Okafor in the 70s in two articles [14,15], but those reviews were incomplete. Synthesis of azaphenothiazines from diazinyl sulfides was also a part in a chapter of the monograph [16]. Reading the chemical literature on the azaphenothiazines, we found misunderstanding chemical names and ring numbering, not to mention some incorrect names. As in the 60s and 70s, there were three nomenclature systems of azaphenothiazines, two based on the azaphenothiazine name (x-azaphenothiazine, x,y-diazaphenothiazine, x,y,z-triazaphenothiazine, and x,y,z,w-tetraazaphenothiazine) but with different numbering of the tricyclic ring system (British and American system **A**, German system **B**) and one based on heterocylic ring system **C** (Scheme 7) as the azino[. . .]benzo [1,4]thiazine, diazino[. . .][1,4]thiazine, or azino[. . .]azino[. . .][1,4]thiazine names (in the last two examples, the two azine rings are the same or different) but with another numbering system. The last system was not always used properly with determination of a place of the ring fusion in square brackets. All those systems were used in Chemical Abstracts after original articles. All of it led to confusion: 1,2-diazaphenothiazines in German articles and patents were in fact 3,4-diazaphenothiazines in American and British articles and patents, 1,3-diazaphenothiazines in fact 2,4-diazaphenothiazines, 2,7-diazaphenothiazines in fact 3,7-diazaphenothiazines. The wrong system numbering causes some misunderstandings, for example: 2,3,6,9-tetraazaphenothiazine should be named as 1,4,7,8-tetraazaphenothiazine. Unfortunately, we found that this confusion is still valid.

It is worth noting that not all azaphenothiazines structures were unequivocally determined, some structures were deduced from chemical properties or spectroscopic

Scheme 3



Scheme 4



X **XI**

data and only a few structures were based on X-ray analysis.

We think that the chemistry of diaza-, triaza-, and tetraazaphenothiazines which consists of over 30 different heterocyclic systems and is published in over 100 articles and patents requires to be reviewed.

The aim of this review is:

1. to arrange and to clarify the chemistry (synthesis and properties) of diazaphenothiazines, triazaphenothiazines, and tetraazaphenothiazines,
2. to discuss the articles and patents of this field up to 2008 and
3. to correct some azaphenothiazine names.

This material has been divided into tricyclic, tetracyclic, and pentacyclic azaphenothiazines with increasing numbers of nitrogen atoms in the systems:

1. diazaphenothiazines (1,2-, 1,3-, 1,4-, 1,6-, 1,9-, 2,3-, 2,4-, 2,7-, 3,4-, 3,6-, and 3,7-),
2. triazaphenothiazines (1,3,4-, 1,3,6-, 1,3,9-, 1,4,6-, 1,4,9-, and 2,3,6-),
3. tetraazaphenothiazines (1,2,6,7-, 1,2,7,8-, 1,3,6,8-, 1,3,6,9-, 1,4,7,8-, 2,3,6,7-, 2,3,6,8-, 2,3,7,8-, 2,4,6,8-, and 3,4,6,7-) and
4. their benzo, dibenzo, and naphtho derivatives.

For this review, to compare the structures of all azaphenothiazines and to clarify discussion, the structures were drawn as the phenothiazine derivatives (the structure **A** in Scheme 7).

Tricyclic diazaphenothiazines. ***1,2-Diazaphenothiazines (pyridazino[4,3-b][1,4]benzothiazines).*** 1,2-Diazaphenothiazines accompanied by 2,3- and 3,4-diazaphenothiazines were achieved in synthesis of the pyridazine derivatives. The first synthesis was carried out by Druey using *o*-aminophenyl 3,6-dichloro-4-pyridazinyl sulfide **1** (obtained from *o*-aminobenzenethiol and 3,4,6-trichloropyridazine) which in acidic medium led to 3-chloro-1,2-diazaphenothiazine **2** (no experimental data included). The same result was obtained when acetylated sulfide **3** was used [17]. Later this first synthesis was repeated giving in concentrated hydrochloric acid expected 3-chloro-1,2-diazaphenothiazine **2** (through postulated its hydrochloride **4**, not isolated) but in diluted hydrochloric acid or acetic acid giving isomeric compound, 2-chloro-3,4-diazaphenothiazine **6** (no yields given), as a product of the Smiles rearrangement to amine **5**. The same product **6** was obtained even from sulfide **7** (Scheme 8) [18,19].

Similar mixtures of isomeric products, 4-chloro-1,2-diazaphenothiazine **10** and 1-chloro-2,3-diazaphenothiazine **11**, were obtained in 51 and 17% yields directly from *o*-aminobenzenethiol **8** and 3,4,5-trichloropyridazine **9** in ethanol in the presence of potassium hydroxide at room temperature. When this reaction of trichloropyridazine **9** was carried out at 30–60°C or with two equivalents of *o*-aminobenzenethiol **8**, the only product was 4-(*o*-aminophenylthio)-1,2-diazaphenothiazine **13**. As 4-chloro-1,2-diazaphenothiazine **10** did not react with aminobenzenethiol **8** in ethanolic potassium hydroxide, the authors postulated the formation of bis-sulfide **12** as an intermediate product (Scheme 9) [20].

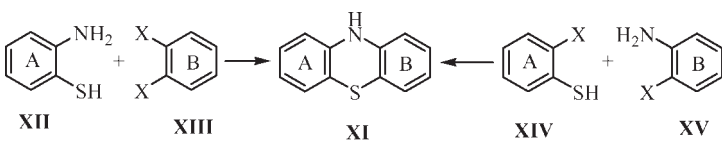
Reaction of 3,4,5-trichloropyridazine **9** with *N*-methylated *o*-aminobenzenethiol **14** (obtained by hydrolysis of 3-methyl-2(3*H*)-benzothiazolinone) in ethanolic potassium hydroxide at 0°C led unexpectedly to 4-chloro-10-methyl-2,3-diazaphenothiazine **15** as the sole product. The same reaction in methanolic potassium hydroxide at room temperature led to expected 4-(*o*-methylaminophenylthio)-1,2-diazaphenothiazine **16** (Scheme 10) [20].

The *N*-methyl analogous of sulfide **1**, sulfide **17**, heated in ethanol (with diluted hydrochloric acid) gave the rearrangement product, 10-methyl-2-chloro-3,4-diazaphenothiazine **18**, but in concentrated hydrochloric acid 10-methyl-3-chloro-1,2-diazaphenothiazine **19** (Scheme 11) [19].

3-Chloro- and 4-chloro-1,2-diazaphenothiazines **10** and **2** were dechlorinated over palladium charcoal to unsubstituted 1,2-diazaphenothiazine **20** what proved the chloro compound structures (Scheme 12) [19,20].

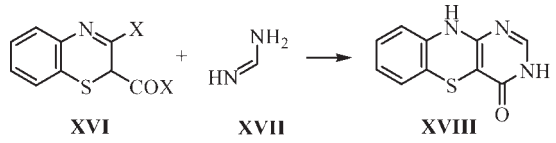
10*H*-3-Chloro-1,2-diazaphenothiazine **2** was alkylated with methyl iodide and diethylaminoethyl chloride in liquid ammonia (with sodium amide) to 10-substituted 1,2-diazaphenothiazines **21** and **22**. The chlorine atom in 3-chloro-1,2-diazaphenothiazines **2** and **21** was

Scheme 5



XII **XIII** **XI** **XIV** **XV**

Scheme 6



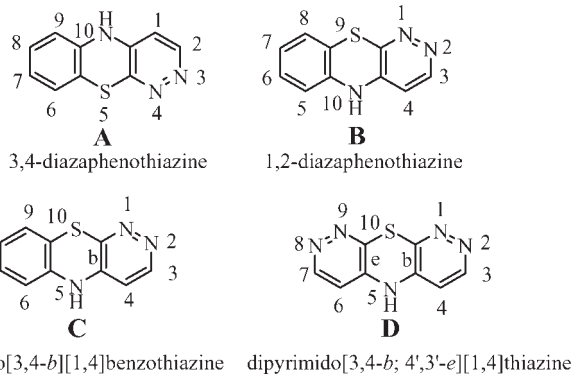
XVI XVII XVIII

substituted in the reactions of with sodium methoxide and diethylaminoethylamine to give 3-substituted diazaphenothiazines **22** and **23**. Diazaphenothiazine **2** was oxidized with hydrogen peroxide to compound **24**, possessing *S,S*-dioxide and *N*-oxide functions (Scheme 13) [17,18].

Similarly, the chlorine atom in 10*H*-4-chloro-1,2-diazaphenothiazine **10** was substituted with the alkoxy group in the reactions with methanol and ethanol in the presence of sodium, and with dimethylamine in a sealed tube at 160°C to give 4-substituted 1,2-diazaphenothiazines **25** (Scheme 14) [20].

The reactions discussed earlier were later patented [21–24]. Diazaphenothiazine **22** (R_1 = OMe, R = $CH_2CH_2NEt_2$) showed antihistaminic activity [17].

Scheme 7



A 3,4-diazaphenothiazine

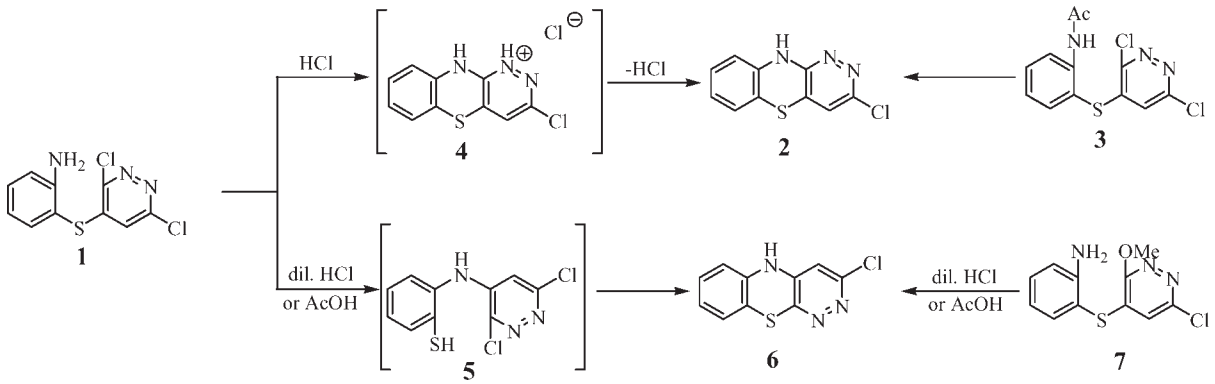
B 1,2-diazaphenothiazine

C pyrimido[3,4-*b*][1,4]benzothiazine

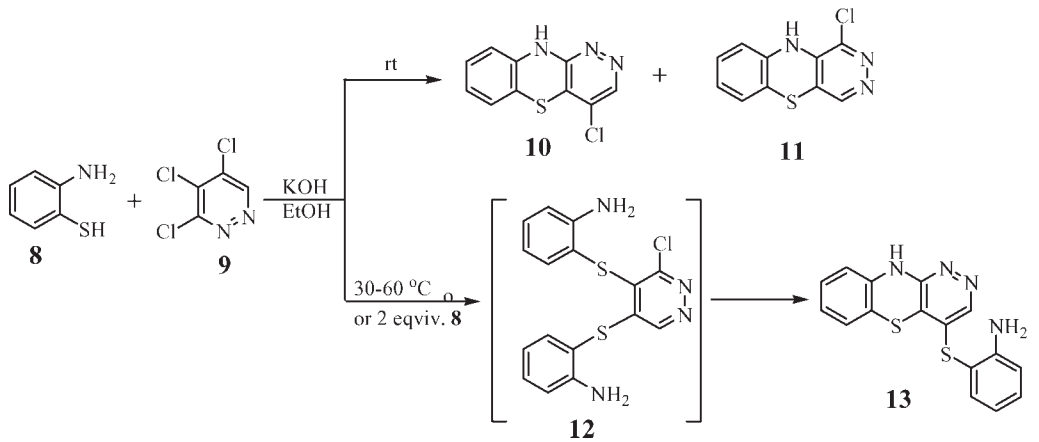
D dipyrimido[3,4-*b*; 4',3'-*e*][1,4]thiazine

1,3-Diazaphenothiazines (pyrimido[5,4-b][1,4]benzothiazines). 1,3-Diazaphenothiazines were obtained with the use of pyrimidine compounds in reactions which also produced 2,4-diazaphenothiazines. The first synthesis of this azaphenothiazine was carried out by Westermann and coworkers in 1958 who underwent a cyclization of *o*-aminophenyl 4-pyrimidinyl sulfide **25** in DMF (with potassium carbonate) under nitrogen atmosphere

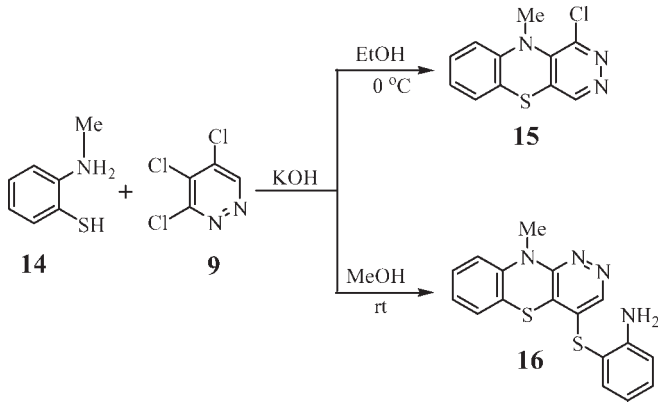
Scheme 8



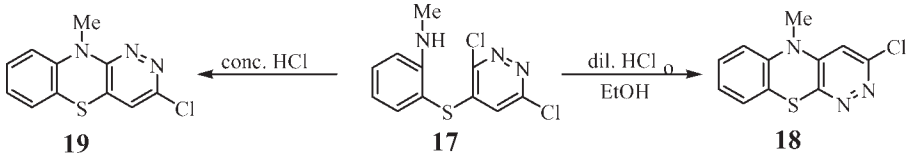
Scheme 9



Scheme 10



Scheme 11

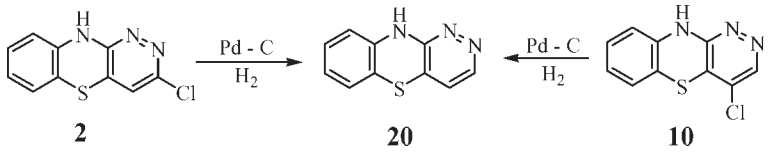


to isomeric 1,3-diazaphenothiazine **26** and 2,4-diazaphenothiazine **27** in very low yield. The discrimination of the isomers was arbitrary. One of the products, diazaphenothiazine **26**, was a result of the Smiles rearrangement occurring during the reaction course (Scheme 15) [25].

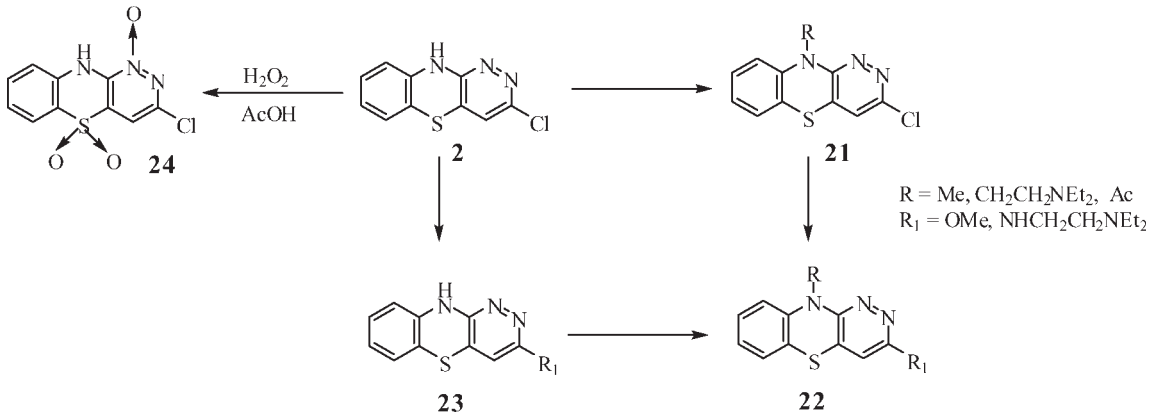
Further cyclizations of substituted sulfides **28** in DMF (with potassium carbonate and copper powder) led to only one product, namely substituted 1,3-diazaphenothiazines **29** in 15–71% yields, through the Smiles rearrangement to the appropriate amines, which, however, were not isolated. Such *o*-mercaptophenyl pyrimidinyl amines **30** (obtained separately) under the same reaction conditions gave 1,3-diazaphenothiazines **29** in moderate yields (42–58%) (Scheme 16) [25].

Later Roth and Phillips with coworkers independently developed a synthesis of 1,3-diazaphenothiazines. Reaction of 4-bromo-5-chloropyrimidine **31** with aminobenzenethiol **8** under basic conditions (ethanol,

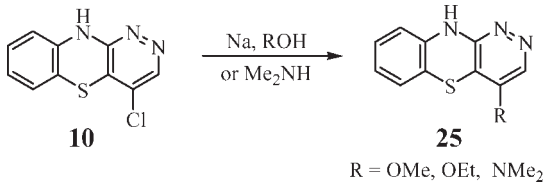
Scheme 12



Scheme 13



Scheme 14

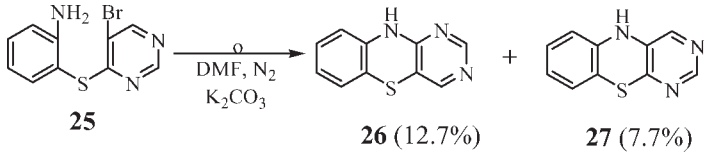


triethylamine) led to aminophenyl 4-pyrimidinyl sulfide **32** which in ethanol and ethanolic hydrogen chloride underwent rearrangement to amine **33** (not isolated) and subsequent acid catalyzed cyclization to 2,4-diamino-1,3-diazaphenothiazine **34** in high yield (95%). The same product was obtained (in 90% yield) directly from compounds **8** and **31** in diluted hydrochloric acid through postulated amine **33** (Scheme 17) [26–28].

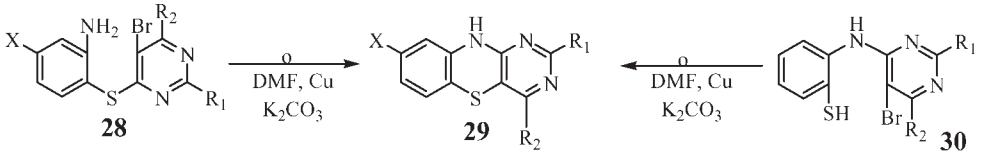
Substituted *o*-aminophenyl 4-hydroxy-5-pyrimidinyl sulfides **35** (obtained from substituted 5-bromoisocytosine or 5-bromouracil and substituted aminobenzenethiols) reacted in a different manner under similar acidic conditions (hydrochloric acid or sulfuric acid in 85% ethanol) to produce various substituted 1,3-diazaphenothiazines **37** without the Smiles rearrangement [29]. Later the authors (Roth and Bunnett) [30] proposed another structure of starting materials, the keto tautomers, *o*-aminophenyl 4-oxo-3,4-dihydro-5-pyrimidinyl sulfides **36** which explains well the attack of the amino group at the carbonyl carbon (at position 4, instead of position 5) and the resulting formation of the thiazine ring. Cyclization of various sulfides **36** led to substituted 1,3-diazaphenothiazines **37**, possessing substituents in positions 2 (mainly), 4, 7, and 8 (Scheme 18). 2-Hydroxy-1,3-diazaphenothiazines **37** (R_1 = OH) were transformed into the chloro derivatives **37** (R_1 = Cl) in the reaction with phosphoryl chloride and further *via* dichloro substitution to other derivatives **37** (R_1 = OMe, OCH_2CH_2OMe, SH, $NHNH_2$, $NHCH_2CH_2NMe_2$, $NHCH_2CH_2CH_2NMe_2$, *etc*). 2-Hydrazino-1,3-diazaphenothiazine **37** (R_1 = NH_2NH_2, R_2 and X = H) was transformed to parent 1,3-diazaphenothiazine **26** in the action of hydrochloric acid and copper sulfate [29].

