Annelated[1,2,4,5]Tetrazines

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I. Introduction.

Increasing interest in the chemistry of [1,2,4,5]tetrazine derivatives has stimulated research on annelated [1,2,4,5]tetrazines and as consequence a considerable number of papers and patents have appeared in the literature. However, no survey dealing with the chemistry of annelated [1,2,4,5]tetrazines has been reported hitherto. Herein we review the various synthetic strategies of the title systems from 1981 to 2000 (Chemical Abstracts Volume 132). The biological activity and industrial applications of the reported compounds, where tested, are also included.

Chart 1

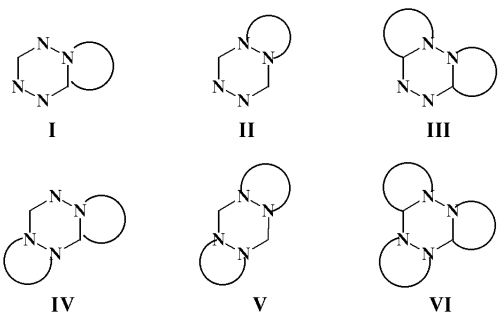


Chart 2

7 [1,2 -*b*] **8** [1,5 - *b*]

The arrangement of this review follows the order of the site of fusion onto the tetrazine ring. Generally the fusion of the tetrazine ring may be on one or more of the C–N and/or N–N bonds of the tetrazine nucleus and thus can lead to six possible annelated tetrazine systems I-VI with one, two, three or four bridgehead nitrogen atoms (Chart 1).

The annelated tetrazines covered in this review are arranged according to the number of fused rings present and each class is subdivided into sections according to the number of bridgehead nitrogen atoms present in the [1,2,4,5]tetrazine ring. Furthermore, the systems of each subclass are arranged in the order of increasing ring size and number of the heteroatoms (nitrogen, oxygen, sulfur and other elements) present. The designation of the site of fusion is indicated by numbers and letters as reported in Chemical Abstracts.

II. Bicyclic[1,2,4,5]tetrazines.

A. With one Bridgehead Nitrogen Atom.

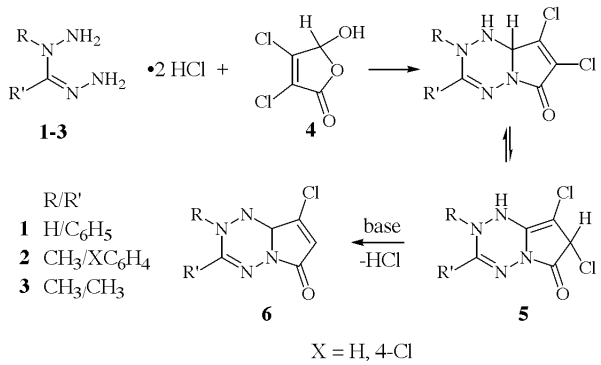
1. Pyrrolo[1,2-*b*][1,2,4,5]tetrazines.

Some derivatives of such ring system namely 7,8-dichloro–1,2-dihydro-pyrrolo[1,2–*b*][1,2,4,5]tetrazin-6-(8a*H*)-ones **5** have been prepared by reaction of the hydrochloride salt of hydrazidines **1-3** with **4**. Treatment of **5** with base resulted in the formation of the respective 8-chloro-2*H*-pyrrolo[1,2-*b*][1,2,4,5]tetrazin-6(2*H*)–ones **6** (Scheme 1) [1].

2. Imidazo[1,2,4,5]tetrazines.

Several derivatives of the ring systems imidazo[1,2-*b*]-[1,2,4,5]tetrazine **7** and imidazo[1,5-*b*][1,2,4,5]tetrazine **8** (Chart 2) have been reported. Reaction of 3,6-di(4-substituted phenyl)[1,2,4,5]tetrazines **9** with potassium hydroxide in methanol was reported to give, in addition to other products, the imidazo[1,2-*b*][1,2,4,5]tetrazine derivatives **12** and triazoles **13**. The mechanism that accounts for the formation of the latter products **12** and **13** is outlined in Scheme 2 [2,3].

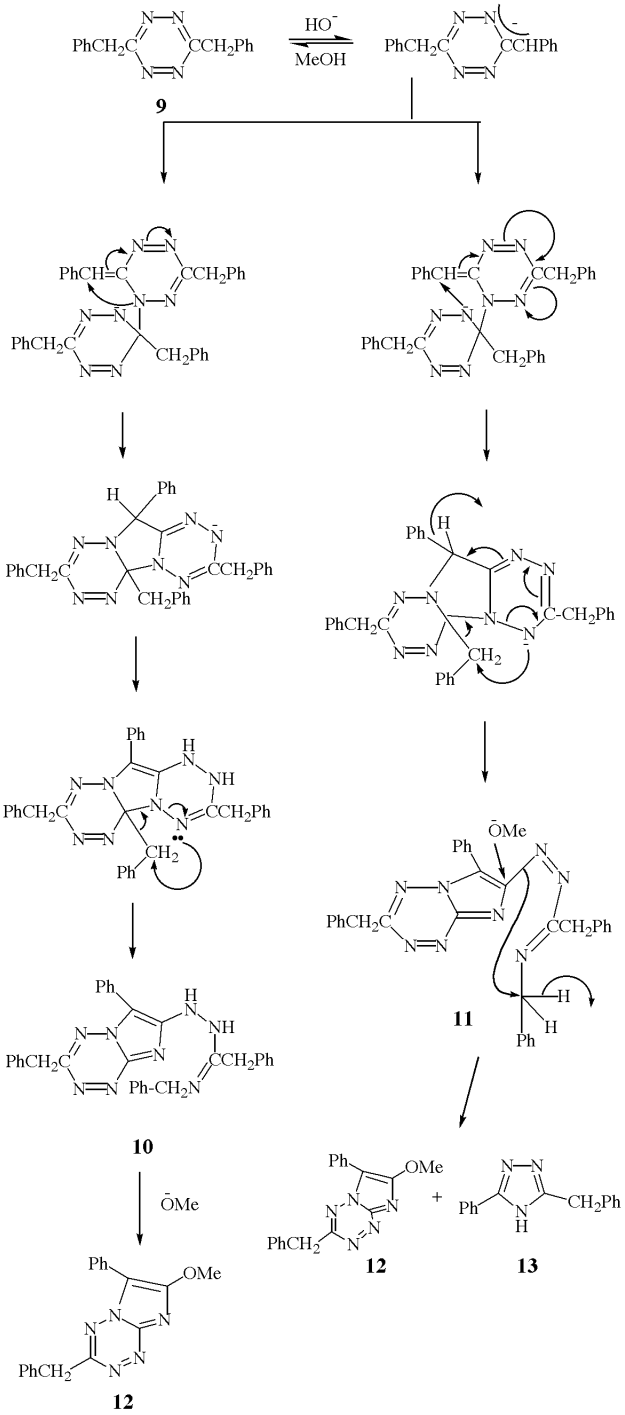
Scheme 1



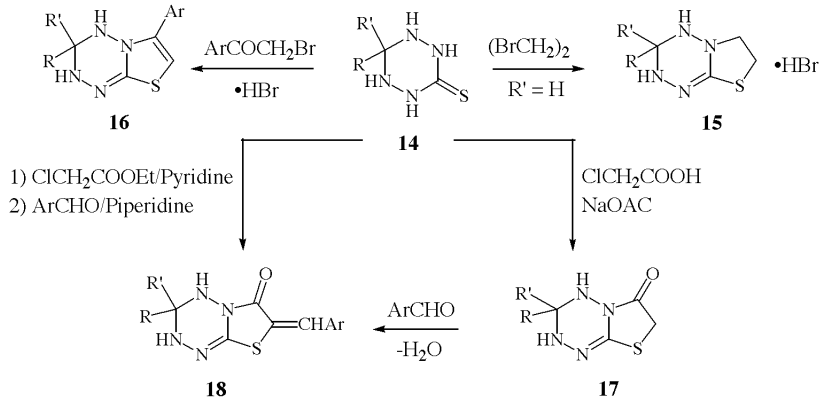
R/R'
1 H/C_6H_5
2 CH_3/XC_6H_4
3 CH_3/CH_3

X = H, 4-Cl

Scheme 2



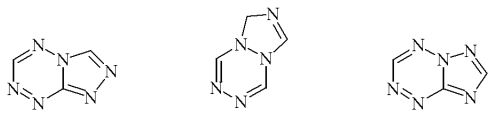
Scheme 3



R/R' = 4-ClC_6H_4/H, 1-Naphoyl/H, Et/H, 2-Furyl/H

R-R' = -$(CH_2)_n$-; n = 3,4,5,6,8,10,-CH_2-CH_2-CH(CH_3)-CH_2-

Chart 3

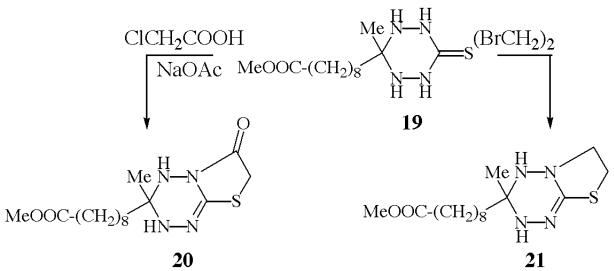


22 [4,3-b] **23** [1,2-a] **24** [1,5-b]

3. 2*H*-Thiazolo[3,2-*b*][1,2,4,5]tetrazines.

The synthesis of 2*H*-thiazolo[3,2-*b*][1,2,4,5]tetrazines **15-17** was generally carried out by cyclocondensation of 6-substituted 1,2,4,5-tetrahydro [1,2,4,5]tetrazine-3(6*H*)-thiones **14** with 1,2-dibromoethane, phenacyl bromides and chloroacetic acid, respectively. 7-Arylidene-2,3,6,7-tetrahydro-3-substituted-4*H*-thiazolo[3,2-*b*][1,2,4,5]tetrazin-6-ones **18** have been prepared either by the condensation of **17** with aldehydes or in a single step by reaction of **14** with ethyl chloroacetate and aldehydes in the presence of pyridine and piperidine (Scheme 3) [4-8,82-88]. The compounds **16** were reported to be active against gram positive *Staphlococcus Aureus* bacteria and the fungus *Candida Albicans*, when treated as neat samples and may be used for local applications in the form of powder or ointment [4-8].

Scheme 4

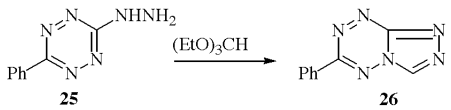


Similar reactions of methyl hexahydro-3-methyl-6-thioxo[1,2,4,5]tetrazine-3-nonanoate **19** with chloroacetic acid and 1,2-dibromoethane afforded the methyl thiazolo[3,2-*b*][1,2,4,5]tetrazine-3-nononoates **20** and **21**, respectively (Scheme 4) [9].

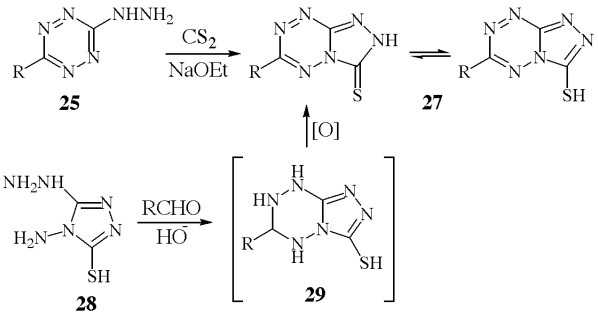
4.[1,2,4]Triazolo[4,3-*b*][1,2,4,5]tetrazines.