Many various multisubstituted 1,3-diazaphenothiazines were obtained using these methods and were patented [30–35]. When alkylamino compounds **38** were

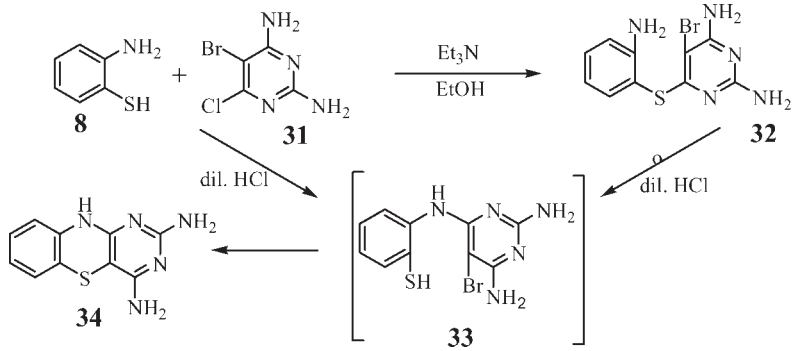
Scheme 15



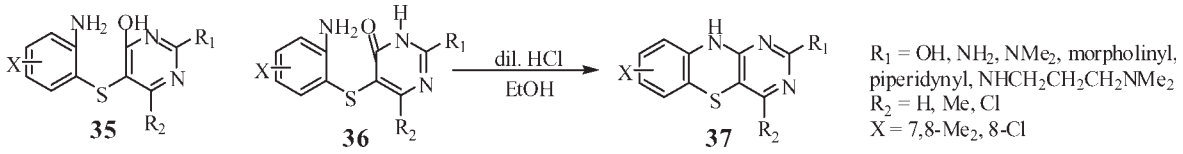
Scheme 16



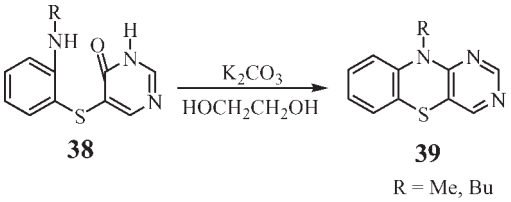
Scheme 17



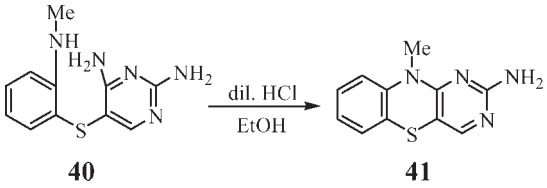
Scheme 18



Scheme 19



Scheme 20



used in ethylene glycol (with potassium carbonate) under nitrogen, the reaction led to 10-alkyl-1,3-diazaphenothiazines **39** (Scheme 19) [36].

The very interesting sulfide **40** possessing three amino groups, reacted by intramolecular substitution of the amino group with the methylamino group in ethanol containing hydrochloric acid, giving 10-methyl-1,3-diazaphenothiazine **41** (Scheme 20) [36].

Reactions of *N*-substituted phenyl uracilyl sulfides **42** (obtained from substituted aminobenzenethiols and bromochlorouracils) in ethanol or DMF underwent the Smiles rearrangement and cyclization to 10-substituted 1,3-diazaphenothiazine-2,4(1*H*,3*H*)-diones **43** in excellent yield (75–93%) [37]. On the contrary, phenyl uracilyl sulfide **44** in acetic acid or in alcohol with hydrochloric acid underwent cyclization without the rearrangement (Scheme 21) [38,39].

Reactions of substituted aminobenzenethiols **45** with 5-bromo- and 5-bromo-5-nitrobarbituric acids **46** and **47** led to 10*H*- and 10*H*-4a-nitro-1,3-diazaphenothiazine derivatives **48** and **49** (Scheme 22) [40].

Reaction of aminobenzenethiol **8** with *N*-substituted chloronitrouracil **50** in benzene (with triethylamine) proceeded *via* the Smiles rearrangement to give 10*H*-1,3-diazaphenothiazine-2,4(1*H*,3*H*)-dione **51** (Scheme 23) [41].

Very interesting transformations were described in Pfizer's patents [42,43]. Substituted anilinouracils **52** underwent cyclization with thionyl chloride in chloroform under nitrogen atmosphere to 4a-chloro derivatives of 1,3-diazaphenothiazine **53**. The chloro derivatives **53** with reducing agents (hydrazines, zinc, or reducing cations and anions) in methylene chloride gave stable radicals **54** or (with excess of agents) 1,3-diazaphenothiazine-2,4(1*H*,-3*H*)-diones **55**. The chloro derivatives **53** were transformed into 4a-substituted derivatives **56** by substitution of the reactive chlorine atom (Scheme 24).

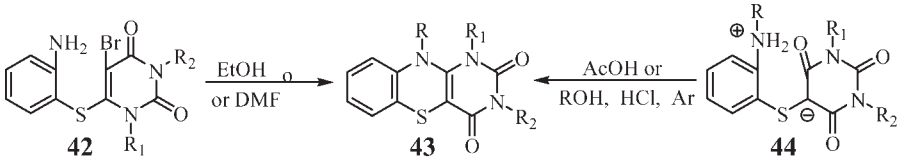
Reaction of *N*-tetraacetylribityl derivative of anilinouracil **57** with sulfur chloride in chloroform led to 10-tetraacetylribityl-1,3-diazaphenothiazinedione **58** which was deacetylated with ammonia in moderate yield (Scheme 25) [44].

Pyrimidobenzothiazepines **60** in the reaction with iodine in morpholine underwent a ring contraction to give 10*H*-1,3-diazaphenothiazinedione **51** but with iodine or *N*-halogenosuccinimide in other solvents gave 4a-substituted derivatives **61** (Scheme 26) [45].

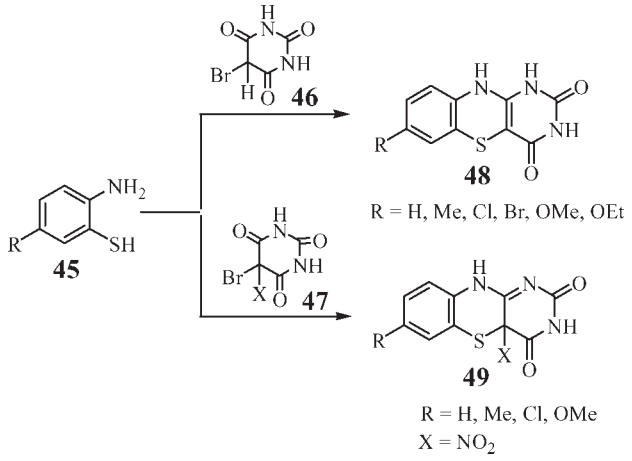
An unusual synthesis was described by Granik and Luszkov who built the 1,3-diazine ring in benzothiazine **62** in reactions with substituted amidines **63** giving 1,3-diazaphenothiazines **64** or **65** (Scheme 27) [46].

10*H*-1,3-Diazaphenothiazines **37** were transformed into 10-substituted 1,3-diazaphenothiazines **66** in the

Scheme 21



Scheme 22



reaction with alkyl and aminoalkyl chlorides in DMF or xylene (with sodium amide or sodium hydride) (Scheme 28) [36,47].

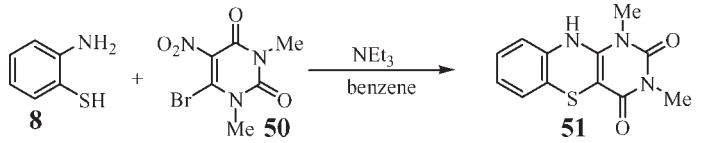
Much more complicated was the alkylation of 1,3-diazaphenothiazine-2,4(1*H*,3*H*)-diones which led to *N*-, *O*-, *C*-, and *N*-alkylated products. The alkylation of 1,3-dialkyl compound **67** with alkyl halides or sulfates in DMF (with sodium hydride) led unexpectedly to the *S*-alkyl ylide **68** alone or with 4a-alkyl derivatives **69** [42,48]. When only allyl iodide was used, 4a-allyl derivative **69** was obtained (Scheme 29) [48]. In contrast to the alkylation of 10*H*-1,3-diazaphenothiazine, the alkylation of 10*H*-1,3-diazaphenothiazinediones **67** (R = H) did not proceed at the nitrogen atom in position 10.

Alkylation of 1,3-unsubstituted 1,3-diazaphenothiazines **70** in DMF (with potassium carbonate) yielded the *N*-, *O*-, and *C*-alkylated products **71-73** (Scheme 30) [39].

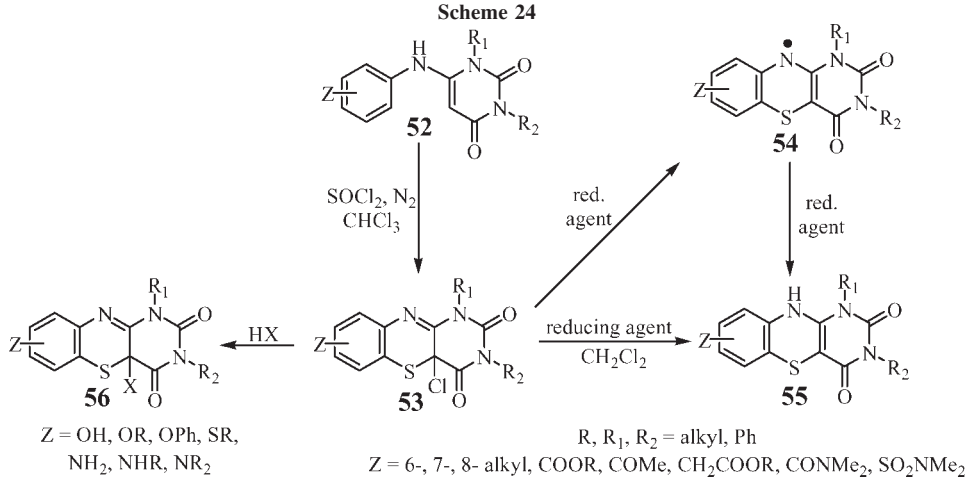
When 3,10-dimethyl-1,3-diazaphenothiazinedione **74** was alkylated in chloroform in the presence of diisopropylethylamine, the *S*-alkyl ylide of another type **75** was obtained in 100% yield (Scheme 31). Alkylation in DMF gave different products depending on the alkyl halide nature [39].

An X-ray analysis of selected sulfonium ylide (provided by Pfizer Co.) confirmed the structure as the *S*-alkyl compound and the major canonical structure was proposed as **76** (Scheme 32) [49].

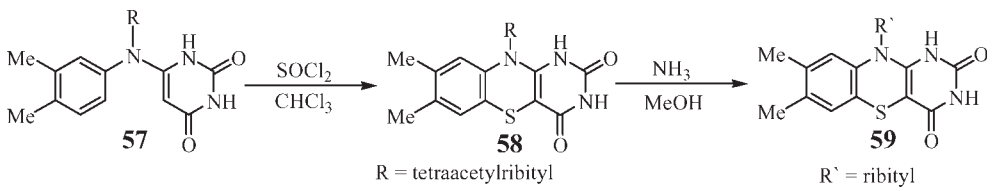
Scheme 23



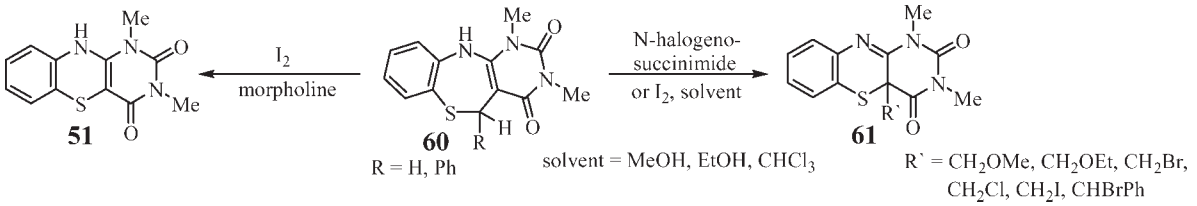
Scheme 24



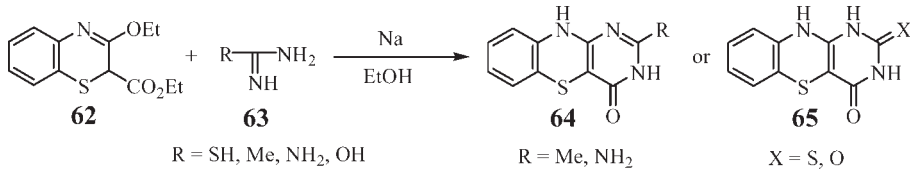
Scheme 25



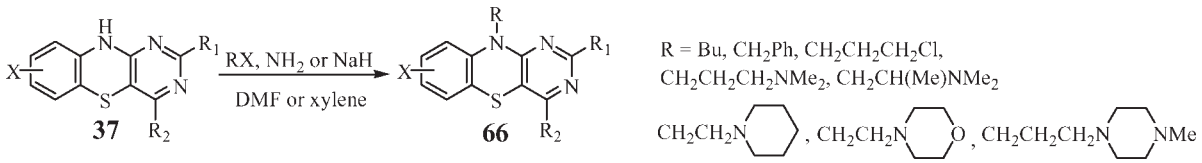
Scheme 26



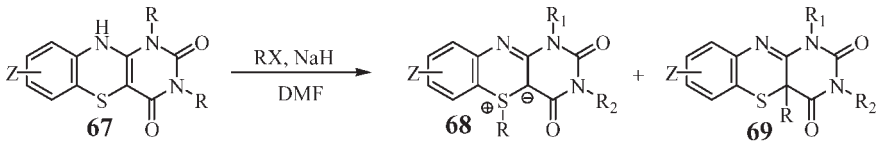
Scheme 27



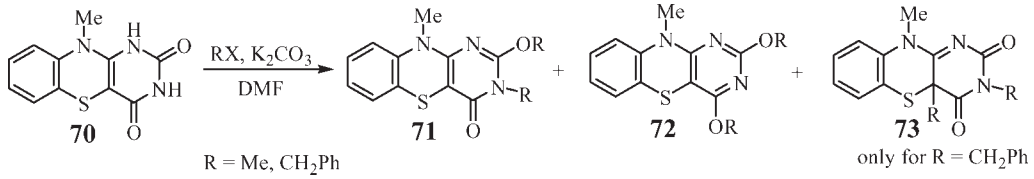
Scheme 28



Scheme 29

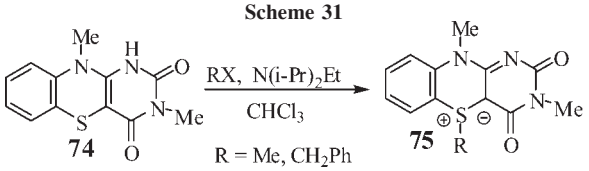


Scheme 30

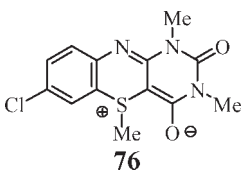


Although alkylation of 10*H*-1,3-dialkyl-1,3-diazaphenothiazinediones **77** proceeded mainly to *S*-ylides, heating those compounds induced thermal rearrangement (the S→N type) to 10-alkyl derivatives **78**. Ultraviolet irradiation induced a ring expansion to pyrimidobenzothiazepines **79** (Scheme 33) [48].

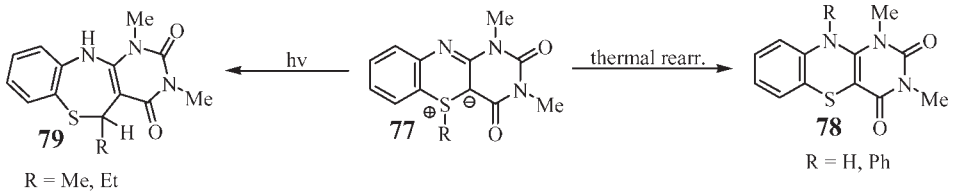
Scheme 31



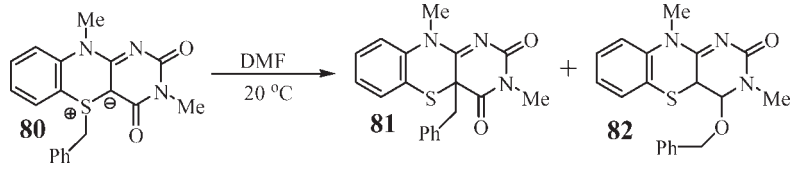
Scheme 32



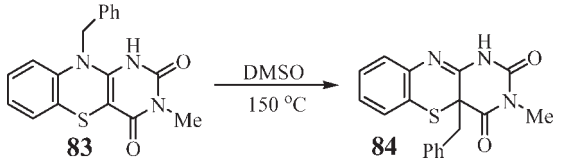
Scheme 33



Scheme 34



Scheme 35



On the other hand, *S*-ylide **80** in DMF underwent the S→C and S→O benzyl group migration to give 4a-benzyl and *O*-benzyl derivatives **81** and **82** (Scheme 34) [49].

The benzyl group in compound **83** during heating in DMSO underwent the N→C migration to give derivative **84** (Scheme 35) [49].

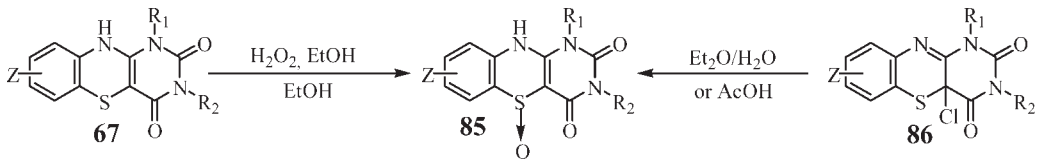
10*H*-1,3-Diazaphenothiazinediones **67** were oxidized with hydrogen peroxide in ethanol giving *S*-oxide derivatives **85**. The same compounds were obtained from 4a-chloro compound **86** in ether/water or acetic acid (Scheme 36) [42].

Both 4a-chloro derivatives **53** and *S*-oxide **85** heated in aqueous acetone or glacial acetic acid on a steam bath underwent degradation to imidazolylbenzothiazole derivatives **87** (Scheme 37) [43].

1,3-Diazaphenothiazine-2,4-diones with sulfuric acid and diacetyl gave a radical cation and a radical, respectively [50]. Several alkyl, amino, and aminoalkyl 1,3-diazaphenothiazines exhibited antibacterial activity against *Streptococcus fecalis, Escherichia coli, Staphylococcus aureus, Proteus vulgaris*, and *Pseudomonas aeruginosa* [31–36], and analgesic and anti-inflammatory activity [37].

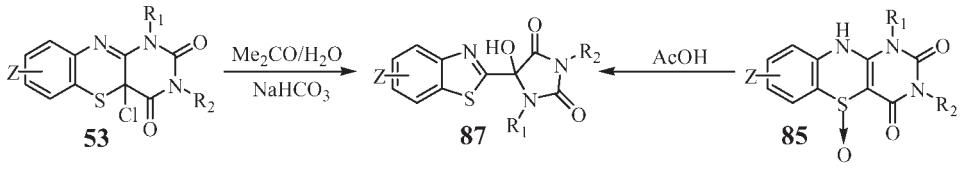
1,4-Diazaphenothiazines (pyrazino[2,3-b][1,4]benzothiazines). The first synthesis of 1,4-diazaphenothiazine was described by Gulbenk and coworkers in their patents in 1972–1974 [51–53]. Reaction of

Scheme 36



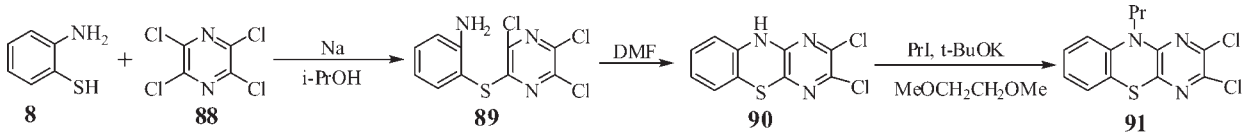
R_1, R_2, Z as in Scheme 24

Scheme 37

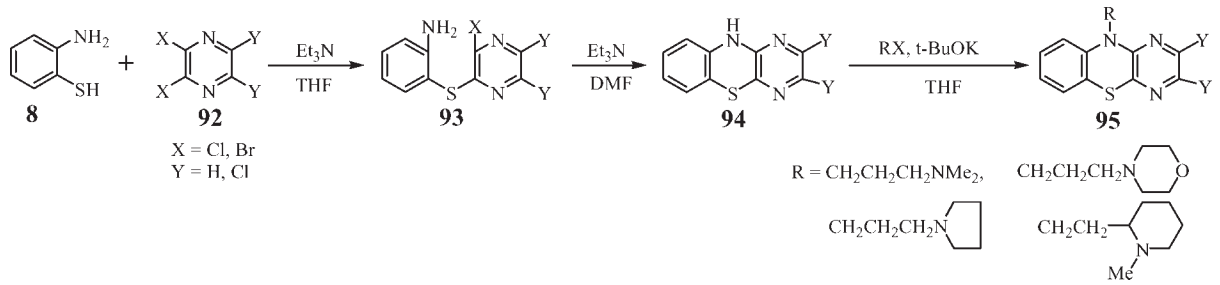


R_1, R_2, Z as in Scheme 24

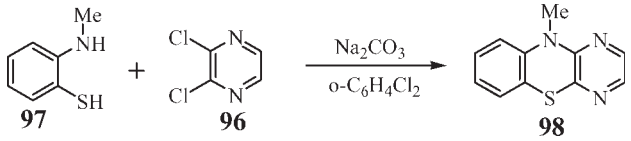
Scheme 38



Scheme 39



Scheme 40



tetrachloropyrazine **88** with aminobenzenethiol **8** in isopropyl alcohol (in the presence of sodium) led to aminophenyl pyrazinyl sulfide **89** which further in DMF cyclized to 2,3-dichloro-1,4-diazaphenothiazine **90**. *N*-Alkylation of compound **90** with propyl iodide in dimethoxyethane (with potassium *t*-butoxide) gave 10-propyl derivative **91** (Scheme 38).

During the same time period, Tong in his patent [54] described reactions of aminobenzenethiol **8** not only with tetrachloropyrazine **88** but also with dichloro- and dibromopyrazine **92** in THF in the presence of triethylamine. The obtained aminophenyl pyrazinyl sulfides **93** underwent cyclization in DMF to yield 1,4-diazaphenothiazines **94** (in 70% yield for unsubstituted product). The last compounds were transformed into the 10-aminoalkyl derivatives **95** in the aminoalkylation with aminoalkyl chlorides in THF (with potassium *t*-butoxide, Scheme 39).

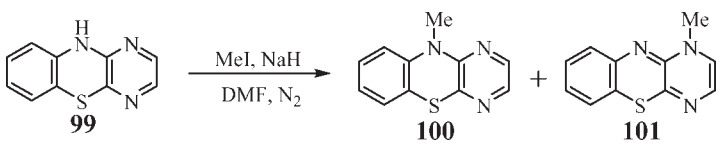
Later other authors [55,56], unaware of those patents, carried out the reaction of 2,3-dichloropyrazine **96** with aminobenzenethiol **8** in *o*-dichlorobenzene (with sodium carbonate) to give 10*H*-1,4-diazaphenothiazine **94** (Y = H) in 62% yield. Excellent yield (94%) of diazaphenothiazine **94** was achieved when this reaction was carried out in DMF (with sodium hydroxide) [57]. When *o*-methylaminobenzenethiol **97** was used instead of compound **8**, 10-methyl-1,4-diazaphenothiazine **98** was obtained in 63% yield (Scheme 40) [55].

Methylation of 10*H*-1,4-diazaphenothiazine **99** with methyl iodide in DMF (in the presence of sodium hydride) under nitrogen atmosphere gave the expected 10-methyl derivative **100** in 75% yield and the unexpected side product **101** (1-methyl derivative) in 1.2% yield (Scheme 41) [55].

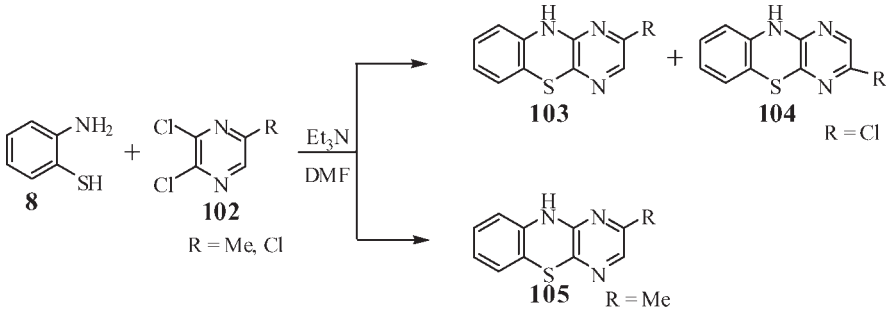
When unsymmetrical pyrazine derivatives, 2,3,5-trichloropyrazine and 2,3-dichloro-5-methylpyrazine **102** were used, one or two diazaphenothiazines were formed because of possibility of accompanying Smiles rearrangement. Reaction of compound **102** (R = Cl) with aminobenzenethiol **8** in DMF led to 2-chloro- and 3-chloro-10*H*-diazaphenothiazines **103** and **104** in 26 and 15% yields. The isomers were discriminated on the basis of NMR long range ^{13}C-^{1}H couplings and confirmed by X-ray analysis of isomer **103**. Reaction with compound **102** (R = Me) led only to one product, 2-methyl derivative **105**, in 66% yield (Scheme 42) [58].

In the reaction of dichloropyrazine **96** with 4-chloro-2-aminobenzenethiol **106** the sulfide **107** was isolated in 57% yield which further heated without solvent at 220°C underwent cyclization to 8-chloro-1,4-diazaphenothiazine **108** in 47% yield (Scheme 43) [58].

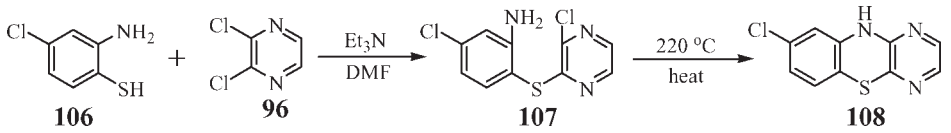
Scheme 41



Scheme 42



Scheme 43

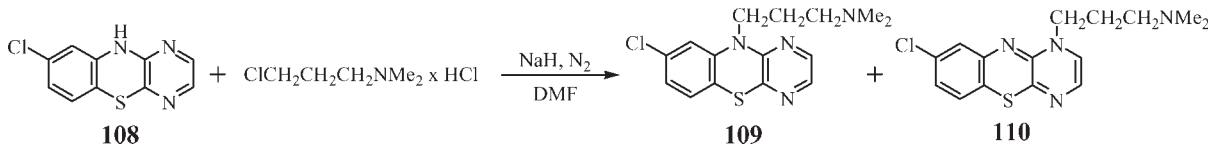


Alkylation of substituted 10*H*-1,4-diazaphenothiazines with aminoalkyl chlorides or their hydrochlorides in DMF (with sodium hydride) in nitrogen atmosphere gave 10-aminoalkyl derivatives which were transformed further into hydrochlorides. Only when 8-chloro-1,4-diazaphenothiazine **108** was alkylated with dimethylaminopropyl chloride hydrochloride two products, 10- and 1-dimethylaminopropyl-1,4-diazaphenothiazine **109** and **110**, were isolated as hydrochlorides in 47 and 17% yields (Scheme 44) [58].

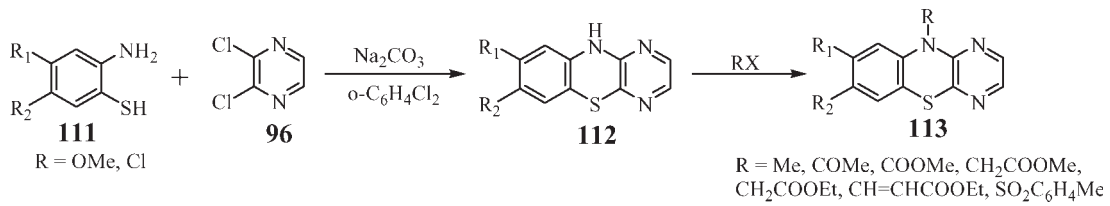
10*H*-1,4-Diazaphenothiazine **99** was once more obtained from sulfide **93** (X = Cl, Y = H) but this time with DBU in pyridine. Using substituted *o*-aminobenzenethiols **111** and 2,3-dichloropyrazine **96** in *o*-dichlorobenzene (with sodium carbonate), 1,4-diazaphenothiazines **112** were obtained, which were further *N*-alkylated, acylated, and sulfonylated to give various derivatives **113** (Scheme 45) [59].

Very recently Kaneko et al. [60–62] synthesized 8-methoxycarbonyl-10*H*-1,4-diazaphenothiazine **115** from 2-amino-4-methoxycarbonylbenzenethiol **114** and 2,3-dichloropyrazine **96** in DMF. The obtained 8-methoxycarbonyl compound was reduced with lithium aluminum hydride to 8-hydroxymethyl derivative **116**. Because of low stability of aminobenzenethiol **114**, a second route was elaborated from phenyl pyrazinyl sulfide **117** (obtained from 3-nitro-4-mercaptobenzyl alcohol and 2,3-dichlo-ropyrazine **96** followed by reduction of the nitro group). Sulfide **117** cyclized in methanol containing hydrochloric acid to give 8-hydroxymethyl derivative **116** in high yield of 99%. This compound was transformed into the chloromethyl derivative **118** by chlorination with methanesulfonyl chloride in DMF/pyridine under nitrogen atmosphere. Reactions of chloromethyl compound **118** with secondary monocyclic and bicyclic amines gave about 60 of 2-aminomethyl

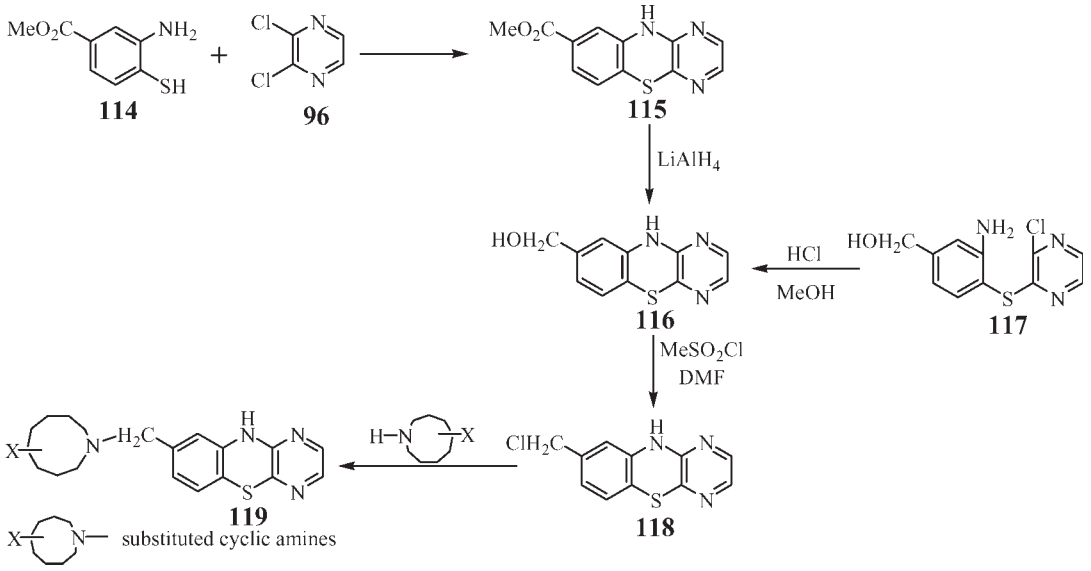
Scheme 44



Scheme 45



Scheme 46



derivatives **119** of biological activity (Scheme 46) [60–62].

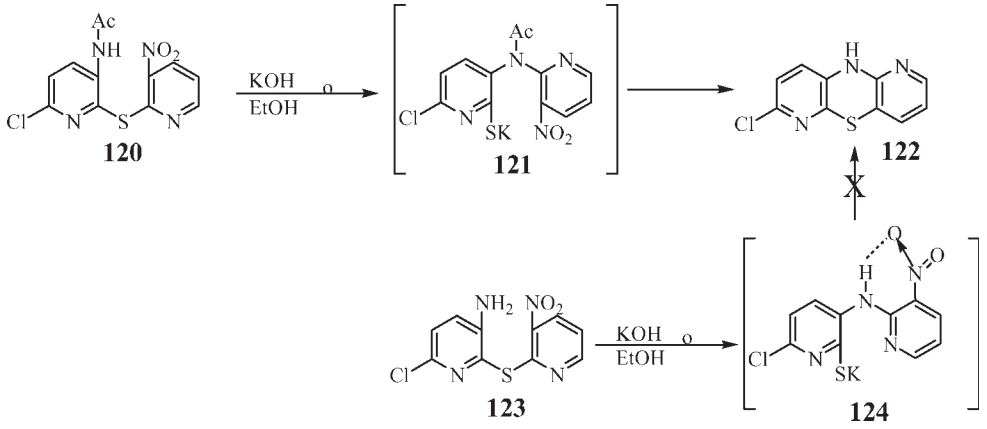
1,4-Diazaphenothiazines were transformed into other derivatives: by oxidation with hydrogen peroxide or potassium permanganate to *S*-oxides and *S,S*-dioxides [55,56,59,63], by nitration to the nitro compounds [55,56] or by reaction with iodobenzene to benzothiazole compound [55]. Most of 1,4-diazaphenothiazines exhibited very interesting biological activities: bactericidal, fungicidal, herbicidal [51–54,63], insecticidal [51–54], helminthicidal, pesticidal [51–53], neuroleptic [58], and are inhibitors of the 5-lipoxygenase enzyme system [59] and promising candidates for the treatment of autoimmune inflammatory diseases [61,62].

1,6-Diazaphenothiazines (dipyrido[2,3-b;2′,3′-e][1,4] thiazines). The first synthesis of 1,6-diazaphenothiazines was described by Maki [64]. Reaction of 3-acetylamino-6-chloro-3′-nitro-2,2′-dipyridinyl sulfide **120** (obtained from 3-amino-6-chloro-2(1*H*)-pyridinethione and 2-chloro-3-nitropyridine followed by acetylation) in ethanol (with sodium hydroxide) underwent cyclization to 7-chloro-10*H*-1,6-diazaphenothiazine **122** in 68% yield through the Smiles rearrangement to dipyridinyl amine **121**. During cyclization the acetyl group was hydrolyzed. It is interesting that the nonacetylated sulfide **123** did not undergo cyclization due to a conformation **124** produced by the hydrogen bondings between the amino and nitro groups (Scheme 47).

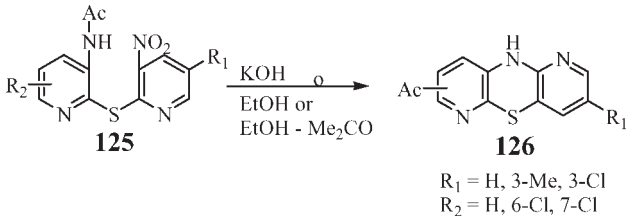
Similar procedures were used to obtain unsubstituted, 3-methyl-, 3,6-dichloro-, and 3,7-dichloro-1,6-diazapheno-thiazines **126** from appropriate dipyridinyl sulfides **125** with acetylamino groups (Scheme 48) [65–67].

Nonacetylated amines **127** (obtained directly from appropriate aminopyridinethiones and chloronitropyridines or from 3-amino-3′-nitro-2,2′-dipyridinyl sulfides *via* the Smiles rearrangement in basic or acidic media)

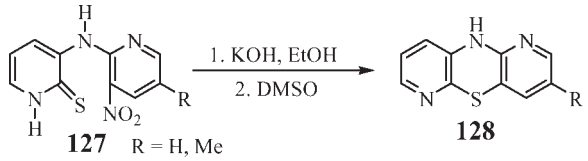
Scheme 47



Scheme 48



Scheme 49



[67,68] were able to undergo cyclization to 1,6-diazaphenothiazines **128** in DMSO (potassium hydroxide and ethanol were used to obtain potassium pyridinethiolate) (Scheme 49) [67].

Very interesting was the reaction of dipyridinyl amine **129** with 2-chloro-3-nitropyridine **130** to give compound **131**, possessing three pyridine units, which cyclized in DMSO through the Smiles rearrangement to 10-(3′-nitro-2′-pyridinyl)-1,6-diazaphenothiazine **132** (in 78% yield, Scheme 50) [67].

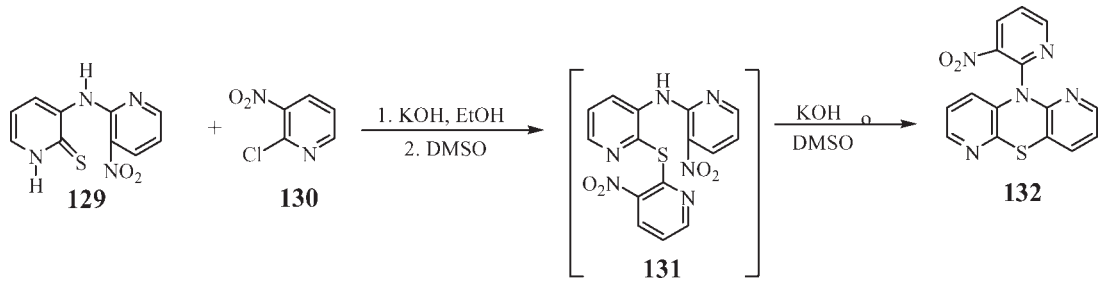
10-Substituted 1,6-diazaphenothiazines **133** and **134** were obtained from unsubstituted compound **126** in the reaction with acrylonitrile and dimethylaminopropyl chlorides (Scheme 51) [65,67].

3-Dimethylaminopropyl derivatives turned out to be more toxic than chlorpromazine and produced CNS depression) [65,67].

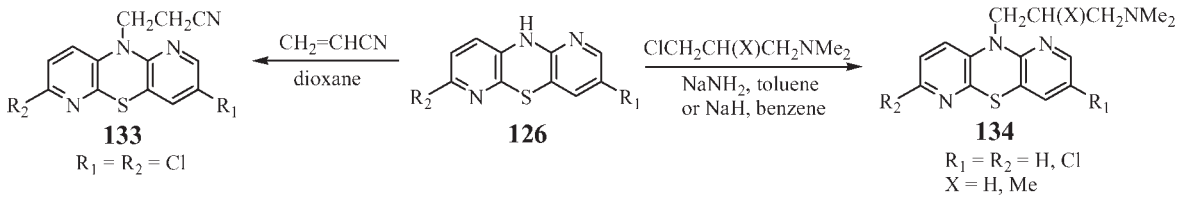
1,9-Diazaphenothiazines (dipyrido[3,2-b;2′,3′-e][1,4]thiazines). 10*H*-1,9-Diazaphenothiazine **136** was obtained by Rath in the sulfurization of 2,2′-dipyridinyl amine **135** with elemental sulfur at higher temperature (no details) and was converted into dimethylaminopropyl derivative **137** using dimethylaminopropyl chloride in xylene (with sodium amide) (Scheme 52) [69].

2,3-Diazaphenothiazines (pyridazino[4,5-b][1,4]benzothiazines). 1-Chloro-2,3-diazaphenothiazine **11** was obtained beside 4-chloro-1,2-diazaphenothiazine **10** in the reaction of aminobenzenethiol **8** with trichloropyridazine **9** as was already mentioned (Scheme 9) [20]. The first synthesis of 2,3-diazaphenothiazine was carried out in 1962 by heating aminophenyl pyridazinyl sulfide **138** in acetic anhydride to give 10-acetyl-2,3-diazaphenothiazin-1(2*H*)-one **139** which was deacetylated to 10*H*-derivative **140** in methanolic potassium hydroxide (Scheme 53) [70].

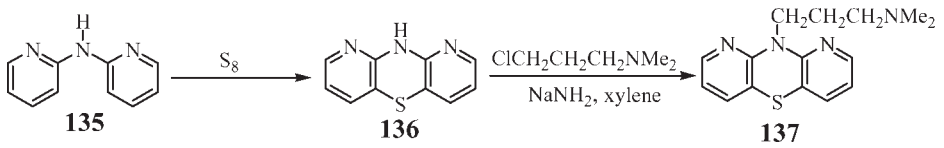
Scheme 50



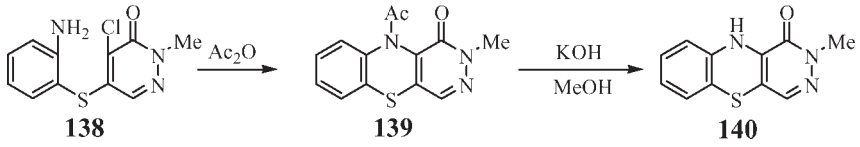
Scheme 51



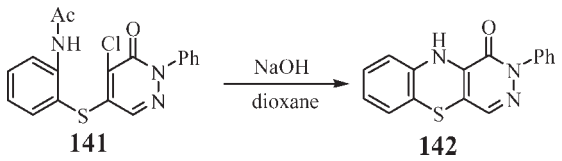
Scheme 52



Scheme 53



Scheme 54



Similarly, *N*-acetylaminophenyl pyridazinyl sulfide **141** heated in dioxane (with sodium hydroxide) gave at once 10*H*-2,3-diazaphenothiazinone **142** (Scheme 54) [70].