Although the [1,2,4]triazole ring may form three condensed systems with [1,2,4,5]tetrazine namely **22-24** (Chart 3), only 1,2,4-triazolo[4,3-*b*][1,2,4,5] tetrazine **22** and its substituted derivatives have been synthesized. The first synthesis of this ring system was

Scheme 5

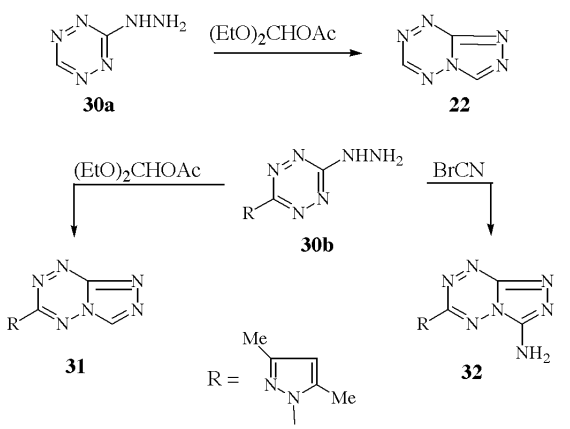


Scheme 6



R = H, CH_3, Et, *n*-Pr, C_6H_5

Scheme 7

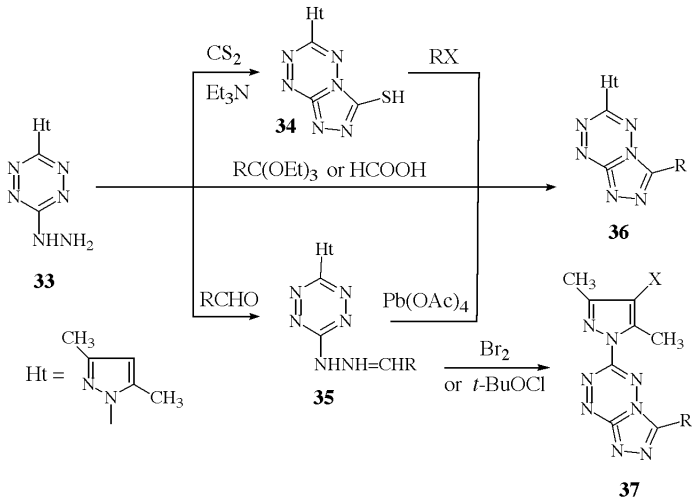


The [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine parent ring system **22** was reported to be obtained in 61% yield by heating 3-hydrazino[1,2,4,5]tetrazine **30a** with diethoxymethyl acetate [14]. Similar treatment of 3-(3,5-dimethylpyrazol-1-yl)-6-hydrazino[1,2,4,5]tetrazine **30b** with diethoxymethyl acetate and cyanogen bromide gave the corresponding substituted [1,2,4]triazolo[4,3-*b*]-[1,2,4,5]tetrazines **31** and **32**, respectively (Scheme 7) [14].

Recently, Rusinov *et al.* [15] reported three alternative routes for 3-substituted 6-(3,5-dimetheylpyrazol-1-yl)[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines **36** and **37** *via* cyclization of 6-hydrazino-3-(3,5-dimetheylpyrazol-1-yl)-[1,2,4,5]tetrazine **33** with ortho esters, carbon disulfide and by oxidation of the corresponding hydrazones **35** (Scheme 8) [15].

When the same cyclization procedure was performed on 3,6-dihydrazino[1,2,4,5]tetrazine **38** in an attempt to get the unknown tri-heterocyclic ring system **40**, the latter was not obtained but the reaction proceeded only to the [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine derivative **39** (Scheme 9) [14].

Scheme 8

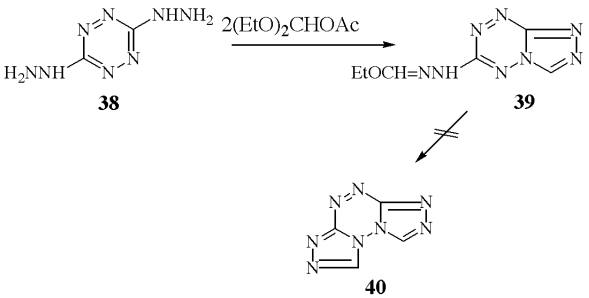


R = H, Me, Ph, MeS, $PhCH_2$, 3-Pyridyl; PhCH=CH, 3,4-$(MeO)_2C_6H_3$, 4-$O_2NC_6H_4$; X/R : Cl/Ph, Br/Ph.

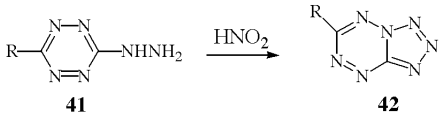
reported in 1968 by Ershov [10]. Compound **26** reported was substituted with a phenyl group at the 6 position and its synthesis involved fusing a triazole ring with a tetrazine using one carbon cyclizing reagent namely triethyl orthoformate and 3-hydrazino-6-phenyl-[1,2,4,5]tetrazine **25** (Scheme 5).

Later, Jacobsen and Dickinson [11-13] prepared 1,2,4-triazolo[4,3-*b*][1,2,4,5]tetrazine **27** by reacting 6-phenyl-3-hydrazino-1,2,4-tetrazine **25** with carbon disulfide or by reacting 4-amino-5-hydrazino[1,2,4]triazole-3-thione **28** with aldehydes in alkaline medium. The reaction involved air oxidation of tetrahydro[1,2,4]triazolo[4,3-*b*]-[1,2,4,5]tetrazine intermediate **29** (Scheme 6). The intense magenta and violet colors exhibited by compounds **27** in alkaline medium were recognized as being the basis of useful quantitative assay of aldehydes [12,13].

Scheme 9



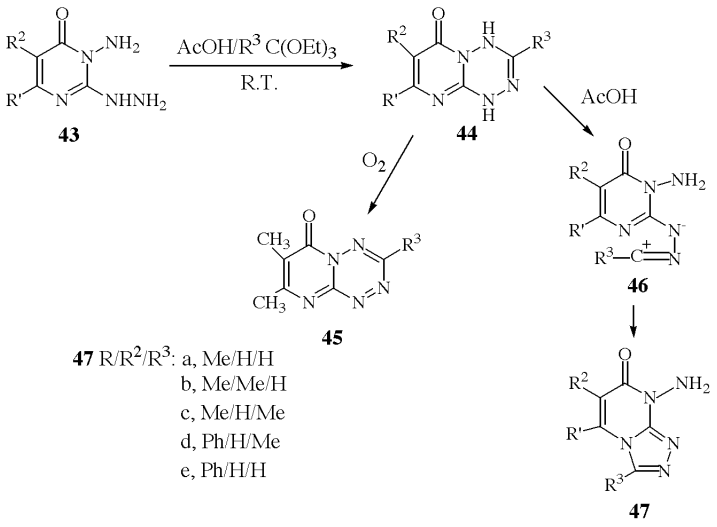
Scheme 10



41 **42**

50 with either 3-amino-2,3-dihydro-6-methyl-2-thioxo-4(1*H*)-pyrimidinone **48** or 3-amino-6-methyl-2-methylthio-4(3*H*)-pyrimidinone **49** in ethanol in the presence of triethylamine or in pyridine at reflux were reported to give the respective pyrimido[1,2-*b*]-

Scheme 11



43 **44** **45** **46** **47**

47 R/R^2/R^3: a, Me/H/H
b, Me/Me/H
c, Me/H/Me
d, Ph/H/Me
e, Ph/H/H

5.Tetrazolo[1,5-*b*][1,2,4,5]tetrazines.

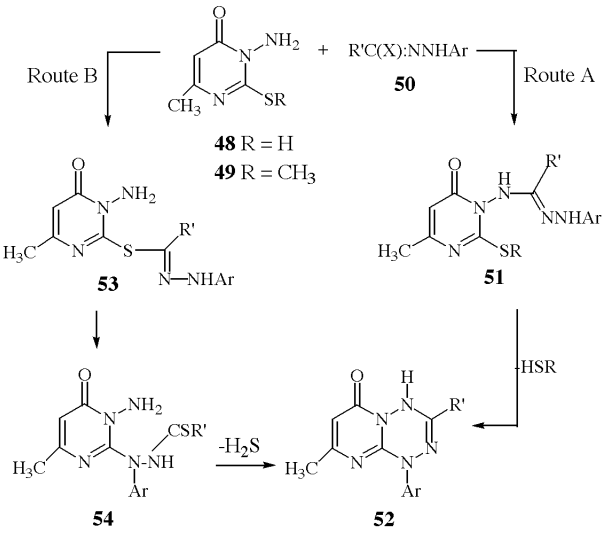
The synthesis of such ring system and its explosive properties were reported recently [16,17]. Thus, treatment of 3-hydrazino-1,2,4,5-tetrazines **41** with nitrous acid gave tetrazolo[1,5-*b*][1,2,4,5]tetrazines **42** (Scheme 10).

6.Pyrimido[1,2-*b*][1,2,4,5]tetrazines.

Treatment of 3-amino-2-hydrazino-6-substituted-4(3*H*)-pyrimidinone **43** with ortho esters in glacial acetic acid at room temperature afforded the respective 1,4-dihydro-6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-ones **44** (Scheme 11) [18,19]. The latter product **44** was oxidized in buffer solution at pH 7.5 by atmospheric oxygen to give **45** [19]. Prolonged refluxing of **44** in acetic acid led to the cleavage of the tetrazine ring leading to the nitrilimine intermediate **46**, which readily underwent 1,5-electrocyclization to give 8-amino[1,2,4]triazolo[4,3-*a*]-pyrimidin-7(8*H*)-ones **47** (Scheme 11) [18]. 1,4-Dihydro-7,8-dimethyl-6*H*-pyrimido[1,2-*b*]-[1,2,4,5]tetrazin-6-one **44** (R_3 = H) was identified to be one of the most potent inhibitors of the human Cytomegalovirus. Its oxidized form **45** (R_3 = H) which is present in solutions of **44** (R_3 = H) was shown to be the actual inhibitory species which irreversibly inactivates the protease [19].

Another new strategy for synthesis of pyrimido-[1,2,4,5]tetrazine derivatives **52** was reported recently by Shawali *et al.* [20]. Thus, reaction of hydrazonoyl halides

Scheme 12

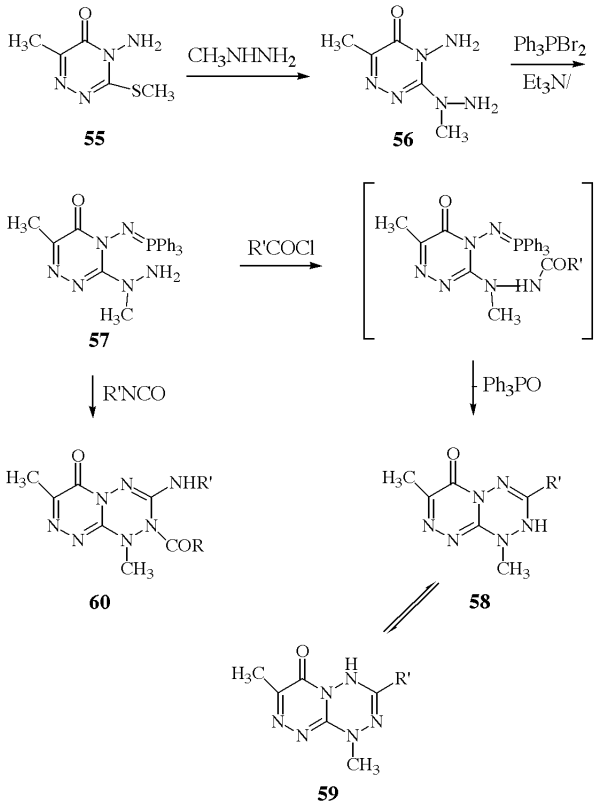


48 R = H
49 R = CH_3
50
51 **52** **53** **54**

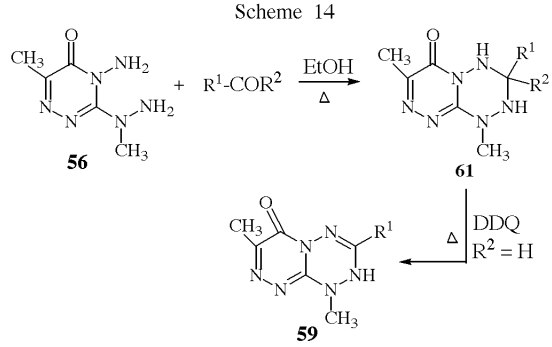
[1,2,4,5]tetrazine derivatives **52**. The formation of the latter products from **48** and **50** can proceed *via* pathway B outlined below (Scheme 12). However, attempts to isolate either thiohydrozonates **53** or their Smiles rearrangement product thiohydrazides **54** failed. This finding indicates that such intermediates are consumed *in situ* as soon as they are formed if the reaction proceed *via* pathway B. On

the other hand, reaction of **49** with **50** leading to **52** can proceed only *via* route A involving the amidrazone intermediates **51**. The latter seem to be consumed also under the reaction conditions employed as attempts to isolate them failed [20].