Later, Yoneda, Nitta, and Ohtaka published and patented reactions of aminophenyl pyrazinyl sulfides **143** which underwent cyclization with or without the Smiles rearrangement to isomeric 10*H*-2,3-diazaphenothiazinones **144** or **145** depending on the reaction conditions (basic or acidic, Scheme 55) [20,71–74].

In the same time Scapini, Duro, and Pappalardo carried out cyclization of sulfide **146** under basic conditions (acetone, potassium hydroxide) to obtain 10*H*-2,3-diazaphenothiazinon-4(3*H*)-ones **147** *via* the Smiles rearrangement (Scheme 56) [75].

Later, two teams (Pappalardo, Duro, and Maki with coworkers) independently carried out a similar cyclization of sulfide **141** under basic conditions to give phenyl derivatives of 10*H*-2,3-diazaphenothiazinon-4(3*H*)-one **148** *via* the Smiles rearrangement [76,77]. Sulfide **141** in acidic medium gave isomeric 10*H*-2,3-diazaphenothiazinon-1(2*H*)-one **142** (Scheme 57) [76].

The same product **142** was obtained in the cyclization of sulfide **149** under acidic conditions. The structure of the product was supported by unequivocal synthesis using amine **150** (Scheme 58) [76].

The 2,3-diazaphenothiazine chemistry was later widely explored mainly by Duro and Pappalardo with coworkers. They used various substituted aminophenyl pyridazinyl sulfides **151** which under basic conditions cyclized *via* the Smiles rearrangement, but under acidic conditions without the rearrangement, to give isomeric substituted 2,3-diazaphenothiazinones **152** and **153**, respectively. Whereas the acetyl group was deacetylated in the acidic medium during the synthesis (to form 10*H*-2,3-diazaphenothiazinones **153**, R = H), in basic medium was most often stable (Scheme 59) [78–84].

A very unusual synthesis was carried out using bis-sulfide **154** which underwent cyclization under basic conditions to 10*H*-2,3-diazaphenothiazin-4-one **155**. The *N*-acetylaminobenzenethiolate group turned out to be a quite good leaving group (Scheme 60) [75].

Similarly, bis-sulfide **156** gave 10*H*- and 10-acetyl-2,3-diazaphenothiazine-1,4-diones **157** (Scheme 61) [85].

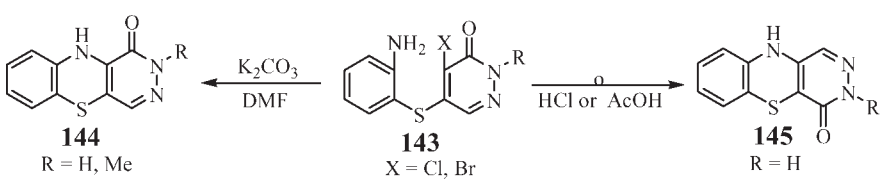
When *N*-methylaminophenyl pyridazinyl sulfide **158** was used in acidic medium, the product was identified as 3,10-dimethylphenothiazinium perchlorate **159** (Scheme 62) [79].

The direct synthesis of 2,3-diazaphenothiazinones with the use of aminobenzenethiols and pyridazine derivatives was less explored. Reactions of *N,S*-diacetyl derivatives of aminobenzenethiol **160** with dibromopyridazinones **161** under basic conditions led to 10*H*-2,3-diazaphenothiazinon-4(3*H*)-ones **147** (Scheme 63) [75].

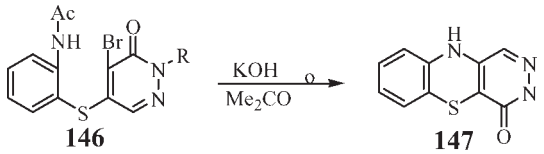
On the other hand, aminobenzenethiol and its acetyl derivatives **162** reacted with dihalogenopyridazinones **163** in the presence of equimolar amount of sodium hydroxide (in methanol) to form 10*H*-2,3-diazaphenothiazin-1(2*H*)-one **164**. The same product **164** was obtained when potassium carbonate in DMF was used. When two equivalents of sodium hydroxide or equimolar amount of potassium hydroxide were used, isomeric 10*H*-2,3-diazaphenothiazinon-4(3*H*)-ones **165** were formed (Scheme 64) [72,86].

Similarly, reaction of *N*-methylaminobenzenethiol **97** with dibromopyridazinedione **166** led to two 2,3-diazaphenothiazine-1,4-diones **167** and **168** depending on the amount of sodium hydroxide (Scheme 65) [82].

Scheme 55



Scheme 56



When potassium hydroxide was used in the reaction of *N*-acetylaminobenzenethiol **14** with dibromopyridazinedione **169** only one 2,3-diazaphenothiazine-1,4-dione **170** was obtained (Scheme 66) [83].

Reaction of *N,S*-diacetyl derivative of aminobenzenethiol **160** with dibromopyridazinediones **171** under basic conditions led to 10*H*- or 10-acetyl-2,3-diazaphenothiazine-1,4-diones **172** (Scheme 67) [85,87].

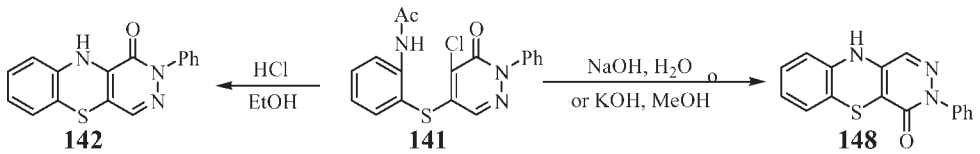
A very rare method of synthesis of an azine ring in the multiazaphenothiazine chemistry was applied by Pappalardo and coworkers. 2,3-Di(ethoxycarbonyl)-1,4-benzothiazine **173** in the annulation reaction with hydrazines led to 10*H*-2,3-diazaphenothiazine-1,4-diones **174** by building of the pyridazinedione ring (Scheme 68) [85,87].

The chemistry of 2,3-diazaphenothiazines involves alkylation, the transformation of the oxo functions, substitution of the chlorine atoms, building an azole ring, nitration and oxidation. Alkylation of 10*H*-2,3-diazaphenothiazine **175** with methyl iodide or sulfate in methanol (with addition of perchloric acid) proceeded smoothly in the pyridazine ring to give a mixture of 2- and 3-methyl-10*H*-2,3-diazaphenothiazinium perchlorates **159** and **176** (Scheme 69) [79].

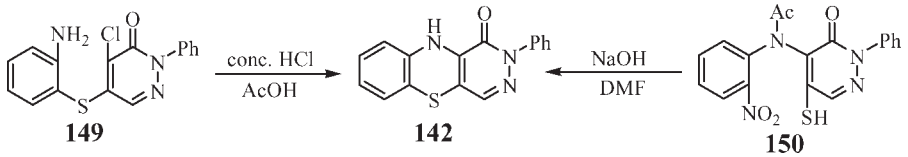
Chloro-2,3-diazaphenothiazines **177** gave only one methylation product with the methyl group farther from the chlorine atom (Scheme 70) [79].

The alkylation of 10*H*-2,3-diazaphenothiazinones **180** and **181** with methyl iodide or aminoalkyl chlorides

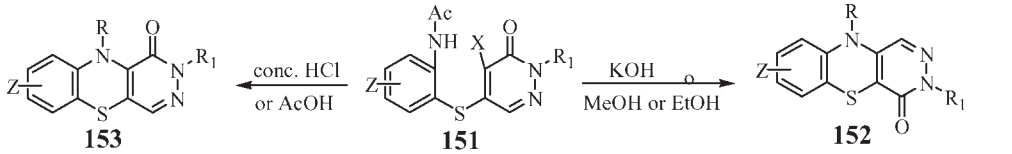
Scheme 57



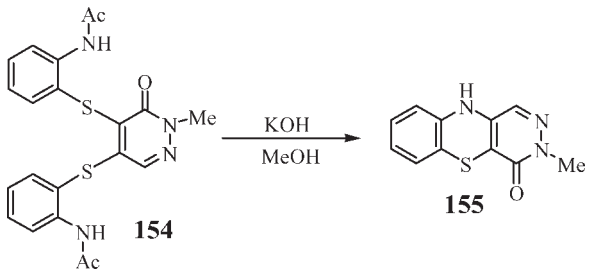
Scheme 58



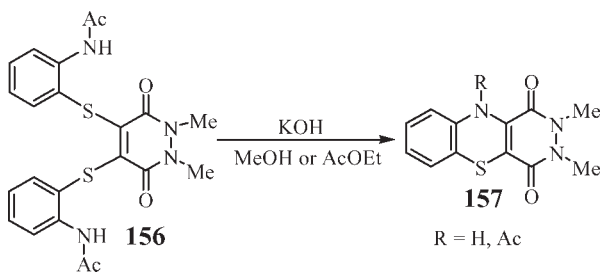
Scheme 59



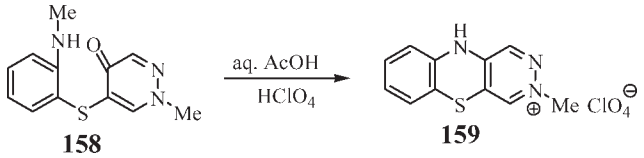
Scheme 60



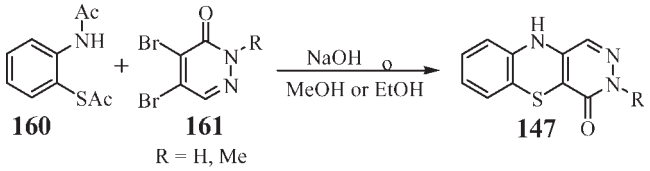
Scheme 61



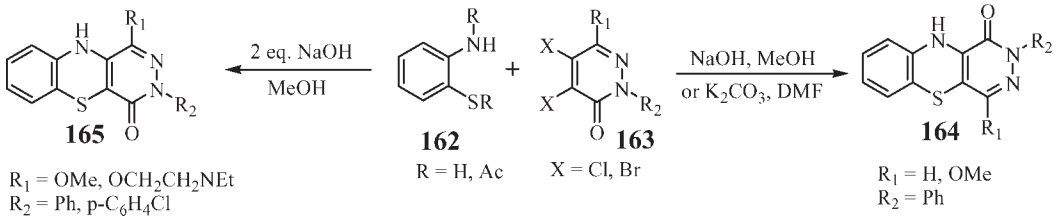
Scheme 62



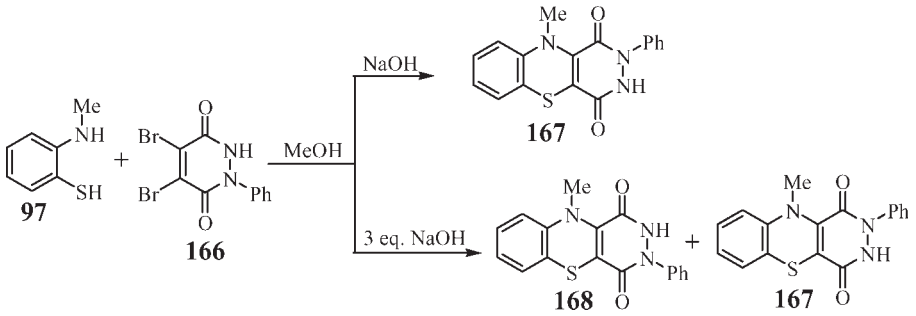
Scheme 63



Scheme 64



Scheme 65

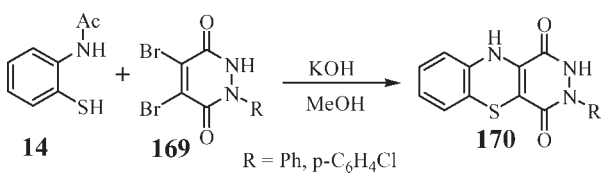


under basic conditions proceeded in the pyridazinone ring to give appropriate 2- and 3-alkyl derivatives **182** and **183** (Scheme 71) [20,71,73,83,84,88,89]. Much more complicated was the alkylation of 10*H*- and 10-methyl-2,3-diazaphenothiazine-1,4-diones giving not only expected *N*-methyl but also *O*-methyl derivatives [77,86].

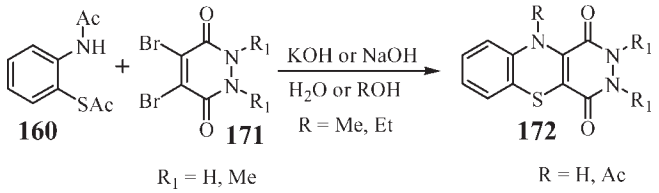
A very interesting distinction of isomeric phenyl derivatives of 10*H*-2,3-phenothiazinones **142** and **148** was carried out by action of sodium ethoxide. Whereas isomer **142** gave the product of a ring contraction **184**, isomer **148** gave sodium salt of diazaphenothiazine **185** which was further methylated to form 10-methyl derivative **186** and dimer **187** (Scheme 72) [76].

Isomeric diazaphenothiazinones **188** and **189** were converted to chloro compounds **11** and **190** which were further transformed to the hydrazine and amine derivatives **191** and **192**. The hydrazine compounds were oxidized with cupric ions to the same parent 10*H*-2,3-diazaphenothiazine **175**. On the other hand, the hydrazine

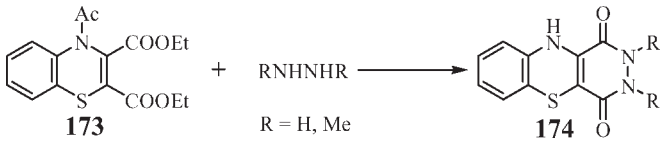
Scheme 66



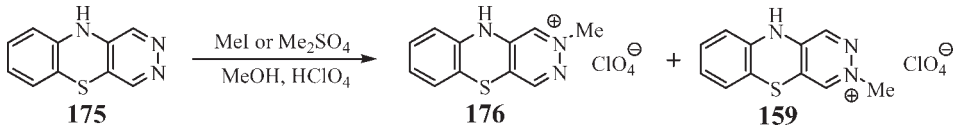
Scheme 67



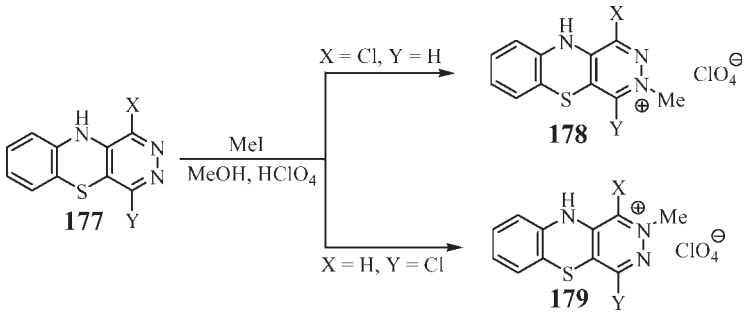
Scheme 68



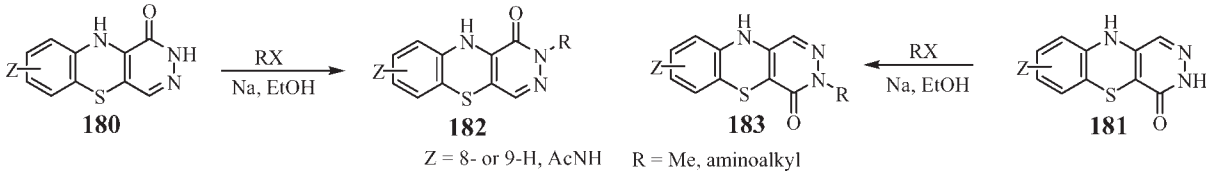
Scheme 69



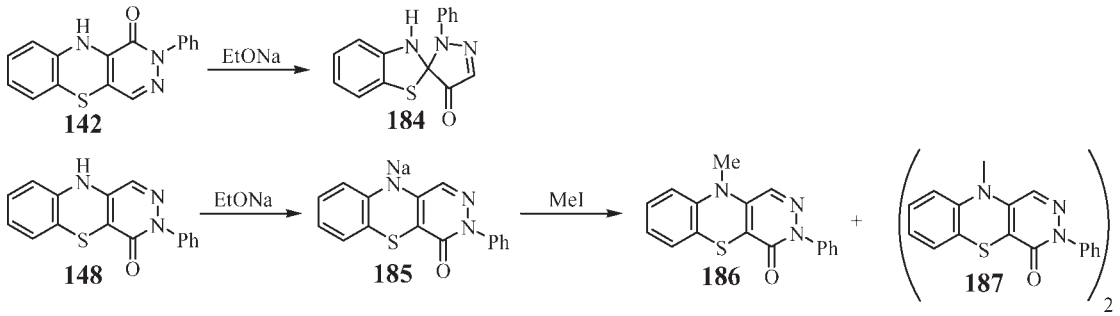
Scheme 70



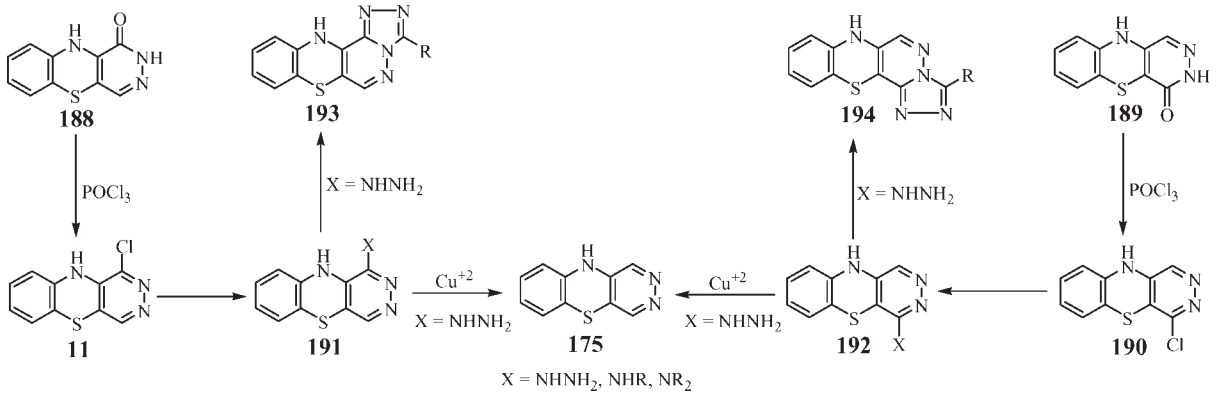
Scheme 71



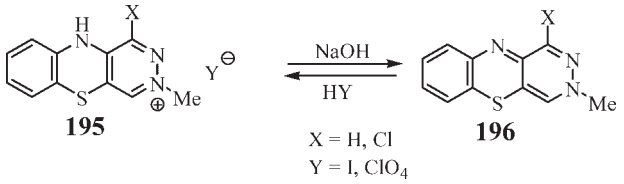
Scheme 72



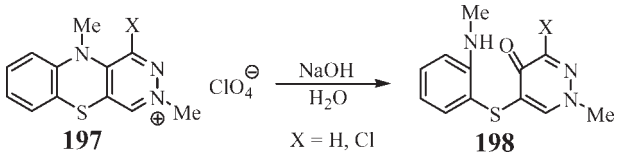
Scheme 73



Scheme 74



Scheme 75



compounds with acetic acid gave tetracyclic triazolodiazaphenothiazines **193** and **194** (R = Me, Scheme 73) [90]. Similar triazolo compounds (R = alkyl, *S*-alkyl, *S*-aminoalkyl) were obtained from the same or other hydrazine substrates [78,80,91].

2,3-Diazaphenothiazinium salts exhibited different properties under basic conditions. Whereas the 10*H*-2-alkyl salt was unreactive, the 10*H*-3-alkyl salt **195** gave 3-methyl-2,3-diazaphenothiazine **196**. This product can be converted back to the thiazinium salt **195** by action of acid (perchloric or hydroiodic, Scheme 74) [79,90].

When position 10 was methylated as in 3,10-dimethyl-2,3-diazaphenothiazinium perchlorate **197**, action of alkali led unexpectedly to opening of the 1,4-thiazine ring to give sulfide **198** (Scheme 75) [79].

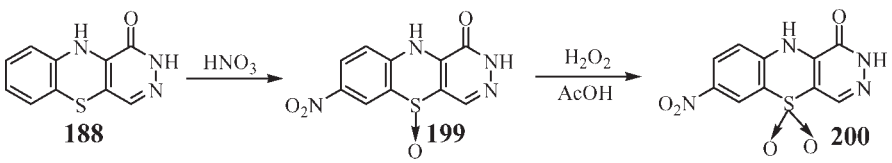
Nitration of 10*H*-diazaphenothiazin-1-one **188** with fuming nitric acid led to 7-nitro-2,3-diazaphenothiazin-1-one *S*-oxide **199**, which can be further converted to *S*,*S*-dioxide **200** by action of hydrogen peroxide in acetic acid (Scheme 76) [81]. Other transformations of 2,3-diazaphenothiazines were connected with the chlorine atom substitution, reduction of the nitro group and acetylation of the 10*H* position [75–78,82–85,90].

The postulated structures of 2,3-diazaphenothiazines and their salts were based on chemical transformations to known compounds (*e.g.*, 2,3-diazaphenothiazin-1(2*H*)-ones and 2,3-diazaphenothiazin-4(3*H*)-ones to chloro-2,3-diazaphenothiazines), on the ^{1}H NMR spectra (a shift of the H-1 proton [92], shielding of the H-1 and H-4 protons in salts [79], long range coupling between the H-4 and H-10 protons [80,90]) and UV spectra (distinction of 1,2-, 2,3-, and 3,4-diazaphenothiazines [20], distinction of 3- and 10-substituted 2,3-diazaphenothiazines [80]). Unquestionable structure evidences came from X-ray analysis of the selected compounds: 10-methyl-2,3-azaphenothiazine, 1-chloro-10-methyl-2,3-azaphenothiazine, 10*H*-2,3-azaphenothiazin-1(2*H*)-one, and 10*H*-2,3-azaphenothiazin-4(3*H*)-one [93–95].

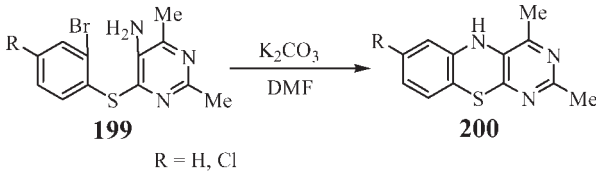
Some 2,3-diazaphenothiazines exhibited wide spectrum of biological activities: anti-inflammatory [88,89,91], analgesic [88,89,91,96], sedative [73,74,89], antiallergic [80], antiparasitic [96], antihistaminic [74,96], and antiarrhythmic [80].

2,4-Diazaphenothiazines (pyrimidino[4,5-b][1,4] benzothiazines). As was shown in Scheme 15, 10*H*-2,4-diazaphenothiazine **27** was the minor product of cyclization of amino-phenyl 4-pyrimidinyl sulfide **25** in DMF

Scheme 76



Scheme 77



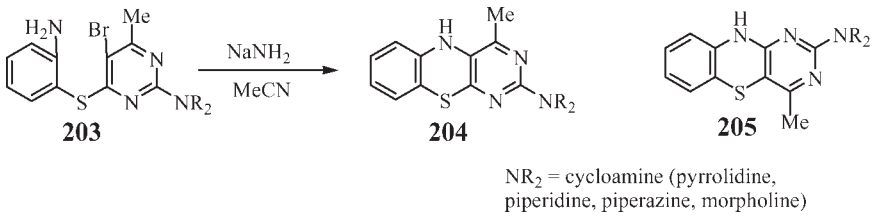
(with potassium carbonate) [25]. Reactions of *o*-bromophenyl 4-pyrimidinyl sulfides **201** in DMF (with potassium carbonate and copper powder), according to the authors, proceeded without the Smiles rearrangement to substituted 10*H*-2,4-diazaphenothiazines **202** (Scheme 77) [25,47].

Very recently an interesting cyclization of substituted *o*-aminophenyl 4-pyrimidinyl sulfides **203** in acetonitrile (with sodium amide) was published. According to the authors, the products were identified on the spectral (^{1}H NMR, IR, and MS) and microanalytical data as 3-substituted 2,4-diazaphenothiazines **204**. As the reaction conditions seem to favor the Smiles rearrangement, the obtained products are rather 1,3-diazaphenothiazines **205** (Scheme 78) [97].

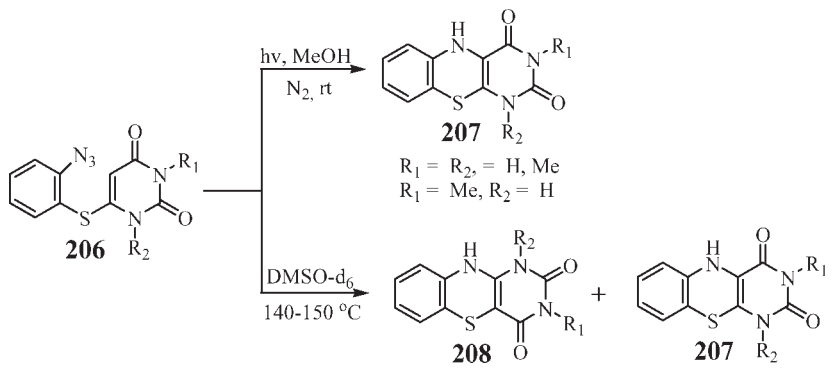
Although an irradiation of 6-(2-azidophenylthio)uracil **206** in methanol with a mercury lamp under nitrogen atmosphere resulted in exclusive formation of 2,4-diazaphenothiazine-1,3-diones **207**, thermolysis in DMSO-d_6 led to 1,3-diazaphenothiazine-2,4-diones **208** and 2,4-diazaphenothiazine-1,3-diones **207** in ratio of 2:1 (Scheme 79) [98].

Japanese groups [99–101] carried out reactions of the uracil compounds **209** with *N*-bromosuccinimide in ethanol followed by reaction with aminobenzenethiol **8** to obtain 2,4-diazaphenothiazinones **210**. It was found that those reactions proceeded through formation of 6-bromouracils which further formed with ethanol the diethoxy derivatives. The isolated diethoxy compound **211** reacted with aminobenzenethiol **8** to give 2,4-diazaphenothiazinedione **210** (R_1, R_2 = H, X = O, Scheme 80) [99].

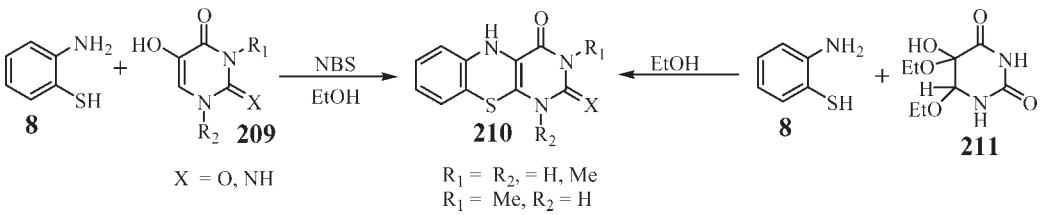
Scheme 78



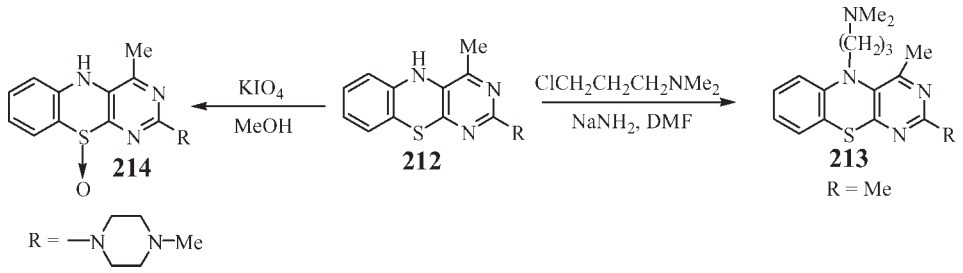
Scheme 79



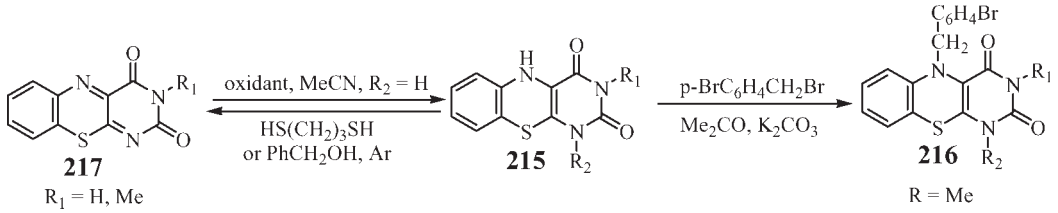
Scheme 80



Scheme 81



Scheme 82



1,3-Disubstituted 10*H*-2,4-diazaphenothiazine **212** was alkylated with dimethylaminopropyl chloride to give 10-aminoalkyl derivative **213** [25] and oxidized with potassium metaperiodate to give the 2,4-diazaphenothiazine *S*-oxide **214** (Scheme 81) [97].

Similarly, 1,3-disubstituted 10*H*-2,4-diazaphenothiazine-1,3-dione **215** was alkylated in acetone with *p*-bromobenzyl bromide to form 10-bromobenzyl derivative **216** [101]. Reaction with an oxidant (*e.g.*, 1,4-benzoquinone) in acetonitrile led to 2,4-diazaphenothiazine-1,3(2*H*)-diones **217** (called also as 10-thiaisoalloxazines). Reduction with propanedithiol or benzyl alcohol gave substrate **215** back (Scheme 82) [98,101]. Compound **217** underwent a smooth ring contraction on reaction with amines [102].

Some 2,4-diazaphenothiazines showed anti-inflammatory, antibacterial, antifungal, and analgesic activities [25–47] and some 2,4-diazaphenothiazine-1,3-diones inhibiting activity to lipoxygenases [97,100].

2,7-Diazaphenothiazines (dipyrido[3,4-b;3′,4′-e][1,4] thiazines). Reactions of 4-chloro-3-nitropyridine **218** with sodium sulfide in DMF led unexpectedly to 10*H*- and 10-(3′-nitro-4′-pyridinyl)-2,7-diazaphenothiazines **219** and **220** as major products (in modest yields) and to isomeric 2,7- and 2,8-diazathianthrenes **221** and **222** as minor products (Scheme 83, the last compounds were only products in DMSO) [103].

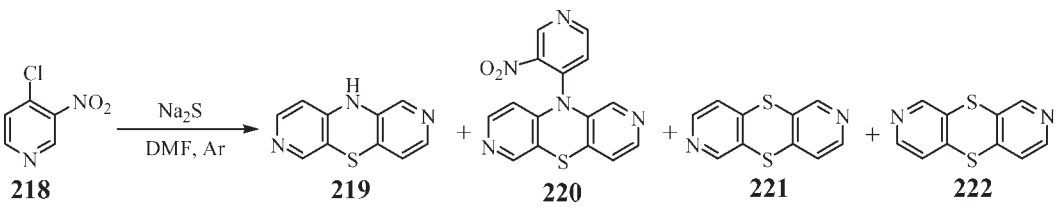
It is worth noting that the unexpected products **219** and **220** were results of single and double Smiles rearrangements of sulfides **224** and **226** and reductive properties of DMF (Scheme 84).

Later the synthesis was improved using sodium 3-nitro-4-pyridinethiolate **223**, or pairs of disubstituted pyridines **218** and **227–229**, or dipyridinyl sulfide **224**. 2,7-Diazaphenothiazine **219** was further transformed into 10-substituted derivatives **230** in reactions with appropriate halogenocompounds in DMF (with sodium hydride) or dioxane (with sodium hydroxide, Scheme 85) [104].

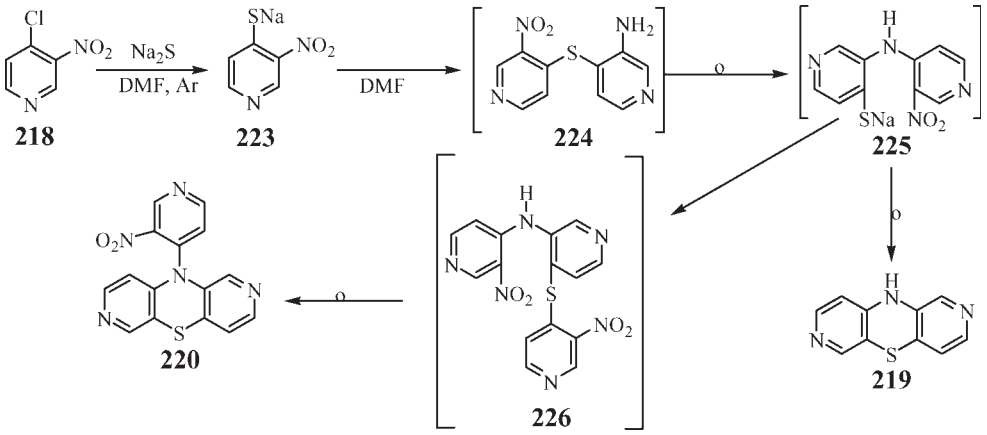
The structures of 2,7-diazaphenothiazines **219**, **220**, and **230** were determined on the basis of spectroscopic analyses (^{1}H NMR, ^{1}H-^{1}H COSY, and NOE) and confirmed by X-ray analysis of compound **220** [103,104]. For selected compounds lipophilic character and promising anti-cancer activities against lung, colon, renal cancers, and leukemia were determined [105,106].

3,4-Diazaphenothiazines (pyridazino[3,4-b][1,4] benzothiazines). The first synthesis of 3,4-diazaphenothiazine was achieved when *o*-aminophenyl 4-pyridazinyl sulfides **1** and **7** were heated in diluted

Scheme 83



Scheme 84



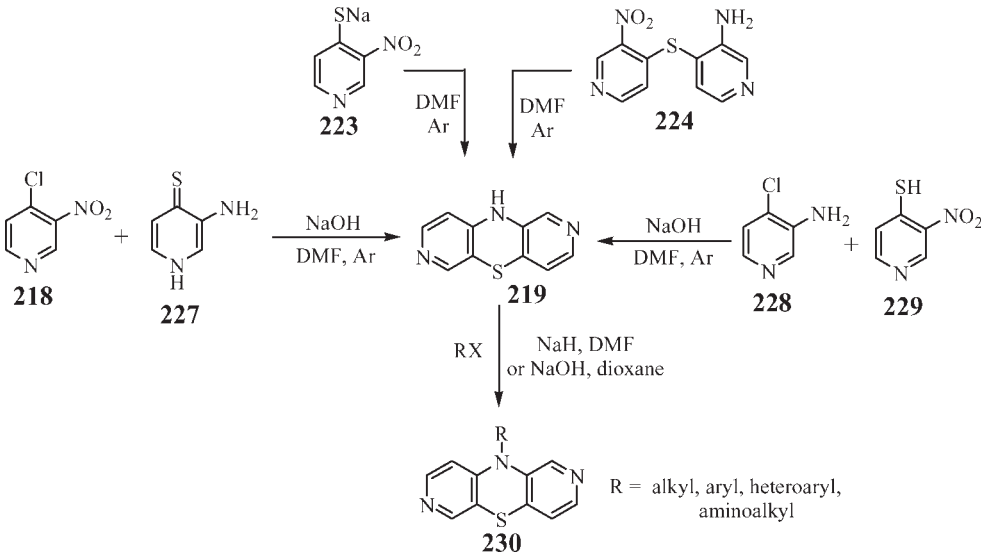
hydrochloric acid or acetic acid to give 2-chloro-3,4-diazaphenothiazine **6** through the Smiles rearrangement as is shown in Scheme 8. It worth noting that sulfide **1** in methanolic potassium hydroxide did not lead to 3,4-diazaphenothiazine **6** but to sulfide **7** which under acidic conditions underwent rearrangement and cyclization. The 10-methyl derivative **18** was obtained under the same conditions when the *N*-methylated sulfide **17** was used as depicted in Scheme 11 [18,19].

Attempts to obtain the parent 10*H*-3,4-diazaphenothiazine **232** from chloro compound **6** with catalytic hydrogenation over palladium charcoal was unsuccessful [19]. Only when aminophenyl 4-cyano-3-pyridazinyl sulfide **231** was stirred in DMSO (with sodium hydride) at room temperature 3,4-diazaphenothiazine **232** was obtained (in 85% yield). Reaction proceeded without the rearrangement (Scheme 86) [107].

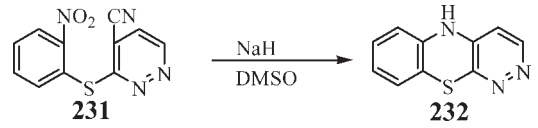
10-Substituted 3,4-diazaphenothiazines **237** were obtained when N-substituted *o*-aminobenzenethiols **233** (obtained from 3-substituted benzothiazolinone by alkaline decomposition) reacted with 3,4,6-trichloropyridazine **234** in ethanol (with potassium hydroxide) to give aminophenyl 4-pyridazinyl sulfide **235** (not always isolated) whose treatment in ethanol (with diluted hydrochloride acid) yielded 10-substituted 3,4-diazaphenothiazine **237** through rearrangement to amine **236** (Scheme 87) [108].

In a German patent [109], 10-substituted 3,4-diazaphenothiazines were described as the products of the reactions of 10*H*-3,4-diazaphenothiazine with dialkylaminoalkyl chlorides but lack of appropriate structures questioned the used 3,4-diazaphenothiazine (rather 1,2-diazaphenothiazine). 2-Chloro-3,4-diazaphenothiazines **6** underwent acetylation with acetic anhydride to

Scheme 85



Scheme 86



derivative **238**, the chlorine atom substitution with methoxy and dimethylamino groups to derivatives **239** and oxidation to *S*,*S*-dioxide *N*-oxide derivative **240** (Scheme 88) [18,19,108]. 2-Methoxy derivatives were also obtained for 10-substituted diazaphenothiazines (**237**, R = benzyl, dimethylaminoethyl) [19,108].

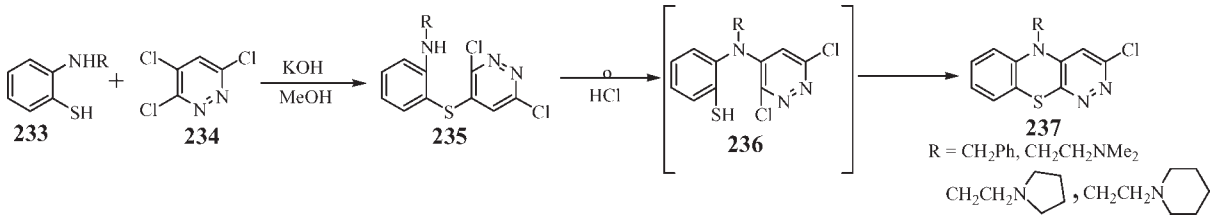
10-Pyrrolidinylethyl and dimethylaminoethyl derivatives **237** exhibited antihistaminic activity [107].

3,6-Diazaphenothiazines (dipyrido[2,3-b;4′,3′-e][1,4] thiazines). The first synthesis was described by Okafor [110] who carried out reactions of 3-amino-2(1*H*)-pyridinethione **241** with 3,5-dinitro-4-chloropyridine **242** in methanolic potassium hydroxide. The reaction proceeds through a formation of dipyridinyl sulfide **243** which undergoes rearrangement to dipyridinyl amine **244** to give 3,6-diazaphenothiazine **245**. The product structure was determined on the basis of strong hydrogen bonding between the NH and NO_2 groups (Scheme 89) [110].