Scheme 13



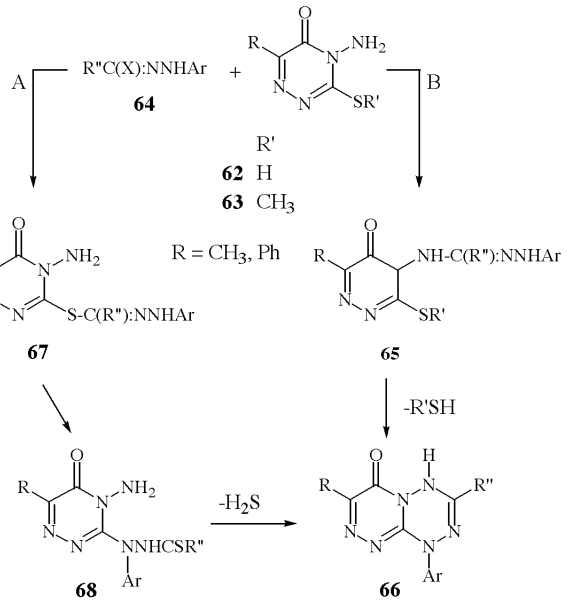
Scheme 14



7.[1,2,4]Triazino[4,3-b][1,2,4,5]tetrazines.

Molina *et al.* [21] reported two methods for the synthesis of [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines **58** and **60**. The first method (Scheme 13) involves reaction of the iminophosphorane **57** derived from 4-amino-6-methyl-3-(1-methylhydrazino)-5-oxo-4,5-dihydro[1,2,4]triazine **56** with acyl chlorides [21,22]. Similar reaction of **57** with isocyanates yielded **60** (Scheme 13) [21].

Scheme 15



The second method is based on the reaction of **56** with carbonyl compounds to give 1,2,3,4-tetrahydro[1,2,4]-triazino[4,3-*b*][1,2,4,5]tetrazines **61** which by dehydrogenation leads to [1,2,4]triazino[4,3-*b*][1,2,4,5] tetrazines **59** (Scheme 14) [22].

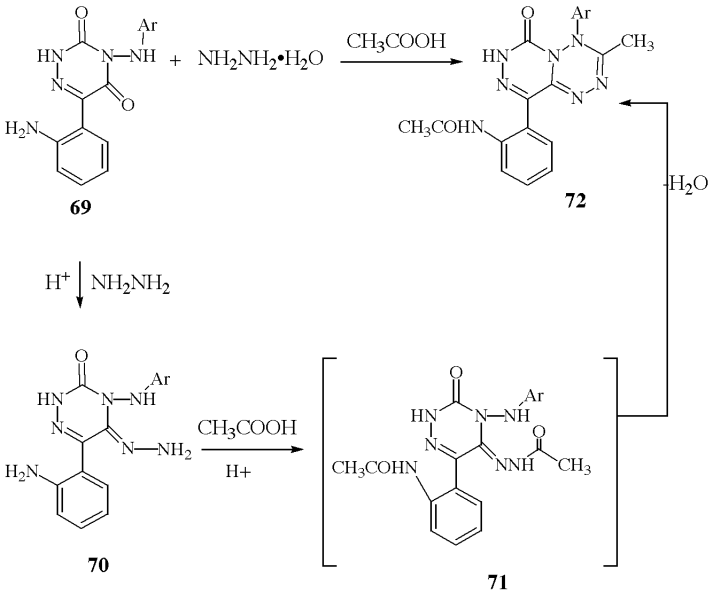
Recently, Shawali *et al*. [23] reported a one-pot synthesis of [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines **66**. Thus, reactions of hydrazonoyl halides **64** with either 4-amino-2,3-dihydro-6-substituted-3-thioxo[1,2,4]-triazin-5(4*H*)ones **62** or 4-amino-3-methylthio-6-substituted[1,2,4]triazin-5(4*H*)ones **63** in ethanol in the presence of triethylamine at reflux afforded the respective derivatives **66** (Scheme 15). The mechanism of formation of the latter from the studied reactions of **64** with **62** and **63** was discussed and it was visualized that they can proceed *via* pathway A and B, respectively as outlined in Scheme 15 [23].

8.4*H*-[1,2,4]Triazino[4,5-b][1,2,4,5]tetrazines.

Abdel-Rahman *et al*. [24] reported the synthesis of 4*H*-[1,2,4]- triazino[4,5-*b*][1,2,4,5]tetrazines derivative **72**. The method reported involves the reaction of 4-aryl-amino-6-(2-aminophenyl)-1,2,4-triazine-3,4-dione **69** with hydrazine hydrate in glacial acetic acid. The reaction seems to proceed *via* the reaction pathway outlined below (Scheme 16).

Heating the 1,2,4-triazinedione derivative **73** with hydrazine hydrate under reflux in presence of piperidine was reported to give the spirotriazino[1,2,4,5]tetrazine derivative **74** (Scheme 17) [24].

Scheme 16

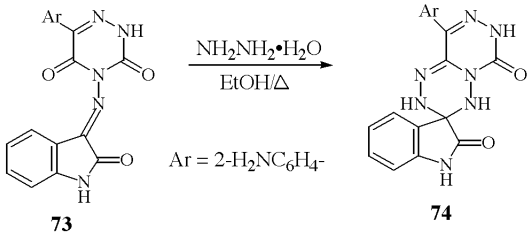


B.With Two Bridgehead Nitrogen Atoms.

1.[1,2,4,5]Tetrazino[1,2-*a*][1,2,4,5]tetrazines.

Octahydro[1,2,4,5]tetrazino[1,2-*a*][1,2,4,5]tetrazine **75** is the only example of such ring system that been reported so far. Its synthesis is based on reaction of hydrazine hydrate with formaldehyde (Scheme 18) [38-43]. This compound was reported to inhibit the germination of twelve plant species except wheat (*Triticum Vulgare*) [40]. In another report, it was indicated that adminstration of compound **75** to Sprague-Dowley rats resulted in methaylation of liver DNA guanine to produce 7-methylguanine [25,41]. In addition compound **75** has been used for preparation of fine particle oxide powders of submicrometer size (< 1 μm) and surface area ranging from 3-20 m^2/g by combustion process [29-39]. For this purpose an aqueous solution of a redox mixture containing the respective metal nitrates and **75** is heated rapidly at 350 °C where it boils, foams and ignite to yield voluminuous fine particle oxide powder. Examples of such fine particle oxides are $MCrO_4$ (M = Mg, Mn, Fe, Co, Ni, Cu, Zn) [30]; Lanthanum cuprate ($La_{2-x}Sr_xCuO_4$) [29], Lanthanum chromite ($LaCrO_3$) and Lanthanum manganite ($LaMnO_3$) [25], and lead based relaxor materials such as $Pb(M_{1/3}N_{2/3})O_3$ (M = Mg, Ni, Zn) [37]. Such fine particle oxides attracted much attention due to their high magnetic and catalytic properties and electronic conductivity, control of automobile emissions and their use in ceramic industry [25].

Scheme 17



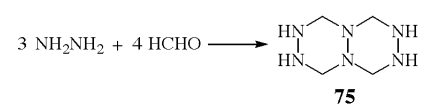
III.Tricyclic[1,2,4,5]tetrazines.

A.With one Bridgehead Nitrogen Atom

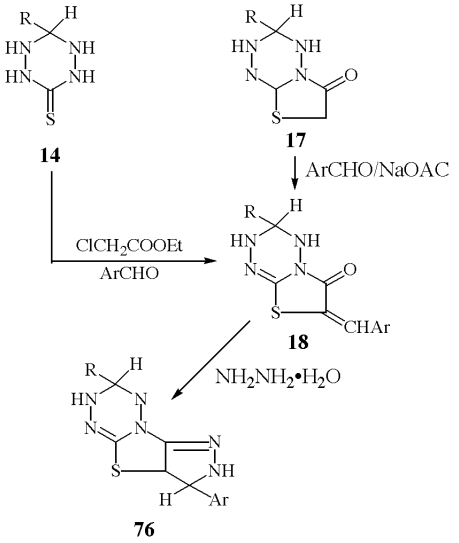
1.Pyrazolo[3',4': 4,5]thiazolo[3,2-*b*][1,2,4,5]-tetrazines.

Condensation of 7-arylidene-2,3,6,7-tetrahydro-4*H*-thiazolo[3,2-*b*][1,2,4,5] tetrazin-6-ones **18** with hydrazine hydrate yielded in one step 3,8-diaryl-2,3,7,8-tetrahydro-4*H*,8a*H*-Pyrazolo[3',4':4,5]thiazolo[3,2-*b*][1,2,4,5]tetrazines **76** (Scheme 19) [4-8,44]. The precursors **18** were prepared by two methods. In the first method the thiazolidinone **17** was condensed with aldehydes, whereas in the second method a mixture of ethyl chloroacetate, the respective aldehyde and the tetrazine **14** was heated in the presence of pyridine and

Scheme 18



Scheme 19



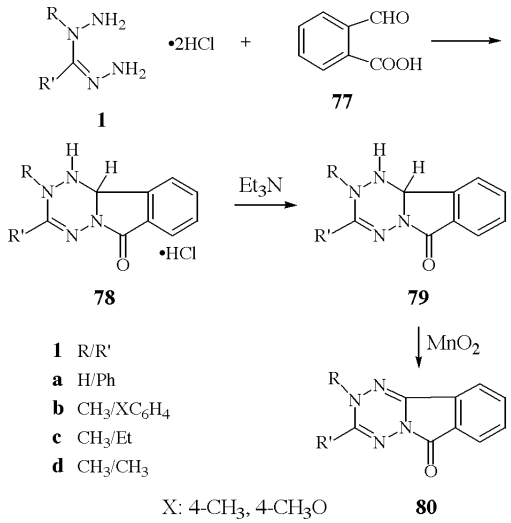
76; R = Et, 2-Furyl, 2-Naphthyl, 4-ClC_6H_4, Ar = XC_6H_4.

piperidine (Scheme 19) [4-8,44]. Compounds **76** (R = 4-ClC_6H_4, 2-furyl), were found to be active against *Staphylococcus Aureus* bacteria and the fungus *Candida Albicans* [4,6,8,44].