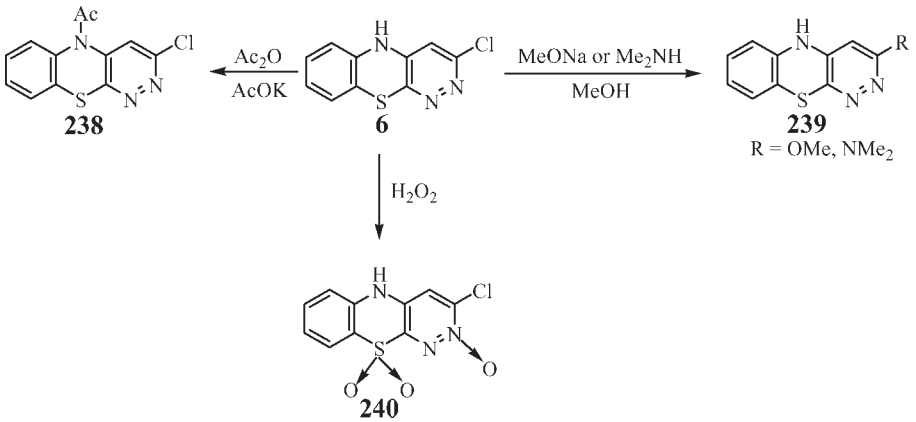
3,6-Diazaphenothiazines **245** were oxidized by sulfuric and nitric acids to *S*-oxide derivatives [111].

3,7-Diazaphenothiazines (dipyrido[3,4-b;4′,3′-e][1,4] thiazines). 10*H*-3,7-Diazaphenothiazine **247** was obtained in very low yield (9 and 6%, respectively) from sulfurization of 4,4′-dipyridinyl amine **246** with elemental sulfur at very high temperature (280–290°C) in the presence of iodine or with disodium tetrasulfide (at 260°C) [112,113]. When the cylization was carried out in *o*-dichlorobenzene with sulfur dichloride or when 3,7-diazaphenothiazine **247** was heated under those conditions, X,X′-dichloro-10*H*-3,7-diazaphenothiazine was formed (where X, X′ are most likely 4 and 4′) [114]. *N*-Alkylation with diethylaminoethyl and

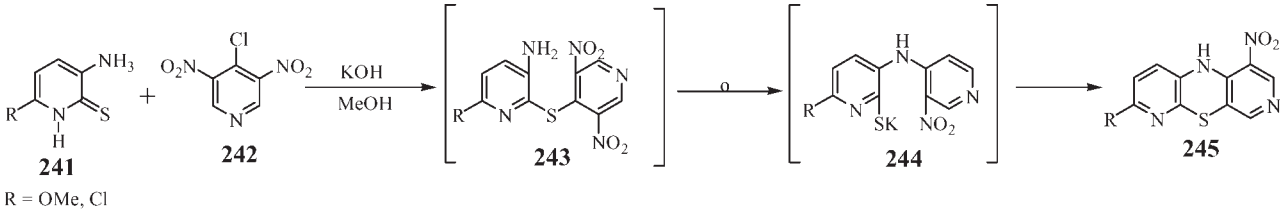
Scheme 87



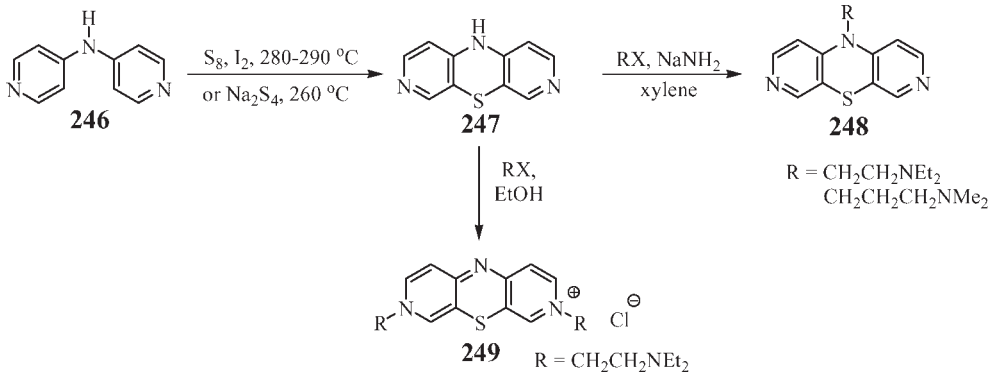
Scheme 88



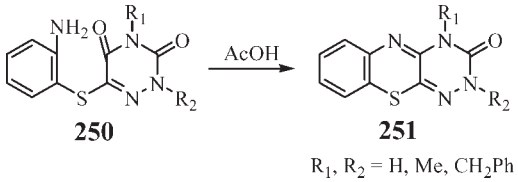
Scheme 89



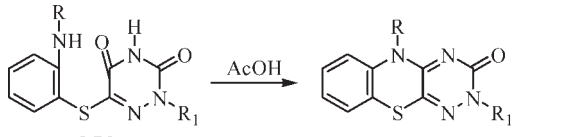
Scheme 90



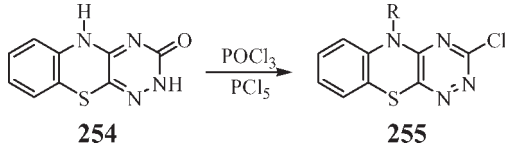
Scheme 91



Scheme 92



Scheme 93



dimethylaminopropyl chlorides proceeded at the thiazine or pyridine nitrogen atoms depending on the reaction conditions (xylene with sodium amide or only ethanol) to give 10-dialkylaminoalkyl derivatives **248** or the ammonium compound **249** (Scheme 90) [115].

3,7-Diazaphenothiazines **248** exhibited antihistaminic activity [115].

Tricyclic triazaphenothiazines. ***1,3,4-Triazaphenothiazines (benzo[1,2,4]triazino-[5,6-e][1,4]thiazines).*** Kaji et al. heated aminophenyl 1,2,4-triazinyl sulfides **250** in acetic acid to give 1*H*-1,3,4-triazaphenothiazin-2(1*H*)-one **251** without the rearrangement (Scheme 91) [116].

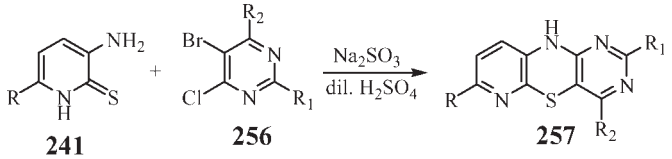
When *N*-benzyl derivative of aminophenyl triazinyl sulfide (with 4*H* function) **252** was used, appropriate 10-benzyl-1,3,4-triazaphenothiazin-2(1*H*)one **253** was obtained in low yield (20%, Scheme 92) [117].

The oxo group was substituted by the chlorine atom in 10*H*-1,3,4-triazaphenothiazinone **254** in the reaction with phosphoryl chloride giving 2-chloro derivative **255** (Scheme 93) [118].

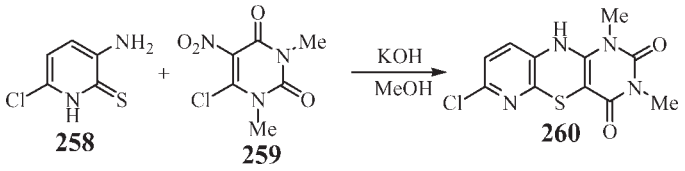
1,3,6-Triazaphenothiazine (pyrido[2,3-b]pyrimido-[4,5-e][1,4]thiazines). Reactions of substituted 3-aminopyridine-2(1*H*)-thiones **241** with chlorobromopyrimidines **256** in highly diluted sulfuric acid (100:1) (with sodium sulfite) led without rearrangement directly to 1,3,6-triazaphenothiazines **257** in low to excellent yields (11–95%, Scheme 94). The structure of the product as 1,3,6-triaza compounds (but not the 2,4,6-triaza isomers) was based on the lack of formation of the 1,10-diazole ring during diazotization of the amino derivative [119,120].

A similar reaction of aminopyridinethione **258** with 1,3-dimethyl-5-nitro-6-chlorouracil **259** in methanol (in the presence of base) led to 1,3,6-triazaphenothiazine-2,4-(1*H*,3*H*)-dione **260** in 66% yield (Scheme 95) [121,122].

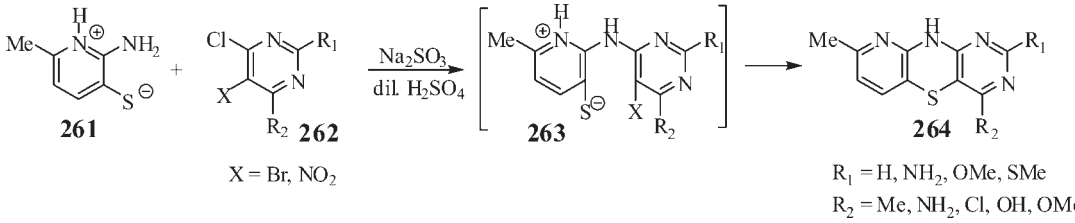
Scheme 94



Scheme 95



Scheme 96



1,3,6-Triazaphenothiazines **257** exhibited appreciable CNS-depressant activities [120].

1,3,9-Triazaphenothiazine (pyrido[3,2-b]pyrimido-[4,5-e][1,4]thiazines). The reaction of the betaine **261** with chlorobromopyrimidines or chloronitropyrimidines **262** in diluted sulfuric acid (with sodium sulfite) led directly to 1,3,9-triazaphenothiazines **264** (Scheme 96) [120,123–125]. The same reaction under basic conditions gave no products. The authors postulated that the reaction proceeded *via* formation of diazinyl amine **263**, which underwent cyclization smoothly, as they isolated compound **263** (X = H, R_1 = R_2 = OMe) from the reaction of compound **261** with 4-chloropyrimidine **262** (without the 5-bromo function, X = H). The structure of the resulting product **264** was reported as the 1,3,9-triaza compound (but not the 2,4,9-triaza isomer) based on the lack of formation of the 1,10-diazole ring during diazotization of the amino derivative [124].

1,3,9-Triazaphenothiazines **264** exhibited appreciable CNS-depressant activities [120].

1,4,6-Triazaphenothiazine (pyrido[2,3-b]pyrimido[2′, 3′-e][1,4]thiazines). Reaction of substituted 3-aminopyridine-2(1*H*)-thiones **241** with 2,3-dichloropyrazine **96** in aqueous propylene glycol (with sodium hydroxide) led to 7-substituted 1,4,6-triazaphenothiazines **265** in 67–89% yield (Scheme 97).

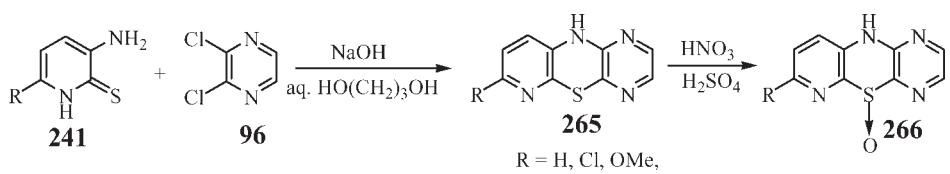
Triazaphenothiazines **265** were converted to their *S*-oxide derivatives **266** by the action of mixed concentrated nitric and sulfuric acids [125].

1,4,9-Triazaphenothiazines (pyrido[3,2-b]pyrazino[2′, 3′-e][1,4]thiazines). The reaction of the betaine **261** with trichloropyrazine **267** in DMA (with sodium hydroxide) aimed at obtaining triazaphenothiazines **268** or **269** gave unexpectedly the bis-sulfide **270** in 82% yield. The formation of the second sulfide function proceeded more smoothly than the thiazine ring closure (Scheme 98) [126].

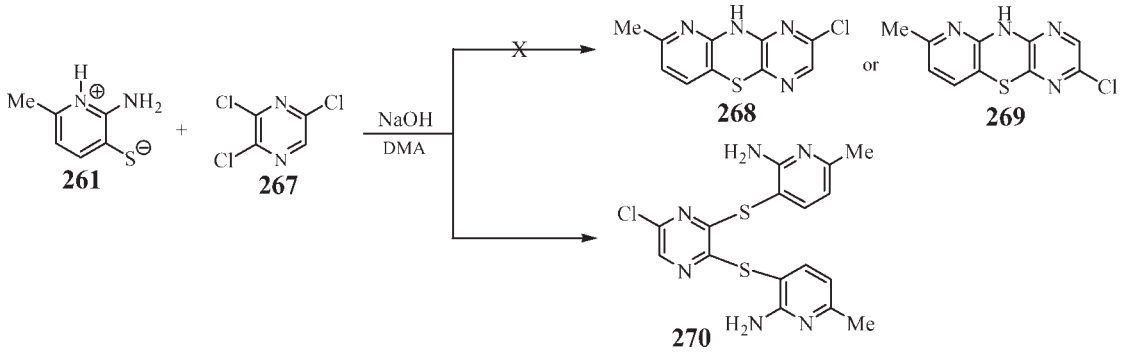
2,3,6-Triazaphenothiazine (pyrido[2,3-b]pyridazino-[4′,5′-e][1,4]thiazines). Reaction of 6-methoxy-3-aminopyridine-2(1*H*)-thione **271** with 4,5-dichloropyridazin-3(2*H*)-one **272** in aqueous DMSO (with sodium hydroxide) gave the pyridinyl pyridazinyl sulfide **273** which further in concentrated hydrochloric acid underwent cyclization to 2,3,6-triazaphenothiazin-1(2*H*)-one **274** in 82% yield. Direct reaction of compounds **271** and **272** in aqueous DMSO (for prolonged periods of time) gave the same triazaphenothiazinone **274** in 41% yield and the sulfide **275** (in 26% yield). Sulfide **273**, when heated in acetic acid, underwent the Smiles rearrangement and cyclization to isomeric 2,3,6-triazaphenothiazin-4(3*H*)-one **276** in 89% yield (Scheme 99). The structure of isomeric triazaphenothiazinones was established on the basis of a very broad signal for 10-H proton of isomer **274** (1-one) because of strong NHO hydrogen bonding [127].

Reaction of 3-aminopyridine-2(1*H*)-thione **277** with 4,5-dichloropyridazine **278** in ethanol (with potassium hydroxide) under nitrogen atmosphere led to 2,3,6-triazaphenothiazine **279** in 63% yield (Scheme 100) [126].

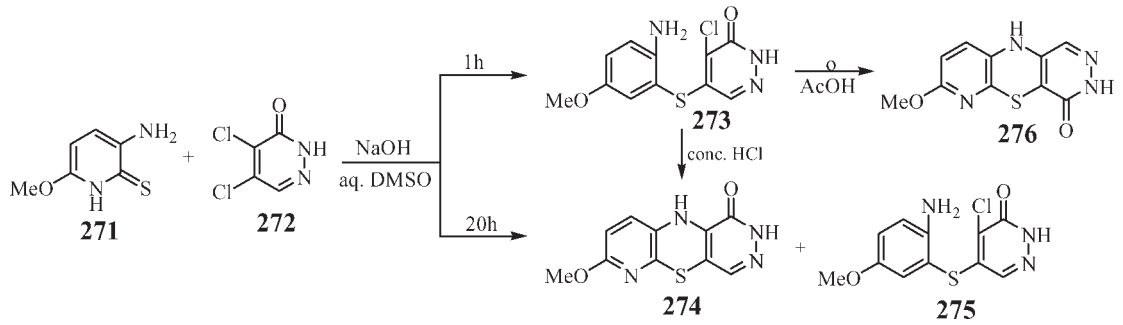
Scheme 97



Scheme 98



Scheme 99

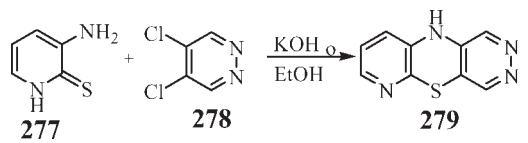


Later, Baltrop and Owen repeated this reaction and questioned the previous result. The obtained product was also identified as 2,3,6-triazaphenothiazine **279** [128] but possessed a different melting point, ^{1}H NMR, UV spectra, and elemental analysis only was similar.

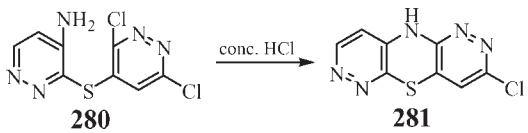
Tricyclic tetraazaphenothiazines. ***1,2,6,7-Tetraazaphenothiazine (dipyridazino[3,4-b;3′,4′-e][1,4]thiazines).*** Heating dipyridazinyl sulfide **280** in concentrated hydrochloric acid led to 1,2,6,7-tetraazaphenothiazine **281** in 61% yield (Scheme 101) [129].

1,2,7,8-Tetraazaphenothiazine (dipyridazino[4,3-b;4′,5′-e][1,4]thiazines). Cyclization of dipyridazinyl sulfide **282** in concentrated hydrochloric acid gave 1,2,7,8-tetraazaphenothiazine **283** in 63% yield (Scheme 102) [129].

Scheme 100



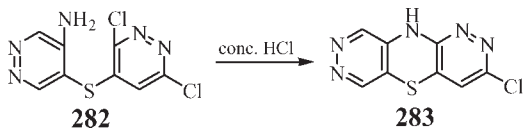
Scheme 101



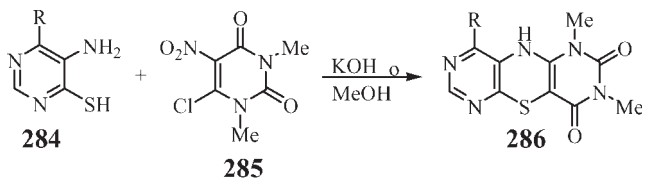
1,3,6,8-Tetraazaphenothiazine (dipyrimido[4,5-b;4′,5′-e][1,4]thiazines). Reactions of substituted 5-aminopyrimidine-4-thiols **284** with 1,3-dimethyl-5-nitro-6-chlorouracil **285** in ethanol (with potassium hydroxide) led to 1,3,6,8-tetraazaphenothiazine-2,4(1*H*,3*H*)-diones **286** in 54–78% yield *via* the Smiles rearrangement (Scheme 103).

When 1,3-dimethyl-5-amino-6-mercaptouracil **287** was used in the reaction, 1,3,6,8-tetraazaphenothiazine-2,4,7,-9(1*H*,3*H*,6*H*,8*H*)-tetraone **288** was obtained in 58% yield (Scheme 104) [121,122].

Scheme 102

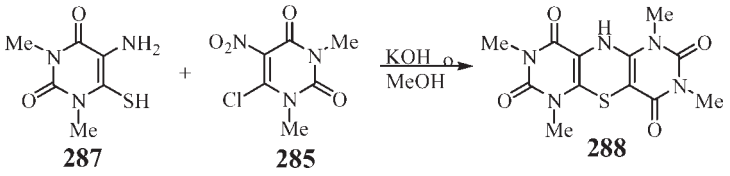


Scheme 103

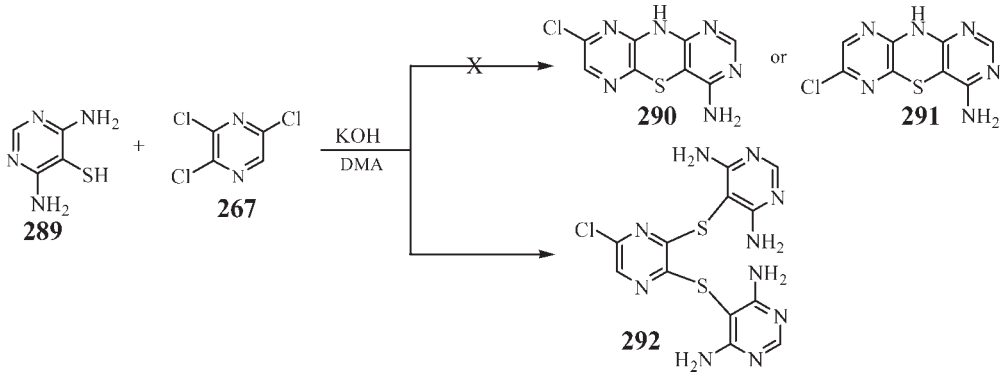


R = OMe, NH_2, NMe_2

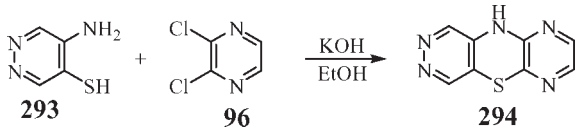
Scheme 104



Scheme 105



Scheme 106



1,3,6,9-Tetraazaphenothiazine (pyrazino[2,3-b]pyrimido[4′,5′-e][1,4]thiazines). Reaction of 4,6-diaminopyrimidine-5-thiol **289** with trichloropyrazine **267** in DMA did not lead to tetraazaphenothiazine **290** or **291** but unexpectedly to the bis-sulfide **292** in high yield (93%, Scheme 105) [126].

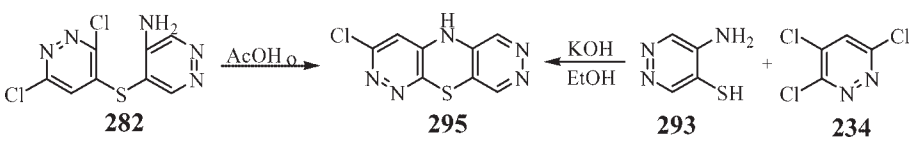
1,4,7,8-Tetraazaphenothiazine (pyrazino[2,3-b]pyridazino[4′,5′-e][1,4]thiazines). Reaction of 4-aminopyridazine-5-thiol **293** with dichloropyrazine **96** (with potassium hydroxide) led to 1,4,7,8-tetraazaphenothiazine **294** in low yield (30%, Scheme 106) [126].

2,3,6,7-Tetraazaphenothiazine (dipyridazino[3,4-b;4′,5′-e][1,4]thiazines). Dipyridazinyl sulfide **282** in acetic acid underwent the Smiles rearrangement and cyclization to give 8-chloro-2,3,6,7-tetraazaphenothiazine **295** in 82% yield. The same product was obtained in the reaction of aminopyridazinethiol **293** with trichloropyridazine **234** in ethanol (with potassium hydroxide) in 88% yield (Scheme 107).

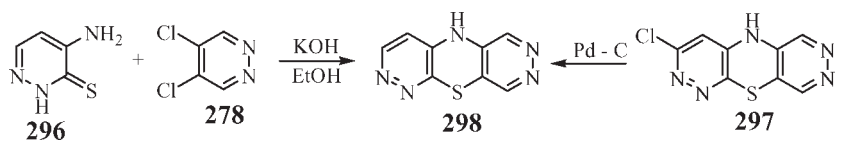
The parent 2,3,6,7-tetraazaphenothiazine **298** was obtained in the reaction of 4-aminopyridazine-3-thione **296** with dichloropyrazine **278** in ethanol (with a base) in 57% yield or by dechlorination of chlorotetraazaphenothiazine **297** in 55% yield with a use of palladium charcoal (Scheme 108).

Alkylation of tetraazaphenothiazine **297** with aminoalkyl chlorides in liquid ammonia (with sodium amide) yielded aminoalkyl derivatives **298** in 43–55% yield (Scheme 109) [129].

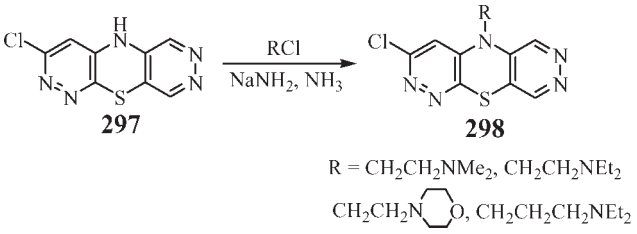
Scheme 107



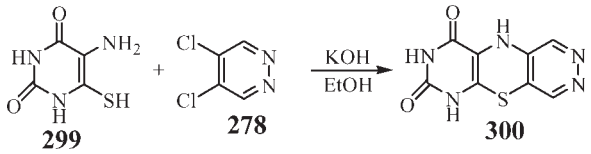
Scheme 108



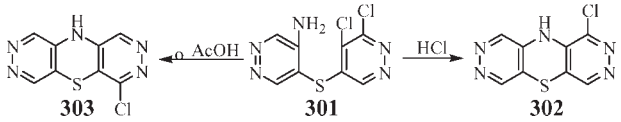
Scheme 109



Scheme 110



Scheme 111



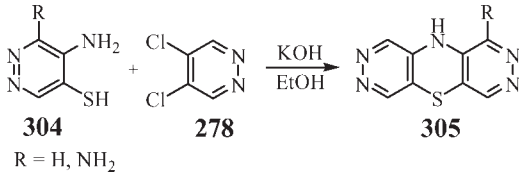
2,3,6,8-Tetraazaphenothiazine (pyridazino[4,5-b]pyrimido[5′,4′-e][1,4]thiazines). Reaction of 5-aminouracil-6-thiol **299** with dichloropyridazine **278** in ethanol (with potassium hydroxide) led to 2,3,6,8-tetraazaphenothiazine-7,9(6*H*,8*H*)-dione **300** in 50% yield (Scheme 110) [126].

2,3,7,8-Tetraazaphenothiazine (dipyridazino[4,5-b;4′,5′-e][1,4]thiazines). Whereas dipyridazinyl sulfide **301** in hydrochloric acid underwent cyclization to 1-chloro-2,3,7,8-tetraazapheno-thiazine **302** in 58% yield, in acetic acid it underwent the Smiles rearrangement and cyclization to isomeric 4-chloro-2,3,7,8-tetraazaphenothiazine **303** in 57% yield (Scheme 111).

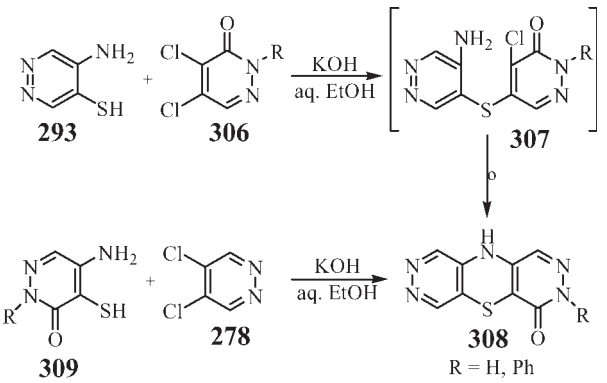
The parent tetraazaphenothiazine and the amino derivative **305** were obtained in the reaction of 4-amino-3-pyridazinethiols **304** with dichloropyridazine **278** in ethanol (with potassium hydroxide) in 66 and 72% yield (Scheme 112).

With dichloropyridazinones **306** in aqueous ethanol (in the presence of a base) the aminopyridazinethiol **293** underwent the Smiles rearrangement and cyclization to 2,3,7,8-tetraazaphenothiazin-4-ones **308**. Crude dipyridazinyl sulfide **307** (R = H) underwent the rearrangement and cyclization during crystallization from ethanol. The

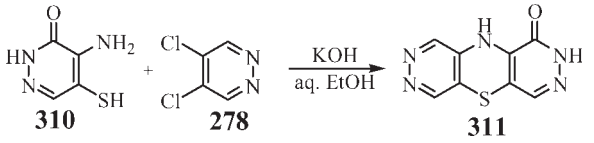
Scheme 112



Scheme 113



Scheme 114



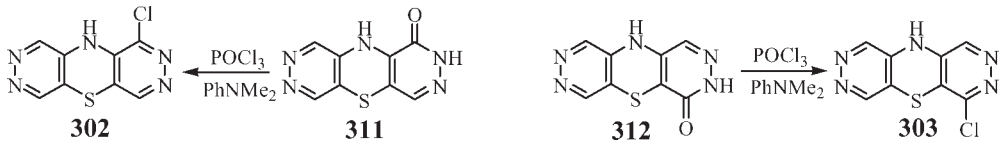
structures of the products **308** were established by independent synthesis using 5-amino-4-mercaptopyridazin-3(2*H*)-one **309** and dichloropyridazine **278** under the same conditions (Scheme 113).

When 5-amino-4-mercaptopyridazin-6(1*H*)-one **310** was used in the reaction with dichloropyridazine **278**, isomeric 2,3,7,8-tetraazaphenothiazin-1-one **311** was obtained in 75% yield (Scheme 114).

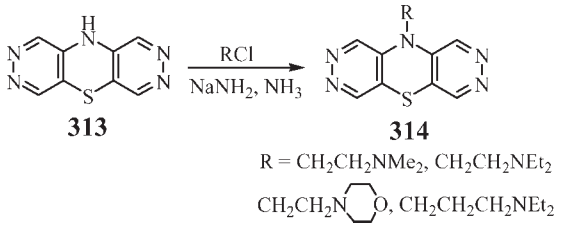
Both tetraazaphenothiazinones **311** and **312** were converted into the chloro derivatives **302** and **303** in low yield (27 and 40%) by the action of phosphoryl chloride with *N*,*N*-dimethylaniline (Scheme 115).

The parent 10*H*-tetraazaphenothiazine **313** was transformed into aminoalkyl derivatives **314** in 39–51% yield by *N*-alkylation with aminoalkyl chlorides in liquid ammonia (in the presence of sodium amide, Scheme 116) [129].

Scheme 115



Scheme 116



2,4,6,8-Tetraazaphenothiazine (dipyrimido[4,5-b;5′,4′-e][1,4]thiazines). Reaction of 5,6-diamino-1,3-dimethyluracil **315** with liquid hydrogen sulfide in pyridine in a sealed tube led unexpectedly to 2,4,6,8-tetraazaphenothiazine-1,3,7,9(2*H*,4*H*,6*H*,8*H*)-tetraone **316** in 55% yield. To establish the correct structure of the product, an independent synthesis (in 58% yield) was carried out using aminomercaptouracil **287** and 5-hydroxy-1,3-dimethyluracil **317** in the presence of N-bromosuccinimide in ethanol (Scheme 117).

N-Alkylation of tetraazaphenothiazine **316** with benzyl and *p*-bromobenzyl bromides in DMF or acetone (with bases) led not only to the expected benzyl derivatives **317** (in 29 and 14% yield) but also to the unexpected benzyl derivatives of the ring contraction product, dipyrimidopyrroles **318** (in 7 and 46% yield, respectively, Scheme 118) [101].

3,4,6,7-Tetraazaphenothiazine (dipyridazino[3,4-b;4′,3′-e][1,4]thiazines). Whereas dipyridazinyl sulfide **280** gave in concentrated hydrochloric acid 1,2,6,7-tetraazaphenothiazine **281** (Scheme 101), in acetic acid gave 2-chloro-3,4,6,7-tetraazaphenothiazine **319** (in 47% yield) as a result of the Smiles rearrangement (Scheme 119).

Reaction of aminopyridazinethione **296** with dichloropyridazine **320** in ethanol (in the presence of potassium hydroxide) led to parent 3,4,6,7-tetraazaphenothiazine **321** in 60% yield (Scheme 120) [129].

Tetracyclic phenothiazines (benzo derivatives of phenothiazines).

Benzo derivatives of 1,4-diazaphenothiazines (quinoxalino[2,3-b]benzo[1,4]thiazines). The first synthesis was carried out by Walter and co-workers as early as 1933 using aminobenzenethiol **8** and 2,3-dichloroquinoxaline **322** (no details). The product structure was postulated as 12*H*-benzo-1,4-diazaphenothiazine **323** (Scheme 121) [130].

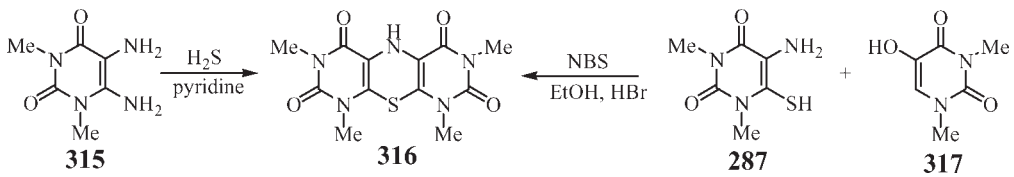
Almost 30 years later Schindler and Peterili (1961) repeated this synthesis using 5-chloro-2-aminobenzenethiol **324** and substituted 2,3-dichloroquinoxalines **325** to obtain substituted 12*H*-8-chlorobenzo-1,4-diazaphenothiazines **326** (Scheme 122) [131].

In the same time Riedel and Deuschel [132] and later Carter with Cheeseman [55] and Okafor [57] carried out the same reaction of aminobenzenethiol **8** with 2,3-dichloroquinoxalines **325** in *o*-dichlorobenzene or DMF (with bases) to obtain postulated 11*H*-benzo-1,4-diazaphenothiazines **327** (Scheme 123). When R ≠ H, the product was assigned as the 2-chloro compound **327** (X = Cl [57]) or was not determined at all (X = Me, Cl, OMe [132]).

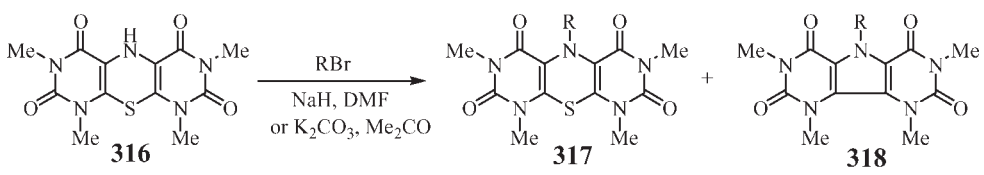
When *N*-substituted aminobenzenethiols **328** and substituted 2,3-dichloroquinoxalines **325** or quinoxaline-2,3-(1*H*,4*H*)-diones **329** were used, the obtained products were assigned as 11-substituted benzo-1,4-diazaphenothiazines **330** (Scheme 124) [55,132].

Whereas 11*H*- or 12*H*-benzo-1,4-diazaphenothiazines **323** or **331** (according to the authors), when methylated with methyl iodide in DMF (with sodium hydride), gave two compounds: the expected 11-methyl derivative as the main product **332** (in 45% yield) and the 12-methyl derivative **333** as the minor product (in 25% yield) [55], alkylated with aminoalkyl chlorides gave only one product: 11- or 12-substituted compound (**334** or **335**, not

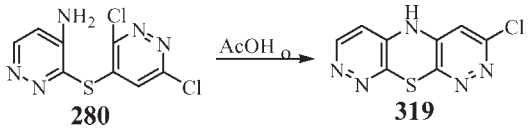
Scheme 117



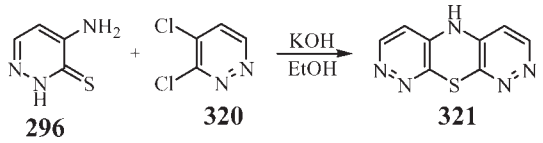
Scheme 118



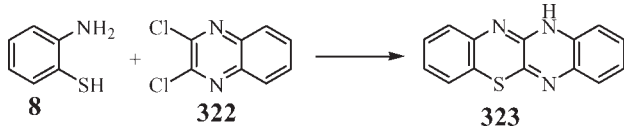
Scheme 119



Scheme 120



Scheme 121



determined) [131]. Acetylation with acetic anhydride gave only one product assigned as the 11-acetyl derivative **336** (Scheme 125) [55].

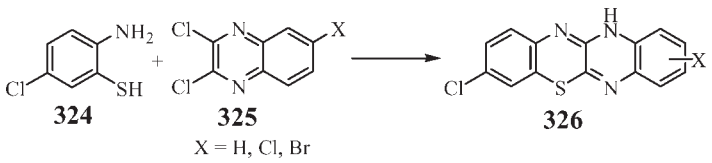
Oxidation of the 11-methyl derivative **332** with iodobenzene dichloride led to *S*-oxide derivative **337**, but with potassium permanganate to *S,S*-dioxide **338** (Scheme 126) [55].

Nitration of benzo-1,4-diazaphenothiazines **339** gave products depending on the nitrating agents. Nitration with sodium nitrate led to the mononitro derivative **340** but with mixed nitric and sulfuric acid to the nitration and oxidation product, the dinitro and *S*-oxide derivative **341** (Scheme 127) [55,57]. The last nitration was carried out to determine the correct structure of chlorobenzo-1,4-diazaphenothiazine (the position of the chlorine atom) **339** (X = Cl) by analysis of the directive influence of the functional groups [57].

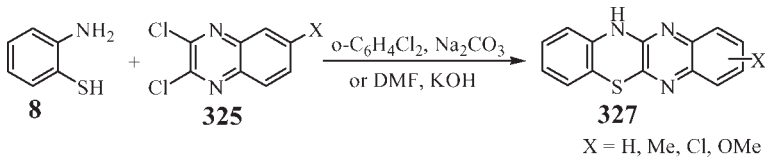
Some benzo-1,4-diazaphenothiazines exhibited antiallergic, anticonvulsive, sedative, adrenolytic, and serotonin-antagonistic activities [131] and yellow pigment dye properties [132].

Benzo derivatives of 3,6-diazaphenothiazines (pyrido[2,3-b]quino[4′,3′-e][1,4]-thiazines). Reactions of 5,12-dialkylthioquinanthrenediinium dichlorides **342** with 3-aminopyridine in pyridine proceeded *via* the 1,4-dithiin ring opening to give 1-alkyl-4-(3-pyridinylamino)-quinolinium-3-thiolate **343** in 63–70% yield or 5-alkyl-12*H*-benzodiazaphenothiazinium chlorides **344** in 60–66% yield, depending on the presence of atmospheric oxygen in the reaction mixture. Quinolinium thiolate **343** in the presence of aniline hydrochloride and air was converted

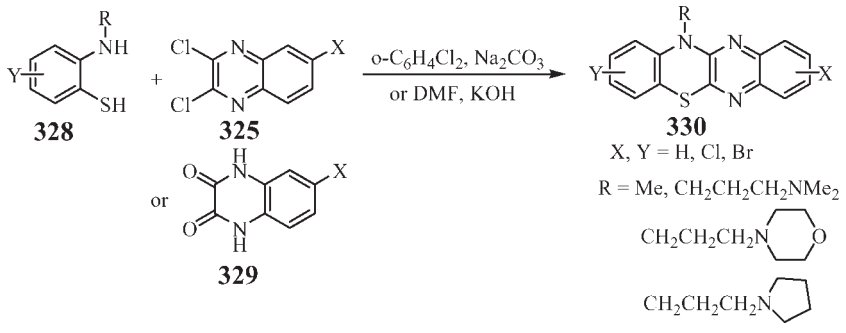
Scheme 122



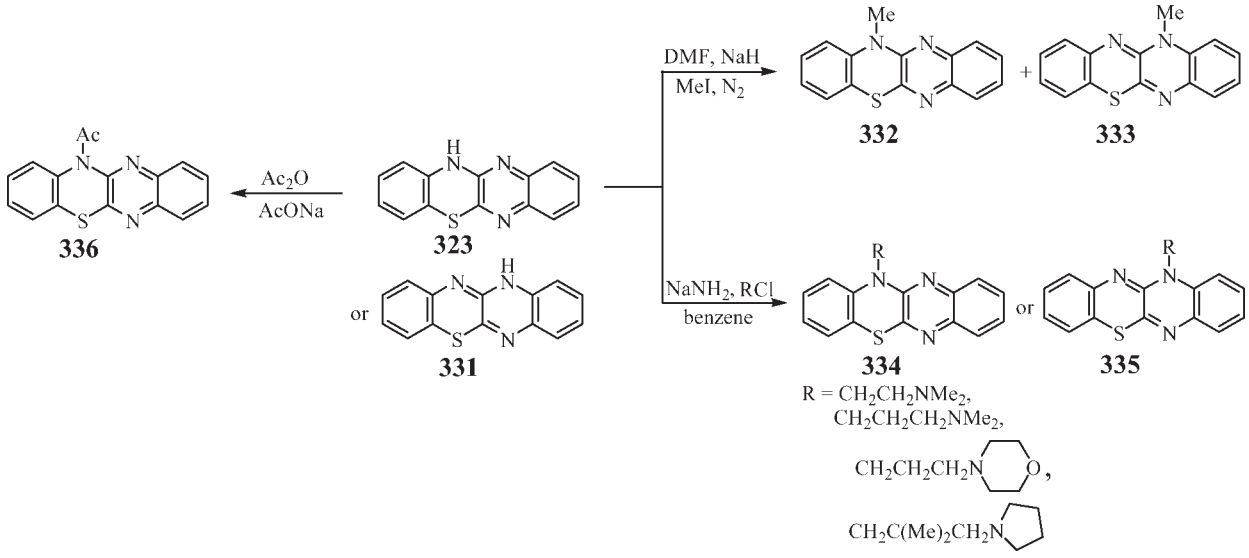
Scheme 123



Scheme 124



Scheme 125



to benzodiazaphenothiazinium salt **344** in 67–69% yield which was further transformed into 5-alkylbenzodiazaphenothiazines **345** in quantitative yield (Scheme 128).

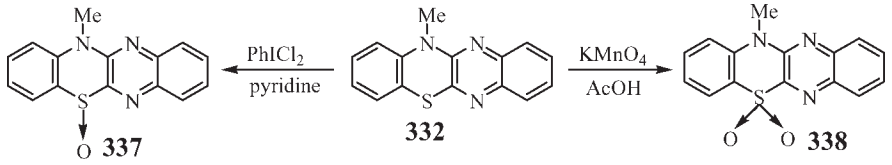
The structure of phenothiazinium salts was determined based on coupling constants analysis and was confirmed by X-ray analysis of the ethyl derivative **344** (R = Et) [133].