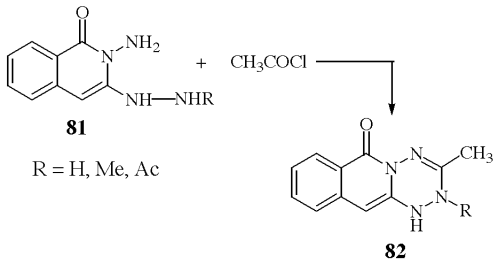
2. [1,2,4,5]Tetrazino[6,1-*a*]isoindoles.

Reaction of the hydrazidine hydrochlorde **1** with 2-formylbenzoic acid **77** in ethanol was reported to give 1,2-dihydro-3-aryl[1,2,4,5]tetrazino[6,1-*a*]isoindol-6-(10b*H*)-one hydrochloride **78**. Treatment of the latter with triethylamine gave the free base **79** which afforded, upon oxidation with manganese dioxide, the corresponding 3-substituted[1,2,4,5]tetrazino[6,1-*a*]isoinodol-6-(2*H*)-one **80** (Scheme 20) [1].

Scheme 20



Scheme 21



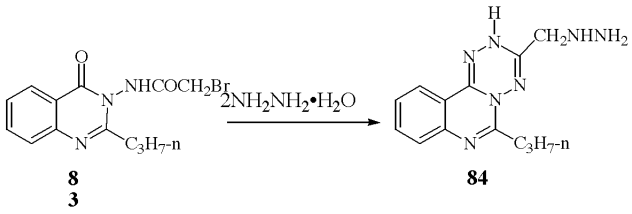
3. [1,2,4,5]Tetrazino[1,6-*b*]isoquinolines.

Reaction of 2-amino-3-hydrazinoisoquinolinone **81** with acyl halides yielded the respective 2*H*-[1,2,4,5]tetrazino-[1,6-*b*]isoquinolin-6(1*H*)-ones **82** (Scheme 21) [45].

4. 2*H*-[1,2,4,5]Tetrazino[1,6-*c*]quinazolines.

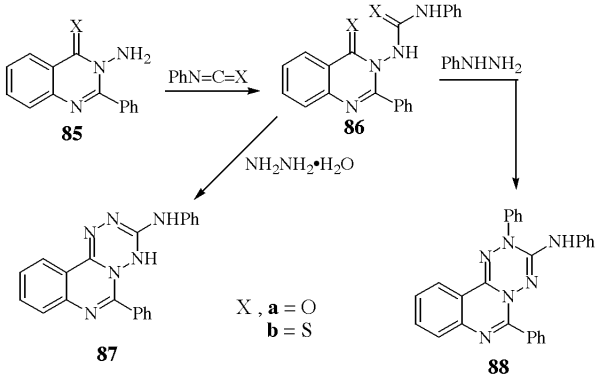
Reaction of 3-(bromoacetylamino)-2-propyl-4(3*H*)-quinazolinone **83** with hydrazine hydrate was reported to give 3-(hydrazinomethyl)-6-propyl-2*H*-[1,2,4,5]-tetrazino[1,6-*c*]quinazoline **84** (Scheme 22) [46].

Scheme 22

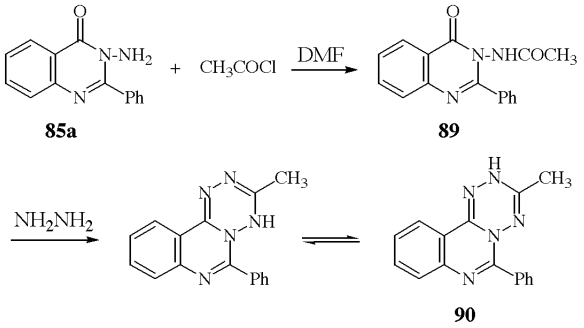


Similar reaction of 3-amino-2-phenylquinazolin-4(3*H*)-one **85a** or its thione analogue **85b** with phenyl isocyanate and phenyl isothiocyanate gave the adducts **86a** and **86b**, respectively. The latter products reacted with hydrazine hydrate and phenylhydrazine to yield the respective fused tetrazines **87** and **88**, (Scheme 23) [47,48].

Scheme 23

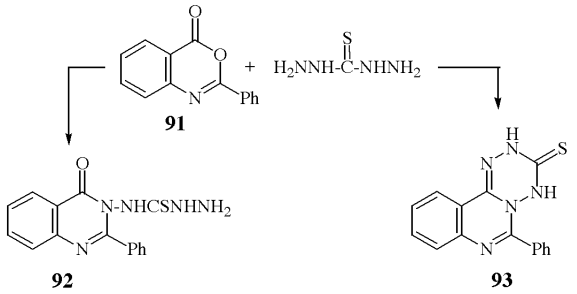


Scheme 24



Also, acylation of **85a** with acetyl chloride in dimethylformamide led to the formation of the *N*-acetyl derivative **89**, which on fusion with hydrazine hydrate afforded 3-methyl-6-phenyl-10-iodo-2*H*-[1,2,4,5]tetrazino[1,6-*c*]-quinazoline **90** (Scheme 24) [49].

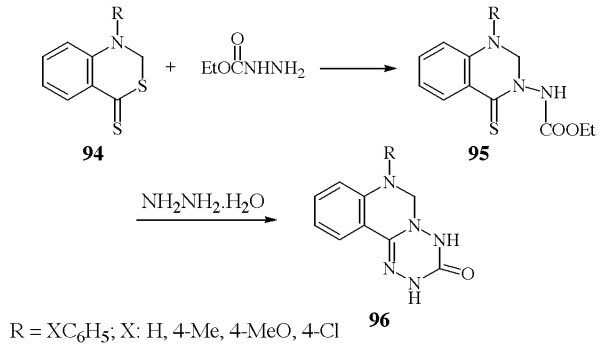
Scheme 25



Recently, it was reported that thioxotetrazinoquinazoline **93** was obtained in 79% yield when 2-phenyl-4*H*-3,1-benzoxazin-4-one **91** was fused with thiocarbohydrazide in an oil bath at 160 °C (Scheme 25) [50]. However, 2-phenyl-3-thiosemicarbazido-4(3*H*)-quinazolinone **92** was obtained when the reaction mixture was refluxed in ethanol (Scheme 25) [50].

Treatment of 1,3-benzothiazine-4-thiones **94** with ethyl carbazate gave 3-ethoxycarbonylaminoquinazoline-4-thiones **95** which upon treatment with hydrazine hydrate afforded the [1,2,4,5]tetrazino[1,6-*c*]quinazolines **96** (Scheme 26) [51].

Scheme 26



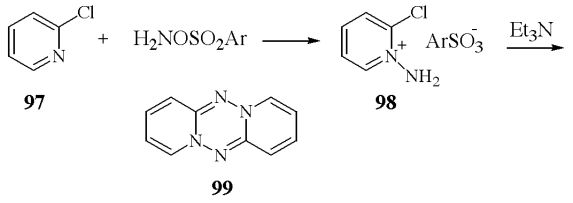
R = XC_6H_5; X: H, 4-Me, 4-MeO, 4-Cl

B. With Two Bridgehead Nitrogen-atoms

1. Bispyrido[1,2-*b*:1',2'-*e*][1,2,4,5]tetrazines.

Reaction of 2-chloropyridine **97** with *O*-arylsulfonyl hydroxylamine was reported to give **98** which, upon treatment with a base catalyst such as triethylamine, was converted into bispyrido[1,2-*b*:1',2'-*e*][1,2,4,5]tetrazine **99** (Scheme 27) [52-55].

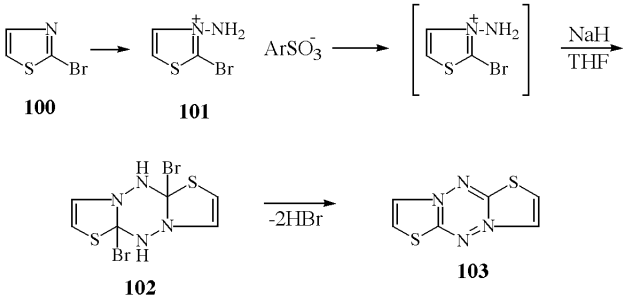
Scheme 27



2. Bisthiazolo[3,2-*b*:3',2'-*e*][1,2,4,5]tetrazines.

N-Amination of 2-bromothiazole **100** with *O*-arylsulfonylhydroxylamine was reported to give the respective *N*-amino salt **101** which was isolated and characterized (Scheme 28). Treatment of the latter with sodium hydroxide in tetrahydrofuran afforded bisthiazolo[3,2-*b*:-3',2'-*e*][1,2,4,5]tetrazine **103** *via in situ* dimerization of the initially formed nitrilium imide to give **102** followed by dehydrobromination of the latter intermediate (Scheme 28) [56].

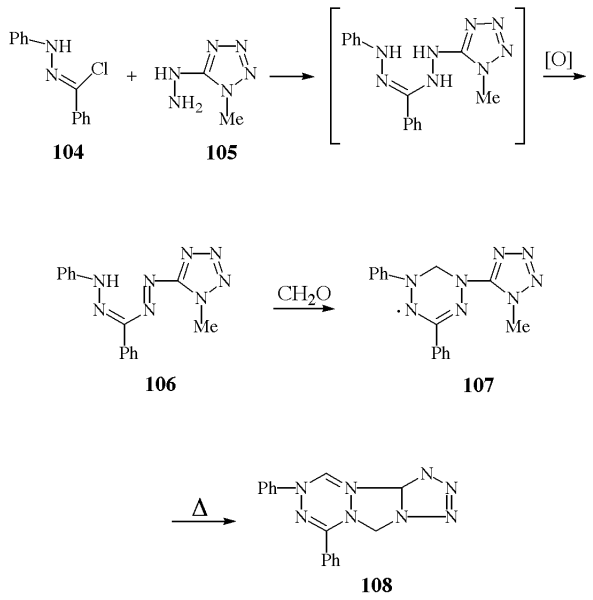
Scheme 28



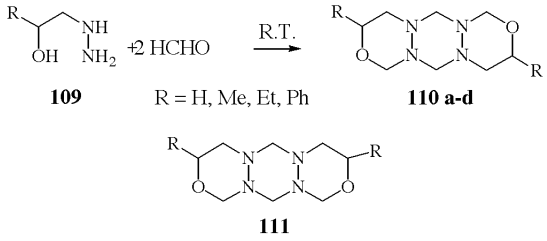
3. Tetrazolo[1,5-*a*][1,2,4]triazolo[1,2-*c*][1,2,4,5]-tetrazines.

Heating the tetrazolylsubstituted verdazyl **107** in boiling acetone was reported to afford the tricyclic system **108** (Scheme 29) [57]. The verdazyl **107** was prepared by heating *N*-phenyl benzenecarbohydrazonoyl chloride **104** with 1-methyl-5-hydrazinotetrazole **105** in diglyme to give the respective formazan **106** which undergo cyclco-condensation with formaldehyde to give the verdazyl **107** (Scheme 29).

Scheme 29



Scheme 30



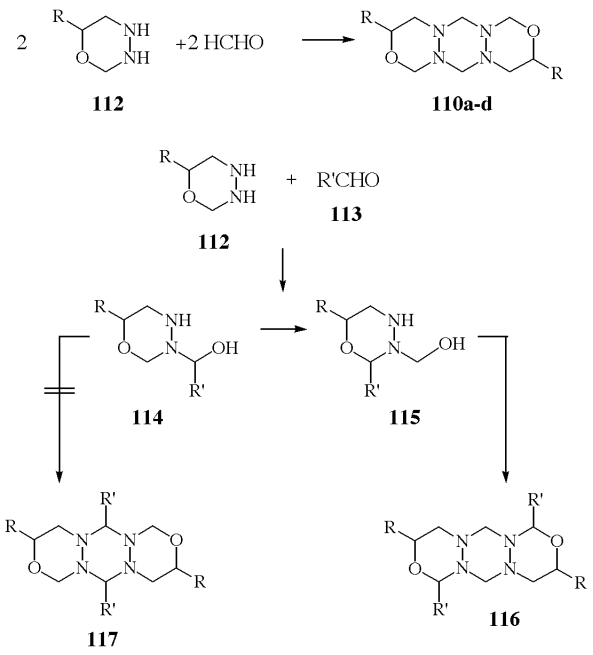
C. With Four Bridgehead Nitrogen Atoms

1. 1*H*,6*H*,8*H*,13*H*-Bis[1,3,4]oxadiazino[3,4-*a*:3',4'-*a*']-[1,2,4,5]tetrazines.

Reaction of 2-hydrazinoethanols **109** with two equivalents of formaldehyde in ethanol at room temperature was reported to give the title derivatives **110a-d** in 29-88% yield [58]. The other isomeric structure **111** was eliminated on the basis of ^{1}H NMR and ^{13}C NMR data (Scheme 30) [58].

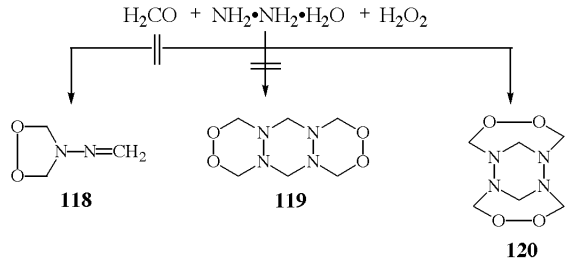
Compounds **110a-d** were also prepared by the reaction of formaldehyde with **112a-d** in ethanol, respectively [58]. However, similar reactions of **100a,b** each with the other aldehydes **113** gave **116** and none of the expected 6,13-disubstituted derivatives **117** were formed (Scheme 31) [58]. The reaction pathway to **116** was considered by the authors [58] to be as depicted in Scheme 31. Intermediate **114** derived from **112** and **113** is converted into another intermediate **115**, which then condenses intermolecularly to give **116** (Scheme 31).

Scheme 31



R/R': **a** = H, CH_3, **b** = H/Et, **c** = Me/Me, **d** = Me/Et

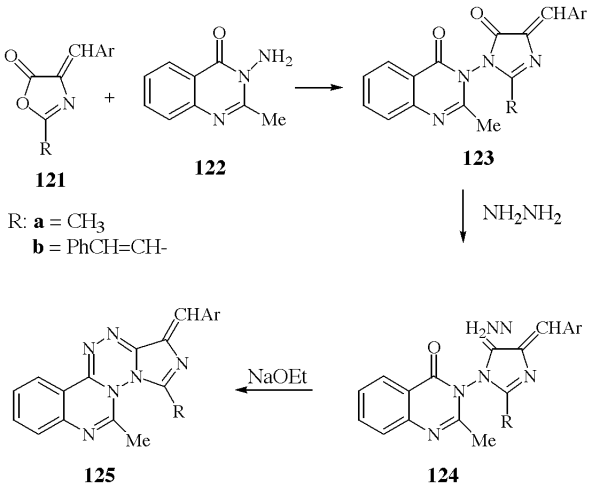
Scheme 32



2. (1*H*,4*H*,6*H*,8*H*,11*H*,13*H*)-[1,2,4,5]Tetrazino[1,2-*d*:-4,5-*d*']bis-[1,2,4,5]dioxadiazines.

Condensation of formaldehyde with hydrazine hydrate in the presence of hydrogen peroxide was reported in 1921 to yield **118** (Scheme 32) [59]. Later, on the basis of infrared and molecular weight data, it was shown that the product of such condensation reaction should be assigned the tricyclic structure 1*H*,4*H*,6*H*,8*H*,11*H*,13*H*-[1,2,4]tetrazino[1,2-*d*:4,5-*d*']-bis[1,2,4,5] dioxadiazine **119** [60]. More recently, the structure of the condensation product was conclusively proven to be **120** by X-ray studies [61]. The latter structure was confirmed by ^{1}H and ^{13}C-NMR (spectral data) [62]. This structure assignment was further confirmed by calculation of heats of formation of both **119** and **120** using a molecular orbital method (AM1). The results

Scheme 33



indicate that the 7:6:7 quinazoline tricyclic structure **120** is more stable than the isomeric 6:6:6 structure **119** [62].

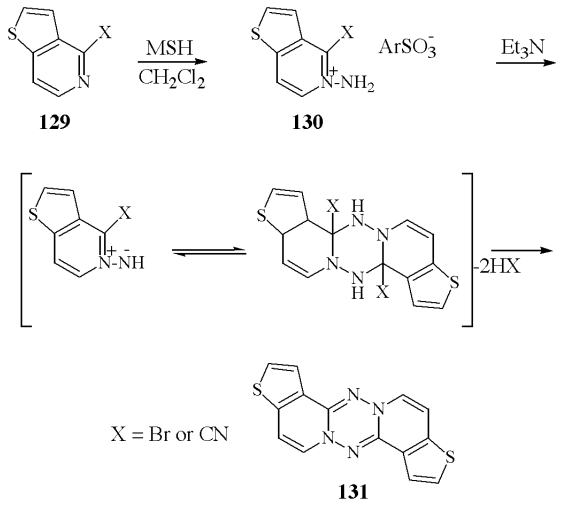
IV. Tetracyclic[1,2,4,5]tetrazines.

A. With Two Bridgehead Nitrogen Atoms.

1. 1*H*-Imidazo[1', 5': 2,3][1,2,4,5]tetrazino[1,6-*c*]-quinazolines.

A convenient method for the synthesis of the title ring system **125** starts with treatment of 2-substituted-4-(aryl-methylene)oxazol-5(4*H*)-one **121** with 2-methyl-3-amino-quinazolin-4(3*H*)-one **122** to give **123**. Hydrazinolysis of the latter afforded the hydrazone **124** which cyclizes upon treatment with sodium ethoxide to give the fused tetrazine derivative **125** (Scheme 33) [63].

Scheme 35



V. Pentacyclic[1,2,4,5]tetrazines.

A. With Two Bridgehead Nitrogen Atoms.

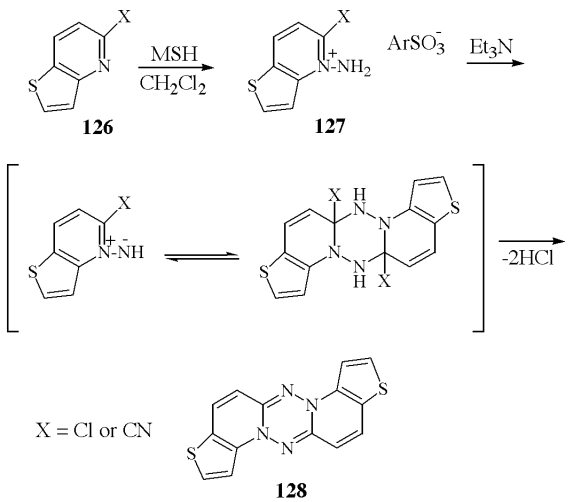
1. Bisthieno[2',3':5,6]pyrido[1,2-*b*:1',2'-*e*][1,2,4,5]-tetrazines.

Treatment of 5-substituted thieno[3,2-*b*]pyridine **126** with *O*-(mesityl- sulfonyl)hydroxylamine in dichloro-methane at room temperature gave the salt **127**, which upon subsequent treatment with triethylamine afforded the title ring system **128** (Scheme 34) [56].

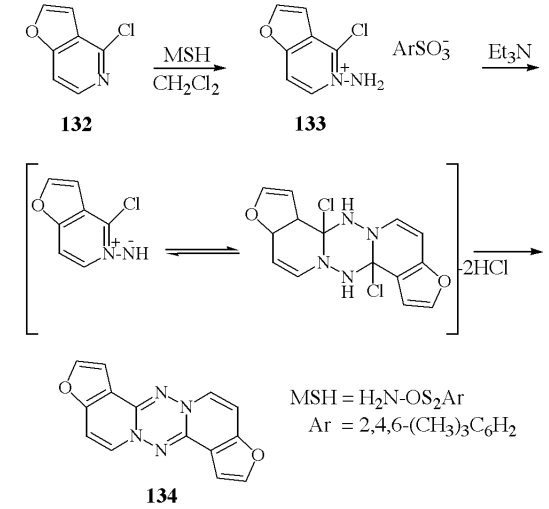
2. Bisthieno[3',2':3,4]pyrido[1,2-*b*:1',2'-*e*][1,2,4,5]-tetrazines.

This ring system was synthesized by a reaction sequence similar to that reported for **128** [56]. Thus, electrophilic *N*-amination of 4-substituted thieno[3,2-*c*]pyridines **129**

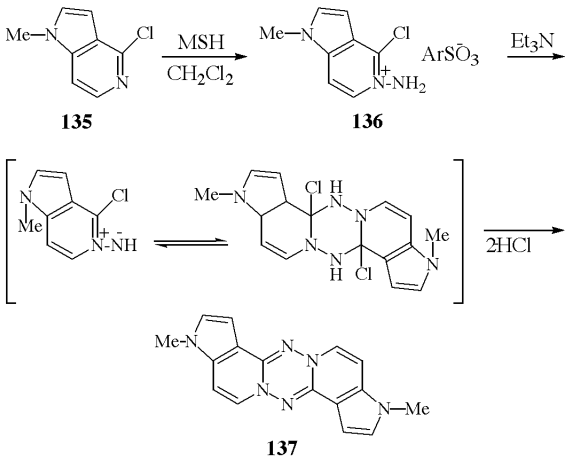
Scheme 34



Scheme 36



Scheme 37

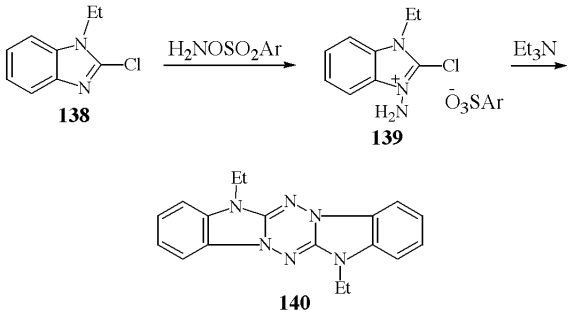


yielded the salt **130**. When the latter was treated with triethylamine in methanol at room temperature, the unsubstituted compound **131** was produced in 81% yield (Scheme 35) [56].

3. Bisfuro[3',2':3,4]pyrido[1,2-*b*:1',2'-*e*][1,2,4,5]-tetrazines.

This ring system was prepared by the reaction sequence outlined in Scheme 36 [56]. Thus, when 4-chlorfuro-[3,2-*c*]pyridine **132** was treated with *O*-(mesitylsulfonyl)-hydroxylamine (MSH) in dichloromethane at room temperature, it afforded the salt of *N*-amino derivative **133**. Subsequent treatment of the latter with triethylamine led to the formation of bisfuro[3',2':3,4]pyrido[1,2-*b*:1',2'-*e*]-[1,2,4,5]tetrazine **134** in 34% yield (Scheme 36) [56].