Benzo derivatives of 1,4,9-triazaphenothiazines (pyrido[3,2-b]quinoxalino[2′,3′-e][1,4]thiazines). Reaction of 2-amino-6-methylpyridine-3-thiol **261** with dichloro- and trichloroquinoxalines **325** in DMF (with sodium hydroxide) did not lead to tetracyclic azaphenothiazines **346** or **347** but unexpectedly to the bis-sulfide **348** in 77 and 71% yield, respectively (Scheme 129) [127].

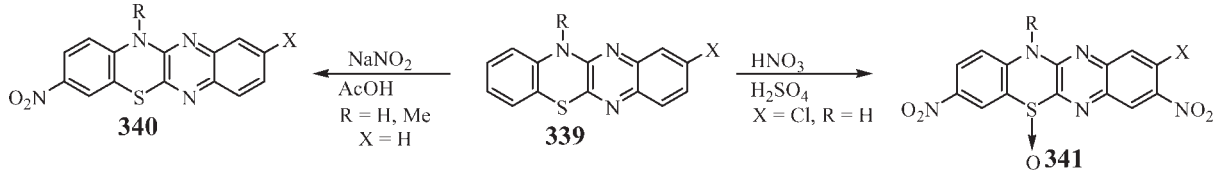
Benzo derivative of 1,3,6,9-tetraazaphenothiazines (pyrimido[5,4-b]quinoxalino[2′,3′,-e][1,4]thiazines. Reactions of substituted 4-aminopyridazine-5-thiols **349** with 2,3-dichloroquinoxalines **325** in aqueous propylene glycol (with potassium hydroxide) led to benzo derivatives of 1,3,6,9-tetraazaphenothiazines **350** in 84–95% yield *via* the Smiles rearrangement. The structures of the products were established on the basis of further nitration under mild conditions and the discussion of the directive influence of the NH group. The products were identified as substituted 8-nitrotetraazabenzophenothiazine-*S*-oxides **351** (Scheme 130) [134].

Benzo derivatives of 1,4,6,8-tetraazaphenothiazines (pyrimido[4,5-b]quinoxalino[2′,3′-e][1,4]thiazines). Reactions of 4,5-diaminopyrimidine-6(1*H*)-thione **352** with 2,3-dichloroquinoxalines **325** in aqueous DMF (with sodium hydroxide) proceeded *via* the Smiles rearrangement to give benzo derivatives of 1,4,6,8-tetraazaphenothiazines **353** in high yield (92 and 85% yield, respectively). The structure of the chloro product was based on further nitration under mild conditions and the discussion of the directive influence of the functional groups. The product

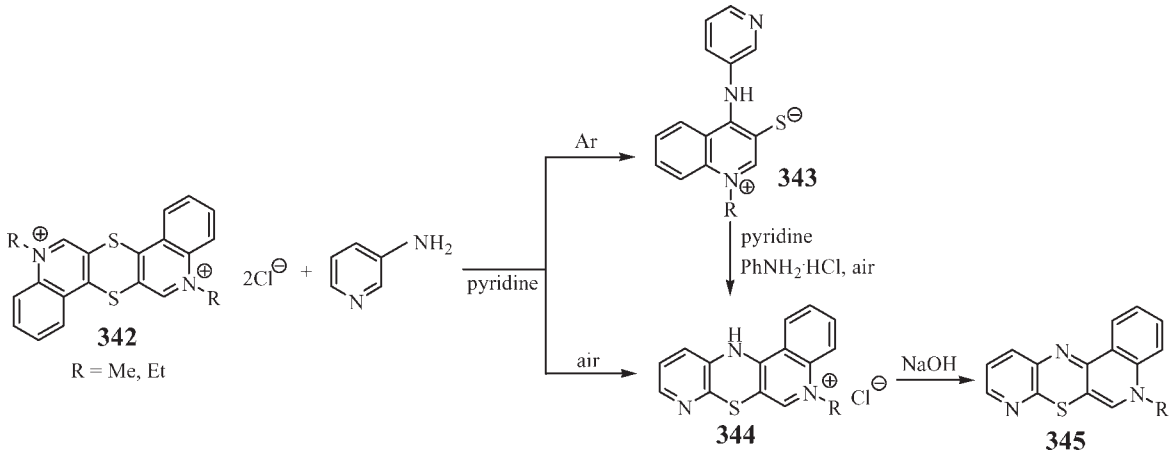
Scheme 126



Scheme 127



Scheme 128



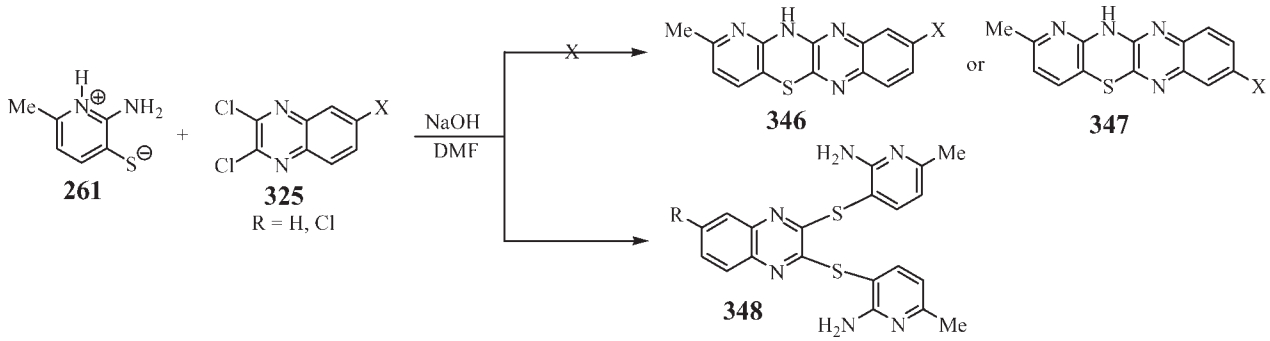
was identified as 10-amino-2-chloro-3-nitrotetraazabenzo[*b*]phenothiazine *S*-oxide **354** (Scheme 131).

To confirm the presence of the proton at the thiazine nitrogen atom compound **353** (R = H) was diazotized and heated to give triazolobenzotetraazaphenothiazine **355** in 81% yield (Scheme 132) [135].

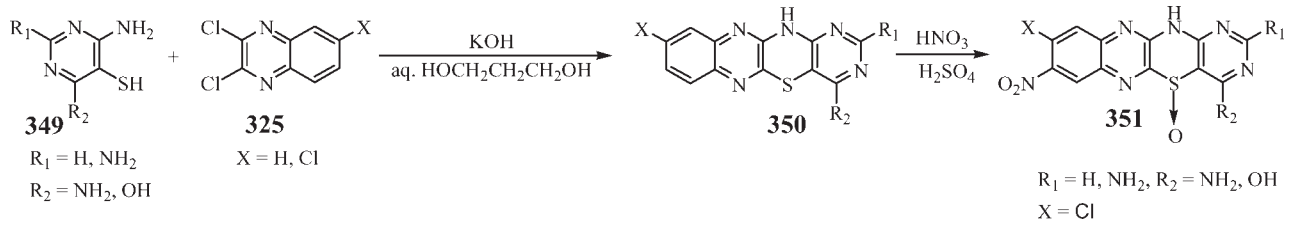
Pentacyclic phenothiazines (dibenzo derivatives of phenothiazines).

Dibenzo derivatives of 1,9-diazaphenothiazines (diquino[3,2-b;2′,3′-e]thiazines). Reaction of dihydroquinolin-2(1*H*)-one **356** with thionyl chloride in DMF led unexpectedly to the diquinothiazine **357** (in 21%

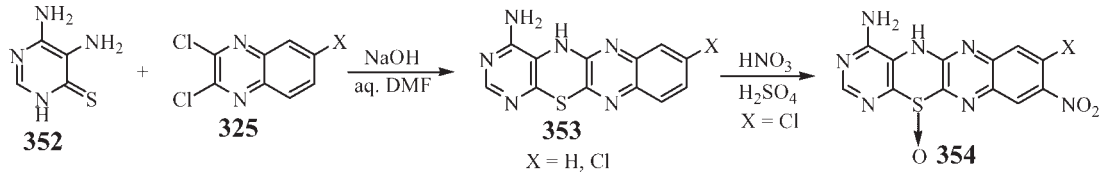
Scheme 129



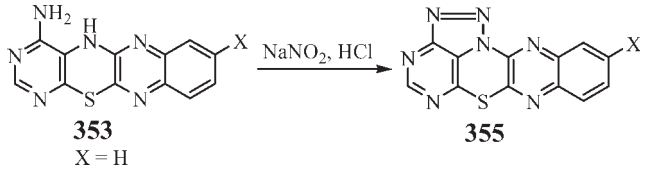
Scheme 130



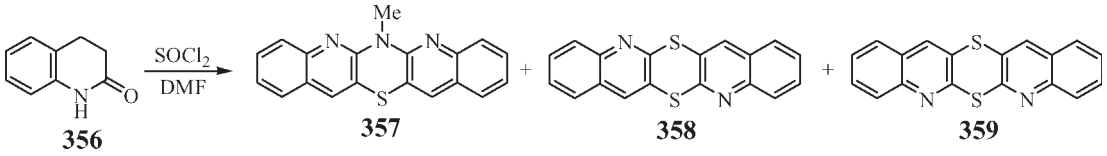
Scheme 131



Scheme 132



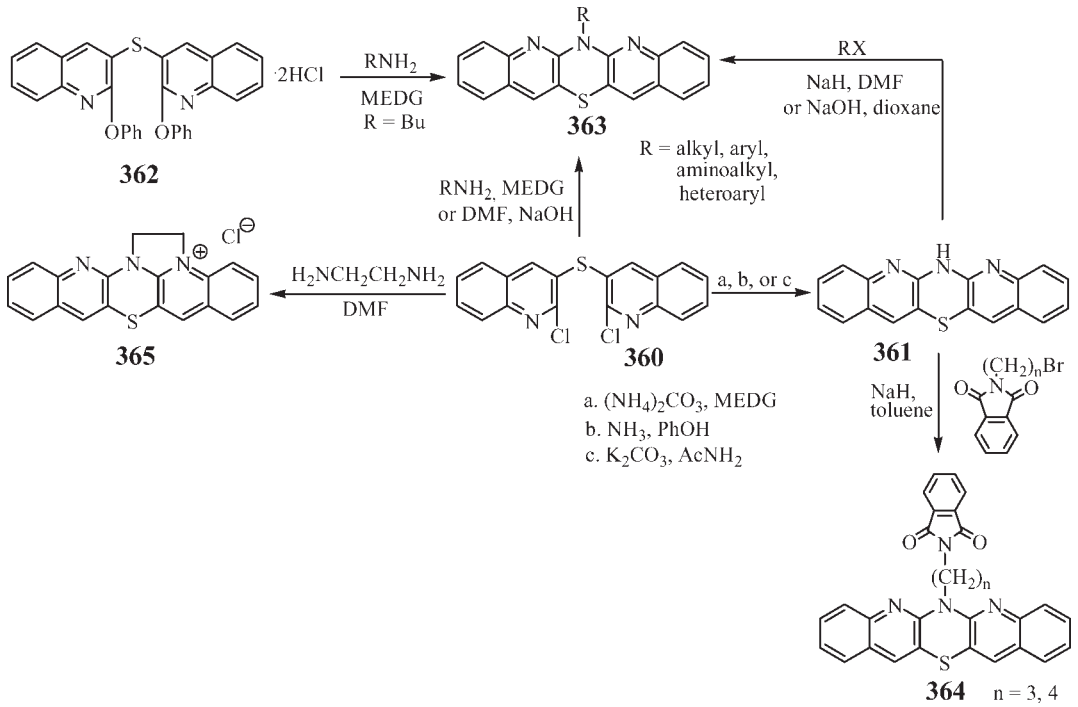
Scheme 133



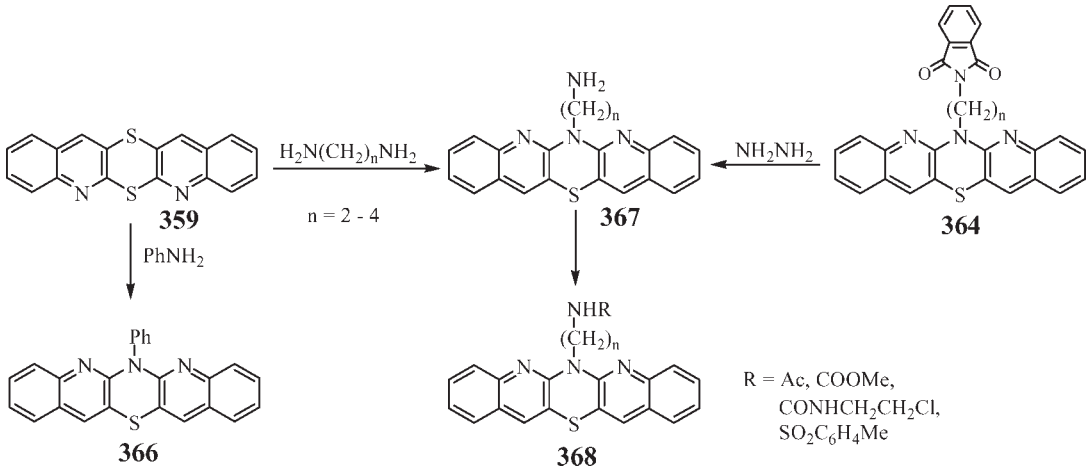
yield) and the isomeric diquinodithiins **358** and **359** (Scheme 133) [136].

Annulation reactions of 2,2′-dichloro-3,3′-diquinolinyl sulfide **360** with ammonium carbonate in MEDG (mono-methyl ether of diethylene glycol) or with gaseous ammonia in phenol or with acetamide (in the presence of potassium carbonate) led to 6*H*-diquinothiazine **361** (the dibenzo derivative of 1,9-diazaphenothiazine) in 10%, 13 and 57% yield, respectively. Further annulation reactions of sulfide **360** with primary aliphatic, aromatic, and heteroaromatic amines in MEDG or with DMF (in the presence of sodium hydroxide) and dihydrochloride of 2,2′-diphenoxy-3,3′-diquinolinyl sulfide **362** (the main product in the reaction of sulfide **360** with ammonia in phenol) with butylamine in MEDG gave various alkyl-, aminoalkyl-, aryl-, and heteroaryldiquinothiazines **363** in low to good yields. The alkyl derivatives were also obtained by alkylation of 6*H*-diquinothiazine **361** with alkyl and aminoalkyl halides in DMF (with sodium hydride) or in dioxane (with sodium hydroxide). Alkylation with phthalimidoalkyl bromides in toluene (with sodium hydride) gave phthalimidoalkyl derivatives **364** in good yields. When 2-chloroethylamine was used, the reaction proceeded through the formation of 2-chloroethyldiquinothiazine which underwent very smoothly intramolecular alkylation to give hexacyclic compound,

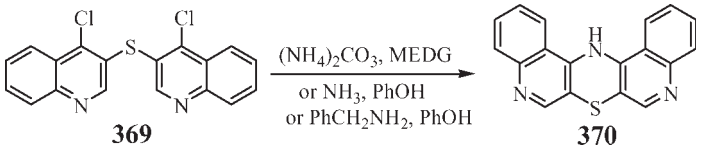
Scheme 134



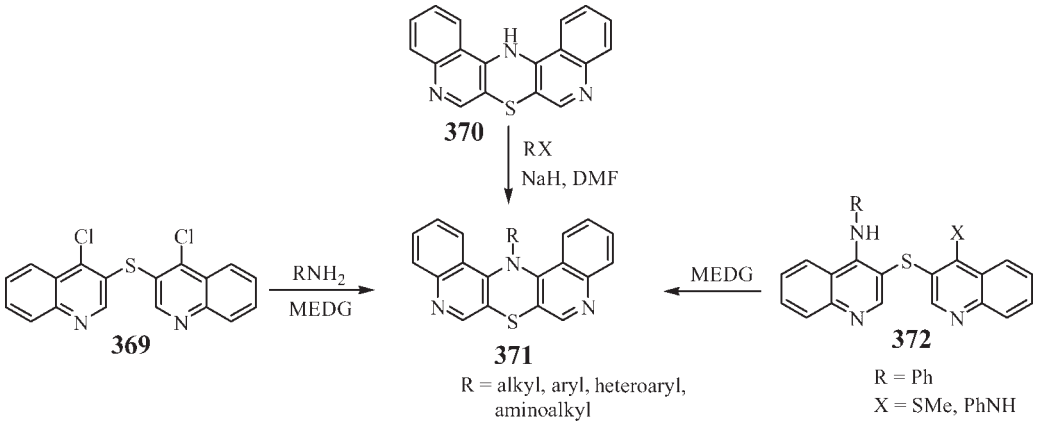
Scheme 135



Scheme 136



Scheme 137



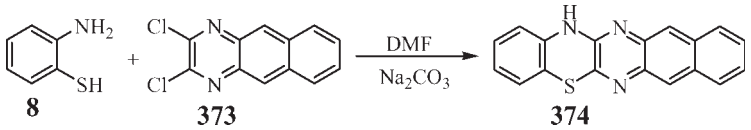
5,6-ethylenediquinothiazinium chloride **365** in 53% yield (Scheme 134) [136–138].

Diquinodithiin **359** turned out to be good substrate in the reaction with aniline and diaminoalkanes to give phenyl and aminoalkyl derivatives **366** and **367** in good yields. The last compounds were also obtained from phthalimidoalkyl derivatives **364** by action of hydrazine. The aminoalkyldiquinothiazines **367** were converted into acyl, sulfonyl, and half-mustard derivatives **368** in 68–90% yield (Scheme 135) [138].

The structures of diquinothiazines were established on the basis of ^{1}H NMR (^{1}H-^{1}H COSY and NOE) spectra and were confirmed by X-ray analysis of the phenyl and 4-nitrophenyl derivatives [137,139]. The diquinothiazine system turned out to be very lipophilic [140,141]. Some selected diquinothiazines exhibited significant anticancer activities against lung, colon, breast, renal and CNS cancers, melanoma and leukemia [138].

Dibenzo derivatives of 3,7-diazaphenothiazines (diquino [3,4-b;4′,3′-e]thiazines). Annulation reactions of 4,4′-dichloro-3,3′-diquinolinyl sulfide **369** with ammonium carbonate in MEDG or with gaseous ammonia in phenol led to 14*H*-diquinothiazine **370** (the dibenzo derivative of 3,7-diazaphenothiazine) in 27 and 65% yield. The same product was formed in 86% yield when benzylamine was used (Scheme 136).

Scheme 138



Further annulation reactions with primary aliphatic, aromatic and heteroaromatic amines in MEDG led to various 14-substituted dibenzodiazaphenothiazines **371**. 14-Alkyl derivatives were also obtained by *N*-alkylation of unsubstituted diquinothiazine **370** with alkyl halides in DMF (with sodium hydride). The phenyl derivative was also formed in cyclization of diquinolinyl sulfides **372** in MEDG (Scheme 137) [142–144].

The structure of dibenzodiazaphenothiazines **371** was based on ^{1}H NMR (^{1}H-^{1}H COSY, NOE) spectra and was confirmed by X-ray analyses of the methyl and phenyl derivatives [145,146].

Naphtho derivative of 1,4-diazaphenothiazine (benzo[g]quinoxalinobenzo[1,4]thiazine). Reaction of aminobenzenethiol **8** with 2,3-dichlorobenzoquinoxaline **373** led to the pentacyclic naphtho-1,4-diazaphenothiazine **374**, an orange pigment dye (Scheme 138) [132].

CONCLUDING REMARKS

Modification of the phenothiazine structures by substitution of the benzene ring with an azine ring brought over 30 different azaphenothiazine systems. The authors hope that this review will provide the arranged knowledge of the diaza-, triaza-, and tetraazaphenothiazine chemistry and will clarify their nomenclature. The reader should take into account that not all the cited authors were aware of the Smiles rearrangement step and not all the azaphenothiazines were identified unequivocally. Re-emergence of classical phenothiazines in the treatment of various diseases perhaps will pay attention to the synthesis and structure of monoaza-, diaza-, triaza-, and tetraazaphenothiazines as potential biological phenothiazine derivatives.

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