Scheme 38



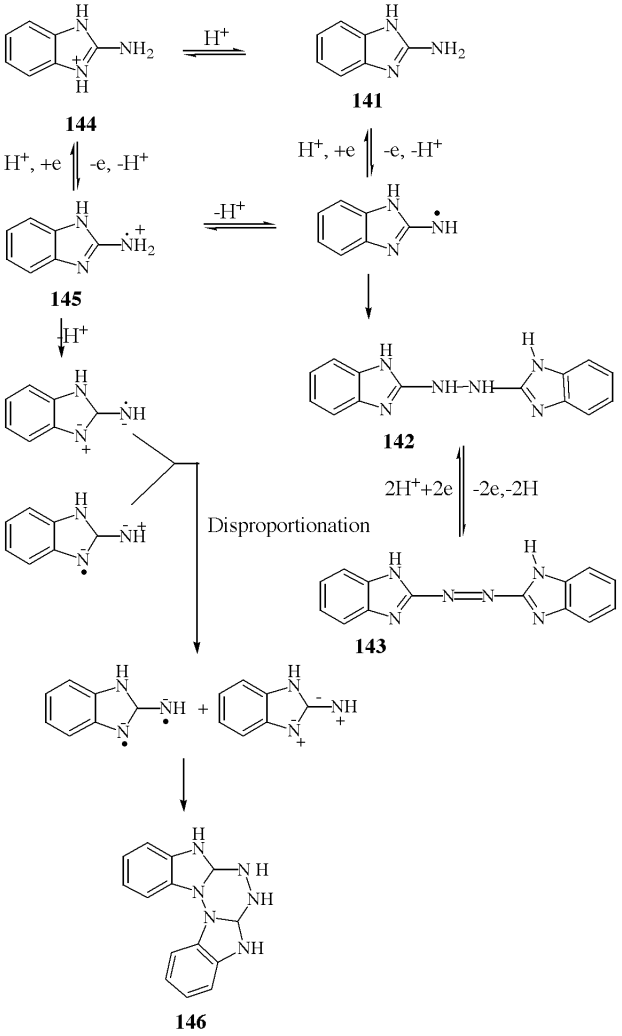
4. 3*H*,10*H*-Bispyrrolo[3',2':3,4]pyrido[1,2-*b*:1',2'-*e*]-[1,2,4,5]tetrazines.

Reaction of 1-methyl-4-chloropyrrolo[3,2-*c*]pyridine **135** with *O*- (mesitylsulfonyl)hydroxylamine was reported to give the *N*-amino salt **136** [56]. Treatment of the latter with triethylamine at room temperature afforded the respective 3,10-dimethyl-3*H*,10*H*-bispyrido[3',2':3,4]-pyrido[1,2-*b*:1',2'-*e*] [1,2,4,5]tetrazines **137** in 30% yield (Scheme 37) [56].

5. 5*H*,12*H*-[1,2,4,5]Tetrazino[1,6-*a*:4,3-*a*']bisbenzimidazole

5,12-Diethyl derivatives of 5H,12H-[1,2,4,5]tetrazino-[1,6-a:4,3-a']bisbenzimidazole **140** was obtained in a two-step synthesis by *N*-aminating of the *N*-substituted benzimidazole derivative **138** to give **139** and treating the latter with triethylamine (Scheme 38) [53-55].

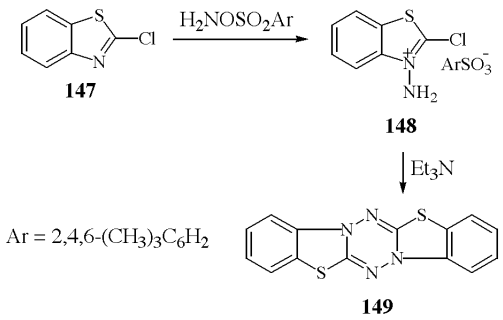
Scheme 39



6. [1,2,4,5]Tetrazino[1,6-*a*:2,3-*a*']bisbenzimidazoles.

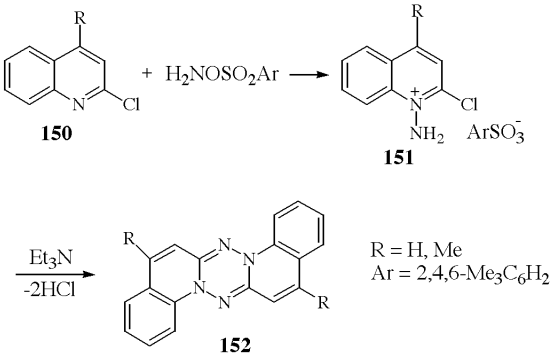
This ring system has been reported as a by-product during the electrochemical oxidation of 2-aminobenzimidazole **141** [64,65]. Such electrochemical oxidation of 2-aminobenzimidazole **141** has been studied in aqueous solution in a wide pH range from 3.0 to 10.8 using a pyrolytic graphite electrode. The initial step in the oxidation was reported to involve a 1e, $1H^+$ reaction

Scheme 40



leading to the formation of free radical species, which rapidly dimerizes to give hydrazo intermediate **142**. Further oxidation of the latter hydrazo species in a 2e, $2H^+$ reaction leads to the formation of azobenzimidazole **143**. Alternatively, the 1e,$1H^+$-oxidation of protonated 2-aminobenzimidazole gives a free radical cation which upon loss of a proton followed by disproportionation gives the fused tetrazine **146** (Scheme 39) [64,65].

Scheme 41



7. [1,2,4,5]Tetrazino[3,4-*b*:6,1-*b*']bisbenzothiazoles.

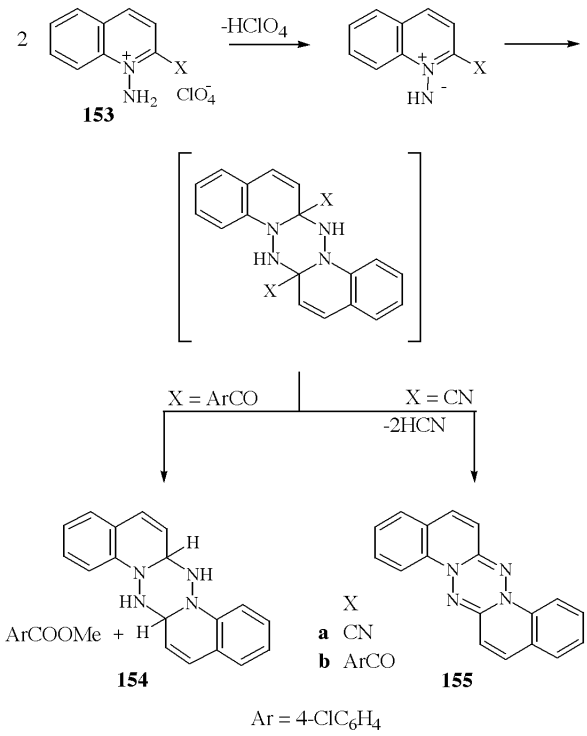
Treatment of 2-chlorobenzothiazole **147** with *O*-(2,4,6-trimethylphenylsulfonyl)hydroxylamine afforded **148** which is converted into **149** upon treatment with triethylamine (Scheme 40) [53-55].

8. [1,2,4,5]Tetrazino[1,6-*a*:4,3-*a*']diquinolines.

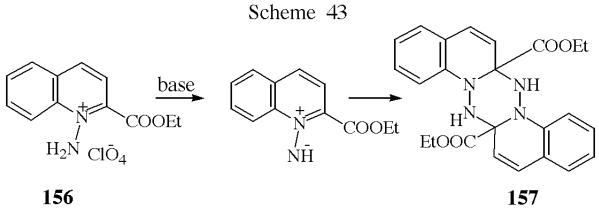
Treatment of 2-chloroquinoline derivative **151** with triethylamine afforded [1,2,4,5]tetrazino[1,6-*a*:4,3-*a*']-diquinolines **152** (Scheme 41) [53-55]. The precursor **151** was prepared by reaction of **150** with *O*-arylsulfonyl-hydroxylamine.

Also, treatment of 1-amino-2-cyanoquinolinium perchlorate **153a** with triethylamine in acetonitrile afforded **155** *via* elimination of hydrogen cyanide from the initially formed dimer of the nitrilium imide (Scheme 42) [66]. Similar treatment of 1-amino-2-(4-chlorobenzoyl)-quinolinium perchlorate **153b** with sodium hydroxide methanol was reported to give **154** *via* methanolysis of the initially formed dimer (Scheme 42) [66].

Scheme 42

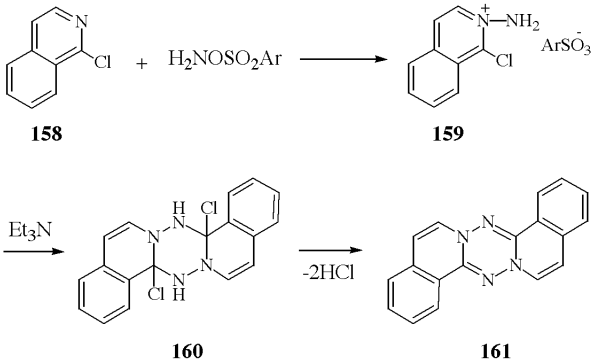


Scheme 43

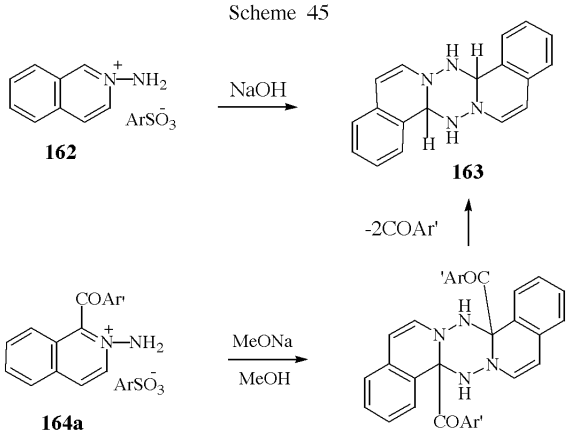


1-Amino-2-ethoxycarbonylquinolinium perchlorate **156** yielded **157** when it was treated with aqueous sodium hydroxide *via* dimerization of the initially formed nitrilium imide (Scheme 43) [66].

Scheme 44



Scheme 45



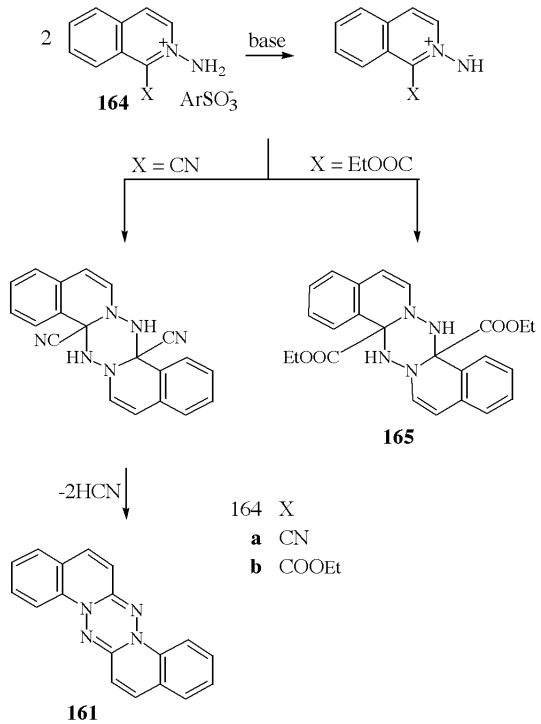
Ar' = XC_6H_4, X = H, 4-Cl, 3-CF_3
Ar = 4-$CH_3C_6H_4$, 2,4,6-$Me_3C_6H_2$

9. [1,2,4,5]Tetrazino[6,1-*a*:3,4-*a*']diisoquinolines.

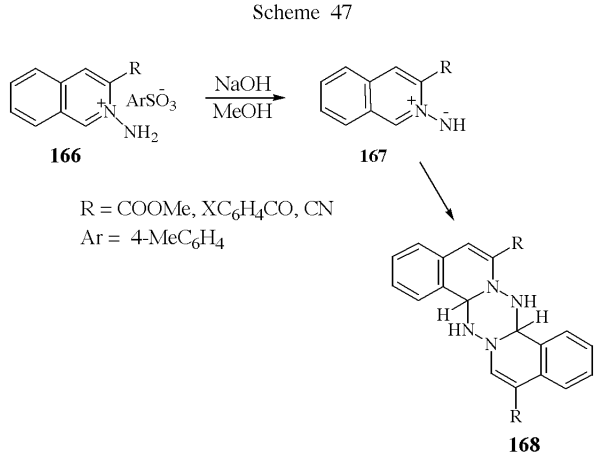
Treatment of **159**, prepared by the reaction of 3-chloroisoquinoline **158** with *O*-arylsulfonylhydroxylamine, with a base such as triethylamine yielded [1,2,4,5]tetrazino-[6,1-*a*:3,4-*a*']diisoquinoline **161** *via* dehyrochlorination of the dichloro derivative **160** (Scheme 44) [53-55].

Also, treatment of the 2-aminoisoquinolinium arylsulfonate **162** with sodium hydroxide was reported to give **163** (Scheme 45) [67]. The latter compound was also obtained by treatment of 2-amino-1-aroylisoquinolinium tosylate **164a** with sodium methoxide in methanol (Scheme 45) [66].

Scheme 46



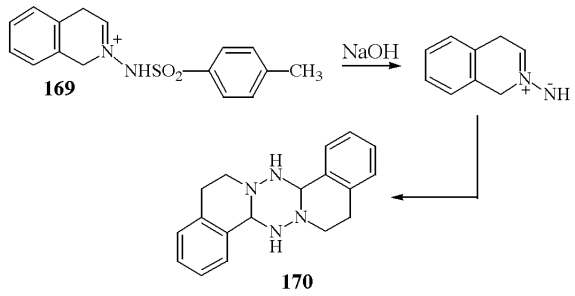
Scheme 47



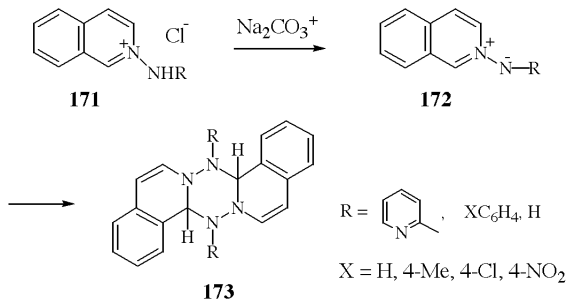
Treatment of 2-amino-1-cyanoisoquinolinium tosylate **164a** with triethylamine in acetonitrile was reported to give **161**, likely *via* elimination of hydrogen cyanide from the initially formed dimer of the nitrilium imide (Scheme 46) [66]. However, similar treatment of 2-amino-1-(ethoxycarbonyl)isoquinolinium tosylate **164b** with sodium methoxide in methanol at room temperature yielded **165** in 51% yield (Scheme 46) [66].

On the other hand, it was reported that treatment of 3-substituted-2-aminoisoquinolinium salts **166** with sodium hydroxide gave the fused tetrazines **168** in every case, and elimination of the substitutuent did not occurre (Scheme 47) [66]. Also treatment of 2-*p*-toluenesulfonamido[1,2,3,4]tetrahydroisoquinoline

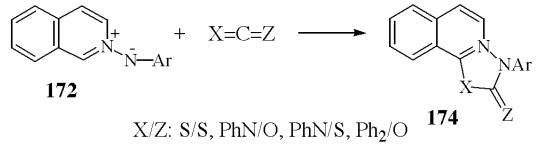
Scheme 48



Scheme 49



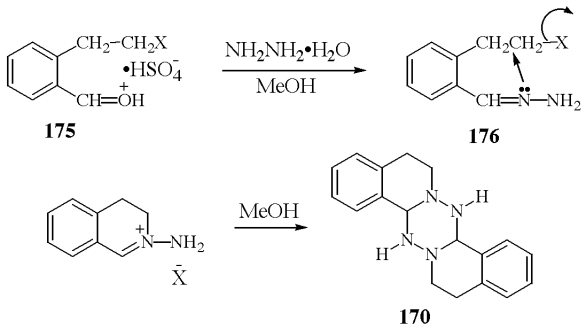
Scheme 50



172 174

X/Z: S/S, PhN/O, PhN/S, Ph_2/O

Scheme 51

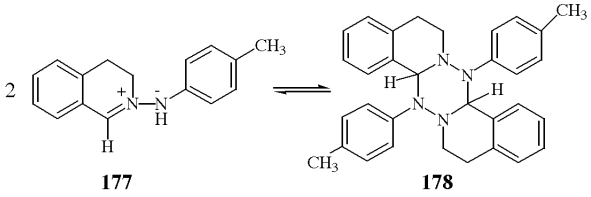


175 176 170

169 with hot aqueous base afforded hexahydro-fused tetrazine **170** in essentially quantitative yield (Scheme 48) [68].

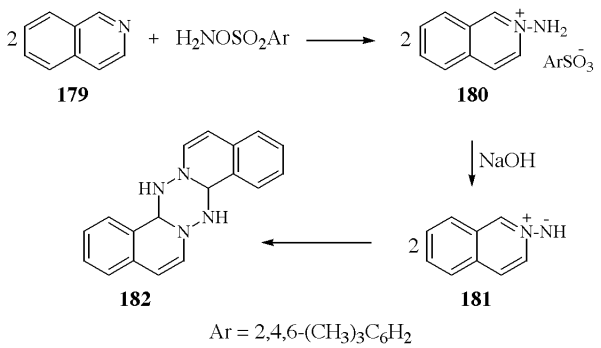
Treatment of 2-(arylamino)isoquinolinium chloride **171** with sodium carbonate in aqueous solution gave the respective isoquinolinium *N*-(2-substituted)imide **172**. When the latter was dissolved in dichloromethane and left for 7 days at room temperature, it underwent dimerization to give 8,8a,16,16a–tetrahydro-8,16a-diaryl[1,2,4,5]tetrazino[6,1-*a*:3,4-*a*']diisoquinoline **173** in 42% yield (Scheme 49) [69,70,73].

Scheme 52



177 178

Scheme 53



179 180 182 181

Ar = 2,4,6-$(CH_3)_3C_6H_2$

Generally the imide **172** is unstable, so that if it is generated by dehydrohalogenation of **171** in the presence of suitable dipolarophile, it affords the respective cycloadduct **174** (Scheme 50) [69].

[1,2,4,5]Tetrazino[6,1-*a*:3,4-*a*']diisoquinoline **170** was reported by Schmitz in 1958 [71]. Thus, treatment of 2-(2-haloethyl)benzaldehyde hydrogen sulphate **175** with hydrazine hydrate yields the respective hydrazone **176** which cyclizes to afford isoquinolinium salt. Treatment of the latter halide salt with a base yields **170** (Scheme 51).

An analogue of compound **176** namely **178** was formed by heating **177** in methanol or ethanol. Otherwise, **178** is interconvertable to **177** by heating in cyclohexane or benzene (Scheme 52) [72], as shown by the following equilibrium.

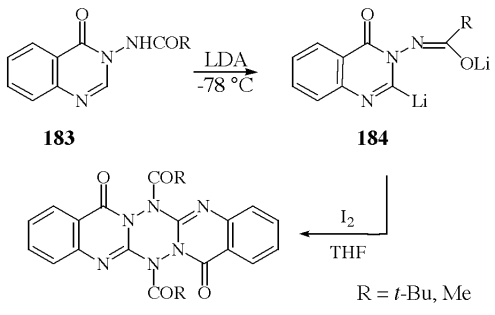
Treatment of isoquinoline **179** with *O*-(2,4,6-trimethylbenzenesulfonyl hydroxylamine) in dichloromethane at room temperature for 1 hour gave 95.8% isoquinolinium mesitylenesulfonate **180** which upon treatment with aqueous sodium hydroxide gave 85% of **182** (Scheme 53) [67].

10. [1,2,4,5]Tetrazino[3,2-*b*:6,5-*b*']diquinazolines

Reaction of 3-acylamino-4(3*H*)quinazolinones **183** with lithium dialkylamide (LDA) at -78 °C in tetrahydrofuran afforded regioselectively the dilithium salt **184**. Treatment of the latter with iodine resulted in oxidative dimerization to give 6H,13H[1,2,4,5] tetrazino[3,2 -*b*:6,5-*b*']diquinazoline–7,14-dione **185** (Scheme 54) [74].

Recently, 6,14-diacetyl[1,2,4,5]tetrazino[3,2-*b*:6,5-*b'*]-diquinolin-8,16 (6*H*,14*H*)-dione **187** was reported to be obtained in 80% yield by boiling 3-amino-2-anilino-4(3*H*)quinazolinone **186** in acetic anhydride for 2 hours (Scheme 54) [75]. However, heating **186** with acetic acid anhydride under mild conditions (5 minutes reflux) caused simple acetylation leading to **188** (Scheme 55) [75] .

Scheme 54

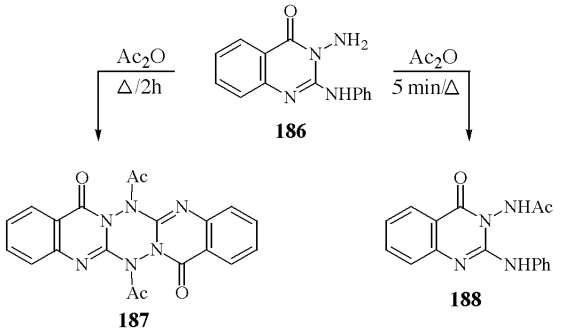


183 184 185

11. [1,2,4,5]Tetrazino[1,6-*c*:4,3-*c*']diquinazolines.

Richter and Buhrow [76] reported that treatment of 2-acyl-4-chloro-phenylisothiocyanate **189** with hydrazine hydrate in dioxane gave 3-amino-6-chloro-4-hydroxy-4-phenyl-2-thioxotetrahydroquinazolines **190**. When the latter was refluxed in methanol, it underwent dehydration to give **191** which cyclized *in situ* to afford **193**. When the latter was refluxed in dioxane in the presence of *p*-toluene-

Scheme 55



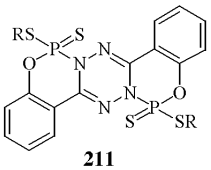
sulfonic acid, in an attempt to give the pentacyclic tetrazine derivative **195**, 7-chloro-8b-phenyl-3-thioxo-2,3,4,8b-tetrahydrodiazino[2,3-*c*]quinazoline **194** was produced instead (Scheme 56) [76].

However, when a mixture of ethyl orthoformate and 3,6-bis(2-aminophenyl)tetrazine **196** was refluxed fo 6 hours, [1,2,4,5]tetrazino[1,6-*c*:4,3-*c*']diquinazoline **197** was produced in 74% yield (Scheme 57) [56]. The other isomer **198** was not reported.

12. [1,2,4,5]Tetrazino[1,6-*a*:4,3-*a*']diquinoxalines.

Reaction of 1,2–benzenediamine **199** with s-*trans*-chloroethanedial dioxime **200** gave **201**. When the latter was treated with $CoCl_2 \cdot 6H_2O$ in ethanol, it afforded [1,2,4,5]tetrazino[1,6-*a*:4,3-*a*']diquinoxaline **202** (Scheme 58) [77].

Chart 4



R = Alkyl, Benzyl, Allyl, $EtOCOCH_2$

13. [1,2,4,5]Tetrazino[1,6-*a*:4,3-*a*']di[1,8]naphthyridines.

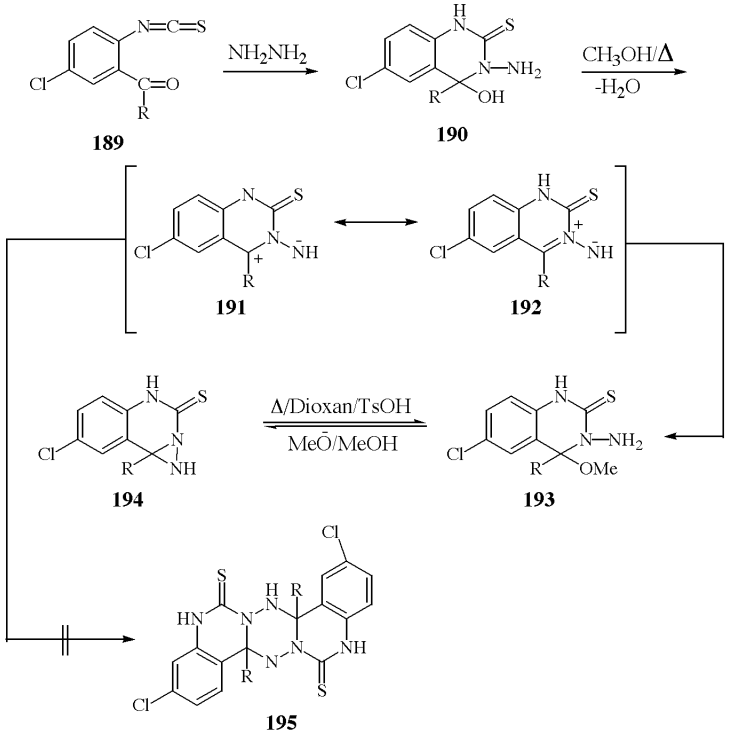
Treatment of the *N*-iminonaphthyridinium salt **204** with potassium carbonate gave the respective fused tetrazine **206** derivative in 65% yield (Scheme 59) [78]. The precursor **204** was prepared by amination of **203** with *O*-arylsulfonylhydroxylamine in dichloromethane [78].

Similar treatment of **208** with potassium carbonate was reported to give [1,2,4,5]tetrazino[1,6-*a*:4,3-*a*']di[1,5]naphthyridine analog **210** (Scheme 60) [78]. The precursor **208** was also prepared by *N*-amination of **207** with *O*-mesitylene sulfonylhydroxylamine in chloroform [78].

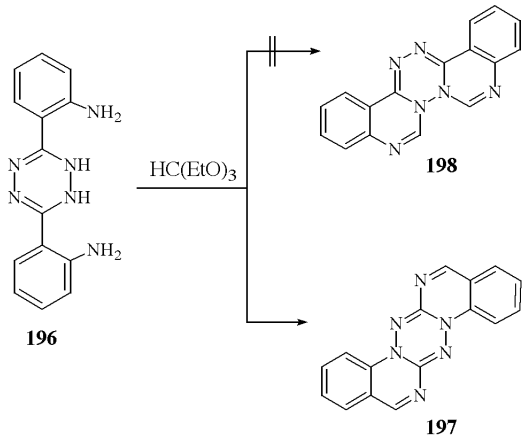
14. [1,2,4,5]Tetrazino[1,6-*c*:4,3-*c*']di[1,3,2]benzoxaphosphorines.

Chen *et al*. [79-81] reported the synthesis of the derivatives **211** of the title ring system (Chart 4). The crystal structures of some derivatives were also determined.

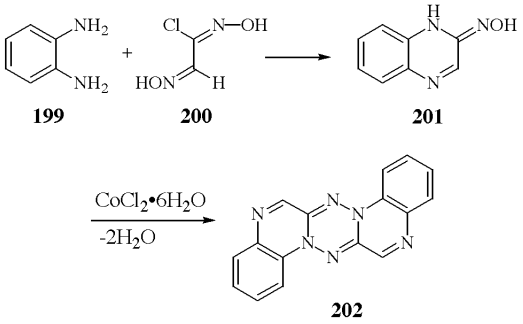
Scheme 56



Scheme 57



Scheme 58



B. With Four Bridgehead Nitrogen Atoms.

1. [1,2,4,5]Tetrazino[1,2-*a*:4,5-*a*']bis[4,1,2]benzoxadiazines and [1,2,4,5]Tetrazino[1,2-*a*:5,4-*a*']bis-[4,1,2]benzoxadiazines.

Reaction of 2-hydrazinocyclohexanol **212** with formaldehyde in ethanol was reported to give a mixture of **213** and **214** in 33% and 16% yields, respectively (Scheme 61) [58].

2. 3,9-Dioxa-3b,6b,9b,12b-tetraazaperylenes

When a mixture of **215** and glutaraldehyde **216** in tetrahydrofuran was stirred for 15 hours at room temperature 3,9-dioxa-3b,6b,9b,12b-tetraaza perhydroperylenes **218** were obtained in 42-72% yield (Scheme 62) [58]. The structures of the latter products were elucidated by ^{13}C NMR3 spectra and confirmed by X-ray crystallography.

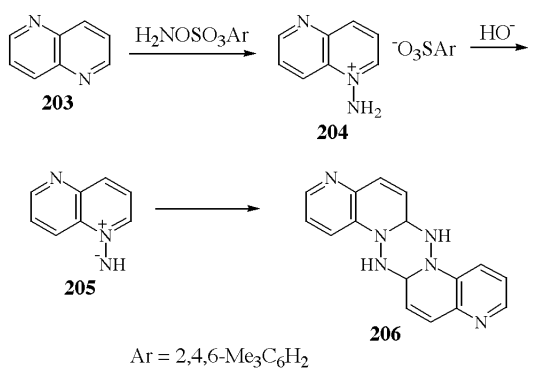
VI. Heptacyclic [1,2,4,5]tetrazines.

A. With Two Bridgehead Nitrogen Atoms.

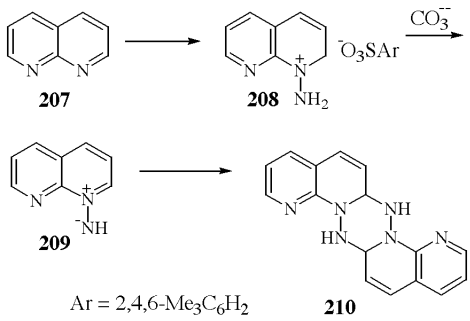
1. [1,2,4,5]tetrazino[1,6-*a*:4,3-*a*']diindole.

So far only one derivative of such ring system has been prepared. Thus, 1-aza-2-chloroacenaphthylene **219** was first *N*-aminated by *O*-arenesulfonylhydroxylamine to give the

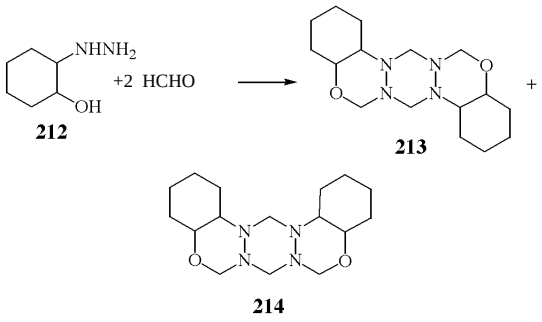
Scheme 59



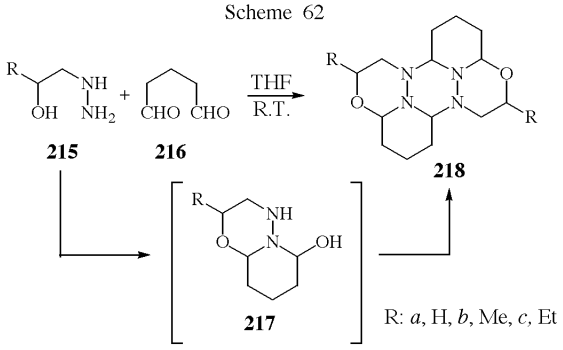
Scheme 60



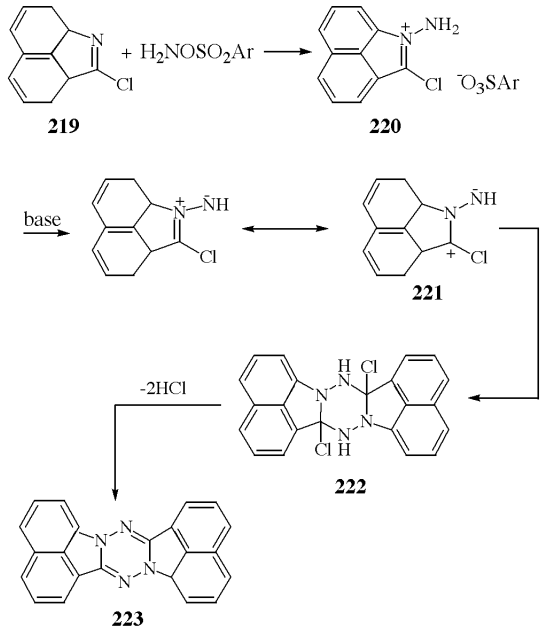
Scheme 61



Scheme 62



Scheme 63



salt **220**. Treatment of the latter with base, resulted in the generation of the 1,3 dipole **221**, which dimerizes to give cycloadduct **222**. Dehydrochlorination of the latter occurs *in situ* to give the end product **223** (Scheme 63) [53-55].

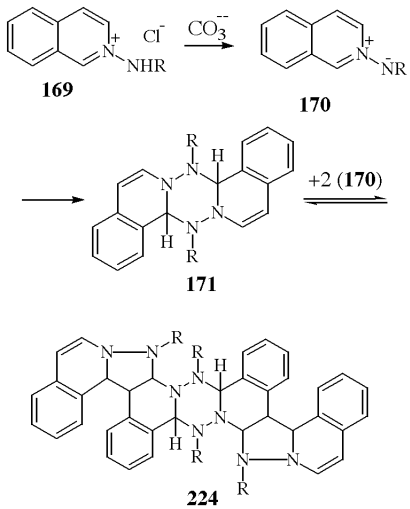
VII. Undecaycyclic [1,2,4,5]Tetrazines.

A. With Two Bridgehead Nitrogen Atoms

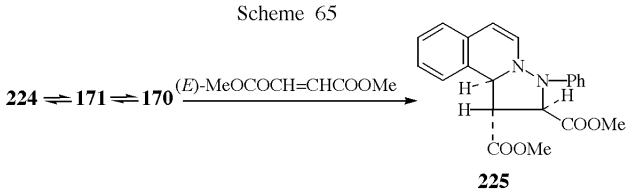
1. Tetramer of Isoquinolinium *N*-phenylimide

When a solution of 2-arylaminoisoquinolinium chloride **169** was treated with aqueous sodium carbonate, the corresponding isoquinolinium *N*-arylimide **170** is produced, which is usually deep in color. Treatment of the latter with

Scheme 64



Scheme 65



petroleum ether results in its dimerization to give a pentacyclic hexahydrotetrazine **171**. The kinetics of dimerization of **169** were studied. It was further indicated that the solid that separated upon generation of **170** appears to be its tetramer, namely **224** (Scheme 64). The latter is thought to be formed *via* cycloaddition of two ene-hydrazine double bonds in **171**. In dichloromethane it was indicated that an equilibrium is established between **224**, **171** and **170**. The fomation of the cycloaddact **225** when dimethyl fumarate was added to the solution of **224** (Scheme 65) [69] is evidence for the equilibrium.

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